(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 2 363 877 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
07.09.2011 Bulletin 2011/36

(51) Int Cl.:
H01J 49/10 *(2006.01)*

(21) Application number: **10405080.2**

(22) Date of filing: **19.04.2010**

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO SE SI SK SM TR
Designated Extension States:
AL BA ME RS

(30) Priority: **02.03.2010 CH 2712010**

(71) Applicant: **Tofwerk AG**
3600 Thun (CH)

(72) Inventor: **Gonin, Marc**
3654 Gunten (CH)

(74) Representative: **Rüfenacht, Philipp Michael et al**
Keller & Partner
Patentanwälte AG
Schmiedenplatz 5
Postfach
3000 Bern 7 (CH)

(54) Method for chemical analysis

(57) In a method for chemical analysis a first group of particles of a sample of interest is ionized using a first ionization method for generating a first group of ions. A second group of particles of the sample of interest is ionized using a second ionization method which is different from the first ionization method for generating a second group of ions. The first group of ions and the second group of ions are analyzed in a mass analyzer (120), whereas ions of the first group and ions of the second group are detected using the same detector (124) of the mass analyzer. At least one of the ionization methods is operated in a pulsed manner and/or the ionized particles of at least one of the groups are transmitted to the mass analyzer in a pulsed manner. At least in a time interval the first ionization method and the second ionization method are operated simultaneously and ions of the first group and ions of the second group are both transmitted to the mass analyzer (120). This method and a corresponding apparatus have an improved capability to identify chemical compounds. In particular, the improvement may be achieved by high-speed multiplexing of the different ionization methods.

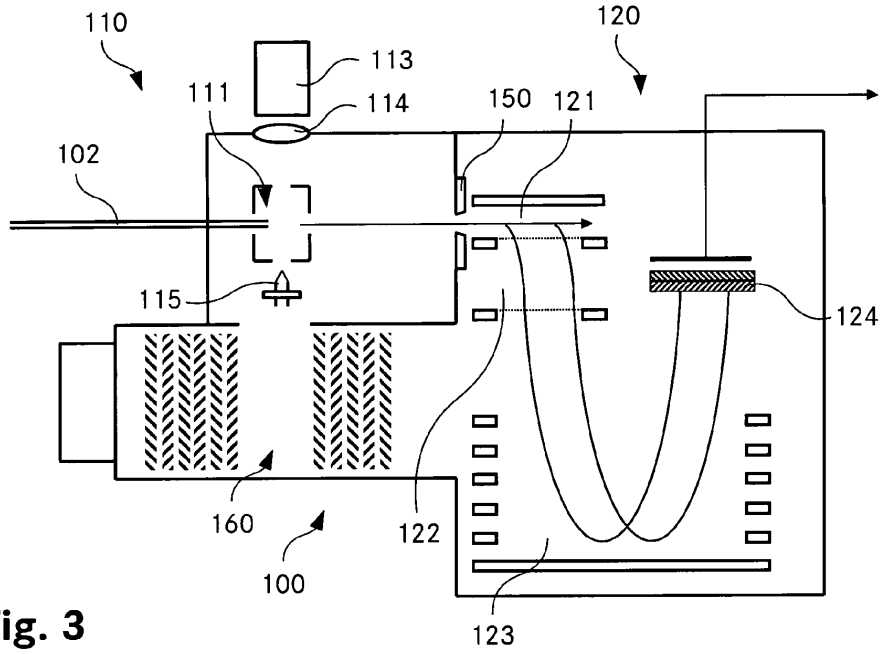

Fig. 3

EP 2 363 877 A1

Description

Technical Field

[0001] The invention relates to a method for chemical analysis as well as to an apparatus for carrying out such a method.

Background Art

Mass Spectrometry

[0002] Mass spectrometry (MS) is a method of chemical analysis that has a wide range of applications. MS is used in many different fields, including the analysis of gases, liquids, solids, plasmas, aerosols, biological aerosols, biological material, tissue, and so forth.

[0003] A mass spectrometer an alyzes gas-phase ions (i.e., molecules or atoms having a net positive or negative electric charge). This implies that the molecule or atom to be analyzed must be converted to the gas phase and ionized prior to the analysis, unless it already exists in this state.

[0004] In analyzing an ion, a mass spectrometer determines the ratio of the ion's mass to its net charge. This quotient is referred to as the ion's mass-to-charge ratio (m/Q).

[0005] Mass spectrometry data are typically presented as a mass spectrum. A mass spectrum of a sample is a histogram showing the abundances of ions separated by their mass-to-charge ratio.

[0006] The mass-to-charge ratios of ions originating from a sample can be used to determine the structures and identities of molecules present in a sample. The abundance of ions can be used to determine concentrations of molecules in the sample.

[0007] Many types of mass spectrometers exist; all are based on the manipulation of ion trajectories using electric and/or magnetic fields.

[0008] Some types of mass spectrometers manipulate trajectories so that ions of only one mass-to-charge ratio are visible to the detector. By varying some parameter(s), the visible mass-to-charge ratio can be changed. To construct a mass spectrum, these filtering mass spectrometers (FMS) make successive measurements at each mass-to-charge ratio of interest. A common type of FMS is the quadrupole mass spectrometer.

