

TIME OF FLIGHT MASS SPECTROMETER

CROSS-REFERENCE TO RELATED APPLICATION

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This application claims priority from and the benefit of United Kingdom patent application No. 2318516.8 filed on 4 December 2023. The entire contents of this application are incorporated herein by reference.

10 FIELD OF THE INVENTION

The present invention relates generally to mass spectrometers and in particular to time of flight mass spectrometers, such as Multi-Reflecting Time-of-Flight (MRTOF) mass spectrometers (MRTOF), and methods of their use.

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BACKGROUND

Time of Flight (TOF) mass analyser are known instruments having a pusher that periodically pushes packets of ions into a time of flight region towards an ion detector. The ions in each ion packet separate according to mass to charge ratio as they travel through the time of flight region towards the ion detector. The mass analyser is then able to determine the mass to charge ratio of the ion from the duration of time between it being pushed by the pusher and it being detected at the ion detector.

It is known to be desirable to change the period of time between consecutive pushes of the pusher. For example, it may be desired to change the push rate of the pusher when it is desired for the mass analyser to mass analyse a different range of mass to charge ratios.

However, it has been realised that known methods of changing the pusher period may adversely affect attributes of the mass analyser, such as mass measurement accuracy and/or mass resolution.

SUMMARY

From a first aspect the present invention provides a Time of Flight mass analyser comprising: an ion detector; a pusher configured to perform a sequence of pushes for pushing packets of ions towards the ion detector; an ion attenuator configured to alternate between a high transmission mode in which it allows ions to reach the ion detector and a low transmission mode in which it prevents ions from reaching the ion detector; and wherein the mass analyser is configured to synchronise the operation of the ion attenuator in the high and low transmission modes with the timings of the pushes such that a first plurality of the pushes result in ions being received at the ion detector and a second different plurality of the pushes do not result in ions being received at the detector.

As the present invention synchronises the timings of the high and low transmission modes of the ion attenuator with the timings of the pushes, in the above-described manner, the frequency with which pushes cause ion packets to arrive at the ion detector can be controlled so as to be different to the frequency of the pushes. As such, the frequency with which pushes cause ion packets to arrive at the ion detector can be reduced relative to the frequency of the pushes. Thus, the frequency with which ion packets are caused to arrive at the ion detector can be reduced without having to alter the timings of the pushes. This is advantageous, as altering the timings of the pushes can be problematic, e.g. because it can reduce the mass accuracy of the TOF mass analyser.

According to the present invention, the ion attenuator operates in the high transmission mode so as to allow or cause the first plurality of the pushes to result in ion packets being received at the ion detector. Conversely, the ion attenuator operates in the low transmission mode so as to prevent the second plurality of the pushes resulting in ion packets being received at the ion detector. The ion attenuator is controlled so as to repeatedly alternate between the high and low transmission modes whilst the pusher performs the sequence of pushes.

For each of the first plurality of pushes, substantially all of the ions in the ion packet that is pushed may arrive at the detector. Alternatively, or additionally, each push in the second plurality of pushes may cause substantially no ions to arrive at the ion detector.

The ion attenuator may be upstream of, downstream of, or within the pusher. When the ion attenuator is within the pusher, it may be configured to accelerate or decelerate the ions within the pusher in a direction other than the direction in which the pusher pushes the ions into the time of flight region.

The pusher comprises one or more electrodes and a voltage supply for applying a sequence of voltage pulses to said one or more electrodes so as to perform said sequence of pushes.

The mass analyser may be configured to receive ions along a first axis and the pusher may be configured to push ions in a direction that is substantially orthogonal to the first axis.

The pusher may be configured to perform the sequence of pushes at a constant rate, or the sequence of pushes may be a pattern of pushes that is repeated; and the mass analyser may be configured to vary the rate or pattern at which ion packets arrive at the ion detector during this sequence of pushes by: (i) varying the duration that the high transmission mode is applied for, for at least some of the times that it is applied; and/or (ii) varying the duration that the low transmission mode is applied for, for at least some of the times that it is applied.

For example, the mass analyser may be configured to cause or allow ion packets to arrive at the ion detector at a first constant rate during a first portion of the sequence of pushes and to then vary the duration that the high and/or low transmission mode is applied for so as to cause or allow ion packets to arrive at the ion detector at a second, different constant rate during a second, later portion of the sequence of pushes. Alternatively, the mass analyser may be configured to cause or allow ion packets to arrive at the ion detector

in a first pattern that is repeated during a first portion of the sequence of pushes, and to then vary the duration that the high and/or low transmission mode is applied for so as to cause or allow ion packets to arrive at the ion detector at a second, different pattern that is repeated during a second, later portion of the sequence of pushes.

5 Accordingly, the mass analyser may be configured to control the ion attenuator such that: during the first portion of the sequence of pushes the ion attenuator alternates between the high and low transmission modes according to a first pattern such that ion packets are allowed or caused to arrive at the ion detector at the first rate or in the first pattern; and during the second, later portion of the sequence of pushes the ion attenuator
10 alternates between the high and low transmission modes according to a second pattern such that ion packets are allowed or caused to arrive at the ion detector at the second rate or in the second pattern.

 The mass analyser may comprise a user interface configured to enable a user to select or input a range of mass to charge ratios to be mass analysed by the mass analyser;
15 or the mass analyser may be pre-configured to select a range of mass to charge ratios to be mass analysed from multiple different ranges of mass to charge ratios. In either case the mass analyser may be configured to control the manner in which the ion attenuator is synchronised with the timings of the pushes in response to, and based on, the selected or input range of mass to charge ratios.

20 The mass analyser may be configured to operate in a first mode by performing the step of synchronising during a first portion of the sequence of pushes such that the pushes that are in said first plurality of pushes are performed at a first rate or in a first repeating pattern; and to operate in a second mode by performing the step of synchronising during a second, later portion of the sequence of pushes such that the pushes that are in said first
25 plurality of pushes are performed at a second, different rate or in a second, different repeating pattern.

 The first and/or second rate may be a constant rate.

 The pushes that are in each of the first and second patterns of pushes may be at non-uniform intervals and such that ions from different ones of these pushes arrive at the
30 ion detector during overlapping time periods so as to form a multiplexed ion signal. The mass analyser may be configured to demultiplex the ion signal using knowledge of the non-uniform intervals. The mass analyser may therefore be operated using an Encoded Frequent Pulsing (EFP) technique.

 The non-uniform intervals may be such that the duration between any two pushes
35 in the first or second pattern of pushes is unique. This first pattern may be repeated during the first portion of the sequence of pushes and the second pattern may be repeated during the second portion of the sequence of pushes.

 During the first mode the step of synchronising may be performed such that ion packets having a first range of mass to charge ratios reach the ion detector, and during the
40 second mode the step of synchronising may be performed such that ion packets having a second, different range of mass to charge ratios reach the ion detector.

The mass analyser may comprise a user interface configured to enable a user to select or input the first and second ranges of mass to charge ratios; or the mass analyser may be pre-configured to select the first and second ranges of mass to charge ratios to be mass analysed from more than two different ranges of mass to charge ratios.

5 The mass analyser may be configured to operate in a first mode by performing the step of synchronising during a first portion of the sequence of pushes such that the pushes in said first plurality of pushes are performed at a constant rate; and to operate in a second mode by performing the step of synchronising during a second, different portion of the sequence of pushes such that the pushes in said first plurality of pushes are performed at
10 non-uniform intervals.

The mass analyser may have a user interface configured to enable a user to select the first or second mode, and the mass analyser may be configured to switch between the two modes in response thereto. Alternatively, the mass analyser may be configured to automatically switch between the two modes whilst analysing a sample.

