

Sterlington

Axion BioSystems, Inc. v. Agilent Technologies, Inc.

Case No.: IPR2024-01467

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

Counsel: Brenton R. Babcock (Reg. No. 39,592)
Yang Wang (Ltd. Recog. No. 800,126)

On Behalf Of: Patent Owner, Agilent Technologies, Inc.

Location: USPTO Southwest Regional Outreach Office (Dallas, TX)

Date: December 12, 2025

Roadmap for Today's Oral Argument

01

The Parties' Core Dispute

Impedance measurements at "**millisecond time resolution**" recited in the challenged patent's claims

02

'508 Patent's Express Definition

The '508 Patent's specification expressly defines the term "**millisecond time resolution**" with specific parameters

03

Jones' Missing Limitation

Jones teaches a "target 1.5-second update period" for its ZMS that fails to meet the "**millisecond time resolution**" limitation

04

Axion's Hindsight Reconstruction

Axion relies on unsupported expert testimony and undisclosed and unsuggested hindsight modifications of Jones' ZMS rather than prior art

05

Axion's Improper New Reply Arguments

Axion's new impermissible introduction and reliance on the Ghosh reference; elimination of Jones' multiplexer switching and settling time; and dismissal of Sciex's CellKey update period

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Axion Fails to Meet Its Burden

Axion has failed to establish unpatentability by a preponderance of the evidence

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The Challenged '508 Patent (Claim 1)

- 65 1. An apparatus for continuous, label free, real-time monitoring of cells using impedance-based analysis, the apparatus comprising:
- a) a multiwell plate comprising a plurality of wells on a nonconductive substrate, wherein each of the plurality of wells comprises an electrode array of a plurality of electrode arrays that is disposed on the nonconductive substrate; 5
 - b) an impedance analyzer that independently measures a cell-substrate impedance at each well, the cell-substrate impedance being measured between a first electrode structure and a second electrode structure of the electrode array and across a cellular sample comprising a plurality of cells disposed within each well, the impedance analyzer including 10
 - at least two analogue-to-digital conversion channels coupled to the plurality of electrode arrays, wherein the impedance analyzer monitors the electrode arrays at millisecond time resolution between first measurements of the cell-substrate impedance and second measurements of the cell-substrate impedance for each well; and 15
 - c) a software program that analyzes the first measurements and the second measurements to produce a time 20 period analysis of the cellular sample.

Claim 1 is the only independent claim.

Claim 1 recites, *inter alia*:

- a multiwell plate with a plurality of wells;
- an impedance analyzer;
- at least two ADC channels; and
- monitoring the plurality of wells at **“millisecond time resolution”**.

The Challenged '508 Patent (Claims 2-8 & 11-15)

2. The apparatus of claim 1, 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. 25

3. The apparatus of claim 1, wherein the plurality of analogue-to-digital conversion channels performs signal conversion in parallel across multiple wells.

4. The apparatus of claim 1, 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. 30

5. The apparatus of claim 1, wherein the apparatus comprises an electromechanical apparatus configured for interfacing the multiwell plate with one or more platforms. 35

6. The apparatus of claim 5, wherein the one or more platforms of the electromechanical apparatus comprise an impedance platform.

7. The apparatus of claim 1, 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. 40

8. The apparatus of claim 1, wherein the nonconductive substrate includes a precoat comprising one or more compounds that improve cell attachment. 45

11. The apparatus of claim 1, wherein the millisecond time resolution between the first measurement and the second measurement is less than 100 milliseconds.

12. The apparatus of claim 1, wherein the millisecond time resolution between the first measurement and the second measurement is less than 40 milliseconds. 55

13. The apparatus of claim 1, wherein the millisecond time resolution between the first measurement and the second measurement is less than 20 milliseconds. 60

14. The apparatus of claim 1, wherein the millisecond time resolution between the first measurement and the second measurement is less than 5 milliseconds.

15. The apparatus of claim 1, wherein the time period analysis lasts at least 12 hours.

Ex. 1001 (the '508 Patent) at 83.

Claims 2-8 & 11-15 all depend (either directly or indirectly) on Claim 1.

Dependent claims not argued separately in this IPR.

Axion's Section 103 Challenge: Xu-752 + Jones

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 PTO during '508 prosecution), describes an improved impedance measurement system that includes the limitations that Xu-752 does not explicitly describe.

Pet. at 31-32.

Axion concedes that Xu-752 does **not** disclose ADCs or "millisecond time resolution"

Axion relies **solely** on Jones to purportedly supply the missing claim limitations.