[0009] Other mass spectrometers disperse ions across a spatial and/or temporal axis in a m/Q-dependent manner and detect ions with a detection system that has resolution along the axis of dispersion. These dispersive mass spectrometers (DMS) can record the abundances of all mass-to-charge ratios of interest in a single measurement.

[0010] A time-of-flight mass spectrometers (TOFMS) is a type of DMS that determines the mass-to-charge ratio of ions by measuring velocities when accelerated to a known kinetic energy or by a known impulse.

[0011] In a standard TOFMS configuration, measurements are made in a pulsed manner, such that unique mass spectra for a selected m/Q range are acquired at frequencies between 10kHz and 100 kHz.

[0012] In this standard TOFMS configuration, each measurement is often referred to as an "extraction".

[0013] For a given TOFMS, sensitivity may be increased by increasing the frequency of extractions, while the range of m/Q values may be increased by increasing the period of the extractions (i.e., lowering the frequency).

[0014] For a given TOFMS extraction frequency, the range of monitored m/Q values depends on the active data acquisition time, relative to the extraction period. For instance, the maximum m/Q value recorded can be reduced by acquiring data for a shorter period within the TOFMS period.

Data Acquisition

[0015] Mass spectrometer operating parameters and data acquisition are generally controlled by a computer. For instance, the control computer may be used to:

- Set and monitor the voltages applied to electrodes within the mass spectrometer
- Set and monitor pressures in the various regions of the mass spectrometer
- Generate start and stop signals for data acquisition
- Synchronize MS acquisition with data recording
- Synchronize MS data acquisition with some external process, such as a chromatographic separation
- Manage the data recording device
- Average successive MS measurements, display MS data, and save MS data

[0016] Instead of having a single control computer for carrying out all these tasks, it is possible to have two or more devices such as all-purpose computing devices or dedicated components between which these tasks are distributed.

[0017] All types of mass spectrometers include a detector that generates a signal in response to the presence of an ion or ions. This output signal is often an analog voltage with magnitude proportional to the number of simultaneously detected ions.

[0018] The signal output by a mass spectrometer must be converted to a digital format in order to be stored in the memory (RAM) of the control computer and/or saved to disk. Mass spectrometers usually use either analog-to-digital (ADC) or time-to-digital converters (TDC) for this conversion.

[0019] Both types of digitizer accept an input signal from the MS, process the signal, and output a digital representation of the signal to the control computer.

[0020] The signal output by an ADC maintains knowledge of the input signal's intensity as a function of time.

[0021] A TDC output time values for which the input signal is greater than a defined value (discriminator threshold). No other knowledge of the input signal's absolute intensity is maintained.

[0022] The number of ions recorded in a single MS measurement (e.g., TOF extraction) is typically low, such that the data from many measurements do not contain all ion types (m/Q values) present in the sample. Thus, for a given sample, data are generally averaged by accumulating data from successive measurements to produce a total mass spectrum.

[0023] In some systems, the ADC or TDC has user-managed memory, and data from successive measurements are averaged in this memory for a fixed duration of time, only after which the averaged data are transferred to the control computer.

[0024] In other systems, data from each measurement are transferred to the control computer, and data from successive measurements are averaged in the RAM of the control computer.

[0025] In some known ADCs and TDCs, the user-managed memory can be divided into several segments and the operator can then direct data from each measurement into a specific segment for averaging.

[0026] Similarly, for instruments averaging data in the PC RAM, the RAM of the PC can be divided into segments, and the operator can direct the transferred data into a specific segment for averaging.

[0027] For some MS applications, data are averaged and saved as a continuous array representing the signal intensity versus time or signal intensity versus mass-to-charge ratio. We refer to such data as a waveform.

[0028] For other MS applications, the averaged and saved data are limited to signal intensities at select times or mass-to-charge ratios. These data are effectively selected sub-sections of the continuous waveform. We refer to such data as a peak picture.

[0029] For other MS applications the peak pictures are evaluated in order to find the important parameters like peak position (e.g. centroid), peak height, peak area and peak width. We refer to such data as a peak list.

Ionization

[0030] The process used to convert sample molecules to gas-phase ions prior to analysis by a mass spectrometer is called ionization.

[0031] Many different ionization methods exist.

[0032] The ion source is the hardware used to produce ions by the ionization method, and it must be directly or indirectly connected to the mass spectrometer in a way that allows transfer of the produced ions into the mass spectrometer.

[0033] The desorption mechanism refers to the process by which the molecule to be analyzed is forced into the gas phase, while the ionization mechanism describes the steps that give the molecule a charge.

[0034] The relationship between desorption and ionization varies with the ionization method: the processes may occur in separate, unrelated steps, or the mechanisms may be strongly interlinked.

[0035] Some ionization methods rely on the bombardment of the sample molecules or sample atoms with particles. The particles can be photons, electrons, atoms, ions, molecules or clusters. In these cases the interaction of the incoming particle and analyte molecule supplies the energy required to ionize the sample molecule. Examples include electron ionization (EI), photon ionization (PI), and fast atom bombardment (FAB).

