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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AXION BIOSYSTEMS, INC.,

Petitioner,

v.

AGILENT TECHNOLOGIES, INC.,

Patent Owner.

Case No. IPR2024-01467

Patent 11,906,508

PATENT OWNER RESPONSE

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PATENT OWNER'S EXHIBIT LIST

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Ex. 2002	File History of U.S. Patent No. 11,906,508
Ex. 2003-1	File History of U.S. Patent No. 9,709,548 (pp. 1-263)
Ex. 2003-2	File History of U.S. Patent No. 9,709,548 (pp. 264-551)
Ex. 2003-3	File History of U.S. Patent No. 9,709,548 (pp. 552-862)
Ex. 2003-4	File History of U.S. Patent No. 9,709,548 (pp. 863-1115)
Ex. 2003-5	File History of U.S. Patent No. 9,709,548 (pp. 1116-1316)
Ex. 2004	Declaration of Brian T. Cunningham, Ph.D.
Ex. 2005	<i>Curriculum Vitae</i> of Brian T. Cunningham, Ph.D.
Ex. 2006	Graf, Modern Dictionary of Electronics (1999) (excerpts)
Ex. 2007	File History of U.S. Patent No. 7,459,918 (Jones)
Ex. 2008	File History of U.S. Patent No. 7,192,752 to Xu et al. ("Xu-752")
Ex. 2009	Declaration of Benjamin Sanchez Terrones, Ph.D.
Ex. 2010	<i>Curriculum Vitae</i> of Benjamin Sanchez Terrones, Ph.D.
Ex. 2011	MDS Sciex - CellKey Brochure (c. 2005)
Ex. 2012	CellKey Specifications (2007)
Ex. 2013	CellKey Press Release (2005)
Ex. 2014	U.S. Patent App. Pub. No. 2008/0043448A1 (Finnerty)
Ex. 2015	U.S. Patent App. Pub. No. 2008/0068790A1 (Lee)
Ex. 2016	U.S. Patent App. Pub. No. 2008/0037218A1 (Sharma)
Ex. 2017	U.S. Patent App. Pub. No. 2008/0298014A1 (Franco)
Ex. 2018	U.S. Patent App. Pub. No. 2008/0257594A1 (Engblom)
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Ex. 2020	2nd Statutory Disclaimer in a Patent Under 37 C.F.R. 1.321(a)

I. INTRODUCTION AND SUMMARY OF ARGUMENT

Patent Owner, Agilent Technologies, Inc. (“Agilent”), is a global leader in life sciences, diagnostics and applied chemical markets. Agilent provides laboratories worldwide with instruments, services, consumables, applications and expertise.¹ Agilent’s U.S. Patent No. 11,906,508 (“the ’508 Patent”) at issue in this *inter partes* review (“IPR”) claims a novel impedance-based cellular analysis system which makes electrical impedance measurements at millisecond time resolution and also claims systems in which an impedance analyzer measures the impedances of multiple wells simultaneously or nearly simultaneously.

Petitioner, Axion Biosystems, Inc.’s (“Axion’s”) Ground 1 alleges that claims 23-30 are anticipated by Xu-752 and is moot in light of Agilent’s statutory disclaimer. Ex. 2001. Contemporaneous with the filing of this Patent Owner Response, Agilent has also statutorily disclaimed Claims 16-22 of the ’508 Patent. Ex. 2020. This statutory disclaimer moots Claims 16-22 of Ground 2 of the Petition. 37 CFR § 42.107 (“The patent owner may file a statutory disclaimer under 35 U.S.C. 253(a) in compliance with § 1.321(a) of this chapter, disclaiming one or more claims in the patent. Additionally, Axion has failed to meet its burden to establish that the challenged Claims 1-8 and 11-15 would have been obvious

¹ <https://www.agilent.com/about/companyinfo/>

over the asserted prior art.