15 In the second mode the pushes in said first plurality of pushes may be performed at non-uniform intervals and such that ions from different ones of these pushes arrive at the ion detector during overlapping time periods so as to form a multiplexed ion signal, and the mass analyser may be configured to demultiplex the ion signal.

20 The mass analyser may be configured to demultiplex the ion signal using knowledge of the sequence of non-uniform intervals.

The non-uniform intervals may be such that, for at least part of the second mode, the duration between any two pushes in the first plurality of pushes is unique.

This unique pattern may be repeated throughout the second mode.

25 The second mode may therefore be operated using an Encoded Frequent Pulsing (EFP) technique.

30 The mass analyser may be configured to operate in a first encoding mode by performing the step of synchronising such that the duration between any two pushes in the first plurality of pushes is unique over a first encoding period; and to operate in a second encoding mode by performing the step of synchronising such that the duration between any two pushes in the first plurality of pushes is unique over a second longer encoding period, or such that the ion packets received at the ion detector are otherwise encoded in a different manner to in the first encoding mode.

For the avoidance of doubt, the first and second encoding periods are performed during said sequence of pushes.

35 The mass analyser may have a user interface configured to enable a user to select the first or second mode, and the mass analyser may be configured to switch between the two modes in response thereto. Alternatively, the mass analyser may be configured to automatically switch between the two modes whilst analysing a sample.

40 In each of the first and second encoding modes, the pushes in said first plurality of pushes are performed at non-uniform intervals and such that ions from different ones of these pushes arrive at the ion detector during overlapping time periods so as to form a

multiplexed ion signal. The mass analyser may be configured to use the non-uniform intervals to demultiplex the ion signal.

The first encoding mode preferably comprises the step of consecutively repeating the first encoding period, i.e. repeating the unique push pattern multiple times. The second
5 encoding mode may be performed before or after the first encoding mode. The second encoding mode preferably comprises the step of consecutively repeating the second encoding period, i.e. repeating that unique push pattern multiple times.

The mass analyser described herein may be configured to vary the mass spectral density of the mass spectral data detected by the ion detector, by varying the manner in
10 which the ion attenuator and pusher are synchronised so as to change the rate at which ion packets are received at the ion detector.

The mass analyser may be configured to: determine the mass spectral density of mass spectral data detected by the ion detector; and (i) determine whether the mass spectral density is above a first threshold value, and if the determined mass spectral
15 density is above the first threshold value then automatically control the synchronisation of the pusher with the ion attenuator so as to reduce the rate that ion packets arrive at the ion detector; and/or (ii) determine whether the mass spectral density is below a second threshold value, and if the determined mass spectral density is below the second threshold value then automatically control the synchronisation of the pusher with the ion attenuator
20 so as to increase the rate that ion packets arrive at the ion detector.

The first threshold value and the second threshold value may be the same value or different values.

The mass spectral data may be determined by determining the number of mass peaks that the mass analyser has detected that are within a pre-selected range of mass to
25 charge ratios.

The ion attenuator may be arranged within or downstream of the pusher, and may be configured such that in the high transmission mode it allows or causes ions pushed in said first plurality of pushes to arrive at the ion detector and prevents ions pushed in said second plurality of pushes from arriving at the ion detector.

The mass analyser may be configured such that, during said second plurality of
30 pushes, the ion attenuator increases or decreases the energy of the ions in a direction that is orthogonal to the direction in which the pusher pushes the ions, relative to the energy that ions have in said direction during the first plurality of pushes.

Said direction may be the same direction that ions travel in when they arrive at the
35 pusher. Additionally, or alternatively, said direction may be a direction in which the ion detector is spaced apart from the pusher (e.g. in the drift direction referred to herein).

The ion attenuator may or may not accelerate or decelerate ions in the said direction during the first plurality of pushes, relative to their velocity in said direction when they arrive at the pusher. For example, during said first plurality of pushes, the ion
40 attenuator may be configured to provide ions passing through the pusher or downstream of the pusher with a first energy in said direction; and, during said second plurality of pushes, the ion attenuator may be configured to provide the ions passing through the pusher or

downstream of the pusher with a second, different energy in said direction. The first energy may be higher or lower than the second energy.

The ion attenuator may comprise one or more electrodes and a voltage supply that are configured to generate an electric field in said direction, wherein the magnitude of the electric field is higher or lower during each of said second plurality of pushes than during
5 each of the first plurality of pushes.

The ion attenuator may provide substantially no electric field in the said direction during the first plurality of pushes. Alternatively, the ion attenuator may be configured to generate said electric field with a first field strength during said first plurality of pushes, and
10 to generate said electric field with a second different field strength during said second plurality of pushes.

Preferably, the ion attenuator acts on the ions within the pusher, rather than downstream of the pusher. This enables the ion attenuator to achieve the above functions using relatively small voltages and without needing to introduce electric fields into the time
15 of flight region that is between the pusher and the ion detector.

The ion attenuator may be an ion gate having an electrode and voltage supply connected thereto that are configured to allow ions to be transmitted through the ion gate in the high transmission mode and to prevent substantially all ions from passing through the ion gate in the low transmission mode.

It is contemplated that the ion attenuator may be arranged upstream of the pusher, and the ion attenuator configured such that in the high transmission mode it allows to pass into the pusher during each of said first plurality of pushes such that they arrive at the ion detector, and prevents ions passing into the pusher during each of said second plurality of pushes such that ions do not arrive at the ion detector.

The ion attenuator may be an ion gate having an electrode and voltage supply connected thereto that are configured to allow ions to be transmitted through the ion gate to the pusher in the high transmission mode and to prevent substantially all ions from passing through the ion gate to the pusher in the low transmission mode.

Alternatively, the ion attenuator may be an ion deflector having an electrode and
30 voltage supply connected thereto that are configured to deflect ions in each low transmission mode such that they do not reach the pusher and to not deflect (or deflect to a lesser extent) ions during each high transmission mode such that they do reach the pusher. However, it is alternatively contemplated that the ion deflector may be configured to deflect ions in each high transmission mode such that they reach the pusher, and to not
35 deflect (or deflect to a lesser extent) ions during each low transmission mode such that they do not reach the pusher.

Alternatively, the ion attenuator may be an ion trap configured to trap ions in the low transmission mode such that they cannot enter the pusher, and to transmit ions downstream to the pusher in the high transmission mode.

The ion attenuator may be located adjacent to the pusher. For example, there may
40 be no ion-optical elements such as lenses between the ion attenuator and the pusher.

The mass analyser may be a Multi-Reflecting Time-of-Flight mass analyser comprising two ion mirrors arranged and configured such that the ions are accelerated into one of the ion mirrors by the pusher and are reflected by each of the mirrors, and between the mirrors, a plurality of times before reaching the ion detector.

5 The mass analyser described herein comprises control circuitry and software that are configured to control the synchronisation of the ion attenuator with the pusher in the various manners described.

The techniques described herein may be performed during a single experimental run, e.g. whilst a sample to be analysed is continually supplied to the mass spectrometer.

10 The present invention also provides a mass spectrometer comprising a mass analyser as described above and elsewhere herein.

The mass spectrometer may be configured to analyse ions according to multiple different techniques, and to automatically change the manner in which the ion attenuator is synchronised with the pusher when changing between the different techniques.

15 The manner in which the ion attenuator is synchronised with the pusher may be pre-set for each of the techniques, such that when the spectrometer switches between the techniques it automatically switches between the pre-set synchronisation modes.

