

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GATOR BIO, INC.,

Petitioner,

v.

SARTORIUS BIOANALYTICAL INSTRUMENTS, INC.,

Patent Owner.

IPR2023-00215

U.S. Patent No. 8,305,585

**PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 8,305,585**

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EXHIBIT LIST¹

Exhibit	Description
1001	U.S. Patent No. 8,305,585 (“’585 patent” or “challenged patent”)
1002	Declaration of David Schaafsma, Ph.D.
1003	USPTO Assignment Records for ’585 Patent
1004	U.S. Provisional Patent Application No. 60/518,068, filed November 6, 2003 (“’068 provisional”)
1005	U.S. Provisional Patent Application No. 60/558,381, filed March 31, 2004 (“’381 provisional”)
1006	File History of U.S. Patent Application No. 12/099,751, filed April 8, 2008 (“’751 FH”)
1007	File History of U.S. Patent Application No. 12/790,736, filed May 28, 2010 (“’736 FH”)
1008	Yuxiao Yang et al., <i>Direct monitoring of antigen-antibody interactions by optical fiber bioprobe</i> , PROCEEDINGS OF SPIE, THIRD INTERNATIONAL CONFERENCE ON PHOTONICS AND IMAGING IN BIOLOGY AND MEDICINE, 5254:431-436 (2003), copy obtained from British Library
1009	Yan Sun et al., <i>Fiber Optic Direct-Sensing Biosensor Applied in Detecting Biolayer Thickness of Nanometer Grade</i> , ACTA PHOTONICA SINICA, 31(6):657-661 (June 2002), copy obtained from British Library

¹ Unless otherwise stated, citations in this Petition are to the original page, column, and line numbers in the exhibits. Brackets ([]) are used in citations to refer to the sequential page numbers added to exhibits pursuant to 37 C.F.R. § 42.63(d)(2)(i).

Exhibit	Description
1010	Certified English Translation of Yan Sun et al., <i>Fiber Optic Direct-Sensing Biosensor Applied in Detecting Biolayer Thickness of Nanometer Grade</i> , ACTA PHOTONICA SINICA, 31(6):657-661 (June 2002) (“Sun”)
1011	Fang Yu et al., <i>Reflectometry Interference Spectroscopy in Detection of Hepatitis B Surface Antigen</i> , CLINICAL CHEMISTRY, 46(9):1489-1490 (September 2000) (“Yu”), copy obtained from U.S. Library of Congress
1012	U.S. Patent No. 5,804,453 (“Chen”)
1013	Andreas Brecht et al., <i>Direct monitoring of antigen-antibody interactions by spectral interferometry</i> , SENSORS & ACTUATORS B: CHEMICAL, 6:96-100 (1992) (“Brecht 1992”)
1014	Andreas Brecht et al., <i>Interferometric Immunoassay in a FIA system: a sensitive and rapid approach in label-free immunosensing</i> , BIOSENSORS & BIOELECTRONICS, 8:387-392 (1993) (“Brecht 1993”)
1015	Andreas Brecht et al., <i>Optimised layer systems for immunosensors based on the RIFS transducer</i> , FRESENIUS J. ANAL. CHEM., 349:360-366 (1994) (“Brecht 1994”)
1016	Andreas Brecht et al., <i>A direct optical immunosensor for atrazine detection</i> , ANALYTICA CHIMICA ACTA, 311:289-299 (1995) (“Brecht 1995”)
1017	Andreas Brecht et al., <i>Recent developments in optical transducers for chemical or biochemical applications</i> , SENSORS AND ACTUATORS B, 38-39:1-7 (1997) (“Brecht 1997”)
1018	W. Rudolf Seitz, <i>Chemical Sensors Based on Immobilized Indicators and Fiber Optics</i> , CRITICAL REVIEWS IN ANALYTICAL CHEMISTRY, 19(2):135-173 (1988) (“Seitz”)
1019	Ping Hua et al., <i>Integrated Optical Dual Mach-Zehnder Interferometer Sensor</i> , IEEE TECHNICAL DIGEST., CLEO/PACIFIC RIM 2001, 4TH PACIFIC RIM CONFERENCE ON LASERS AND ELECTRO-OPTICS (Chiba, Japan July 15-19, 2001) (“Hua”)

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1020	Maura Kasper et al., <i>Quantification of quaternary mixtures of alcohols: a comparison of reflectometric interference spectroscopy and surface plasmon resonance spectroscopy</i> , MEASUREMENT SCIENCE & TECHNOLOGY, MEAS. SCI. TECHNOL., 15:540-548 (Feb. 2004) (“Kasper”)
1021	Piotr Zalicki et al., <i>Cavity ring-down spectroscopy for quantitative absorption measurements</i> , J. CHEM. PHYS., 102(7):2708-2717 (1995) (“Zalicki”)
1022	Jay L. Bock, <i>The New Era of Automated Immunoassay</i> , AM. J. CLIN. PATHOL., 113:628-646 (2000) (“Bock”)
1023	Peter B. Lippa et al., <i>Immunosensors- principles and applications to clinical chemistry</i> , CLINICA CHIMICA ACTA, 314:1-26 (2001) (“Lippa”)
1024	Peter E. Andreotti et al., <i>Immunoassay of infectious agents</i> , BIOTECHNIQUES EURO EDITION, 850-859 (“Andreotti”)
1025	Excerpt of Tuan Vo-Dinh et al., <i>Biosensors for Medical Applications</i> , in BIOMEDICAL PHOTONICS HANDBOOK 20 (2003) (“Vo-Dinh”)
1026	Aldo Roda, <i>Discovery and development of the green fluorescent protein</i> , GFP: the 2008 Nobel Prize, ANAL. BIOANAL. CHEM., 396:1619-1622 (2010) (“Roda”)
1027	P. H. Harding et al., <i>The Adhesion Promotion Mechanism of Organofunctional Silanes</i> , J. APPLIED POLYMER SCIENCES, 67:1025-1033 (1998) (“Harding”)
1028	Weiping Qian et al., <i>Immobilization of Antibodies on Ultraflat Polystyrene Surfaces</i> , CLINICAL CHEMISTRY, 46(9):1456-1463 (2000) (“Qian”)
1029	John D. Lytle et al., <i>Wideband optical transmission properties of seven thermoplastics</i> , APPLIED OPTICS, 18(11):1842-1846 (1979) (“Lytle”), copy obtained from University of Wisconsin-Madison Library
1030	N. F. Leite et al., <i>Dielectric constant, optical transmission, and thermal diffusivity monitoring of iodine-impregnated polystyrene films</i> , J. APPLIED POLYMER SCIENCE, 39:1361-1373 (1990) (“Leite”)

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1031	Sonja Krause et al., <i>Refractive Index-Temperature Measurements on Anionically Polymerized Polystyrene</i> , J. POLYMER SCIENCE, 19:1925-1928 (1981) (“Krause”)
1032	U.S. Patent No. 6,174,291 (“McMahon”)
1033	U.S. Department of Defense, Interface Standard, MIL-STD-348B (April 20, 1988) (“MIL-STD-348B”)
1034	Thomas S. Laverghetta, <i>Microwave Materials and Fabrication Techniques</i> (Artech House Publishers 2000) (“Laverghetta”), copy obtained from U.S. Library of Congress
1035	MetroTek 2004 Product Catalog
1036	Xiao Ying Lu et al., <i>Evaluation of Protein Adsorption on Chitosan Surfaces with Reflectometry Interference Spectroscopy</i> , BIOSENSORS 1(5):148-160 (2001) (“Lu”)
1037	<i>Sartorius Bioanalytical Instruments, Inc. v. Gator Bio, Inc.</i> , Case No. 5:22-cv-01417, ECF No. 28, Amended Complaint (“Sartorius Amended Complaint”)
1038	R.G. Heideman et al., <i>Remote opto-chemical sensing with extreme sensitivity: design, fabrication and performance of a pigtailed integrated optical phase-modulated Mach–Zehnder interferometer system</i> , SENSORS & ACTUATORS B, 61:100-127 (1999).
1039	Luna Website, <i>About Luna</i> , available at https://lunainc.com/about-luna
1040	Jennifer L. Elster et al., <i>Optical fiber extrinsic Fabry-Perot interferometric (EFPI)-based biosensors</i> , PROC. SPIE 3911, BIOMEDICAL DIAGNOSTIC, GUIDANCE, AND SURGICAL-ASSIST SYSTEMS II (2000)
1041	Hiroshi Terui et al., <i>Refractive-index-adjustable SiO₂-Ta₂O₅ films for integrated optical circuits</i> , APPL. PHYS. LETT. 32: 666 (1978)
1042	Zhenxin Cao et al., <i>Gold and Silver Film Optical Fiber SPR Sensors</i> , ACTA PHOTONICA SINICA, 33(10):1169-1171 (Oct 2004) (“Cao”)
1043	Declaration of Seema Rampersad regarding Sun

Exhibit	Description
1044	Declaration of Seema Rampersad regarding Yang
1045	British Library Certification regarding Yu
1046	British Library Certification regarding Brecht 1997
1047	British Library Certification regarding Cao
1048	Declaration of Rachel J. Waters regarding Lytle
1049	Declaration of Rachel J. Waters regarding Vo-Dinh
1050	Declaration of Gordon MacPherson regarding Hua
1051	Library of Congress Certification regarding Laverghetta
1052	Certificate of Copyright Registration regarding Yu
1053	Certificate of Copyright Registration regarding Yang
1054	Certificate of Copyright Registration regarding Hua
1055	Certificate of Copyright Registration regarding Bock
1056	Certificate of Copyright Registration regarding Laverghetta
1057	Certificate of Copyright Registration regarding Vo-Dinh
1058	The Fiber Optic Association, Inc., <i>Reference Guide, Connector Types and Terminology – What’s In A Name?</i> , available at https://www.foa.org/tech/ref/termination/names.html (“FOA Reference Guide”)
1059	Jim Hayes, <i>Fiber Optics, Technician’s Manual</i> , Ch. 6 (Delmar Cengage Learning, 2d ed. 2000) (“Hayes”)
1060	<i>In the Matter of Certain Bio-Layer Interferometers and Components Thereof</i> , Docket No. 3652, Complaint Exhibit 54 (“Sartorius ’585 Patent ITC Claim Chart”)

Petitioner respectfully requests *inter partes* review of claims 1-19 of U.S. Patent No. 8,305,585 (“’585 patent”). The ’585 patent is directed to a fiber-optic probe for detecting the presence of a substance of interest (analyte) in a biological sample. (EX1001, 1:25-29.) The probe’s sensing surface includes a layer of analyte-binding molecules (e.g., antibodies) capable of binding analyte in a sample, and the presence of analyte in the sample is determined based on variations in the interference pattern produced by light reflected from the sensing surface. (*Id.*, 2:26-34.) This technique, however, was hardly new. Those in the art had coined a name for it—“reflectometric interference spectrometry” (“RIfS”)—and had been applying it for over a decade before the earliest possible priority date of the challenged claims. As detailed below, references such as Yang and Sun disclosed substantially identical RIfS probes that that when considered in the context of the art, exemplified by Yu, render the challenged claims obvious.

I. GROUNDS FOR STANDING – 37 C.F.R. § 42.104(a)

Petitioner certifies the ’585 patent is available for *inter partes* reviews and Petitioner is not barred or estopped from requesting review on the grounds herein.

II. IDENTIFICATION OF CHALLENGE – 37 C.F.R. § 42.104(b)

A. Prior Art

1. Yang

Yang is a printed publication entitled “Direct monitoring of antigen-antibody interactions by optical fiber bioprobe.” (EX1008.) It was published to participants

of the Third International Conference on Photonics and Imaging in Biology, held in Wuhan, China on June 8-11, 2003, and later republished on December 8, 2003 in Proceedings of SPIE, volume 5254, pages 431-436. (*Id.*, [2].)

Yang is prior art under 35 U.S.C. § 102(a).² It was publicly accessible before the applicable priority date,³ as early as June 2003 when it was made available to conference participants and no later than February 5, 2004 when it was made available at the British Library. (*Id.* (bearing stamp date of February 5, 2004); EX1044, [1], [5]-[6], [13] (explaining Yang was cataloged and publicly available at British Library by February 5, 2004; attaching pages with library stamps bearing same date); EX1002, 45 n.86 (explaining that SPIE conference papers are made available to conference participants at beginning of conference); EX1053 (copyright registration identifying publication date as June 8, 2003).

2. Sun

Sun is a printed publication entitled “Fiber Optic Direct-Sensing Biosensor Applied in Detecting Biolayer Thickness of Nanometer Grade.” (EX1009.) It was published in June 2002 in the periodical journal Acta Photonica Sinica, volume 31,

² Citations to 35 U.S.C. §§ 102 and 103 are to the pre-AIA versions applicable here.

³ As addressed in Section IV.C, the priority date is no earlier than March 31, 2004.

issue 6, pages 657-61. (*Id.*, [2].) Petitioner submits herewith a certified translation of Sun (EX1010) and refers to this translation when citing Sun.

Sun is prior art under 35 U.S.C. § 102(b). It was publicly accessible before the applicable priority date, no later than July 17, 2002 when it was made available at the British Library. (EX1043, [1], [5], [7] (explaining Sun was cataloged and publicly available at British Library by July 17, 2002; attaching page with library stamp bearing same date); EX1042, 1171 (later publication received by publisher in August 2003 and citing Sun, confirming Sun was actually accessed by public).

3. Yu

Yu is a printed publication entitled “Reflectometry Interference Spectroscopy in Detection of Hepatitis B Surface Antigen.” (EX1011.) It was published in September 2000 in the periodical journal Clinical Chemistry, volume 46, issue 9, pages 1489-90. (*Id.*, [4]-[6], [12]-[13].)

Yu is prior art under 35 U.S.C. § 102(b). It was publicly accessible before the applicable priority date of the challenged claims, no later than September 27, 2000 when it was made available at the Library of Congress. (EX1011, [1], [9] (certified Library of Congress stamp date of September 27, 2000); EX1045, [1], [3], [6] (British Library certification of public availability by October 11, 2000); EX1052 (copyright registration dated September 27, 2000 and identifying publication date as

September 5, 2000); EX1036, 148, 160 (article published in 2001 and citing Yu, confirming Yu was actually accessed by public).)

B. Challenged Claims and Statutory Grounds

Ground	Claims	Basis	References
1	1-19	§ 103(a)	Yang (EX1008) and Yu (EX1011)
2	1-19	§ 103(a)	Sun (EX1009, EX1010) and Yu (EX1011)

C. Claim Construction

Petitioner does not believe any terms need construction to resolve the prior-art issues presented in this Petition but reserves the right to identify terms for construction in any related litigation that may be relevant to issues there.

D. How the Challenged Claims Are Unpatentable

Petitioner provides an explanation of how the challenged claims are unpatentable in Sections V-0.⁴

E. Evidence Supporting Challenge

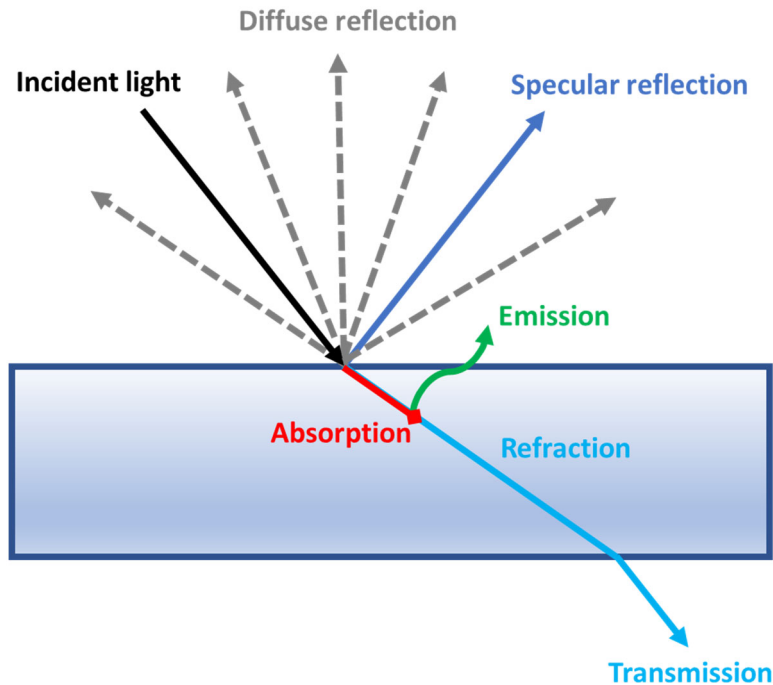
Petitioner submits herewith an expert declaration by David Schaafsma, Ph.D. (EX1002) and an Appendix of Exhibits, and further sets forth in Sections V-0 the relevance of this evidence and the specific portions that support the challenge.

⁴ All internally cross-referenced sections are incorporated by reference.

III. TECHNICAL BACKGROUND

A. General Principles of Optical Sensors

All optical sensors rely on the interaction of light with matter. (EX1002 ¶21.) As illustrated below, when a light ray is incident on a surface, there are three basic effects: (1) it can be transmitted through the surface into the medium; (2) it can be reflected at the same angle as the incident ray (specular or mirror-like reflection); and (3) it can be reflected at a different angle (diffuse reflection or scattering). (*Id.* ¶21.) If transmitted into the medium beyond the surface, the light can be absorbed by the medium, and potentially re-emitted at a different wavelength. (*Id.*) The light also can transit the medium, in which case the medium may affect the properties of the transmitted light. (*Id.*) For example, the transmitted light may experience refraction, where the incident light is transmitted at a different angle than the incident angle. (*Id.*) The transmitted light also may experience a phase shift, where the light actually slows down from its (near) maximal value in air.