[0036] In some methods, such as EI, it is the kinetic energy of the bombarding particle that is the source of the ionization energy.

[0037] In other cases it is a chemical reaction that ionizes the sample substance, by spontaneous transfer of electrons, protons or other ions between the incident molecule or ion and the sample molecule. These ionization methods are summarized as chemical ionization (CI).

[0038] A common method that involves the transfer of an electron from the analyte molecule to an incident metastable atom is called Penning ionization.

[0039] Chemical ionization mechanisms are key to many atmospheric pressure (AP) ionization methods (APCI, APPI, APEI) and ambient ionization methods (DESI, DART), where primary/reagent ions or metastable atoms are formed in a plasma or by irradiation of particles or photons and then ionize the analyte by charge exchange or Penning ionization.

[0040] Neutral molecules can also be ionized by high temperatures using high temperature surfaces (thermal ionization) or in hot plasmas.

[0041] Ionization of neutral molecules can also occur in strong electric fields, using field ionization (FI).

[0042] Ionization methods may be continuous, producing an effectively constant current of ions, or pulsed, producing ions in bursts. A continuous ionization method may be run in a pulsed manner by modulating the method between active and inactive states.

[0043] EI, which bombards samples with a continuous stream of electrons, is an example of a continuous source.

[0044] PI using photons generated by a pulsed laser is an example of a pulsed source.

[0045] For any MS analysis, the choice of ionization method depends on the physical and chemical nature of the sample.

[0046] Use of a given ionization method might require that the sample is a solid, liquid, or a gas. And, the desorption and ionization mechanisms may rely on properties of the sample molecules. For instance, certain CI mechanisms are selective for molecules that have proton affinities within a specific range of values. The spontaneity of EI and Penning ionization mechanisms depend on the energy required to remove an electron from the analyte molecule. PI requires that the analyte molecule absorbs light at the wavelength of the incident photons. And, ionization methods based on a thermal desorption mechanism may be limited to use with molecules of high volatility.

[0047] Such selectivity can limit the application of a method, or it can be exploited to detect specific classes of molecules within complex sample mixtures or matrixes.

[0048] The choice of ionization method also depends on the nature of the desired analysis. As such, ionization methods are characterized based on the types of ions and data they produce. For instance, methods may be quantitative, thereby enabling determination of sample concentrations. Or, methods for ionization of solid samples may or may not have spatial resolution sufficient for surface mapping.

[0049] A critical characteristic of an ionization method is the tendency of the desorption and/or ionization mechanisms to break the intact molecule or molecular ion into smaller fragments. An ionization method is described as "hard" or "soft" according to its tendency to produce fragments. Both hard and soft ionization methods are desirable for different reasons.

[0050] "Hard" ionization methods yield ions that are fragments of the original sample molecules. As an example, a mass spectrum of EI-generated ions typically contains many fragment ions with mass lower than the sample molecule.

[0051] The analysis of fragment ions generated by hard ionization methods can be useful for deducing the structure of sample molecules, particularly if the sample contained only one type of molecule (a "pure sample"), such that all fragments can be assumed to originate from the same molecular structure.

[0052] Structural analysis based on fragments is very complicated for mass spectra of mixed samples.

[0053] For any "hard" method, the degree of observed fragmentation depends on the properties of the specific analyte molecule and may depend on instrumental parameters. All hard methods do not produce the same types of fragments or the same degree of fragmentation.

[0054] Very hard methods break a molecule into bare atomic ions, enabling elemental analysis.

[0055] Ionization with soft methods yields little to no fragmentation of the sample molecules. A mass spectrum of a pure sample ionized by a soft method will have a dominant peak corresponding to the intact molecular ion. Depending on what is known about the sample, this may or may not enable molecular identification.

[0056] For samples that are complex mixtures of molecules, soft ionization produces simpler mass spectra containing fewer ion peaks, and therefore reduces data-analysis complications related to interferences between mass spectral peaks of similar mass-to-charge.

[0057] The fraction of sample molecules that is ionized when a given method is applied using a given source is termed the ionization efficiency.

[0058] The ionization efficiency of different methods and different sources vary greatly. And, for a given source and method, the ionization efficiency will not be equal for all molecule types.

[0059] For many types of analysis it is desirable to acquire mass spectra for a single sample ionized by multiple methods. The complimentary data produced by the various ionization methods can facilitate more thorough characterization of a sample.

[0060] For example, many mass spectrometers (MS) that are used in combination with gas chromatographs (GC) are equipped to run with both hard and soft ionization methods. The soft ionization enables determination of the mass of the molecule or the purity (number of molecule types in the sample), while the hard ionization enables structural analysis based on fragments.

[0061] Many reasons for wanting to alternate between ionization methods can be imagined, and alternation schemes are not limited to methods that are opposite in their tendency to cause fragmentation. For example, it may be desired to alternate between a universal and quantitative ionization method that enables determination of the total concentration of molecules in the sample and a selective method that will help determine the presence or absence of a specific molecule.

