UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Bio-Techne Corporation and ProteinSimple,
Petitioners

v.

Caliper Life Sciences, Inc. and/or PerkinElmer, Inc.[1],
Patent Owners

U.S. Patent No. 6,834,240
Filing Date: May 22, 2003
Issue Date: Dec. 21, 2004
Title: Software for the Display of Chromatographic Separation Data

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Inter Partes Review No. _____

Petition for *Inter Partes* Review of U.S. Patent No. 6,834,240

[1] Caliper was acquired by PerkinElmer in 2011 but Caliper is still listed as assignee of U.S. Patent No. 6,834,240. It is unclear who the true and correct assignee of this patent is so Petitioners include both Caliper and PerkinElmer for completeness.

Table of Contents

Page

Table of Contents
(continued)

Page

EXHIBITS

Exhibit No.	Description of Document
1001	U.S. Patent No. 6,834,240 ("the '240 patent")
1002	Declaration of Dr. Karl Voss
1003	U.S. Patent No. 5,963,456 ("Klein")
1004	U.S. Patent No. 5,228,960 ("Liu")
1005	U.S. Patent No. 5,139,630 ("Chen")
1006	Paula B. Hietpas, *et al*., "Ultrathin Slab Gel Separation of DNA Using a Single Capillary Sample Introduction System," Analytical Chemistry (Jul. 1, 1997)
1007	Curriculum Vitae of Dr. Karl Voss
1008	R. Kuhn and S. Hoffstetter-Kuhn, "Capillary Electrophoresis: Principles and Practice," Springer Laboratory (1993)
1009	Dorland's Illustrated Medical Dictionary (1994)
1010	Stedman's Medical Dictionary (1993)
1011	Daniel C. Carter, *et al*., "Structure of Serum Albumin," Advances in Protein Chemistry, Academic Press, Vol. 45 (1994)
1012	Frank W. Putnam, "The Plasma Proteins: Structure, Function, and Genetic Control," Academic Press, 2d ed. (1975)
1013	U.S. Patent No. 5,413,686 ("Klein '686")
1014	Mark Brownstein, "Technology Tutorial: Memory Caches Speed Access to Data," Info World, Vol. 12, Iss. 8 (Feb. 19, 1990)
1015	IBM Dictionary of Computing (10^{th} ed. 1993)
1016	Janice T. Busher, "Serum Albumin and Globulin," Clinical Methods: The History, Physical, and Laboratory Examinations, Chap. 101 (3 ed. 1990)
1017	Robert G. Hamilton, "Human IgG Subclass Measurements in the Clinical Laboratory," Clin. Chem., Vol. 33, No. 10 (1987)
1018	Webster's Ninth New Collegiate Dictionary (1988)
1019	James P. Landers, "Handbook of Capillary Electrophoresis," (2d ed. 1996)
1020	Lloyd R. Snyder, "Introduction to Modern Liquid Chromatography" (1979)

EXHIBITS

Exhibit No.	Description of Document
1021	"Gel Electrophoresis: How Does It Work?," Purdue University Van Project (May 11, 1996)
1022	Galen Hunt, *et al*., "Detours: Binary Interception of WIN32 Functions," Proceedings of the 3rd USENIX Windows NT Symposium (July 12-13, 1999)
1023	Barnett B. Rosenblum, *et al.*, "Improved single-strand DNA sizing accuracy in capillary electrophoresis," Nucleic Acids Research, Vol. 25, No. 19 (1997)
1024	IUPAC Compendium of Chemical Terminology (1990)
1025	IUPAC Compendium of Chemical Terminology (1996)
1026	IUPAC Compendium of Chemical Terminology (1992)
1027	Christopher K. Mathews, *et al.*, "Biochemistry," The Benjamin/Cummings Publishing Co., Inc. (1990)
1028	S. Wieman, *et al.*, "Simultaneous On-line DNA Sequencing on Both Strands with Two Fluorescent Dyes," Anal Biochem (Jan. 1995)(Abstract)
1029	Miguel Garcia-Sancho, "Biology, Computing and the History of Molecular Sequencing From Proteins to DNA 1945-2000," Science, Technology and Medicine in Modern History (2012)
1030	File History for U.S. Patent No. 6,834,240
1031	Heather A. Drury, *et al.*, "Spatial Normalization of One-Dimensional Electrophoretic Gel Images," Genomics 8 (1990)
1032	E.M. Southern, "Measurement of DNA Length by Gel Electrophoresis," Analytical Biochemistry 100 (1979)
1033	Adam T. Woolley, *et al.*, "High-Speed DNA Genotyping Using Microfabricated Capillary Array Electrophoresis Chips," Anal. Chem. (June 1, 1997)

I. INTRODUCTION

Bio-Techne Corporation ("Bio-Techne") and ProteinSimple (collectively "Petitioners") petition for *inter partes* review ("IPR") under 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42 of claims 1, 3, 5-7, 14, 15 and 17-20 ("the Petitioned Claims") of U.S. Patent No. 6,834,240 (Ex. 1001).

The '240 patent is generally directed to displaying data associated with the analysis of macromolecular structures. The '240 patent claims subjecting a first sample to a chromatographic separation process and receiving a series of measurements indicating a presence of constituents in the first sample at a scanning location over time. The '240 patent also claims subjecting a second sample to the chromatographic separation process, receiving a series of measurements indicating a presence of constituents in the second sample at a scanning location over time, and then normalizing the measurements from the second sample using the measurements from the first sample.

The Klein reference (Ex. 1003) anticipates the Petitioned Claims and renders them obvious when combined with the other prior art discussed below.

II. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8(A)(1)

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

Bio-Techne Corporation and ProteinSimple are the real parties-in-interest. ProteinSimple is a wholly owned subsidiary of Bio-Techne Corporation.

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

There are no related judicial or administrative matters that would affect, or be affected by, a decision in this proceeding. Caliper Life Sciences, Inc. and/or PerkinElmer, Inc. (collectively "Patent Owner") has not yet asserted the '240 patent against Petitioners but litigation is anticipated. Petitioners will supplement this section when and if Patent Owner files suit against Petitioners.

C. Lead and Back-Up Counsel under 37 C.F.R. § 42.8(b)(3)

Lead Counsel: Erik B. Milch (Reg. No. 42,887) / emilch@cooley.com
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D. Service Information

The Petition is being served by FEDERAL EXPRESS to the '240 Patent Owner's attorneys of record, Cardinal Law Group, Ltd. and the known outside counsel to PerkinElmer, Day Pitney LLP. Petitioners Bio-Techne and ProteinSimple consent to service by e-mail at the addresses provided above.

E. Power of Attorney

Filed concurrently with this petition per 37 C.F.R. § 42.10(b).

III. PAYMENT OF FEES - 37 C.F.R. § 42.103

This Petition requests review of claims 1, 3, 5-7, 14, 15 and 17-20 of the '240 patent (a total of 11 claims) and is accompanied by a payment of $23,000. 37

C.F.R. § 42.15. This Petition meets the fee requirements of 35 U.S.C. § 312(a)(1).

IV. REQUIREMENTS FOR *INTER PARTES* REVIEW UNDER 37 C.F.R. §§ 42.104 AND 42.108

A. Grounds for Standing Under 37 C.F.R. § 42.104(a)

Petitioners certify that the '240 patent is eligible for IPR and further certify that Petitioners are not barred or estopped from requesting IPR.

B. Identification of Challenge Under 37 C.F.R. § 42.104(b) and Statement of Precise Relief Requested

Petitioners request that the Board institute *inter partes* review of claims 1, 3, 5-7, 14, 15 and 17-20 of the '240 patent and request that each claim be found unpatentable as anticipated under 35 U.S.C. § 102(e) and/or obvious under 35 U.S.C. § 103(a) on the following grounds:

Ground	'926 Claim(s)	Basis for Challenge
1.	1, 3, 5-7, 14, 15 and 17-20	Anticipated by Klein[2] under 35 U.S.C. § 102(e).

[2] Klein incorporates by reference U.S. Patent No. 5,228,960 ("Liu" Ex. 1004) and U.S. Patent No. 5,139,630 ("Chen" Ex. 1005). It is therefore appropriate to rely on the disclosure of Liu and Chen as incorporated in Klein to support anticipation. *See Intelligent Bio-Systems, Inc. v. Illumina Cambridge Limited*, Case IPR2013-000128, Paper 23 (July 29, 2013) at 9-11 (citing to *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000); *Callaway Golf Co. v.*

Ground	'926 Claim(s)	Basis for Challenge
2.	1, 3, 5-7, 14, 15 and 17-20	Obvious over Klein in view of Liu under 35 U.S.C. § 103(a).
3.	1, 3, 5-7, 14, 15 and 17-20	Obvious over Klein in view of Hietpas under 35 U.S.C. § 103(a).

This petition is accompanied by the Declaration of Dr. Karl Voss (Ex. 1002, "Dr. Voss"), an expert in the field.

C. Threshold Requirement for *Inter Partes* Review 37 C.F.R. § 42.108(c)

Inter partes review of claims 1, 3, 5-7, 14, 15 and 17-20 should be instituted because this Petition establishes a reasonable likelihood that Petitioners will prevail with respect to each of the claims challenged. 35 U.S.C. § 314(a).

V. BACKGROUND OF TECHNOLOGY RELATED TO THE '240 PATENT

Dr. Voss provides a technology tutorial in his declaration. (Ex. 1002 at ¶¶ 33-53.)

VI. SUMMARY OF THE '240 PATENT

A. Brief Description of the '240 Patent

The specification of the '240 patent is directed to techniques for displaying chromatographic separation data using a graphical interface. The chromatographic separation data includes a series of measurements for samples at a scanning

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Acushnet Co., 576 F.3d 1331, 1347-48 (Fed. Cir. 2009); *Net MoneyIN, Inc. v. VeriSign, Inc.* 545 F.3d 1359, 1369 (Fed. Cir. 2008)).

location over time that can be displayed in a series of bands that are aligned. (Ex. 1001 at Abstract.) Specifically, the '240 patent discloses a system for displaying measurements acquired from microfluidic capillary separation experiments, in a gel-like format. The measured data is output as a series of bands to allow the side-by-side display of chromatographic separation data from multiple samples, which can be normalized for easier comparison. (*Id.* at 2:29-46, 16:28-29.)

In one application, using capillary electrophoresis, materials are separated based on their size. The materials are introduced into a capillary channel having a separation matrix and an applied electric field causes the sample to be drawn through the capillary channel. The single capillary channel is used to serially analyze multiple samples. (*Id.* at 3:26-41.) Separated species are detected at a single point along the length of the capillary channel as the species move past a detector located at that point. The collected data are then displayed as a series of bands and normalized to a standard. (*Id.* at 3:58-4:15.) FIG. 10D, reproduced at right, illustrates a screen display in which the series of bands from successive series of data are normalized to a particular marker. The methods are disclosed as being useful in capillary electrophoresis systems, but can be useful in other systems such

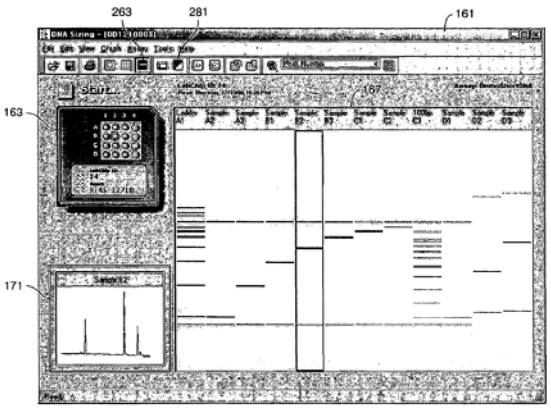


FIG. 10D

as, for example, conventional column chromatography, HPLC, FPLC, mass spectrometry, scanned slab gel methods and the like. (*Id.* at 5:31-37.)