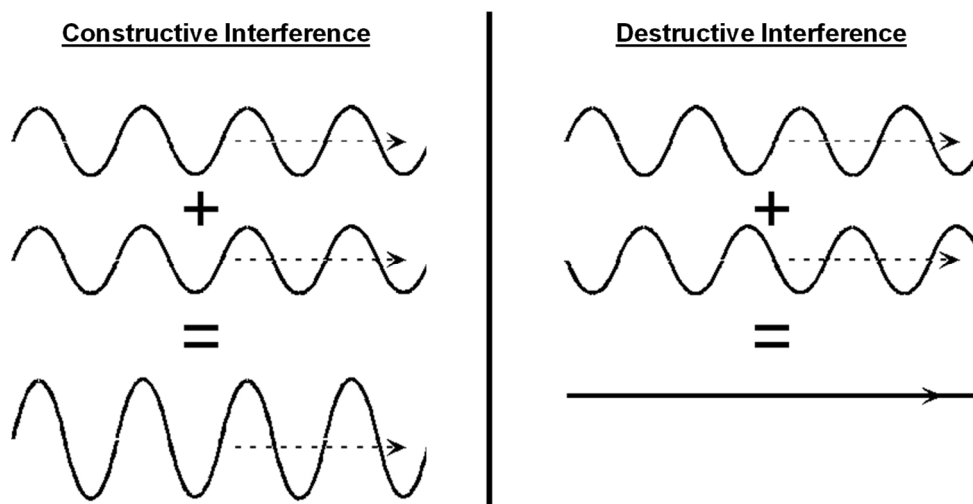
(*Id.*)

These effects occur because all materials, including air, have an index of refraction that is both different from that of a vacuum and varies with the wavelength of light. (*Id.* ¶23.) The index of refraction is an intrinsic property of a material that has a real and an imaginary part (i.e., it is a complex number), which is a mathematical way of expressing the fact that some portion of the light will propagate through the material as a refracted ray having a slower speed relative to the speed of light in a vacuum (due to the real part), and some portion of the light will be absorbed by the material (due to the imaginary part). (*Id.*) In contexts where only the real part of the refractive index is at issue, the imaginary part is omitted. (*Id.*)

When light passes from a material having a lower refractive index (real part) to a transparent material having a higher refractive index, the interface between the

materials functions as a partially reflecting surface. (*Id.* ¶24.) That is, some portion of the light will be reflected at the interface, while some portion is transmitted (continues on) and refracted. (*Id.*) Generally, the greater the disparity between the refractive indices of the two materials, the more light that is reflected at the interface. (*Id.*) Taking advantage of this property, high-refractive-index materials are often incorporated into optical systems when a higher reflectance is desired. (*Id.*)

Because light propagates as an electromagnetic wave, light beams of the same wavelength may differ in phase, and thus constructively or destructively interfere with one another. (*Id.* ¶25.) The figures below illustrate such interference between two coherent waves, which have the same wavelength and waveform. (*Id.*) When in phase, the waves constructively interfere to produce a larger-amplitude wave. (*Id.*) Conversely, when out of phase, the waves destructively interfere to produce smaller-amplitude wave, potentially cancelling out one another. (*Id.*) Depending on the phase difference, there may be both constructive and destructive interference.



(*Id.*) The optical phase of light has been used for nearly two centuries as a means of probing various physical effects, including light-matter interaction. (*Id.* ¶26.) Phase differences between beams of light can be discriminated using instruments called “interferometers.” (*Id.*)

B. Optical Biosensors

Optical biosensors are devices that employ one or more assay techniques to detect the presence of an analyte molecule in a biological sample based on changes in the optical properties of the system. (EX1002 ¶29.) Nearly all optical biosensors employ some type of analyte-binding mechanism, where analyte molecules of the particular compound to be detected are “captured” by analyte-binding molecules immobilized on a surface or substrate. (*Id.*; EX1023, 2, 6, Fig. 1; EX1024, 840.) When the target analyte binds to the analyte-binding molecules, and other potentially interferant molecules are washed away, what remains will affect the optical properties of the system, which the biosensor measures to detect the presence of analyte. (EX1002 ¶29; EX1023, 2, 6, Fig. 1; EX1022, 629.)

Before the 2003/2004 timeframe, biosensors applying various readout methods were known, including methods that detect changes in color or the emitted fluorescence of labeled reagents, as well as “label-free” interferometric methods that detect phase shifts in light to determine how much analyte is present. (EX1002 ¶¶30-37; EX1024, 853; EX1018, 145, 168; EX1013, abstract.)

C. Reflectometric Interference Spectroscopy (RIfS)

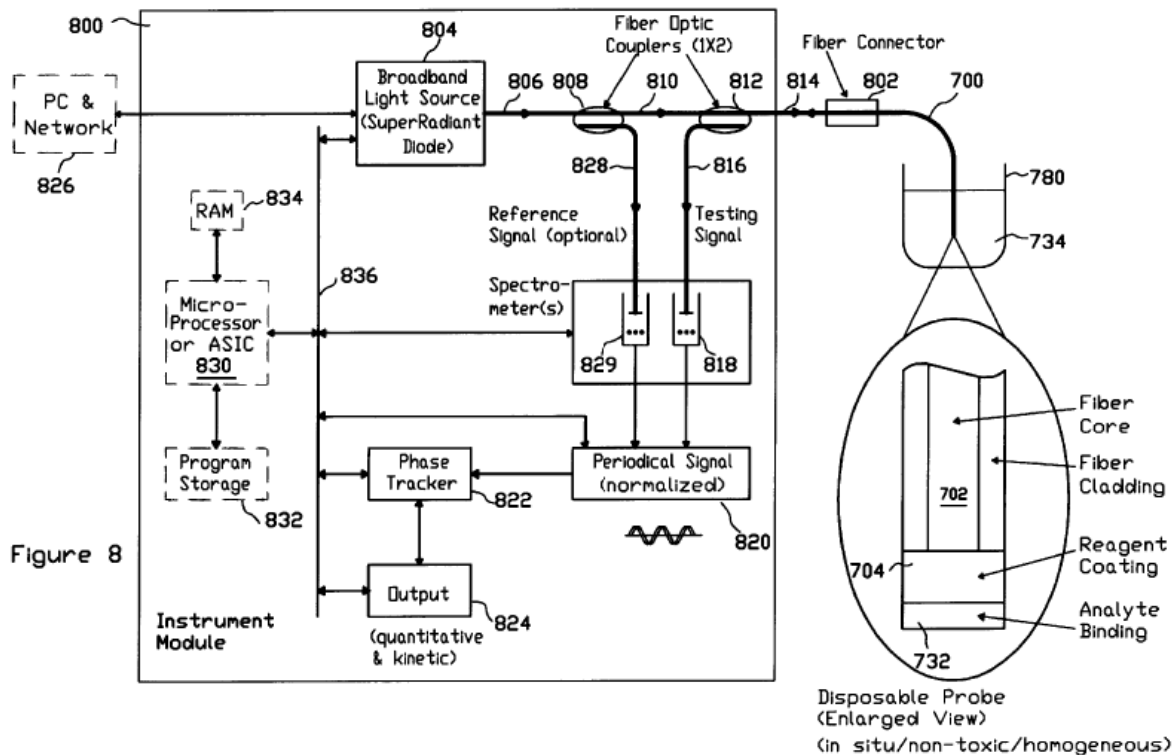
By the early 1990s, Brecht et al. developed and described the use of a label-free fiber-optic biosensor employing a method they called “reflectometric interference spectroscopy” (“RIfS”). (EX1002 ¶38; EX1013, abstract; EX1014, abstract; *see also* EX1012, 1:10-14.)

RIfS uses a thin film on a substrate or the end of an optical fiber to interact with analyte in a sample and provide an interferometric readout. (EX1002 ¶38; EX1015, 361; EX1016, 290.) The underlying principle is that when a beam of white light passes through the thin film, it generates two partially reflected light beams, one at each interface of the film. (EX1002 ¶38.) The reflected beams interfere with one another, resulting in an interference pattern that varies with wavelength and can be measured using a spectrometer and that is indicative of the optical thickness (optical path length) of the film (i.e., the product of the actual film thickness and its refractive index). (*Id.*) The binding of analyte to the film, in turn, increases the film thickness, resulting in a phase shift in the interference pattern that can be measured to detect the presence of analyte in a sample. (*Id.*)

1. Admitted Prior Art Chen

U.S. Patent No. 5,804,453 (“Chen”) (EX1012), an admitted prior-art patent, describes a basic RIfS setup. As shown in Figure 8 (copied below), white light from a light source 804 is transmitted through a Y-shaped optical-fiber coupler 812 and

an optical waveguide/fiber 814 to a probe 700, where at the distal end⁵ of the probe the light is reflected back through the optical coupler to a detector (spectrometer):



(EX1012, 11:29-43, FIG. 8; EX1002 ¶39.)

Chen explains that the probe 700 is “disposable” and is optically connected to optical fiber/waveguide 814 via a connector 802, which “may be part no. BFA-MM manufactured by MetroTek.” (EX1012, 12:25-26, 13:9-11.) Part no. BFA-MM is a “strong ‘clothespin’ type adaptor” for holding an optical fiber in place. (EX1035, 7; EX1002 ¶39.) Other standard connectors, including screw-type SMA

⁵ The terms “proximal” and “distal” refer to the ends closest to and furthest from the light source, respectively.

(SubMiniature-Type-A) connectors, also were known in the art and commercially available. (EX1034, 266; EX1033, 310-1-310-2; EX1002 ¶39.)

As shown in Figures 7a-7b of Chen, the probe itself comprises an optical fiber/waveguide 702 that is coated at the distal end with a layer of analyte-binding reagent 704 (e.g., an antibody, antigen, or other molecule) that binds analyte 732 in a sample solution to form a biolayer.

Figure 7a

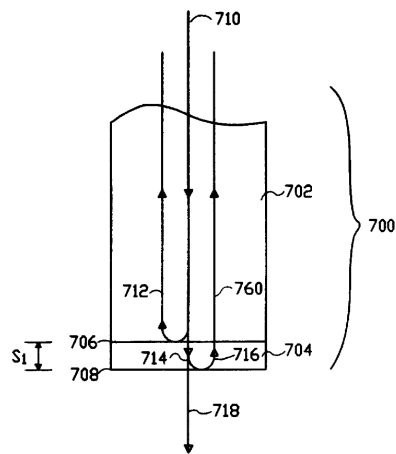
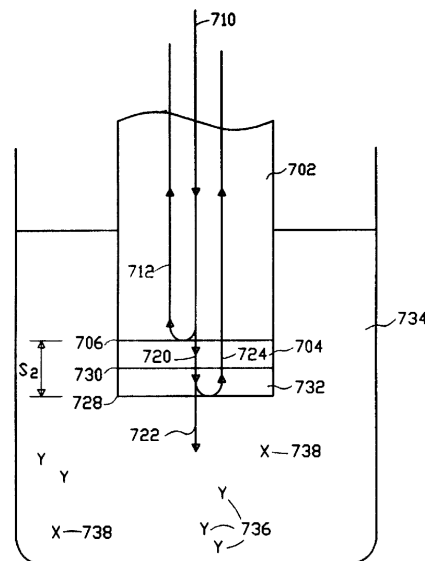


Figure 7b

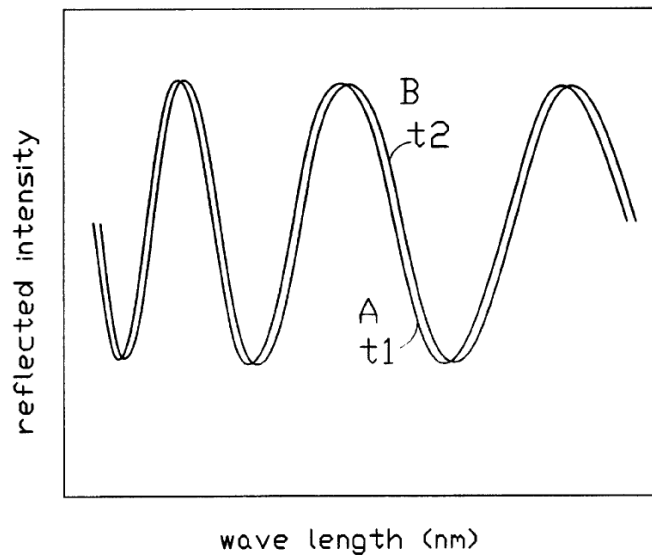


(EX1012, 9:10-20, 10:45-57, FIGS. 7a-7b.)

During a detection operation, incident light is partially reflected at the interfaces (reflecting surfaces) on either side of this biolayer (i.e., the interface between the optical fiber and the biolayer and the interface between the biolayer and the sample solution). (*Id.*, 6:60-7:2, 7:50-60, 10:25-30, 11:33-44.) The light reflected back to the detector from these interfaces generates an interference pattern

(reflectance spectrum) that is indicative of the optical thickness of the biolayer, and changes in the biolayer thickness due to analyte binding are detected as phase shifts in the interference pattern, similar to that shown in Figure 4.

Figure 4
(Prior Art)



(*Id.*, 5:34-40, FIG. 4.)

2. Biolayer Films Used with RI_fS

Chen states that the analyte-binding reagent that comprises the biolayer may be formed by “coating the [probe] tip with a solution having a predetermined concentration of the [analyte binding] reagent for a predetermined time period” and notes that “[o]ther methods...will be apparent to those skilled in the art.” (EX1012, 9:16-24.) In this regard, it was well established before the 2003/2004 timeframe that the substrate/optical-fiber portion of a RI_fS sensor may be first coated with a

polymer layer to help adsorb and immobilize antibodies (or other analyte-binding molecules). (EX1002 ¶45; EX1010, 659; EX1011, 1489; EX1017, 4.)

It also was well established that the polymer layer should have a refractive index similar to that of the biolayer (formed by the analyte-binding molecules and bound analyte) so that it functions as an “interference layer” that is effectively an extension of the biolayer and increases the separation between the reflecting surfaces on either side of the biolayer. (EX1002 ¶46; EX1017, 4; EX1015, 362; EX1011, 1489; EX1010, 659.) Thus, when the thickness of the biolayer increases due to analyte binding, the result is an increase in the optical thickness (optical path length) of the interference layer, which can be measured “very sensitively” based on the interference pattern of the reflected light. (EX1002 ¶46; EX1017, 3-4.) To maximize sensitivity, it is necessary to keep the interference layer thin, so that small changes will represent a larger fraction of the total optical path. (EX1002 ¶47.) The use of such thin interference layers (from a few hundred nanometers to a few micrometers) likewise was well established. (*Id.*; EX1017, 3; EX1010, 659; EX1011, 1489.)

Further, it was known that the sensitivity of a RIfS system improves with the strength of the reflected light signal and that the signal strength may be enhanced by incorporating a thin layer of a relatively high-refractive-index material (e.g., tantalum pentoxide (Ta_2O_5)) as a reflecting surface at the interface between the

substrate/optical-fiber portion and the interference layer. (EX1002 ¶¶48-49; EX1011, 1489; EX1008, 430; EX1016, 291-92; EX1015, 362-63; *see also* EX1019.) In fact, by 1995, “[i]nterference layers for RIFS” that incorporated a reflecting surface of “10 nm Ta₂O₅” were commercially available. (EX1002 ¶¶48-49; EX1016, 291-92.)

IV. THE ’585 PATENT

A. Overview

The ’585 patent is directed to an apparatus for “detecting the presence, amount, or rate of binding of one or more analytes in a sample...based on fiber optic interferometry.” (EX1001, 1:25-28.) In the “Background of the Invention,” the ’585 patent acknowledges that “[d]iagnostic tests based on a binding event between members of an analyte-anti-analyte binding pair are widely used in medical, veterinary, agricultural and research applications.” (*Id.*, 1:30-33, 1:55.) The ’585 patent further acknowledges that the prior-art Chen patent (discussed above) “discloses a fiber-optic interferometer assay device designed to detect the binding analyte to a fiber-optic end surface” based on “phase shifts” in the “interference signal” produced by light reflected from the surface. (*Id.*, 1:55-67.)

According to the ’585 patent, “[t]he present invention is designed to overcome [a] limitation” in Chen’s apparatus, namely that it does not produce “readily observable changes” in the spectral extrema (peaks and valleys) of the interference

signal “within the range of a conventional visible-light spectrometer” “between about 450-700 nm.” (*Id.*, 2:1-15.) The ’585 patent does not explain the basis for this conclusion, as Chen in fact describes the use of a “tungsten halogen source” and a “600 to 700 nm spectrometer.” (EX1012, 7:60-62, 11:1-15; EX1002 ¶54.)

The ’585 patent nonetheless proceeds to describe a probe (depicted below in Figure 2) substantially similar to Chen’s and other existing RfS sensors. The disclosed probe comprises an optical assembly 26. (EX1001, 7:14-17, FIG. 2.) The optical assembly includes an optical-fiber portion 32 and a transparent optical element 38 that is sandwiched between two reflecting surfaces: (1) a first reflecting surface 42 that is formed as a layer of analyte-binding molecules 44 on the distal end of the optical element 38, and (2) a second reflecting surface 40 that is provided at the interface between the optical-fiber portion 32 and the optical element 38.

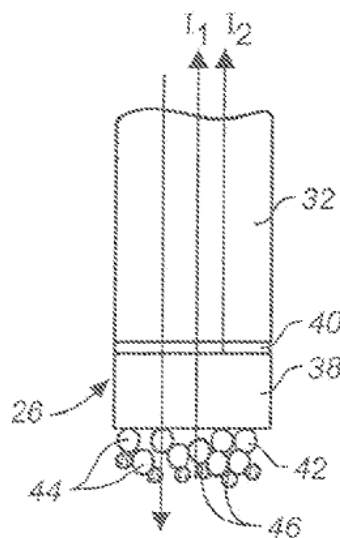


FIG. 2

(*Id.*, 7:17-33, 7:50-60, FIG. 2.)