Patent Claims Currently At Issue (Claims 1-8 & 11-15)

Axion's Ground 2 Challenge:

- **Claims 1-8 and 11-15** are at issue based on the combination of **Xu-752** and **Jones** (Section 103)
- Agilent's statutory disclaimers have significantly streamlined this IPR proceeding, narrowing the technological and legal issues.
 - Ex. 2001 – pre-institution (disclaimed claims 9, 10, & 23-30)
 - Ex. 2020 – post-institution (disclaimed claims 16-22)

The Central Question:

The dispute is now focused squarely on one key limitation that determines the outcome of this case:

| **“millisecond time resolution”**

| Neither Xu-752 nor Jones, separately or together, disclose or suggest the “millisecond time resolution” limitation

Missing Limitation (Reason to Combine *not* at issue)

Missing Limitation

- Combination of Xu-752 + Jones does **not** disclose or suggest “millisecond time resolution”
- Thus, no need to consider whether POSA would be **motivated** to combine Xu-752 + Jones

Axion's Arguments Directed to Reason to Combine Are Not Relevant Here

In any event, “a given course of action often has simultaneous advantages and disadvantages, and this does not necessarily obviate motivation to combine.”

Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1165 (Fed. Cir. 2006).

E.g., Reply at 16-17.

Missing Limitation – “Millisecond Time Resolution”

In sum, the '508 patent's claims include an apparatus capable of monitoring impedance for two (or more) wells, where the time between two consecutive measurements for the wells is within the claimed **millisecond time resolutions**. Jones discloses exactly such a system.

Scope of Claim 1	Jones
“plurality of wells” (<i>i.e.</i> , at least two)	“The present technology provides an Impedance Measurement System (ZMS) for measuring the complex impedance of each well of a <i>single well or multiwell microtiter plate</i> .” EX1006, ¶[0003]; <i>see also id.</i> , Abstract.
measurements at a single frequency or multiple frequencies	“The system can be used for impedance measurements of varying time periods, <i>single or multiple frequencies</i> , and various measurement rates.” <i>Id.</i> , ¶[0003].
serial or parallel measurements	“Additionally, the ZMS <i>employs parallelism to obtain the required throughput</i> ” <i>Id.</i>

Axion's Reply includes a claim chart comparing Claim 1 of '508 Patent to Jones.

The chart completely omits the "millisecond time resolution" limitation ***because Jones does not teach or suggest “millisecond time resolution”.***

Sur-reply at 11 (quoting Reply at 8-9).

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Express Definition Of “Millisecond Time Resolution”

A. Definitions

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

Ex. 1001 (the '508 Patent), Col. 9:36-47.

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 (the '508 Patent), Col. 10:7-25.

Axion's "Plain Meaning" Ignores Express Definition

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-

Pet. at 13.

Axion ignored the '508 Patent's express definition.

Axion proposed **no construction**, arguing "plain meaning." Pet. at 13.

"Millisecond time resolution" should be construed using the patent's own explicit definition.

At Least Two Consecutive Measurements For Each And Every Well With Millisecond Time Resolution

compounds that improve attachment. In embodiments where the device includes multiple wells, the impedance analyzer 25 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. 30

Ex. 1001 (the '508 Patent), Col. 3:24-32.

number therebetween. Throughout the present application 65 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 5 subsets of all wells of a device, are monitored a group of wells may be monitored using millisecond time resolution.

Ex. 1001 (the '508 Patent), Cols. 3:65 – 4:6.

or 96 wells. For example, if the system comprises a device having 96 wells, the system hardware and software should be capable of, for a given time period, measuring the 25 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 30 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. 35 Similarly, if a 96 well device is provided, a group of

Ex. 1001 (the '508 Patent), Col. 24:22-35.

At Least Two Consecutive Measurements For Each And Every Well With 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.
(emphases added)

Ex. 1001 (the '508 Patent), Col. 10:8-15.

"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 milliseconds 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 evaluated in the claimed apparatus or system.
(emphases added)

POR at 2-3.

“Less Than 500 Milliseconds”

In preferred embodiments the impedance analyzer is capable of impedance measurements at millisecond time resolution. The required or desired time resolution may vary depending on the excitation cycle of the excitable cell. 50 Excitable cells having shorter excitation cycles would tend to require faster time resolution. In some embodiments 500 millisecond time resolution is sufficient, such that at least two consecutive impedance measurements are between about 300 milliseconds and about 500 milliseconds apart. 55 In preferred embodiments, impedance measurement at millisecond time resolution includes at least two consecutive impedance measurements less than 100 milliseconds apart. In some instances the at least two consecutive impedance measurements are less than 50 milliseconds or less than 40 60 milliseconds apart. In some instances the at least two consecutive impedance measurements are less than 20 milliseconds apart. In some instances at least two consecutive impedance measurements are less than 10 milliseconds apart. In some instances millisecond time resolution 65 includes two consecutive impedance measurements between 1 millisecond and 5 milliseconds, between 5 milliseconds