B. The Petitioned Claims of the '240 Patent

The Declaration includes a chart that lists and labels the elements of the Petitioned Claims. (Ex. 1002 at ¶ 58.) Petitioners refer to the various elements of the Petitioned Claims using the same claim element identifiers as the Declaration.

VII. CLAIM CONSTRUCTION UNDER 37 C.F.R. § 42.104(b)(3)

A. Legal Overview

A claim subject to IPR is given its "broadest reasonable construction in light of the specification of the patent in which it appears."[3] 37 C.F.R. § 42.100(b).

B. "At A Scanning Location Over Time" (Claims 1, 17 & 19)

The broadest reasonable interpretation of "at a scanning location over time" is "at a location on the structure containing the sample as constituents within the sample move past the location during a period of time." This construction is consistent with the '240 patent specification.

The microfluidic devices in the '240 patent are described as including one or more detectors, such as "optical sensors, temperature sensors, pressure sensors, pH

[3] Petitioners reserve the right to pursue different constructions in litigation. *In re Zletz*, 893 F.2d 319, 321 (Fed. Cir. 1989).

sensors, conductivity sensors, and the like." (Ex. 1001 at 11:1-5.) These detectors are "placed either within or adjacent to the microfluidic device or one or more channels, chambers or conduits of the device" so the detector is "capable of detecting the property of the microfluidic device, a portion of the microfluidic device, or the *contents of a portion* of the microfluidic device, for which that detector was intended." (*Id.* at 11:7-17 (emphasis added); *see also, id.* at 9:18-30, 10:65-12:11.)

The '240 patent discloses that the detectors take measurements or "scan" the sample as the constituents within the sample move past the detector. (*See e.g.*, Ex. 1001 at 6:50-52, 13:39-42.) For example, in one embodiment, the specification describes taking measurements "at the scanning location of the microfluidic device as a sample [is] electrokinetically pulled through the separation channel." (*Id*. at 13:51-55.) In another embodiment, the specification describes taking measurements as "the material pass[es] through the detector." (Ex. 1001 at 16:57-62; *see also, id.* at 17:43-48.)

The '240 patent discloses that detectors take measurements over a period of time at specific locations. The measurements are plotted in a graph showing, for example, measured intensity vs. time. (*See, e.g.*, Ex. 1001 at 6:50-52, 13:37-42, 14:43-48, 15:39-42.) The time axis in FIGS. 10C and 10E of the '240 patent shows that a detector took measurements at a specific location over a 70 second period.

Thus, the broadest reasonable interpretation for "at a scanning location over time" is "at a location on the structure containing the sample, as constituents within the sample move past the location during a period of time." (*See also*, Ex. 1002 at ¶¶ 59-66 .)

VIII. PERSON HAVING ORDINARY SKILL IN THE ART & STATE OF THE ART

The '240 patent is directed to displaying data associated with the analysis of macromolecular structures. (Ex. 1002 at ¶¶ 54-57.) At the time of the alleged invention, a person having ordinary skill in the art ("POSA") as of 1997 would hold a bachelor's degree or the equivalent in analytical chemistry (or related academic fields) and at least five years of additional work experience in the area of laboratory diagnostics and experimentation. (*Id*. at ¶¶ 20-27.)

IX. CLAIMS 1, 3, 5-7, 14, 15 AND 17-20 OF THE '240 PATENT ARE UNPATENTABLE

As detailed in the sections below, claims 1, 3, 5-7, 14, 15 and 17-20 of the '240 patent are anticipated by Klein, obvious in light of Klein and Liu, and obvious in light of Klein and Hietpas.

A. Overview Of The Prior Art

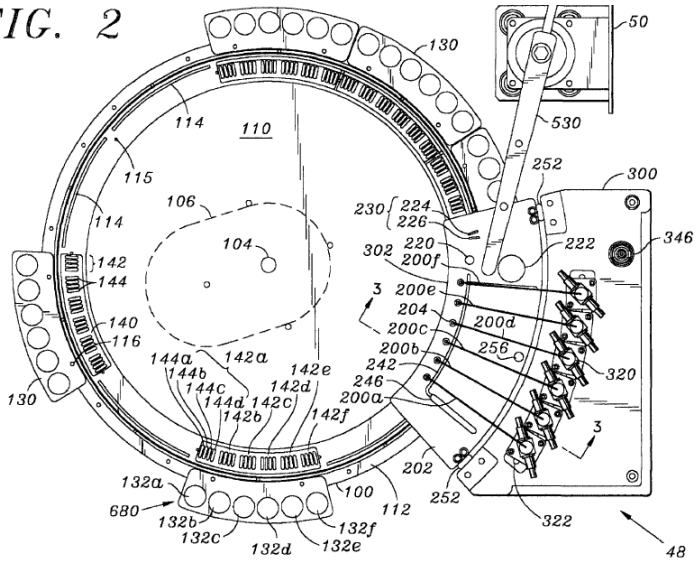
1. Overview of Klein

Klein was filed on November 27, 1996 and is a continuation of two U.S. patent applications with an earliest priority date of July 17, 1992. (Ex. 1003 at 1:5-8.) Klein issued on October 5, 1999. Because Klein was filed before the earliest

priority date of the '240 patent (December 30, 1997), the Klein patent qualifies as prior art under 35 U.S.C. § 102(e).

Klein describes a method and apparatus for displaying capillary electrophoresis data showing, for example, absorbance with respect to time related to graphic values within a range or scale. (Ex. 1003 at Abstract.) The output of the collected data can be in the form of a quantitative (electrophoretogram absorbance values) and/or qualitative (graphic stripe) display. (*Id.*) Klein discloses a microfluidic device (i.e., a capillary) on which a sample is subjected to an electrophoretic separation process. (*Id.* at 5:60-6:3, 13:58-63.) Klein discloses a microfluidic instrument including a detection system that detects the results of the electrophoretic separation process. (*See, e.g.*, *id.* at FIG. 2, reproduced above).

FIG. 2



Klein discloses a method including electrophoresis of fluid samples in a capillary and detecting a plurality of values related to the absorbance of the fluid in the capillary. (Ex. 1003 at 3:34-37.) The device of the invention includes, for

example, six capillaries that are each connected to an optical detector. (*Id.* at 6:4-7, 8:7-16.) The "detection end" of each capillary is the end proximate to the detector used to detect the results of electrophoretic separation occurring along the length of the capillary. (*Id.* at 5:67-6:3.) Klein discloses that the measurements indicating presence of certain constituents are taken at a single location over time. (*Id.* at 13:58-67.) When an electrophoresising voltage is applied across the capillaries, separation occurs and separated samples flow past the window 432 within each of the capillaries 200. (*Id.* at 13:58-63.) The light directed through the windows between the input and output optical fiber optic light guides and thus through the bores of the capillaries is periodically sampled and processed. (*Id.* at 13:58-14:3.) Klein also discloses a computer system, including a processor (e.g., a type i386 available from Intel Corporation), that displays electrophoretic separation data corresponding to results received from the microfluidic instrument. (*Id.* at 10:10-30.)

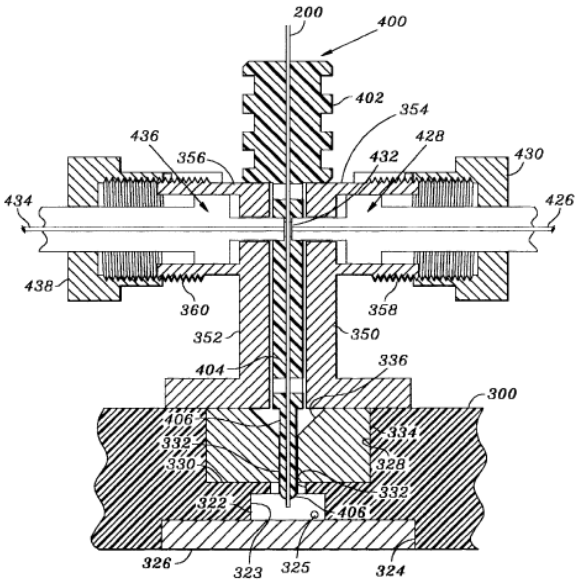


FIG. 7

Klein discloses that electrophoretic separation data from the samples can be displayed as a graph. (*See* Ex. 1003 at FIG. 10 (reproduced at the right).) Peaks 762, 764, 766 and 768 represent increasing absorbance on the graph 750. (*Id.* at 16:23-24.) Corresponding bands 772, 774, 776 and 778, respectively, serve to visualize increasing dark graphic values in the stripe 760 with respect to the increasing absorbance peaks 762, 764, 766 and 768. (*Id.* at 16:24-29.)

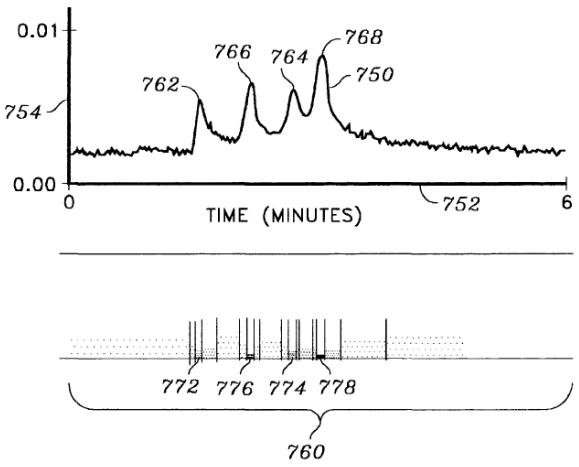


FIG. 10

Klein further discloses that separation data can be presented in a first lane comprising a series of bands from chromatographic separation data from a first sample and a second lane comprising a series of bands from chromatographic separation data from a second sample as a parallel set of lanes. (*See* Ex. 1003 at FIG. 13 (reproduced at the right).) Each of the capillaries analyzed includes its own area, 850a-850f, respectively. Each of the areas 850a-850f may display the absorbance data as a stripe similar to the stripe 760 of FIG. 10, or may display a stripe overlaid with an absorbance

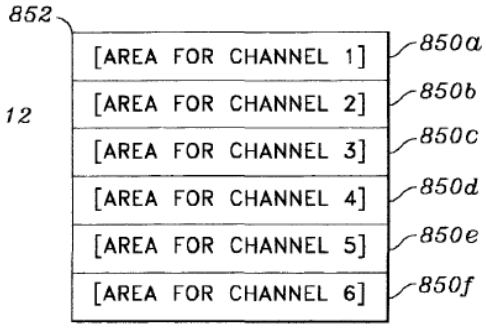


FIG. 13

graph similar to that illustrated in FIG. 12. (*Id.* at 17:35-47.) The display arrangement of FIG. 13 allows the direct comparison of the results for each of the capillaries 200. (*Id*.)