The disclosed probe uses known RIfS principles to detect analyte binding. (EX1002 ¶56.) When light is transmitted to the optical assembly, some of the light is partially reflected at the second reflecting surface 40 (forming reflected beam I₂), while some of the light continues on and is further partially reflected at the first reflecting surface 42 (forming reflected beam I₁). (EX1001, 2:28-30, 7:17-28, FIG. 2.) These reflected beams interfere with one another and are routed back through the optical fiber to a detector unit 28 where they are detected as an interference pattern or signal (reflectance spectrum). (*Id.*, 2:30-31, 6:33-35, 8:17-27.) As the analyte-binding molecules 44 bind analyte molecules 46 in a sample, the optical thickness of the optical element/biolyer increases, which is detected as a phase shift in the resulting interference pattern. (*Id.*, 8:21-27.)

Purportedly to enhance such detection, the '585 patent states that “an important feature of the invention” is that “the thickness ‘d’ of the optical element between its distal and proximal surfaces, i.e., between the two reflecting surfaces, is at least 50 nm, and preferably at least 100 nm,” further noting an “exemplary thickness...between about 100-5,000 nm, preferably 400-1,000 nm.” (*Id.*, 7:20-25.) The described thicknesses, however, simply follow from the free spectral range of an interferometer (i.e., the spacing between peaks in a reflectance spectrum), which can be determined through routine calculations, and as discussed above, the use of interference layers of such thicknesses were known. (EX1002 ¶¶47, 57.)

The '585 patent also states that the “second reflecting surface in the optical assembly [is] formed as a layer of transparent material having an index of refraction that is substantially higher than that of the optical element, such that this layer functions to reflect a portion of the light directed onto the optical assembly.” (EX1001, 7:50-54.) According to the '585 patent, this “second reflecting layer” preferably has a “refractive index greater than 1.8,” such as tantalum pentoxide (Ta_2O_5), and a “thickness of less than 50 nm, typically between 5 and 30 nm.” (*Id.*, 7:55-60.) As noted above, however, the use of such high-refractive-index materials was likewise well established. (EX1002 ¶58; EX1016, 291-92.)

Figure 4 shows another embodiment in which an optical assembly 50 is “removably carried on the distal end of an optical fiber 52.”

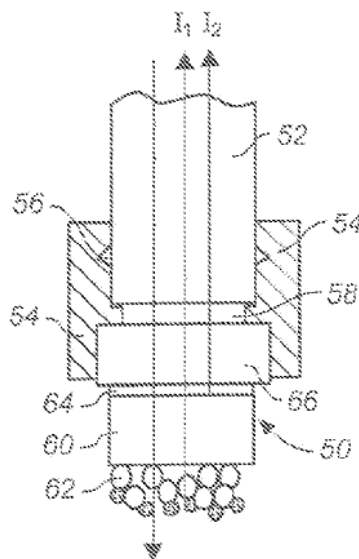


FIG. 4

(EX1001, 9:27-29, FIG. 4.) The optical assembly 50 “includes a plurality of flexible

gripping arms, such as arms 54, that are designed to slide over the end of [a] fiber and grip the fiber by engagement of an annular rim or detente 56 on the fiber with complementary shaped recesses formed in the arms.” (*Id.*, 9:29-33, FIG. 4.) Similar to the first embodiment, the optical assembly 50 includes an optical element 60 and “further includes a second optical element 66 whose thickness is preferably greater than 100 nm, typically at least 200 nm, and whose index of refraction is similar to that of first optical element 60.” (*Id.*, 9:42-50, FIG. 4.) The optical elements are not limited to any particular material but are preferably constructed of “glass” or a “polymer.” (*Id.*, 7:44-49, 9:50-52)

B. Prosecution History

The ’585 patent issued from Application No. 12/790,736, filed on May 28, 2010 (“’736 application”). The ’736 application is a continuation of Application No. 12/099,751, filed on April 8, 2008 (“’751 application”), which in turn is a continuation of Application No. 10/981,901, filed on November 4, 2004.

1. Parent ’751 Application

The ’751 application, which issued as U.S. Patent No. 7,728,982 (“’982 patent”), was filed on April 8, 2008.⁶ On September 26, 2008, the Patent Office

⁶ At the time, this patent family was assigned to ForteBio, Inc. (a predecessor entity of Patent Owner). (EX1003.) Dr. Hong Tan, the lead named inventor and a real

(continued...)

examiner issued rejections finding claims 1-19 (among others) unpatentable for various reasons.⁷

The examiner rejected claims 1, 3-4, 11-13, and 15-18 (among others) as obvious over the combination of Brecht 1997 (EX1017) and Chen (EX1012). (EX1006, [60].) Specifically, the examiner found that Brecht 1997 taught all the elements of these claims with the exception of (1) a detachable optical assembly that is “adapted for coupling to [a] light source through a mechanical coupling that engages [the] optical element with [the optical] fiber” and (2) a second optical element having a thickness “greater than 100 nm” or “200 nm.” (*Id.*, [61]-[65].) Regarding the mechanical coupling, the examiner noted that “Chen teaches a fiber connector (Fig. 8, 802) which removably attaches the optical assembly (Fig. 8, 700) to the fiber tip (Fig. 8, the tip of fiber 814)” and found that it would have been “obvious...to modify Brecht [1997] by adding a fiber connector.” (*Id.*, [65]-[66].)

party-in-interest, was employed by ForteBio but left the company before any substantive office actions were issued and was not involved in prosecuting the '751 application or the later-filed '736 application.

⁷ The examiner only rejected claim 19 for obviousness-type double patenting based on the claims of U.S. Patent No. 7,394,547, which Patent Owner overcame via a terminal disclaimer. (EX1006, [73], [127].)

And the examiner found that it would have been obvious to determine the “optimum or workable range” for the thickness of the second optical element. (*Id.*, [66].)

The examiner also rejected claims 2 and 8-10 (among others) as obvious over the combination of Brecht 1997, Chen, and Yang. (*Id.*, [66].) The examiner found that Brecht 1997 and Chen taught all the elements of these claims with the exception of a “second reflecting surface” that (1) has “an index of refraction greater than the refractive index of said transparent material [optical element]” and “greater than 1.8,” (2) “comprises Ta₂O₅,” and (3) has a thickness “between 5 nm and 50 nm.” (*Id.*, [67].) The examiner, however, found that a second reflecting surface having these properties would have been obvious based on Yang, which the examiner explained “teach[es] the use of Ta₂O₅ with a thickness of 10-20nm...and a transparent binding layer having a thickness of 550-600nm.” (*Id.*, [68]-[69].)

The examiner further rejected claims 5-7 as obvious over the combination of Brecht 1997, Chen, and Brecht 1992 (EX1013), finding that Brecht 1992 taught the additional requirements of these claims of the use of a transparent layer of polystyrene or SiO₂ having a refractive index less than 1.8. (*Id.*, [69]-[70].) And the examiner rejected claim 14 as obvious over the combination of Brecht 1997, Chen, and Hjelme (U.S. Patent Publication No. 2003/0112443), finding that Hjelme taught a “lens system” as required by this claim. (*Id.*, [70]-[71].)

In a response dated December 19, 2008, Patent Owner amended the independent claims to require an “optical element [that] compris[es] flexible gripping arms that slide over and grip the optical fiber to removably attach [the] optical element to the optical fiber.” (EX1006, [92], [95].) Relying on this amendment, Patent Owner asserted that “Chen does not [] describe any detachment mechanism and does not describe detachment of the probe,” and that Chen “also fails to disclose flexible gripping arms that slide over and grip the fiber.” (*Id.*, [97]-[98], [100].) Notably, Patent Owner did not address the examiner’s findings that the prior art taught an optical assembly having the other claim elements.

Accepting Patent Owner’s assertion, the examiner issued a notice of allowance on April 6, 2009, reasoning that “the prior art of record fails to teach an optical element comprising flexible gripping arms that slide over and grip the optical fiber to removably attach the optical element to the optical fiber... in combination with the remaining limitations of claim 1.” (EX1006, [127].)

2. ’736 Application

The ’736 application, which issued as the ’585 patent, was filed on May 28, 2010 and overseen by a different examiner than the parent ’751 application. Notably, claims 1-19 submitted with the ’736 application (corresponding to issued claims 1-19 of the ’585 patent) were identical to claims 1-19 submitted with the parent ’751 application. (*Compare* EX1006, [42]-[43], *with* EX1007, [42]-[43].)

But although the examiner in the '751 prosecution rejected these claims and allowed them only after they were amended to require a specific attachment mechanism with “flexible gripping arms,” the examiner in the '736 prosecution allowed these same claims without issuing any prior-art rejections or requiring any amendments, and without providing any substantive comments or explanation. Rather, the only rejection the examiner in the '736 prosecution issued was for obviousness-type double patenting based on the '751 application ('982 patent), which Patent Owner overcame by submitting a terminal disclaimer. (EX1007, [202]-[209], [241].)

C. Priority Date

The '585 patent purports to claim priority to U.S. Provisional Application No. 60/558,381, filed on March 31, 2004 (“’381 provisional”) (EX1004), and No. 60/518,068, filed on November 6, 2003 (“’068 provisional”) (EX1005). For a patent claim to be entitled to the filing date of a provisional application, the provisional application must provide written-description and enablement support for the later-issued claim. 35 U.S.C. § 119(e)(1); *New Railhead Mfg., LLC v. Vermeer Mfg. Co.*, 298 F.3d 1290, 1294-95 (Fed. Cir. 2002). The '068 provisional, however, does not provide any written-description support for an optical element that is “removably attached to the tip of [an] optical fiber,” as recited in independent claim 1 and

required by all the challenged claims.⁸ (*Compare* EX1004, with EX1005, FIG. 4; EX1002 ¶61.) The lack of disclosure is notable given Patent Owner’s assertions during prosecution that the prior art failed to teach “any detachment mechanism.” (EX1006, [97]-[98], [100].) Thus, Petitioner assumes the challenged claims have a priority date no earlier than the March 31, 2004 filing date of the ’381 provisional.

D. Person of Ordinary Skill in the Art

A person of ordinary skill in the art (“POSA”) pertaining to the ’585 patent would have had the equivalent of a master’s degree in physics, optics, or a related discipline providing knowledge of optics and optical materials, and 2-3 years of experience designing, developing, or testing fiber-optic biosensors. (EX1002 ¶63.)

V. GROUND 1: THE COMBINATION OF YANG AND YU RENDERS CLAIMS 1-19 OBVIOUS UNDER 35 U.S.C. § 103(a)

A. Yang

Yang is directed to applications of “[r]eflectometric interference spectroscopy (RIfS),” which Yang explains is “a successful label-free method” of detecting analytes in a sample. (EX1008, 431.) As shown in Figure 3, Yang describes a RIfS setup in which white light from a “light source” is transmitted through a “‘Y’ type

⁸ To the extent this feature would have been obvious, obviousness does not satisfy the written-description requirement. *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997).

[Y-shaped] optical fiber” to the distal end of a “bioprobe” and then reflected back to a detector (“spectrometer”):

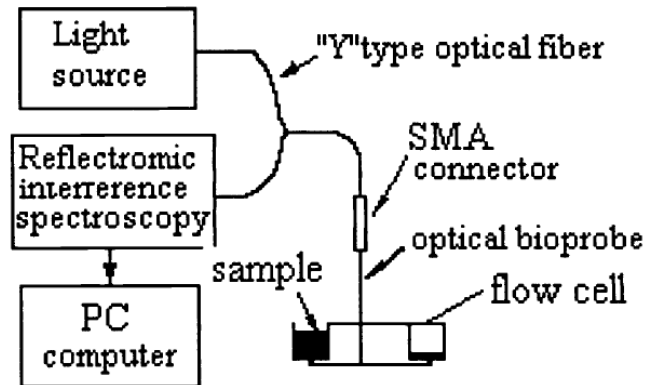


Fig 3 Sketch map of the Rifs testing system

(*Id.*, 433, Fig. 3.) The probe includes an optical-fiber portion (shown in Fig. 1b) that is separate from the Y-shaped fiber, and the two fibers are connected via a “standard SMA905 connector,” a common screw-type coupling with male and female components that removably engage one another. (*Id.*, 433, Fig. 1b; EX1034, 266; EX1033, 310-1-310-2; EX1002 ¶¶46, 92.)

The optical-fiber portion of the probe is coated on its distal end with a thin layer of tantalum pentoxide (Ta_2O_5) having a thickness of approximately “10~20nm” and a “transparent interference layer” of “special material” (referred to

throughout this Petition as the “SM-interference layer”)⁹ having a thickness of approximately “550~650nm.” (EX1008, 432-33, Fig. 1b.) Yang explains that the purpose of the SM-interference layer is to serve as a “transducer” for “biomolecular interaction analysis.” (*Id.*) For example, as shown in Figure 1b, a layer of antibodies is immobilized on the distal surface of the SM-interference layer to bind antigen molecules (“analyte”) present in a sample.

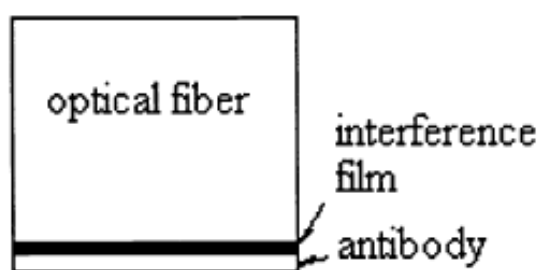


Fig 1b Structure of the bioprobe

(*Id.*, 432, 434, Fig. 1b.)

As shown in Figure 1a, during the operation of Yang’s system, when incident light is transmitted to the distal end of the probe, the light is partially reflected from each side of the SM-interference layer, resulting in a measurable interference pattern (reflectance spectrum).

⁹ Because Yang also refers to the Ta₂O₅ layer as an “interference layer” (EX1008, Yang, 432), Petitioner uses the term “SM-interference layer” where possible to refer to the interference layer of “special material.”

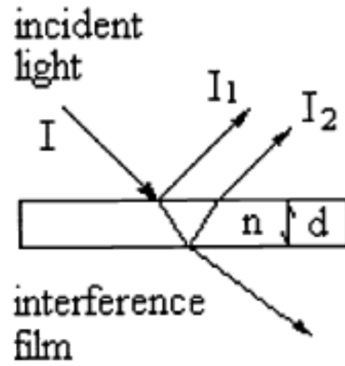


Fig 1a Schematic of the light path in the bioprobe

(*Id.*, 432, Figs. 1a, 2, 4.)

The binding of analyte to the immobilized antibodies increases the “optical thickness” of the SM-interference layer, which is manifested as a “phase shift” in the interference pattern, as shown in Figure 6.

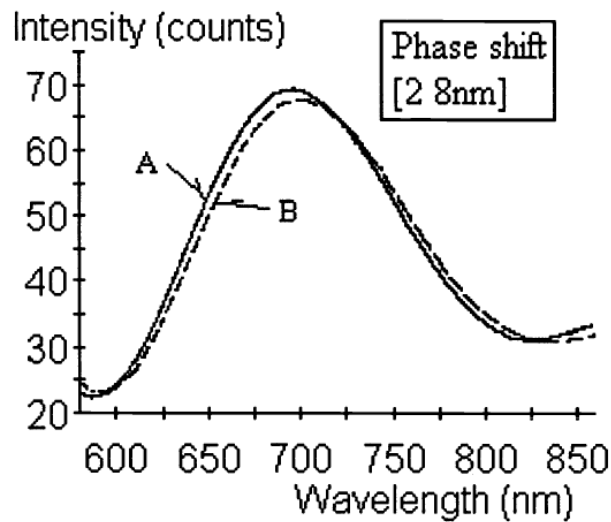


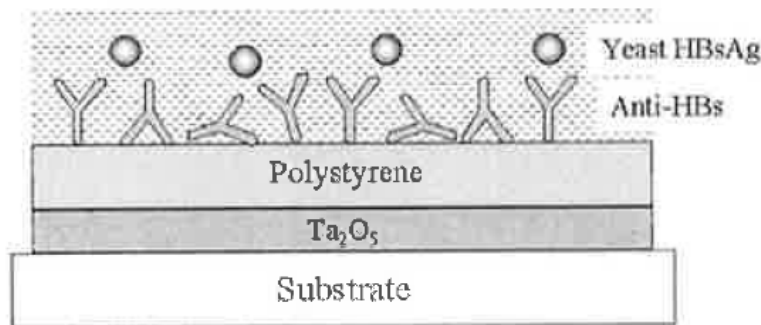
Fig 6 Caused shifting of the reflectance spectrum by the binding of protein

(*Id.*, 433-34, Fig. 6.) Yang explains that this allows “binding events [to be] observed by detection of changes of optical thickness in real time.” (*Id.*, 432.)

B. Yu

Yu states at the outset that “[o]ptical biosensors are of increasing interest for real-time detection of analytes without the use of additional labeled reagents” and proceeds to describe an application of “[r]eflectometry interference spectrometry (RIfS).” (EX1011, 1489.) Specifically, Yu describes an RIfS setup in which white light from a light source is directed through a “Y-shaped” optical fiber to a “transducer chip” and reflected back to a detector (spectrometer). (*Id.*)

Yu’s Figure 1(A) illustrates an exemplary “transducer chip” that comprises a substrate coated with a “10-nm” layer of tantalum pentoxide (Ta_2O_5) and a “~650 nm” interference layer of polystyrene, on which a layer of antibodies (anti-HBg) is adsorbed and immobilized. (*Id.*, 1489, Fig. 1(A).) When antigen (HBgAg) binds to the antibody layer, the optical thickness of the interference layer/biolyer increases.

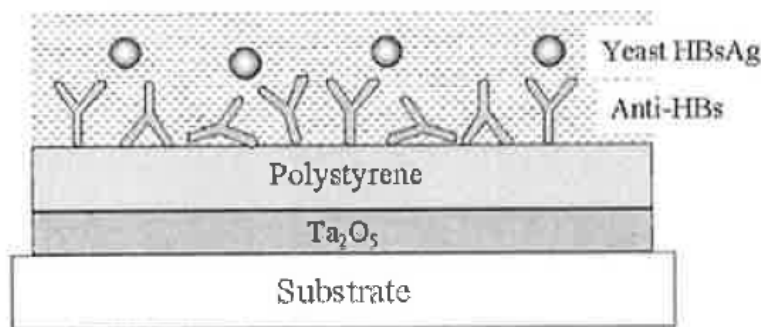


(*Id.*) Yu explains that the polystyrene layer “serve[s] as both [an] interference film and [a] hydrophobic surface for immobilization of antibodies.” (*Id.*) Citing to earlier work by Brecht et al, Yu further explains that the purpose of the thin layer of Ta_2O_5 is to “enhance the interference contrast.” (*Id.*; EX1015, 362-363.)

