

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AXION BIOSYSTEMS, INC.
Petitioner

v.

AGILENT TECHNOLOGIES, INC.
Patent Owner

U.S. Patent No. 11,906,508

PETITION FOR *INTER PARTES* REVIEW

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EX1001	U.S. Patent No. 11,906,508 (the “’508 patent”)
EX1002	File History for U.S. Patent No. 11,906,508
EX1003	Declaration of Dr. Bruce Kim
EX1004	Curriculum Vitae of Dr. Bruce Kim
EX1005	U.S. Patent No. 7,192,752 to Xu et al. (“Xu-752”)
EX1006	U.S. Patent Application Publication No. 2007/0057680 to Jones et al. (“Jones”)
EX1007	U.S. Patent No. 7,459,918 to Jones et al.
EX1008	“Real-Time Monitoring of Morphological Changes in Living Cells by Electronic Cell Sensor Arrays: An Approach To Study G Protein-Coupled Receptors,” by Naichen Yu et al., <i>Analytical Chemistry</i> , Vol. 78, No. 1, 35-43 (January 2006) (“Yu”)
EX1009	Reserved
EX1010	Scheduling Order in <i>Agilent Technologies, Inc. v. Axion BioSystems, Inc.</i> , Case No. 1:24-cv-300-CJB (D. Del.) (D.I. 24, dated June 21, 2024)
EX1011	Reserved
EX1012	PDF of Agilent’s Technology Tutorial for Xu-752 and related patents in <i>Agilent Technologies, Inc. v. Axion BioSystems, Inc.</i> , Case No. 1:23-cv-198-CJB (D. Del.) (D.I. 127) (April 5, 2024)
EX1013	U.S. Patent No. 9,709,548 to Wang et al. (“Wang-548”)
EX1014	File History Excerpts for Wang-548 (U.S.P.N. 9,709,548)
EX1015	U.S. Patent No. 7,459,303 to Wang et al. (“Wang-303”)
EX1016	U.S. Patent No. 7,470,533 to Xu et al. (“Xu-533”)

LIST OF PETITIONER EXHIBITS

(continued)

- EX1017 “Monitoring electroporabilization in the plasma membrane of adherent mammalian cells,” by Paramita M. Ghosh et al., Biophysical Journal, Vol. 64(5), 1602-1609 (May 1993) (“Ghosh”)
- EX1018 “Performance of a thin film microelectrode array for monitoring electrogenic cells in vitro,” by A. Mohr et al., Sensors and Actuators, B 34, 265-269 (1996) (“Mohr”)
- EX1019 “Portable cell-based biosensor system for toxin detection,” by Joseph J. Pancrazio et al., Sensors and Actuators, B 53, 179-185 (1998) (“Pancrazio”)
- EX1020 Reserved
- EX1021 “CMOS microelectrode array for the monitoring of electrogenic cells,” by F. Heer et al., Biosensors and Bioelectronics 20, 358-366 (March 2004) (“Heer”)
- EX1022 “A novel microfluidic impedance assay for monitoring endothelin-induced cardiomyocyte hypertrophy,” by Mo Yang et al., Biosensors and Bioelectronics (2006) (“Yang”)
- EX1023 “Real Time Monitoring Primary Cardiomyocyte Adhesion Based on Electrochemical Impedance Spectroscopy and Electrical Cell-Substrate Impedance Sensing,” by Yiling Qiu et al., Analytical Chemistry, Vol. 80, No. 4, 990-996 (February 2008) (“Qiu”)
- EX1024 Operating Manual for Solartron Analytical 1260 Impedance/Gain-Phase Analyzer (January 1996)
- EX1025 “Monitoring fibroblast behavior in tissue culture with an applied electric field,” by Ivar Giaever et al., Proc. Natl. Acad. Sci. (USA), Vol. 81, 3761-3764 (June 1984) (“Giaever-1984”)
- EX1026 “A new planar multielectrode array for extracellular recording: application to hippocampal acute slice,” by Hiroaki Oka et al., Journal of Neuroscience Methods, Vol. 93(1), 61-67 (October 1999) (“Oka”)
- EX1027 Librarian Declaration

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I. INTRODUCTION

Blinded by desire to harm Axion—a competitor against whom Agilent was already litigating other, now-expired patents—Agilent pursued claims that the PTO should never have issued in the application that led to the '508 patent. Indeed, the key prior-art references include some of the '508 patent co-inventors' own work that was published years before the '508 patent's earliest claimed priority date. That earlier work anticipates some claims, would have rendered claims obvious, and, for the remaining claims, is missing only trivial features that were otherwise well known in the art and cannot possibly salvage patentability. Axion requests institution of IPR and cancellation of claims 1-30.

II. REQUIREMENTS FOR IPR UNDER 37 C.F.R. § 42.204

A. Grounds For Standing Under 37 C.F.R. § 42.204(a)

Axion certifies that the '508 patent is eligible for IPR, and Axion is not barred or estopped from requesting IPR of claims 1-30 on the challenged grounds.

B. Identification Of Challenge Under 37 C.F.R. § 42.204(b) And Relief Requested

Axion requests IPR on the following grounds:

Ground	Claims	Basis
Ground 1	23-30	§ 102 and § 103 based on U.S. Patent No. 7,192,752 to Xu et al. ("Xu-752")
Ground 2	1-22	§ 103 based on Xu-752 and U.S. Patent Application Publication No. 2007-0057680 to Jones et al. ("Jones")

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The earliest filing date to which the '508 patent could potentially claim priority is May 5, 2008. EX1001, 2. Xu-752 and Jones are prior art to the '508 patent under at least 35 U.S.C. § 102(b) (pre-AIA): Xu-752 issued on March 20, 2007 (EX1005), and Jones was published on March 15, 2007 (EX1006). Neither reference was cited by the PTO or applied during prosecution of the '508 patent. EX1002. The patentee disclosed Xu-752 in an IDS that listed over 330 documents. EX1002, 131-52.

The PTO applied the pre-grant publication version of Xu-752 (US 2005/0153425) in at least one of the parent applications to the '508 patent: U.S. Application No. 12/435,569 (issued as U.S.P.N. 9,709,548 ("Wang-548," EX1013)). But, as discussed below (§ III.C), the application for the '508 patent is a sixth-generation continuation of Wang-548, the PTO Examiner for Wang-548 and the '508 patent was not the same, and the PTO did not apply Xu-752 in examining the claims that ultimately issued as the '508 patent.

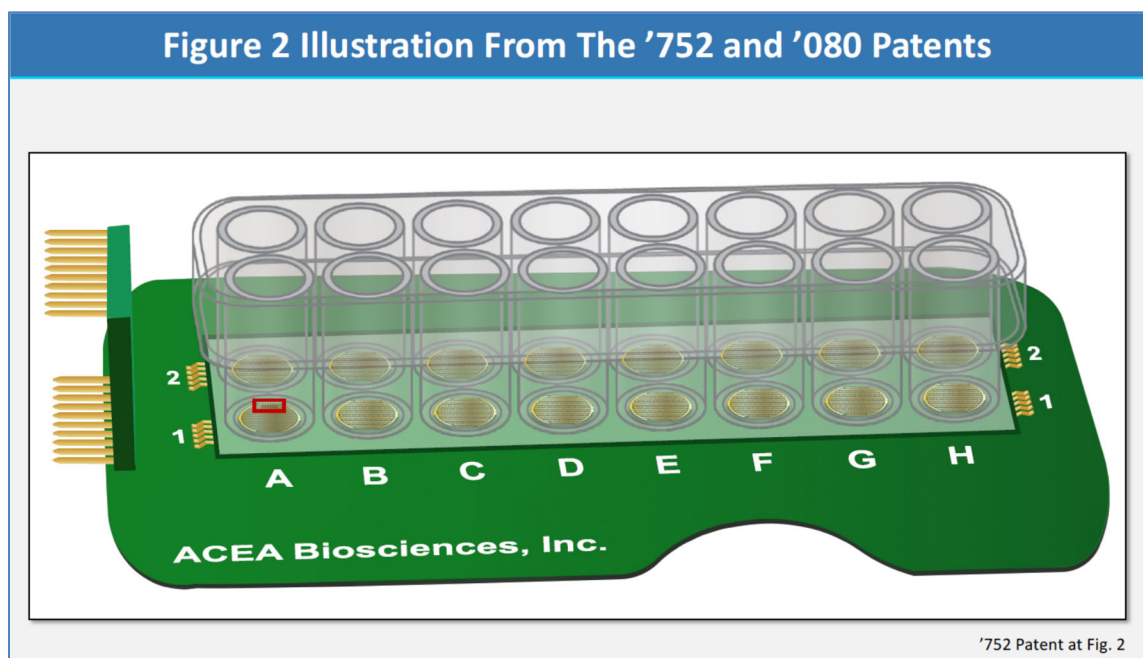
III. THE '508 PATENT AND CLAIM CONSTRUCTION

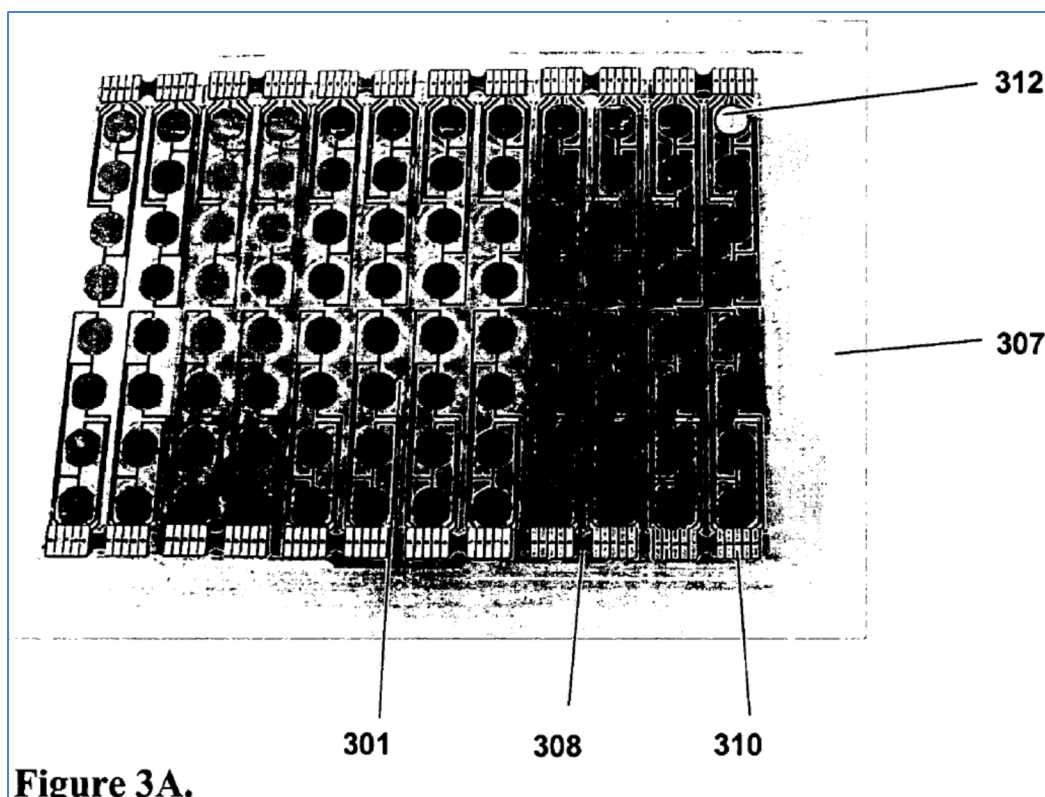
A. Technology Background

The technology here is old and not complex. EX1003, ¶¶39-60. As early as 1984, Giaever and Keese described using electrical cell-substrate impedance sensing for real-time analysis of cellular processes. *Id.*, ¶40; EX1025; EX1015, 3:44-52 (referencing Giaever and Keese's work); EX1016, 2:16-21 (same).

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Impedance-based cell analysis systems generally work by applying a voltage or current to electrode(s) in the bottom of a well in a multiwell microtiter plate so that the impedance of the well can be measured. EX1003, ¶41. Xu-752's 16-well and 96-well plates (EX1005, Figs. 2, 3A) are shown below, with a cleaned-up version of Xu-752's Figure 2 that was prepared by Agilent. EX1012, 53.





When a voltage is applied to an electrical element, an electrical current is conducted. EX1003, ¶42. Impedance is the opposition of the electrical element to an alternating current and has two components: resistance and reactance. EX1005, 26:31-35; EX1003, ¶42. When a voltage is applied, a higher impedance object will allow less current to be conducted (and vice versa). EX1003, ¶42.

In impedance-based systems, biological cells present in a well of a plate will block some of the current and thus act as an impedance. *Id.*, ¶43. As a result, the behavior of cells can be observed by monitoring their impedance. *Id.* Prior-art impedance-based cell analysis systems utilized multiwell plates or devices

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connected to an impedance analyzer, and a software program to record and/or analyze the impedance data. *Id.*; EX1005, Abstract, 24:48-61.

B. ACEA Entered the Market in the Early 2000s, Filing Patent Applications from 2002-2004 on Impedance-Based Cell Analysis Systems.

Almost 20 years after Giaever and Keese first reported using impedance-based cell analysis, a small, southern-California company—ACEA—entered the market. ACEA didn't claim to invent impedance-based cell analysis systems, nor could it given the earlier work of Giaever and Keese. ACEA began its patent activity in 2002, and one of its earliest-issued patents was Xu-752, issued in March 2007.

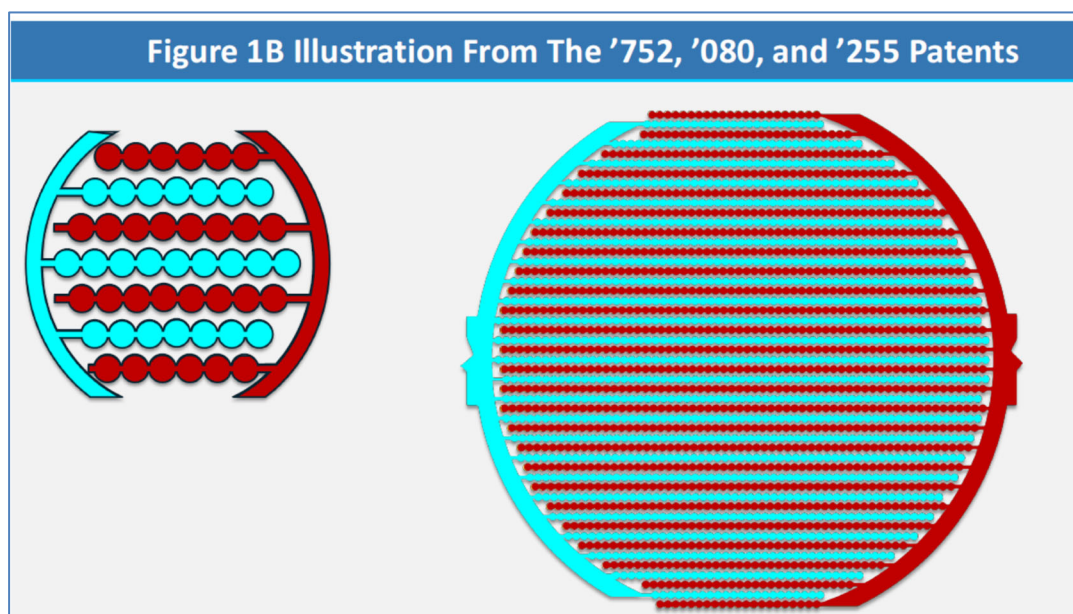
Xu-752 states that its “invention provides a real time cell electronic sensing system for conducting cell-based assays based on measurement of cell-substrate impedance and provides the method for using such a system to perform cell-based assays.” EX1005, 3:49-53. Xu-752's system includes four main components: (a) a multiwell plate or device with an electrode array in the bottom of each well (*id.*, 4:17-19, 22:50-52, 23:4-8); (b) an impedance analyzer (*id.*, 4:19-20, 22:62-23:3, 23:49-60); (c) electronic circuitry that connects the electrode arrays to the impedance analyzer (*id.*, 22:44-52, 23:44-52); and (d) a software program that performs data acquisition and data analysis on data from the impedance analyzer (*id.*, 4:24-26, 22:58-61, 23:66-24:12). *Id.*, claim 1; EX1003, ¶44. Xu-752's specification is focused largely on cell-based assays and methods of using its cell analysis system

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(*id.*, 24:56-70:46, Figs. 6A-18), as well as the design of the electrode arrays in the wells of the multiwell plates (*id.*, 15:50-22:30, Figs. 1A-5).

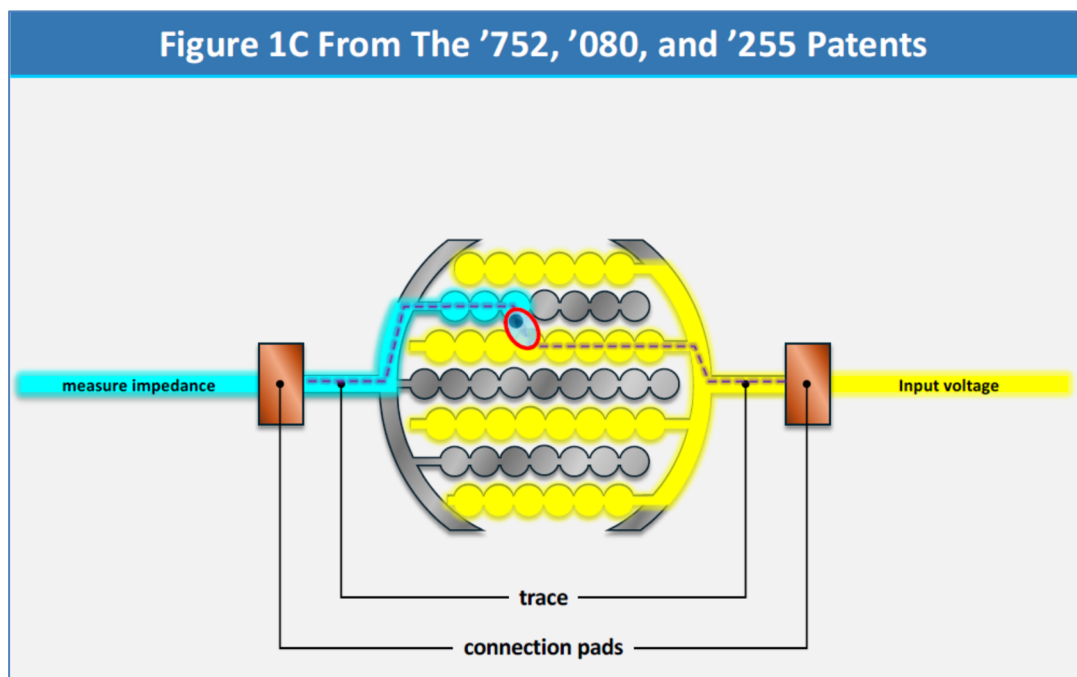
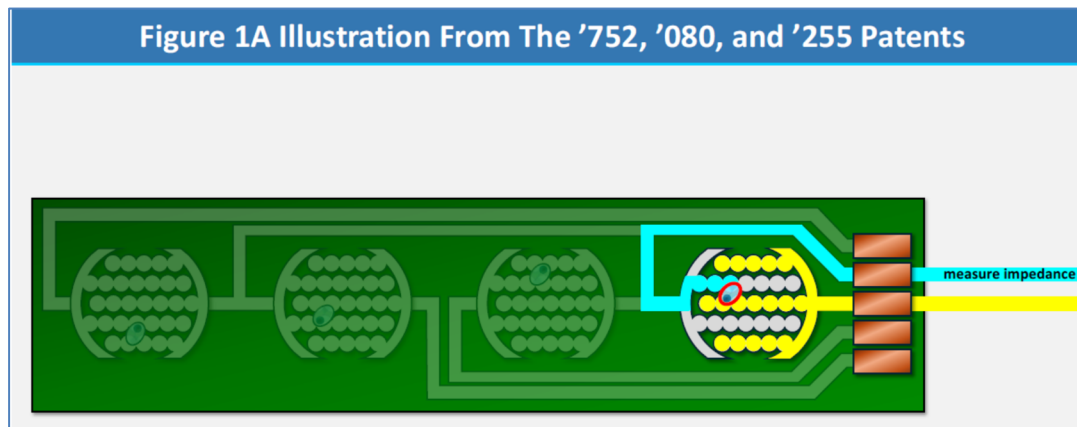
Agilent acquired ACEA in 2018. <https://www.agilent.com/about/newsroom/presrel/2018/14nov-gp18062.html> (last visited September 12, 2024). In addition to Agilent's pending litigation against Axion on the '508 patent, Agilent is also currently asserting that Axion infringes claims 11-20 of Xu-752 (and two other patents) in another Delaware litigation (Case No. 1:23-cv-198-CJB). In the litigation based on Xu-752, Agilent submitted a technology tutorial to the court, including annotated versions of Xu-752's Figs. 1A-1C to explain the structure of Xu-752's electrode arrays. EX1012.

Annotated Figure 1B (below) shows an electrode array in Xu-752, with a first electrode structure in blue and a second electrode structure in red. EX1003, ¶45.



