

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
8 April 2004 (08.04.2004)

PCT

(10) International Publication Number  
**WO 2004/030025 A1**

(51) International Patent Classification<sup>7</sup>: **H01J 49/40**

(21) International Application Number:  
PCT/US2003/029950

(22) International Filing Date:  
24 September 2003 (24.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/413,406 24 September 2002 (24.09.2002) US  
10/424,351 24 April 2003 (24.04.2003) US  
60/476,714 6 June 2003 (06.06.2003) US

(71) Applicant (for all designated States except US): **CIPHER-  
GEN BIOSYSTEMS, INC.** [US/US]; 6611 Dumbarton  
Circle, Fremont, CA 94555 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **BUTTRILL, Sidney,  
E., Jr.** [US/US]; 1417 Parkinson Avenue, Palo Alto, CA  
94301 (US).

(74) Agents: **BECKER, Daniel, M.** et al.; c/o Fish & Neave,  
1251 Avenue of the Americas, New York, NY 10020 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,  
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,  
KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,  
MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT,  
RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR,  
TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

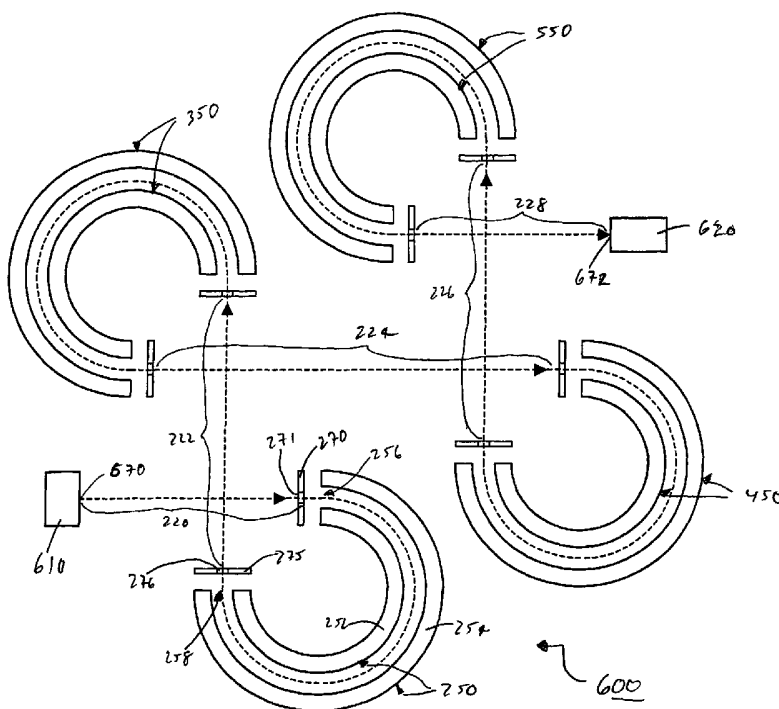
(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,  
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,  
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,  
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17:**

— as to applicant's entitlement to apply for and be granted  
a patent (Rule 4.17(ii)) for the following designations AE,  
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,  
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES,

[Continued on next page]

(54) Title: ELECTRIC SECTOR TIME-OF-FLIGHT TANDEM MASS SPECTROMETER



(57) Abstract: The invention provides apparatus and methods for performing tandem mass spectrometry. A tandem mass spectrometer (600) of the present invention comprises a first mass analyzer (250, 350) and a second mass analyzer (450, 550). At least one of the mass analyzers is a time-of-flight mass analyzer and comprises at least one electric sector (250, 350, 450 or 550).

WO 2004/030025 A1

— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ,

as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, SE, SI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

## ELECTRIC SECTOR TIME-OF-FLIGHT TANDEM MASS SPECTROMETER

## CROSS-REFERENCE TO RELATED APPLICATIONS

- 5     **[0001]**     This application claims the benefit of U.S. provisional application no. 60/413,406, filed 24 September 2002; and is a continuation-in-part of U.S. patent application no. 10/424,351, filed 24 April 2003; and claims the benefit of U.S. provisional application no. 60/476,714, filed 06 June 2003, the disclosures of which are incorporated herein by reference in their entireties.

10

## FIELD OF THE INVENTION

- [0002]**             This invention is in the field of mass spectrometry.

## BACKGROUND OF THE INVENTION

- 15     **[0003]**             Tandem, or sequential, mass spectrometry, in which successive phases of mass analysis are conducted in a single device, has brought significant analytical power to the study of macromolecules, including biomolecules. In the study of proteins, for example, tandem mass spectrometry has made possible the rapid identification of proteins present within complex biological samples.
- 20     **[0004]**             Given the power of tandem mass spectrometry, a variety of spectrometers have been developed that are capable of performing successive phases of mass spectral analysis ( $MS^n$ ), either tandem in space, using multiple mass analyzers positioned

successively along the ion flight path, or tandem in time, typically with at least one ion trap for selective retention and/or passage of ions.

**[0005]** The well-recognized advantages of time-of-flight (TOF) mass analyzers -- including their ability to function without time-dependent changing magnetic or electric fields, and their ability to scan a wide spectral range in a small time window -- have led to the development of a variety of tandem mass spectrometers having at least one TOF mass analyzer. Loboda et al., Rapid Commun. Mass Spectrom. 14:1047 - 1057 (2000), for example, describe a quadrupole time-of-flight tandem mass spectrometer (Qq-TOF) having a matrix-assisted laser desorption/ionization (MALDI) source. U.S. Patent Application Publication No. 2002/0195555 and corresponding international patent publication no. WO 02/31491 describe a Qq-TOF tandem MS with an interface particularly adapted to engage surface-enhanced laser desorption/ionization (SELDI) probes.

**[0006]** TOF mass analyzers nonetheless have several drawbacks.

**[0007]** One is size.

**[0008]** Particularly when arranged in tandem, the multiple free-flight regions necessitate a long ion flight path that demands a commensurately large device. Increased size, in turn, demands larger or higher-performance peripherals, such as vacuum pumps, which adds to the overall cost, complexity, and may reduce system performance.

**[0009]** Another is resolution.

**[0010]** At the theoretical optimum, ions having exactly the same mass and kinetic energy traverse the free-flight region of a time-of-flight mass analyzer as a highly compact parcel.

**[0011]** In practice, however, it is difficult to achieve these optimal circumstances using a TOF mass spectrometer. Several stochastic factors conspire to impart a distribution of energies to the ions formed in the ion source. This distribution may arise due to inhomogeneities among the ions during their initial formation, such as differences in their thermal energies, velocities, spatial positions, or times of formation. As a result, parcels of identical ions disperse in the free-flight region and hence arrive at the ion detector with a broader distribution of times-of-flight. This broader distribution decreases the resolving power of the spectrometer.

**[0012]** These problems have imposed limitations on the resolution, and thus utility, of TOF mass spectrometers, whether used for a single phase of mass analysis or as one or multiple phases in a tandem mass spectrometer.

**[0013]** Various techniques, known generally as ion focusing, have been described  
5 that attempt to offset this mass-independent dispersion of ions during free-flight. Some of these focusing techniques, such as time-lag focusing, post-source focusing, and dynamic pulse focusing, manipulate the electric field during ion acceleration. Other methods include ion mirrors or reflectrons that provide ion focusing by altering the flight path length, such that higher energy ions are made to travel proportionally longer paths. However, these  
10 techniques are typically limited to focusing ions in a limited mass range.

**[0014]** Another ion focusing technique uses curved deflecting fields provided by electric sectors. U.S. Patent Nos. 3,576,992 (Moorman, et al.) and 3,863,068 (Poschenrieder) describe ion focusing techniques using electric sectors. In 1985, Matsuda and co-workers published an analysis of the advantages and preferred configurations of  
15 time-of-flight mass spectrometers incorporating multiple electric sectors. Sakurai et al., Int. J. Mass Spectrom. Ion Processes 63:273-287 (1985). Subsequently, the same group described the construction and performance of an instrument based on the best of the four sector designs. Sakurai et al., Int. J. Mass Spectrom. Ion Processes 66:283-290 (1985).

**[0015]** Although certain advantages have been demonstrated, several  
20 disadvantages have limited use of electric sectors in TOF mass spectrometers.

**[0016]** In particular, the ion focusing abilities of an electric sector are highly dependent on and sensitive to its electric field properties and physical parameters. Small deviations in these parameters can profoundly affect its ion focusing abilities. Hence, electric sectors are difficult to construct and install so as to achieve the desired results.  
25 Furthermore, modifying or correcting these parameters by mechanical means after their construction and installation is also exceedingly difficult.

**[0017]** There thus exists a need in the art for tandem mass spectrometers having at least one time-of-flight mass analyzer in which the ion flight path can nonetheless be accommodated in a reasonably-sized enclosure. There exists a further need in the art for  
30 TOF tandem mass spectrometers with improved ion focusing capabilities. There exists a need for tandem mass spectrometers in which one or more electric sectors can be used for time-of-flight mass analysis in which the ion focusing abilities of the electric sectors are less

dependent on and sensitive to small deviations in the sector's electric field properties and physical parameters. And there also exists a need for tandem mass spectrometers with decreased size, cost, and improved performance.

## 5 SUMMARY OF THE INVENTION

**[0018]** The present invention solves these and other needs in the art by providing, in a first aspect, a tandem mass spectrometer.

**[0019]** The tandem mass spectrometer comprises an ion source; a first mass analyzer; a second mass analyzer; and an ion detector. The ion source is in ion  
10 communication with the first mass analyzer; the first mass analyzer is in ion communication with the second mass analyzer; the second mass analyzer is in ion communication with the ion detector; and at least one of the mass analyzers is a time-of-flight mass analyzer that comprises at least one electric sector. In one particularly useful embodiment, the first mass analyzer is a time-of-flight mass analyzer that comprises at least one electric sector.

15 **[0020]** In further embodiments, the tandem mass spectrometer of the present invention can usefully further comprise at least one field free region, wherein the at least one electric sector and the at least one field free region define an ion flight path. The tandem mass spectrometer may comprise ion fragmentation means, typically situated between and in ion communication with both first and second mass analyzers.

20 **[0021]** The tandem mass spectrometer of the present invention can further comprise ion selection means in ion communication with both the first and second mass analyzer. The ion selection means are capable of selecting ions from among a plurality of ions provided by the first mass analyzer.

**[0022]** In some embodiments, the ion selection means comprises an aperture in  
25 ion communication with the second mass analyzer and means for sweeping an ion beam across the aperture. In some embodiments, the ion deflection means comprises electric field means. In some embodiments, the ion selection means comprises a plurality of consecutive ion gates.

**[0023]** The ion source can, in some embodiments, usefully be selected from the  
30 group consisting of: laser desorption/ionization means, chemical ionization means, photoionization means, and electrospray ionization means.

5       **[0024]**       The ion source can comprise means for extracting ions from a pulsed or continuous ion beam in either a substantially axial or substantially orthogonal direction. Further, the ion source can comprise means for accelerating a pulse of ions from the ion source, such as voltage pulsing means capable of applying a pulse subsequent to formation of the ions.

10       **[0025]**       So long as the tandem mass spectrometer includes a time-of-flight mass analyzer having an electric sector, the first mass analyzer can include an analyzer selected from the group consisting of: an electric sector time-of-flight mass analyzer, a linear time-of-flight mass analyzer, a reflecting time-of-flight mass analyzer, a linear ion trap, a quadrupole ion trap, a quadrupole ion filter, a magnetic sector mass analyzer, an ion cyclotron resonance mass analyzer, an electric sector/magnetic sector mass analyzer, an ion trap/linear time-of-flight mass analyzer, an ion trap/reflecting time-of-flight mass analyzer, and an electrostatic mass analyzer.

15       **[0026]**       Analogously, so long as the tandem mass spectrometer includes a time-of-flight mass analyzer having an electric sector, the second mass analyzer can comprise a mass analyzer selected from the group consisting of: an electric sector time-of-flight mass analyzer, a linear time-of-flight mass analyzer, a reflecting time-of-flight mass analyzer, a linear ion trap, a quadrupole ion trap, a quadrupole ion filter, a magnetic sector mass analyzer, ion cyclotron resonance mass analyzer, an electric sector/magnetic sector mass analyzer, an ion trap/ linear time-of-flight mass analyzer, an ion trap/reflecting time-of-flight mass analyzer, and an electrostatic mass analyzer.

25       **[0027]**       In some embodiments, the mass spectrometer of the present invention includes at least one time-of-flight mass analyzer having two or four electric sectors and a field-free region separating each of the electric sectors, the electric sectors and the field-free regions defining an ion flight path. In one such embodiment, the at least one mass analyzer is a time of flight mass analyzer that comprises four electric sectors and a field-free region separating each of the electric sectors, each of the electric sectors having a deflection angle of about 270 degrees, the electric sectors and the field-free regions defining an ion flight path therein.

30       **[0028]**       In embodiments having a plurality of electric sectors, the electric sectors can be arranged in a symmetrical arrangement.

[0029] In further embodiments, a field-free region can precede and alternatively, or in addition, follow at least one electric sector.

[0030] In some embodiments, at least one of the mass analyzers is a time-of-flight mass analyzer that comprises two or four electric sectors and a field free region before the first electric sector, after the last electric sector, and between each of the electric sectors, the electric sectors and the field-free regions defining an ion flight path therein.

[0031] The electric sector time-of-flight mass analyzer in the tandem mass spectrometer of the present invention can further comprise at least one Herzog shunt having an aperture: the Herzog shunt is associated with either the entry or the outlet of an electric sector such that the ions pass through the aperture. In one series of embodiments, the Herzog shunt is an aperture in a housing enclosing the electric sector.

[0032] The tandem mass spectrometer of the present invention can further comprise means for fragmenting ions provided by the first mass analyzer. The fragmenting means can, for example, include a collision cell.

[0033] Usefully, at least one electric sector is associated with at least one ionic optical element, wherein the at least one ion optical element modifies the potential experienced by an ion entering or exiting the electric sector.

[0034] In certain embodiments, for example, the ion optical element comprises at least one adjustable trim electrode capable of adjustably modifying the potential experienced by an ion entering or exiting an electric sector. The at least one adjustable trim electrode can usefully be disposed between the entry and the outlet of the electric sector.

[0035] The tandem mass spectrometer can include a pair of adjustable trim electrodes disposed so that the ions pass between the adjustable trim electrodes of the pair, wherein the pair is associated either with an entry or an outlet of an electric sector. In other embodiments, the device includes a plurality of pairs of adjustable trim electrodes, each pair disposed so that the ions pass between the adjustable trim electrodes of the pair, wherein a pair is associated with each entry and each outlet of each electric sector.

[0036] The electric sector time-of-flight mass analyzer within the tandem mass spectrometer can comprise four electric sectors, each electric sector having a deflection angle of about 270 degrees, wherein a field free region separates each electric sector.



**[0037]** In one series of embodiments, the ion source comprises means for extracting ions from a pulsed or continuous ion beam in either a direction substantially parallel to (axial to) the ion beam, or substantially orthogonal to the direction of the beam.

**[0038]** In embodiments having trim electrodes, the trim electrode potentials can be controlled by a control system, which can comprise a software program.

**[0039]** In another aspect, the invention provides a tandem mass spectrometer, the tandem mass spectrometer comprising an ion source; a first mass analyzer; a second mass analyzer; and an ion detector, wherein the first mass analyzer is capable of stigmatic and time focusing of ions to a substantially coincident spatial location on an ion flight path.

**[0040]** The mass spectrometer can further comprise ion selection means in ion communication with both the first and second mass analyzer, the ion selection means capable of selecting ions from among a plurality of ions provided by the first mass analyzer. The ion selection means can usefully comprise an aperture in ion communication with the second mass analyzer and means for sweeping an ion beam across the aperture. The ion deflection means, in certain embodiments, can further comprise electric field means.

**[0041]** In these embodiments, the mass spectrometer can further comprise ion fragmentation means, wherein the ions are fragmented following the first mass analysis. Usefully, the first mass analyzer is a time-of-flight mass analyzer, including, e.g., a time-of-flight mass analyzer that includes at least one electric sector.

**[0042]** In a further aspect, the invention provides a tandem mass spectrometer comprising means for providing a plurality of ions; means for performing a first mass analysis; means for performing a second mass analysis; and means for detecting a plurality of ions. The means for performing the first mass analysis is capable of stigmatic and time focusing of ions to a substantially coincident spatial location on an ion flight path.

**[0043]** Such devices can further comprise means for selecting ions, wherein the ion selecting means is positioned in ion communication with both the means for performing a first mass analysis and means for performing a second mass analysis. In such embodiments, the means for performing a first mass analysis can be capable of coincident temporal and stigmatic ion focusing at a location substantially coincident with the means for selecting ions.

**[0044]** In a further series of embodiments, the mass spectrometer further comprises means for fragmenting ions, wherein the ions are fragmented following the

means for performing a first mass analysis. The means for performing a first mass analysis can be capable of coincident ion focusing at a location substantially coincident with the means for fragmenting ions.

5 [0045] In another aspect, the invention provides a method for performing tandem mass spectrometry, the method comprising performing a first mass analysis on a plurality of ions provided by an ion source, using a first mass analyzer; performing a second mass analysis on at least a subset of said plurality of ions using a second mass analyzer; and detecting a plurality of ions using an ion detector, wherein at least one of the mass analyzers comprises a time-of-flight mass analyzer that has at least one electric sector.

10 [0046] In these methods, the electric sector time-of-flight mass analyzer can further comprise at least one field free region, wherein the at least one electric sector and the at least one field free region define an ion flight path. The electric sector time-of-flight mass analyzer can be the first mass analyzer.

15 [0047] In another aspect, the invention provides a method for performing tandem mass spectrometry, the method comprising: stigmatically and temporally focusing at least a plurality of ions provided by an ion source using a first mass analyzer, wherein the ions are stigmatically and temporally focused to a substantially coincident spatial location on an ion flight path; performing a second mass analysis on at least a subset of the focused ions using a second mass analyzer; and detecting a plurality of ions using an ion detector.

20 [0048] In yet a further aspect, the invention provides a method for tuning a tandem mass spectrometer of the present invention having trim electrodes adjacent to one or more electric sectors in a time-of-flight mass analyzer. The method comprises: a) determining the resolution or sensitivity of detection of ions at a first setting by: i) applying a potential to at least one adjustable trim electrode; ii) obtaining a first mass spectrum of ions from the ion source; and iii) determining resolution and/or sensitivity of detection from the first mass spectrum; b) determining the resolution or sensitivity of detection of ions at a second setting by: i) adjusting the potential applied to at least one adjustable trim electrode; ii) obtaining a second mass spectrum of ions from the ion source; and iii) determining resolution or sensitivity of detection from the second mass spectrum; and c) determining whether  
25  
30 resolution or sensitivity of detection of ions is improved or degraded at the second setting.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0049]** The above and other objects and advantages of the present invention will be apparent upon consideration of the following detailed description taken in conjunction with the accompanying drawings, in which like characters refer to like parts throughout, and  
5 in which:

FIG. 1 is a schematic view of a tandem mass spectrometer of the present invention;

FIG. 2 is a schematic top cross-sectional view of a mass analyzer of the present invention;

10 FIG. 3 is a schematic top cross-sectional view of a mass analyzer of the present invention;

FIG. 4 is a schematic view of a tandem mass spectrometer of the present invention;

15 FIGS. 5A-C present a schematic view of an ion selection means of the present invention;

FIG. 6 is a schematic top cross-sectional view of a mass analyzer of the present invention;

FIG. 7 is a schematic view of an electric sector opening of the present invention with the reference ion flight path normal to the plane of the drawing;

20 FIG. 8 is a schematic top cross-sectional view of another mass analyzer of the present invention;

FIG. 9 is a schematic view of an electric sector opening of the present invention with the reference ion flight path normal to the plane of the drawing and with dimensions labeled;

25 FIGS. 10A and 10B are a schematic top cross-sectional view and an exploded isometric view, respectively, of an electric sector opening of the present invention;

FIGS. 11A, 11B and 11C are portions of an exemplary mass spectrum of IgG (immunoglobulin G) obtained using an apparatus in accordance with the present invention;

30 FIGS. 12A-12H are portions of an exemplary mass spectrum of a tryptic digest of bovine serum albumin using an apparatus in accordance with the present invention;

FIGS. 13A and 13B are portions of an exemplary mass spectrum of a tryptic digest of bovine serum albumin using an apparatus in accordance with the present invention;

FIG. 14 is an exemplary mass spectrum of adrenocorticotrophic hormone  
5 using an apparatus in accordance with the present invention; and

FIG. 15 is a schematic top cross-sectional view of another mass analyzer of the present invention.

#### DETAILED DESCRIPTION

##### 10 Definitions

**[0050]** As used herein, the terms set forth with particularity below have the following definitions. If not otherwise defined, all terms used herein have the meaning commonly understood by a person skilled in the arts to which this invention belongs.

**[0051]** "Ion source" refers to a sub-assembly of a mass spectrometer that provides  
15 gas phase ions. In one embodiment, the ion source provides ions through a desorption/ionization process. Such embodiments generally comprise a probe interface that positionally engages a probe in an interrogatable relationship to a source of ionizing energy and in concurrent communication at atmospheric or subatmospheric pressure with a detector of a gas phase ion spectrometer. Ion sources are indicated by reference number  
20 410 in FIG. 1, reference number 710 in FIG. 4, reference number 110 in FIGS. 5 and 15, and by reference number 210 in FIG. 8.