As above, in preferred embodiments, the time difference between two consecutive impedance measurement for a well is in the range of milliseconds (e.g., less than 500 milliseconds, less than 300 milliseconds, less than 100 milliseconds, less than 10 milliseconds, or less than about 1 millisecond or faster). The millisecond kinetic readout is required to resolve the individual beat cycles of the cells. Thus, the time resolution for the impedance measurement should allow the system to perform measurement using at least two time 50 points for each beat cycle. In some embodiments more than two time points are resolved for each beating cycle. 55

Ex. 1001 (the '508 Patent), Col. 38:47-56.

Ex. 1001 (the '508 Patent), Col. 23:47-65.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

300 Milliseconds Versus 500 Milliseconds Is Immaterial For This Proceeding

“Th[e Board’s] concern [about Petitioner’s showing] 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.

“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.”

POR at 15; Ex. 2009 (Sanchez Decl.) ¶¶ 33, 40.

For This Proceeding, Agilent Proposes 500ms:

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.

POR at 15; Ex. 2009 (Sanchez Decl.) ¶ 33.

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Jones Teaches A “Target 1.5-Second Update Period”

(73) Assignee: **MDS Sciex (US) a division of MDS Pharma Services (US) Inc.**, South San Francisco, CA

Jones discloses a small form factor “Impedance Measurement System (ZMS)”.

Jones **ONLY** discloses a single embodiment with a “**target 1.5 second update period**” with precise timing calculations.

The 1.5 second target update period is at least **3X longer** than the claimed “millisecond time resolution” in the ‘508 Patent.

Jones' disclosed embodiment operates at speeds fundamentally incompatible with the “millisecond time resolution” limitation claimed in the ‘508 Patent.

[0030] 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 (Jones) ¶ [0030].

Jones Teaches Multiplexing Each Well

Each daughter board has multiplexing circuitry allowing one or more measurement channels to address the sensors for each well in the row.

Ex. 1006 (Jones) ¶ [0012].

What is claimed is:

1. An impedance measurement system for measuring the complex impedance of each well of a microtiter plate, the microtiter plate wells being formed in an array of rows and columns, the microtiter plate having a topside and an underside, the microtiter plate comprising sensors in the well bottoms and contact pads on the underside of the microtiter plate, the impedance measurement system comprising:

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

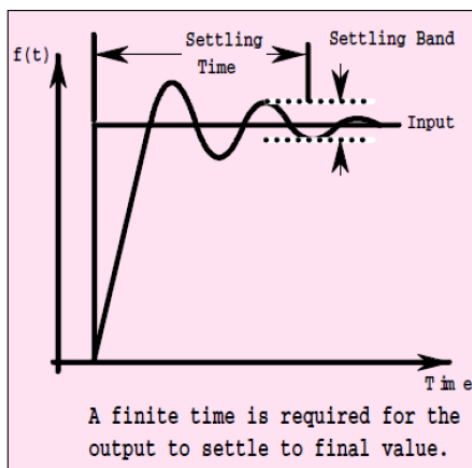
Ex. 1006 (Jones), Claim 1.

[0030] 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 (Jones) ¶ [0030].

Multiplexing Requires Time To Maintain Accuracy

Settling Time. The time interval between the application of an input and the time when the output is within an acceptable band of the final steady-state value.



High sampling rates. With an ADC per channel, the sampling rate is not encumbered with considerations such as multiplexing and post-amplifier settling time.

(22)	A. It would because as I mentioned before, with
(23)	reduced measurement times there is a compromise on
(24)	measurement accuracy, right? And part of my PhD was
(25)	precisely to move forward the body of knowledge and
(1)	scientific knowledge to balance this trade off, and

Sur-reply at 14-15 (quoting Ex. 1028 (Sanchez Depo. Tr.) at 93:22 – 94:1).

Jones' "1.5 Second Update Rate" System Specification

For each ZMS "daughter board":

12 wells + 4 reference channels = 16 channels

68.2 ms/channel x 16 channels = 1.091 seconds

Target update period = 1.5 seconds

Time left for "multiplexer switching and signal settling":

1.5 seconds - 1.091 seconds = 409 ms

Note: Axion eliminates reference to the "multiplexer" and "switching and signal settling" time in its Reply.

