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Application Number: 17993716 Document Date: 11/23/2022

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Form Revision Date: March 1, 2019

Agilent Ex. 2002
Axion v. Agilent, IPR2024-01467

PTO/AIA/15 (10-17)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995 no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	20191134-16
First Named Inventor	Xiaobo Wang
Title	
Priority Mail Express® Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. [✔] **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. [ ] **Applicant asserts small entity status.** See 37 CFR 1.27
3. [ ] **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. [✔] **Specification** [*Total Pages* 74] Both the claims and abstract must start on a new page. *(See MPEP § 608.01(a) for information on the preferred arrangement)*
5. [✔] **Drawing(s)** (35 U.S.C. 113) [*Total Sheets* 53]
6. **Inventor's Oath or Declaration** [*Total Pages* 4] *(including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))*
   a. [ ] Newly executed (original or copy)
   b. [✔] A copy from a prior application (37 CFR 1.63(d))
7. [✔] **Application Data Sheet** ** See note below.* See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. **CD-ROM or CD-R** in duplicate, large table, or Computer Program (*Appendix*)
   [ ] Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission** (*if applicable, items a. – c. are required*)
   a. [ ] Computer Readable Form (CRF)
   b. [ ] Specification Sequence Listing on:
      i. [ ] CD-ROM or CD-R (2 copies); or
      ii. [ ] Paper
   c. [ ] Statements verifying identity of above copies

ADDRESS TO:

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ACCOMPANYING APPLICATION PAPERS

10. [ ] **Assignment Papers** (cover sheet & document(s))
    Name of Assignee _____
11. [ ] **37 CFR 3.73(c) Statement** (*when there is an assignee*) [ ] **Power of Attorney**
12. [ ] **English Translation Document** (*if applicable*)
13. [ ] **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    [ ] Copies of citations attached
14. [ ] **Preliminary Amendment**
15. [ ] **Return Receipt Postcard** (*MPEP § 503*) (*Should be specifically itemized*)
16. [ ] **Certified Copy of Priority Document(s)** (*if foreign priority is claimed*)
17. [ ] **Nonpublication Request** Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
18. [✔] **Other:** Request for Prioritized Examination

***Note**: (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS

[✔] The address associated with Customer Number: 22878 **OR** [ ] Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/Raymond Wagenknecht/	Date	11/23/2022
Name (Print/Type)	Raymond Wagenknecht	Registration No. (Attorney/Agent)	50948

This collection of information is required by 37 CFR 1.53(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Type text here

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION
First Named Inventor/Applicant Name:	Xiaobo Wang
Filer:	Raymond C. Wagenknecht
Attorney Docket Number:	20191134-16

Filed as Large Entity

Filing Fees for Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	320	320
UTILITY SEARCH FEE	1111	1	700	700
UTILITY EXAMINATION FEE	1311	1	800	800
REQUEST FOR PRIORITIZED EXAMINATION	1817	1	4200	4200
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	1202	10	100	1000
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**7160**

Electronic Acknowledgement Receipt

EFS ID:	47086741
Application Number:	17993716
International Application Number:	
Confirmation Number:	1061
Title of Invention:	LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION
First Named Inventor/Applicant Name:	Xiaobo Wang
Customer Number:	22878
Filer:	Raymond C. Wagenknecht
Filer Authorized By:	
Attorney Docket Number:	20191134-16
Receipt Date:	23-NOV-2022
Filing Date:	
Time Stamp:	17:43:51
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$7160
RAM confirmation Number	E2022AMH45230958
Deposit Account	504352
Authorized User	Raymond Wagenknecht

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.16 (National application filing, search, and examination fees)

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	20191134-16_ADS.pdf	2226832 b710babf18b38c6d3eedaa1a74b0d6ef41e71ba1	no	10
Warnings:					
Information:					
2		20191134-16_FILED_Application.pdf	7237569 4f4b491716d4296024b35e8bc01db23ff680b092	yes	130

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	71
Claims	72	76
Abstract	77	77
Drawings-only black and white line drawings	78	130

Warnings:					
Information:					
3	Internet Communications Authorization	20191134-16_Internet-Comm.pdf	186086 4bffa01b6cc8670651e8bb694dbf767df619fd2a	no	2
Warnings:					
Information:					
4	Oath or Declaration filed	20191134-16_Parent-Declaration.pdf	1790095 71a8546078975a35ff227830a2f847e827af9b4e	no	4
Warnings:					
Information:					

5	Track One Request	20191134-16_Track-1-Request.pdf	124417 678e6e42e707f4cc892940d80d1cfb6891053cc3	no	2
Warnings:					
Information:					
6	Transmittal of New Application	20191134-16_Transmittal.pdf	285557 75e1d6b31e651059058c9fa3425b73d872623865	no	2
Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	53388 240672647e7e0927e08e23ce8439dbb7c5ef76eb	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	11903944	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/14 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	20191134-16
	Application Number	
Title of Invention	LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Xiaobo		Wang	

Residence Information (Select One) ● US Residency Non US Residency Active US Military Service

City	State/Province	Country of Residence
San Diego	CA	

Mailing Address of Inventor:

Address 1	Agilent Technologies, Inc.
Address 2	6779 Mesa Ridge Road, Suite 100
City	San Diego
State/Province	CA
Postal Code	92121
Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Yama	A.	Abassi	

Residence Information (Select One) ◉ US Residency Non US Residency Active US Military Service

City	State/Province	Country of Residence
San Diego	CA	

Mailing Address of Inventor:

Address 1	Agilent Technologies, Inc.
Address 2	6779 Mesa Ridge Road, Suite 100
City	San Diego
State/Province	CA
Postal Code	92121
Country	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Biao		Xi	

Residence Information (Select One) ◉ US Residency Non US Residency Active US Military Service

PTO/AIA/14 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	20191134-16
	Application Number	
Title of Invention	LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION	

City	San Diego	State/Province	CA	Country of Residence	

Mailing Address of Inventor:

Address 1	Agilent Technologies, Inc.
Address 2	6779 Mesa Ridge Road, Suite 100
City	San Diego
State/Province	CA
Postal Code	92121
Country	US

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Wen	Fu	Zhang	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	San Diego	State/Province	CA	Country of Residence	

Mailing Address of Inventor:

Address 1	Agilent Technologies, Inc.
Address 2	6779 Mesa Ridge Road, Suite 100
City	San Diego
State/Province	CA
Postal Code	92121
Country	US

Inventor 5 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Xiao		Xu	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	San Diego	State/Province	CA	Country of Residence	

Mailing Address of Inventor:

Address 1	Agilent Technologies, Inc.
Address 2	6779 Mesa Ridge Road, Suite 100
City	San Diego
State/Province	CA
Postal Code	92121
Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	20191134-16
	Application Number	
Title of Invention	LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION	

Customer Number	22878		
Email Address		Add Email	Remove Email

Application Information:

Title of the Invention	LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION		
Attorney Docket Number	20191134-16	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	53	**Suggested Figure for Publication (if any)**	1A

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	59538		

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	20191134-16
	Application Number	
Title of Invention	LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)	
	Continuation of	17824782	2022-05-25	
Prior Application Status	Patented			Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
17824782	Continuation of	16733781	2020-01-03	11360072	2022-06-14

Prior Application Status	Patented			Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16733781	Continuation of	16020679	2018-06-27	10533985	2020-01-14

Prior Application Status	Patented			Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16020679	Continuation of	15651882	2017-07-17	10012636	2018-07-03

Prior Application Status	Patented			Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15651882	Continuation of	12435569	2009-05-05	9709548	2017-07-18

Prior Application Status	Expired			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)	
12435569	Claims benefit of provisional	61191684	2008-09-11	
Prior Application Status	Expired			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)	
12435569	Claims benefit of provisional	61126533	2008-05-05	

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	20191134-16
	Application Number	
Title of Invention	LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION	

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	20191134-16
	Application Number	
Title of Invention	LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	20191134-16
	Application Number	
Title of Invention	LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	20191134-16
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LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This is a continuation of US patent application serial no. 17/824,782, filed May 25, 2022, which is a continuation of US patent application serial no. 16/733,781, filed January 3, 2020, now US patent 11,360,072, which is a continuation of US patent application serial no. 16/020,679, filed June 27, 2018, now US patent 10,533,985, which is a continuation of US patent application serial no. 15/651,882, filed July 17, 2017, now US patent 10,012,636, which is a continuation of US patent application serial no. 12/435,569, filed May 5, 2009, now US patent 9,709,548, which claims benefit of priority to U.S. provisional patent application serial no. 61/191,684, filed on September 11, 2008, and U.S. provisional patent application serial no. 61/126,533, filed on May 5, 2008; the content of each is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates generally to impedance-based monitoring of cells and more particularly to systems and methods for monitoring excitation-contraction coupling and excitable cells using impedance based systems with millisecond time resolution.

BACKGROUND OF THE INVENTION

[0003] Excitation-contraction coupling (ECC) is a term used to describe the physiological process of converting an electrical stimulus to a mechanical response. The process is fundamental to muscle physiology, wherein the electrical stimulus may be an

action potential and the mechanical response is contraction. Although ECC has been known generally over half a century, it is still an active area of biomedical research.

[0004] Cardiomyocytes are specialized muscle cells of the myocardium that are capable of excitation-contraction coupling. Cardiomyocytes are commonly used in biomedical research to assess the cardiotoxicity of potential drugs or treatments. Two conventional approaches to assess cardiotoxicity are primarily used. A first approach involves isolation of cardiomyocytes directly from a mammalian species such as rats and dogs followed by electrophysiological studies on the isolated cardiomyocytes. However, this approach suffers from being extremely labor-intensive, time consuming and costly and at the same time not very amenable to the high throughput demands of pharmaceutical industry. An alternative approach utilizes cell-based assay models, which heterologously express specific ion channels such as hERG channels or voltage-gated calcium channels. These cardiac ion channels have been envisioned as possible molecular targets through which drugs could induce cytotoxicity. These cell-based systems allow assessment of drug-channel interaction by monitoring the effect of the drug on currents produced by different channels in cultured cells using a technique known as "patch clamping." Patch clamping isolates regions of the cell membrane containing channel proteins and measures changes in electrical potential difference. However, use of this method in high throughput requires automation of patch clamping in an array format, which even though is becoming increasing available, is not yet widespread. In addition, cardiac toxicity may occur by other mechanisms that may be missed by this type of targeted approach.

[0005] An alternative to in vitro ion-channel recording assays as well as the labor-intensive isolation of primary tissue is the differentiation of embryonic stem (ES) cells into cardiomyocytes. The utility of ES cells as a treatment for various chronic diseases has received much attention in recent years. Mammalian ES cells are self renewing cells derived from the inner cell mass of a blastocyst stage embryo which can be differentiated into multiple different cell types. It has been demonstrated that the mouse ES cells as well as human ES cells can be differentiated into cardiomyocytes which retain the ability to beat in culture. Differentiation of ES cells first involves an intermediate in vitro developmental stage in which ES cells form compact cell structures known as embryoid

bodies. These embryoid bodies can induce the developmental program of ES cell differentiation into multiple cell types including cardiomyocytes, which are distinguished in culture by their ability to undergo spontaneous beating. These ES derived in vitro differentiated cardiomyocytes recapitulates the normal development of cardiomyocytes as evidenced by the stage-specific expression of cardiomyocyte specific genes. All the known transcription factors, ion channels and structural proteins that are part of normal heart development and function in vivo are also expressed in ES-derived cardiomyocytes.

[0006] Even though high throughput to medium throughput systems have been developed for functional characterization of cell lines heterologously expressing the gene for specific ion channels, high throughput techniques for functional characterization of more complex systems such as cardiomyocytes have been limited. Technologies designed to assess cardiomyocyte behaviour and function and the effect of drugs and other manipulations *in vitro* can be divided into two different approaches. One approach involves long term assessment of cardiomyocyte viability for example in response to certain compounds. Such assays are typically end point assays designed to measure a cellular component such as ATP which correlates with the degree of viability of the cells. The other approach involves studying short term effect of drugs and compounds on beating function of cardiomyocytes. High throughput techniques for short term functional characterization of ion channels and other targets in cardiomyocytes has been rather challenging and limited. The available systems typically only monitor a single cardiomyocyte or a small number of cardiomyocytes at a time and with very limited throughput.

SUMMARY OF THE INVENTION

[0007] The present invention addresses the need to provide systems and methods for improved monitoring of excitation-contraction coupling and excitable cells and provides related benefits. Specifically, embodiments of the invention describe label-free methods for monitoring excitable cells, such as cardiomyocytes, in vitro. The system is capable of continuously monitoring excitation-contraction coupling in a relatively high-

throughput manner. The systems and methods can be used for pharmacological safety assessment, screening for novel compounds which modulate cardiomyocyte function in a specific manner, and assessment of genes involved or potentially involved in cardiac function. In addition the system and methods may study the role of different genes and proteins in cardiac function and development through the use of embryonic stem (ES) derived cardiomyocytes.

[0008] In one aspect of the presence invention a system for monitoring impedance of excitable cells in vitro is provided including a device for monitoring cell-substrate impedance, an impedance analyzer capable of impedance measurements at millisecond time resolution, electronic circuitry that can engage the device and selectively connect two or more electrode arrays of the device to the impedance analyzer and a software program that controls the electronic circuitry and records and analyzes data obtained from the impedance analyzer. Embodiments of the device for monitoring substrate impedance include a nonconductive substrate having one or more individually addressable electrode arrays fabricated thereon and one or more wells. Preferably, each of the one or more arrays is associated with one of the one or more wells and each electrode array is individually addressable. In further embodiments, a surface of the substrate is suitable for cell attachment, wherein cell attachment results in a detectable change in impedance between electrodes within the array. Attachment or growth along the surface may be enhanced by applying a precoat having one or more compounds that improve attachment. In embodiments where the device includes multiple wells, the impedance analyzer has the capability to allow impedance measurements for each and every well at millisecond time resolution. That is to say, for a selected time period, the impedance data for each and every well of the system is measured at millisecond time resolution. Further, when groups of wells are monitored, the groups are monitored at millisecond time resolution.

[0009] Embodiments of the system include electrode arrays having two electrode structures that have substantially the same surface area. The electrodes themselves may be formed from suitable electrically conductive materials such as metal, gold, platinum, titanium, chromium and the like. The electrode arrays may be organized in a variety of configurations, including interdigitated, circle-on-line, diamond-on-line, concentric,

sinusoidal, and castellated. The widths of the electrode structures may be between 20 microns and 500 microns or 5 microns and 100 microns.

[0010] Embodiments of the invention include impedance monitoring using millisecond time resolution. Millisecond time resolution allows monitoring of at least two consecutive impedance measurements with an excitation cycle of excitable cells, which are introduced into the well. Further, millisecond time resolution enhances measurement such that excitation-contraction coupling of excitable cells may be effectively monitored. In some embodiments the excitation cycle is a beating cycle, such as a beating cycle of a cardiomyocyte. In some embodiments at least two consecutive impedance measurements are performed in less than 100 milliseconds. In other embodiments at least two consecutive impedance measurements are performed in less than 40 milliseconds. In still further embodiments at least two consecutive impedance measurements are performed in less than 20 milliseconds. In still further embodiments the at least two consecutive impedance measurements are performed in less 10 milliseconds.

[0011] In some embodiments the device is provided as a multiwell device or a multiwell plate. In some embodiments, the multiwell device or multiwell plate may including 6 wells, 8 wells, 16 wells, 32 wells, 96 wells, 384 wells or any number therebetween. Throughout the present application where the device includes multiple wells each of which is associated with an electrode array, millisecond time resolution refers to that for any selected time period, the impedance measurement for each and every well can be performed with two consecutive measurements separated with millisecond resolution. Further, when groups of wells, such as subsets of all wells of a device, are monitored a group of wells may be monitored using millisecond time resolution.

[0012] Embodiments of the present invention provide impedance-based monitoring with millisecond time resolution in combination with longer term monitoring of cells. By combining millisecond time resolution technology with impedance monitoring having longer time periods, both short term and long term effects on excitable cells can be evaluated. In some embodiments impedance readouts can be used to monitor

both short term beating and long term viability status of cardiomyocytes in the same well or the same population. Such monitoring addresses needs where certain manipulations such as drug treatment may not manifest its effect on cardiomyocyte beating and/or viability until a later time period.

[0013] In some embodiments methods for assessing and quantifying excitable cells in vitro include providing the impedance-based system with millisecond time resolution; adding excitable cells to one or more wells; monitoring impedance of the one or more wells over a first time period, which is characterized as a longer time period, such as seconds, minutes, hours or days; monitoring impedance of the one or more wells over a second time period in millisecond time resolution; determining a characteristic, such as cell attachment, cell growth and cell viability from monitoring over the first time period; and resolving individual cycles of the excitable cells from monitoring over the second time period. In such embodiments, monitoring impedance over the second time period may be performed at regular or irregular time intervals within monitoring impedance over the first time period.

[0014] Among the benefits, embodiments of the invention permit impedance readouts to monitor the morphological or differentiative behavior of cardiomyocytes in vitro. Certain treatments can induce changes in morphological behavior of cardiomyocytes, such as inducing hypertrophy which is associated with cardiomyocyte elongation and expansion. Because impedance monitoring can detect changes in cell morphology, it can be used to for detection of hypertrophy in cardiomyocytes.

[0015] In another aspect of the present invention a method for assessing or quantifying excitable cells in vitro is provided. An exemplary method includes providing the impedance based system having millisecond time resolution, adding excitable cells to the one or more wells, monitoring impedance of the one or more wells, and resolving individual cycles of the excitable cells. The method has particular utility with cells that are known or suspected to be capable of or undergo excitation-contraction coupling, such as cardiomyocytes. The method may also be useful for monitoring neurological cells or neurological systems. Impedance measurements may be performed in millisecond time resolution. In some embodiments, two consecutive impedance measurements for each

and every well of the system are performed less than 300 milliseconds apart. In further embodiments, at least two consecutive impedance measurements for each and every well of the system are performed less than 100 milliseconds apart. In further embodiments, at least two consecutive impedance measurements for each and every well of the system are performed less than 40 milliseconds apart. In further embodiments, at least two consecutive impedance measurements for each and every well of the system are less than 10 milliseconds apart.

[0016] In some embodiments methods of determining whether a compound modulates a beating cycle of an excitable cell is provided. An exemplary method includes providing the impedance based system having millisecond time resolution, wherein the system includes at least two wells; adding excitable cells to the at least two wells; monitoring impedance of the at least two wells; adding a compound suspected of modulation of the beating cycle to a first of the at least two wells to provide a test well, wherein a second well lacking compound or having a control compound is provided as a control well; resolving the beating cycle of both test well and control well; and comparing the beating cycles between the test well and control well, wherein a difference in beating cycles indicates the compound modulates the beating cycle of the excitable cell. In some embodiments, beating cycles are compared to identify changes in beating magnitude or amplitude. In other embodiments, beating cycles are compared to identify changes in beating frequency, which may be regular changes or irregular changes. In further embodiments the method includes determining a cell index for each of the test well and control well such that the step of comparing the beating cycles includes comparing the cell indices between test well and control well. Peak magnitude or amplitude and/or frequency may be compared. The method may also include monitoring impedance over longer time periods of time. Such embodiments may provide long term impedance monitoring with intermittent monitoring using millisecond resolution. Thus short term and long term monitoring may be performed.

[0017] In another exemplary methods include providing a device for measuring cell-substrate impedance operably connected to an impedance analyzer, wherein the device includes at least two wells; adding ES cells, adult stem-cell derived cardiomyocytes or primary cardiomyocytes to at least two wells; monitoring impedance

of the at least two wells at different or similar time intervals over a period of time and optionally determining cell indices from impedance values; generating an impedance-based curve or optionally a cell index curve for each of the at least one known biologically active agent and the control; comparing the impedance-based curves or optionally the cell index curves between the at least one known biologically active agent well and the control well. The impedance-based curves may be direct measurement of cardiomyocyte excitation-contraction coupling and if significantly different, concluding that the biologically active agent modulates cardiomyocyte function. Optionally, impedance-based curves or optionally cell index curves are used to calculate average rate of beats of cardiomyocytes per unit time, average amplitude intensity in a unit time as well as the average length of time between the beats, comparison of these optionally derived parameters is made between the at least one known biologically active agent well and the control well, and if significant differences exist, one may optionally conclude that the biologically active agents modulate cardiomyocyte functions.

[0018] In other embodiments of the present invention, a method of characterizing rhythmic beating of a cardiomyocyte is provided. An exemplary method includes providing the impedance based system with millisecond time resolution; adding excitable cells to the one or more wells; monitoring impedance of the one or more wells in millisecond time resolution; determining a plurality of beating cycle peaks; and comparing magnitude or amplitude or frequency of the peaks over a time unit. Various methods can be used for determining beating cycle peaks. For example, time dependent impedance values or cell index values for a well are analyzed by deriving their first order derivatives and second order derivatives using numerical methods. The beating cycle peaks are those data points where the first order derivatives of impedance values or cell index values are zero or close to zero in its absolute value. If the beating cycle peak is a positive peak (i.e. peak corresponds to a maximum value in measured impedance or cell index over the beating cycle), then the peak would correspond to the data points where the second order derivatives of the impedance values or cell index values is negative and where the first order derivatives of the impedance values or cell index values is zero or close to zero in its absolute value. If the beating cycle peak is a negative peak (i.e. peak corresponds to a minimum value in measured impedance or cell index over the

beating cycle), then the peak would correspond to the data points where the second order derivatives of the impedance values or cell index values is positive and where the first order derivatives of the impedance values or cell index values is zero or close to zero in its absolute value. The step of determining a plurality of beating cycle peaks may include determining a rise in impedance and a decay in impedance and extrapolating a peak from each rise and decay. The method may further include determining a cell index for each of the one or more wells, which may allow improved comparison of beating cycles. Further, beating cycle peaks may be determined by identifying frequency components having largest magnitude in Fourier transformed impedance data. The method may also include monitoring impedance over longer time periods of time. Such embodiments may provide long term impedance monitoring with intermittent monitoring using millisecond resolution.

[0019] A variety of agents and compounds may be tested for modulation of excitable cells and for modulation of rhythmic beating of cardiomyocytes. Examples include compounds, peptides, proteins, antibodies or antibody fragments, siRNA, shRNA, lipid or any combination of thereof.

[0020] In another aspect of the present invention a method of assessing genetic manipulation of an embryonic stem cell is provided including providing the impedance based system having millisecond time resolution, mutating embryonic stem cells to include a genetic mutation; adding mutated embryonic stem cells to a first well of at least two wells to form a test well and control embryonic stem cells to a second of at least two wells to form a control well; monitoring impedance of the at least two wells in millisecond time resolution; resolving the beating cycles of both test well and control well, if any; and comparing the beating cycles between the test well and control well, wherein a difference in beating cycles indicates the genetic mutation modulates embryonic stem cell differentiation. In some embodiments the embryonic stem cell differentiation is differentiation into a cardiomyocyte. In some embodiments the genetic mutation is selected from the group consisting of a genetic knock out, a knock down and an inserted transgene. The method may also include monitoring impedance over longer time periods of time. Such embodiments may provide long term impedance monitoring

with intermittent monitoring using millisecond resolution. Thus short term and long term monitoring may be performed.

BRIEF DESCRIPTION OF THE DRAWNGS

[0021] Those skilled in the art will recognize that the drawings described below are for illustrative purposes only. The drawings are not intended to limit the scope of the invention but to provide exemplary embodiments.

[0022] FIGS.1A-1B depict schematic drawings of one design of a cell-substrate impedance measurement device of the present invention. **FIG. 1A** shows a nonconductive substrate (**101**) shown with 16 electrode arrays fabricated on the substrate. Each electrode array (**102**) comprises two electrode structures (shown in detail in **FIG. 1B**). Each electrode structure comprises multiple electrode elements. Each electrode array connects to two electrical traces (**103**), with each of the two traces connected one of the two electrode structures. These electrical connection traces (**103**) from the electrode array (**102**) are connected to the connection pads (**104**) at the edges of the substrate (**101**). As shown in **FIG. 1A**, each the four electrode arrays in each of four quarters on the substrate (**101**) have one of their electrical connection traces (**103**) connected to a common connection pad (**104**). Thus, for the entire device there are four common connection pads (**104**), one for each quarter of the device. In addition, each electrode array has a separate electrical connection trace (**103**), connecting to an independent connection pad (**104**). Thus, there are total 20 connection pads (**104**) at the edges of the substrate (**101**). In **FIG. 1B** a single exemplary electrode array is shown. The electrode array has two electrode structures, where each electrode structure comprises multiple electrode elements (**105**) shown here having a circle-on-line geometry. In this electrode array structure, electrode elements (**105**) of one electrode structure of the array alternate with electrode elements (**105**) of the other electrode structure of the array. Each of the electrode structures is independently connected to its electrode bus (**106**), in this case, by means of direct connection of the electrode elements (**105**) to the electrode bus (**106**). Each electrode bus (**106**) forms an arc around the perimeter of the array, where the two buses of the array do not abut or overlap. The electrically conductive connection traces

(**103** in **FIG. 1A**) connect each bus with a connection pad (**104** in **FIG. 1A**) on the edge of the substrate (**101** in **FIG. 1A**).

[0023] FIG. 2A is a schematic representation of a device **100** with two electrode structures of same or similar areas deposited on a substrate. First electrode structure has electrode elements **110a**, **110b**, **110c** and second electrode structure has electrode elements **120a**, **120b**, **120c** and **120d**. Electrode elements within an electrode structure are connected to each other by arc-shaped connection electrode bus **125**. Like the electrode elements, such connection-buses (**125**) are also made of electrically conductive material (e.g. gold film, platinum film, gold film over a chromium or titanium film). These electrically conductive connection-paths or connection buses (**125**) may have an insulating coating. Electrode elements **110a-110c** and **120a-120d** comprise electrode lines with connected circles added on the line. The overall area of electrode elements and gaps between electrode elements may correspond to, or may be slightly larger than, or may be slightly smaller than, the bottom of a well (e.g., a cylinder shaped well, a conical shaped well, or a cubic shaped well), for example, a 24 well-plate, a 96-well plate, or 384 well plate that are commonly used. The whole surfaces of the wells may be covered with electrodes to ensure that the cell attachment at nearly any locations of the bottom surface of the well can contribute to the impedance change. This arrangement has an advantage that non-uniform landing and attachment of cells on the bottom surface of the different wells would result in only a small variation in the impedance measured between electrode structures **110** and **120**. **150** are connection pads that can be connected to an external impedance measurement circuit. **130** is the electrical connection traces that connects the connection pad to the electrode structures **110** and **120**. Such connection traces can extend in any direction in the plane of the electrodes. **FIG. 2B** is a schematic representation of a device **200** with two electrode structures of similar areas deposited on a substrate. Electrode structures **210** and **220** comprise multiple interconnected electrode elements. Electrode elements (**210a-210c**, **220a-220d**) are rectangular lines and together form an interdigitated electrode structure unit. Similar to **FIG. 2A**, the electrode elements (**210a-210c**, **220a-220d**) within each electrode structure are connected through arc-shaped, electrically conductive paths or electrode buses (**225**). Connection pads **250** are connected to electrode structures through the electrical connection traces **230**. **FIG.**

2C is a schematic representation of a device **300** with two electrode structures of similar areas deposited on a substrate. Electrode structures **310** and **320** comprise multiple interconnected electrode elements (**310a-310f**, **320a-320f**). Electrode elements (**310a-310c**, **320a-320d**) are rectangular lines and together form an interdigitated electrode structure unit. Different from **FIG. 2A** and **FIG. 2B**, the electrode structures having electrode elements **310a-310c** and **320a-320c** are connected to connection pads **350**.

[0024] FIG. 3 shows the cell index curves measured on RT-CES system for 4 different seeding densities (3750, 7500, 15,000 and 30,000 cells per well) of mouse ES-derived cardiomyocytes. In this example, the impedance measurement was taken with a time resolution of 1 hour between any two consecutive data points for each well.

[0025] FIG. 4A provides a plot of normalized cell index values for cells in different wells treated with different concentrations of sodium dichromate dehydrate (SDD). **FIG. 4B** provides the corresponding sigmoidal curve for deriving the IC-50 of the compound.

[0026] FIG. 5A provides a graph of normalized impedance data over time showing shifts in morphology in response to isproteranol, a β2 adrenergic receptor agonist. **FIG. 5B** shows a plot of the normalized cell indices against the log of the corresponding isoproteranol concentrations to calculate the EC-50.

[0027] FIG. 6 shows the cell index curves measured on RT-CES system for 4 individual wells, with cell culture medium as background starting from cell seeding to about 86 hrs after cell seeding. For such long term measurement, cell electrode impedance and corresponding cell indices were measured at about 15 minute intervals. Thus for each well, the impedance measurement was performed with a time resolution of 15 minutes.

[0028] FIGS. 7A-D provides a series of graphs showing cardiomyocyte beating throughout attachment and growth phases.

[0029] FIG. 8A and **FIG. 8B** are a pair of cell index curves and the corresponding beat rate derived from Fourier transformation of impedance values

[0030] FIGS. 9A-D show cardiomyocyte beating data from mouse cardiomyocytes treated with sotalol. In **FIGS. 9C** and **9D**, the time resolution between two adjacent points is 40 milliseconds. In other words, a second in **FIGS. 9C** and **9D** is equivalent to 40 milliseconds.

[0031] FIG 10A depicts graphs of agents which slow down heart rate and cardiomyocyte beating. **FIG. 10B** depicts graphs of agents which increase heart rate and cardiomyocyte beating.

[0032] FIGS. 11A-T depict impedance data of cardiomyocyte patterns associated with testing of a variety of known compounds, which are further described in **Table II**.

[0033] FIG. 12 depicts impedance based cardiotoxic patterns from known compounds.

[0034] FIG. 13 shows an example of dose dependent effects of Astemizole on cardiomyocytes beating at different concentrations.

[0035] FIGS. 14A - H are graphical depictions of real time impedance-based millisecond time resolution of cardiomyocyte beating in response to Haloperidol treatment. The Y-axis is the cell index value.

[0036] FIGS. 15A-H depict graphical analysis of the impedance beating frequency from impedance plots (cell index plots) shown in **FIGS. 14A – H**.

[0037] FIGS. 16A-H depict additional graphical analysis of the magnitude or amplitude of the beating cycle peaks from impedance plots (cell index plots) shown in **FIGS. 14A–H.**

[0038] FIGS. 17A-I are graphical depictions of real time impedance-based millisecond time resolution of cardiomyocyte beating in response to Erythromycin treatment. The Y-axis is the cell index value.

[0039] FIGS. 18A-I depict graphical analysis of the impedance beating frequency from impedance plots (cell index plots) shown in **FIGS. 17A – I**.

[0040] FIGS. 19A-I depict additional graphical analysis of beating magnitude or amplitude of the beating cycle peaks shown from impedance plots (cell index plots) shown in **FIGS. 17A – I.**

DETAILED DESCRIPTION OF THE INVENITON

[0041] Detailed descriptions of preferred embodiments of the provided herein. It is to be understood; however, that the present invention may be embodied in various forms. Therefore specific reference to various forms are provided as a basis for the claims and for teaching one skilled in the present art to employ the present invention in appropriate system, structure or manner.

A. Definitions

[0042] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this invention belongs. All patents, applications, published applications and other publications referred to herein are incorporated by reference in their entirety. If a definition set forth in this section is contrary to or otherwise inconsistent with a definition set forth in the patents, applications, published applications and other publications that are herein incorporated by reference, the definition set forth in this section prevails over the definition that is incorporated herein by reference.

[0043] As used herein, "a" or "an" means "at least one" or "one or more."

[0044] As used herein, "membrane" is a sheet of material.

[0045] As used herein, "biocompatible polymer" means a polymeric material that does not have deleterious effects on cells, including the viability, attachment, spreading, motility, growth, or cell division.

[0046] As used herein, "suitable for attachment" refers to structural features that permit attachment of cells thereto. A surface is "suitable for cell attachment" when a

significant percentage of the cells attach or adhere to the surface within twelve hours. Preferably, at least 50% of the cells are adhered to the surface within twelve hours. More preferably, at least 70% of the cells are adhered to the surface within twelve hours of plating (i.e., adding cells to the well or fluid container). Even more preferably, the surface properties of a surface that is suitable for cell attachment results in at least 90% of the cells adhering to the surface within twelve hours of plating. Most preferably, the surface properties of a surface that is suitable for cell attachment results in at least 90% of the cells adhering to the surface within eight, six, four, two hours of plating. To have desired surface properties for cell attachment, the surface may need to chemically-treated (e.g. treatment with an acid and/or with a base), and/or physically treated (e.g. treatment with plasma), and/or biochemically treated (e.g. coated with one or more molecules or biomolecules that promotes cell attachment).

[0047] As used herein, "impedance measurement at millisecond time resolution" refers to the ability to perform a series of at least two consecutive impedance measurements within milliseconds of one another for each and every well of the system where each well is associated with an electrode array for impedance measurement. In each instance the time between two consecutive impedance measurements are less than 300 milliseconds from one another. Preferably, consecutive impedance measurements are less than 200 milliseconds from one another. More preferably impedance measurements are less than 100 milliseconds from one another. For example, the time between two consecutive impedance measurements are 40 milliseconds from one another for each and every well of the system. To be clear, that is to say, in a time period of 40 milliseconds, the system has the ability to measure two impedance data points for each and every well of the system.

[0048] As used herein, "excitable cells" refers to a cell population that is capable of propagation and spreading action potentials to surrounding cells. These cells are able to produce and respond to electrical signals. Some excitable cells are capable of excitation-contraction coupling. Examples of "excitable cells" include cardiomyocytes, cells that beat, some skeletal muscle cells, some smooth muscle cells and some neural cells. Identification of excitable cells may be found in cell biology literature.

[0049] As used herein, "excitation-contraction coupling" refers to the physiological process of converting an electrical stimulus to mechanical response. This process is fundamental to muscle physiology, whereby the electrical stimulus is usually an action potential and the mechanical response is contraction. EC coupling can be dysregulated in many disease conditions.

[0050] As used herein, "beating cycle" refers the time between which a cardiomyocyte sequentially beats. The "beating cycle" may vary depending on organism and developmental stage of the cardiomyocyte. A beating cycle may be as short as between 100 and 200 milliseconds, translating to a beating rate of 600 to 300 beats per minute. A beating cycle may be as long as between 1000 millisconds and 10,000 milliseconds, translating to a beating rate of 60 to 6 beats per minute.

[0051] As used herein, "biomolecular coating" or "coated with a biomolecule" refers to is a coating on a surface that comprises a molecule that is a naturally occurring biomolecule or biochemical, or a biochemical derived from or based on one or more naturally occurring biomolecules or biochemicals. For example, a biomolecular coating can comprise an extracellular matrix component (e.g., fibronectin, collagens), or a derivative thereof, or can comprise a biochemical such as polylysine or polyornithine, which are polymeric molecules based on the naturally occurring biochemicals lysine and ornithine. Polymeric molecules based on naturally occurring biochemicals such as amino acids can use isomers or enantiomers of the naturally-occuring biochemicals.

[0052] As used herein, "extracellular matrix component" refers to a molecule that occurs in the extracellular matrix of an animal. It can be a component of an extracellular matrix from any species and from any tissue type. Nonlimiting examples of extracellular matrix components include laminins, collagens fibronectins, other glycoproteins, peptides, glycosaminoglycans, proteoglycans, etc. Extracellular matrix components can also include growth factors.

[0053] As used herein, "electrode" refers to a structure having a high electrical conductivity, that is, an electrical conductivity much higher than the electrical conductivity of the surrounding materials.

[0054] As used herein "electrode structure" refers to a single electrode, particularly one with a complex structure (as, for example, a spiral electrode structure), or a collection of at least two electrode elements that are electrically connected together. All the electrode elements within an "electrode structure" are electrically connected.

[0055] As used herein, "electrode element" refers to a single structural feature of an electrode structure, such as, for example, a fingerlike or branched projection of an interdigitated electrode structure.

[0056] As used herein "electrode structure unit" refers to two or more electrode structures that are constructed to have dimensions and spacing such that they can, when connected to a signal source, operate as a unit to generate an electrical field in the region of spaces around the electrode structures. Preferred electrode structure units of the present invention can measure impedance changes due to cell attachment to an electrode surface. Non-limiting examples of electrode structure units are interdigitated electrode structure units and concentric electrode structure units.

[0057] As used herein, "electrode traces" refer to electrically conductive paths that extend from electrodes or electrode elements or electrode structures toward one end or boundary of a device or apparatus for connecting the electrodes or electrode elements or electrode structures to an impedance analyzer. The end or boundary of a device may correspond to the connection pads on the device or apparatus.

[0058] As used herein, "connection pad" refers to an area on an apparatus or a device of the present invention which is electrically connected to at least one electrode or all electrode elements within at least one electrode structure on an apparatus or a device and which can be operatively connected to external electrical circuits (e.g., an impedance measurement circuit or a signal source). The electrical connection between a connection pad and an impedance measurement circuit or a signal source can be direct or indirect, through any appropriate electrical conduction means such as leads or wires. Such electrical conduction means may also go through electrode or electrical conduction paths located on other regions of the apparatus or device.

[0059] As used herein, "interdigitated" refers to having projections coming from one direction that interlace with projections coming from a different direction in the

manner of the fingers of folded hands (with the caveat that interdigitated electrode elements preferably do not contact one another).

[0060] As used herein, "high probability of contacting an electrode element" refers to if a cell is randomly positioned within the sensor area of a device or apparatus of the present invention, the probability of a cell (or particle) contacting on an electrode element, calculated from the average diameter of a cell used on or in a device or apparatus of the present invention, the sizes of the electrode elements, and the size of the gaps between electrode elements, is greater than about 50%, more preferably greater than about 60%, yet more preferably greater than about 70%, and even more preferably greater than about 80%, greater than about 90%, or greater than about 95%.

[0061] As used herein, "at least two electrodes fabricated on said substrate" refers to at least two electrodes are fabricated or made or produced on the substrate. The at least two electrodes can be on the same side of the substrate or on the different side of the substrate. The substrate may have multiple layers, the at least two electrodes can be either on the same or on the different layers of the substrate.

[0062] As used herein, "at least two electrodes fabricated to a same side of said substrate" refers to at least two electrodes are fabricated on the same side of the substrate.

[0063] As used herein, "at least two electrodes fabricated to a same plane of said substrate" refers to, if the nonconducting substrate has multiple layers, the at least two electrodes are fabricated to the same layer of the substrate.

[0064] As used herein, "electrodes have substantially same surface area" refers to the surface areas of the electrodes referred to are not substantially different from each other, so that the impedance change due to cell attachment or growth on any one of the electrodes referred to will contribute to the overall detectable change in impedance to a same or similar degree as the impedance change due to cell attachment or growth on any other of the electrodes referred to. In other words, where electrodes have substantially the same surface area, any one of the electrodes can contribute to overall change in impedance upon cell attachment or growth on the electrode. In most cases, the ratio of surface area between the largest electrode and the smallest electrode that have

"substantially the same surface area" is less than 10. Preferably, the ratio of surface area between the largest electrode and the smallest electrode of an electrode structure is less than 5, 4, 3, 2, 1.5, 1.2 or 1.1. More preferably, the at least two electrodes of an electrode structure have nearly identical or identical surface area.

[0065] As used herein, "said device has a surface suitable for cell attachment or growth" refers to the electrode and/or non-electrode area of the apparatus has appropriate physical, chemical or biological properties such that cells of interest can viably attach on the surface and new cells can continue to attach, while the cell culture grows, on the surface of the apparatus. However, it is not necessary that the device, or the surface thereof, contain substances necessary for cell viability or growth. These necessary substances, e.g., nutrients or growth factors, can be supplied in a medium. Preferably, when a suspension of viable, unimpaired, excitable cells is added to the "surface suitable for cell attachment" at least 50% of the cells adhere to the surface within twelve hours. More preferably, a surface that is suitable for cell attachment has surface properties so that at least 70% of the cells are adhering to the surface within twelve hours of plating (i.e., adding cells to the chamber or well that comprises the said device). Even more preferably, the surface properties of a surface that is suitable for cell attachment results in at least 90% of the cells adhering to the surface within twelve hours of plating. Most preferably, the surface properties of a surface that is suitable for cell attachment results in at least 90% of the cells adhering to the surface within eight, six, four, two hours of plating.

[0066] As used herein, "detectable change in impedance between or among the electrodes" refers to the impedance between or among the electrodes would have a significant change that can be detected by an impedance analyzer or impedance measurement circuit when molecule binding reaction or cell attachment or cell adhesion or cell presence occurs on the electrode surfaces. The impedance change refers to the difference in impedance values when cell attachment or cell adhesion or cell presence or molecule binding reaction occurs on the electrode surface of the apparatus and when no molecular reaction occurs on the electrode surface or no cell is present on the electrode surface. The impedance change may occur upon the presence or decay of a beat from a cardiomyocyte. Alternatively, the impedance change refers to the difference in

impedance values when cells are attached to the electrode surface and when cells are not attached to the electrode surface, or when the number, type, activity, or morphology of cells attached to the electrode-comprising surface of the apparatus changes. In most cases, the change in impedance is larger than 0.1% to be detectable. Preferably, the detectable change in impedance is larger than 1%, 2%, 5%, or 8%. More preferably, the detectable change in impedance is larger than 10%. Impedance between or among electrodes is typically a function of the frequency of the applied electric field for measurement. "Detectable change in impedance between or among the electrodes" does not require the impedance change at all frequencies being detectable. "Detectable change in impedance between or among the electrodes" only requires a detectable change in impedance at any single frequency (or multiple frequencies). In addition, impedance has two components, resistance and reactance (reactance can be divided into two categories, capacitive reactance and inductive reactance). "Detectable change in impedance between or among the electrodes" requires only that either one of resistance and reactance has a detectable change at any single frequency or multiple frequencies. In the present application, impedance is the electrical or electronic impedance. The method for the measurement of such impedance is achieved by, (1) applying a voltage between or among the electrodes at a given frequency (or multiple frequencies, or having specific voltage waveform) and monitoring the electrical current through the electrodes at the frequency (or multiple frequencies, or having specific waveform), dividing the voltage amplitude value by the current amplitude value to derive the impedance value; (2) applying an electric current of a single frequency component (or multiple frequencies or having specific current wave form) through said electrodes and monitoring the voltage resulted between or among the electrodes at the frequency (or multiple frequencies, or having specific waveform), dividing the voltage amplitude value by the current amplitude value to derive the impedance value; (3) other methods that can measure or determine electric impedance. Note that in the description above of "dividing the voltage amplitude value by the current amplitude value to derive the impedance value", the "division" is done for the values of current amplitude and voltage amplitude at same frequencies. Measurement of such electric impedance is an electronic or electrical process that does not involve the use of any reagents.

[0067] As used herein, "multiple pairs of electrodes or electrode structures spatially arranged according to wells of a multi-well microplate" refers to multiple pairs of electrodes or electrode structures of a device or apparatus are spatially arranged to match the spatial configuration of wells of a multi-well microplate so that, when desirable, the device can be inserted into, joined with, or attached to a multiwell plate (for example, a bottomless multiwell plate) such that multiple wells of the multi-well microplate will comprise electrodes or electrode structures.

[0068] As used herein, "arranged in a row-column configuration" refers to that, in terms of electric connection, the position of an electrode, an electrode array or a switching circuit is identified by both a row position number and a column position number.

[0069] As used herein, "each well contains substantially same number . . . of cells" refers to the lowest number of cells in a well is at least 50% of the highest number of cells in a well. Preferably, the lowest number of cells in a well is at least 60%, 70%, 80%, 90%, 95% or 99% of the highest number of cells in a well. More preferably, each well contains an identical number of cells.

[0070] As used herein, "each well contains . . .same type of cells" means that, for the intended purpose, each well contains same type of cells; it is not necessary that each well contains exactly identical type of cells. For example, if the intended purpose is that each well contains mammalian cells, it is permissible if each well contains same type of mammalian cells, *e.g.*, human cells, or different mammalian cells, *e.g.*, human cells as well as other non-human mammalian cells such as mice, goat or monkey cells, etc. In some instances the "same type of cells" may initially refer to embryonic stem cells; however, the stage of differentiation into cardiomyocytes may be differ.

[0071] As used herein, "each well contains . . . serially different concentration of a test compound" means that each well contains a test compound with a serially diluted concentrations, *e.g.*, an one-tenth serially diluted concentrations of 1 M, 0.1 M, 0.01 M, etc.

[0072] As used herein, "dose-response curve" means the dependent relationship of response of cells on the dose concentration of a test compound. The

response of cells can be measured by many different parameters. For example, a test compound is suspected to be cardiotoxic if it impairs cardiomyocyte beating, whether magnitude or amplitude or frequency, or if it causes cell death. Then the response of cells can be measured by percentage of non-viable (or viable) cardiac cells after the cells are treated by the test compound.

[0073] As used herein, "microelectrode strip or electrode strip" refers to a non-conducting substrate strip on which electrodes or electrode structure units are fabricated or incorporated. The non-limiting examples of the non-conducting substrate strips include polymer membrane, glass, plastic sheets, ceramics, insulator-on-semiconductor, fiber glass (like those for manufacturing printed-circuits-board). Electrode structure units having different geometries can be fabricated or made on the substrate strip by any suitable microfabrication, micromachining, or other methods. Non-limiting examples of electrode geometries include interdigitated electrodes, circle-on-line electrodes, diamond-on-line electrodes, castellated electrodes, or sinusoidal electrodes. Characteristic dimensions of these electrode geometries may vary from as small as less than 5 micron, or less than 10 micron, to as large as over 200 micron, over 500 micron, over 1 mm. The characteristic dimensions of the electrode geometries refer to the smallest width of the electrode elements, or smallest gaps between the adjacent electrode elements, or size of a repeating feature on the electrode geometries. The microelectrode strip can be of any geometry for the present invention. One exemplary geometry for the microelectrode strips is rectangular shape – having the width of the strip between less than 50 micron to over 10 mm, and having the length of the strip between less than 60 micron to over 15 mm. An exemplary geometry of the microelectrode strips may have a geometry having a width of 200 micron and a length of 20 mm. A single microelectrode strip may have two electrodes serving as a measurement unit, or multiple such two-electrodes serving as multiple measurement units, or a single electrode structure unit as a measurement unit, or multiple electrode structure units serving as multiple electrode structure units. In one exemplary embodiment, when multiple electrode structure units are fabricated on a single microelectrode strip, these electrode structure units are positioned along the length direction of the strip. The electrode structure units may be of

squared-shape, or rectangular-shape, or circle shapes. Each of electrode structure units may occupy size from less than 50 micron by 50 micron, to larger than 2 mm x 2mm.

[0074] A “compound” or "test compound" is any compound whose activity or direct or indirect effect or effects on cells is investigated in any assay. A test compound can be any compound, including, but not limited to, a small molecule, a large molecule, a molecular complex, an organic molecule, an inorganic molecule, a biomolecule or biological molecule such as but not limited to a lipid, a steroid, a carbohydrate, a fatty acid, an amino acid, a peptide, a protein, a nucleic acid, or any combination thereof. A test compound can be a synthetic compound, a naturally occurring compound, a derivative of a naturally occurring compound, etc. The structure of a test compound can be known or unknown. In one application of the present invention, a compound is capable of, or is suspected of, modulating the beating cycle of a cardiomyocyte cell population, whether by beating amplitude or frequency. In still another application, a compound is capable of, or is suspected of, interacting with cells (for example, binding to cell surface receptor, or inhibiting certain intracellular signal transduction pathway, or activating cells).

[0075] A "known compound" is a compound for which at least one activity is known. In the present invention, a known compound preferably is a compound for which one or more direct or indirect effects on cells is known. Preferably, the structure of a known compound is known, but this need not be the case. Preferably, the mechanism of action of a known compound on cells is known, for example, the effect or effects of a known compound on cells can be, as nonlimiting examples, effects on cardiotoxicity or embryonic stem cell development, etc.

[0076] An "impedance value" is the impedance measured for electrodes in a well with or without cell present. Impedance is generally a function of the frequency, i.e., impedance values depend on frequencies at which the measurement was conducted. For the present application, impedance value refers to impedance measured at either single frequency or multiple frequencies. Furthermore, impedance has two components, one resistance component and one reactance component. Impedance value in the present application refers to resistance component, or reactance component, or both resistance

and reactance component. Thus, when "impedance value" was measured or monitored, we are referring to that, resistance, or reactance, or both resistance and reactance were measured or monitored. In many embodiments of the methods of the present application, impedance values also refer to parameter values that are derived from raw, measured impedance data. For example, cell index, or normalized cell index, or delta cell index could be used to represent impedance values.

[0077] A "Cell Index" or "CI" is a parameter that can derived from measured impedance values and that can be used to reflect the change in impedance values. There are a number of methods to derive or calculate Cell Index.

[0078] A "Normalized Cell Index" at a given time point is calculated by dividing the Cell Index at the time point by the Cell Index at a reference time point. Thus, the Normalized Cell Index is 1 at the reference time point.

[0079] A "delta cell index" at a given time point is calculated by subtracting the cell index at a standard time point from the cell index at the given time point. Thus, the delta cell index is the absolute change in the cell index from an initial time (the standard time point) to the measurement time.

[0080] A "Cell Change Index" or "CCI" is a parameter derived from Cell Index and "CCI" at a time point is equal to the 1st order derive of the Cell Index with respect to time, divided by the Cell Index at the time point. In other words, CCI is calculated as

$$CCI(t) = \frac{dCI(t)}{CI(t) \cdot dt}.$$

[0081] As used herein, "primary cell" or "primary cells" refers to any non-immortalized cell that has been derived from various tissues and organs of a patient or an animal.

B. Introduction to Impedance-Based Systems and Methods having Millisecond Time Resolution

[0082] The impedance-based system and methods of the present invention fill a major technological gap in monitoring of excitation-contraction coupling and excitable cells, such as cardiomyocytes, in vitro. This is accomplished, in part, from the development of an impedance-based system and monitoring method that employs millisecond time resolution. Millisecond timer resolution permits effective monitoring of excitable cells for short durations, such as less than about 100 milliseconds. Further by coupling millisecond time resolution with longer duration time periods, both short term and long term effects of drugs, such as cell viability, changes in morphology and adhesion can also be assessed. These combination studies permit further data collection with respect to compounds such as β-2 adrenergic receptor agonists, well known and characterized modulators of heart function in vivo and in vitro, which can induce long term hypertrophic responses in cardiomyocytes, which is associated with elongated morphology of the cells. When combining long term monitoring and short term monitoring it may be desirable to provide long term monitoring coupled to intermittent short term monitoring periods.

[0083] The devices, systems and methods provided permit impedance-based monitoring of excitable cells using millisecond time resolution. It has been discovered that by developing enhanced impedance based systems, detailed analysis of excitable cells, the excitation cycle of cells and potential modulators of excitable cells can be performed. Further, by studying the excitation cycle with increased resolution embodiments of the invention permit the effective evaluation of factors that may alter normal or abnormal cycling. Without millisecond time resolution, it would not be possible to perform detailed analysis of the beating cycle of the excitable cells. For example, for cardiomyocytes, if the impedance is measured at seconds time-resolution such as a ten-second or even one-second resolution, it would not be possible to observe beating of the cardiomyocytes or resolve a beating cycle of the cardiomyocytes with an impedance measurement. The cardiomyocytes-beating-resulted impedance change would be shown as "noise" on the impedance curves measured at seconds or minutes time-resolution. Indeed, it was a surprise that the beating of the cardiomyocytes on the electrode surfaces would result in periodic change in impedance and even more surprise that the impedance measurement, when performed at appropriate time resolution of milli-

seconds, could resolve such beating cycles. After we discovered that cardiomyocyte beating, when cultured on electrode surfaces, can be monitored via impedance measurement, we interpreted that such dynamic monitoring of cardiomyocyte beating is based on quantification in real time of the rhythmic changes in cardiomyocyte morphology and/or attachment as a result of the excitation contraction coupling of the electrically excitable cardiomyocytes growing on microelectrodes' surface in E-PLATES (ACEA Biosciences, San Diego, CA). The quantification of the rhythmic changes in cardiomyocyte morphology and/or attachment is achieved via the fast (millisecond resolution) and continuous measurement of electrode impedance. The method essentially provides a cellular cardio-gram which can provide incisive information about the status of cardiomyocytes especially upon treatment with pharmacological agents.

[0084] When combining long term impedance monitoring and short term monitoring it may be desirable to provide long term monitoring coupled to intermittent short term monitoring. In other words, while long term impedance monitoring is able to identify long term effects on excitable cells, short term impedance monitoring, such as at millisecond time resolution may be employed at particular time points to assess short term effects. In some instances, impedance monitoring with millisecond time resolution is performed at regular or irregular time intervals. In these instances, time intervals may be preprogrammed in the system or may be initiated by the user. In some instances intermittent measuring at millisecond time resolution is initiated upon the occurrence of an event, such as an event detected or determined while long term monitoring of impedance. Such events may be changes in measured impedance data, changes in optical property and the like. Monitoring at millisecond time resolution may continue until a programmed event occurs, such as expiration of a time period. After or during which, long term impedance monitoring may continue.

[0085] In some embodiments, long term and short term monitoring of excitation-contraction coupling or excitable cells is provided in combination. Exemplary methods include providing the impedance-based system with millisecond time resolution; adding excitable cells or cells suspected of excitation-contraction coupling to one or more wells; monitoring impedance of the one or more wells over a first time period, which is characterized as a longer time period, such as seconds, minutes, hours or days;

monitoring impedance of the one or more wells over a second time period in millisecond time resolution; determining a characteristic, such as cell attachment, cell growth and cell viability from monitoring over the first time period; and resolving individual cycles of the excitable cells from monitoring over the second time period. In such embodiments, monitoring impedance over the second time period may be performed at regular or irregular time intervals within monitoring impedance over the first time period. Further, test agents may be added to assess their short term effects and long term effects on the cells.

[0086] Impedance monitoring using, at least in part, millisecond time resolution will be useful in the testing of compounds such as drugs for the treatment or prevention of various medical conditions or their safety. In some embodiments the systems and methods are used to test or evaluate potential compounds, drugs or treatments for cardiotoxicity data. In some embodiments potential compounds, drugs or treatments are tested for cardioprotective data. In some embodiments potential compounds, drugs or treatments are tested for potential applicability for cardiovascular treatments, including hypertension or congestive heart failure. In some embodiments potential compounds, drugs or treatments are tested for modulation of embryonic stem cell development, such as development into cardiomyocytes. In other embodiments the systems and methods are used to test or assess potential drugs or treatments for neurological data, such as beneficial or deleterious neurological effects. As will be understood by those skilled n the present art, the impedance based system and methods including millisecond time resolution permits evaluation across multiple cell populations or systems that including excitation-contraction coupling.

[0087] One skilled in the art will understand embodiments of the present invention may be used for studying a variety of excitable cells or effects thereon. As nonlimiting examples cells may be cardiac muscle cells, neurological cells, differentiating stem cells, embryonic stem cells, adult stem cells and the like. Smooth muscle cells and skeletal muscle cells that undergo excitation-contraction coupling may also be studied.

[0088] In some embodiments of the present invention the excitation cycle or beating of cardiomyocytes is studied. Cardiomyocytes are specialized muscle cells, which make up the majority of the volume of the myocardium. The myocardium also includes epithelial cells and fibroblasts. Cardiomyocytes are arranged largely in a circumferential and spiral orientation around the left ventricle, the chamber that pumps blood to the systemic circulation. Atrial myocytes, also cardiomyocytes, are smaller in diameter and less structured than their ventricular counterparts. Cardiomyocytes have five major components: cell membrane (sarcolemma) and T-tubules, for impulse conduction; sarcoplasmic reticulum, a calcium reservoir needed for contraction; contractile elements; mitochondria; and nucleus. Cellularly, cardiomyocytes may be identified by the presence of cardiac tropnin T (TnT) and atrial natriuretic peptide (ANP).

[0089] The functional intracellular contractile unit of cardiac muscle (like skeletal muscle) is the sarcomere, an orderly arrangement of thick filaments composed principally of myosin, and thin filaments containing actin. Contraction of cardiac muscle occurs by the cumulative effort of sliding of the actin filaments between the myosin filaments toward the center of each sarcomere.

[0090] Cardiomyocytes may be obtained or isolated from cardiac tissue directly, may be cultured from cardiomyocyte cells or may be differentiated from stem cells, such as embryonic stem cells. In some embodiments embryonic or adult stem cells are used. Methods for obtaining or isolating cardiomyocytes from cardiac tissue may be found in the literature.

[0091] Since embryonic stem (ES) cells are self renewing cells in culture they can serve as an excellent source for continuous production of cardiomyocytes. These derived cardiomyocytes, which behave in every way like normal cardiomyocytes isolated from the heart tissue itself, addresses the ever important supply problem and for the first time allows for assessment of cardiac function and its modulation by lead candidate drugs and compounds in relatively large scale. Furthermore, because the technology exists to selectively knockout or express trans-genes in ES cells, it provides an excellent model system to study the role of certain genes in cardiac development and function without concern of adverse affects on overall embryonic development in transgenic animals.

Further, the ability to express transgenes in ES cells has been utilized as a way to enrich for preparation of cardiomyocytes that are 100% pure. For example, the gene encoding GFP has been cloned downstream of a cardiac-specific promoter and then introduced into ES cells. Embryoid cells which ultimately differentiate into cardiomyocytes express the GFP transgenes and can be easily identified and isolated by cell sorting techniques and therefore an enriched cardiomyocyte population can be obtained.

C. Impedance-Based Systems Having Millisecond Time Resolution

[0092] In preferred embodiments the system for monitoring impedance of excitable cells in vitro includes a device for monitoring cell-substrate impedance, an impedance analyzer capable of impedance measurements at millisecond time resolution, electronic circuitry that can engage the device and selectively connect two or more electrode arrays of the device to the impedance analyzer and a software program that controls the electronic circuitry and records and analyzes data obtained from the impedance analyzer. By providing the impedance based system with millisecond time resolution, excitation-contraction coupling cells can be efficiently monitored and studied. Accordingly, the systems provided herein are able to identify and evaluate changes in excitation-contraction events, which may be used for high throughput analysis of potential therapeutics. Millisecond time resolution measurements may be coupled with longer term impedance monitoring, such as longer than seconds, hours or days. In some embodiments, long term impedance monitoring is performed with intermittent periods of impedance monitoring at millisecond time resolution.

[0093] Embodiments of the device for monitoring substrate impedance include a nonconductive substrate having one or more individually addressable electrode arrays fabricated thereon and one or more wells. A surface of the substrate may be suitable for cell attachment, wherein the cell attachment results in a detectable change in impedance between electrodes within the array. Preferably, the nonconducting substrate is planar, and is flat or approximately flat. The substrates may be constructed from a variety of nonconductive materials known in the present art, including, but not limited to, silicon dioxide on silicon, silicon-on-insulator (SOI) wafer, glass (e.g., quartz glass, lead glass or

borosilicate glass), sapphire, ceramics, polymer, fiber glass, plastics, *e.g.*, polyimide (e.g. Kapton, polyimide film supplied by DuPont), polystyrene, polycarbonate, polyvinyl chloride, polyester, polypropylene and urea resin. Preferably, the substrate is biocompatible with excitable cells; however, materials that are not biocompatible can be made biocompatible by coating with a suitable material, such as a biocompatible polymer or coating. Further, attachment or growth along the substrate or electrodes may be enhanced by precoating the substrate with a protein or compound that facilitates attachment or growth. Such compounds may be chosen according to techniques known in the cellular biology arts; however, in some embodiments fibronectin is effective. Alternatively, the substrate may be chemically modified to display reactive groups that enhance cell attachment, particularly ES cells or cardiomyocytes.

[0094] Each electrode array includes two or more electrode structures that are constructed to have dimensions and spacing such that they can, when connected to a signal source, operate as a unit to generate an electrical field in the region of spaces around the electrode structures. Preferably the electric field is substantially uniform across the array. An electrode structure refers to a single electrode, particularly one with a complex structure. Specifically, an electrode array includes two electrode structures, each of which includes multiple electrode elements, or substructures, which branch from the electrode structure. In preferred embodiments, the electrode structures of each of the two or more electrode arrays of a device have substantially the same surface area.

[0095] Each of the two electrode structures of an electrode array is connected to a separate connection pad that is preferably located at the edge of the substrate. Specifically, for each of the two or more electrode arrays of the device, preferably the first of the two electrode structures is connected to one of the two or more connection pads, and the second of the two electrode structures is connected to another of the two or more connection pads. Preferably, each array of a device is individually addressed, meaning that the electrical traces and connection pads of the arrays are configured such that an array can be connected to an impedance analyzer in such a way that a measuring voltage can be applied across a single array at a given time by using switches (such as electronic switches).

[0096] Preferably, each electrode array of the device has an approximately uniform electrode resistance distribution across the entire array. By "uniform resistance distribution across the array" is meant that when a measurement voltage is applied across the electrode structures of the array, the electrode resistance at any given location of the array is approximately equal to the electrode resistance at any other location on the array. Preferably, the electrode resistance at a first location on an array of the device and the electrode resistance at a second location on the same array does not differ by more than 30%. More preferably, the electrode resistance at a first location on an array of the device and the electrode resistance at a second location on the same array does not differ by more than 15%. Even more preferably, the electrode resistance at a first location on an array of the device and a second location on the same array does not differ by more than 5%. More preferably yet, the electrode resistance at a first location on an array of the device and a second location on the same array does not differ by more than 2%.

[0097] Preferred arrangements for electrode elements and gaps between the electrodes and electrode buses in a given electrode array are used to allow all cells, no matter where they land and attach to the electrode surfaces and to contribute similarly to the total impedance change measured for the electrode array. Thus, it is desirable to have similar electric field strengths at any two locations within any given array of the device when a measurement voltage is applied to the electrode array. At any given location of the array, the field strength is related to the potential difference between the nearest point on a first electrode structure of the array and the nearest point on a second electrode structure of the array. It is therefore desirable to have similar electric potential drops across the electrode elements and across the electrode buses of a given array. Based on this requirement, it is preferred to have an approximately uniform electrode resistance distribution across the whole array where the electrode resistance at a location of interest is equal to the sum of the electrode resistance between the nearest point on a first electrode structure (that is the point on the first electrode structure nearest the location of interest) and a first connection pad connected to the first electrode structure and the electrode resistance between the nearest point on a second electrode structure (that is the point on the first electrode structure nearest the location of interest) and a second connection pad connected to the second electrode structure.

[0098] Preferably, devices of the present invention are designed such that the arrays of the device have an approximately uniform distribution across the whole array. This can be achieved, for example, by having electrode structures and electrode buses of particular spacing and dimensions (lengths, widths, thicknesses and geometrical shapes) such that the resistance at any single location on the array is approximately equal to the resistance at any single other location on the array. In most embodiments, the electrode elements (or electrode structures) of a given array will have even spacing and be of similar thicknesses and widths, the electrode buses of a given array will be of similar thicknesses and widths, and the electrode traces leading from a given array to a connection pad will be of closely similar thicknesses and widths. Thus, in these preferred embodiments, an array is designed such that the lengths and geometrical shapes of electrode elements or structures, the lengths and geometrical shapes of electrode traces, and the lengths and geometrical shapes of buses allow for approximately uniform electrode resistance distribution across the array.