**[0052]** Forms of ionizing energy for desorbing/ionizing an analyte from a solid phase include, for example: (1) laser energy; (2) fast atoms (used in fast atom bombardment); (3) high energy particles generated via beta decay of radionuclide (used in  
25 plasma desorption); and (4) primary ions generating secondary ions (used in secondary ion mass spectrometry). A typical form of ionizing energy for solid phase analytes is a laser (used in laser desorption/ionization), in particular, nitrogen lasers, Nd-Yag lasers and other pulsed laser sources.

**[0053]** Other forms of ionizing energy for analytes include, for example: (1)  
30 electrons that ionize gas phase neutrals; (2) strong electric field to induce ionization from gas phase, solid phase, or liquid phase neutrals; and (3) a source that applies a

combination of ionization particles or electric fields with neutral chemicals to induce chemical ionization of solid phase, gas phase, and liquid phase neutrals.

**[0054]** "Ion flight path" refers to the path taken by the ions within the mass spectrometer apparatus between the "ion entrance" and the "ion exit". Ion flight paths may  
5 be exemplified by the path followed by a reference ion, such as those indicated by reference numbers 50, 52, and 54 in FIGS. 2, 6, and 15, and by reference number 60 in FIGS. 3 and 8.

**[0055]** "Ion flight path means" refers to the components of the mass spectrometer apparatus that define the ion flight path. Ion flight path means have an ion entrance and an  
10 ion exit, and may comprise at least one field-free region, at least one electric sector, and at least one ion optical element. Exemplary ion flight path means in FIGS. 6 and 15 comprise free-flight regions 120 and 125, electric sector 150, and ion optical elements 166 and 167. The ion flight path means of the embodiment depicted in FIG. 8 comprises free-flight regions 220, 222, 224, 226, and 228; electric sectors 250, 350, 450, and 550; and the ion  
15 optical elements associated with the electric sectors. Exemplary ion flight path means in FIG. 2 comprise free-flight regions 120 and 125, and electric sector 150. The ion flight path means of the embodiment depicted in FIG. 3 comprises free-flight regions 220, 222, 224, 226, and 228 and electric sectors 250, 350, 450, and 550.

**[0056]** "Field free region" refers to a one or more segments of an ion flight path in  
20 which the ions are allowed to travel without linear or angular acceleration. Field free regions are indicated by reference numbers 120 and 125 in FIGS. 2, 6 and 16 and by reference numbers 220, 222, 224, 226, and 228 in FIGS. 3 and 8.

**[0057]** "Electric sector" refers to a component of the mass spectrometer apparatus that defines a curved deflection region of the ion flight path. The electric sector comprises  
25 two deflecting electrodes with an electric field therebetween that is configured to deflect ions such that the ions follow a curved path by angular acceleration. Electric sectors are illustrated in the drawings, e.g., by reference numbers 150, 250, 350, 450, and 550.

**[0058]** "Ion optical element" refers to a component of the mass spectrometer apparatus distinct from the electric sectors that is configured to modify the potential  
30 experienced by ions in the ion flight path. When the ion optical element is in association with an electric sector, the modification of the potential is imposed on the ions as the ions enter, exit, or pass through the electric sector. Ion optical elements are, e.g., indicated by

reference numbers 166 and 167 of FIGS. 6 and 15 and by reference numbers 266 and 267 of FIGS. 8, 10A and 10B.

**[0059]** "Ion detector" refers to a component of the mass spectrometer apparatus that is suitable for detecting ions after exiting the ion flight path. The detection of the arriving ions is used to determine the time-of-flight of the ions. For illustration, ion detectors are indicated by reference number 440 in FIG. 1, by reference number 740 in FIG. 4, by reference number 180 in FIGS. 6 and 15, and by reference number 280 in FIG. 8.

**[0060]** "Trim electrode" refers to one or more components of an ion optical element that are configured to modify the potential experienced by ions on the ion flight path. In some embodiments, the present invention includes trim electrodes that are adjustable. Illustrative trim electrodes are indicated by reference numbers 160-163 on FIGS. 1 and 10 and reference numbers 260-263 on FIGS. 3, 5A and 5B.

**[0061]** "Fragments" refers to ions that result from the decomposition of molecular ions. Fragments may be formed during or after ionization of the sample.

**[0062]** "Deflection angle" refers to the angle spanned by the arc of the electric sector over which the ions on the ion flight path are deflected. For example, the deflection angle of the electric sector in FIGS. 2, 6, and 15 is approximately 180° and the deflection angle of each electric sector in FIGS. 3 and 8 is approximately 270°.

**[0063]** "Ion trap" refers to a component that is suitable for trapping ions. Ion traps use electric fields configured to selectively trap and provide ions of one or more masses or range of masses, or fragments thereof. Ion traps may include quadrupole ion traps and linear ion traps.

**[0064]** "Herzog shunt" refers to a component or structure in a mass spectrometer apparatus suitable for limiting the terminal electric fields of an electric sector. A Herzog shunt has an aperture to allow passage of the ion flight path therethrough. Illustrative Herzog shunts are indicated by reference numbers 170 and 171 in FIGS. 2, 6 and 15 and by reference numbers 270 and 275 in FIGS. 3, 8, 10A and 10B. The enclosure and apertures indicated by reference number 370 and 375-376, respectively, on FIG. 15 also function as Herzog shunts.

**[0065]** "Einzel lens" is a component of an ion optical element that comprises one or more electrodes suitable for focusing the radial distribution of ions on the ion flight path.

**[0066]** "Resolution" refers to the ability to distinguish ions of similar but non-identical masses (or  $m/z$ ) as separate signals and/or the width of a measured mass signal as a ratio of its determined mass.

5 **[0067]** "Sensitivity" refers to the ability to detect and distinguish signals over the noise of the spectrum, thereby establishing the minimum amount of sample required to detect a signal.

**[0068]** "Accuracy" refers to the ability of a calibrated mass spectrometer to provide a mass value for an ion that is close to the predicted mass for that ion.

10 **[0069]** "Spectral range" refers to the extent to which the spectrometer can detect and measure a range of masses and/or times-of-flight from a given sample within a single spectrum. Ions outside of the spectral range of a mass spectrum are usually not detectable.

**[0070]** "Tandem mass spectrometer" refers to any mass spectrometer that is capable of performing two or more successive stages of  $m/z$ -based discrimination or measurement of ions, including ions in an ion mixture. The phrase includes mass spectrometers having two mass analyzers that are capable of performing two successive stages of  $m/z$ -based discrimination or measurement of ions tandem-in-space. The phrase further includes mass spectrometers having a single mass analyzer that is capable of performing two successive stages of  $m/z$ -based discrimination or measurement of ions tandem-in-time. For illustration, a schematic view of a tandem mass spectrometer is indicated by reference number 400 in FIG. 1.

15 **[0071]** "Mass analyzer" refers to a sub-assembly of a mass spectrometer that comprises means for measuring a parameter that can be translated into mass-to-charge ratio ( $m/z$ ) of gas phase ions. For illustration, mass analyzers are indicated by reference numbers 420 and 430 in FIG. 1, by reference numbers 720 and 730 in FIG. 4, by reference number 500 in FIG. 2, by reference number 600 in FIG. 3, by reference numbers 1100 and 1200 in FIG. 5, by reference number 100 in FIG. 6, reference number 200 in FIG. 8, and reference number 300 in FIG. 15.

25 **[0072]** "Ion selector" refers to a component of the mass spectrometer apparatus that is suitable for selecting ions of a desired mass from a plurality of ions. The selected ions may be subjected to further mass analysis. For illustration, ion selectors are indicated by reference number 1000 in FIG. 5 and by reference number 750 in FIG. 4.

**[0073]** "Ion fragmentor" refers to a component of the mass spectrometer apparatus that is suitable for fragmenting larger ions into smaller secondary (product) ion fragments. The secondary ions may be subjected to further mass analysis. For illustration, ion fragmentors are indicated by reference number 750 in FIG. 4.

5

#### Description of Embodiments of the Present Invention

**[0074]** In the present invention, a tandem mass spectrometer apparatus includes an ion source, a first mass analyzer, a second mass analyzer, and an ion detector. At least one of the mass analyzers comprises a time-of-flight mass analyzer that comprises at least one electric sector ("an electric sector TOF mass analyzer"). In some useful embodiments of the present invention, the first mass analyzer is an electric sector TOF mass analyzer.

**[0075]** Although embodiments of the tandem mass spectrometers of the present invention include two mass analyzers, such in the examples shown herein, it is understood that in other embodiments the tandem mass spectrometers of the present invention include three or more mass analyzers, wherein each mass analyzer may perform successive ion discrimination or measurement steps.

**[0076]** Referring to FIG. 1, a schematic view of tandem mass spectrometer apparatus 400 of the present invention is depicted, illustrating the component sub-assemblies. Apparatus 400 comprises ion source 410, a first mass analyzer 420, a second mass analyzer 430, and ion detector 440. Each component is in ionic communication with the other components as indicated, thereby allowing ions to move therebetween. Other components that are or may be present in a tandem mass spectrometer of the present invention, such as additional mass analyzers, ion fragmentors, ion selectors, etc. are not depicted in this figure.

**[0077]** Ion source 410 includes means for generating ions that are known in the art, including any of the means or methods known in the art for producing a plurality of ions within a relatively small volume and within a relatively short time. Also included are any of the means or methods known in the art for producing a pulse of ions, such that the pulse of ions has the appearance of or behaves as if the ions were produced within a relatively small volume and within a relatively short time. Ion source 410 may include means to form ions in a continuous or pulsed manner. The ion source may also include means to concentrate the ions, such as a quadrupole ion trap or a linear ion trap. In certain embodiments, the means

30



for accelerating the pulse of ions comprises means for creating a voltage pulse subsequent to the formation of the ions. The ion source may include means to extract a group of ions from a pulsed or continuous ion beam in a direction substantially orthogonal to or parallel to the direction of the beam.

5     **[0078]**           Ion source 410 may, e.g., include means that employ a pulsed laser interacting with a solid surface, a pulsed focused laser ionizing a gas within a small volume, or a pulsed electron or ion beam interacting with a gas or solid surface. In another embodiment, ion source 410 may employ means for generating a pulse of ions that uses a rapidly sweeping, continuous ion beam passed over a narrow slit, in which a brief pulse of  
10    ions is produced by the ions passing through the slit when the ion beam passes thereover. Ion source 410 may employ, but is not limited to use of, electrospray ionization, laser desorption/ionization ("LDI"), matrix-assisted laser desorption/ionization ("MALDI"), surface-enhanced laser desorption/ionization ("SELDI"), surface-enhance neat desorption ("SEND"), fast atom bombardment, surface-enhanced photolabile attachment and release, pulsed ion  
15    extraction, plasma desorption, multi-photon ionization, electron impact ionization, inductively coupled plasma, chemical ionization, atmospheric pressure chemical ionization, and hyperthermal source ionization.

**[0079]**           Furthermore, ion source 410 may also include means for selectively providing ions of one or more masses or ranges of masses, or fragments therefrom. Such  
20    means may be accomplished by combining a TOF mass spectrometer of the present invention in tandem fashion with a plurality of analyzers, including magnetic sector, electrostatic analyzer, ion traps, quadrupole ion traps, quadrupole mass filters, and TOF devices.

**[0080]**           Ion source 410 also includes means for ion extraction or acceleration from  
25    the ion source to the ion flight path. The extraction methods may be parallel or orthogonal to the ion beam generated in ion source 410. In addition, extraction or acceleration of the ions may occur subsequent to the formation of the ions, such as by application of a voltage pulse.

**[0081]**           The sample ions subsequently enter first mass analyzer 420, in which the  
30    sample ions may be separated and resolved. In certain useful embodiments, the first mass analyzer preferably includes an electric sector TOF mass analyzer. Accordingly, in such embodiments the first mass analyzer may perform ion focusing, such as stigmatic and time

focusing, of the ions therein. When the ions are focused in this manner, the ion beam may be focused at a defined spatial location after exiting the first mass analyzer.

**[0082]** The first mass analyzer may comprise mass analyzers known to one of ordinary skill in the art. Examples of suitable mass analyzers include an electric sector time-of-flight mass analyzer, a linear time-of-flight mass analyzer, a reflecting time-of-flight mass analyzer, a linear ion trap, a quadrupole ion trap, a quadrupole ion filter, a magnetic sector mass analyzer, ion cyclotron resonance mass analyzer, an electric sector/magnetic sector mass analyzer, an ion trap/ linear time-of-flight mass analyzer, an ion trap/reflecting time-of-flight mass analyzer, and an electrostatic mass analyzer.

**[0083]** In succession with the first mass analyzer, ions may undergo a second mass analysis using second mass analyzer 450. As with the first mass analyzer, the second mass analyzer may comprise mass analyzers known to one of ordinary skill in the art. Examples of suitable mass analyzers include an electric sector time-of-flight mass analyzer, a linear time-of-flight mass analyzer, a reflecting time-of-flight mass analyzer, a linear ion trap, a quadrupole ion trap, a quadrupole ion filter, a magnetic sector mass analyzer, ion cyclotron resonance mass analyzer, an electric sector/magnetic sector mass analyzer, an ion trap/ linear time-of-flight mass analyzer, an ion trap/reflecting time-of-flight mass analyzer, and an electrostatic mass analyzer.

**[0084]** Following the second mass analysis by the second mass analyzer, ion products are then detected and recorded by ion detector 440 to generate a mass spectrum. For example, ion detector 440 includes known means for detecting ions and amplifying their signals. Ion detector 440 may also include means for recording ions detected therein, such as a computer or other electronic apparatus.

**[0085]** Tandem mass spectrometers of the present invention may also include one or more mass analyzers in addition to mass analyzers 420 and 430 to provide further mass analysis steps. These and other tandem mass spectrometers of the present invention are particularly useful for the analysis and identification of large molecules, such as proteins, peptides, and other biopolymers.

**[0086]** Tandem mass spectrometers of the present invention may also include one or more ion selectors for the selection of primary ions from among a plurality of sample ions. Ion selectors may be situated in ionic communication with the other components of the

tandem mass spectrometer. In certain useful embodiments, an ion selector is situated to receive ions exiting the first mass analyzer.

5       **[0087]**        Tandem mass spectrometers of the present invention may also include one or more ion fragmentors for ion fragmentation, thereby yielding secondary (product) ions. In certain useful embodiments, an ion selector is situated to receive ions exiting the first mass analyzer. An ion selector may also be situated to receive ions after an ion selection or filtration step, such as by a mass analyzer or an ion selector. Alternatively, or in addition to ion fragmentors, the apparatus of the present invention may be configured to allow ions to decay within or after the source.

10       **[0088]**        Likewise, ion detector 440 includes means for detecting ions and amplifying their signals that are known, and also will not be discussed in detail here. For example, ion detector 440 may include continuous electron multipliers, discrete dynode electron multipliers, scintillation counters, Faraday cups, photomultiplier tubes, and the like. Ion detector 440 may also include means for recording ions detected therein, such as a  
15        computer or other electronic apparatus.

**[0089]**        As described above, a tandem mass spectrometer of the present invention includes at least one mass analyzer that includes an electric sector TOF mass analyzer. An electric sector TOF mass analyzer comprises at least one electric sector and, typically, at least one free-flight region, such that the electric sectors and the free-flight regions define  
20        an ion flight path. In certain useful embodiments of this mass analyzer in which there are multiple electric sectors, each electric sector is separated from adjacent electric sectors by a free-flight region.

**[0090]**        Referring to FIG. 2, an exemplary electric sector TOF mass analyzer suitable for use as a mass analyzer of the tandem mass spectrometer is depicted. Mass  
25        analyzer 500, shown in top cross-section view taken through a plane defined by ion flight path 50, comprises free-flight regions 120 and 125, electric sector 150, and Herzog shunts 170 and 171. Reference number 510 is in ionic communication with mass analyzer 500, and indicates the source of the ions that enter electric sector TOF mass analyzer 500. In the context of a tandem mass spectrometer of the present invention, source 510 may  
30        include, for example, an ion source, a preceding mass analyzer, an ion trap, an ion selector, an ion fragmentor, or other suitable source. Reference number 520 is in ionic communication with mass analyzer 500 indicates the destination of the ions that exit electric

sector TOF mass analyzer 500. In the context of a tandem mass spectrometer of the present invention, source 520 may include, for example, an ion detector, a successive mass analyzer, an ion trap, an ion selector, an ion fragmentor, or other suitable destination. For example, in an embodiment in which first mass analyzer 420 in FIG. 1 includes mass  
5 analyzer 500, source 510 may therefore represent ion source 410 and destination 520 may therefore represent second mass analyzer 430.

**[0091]** During typical operation of a tandem mass spectrometer of the present invention that includes electric sector TOF mass analyzer 500, ions are provided by source 510, separate in free-flight region 120, pass through aperture 175 of shunt 170, and enter  
10 electric sector 150 via entry opening 156. Outer and inner deflecting electrodes 154 and 152, respectively, provide a deflecting electric field therebetween that deflects the ions into a curved path. The ions then exit via outlet opening 158, pass through aperture 176 of shunt 171, separate in free-flight region 125, and continue to destination 520. Flight path 50  
15 is the path of a reference ion, while flight paths 52 and 54 are schematic representations of the paths taken by ions leaving ion source 110 with angles which are slightly larger or smaller than the angle of the reference ion. Further details on the specific features of mass analyzer 500 are discussed hereinbelow with respect to like reference numbers in FIG. 6.

**[0092]** Accordingly, an ion flight path is defined within mass analyzer 500, for which flight path 50 is a representative example. Flight path 50 comprises ion entrance 540  
20 at which source 510, in communication with free-flight region 120, causes the ions to enter flight path 50. Correspondingly, flight path 50 further comprises ion exit 542, at which the ions exit flight path 50 upon arrival at destination 542 which is in communication with free-flight region 125.

**[0093]** With respect to FIG. 3, a preferred embodiment of an electric sector TOF mass analyzer in a tandem mass spectrometer of the present invention is schematically  
25 illustrated in a top cross-sectional view. The cross-section is taken through a plane defined by reference ion flight path 60. Mass analyzer 600 is a TOF mass analyzer comprising four identical electric sectors 250, 350, 450, and 550, each defining a curved deflection field of approximately 270° of arc. Each of the four electric sectors are preceded and followed by a  
30 free-flight region, namely 220, 222, 224, 226, and 228. This symmetrical arrangement of the electric sectors and free-flight regions provides several advantages, including both isochronous and spatial focusing, as described in Sakurai, et al., "Ion Optics For Time-Of-

Flight Mass Spectrometers With Multiple Symmetry", *Int. J. of Mass Spectrom. Ion Proc.* 63, pp273-287 (1985). This symmetric arrangement also provides the advantage of allowing a relatively long flight path 60 to be compactly contained within a space of significantly smaller dimensions, thereby allowing the overall size of the mass spectrometer to decrease. In a preferred arrangement, each of the four electric sectors is positioned such that the plane defined by each sector is approximately parallel to and coplanar with those of the other sectors, while accommodating the free-flight regions therebetween.

5 [0094] Reference number 610 is in ionic communication with mass analyzer 600, and indicates the source of the ions that enter electric sector TOF mass analyzer 600. In the context of a tandem mass spectrometer of the present invention, source 610 may include, for example, an ion source, a preceding mass analyzer, an ion trap, an ion selector, an ion fragmentor, or other suitable source. Reference number 620 is in ionic communication with mass analyzer 600 indicates the destination of the ions that exit electric sector TOF mass analyzer 600. In the context of a tandem mass spectrometer of the present invention, source 620 may include, for example, an ion detector, a successive mass analyzer, an ion trap, an ion selector, an ion fragmentor, or other suitable destination. For example, in an embodiment in which first mass analyzer 420 in FIG. 1 includes mass analyzer 600, source 610 may therefore represent ion source 410 and destination 620 may therefore represent second mass analyzer 430.

15 [0095] During typical operation of a tandem mass spectrometer of the present invention that includes electric sector TOF mass analyzer 600, ions are provided by source 610, are separated and focused along flight path 60, and continue to destination 520. Flight path 60 comprises ion entrance 670 and ion exit 672, and is defined by the four electric sectors (250, 350, 450, and 550) and the five free-flight regions (220, 222, 224, 226, and 25 228), which are arranged as shown and each of which communicates with its neighbors. Ions enter flight path 60 via ion entrance 670 from source 610 and entering free-flight region 220. Correspondingly, ions exit flight path 60 via ion exit 672 upon arrival at destination 620 from free flight region 228. Further details on the specific features of mass analyzer 600 are discussed hereinbelow with respect to like reference numbers in FIG. 8.

30 [0096] As described above, an electric sector TOF mass analyzer of a tandem mass spectrometer of the present invention comprises a time-of-flight mass analyzer that comprises at least one electric sector. Exemplary versions of such mass analyzers suitable

for the present invention are shown in FIGS. 2 and 3. Other suitable combinations and arrangements of electric sectors and field-free regions may also serve as mass analyzers in a tandem mass spectrometer of the present invention. For example, suitable electric sector TOF mass analyzers may include one, two, or four electric sectors. In mass analyzers with multiple electric sectors, it may be preferred to separate each electric sector with a free-flight region. Moreover, it is desired to arrange the electric sectors and the free-flight regions in a geometrically symmetric configuration, also shown by the examples of FIGS. 2 and 3.