Jones explains that the specification to meet (or the "target update period") is 1.5 seconds. Thus, *Jones allocates any time after the individual well measurements "for multiplexer switching and signal settling".*

[0030] 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 (Jones) ¶ [0030].

Sur-reply at 15 (quoting Ex. 2009 (Sanchez Decl.) ¶ 37 (emphasis added)).

Axion Misunderstands Jones' Teaching

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].

Pet. at 35.

The **68.2ms** discussed in Jones is the time required to measure a **single well**, NOT the total measurement time necessary to perform two consecutive measurements of at least two wells.

POR at 2-3.

Jones' Goals of Compactness & Thermal Stability

"The ZMS employs parallelism to obtain the **required** throughput . . . as well as internal temperature control **to ensure increased measurement accuracy and stabilization against thermal drift.**"

Ex. 1006 (Jones) ¶ [0003] (emphases added).

Critical Distinction: Jones was designed to maintain "required [*i.e.*, specified] throughput" in a more compact, thermally stable package — not to **increase** measurement speed.

SUMMARY OF THE INVENTION

[0003] 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. Additionally, 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.**

Jones Does *Not* Teach Decreasing Throughput Time

[0023] 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.

[0024] 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.

Thermal Control

[0044] In addition to the temperature compensation provided by the self calibration and in-run calibration networks, the ZMS requires a stable controlled thermal environment. To achieve the desired rate of ZMS accuracy and repeatability, temperature control to within $\pm 1.5^{\circ}\text{C}$ is necessary. In an additional embodiment, the temperature control must be within $\pm 1.0^{\circ}\text{C}$. In yet a further embodiment, the temperature control must be within $\pm 0.5^{\circ}\text{C}$.

[0045] The ZMS thermal control system includes a high flow rate, forced air circulation system to provide spatial temperature uniformity ability to remove waste heat generated by ZMS heating to maintain optimum operating temperature monitoring of gross air temperature and gradients a heat exchanger to prevent build-up of contaminants causing surface leakage currents

Ex. 1006 (Jones) ¶¶ [0023]-[0024].

Ex. 1006 (Jones) ¶¶ [0044]-[0045].

Jones Teaches A “1.5 Second Update Period” System Specification

Jones mentions the ZMS system “update rate” or “throughput” in two places:

SUMMARY OF THE INVENTION

Additionally, 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 (Jones) ¶ [0003].

42. I note that the times for the “multiplexer switching and signal settling” in the above illustration would be interspersed throughout the entire 1.5 second update period, with electrical transients occurring after each multiplexer switching operation between wells and reference channels within a row in the microtiter plate.

Ex. 2009 (Sanchez Decl.) ¶ 42.

[0030]

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 (Jones) ¶ [0030].

Jones’ ZMS “throughput” or “update period” specification is **1.5 seconds** – the time between **two consecutive impedance measurements of all of multiple wells** being evaluated.

- Not simply “measurement” period or rate
- Not simply “multiplexer switching” time
- Not simply “signal settling” time

Sciex's Commercial CellKey: "2 Second Update Rate"

Contemporaneous Evidence / Commercial Reality

Sciex's (the **assignee** of Jones) circa-2006 commercial CellKey product:
System specification for a **"2 or 10 second update rate."**



CellKey™ Instrument Specifications
The CellKey™ System integrates a proprietary impedance measurement system, custom 96-well microtiter plates, on-board 96-well fluidics, environmental control, and custom acquisition and analysis software in a full solutions package.

Measurement principles	Impedance
Measurement frequency range	1 kHz–10 MHz
Assay type	Homogenous, cell-based
Measurement modes	Endpoint or kinetic measurements
Update rate	2 or 10 second update rate
96-well	

2 or 10 second update rate

Ex. 2011 at 6.



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CELLKEY™ SYSTEM

- KEY FEATURES & BENEFITS
- SPECIFICATIONS
- PRODUCT BROCHURE
- PRODUCT VIDEO
- TECHNOLOGY
- APPLICATIONS
- TECHNOLOGY FAQ

CellKey™ System Specifications

CELLKEY INSTRUMENT SPECIFICATIONS	
Measurement Principles	Impedance
Measurement Frequency Range	1 kHz - 10 MHz
Assay Type	Homogenous, cell-based
Measurement Modes	Endpoint and kinetic measurements
Update Rate	2- or 10-second update rate
96-well	

2- or 10-second update rate

Ex. 2012 at 1.

POSAs' Recognition Of "2 Second Update Rate"

This real-world evidence confirms that a POSA would understand Jones' "target 1.5 second update period" as its operational specification, not a starting point for system modifications. Sur-reply at 16-20.