[0062] Possible schemes are also not limited to alternation between only two methods. For instance, in selected ion flow tube (SIFT) MS, analysis alternates between different CI methods. Because CI methods are selective, analysis with SIFT-MS can produce multiple different mass spectra for the same sample, and each mass spectrum gives unique insight into the nature of the sample.

[0063] Traditionally, switching between ionization methods is a rather cumbersome procedure. It can involve the

exchange of the whole ion source or of parts of the ion source. It can also involve the addition of gases into the ionization source. This makes the transition of one mode to the other slow, and therefore it is usually not possible to record the mass spectra from the different ionization methods within the duration of a single sample injection. For example, it is common to carry out two successive GC-MS runs with duplicate samples in order to record mass spectra with both a soft and a hard ionization method mass spectra. Due to the fact of that GC is a rather slow method, this substantially increases the time to carry out the analysis.

[0064] It is also already known to obtain complimentary mass spectra from different ionization methods in the same sample analysis. Up to now, this has been achieved in different ways:

- It is possible to run two mass spectrometers in parallel, each running with a different ionization method. This approach has the cost disadvantage of having two mass spectrometers.

- It is also possible to switch the same ion source between different ionization modes such as a hard ionization mode and a soft ionization mode.

- US 6,469,297 (Hitachi) describes hardware for interfacing multiple ionization sources to a single mass spectrometer. Alternation between the multiple ionization sources is controlled with an electrostatic or quadrupole deflector that deflects the ions from one of the ion sources into the mass spectrometer. This hardware is applicable to nearly any ion source.

- Furthermore, it is possible to have two ion sources sharing a mass analyzer or at least parts of a mass analyzer. For example, US 7,294,830 (Indiana University Research and Technology Corporation) discloses running an electrospray ionization (ESI) source and an inductively coupled plasma (ICP) ionization source on the same TOF analyzer. In this method, a flowing liquid sample is split between the two sources. Ions are simultaneously created in the two sources and introduced to a TOFMS by separate ion optical interfaces, which direct ions into the TOFMS extraction region on parallel paths, but from opposite sides. Ions from the two sources are analyzed in a shared mass TOF drift chamber, but have different trajectories related to the direction from which they were introduced into the extraction region. Ions from the two sources are recorded on separate detectors, positioned according to the different trajectories.

[0065] The latter approaches eliminate the need for two separate mass detectors, however a specific design of the mass analyzer and/or a specific deflector between the ion sources and the mass analyzer is required and the number of different ion sources that may be coupled to the mass analyzer is limited.

[0066] Switching between different ionization methods depends on an ability to (1) enable/ disable ionization methods in a controlled manner and (2) sort acquired data according to the active ionization method. Errors in either regard lead to ambiguity in data processing.

[0067] Many samples have chemistry that is changing in time. Anal yzing such samples with multiple ionization methods requires alternation schemes that are more rapid than the time scale of chemical change.

[0068] In some cases the physical method for alternation determines the maximum rate at which methods can be alternated. In other cases, it is the sorting of data that determines this rate. In particular, standard methods of alternation save a data file each time the method is changed. Thus, at the completion of analysis with each method, data must be transferred from the digitizer to the PC, processed (optional), and saved to disk. This step is potentially slower than the rate at which methods can be changed. And, even if rapid, this method of sorting data can require undesirable breaks in acquisition.

[0069] Further, in cases where ionization methods are rapidly alternated, frequent saves to disk in order to avoid ambiguity in data may consume more hard disk space than is necessary.

Summary of the invention

[0070] It is the object of this invention to create a method as well as an apparatus for chemical analysis that allow for rapid switching between different ionization methods when analyzing ions generated from a single sample.

[0071] The object is achieved using a method for chemical analysis, comprising the steps of

a) ionizing a first group of particles of a sample of interest using a first ionization method for generating a first group of ions;

b) ionizing a second group of particles of the same sample of interest using a second ionization method which is different from the first ionization method for generating a second group of ions;

c) analyzing the first group of ions and the second group of ions in a mass analyzer, preferably in a time-of-flight mass spectrometer;
whereas

d) ions of the first group and ions of the second group are detected using a same detector of the mass analyzer;

e) at least one of the ionization methods is operated in a pulsed manner and/or the ionized particles of at least one of the groups is transmitted to the mass analyzer in a pulsed manner;

f) at least in a time interval the first ionization method and the second ionization method are operated simultaneously and ions of the first group and ions of the second group are both transmitted to the mass analyzer.

[0072] The method may involve more than two different ionization methods. In that case, it is preferred that all but one or all of the ionization methods are operated in a pulsed manner. It is crucial that the method allows the ionization of particles of the same sample by different ionization methods, thus allowing for multiplexing the ionization methods and thus to obtain additional information compared to the sequential application of different ionization methods to different samples.

[0073] A preferred architecture of a multiplexing sequence is organized as follows. The mass analyzer acquires passes, i. e. single mass spectra. Acquisition of passes is synchronized with the controlled alternation of active ionization methods and mass spectrometer settings. The control sequence that determines this alternation is constructed of elements. A specific combination of ionization methods and mass sprectrometer settings is termed an element type. Application of the multiplexing sequence is synchronized with passes, such that transitions between elements occurs between passes. A number of successive sequence elements passes relating to the same ionization met hod or combination of ionization methods respectively, constitute a sequence segment. A plurality of sequence segments, all having the same length (number of elements), follow one another, constituting a sequence block. The multiplexing sequence follows a cyclical sequence of segments. It is the pattern of segments that is repeated that is called the sequence block.