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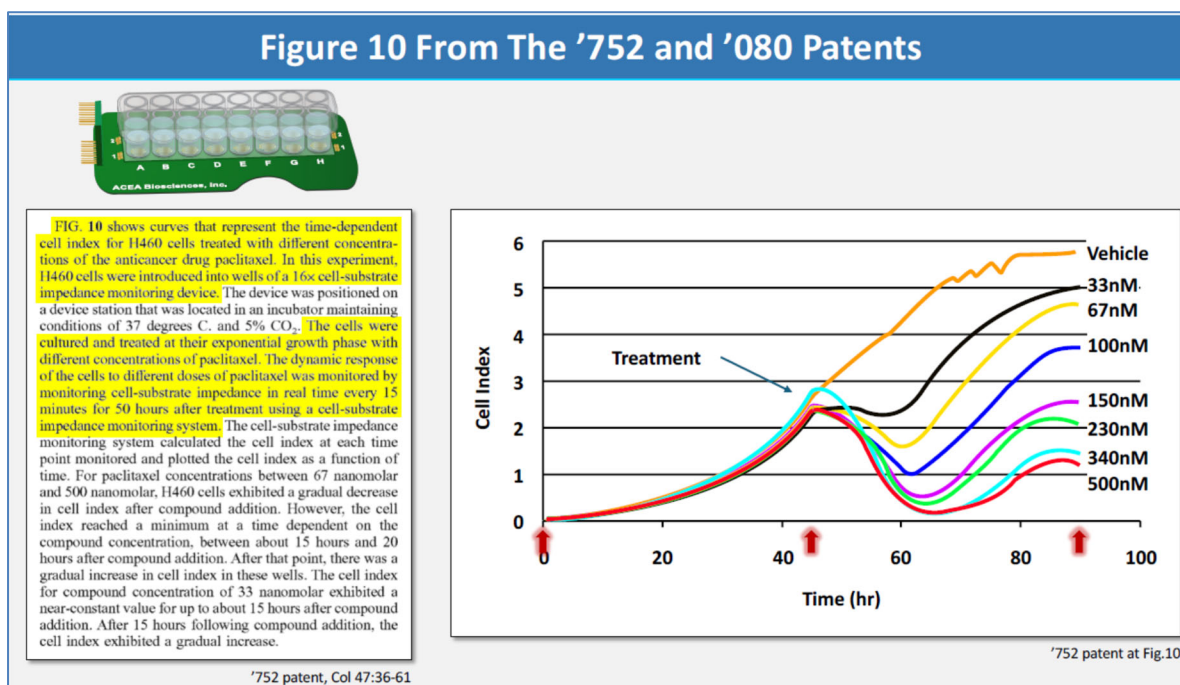
EX1012, 50; EX1005, 19:36-20:5. Annotated Figures 1A and 1C (below) show how an input voltage (yellow) is applied across an electrode array (including the path to ground (blue)) to measure the impedance across a cell sample (the red oval) that is depicted on the array. EX1003, ¶46.



EX1012, 40, 34; EX1005, 40:1-7.

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Xu-752 provides only brief descriptions of the functionality of its impedance analyzer and software program, most likely because these components were well known at the time Xu-752 was filed. EX1005, 24:4-5, 62:36-41. Annotated Figure 10 below (from Agilent's litigation tutorial) depicts an analysis over a period of time by Xu-752's system for multiple wells, each having cells and different concentrations of an anti-cancer drug. EX1003, ¶¶47-48.



EX1012, 65; EX1005, 47:36-61, Fig. 10.

C. ACEA Initiated a New Patent Family in 2009, and, 15 Years Later, Agilent Obtained the '508 Patent Out of This Family

1. ACEA Filed An Application in May 2009 That Issued in 2017 as U.S. Patent No. 9,709,548 (Wang-548)

In May 2009, ACEA filed a new nonprovisional application, No. 12/435,569.

EX1013. This new application claimed priority to two provisional applications, but

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did not claim priority to Xu-752 or its family. This new family shared three co-inventors (Wang, Abassi, and Xu) with Xu-752, and the specification includes significant common subject matter with the Xu-752 specification.

The first application, No. 12/435,569, issued in 2017 as U.S.P.N. 9,709,548 (Wang-548). EX1013. Wang-548's claims are directed to methods of monitoring excitable cells using impedance-based cell analysis systems. EX1013, 47:1-51:2. Although method claims, many of Wang-548's claims recite "providing a system ..." and set forth the same structural components of the "system" that are described in Xu-752 (multiwell plate, impedance analyzer, circuitry to connect the electrode arrays of the plate to the impedance analyzer, and software program). *Id.*

During prosecution of Wang-548, the PTO cited the pre-grant publication version of Xu-752 as a lead reference in rejecting the claims under § 103, and also cited, as a secondary reference, "Real-Time Monitoring of Morphological Changes in Living Cells by Electronic Cell Sensor Arrays: An Approach To Study G Protein-Coupled Receptors," by Naichen Yu et al. ("Yu") (EX1008). EX1014, 235-253. The PTO explained that Xu-752 described all of the structural elements in the claims, but relied on secondary references for some of the method steps/functionality. EX1014, 240-243. ACEA amended the claims and traversed the § 103 rejections based on Xu-752 and Yu, arguing that (i) Xu-752 and Yu did not describe using impedance-based cell analysis to resolve beating cycles/monitor excitable cells/cardiomyocytes, as

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required by all claims; and (ii) Xu-752 did not describe taking measurements at millisecond time resolution and Yu confirmed that it can only achieve 50 millisecond time resolution between measurements, which is 2.5 times greater than the limitation present in all amended claims requiring “at least two consecutive impedance measurements less than 20 milliseconds apart.” *Id.*, 254-275.

2. In November 2022, Agilent Filed a New Continuation in the Wang-548 Family, Dropped Key Claim Elements from Wang-548, and Obtained the ’508 Patent.

Agilent filed Application No. 17/993,716—a sixth generation continuation application that claims priority back to Wang-548—with a Track One Request in November 2022, and this application issued as the ’508 patent in February 2024. EX1001; EX1002. The ’508 patent claims do not have any limitations regarding resolving beating cycles/monitoring excitable cells/cardiomyocytes that ACEA argued for allowance of Wang-548 over Xu-752 and Yu. EX1001, 46:65-50:24. And only two dependent claims in the ’508 patent (claims 13-14) require taking measurements less than 20 milliseconds apart, as required by all claims in Wang-548. EX1001, 47:57-62. ’508 patent claim 1 is the only independent claim that recites anything at all about “millisecond time resolution,” as claims 16 and 23 have no time resolution limitations. Claims 1 and 16 of the ’508 patent also include limitations concerning two analog-to-digital conversion (ADC) channels, or parallel ADCs, that are not in the Wang-548 claims.

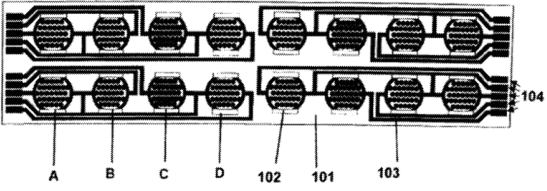
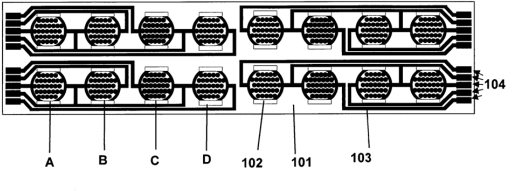
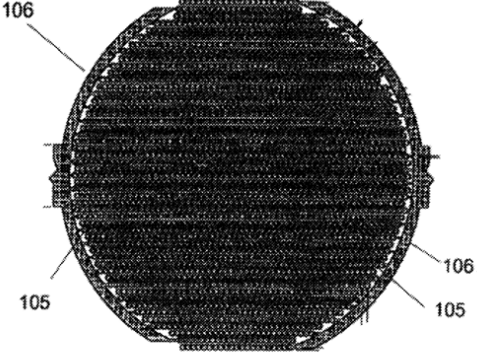
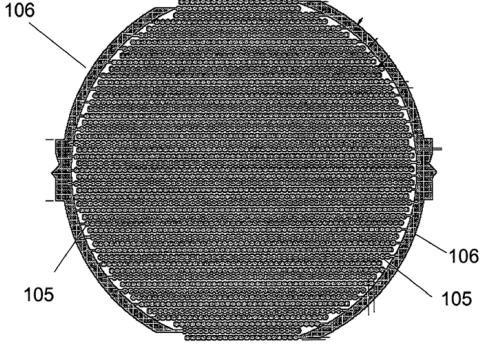
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The '508 patent claims should never have issued. The PTO Examiner, unfortunately, did not apply the best available prior art of which the PTO was already aware (Xu-752, Yu) and was missing other relevant art (Jones). EX1003, ¶¶56-60. The PTO Examiner for the '508 patent was different from the PTO Examiner who had cited Xu-752 and Yu when examining Wang-548. Moreover, the '508 prosecution was not rigorous—one rejection, one interview, one response with claim amendments, and allowance. EX1002. Of the 330+ references cited in Agilent's November 2022 IDS, the lone Office Action cited only one, "Oka." EX1002, 153-64; EX1026. Agilent easily distinguished Oka, arguing that Oka does not teach (i) a plate with multiple wells, (ii) each well having an electrode array, (iii) taking a measurement from each well, or (iv) even measuring cell-substrate impedance (EX1002, 184-94)—all features that Xu-752 describes.

3. Using a Faster Measurement Rate and Parallel ADCs—the Only "New" Features in the '508 Patent Claims—Were Old and Not Inventive.

The Xu-752 and '508 patent disclosures share common subject matter, and the '508 patent incorporates Xu-752 by reference. EX1001, 23:15-23 (also stating that a device of the alleged invention "preferably has between 2 and 1,536 wells"). The '508 patent reuses Xu-752's figures to show its multiwell plates and electrode arrays:

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'508 patent (EX1001)	Xu-752 (EX1005)
 FIG. 1A	 Figure 1A
 FIG. 1B	 Figure 1B

The '508 patent suggests that it has made improvements over the prior art, for example so that excitable cells, beating activity of cardiomyocytes, and the like, can be monitored with less time between measurements of the cell samples using impedance-based systems. EX1001, 1:36-6:58. But using parallel ADCs or ADC channels (claims 1, 16) and taking samples at “millisecond time resolution” (claim 1) were already well known and conventional, and clearly not inventive. Indeed, the desire to improve products by increasing throughput and speed was ubiquitous across numerous electronics fields long before 2009, and parallel processing of data streams

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was a well-known technique to improve throughput and speed in electronics for decades before the earliest claimed priority date of the '508 patent.

The '508 patent's description of its "improvements" of impedance-based cell analysis systems is telling. EX1003, ¶¶49-55; EX1001, 24:53-25:44. The patent asserts that three "improvements" are used to achieve millisecond time resolution, *i.e.*, (1) fast ADC hardware, (2) the use of parallel ADCs, and (3) measuring the impedance of multiple wells simultaneously. EX1001, 24:53-25:44. But as detailed herein, these alleged advances of the '508 patent were not new. EX1003, ¶¶53-54. And, significantly, the '508 patent provides no circuit diagrams or technical detail regarding its ADCs; instead, the ADCs are described only by the desired functionality of allowing for faster measurements. *Id.*, ¶55.

D. Claim Construction And The Level Of Ordinary Skill In The Art

1. Claim Construction

In this Petition, all of the claim terms are given their plain meaning, as understood by the POSA, unless indicated otherwise.

The '508 patent contains a "Definitions" section. EX1001, 9:34-16:14. Petitioner does not believe there is any need to adopt any definitions from this section to address the grounds below. Xu-752 describes the exact same electrode-related structures recited in the '508 patent claims (EX1003, ¶¶26-27), and so it is not necessary to construe any of the electrode-related terms discussed at 11:5-36 of

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the “Definitions” section. In this section, the disclosure (at 10:8-24) suggests that measurements must occur at less than 300 milliseconds for “impedance measurement at millisecond time resolution,” but other portions of the specification discuss measurements at 500 milliseconds (and also claims 9-10). EX1001, 23:52-55, 24:37-39, 39:47-52, 43:27-33, 47:46-51; EX1003, ¶28. The prior art shows measurements taken at 500 or fewer milliseconds, as discussed below, and the Board does not need to construe “millisecond time resolution” to find the claims unpatentable on the stated grounds.

2. The POSA’s Skill Level

In this proceeding, a POSA at the time of the invention of the ’508 patent (circa May 2009) would have had a B.S in electrical/mechanical/biomedical engineering or biological science, or a related field, and approximately 2 years of relevant experience or equivalent study in systems and methods for bioanalysis of cells. Additional graduate education (such as master’s or doctorate or additional degree in another field) could substitute for experience, or significant experience in the field could substitute for formal education. EX1003, ¶¶23-25.

IV. CLAIMS 1-30 ARE UNPATENTABLE

A. Ground 1: Xu-752 Anticipates, and Would Have Rendered Obvious, Claims 23-30

1. Summary of Xu-752

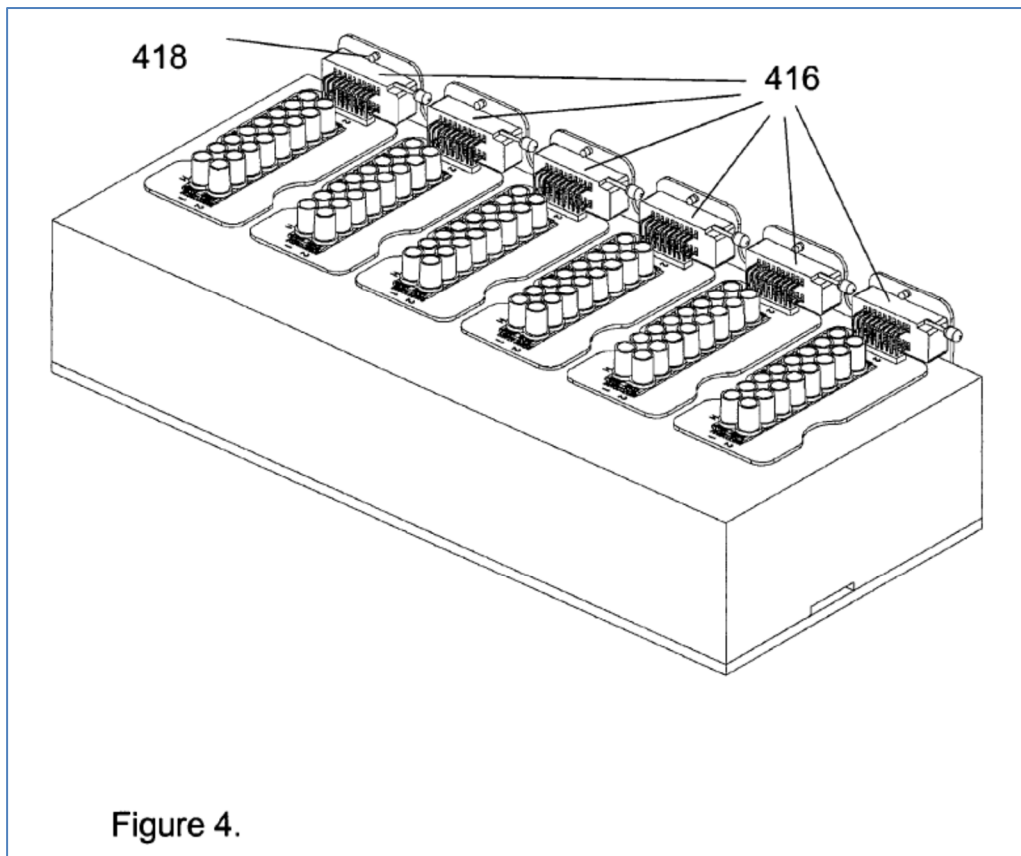
Xu-752 was discussed extensively above, and its abstract is illustrative:

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The present invention includes devices, systems, and methods for assaying cells using cell-substrate impedance monitoring. In one aspect, the invention provides cell-substrate impedance monitoring devices that comprise electrode arrays on a nonconducting substrate, ... In another aspect, the invention provides cell-substrate monitoring systems comprising one or more cell-substrate monitoring devices comprising multiple wells each having an electrode array, an impedance analyzer, a device station that connects arrays of individual wells to the impedance analyzer, and software for controlling the device station and impedance analyzer. In another aspect, the invention provides cellular assays that use impedance monitoring to detect changes in cell behavior or state.

EX1005, Abstract. EX1003, ¶¶43-48, 61-63.

Xu-752's multiwell plate design, including the electrode array in each well, is identical to that in the '508 patent. Xu-752's software program has the same functionality in the '508 claims, and Xu-752 also describes circuitry connecting the electrode arrays to the impedance analyzer, as in the '508 claims. Xu-752's Figure 4 shows an exemplary device station with six 16-well devices connected.



Xu-752 describes the combination of every structural component in claims 23-30, as well as the recited functionality, thus anticipating these claims and rendering them obvious. To the extent that Agilent argues that Xu-752 does not anticipate a particular claim because some aspect of the claim is purportedly not arranged in Xu-752 exactly as claimed or not stated *in haec verba* in Xu-752, the claim would nevertheless have been obvious in view of Xu-752's disclosure and the knowledge of a POSA at the time of the purported invention.

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2. Claim 23

- (a) **Preamble: “A system for continuously monitoring cells in real time, label free, with impedance-based analysis, the system comprising:”**

To the extent the preamble is limiting, Xu-752 discloses it. EX1003, ¶76. Xu-752 describes “a real time cell electronic sensing system for conducting cell-based assays based on measurement of cell-substrate impedance[.]” EX1005, 3:49-53. Xu-752 allows “cell behavior” or “cell conditions” to be assessed “continuously at regular or irregular intervals” and in “real-time and label-free.” *Id.*, 39:16-22, 64:4-6, 67:61-65, 68:61-65.

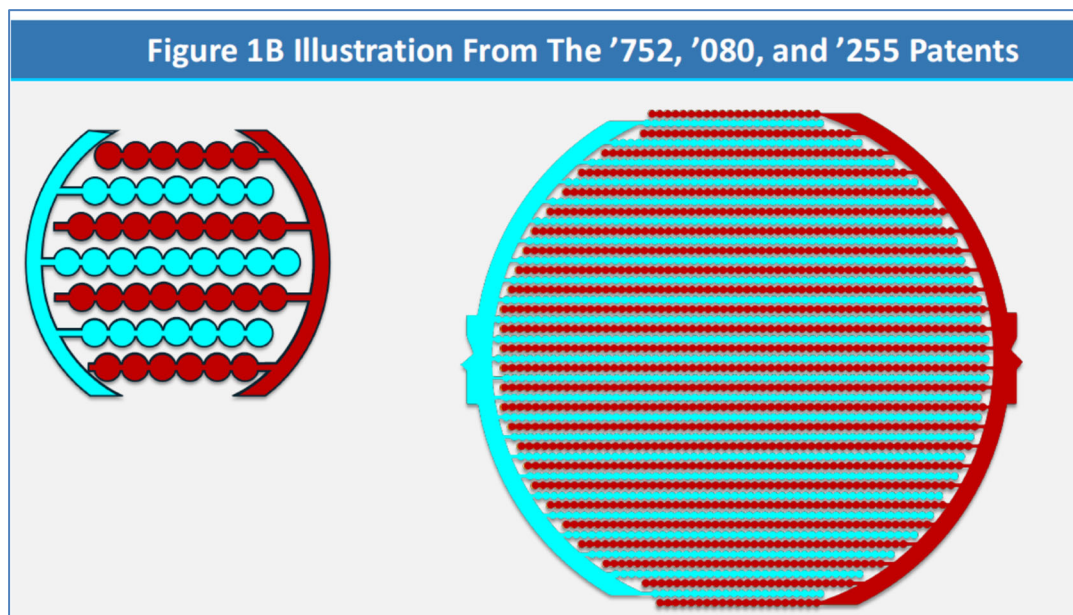
- (b) **Element 1: “a) a well plate comprising a plurality of electrode arrays formed on a nonconductive substrate,”**

Xu-752 discloses this claim element. EX1003, ¶77. Xu-752 describes multiwell plates, including 16-well and 96-well plates, with a plurality of electrode arrays that are fabricated on, and thus formed on, a nonconductive substrate including, *e.g.*, glass or plastic. EX1005, Abstract, 3:60-66, 7:28-32, 14:49-53, 15:52-56, 19:36-42, 20:17-55, 21:24-48, 21:63-22:8, 24:25-34, Fig. 1A, Figs. 2-5.

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- (c) **Element 2: “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;”**

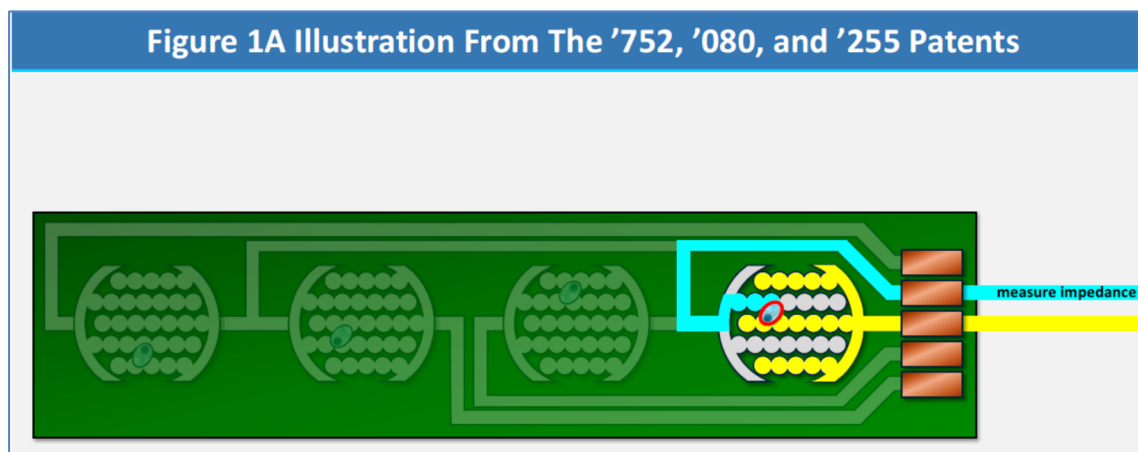
Xu-752 discloses this claim element. EX1003, ¶78. Xu-752 discloses that the plate “is assembled such that a single array of the substrate is at the bottom of a receptacle or well,” and, “[p]referably, each array of a device is associated with a well of a multiwell plate.” EX1005, 21:26-33, Abstract, 4:4-17, 21:63-22:8, 22:50-52, 23:4-8, Fig. 2. Xu-752 describes that an electrode array includes first and second electrode structures. EX1005, 3:60-4:12, 10:50-11:36, 19:36-20:5, Fig. 1B (annotated version below showing first (blue) and second (red) electrode structures, EX1012, 50).