**[0097]** Electric sector TOF mass analyzers have properties that are particularly useful in the context of a tandem mass spectrometer of the present invention. For example, electric sector TOF mass analyzers are capable of improved ion focusing, whereby the dispersion of the ion beam or ion parcels along one or more axes upon entry of the mass analyzer are decreased or minimized after exit.

**[0098]** Such ion focusing by electric sector TOF mass analyzers may be spatial, such as stigmatic focusing, whereby such focusing reduces the dispersion of the ion beam or parcels lateral to the ion flight path. Ion focusing may also be temporal, such as time focusing, whereby such focusing reduces the mass-independent dispersion of the ion beam or parcels along or parallel to the flight patch. Time focusing may also result in increased mass resolution between ion parcels of different mass during time-of-flight.

**[0099]** Advantages are also available when an electric sector TOF mass analyzer provides ions to an ion selector or an ion fragmentor. Referring to FIG. 4, an embodiment of such a tandem mass spectrometer is depicted using a schematic view. Tandem mass spectrometer apparatus 700 comprises ion source 710, first mass analyzer 720, second mass analyzer 730, and ion detector 740. Reference number 750 indicates the position of a component, wherein component 750 may include an ion selector means or an ion fragmentor means. In a preferred embodiment, first mass analyzer 720 comprises an electric sector TOF mass analyzer. Each component is in ionic communication with the other components as indicated, thereby allowing ions to move therebetween. Other components that are or may be present in a tandem mass spectrometer of the present invention, such as additional mass analyzers, additional ion fragmentors, additional ion selectors, etc. are not depicted in this figure. Features and uses of ion source 710 and ion

detector 740 may be considered substantially the same as the corresponding ion source 410 and ion detector 440 described hereinabove.

**[0100]** In an embodiment of apparatus 700 in which first mass analyzer 720 is an electric sector TOF mass analyzer, sample ions are provided by ion source 710 and travel  
5 to the first mass analyzer. The sample ions may be separated and resolved in this first mass analysis step by time-of-flight, such that ions of lower mass travel faster and hence exit first mass analyzer 720 before than those ions of larger mass. In addition, in this embodiment the electric sector TOF mass analyzer may perform ion focusing, such as stigmatic and time focusing, of the sample ions. Both stigmatic and time focusing may be  
10 performed on the sample ion beam. The mass analyzer may be configured such that a minimum sized ion beam may be provided at a point in space coincident with the minimum dispersion in flight-times for a particular ion mass or ( $m/z$ ).

**[0101]** Such ion focusing by the mass analyzer has several advantages within the context of a tandem mass spectrometer of the present invention. For example, reduced or  
15 minimized dispersion, such as increased mass resolution, may result in a mass spectrum output with improved quality, sensitivity, and mass resolution. Another advantage arises because in some useful embodiments of the present invention, ions from the electric sector TOF mass analyzer are provided to one or more successive components of the tandem mass spectrometer. Such components may include another mass analyzer, an ion trap, an  
20 ion selector, an ion fragmentor, or other suitable components. By providing a focused ion beam or ion parcels having reduced dispersion and improved mass resolution to a successive component, the component's subsequent performance on the provided ions may also be improved. In still another advantage, the successive component in the tandem mass spectrometer may be reduced in size, cost, and performance by the reduced size of  
25 the provided ion beam or parcels. For example, a larger sample ion beam may require larger enclosures, larger apertures, etc. These demands may, in turn, increase the size, cost and complexity of the component or its peripherals, as well as the size, cost and complexity of the apparatus as a whole. Therefore, decreasing the ion beam or parcel size may decrease the size, cost, and complexity of the component, its peripherals, or the overall  
30 tandem mass spectrometer.

**[0102]** In one useful embodiment of the present invention, a tandem mass spectrometer may include an ion selection means and/or an ion fragmentation means. An

ion selector refers to a component of the mass spectrometer apparatus that is suitable for selecting ions of a desired mass from a plurality of ions. An ion fragmentor refers to a component of the mass spectrometer apparatus that is suitable for fragmenting larger ions into smaller secondary ion fragments. These secondary ions may be subjected to further mass analysis. In some useful embodiments, ion fragmentation occurs after an ion selection step.

**[0103]** As described above, the first mass analyzer comprising an electric sector TOF mass analyzer may be configured to provide a minimum sized ion beam with minimal dispersion at a particular spatial location upon exiting the first mass analyzer. In typical embodiments, a sub-assembly component that serves as an ion fragmentation means or an ion selection means may be situated at that spatial location; thus, the fragmentation means or the selection means may act on a minimum-sized ion beam. The small ion beam may allow the component to be of correspondingly smaller size, which may in turn reduce its cost while increasing its performance. Some specific advantages are described below for certain components. It is understood that similar advantages may be apparent and understood by one of ordinary skill in the art for other suitable components for use in tandem mass spectroscopy.

**[0104]** In one example, ion selector 750 of tandem mass spectrometer 700 of the present invention may include consecutive ion gates for the selection of primary ions. These consecutive ion gates, as are known in the art, include gate electrodes that are controlled by pulsed voltages. Selective opening and closing of the ion gates in response to the pulsed voltages allows selection of ion peaks from the sample ion beam. By providing a smaller sample ion beam with the first mass analyzer of the present invention, as described above, the consecutive ion gate electrodes may be positioned more closely together. As a result, the ion gates may be controlled by providing pulsed voltages of smaller amplitude, thereby allowing improved and faster control of the ion gates, and therefore increasing the efficiency and selectivity of the primary ion selection.

**[0105]** In another example, the tandem mass spectrometer of the present invention may perform primary ion selection from a sample ion beam by sweeping the sample ion beam over a narrow aperture. In a preferred embodiment of the present invention, this aperture is disposed between the first mass analyzer and the second mass analyzer and is in ion communication with both mass analyzers. Referring to FIGS. 5A-C, a



schematic illustration of this means of ion selection is illustrated. Ion selector 1000 is in ion communication with first mass analyzer 1100, from which sample ion beam 1400 is provided. Sample ion beam comprises a plurality of ions 1610-1650. When first mass analyzer 1100 is a time-of-flight mass analyzer, ions 1610-1650 travel within sample ion beam 1400 essentially in mass order, with the lower mass ions arriving earlier than the heavier ions.

**[0106]** Ion selector 1000 is also in ion communication with second mass analyzer 1200. In some embodiments, an ion fragmentor may be situated to receive ions from the ion selector. Within the ion selector is aperture 1350 disposed within plane 1300, such that only the ions that pass through aperture 1350 are able to exit ion selector 1000 and thus enter second mass analyzer 1200.

**[0107]** Deflection electrodes 1500 and 1550 are situated to flank the sample ion beam such that ions in the beam travel therebetween and may respond to the electrodes' potentials. These electrodes are configured such that potentials may be independently applied to and controlled for each of electrodes 1500 and 1550. As illustrated in FIG. 5A, if the same potential is applied to both electrodes such that the potential difference between electrodes 1500 and 1550 is essentially zero, no net electrostatic deflection is imposed on the ions in the sample beam traveling therethrough. In this situation, because the sample ion beam and all of the ions therein continue through aperture 1350 to second mass analyzer 1200, ion selector 1000 provides no ion selectivity.

**[0108]** In FIG. 5B, an appropriately greater potential is applied to electrode 1500 than that applied to electrode 1550. Accordingly, an electrostatic force is applied on all of the ions in beam 1400 traveling therebetween such that the ions are deflected towards electrode 1550. As a result of this deflection, ions 1610-1650 are deflected away from aperture 1350 and strike plane 1300. Therefore, no ions are selected in this scenario.

**[0109]** A method to select a desired primary ion is illustrated in FIG. 5C. In this scenario, the potential difference between electrodes 1500 and 1550 changes in a time-dependent manner. As a result, the electrostatic deflection imposed on the ions in ion beam 1400 may also change in magnitude and direction in a time dependent manner, thereby causing sample ion beam to "sweep". For example, the electrodes may begin at time zero with a greater potential on electrode 1500, thus deflecting the ions towards electrode 1550. By, for example, decreasing the potential on electrode 1500 with time, the potential

difference between the electrodes and the corresponding deflection force also decreases. As a result, ion beam 1400 will "sweep" towards electrode 1500 as the magnitude of deflection decreases. If the potential on electrode 1500 continues to decrease such that the polarity of the potential difference is in the opposite direction, ion beam 1400 will continue its sweep until it is deflected towards electrode 1500.

5       **[0110]**       During the foregoing sweeping of the ion beam, ions 1610-1650 in beam 1400 travel towards plane 1300 in a direction essentially following the angle of beam 1400 at the time of the ion's passage between the electrodes. Therefore, in the above example, ion 1650 (having a low mass) arriving at electrodes 1500 and 1550 at an early time point, and thus is strongly deflected towards electrode 1550. As a result of this strong deflection, ion 1650 strikes plane 1300 well below aperture 1350. Arriving at a later time point, the higher mass ion 1640 is deflected with a lesser force due to the small potential difference at this time point. Accordingly, ion 1640 contacts plane 1300 at point closer to aperture 1350.

10       **[0111]**       Therefore, at the instant there is essentially no potential difference between the electrodes, an ion passing at that point receives essentially no net deflection. Accordingly, this ion (in this case, ion 1630) travels towards and through aperture 1350. Ion 1630 is therefore selected by ion selector 1000 and continues towards second mass analyzer 1200. Because the heavier ions 1620 and 1610 arrive at the electrodes after ion 1630, these ions receive a net deflection towards electrode 1500 and thus strike plane 1300 at locations on the other side of aperture 1350.

15       **[0112]**       Therefore, to select a particular ion using ion selector 1000, the time-dependent changing potential is configured such that the time point at which the potential difference between electrodes 1500 and 1550 is essentially zero substantially coincides with the arrival of the desired ions at the electrodes. For example, if the arrival time of the desired ion is known, the starting time of the ramping potential may be set accordingly. Other variations on this method may be appreciated by one of ordinary skill and implemented accordingly. For example, aperture 1300 may be situated such that an ion requires a deflection angle to pass through. Thus the ramping potential is configured to provide the necessary potential difference at the time the desired ion arrives at the electrodes.

20       **[0113]**       Ions of a desired mass may therefore be selected by configuring the voltage ramping parameters such that the passage of the desired ions through deflection

electrodes 1550 and 1500 is substantially coincident with the voltage at which no deflection is imposed. Configurable parameters include, for example, the shape and/or slope of the voltage ramping profile, the starting time of the voltage ramping, and other like parameters. These parameters may be configured based on the time of entry of the sample ions into the ion flight path of the tandem mass spectrometer and the expected time-of-flight of the desired ions. In this manner, the timing between the voltage ramping and the arrival of the ions at ion selector 1000 may be coordinated to effect selection of the desired ions.

5 [0114] As with the consecutive ion gates described above, the enhanced ion focusing properties of the first mass analyzer of the tandem mass spectrometer of the present invention may result in enhanced selectivity and efficiency of primary ion selection using this method of primary ion selection. As described above, the electric sector TOF mass analyzer of the first mass analyzer may be configured to minimize the time-of-flight and lateral dispersion of the sample ions by adjusting the ion optical elements of the present invention, hence reducing the size and dispersion of the desired ion parcels. Without the enhanced ion focusing of the present invention, lateral dispersion of the ions with respect to the ion flight path may decrease the efficiency of selection by not allowing a sufficient amount of the desired ion parcel to pass through the slit, or by decreasing selectivity of primary ion selection by requiring a larger slit. Similarly, increased mass-independent time-of-flight dispersion may subject ions of the same mass within the dispersed ion parcel to different deflection voltages, thereby also reducing the efficiency of selection.

15 [0115] Referring again to FIG. 4, apparatus 700 comprises an ion fragmentor as indicated by reference number 750. In some useful embodiments, ion fragmentor 750 may include a collision cell. Collision cells, as are known in the art, are typically partially enclosed volumes within the vacuum chamber of the tandem mass spectrometer apparatus. The cell has apertures to allow entry of the ions and exit of the secondary ion fragments. The collision cell contains gas particles at a suitable pressure in order to collide with and thus fragment a significant fraction of the primary ions entering the cell. However, gas escapes the cells via its entry and exit apertures and thus enters the vacuum chamber of the spectrometer. To prevent contamination or extraneous collisions, vacuum pumps are required to continuously pump out the escaped gas in the vacuum chamber. In tandem mass spectrometer 700 of the present invention, the electric sector TOF mass analyzer of the first mass analyzer may provide a small-size sample ion beam by enhanced ion

20  
25  
30

focusing, as described above. Accordingly, the size of the collision cell apertures, or the cell itself, may also be reduced. The smaller apertures may decrease the amount of escaping gas from the collision cell, and thus reduce the size and the cost of the pumps required to maintain the chamber free of contamination. In addition, a collision cell of reduced size and cost may also reduce the cost of the overall apparatus.

**[0116]** The above-described exemplary embodiments of tandem mass spectrometers of the present invention are neither limiting nor exclusive of other embodiments. Other configurations will be apparent to or envisioned by one of ordinary skill in the art. For example, in embodiments in which the first mass analyzer includes an electric sector TOF mass analyzer, the second mass analyzer may include an electric sector TOF mass analyzer, a linear TOF mass spectrometer (with or without delayed extraction), a reflecting TOF mass spectrometer, an ion trap in combination with a TOF mass spectrometer (linear or reflecting), and other mass analyzers known in the art. Moreover, in embodiments comprising ion fragmentation means, exemplary means may include a collision cell (as described above), surface induced dissociation, laser photodissociation, electron-impact induced dissociation, and other methods known in the art. Finally, it is understood that tandem mass spectrometers having at least one electric sector TOF mass analyzer in combination with other suitable mass analyzers, ion selectors, ion sources, ion fragmentors, and ion detectors may be apparent to or envisioned by one of ordinary skill in the art and hence are within the scope of the present invention.

**[0117]** In addition to the embodiments of tandem mass spectrometers of the present invention described above, I have also discovered improved electric sector TOF mass analyzers that may be used as one or more of the mass analyzers of the present invention. These improved electric sector TOF mass analyzers may be used in a tandem mass spectrometer with any suitable mass analyzer described above or otherwise known in the art. Alternatively, these improved electric sector TOF mass analyzers may be used exclusively as the mass analyzer in a tandem mass spectrometer according to the present invention. The advantages and features of these improved electric sector TOF mass analyzers are described below.

**[0118]** An improved electric sector TOF mass analyzer comprises one or more electric sectors. At least one of the electric sectors is associated with one or more ion optical elements. The ion optical elements are disposed at either or both the entry or the

outlet of the electric sector, such that the optical element modifies the potential experienced by an ion entering or exiting the electric sector with which it is associated. Each ion optical element comprises at least one trim electrode, wherein the potential of the trim electrode is adjustable. Furthermore, each trim electrode may be independently adjustable with respect to others of the adjustable trim electrodes and the electric sectors. Therefore, each adjustable trim electrode may provide an additional degree of freedom with which to modify the ion focusing properties of the electric sectors without requiring the more difficult mechanical adjustment or modification of the electric sectors themselves.

**[0119]** In another embodiment of the present invention, a TOF mass analyzer further comprises a plurality of electric sectors in a symmetric arrangement. This arrangement of electric sectors deflects the ions into a correspondingly symmetric flight path, thereby providing additional ion focusing abilities in a compact space. At least one of the electric sectors is associated with one or more ion optical elements. Each ion optical element comprises at least one independently adjustable trim electrode as described above.

**[0120]** In another aspect, methods are provided that allow tuning of a TOF mass spectrometer of the present invention to improve the mass resolution or sensitivity of the resulting mass spectra. The tuning is performed by adjusting the adjustable trim electrodes of one or more of the ion optical elements present therein, thereby modifying the ion focusing properties of the mass spectrometer. Observing and comparing the effects of the adjustment on the mass spectrum may be used to guide further trim electrode adjustments until a desired mass spectrum is achieved.

**[0121]** Referring to FIG. 6, apparatus 100 comprises a TOF mass spectrometer in accordance with the present invention, shown in a top cross-sectional view. The cross-section is taken through a plane defined by flight path 50 of a reference ion traveling therethrough. Apparatus 100 comprises ion source 110, free-flight regions 120 and 125, electric sector 150, ion optical elements 166 and 167, Herzog shunts 170 and 171, and ion detector 180. During typical operation of the TOF mass spectrometer, ions are generated and accelerated in ion source 110, separate in free-flight region 120, pass through aperture 175 of shunt 170, pass between paired trim electrodes 160 and 161 of ion optical element 166, and enter electric sector 150 via entry opening 156. Outer and inner deflecting electrodes 154 and 152, respectively, provide a deflecting electric field therebetween that deflects the ions into a curved path. The ions then exit via outlet opening 158, pass

between paired trim electrodes 162 and 163 of ion optical element 167, pass through aperture 176 of shunt 171, separate in free-flight region 125, and are detected on arrival at ion detector 180. Flight path 50 is the path of a reference ion, while flight paths 52 and 54 are schematic representations of the paths taken by ions leaving ion source 110 with angles which are slightly larger or smaller than the angle of the reference ion.

5 [0122] Accordingly, an ion flight path is defined within apparatus 100, for which flight path 50 is a representative example. Flight path 50 comprises ion entrance 40 at which ion source 110, in communication with free-flight region 120, causes the ions to enter flight path 50. Correspondingly, flight path 50 further comprises ion exit 42, at which the ions exit flight path 50 upon arrival at ion detector 180 which is in communication with free-flight region 125.

[0123] Ion source 110 includes means for generating ions that are known in the art, including any of the means or methods known in the art for producing a plurality of ions within a relatively small volume and within a relatively short time. Also included are any of the means or methods known in the art for producing a pulse of ions, such that the pulse of ions has the appearance of or behaves as if the ions were produced within a relatively small volume and within a relatively short time. Ion source 110 may include means to form ions in a continuous or pulsed manner. The ion source may also include means to concentrate the ions, such as a quadrupole ion trap or a linear ion trap.

20 [0124] Ion source 110 may, e.g., include means that employ a pulsed laser interacting with a solid surface, a pulsed focused laser ionizing a gas within a small volume, or a pulsed electron or ion beam interacting with a gas or solid surface. In another example, ion source 110 may employ means for generating a pulse of ions that uses a rapidly sweeping, continuous ion beam passed over a narrow slit, in which a brief pulse of ions is produced by the ions passing through the slit when the ion beam passes thereover. Ion source 110 may employ, but is not limited to use of, electrospray ionization, laser desorption/ionization ("LDI"), matrix-assisted laser desorption/ionization ("MALDI"), surface-enhanced laser desorption/ionization ("SELDI"), surface-enhance neat desorption ("SEND"), fast atom bombardment, surface-enhanced photolabile attachment and release, pulsed ion extraction, plasma desorption, multi-photon ionization, electron impact ionization, inductively coupled plasma, chemical ionization, atmospheric pressure [0125] Furthermore, ion source 110 may also include means for selectively providing ions of one or more masses or

ranges of masses, or fragments therefrom. Such means may be accomplished by combining a TOF mass spectrometer of the present invention in tandem fashion with a plurality of analyzers, including magnetic sector, electrostatic analyzer, ion traps, quadrupole ion traps, quadrupole mass filters, and TOF devices.

5     **[0126]**         Ion source 110 also includes means for ion extraction or acceleration from the ion source to ion entrance 40 of the ion flight path. The extraction methods may be parallel or orthogonal to the ion beam generated in ion source 110. In addition, extraction or acceleration of the ions may occur subsequent to the formation of the ions, such as by application of a voltage pulse.

10    **[0127]**         Likewise, ion detector 180 includes means for detecting ions and amplifying their signals that are known, and also will not be discussed in detail here. For example, ion detector 180 may include continuous electron multipliers, discrete dynode electron multipliers, scintillation counters, Faraday cups, photomultiplier tubes, and the like. Ion detector 180 may also include means for recording ions detected therein, such as a  
15    computer or other electronic apparatus.

**[0128]**         Electric sector 150 comprises inner deflecting electrode 152 and outer deflecting electrode 154. Referring to FIG. 7, a view of entry opening 156 of electric sector 150 is shown, such that the ion flight path is approximately normal to the plane of the figure. As shown, the electric sector further comprises top and bottom Matsuda plates 190 and  
20    192, respectively. In a preferred embodiment, both deflecting electrodes are cylindrical sections with outer electrode 154 having a larger radius than inner electrode 152. Alternatively, the electrostatic plates may conform to other forms, such as toroidal or spherical sections. Further alternative embodiments include electrostatic plates in which the radii of the inner and outer plates are substantially the same and hence converge at the top  
25    and bottom, such as when toroidal sections are employed. Matsuda plates 190 and 192 are themselves electrodes which are configured to further confine ions traversing electric sector 150 by preventing ions from exiting the top or bottom of the electric sector, thereby increasing the ion transmission yield of the electric sector.

