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**Covey et al.**

(54) **MASS ANALYSIS SYSTEM WITH LOW PRESSURE DIFFERENTIAL MOBILITY SPECTROMETER**

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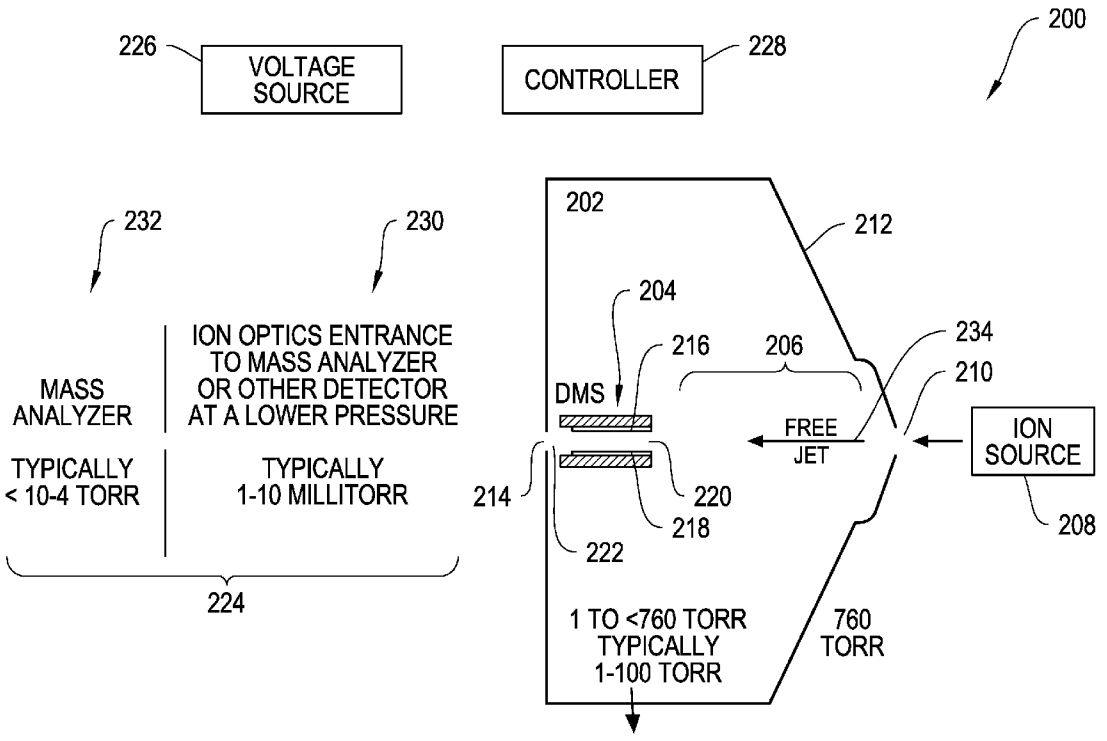
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(57) **ABSTRACT**

A mass analysis system including a low pressure dissociation region and a differential mobility spectrometer. The differential mobility spectrometer including at least one pair of filter electrodes defining an ion flow path where the filter electrodes generate an electric field for passing through a selected portion of the sample ions based on the mobility characteristics of the sample ions. The differential mobility spectrometer also includes a voltage source that provides DC and RF voltages to at least one of the filter electrodes to generate the electric field, an ion inlet that receives sample ions that have passed through the low pressure dissociation region, and an ion outlet that outputs the selected portion of the sample ions. A mass spectrometer receives some or all of the selected portion of the sample ions.



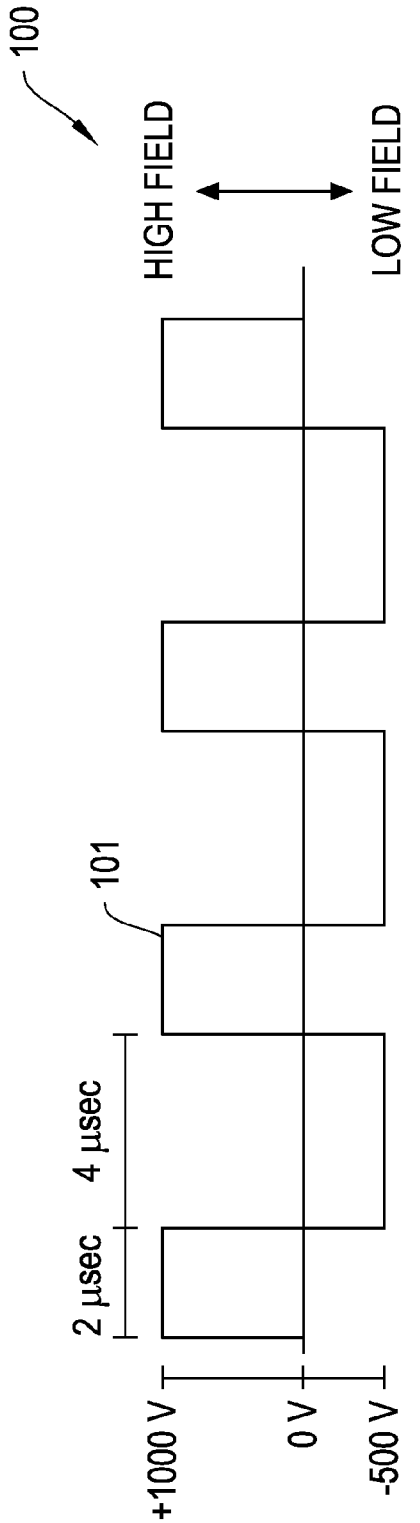



Figure 1A (Prior Art)

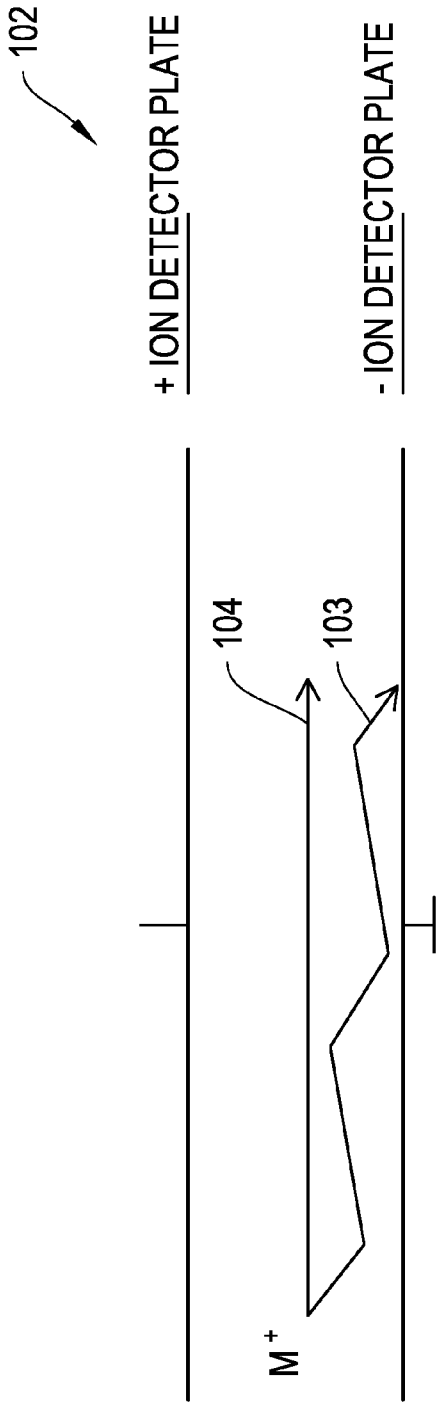



Figure 1B (Prior Art)

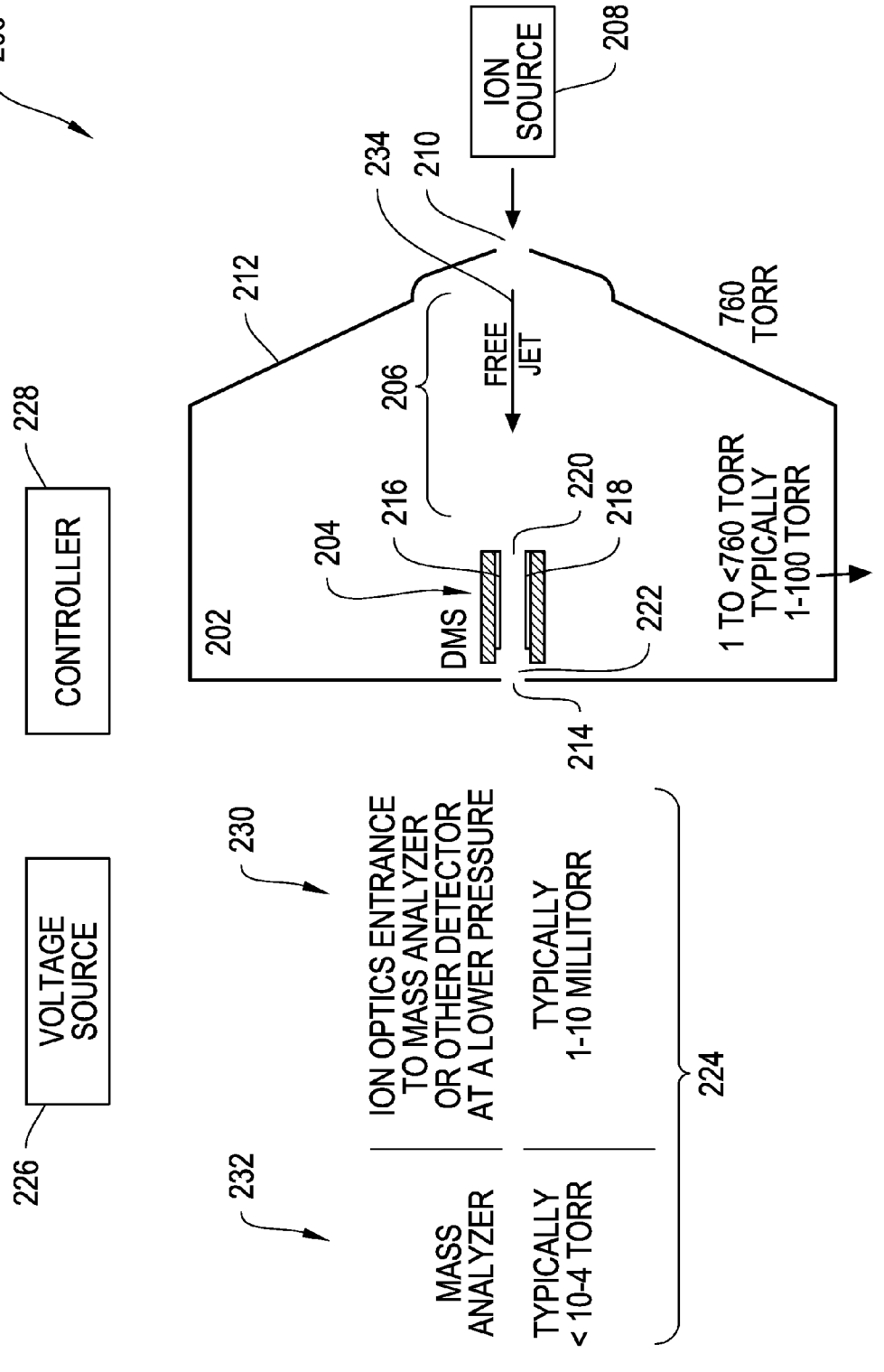

200
ION SOURCE
208
234
210
212
760 TORR
FREE JET
206
228
CONTROLLER
216
204
220
218
202
DMS
222
1 TO <760 TORR TYPICALLY 1-100 TORR
214
230
ION OPTICS ENTRANCE TO MASS ANALYZER OR OTHER DETECTOR AT A LOWER PRESSURE
TYPICALLY 1-10 MILLITORR
VOLTAGE SOURCE
226
232
MASS ANALYZER
TYPICALLY < 10-4 TORR
224

Figure 2

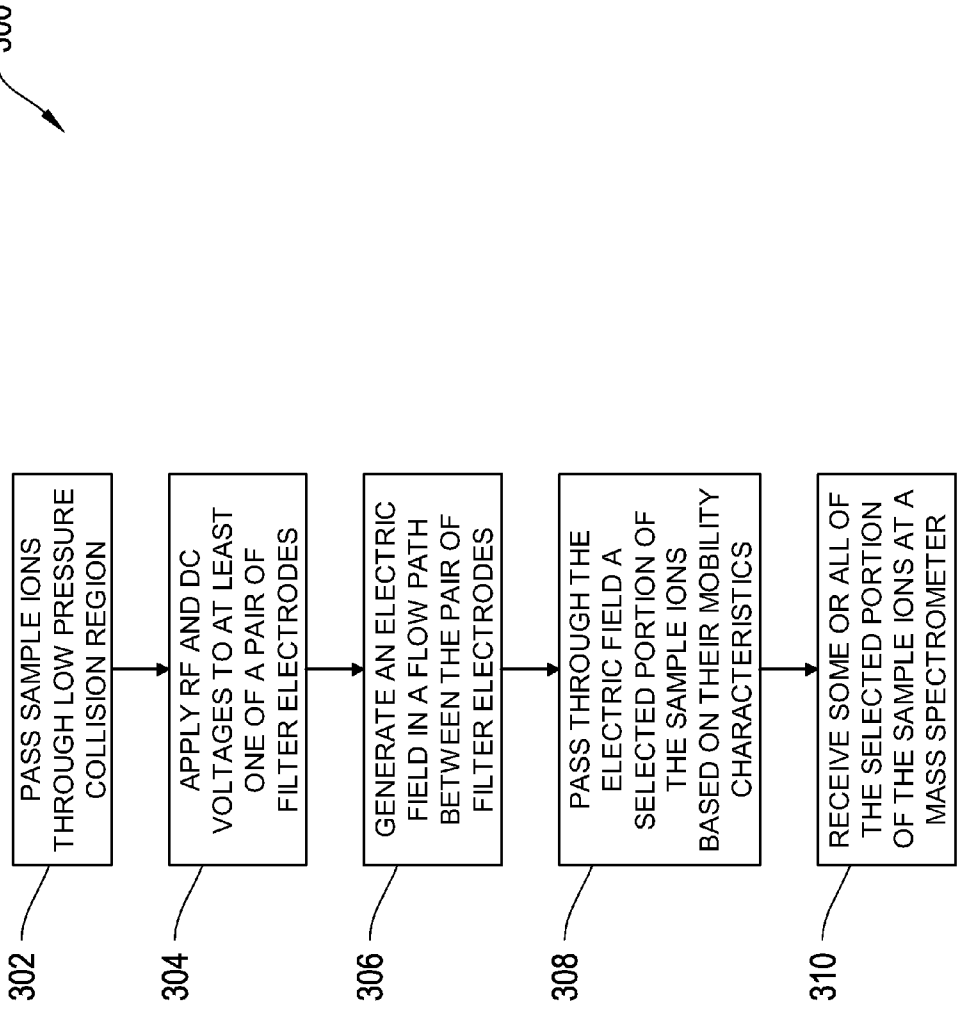

300
PASS SAMPLE IONS THROUGH LOW PRESSURE COLLISION REGION
APPLY RF AND DC VOLTAGES TO AT LEAST ONE OF A PAIR OF FILTER ELECTRODES
GENERATE AN ELECTRIC FIELD IN A FLOW PATH BETWEEN THE PAIR OF FILTER ELECTRODES
PASS THROUGH THE ELECTRIC FIELD A SELECTED PORTION OF THE SAMPLE IONS BASED ON THEIR MOBILITY CHARACTERISTICS
RECEIVE SOME OR ALL OF THE SELECTED PORTION OF THE SAMPLE IONS AT A MASS SPECTROMETER
302
304
306
308
310

Figure 3

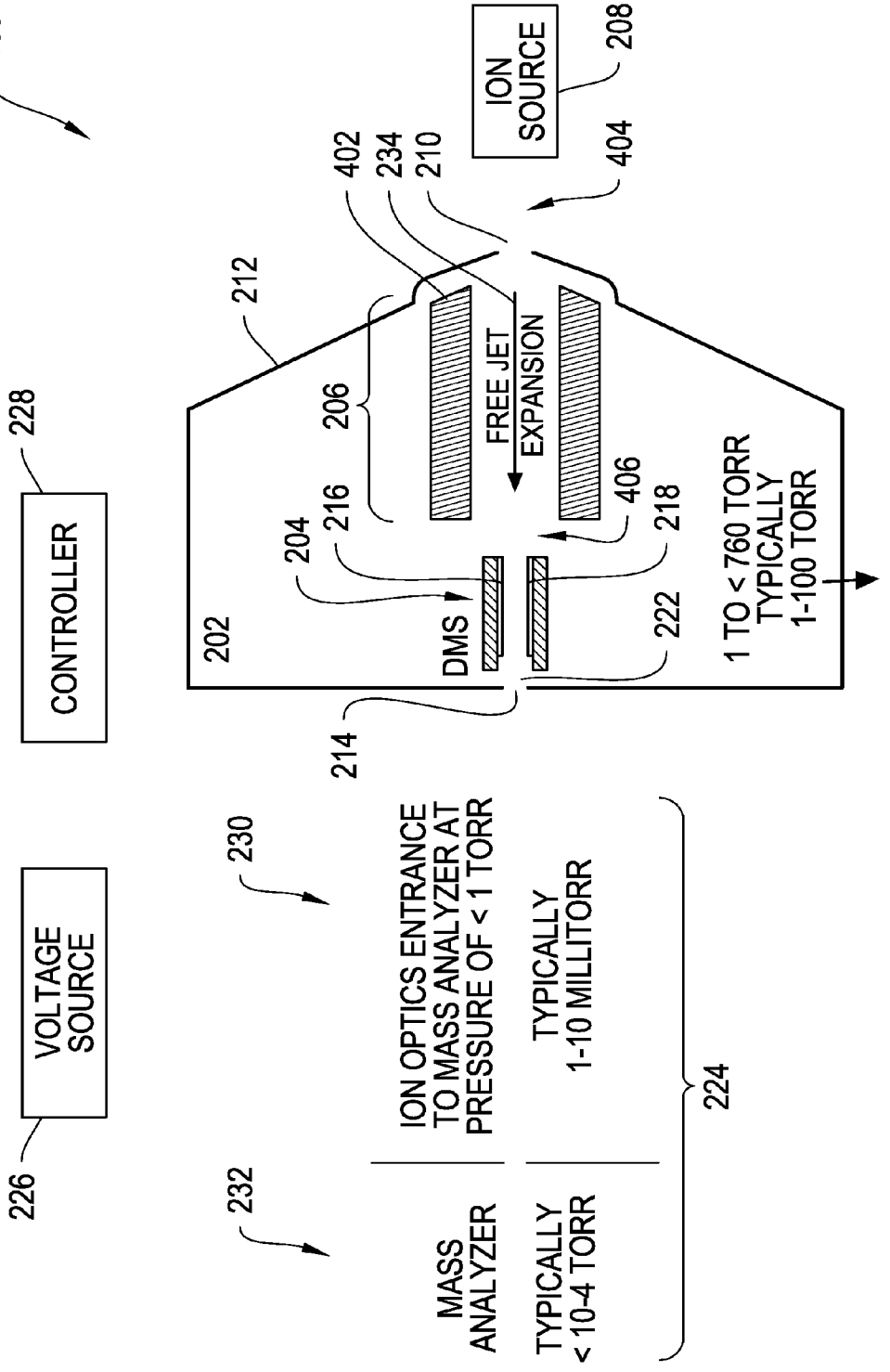

400
ION SOURCE
208
402
234
210
404
212
206
FREE JET EXPANSION
406
218
216
204
202
DMS
222
214
1 TO < 760 TORR TYPICALLY 1-100 TORR
228
CONTROLLER
230
ION OPTICS ENTRANCE TO MASS ANALYZER AT PRESSURE OF < 1 TORR
TYPICALLY 1-10 MILLITORR
224
VOLTAGE SOURCE
226
232
MASS ANALYZER
TYPICALLY < 10-4 TORR