Alternatively, when the spectrometer switches between the techniques it may automatically adjust the manner in which the ion attenuator is synchronised with the pusher based on the ion signal being detected by the detector, e.g. in real time. For example, the mass analyser may be configured such that when it switches to a different analysis technique it: determines the mass spectral density of mass spectral data detected by the ion detector; and (i) determines whether the mass spectral density is above a first threshold value, and if the determined mass spectral density is above the first threshold value then
20 automatically control the synchronisation of the pusher with the ion attenuator so as to reduce the rate that ion packets arrive at the ion detector; and/or (ii) determines whether the mass spectral density is below a second threshold value, and if the determined mass spectral density is below the second threshold value then automatically control the
25 synchronisation of the pusher with the ion attenuator so as to increase the rate that ion
30 packets arrive at the ion detector.

The first threshold value and the second threshold value may be the same value or different values.

35 The mass spectral data may be determined by determining the number of mass peaks that the mass analyser has detected that are within a pre-selected range of mass to charge ratios.

The mass spectrometer may comprise a fragmentation or reaction device, and the mass spectrometer may be configured to perform a first of said different techniques in which precursor ions are transmitted to the pusher for mass analysis, and to perform a second of said different techniques in which the precursor ions are fragmented or reacted
40 in the fragmentation or reaction device and the resulting fragment or other product ions are then transmitted to the pusher for mass analysis.

The mass spectrometer may further comprise a mass filter and the spectrometer may be configured such that in said second of the different techniques it mass filters the precursor ions in the mass filter so as to transmit precursor ions having a restricted range of mass to charge ratios to the fragmentation or reaction device.

5 The ion attenuator may be synchronised with the pusher in the first of said different techniques such that ion packets arrive at the ion detector at a relatively low rate, whereas the ion attenuator may be synchronised with the pusher in the second of said different techniques such that ion packets arrive at the ion detector at a higher rate.

10 The present invention also provides a method of mass spectrometry comprising: using a mass analyser or mass spectrometer as described above or elsewhere herein to mass analyse ions.

The method may comprise operating the mass analyser or spectrometer according to any of the embodiments described herein.

15 The pusher may perform the pushes in said sequence of pushes at a constant rate throughout the entire method; or the sequence of pushes may consist of a single pattern of pushes that is repeated throughout the entire method.

BRIEF DESCRIPTION OF THE DRAWINGS

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

Fig. 1 illustrates an TOF mass analyser according to an embodiment of the present invention;

25 Figs. 2A to 2C illustrate the operation of an embodiment in which an ion attenuator is arranged upstream of the pusher in a TOF mass analyser;

Fig. 3A illustrates the operation of an embodiment in which an ion attenuator is arranged within the pusher of a TOF mass analyser; and Fig. 3B illustrates the operation of an embodiment in which an ion attenuator is arranged downstream of the pusher of a TOF mass analyser; and

30 Figs. 4-8 show schematics of embodiments of mass spectrometers according to the present invention.

DETAILED DESCRIPTION

35 Fig. 1 illustrates a multi-reflecting time-of-flight (MRTOF) mass analyser 1 according to an embodiment of the present invention. The mass analyser comprises two ion mirrors 2 for reflecting ions that are each elongated along a drift dimension (z-dimension), a pusher 3 for injecting ions into a time of flight region between the mirrors, and an ion detector 4 for detecting the ions that impact thereon at the end of their folded flight path through the mass analyser. In Fig. 1 the x-axis corresponds to the main dimension of time-of-flight (i.e. the direction of ion reflections between the ion mirrors), the z-axis corresponds to the drift

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direction that the ions drift in as they are reflected between the mirrors, and the y-axis is orthogonal to both the x- and z- axes.

In use ions are supplied into the pusher 3, e.g. along the y-axis or z-axis. The pusher includes one or more electrodes and a voltage supply that is configured to apply a sequence of voltage pulses to the one or more electrodes so as to perform a sequence of
5 respective pushes of ion packets towards one of the ions mirrors 2. The ions travel from the pusher at an inclination angle α to the X-axis, e.g. because ions are supplied to the pusher along the z-axis and retain at least some of their velocity in this direction or because the pusher imparts a velocity to the ions along the z-axis. The ions are therefore
10 provided with a velocity along the x-axis and also a drift velocity along the z-axis. The ions enter into a first of the ion mirrors and are reflected back towards a second of the ion mirrors. The ions then enter the second mirror and are reflected back to the first ion mirror. The first ion mirror may then reflect the ions back to the second ion mirror. This pattern may continue, with the ions being continually reflected between the two ion mirrors as they
15 drift along the mass analyser in the z-dimension until the ions impact upon ion detector 4. The ions therefore follow a substantially sinusoidal mean trajectory within the x-z plane. Although the ions are shown as performing nine ion mirror reflections between the pusher and the ion detector, any number of ion mirror reflections may take place.

The pusher 3 repeatedly pushes packets of ions such that the above process is
20 repeated. The period of time between pushes that cause ions to reach the detector may be selected based on a range of mass to charge ratios of the ions that are desired to be analysed. More specifically, it may be desired for the highest mass to charge ratio ion of interest in any given ion packet that is pushed by the pusher to reach the ion detector before the next ion packet is pushed by the pusher. This prevents a lower mass to charge
25 ratio ion in an ion packet that is subsequently pushed by the pusher from arriving at the ion detector before the highest mass to charge ratio ion in the preceding ion packet, which could cause mass spectral confusion. As such, it may be desirable for the period of time between consecutive packets of ions being pushed into the time of flight region to be selected to be the same as, or longer than, the duration required for the highest mass to
30 charge ratio ion of interest to travel from the pusher to the ion detector.

Accordingly, if the range of mass to charge ratios that is desired to be mass analysed by the mass analyser is changed, then it may be desired to change the period of time between consecutive packets of ions being pushed into the time of flight region. For example, if the maximum mass to charge ratio that is desired to be mass analysed is
35 increased, then the period of time between consecutive packets of ions being pushed into the time of flight region may be increased so as to allow the higher mass to charge ratio ions more time to travel from the pusher to the detector before the next packet of ions is pushed by the pusher. Conversely, if the maximum mass to charge ratio that is desired to be mass analysed is decreased, then the period of time between consecutive packets of
40 ions being pushed into the time of flight region may be decreased as the highest mass to charge ratio ions do not require as much time to travel from the pusher to the detector.

This enables the pusher to push packets of ions more frequently, and so may increase the duty cycle of the mass analyser.

Conventionally the period of time between consecutive packets of ions being pushed into the time of flight region has been changed simply by changing the period between adjacent pushes of the pusher. However, it has been realised that this can have undesired effects, such as changing the mass to charge ratio accuracy and/or resolving power of the mass analyser. For example, after the pusher rate has been changed the power supply takes time to settle and also the temperature of the mass analyser may vary, which may result in the calibration/relationship between the ion flight time in the mass analyser and the mass to charge ratio changing. Also, this can result in problems synchronising the pusher pulses with the timings of other operations of the mass spectrometer.

MRTOF mass analysers are able to mass analyse ions with a relatively high mass resolution, due to the relatively long ion flight path. However, as the ions have a relatively long flight time through such mass analysers, the highest mass to charge ratio ion in any given ion packet will take a relatively long time to travel from the pusher to the ion detector. As such, the period of time between consecutive packets of ions being pushed into the time of flight region is required to be set to be relatively long, if it is desired to prevent relatively low mass to charge ratio ions in an ion packet pushed by the pusher from arriving at the ion detector before higher mass to charge ratio ions in the preceding ion packet have arrived at the detector. This leads to the mass analyser having a relatively low sampling duty cycle, because the mass analyser is only able to push ions relatively infrequently.