**[0129]**         Referring again to FIG. 6, entry Herzog shunt 170 and outlet Herzog shunt  
30    171 are disposed at the respective openings of electric sector 150. These Herzog shunts are electrodes that have potentials that are approximately the same as the average potential within the electric sector. The purpose of the Herzog shunts, as is known in the

art, is to terminate the electric field of the electric sector as near as possible to its openings, thereby approaching an ideal deflection field. Furthermore, as ions pass through apertures 175 and 176 of the Herzog shunts, the apertures serve to select for a narrower range of ion trajectories as the ions enter and exit the electric sector. It is preferred that the shape of Herzog shunt apertures 175 and 176 conform to the shape of the electric sector opening with which they are associated. For example, in embodiments in which inner electrode 152 and outer electrode 154 are cylindrical sections, a preferred shape of the Herzog shunt aperture associated with entry opening 156 or outlet opening 158 is conformally rectangular in shape. It is also preferred that the aperture of a Herzog shunt have smaller dimensions than the electric sector entry opening or outlet opening with which the shunt is associated.

**[0130]** Ion optical element 166 is associated with electric sector 150, being disposed at entry opening 156. Similarly, ion optical element 167 is disposed at outlet opening 158. Ion optical element 166 comprises a pair of trim electrodes 160 and 161; similarly, element 167 comprises trim electrodes 162 and 163. Both pairs of trim electrodes allow flight path 50 to pass between the paired trim electrodes. It is preferred that the pair of trim electrodes of a given ion optical element be separated by a distance that is less than the separation of the inner and outer electrodes of the electric sector entry or outlet with which the ion optical element is associated. Each trim electrode has an electric potential that may be independently adjustable with respect to others of the adjustable trim electrodes, as well as with respect to deflecting electrodes 152 and 154. Thus, each adjustable trim electrode provides an additional degree of freedom with which to adjust the ion focusing properties of electric sector 150.

**[0131]** As with the Herzog shunt apertures, it is preferred that the inner edges of the trim electrodes conform to the shape of the electric sector opening with which they are associated. For example, in the embodiment illustrated in FIG. 6, the inner edge of trim electrode 160 preferably conforms to the shape of the inner edge of outer deflecting electrode 154. The inner edges of the other trim electrodes are correspondingly conformal to their respective electric sector openings.

**[0132]** In embodiments in which a pair of trim electrodes (forming an ion optical element) and a Herzog shunt are associated with a given electric sector opening (entry or outlet), it is preferred that the separation of the inner and outer electric sector electrodes is greater than the distance separating the pair of trim electrodes, as described above.



Moreover, it is also preferred that the separating distance between the trim electrodes is, in turn, greater than the width of the Herzog shunt aperture associated therewith.

**[0133]** Ion optical elements of the present invention comprising trim electrodes provide a means for modifying the potential experienced by ions in the ion flight path as the ions exit or enter an electric sector. Trim electrodes of the present invention provide a means for providing an adjustable potential. For example, by positioning ion optical elements 166 and 167 with respect to the openings of electric sector 150 and ion flight path 50 in the manner illustrated, each element is able to affect the potential experienced by an ion as it enters or exits electric sector 150. Accordingly, adjusting the potential of an ion optical element correspondingly modifies the potential experienced by the ion. These adjustments may be performed without adjusting the potential of Herzog shunts 170 and 171 or deflecting electrodes 152 and 154. In this manner, subtle adjustments may readily and advantageously be made to the ion optical properties of electric sector 150 without requiring direct adjustments to the electric sector itself. Examples of advantages provided by the ion optical elements are described below.

**[0134]** The ion optical elements of the present invention may be used to modify the deflection angle of electric sector 150 without significant effect on its other ion optical properties. Electric sectors of the prior art time-of-flight mass spectrometers do not include any means to modify selectively or specifically the potential experienced by an entering or exiting ion. Changing the potential of either deflecting electrode 152 or 154 changes the ion optical properties of the entire electric sector, and hence is not specific for the electric field at either entry opening 156 or outlet opening 158. More specifically, adjusting deflecting electrodes 152 or 154 would have a significant effect on the ion focusing properties and the energy range that the electric sector is configured to select. Adjusting ion optical elements 166 and 167 of the present invention to provide increased or decreased deflection of the ions allows for more subtle and more readily made adjustments to the deflection angle without significantly altering the other properties of the electric sector.

**[0135]** Another advantage provided by the ion optical elements of the apparatus of the present invention is to alter the ion focusing properties of electric sector 150. For example, adjusting ion optical element 167 (by applying equal, non-zero potentials to trim electrodes 162 and 163) at exit opening 158 may be used to alter the location of the point at which ions with flight paths similar to flight path 54 and flight path 52 cross or intersect near

flight path exit 42. Such changes to the flight paths may result in changes to the ion focusing properties of electric sector 150 and improvements to the sensitivity and/or resolution of the time-of-flight mass spectrum.

5       **[0136]**       The present invention provides at least two types of advantages. The first advantage results from the use of the ion optical elements of the present invention to correct or alter the performance of the associated electric sectors in TOF mass spectrometers so that the electric sectors have the ion optical properties expected from the design specification. The use of the ion optical elements in this manner may compensate for errors, defects, or deviations in fabrication or mechanical design of the electric sectors. The  
10       second advantage results from the use of combinations of ion optical properties that are not available with electric sectors which lack the present invention. In addition, because these properties are adjustable, the performance of TOF mass spectrometers incorporating the present invention may actually exceed the theoretical performance of designs based on conventional electric sectors .

15       **[0137]**       For example, increasing the potential on each of the four trim electrodes described above by the same magnitude may result in changing the focusing of the ions in the radial plane. In another example, a small deflection of the ion beam may be applied at the entrance of the electric sector using a first ion optical element and an opposite deflection may be applied at the exit using a second ion optical element. Although this particular  
20       adjustment results in no change in the net deflection over the electric sector, the path taken by the ions through the electric sector is slightly altered. As a result, the overall performance of the TOF mass spectrometer of the present invention may be changed because of the change in the effective path length within the electric sector with respect to the path length through the field free (e.g., free-flight) regions.

25       **[0138]**       I have demonstrated that by adjusting the potentials of the trim electrodes, the resolution and other figures of merit of a TOF mass spectrometer that can be used as a mass analyzer in the tandem mass spectrometer of the present invention can be greatly improved compared to prior electric sector containing mass analyzers. Other applications and advantages arising from adjusting the potentials on the trim electrodes of the present  
30       invention may be envisioned by one of ordinary skill in this art, and such applications and advantages are within the scope of the present invention.

**[0139]** Providing an adjustable potential field using an ion optical element of the present invention may be accomplished by using one or more trim electrodes that conforms to a physical shape corresponding to the shape of the potential. Trim electrodes of the present invention may also provide adjustable potentials of similar or equivalent shape  
5 without requiring the trim electrode to have the corresponding physical shape. Such electrodes may be fabricated from, for example, semiconductive or poorly conductive material, or insulative material fully or partially coated with conductive or semiconductive material. The foregoing conductive or semiconductive material may be formed as, for example, films or wires. It is understood that trim electrodes of any shape which produce  
10 the desired adjustable potentials are within the scope of this invention.

**[0140]** Ion optical elements of the present invention need not be limited to a single pair of trim electrodes. For example, a plurality of three or more trim electrodes may be positioned at the entry or outlet of an electric sector such that they compose an ion optical element. Such a plurality of trim electrodes may be arranged with trim electrodes in  
15 opposing pairs, in a point-symmetric arrangement, or any other suitable arrangement. Additional trim electrodes in an ion optical element configured in the foregoing manner not only provide additional degrees of freedom for modifying the potential experienced by the ions, but may also provide additional advantages. For example, additional trim electrodes may allow the operator to deflect the ions entering or exiting the electric sector associated  
20 therewith in a direction perpendicular to the plane of the electric sector and overall ion flight path. Trim electrodes used for perpendicular deflection may have edges that do not necessarily conform to the shape of the electric sector deflection electrodes, nor is it necessary that trim electrodes of the present invention conform to any particular shape.

**[0141]** Although ion optical elements of the present invention are disposed at both  
25 the entry and the outlet of the associated electric sectors of a preferred embodiment, other configurations and arrangements of ion optical elements with respect to electric sectors are within the scope of the invention.

**[0142]** The trim electrodes of an ion optical element are preferably positioned close to their associated electric sector entry or outlet, while maintaining a spacing with  
30 respect to the deflection electrodes sufficient to sustain the potential differences required by the design of the apparatus. Similarly, a Herzog shunt is also preferably positioned closely to its associated ion optical element and electric sector. In a preferred embodiment, the

spacing between the Herzog shunt and the trim electrodes is the same as the spacing between the trim electrode and the electric sector opening. However, variations in the positions of the foregoing components, resulting in different spacings or different spacing ratios, are within the scope of the present invention. For example, the distance between the trim electrodes and the electric sector, or between the Herzog shunt and the trim electrodes, may be increased without departing from the spirit of the present invention. Also, the position of the trim electrodes may be moved arbitrarily close to the entrance or exit of an electric sector. In fact, the trim electrodes may even be moved into the region between the deflection electrodes of the electric sector. Those skilled in the art will recognize that all such variations in trim electrode geometry provide a means for modifying the potential experienced by ions in the ion flight path as the ions exit or enter an electric sector, and hence are within the scope of the present invention.

**[0143]** In a preferred embodiment, the thicknesses of the trim electrodes of a given ion optical element are less than the spacing separating the trim electrodes. However, the dimensions of the trim electrodes may be varied from this embodiment over a wide range while remaining within the scope of the present invention. For example, the thickness of the trim electrodes may be increased to a point where the distance traveled by an ion through the ion optical element is greater than the separation spacing of the trim electrodes or even the separation spacing of the electric sector. In a preferred embodiment, the thickness of the trim electrodes is approximately the same as that of the associated Herzog shunt. Again, deviations from this relationship are within the spirit of the present invention.

**[0144]** Electrodes of the present invention, including the deflecting electrodes, trim electrodes, Herzog shunts and Matsuda plates are made from materials known in the art. In general, suitable materials for the electrodes would include metals, metal alloys, composites, polymers, ionic solids, and combinations or mixtures thereof upon which a voltage may be applied from an external source. Electrodes of the present invention may be made from materials that are conductive, semiconductive, and/or poorly conductive. Electrodes may also be made from insulating material that has been coated with or supports a conductive, semi-conductive, or poorly conductive material, such as films, wiring, or the like.

[0145] As described above, ion optical elements and trim electrodes of the present invention may each have different and independent characteristics, such as with respect to their material composition, configuration, arrangement, shape, disposition with respect to electric sectors and other electrodes, etc. Accordingly, it is understood that any suitable combination of ion optical elements and trim electrodes having different or similar characteristics may be implemented within a TOF mass spectrometer and hence are within the scope of this invention.

[0146] With respect to FIG. 8, a preferred embodiment of a TOF mass spectrometer of the present invention is schematically illustrated in a top cross-sectional view. The cross-section is taken through a plane defined by reference ion flight path 60. Apparatus 200 is a TOF mass spectrometer comprising four identical electric sectors 250, 350, 450, and 550, each defining a curved deflection field of approximately 270° of arc. Each of the four electric sectors are preceded and followed by a free-flight region, namely 220, 222, 224, 226, and 228. This symmetrical arrangement of the electric sectors and free-flight regions provides several advantages, including both isochronous and spatial focusing, as described in Sakurai, et al., "Ion Optics For Time-Of-Flight Mass Spectrometers With Multiple Symmetry", *Int. J. of Mass Spectrom. Ion Proc.* 63, pp273-287 (1985). This symmetric arrangement also provides the advantage of allowing a relatively long flight path 60 to be compactly contained within a space of significantly smaller dimensions, thereby allowing the overall size of the mass spectrometer to decrease. In a preferred arrangement, each of the four electric sectors is positioned such that the plane defined by each sector is approximately parallel to and coplanar with those of the other sectors, while accommodating the free-flight regions therebetween.

[0147] Apparatus 200 further comprises ion source 210 and ion detector 280, both of which are functionally analogous to the corresponding features in apparatus 100 illustrated in FIG. 6. Likewise, each of electric sectors 250, 350, 450, and 550 comprises essentially the same elements as the others and has essentially the same functions as electric sector 150 described above. Hence, reference will only be made to the elements of electric sector 250, with the understanding that the following descriptions apply to the other electric sectors.

[0148] During typical operation of apparatus 200, sample-derived ions are generated in and extracted from ion source 210, separated and focused along flight path

60, and are finally detected upon arrival at ion detector 280. Flight path 60 comprises ion entrance 70 and ion exit 72, and is defined by the four electric sectors (250, 350, 450, and 550) and the five free-flight regions (220, 222, 224, 226, and 228), which are arranged as shown and each of which communicates with its neighbors. Ions enter flight path 60 via ion entrance 70 by exiting ion source 210 and entering free-flight region 220. Correspondingly, ions exit flight path 60 via ion exit 72 by entering ion detector 280 from free flight region 228.

**[0149]** In a preferred embodiment of apparatus 200, the lengths of the free-flight regions are defined by parameters designated "D1" and "D2," values for which are listed in Tables 1 and 3. In a preferred embodiment, the lengths of free-flight regions 222 and 226 are substantially the same length, wherein this length is two times "D2." It is also preferred that the length of free-flight region 224 is substantially two times the length of free-flight regions 220 and 228, wherein the lengths of free-flight regions 220 and 228 are defined by "D1." However, it would be understood by one skilled in the art that these default lengths may be further adjusted and/or modified to alter the performance or other desired characteristics of the apparatus. For example, the lengths of free-flight regions 220 and 228, which are associated respectively with the ion source 210 and ion detector 280, may be modified from the default lengths described above depending on the actual ion source and/or ion detector used in the apparatus.

**[0150]** First electric sector 250 comprises inner deflecting electrode 252 and outer deflecting electrode 254. Entry opening 256 of the electric sector is associated with Herzog shunt 270 having aperture 271. Similarly, Herzog shunt 275 with aperture 276 associates with the electric sector at outlet opening 258.

**[0151]** Also associated with entry 256 and outlet 258 are ion optical elements 266 and 267, respectively. Ion optical element 266 comprises trim electrodes 260 and 261, and similarly ion optical element 267 comprises trim electrodes 262 and 263. In this particular embodiment, electric sectors 350, 450, and 550 comprise the same elements as electric sector 250, and hence will not be discussed separately.

**[0152]** FIG. 9 shows a schematic drawing of entry 256 to electric sector 250 of FIG. 8, such that a reference ion flight path is approximately normal to the plane of the figure. This figure defines the dimensions  $S_s$ , the space between the inner deflecting electrode 252 and the outer deflecting electrode 254 of electric sector 250;  $W_M$ , the width of the Matsuda plates 284 and 285;  $H_s$ , the height of the electric sector deflecting electrodes

252 and 254; and  $S_M$ , the spacing between the Matsuda plates 284 and 285 and the electric sector deflecting electrodes 252 and 254.

[0153] FIG. 10A shows a top cross-sectional view of electric sector entry 256 to electric sector 250, including inner deflecting electrode 252 and outer deflecting electrode 254. The Matsuda plates shown in FIG. 9 are omitted for illustrative purposes. Also depicted in this view are ion optical element 266 (including trim electrodes 260 and 261) and Herzog shunt 270 (including Herzog shunt aperture 271). Various dimensions, values for which are listed in Tables 1 and 3 (see below), are labeled in this view. These dimensions include the trim electrode thickness ( $T_T$ ), the trim electrode spacing ( $T_S$ ), the trim electrode to deflecting electrode space ( $TE_S$ ), Herzog shunt thickness ( $H_T$ ), Herzog shunt spacing to trim electrode ( $HT_S$ ), Herzog shunt opening height ( $H_H$ ) and Herzog shunt opening width ( $H_W$ ).

[0154] FIG. 10B shows a corresponding exploded isometric view of entry 256 to electric sector 250, with various dimensions labeled, values for which are listed in Table 1 and 3 (see below). As with FIG. 10A, values for these dimensions are considered representative of all four electric sectors depicted in FIG. 8. All dimensions are given in inches, unless otherwise indicated.

[0155] In various embodiments, the ion optical elements may include an Einzel lens. As is known in the art, an Einzel lens comprises multiple electrodes configured to focus the ion beam. The Einzel lens may be used instead of, or in combination with, the adjustable electrodes already described.

[0156] A TOFMS apparatus, the electric sector mass analyzer of which is useful in the tandem mass spectrometers of the present invention, was first modeled using SIMION 7, a commercially available ion optic modeling program (SIMION 7, P.O. Box 2726, Idaho Falls, ID 83403, USA), and then a prototype constructed to test the performance and compare the figures of merit to values reported in the prior art.

[0157] The addition of the four trim electrodes to an electric sector provides up to four additional adjustments, or degrees of freedom, for tuning the ion optical properties of each of the electric sectors. It is not necessary or even desirable in modeling the ion optics to use all of these degrees of freedom. In the model, it is not necessary to correct for small errors in the mechanical alignment of the sectors, so these adjustments are not needed.

[0158] Thus, for modeling purposes, only the sum and the difference of the potentials on the inner and outer trim electrodes were used as adjustable parameters in the tuning of the spectrometer. The same potential is applied to all of the outer trim electrodes and yet another potential is applied to all of the inner trim electrodes. It is understood that the present invention is not limited to potentials applied in this pattern, and that other possible subsets (up to and including individual trim electrodes) may each have different applied potentials.

TABLE 1  
Modeled Invention Embodiment Dimensions and Potentials

Parameter	Modeled Invention Embodiment
Electric Sector Radius	2.00
Deflection Angle	270 degrees
D1	4.76
D2	3.12
S <sub>s</sub>	0.36
W <sub>M</sub>	0.20
H <sub>s</sub>	1.12
S <sub>M</sub>	0.12
Trim Electrode Thickness (T <sub>T</sub> )	0.16
Trim Electrode Spacing (T <sub>S</sub> )	0.22
Trim Electrode to Sector Electrode Space (T <sub>ES</sub> )	0.14
Herzog shunt thickness (H <sub>T</sub> )	0.16
Herzog shunt spacing to Trim Electrode (H <sub>TS</sub> )	0.14
Herzog shunt opening height (H <sub>H</sub> )	0.40
Herzog shunt opening width (H <sub>W</sub> )	0.20
Ion Acceleration Voltage	10,000 volts
Potential on Electric Sector Outer Electrode	1739 volts
Potential on Electric Sector Inner Electrode	-1971 volts
Potential on Matsuda Plates	183 volts
Potential on Inner Trim Electrodes	339 volts
Potential on Outer Trim Electrodes	343 volts

[0159] The set of operating potentials given in Table 1 is the best of many combinations found during modeling which produces a maximum resolution for 10 kV ions in this particular geometry. The tuning of the model was carried out by minimizing the sum of the absolute magnitudes of all of the first and second order aberration coefficients for the time-of-flight. Because the deviations in x (in the plane of the ion flight path, perpendicular to the path of the reference ion) and the corresponding angle  $\theta$  are not symmetrical for this



design, the aberrations for these deviations were also calculated, adding an additional 11 terms to the 20 normally included in the sum. The values for the deviations  $x_0$ ,  $l_0$ ,  $y_0$ ,  $l_1$ , and  $\theta$  used for the optimization were 0.2 mm, 0.2 degrees, 0.2 mm, 0.2 degrees, and 0.001 which gave an optimized resolution of over 16,000 when all 31 aberration terms are included in the calculation.

**[0160]** The results of these calculations for this set of potentials are compared in Table 2 with the aberration coefficients disclosed in Sakurai *et al.*, "A New Time-Of-Flight Mass Spectrometer", *Int. J. Mass. Spectrom. Ion Proc.* 66, pp283-290 (1985) ("Sakurai I"); definitions of the aberration coefficients are as described in "Sakurai I" and in Sakurai *et al.*, "Ion Optics For Time-Of-Flight Mass Spectrometers With Multiple Symmetry", *Int. J. Mass. Spectrom. Ion Proc.* 63, pp273-287 (1985) ("Sakurai II").

TABLE 2.  
Comparison of Aberration Coefficients

Aberration Coefficient	Sakurai I	Modeled Invention Embodiment
$L_x$	0.0000	0.0005
$L_l$	0.0000	0.0003
$L_l$	0.0000	0.0000
$L_{xx}$	137.94	115.00
$L_{xl}$	18.75	3.72
$L_{xl}$	5.66	2.00
$L_{ll}$	1.79	0.67
$L_{ll}$	1.08	0.26
$L_{ll}$	0.73	2.90
$L_{yy}$	0.00	0.0000
$L_{yl}$	0.00	1.00
$L_{ll}$	-0.02	0.39

**[0161]** While some of the aberration coefficients of the modeled embodiment of the present invention are smaller and some are larger than those of Sakurai, the two which make the largest contribution to the peak width,  $L_{ll}$  and  $L_{ll}$ , are significantly smaller, with the result that the overall spectrometer resolution of the modeled embodiment of the present invention is improved over that reported in the prior art.

**[0162]** For example, with  $x_0 = y_0 = 0.0002$  meters and  $l_1 = l_1 = 0.00349$  radians and  $\theta = 0.001$ , the predicted resolution using the calculation of Sakurai I, which includes only the aberration coefficients listed in Table 2, is about 19,000 for the original design, but is over 30,000 for the modeled embodiment of the present invention.