Klein further discloses that the data can be normalized for more ready comparison. Klein incorporates by reference U.S. Patent No. 5,228,960 to Liu *et al*. ("Liu," Ex. 1004), which discloses normalizing electrophoretic data based on markers. (*See* Ex. 1003 at 17:47-55.)

2. Overview of Liu

Liu issued as a patent on July 20, 1993. Because Liu published more than one year before the earliest priority date of the '240 patent (December 30, 1997), Liu qualifies as prior art under 35 U.S.C. § 102(b). Liu is entitled "Analysis of Samples by Capillary Electrophoretic Immunosubtraction."

As disclosed in Liu, "to compare the two electropherograms … it is preferred that the electropherograms be normalized, i.e., variations between the conditions of the first run and the second run are adjusted such that direct comparisons between the different separations can be conducted." (Ex. 1004 at 8:28-33.)

Liu discloses that normalization can be accomplished by the use of two "markers" which are added to the sample prior to the analysis of the samples. (Ex. 1004 at 9:13-20.) To the degree that the detected sample constituents are detected

at different times (due to, for example, environmental or experimental variations), the relative detection times of the two sets of constituents can be normalized using the markers. (*Id.* at 9:13-49.)

Liu incorporates U.S. Patent No. 5,139,630 to Chen ("Chen," Ex. 1005) by reference for purposes of describing the methodologies and protocols for selecting appropriate markers for an assay.[4] (Ex. 1004 at 9:21-28.) It is therefore appropriate to rely on the disclosure of Chen as incorporated in Klein. (*See also,* Ex. 1003 at 4:67-5:3 (illustrating that Klein references the marker teachings of Chen but does not incorporate Chen by reference).)

3. Overview of Hietpas

Hietpas was published on July 1, 1997. Because Hietpas published before the earliest priority date of the '240 patent (December 30, 1997), Hietpas qualifies as prior art under 35 U.S.C. § 102(a).

Hietpas discloses a method for DNA separation combining parallel processing capabilities of slab gels with the advantages of capillary sample

[4] Klein, Chen and Liu are commonly owned. Liu also has one named inventor in common with each of Klein and Chen. For example, Liu and Chen both name Fu-Tai A. Chen as an inventor. And, Klein and Liu name Gerald L. Klein as an inventor.

introduction. (Ex. 1006 at 1 (col. 1).) Detection of the sample separation is resolved with an ion laser focused to a line for excitation and a charge-coupled device (CCD) for collection of fluorescence. (*Id.*) Hietpas discloses a computer program that identifies a band in the first set of bands that corresponds to a marker in the first sample, identifies a band in the second set of bands that corresponds to the same marker in the second sample, and aligns the bands when presenting the two sets of bands adjacent to each other. (*See id.* at 5 (section entitled "Normalization of Separations for Injection Time and Curvature along the Gel".)

B. Klein, Liu, Chen and Hietpas Are Analogous Art

Each of the prior art references combined in this Petition is analogous art to the '240 patent and to each other, as each reference is in the same field of endeavor as the '240 patent. (Ex. 1002 at ¶¶ 77-78.) The '240 patent is directed to the field of biochemistry and, more particularly, to separation of constituents and displaying data derived therefrom. The '240 patent specifically discloses using an electrophoretic separation technique. (*See e.g.,* Ex. 1001 at claim 7.) Both Klein and Hietpas are similarly directed to electrophoretic separation. (Ex. 1003 at Abstract; Ex. 1006 at 1 (col. 2).) Both are also directed to displaying data derived from their respective electrophoresis experiments. (Ex. 1003 at Abstract; Ex. 1006 at 5 (col. 1) and FIGS. 3-4.)

Liu and Chen, which are incorporated by reference into Klein, are also in the

same field of endeavor as the '240 patent. Liu is directed to capillary electrophoresis applied to a sample that has been specifically processed prior to separation. (Ex. 1003 at 17:46-58; Ex. 1004 at Abstract.) Liu is also directed to displaying data derived from the separation process. (Ex. 1004 at Abstract, 12:1-21.) Chen is also directed to electrophoresis analysis and concerns the presentation of the results of that analysis as well. (Ex. 1005 at Abstract.)

C. Grounds 1 & 2 – Claims 1, 3, 5-7, 14, 15 and 17-20 Are Anticipated by Klein Under 35 U.S.C. § 102(e) or, Alternatively, Are Obvious over Klein in view of Liu Under 35 U.S.C. § 103(a)

Under Ground 1, Klein anticipates independent claims 1, 17 and 19 and dependent claims 3, 5-7, 14, 15, 18 and 20 under 35 U.S.C. § 102(e). The arguments presented for Klein in Ground 1 rely on incorporated disclosures from Liu. If, for any reason, the Board determines that the incorporated disclosure of Liu in Klein cannot form the basis of anticipation, an alternative Ground 2 is presented, which combines the teachings of Klein and Liu under 35 U.S.C. 103(a).

1. Independent Claim 1

a. Klein discloses claim element 1[a] – Grounds 1 & 2

[1a]	*A method of analyzing data from a chromatographic separation process, the method comprising:*

Klein discloses claim element 1[a]. Specifically, Klein discloses a "method and apparatus for displaying capillary electrophoresis data." (Ex. 1003 at Abstract; *see also*, *id.* at 3:15-33.) Capillary electrophoresis is a well-known separation

process. (Ex. 1002 at ¶¶ 43-44.) The '240 patent discloses that the chromatographic separation process can be a capillary electrophoresis process, and even describes its preferred embodiment in the context of electrophoretic separation. (Ex. 1001 at 3:26-32, 4:61-5:7, 5:31-40, 13:35-46.) Notably, claim 7 of the '240 patent recites "wherein the separation process is capillary electrophoresis." (*Id.* at 20:15-16; s*ee also* § IX.C.5, below.) Thus, consistent with the '240 patent and its claims, the capillary electrophoresis described in Klein is a "chromatographic separation process." As will be demonstrated in the following sections, the electrophoretic data collected in Klein is analyzed.

b. Klein discloses claim element 1[b] – Grounds 1 & 2

[1b]	[b.1]*subjecting a first sample comprising* [b.2]*constituents having known characteristics to the chromatographic separation process;*

Klein discloses claim element 1[b]. Klein discloses performing electrophoresis on a sample loaded into a capillary (i.e., "sub-element [b.1]"). The loaded sample in Klein includes constituents having known characteristics (i.e., "sub-element [b.2]").

(1) Sub-element [b.1], "subjecting a first sample comprising constituents … to the chromatographic separation process"

Klein explains the process of an analysis cycle for analyzer 40 starting on line 8 of column 11. The cycle begins by loading a sample into a "sample end" of a capillary 200. (Ex. 1003 at 13:20-37 ("a predetermined volume of diluted samples

from the six reservoirs 144a in the reservoir groups 142a-142f are drawn to the six respective sample ends of the capillaries 200a-200f"), and 5:53-66 (a "sample end" is defined as "the end into which a sample is introduced into the capillary before electrophoretic separation along the length of the capillary").)

Next, the sample end of the capillary 200 is positioned with electrodes 240 in a reservoir containing a buffer solution and then electrophoresis is initiated by activating the electrodes 240. (Ex. 1003 at 13:38-45; *see also, id*. at 15:4-14.) Klein describes:

> The high voltage power supply 248 is commanded to apply a high voltage across the capillaries 200. More particularly, the high voltage power supply is connected to the wire 244 which is [in] turn connected to the six electrodes 240 that are now disposed within the buffer reservoirs 144b … By the application of this voltage, preferably in the range of approximately 6000 to 10,000 volts DC, ***capillary electrophoresis begins with the samples*** previously drawn into the sample end of the capillaries 200.

(*Id.* at 13:45-57 (emphasis added).) This high voltage is referred to in Klein as an "electrophoresising voltage." (*Id.* at 13:58-63.) And, as indicated, electrophoretic separation occurs when this electrophoresising voltage is applied across the capillary containing the sample. (*Id.*) Klein discloses subjecting the sample to the

electrophoresising voltage for an "electrophoresising period", which can be anywhere from two minutes to four minutes or longer. (Ex. 1003 at 13:58-63; *see also, id.* at 15:39-43.) Thus, Klein discloses subjecting a sample to a chromatographic separation process and, specifically to capillary electrophoresis.

(2) Sub-element [b.2], "constituents having known characteristics"

Klein discloses that the "first sample" subjected to electrophoresis includes constituents having known characteristics. (*See, e.g.*, Ex. 1003 at 8:8 and 14:3, both of which refer to "sample constituents".) Klein discloses that a sample can comprise human blood serum, which necessarily includes the albumin protein and the gamma-globulin proteins. (Ex. 1003 at 11:25-27, 5:38-41; Ex. 1002 at ¶¶ 100-108.) Albumin and gamma-globulins have many known characteristics, such as, for example, molecular weights, (normal) serum concentration ranges and isoelectric points (pI). *See* § IX.C.3-IX.C.5, below. Klein also describes an embodiment where "specific chemical reference markers" are added to a sample before electrophoresis. (*Id.* at 4:65-5:3 (referencing Chen as an example of how these markers can be selected), 11:8-12:20 (describing a sample dilution cycle where diluent including "specific chemical reference markers" is added to a sample before electrophoresis).) For the reasons that follow, the markers described in Klein inherently have known characteristics. (Ex. 1002 at ¶¶ 79-84.)

Klein explicitly identifies the markers as references ("chemical *reference*

markers"). It was well known in the chemical arts at the time of the '240 patent that the only reason markers are added to samples is so that they can serve as a reference point for an assay. (Ex. 1002 at ¶¶ 81-82, 84.) The only way a marker can serve as a reference point is if certain characteristics of that marker are known. (Ex. 1009 at 3 ("marker" is defined as "a characteristic [] by which [a] molecule can be recognized or identified").) Without any known characteristics, the marker measurements would be unidentifiable from the other sample constituent measurements and its use as a "reference" would have no utility, which would entirely defeat the purpose of the marker.

Klein also describes the markers as being "specific." (Ex. 1003 at 4:65-5:3). The term "specific" means "designed or selected for a particular purpose." (Ex. 1018 at 4.) The only way the markers in Klein can be designed or selected for a particular purpose is if the markers have known characteristics, such as concentration level, mobility, charge, molecular weight and the like. (Ex. 1002 at ¶ 82.) If a "marker" and its characteristics are unknown, then there is nothing specific about the "marker" and it serves no purpose in the sample.

Furthermore, Klein specifically identifies Chen as an exemplary reference for disclosing adding "specific chemical reference markers" to a sample. (Ex. 1003 at 4:65-5:3 ("diluent may additionally include if desired specific chemical reference markers, such as disclosed in U.S. patent application Ser. No.

