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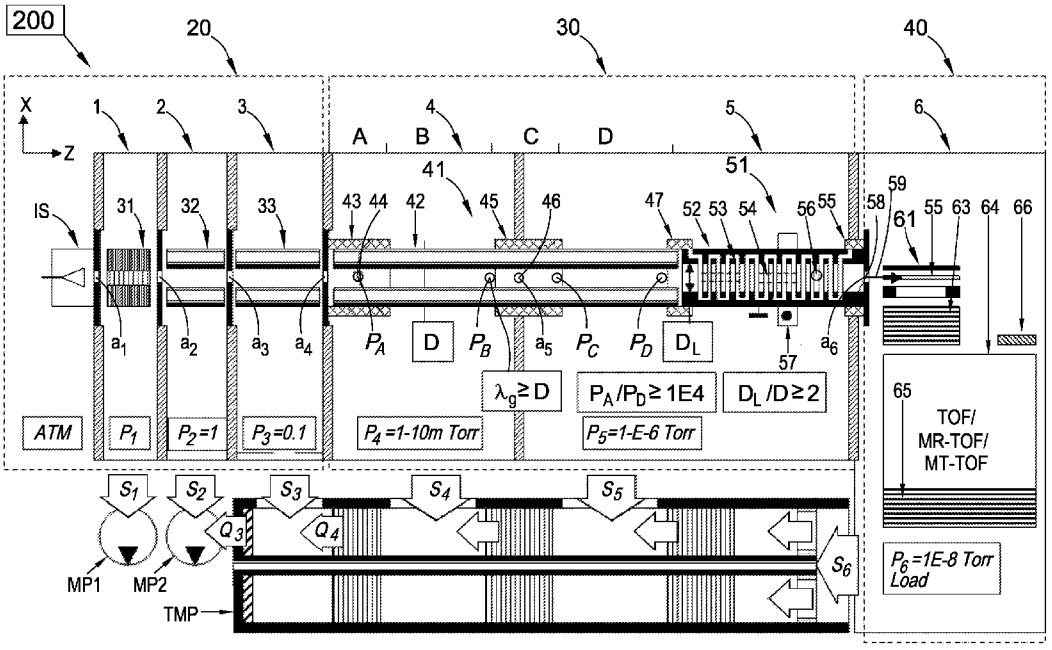

Fig.2

(57) **Abstract:** A combination (200) of protruding RF ion guide (41) and of periodic lens (51) is proposed for non distorting transferring of ions from a region of effective collisional dampening into an orthogonal accelerator (61) of singly or multi-reflecting or multi -turn TOF mass spectrometer (60). The system allows substantial reduction of ion beam phase space and energy spread, in turn providing for an improved combination of time and energy spread of ion packets in TOF MS. In one embodiment (700), the transfer interface is arranged spiral around multi-port turbo-molecular pump for significant reduction of the interface length.

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ION TRANSFER INTERACE FOR TOF MS

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority from and the benefit of United Kingdom patent application No. 1812329.9 filed on 27 July 2018. The entire content of this application is incorporated herein by reference.

FIELD OF INVENTION

The invention relates to the area of time-of-flight (TOF) mass spectrometers, such as multi-reflecting time-of-flight (MRTOF) mass spectrometers, and is particularly concerned with the ion transfer interface to the TOF region.

BACKGROUND

Time-of-flight mass spectrometers (TOF MS) are widely used for their combination of sensitivity and speed, and lately with the introduction of various multi-pass schemes, for their high resolution and mass accuracy. In the last two decades, the resolution of TOF MS analyzers has been substantially improved by using multiple ion passes in multi-pass TOFMS (MPTOF) instruments. These instruments have either ion mirrors for multiple ion reflections (i.e. a multi-reflecting TOF (MRTOF)), such as described in SU1725289, US6107625, US6570152, GB2403063, and US6717132, or between have electrostatic sectors for multiple ion turns (i.e. a multi-turn TOF (MTTOF)) such as described in US7504620 and US7755036.

WO9103071 proposed an orthogonal accelerator for coupling a reflecting TOF MS analyzer with a continuous ion source. A continuous ion beam enters an orthogonal accelerator (OA) in a first direction. Periodic electrical pulses are used to extract ion packets in an orthogonal direction. The duty cycle of the pulsed conversion is strongly enhanced by using long ribbons of continuous ion beams. It was recognized that the product of ion beam width and angular divergence, called emittance, defines the balance between time and energy spreads of ion packets. At limited energy acceptance of TOF MS analyzers, the beam emittance defines the lowest reachable turn around time (TAT), in turn, being one major limit of the TOF MS resolving power. The axial energy spread of the continuous beam (along the beam) defines the angular divergence of orthogonally extracted ion packets, being important for MR TOF MS transmission, where meniscus angular divergence of a few mrad still induces ion losses at prolonged ion paths. In other words, OA-TOF MS and OA-MRTOF MS performances are defined and limited by parameters of continuous ion beams formed within upstream ion transfer interfaces.

OA-TOF MS are widely used in combination with gaseous ion sources like Electrospray (ESI), Atmospheric pressure ionization (APPI), atmospheric Pressure Chemical Ionization (APCI), Inductively coupled Plasma (ICP) and gaseous (MALDI) ion sources. Ion transfer interfaces are used to deliver ions from gas filled (mostly atmospheric) ion sources into the OA located at deep vacuum. Transfer interfaces are arranged with multiple stages of differential pumping and employ radio-frequency (RF) ion guides at intermediate gas pressures, followed by a lens transfer optics in a deeper vacuum, the latter of which shape the ion beam before the OA. The interface performance defines ion beam parameters, which in turn limit the performance of the OA-TOF MS, as explained in the previous section.

Gas filled RF ions guides became an intrinsic part of transfer interfaces since the 1990s, after discovering advantages of collisional ion dampening within radially confining RF guides, initially quadrupoles, proposed in US4963736. Collisional dampening strongly improves ion beam emittances and energy spreads for better ion admission by various MS systems. To arrange a sufficient number of ion to gas collisions, ion guides are placed within intermediate pumping stages at ~10mTorr gas pressures. RF ion guides are terminated by fine apertures (usually 1mm or less) for limiting gas flow into downstream ion optics in the next vacuum stage. Relatively strong extracting fields (few Volts/mm) at the ion guide exit help nearly full ion transmission through the exit aperture. The extracted ion beam is then shaped within a lens system for injection into an OA of a TOF MS. Problems of conventional ion beam extraction through fine apertures are detailed in the specification.

Xu at. el. in Nuclear Instr. and Methods in Physics Research, Vol. 333, p. 274, 1993 describes a hexapole ion guide which extends through a wall, separating two vacuum pumping stages. An RF multipole ion guide that extends continuously between vacuum pumping stages for delivering ions into a TOF MS is proposed in US5652427. The guide may protrude through the differential pumping wall of a CID cell, as proposed in US6753523 for improving ion transmission. Those and other related inventions by C. Whitehouse, incorporating segmented guides, are primarily concerned with improved transmission between stages (segments) of RF multipoles, while minimizing the amount of neutral gas transferred for lowering vacuum pumping cost.

Lens systems of commercial OA-TOF MS are characterized by a number of common features. A fine (1mm) exit aperture at the end of the ion guide serves for reducing the gas downstream of the ion guide. For better ion transmission the ion extraction is arranged to form ion focusing at the aperture plane. The downstream lens optics starts from a point ion source and forms a nearly parallel ion beam at the entrance slit of the OA converter. Preferably, the lens magnifies the spatial ion spread while reducing angular ion spread for a smaller turn around time downstream of the OA. When starting from a point and widely diverging beam, the lens system comprises at least one short focusing lens, which is highly chromatic (i.e. sensitive to ion beam axial energy spread) and is very sensitive to minor misalignments of electrodes. Practical experience tells us that such lens systems shall use side steering to compensate for negative effects produced by the fine apertures and for misalignments of short focusing lens systems. Further improvements of lens systems, such as forming telescopes with strong intermediate acceleration lead to complexity of lens tuning and reduces reproducibility and stability.

The periodic Einzel lens is long known in nuclear physics, as described in: "The current transmission of a periodic electrostatic lens system", W. Huizenga and W. Schuurman, J. Nuclear Energy, Part C, Plasma Physics, Accelerators, Thermonuclear Research, v.6, No5, 1964. The theory of periodic lens is based on transformation matrices, defining phase-space transformation and stability conditions, and can be found. e.g. in "Principles of Charged Particle Acceleration", Stanley Humphries, 2015, Science, originally published in 1986, or in H. Wollnik, "Optics of Charged Particles", Acad. Press, Orlando, FL (1987). Nonlinear effects and fundamental stability in effective potential terms are described in "Stable ion beam transport through periodic electrostatic structures: linear and non-linear effects", A. Verentchikov et. al, Science Direct, Physics Procedia, 1 (2008) 87-97. A periodic lens system provides stable and indefinite ion beam confinement, and may be controlled with a single voltage, applied to periodically repeated lens elements, where a second different potential may be at ground. Though the periodic lens is long known, however, it was never applied as a lens system between RF ion guides and an OA in a TOF MS for multiple practical reasons, including: (i) lens termination on both ends would be

suspected to distort the phase space of the ion beam; (ii) non-linear lens effects may spread and swirl the beam phase space; (iii) advantages for use were not apparent; and (iv) a multi-element system would naturally be viewed as being more complex mechanically.

In summary, ion transfer interfaces for TOF and MRTOF mass spectrometers with orthogonal accelerators employ RF ion guides and lens systems. However, the interfaces of the prior art are characterized by distortion of the ion beam parameters, producing ion beams with higher energy spread and emittances compared to ion beam parameters obtained using collisional dampening of the ions in RF ion guides at intermediate gas pressures, meaning that the interfaces are distorting the collisional dampened ion beams. This in turn limits the resolution and sensitivity of the TOF MS and MRTOF MS.

SUMMARY

The present invention provides a mass or mobility spectrometer comprising:

a first pumping stage and a second pumping stage that is separated from the first pumping stage by a wall having an orifice;

at least one vacuum pump for differentially pumping the pumping stages such that the second pumping stage is at a lower pressure than the first pumping stage;

an ion guide extending continuously from the first pumping stage to the second pumping stage, through the orifice, such that an upstream end of the ion guide is in the first pumping stage and a downstream portion of the ion guide is in the second pumping stage;

wherein the ion guide comprises a plurality of electrodes for radially confining ions and wherein the electrodes define radially extending gaps therebetween;

wherein, in the downstream portion of the ion guide, the gaps are open such that gas is evacuated, in use, radially out of the downstream portion through said gaps; and

wherein, at the upstream end of the ion guide, the gaps are either: (i) blocked such that gas cannot be evacuated radially at the upstream end; or (ii) restricted relative to the gaps in said downstream portion of the ion guide for restricting the evacuation of gas radially at the upstream end.

As the ion guide has an upstream end at which the gaps are blocked or restricted and a downstream portion in which the gaps are open, the ion guide may simultaneously enable both a high pressure within the ion guide at the upstream end and a low pressure within the ion guide at the downstream portion. This enables collisional damping of the ions entering the ion guide in the first pumping stage so that these ions are conditioned for transport through the ion guide into the second, lower pressure pumping stage. This may also enable substantially collision-free passage of the ions at the downstream portion, e.g. such that the ions are conditioned for downstream transmission through an aperture and/or into a mass or mobility analyser.

It is known to arrange an ion guide to extend continuously between adjacent pumping stages, such that the ion guide replaces the conventional differential pumping aperture arranged between such pumping stages and hence minimises ion losses (e.g. see Fig. 1). In such arrangements the ion guide is supported at the junction between the two pumping stages by an insulating support structure. However, it is believed that it is not known to block or restrict the gaps between the electrodes at an upstream end of an ion guide that extends continuously between two pumping stages, so as to effectively raise the pressure at the upstream end of the ion guide (as compared to if the gaps were not blocked or restricted) and enhance collisional damping of ions entering the ion guide.

According to embodiments of the present invention, the gaps at the upstream end may be blocked or restricted such that, in use, the pressure within the upstream end is higher than the pressure within the rest of the ion guide and causes the ions to be collisionally

dampened, whereas the gaps in the downstream portion are open such that the gas is radially evacuated and the pressure therein is such that ions passing therethrough substantially do not collide with gas molecules or collide with gas at a lower rate than in the upstream end portion.

For example, $\leq x\%$ of the ions may collide with gas molecules within the downstream portion of the ion guide, wherein x is selected from: 1; 2; 3; 4 or 5.

The pumping stages are evacuated by the at least one vacuum pump. It will be appreciated that it is one of the at least one vacuum pumps that radially evacuates the gas from the downstream portion of the ion guide. The multiple pumping stages comprise multiple respective vacuum chambers that are evacuated through respective gas exhaust ports by the at least one vacuum pump. The multiple pumping stages are differentially pumped such that stages located further in the downstream direction (away from the ion source and towards the mass or mobility analyser) are pumped to lower pressures. The at least one vacuum pump therefore evacuates the gas from within the ion guide.

Said gaps at the upstream end of the ion guide may be blocked or restricted from a point at the distal upstream end of the ion guide and for a length downstream thereof.

In the embodiments where the gaps at the upstream end are restricted relative to the gaps in said downstream portion of the ion guide, the gaps in the upstream end are not blocked, and instead gas can be evacuated radially from the upstream end. However, as the gaps are restricted relative to those in the downstream portion, gas will be radially evaluated from the upstream end at a lower rate than from the downstream portion.

The gaps in the upstream end may be restricted relative to the gaps in the downstream portion by the gaps between adjacent electrodes in the upstream end being made narrower (orthogonal to the radial direction) than in the downstream portion, such that the gas flow through the gaps is more restricted.

It will be appreciated that the upstream direction referred to herein means in a direction towards the ion source (i.e. the opposite direction to the ion flow). The spectrometer described may comprise an ion source such as a gaseous ion source.

Each of the plurality of electrodes of the ion guide may extend continuously from an upstream distal end of the ion guide to a downstream distal end of the ion guide. In other words, the ion guide is not axially segmented.

The ion guide may further comprises: an intermediate sealed portion between the upstream end and the downstream portion, wherein the gaps of the intermediate sealed portion are blocked such that gas cannot be radially evacuated from within the intermediate sealed portion; and an intermediate open portion between the upstream end and the intermediate sealed portion, wherein the gaps of the intermediate open portion are open such that gas is evacuated, in use, from within the intermediate open portion through said gaps.

The gaps in the intermediate sealed portion (and/or the upstream end) of the ion guide may be blocked by a seal extending circumferentially around the outside of the electrodes such that gas cannot be radially evacuated from that portion; or the gaps may be blocked by plugs located in the gaps between the electrodes.

The seals or plugs described herein may be an electrically insulating material so that they do not electrically connect the electrodes of the ion guide that are in contact with them.

Alternatively, rather that the gaps of the intermediate sealed portion being blocked, the gaps may be restricted relative to the gaps of the downstream portion of the ion guide.

The intermediate sealed portion may extend axially upstream and/or downstream from said orifice.

The intermediate sealed portion may have an axial length selected from the group of: $\geq 10D$, where D is the inscribed diameter of said ion guide; ≥ 20 mm; ≥ 30 mm; ≥ 40 mm; $\geq$

50 mm; and ≥ 60 mm; and/or the intermediate sealed portion may have an axial length L_C, wherein the ion guide has an inscribed diameter D, and wherein $D^3/L_C < 1\ mm^2$.

The gas pressure at the upstream entrance of the intermediate sealed portion may be arranged low enough such that the gas mean free path $\lambda g \geq D$, for suppression of gas conductance through the channel of the intermediate sealed portion by a factor L_C/D, where L_C is the axial length of the intermediate sealed portion and D is the inscribed diameter of said ion guide.

It is contemplated that the downstream distal end of the ion guide may be located in the second pumping stage, or alternatively, that the ion guide may continuously extend through one or more further pumping stage arranged downstream of the second pumping stage. In the latter embodiment, there will be one or more further orifice between the pumping stages, and one or more further intermediate sealed portion may be provided extending axially upstream and/or downstream from each of the one or more further orifice. The radially extending gaps in the axial portion of ion guide between the intermediate sealed portions may be open such that gas is evacuated, in use, from within these portions through the gaps. The axial portion of the ion guide immediately downstream of the most downstream sealed portion may be open such that gas is evacuated, in use, from within this portions through its gaps.