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- (d) **Element 3: “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,”**

Xu-752 discloses this claim element. EX1003, ¶¶79-80. Xu-752 describes that “the impedance analyzer can automatically select wells to be measured and continuously conduct impedance measurements.” EX1005, 62:36-41. Xu-752 states that “[t]he 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. The switches of the device station allow the selected individual arrays to be monitored in rapid succession for each desired monitoring time point.” *Id.*, 23:57-62. Xu-752 describes the operation of switching from “measuring impedance over an array in one well to measuring impedance over an array in another well.” *Id.*, 23:1-3. Agilent’s litigation tutorial shows how Xu-752 measures impedance in association with an individual well of a multiwell configuration (annotated Figure 1A below (EX1012, 40)).

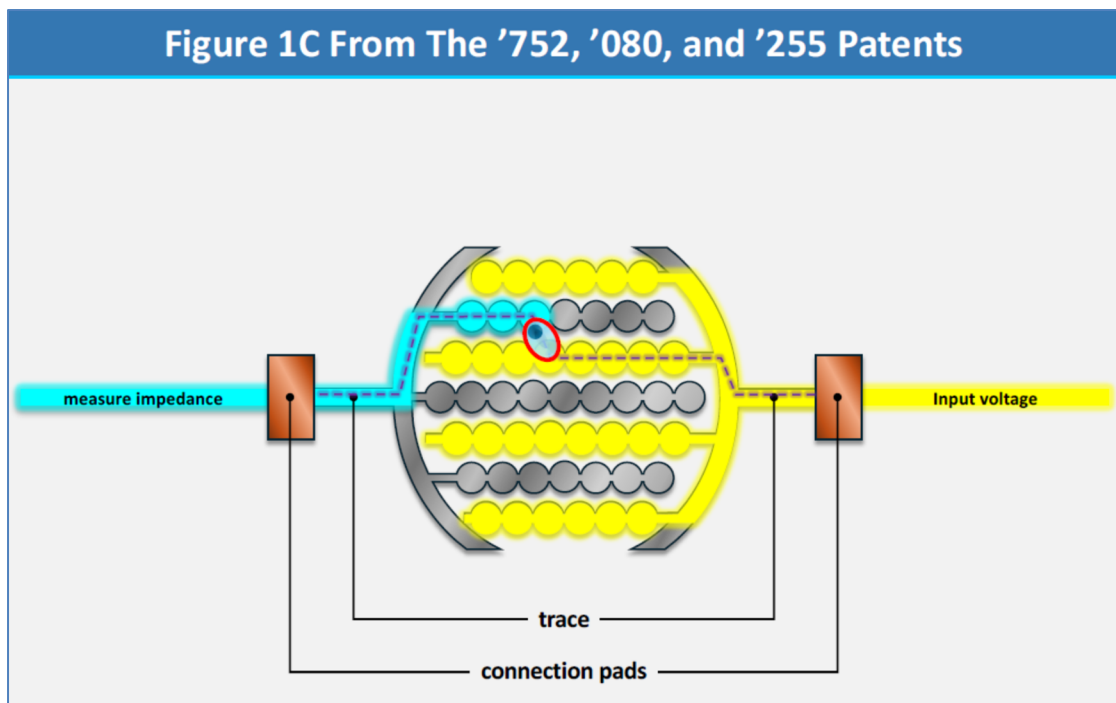


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Xu-752 describes the impedance analyzer monitoring impedance of cell samples in multiple individual wells over various time intervals. EX1005, 7:56-62, 8:52-64, 38:36-67, 39:16-28, 62:24-55; Figs. 6E, 7-15, 16A-17 (and associated descriptions in specification).

- (e) **Element 4: “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;”**

Xu-752 discloses this claim element. EX1003, ¶81. Xu-752 states that, for the substrate on which the electrode arrays are fabricated, “cell attachment or growth on said substrate can result in a detectable change in impedance between or among the electrode structures.” EX1005, 4:4-12, 15:52-64. Xu-752 describes that “[m]easuring the impedance between and among electrodes provides important information about biological status of cells present on the sensors.” *Id.*, 40:1-3. Xu-752 describes numerous examples of cellular samples that comprise a plurality of cells being deposited in wells for impedance measurement/monitoring. *Id.*, Figs. 6-18 (and their associated descriptions in the specification), 60:35 *et seq.* (describing Examples 1 and 2); EX1003, ¶81. Agilent’s litigation tutorial shows how Xu-752 measures impedance between the two electrode structures of an array and across a cell sample (the red oval) in annotated Figure 1C below. EX1012, 34; Ex 1003, ¶81.



(f) Element 5: “(c) electronic circuitry that electrically connects the plurality of electrode arrays to the impedance analyzer; and”

Xu-752 discloses this claim element. EX1003, ¶82. Xu-752 discloses that its impedance analyzer is electrically connected to the plurality of electrode arrays. EX1005, Abstract, 4:19-23, 4:34-35, 16:23-29, 18:26-29, 22:48-61, 22:63-23:3, 23:48-62, 62:21-41, claim 1. Xu-752 describes a device station with “electronic circuitry capable of selecting and connecting electrode arrays within any of the multiple wells to the impedance analyzer.” EX1005, 22:54-58, 24:31-34.

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- (g) Element 6: “d) a software program that 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.”**

Xu-752 discloses this claim element. EX1003, ¶¶83-86. Xu-752 describes “a software program to ... perform data acquisition and data analysis on impedance values measured by the impedance analyzer.” EX1005, 4:24-26; *id.*, 22:58-61. Xu-752 explains that the “software is programmable to direct impedance monitoring of any of the wells of the device that comprise arrays at chosen time intervals.” *Id.*, 23:66-24:12. The software can analyze, store, and display impedance data, including for multiple time points and intervals. *Id.*, 23:66-24:12, 24:35-54, 39:17-28, 62:36-41, claims 3-10.

The software includes a “[t]est time setting page [that] allows for the recording and control of time intervals used for performing cell-substrate impedance measurement and multiple experimental steps each having different time interval values and different length times can be setup.” *Id.*, 7:44-49; 24:43-47. Xu-752’s Figure 6E (below) shows a software “page” that includes a time period analysis (X-axis of plot) of a cellular sample (“Cell Type” and “Cell Number” fields) produced from multiple measurements.

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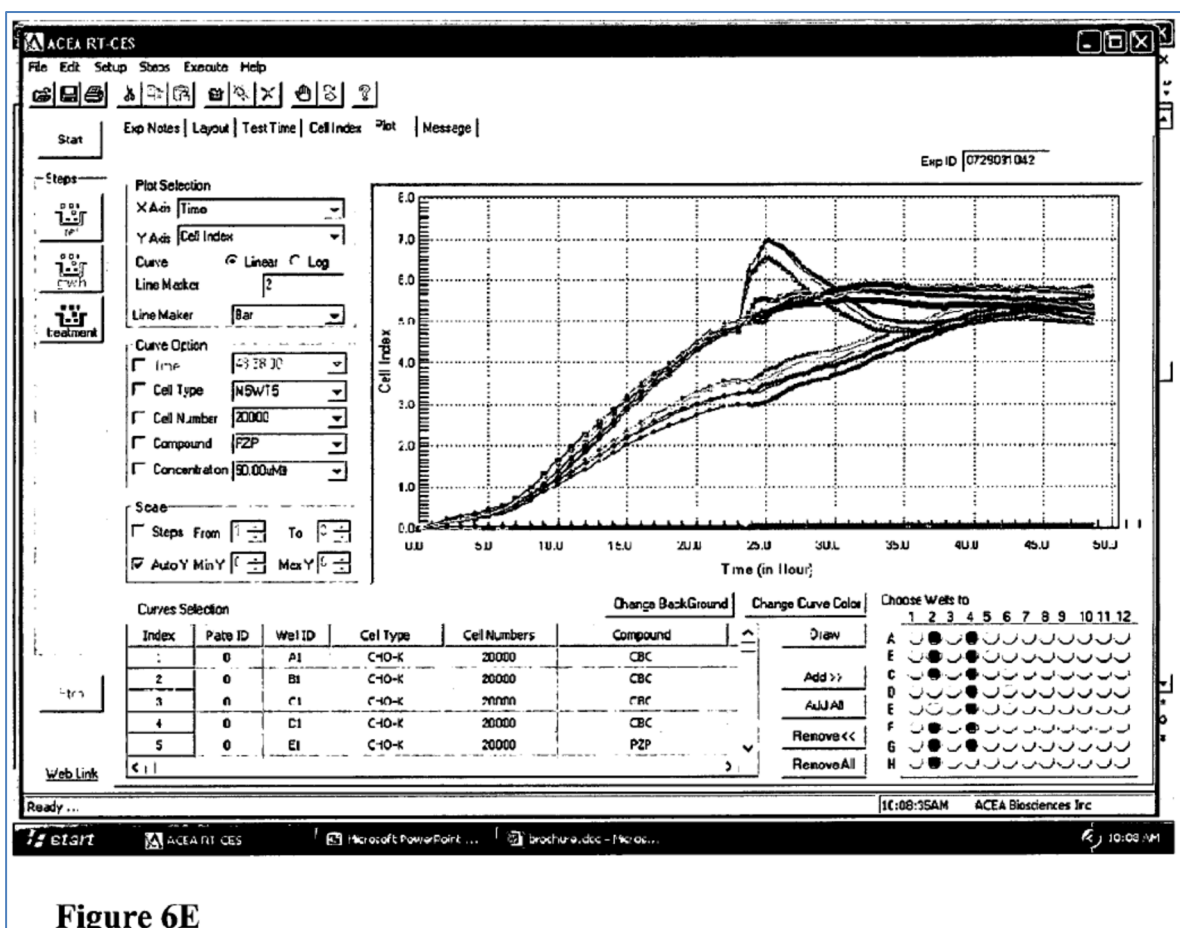
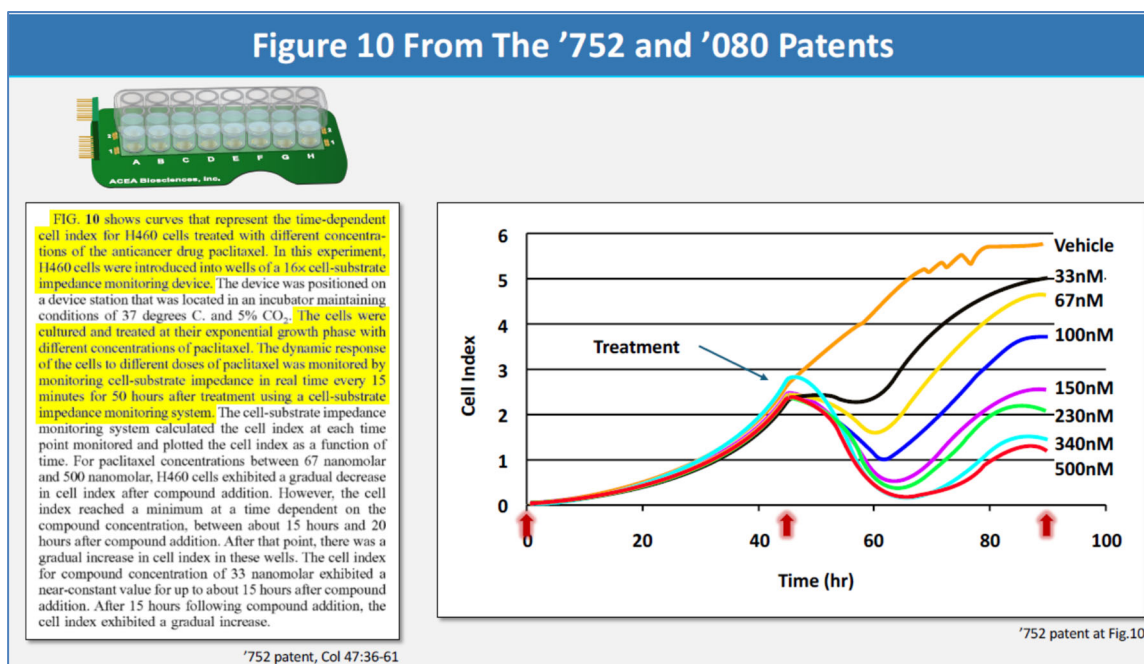


Figure 6E

Id., Fig. 6E, 7:38-55, 24:35-54. Xu-752 describes numerous examples of time period analyses of cellular samples, with various sampling time resolutions. *Id.*, Figs. 6-18 (and their associated descriptions in the specification), 42:49-65, 60:35 *et seq.* (describing Examples 1 and 2); EX1003, ¶85. An annotated version of Xu-752's Figure 10 (and its associated description) from Agilent's litigation tutorial is shown below.



EX1012, 65; EX1005, 47:36-61, Fig. 10.

3. Claims 24-26

Claims 24-26 each depend from claim 23 and add: “wherein the impedance analyzer monitors the impedance using a voltage applied at a single frequency” (claim 24); “wherein the impedance analyzer monitors the impedance using a voltage applied with multiple frequencies” (claim 25); and “wherein the impedance analyzer monitors the impedance using a voltage applied with a specified voltage waveform” (claim 26). Xu-752 discloses each of these limitations. EX1003, ¶¶87-89.

Xu-752 describes that “[d]uring impedance monitoring, the impedance analyzer can monitor impedance at one frequency or at more than one frequency.” EX1005, 23:52-54; *see also* 26:11-35, 40:64-41:3, 42:66-43:6, 51:17-19, 53:38-39,

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56:9-10, 58:26-27, 60:7-9, claim 4. Xu-752 explains that “a method for the measurement of such impedance is ... applying a voltage between or among said electrodes at a given frequency (or multiple frequencies, or having specific voltage waveform) and monitoring the electrical current through said electrodes at the frequency (or multiple frequencies, or having a specific waveform)[.]” *Id.*, 13:11-19; *see also* 16:23-29, 26:42-50.

4. Claim 27

Claim 27 depends from claim 23 and adds: “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.” Xu-752 discloses this limitation. EX1003, ¶¶90-92.

As discussed above for claim 23 elements 3 and 4, Xu-752 describes the impedance analyzer monitoring a plurality of impedances between the electrode arrays and cell samples in corresponding wells that are associated with individual cell samples in the individual wells.

5. Claims 28 and 29

Claim 28 depends from claim 23 and adds: “wherein the impedance analyzer separates the cell-substrate impedances from a background electrode impedance

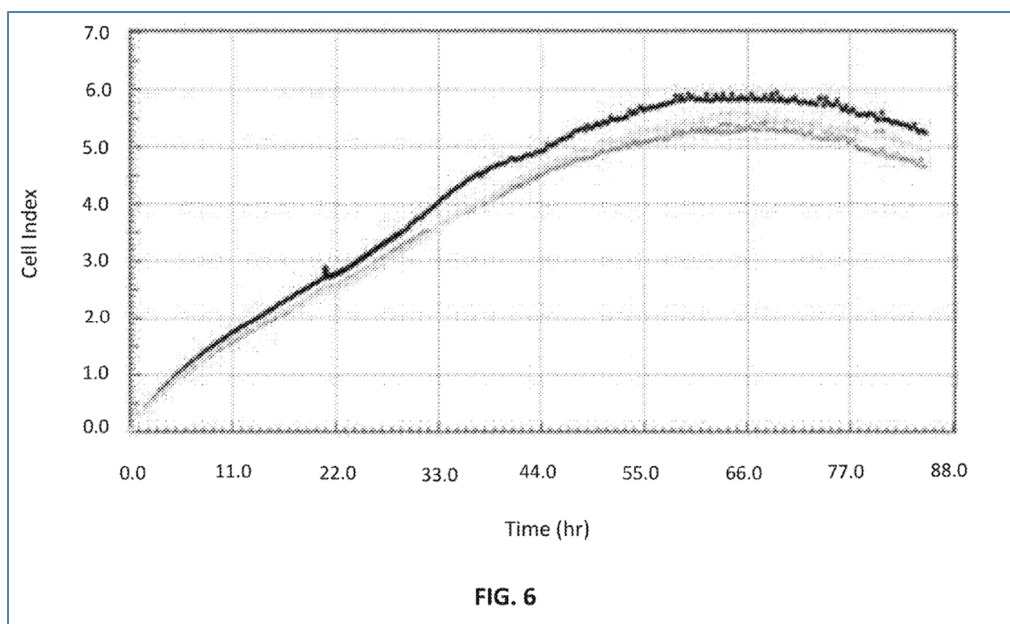
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measured with the cell sample inside the corresponding well.” Claim 29 depends from claim 23 and adds: “wherein the impedance analyzer separates the cell-substrate impedances from a background electrode impedance measured with a cell culture media inside the corresponding well.” Xu-752 discloses the limitations in these two claims. EX1003, ¶¶93-101.

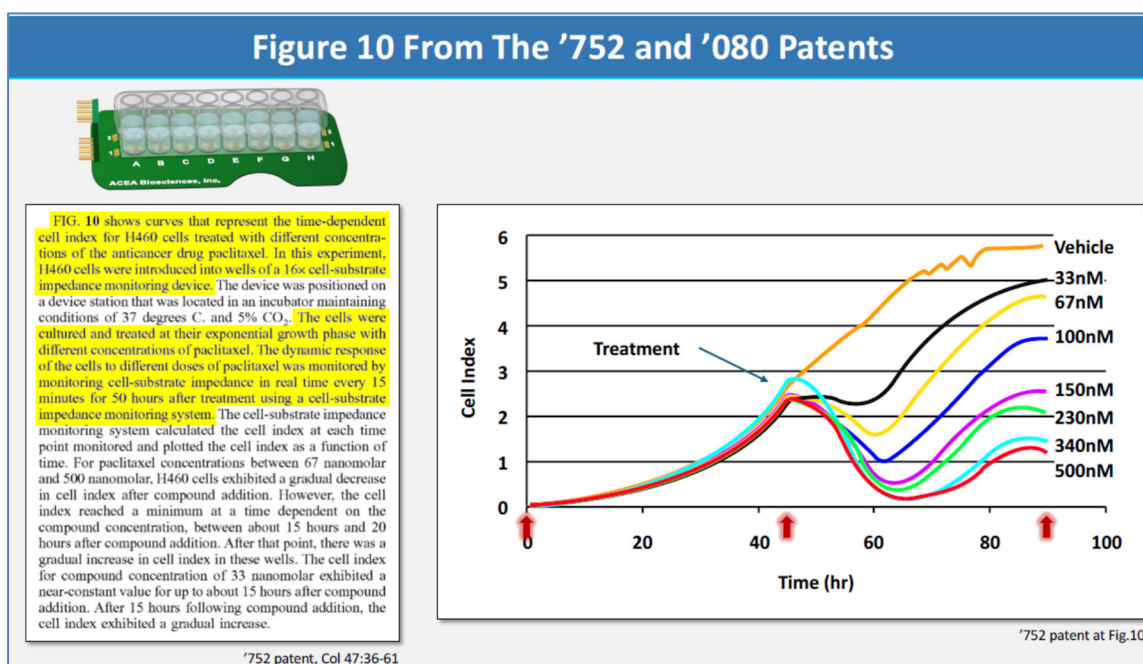
The ’508 patent describes two ways to measure a background impedance of a well, against which later impedance measurements for the cell sample can be compared or analyzed to evaluate the impedance changes—measuring background impedance with cells inside the well, or measuring impedance with cell culture media in the well. EX1001, 40:24-32, 40:50-54, 8:39-46. Xu-752 describes the same measurements of a background (or baseline) impedance—“the impedance measured shortly (e.g. 10 minutes) after the cell-containing medium was applied to the wells,” or “the impedance measured for the electrode structures with a cell-free culture medium introduced into the well.” EX1005, 27:21-34. Xu-752 also, like the ’508 patent, describes that later impedance measurements for the cell sample can be compared or analyzed to evaluate the impedance changes against the baseline. *Id.*, 37:61-63, 38:4-10, 38:34-36.

The ’508 patent’s impedance-based system produces “cell index” curves measured against background impedance, such as shown in Figure 6 below (using cell culture media as background). EX1001, 40:24-32, 40:50-54, 8:39-46, Fig. 6.

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Xu-752's impedance-based system likewise produces "cell index" curves and describes that calculating cell index includes comparison of cell-substrate impedances against a baseline or background impedance. EX1005, 27:41-30:44. One example of Xu-752's cell index curves is shown in annotated Figure 10 below.



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EX1012, 65; EX1005, 47:36-61, Fig. 10.

