

UNITED STATES PATENT AND TRADEMARK OFFICE

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**BEFORE THE PATENT TRIAL AND APPEAL BOARD**

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AXION BIOSYSTEMS, INC.,

Petitioner,

v.

AGILENT TECHNOLOGIES, INC.,

Patent Owner.

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Case No. IPR2024-01467

Patent 11,906,508

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**DECLARATION OF BRIAN T. CUNNINGHAM, Ph.D., IN SUPPORT OF  
PATENT OWNER AGILENT TECHNOLOGIES, INC.'S  
PRELIMINARY RESPONSE**

I, Brian T. Cunningham, Ph.D., being over the age of 18 and competent to make the statements herein, hereby declare that:

## **I. INTRODUCTION**

1. My name is Brian Cunningham. I am a Professor of Electrical & Computer Engineering, a Professor of Bioengineering, and Director, Center for Genomic Diagnostics, University of Illinois at Urbana-Champaign. I was named the Donald Biggar Willett Professor in Engineering in 2015, and as the Intel Alumni Endowed Chair in 2020.

2. As provided in greater detail my *curriculum vitae* (Ex. 2005), I have an educational and research background in electrical engineering and bioengineering. One of my research focus and interest is biosensors. I have applied electrical engineering principles to biosensing applications such as disease diagnostics.

3. I have authored or co-authored over 200 peer-reviewed articles, given over 160 conference talks, and delivered 190 invited lectures.

4. I have been awarded over 90 patents covering a broad range of technology, including biosensors and biosensing.

5. I have received numerous awards in research and teaching, including the IEEE Sensors Council Technical Achievement Award (2010), the IEEE

Engineering in Medicine and Biology Society (EMBS) Technical Achievement Award (2014), and the Optica Michael S. Feld Biophotonics Award (2023).

6. I have been elected to be a fellow of several well-known organizations: IEEE, AIMBE, Optica, AAAS, National Academy of Inventors, and Royal Society of Chemistry.

7. I have been retained as an expert on behalf of Patent Owner Agilent Technologies, Inc. (“Agilent”). As part of this engagement, I have been asked to provide opinions regarding the subject matter disclosed and claimed by U.S. Patent No. 11, 906,508 (“the ’508 Patent”) (Ex. 1001) and the primary prior art references relied upon by Petitioner Axion BioSystems, Inc. (“Axion”). Those prior art references are U.S. Patent Application No. 2007/0057680 A1 to Jones, et al. (“Jones”) (Ex. 1006) and U.S. Patent No. 7,192,752 to Xu, et al. (“Xu-752”) (Ex. 1005).

8. I have been informed that the ’508 Patent was filed on November 23, 2022 and issued on February 20, 2024. I also understand that the ’508 Patent is a continuation of a series of patent applications, including U.S. Patent Application No. 12/435,569, filed on May 5, 2009. The ’508 Patent claims priority to provisional U.S. Patent Application No. 61/126,533, filed on May 5, 2008.

9. I am not and have never been an employee of Agilent. I also have not consulted with or provided any other services to Agilent in the past. I have been

retained by Agilent in this proceeding to provide my independent analysis of the issue raised by the Petition for *inter partes* review of the '508 Patent.

10. I am being compensated at my normal hourly consulting rate of \$300/hour for my work in this proceeding, including studying this matter, preparing this declaration, and providing any cross-examination testimony. My compensation is not contingent upon the outcome of this proceeding or the particular testimony or opinions that I express. I have personal knowledge of the facts stated in the declaration, and I am willing to competently testify to them if and when called to do so.

11. Between now and such time that I may be asked to testify, I expect to continue my review, evaluation, and analysis of evidence presented during this proceeding. I expect to review the declarations and other evidence submitted by Axion's expert(s). I expressly reserve the right to amend or supplement this declaration, as appropriate, after considering the opinions set forth by Axion's expert(s). I also reserve the right to review and consider that information in further developing or refining my opinions.

## **II. QUALIFICATIONS AND PROFESSIONAL EXPERIENCE**

12. My experience and qualifications are further provided in my *curriculum vitae*, which is submitted with this Declaration. Ex. 2005. My *curriculum vitae* also provides a listing of my publications, conference

presentations, chapter books, invited lectures, patents, and other professional activities and services.

13. I graduated with a Bachelor of Science degree in Electrical and Computer Engineering from the University of Illinois at Urbana-Champaign in 1986. I received a Master of Science degree in Electrical and Computer Engineering from the University of Illinois at Urbana-Champaign in 1987. I completed a Ph.D. in Electrical and Computer Engineering from the University of Illinois at Urbana-Champaign in 1990.

14. After completing a 9-month term as a postdoctoral scholar at Sandia National Laboratory, I joined the Research Division of Raytheon (Lexington, MA) as a staff scientist in 1991, where I contributed to the development of infrared detectors and image sensors used in night vision systems and heat-seeking missile guidance systems. My research activities included development of micro-electromechanical sensors (MEMS) to improve sensitivity performance and miniaturization. In 1995, I joined the MEMS Sensors group at the Charles Stark Draper Laboratory (Cambridge, MA) as a Principal Member of the Technical Staff, where I later served as Group Leader and Director of Bioengineering Programs. During my time at Draper Laboratory, I began to pursue research in the field of biosensors, aimed initially at detection of biological and chemical weapons. My interests extended into development of biosensing applications that included

detection of proteins in clinical samples to measure cardiac health, and detection of antibiotic-resistant bacteria in the context of the intensive care unit. I left Draper Laboratory in 2000 to become the founder of a startup company, SRU Biosystems, with the goal of developing optics-based biosensors and detection instruments for applications in pharmaceutical drug discovery, including high throughput screening of the effects of chemical compounds upon live cells. SRU Biosystem's products included incorporation of optical biosensors into the bottom surfaces of the wells in 96-, 384-, and 1536-well microplates. SRU Biosystem's product line also included detection instruments that performed automated measurement of cell attachment to the biosensors in every well in the plate, including recording the effects of chemical compounds upon cell attachment over extended periods of time.