The upstream distal end of the ion guide may be spaced from the upstream wall and downstream wall of the first pumping stage. In other words, the upstream end of the ion guide (having blocked or restricted radially extending gaps) does not correspond to a portion of an ion guide that extends through an orifice in a wall between two pumping stages. The upstream distal end of the ion guide therefore may not be upstream of the first pumping stage.

The ion guide may not pass through or reside within a differential pumping aperture in an upstream wall of the first pumping stage.

The spectrometer may be configured such that, in use, a pressure within the upstream end is ≥ 10 mTorr and/or a pressure within the downstream end of the ion guide is ≤ 1E-6 Torr; and/or such that the ratio of the pressure within the upstream end P_A to the pressure within the downstream end portion P_D is $P_A/P_D \geq 1E+4$.

The portion of the ion guide at the upstream end having said blocked or restricted gaps may have an axial length selected from the group of: ≥ 5 mm; ≥ 10 mm; ≥ 15 mm; ≥ 20 mm; ≥ 30 mm; ≥ 40 mm; ≥ 50 mm; and ≥ 60 mm.

The downstream portion may have an axial length of ≥10D, where D is the inscribed diameter of said ion guide; and/or the downstream portion may have an axial length selected from the group of: ≥ 20 mm; ≥ 30 mm; ≥ 40 mm; ≥ 50 mm; and ≥ 60 mm.

The downstream portion may have an axial length $L_D \geq D^2/2h$ for sufficient gas evacuation, wherein h is the minimum width of the open gaps, perpendicular to the radial direction of the ion guide, and D is the inscribed diameter of said ion guide.

The radial length of each gap defined between adjacent electrodes of the ion guide, in at least the upstream end and/or intermediate sealed portion, may be at least three times the minimum width h of the gap, perpendicular to the radial direction of the ion guide. This relatively long and narrow gap helps prevent stray ions from charging the seal that blocks the exit of the gap in the upstream end and/or intermediate sealed portion.

The inscribed diameter D of said ion guide may be between 2 and 5 mm, or about 3 mm.

The inscribed diameter may be constant along the entire length of the ion guide.

The gaps in the upstream end of the ion guide may be blocked by a seal extending circumferentially around the outside of the electrodes such that gas cannot be radially

evacuated from within the upstream end; or wherein the gaps in the upstream end of the ion guide are blocked by plugs located in the gaps between the electrodes.

The seal or plugs may be an electrically insulating material so that they do not electrically connect the electrodes of the ion guide that are in contact with them.

The ion guide may be a multipole RF ion guide having rod electrodes, such as a quadrupole ion guide.

RF voltage supplies are connected to the electrodes of the RF ion guide so as to supply the RF voltages for radially confining the ions.

The spectrometer may further comprise a lens system arranged downstream of the ion guide for shaping the ion beam received therefrom, wherein the ion path from the ion guide into the lens system is free from apertures having a diameter that is less than the inscribed diameter of said ion guide.

The lens system may comprise electrodes defining an inscribed diameter that is at least twice as large as the inscribed diameter of the ion guide.

The lens system may comprise a plurality of DC electrodes spaced along a longitudinal axis on which ions are received from the ion guide, and DC voltage supplies configured to apply different DC potentials to different ones of said DC electrodes such that when ions travel through the lens system along the longitudinal axis they experience an ion confining force, generated by the DC potentials, in at least one dimension orthogonal to the longitudinal axis.

The plurality of DC electrodes may be apertured electrodes having apertures through which the ions travel as they pass along the longitudinal axis. For example, each DC electrode may be an annular ring electrode or may be a segment of an annulus (i.e. an annular strip).

The DC voltage supplies may be configured to maintain adjacent DC electrodes at different DC potentials, and alternating DC electrodes at the same DC potential.

One of the DC potentials may be a ground potential; optionally wherein the DC electrodes at the distal ends of the lens system are maintained at ground potential in use.

The DC electrode at one or both longitudinal ends of the lens system may have a length, in the longitudinal direction, that is longer than the length of each DC electrode arranged between the end electrodes.

The lens system may pass between at least two differentially pumped stages of the spectrometer.

The spectrometer may comprise a heater for heating electrodes of the lens system.

The downstream end electrode of the lens system may comprise the differential pumping aperture between two pumping stages. This electrode may be heated by the heater.

The ion guide and/or lens system may have a curved longitudinal axis for guiding ions in a curved path.

The may comprise a mass or mobility analyser arranged to receive ions from the ion guide or lens system.

The mass analyser may be a time of flight mass analyser comprising an orthogonal ion accelerator arranged to receive the ions from the ion guide or lens system.

The time-of-flight mass analyser may be: (i) a multi-reflecting time of flight mass analyser having two ion mirrors that are elongated in a drift direction and configured to reflect ions multiple times in an oscillation dimension that is orthogonal to the drift direction, wherein the orthogonal ion accelerator is arranged to receive ions and accelerate them into one of the ion mirrors; or (ii) a multi-turn time of flight mass analyser having at least two electrostatic sectors configured to turn ions multiple times in an oscillation plane,

wherein the orthogonal accelerator is arranged to receive ions and accelerate them into one of the sectors.

The present invention also provides a method of mass spectrometry or ion mobility spectrometry comprising: providing a spectrometer as described herein above; operating the at least one vacuum pump so as to evacuate gas from the ion guide such that the pressure within the upstream end portion of the ion guide is higher than the pressure within the rest of the ion guide; transmitting ions through the ion guide, wherein the ions are collisionally dampened by gas in the upstream end portion but substantially do not collide with gas molecules in the downstream portion, or collide with gas at a lower rate in the downstream portion than in the upstream end portion; and mass analysing or ion mobility analysing ions downstream of the ion guide.

It is contemplated that the upstream end portion of the ion guide (or all portions thereof) need not have gaps that are blocked or restricted. For example, the upstream end portion of the RF ion guide may instead protrude into an upstream pumping stage such that the upstream end portion is at the higher pressure (as compared to the downstream portion in the downstream pumping stage) required to perform the collisional damping.

Accordingly, the present invention also provides a time of flight mass spectrometer comprising: first, second and third interconnected pumping stages; at least one vacuum pump for evacuating the pumping stages; an ion guide continuously extending from first pumping stage to the second pumping stage; an orthogonal ion accelerator and at least one ion mirror or electrostatic sector arranged in the third pumping stage, wherein the orthogonal ion accelerator is configured to pulse ions into the ion mirror or electrostatic sector; and a lens system between the ion guide and orthogonal ion accelerator, wherein the ion path from the ion guide into the lens system is free from apertures having a diameter that is less than the inscribed diameter of said ion guide.

The spectrometer may have any of the features described above in relation to the first aspect, except that the upstream end of the ion guide need not have gaps that are blocked or restricted.

For example, the pressure within the upstream end portion may be $\geq$ 10 mTorr and/or the pressure within the downstream end portion of the ion guide may be $\leq$ 1E-6 Torr; and/or the ratio of the pressure within the upstream end portion P_A to the pressure within the downstream end portion P_D may be $P_A/P_D \geq 1E+4$.

Further pumping stages may be provided between the first and second pumping stages, and the ion guide may continuously extend through those further pumping stages.

The spectrometer may be configured such that the at least one vacuum pump pumps the first and second pumping stages such that, in use, the pressure within the upstream end portion of the ion guide is higher than the pressure within a downstream end portion of the ion guide and such that the ions are collisionally dampened in the upstream end portion but substantially do not collide with gas molecules in the downstream end portion, or collide with gas at a lower rate than in the upstream end portion.

The lens system may comprise a plurality of DC electrodes spaced along a longitudinal axis on which ions are received from the ion guide, and DC voltage supplies configured to apply different DC potentials to different ones of said DC electrodes such that when ions travel through the lens system along the longitudinal axis they experience an ion confining force, generated by the DC potentials, in at least one dimension orthogonal to the longitudinal axis.

The lens system may comprise electrodes defining an inscribed diameter that is at least twice as large as the inscribed diameter of the ion guide.

The plurality of DC electrodes may be apertured electrodes having apertures through which the ions travel as they pass along the longitudinal axis. For example, each DC

electrode may be an annular ring electrode or may be a segment of an annulus (i.e. an annular strip).

The DC voltage supplies may be configured to maintain adjacent DC electrodes at different DC potentials, and alternating DC electrodes at the same DC potential.

One of the DC potentials may be a ground potential; optionally wherein the DC electrodes at the distal ends of the lens system are maintained at ground potential in use.

The DC electrode at one or both longitudinal ends of the lens system may have a length, in the longitudinal direction, that is longer than the length of each DC electrode arranged between the end electrodes.

The lens system may pass between at least two differentially pumped stages of the spectrometer, e.g. between the second and third pumping stages.

The spectrometer may comprise a heater for heating electrodes of the lens system.

The downstream end electrode of the lens system may comprise the differential pumping aperture between two pumping stages. This electrode may be heated by the heater.

The ion guide and/or lens system may have a curved longitudinal axis for guiding ions in a curved path.

The spectrometer may comprise a mass or mobility analyser arranged to receive ions from the ion guide or lens system.

The time-of-flight mass spectrometer may comprise: (i) a multi-reflecting time of flight mass analyser having two ion mirrors that are elongated in a drift direction and configured to reflect ions multiple times in an oscillation dimension that is orthogonal to the drift direction, wherein the orthogonal ion accelerator is arranged to receive ions and accelerate them into one of the ion mirrors; or (ii) a multi-turn time of flight mass analyser having at least two electrostatic sectors configured to turn ions multiple times in an oscillation plane, wherein the orthogonal accelerator is arranged to receive ions and accelerate them into one of the sectors.

The second aspect also provides a method of time of flight mass spectrometry comprising: providing a time of flight spectrometer as described herein; operating the at least one vacuum pump so as to evacuate gas from the ion guide such that the pressure within the upstream end portion of the ion guide is higher than the pressure within the rest of the ion guide; transmitting ions through the ion guide, wherein the ions are collisionally dampened by gas in the upstream end portion but substantially do not collide with gas molecules in the downstream end portion, or collide with gas at a lower rate in the downstream end portion than in the upstream end portion; transmitting the ions to the orthogonal ion accelerator using the lens system; and pulsing the ions into the ion mirror or sector for time of flight mass analysing the ions.

The inventor has identified several problems of prior art ion transfer interfaces for OA-TOF MS: e.g. ion extraction from gas filled RF ion guides distort the ion beam parameters by a strong extracting field at the presence of fringing RF fields and at the presence of gas collisions; extraction through fine apertures produces surface charging (say, of oil or droplet coated metal); extraction through a fine aperture forms a short-focusing lens being highly chromatic and having large aberrations; coupling between RF ion guides and lens systems are not optimized; lens systems are not robust, they are difficult for tune, and are susceptible to misalignments; lens systems operate at elevated pressures at 1E-4 to 1E-5Torr, spreading the ion beam in gas collisions; if using beam collimators for limiting ion beam phase space, the effect of ion on surface sliding collisions produce a beam halo. Those effects deteriorate parameters of continuous ion beams, which in turn limit parameters of OA-TOF and of OA-MRTOF mass spectrometers.

All those problems are linked to relatively high gas pressure at the exit of RF ion guide and the use of a fine exit aperture. Dropping the gas pressure at the ion guide exit was unthinkable because of ion beam distortions during passage between ion guides, separated by apertures. Using protruding ion guides was unthinkable because of the limited gas pressure ratio (limited to a factor of 100 to 1000 in the prior art), where vacuum conditions at the exit end were not compatible with collisional dampening conditions at the entrance end.

The inventor realized that, in embodiments of the present invention, a protruding RF ion guide, most favorably quadrupolar, may be used for non-distorting ion transfer between regions with dampening gas collisions and deep vacuum, if arranging long radially sealed channels, alternated with open areas for gas evacuation, and if optimizing parameters of the ion guide for a substantial pressure drop above a factor of 1E+5 along the ion guide. While the collisional dampening may require gas pressures above 1E-1mTorr if using short (e.g. a few cm) ion guides, the collision free ion beam formation in the lens system may require gas pressures under 1E-6Torr to scatter less than 1% of ion beam during a 10cm long ion path. To reach such an unprecedented pressure drop, embodiments of the invention propose: (a) arranging alternating segments of radially sealed and open segments of a continuous ion guide (b) a local rise of gas pressure within a first radially sealed channel with continuum gas flow conditions; (c) substantial suppression of gas conductance in the second radially sealed channel at rarified gas flow conditions; and (d) arrangement of sufficient gas conductance in open segments; where ion guide parameters are balanced for satisfying all the requirements and to form a sweet spot range, as described below.

The inventor further realized that the optimized protruding ion guide allows using wide extracting apertures and soft extracting fields. The proposed extraction methods and parameters overcome most of the prior art faults and according to simulations, allow reaching unprecedented small emittance of the ion beam, being under 0.5mm*deg at 30eV beam energy, which is three to five times lower compared to reported prior art ion beam parameters.

The inventor further realized that using a periodic lens, being novel for TOFMS interfaces, appears an effective replacement for lens systems downstream of RF ion guides for a number of reasons: it is robust since it may be controlled by varying a single voltage; it is insensitive to minor misalignments and does not require ion beam steering; it passes ion beams without non linear distortions and allows retaining small phase space and energy spread of ion beams; it avoids ion on surface scattering; it appears a strong gas flow restrictor; and finally, it can be bent, curved or passed between differential pumping stages.

The proposed ion guide and periodic lens may form continuous ion channels with constant radial ion confinement. Both of those components may be bent at large radius (compared to inner diameter), which helps more compact interface packaging, including a spiral interface arranged around a split flow turbo-molecular pump cartridge.

According to an embodiment of the invention, there is provided a time-of-flight mass spectrometer, comprising conventional components: a gaseous ion source, generating an ion beam; a multi-stage differentially pumped ion transfer interface with stages separated by differential apertures; a gas filled radio-frequency (RF) ion guides for collisional dampening and transfer of said ion beam; a lens system for transferring and shaping said ion beam past said ion guide; an orthogonal accelerator for pulsed extracting of ion packets from the ion beam past said lens system; and a singly reflecting, or multi-reflecting, or multi-turn electrostatic analyzer for mass separation of said ion packets;

wherein for the purpose of non distorting ion transfer of collisional dampened ion beam into said orthogonal accelerator, one of said RF ion guides satisfies the following range of parameters:

a) said RF ion guide is quadrupolar, i.e. composed of four parallel rods, wherein the inner bore between rods with the inscribed diameter d is continuous and non distorted at the entire guide length;

b) the guide comprises at least four segments A to D, formed by electrically insulating radial seals around said rods, alternated with open rod areas having gaps between rods for gas evacuation;

c) the entrance segment A of said RF ion guide has said radial seal, which either serves as a differential aperture, or the segment A resides past a differential aperture and said radial seal has length L_A>1mm/P_A(Torr), where P_A - is the gas pressure within segment A, accounting local raise of the gas pressure at a limited gas conductance along the guide rods;

d) the next segment B is open (no radial seal) and is arranged for sufficient radial gas evacuation, achieved at segment length $L_B \geq 10d$ and at the gap width h between the guide rods being $h>d/4$;

e) the next segment C has said radial seal which protrudes through the differential pumping wall, thus forming a differential channel of length $L_C \geq 10d$;

f) the gas pressure P_C at the entrance of segment C is arranged low enough for gas mean free path $\lambda g \geq d$ for suppression of gas conductance of said channel by factor L_C/d;

g) the exit segment D is open (no radial seal), it has length $L_D \geq d^2/2h$ for sufficient gas evacuation, and the gas pressure P_D at the segment end is arranged $P_D \leq$1E-6Torr for collisional free ion beam formation in the subsequent lens system; and

h) the exit of said ion guide is open and aligned with the entrance of said lens system without using any aperture with diameter less than d.

Optionally, said lens system may be a periodic lens, energized by at least two distinct DC potentials with one potential optionally being at ground; wherein inscribed diameter of said periodic lens is at least twice larger than D.

Optionally, P_A/P_D>1E+4; wherein the inscribed diameter D of said ion guide may be between 2 and 5mm, preferably 3mm; and wherein D^3/L_C<1mm^2.

Optionally, to prevent charging of said radial seals, the gap between electrodes of said quadrupole may be at least three calibers long H: $H/h \geq 3$.

Optionally, the electrode shape at the entrance of said periodic lens attenuate the filed of said periodic lens to provide for acceleration of continuous ion beam at the exit cross section of said ion guide being less than 10% the beam mean energy at the entrance of said orthogonal accelerator.