Figure 4

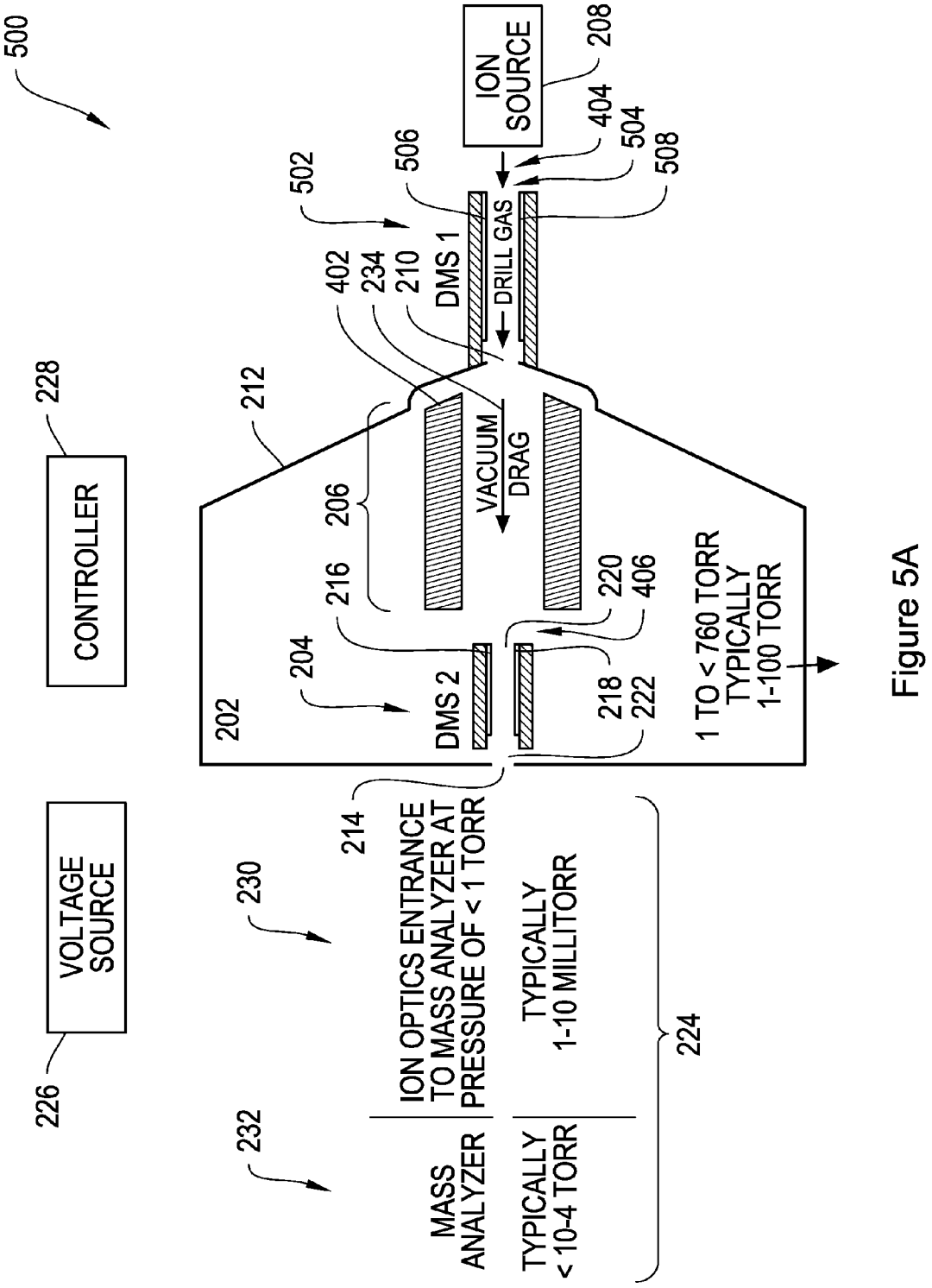

500
ION SOURCE
208
404
504
508
506
502
DMS 1
DRILL GAS
402
234
210
212
228
CONTROLLER
VACUUM DRAG
206
216
220
406
204
DMS 2
218
222
202
1 TO < 760 TORR TYPICALLY 1-100 TORR
214
ION OPTICS ENTRANCE TO MASS ANALYZER AT PRESSURE OF < 1 TORR
230
TYPICALLY 1-10 MILLITORR
224
226
VOLTAGE SOURCE
232
MASS ANALYZER
TYPICALLY < 10-4 TORR

Figure 5A

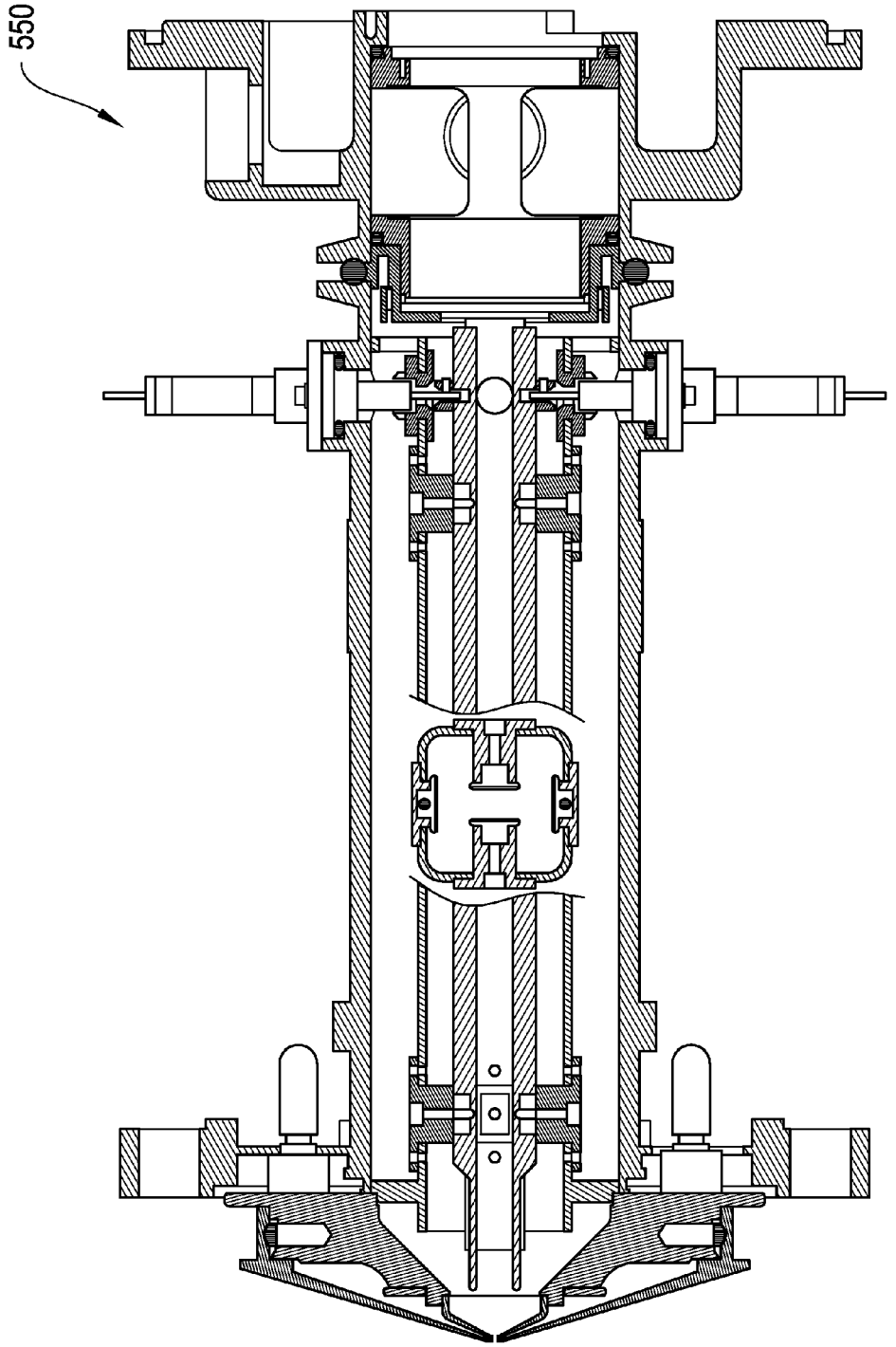



Figure 5B

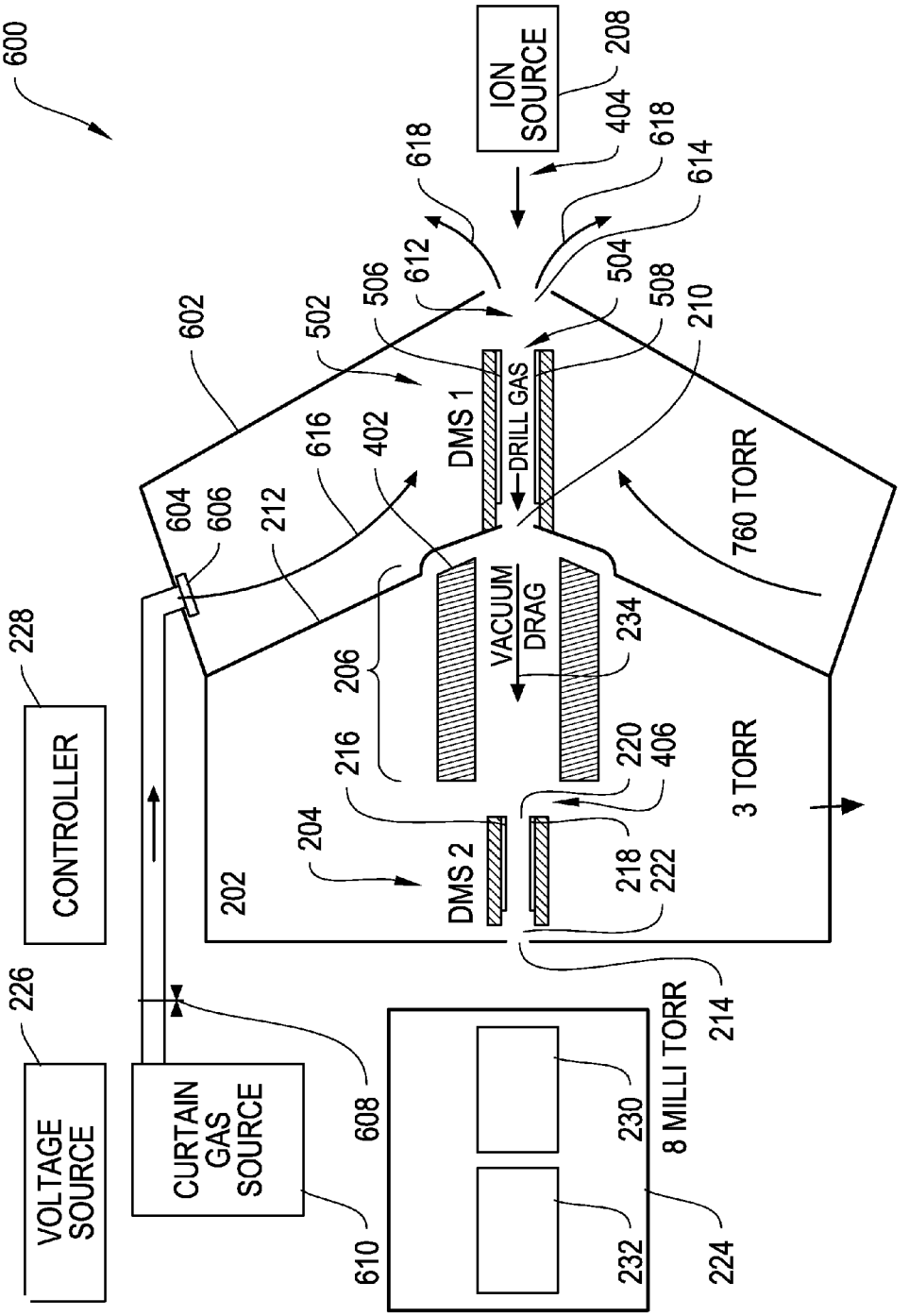

600
ION SOURCE
208
404
618
614
618
612
506
504
508
210
602
502
DMS 1
DRILL GAS
616
402
760 TORR
604
606
212
VACUUM DRAG
234
206
228
CONTROLLER
216
220
406
204
3 TORR
DMS 2
218
222
202
226
214
608
VOLTAGE SOURCE
CURTAIN GAS SOURCE
230
8 MILLI TORR
610
232
224

Figure 6

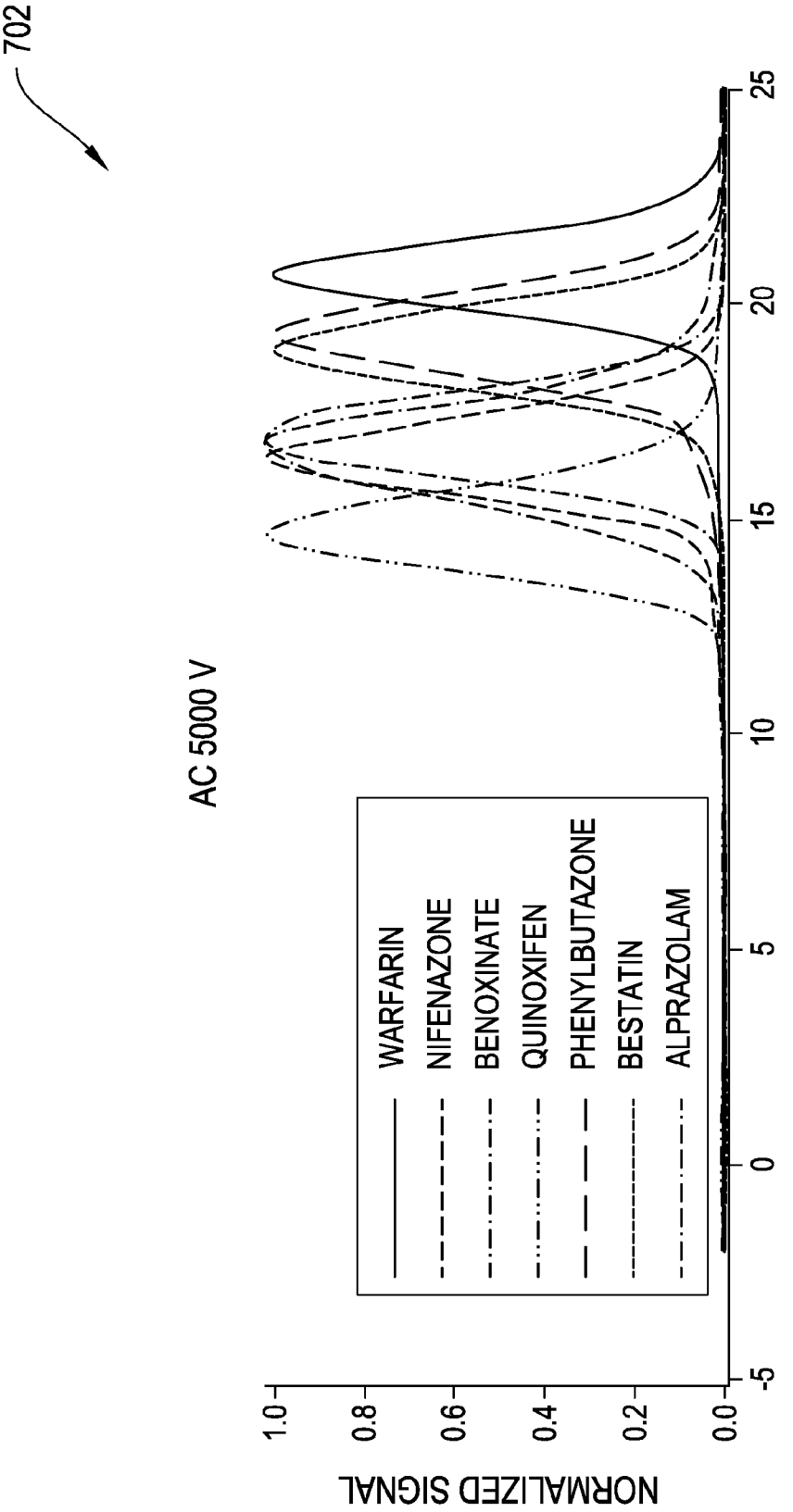



Figure 7A (part 1)

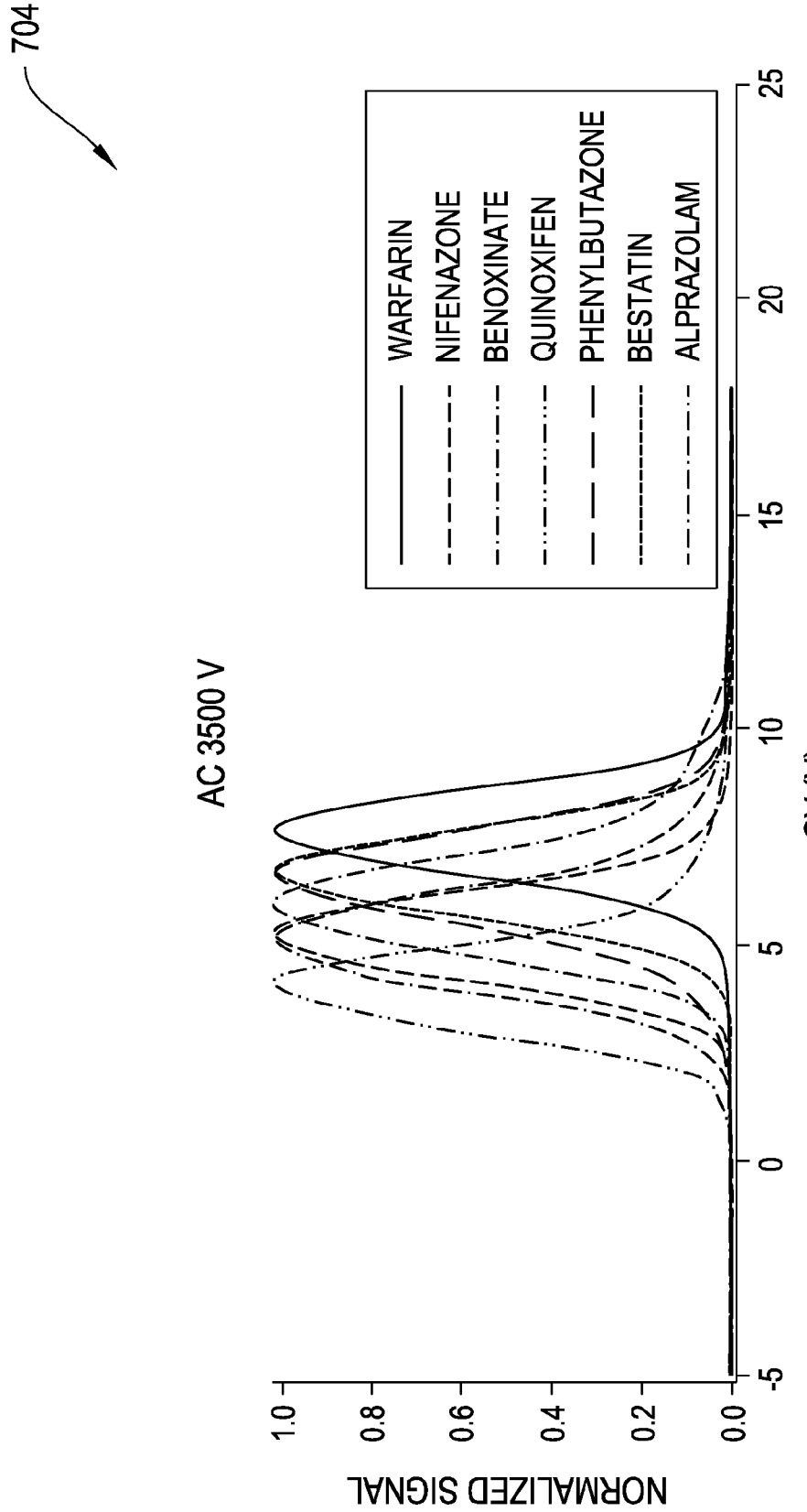



Figure 7A (part 2)