### **III. MATERIALS CONSIDERED AND BASIS FOR TESTIMONY**

15. In forming my opinions, I have reviewed the '508 Patent, portions of its file history, and the other materials cited in my declaration. The bases for my opinions include the following: (i) my education in electrical and computer engineering; (ii) my more than thirty years of experience in electrical engineering, computer engineering, and bioengineering, including my over twenty-five years of research experience with biosensing; and (iii) my review of certain documents as cited in my declaration. These documents include:

- a. Petition for Inter Partes Review by Axion BioSciences, Inc.
- b. U.S. Pat. No. 11,906,508 (“the ’508 Patent”) (Ex. 1001)
- c. Excerpts of the Prosecution History of U.S. Patent No. the ’508 Patent (Ex. 1002)
- d. Declaration of Bruce C. Kim, Ph.D. (Ex. 1003)
- e. Curriculum Vitae of Declaration of Bruce C. Kim, Ph.D. (Ex. 1004)
- f. U.S. Patent No. 7,192,752 to Xu, et al. (“Xu-752”) (Ex. 1005)
- g. U.S. Patent Application No. 2007/0057680 A1 to Jones, et al. (“Jones”) (Ex. 1006)
- h. U.S. Patent No. 7,459,918 o Jones, et al. (“Jones Patent”) (Ex. 1007)
- i. Statutory Disclaimer (Ex. 2001)
- j. Modern Dictionary of Electronics (1999) (excerpts) (Ex. 2006)
- k. The above-referenced materials are in addition to any other materials referenced directly or indirectly in this Declaration.

#### **IV. LEGAL PRINCIPLES**

##### **A. Person of Ordinary Skill in the Art**

16. I understand that a patent claim is evaluated from the perspective of a “person of ordinary skill in the art” (“POSA”), which I understand is a hypothetical person considered to have the skill level and knowledge of a particular field related to an alleged invention claimed in a patent. I further understand that this

hypothetical skilled artisan is presumed to have before him or her all of the relevant prior art. I understand that this “hypothetical person” can be more than one person or a team of people of different disciplines. The discussions in this declaration are intended to convey the state of the art and the knowledge of a POSA generally prior to the earliest effective filing date of the patent application that issued as the respective ’508 Patent, which I understand is May 5, 2008, based on the filing date of the provisional application to which the ’508 Patent claims priority.

17. I have been asked to define the level of a POSA with regard to this proceeding. In defining the level of a POSA, I have been informed that a list of non-exhaustive factors to consider include: (1) the type of problems encountered in the art; (2) the prior art solutions to those problems; (3) the rapidity with which inventions are made; (4) the sophistication of the technology; and (5) the education level of active workers in the field. In my opinion, a POSA in the field of the ’508 Patent (*i.e.*, systems for electrical impedance-based monitoring of cells) at the time of the invention (*i.e.*, in the 2008 time frame) would be a person who had a bachelor’s degree in electrical and/or computer engineering, or similar field of study, and at least 2 years of academic and/or professional experience researching, re-engineering, designing, and developing electronic systems and devices for

biomedical applications. As of the time of the invention, I was at least at the level of a POSA with respect to the '508 Patent.

## **B. Claim Construction**

18. I understand that the first step in analyzing a patent claim begins with an analysis of the wording of the claim itself, also referred to as “claim construction.”

19. I understand that claim terms in an *inter partes* review should be accorded their ordinary and customary meaning as understood by a POSA at the time of the invention, in light of the patent specification and the prosecution history pertaining to the patent. I further understand that when the specification expressly defines terms used in the claims or when it defines terms by implication, it acts as a dictionary.

20. As set forth herein, I apply these principles to my discussion of the '508 Patent's claim terms “millisecond time resolution” and “wherein the impedance analyzer measures, . . . , a first plurality of cell-substrate impedances at a first time and a second plurality of cell-substrate impedances at a second time” (“an impedance analyzer which measures multiple wells' impedances at a time”).

## **V. OVERVIEW OF THE TECHNOLOGY OF THE '508 PATENT**

21. The '508 Patent is directed to impedance-based cellular analysis systems and methods for monitoring excitation-contraction coupling and excitable

cells. Ex. 1001, Col. 1:28-32. Although impedance-based cellular analysis had been known in 2008, the '508 Patent was the first to describe an impedance-based cellular analysis with “millisecond time resolution.” This is particularly helpful to monitor fast cellular activities, such as excitation and contraction coupling of cardiomyocytes, cardio safety profiling/analysis for drugs or drug candidates, functional studies of cardiomyocytes derived from stem cells, cardio disease modelling by gene modification of cardiomyocyte, and physiological and disease processes of muscle cells in a high throughput manner.

22. “Impedance” is defined as “[t]he total opposition (i.e., resistance and reactance) a circuit offers to the flow of alternating current at a given frequency . . . . It is measured in ohms . . . . Symbol: Z.” Ex. 2006 at 10; Ex. 1001, Col. 13:21-23 (“[I]mpedance has two components, resistance and reactance (reactance can be divided into two categories, capacitive reactance and inductive reactance).” In my opinion, these statements are accurate.

## **VI. PERSON OF ORDINARY SKILL IN THE ART**

23. As discussed above, for purposes of this IPR, a POSA in the field of the '508 Patent (*i.e.*, systems for electrical impedance-based monitoring of cells) at the time of the invention (*i.e.*, in the 2008 time frame) would be a person who had a bachelor's degree in electrical and/or computer engineering, or similar field of study, and at least 2 years of academic and/or professional experience researching,

re-engineering, designing, and developing electronic systems and devices for biomedical applications.

24. I understand that the Axion's expert, Bruce C. Kim, Ph.D., has also provided a POSA definition:

[A] POSA for the '508 patent on or around May 5, 2008 would have had a B.S[.] in electrical, mechanical, or biomedical engineering or biological science/biology, 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.