Optionally, said periodic lens may be a rigid structure made by cutting conductive tube with electro erosion into two combs; and wherein ends of said periodic lens may be aligned with axis of said RF ion guide and of said orthogonal accelerator.

Optionally, said periodic lens may be heated to at least 150^{o}C for reducing oil deposits on the hot lens surface, this way avoiding surface charging by ions.

Optionally, said periodic lens may pass between at least two differentially pumped stages.

Optionally, said periodic lens may continue through fringing fields and electrode boundaries of said orthogonal accelerator.

Optionally, at least one of said periodic lens or said RF ion guide may be curved.

According to an embodiment of the invention, there is provided an ion transfer interface between a gaseous ion source and a mass spectrometer comprising

a) a cartridge multi-stage turbo-molecular pump;

b) at least one ion optical component of the list: (i) RF ion guides; (ii) analytical quadrupole; (iii) ion mobility separator; (iv) CID cell; and (iv) periodic lens; and

c) wherein said ion optical component are arranged spiral, thus forming a spiral ion path, surrounding said cartridge pump.

BRIEF DESRIPTION OF THE FIGURES

Various embodiments will now be described, by way of example only, and with reference to the accompanying drawings in which:

Fig.1 shows a prior art time-of-flight mass spectrometer with an orthogonal accelerator (OA-TOF MS), incorporating a protruding RF ion guide within an ion transfer interface, arranged for improved ion transmission and for reduced gas load onto pumping system;

Fig.2 shows an embodiment of an OA-TOF MS of the present invention, incorporating an ion transfer interface with an improved protruding ion guide, with an optimized ion extraction downstream of the guide, and with a periodic lens for ion transfer - arranged and improved for collisional ion dampening and for the non-distorted ion transfer of the dampened ion beam all the way to orthogonal accelerator;

Fig.3 shows an improved protruding RF ion guide, providing pressure drop over 10,000 times to satisfy both sufficient dampening at the guide entrance and collision free vacuum conditions at the guide exit;

Fig.4A shows results of ion optical simulations of ion extraction downstream of the RF ion guide through a wide open aperture, while accurately accounting for three-dimensional fields and considering effects of mutual component misalignment;

Fig.4B presents graphs summarizing the results of simulations in Fig.4A;

Fig.5 shows an embodiment of a periodic lens downstream of the improved ion guide, having a wide open exit at deep vacuum conditions;

Fig.6A shows results of ion optical simulations of ion beam extraction downstream of the RF ion guide and of ion beam formation within periodic lens systems considering effects of mutual component misalignment;

Fig.6B presents graphs summarizing the results of simulations in Fig.6A; and

Fig.7 shows and embodiment of a spiral ion transfer interface arranged around a cartridge multi-stage turbo-molecular pump, arranged for compact interface size.

DETAILED DESCRIPTION

Fig.1 shows a prior art OA-TOF MS 100 comprising: a gaseous Electrospray ion source ESI; an ion transfer interface 10; and a TOF mass analyzer 20 with an orthogonal accelerator 24. Ion transfer interface 10 comprises: multiple stages of differential pumping 11-14, interconnected by fine differential pumping apertures and evacuated by pumps S1-S4; an ion guide 15 (here an RF multipole), continuously extending between stages 12 and 13; a terminating differential aperture 19 downstream of ion guide 15; and a lens 22. The feature of RF ion guide 15 is common for US5689111, US5652427, US6753523, and US7034292, and is claimed to enhance ion transmission, thus reducing requirements on the pumping systems.

In operation, ions are sampled together with gas from atmospheric pressure ESI source via a set of separating apertures. Differential pumping in stages 11-14 helps quick reduction of the gas pressure, described as: P1=1Torr, P2>50mTorr (but less than P1), and P3=1mTorr (but less than P2). P2>50mTorr is claimed as necessary for collisional ion dampening. The prior art recognizes that P4 shall be under 1E-6Torr for non-scattered ion transmission in the TOF 20, thus, requiring aperture 19 to have a diameter less than 1mm.

Ion transmission is claimed to be improved by the RF ion guide 15 extending between vacuum chambers. Gas collisions in RF ion guide 15 help dampen the ion beam diameter and the axial energy and enhance the ion transmission through the channel 17 and

through aperture 19. The exiting ion beam 21 is focused by lens 22 into a parallel ion beam 23 at the entrance of OA 24. Ion beam energy is described as being 5eV, while axial energy spread has been measured as being about 1eV, meaning that lens 22 is strongly chromatic.

The cross section of ion guide 15 is described in US5689111 and is shown in Fig.1. The guide is a hexapole of six rods 16 mounted on the inner surface of an insulating ring 18, which arrangement exposes the insulating surface to stray ions. To reduce the gas conductance, the inner diameter D of ring 18 is chosen to be small (D=2mm, which is small relative to most prior art ion guides having D from 5 to 10mm), which still allows effective ion transmission at P2/P3>50. Channel 17 through ring 18 is depicted short, less than D. Indeed, the chosen P2>50mTorr gas pressure corresponds to continuous (Vs rarified) gas flow, and an elongation of channel 17 would have minimal effect on gas conductance, while increasing the harm due to a greater amount of exposed insulating surface of ring 18. The radial RF field confines the ion beam to a width w being smaller than D, thus, the guide provides nearly full ion transmission for a wide m/z range of ion species. The guide 15 is terminated by aperture 19, which reduces gas load into stage 14, while stated as being sufficient for nearly lossless ion transfer into optics 22.

Though the aperture 19 and lens system 22 are not explicitly described within the cited prior art, they may be generalized based on common properties of commercial interfaces for OA-TOF MS. The exit aperture 19 is chosen to be small, in the range of 0.5-1mm, but still sufficient for ion transfer at minimal gas flow into the TOF analyzer 20 to sustain a vacuum better than 1E-6Torr. Ions are extracted from the RF guide 15 by DC fields of aperture 19. The extracting fields shall be sufficiently strong to form a short focusing lens in order to transfer the ion beam through the aperture 19, thus forming a widely diverging beam downstream of the aperture. Lens 22 (looking like the Einzel lens of Fig.1) forms a nearly parallel and expanded ion beam 23 at the entrance of the OA 24. Because of the short focal distance at ion extraction into aperture 19, the lens system is very sensitive to minor side misalignments, which requires additional ion beam steering in the lens 22.

Prior art interfaces for OA-TOF MS (similar to interfaces for other MS, like 3Q) are known to provide nearly 100% ion transmission through the stages at intermediate gas pressures, regardless of whether using protruding RF ion guides of the type described above or using RF guides separated by apertures. Split flow turbo-molecular pumps with multiple ports allow economic arrangement of multiple pumping stages, in turn allowing larger size apertures between stages, this way providing very effective ion transmission all the way downstream of the first sampling nozzle. Thus, the goal of high ion transmission is solved regardless of using protruding RF ion guides (i.e. ion guides that continuously extend between multiple stages), which in turn explains why protruding ion guides are not popular in commercial TOF MS. However, known interfaces still bare several principal mistakes in the arrangement of the final RF guide stage and of the following ion optics, which spreads the ion beam phase space and energy spread of continuous ion beams, directly affecting the combination of Turn-around time (TAT) and energy spread (dK) of ion packets within TOF and MR-TOF analyzers, in turn, limiting TOF MS and MRTOF MS resolution and sensitivity.

The exemplary OA-TOF MS of Fig.1 has the following problems:

(i) exposure of insulating surfaces in the separating channel of protruding RF ion guide, whose charging distorts the ion beam emittance and energy spread;

(ii) too high pressure at RF ion guide exit (P3=1mTorr) requires a small size of the exit aperture 19, otherwise causing ion on gas scattering in the subsequent lens system;

(iii) to pass ions through fine aperture 19, the extracting DC field shall be a few Volts/mm, which causes ion on gas scattering at ion extraction and also may produce the non-adiabatic termination of RF fields;

(iv) because of residual oil coatings and because of contamination by droplets, fine aperture 19 is partially charged by ions,

(v) the fine aperture acts as a distorting lens, and is susceptible to minor side displacements, which requires subsequent ion beam steering;

(vi) the chromatic regime of lens operation produces angular beam spreading; and

(vii) too high a gas pressure in the lens system spreads the ion beam.

Embodiments of the invention collisionally dampen ions within the RF ion guide and retain the thus achieved small phase space and energy spread of the dampened ion beams all the way through to the final stage of the RF ion guide, through the lens system, and into the orthogonal accelerator.

Embodiments of the invention provide: an improved protruding RF ion guide (i.e. an ion guide that extends continuously between multiple stages); a set of optimal parameters (sweet spot) of the protruding RF ion guide; termination of the guide with a wide open aperture; and optimal parameters of ion extraction downstream of the guide. The guide may be coupled to a periodic lens for ease of tuning and for the ability of curving the interface between the ion source and mass analyser.

Fig.2 shows an embodiment 200 of an OA-TOF mass spectrometer of the present invention comprising: a front-end interface 30 with an ESI source at atmospheric pressure; a low pressure interface 40; and TOF or MRTOF analyzer 60. Those main components share differentially pumped stages 1 to 6, evacuated by mechanical pumps MP1 and MP2, and by differential ports S3 to S6 of turbo-molecular pump TMP.

Interface 30 is exemplified by differential stages 1-3, comprising: an RF ion funnel or tunnel ion guide 31 at pressure P1~10 Torr; an RF funnel, or tunnel, or multipole ion guide 32 at pressure P2~1 Torr; and an RF quadrupole 33 at pressure P3~0.1 Torr. At typical pumping speeds of mechanical pumps S1 and S2 and of the drag stage S3 of turbo-molecular pump TMP (S1~S2~S3~10 L/s), the diameter of the differential pumping apertures sizes may be: a1 is from 0.5 to 1mm (or a heated 1 mm inner diameter capillary), and a2~a3~2mm, which is known to be sufficient for nearly lossless ion transmission all the way downstream of nozzle a1. Front end interface 30 may be arranged similar to a variety of prior art front ends, although it is desired that P_3>10mTorr, and that the gas flux Q_4 through aperture a4 remains under 1Torr*L/s, for optimal operation of the low pressure interface 40. The gas pressures P1-P6 may be as given in Fig. 2, assuming approximately S4~S5~S6~100 L/s pumping speeds of differential ports of the split flow turbo-molecular pumps, constructed from (most popular in mass spectrometry) 300L/s turbo-pumps.

Interface 40 comprises: a protruding ion guide 41 and periodic lens 51, located within differentially pumped stages 4 and 5. Ion guide 41 is preferably a quadrupole (for stronger ion beam confinement between known RF ion guides) and comprises a set of four rods 42 that are connected to radially sealed and insulating supports 43 and 45, thus forming longitudinal channels 44 and 46 and defining four segments A-D of the otherwise continuous guide. The term "continuous" means that the inner bore of the ion guide with diameter D and surrounding features of the guide rods remain constant and non-distorted through the entire guide length. The guide 41 may be aligned with the lens 51 by centering ring 47. The periodic lens 51 comprises; two conductive combs 52, forming alternating potential rings with inner channel 56 of diameter D_L, where inner lens diameter is wide D_L>2D to reduce lens non-linear effects; slits and slots 53 and 54, serving for electrodes 52 separation and alignment; an aligning support 55; a heater 57 for heating the lens assembly above 150 Celsius; and an exit collimating slit 58.

In operation, ions are sampled together with gas from gaseous ion source IS through apertures a1 to a6. Ions are confined radially by RF ion guides 31, 32, 33 and 41, while gas is evacuated via differential pumping ports of mechanical pumps MP1 and MP2 and of multi-stage turbo pump TMP. The gas pressure drops along the interface from 1 atmosphere down to less than 1E-8Torr in TOF analyzer at stage 6.

Rarified gas flow at $P_5 \leq$1E-6Torr is already achieved in stage 5, where the ion beam transfer is controlled by fields of periodic lens 51, while the vacuum is strong enough to limit the scattering of ion due to gas collisions to less than 1% of the ions. At the same time, the embodiment provides a sufficiently high gas pressure at the entrance of the ion guide 41 for collisional ion dampening at the ion guide 41 entrance. The rest of the guide 41 is arranged for non-distorting ion transfer through guide 41, thus delivering a well dampened ion beam into the strong vacuum of P5.

At the exit of RF ion guide 41 ions are extracted into a wide bore of periodic lens 51, in contrast to the fine aperture at the ion guide exit of known instruments. This becomes possible because of the high vacuum at the guide 41 exit. As described below, the ion extraction may be optimized at extracting DC fields of less than 1V/mm (preferably 0.5V/mm) to form a slowly diverging ion beam. The beam may then be refocused by periodic lens 51 to form a parallel ion beam of a few mm width. Focused and collimated beam 59 enters OA 61. Periodic voltage pulses are applied to OA61 to extract ion packets in the orthogonal (X) direction for mass spectrometric analysis in the TOF analyzer, presented here by the orthogonal accelerator 61, drift space 64, ion mirror 65 and detector 66.

Referring to **Fig.3**, equation 300 states an optional goal for the protruding ion guide 41, schematic 301 shows ion guide 41 in the XZ-plane, view 302 shows a cross section of segment A or C in the XY-plane, and gas flow model 303 illustrates the efficiency of gas evacuation between the guide rods in segments B and D.

Equation 300 set limits onto two gas pressures, i.e. the pressure P_A at the entrance part of protruding guide 41, and pressure P_D at the guide exit. The relationships provide three features of the protruding ion guide: (a) to dampen the ion beam in a dense gas at P_A>10mTorr and $L_A P_A$>1Torr*mm (where LA is the length of radially sealed section A of the ion guide), which are known to be sufficient for achieving smallest phase space and energy spread of the ion beam; (b) to preserve the achieved beam parameters all the way to vacuum conditions, which is achieved by continuation of the non-distorted rod geometry through the differential pumping wall of the pumping system; and (c) to reach high vacuum conditions at the guide exit with P_D<1E-6Torr, where ion on gas collisions are practically avoided at the exit of the ion guide and within the subsequent lens system.

The pressure limits in relation equation 300 are defined by the mean free path λ_i =1cm/P(mTorr) for mid-size 1000amu ions. Accounting for realistic lengths of the ion guide and lens system being in the range of 10cm, the pressure P_A>1E-2Torr (preferably 30 to 100mTorr) is required to provide for approximately 100% ion to gas collisions at the ion guide entrance, while P_D<1E-6Torr is needed at the guide exit to reduce the amount of scattered ions to under 1% of the ions.

Note that to reach such a large pressure ratio (e.g. P_A/P_D>1E4) at realistic pumping rates (e.g. S_5=100L/s) of a mid-sized TMP, and if using a single separating aperture within the ion guide, the a5 aperture diameter of the protruding ion guide shall be under 0.3mm, which does not allow making a non-distorted cross section of the ion guide without strongly compromising the guide acceptance at the entrance part.

This problem is solved in the embodiments of the present invention by arranging electrically insulating and longitudinally elongated radial seals 43 and 45, this way splitting the otherwise continuous ion guide into four segments A to D. This provides four features: (i) the longitudinal channel 44 within radial seal 43 at the guide entrance provides for a

local rise of gas pressure, since the gas within channel 44 cannot be radially evacuated; (ii) longitudinal channel 46 within radial seal 45 may operate in the free molecular regime at Knudsen number Kn>1, so that the gas conductance of channel 46 becomes suppressed proportionally to the number of channel calibers that the length of the channel corresponds to; and (iii) segments B and D provide for sufficient gas evacuation at moderate elongation if accounting for gas pressure drop along those sections (since segments B and D are not radially sealed and so are able to be radially evacuated). In addition, improved shapes of the electrodes may be used to prevent the insulators 43,45 electrically charging within radially sealed channels 44 and 46 due to ion strikes.

Referring to views 301 and 302 in Fig. 2, the guide may comprise four rods 42 with a small inscribed diameter D, selected in the range between 2 and 5mm, and preferably being about 3mm. Radial seals 43 and 45, which may also be used as holders for the electrodes, may be arranged to separate guide 41 into four longitudinal segments A-D with lengths L_A-L_D of otherwise continuous ion guide 41. The three last segments may be at least ten calibers long, i.e.:

$$L_B/D \geq 10;\ L_C/D \geq 10 \text{ and } L_D/D \geq 10 \qquad (1)$$

The gas pressures and parameters of the segments may be chosen to be optimal to provide for:

- in segment A, ion dampening at a locally raised gas pressure in channel 44;
- in segment B, effective gas evacuation, e.g. to P_4=1-10mTorr;
- in segment C, strongly restricted gas flow through channel 46, e.g. at Kn>1;
- in segment D, effective gas evacuation, e.g. to $P_4 \leq$1E-6Torr, for a collision free ion beam in lens 51;
- between segments, efficient ion transfer of ion beam without distorting the small ion beam phase space and axial energy spread, earlier achieved in front segment A;
- at the exit of segment D, collision free and optionally adiabatic (more than two RF cycles) ion extraction with weak DC electric fields to avoid spreading of the ion beam phase space and energy;
- at the exit of segment D, ion extraction with weak electrostatic fields, while avoiding use of a fine aperture, where the exit aperture may be the front portion of a wide open periodic lens 51.