[0099] In some preferred embodiments of impedance measurement devices, electrode structures comprise multiple electrode elements, and each electrode element connects directly to an electrode bus. Electrode elements of a first electrode structure connect to a first electrode bus, and electrode elements of a second electrode structure connect to a second electrode bus. In these embodiments, each of the two electrode buses connects to a separate connection pad via an electrical trace. Although the resistances of the traces contribute to the resistance at a location on the array, for any two locations on the array the trace connections from the first bus to a first connection pad and from the second bus to a second connection pad are identical. Thus, in these preferred embodiments trace resistances do not need to be taken into account in designing the geometry of the array to provide for uniform resistances across the array.

[00100] In preferred embodiments of the present invention, a device for monitoring cell-substrate impedance has two or more electrode arrays that share a connection pad. Preferably one of the electrode structures of at least one of the electrode arrays of the device is connected to a connection pad that also connects to an electrode structure of at least one other of the electrode arrays of the device. Preferably for at least two arrays of the device, each of the two or more arrays has a first electrode structure

connected to a connection pad that connects with an electrode structure of at least one other electrode array, and each of the two or more arrays has a second electrode structure that connects to a connection pad that does not connect with any other electrode structures or arrays of the device. Thus, in preferred designs of a device there are at least two electrode arrays each of which has a first electrode structure that is connected to a common connection pad and a second electrode structure that is connected to an independent connection pad.

[00101] In some preferred embodiments of the present invention, each of the electrode structures of an array is connected to an electrode bus that is connected to one of the two or more connection pads of the device via an electrically conductive trace. In preferred embodiments, each of the two electrode structures is connected to a single bus, such that each array connects to two buses, one for each electrode structure. In this arrangement, each of the two buses connects to a separate connection pad of the substrate.

[00102] The electrically conductive traces that connect a bus with a connection can be fabricated of any electrically conductive material. The traces can be localized to the surface of the substrate and can be optionally covered with an insulating layer. Alternatively the traces can be disposed in a second plane of the substrate. Description of arrangements and design of electrically conductive traces on impedance measurement devices can be found in U.S. Patent No. 7,470,533, herein incorporated by reference for all disclosure on fabrication and design of electrically conductive trace on substrates.

[00103] Appropriate electronic connection means such as metal clips engaged onto the connection pads on the substrate and connected printed-circuit-boards can be used for leading the electronic connections from the connection pads on the devices to external electronic circuitry (e.g. an impedance analyzer). Description of the design of cell-substrate impedance devices and their manufacture can be found in U.S. Patent 7,470,533, herein incorporated by reference for all description and disclosure of the design, features, and manufacture of impedance device comprising electrode arrays.

[00104] Descriptions of electrode arrays used for impedance measurement that apply to the devices of the present invention are described in U.S. Patent No. 7,470,533, herein incorporated by reference for all disclosure relating to electrode arrays (or structural units), electrode structures, electrode materials, electrode dimensions, and methods of manufacturing electrodes on substrates.

[00105] Preferred electrode arrays for devices of the present invention include arrays comprising two electrode structures, such as, for example, spiral electrode arrays and interdigitated arrays. In some preferred devices of the present invention, electrode arrays are fabricated on a substrate, in which the arrays comprises two electrode structures, each of which comprises multiple circle-on-line electrode elements, in which the electrode elements of one structure alternate with the electrode elements of the opposite electrode structure. Electrode arrays may be provided in configurations, such as interdigitated, circle-on-line, diamond-on-line, concentric, sinusoidal and castellated.

[00106] Preferably, the electrode elements (or electrode structures) of an array of the present device of the present invention are of approximately equal widths. Preferably the electrode elements (or electrode structures) of an array of the present device of the present invention are greater than 20 microns and less than 500 microns in width, more preferably from about 50 to about 300 microns in width.

[00107] Preferably, the electrode elements (or electrode structures) of an array of the present device of the present invention are approximately evenly spaced. Preferably, the gap between electrode elements (or electrode structures) of an array of the present device of the present invention is less than 100 microns and more than 5 microns in width, more preferably from about 10 to about 80 microns in width.

[00108] A device of the present invention can include one or more fluid-impermeable receptacles which serve as fluid containers or wells. Such receptacles may be reversibly or irreversibly attached to or formed within the substrate or portions thereof (such as, for example, wells formed as in a microtiter plate). In another example, the device of the present invention includes microelectrode strips reversibly or irreversibly attached to plastic housings that have openings that correspond to electrode structure units located on the microelectrode strips. Suitable fluid container materials comprise

plastic, glass, or plastic-coated materials such as a ceramic, glass, metal, etc. Descriptions and disclosure of devices that comprise fluid containers can be found in U.S. Patent Application No. 7,470,533, herein incorporated by reference for all disclosure of fluid containers and fluid container structures that can engage a substrate comprising electrodes for impedance measurements, including their dimensions, design, composition, and methods of manufacture.

[00109] In preferred embodiments, each electrode array on the substrate of a device of the present invention is associated with a fluid-impermeable container or receptacle, such as, for example, a well. Preferably, the device of the present invention is assembled to a bottomless, multiwell plastic plate or strip with a fluid tight seal. The device is assembled such that a single array of the substrate is at the bottom of a receptacle or well. Preferably, each array of a device is associated with a well of a multiwell plate. In some preferred embodiments, a multiwell device for cell-substrate impedance measurement has "non-array" wells that are attached to the substrate but not associated with arrays. Such wells can optionally be used for performing non-impedance based assays, or for viewing cells microscopically.

[00110] The design and assembly of multiwell impedance measurement devices is described in U.S. Patent No. 7,470,533, and also in U.S. Patent No. 7,192,752, both herein incorporated by reference for disclosure of multiwell impedance measurement devices, including their design, composition, and manufacture. A device of the present invention preferably has between 2 and 1,536 wells and more preferably between 4 and 384 wells. In some embodiments the device includes 6 wells, 16 wells, 32 wells, 96 wells or 386 wells.

[00111] In some preferred embodiments, commercial tissue culture plates can be adapted to fit a device of the present invention. Bottomless plates may also be custom-made to preferred dimensions. Preferably, well diameters are from about 1 millimeter to about 20 millimeters, more preferably from about 2 millimeters to about 8 millimeters at the bottom of the well (the end disposed on the substrate). The wells can have a uniform diameter or can taper toward the bottom so that the diameter of the

container at the end in contact with the substrate is smaller than the diameter of the opposing end.

[00112] In the system for monitoring impedance of excitable cells the impedance analyzer engages connection pads of one or more multi-well devices to measure impedance. In one embodiment of the above system, the impedance analyzer is capable of measuring impedance between 0.1 ohm and 10^5 ohm in frequency range of 1Hz to 1 MHz. The impedance analyzer is preferably capable of measuring both resistance and reactance (capacitive reactance and inductive reactance) components of the impedance. In a preferred embodiment of the above system, the impedance analyzer is capable of measuring impedance between 1 ohm and 10^3 ohm in frequency range of 1.00 Hz to 300 kHz.

[00113] In preferred embodiments the impedance analyzer is capable of impedance measurements at millisecond time resolution. The required or desired time resolution may vary depending on the excitation cycle of the excitable cell. Excitable cells having shorter excitation cycles would tend to require faster time resolution. In some embodiments 500 millisecond time resolution is sufficient, such that at least two consecutive impedance measurements are between about 300 milliseconds and about 500 milliseconds apart. In preferred embodiments, impedance measurement at millisecond time resolution includes at least two consecutive impedance measurements less than 100 milliseconds apart. In some instances the at least two consecutive impedance measurements are less than 50 milliseconds or less than 40 milliseconds apart. In some instances the at least two consecutive impedance measurements are less than 20 milliseconds apart. In some instances at least two consecutive impedance measurements are less than 10 milliseconds apart. In some instances millisecond time resolution includes two consecutive impedance measurements between 1 millisecond and 5 milliseconds, between 5 milliseconds and 10 milliseconds, between 10 milliseconds and 20 milliseconds, between 20 milliseconds and 40 milliseconds, or between 40 milliseconds and 50 milliseconds apart. In some instances millisecond time resolution includes at least two consecutive impedance measurements between 50 milliseconds and 100 milliseconds apart. In some instances millisecond time resolution includes at least

two consecutive impedance measurements between 100 milliseconds and 150 milliseconds or between 150 and 300 milliseconds apart.

[00114] Millisecond time resolution of impedance-based devices provides a significant technical step over traditional impedance measuring devices, which are typically limited to second or minute resolution. That is, substantial reconfiguration of a traditional impedance-based system is required to obtain millisecond time resolution. Advances in multiple steps are required to achieve millisecond time resolution, including the impedance measurement circuitry together with electronic switching circuitry. Technological advances are further required when performing millisecond time resolution over multiple wells, such as 4 wells, 8 wells, 16 wells or 96 wells. For example, if the system comprises a device having 96 wells, the system hardware and software should be capable of, for a given time period, measuring the impedances of all 96 wells with millisecond time resolution between two adjacent or consecutive impedance measurement points for each and every well. Thus, comparing two impedance analyzers, one for impedance measurement of 96 wells with millisecond resolution and another for impedance measurement of a single well with millisecond time resolution, the one for 96 well measurement is effectively 96-times faster than one for a single well measurement since it is required to have a capability for performing impedance measurement for all 96 wells with millisecond time resolution. Similarly, if a 96 well device is provided, a group of wells, such as a group of 2, 4, 6, 12, 24 or 48 wells, may be measured in millisecond time resolution. Preferably, the time difference between two adjacent measurement points for each and every given well is less than 500 milliseconds. More preferably, the time difference between two adjacent measurement points for each and every given well is less than 300 milliseconds. Still more preferably, the time difference between two adjacent measurement points for each and every given well is less than 100 milliseconds. Still more preferably, the time difference between two adjacent measurement points for each and every given well is less than 40 milliseconds. Still more preferably, the time difference between two adjacent measurement points for each and every given well is less than 20 milliseconds. Still more preferably, the time difference between two adjacent measurement points for each and every given well is less than 10 milliseconds.

[00115] A number of improvements in the impedance measurement circuitry, electronic switching circuitry, communication between impedance measurement circuitry and software can be used to achieve such millisecond time resolution. For instance, improvement likely requires the use of fast processing electronic chips for analogue-to-digital conversion, for parallel digital signal processing and data calculation with field-programmable gate array (FPGA) and for fast communication between the impedance measurement circuitry and software. Another example of improvements includes the use of multiple analogue-to-digital (AD) conversion channels so that analog electronic signals from multiple channels can be converted to digital signals simultaneously. Such parallel AD conversion is important, particular for the system having multiple wells, each of which's measurement time resolution is required to be in the millisecond resolution. And, a very important is to replace previous working mode of "measurement of one-well's impedance at a time" with a mode of "measurement of multiple-wells' impedances at a time". In "one-well at a time" mode, when the software issue a command for measuring one well's impedance, the measurement circuitry would perform the measurement for one well including signal generation to the well, converting the voltage signal and the electric current signal for the well to digital signal, digitally processing the signals to do impedance calculation and sending the well's impedance data to the computer over the communication line between the impedance measurement circuitry and the computer. The system will not perform any measurement for another well until the completion of the measurement of this well and until receiving another command for the measurement of another well. In "multiple-wells at a time" mode, the software would issue a command for measuring multiple wells' impedances. The measurement circuitry would simultaneously or nearly simultaneously perform signal conversion, signal processing and impedance calculation for multiple wells. The multiple impedance data for the multiple wells would be sent over the communication lines to the computer sequentially with one well's data at the same time or simultaneously with more than one well's data being sent at a time. In this "measurement of multiple-wells' impedances at a time" mode, the system may be performing multiple tasks simultaneously, for example, while one well's impedance data

is being measured and calculated, another well's impedance data may be communicated and sent over the communication lines to the computer.

[00116] With millisecond time resolution for impedance measurement, it becomes possible to resolve individual beating cycles of cardiomyocytes cultured on electrodes. Whilst theoretically one needs at least two data points for each beating cycle, in practice more than 2 data points are needed for each beating cycle. For example, if cells have a beating rate of 60 beats per minute, i.,e, one beat per second. It would be preferred to have a time resolution of at least 200 milliseconds so that each beating cycle consists of 5 data points. More preferably, the measurement time resolution is 100 milliseconds. Still more preferably, the time resolution is 50 millisconds or less.

[00117] One skilled in the art will understand that the cell-substrate impedance measurement or monitoring system with millisecond time resolution can be used to efficiently and simultaneously perform multiple assays by using circuitry of the device station to digitally switch from recording from measuring impedance over an array in one well to measuring impedance over an array in another well. Similarly, groups of wells may be monitored simultaneously and switching between occur between designated groups. In one embodiment of the above system, the system under software control is capable of completing an impedance measurement for an individual well at a single frequency within milliseconds, such as less than 100 milliseconds, less than 40 milliseconds, less than 20 milliseconds, less than 10 milliseconds or between 1 millisecond and 40 milliseconds. In some embodiments the user may choose the frequency of measurement for millisecond time resolution.

[00118] A multiple-well cell-substrate impedance measuring device in a system of the present invention can be any multiple-well cell-substrate impedance measuring device in which at least two of the multiple wells comprise an electrode array at the bottom of the well, and in which at least two of the multiple wells comprise an electrode array are individually addressed. In one embodiment of the above system, the multi-well device takes the form of a specialized microtiter plate which has microelectronic sensor arrays integrated into the bottom of the wells.

[00119] A device used in a system of the present invention, when connected to an impedance analyzer, can measure differences in impedance values that relate to cell behavior. For example, a cell-substrate impedance measuring device used in a system of the present invention can measure differences in impedance values when cells are attached to the electrode array and when cells are not attached to the electrode array, or can detect differences in impedance values when the number, type, activity, adhesiveness, or morphology of cells attached to the electrode-comprising surface of the apparatus changes. Further, by using millisecond time resolution differences in impedance may be detected or monitored that relate to excitation-contraction coupling, including the beating of cardiomyocytes or stem cells differentiating into cardiomyocytes, and the signaling between neurological cells. Impedance monitoring of the excitation cycle of excitable cells may be determined and monitored before, during or after adding a test compound, which is suspected of affecting the excitation cycle. Thus, by monitoring the excitation cycle of the excitable cell before, during or after adding a test compound the system provides data corresponding to the potential affect of the compound on the cardiovascular system, the heart, the nervous system, and the like. In some embodiments monitoring the excitation cycle of the cell before, during or after adding a compound provides cardiotoxicity data useful in drug screening.

[00120] In some embodiments a device station or electromechanical apparatus or assembly capable of interfacing multiwell devices can include one or more platforms or one or more slots for positioning one or more multiwell devices. The one or more platforms or one or more slots can comprise sockets, pins or other devices for electrically connecting the device to the device station. The device station or electromechanical apparatus or assembly capable of interfacing multiwell devices preferably can be positioned in a tissue culture incubator during cell impedance measurement assays. It can be electrically connected to an impedance analyzer and computer that are preferably located outside the tissue culture incubator.

[00121] The device station or electromechanical apparatus or assembly capable of interfacing multiwell devices includes electronic circuitry that can connect to the impedance monitoring device and an impedance analyzer and electronic switches that can switch on and off connections to each of the two or more electrode arrays of the

multiwell devices used in the system. The switches of the device station or electromechanical apparatus or assembly capable of interfacing multiwell devices are controlled by a software program, each of which has been improved to provide millisecond time resolution. The software program directs the device station to connect arrays of the device to an impedance analyzer and monitor impedance from one or more of the electrode arrays. During impedance monitoring, the impedance analyzer can monitor impedance at one frequency or at more than one frequency. Preferably, impedance monitoring is performed at more than one time point for a given assay, and preferably, impedance is monitored using at least two time points. The device station can connect individual arrays of a device to an impedance analyzer to monitor one, some, or all of the arrays of a device for a measurement time point. In some preferred embodiments of the present invention, the device station software is programmable to direct impedance monitoring of any of the wells of the device that comprise arrays at chosen time intervals.

[00122] The software of the impedance monitoring system can also store and display data. Data can be displayed on a screen, as printed data, or both. Preferably the software can allow entry and display of experimental parameters, such as descriptive information including cells types, compound concentrations, time intervals monitored, etc.

[00123] Preferably, the software can also analyze impedance data. In preferred embodiments, the software can calculate a cell index (CI) for one or more time points for one or more wells of the multiwell device. In some preferred embodiments, the software can calculate a cell change index (CCI) from impedance measurements of one or more wells of the multiwell device. The software can preferably generate plots of impedance data and impedance values, such as but not limited to CI or CCI, with respect to time. The software may perform other analysis as well, such as calculate cell number from CI, generate dose-response curves based on impedance data, calculate IC values based on impedance values, and calculate kinetic parameters of the excitation cycle cell based on impedance values and impedance value curves. In some embodiments the beating cycle of a cardiomyocyte population is determined, which may include initiation and decay of individual beats. Peaks may be derived from the detection of vectors

associated with initiation of beating or beating decay. Peaks may be derived with other methods. In further embodiments the change in beating cycle of a cardiomyocyte population is determined in response to a stimulus such as a pharmacological agent. The software of the impedance monitoring system can also store and display analyses of the data, such as calculated impedance values and kinetic parameters derived therefrom, Data can be displayed on a screen, as printed data, or both. Data may be stored on a hard drive for exportation into compatible programs for further analysis or data storage

[00124] Further information regarding how to calculate a cell index, cell change index, normalized cell index, and delta cell index may be found in US patent application no. 11/235,938, and U.S. Patent No. 7,470,533, the contents of which are herein incorporated by reference with respect to the cell index, cell index number, cell change index, and cell change index number. However each is briefly summarized.

[00125] The cell index obtained for a given well reflects: 1) how many cells are attached to the electrode surfaces in this well, 2) how well cells are attached to the electrode surfaces in the well. In this case, a zero or near-zero "cell index or cell number index" indicates that no cells or very small number of cells are present on or attached to the electrode surfaces. In other words, if no cells are present on the electrodes, or if the cells are not well-attached onto the electrodes cell index =0. A higher value of "cell number index" indicates that, for same type of the cells and cells under similar physiological conditions, more cells are attached to the electrode surfaces. Thus Cell Index is a quantitative measure of cell number present in a well. A higher value of "cell index" may also indicate that, for same type of the cells and same number of the cells, cells are attached better (for example, cells spread out more, or cell adhesion to the electrode surfaces is stronger) on the electrode surfaces.

[00126] A "Normalized Cell Index" at a given time point is calculated by dividing the Cell Index at the time point by the Cell Index at a reference time point. Thus, the Normalized Cell Index is 1 at the reference time point. Normalized cell index is cell index normalized against cell index at a particular time point. In most cases in the present applications, normalized cell index is derived as normalized relative to the time point immediately before a compound addition or treatment. Thus, normalized cell index

at such time point (immediately before compound addition) is always unit one for all wells. One possible benefit for using such normalized cell index is to remove the effect from difference in cell number in different wells. A well having more cells may produce a larger impedance response following compound treatment. Using normalized cell index, it helps to remove such variations caused by different cell numbers.

[00127] A "delta cell index" at a given time point is calculated by subtracting the cell index at a standard time point from the cell index at the given time point. Thus, the delta cell index is the absolute change in the cell index from an initial time (the standard time point) to the measurement time.

[00128] The time-dependent cellular response (including cardiotoxicity response) may be analyzed by deriving parameters that directly reflect the changes in cell status. For example, time dependent cellular response may be analyzed by calculating the slope of change in the measured impedance responses (that is equivalent to the first order derivative of the impedance response with respect to time, impedance response here can be measured impedance data or derived values such as cell index, normalized cell index or delta cell index). In another example, the time-dependent cellular responses (including cardiotoxic resposnes) may be analyzed for their higher order derivatives with respect to time. Such high order derivatives may provide additional information as for how cells responding to different compounds and as for the mechanisms of compound action.

[00129] Thus CCI is the normalized rate of change in cell index. CCI values can be used to quantify the cell status change. For cells in an exponential growth under regular cell culture condition, the cell index determined by a cell-substrate impedance monitoring system described herein is expected to be a proportionate measure of the cell number in the well since the cell morphology and average extent of cell adhesion to the electrode surfaces among the whole cell population do not exhibit significant changes over time.

[00130] After measuring and recording time dependent impedance data for excitable cells cultured on electrodes, various methods can be used for determining beating cycle peaks. For example, time dependent impedance values or cell index values

for a well are analyzed by deriving their first order derivatives and second order derivatives using numerical methods. The beating cycle peaks are those data points where the first order derivatives of impedance values or cell index values are zero or close to zero in its absolute value. If the beating cycle peak is a positive peak (i.e. peak corresponds to a maximum value in measured impedance or cell index over the beating cycle), then the peak would correspond to the data points where the second order derivatives of the impedance values or cell index values is negative and where the first order derivatives of the impedance values or cell index values is zero or close to zero in its absolute value. If the beating cycle peak is a negative peak (i.e. peak corresponds to a minimum value in measured impedance or cell index over the beating cycle), then the peak would correspond to the data points where the second order derivatives of the impedance values or cell index values is positive and where the first order derivatives of the impedance values or cell index values is zero or close to zero in its absolute value. In another example, the method of determining a beating cycle peak is to search for the data point where the trend of the data changes direction from "increasing" to "decreasing" with time (for a positive peak), or from "decreasing" to "increasing" (for a negative peak). After the identification of the beating cycle peaks, the impedance or cell index values at such peak time points are the magnitude or amplitude of the beating cycle peaks.

[00131] After determining the beating cycle peaks, various methods can be used to calculate the beating rate. The beating rate can be determined by dividing a unit time (e.g., 1 minute) by the time period between two adjacent peaks. For example, if two adjacent peaks are separated by 500 milliseconds, then the beating rate for this 500 milliseconds can be determined as 120 beats per minute. Another method is simply to count how many peaks in a unit time by software. For example, if there are 2 peaks in one second interval, then the beating rate should be 2 beats per second, or 120 beats per minute.

D. Assessing or Quantifying Excitable Cells, Excitation Contraction-Coupling and Cardiomyocytes In Vitro

[00132] In another aspect of the present invention a method for assessing or quantifying excitable cells in vitro is provided. The methods including detecting or monitoring excitable cells using impedance monitoring with millisecond time resolution. In preferred embodiments, the method includes providing the impedance based system having millisecond time resolution system, adding excitable cells to one or more wells of the device, monitoring impedance of the one or more wells with millisecond time resolution, and resolving individual cycles of the excitable cells. In some embodiments monitoring impedance further includes determining cell indices from impedance values, calculating average rate of excitation events per unit time (such as beats per unit time when using cardiomyocytes), determining amplitude intensity or average amplitude intensity in a unit time, and/or determining the length of time between excitation cycles (or beating cycles). These additional determinations may be compared to further assess excitable cells.

[00133] The methods have particular utility with cells that are known or suspected to be capable of or undergo excitation-contraction coupling, such as cardiomyocytes. Thus the methods may monitor, detect or determine excitation contraction-coupling of excitable cells. Further, even minor variations in excitation-contraction coupling may be detected.

[00134] Preferably impedance measurements are performed with millisecond time resolution. In some embodiments, two consecutive impedance measurements are performed at less than 300 milliseconds apart. In further embodiments, at least two consecutive impedance measurements are performed less than 100 seconds apart. In further embodiments, at least two consecutive impedance measurements are performed less than 40 milliseconds apart. In further embodiments, at least two consecutive impedance measurements are performed less than 10 milliseconds apart. In som embodiments at least two impedance measurements are between 1 millisecond and 50 milliseconds apart.

[00135] Cardiomyocytes are a subset of cells that are involved in excitation-contraction coupling. Embodiments of the present invention include

applications for studying cardiomyocyte activity, function and its modulation. By monitoring the continuous rhythmic beating of cardiomyocytes, methods of the present invention allow the study of cardiomyocytes themselves as well as screening for pharmacological agents which may alter cardiomyocyte rhythmic beating. Thus the methods permit screening of compounds or conditions that affect cardiomyocyte function or induce cardiotoxicity. Specifically, methods may assess or quantify cardiomyocyte beating in vitro using impedance-based technology having millisecond time resolution. In preferred embodiments, the methods are based on quantification in real time of the rhythmic changes in cardiomyocyte morphology as a result of the excitation contraction coupling of the electrically excitable cardiomyocytes growing on microelectrodes' surface in E-PLATES (ACEA Biosciences, Inc. San Diego, CA). Thus quantification of the rhythmic changes in cardiomyocyte morphology is achieved via the measurement of electrode impedance, which may be performed with millisecond time resolution. In summary, some methods provide a cellular cardio-gram, which can provide incisive information about the status of cardiomyocytes especially upon treatment with pharmacological agents.

[00136] Cardiomyocytes used in the present invention may be any known or experimental cardiomyocyte population. Human cardiomyocytes will be particularly desirable when studying the effect of pharmacological agents for human use; however, cardiomyocytes may also be murine or mouse, rat, rabbit, dog, and the like. Further, the cardiomyocytes may be primary cardiomyocytes isolated from cardiac tissue or may be cultured cardiomyocytes, which are cultured over time. In some embodiments, ES cells destined to differentiate into cardiomyocytes are used. Isolated primary cardiomyocytes as well as ES-derived cardiomyocytes retain the ability to beat in culture. Thus, these cells provide a desirable model system to study cardiomyocyte function in vitro.

[00137] Cardiomyocytes have an innate ability to undergo mechanotransduction. In other words, the spontaneous force generated from the beating cardiomyocyte is translated to intracellular biochemical signals. Membrane receptors such as integrins, ion channels and other proteins have been shown to play a crucial role in cardiac mechanotransduction and lead to a continuous and rhythmic dynamics of the cardiac actin cytoskeleton and morphology. Because the impedance-based system can

sensitively and precisely detect transient changes in morphology and adhesive capacity of the cells, it can be used to monitor cardiac function in vitro. Further, the development of millisecond time resolution permits impedance monitoring of the cardiomyocyte beating cycle as well as fluctuations, even minor alterations, in response to external stimuli.

[00138] Exemplary steps involved in using an impedance-measurement system for measurement of cardiomyocyte function include: providing a system for monitoring impedance of excitable cells, in vitro, which is capable of millisecond time resolution, optionally coating wells of the device with either fibronectin or other matrix proteins; seeding either embryonic stem cells (ES cells) of mammalian origin or primary cardiomyocytes at sufficient seeding densities into the wells of the device; allowing the cells to attach and spread; after a period of time unique to ES-derived cardiomyocytes or primary cardiomyocytes, monitoring cardiomyocyte beating using the impedance-monitoring system to monitor electrode impedance by using millisecond kinetic readout to resolve the individual beat cycles of the cells.

[00139] The millisecond kinetic readout requires the impedance measurement system be capable of obtaining impedance measurement data at millisecond time resolution. Preferably, the time difference between two consecutive impedance measurements for a well is within the range of milliseconds (e.g., less than 300 millisecond, less than 100 milliseconds, less than 50 milliseconds, less than 20 milliseconds, less than 10 milliseconds, or less than or about 1 millisecond). Due to the fast nature of beating cycles of cells, millisecond kinetic readout is required for proper resolution. Thus, the time resolution for the impedance measurement should allow the system to perform measurement using at least two time points for each beat cycle, or at more than two points for each beating cycle. In some embodiments, three, four, five or even ten, or fifteen or twenty or more time points within each beating cycle are obtained.

[00140] Embodiments of the present invention include methods of assessing or quantifying cardiomyocytes include providing the system for monitoring impedance of excitable cells in vitro, which includes millisecond time resolution, adding cardiomyocytes to one or more wells, monitoring impedance of the one or more wells, such as using millisecond time resolution, and resolving excitation cycle or beating cycle

of the cardiomyocytes In further embodiments, the method also includes determining cell indices from impedance values, optionally calculating average rate of beats per unit time, average amplitude intensity in a unit time as well as the average length of time between the beats. In preferred embodiments, millisecond time resolution permits measurement of at least two consecutive impedance measurements within a beating cycle. In some embodiments at least three consecutive impedance measurements are performed with millisecond time resolution.

[00141] Isolated primary cardiomyocytes as well as ES-derived cardiomyocytes retain the ability to beat in culture. These cells provide an excellent model system to study cardiomyocyte function in vitro, especially with regards to cardiotoxicity. A number of cardiotoxic drugs are known to affect certain heart channels, such as the ERG channels, that are involved in excitation-contraction coupling of cardiomyocytes. Cardiomyocytes have an innate ability to undergo mechanotransduction, that is that the spontaneous force generation of the beating cardiomyocyte is translated to intracellular biochemical signals. Membrane receptors such as integrins, ion channels and other proteins have been shown to play a crucial role in cardiac mechanotransduction and lead to a continuous and rhythmic dynamics of the cardiac actin cytoskeleton and morphology. Because the impedance-based system can sensitively and precisely detect transient changes in morphology and adhesive capacity of the cells, the it can be used to monitor cardiomyocyte beating in vitro.

[00142] Another exemplary method for impedance based measurement of cardiomyocyte beating includes: providing a single-well or multi-well device that comprise microelectrode arrays in well(s) of the device, which can be used for monitoring cell-substrate impedance; optionally coating wells of the device with either fibronectin or other matrix proteins; seeding either embryonic stem cells (ES cells) of mammalian origin or primary cardiomyocytes at specific seeding densities to the wells of the device; allowing the cells to attach and spread; after a specified period of time unique to ES-derived cardiomyocytes or primary cardiomyocytes, monitoring cardiomyocyte beating using the impedance-monitoring system to monitor electrode impedance by using millisecond kinetic readout to resolve the individual beat cycles of the cells.

[00143] In another exemplary embodiment for measurement of cardiomyocyte function the method includes: optionally coating E-PLATES with either fibronectin or other matrix proteins; seeding either ES cells of mammalian origin or primary cardiomyocytes at specific seeding densities; allowing the cells to attach and spread; after a specified period of time unique to ES-derived cardiomyocytes or primary cardiomyocytes, monitoring cardiomyocyte beating using an impedance-based system by using millisecond kinetic readout to resolve the individual beat cycles of the cells.

[00144] Dynamic monitoring of cardiomyocyte beating is based on quantification in real time of the rhythmic changes in cardiomyocyte morphology as a result of the excitation contraction coupling of the electrically excitable cardiomyocytes growing on microelectrodes' surface of E-PLATES. The quantification of the rhythmic changes in cardiomyocyte morphology is achieved via the fast, millisecond resolution and continuous measurement of electrode impedance. The method essentially provides a cellular cardio-gram which can provide incisive information about the status of cardiomyocytes especially upon treatment with pharmacological agents. An exemplary method includes providing a device for measuring cell-substrate impedance operably connected to an impedance analyzer, wherein the device includes at least one well optionally coated with fibronectin to expedite attachment; adding cells to the at least one well, where the cells can be mouse or human or other mammalian ES cells or adult stem cells destined to differentiate into cardiomyocytes or primary cardiomyocytes isolated directly from the heart of an experimental system including mice, rats, rabbits or dog; monitoring impedance of the at least one well at time intervals over a period of time and optionally determining cell indices from impedance values; optionally calculating average rate of beats per unit time, average amplitude intensity in a unit time as well as the average length of time between the beats.

[00145] Certain cardiotoxic drugs can illicit their effect by affecting the morphological aspects of cardiomyocyte morphology. For example, it is well known that compounds such as β-2 adrenergic receptor agonists can induce morphological changes resulting in an elongated cardiomyocyte morphology, otherwise known as hypertrophy. Morphological changes can occur immediately in the order of minutes as with certain GPCR agonists or can be of longer duration detectable over several days. The time

resolution of the impedance-based system can be used to distinguish between different kinds of morphological effects. The steps involved in using an impedance-monitoring system for measurement of morphological modulation of cardiomyocytes may include: optionally coating E-PLATES with either fibronectin or other matrix proteins; seeding either embryonic stem cells (ES cells) of mammalian origin, mammalian adult stem cell-derived cardiomyocytes or primary cardiomyocytes isolated directly from mammalian heart tissue at specific seeding densities to the wells of the device; allowing the cells to attach and spread; monitoring cardiomyocyte viability over time using the impedance-monitoring system at prespecified intervals of time for 12, 24, 48, 72 hours or longer; at certain times after cell seeding, treat the cell with agents that may cause morphology changes at one or more concentration; using the vehicle that the agent is dissolved in as a control; continuing to monitoring the cardiomyocytes at 1 minute intervals for at least 1-2 hours to capture any immediate morphological changes and continue to monitor at 30 minutes intervals of time for additional 12, 24, 48, 72 hours or longer to detect long term morphological changes; and quantifying the extent of morphological change by normalizing the cell index values immediately prior to agent addition and determine the normalized cell index at a given time point after agent addition. The extent of morphological change can be expressed as EC-50 value which quantifies the activity of the agent with respect to the cardiomyocyte shape changes.

[00146] Once regular cardiomyocyte beating can be effectively monitored compounds may be added to the wells to assess whether or not beating frequency is altered, beating amplitude is altered and the like. Thus, compounds that adversely affect the normal cardiomyocyte beating are suspected of being cardiotoxic. However, cardioprotective agents can also be assessed by adding an agent suspected of being cardioprotective to the well and inducing a cardiotoxic response.

[00147] Accordingly, methods of identifying or screening for potential agents that modulate ES- derived cardiomyocyte beating or primary cardiomyocyte beating by monitoring and measuring the excitation-contraction coupling of cardiomyocytes upon treatment with pharmacological agents are also provided. The methods may include providing the system for monitoring impedance at millisecond resolution of excitable cells in vitro, adding ES cells or primary cardiomyocytes to two or

more wells, adding a test agent suspected of modulating ES-derived or primary cardiomyocyte beating to a first well to provide a test well and either no agent or a control agent to a second well to form a control well, monitoring impedance of the two or more wells at different or similar time intervals using millisecond time resolution at least in part, and optionally determining cell indices from impedance values, generating an impedance-based curve or optionally a cell index curve for each of the test well and control well, and comparing the impedance-based curves or optionally the cell index curves between the test well and the control well. If significantly different, the test agent is concluded to modulate cardiomyocyte function. In preferred embodiments, the impedance-based curves may be direct measurement of cardiomyocyte excitation-contraction coupling; however, the methods may also include long term monitoring of the viability and or morphology of the cardiomyocytes. The methods may show whether the test agent increases cardiomyocyte beating, which is indicative of increased heart rate, or whether the cardiomyocyte beating is slowed, which is indicative of lowered heart rate.

[00148] In another exemplary embodiment a method for screening for modulators of cardiomyocyte beating using an impedance-measurement system in vitro may include: providing a single-well or multi-well device that comprise microelectrode arrays in well(s) of the device, which can be used for monitoring cell-substrate impedance; optionally coating wells of the device with either fibronectin or other matrix proteins; seeding either embryonic stem cells (ES cells) of mammalian origin, mammalian adult stem cell-derived cardiomyocytes or primary cardiomyocytes at specific seeding densities to the wells of the device; allowing the cells to attach and spread; after a specified period of time unique to ES-derived cardiomyocytes or primary cardiomyocytes, monitoring cardiomyocyte beating using the impedance-monitoring system to monitor electrode impedance by using millisecond kinetic readout to resolve the individual beat cycles of the cells; and adding the pharmacological agents at one or more doses and continue monitoring the cardiomyocyte beating frequency. Preferably, the step of monitoring impedance of beating is performed immediately prior to addition of pharmacological agent, in order to obtain a baseline of the cardiomyocyte beating frequency using fast measurement software and hardware to ensure milli-second kinetic readout signals.

[00149] In another exemplary embodiment, a method of screening for modulators of cardiomyocyte beating using an impedance-based system in vitro includes seeding cardiomyocytes, in E-PLATES exactly as described in the previous exemplary embodiment; however, prior to addition of pharmacological agent, obtaining a baseline of the cardiomyocyte beating frequency using the impedance measurement system with millisecond time resolution; and adding the pharmacological agents at one or more doses and continue monitoring the cardiomyocyte beating frequency.

[00150] It is well established that certain pharmacological treatments and disease conditions can result in cardiac hypertrophy or atrophy culminating in changes in the morphology of cardiomyocyte. Cell substrate impedance can be used to precisely measure and quantify these changes in cell morphology and shape. Certain treatments can also affect the differentiative process of ES cells to cardiomyocytes which may involve specific morphological and adhesive changes. In some embodiments the present invention is directed to a method to screen for potential agents that may modulate the morphology of ES- derived cardiomyocyte, adult stem cell-derived cardiomyocyte or primary cardiomyocyte or its differentiation. The agent may include but is not limited to compounds, drugs, peptides, proteins, antibodies, siRNA, shRNA, miRNA, cDNA, lipids and any combination thereof. The method includes providing a device for measuring cell-substrate impedance operably connected to an impedance analyzer, wherein the device includes at least two wells; adding ES cells, adult stem-cell derived cardiomyocytes or primary cardiomyocytes to at least two wells; monitoring impedance of the at least two wells at different or similar time intervals over a period of time and optionally determining cell indices from impedance values; generating an impedance-based curve or optionally a cell index curve for each of the at least one known factor and the control; comparing the impedance-based curves or optionally the cell index curves between the at least one known biologically active agent well and the control well; the impedance-based curves could be direct measurement of changes in cell morphology and if significantly different, concluding that the biologically active agent modulates cardiomyocyte function. Optionally, impedance-based curves or optionally cell index curves are used to calculate the compound dose-dependent changes in cardiomyocyte morphology and generate an EC-50 value for the potency of the compound.

[00151] The method of the present invention is to devise a label-free cell-based assay system for continuous monitoring of cardiomyocyte viability, the rhythmic beating of cardiomyocytes and cardiomyocyte morphology and differentiation and to screen for pharmacological agents which may modulate these processes and induce cardiotoxicity. In some embodiments, viability is monitored based on long term impedance monitoring of cardiomyocytes seeded in microelectronic plates (E-Plates). Viable cells will continue to generate impedance signal and any changes in viability, especially due to cytotoxic or cardiotoxic drugs will be reflected by changes in impedance. In one respect, the method includes providing a device for measuring cell-substrate impedance operably connected to an impedance analyzer, wherein the device includes at least one well optionally coated with fibronectin to expedite attachment; adding cells to the at least one well, where the cells can be mouse or human or other mammalian ES cells or adult stem cells destined to differentiate into cardiomyocytes or primary cardiomyocytes isolated directly from the heart of an experimental system including mice, rats, rabbits or dog; monitoring impedance of the at least one well over a period of time and optionally determining cell index from impedance values; In another aspect, the method includes providing a device for measuring cell-substrate impedance operably connected to an impedance analyzer, wherein the device includes at least two wells optionally coated with fibronectin to expedite attachment; adding cells to the at least two wells, where the cells can be mouse or human or other mammalian ES cells or adult stem cells destined to differentiate into cardiomyocytes or primary cardiomyocytes isolated directly from the heart of an experimental system including mice, rats, rabbits or dog; monitoring impedance of the at least two wells over a period of time and optionally determining cell index from impedance values. Treating at least one well with an agent; where the agent could include but is not limited to a compound, peptide, protein, antibody, siRNA, shRNA, lipid or any combination of thereof and the other well is treated with an appropriate control; continue monitoring of control and treated well over a period of time preoptimized for the experiment of interest; concluding that the factor may affect cell viability if the impedance or alternatively the cell index of the treated well is significantly different than the impedance or cell index of the treated well.

[00152] In other preferred embodiments short term measurement using millisecond time resolution is combined with longer term impedance monitoring, such as over seconds, hours, days and the like. Certain cardiotoxic drugs can directly affect the viability of cardiomyocytes. Thus, long term impedance monitoring may be used to assess loss of viability of cardiomyocytes. An exemplary long term method to assess loss of viability includes: optionally coating E-PLATES with either fibronectin or other matrix proteins; seeding either embryonic stem cells (ES cells) of mammalian origin , mammalian adult stem cell-derived cardiomyocytes or primary cardiomyocytes isolated directly from mammalian heart tissue at seeding densities to the wells of the device; allowing the cells to attach and spread; monitoring cardiomyocyte viability over time using the impedance-monitoring system to monitor electrode impedance at pre-specified intervals of time for specified length of time such as 12, 24, 37, 48, 72 hours or longer; at certain time after cell seeding, treating the cell with a cytotoxic agent at one or more concentration; using the vehicle that the agent is dissolved in as a control; continue monitoring the cardiomyocytes at pre-specified intervals of time for specified length of time such as additional 12, 24, 48, 72 hours or longer, quantify the extent of cardiotoxicity by normalizing the cell index values immediately prior to agent addition and determining the normalized cell index at a given time point after agent addition; alternatively the rate of cytotoxicity can also be quantified for a given time period after compound addition for a given agent concentration or a group of concentrations. The extent of cytotoxicity can be expressed as IC-50 value which quantifies the activity of the agent with respect to the cardiomyocytes.

[00153] In another aspect of the present invention, direct optical monitoring of cardiomyocytes is used to quantify and measure the beating of cardiomyocytes. The method includes providing a device for optically monitoring cells and monitoring cell morphology operably connected to an optical measurement system, where the device includes at least two wells optionally coated with fibronectin to expedite attachment; adding cells to the at least two wells, where the cells can be mouse or human or other mammalian ES cells destined to differentiate into cardiomyocytes or primary cardiomyocytes isolated directly from the heart of an experimental system including mice, rats, rabbits or dog; optically monitoring the cells of at least two wells at time

intervals over a period of time via the optical measurement system; optionally calculating average rate of beats per unit time, average amplitude intensity in a unit time as well as the average length of time between the beats. The device for such optical measurement of cells may include microtiter plates. The optical system may include optical magnification instrument such as microscope, optical CCD camera, optical-signal processing algorithm to quantify cell beating and to derive cell-beating parameters (such as calculating average rate of beats per unit time, average amplitude intensity in a unit time as well as the average length of time between the beats) based on cell morphology images.

[00154] On skilled in the art will recognize that any agent may be tested. The agent may be a biologically active agent. Exemplary test agents include compounds, drugs, peptides, proteins, antibodies, antibody fragments, siRNA, shRNA, miRNA, cDNA, lipids and any combination thereof. Optionally, impedance-based curves or optionally cell index curves are used to calculate average rate of beats of cardiomyocytes per unit time, average amplitude intensity in a unit time as well as the average length of time between beats, comparison of these optionally derived parameters is made between the test well and the control well, and if significant differences exist, one may optionally conclude that the test agent modulates cardiomyocyte functions.

[00155] The study of cardiomyocyte function and modulation has particular utility in the biomedical arts. For example, the methods of the present invention may be used to assess whether a potential agent is cardiotoxic, cardioprotective and the like. If normal cardiomyocyte beating is altered, the result likely demonstrates the potential agent is cardiotoxic. Such information would permit effective screening prior to testing in live animals or in humans. Further, by coupling millisecond time resolution over extended time periods, the methods may assess short term and long term effects on cardiomyocytes. Since it is well established that certain pharmacological treatments and disease conditions can result in cardiac hypertrophy or atrophy culminating in changes in the morphology of cardiomyocyte, the systems and methods are able to precisely measure and quantify these changes in cell morphology and shape. Thus the methods and systems have particular utility in the areas of biomedical research.

[00156] In some embodiments, potential agents are tested to assess whether they are cardioprotective, or protect against adverse affects. In such embodiments the agent suspected of being cardioprotective is added to the cardiomyocytes prior to, simultaneously or after adding a cardiotoxic agent or a cardiotoxic event. Thus, a cardioprotective agent may prevent abnormal shifts in beating cycle, which would naturally occur in the presence of a cardiotoxic agent. In further embodiments, cardiomyocytes having abnormal beating cycles are treated with potential agents to assess whether normal beating may be induced, such as through administration of a cardioprotective pharmacological agent.

[00157] Certain treatments can also affect the differentiative process of ES cells to cardiomyocytes which may involve specific morphological and adhesive changes. In another aspect of the present invention a method is provide to screen or potential agents that may modulate the morphology of ES- derived cardiomyocyte, adult stem cell-derived cardiomyocyte or primary cardiomyocyte or its differentiation.

[00158] Impedance-based curves and optionally cell index curves may be used to calculate average rate of beats per unit time, average amplitude intensity in a unit time as well as the average length of time between the beats. Significant difference between measurements or data of a test well and a control well support a finding that the biologically active agent within the test well modulates cardiomyocyte function.

E. Assessing the Developmental or Functional Consequence of Gene Knockout and Transgene Expression in Embryonic Stem Cell-Derived Cardiomyocytes

[00159] Embodiments of the present invention also include assessing the developmental consequence of genetically manipulated ES cells or their derived cardiomyocytes. ES cells offer a suitable experimental model system that is amenable to genetic manipulation. Therefore, specific genes can be targeted in knockout experiment as well as genes can be expressed in a developmental or stage specific manner under the control of special promoters. The impedance-based measurement system with

millisecond time resolution can be used to evaluate the role of these genes in cardiac development and or function.

[00160] Steps involved in assessing the developmental and functional effect of gene knockout or transgene expression may include: obtaining ES cells harboring specific knockout of genes or which expresses a particular transgene; provide the system for monitoring impedance of excitable cells having millisecond time resolution; optionally coating wells of the device with either fibronectin or other matrix proteins; seeding the embryonic stem cells (ES cells) of mammalian origin at desired seeding densities into the wells of the device; allowing the cells to attach and spread; after a time period unique to ES-derived cardiomyocytes or primary cardiomyocytes, and monitoring cardiomyocyte beating using the impedance-monitoring system using millisecond kinetic readout to resolve the individual beat cycles of the cells. If a particular gene is required for development of cardiomyocytes from ES cells, it is likely that the knockout of that gene will either block or delay the differentiation of ES cells to cardiomyocytes. Since the impedance-based measurement system is capable of functional monitoring of cardiomyocyte, it can be used as a specific way to monitor the effect of either gene knockout or transgene expression on cardiomyocyte function. In alternative embodiments, the ES cells can be transfected with specific siRNA to "knockdown" the product of a particular transcript and then monitor cardiomyocyte differentiation and function in vitro using the impedance-based measurement system with millisecond time resolution.

[00161] In other exemplary embodiments an impedance-based measurement system is used to evaluate the role of genes in cardiac viability, morphology, development and or beating function. The steps involved in assessing the developmental and functional effect of gene knockout or transgene expression may include: obtaining ES cells harboring specific knockout of genes or which expresses a particular transgene; providing a single-well or multi-well device that comprise microelectrode arrays in well(s) of the device, which can be used for monitoring cell-substrate impedance; optionally coat wells of the device with either fibronectin or other matrix proteins; seeding the embryonic stem cells (ES cells) of mammalian origin or adult stem cells of mammalian origin at specific seeding densities to the wells of the

device; allowing the cells to attach and spread and monitor the growth and viability of the cells using the impedance-based system; after a specified period of time unique to ES-derived cardiomyocytes or primary cardiomyocytes, monitoring cardiomyocyte beating using the impedance-monitoring system to monitor electrode impedance by using milli-second kinetic readout to resolve the individual beat cycles of the cells. If a particular gene is required for development of cardiomyocytes from ES cells, it is likely that the knockout of that gene will either affect the viability of the cells or block or delay the differentiation of ES cells to cardiomyocytes. Since the impedance-based measurement system is capable of functional monitoring of cardiomyocyte both in long term assays and short term assays, it can be used as a specific way to monitor the effect of either gene knockout or transgene expression on cardiomyocyte function. In related embodiments, the ES cells can be transfected with specific siRNA to "knockdown" the product of a particular transcript and then monitor cardiomyocyte viability, differentiation and function in vitro using the impedance-based measurement system.

[00162] In another exemplary embodiment, steps involved in assessing the developmental and functional effect of gene knockout or transgene expression using an impedance-based system in vitro are provided, which include: obtaining ES cells harboring specific knockout of genes or which expresses a particular transgene; optionally coating E-PLATES with either fibronectin or other matrix proteins; seeding either ES cells of mammalian origin or primary cardiomyocytes at specific seeding densities; allowing the cells to attach and spread; and after a specified period of time unique to ES-derived cardiomyocytes or primary cardiomyocytes, monitoring cardiomyocyte beating using the impedance-based system by using millisecond kinetic readout to resolve the individual beat cycles of the cells. If a particular gene is required for development of cardiomyocytes from ES cells, it is likely that the knockout of that gene will either block or delay the differentiation of ES cells to cardiomyocytes. Since the impedance-based system is capable of functional monitoring of cardiomyocyte, it can be used as a specific way to monitor the effect of either gene knockout or transgene expression on cardiomyocyte function. Alternatively, the ES cells can be transfected with specific siRNA to "knockdown" the product of a particular transcript and then monitor cardiomyocyte differentiation and function in vitro using the impedance-based system.

[00163] In another aspect, the present invention is directed to method to establish an assay to assess the effect of gene knockout or transgene expression in ES cells differentiated to cardiomyocytes and functionally monitored by the impedance-based system. The method includes providing a device for measuring cell-substrate impedance operably connected to an impedance analyzer, wherein the device includes at least two wells; adding wildtype ES cells as control to at least 1well and ES cells with a gene knockout or a transgene in at least 1 other well; monitoring impedance of the at least two wells at time intervals over a period of time and optionally determining cell indices from impedance values; comparing the impedance-based curves or optionally the cell index curves between the control well and the well containing the ES cells harboring a knockout of a specific gene or expressing a specific transgene; and if significantly different, concluding that the gene knockout or the transgene can affect either cardiomyocyte viability, morphology from ES cells or cardiomyocyte function as monitored by observing the excitation-contraction coupling.

[00164] As above, in preferred embodiments, the time difference between two consecutive impedance measurement for a well is in the range of milliseconds (e.g., less than 500 milliseconds, less than 300 milliseconds, less than 100 milliseconds, less than 10 milliseconds, or less than about 1 millisecond or faster). The millisecond kinetic readout is required to resolve the individual beat cycles of the cells. Thus, the time resolution for the impedance measurement should allow the system to perform measurement using at least two time points for each beat cycle. In some embodiments more than two time points are resolved for each beating cycle.

EXAMPLES

Example 1

Impedance Monitoring of Attachment, Growth and Viability of Mouse ES Cell-Derived Cardiomyocytes

[00165] Since isolated primary cardiomyocytes, ES-derived cardiomyocytes and adult stem cell-derived cardiomyocytes can be maintained in culture, these cells provide a desirable model system to study cardiomyocytes as well as cardiomyocyte modulation. The present example demonstrates the use of the ACEA RT-CES system to measure and monitor the attachment, growth and viability of mouse ES-derived cardiomyocytes which were seeded at different seeding densities.

[00166] Mouse ES cells were seeded at a density ranging from 3000 cells to 50,000 cells per well in E-PLATES (Acea Biosciences, San Diego, CA) precoated with fibronectin. The attachment, growth and viability of the cells were monitored on RT-CES system measuring impedance signal in the form of cell index every 30 minute for 48 hours. At about 48 hrs after cell seeding, the growth of the cells had ceased and the appearance of beating cardiomyocytes were evident as judged by looking at the cells inside the E-PLATE under the microscope.

[00167] **FIG. 3** shows the cell index curves measured on RT-CES system for 4 different seeding densities (3750, 7500, 15,000 and 30,000 cells per well) of mouse ES-derived cardiomyocytes. For such long term measurement, cell electrode impedance and corresponding cell indices were measured at about 15 minute intervals. Based on the cell index growth and viability curves, it is evident that the extent of the impedance signal correlates well with the seeding density of viable ES-derived cardiomyocytes.

Example 2

Detection of Cardiotoxic Effects Using Real Tim Impedance Monitoring

[00168] As an example, we describe here the use of the ACEA RT-CES system to measure and monitor the attachment and growth of mouse ES cells derived cardiomyocytes and subsequently treated with a cytotoxic agent (**FIG. 4A-B**).

[00169] Mouse ES-derived cardiomyocytes were seeded at a density of 25,000 cells per well in E-PLATES precoated with fibronectin. The attachment and growth of cells were monitored on RT-CES system for 72 hours and then treated with

increasing doses of the compound of sodium dichromate dehydrate which is known to induce cytotoxicity. According to **FIG. 4A** the plot of normalized cell index for cells in different wells treated with different concentrations of sodium dichromate dehydrate (SDD), SDD causes a concentration dependent decrease in viability of ES-derived cardiomyocytes. To quantify the extent of sodium dichromate dehydrate activity against the cardiomyocytes, the normalized cell indices at 24 hrs after compound treatment were plotted against the log of the corresponding sodium dichromate dehydrate concentrations. From the sigmoidal curve, shown in **FIG. 4B**, half maximal activity or IC-50 value of 1.48 uM was derived for the compound.

Example 3

Real time Monitoring of Mouse ES Cell-Derived Cardiomyocytes and Inducing Hypertrophy

[00170] As an example, we describe here the use of the ACEA RT-CES system to measure and monitor the attachment and growth of mouse ES cells derived cardiomyocytes and subsequently treated with isoproteranol, a β2 adrenergic receptor agonist known to induce hypertrophy (**FIG. 5A**).

[00171] Mouse ES-derived cardiomyocytes were seeded at a density of 25,000 cells per well in E-PLATES precoated with fibronectin. The attachment and growth of the cells were monitored on RT-CES system for 72 hours and then treated with increasing doses of the compound isoproteranol. According to **FIG. 5A**, isoproteranol causes a concentration dependent change in cell index readings. The timing of the cell index change is consistent with a change in the morphology of the cells which we have shown previously for other GPCR agonists in primary cells (Yu et al (2006): Real-time monitoring of morphological changes in living cells by electronic cell sensor arrays: an approach to study G protein-coupled receptors; Analytical Chemistry, Vol 78, pages 35-43). To quantify the extent of isoproteranol-induced morphological changes in mouse ES-derived cardiomyocytes, the normalized cell indices were plotted against the log of

the corresponding isoproteranol concentrations (**FIG. 5B**). From the sigmoidal curve generated a half maximal activity or IC-50 value of 3.1 nM was derived for the compound.

Example 4

Real Time Impedance Monitoring with Millisecond Resolution of Beating Cardiomyocytes

[00172] As an example, we describe here the use of an improved impedance-based system with millisecond time resolution to measure and monitor the beating of cardiomyocytes using fast kinetic software.

[00173] Mouse ES cells were seeded at a density of between 3,000 to 50,000 cells per well in E-PLATES precoated with fibronectin. The attachment and growth of the cells were monitored on RT-CES system. **FIG. 6** shows the cell index curves measured on RT-CES system for 4 individual wells, with cell culture medium as background starting from cell seeding to about 86 hrs after cell seeding. For such long term measurement, cell electrode impedance and corresponding cell indices were measured at about 15 minute intervals. As evidenced on these plots, the cell index curves were rather smooth up to about 44-48 hrs, after which there were "noises" or "small-spikes" on the cell index curves. Such spikes were most evident after about 60 hrs. We now understand the origins of such "small-spikes" and interpret that such spikes in the impedance or cell index readout are associated with the beating of the cells. During the synchronized beating of the cells, the cell morphology and cell adhesion/attachment to the electrodes change regularly in synchrony with the cell beating. Such regular or periodic changes in cell morphology and cell adhesion/attachment are then reflected in the changes in cell-electrode or cell-substrate impedances.

[00174] In order to monitor beating of cardiomyocytes, a specially designed software and measurement circuit hardware that are capable of millisecond

impedance data acquisition (e.g., typically with time resolution between consecutive impedance measurement for a same well being less than 40 milliseconds) was used to monitor the quick rhythmic beating of the cardiomyocytes. For such measurement, the background electrode impedance is measured with the cells inside the wells (note, this is in contrast with **FIGS. 3** and **6**, where the background measurement is performed using cell culture media). The software was used to measure cardiomyocyte beating at distinct stages throughout its attachment and growth phases (**FIG. 7**). For a baseline reference, the impedance measurement was done on the ES cells at 24 hours where the cells had not fully spread and formed a tight monolayer and even though the cells appear to beat when visualized under a microscope, they do so asynchronously and as a result no net beating signal is detected (**FIG. 7A**). For plot, impedance readout has been converted into dimensionless cell indices. **FIGS. 7B** and **7C** show that ES cells that had fully spread and formed tight junctions with neighboring cells at 48 hours and 72 hours respectively, show regular impedance-spikes which correlate with the beating frequency of cardiomyocytes as judged by microscopic observation .

[00175] To use the measured cell index curves, it is important to further derive various physiologically relevant parameters. Several important parameters may include, the beating rate of the cardiomyocytes (i.e., how many times the cells beat within a unit of time for example, a minute), the beating amplitude (i.e. the magnitude of the beating of cells in terms of impedance change) the average amplitude intensity in a unit time as well as the average length of time between the beats, time of rise for a beat, time of decay for a beat. Because of the unique and complex nature of the impedance readout signals (smaller signal amplitude, sampling time resolution may be limited by the hardware and the software used), appropriate methods or techniques are required for analyzing cell index curves to derive the above mentioned parameters.

[00176] For deriving the beating rates of cardiomyocytes, one method may be by counting how many peaks there are within a given time frame (for example, one minute). For this approach to work, the sampling time resolution has to be sufficiently high so that the each beat of the cells does show a peak on the recorded cell index curves. In addition, determining a peak "automatically" also require some algorithm. For example, each peak would have to have one "rise" in cell index and also one "decay" in

cell decay. Each "rise"-and-"decay" pair forms a single peak. The algorithm needs to determine such "rise" and "decay" portions of the curves and then counts a peak.

[00177] Another method to derive or count the beating rates of cardiomyocytes is to perform a detailed signal analysis to derive the frequency components of the cell index curves and to derive the magnitude of each frequency components. One method of signal analysis is Fourier transform of the cell index curve (of the time domain). Like above method, the sampling time-resolution needs to be sufficiently high so that each beat of the cells has at least three time points being measured. After performing Fourier transform, we would look for the frequency components having the largest magnitude and such frequency would correspond to, or be very close to, the beating frequency. In addition, for such analysis, giving a fixed sampling time resolution, the more time points sampled for analysis, the more accurate it is for the analyzed beating frequency. **FIG. 8A** and **FIG. 8B** shows a pair of cell index curves and the corresponding beat rate based the above described Fourier transform. In **FIG. 8B**, the cell index curves last from time zero to time 42 seconds. In **FIG. 8B**, the beating frequency for the traces in **FIG. 8A** is analyzed using the method described here, i.e., Fourier transform followed by picking up the highest-magnitude frequency component. For each derived frequency data at one time moment in **FIG. 8B**, cell index data from multiple time points (starting from previous 98 time points plus the time moment of interest) is used for analysis. Thus, the time axis in **FIG. 8B** starts from about 20 seconds to 42 seconds.

[00178] Another method deriving the beating rates of cardiomyocytes is to first determine the time length (ΔT in seconds) between two consecutive peaks and then calculate the beating rate according to the formula of "beats per minute =60/ ΔT". Thus for each two-consecutive peaks, one can calculate one beating rate. Furthermore, one can plot this beating rate as a function of the time (of the first of the two consecutive peaks) to obtain the time dependency of the beating rates. **FIG. 9A** shows an example of the time-dependent beat rates derived using this method, for mouse ES-derived cardiomyocytes treated with compound sotalol at a concentration of 4.4 uM. Corresponding cell index data is shown in **FIGS. 9C** and **9D**, where the time resolution

between two adjacent points is 40 milliseconds. In other words, a second in **FIGS. 9C** and **9D** is equivalent to 40-milliseconds.

[00179] For deriving the amplitude of the beating of the cardiomyocytes, there may also be different methods. One method is to analyze each peak and finding the peak maximum and the peak minimum. The amplitude is calculated by subtracting peak maximum by the peak minimum. Then, one can plot the peak amplitude as a function of the time of the peak to obtain the time dependency of the peak amplitude. **FIG. 9B** shows an example of the time-dependent peak amplitudes derived using this method, for mouse ES-derived cardiomyocytes treated with compound sotalol at a concentration of 4.4 uM. Another approach may also be to use Fourier transform described above. Then based on derived Fourier coefficients, one can re-simulate time domain cell index curves and look for the peak magnitude from the simulated curves.

[00180] For deriving the averaged length of time between the beats, there may also be different methods. For each identified peak, one can first determine a starting point of the peak. Then the time difference between two consecutive peaks at the two starting points of the peak can be used for the length of time between the beats.

[00181] With the method of determining each peak, one can also calculate the time-of-rise of the peak and the time-decay-of the peak.

Example 5

Identifying Modulators of Cardiac Function Using Real Time Impedance Monitoring with Millisecond Resolution

[00182] Similar to Example 4, the millisecond kinetic readout requires that the impedance measurement system can provide impedance measurement data at millisecond time resolution. In other words, the time difference between two consecutive impedance measurement for a well shall be in the range of milliseconds (e.g., less than 500 millisecond, less than 300 millisecond, less than 100 millisecond, less than 10 millisecond, or less than 1 millisecond or faster). The millisecond kinetic readout is

required to resolve the individual beat cycles of the cells. Thus, the time resolution for the impedance measurement should allow the system to perform measurement at least two time points for each beat cycle, or at more than two points for each beat cycle.

[00183] In order to demonstrate the utility of the millisecond kinetic impedance-measurements, we first used two pharmacological agents, one known to suppress the heart rate and consequently cardiomyocyte beating and the other known to increase the heart rate and consequently the rate of cardiomyocyte beating. As Mouse ES cells were seeded in FN-coated E-PLATES and monitored for about 72 hours when the cells differentiated into beating cardiomyocytes, as described in Section 4. A baseline of the cardiomyocyte was taken for approximately 40 seconds using the specially designed fast kinetic data acquisition hardware and software which is capable of millisecond data acquisition and display. An agonist of muscarinic receptors, carbachol, which is known to slow down the heart rate was added to one well at a final concentration of 333 nM and cardiomyocyte beating was monitored for 10 minutes (**FIG. 10A**). The data clearly shows that carbachol significantly slows down the rate of cardiomyocyte beating from ~ 80 beats/min prior to carbachol addition to ~ 60 beats/min after carbachol addition (Table I). Alternatively, addition of isoproteranol at a final concentration of 4.4 uM significantly increased the rate of cardiomyocyte beating from ~ 65 beats/min to 115-135 beats/min (**FIG. 10B** and **Table I**). These data clearly show that the readout system and the fast kinetic software are sufficiently robust and sensitive to detect these changes in rate of cardiomyocyte beating even at very low compound concentrations. Similar to the cell index plot shown in **FIGS. 9C** and **9D**, the time resolution between two adjacent points in **FIGS. 10A** and **10B** is 40 milliseconds. In other words, a second in **FIGS. 10A** and **10B** is equivalent to 40 millisecond.

Table I.

Compound	Mechanism	Concentration	Beat Rate	Amplitude	Pattern Change
Carbachol	Muscarnic receptor agonist	333 nM	From ~ 80 to ~ 60	From 0.07 to 0.06	Beating rate decreased
Isoproteranol	b2 Adrenergic receptor agonist	4.4 uM	From ~ 65 to 115-136	From 0.19 to 0.16	Beating rate increased

[00184] To further demonstrate the capabilities of the improved impedance-based monitoring of cardiomyocyte beating in detecting drugs which may adversely affect heart function, a number of drugs which have been pulled out of the market due to cardiotoxic side effects such as ERG channel inhibition and QT elongation were compiled and tested in a dose-dependent manner. The list of these compounds, their mechanism and adverse side affects are shown in **Table II**. For these tests, mouse ES derived cardiomyocytes were seeded at a final density of 25,000 cells in ACEA E-Plates and continually monitored by the RT-CES system. Approximately, 72 hours after cell seeding the improved, impedance-measurement system with millisecond time resolution was used to establish a baseline reading of cardiomyocyte beating for each well for about 40 seconds. Subsequently, the cells in each well were treated with the indicated drug and dose shown in **FIGS. 11A-11T**. Similar to the cell index plot shown in **FIGS. 9C** and **9D**, the time resolution between two adjacent points in all the figures in **FIG. 9** is 40 milliseconds. In other words, a second in **FIG. 9** is equivalent to 40-milliseconds.