Axion argues that Jones (Ex. 2007) “describes an improved impedance measurement system that includes the limitations that Xu-752 does not explicitly describe”, and thus the combination of Xu-752 and Jones renders Claims 1-8 and 11-15 obvious. Pet. at 31-32. Even assuming *arguendo* that Xu-752 includes the elements as Axion asserts, this obviousness argument still fails because Jones does not teach or suggest the “millisecond time resolution” limitation of Claims 1-8 and 11-15.

With respect to Claims 1-8 and 11-15, the “millisecond time resolution” limitation requires that the system or apparatus perform at least two consecutive impedance measurements across all of multiple wells being evaluated within no more than 500 milliseconds² of each other. This claim term is ***not directed to the time span required to take a single measurement*** of the electrical impedance ***of one well***, as Axion incorrectly argues throughout its Petition. Rather, as the ’508 Patent expressly defines and explains, this claim term is directed at the time between ***two consecutive impedance measurements of all of multiple wells*** being

² See *infra* Section IV.B for a discussion of the 300ms versus 500ms issue raised by the Board. DI at 10-11, 25.

evaluated in the claimed apparatus or system. The disclosure of Jones, in which impedance measurements are taken over a period of seconds, does not teach or suggest the millisecond time resolution recited in Claims 1-8 and 11-15.

Indeed, Jones nowhere discusses any objective of measuring impedance in millisecond time resolution. Ex. 2009 ¶ 55. And Jones does not discuss the types of cells that are to be measured by the disclosed system. *Id.* Thus, even if Axion's argument that Xu-752 teaches (and it does not) that a POSA would have been motivated to develop an impedance system that would be capable of millisecond time resolution, a POSA would not look to Jones because Jones does not teach an impedance system capable of millisecond time resolution, or even suggest any solution or reason to increase the "target *1.5 second* time period" of Jones' disclosed system, as explained further below in Section V.B. Ex. 2009 ¶¶ 54, 56.

II. JONES' OBJECTIVE WAS TO STABILIZE THE SYSTEM FROM THERMAL DRIFT IN A COMPACT FORM FACTOR

Jones does not disclose or suggest improving the speed of making impedance measurements resulting in an "increased throughput", as Axion incorrectly argues (Pet. at 42), or improving the speed of making impedance measurements. Ex. 2009 ¶ 56. In particular, Jones does not teach or suggest a system or apparatus which performs at least two consecutive impedance measurements across all of multiple wells being evaluated with millisecond time resolution. To the contrary, Jones explains that the purpose of its systems' parallel

physical arrangement is to maintain specified accuracy and repeatability within a smaller and denser form factor (because the daughter boards are arranged physically in parallel next to each other, the overall system dimensions are reduced):

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*.

* * *

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.

Ex. 1006 ¶¶ [0021], [0023]-[0024] (emphases added); Ex. 2009 ¶ 55.

While in the DI the Board cites Axion’s partial and out-of-context quote from Jones that its system “employs parallelism to obtain the required throughput”, the entire sentence and the complete context of Jones’ disclosure reveal that sentence teaches nothing about “improving” or “increasing” throughput, but is actually directed to “increased measurement *accuracy and stabilization against thermal drift*”:

The ZMS employs 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*.

Ex. 1006 ¶ [0003] (emphases added); Ex. 2009 ¶ 49. And in the context of Jones, the “required throughput” is clearly stated: “the *target* 1.5 second update period.” Ex. 1006 ¶ [0030] (emphasis added); Ex. 2009 ¶ 58. This target 1.5 second throughput requirement is consistent with the “2 or 10 second update rate” specified for the commercial CellKey impedance measurement system introduced on September 8, 2005, by MDS Sciex, the assignee of the Jones application (filed on September 9, 2005):

Update rate	
96-well	2 or 10 second update rate

Ex. 2011 (MDS Sciex CellKey Brochure (c. 2005) (Instrument Specifications)) at 6; Ex. 1006 at 1 (INID code (73)); Ex. 2012 (CellKey Specifications (2007)); Ex.