**[0163]** The predicted resolution depends on the magnitudes assumed for the deviations  $x_0$ ,  $y_0$ ,  $\Delta_0$ ,  $\Delta_0$ , and  $\Delta$ . Furthermore, with the present invention, the properties of the time-of-flight spectrometer may be adjusted to provide the best performance for the actual deviations expected from the reference ion properties. For example, it is well known that ions produced by commonly employed matrix-assisted laser desorption ionization (MALDI) methods have on average considerable excess energy and that the average amount of this extra energy is proportional to the mass of the ion. The magnitude of this excess energy is approximately one electron volt per 1000 daltons. Thus, the ions formed from large proteins can have over 100 eV of extra energy, on average, with a distribution in energies of this same magnitude. A MALDI time-of-flight mass spectrometer operating at 10,000 volt nominal ion energy would have an energy deviation  $\Delta$  of 0.01 or more for large proteins, but the value would be only 0.0002 or less for small peptides with masses below 2000 daltons. A time-of-flight spectrometer according to this invention has ion optical properties which may be changed by changing the potentials applied to the various elements, including the trim electrodes. Thus, this invention makes it possible to tune the spectrometer for best performance with larger  $\Delta$  which gives best resolution for large proteins, or to tune for best resolution with small  $\Delta$  which gives the best performance for peptides. Furthermore, the desired tuning condition may be obtained by simply changing the potentials applied to the electrodes of the spectrometer.

**[0164]** Each of the trim electrodes of apparatus 200 has an electric potential that may be independently adjustable with respect to others of the adjustable trim electrodes and with respect to the electric sector deflecting electrodes. Therefore, each ion optical element may be configured to modify specifically the potential experienced by an ion entering or exiting the electric sector with which the ion optical element is associated. The effects of these adjustments are similar to those described hereinabove for apparatus 100. Therefore, each element and trim electrode may constitute an additional degree of freedom to modify the ion focusing properties of the electric sectors. These adjustments, in combination with the known advantages of the symmetric arrangement of flight path 60, allow even greater control over and improvement of the mass resolution and/or sensitivity.

**[0165]** An exemplary electric sector time-of-flight mass spectrometer, the mass analyzer of which is useful in the tandem mass spectrometer of the present invention

("Physical Embodiment A" or equivalently, "Embodiment A") was constructed with the parameters provided in Table 3.

5

TABLE 3  
Dimensions and Potentials of Embodiment A

Parameter	Physical Embodiment A
Electric Sector Radius	3.00
Deflection Angle	270 degrees
D1	7.14
D2	4.68
S <sub>s</sub>	0.54
W <sub>M</sub>	0.30
H <sub>s</sub>	1.68
S <sub>M</sub>	0.18
Trim Electrode Thickness (T <sub>T</sub> )	0.24
Trim Electrode Spacing (T <sub>S</sub> )	0.33
Trim Electrode to Sector Electrode Space (T <sub>ES</sub> )	0.21
Herzog shunt thickness (H <sub>T</sub> )	0.24
Herzog shunt spacing to Trim Electrode (H <sub>TS</sub> )	0.21
Herzog shunt opening height (H <sub>H</sub> )	0.60
Herzog shunt opening width (H <sub>W</sub> )	0.30
Ion Acceleration Voltage	20,000 volts
Potential on Electric Sector Outer Electrode	3224 volts
Potential on Electric Sector Inner Electrode	-4181 volts
Potential on Matsuda Plates	549 volts
Potential on Inner Trim Electrodes	655 volts
Potential on Outer Trim Electrodes	676 volts

[0166] The apparatus of the present invention designated Embodiment A was constructed in accordance with the dimensions provided in Table 3 and is schematically depicted in FIGS. 8, 9, 10A and 10B. Other attributes of this embodiment, unless specified otherwise hereinbelow or in Table 3, are substantially similar to those described above with respect to the theoretical embodiment described above.

[0167] To demonstrate the features and/or advantages of electric sector mass analyzers having adjustable trim electrodes, representative mass spectrometer experiments were performed with the Embodiment A electric sector time-of-flight mass spectrometer. Unless otherwise specified, the preparation of the samples, the operation of the mass spectrometer, and acquisition of the time-of-flight mass spectrum were performed in accordance with methods and protocols known and understood by one of ordinary skill in

the art. The potentials of the electrodes in Embodiment A were applied as set forth in Table 3. The experiments and results described below are illustrative and exemplary only, and are not meant to be limiting with respect to the features, advantages and uses of the present invention.

5

#### EXAMPLE 1: Spectral Range (IgG)

**[0168]** The TOF electric sector mass spectrometer of Embodiment A provides well-defined signals over a large spectral range. Spectral range is a characteristic of the mass spectrum and refers to the spectrometer's ability to detect and measure a broad range of masses from a given sample within a single spectrum. Ions outside the spectral range are usually not detectable and hence do not appear on the mass spectrum. Therefore, a spectrometer that provides a mass spectrum with a large mass range of interest may allow detection and measurement of a larger number of ions than one with a smaller spectral range.

**[0169]** To demonstrate the spectral range of Embodiment A, the apparatus of Embodiment A was used to obtain a TOF mass spectrum of IgG in a sinapinic acid ("SPA") matrix on a gold chip. The sample was ionized by delayed extraction laser desorption ionization and the ions were detected with a sampling rate of 250 MHz. Referring to FIGS. 11A-11C, three portions of the TOF mass spectrum are shown, each portion rescaled along its horizontal axis. In this mass spectrum, signals representing ions having masses from 1.3 kDa to 146.4 kDa were observed. Therefore, this example demonstrates that the apparatus of Embodiment A can provide a single mass spectrum with a large spectral range.

**[0170]** This experiment was performed to determine the spectral range and sensitivity of the apparatus with a peptide sample. In a manner similar to that described in Example 1, a tryptic digest of 100 fmole of bovine serum albumin ("BSA") was prepared on a SEND-C18 chip (Ciphergen Biosystems™) and a mass spectrum was obtained. Referring to FIG. 12A-12H, eight portions from the single mass spectrum obtained are shown. The measured masses and resolutions of the peaks indicated are listed in Table 4 below. This experiment demonstrates that the masses of individual peptides may be obtained with high accuracy and resolution as measured in a single mass spectrum.

TABLE 4: Selected Peptide Masses and Resolution

Peak	Mass	Resolution
1	545.334	1560
2	572.323	1460
3	922.467	3180
4	927.464	2390
5	1399.7	3920
6	1419.76	3990
7	1795.85	5290
8	2019.96	5400
9	2458.19	6710
10	3038.2	7530
11	3511.57	8540

[0171] In order to determine the sensitivity of the apparatus, the experiment was repeated with decreasing amounts of BSA digest. As listed in Table 5 below, the sensitivity of the apparatus allows detection of a significant number of peptides constituting a substantial percentage of the original protein sequence, even when starting with low-femtomolar quantities of the sample protein. FIG. 13A depicts the TOF mass spectrum of a tryptic digest of 1 fmole of BSA. FIG. 13B depicts an expanded section of the mass spectrum of FIG. 13A.

TABLE 5: Sensitivity of Peptide Detection

Amount of BSA Digest	Number of BSA Peptides Detected	Percent Coverage of BSA Sequence
100 fmole	92	93
10 fmole	64	81
1 fmole	44	66

## EXAMPLE 3: Mass Accuracy

[0172] To determine the mass accuracy of Embodiment A, the mass spectra of eight samples of a peptide mixture were acquired using the mass spectrometer of Embodiment A. All eight samples were introduced on a single gold chip in a cyanohydroxycinnamic acid ("CHCA") matrix. The numbers listed in Table 6 were calculated from the corresponding peptide signals measured by these mass spectra. As shown below, accurate masses for all five peptides were obtained using the Embodiment A mass spectrometer apparatus.

TABLE 6: TOF Mass Spectra of Peptide Mixture (8 measurements)

	<b>Arg8- Vaso- pressin</b>	<b>Somato- statin</b>	<b>Dynor- phin A</b>	<b>Insulin β-chain</b>	<b>Insulin αβ- chains</b>
True Mass	1083.438	1636.717	2146.191	3493.644	5807.653
Average Mass	1083.405	1636.700	2146.192	3493.569	5806.877
SD (ppm)	37.3	32.1	26.2	26.5	57.9
Range (ppm)	116.2	103.0	80.7	72.8	155.3
Avg. Err. (ppm)	40.1	23.7	18.9	26.6	133.7
Avg.-True (ppm)	-30.1	10.2	0.1	-21.3	-133.7
TOF Avg. (μsec)	45.8447	56.3129	64.4642	82.2101	105.9537
TOF SD (ppm)	18.6	16.0	13.1	13.2	28.9

## EXAMPLE 4: Mass Resolution

- 5     **[0173]**             To demonstrate the mass resolution of Embodiment A, the mass of adrenocorticotrophic hormone ("ACTH") was measured using the Embodiment A apparatus. The resulting mass spectrum is shown in FIG. 14, and the mass and resolution of each labeled peak in the mass spectrum is listed below in Table 7.

10     TABLE 7: Measured masses and resolutions of ACTH Spectrum

<b>Peak</b>	<b>Mass</b>	<b>Resolution</b>
1	4540.28	10394.6
2	4541.33	10306
3	4542.31	10651.1
4	4543.29	10305.6
5	4544.3	9178.79
6	4545.34	9105.81
7	4546.31	8430.71

- [0174]**             It is understood that the foregoing experiments and their results are only examples and illustrations of the uses, parameters, and advantages of the present invention. These experiments and results are therefore not meant to be limiting with respect to the type or scope of the features, advantages and uses of the present invention. Other uses, applications and advantages of the present invention will be apparent to those skilled in the art upon review of the specification.

**[0175]**             It is understood that the apparatuses described herein are only examples of the many alternative embodiments contemplated by the present invention. For example,

although these embodiments illustrate ion optical elements disposed at every entry and outlet of all electric sectors, this configuration is not a requirement. For example, in a TOF mass spectrometer comprising more than one electric sector, it may be desirable to situate ion optical elements only at the entry of the first electric sector and only at the outlet of the final electric sector, with no ion optical elements between contiguous electric sectors. Other similar combinations are easily conceivable. Likewise, the present invention contemplates alternative embodiments in which the quantity, shape, size, relative position, and other properties of the ion optical elements and trim electrodes are different from those illustrated in FIGS. 6, 7, 8, 9, 10A, 10B and 15.

10 **[0176]** Furthermore, it is not required that all of the electric sectors in a TOF mass spectrometer be identical in geometry, size, ion focusing, or other properties. Similarly, the present invention is not limited to any particular arrangement, symmetric or otherwise, of the multiple electric sectors and free-flight regions.

15 **[0177]** It is also understood that one of ordinary skill would recognize that the Herzog shunts or Matsuda plates, as described above, are dispensable elements. They would also recognize that the Herzog shunts or Matsuda plates could be incorporated into a partial or full enclosure of the electric sector or sectors of the time-of-flight mass spectrometer, as depicted schematically in FIG. 15 in a top cross-sectional view. With respect to FIG. 15, apparatus 300 comprises enclosure 370 that incorporates the  
20 functionalities of Herzog shunts and/or Matsuda plates. Enclosure 370 further comprises aperture 375 and 376 that allow entry and exit, respectively, of the ion flight path. These and other embodiments are within the scope of the present invention and would be apparent to one of ordinary skill in the art, and their suitability would depend on the analytical circumstances or desired features.

25 **[0178]** A TOF mass spectrometer of the present invention may also comprise electronic and/or computational means for controlling and adjusting the trim electrodes. For example, a control system such as a computer may be configured to monitor and adjust the potentials on one or more of the trim electrodes. Such a control system is capable of monitoring and adjusting the adjustable trim electrodes with a high degree of accuracy and  
30 precision. The control system may further comprise a software program configured to control the adjustable trim electrodes. For example, the software may be programmed to

confer potentials to each of the adjustable trim electrodes in arrangements suitable for a particular sample or analytical application.

5       **[0179]**       In another aspect of the invention, the present invention provides methods for tuning a TOF mass spectrometer in order to improve the mass resolution or sensitivity of the mass spectrum. The TOF mass spectrometer includes one or more ion focusing electric sectors, at least one of which is associated with at least one ion optical element. Each ion optical element comprises at least one adjustable electrode. Suitable TOF mass spectrometers for this method include, but are not limited to, the embodiments described hereinabove.

10       **[0180]**       In one embodiment, the method comprises determining a first mass spectrum using a mass spectrometer of the present invention, from which a first mass resolution or sensitivity is determined. A potential may be applied to at least one trim electrode prior to determining the first mass spectrum.

15       **[0181]**       Following the first mass determination, the potential of at least one trim electrode of the apparatus is adjusted. A second mass spectrum is subsequently determined, from which a corresponding second mass resolution or sensitivity is determined. By comparing the relative improvement or degradation of the mass resolution or sensitivity between the first and second mass spectra, the improvement or degradation may be correlated with the intervening adjustment made to the ion optical elements. If, for  
20       example, the second spectrum demonstrates a higher mass resolution or sensitivity relative to the first spectrum, further improvement may be pursued by determining a third mass spectrum after further adjustment of the trim electrode in the same direction. Accordingly, adjustment in the opposite direction may be required if the second spectrum is demonstrated to be degraded with respect to the first spectrum as a result of the intervening  
25       adjustment.

30       **[0182]**       Further tuning may be performed in this iterative manner until a desired or sufficient mass resolution or sensitivity is achieved. The tuning method of the present invention may be used to attain the desired resolution and/or sensitivity for particular samples and analytical applications. For example, the trim electrodes of the mass spectrometer may be tuned to optimize the mass spectrometer for determining a mass spectrum for a peptide sample. Similarly, the mass spectrometer may instead be tuned for the optimal determination of a mass spectrum of a protein sample. One skilled in the art



would understand that tuning in this manner may be performed to provide optimal settings for any suitable substrate. Furthermore, optimal tuning settings for a given substrate type may be determined beforehand by the manufacturer and/or the operator. These settings may be available in the documentation or pre-programmed for the apparatus.

5     **[0183]**         This tuning method, as well as adjustments of the trim electrodes in general, may be performed more quickly, precisely, and/or accurately by using an apparatus that further comprises the control system as described above. The control system may be configured to, for example, compare the properties of the mass spectra determined at different settings and/or adjust the trim electrode settings accordingly. The control system  
10    may comprise a computer, electronics, software programs, algorithms, and the like. Predetermined optimized settings, as described above, may be stored in the apparatus and used by the software program to quickly and accurately set the trim electrodes to the appropriate settings.

15    **[0184]**         All patents, patent publications, and other published references mentioned herein are hereby incorporated by reference in their entireties as if each had been individually and specifically incorporated by reference herein. By their citation of various references in this document, applicants do not admit that any particular reference is "prior art" to their invention.

20    **[0185]**         While specific examples have been provided, the above description is illustrative and not restrictive. Any one or more of the features of the previously described embodiments can be combined in any manner with one or more features of any other embodiments in the present invention. Furthermore, many variations of the invention will become apparent to those skilled in the art upon review of the specification. The scope of the invention should, therefore, be determined not with reference to the above description,  
25    but instead should be determined with reference to the appended claims along with their full scope of equivalents.

What is Claimed is:

1. A tandem mass spectrometer, comprising:  
an ion source;  
a first mass analyzer;  
a second mass analyzer; and  
an ion detector, wherein:  
the ion source is in ion communication with the first mass analyzer;  
the first mass analyzer is in ion communication with the second  
mass analyzer;  
the second mass analyzer is in ion communication with the ion  
detector; and  
at least one of the mass analyzers is a time-of-flight mass analyzer  
that comprises at least one electric sector.
2. The mass spectrometer of claim 1, wherein the first mass analyzer is a  
time-of-flight mass analyzer that comprises at least one electric sector.
3. The mass spectrometer of claim 1 or claim 2, wherein the electric sector  
time-of-flight mass analyzer further comprises at least one field free region, wherein the at  
least one electric sector and the at least one field free region define an ion flight path.
4. The mass spectrometer of any of claims 1 - 3, further comprising ion  
fragmentation means.
5. The mass spectrometer of any one of claims 1 - 4, further comprising ion  
selection means in ion communication with both the first and second mass analyzer, said  
ion selection means capable of selecting ions from among a plurality of ions provided by the  
first mass analyzer.
6. The mass spectrometer of claim 5, wherein the ion selection means  
comprises an aperture in ion communication with the second mass analyzer and means for  
sweeping an ion beam across the aperture.

7. The mass spectrometer of claim 6, wherein the ion deflection means comprises electric field means.

8. The mass spectrometer of any one of claims 1 – 7, wherein the ion source comprises ionization means selected from the group consisting of: laser desorption/ionization means, chemical ionization means, photoionization means, and electrospray ionization means.

9. The mass spectrometer of claim 8, wherein the ion source comprises laser desorption/ionization means.

10. The mass spectrometer of any one of claims 1 – 9, wherein the ion source comprises means for extracting ions from a pulsed or continuous ion beam in a direction selected from the group consisting of substantially axial to the direction of the ion beam and substantially orthogonal to the direction of the ion beam.

11. The mass spectrometer of any one of claims 1 - 10, wherein the ion source comprises means for accelerating a pulse of ions from the ion source.

12. The mass spectrometer of claim 11, wherein the means for accelerating a pulse of ions comprises a voltage pulsing means capable of applying a pulse subsequent to formation of the ions.

13. The mass spectrometer of any one of claims 1 – 12, wherein the first mass analyzer comprises a mass analyzer selected from the group consisting of: an electric sector time-of-flight mass analyzer, a linear time-of-flight mass analyzer, a reflecting time-of-flight mass analyzer, a linear ion trap, a quadrupole ion trap, a quadrupole ion filter, a magnetic sector mass analyzer, an ion cyclotron resonance mass analyzer, an electric sector/magnetic sector mass analyzer, an ion trap/ linear time-of-flight mass analyzer, an ion trap/reflecting time-of-flight mass analyzer, and an electrostatic mass analyzer.

14. The mass spectrometer of any one of claims 1 – 12, wherein the second mass analyzer comprises a mass analyzer selected from the group consisting of: an electric sector time-of-flight mass analyzer, a linear time-of-flight mass analyzer, a reflecting time-of-flight mass analyzer, a linear ion trap, a quadrupole ion trap, a quadrupole ion filter, a magnetic sector mass analyzer, ion cyclotron resonance mass analyzer, an electric sector/magnetic sector mass analyzer, an ion trap/ linear time-of-flight mass analyzer, an ion trap/reflecting time-of-flight mass analyzer, and an electrostatic mass analyzer.

15. The mass spectrometer of any one of claims 3 – 12 and 14, wherein the first mass analyzer is a time-of-flight mass analyzer and comprises at least one electric sector.

16. The mass spectrometer of claim 15, wherein the second mass analyzer is a time-of-flight mass analyzer and comprises at least one electric sector.

17. The mass spectrometer of any one of claims 1 – 16, wherein at least one of the mass analyzers is a time-of-flight mass analyzer that comprises two or four electric sectors and a field-free region separating each of the electric sectors, the electric sectors and the field-free regions defining an ion flight path therein.

18. The mass spectrometer of claim 17, wherein said at least one mass analyzer is a time of flight mass analyzer that comprises four electric sectors and a field-free region separating each of the electric sectors, each of the electric sectors having a deflection angle of about 270 degrees, the electric sectors and the field-free regions defining an ion flight path therein.

19. The mass spectrometer of claim 17 or claim 18, wherein the electric sectors are arranged in a symmetrical arrangement.

20. The mass spectrometer of any one of claims 17 – 19, wherein at least one of the mass analyzers is a time-of-flight mass analyzer that comprises two or four electric sectors and a field free region before the first electric sector, after the last electric sector,

and between each of the electric sectors, the electric sectors and the field-free regions defining an ion flight path therein.

21. The mass spectrometer of any one of claims 1 – 20, further comprising at least one Herzog shunt having an aperture, wherein each Herzog shunt is associated with either the entry or the outlet of an electric sector such that the ions pass through the aperture.

22. The mass spectrometer of claim 21, wherein said Herzog shunt is an aperture in a housing enclosing said electric sector.

23. The mass spectrometer of any one of claims 1 – 22, further comprising ion selection means in ion communication with both the first and second mass analyzers, wherein said ion selection means are capable of selecting ions from among a plurality of ions provided by the first mass analyzer.

24. The mass spectrometer of claim 23, wherein the ion selection means comprises a plurality of consecutive ion gates.

25. The mass spectrometer of any one of claims 1 – 24, further comprising means for fragmenting ions provided by the first mass analyzer.

26. The mass spectrometer of claim 25, wherein the means for fragmenting ions is a collision cell.

27. The mass spectrometer of any one of claims 1-26, wherein at least one electric sector is associated with at least one ionic optical element, wherein each ion optical element modifies the potential experienced by an ion entering or exiting the electric sector.

28. The mass spectrometer of claim 27, wherein the ion optical element comprises an Einzel lens.

29. The mass spectrometer of claim 27 or claim 28, wherein the ion optical element comprises at least one adjustable trim electrode capable of adjustably modifying the potential experienced by an ion entering or exiting an electric sector.

30. The mass spectrometer of any one of claims 1 – 29, wherein the ion source comprises laser desorption/ionization means.

31. The mass spectrometer of any one of claims 1 - 30, wherein the ion source includes means for selectively providing one or more masses or ranges of masses.

32. The mass spectrometer of claim 31, wherein the ion source further includes means for providing fragments of the selected masses or ranges of masses.

33. The mass spectrometer of claim 29, wherein the at least one adjustable trim electrode is disposed between the entry and the outlet of the electric sector.

34. The mass spectrometer of claim 29 or 33, comprising a pair of adjustable trim electrodes disposed so that the ions pass between the adjustable trim electrodes of the pair, wherein the pair is associated either with an entry or an outlet of an electric sector.