During the operation of Yu's system, incident light is partially reflected from the Ta_2O_5 layer and is further partially reflected from the distal surface of the biolayer (formed by the antibody layer and any bound analyte). (EX1011, 1489; EX1002 ¶74.) The reflected light beams are guided back through the Y-shaped optical fiber to the spectrometer, where changes in the optical thickness are detected based on phase shifts in the interference pattern produced by the reflected light. (EX1011, 1489; EX1002 ¶74.)

C. Motivation to Combine Yang and Yu

Yang discloses a RIfS sensor comprising a “transparent interference layer” of “special material” (SM-interference layer) having a thickness of approximately “550~600nm.” (EX1008, 432-33, Figs. 1a, 1b; EX1002 ¶76; *see* Section V.A above.) Although Yang does not expressly identify this “special material,” such transparent interference layers were commonly used in this type of device and were made from materials familiar to POSAs. (EX1002 ¶77.) Yu, in turn, provides a known example of a RIfS sensor using a polystyrene interference layer.



(*Id.* ¶78; EX1011, 1489, Fig. 1(A); *see* Section V.B above.)

A POSA would have been motivated to use polystyrene as the SM-interference layer of Yang's probe for several reasons. As an initial matter, this would have merely substituted a well-known element (an interference layer) of a similarly structured RIfS sensor according to its established function to yield predictable results. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 417 (2007). Indeed, both Yang and Yu describe RIfS sensors with transparent interference layers having similar thicknesses of approximately "550~600nm" (Yang) and "~650 nm" (Yu). (EX1008, 432; EX1011, 1489; EX1002 ¶80.) Both sensors incorporate a thin Ta₂O₅ layer as a reflecting surface between the optical fiber/substrate and the interference layer, and both utilize a layer of antibodies that are immobilized on the interference layer to bind analyte in a sample. (EX1008, 432, Fig. 1a; EX1011, 1489, Figure 1(A); EX1002 ¶80.) Further, both sensors detect analyte binding based on phase shifts in the interference pattern of white light reflected from each side of the interference layer. (EX1008, 432-434, Figs. 1a, 2, 6; EX1011, 1489, Figure 1(A); EX1002 ¶80.)

To be sure, Yu's sensor is a "transducer chip" that comprises a flat "substrate," while Yang's sensor is a probe in which the "substrate" is the optical-fiber portion of a probe. (EX1008, 432-33, Figs. 1b, 3; EX1011, 1489, Figure 1(A); EX1002 ¶81.) A POSA, however, would not have found this significant in applying Yu's teachings to Yang's probe, particularly given that Yu's chip and Yang's probe

operate based on the same RIfS principle of white-light interference at a transparent thin film, and given that the interference layer would serve the same purpose in both. (EX1002 ¶¶81.) Coating the end of an optical fiber with a polymer layer also was well known in the art, and commercial services for this type of coating existed at the time. (*Id.* ¶¶81, 84.) Moreover, the transition from a larger substrate to an optical fiber was a standard progression in the development of optical-fiber systems. (*Id.*)

Yu further provides explicit motivations for using polystyrene as the SM-interference layer of Yang's probe. For example, Yu motivates a POSA to use a "transparent polystyrene layer" in a RIfS sensor by explaining that it "serves as both [an] interference film and [a] hydrophobic surface for immobilization of antibodies." (EX1011, 1489; EX1002 ¶82.) This is the same purpose Yang's "special material" serves, which Yang explains functions as an "interference layer" and a "transducer" for "biomolecular interaction analysis." (EX1008, 432, 434; EX1002 ¶82.)

Yu also motivates the use of polystyrene as the SM-interference layer of Yang's probe by explaining that the purpose of the thin layer of Ta₂O₅ (used in both sensors) is to "enhance the interference contrast." (EX1011, 1489; EX1002 ¶83.) Others had similarly reported that the signal-to-noise ratio and sensitivity of reflectometric analyses could be improved by incorporating a thin layer of a relatively high-refractive-index material, such as Ta₂O₅, as a reflecting surface. (EX1016, 291-92; EX1015, 362-63; EX1019, 156-157; EX1002 ¶83.) Significantly,

as a POSA would have recognized, for Yang's Ta₂O₅ layer to provide these benefits, the "special material" must be selected so that the Ta₂O₅ layer has a greater refractive index. (EX1002 ¶83.) This provides further motivation to use polystyrene (which has a lower refractive index than Ta₂O₅) as the "special material" comprising the SM-interference layer of Yang's probe. (*Id.*)

D. Claims 1-19 Would Have Been Obvious in View of Yang and Yu

1. Claim 1

a. [1P]: "An optical assembly for use in detecting an analyte in a sample based on interference"

To the extent the preamble is limiting, Yang discloses "[a]n optical assembly for use in detecting an analyte in a sample based on interference." In Yang's RIfS system, the "optical assembly" comprises a "'Y' type [Y-shaped] optical fiber" coupled to an "optical fiber bioprobe" that detects the binding of antigen (i.e., "analyte") to an immobilized layer of antibodies (i.e., "analyte-binding molecules"), as shown in Figures 1b and 3 and described above in Section V.A.

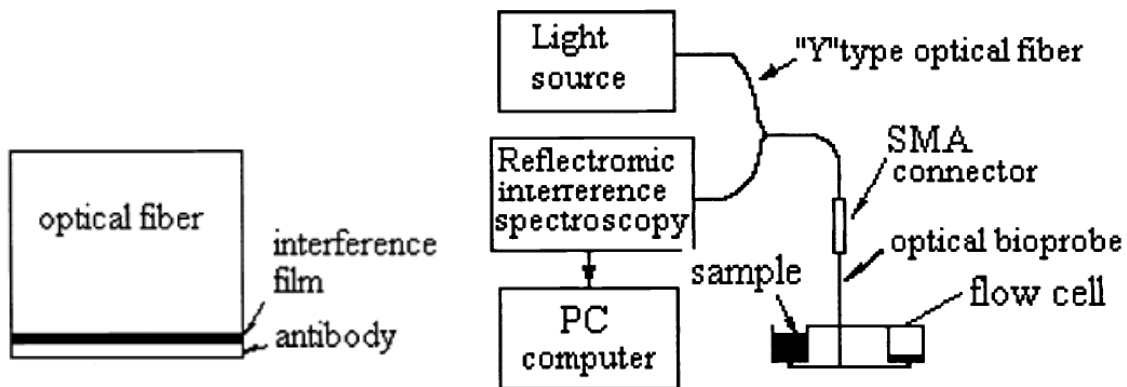


Fig 1b Structure of the bioprobe

Fig 3 Sketch map of the Rifs testing system

(EX1008, 432-33, Figs. 1b, 3; EX1002 ¶86.) Yang explains that the “[t]he detection is based on the theory of multiple-reflection principles in white-light interferometry.” (EX1008, abstract.) Specifically, analyte binding is detected based on phase shifts in the interference pattern produced by light reflected from the distal end of the probe. (*Id.*, 433-34, Fig. 6; EX1002 ¶87.)

b. [1A]: “an optical fiber having a tip”

Yang discloses “an optical fiber having a tip.” For example, as shown in Figure 3, Yang’s setup includes a “‘Y’ type [Y-shaped] polymer fiber coupler” that comprises a “Φ0[.]6mm optical fiber.”

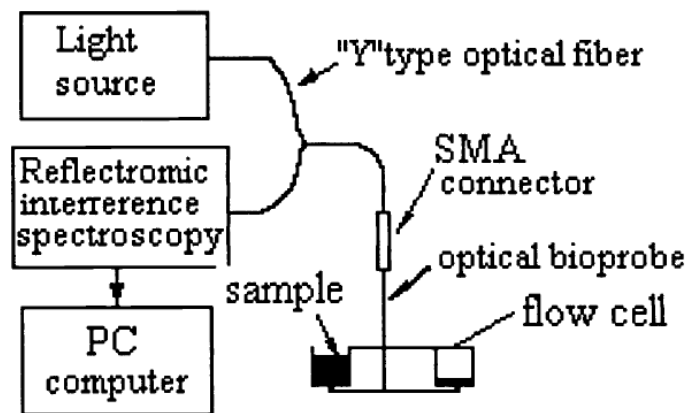


Fig 3 Sketch map of the Rifs testing system

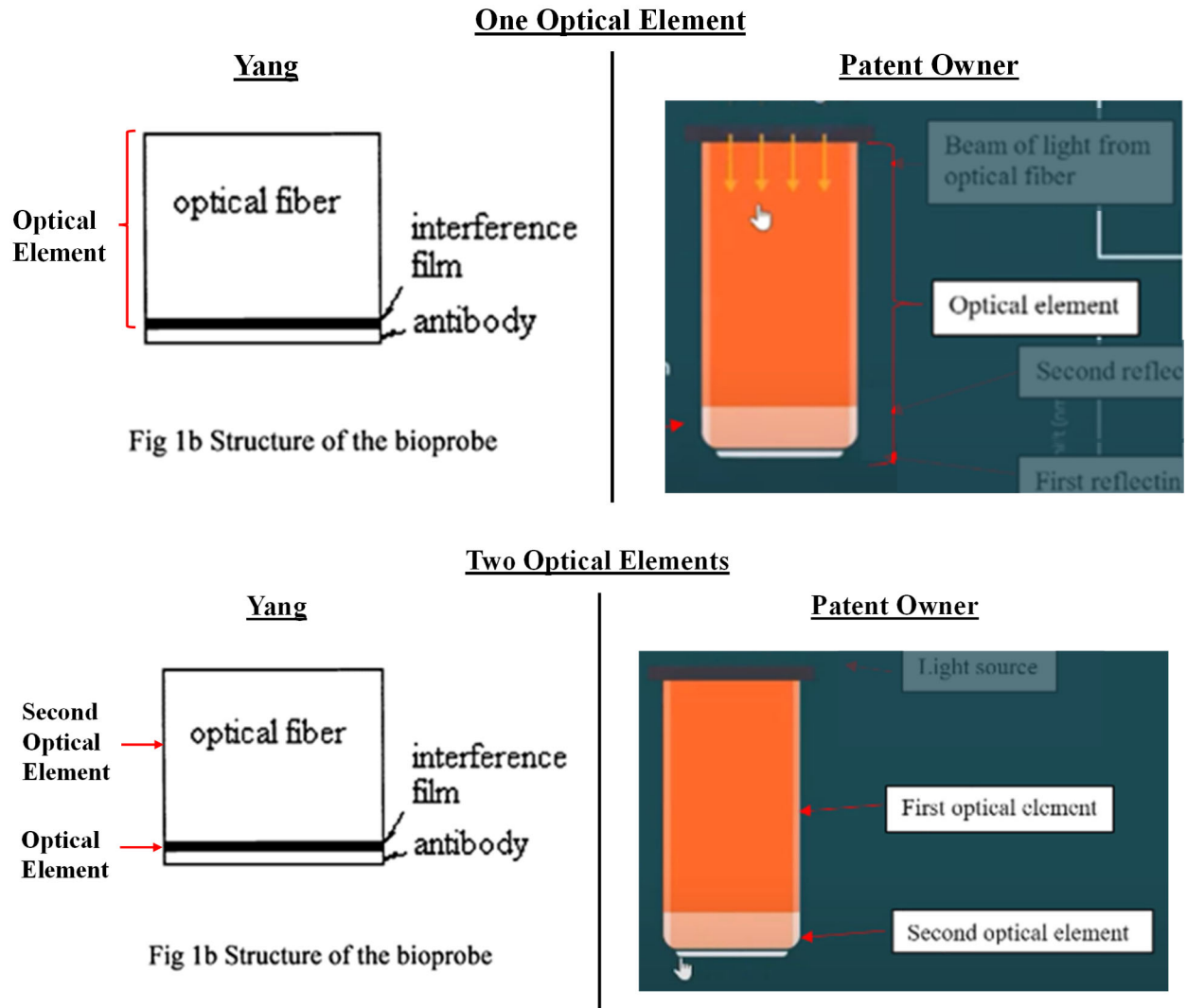
(EX1008, 433, Fig. 3.) The distal end (i.e., “tip”) of this Y-shaped optical fiber is connected via a “standard SMA905 connector” to Yang’s probe. (*Id.*; EX1002 ¶88.)

c. [1B]: “an optical element removably attached to the tip of the optical fiber and configured for receiving a beam of light from the optical fiber”

Yang, alone and in combination with Yu, teaches an “optical element.” As addressed in Sections V.A-V.B, Yang discloses a probe comprising an optical-fiber portion coated on its distal end with an “transparent interference layer” of “special material” (SM-interference layer), which a POSA would have found obvious to substitute with a “transparent polystyrene layer” as described in Yu. (EX1008, 432-33, Fig. 1b; EX1011, 1489, Figure 1(A); EX1002 ¶¶76-84.)

In the related litigations, depending on whether the claim at issue requires only one “optical element” (e.g., claim 1) or also requires a “second optical element” (e.g., claim 15), Patent Owner refers to the interference layer of the accused probes and the structure to which it is attached as either a single “optical element” or two “optical element[s],” respectively. (EX1037, ¶¶62, 120, Figs. 2, 7; EX1060, 5, 18.) Thus, based on Patent Owner’s infringement positions, the “optical element” of Yang’s probe includes both the SM-interference layer and the optical-fiber portion to which it is attached, or alternatively just the SM-interference layer.¹⁰

¹⁰ In the latter case, as addressed below regarding claim 15, the optical-fiber portion comprises a “second optical element.”



(EX1002 ¶¶90-91; EX1008, 433, Fig. 1b (annotated); EX1037, ¶¶62, 120, Figs. 2, 7 (background deemphasized); *see also* EX1060, 5, 18.) In either case, the “optical element” is an element of Yang’s optical assembly that conveys and affects the optical properties of light, including the phase of the measured interference pattern (reflectance spectrum). (EX1002 ¶90; EX1008, 433-34, Fig. 6.)

Moreover, in either case, the “optical element” is “removably attached to the tip of [an] optical fiber.” As shown in Figure 3, the optical-fiber portion of Yang’s

probe is removably attached to the tip of a “Y” type (Y-shaped) optical fiber via a “standard SMA905 connector,” a common screw-type coaxial coupling with male and female components that removably attach to one another.

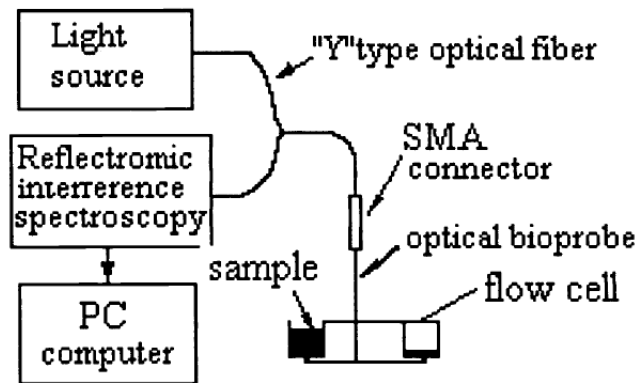


Fig 3 Sketch map of the Rifs testing system

(EX1008, 433, Fig. 3; EX1034, 266; EX1033, 310-1-310-2; EX1002 ¶92.) Because the SM-interference layer is attached to the optical-fiber portion, it too is “removably attached” to the tip of the Y-shaped optical fiber. (EX1002 ¶92.)

Further, because the purpose of the SMA connectors is to couple and convey light from the Y-shaped optical fiber to the optical-fiber portion and onto the SM-interference layer, the optical-fiber portion and the SM-interference layer are both “configured for receiving a beam of light from the optical fiber.” (*Id.* ¶93.)

- d. [1C]: “said optical element comprising a transparent material, a first reflecting surface, and a second reflecting surface separated from the first reflecting surface by the transparent material”

Yang, alone and in combination with Yu, teaches an “optical element comprising a transparent material.” Regardless of whether the “optical element” of

Yang's probe includes just the SM-interference layer or alternatively also includes the optical-fiber portion of the probe, the "optical element" comprises a "transparent material," namely the SM-interference layer. (EX1002 ¶94.) Yang expressly describes the SM-interference layer as "transparent," and to the extent it is a polystyrene layer as described in Yu, Yu likewise describes this polystyrene interference layer as "transparent." (EX1008, 433 ("transparent interference layer"); EX1011, 1489 ("transparent polystyrene layer").) Polystyrene also is a known transparent polymer. (EX1029, Lytle; EX1030, Leite; EX1002 ¶94.) Additionally, by its nature, the SM-interference layer is necessarily transparent because light must be able to pass through (and be reflected back through) it for the RfS system to be able to detect analyte binding. (EX1002 ¶94); *see Persion Pharms. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1190-91 (Fed. Cir. 2019).

The SM-interference layer of Yang's probe also separates "a first reflecting surface" and "a second reflecting surface." For example, as shown in Figure 1a, when light is transmitted to the distal end of the probe, the incident light is partially reflected at the interface between the optical-fiber portion and the SM-interference layer, thereby producing a first reflected light beam ("I₁").