708,424").) Chen specifically discloses selecting two markers based on their known mobility. In Chen, the first marker is selected to have a faster mobility than the other sample constituents, and the second marker is selected to have a slower mobility than the other sample constituents. (Ex. 1005 at 5:31-9:37 (where the "neutral charge species" marker has the faster mobility, and the "ionic species" marker has the slower mobility).) Chen also discloses that these markers have additional known characteristics, such as a known molecular weight (*id.* at 7:41-55), known absorbance (*id.* at 5:64-68, 6:13-15, 7:30-34, 8:34-38, 9:1-9) and a known charge density (*id.* at 6:35-42, 6:56-7:14). The markers in Chen served as specific reference points used to assist in identifying and normalizing the sample constituents. (*See e.g.,* Ex. 1005 at Abstract, 9:40-10:36.) Chen therefore provides direct evidence that the types of "specific chemical reference markers" described in Klein inherently included known characteristics such as mobility, molecular weight, absorbance and/or charge density.

For these reasons, the "specific chemical reference markers" disclosed in Klein correspond to the claimed "constituents having known characteristics." As such, Klein discloses claim element 1[b].

c. Klein discloses claim element 1[c] – Grounds 1 & 2

[1c]	[c.1] *receiving a series of measurements* [c.2] *indicating presence of the constituents having known characteristics at a scanning location over time;*

Klein discloses claim element 1[c]. For clarity, this element is divided into two sub-elements. Each sub-element is addressed separately below.

(1) Sub-element 1[c.1], "receiving a series of measurements"

Klein discloses a detector 640 that "periodically sample[s]" light that passes through a window 432 of the capillary 200 during the electrophoresising period. (Ex. 1003 at 13:63-14:3.) In other words, the detector 640 in Klein takes a number of light measurements one right after another during the electrophoresis period. Klein explains that the sampled light measurements are processed by the detector 640 and other components of the analyzer 40 "to create digital values related to the absorbance of the sample constituents." (*Id.* at 13:63-14:9.) These digital values are the claimed "series of measurements". For simplicity, the series of measurements related to the first sample is referred to herein as the "first series of measurements."

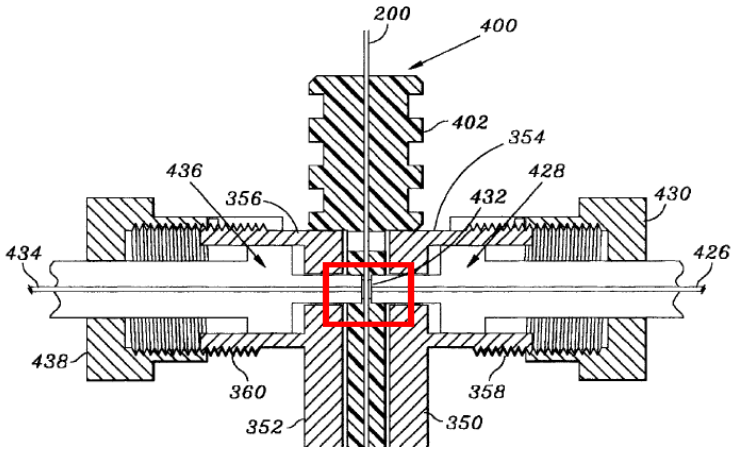
Klein discloses a computer-based control system 590 that receives the digital values or "first series of measurements" from the analyzer 40. The control system 590 can be, for example, a computer 592, such as "a conventional IBM compatible personal computer." (Ex. 1003 at 10:10-30.) As shown in Figure 8 of Klein, the light measurements taken by the detector 640 are passed from the detector 640 to an analog signal interface 644 and further to an A/D converter 612. (*Id.* at 10:31-42, 13:63-14:9.) The A/D converter 612 converts the light measurements to digital

values and then sends those digital values to the computer 592 for analysis and additional processing. (*Id.* at 10:31-42, 13:63-14:9, 15:30-44.) Thus, Klein discloses receiving a series of measurements.

(2) Sub-element 1[c.2], "indicating presence of the constituents having known characteristics at a scanning location over time"

The broadest reasonable interpretation of "at a scanning location over time" is "at a location on the structure containing the sample as constituents within the sample move past the location during a period of time." Klein discloses that the series of measurements of sub-element 1[c.1] indicate the presence of the constituents at a scanning location over time.

As discussed above, the detector 640 in Klein samples light that passes through a window 432 of the capillary 200 during the electrophoresising period. (Ex. 1003 at 13:63-14:3.) This capillary window 432 in Klein is the claimed "scanning location" and the "electrophoresising period" is the "period of time" (or the claimed "over time" limitation). The capillary window 432 in Klein is described as an uncoated section of the capillary wall that "allow[s] the passage of



UV light from the end of the input optical fiber light guide 426 through the capillary to an output optical fiber light guide 434." (*Id.* at 8:23-38.) Figure 7 of Klein (annotated and excerpted above) shows the capillary window 432 in relation to the input and output optical fiber light guides 426 and 434.

Klein discloses that the other end of the output optical fiber light guide 434 is connected to the detector 640 such that the detector 640 can "detect the light that passes through the capillary 200." (*Id.* at 8:39-45.)

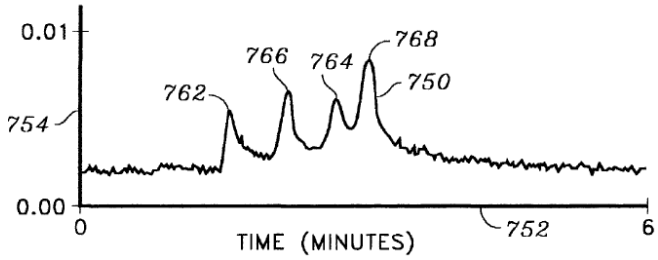
The light sampled by the detector 640 in Klein provides information about constituents moving through the capillary during electrophoresis. Klein explains:

> As the sample nears the other end of the capillary, the small volume of sample becomes separated into bands of different molecules according to the relative migration rates of the molecules. These bands or groups of different molecules are detected near the end of the capillary by, for example, passing a light beam through the bore of the capillary. ***Changes to the light beam, such as absorbance caused by the different molecules, are detected as the separated molecules pass through the beam, thus identifying the different molecules or the classes or categories of molecules in the sample and the relative concentration of such molecules***.

(Ex. 1003 at 2:18-53 (describing capillary electrophoresis detection generally)(excerpt)(emphasis added); *see also*, *id.* at FIG. 10, 16:23-24.) In other

words, when detector 640 in Klein detects a change in the UV light passing through the capillary window 432, it means that constituents (including markers) are passing by the capillary window 432. (*Id*. at 13:58-4:3.) A change in the UV light therefore indicates the presence of constituents (including markers) at the location of the capillary window 432. The "digital values" (or the claimed "series of measurements") are derived from the UV light samples and therefore also indicate the presence of constituents (including markers) at the location of the capillary window 432.

Klein discloses sampling the light over the electrophoresising period. For example, Figure 10 of Klein (excerpted below) shows an electrophoretogram generated from the series of measurements at the scanning location of the capillary 200 over a six minute period. (Ex. 1003 at 13:63-14:9.) The horizontal axis 752 of this figure is described as



"illustrat[ing] electrophoresising time in a range beginning with the application of electrophoresising voltage at zero minutes to the end of the capillary electrophoresis analysis at, for example, six minutes." (*Id.* at 15:30-44.) The "peaks 762, 764, 766 and 768 represent increasing absorbance" – i.e., a change in the UV light at the capillary window 432 – during the electrophoresising time when the UV light was sampled. (*Id.* at 16:23-24.)

For the reasons discussed above, Klein discloses receiving a series of measurements indicating the presence of the constituents (including markers) at a scanning location over time – i.e., over the electrophoresising period.

d. Klein discloses claim element 1[d] – Grounds 1 & 2

[1d]	*subjecting a second sample to the chromatographic separation process;*

Klein discloses claim element 1[d]. The evidence provided for claim element 1[b] is applicable here for claim element 1[d] for the reasons that follow.

Klein specifically discloses that the analyzer 40 includes six identical capillaries 200 that can perform six identical functions. (Ex. 1003 at 6:4-14.) For example, each of the capillaries 200 can be loaded with a sample in the same manner described above with respect to claim element 1[b]. (*See* Ex. 1003 at 11:25-27, 12:28-43, 13:33-37 ("a predetermined volume of diluted samples from the ***six reservoirs*** 144a in the reservoir groups 142a-142f are drawn to the ***six respective sample ends of the capillaries 200a-200f***")(emphasis added).) The sample disclosed for claim element 1[b] is the "first sample" and any one of the samples loaded into the remaining five capillaries in Klein corresponds to the "second sample."

Klein discloses that all six of these capillaries are subjected to the same electrophoresis process described above for claim element 1[b]. (*Id.* at 13:58-60.) In particular, the electrophoresising voltage in Klein is applied across all six of the

capillaries 200 such that both the first sample and the second sample are subjected to the same electrophoretic separation process. (*Id.*) Klein therefore discloses subjecting a second sample to the same capillary electrophoresis process as the first sample in claim element 1[b].

e. Klein discloses claim element 1[e] – Grounds 1 & 2

[1e]	[e.1]*receiving a series of measurements*[e.2] *indicating presence of constituents in the second sample at a scanning location over time; and*

Klein discloses claim element 1[e]. In Klein, each capillary 200a-200f and its contents are analyzed in the same manner. Therefore, the evidence provided for claim element 1[c] is applicable here for the second capillary 200b containing the second sample.

(1) Sub-element [e.1], "receiving a series of measurements"

Klein discloses a computer-based control system 590 that receives a series of measurements from a detector 640. The evidence provided for claim sub-element 1[c.1] is applicable here for the reasons that follow.

The six capillaries 200 in Klein are identical. Each capillary 200 has a window 432 that passes light from its own input optical fiber light guide 426. (Ex. 1003 at 8:7-20 ("single optical fiber light guide 422 (FIG. 3) … [is] split at an optical fiber splitter 424 into six input optical fiber light guides 426").) Each capillary 200 also has its own output optical fiber light guide 434 that is connected

to its own detector 640. (*Id.* at 10:31-37 ("output optical fiber light guides 434 are directed towards six solid state detectors 640"); *see also*, FIG. 8.) Therefore there are six detectors 640 – one for each of the capillaries 200 – that perform the exact same operation during the electrophoresising period. Thus, the detector 640 for the capillary 200b holding the second sample will periodically sample the light passing through that capillary window 432 in the same manner described above with respect to claim sub-element 1[c.1]. (*See id.* at 13:58-67 ("separated sample**s** … flow past the window**s** 432 within each of the capillaries 200" and "[t]he light directed through the window**s** 432 … of the capillaries is periodically sampled and processed by the detector**s** 640")(emphasis added).) Digital values related to the absorbance of the second sample constituents can be derived from the light measurements taken by the detector 640 for capillary 200b in the same manner described for the first sample in claim sub-element 1[c.1]. (*Id.* at 13:63-14:9 ("the values are arranged and stored for each of the capillaries 200a-200f creating six channels or arrays of data corresponding to the six capillaries 200a-200f").) The light measurements or digital values related to capillary 200b are synonymous with the claimed "series of measurements."

The computer-based control system 590 in Klein receives the digital values or "series of measurements" for all of the capillaries from the analyzer 40. (Ex. 1003 at 10:31-42, 13:63-14:9, 15:30-44.) For example, as shown in FIG. 8 of

Klein, the output from each of the detectors 640 is fed directly to the microprocessor 600 of the computer 592, which is part of the system 590. Thus, Klein discloses receiving a series of measurements related to the second sample.