35. The mass spectrometer of claim 34, comprising a plurality of pairs of adjustable trim electrodes, each pair disposed so that the ions pass between the adjustable trim electrodes of the pair, wherein a pair is associated with each entry and each outlet of each electric sector.

36. The mass spectrometer of any one of claims 1 – 35, wherein at least one mass analyzer is a time-of-flight mass analyzer that comprises four electric sectors, each electric sector having a deflection angle of about 270 degrees, wherein a field free region separates each electric sector.

37. The mass spectrometer of any one of claims 1 – 36, wherein at least one mass analyzer is a time-of-flight mass analyzer that comprises a plurality of electric sectors

and at least one adjustable trim electrode, wherein the at least one adjustable trim electrode comprises a first and second pair of adjustable trim electrodes, each pair disposed so that the ions pass between the adjustable trim electrodes of the pair, wherein the first pair is associated with the entry of the electric sector closest to the entrance of the ion flight path and the second pair is associated with the outlet of the electric sector closest to the exit of the ion flight path.

38. The mass spectrometer of claim 37, wherein at least one mass analyzer is a time-of-flight mass spectrometer that comprises four electric sectors, each electric sector having a deflection angle of about 270 degrees, wherein a field free region separates each electric sector.

39. The mass spectrometer of claim 38, wherein the ion source includes laser desorption/ionization means.

40. The mass spectrometer of claim 38, wherein the ion source includes chemical ionization means, electron impact ionization means, photoionization means or electrospray ionization means.

41. The mass spectrometer of any one of claims 1 – 40, wherein the ion source includes means for selectively providing ions of one or more masses or ranges of masses.

42. The mass spectrometer of claim 41, wherein the ion source comprises a quadrupole ion trap.

43. The mass spectrometer of any one of claims 1 – 42, wherein the ion source comprises a means for extracting ions from a pulsed or continuous ion beam in a direction selected from the group consisting of: a direction substantially axial to the direction of the beam and a direction substantially orthogonal to the direction of the beam.

44. The mass spectrometer of any one of claims 1 – 43, wherein the ion source comprises means for accelerating a pulse of ions from the ion source.

45. The mass spectrometer of claim 44, wherein the means for accelerating a pulse of ions comprises voltage pulsing means capable of applying a voltage pulse subsequent to formation of the ions.

46. The mass spectrometer of any one of claims 1 – 45, wherein at least one electric sector is associated with at least one ion optical element, wherein said at least one ion optical element includes at least one trim electrode capable of adjustably modifying the potential experienced by an ion entering or exiting an electric sector, and further comprising a control system configured to adjust the potential of the at least one trim electrode, wherein the adjustment adjustably modifies the potential experienced by an ion entering or exiting an electric sector.

47. The mass spectrometer of claim 46, wherein the control system comprises a software program.

48. A tandem mass spectrometer comprising:  
an ion source;  
a first mass analyzer;  
a second mass analyzer; and  
an ion detector,  
wherein the first mass analyzer is capable of stigmatic and time focusing of ions to a substantially coincident spatial location on an ion flight path.

49. The mass spectrometer of claim 48, further comprising ion selection means in ion communication with both the first and second mass analyzer, said ion selection means capable of selecting ions from among a plurality of ions provided by the first mass analyzer.

50. The mass spectrometer of claim 49, wherein the ion selection means comprises an aperture in ion communication with the second mass analyzer and means for sweeping an ion beam across the aperture.



51. The mass spectrometer of claim 50, wherein the ion deflection means further comprises electric field means.

52. The mass spectrometer of any one of claims 48 – 52, further comprising ion fragmentation means, wherein the ions are fragmented following the first mass analysis.

53. The mass spectrometer of any one of claims 48 – 52, wherein the first mass analyzer is a time-of-flight mass analyzer.

54. The mass spectrometer of claim 53, wherein the time-of-flight mass analyzer includes at least one electric sector.

55. A tandem mass spectrometer comprising:  
means for providing a plurality of ions;  
means for performing a first mass analysis;  
means for performing a second mass analysis; and  
means for detecting a plurality of ions,  
wherein the means for performing the first mass analysis is capable of stigmatic and time focusing of ions to a substantially coincident spatial location on an ion flight path.

56. The mass spectrometer of claim 55, further comprising means for selecting ions, wherein the ion selecting means is positioned in ion communication with both the means for performing a first mass analysis and means for performing a second mass analysis.

57. The mass spectrometer of claim 56, wherein the means for performing a first mass analysis is capable of said coincident ion focusing at a location substantially coincident with the means for selecting ions.

58. The mass spectrometer of any one of claims 55 - 57, further comprising means for fragmenting ions, wherein the ions are fragmented following the means for performing a first mass analysis.

59. The mass spectrometer of claim 58, wherein the means for performing a first mass analysis is capable of said coincident ion focusing at a location substantially coincident with the means for fragmenting ions.

60. A method for performing tandem mass spectrometry, the method comprising:  
performing a first mass analysis on a plurality of ions provided by an ion source, using a first mass analyzer;  
performing a second mass analysis on at least a subset of said plurality of ions using a second mass analyzer; and  
detecting a plurality of ions using an ion detector,  
wherein at least one of the mass analyzers comprises a time-of-flight mass analyzer that has at least one electric sector.

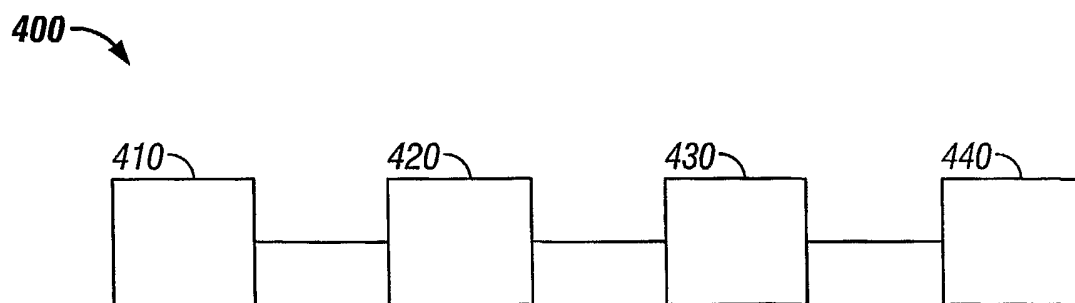
61. The method of claim 60, wherein the electric sector time-of-flight mass analyzer further comprises at least one field free region, wherein the at least one electric sector and the at least one field free region define an ion flight path.

62. The method of claim 61 or claim 62, wherein said electric sector time-of-flight mass analyzer is the first mass analyzer.

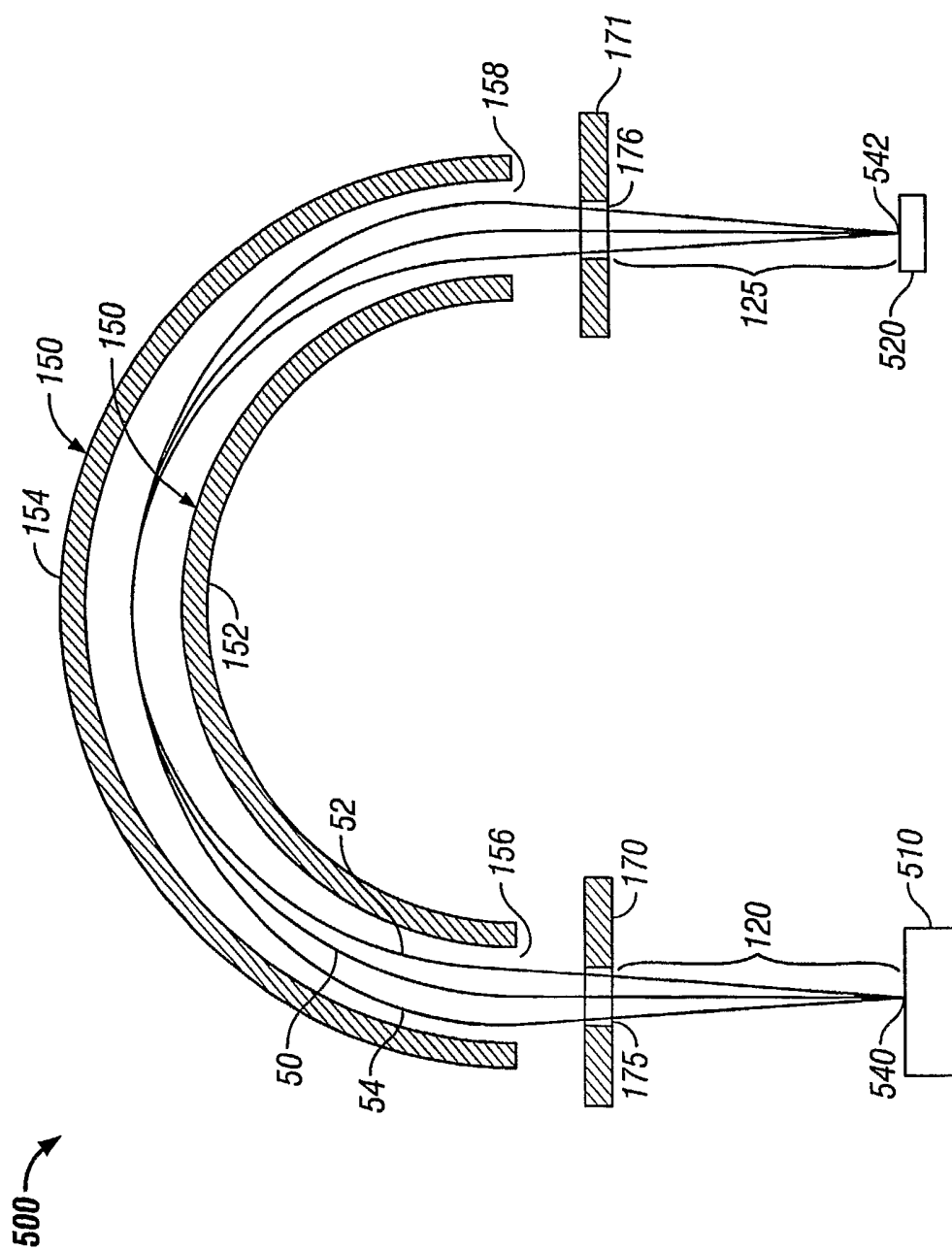
63. A method for performing tandem mass spectrometry, the method comprising:  
stigmatically and temporally focusing at least a plurality of ions provided by an ion source using a first mass analyzer, wherein the ions are stigmatically and temporally focused to a substantially coincident spatial location on an ion flight path;  
performing a second mass analysis on at least a subset of said focused ions using a second mass analyzer; and  
detecting a plurality of ions using an ion detector.

67. A method for tuning a tandem mass spectrometer comprising:
- a) with a tandem mass spectrometer according to claim 29, determining the resolution or sensitivity of detection of ions at a first setting by:
    - i) applying a potential to at least one adjustable trim electrode;
    - ii) obtaining a first mass spectrum of ions from the ion source; and
    - iii) determining resolution or sensitivity of detection from the first mass spectrum;
  - b) determining the resolution or sensitivity of detection of ions at a second setting by:
    - i) adjusting the potential applied to at least one adjustable trim electrode;
    - ii) obtaining a second mass spectrum of ions from the ion source;and
    - iii) determining resolution or sensitivity of detection from the second mass spectrum; and
  - c) determining whether resolution or sensitivity of detection of ions is improved or degraded at the second setting.