Referring to view 302, segment C is shown in XY-cross section (although segment A would have the same cross section). Radial seal 45 is representative for the seal in segments A and C, while rods 42 are representative for all segments of the smooth and non-interrupted ion guide 41. Rods 42 may be split from a single block or tube by electrical discharge machining (EDM), e.g. from stainless steel. Machining may be used for materials with lesser internal stress, e.g. low stress grades of Ti. For better mechanical stability, the rods may use materials like ceramics of aluminium, further chemically coated with electroless nickel. The rods may be arranged such that circumferentially adjacent rods are separated by a narrow gap (e.g. h~1mm) and such that these gaps define relatively long conduits 48 in the radial direction (e.g. H/h>3) so that stray ions do not impact on the insulator seals 43,45. This prevents electrical charging of insulators 43 and 45, this way avoiding ion beam distortions of the confined ions passing through channels 44 and 46.Slots 49 may be made either in rods 42 or in the insulating supports 43 and 45 to prevent surface electrical leaks or discharges between opposite RF phases that may occur due to the RF voltages applied to the rods (typically having V_{RF}=0.3-0.5kV amplitudes, measured zero to peak). Both gaps 48 and slots 49 increase the gas conductance of channels 44 and 46. However, the effect is moderate in channel 44 (less than a factor of two) and is negligible in

channel 46, accounting for free-molecular gas flow regime within long and narrow gaps, where the conductance of slots and gaps is further suppressed at larger number of channel calibers.

The entrance channel 44 in segment A is sealed radially, either by insulating holder 43, or by insulating plugs inserted between circumferentially adjacent rod electrodes, or by locally narrowing the gaps h between circumferentially adjacent rod electrodes. The gas conductance along ion guide 41, i.e. along the z-axis, is about 1.5L/s at D=3mm. As shown below, the effective gas conductance between rods within segment B exceeds the pumping speed S_4=100L/s, i.e. it is the pump speed S_4 which controls pumping efficiency in segment B. Thus, the limited conductance of channel 43 provides for a local rise of gas pressure P_A at the guide entrance, estimated to be about 30-50 times higher than the pressure at the downstream end of segment B ($P_B \cong P_4$). With flexible choice of the gas pressure P_3 upstream of the ion guide 41 and of the aperture $a4$ size, the local rise of gas pressure P_A may be primarily limited by requirements of the downstream pumping, where the gas flux from the upstream pumping stages may be adopted using flexible parameters of the upfront interface 30.

It has been recognized that there are at least two ways of producing a local rise of the entrance gas pressure P_A. In one embodiment, the upstream gas pressure P_3, the entrance aperture conductance $a4$ and the length of the entrance channel L_A of segment A of the ion guide 41 are chosen for sufficient collisional ion dampening, while keeping sufficiently low pressure P_4, e.g. :

$$P_A L_A > 1\text{Tor*mm at } P_4 < 10\text{mTorr} \qquad (2)$$

The above estimates of the channel gas conductance and of the pumping speed behind the entrance channel support the opportunity for satisfying equation (2).

In another embodiment, the entrance channel of ion guide 41 is formed by protrusion of the guide 41 into the upstream pumping stage 3, this way supporting collisional gas dampening at the entrance of continuous ion guide 41.

Again referring to **Fig.3**, segment B is shown by an equivalent pumping scheme 303. A long channel with diameter D is continuously evacuated through four side slots having width h. Efficiency of gas evacuation between rods is greatly enhanced because of the axial gas pressure gradient (the effect is similar to efficiency of differential pumping). Axial conductance S_A of the guide is proportional to D^2, while radial conductance through four gaps S_R per caliber is proportional to $4hD$. Relatively long radial slots, e.g. with H/h>3, do not affect the radial conductance through the gaps 48, unless gas pressure drops to a few mTorr, i.e. gas flow is in the continuum regime at the slot beginning and in the transition regime downstream. Using a simple model of multi-stage dilution, the gas pressure drops per single caliber (i.e. per length equal D) by a factor $1/(1+S_R/S_A) = 1/(1+4h/D)$. If supported by infinitive pumping S_4, the pressure would drop by a factor:

$$P_B/P_A = 1(1+4h/D)\text{^}N \qquad (3)$$

For arranging sufficient gas evacuation between rods, embodiments of the invention propose a combination of $L_B/D \geq 10$ and $h > D/4$, sufficing for up to P_B/P_A = 2^10 =1000 pressure drop along segment B.

Note that similarly accounting for narrow and long gaps H/h>3, and accounting for free molecular gas flow regime in the exit segment D, one may derive the safe requirement $L_D/D \geq 20$ and $h > D/4$ for providing sufficient gas evacuation in the last segment D.

The proposed ion guide capitalizes on the effect of limited gas conductance at free-molecular and transition gas flows, achieved at the small inscribed diameter D of ion guide 41 ($2 \leq D \leq 5$mm) and at low (compared to 50mTorr in prior art US5652427) gas pressures P_B at the entrance of channel 46 (e.g. $1 < P_B < 10$mTorr). The molecular flow is characterized by Knudsen number $Kn = \lambda_g / D > 10$, and the transition flow is characterized by $10 > Kn < 0.1$, where λ_g is a mean free path in gas. In air, $\lambda_g \cong 50$mm/P(mTorr), then for the largest proposed diameter D=5mm and P_B=1 to 10mTorr, one can calculate the Knudsen number for separating channel (in segment C) as $1 < Kn < 10$, i.e. safely $Kn \geq 1$.

In free molecular flow ($Kn > 10$) the gas conductance drops proportionally to the number of calibers L_C/D that the length of the channel 46 corresponds to. In transition flow ($10 > Kn < 0.1$), the effect is corrected by a coefficient f depending on Knudsen number $f(Kn)$, however with correction being minor $f \cong 1$ at $Kn \geq 1$ (see www.springer.com/978-3-658-13535-5). Then at $Kn \geq 1$ the pressure ratio $P_B/P_D \cong P_5/P_4$ between stages surrounding channel 46 is:

$$P_B/P_D \cong \upsilon * \pi D^3 / 12 L_C S_5 \cong \upsilon D^3 / 4 L_C S_5 \qquad (4)$$

where $\upsilon = sqrt(kT/m)$ is an average gas velocity, $\upsilon \cong 400$m/s in air

To reach $P_B/P_D < 1E\text{-}3$ at S_5=100L/s, one shall satisfy a reduced geometrical relation:

$$D^3/L \leq 1 \text{ mm}^2 \qquad (5)$$

The reduced equation (5) sets limits as $L_C \geq 8$mm at D=2mm; $L_C \geq 27$mm at D=3mm, and $L_C \geq 64$mm at D=4mm - all being realistic, and extending the prior set limit $L_4/D > 10$ at D>2.2mm. This allows keeping very low gas pressure P_D past channel 46:

$$P_D < 1E\text{-}6 \text{ Torr} \qquad (6)$$

Summarizing the above, embodiments of the invention propose an improved arrangement of the protruding ion guide with at least two longitudinally extending radial seals, and the following range of "sweet spot" parameters may be used for the protruding RF ion guide 41.

To simultaneously provide collisional dampening at the guide entrance and collision free ion transfer at the guide exit, the protruding ion guide may have at least four segments A-D. The radial gas seal in segment A (or protrusion into an upstream pumping stage) arranges a local rise of gas pressure, e.g. with $P_A L_A >$ 1Tor*mm, accounting for a limited gas conductance along the rods. In second segment B, sufficient gas evacuation is provided, e.g. at length $L_B/D \geq 10$ and gap $h > D/4$. In third segment C, a longitudinal channel, e.g. at $L_C/D \geq 10$, may be arranged for the substantial reduction of the channel gas conductance, e.g. where gas pressure may be $P_C < 10$mT and $D < 5$mm for arranging free molecular or transition gas flow at Kn>1. The conductance of channel C may be further reduced to $D^3/L \leq 1 \text{ mm}^2$ for ensuring a high vacuum at the guide exit, e.g. with $P_D < 1E\text{-}6$Torr. In segment D, a yet longer channel, e.g. $L_D/D \geq 20$, may be used for sufficient gas evacuation, e.g. at $H/h > 3$ and $h > D/4$. As shown below, the gas evacuation past segment D may be enhanced by a gap between the guide and the lens and by slots of the lens. As shown below, the periodic lens may also serve as a long channel suppressing gas flow into the TOF spectrometer.

To summarise, the elongated radial gas seals of the ion guide provide for a substantial drop in gas pressure from a collisional dampening region to high vacuum conditions, while providing for sufficient flexibility in guide parameters. The gas limits in the various segments A-D of the ion guide may be as follows: (i) $P_A/P_D > 1E+4$; (ii) $P_B < 1E$-

6Torr and P_A>1E-2Torr; and (iii) P_B<1E-6Torr and P_A>1Torr/L_A(mm), where L_A is the length of said first segment.

Figs.4A and **4B** present results of ion optical simulations of ion extraction from RF ion guide 41 to ion optical system 51. Picture 400 shows ion trajectories at various extraction potentials U_E. Energy distributions 405 are compared for high 1E-2Torr and low 1E-6Torr pressures at the ion guide exit. Set of plots 406-409 present various ion beam parameters as a function of the normalized extraction potential.

Referring to **Fig.4A**, ion trajectories 400 are shown for the extraction of 1000amu ions from a 3mm inner diameter quadrupolar RF ion guide 41, running at an RF frequency of 5MHz and an amplitude of 330V. In the simulations, ions are dampened in gas collisions within an upstream segment (not shown) of the RF ion guide (having the same RF confinement) and are driven at a (typical) 10m/s axial velocity (usually induced by self charge) to the exit portion 401 of the RF ion guide 41, which is located at a high vacuum. The guide 41 and its exit portion 401 are biased at U=30V DC, controlling the ion injection energy into the downstream OA. The guide 401 is terminated by a shielding aperture 402, also kept at 30V DC. The beam is accelerated downstream to 30eV energy when it enters the grounded entrance section 404 of the lens system 52, and of course, later within the grounded storage region (ion acceptance region) of OA 61. An extraction electrode 403 at variable potential U_E is used to control the strength E of the extracting electric field at the exit of exit portion 401, and also to vary the ion beam focusing within two stages of unavoidable ion acceleration: from 401 to 403, and from 403 to 404.

Contrary to the prior art, as the pressure (e.g. 1E-6Torr) at the exit of ion guide 41 is low, this removes the problem of gas load into the lens system and now allows termination of guide 41 by a wide open aperture with a diameter exceeding the guide inscribed diameter D (here simulated at 2D diameter).

Using a wide extraction aperture is beneficial. The aperture diameter D_L may be at least equal to or larger than inscribed diameter of ion guide D, i.e. $D_L \geq D$, and yet more preferably $D_L \geq 2D$. Using a wide aperture eliminates exposure of the aperture walls to stray ions and avoids surface charging. While metal electrodes are considered fully conductive, nevertheless, the metal surfaces are usually coated by residual pumping oil and may be contaminated by electrically insulating sample material. If exposing surfaces to large currents, the charge builds up. The extracting apertures downstream of RF guides appear sensitive to those effects because of the unfavorable combination of: (1) large currents downstream of ion guide 41, e.g. up to several nA; (2) aperture contamination by the sample and droplets from an ESI source; (3) small potentials of one Volt or so, preferable for ion extraction downstream of the RF ion guide, where the ion beam is sensitive to the likely build up of the charge on the aperture surfaces.

Using a wide extraction aperture also solves the problem of non-linear lens effects associated with the small apertures of the prior art, since now the ion beam occupies a small fraction of the aperture opening. However, use of a wide extraction aperture may result in the voltages used for the downstream acceleration of the ion beam producing strong extraction DC fields E at the RF guide exit. However, simulations demonstrate that the acceleration from U=30V to ground may be distributed between two acceleration stages to form a nearly uniform and relatively weak extraction field, calculated as being about 0.5V/mm in case C (at U_E=26V) shown in Fig. 4A.

Referring to **Fig.4A**, and contrary to the prior art, reaching a much lower (e.g. 1E-6Torr) gas pressure at the exit of ion guide 41 strongly reduces the energy spread of the ion beam, as seen in distributions 405 simulated at 1E-2 Torr and 1E-6 Torr for system 400 at U_E=0V. This causes at least two positive effects. First, the downstream ion optical system does not produce chromatic aberrations which helps obtaining minimal phase space of the

ion beam. Second, the small energy spread minimizes the ion packets angular divergence in MR-TOF systems, which are described in co-pending applications WO2019/030476, WO2019/030477, WO2019/030472, WO2019/030471 and WO2019/030473.

To analyze the effect of electrode misalignment, in the simulations shown by the trajectories in picture 400 of Fig. 4A, the RF ion guide 401 is shifted vertically by 0.2mm from the axis of other electrodes 402-404. Pictures of ion trajectories at various extraction potentials U_E, varying from 30V to 0V show that the extraction potential affects both the ion beam divergence and ion beam sensitivity to vertical misalignment. The most parallel beam and the least sensitive to misalignments is obtained at U_E=26V, where E<0.5V/mm.

Again referring to **Fig.4B**, the above simulations are summarized with plots 406-409. Each graph includes three plots, corresponding to the diameter the shield aperture 402 being 2, 3 and 5mm. The plots allow the derivation of the following conclusions:

- From plot 406, at U_E/U<0.8, the beam crossover position (either virtual when negative, or actual when positive) stays within few mm from shield aperture 402, which forms stable initial conditions for the downstream periodic lens or for any other lens system.
- From plot 406, at U_E/U~0.9, the focal distance becomes long (25mm), which may cause instability if using a standard lens system, but it is not a problem when using periodic lens 52 with easily adaptable focal distance, as will be explained below.
- From plot 407, the sensitivity of the lens system to electrode misalignment drops at larger U_E/U, and becomes zero at U_E/U~0.9.
- Thus, it is preferable to use a weak extraction field E<0.5V/mm at U_E/U~0.9 for obtaining the least sensitivity to lens misalignments. This allows eliminating ion beam steering systems within the lens system 52. The extracted beam is nearly parallel and has a desirable width as seen in picture 400 (Fig. 4A) in case C (U_E=26V).
- From plots 408 and 409, the ion beam phase space, i.e. the product of beam diameter and angle, remains about the same in all simulated cases, which indicates that RF field termination is sufficiently adiabatic.
- The simulated phase space is in the order of $E\mu$=0.5mm*deg at 30eV beam energy, which is three to five times lower than reported in the prior art and experimentally measured for conventional ion guides. This proves that the ion beam emittance was affected within prior art interfaces, but that the distortion may be avoided and the ion beam phase space may be substantially reduced by using the combination of the improved ion guide and ion extraction by ion optics that are described herein.

Though the protruding ion guide 41 described herein may be used with a conventional Einzel lens or telescopic lens, it is preferable to use the periodic lens 51 at least for reasons of: (a) natural optimal ion optical coupling between the guide and the lens, as detailed below; (b) easy adjustments of the periodic lens to compensate for variations of the extracted ion beam, as explained below; (c) easy lens tuning by a single voltage; (d) ease of arranging accurate mutual alignment, here shown with centering ring 47; (e) guaranteed ion beam confinement within periodic lens which eliminates the ion on surface collisions, and (f) ability to bend and twist the overall interface, as described in Fig.7 below.

Fig.5 shows a portion 500 of the embodiment 200 shown in Fig. 2 and shows an embodiment of the periodic lens 51 of the present invention. View 501 shows a cross-sectional view along the lens 51. View 502 illustrates another embodiment of the periodic lens, protruding between differentially pumped stages.