We designed a system capable of producing impedance measurements simultaneously across a large range of frequencies (from 1 kHz to 10 MHz) before, during, and after receptor activation. This approach facilitates *the measurement of early events within seconds to minutes* of ligand addition in receptor signaling cascades.... (15 min assay with **2 s update rate**).

Ex. 2026 at 256, 259 (emphases added).

Small-amplitude AC voltage at 24 frequencies, from 1 KHz to 10 MHz, is applied to a monolayer of cells, and the resultant current is measured at an **update rate of 2 s**.... The **quick update rate (2 s)** of the CellKey system allows detection of these *immediate changes in impedance*.

Ex. 2027 at 611 (emphases added).

The instrument applies small voltages at 24 discrete frequencies, from 1 kHz to 10 MHz, once every 2 s.... 10 min of cellular activation were recorded at an **update rate of 2 s** per 96 wells.

Ex. 2028 at 813-15 (emphasis added).

The electrical impedance of the cells was measured using CellKey™ (MDS Sciex, Concord, Ontario) *according to the protocol of the manufacturer* [Ex. 2030]. In particular, 100 mV voltage was applied to the cells with a sweeping frequency range of 1 kHz to 10 mHz.

Ex. 2029 ¶ [0069] (emphasis added) (referencing Ex. 2030 (prototype CellKey));

Sur-reply at 18-19.

Sur-reply at 18.

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Dr. Kim's Examples: Hindsight Reconstruction

Dr. Kim's Fabricated "Examples"

EX1003	Number of Wells	Number of Frequencies	Daughter Boards	Reference Channels	Update Period
¶72	96-well	Single freq. (10, 50, or 100 kHz)	8	4	412-433 ms
¶137	16-well	Multi-freq. sweep	8	3	470 ms
¶139	16-well	Single freq. (10 kHz)	8	3	136 ms
¶173	16-well	Single freq. (10 kHz)	16	0	1.5 ms
¶175	16-well	Single freq. (10 kHz)	2	0	55 ms

Dr. Kim contorts Jones' single 135-word example Paragraph 30 into pages of complex, contrived configurations that appear nowhere in Jones.

Critical Distinction: These are Dr. Kim's hypothetical examples created with after-the-fact knowledge of the '508 patent – not configurations disclosed, taught, or suggested by Jones.

Sur-reply at 5-7.

Reply at 6 (citing Ex. 1003).

Dr. Kim's Examples: Hindsight Reconstruction

What's in Jones?

[0030] 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 (Jones) ¶ [0030].



**NO TEACHING
IN JONES**

Dr. Kim's Hypothetical Examples

Number of Wells / Channels	Time for Measuring One Well / Channel (see Jones, ¶[0030])	Switching / Settling Time for One Well / Channel	Measurement Time	Switching / Settling Time	Total Time
5	68.2 ms	25.6 ms ¹	5 * 68.2 ms = 341 ms	5 * 25.6 ms = 128 ms	~ 470 ms

Ex. 1004 ¶ 137.

Frequency	Number of Wells / Channels	Time for 15-Cycle Burst (see Table 1)	Measurement Time	Switching / Settling Time	Total Time
10 kHz	5	1.5 ms	5 * 1.5 ms = 7.5 ms	5 * 25.6 ms = 128 ms	~ 136 ms

Ex. 1004 ¶ 139.

Frequency	Number of Wells / Channels	Time for 15-Cycle Burst (see Table 1)	Measurement Time	Switching / Settling Time	Total Time
10 kHz	1	1.5 ms	1 * 1.5 ms = 1.5 ms	N/A	1.5 ms

Ex. 1004 ¶ 173.

Frequency	Number of Wells / Channels	Time for 15-Cycle Burst (see Table 1)	Measurement Time	Switching / Settling Time	Total Time
10 kHz	2	1.5 ms	2 * 1.5 ms = 3.0 ms	2 * 25.6 ms = 51.2 ms	~ 55 ms

Ex. 1004 ¶ 175.

Dr. Kim's Modifications Are Unsupported

Fewer Wells & Channels:

Jones specifies a 96-well plate with 4 reference channels. Dr. Kim uses 16 wells and 3 or 0 references.

Dr. Kim (or another expert witness) provided no supplemental declaration.

Single Frequency:

Jones teaches a "stepped sweep" of multiple frequencies. Dr. Kim assumes a single frequency.

Eliminating/Discounting Settling Time:

Jones explicitly "leaves" 409 ms for "multiplexer switching and signal settling" – the remainder from the 1.5 second target throughput. Dr. Kim's examples treat these times as a negligible constant or eliminates them altogether.

"Axion's arguments are nothing more than hindsight-induced attempts to overhaul and reengineer the system described in Jones after viewing the '508 Patent. . . ."