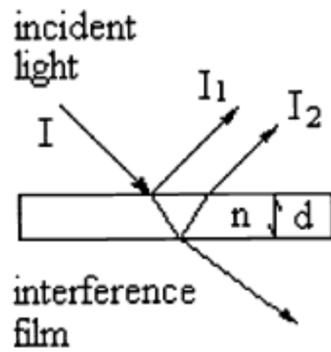
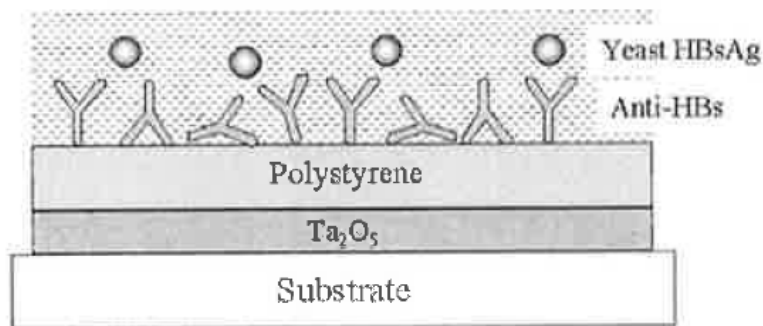


Fig 1a Schematic of the light path in the bioprobe

(EX1008, 432, Fig. 1a; EX1002 ¶¶95-96.) Yang further explains that this interface includes a thin “10~20nm” layer of tantalum pentoxide (Ta_2O_5). (EX1008, 432; EX1002 ¶96.) Although Yang does not show the Ta_2O_5 layer in Figure 1a, Yu shows the Ta_2O_5 layer as sandwiched between the substrate (corresponding to the optical-fiber portion of Yang’s probe) and the polystyrene interference layer.



(EX1011, 1489, Figure 1(A); EX1002 ¶96.) In the context of the ’585 patent, the Ta_2O_5 layer (or more specifically, its proximal surface) comprises the “second reflecting surface.” (EX1001, 3:4-7, 7:50-57 (describing Ta_2O_5 layer as “second reflecting surface”); EX1002 ¶96.)

The light that continues through the SM-interference layer is further partially reflected at the interface between the biolayer (i.e., the antibody layer and any bound antigen) and the sample solution, thereby producing a second reflected light beam (“I₂”).¹¹ (EX1008, 432, Fig. 1a; EX1002 ¶97.) In the context of the ’585 patent, the biolayer (or more specifically, its distal surface) comprises the “first reflecting surface.” (EX1001, 3:2-4, 7:25-33 (describing biolayer of immobilized antibodies as “first reflecting surface”); EX1002 ¶97.)

e. [1D]: “said first and second reflecting surfaces separated by at least 50 nm”

As addressed in Section V.D.1.d (Element [1C]), Yang, alone and in combination with Yu, teaches an SM-interference layer that separates the “first and second reflecting surfaces.” (EX1008, 432-33, Fig. 1a; EX1011, 1489, Figure 1(A); EX1002 ¶98.) Determining the thickness of the SM-interference layer (and hence the separation between the reflecting surfaces) would have been a matter of routine optimization well within a POSA’s capability. (EX1002 ¶98); *see In re Geisler*, 116 F.3d 1465, 1470-71 (Fed. Cir. 1997) (explaining “it is not inventive to discover the optimum or workable ranges by routine experimentation”). Yang and Yu also

¹¹ Figure 1a omits the antibody/antigen layers for simplicity, but given Yang’s discussion of changes in optical thickness due to analyte binding, it is understood that beam I₂ forms at the biolayer-sample solution interface. (EX1002, 67 n.143.)

provide express guidance by disclosing interference-layer thicknesses of approximately “550~600nm” and “~650 nm,” respectively, which are “greater than 50 nm.” (EX1008, 432; EX1011, 1489; EX1002 ¶98.)

- f. [1E]: “wherein said first reflecting surface binds a layer of analyte binding molecules positioned so that interference between a beam of light reflected from the first reflecting surface into the optical fiber and a beam of light reflected from the second reflecting surface into the optical fiber varies as analyte binds to the layer of analyte binding molecules”

As addressed in Section V.D.1.d (Element [1C]), Yang, alone and in combination with Yu, teaches a RIfS probe with an SM-interference layer that separates “a first reflecting surface” and “a second reflecting surface,” and incident light reflected from these surfaces forms two light beams, “ I_2 ” and “ I_1 ,” respectively.

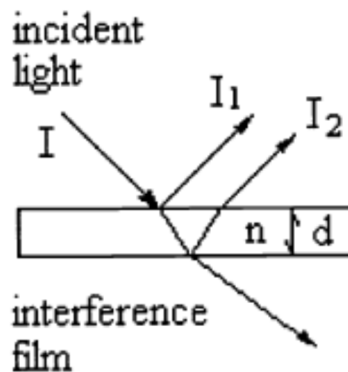


Fig 1a Schematic of the light path in the bioprobe

(EX1008, 432, Fig. 1a; EX1002 ¶99.)

Moreover, as addressed in Section V.A, Yang’s RIfS setup detects analyte binding based on the fact that these reflected light beams interfere with one another

to form an interference pattern (reflectance spectrum) that varies based on the binding of analyte. (EX1008, 432-33; EX1002 ¶100.) Specifically, when analyte molecules bind to the immobilized antibody layer during a test, the “optical thickness” of the SM-interference layer (and hence the separation between the two reflecting surfaces) “increases.” (EX1008, 433; EX1002 ¶100.) This increase is manifested as a “phase shift” (i.e., variance) in the reflectance spectrum (depicted in Figure 6) and “can be detected by [the] Rifs setup in real time.”

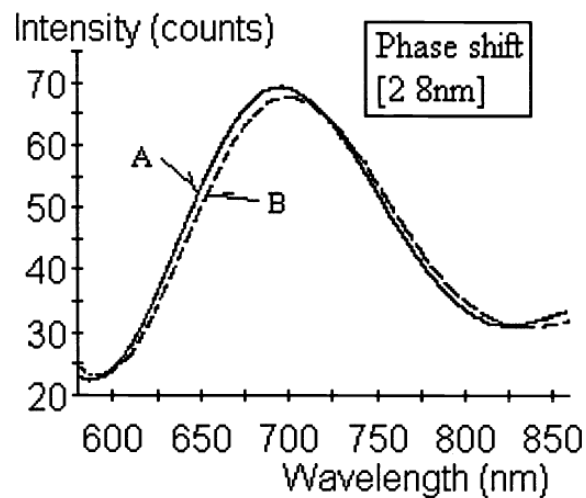


Fig 6 Caused shifting of the reflectance spectrum by the binding of protein

(EX1008, 433, Fig. 6; EX1002 ¶100.) As Yang explains, one “can directly determine the [analyte] concertation” based on “changes [in the reflectance] spectrum and the speed of phase shifting [in the] spectrum.” (EX1008, 433.)

Further, Yang provides an example of a probe in which a layer of immobilized rabbit-IgG antibodies binds goat anti-rabbit-IgG antibodies that, in turn, bind rabbit anti-goat-IgG antibodies present in a sample, forming a three-layer “sandwich”

structure. (EX1008, 434; EX1002 ¶99.) In this example, the first two layers of antibodies may be considered (individually or collectively) as a “layer of analyte binding molecules” and the third layer of antibodies is the “analyte” that is detected. (EX1002 ¶99.)

In summary, Yang, alone and in combination with Yu, teaches an optical assembly comprising each element of claim 1 and renders claim 1 obvious.

2. Claims 2 and 5-10

Yang, alone and in combination with Yu, teaches claims 2 and 5-10, which recite characteristics of the “second reflecting surface” and the “transparent material” that comprises the “optical element” of claim 1.

As discussed in Sections V.B and V.D.1.d (Element [1C]), the “second reflecting surface” in Yang’s probe comprises a Ta₂O₅ layer having a thickness of approximately “10~20nm” and a POSA would have been motivated to use a “transparent polystyrene layer” as the SM-interference layer. (EX1008, 432; EX1011, 1489, Figure 1(A) (describing “10-nm Ta₂O₅ film”); EX1002 ¶103.)

This configuration meets the elements of claims 2 and 5-10. For example, the “optical element transparent material” is a “transparent polymer” (claim 6), namely “polystyrene” (claim 7). (EX1002 ¶103.) Polystyrene has a refractive index of approximately 1.55-1.59, which is “less than 1.8” (claim 5). (EX1031, Krause, 1926; EX1002 ¶103.) Further, the “second reflecting surface” is a layer of material

that “comprises Ta₂O₅” (claim 9) having a thickness (approximately “10~20nm”) that is “between 5 nm and 50 nm” (claim 10) and having a refractive index (approximately 2.1) that is greater than that of the polystyrene SM-interference layer (claim 2) and “greater than 1.8” (claim 8). (EX1001, 7:56-57; EX1002 ¶103.)

3. Claims 3-4

Claim 3 recites that “the separation between [the] first and second reflecting surfaces is between 100 nm and 5,000 nm,” which claim 4 narrows to “between 400 nm and 1,000 nm.” As addressed in Sections V.D.1.d (Element [1C]) and V.D.1.e (Element [1D]), determining the thickness of the SM-interference layer (and hence the separation between the “first and second reflecting surfaces”) would have been a matter of routine optimization well within a POSA’s capability. (EX1002 ¶¶98, 105); *see Geisler*, 116 F.3d at 1470-71. Yang and Yu also provide express guidance by disclosing interference-layer thicknesses of approximately “550~600nm” and “~650 nm,” respectively, which are within the claimed ranges. (EX1008, 432; EX1011, 1489; EX1002 ¶105.)

4. Claims 11-12

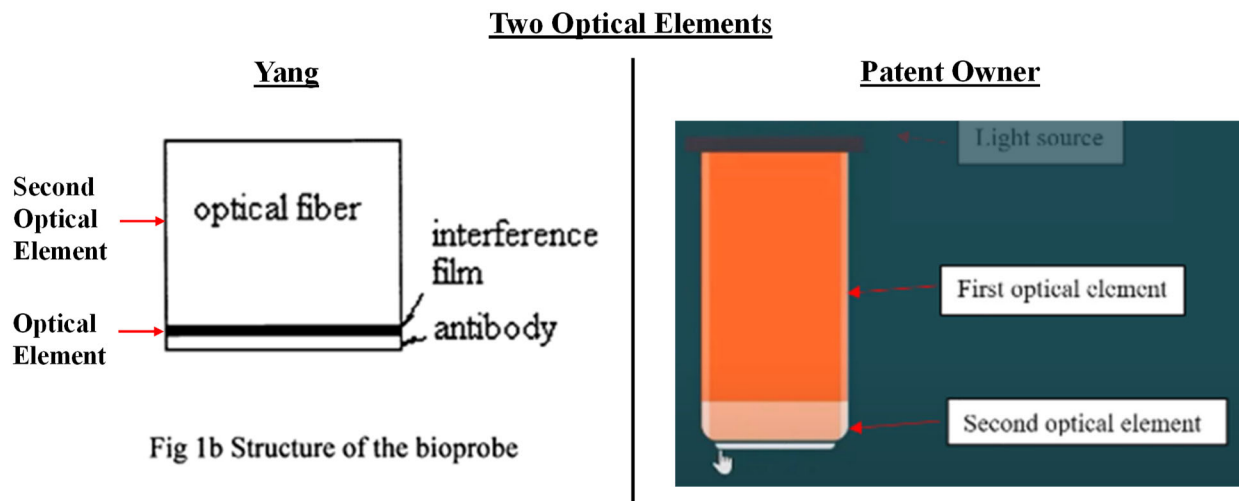
Claims 11-12 specify that the “layer of the analyte binding molecules” is selected from a group that includes a “protein” and that this “protein” is selected from a group that includes “an antibody.” As addressed in Section V.D.1.f (Element

[1E]), the “layer of analyte binding molecules” in Yang’s probe comprises antibodies (a type of protein). (EX1008, 432, 434, Fig. 1b; EX1002 ¶107.)

5. Claims 15-17

Claim 15 recites that the “optical assembly” of claim 1 “further compris[es] a second optical element overlaying [the] second reflecting surface.” Claims 16-17 specify that “the thickness of [the] second optical element is greater than 100 nm” and “200 nm,” respectively.

As addressed in Section V.D.1.c (Element [1B]), and as shown in Figure 1b, Yang describes a probe that includes an optical-fiber portion coated on its distal end with an SM-interference layer. (EX1008, 432, 434; Figs. 1b; EX1002 ¶108.) In the context of claims 15-17 and based on Patent Owner’s infringement positions in the related litigations, the SM-interference layer comprises an “optical element” and the optical-fiber portion comprises “a second optical element,” as both are elements of Yang’s optical assembly that convey and affect the optical properties of light.



(EX1002 ¶108; EX1008, Fig. 1b (annotated); EX1037, ¶62, Figure 2 (background deemphasized); *see also* EX1060, 18.)

Moreover, regarding claim 15, the optical-fiber portion (“second optical element”) “overlay[s] [the] second reflecting surface,” which is the interface between the optical-fiber portion and the SM-interference layer, namely a thin layer of “10~20nm Ta₂O₅.” (EX1008, 432, Fig. 1b; *see also* EX1011, 1489, Figure 1(A) (showing Ta₂O₅ layer sandwiched between the substrate (corresponding to the optical-fiber portion of Yang’s probe) and interference layer); EX1002 ¶109.)

Regarding claims 16-17, Yang does not expressly state the thickness of the optical-fiber portion, but it is necessarily “greater than 100 nm” and “200 nm” (i.e., greater than 0.1 µm and 0.2 µm). *See Persion*, 945 F.3d at 1190-91. To put this into perspective, a typical human hair is about 100 µm thick, so this thickness is roughly 1/1000th of a human hair. (EX1002 ¶110.) Notably, Yang states that the optical-fiber portion of the probe is coupled to a Y-shaped optical fiber via a “standard SMA905 connector,” which requires the thickness (or more appropriately, the length) of the optical-fiber portion to be substantially greater than a few micrometers, or even a few millimeters in practice. (EX1008, 433, Fig. 3; EX1002 ¶111.) Yang also describes the thickness of the SM-interference layer as approximately “550~600nm,” which indicates that the optical-fiber portion to which it is attached has a thickness greater than 100 or 200 nm. (EX1008, 432; EX1002

¶112.) Further, Figure 3 shows Yang's probe as substantially longer than the width of its distal end, and only a portion (the distal end) is shown as being immersed in a sample solution, while most of the probe is not immersed.

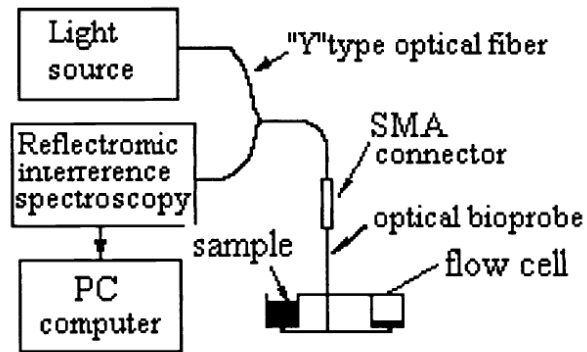


Fig 3 Sketch map of the Rifs testing system

(EX1008, 433, Fig. 3; EX1002 ¶113.) Thus, even if not drawn to scale, Figure 3 indicates that the thickness (length) of the optical-fiber portion of the probe is substantially greater than a few micrometers. (EX1002 ¶113.)

6. Claims 13-14 and 18-19

Claims 13 and 18 recite that the “optical assembly is adapted for coupling to [the] light source through a mechanical coupling that engages” either the “optical element” (claim 13) or the “second optical element” (claim 18) “with [the] fiber.” Claim 19 recites that the mechanical coupling provides “an air gap between [the] second optical element and [the] fiber.” Claim 14 recites that the “optical element is adapted for coupling to [the] light source through a coupling assembly that comprises a lens system.”

As addressed in Sections V.D.1.c (Element [1B]) and V.D.5 (claims 15-17), the SM-interference layer and the optical-fiber portion of Yang's probe collectively comprise an "optical element" (claim 1), or alternatively comprise an "optical element" and a "second optical element," respectively (claim 15). (EX1002 ¶115.) In either case, Yang's probe, which comprises both the "optical element" and "second optical element," is coupled to the tip of a "Y" type (Y-shaped) optical fiber, and in turn a "light source," via a "standard SMA905 connector."

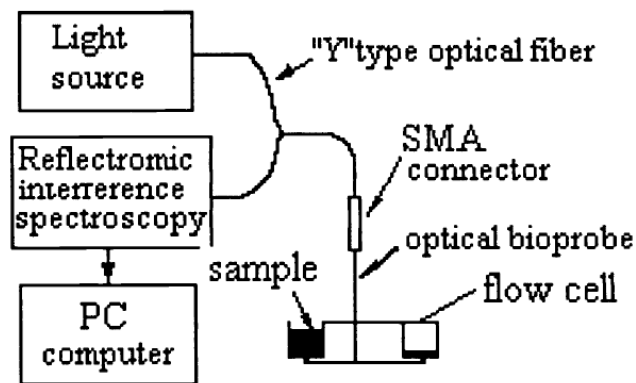


Fig 3 Sketch map of the Rifs testing system

(EX1008, 433, Fig, 3; EX1002 ¶115.)

Regarding claims 13-14 and 18-19, the SMA connectors are a screw-type coaxial "mechanical coupling" or "coupling assembly" with male and female components that removably engage one another. (EX1034, 175, 266; EX1033, 310-1-310-2; EX1002 ¶116.) The SMA connectors couple Yang's optical assembly to a light source by engaging the optical-fiber portion of the probe (whether it is a part

of the “optical element” of claim 1 or the “second optical element” of claim 15) with the Y-shaped optical fiber. (EX1008, 433, Fig. 3; EX1002 ¶117.)

Regarding claim 14, Yang and Yu do not explicitly describe using a “lens system.” Nonetheless, a POSA would have found it obvious to incorporate a “lens system.” As an initial matter, any free-space light source (such as the halogen lamp used in Yang’s setup) will require lenses to couple light into a fiber, and Patent Owner has asserted that such lenses suffice as the claimed “lens system.” (EX1002 ¶118; EX1008, 433; EX1060, 16.) A POSA also would have found it obvious to incorporate a lens system into Yang’s SMA coupling assembly to focus the light from the Y-shaped optical fiber and direct it into the optical-fiber portion of Yang’s probe, and vice versa, recognizing that this would improve the signal-to-noise ratio of the system. (EX1002 ¶119.) Yang and Yu, in fact, are concerned with noise and contemplate further improvements to address the effects of noise. (*Id.*; EX1008, 435; EX1011, 1490.) As would have been apparent a POSA, enhancing the signal strength, for example by focusing the incident light using a lens system, would improve the signal-to-noise ratio. (EX1002 ¶119; EX1015, 360.)