Claims 28 and 29 would also have been obvious over Xu-752. EX1003, ¶¶97-101. Agilent may argue that Xu-752 does not disclose that the impedance analyzer is what separates the measured impedances from the background impedance. But even if that were so, the disclosures in Xu-752, combined with the knowledge of a POSA, would have rendered claims 28 and 29 obvious. Xu-752's impedance-based cell analysis system includes only two components able to subtract or separate background impedance as described: the impedance analyzer and the software program. EX1003, ¶97. It would have been obvious to a POSA that she could use the impedance analyzer to separate cell-substrate impedances from a background impedance, as claimed in claims 28 and 29. *Id.* Furthermore, Xu-752 describes that it is the software that controls and directs the activities of the impedance analyzer. EX1003, ¶98; EX1005, 62:36-39; *see also* 7:38-55, Figs. 6A-6E, 24:35-54, 60:44-46.

It was also well known to a POSA that impedance analyzers available at the time of Xu-752 had settings to allow a user to separate impedance measurements, such as cell-substrate impedances, from a background electrode impedance—this is called normalization. EX1003, ¶99. For example, the Solartron 1260 impedance analyzer is referenced in a priority application (U.S. Application No. 10/705,615 that issued as U.S.P.N. 7,459,303 (“Wang-303,” EX1015)) that Xu-752 incorporates by reference into its specification. EX1005, 1:15-24, 39:36-55; EX1015, 47:54-57, 49:25-28

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(referencing the Solartron 1260); EX1003, ¶99. The Solartron 1260 impedance analyzer included normalization settings that allowed the user to separate measurement results from background data. EX1024, 5-6, 5-31, 10-3, 10-4; EX1003, ¶99.

6. Claim 30

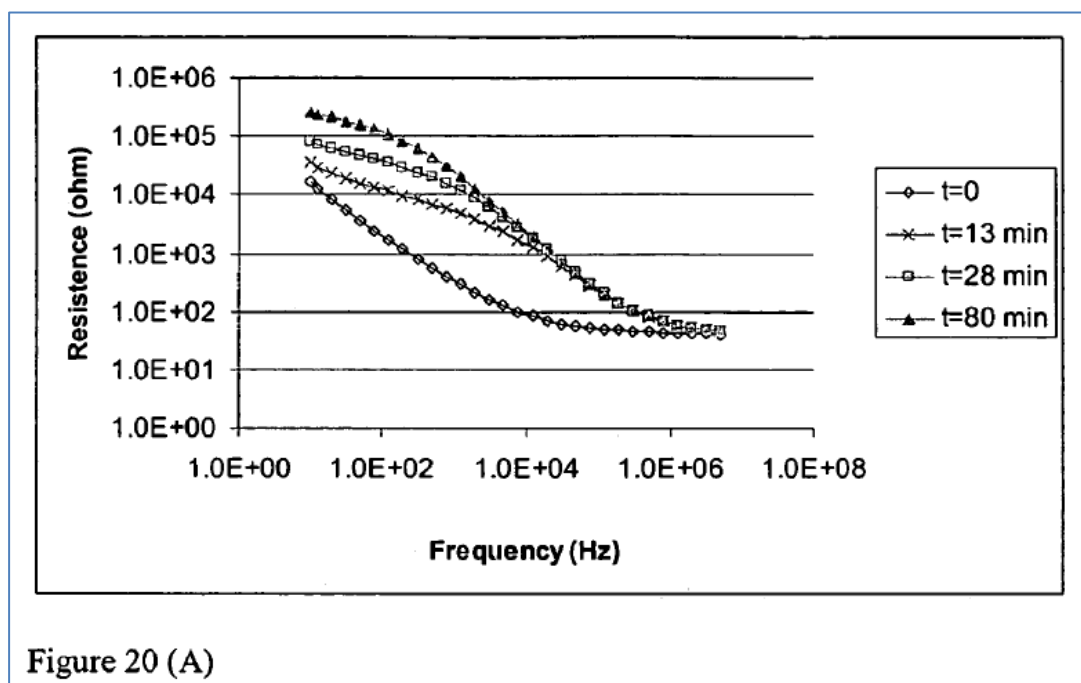
Claim 30 depends from claim 23 and adds: “wherein the impedance analyzer measures impedances between 0.1 ohms and 10^5 ohms via an alternating current applied in a frequency range of 1 Hertz (Hz) to 1 Megahertz (MHz).” Xu-752 discloses these limitations. EX1003, ¶¶102-106.

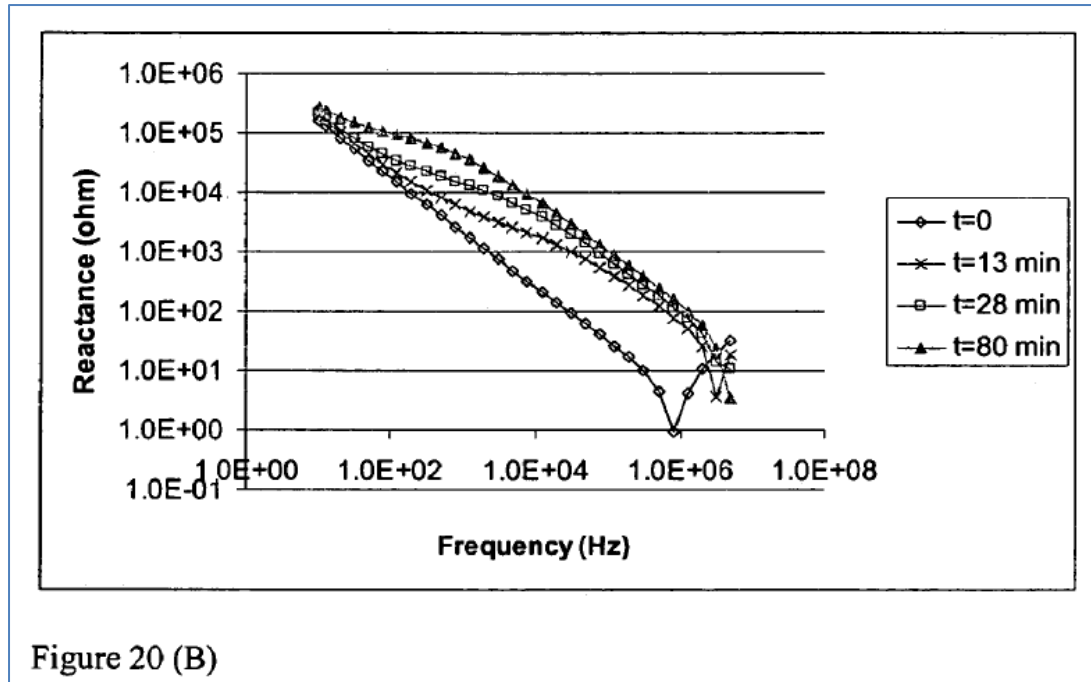
Xu-752 explains that “[i]mpedance between or among electrodes is typically a function of the frequency of the applied electric field for measurement.” EX1005, 12:63-65. Xu-752 states that impedance can be measured in range from “about 1 Hz to about 100 MHz.” *Id.*, 26:20-24, 40:64-41:3, 43:3-6. Xu-752 states that one method for measuring impedance is applying a current at a frequency through the electrodes. *Id.*, 13:11-26, 26:36-58. It was well known to a POSA at the time of the alleged invention that impedance is measured using alternating current applied at a specified frequency. EX1003, ¶103.

In discussing methods for measuring electrical impedance, Xu-752 refers to, and incorporates by reference, priority application No. 10/705,447 that issued as U.S.P.N. 7,470,533 (“Xu-533,” EX1016)). EX1005, 26:11-60; *see also* 1:5-14,

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19:30-35, 20:11-16, 20:38-44, 21:16-23, 21:39-47, 22:41-46, 23:21-27, 25:1-18, 27:5-13, 30:26-35, 39:36-55, 43:18-22, 44:38-44. The incorporated Xu-533 disclosure describes that “impedance may be measured at a frequency ranging from about 1 Hz to about 1 MHz” by the impedance analyzer. EX1016, 6:31-36; *see also* 73:41-46, 28:65-29:3, 63:59-61. The incorporated Xu-533 disclosure includes numerous figures showing plots of impedance over various frequency ranges, including measurements of impedance components in the range from 0.1 ohms to 10^5 ohms (*i.e.*, 100,000 ohms). EX1016, Figs. 20(A)-(B), 26A(1)-(4), 38(A)-(B), 39(A)-(B), 40(A)-(B), 42A; EX1003, ¶104. For example, Figures 20(A)-(B), reproduced below, show “typical frequency spectra” of measured resistance and reactance “for circle-on-line electrode structures.” EX1016, 14:42-15:11, Figs. 20(A)-(B).





Claim 30 would also have been obvious over Xu-752. EX1003, ¶¶105-106. The claimed impedance measurement and frequency ranges were known, and it was well known that commercially available impedance analyzers at the time of Xu-752 were capable of measuring and operating in the claimed ranges. EX1003, ¶105. For example, the Solartron 1260 impedance analyzer (referenced in the incorporated Wang-303 disclosure, and discussed above for claims 28-29) operated over the recited impedance and frequency ranges. *Id.*; EX1024, 1-4, 1-5.

B. Ground 2: Claims 1-22 Would Have Been Obvious in View of Xu-752 and Jones

Xu-752 describes the combination of every structural component in claims 1-22, except for ADCs, and also describes the claimed functionality, except for sampling at “millisecond time resolution.” Jones, published in early 2007 (and not before the

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PTO during '508 prosecution), describes an improved impedance measurement system that includes the limitations that Xu-752 does not explicitly describe. As explained in detail below, a POSA would have been motivated to combine Xu-752 with Jones for several reasons. Accordingly, claims 1-22 are unpatentable as obvious.

1. Summary of Jones

Jones “provides an impedance measurement system with massive parallelism, high temporal sampling, and a means for interconnecting multiple microtiter plate sensors to impedance measurement channels.” EX1006, ¶[0002]; EX1003, ¶¶64-75.

Jones states:

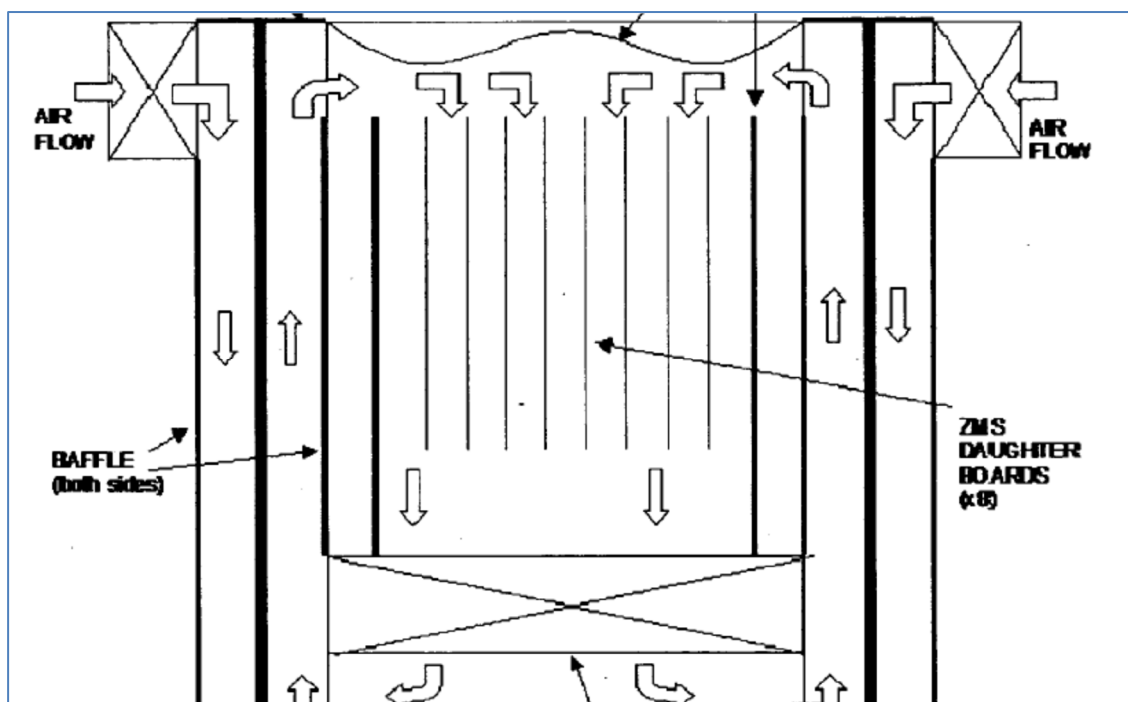
The present technology provides an Impedance Measurement System (ZMS) for measuring the complex impedance of each well of a single well or multiwell microtiter plate. The ZMS utilizes a novel combination of parallel impedance measurement channels and the multiplexing of impedance measurement channels for interconnecting multiple microtiter plate sensors and reference impedance networks to the channels, allowing internal correction of impedance measurement drift, maximized measurement accuracy, and minimized system size. The system is self-contained, thermally controlled, provides well excitation and measurement, and allows the measurement data to be stored or communicated to an external host computer. The system can be used for impedance measurements of varying time periods, single or multiple frequencies, and various measurement rates.

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EX1006, ¶[0003]. Jones notes that “the ZMS employs parallelism to obtain the required throughput.” *Id.*

As relevant to the ADC limitations of the ’508 patent, Jones describes that (i) each row of sensors/wells of a microtiter plate has an associated daughter board, and (ii) each daughter board has an ADC, and multiplexing circuitry enables each well within a given row to be addressed. *Id.* ¶¶[0012], [0018]. Jones explains that: “[t]he ZMS daughter boards mate at their lowest edge with the mother board.... The mother board processes the impedance measurement data, at a specific time and frequency, of all wells of the microtiter plate and communicates the results to the system controller.” *Id.* ¶[0020].

Further, Jones states that “[a] high speed, high resolution ADC is used for each of the current and the voltage channels. The ADCs are 14 bit, 60 Mega Samples per second to provide high speed and accuracy (especially at the lower current values anticipated n [*sic*] some circumstances).” *Id.* ¶[0035]. Jones explains that “[t]he current through and the voltage across each well is scaled, converted to digital values, and transmitted via the measurement channels to either a storage device or an associated computer.” *Id.* ¶[0037]. Jones Figure 4, an excerpt of which is reproduced below, shows eight daughter boards, arranged in parallel.



Id., Fig. 4; see also Fig. 2, ¶[0036].

As relevant to the “millisecond time resolution” limitations of the ’508 patent, Jones’ impedance analyzer is capable of monitoring each well at a millisecond time resolution between two measurements of the cell-substrate impedance of the well. EX1003, ¶¶69-75. In an embodiment, Jones describes an exemplary 1.5-second update period for an entire 96-well plate, where the 1.5-second period includes 1091 milliseconds of measurement time, leaving 409 milliseconds for multiplexer switching and signal settling. EX1006, ¶[0030].

Jones describes that “no more than 68.2 ms per well for all frequencies is required to obtain sufficient samples” and this is where “[e]ach well is subject to a stepped sweep (a series of single-frequency bursts-one burst for each selected

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frequency). The bursts consist of an integral number of cycles. In one embodiment, the number of cycles is typically 15.” EX1006, ¶[0030]; EX1003, ¶¶69-75 (Dr. Kim explaining example measurement times for several frequencies, showing millisecond time resolution). This disclosure in Jones also describes taking first and second measurements of impedance in a well milliseconds apart as part of the stepped frequency sweep that is completed for each well in “no more than 68.2 ms per well.” EX1006, ¶[0030].

In addition, Jones explains that its parallel daughter boards may be used in different numbers and configurations. EX1003, ¶74. As one example, Jones states that another embodiment would utilize one daughter board for each column, rather than each row, of wells. EX1006, ¶[0025]. Thus, for an 8 row, 12 column 96-well plate, twelve daughter boards would be used, lowering the time needed to measure impedance in each well when compared to the configuration using only eight daughter boards. EX1003, ¶74.

As noted above, Jones states that its system “can be used for impedance measurements of varying time periods, *single* or multiple *frequencies*, and *various measurement rates*.” EX1006, ¶[0003] (emphasis added). And, as Dr. Kim explains, the measurement rate for a single-frequency sampling (rather than a stepped sweep) in Jones for the entire 96-well plate would be significantly less than 1.5 seconds, such that first and second measurements in each well are taken at a millisecond time

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resolution. EX1003, ¶¶71-73, 75. And for a multiwell plate having even fewer wells, or where the user only wanted to monitor a more limited number of wells in a 96-well plate, Jones discloses providing a higher measurement rate with less time between two measurements in each well. *Id.*, ¶75.

2. Motivations To Combine

A POSA would have had numerous reasons to combine Xu-752 and Jones. EX1003, ¶¶107-126. As noted above, Xu-752 does not explicitly describe the ADC limitations of independent claims 1 and 16 (and dependent claims 2-4) or the “millisecond time resolution” limitation of independent claim 1 (and dependent claims 9-14). It would have been obvious to a POSA at the time of the ’508 patent’s purported invention to modify Xu-752’s system for monitoring cells using impedance-based analysis with an impedance analyzer, such as Jones’s device, having the claimed ADC and “millisecond time resolution” features. EX1003, ¶¶107-108.

First, it would have been obvious to implement Xu-752’s impedance analyzer such that it would “monitor[] the electrode arrays at millisecond time resolution” between two measurements for each well. *Id.*, ¶¶109-116. As detailed above, Xu-752 describes systems for continuous, label-free, real-time monitoring of cells using impedance-based analysis. Several known applications of such impedance-based cell analysis systems involved monitoring cell behavior over time, including cell behavior known to occur in very short time windows (*e.g.*, in milliseconds). *Id.*

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For example, one known application of impedance-based cell analysis was studying cell pores formed via electroporation. *Id.*, ¶¶110-111. Ghosh, published in 1993, explains that “by constantly monitoring the impedance of the electrode with a low-amplitude AC signal, small changes in cell morphology, cell motion, and membrane resistance can be detected.” EX1017, 1602. Ghosh describes the use of millisecond-time resolution between two measurements for a well to monitor impedance while studying electroporation. EX1017, 1604; EX1003, ¶110.

Ghosh explains that a relatively high voltage pulse (1-5 V) is applied for 200 milliseconds to cause the formation of cell pores. *Id.*, ¶111; EX1017, 1604. “These pores start resealing as soon as the high voltage is turned off” (EX1017, 1608), and so Ghosh describes “tak[ing] data once every 10 milliseconds” and also notes the capability to “take readings as fast as once every 5 milliseconds” (*id.*, 1604). EX1003, ¶111. Ghosh concludes by saying that “the method can be improved by using an amplifier that has a faster response time and can take data more frequently. This will allow us to look at further details in the formation and resealing of membrane pores.” EX1017, 1609; EX1003, ¶111. Thus, at least as early as the 1990s, applications of impedance-based cell analysis systems using fast, millisecond-time resolution between measurements were known to POSAs, and further, even for such

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applications, POSAs were seeking faster sampling times to obtain data more frequently. EX1003, ¶111.

In addition, Yu also describes assays based on using “cell-electrode impedance to measure minute changes in cellular morphology as a result of ligand-dependent GPCR activation. ... Our data indicate that cell-electrode impedance measurements offer a convenient, sensitive, and quantitative method for assessing GPCR function.” EX1008, 35. Yu concludes that “[u]sing molecular, cellular, and biochemical assays, we demonstrate that the impedance readout correlates with specific changes in cell morphology and activation of signaling pathways” *Id.*, 36. Yu further explains that:

The addition of the agonist for different GPCRs will affect cell morphology in a very specific manner depending on the pathways being activated, and further change in impedance is a reflection of the morphological dynamics that are induced by the ligand ($Z_{\text{activated cell}}$). Because the readout *can be sampled in as little as 50 ms/well*, the rate of change, magnitude, and duration of the response can be precisely measured.

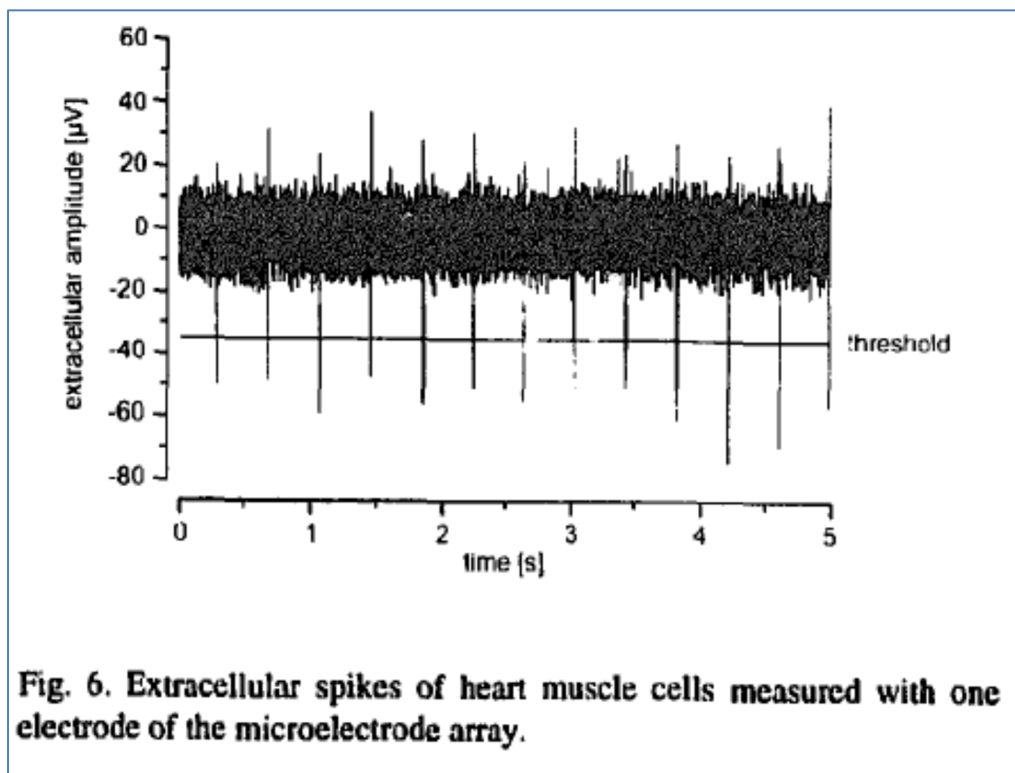
Id., 37 (emphasis added); EX1003, ¶112.