[00185] **Table II** shows a summary of the results, clearly demonstrating that compounds which have been shown to affect ERG channels do affect various aspects of cardiomyocyte beating and function such as frequency of beating, magnitude of beating. Furthermore, as shown in **FIG. 12** some of these compounds can lead to qualitatively different or similar patterns. For example, the compounds E4031, Astezimole and dofetilide which are ERG channel inhibitors do contain patterns with similar features. In summary these results clearly indicate that using the impedance-measurement system with millisecond time resolution do lead to a sensitive and robust readout for cardiomyocyte beating that can also detect drugs which are known to be cardiotoxic. Similar to the cell index plot shown in **FIGS. 9C** and **9D**, the time resolution between two adjacent points in all the figures in **FIGS. 10A-10B** is 40 milliseconds. In other words, a second in a figure in **FIGS. 10A-10B** is equivalent to 40-millisecond.

Table II.

Compound	Mechanism	Concentration	Beat Rate	Amplitude	Pattern Change
Astemizole	anti-histamine	400 nM	0	<0.01	From 68-72 bpm to irregular being to beating stopped
Terfenadine	anti-histamine	200 nM	0	<0.01	From 71-78 bpm to irregular beating to beating stopped
Erythromycin	anti-biotic	13.3 uM	From ~ 60 to ~ 80	0.09 to 0.07	No pattern change
Moxifloxacin	anti-biotic	20 uM	From ~ 80 to ~73	From 0.055 to 0.060	No pattern change
Pentamidine	anti-infective	20 uM	From 71~78 to ~71	From 0.24 to 0.21	No pattern change
Amitriptyline	Serotonergic Inhibitor	4.4 uM	From ~70 to ~ 90	From 0.22 to 0.17	No pattern change
Verpamil	Ca channel blocker	130 nM	From ~ 65 to 0	From 0.13 to 0.06	From ~ 65 bpm to only occasional single beating.
Rosglitazone	PPAR agonist	13.3 uM	From ~79 to ~ 75	From 0.22 to 0.17	No pattern change
Dofitlite		500 nM	From ~ 80 to ~ 180	From 0.09 to 0.02	Pattern changed, much faster
Rofecoxib	COX-2 Inhibitor	13.3 uM	From ~ 68 to ~ 60	From 0.2 to 0.19	No pattern change
Rofecoxib	COX-2 Inhibitor	40 uM	From ~ 62 to ~ 60	From 0.16 to 0.10	Pattern change, no beating after initial treatment, then recovers
Celecoxib	COX-2 Inhibitor	4.4 uM	From ~ 60 to (~20 - ~ 50)	From ~0.2 to ~0.12	Pattern change
Doxirubicin	Anthracycline	40 uM	~ 70	~ 0.16	No pattern change (initially). Beating pattern changes after 2 hrs.
Cyclosporin A	Calcineurin inhibitor	13.3 uM	From ~70 to ~ 80	From 0.18 to 0.15	No pattern change
Propalanol	β2-adrenergic receptor antagonist	4.4 uM	From ~70 to over 150	From 0.25 to 0.025	Pattern changed, much faster and irregular
Sotalol		13.3 uM	From ~ 80 to ~ 160	From 0.27 to 0.07	Much faster, pattern changed
E4031	K channel inhibitor	120 nM	From 80 to 160	From 0.09 to 0.03	Pattern changed, much faster
DDT	Pesticide	8 uM	From 80 to 140, then to ~ 80	From 0.25 to 0.02	Initially become faster, later irregular beating
PCB	Organic toxicant	8 uM	From ~ 65 to o	From 0.2 to 0	Beating stopped
Endosulfan	insecticide	8 uM	From ~ 75 to o	From 0.2 to 0	Beating stopped

[00186] To further demonstrate the capabilities of the fast impedance-measurement-system-based monitoring of cardiomyocyte beating in detecting drugs which may adversely affect heart function, compounds at different concentrations were tested to demonstrate the dose-dependent effects of these compounds on cardiomyocytes. Approximately, 72 hours after cell seeding the impedance-measurement system with millisecond time resolution was used to establish a baseline reading of cardiomyocyte beating for each well for about 40 seconds. Subsequently, the cells in each well were treated with drugs at different dose concentrations. **FIG. 13** shows an example of dose dependent effects of Astemizole on cardiomyocytes beating at different concentrations. At high concentration of 400 nM, Astemizole had such a strong effect on the beating of cardiomyocytes that the beating almost stopped. The effect of Astemizole on the beating of the cardiomyocytes is clearly does-dependent. At low concentration of 40 pM, its effect on the beating of the cardiomyocytes is small that the cardiomyocyte beating rate was not affected. Similar to the cell index plot shown in **FIGS. 9C** and **9D**, the time resolution between two adjacent points in all the figures in **FIGS. 11A-11T** is 40 milliseconds. In other words, a second in **FIG. 13** is equivalent to 40 milliseconds.

Example 6

Modulation of Cardiomyocyte Beating In Response to Haloperidol Treatment Using Millisecond Time Resolution

[00187] To further demonstrate the capabilities of the improved impedance measurement system for monitoring of cardiomyocyte beating in detecting drugs which may adversely affect heart function, 500nM Haloperidol was tested to demonstrate its time-dependent effects on cardiomyocytes. Approximately, 72 hours after cell seeding the improved impedance system was used to establish a baseline reading of cardiomyocyte beating for each well for about 16 seconds (**FIG. 14A**). Note that in **FIG. 14A**, each minute showed on the x-axis of **FIG. 14A** corresponds to one second in real measurement. Subsequently, the cells in the well treated with 500 nM Haloperidol.

FIGS. 14B, **C**, **D**, **E**, **F**, **G** and **H** show the impedance-based monitoring of beating of the cardiomyocytes at time points of first 30 seconds, about 1 minute, about 2 minutes, about 4 minutes, about 5.5 minutes, about 1 hour and about 21 hours after the compound treatment. In **FIGS. 14B** through **14H**, each minute showed on the x-axis corresponds to one second in real measurement. It is clear that within 1 hr of compound treatment, the cardiomyocytes exhibit significant, time-dependent change in their impedance responses. Even at ~ 21 hrs after compound treatment, the impedance pattern did not restore and the beating frequency (50 ~ 60 beats per minute) appeared to become about half of that before compound treatment (90 ~ 100 beats per minute before treatment). Yet the amplitude of the impedance response spikes nearly doubled compared with that before compound treatment. **FIGS. 15A-H** and **FIGS. 16A-H** show the analysis results of the impedance beating pattern of **FIGS. 14A-H** in terms of the beating frequency (beats per minute) and the beating magnitude For **FIGS. 15A-H** and **FIG. 16A-H**, each unit (1) on the x-axis corresponds to 0.016 second (16 milliseconds) in real measurement.

Example 7

Modulation of Cardiomyocyte Beating In Response to Eryromycin Treatment Using Millisecond Time Resolution

[00188] To further demonstrate the capabilities of the improved impedance measurement system for monitoring of cardiomyocyte beating in detecting drugs which may adversely affect heart function,300 uM erythromycin was tested to demonstrate its time-dependent effects on cardiomyocytes. Approximately, 72 hours after cell seeding the improved impedance system was used to establish a baseline reading of cardiomyocyte beating for each well for about 15 seconds (**FIG. 17A**). Note that in **FIG. 17A**, each minute showed on the x-axis of **FIG. 17A** corresponds to one second in real measurement. Subsequently, the cells in the well treated with 300 uM erythromycin. **FIGS. 17B-I** show the impedance-based monitoring of beating of the cardiomyocytes at time points of first 30 seconds, about 1 minute, about 2 minutes, about 4 minutes, about 5.5 minutes, about 1 hour, about 3hr and about 21 hours after the compound treatment.

In **FIGS. 17B-H**, each minute showed on the x-axis corresponds to one second in real measurement. It is clear that within 3 hr of compound treatment, the cardiomyocytes exhibit significant, time-dependent change in their impedance responses. For example, at about 1 hr after the treatment, the frequency of the impedance-based beating spikes is much higher than that for the cardiomyocytes before treatment, yet the magnitude is much smaller. On the other hand, at about 3 hr after treatment, the impedance-based beating pattern becomes rather irregular whilst the magnitude of the beating pattern has somewhat restored. Still, even at ~ 21 hrs after compound treatment, the impedance pattern did not restore and the beating frequency appeared to about 70% (at 50 ~ 60 beats per minute) of that before compound treatment (at 80 ~ 90 beats per minute). Yet the amplitude of the impedance response spikes increased by about 50% compared with that before compound treatment. **FIGS. 18A-I** and **FIGS. 19A-I** show the analysis results of the impedance beating pattern of **FIGS. 17A-I** in terms of the beating frequency (beats per minute) and the beating magnitude. For **FIGS. 18A-I** and **FIGS. 19A-I**, each unit (1) on the x-axis corresponds to 0.016 second (16 milli-seconds) in real measurement.

CLAIMS

What is claimed is:

1. A system for monitoring cells, the system comprising:

a) a device for monitoring cell-substrate impedance, the device comprising a plurality of wells on a nonconductive substrate, wherein each of the plurality of wells comprises an electrode array fabricated on the substrate for measurement of cell-substrate impedance;

b) an impedance analyzer that measures cell-substrate impedance from the plurality of wells.

c) electronic circuitry comprising multiple analogue-to-digital conversion channels, wherein the electronic circuitry electrically connects the electrode arrays to the impedance analyzer such that the electrode arrays are electrically monitored at millisecond time resolution; and

d) a software program that analyzes the measured cell-substrate impedance.

2. The system of claim 1, wherein the multiple analogue-to-digital conversion channels are configured to convert analog electronic signals from multiple wells to digital signals simultaneously.

3. The system of claim 1, wherein the electronic circuitry allows parallel analogue-to-digital (AD) conversion of impedance signals from multiple wells.

4. The system of claim 1, wherein the electronic circuitry performs signal conversion in parallel across multiple wells.

5. The system of claim 4, wherein said parallel signal conversion allows for parallel signal processing and impedance calculation for measurements obtained from multiple wells.

6. The system of claim 1, wherein the electronic circuitry is configured for monitoring cell-substrate impedance in a plurality of wells at approximately the same time.

7. The system of claim 1, wherein the electronic circuitry performs parallel analogue-to-digital (AD) conversion of impedance signals from multiple wells.

8. The system of claim 1, wherein the electronic circuitry performs signal conversion, signal processing, and impedance calculation in parallel across multiple wells.

9. The system of claim 1, wherein the system comprises an electromechanical apparatus capable of interfacing a multiwell device with one or more platforms.

10. The system of claim 9, wherein the one or more platforms of the electromechanical apparatus comprise an impedance platform and an optical platform.

11. The system of claim 1, wherein the device for monitoring cell-substrate impedance comprising a two-piece structure wherein the nonconductive substrate is attached to a bottomless plate to form a bottom surface of the wells.

12. The system of claim 1, wherein the substrate is suitable for cell attachment via a precoat comprising one or more compounds that improve attachment.

13. The system of claim 1, wherein the electronic circuitry is configured to measure with a time difference between two adjacent impedance measurements is less than 500 ms.

14. The system of claim 1, wherein the measurement at millisecond time resolution is initiated by a change in an optical property.

15. The system of claim 14, wherein the change in the optical property is determined by the device for optically monitoring the one or more wells.

16. The system of claim 1, wherein the electrode array comprises electrical traces and connection pads configured to connect the electrode array to the impedance analyzer, wherein the electrical traces are covered with an insulating layer.

17. The system of claim 1, wherein the electrode array comprises a plurality of electrode elements that are evenly spaced.

18. A system for monitoring cells, the system comprising:

a) a device for monitoring cell-substrate impedance, the device comprising a plurality of wells on a nonconductive substrate, wherein each of the plurality of wells comprises an electrode array fabricated on the substrate for measurement of cell-substrate impedance;

b) an impedance analyzer that measures cell-substrate impedance from the plurality of wells.

c) electronic circuitry that electrically connects the electrode arrays to the impedance analyzer, wherein the electronic circuitry performs signal conversion in parallel across multiple wells such that the electrode arrays are electrically monitored at millisecond time resolution; and

d) a software program that analyzes the measured cell-substrate impedance.

19. The system of claim 18, wherein the electronic circuitry comprises multiple analogue-to-digital conversion channels.

20. The system of claim 19, wherein the multiple analogue-to-digital conversion channels are configured to convert analog electronic signals from multiple wells to be converted to digital signals simultaneously.

21. The system of claim 18, wherein the electronic circuitry allows parallel analogue-to-digital (AD) conversion of impedance signals from multiple wells.

22. The system of claim 18, wherein said parallel signal conversion allows for parallel signal processing and impedance calculation for measurements obtained from multiple wells.

23. The system of claim 22, wherein the electronic circuitry performs signal conversion, signal processing, and impedance calculation in parallel across multiple wells.

24. A system for monitoring cells, the system comprising:

a) a device for monitoring cell-substrate impedance, the device comprising a plurality of wells on a nonconductive substrate, wherein each of the plurality of wells comprises an electrode array fabricated on the substrate for measurement of cell-substrate impedance;

b) an impedance analyzer that measures cell-substrate impedance from the plurality of wells;

c) electronic circuitry that electrically connects the electrode arrays to the impedance analyzer to electrically monitor the electrode arrays such that a time difference between two adjacent measurements is less than 500 ms; and

d) a software program that analyzes the measured cell-substrate impedance.

25. The system of claim 24, wherein the electronic circuitry comprises multiple analogue-to-digital conversion channels.

26. The system of claim 25, wherein the multiple analogue-to-digital conversion channels are configured to convert analog electronic signals from multiple wells to digital signals simultaneously.

27. The system of claim 24, wherein the electronic circuitry allows parallel analogue-to-digital (AD) conversion of impedance signals from multiple wells.

28. The system of claim 24, wherein the electronic circuitry performs signal conversion in parallel across multiple wells.

29. The system of claim 28, wherein said parallel signal conversion allows for parallel signal processing and impedance calculation for measurements obtained from multiple wells.

30. The system of claim 24, wherein the electronic circuitry performs signal conversion, signal processing, and impedance calculation in parallel across multiple wells.

ABSTRACT

A system for monitoring cells, which includes a device for monitoring cell-substrate impedance, the device having a plurality of wells on a nonconductive substrate, where each of the plurality of wells has an electrode array fabricated on the substrate for measurement of cell-substrate impedance; an impedance analyzer that measures cell-substrate impedance from the plurality of wells; electronic circuitry with multiple analogue-to-digital conversion channels, where the electronic circuitry electrically connects the electrode arrays to the impedance analyzer such that the electrode arrays are electrically monitored at millisecond time resolution; and a software program that analyzes the measured cell-substrate impedance.

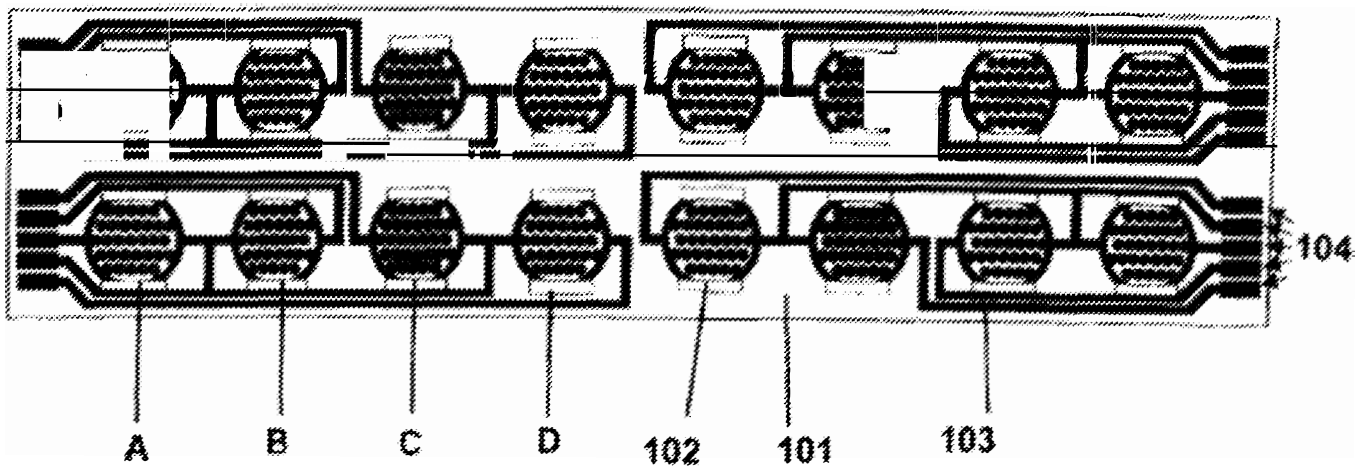


FIG. 1A

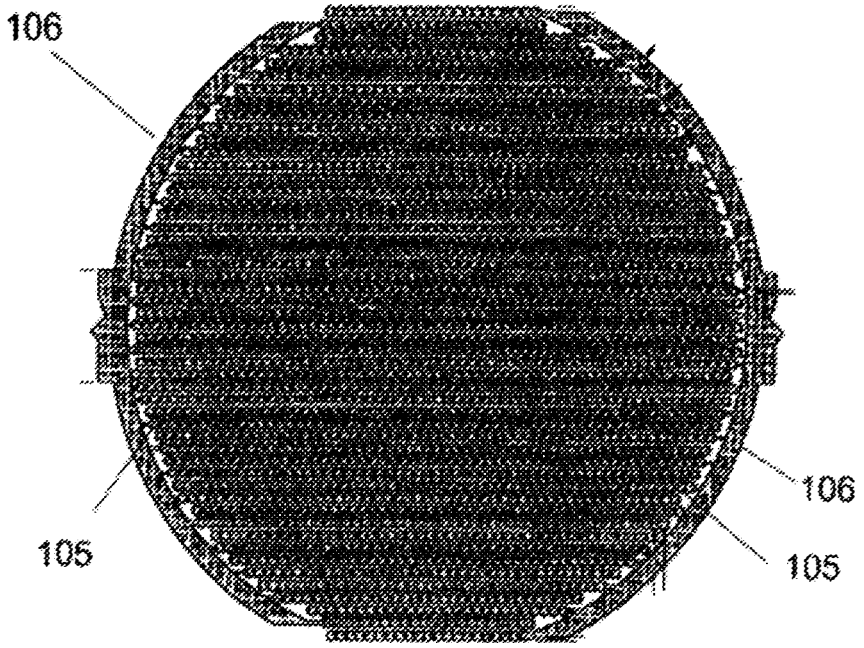


FIG. 1B

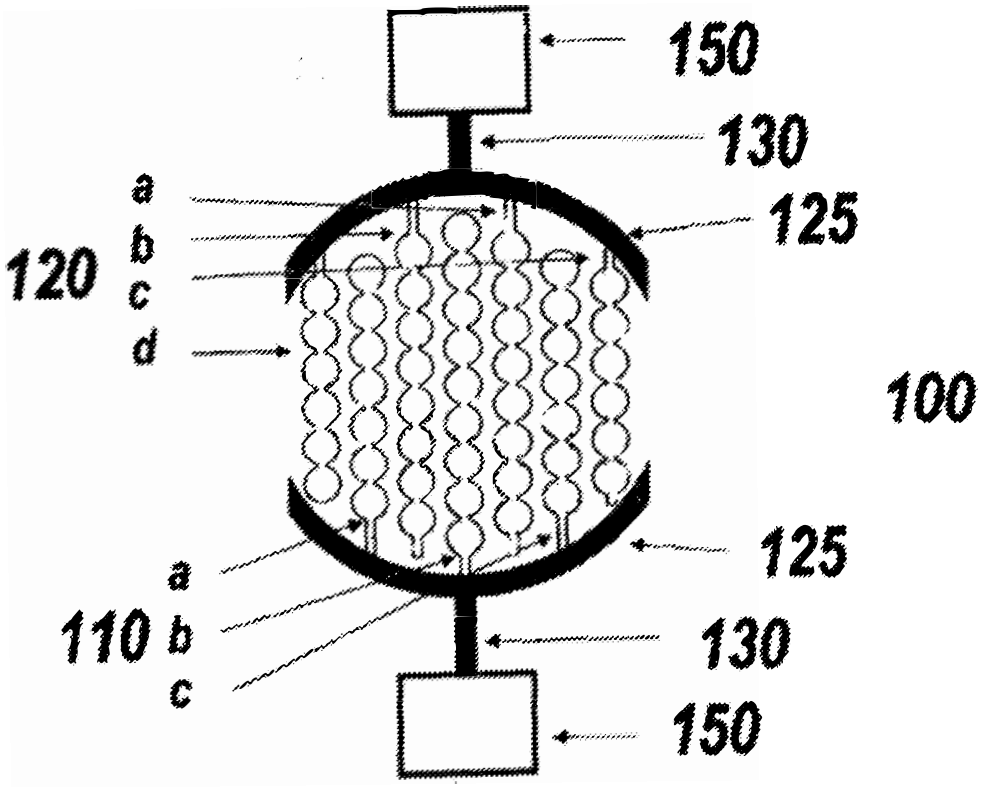


FIG. 2A

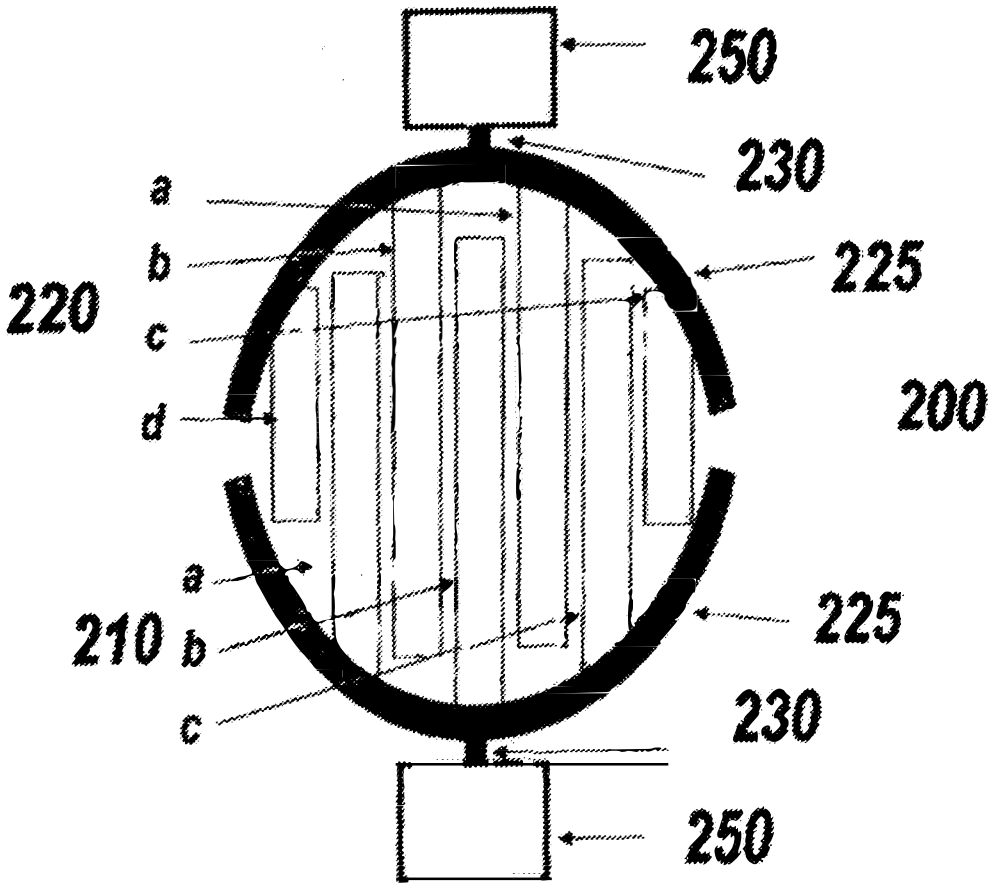


FIG. 2B

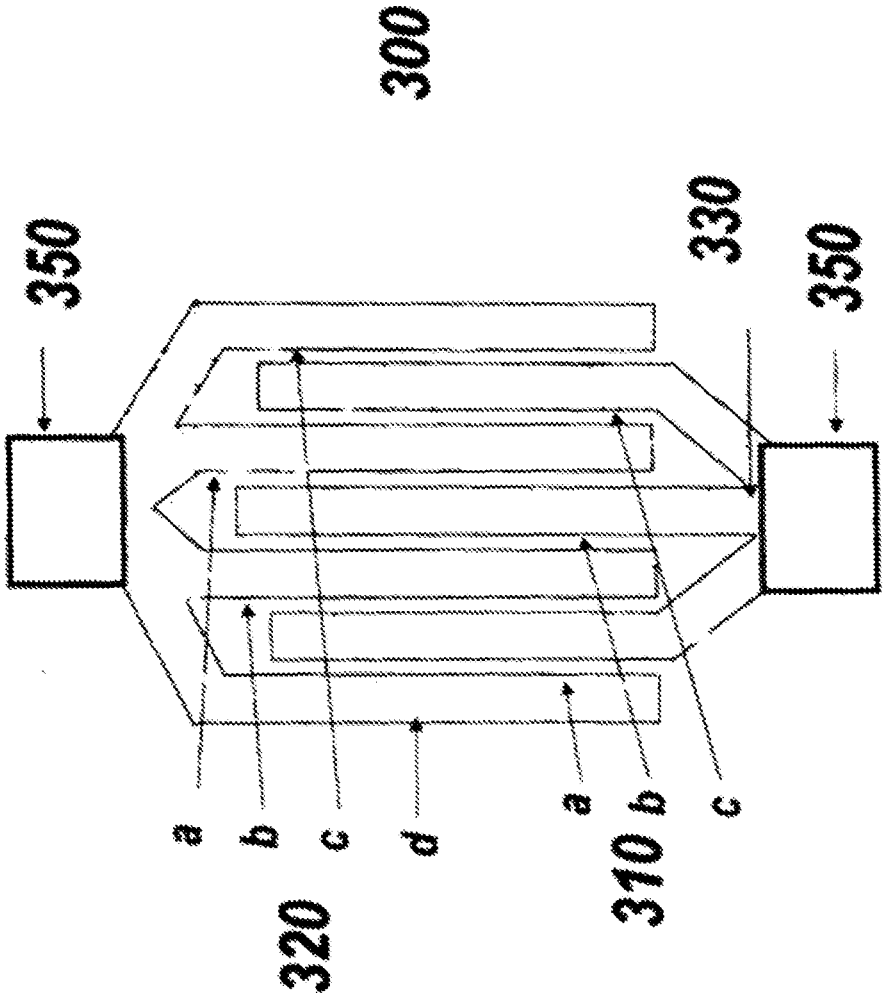


FIG. 2C

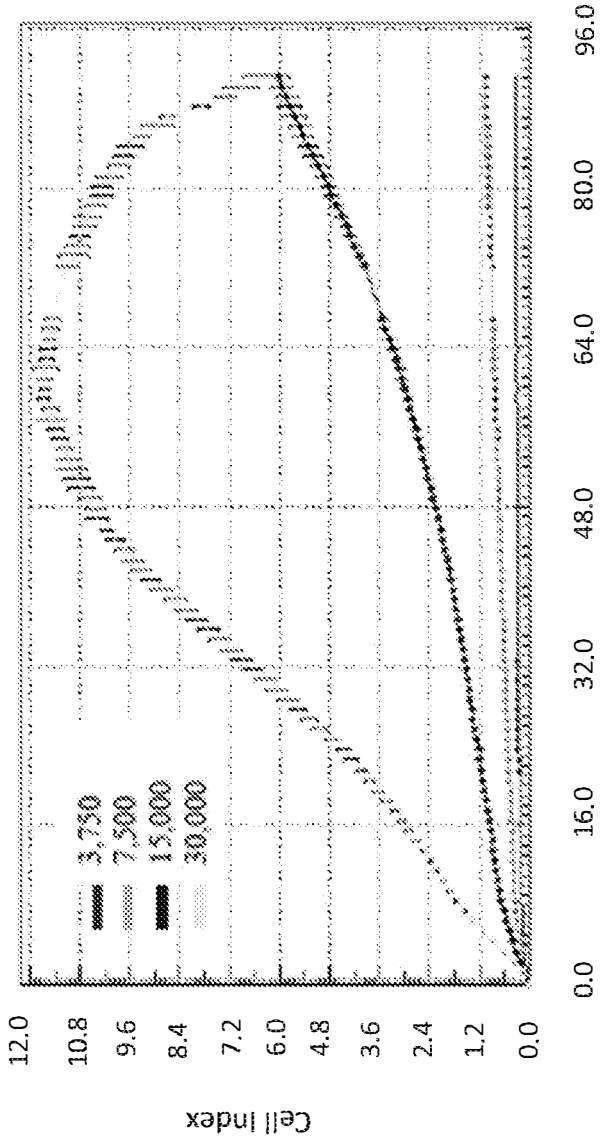

12.0
10.8
9.6
8.4
7.2
6.0
4.8
3.6
2.4
1.2
0.0
Cell Index
0.0
16.0
32.0
48.0
64.0
80.0
96.0
Time (hr)
3,750
7,500
15,000
30,000

FIG. 3

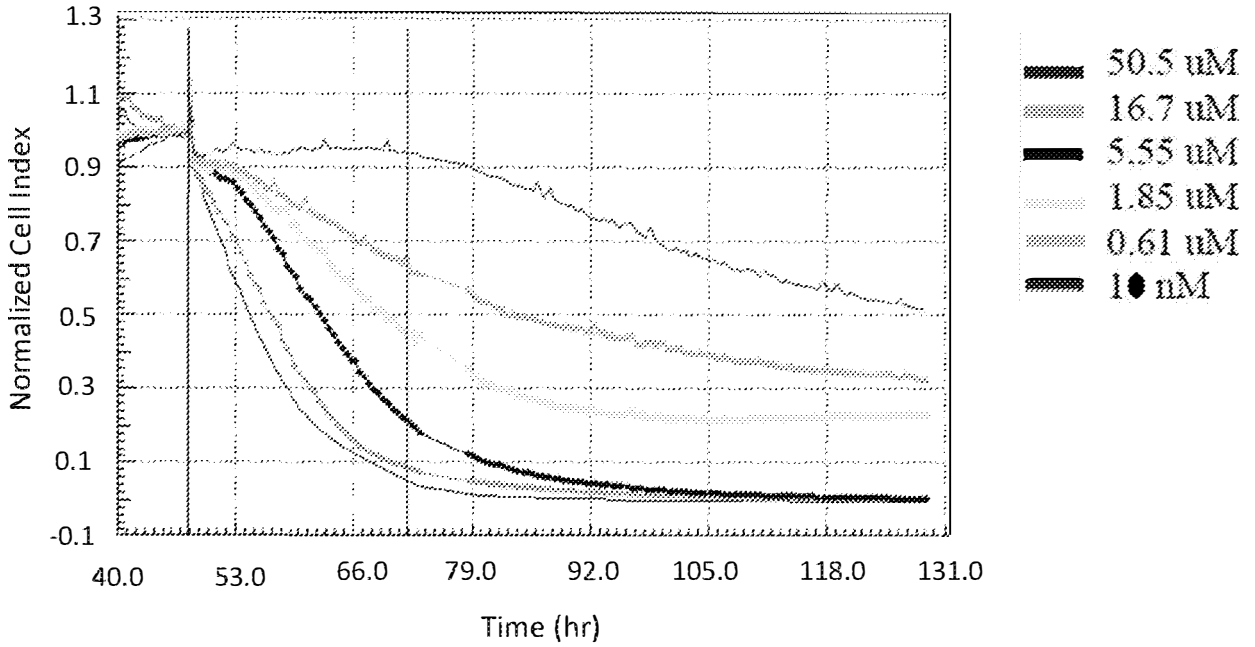

1.3
1.1
0.9
0.7
0.5
0.3
0.1
-0.1
Normalized Cell Index
40.0
53.0
66.0
79.0
92.0
105.0
118.0
131.0
Time (hr)
50.5 uM
16.7 uM
5.55 uM
1.85 uM
0.61 uM
1♦ nM

FIG. 4A

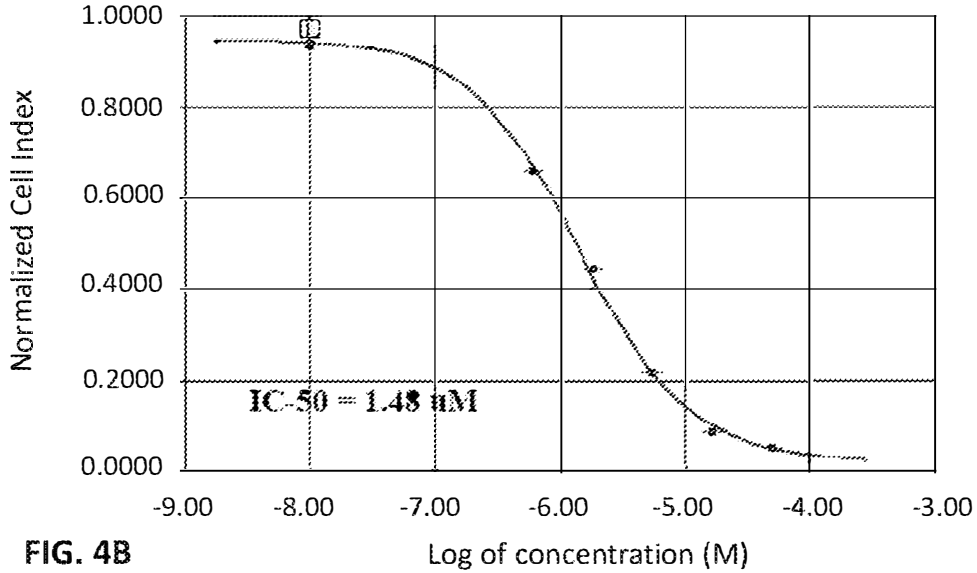

1.0000
0.8000
0.6000
0.4000
0.2000
0.0000
Normalized Cell Index
IC-50 = 1.48 nM
-9.00
-8.00
-7.00
-6.00
-5.00
-4.00
-3.00
Log of concentration (M)

FIG. 4B

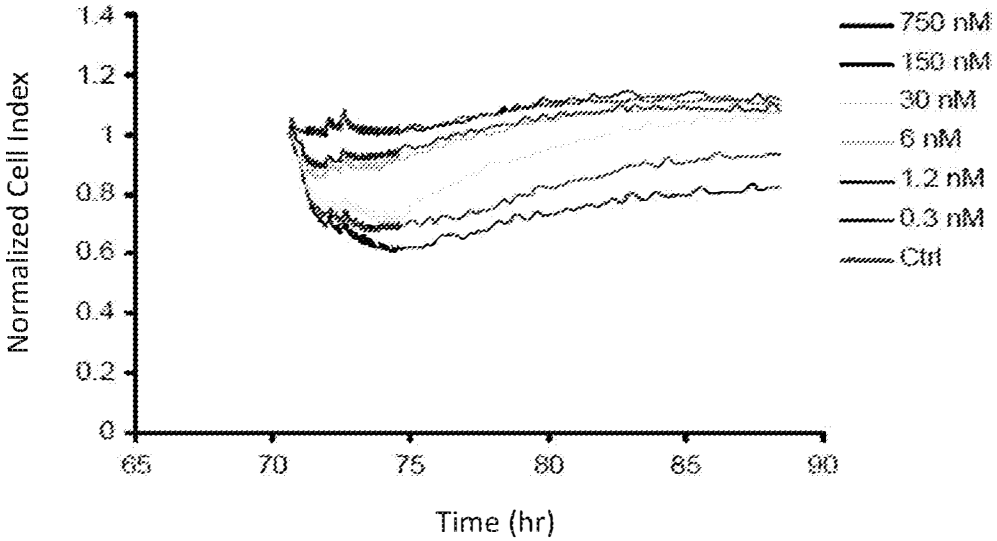

Normalized Cell Index
1.4
1.2
1
0.8
0.6
0.4
0.2
0
65
70
75
80
85
90
Time (hr)
750 nM
150 nM
30 nM
6 nM
1.2 nM
0.3 nM
Ctrl

FIG. 5A

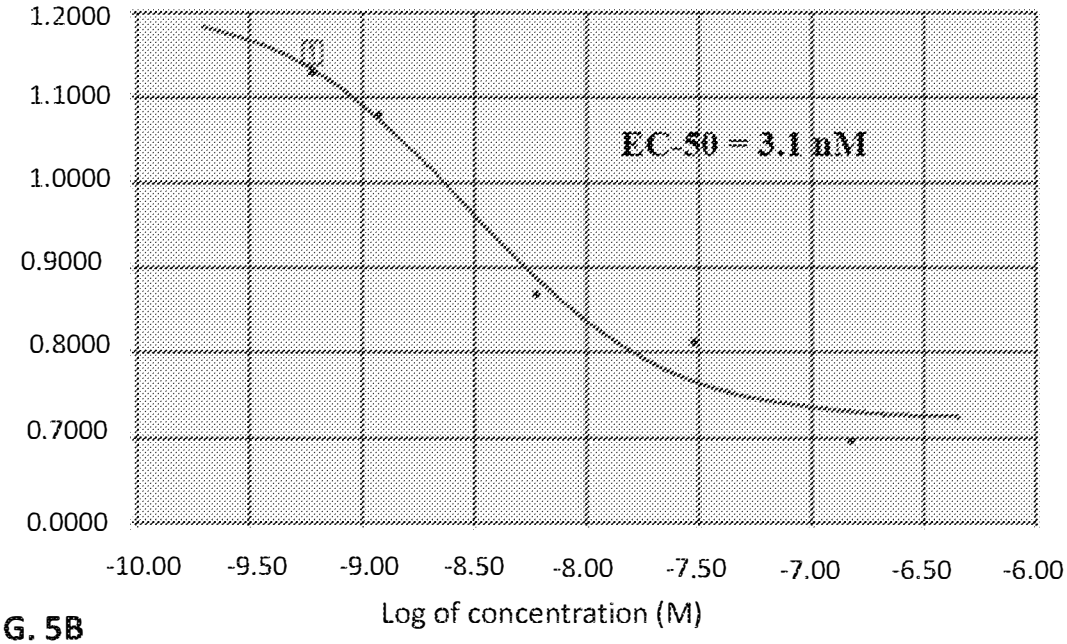

1.2000
1.1000
1.0000
0.9000
0.8000
0.7000
0.0000
EC-50 = 3.1 nM
-10.00
-9.50
-9.00
-8.50
-8.00
-7.50
-7.00
-6.50
-6.00
Log of concentration (M)

FIG. 5B

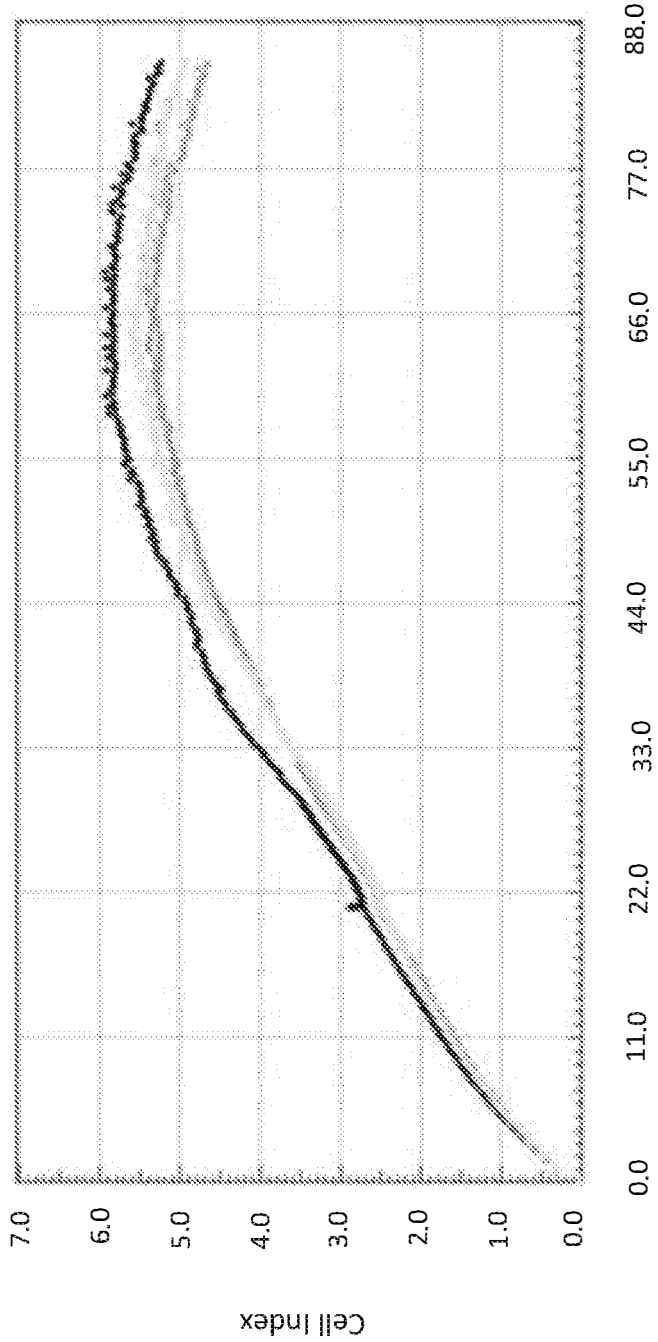

Cell Index
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.0
11.0
22.0
33.0
44.0
55.0
66.0
77.0
88.0
Time (hr)

FIG. 6

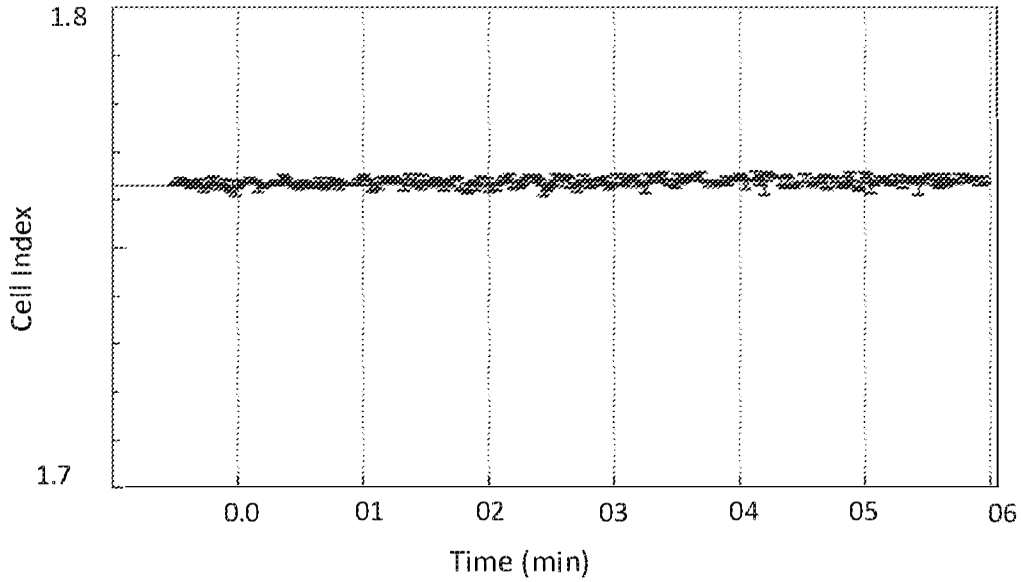


FIG. 7A

105

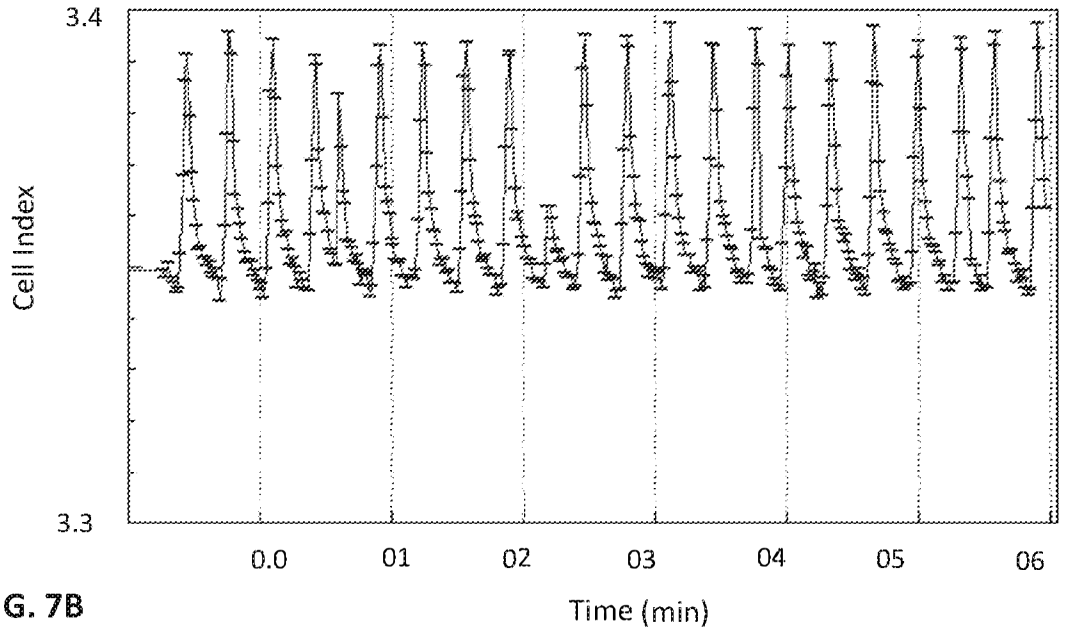


FIG. 7B

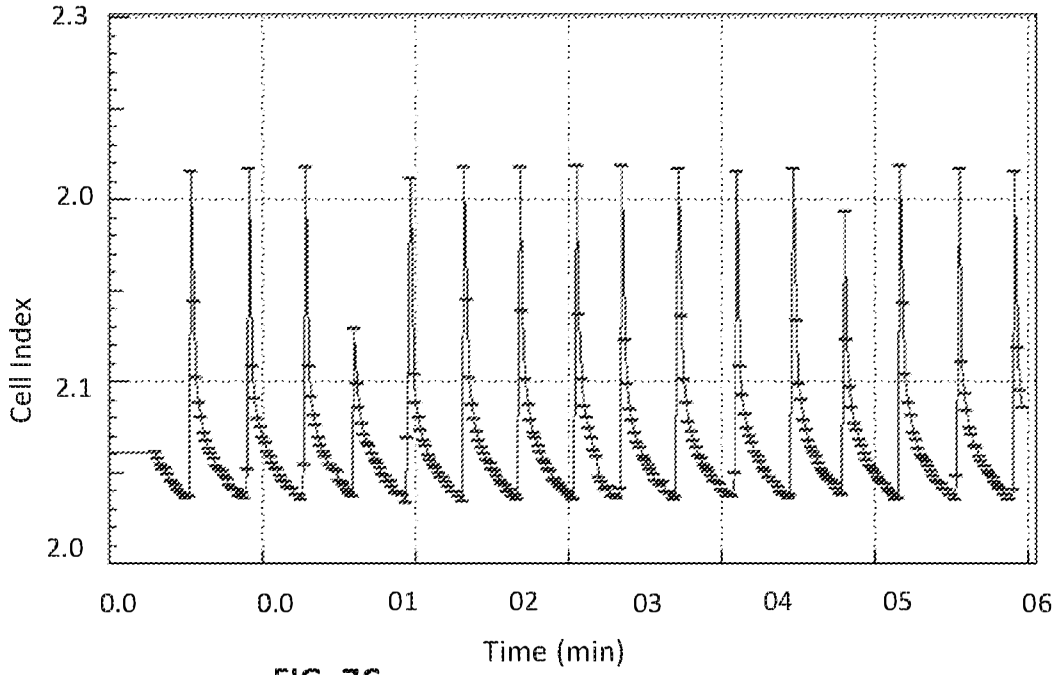

2.3
2.0
2.1
2.0
Cell Index
0.0
0.0
01
02
03
04
05
06
Time (min)

FIG. 7C

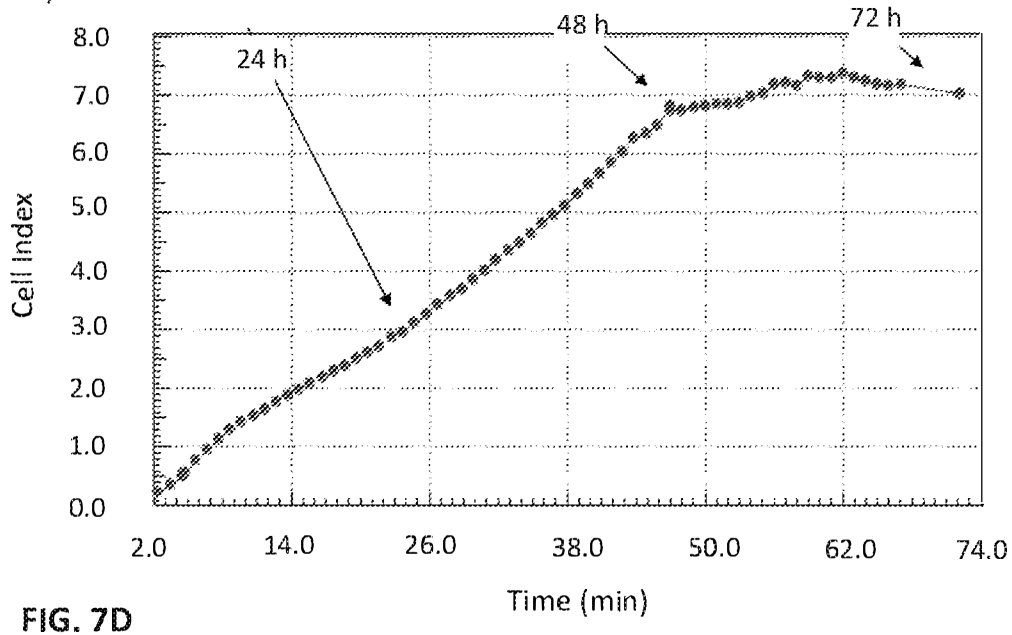

48 h
72 h
24 h
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Cell Index
2.0
14.0
26.0
38.0
50.0
62.0
74.0
Time (min)

FIG. 7D

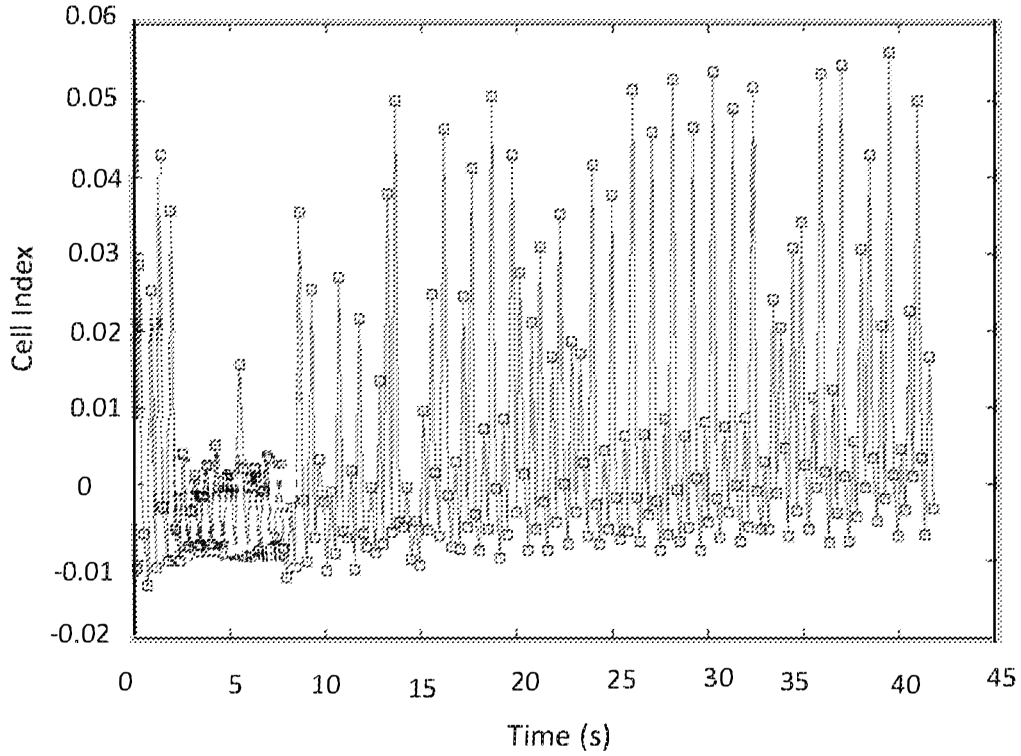

0.06
0.05
0.04
0.03
0.02
0.01
0
-0.01
-0.02
Cell Index
0
5
10
15
20
25
30
35
40
45
Time (s)

FIG. 8A

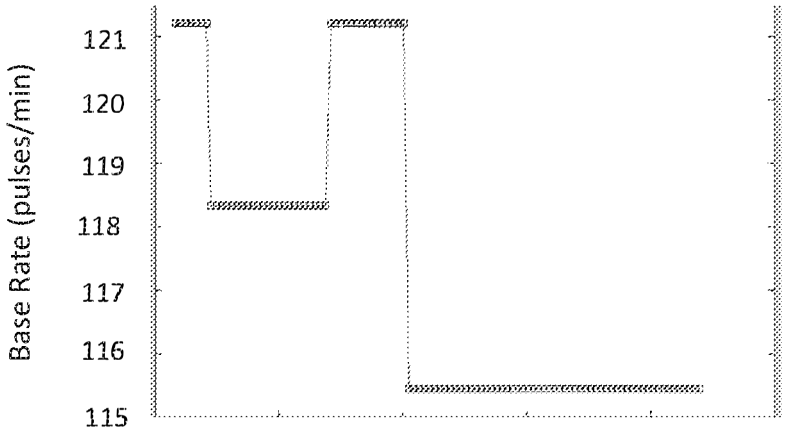

121
120
119
118
117
116
115
Base Rate (pulses/min)

FIG. 8B

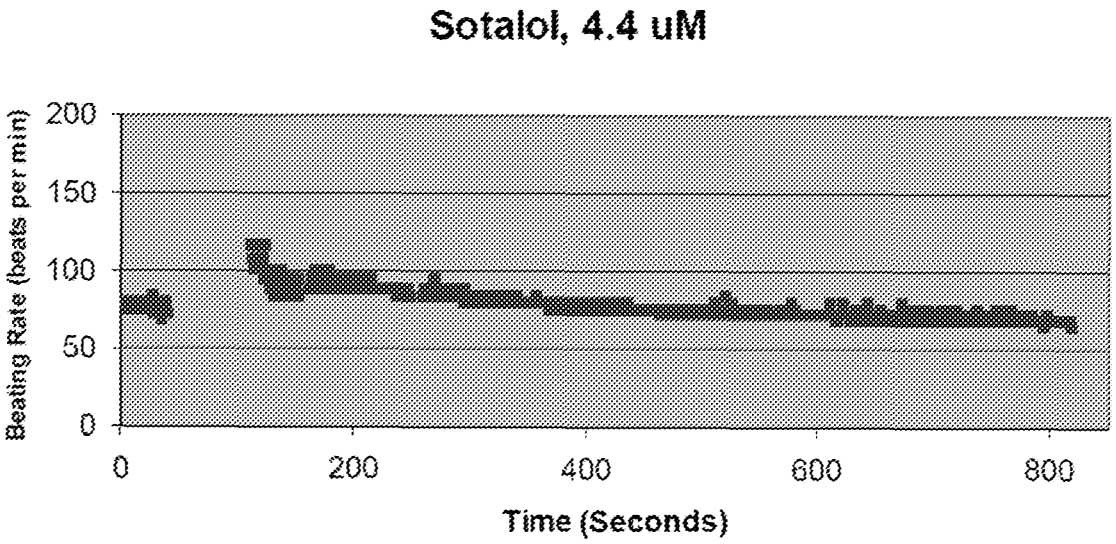

Sotalol, 4.4 uM
Beating Rate (beats per min)
200
150
100
50
0
0
200
400
600
800
Time (Seconds)

FIG. 9A

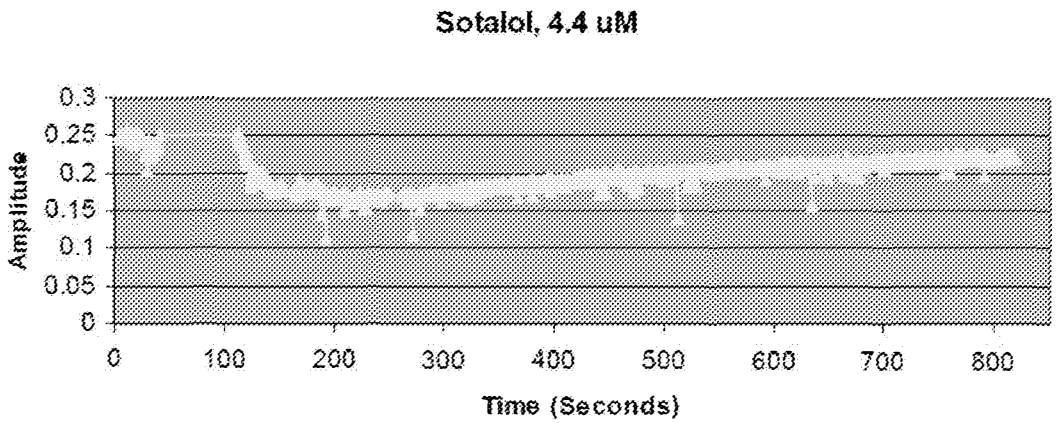

Sotalol, 4.4 uM
Amplitude
0.3
0.25
0.2
0.15
0.1
0.05
0
0
100
200
300
400
500
600
700
800
Time (Seconds)

FIG. 9B

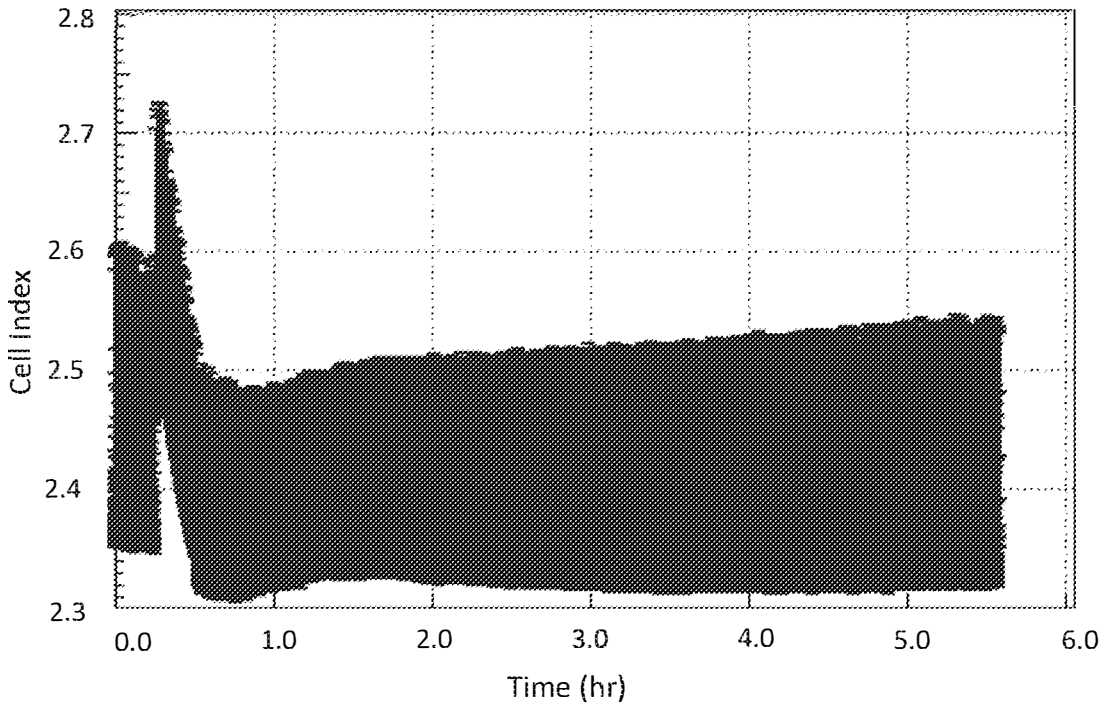

2.8
2.7
2.6
2.5
2.4
2.3
Cell Index
0.0
1.0
2.0
3.0
4.0
5.0
6.0
Time (hr)

FIG. 9C

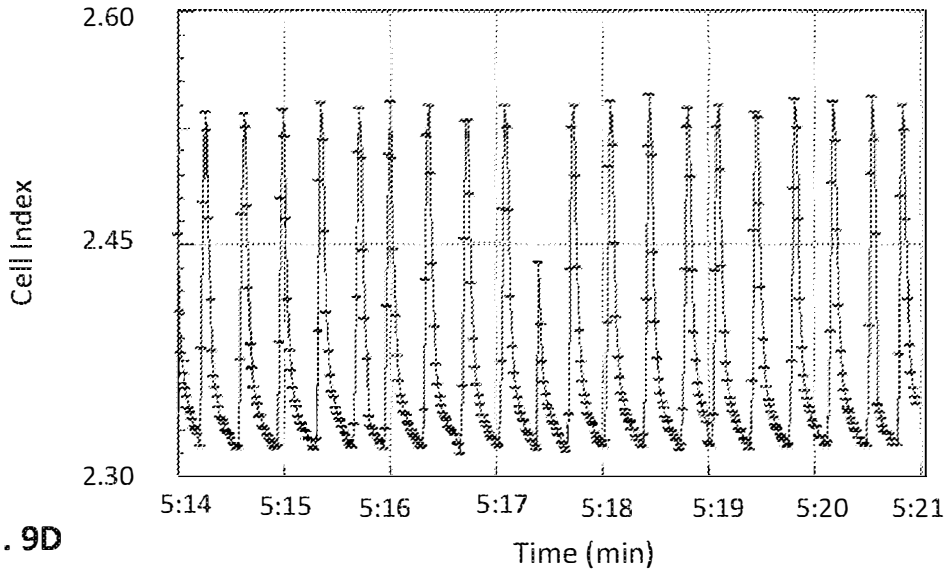

2.60
2.45
2.30
Cell Index
5:14
5:15
5:16
5:17
5:18
5:19
5:20
5:21
Time (min)