Ex. 1003 ¶ 24.

25. In my opinion, a comparison of the two definitions reveals that the differences are not significant with respect to the substantive issues that I am discussing in this Declaration with respect to Agilent's Preliminary Patent Owner Response. Accordingly, my analysis and opinions herein would not change regardless of which definition the Board adopts.

26. All of my opinions set forth herein are provided from the perspective of a POSA at the time of the invention of the '508 Patent.

## VII. STATUTORY DISCLAIMER

27. I understand that on December 20, 2024, Agilent filed a statutory disclaimer of Claims 9, 10, and 23-30 of the '508 Patent. Ex. 2001. I understand that the statutory disclaimer effectively cancels all of those claims from the '508 Patent and that those claims cannot be considered in determining whether the Petition should be granted.

## VIII. THE TERM “MILLISECOND TIME RESOLUTION”

28. I have reviewed the claims and specification of the '508 Patent in order to determine the ordinary and customary meaning of the claims in view of the patent's specification.

29. The specification of the '508 Patent includes a “Definitions” section, which defines numerous terms including “millisecond time resolution.” Ex. 1001, Cols. 9:35 – 16:14. The specification also explains that “the definition set forth in this section prevails over the definition that is incorporated herein by reference.” *Id.*, Col. 9:45-47.

30. Specifically, the “Definitions” section of the '508 Patent defines the term “millisecond time resolution” as follows:

As used herein, “**impedance measurement at millisecond time resolution**” refers to the ability to perform a series of at least two consecutive impedance measurements within milliseconds of one another for each and every well of the system where each well is

associated with an electrode array for impedance measurement. In each instance the time between two consecutive impedance measurements are less than 300 milliseconds from one another. Preferably, consecutive impedance measurements are less than 200 milliseconds from one another. More preferably impedance measurements are less than 100 milliseconds from one another. For example, the time between two consecutive impedance measurements are 40 milliseconds from one another for each and every well of the system. To be clear, that is to say, in a time period of 40 milliseconds, the system has the ability to measure two impedance data points for each and every well of the system.

Ex. 1001, Col. 10:8-24 (emphasis added).

31. Under this definition, the term “millisecond time resolution” means that at least two consecutive impedance measurements for each and every well being evaluated in the claimed apparatus or system can be performed in less than 300 milliseconds from one another.

32. This definition is consistent with other disclosures in the specification of the '508 Patent:

In embodiments where the device includes multiple wells, the impedance analyzer has the capability to allow impedance measurements for each and every well at millisecond time resolution. That is to say, for a selected time period, the impedance data for each and every well of the system is measured at millisecond time

resolution. Further, when groups of wells are monitored, the groups are monitored at millisecond time resolution.

*Id.*, Col. 3:24-32.

Throughout the present application where the device includes multiple wells each of which is associated with an electrode array, millisecond time resolution refers to that for any selected time period, the impedance measurement for each and every well can be performed with two consecutive measurements separated with millisecond resolution. Further, when groups of wells, such as subsets of all wells of a device, are monitored a group of wells may be monitored using millisecond time resolution.

*Id.*, Cols. 3:65 – 4:6.

For example, if the system comprises a device having 96 wells, the system hardware and software should be capable of, for a given time period, measuring the impedances of all 96 wells with millisecond time resolution between two adjacent or consecutive impedance measurement points for each and every well. Thus, comparing two impedance analyzers, one for impedance measurement of 96 wells with millisecond resolution and another for impedance measurement of a single well with millisecond time resolution, the one for 96 well measurement is effectively 96-times faster than one for a single well measurement since it is required to have a capability for performing impedance measurement for all 96 wells with millisecond time resolution.

*Id.*, Col. 24:22-35.

33. Axion appears to solely rely on Jones' Paragraph [0030] to support the "millisecond time resolution." Paragraph [0030] states in its entirety:

Each well is subject to a stepped sweep (a series of single frequency bursts-one burst for each selected frequency). The bursts consist of an integral number of cycles. In one embodiment, the number of cycles is typically 15. The number of cycles for additional embodiments are chosen to be sufficient for well and gain multiplexer switching transients to settle and to obtain the necessary number of sample points. From preliminary modeling and testing, no more than 68.2 ms per well for all frequencies is required to obtain sufficient samples. For an embodiment in which a 96 well plate with 12 wells per row plus four reference network channels, calculations to determine sufficient samples suggest a 1091 mS measurement period, leaving 409 mS for multiplexer switching and signal settling within the target 1.5 second update period.

Ex. 1006 ¶ [0030].

34. A "multiplexer" is defined as "[a]n analog or linear device for selecting one of a number of inputs and switching its information to the output[.]"

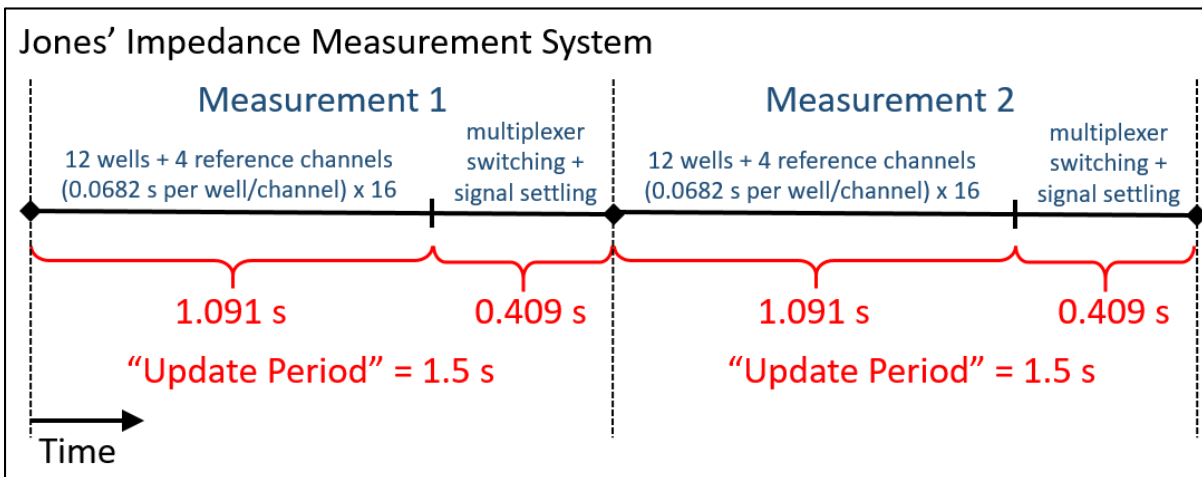
Ex. 2006 at 12. Similarly, an "analog multiplexer" is defined as a "[c]ircuit used for time-sharing of analog-to-digital converters between a number of different analog information channels. . . . Multiplexing is performed by sequentially turning on each switch one at a time, switching each individual input to a common output." Ex. 2006 at 9. Further, "switching time" is defined as "[t]he time for a