(2) Sub-element [e.2], "indicating presence of constituents in the second sample at a scanning location over time"

The broadest reasonable interpretation of "at a scanning location over time" is "at a location on the structure containing the sample as constituents within the sample move past the location during a period of time." Klein discloses that the series of measurements of sub-element 1[e.1] indicate the presence of the constituents in the second sample at a scanning location over time for the same reasons provided in § IX.C.1.c.(2) for claim sub-element 1[c.2]. This is at least because the windows 432 in each of the capillaries 200 are exactly the same and the detectors 640 for each of the capillaries 200 perform the same functions over the electrophoresising period.

f. Claim element 1[f] – Grounds 1 & 2

[1f]	*normalizing the series of measurements from the second sample using the series of measurements from the first sample.*

For purposes of Ground 1, Klein discloses claim element 1[f] through its incorporation of Liu. For purposes of Ground 2, Klein in view of Liu discloses claim element 1[f].

Liu discloses a process of normalizing raw data derived from capillary electrophoresis (and more particularly from capillary electrophoresis immunosubtraction or "CEI"). (Ex. 1004 at 7:27-40, 8:1-9:49.) The sample to-be-analyzed in Liu contains immunoglobulins (e.g., IgA, IgM and IgG (gamma-globulins)). (*Id*. at 1:24-39, 3:26-29, 8:1-9:49, 12:22-41, 13:65-15:18, 15:45-16:8, FIGs. 1, 5A-5E.) This sample is divided into two parts. The first part is subjected to conventional capillary electrophoresis ("first run") while the second part is mixed with a specific binding partner and then subjected to capillary electrophoresis ("second run"). (*Id.* at 7:3-26.) The results of each electrophoretic process are plotted in an electropherogram, such as the one shown at the right. (*Id.* at FIG. 2.)

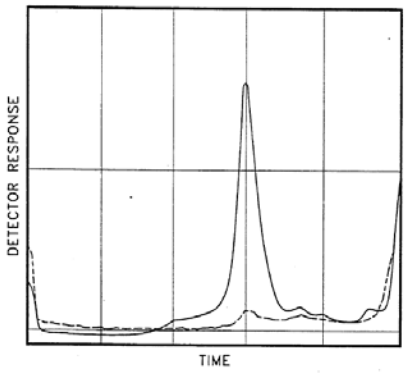


FIG. 2

Liu explains that there may be some "variations between the conditions of the first run and the second run" so the results are normalized "such that direct comparisons between the different separations can be conducted." (Ex. 1004 at 8:28-36.) Liu describes several types of normalization techniques, including time normalization. Time normalization involves the use of two external "markers" in the sample. (*Id.* at 9:13-49.) Markers are described in Liu as "being capable of traversing the capillary column and being detected within the approximate same

time period as the sample constituents are detected." (*Id.*) When markers are added to the sample, "the first marker in each aliquot [is] detected at approximately the same time and the second marker in each aliquot [is] detected at approximately the same time, preferably with the separated constituents appearing between the first and second markers." (*Id.*; *see also id.* at 9:50-68.) Liu discloses that "the relative detection times of the two [runs] can be normalized using the markers." (*Id.* at 9:13-49.) In other words, the markers of the first run are aligned with the markers of the second run or vice versa so that a pathologist can directly compare the electropherograms from both runs over the same detection period.

(1) Klein discloses claim element 1[f] – Ground 1

Based on the above teachings in Liu, Klein discloses normalizing the series of measurements from the second sample using the series of measurements from the first sample. For simplicity, the series of measurements from the second sample will be referred to herein as "the second series of measurements" and the series of measurements from the first sample will be referred to as "the first series of measurements." *See* §§ IX.C.1.c. and IX.C.1.e., above.

Applying the text of Liu, Klein discloses that the first sample in capillary 200a and the second sample in capillary 200b each include "specific chemical reference markers". (Ex. 1003 at 4:65-5:3 (disclosing that diluent can include "specific chemical reference markers"), 11:8-12:33 (explaining that the same

diluent is used for all samples so that all samples will have the same markers).) Klein's incorporated disclosure teaches that there can be two such markers and that they can be used to time normalize the two samples. (Ex. 1004 at 9:13-68.) The first marker in each sample will produce a "first detected peak" and the second marker in each sample will produce the "last detected peak". (Ex. 1004 at 9:58-68.) As explained in Liu, the non-marker sample constituents will produce the peaks in-between the "first detected peak" and the "last detected peak". (*Id.*) The peaks produced by the sample constituents will therefore be bound by the first and last detected peaks produced by the markers. (The "first detected peak", the "last detected peak" and all peaks in-between are part of the series of measurements collected by a respective detector 640.) From here, the first and second series of measurements in Klein can be *time normalized* based on their respective first and last detected peaks. (Ex. 1004 at 9:38-49 ("the relative detection times of the two [runs] can be normalized ***using*** the markers")(emphasis added).)

Klein does not explicitly disclose, either in its text or its incorporated disclosure, that the results from the second run are time normalized using the results from the first run. (Ex. 1004 at 8:28-36, 9:13-68.) However, time normalization using markers can only be achieved in one of two ways in Liu – the marker results from the first run are aligned to the marker results from the second run OR the marker results from the second run are aligned to the marker results

from the first run. (Ex. 1002 at ¶ 89.) Selecting one run over the other is completely arbitrary. And, regardless of which run is selected as the "base", the end result is that all electropherograms are confined to a constant region so that the measurements can be directly and accurately compared. (Ex. 1004 at 8:28-33, 9:13-49.) Thus, both electropherograms are normalized.

As an aside, there is nothing in Klein that specifically limits which samples are considered the first sample or the second sample. The samples can be processed simultaneously so, technically, there is no "first" or "second" sample. Also, both samples can include human blood serum and markers so there is no discernable difference between the samples (except, maybe, their source). The "first" and "second" samples can be selected in Klein so that the second series of measurements is always aligned using the first series of measurements. For example, depending on the approach selected, the sample in capillary 200a can be either the first sample or the second sample and the sample in capillary 200b is the other sample. Therefore, after applying the incorporated teachings of Liu, Klein inherently discloses that the second series of measurements are normalized using the first series of measurements.

(2) Klein and Liu discloses claim element 1[f] – Ground 2

In addition to the arguments set forth in Ground 1, Petitioners propose an alternative Ground 2 in which Liu is combined with Klein without incorporation.

Under Ground 2, similar to Ground 1, the "chemical reference markers" are present in the multiple samples in Klein and the teachings of Liu suggest that the series of measurements corresponding to the multiple samples can be time normalized using those markers. For example, for the same reasons discussed under Ground 1, any one of the samples in Klein can be selected as the first or second sample so that the second series of measurements is aligned (or normalized) using the first series of measurements. Nothing in Klein limits how a first or second sample is characterized or used.

In an effort to streamline discussions, assume that the sample from capillary 200a is the claimed "first sample" and the sample from capillary 200b is the claimed "second sample". A person of ordinary skill in the art at the time of the '240 patent would understand based on the disclosures in Liu that the first peak from the second series of measurements from the second sample can be adjusted to match up with the first peak from the first series of measurements from the first sample. (Ex. 1002 at ¶ 86.) As such, Klein in view of Liu discloses normalizing the series of measurements from the second sample using the series of measurements from the first sample, as recited in claim element 1[f].

A POSA would be motivated to combine the normalization teachings of Liu with the teachings of Klein for several reasons, including MPEP's "Exemplary Rationale G" (i.e., "some teaching, suggestion, or motivation in the prior art") and

"Exemplary Rationale D" (i.e., "applying a known technique to a known device ready for improvement to yield predictable results"). (Ex. 1002 at ¶¶ 85-99.)

"Exemplary Rationale G": Klein incorporates Liu by reference, which provides express motivation to combine the teachings of Liu and Klein. *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1348 (Fed. Cir. 2000)("Evidence of a suggestion, teaching, or motivation to combine prior art references may flow, inter alia, from the references themselves."). Additionally, Liu provides express motivation to combine its teachings with Klein because it incorporates by reference U.S. Patent Appl. No. 07/916,308 (now U.S. Patent No. 5,413,686, "Ex. 1013"), which has the *same exact* multi-channel capillary electrophoresis disclosure found in columns 4 through 15 of Klein. (Ex. 1004 at 12:36-41; *see* Ex. 1013 at 4:48-60, FIGs. 1-8; *compare to* Ex. 1003 at 4:50-15:29, FIGs. 1-8.) Liu expressly states in column 12, lines 22-41 that the normalization techniques disclosed in Liu are directly applicable to and useable within the Klein system. (*See e.g.*, Ex. 1004 at 12:22-41.) Liu also incorporates by reference the parent application of Klein – i.e., U.S. Patent Appl. No. 07/916,307 (mis-numbered as 07/911,307 in Liu), which was abandoned during prosecution and never published. (Ex. 1004 at 12:12-21; Ex. 1002 at ¶¶ 92-94.)

Klein indicates that the display arrangement shown in FIG. 13 (reproduced above in § IX.A.1.) would be a useful tool for Liu because it allows several

electropherograms to be displayed on a single screen, thereby allowing for direct comparison of more than one electropherogram at a given time. (Ex. 1003 at 17:46-60.) However, a person of skill in the art would understand that the electropherograms generated from the assays in Liu would still need to be time normalized for *useful* direct comparison of the electropherograms. (Ex. 1002 at ¶ 92.) A POSA would be motivated to perform the same time normalization technique on the graphs 750 displayed in Klein so that these graphs 750 also provide useful direct comparisons. (*Id.* at ¶¶ 92-95.)

The fact that the first and second series of measurements in Klein are taken over the same electrophoresising period would not deter a POSA from combining the time normalization teaching in Liu with the teachings of Klein. (Ex. 1002 at ¶¶ 87-90.) Dr. Voss explains that each of the six capillaries 200 in Klein will inevitably have slightly different characteristics (e.g., slight variations in inner or outer capillary diameters, temperature differences, etc.) that change the absolute detection times for sample constituents even though detection across all capillaries 200 occurs over the same period of time. (*Id*.) Therefore a POSA would need to perform some sort of normalization or re-alignment so that the results are useful for direct comparison. (*Id.*) Even Liu recognizes that time normalization after multi-channel capillary electrophoresis is needed. (Ex. 1004 at 12:36-41.)

“Exemplary Rationale D”: It would also be obvious to apply the known

time normalization technique disclosed in Liu to Klein's known system. At the time of the '240 patent, time normalization was a well-known technique for adjusting values so that displayed results could be accurately compared. (Ex. 1002 at ¶¶ 86,- 96.) According to Dr. Voss, all analyses included markers for normalization purposes when constituent mobility was being compared – it was a rudimentary step that no experienced technician would forget. (Ex. 1002 at ¶ 97.)

Dr. Voss also explains that modifying the system in Klein to perform time normalization would have been routine for a POSA because only minimal software enhancements would have been needed. (Ex. 1002 at ¶ 98.) Markers are already present in Klein. A programmer could simply write code to align the first peak from the second series of measurements with the first peak from the first series of measurements in Klein. (*Id*.) This could be accomplished using a relatively simple mathematical equation. (*Id*.) The end result is two graphs 750 that could be displayed in area 850a and 850b of FIG. 13 in normalized form. Again, this provides a useful direct comparison.