FIG. 9D

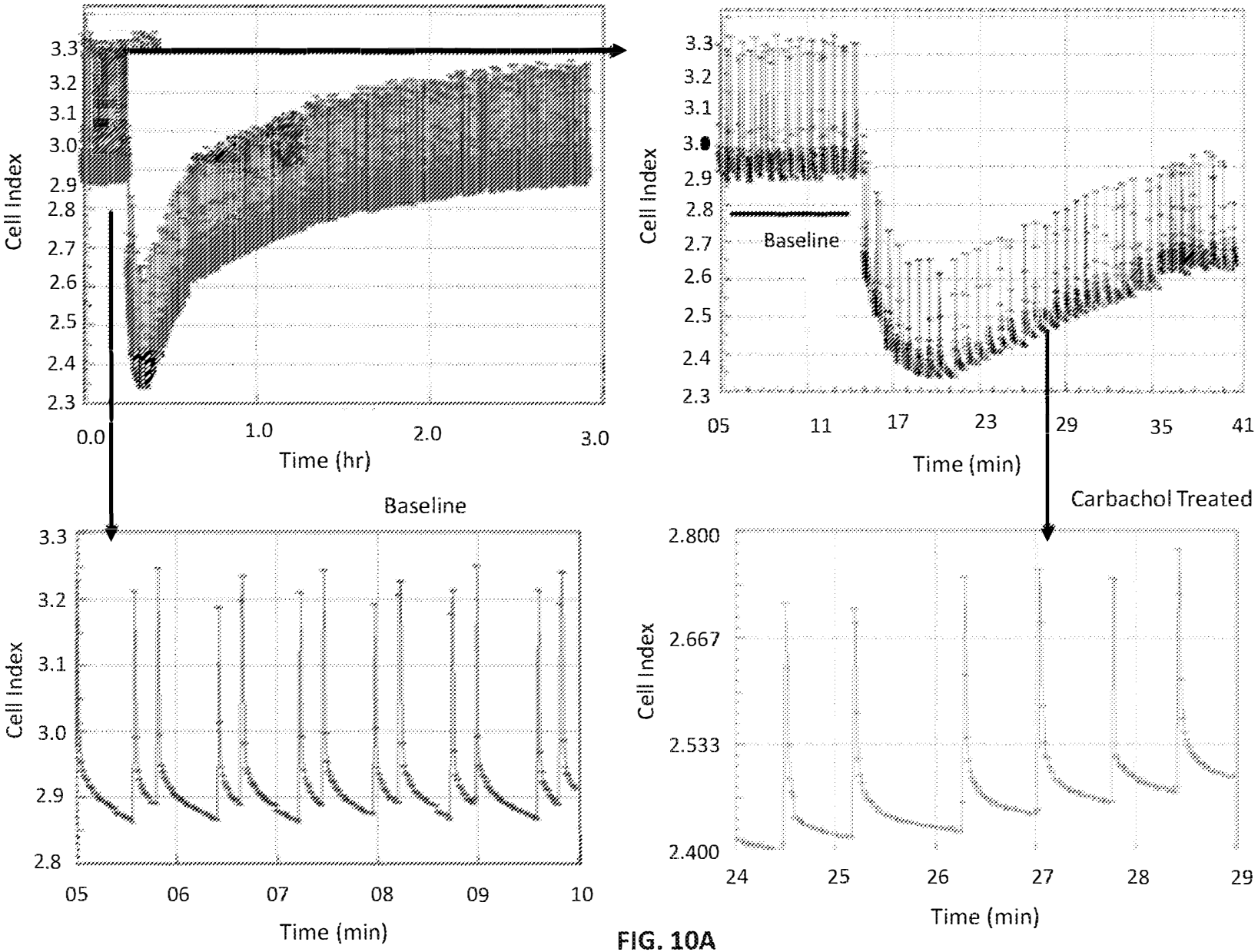

Cell Index
3.3
3.2
3.1
3.0
2.9
2.8
2.7
2.6
2.5
2.4
2.3
0.0
1.0
2.0
3.0
Time (hr)
Baseline
05
11
17
23
29
35
41
Time (min)
Carbachol Treated
2.800
2.667
2.533
2.400
24
25
26
27
28
29
Time (min)
06
07
08
09
10

FIG. 10A

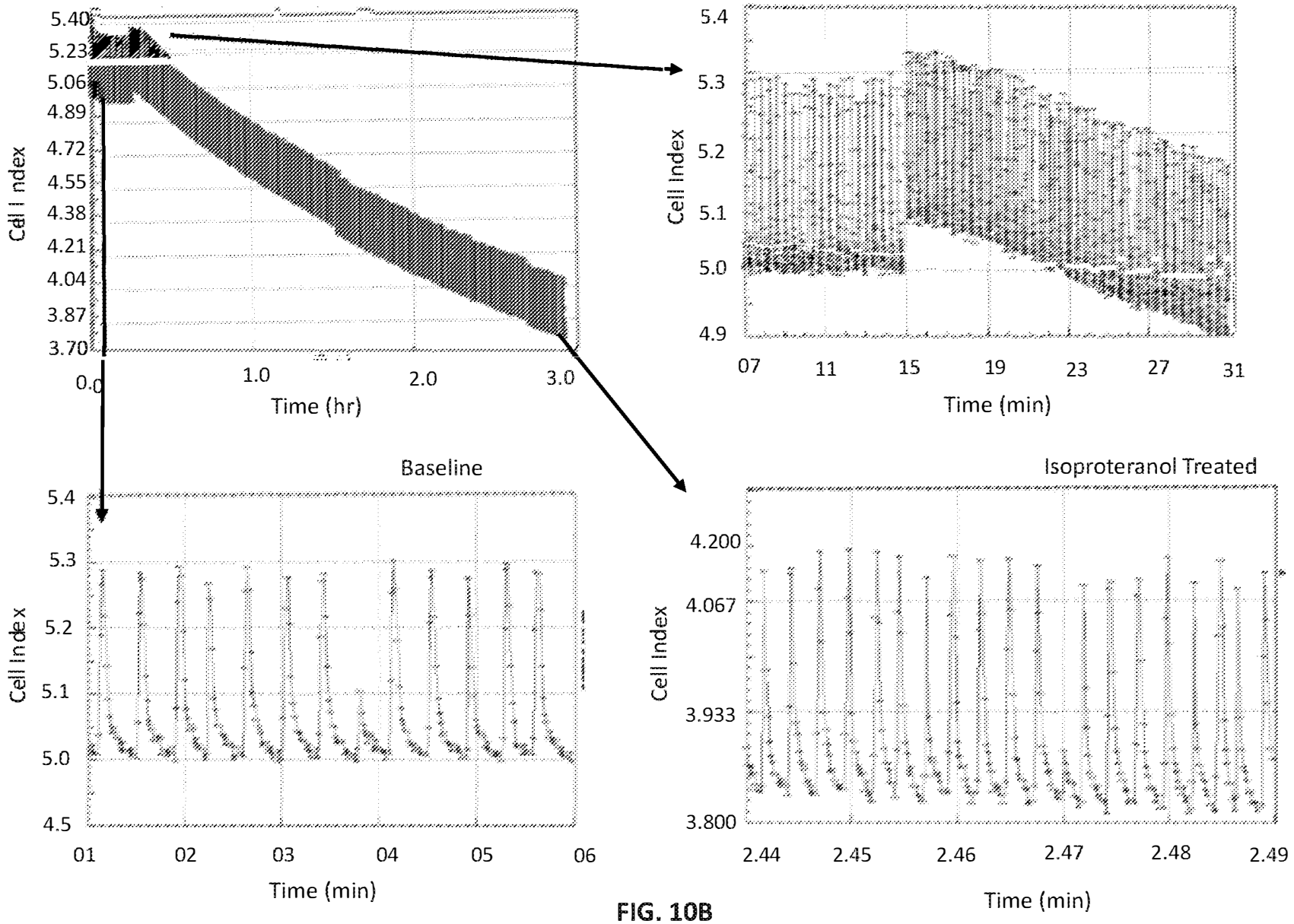

5.40
5.23
5.06
4.89
4.72
4.55
4.38
4.21
4.04
3.87
3.70
Cell Index
0.0
1.0
2.0
3.0
Time (hr)
5.4
5.3
5.2
5.1
5.0
4.9
Cell Index
07
11
15
19
23
27
31
Time (min)
Baseline
5.4
5.3
5.2
5.1
5.0
4.5
Cell Index
01
02
03
04
05
06
Time (min)
Isoproteranol Treated
4.200
4.067
3.933
3.800
Cell Index
2.44
2.45
2.46
2.47
2.48
2.49
Time (min)

FIG. 10B

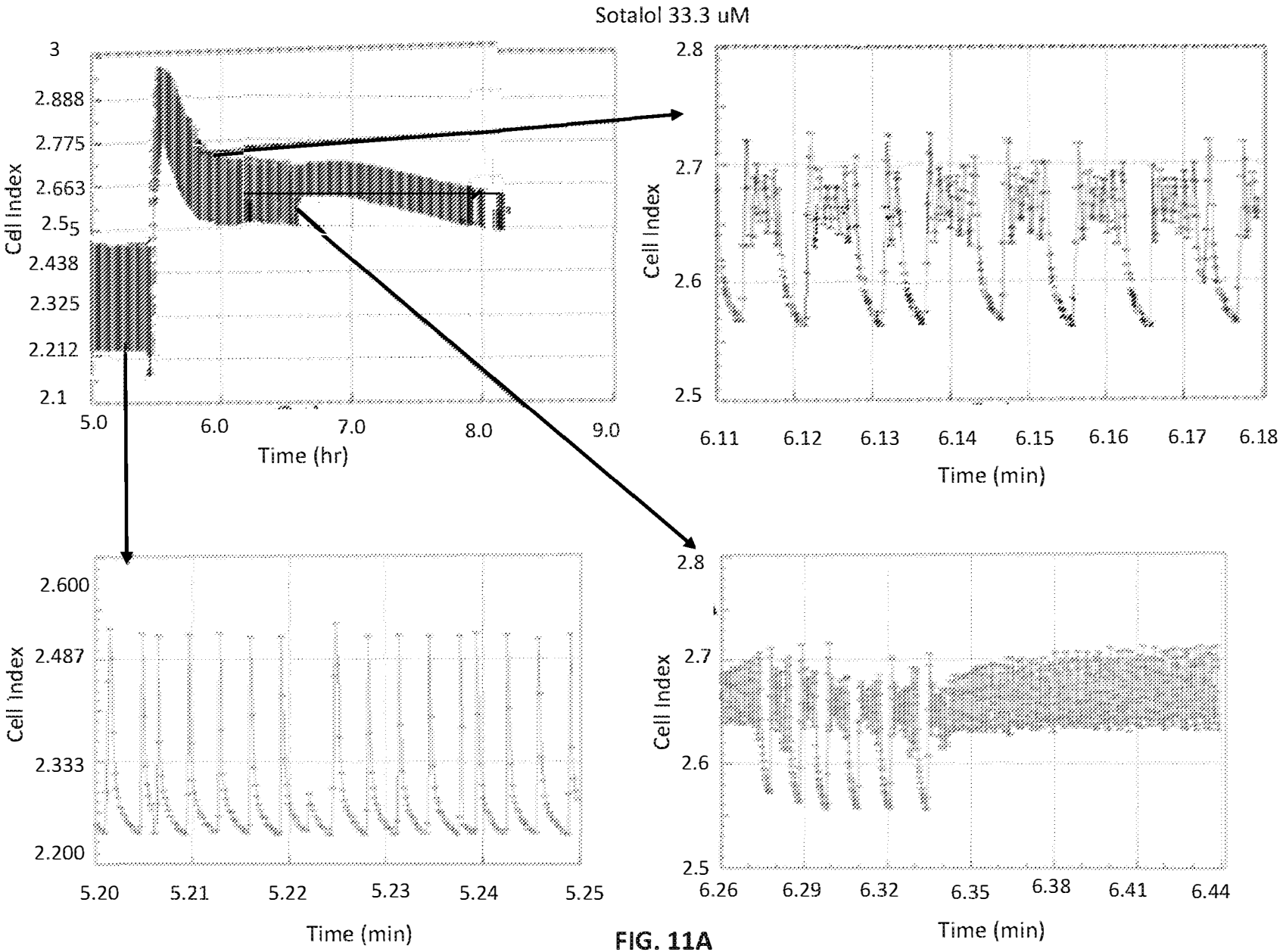

Sotalol 33.3 uM
Cell Index
3
2.888
2.775
2.663
2.55
2.438
2.325
2.212
2.1
5.0
6.0
7.0
8.0
9.0
Time (hr)
Cell Index
2.8
2.7
2.6
2.5
6.11
6.12
6.13
6.14
6.15
6.16
6.17
6.18
Time (min)
Cell Index
2.600
2.487
2.333
2.200
5.20
5.21
5.22
5.23
5.24
5.25
Time (min)
Cell Index
2.8
2.7
2.6
2.5
6.26
6.29
6.32
6.35
6.38
6.41
6.44
Time (min)

FIG. 11A

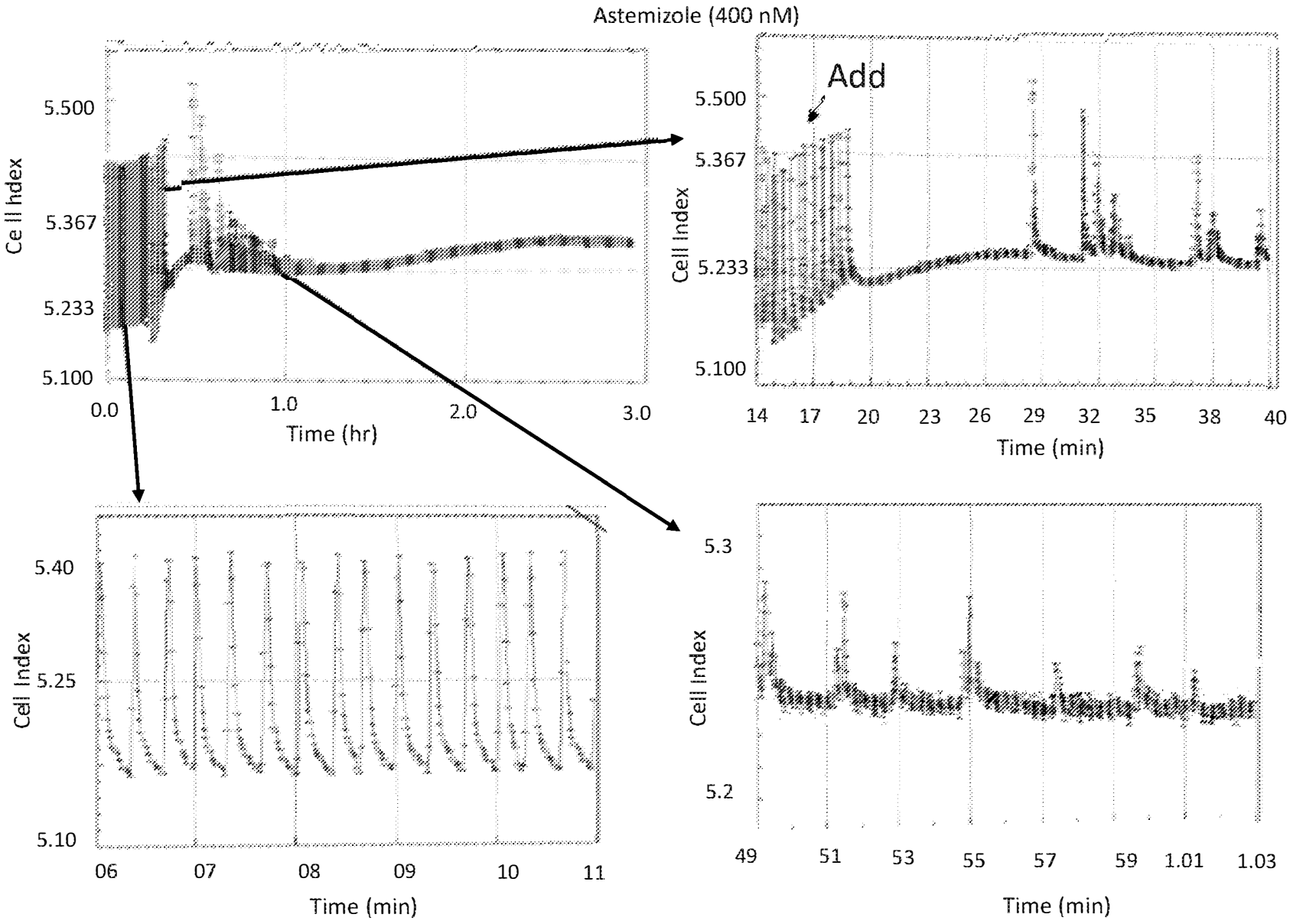

Astemizole (400 nM)
Add
Ce ll hdex
5.500
5.367
5.233
5.100
0.0
1.0
2.0
3.0
Time (hr)
Cell Index
5.500
5.367
5.233
5.100
14
17
20
23
26
29
32
35
38
40
Time (min)
Cell Index
5.40
5.25
5.10
06
07
08
09
10
11
Time (min)
Cell Index
5.3
5.2
49
51
53
55
57
59
1.01
1.03
Time (min)

FIG. 11B

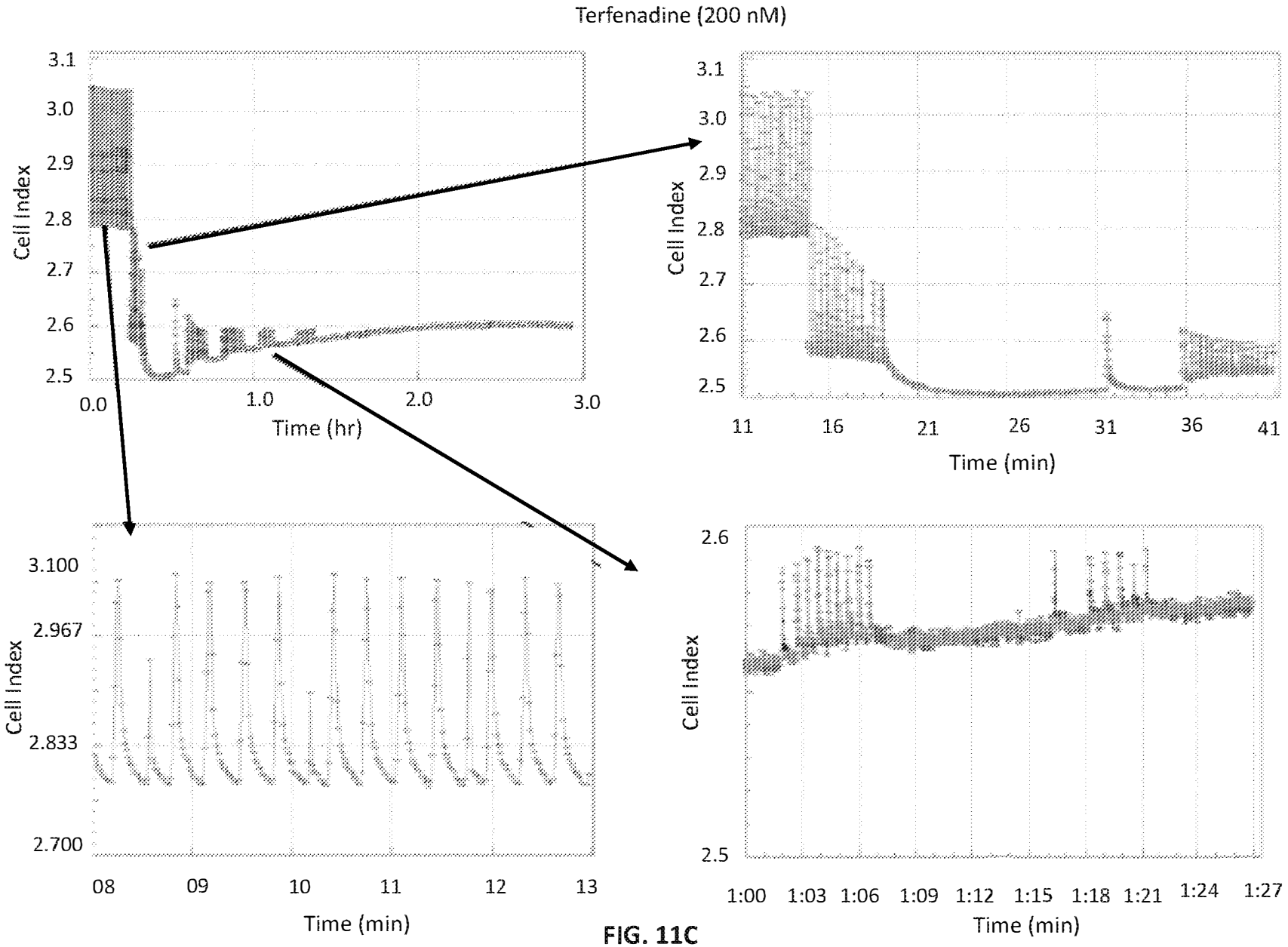

Terfenadine (200 nM)
Cell Index
3.1
3.0
2.9
2.8
2.7
2.6
2.5
0.0
1.0
2.0
3.0
Time (hr)
Cell Index
3.1
3.0
2.9
2.8
2.7
2.6
2.5
11
16
21
26
31
36
41
Time (min)
Cell Index
3.100
2.967
2.833
2.700
08
09
10
11
12
13
Time (min)
Cell Index
2.6
2.5
1:00
1:03
1:06
1:09
1:12
1:15
1:18
1:21
1:24
1:27
Time (min)

FIG. 11C

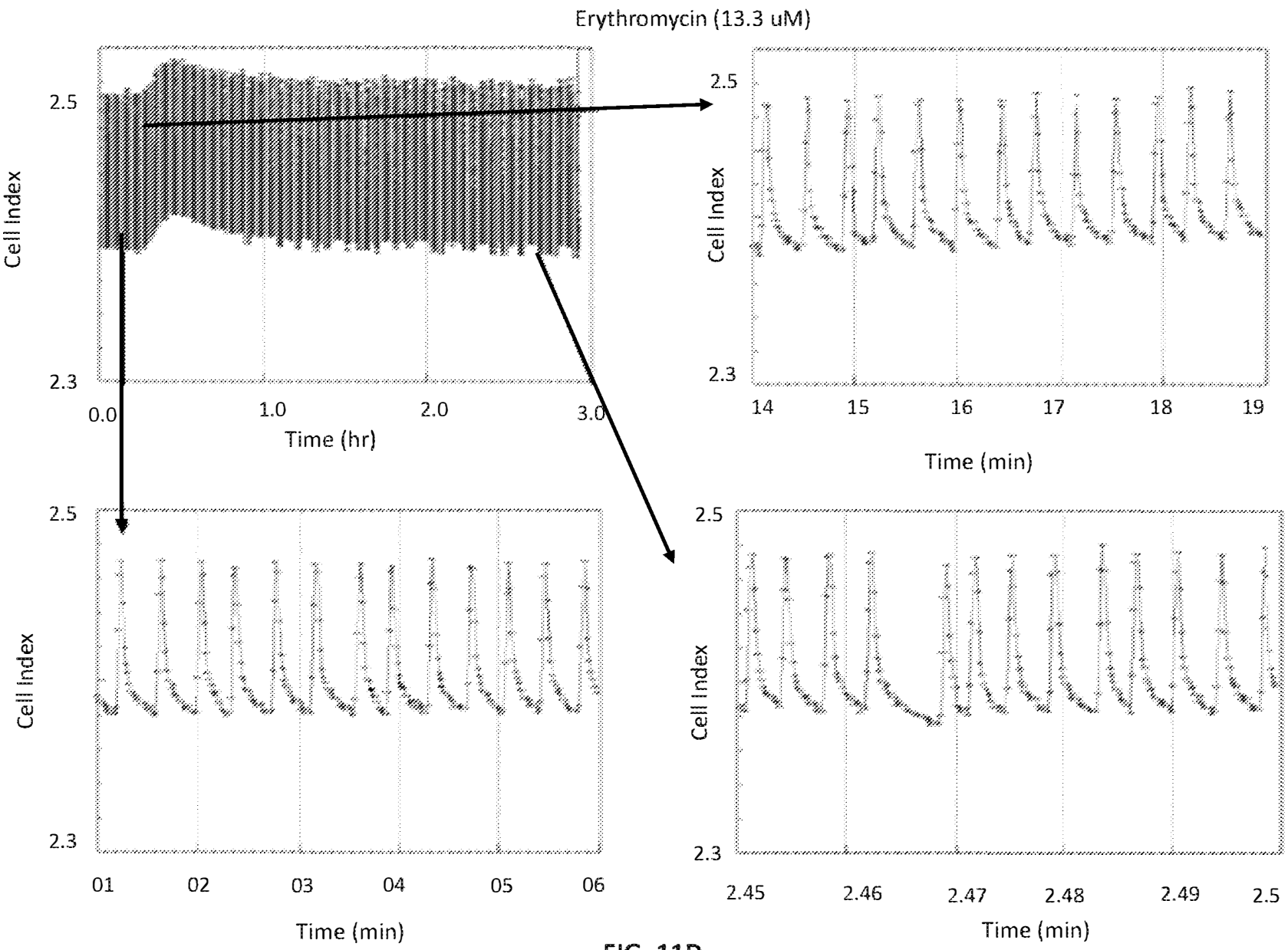

Erythromycin (13.3 uM)
Cell Index
2.5
2.3
0.0
1.0
2.0
3.0
Time (hr)
Cell Index
2.5
2.3
14
15
16
17
18
19
Time (min)
Cell Index
2.5
2.3
01
02
03
04
05
06
Time (min)
Cell Index
2.5
2.3
2.45
2.46
2.47
2.48
2.49
2.5
Time (min)

FIG. 11D

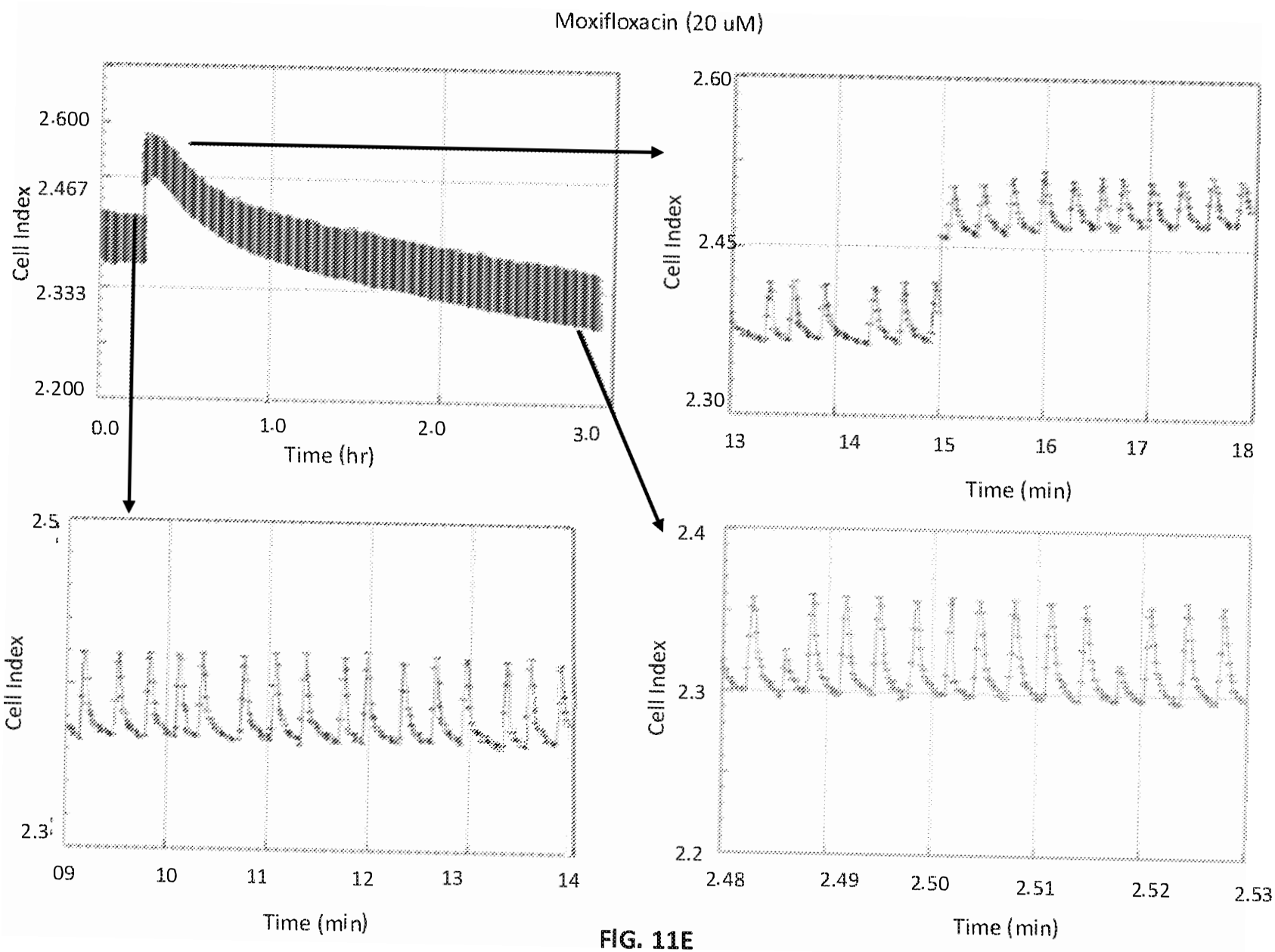

Moxifloxacin (20 uM)
Cell Index
2.600
2.467
2.333
2.200
0.0
1.0
2.0
3.0
Time (hr)
2.60
2.45
2.30
13
14
15
16
17
18
Time (min)
2.5
2.3
09
10
11
12
13
14
Time (min)
2.4
2.3
2.2
2.48
2.49
2.50
2.51
2.52
2.53
Time (min)

FIG. 11E

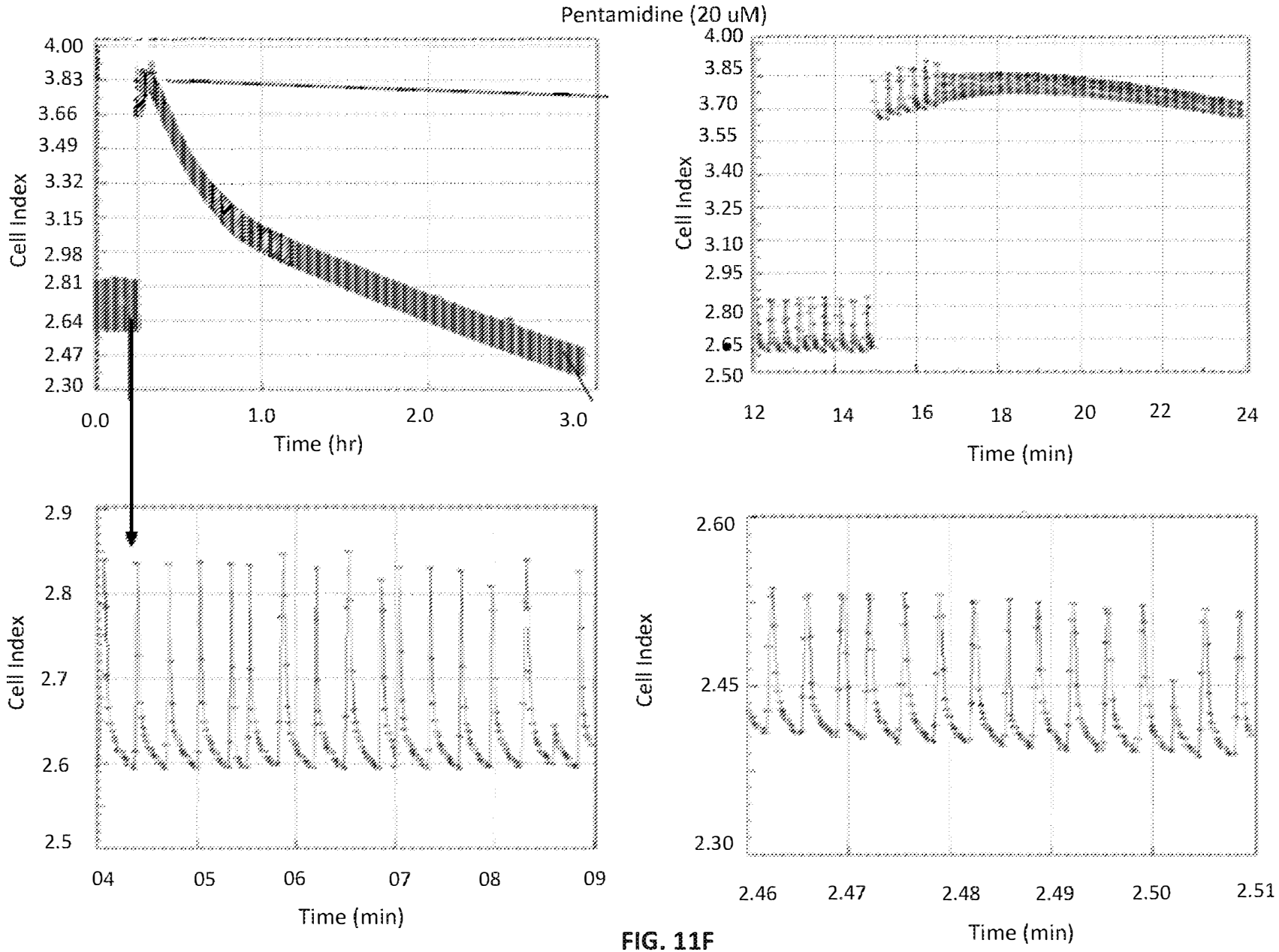

Pentamidine (20 uM)
Cell Index
4.00
3.83
3.66
3.49
3.32
3.15
2.98
2.81
2.64
2.47
2.30
0.0
1.0
2.0
3.0
Time (hr)
Cell Index
4.00
3.85
3.70
3.55
3.40
3.25
3.10
2.95
2.80
2.65
2.50
12
14
16
18
20
22
24
Time (min)
Cell Index
2.9
2.8
2.7
2.6
2.5
04
05
06
07
08
09
Time (min)
Cell Index
2.60
2.45
2.30
2.46
2.47
2.48
2.49
2.50
2.51
Time (min)

FIG. 11F

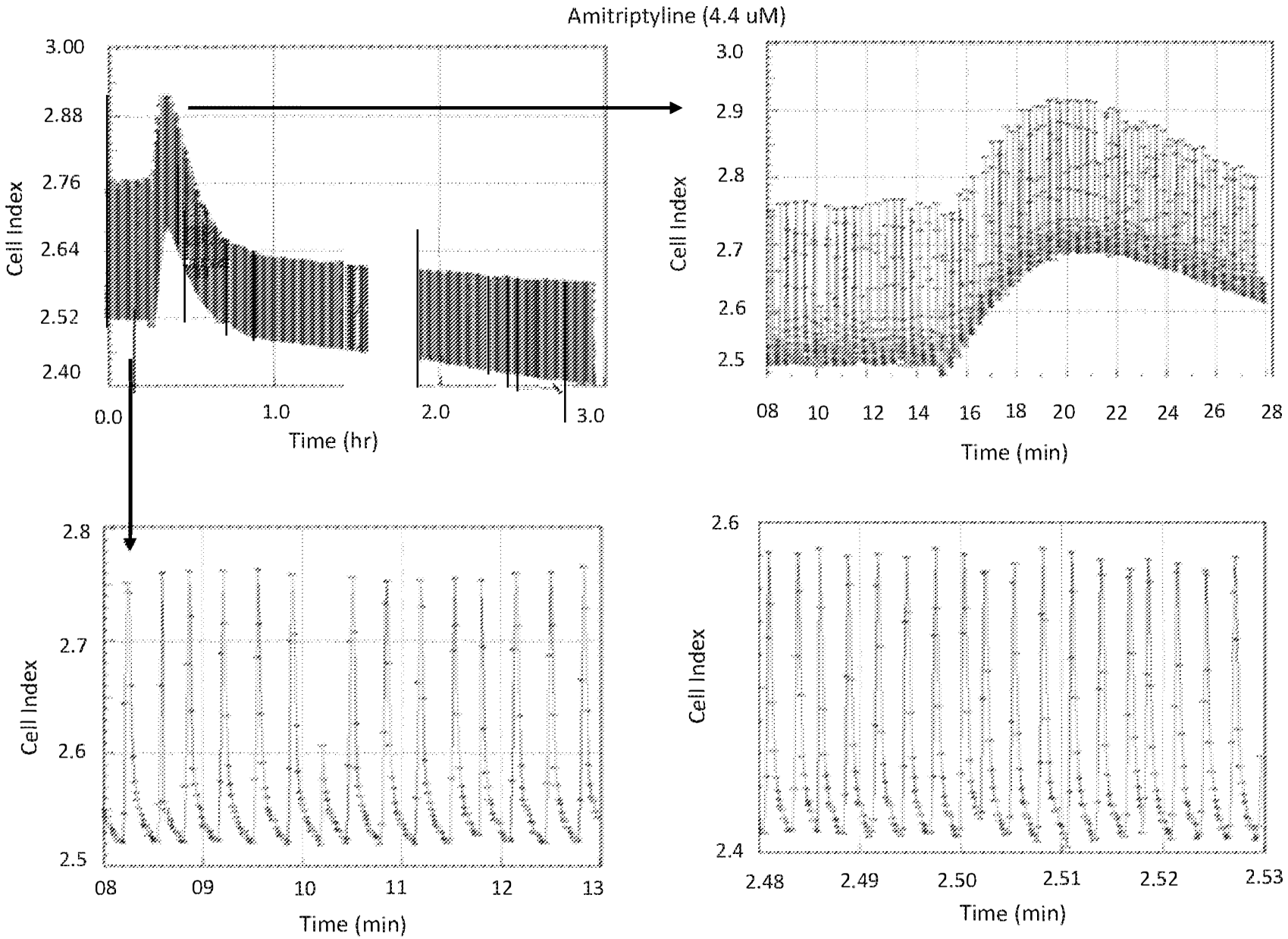

Amitriptyline (4.4 uM)
3.00
2.88
2.76
2.64
2.52
2.40
Cell Index
0.0
1.0
2.0
3.0
Time (hr)
3.0
2.9
2.8
2.7
2.6
2.5
Cell Index
08
10
12
14
16
18
20
22
24
26
28
Time (min)
2.8
2.7
2.6
2.5
Cell Index
08
09
10
11
12
13
Time (min)
2.6
2.4
Cell Index
2.48
2.49
2.50
2.51
2.52
2.53
Time (min)

FIG. 11G

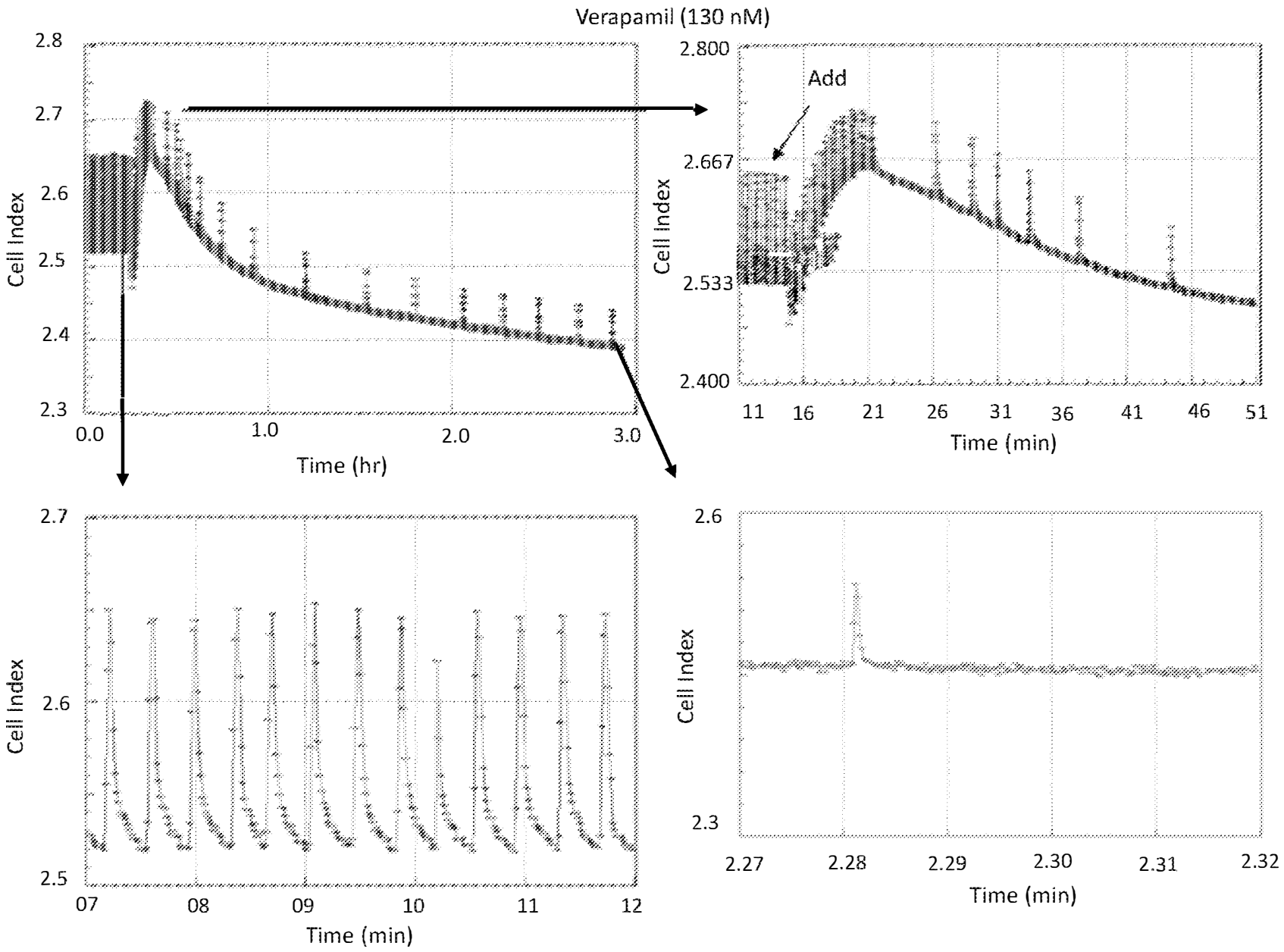

Verapamil (130 nM)
Cell Index
Time (hr)
Add
Time (min)
Cell Index
Time (min)
Cell Index
Time (min)

FIG. 11H

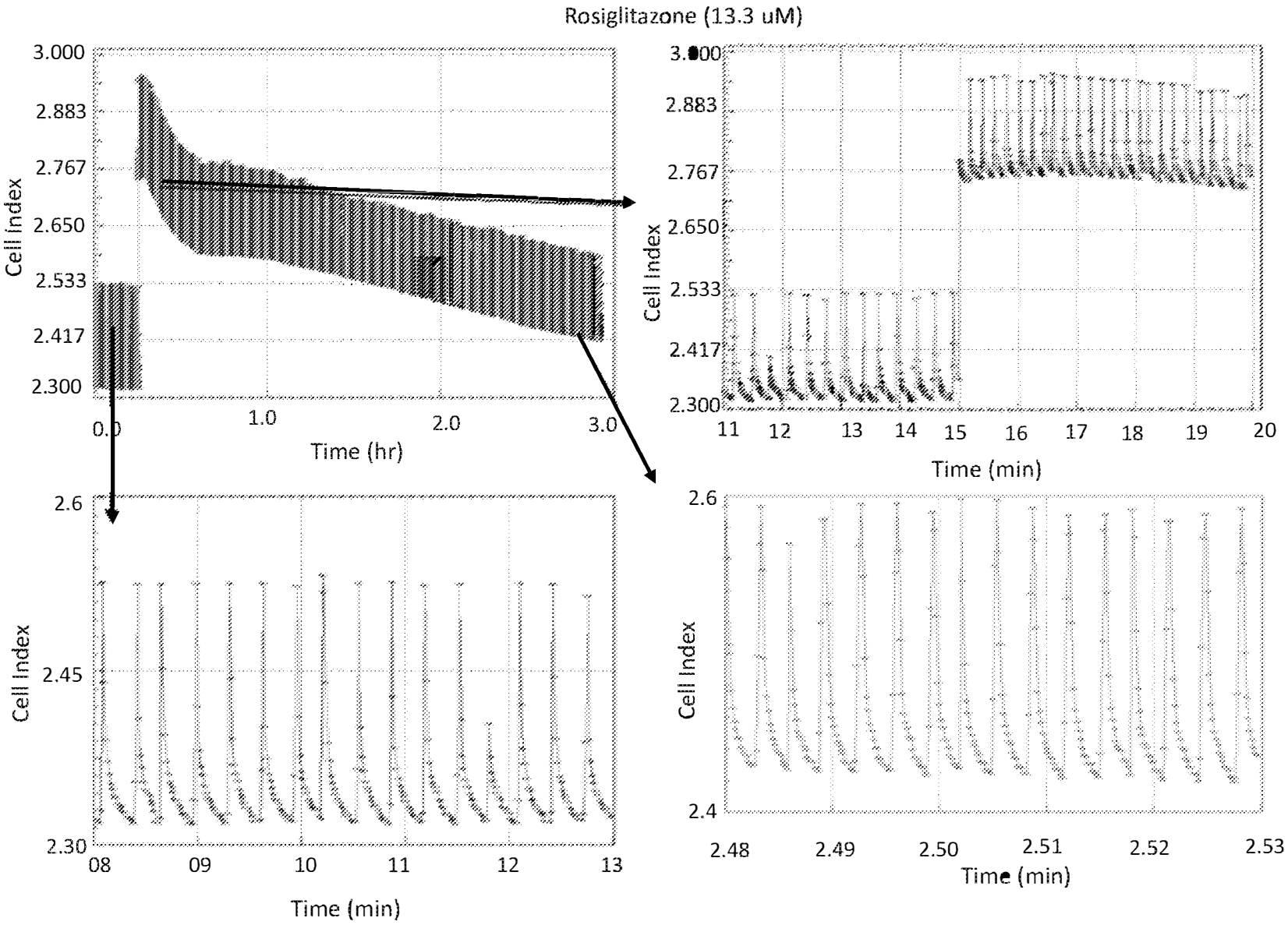

Rosiglitazone (13.3 uM)
Cell Index
3.000
2.883
2.767
2.650
2.533
2.417
2.300
0.0
1.0
2.0
3.0
Time (hr)
Cell Index
3.000
2.883
2.767
2.650
2.533
2.417
2.300
11
12
13
14
15
16
17
18
19
20
Time (min)
Cell Index
2.6
2.45
2.30
08
09
10
11
12
13
Time (min)
Cell Index
2.6
2.4
2.48
2.49
2.50
2.51
2.52
2.53
Time (min)

FIG. 11I

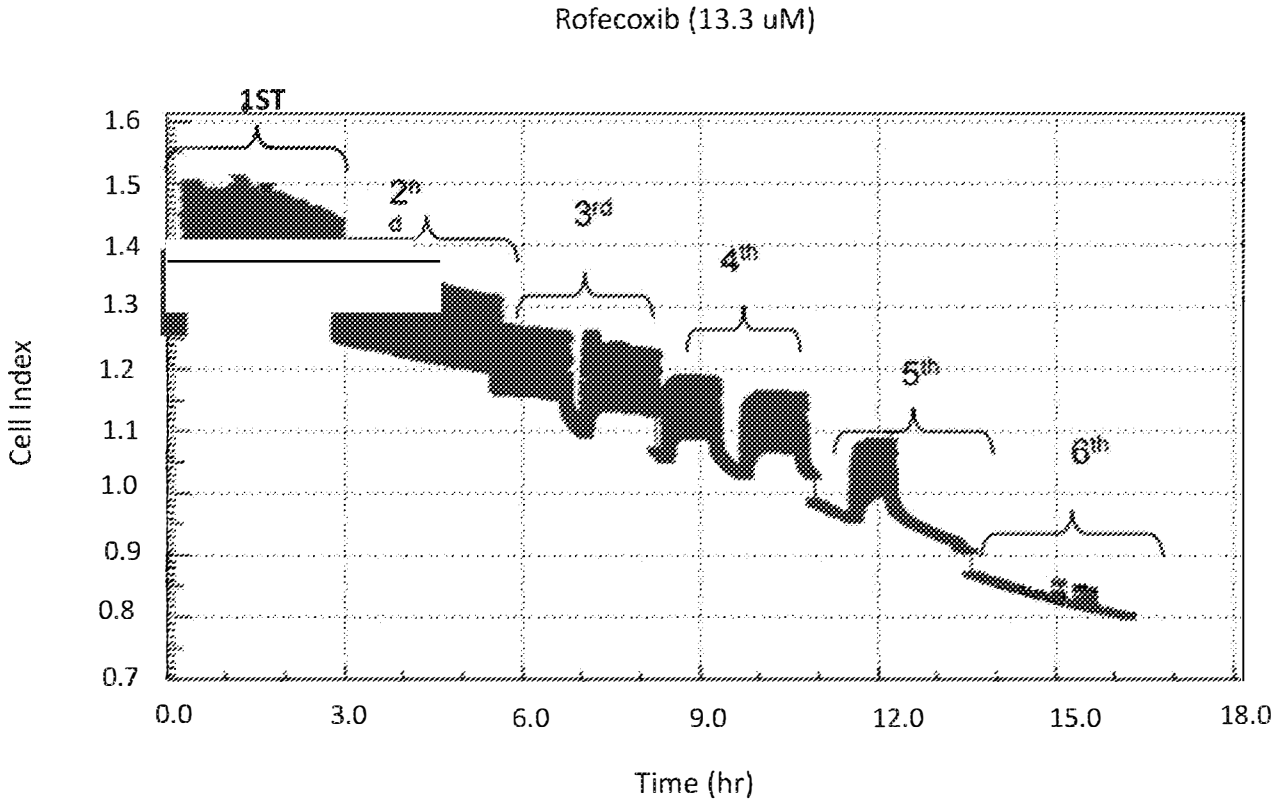

Rofecoxib (13.3 uM)
1ST
2nd
3rd
4th
5th
6th
Cell Index
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.0
3.0
6.0
9.0
12.0
15.0
18.0
Time (hr)

FIG. 11J

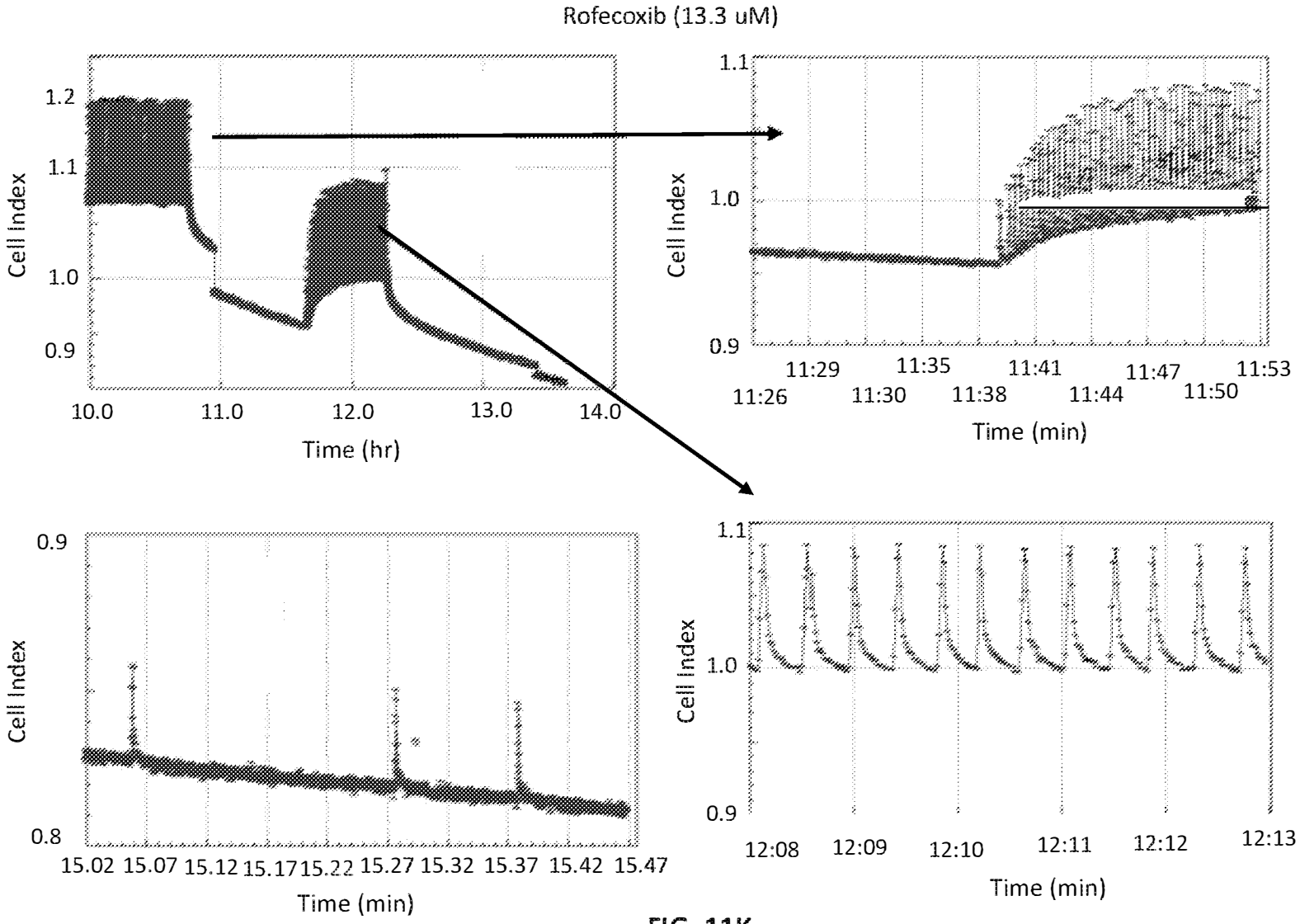

Rofecoxib (13.3 uM)
Cell Index
1.2
1.1
1.0
0.9
10.0
11.0
12.0
13.0
14.0
Time (hr)
Cell Index
1.1
1.0
0.9
11:26
11:29
11:30
11:35
11:38
11:41
11:44
11:47
11:50
11:53
Time (min)
Cell Index
0.9
0.8
15.02
15.07
15.12
15.17
15.22
15.27
15.32
15.37
15.42
15.47
Time (min)
Cell Index
1.1
1.0
0.9
12:08
12:09
12:10
12:11
12:12
12:13
Time (min)

FIG. 11K

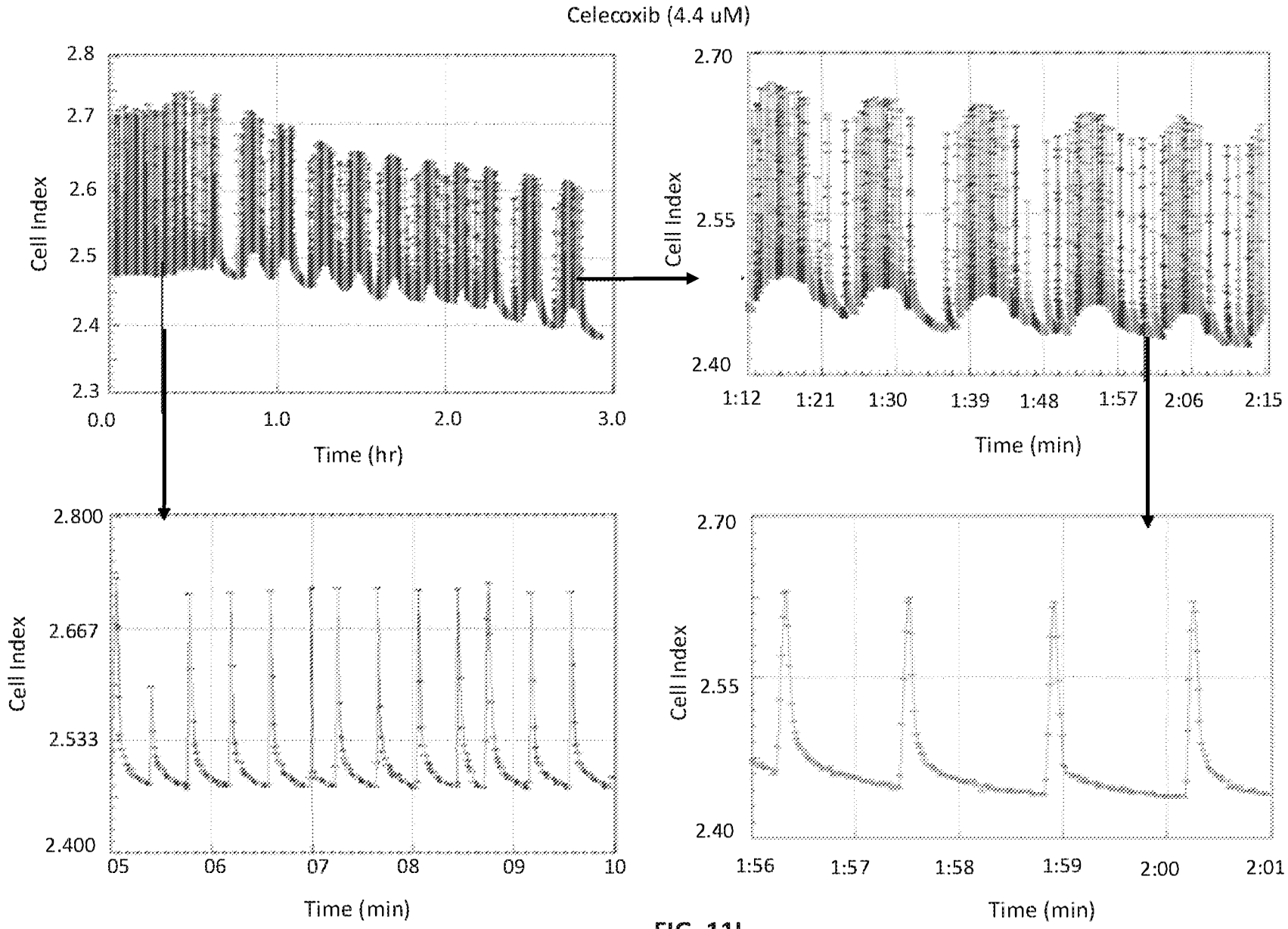

Celecoxib (4.4 uM)
Cell Index
2.8
2.7
2.6
2.5
2.4
2.3
0.0
1.0
2.0
3.0
Time (hr)
Cell Index
2.70
2.55
2.40
1:12
1:21
1:30
1:39
1:48
1:57
2:06
2:15
Time (min)
Cell Index
2.800
2.667
2.533
2.400
05
06
07
08
09
10
Time (min)
Cell Index
2.70
2.55
2.40
1:56
1:57
1:58
1:59
2:00
2:01
Time (min)

FIG. 11L

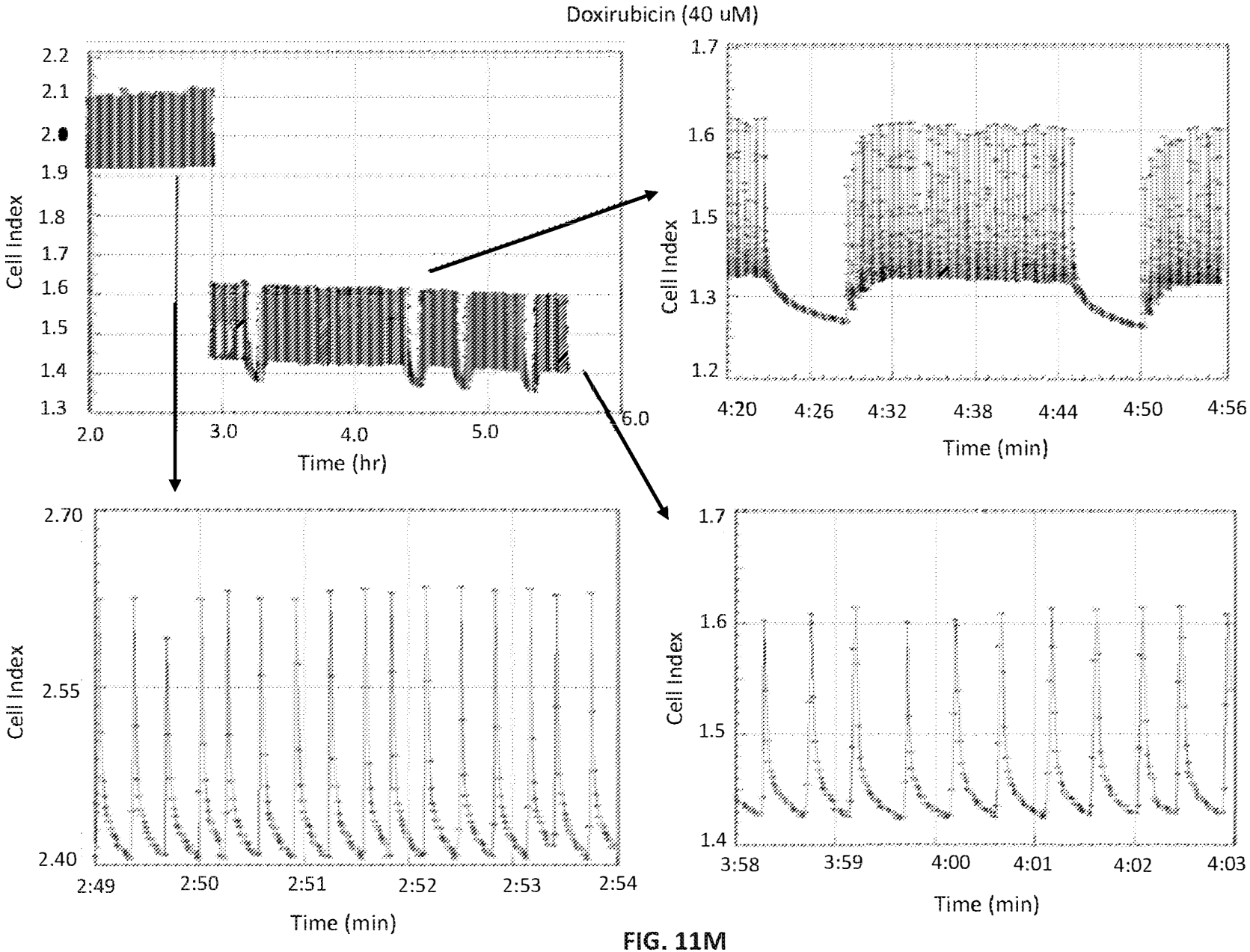

Doxirubicin (40 uM)
Cell Index
Time (hr)
Time (min)
Cell Index
Time (min)
Cell Index
Time (min)