2013 (CellKey Press Release (2005)) at 1; Ex. 2009 ¶ 41. Thus, the objective taught by Jones' was to maintain existing throughput and repeatability requirements (*i.e.*, specifications) in a smaller, more compact system. Ex. 2009 ¶ 55.

Moreover, Jones' express focus on a compact form factor and temperature control in conjunction with closely packed parallel daughter boards is consistent with contemporaneous patent applications discussing the growing adoption of, for example, the PCI Mezzanine Card (PMC) standard and the PCI eXtensions for Instrumentation (PXI) standard to achieve those competing goals. *See, e.g.*, Ex. 2014 (Finnerty, filed 2006) ¶ [0003] ("One solution to this problem is the use of a supplemental card portion called a 'mezzanine' card (sometimes referred to as a 'daughter card') that is mounted to the main circuit card (referred to generically as the carrier card) [T]he confined area between the main circuit card and the mezzanine card also makes heat dissipation an issue."); Ex. 2015 (Lee, filed 2006) ¶¶ [0002]-[0003] ("Developments in computer hardware have also resulted in space constraints, particularly in small form factors and modular computer platforms. . . . To increase heat dissipation further, fans may be used to provide forced convection within a computer or electronic system"); Ex. 2016 (Sharma, filed 2006) ¶ [0028] ("The cooling units [are] . . . operative . . . to deliver the standards-defined cooling performance in a compact, cost-effective package

that maximizes the volume of the enclosure available for housing modules.”); *see* Ex. 2009 ¶¶ 60-65 (discussing these and other similar references).

Accordingly, Xu-752 and Jones relied upon by Axion in the Petition, neither alone nor in combination, disclose or suggest the “millisecond time resolution” limitation of Claims 1-8 and 11-15. There is, therefore, no need to further elaborate on why a POSA would not have been motivated to combine those two references. Even if Xu-752 and Jones could be properly combined, that combination would not contain each and every element of the invention claimed in the ’508 Patent because it would be missing at least the key “millisecond time resolution” invention claimed in the ’508 Patent.

III. BACKGROUND

The Board instituted IPR proceedings for claims 1-8, 11-15, and 16-22 of the ’508 Patent, pursuant to 35 U.S.C. § 314, based on the challenges of obviousness over Xu-752 and Jones. In instituting a trial, the Board will not institute on fewer than all claims or all challenges in a petition. *See SAS Institute Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018). As a result, the Board stated that it “need not resolve the parties’ disputes regarding the ‘millisecond time resolution’ limitation at this stage, nor do we need to determine whether Petitioner has demonstrated a reasonable likelihood of prevailing on its challenge to claims 1–8 and 11–15.” DI at 23. Additionally, the Board expressed “some initial concerns

we have regarding Petitioner’s showing for the ‘millisecond time resolution’ limitation” by relying on the calculation in Axion’s expert report (Ex. 1003). *Id.* at 24-25. This POR addresses challenged Claims 1-8 and 11-15 in Ground 2, for which a trial was instituted.

A. Overview of the Challenged ’508 Patent

The USPTO issued the ’508 patent on February 20, 2024, which claims priority to a series of applications, the earliest of which was filed on May 5, 2008. Ex. 2002 at 1. The ’508 Patent describes “[a] system for monitoring cells, which includes a device for monitoring cell-substrate impedance, the device having a plurality of wells on a nonconductive substrate” where each well has an electrode array for measuring the cell-substrate impedance. Ex. 2002, Abstr. Additionally, the ’508 Patent discloses that “electronic circuitry with multiple analogue-to-digital conversion channels” connects the electrode arrays to an “impedance analyzer” that measures the impedance with “millisecond time resolution”. *Id.* The system further includes “a software program that controls the electronic circuitry and records and analyzes data obtained from the impedance analyzer.” *Id.*, Col. 3:11-13.