Periodic lens 51 comprises: two comb electrodes 52, radially separated by slot 53, and having slots 54 for mutual alignment of the comb electrodes 52; heater 57 (e.g. at 150-200°C); aligning thermal insulator 55 for aligning the lens 51; and a terminating slit 58

through which ions exit. Each comb electrode comprises a plurality of apertured electrodes, such as ring electrodes, that depend from a common spine such that the apertured electrodes are maintained at the same potential in use. The ring electrodes may be attached to a rigid spine or may be integral therewith. For example, the comb electrodes 52 may be made by EDM from a single conductive tube. Alternatively, the ring electrodes in each comb may not be rigidly connected to a spine, but may simply be electrically connected to each other so as to be at the same potential. The two comb electrodes are interleaved such that the apertured electrodes of one comb are arranged between the apertured electrodes of the other comb, and are aligned such that ions are guided longitudinally along the lens 51 through the apertures in the combs. The comb electrodes 52 are connected to a pair of power supplies with DC voltages U1 and U2, where U2 is preferably grounded U2=0 and U1 is a single voltage controlling lens focusing. Lens 51 is aligned with rods of guide 41 by an insulating ring 47, which may be ceramic or Vespel. The lens 51 inner diameter D_L is chosen larger than the inscribed diameter of the ion guide D, optionally $D_L \sim 2D$. Contrary to the prior art, the embodiment does not use any fine apertures between guide 41 and lens 51. The grounded comb 52 of large inner diameter gently extracts ions from the guide 41, e.g. at $E<0.5$V/mm. Similarly, the exit grounded section of the lens 51 is elongated for minimizing the field strength at the exit aperture 58.

Referring to view 502, the exit slit 58 may function as a differential aperture between stages 5 and 6 of embodiment 200 (Fig. 2), and/or the lens channel 56 itself may act as a differential channel, in particular when using an elongated L_L radial seal 55 around the protruding portion of the lens (i.e. the portion extending through aperture between stages 5-6), thanks to suppressed gas conductance of long channels at vacuum and to satisfying Kn>>1.

The ion optical properties of the lens 51 will now be discussed. The two combs 52 form a set of ring electrodes to which potentials U1 and U2 are alternately applied, e.g. at spatial period p (i.e. each potential may be applied to electrodes arranged at pitch p). Ions traveling at some axial velocity Vz through the DC electrodes experience an effective radio-frequency field with frequency $F=p/Vz$ and angular frequency $\omega=2\pi F$. Similarly to in ion guides having time variable RF fields applied thereto, the effective radio-frequency field sensed by moving ions is also characterized by an effective potential $D=E^2q/m\omega^2$, being independent on ion mass for beams with mass independent axial ion energy $K=mV_Z^2/2$. The radially non-uniform field confines ions towards the smaller field gradient, i.e. towards the center of the ring channel. The soft radially confining effective field forms a spatially distributed lens. The ion beam parameters downstream of the lens depend on the initial ion beam parameters, formed at ion extraction from the guide 41.

The ion extraction from the RF ion guide 41 will now be described. Ion guide 41 is floated at a DC bias voltage U_{DC}, of say 30V, thereby controlling the ion beam energy in the OA. The grounded comb electrode 52 form a gentle extracting field with strength $E_{EX} \sim U_{DC}/5D_L$ at the exit of RF guide 41. By way of example, at U_{DC}=30V and D_L=10mm, E_{EX}~0.6V/mm. Note, that using a wide grounded section of the periodic lens 51 allows obtaining a similar extraction field E~0.5V/mm as at the optimal extraction in Fig.4, corresponding case C of view 400. Slowly extracted ions experience multiple RF oscillations in the fringing RF fields, i.e. the RF field termination is adiabatic and does not introduce additional angular or energy spread to the ion beam. The guide exit is at vacuum conditions, so there are no ion on gas collisions at ion extraction. As confirmed in simulations, the proposed soft ion extraction at vacuum conditions is expected to form ion beams with $dKz<0.1$eV energy spread, being drastically different from conventional ion extraction from gas filled ion guides and through fine apertures, where both the simulated and experimentally observed energy spread is dKz~1eV. Such substantial reduction of the

axial energy spread helps the OA-TOF and OA-MRTOF in multiple ways: (i) the lens system operates with a chromatic beam, i.e. does not introduce chromatic aberrations, which helps reduce the angular spread in the beam and, thus, turn around times of ion packets; (ii) the OA may use smaller beam energies for higher duty cycles; (iii) within the OA-MRTOF of co-pending applications WO2019/030476, WO2019/030477, WO2019/030472, WO2019/030471 and WO2019/030473, the angular divergence of ion packets is reduced which reduces ion losses in the analyzer and allows an increasing number of mirror reflections for higher MRTOF resolutions.

As shown below, a single potential U1 of periodic lens 51 may be used to control all the processes downstream of the ion guide, such as soft ion extraction, formation of intermediate beam crossover, and formation of a parallel ion beam at the lens exit with a preset magnification of the beam diameter. The system design (e.g. manufacturing the periodic lens from a single tube) allows precise axial alignment between the RF ion guide 41 and periodic lens 51, expected to be better than 0.05mm, while providing low sensitivity to misalignments by its ion optical properties (elongated focal length at ion extraction). Thus, no other steering or adjustment is needed. The proposed system provides exceptional ion beam parameters and is easy to tune by a single potential.

Referring to **Fig.6A** and **Fig.6B**, ion optical simulations of the interface are presented by: set 600 of simulated parameters for the protruding RF ion guide 41 and periodic lens 51; by picture 601 of ion trajectories in the set 600; by graphs 602 and 603 for ion beam parameters in the middle of the orthogonal accelerator obtained using the set 600; and by ion beam emittance in the case of complimenting the set 600 by an extraction system 401 and 402, similar to one used in Fig.4. It is to be noted that the presented geometry 600 is strongly expanded in vertical direction for a better view of proportionally expanded ion trajectories in view 601.

In the simulation example shown in set 600, quadrupolar ion guide 41 has a 3mm inscribed diameter, the guide is floated at a 30V DC mid line bias U_{DC}=30V and is fed by an RF signal with 300V zero to peak amplitude at 5MHz frequency, which allows RF stability of 100amu low mass ions. The gas pressure in the guide is varied from 10mTorr at the upstream ion guide segment (not shown) and down to 1uTorr at the downstream end (shown). Ions are moved axially by superimposed gas flow at 10m/s velocity, so that they spend at least 1ms at higher gas pressure for sufficient collisional dampening. Such motion represents typical axial ion propagation, normally induced by a combination of gas flow and self space charge propagation.

The periodic lens 51 has a $\mathbf{D_L}$=10mm inner diameter and 7mm long ring sections. Alternating potentials of U1~ -60V and 0V are applied to rings of the periodic lens (the potentials are actually applied to the two comb electrodes from which the ring electrodes depend). The overall length of the periodic lens 51 is 133mm. The entrance and exit sections of the lens 51 are formed from grounded rings having lengths of 7mm and 26mm respectively.

Referring to ion trajectories 601, ions are extracted from ion guide 41 by the ground potential of the entrance ring of the lens 51. Penetration of the extraction field between the ion guide rods forms a weak electrostatic lens with E~0.5V/mm at the exit cross section of the guide 41. The combination of a slowly (spatially) decaying RF field and of the extracting DC field forms an intermediate beam crossover 605. The periodic lens 51 refocuses the beam once in section 606 and forms a parallel beam 607 at the lens exit segment at U1=0V. The exit ring of the lens 51 is at ground for shielding the lens field at slit 608. A 1.4mm high slit 608 trims the beam halo at the entrance of OA 61.

Referring to **Fig.6B,** graphs 602 and 603 show that the exiting ion beam 608 has a very small angular beam divergence with FWHM 0.3deg and the beam emittance is less

than 0.5mm*deg at 30eV energy, both of which are considered to be much superior to the parameters reported in the prior art and measured in experiments. The trimmed beam is highly parallel and travels through the 60mm long OA 61 without any notable spatial spreading. The radial velocity spread (in the TOF direction) is 20m/s for 1000amu ions, which allows a 0.5ns turn around time at an E=400V/mm pulsed field in OA.

Referring to graph 604, a yet smaller beam divergence FWHM~0.15deg is predicted in simulations, if using an additional extracting system 401 and 402, similar to one used in Fig.4. The extraction system allows flexible adjustments between OA-TOF MS resolution and sensitivity, however, once the optimal compromise if found, a similar reduction of the angular beam divergence and beam spatial magnification may be obtained with optimization of the lens extracting part (say using larger lens diameter).

Separate simulations were made to examine misalignment effects. Trajectory picture 601 corresponds to a 50um vertical shift of the ion guide rods. Such accuracy is easy to achieve if using an aligning ring 47 (as in Fig,4) and the rigid structure of periodic lens 51, described in Fig.5. The 0.05mm radial misalignment tilts the exiting beam by less than 0.05deg, staying well within the beam divergence. The tilt displaces the entire beam across the exit slit 608, and drops ion transmission from 90% to 80%, which is not considered problematic or requiring additional beam steering. Thus, the proposed system, first, allows precise coaxial alignment between the RF ion guide and periodic lens (by rigidity and alignment of the lens design, so as with use of the aligning ring 47) and, second, is insensitive to minor misalignments at standard manufacturing accuracy. This allows avoiding ion steering elements (typical for prior art lens systems) and the entire lens may be controlled by a single voltage.

The simulated beam parameters are notably (three to five times) better than the phase space of experimentally measured ion beams within conventional interfaces, meaning that prior art interfaces were affecting ion beam phase space and axial energy spread. The above description lists multiple possible reasons, such as: ion extraction from the RF guide by a strong field through gas; ion extraction by a strong field through fringing RF fields; extraction via a small size aperture; exposure and charging of a small exit aperture (in particular if the aperture is not heated); non-linear lens effects of the fine aperture; ion on gas scattering within the lens; misalignment of components, where standard optics are highly sensitive to such misalignments. The proposed combination of (a) the improved protruding ion guide with at least two long radial seals, (b) optimal extraction parameters and (c) the periodic lens solves problems associated with prior art interfaces.

Both the RF ion guide 41 and periodic lens 51 are characterized by radially confining fields, being axially uniform, effectively forming an ion confining trough. With known examples of curved ion guides, there exists a confidence in the non-distorted ion transfer within curved guides, in particular, when the bending radius is much larger than the inner channel diameter.

A gentle bending of either one or both of the protruding RF ion guide and periodic lens would have moderate or negligible effect on the ion beam parameters. Such an ion path curvature may be used to gain an advantage of compact instrument packaging and would improve protection of the instrument against dust and droplets from the ion source.

Fig.7 shows the compact packaging 700 of the ion transfer interface for minimization of the vacuum connections when a turbo-molecular pump cartridge TMP is installed on the axis of the interface, and while the central ion path 603 is arranged to spiral around the TMP. The ion transfer interface may comprise a combination helical ion optical elements 701 and 702, such as the described RF ion guides 41 and periodic lens 51, analytical quadrupoles, CID cells and mobility spectrometers. The helical packaging strongly improves the gas conductance to pumping ports S3, S4 and S5, which in turn

allows making the intra-stage gaps and whole TMP notably shorter. Currently produced commercial interfaces for Q-TOF and IMS-TOF instruments are 0.5-1m long. With the helical packaging, their length may be reduced to 200-300mm, in particular when using smaller size (e.g. 70L/s) pumps, but a larger number of pumping stages. Schemes 704 and 705 illustrate how the helical path may be formed with circular C-shaped elements 701 and 702, whilst 705 illustrates matching the RF phases between the elements.

Although the present invention has been describing with reference to preferred embodiments, it will be apparent to those skilled in the art that various modifications in form and detail may be made without departing from the scope of the present invention as set forth in the accompanying claims.

For example, although the described embodiments include time-of-flight mass analysers, it is contemplated that other mass analysers (or ion mobility analysers) may be used to benefit from embodiments of the invention.

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CLAIMS:

1. A mass or mobility spectrometer comprising:

a first pumping stage and a second pumping stage that is separated from the first pumping stage by a wall having an orifice;

at least one vacuum pump for differentially pumping the pumping stages such that the second pumping stage is at a lower pressure than the first pumping stage;

an ion guide extending continuously from the first pumping stage to the second pumping stage, through the orifice, such that an upstream end of the ion guide is in the first pumping stage and a downstream portion of the ion guide is in the second pumping stage;

wherein the ion guide comprises a plurality of electrodes for radially confining ions and wherein the electrodes define radially extending gaps therebetween;

wherein, in the downstream portion of the ion guide, the gaps are open such that gas is evacuated, in use, radially out of the downstream portion through said gaps; and

wherein, at the upstream end of the ion guide, the gaps are either: (i) blocked such that gas cannot be evacuated radially at the upstream end; or (ii) restricted relative to the gaps in said downstream portion of the ion guide for restricting the evacuation of gas radially at the upstream end.

2. The spectrometer of claim 1, wherein the gaps at the upstream end are blocked or restricted such that, in use, the pressure within the upstream end is higher than the pressure within the rest of the ion guide and causes the ions to be collisionally dampened, whereas the gaps in the downstream portion are open such that the gas is radially evacuated and the pressure therein is such that ions passing therethrough substantially do not collide with gas molecules or collide with gas at a lower rate than in the upstream end portion.

3. The spectrometer of claim 1 or 2, wherein each of the plurality of electrodes of the ion guide extend continuously from an upstream distal end of the ion guide to a downstream distal end of the ion guide.

4. The spectrometer of claim 1, 2 or 3, wherein the ion guide further comprises: an intermediate sealed portion between the upstream end and the downstream portion, wherein the gaps of the intermediate sealed portion are blocked such that gas cannot be radially evacuated from within the intermediate sealed portion; and an intermediate open portion between the upstream end and the intermediate sealed portion, wherein the gaps of the intermediate open portion are open such that gas is evacuated, in use, from within the intermediate open portion through said gaps.

5. The spectrometer of claim 4, wherein the intermediate sealed portion extends axially upstream and/or downstream from said orifice.

6. The spectrometer of claim 4 or 5, wherein the intermediate sealed portion has an axial length selected from the group of: $\geq$10D, where D is the inscribed diameter of said ion guide; $\geq$ 20 mm; $\geq$ 30 mm; $\geq$ 40 mm; $\geq$ 50 mm; and $\geq$ 60 mm; and/or

wherein the intermediate sealed portion has an axial length L_C, wherein the ion guide has an inscribed diameter D, and wherein $D^3/L_C < 1$ mm^2.

7. The spectrometer of any preceding claim, wherein the upstream distal end of the ion guide is spaced from the upstream wall and downstream wall of the first pumping stage.

8. The spectrometer of any preceding claim, wherein the ion guide does not pass through or reside within a differential pumping aperture in an upstream wall of the first pumping stage.

9. The spectrometer of any preceding claim, configured such that in use a pressure within the upstream end is ≥ 10 mTorr and/or a pressure within the downstream end of the ion guide is ≤ 1E-6 Torr; and/or

wherein the ratio of the pressure within the upstream end P_A to the pressure within the downstream end portion P_D is $P_A/P_D \geq 1E+4$.

10. The spectrometer of any preceding claim, wherein the portion of the ion guide at the upstream end having said blocked or restricted gaps has an axial length selected from the group of: ≥ 5 mm; ≥ 10 mm; ≥ 15 mm; ≥ 20 mm; ≥ 30 mm; ≥ 40 mm; ≥ 50 mm; and ≥ 60 mm.

11. The spectrometer of any preceding claim, wherein the downstream portion has an axial length of ≥10D, where D is the inscribed diameter of said ion guide; and/or wherein the downstream portion has an axial length selected from the group of: ≥ 20 mm; ≥ 30 mm; ≥ 40 mm; ≥ 50 mm; and ≥ 60 mm.

12. The spectrometer of any preceding claim, wherein the radial length of each gap defined between adjacent electrodes of the ion guide, in at least the upstream end and/or intermediate sealed portion, is at least three times the minimum width h of the gap, perpendicular to the radial direction of the ion guide.

13. The spectrometer of any preceding claim, wherein the inscribed diameter D of said ion guide is between 2 and 5 mm, or about 3 mm.

14. The spectrometer of any preceding claim, wherein the gaps in the upstream end of the ion guide are blocked by a seal extending circumferentially around the outside of the electrodes such that gas cannot be radially evacuated from within the upstream end; or wherein the gaps in the upstream end of the ion guide are blocked by plugs located in the gaps between the electrodes.

15. The spectrometer of any preceding claim, wherein the ion guide is a multipole RF ion guide having rod electrodes, such as a quadrupole ion guide.