FIG. 11M

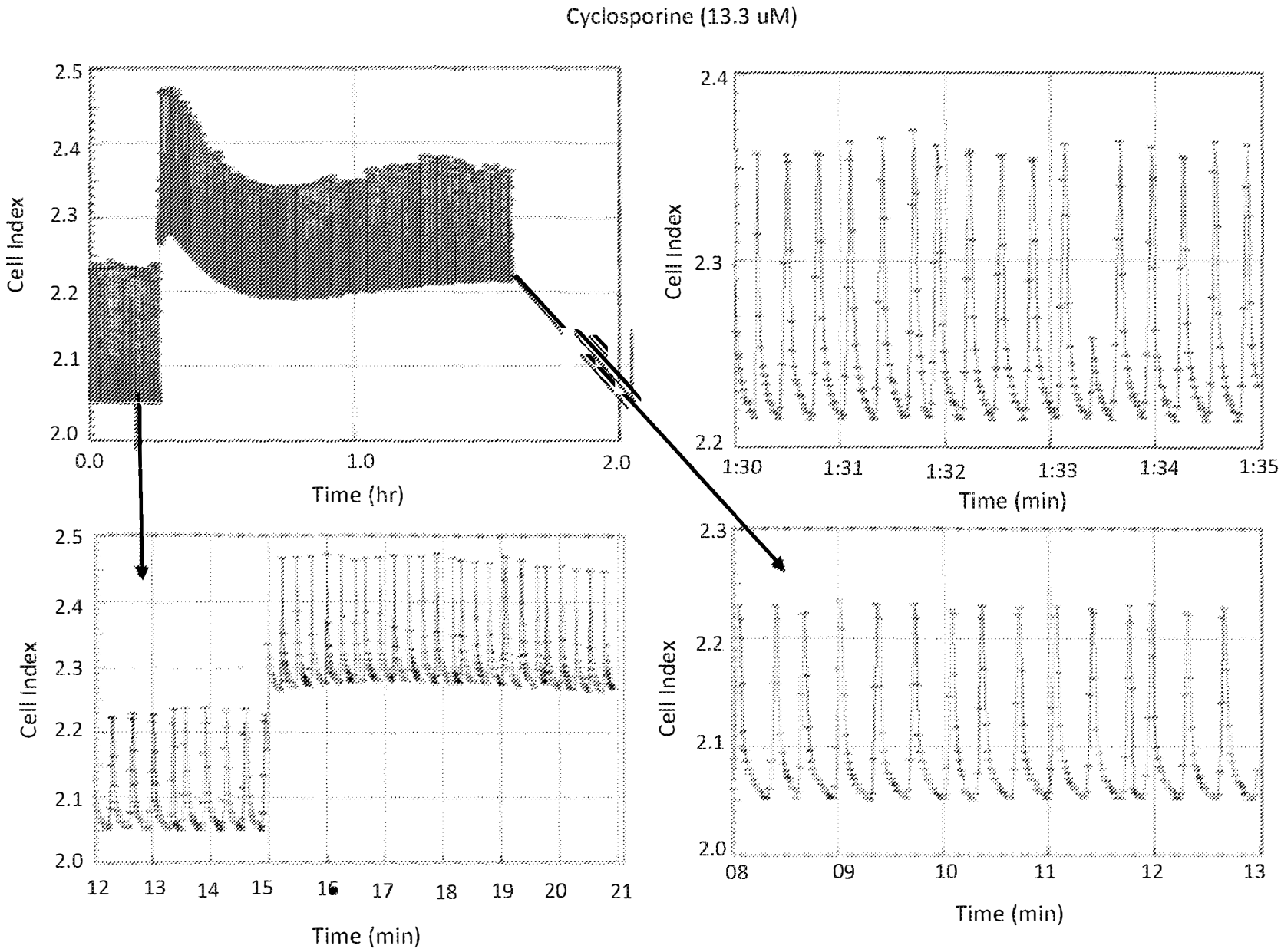

Cyclosporine (13.3 uM)
Cell Index
Time (hr)
Time (min)
Time (min)
Time (min)

FIG. 11N

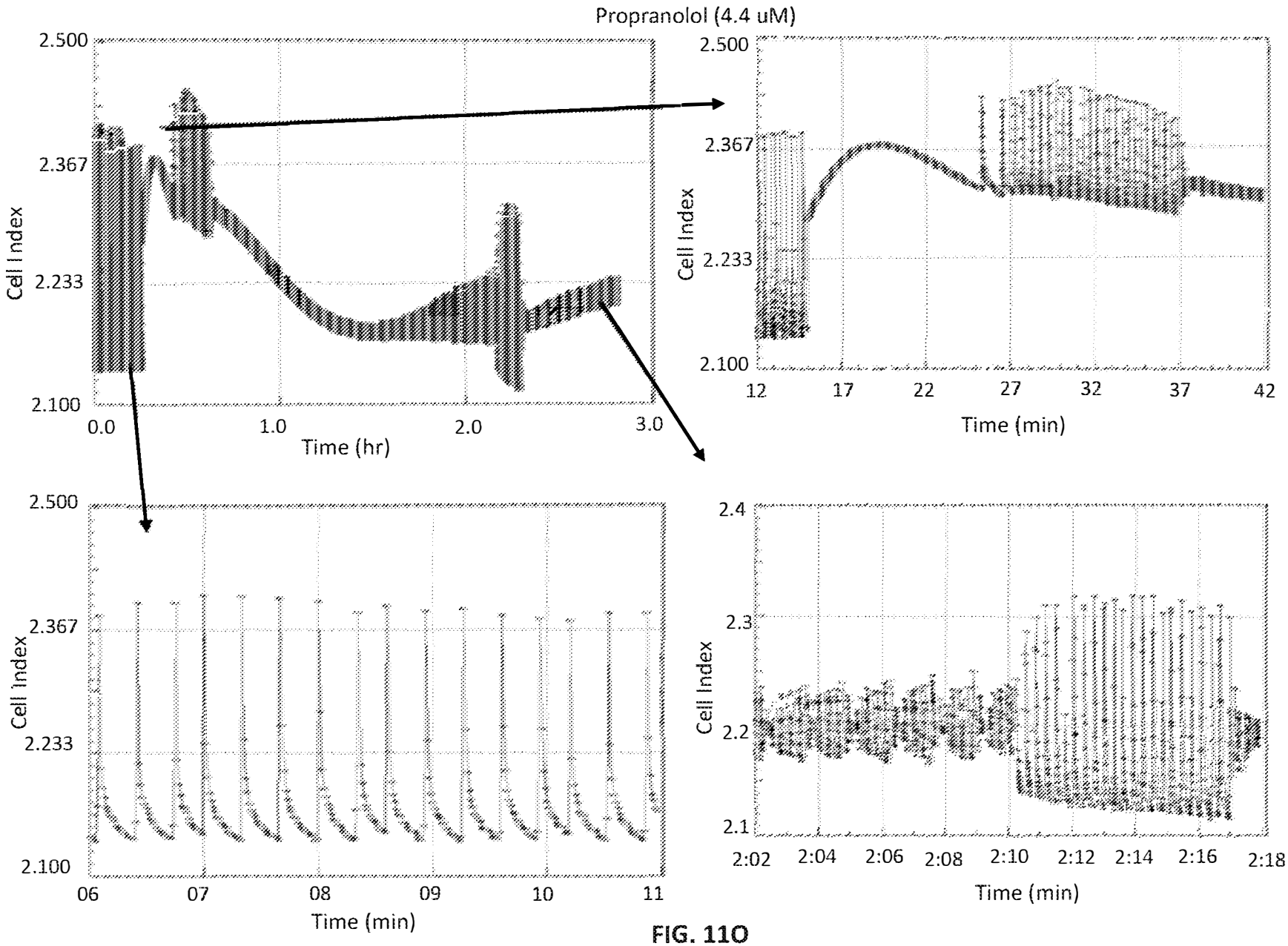

Propranolol (4.4 uM)
2.500
2.367
2.233
2.100
Cell Index
0.0
1.0
2.0
3.0
Time (hr)
2.500
2.367
2.233
2.100
Cell Index
12
17
22
27
32
37
42
Time (min)
2.500
2.367
2.233
2.100
Cell Index
06
07
08
09
10
11
Time (min)
2.4
2.3
2.2
2.1
Cell Index
2:02
2:04
2:06
2:08
2:10
2:12
2:14
2:16
2:18
Time (min)

FIG. 11O

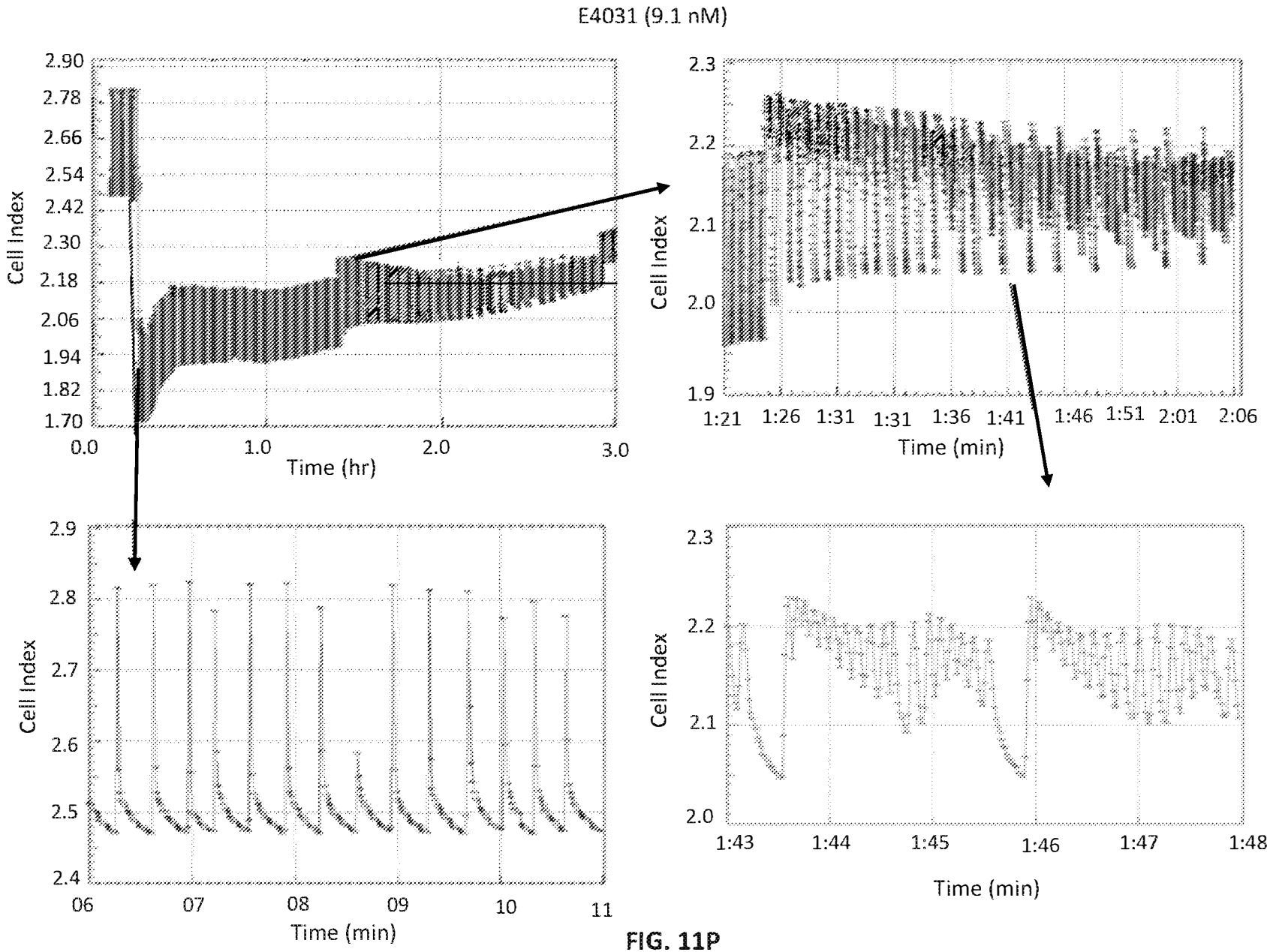

E4031 (9.1 nM)
Cell Index
2.90
2.78
2.66
2.54
2.42
2.30
2.18
2.06
1.94
1.82
1.70
0.0
1.0
2.0
3.0
Time (hr)
Cell Index
2.3
2.2
2.1
2.0
1.9
1:21
1:26
1:31
1:31
1:36
1:41
1:46
1:51
2:01
2:06
Time (min)
Cell Index
2.9
2.8
2.7
2.6
2.5
2.4
06
07
08
09
10
11
Time (min)
Cell Index
2.3
2.2
2.1
2.0
1:43
1:44
1:45
1:46
1:47
1:48
Time (min)

FIG. 11P

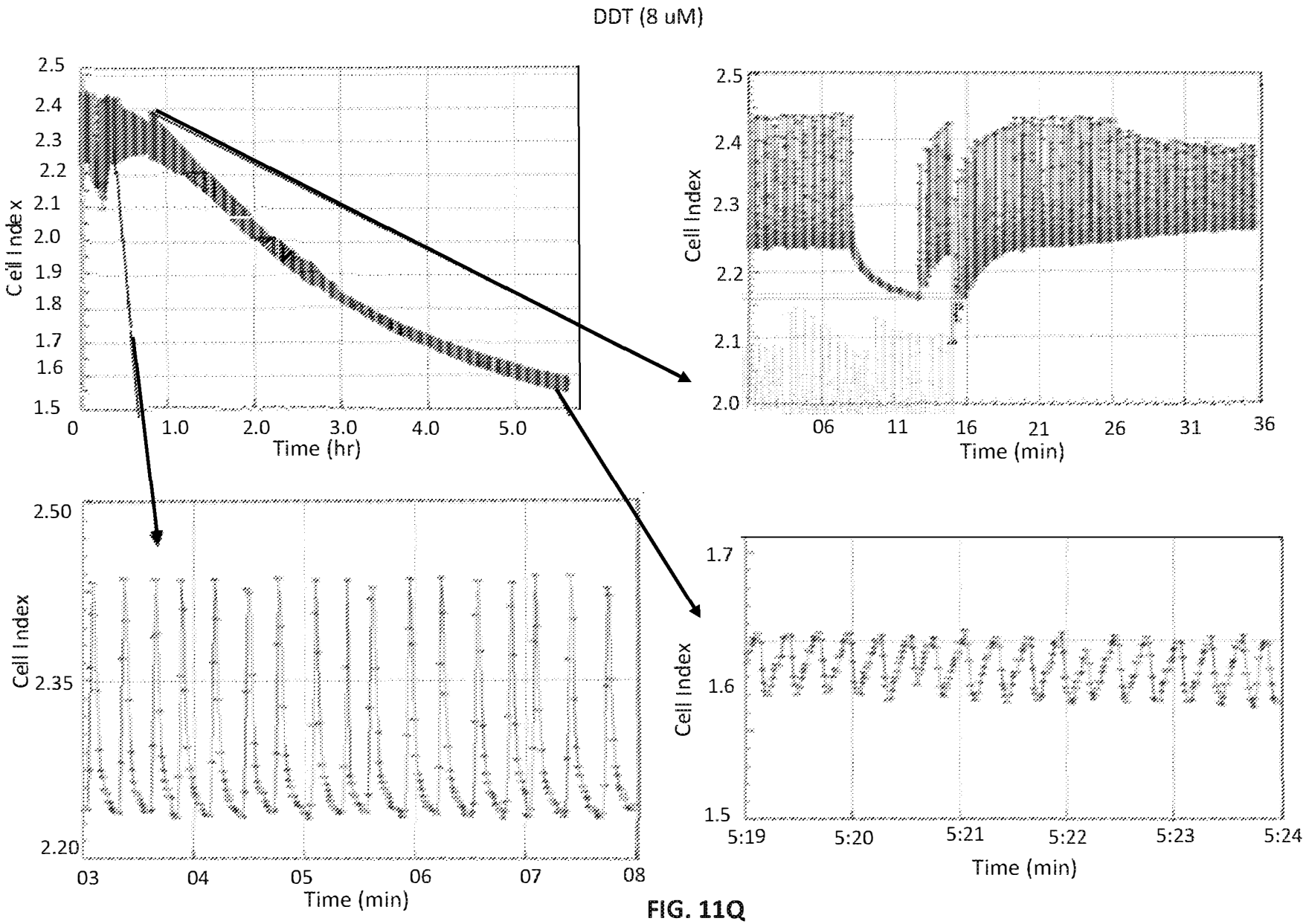

DDT (8 uM)
Cell Index
Time (hr)
Time (min)
Cell Index
Time (min)
Cell Index
Time (min)

FIG. 11Q

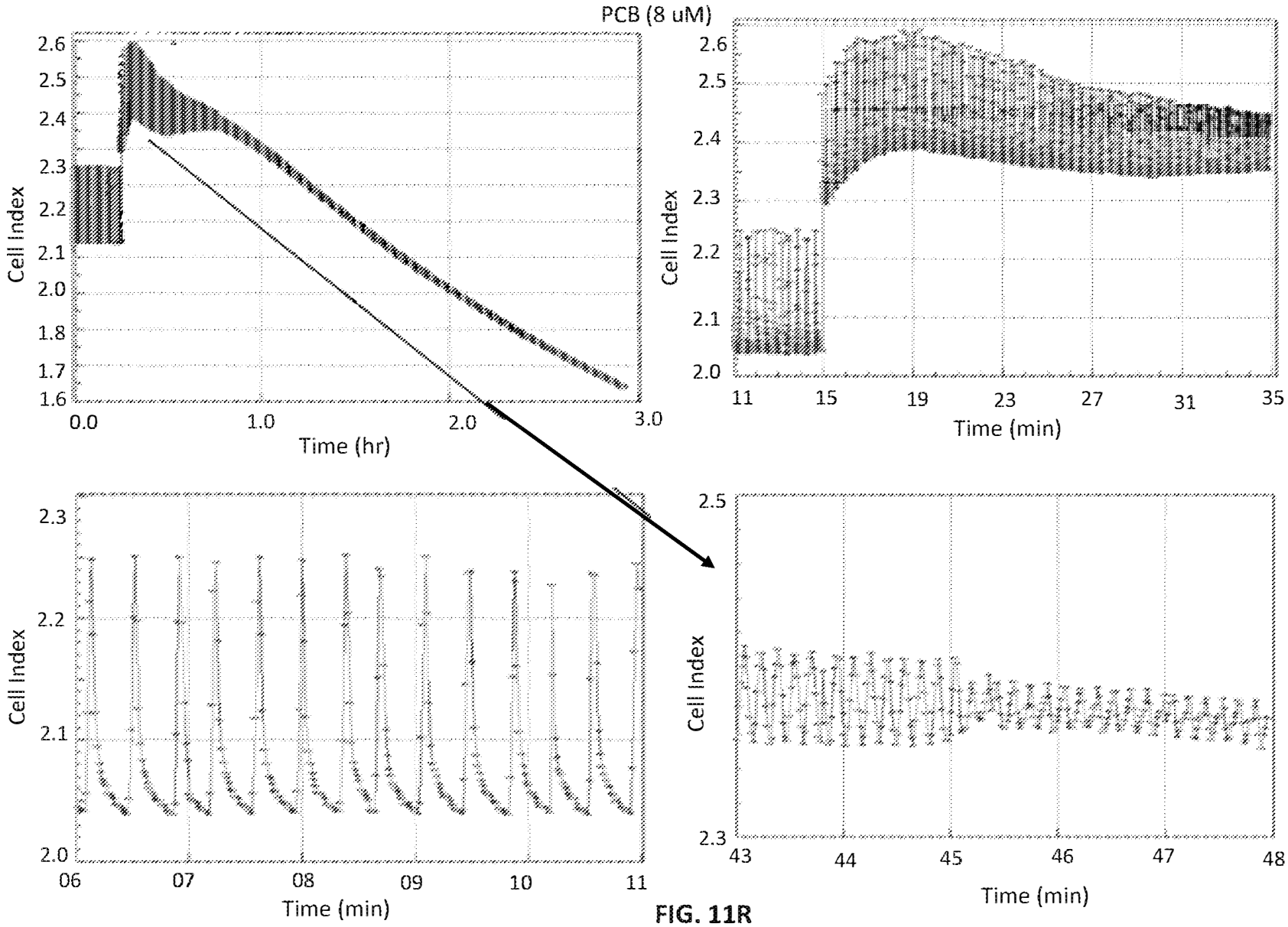

PCB (8 uM)
Cell Index
Time (hr)
Time (min)
Cell Index
Time (min)
Cell Index
Time (min)

FIG. 11R

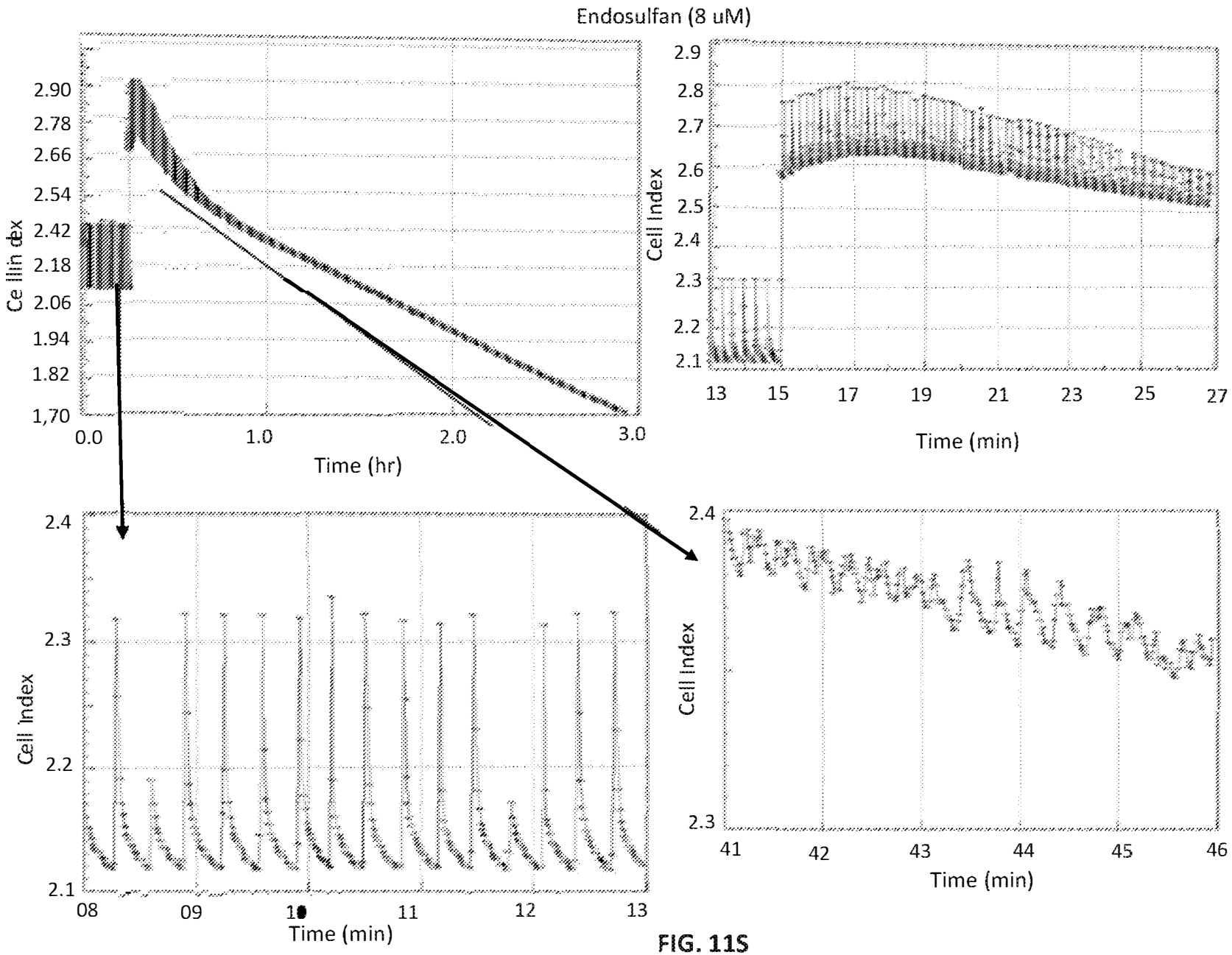

Endosulfan (8 uM)
Cell Index
2.90
2.78
2.66
2.54
2.42
2.18
2.06
1.94
1.82
1,70
0.0
1.0
2.0
3.0
Time (hr)
2.9
2.8
2.7
2.6
2.5
2.4
2.3
2.2
2.1
13
15
17
19
21
23
25
27
Time (min)
2.4
2.3
2.2
2.1
08
09
10
11
12
13
Time (min)
2.4
2.3
41
42
43
44
45
46
Time (min)

FIG. 11S

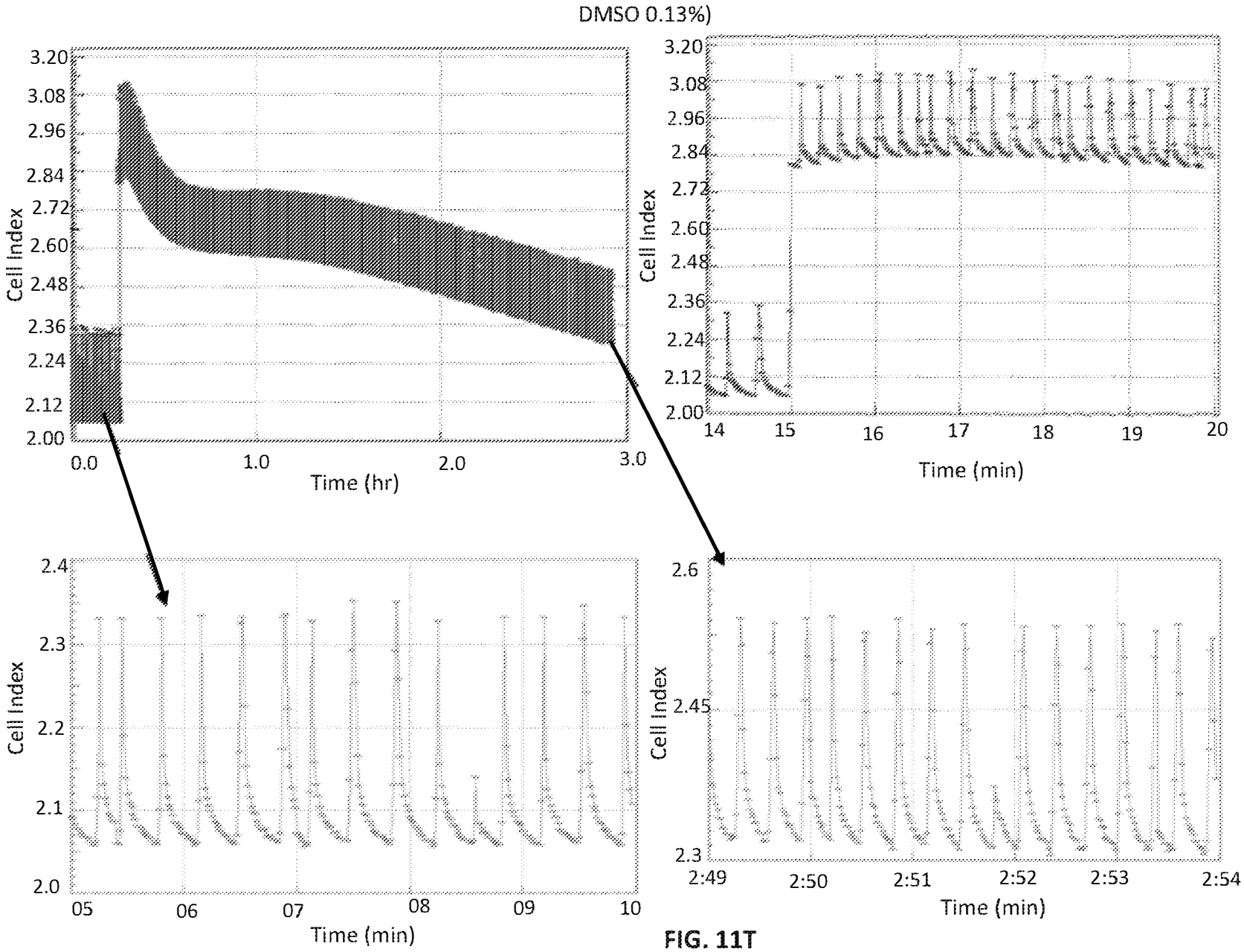

DMSO 0.13%)
Cell Index
Time (hr)
Time (min)
Cell Index
Time (min)
Cell Index
Time (min)

FIG. 11T

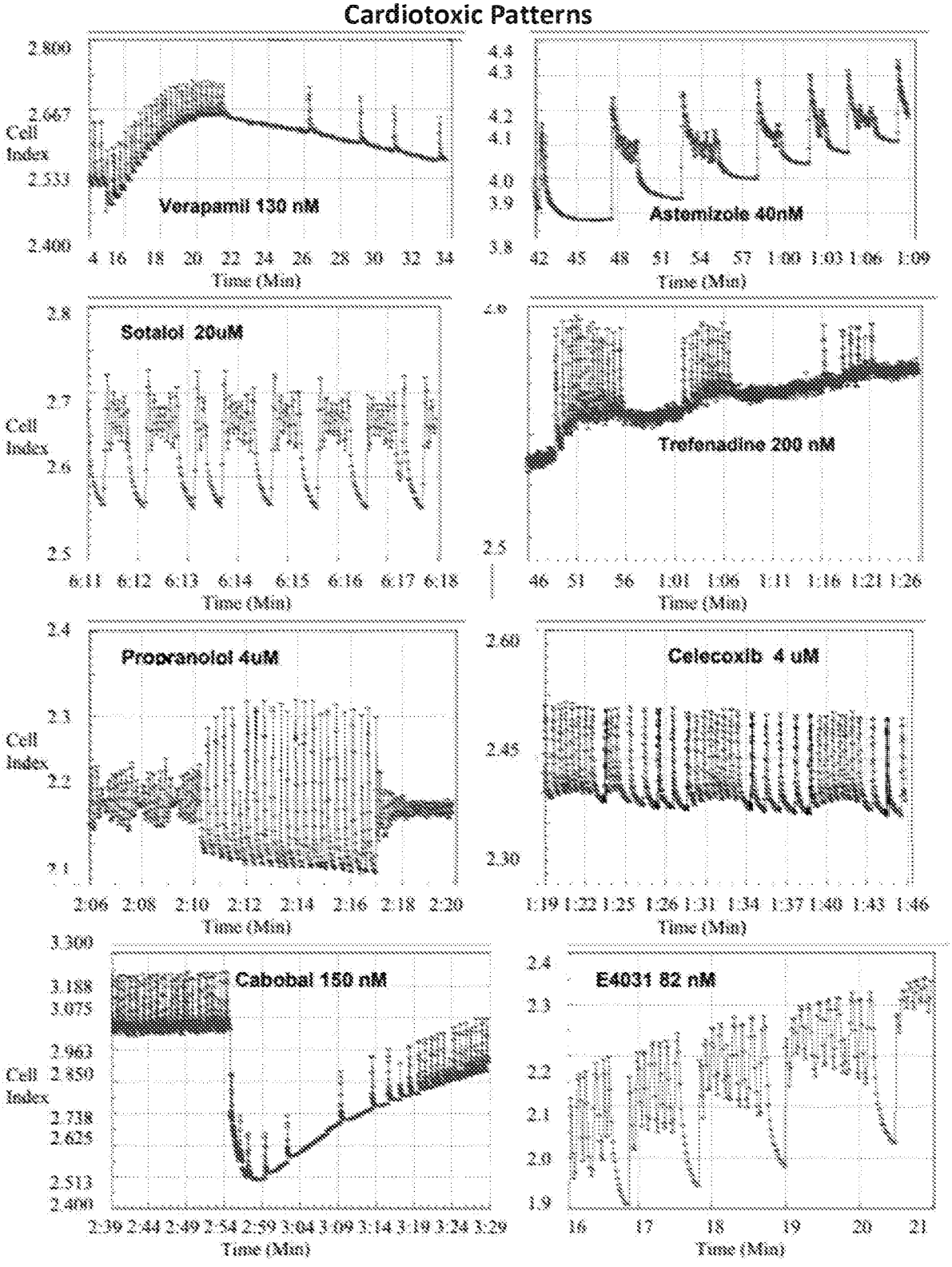

Cardiotoxic Patterns
Verapamil 130 nM
Astemizole 40nM
Sotalol 20uM
Trefenadine 200 nM
Propranolol 4uM
Celecoxib 4 uM
Cabobal 150 nM
E4031 82 nM
Cell Index
Time (Min)

FIG. 12

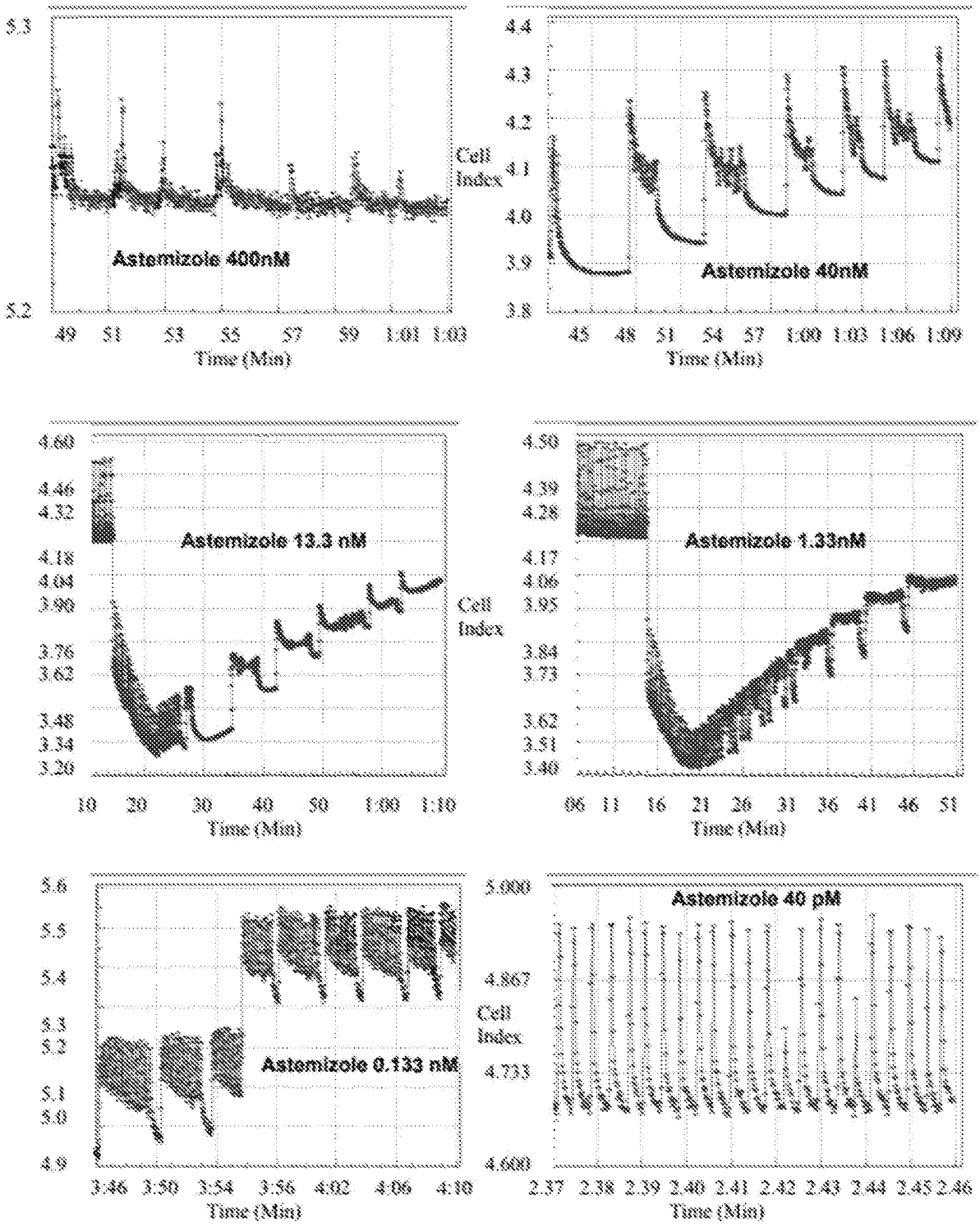

Astemizole 400nM
Astemizole 40nM
Astemizole 13.3 nM
Astemizole 1.33nM
Astemizole 0.133 nM
Astemizole 40 pM
Cell Index
Time (Min)