**1/17**



**FIG. 1**



**FIG. 2**

3/17

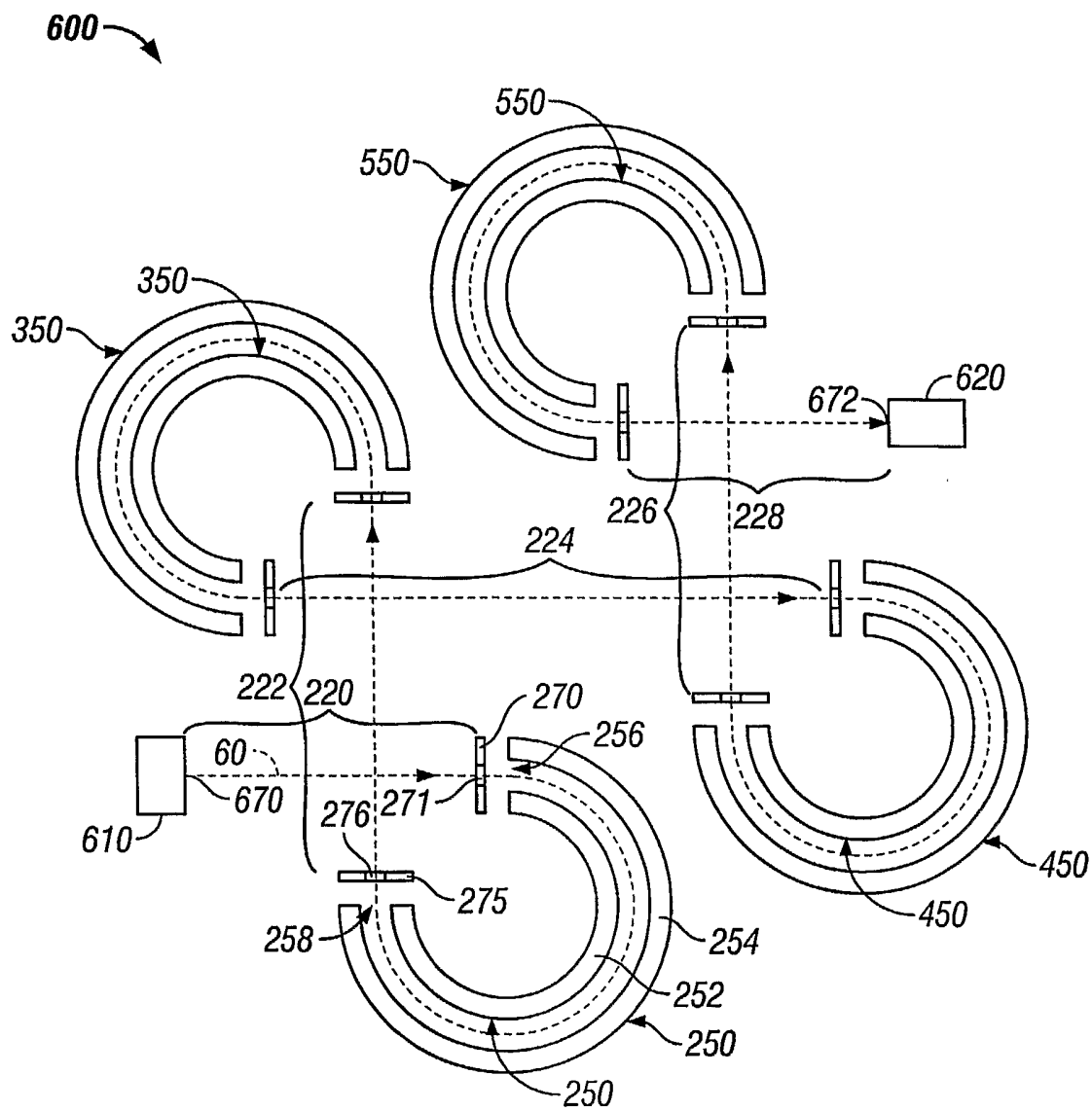


FIG. 3

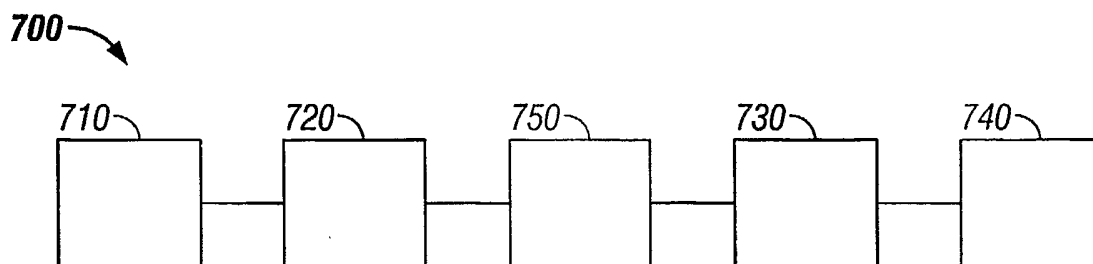


FIG. 4

4/17

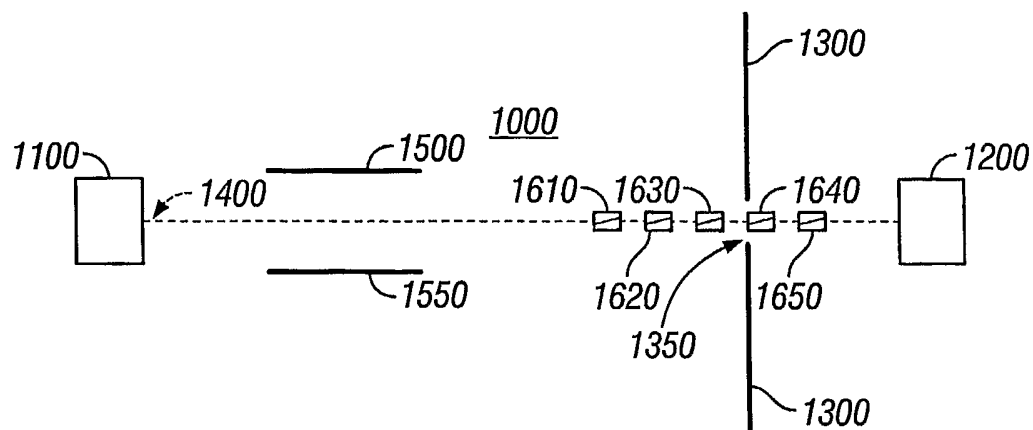


FIG. 5A

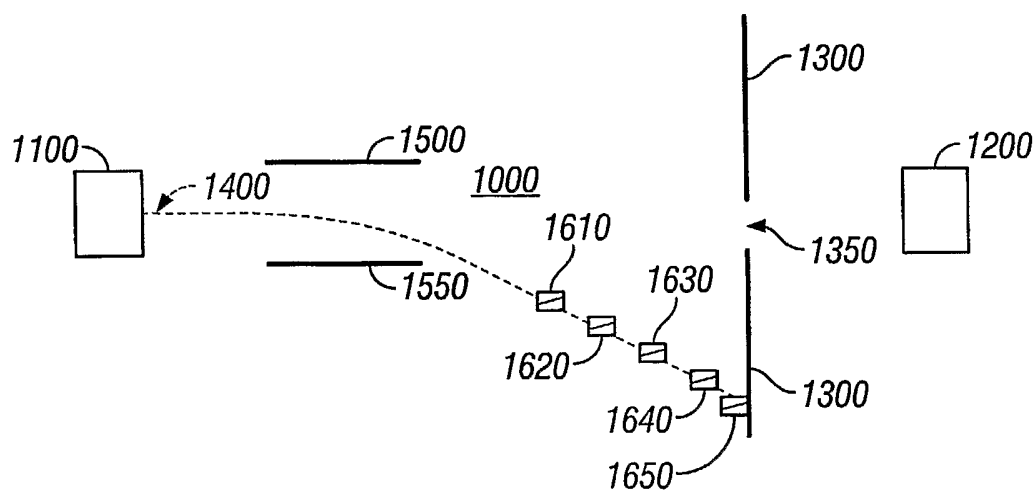


FIG. 5B

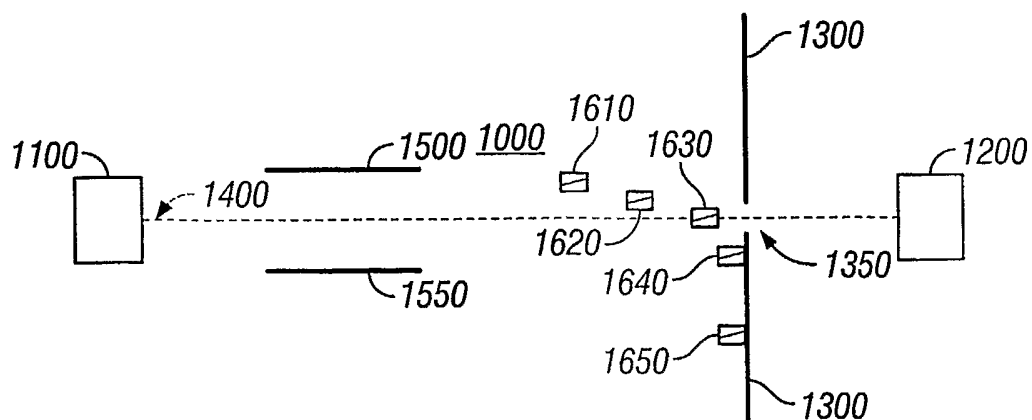


FIG. 5C

5/17

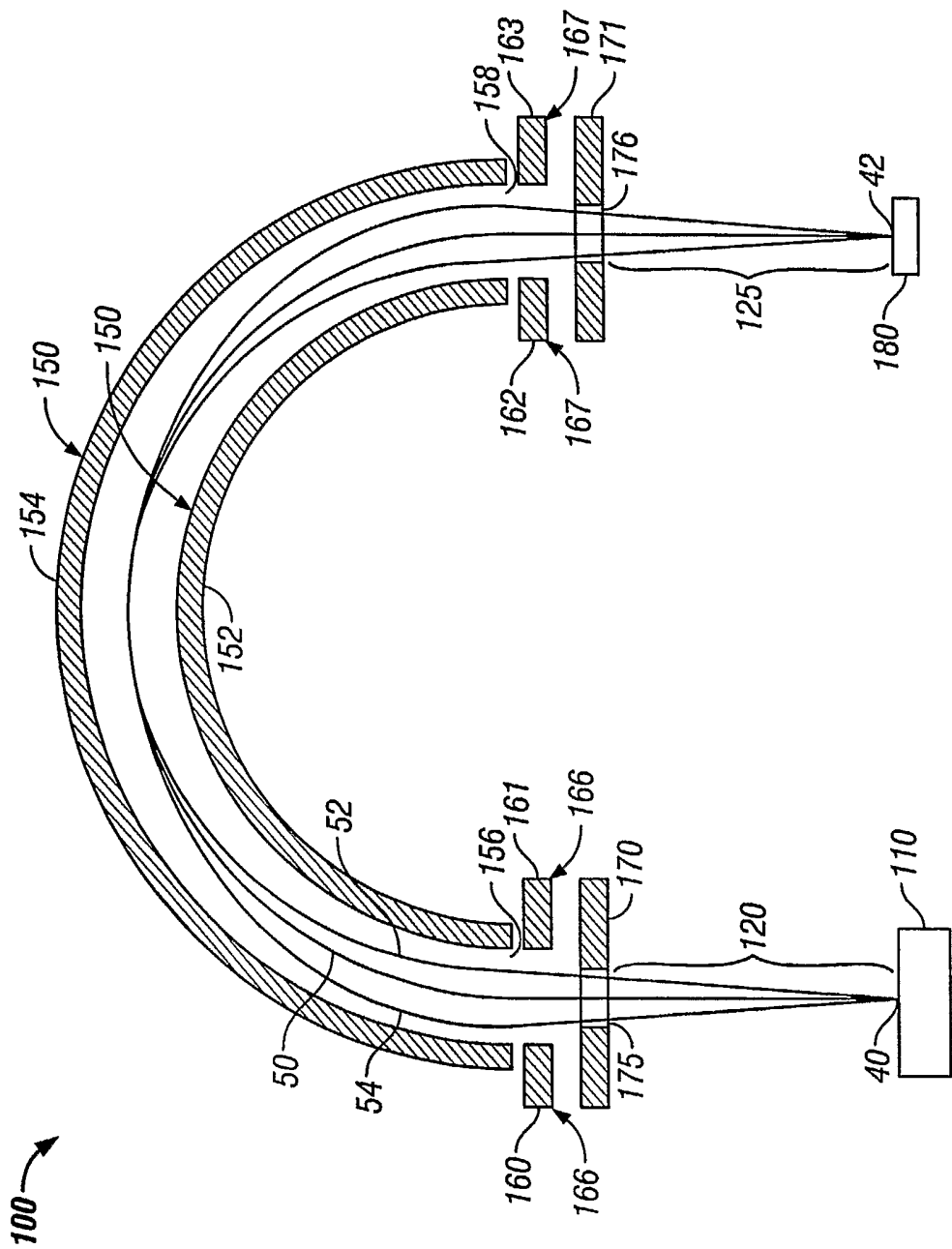


FIG. 6



6/17

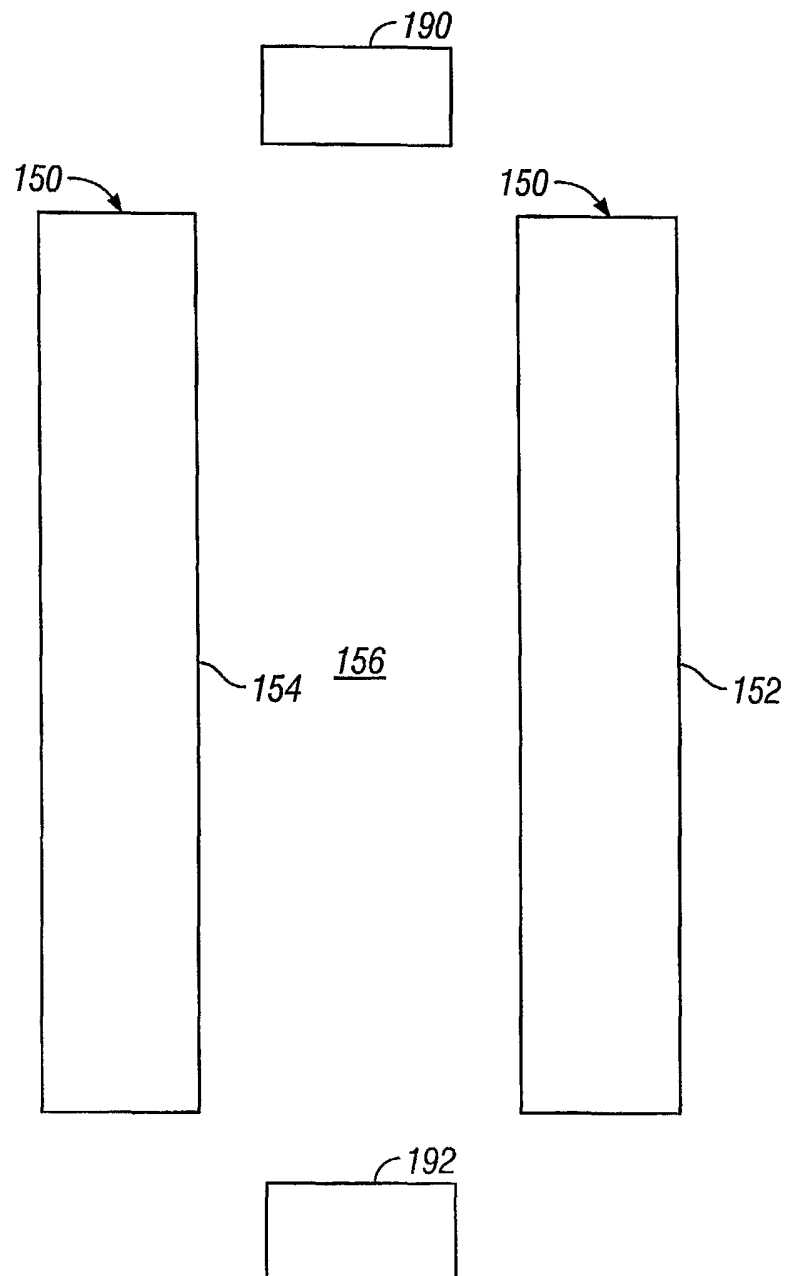


FIG. 7

7/17

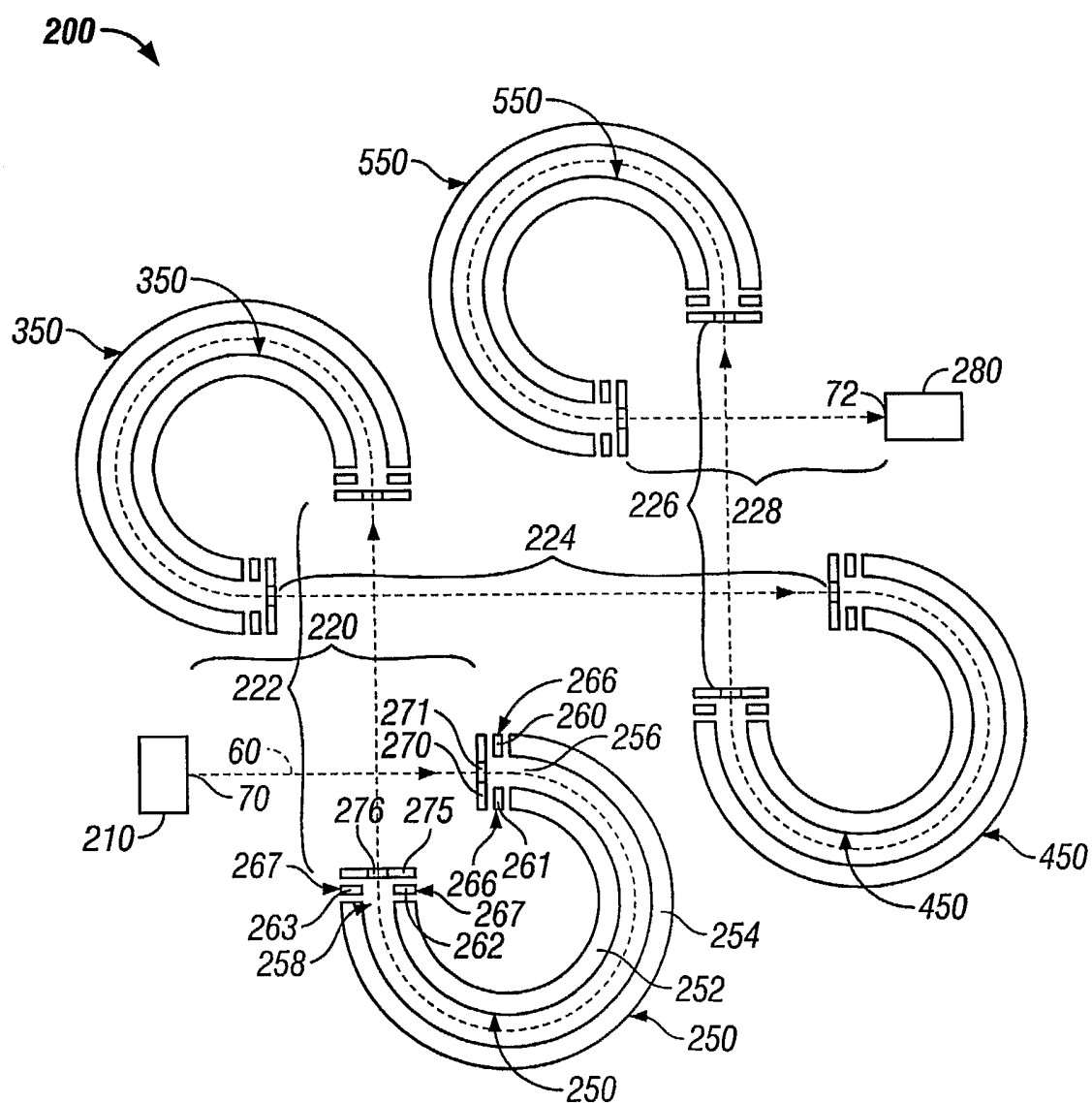


FIG. 8

8/17

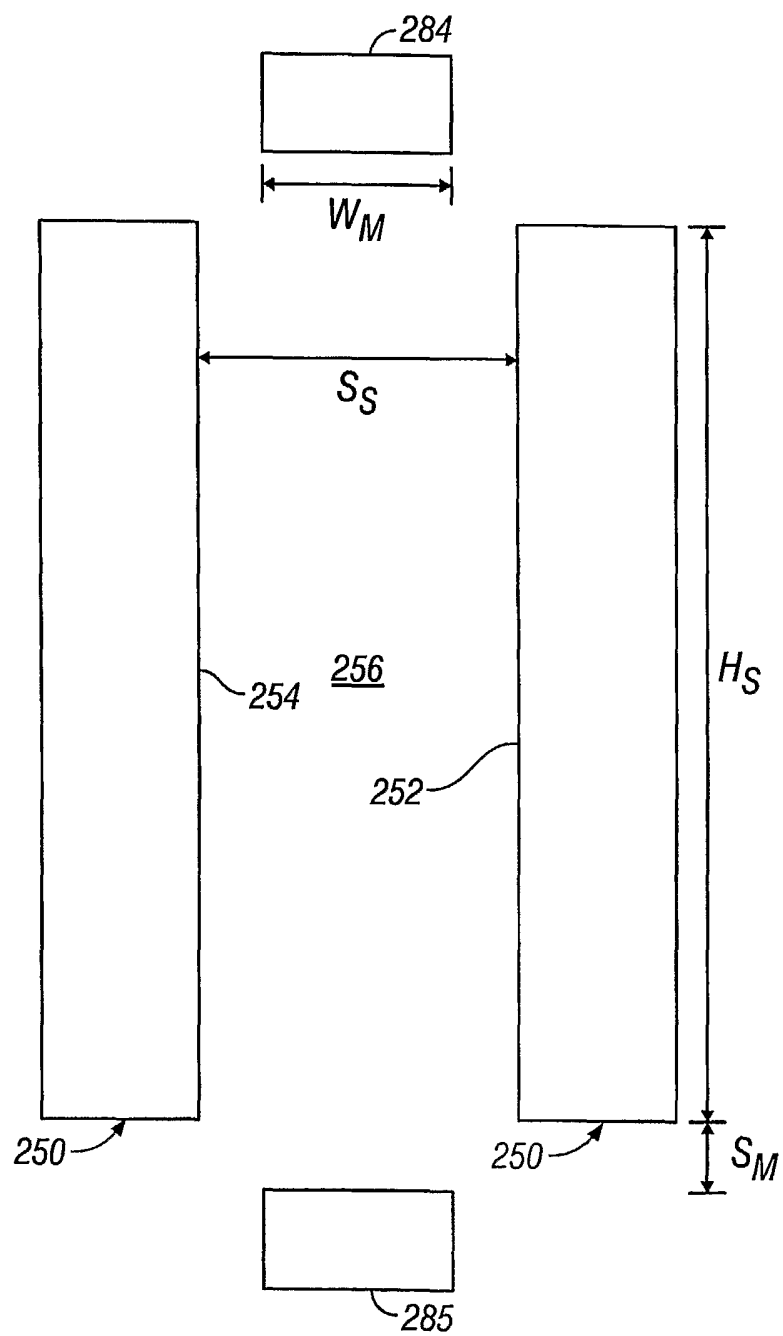


FIG. 9

9/17

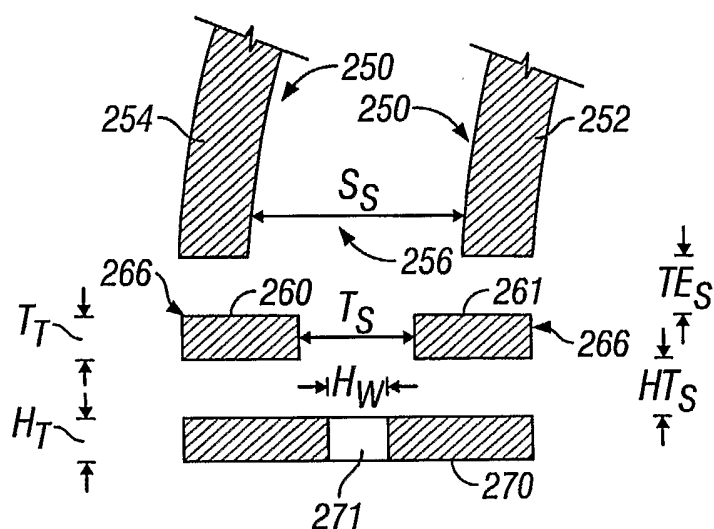


FIG. 10A

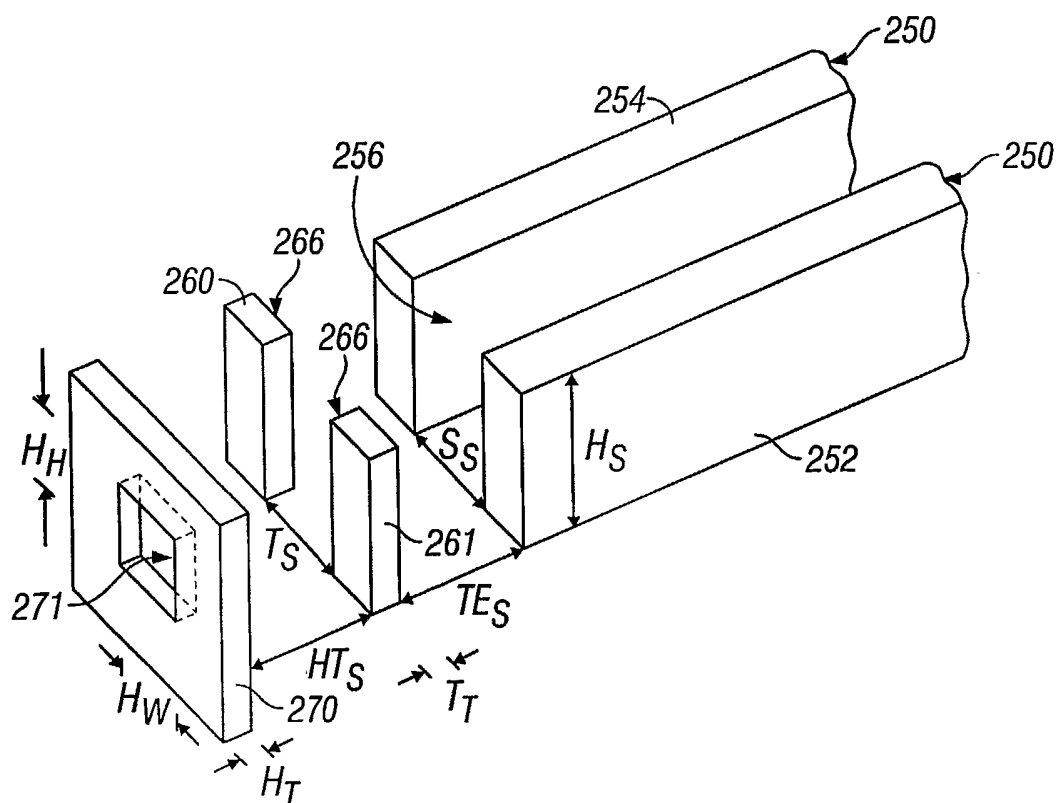
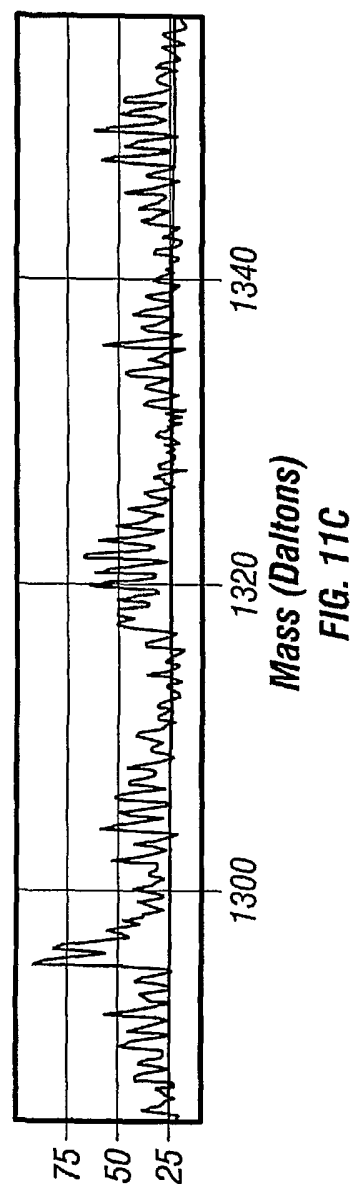
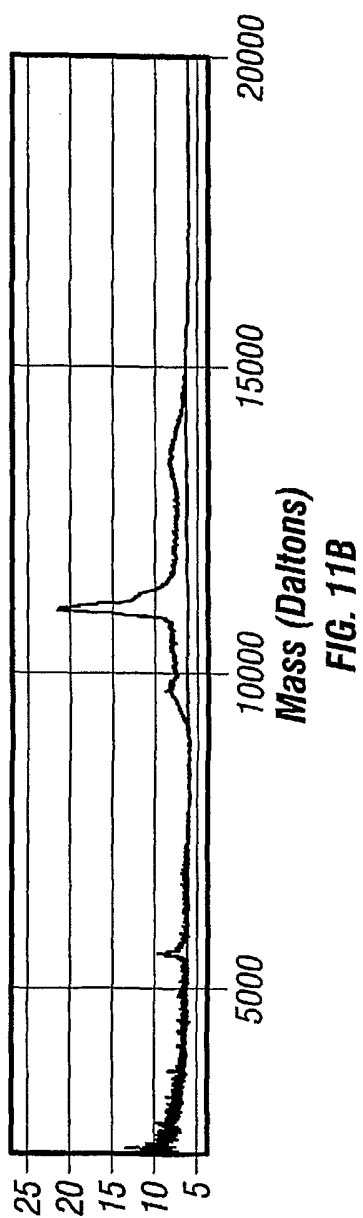
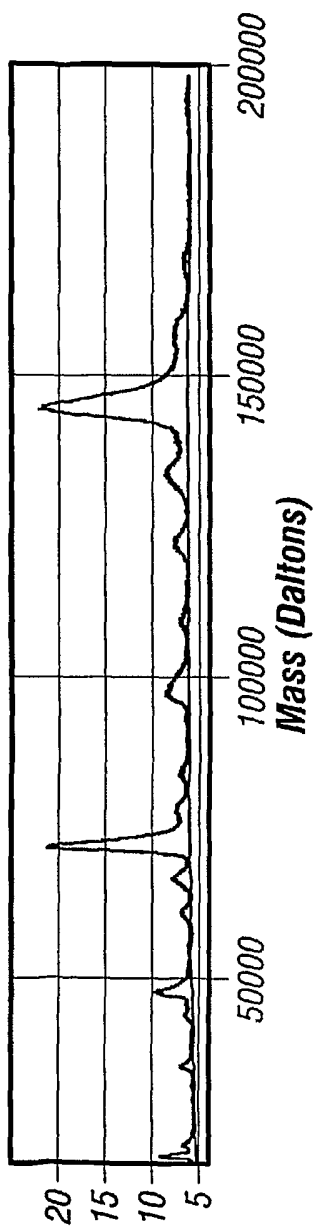
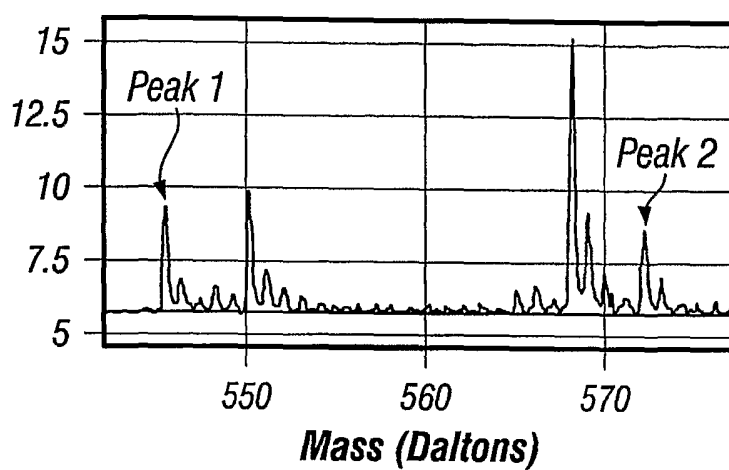
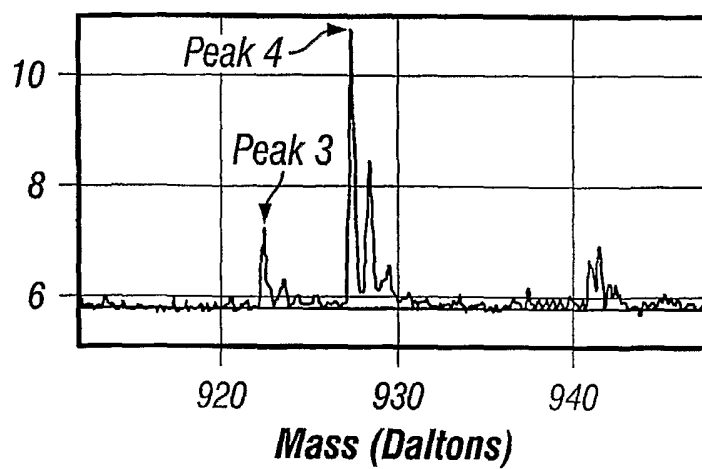
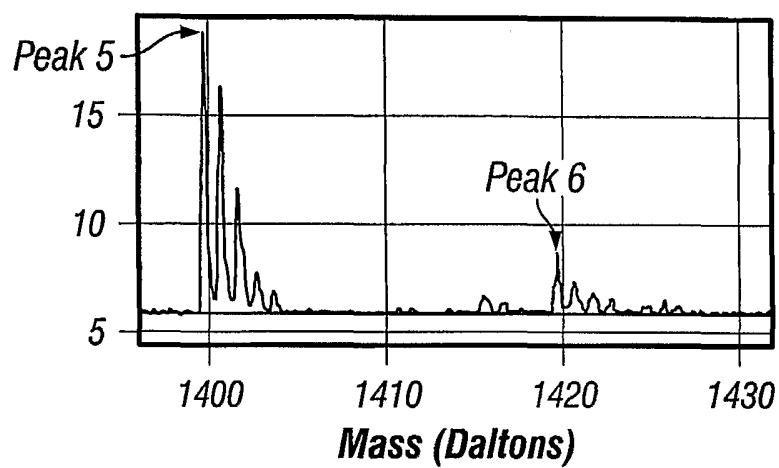
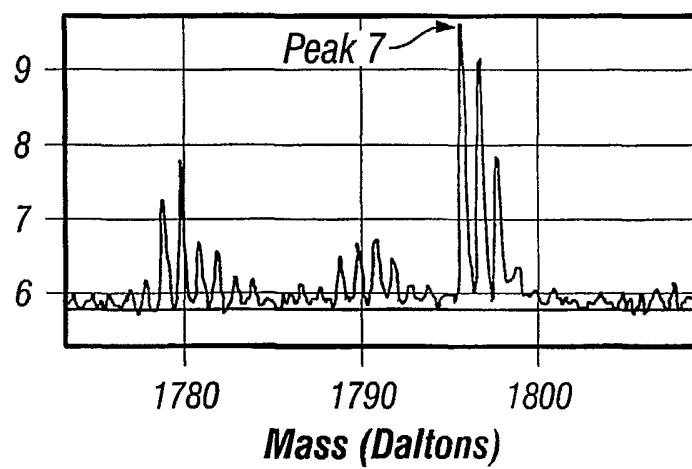