It is known to improve the duty cycle of such mass analysers by “over-pushing” the pusher, such as by using an Encoded Frequent Pulsing (EFP) technique. In such techniques the packets of ions are pushed into the time of flight region by the pusher before waiting for all of the ions from the preceding ion packet to fully traverse the time of flight region. This is enabled by the pusher being controlled to push the packets of ions into the time of flight region with a known push sequence in which the duration between any two pushes in the sequence is unique, i.e. to encode the ion signal. The pusher may be controlled to repeat this push sequence. The ion detector then detects mass spectral data for the ions from the different pushes, which has been multiplexed, and the mass analyser is able to decode/demultiplex this data using knowledge of the push sequence.

In practice, the success of the decoding process depends on characteristics of the mass spectral data that is detected, and in particular the spectral density or the proportion of the time domain that is populated in the encoded multiplexed mass spectral data. For relatively densely populated mass spectra the decoding process can effectively discard low level mass peaks, resulting in low sensitivity and dynamic range. In these instances it is desirable to reduce the mass spectral density by reducing the number of mass spectra that are multiplexed together, i.e. by increasing the period between consecutive pushes of the pusher. However, simply reducing the pusher rate in this way can be problematic for the above-mentioned reasons. For example, this may result in mass measurement changes, e.g. because after the pusher rate is changed the power supply takes time to settle and the

temperature in the mass analyser varies, which may result in the calibration/relationship between the ion flight time in the mass analyser and the mass to charge ratio changing.

Although the above problems have been described in relation to an MRTOF mass analyser having multiple reflectrons, they can also be problems with other forms of time of flight (TOF) mass analysers, such as those that only reflect the ions in an ion mirror (i.e. reflectron) a single time before they are detected or those that do not reflect the ions in an ion mirror. As such, the present invention relates to all such mass analysers.

Embodiments of the present invention enable the mass to charge ratio range being mass analysed by the mass analyser, or the mass spectral density detected by the ion detector, to be varied without having to change the way in which the pusher is operating, e.g. without changing the push rate or push pattern of the pusher. This is achieved by providing an ion attenuator that alternates between a high transmission mode in which it allows or causes ions to reach the ion detector of the mass analyser and a low transmission mode in which ions are prevented from reaching the ion detector. The timings at which the ion attenuator is switched between the high and low transmission modes are synchronised with the timings of the pushes of the pusher such that only a first plurality of the pushes result in ions being received at the ion detector and a second, different plurality of the pushes do not result in ions being received at the detector. This helps avoid problems such as those mentioned above.

According to embodiments of the present invention, an ion attenuator may be provided upstream of the pusher for attenuating ions that travel towards the pusher. The ion attenuator is alternated between operating in the low transmission mode in which it transmits a relatively low proportion of ions (e.g. substantially no ions) and the high transmission mode in which it transmits a relatively higher proportion of ions (e.g. substantially all ions). The timings at which the ion attenuator is switched between the high and low transmission modes is synchronised with the timings at which the pusher pushes, such that substantially no ions (or relatively few ions) reach the pusher whilst some of the pushes occur, and such that a greater proportion of ions (e.g. substantially all ions) are allowed to reach the pusher when other pushes occur.

Alternatively, the ion attenuator may be provided within or downstream of the pusher for attenuating ions pushed by the pusher towards the ion detector. Ions may be allowed or caused to reach the pusher during substantially all of the pushes. The ion attenuator is alternated between operating in the low transmission mode in which it causes a relatively low proportion of ions in each ion packet (e.g. substantially no ions) to reach the ion detector, and the high transmission mode in which it causes a relatively higher proportion of ions in each ion packet (e.g. substantially all ions) to reach the ion detector. The timings at which the ion attenuator is switched between the high and low transmission modes is synchronised with the timings at which the pusher pushes packets of ions into the time of flight region such that substantially no ions (or relatively few ions) from some of the pushes reach the ion detector, and such that a greater proportion of ions from other pushes (e.g. substantially all ions) are allowed to pass from the pusher to the ion detector.

The ion attenuator may take various different forms, as described elsewhere herein. For example, the ion attenuator may be configured such that in the low transmission mode it does any one of the following: deflects ions, block ions, neutralises ions, trap ions, or changes the energy of the ions.

5 Figs. 2A to 2C show the operation of an embodiment that has the ion attenuator arranged upstream of the pusher.

Fig. 2A shows a schematic in which the ion attenuator 5 is arranged upstream of the pusher 3. In this example a series of ion-optical lenses 7 is interposed between the ion attenuator and the pusher, e.g. for focussing or otherwise conditioning the ion beam entering the pusher. However, it is contemplated that the lenses may be excluded and the
10 ion attenuator may be located adjacent to the pusher, as best practice is to attenuate the ions as close to the pusher as possible.

Ions 8 are supplied to the ion attenuator 5, which alternates between the high and low transmission modes. Ions that are transmitted each time that the high transmission
15 mode is performed travel through the ion-optical lenses 7, if present, and into the pusher 3. As described above, a voltage pulse is applied to the electrode(s) of the pusher, either at a constant rate or in a repeating pattern, for pushing ions into the time of flight region towards the ion detector 4.

Fig. 2B shows how the ion beam may be modulated by the ion attenuator in an
20 embodiment in which the ion attenuator fully attenuates the ions in the low transmission mode. This figure shows the magnitude of the ion current at the exit of ion attenuator, as a function of time. The peaks represent the ions that are transmitted to the exit of the ion attenuator in the high transmission mode. Ions of all mass to charge ratios may be transmitted with substantially the same temporal profile. The peaks are spaced apart by
25 periods in which the ion attenuator fully attenuates ions in the low transmission mode and does not transmit ions. The duration of each peak and the duration between each pair of adjacent peaks may be selected so that ions arrive at the pusher during only some of the pushes, as described elsewhere herein. The durations of the peaks may be the same or may differ from each other. Additionally, or alternatively, the durations between adjacent
30 pairs of peaks may be the same or may differ from each other.

Fig. 2C shows the temporal profiles of the ions at the point that they arrive at the pusher 3 of the time of flight mass analyser, when using the ion attenuator as shown in Fig. 2B. It will be appreciated that the ions in each packet of ions that is transmitted by the ion attenuator in the high transmission mode will separate according to mass to charge ratio as
35 they pass downstream to the pusher. Fig. 2C shows three groups of ions that arrive at the pusher due to three respective durations that the high transmission mode is applied. First ions having a relatively low mass to charge ratio (M_{low}) that are transmitted by the ion attenuator during a first duration that the high transmission mode is applied will arrive at the pusher first, as illustrated by the temporal profile shown by the solid line. Second ions
40 having a higher mass to charge ratio (M_{middle}) that are transmitted by the ion attenuator during the first duration that the high transmission mode is applied begin to arrive at the pusher later than the first ions begin to arrive at the pusher, and the second ions continue

to arrive at the pusher until a time that is after all of the first ions have arrived at the pusher, as illustrated by the temporal profile shown by the dashed line. Third ions having a still higher mass to charge ratio (M_{high}) that are transmitted by the ion attenuator during the first duration that the high transmission mode is applied begin to arrive at the pusher later than the second ions (M_{middle}) begin to arrive at the pusher, and the third ions continue to arrive at the pusher until a time that is after all of the second ions have arrived at the pusher, as illustrated by the temporal profile shown by the dotted line. Then there follows a period of time 10 during which substantially no ions arrive at the pusher, due to the ion attenuator operating in the low transmission mode.