[0074] The disclosed method may involve the multiplexing of any number of ionization methods. At least one of the ionization methods is to be applied in a pulsed manner, with a pulsing frequency that is less than or equal to the rate at which the mass spectrometer acquires passes.

[0075] In some embodiments, multiple methods are multiplexed for the analysis of a single sample, where at least one of the methods is applied continuously and the others are applied in a pulsed manner.

[0076] In some embodiments, multiple ionization methods are multiplexed for the analysis of a single sample, where all the methods are applied in pulsed manner. The multiplexing sequence contains at least one element for which more than one ionization method is active.

[0077] The method may be carried out by an apparatus comprising

a) at least one ionization source being capable of ionizing a first group of particles using a first ionization method for generating a first group of ions and of ionizing a second group of particles using a second ionization method which is different from the first ionization method for generating a second group of ions;

b) a mass analyzer, in particular a time-of-flight mass spectrometer;

c) a modulator for modulating at least one of the ionization methods and/or a transmission of the ionized particles of at least one of the groups to the mass analyzer between active and inactive states;
whereas

d) the mass analyzer is coupled to the at least one ionization source such that ions of the first group and ions of the second group may be simultaneously analyzed by the mass analyzer, whereas ions of the first group and ions of the second group are detected using a same detector of the mass analyzer;

e) the modulator is capable of modulating the at least one of the ionization methods in a manner synchronized with the acquisition of successive mass spectra;

f) at least in a time interval the at least one ionization source is operable to carry out the first ionization method and the second ionization method simultaneously and to transmit ions of the first group and ions of the second group simultaneously to the mass analyzer.

[0078] The apparatus may have a single ion source which allows for simultaneously carry out two or more different

ionization methods. As well, the apparatus may have two or more ion sources. Preferably, all or all but one of the ionization methods are operated in a pulsed manner in order to allow true multiplexing.

[0079] It is to be noted that the term "mass analyzer" encompasses devices that allow discrimination of different particles depending on their mass (and possibly other quantities). In particular, the term "mass analyzer" according to that specification encompasses mass spectrometers discriminating particles according to their mass-to-charge ratio m/Q.

[0080] The mass analyzer comprises data acquisition electronics including a digitizer and a control computer. The apparatus further comprises circuitry and/or hardware for multiplexing the multiple ionization methods according to a known sequence with high temporal precision.

[0081] In the disclosed method, ions may be generated by any ionization method and any ionization methods may be applied together or in alternation, provided the numerous methods are applied to the same sample.

[0082] The inventive method and apparatus allow for quasi-simultaneous analysis, i. e. mass spectra of ions generated by the various ionization methods are recorded on a timescale faster than the relevant chemistry of the sample is changing. Compared to prior art methods and apparatuses, the improvement is achieved by high-speed multiplexing of different ionization methods applied to a single sample with a single mass spectrometer having an acquisition system.

[0083] The disclosed method allows for increasing the comprehensiveness and sensitivity of MS analysis by multiplexing the applied ionization methods, such that at any time interval during the analysis one ionization method or some set of ionization methods is active and data representing ions originating from one, some, or all of the different ionization methods that were operational at said time interval are recorded with a single mass spectrometer. For some duration of time during any such multiplexed analysis, two or more ionization methods are simultaneously active.

[0084] This multiplexing can be contrasted with sequential alternation schemes, in which ionization methods are applied sequentially and only one ionization method is active at any point during the analysis of a sample.

[0085] In the disclosed multiplexing method, the active method or sets of methods is changed in a controlled manner.

[0086] Application of an ionization method may e. g. be modulated by mechanical modulation of a beam of primary particles, electromagnetic deflection of a beam of primary charged particles, pulsed regulation of a voltage necessary to generate the beam of primary particles, or pulsed regulation of a gas necessary to generate the beam of primary particles.

[0087] In some embodiments, multiple ionization methods are multiplexed for the analysis of an unknown sample (pure or mixture), and at least one of the methods is considered selective for a unique class of compounds. In one such embodiment, the multiplexing sequence contains element types corresponding to independent application of each of the selective ionization methods.

[0088] In some embodiments, multiple ionization methods are multiplexed, whereby data from at least one provides quantitative information. In one such embodiment, the quantitative ionization method is solely active during at least one sequence element. In another such embodiment, the quantitative ionization has a much greater ionization efficiency than some or all of the other applied ionization methods, such that ions from less efficient methods are negligible in passes acquired with the quantitative and less efficient methods simultaneously active.

[0089] In some embodiments, the mass analyzer is used for detection of a chromatographic experiment, such as a gas chromatographic experiment, and multiple ionization methods are multiplexed during the analysis. The multiplexing sequence repeats multiple times during the chromatographic experiment, and data are saved at the completion of each sequence. Each save includes data from the multiple memory segments.