The advancements of the ’508 Patent opened up a whole new field of applications previously unavailable in impedance-based cellular analysis. Ex. 2009 ¶ 25. In particular, with the improved apparatus and system described and

claimed in the '508 Patent, researchers and scientists were, for the first time, able to conduct studies of exceedingly fast cellular activities requiring measurements with millisecond time resolution, such as the mechanism of 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.

Id.

B. Level of Ordinary Skill in the Art

The Petition defines a person of ordinary skill in the art as having “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.” Pet. 14 (citing Ex. 1003 ¶¶ 23–25). The Board adopted this definition for purposes of the DI. DI at 7. Accordingly, Agilent uses this definition for purposes of this IPR proceeding, although Agilent reserves the right to adopt a different definition in other contexts and proceedings. Ex. 2009 ¶ 19.

C. Overview of the Two Asserted References

The following is a summary of the references that Axion relies upon in its Petition.

1. Xu-752

Xu-752 (U.S. Patent No. 7,192,752) issued on March 20, 2007. Ex. 2008 at 1. At a minimum, and as Axion acknowledges, Xu-752 does not disclose or suggest the limitation of “millisecond time resolution” in the ‘508 patent. Pet. at 31. Thus, Axion combines Xu-752 with Jones to challenge the claims in the ‘508 Patent for alleged obviousness.

Additionally, Axion wrongfully asserts that Xu-752 was not “cited by the PTO or applied during prosecution of the ‘508 Patent.” Pet. at 2. But Xu-752 was disclosed to the USPTO in an IDS during the prosecution of the ‘508 Patent. Pet. at 2; Ex. 1002 at 133; Ex. 2002 at 159. The IDS was initialed by the examiner, indicating that references listed on the IDS, including Xu-752, were received and considered by the examiner. Ex. 2002 at 234.

2. Jones

Jones published on March 15, 2007 (U.S. Patent Application Publication No. 2007/0057680 A1). Ex. 1006 at 1. The subsequent Jones patent issued on December 2, 2008 (U.S. Patent No. 7,459,918 B2). Ex. 1007 at 1. Notably, the Jones *patent* includes significant post-publication amendments to the application’s specification, including deletion of one figure (original Fig. 3) and addition of two new figures (new Figs. 2 & 3). *Compare* Ex. 1006, Fig. 2 *with* Ex. 1007, Figs. 2 & 3; Ex. 2007 at 67, 87-91. Jones represented to the USPTO that “no new matter has

been added with these amendments.” Ex. 2007 at 67, 87.

With regard to the “millisecond time resolution” claim limitation, Jones only mentions the term “millisecond” in the sentence quoted below:

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 [sic] 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 setting within the target **1.5 second update period**.

Ex. 1006 ¶ [0030] (emphases added); Ex. 2009 ¶¶ 34-35.

The expressly disclosed 68.2 milliseconds in Jones is the time required to scan a single well once. Ex. 2009 ¶ 35. The suggested 1,091 millisecond measurement period is exactly 16 times 68.2 milliseconds, which is consistent with Jones’ teaching of multiplexing 12 rows plus 4 reference channels (*i.e.*, making one measurement at a time). *Id.* Accordingly, Jones uses a multiplexer and measurement circuitry to address each row on the well plate sequentially (one well at a time), resulting in a 1.5 second update period. *Id.* This update period is at least three times slower than the claimed “millisecond time resolution” in the ’508 Patent. *Id.*

In its Petition, Axion erroneously treats the 68.2 milliseconds as a benchmark for calculating the time between consecutive measurements of all of the

wells being evaluated in the '508 patent. *E.g.*, Pet. at 53-54; Ex. 2009 ¶ 36. As discussed herein, Jones only discloses a time of 1.5 seconds between consecutive measurements of all the wells being evaluated. Ex. 2009 ¶ 36.