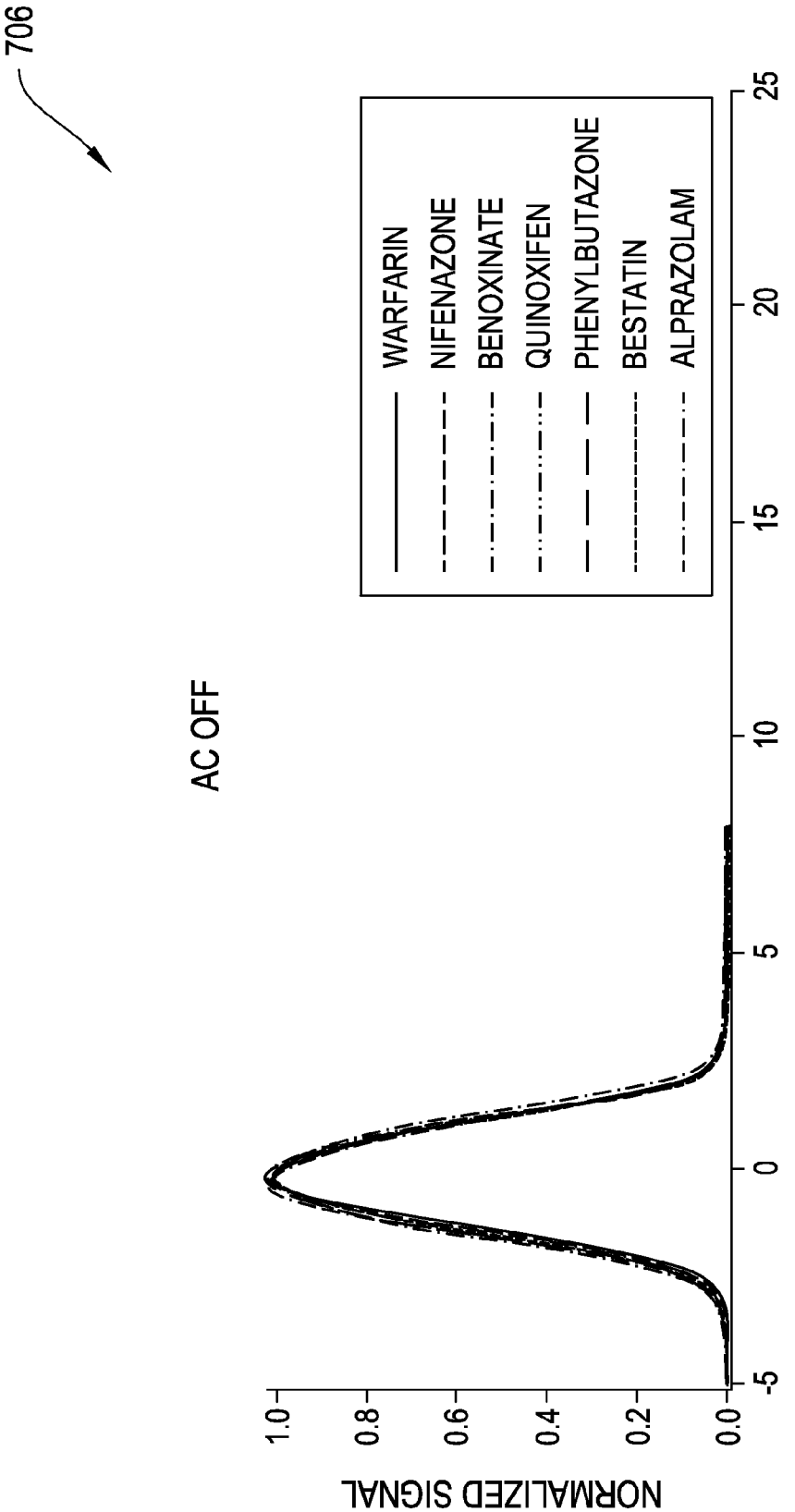



Figure 7A (part 3)

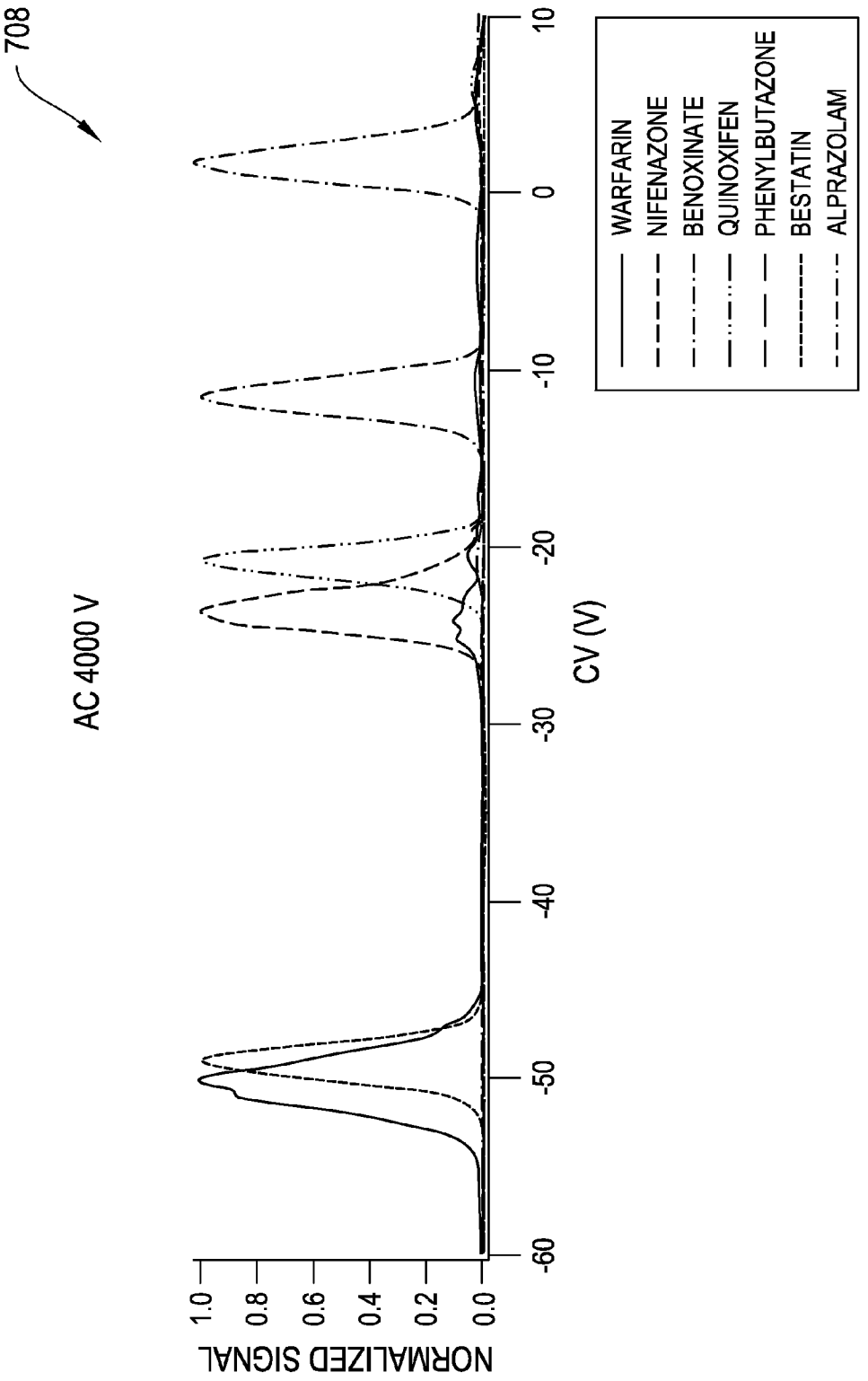



Figure 7B (part 1)

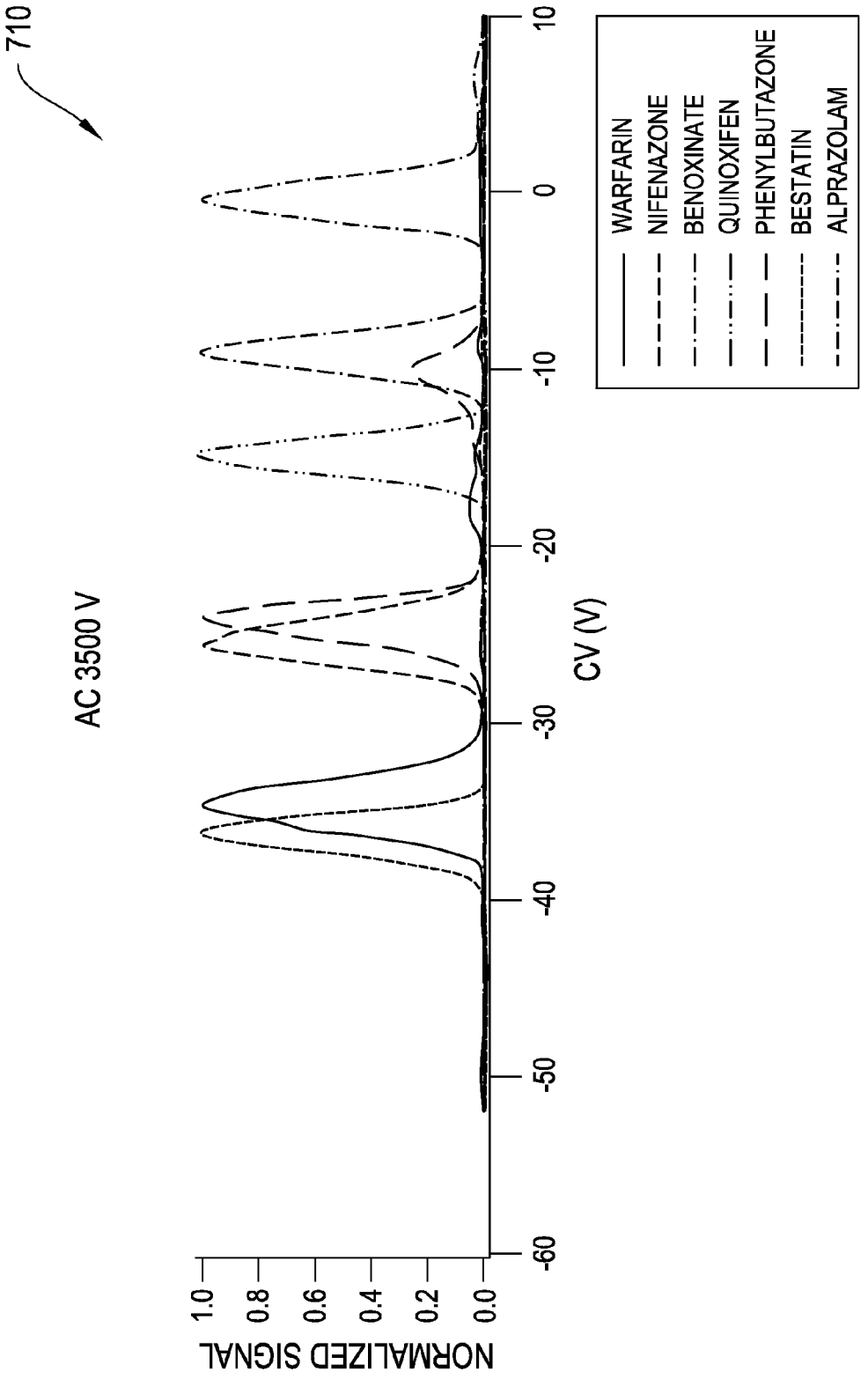



Figure 7B (part 2)

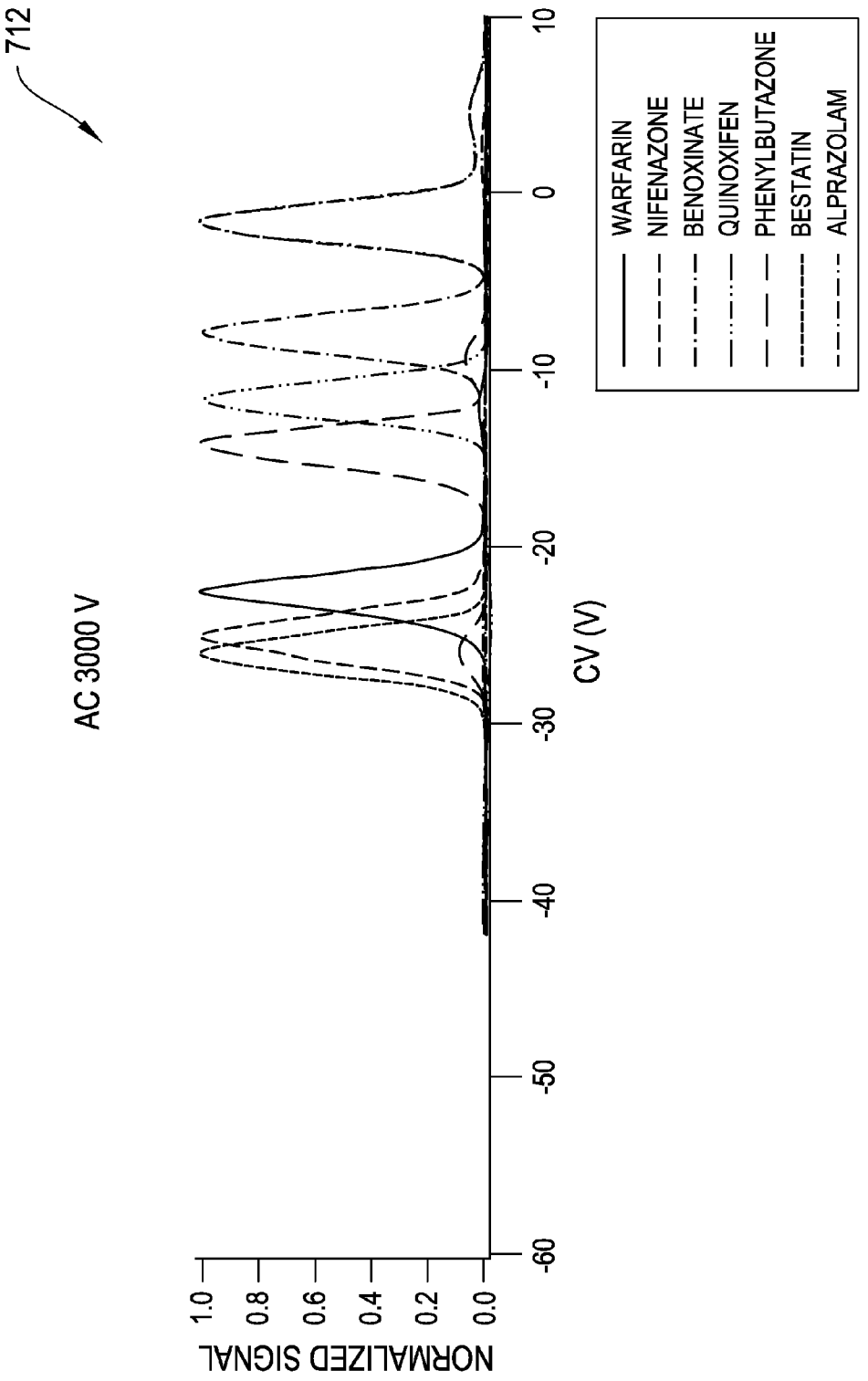



Figure 7B (part 3)

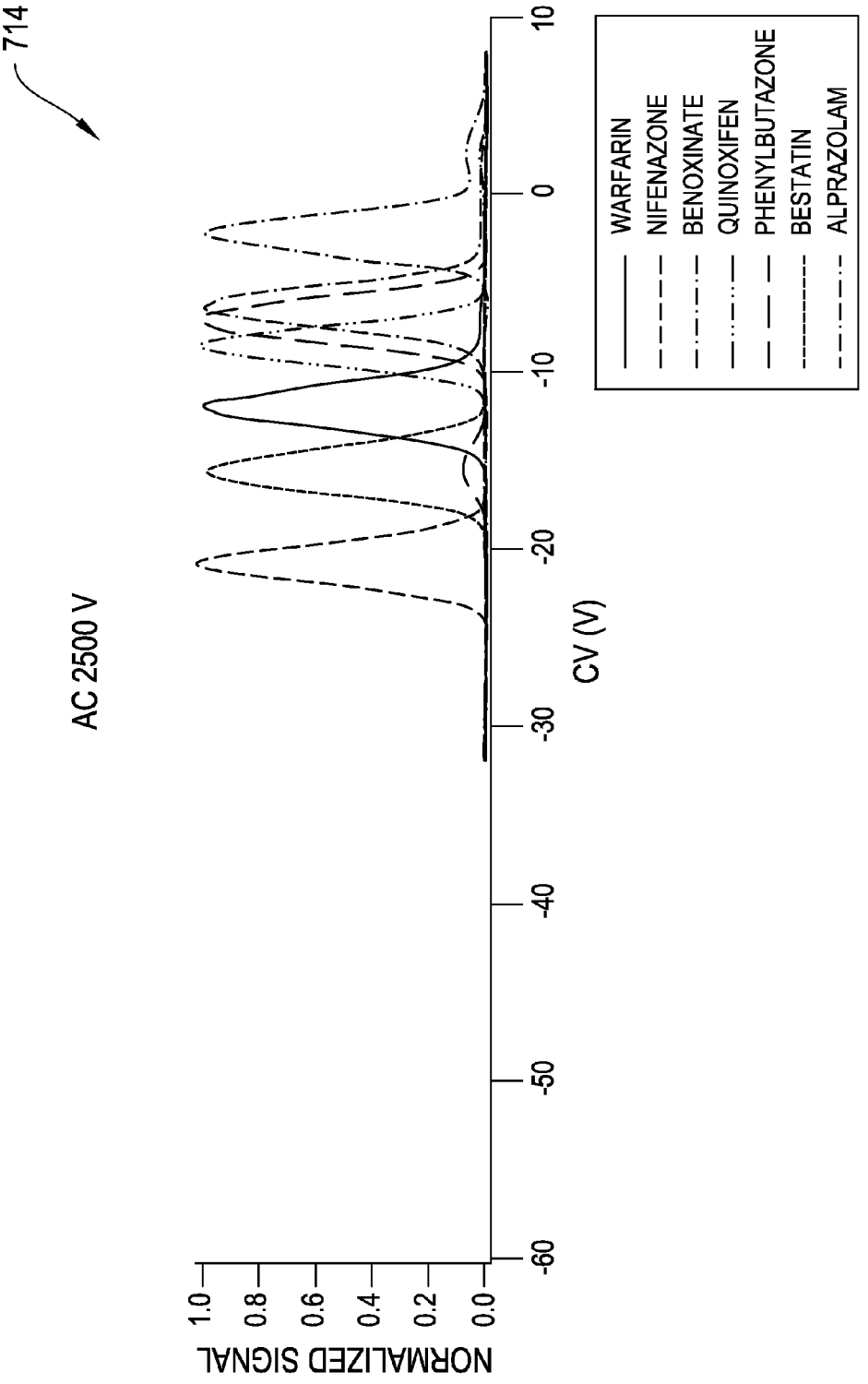



Figure 7B (part 4)