Further, SMA coupling assemblies incorporating lenses were known and available in the art. (EX1002 ¶120.) For example, as addressed below (Section VI.C.6), Sun describes a similar fiber-optic RfS probe that is coupled to a Y-shaped optical fiber using a lens system employing standard SMA connectors. (EX1010,

658, Figure 3.) As another example, U.S. Patent No. 6,174,291 describes an optical system capable of interferometric applications that uses an “optical coupler 210” comprising a lens assembly to connect a “diagnostic optical fiber 135” to a light source (“laser 200”) via a “Subminiature type A (SMA) 905 interface.” (EX1001, 12:65-13:37, FIG. 2.) Thus, the inclusion of a lens system in Yang’s SMA coupling assembly would have merely combined and substituted known elements of optical systems to obtain predictable results. (EX1002 ¶120); *KSR*, 550 U.S. at 417.

Regarding claim 19, because the SMA connectors used in Yang’s system are able to rotate, they inherently incorporate an “air gap” between the distal end of the Y-shaped optical fiber and the optical-fiber portion of the probe (“second optical element”) to prevent the respective fiber ends from directly contacting one another and becoming scratched, for example as shown in the figure below.



(EX1002 ¶121; EX1058, 2; EX1059, 81, 83, Figure 6-4.) In any event, a POSA would have found the use of a mechanical coupling that provides an “air gap” to be an obvious design choice to reduce the likelihood of fiber ends from becoming scratched or otherwise coated with debris or foreign substances, particularly in a setup such as Yang’s where the Y-shaped optical fiber is intended to be a permanent fixture to which different probes may be removably attached. (EX1002 ¶122.)

VI. GROUND 2: THE COMBINATION OF SUN AND YU RENDERS CLAIMS 1-19 OBVIOUS UNDER 35 U.S.C. § 103(a)**A. Sun**

Sun relates to a fiber-optic RIfS probe for “detect[ing] the thickness of nm level biolayers.” (EX1010, abstract.) At the outset, Sun explains that a “common approach” in diagnostic testing involves deploying a biosensor to “detect whether a sample contains a specific biological substance” (analyte) and provides an example of detecting whether a specific antibody is present in blood plasma. (*Id.*, 657.) Sun then proceeds to describe a biosensor that “detect[s] whether a substance is present in a solution” by “detect[ing] whether the thickness of a biolayer on probe terminal surface changes based on changes in the spectral phase of the interference pattern” produced by reflected light. (*Id.*)

As shown in Figure 3, Sun employs a RIfS setup that includes “a white light source, a ‘Y’ shaped [or ‘Y’ type] optical fiber, a fiber optic connector, a fiber optic probe, a spectrophotometer, and a computer.”

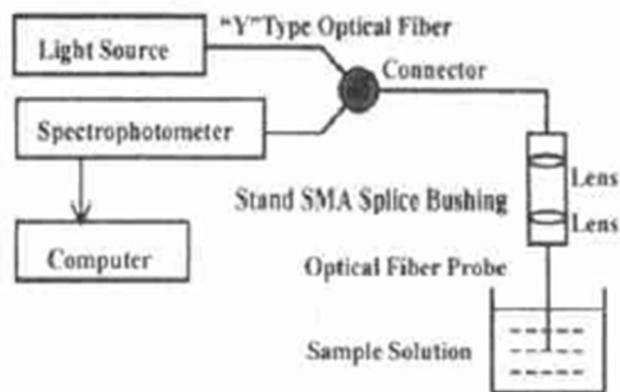


Figure 3 Detecting system structure

(*Id.*, 658, Figure 3.) The probe includes an “optical fiber” portion (shown in Figure 1) that is separate from the Y-shaped optical fiber (shown in Figure 3), and these two fiber structures are connected by a “standard SMA connector,” which again is a common screw-type mechanical coupling with male and female components that removably engage one another. (EX1010, at 657-658, Figures 1, 3; EX1034, 266; EX1033, 310-1-310-2; EX1002 ¶126.) In Sun’s setup, light from the light source travels through the Y-shaped optical fiber to the probe via the connector, and light that is reflected from the probe’s distal end is directed back through the connector and Y-shaped optical fiber to the spectrophotometer. (EX1010, 658, Figure 3.)

Figure 1 illustrates Sun’s probe but omits for simplicity certain elements such as an interference layer, which Sun discusses throughout and refers to as a “siliconization film.”

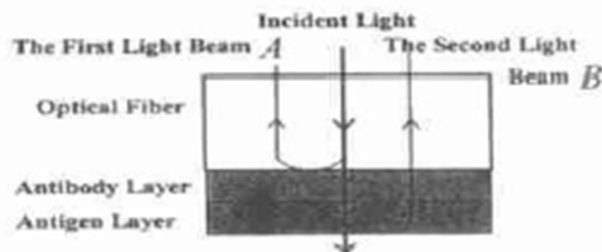
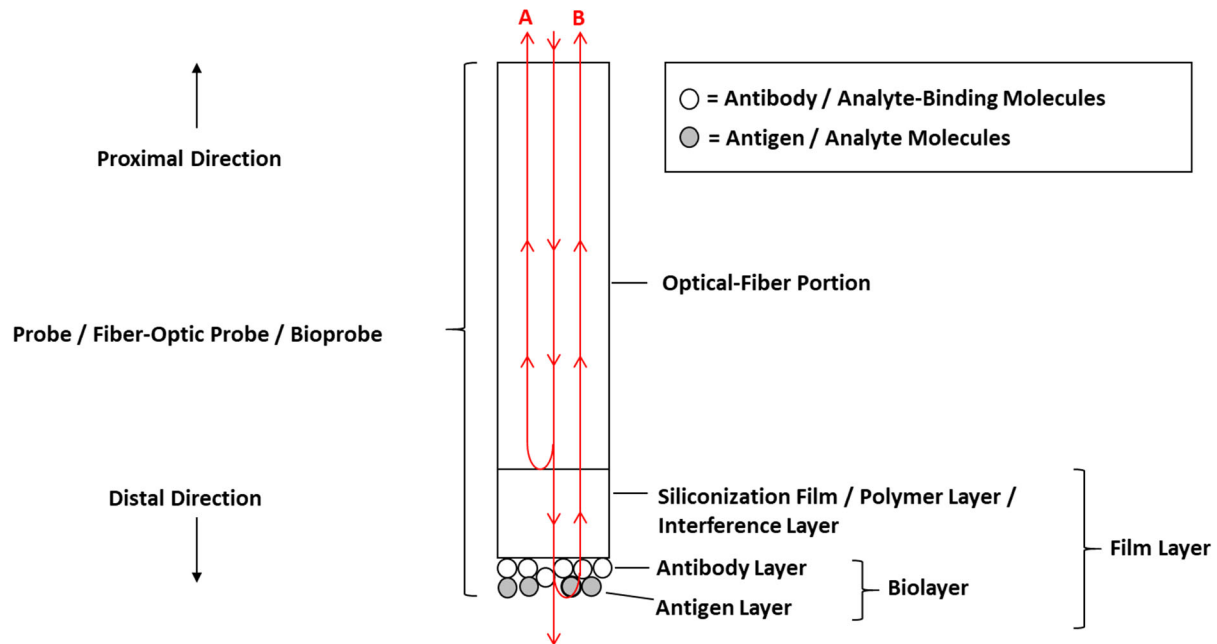


Figure 1 Light reflection at the bottom of a bioprobe

(EX1010, 657, 659, Figure 1; EX1002, ¶127.) For ease of reference, Petitioner refers to the demonstrative diagram below to illustrate Sun’s probe (including the interference layer) and identify the various corresponding terminology:



(EX1002 ¶127.)

As shown, the distal end of the optical-fiber portion of Sun's probe is covered by an interference layer, which Sun refers to as a "siliconization film," on which a layer of antibodies is immobilized. (EX1010, 657, 659.) The immobilized antibodies, in turn, bind antigen (analyte) molecules present in a sample solution. (*Id.*; EX1002 ¶128.) Sun refers to the immobilized antibody layer and bound antigen together as a "biolayer." (EX1010, 657.)

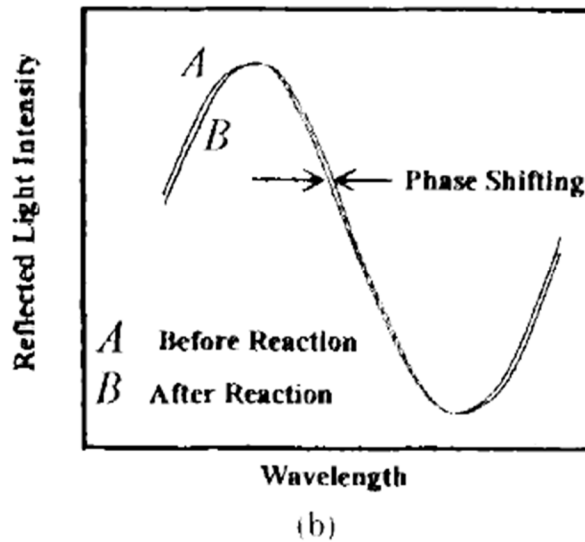
According to Sun, the "siliconization film" is formed through a "siliconization method" that results in "a film of a polymer (the main component [of which] is polystyrene)." (EX1010, 659.) For this reason, Sun also refers to the "siliconization film" as a "polymer layer" or "polymer film." (*Id.*) Sun further explains the "siliconization film" serves as an interference layer that "increas[es] the thickness of

the [overall] film layer” and “increas[es] the adhesion ability of the optical fiber to the antibody.” (*Id.*)

Referring again to the diagram above, during the operation Sun’s system, light travels along the optical fiber toward the distal end of the probe, where there are two reflection events. (EX1010, 657, Figure 1.) First, light is partially reflected at the interface between the optical-fiber portion and the interference layer (“siliconization film”), thereby producing a first reflected light beam (“A”). (*Id.*; EX1002 ¶130.) Second, some of the light continues forward and is further partially reflected at the interface between the biolayer (i.e., the antibody layer and any bound antigen) and the external environment, thereby producing a second reflected light beam (“B”). (EX1010, 657, Fig. 1; EX1002 ¶130.)

Sun explains that because these reflective interfaces are separated by a thickness, there is a difference in the distance traveled by the reflected light beams (and hence the optical path length). (EX1010, 658.) As a result, the reflected light beams are out of phase and interfere with one another to produce an interference pattern (reflectance spectrum) that is measured by the spectrophotometer. (*Id.*) When “the antigen [molecules] and the antibody [molecules] react” during a test, the thickness that separates the reflective interfaces increases, which is manifested as a “phase shift” in the “interference pattern.” (*Id.*, 658.) Thus, if a phase shift is detected, Sun explains that it can be concluded that analyte molecules are present.

(*Id.*) Sun's Figure 5(b) provides an example of a phase shift in the interference pattern resulting from the binding of antigen to the antibody layer.



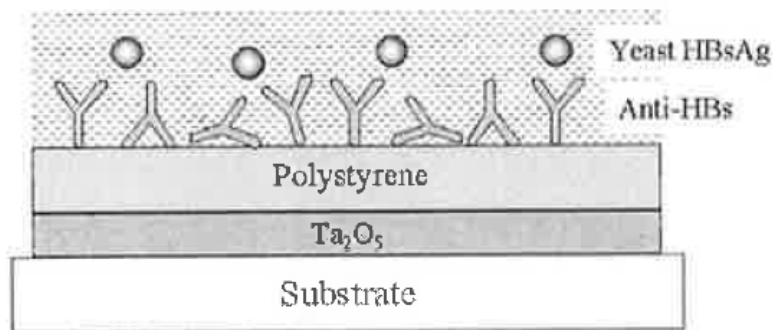
(*Id.*, 659, Figure 5(b); *see also id.*, 658, Figure 2.) Sun further describes the results of a test in which the thickness of the overall film layer (including the interference layer, antibody layer, and antigen layer) was about 0.987 μm (987 nm), and the increase in thickness due to analyte binding was about 7 nm. (*Id.*, 659.)

B. Motivation to Combine Sun and Yu

Sun describes a RI_fS sensor with an interference layer that it refers to as a “siliconization film” that comprises a polymer layer (of which “the main component is polystyrene”) and is formed through a “siliconization method.” (EX1010, 659; EX1002 ¶133; *see* Section VI.A above.) Sun, however, does not explain this “siliconization method” or identify what other components may comprise the “siliconization film.” (EX1002 ¶134.) Sun also does not explicitly address known

aspects of this type of RI/S sensor such as the incorporation of a relatively high-refractive-index reflective material at the interface between the optical-fiber portion of the probe and the interference layer to enhance the sensitivity of the system. (*Id.*)

In this regard, Yu describes a RI/S sensor comprising a “transparent polystyrene layer with thickness of ~650 nm” that “serve[s] as both the interference film and the hydrophobic surface for immobilization of antibodies,” and further describes a thin “10-nm Ta₂O₅ film” at the interface between the interference film and the substrate “to enhance the interference contrast.”



(EX1011, 1489, Fig. 1(A); EX1002 ¶135; *see* Section V.B above.)

Based on Yu’s teachings, a POSA would have found it obvious to modify Sun’s probe by (1) using a “transparent polystyrene layer” as the interference layer, as opposed to a “siliconization film” in which polystyrene is simply the “main component,” and (2) incorporating an approximately 10 nm layer of Ta₂O₅ as a reflecting surface between the optical-fiber portion of the probe (equivalent to the substrate in Yu) and the interference layer. (EX1002 ¶136.)

A POSA would have been motivated to make these modifications for several reasons. As an initial matter, the modifications would have simply combined or substituted well-known elements of RIfS sensors according to their established functions to yield predictable results. *See KSR*, 550 U.S. at 417. Indeed, as noted, both Sun and Yu employ very similar RIfS sensors. Both utilize an interference layer comprising polystyrene. (EX1010, 657, 659, Figure 1; EX1011, 1489; EX1002 ¶137.) Both utilize a layer of antibodies immobilized on the interference layer to bind analyte present in a sample. (EX1010, 657, 659, Figure 1; EX1011, 1489, Figure 1(A); EX1002 ¶137.) And both detect the analyte binding based on phase shifts in the interference pattern of white light reflected from each side of the interference layer. (EX1010, 657-658, Figures 1, 2; EX1011, 1489, Figure 1(A); EX1002 ¶137.)

To be sure, Yu's sensor is a "transducer chip" that comprises a flat "substrate," while Sun's sensor is a probe in which the "substrate" is the optical-fiber portion of the probe. (EX1010, 657-58, Figures 1, 3; EX1011, 1489, Figure 1(A); EX1002 ¶138.) A POSA, however, would not have found this significant in applying Yu's teachings to Sun's probe, particularly given that Yu's chip and Sun's probe operate based on the same RIfS principle of white-light interference at a transparent thin film, and given that the interference layer and the Ta₂O₅ layer would serve the same purpose in both. (EX1002 ¶138.) Coating the end of an optical fiber with an oxide

and/or polymer also was well known in the art, and commercial services for this type of coating existed at the time. (*Id.* ¶¶138, 142.) Moreover, the transition from a larger substrate to an optical fiber was a standard progression in the development of optical-fiber systems. (*Id.*)

Yu also provides explicit motivations for these modifications. For example, Yu motivates a POSA to use a “transparent polystyrene layer” in a RIfS setup by explaining that it “serve[s] as both [an] interference film and [a] hydrophobic surface for immobilization of antibodies.” (EX1011, 1489.) This is the same purpose Sun’s “siliconization film” serves, which Sun explains “increas[es] the thickness of the film layer [i.e., serve as an interference layer] and increas[es] the adhesion ability of the optical fiber to the antibody.” (EX1010, Sun 659; EX1002 ¶139.)

Similarly, Yu motivates a POSA to incorporate a thin layer of Ta₂O₅ layer on the order of 10 nm as a reflecting surface between the optical-fiber portion of Sun’s probe and the interference layer by explaining that it “enhance[s] the interference contrast.” (EX1011, 1489; EX1002 ¶140.) This was not a novel suggestion—others had long established that the signal-to-noise ratio and sensitivity of RIfS and other reflectometric analyses could be improved by incorporating a thin layer of a relatively high-refractive-index material, such as Ta₂O₅, as a reflecting surface. (EX1015, 362-363; EX1019, 156-157; EX1002 ¶140.) In fact, by 1995,

“[i]nterference layers for RIFS” incorporating a “10 nm Ta₂O₅” reflecting surface were commercially available. (EX1016, 291-92.)

Further, as a POSA would have recognized, for a reflective Ta₂O₅ layer to provide these benefits, the adjacent interference layer must be selected so that the Ta₂O₅ layer has a greater refractive index. (EX1002 ¶141.) This provides further motivation to use polystyrene (which has a lower refractive index than Ta₂O₅) as the interference layer in Sun’s probe. (*Id.*)

C. Claims 1-19 Would Have Been Obvious in View of Sun and Yu

1. Claim 1

a. [1P]: “An optical assembly for use in detecting an analyte in a sample based on interference”

To the extent the preamble is limiting, Sun discloses “[a]n optical assembly for use in detecting an analyte in a sample based on interference.” In Sun’s RIFS system, the “optical assembly” comprises a “‘Y’ shaped [or ‘Y’ type] optical fiber” coupled to a “fiber optic probe” that detects the binding of antigen (i.e., “analyte”) to an immobilized layer of antibodies (i.e., “analyte-binding molecules”), as shown in Figures 1 and 3 and described in Section VI.A.