FIG. 13

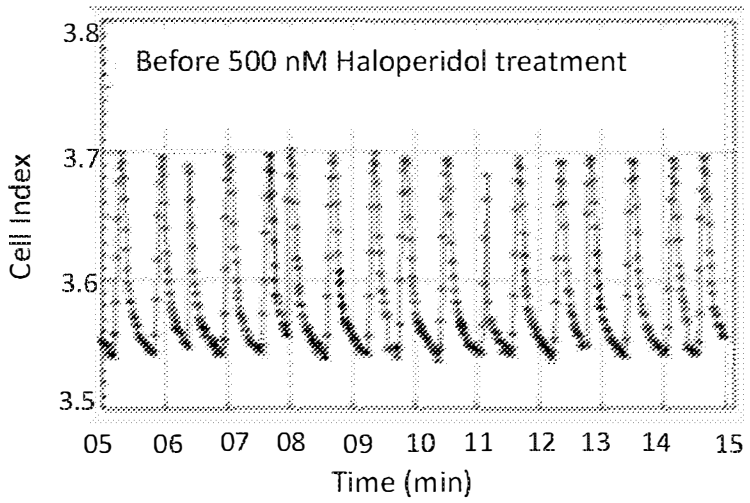


FIG. 14A

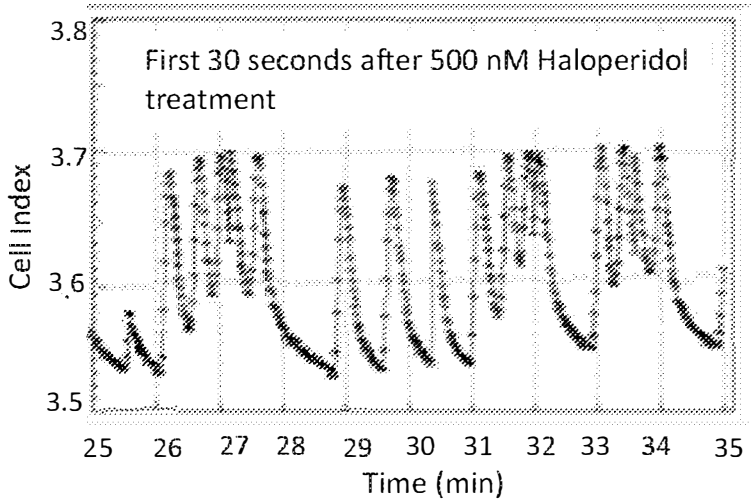


FIG. 14B

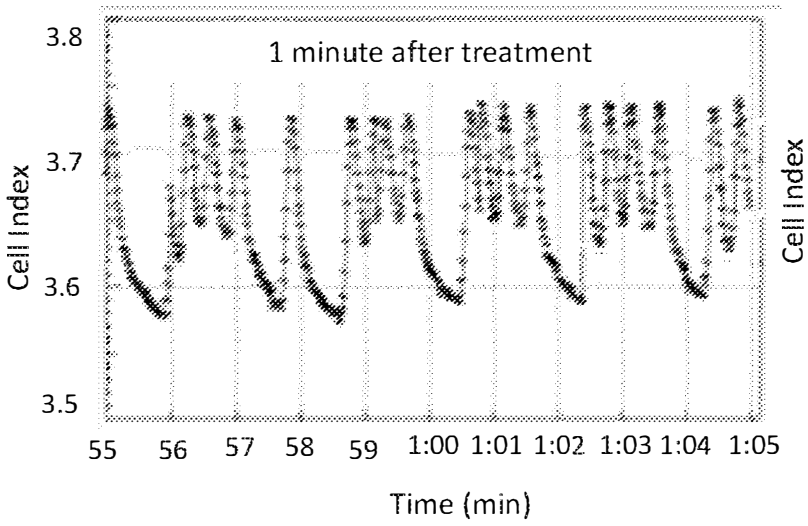


FIG. 14C

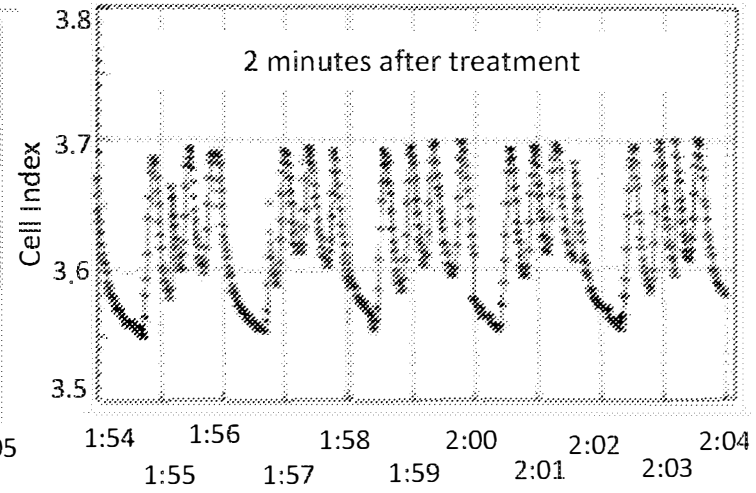


FIG. 14D

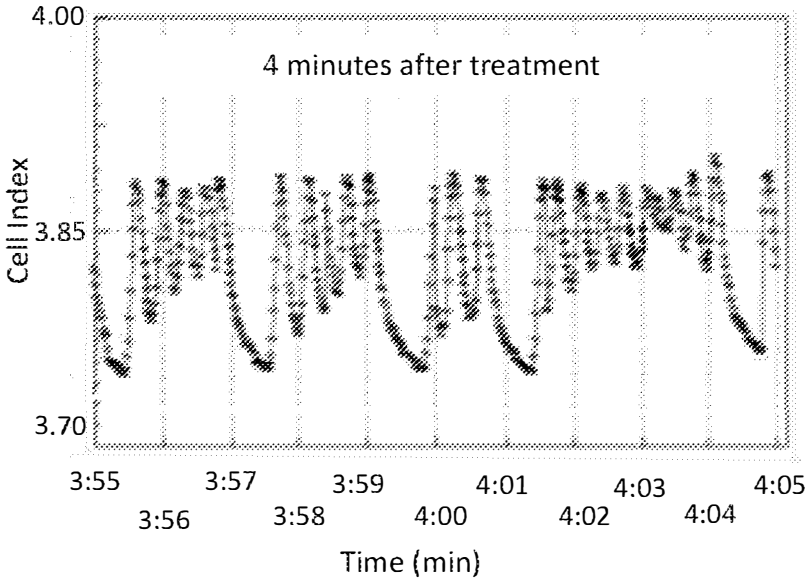


FIG. 14E

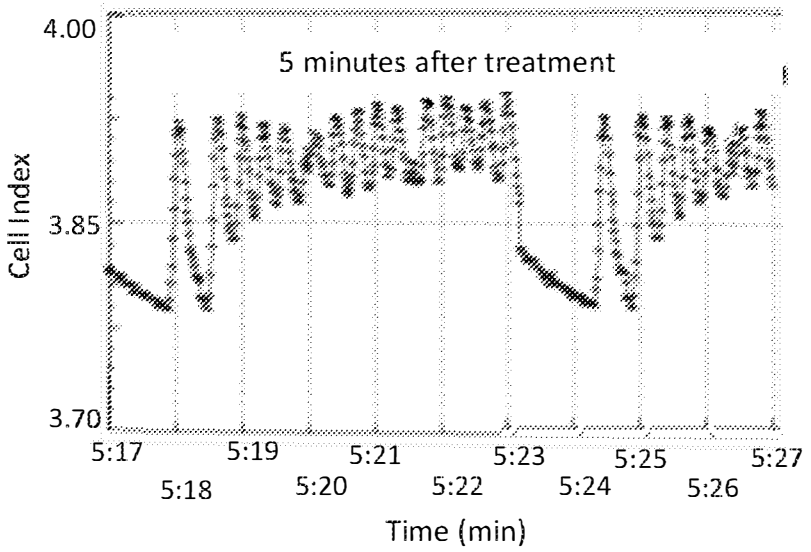


FIG. 14F

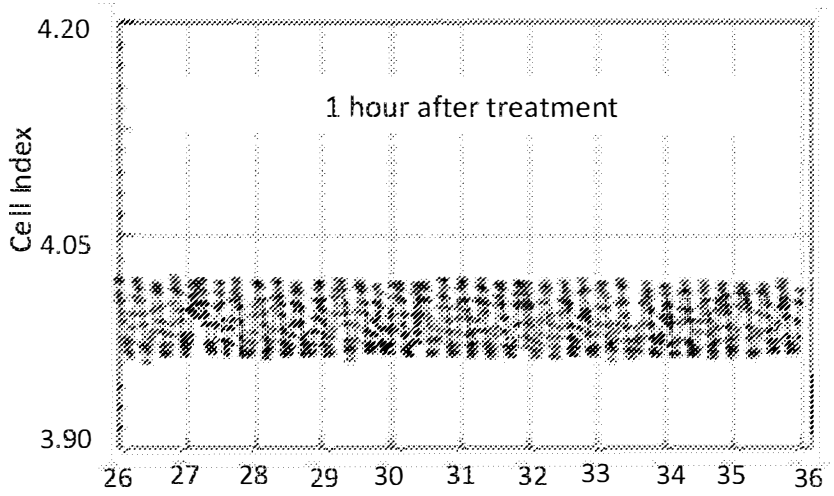


FIG. 14G

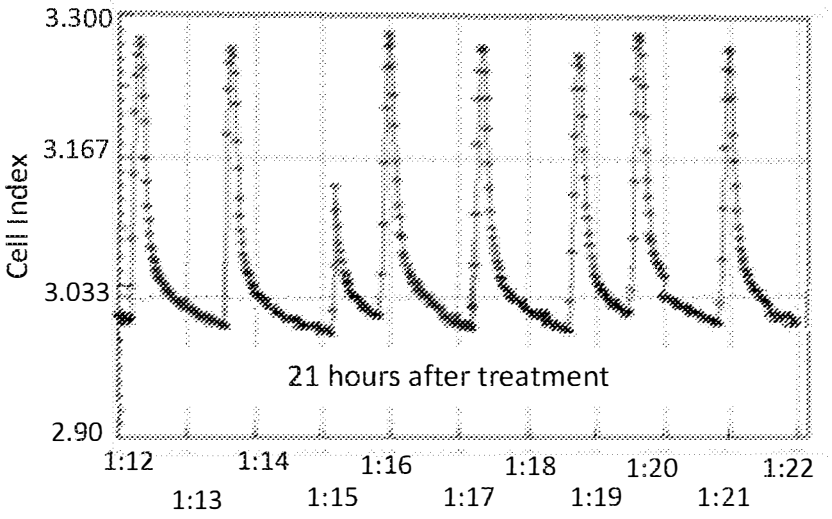


FIG. 14H

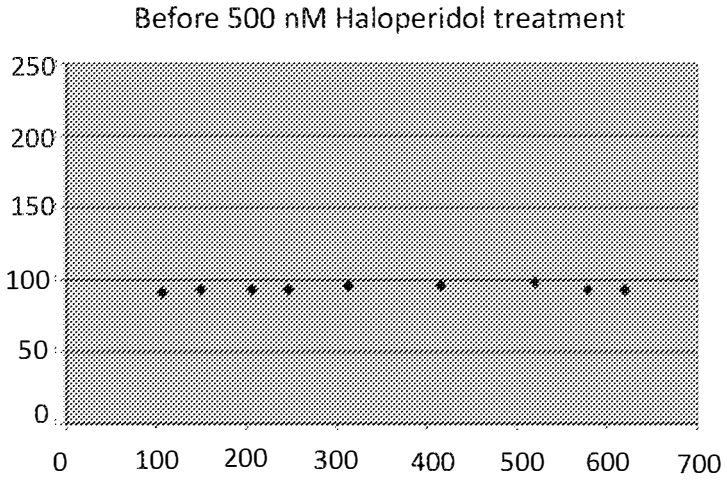


FIG. 15A

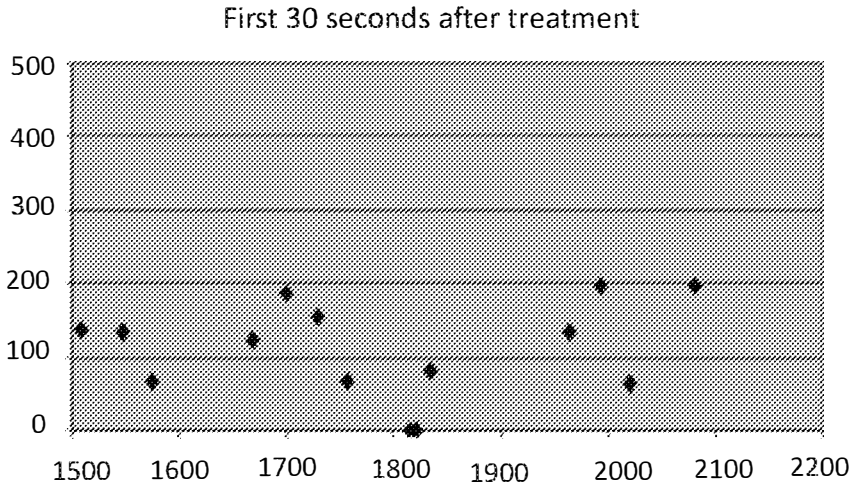


FIG. 15B

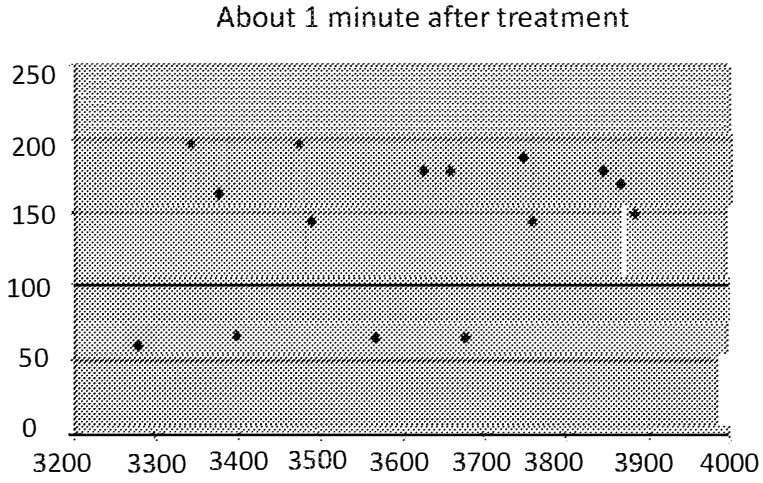


FIG. 15C

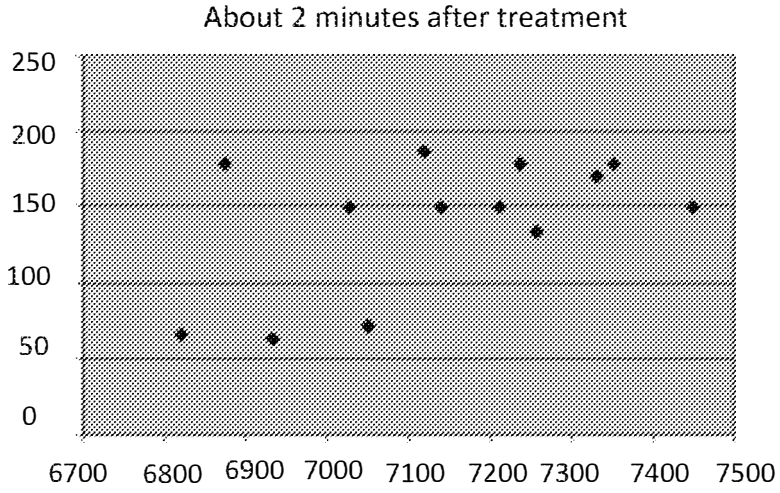


FIG. 15D

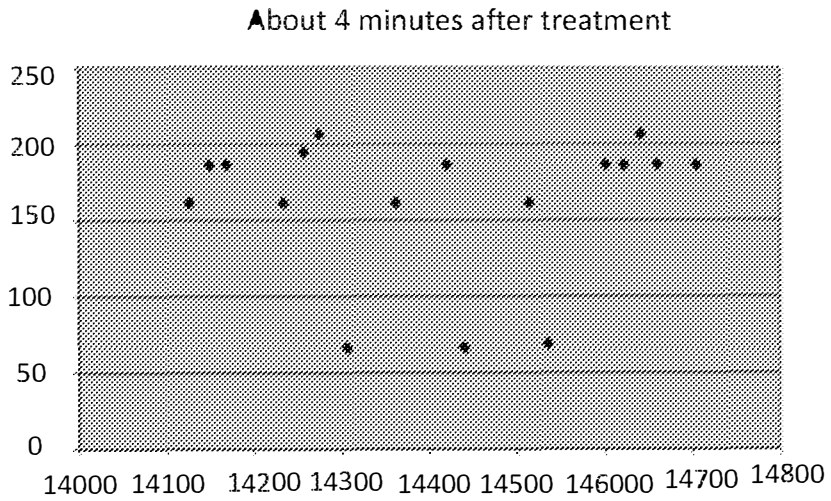


FIG. 15E

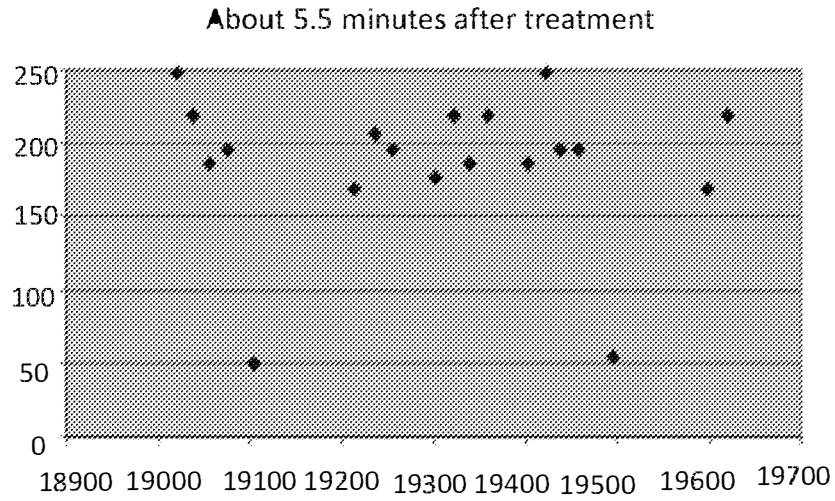


FIG. 15F

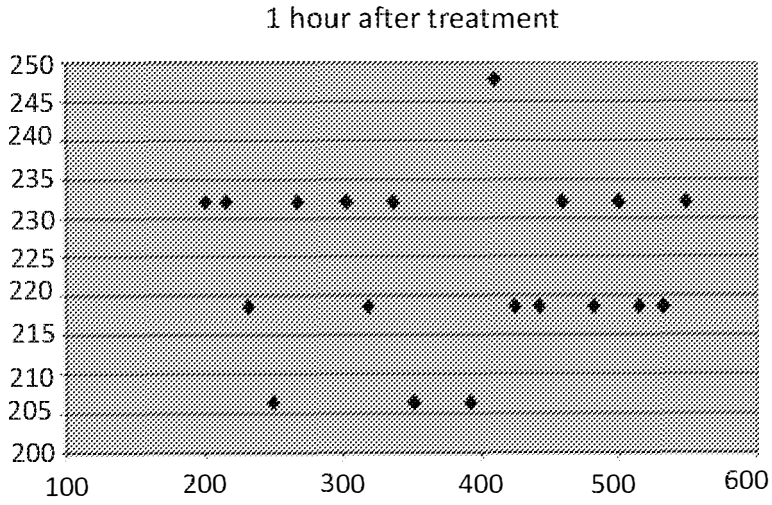


FIG. 15G

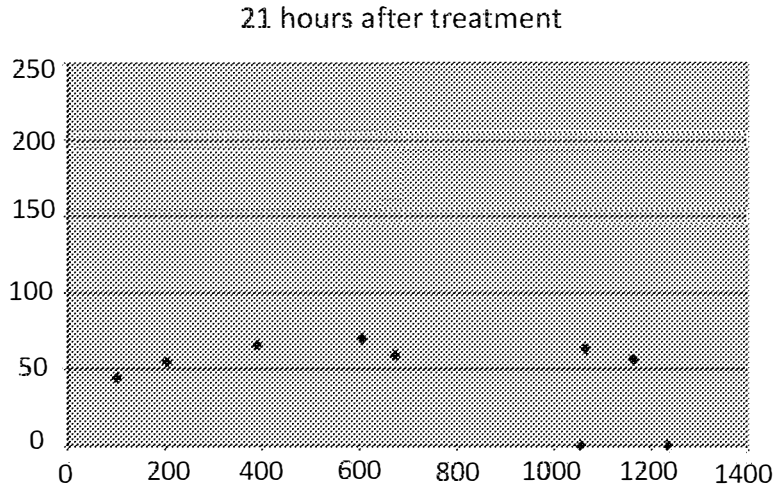


FIG. 15H

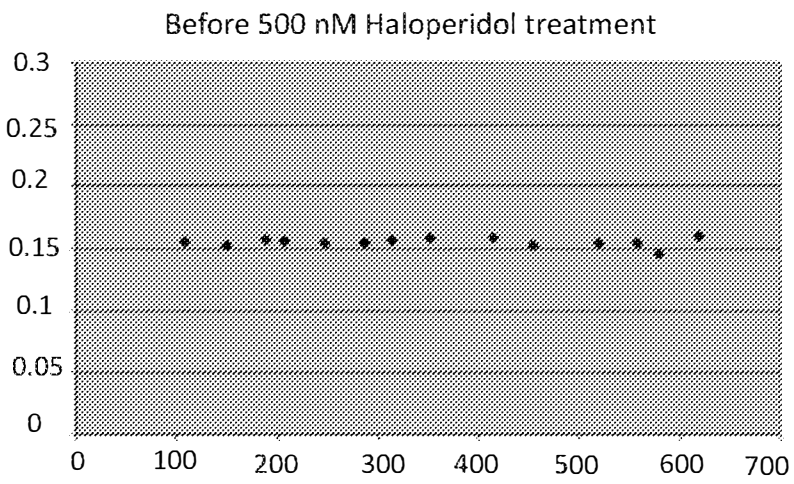


FIG. 16A

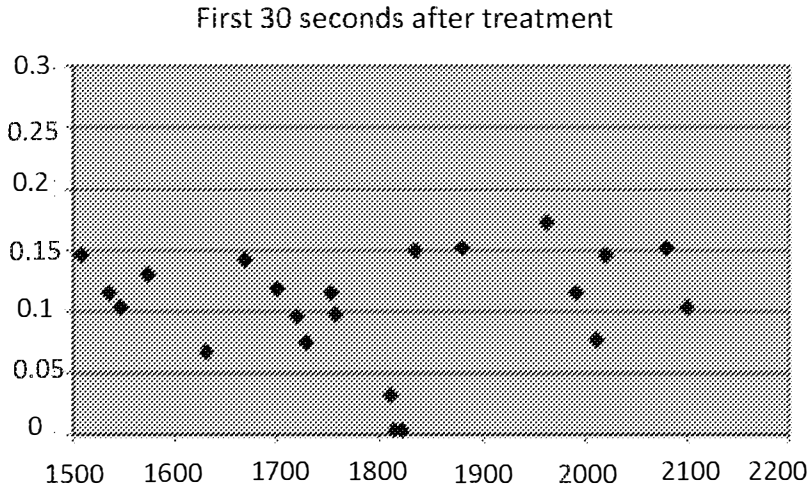


FIG. 16B

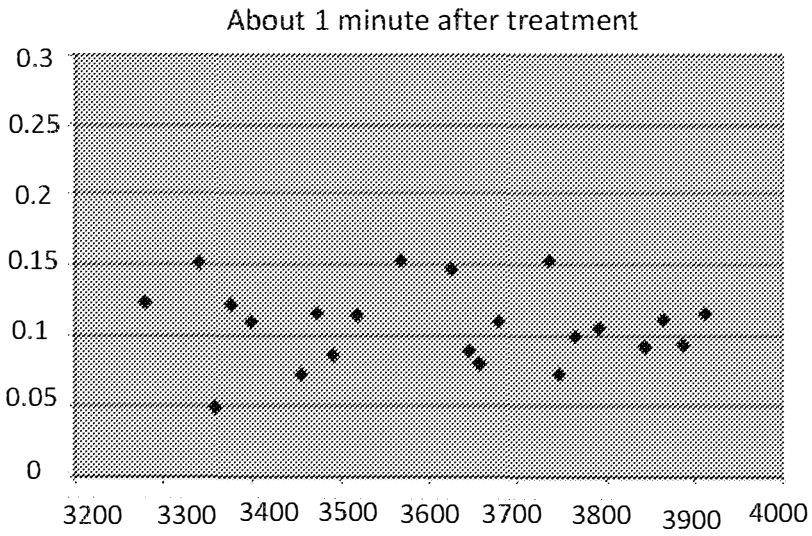


FIG. 16C

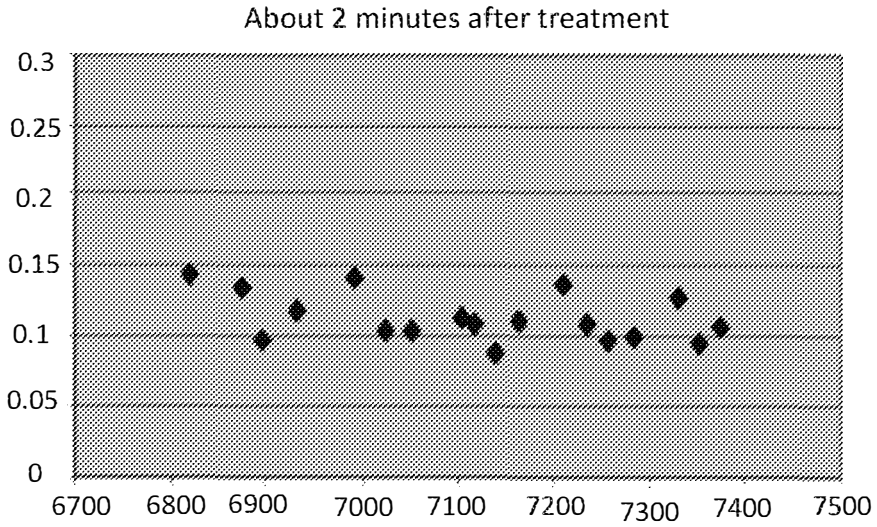


FIG. 16D

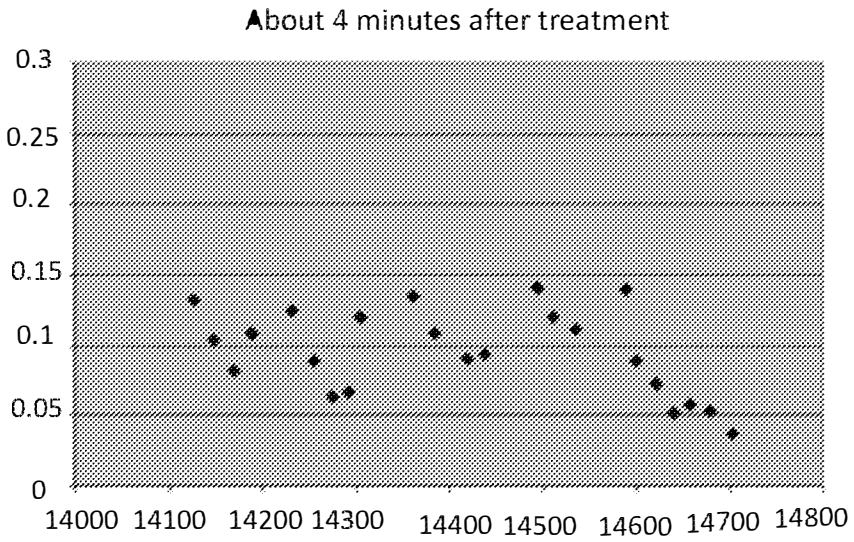


FIG. 16E

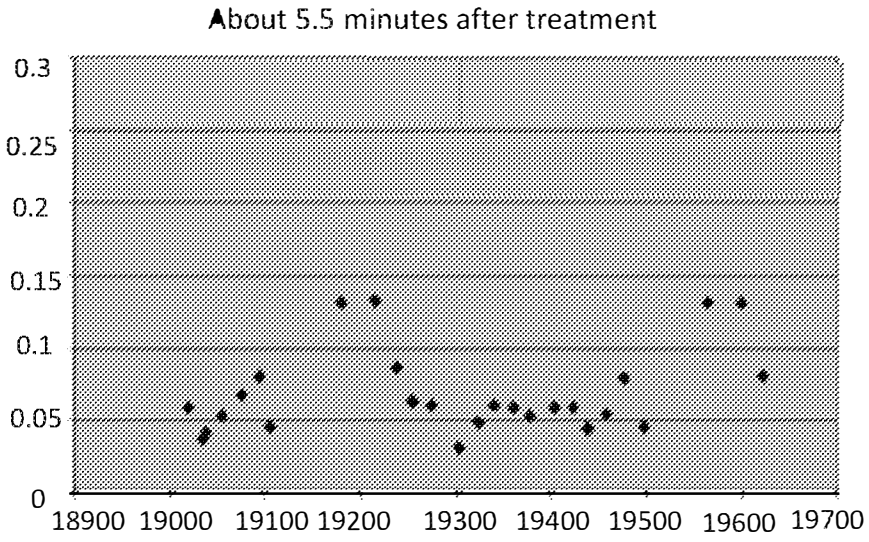


FIG. 16F

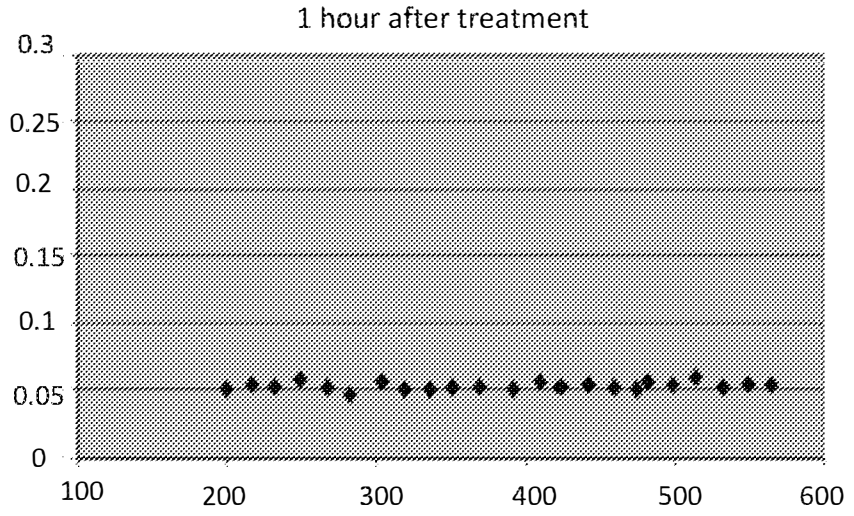


FIG. 16G

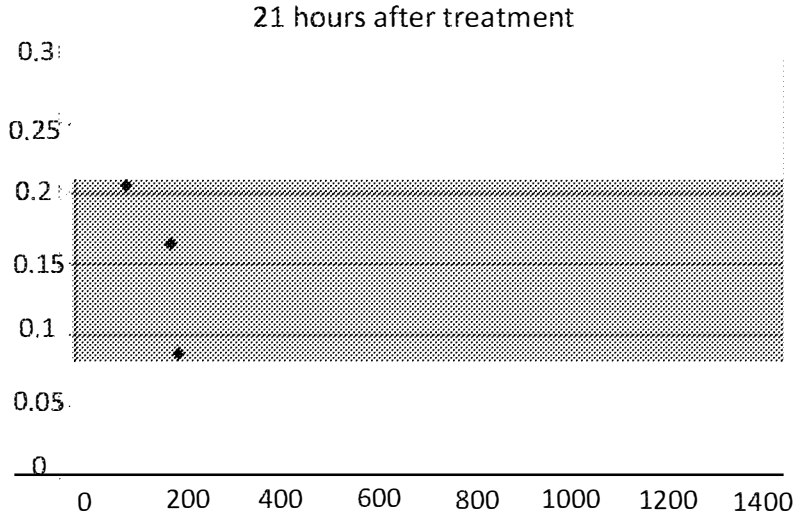


FIG. 16H

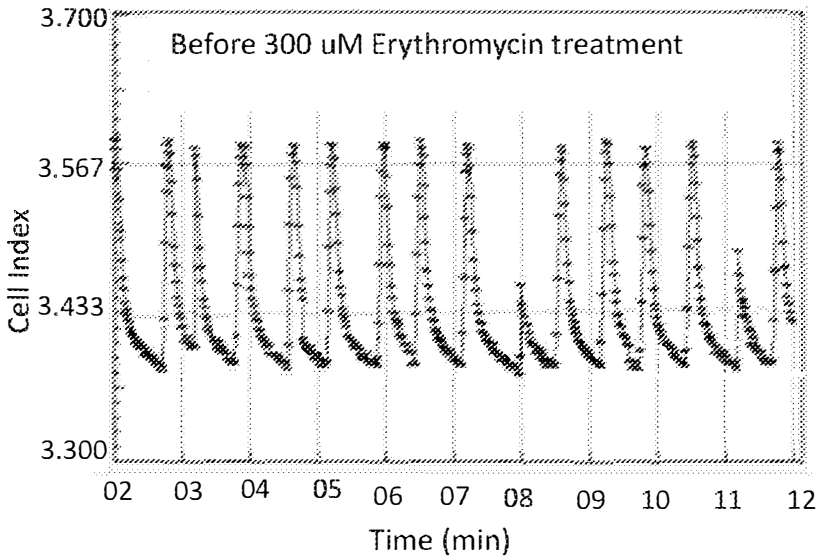


FIG. 17A

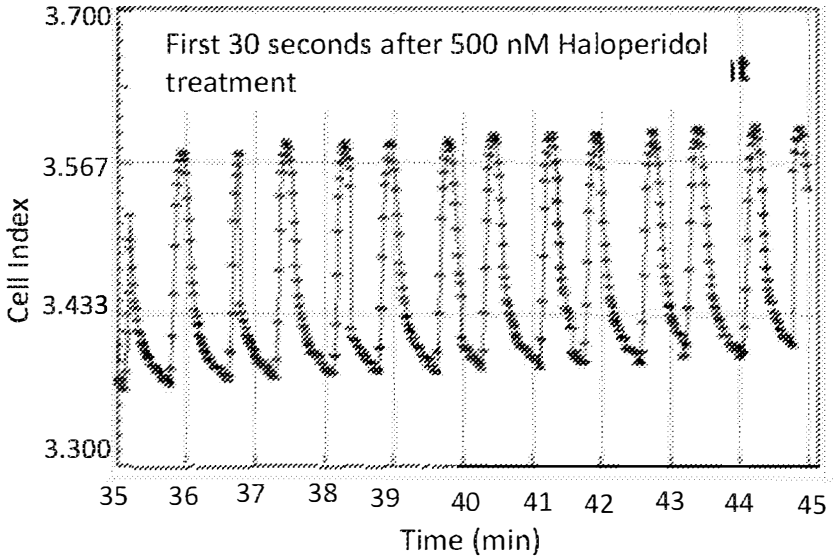


FIG. 17B

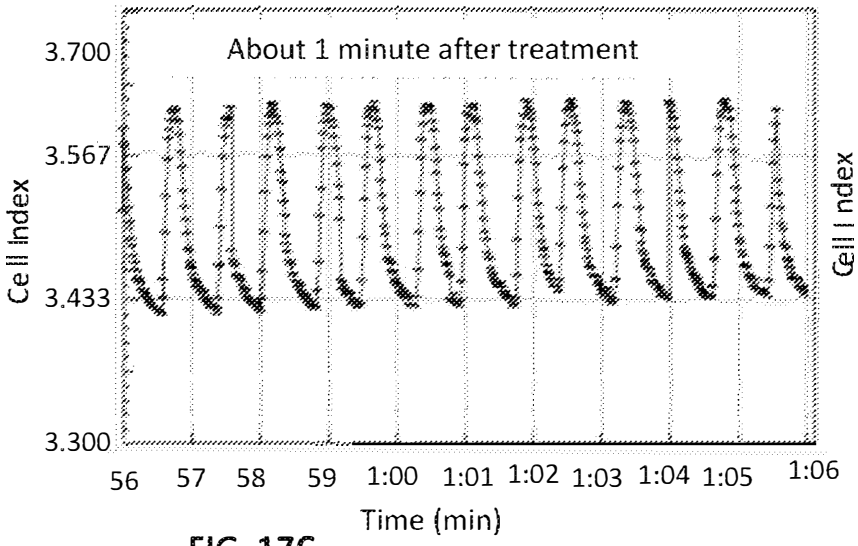


FIG. 17C

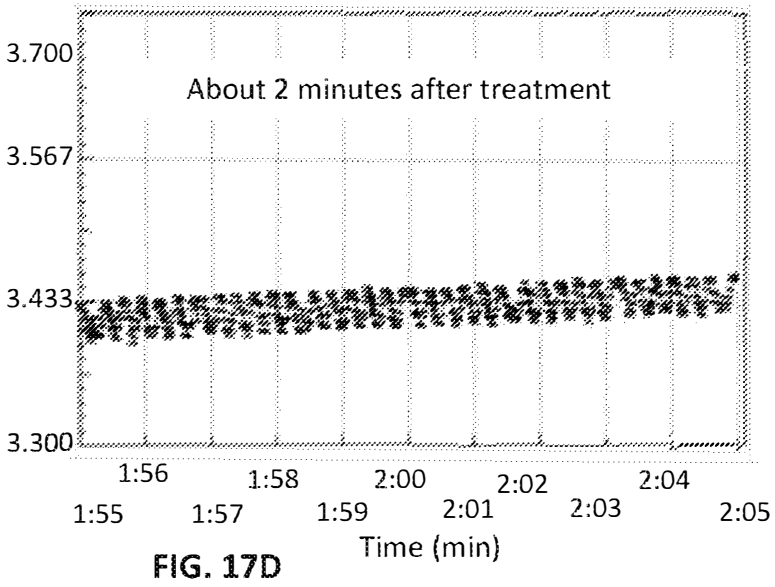


FIG. 17D

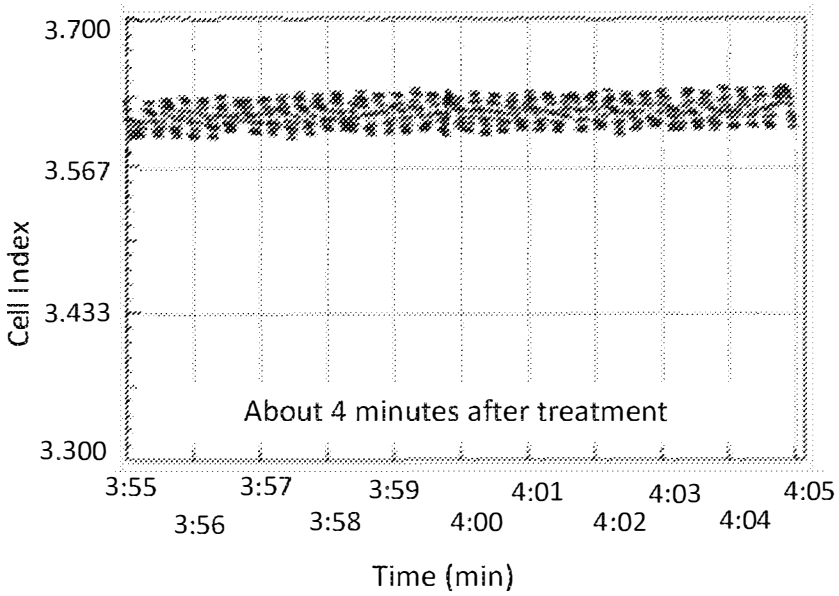


FIG. 17E

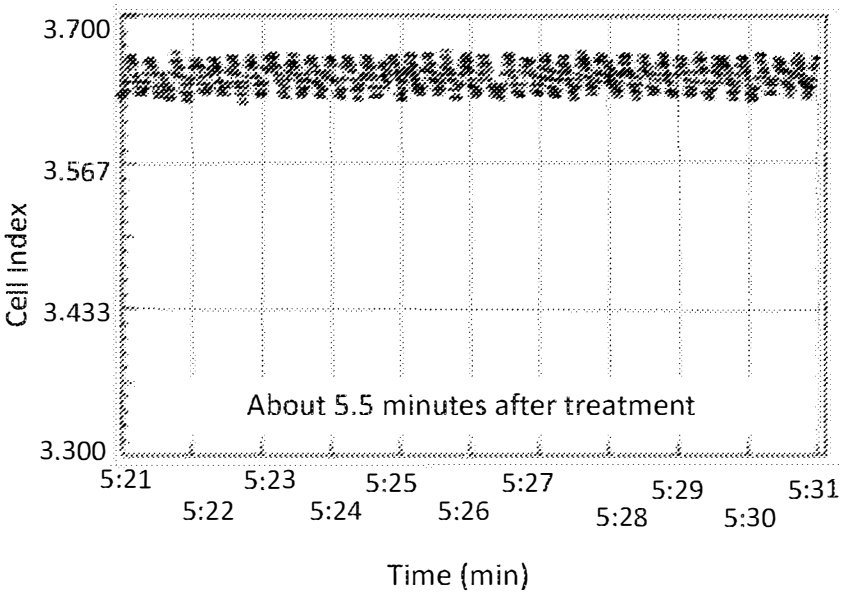


FIG. 17F

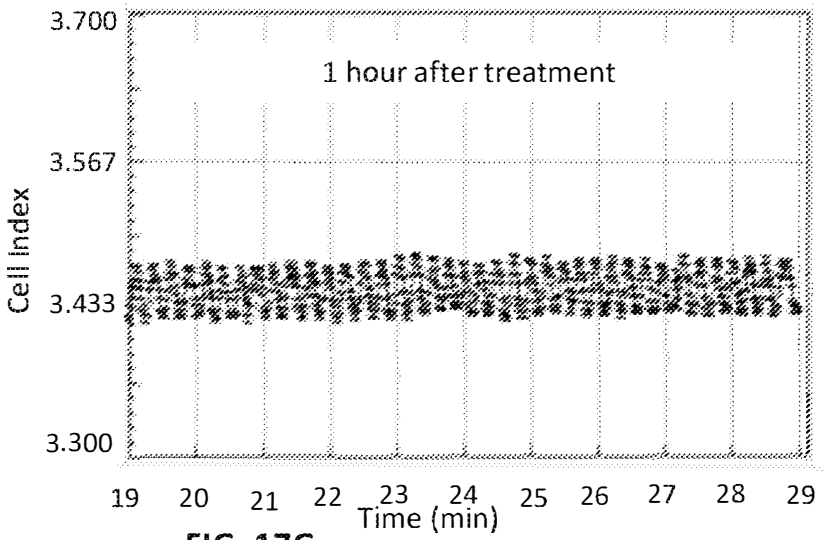


FIG. 17G

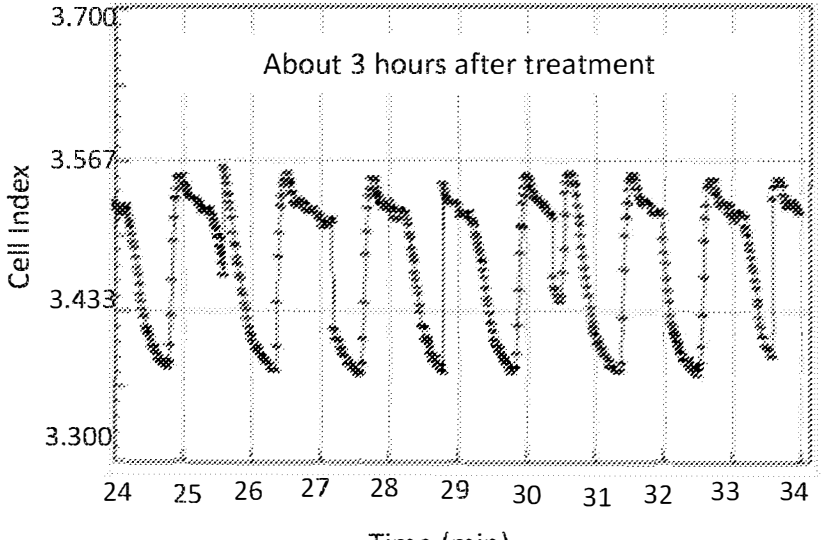


FIG. 17H

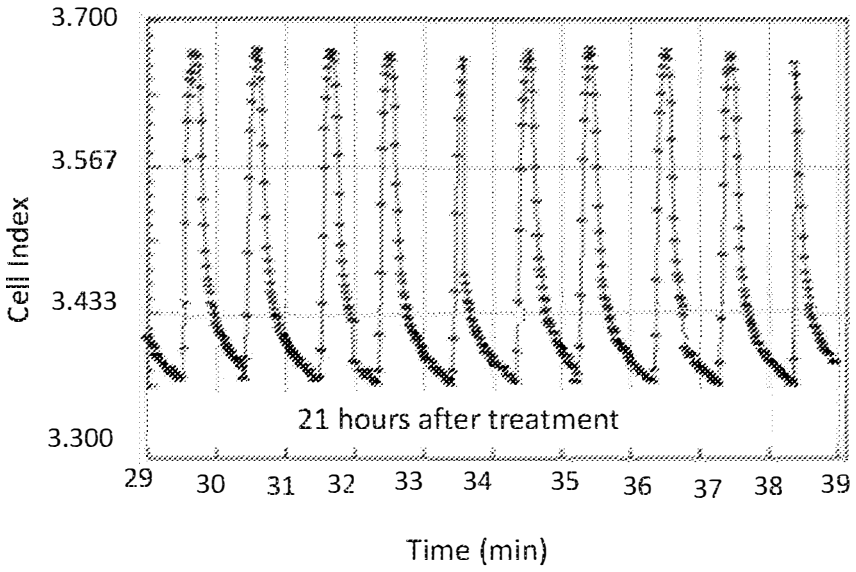

3.700
3.567
3.433
3.300
Cell Index
21 hours after treatment
29
30
31
32
33
34
35
36
37
38
39
Time (min)

FIG. 17I

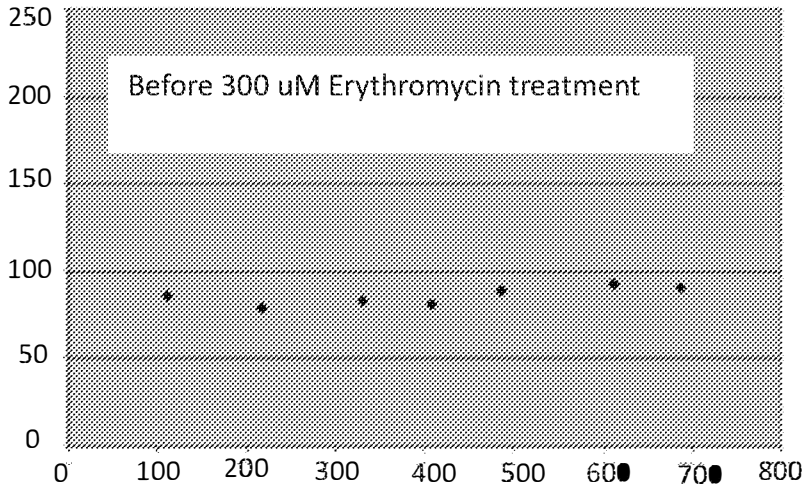


FIG. 18A

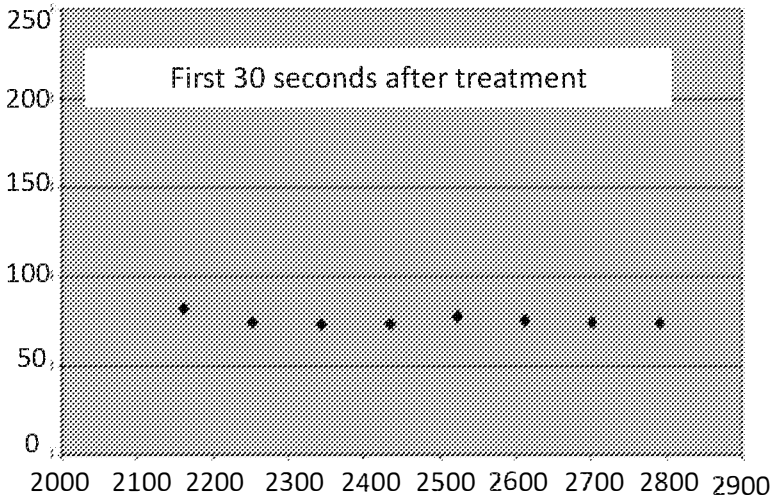


FIG. 18B

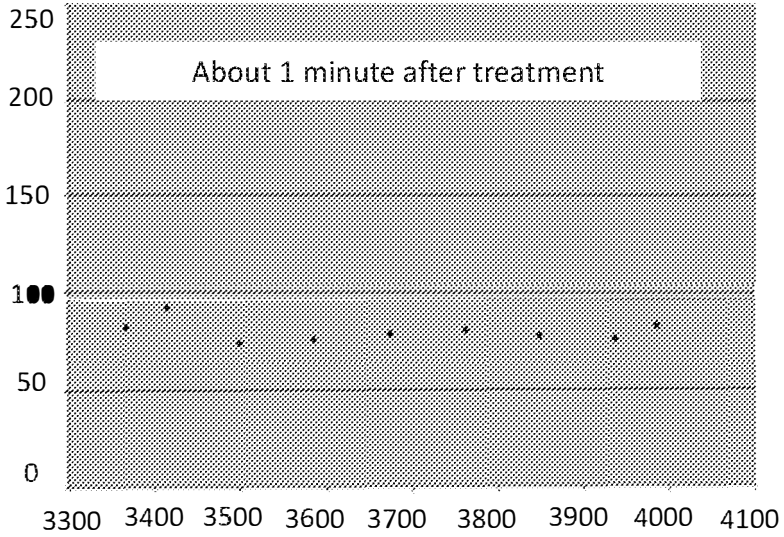


FIG. 18C

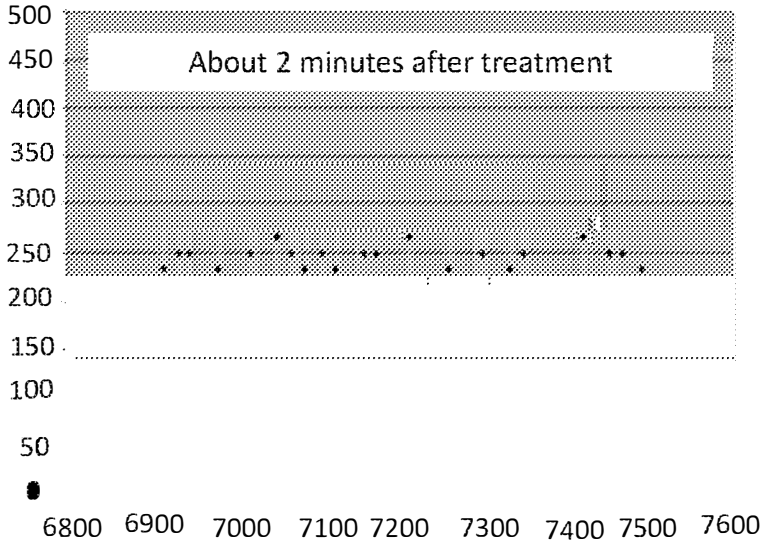


FIG. 18D

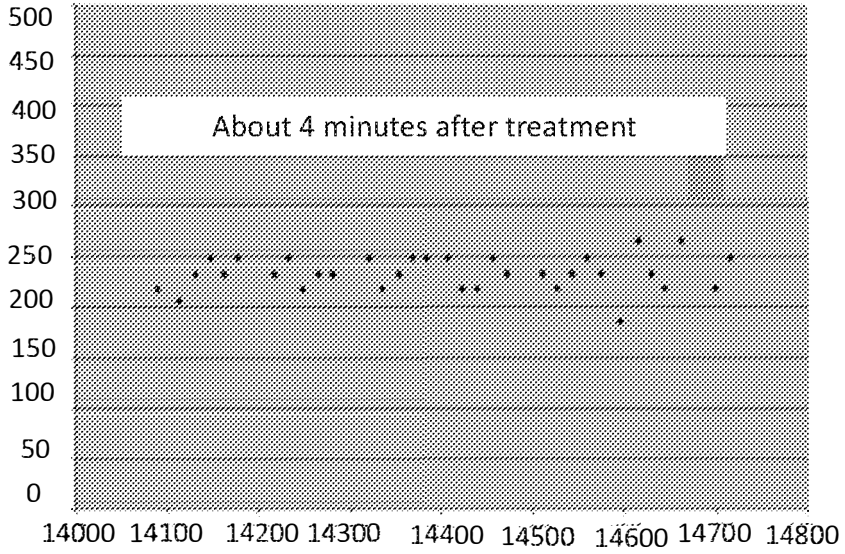


FIG. 18E

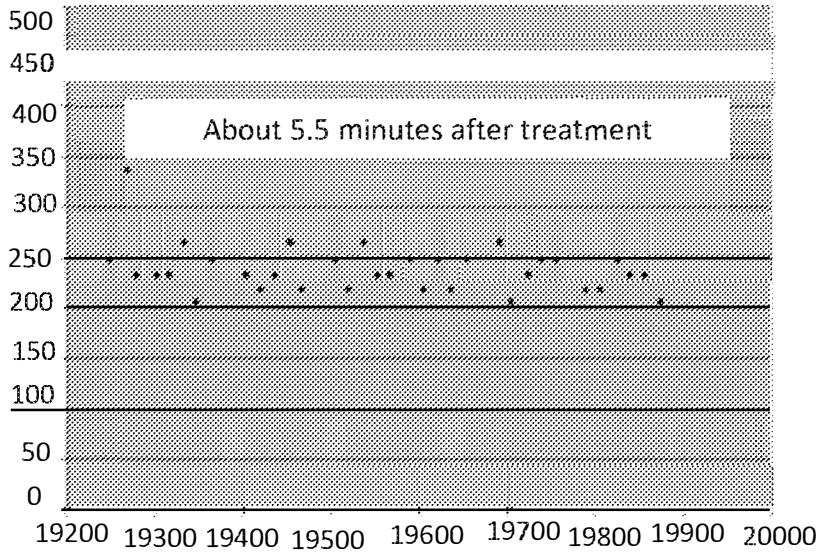


FIG. 18F

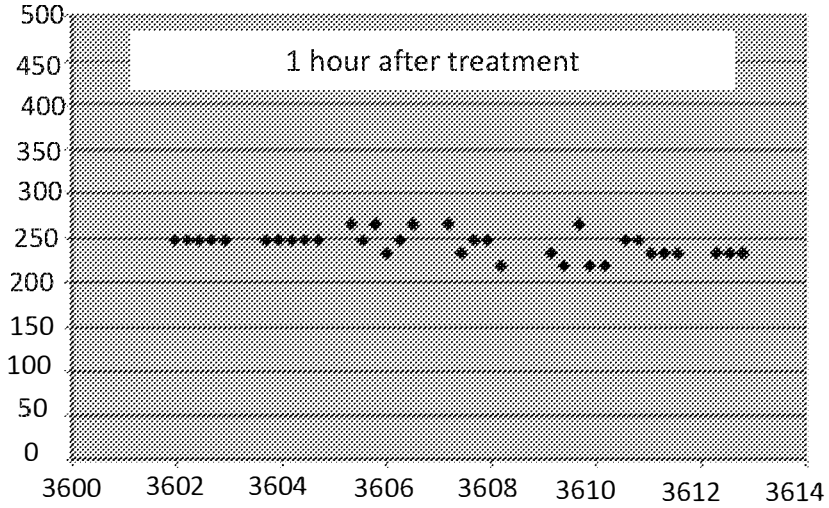


FIG. 18G

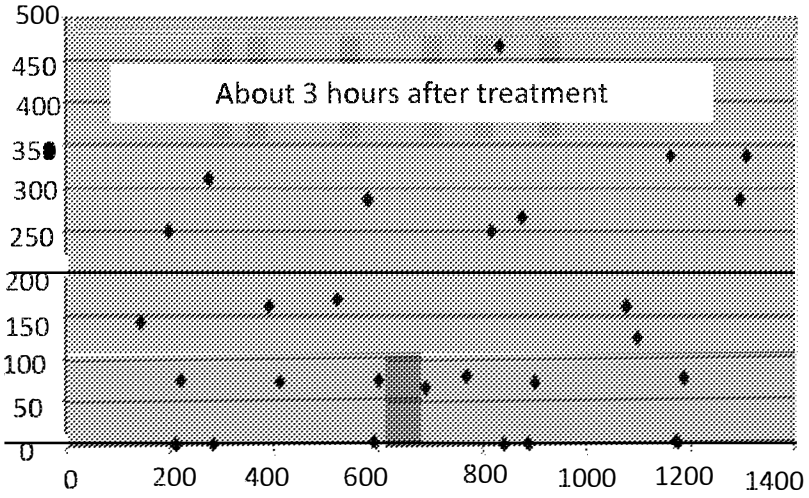


FIG. 18H

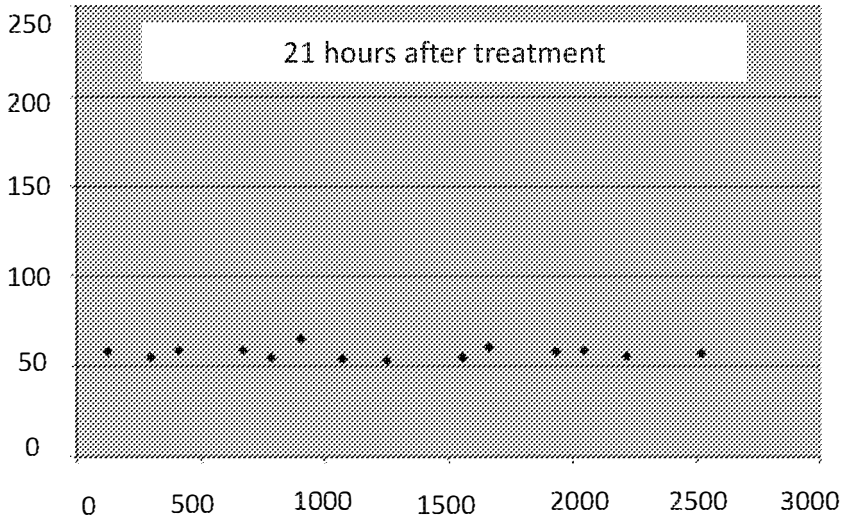

21 hours after treatment
250
200
150
100
50
0
0
500
1000
1500
2000
2500
3000

FIG. 18I

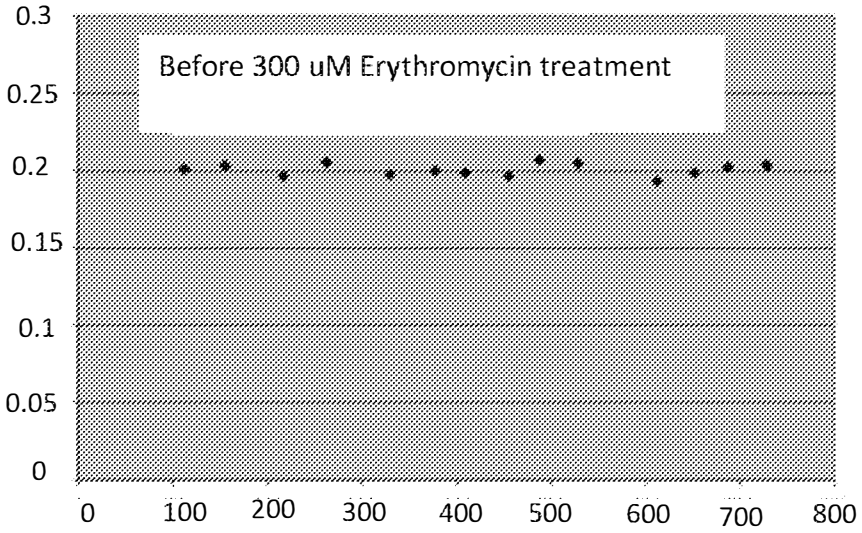


FIG. 19A

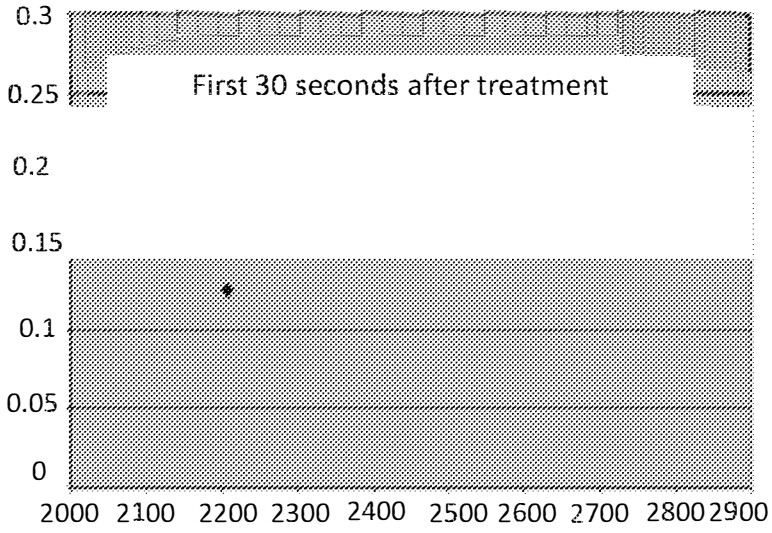


FIG. 19B

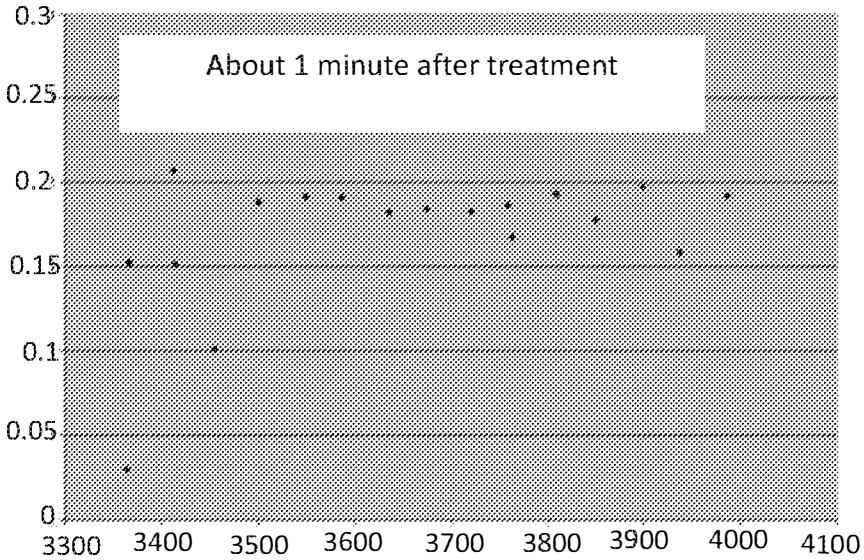


FIG. 19C

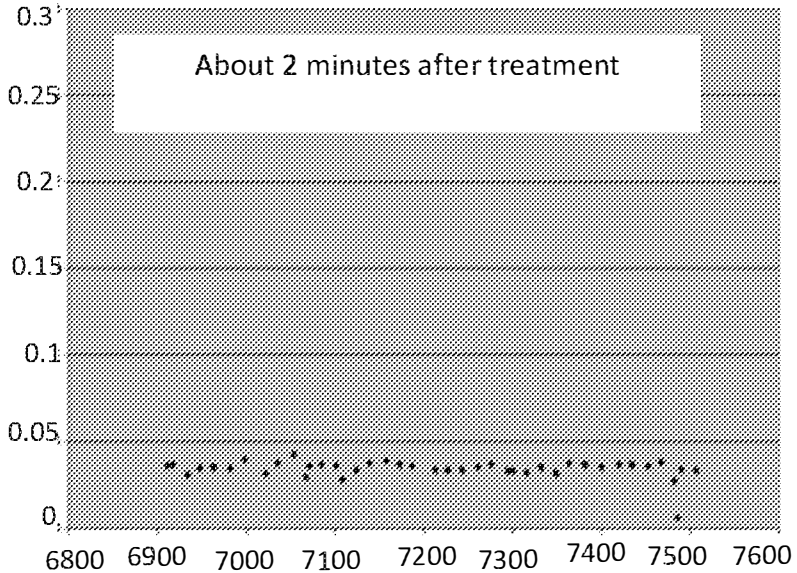


FIG. 19D

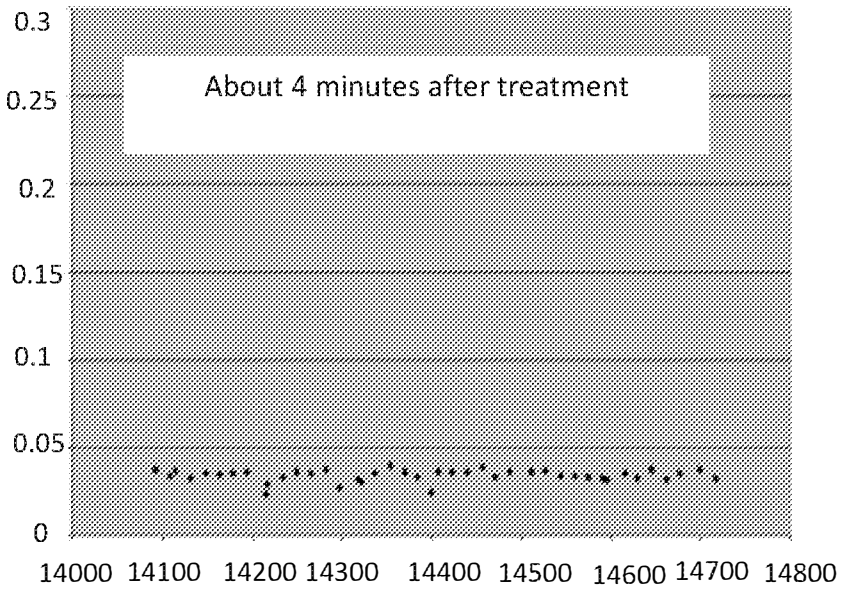


FIG. 19E

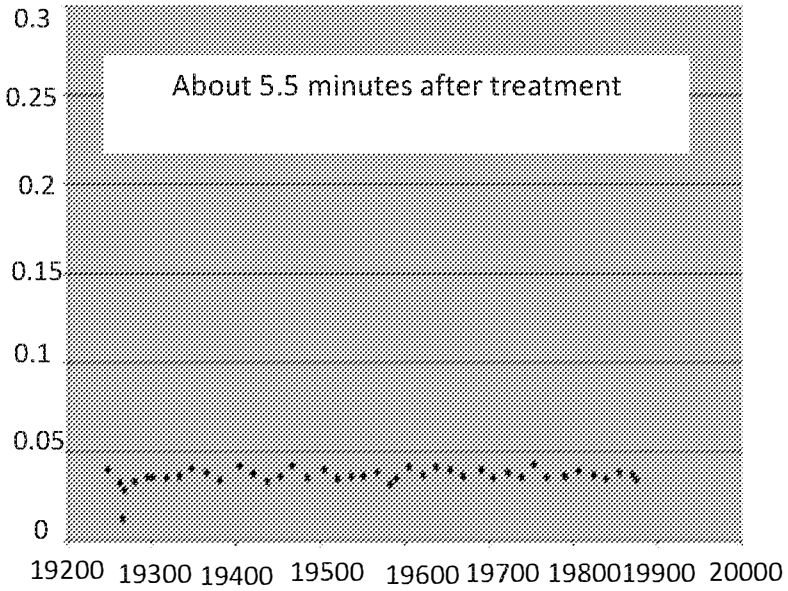


FIG. 19F

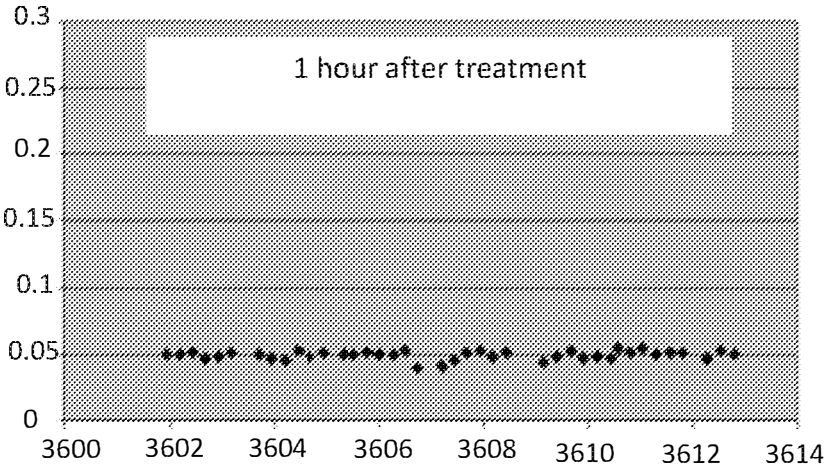


FIG. 19G

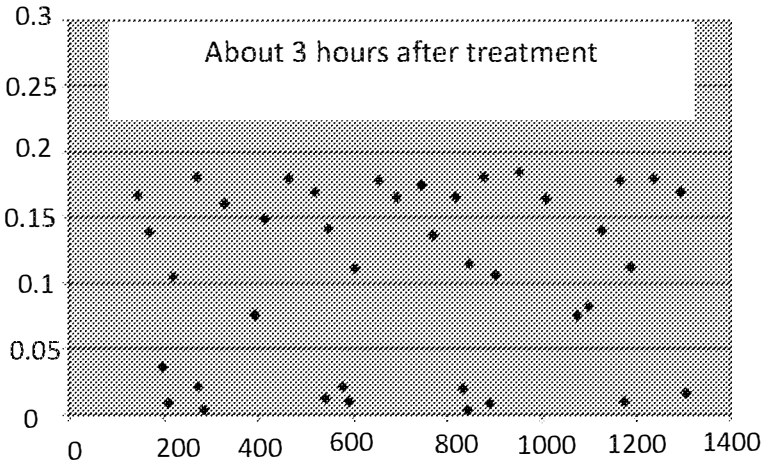


FIG. 19H

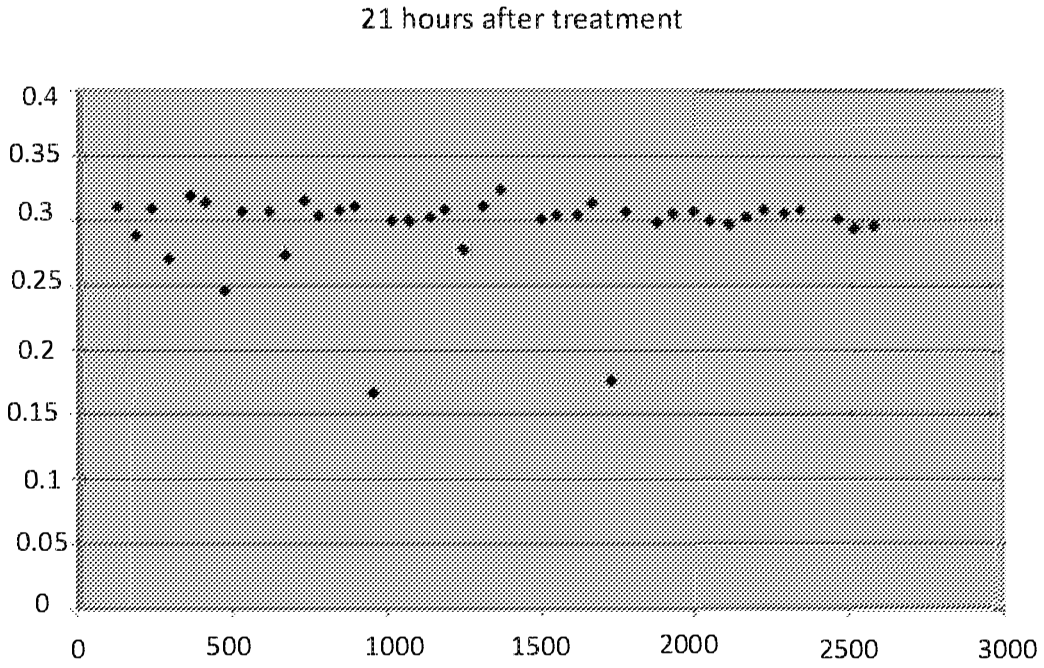

21 hours after treatment
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0
500
1000
1500
2000
2500
3000

FIG. 19I

Doc Code: ECOMM.AUTH/ECOMM.WTDW
Doc Description: Internet Communications Authorization/Internet Communications Authorization Withdrawal

PTO/SB/439 (11-15)

AUTHORIZATION FOR INTERNET COMMUNICATIONS IN A PATENT APPLICATION OR REQUEST TO WITHDRAW AUTHORIZATION FOR INTERNET COMMUNICATIONS		
	Application No.	
	Filing Date	Herewith
	First Named Inventor	Xiaobo Wang
	Art Unit	
	Examiner Name	
	Practitioner Docket No.	20191134-16

To: Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I. To authorize permission for Internet Communications.

☒ Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned and practitioners in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via video conferencing, instant messaging, or electronic mail. I understand that a copy of these communications will be made of record in the application file. (MPEP 502.03)

II. To withdraw authorization for Internet Communications.

☐ The authorization given on _____, to the USPTO to communicate with the undersigned and any practitioner in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via Internet communications such as video conferencing, instant messaging, or electronic mail is hereby withdrawn. I understand that the withdrawal is effective when approved rather than when received.

I am the

☐ applicant.

☒ attorney or agent of record. Registration number 50948.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Raymond Wagenknecht/ — Signature

11/23/2022 — Date

Raymond Wagenknecht — Typed or printed name

858-592-4141 ext. 1100 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Juristic entities must be represented by a patent practitioner (see 37 CFR 1.31, which is applicable to any paper filed on or after September 16, 2012, that is presented on behalf of a juristic entity, regardless of application filing date). Submit multiple forms if more than one signature is required, see below*.

☐ * Total of _____ forms are submitted.

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc Code: Oath

Document Description: Oath or declaration filed

PTO/AIA/08 (06-12)

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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted With Initial Filing OR ▩ Declaration Submitted After Initial Filing (surcharge (37 CFR 1.16(f)) required)

Attorney Docket Number	10101-101483
First Named Inventor	Wang et al.
COMPLETE IF KNOWN	
Application Number	15/651,882
Filing Date	July 17, 2017
Art Unit	1636
Examiner Name	Ghafoorian, Reza

LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

(Title of the invention)

As a below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application,

OR

▩ United States Application Number or PCT International application number 15/651,882 filed on July 17, 2017

The above-identified application was made or authorized to be made by me.

I believe I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

Authorization To Permit Access To Application by Participating Office

☑ If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the above-identified patent application is filed access to the above-identified patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the above-identified patent application is filed to have access to the above-identified patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the above-identified patent application with respect to: 1) the above-identified patent application-as-filed; 2) any foreign application to which the above-identified patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the above-identified patent application; and 3) any U.S. application-as-filed from which benefit is sought in the above-identified patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing the Authorization to Permit Access to Application by Participating Offices.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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DECLARATION — Utility or Design Patent Application

Direct all correspondence to:	☒	The address associated with Customer Number:	59538	OR ☐	Correspondence address below

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Address		
City	State	Zip
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WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available. Petitioner/applicant is advised that documents which form the record of a patent application (such as the PTO/SB/01) are placed into the Privacy Act system of records DEPARTMENT OF COMMERCE, COMMERCE-PAT-7, System name: *Patent Application Files*. Documents not retained in an application file (such as the PTO-2038) are placed into the Privacy Act system of COMMERCE/PAT-TM-16, System name: *Deposit Accounts and Electronic Funds Transfer Profiles*.

LEGAL NAME OF SOLE OR FIRST INVENTOR:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Xiaobo Wang

Inventor's Signature		Date (Optional)	5/21/2018
Residence: City	State	Country	
San Diego	CA	US	

Mailing Address

ACEA Biosciences, Inc., 6779 Mesa Ridge Road, Suite 100

City	State	Zip	Country
San Diego	CA	92121	US

☒ Additional inventors are being named on the 2 supplemental sheet(s) PTO/AIA/10 attached hereto

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SUPPLEMENTAL SHEET FOR DECLARATION | **ADDITIONAL INVENTOR(S)**
Supplemental Sheet (for PTO/AIA/08,09) Page 3 of 4

Legal Name of Additional Joint Inventor, if any:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)
Yama A. Abassi

Inventor's Signature | Date (Optional) 5/17/2018

Residence: City San Diego | State CA | Country US

Mailing Address: ACEA Biosciences, Inc.
6779 Mesa Ridge Road, Suite 100

City San Diego | State CA | Zip 92121 | Country US

Legal Name of Additional Joint Inventor, if any:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)
Biao Xi

Inventor's Signature | Date (Optional) 5/16/2018

Residence: City San Diego | State CA | Country US

Mailing Address: ACEA Biosciences, Inc., 6779 Mesa Ridge Road, Suite 100

City San Diego | State | Zip 92121 | Country US

Legal Name of Additional Joint Inventor, if any:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)
Wen Fu Zhang

Inventor's Signature | Date (Optional) 5/16/18

Residence: City San Diego | State CA | Country US

Mailing Address: ACEA Biosciences, Inc., 6779 Mesa Ridge Road, Suite 100

City San Diego | State CA | Zip 92121 | Country US

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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SUPPLEMENTAL SHEET FOR DECLARATION | **ADDITIONAL INVENTOR(S)**
Supplemental Sheet (for PTO/AIA/08.09) Page 4 of 4

Legal Name of Additional Joint Inventor, if any:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Xiao Xu

Inventor's Signature | Date (Optional)

Residence: City: San Diego | State: CA | Country: US

Mailing Address:
ACEA Biosciences, Inc.
6779 Mesa Ridge Road, Suite 100

City: San Diego | State: CA | Zip: 92121 | Country: US

Legal Name of Additional Joint Inventor, if any:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Inventor's Signature | Date (Optional)

Residence: City | State | Country

Mailing Address

City | State | Zip | Country

Legal Name of Additional Joint Inventor, if any:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Inventor's Signature | Date (Optional)

Residence: City | State | Country

Mailing Address

City | State | Zip | Country

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Doc Code: TRACK1.REQ
Document Description: **TrackOne Request**

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Xiaobo Wang	Nonprovisional Application Number (if known):	
Title of Invention:	LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

I. ☑ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Raymond Wagenknecht/	Date 11/23/2022
Name (Print/Typed) Raymond Wagenknecht	Practitioner Registration Number 50948

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☐ *Total of _____ forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT		
	Application Number	17/993,716
	Filing Date	2022-11-23
	First Named Inventor	Xiaobo Wang
	Art Unit	
	Examiner Name	
	Attorney Docket Number	20191134-16

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
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	2	3259842	A	1966-07-05	Coulter, et al.	
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	Examiner Name	
	Attorney Docket Number	20191134-16

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	Filing Date	2022-11-23
	First Named Inventor	Xiaobo Wang
	Art Unit	
	Examiner Name	
	Attorney Docket Number	20191134-16

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	First Named Inventor	Xiaobo Wang
	Art Unit	
	Examiner Name	
	Attorney Docket Number	20191134-16

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	95	9612234	B2	2017-04-04	Li, et al.	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT		
	Application Number	17/993,716
	Filing Date	2022-11-23
	First Named Inventor	Xiaobo Wang
	Art Unit	
	Examiner Name	
	Attorney Docket Number	20191134-16

	97	9709548	B2	2017-07-18	Wang, et al.	
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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

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Name/Print	Raymond Wagenknecht	Registration Number	50948

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International Application Number:	
Confirmation Number:	1061
Title of Invention:	LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION
First Named Inventor/Applicant Name:	Xiaobo Wang
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Filer:	Raymond C. Wagenknecht
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Receipt Date:	25-NOV-2022
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronic Acknowledgement Receipt

EFS ID:	47090488
Application Number:	17993716
International Application Number:	
Confirmation Number:	1061
Title of Invention:	LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION
First Named Inventor/Applicant Name:	Xiaobo Wang
Customer Number:	22878
Filer:	Raymond C. Wagenknecht
Filer Authorized By:	
Attorney Docket Number:	20191134-16
Receipt Date:	25-NOV-2022
Filing Date:	
Time Stamp:	18:40:17
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronic Acknowledgement Receipt

EFS ID:	47090510
Application Number:	17993716
International Application Number:	
Confirmation Number:	1061
Title of Invention:	LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION
First Named Inventor/Applicant Name:	Xiaobo Wang
Customer Number:	22878
Filer:	Raymond C. Wagenknecht
Filer Authorized By:	
Attorney Docket Number:	20191134-16
Receipt Date:	25-NOV-2022
Filing Date:	
Time Stamp:	18:59:29
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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Information:					

51	Non Patent Literature	NPL141-Zimmermann.pdf	2059679 a8277b1b3d5e45302cab8200ceb34d7a90511171	no	8
Warnings:					
Information:					
52	Non Patent Literature	NPL125-Wang.pdf	311222 be3dccbd8d6bd1df6cfc50cabaf96d8d8014cfc3	no	13
Warnings:					
Information:					
		Total Files Size (in bytes):	52492242		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
17/993,716	11/23/2022		2820	20191134-16	30	3

CONFIRMATION NO. 1061

FILING RECEIPT



22878
Agilent Technologies, Inc.
Global IP Operations
5301 Stevens Creek Blvd, 1A-PB
Santa Clara, CA 95051

Date Mailed: 12/16/2022

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Xiaobo Wang, San Diego, CA;
Yama A. Abassi, San Diego, CA;
Biao Xi, San Diego, CA;
Wen Fu Zhang, San Diego, CA;
Xiao Xu, San Diego, CA;

Applicant(s)

Agilent Technologies, Inc., Santa Clara, CA;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 17/824,782 05/25/2022
which is a CON of 16/733,781 01/03/2020 PAT 11,360,072
which is a CON of 16/020,679 06/27/2018 PAT 10,533,985
which is a CON of 15/651,882 07/17/2017 PAT 10,012,636
which is a CON of 12/435,569 05/05/2009 PAT 9,709,548
which claims benefit of 61/191,684 09/11/2008
and claims benefit of 61/126,533 05/05/2008

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 12/13/2022

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 17/993,716**

Projected Publication Date: 03/23/2023

Non-Publication Request: No

Early Publication Request: No

Title

LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 17/993,716

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	320
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	700
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	800
TOTAL CLAIMS (37 CFR 1.16(i))	30 minus 20 =	* 10			OR	x 100 =	1000
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*				x =	0
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1820

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/993,716	11/23/2022	Xiaobo Wang	20191134-16	1061

22878 7590 01/23/2023

Agilent Technologies, Inc.
Global IP Operations
5301 Stevens Creek Blvd, 1A-PB
Santa Clara, CA 95051

EXAMINER	

ART UNIT	PAPER NUMBER
2858	

NOTIFICATION DATE	DELIVERY MODE
01/23/2023	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Agilentdocketing@cpaglobal.com
ipopsadmin@agilent.foundationip.com

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 17/993,716	**Applicant(s)** Wang et al.	
	Examiner CHERYL P GIBSON BAYLOR	**Art Unit** OPET	**AIA (FITF) Status** No

1. THE REQUEST FILED 23 November 2022 IS **GRANTED** .

The above-identified application has met the requirements for prioritized examination

A. ☑ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination**. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims** , or a multiple dependent claim;

C. filing a **request for continued examination** ;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to CHERYL GIBSON BAYLOR at (571)272-3213. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/CHERYL GIBSON BAYLOR/ Paralegal Specialist, OPET	

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/993,716	11/23/2022	Xiaobo Wang	20191134-16	1061

22878 7590 03/28/2023

Agilent Technologies, Inc.
Global IP Operations
5301 Stevens Creek Blvd, 1A-PB
Santa Clara, CA 95051

EXAMINER	
HE, AMY	

ART UNIT	PAPER NUMBER
2858	

NOTIFICATION DATE	DELIVERY MODE
03/28/2023	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Agilentdocketing@cpaglobal.com
ipopsadmin@agilent.foundationip.com

Office Action Summary	Application No. 17/993,716	Applicant(s) Wang et al.	
	Examiner AMY HE	Art Unit 2858	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-30 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-30 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 23 November 2022 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 11/25/2022

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A

web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

2. Claims 1-8, 13, 18-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 and 4 of U.S. Patent No. 9,709,548 (thereafter referred to as Patent '548) in view of Oka et al. "A new planar multielectrode array for extracellular recording: application to hippocampal acute slice", Journal of Neuroscience Methods, 1999, Vol. 93, 61-67.

As for claims 1, 18-19 and 24-25, Patent'548 discloses a system (see the system in claim 1, lines 3-26 of Patent '548) for monitoring cells, the system comprising:

a) a device for monitoring cell-substrate impedance (see the device in claim 1, lines 5-6), the device comprising a plurality of wells (see claim 1, line 10) on a nonconductive substrate (see claim 1, line 7), wherein each of the plurality of wells comprises an electrode array (see claim 1, lines 8-9) fabricated on the substrate for measurement of cell-substrate impedance;

b) an impedance analyzer (see the impedance analyzer in claim 1, lines 19-20) that measures cell-substrate impedance from the plurality of wells.

c) electronic circuitry (see the electronic circuitry in claim 1, lines 21-23), wherein the electronic circuitry electrically connects the electrode arrays to the impedance analyzer such that the electrode arrays are electrically monitored at millisecond time resolution, or that a time difference between two adjacent measurement is less than 500ms (see claim 1, lines 31-33); and

d) a software program (see the software program in claim 1, lines 24-25) that analyzes the measured cell-substrate impedance.

Still referring to claims 1, 18-19 and 24-25, Patent '548 does not specifically disclose that the electronic circuitry comprising multiple analogue-to-digital conversion channels to perform signal conversion in parallel across multiple wells.

Oka et al. discloses a system for monitoring cells, the system comprising electronic circuitry including multiple analogue-to-digital conversion channels to perform signal conversion in parallel across multiple wells (see the multiple AD-C channels as shown in Figs. 1 and 2; also see pages 62-64).

In view of Oka et al., a person of ordinary skill in the art would recognize that using a conventional multiple analogue-to-digital conversion channels to performs signal conversion in parallel across the multiple wells, as suggested in Oka et al., for the purpose of reducing the overall measurement time, would not make the current application patentably distinct from Patent' 548.

As for claims 2, 20 and 26, Oka et al. discloses wherein the multiple analogue-to-digital conversion channels are configured to convert analog electronic signals from multiple wells to digital signals simultaneously (see claim 4 of Patent '548).

As for claims 3, 21 and 27, Patent'548 in view of Oka et al. discloses wherein the electronic circuitry allows parallel analogue-to-digital (AD) conversion of impedance signals from multiple wells (by using the multiple AD-C channels as shown in Figs. 1 and 2; also see pages 62-64 of Oka et al.)

As for claims 4-5, 22-23, and 28-30, Patent'548 in view of Oka et al. discloses wherein the electronic circuitry performs signal conversion in parallel across multiple wells, wherein said parallel signal conversion allows for parallel signal processing and impedance calculation for measurements obtained from multiple wells (by using the multiple AD-C channels as shown in Figs. 1 and 2; also see pages 62-64 of Oka et al.).

As for claim 6, Patent'548 in view of Oka et al. discloses the system of claim 1, wherein the electronic circuitry is configured for monitoring cell-substrate impedance in a plurality of wells at approximately the same time (see claim 4 of Patent '548).

As for claim 7, Patent'548 in view of Oka et al. discloses the system of claim 1, wherein the electronic circuitry performs parallel analogue-to- digital (AD) conversion of impedance signals from multiple wells (by using the multiple AD-C channels as shown in Figs. 1 and 2; also see pages 62-64 of Oka et al.).

As for claim 8, Patent'548 in view of Oka et al. discloses the system of claim 1, wherein the electronic circuitry performs signal conversion, signal processing, and impedance calculation in parallel across multiple wells (see claim 4 of Patent '548).

As for claim 13, Patent'548 in view of Oka et al. discloses the system of claim 1, wherein the electronic circuitry is configured to measure with a time difference between two adjacent impedance measurements is less than 500 ms (see claim 1, lines 31-33 of Patent'548).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-13 and 16-30 are rejected under pre-AIA 35 U.S.C. 102(a)(1), 102(a)(2) as being anticipated by Oka et al. "A new planar multielectrode array for extracellular recording: application to hippocampal acute slice", Journal of Neuroscience Methods, 1999, Vol. 93, 61-67.

As for claims 1, 18-19 and 24-25, Oka et al. discloses a system (see the MED system in Fig. 2) for monitoring cells (i.e., the brain cells of rat), the system comprising:

a) a device (the MED probe in Fig. 1) for monitoring cell-substrate impedance (see page 62, section 2.1), the device comprising a plurality of wells (see the plurality of wells/microelectrodes in Fig. 1A) on a nonconductive substrate (glass plate in Fig. 1B), wherein each of the plurality of wells comprises an electrode array (see the 8 arrays of microelectrodes in Fig. 1A) fabricated on the substrate for measurement of cell-substrate impedance;

b) an impedance analyzer (the LCR meter for measuring the impedance; or the means for measuring impedance for coating effectiveness, see page 64, section 3.1; or the impedance analyzing means in the computer shown in Fig. 2) that measures cell-substrate impedance from the plurality of wells.

c) electronic circuitry comprising multiple analogue-to-digital conversion channels to perform signal conversion in parallel across multiple wells(see the multiple AD-C channels as shown in Fig. 2; also see page 63, section 2.2), wherein the electronic circuitry electrically connects the electrode arrays (electrode arrays in the MED probe) to the impedance analyzer such that the electrode arrays are electrically monitored at millisecond time resolution, or that a time difference between two adjacent measurement is less than 500ms (see Fig. 5B); and

d) a software program (see the software in the controlling unit in Fig. 2) that analyzes the measured cell-substrate impedance.

As for claims 2, 20 and 26, Oka et al. discloses wherein the multiple analogue-to-digital conversion channels are configured to convert analog electronic signals from multiple wells to digital signals simultaneously (see the multiple AD-C in Fig. 2; and section 2.2.4 on page 64).

As for claims 3, 21 and 27, Oka et al. discloses wherein the electronic circuitry allows parallel analogue-to- digital (AD) conversion of impedance signals from multiple wells (see the multiple channels of AD-C in Fig. 2; and section 2.2.4 on page 64).

As for claims 4-5, 22-23, and 28-30, Oka et al. discloses wherein the electronic circuitry performs signal conversion in parallel across multiple wells, wherein said parallel signal conversion allows for parallel signal processing and impedance calculation for measurements obtained from multiple wells (see the multiple AD-C used for analog to digital conversion in parallel as shown in Fig. 2; and section 2.2.4 on page 64).

As for claim 6, Oka et al. discloses the system of claim 1, wherein the electronic circuitry is configured for monitoring cell-substrate impedance in a plurality of wells at approximately the same time (i.e., monitoring simultaneously by using the multiple channels as shown in Fig. 2; and section 2.2.4 on page 64).

As for claim 7, Oka et al. discloses the system of claim 1, wherein the electronic circuitry performs parallel analogue-to- digital (AD) conversion of impedance signals from multiple wells (see the multiple AD-C used in Fig. 2; and section 2.2.4 on page 64).

As for claim 8, Oka et al. discloses the system of claim 1, wherein the electronic circuitry performs signal conversion, signal processing, and impedance calculation in parallel across multiple wells (see the multiple AD-C and amplifiers used in Fig. 2; and section 2.2.4 on page 64).

As for claim 9, Oka et al. discloses the system of claim 1, wherein the system comprises an electromechanical apparatus (8/64 switch box in Fig. 2) capable of interfacing a multiwell device MED probe) with one or more platforms (isolator and computer and software in Fig. 2).