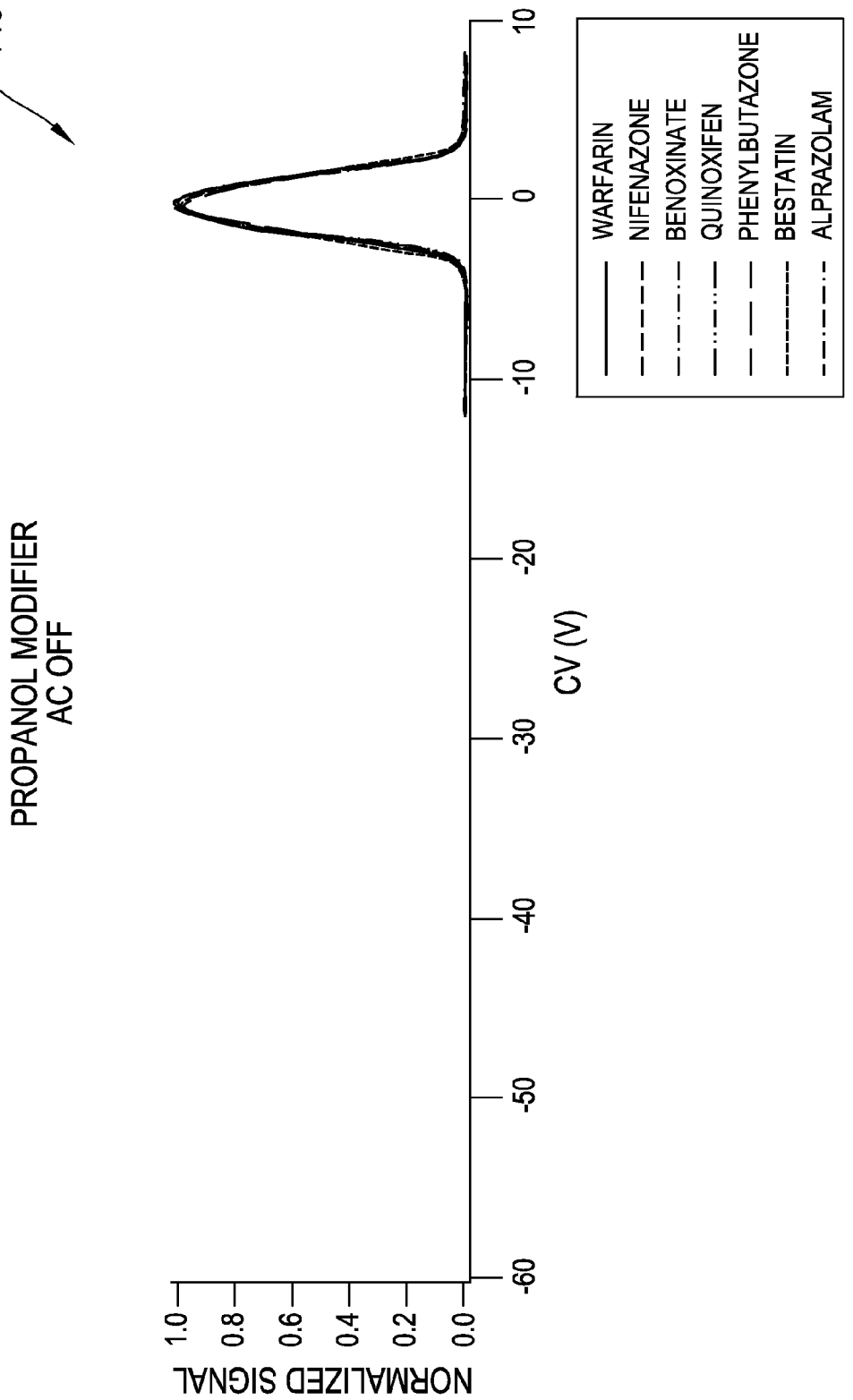



Figure 7B (part 5)

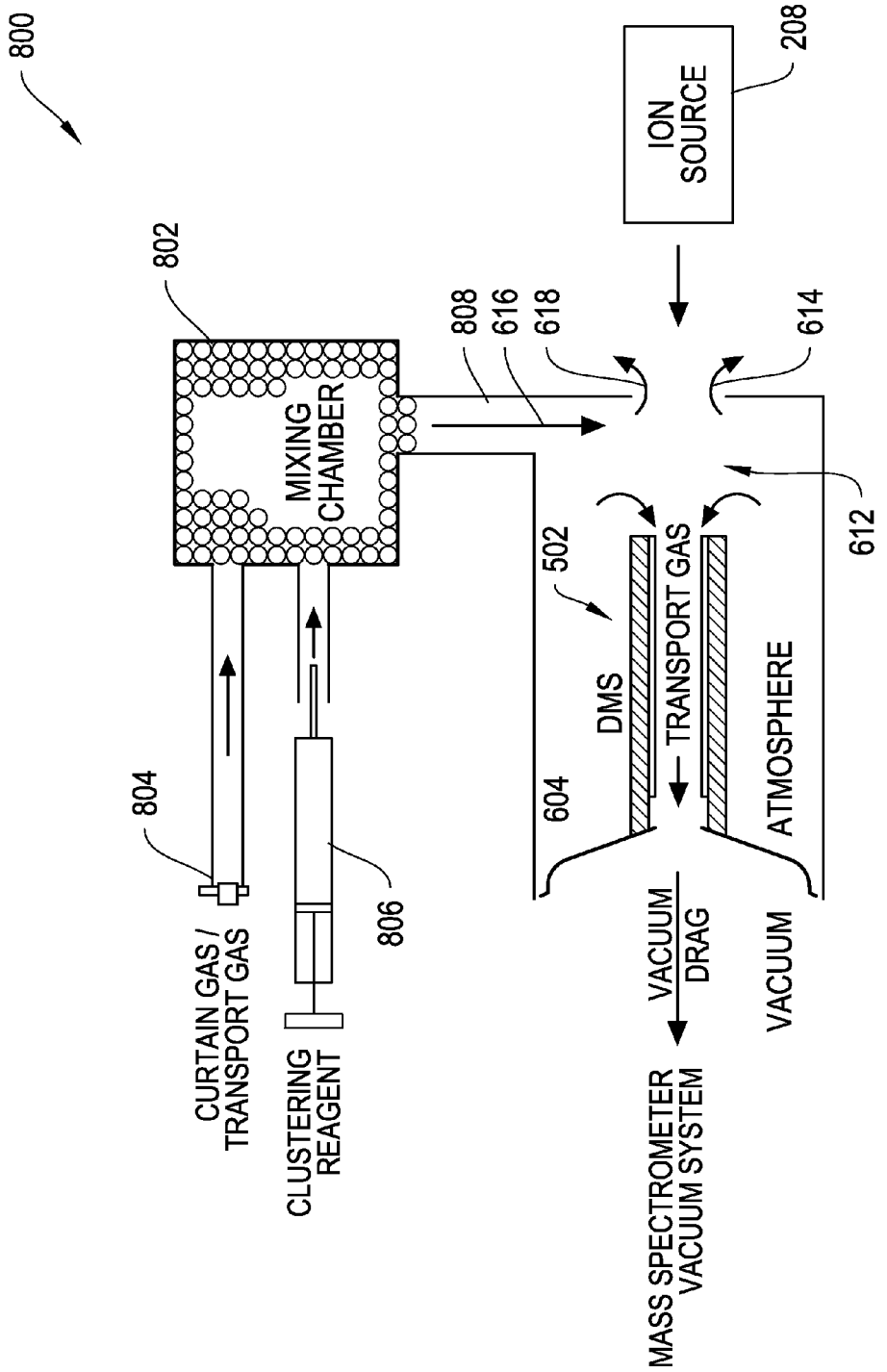

800
208
ION SOURCE
802
MIXING CHAMBER
808
616
618
614
612
502
DMS
TRANSPORT GAS
ATMOSPHERE
604
804
806
CURTAIN GAS / TRANSPORT GAS
CLUSTERING REAGENT
VACUUM DRAG
VACUUM
MASS SPECTROMETER VACUUM SYSTEM

Figure 8

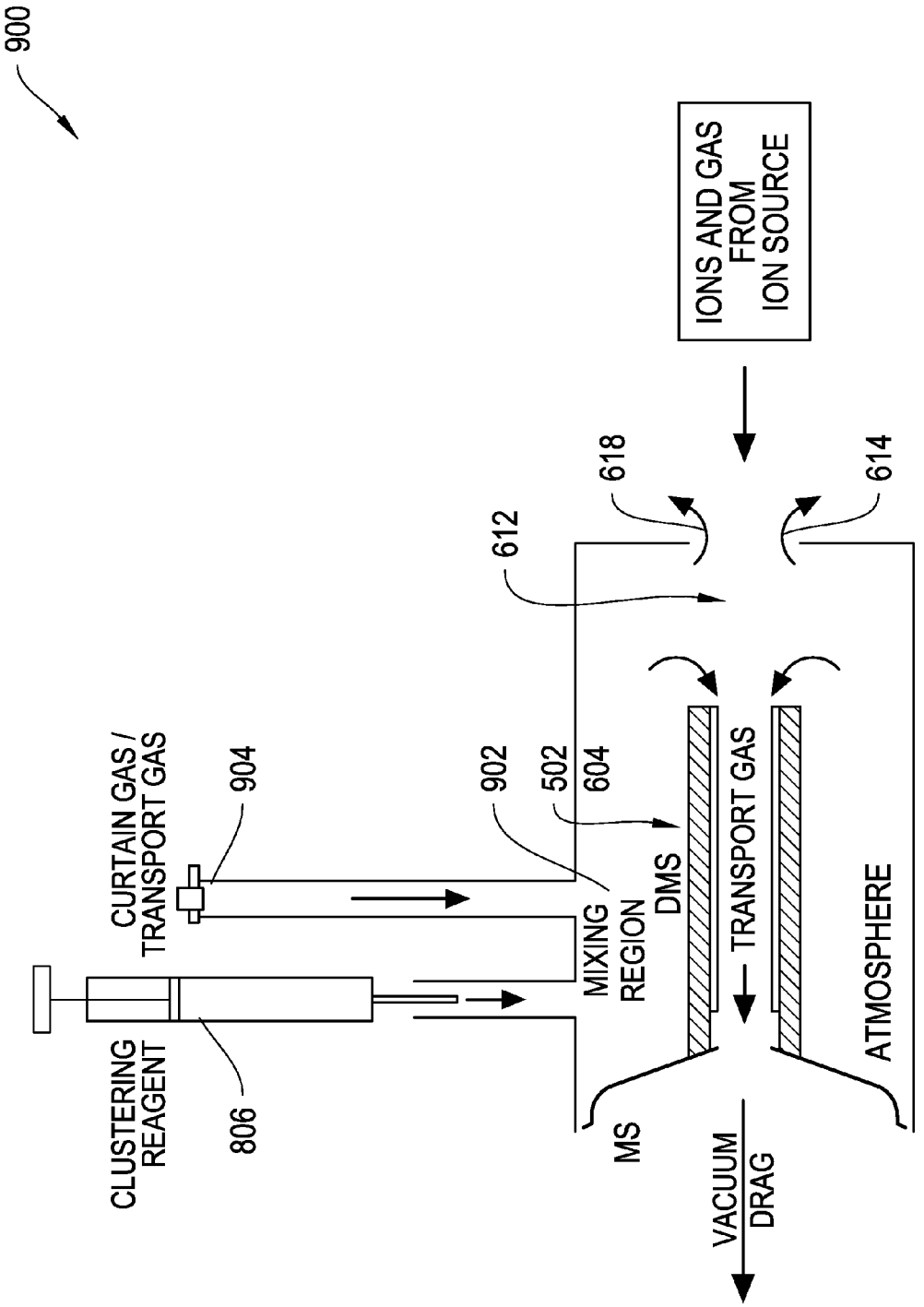

900
IONS AND GAS FROM ION SOURCE
618
614
612
CURTAIN GAS / TRANSPORT GAS
904
902
502
604
MIXING REGION
DMS
TRANSPORT GAS
ATMOSPHERE
CLUSTERING REAGENT
806
MS
VACUUM DRAG

Figure 9

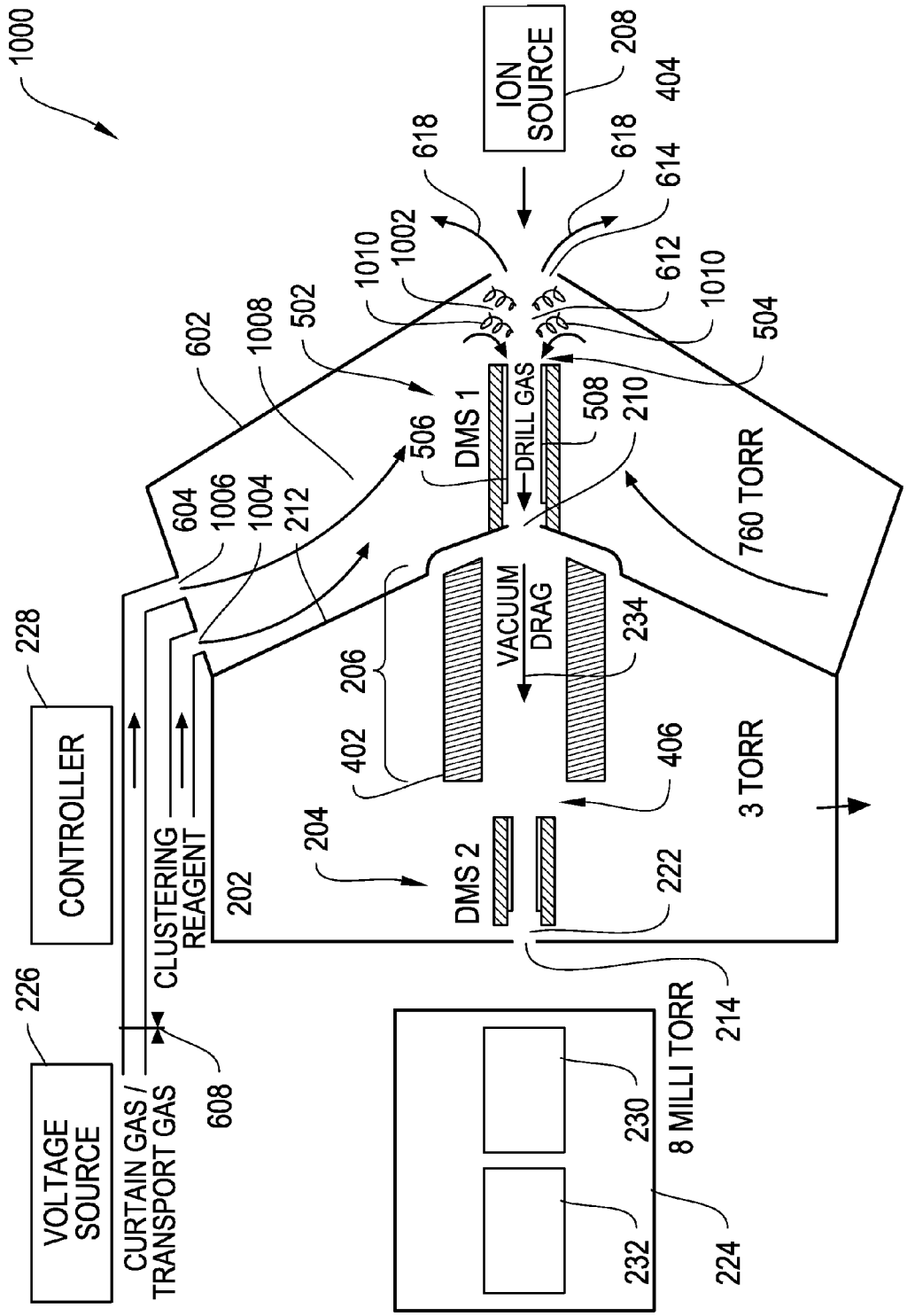

1000
ION SOURCE
208
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618
614
1010
1002
612
1010
602
1008
502
504
DMS 1
DRILL GAS
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508
210
604
1006
1004
212
760 TORR
VACUUM DRAG
234
206
402
406
3 TORR
204
DMS 2
222
202
228
CONTROLLER
CLUSTERING REAGENT
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VOLTAGE SOURCE
CURTAIN GAS / TRANSPORT GAS
608
214
230
8 MILLI TORR
232
224

Figure 10

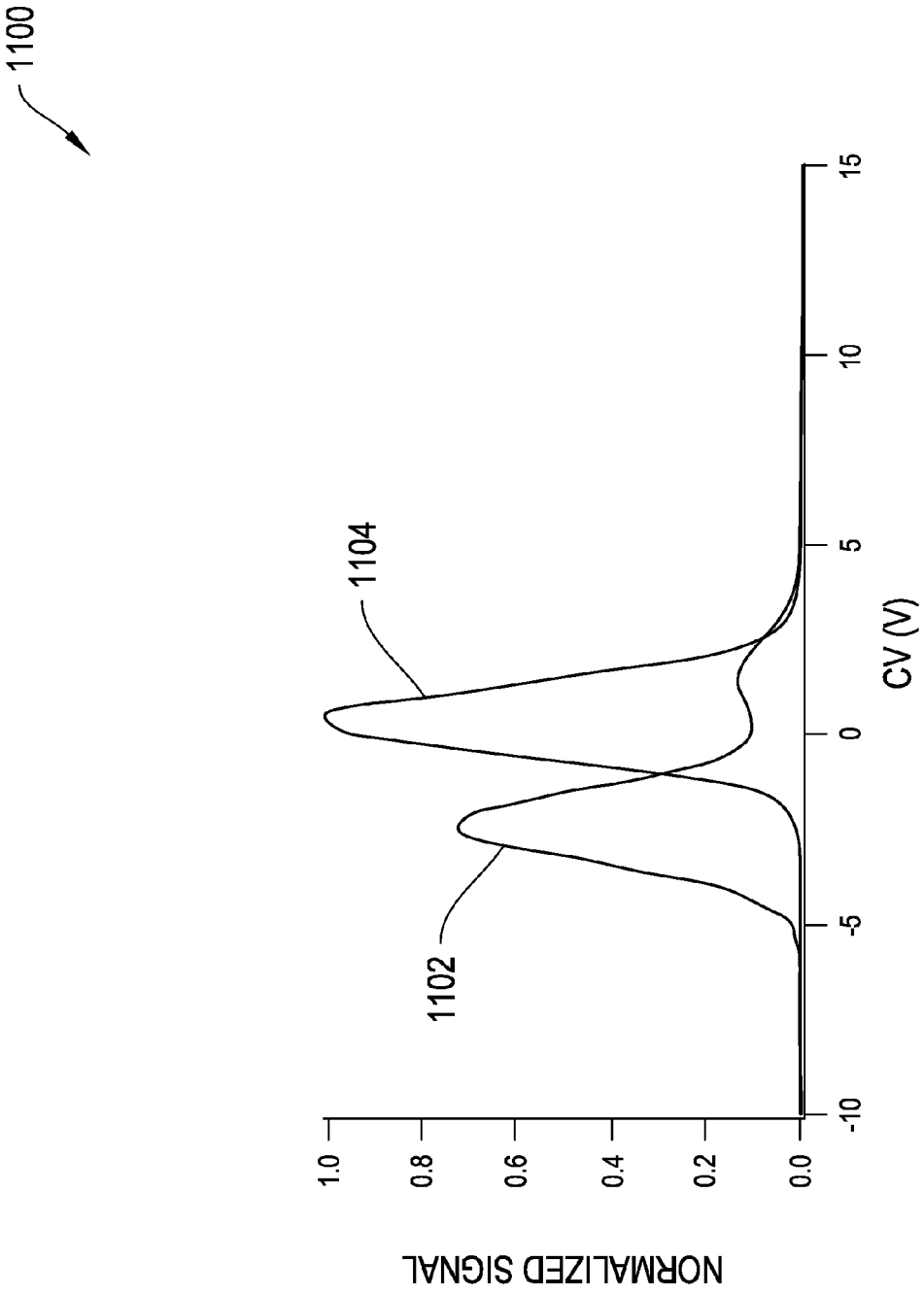

1100
1104
1102
NORMALIZED SIGNAL
1.0
0.8
0.6
0.4
0.2
0.0
-10
-5
0
5
10
15
CV (V)