16. The spectrometer of any preceding claim, further comprising a lens system arranged downstream of the ion guide for shaping the ion beam received therefrom, wherein the ion path from the ion guide into the lens system is free from apertures having a diameter that is less than the inscribed diameter of said ion guide.

17. The spectrometer of claim 16, wherein the lens system comprises electrodes defining an inscribed diameter that is at least twice as large as the inscribed diameter of the ion guide.

18. The spectrometer of claim 16 or 17, wherein the lens system comprises a plurality of DC electrodes spaced along a longitudinal axis on which ions are received from the ion guide, and DC voltage supplies configured to apply different DC potentials to different ones of said DC electrodes such that when ions travel through the lens system along the longitudinal axis they experience an ion confining force, generated by the DC potentials, in at least one dimension orthogonal to the longitudinal axis.

19. The spectrometer of claim 18, wherein the plurality of DC electrodes are apertured electrodes having apertures through which the ions travel as they pass along the longitudinal axis.

20. The spectrometer of claim 18 or 19, wherein the DC voltage supplies are configured to maintain adjacent DC electrodes at different DC potentials, and alternating DC electrodes at the same DC potential.

21. The spectrometer of claim 20, wherein one of the DC potentials is a ground potential; optionally wherein the DC electrodes at the distal ends of the lens system are maintained at ground potential in use.

22. The spectrometer of any one of claims 18-21, wherein the DC electrode at one or both longitudinal ends of the lens system has a length, in the longitudinal direction, that is longer than the length of each DC electrode arranged between the end electrodes.

23. The spectrometer of any one of claims 16-22, wherein the lens system passes between at least two differentially pumped stages of the spectrometer.

24. The spectrometer of any one of claims 16-23, comprising a heater for heating electrodes of the lens system.

25. The spectrometer of any preceding claim, wherein the ion guide and/or lens system has a curved longitudinal axis for guiding ions in a curved path.

26. The spectrometer of any preceding claim, comprising a mass or mobility analyser arranged to receive ions from the ion guide or lens system.

27. The spectrometer of claim 26, wherein the mass analyser is a time of flight mass analyser comprising an orthogonal ion accelerator arranged to receive the ions from the ion guide or lens system.

28. The spectrometer of claim 27, wherein the time-of-flight mass analyser is:

(i) a multi-reflecting time of flight mass analyser having two ion mirrors that are elongated in a drift direction and configured to reflect ions multiple times in an oscillation dimension that is orthogonal to the drift direction, wherein the orthogonal ion accelerator is arranged to receive ions and accelerate them into one of the ion mirrors; or

(ii) a multi-turn time of flight mass analyser having at least two electrostatic sectors configured to turn ions multiple times in an oscillation plane, wherein the orthogonal accelerator is arranged to receive ions and accelerate them into one of the sectors.

29. A method of mass spectrometry or ion mobility spectrometry comprising:

providing a spectrometer as claimed in any preceding claim;

operating the at least one vacuum pump so as to evacuate gas from the ion guide such that the pressure within the upstream end portion of the ion guide is higher than the pressure within the rest of the ion guide;

transmitting ions through the ion guide, wherein the ions are collisionally dampened by gas in the upstream end portion but substantially do not collide with gas molecules in the downstream portion, or collide with gas at a lower rate in the downstream portion than in the upstream end portion; and

mass analysing or ion mobility analysing ions downstream of the ion guide.

30. A time of flight mass spectrometer comprising:

first, second and third interconnected pumping stages;

at least one vacuum pump for evacuating the pumping stages;

an ion guide continuously extending from first pumping stage to the second pumping stage;

an orthogonal ion accelerator and at least one ion mirror or electrostatic sector arranged in the third pumping stage, wherein the orthogonal ion accelerator is configured to pulse ions into the ion mirror or electrostatic sector; and

a lens system between the ion guide and orthogonal ion accelerator, wherein the ion path from the ion guide into the lens system is free from apertures having a diameter that is less than the inscribed diameter of said ion guide.

31. The spectrometer of claim 30, configured such that the at least one vacuum pump pumps the first and second pumping stages such that, in use, the pressure within the upstream end portion of the ion guide is higher than the pressure within a downstream end portion of the ion guide and such that the ions are collisionally dampened in the upstream end portion but substantially do not collide with gas molecules in the downstream end portion, or collide with gas at a lower rate than in the upstream end portion.

32. The spectrometer of claim 30 or 31, wherein the lens system comprises a plurality of DC electrodes spaced along a longitudinal axis on which ions are received from the ion guide, and DC voltage supplies configured to apply different DC potentials to different ones of said DC electrodes such that when ions travel through the lens system along the longitudinal axis they experience an ion confining force, generated by the DC potentials, in at least one dimension orthogonal to the longitudinal axis;

33. A time-of-flight mass spectrometer, comprising conventional components: a gaseous ion source, generating an ion beam; a multi-stage differentially pumped ion transfer interface with stages separated by differential apertures; a gas filled radio-frequency (RF) ion guides for collisional dampening and transfer of said ion beam; a lens system for transferring and shaping said ion beam past said ion guide; an orthogonal accelerator for pulsed extracting of ion packets from the ion beam past said lens system; and a singly reflecting, or multi-reflecting, or multi-turn electrostatic analyzer for mass separation of said ion packets; wherein for the purpose of non distorting ion transfer of collisional dampened ion beam into said orthogonal accelerator, one of said RF ion guides satisfies the following range of parameters:

a) said RF ion guide is quadrupolar, i.e. composed of four parallel rods, wherein the inner bore between rods with the inscribed diameter d is continuous and non distorted at the entire guide length;

b) the guide comprises at least four segments A to D, formed by electrically insulating radial seals around said rods, alternated with open rod areas having gaps between rods for gas evacuation;

c) the entrance segment A of said RF ion guide has said radial seal, which either serves as a differential aperture, or the segment A resides past a differential aperture and said radial seal has length L_A>1mm/P_A(Torr), where P_A - is the gas pressure within segment A, accounting local raise of the gas pressure at a limited gas conductance along the guide rods;

d) the next segment B is open (no radial seal) and is arranged for sufficient radial gas evacuation, achieved at segment length $L_B \geq 10d$ and at the gap width h between the guide rods being $h>d/4$;

e) the next segment C has said radial seal which protrudes through the differential pumping wall, thus forming a differential channel of length $L_C \geq 10d$;

f) the gas pressure P_C at the entrance of segment C is arranged low enough for gas mean free path $\lambda g \geq d$ for suppression of gas conductance of said channel by factor L_C/d;

g) the exit segment D is open (no radial seal), it has length $L_D \geq d^2/2h$ for sufficient gas evacuation, and the gas pressure P_D at the segment end is arranged $P_D \leq$1E-6Torr for collisional free ion beam formation in the subsequent lens system; and

h) the exit of said ion guide is open and aligned with the entrance of said lens system without using any aperture with diameter less than d.

34. A spectrometer as in claim 33, wherein said lens system is a periodic lens, energized by at least two distinct DC potentials with one potential optionally being at ground; wherein inscribed diameter of said periodic lens is at least twice larger than D;

35. A spectrometer as in claim 33 or 34, wherein P_A/P_D>1E+4; and wherein the inscribed diameter D of said ion guide is between 2 and 5mm, preferably 3mm; and wherein D^3/L_C<1mm^2.

36. A spectrometer as in claims 33-35, wherein to prevent charging of said radial seals, the gap between electrodes of said quadrupole is at least three calibers long H: H/h≥3.

37. A spectrometer as in claims 33-36, wherein electrode shape at the entrance of said periodic lens attenuate the filed of said periodic lens to provide for acceleration of continuous ion beam at the exit cross section of said ion guide being less than 10% the beam mean energy at the entrance of said orthogonal accelerator.

38. A spectrometer as in claims 33-37, wherein said periodic lens is a rigid structure made by cutting conductive tube with electro erosion into two combs; and wherein ends of said periodic lens are aligned with axis of said RF ion guide and of said orthogonal accelerator.

39. A spectrometer as in claims 33-38, wherein said periodic lens is heated to at least 150°C for reducing oil deposits on the hot lens surface, this way avoiding surface charging by ions.

40. A spectrometer as in claims 33-39, wherein said periodic lens passes between at least two differentially pumped stages.

41. A spectrometer as in claims 33-40, wherein said periodic lens continues through fringing fields and electrode boundaries of said orthogonal accelerator.

42. A spectrometer as in claims 33-41, wherein at least one - said periodic lens or said RF ion guide is curved.

43. An ion transfer interface between a gaseous ion source and a mass spectrometer comprising

a) a cartridge multi-stage turbo-molecular pump;

b) at least one ion optical component of the list: (i) RF ion guides; (ii) analytical quadrupole; (iii) ion mobility separator; (iv) CID cell; and (iv) periodic lens; and

c) wherein said ion optical component are arranged spiral, thus forming a spiral ion path, surrounding said cartridge pump.

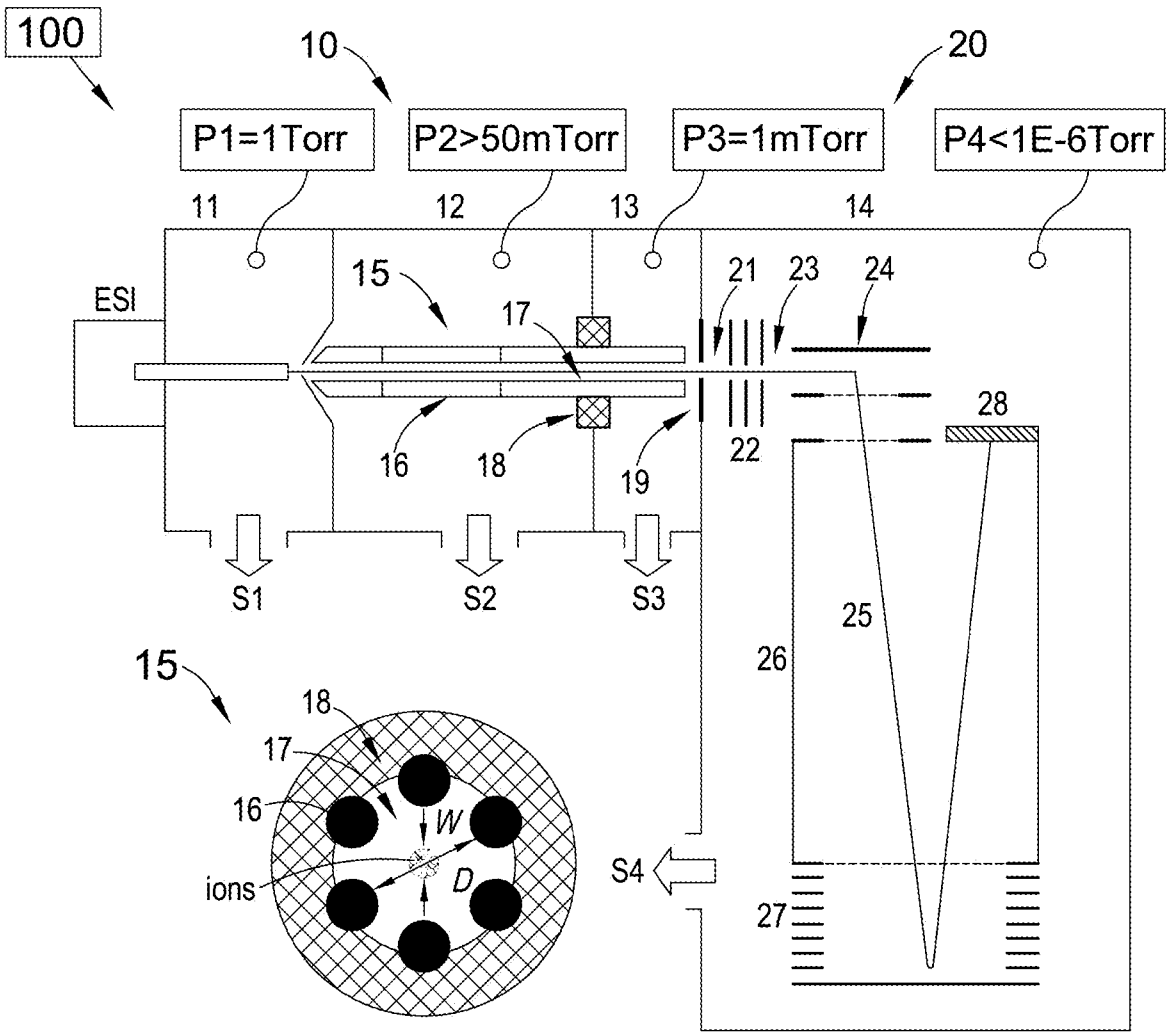


Fig.1
Prior Art

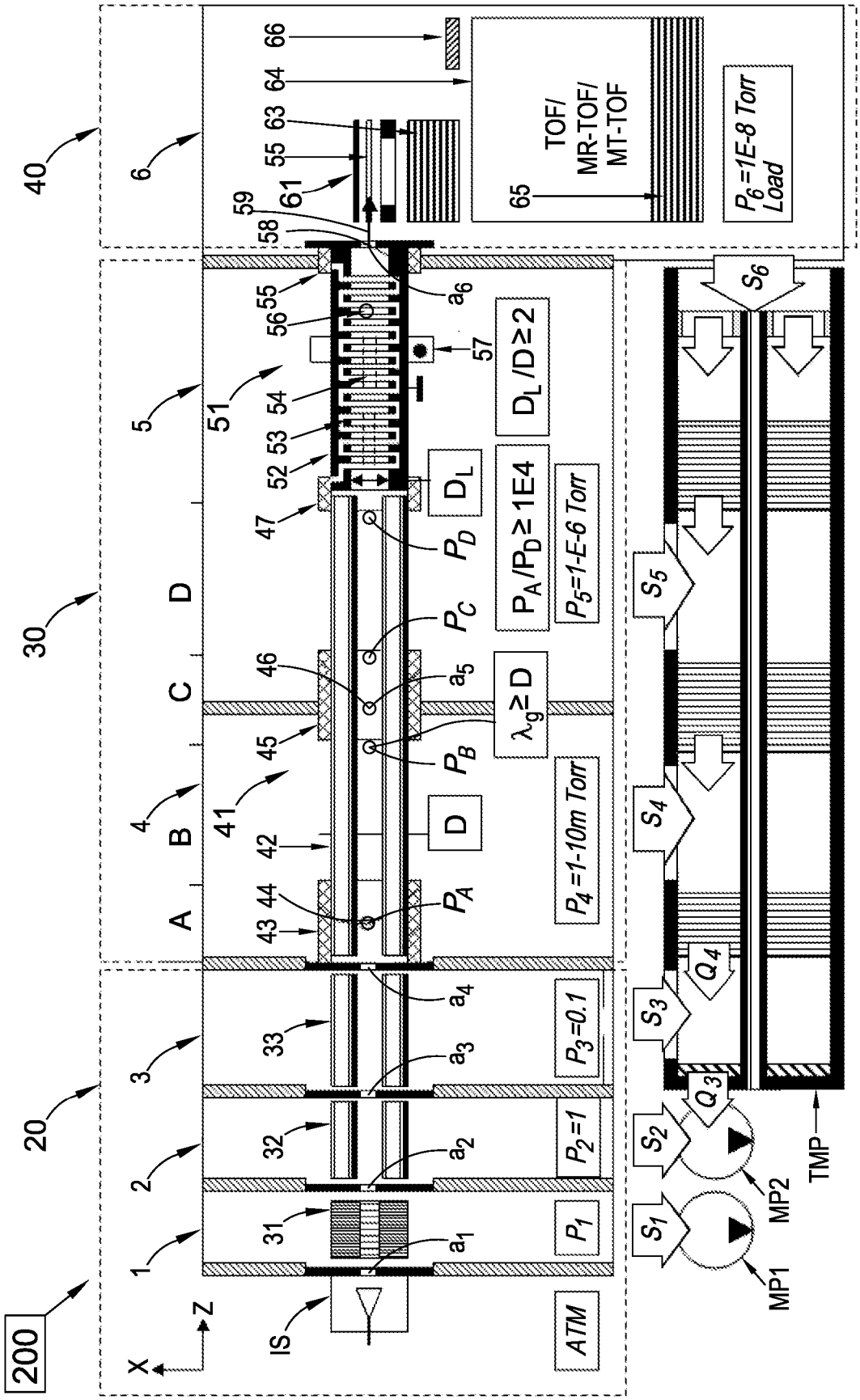

200
20
30
40
A
B
C
D
1
2
3
4
5
6
31
32
33
41
42
43
44
45
46
47
51
52
53
54
55
56
57
58
59
61
63
64
65
66
IS
X
Z
ATM
P1
P2=1
P3=0.1
P4 =1-10m Torr
P5=1-E-6 Torr
P6=1E-8 Torr Load
TOF/ MR-TOF/ MT-TOF
DL /D≥2
PA/PD≥ 1E4
λg≥ D
DL
D
PA
PB
PC
PD
a1
a2
a3
a4
a5
a6
S1
S2
S3
S4
S5
S6
Q3
Q4
MP1
MP2
TMP