Another cell-analysis application known as early as the 1990s that required millisecond-time resolution between measurements was studying the beating activity of cardiomyocytes (as later described in the '508 patent). EX1003, ¶113. Prior art describes using various microelectrode array-based biosensors to monitor

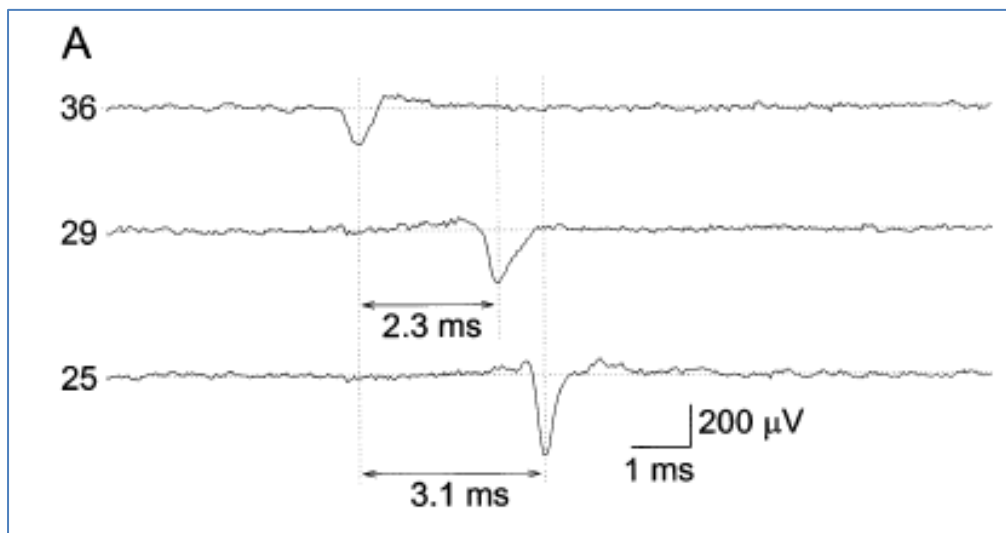
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cardiomyocyte beating activity in millisecond-time resolution, including, for example, Mohr, Pancrazio, and Heer (excerpts of which are reproduced below).

- Mohr Figure 6 (EX1018, 267):

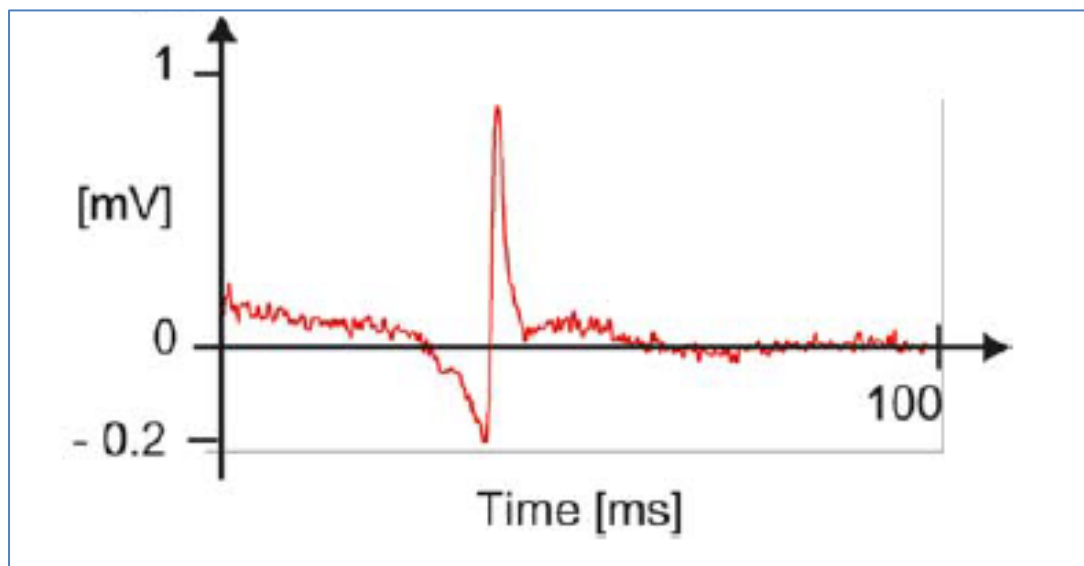


- Pancrazio Figure 5A (EX1019, 184).



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- Heer Figure 8B is below (EX1021, 364), and Heer also describes using one ADC for each row of the microelectrode array (*id.*, 359-60, Fig. 1).



EX1003, ¶113. POSAs knew, years before the time of the '508 patent's alleged invention, that cardiomyocytes' beating function occurs on a very short time scale, in milliseconds, as shown in these exemplary references. *Id.*, ¶114. The '508 patent also admits that studying the short term effects of drugs on the beating function of cardiomyocytes was already known. *Id.*; EX1001, 1:44-2:51. Thus, it was well known to POSAs before the '508 patent that cardiomyocyte beating activity should be monitored at millisecond-time resolution between measurements. EX1003, ¶114.

Further, and also years before the '508 patent, others in the art had reported using impedance-based cell analysis systems to monitor cardiomyocytes more generally. *Id.*, ¶115. For example, Yang describes an impedance-based assay for monitoring cardiomyocyte hypertrophy. *Id.*; EX1022. As another example, Qui

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describes monitoring cardiomyocyte adhesion using an impedance-based cell analysis system. EX1023; EX1003, ¶115.

In sum, there were applications of impedance-based cell analysis known to a POSA at the time of the '508 patent that used millisecond-time resolution between measurements, and further there were also specific cell behaviors (*e.g.*, cardiomyocyte beating activity) that were known to a POSA to occur in short time periods (*e.g.*, milliseconds), such that millisecond-time resolution for measurements would be necessary and/or advantageous for any cell analysis system used to monitor such behaviors. EX1003, ¶116. Thus, it would have been obvious to a POSA to implement Xu-752's impedance-based cell analysis system using an impedance analyzer that would "monitor[] the electrode arrays at millisecond time resolution," as recited in claim 1. *Id.*

Second, it would have been obvious to a POSA to modify the impedance analyzer of Xu-752's impedance-based cell analysis system to provide "at least two analogue-to-digital conversion channels" to achieve the millisecond time resolution needed for certain applications analyzing cell behavior that occurs in less than a second (*i.e.*, milliseconds) such as studying electroporabilization and cardiomyocyte beating function. *Id.*, ¶117. Xu-752 acknowledges that its impedance-based system already uses analog-to-digital conversion, describing "convert[ing]" to "digital signals for processing and for analysis" (EX1005, 40:3-7), and a POSA would

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have readily understood that the use of parallel ADCs for simultaneously measuring multiple impedances would have advantageously enabled increased throughput for achieving millisecond-time resolution measurements. EX1003, ¶117. Further, as discussed above, Jones explicitly describes an impedance analyzer with parallel ADCs in an impedance measurement system with “massive parallelism, high temporal sampling, and a means for interconnecting multiple microtiter plate sensors to impedance measurement channels” and that such system “employs parallelism to obtain the required throughput.” *Id.*; EX1006, ¶¶[0002]-[0003].

Third, a POSA would have been motivated to improve Xu-752’s impedance-based cell analysis system more generally by improving its impedance analyzer, such as by using Jones’s improved impedance analyzer (with parallel ADCs and the capability for millisecond-time resolution measurements) in place of Xu-752’s impedance analyzer. EX1003, ¶¶118-121. There is no suggestion in Xu-752 that its impedance analyzer is anything other than an off-the-shelf impedance analyzer that was available circa 2002 (or earlier). *Id.*, ¶118; EX1005, 62:23-41 (stating electrical cables connect an external impedance analyzer to the device station/circuitry that holds Xu-752’s multiwell plates).

Xu-752 incorporates by reference a number of priority applications, including Wang-303 and Xu-533 as discussed above (for claims 28-30). EX1005, 1:5-24, 39:36-55; EX1003, ¶119. The incorporated Xu-533 disclosure states that

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“[i]mpedance analyzers are well known in the art.” EX1016, 7:45-46. The incorporated Wang-303 disclosure states that a 1260 Impedance Analyzer from Solartron Analytical was used in the experiments described. EX1015, 47:54-57, 49:25-28. Xu-752 otherwise provides no technical details about its impedance analyzer. EX1003, ¶119.

A POSA reading Xu-752, including the incorporated Xu-533 and Wang-303 disclosures, would have understood at the time of the '508's purported invention that known impedance analyzers would have been suitable for use in Xu-752's impedance-based cell analysis system. EX1003, ¶120. Further, a POSA, at that time, would have been motivated to use a more current, and improved, impedance analyzer, such as, for example, Jones's impedance analyzer. *Id.*

Beyond the advantages of parallelism, speed, and efficiency that would have provided motivations to a POSA (EX1006, ¶¶[0002]-[0003]), Jones also describes a number of additional advantages of its device that would have motivated a POSA to modify Xu-752's system to use Jones's impedance analyzer, including “allowing internal correction of impedance measurement drift, maximized measurement accuracy, and minimized system size.” *Id.*, ¶[0003], Abstract; EX1003, ¶121. Jones employs “novel calibration, self-check, and in-run compensation schemes as well as internal temperature control to ensure increased measurement accuracy and stabilization against thermal drift.” EX1006, ¶[0003]. These additional advantages

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Jones describes would have further motivated a POSA to modify Xu-752's impedance-based cell analysis system to improve its impedance analyzer based on the improved Jones device. EX1003, ¶121.

Fourth, a POSA would have had a reasonable expectation of success in combining Xu-752 and Jones. *Id.*, ¶¶122-123. Xu-752 describes the use of a known, generic, off-the-shelf impedance analyzer. Substituting a known, improved impedance analyzer, like that in Jones, would have been a straightforward substitution well within the capability of the POSA. *Id.*, ¶122. Xu-752's impedance analyzer (i) connects to the electrode arrays of multiwell plates to measure impedance in each well and (ii) also connects to a computer. *Id.*; EX1005, 16:23-29, 18:26-29, 20:6-16, 22:48-65, 55:21-25, 62:22-41. Jones's impedance analyzer is likewise for use in cell analysis to "measur[e] the complex impedance of each well of a single well or multiwell microtiter plate," and (i) connects to sensors in each well of the plate and (ii) also connects to a computer. EX1006, Abstract, ¶¶[0012], [0015]-[0020], [0037]-[0038], [0042]; EX1003, ¶122. Jones also provides a detailed description of the design and manufacture of its impedance analyzer, unlike Xu-752, and Jones describes the interface and electrical connections with the wells of a microtiter plate. EX1003, ¶122. Any modifications of the electronics, connections, or interface necessary to utilize Jones's impedance analyzer with components of Xu-752's impedance-based cell analysis system, including Xu's multiwell plates, would have

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been routine, non-complex modifications based on the descriptions in Jones and Xu-752 and the capabilities and knowledge of a POSA at the time of the '508 patent's alleged invention. EX1003, ¶122.

In addition, a POSA would have had a reasonable expectation of success in implementing millisecond time resolution between measurements with the modification of Xu-752 to use Jones's impedance analyzer. *Id.*, ¶123. As described above, Jones's impedance analyzer is capable of millisecond-time resolution between measurements of each well, and a POSA would have been able to use Jones's "massive parallelism" in design and "high temporal sampling" to provide the claimed millisecond-time resolution. *Id.*; EX1006, ¶[0002]. Moreover, a POSA would have been able to further adapt a combination of Xu-752 and Jones to provide an appropriate number of parallel ADCs and measurement channels, in addition to the eight and twelve parallel ADCs described in Jones's exemplary embodiments, as desired to further increase speed of sampling time for each well, to monitor multiwell plates with higher numbers of wells, and/or to monitor multiple plates. EX1003, ¶123.

Finally, it would also have been obvious to a POSA at the time of the '508 patent's purported invention to combine Jones's impedance measurement system with both Xu-752's multiwell plates and software that produces time period analyses for individual cell samples in the wells of such plates. *Id.*, ¶¶124-126. Jones describes using its impedance measurement system with multiwell plates and taking

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measurements of each individual well. EX1006, ¶[0037]; *see also* ¶¶[0003], [0012], [0018], [0020]. Xu-752 describes advantages associated with its electrode array structure found in each well, including that they provide uniform resistance distribution across the electrode array. EX1005, 15:50-22:30; EX1003, ¶125. Xu-752 provides extensive details regarding the design and construction of its multiwell plates and electrode arrays, allowing for easy implementation by a POSA. EX1005, 15:50-22:30. Xu-752 also describes the design details for connecting its multiwell plates for impedance analysis, including the use of POGO pins (24:30) (which are also described by Jones (EX1006, ¶[0015])). EX1005, 24:13-35; EX1003, ¶125. It would have been obvious to a POSA at the time of the '508 patent's alleged invention to use the known Xu-752 multiwell plates with Jones's impedance measurement system, including for the advantages described in Xu-752. EX1003, ¶125.

Jones also describes acquiring and processing significant amounts of impedance data, including the transmission of measurement data for each well to a storage device or computer and the capability to process "approximately 5000 data points per second." *Id.*, ¶126; EX1006, ¶¶[0037]-[0038]. Xu-752 describes using software to produce time period analyses for multiple wells of a plate from the measured impedance data, including to produce many of the plots and figures in Xu-752's Figures 6-18, and the benefits of being able to monitor numerous cell behaviors at multiple time points over a time interval. EX1005, 4:24-26, 7:38-9:29, 22:58-61,

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23:66-24:12, 24:35-54, 39:1 *et seq.* (describing numerous time period analyses for various assays associated with Figs. 6-18 and Examples 1 and 2); EX1003, ¶126. It would have been obvious to a POSA at the time of the purported invention of the '508 patent to use Xu-752's (or similar) software to further analyze the impedance data that Jones describes collecting and storing, including to produce time period analyses like those described in Xu-752 and for the reasons that Xu-752 describes producing such time period analyses. EX1003, ¶126. Any modifications of hardware or software necessary to utilize Jones's impedance measurement system with Xu-752's software or multiwell plates would have been routine, non-complex modifications based on the descriptions in Xu-752 and Jones and the capabilities and knowledge of a POSA at the time of the '508 patent's alleged invention. *Id.*

3. Claim 1

(a) Preamble: “An apparatus for continuous, label free, real-time monitoring of cells using impedance-based analysis, the apparatus comprising:”

To the extent the preamble is limiting, Xu-752 discloses this claim language as discussed above for claim 23's preamble (§ IV.A.2.(a)). EX1003, ¶127. Jones also discloses a system “for measuring the complex impedance of each well of a ... multiwell microtiter plate.” EX1006, Abstract, ¶[0003], claim 1.

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(b) Element 1: “a) a multiwell plate comprising a plurality of wells on a nonconductive substrate”

Xu-752 discloses this claim element. EX1003, ¶128. Xu-752 describes multiwell plates with a plurality of wells, including 16-well and 96-well plates. EX1005, 7:28-32, 13:49-58, 21:39-22:30, 24:25-34, 49:16-18, 51:31-34, Figs. 2-5. Xu-752’s multiple wells are on nonconductive substrate, including, *e.g.*, glass or plastic. EX1005, Abstract, 3:60-66, 14:49-53, 15:52-56, 19:36-42, 20:17-37, 21:63-22:8. Jones also discloses multiwell plates, including 96-well plates. EX1006, ¶[0030], claim 2.

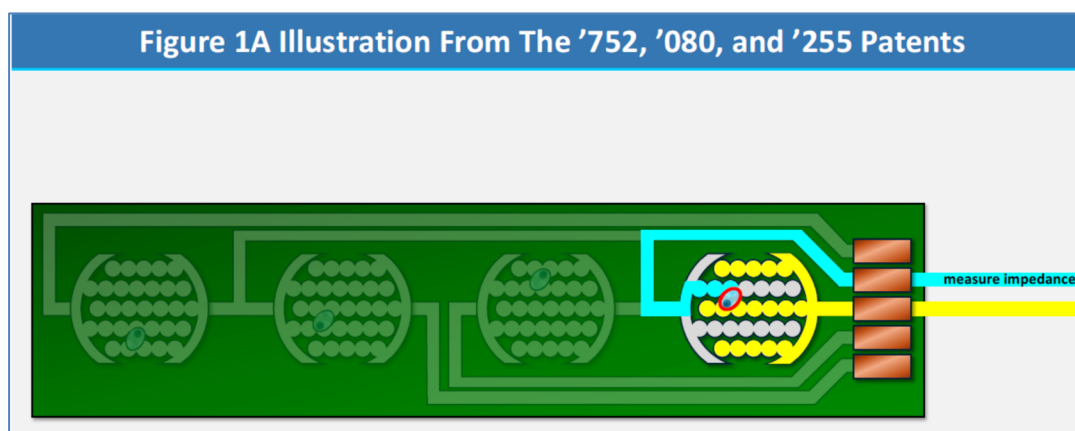
(c) Element 2: “wherein each of the plurality of wells comprises an electrode array of a plurality of electrode arrays that is disposed on the nonconductive substrate;”

Xu-752 discloses this claim element. EX1003, ¶129. Xu-752 describes plates where each well of the plurality of wells includes an electrode array (meaning there are a plurality of electrode arrays), where the arrays are fabricated on, and thus disposed on, the nonconductive substrate. *Id.*; EX1005, Abstract, 3:60-66, 15:52-56, 19:36-42, 20:37-55, 21:24-48, 21:63-22:8, 22:50-52, Fig. 1A. Jones also discloses that plates include sensors or electrodes in the well bottoms. EX1006, ¶¶[0012], [0016], [0018], claim 1; EX1003, ¶129.

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(d) Element 3: “b) an impedance analyzer that independently measures a cell-substrate impedance at each well,”

Xu-752 discloses this claim element. EX1003, ¶¶130-131. Xu-752 describes that “the impedance analyzer can automatically select wells to be measured and continuously conduct impedance measurements.” EX1005, 62:36-41. Xu-752’s system includes circuitry that connects the electrode array in each well to Xu-752’s impedance analyzer. *Id.*, 4:19-23, 16:23-29, 18:26-29, 22:52-58, 22:63-23:3, 23:48-62, 62:22-41. Xu-752 describes the operation of switching from “measuring impedance over an array in one well to measuring impedance over an array in another well,” and further notes that switches “allow the selected individual arrays to be monitored in rapid succession for each desired monitoring time point.” *Id.*, 23:1-3, 23:60-62. Agilent’s litigation tutorial on Xu-752 illustrates how impedance is independently measured in one well of a multiwell configuration, with the annotated version of Xu-752’s Figure 1A below (EX1012, 40).

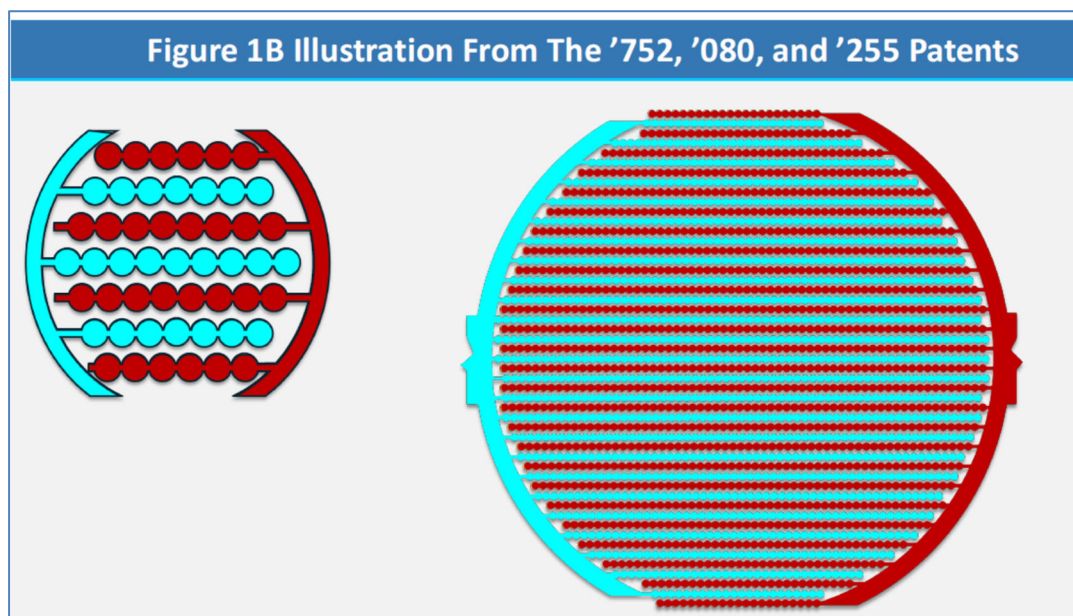


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Jones also describes a system “for measuring the complex impedance of each well.” EX1006, Abstract, ¶¶[0003], [0026], claim 1; EX1003, ¶131.