[0090] In some embodiments, a solid surface is analyzed by mass spectrometry and ions are generated from the surface using multiplexed ionization methods. In one such embodiment, one of the ionization methods has spatial resolution sufficient for chemical mapping of the surface, and the focus of this ionization method is scanned across the surface. Data files are saved at a rate greater than or equal to the rate at which the spatial resolved method is moved.

[0091] In some embodiments, multiple ionization methods are multiplexed. One of these methods may be very hard, producing atomic ions enabling elemental analysis. At least one of the other methods should not produce atomic ions. The method producing atomic ions is pulsed, such that analysis produces both molecular and atomic data.

[0092] In any of the previous embodiments, the relative duty cycle of any of the ionization methods may be adjusted by customization of the defined multiplexing sequence. In one such embodiment, a very sensitive method is multiplexed with a less sensitive method. The less sensitive method is included in all sequence elements, while the more sensitive method is pulsed and only included in a fraction of the elements.

[0093] In some embodiments the simultaneous application of ionization methods produces a mass spectrum that can be considered the sum of the mass spectra that are produced when each method is applied individually, where each of these individual mass spectra are normalized according to the methods' ionization efficiency. In such embodiments, mass spectra corresponding to passes from sequence elements with multiple methods applied can be deconstructed linearly to produce the spectra corresponding to each method.

[0094] In some embodiments the multiplexing sequence contains elements that apply multiple methods simultaneously, where one method has ionization efficiency much greater than the other applied method or methods, such that the spectrum recorded during these elements can be treated as originating only from the ionization method with the high

ionization efficiency.

[0095] In some embodiments the multiplexing sequence contains elements that apply multiple methods simultaneously, the combination of which produces a spectrum having features not visible when any of the methods are applied individually. In such cases, the combination of methods can be treated as a unique method.

[0096] Preferably, the first ionization method is a hard ionization method and the second ionization method is a soft ionization method. At least the first ionization method is operated in a pulsed manner. The ionization efficiency of the hard ionization method is sufficiently large, such that fragment ions can be identified in the data from passes recording ions originating from the combination of these two methods.

[0097] Alternatively, the method exclusively includes two or more hard ionization methods or two or more soft ionization methods, respectively. Due to the differences between different hard ionization methods or between different soft ionization methods, multiplexing and obtaining additional information is possible even in that case.

[0098] In a preferred embodiment, the first ionization method is electron impact ionization (also called electron ionization, EI). This method produces a wide range of molecular fragments and therefore allows for obtaining comprehensive structural information. It is well suited for gases and volatile organic molecules.

[0099] In another preferred embodiment the first ionization method is field ionization (FI, also called field desorption). This method is advantageous in that it may be switched on and off with a very short delay, thus allowing for high pulsing frequencies.

[0100] Alternatively or additionally, other suitable hard ionization methods are employed.

[0101] A preferred soft (i. e. second) ionization method is single photon ionization (SPI), such as atmospheric pressure photo ionization. Choosing a suitable wavelength, optimum cross-section for given species of particles may be achieved.

[0102] Alternatively, the second ionization method is Penning ionization, which involves reactions between a gas-phase excited state particle and the target molecule having an ionization potential that is lower than the internal energy of the excited state particle.

[0103] In another alternative, the second ionization method is chemical ionization (CI). This involves the collision of the analyte with ions of a reagent gas such as methane. CI is particularly suited for the ionization of particles that are usually analyzed by the succession of gas chromatography and time-of-flight mass spectrometry.

[0104] In principle, the disclosed method may be used with any type of mass spectrometer.

[0105] In some embodiments, the mass analyzer is a filtering mass spectrometer, which allows the user to monitor select collections of m/Q values. The collection of m/Q values is uniquely defined for each sequence element type. A pass includes measurements at all m/Q values in the defined collection. In some such embodiments, all element types monitor the same collection of m/Q values. In other such embodiments, the monitored collection of m/Q values varies between element types.

[0106] In some embodiments, the mass analyzer is a dispersive mass spectrometer and passes correspond to the measurement of all ions within a user-defined m/Q range. In a preferred of these embodiments, the mass analyzer is a time-of-flight mass spectrometer (TOFMS), and the monitored m/Q range can be varied by varying the extraction frequency, TOFMS voltages, and/or the data acquisition timing parameters between element types.

[0107] Preferably, an acquisition of data from the mass analyzer is synchronized with the operation of the ionization methods such that an origin of ions in a data set from the different ionization methods is always known. This allows for true multiplexing of the measurements obtained from ions originating from the different ionization methods.

[0108] The quasi-simultaneous, multiplexed analysis depends on an ability to rapidly modulate at least one of the applied ionization methods between active and inactive states in a controlled manner and to synchronize this modulation with a data-storage routine that averages data from a single sample analysis in multiple discrete memory segments, each of which is associated with a unique ionization mechanism or combination of ionization mechanisms.

[0109] The disclosed method enables quasi-simultaneous analysis of ions generated by multiple pulsed methods or by one or more continuous methods and one or more pulsed or modulated methods.

[0110] Multiplexing enables alternation schemes that include continuous ionization methods which may be difficult to modulate in a controlled manner, as is necessary for sequential alternation schemes.