Applying the normalization process to Klein's system would improve the output of the system and provide images for easy comparison. (Ex. 1002 at ¶ 99.) In addition, the overall value of the system would be enhanced because of the normalization of the images. (*Id*.) Dr. Voss explains that electropherograms were originally used for gel electrophoresis and provided clean visual results that did not

need to be normalized. (*Id*.) But, scientists would "fit" the data from capillary electrophoresis into an electropherogram image because it was a format with which they were familiar. (*Id*.) Unfortunately, without normalization, the graphs / images generated from capillary electrophoresis would appear distorted next to each other and any comparison made with these "distorted" images / graphs would have little – if any – value to pathologists. (*Id.*)

2. Dependent Claim 3

[3]	*The method of claim 1, wherein the known characteristics of the constituents of the first sample are the sizes of the constituents.*

Klein discloses dependent claim 3 under Grounds 1 & 2. Klein discloses that a sample can consist of human blood serum, which necessarily includes the albumin protein and the gamma-globulin proteins. (Ex. 1003 at 11:25-27, 5:38-41; Ex. 1005 at 1:31-34.) Dr. Voss explains that albumin is the most prevalent protein in blood serum and that gamma-globulins are the next prevalent. (Ex. 1002 at ¶¶ 100-105; Ex. 1005 at 2:20-21.) Both have many known characteristics, including molecular weight, (normal) concentration range in human serum and pI (isoelectric point). (Ex. 1002 at ¶¶ 100-108; Ex. 1005 at 2:20-21; Ex. 1012 at 3, 6 (Table 1); Ex. 1017 at 4, 2 (Table 1).)

At the time of the '240 patent, the albumin found in human blood serum had a known molecular weight of 66.3 kDa. (Ex. 1002 at ¶¶ 100-108; Ex. 1012 at 3 (Table 1).) The gamma-globulins ("IgG") are a type of immunoglobulin and are

comprised of four subclasses (IgG1, IgG2, IgG3, IgG4) that have known molecular weights of 146 kDa (IgG1, IgG2, IgG4) and 170 kDa (IgG3). (Ex. 1002 at ¶¶ 106-108; Ex. 1017 at 2 (Table 1)(identified as "molecular mass".) A "molecular weight" (or "molecular mass") is a "size" and, as Dr. Voss explains, these terms are often used interchangeably because they generally mean the same thing. (Ex. 1002 at ¶¶ 106-108.)

Furthermore, albumin is known to have a high absorbance rate so it is generally easily detected and typically has the tallest peak on an electropherogram. (Ex. 1004 at 8:47-9:12.) Gamma-globulins are also detectable and have visible, identifiable peaks on an electropherogram . (Ex. 1005 at 2:63-32, Ex. 1004 at 3:3-29, FIG. 1, 15:1-18, 15:45-64, FIGS. 2, 5A-5E.) Therefore, because of albumin's inherent characteristics and gamma-globulin's inherent characteristics, they will be detected by detectors 640 at the capillary windows 432 during the electrophoresising period in Klein. *See* §§ IX.C.1.c.(2) and IX.C.1.2.(2), above.

Because albumin and gamma-globulin are constituents of the first sample in Klein and the sizes of albumin and gamma-globulin are known, Klein discloses dependent claim 3 under Grounds 1 & 2.

Alternatively, the "specific chemical reference markers" in Klein, as evidenced by Chen and Liu, had a known size / molecular weight. *See* § IX.C.1.b.(2), above.

3. Dependent Claim 5

[5]	*The method of claim 3, wherein the constituents having known size are molecules having known molecular weights.*

As discussed directly above, Klein discloses that a sample can consist of human blood serum, which necessarily includes albumin and gamma-globulins. *See* § IX.C.2, above. At the time of the '240 patent, albumin and gamma-globulins had known molecular weights. (Ex. 1002 at ¶ ¶¶ 100-108; *see* § IX.C.2, above.) Alternatively, the "specific chemical reference markers" in Klein, as evidenced by Chen and Liu, had a known size / molecular weight. *See* § IX.C.1.b.(2), above. Thus, Klein discloses claim 5 under Grounds 1 & 2.

4. Dependent Claim 6

[6]	*The method of claim 5, wherein the constituents having known molecular weights are proteins.*

As discussed directly above, Klein discloses that a sample can consist of human blood serum, which necessarily includes albumin and gamma-globulins. *See* § IX.C.2. Both albumin and gamma-globulins are proteins. (Ex. 1004 at 8:45-47, 1:14-41; *see also* Ex. 1002 at ¶¶ 109-110.)

5. Dependent Claim 7

[7]	*The method of claim 1, wherein the separation process is capillary electrophoresis.*

Klein expressly discloses performing capillary electrophoresis on the first and second samples. (*See* Ex. 1003 at 1:11-16 ("The present invention relates

generally to the field of electrophoresis and more particularly to capillary electrophoresis"), 2:18-53, 3:16-18 ("for use in a clinical chemistry capillary electrophoresis analyzer"), 3:34-37 ("A method according to the present invention may include electrophoresising a fluid in a capillary"), 6:2-3 ("electrophoretic separation occurring along the length of the capillary"), 13:45-63; *see also*, § IX.C.1.a through IX.C.1.f above.) Thus, Klein discloses dependent claim 7 such that the claim is anticipated under Ground 1 or obvious under Ground 2 based on its dependence on claim 1.

6. Dependent Claim 14

[14]	*The method of claim 1, wherein the first and second samples comprise proteins.*

Klein discloses that the first and second samples can consist of human blood serum, which necessarily includes proteins. (Ex. 1003 at 11:25-27 ("sector 130 holds six sample tubes 132a through 132f, each containing a suitable sample for analysis, such as human blood serum"), 5:38-41; Ex. 1002 at ¶ 111; *see also*, §§ IX.C.2 to IX.C.4, above.) Examples of proteins found in human blood serum include albumin, alpha-1 lipoprotein, alpha-2 macroglobulin, beta-1 lipoprotein and immunoglobulins. (Ex. 1002 at ¶ 111; *see also*, Ex. 1005 at 1:31-34; *see also* Ex. 1004 at 3:5-12 (immunoglobulins).) Klein therefore discloses claim 14 such that the claim is anticipated under Ground 1 or obvious under Ground 2 based on its dependence on claim 1.

7. Dependent Claim 15

[15]	*The method of claim 1, wherein normalizing step comprises comparing the migration time of one or more markers in the second sample with the migration time of the same markers in the first sample.*

Ground 1: Klein discloses dependent claim 15 through its incorporation of Liu. The time normalization described in Liu necessarily requires that the markers and their migration time be compared. Each sample in Liu includes the same markers and each marker is detected at approximately the same time in each sample: "i.e., the first marker in each aliquot will be detected at approximately the same time and the second marker in each aliquot will be detected at approximately the same time." (Ex. 1004 at 9:28-38.) "Thus, to the degree that the detected sample constituents are detected at different times … the relative detection times of the two sets of constituents can be normalized using the markers." (*Id.* at 9:38-49.) The detection time of each constituent was (and still is) known in the art as its "migration time." (Ex. 1002 at ¶ 112.)

The migration times of the "first detected peaks" of all the samples and the "last detected peaks" of all the samples in Liu must be directly compared in order to determine whether "sample constituents are detected at different times." (Ex. 1004 at 9:38-49; *see also,* Ex. 1004 at FIGs. 2-10 (illustrating that all of the first and last peaks are matched on the normalized electropherograms).) Liu discloses that "[t]ime normalization is principally accomplished in order to place the

resulting electropherogram results within a constant region." (Ex. 1004 at 9:13-20.) This would necessarily require that the migration times of the first and last peaks of all of the samples be compared so that the "constant region" can be determined and the electropherograms can be normalized accordingly. (Ex. 1002 at ¶¶ 112-115.) This is the only way normalization can be accomplished in Liu.

Ground 2: The arguments raised above under Ground 1 are applicable under Ground 2 except that Liu is applied as an independent reference under Ground 2. Thus, Klein in view of Liu renders dependent claim 15 obvious. It would be obvious to combine the migration time comparison teachings of Liu with Klein for all of the reasons discussed in § IX.C.1.f. for claim 1.

8. Independent Claim 17

a. Klein discloses claim element 17[a] – Grounds 1 & 2

[17a]	*A computer system, comprising:*

Klein discloses a computer system. For example, Klein discloses a computer-based control system 590 that "control[s] the automated features of the analyzer 40." (Ex. 1003 at 10:10-30.) Klein therefore discloses claim element 17[a].

b. Klein discloses claim element 17[b] – Grounds 1 & 2

[17b]	*a processor;*

Klein discloses that the computer-based control system 590 includes a

central computer 592, which has a microprocessor 600. (Ex. 1003 at 10:10-30 ("system 590 includes a central computer 592 which includes a microprocessor board 600," "[t]he microprocessor may be, for example, a type i386 available from Intel Corporation"), FIG. 8.) Klein therefore discloses claim element 17[b].

c. Klein discloses claim element 17[c] – Grounds 1 & 2

[17c]	[c.1]*a computer readable medium coupled to the processor* [c.2]*that stores a computer program* [c.3]*that analyzes data from a chromatographic separation process, the computer program comprising:*

Klein discloses claim element 17[c] for the reasons that follow.

(1) Sub-element [c.1], "a computer readable medium coupled to the processor"

Klein discloses that the microprocessor 600 is coupled to (or "interfaced with") a memory board 602 and, through the memory board 602, to floppy and hard disk drives 604. (Ex. 1003 at 10:16-19, FIG. 8.) This memory board 602 is the claimed "computer readable medium." Alternatively, the memory board 602 and the disk drives 604 collectively form the "computer readable medium."

(2) Sub-element [c.3], "a computer program that analyzes data from a chromatographic separation process"

Sub-element [c.3] is addressed before sub-element [c.2] because understanding the details of the computer program is a pre-requisite for understanding where that program is stored.

The control system 590 in Klein analyzes the data from the capillary electrophoresis. For the same reasons discussed above in § IX.C.1.a., the capillary electrophoresis process described in Klein is the claimed "chromatographic separation process."