POR at 27, n.3; Ex. 2009 (Sanchez Decl.) ¶ 52.

The Board's Institution Decision Expressed Concerns About Dr. Kim's "Examples"

“The current record supports Patent Owner’s position that ***Jones’s 96-well embodiment, which “operates on a time resolution on the scale of seconds,” does not teach or suggest monitoring at “millisecond time resolution”*** as recited in claim 1.

DI at 23 (emphasis added).

“Instead of relying on the 96-well embodiment in paragraph 30, or any other embodiment expressly described in Jones, ***Petitioner relies on “examples” evidenced by Dr. Kim’s testimony*** and based on modifications of the 96-well embodiment taught in Jones.

DI at 23 (emphasis added).

“In sum, this leads us to question ***whether the parameters for Dr. Kim’s examples were chosen not because they were obvious, but because they would result in a time between measurements of 500 milliseconds or less***, and thereby accord with Petitioner’s apparent interpretation of the term “millisecond time resolution” (see supra § III.C).

DI at 24 (emphasis added).

“If so, ***such 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.

DI at 24-25 (emphases added).

Axion Failed To Address The Board's Concerns With Evidence

What The Board Implicitly Requested From Axion?

To meet its burden, Axion needed to provide substantial additional factual support (*i.e.*, evidence) to overcome the deficiencies in Dr. Kim's declaration.

What Axion Provided?

No New Expert Testimony Or Other Evidence

Dr. Kim (or another expert witness) provided no supplemental declaration attempting to address the Board's concerns. Axion presented no additional factual evidence.

Only Attorney Argument

Petitioner's Reply attempts to fill evidentiary gaps with counsel's arguments and characterizations.

"Argument of counsel cannot take the place of objective evidence."

Qualcomm Inc. v. UNM Rainforest Innovations, IPR2021-00582, Paper 63 at 16-17; Sur-reply at 4.

"These attorney arguments are entitled to little, if any, weight."

Apple Inc. v. LBT IP I LLC, IPR2020-01191, Paper 39, at 29; Sur-reply at 3-4.

Expert Witness Cannot Supply Missing Limitation

Axion's Expert Witness, Dr. Kim, Cannot Supply the Missing Claim Limitation

- Axion effectively asserts combination of Xu-752 + Jones + **Dr. Kim Testimony**
- Legally improper to attempt to “fill in the gap” with expert testimony:

Furthermore, because an *inter partes* review may only be requested “on the basis of prior art consisting of patents or printed publications,” 35 U.S.C. § 311(b), expert testimony cannot take the place of disclosure from patents or printed publications. In other words, expert testimony may explain “patents and printed publications,” but is not a substitute for disclosure in a prior art reference itself.

PTAB Consolidated Trial Practice Guide, at 36 (Nov. 2019) (Sur-Reply at 6-7).

Agilent Consistently Contested Dr. Kim's Testimony

Axion argues that Dr. Kim's testimony is "uncontested." (Reply at 4-5). **This argument is incorrect.**

Examples of Agilent's contesting Dr. Kim's Testimony:

In the POR: Agilent contrasted Dr. Kim's testimony with Jones' actual disclosure. (POR at 14-17, 22)

Dr. Sanchez's Rebuttal: "I have reviewed Dr. Kim's lengthy analysis, and in my opinion it is an exercise in hindsight reconstruction in an attempt to meet the limitations of the '508 Patent's claims." (Ex. 2009 ¶ 52)

Cross-Examination: Dr. Sanchez confirmed his analysis. (Ex. 1028 at 93:22 – 94:8)

Sur-reply at 7-10.

Roadmap for Today's Oral Argument

01

The Parties' Core Dispute

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02

'508 Patent's Express Definition

The '508 Patent's specification expressly defines the term "**millisecond time resolution**" with specific parameters

03

Jones' Missing Limitation

Jones teaches a "target 1.5-second update period" for its ZMS that fails to meet the "**millisecond time resolution**" limitation

04

Axion's Hindsight Reconstruction

Axion relies on unsupported expert testimony and undisclosed and unsuggested hindsight modifications of Jones' ZMS rather than prior art

05

Axion's Improper New Reply Arguments

Axion's new impermissible introduction and reliance on the Ghosh reference; elimination of Jones' multiplexer switching and settling time; and dismissal of Sciex's CellKey update period

06

Axion Fails to Meet Its Burden

Axion has failed to establish unpatentability by a preponderance of the evidence

Axion's Reply Attempts To Introduce Ghosh As A New Ground Of Unpatentability

Ghosh (Ex. 1017) was NOT a ground of unpatentability in the Petition

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")

Pet. at 1.