As for claim 10, Oka et al. discloses the system of claim 9, wherein the one or more platforms of the electromechanical apparatus comprise an impedance platform and an optical platform (impedance analyzer and an optical display that may be within the computer in Fig. 1).

As for claim 11, Oka et al. discloses the system of claim 1, wherein the device for monitoring cell-substrate impedance comprising a two-piece structure wherein the nonconductive substrate (glass plate in Fig. 1B) is attached to a bottomless plate (conducting layer in Fig. 1B) to form a bottom surface of the wells.

As for claim 12, Oka et al. discloses the system of claim 1, wherein the substrate is suitable for cell attachment via a precoat comprising one or more compounds that improve attachment (i.e., the coating of the MED probe by polyethylenimine and serum, see page 65, the last paragraph).

As for claim 13, Oka et al. discloses the system of claim 1, wherein the electronic circuitry is configured to measure with a time difference between two adjacent impedance measurements is less than 500 ms (see Fig. 5B).

As for claim 16, Oka et al. discloses the system of claim 1, wherein the electrode array comprises electrical traces and connection pads (i.e., the connecting pad and wires/traces for connecting the MED probe to the impedance measuring device or the computer and software) configured to connect the electrode array to the impedance analyzer, wherein the electrical traces are covered with an insulating layer (e.g., the insulation layer in Fig. 1B).

As for claim 17, Oka et al. discloses the system of claim 1, wherein the electrode array comprises a plurality of electrode elements that are evenly spaced (see the evenly spaced microelectrode arrays shown in Fig. 1).

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 14 and 15 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Oka et al. “A new planar multielectrode array for extracellular recording: application to hippocampal acute slice”, Journal of Neuroscience Methods, 1999, Vol. 93, 61-67.

As for claims 14 and 15, Oka et al. discloses the system of claim 1 as discussed above.

Oka et al. does not specifically disclose wherein the measurement at millisecond time resolution is initiated by a change in an optical property, wherein the change in the optical property is determined by the device for optically monitoring the one or more wells.

It would have been obvious to a person of ordinary skill in the art, before the effective filing date of the claimed invention, to modify Oka et al., to disclose optically monitoring the wells and initiate the impedance measurement when there is a change in an optical property, for the purpose of optically controlling the on and off of the cell-substrate impedance measurement as maybe desirable in a specific application on hands.

Conclusion

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY HE whose telephone number is (571)272-2230. The examiner can normally be reached 9:00am--5:00pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Huy Phan can be reached on (571) 272-7924. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like

assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or

571-272-1000.

/AMY HE/
Primary Examiner, Art Unit 2858

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/993,716	Wang et al.
	Examiner	Art Unit
	AMY HE	2858

CPC - Searched*		
Symbol	Date	Examiner
G01N33/4836 OR G01N27/02 OR G01N33/4833 OR G01N33/48728 OR G01N33/5438	03/15/2023	AH

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
G01N33/4836 OR G01N27/02 OR G01N33/4833 OR G01N33/48728 OR G01N33/5438 COMBINED WITH TEXT SEARCH	03/15/2023	AH
PE2E TEXT SEARCH	03/15/2023	AH
similarity and more like search	03/15/2023	AH
references used in related applications checked	03/15/2023	AH
PE2E text search	03/22/2023	AH

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
G01N	33/4836; 33/4833; 33/48728; 33/5438; 27/02	03/22/2023	AH

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/993,716	Wang et al.
	Examiner	Art Unit
	AMY HE	2858

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/993,716	Wang et al.
	Examiner	Art Unit
	AMY HE	2858

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	03/22/2023								
	1	✓								
	2	✓								
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	29	✓								
	30	✓								

Bibliographic Data

Application No: 17/993,716

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☑ No ☐ Met After Allowance

Verified and Acknowledged: /AMY HE/ Examiner's Signature | Initials

Title: LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/23/2022	506	2858	20191134-16
RULE			

APPLICANTS

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Wen Fu Zhang, San Diego, CA,

Xiao Xu, San Diego, CA,

CONTINUING DATA

This application is a CON of 17824782 05/25/2022

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FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

12/13/2022

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FILING FEE RECEIVED

$7,160

INFORMATION DISCLOSURE STATEMENT BY APPLICANT		
	Application Number	17/993,716
	Filing Date	2022-11-23
	First Named Inventor	Xiaobo Wang
	Art Unit	2858
	Examiner Name	Amy He
	Attorney Docket Number	20191134-16

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	Attorney Docket Number	20191134-16

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]
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/A.H/	107	RICHARDS, KAREN L, et al. , "A Modified Microchamber Method For Chemotaxis And Chemokinesis" , Immunological Communications, Vol. 13, No. 1 , 1984 , 49-62	☐
/A.H/	108	RISHPON, J , et al. , "An Amperometric Enzyme-Channeling Immunosensor" , Biosensors & Bioelectronics, Vol. 12, No. 3 , 195-204 Date: 1997	☐
/A.H/	109	SATHAYE, ALOK , et al. , "Electrical Pacing Counteracts Intrinsic Shortening of Action Potential Duration of Neonatal Rat Ventricular Cells in Culture" , Journal of Molecular and Cellular Cardiology, Vol. 41 , 633-641 Date: 2006	☐
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT		
	Application Number	17/993,716
	Filing Date	2022-11-23
	First Named Inventor	Xiaobo Wang
	Art Unit	
	Examiner Name	
	Attorney Docket Number	20191134-16

/A.H/	112	SLAUGHTER, GYMAMA E, et al. , "Artificial Neural Network for Temporal Impedance Recognition of Neurotoxins" , 2006 International Joint Conference on Neural Networks , July 16-21, 2006 , 2001-2008	☐
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/A.H/	114	STEINEM, CLAUDIA , et al. , "Impedance and Shear Wave Resonance Analysis of Ligand-Receptor Interactions at Functionalized surfaces and of Cell Monolayers" , Biosensors & Bioelectronics, Vol. 12, No. 8 , 787-808 Date: 1997	☐
/A.H/	115	STENGER, DAVID A, et al. , "Detection Of Physiologically Active Compounds Using Cell-Based Biosensors" , Trends In Biotechnology; Vol. 19, No.8 , August 2001 , 304-309	☐
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/A.H/	117	TAKAHASHI, KAZUTOSHI , et al. , "Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors" , Cell, Vol. 131 , 861-872 Date: 2007	☐
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	Application Number	17/993,716
	Filing Date	2022-11-23
	First Named Inventor	Xiaobo Wang
	Art Unit	
	Examiner Name	
	Attorney Docket Number	20191134-16

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/A.H/	127	WARBURG, VON E , "Ueber Die Polarisationscapacitat Des Platins" , Annals of Physics, Vol. 6 , 1901 , 125-135	☐
/A.H/	128	WEGENER, JOACHIM , et al. , "Electric Cell-Substrate Impedance Sensing (ECIS) As A Noninvasive Means To Monitor The Kinetics Of Cell Spreading To Artificial Surfaces" , Experimental Cell Research, Vol. 259 , 158-166 Date: 2000	☐
/A.H/	129	WEGENER, JOACHIM , et al. , "Use Of Electrochemical Impedance Measurements To Monitor β-Adrenergic Stimulation Of Bovine Aortic Endothelial Cells" , European Journal Of Physiology, Vol. 437 , 925-934 Date: 1999	☐
/A.H/	130	WERLEY, CHRISTOPHER A, et al. , "Geometry-Dependent Functional Changes In iPSC-Derived Cardiomyocytes Probed By Functional Imaging And RNA Sequencing" , PLOS One, Vol. 12, No. 3;e0172671 , 3/23/2017 , 1-22	☐
/A.H/	131	WOLF, BERNHARD , et al. , "Monitoring Of Cellular Signalling And Metabolism With Modular Sensor-Technique: The PhysioControl-Microsystem (PCM)" , Biosensors and Bioelectronics, Vol. 13 , 501-509 Date: 1998	☐
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/A.H/	133	XIAO, CAIDE , et al. , "Assessment Of Cytotoxicity Using Electric Cell-Substrate Impedance Sensing: Concentration And Time Response Function Approach" , Analytical Chemistry, Vol. 74, No. 22 , 5748-5753 Date: 2002	☐
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	Filing Date	2022-11-23
	First Named Inventor	Xiaobo Wang
	Art Unit	
	Examiner Name	
	Attorney Docket Number	20191134-16

/A.H/	136	YAMAUCHI, FUMIO , et al. , "Spatially And Temporally Controlled Gene Transfer By Electroporation into Adherent Cells On Plasmid DNA-Loaded Electrodes" , Nucleic Acids Research, Vol. 32, No. 22 e187 , 1-8 Date: December, 2004	☐
/A.H/	137	YANG, JUN , et al. , "Cell Separation On Microfabricated Electrodes Using Dielectrophoretic/Gravitational Field-Flow Fractionation" , Analytical Chemistry, Vol. 71, No. 5 , 911-918 Date: 1999	☐
/A.H/	138	YANG, MO , et al. , "A Novel Microfluidic Impedance Assay for Monitoring Endothelin-Induced Cardiomyocyte Hypertrophy" , Biosensors and Bioelectronics, Vol. 22 , 1688-1693 Date: 2006	☐
	139	YANG, XIULAN , et al. , "Tri-iodo-L-Thyronine Promotes the Maturation of Human Cardiomyocytes-Derived from Induced Pluripotent Stem Cells" , Journal of Molecular Cell Cardiology, Vol. 72 , 296-304 No copy provided	☐
/A.H/	140	YU, NAICHEN , et al. , "Real-Time Monitoring of Morphological Changes in Living Cells by Electronic Cell Sensor Arrays: An approach To Study G Protein-Coupled Receptors" , Analytical Chemistry, Vol. 78, No.1 , 35-43 Date: 2006	☐
/A.H/	141	ZIMMERMANN, W H, et al. , "Tissue Engineering of a Differentiated Cardiac Muscle Construct" , Circulation Research, Vol. 90 , 2/8/2002 , 223-230	☐

EXAMINER SIGNATURE

Examiner Signature	/AMY HE/	Date Considered	03/16/2023

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.
[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	47	(Artificial Intelligence) Similar to: 17/993,716 with 0 CPC Selections and 0 Text Selections Text: (US-9709548-B2 OR US-20180306771-A1 OR US-10533985-B2 OR US-11360072-B2 OR US-20210164961-A1 OR US-20220291191-A1 OR WO-2009137440-A1 OR EP-2291645-A1 OR US-20100029506-A1 OR CA-2723223-A1 OR CA-2723223-C OR US-10012636-B2 OR US-20180095064-A1 OR EP-2291645-B1 OR US-20170205391-A1 OR US-9612234-B2 OR US-20110300569-A1 OR WO-2011146531-A9 OR WO-2011146531-A1 OR US-10761081-B2 OR WO-2017216694-A1 OR US-20180100849-A1 OR WO-2015196957-A1 OR US-20170151574-A1 OR JP-6119888-B2 OR EP-3159400-A1 OR CN-104789443-B OR US-20160305927-A1 OR JP-2017519524-A OR US-20090309618-A1 OR US-9404140-B1 OR CN-104789443-A OR US-9399787-B2 OR US-20160320365-A1 OR US-7876108-B2 OR US-20050213374-A1 OR US-20230014082-A1 OR US-20110117542-A1 OR US-8344742-B2 OR US-20130123136-A1 OR US-7560269-B2 OR CA-3187430-A1 OR WO-2021257705-A1	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO))	OR	ON	ON	2023/03/15 10:43 AM

		OR GB-2576429-A OR US-20100120626-A1 OR AU-2018224829-A1 OR CA-3053191-A1 OR WO-2018157073-A1 OR WO-2015068530-A1 OR JP-6370544-B2).did.					
L2	3	"9709548".pn.	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO))	OR	ON	ON	2023/03/15 11:37 AM
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L4	94	L1 L3	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO,	OR	ON	ON	2023/03/15 12:20 PM

			MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L5	4101327	(A$1D(Analog$2 near3 digital)) WITH conver$4	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/15 12:21 PM
L6	20	L4 AND L5	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/15 12:21 PM
L7	32	(Artificial Intelligence) More like doc: US-20100029506-A1 Text: (EP-2291645-A1 OR WO-2009137440-A1 OR CA-2723223-A1 OR US-9709548-B2 OR EP-2291645-B1 OR CA-2723223-C OR US-20180095064-A1 OR US-10012636-B2 OR US-10533985-B2 OR US-20180306771-A1 OR US-20220291191-A1 OR US-20210164961-A1 OR US-11360072-B2 OR	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/15 05:12 PM

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L9	619	((A$1D(Analog$2 near3 digital)) WITH conver$4) SAME (millisecond SAME impedance)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/15 05:19 PM
L10	726190	(measur$4 detect$3 sens$3 inspect$3 monitor$3 test$4 calculat$3 evaluat$3) WITH (cell membrane well) WITH (impedance parameter)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/15 05:21 PM
L11	95	L9 AND L10	(US-PGPUB; USPAT;	OR	ON	ON	2023/03/15

			USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				05:21 PM
L12	43365	(G01N33/4836 or G01N27/02 or G01N33/4833 or G01N33/48728 or G01N33/5438).cpc.	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/15 05:52 PM
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L18	2	"20220291191".pn.	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY,	OR	ON	ON	2023/03/22 01:44 PM

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L19	7	L17 L18	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/22 01:44 PM
L20	4	L19 AND optical	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/22 01:44 PM
L21	32	(Artificial Intelligence) More like doc: US-20100029506-A1 Text: (EP-2291645-A1 OR WO-2009137440-A1 OR CA-2723223-A1 OR US-9709548-B2 OR EP-2291645-B1 OR CA-2723223-C OR US-20180095064-A1 OR US-10012636-B2 OR	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK,	OR	ON	ON	2023/03/22 01:49 PM

		US-10533985-B2 OR US-20180306771-A1 OR US-20220291191-A1 OR US-20210164961-A1 OR US-11360072-B2 OR US-10539523-B2 OR EP-2291645-A4 OR US-20200158670-A1 OR US-20140203818-A1 OR US-10551371-B2 OR CA-2760941-C OR WO-2010129725-A1).did.	TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L22	35	(Artificial Intelligence) More like doc: US-10551371-B2 Text: (US-20110039294-A1 OR US-20200278339-A1 OR WO-2010129725-A1 OR EP-2427543-A1 OR CA-2760941-A1 OR CA-2760941-C OR WO-2014085727-A1 OR US-10539523-B2 OR WO-2009137440-A1 OR EP-2291645-A1 OR CA-2723223-A1 OR US-20140203818-A1 OR US-20100029506-A1 OR US-20200158670-A1 OR EP-2291645-B1 OR US-10533985-B2 OR US-20180306771-A1 OR CA-2723223-C OR US-9709548-B2 OR US-10012636-B2).did.	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/22 01:49 PM
L23	41	L21 L22	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/22 01:49 PM
L24	18	L23 AND optical	(US-PGPUB; USPAT;	OR	ON	ON	2023/03/22

			USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				01:49 PM
L25	43427	(G01N33/4836 or G01N27/02 or G01N33/4833 or G01N33/48728 or G01N33/5438).cpc.	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/22 01:52 PM
L26	1890658	(measur$4 detect$3 sens$3 inspect$3 monitor$3 test$4 calculat$3 evaluat$3) WITH (cell membrane well) WITH (impedance resistance capacitance voltage current)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/22 01:54 PM
L27	7949	L25 AND L26	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL,	OR	ON	ON	2023/03/22 01:55 PM

			PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L28	1961	L27 AND (optical WITH (cell well))	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/22 01:55 PM
L29	84	L27 AND (optical WITH (cell well) WITH (initiat$3 start$3))	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/22 01:55 PM
L30	47	(Artificial Intelligence) Similar to: 17/993,716 with 0 CPC Selections and 0 Text Selections Text: (US-9709548-B2 OR US-20180306771-A1 OR US-10533985-B2 OR US-11360072-B2 OR US-20210164961-A1 OR US-20220291191-A1 OR EP-2291645-A1 OR WO-2009137440-A1 OR US-20100029506-A1 OR CA-2723223-A1 OR CA-2723223-C OR US-10012636-B2 OR	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO))	OR	ON	ON	2023/03/22 02:07 PM

		US-20180095064-A1 OR EP-2291645-B1 OR US-20170205391-A1 OR US-9612234-B2 OR US-20110300569-A1 OR WO-2011146531-A9 OR WO-2011146531-A1 OR US-10761081-B2 OR WO-2017216694-A1 OR US-20180100849-A1 OR WO-2015196957-A1 OR US-20170151574-A1 OR JP-6119888-B2 OR EP-3159400-A1 OR CN-104789443-B OR US-20160305927-A1 OR JP-2017519524-A OR US-10107792-B2 OR US-20090309618-A1 OR US-9404140-B1 OR CN-104789443-A OR US-9399787-B2 OR US-20160320365-A1 OR US-7876108-B2 OR US-20050213374-A1 OR JP-2016212083-A OR US-20230014082-A1 OR US-20110117542-A1 OR US-8344742-B2 OR US-20130123136-A1 OR US-7560269-B2 OR CA-3187430-A1 OR WO-2021257705-A1 OR GB-2576429-A OR US-20100120626-A1 OR AU-2018224829-A1 OR CA-3053191-A1 OR WO-2018157073-A1).did.					
L31	43	(Artificial Intelligence) Similar to: 17/993,716 with 0 CPC Selections and 2 Text Selections Text: (CA-2723223-C OR US-20100029506-A1 OR EP-2291645-A1 OR US-9709548-B2 OR CA-2723223-A1 OR EP-2291645-B1 OR WO-2009137440-A1 OR US-10533985-B2 OR US-20180306771-	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO))	OR	ON	ON	2023/03/22 02:08 PM

		A1 OR US-20220291191-A1 OR US-20180095064-A1 OR US-20210164961-A1 OR US-10012636-B2 OR US-11360072-B2 OR US-9612234-B2 OR WO-2011146531-A9 OR US-20110300569-A1 OR WO-2011146531-A1 OR US-20050095578-A1 OR US-20070269875-A1 OR WO-2005044367-A2 OR WO-2020185817-A1 OR CA-3148918-A1 OR EP-3938530-A1 OR AU-2020237460-A1 OR US-9360468-B2 OR US-20160245787-A1 OR US-20170205391-A1 OR US-8697431-B2 OR US-10551371-B2 OR EP-3173769-A1 OR JP-2022180500-A OR US-20120043969-A1 OR EP-2429395-A1 OR US-20100227385-A1 OR US-20070238165-A1 OR US-7638321-B2 OR US-10539523-B2 OR US-20220026364-A1 OR EP-3568677-A1 OR WO-2018132487-A1 OR US-11041806-B2 OR US-20190346368-A1 OR JP-2020509391-A OR JP-2022525087-A OR DE-102016225817-A1 OR CA-2491166-A1 OR ES-2273868-T3 OR DE-60123797-T2 OR US-20200347337-A1).did.					
L32	41	L31 AND optical	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH,	OR	ON	ON	2023/03/22 02:08 PM

			TN, TR, TW, UA, VN, WO))				
L33	5	((US-10551371-B2 OR US-9709548-B2).did. AND USPT.dbnm.) OR ((US-20100029506-A1).did. AND PGPB.dbnm.) OR ((AU-2002365810-A1 OR EP-0566725-B1).did. AND FTDB.dbnm.)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/22 02:14 PM
L34	3	L33 AND optical AND initiat$3	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/22 02:15 PM
L35	460961	(optical microscope) WITH (measur$4 detect$3 sens$3 determin$4 evaluat$3 monitor$3 test$3) WITH (cell cardiomyocyte beating)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/22 02:22 PM
L36	1142	((optical microscope) WITH (measur$4 detect$3 sens$3 determin$4 evaluat$3 monitor$3 test$3) WITH ((cell cardiomyocyte) AND	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS,	OR	ON	ON	2023/03/22 02:22 PM

		beating))	IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L37	59	((optical microscope) WITH (measur$4 detect$3 sens$3 determin$4 evaluat$3 monitor$3 test$3) WITH ((cell cardiomyocyte) AND beating)).clm.	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/22 02:22 PM

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N1	7478	(G01N33/4836 OR G01N27/02 OR G01N33/4833 OR G01N33/48728 OR G01N33/5438).cpc.	(US-PGPUB; USPAT)	OR	ON	ON	2023/03/22 02:32 PM
N2	182608	(measur$4 detect$3 sens$3 inspect$3 monitor$3 test$4 calculat$3 evaluat$3) WITH (cell membrane well) WITH (impedance parameter)	(US-PGPUB; USPAT)	OR	ON	ON	2023/03/22 02:32 PM
N3	937	N1 AND N2 AND optical	(US-PGPUB; USPAT)	OR	ON	ON	2023/03/22 02:32 PM

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/993,716	11/23/2022	Xiaobo Wang	20191134-16

CONFIRMATION NO. 1061

PUBLICATION NOTICE

22878
Agilent Technologies, Inc.
Global IP Operations
5301 Stevens Creek Blvd, 1A-PB
Santa Clara, CA 95051

OC000000137823234

Title:LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

Publication No.US-2023-0130050-A1
Publication Date:04/27/2023

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/993,716	11/23/2022	Xiaobo Wang	20191134-16	1061

22878 7590 05/08/2023

Agilent Technologies, Inc.
Global IP Operations
5301 Stevens Creek Blvd, 1A-PB
Santa Clara, CA 95051

EXAMINER	
HE, AMY	

ART UNIT	PAPER NUMBER
2858	

NOTIFICATION DATE	DELIVERY MODE
05/08/2023	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Agilentdocketing@cpaglobal.com
ipopsadmin@agilent.foundationip.com

Applicant-Initiated Interview Summary	**Application No.** 17/993,716	**Applicant(s)** Wang et al.		
	Examiner AMY HE	**Art Unit** 2858	**AIA (First Inventor to File) Status** No	**Page** 1 of 2

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
AMY HE	Examiner	Telephonic
Robert Kramer	Attorney	
Ray Wagenknecht	Attorney	

Date of Interview: 03 May 2023

Issues Discussed:

35 U.S.C. 102

The 102 rejection of claims 1-13 and 16-30 in view of Oka reference were discussed. Applicant's representatives argue that:1) Oka et al. discloses extracellular recording and extracellular field potential measurement, not an impedance measurement at the cell-electrode substrate; 2) the LCR meter is used for testing the MED probe and is not included in the device in Fig. 2; and 3) the Oka device shows a probe with a single electrode array of electrodes, not a multiwell device.
In response, the examiner believes that: 1) Oka et al. does disclose an impedance analyzer for monitoring the impedance of the each 64 microelectrodes with or without the cell attachment (see section 2.1). In addition, an impedance can always be calculated from the measured voltages/current in response to a stimulating signal of current/voltage (see 2.2.1). And the current specification and drawings do not show the specific structure/device used for the impedance measurement/analyzer; and 2) a system, not an apparatus is claimed in the current application. The system can be considered to include the LCR meter for measuring the impedance; and 3) the structure of MED probe including the 64 microelectrodes in Fig. 1 of Oka can be considered as the multiwell device, in which each row of microelectrodes is considered as one array of microelectrodes array.
No agreement was reached.

Non-statutory Double Patenting

The double patent rejection still applies since in view of Oka et al. reference, the addition of an ADC for signal conversion and signal processing does not make the current application patentably distinct from the cited Patent '548.

/AMY HE/ Primary Examiner, Art Unit 2858	

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant-Initiated Interview Summary	**Application No.** 17/993,716	**Applicant(s)** Wang et al.		
	Examiner AMY HE	**Art Unit** 2858	**AIA (First Inventor to File) Status** No	**Page** **2 of 2**

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 17/993,716	Filing Date 11/23/2022	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $480 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	06/23/2023	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 30	Minus	** 30	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	*** 3	= 0		x $480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/TERRANCE R LAWRENCE/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

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PTO/AIA/82A (07-13)
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NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	17/993,716
Filing Date	November 23, 2022
First Named Inventor	Xiaobo Wang et al.
Title	LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION
Art Unit	2858
Examiner Name	AMY HE
Attorney Docket Number	20191134-16 (A2185-9003)

SIGNATURE of Applicant or Patent Practitioner

Signature	/William Fortunato/	Date (Optional)	June 23, 2023
Name	William Fortunato	Registration Number	76,212
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of 2 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 03/31/2021. OMB 0651-0035
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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 188545

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

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☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Agilent Technologies, Inc.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	/Jasbir Sagoo/	Date (Optional)	Nov 23, 2022
Name	Jasbir Sagoo		
Title	Associate Vice President of IP, LSAG, Agilent Technologies, Inc.		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ Total of 2 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Electronic Patent Application Fee Transmittal

Application Number:	17993716
Filing Date:	23-Nov-2022
Title of Invention:	LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION
First Named Inventor/Applicant Name:	Xiaobo Wang
Filer:	William Fortunato/Brynn Kooyenga
Attorney Docket Number:	20191134-16

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	1202	10	100	1000
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1000**

Electronic Acknowledgement Receipt

EFS ID:	48199715
Application Number:	17993716
International Application Number:	
Confirmation Number:	1061
Title of Invention:	LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION
First Named Inventor/Applicant Name:	Xiaobo Wang
Customer Number:	22878
Filer:	William Fortunato/US Patent Mail
Filer Authorized By:	William Fortunato
Attorney Docket Number:	20191134-16
Receipt Date:	23-JUN-2023
Filing Date:	23-NOV-2022
Time Stamp:	17:06:12
Application Type:	Utility under 35 USC 111(a)

Payment information:

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Payment was successfully received in RAM	$1000
RAM confirmation Number	E20236MH06358204
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37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.16 (National application filing, search, and examination fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment/Request for Reconsideration-After Non-Final Rejection	20191134-16_Amendment_and_Response_to_NFOA.pdf	369114 560ce9705b79be2206fff9b24d4361888ffe06c3	no	29
Warnings:					
Information:					
2	Power of Attorney	20191134-16_POA.pdf	201739 6943447fa9012e6ef42657d72f7104930d1d47eb	no	2
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	38035 9d920a4755f129da13992c1ef7d217d918e2ba5e	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	608888		

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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: June 23, 2023
Electronic Signature for William Fortunato: / William Fortunato /

Docket No.: 20191134-16 (A2185-9003)
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Xiaobo Wang et al.

Application No.: 17/993,716 Confirmation No.: 1061

Filed: November 23, 2022 Art Unit: 2858

For: LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

Examiner: AMY HE

AMENDMENT AND RESPONSE TO NON-FINAL OFFICE ACTION

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

RESPONSE TO NON-FINAL OFFICE ACTION

In response to the Non-Final Office Action dated March 28, 2023, please enter the following amendments and consider the following remarks.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims begin on page 12 of this paper.

Remarks begin on page 19 of this paper.

Amendments to the Specification

Please replace ¶¶ [00115], [00145], [00154], and [00163] of the Specification as filed with the following amended ¶¶ [00115], [00145], [00154], and [00163].

[00115] A number of improvements in the impedance measurement circuitry, electronic switching circuitry, communication between impedance measurement circuitry and software can be used to achieve such millisecond time resolution. For instance, improvement likely requires the use of fast processing electronic chips for analogue-to-digital conversion, for parallel digital signal processing and data calculation with field-programmable gate array (FPGA) and for fast communication between the impedance measurement circuitry and software. Another example of improvements includes the use of multiple analogue-to-digital (AD) conversion channels so that analog electronic signals from multiple channels can be converted to digital signals simultaneously. Such parallel AD conversion is important, particular for the system having multiple wells, each of which's measurement time resolution is required to be in the millisecond resolution. And, a very important improvement is to replace previous working mode of "measurement of one-well's impedance at a time" with a mode of "measurement of multiple-wells' impedances at a time". In "one-well at a time" mode, when the software ~~issue~~ issues a command for measuring one well's impedance, the measurement circuitry would perform the measurement for one well including signal generation to the well, converting the voltage signal and the electric current signal for the well to digital signal, digitally processing the signals to do impedance calculation and sending the well's impedance data to the computer over the communication line between the impedance measurement circuitry and the computer. The system will not perform any measurement for another well until ~~the completion of~~ completing the measurement of this well and until receiving another command for the measurement of another well. In "multiple wells at a time" mode, the software would issue a command for measuring multiple wells' impedances. The measurement circuitry would simultaneously or nearly simultaneously perform signal conversion, signal processing and impedance calculation for multiple wells. The multiple impedance data for the multiple wells would be sent over the communication lines to the computer sequentially with one well's data at the same time or simultaneously with more than one well's data being sent at a

time. In this "measurement of multiple-wells' impedances at a time" mode, the system may be performing multiple tasks simultaneously, for example, while one well's impedance data is being measured and calculated, another well's impedance data may be communicated and sent over the communication lines to the computer.

[00145] Certain cardiotoxic drugs can ~~illicit~~ elicit their effect by affecting the morphological aspects of cardiomyocyte morphology. For example, it is well known that compounds such as β-2 adrenergic receptor agonists can induce morphological changes resulting in an elongated cardiomyocyte morphology, otherwise known as hypertrophy. Morphological changes can occur immediately in the order of minutes as with certain GPCR agonists or can be of longer duration detectable over several days. The time resolution of the impedance-based system can be used to distinguish between different kinds of morphological effects. The steps involved in using an impedance-monitoring system for measurement of morphological modulation of cardiomyocytes may include: optionally coating E-PLATES with either fibronectin or other matrix proteins; seeding either embryonic stem cells (ES cells) of mammalian origin, mammalian adult stem cell derived cardiomyocytes or primary cardiomyocytes isolated directly from mammalian heart tissue at specific seeding densities to the wells of the device; allowing the cells to attach and spread; monitoring cardiomyocyte viability over time using the impedance monitoring system at prespecified intervals of time for 12, 24, 48, 72 hours or longer; at certain times after cell seeding, treat the cell with agents that may cause morphology changes at one or more concentration; using the vehicle that the agent is dissolved in as a control; continuing to monitoring the cardiomyocytes at 1 minute intervals for at least 1-2 hours to capture any immediate morphological changes and continue to monitor at 30 minutes intervals of time for additional 12, 24, 48, 72 hours or longer to detect long term morphological changes; and quantifying the extent of morphological change by normalizing the cell index values immediately prior to agent addition and determine the normalized cell index at a given time point after agent addition. The extent of morphological change can be expressed as EC-50 value which quantifies the activity of the agent with respect to the cardiomyocyte shape changes.

[00154] [[On]] One skilled in the art will recognize that any agent may be tested. The agent may be a biologically active agent. Exemplary test agents include compounds, drugs, peptides, proteins, antibodies, antibody fragments, siRNA, shRNA, miRNA, cDNA, lipids and any combination thereof. Optionally, impedance-based curves or optionally cell index curves are used to calculate average rate of beats of cardiomyocytes per unit time, average amplitude intensity in a unit time as well as the average length of time between beats, comparison of these optionally derived parameters is made between the test well and the control well, and if significant differences exist, one may optionally conclude that the test agent modulates cardiomyocyte functions.

[00163] In another aspect, the present invention is directed to method to establish an assay to assess the effect of gene knockout or transgene expression in ES cells differentiated to cardiomyocytes and functionally monitored by the impedance based system. The method includes providing a device for measuring cell-substrate impedance operably connected to an impedance analyzer, wherein the device includes at least two wells; adding wildtype ES cells as control to at least ~~1well~~ one well and ES cells with a gene knockout or a transgene in at least [[1]] one other well; monitoring impedance of the at least two wells at time intervals over a period of time and optionally determining cell indices from impedance values; comparing the impedance-based curves or optionally the cell index curves between the control well and the well containing the ES cells harboring a knockout of a specific gene or expressing a specific transgene; and if significantly different, concluding that the gene knockout or the transgene can affect either cardiomyocyte viability, morphology from ES cells or cardiomyocyte function as monitored by observing the excitation-contraction coupling.

Please replace the section header appearing on lines 20-21 of page 60, between ¶¶ [00167] and [00168], with the following amended section header.

Example 2
Detection of Cardiotoxic Effects Using Real [[Tim]] Time Impedance Monitoring

Please replace ¶¶ [00169], [00178-79], and [00182-83] of the Specification as filed with the following amended ¶¶ [00169], [00178-79], and [00182-83].

[00169] Mouse ES-derived cardiomyocytes were seeded at a density of 25,000 cells per well in E-PLATES precoated with fibronectin. The attachment and growth of cells were monitored on RT-CES system for 72 hours and then treated with increasing doses of the compound of sodium dichromate dehydrate which is known to induce cytotoxicity. According to FIG. 4A the plot of normalized cell index for cells in different wells treated with different concentrations of sodium dichromate dehydrate ~~(SDD),~~ (SDD). SDD causes a concentration dependent decrease in viability of ES-derived cardiomyocytes. To quantify the extent of sodium dichromate dehydrate activity against the cardiomyocytes, the normalized cell indices at 24 [[hrs]] hours after compound treatment were plotted against the log of the corresponding sodium dichromate dehydrate concentrations. From the sigmoidal curve, shown in FIG. 4B, half maximal activity or IC-50 value of 1.48 [[uM]] μM was derived for the compound.

[00178] Another method for deriving the beating rates of cardiomyocytes is to first determine the time length (ΔT in seconds) between two consecutive peaks and then calculate the beating rate according to the formula of "beats per minute =60/ ΔT". Thus for each two-consecutive peaks, one can calculate one beating rate. Furthermore, one can plot this beating rate as a function of the time (of the first of the two consecutive peaks) to obtain the time dependency of the beating rates. FIG. 9A shows an example of the time-dependent beat rates derived using this method, for mouse ES-derived cardiomyocytes treated with compound sotalol at a concentration of 4.4 [[uM.]] μM. Corresponding cell index data is shown in FIGS. 9C and 9D, where the time resolution between two adjacent points is 40 milliseconds. In other words, a second in FIGS. 9C and 9D is equivalent to 40 milliseconds. ~~40-milliseconds.~~

[00179] For deriving the amplitude of the beating of the cardiomyocytes, there may also be different methods. One method is to analyze each peak and ~~finding~~ to find the peak maximum and the peak minimum. The amplitude is calculated by subtracting peak maximum by the peak minimum. Then, one can plot the peak amplitude as a function of the time of the peak to obtain the time dependency of the peak amplitude. FIG. 9B shows an example of the time-dependent peak amplitudes derived using this method, for mouse ES-derived cardiomyocytes treated with

compound sotalol at a concentration of 4.4 [[uM.]] μM. Another approach may also be to use Fourier transform as described above. Then based on derived Fourier coefficients, one can re-simulate time domain cell index curves and look for the peak magnitude from the simulated curves.

[00182] Similar to Example 4, the millisecond kinetic readout requires that the impedance measurement system can provide impedance measurement data at millisecond time resolution. In other words, the time difference between two consecutive impedance measurement for a well shall be in the range of milliseconds (e.g., less than 500 millisecond, less than 300 millisecond, less than 100 millisecond, less than 10 millisecond, or less than 1 millisecond or faster). The millisecond kinetic readout is required to resolve the individual beat cycles of the cells. Thus, the time resolution for the impedance measurement should allow the system to perform measurement at at least two time points for each beat cycle, or at more than two points for each beat cycle.

[00183] In order to demonstrate the utility of the millisecond kinetic impedance-measurements, we first used two pharmacological agents, one known to suppress the heart rate and consequently cardiomyocyte beating and the other known to increase the heart rate and consequently the rate of cardiomyocyte beating. As Mouse ES cells were seeded in FN-coated E-PLATES and monitored for about 72 hours when the cells differentiated into beating cardiomyocytes, as described in Section 4. A baseline of the cardiomyocyte was taken for approximately 40 seconds using the specially designed fast kinetic data acquisition hardware and software which is capable of millisecond data acquisition and display. An agonist of muscarinic receptors, carbachol, which is known to slow down the heart rate was added to one well at a final concentration of 333 nM and cardiomyocyte beating was monitored for 10 minutes (FIG. 10A). The data clearly shows that carbachol significantly slows down the rate of cardiomyocyte beating from ~ 80 beats/min prior to carbachol addition to ~ 60 beats/min after carbachol addition (Table I). Alternatively, addition of isoproteranol at a final concentration of 4.4 [[uM]] μM significantly increased the rate of cardiomyocyte beating from ~ 65 beats/min to 115-135 beats/min (FIG. 10B and Table I). These data clearly show that the readout system and the fast kinetic software are sufficiently robust and sensitive to detect these changes in rate of cardiomyocyte beating even at very low compound concentrations. Similar to the cell index plot shown in FIGS. 9C and 9D, the

time resolution between two adjacent points in FIGS. 10A and 10B is 40 milliseconds. In other words, a second in FIGS. 10A and 10B is equivalent to 40 millisecond.

Please replace Table I appearing on page 60, after ¶¶ [00183], with the following amended Table I.

Table I.

Compound	Mechanism	Concentration	Beat Rate	Amplitude	Pattern Change
Carbachol	Muscamic receptor agonist	333 nM	From ~80 to ~60	From 0.07 to 0.06	Beating rate decreased
Isoproteranol	[[b2]] β2 Adrenergic receptor agonist	4.4 [[uM]] μM	From ~65 to 115-136	From 0.19 to 0.16	Beating rate increased

Please replace Table II appearing on page 68 with the following amended Table II.

Table II

Compound	Mechanism	Concentration	Beat Rate	Amplitude	Pattern Change
Astemizole	anti-histamine	400 nM	0	<0.01	From 68-72 bpm to irregular being to beating stopped
Terfenadine	anti-histamine	200 nM	0	<0.01	From 71-78 bpm to irregular beating to beating stopped

Erythromycin	anti-biotic	13.3 [[uM]] μM	From ~ 60 to ~ 80	0.09 to 0.07	No pattern change
Moxifloxacin	anti-biotic	20 [[uM]] μM	From ~ 80 to ~73	From 0.055 to 0.060	No pattern change
Pentamidine	anti-infective	20 [[uM]] μM	From 71~78 to ~71	From 0.24 to 0.21	No pattern change
Amitriptyline	Serotonergic Inhibitor	4.4 [[uM]] μM	From ~70 to ~ 90	From 0.22 to 0.17	No pattern change
Verpamil	Ca channel blocker	130 nM	From ~ 65 to 0	From 0.13 to 0.06	From ~ 65 bpm to only occasional single beating.
Rosglitazone	PPAR agonist	13.3 [[uM]] μM	From ~79 to ~ 75	From 0.22 to 0.17	No pattern change
Dofitlite		500 nM	From ~ 80 to ~ 180	From 0.09 to 0.02	Pattern changed, much faster
Rofecoxib	COX-2 Inhibitor	13.3 [[uM]] μM	From ~ 68 to ~ 60	From 0.2 to 0.19	No pattern change
Rofecoxib	COX-2 Inhibitor	40 [[uM]] μM	From ~ 62 to ~ 60	From 0.16 to 0.10	Pattern change, no beating after initial treatment, then recovers
Celecoxib	COX-2 Inhibitor	4.4 [[uM]] μM	From ~ 60 to (~20 - ~ 50)	From ~0.2 to ~0.12	Pattern change
Doxirubicin	Anthracycline	40 [[uM]] μM	~ 70	~ 0.16	No pattern change (initially). Beating

					pattern changes after 2 hrs.
Cyclosporin A	Calcineurin inhibitor	13.3 [[uM]] μM	From ~70 to ~ 80	From 0.18 to 0.15	No pattern change
Propalanol	β2-adrenergic receptor antagonist	4.4 [[uM]] μM	From ~70 to over 150	From 0.25 to 0.025	Pattern changed, much faster and irregular
Sotalol		13.3 [[uM]] μM	From ~ 80 to ~ 160	From 0.27 to 0.07	Much faster, pattern changed
E4031	K channel inhibitor	120 nM	From 80 to 160	From 0.09 to 0.03	Pattern changed, much faster
DDT	Pesticide	8 [[uM]] μM	From 80 to 140, then to ~ 80	From 0.25 to 0.02	Initially become faster, later irregular beating
PCB	Organic toxicant	8 [[uM]] μM	From ~ 65 to [[o]] 0	From 0.2 to 0	Beating stopped
Endosulfan	insecticide	8 [[uM]] μM	From ~ 75 to [[o]] 0	From 0.2 to 0	Beating stopped

Please replace ¶¶ [00186-88] of the Specification as filed with the following amended ¶¶ [00186-88].

[00186] To further demonstrate the capabilities of the fast impedance measurement- system-based monitoring of cardiomyocyte beating in detecting drugs which may adversely affect heart function, compounds at different concentrations were tested to demonstrate the dose-dependent effects of these compounds on cardiomyocytes. Approximately, 72 hours after cell seeding the impedance-measurement system with millisecond time resolution was used to establish a baseline reading of cardiomyocyte beating for each well for about 40 seconds. Subsequently, the cells in each well were treated with drugs at different dose concentrations. FIG. 13 shows an example of dose dependent effects of Astemizole on cardiomyocytes beating at different concentrations. At

high concentration of 400 nM, Astemizole had such a strong effect on the beating of cardiomyocytes that the beating almost stopped. The effect of Astemizole on the beating of the cardiomyocytes is clearly ~~does-dependent.~~ dose-dependent. At low concentration of 40 pM, its effect on the beating of the cardiomyocytes is small enough that the cardiomyocyte beating rate was not affected. Similar to the cell index plot shown in FIGS. 9C and 9D, the time resolution between two adjacent points in all the figures in FIGS. 11A-11T is 40 milliseconds. In other words, a second in FIG. 13 is equivalent to 40 milliseconds.

[00187] To further demonstrate the capabilities of the improved impedance measurement system for monitoring of cardiomyocyte beating in detecting drugs which may adversely affect heart function, ~~500nM~~ 500 nM Haloperidol was tested to demonstrate its time-dependent effects on cardiomyocytes. Approximately, 72 hours after cell seeding the improved impedance system was used to establish a baseline reading of cardiomyocyte beating for each well for about 16 seconds (FIG. 14A). Note that in FIG. 14A, each minute ~~showed~~ shown on the x-axis of FIG. 14A corresponds to one second in real measurement. Subsequently, the cells in the well treated with 500 nM Haloperidol. FIGS. ~~14B, C, D, E, F, G and H~~ 14B-H show the impedance-based monitoring of beating of the cardiomyocytes at time points of first 30 seconds, about 1 minute, about 2 minutes, about 4 minutes, about 5.5 minutes, about 1 hour and about 21 hours after the compound treatment. In FIGS. 14B through 14H, each minute ~~showed~~ shown on the x-axis corresponds to one second in real measurement. It is clear that within 1 hr of compound treatment, the cardiomyocytes exhibit significant, time-dependent change in their impedance responses. Even at ~ 21 hrs after compound treatment, the impedance pattern did not restore and the beating frequency (50 ~ 60 beats per minute) appeared to become about half of that before compound treatment (90 ~ 100 beats per minute before treatment). Yet the amplitude of the impedance response spikes nearly doubled compared with that before compound treatment. FIGS. 15A-H and FIGS. 16A-H show the analysis results of the impedance beating pattern of FIGS. 14A-H in terms of the beating frequency (beats per minute) and the beating ~~magnitude~~ magnitude. For FIGS. 15A-H and FIG. 16A-H, each unit (1) on the x-axis corresponds to 0.016 second (16 milliseconds) in real measurement.

[00188] To further demonstrate the capabilities of the improved impedance measurement system for monitoring of cardiomyocyte beating in detecting drugs which may adversely affect heart ~~function,300 uM~~ function, 300 μM erythromycin was tested to demonstrate its time-dependent effects on cardiomyocytes. Approximately, 72 hours after cell seeding the improved impedance system was used to establish a baseline reading of cardiomyocyte beating for each well for about 15 seconds (FIG. 17A). Note that in FIG. 17A, each minute ~~showed~~ shown on the x-axis of FIG. 17A corresponds to one second in real measurement. Subsequently, the cells in the well treated with 300 [[uM]] μM erythromycin. FIGS. 17B-I show the impedance-based monitoring of beating of the cardiomyocytes at time points of first 30 seconds, about 1 minute, about 2 minutes, about 4 minutes, about 5.5 minutes, about 1 hour, about [[3hr]] 3 hours and about 21 hours after the compound treatment. In FIGS. 17B-H, each minute ~~showed~~ shown on the x-axis corresponds to one second in real measurement. It is clear that within 3 [[hr]] hours of compound treatment, the cardiomyocytes exhibit significant, time-dependent change in their impedance responses. For example, at about 1 hr after the treatment, the frequency of the impedance-based beating spikes is much higher than that for the cardiomyocytes before treatment, yet the magnitude is much smaller. On the other hand, at about 3 [[hr]] hours after treatment, the impedance-based beating pattern becomes rather irregular whilst the magnitude of the beating pattern has somewhat restored. Still, even at ~ 21 hrs after compound treatment, the impedance pattern did not restore and the beating frequency appeared to be about 70% (at 50 ~ 60 beats per minute) of that before compound treatment (at 80 ~ 90 beats per minute). Yet the amplitude of the impedance response spikes increased by about 50% compared with that before compound treatment. FIGS. 18A-I and FIGS. 19A-I show the analysis results of the impedance beating pattern of FIGS. 17A-I in terms of the beating frequency (beats per minute) and the beating magnitude. For FIGS. 18A-I and FIGS. 19A-I, each unit (1) on the x-axis corresponds to 0.016 ~~second~~ seconds (16 milli-seconds) in real measurement.

Amendments to the Claims

The following listing of claims in intended to replace all prior listings of claims.

CLAIMS

What is claimed is:

1. (Currently Amended) ~~A system~~ An apparatus for continuous, label free, real-time monitoring of cells[[,]] using impedance-based analysis, the ~~system~~ apparatus comprising:

a) a ~~device for monitoring cell-substrate impedance, the device~~ multiwell plate comprising a plurality of wells on a nonconductive substrate, wherein each of the plurality of wells comprises an electrode array of a plurality of electrode arrays that is disposed on the nonconductive substrate; ~~substrate for measurement of cell-substrate impedance;~~

b) an impedance analyzer that independently measures a cell-substrate impedance at each well, the cell-substrate impedance being measured between a first electrode structure and a second electrode structure of the electrode array and across a cellular sample comprising a plurality of cells disposed within each well, the impedance analyzer including ~~cell-substrate impedance from the plurality of wells.~~

~~c) electronic circuitry comprising multiple~~ at least two analogue-to-digital conversion channels[[,]] coupled to the plurality of electrode arrays, wherein ~~the electronic circuitry electrically connects the electrode arrays to~~ the impedance analyzer ~~such that the electrode arrays are electrically monitored~~ monitors the electrode arrays at millisecond time resolution[[;]] between first measurements of the cell-substrate impedance and second measurements of the cell-substrate impedance for each well; and

[[d)]] c) a software program that analyzes the first measurements and the second measurements to produce a time period analysis of the cellular sample. ~~the measured cell-substrate impedance.~~

2. (Currently Amended) The ~~system~~ apparatus of claim 1, wherein the ~~multiple~~ plurality of analogue-to-digital conversion channels are configured to simultaneously convert analog

electronic signals from multiple individual wells to digital signals associated with at least two individual wells. ~~simultaneously.~~

3. (Cancelled)

4. (Currently Amended) The ~~system~~ apparatus of claim 1, wherein the ~~electronic circuitry~~ plurality of analogue-to-digital conversion channels performs signal conversion in parallel across multiple wells.

5. (Cancelled)

6. (Currently Amended) The ~~system~~ apparatus of claim 1, wherein the ~~electronic circuitry~~ plurality of analogue-to-digital conversion channels is configured for monitoring multiple cell-substrate ~~impedance~~ impedances in [[a]] different wells of the plurality of wells at approximately the same time.

7. (Cancelled)

8. (Cancelled)

9. (Currently Amended) The ~~system~~ apparatus of claim 1, wherein the ~~system~~ apparatus comprises an electromechanical apparatus ~~capable of~~ configured for interfacing ~~a multi well device~~ the multiwell plate with one or more platforms.

10. (Currently Amended) The ~~system~~ apparatus of claim 9, wherein the one or more platforms of the electromechanical apparatus comprise an impedance platform ~~and an optical platform~~.

11. (Currently Amended) The ~~system~~ apparatus of claim 1, wherein the ~~device for monitoring cell substrate impedance comprising~~ the multiwell plate comprises a two-piece

structure wherein the nonconductive substrate is attached to a bottomless plate to form a bottom surface of the wells.

12. (Currently Amended) The ~~system~~ apparatus of claim 1, wherein the nonconductive substrate ~~is suitable for cell attachment via~~ includes a precoat comprising one or more compounds that improve cell attachment.

13. (Currently Amended) The ~~system~~ apparatus of claim 1, wherein the ~~electronic circuitry is configured to measure with a time difference between two adjacent impedance measurements~~ millisecond time resolution between the first measurements and the second measurements is less than 500 [[ms.]] milliseconds.

14-17. (Cancelled)

18. (Currently Amended) A system for continuously monitoring cells[[,]] in real time, label free, with impedance-based analysis, the system comprising:

a) a plurality of analog-to-digital (A2D) signal converters electrically arranged in parallel to one another;

~~a) a device for monitoring cell-substrate impedance, the device~~ b) a well plate comprising a plurality of wells on a nonconductive substrate, wherein each well of the plurality of wells comprises [[an]] one electrode array of a plurality of electrode arrays disposed on the nonconductive substrate that is connected to the plurality of A2D signal converters; ~~substrate for measurement of cell-substrate impedance;~~

[[b)]] c) an impedance analyzer connected to or including the plurality of A2D signal converters, wherein the impedance analyzer ~~that~~ measures, via digitally converted signals from the A2D signal converters, a first plurality of cell-substrate impedances at a first time and a second plurality of cell-substrate impedances at a second time, the first plurality of cell-substrate impedances and the second plurality of cell-substrate impedances being measured between a first electrode structure and a second electrode structure in each electrode array and across a cell

sample attached within each well of the plurality of wells; and ~~cell-substrate impedance from the plurality of wells.~~

~~c) electronic circuitry that electrically connects the electrode arrays to the impedance analyzer, wherein the electronic circuitry performs signal conversion in parallel across multiple wells such that the electrode arrays are electrically monitored at millisecond time resolution; and~~

d) a software program that analyzes the first plurality of cell-substrate impedances from the first time and the second plurality of cell-substrate impedances from the second time to produce a plurality of time period analyses of the plurality of cell samples, wherein individual time period analyses of the plurality of time period analyses are associated with individual wells of the plurality of wells. ~~measured cell-substrate impedance.~~

19-23. (Cancelled)

24. (Currently Amended) A system for continuously monitoring cells[[,]] in real time, label free, with impedance-based analysis, the system comprising:

a) ~~a device for monitoring cell-substrate impedance, the device~~ a well plate comprising a plurality of electrode arrays formed ~~a plurality of wells~~ on a nonconductive substrate, wherein each electrode array of the plurality of ~~wells~~ electrode arrays is disposed in a corresponding well of a plurality of wells defined by the well plate and includes a first electrode structure and a second electrode structure; ~~comprises an electrode array fabricated on the substrate for measurement of cell-substrate impedance;~~

b) an impedance analyzer that monitors, in association with individual cell samples in individual wells of the plurality of wells via each individual electrode array of the plurality of electrode arrays, a cell-substrate impedance between the first electrode structure and the second electrode structure across a cell sample disposed in a corresponding well of the plurality of wells; ~~measures cell-substrate impedance from the plurality of wells;~~

c) electronic circuitry that electrically connects the plurality of electrode arrays to the impedance analyzer ~~to electrically monitor the electrode arrays such that a time difference between two adjacent measurements is less than 500 ms~~; and

d) a software program that ~~analyzes the~~ continuously monitors each cell sample via the plurality of cell-substrate impedances across an analysis period of time with measurements recorded at a sampling time resolution during the period of time. ~~measured cell-substrate impedance.~~

25-30. (Cancelled)

31. (New) The apparatus of claim 13, wherein the millisecond time resolution between the first measurement and the second measurement is between 500 and 100 milliseconds.

32. (New) The apparatus of claim 1, wherein the millisecond time resolution between the first measurement and the second measurement is less than 100 milliseconds.

33. (New) The apparatus of claim 1, wherein the millisecond time resolution between the first measurement and the second measurement is less than 40 milliseconds

34. (New) The apparatus of claim 1, wherein the millisecond time resolution between the first measurement and the second measurement is less than 20 milliseconds

35. (New) The apparatus of claim 1, wherein the millisecond time resolution between the first measurement and the second measurement is less than 5 milliseconds.

36. (New) The apparatus of claim 1, wherein the time period analysis lasts at least 12 hours.

37. (New) The system of claim 18, wherein:
the first electrode structure includes a first set of electrode elements;
the second electrode structure includes a second set of electrode elements;
the first electrode structure opposes the second electrode structure; and
the first set of electrode elements alternate with the second set of electrode elements in an interdigitated pattern.

38. (New) The system of claim 18, wherein each cell sample disposed in the corresponding wells is cultured from a cell seeding placed in the corresponding wells at a setup time before the first time that viably attaches to a bottom of the well by growing from the setup time to the first time and are observed from the first time to the second time for dynamic cellular responses that alter signal impedance between the first electrode structure and the second electrode structure including at least one of:

changes in cell attachment,

cell spreading, or

excitation-contraction coupling of the cell sample.

39. (New), The system of claim 38, wherein the changes in cell attachment at the bottom of the well include changes in a number of cells attached to at least one of:

the first electrode structure;

the second electrode structure; and

the nonconductive substrate between the first electrode structure and second electrode structure.

40. (New) The system of claim 18, wherein each cell sample disposed in the corresponding wells is an in vitro sample that is measured between the first time and the second time for changes in impedance that are associated with morphological changes in each cell sample across the time period analyses.

41. (New) The system of claim 18, wherein each cell sample disposed in the corresponding wells is an in vitro sample that is measured between the first time and the second time for changes in impedance that are associated with changes in a number of cells attached to at least one of the first electrode structure or the second electrode structure.

42. (New) The system of claim 18, wherein the plurality of wells isolate the individual cell samples from one another.

43. (New) The system of claim 24, wherein the impedance analyzer monitors the impedance using a voltage applied at a single frequency.

44. (New) The system of claim 24, wherein the impedance analyzer monitors the impedance using a voltage applied with multiple frequencies.

45. (New) The system of claim 24, wherein the impedance analyzer monitors the impedance using a voltage applied with a specified voltage waveform.

46. (New) The system of claim 24, wherein the impedance analyzer is further configured to monitor a plurality of cell-electrode impedances between the cell sample disposed in the corresponding well of the plurality of wells and the electrode arrays, the cell-electrode impedances being associated with individual cell samples in the individual wells of the plurality of wells.

47. (New) The system of claim 24, wherein the impedance analyzer separates the cell-substrate impedances from a background electrode impedance measured with the cell sample inside the corresponding well.

48. (New) The system of claim 24, wherein the impedance analyzer separates the cell-substrate impedances from a background electrode impedance measured with a cell culture media inside the corresponding well.

49. (New) The system of claim 24, wherein the impedance analyzer measures impedances between 0.1 ohms and 10^5 ohms via an alternating current applied in a frequency range of 1 Hertz (Hz) to 1 Megahertz (MHz).

Remarks

This response is submitted in reply to the Non-Final Office Action of March 28, 2023. In the Office Action, claims 1-30 were pending. With entry of this response, claims 1, 2, 4, 6, 9-13, 18, 24, and 31-49 shall be pending. Claims 1, 2, 4, 6, 9-13, 18, and 24 are amended; claims 3, 5, 7, 8, 14-17, 19-23, and 25-30 are cancelled; and claims 31-49 are newly introduced. Paragraphs [00145], [00154], [00163], [00169], [00178-79], [00182-83], and [00186-88] and Tables I and II of the Specification are amended to address minor typographical and grammatical informalities. Applicant submits that no new matter is added with these amendments and new claims. Support for the amendments can be found at least in ¶¶ [0014], [0024-25], [0065-66], [0112], [0128], [0138], [0145-48], [0167], and [0173-74] of the Specification as originally filed. Favorable reconsideration of this application is respectfully requested in view of these amendments and the following remarks.

Statement of Substance of Interview

On May 3, 2023, Applicant's representatives Robert Kramer (Reg. No.: 51,242) and Raymond Wagenknecht (Reg. No.: 50,948) conducted a telephonic interview with Examiner He. During the interview, the parties discussed the rejections under 35 U.S.C. § 102 and the double patenting rejections with focus on how the *Oka* reference differs from the present invention. The parties discussed proposed amendments to clarify the differences in the claims from the *Oka* reference. Although the parties could not come to agreement on the allowability of the claims, Applicant thanks Examiner He for the courtesies extended during the interview and the opportunity to better understand the reasoning behind the rejection.

Amendments to the Specification

Applicant submits that the amendments to ¶¶ [00145], [00154], [00163], [00169], [00178-79], [00182-83], and [00186-88] and Tables I and II of the Specification as filed add no new matter, and merely correct typographical and grammatical informalities.

Double Patenting

In the Office Action, claims 1-8, 13, and 18-30 stand rejected on the grounds of nonstatutory double patenting as allegedly being unpatentable over claims 1 and 4 of U.S. Patent No.: 9,709,548 (hereinafter, the '548 patent) in view of Non-Patent Literature "A new planar multielectrode array for extracellular recording: application to hippocampal acute slice" (hereinafter, *Oka*).

The Office Action admits that claims 1 and 4 of the '548 patent do not cover that the electronic circuity comprises multiple analogue-to-digital conversion channels, and cites to *Oka* to cure these deficiencies. The Office Action alleges on page 4 that *Oka* discusses "a system for monitoring cells, the system comprising electronic circuitry including multiple analogue-to-digital conversion channels to perform signal conversion in parallel across multiple wells."

Claim 1, as amended, recites, in part, an "impedance analyzer including a plurality of analogue-to-digital conversion channels coupled to the plurality of electrode arrays, wherein the impedance analyzer monitors the electrode arrays at millisecond time resolution between first measurements of the cell-substrate impedance and second measurements of the cell-substrate impedance for each well".

Applicant submits that *Oka* does not discuss the above elements claim 1 as *Oka* does not include any analogue-to-digital conversion channels in an impedance analyzer. Indeed, Figure 2 of *Oka* shows that the elements identified from *Oka* as analogue-to-digital conversion channels are not included in the element identified as the impedance analyzer.

Moreover, *Oka* uses a switch to connect the AD-C to different electrodes at different times and is therefore not performing measurements for each well's electrode as is claimed for the independent analysis of samples in the wells, but rather processing measurements from among a collective of several electrodes (e.g., **inter**-array processing vs. **intra**-array). Stated differently, *Oka* does not monitor individual electrode arrays of the plurality of electrode arrays. Indeed, *Oka* states in § 2.2.3 that the sample is "positioned to cover the 8x8 array" indicating that the measurement of the sample is not conducted from the individual wells, but from the entire MED probe as a collective. Figure 3A of *Oka* shows the sample placed over the probe to cover a

collective set of the electrodes; not in individual wells holding individual samples. Figure 3A of *Oka* shows the sample placed over the probe to cover a collective set of the electrodes; not in individual wells holding individual samples. Indeed, *Oka* discusses in relation to the caption for Figure 3 that eight electrodes (indicated in Figure 3A as 1-8) are used to measure, in common, a field potential generated in a cell sample by two additional electrodes (indicated in Figure 3A as + and -). As each of the electrodes 1-8 receive the same signal from electrodes + and - in *Oka*, these measurements are not performed by each individual electrode array. Moreover, as electrodes + and - are used to deliver the impulse that generates the field effect in the sample that electrodes 1-8 measure, at least electrodes + and - are not measuring, analyzing, or monitoring an impedance, as is recited.

Claim 18, as amended, recites, in part, "a plurality of analog-to-digital (A2D) signal converters arranged in parallel to one another … wherein each well comprises one electrode array of a plurality of electrode arrays fabricated on the nonconductive substrate that is connected the plurality of A2D signal converters"

Applicant submits that *Oka* does not discuss the above elements of claim 18 as *Oka* is performing **inter**-array processing as is claimed for the independent analysis of samples in the wells, but rather **intra**-array processing from among a collective of several electrodes. Indeed, *Oka* states in section 2.2.3 that the sample is "positioned to cover the 8x8 array" indicating that the measurement of the sample is not conducted from the individual wells, but from the entire MED probe as a collective. Figure 3A of *Oka* shows the sample placed over the probe to cover a collective set of the electrodes; not in individual wells holding individual samples. Figure 3A of *Oka* shows the sample placed over the probe to cover a collective set of the electrodes; not in individual wells holding individual samples. Indeed, *Oka* discusses in relation to the caption for Figure 3 that eight electrodes (indicated in Figure 3A as 1-8) are used to measure, in common, a field potential generated in a cell sample by two additional electrodes (indicated in Figure 3A as + and -). As each of the electrodes 1-8 receive the same signal from electrodes + and - in *Oka*, these measurements are not performed by each individual electrode array. Moreover, as electrodes + and - are used to deliver the impulse that generates the field effect in the sample that electrodes 1-8

measure, at least electrodes + and - are not measuring, analyzing, or monitoring an impedance, as is recited.

Claim 24, as amended, recites, in part, "an impedance analyzer that monitors, in association with individual cell samples in individual wells of the plurality of wells via each individual electrode array of the plurality of electrode arrays, a cell-substrate impedance between the first electrode structure and the second electrode structure across a cell sample attached in a corresponding well of the plurality of wells;

Applicant submits that *Oka* does not monitor a plurality of cell-substrate impedances associated with individual cell samples in individual wells of the plurality of wells. Indeed, *Oka* states in section 2.2.3 that the sample is "positioned to cover the 8x8 array" indicating that the measurement of the sample is not conducted from the individual wells, but collectively from the entire MED probe as a collective. Figure 3A of *Oka* shows the sample placed over the probe to cover a collective set of the electrodes; not in individual wells holding individual samples. Indeed, *Oka* discusses in relation to the caption for Figure 3 that eight electrodes (indicated in Figure 3A as 1-8) are used to measure, in common, a field potential generated in a cell sample by two additional electrodes (indicated in Figure 3A as + and -). As each of the electrodes 1-8 receive the same signal from electrodes + and - in *Oka*, these measurements are not performed by each individual electrode array. Moreover, as electrodes + and - are used to deliver the impulse that generates the field effect in the sample that electrodes 1-8 measure, at least electrodes + and - are not measuring, analyzing, or monitoring an impedance, as is recited. Figure 3A of *Oka* shows the sample placed over the probe to cover a collective set of the electrodes; not in individual wells holding individual samples. Indeed, *Oka* discusses in relation to the caption for Figure 3 that eight electrodes (indicated in Figure 3A as 1-8) are used to measure, in common, a field potential generated in a cell sample by two additional electrodes (indicated in Figure 3A as + and -). As each of the electrodes 1-8 receive the same signal from electrodes + and - in *Oka*, these measurements are not performed by each individual electrode array. Moreover, as electrodes + and - are used to deliver the impulse that generates the field effect in the sample that electrodes 1-8 measure, at least electrodes + and - are not measuring, analyzing, or monitoring an impedance, as is recited.

As *Oka* does not describe the claimed elements in any of claims 1, 18, or 24 related to the electronic circuitry as set forth in the claims, Applicant respectfully submits that *Oka* cannot be used to maintain a rejection of double patenting. Accordingly, Applicant respectfully requests that the rejections be withdrawn.

Rejections Under 35 U.S.C. § 102

In the Office Action, claims 1-13 and 16-30 stand rejected under 35 U.S.C. § 102 as allegedly being anticipated by Non-Patent Literature "A new planar multielectrode array for extracellular recording: application to hippocampal acute slice" (hereinafter, *Oka*).