IV. CLAIM CONSTRUCTION

A. The *Phillips* Standard

In an IPR proceeding, the Board applies the same *Phillips* claim construction standard as federal courts. *See* 37 C.F.R. § 42.100(b). Under the *Phillips* standard, “the words of a claim are generally given their ordinary and customary meaning.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (*en banc*) (internal quotation marks and citation omitted). However, “the specification acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication.” *Id.* at 1321 (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996) (citing *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (*en banc*), *aff'd*, U.S. 116 S. Ct. 1384, 1393 (1996))); *Irdeto Access, Inc. v. Echostar Satellite Corp.*, 383 F.3d 1295, 1300 (Fed. Cir. 2009) (“Even when guidance is not provided in explicit definitional format, the specification may define claim terms by implication such that the meaning may be found in or ascertained by a reading of the patent documents.”).

Axion recognizes that the '508 Patent “contains a ‘Definitions’ section.” Pet. at 13. However, Axion does not propose any construction for any claim term.

Without any explanation whatsoever, Axion then simply concludes that

“[p]etitioner does not believe there is any need to adopt any definitions from [the Definitions] section to address the grounds below.” *Id.* Instead, Axion argues that “[i]n this Petition, all of the claim terms are given their plain meaning, as understood by the POSA, unless indicated otherwise.” *Id.*

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

Accordingly, the definitions provided in the ’508 Patent provide the POSA with essential understandings of the meanings of the claim terms.

Axion’s approach contradicts with the governing case law cited above regarding claim construction. The Board should explore the construction of the key disputed terms by considering both intrinsic and extrinsic evidence in the prosecution history of the ’508 Patent, including particularly any express definitions set forth in the ’508 Patent’s specification.

B. “Millisecond Time Resolution”

The “Definitions” section of the ’508 Patent sets forth the meaning for the term “millisecond time resolution”:

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 (emphases added).

In the DI, the Board correctly noted that while the ’508 Patent expressly defines “millisecond time resolution” using the “less than 300 milliseconds” formulation, several other instances in the patent (including now-disclaimed Claims 9 and 10) state “less than 500 milliseconds”. DI at 10-11, 25. In general, a patent’s entire disclosure may be used for claim construction purposes. *E.g., Netcraft Corp. v. eBay, Inc.*, 549 F.3d 1394, 1398 (Fed. Cir. 2008) (noting that disputed claim language “must be read in the context of the entire specification and prosecution history”); *Lucent Techs., Inc. v. Gateway, Inc.*, 525 F.3d 1200 (Fed.

Cir. 2008) (examining the entirety of the specification in performing claim construction). And particularly important here, the distinction between 300 milliseconds and 500 milliseconds is immaterial to the dispute in this IPR because Jones teaches a 1.5 second update period, thus at least three times longer than the 500 milliseconds formulation. Ex. 2009 ¶¶ 33, 40. In the DI, the Board recognized that the distinction between 300 milliseconds and 500 milliseconds is likely not material in this IPR:

[S]uch cherry-picking suggests that Petitioner’s showing for claims 1-8 and 11-15 is improperly premised on hindsight knowledge of the ’508 patent as opposed to what Jones teaches or reasonably suggests to a POSA regarding the “millisecond time resolution” limitation. This concern exists whether the term “millisecond time resolution” is construed to mean that the time between consecutive measurements for each well is under 300 milliseconds . . . or more broadly to encompass consecutive measurements made in 500 milliseconds or less.

DI at 24-25.

Accordingly, for purposes of this IPR, Agilent proposes that the term “millisecond time resolution” be construed to mean the time between two consecutive impedance measurements for each and every well being evaluated in the claimed apparatus or system, which can be performed in less than 500 milliseconds from one another. Ex. 2009 ¶ 33.

**V. AXION HAS FAILED TO DEMONSTRATE UNPATENTABILITY
OF CHALLENGED CLAIMS 1-8 AND 11-15**

A. Legal Standards for Obviousness

Axion bears the burden of proving that the challenged claims are unpatentable as obvious. 35 U.S.C. § 316(e). A claim is obvious only if “the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.” 35 U.S.C. § 103.