Figure 11

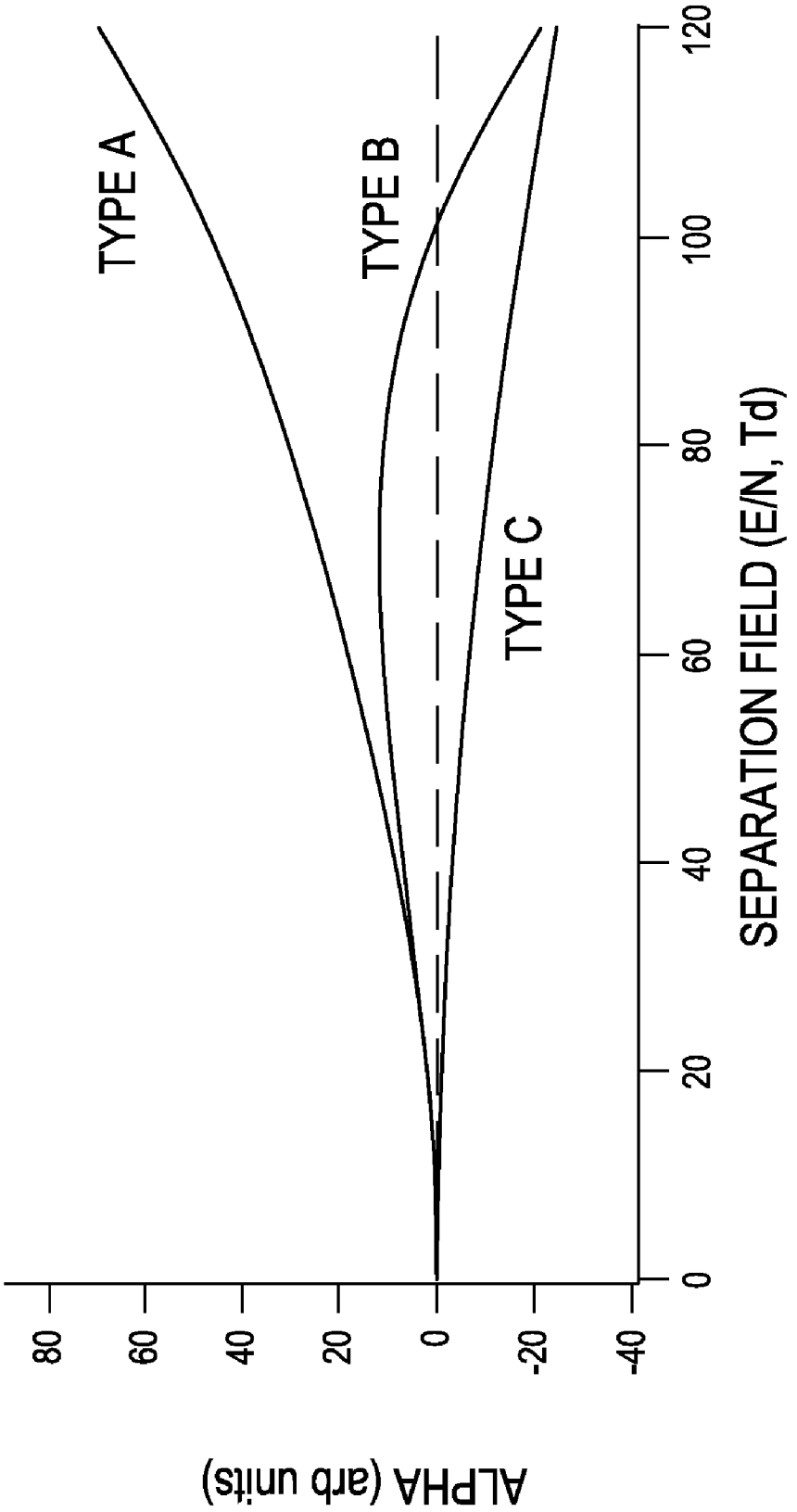

TYPE A
TYPE B
TYPE C
80
60
40
20
0
-20
-40
0
20
40
60
80
100
120
SEPARATION FIELD (E/N, Td)
ALPHA (arb units)

Figure 12

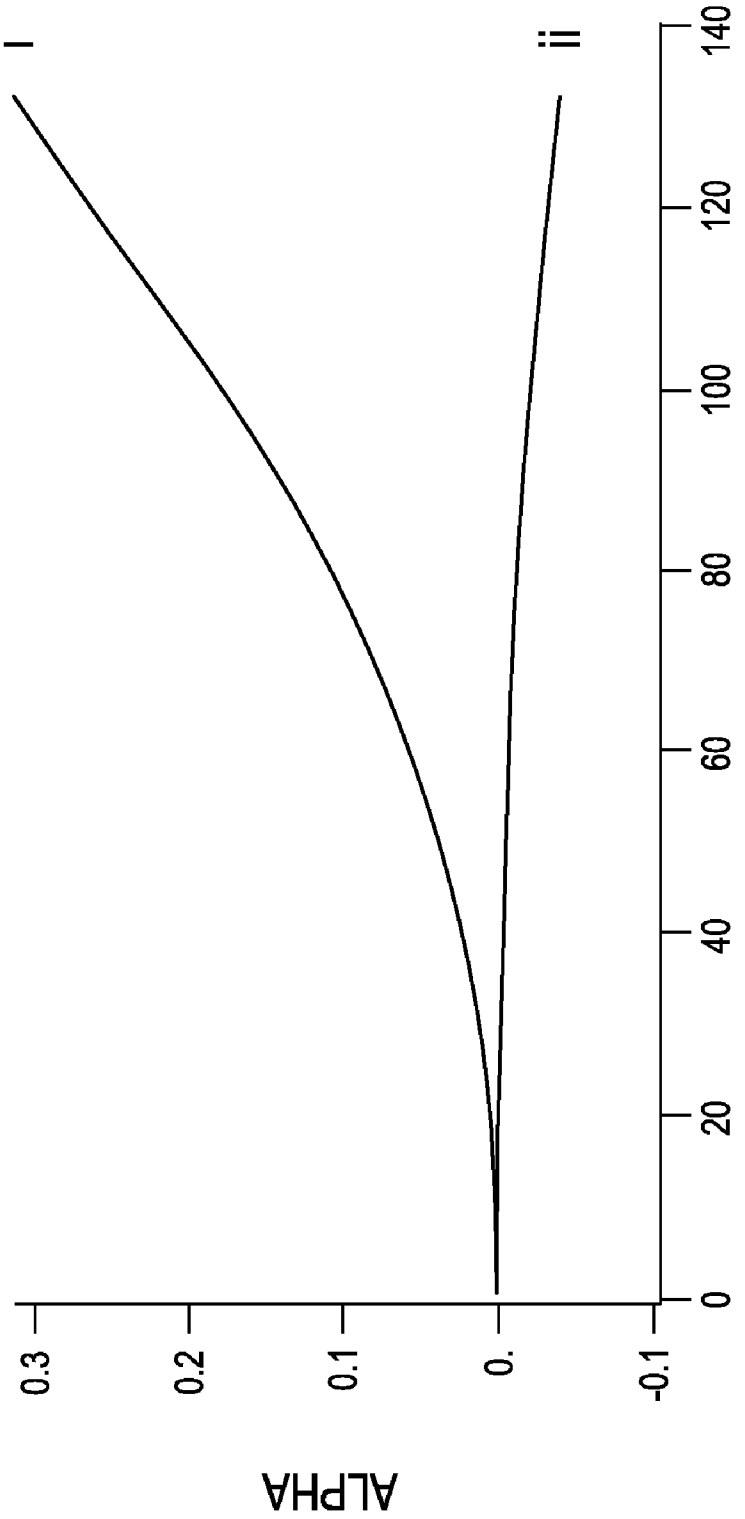

i
ii
0.3
0.2
0.1
0.
-0.1
ALPHA
0
20
40
60
80
100
120
140
SEPARATION FIELD (E/N, Td)

Figure 13

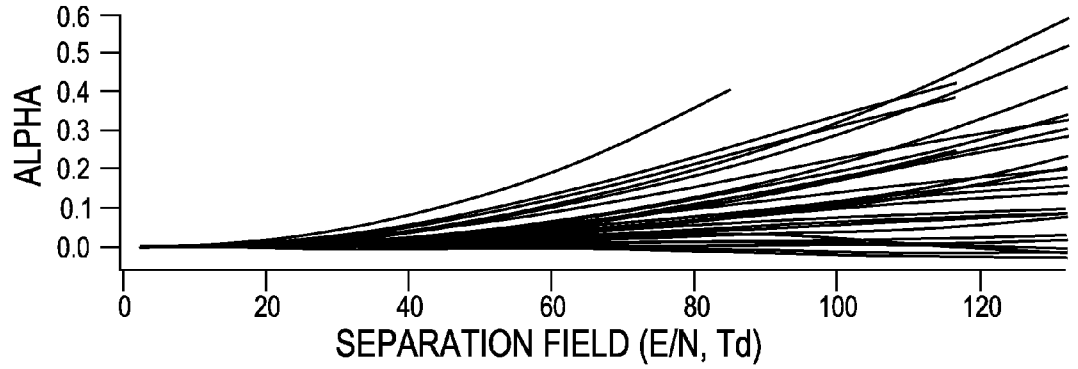



Figure 14A

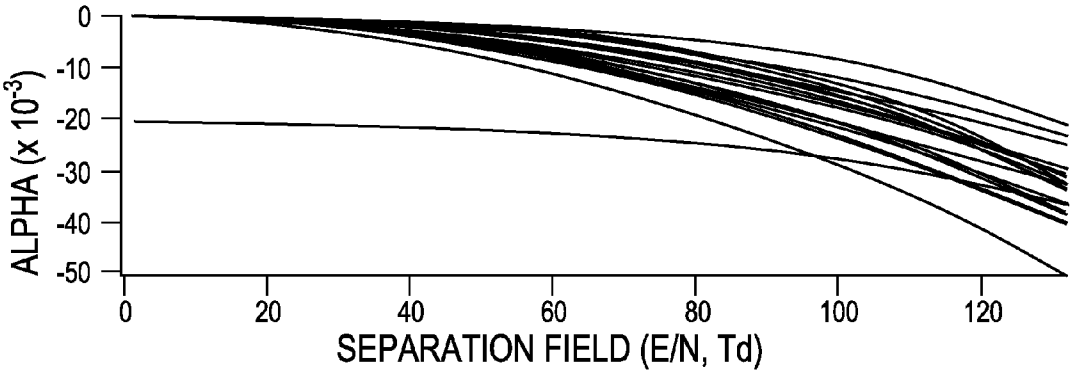



Figure 14B

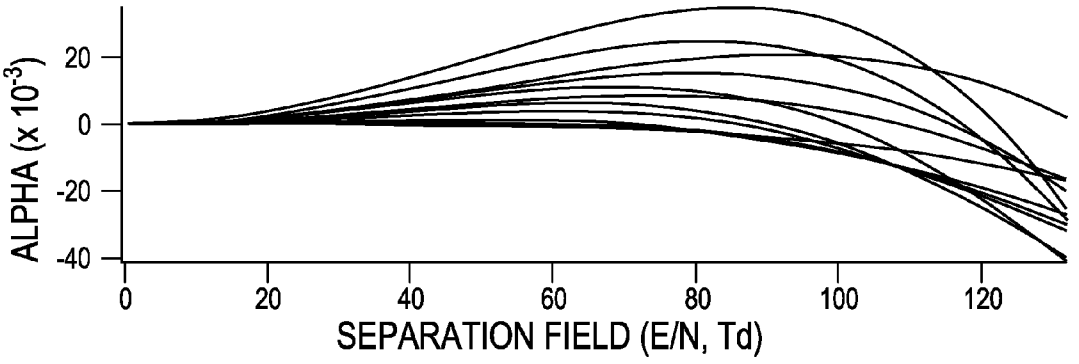



Figure 14C

# MASS ANALYSIS SYSTEM WITH LOW PRESSURE DIFFERENTIAL MOBILITY SPECTROMETER

## REFERENCE TO RELATED APPLICATIONS

**[0001]** This application claims benefit of U.S. Provisional Application No. 61/299,086 filed Jan. 28, 2010 and entitled "Mass Analysis System With Low Pressure Differential Mobility Spectrometer" the entirety of which is incorporated herein by reference.

## INTRODUCTION

**[0002]** A Differential Mobility Spectrometer (DMS), also referred to as a Field Asymmetric Waveform Ion Mobility Spectrometer (FAIMS) or Field Ion Spectrometer (FIS), typically performs gas phase ion sample separation and analysis. In some circumstances, a DMS has been interfaced with a mass spectrometer (MS) to take advantage of the atmospheric pressure, gas phase, and continuous ion separation capabilities of the DMS and the detection accuracy of the MS.

**[0003]** By interfacing a DMS with an MS, numerous areas of sample analysis, including proteomics, peptide/protein conformation, pharmacokinetic, and metabolism analysis have been enhanced. In addition to pharmaceutical and biotech applications, DMS-based analyzers have been used for trace level explosives detection and petroleum monitoring.

**[0004]** A DMS, like an ion mobility spectrometer (IMS), is considered an ion mobility based analyzer because the DMS separates and analyzes ions based on the mobility characteristics of the ions. In an IMS, ions are pulsed into and pass through a drift tube while being subjected to a constant electric field. The ions interact with a drift gas in the drift tube and the interactions affect the time it takes for the sample ions to pass through the drift tube, e.g., the time-of-flight (TOF). These interactions are specific for each analyte ion of a sample, leading to an ion separation based on more than just mass/charge ratio. In contrast, in a TOF MS, there is a vacuum in the drift region of the MS and, therefore, an ion's time through the MS drift region is based on the ion's mass-to-charge ratio (m/z) in the collision-free environment of the vacuum.

**[0005]** A DMS is similar to an IMS in that the ions are separated in a drift gas. However, unlike an IMS, the DMS uses an asymmetric electric field waveform that is applied between at least two parallel electrodes through which the ions pass, typically, in a continuous manner. The electric field waveform typically has a high field duration at one polarity and then a low field duration at an opposite polarity. The duration of the high field and low field portions are applied such that the net voltage being applied to the DMS filter electrodes is zero.

**[0006]** FIG. **1**A shows a plot **100** of the time-varying, RF, and/or asymmetric high and low voltage waveform **101** (e.g., Vrf) that can be applied to generate an asymmetric electric field. FIG. **1**B shows a diagram of a DMS filter **102** where the path of an ion $M^-$ is subjected to an asymmetric electric field resulting from the asymmetric voltage waveform **101**. The ion's mobility in the asymmetric electric field indicates a net movement **103** towards the bottom electrode plate of the DMS filter **102**. This example shows that, in a DMS, an ion's mobility is not constant under the influence of the low electric field compared to the high electric field. Since an ion may experience a net mobility towards one of the filter electrode plates during its travel between the plates, a compensation voltage (Vc) is applied to the filter electrodes to maintain a safe trajectory **104** for the ion through the DMS filter **102** without striking one of the filter electrodes. The ions are passed between the two filter electrodes by either being pushed through with a pressurized gas flow upstream of the filter electrodes or pulled through by a pump downstream from the filter electrodes.

**[0007]** In a DMS or IMS, ions are typically separated in a gas at pressures sufficient to enable collisions between sample ions and neutral drift gas molecules. The smaller the ion, the fewer collisions it will experience as it is pulled through the drift gas. Because of this, an ion's cross sectional area can effect the ion's mobility through the drift gas. As shown in FIG. **1**B, an ion's mobility is not constant under the influence of a low electric field compared to a high electric field. This difference in mobility may be related to clustering/de-clustering reactions taking place as an ion experiences the weak and strong electric fields. An ion typically experiences clustering with neutral molecules in the drift gas during the weak field portion of the waveform, resulting in an increased cross sectional area. During the strong field portion of the waveform, the cluster may be dissociated, reducing the ion's cross sectional area. Alternatively, differences between high and low field mobility behavior may be due to different collision dynamics due to changes that occur in ion translational energy.

**[0008]** The integration of a DMS with a MS can provide added selectivity that can be used for purposes such as chemical noise reduction and elimination of isobaric interferences. This general reduction of the chemical background can provide improvements in the detection limit (defined for example as $3\sigma$/slope of the calibration curve) for various assays. One of the key factors limiting general applicability of DMS technology with MS analysis is the reduction in instrument sensitivity that is observed upon installation of the DMS. Experiments have demonstrated that the observed sensitivity reduction due to the DMS has a flow rate dependence, with typical values being 3× down at low solvent flows (10 μL/min) and 10× down at high flows (500 μL/min) These sensitivity reductions may occur as a result of three different phenomena: 1) diffusion losses in the DMS itself, 2) inefficiencies in ion transport into and out of the DMS, and 3) ion clustering. Our experiments provide strong evidence that the bulk of losses currently being observed with the DMS at high solvent flows are a result of sampling a "wet spray" into the DMS and subsequently filtering clusters that do not transmit at the same Vc as the unclustered parent ion. This hypothesis is supported by modeling of diffusion behavior, as well as experimental data showing improvements in the coefficient of transmission with additional heaters located in front of the DMS.

**[0009]** In existing DMS-MS systems, there are several approaches where desolvation or declustering are utilized including: 1) the source region where turbo heaters can be operated up to 750° C., 2) a counter-current gas flow region established by the heated curtain gas, and 3) a declustering region within the first vacuum stage where the potential difference between the inlet orifice and first vacuum lens element provides some declustering. Existing DMS-MS systems typically locate the DMS before the orifice of the MS, which results in a limitation in that ions and clusters are filtered prior to the orifice, eliminating the ability to decluster within the first vacuum stage. Elimination of this stage of

declustering results in sensitivity reduction with the DMS, with higher solvent flows being most problematic. Efforts to add additional heating and provide additional desolvation prior to the DMS have shown some improvement in sensitivity, however, have imparted very significant challenges with respect to commercialization due to the critical importance of maintaining a constant temperature and the difficulty of monitoring temperature in close proximity to very high AC potentials. The range of assays that can exhibit detection limit improvements with the DMS is limited by the magnitude of the sensitivity reduction that is observed with the DMS device. For instance with a 10× sensitivity reduction, this number may be as low as 5-10%. Mobility based separations have also been known to be of low resolution and limited in peak capacity.

**[0010]** Accordingly, there is a need to improve mobility based resolution and specificity, and to increase the applicability of DMS-MS analyses by providing improved sensitivity and selectivity, including for high flow analyses.

## SUMMARY

**[0011]** The application, in various embodiments, addresses the deficiencies of current DMS-MS systems by providing systems and methods including a mass analysis system that combines a MS with a low pressure DMS to enable enhanced sample analysis sensitivity and/or selectivity. In certain aspects, a tandem DMS device advantageously includes first and second DMS filters that utilize separation mechanisms based on two different separation models.

**[0012]** With the tandem device, a cell, including the first DMS, operates at about atmosphere where clustering is done efficiently and a second cell, including the second DMS, operates in a vacuum where declustering to the bare ion is done efficiently. Separation at about atmosphere is done according to a "clusterization model" which derives it's specificity from the differences in the chemical interactions of an ion and its immediate surroundings. For instance, Hydrogen bonding, Vanderwaals forces, steric hindrance, where all of these actions come into play in the clusterization model. The addition of modifiers (e.g., dopants) to the transport gas can assure that separations occur according to this mechanism.

**[0013]** In a vacuum, the tandem device creates dry ions with energetic collisions in, for example, a free jet expansion by accelerating the clusters into a background gas. Because there is a substantially greater mean free path under the vacuum, as compared to atmosphere to accelerate and collide ions, declustering can be done most efficiently in or near the free jet gas expansion. The declustered ions are then separated in the second vacuum DMS according to a "hard sphere collision model". This mechanism is based upon a more "physical" process where the ion mobility is related to the interaction and scattering of ions during collisions with the inert background gas molecules. Ion mobility based separation using the combination of both models advantageously provides orthogonal separation mechanisms that substantially enhance ion analysis with respect to conventional techniques. These and other features of the applicant's teachings are set forth herein.

**[0014]** In one aspect, a mass analysis system includes a low pressure dissociation region, a low pressure DMS that filters sample ions, and a mass spectrometer that receives some or all of the selected portion of the sample ions. The dissociation region may include, without limitation, a collision region, a fragmentation region, an expansion region, a desolvation region, radiation region, high temperature region, and/or the like. The dissociation region may utilize a laser, radiation source, collision gas source, thermal source, gas expansion mechanism, and the like to effect the dissociation process. In one configuration, the DMS includes at least a pair of filter electrodes defining an ion flow path where the filter electrodes generate an electric field for passing through a selected portion of the sample ions based on their ion mobility characteristics. In certain embodiments, the DMS can include a plurality of filter electrode pairs. The DMS also includes a voltage source that provides RF and DC voltages to at least one of the filter electrodes to generate the electric field. The DMS further includes an ion inlet that receives sample ions that have passed through the low pressure collision region and an ion outlet that outputs the selected portion of the sample ions.

**[0015]** In one feature, the low pressure dissociation region is configured to accelerate the sample ions and collide the sample ions with a collision gas. The low pressure dissociation region may be configured to perform at least one of declustering and fragmenting the sample ions. The pressure of the DMS and/or a portion of the low pressure dissociation region may be set at less than about atmospheric pressure. The pressure of the DMS and/or portion of the low pressure dissociation region may be set at about 50 to about 760 Torr. The pressure of the DMS and/or a portion of the low pressure dissociation region may be set at less than about 100 Torr. In certain configurations, the DMS operates from about 200 to about 500 Torr. In certain configurations, the DMS operates at about 200 Torr. In certain configurations, the DMS can operate at less than about 50 Torr, less than about 25 Torr, less than about 15 Torr, less than about 5 Torr, less than about 3 Torr, and less than about 1 Torr. The DMS may be operated at about 2-4 Torr. In one configuration, the pressure of the ion flow path in the DMS is substantially the same as the pressure of a portion of the low pressure dissociation region.