multiplexer to change from one channel to the next with the new output signal remaining within a specified percentage of its final value.” Ex. 2006 at 14. I agree with these definitions.

35. Jones’ Paragraph [0030] describes a system that requires a measurement time for a single well to be “no more than 68.2 ms *per well*,” to achieve a “target 1.5 second update period.” Ex. 1006 ¶ [0030] (emphasis added). Thus, Jones teaches that it requires 1.5 seconds between two measurements of each well (the “update period”): 12 wells plus the 4 reference channels on a daughter board measured sequentially (in series), with an additional 0.409 seconds for “multiplexer switching and signal settling” ( $0.0682 \text{ seconds} \times (12 + 4) + 0.409 \text{ seconds} = 1.5 \text{ seconds}$ ). *Id.* This further teaches that the 12 wells in a row (with 4 additional channels) are measured one at a time, *i.e.*, in series, such that a measurement time of 68.2 ms per well provides a total measurement time of  $(12 + 4) \times 68.2 \text{ ms} = 1.091 \text{ seconds}$ . *Id.* Because the 12 wells in the row are measured in series, an additional 0.409 seconds is included for “multiplexer switching and signal settling.” *Id.* The total of the measurement time and the “multiplexer switching and signal settling” time is the 1.5 seconds of the “updated period.” Accordingly, the system disclosed in Jones operates on a time resolution on the scale of seconds, which is nearly an order of magnitude slower than the 300 millisecond time resolution described and claimed in the ’508 Patent, and more

than an order of magnitude slower than the 100ms, 40ms, 20ms, and 5ms time resolutions described and claimed in the patent.

36. The diagram below illustrates the impedance measurement system described in Paragraph [0030] of Jones:



37. The '508 Patent explains this order-of magnitude difference in measurement speed with an illustrative example:

Thus, comparing two impedance analyzers, one for impedance measurement of 96 wells with millisecond resolution and another for impedance measurement of a single well with millisecond time resolution, the one for 96 well measurement is effectively **96-times faster** than one for a single well measurement since it is required to have a capability for performing impedance measurement for all 96 wells with millisecond time resolution.

Ex. 1001, Col. 24:27-35.

38. As its specification describes, the '508 Patent is directed to "systems and methods for monitoring excitation-contraction coupling and excitable cells

using impedance based systems with millisecond time resolution.” Ex. 1001, Col. 1:28-32. Thus, the invention claimed in the ’508 Patent “fill[s] a major technological gap in monitoring of excitation-contraction coupling and excitable cells, such as cardiomyocytes, in vitro[,] . . . in part, [by] the development of an impedance-based system and monitoring method that employs millisecond time resolution.” *Id.*, Col. 16:19-24; *see also id.*, Col. 3:48-54 (“[M]illisecond time resolution enhances measurement such that excitation-contraction coupling of excitable cells may be effectively monitored. In some embodiments the excitation cycle is a beating cycle, such as a beating cycle of a cardiomyocyte.”), Col. 30:38-41 (“[T]he development of millisecond time resolution permits impedance monitoring of the cardiomyocyte beating cycle as well as fluctuations, even minor alterations, in response to external stimuli.”). In my opinion, these statements are accurate.

39. For example, for cardiomyocytes, “[a] beating cycle may be as short as between 100 and 200 milliseconds, translating to a beating rate of 600 to 300 beats per minute.” *Id.*, Col. 10:44-46. Because of the important applications repeatedly discussed, the ’508 Patent focuses on time resolutions between two measurements of “less than 300 milliseconds”:

The method has particular utility with cells that are known or suspected to be capable of or undergo excitation-contraction coupling,

such as cardiomyocytes. The method may also be useful for monitoring neurological cells or neurological systems. Impedance measurements may be performed in **millisecond time resolution**. In some embodiments, two consecutive impedance measurements for each and every well of the system are performed **less than 300 milliseconds apart**.

*Id.*, Col. 4:51-59; *see id.*, Col. 47:15 (“millisecond time resolution”) (Cl. 1), Col. 47:54 (“less than 100 milliseconds”) (Cl. 11), Col. 47:57 (“less than 40 milliseconds”) (Cl. 12), Col. 47:59 (“less than 20 milliseconds”) (Cl. 13), Col. 47:62 (“less than 5 milliseconds”) (Cl. 14). In my opinion, these statements are accurate.

40. The specification of the '508 Patent explains that these kinds of applications may require time resolutions much less than 300 milliseconds:

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

*Id.*, Col. 25:33-44. In my opinion, these statements are accurate.

41. To monitor these kinds of cellular activities, the '508 Patent discloses multiple experiments using a 40-millisecond resolution for impedance measurements of cardiomyocytes. *See, e.g.*, Figs. 9C, 9D, 11A-T, Col. 45:32-34 (“Similar to the cell index plot shown in FIGS. 9C and 9D, the time resolution between two adjacent points in all the figures in FIGS. 11A-11T is 40 milliseconds.”).