- (e) **Element 4: “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”**

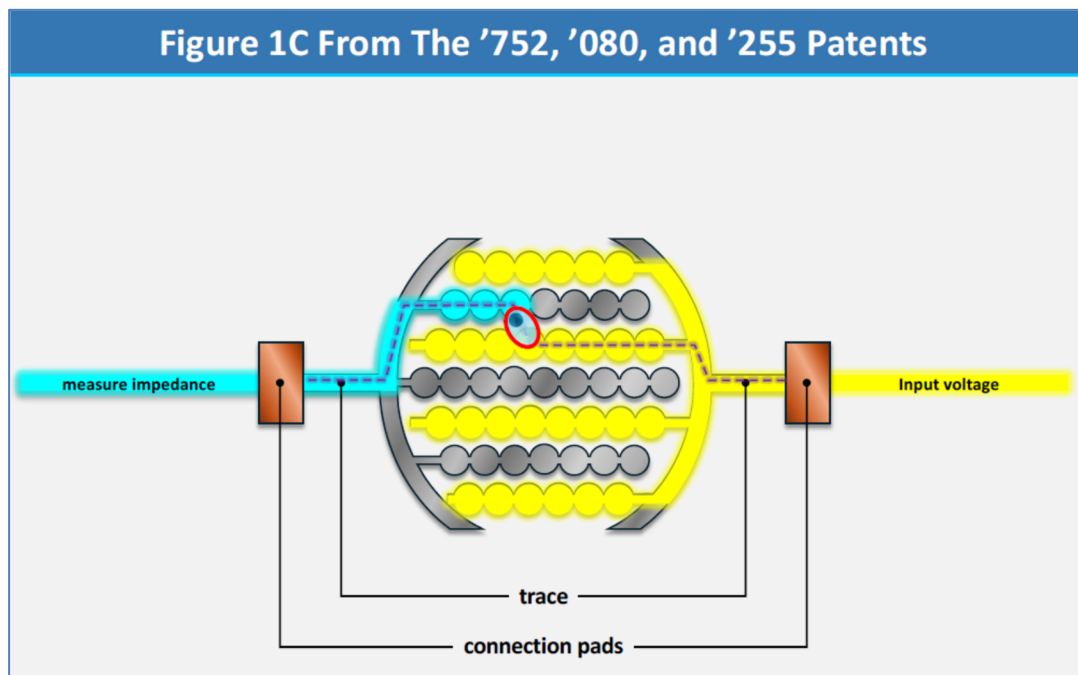
Xu-752 discloses this claim element. EX1003, ¶¶132-133. Xu-752 describes electrode arrays with first and second electrode structures. EX1005, 3:60-4:12, 10:50-11:36, 19:36-20:5, Fig. 1B (annotated version from Agilent’s litigation tutorial below); EX1012, 50.



Xu-752 states that, for the substrate on which the electrode arrays are fabricated, “cell attachment or growth on said substrate can result in a detectable change in impedance between or among the electrode structures.” EX1005, 4:4-12;

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see also 15:52-64. Xu-752 describes that “[m]easuring the impedance between and among electrodes provides important information about biological status of cells present on the sensors.” *Id.*, 40:1-3. Xu-752 describes numerous examples of cellular samples that comprise a plurality of cells being deposited in wells for impedance measurement/monitoring. *Id.*, Figs. 6-18 (and their associated descriptions in the specification), 60:35 *et seq.* (describing Examples 1 and 2); EX1003, ¶133. Agilent’s litigation tutorial shows how Xu-752 measures impedance between the two electrode structures of an array and across a cell sample in annotated Figure 1C below. EX1012, 34; Ex 1003, ¶133.



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(f) Element 5: “the impedance analyzer including at least two analogue-to-digital conversion channels coupled to the plurality of electrode arrays,”

The combination of Xu-752 and Jones discloses this claim element. EX1003, ¶¶134-135. As noted above, Xu-752 discloses that its impedance analyzer is coupled to the plurality of electrode arrays. EX1005, Abstract, 4:19-23, 4:34-35, 16:23-29, 18:26-29, 22:48-61, 22:63-23:3, 23:48-62, 62:21-41. Xu-752 does not explicitly describe that its impedance analyzer has at least two ADC channels.

Jones discloses that its impedance analyzer utilizes at least two ADC channels, and that such channels are coupled to the sensors at the bottom of each well of the plate. EX1003, ¶135. Jones describes “parallel impedance measurement channels” and, more specifically, using multiple daughter boards (e.g., eight daughter boards, one for each row of wells of a plate) where each daughter board has multiple ADCs and a digital signal processor to process impedance data. EX1006, ¶¶[0003], [0012], [0018], [0035]. Jones states that “[t]he interconnection of each sensor from a particular well in a particular row of the microtiter plate to the associated daughter board is made through a Top Contact printed circuit board assembly (PCBA), which carries all sensor signals.” *Id.* ¶[0012]. Jones states that “[f]or each impedance datum in the domain (characterized by well number, frequency, and time), each well is excited with a sinusoidally-varying voltage wave, and the resultant voltage across and current through the well are measured.” *Id.* ¶[0026].

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- (g) Element 6: “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”**

The combination of Xu-752 and Jones discloses this claim element. EX1003, ¶¶136-141. Xu-752 describes the impedance analyzer monitoring electrode arrays in each well “continuously” over various time periods, and thus taking multiple measurements of each well over such time intervals. EX1005, 7:56-62, 8:52-64, 38:36-67, 39:16-28; *see also* Figs. 6E, 7-15, 16A-17 (and associated descriptions in specification). Xu-752 does not explicitly describe a “millisecond time resolution” between two measurements in a well.

As explained in § IV.B.1-2 above, Jones describes an impedance analyzer that can monitor electrode arrays in wells at millisecond-time resolution between two measurements of cell-substrate impedance for each well. EX1006, ¶¶[0003], [0025], [0030], [0038], Fig. 4; EX1003, ¶¶69-75, 137-140. As one simple example, Dr. Kim explains that for a 16-well plate with an 8 x 2 configuration (such as in one of Xu-752’s preferred plates) with Jones’s exemplary impedance analyzer that uses three reference network channels and eight daughter boards (EX1006, ¶[0042]), each daughter board would take impedance measurements for its two wells and the three reference network channels in less than 470 milliseconds, and thus a set of measurements would be made for all 16 wells of the plate in less than 500

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milliseconds. EX1003, ¶137. Two sets of measurements for all 16 wells of the plate would be completed in less than 940 milliseconds (*i.e.*, 470 milliseconds multiplied by two). EX1006, ¶[0030]. Thus, with measurements of any given well being repeated every 470 milliseconds in this example, monitoring of the wells is performed “at millisecond time resolution between first measurements of the cell-substrate impedance and second measurements of the cell-substrate impedance for each well,” as required by claim 1. EX1003, ¶137.

Jones’s parallelism, including use of parallel ADCs, allows this millisecond-time resolution sampling. *Id.*, ¶138. Furthermore, the above example includes taking measurements for each well at multiple frequencies by using a stepped (frequency) sweep, as Jones describes in its preferred embodiment, but taking measurement samples at multiple frequencies is neither needed nor required by claim 1. *Id.* Taking measurements at a single frequency, which Jones also describes, for each well would provide for even faster measurements than in the above example. *Id.* As Dr. Kim explains, for instance, measuring all 16 wells of a 16-well plate with an 8 x 2 configuration at a single frequency of 10 kHz would take less than 136 milliseconds. *Id.*, ¶139. Because measurements of a given well are repeated every 136 milliseconds in this example, monitoring of the wells occurs at millisecond time resolution between first and second measurements of each well, as required by claim 1. *Id.*, ¶140. Dr. Kim explains several additional examples of how a POSA would use Jones’s

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impedance analyzer for impedance measurements with millisecond-time resolution between measurements to monitor multiple wells. *Id.*, ¶¶69-75, 141, 169-177.

(h) Element 7: “c) a software program that analyzes the first measurements and the second measurements to produce a time period analysis of the cellular sample.”

Xu-752 discloses this claim element. EX1003, ¶¶142-148. Xu-752 describes “a software program to ... perform data acquisition and data analysis on impedance values measured by the impedance analyzer.” EX1005, 4:24-26; *id.*, 22:58-61. The software can analyze, store, and display impedance data, including for multiple time points and intervals. *Id.*, 23:66-24:12, 24:35-54, 62:36-41, claims 3-10.

The software includes a “[t]est time setting page [that] allows for the recording and control of time intervals used for performing cell-substrate impedance measurement and multiple experimental steps each having different time interval values and different length times can be setup.” *Id.*, 7:44-49; *see also* 24:43-47. Xu-752’s Figure 6E (below) shows a “page” from the “software” that includes a time period analysis (X-axis of plot) of a cellular sample (“Cell Type” and “Cell Number” fields) produced from multiple measurements.

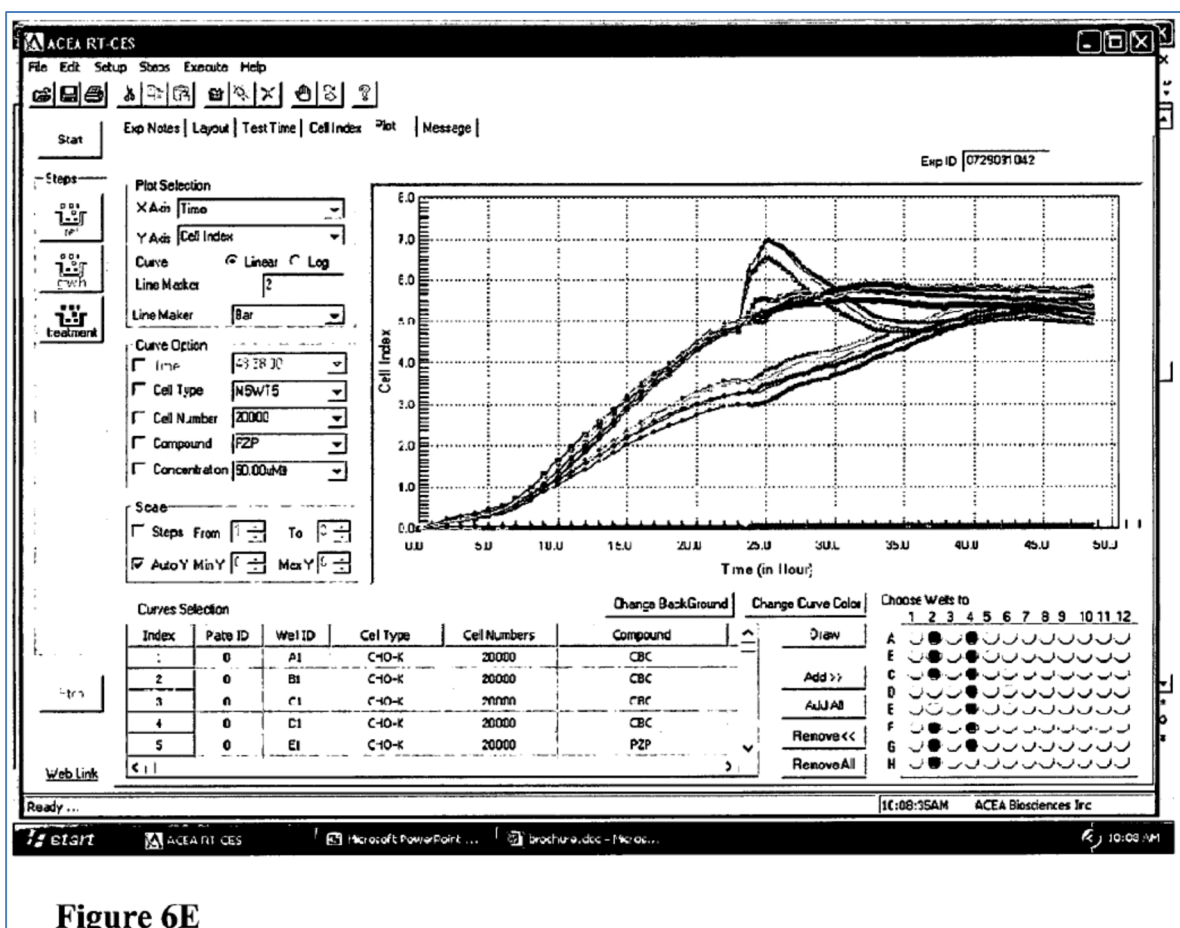
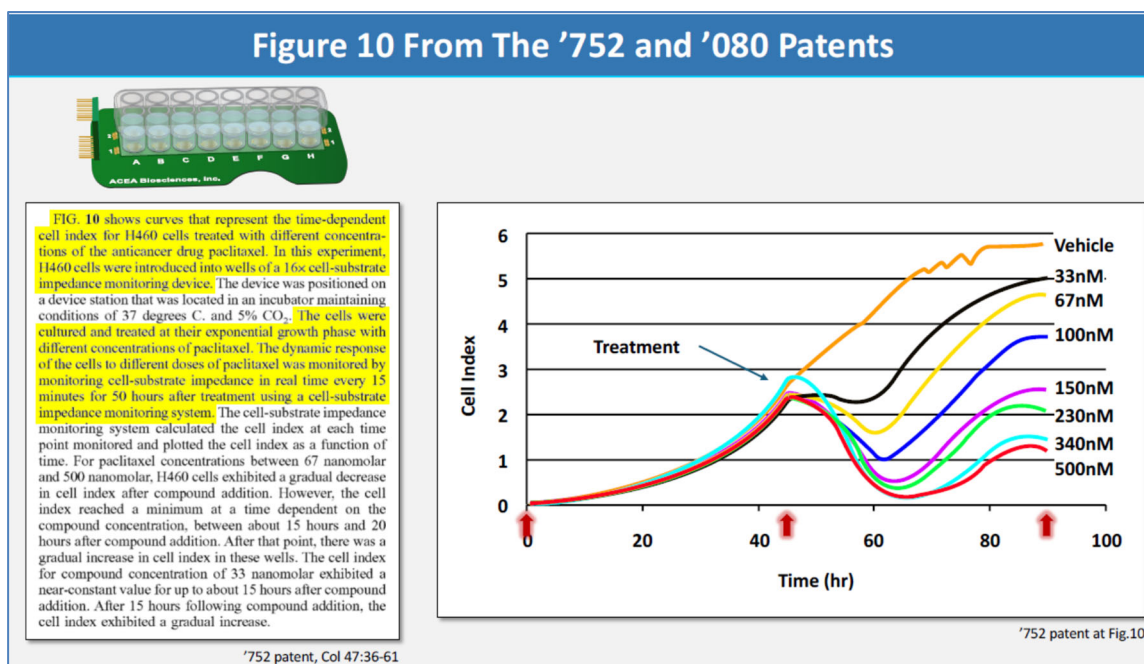


Figure 6E

Id., Fig. 6E, 7:38-55, 24:35-54. Xu-752 describes numerous examples of time period analyses of cellular samples. *Id.*, Figs. 6-18 (and their associated descriptions in the specification), 60:35 *et seq.* (describing Examples 1 and 2); EX1003, ¶¶143-144. An annotated version of Xu-752's Figure 10 (and its associated description) from Agilent's litigation tutorial is shown below.



EX1012, 65; EX1005, 47:36-61, Fig. 10.

Xu-752 thus discloses the claimed “software program that analyzes the first measurements and the second measurements to produce a time period analysis of the cellular sample.” EX1003, ¶145. Notably, claim 1 at most requires the impedance analyzer’s *monitoring* of cells/electrode arrays to be performed in real time, at a millisecond time resolution, but the claim does not apply the “real-time” and “millisecond time resolution” requirements to the production of the time period analysis by the software program. *Id.*, ¶146. And, in prosecuting Wang-548 (a grandparent application to the '508 patent, *see* § III.C.1-2 above), ACEA did not attempt to distinguish the prior art by arguing that the claimed “software program” analyzed data at millisecond time resolution. EX1014, 145-159, 179-198, 215-234, 254-276. In any event, as Dr. Kim explains, the combination of Xu-752 and Jones

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would have rendered obvious the production of the time period analysis in real time or at a millisecond time resolution. EX1003, ¶¶147-148.

4. Claim 2

Claim 2 depends from claim 1 and adds: “wherein the 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.” The combination of Xu-752 and Jones discloses this limitation. EX1003, ¶¶149-151.

As discussed above for claim 1 (element 5), Jones describes using “parallel impedance measurement channels,” including, for example, eight daughter boards in parallel. EX1006, ¶¶[0003], [0012], [0018], [0026], [0035]. Jones states that “each row of sensors on a microtiter plate is addressed by measurement circuitry (in the form of analog signal conditioning circuits, multiplexing circuits, analog-digital converters, and digital signal processors) on a single daughter board. ... Each daughter board has multiplexing circuitry allowing one or more measurement channels to address the sensors for each well in the row.” *Id.* ¶[0012]; *see also* ¶¶[0018], [0030]-[0031], [0035], [0037]-[0038]. “The impedance data for a microtiter plate row is processed by a digital signal processor dedicated to each row and located on the daughter boards.” *Id.* ¶[0018]. The “daughter boards mate at their lowest edge with the mother board” and the “mother board processes the impedance measurement data ... of all

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wells of the microtiter plate....” *Id.* ¶[0020]. “The current through and the voltage across each well is scaled, converted to digital values, and transmitted via the measurement channels to either a storage device or an associated computer.” *Id.* ¶[0037].

5. Claim 3

Claim 3 depends from claim 1 and adds: “wherein the plurality of analogue-to-digital conversion channels performs signal conversion in parallel across multiple wells.” The combination of Xu-752 and Jones discloses this limitation. EX1003, ¶¶152-154.

As discussed above for claims 1 and 2, Jones describes that its parallel ADC channels on its multiple daughter boards perform signal conversion in parallel across multiple wells, emphasizing its “massive parallelism” and “parallel impedance measurement channels.” EX1006, ¶¶[0002]-[0003]; *see also* ¶¶[0012], [0018], [0020], [0030]-[0031], [0035], [0037]-[0038].

6. Claim 4

Claim 4 depends from claim 1 and adds: “wherein the plurality of analogue-to-digital conversion channels is configured for monitoring multiple cell-substrate impedances in different wells of the plurality of wells at approximately the same time.” The combination of Xu-752 and Jones discloses this limitation. EX1003, ¶¶155-157.

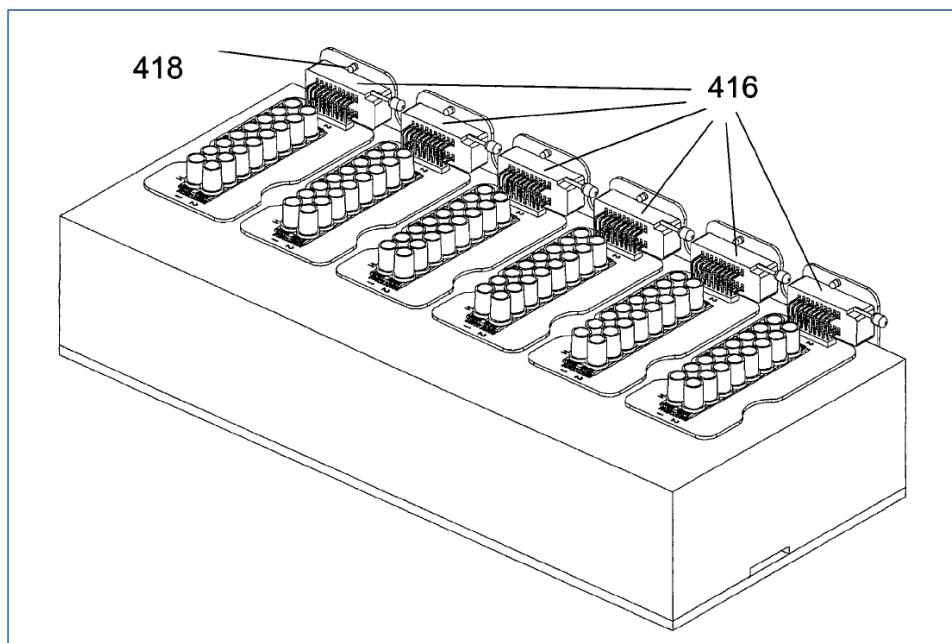
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As discussed above for claims 1 and 2, Jones describes that its parallel ADC channels on its multiple daughter boards monitor impedances in different wells of multiwell plates at approximately the same time, emphasizing its “massive parallelism” and “parallel impedance measurement channels.” EX1006, ¶¶[0002]-[0003]; *see also* ¶¶[0012], [0018], [0020], [0030]-[0031], [0035], [0037]-[0038].

7. Claims 5 and 6

Claim 5 depends from claim 1 and adds: “wherein the apparatus comprises an electromechanical apparatus configured for interfacing the multiwell plate with one or more platforms.” Claim 6 depends from claim 5 and adds: “wherein the one or more platforms of the electromechanical apparatus comprise an impedance platform.” Xu-752 discloses these limitations. EX1003, ¶¶158-161.

Xu-752 describes that its “device station,” an example of which is shown in Figure 4 below, “can comprise one or more platforms or one or more slots for position one or more multiwell devices,” and “can comprise sockets, pins or other devices for electrically connecting the device to the device station.” EX1005, 23:31-43, Fig. 4, 24:13-24; *compare* EX1001, 26:32-44 *with* EX1005, 23:31-43.



Xu-752 discloses that the device station “can be electrically connected to an impedance analyzer.” EX1005, 23:41-42. Xu-752’s device station connects “to an impedance analyzer and [has] 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. ... [to] monitor impedance from one or more of the electrode arrays.” EX1005, 23:44-52; *see also* 22:54-58.