After this period 10, first ions having a relatively low mass to charge ratio ions (M_{low}) that are transmitted by the ion attenuator in during a second duration that the high transmission mode is applied begin to arrive at the pusher, as illustrated by the temporal profile shown by the solid line. Second ions having a higher mass to charge ratio (M_{middle}) that are transmitted by the ion attenuator in this second duration begin to arrive at the pusher later than the first ions begin to arrive at the pusher, and the second ions continue to arrive at the pusher until a time that is after all of the first ions have arrived at the pusher, as illustrated by the temporal profile shown by the dashed line. Third ions having a still higher mass to charge ratio (M_{high}) that are transmitted by the ion attenuator in the second duration that the high transmission mode is applied begin to arrive at the pusher later than the second ions (M_{middle}) begin to arrive at the pusher, and the third ions continue to arrive at the pusher until a time that is after all of the second ions have arrived at the pusher, as illustrated by the temporal profile shown by the dotted line. Then there follows another period of time 10 during which substantially no ions arrive at the pusher, due to the ion attenuator operating in the low transmission mode another time.

The above described pattern of ion transmission may be repeated with time. Fig. 2C shows this in respect of low mass to charge ratio ions (M_{low}), higher mass to charge ratio ions (M_{middle}) and still higher mass to charge ratio ions (M_{high}) from a third duration that the high transmission mode is applied arriving at the pusher. However, it will be appreciated that the ion attenuator may operate additional (non-illustrated) high and low transmission modes.

As can be seen from Fig. 2C there are time periods 10 during which no ions arrive at the pusher. There are also time periods during which only ions having some of the mass to charge ratios that are transmitted (in each high transmission mode) are received at the pusher, such as the period between the lowest m/z ions (M_{low}) beginning to arrive at the pusher and the highest m/z ions (M_{high}) beginning to arrive at the pusher, or the period between the lowest m/z ions (M_{low}) finishing arriving at the pusher and the highest m/z ions (M_{high}) finishing arriving at the pusher. There are also time periods 11 during which ions having substantially all of the mass to charge ratios that are transmitted (in each high transmission mode) are received at the pusher.

As has been described above, embodiments of the present invention synchronise the operation of the ion attenuator in the high and low transmission modes with the operation of the pusher such that substantially no ions (or relatively few ions) reach the

pusher whilst some of the pushes occur, and such that a greater proportion of ions (e.g. substantially all ions) are allowed to reach the ion attenuator when other pushes occur. The spectrometer may control this synchronisation by controlling the duration of time between the start or end of the high transmission mode and the time at which the pusher pushes. For example, the pusher rate may be maintained at a substantially constant push rate, whereas the ion attenuator may be controlled to vary the duration of at least some of the occurrences of the high transmission mode and/or to vary the duration of at least some of the occurrences of the low transmission mode.

The spectrometer may synchronise the operation of the ion attenuator in the high and low transmission modes with the operation of the pusher such that only ions having a first selected range of mass to charge ratios are able to be located within the pusher when it pushes. The spectrometer may then change the manner in which the high and low transmission modes are synchronised with the pushes such that only ions having a different selected range of mass to charge ratios are able to be located within the pusher when it pushes.

Alternatively, the spectrometer may synchronise the operation of the ion attenuator in the high and low transmission modes with the operation of the pusher such that substantially no ions (or relatively few ions) reach the pusher whilst some of the pushes occur, and such that other pushes occur when ions having the full range of mass to charge ratios that were transmitted by the ion attenuator in the low transmission mode are present in the pusher. These embodiments may be used to reduce the spectral density detected by the ion detector, since some pushes are prevented from causing ions to reach the ion detector.

Alternatively, the spectrometer may synchronise the operation of the ion attenuator in the high and low transmission modes with the operation of the pusher such that no ions (or relatively few ions) reach the pusher whilst some of the pushes occur, and such that other pushes activate when ions having only a subset of the full range of mass to charge ratios that are transmitted by the ion attenuator in the high transmission mode are present in the pusher. For example, the manner in which the ion attenuator and pusher are synchronised may be selected so that only ions having a selected range of mass to charge ratios are able to be located within the pusher when it pushes.

The ion attenuator may be a device that discards ions at a high rate in the low transmission mode (e.g. all ions) and that discards ions at a lower rate in the high transmission mode (e.g. substantially no ions). For example, the ion attenuator may be configured to transmit ions along an axis in the high transmission mode and deflect ions off the axis in the low transmission mode. The ions may be deflected onto an electrode and neutralised.

Alternatively, the ion attenuator may not necessarily discard or neutralise ions in the low transmission mode. For instance, the ion attenuator may be an ion trap that releases ions downstream in the high transmission mode and that traps ions such that they are not released downstream in the low transmission mode. Alternatively, the ion attenuator may be an ion bunching device that decelerates and/or accelerates ions, in the high

transmission mode, so to form the ions into a bunch that is transmitted downstream each time the mode is performed. For example, the ion bunching device may comprise electrodes and a voltage supply that applies voltages to the electrodes so as to decelerate the ions such that they do not travel downstream during a period after these voltages have
5 been applied, i.e. in the low transmission mode. These voltages may then be deactivated, of the voltage supply may apply voltages to the electrodes so as to accelerate ions, such that ions do travel downstream during a period thereafter, i.e. in the high transmission mode. For example, an ion gate may be used to bunch the ions. Other types of ion attenuator are also contemplated, such as those that defocus the ion beam in the low
10 transmission mode and maintain the beam focussed in the high transmission mode.

Although embodiments have been described in which the ion attenuator is arranged upstream of the pusher so as to prevent ions from reaching the pusher during some of the pushes, it may alternatively be arranged within or downstream of the pusher so as to prevent ions, or reduce the number of ions, in some of the pushes from reaching the ion
15 detector. Figs. 3A and 3B show schematics of such embodiments.

Fig 3A shows a schematic of an embodiment in which the ion beam 8 is received at the pusher 3, which repeatedly pushes the ions orthogonally into the time of flight region of the TOF mass analyser. Ion lenses 7 may be provided upstream of the pusher, e.g. for focussing or otherwise conditioning the ion beam entering the pusher. Fig. 3A depicts
20 three ion packets 12-14 that have been pushed by the pusher. As will be appreciated, the ions in each ion packet separate according to their mass to charge ratio as they pass through the time of flight region, since ions having a lower mass to charge ratio travel faster than ions having a higher mass to charge ratio. As such, any given ion packet elongates in the direction that it is travelling as it moves away from the pusher.

In the depicted embodiment, the ion attenuator allows (or causes) ion packets that are pushed by the pusher to travel away from the pusher at a first angle that is optimised for the ions to be detected at the ion detector (not shown), when the ion attenuator is operating in the high transmission mode. In contrast, when the ion attenuator is operated in the low transmission mode it causes (or allows) ion packets that are pushed by the
30 pusher to travel away from the pusher at a second, different angle such that none or fewer of these ions are detected at the ion detector. Fig. 3A only shows three of the ion packets. The ion attenuator operates in the high transmission mode so as to allow (or cause) the first ion packet 12 and third ion packet 14 to travel at the first angle that is optimised for the ions to be detected at the ion detector, and operates in the low transmission mode to cause
35 (or allow) the second ion packet 13, that was pushed by the pusher between the first and third ion packets, to travel at the second angle such that none or fewer of these ions are detected at the ion detector.