42. The specification of the '508 Patent further explains why then-existing systems that use seconds time resolution between consecutive impedance measurements (like Jones' 1.5 seconds “update period”) would not accomplish the objectives of the invention:

Millisecond time resolution of impedance-based devices provides a significant technical step over traditional impedance measuring devices, which are typically limited to **second** or minute **resolution**.

\* \* \*

Without millisecond time resolution, it would not be possible to perform detailed analysis of the beating cycle of the excitable cells. For example, for cardiomyocytes, if the impedance is measured at **seconds time-resolution** such as a ten-second or **even one-second resolution**, it would not be possible to observe beating of the cardiomyocytes or resolve a beating cycle of the cardiomyocytes with an impedance measurement. The cardiomyocytes-beating-resulted

impedance change would be shown as “noise” on the impedance curves measured at seconds or minutes time-resolution.

*Id.*, Cols. 24:11-14, 16:40-58. In my opinion, these statements are accurate. Thus, the impedance measuring system disclosed in Jones with the 1.5 seconds “update period” would not be able to effectively perform the analysis of the excitable cells repeatedly discussed and emphasized in the ’508 Patent.

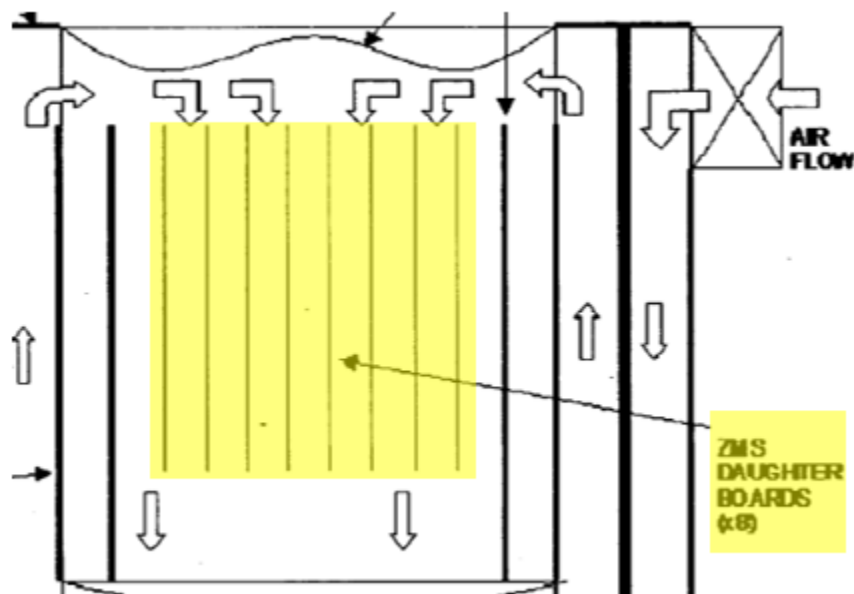
43. Jones is directed to the physical arrangement of its system, with the goal of improving “internal correction of impedance measurement drift, maximized measurement accuracy, and minimized system size.” Ex. 1006, Abstract. Jones does not describe any particular applications for its system, including the types of cells to be monitored or their particular nature (such as excitable cells or cardiomyocytes). Nor does Jones disclose millisecond time resolution or include any discussion about improving measurement time resolution.

44. Jones discloses hardware “parallelism” to achieve its goal of increased measurement accuracy and stabilization:

[T]he ZMS employs [hardware] parallelism to obtain the required throughput at the repeatability required and incorporates 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.

*Id.* ¶ [0003].

45. According to Axion, Jones illustrated the hardware parallelism in figures, such as the eight daughter boards arrange in parallel:



Ex. 1006, Fig. 4 (excerpt); Pet. at 33 “Jones Figure 4 . . . shows eight daughter boards, arranged in parallel.”).

46. Thus, the '508 Patent's described and claimed “millisecond time resolution” provides a substantial improvement in cellular impedance measurements, particularly with respect to applications such as excitation-contraction coupling and excitable cells.

**IX. THE TERM “AN IMPEDANCE ANALYZER MEASUR[ING] . . . A FIRST PLURALITY OF CELL-SUBSTRATE IMPEDANCES AT A FIRST TIME AND A SECOND PLURALITY OF CELL-SUBSTRATE IMPEDANCES AT A SECOND TIME”**

47. Claim 16 of the '508 Patent recites a system for impedance analysis, comprising:

- a) a plurality of analog-to-digital (A2D) signal converters electrically arranged in parallel to one another;
- b) a well plate comprising a plurality of wells on a nonconductive substrate, wherein each well of the plurality of wells comprises one electrode array of a plurality of electrode arrays disposed on the nonconductive substrate that is connected to the plurality of A2D signal converters;
- c) an impedance analyzer connected to or including the plurality of A2D signal converters, 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 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; . . . .

Ex. 1001, Col. 48:1-20 (Cl. 16).

48. Element a) of Claim 16 recites “a plurality of analog-to-digital (A2D) signal converters electrically arranged in parallel to one another.” *Id.* Element b) of Claim 16 recites “a well plate comprising a plurality of wells” wherein the plurality of wells are connected to the plurality of A2D signal converters of Element a) through electrode arrays. Element c) of Claim 16 recites “an impedance analyzer” that is “connect[ed] to or include[es] the plurality of A2D

signal converters [of Element a)],” which are “electrically arranged in parallel to one other.” The impedance analyzer of Element c) “measures, via digitally converted signals from the A2D signal converters [of Element a)], a first plurality of cell-substrate impedances at a first time and a second plurality of cell-substrate impedances at a second time[.]” *Id.*

49. This means that the “impedance analyzer” of claim 16 measures more than one impedance at a time via the plurality of A2D signal converters that are electronically arranged in parallel. This is achieved by measuring the impedances of multiple wells in parallel, *i.e.*, at the same time (or nearly the same time), via the plurality of A2D signal converters that are “electronically arranged in parallel to one another.” Claim 16 also emphasizes the measuring of a plurality of wells’ impedances at the same time (or nearly the same time) by reciting that “the impedance analyzer measures . . . a first plurality of cell-substrate impedances at a first time and a second plurality of cell-substrate impedances at a second time . . . .” *Id.*