8. Claim 7

Claim 7 depends from claim 1 and adds: “wherein 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.” Xu-752 discloses this limitation. EX1003, ¶¶162-164.

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Xu-752 states that “each electrode array on the substrate” of a multiwell plate “is associated with a fluid-impermeable container or receptable,”; “[p]referably, the device ... is assembled to a bottomless, multiwell plastic plate or strip with a flight tight seal, as shown, for example, in FIG. 2 and FIG. 3”; and “[t]he device is assembled such that a single array of the substrate is at the bottom of a receptable or well.” EX1005, 21:24-31; *compare* EX1001, 23:1-14 *with* EX1005, 21:24-38.

9. Claim 8

Claim 8 depends from claim 1 and adds the following limitations: “wherein the nonconductive substrate includes a precoat comprising one or more compounds that improve cell attachment.” Xu-752 discloses this limitation. EX1003, ¶¶165-167.

The '508 patent states that fibronectin is an example of a compound used to precoat the substrate to improve cell attachment. EX1001, 19:48-54. Xu-752 also describes using fibronectin as a precoat for wells to improve cell attachment. EX1005, 41:19-31, 7:63-8:2, 10:25-45, Fig. 8. Xu-752 describes that the nonconducting substrate “has a surface suitable for cell attachment or growth” (*id.*, 4:4-12, 15:52-64), which may require that the surface be “chemically-treated (e.g. treatment with an acid and/or with a base),” physically treated, and/or “biochemically treated (e.g. coated with one or more molecules or biomolecules that promotes cell attachment)” (*id.*, 9:65-19). *See also id.*, 20:17-33.

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10. Claims 9-14

Claim 9 depends from claim 1 and adds: “wherein the millisecond time resolution between the first measurement and the second measurements is less than 500 milliseconds.” Claims 10-14 recite measurement time resolutions within this window: between 500 and 100 milliseconds (claim 10), less than 100 milliseconds (claim 11), less than 40 milliseconds (claim 12), less than 20 milliseconds (claim 13), and less than 5 milliseconds (claim 14). Claims 9-14 would have been obvious over Xu-752 and Jones. EX1003, ¶¶168-182.

First, claims 9-14 are obvious because they fail to “specify a device which perform[s] and operate[s] any differently from the prior art.” *Gardner v. TEC Sys., Inc.*, 725 F.2d 1338, 1349 (Fed. Cir. 1984); EX1003, ¶¶169-177. For instance, in an example of the Xu-752/Jones system using a 96-well plate with an 8 row by 12 column configuration, so that there are 12 wells per row plus 4 reference channels, measuring all 16 wells/channels with a single frequency burst of 15 cycles would take less than 412 milliseconds for a 100 kHz measurement frequency, reading on claims 9 and 10. EX1003, ¶169; *see also* ¶170.

Further, in applying the Xu-752/Jones system to study biological cell phenomena like electroporation, where cell changes occur on the order of “a few milliseconds” (EX1017, 1604, 1609), a POSA would have recognized that the desired measurement resolutions on the order of a few milliseconds would be

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achieved by eliminating unnecessary measurements of Jones's reference channel networks. EX1003, ¶171. As Dr. Kim explains, for instance, in an example of the Xu-752/Jones system using a 16-well plate and 16 daughter boards, the elimination of such unnecessary measurements would enable all 16 wells to be measured in approximately 1.5 milliseconds using a single frequency burst at a 10 kHz measuring frequency and 15 cycles per burst, thus reading on claims 9 and 11-14. *Id.*, ¶¶172-174; *see also* ¶¶175-176.

Further, it would have been an obvious design choice to configure the Xu-752/Jones system to operate at the millisecond time resolutions of claims 9-14. A POSA would have understood, well before the '508's alleged invention, that the biological cell phenomenon to be studied drives the requisite measurement speed (*id.*, ¶178), and each of the ranges recited in claims 9-14 therefore would have been obvious. To apply the Xu-752/Jones system to study electroporabilization, for instance, where cell pores "start resealing within a few milliseconds," it would have been obvious to configure the system to provide an adequate measurement resolution, *e.g.*, "less than 5 milliseconds" (claim 14). EX1017 (Ghosh), 1604, 1609; EX1003, ¶178. The other resolutions of claims 9-14 would have been obvious for the same reason—there is nothing inventive or non-obvious about selecting a measurement speed sufficient for the application. *Id.*

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A POSA would have also understood how to configure the Xu-752/Jones system to achieve the millisecond time resolutions recited in claims 9-14, *i.e.*, by choosing system parameters in a manner suitable for achieving the desired time resolution. *Id.*, ¶179. Further, Xu-752 and Jones both tout their flexibility and ability to operate in a variety of configurations (*id.*, ¶180), further confirming a POSA's reasonable expectation of success in achieving resolutions within the ranges of claims 9-14 using the combination of Xu-752 and Jones. EX1005, 21:39-47, 26:11-35, 38:34-67, 40:28-47; EX1006, ¶[0003], ¶[0025], ¶[0030].

Finally, nothing in the '508 patent indicates that the ranges of claims 9-14 are critical aspects of the alleged invention or that they achieve unexpected results. EX1003, ¶181. Instead, the '508 patent simply lists off various millisecond time resolutions without distinguishing them in any way. EX1001, 3:52-60, 4:55-67, 10:8-24, 23:47-24:10, 24:37-52, 25:53-59. Higher resolution measurements enable faster measurements, of course, but that is not unexpected. EX1003, ¶181. And while the '508 patent alleges that "substantial reconfiguration" is required to achieve "millisecond time resolution," generally (*id.*, 24:12-37, 24:53-57), the '508 patent never suggests that achieving the faster claimed measurements (*e.g.*, "less than 5 milliseconds," claim 14) requires any technological advancement versus the slower ones (*e.g.*, "less than 500 milliseconds," claim 9).

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11. Claim 15

Claim 15 depends from claim 1 and adds: “wherein the time period analysis lasts at least 12 hours.” Xu-752 discloses this limitation. EX1003, ¶¶183-185.

Xu-752 discloses that “[t]he cell response during an assay can be monitored essentially continuously over a selected time period,” and, for example, this time period can be “for several hours to several days.” EX1005, 39:18-28; Figs. 6E, 7, 9-15, 16A-17 (and their associated descriptions in the specification), 60:35 *et seq.* (describing Examples 1 and 2) (all showing/describing time period analyses of over 12 hours).

12. Claim 16

(a) Preamble: “A system for continuously monitoring cells in real time, label free, with impedance-based analysis, the system comprising:”

To the extent the preamble is limiting, Xu-752 discloses this claim language as discussed above for claim 23’s preamble (§ IV.A.2.(a)). EX1003, ¶186. Jones also discloses a system “for measuring the complex impedance of each well of a ... multiwell microtiter plate.” EX1006, Abstract, ¶¶[0003], claim 1.

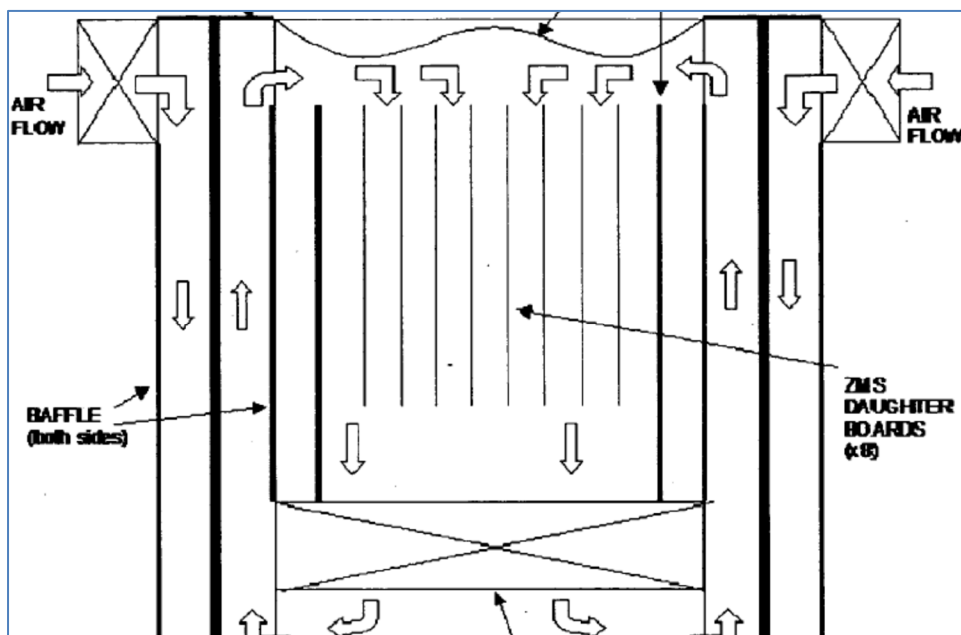
(b) Element 1: “a) a plurality of analog-to-digital (A2D) signal converters electrically arranged in parallel to one another;”

The combination of Xu-752 and Jones discloses this claim element. EX1003, ¶¶187-189. Xu-752 describes the use of analog-to-digital conversion, describing

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“convert[ing]” to “digital signals for processing and for analysis” (EX1005, 40:3-7), but does not explicitly describe that its impedance-based cell analysis system has a plurality of ADCs electrically arranged in parallel to one another.

Jones discloses that its impedance measurement system includes a plurality of ADCs electrically arranged in parallel to one another. EX1003, ¶188. Jones describes, as shown in Figure 4 below, eight daughter boards electrically arranged in parallel to one another. EX1006, ¶¶[0002]-[0003], [0012], [0014], [0018], [0020], Figs. 2, 4.



Each daughter board has multiple ADCs and a digital signal processor to process impedance data. *Id.*, ¶¶[0003], [0012], [0018], [0035], Fig. 3; EX1003, ¶189.

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(c) Element 2: “b) a well plate comprising a plurality of wells on a nonconductive substrate,”

Xu-752 discloses this claim element. EX1003, ¶190. Xu-752 describes multiwell plates with a plurality of wells, including 16-well and 96-well plates. EX1005, 7:28-32, 13:49-58, 21:39-22:30, 24:25-34, 49:16-18, 51:31-34, Figs. 2-5. Xu-752’s multiple wells are on nonconductive substrate, including, *e.g.*, glass or plastic. EX1005, Abstract, 3:60-66, 14:49-53, 15:52-56, 19:36-42, 20:17-37, 21:63-22:8. Jones also discloses multiwell plates, including 96-well plates. EX1006, ¶[0030], claim 2.

(d) Element 3: “wherein each well of the plurality of wells comprises one electrode array of the plurality of electrode arrays disposed on the nonconductive substrate that is connected to the plurality of A2D signal converters;”

The combination of Xu-752 and Jones discloses this claim element. EX1003, ¶¶191-192. Xu-752 describes plates where each well of the plurality of wells includes an electrode array (meaning there are a plurality of electrode arrays), where the arrays are fabricated on, and thus disposed on, the nonconductive substrate. EX1005, Abstract, 3:60-66, 15:52-56, 19:36-42, 20:37-55, 21:24-48, 21:63-22:8, 22:50-52, Fig. 1A. Jones also discloses multiwell plates including sensors or electrodes in the well bottoms. EX1006, ¶¶[0012], [0016], [0018], claim 1. Xu-752 does not explicitly describe the connection to a plurality of ADCs.

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As discussed above for claim 16 element 1, Jones's daughter boards each include ADCs and a digital signal processor to process impedance data, and Jones explains that "[t]he interconnection of each sensor from a particular well in a particular row of the microtiter plate to the associated daughter board is made through a Top Contact printed circuit board assembly (PCBA), which carries all sensor signals." *Id.* ¶[0012]. Jones thus describes the connection of well sensors to the plurality of ADCs. EX1003, ¶192.

(e) Element 4: "c) an impedance analyzer connected to or including the plurality of A2D signal converters,"

The combination of Xu-752 and Jones discloses this claim element. EX1003, ¶193. Xu-752 describes that "the impedance analyzer can automatically select wells to be measured and continuously conduct impedance measurements." EX1005, 62:36-41. As noted above, Xu-752 describes the use of analog-to-digital conversion, describing "convert[ing]" to "digital signals for processing and for analysis" (*id.*, 40:3-7), but does not explicitly describe use of a plurality of ADCs. As discussed above for claim 16 element 1, Jones discloses that its impedance analyzer is connected to or includes a plurality of ADCs. Jones describes "parallel impedance measurement channels" and, more specifically, using multiple daughter boards (*e.g.*, eight daughter boards, one for each row of wells of a plate) where each daughter board has multiple ADCs and a digital signal processor to process impedance data. EX1006, ¶¶[0003], [0012], [0018], [0035].

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- (f) Element 5: “wherein the impedance analyzer 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 combination of Xu-752 and Jones discloses this claim element. EX1003, ¶¶194-195. Xu-752 describes the impedance analyzer monitoring electrode arrays in each well “continuously” over various time periods, and thus taking multiple measurements of each well over such periods. EX1005, 7:56-62, 8:52-64, 38:36-67, 39:16-28; *see also* Figs. 6E, 7-15, 16A-17 (and associated descriptions in specification). Xu-752 does not explicitly describe measuring pluralities of impedances via digitally converted signals from the plural ADCs.

Jones describes an impedance analyzer that uses digitally converted signals from the plural ADCs to measure pluralities of impedances, as claimed. EX1003, ¶195. Jones describes using “parallel impedance measurement channels.” EX1006, ¶¶[0003], [0012], [0018], [0026], [0035]. Jones states that “[f]or each impedance datum in the domain (characterized by well number, frequency, and time), each well is excited with a sinusoidally-varying voltage wave, and the resultant voltage across and current through the well are measured.” *Id.* ¶[0026]. Jones states that “each row of sensors on a microtiter plate is addressed by measurement circuitry (in the form of analog signal conditioning circuits, multiplexing circuits, analog-digital converters, and digital signal processors) on a single daughter board. ... Each daughter board has

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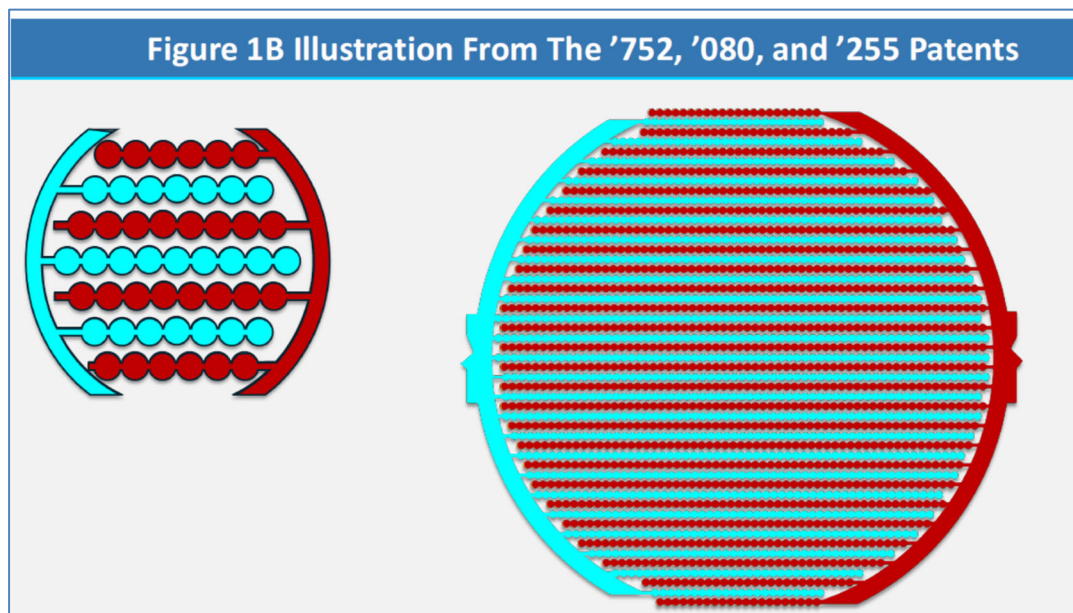
multiplexing circuitry allowing one or more measurement channels to address the sensors for each well in the row.” *Id.* ¶[0012]; *see also* ¶¶[0018], [0030]-[0031], [0035], [0037]-[0038]. “The impedance data for a microtiter plate row is processed by a digital signal processor dedicated to each row and located on the daughter boards.” *Id.* ¶[0018]. The “daughter boards mate at their lowest edge with the mother board” and the “mother board processes the impedance measurement data ... of all wells of the microtiter plate....” *Id.* ¶[0020]. “The current through and the voltage across each well is scaled, converted to digital values, and transmitted via the measurement channels to either a storage device or an associated computer.” *Id.* ¶[0037].

- (g) Element 6: “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”**

The combination of Xu-752 and Jones discloses this claim element. EX1003, ¶¶196-198. As noted above for claim 16 element 5, Jones describes measuring the pluralities of impedances recited here, while Xu-752 describes how impedance is measured between two electrode structures across a cell sample.

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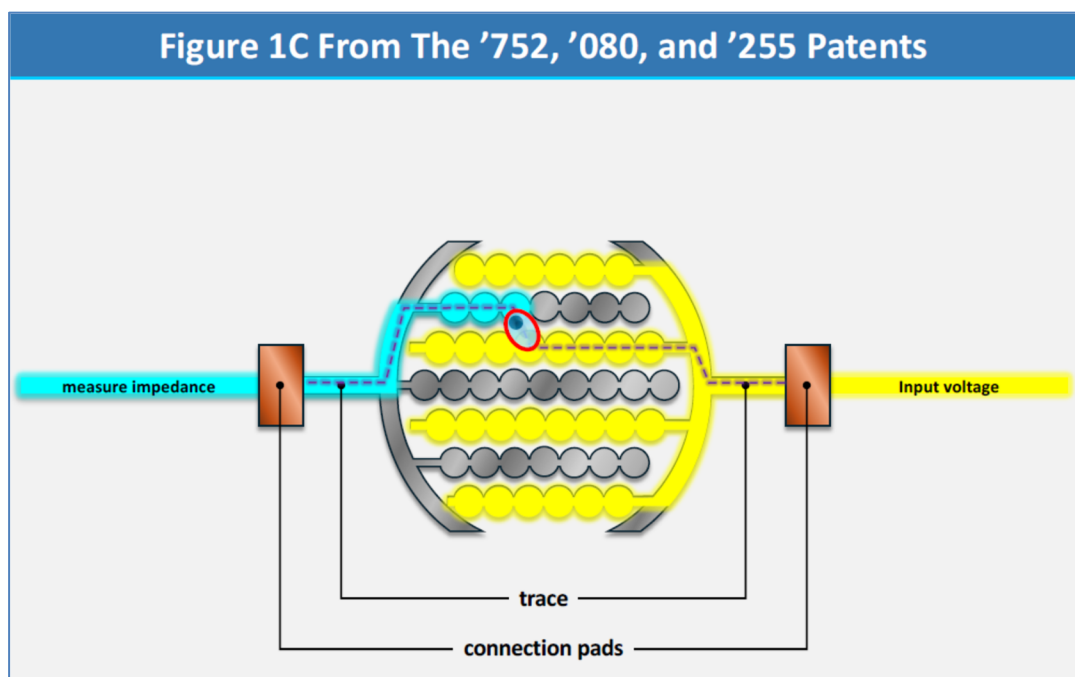
Xu-752 describes electrode arrays, with each array having first and second electrode structures. EX1005, 3:60-4:12, 10:50-11:36, 19:36-20:5, Fig. 1B (annotated version from Agilent's litigation tutorial below); EX1012, 50.



Xu-752 states that, for the substrate on which the electrode arrays are fabricated, “cell attachment or growth on said substrate can result in a detectable change in impedance between or among the electrode structures.” EX1005, 4:4-12. Xu-752 describes that “[m]easuring the impedance between and among electrodes provides important information about biological status of cells present on the sensors.” *Id.*, 40:1-3. Xu-752 describes numerous examples of cellular samples that comprise a plurality of cells being deposited in wells for impedance measurement/monitoring. *Id.*, Figs. 6-18 (and their associated descriptions in the specification), 60:35 *et seq.* (describing Examples 1 and 2); EX1003, ¶¶197-198. Agilent's litigation tutorial

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shows how Xu-752 measures impedance between the two electrode structures of an array and across a cell sample in annotated Figure 1C below. EX1012, 34; Ex 1003, ¶198.



- (h) **Element 7: “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,”**

Xu-752 discloses this claim element. EX1003, ¶¶199-202. Xu-752 describes “a software program to ... perform data acquisition and data analysis on impedance values measured by the impedance analyzer.” EX1005, 4:24-26; *id.*, 22:58-61. Xu-752’s software can analyze, store, and display impedance data, including for

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multiple time points and intervals. *Id.*, 23:66-24:12, 24:35-54, 62:36-41, claims 3-10.

The software includes a “[t]est time setting page [that] allows for the recording and control of time intervals used for performing cell-substrate impedance measurement and multiple experimental steps each having different time interval values and different length times can be setup.” *Id.*, 7:44-49; *see also* 24:43-47. Xu-752’s Figure 6E (below) shows a software “page” that includes a plurality of time period analyses (X-axis of plot) of cell samples (“Cell Type” and “Cell Number” fields) in multiple wells produced from multiple measurements (*see* multiple lines on the plot).