**[0016]** In another feature, the mass analysis system includes at least one ion guide located in at least the low pressure dissociation region or an intermediate region between the low pressure DMS and the low pressure dissociation region. The ion guide may include at least one ion focusing element. The ion focusing element may include an RF rod, RF ring, RF lens, DC lens, DC ring, deflector plate, and/or grid.

**[0017]** The low pressure dissociation region may be configured to receive a flow of the sample ions from an ion source. The ion source may include a second DMS that operates at substantially atmospheric pressure or above. The low pressure dissociation region may be configured to accelerate ions within a free jet expansion. In one configuration, a housing substantially encloses the low pressure DMS and the low pressure dissociation region. The housing may include a housing or vacuum inlet for receiving sample ions. The housing may also include a housing outlet, in communication with an outlet of the low pressure DMS, for outputting a portion of selected sample ions into the mass spectrometer. In various aspects, the ion guide located in the low pressure dissociation region can be removed, and the low pressure DMS can comprise four electrodes.

**[0018]** In another configuration, the mass spectrometer includes at least one ion optics element that receives the selected portion of the sample ions via the housing outlet. The mass spectrometer may include a mass analyzer in communication with at least one ion optics element. In certain fea-

tures, an insulating material is in communication with and/or supports at least one of the DMS filter electrodes. In certain configurations, the mass analysis system includes one or more heated regions that are configured to perform i) declustering ions, ii) desolvating ions, iii) accelerating the reclustering of ions with reagents, and/or iv) shifting the clustering equilibrium for ions with dopant or reagents.

**[0019]** In another aspect, a sample analysis system includes a first pressure region that operates at a pressure of about atmospheric pressure or greater. The first pressure region includes a first DMS filter that receives sample ions from an ion source and passes through a first set of selected sample ions. The system also includes a second pressure region, in communication with the first pressure region, that operates at less than about atmospheric pressure. The second pressure region includes a dissociation and/or collision region where the first set of selected sample ions are accelerated and collided with a collision gas to desolvate and/or fragment the sample ions. The second pressure region also includes a second DMS filter that passes through a second set of selected sample ions based on their ion mobility characteristics.

**[0020]** In one configuration, the system includes a third pressure region, in communication with the second pressure region, that operates at less than about 1 Torr. The third pressure region may include an ion optics element that receives the second set of selected sample ions. In another configuration, the system includes a fourth pressure region, in communication with the third pressure region, that operates at less than about $10^{-4}$ torr and includes a mass analyzer. In certain embodiments, a vacuum drag is established from a lower pressure region to a higher pressure region to facilitate the transport of ions. For instance, a vacuum drag may be utilized to pull ions into and/or through the first and/or second DMS, or through other components of the ion analyzer.

**[0021]** In another aspect, an ion analysis system comprises an ion inlet and a first low pressure region maintained at a pressure in the range of about 50 to about 760 Torr including a first dissociation region and a differential mobility spectrometer. Second and third low pressure regions maintained at less than about 50 Torr and less than about 1 Torr, respectively, with RF ion guides for directing ions to a fourth low pressure region comprising a mass analyzer.

**[0022]** In a further aspect, an ion analyzer includes an ion source, a flow of ions from the ion source, a reaction region that introduces at least one chemical modifier to the flow of ions, and a first DMS, operating substantially at atmospheric pressure, that receives the flow of ions from the reaction region and performs a first mobility based filter operation on the flow of ions. The analyzer also includes a declustering region, operating at less than atmospheric pressure, that receives the flow of ions from the first DMS. The analyzer further includes a second DMS, operating at less than atmospheric pressure, that receives the flow of ions from the declustering region and performs a second mobility based filter operation on the flow of ions. As discussed above, the ion analyzer may advantageously employ an orthogonal separation approach where the first DMS, operating at about atmospheric pressure, performs ion mobility based separations based on the clusterization model, while the second DMS, operating at less than atmospheric pressure, performs ion mobility based separations based on the hard or rigid sphere collision model. Further details regarding these separation models are provided later herein.

**[0023]** In one configuration, the ion analyzer includes a mass spectrometer that receives the flow of ions from the second DMS. In another configuration, the mass spectrometer includes a mass analyzer. The ion analyzer may include at least one heated region configured to perform at least one of i) declustering ions, ii) desolvating ions, iii) accelerating the reclustering of ions with reagents, and iv) shifting the clustering equilibrium for ions with dopant or reagents.

**[0024]** In yet another aspect, an ion analysis system includes an ion source, a flow of ions from the ion source, a first means for modifying a first portion of ions from the flow of ions to provide a specific $\alpha$-function for each of the ion species associated with the first portion of ions, a first DMS configured to receive the first portion of ions, conduct a differential mobility separation, and output a second portion of ions, a second means for modifying the second portion of ions to alter the $\alpha$ function associated with the second portion of ions, and a second DMS configured to receive the second portion of ions, conduct a differential mobility separation, and output a third portion of ions. The means for modifying may include a reaction region, clustering region, dissociation region, and/or declustering region.

## DRAWINGS

**[0025]** The foregoing and other objects and advantages of the invention will be appreciated more fully from the following further description thereof, with reference to the accompanying drawings. The skilled person in the art will understand that the drawings, described below, are for illustration purposes only. The drawings are not intended to limit the scope of the applicant's teachings in any way.

**[0026]** FIG. **1**A shows a plot of a time-varying and/or asymmetric high and low voltage waveform that may be applied to generate an asymmetric electric field in a differential mobility spectrometer (DMS);

**[0027]** FIG. **1**B shows a diagram of a DMS filter where the path of an ion $M^{I}$ is subjected to an asymmetric electric field resulting from the asymmetric voltage waveform of FIG. **1**A;

**[0028]** FIG. **2** shows a diagram of a mass analysis system with a vacuum chamber including a DMS and collision region according to an illustrative embodiment of the invention;

**[0029]** FIG. **3** is a flow diagram of a process for analyzing ions using the system of FIG. **2** according to an illustrative embodiment of the invention;

**[0030]** FIG. **4** shows a diagram of a mass analysis system as in FIG. **2** with an ion guide according to an illustrative embodiment of the invention;

**[0031]** FIG. **5**A shows a diagram of a mass analysis system as in FIG. **4** with an atmospheric pressure DMS pre-filter according to an illustrative embodiment of the invention;

**[0032]** FIG. **5**B shows a diagram of a mass analysis system as in FIG. **5**A but without an RF ion guide, and a DMS comprising four electrodes according to an illustrative embodiment of the invention;

**[0033]** FIG. **6** shows a diagram of a mass analysis system as in FIG. **5**A with a clustering and/or reaction region prior to the atmospheric pressure DMS according to an illustrative embodiment of the invention;

**[0034]** FIG. **7**A includes plots of normalized ion intensity peaks in a DMS without reagent modifiers at various Vrf settings;

**[0035]** FIG. **7**B includes plots of normalized ion intensity peaks in a DMS with reagent modifiers introduced at various Vrf settings;

**[0036]** FIG. **8** shows a diagram of dopant introduction system via a mixing chamber according to an illustrative embodiment of the invention;

**[0037]** FIG. **9** shows a diagram of an alternative dopant introduction system according to an illustrative embodiment of the invention;

**[0038]** FIG. **10** shows a diagram of a mass analysis system as in FIG. **6** with a turbulent heated region according to an illustrative embodiment of the invention; and

**[0039]** FIG. **11** is a graph including plots of normalized ion intensity vs. compensation voltage when the inlet to the atmospheric pressure DMS is heated and not heated respectively;

**[0040]** FIG. **12** is a graph of the of alpha behavior for type A, B, and C ion mobility behavior;

**[0041]** FIG. **13** is a graph showing the dramatic changes that occur in the alpha function for a sample of norfentanyl with inert transport gases and the inclusion of a clustering modifier; and

**[0042]** FIGS. **14**A-C includes a series of graphs showing alpha function data for 36 compounds under different conditions.

## DESCRIPTION OF VARIOUS EMBODIMENTS

**[0043]** While the applicant's teachings are described in conjunction with various embodiments, it is not intended that the applicant's teachings be limited to such embodiments. On the contrary, the applicant's teachings encompass various alternatives, modifications, and equivalents, as will be appreciated by those of skill in the art.

**[0044]** A common problem with electrospray ionization sources is that they typically produce heterogeneous ion clusters that can adversely affect the resolution of ion analyzer systems. Clustering of ions and neutral gas phase molecules typically results from ionization at atmospheric pressure. Ions generated during the electrospray process are a combination of bare molecular ions and ions clustered or contained in small droplets of the electrospray solvent. The relative proportion of ions, ion-clusters, and charged droplets is highly dependent on the degree to which the charged nebulized liquid is desolvated.

**[0045]** When a mobility based analyzer, such as a DMS, is used with an electrospray ionization source, the extent of the production of these heterogeneous cluster ion populations is related to mobile phase introduction flow rate. When the mobile phase flow rates extend into the hundreds of microlitres per minute range, a large proportion of the ions produced by the ion evaporation process are created as clusters and small droplets of widely varying composition. Cluster ion populations formed in this way are highly heterogeneous and different from the relatively homogeneous cluster ion populations formed in the gas phase during the interaction of an ion with the background transport gas.

**[0046]** A particular ion can exist in a wide variety of different clustered states covering a broad distribution of molecular weights and chemical compositions. This occurs whether or not high desolvation temperatures are used to evaporate the pneumatically nebulized electrospray, although the problem is exacerbated at low temperatures. A mobility based analyzer such as a DMS, operating at atmospheric pressure, can separate the components of the distribution. However, the sensitivity for the targeted analyte, as detected by, for example, a MS, will be reduced in addition to the mobility resolution and peak capacity. Under conditions of incomplete electrospray desolvation, heterogeneous clusters of different sizes and compositions may be present in addition to small droplets. These clusters will show a much greater range of differential mobility values and a correspondingly greater peak width.

**[0047]** Electrospray sources operating at liquid flows in the nanolitre to low microlitre per minute range produce fewer clusters and, depending on the analyte and solvent chemistry, will often produce unclustered molecular ions prior to the vacuum inlet of an MS. This is apparent when Vc scans of an electrosprayed solution of a standard compound are done at high and low liquid flow rates. The apparent loss of resolution as the flow rate is raised can be attributed to the formation of increasingly heterogeneous analyte/cluster ion populations and possibly the persistence of small droplets within the mobility based analyzer.

**[0048]** One approach to addressing the resolution problem at relatively high flow rates is by dissociating ion clusters prior to mobility based filtering. In certain embodiments, a dissociation region is established before ion mobility based filtering. In some embodiments, a low pressure DMS is used to filter ions based on the rigid sphere collision (or scattering) model after dissociation of ion clusters. In other embodiments, where ion mobility based filter of ion clusters is preferred, an atmospheric pressure DMS provides ion mobility based filter based on the clusterization model. In further embodiments, an ion analyzer system includes both a low pressure DMS and atmospheric pressure DMS that combines the advantages of ion mobility based filtering using both models. Further details regarding the rigid sphere collision and clustering models are provided later herein with respect to FIG. **12**.

**[0049]** FIG. **2** shows a diagram of a mass analysis system **200** with a vacuum chamber **202** including a DMS **204** and dissociation region **206** according to an illustrative embodiment of the invention. The system **200** also includes an ion source **208**, vacuum chamber inlet and/or orifice **210**, vacuum plate **212**, an outlet orifice **214**, a mass spectrometer **224**, a voltage source **226**, and controller **228**. The DMS **204** includes filter electrodes **216** and **218**, a DMS inlet **220**, and DMS outlet **222**. The mass spectrometer **224** includes an ion optics assembly **230** and mass analyzer **232**, and ion detector (not shown). In certain embodiments, the dissociation region **206** includes at least one of a collision region, declustering region, desolvation region, and gas expansion region.

**[0050]** The vacuum chamber inlet **210** is in communication with the ion source **208** and may include an orifice, a pipe, a heated capillary, a resistive capillary, or any suitable sample inlet configuration known to one of ordinary skill in the art. The vacuum chamber inlet **210** may be part of a sample inlet system that includes components such as a source extension ring or the like to facilitate ion introduction into the vacuum chamber **202** via the sample inlet **210**. The ion source **208** may be integrated with the vacuum chamber inlet **210** or an inlet system or, alternatively, may be separate from the inlet system. The ion source **208** may be any suitable ion source known to one of skill in the art. For example, the ion source **208** may include an electrospray ionization source with the ability to generate ions from a sample analyte dissolved in solution. Other example arrangements of the ion source **208** may include an atmospheric pressure chemical ionization (APCI), atmospheric pressure photo-ionization (APPI), direct analysis in real time (DART), desorption electrospray (DESI), atmospheric pressure matrix-assisted laser desorption ionization (AP MALDI), liquid chromatography (LC) column, gas chromatography (GC) column, multimode ion-

ization sources, surface analysis sources, or configurations with multiple inlet systems and/or sources.

**[0051]** The vacuum chamber **202**, in certain embodiments, is configured to include a low pressure dissociation region **206** and/or declustering region located upstream of the DMS **204**. The low pressure dissociation region **206** may be configured to accelerate sample ions from the vacuum chamber inlet **210** within a free jet expansion. The vacuum chamber **202** may be defined or bounded by a vacuum plate **212** and/or housing. Sample ions travel through the inlet **210**, where a vacuum expansion occurs, as a result of the pressure differential on either side of the inlet **210**. The low pressure dissociation region **206** may include a pressure gradient along the sample ion flow path **234** whereby the pressure is reduced from about atmospheric pressure in proximity to the vacuum chamber inlet **210** to a set pressure below atmospheric pressure in proximity to the DMS inlet **220**. The pressure in proximity to the DMS inlet may be from about 1 Torr to less than atmospheric pressure (e.g., 760 Torr). In some embodiments, the DMS can operate at about 50 to about 760 Torr. In certain configurations, the DMS can operate from about 200 to about 500 Torr. In certain configurations, the DMS can operate at about 200 Torr. In some embodiments, the pressure may be from about 1 Torr to less than or equal to about 100 Torr. In certain circumstances, the sample ions are accelerated in the low pressure dissociation region **206** with voltage and collided into a background gas to effect declustering and/or fragmentation prior to delivery of the sample ions to the DMS **204**.

**[0052]** DMS residence time and gap height can be affected by the operating pressure, with lower pressures requiring wider gaps and longer residence time. For example, Table 1 below shows typical gap widths and residence times for the DMS at different operating pressures. Long residence times can limit sample throughput, therefore it may be advantageous to operate the DMS in the about 100 to about 760 Torr pressure regime.

TABLE 1

| Pressure (Torr) | Gap Height (mm) | Residence Time (ms) |
|---|---|---|
| 2.5 | 240 | 1579 |
| 10 | 60 | 385 |
| 20 | 30 | 193 |
| 50 | 15 | 93 |
| 100 | 7 | 44 |
| 200 | 3.5 | 22 |
| 300 | 2.1 | 13.5 |
| 500 | 1.3 | 8.4 |
| 760 | 0.8 | 5.1 |

**[0053]** The DMS **204**, also referred to as a field asymmetric ion mobility spectrometer (FAIMS), may include filter electrodes **216** and **218** that are formed and/or configured as parallel plates, curved plates, concentric rings/surface, and the like. The DMS **204** may include a plurality of filter electrode pairs. The filter electrodes **216** and **218** may be formed on or connected to insulating surfaces or components. The DMS **204** may have form factor including a generally planar, circular, concentric, and/or curved structure. The voltage source **226** applies RF and DC voltages to at least one of the filter electrodes **216** and **218** to generate an electric field to enable sample ion filtering based on the mobility characteristics of the sample ion species while traveling through the DMS **204**. The DC voltage is referred to as the compensation voltage, Vc, because the Vc may be adjusted to select a desired ion species to pass through the DMS **204**. The controller **228** may control the voltage **226** so that the voltage source **226** sweeps Vc over a range of DC voltages to produce a ionogram or spectrum of sample ion species that are allowed to pass through the DMS **204**. It will be appreciated that other ion mobility based separation devices and/or filters may be used in the system **200** such as, without limitation, an Ion Mobility Spectrometry (IMS), a Differential Mobility Analyzer (DMA), a hybrid ion mobility based analyzer, a high-field/low-field filter, and the like. The DMS assembly **204** may be mounted so as to provide vacuum seal to exit aperture **214** so that gas drag through aperture **214** establishes a laminar gas flow through the DMS **204**. Additionally, DC potentials may be provided to electrodes **216** and/or **218** to adjust the DC offset potential between DMS **204** and aperture **214** to optimize transmission.

**[0054]** The ion optics assembly **230** may use RF fields to focus the sample ions from the orifice **214** on to an ion optical path and direct the ions toward the mass analyzer **232**. It will be appreciated that the ion optics assembly **230** used in system **200** may be made up of any ion optics known to one of skill in the art, such as, without limitation, a multipole array, a ring guide, a resistive ion guide, an ion funnel, a traveling wave ion guide, or the like. In certain embodiments, the ion optics assembly is operated at a pressure in the range of about 1-10 millitorr.

**[0055]** In some embodiments, the ion optics assembly **230** is connected with the mass analyzer **232** to enable sample ions to travel via ion optical path to mass analyzer **232** where the ions are separated based on their mass-to-charge ratios (m/z) and detected. The detected ion data may be stored in memory and analyzed by a processor or computer software. In certain embodiments, the controller **228** includes a processor and memory or data storage. The controller **228** may also control the operation of the mass analyzer **232**. The mass analyzer **232** may function as at least one of a linear ion trap and a quadrupole analyzer, time-of-flight MS, or include multiple mass analyzers. In certain embodiments, the ion optics assembly may include the Q0 RF ion guide or any like ion guide. An ion guide may be used to capture and focus sample ions from the orifice **214** using a combination of gas dynamics and radio frequency fields. An ion guide, such as Q0, may then transfer sample ions from the orifice **214** to subsequent ion optics or the mass analyzer **232**.

**[0056]** The API 5000™ system, manufactured by AB Sciex is one type of exemplary mass spectrometer **224** that may be utilized by the mass analysis system **200**. Such a mass spectrometer typically includes instrumental optics, a mass analyzer, curtain plate and orifice. Instrumental optics comprise a QJET® RF ion guide and Q0 RF ion guide separated by an IQ0 lens. The QJET® RF ion guide is used to capture and focus ions using a combination of gas dynamics and radio frequency fields. The QJET® transfers ions from the orifice to subsequent ion optics such as the Q0 RF ion guide. The Q0 RF ion guide transports ions through an intermediate pressure region (e.g., at about ≈6 mTorr) and delivers ions through an IQ1 lens to a high vacuum chamber containing a mass analyzer. The mass analyzer region comprises a Q1 quadrupole analyzer, Q2 quadrupole collision cell, Q3 quadrupole analyzer and CEM detector.

**[0057]** The instrumental optics comprising an ion guide and/or Q0 RF ion guide are an example of optics that can be used in ion optics assembly **230** of FIG. **2**. However, in some

embodiments the elements can be used individually, in combination with other types of ion optics, or not used in mass spectrometer system **224** at all. In some instances, a Q0 ion guide may be capacitively coupled to either the Q1 or Q3 quadrupole. In some configurations, the ion optics and mass analyzer can include one or more pressure regions, separated by apertures, operating at various range of pressures. For example, the first region may be set at 2.5 Torr, Q0 set at 6 mTorr and mass analyzer, comprising Q1, Q2 and Q3, may be set at $10^{-5}$ Torr. It will be apparent to those of skill in the art that Q2 can comprises a collision cell for fragmenting ions, and the gas pressure within the Q2 cell may be substantially higher than the pressure in Q1 and Q3 of the API 5000™ device.

**[0058]** In some embodiments that require short residence times, the first region can be set to 50 to 760 Torr, the second QJET® region can be set to 2.5 Torr, Q0 can be set to 6 mTorr, and the mass analyzer comprising Q1, Q2, and Q3 can be set to $10^{-5}$ Torr.