The ion attenuator may switch between the high and low transmission modes by varying the energy of the ions in a direction orthogonal to the time of flight direction (x-direction) in which the ions are primarily pushed by the pusher. For example, the ion
40 attenuator may switch between the high and low transmission modes by varying the energy of the ions in the drift direction (z-direction). In embodiments, the drift direction may be the

direction along which ions enter the pusher. Alternatively, the ion attenuator may switch between the high and low transmission modes by varying the energy of the ions in a direction that is orthogonal to both the time of flight direction (x-direction) and the drift direction (z-direction).

5 The ion attenuator may 5 may be within the pusher and may vary the energy of the ions in the direction orthogonal to the time of flight direction (x-direction) whilst the ions are travelling within the pusher, e.g. by varying an electric field. For example, the ion attenuator may vary the energy of the ions in the drift direction (z-direction) whilst the ions are travelling within the pusher by varying an electric field arranged in the drift direction (z-
10 direction). For instance, the ion attenuator may be configured to increase the drift direction energy of the ions in the low transmission mode, relative to the drift direction energy of the ions in the high transmission mode. This is advantageous as only relatively small voltage changes are required to achieve the desired result, e.g. in the order of tens of volts.

 Although embodiments have been described in which the ion attenuator is within
15 the pusher, less preferred embodiments are contemplated in which the ion attenuator is downstream of the pusher, e.g. as shown in Fig. 3B.

 Fig. 3B shows a schematic of a less preferred embodiment in which the ion beam 8 is received at the pusher 3, which periodically pushes the ions orthogonally into the time of flight region of the TOF mass analyser. Ion lenses 7 may be provided upstream of the
20 pusher, e.g. for focussing or otherwise conditioning the ion beam entering the pusher. An ion attenuator 5 is provided downstream of the pusher, in the time of flight region. Fig. 3B depicts the positions that three ion packets 12-14 that have been consecutively pushed by the pusher would have if the ion attenuator was only operated in the high transmission mode. However, in this embodiment, the ion attenuator is switched between the high and
25 low transmission modes such that it operates in the high transmission mode so as to transmit the first ion packet 12 to the detector, then operates in the low transmission mode so as to block the passage of the second ion packet 13 such that it does not reach the detector, and then operates again in the high transmission mode so as to transmit the third ion packet 14 to the detector. In this example the second ion packet 13 is fully attenuated
30 by the ion attenuator, which is depicted by the ion packet being illustrated more lightly. It will be appreciated that the second ion packet 13 would not actually be present downstream of the attenuator 5.

 As described above, the ions in each ion packet separate according to their mass to charge ratio as they pass through the time of flight region. As such, any given ion packet
35 elongates in the time of flight direction as it moves away from the pusher. Preferably, the ion attenuator 5 is positioned in the time of flight region at a distance from the pusher 3 such that ions from any given push are not able to overtake any ions from the preceding push before they reach the ion attenuator.

 The mass analyser described herein comprises control circuitry and software that
40 controls the synchronisation of the ion attenuator with the pusher. The ion attenuator may be synchronised with the pusher such that ions in any given ion packet arrive at the ion

detector over a time period that does not overlap with the time period that ions in any other ion packet reach the ion detector.

Alternatively, the ion attenuator may be synchronised with the pusher such that ions from different ion packets arrive at the ion detector during overlapping time periods, i.e.

- 5 such that the mass spectral data of ions from different ion packets is multiplexed. This may be useful to improve the duty cycle of the mass analyser. For example, the ion attenuator may be synchronised with the pusher such that an Encoded Frequent Pulsing (EFP) technique is performed. In such techniques the packets of ions are pushed into the time of flight region by the pusher before waiting for all of the ions from the preceding ion packet to
- 10 fully traverse the time of flight region, and such that ions from different ion packets arrive at the ion detector during partially overlapping time periods.

When the ion attenuator is arranged upstream of the pusher, the ion attenuator may be synchronised with the pusher such that the pushes that actually push ion packets into the time of flight region follow a push pattern in which the duration between any two pushes

15 in the pattern is unique, i.e. to encode the ion signal. The pusher may be controlled so that this push pattern is repeated. Alternatively, when the ion attenuator is arranged within or downstream of the pusher, the ion attenuator may be synchronised with the pusher such that the pushes that actually cause ion packets to reach the ion detector follow a push pattern in which the duration between any two pushes in the pattern is unique, i.e. to

20 encode the ion signal. The pusher and ion attenuator may be controlled so that this push pattern is repeated. In these embodiments the ion detector detects mass spectral data for the ions from the different ion packets, which has been multiplexed, and the mass analyser is able to decode/demultiplex this data using knowledge of said pattern.

- However, the success of the decoding/demultiplexing step depends on the spectral
- 25 density of the encoded/multiplexed mass spectral data. Embodiments of the present invention vary the mass spectral density of the mass spectral data detected by the ion detector by varying the rate at which ion packets are received at the ion detector. For example, the mass analyser may determine the mass spectral density of mass spectral data from the ion detector, determine if this is within a pre-set (acceptable) range relative to a target or threshold value, and if the determined mass spectral density is outside of this
- 30 range then the mass analyser may automatically control the synchronisation of the pusher and ion attenuator so as to reduce the rate that ion packets arrive at the ion detector if the spectral density is too high or to increase the rate that ion packets arrive at the ion detector if the spectral density is too low. The decoding/demultiplexing process may also be
- 35 changed to reflect the different rate at which ion packets arrive at the detector.

- In the mass analysers described herein, the ion attenuator is preferably arranged proximate to, adjacent to or within the pusher, e.g. such that the ions travel less than 200 mm between the ion attenuator to the pusher. This reduces the effects on the ions due their time of flight between the ion attenuator and the pusher, and allows a greater variation
- 40 of encoding sequences to be performed. Ideally the ion attenuator, and optionally also any region between the ion attenuator and the pusher, is maintained at a pressure such as <

10^{-3} mbar. This may reduce the scattering of the ions due to the background gas molecules.

The techniques described herein are particularly applicable to a wide range of instrument geometries that incorporate TOF mass analysers, such as those having a relatively long ion flight path. For example, a multi-reflecting time of flight (MRTOF) mass analyser may be used as the TOF mass analyser. In such an instrument, ions are pushed into the TOF flight region and are reflected between ion mirrors multiple times before the impact on the TOF detector. Examples of various geometries that may be used according to embodiments of the present invention, with or without an MRTOF mass analyser, are shown in Figs. 4-8.

Fig. 4 shows a schematic of an embodiment of the present invention comprising an ion source 20, a mass filter 21 (such as a quadrupole mass filter), a fragmentation or reaction device 22 (such as a Collision Induced Dissociation cell) and a TOF mass analyser 1. In use, ions are transmitted from the ion source 20 into the mass filter 21, which is set so as to be capable of only transmitting ions within a certain mass to charge ratio window, which may be a single mass to charge ratio or a range, at any given time. The mass to charge ratio(s) capable of being transmitted by the mass filter 21 at any instant varies with time such that ions of different mass to charge ratio are transmitted the fragmentation or reaction cell 22 at different times. The mass filter therefore effectively separates the ions upstream of the TOF mass analyser 1. The ions are then fragmented or reacted in the fragmentation or reaction cell 22 so as to form fragment or product ions. The fragment or product ions, and remaining precursor ions, are then transmitted into the TOF mass analyser 1 for analysis as described above.