"We disregard Petitioner's alternative position as it was an attempt to raise a new theory of unpatentability improperly for the first time in the Reply."

Henny Penny Corp. v. Frymaster L.L.C., IPR2016-01435, Paper 47, at 17 (PTAB Dec. 21, 2017); Sur-Reply at 21.

Fifteen

years before the '508 patent's alleged priority date, Ghosh described "monitor[ing] the impedance of [a] sample" by "tak[ing] data once every 10 milliseconds" and noting the capability to "take readings as fast as once every 5 milliseconds."

EX1017, 1604, 1609. Ghosh thus described impedance-based cellular analysis with millisecond time resolution measurements, contrary to Dr. Sanchez's

unsubstantiated opinion.⁷ The '508 patent's alleged invention (measuring *two or*

more wells at a millisecond time resolution) is, at most, a minor variation on

Ghosh (measuring *a single sample* at a millisecond time resolution), and would

have been obvious for all of the reasons stated in the Petition.

Reply at 12.

Ghosh Is Fundamentally Different And Irrelevant

B. Ghosh Describes An Entirely Dissimilar Single-Sample System For Studying Electroporation In A Large Tissue Culture Dish

Ghosh describes a single-sample system for “the measurement of pore formation and closure in anchored mammalian cells”, called “electroporation”. Ex. 1017, Abstract. Ghosh measures when “small transient pores are formed in the membrane” by applying a “low voltage (1V-5V) pulse” using a single sample of cells growing on a “[p]olystyrene dish (60 mm)” of tissue culture optical quality....” *Id.* at 1063-64; Ex. 2036 at 3761; Ex. 1017, Abstract (“[T]he application of a few volts across the cell-covered electrode causes pore formation in the cell membrane.”). While Axion acknowledges that Ghosh is used for “measuring α

Sur-reply at 22.

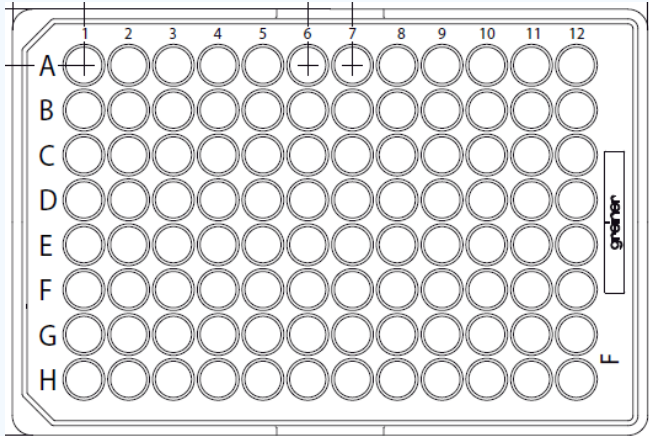
Ghosh is directed to a **completely different field and problem**. The systems, purposes, and scales are entirely dissimilar.

The dimensions of the large electrode in Ghosh are incompatible with microtiter well dimensions.

A POSA would not look to Ghosh to solve the problem of high-throughput, multi-well impedance analysis.

Sur-reply at 22-24.

Ghosh Is Fundamentally Different And Irrelevant



Feature	Ghosh (Ex. 1017)	'508 Patent (Ex. 1001)
Purpose	Electroporation (pore formation)	Cell monitoring (<i>e.g.</i> , cardiomyocyte beating)
Electrode Size	2 square centimeters	micron or millimeter
Apparatus	Single large tissue culture dish (60mm)	Multi-well (<i>e.g.</i> , 96) microtiter plate (~7mm wells)
Scale	Single sample	High-throughput, multiple wells
Voltage	1-5 V (to porate membranes)	~100 mV (non-invasive)

Sur-reply at 22-24; Ex. 2037.

Ghosh Is Fundamentally Different And Irrelevant

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.

Pet. at 3.

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

Pet. at 4.

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

Pet. at 37.

Ghosh is directed to a **completely different field and problem**. The systems, purposes, and scales are entirely dissimilar.

Sur-reply at 22-24.

The 15-Year Time Gap Suggests *Non*-Obviousness

Ghosh was Published in 1993

Monitoring electroporabilization in the plasma membrane of adherent mammalian cells

Paramita M. Ghosh, Charles R. Keese, and Ivar Giaever
School of Science, Rensselaer Polytechnic Institute, Troy, New York 12180-3590 USA

Biophys. J. © Biophysical Society
Volume 64 May 1993 1602-1609

Ex. 1017 (Ghosh) at 1.