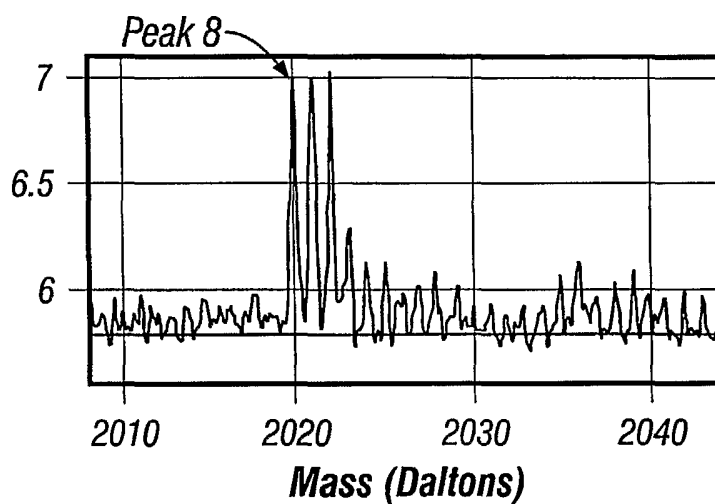
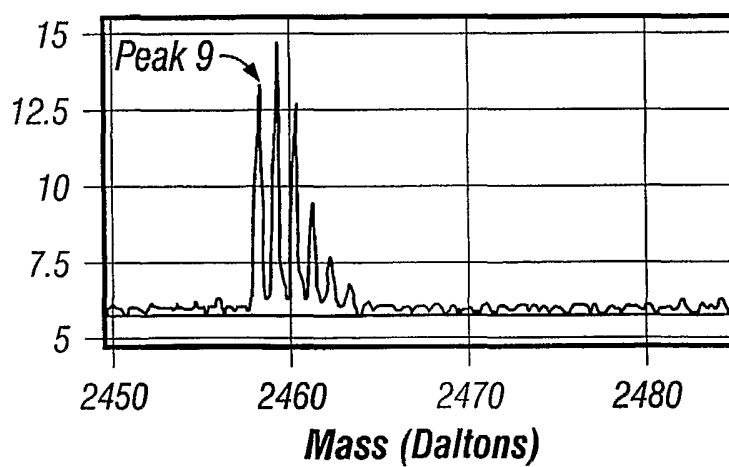
FIG. 10B

10/17

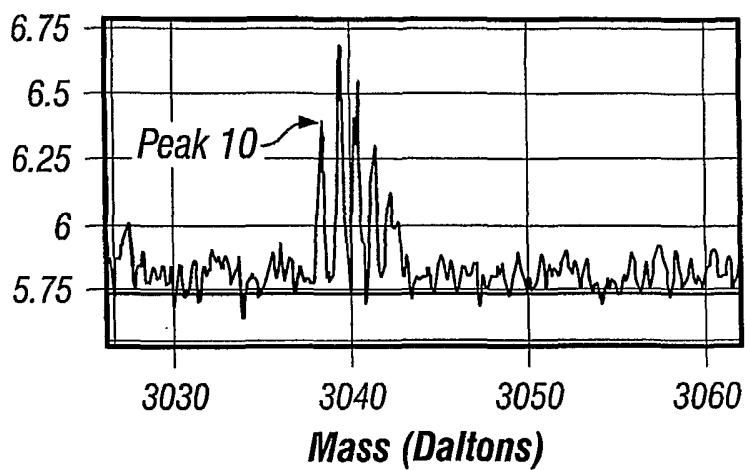
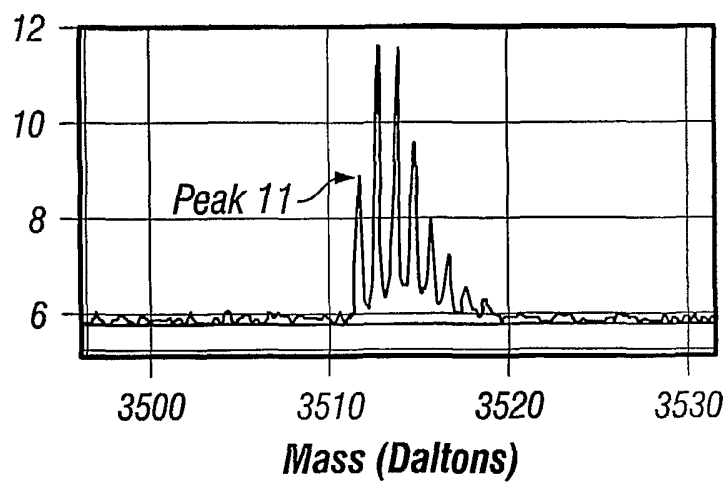


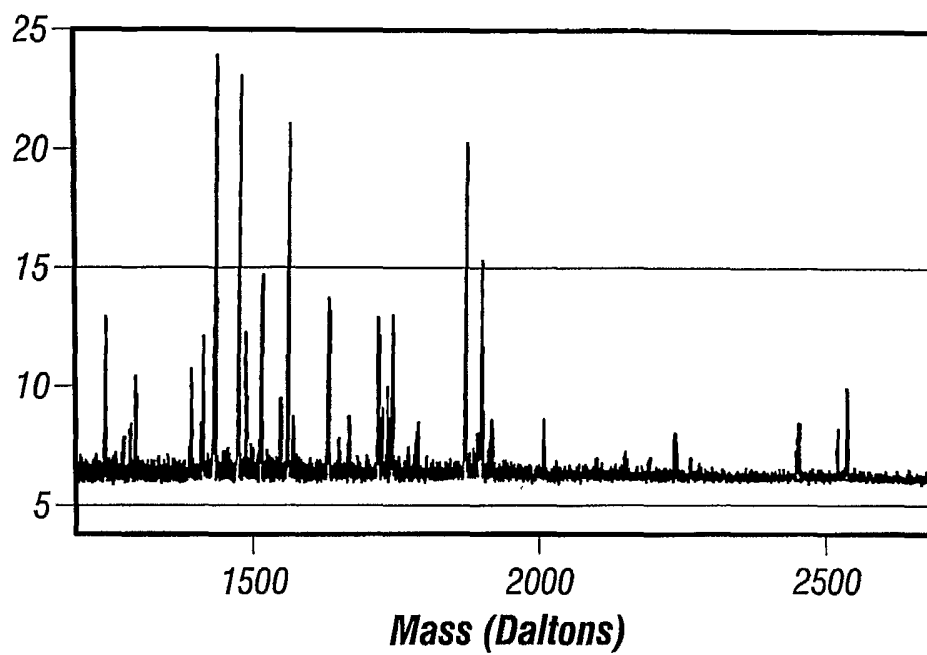
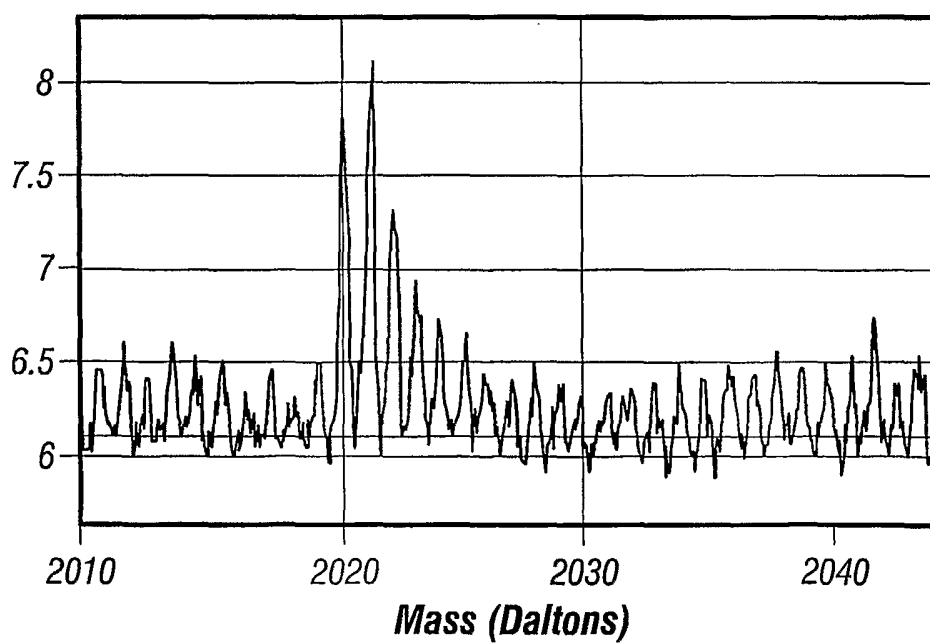
**11/17****FIG. 12A****FIG. 12B**

**12/17****FIG. 12C****FIG. 12D**

**13/17****FIG. 12E****FIG. 12F**



**14/17****FIG. 12G****FIG. 12H**

**15/17****FIG. 13A****FIG. 13B**

16/17

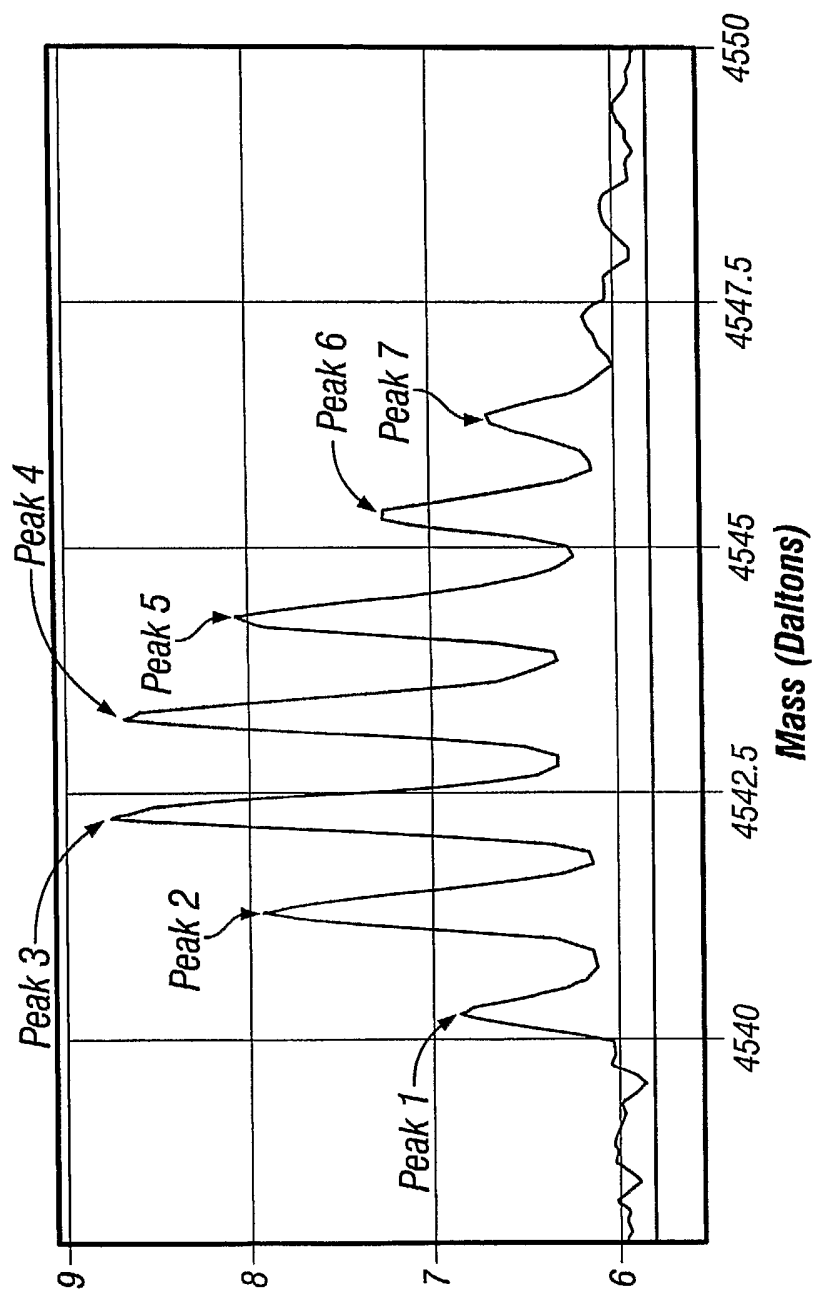
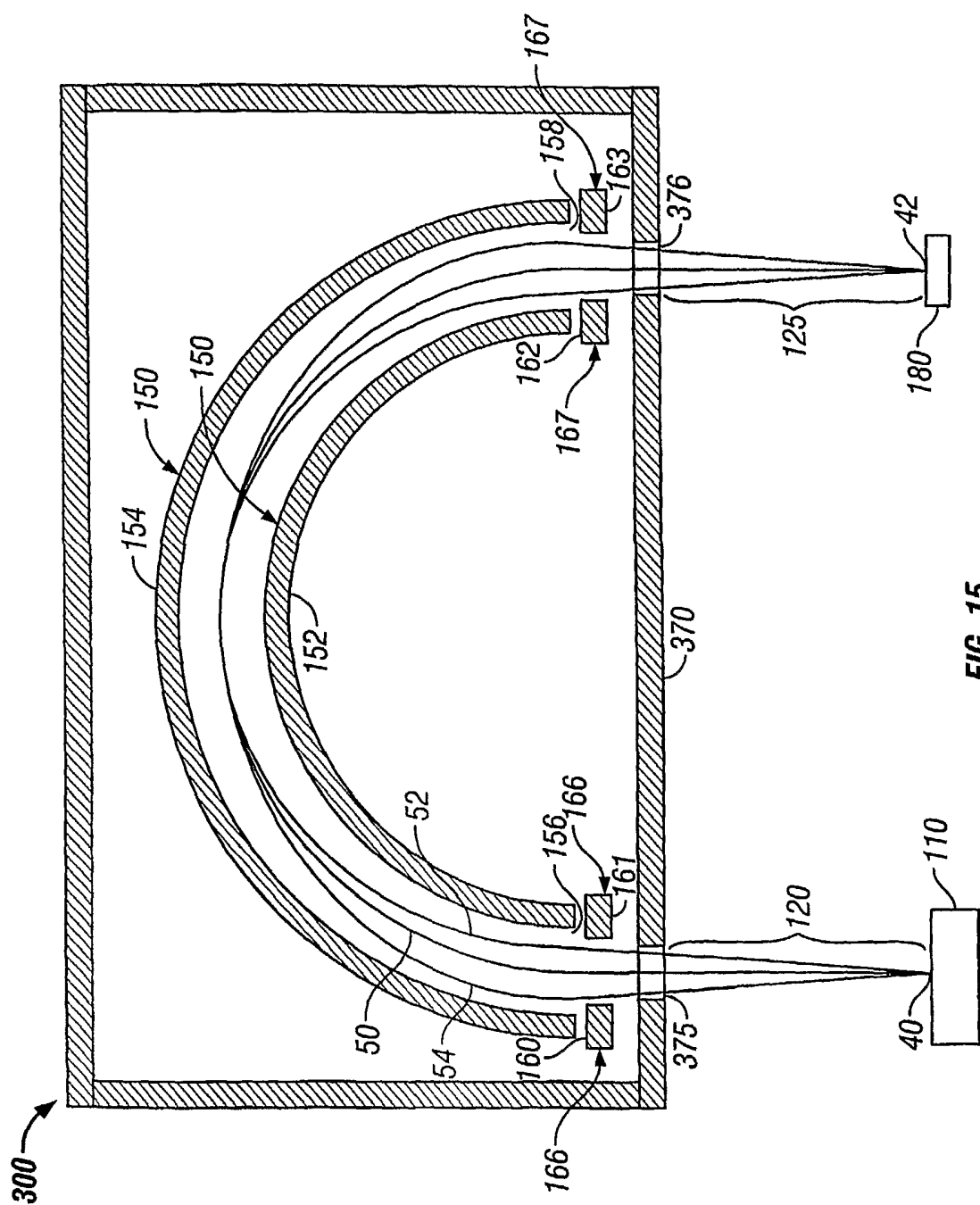


FIG. 14

**17/17**



**FIG. 15**

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/29950

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : H01J 49/40

US CL : 250/287, 281, 283, 396R, 398.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 250/287, 281, 283, 396R, 398.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,472,631 A (ENKE et al.) 18 September 1984 (18.09.1984), Figs. 2 and 8, col. 28, lines 14-35 and 57-68.	1-67
X	US 6,674,069 B1 (MARTIN et al.) 6 January 2004 (06.01.2004), Fig. 1, col. 1, lines 22-57, col. 3, lines 36-57, and col. 4, lines 47-67.	1-67



Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

09 January 2004 (09.01.2004)

Date of mailing of the international search report

23 FEB 2004

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Authorized officer

John R Lee

Telephone No. (703) 308-0956