Fig. 5 shows a schematic of an embodiment of the present invention having the same components as Fig. 4, but also an ion mobility separator 23 between the ion source 20 and the fragmentation or reaction device 22. In use, ions are transmitted from the ion source into the IMS device, which separates the ions according to their ion mobility. For example, the IMS device may be a drift time IMS device and ions may be pulsed in the IMS device such that ions of different ion mobility are separated by differing levels of interaction with a buffer gas therein. However, other IMS devices may be used such as a travelling wave IMS device. The ions elute from the IMS device according to their ion mobility and may pass into the mass filter. The mass filter 32 may be set so as to be capable of only transmitting ions within a certain mass to charge ratio window, which may be a single mass to charge ratio or a range, at any given time. The mass to charge ratio(s) capable of being transmitted by the mass filter at any instant may remain constant, or may vary with time such that ions of different mass to charge ratio are transmitted the fragmentation or reaction cell at different times. The mass to charge ratio(s) capable of being transmitted by the mass filter at any instant may be scanned, either once or multiple times for each ion mobility separation cycle of the IMS device (e.g. between pulses of ions into the IMS device). The onwardly transmitted ions are then fragmented or reacted in the fragmentation or reaction cell so as to form fragment or product ions. The fragment or

product ions, and remaining precursor ions, are then transmitted into the TOF mass analyser 1 for analysis as described above.

Fig. 6 shows a schematic of an embodiment of the present invention having the same components as Fig. 5, except that the IMS device 23 is downstream of the mass filter 21. In use, ions are transmitted from the ion source 20 into the mass filter 21. The mass filter may be set so as to be capable of only transmitting ions within a certain mass to charge ratio window, which may be a single mass to charge ratio or a range, at any given time. The mass to charge ratio(s) capable of being transmitted by the mass filter at any instant may remain constant, or may vary with time such that ions of different mass to charge ratio are transmitted the fragmentation or reaction cell 2 at different times. The mass to charge ratio(s) capable of being transmitted by the mass filter at any instant may be scanned, either once or multiple times. The onwardly transmitted ions then pass into the IMS device, which separates the ions according to their ion mobility. The ions elute from the IMS device according to their ion mobility and may pass into the collision or reaction device. The ions are then fragmented or reacted in the fragmentation or reaction cell so as to form fragment or product ions. The fragment or product ions, and remaining precursor ions, are then transmitted into the TOF mass analyser 1 for analysis as described above.

Fig. 7 shows a schematic of an embodiment of the present invention having the same components as Fig. 6, except also comprising a collision or reaction device 24 between the mass filter 21 and IMS device 23. This arrangement allows first generation fragment or product ions to be formed in the upstream collision or reaction device 24 and second generation fragment or product ions to be formed in the downstream collision or reaction device 22.

Fig. 8 shows a schematic of an embodiment of the present invention comprising an ion source 20, a mass selective ion trap 25 such as a quadrupole ion trap, a fragmentation or reaction device 22 such as a Collision Induced Dissociation cell, and a TOF mass analyser 1. In use, ions are transmitted from the ion source into the ion trap, which is set so as to be capable of only ejecting ions within a certain mass to charge ratio window, which may be a single mass to charge ratio or a range, at any given time. The mass to charge ratio(s) capable of being ejected by the ion trap at any instant varies with time such that ions of different mass to charge ratio are ejected from the trap and into the fragmentation or reaction cell at different times. The ion trap therefore effectively separates the ions upstream of the TOF mass analyser. The ions are then fragmented or reacted in the fragmentation or reaction cell so as to form fragment or product ions. The fragment or product ions, and remaining precursor ions, are then transmitted into the TOF mass analyser 1 for analysis as described above. In a non-illustrated embodiment, the ion trap 25 may be omitted. Additionally, or alternatively, in another non-illustrated embodiment the fragmentation or reaction device 22 may be replaced with a device for reducing the energy of the ions, such as a collision cell that is provided with a background gas so as to collisionally cool ions received therein.

Although several embodiments have been described above which include one or more collision or reaction device, it is contemplated that the one or more collision or reaction device may be omitted, for example, and that the TOF mass analyser 1 analyses the precursor ions.

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

 For example, the mass spectrometer may be configured to perform multiple
10 different methods of analysing ions, and to automatically change the manner in which the ion attenuator is synchronised with the pusher when changing between the different methods. The manner in which the ion attenuator is synchronised with the pusher may be pre-set for each of the methods. Alternatively, the spectrometer may automatically adjust the manner in which the ion attenuator is synchronised with the pusher based on the ion
15 signal detected by the detector in a given mode, e.g. in real time. For example, in a given mode, the mass analyser may determine the spectral density of the mass spectral data that is detected by the ion detector, determine if this is within a pre-set (acceptable) range of a target or threshold value, and if the determined mass spectral density is outside of this range then the mass analyser may automatically control the synchronisation of the pusher
20 and ion attenuator so as to reduce or increase the rate that ion packets arrive at the ion detector.

 By way of example, the mass spectrometer may be configured to perform a first method of mass analysing precursor ions by transmitting precursor ions to the pusher for mass analysis, and to perform a second method in which the precursor ions are mass
25 filtered so as to select a range of mass to charge ratios to be fragmented or reacted to produce fragment or other product ions (e.g. adduct ions), which are then transmitted to the pusher for mass analysis. The spectrometer may be configured such that it automatically synchronises the ion attenuator with the pusher in a first manner when the first method is being performed, and such that it automatically synchronises the ion attenuator with the
30 pusher in a second, different manner when the second method is being performed. For instance, the ion attenuator may be synchronised with the pusher in the first method such that ion packets arrive at the ion detector at a relatively low rate, whereas the ion attenuator may be synchronised with the pusher in the second method such that ion packets arrive at the ion detector at a higher rate. In contrast, conventionally ion packets
35 would arrive at the ion detector at the same rate in both the first and second methods, and so the mass spectral data in the second method would typically be more sparsely populated than the mass spectral data in the first method.

 For example, it has also been recognised that providing the ion attenuator upstream of the pusher may be used to prevent ions from undesirably striking downstream surfaces
40 within the spectrometer, which may lead to surface charging and/or contamination issues that may reduce the performance of the spectrometer. For instance, a well-known example of this is that an apertured plate is typically provided on the upstream side of the pusher in

order to restrict the phase-space and control the energy spread of ions by only allowing those that pass through the aperture into the pusher, thus improving TOF focusing and mass resolution. However, as ions strike the apertured plate this causes contamination and surface charging. This ultimately results in the local electrical potentials deviating from the desired values, causing the mass resolution, mass accuracy and ultimately sensitivity of the mass analyser to be affected. Whilst these effects can be alleviated in the short term by re-tuning the mass analyser, this adds extra complexity to the system, and the system may ultimately reach a level of contamination such that it can no longer be satisfactorily re-tuned.

10 An orthogonal acceleration TOF mass analyser typically only has a maximum sampling duty cycle of between 5% and 50%, depending on geometry, meaning that the proportion of ions sampled into the TOF mass analyser can be relatively low. However, conventionally, the ions that are not sampled are still free to strike the apertured plate, resulting in the previously mentioned contamination and surface charging. The inventors

15 have recognised that providing the ion attenuator upstream of the pusher reduces downstream contamination and surface charging. In embodiments, the ion attenuator is configured such that in the low transmission mode it directs ions to a region where contamination does not affect performance of the TOF mass analyser.