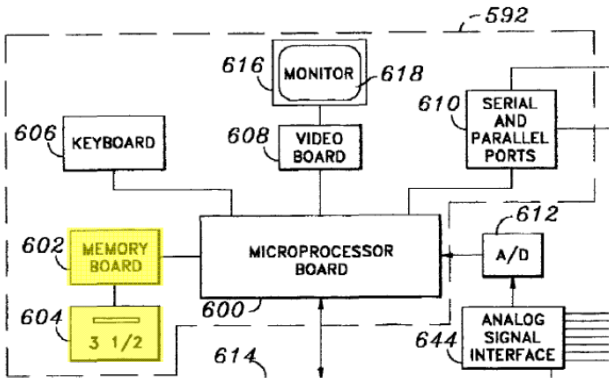
It is inherent from the disclosure in Klein that the control system 590 includes a computer program that performs the capillary electrophoresis data analysis recited in claim 17, including subjecting samples to electrophoresis, receiving series of measurements and normalizing data. (Ex. 1002 at ¶¶ 116-117.) Klein specifically states that this control system 590 is a ***computer-based*** control system that is used to "control the ***automated*** features of the analyzer 40" and to "provide the operator interface and ***graphic display*** functions." (Ex. 1003 at 10:10-30 (emphasis added), 19:66-20:2 (emphasis added).) Each highlighted term indicates the use of a computer program. Regarding a "computer-based" control system, a computer itself cannot function without a computer program or its corresponding computer code; thus, it is inherent that the system 590 functions according to a computer program. Regarding "automated" features, Klein discloses that those features can include subjecting the capillary and its contents to electrophoresis (*id.* at 13:46-63) and collecting data associated with the electrophoretic process (*id.* at 13:58-14:9). The term "automate" necessarily requires the use of a computer because something that is automated functions

without any human interaction. (Ex. 1002 at ¶¶ 116-117; Ex. 1015 at 3 (definitions for "automate" and "automatic").) Because this is a "computer-based" system, the "automated" features in Klein operate based on a computer program. Furthermore, Klein explicitly discloses that the graphic display functions are "implemented in the C programming language." (Ex. 1003 at 19:62-66, 15:30-65.)

Thus, Klein discloses a computer program that analyzes data from an electrophoretic separation process. The below sub-sections d.(1) to d.(3) provide further evidence that Klein discloses a computer program that analyzes data according to claim 17.

(3) Sub-element [c.2], "a computer readable medium … that stores a computer program"

It is inherent that the computer program from sub-element [c.3] is stored within the memory board 602 in Klein or is stored collectively within the memory board 602 and disk drives 604. The memory board 602 and disk drives 604 are the only storage units disclosed in Klein (see excerpted and annotated FIG. 8 below); therefore, the computer program must be stored in one or more of those locations.



Furthermore, even if the computer program (or a portion thereof) originated from the disk drives 604 or another source in Klein, that computer program (or the

portion thereof) must first be loaded onto the memory board 602 before the program is executed by the processor 600. (Ex. 1014 at 1.) Therefore, regardless of where the program originates in Klein, the memory board 602 necessarily stores the computer program for the control system 590. Thus, Klein discloses claim element 17[c].

d. Klein discloses claim elements 17[d]-17[h]

As illustrated in the below chart, the language of claim elements 17[d] to 17[h] is substantively identical to that of claim elements 1[b] to 1[f] except for the underlined language:

Claim 1		**Claim Elements 17[d] to 17[h]**	
[1a]	A method of analyzing data from a chromatographic separation process, the method comprising:	[redacted]	
[1b]	subjecting a first sample comprising constituents having known characteristics to the chromatographic separation process;	[17d]	<u>computer code that subjects</u> a first sample comprising constituents having known characteristics to the chromatographic separation process;
[1c]	receiving a series of measurements indicating presence of the constituents having known characteristics at a scanning location over time;	[17e]	<u>computer code that receives</u> a series of measurements indicating presence of the constituents having known characteristics at a scanning location over time;
[1d]	subjecting a second sample to the chromatographic separation process;	[17f]	<u>computer code that subjects</u> a second sample to the chromatographic separation process;

[1e]	receiving a series of measurements indicating presence of constituents in the second sample at a scanning location over time; and	[17g]	<u>computer code that receives</u> a series of measurements indicating presence of constituents in the second sample at a scanning location over time; and
[1f]	normalizing the series of measurements from the second sample using the series of measurements from the first sample.	[17h]	<u>computer code that normalizes</u> the series of measurements from the second sample using the series of measurements from the first sample.

The difference highlighted by the underlined language is that the claim elements in the first column recite a specific operation (e.g., subjecting, receiving, normalizing) while the claim elements in the second column recite a computer code that performs that same operation (e.g., computer code that subjects, computer code that receives, computer code that normalizes). Klein discloses computer code that performs these claimed operations for the reasons set forth below.

(1) Claim elements 17[d] & 17[f] – Grounds 1 & 2

As previously discussed, the control system 590 in Klein inherently includes a computer program. A computer program necessarily includes computer code.

Klein discloses that the control system 590, via the microprocessor 600, controls the electrophoresising voltage applied to all six capillaries 200. (Ex. 1003 at 13:46-47 ("high voltage power supply 248 is ***commanded*** to apply a high voltage across the capillaries 200"), 14:10-14 ("microprocessor board 600 controls

the high voltage power supply 248 to remove the electrophoresising voltage from the capillaries 200").) Because the control system 590 (and microprocessor 600) operates according to the computer program, Klein discloses computer code that subjects a first sample (e.g., in capillary 200a) and a second sample (e.g., in capillary 200b) to a capillary electrophoretic separation process. The arguments provided with respect to claim elements 1[b] and 1[d] apply to claim elements 17[d] and 17[f], respectively.

(2) Claim elements 17[e] & 17[g] – Grounds 1 & 2

Klein discloses that the control system 590, via microprocessor 600, receives the digital values or "series of measurements" for all of the capillaries 200 from the analyzer 40. (Ex. 1003 at 10:31-42, 13:63-14:9, 15:30-44.) For example, as shown in FIG. 8 of Klein, the output from each of the detectors 640 is passed to the microprocessor 600, which is part of the control system 590. Because the control system 590 (and microprocessor 600) operates according to the computer program, Klein discloses computer code that receives a series of measurements according to elements 17[e] and 17[e]. The arguments provided with respect to claim elements 1[c] and 1[e] apply to claim elements 17[e] and 17[g], respectively.

(3) Claim element 17[h] – Grounds 1 & 2

Ground 1: Liu explicitly discloses that normalization is "accomplished by an on-board computer." (Ex. 1004 at 14:54-60.) Applying the text of Liu, Klein

discloses computer code that normalizes the series of measurements from the second sample using the series of measurements from the first sample.

Klein explicitly discloses that the computer system 590 is responsible for processing collected electrophoretic data and displaying that data as an electrophoretogram on a computer screen. (Ex. 1003 at 15:30-65.) Performing time normalization is part of processing and displaying data; therefore, the computer system 590 in Klein performs the normalization process disclosed in Liu. (Ex. 1002 at ¶¶ 118-119.) This is necessarily the case because it is the only feature in Klein that is capable of performing the computerized normalization process. (*Id*.) Again, all data processing and display is controlled by the computer system 590. (Ex. 1003 at 15:30-65.) The arguments provided in § IX.C.1.f apply to claim element 17[h] under Ground 1.

Ground 2: Alternatively, claim element 17[h] is rendered obvious over the combined disclosures of Klein and Liu. The arguments in § IX.C.1.f apply to claim element 17[h] under Ground 2.

In the modified Klein system, the control system 590 would perform the time normalization process described in Liu. (Ex. 1004 at 14:54-60.) As previously discussed, the control system 590 already controls the tasks for processing and displaying electrophoretic data (including the first and second series of measurements). (Ex. 1003 at 15:30-65.) It would be obvious for all the same

reasons set out above in § IX.C.1.f to normalize the first and second series of measurements of Klein based on the disclosures in Liu. Furthermore, it would be obvious for the control system 590 and its corresponding computer code to carry out that time normalization process. (Ex. 1002 at ¶¶ 118-119.) The code required to perform the time normalization process would be minimal and the resulting modifications to the Klein system would be insignificant when viewed from the perspective of one skilled in the art. (Ex. 1002 at ¶¶ 118-119.)

9. Independent Claim 19

As illustrated in the below chart, the language of claim elements 19[a] - 19[g] are substantively identical to that of claim elements 17[c] - 17[h]:

Claim Elements of 17[c]-17[h]		**Claim 19**	
[17c]	a computer readable medium coupled to the processor that stores a computer program that analyzes data from a chromatographic separation process, the computer program comprising:	[19a]	A computer program product that analyzes data from a chromatographic separation process, comprising:
[17d]	computer code that subjects a first sample comprising constituents having known characteristics to the chromatographic separation process;	[19b]	computer code that subjects a first sample comprising constituents having known characteristics to the chromatographic separation process;
[17e]	computer code that receives a series of measurements indicating presence of the constituents having known	[19c]	computer code that receives a series of measurements indicating presence of the constituents having known

	characteristics at a scanning location over time;		characteristics at a scanning location over time;
[17f]	computer code that subjects a second sample to the chromatographic separation process;	[19d]	computer code that subjects a second sample to the chromatographic separation process;
[17g]	computer code that receives a series of measurements indicating presence of constituents in the second sample at a scanning location over time; and	[19e]	computer code that receives a series of measurements indicating presence of constituents in the second sample at a scanning location over time;
[17h]	computer code that normalizes the series of measurements from the second sample using the series of measurements from the first sample.	[19f]	computer code that normalizes the series of measurements from the second sample using the series of measurements from the first sample; and
		[19g]	a computer readable medium that stores the computer codes.

Elements 19[b] to 19[f] are identical to elements 17[d] to 17[h]. Thus, they are found either in Klein alone or in combination with Liu for the reasons described above in § IX.C.8.d.

The only noticeable difference between claim elements 17[c]-17[h] and 19[a]-19[g] is that claim element 17[c] recites an amalgamation of claim elements 19[a] and 19[g]. The below chart clearly illustrates this point. (Claim element 19[g] appears above element 19[a] because element 19[g] aligns with the first half of element 17[c] while element 19[a] aligns with the second half of element 17[c].)

[17c]	*a computer readable medium coupled to the processor that stores a computer program* that analyzes data from a chromatographic separation process, the computer program comprising:	[19g]	*a computer readable medium that stores the computer codes*.
		[19a]	A computer program product that analyzes data from a chromatographic separation process, comprising:

As illustrated in the above chart, the underlined portion of claim element 17[c] relates directly to claim element 19[a]. The italicized portion of claim element 17[c] relates directly to claim element 19[g] – the only variation being that claim 19[g] recites storing "computer codes" as opposed to storing the "computer program." A computer program is necessarily comprised of codes; therefore, storing the computer program is the same as storing the computer codes. *See* § IX.C.8.d.(1), above. This variation of format of presenting this feature does not render the anticipation or obviousness analyses presented for claim 17 inapplicable to claim 19 – that variation has no impact on the analyses at all.

Thus, under Ground 1, Klein anticipates each of claim elements 19[a] - 19[g] for the reasons discussed above in §§ IX.C.8.c and IX.C.8.d for claim elements 17[c] - 17[h]. Under alternative Ground 2, Klein in view of Liu renders the claim elements obvious. Klein discloses each of elements 19[a] - 19[e] and 19[g] for reasons discussed above in §§ IX.C.8.c and IX.C.8.d for claim elements 17[c] - 17[g]. Liu discloses claim element 19[f] for the reasons discussed above in

§ IX.C.8.d.(3) for claim element 17[h].

10. Dependent Claims 18 & 20

Claim 18 depends from claim 17 and claim 20 depends from claim 19. Both recite "*wherein the computer readable medium is selected from the group consisting of CD-ROM, floppy disk, tape, flash memory, system memory, hard drive, and data signal embodied on a carrier wave*." Klein discloses the memory board 602 and disk drives 604 as part of the computer 592. (Ex. 1003 at 10:10-30.) As previously discussed, the computer program driving the control system 590 in Klein is stored within the memory board 602 or is stored collectively within the memory board 602 and disk drives 604. *See* § IX.C.8.c., above. The memory board 602 is the claimed "system memory." The floppy or hard disk drives 604 are the claimed "floppy disk" or "hard drive."