“Whether a claim is invalid for obviousness is determined from the perspective of one of ordinary skill in the art.” *Cheese Sys. v. Tetra Pak Cheese & Powder Sys.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013). Obviousness analysis requires an assessment of the well-known *Graham* factors: (1) the scope and content of the prior art; (2) any differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) where in evidence, objective indicia of nonobviousness. *KSR Int’l v. Teleflex Inc.*, 550 U.S. 398, 406 (2007) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966)).

Further, “[o]bviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention.” *Cheese Sys.*, 725 F.3d at 1352 (internal quotation marks and citation omitted); *see also KSR*, 550 U.S. at 421 (“A factfinder should be aware, of

course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning.”); *Graham*, 383 U.S. at 36 (warning against a “temptation to read into the prior art the teachings of the invention in issue” and instructing courts to “guard against slipping into the use of hindsight” (citation omitted)).

“[T]he proper analysis requires a form of amnesia that ‘forgets’ the invention and analyzes the prior art and understanding of the problem at the date of invention.” *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1379 (Fed. Cir. 2012). “Care must be taken to avoid hindsight reconstruction by using the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.” *In re NTP, Inc.* 654 F.3d 1279, 1299 (Fed. Cir. 2011) (internal quotation marks and citations omitted).

B. Ground 2, Claims 1-8 and 11-15: Jones Does Not Disclose the “Millisecond Time Resolution” Claim Limitation

Axion fails to show that Jones discloses or suggests the “millisecond time resolution” claim limitation of Claims 1-8 and 11-15. As discussed below, Axion relies on an incorrect understanding of the claim term “millisecond time resolution” to support its Ground 2 challenge. Under the correct claim construction, Axion does not (and cannot) show that Jones teaches or suggests the “millisecond time resolution” claim limitation. Jones does not teach or suggest the “millisecond time resolution” limitation, which requires that the system or

apparatus must be capable of performing at least two consecutive impedance measurements within a time span of no more than 500 milliseconds across all of the wells being evaluated on a well plate. Ex. 2009 ¶ 38.

1. The '508 Patent Explains That the Term “Millisecond Time Resolution” Means the Time Between Two Consecutive Impedance Measurements for Each and Every Well Being Evaluated in the Claimed Apparatus or System Is Under 500 Milliseconds From One Another

The '508 Patent expressly defines the “millisecond time resolution” as follows:

A. Definitions

* * *

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, Cols. 9:34, 10:8-24 (emphases added); Ex. 2009 ¶ 30.

The specification of the '508 Patent contains numerous teachings that are entirely consistent with and support the explicit definition of the “millisecond time resolution” claim term, include but not limited to the following discussions:

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.

Ex. 1001, Cols. 3:65 – 4:6 (emphasis added); Ex. 2009 ¶ 32.

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.

Ex. 1001, Col. 24:22-35 (emphasis added); Ex. 2009 ¶ 32.

Therefore, in accordance with the patentees' express definition in the '508 Patent, and the patentees' discussion of that term elsewhere in the patent's specification, the term "millisecond time resolution" means the time between two consecutive impedance measurements for each and every well being evaluated in the claimed apparatus or system is under 500 milliseconds from one another. Ex. 2009 ¶ 33. And the term "millisecond time resolution" does not mean, as Axion repeatedly asserts, taking a single impedance measurement of a single well over a period of milliseconds. *See infra* Section VI.B; Ex. 2009 ¶ 34.

Axion argues that "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." Pet. at 34. This argument is theorized from Jones' single disclosure of "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." *Id.*; Ex. 1006 ¶ [0030]. Axion's arguments that Jones discloses the "millisecond time resolution" limitation are based on Paragraph [0030] of Jones, which states that "[f]rom preliminary modeling and testing, no more than 68.2 ms per well for all frequencies is required to obtain sufficient samples." Ex. 1006

¶ [0030]; Ex. 2009 ¶ 34.