50. The ’508 Patent teaches that measuring the impedances of multiple wells at a time is a very important improvement over the conventional measuring the impedance of one well at a time:

[A] very important improvement is to replace previous working mode of “measurement of one-well’s impedance at a time” with a mode of

“measurement of multiple-wells’ impedances at a time”. In “one-well at a time” mode, when the software issues a command for measuring one well’s impedance, the measurement circuitry would perform the measurement for one well including signal generation to the well, converting the voltage signal and the electric current signal for the well to digital signal, digitally processing the signals to do impedance calculation and sending the well’s impedance data to the computer over the communication line between the impedance measurement circuitry and the computer. The system will not perform any measurement for another well until completing the measurement of this well and until receiving another command for the measurement of another well. In “multiple wells at a time” mode, the software would issue a command for measuring multiple wells’ impedances. The measurement circuitry would simultaneously or nearly simultaneously perform signal conversion, signal processing and impedance calculation for multiple wells.

Ex. 1001, Col. 25:2-22. In my opinion, these statements are accurate.

51. The impedance analyzer recited in Claim 16 of the ’508 Patent performs its measurements in a “multiple wells at a time” mode, meaning measuring multiple well’s impedance at a time in reliance on the measurement circuitry, including the A2D converters electrically arranged in parallel to one another. Thus, the “an impedance analyzer which measures multiple wells’ impedances at a time” limitation means an impedance analyzer measures multiple

wells' impedances on a well plate at the same (or nearly the same) time, i.e., in parallel.

52. In contrast, Jones does not disclose an impedance analyzer which measures the impedances of multiple wells at the same time. Paragraph 12 of Jones teaches that each row of wells of a well plate (or 'microtiter plate') is addressed by a "daughter board" that includes an impedance analyzer for measuring the plate's wells *in series*:

In one embodiment, 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**.

Ex. 1006 ¶ [0012]. This shows that the impedance measurement is accomplished by the "measurement circuitry" on each daughter board. *Id.* The "measurement circuitry" is "in the form of analog signal conditioning circuits, multiplexing circuits, analog-digital converters, and digital signal processors." *Id.* The "measurement circuitry" and "multiplexing circuits" are further illustrated in the Jones Patent:

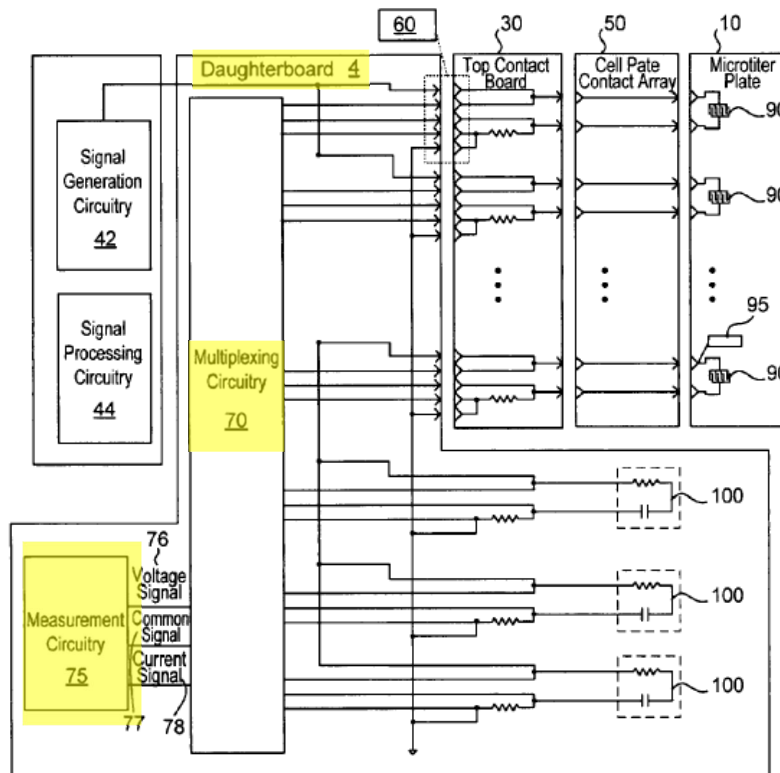


**FIG. 3**

Ex. 1007, Fig. 3. Jones further discloses that:

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.

Ex. 1006 ¶ [0018]. Thus, Jones teaches that the “measurement circuitry” on each daughter board measures the “impedance data for a microtiter plate row,” which is “processed by a digital signal processor dedicated to each row and located on the daughter boards.” *Id.* Jones has additional disclosures that confirm this configuration:

In an additional embodiment, each column of sensors, rather than each row of sensors, on a microtiter plate is addressed by measurement circuitry on a single daughter board with the system arrangement of the boards remaining the same.

*Id.* ¶ [0025].

(1) at least one daughter board comprising measurement and multiplexing circuitry . . .

*Id.*, Cl. 1(1), Cl. 15(1).

53. Jones also emphasizes that its “mother board” receives the “impedance measurement data” from each of the daughter boards:

The 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].

54. Jones teaches that each daughter board uses multiplexing circuitry, which confirms that each well on the microtiter plate is measured sequentially (*i.e.*, in series). *E.g.*, *id.*, Abstract (“multiplexing”), ¶ [0003] (“multiplexing of impedance measurement channels”), ¶ [0012] (“[E]ach 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.”), ¶ [0012] (“Each daughter board

has multiplexing circuitry allowing one or more measurement channels to address the sensors for each well in the row.”), ¶ [0030] (“The number of cycles for additional embodiments are chosen to be sufficient for well and gain multiplexer switching transients to settle and to obtain the necessary number of sample points.”), ¶ [0030] (“leaving 409 mS for multiplexer switching and signal settling within the target 1.5 second update period.”).