Fig.2

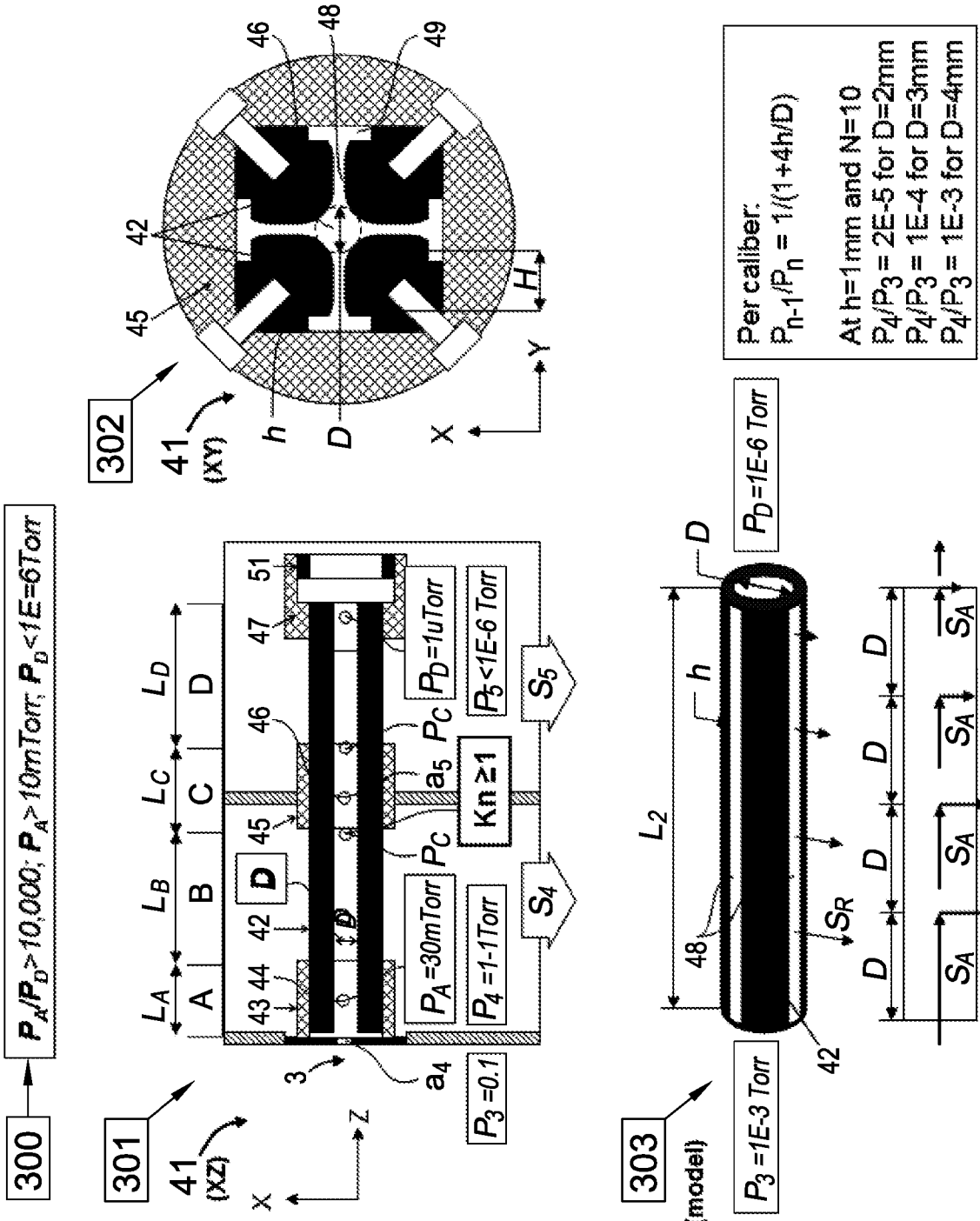

300
P_A/P_D>10,000; P_A>10mTorr; P_D<1E=6Torr
301
41 (XZ)
X
Z
3
a_4
P_3 =0.1
L_A
L_B
L_C
L_D
A
B
C
D
43 44
42
45
46
47
51
P_A =30mTorr
P_4 =1-1Torr
P_C
a_5
Kn≥1
P_D=1uTorr
P_3<1E-6 Torr
S_4
S_5
302
41 (XY)
45
42
46
48
49
h
D
H
X
Y
303
(model)
P_3 =1E-3 Torr
P_D=1E-6 Torr
L_2
h
D
48
42
S_R
S_A
S_B
Per caliber:
P_{n-1}/P_n = 1/(1+4h/D)
At h=1mm and N=10
P_4/P_3 = 2E-5 for D=2mm
P_4/P_3 = 1E-4 for D=3mm
P_4/P_3 = 1E-3 for D=4mm

Fig.3

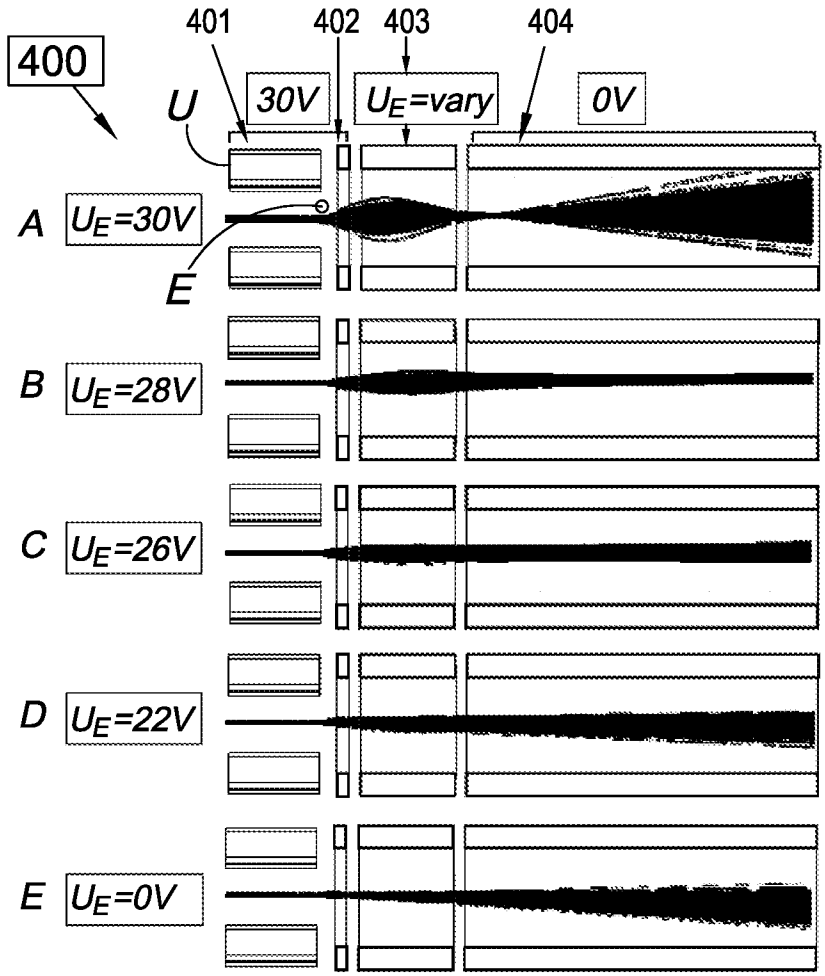
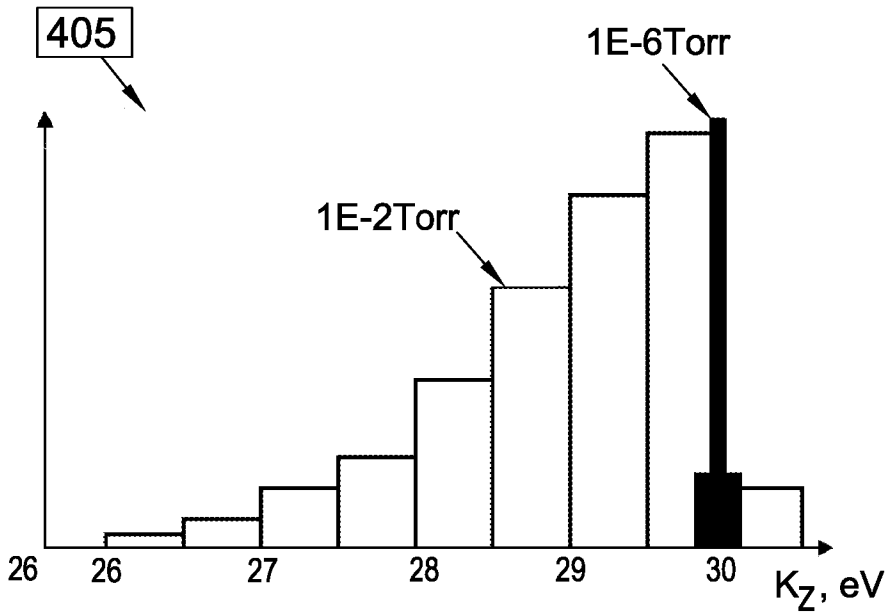

400
401
402
403
404
U
30V
U_E=vary
0V
A
U_E=30V
E
B
U_E=28V
C
U_E=26V
D
U_E=22V
E
U_E=0V

Fig.4A


405
1E-6Torr
1E-2Torr
26
26
27
28
29
30
K_Z, eV

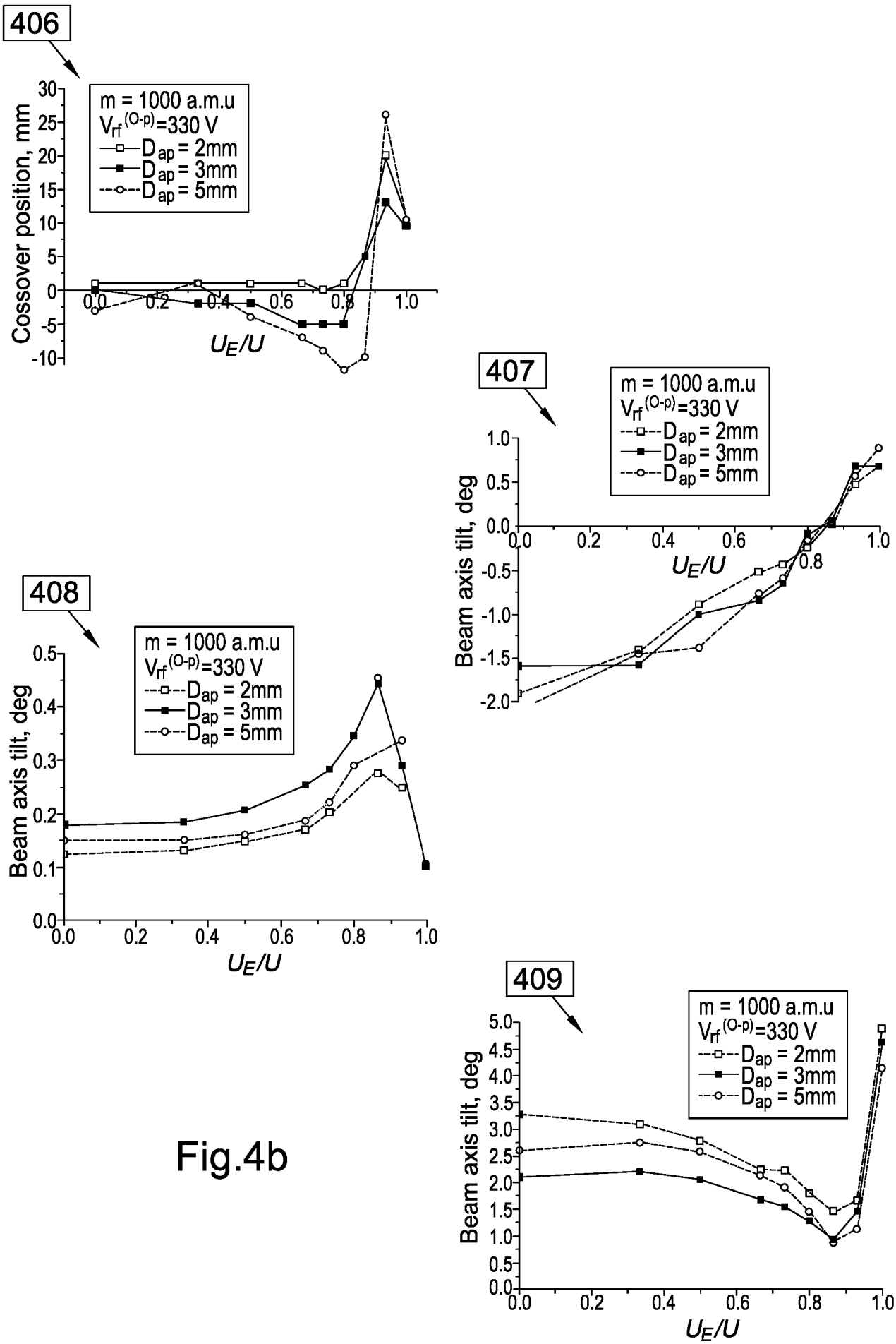

406
m = 1000 a.m.u
$V_{rf}^{(O-p)}$=330 V
D_{ap} = 2mm
D_{ap} = 3mm
D_{ap} = 5mm
Cossover position, mm
U_E/U
407
m = 1000 a.m.u
$V_{rf}^{(O-p)}$=330 V
D_{ap} = 2mm
D_{ap} = 3mm
D_{ap} = 5mm
Beam axis tilt, deg
U_E/U
408
m = 1000 a.m.u
$V_{rf}^{(O-p)}$=330 V
D_{ap} = 2mm
D_{ap} = 3mm
D_{ap} = 5mm
Beam axis tilt, deg
U_E/U
409
m = 1000 a.m.u
$V_{rf}^{(O-p)}$=330 V
D_{ap} = 2mm
D_{ap} = 3mm
D_{ap} = 5mm
Beam axis tilt, deg
U_E/U