[0111] The first ionization method and the second ionization method may operate in the same ionization volume. This allows for a compact and cost-effective construction of the ion source. Furthermore, the ions generated by the different ionization methods may be transferred to the mass analyzer by the same ion optics. A potentially continuous ionization method may be used in a pulsed manner by modulating the application of the method to the sample molecules.

[0112] In other embodiments, the sample flow may be split so that ions are generated in different ionization volumes and transported into the mass spectrometer on different trajectories.

[0113] In this case, a potentially continuous ionization method may be used in a pulsed manner by modulating the transport of sample into the ionization volume, modulating the application of the method to the sample molecules, or by modulating the transport of generated ions from the ionization volume into the mass spectrometer.

[0114] In a preferred embodiment of the invention employing different ionization volumes,

a) a first pressure in a first of the ionization volumes is higher than a second pressure in a second of the ionization volumes,

b) a soft ionization method is used in the first ionization volume,

c) a hard ionization method is used in the second ionization volume, whereas the hard ionization method is operated in a pulsed manner,

d) ions generated in the first ionization volume are accelerated and transmitted to the second ionization volume in such a way that they traverse the second ionization volume and arrive at the mass analyzer essentially unaffected by the second ionization method.

[0115] The ions generated in the first ionization volume are "shot through" the second ionization volume. The dwell time of the softly ionized particles in the second volume as well as their cross section and the intensity of the hard ionization are chosen such that a majority (such as 99% or more) of the ions generated in the first ionization volume pass the second volume unaffected. Between the first ionization volume and the second ionization volume which is arranged in between the first ionization volume and the mass analyzer, a pressure interface known as such is arranged. In order to achieve the desired pressures components known as such like a split-flow pump may be employed.

[0116] This particular variant of the inventive method may be advantageous even in cases where no multiplexing is desired, as it allows for very fast switching between different ionization methods. Therefore, features a) - d) as mentioned before may even be employed in the context of a method or apparatus for chemical analysis where a given sample is always ionized by only one ionization method, where it is desired however that switching to another method (for the analysis of the same or another sample) should be easy and quick.

[0117] Preferably, the method further comprises the step of storing data relating to unique ionization methods and/or unique combinations of ionization methods in multiple discrete memory segments, whereas storing is synchronized with the operation of the ionization methods.

[0118] Sorting data across user-managed memory enables alternation of ionization methods without interruption for save each time the applied ionization method or set of methods is changed, implying that ionization methods can be varied at rates greater than at which data are saved.

[0119] The disclosed multiplexing method can be used without such memory management. It may not be necessary, for instance, if desired rates of save are faster than the rate at sample chemistry is changing (hence quasi-simultaneous acquisition would still be achieved) or if the quasi-simultaneous acquisition was not a requirement.

[0120] In particular, the method further comprises the further step of averaging data for ions originating from multiple ionization methods in at least one of the memory segments prior to save to a mass storage (such as a disk, flash memory, tape etc.).

[0121] In the disclosed method, mass spectra are acquired at a rate faster than the rate at which unique mass spectra are saved to disk. This requires averaging in memory. For cases where the rate of alternation between ionization methods is faster than the rate at which unique mass spectra are saved to the mass storage, e. g. the computer hard disk, this temporary memory has multiple accessible segments.

[0122] Data from these segments can be saved by three mechanisms:

(1) Data from a given segment is written to a mass storage (saved) after the final write of mass spectral data to that segment, during which time the system goes idle.

(2) Write all segments to the mass storage at the completion of the final write of mass spectral data to the final segment, during which time the system goes idle.

(3) Write data to the mass storage from one or more segments in parallel to averaging of new data in a separate segment without breaks in acquisition.

[0123] In each case, averaging reduces the total mass storage space used. Mechanisms (1) and (2) reduce the total dead time associated with data transfer and write to mass storage events, and because data can be averaged in memory at a rate faster than at which data can be saved to the mass storage, both allows alternation at faster rates compared to methods which might save a unique file each time the active ionization method is changed. This is of particular advantage for pulsed ionization methods that operate at high repetition frequencies and for analysis of fast transient samples.

[0124] Mechanism (3) has no dead times, enabling continuous acquisition.

[0125] Averaging reduces memory usage at the level of the mass storage and reduces the required data rate of the

communication channel between the acquisition electronics and the mass storage.

[0126] In order to carry out these further steps, the data acquisition electronics preferably comprises a time-to-digital converter or an analog-to-digital converter and a main computing unit (such as a general purpose Personal Computer), whereas the user-manageable memory is comprised by the time-to-digital converter, the analog-to-digital converter and/or the main computing unit.

[0127] The user-manageable memory is dividable into segments for recording and possibly averaging ion data relating to unique ionization methods and/or unique combinations of ionization methods in multiple discrete memory segments.

[0128] In some embodiments, pass data are averaged in memory that is a component of the digitizer used for data acquisition. This digitizer may be an analog-to-digital converter (ADC) or a time-to-digital converter (TDC).