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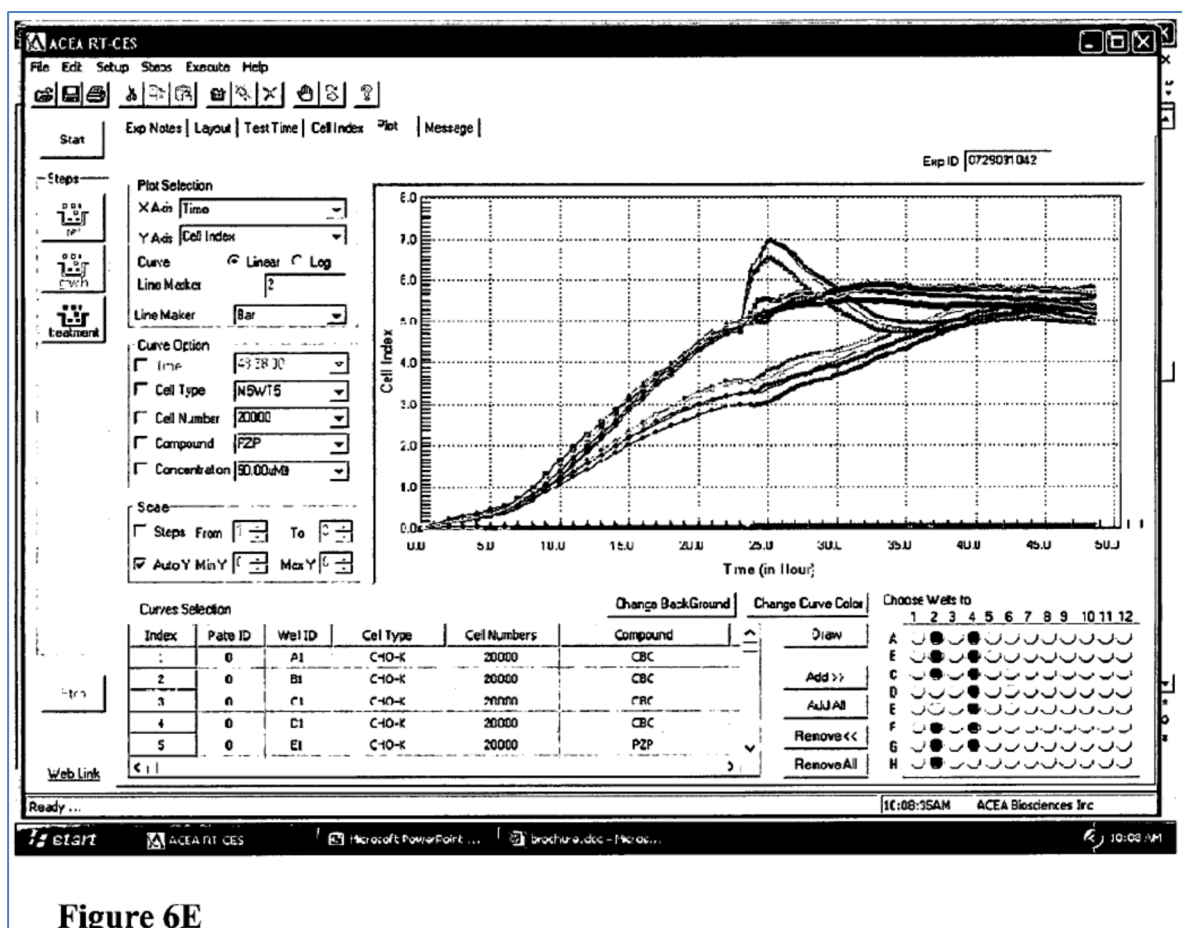
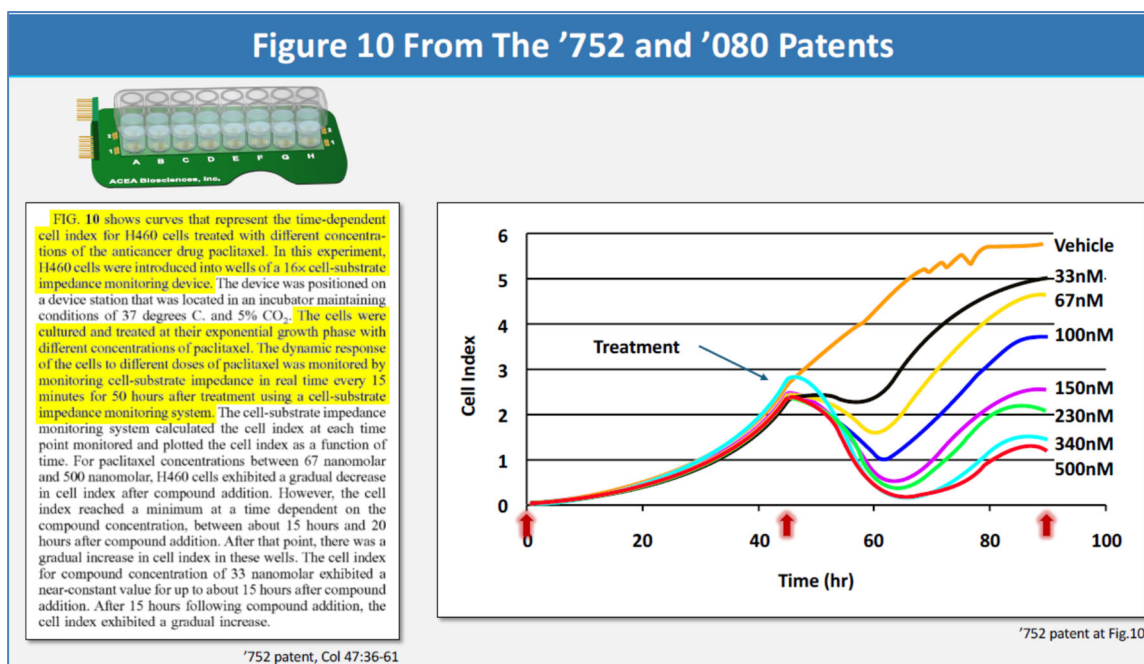


Figure 6E

Id., Fig. 6E, 7:38-55, 24:35-54. Xu-752 describes numerous examples of time period analyses of pluralities of cell samples from multiple wells. *Id.*, Figs. 6-18 (and their associated descriptions in the specification), 60:35 *et seq.* (describing Examples 1 and 2); EX1003, ¶¶201-202. An annotated version of Xu-752's Figure 10 (and its associated description) from Agilent's litigation tutorial is shown below.



EX1012, 65; EX1005, 47:36-61, Fig. 10.

- (i) **Element 8: “wherein individual time period analyses of the plurality of time period analyses are associated with individual wells of the plurality of wells.”**

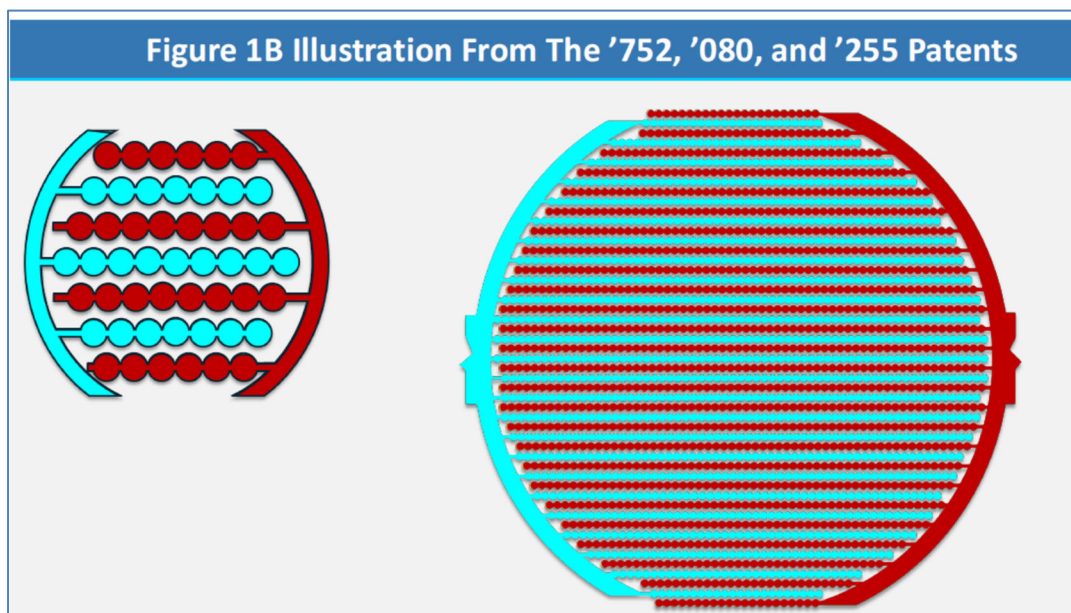
Xu-752 discloses this claim element. EX1003, ¶¶203-204. Agilent’s annotated Figure 10 of Xu-752 shows individual time period analyses for eight individual wells over 90 hours. *Id.*, ¶203; EX1005, Fig. 10, 47:36-61. Xu-752 describes other examples of this as well, including for its Example 2 assay: “20,000 RBL-2H3 cells were seeded per well of a 16x microtiter device and monitored by the impedance measuring system. The cells were allowed to attach and spread for 5–24 hours prior to the addition of IgE at the indicated final concentration. The cell-electrode impedance was continuously measured and the corresponding, time dependent Cell-

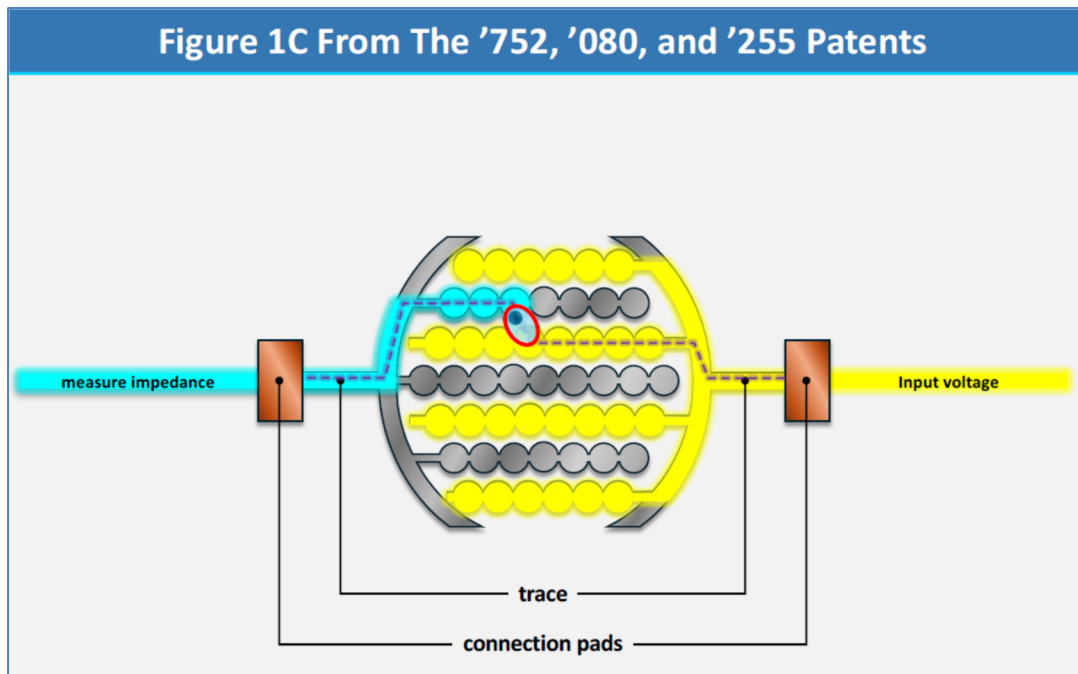
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Index values were derived and recorded.” EX1005, 63:42-49; *see also* 7:38-55, 24:35-54, claims 7-9, Figs 6A-6E.

13. Claim 17

Claim 17 depends from claim 16 and adds: “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.” Xu-752 discloses these limitations. EX1003, ¶¶205-206. Xu-752’s Figures 1B and 1C, with annotated versions from Agilent’s litigation tutorial on Xu-752 below, show the structure recited in claim 17.





EX1012, 50, 34; EX1005, 10:49-11:36, 19:36-20:5, 20:45-55, Figs. 1A-1C.

14. Claim 18

Claim 18 depends from claim 16 and adds: “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.” Xu-752 discloses these limitations. EX1003, ¶¶207-211.

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Xu-752 describes numerous assays that meet the limitations of claim 18. *Id.*, ¶¶208-210. As discussed above for claim 16 element 6, Xu-752 describes taking multiple measurements of impedance between first and second electrode structures of an array in each well, as restated in claim 18. Xu-752 explains that “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.” EX1005, 12:19-24; *compare* EX1001, 12:35-40 (same disclosure). Xu-752 also explains that detectable impedance changes may refer to the difference in impedance values when cells are attached (or not), or the difference in impedance values “when the number, type, activity, adhesiveness, or morphology of cells attached to the electrode-comprising surface of the apparatus changes.” EX1005, 12:43-59; *compare* EX1001, 12:58-13:8.

Xu-752 describes that cell samples may be cultured from a cell seeding placed in a well that viably attaches to a bottom of the well and grows, in at least the Xu-752 assays associated with Figures 7-9, 12-14, and 16 and Examples 1 and 2. EX1005, Figs. 7-9, 12-14, 16; 7:55-9:20, 30:52-61, 39:1-29, 41:4-42:20, 48:21-35, 59:12-23, 60:20 *et seq.* Xu-752 also describes measuring/monitoring impedance in seeded wells, including continuously from a time when the cells are placed in the well, until the cells attach, and for hours after attachment. *Id.*

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For example, the Example 2 assay discussed above for claim 16 element 8 states: “20,000 RBL-2H3 cells were seeded per well of a 16x microtiter device and monitored by the impedance measuring system. The cells were allowed to attach and spread for 5–24 hours prior to the addition of IgE at the indicated final concentration. The cell-electrode impedance was continuously measured and the corresponding, time dependent Cell-Index values were derived and recorded.” *Id.*, 63:42-49. In discussing the Example 2 assay, Xu-752 also states: “[i]n the presence of cells, cells attached to the electrode sensor surfaces will alter the local ionic environment at the electrode/solution interface, leading to an increase in the impedance. The more cells there are on the electrodes, the larger the increase in cell-electrode impedance. Furthermore, the impedance change also depends on cell morphology and the extent to which cells attach to the electrodes.” *Id.*, 62:48-55.

15. Claim 19

Claim 19 depends from claim 18 and adds: “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.” Xu-752 discloses this limitation. EX1003, ¶¶212-213. As discussed above for claim 18, Xu-752 describes measuring differences in impedance values that show changes in cell attachment including changes in the number of cells

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attached to the electrodes (which includes the substrate, and the first and second electrode structures). EX1005, 12:19-59, 23:10-20, 27:51-28:11, 39:1-29, 40:28-47, 41:62-42:20, 43:49-44:7, 48:57-49:7, 50:7-36, 52:1-8, 54:56-67, 57:12-23, 59:12-23, 62:42-63:11.

16. Claim 20

Claim 20 depends from claim 16 and adds: “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.” Xu-752 discloses this limitation. EX1003, ¶¶214-216.

As discussed above for claim 18, Xu-752 describes seeding cell samples into wells (*i.e.*, in vitro or “in glass” samples) and measuring impedance between first and second times for impedance differences/changes, including changes associated with morphological changes in the sample. EX1005, 5:58-6:6, 8:3-11, 12:43-59, 23:10-20, 39:1-29, 40:28-47, 41:32-46, 41:62-42:20, 43:49-44:7, 48:57-49:7, 50:7-36, 51:19-21, 52:1-8, 53:39-42, 54:56-67, 56:19-26, 57:12-23, 59:12-23, 59:50-60:19, 60:35-61:40, 62:42-63:11.

17. Claim 21

Claim 21 depends from claim 16 and adds: “wherein each cell sample disposed in the corresponding wells is an in vitro sample that is measured between

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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.” Xu-752 discloses this limitation. EX1003, ¶¶217-219.

As discussed above for claims 18-19, Xu-752 describes seeding cell samples into wells (*i.e.*, in vitro or “in glass” samples) and measuring impedance between first and second times for impedance differences/changes, including changes associated with the number of cells attached to the first and/or second electrode structure. *See* portions of Xu-752 cited for claims 18-19.

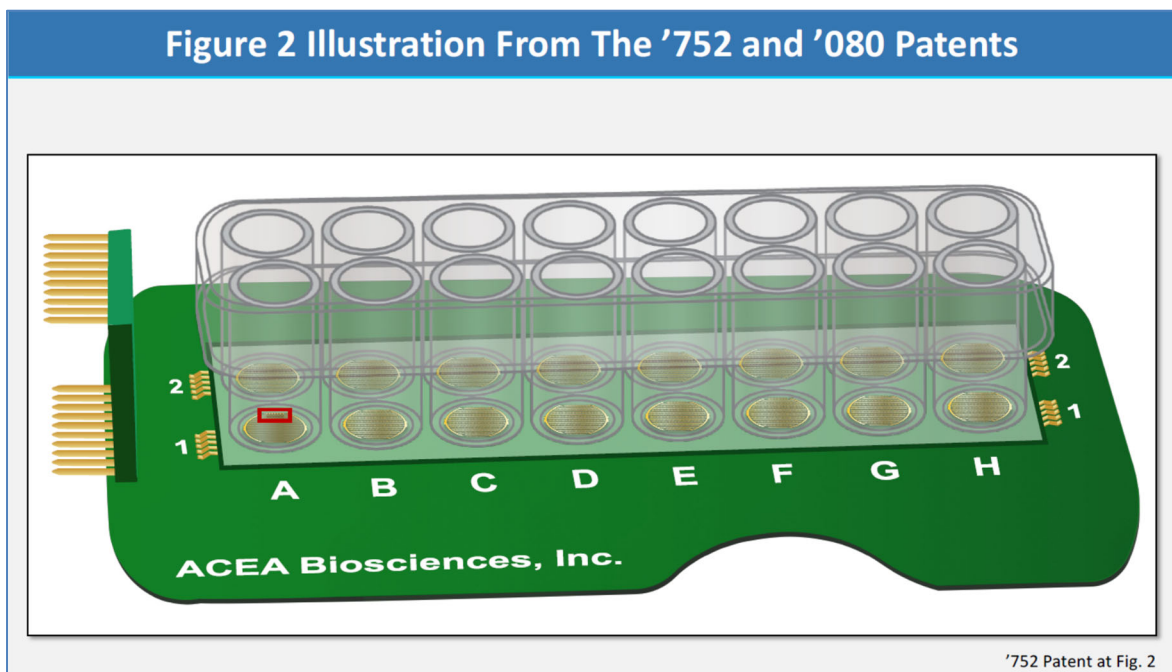
18. Claim 22

Claim 22 depends from claim 16 and adds: “wherein the plurality of wells isolate the individual cell samples from one another.” Xu-752 discloses this limitation. EX1003, ¶¶220-222.

Xu-752 states that “each electrode array on the substrate of a device of the present invention is associated with a fluid-impermeable container or receptacle. Preferably, the device ... is assembled to a bottomless, multiwell plastic plate or strip with a fluid tight seal, as shown, for example, in FIG. 2 and FIG. 3. The device is assembled such that a single array of the substrate is at the bottom of a receptacle or well.” EX1005, 21:24-31, Figs. 2-3B. Agilent’s annotated Figure 2 from its

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litigation tutorial for Xu-752 shows how the wells would isolate cell individual samples, as described.



EX1012, 53.

V. CONCLUSION

Petitioner respectfully requests IPR of claims 1-30.

VI. MANDATORY NOTICES PURSUANT TO 37 C.F.R. § 42.8(a)(1)

Pursuant to 37 C.F.R. § 42.8(a)(1), the mandatory notices identified in 37 C.F.R. § 42.8(b) are provided below as part of this petition.

A. 37 C.F.R. § 42.8(b)(1): Real Parties-In-Interest

The real parties-in-interest are Axion BioSystems, Inc.

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B. 37 C.F.R. § 42.8(b)(2): Related Matters

Pursuant to 37 C.F.R. § 42.8(b)(2), Petitioner is aware of the following patent infringement lawsuit that involves the '508 patent:

- *Agilent Technologies, Inc. v. Axion BioSystems, Inc.*, 1:24-cv-00300-CJB (D. Del.).

C. 37 C.F.R. § 42.8(b)(3), (4): Lead And Back-Up Counsel And Service Information

Petitioner provides the following designation of counsel:

Lead Counsel	Back-up Counsel
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Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney for Petitioner accompanies this petition. Please address all correspondence to lead and back-up counsel at the addresses above. Petitioner also consents to electronic service by email at the email addresses listed above.

Dated: September 20, 2024

Respectfully submitted,

/Joshua R. Nightingale/

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing petition for *Inter Partes* Review of U.S. Patent No. 11,906,508, including all exhibits, was served on September 20, 2024 via Express Mail delivery directed to the attorney of record for the patent at the following address:

Agilent Technologies, Inc./K&L Gates LLP
Attn: Daniel Hart
Global IP Operations
5301 Stevens Creek Blvd, 1A-PB
Santa Clara, CA 95051
UNITED STATES

In addition, a courtesy copy of the foregoing petition for *Inter Partes* Review of U.S. Patent No. 11,906,508, including all Exhibits, was served on litigation counsel for assignee Agilent Technologies, Inc. at the following address:

Peter J. Chassman
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Date: September 20, 2024

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CERTIFICATE OF WORD COUNT UNDER 37 C.F.R. § 42.24(a)

I, the undersigned, do hereby certify that the attached petition contains 13,983 words, as measured by the Word Count function of Microsoft Word. This is less than the limit of 14,000 words as specified by 37 C.F.R. § 42.24(a)(1)(i).

Date: September 20, 2024

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