**[0059]** In certain embodiments, the controller **220** includes a processor that enables the control of the various components of the mass analysis system **200** including the DMS **204**, the voltage source **226**, the ion source **208**, the mass spectrometer **224**, and, more particularly, the ion optics **230**, and mass analyzer **232**. The controller may include a user interface, network interface, and data storage. The processor may include an interface with a memory having software and/or hardware code configured to enable the control of the system **200**. The controller **228** may include program code embedded on program media to enable the processor to perform instructions to effect control of the system **200** and/or analysis or processing of data acquired from the operation of the system **200**.

**[0060]** The mass spectrometer **224** may include at least one electrode, e.g., a linear accelerator (LINAC) in close proximity to the ion optics assembly **230**. The electrode or electrodes may be used for accelerating ions through an RF multipole or expelling residual ions from the RF multipole. The voltage source **226** (e.g., power supply) may be connected to and apply a DC potential to the electrode(s), causing the electrodes to generate an electric field to axially expel ions, including residual ions, out of the ion optics assembly **230**, or out of another component of the system **200**. The electrodes may also accelerate ions to reduce the residence time within the ion optics assembly **230** and, thereby, reduce or substantially eliminate ion beam spreading.

**[0061]** The voltage source **226** may include an RF/DC auxiliary alternating current (AC) power supply that supplies RF and/or DC signals, and/or an auxiliary AC signal to a quadrupole rod set of the mass analyzer **232**. The system **200** may include a shortened quadrupole rod set, which can act as Brubaker lenses, adjacent to the mass analyzer **232** or other component of the system **200**.

**[0062]** In certain embodiments, the mass spectrometer **224** may include a collision cell having an inert gas (for example, helium, nitrogen, argon, or the like) that can be pumped into the collision cell to initiate collision induced dissociation (CID) of ions. Ions in a collision cell, such as parent ions, can collide with gas molecules and break into fragments, referred to as daughter ions. In certain embodiments, when a component of the mass spectrometer **224** functions in an ion trap mode, an RF power supply can be used to create an electric field within a quadrupole rod set of the ion trap. By changing the amplitude and waveform of the applied field, ions of a selected m/z can be trapped within the quadrupole rod set. In some configurations, the mass analysis system **200** performs Multiple reaction monitoring (MRM).

**[0063]** FIG. **3** is a flow diagram of a process **300** for analyzing ions using the system **200** of FIG. **2** according to an illustrative embodiment of the invention. In one embodiment, the ion source **208** includes an electrospray ionization source that delivers sample ions from a solution to the vacuum inlet **210**. As discussed previously, electrospray ionization, particularly at high flow rates, can produce heterogeneous ions which are undesirable. One approach to mitigating the adverse effects of heterogeneous clusters is to dissociate the ion clusters before ion mobility based filtering.

**[0064]** The pressure at the ion source **208** may be at about atmospheric pressure, while the pressure inside the vacuum chamber may be at a pressure less that atmospheric pressure. Thus, the pressure differential across the vacuum inlet **210** can create a free jet within the vacuum chamber **202** to pass and accelerate sample ions through the low pressure collision region **206** along the flow path **234** toward the DMS inlet (Step **302**). The arrangement and use of the low pressure collision region **206** advantageously enables declustering of the heterogeneous sample/solvent cluster ions because the sample ion clusters in the wet spray from the ion source **208** are accelerated within the free jet expansion of the low pressure collision region **206**. By declustering and/or desolvating the sample ions in the low pressure collision region **206** before entry into the DMS **204**, the sensitivity of the system **200** is advantageously improved because the DMS **204** is allowed to filter the desired sample ions, as opposed to filtering clusters.

**[0065]** As discussed previously, when creating clusters in the gas phase, as opposed to during electrospray ionization, clusters are homogeneous and, therefore, form well-defined structures and resulting well-defined detection peaks. Unlike heterogeneous ion clusters, homogeneous cluster ion populations are formed in the gas phase during the interaction of an ion with the background transport gas (e.g., neutral molecules). In certain instances, a modifier and/or dopant may be introduced into the gas flow that drives the equilibrium toward a desired homogeneous cluster ion population. Homogeneous clusters have well-defined DMS characteristics.

**[0066]** Once the sample ions enter the DMS inlet **220**, the voltage source applies RF (Vrf) and DC (Vc) voltages to at least one of a pair of filter electrodes **216** and **218** (Step **304**). With the applied RF and DC voltages, the filter electrodes **216** and **218** generate an electric field in the flow path between the pair of filter electrodes **216** and **218** (Step **306**). In certain embodiments, the controller **228** controls the RF and DC voltages applied from the voltage source **226** to the filter electrodes **216** and **218** so as to pass through the electric field a selected portion of the sample ions based on the mobility characteristics of the sample ions (Step **308**). Some or all of the selected portion of sample ions that exit the DMS outlet **222** may then be received at a mass spectrometer **224** (Step **310**) via the orifice **214**. The transfer of ions from the DMS to mass spectrometer **224** may be effected by sealing the outlet of the DMS with the aperture **214** to establish a vacuum drag of gas from the DMS **204** into the mass spectrometer **224**. The mass spectrometer **224** may employ any number of known techniques and operations using the ion optics assembly **230** and mass analyzer **232** to analyze and detect the sample ions from the DMS **204**.

**[0067]** FIG. **4** shows a diagram of a mass analysis system **400** like system **200** in FIG. **2** with the addition of an ion guide **402** according to an illustrative embodiment of the invention. In certain embodiments, the ion guide **402** is included in the low pressure collision region **206** to focus and direct sample ions from the vacuum inlet **210**. In the region between aperture **210** and ion guide **402**, a potential may be applied to accelerate the sample ions and facilitate declustering and/or desolvation of the sample ions before entry into the DMS **204**. The ion guide may include a QJET®. Under certain conditions, a potential difference between the vacuum inlet and the QJET® may enable acceleration and declustering of sample ions from the ion source **208**. The system may also include a free jet expansion due to the pressure differential across the vacuum inlet/orifice **210** that also propels ions through the ion guide **402** toward the DMS inlet **220**. In one embodiment, the ion guide **402** may include a quadrupole ion guide. In another embodiment, the ion guide **402** may include dual ion guides or a plurality of ion guides to effect acceleration of sample ions and declustering. The inclusion of an ion guide **402** enables the introduction of substantially dry sample ions into the DMS inlet **220**. The ion guide **402**, operating as an ion focusing element, may focus and guide sample ions entering the vacuum chamber **202** via the vacuum inlet **210** toward the DMS inlet **220**. Collisions between the sample ions and a collision gas may occur before, within, or after the ion guide **402**. The ion guide **402** may include RF rods, DC lenses, and/or RF lenses.

**[0068]** In one embodiment, the vacuum chamber **202** includes an intermediate region **406**, located downstream of the ion guide **402** and upstream of the DMS **204**. The intermediate region may include some type of ion control element such as, without limitation, a second ion guide and/or an RF multipole, or the like to further effect control of the sample ions in the vacuum chamber **202**. In addition, a lens element may be included in region **406** to limit electrical interference for the RF potentials applied to the ion guide **402** and DMS **204**.

**[0069]** Thus, in certain embodiments, the DMS **204** is moved from a location within the atmospheric pressure source region **404** to a new location within the vacuum region and/or chamber **202** of the system **400**. This may be accomplished on systems that include a QJET® or dual QJET® ion optics configuration. For instance, on the AB Sciex 5500 QTRAP platform, the DMS **204** could be located in the first vacuum region downstream of a slightly shortened QJET quadrupole ion guide. With this configuration, the DMS/MS system, such as the system **400**, would retain the identical desolvation/declustering configuration of a standard 5500 QTRAP® platform, however, ion filtering can be accomplished for dry ions downstream of the QJET®. Other benefits and advantages of employing a low pressure collision region **206** and/or ion guide **402** upstream of the low pressure DMS **204** may include:

**[0070]** Complete elimination of sensitivity losses due to solvent clustering within the source region and ion source **208**.

**[0071]** Dramatically simplified DMS power supply that requires much lower AC amplitudes since the same E/N ratio would be achieved in a region of much lower number density.

**[0072]** Elimination of any ion optics crosstalk within the QJET® region, since ion filtering would occur downstream from this optic.

**[0073]** Simplification of the design of a tandem DMS as "doped separations" can be performed in the atmospheric pressure curtain chamber with a standard DMS.

**[0074]** Separations under the presence of modifiers (dopants) are done according to a cluster/decluster model and/or process to be discussed later herein. A collision region that strips the clusters and then allows for a second mobility based separation based on a second different separation mechanism, e.g., hard sphere collision model, to be discussed later herein. The use of two orthogonal separation mechanism enhances the specificity of the analysis process.

In certain embodiments, at least a portion of the vacuum chamber **202** and/or DMS **204** can be operated at about 50 to about 760 Torr. In certain configurations, the DMS can operate from about 200 to about 500 Torr. In certain configurations, the DMS can operate at about 200 Torr. In certain embodiments, the DMS can be operated at about 2-4 Torr. The DMS **204** may be operated at less than or equal to about 100 Torr, 50 Torr, 25 Torr, 10 Torr, 5 Torr, 4 Torr, 2 Torr, 1 Torr, 0.5 Torr, 0.3 Torr, and/or 0.1 Torr. However, at a certain pressure setting, due to some signal loss, the Vrf waveform frequency and/or gap height between DMS filter electrodes **216** and **218** may need to be adjusted to account for the increased oscillation amplitude of the sample ions in the DMS **204** that may occur due to reduced pressure.

**[0075]** Alternatively, in certain embodiments, an additional vacuum stage can be included prior to region **202**. The pressure can be set to about 50 to 760 Torr, and the region can include the DMS and a declustering region as well as an optional ion guide. With this configuration, the region **202** would not include a DMS.

**[0076]** FIG. **5**A shows a diagram of a mass analysis system **500**, like the system **400** shown in FIG. **4**, with an additional atmospheric pressure DMS **502** pre-filter according to an illustrative embodiment of the invention. The DMS **502** is located in the atmospheric pressure source region **404** and receives sample ions from the ionization source **208** at the DMS inlet **504**. In the same manner as DMS **204**, the DMS **502** passes through selected sample ions by applying an asymmetric RF field and DC compensation field between the DMS filter electrodes **506** and **508**. The voltage source, under the control of controller **228**, applies both a Vrf and Vc voltage to at least one of the DMS filter electrodes **506** and **508** to generate the RF and DC electric field. Sample ions passing through the filtering electric field of the DMS **502** are separated based upon their ion mobility characteristics in the drift gas and the electric field of the DMS **502**. FIG. **5**A also shows that the ion flow **234** in the low pressure collision region **206** is at least partially due to a vacuum drag created by the difference in pressure from the DMS **502**, operating at or near atmospheric pressure, and the vacuum chamber **202**, operating at about 1 Torr to about atmospheric pressure.

**[0077]** The mass analysis system **500** advantageously combines an atmospheric pressure DMS **502** with a low pressure DMS **204** to combine the benefits of performing ion mobility based separation at both conditions. This can provide a dramatic improvement in separation power and peak capacity when the separation conditions are different in the 2 mobility analyzers.

**[0078]** Ion separation in DMS occurs as a result of differences in ion mobility at high and low electric fields. The field dependence of the ion mobility can be symbolically represented as the $\alpha$ function, as shown in the following equation,

$$\alpha\left(\frac{E}{N}\right) = \frac{K(E) - K(0)}{K(0)}$$

where K(E) is the high field mobility and K(0) is the low field mobility. Thus the alpha function describes changes that occur to the mobility coefficient with electric field strength at constant gas number density. FIG. **12** illustrates the 3 general types of mobility behavior observed in a DMS, including monotonically increasing α (Type A), monotonically decreasing α (Type C), and first increasing then decreasing α (Type B).

**[0079]** The addition of polar modifiers to the transport gas within a DMS cell can improve selectivity as a result of cluster formation. Different chemical species cluster to different extents with chemical modifiers, and this imparts additional selectivity. The asymmetric waveform used in DMS varies between high field and low field regimes at a rate in the MHz range. This variation can be modeled as a field-dependent effective temperature synchronous with the Vrf field because of the high collision frequency at atmospheric pressure. When ion-neutral clustering is occurring to a significant extent, the time-varying effective temperature can cause a time-varying change in ion size and, therefore, a synchronous change in ion-mobility cross-section. Ions are clustered during the low field portion of the waveform and undergoing declustering due to heating during the high field portion of the waveform. The extent of clustering and the relative change in mobility due to clustering dictates the magnitude of Vc shift observed for the compounds, and the structural and chemical differences of compounds leads to a spread in peak position in the presence of clustering modifiers or dopants. This reversible cluster formation provides a method for the amplification of differential mobility effects in DMS. Because the change in cluster number occurs between the low and high field regimes during the SV waveform in DMS, the differential mobility is greatly enhanced.

**[0080]** In the absence of clustering modifiers, the hard sphere collision model can be used to predict the motion of colliding particles at high separation fields. Such predictions are widely used in molecular dynamics (MD) to understand and predict properties of physical systems at the particle level. The hard sphere collision model is based on the kinetic theory of gases in which, unlike the viscous damping models, the individual collisions between ion and gas particles are modeled. The expected frequency of collisions, measured as a distance (the mean-free-path) is predicted by the kinetic theory of gases as a function of the known pressure, temperature, and collisional cross sections of colliding particles. Collisions between ion and gas particles result in positive and negative energy transfers as well as scattering (deflection of ion velocity vectors), or even absorptions (e.g. in electron-gas collisions). The energy transfers provide for the kinetic cooling of a fast moving ion as well as the kinetic heating of a slow moving ion. Usually, colliding particles are treated as hard spheres. Generally, the background gas is non-stationary and has a Maxwell-Boltzmann distribution of velocities, which can be a function of temperature.

**[0081]** Such a configuration of an atmospheric pressure DMS **502** with a low pressure DMS **204**, in combination with the mass spectrometer **224**, provides for enhanced system **500** analysis selectivity. Such solution as in system **500** can simplify the incorporation of DMS into existing analyzer instruments such as, for example, the QTRAP® 5500 system, and provide substantial improvements in detection limits. This will increase the number of assays where DMS and ion mobility based filtering is useful.

**[0082]** In some embodiments, the region **202** may not include an RF ion guide. For these embodiments, only a DMS would be included. The DMS can include a plurality of filter electrode pairs. As shown in mass analysis system **550** of FIG. **5**B, the DMS can comprise four electrodes, and the separation voltage can be applied across two of the electrodes. A focusing potential can be applied to the other two electrodes.

**[0083]** FIG. **6** shows a diagram of a mass analysis system **600**, like the system **500** shown in FIG. **5**A, with a clustering and/or reaction region **612** prior to the atmospheric pressure DMS **502** according to an illustrative embodiment of the invention. The mass analysis system **600** also includes a curtain plate **602**, a curtain chamber **604**, curtain gas inlet **606**, curtain gas control valve **608**, curtain gas source **610**, and aperture **614**.

**[0084]** The curtain plate **602** may be configured to direct the curtain gas flow **616** and **618** out of the aperture **614** and towards the ion source **208**. In one embodiment, a high-purity curtain gas (e.g., $N_2$) flows between curtain plate **602** and vacuum plate **212** and out of the orifice **614** to provide a counter flow of gas that aids in keeping the mass analysis system **600** clean by desolvating and evacuating large neutral particles. The counter current gas flow (e.g., curtain gas) serves to decluster ions and prevent neutrals from entering the curtain chamber **604** and reaction region **612**.

**[0085]** In operation, a curtain gas is delivered to the curtain chamber **604** from a source **610** via a control valve **608** and inlet **606**. In addition to the curtain gas, the source **610** may provide a clustering reagent (e.g., a dopant or modifier) with the curtain gas. The reagent may be in the form of a gas, vapor, and/or liquid. By including a clustering reagent, the system **600** enables selected clustering of the sample ions in the reaction/clustering region **612** prior to ion mobility based filtering by the DMS **502**.

**[0086]** Thus, the DMS **502** performs ion mobility based filtering and/or separation consistent with the clusterization model. Under the clusterization model (shown as the Type A curve in FIG. **12**), the alpha function becomes increasingly positive, indicating that the mobility under high field conditions is getting larger as an ion becomes smaller with increasing amounts of declustering. The mobility during the low field portion of the waveform becomes smaller relative to the high field condition because the ion is larger and highly clustered. The declustering mechanism dominates the separation process and the selectivity achieved is highly influenced by the chemical characteristics of the ion in relation to its immediate surroundings. Higher fields typically improve the declustering which accentuates the difference in the state of the ion, and thus mobility, under the two field conditions. Clusterization model separations are considered to be chemically dominated separations (Type A).

**[0087]** The mass analysis system **600** enables tandem DMS operations, using atmospheric pressure DMS **502** and low pressure DMS **204** where the DMS **502** advantageously filters doped sample ions (e.g., reagent clustered sample ions) that were formed in the reaction/clustering region **612** due to mixing with the clustering reagent. But, after filtering by the DMS **502**, the sample ions are then declustered in the low pressure collision region **206** to remove the clustering reagent and/or other clustering. Once declustering/desolvation is per-

formed, the dry and/or declustered sample ions then are subjected to further ion mobility based filtering by the low pressure DMS **204**.

**[0088]** Thus, the DMS **204** performs ion mobility based filtering and/or separation consistent with the hard sphere collision model. Under transport gas conditions where clustering and adduct ion formation are minimized or nonexistent, the behavior of the sample ions shift towards a Type C classification. Under high field conditions the mobility is decreasing relative to the low field condition which remains constant. In high fields and in the absence of clusters, the hard sphere collision (or rigid sphere scattering) mechanism becomes dominant At high interaction energies, the short-range repulsive potential becomes important, resulting in a decreasing mobility. In contrast to the situation with modifiers present, the separation process and the selectivity achieved is less under these conditions, since it has more to do with collision dynamics. The negative shift in $\alpha$ shifts the compensation voltage in the opposite direction of what is observed when clustering phenomena dominate. The sample ions that pass through the second DMS **204** are then analyzed and detected by the mass spectrometer **224**.

**[0089]** Thus, the configuration of the system **600** illustrates an enhanced design concept for a tandem DMS system. Accordingly, a DMS analyzer, e.g., DMS **204**, may be located within the first reduced vacuum pressure stage, e.g., vacuum chamber **202**, with an additional DMS analyzer, e.g., DMS **502**, located within an atmospheric pressure region between the curtain plate **602** and gas restricting orifice **210**. In this fashion, modifiers may be added in the typical manner to the curtain gas stream to provide a DMS separation based upon clustering modifiers. As demonstrated, the clusters are lost upon expansion into the first vacuum chamber **202**, and this can be further facilitated by increasing the potential difference between the orifice **210** and QJET® ion guide **402**. Subsequently, a second ion mobility based separation can be achieved within the first vacuum chamber **202**, in the absence of modifiers. The tandem mobility analyzer, e.g., system **600**, can provide a substantial improvement in mobility peak capacity over a single DMS configuration. Hence, the transmitted ion population is modified between the stages of DMS mobility based separation. In addition, if desired, ions may be fragmented by application of a high potential difference between the orifice **210** and QJET ion guide **402** to provide additional selectivity. This workflow would involve mobility selection of a particular ion in DMS **502**, followed by fragmentation in the interface, e.g., low pressure collision region **206**, followed by mobility selection in DMS **204** of a particular daughter ion. It will be apparent to those skilled in the art that the RF ion guide **402** can be removed, and the DMS can comprise for electrodes as shown in FIG. **5**B.

**[0090]** FIG. **7**A includes plots **702**, **704**, and **706** of normalized ion intensity peaks in a DMS without reagent modifiers at various Vrf settings. As shown in the plots **702**, **704**, **706**, is can be difficult to differentiate or separate the ion intensity peaks associated with this particular series of isobaric compounds under conditions where no dopant or modifier is added to sample ions passing through a DMS such as DMS **502**. As shown in FIG. **7**A, there is a shift toward positive Vc values in all the compounds tested under these "dry ion" conditions.

**[0091]** FIG. **7**B includes plots **708**, **710**, **712**, **714**, and **716** of normalized ion intensity peaks in a DMS with reagent modifiers introduced at various Vrf settings. The various plots **708**, **710**, **712**, **714**, **716** illustrate the advantageous effect of adding a modifier, e.g., n-Propanol, 2-Propanol, and/or water, to the curtain gas which illustrate substantially improved peak capacity and substantially improved peak separation for many compounds in a DMS such as DMS **502**. As shown in FIG. **7**B, there is a shift toward negative Vc values in all the compounds tested with a modifier and/or dopant added to the transport gas which is described based upon the clusterization model.