D. Ground 3 – Claims 1, 3, 5-7, 14, 15 and 17-20 Are Obvious Under 35 U.S.C. § 103(a) Over Klein in view of Hietpas

The teachings of Klein in view of Hietpas render independent claims 1, 17 and 19 and corresponding dependent claims 3, 5-7, 14, 15, 18 and 20 obvious under 35 U.S.C. § 103(a) for the reasons set forth below.

1. Independent Claim 1

a. Klein discloses claim elements 1[a]-1[e]

Klein discloses claim elements 1[a] to 1[e] for the same reasons discussed above in §§ IX.C.1.a through IX.C.1.e under Ground 1. For this reason, elements

1[a] to 1[e] are not addressed again here under Ground 3.

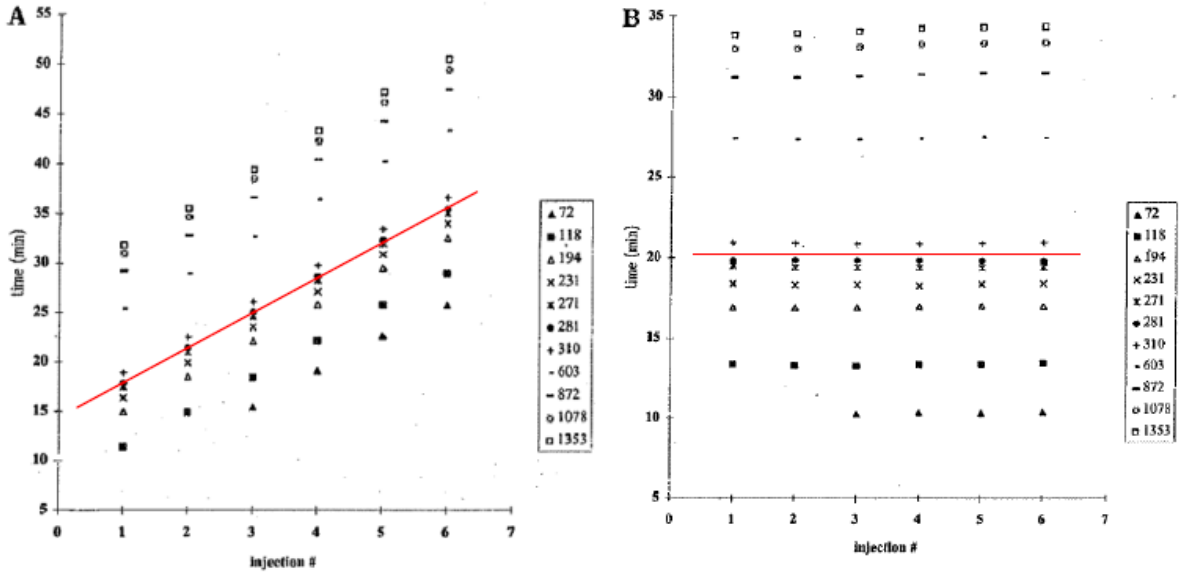
b. Klein and Hietpas render obvious claim element 1[f]

[1f]	*normalizing the series of measurements from the second sample using the series of measurements from the first sample.*

The teachings of Klein in view of Hietpas render claim element 1[f] obvious. Hietpas discloses normalizing a series of measurements from a second sample using a series of measurements from a first sample.

Hietpas discloses methods for applying electrophoresis across ultrathin slab gels containing DNA fragments. (Ex. 1006 at 1 (col. 1).) Figure 4A of Hietpas (annotated and reproduced below left) is a plot of the *raw data* collected during electrophoresis. Hietpas explains that, as shown in Figure 4A, there are inevitable variations in DNA fragment detection as a result of staggered injection times and a "smiling phenomenon" which caused fragments to move faster in warmer zones in the gel. (*Id.* at 5 (col. 1).) To account for this variation, Hietpas "normalized [the data] to fragment 281 in injection 1." (*Id.*) In other words, each detected fragment 281 from injections 2-6 was aligned with the detected fragment 281 in injection 1. This normalization – or realignment – is illustrated in FIG. 4B of Hietpas (annotated and reproduced below right). The red annotated line in the figures clearly illustrates the "before" and "after" of normalization in Hietpas and demonstrates how displaying normalized data in parallel is useful for review.

Raw Data (FIG. 4A) **Normalized Data (FIG. 4B)**



In the modified Klein system, the electrophoretic data resulting from a constituent in the second series of measurements in Klein can be aligned to the data resulting from the same constituent in the first series of measurements according to the teachings in Hietpas. The constituent can be the "specific chemical reference markers" or albumin and gamma-globulins. *See* IX.C.1.f and IX.C.2, above. The markers and albumin constituents would generate an identifiable peak that can be used to normalize the electropherograms. (Ex. 1002 at ¶ 125.)

A POSA would be motivated to combine the normalization teachings of Hietpas with the teachings of Klein for several reasons, including MPEP's "Exemplary Rationale G" (i.e., "some teaching, suggestion, or motivation in the prior art") and "Exemplary Rationale D" (i.e., "applying a known technique to a

known device ready for improvement to yield predictable results").

"Exemplary Rationale G": Klein already discloses time normalization through its incorporation of Liu. Because some form of normalization is disclosed in Klein, a person of ordinary skill in the art would be motivated to combine the normalization teachings of Hietpas with Klein. *Winner Int'l Royalty*, 202 F.3d at 1348 ("Evidence of a suggestion, teaching, or motivation to combine prior art references may flow, inter alia, from the references themselves."). Also, the normalization technique disclosed in Hietpas is so basic that a POSA could perform the technique without any significant effort. (Ex. 1002 at ¶ 126.)

For the same reasons discussed above in § IX.C.1.f.(2), the fact that the first and second series of measurements in Klein are taken over the same electrophoresising period would not deter a POSA from combining the time normalization teaching in Hietpas with the teachings of Klein. (Ex. 1002 at ¶ 126.)

"Exemplary Rationale D": It would also be obvious to apply the known normalization technique disclosed in Hietpas to Klein's known system. At the time of the '240 patent, normalization was a well-known technique for adjusting values so that displayed results could be accurately compared. (Ex. 1002 at ¶ 127; *see also* § IX.C.1.f.(2), above.) Dr. Voss explains that modifying the system in Klein to perform the normalization disclosed in Hietpas would have been routine for a POSA because only minimal software enhancements would have been needed.

(Ex. 1002 at ¶127.) A programmer could simply write code to align a known peak from the second series of measurements with a known peak from the first series of measurements. (*Id*.) This could be accomplished using a relatively simple mathematical equation. (*Id*.) The end result is two graphs 750 that could be displayed in area 850a and 850b of FIG. 13 in normalized form for useful direct comparison.

Furthermore, for the same reasons discussed above in § IX.C.1.f.(2), a POSA would recognize that data collected based on multiple capillary experiments will inevitably result in (minor) variations and normalization of some kind is needed to enhance the usefulness of the results. (Ex. 1002 at ¶ 127.) A POSA would be motivated to perform the same time normalization technique from Hietpas on the graphs 750 displayed in Klein so that these graphs 750 provide useful direct comparisons. (*Id.*) Moreover, for the same reasons discussed in § IX.C.1.f.(2), applying the normalization process to Klein's system would improve the output of the system and provide images for easy comparison.

For these reasons, Klein in view of Hietpas disclose claim element 1[f].

2. Dependent Claims 3, 5-7, 14 and 15

Dependent claims 3, 5-7, 14 and 15 are disclosed by Klein as discussed above in §§ IX.C.2 through IX.C.7 under Ground 1. The rationales for combining Klein and Hietpas explained above for claim 1 under Ground 3 applies equally to

claims 3, 5-7, 14 and 15.

3. Independent Claim 17

a. Klein discloses claim elements 17[a]-17[g]

Klein discloses claim elements 17[a] to 17[c] for the same reasons discussed above in §§ IX.C.8.a through IX.C.8.c under Ground 1. Klein also discloses claim elements 17[d] to 17[g] for the same reasons discussed above in §§ IX.C.8.d(1) and (2) as well as §§ IX.C.1.b through IX.C.1.e under Ground 1. For these reasons, elements 17[a] to 17[g] are not addressed again here under Ground 3.

b. Klein and Hietpas render obvious claim element 17[h]

[17h]	*computer code that normalizes the series of measurements from the second sample using the series of measurements from the first sample.*

The teachings of Klein in view of Hietpas render claim element 17[h] obvious for the same reasons discussed above in § IX.D.1.b for claim 1 under Ground 3. Claim 1 recites "normalizing" while claim 17 recites "computer code that normalizes," otherwise the claim language is exactly the same.

Klein explicitly discloses that the computer system 590 is responsible for processing collected electrophoretic data and displaying that data as an electrophoretogram on a computer screen. (Ex. 1003 at 15:30-65.) The computer system 590 in Klein would perform the normalization process described in Hietpas – e.g., aligning a data point from the second series of measurements with a data point from the first series of measurements. As previously discussed in §

IX.C.8.c.(3), the control system 590 already controls the tasks for processing and displaying electrophoretic data (including the first and second series of measurements). Therefore, it would be obvious for the control system 590 and its corresponding computer code to perform the time normalization process described in Hietpas. (Ex. 1002 at ¶¶ 128-129.) The code required to perform the time normalization process would be minimal and the resulting modifications to the Klein system would be insignificant. (Ex. 1002 at ¶ ¶¶ 128-129.)

4. Independent Claim 19

Klein discloses claim elements 19[a] to 19[e] and claim element 19[g] for the same reasons discussed above in § IX.C.9 and §§ IX.C.8.d(1) and (2) under Ground 1. For this reason, elements 19[a] to 19[e] and element 19[g] are not addressed again here under Ground 3.

Claim element 19[f] is exactly the same as claim element 17[h]. Thus, Klein in view of Hietpas render claim element 19[f] obvious for the same reasons discussed above in § IX.D.3.b under Ground 3.

5. Claims 18 & 20

Dependent claims 18 and 20 are disclosed by Klein as discussed above in § IX.C.10 under Ground 1. The rationales for combining Klein and Hietpas explained above for claims 17 and 19 under Ground 3 are applicable here to claims 18 and 20. *See* § IX.D.3.b.

E. No Secondary Considerations of Non-Obviousness Exist

Patent Owner has not identified any evidence of secondary indicia of non-obviousness for the '240 patent. Accordingly, there is no objective evidence of non-obviousness that might warrant a finding that the Petitioned Claims are patentable. (Ex. 1002 at ¶ 130.)

X. CONCLUSION

Petitioners respectfully request that the Board institute *inter partes* review of claims 1-5, 8-12, 15-19, 22-26 and 29-30.

Respectfully submitted,
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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(b), the undersigned certifies that on November 3, 2015, a complete and entire copy of this **Petition for *Inter Partes* Review of Patent No. 6,834,240**, including Exhibit Nos. 1001-1033 and a Power of Attorney, was served via FEDERAL EXPRESS, costs prepaid, to the Patent Owner by serving the correspondence address of record as follows:

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