55. As explained above, Jones discloses an impedance measurement system with multiple daughter boards, each daughter board having a dedicated impedance analyzer or “measurement circuitry”. Ex. 1006 ¶ [0012]. Each daughter board sequentially takes impedance measurements of one well at a time for each of the wells in a row. *Id.* ¶ [0030]. Thus, the impedance analyzer described in Jones measures impedance of a single well at a time, which is not the same as the impedance analyzer described and claimed in the ’508 Patent.

56. Paragraph [0018] of Jones further teaches “one-well at a time” for the measurement of impedance by way of a daughter board (*i.e.*, the wells measured in series):

The daughter boards carry the electronic components to drive and process a row of wells. One daughter board is assigned to each row of the microtiter plate. In one embodiment, the top edge of the daughter boards is equipped with a row of well drivers and an interlaced set of multiplexing field effect transistors (or FETs, a type of transistor

commonly used for signal switching or amplification) for well selection within a row. . . . A digital-to-analog converter may be used to provide DC offset correction to the current channel to ensure the analog-to-digital converter input is centered on the common mode range. Additionally, the daughter boards may be equipped with multiple analog-to-digital converters (including one for the voltage channel and one for the current channel), digital control circuitry (e.g., digital signal processors, memory devices, field programmable gate arrays, and/or electrically programmable logic devices), and voltage regulation circuitry. In one embodiment, these additional components are arranged below and to the side of the analog sections. 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.

Ex. 1006 ¶ [0018].

57. As discussed in Paragraph 45, above, the “parallelism” mentioned in Jones is directed to the physical configuration of the components in the impedance measurement system. Axion also recognizes this:

U.S. Patent No. 7,459,918, the patent that issued on December 2, 2018 from Jones, includes a Figure 2 that shows the spatial relationship of the plate 10 to the top contact PCBA 30 to the daughter boards 4 to the motherboard 40, as described in Jones.

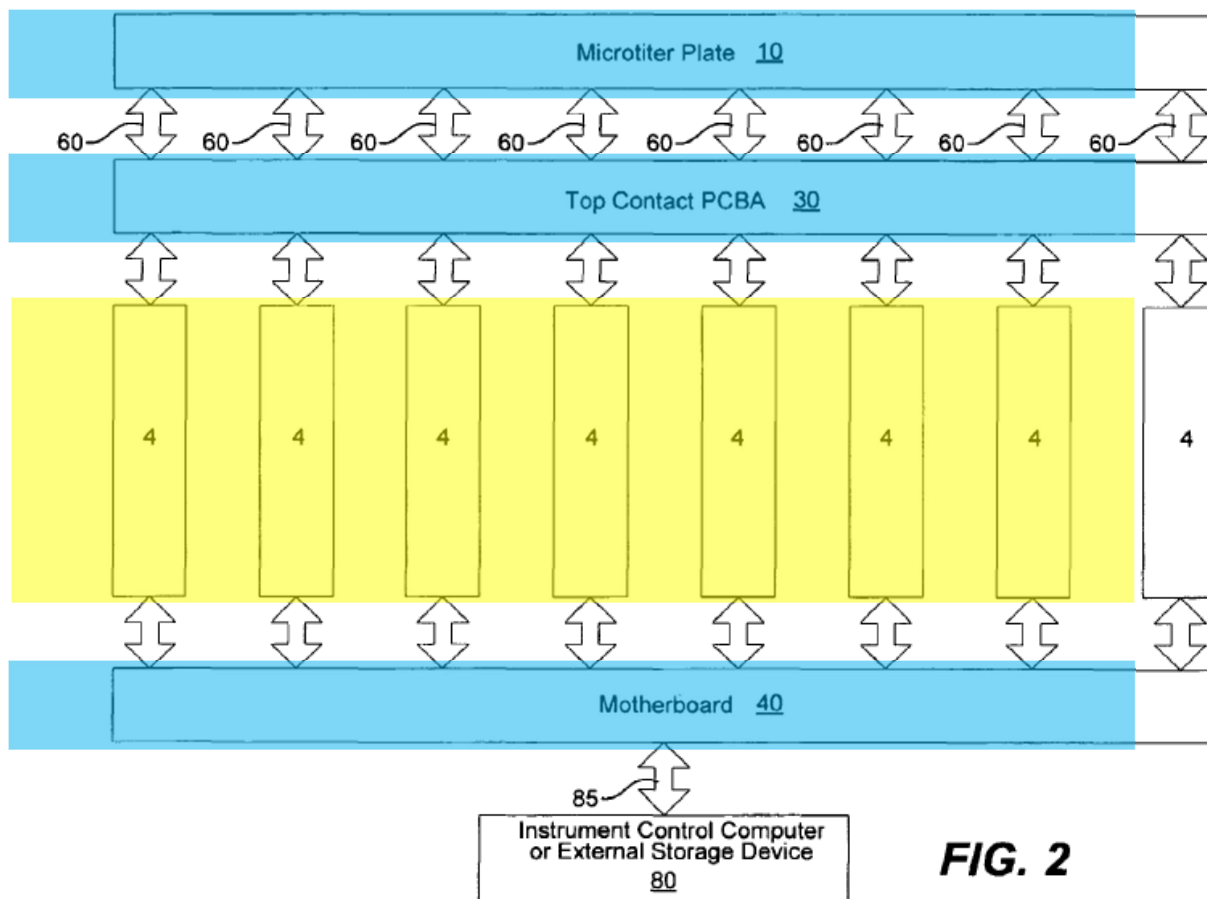


**FIG. 2**

Ex. 1003 ¶ 67 (citing Ex. 1007 at Fig. 2, 2:1-48; Ex. 1006, ¶¶ [0012]-0016)). Jones further teaches “parallelism” in physical configuration in Paragraph [0014]:

Within the Impedance Measurement System the top contact PCBA lies in a plane **parallel** to and immediately below the microtiter plate, while the daughter boards are **perpendicular** to the plane of the microtiter plate. A **horizontal** mother board is located below the daughter boards.