Claims

- 5 1. A Time of Flight mass analyser comprising:
 an ion detector;
 a pusher configured to perform a sequence of pushes for pushing packets of ions
 towards the ion detector;
 an ion attenuator configured to alternate between a high transmission mode in
10 which it allows ions to reach the ion detector and a low transmission mode in which it
 prevents ions from reaching the ion detector; and
 wherein the mass analyser is configured to synchronise the operation of the ion
 attenuator in the high and low transmission modes with the timings of the pushes such that
15 a first plurality of the pushes result in ions being received at the ion detector and a second
 different plurality of the pushes do not result in ions being received at the detector.
2. The mass analyser of claim 1, wherein the pusher is configured to perform the
 sequence of pushes at a constant rate, or wherein the sequence of pushes is a pattern of
 pushes that is repeated; and
20 wherein the mass analyser is configured to vary the rate or pattern at which ion
 packets arrive at the ion detector during this sequence of pushes by: (i) varying the
 duration that the high transmission mode is applied for, for at least some of the times that it
 is applied; and/or (ii) varying the duration that the low transmission mode is applied for, for
 at least some of the times that it is applied.
- 25 3. The mass analyser of claim 1 or 2, wherein: (i) the mass analyser comprises a user
 interface configured to enable a user to select or input a range of mass to charge ratios to
 be mass analysed by the mass analyser; or (ii) wherein the mass analyser is pre-
 configured to select a range of mass to charge ratios to be mass analysed from multiple
30 different ranges of mass to charge ratios; and
 wherein in either (i) or (ii) the mass analyser is configured to control the manner in
 which the ion attenuator is synchronised with the timings of the pushes in response to, and
 based on, the selected or input range of mass to charge ratios.
- 35 4. The mass analyser of claim 1, 2 or 3, wherein the mass analyser is configured to
 operate in a first mode by performing the step of synchronising during a first portion of the
 sequence of pushes such that the pushes that are in said first plurality of pushes are
 performed at a first rate or in a first repeating pattern; and to operate in a second mode by
 performing the step of synchronising during a second, later portion of the sequence of
40 pushes such that the pushes that are in said first plurality of pushes are performed at a
 second, different rate or in a second, different repeating pattern.

5. The mass analyser of claim 4, wherein during the first mode the step of synchronising is performed such that ion packets having a first range of mass to charge ratios reach the ion detector, and during the second mode the step of synchronising is performed such that ion packets having a second, different range of mass to charge ratios reach the ion detector.
6. The mass analyser of claim 3, wherein the mass analyser is configured to operate in a first mode in response to the selection or input of a first range of mass to charge ratios to be mass analysed, wherein in the first mode said synchronising is performed such that the pushes that are in said first plurality of pushes are performed at a first rate or in a first repeating pattern; and wherein the mass analyser is configured to operate in a second mode in response to the selection or input of a second, different range of mass to charge ratios to be mass analysed, wherein in the second mode said synchronising is performed such that the pushes that are in said first plurality of pushes are performed at a second rate or in a second repeating pattern.
7. The mass analyser of claim 1, 2 or 3, wherein the mass analyser is configured to operate in a first mode by performing the step of synchronising during a first portion of the sequence of pushes such that the pushes in said first plurality of pushes are performed at a constant rate; and to operate in a second mode by performing the step of synchronising during a second, different portion of the sequence of pushes such that the pushes in said first plurality of pushes are performed at non-uniform intervals.
8. The mass analyser of claim 7, wherein in the second mode the pushes in said first plurality of pushes are performed at non-uniform intervals and such that ions from different ones of these pushes arrive at the ion detector during overlapping time periods so as to form a multiplexed ion signal, and wherein the mass analyser is configured to demultiplex the ion signal.
9. The mass analyser of claim 1, 2 or 3, wherein the mass analyser is configured to operate in an encoding mode by alternating the ion attenuator between the high transmission mode and the low transmission mode so that these modes of the ion attenuator define the duration between any two pushes in the first plurality of pushes as being unique over an encoding period.
10. The mass analyser of claim 1, 2 or 3, wherein the mass analyser is configured to operate in a first encoding mode by performing the step of synchronising such that the duration between any two pushes in the first plurality of pushes is unique over a first encoding period; and to operate in a second encoding mode by performing the step of synchronising such that the duration between any two pushes in the first plurality of pushes is unique over a second longer encoding period, or such that the ion packets received at the ion detector are otherwise encoded in a different manner to in the first encoding mode.

11. The mass analyser of any preceding claim, wherein the mass analyser is configured to vary the mass spectral density of the mass spectral data detected by the ion detector, by varying the manner in which the ion attenuator and pusher are synchronised so as to change the rate at which ion packets are received at the ion detector.
12. The mass analyser of claim 11, wherein the mass analyser is configured to:
determine the mass spectral density of mass spectral data detected by the ion detector; and
(i) determine whether the mass spectral density is above a first threshold value, and if the determined mass spectral density is above the first threshold value then automatically control the synchronisation of the pusher with the ion attenuator so as to reduce the rate that ion packets arrive at the ion detector; and/or
(ii) determine whether the mass spectral density is below a second threshold value, and if the determined mass spectral density is below the second threshold value then automatically control the synchronisation of the pusher with the ion attenuator so as to increase the rate that ion packets arrive at the ion detector.
13. The mass analyser of any preceding claim, wherein the ion attenuator is arranged within or downstream of the pusher, and is configured such that in the high transmission mode it allows or causes ions pushed in said first plurality of pushes to arrive at the ion detector and prevents ions pushed in said second plurality of pushes from arriving at the ion detector.
14. The mass analyser of claim 13, wherein the mass analyser is configured such that, during said second plurality of pushes, the ion attenuator increases or decreases the energy of the ions in a direction that is orthogonal to the direction in which the pusher pushes the ions, relative to the energy that ions have in said direction during the first plurality of pushes.
15. The mass analyser of claim 14, wherein the ion attenuator comprises one or more electrodes and a voltage supply that are configured to generate an electric field in said direction, wherein the magnitude of the electric field is higher or lower during each of said second plurality of pushes than during each of the first plurality of pushes.
16. The mass analyser of any preceding claim, wherein the ion attenuator is located adjacent to the pusher.
17. The mass analyser of any preceding claim, wherein the mass analyser is a Multi-Reflecting Time-of-Flight mass analyser comprising two ion mirrors arranged and configured such that the ions are accelerated into one of the ion mirrors by the pusher and

are reflected by each of the mirrors, and between the mirrors, a plurality of times before reaching the ion detector.

5 18. A mass spectrometer comprising a mass analyser as claimed in any preceding claim.

10 19. The mass spectrometer of claim 18, wherein the mass spectrometer is configured to analyse ions according to multiple different techniques, and to automatically change the manner in which the ion attenuator is synchronised with the pusher when changing between the different techniques.

15 20. The mass spectrometer of claim 19, further comprising a fragmentation or reaction device, wherein the mass spectrometer is configured to perform a first of said different techniques in which precursor ions are transmitted to the pusher for mass analysis, and to perform a second of said different techniques in which the precursor ions are fragmented or reacted in the fragmentation or reaction device and the resulting fragment or other product ions are then transmitted to the pusher for mass analysis.

20 21. The mass spectrometer of claim 20, further comprising a mass filter and wherein the spectrometer is configured such that in said second of the different techniques it mass filters the precursor ions in the mass filter so as to transmit precursor ions having a restricted range of mass to charge ratios to the fragmentation or reaction device.

25 22. The mass spectrometer of claim 20 or 21, wherein the ion attenuator is synchronised with the pusher in the first of said different techniques such that ion packets arrive at the ion detector at a relatively low rate, whereas the ion attenuator is synchronised with the pusher in the second of said different techniques such that ion packets arrive at the ion detector at a higher rate.

30 23. A method of mass spectrometry comprising:
using a mass analyser or mass spectrometer as claimed in any preceding claim to mass analyse ions.

35 24. The method of claim 23, wherein the pusher performs the pushes in said sequence of pushes at a constant rate throughout the entire method; or wherein the sequence of pushes consists of a single pattern of pushes that is repeated throughout the entire method.