**[0092]** FIG. **8** shows a diagram of dopant introduction system **800** via a mixing chamber **802** according to an illustrative embodiment of the invention. The system **800** may be included in the source **610** of FIG. **6** or may be included in the system **600** in addition to the source **610**. The system **800** also includes a curtain/transport gas inlet **804**, a clustering reagent reservoir **806**, and a curtain chamber inlet **808**.

**[0093]** In operation, clustering reagent is stored in a liquid reservoir **806** and mixed in mixing chamber **802** with the curtain/transport gas. The mixture of curtain gas and modifier are then delivered via the inlet **808** to the curtain gas chamber **604** and, more particularly, to the reaction/clustering region **612**. Conversely, the clustering reagent may be added to carrier/transport gas prior to introduction into the mixing chamber **802**.

**[0094]** FIG. **9** shows a diagram of an alternative dopant introduction system **900** according to an illustrative embodiment of the invention. The system **900** includes a mixing region **902** within the curtain chamber **604**, a curtain/transport gas inlet **904**, and a clustering reagent reservoir **906**. Instead of pre-mixing the curtain and reagent in a mixing chamber **802** according to FIG. **8**, in this embodiment, the clustering reagent and curtain gas are mixed in a mixing region **902** of the curtain gas chamber **604**. Conversely, the clustering reagent may be added to carrier/transport gas prior to introduction into the mixing chamber **902**.

**[0095]** FIG. **10** shows a diagram of a mass analysis system **1000**, like the system **600** in FIG. **6**, with a turbulent heated region **1002** according to an illustrative embodiment of the invention. The system **1000** also includes a clustering reagent inlet **1004**, curtain gas inlet **1006**, and reagent/curtain gas mixing region **1008**. In some embodiments, the system **1000** employs a dopant introduction system like system **900** of FIG. **9**. In other embodiments, the system **1000** employs a dopant introduction system like system **800** of FIG. **8**. Alternatively, the clustering reagent may be added directly to carrier/transport gas prior to introduction into the system. The system **1000** also advantageous employs a turbulent heated region **1002** to enable turbulent heating of the sample ions from the ion source **208**.

**[0096]** By heating the sample ions, declustering and/or desolvation of the sample ions is enhanced before introducing the sample ions into the DMS **502**. One or more heating elements **1010** may be included in the heated region **1002** to generate a selected temperature for heating the sample ions. A heating element **1010** may include a resistive element. The controller **228** may control the application of current and/or voltage to a heating element **1010** via the voltage source **226** to regulate the temperature in the heated region **1002**. One or more temperature sensors may be in communication with the controller **228** to enable the controller to regulate the temperature of the heated region.

**[0097]** The number and location of heating elements may vary in the system **1000**. For example, one or more heating elements may be located in the atmospheric pressure ion

source region **404**, in the curtain chamber **604**, in the vacuum chamber **202**, in the intermediate region **406**, in the low pressure collision region **206**, or in any combination of the regions/locations within the system **1000**. By employing one or more heated regions, such as turbulent heated region **1002**, the sensitivity of the system **1000** is enhanced by improving declustering/desolvation at desired locations within the system **1000**. The RF multipole **402** can be removed, and the DMS can comprise four electrodes as shown in FIG. **5**B.

**[0098]** FIG. **11** is a graph **1100** including plots **1102** and **1104** of normalized ion intensity vs. compensation voltage when the inlet to the atmospheric pressure DMS is not heated and heated respectively (**1102** includes the data without heat). Plot **1102** shows the Vc (CV) at about −2.5 volts with substantial peak tailing which is likely due to undesired clustering from moisture, for example, due to wet spray from an electrospray ionization source. Plot **1104** shows a shift in Vc to about 0 volts with an increased ion intensity and improved peak shape after the DMS inlet is heated, which illustrates how heating can improve declustering and/or desolvation and enhance analysis system sensitivity such as for system **1000**. As described earlier, heterogeneous clusters can be eliminated or reduced by employing heating techniques.

**[0099]** RF ion heating and bulk gas heating effects in DMS are closely related. For example, bulk heating can reduce the heterogeneous cluster ion population in an ion analyzer system. The goal is to desolvate/decluster electrospray generated clusters, and then recluster with a desired gas-phase reaction forming a homogeneous population in the DMS cell and/or filter. Heat transfer is highly efficient at atmospheric pressure due to the high frequency of molecular collisions and radiative heat transfer. Various means for heating the cluster ions in the gas prior to the entrance of a DMS filter can be envisioned in addition to RF heating just described. One approach, uses a wall-less mixing region with counter-current gas flows to accomplish this. Hot desolvation gas containing a mixture of the inert nitrogen curtain/transport gas with the modifier/dopant flows counter to the incoming ion clusters and source gas in a wall-less area.

**[0100]** Flow can be non-laminar in this region which maximizes the residence time of the cluster ion species in the heated region to drive desolvation to the extent possible. The background gas may have a high concentration of modifier/dopant that drives the equilibrium toward the desired homogeneous cluster ion population. The outflow of drying gas in front of the DMS analyzer region also helps to prevent neutral solvents and very large droplets from entering and contaminating the mobility analyzer region. Heterogeneous ion clusters can be reduced using this approach. In certain embodiments, the controller **228** controls various parameters of the analysis process such as, without limitation, dopant concentration, temperature, flow rate, Vc, Vrf, and pressure within the various portions of the analyzer system, such as system **1000**.

**[0101]** FIG. **12** is a graph of the alpha behavior for type A, B, and C ion mobility behavior. The Type A curve is associated with the clusterization model and exhibits a monotonic increase in alpha (a) with the increase in field strength. The Type C curve is associated with the hard sphere collision model and exhibits a monotonic decrease in alpha with the increase in field strength. The Type B curve is associated with a bi-model mode (combination of Type A first, then Type C) where an initial increase then decrease in alpha occurs with an increase in field strength. As is demonstrated in these curves, the classification describes the dominant separation mechanism at play which in turn is controlled by the degree to which an ion is clustered or adducted to neutral molecules. Types A and C represent limits (extremes) where one mechanism dominates, and type B is observed under conditions such that a mixture of mechanisms is apparent.

**[0102]** Type A

**[0103]** Under Type A conditions and/or clusterization model, the alpha function becomes increasingly positive indicating that the mobility under high field conditions is getting larger as the ion becomes smaller with increasing amounts of declustering. The mobility during the low field portion of the waveform becomes smaller relative to the high field condition because the ion is larger and highly clustered. The declustering mechanism dominates the separation process and the selectivity achieved is highly influenced by the chemical characteristics of the ion in relation to its immediate surroundings. The alpha function rapidly climbs with increasing Rf field.

**[0104]** Type C

**[0105]** Under transport gas conditions where clustering and adduct ion formation are minimized or nonexistent (e.g., low pressure condition), the behavior of a sample ion shifts to a Type C classification and/or hard sphere collision model. With increasing field strength, the alpha function becomes increasingly negative. Under high field conditions the mobility is decreasing relative to the low field condition which remains constant. In high fields and in the absence of clusters, the rigid sphere scattering mechanism becomes dominant At high interaction energies, the short-range repulsive potential becomes important resulting in a decreasing mobility. In contrast to the situation with modifiers present, the separation process and the selectivity achieved is less under these conditions, since it has more to do with collision dynamics.

**[0106]** Type B

**[0107]** Under inert transport gas conditions, the separation mechanism exhibits declustering behavior at low Rf amplitudes. Compounds that exhibit this behavior are present as adducts or clusters even under dry transport gas conditions. As the field strength increases, the Vc reverses direction and shifts toward positive values exhibiting a negative trend in alpha. This bimodal behavior is illustrated in the Type B alpha plot of FIG. **12**.

**[0108]** In a dry inert gas flow, the alpha function for a given ion within a DMS is constant, regardless of instrumental variations such as potential and pressure. This principal forms the basis for DMS sensors employing ionization sources such as nickel 63 beta emitters in combination with ion current detectors. The correlation of peaks at various Vc positions at different locations in the world necessitates this. The practical consequence of this is that DMS peak capacity can not be significantly improved by simply providing two DMS filters and conducting two separations on the same ion population rather than one. Dramatic improvements in peak capacity can require significant alterations of the alpha function for a given ion population between the two separations. Therefore, in one embodiment of the current invention, an ion population passes through a reaction/cluster region and is carried through a first DMS with a transport gas containing clustering modifiers. The $\alpha$ function for the clustered ions may have the form of the Type A behavior illustrated in FIG. **12**. The selected subset of the ion population then passes through the dissociation region where the equilibrium is driven towards the declustered ion species. Finally, a second DMS separation

is carried out on the subset of ions, where the α function may display either Type B or Type C behavior.

**[0109]** FIG. **13** shows an example of the transformation of the α function for norfentanyl ions. The trace labeled i) shows the alpha function for this ion under modified DMS separations where 1.5% 2-propanol was added to the nitrogen transport gas. The trace labeled ii) shows a radically different alpha function that is obtained when operating with nitrogen transport gas. The compound dependencies observed in the alpha functions under the two different conditions present the opportunity to dramatically improve peak capacity.

**[0110]** FIGS. **14**A-C show the alpha functions for a series of ion separations in a DMS. FIG. **14**A shows chemically modified separations using 2-propanol modifier, while FIGS. **14**B and **14**C show separations with inert nitrogen transport gas, respectively. In the presence of the clustering modifier, 36 compounds showed predominantly Type A behavior with positive values for the alpha function. In the absence of the clustering modifier, none of the 36 ions displayed Type A behavior, with all of them displaying a shift towards negative alpha values at high field. Under the instrumental conditions used to gather these data points, the observed compensation voltages Vc for the chemical species were predominantly negative for the modified separation and positive for the inert gas separation. In a number of cases, peaks that were not separated in the absence of modifiers were separated in the DMS that had modifiers in the transport gas flow. In a few cases, peaks that were not separated with the chemically modified separation were separated in the DMS that used inert transport gas. This simple example illustrates the peak capacity improvements that are possible when the alpha functions for a population of ions are dramatically altered between DMS separations in a tandem device. While this example describes altering the alpha function by changing the concentration of clustering modifiers in the transport gas flow, it will be apparent to those of skill in the relevant arts that the alpha function may also be altered in other ways including but not limited to a) maintaining a constant concentration of clustering modifier and varying the temperature within the two DMS analyzers to effect the degree of clustering, altering the transport gas composition without adding liquid modifiers, and fragmenting the ion of interest in the dissociation region such that the ion monitored in the second DMS has a different m/z than the ion monitored in the first DMS cell.

**[0111]** It will be apparent to those of ordinary skill in the art that certain aspects involved in the operation of the controller **228** may be embodied in a computer program product that includes a computer usable and/or readable medium. For example, such a computer usable medium may consist of a read only memory device, such as a CD ROM disk or conventional ROM devices, or a random access memory, such as a hard drive device or a computer diskette, or flash memory device having a computer readable program code stored thereon. It will also be apparent to those of skill in the relevant art that the dissociation region may comprise other means of heating ions including a source of radiation such as a laser, or other devices.

**[0112]** Those skilled in the art will know or be able to ascertain using no more than routine experimentation, many equivalents to the embodiments and practices described herein. Accordingly, it will be understood that the invention is not to be limited to the embodiments disclosed herein, but is to be understood from the following claims, which are to be interpreted as broadly as allowed under the law.

What is claimed is:

**1**. A mass analysis system comprising:
a low pressure dissociation region,
a differential mobility spectrometer including:
at least a pair of filter electrodes defining an ion flow path therebetween, the filter electrodes generating an electric field for passing through a selected portion of the sample ions based on the mobility characteristics of the sample ions,
a voltage source for providing RF and DC voltages to at least one of the filter electrodes to generate the electric field,
an ion inlet for receiving sample ions that have passed through the low pressure dissociation region, and
an ion outlet for outputting the selected portion of the sample ions, and
a mass spectrometer for receiving some or all of the selected portion of the sample ions.

**2**. The system of claim **1**, wherein the dissociation region includes at least one of a collision region, desolvation region, and declustering region.

**3**. The system of claim **2**, wherein the low pressure dissociation region is configured to accelerate the sample ions.

**4**. The system of claim **3**, wherein the low pressure dissociation region is configured to perform at least one of declustering and fragmenting the sample ions.

**5**. The system of claim **1**, wherein the pressure of the differential mobility spectrometer and a portion of the low pressure dissociation region is less than about atmospheric pressure.

**6**. The system of claim **5**, wherein the pressure of the differential mobility spectrometer and a portion of the low pressure dissociation region is less than about 100 torr.

**7**. The system of claim **1**, wherein the pressure of the ion flow path is substantially the same as the pressure of a portion of the low pressure dissociation region.

**8**. The system of claim **1** comprising at least one ion guide located in at least one of the low pressure dissociation region and an intermediate region between the differential mobility spectrometer and the low pressure dissociation region.

**9**. The system of claim **7**, wherein the at least one ion guide includes at least one ion focusing element.

**10**. The system of claim **8**, wherein the ion focusing element includes at least one of an RF rod, RF ring, RF lens, DC lens, DC ring, deflector plate, and grid.

**11**. The system of claim **1**, wherein the low pressure dissociation region is configured to receive a flow of the sample ions from an ion source.

**12**. The system of claim **11**, wherein the flow is formed by a vacuum drag from the dissociation region.

**13**. The system of claim **10**, wherein the ion source includes a second differential mobility spectrometer.

**14**. The system of claim **11**, wherein the second differential mobility spectrometer operates at substantially atmospheric pressure or above.

**15**. The system of claim **10**, wherein the low pressure dissociation region is configured to accelerate ions within a free jet expansion.

**16**. The system of claim **1** comprising a housing, the housing substantially enclosing the differential mobility spectrometer.

**17**. The system of claim **16**, wherein the housing substantially encloses the low pressure dissociation region.

**18**. The system of claim **17**, wherein the housing includes a housing inlet for receiving the sample ions.

**19**. The system of claim **16**, wherein the housing includes a housing outlet, in communication with the ion outlet, for outputting the portion of selected sample ions into the mass spectrometer.

**20**. The system of claim **19**, wherein the mass spectrometer includes at least one ion optics element for receiving the selected portion of the sample ions via the housing outlet.

**21**. The system of claim **20**, wherein the mass spectrometer includes a mass analyzer in communication with the at least one ion optics element.

**22**. The system of claim **1** comprising an insulating material in communication with at least one of the filter electrodes.

**23**. The system of claim **1** comprising at least one heated region configured to perform at least one of i) declustering ions, ii) desolvating ions, iii) accelerating the reclustering of ions with reagents, and iv) shifting the clustering equilibrium for ions with dopant or reagents.

**24**. The system of claim **1**, wherein the pressure of the differential mobility spectrometer and a portion of the low pressure dissociation region is about 50 to about 760 torr.

**25**. The system of claim **1**, wherein the differential mobility spectrometer comprises four electrodes.

**26**. A method for analyzing a sample comprising:

passing sample ions through a low pressure dissociation region,

applying RF and DC voltages to at least one of at least one pair of filter electrodes,

generating an electric field in a flow path between the at least one pair of filter electrodes,

passing through the electric field a selected portion of the sample ions based on the mobility characteristics of the sample ions, and

receiving some or all of the selected portion of the sample ions at a mass spectrometer.

**27**. The method of claim **26** comprising accelerating the sample ions in the low pressure dissociation region.

**28**. The method of claim **27** comprising performing at least one of declustering and fragmenting the sample ions in the low pressure dissociation region.

**29**. The method of claim **26**, wherein the pressure of the flow path and a portion of the low pressure dissociation region is less than about 760 torr.

**30**. The method of claim **29**, wherein the pressure of the flow path and a portion of the low pressure dissociation region is less than about 100 torr.

**31**. The method of claim **26**, wherein the pressure of the ion flow path is substantially the same as a portion of the pressure of the low pressure dissociation region.

**32**. The method of claim **26** comprising guiding the sample ions through at least one of the low pressure dissociation region and an intermediate region.

**33**. The method of claim **32**, wherein the guiding is performed by an ion guide including at least one ion focusing element.

**34**. The method of claim **33**, wherein the ion focusing element includes at least one of an RF rod, RF ring, RF lens, DC ring, DC lens, deflector plate, and grid.

**35**. The method of claim **26** comprising receiving a flow of the sample ions at the low pressure dissociation region from an ion source.

**36**. The method of claim **26** comprising providing at least one heated region configured to perform at least one of i) declustering ions, ii) desolvating ions, iii) accelerating the reclustering of ions with reagents, and iv) shifting the clustering equilibrium for ions with a dopant or reagent.

**37**. The method of claim **26**, wherein the at least one pair of filter electrodes comprises four electrodes.

**38**. A sample analysis system comprising:

a first pressure region operating at a pressure of about atmospheric pressure or greater including:

a first DMS filter for receiving sample ions from an ion source and passing through a first set of selected sample ions, and

a second pressure region, in communication with the first pressure region, operating at less than about atmospheric pressure including:

a dissociation region for accelerating the first set of selected sample ions, and

a second DMS filter for passing through a second set of selected sample ions.

**39**. The system of claim **38** comprising:

a third pressure region, in communication with the second pressure region, operating at less than about 1 torr including:

an ion optics element for receiving the second set of selected sample ions.

**40**. The system of claim **39** comprising:

a fourth pressure region, in communication with the third pressure region, operating at less than about $10^{-4}$ torr including:

a mass analyzer.

**41**. The system of claim **38** comprising a dopant inlet, in communication with the first pressure region, for introducing at least one reagent.

**42**. The system of claim **38** comprising a gas inlet, in communication with first pressure region, for introducing at least one of a curtain gas and a transport gas.

**43**. The system of claim **38** comprising at least one heated region configured to perform at least one of i) declustering ions, ii) desolvating ions, iii) accelerating the reclustering of ions with reagents, and iv) shifting the clustering equilibrium for ions with dopant or reagents.

**44**. The system of claim **43** comprising at least one adjustable heating element for controlling the temperature in the at least one heated region.

**45**. The system of claim **41** comprising a heated region located within the first or second pressure region, wherein the heated region is configured to perform at least one of remove unwanted clusters of the sample ions and accelerate reclustering of the sample ions with the at least one reagent.

**46**. The system of claim **41** comprising a reaction region in the first pressure region for clustering a portion of the sample ions using the at least one reagent.

**47**. An ion analyzer comprising:

a ion source,

a flow of ions from the ion source,

a reaction region for introducing at least one modifier to the flow of ions,

a first DMS, operating substantially at atmospheric pressure, for receiving the flow of ions from the reaction region, the first DMS performing a first mobility based filter operation on the flow of ions,

a declustering region, operating at less than atmospheric pressure, for receiving the flow of ions from the first DMS, and

a second DMS, operating at less than atmospheric pressure, for receiving the flow of ions from the declustering region and performing a second mobility based filter operation on the flow of ions.

**48**. The analyzer of claim **47** comprising a mass spectrometer for receiving the flow of ions from the second DMS.

**49**. The analyzer of claim **48**, wherein the mass spectrometer includes a mass analyzer.

**50**. The analyzer of claim **47** comprising at least one heated region configured to perform at least one of i) declustering ions, ii) desolvating ions, iii) accelerating the reclustering of ions with reagents, and iv) shifting the clustering equilibrium for ions with dopant or reagents.

**51**. The analyzer of claim **47**, wherein the first DMS performs separations based on a clustering model mechanism.

**52**. The analyzer of claim **51**, wherein the second DMS performs separations based on a rigid sphere collision model mechanism.

**53**. The analyzer of claim **47** comprising an ion guide upstream of the second DMS for providing the flow of ions to the second DMS.

**54**. An ion analysis system comprising:

an ion source,

a flow of ions from the ion source,

a first means for modifying a first portion of ions from the flow of ions to alter the $\alpha$ function associated with the first portion of ions,

a first DMS configured to receive the first portion of ions, conduct a differential mobility separation, and output a second portion of ions,

a second means for modifying the second portion of ions to alter the $\alpha$ function associated with the second portion of ions, and

a second DMS configured to receive the second portion of ions, conduct a differential mobility separation, and output a third portion of ions.

**55**. The system of claim **54**, wherein the means for modifying includes at least one of a reaction region, clustering region, dissociation region, and declustering region.

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