Fig.4b

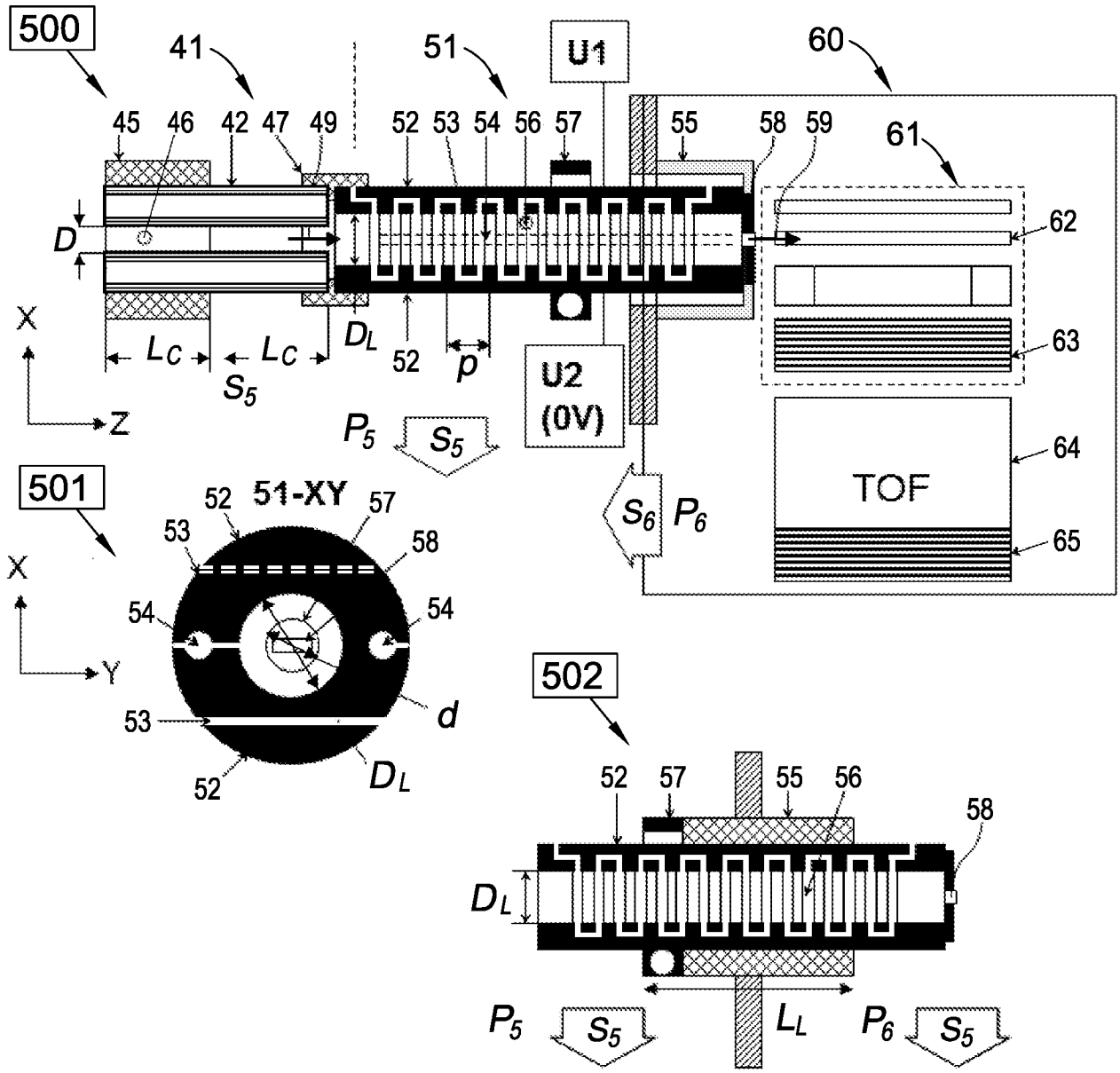

500
41
51
U1
60
45
46
42
47
49
52
53
54
56
57
55
58
59
61
62
63
64
65
D
X
Z
L_C
L_C
S_5
D_L
52
p
U2
(0V)
P_5
S_5
S_6
P_6
TOF
501
51-XY
X
Y
d
D_L
502
L_L

Fig.5

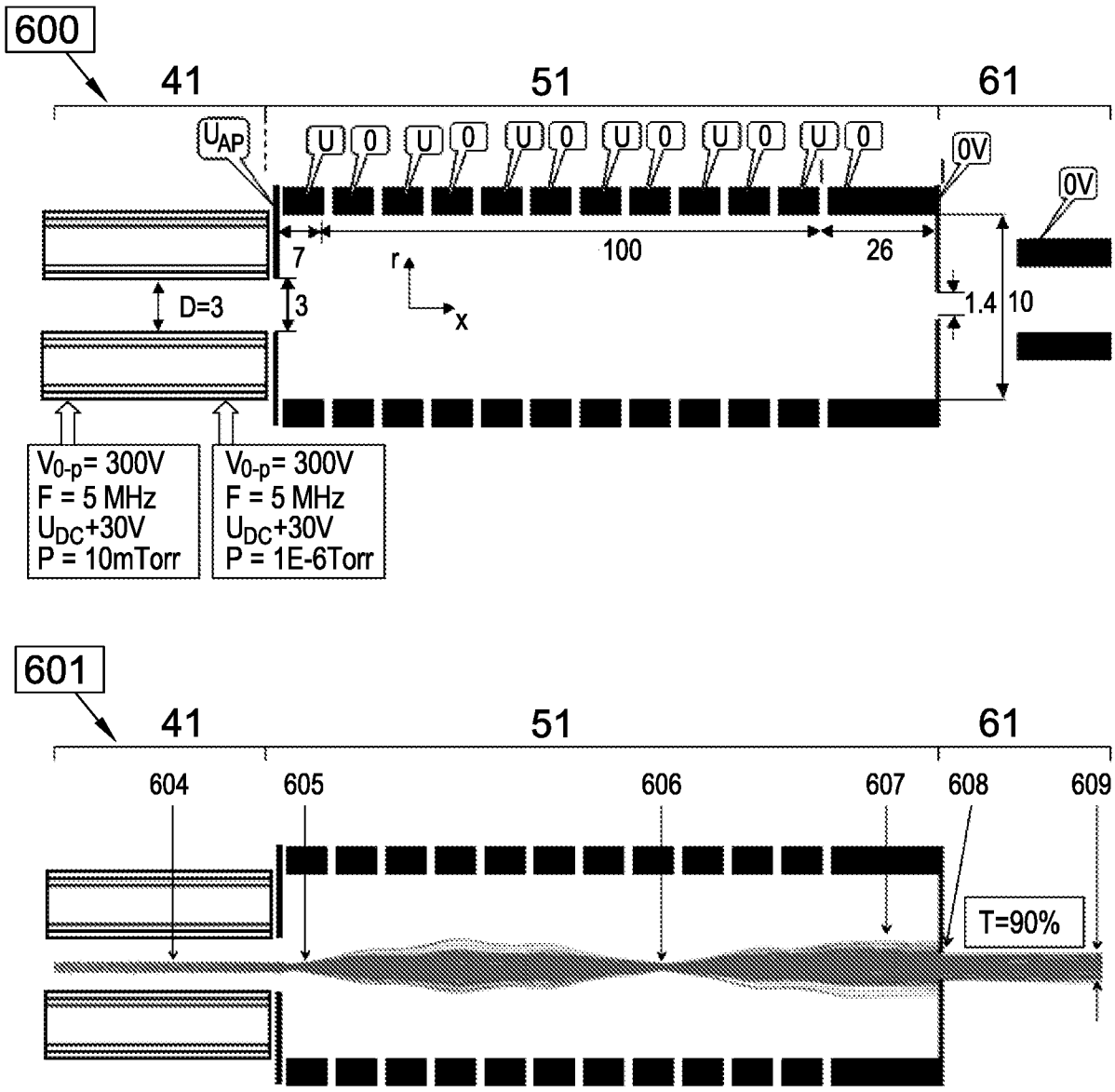

600
41
51
61
U_{AP}
U
0
0V
7
100
26
r
x
D=3
3
1.4
10
V_{0-p}= 300V
F = 5 MHz
U_{DC}+30V
P = 10mTorr
V_{0-p}= 300V
F = 5 MHz
U_{DC}+30V
P = 1E-6Torr
601
604
605
606
607
608
609
T=90%

Fig.6A

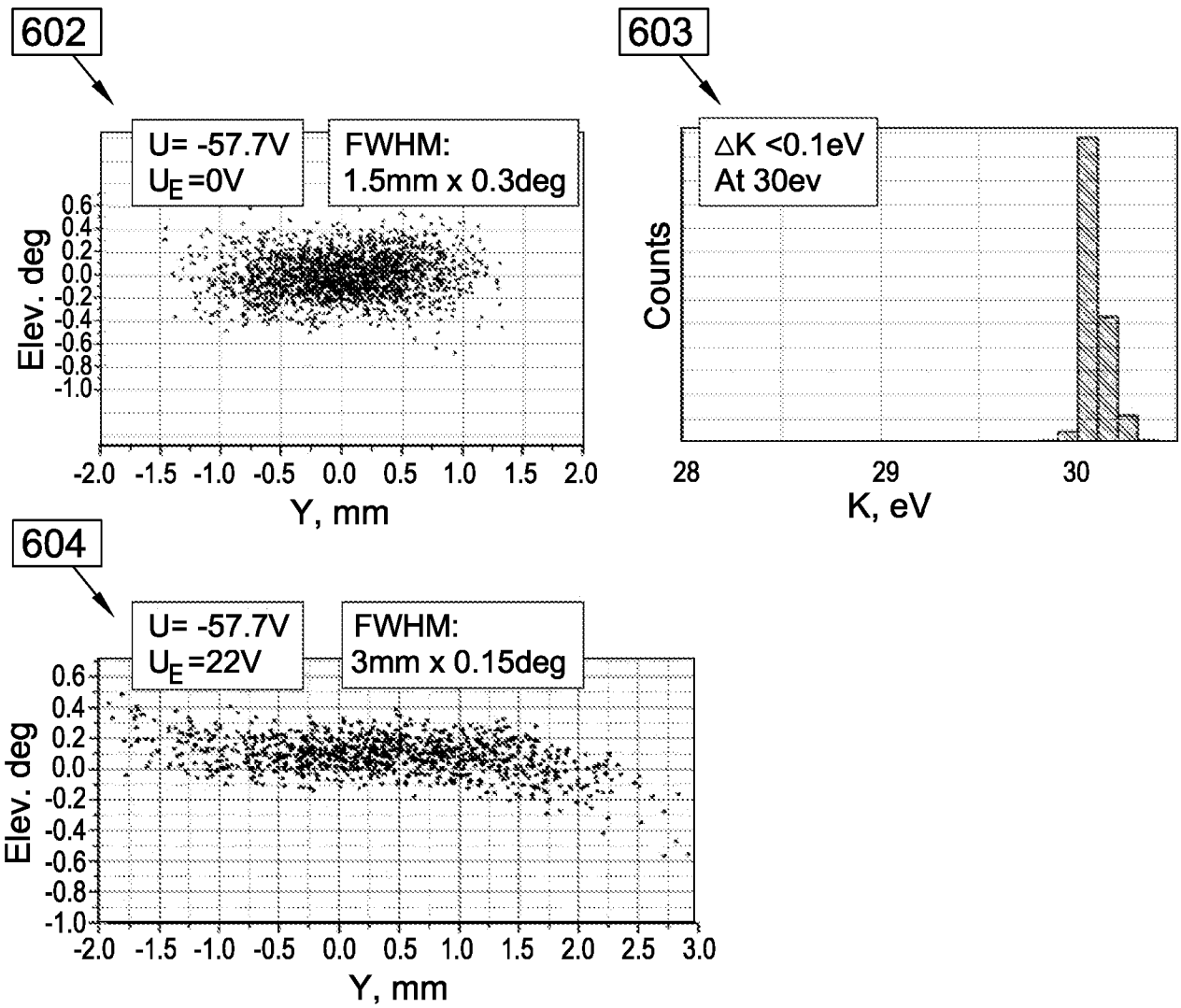

602
U= -57.7V
U_E=0V
FWHM:
1.5mm x 0.3deg
Elev. deg
Y, mm
603
ΔK <0.1eV
At 30ev
Counts
K, eV
604
U= -57.7V
U_E=22V
FWHM:
3mm x 0.15deg
Elev. deg
Y, mm

Fig.6B

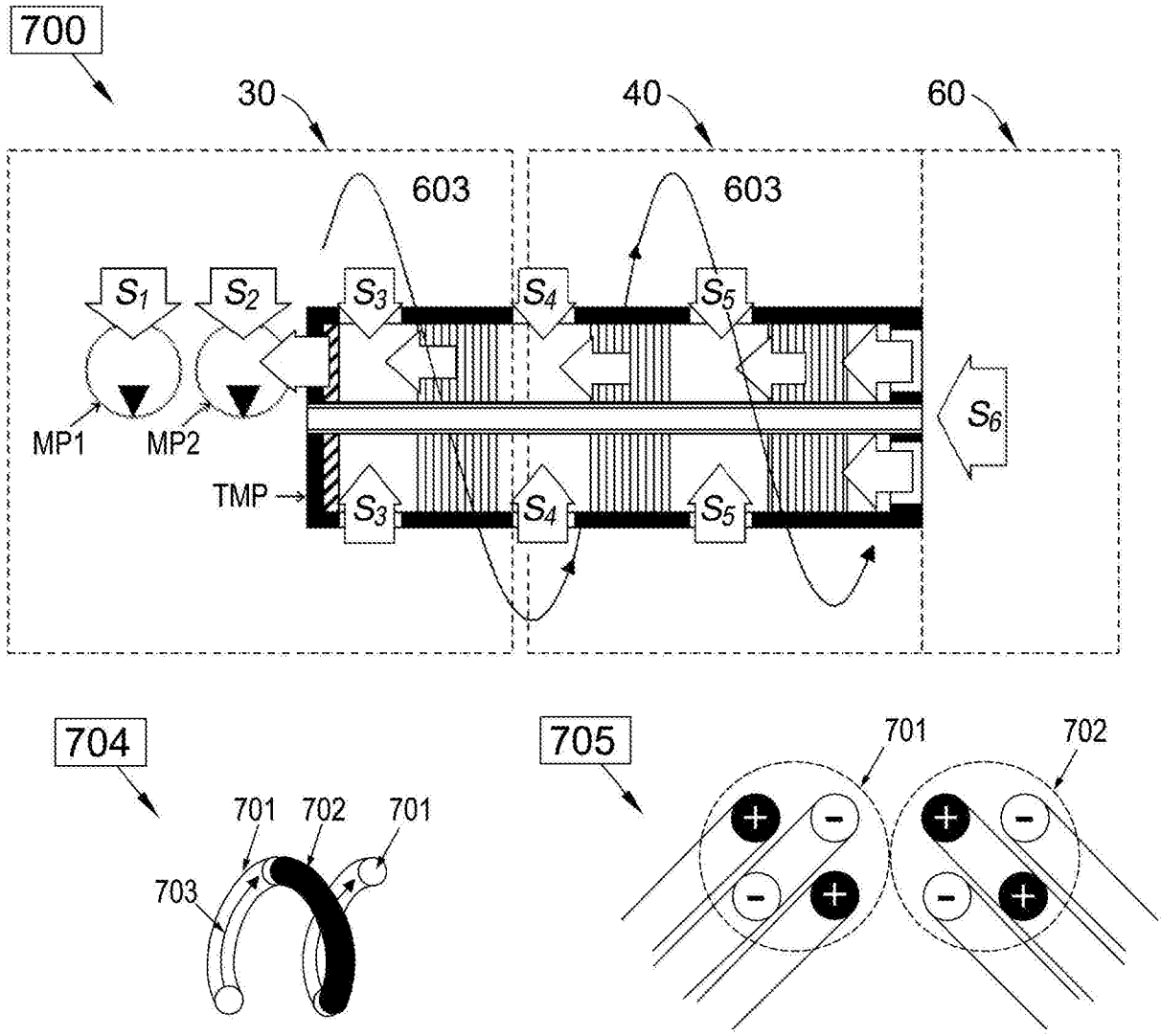

700
30
40
60
603
603
S1
S2
S3
S4
S5
S6
MP1
MP2
TMP
S3
S4
S5
704
701
702
701
703
705
701
702

Fig.7

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2019/052066

A. CLASSIFICATION OF SUBJECT MATTER
INV. H01J49/06 H01J49/24
ADD.

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)
H01J

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)

EPO-Internal, INSPEC, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 7 034 292 B1 (WHITEHOUSE CRAIG M [US] ET AL) 25 April 2006 (2006-04-25) cited in the application column 24; figure 2A	1-6, 9-15, 25-29
A	EP 0 237 259 A2 (FINNIGAN CORP [US]) 16 September 1987 (1987-09-16) abstract; figure 2 column 3, lines 14-55	25
A	US 2007/187614 A1 (SCHNEIDER BRADLEY B [CA] ET AL) 16 August 2007 (2007-08-16) the whole document	1

☐ 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 but 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	Date of mailing of the international search report
14 October 2019	16/12/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Loiseleur, Pierre

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2019/052066

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-15, 25-29

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2019/052066

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 7034292 B1	25-04-2006	US 7034292 B1	25-04-2006
		US 7858926 B1	28-12-2010
EP 0237259 A2	16-09-1987	CA 1249381 A	24-01-1989
		EP 0237259 A2	16-09-1987
		JP S62264546 A	17-11-1987
US 2007187614 A1	16-08-2007	CA 2641561 A1	16-08-2007
		EP 1984934 A1	29-10-2008
		JP 5555428 B2	23-07-2014
		JP 2009526353 A	16-07-2009
		US 2007187614 A1	16-08-2007
		WO 2007090282 A1	16-08-2007

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-15, 25-29

   Mass or mobility spectrometer with an ion guide crossing differentially pumped vacuum stages, comprising a higher pressure upstream end portion; corresponding method.

   ---

2. claims: 16-24, 30-42

   Mass or mobility spectrometer with an ion guide and a wide bore periodic extraction lens system

   ---

3. claim: 43

   Ion transfer interface with a spiral ion path surrounding a central turbo-molecular pump

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