Axion incorrectly asserts that “[t]he disclosure in Jones also describes taking first and second measurements of impedance of *a single well* of a 96-well plate 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].” Pet. at 35 (emphasis added). Axion misunderstands that the 68.2 ms discussed by Jones is the time to scan *a single well*, not the time period between two consecutive scans of that well. Ex. 2009 ¶ 36. Indeed, in the very next sentence, Jones explains that the time between consecutive scans of a given well is 1.5 seconds. Ex. 1006 ¶ [0030]; Ex. 2009 ¶ 36.

Finally, Axion asserts, again incorrectly, that “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*.” Pet. at 36 (emphasis added). Jones nowhere “discloses providing a higher measurement rate” or “monitor[ing] a more limited number of wells”. Ex. 2009 ¶ 37. To the contrary, Jones explains that the specification to meet (or the “target update period”) is 1.5 seconds. Ex. 1006 ¶ [0030]; Ex. 2009 ¶ 37. And Jones allocates any time after the individual scans “for multiplexer switching and signal settling”, which would be necessary in Jones’ system. *Id.*

In an exercise of pure hindsight reconstruction, Axion contorts the single-paragraph disclosure in Jones into pages of complex calculations and results-oriented interpretations. *E.g.*, Pet. at 34-35. A POSA would understand that Jones provides a single disclosure of a 68.2 ms time to scan a single well, plus a 1091 ms time to scan 12 wells and 4 references in series (one at a time), plus a 409 ms time for “multiplexer switching and signal settling,” resulting in a combined “update period” of 1.5 seconds between two consecutive scans. Ex. 1006 ¶ [0030]; Ex. 2009 ¶ 35. This teaching is consistent with the commercial impedance analyzer that Jones’ assignee, MDS Sciex, was selling at the time, with a specification for a “2 or 10 second update rate”:

Update rate	
96-well	2 or 10 second update rate

Ex. 2011 (MDS Sciex CellKey Brochure (c. 2005) (Instrument Specifications)) at 6; Ex. 1006 at 1 (INID code (73)); Ex. 2012 (CellKey Specifications (2007)); Ex. 2013 (CellKey Press Release (2005)) at 1; Ex. 2009 ¶ 41.

Contrary to Axion’s arguments, Jones’ Paragraph [0030] explains that its 8-row, 96-well system requires a measurement time for a single well to be “no more than 68.2 ms *per well*,” with a “target 1.5 second update period”. Ex. 1006 ¶ [0030] (emphasis added); Ex. 2009 ¶ 40. Thus, Jones only teaches that 1.5 seconds are required between two consecutive measurements of each well (the “target 1.5 second update period”): 12 wells plus the 4 reference channels on a

daughter board measured sequentially, with an additional 0.409 seconds for “multiplexer switching and signal settling”: $(0.0682 \text{ seconds} \times (12 + 4)) + 0.409 \text{ seconds} = 1.5 \text{ seconds}$). Ex. 1006 ¶ [0030]; Ex. 2009 ¶ 40. It should be understood that the times for the “multiplexer switching and signal settling” would be interspersed throughout the entire 1.5 second update period, with electrical transients occurring after each multiplexer switching operation. Ex. 2009 ¶ 42.

Axion therefore misinterprets the “millisecond time resolution” limitation to simply mean the time required to take one measurement of the impedance of a single well—not the time required between two impedance measurements of each and every well of the claimed apparatus or system being evaluated, contrary to the express definition set forth in the ’508 Patent. *Id.*

2. The ’508 Patent Explains the Importance of “Millisecond Time Resolution” for Applications Such as Cardiomyocytes, While Jones’ “Target 1.5 Second Update Period” Would Be Inadequate for Such Applications

The ’508 Patent is directed to “impedance-based monitoring of cells and more particularly to systems and methods for monitoring excitation-contraction coupling and excitable cells using impedance-based systems with millisecond time resolution.” Ex. 1001, Col. 1:28-32; Ex. 2009 ¶ 44. The claimed invention “fill[s] a major technological gap in monitoring of excitation-contraction coupling and excitable cells, such as cardiomyocytes, *in vitro*. This is accomplished, in part, from the development of an impedance-based system and monitoring method that

employs millisecond time resolution.” Ex. 1001, 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.”); Ex. 2009 ¶ 44.