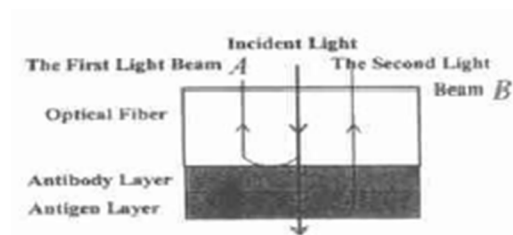


Figure 1 Light reflection at the bottom of a bioprobe

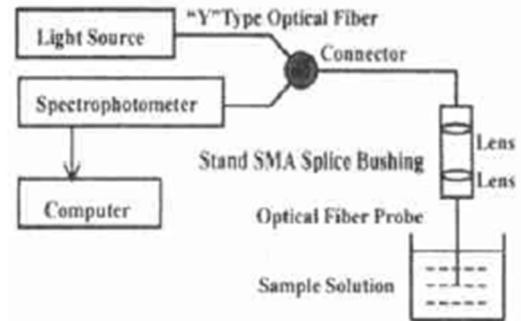


Figure 3 Detecting system structure

(EX1010, 657-58, Figures 1, 3; EX1002 ¶144.)

Sun discloses that analyte binding is detected based on interference, specifically by measuring “changes in spectral phase of the interference pattern” produced by light reflected from the distal end of the probe. (EX1010, 657-59, Figures 2, 5; EX1002 ¶144.) Sun also discloses an exemplary use case in which the probe is used to detect “whether a specific antibody [analyte] is present in [a sample of blood] plasma.” (EX1010, 657-59, Figures 2, 5; EX1002 ¶144.)

b. [1A]: “an optical fiber having a tip”

Sun discloses “an optical fiber having a tip.” For example, as shown in Figure 3, Sun’s setup includes a “‘Y’ shaped [or ‘Y’ type] optical fiber.”

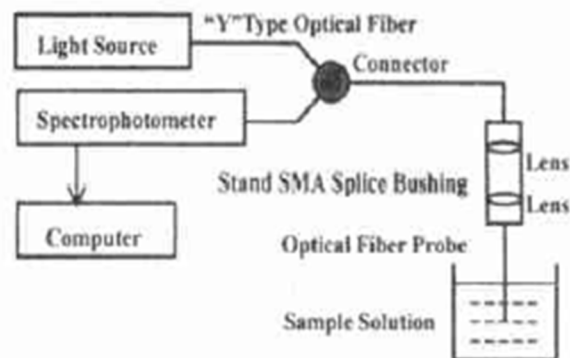


Figure 3 Detecting system structure

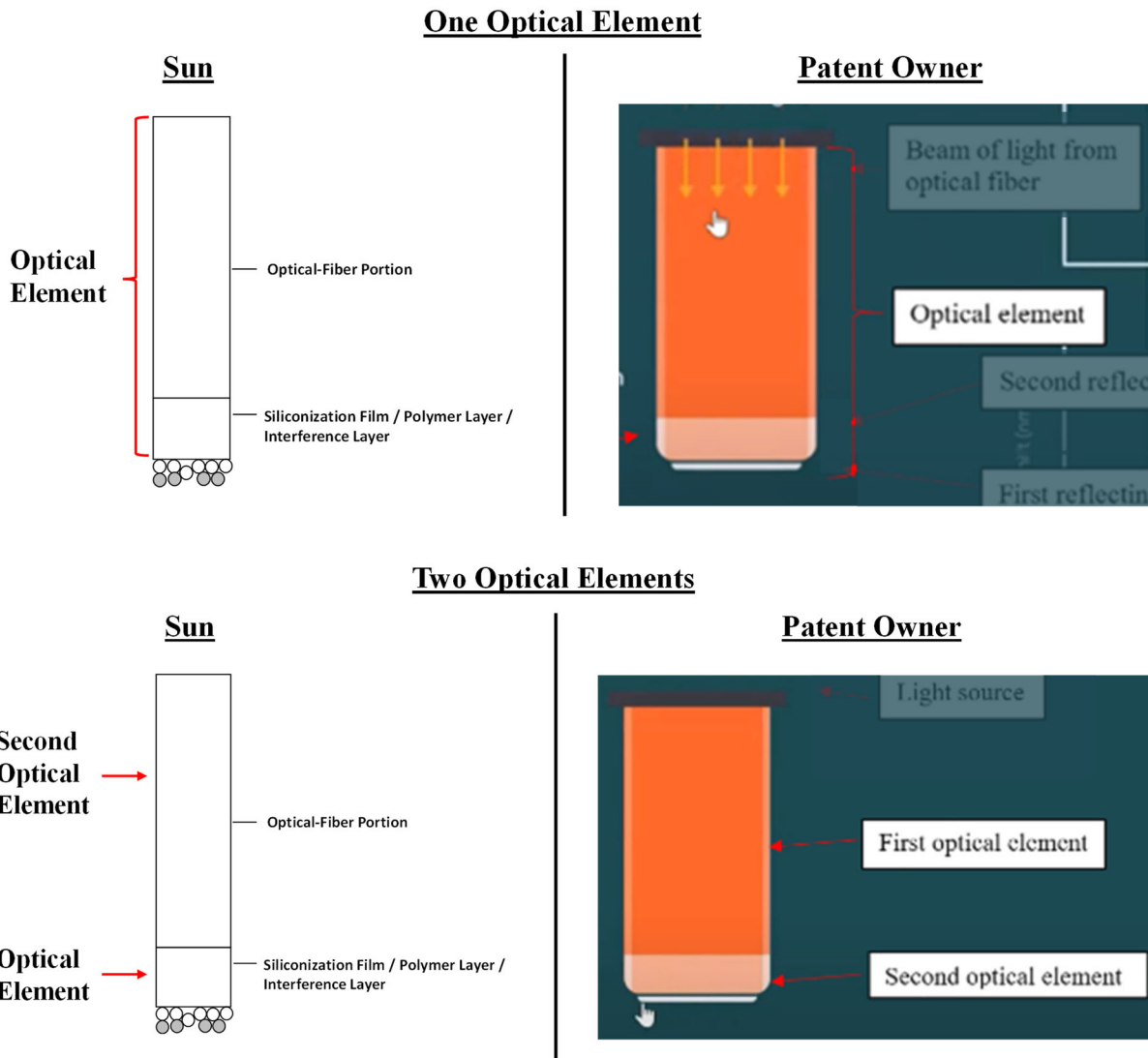
(EX1010, 658, Figure 3.) The Y-shaped optical fiber has a distal end (i.e., a “tip”) that connects via a standard SMA connector to Sun’s probe. (*Id.*; EX1002 ¶145.)

c. [1B]: “an optical element removably attached to the tip of the optical fiber and configured for receiving a beam of light from the optical fiber”

Sun, alone and in combination with Yu, teaches an “optical element.” As addressed in Sections VI.A-VI.B, Sun discloses a probe with an optical-fiber portion that is coated on its distal end with an interference layer, namely a “siliconization layer” of which the “main component is polystyrene,” which a POSA would have found obvious to substitute with a “transparent polystyrene layer” as described in Yu. (EX1010, 657, 659, Figure 1; EX1011, 1489, Figure 1(A); EX1002 ¶¶133-140.)

In the related litigations, depending on whether the claim at issue requires only one “optical element” (e.g., claim 1) or also requires a “second optical element” (e.g., claim 15), Patent Owner refers to the interference layer of the accused probes and the structure to which it is attached as either a single “optical element” or two “optical element[s],” respectively. (EX1037, ¶¶62, 120, Figs. 2, 7; EX1060, 5, 18.) Thus, based on Patent Owner’s infringement positions, the “optical element” of

Sun's probe includes both the interference layer and the optical-fiber portion to which it is attached, or alternatively just the interference layer.¹²



(EX1002 ¶¶147-148; EX1010, Figure 1 (adapted); EX1037, ¶¶62, 120, Figs. 2, 7 (background deemphasized); *see also* EX1060, 5, 18.) In either case, the “optical

¹² In the latter case, as addressed below regarding claim 15, the optical-fiber portion comprises a “second optical element.”

element” is an element of Sun’s RIfS-based optical assembly that conveys and affects the optical properties of light, including the phase of the interference pattern (reflectance spectrum) produced by the reflected light. (EX1010, 658-59, Figures 2, 5; EX1002 ¶147.)

Moreover, in either case, the optical element is “removably attached to the tip of [an] optical fiber.” For example, as shown in Figure 3, the optical-fiber portion of Sun’s probe is removably attached to the tip of a Y-shaped optical fiber via a “standard SMA connector,” a common screw-type coaxial coupling mechanism with male and female components that removably attach to one another.

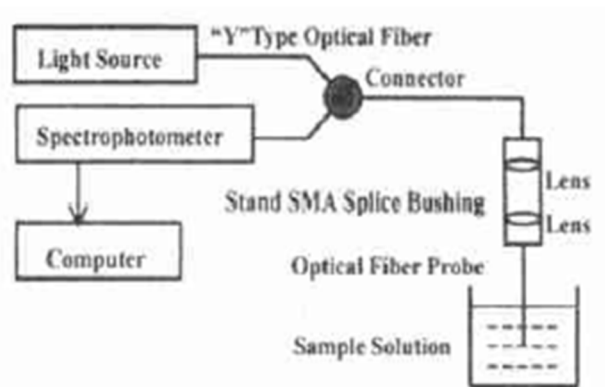


Figure 3 Detecting system structure

(EX1010, 658, Figure 3; EX1034, 175, 266; EX1033, 310-1-310-2; EX1002 ¶149.)

Because the interference layer is attached to the optical-fiber portion, it too is “removably attached” to the tip of the Y-shaped optical fiber. (EX1002 ¶149.)

Further, because the purpose of the SMA connectors is to couple and convey light from the Y-shaped optical fiber to the optical-fiber portion and onto the

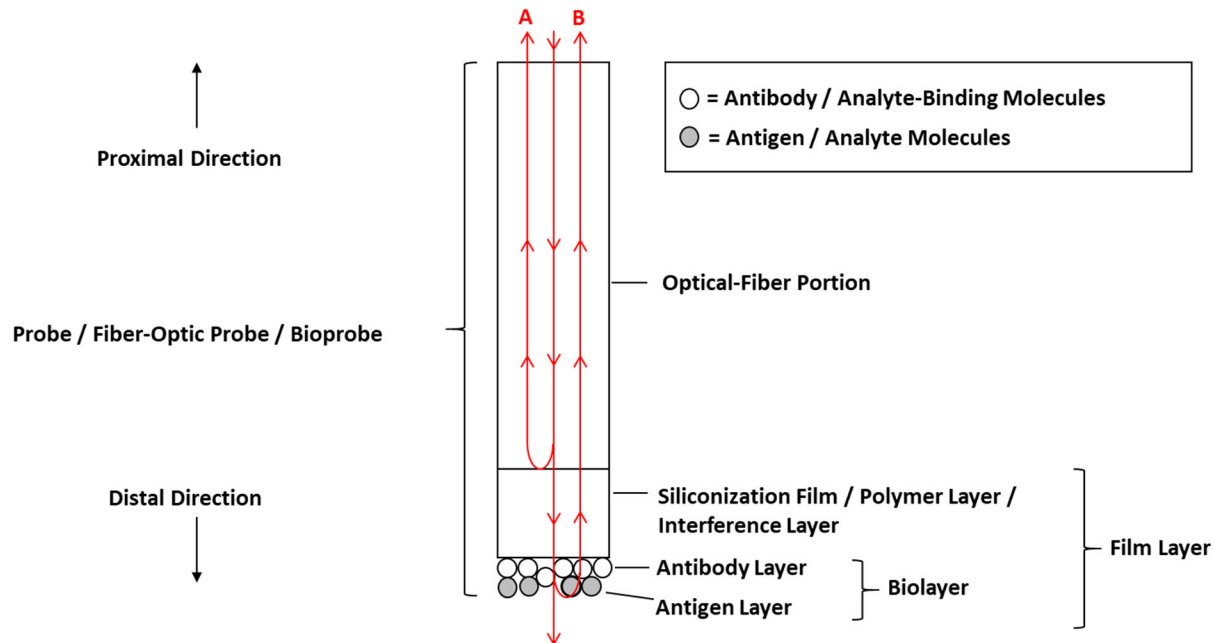
interference layer, the optical-fiber portion and the interference layer are both “configured for receiving a beam of light from the optical fiber.” (*Id.* ¶150.)

- d. [1C]: “said optical element comprising a transparent material, a first reflecting surface, and a second reflecting surface separated from the first reflecting surface by the transparent material”

Sun, alone and in combination with Yu, teaches an “optical element comprising a transparent material.” Regardless of whether the “optical element” of Sun’s probe includes just the interference layer or alternatively also includes the optical-fiber portion of the probe, the “optical element” comprises a “transparent material,” namely the interference layer. (EX1002 ¶151.) As addressed in Section VI.B, Sun describes its interference layer as a “siliconization film” of which the “main component is polystyrene,” and a POSA would have found it obvious to substitute a “transparent polystyrene layer” as described in Yu. Polystyrene is a known transparent polymer, and Yu expressly describes its polystyrene interference layer as “transparent.” (EX1011, 1489; EX1029, Lytle; EX1030, Leite; EX1002 ¶152.) Additionally, by its nature, the interference layer of Sun’s probe is necessarily transparent because light must be able to pass through (and be reflected back through) it for the RIfS system to be able to detect analyte binding. (EX1002 ¶151); *see Persion*, 945 F.3d at 1190-91.

Moreover, Sun, alone and in combination with Yu, teaches “a first reflecting surface” and “a second reflecting surface” that are separated by the transparent

interference layer. As illustrated below, when light travels toward the distal end of Sun's probe, the incident light is partially reflected at the interface ("interface 1") between the optical-fiber portion and the interference layer, thereby producing a first reflected light beam ("A").



(EX1002 ¶¶153-154; EX1010, 657, Figure 1 (adapted).)

In the context of the '585 patent, interface 1 of Sun's probe comprises the "second reflecting surface." (EX1002 ¶154.) Also, as addressed in Section VI.B, a POSA would have found it obvious based on Yu to incorporate a thin layer of tantalum pentoxide (Ta_2O_5) on the order of 10 nm as a reflecting surface at interface 1, in which case the Ta_2O_5 layer (or more specifically its proximal surface) comprises the "second reflecting surface." (EX1011, 1489, Figure 1(A); EX1002 ¶154; EX1001, 3:4-7, 7:50-57 (describing Ta_2O_5 layer as "second reflecting surface").)

Further, as Sun explains, some of the incident light continues through the interference layer and is further partially reflected at the interface (“interface 2”) between the biolayer (i.e., the antibody layer and any bound analyte) and the external environment, thereby producing a second reflected light beam (“B”). (EX1010, 657, Fig. 1; EX1002 ¶155.) In the context of the ’585 patent, this biolayer (or more specifically, its distal surface) comprises the “first reflecting surface.” (EX1001, 3:2-4, 7:25-33 (describing immobilized antibody layer as “first reflecting surface”); EX1002 ¶155.)

e. [1D]: “said first and second reflecting surfaces separated by at least 50 nm”

As addressed in Section VI.C.1.d (Element [1C]), Sun, alone and in combination with Yu, teaches an interference layer that separates the “first and second reflecting surfaces.” (EX1010, 657, 659, Fig. 1; EX1011, 1489, Figure 1(A); EX1002 ¶155.) Determining the thickness of the interference layer (and hence the separation between the reflecting surfaces) would have been a matter of routine optimization well within a POSA’s capability. (EX1002 ¶156); *see Geisler*, 116 F.3d at 1470-71. Sun and Yu also provide express guidance in this regard. (EX1002 ¶157.) For example, Sun discloses that the interference layer may be a “siliconization film” with a thickness “from 1 to 2 μm ” (1000 to 2000 nm). (EX1010, 657.) Sun additionally describes a test in which the “siliconization film” along with the antibody and antigen layers had a collective thickness of “about 0.987

μm” (987 nm). (EX1010, 657, 659.) Because the antibody and antigen layers account for only a small fraction of the 987 nm, the separation between the reflecting surfaces due to the thickness of the interference layer was necessarily “greater than 50 nm.” (EX1002 ¶157); *see Persion*, 945 F.3d at 1190-91.

Further, as addressed in Section VI.B, a POSA would have found it obvious to substitute Sun’s interference layer with a “transparent polystyrene layer” as described in Yu. (EX1011, 1489, Figure 1(A); EX1002 ¶158.) Yu discloses that this “transparent polystyrene layer” may have a thickness of about “~650 nm,” which likewise is “greater than 50 nm.” (EX1011, 1489; EX1002 ¶158.)

- f. **[1E]: “wherein said first reflecting surface binds a layer of analyte binding molecules positioned so that interference between a beam of light reflected from the first reflecting surface into the optical fiber and a beam of light reflected from the second reflecting surface into the optical fiber varies as analyte binds to the layer of analyte binding molecules”**

As addressed in Section VI.C.1.d (Element [1C]), Sun, alone and in combination with Yu, teaches a RIfS probe with an interference layer that separates “a first reflecting surface” and “a second reflecting surface,” and incident light reflected from these surfaces forms two light beams, “B” and “A,” respectively. (EX1010, 657, Figure 1; EX1002 ¶159.)

Moreover, as addressed in Section VI.A, Sun’s RIfS setup detects analyte binding based on the fact that the reflected light beams interfere with one another to

form an interference pattern (reflectance spectrum) that varies based on the binding of analyte. (EX1010, 657, Figure 1; EX1002 ¶160.) Specifically, when analyte molecules bind to the immobilized antibody layer during a test, the separation between the two reflecting surfaces increases, which is manifested as a “phase shift” (i.e., a variance) in the “interference pattern,” as shown in Figures 2 and 5.