Applicant respectfully disagrees that *Oka* anticipates the currently presented claims for at least the following reasons:

I. *Oka* does not discuss a plurality of wells as is claimed

As amended, claim 1 recites, in part, "a multiwell plate **comprising a plurality of wells** on a nonconductive substrate, wherein each of the plurality of wells comprises an electrode array of a plurality of electrode arrays." (emphasis added).

As amended, claim 18 recites, in part, "a well plate **comprising a plurality of wells** on a nonconductive substrate, wherein **each well comprises one electrode array of a plurality of electrode arrays**". (emphasis added).

As amended, claim 24 recites, in part, "a well plate **comprising a plurality of electrode arrays** formed on a nonconductive substrate, wherein **each electrode array of the plurality of electrode arrays is disposed in a corresponding well of a plurality of wells** defined by the well plate and includes a first electrode structure and a second electrode structure" (emphasis added).

Although the Examiner identifies a plurality of wells/microelectrodes in Figure 1A of Oka, (see, Office Action, page 6), Applicant respectfully submits that the Examiner is either conflating the microelectrodes and wells or is engaging in hindsight to describe the device of *Oka* as having a plurality of wells, and that *Oka* only discusses either no wells or a single well; not a plurality.

Applicant notes that *Oka* is titled "A new **planar** multielectrode array for extracellular recording: application to hippocampal acute slice" (emphasis added). As will be commonly

understood, a "well" refers to a structure having a depth - and is therefore not a planar structure. At no point in *Oka* are the electrodes of the multielectrode array discussed as being disposed in a well, depression, or other non-planar feature. Indeed, *Oka* discusses in § 2.1 that the electrodes are surrounded by a glass ring "to form a culture chamber", but that the height of that glass ring is "0 mm". This is consistent with the image shown in Figure 3A of Oka in §3.1, which shows a "contrast microphotograph of the rat hippocampal slice as positioned on the MED probe" that covers the planar probe and extends outward therefrom with no sign of being affected by a non-planar structure. As *Oka* is silent on its MED probe having a depth, and indicates that the samples are placed in a planar arrangement with no indication of containment, Applicant submits that *Oka* does not discuss or suggest even one well, let alone a plurality of wells. However, even assuming, for the sake of argument, that the multi-electrode dish (MED) of *Oka* were non-planar, such a structure would only describe a single well - not a plurality of wells.

Although *Oka* recites in § 2.1 a "square hole centered on each" of the microelectrodes, a review of Figure 1B of *Oka* that these square holes are filled with platinum black - indeed *Oka* later in § 2.1 after introducing these holes that "Finally, 64 microelectrodes were electroplated with platinum black"; indicating that the array does not include the holes in its final form. However, for the sake of argument, if these filled square holes were considered to describe a plurality of wells, application notes that these holes do not comprise "an electrode array" as each is associated with a single electrode; not an array, which is described in each of the independent claims as including two structures.

Accordingly, Applicant submits that *Oka* cannot anticipate claims 1, 18, or 24 for at least not describing a plurality of wells as claimed.

II. *Oka* does not discuss measuring a cell-substrate impedance as is claimed

As amended, claim 1 recites, in part, "an impedance analyzer that independently measures a cell-substrate impedance in each well, the cell-substrate impedance being measured between a first electrode structure and a second electrode structure of the electrode array and across a cellular sample comprising a plurality of cells attached within each well".

As amended, claim 18 recites, in part, "the impedance analyzer measures… a first plurality of cell-substrate impedances at a first time and a second plurality of cell-substrate impedances at

a second time, the first plurality of cell-substrate impedances and the second plurality of cell-substrate impedances being measured between a first electrode structure and a second electrode structure in the electrode array and across a cell sample attached within each well of the plurality of wells".

As amended, claim 24 recites, in part, "an impedance analyzer that monitors, in association with individual cell samples in individual wells of the plurality of wells via each individual electrode array of the plurality of electrode arrays, a cell-substrate impedance between the first electrode structure and the second electrode structure across a cell sample attached in a corresponding well of the plurality of wells".

Applicant submits that a cell-substrate impendence, as defined in the independent claims, is not the same as the impedance measured in *Oka*. The Examiner in page 6 of the Office Action identifies the LCR meter of *Oka* from § 3.1 or the computer shown in Figure 2 as measuring an impedance; neither of which is the same as a cell-substrate impedance as claimed.

The LCR meter from § 3.1 of *Oka* is discussed in relation to the effectiveness of various coating procedures for the electrodes. This effectiveness was "investigated by impedance measurement at 1 kHz between the microelectrode and the medium" which was suggested by different impedances with a slice of hippocampal tissue on different coatings of the electrodes. An impedance between an electrode and a medium, even with a tissue sample placed therebetween, is not the same as "an impedance between the first electrode structure and the second electrode structure" nor does such a measurement determine whether such as sample is attached to "the nonconductive substrate between the first electrode structure and the second electrode structure". As recited in §2.2.3 of *Oka*, the medium is "DMEM:F-12 mixed medium containing 10% fetal bovine serum and 10% horse serum," which is neither nonconductive, nor the substrate on which the electrode structures are disposed. Accordingly, the measurement performed by the LCR meter of *Oka* is not a cell-substrate impedance as is claimed.

Oka is also silent with respect to the computer from Figure 2 on monitoring a cell-substrate impedance as is claimed. *Oka* discusses in § 3.2 that field potentials are recorded at the microelectrodes in the recording region, which are reported to the computer. Even if these readings were for an electrical value "between the first electrode structure and the second electrode structure across a cell sample" such a reading is not an impedance - and at best would merely be a resistance

or a resistance component of an impedance. These readings are reported (as per § 3.3) in millivolts (mV) in response to a **constant current** pulse measured in microamperes (μA) (as per the discussion in relation to Figure 3). Applicant submits that a signal of a "constant current" would be understood by one of ordinary skill in the art to refer to a direct current (DC) signal; not an alternating current (AC) signal. Because, as is explained in ¶ [0066] of Applicant's specification and will be understood by one of ordinary skill in the relevant art, impedance includes both resistance and reactance components, and a reactance component is measured via an AC signal having a frequency or known waveform. Although a DC signal, such as the constant current pulse of *Oka*, can be used to derive the resistance component of an impedance, such a signal cannot determine the reactance component of the impedance. Accordingly, the constant current pulses of *Oka* cannot be used by the computer of *Oka* to measure, monitor, or derive an impedance as is claimed.

Accordingly, Applicant submits that *Oka* cannot anticipate claims 1, 18, or 24 for at least not describing a cell-substrate impedance as claimed.

III. *Oka* does not discuss that each of the electrode arrays are disposed in corresponding wells as is claimed

As amended, claim 1 recites, in part, "an impedance analyzer that independently measures a cell-substrate impedance **in each well**, the cell-substrate impedance being **measured between a first electrode structure and a second electrode structure of the electrode array**" (Emphasis added).

As amended, claim 18 recites, in part, "wherein **each well comprises one electrode array of a plurality of electrode arrays**… the impedance analyzer-measures, … a first plurality of cell-substrate … measured between **a first electrode structure and a second electrode structure in each electrode array** and across a cell sample attached within each well of the plurality of wells" (Emphasis added).

As amended, claim 24 recites, in part, "wherein **each electrode array of the plurality of electrode arrays is disposed in a corresponding well** of a plurality of wells defined by the well plate and **includes a first electrode structure and a second electrode structure**" (emphasis added).

As discussed in relation to section I of the present response, Applicant submits that *Oka* does not discuss a plurality of wells that each include an electrode array. As discussed in relation to section II of the present response, Applicant submits that *Oka* does not measure an impedance as claimed. However, for sake of argument, even if *Oka* did discuss a well that includes an electrode array and measuring a cell-substrate impedance in that well, *Oka* is silent on each well having an electrode array including a first electrode structure and a second electrode structure.

Under the interpretation that the entire MED probe of *Oka* is equivalent to a well, *Oka* cannot not include each electrode array in a corresponding well, as there would be only one well in which the collection of electrodes of *Oka* be disposed in. Therefore, no other well with electrodes exists in *Oka* to comprise a plurality of electrode arrays. Stated differently, if the region of *Oka*'s probe that contains the electrodes were a well, that one well would contain all of the electrodes and therefore no other electrode array would exist to be disposed in another well of a plurality of wells.

Under the interpretation that the square holes of *Oka* are equivalent to wells, those holes do not include an electrode array that includes a first electrode structure and a second electrode structure - each hole includes a single structure.

Accordingly, Applicant submits that *Oka* cannot anticipate claims 1, 18, or 24 for at least not describing each well including an electrode with first and second electrode structures as claimed.

IV. *Oka* does not discuss taking any sort of measurements from each of the electrode arrays as is claimed

As amended, claim 1 recites, in part, "an impedance analyzer that independently measures a cell-substrate impedance in each well".

As amended, claim 18 recites, in part, "wherein individual time period analyses of the plurality of time period analyses **are associated with individual wells of the plurality of wells**" (emphasis added).

As amended, claim 24 recites, in part, "an impedance analyzer that monitors, in association with individual cell samples in individual wells of the plurality of wells **via each individual electrode array** of the plurality of electrode arrays, a cell-substrate impedance between the first

electrode structure and the second electrode structure across a cell sample attached in a corresponding well of the plurality of wells" (emphasis added).

Regardless of what type of measurements *Oka* actually discusses, Applicant submits that *Oka* explicitly does not **independently** measure, analyze, monitor or otherwise take *any sort of measurements* from **each of the wells**, as defined in the independent claims. Indeed, *Oka* discusses in relation to Figure 3 that eight electrodes (indicated in Figure 3A as 1-8) are used to measure, in common, a field potential generated in a cell sample by two additional electrodes (indicated in Figure 3A as + and -). As each of the electrodes 1-8 receive the same signal from electrodes + and - in *Oka*, these measurements are not performed by each individual electrode array. Moreover, as electrodes + and - are used to deliver the impulse that generates the field effect in the sample that electrodes 1-8 measure, at least electrodes + and - are not measuring, analyzing, or monitoring an impedance, as is recited in the independent claims that each of the individual electrode arrays do.

Accordingly, Applicant submits that *Oka* cannot anticipate claims 1, 18, or 24 for at least not describing taking measurements from each of the electrode arrays as claimed.

Applicant notes that the dependent claims include the elements not anticipated by *Oka* found in their respective independent claims 1, 18, or 24. Accordingly, for at least the reasons set forth above, the dependent claims are not anticipated by *Oka*. Moreover, the dependent claims include additional elements that further differentiate the claims from what is discussed in *Oka*. Accordingly, Applicant respectfully requests that the rejections under 35 U.S.C. § 102 be withdrawn, and the claims be allowed.

Rejections Under 35 U.S.C. § 103

In the Office Action, claim 14 and 15 stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable over *Oka* in view of the alleged skill of the person of ordinary skill in the art at the effective filing date of the invention.

Applicant submits that claims 14 and 15 have been cancelled in this response; rendering the rejections moot.

Conclusion

For the foregoing reasons, Applicant respectfully requests reconsideration of the above identified patent application, and earnestly requests an early allowance of the same. In the event there remains any impediment to allowance of the claims that could be clarified in a telephonic interview, the Examiner is respectfully requested to initiate such an interview with the undersigned.

Applicant does not believe any fee is due in connection with this response. However, the Commissioner is authorized to charge any fee that may be required or to credit any overpayment to Deposit Account No. 02-1818. If any such charges are applied, please indicate Attorney Docket No. A2185-9003 (20191134-16) (0528696.00002) on the account statement.

Dated: June 23, 2023

Respectfully submitted,

Electronic signature: /William Fortunato /

William Fortunato
Registration No.: 76,212
K&L GATES LLP
301 Hillsborough Street
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/993,716	11/23/2022	Xiaobo Wang	20191134-16

CONFIRMATION NO. 1061

188545
Agilent Technologies, Inc./K&L Gates LLP
Global IP Operations
5301 Stevens Creek Blvd, 1A-PB
Santa Clara, CA 95051

POA ACCEPTANCE LETTER

OC000000059009993

Date Mailed: 07/06/2023

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 06/23/2023.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/mteklemichael/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

188545 7590 07/19/2023

Agilent Technologies, Inc./K&L Gates LLP
Global IP Operations
5301 Stevens Creek Blvd, 1A-PB
Santa Clara, CA 95051

EXAMINER	
HE, AMY	
ART UNIT	PAPER NUMBER
2858	

DATE MAILED: 07/19/2023

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/993,716	11/23/2022	Xiaobo Wang	20191134-16	1061

TITLE OF INVENTION: LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	10/19/2023

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

188545 7590 07/19/2023

Agilent Technologies, Inc./K&L Gates LLP
Global IP Operations
5301 Stevens Creek Blvd, 1A-PB
Santa Clara, CA 95051

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/993,716	11/23/2022	Xiaobo Wang	20191134-16	1061

TITLE OF INVENTION: LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	10/19/2023

EXAMINER	ART UNIT	CLASS-SUBCLASS
HE, AMY	2858	506-010000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1_____
2_____
3_____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via Patent Center or EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (08-18) Approved for use through 01/31/2020 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/993,716	11/23/2022	Xiaobo Wang	20191134-16	1061

188545 7590 07/19/2023

Agilent Technologies, Inc./K&L Gates LLP
Global IP Operations
5301 Stevens Creek Blvd, 1A-PB
Santa Clara, CA 95051

EXAMINER	
HE, AMY	

ART UNIT	PAPER NUMBER
2858	

DATE MAILED: 07/19/2023

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 17/993,716	Applicant(s) Wang et al.	
	Examiner AMY HE	Art Unit 2858	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the amendment dated June 23, 2023.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/AMY HE/
Primary Examiner, Art Unit 2858

Continuation of 3. The allowed claim(s) is/are: 1-2,4,6,9-13,18,24 and 31-49

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.

2. Claims 1, 2, 4, 6, 9-13, 18, 24, 31-49 are allowed.

REASONS FOR ALLOWANCE

3. The following is an examiner's statement of reasons for allowance:

Claims 1, 2, 4, 6 and 9-13 and 31-36 are allowable because none of the prior art discloses or fairly suggests an apparatus for continuous, label free, real-time monitoring of cells using impedance-based analysis, the apparatus comprising: a) multiwell plate comprising a plurality of wells on a nonconductive substrate, wherein each of the plurality of wells comprises an electrode array of a plurality of electrode arrays; b) an impedance analyzer that independently measures a cell-substrate impedance at each well, the cell-substrate impedance being measured between a first electrode structure and a second electrode structure of the electrode array and across a cellular sample comprising a plurality of cells disposed within each well, the impedance analyzer including at least two analogue-to-digital conversion channels, wherein the impedance analyzer monitors the electrode arrays at millisecond time resolution between first measurements of the cell-substrate impedance and second measurements of the cell-substrate impedance for each well; and c) a software program that analyzes the first measurements and the second measurements to produce a time period analysis of the cellular sample, and in the combination as claimed in claim 1.

Claims 18 and 37-42 are allowable because none of the prior art discloses or fairly suggest a system for continuously monitoring cells in real time, label free, with impedance-based analysis, the system comprising: a) a plurality of analog-to-digital (A2D) signal converters electrically arranged in parallel to one another; b) a well plate comprising a plurality of wells on a nonconductive substrate, wherein each well comprises one electrode array of a plurality of electrode arrays disposed on the

nonconductive substrate; c) an impedance analyzer that measures a first plurality of cell-substrate impedances at a first time and a second plurality of cell-substrate impedances at a second time, the first plurality of cell-substrate impedances and the second plurality of cell-substrate impedances being measured between a first electrode structure and a second electrode structure in each electrode array and across a cell sample attached within each well of the plurality of wells; and d) a software program that analyzes the first plurality of cell-substrate impedances and the second plurality of cell-substrate impedances to produce a plurality of time period analyses associated with individual wells of the plurality of wells, and in the combination as claimed in claim 18.

Claims 24 and 43-49 are allowable because none of the prior art discloses or fairly suggests a system for continuously monitoring cells in real time, label free, with impedance-based analysis, the system comprising: a) a well plate comprising a plurality of electrode arrays, wherein each electrode array is disposed in a corresponding well of a plurality of wells defined by the well plate and includes a first electrode structure and a second electrode structure; b) an impedance analyzer that monitors, in association with individual cell samples in individual wells of the plurality of wells via each individual electrode array of the plurality of electrode arrays, a cell-substrate impedance between the first electrode structure and the second electrode structure across a cell sample disposed in a corresponding well of the plurality of wells; c) electronic circuitry that electrically connects the plurality of electrode arrays to the impedance analyzer; and d) a software program that analyzes the continuously monitors each cell sample via the plurality of cell-substrate impedances across an analysis period of time with measurements recorded at a sampling time resolution during the period of time, and in the combination as claimed in claim 24.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled “Comments on Statement of Reasons for Allowance.”

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY HE whose telephone number is (571)272-2230. The examiner can normally be reached 9:00am--5:00pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Huy Phan can be reached on (571) 272-7924. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/AMY HE/
Primary Examiner, Art Unit 2858

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/993,716	Wang et al.
	Examiner	**Art Unit**
	AMY HE	2858

CPC								
Symbol							**Type**	**Version**
G01N	/	33	/	4836			F	2013-01-01
G01N	/	33	/	4833			I	2013-01-01
G01N	/	33	/	48728			I	2013-01-01
G01N	/	33	/	5438			I	2013-01-01
G01N	/	27	/	02			I	2013-01-01

CPC Combination Sets									
Symbol							**Type**	**Set**	**Ranking**	**Version**
	/		/							

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	30	
/AMY HE/ Primary Examiner, Art Unit 2858	13 July 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	1A

U.S. Patent and Trademark Office — Part of Paper No.: 20230713

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/993,716	Wang et al.
	Examiner	**Art Unit**
	AMY HE	2858

INTERNATIONAL CLASSIFICATION				
CLAIMED				
G01N33/483	/	33	/	483
G01N33/487	/	33	/	487
G01N33/543	/	33	/	543
G01N27/02	/	27	/	02

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE (Assistant Examiner) (Date)	**Total Claims Allowed:** 30	
/AMY HE/ Primary Examiner, Art Unit 2858 (Primary Examiner) 13 July 2023 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 1A

U.S. Patent and Trademark Office Part of Paper No.: 20230713

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/993,716	Wang et al.
	Examiner	**Art Unit**
	AMY HE	2858

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	6	10		19		28	17	37	27	46				
2	2	7	11		20		29	18	38	28	47				
	3	8	12		21		30	19	39	29	48				
3	4	9	13		22	10	31	20	40	30	49				
	5		14		23	11	32	21	41						
4	6		15	23	24	12	33	22	42						
	7		16		25	13	34	24	43						
	8		17		26	14	35	25	44						
5	9	16	18		27	15	36	26	45						

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 30	
/AMY HE/ Primary Examiner, Art Unit 2858 (Primary Examiner)	13 July 2023 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 1A

U.S. Patent and Trademark Office

Part of Paper No.: 20230713

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/993,716	Wang et al.
	Examiner	Art Unit
	AMY HE	2858

CPC - Searched*		
Symbol	Date	Examiner
G01N33/4836 OR G01N27/02 OR G01N33/4833 OR G01N33/48728 OR G01N33/5438	07/12/2023	AH

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
G01N33/4836 OR G01N27/02 OR G01N33/4833 OR G01N33/48728 OR G01N33/5438 COMBINED WITH TEXT SEARCH updated	07/12/2023	AH
similarity search updated	07/12/2023	AH
more like search updated	07/13/2023	AH

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
G01N	33/4836; 33/4833; 33/48728; 33/5438; 27/02	07/13/2023	AH

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L50	10	((US-10551371-B2 OR US-9709548-B2 OR US-5810725-A).did. AND USPT.dbnm.) OR ((US-20100029506-A1 OR US-20050279634-A1 OR US-20050118565-A1 OR US-20030111343-A1 OR US-20230130050-A1).did. AND PGPB.dbnm.) OR ((AU-2002365810-A1 OR EP-0566725-B1).did. AND FTDB.dbnm.)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/07/12 09:34 AM
L51	2	"20230130050"	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/07/12 09:35 AM
L52	2	"20230130050" AND (vitro morphological)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/07/12 10:49 AM
L53	10	((US-10551371-B2 OR US-9709548-B2 OR US-5810725-A).did. AND USPT.dbnm.) OR	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU,	OR	ON	ON	2023/07/12 10:56 AM

		((US-20100029506-A1 OR US-20050279634-A1 OR US-20050118565-A1 OR US-20030111343-A1 OR US-20230130050-A1).did. AND PGPB.dbnm.) OR ((AU-2002365810-A1 OR EP-0566725-B1).did. AND FTDB.dbnm.)	CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L54	48	(Artificial Intelligence) Similar to: 17/993,716 with 0 CPC Selections and 0 Text Selections Text: (US-20190322094-A1 OR US-9709548-B2 OR US-20180306771-A1 OR US-10533985-B2 OR WO-2009137440-A1 OR US-20210164961-A1 OR US-20220291191-A1 OR EP-2291645-A1 OR US-20040045839-A1 OR US-20230130050-A1 OR CA-2723223-A1 OR CA-2723223-C OR US-10012636-B2 OR US-20180095064-A1 OR EP-2291645-B1 OR US-20170205391-A1 OR US-9612234-B2 OR US-20110300569-A1 OR WO-2011146531-A9 OR WO-2011146531-A1 OR CN-102549141-A OR WO-2017216694-A1 OR US-20040000901-A1 OR WO-2015196957-A1 OR US-20170151574-A1 OR WO-2010022391-A9 OR CN-104789443-B OR US-20190374947-A1 OR JP-2017519524-A OR US-10107792-B2 OR US-20090309618-A1 OR US-9404140-B1 OR CN-104789443-A OR US-9399787-B2 OR US-20160320365-A1	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO))	OR	ON	ON	2023/07/12 11:00 AM

		OR US-7876108-B2 OR US-20050213374-A1 OR JP-2016212083-A OR US-20230014082-A1 OR US-20110117542-A1 OR US-8344742-B2 OR US-20130123136-A1 OR US-7560269-B2 OR WO-2021257705-A1 OR CN-104737010-A OR GB-2576429-A OR US-20100120626-A1 OR EP-2556371-B1 OR CA-3053191-A1 OR WO-2018157073-A1).did.					
L55	43	(Artificial Intelligence) Similar to: 17/993,716 with 0 CPC Selections and 4 Text Selections Text: (JP-2021500537-A OR US-20210142182-A1 OR EP-2494400-A1 OR KR-100952330-B1 OR US-20030206001-A1 OR US-20100143944-A1 OR US-20220325329-A1 OR US-10676774-B2 OR CA-2778725-A1 OR US-10481076-B2 OR WO-2007106306-A2 OR US-20170285059-A1 OR WO-2008155072-A1 OR CN-115335531-A OR CN-1426534-A OR JP-2014110780-A OR ES-2352344-T3 OR US-20190086388-A1 OR EP-1907966-A1 OR EP-0980516-A1 OR CN-107917940-B OR WO-2012143463-A1 OR JP-2009528515-A OR US-10299711-B2 OR EP-3851516-A1 OR US-20230105724-A1 OR CN-103460224-B OR CN-109932398-A OR JP-20180538240-A5 OR RU-2553371-C2 OR WO-2004037405-A1 OR WO-	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO))	OR	ON	ON	2023/07/12 11:02 AM

		2012128962-A1 OR JP-4206900-B2 OR RU-2013115758-A OR KR-20230099647-A OR RU-2606938-C2 OR DE-69918389-T2 OR US-20100015697-A1 OR WO-2009083814-A2 OR WO-2017131726-A1 OR US-20120058547-A1 OR JP-20050515475-A5 OR US-10241054-B2 OR US-20180052181-A1 OR CA-3115287-A1 OR WO-2021191793-A1 OR EP-2356448-A1 OR US-20150198615-A1 OR US-20180356397-A1 OR KR-101872380-B1).did.					
L56	4383	N4 AND (well array cell converter)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/07/12 11:14 AM
L57	32	(Artificial Intelligence) More like doc: US-10551371-B2 Text: (US-20110039294-A1 OR US-20200278339-A1 OR EP-2427543-A1 OR WO-2010129725-A1 OR CA-2760941-A1 OR CA-2760941-C OR WO-2014085727-A1 OR EP-2291645-A1 OR CA-2723223-A1 OR US-20100029506-A1 OR EP-2291645-B1 OR US-10533985-B2 OR US-20180306771-A1 OR CA-2723223-C OR US-9709548-B2 OR	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/07/12 11:18 AM

		US-10012636-B2 OR US-20180095064-A1 OR US-20210164961-A1 OR US-11360072-B2 OR US-20220291191-A1).did.					
L58	29	(Artificial Intelligence) More like doc: US-20100029506-A1 Text: (WO-2009137440-A1 OR EP-2291645-A1 OR CA-2723223-A1 OR US-9709548-B2 OR EP-2291645-B1 OR CA-2723223-C OR US-20180095064-A1 OR US-10012636-B2 OR US-10533985-B2 OR US-20180306771-A1 OR US-20220291191-A1 OR US-20210164961-A1 OR US-11360072-B2 OR US-20230130050-A1 OR US-9612234-B2 OR US-20170205391-A1 OR US-20110300569-A1 OR WO-2011146531-A1 OR WO-2011146531-A9 OR US-10551371-B2).did.	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/07/12 11:22 AM
L59	41	(Artificial Intelligence) More like doc: US-20050279634-A1 Text: (US-7678249-B2 OR US-20100133122-A1 OR US-8435393-B2 OR CN-1809628-A OR JP-3801617-B2 OR CN-100372920-C OR WO-2005001018-A1 OR JP-WO2005001018-A1 OR JP-WO2002055653-A1 OR WO-02099408-A1 OR JP-WO2002099408-A1 OR JP-3570715-B2 OR KR-20020086625-A OR US-20040167723-A1 OR WO-2017061171-A1 OR US-8702922-B2 OR WO-2019069707-A1 OR KR-101993943-B1 OR KR-	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/07/12 11:41 AM

		20140084139-A OR US-7326384-B2).did.					
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L61	1030563	("ABASSI Y".ine. OR "ABASSI Y A".ine. OR "ABASSI; YAMA A.".ine. OR "LI N".ine. OR "WANG X".ine. OR "WANG; XIAOBO".ine. OR "XI B".ine. OR "XI; BIAO".ine. OR "XU X".ine. OR "XU; XIAO".ine.)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/07/12 11:48 AM
L62	11	((US-10551371-B2 OR US-9709548-B2 OR US-5810725-A).did. AND USPT.dbnm.) OR ((US-20100029506-A1 OR US-20050279634-A1 OR US-20050118565-A1 OR US-20030111343-A1 OR US-20230130050-A1 OR US-20040167723-A1).did. AND PGPB.dbnm.) OR ((AU-2002365810-A1 OR EP-0566725-B1).did. AND FTDB.dbnm.)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/07/13 10:39 AM
L63	6	L62 AND milliseconds	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB,	OR	ON	ON	2023/07/13 10:39 AM

			HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
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L65	1	"20230130050" AND interdigitated	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/07/13 11:45 AM
L66	672069	(cell ADJ seeding)(cell ADJ attach$3)(impedance WITH time)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT;	OR	ON	ON	2023/07/13 11:54 AM

			IBM_TDB)				
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L68	672070	L65and L66	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/07/13 11:56 AM
L69	1	L65 AND L68	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/07/13 11:56 AM
L70	35	(Artificial Intelligence) More like doc: US-5810725-A Text: (US-6151519-A OR EP-0585933-A2 OR EP-0585933-B1 OR DE-	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV,	OR	ON	ON	2023/07/13 11:58 AM

		69333945-T2 OR JP-H06296595-A OR JP-3193471-B2 OR JP-H0678889-A OR JP-3101122-B2 OR JP-3909738-B2 OR US-7041492-B2 OR WO-0206809-A1 OR JP-2002031617-A OR US-20030111343-A1 OR TW-541433-B OR KR-20020064283-A OR EP-1398625-A1 OR US-6894511-B2 OR WO-02099408-A1 OR US-20020113607-A1 OR CA-2377813-C).did.	MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L71	34	(Artificial Intelligence) More like doc: US-20030111343-A1 Text: (EP-1398625-A1 OR US-7041492-B2 OR WO-03001194-A1 OR KR-100481743-B1 OR KR-20030031463-A OR CN-1440505-A OR CN-1204396-C OR TW-524973-B OR JP-2001281201-A OR US-6894511-B2 OR EP-1300678-B1 OR CA-2377813-C OR US-20020113607-A1 OR EP-1300678-A1 OR EP-1398625-A4 OR KR-20020064283-A OR JP-H11187865-A OR JP-2002523726-A OR TW-541433-B OR JP-2002031617-A).did.	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/07/13 11:58 AM

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N4	1399	N1 AND N2	(US-PGPUB; USPAT)	OR	ON	ON	2023/07/12 11:12 AM
N5	1397	N4 AND (well array cell converter)	(US-PGPUB; USPAT)	OR	ON	ON	2023/07/12 11:14 AM

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/993,716	09/25/2023 04:46:12 PM ET	20191134-16

Title of Invention

LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1061	FILED BY	Brynn Kooyenga
PATENT CENTER #	62861543	AUTHORIZED BY	William Fortunato
CUSTOMER #	188545	FILING DATE	11/23/2022
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Xiaobo Wang

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 021818	E20239OG47207546	US Patent Mail

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
021818	37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees)

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1501	UTILITY ISSUE FEE	1200.00	1	1200.00
			TOTAL AMOUNT:	$1,200.00

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PART B–FEE(S) TRANSMITTAL

Complete and send this form, together with the applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

By fax, send to: (571) 273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

Agilent Technologies, Inc./K&L Gates LLP
Global IP Operations
5301 Stevens Creek Blvd. 1A-PB
Santa Clara, CA 95051

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

William Fortunato	(Typed or printed name)
/William Fortunato/	(Signature)
September 25, 2023	(Date)

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
17/993,716	11/23/2022	Xiaobo Wang	A2185-9003	1061

TITLE OF INVENTION: LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

APPLN: TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1,200.00	$0.00	$0.00	$1,200.00	10/19/2023

EXAMINER	ART UNIT	CLASS-SUBCLASS
HE, AMY	2858	506-010000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363)

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1. K&L Gates LLP
2.
3.

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE	(B) RESIDENCE: (CITY and STATE or COUNTRY)
AGILENT TECHNOLOGIES, INC.	SANTA CLARA, CA

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees Submitted: ☒ Issue Fee ☐ Publication Fee (if required)

4b. Method of Payment (*Please first reapply any previously paid fee shown above*):

☒ Electronic Payment via Patent Center or EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 02-1818

5. Change of Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29. NOTE: Absent a valid Certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27. NOTE: If the application was previously under micro entity status, checking this box will be taken as a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status. NOTE: Checking this box will be taken as a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /William Fortunato/ Date September 25, 2023

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PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/993,716	**09/25/2023 04:46:12 PM ET**	**20191134-16**

Title of Invention

LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1061	FILED BY	Brynn Kooyenga
PATENT CENTER #	62861543	FILING DATE	11/23/2022
CUSTOMER #	188545	FIRST NAMED INVENTOR	Xiaobo Wang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	William Fortunato

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
A2185-9003 -- 21091134-16 -- Issue Fee Transmittal.pdf	1	Issue Fee Payment (PTO-85B)	140 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
A2185-9003 -- 21091134-16 -- Issue Fee Transmittal.pdf	320E8E264A40468A5C298310A05E40659950169A55EEB0D71A0027F2B1271EF4C8DC5114EDB38481AD42B53328DA756C354561B6A2593454FAC685A84D83530C

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/30EFS (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	17993716	Filing Date	2022-11-23	Docket Number (if applicable)	A2185-9003 (20191134-16)	Art Unit	2858
First Named Inventor	Xiaobo Wang			Examiner Name	A. He		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☐ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☒ Other PETITION TO WITHDRAW APPLICATION FROM ISSUE PURSUANT TO 37 C.F.R. § 1.313(c)(2)

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 02-1818

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Signature of Registered U.S. Patent Practitioner			
Signature	/David Lu/	Date (YYYY-MM-DD)	2023-11-23
Name	David Lu	Registration Number	65,769

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/SB/08a (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(**Not for submission under 37 CFR 1.99)**

Application Number	17993716
Filing Date	2022-11-23
First Named Inventor	Xiaobo Wang
Art Unit	2858
Examiner Name	A. He
Attorney Docket Number	A2185-9003 (20191134-16)

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	17993716
	Filing Date	2022-11-23
	First Named Inventor	Xiaobo Wang
	Art Unit	2858
	Examiner Name	A. He
	Attorney Docket Number	A2185-9003 (20191134-16)

	1	YANG et al., "Tri-iodo-L-Thyronine Promotes the Maturation of Human Cardiomyocytes-Derived from Induced Pluripotent Stem Cells," Journal of Molecular and Cell Cardiology (2014) Vol. 72, 296-304	☐
	2	International Search Report and Written Opinion for International Application No. PCT/US2009/033801 dated October 30, 2009.	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	17993716
	Filing Date	2022-11-23
	First Named Inventor	Xiaobo Wang
	Art Unit	2858
	Examiner Name	A. He
	Attorney Docket Number	A2185-9003 (20191134-16)

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/David Lu/	Date (YYYY-MM-DD)	2023-11-23
Name/Print	David Lu	Registration Number	65,769

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/993,716	**11/22/2023 02:47:43 PM Z ET**	**20191134-16**

Title of Invention

LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1061	FILED BY	David Lu
PATENT CENTER #	63359392	FILING DATE	11/23/2022
CUSTOMER #	188545	FIRST NAMED INVENTOR	Xiaobo Wang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 6

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
petition-request.pdf	2	ePetition Request Form	31 KB
317100209_1.pdf	2	Transmittal Letter	105 KB
317100144_1.pdf	4	Information Disclosure Statement (IDS) Form (SB08)	1234 KB
317100181_1.pdf	3	Request for Continued Examination (RCE)	1628 KB
Yang2014_NPL.pdf	14	Non Patent Literature	5443 KB
PCTUS2009033801	8	Other reference-	267 KB

International Search Report and Written Opinion.pdf	Patent/Application/Search Documents

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
petition-request.pdf	0A7AC2EACC02A35FD4F09C3CDA45CD325B65EB7D2CA0977 67D37EBB050A95A4638B3B8EF2D5BEB9E3933507B7B08357D 8A19ADAC88ECADA85204EB96C9BD27BF
317100209_1.pdf	261A8CB1BD71969F65C41922FD8301EBD59B0AFC4E8EC7ED 259797947A90CDBA21FE9E808FD3A882D58EB659C26283283 BD90202345653633ECD4D8C838C19B1
317100144_1.pdf	7DFF635BE038F0230905E1650103F06641F71FF89B64C5B3DB 3EC1C9BB8B0CCB1E4519803D9F02839CEA3C7B612A64F03A 5927F6A06756AE6929A0BBDC29AD81
317100181_1.pdf	61D84F9C167D826B81CEBCE1B36C4EA156C4BCD701964CEC A6ED2F72028571C544C7ECC62A0DE2E56E4154BE8325428FD 9A005FF8352BAD381F6548A85F4C4BB
Yang2014_NPL.pdf	481460374293DBB53998A04E8A22A1810EF0CC0AC6C6CD903 C6C76964355FC83D2C059CB92B243AA4D1027B346EBE3BCE D812324E5959283B4BCC4B242B98400
PCTUS2009033801 International Search Report and Written Opinion.pdf	31D759BB208590048D273FE4DE24EF9DE58205BCF77834CBC 3ED02B769455560E452642BD0B89D25B65B50655488639FBD4 D525E92307CD7261705285539659A

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: November 22, 2023
Electronic Signature for David Lu: /David Lu/

Docket No.: A2185-9003 (20191134-16)
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Xiaobo Wang et al.	Allowed: July 19, 2023
Application No.: 17/993,716	Confirmation No.: 1061
Filed: November 23, 2022	Art Unit: 2858
For: LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION	Examiner: A. He

INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement, pursuant to 37 C.F.R. § 1.114(c), accompanies the Request for Continued Examination (37 C.F.R. § 1.114) submitted herewith.

In accordance with 37 C.F.R. § 1.98(a)(2)(ii), copies of U.S. patents and U.S. patent application publications are not submitted. Submitted herewith are copies of foreign patents and non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2).

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made. In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

The Director is hereby authorized to charge any additional fees which may be required with respect to this communication, or credit any overpayment, to Deposit Account No. 02-1818, under Order No. A2185-9003 (20191134-16) (0528696.00002).

Dated: November 22, 2023

Respectfully submitted,

Electronic signature: /David Lu/
David Lu
Registration No.: 65,769
William Fortunato
Registration No.: 76,212
K&L GATES LLP
1 Congress Street
Suite 2900
Boston, Massachusetts 02114
(617) 261-3100

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
11027A PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2009/033801	11/02/2009	
Applicant		
BRISTOL-MYERS SQUIBB COMPANY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

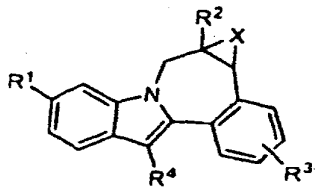
4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

Box No. IV **Text of the abstract (Continuation of item 5 of the first sheet)**

The invention encompasses selected compounds of formula I as well as compositions and methods of using the compounds. The compounds have activity against hepatitis C virus (HCV) and are useful in treating those infected with HCV.



I

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/033801

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/55 A61P31/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2009/029384 A (SQUIBB BRISTOL MYERS CO [US]; MARTIN SCOTT W [US]; BERGSTROM CARL P [U) 5 March 2009 (2009-03-05) the whole document	1-5
A	WO 2007/092888 A (SQUIBB BRISTOL MYERS CO [US]; BERGSTROM CARL P [US]; MARTIN SCOTT W [U) 16 August 2007 (2007-08-16)	1-5
A	WO 2007/033175 A (SQUIBB BRISTOL MYERS CO [US]; BERGSTROM CARL P [US]; BENDER JOHN A [US) 22 March 2007 (2007-03-22)	1-5

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 October 2009	30/10/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bardili, Burkhart

2

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/033801

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 2009029384	A	05-03-2009	CL	23532008 A1	24-10-2008
			PE	06182009 A1	16-05-2009
			US	2009074715 A1	19-03-2009
WO 2007092888	A	16-08-2007	AU	2007211988 A1	16-08-2007
			CN	101379066 A	04-03-2009
			EP	1987038 A2	05-11-2008
			JP	2009526081 T	16-07-2009
			KR	20080102161 A	24-11-2008
			US	2007185083 A1	09-08-2007
WO 2007033175	A	22-03-2007	AR	055165 A1	08-08-2007

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2009/033801	11.02.2009	

International Patent Classification (IPC) or both national classification and IPC
INV. C07D487/04 A61K31/55 A61P31/14

Applicant
BRISTOL-MYERS SQUIBB COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Bardili, Burkhart Telephone No. +49 89 2399-2132

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-5
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The documents D1/ WO 2007/092888 and D2/ WO 2007/033175 disclose compounds comprising a 7H-indolo[2,1-a][2]benzazepine ring system for the treatment of hepatitis C. The compounds recited in claim 1 are distinguished from D1 in the substituents attached to the 5-membered heterocyclic radical at position 6 of the parent ring system. They are distinguished from the compounds of D2 on account of the 5-membered heterocyclic radical directly attached to position 6 of the parent ring system.

The activity of the claimed compounds against hepatitis could not have been expected at the filing date of the application. Hence, inventive step is acknowledged.

Claims 3 and 4 relate to the medical treatment of the human body which is covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. The patentability of claims relating to the use of pharmaceutical compounds can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 2009/029384	05.03.2009	01.08.2008	

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

PETITION TO WITHDRAW AN APPLICATION FROM ISSUE AFTER PAYMENT OF THE ISSUE FEE UNDER 37 CFR 1.313(c)(2)

APPLICATION #	ATTORNEY DOCKET #	FILING DATE
17993716	20191134-16	11/23/2022

Title of Invention

LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

Application Information

CONFIRMATION #	1061	FILING DATE	11/23/2022
ART UNIT	2858	FIRST NAMED INVENTOR	Xiaobo Wang
EXAMINER	AMY HE		

An application may be withdrawn from issue for further action upon petition by the applicant. To request that the Office withdraw an application from issue, applicant must file a petition under this section including the fee set forth in § 1.17(h) and a showing of good and sufficient reasons why withdrawal of the application from issue is necessary.

APPLICANT HEREBY PETITIONS TO WITHDRAW THIS APPLICATION FROM ISSUE UNDER 37 CFR 1.313(c).

A grantable petition requires the following items:

(1) Petition fee; and
(2) One of the following reasons: A grantable petition requires the following items: (a) Unpatentability of one or more claims, which must be accompanied by an unequivocal statement that one or more claims are unpatentable, an amendment to such claim or claims, and an explanation as to how the amendment causes such claim or claims to be patentable;
(b) Consideration of a request for continued examination in compliance with § 1.114 (for a utility or plant application only); or
(c) Express abandonment of the application. Such express abandonment may be in favor of a continuing application, but not a CPA under 37 CFR 1.53(d).

Reason for withdrawal

Consideration of a request for continued examination - RCE request, submission, and fee are attached

Applicant claims the following entity status

Regular Undiscounted

Signature

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:
An attorney or agent registered to practice before the Patent and Trademark Office who has been given power of attorney in this application

Signature	Name	Registration #
/David Lu/	David Lu	65769

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

GRANT LETTER

APPLICATION #	DECISION DATE	DECISION ON PETITION #	ATTORNEY DOCKET NUMBER
17/993,716	11/22/2023	37 CFR 1.313(c)(2)	20191134-16

Title of Invention

LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

In re Application of Xiaobo Wang

This is an electronic decision on the petition under 37 CFR 1.313(c)(2), filed November 22, 2023 to withdraw the above-identified application from issue after payment of the issue fee.

The request is **GRANTED.**

The above-identified application is withdrawn from issue for consideration of a submission under 37 CFR 1.114 (request for continued examination). See 37 CFR 1.313(c)(2).

Petitioner is advised that the issue fee paid in this application cannot be refunded. If, however, this application is again allowed, petitioner may request that it be applied towards the issue fee required by the new Notice of Allowance.

The application is being referred to Technology Center AU for processing of the request for continuing examination under 37 CFR 1.114 .

Telephone inquired concerning this decision should be directed to the Patent Electronic Business Center (EBC) at 866-217-9197.

Office of Petitions

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/993,716	**11/22/2023 02:47:43 PM Z ET**	**20191134-16**

Title of Invention

LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1061	FILED BY	David Lu
PATENT CENTER #	63359392	AUTHORIZED BY	-
CUSTOMER #	188545	FILING DATE	11/23/2022
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Xiaobo Wang

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 021818	**E2023ALE48475018**	**David Lu**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1464	PETITIONS REQUIRING THE PETITION FEE SET FORTH IN 37 CFR 1.17(H) (GROUP III)	140.00	1	140.00
1801	REQUEST FOR CONTINUED EXAMINATION (RCE) - 1ST REQUEST (SEE 37 CFR 1.114)	1360.00	1	1360.00
			TOTAL AMOUNT:	**$1,500.00**

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

188545 7590 12/13/2023

Agilent Technologies, Inc./K&L Gates LLP
Global IP Operations
5301 Stevens Creek Blvd, 1A-PB
Santa Clara, CA 95051

EXAMINER	
HE, AMY	
ART UNIT	PAPER NUMBER
2858	

DATE MAILED: 12/13/2023

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/993,716	11/23/2022	Xiaobo Wang	20191134-16	1061

TITLE OF INVENTION: LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$1200.00	$0	03/13/2024

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

188545 7590 12/13/2023

Agilent Technologies, Inc./K&L Gates LLP
Global IP Operations
5301 Stevens Creek Blvd, 1A-PB
Santa Clara, CA 95051

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/993,716	11/23/2022	Xiaobo Wang	20191134-16	1061

TITLE OF INVENTION: LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$1200.00	$0	03/13/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
HE, AMY	2858	506-010000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/993,716	11/23/2022	Xiaobo Wang	20191134-16	1061

188545 7590 12/13/2023

Agilent Technologies, Inc./K&L Gates LLP
Global IP Operations
5301 Stevens Creek Blvd, 1A-PB
Santa Clara, CA 95051

EXAMINER	
HE, AMY	

ART UNIT	PAPER NUMBER
2858	

DATE MAILED: 12/13/2023

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
2) a federal, state, local, or international agency, in response to its request;
3) a contractor of the USPTO having need for the information in order to perform a contract;
4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 17/993,716	Applicant(s) Wang et al.	
	Examiner AMY HE	Art Unit 2858	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the IDS and RCE dated November 22, 2023.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 11/22/2023.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/AMY HE/
Primary Examiner, Art Unit 2858

Continuation of 3. The allowed claim(s) is/are: 1-2,4,6,9-13,18,24 and 31-49

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.

2. Claims 1, 2, 4, 6, 9-13, 18, 24, 31-49 are allowed.

REASONS FOR ALLOWANCE

3. The following is an examiner's statement of reasons for allowance:

Claims 1, 2, 4, 6 and 9-13 and 31-36 are allowable because none of the prior art discloses or fairly suggests an apparatus for continuous, label free, real-time monitoring of cells using impedance-based analysis, the apparatus comprising: a) multiwell plate comprising a plurality of wells on a nonconductive substrate, wherein each of the plurality of wells comprises an electrode array of a plurality of electrode arrays; b) an impedance analyzer that independently measures a cell-substrate impedance at each well, the cell-substrate impedance being measured between a first electrode structure and a second electrode structure of the electrode array and across a cellular sample comprising a plurality of cells disposed within each well, the impedance analyzer including at least two analogue-to-digital conversion channels, wherein the impedance analyzer monitors the electrode arrays at millisecond time resolution between first measurements of the cell-substrate impedance and second measurements of the cell-substrate impedance for each well; and c) a software program that analyzes the first measurements and the second measurements to produce a time period analysis of the cellular sample, and in the combination as claimed in claim 1.

Claims 18 and 37-42 are allowable because none of the prior art discloses or fairly suggest a system for continuously monitoring cells in real time, label free, with impedance-based analysis, the

system comprising: a) a plurality of analog-to-digital (A2D) signal converters electrically arranged in parallel to one another; b) a well plate comprising a plurality of wells on a nonconductive substrate, wherein each well comprises one electrode array of a plurality of electrode arrays disposed on the nonconductive substrate; c) an impedance analyzer that measures a first plurality of cell-substrate impedances at a first time and a second plurality of cell-substrate impedances at a second time, the first plurality of cell-substrate impedances and the second plurality of cell-substrate impedances being measured between first electrode structure and a second electrode structure in each electrode array and across a cell sample attached within each well of the plurality of wells; and d) a software program that analyzes the first plurality of cell-substrate impedances and the second plurality of cell-substrate impedances to produce a plurality of time period analyses associated with individual wells of the plurality of wells, and in the combination as claimed in claim 18.

Claims 24 and 43-49 are allowable because none of the prior art discloses or fairly suggests a system for continuously monitoring cells in real time, label free, with impedance-based analysis, the system comprising: a) a well plate comprising a plurality of electrode arrays, wherein each electrode array is disposed in a corresponding well of a plurality of wells defined by the well plate and includes a first electrode structure and a second electrode structure; b) an impedance analyzer that monitors, in association with individual cell samples in individual wells of the plurality of wells via each individual electrode array of the plurality of electrode arrays, a cell-substrate impedance between the first electrode structure and the second electrode structure across a cell sample disposed in a corresponding well of the plurality of wells; c) electronic circuitry that electrically connects the plurality of electrode arrays to the impedance analyzer; and d) a software program that analyzes the continuously monitors each cell sample via the plurality of cell-substrate impedances across an analysis period of time with

measurements recorded at a sampling time resolution during the period of time, and in the combination as claimed in claim 24.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY HE whose telephone number is (571)272-2230. The examiner can normally be reached 9:00am--5:00pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Huy Phan can be reached on (571) 272-7924. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/AMY HE/
Primary Examiner, Art Unit 2858

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/993,716	Wang et al.
	Examiner	Art Unit
	AMY HE	2858

CPC - Searched*		
Symbol	Date	Examiner
G01N33/4836 OR G01N27/02 OR G01N33/4833 OR G01N33/48728 OR G01N33/5438	12/04/2023	AH

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
G01N33/4836 OR G01N27/02 OR G01N33/4833 OR G01N33/48728 OR G01N33/5438 COMBINED WITH TEXT SEARCH updated	12/04/2023	AH
similarity search updated	12/04/2023	AH
more like search updated	12/04/2023	AH

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
G01N	33/4836; 33/4833; 33/48728; 33/5438; 27/02	12/04/2023	AH

/AMY HE/ Primary Examiner, Art Unit 2858	

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/993,716	Wang et al.
	Examiner	**Art Unit**
	AMY HE	2858

CPC							
Symbol						**Type**	**Version**
G01N	/	33	/	4836		F	2013-01-01
G01N	/	33	/	4833		I	2013-01-01
G01N	/	33	/	48728		I	2013-01-01
G01N	/	33	/	5438		I	2013-01-01
G01N	/	27	/	02		I	2013-01-01

CPC Combination Sets								
Symbol						**Type**	**Set**	**Ranking**	**Version**
	/		/						

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	30	
/AMY HE/ Primary Examiner, Art Unit 2858	05 December 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	1A

U.S. Patent and Trademark Office — Part of Paper No.: 20231205

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/993,716	Wang et al.
	Examiner	**Art Unit**
	AMY HE	2858

INTERNATIONAL CLASSIFICATION				
CLAIMED				
G01N33/483	/	33	/	483
G01N33/487	/	33	/	487
G01N33/543	/	33	/	543
G01N27/02	/	27	/	02

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE (Assistant Examiner) (Date)	**Total Claims Allowed:** 30	
/AMY HE/ Primary Examiner, Art Unit 2858 (Primary Examiner) 05 December 2023 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 1A

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/993,716	Wang et al.
	Examiner	**Art Unit**
	AMY HE	2858

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	6	10		19		28	17	37	27	46				
2	2	7	11		20		29	18	38	28	47				
	3	8	12		21		30	19	39	29	48				
3	4	9	13		22	10	31	20	40	30	49				
	5		14		23	11	32	21	41						
4	6		15	23	24	12	33	22	42						
	7		16		25	13	34	24	43						
	8		17		26	14	35	25	44						
5	9	16	18		27	15	36	26	45						

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	30	
/AMY HE/ Primary Examiner, Art Unit 2858	05 December 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	1A

U.S. Patent and Trademark Office Part of Paper No.: 20231205

PTO/SB/08a (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(**Not for submission under 37 CFR 1.99)**

Application Number	17993716
Filing Date	2022-11-23
First Named Inventor	Xiaobo Wang
Art Unit	2858
Examiner Name	A. He
Attorney Docket Number	A2185-9003 (20191134-16)

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	17993716
	Filing Date	2022-11-23
	First Named Inventor	Xiaobo Wang
	Art Unit	2858
	Examiner Name	A. He
	Attorney Docket Number	A2185-9003 (20191134-16)

/A.H/	1	YANG et al., "Tri-iodo-L-Thyronine Promotes the Maturation of Human Cardiomyocytes-Derived from Induced Pluripotent Stem Cells," Journal of Molecular and Cell Cardiology (2014) Vol. 72, 296-304	☐
/A.H/	2	International Search Report and Written Opinion for International Application No. PCT/US2009/033801 dated October 30, 2009.	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/AMY HE/	Date Considered	12/04/2023

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L73	12	((US-10551371-B2 OR US-9709548-B2 OR US-5810725-A).did. AND USPT.dbnm.) OR ((US-20100029506-A1 OR US-20050279634-A1 OR US-20050118565-A1 OR US-20030111343-A1 OR US-20230130050-A1 OR US-20040167723-A1 OR US-20020113607-A1).did. AND PGPB.dbnm.) OR ((AU-2002365810-A1 OR EP-0566725-B1).did. AND FTDB.dbnm.)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/12/04 11:05 AM
L74	0	"17993716".pn.	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/12/04 11:06 AM
L75	133386	((wang near2 xiaobo)(Abassi near2 yama)(Xi near2 biao)(zhang near2 wen$1fu)(xu near2 xiao)).inv.	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/12/04 11:34 AM
L76	15218	(Agilent ADJ technologies).as.	(US-PGPUB; USPAT; USOCR; FIT (AP, AT,	OR	ON	ON	2023/12/04 11:35 AM

			AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L77	45114	(G01N33/4836 or G01N27/02 or G01N33/4833 or G01N33/48728 or G01N33/5438).cpc.	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/12/04 11:36 AM
L78	193467	L75 L76 L77	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/12/04 11:36 AM
L79	5293	L78 AND ((cell ADJ seeding)(cell ADJ attach$3)(impedance WITH time))	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE,	OR	ON	ON	2023/12/04 11:38 AM

			SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L80	409	L79 AND milliseconds	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/12/04 11:38 AM
L81	2212	L79 AND (impedance WITH (cell well plate))	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/12/04 01:12 PM
L82	1002	L81 AND (impedance WITH (frequency AND voltage))	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/12/04 01:13 PM
L83	111	L82 AND milliseconds	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU,	OR	ON	ON	2023/12/04 02:53 PM

			CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L84	36	L83 AND (cell near4 beat$3)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/12/04 03:14 PM
L85	35	(Artificial Intelligence) More like doc: US-20200158670-A1 Text: (WO-2014085727-A1 OR US-10539523-B2 OR US-20140203818-A1 OR US-11346797-B2 OR US-9709548-B2 OR EP-2291645-B1 OR US-10533985-B2 OR US-20180306771-A1 OR US-20220291191-A1 OR US-10012636-B2 OR US-20180095064-A1 OR US-20210164961-A1 OR US-11360072-B2 OR EP-2427543-A1 OR WO-2010129725-A1 OR US-20230130050-A1 OR CA-2575297-C OR CA-2575297-A1 OR CA-2575573-A1 OR AU-2003252155-B2).did.	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/12/04 03:20 PM
L86	30	(Artificial Intelligence) More like doc: US-20110300569-A1	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY,	OR	ON	ON	2023/12/04 03:24 PM

		Text: (WO-2011146531-A1 OR WO-2011146531-A9 OR US-9612234-B2 OR US-20170205391-A1 OR US-20220291191-A1 OR US-20210164961-A1 OR US-11360072-B2 OR US-10012636-B2 OR US-20180095064-A1 OR WO-2009137440-A1 OR EP-2291645-A1 OR CA-2723223-C OR EP-2291645-B1 OR CA-2723223-A1 OR US-20180306771-A1 OR US-10533985-B2 OR US-20100029506-A1 OR US-9709548-B2 OR US-20230130050-A1 OR CA-2760941-C).did.	CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L87	46	(Artificial Intelligence) Similar to: 17/993,716 with 0 CPC Selections and 0 Text Selections Text: (US-20230130050-A1 OR US-9709548-B2 OR US-20180306771-A1 OR US-10533985-B2 OR US-11360072-B2 OR US-20210164961-A1 OR US-20220291191-A1 OR WO-2009137440-A1 OR EP-2291645-A1 OR US-20100029506-A1 OR CA-2723223-A1 OR CA-2723223-C OR US-10012636-B2 OR US-20180095064-A1 OR EP-2291645-B1 OR US-20170205391-A1 OR US-9612234-B2 OR US-20110300569-A1 OR WO-2011146531-A9 OR WO-2011146531-A1 OR US-10761081-B2 OR WO-2017216694-A1 OR US-20180100849-A1 OR WO-2015196957-A1 OR EP-3159400-A1 OR	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO))	OR	ON	ON	2023/12/04 03:26 PM

		CN-104789443-B OR US-20160305927-A1 OR JP-2017519524-A OR US-20090309618-A1 OR US-9404140-B1 OR CN-104789443-A OR US-9399787-B2 OR US-7876108-B2 OR US-20050213374-A1 OR JP-2016212083-A OR US-20230014082-A1 OR US-8344742-B2 OR US-20130123136-A1 OR US-7560269-B2 OR US-11774396-B2 OR JP-2023530702-A OR EP-4168172-A1 OR WO-2021257705-A1 OR GB-2576429-A OR US-20100120626-A1 OR AU-2018224829-A1 OR CA-3053191-A1 OR WO-2018157073-A1 OR WO-2015068530-A1 OR JP-6370544-B2).did.					
L88	41	(Artificial Intelligence) Similar to: 17/993,716 with 1 CPC Selection and 2 Text Selections Text: (US-20170205391-A1 OR US-9612234-B2 OR CA-2760941-C OR CA-2760941-A1 OR EP-2427543-A1 OR WO-2010129725-A1 OR US-20110300569-A1 OR WO-2011146531-A9 OR WO-2011146531-A1 OR WO-9854294-A1 OR US-5981268-A OR EP-1244910-B1 OR JP-2010539462-A OR US-6051422-A OR US-20060228771-A1 OR EP-2037268-A1 OR EP-2199783-A1 OR WO-2010070538-A1 OR WO-2009033987-A1 OR EP-2198297-A1 OR US-20110074449-A1 OR US-20230130050-A1 OR DE-60018473-T2 OR	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO))	OR	ON	ON	2023/12/04 03:27 PM

		US-8642287-B2 OR US-11747321-B2 OR US-20180306771-A1 OR US-10533985-B2 OR US-20030107386-A1 OR EP-1244910-A1 OR WO-0148474-A1 OR US-20130037423-A1 OR US-11768196-B2 OR EP-2458373-A1 OR KR-20170133976-A OR US-11774396-B2 OR US-20120119762-A1 OR CA-3187265-A1 OR EP-4168528-A1 OR WO-2021257701-A1 OR DE-10254158-A1 OR JP-WO2011010721-A1 OR US-20040055901-A1 OR US-20230014082-A1 OR US-6151519-A OR US-11360072-B2 OR US-20210164961-A1 OR CA-2385482-A1 OR WO-9822819-A1 OR EP-0938674-A1 OR US-20220291191-A1).did.					

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N6	66689	(impedance WITH (frequency AND voltage))	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/04 03:42 PM
N7	382	N4 AND N6	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/04 03:43 PM
N8	54	N7 AND milliseconds	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/04 03:43 PM

PART B–FEE(S) TRANSMITTAL

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William Fortunato	(Typed or printed name)
/William Fortunato/	(Signature)
December 29, 2023	(Date)

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
17/993,716	11/23/2022	Xiaobo Wang	A2185-9003	1061

TITLE OF INVENTION: LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

APPLN: TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200.00	$0.00	$1200.00	$0.00	03/13/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
HE, AMY	2858	506-010000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363)

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1. K&L Gates LLP
2.
3.

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: AGILENT TECHNOLOGIES, INC.

(B) RESIDENCE: (CITY and STATE or COUNTRY): SANTA CLARA, CA

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees Submitted: ☐ Issue Fee ☐ Publication Fee (if required)

4b. Method of Payment (*Please first reapply any previously paid fee shown above*):

☒ Electronic Payment via Patent Center or EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 02-1818

5. Change of Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29. NOTE: Absent a valid Certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27. NOTE: If the application was previously under micro entity status, checking this box will be taken as a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status. NOTE: Checking this box will be taken as a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /William Fortunato/ Date December 29, 2023

UNITED STATES
PATENT AND TRADEMARK OFFICE

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Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/993,716	**12/29/2023 07:42:02 PM Z ET**	**20191134-16**

Title of Invention

LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1061	FILED BY	Brynn Kooyenga
PATENT CENTER #	63796141	FILING DATE	11/23/2022
CUSTOMER #	188545	FIRST NAMED INVENTOR	Xiaobo Wang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	William Fortunato

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
12.29.23 A2185-9003 -- 20191134-16 -- Issue Fee Transmittal.pdf	1	Issue Fee Payment (PTO-85B)	191 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
12.29.23 A2185-9003 -- 20191134-16 -- Issue Fee Transmittal.pdf	14AF96A5D2951BB3299610D7615B4D7D5403C34DC627A6AFD01D0E8A7F275F7D4A755AAE67C499A905C08D9F147FC6FD9E35EA9C68C4AA2C4C5C323F7089292D

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New Applications Under 35 U.S.C. 111

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National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

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PART B–FEE(S) TRANSMITTAL

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William Fortunato	(Typed or printed name)
/William Fortunato/	(Signature)
December 29, 2023	(Date)

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
17/993,716	11/23/2022	Xiaobo Wang	A2185-9003	1061

TITLE OF INVENTION: LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

APPLN: TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200.00	$0.00	$1200.00	$0.00	03/13/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
HE, AMY	2858	506-010000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363)

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1. K&L Gates LLP
2.
3.

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: AGILENT TECHNOLOGIES, INC.

(B) RESIDENCE: (CITY and STATE or COUNTRY): SANTA CLARA, CA

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees Submitted: ☐ Issue Fee ☐ Publication Fee (if required)

4b. Method of Payment (*Please first reapply any previously paid fee shown above*):

☒ Electronic Payment via Patent Center or EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 02-1818

5. Change of Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29. NOTE: Absent a valid Certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27. NOTE: If the application was previously under micro entity status, checking this box will be taken as a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status. NOTE: Checking this box will be taken as a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /William Fortunato/ Date December 29, 2023

United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :Sofia Mohammed

Refund Accounting Date:01/03/2024

Effective Date	Sale Item Reference Number	Refund Total
09/25/2023	17993716	$1,200.00

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method	Account Number
I202412M25287760	1501	UTILITY APPL ISSUE FEE	$1,200.00	DA	021818

United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :Sofia Mohammed

Sale Adjustment Accounting Date:01/03/2024

Effective Date	Sale Accounting Date	Sale Item Reference Number
09/25/2023	01/03/2024	17993716

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I202412M25287760	1501	UTILITY APPL ISSUE FEE	$1,200.00	DA

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Office of the Chief Financial Officer

Document Code:WFEE

User :Sofia Mohammed

Sale Accounting Date:01/03/2024

Sale Item Reference Number	Effective Date
17993716	12/29/2023

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I202412M29147640	1501	UTILITY APPL ISSUE FEE	$1,200.00	Deposit Account

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/993,716	02/20/2024	11906508	20191134-16	1061

188545 7590 01/31/2024

Agilent Technologies, Inc./K&L Gates LLP
Global IP Operations
5301 Stevens Creek Blvd, 1A-PB
Santa Clara, CA 95051

ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at https://patentcenter.uspto.gov/. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at https://certifiedcopycenter.uspto.gov/index.html. The Certified Copy Center may be reached at (800)972-6382.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Center (https://patentcenter.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional inventors):

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APPLICANT(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional applicants):

Agilent Technologies, Inc., Santa Clara, CA;

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188545 7590 02/20/2024

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Santa Clara, CA 95051

EXAMINER	
HE, AMY	

ART UNIT	PAPER NUMBER
2858	

NOTIFICATION DATE	DELIVERY MODE
02/20/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Agilentdocketing@cpaglobal.com
ipopsadmin@agilent.foundationip.com
uspatentmail@klgates.com

APPLICATION NO.	ISSUE DATE	PATENT NO.
17/993,716	20-Feb-2024	11906508

Agilent Technologies, Inc./K&L Gates LLP
Global IP Operations
5301 Stevens Creek Blvd, 1A-PB
Santa Clara, CA 95051

EGRANT NOTIFICATION

Your electronic patent grant (eGrant) is now available, which can be accessed via Patent Center at https://patentcenter.uspto.gov

The electronic patent grant is the official patent grant under 35 U.S.C. 153. For more information, please visit https://www.uspto.gov/electronicgrants