With respect to cardiomyocytes in particular, “[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.” Ex. 1001, Col. 10:44-46; Ex. 2009 ¶ 45. Because of the important applications repeatedly discussed, the ’508 Patent focuses on time resolutions between two impedance measurements of “less than 300 milliseconds” (emphasis added):

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*.

Ex. 1001, Col. 4:51-59 (emphases added); *see id.*, Col. 47:15 (“millisecond time resolution”) (Claim 1), Col. 47:54 (“less than 100 milliseconds”) (Claim 11), Col. 47:57 (“less than 40 milliseconds”) (Claim 12), Col. 47:59 (“less than 20 milliseconds”) (Claim 13), Col. 47:62 (“less than 5 milliseconds”) (Claim 14); Ex. 2009 ¶ 45.

In sharp contrast, and particularly relevant here, the ’508 Patent explains why then-existing systems that used “seconds” time resolution between consecutive impedance measurements (like Jones’ “target 1.5 second update period”) would be incapable of accomplishing the objectives of the invention (emphasis added):

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*.

Ex. 1001, Cols. 24:11-14, 16:40-58 (emphases added); Ex. 2009 ¶ 47. Thus, the 1.5 second update period disclosed in Jones would be unable to effectively perform the analysis of the excitable cells repeatedly discussed and emphasized in the '508 Patent. *Id.*; Ex. 2009 ¶ 54.

Moreover, Jones does not mention any particular applications for its system, including the types of cells to be monitored or their particular nature (such as excitable cells or cardiomyocytes). Ex. 2009 ¶ 54. And Jones does not disclose millisecond time resolution or include any discussion about improving measurement time resolution. *Id.* Instead, as discussed previously, 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, Abstr.

[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] (emphasis added); Ex. 2009 ¶ 49. Indeed, Jones is titled “Impedance Measurement System With Incorporated Internal Measurement Drift Compensation Networks”, emphasizing the nature of Jones’ disclosure. Ex. 1006.

VI. CONCLUSION

Xu-752 in combination with Jones does not render obvious Claims 1-8 and 11-15 of the '508 Patent because those references both, individually and in combination, fail to disclose or suggest the “millisecond time resolution” of those claims. This claim limitation was neither well-known nor common knowledge in the 2008-time frame, and Axion does not assert as much. And Axion nowhere suggests (nor could it reasonably do so) that a POSA would have modified the Xu-752 and/or Jones references to satisfy the above claim limitation.³ Thus, for the foregoing reasons, the Petition fails to demonstrate that Claims 1-8 and 11-15 of the '508 Patent (Ground 2) would have been obvious over the combination of Xu-

³ Axion argues that the Impedance Measurement System disclosed in Jones could be modified in some unspecified manner and operated somehow differently to shorten the expressly disclosed times of 68.2 ms/well with a 1.5 second “update period.” *E.g.*, Pet. at 53-54. However, Axion’s arguments are nothing more than hindsight-induced attempts to overhaul and reengineer the system described in Jones after viewing the '508 Patent, purposely disregarding Jones’ express and straightforward disclosure. Ex. 2009 ¶ 52. There is no teaching or suggestion in Jones to make any such modifications. *Id.* And there is no teaching or suggestion in Jones why any such modifications would be particularly desirable. *Id.*

752 and Jones. Agilent therefore respectfully requests that the Board confirm the patentability of those claims.

Respectfully submitted,

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Dated: June 19, 2025

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that foregoing Patent Owner Response, exclusive of the parts exempted as provided in 37 C.F.R. § 42.24(A), contains 6,082 words and therefore complies with the type-volume limitations of 37 C.F.R. § 42.24(b).

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the **PATENT OWNER RESPONSE** is being served on June 19, 2025, electronically via P-TACTS and via electronic mail to the email addresses below:

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