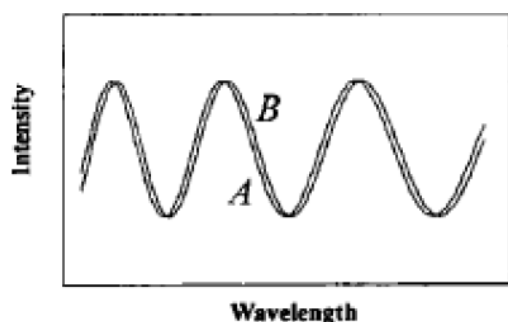
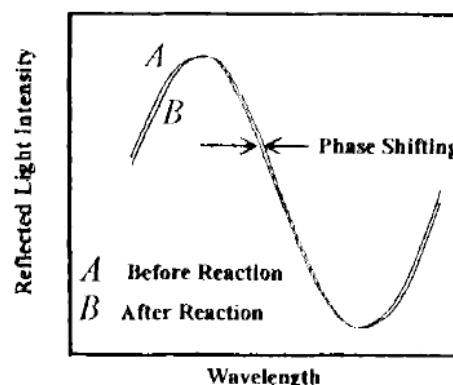


Figure 2, The relationship between wavelength (λ) and reflected light intensity (I), curve *A* indicates initial value of Δ , curve *B* indicates that Δ has increased



(b)
Figure 5 Testing results

(EX1010, 658-59, Figures 2, 5; EX1002 ¶¶160-161.) Thus, if a phase shift is detected, Sun explains it can be concluded that analyte molecules are present in the sample. (EX1010, 658.) Sun further describes the results of a test using a probe in which a layer of immobilized goat-IgG antibodies (“analyte binding molecule”) is used to bind and detect human-IgG antibodies (“analyte”) in a sample. (*Id.*, 659; EX1002 ¶161.)

In summary, Sun, alone and in combination with Yu, teaches an optical assembly comprising each element of claim 1 and renders claim 1 obvious.

2. Claims 2 and 5-10

Sun in combination with Yu teaches claims 2 and 5-10, which recite characteristics of the “second reflecting surface” and the “transparent material” that comprises the “optical element” of claim 1.

As discussed in Sections VI.B and VI.C.1.d (Element [1C]), a POSA would have been motivated based on Yu to modify Sun’s probe by (1) using a “transparent polystyrene layer” as the interference layer, and (2) incorporating an approximately 10 nm layer of tantalum pentoxide (Ta_2O_5) as the “second reflecting surface.” (EX1010, 657-59, Figures 1, 2; EX1011, 1489, Figure 1(A); EX1002 ¶163.)

This configuration meets the elements of claims 2 and 5-10. For example, the “optical element transparent material” is a “transparent polymer” (claim 6), namely “polystyrene” (claim 7). (EX1002 ¶163.) Polystyrene has a refractive index (approximately 1.58-1.59) that is “less than 1.8” (claim 5). (EX1031, Krause, 1926, Table 1; EX1002 ¶163.) Further, the “second reflecting surface” is a layer of material that “comprises Ta_2O_5 ” (claim 9) having a thickness (approximately 10 nm) that is “between 5 nm and 50 nm” (claim 10) and having a refractive index (approximately 2.1) that is greater than that of the polystyrene interference layer (claim 2) and “greater than 1.8” (claim 8). (EX1001, 7:56-57; EX1002 ¶163.)

3. Claims 3-4

Claim 3 recites that “the separation between [the] first and second reflecting surfaces is between 100 nm and 5,000 nm,” which claim 4 narrows to “between 400 nm and 1,000 nm.” As addressed in Sections VI.C.1.d (Element [1C]) and VI.C.1.e (Element [1D]), determining the thickness of the interference layer (and hence the separation between the “first and second reflecting surfaces”) would have been a matter of routine optimization well within a POSA’s capability. (EX1002 ¶¶98, 165); *Geisler*, 116 F.3d at 1470-71. Yu and Sun also provide express guidance by disclosing interference-layer thicknesses of “~650 nm” and approaching 987 nm, respectively, which are within the claimed ranges. (EX1010, 657, 659; EX1011, 1489; EX1002 ¶¶166-67).

4. Claims 11-12

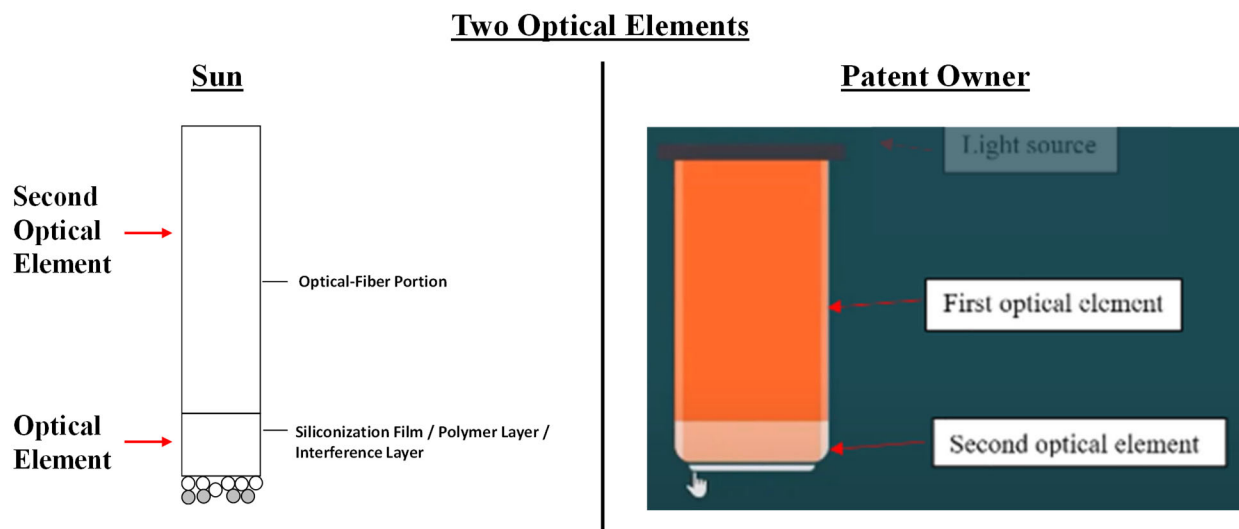
Claims 11-12 specify that the “layer of the analyte binding molecules” is selected from a group that includes a “protein” and that this “protein” is selected from a group that includes “an antibody.” As addressed in Section VI.C.1.f (Element [1E]), the “layer of analyte binding molecules” in Sun’s probe comprises antibodies (a type of protein). (EX1010, 657, 659, Fig. 1; EX1002 ¶169.)

5. Claims 15-17

Claim 15 recites that the “optical assembly” of claim 1 “further compris[es] a second optical element overlaying [the] second reflecting surface.” Claims 16-17

specify that “the thickness of [the] second optical element is greater than 100 nm” and “200 nm,” respectively.

As addressed in Sections VI.C.1.c (Element [1B]), Sun describes a probe that includes an optical-fiber portion coated on its distal end with an interference layer. In the context of claims 15-17 and based on Patent Owner’s infringement positions in the related litigations, the interference layer comprises an “optical element” and the optical-fiber portion comprises “a second optical element,” as both are elements of Sun’s optical assembly that convey and affect the optical properties of light.



(EX1002 ¶171; EX1010, 657, Figure 1 (adapted); EX1037, ¶62, Figure 2 (background deemphasized); *see also* EX1060, 18.)

Moreover, regarding claim 15, the optical-fiber portion (“second optical element”) “overlay[s] [the] second reflecting surface,” which is the “interface 1” between the optical-fiber portion and the interference layer, or alternatively a thin layer of Ta₂O₅ incorporated at this interface as described in Yu. (EX1010, 657,

Figure 1; EX1011, 1489, Figure 1(A) (showing Ta₂O₅ layer sandwiched between the substrate (corresponding to the optical-fiber portion of Yang's probe) and interference layer); EX1002 ¶172.)

Regarding claims 16-17, Sun does not expressly state the thickness of the optical-fiber portion of the probe, but it is necessarily “greater than 100 nm” and “200 nm” (i.e., greater than 0.1 μm and 0.2 μm), which is roughly a thousandth of the thickness of a human hair. (EX1002 ¶173); *see Persion*, 945 F.3d at 1190-91. Notably, Sun discloses that the optical-fiber portion of the probe is coupled to a Y-shaped optical fiber via a “standard SMA connector,” which requires the thickness (length) of the optical-fiber portion to be substantially greater than a few micrometers, or even a few millimeters in practice. (EX1010, 658, Figure 3; EX1002 ¶174.) Sun also describes the interference layer as having a thickness “at the level of μm,” which similarly indicates that the optical-fiber portion to which it is attached has a thickness (length) greater than 100 or 200 nanometers. (EX1010, 659; EX1002 ¶175.) Further, Figure 3 shows the Sun's probe as substantially longer than the width of its distal end, and only a portion (the distal end) is shown as being immersed in a sample solution, while most of the probe is not immersed.

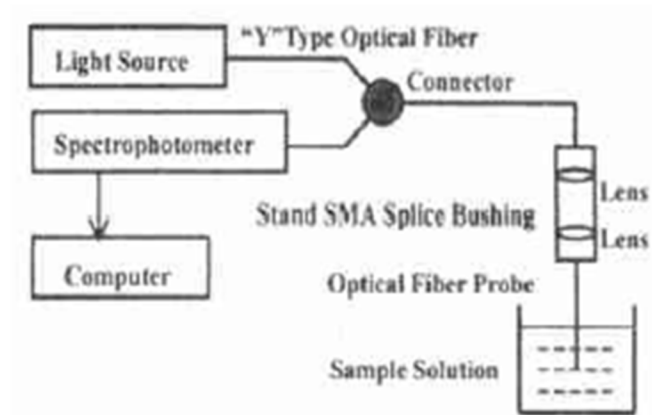


Figure 3 Detecting system structure

(EX1010, Figure 3; EX1002 ¶176.) Thus, even if not drawn to scale, Figure 3 indicates that the thickness (length) of the optical-fiber portion is substantially greater than submicron levels. (EX1002 ¶176.)

6. Claims 13-14 and 18-19

Claims 13 and 18 recite that the “optical assembly is adapted for coupling to [the] light source through a mechanical coupling that engages” either the “optical element” (claim 13) or the “second optical element” (claim 18) “with [the] fiber.” Claim 19 recites that the mechanical coupling provides “an air gap between [the] second optical element and [the] fiber.” Claim 14 recites that the “optical element is adapted for coupling to [the] light source through a coupling assembly that comprises a lens system.”

As addressed in Sections VI.C.1.c (Element [1B]) and VI.C.5 (claims 15-17), the interference layer and the optical-fiber portion of Yang’s probe collectively comprise an “optical element” (claim 1), or alternatively comprise an “optical

element” and a “second optical element,” respectively (claim 15). (EX1002 ¶178.)

In either case, Sun’s probe, which comprises both the “optical element” and “second optical element,” is coupled to the tip of a Y-shaped optical fiber, and in turn a “light source,” via a “standard SMA connector.”

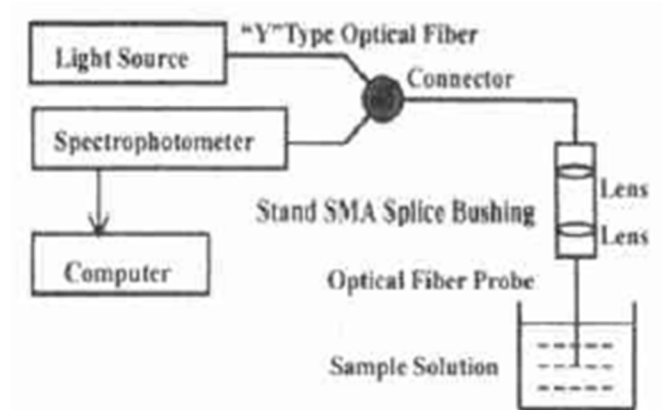


Figure 3 Detecting system structure

(EX1010, 658, Figure 3; EX1002 ¶178.)

Regarding claims 13-14 and 18-19, the SMA connector is a screw-type coaxial “mechanical coupling” or “coupling assembly” with male and female components that removably engage one another. (EX1002 ¶179; EX1034, 175, 266; EX1033, 310-1-310-2.) The SMA connector couples Sun’s optical assembly to a light source by engaging the optical-fiber portion of the probe (whether it is a part of the “optical element” of claim 1 or the “second optical element” of claim 15) with the Y-shaped optical fiber. (EX1010, 658, Figure 3; EX1002 ¶180.)

Regarding claim 14, Sun discloses that “coupling assembly” includes “lenses” that comprise a “lens system” and depicts in Figure 3 (above) an “SMA splice bushing” with at least two lenses. (EX1010, 658, Figure 3; EX1002 ¶181.)

Regarding claim 19, because the SMA connectors used in Sun’s system are able to rotate, they inherently incorporate an “air gap” between the distal end of the Y-shaped optical fiber and the optical-fiber portion of the probe (“second optical element”) to prevent the respective fiber ends from directly contacting one another and becoming scratched, for example as shown in the figure below.



(EX1002 ¶182; EX1058, 2; EX1059, 81, 83, Figure 6-4.) In any event, a POSA would have found the use of a mechanical coupling that provides an “air gap” to be an obvious design choice to reduce the likelihood of fiber ends from becoming scratched or otherwise coated with debris or foreign substances, particularly in a setup such as Sun’s where the Y-shaped optical fiber is intended to be a permanent fixture to which different probes may be removably attached. (EX1002 ¶183.)

VII. THE BOARD SHOULD REACH THE MERITS OF THE PETITION

The *Advanced Bionics* framework and *Becton* factors considered under 35 U.S.C. § 325(d) all weigh in favor of institution and against discretionary denial. See *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (PTAB Dec. 15, 2017); *Advanced Bionics, LLC v. MED-EL Elektromedizinische Gerate GmbH*, IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020).

As an initial matter, the first part of the *Advanced Bionics* framework and *Becton* factors (a), (b), and (d) strongly favor institution given that Petitioner bases its grounds on noncumulative references or combinations of references that were not previously presented or considered during prosecution. Notably, Yu (Grounds 1 and 2) and Sun (Ground 2) were not previously presented or considered. As addressed in Sections V.B-V.C and VI.A-VI.B, Sun discloses a RfS probe substantially similar to that described in the '585 patent, while Yu discloses the use of a polystyrene interference layer and tantalum pentoxide layer in a RfS sensor, along with express motivations to combine.

To the extent the Board reaches the second part of the *Advanced Bionics* framework, it too, along with *Becton* factors (c), (e), and (f), favors institution. The only reference that was arguably previously presented during prosecution is Yang (Ground 1). Notably, Yang was cited only during prosecution of the parent '751 application and not the '736 application that issued as the challenged '585 patent.

Regardless, the record confirms that the examiners who oversaw these applications did not appreciate the relevant scope of Yang's disclosure. For example, during the '751 prosecution, the examiner cited Yang merely as a secondary reference and relied instead on a combination of other references to address most of the claim limitations, whereas here Petitioner presents Yang in a new light as a primary reference that discloses nearly all of the claimed subject matter. (EX1006, [60]-[69].) Moreover, the examiner rejected claim 19 only for obviousness-type double patenting and did not appreciate that Yang disclosed SMA connectors that inherently included an "air gap" as claimed. (EX1006, [71], [73].)

Significantly, even without appreciating the full scope of Yang's disclosure, the examiner in the '751 prosecution allowed the pending claims only after they were amended to require a specific attachment mechanism comprising "flexible gripping arms." (EX1006, [42]-[43], [92]-[93], [95], [127].) Conversely, during the '736 prosecution, a different examiner allowed these exact same claims without issuing any prior-art rejections or requiring any amendments, and without providing any substantive comments or explanation that would suggest consideration of Yang's disclosure. (EX1007, [42]-[43], [208]-[209], [241].)

Petitioner further presents additional evidence here in the form of an expert declaration and supporting exhibits showing how the combinations in each ground teach every element of the challenged claims, as well as the reasons why a POSA

would have pursued such a combination. *See Mylan Pharms. Inc. v. Merck Sharp & Dohme Corp.*, IPR2020-00040, Paper 21, 20 (PTAB May 12, 2020) (emphasizing new expert testimony). Thus, the Board should reach the merits of the Petition.

VIII. MANDATORY NOTICES – 37 C.F.R. § 42.8

A. Real Parties-in-Interest (§ 42.8(b)(1))

The Petitioner and real parties-in-interest are Gator Bio Inc. and Hong Tan. Out of an abundance of caution, Petitioner also identifies Access Medical Systems, Ltd., the parent company of Gator Bio Inc., as a real party-in-interest.

B. Related Matters (§ 42.8(b)(2))

Patent Owner has asserted the '585 patent in a civil action in the Northern District of California: *Sartorius Bioanalytical Instruments, Inc. v. Gator Bio Inc. and Hong Tan*, Case No. 5:22-CV-01417 (N.D. Cal.). Petitioner has moved to dismiss the complaint in this action and the district court has not issued a scheduling order.

Additionally, Patent Owner has asserted the '585 patent in a complaint filed with the International Trade Commission: *In the Matter of Certain Bio-Layer Interferometers and Components Thereof*, Docket No. 3652 (ITC). The Commission has not yet issued a ruling regarding the institution of an investigation in this matter. To the extent an investigation is instituted, and the district court action is not dismissed, it is anticipated that the district court action will be stayed pursuant to 28 U.S.C. § 1659.

C. Lead and Back-Up Counsel (§ 42.8(b)(3))

Petitioner designates the following lead and back-up counsel, and submits herewith a Power of Attorney pursuant to 37 C.F.R. § 42.10(b).

Lead Counsel	Back-up Counsel
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D. Service Information (§ 42.8(b)(4))

Petitioner consents to electronic service by email at GatorBio_IPR@perkinscoie.com.

Date: November 17, 2022

Respectfully submitted,

/ Hari Santhanam /

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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), the undersigned hereby certifies that the foregoing Petition includes 13,846 words, excluding the parts exempted by § 42.24(a)(1), and is in compliance with § 42.24(a)(1)(i).

/ Hari Santhanam /
Hari Santhanam

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true copy of the foregoing Petition for Inter Partes Review of U.S. Patent No. 8,305,585 along with all exhibits and powers of attorney were served on November 17, 2022, via FedEx Overnight delivery to the assignee of the patent at the correspondence address of record:

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