Ex. 1006 ¶ [0014].

58. Jones emphasizes the importance of this physical parallel configuration: “Electrical performance dictates that the daughter board assembly

be closely coupled to the top contact board and that the circuitry be kept as tightly arranged as possible.” *Id.* ¶ [0021].

59. In Jones, only Paragraph [0003] uses the term “parallel impedance measurement *channels*,” which refers to the *physical arrangement* of multiple daughter boards (each board having “measurement channels”) placed in parallel with one another within an “Impedance Measurement System”. Ex. 1006 ¶ [0003]; *see id.* ¶ [0012] (“Each daughter board has multiplexing circuitry allowing one or more *measurement channels* to address the sensors for each well in the row.”) (emphasis added).

60. Thus, Jones’ disclosure of “parallelism” are primarily directed to the *form factor* of the Impedance Measurement System (or “ZMS”):

This physical arrangement and electrical configuration maximizes the accuracy of the impedance measurements by minimizing the electrical path length and stray impedances associated with connecting the microtiter plate sensor to the measurement circuit. The minimized path length also optimizes phase and gain tracking, and maximizes the immunity to noise.

The physical configuration minimizes the number of needed mechanical supports and eliminates key thermal expansion problems associated with other designs. The configuration minimizes the size of the Impedance Measurement System thereby allowing more efficient internal packaging and thermal stabilization of the electronic components (due to reduced convection). The minimized path length

also optimizes phase and gain tracking, and maximizes the immunity to noise.

*Id.* ¶¶ [0023]-[0024]

61. Although Jones teaches that a “mother board” is connected to each of the daughter boards that are physically arranged in parallel (*id.* ¶ [0020] (“The ZMS daughter boards mate at their lowest edge with the mother board.”)), and the mother board receives the impedance measurements from the daughter boards, Jones does not teach or suggest that the mother board performs any impedance measurements, and does not disclose that any processing of the received measurements from the “measurement circuitry” on the daughter boards is performed in parallel:

The mother board accommodates various electrical components and functions, including the digital signal source, excitation low pass filtering, supervisory processing, ROM/RAM, host data communications, and may control enclosure temperature. 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].

62. As explained above, the “parallelism” referred to by Jones is the physical arrangement of the system’s hardware, such as the parallel daughter

boards and the parallel mother board/top contact board/microtiter plate. *See* Ex. 1007, Fig. 2.

63. The '508 Patent expressly distinguishes the “one-well at a time” system of the prior art, such as the system taught by Jones:

For example, if the system comprises a device having 96 wells, the system hardware and software should be capable of, for a given time period, measuring the impedances of all 96 wells with millisecond time resolution between two adjacent or consecutive impedance measurement points for each and every well. Thus, comparing two impedance analyzers, one for impedance measurement of 96 wells with millisecond resolution and another for impedance measurement of a single well with millisecond time resolution, the one for 96 well measurement is effectively 96-times faster than one for a single well measurement since it is required to have a capability for performing with millisecond time resolution.

Ex. 1001, Col. 24:22-35. In my opinion, these statements are accurate.

64. The '508 Patent explains that the “an impedance analyzer which measures multiple wells’ impedances at a time” represents a “very important improvement”:

Another example of improvements includes the use of multiple analogue-to-digital (AD) conversion channels so that analog electronic signals from multiple channels can be converted to digital signals simultaneously. Such parallel AD conversion is important, particular for the system having multiple wells, each of which’s

measurement time resolution is required to be in the millisecond resolution. And, a very important improvement is to replace previous working mode of “measurement of one-well’s impedance at a time” with a mode of “measurement of multiple-wells’ impedances at a time”. In “one-well at a time” mode, when the software issues a command for measuring one well’s impedance, the measurement circuitry would perform the measurement for one well including signal generation to the well, converting the voltage signal and the electric current signal for the well to digital signal, digitally processing the signals to do impedance calculation and sending the well’s impedance data to the computer over the communication line between the impedance measurement circuitry and the computer. The system will not perform any measurement for another well until completing the measurement of this well and until receiving another command for the measurement of another well. In “multiple wells at a time” mode, the software would issue a command for measuring multiple wells’ impedances. The measurement circuitry would simultaneously or nearly simultaneously perform signal conversion, signal processing and impedance calculation for multiple wells.

Ex. 1001, Col. 24:62 – 25:32. In my opinion, these statements are accurate.

65. The ’508 Patent also explains why the new and improved system measuring “multiple wells at a time” would be a dramatic improvement over a conventional “one well at a time” system:

[C]omparing two impedance analyzers, one for impedance measurement of 96 wells with millisecond resolution and another for

impedance measurement of a single well with millisecond time resolution, the one for 96 well measurement is effectively 96-times faster than one for a single well measurement since it is required to have a capability for performing impedance measurement for all 96 wells with millisecond time resolution.

*Id.*, Col. 24:27-35. In my opinion, these statements are accurate.

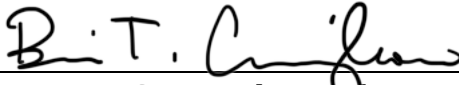
66. The '508 Patent further explains that measuring “multiple wells at a time” would also allow the impedance measurements at “millisecond time resolution.”

[W]here the device includes multiple wells, the impedance analyzer has the capability to allow impedance measurements for each and every well at millisecond time resolution. That is to say, for a selected time period, the impedance data for each and every well of the system is measured at millisecond time resolution. Further, when groups of wells are monitored, the groups are monitored at millisecond time resolution.

*Id.*, Col. 3:24-32. In my opinion, these statements are accurate.

I declare under penalty of perjury under the law of the United States that all statements made herein of my own knowledge are true and that all statements made on information and believe are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: December 26, 2024

  
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Brian T. Cunningham, Ph.D.