The '508 Patent has a 2008 Priority Date

(12) United States Patent
Wang et al.

(10) Patent No.: US 11,906,508 B2
(45) Date of Patent: Feb. 20, 2024

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

(58) Field of Classification Search
CPC G01N 33/4836; G01N 27/02; G01N
33/4833; G01N 33/48728; G01N 33/5438
See application file for complete search history.

(71) Applicant: Agilent Technologies, Inc., Santa Clara,
CA (US)

(56) References Cited
U.S. PATENT DOCUMENTS

(60) Provisional application No. 61/191,684, filed on Sep.
11, 2008, provisional application No. 61/126,533,
filed on May 5, 2008.

Ex. 1001 (the '508 Patent) at 1.

A 15-year gap without a multi-well millisecond-resolution system actually suggests the invention would not have been obvious.

Sur-reply at 24-25 (citing *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1359 (Fed. Cir. 2013)).

Axion Acknowledged Jones' Multiplexing Architecture And Switching And Settling Times In The Petition

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].

Pet. at 34.

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 multiplexing circuitry allowing one or more measurement channels to address the

Pet. at 70-71.

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],

Pet. at 58.

Axion's Petition repeatedly acknowledges Jones' 409 milliseconds “multiplexer switching and signal settling” time and “multiplexing circuits”.

Axion Eliminated Jones' Multiplexing Architecture And Switching And Settling Times In The Reply

Jones's ¶[0030] is a result of each of eight daughter boards “measuring 16 wells/channels (12 wells plus 4 reference network channels) at 68.2 milliseconds per object (68.2 milliseconds * 16 = 1091.2 milliseconds)”).

Reply at 20.

Axion's Reply eliminates all mention of Jones' 409 milliseconds “multiplexer switching and signal settling” time and “multiplexing circuits”.

Axion Argues That Sciex's Commercial CellKey System, With A 2-Second Update Rate, Is Irrelevant

³ Agilent's Exs. 2011-2013, indicating 2-10 second update periods for a 96-well plate in MDS Sciex's commercial product, are beside the point.

Reply at 7, n.3.

Axion made no previous objection to these exhibits, including under Fed. R. Evid. 401.

Sciex's commercial CellKey system is probative evidence showing that in the 2008-time frame, POSAs were **not** endeavoring to alter the manufacturer's system specifications for increased throughput or reduce the seconds-long update periods to obtain millisecond time resolution.

Sur-reply at 17-20.



Sur-reply at 17 (taken from Ex. 2025 at 14).

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Axion Fails to Meet Its Burden

Axion has failed to establish unpatentability by a preponderance of the evidence

Axion Fails To Demonstrate Obviousness

Axion bears the burden of proving unpatentability by a preponderance of the evidence.
35 U.S.C. § 316(e).

"Obviousness 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. v. Tetra Pak Cheese & Powder Sys., 725 F.3d 1341, 1352 (Fed. Cir. 2013) (emphasis added)

| Axion's case is a textbook example of hindsight reconstruction.

See DI at 23-24 ("If so, such ***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." (emphases added)).

Summary Of Key Deficiencies In Axion's Arguments

1. **Misconstrues the Claim Term:** Ignores the patent's express definition of "millisecond time resolution" as a system-wide throughput metric.
2. **Relies on Undisclosed and Unsuggested Modifications to Jones:** Depends solely on expert-contrived "examples" not disclosed in or suggested by Jones.
3. **Uses Hindsight Reconstruction:** Reverse engineers Jones by attempting to retrofit parameters from the '508 Patent to modify Jones.
4. **Fails to Provide Evidence-Based Rationale:** Offers no evidence to support *why* a POSA would make the many modifications to Jones to achieve millisecond time resolution.
5. **Introduces New Arguments on Reply:** Improperly relies on Ghosh; eliminates Jones' multiplexer switching and settling time; and argues that Sciex's CellKey 2-second update rate is irrelevant.

Conclusion – Axion Has Not Met Its Burden

For the foregoing reasons, as set forth more fully in Agilent's POR and Sur-Reply, and the testimony of Dr. Sanchez:

Axion has failed to meet its burden of demonstrating that **Claims 1–8 and 11–15** of the '508 Patent would have been obvious over **Xu-752** and **Jones**.

Claims 9-10 & 16-30:

Because Agilent has voluntarily disclaimed Claims 9-10 & 16-30 of the '508 Patent, Agilent respectfully requests that the Board determine that Axion's challenges to those claims are moot.

Claims 1-8 & 11-15:

Agilent respectfully requests that the Board confirm the patentability of Claims 1-8 and 11-15 of the '508 Patent.

Sterlington

Thank you!