[0129] In one such embodiment, the digitizer has memory with a number of segments greater than or equal to the number of unique element types in the multiplexing sequence and pass data are averaged in a memory segment associated with the active element type. Data are transferred to PC memory, which is dimensioned in a manner that maintains knowledge of the correlation between data and the applied multiplexing sequence. Data may be transferred to the PC at the completion of the sample analysis and immediately prior to data save, or averaged data are transferred more frequently than data are saved, and additional averaging of data may take place in PC memory.

[0130] In another such embodiment the digitizer has only one segment. Data are accumulated in the digitizer memory segment for successive passes of identical element type. Accumulated data are transferred to the PC each time the active element type changes. In that case, the PC memory may have a number of segments greater than or equal to the number of element types in the multiplexing sequence. After transfer from the digitizer, data are accumulated in a PC memory segment associated with the active element type. Alternatively, data are saved to the hard disk immediately after data transfer.

[0131] In further embodiments, pass data are only averaged in memory that is a component of the PC.

[0132] In one such embodiment, the PC memory is divided into a number of segments equal to or greater than the number of element types in the multiplexing sequence. Data may be transferred from the digitizer to the PC after acquisition of each pass and pass waveforms are accumulated in the segments associated with the active element type. Alternatively, digitizer output values are transferred to the PC immediately after they are acquired and are added to the memory position associated with the recorded mass-to-charge ratio within the segment associated with the active element type.

[0133] In some embodiments, data from a specific memory segment are saved after the last pass to be summed in that segment has been recorded.

[0134] In other embodiments, data from all memory segments are saved after the last pass in the multiplexing sequence has been recorded.

[0135] In even further embodiments, data acquisition occurs simultaneous to the transfer and/or saving of previously recorded data.

[0136] Other advantageous embodiments and combinations of features come out from the detailed description below and the totality of the claims.

Brief description of the drawings

[0137] The drawings used to explain the embodiments show:

Fig. 1 a block diagram of an inventive apparatus;

Fig. 2A a block diagram of a first embodiment of an ion source for the inventive apparatus;

Fig. 2B a block diagram of a second embodiment of an ion source for the inventive apparatus;

Fig. 3 a schematic representation of a first embodiment of an inventive apparatus;

Fig. 4 a schematic representation of a second embodiment of an inventive apparatus;

Fig. 5 a schematic representation of a third embodiment of an inventive apparatus;

Fig. 6 a block diagram representing the structure of a segmented memory of an inventive apparatus;

Fig. 7 a schematic representation of a sample train of TOF extraction start pulses and the synchronization with ADC acquisition;

Fig. 8 a schematic representation of sequence elements and sequence segments of a possible multiplexing sequence;

Fig. 9 a schematic representation of sequence blocks of the multiplexing sequence;

Fig. 10 signals representative for the timing of a first multiplexed sequence;

Fig. 11 signals representative for the timing of a second multiplexed sequence; and

Fig. 12 signals representative for the timing of a third multiplexed sequence.

[0138] In the figures, the same components are given the same reference symbols.

Preferred embodiments

[0139] The Figure 1 shows a block diagram of an inventive apparatus. The apparatus 1 comprises an ion source 10 providing ions generated by two different ionization methods. For that purpose it comprises two ionizers, namely a soft ionizer 11 as well as a hard ionizer 12. The ions generated by the ion source 10 are transmitted into a time-of-flight mass spectrometer (TOFMS 20). The detector of TOFMS 20 is connected to an analog-to-digital converter (ADC 30) for acquisition of the signals generated by TOFMS 20. The ADC 30 comprises a user managed ADC memory 31 for temporarily storing data. It is connected to a control computer, namely a Personal Computer (PC 40). The control computer comprises memory 41 and provides the multiplexing logic 42 controlling the ionizers 11, 12 of the ion source 10 as well as the TOFMS 20 and the ADC 30. For that purpose the PC 40 runs software that controls (inter alia) the following steps:

- Generation of the multiplexing sequence;
- Generation of digital signals for triggering TOFMS extraction pulses;
- Controlling voltages that enable or disable the employed ionization methods, and changing the value of these voltages according to the active sequence element;
- Synchronizing TOFMS extractions and data acquisition with the ADC 30;
- Synchronizing TOFMS extractions with the application of the multiplexing sequence;
- Configuration of the ADC memory 31 prior to the start of the analysis;
- Storage of averaged data after transfer from the ADC 30.

[0140] In order to allow multiplexing, an acquisition of data from the mass analyzer is synchronized with the operation of the ionization methods such that an origin of ions in a data set from the different ionization methods is always known.

[0141] The Figures 2A, 2B show block diagrams of a first embodiment of an ion source for the inventive apparatus and of a second embodiment of an ion source for the inventive apparatus, respectively.

[0142] The first embodiment of an ion source 110 depicted in Figure 2A features a single ionization volume 111. In this volume, a hard ionization method such as electron-impact ionization (EI) as well as a soft ionization method such as single photon ionization (PI) may be applied to the particles of the flow coming from the sample 2, whereas both methods operate in the same volume, at the same pressure. The ions generated in the volume 111 are further transmitted to the mass spectrometer 120, whereas the same ion optics arranged between the ion source 110 and the mass spectrometer 120 is employed for ions originating from both ionization methods.

[0143] The second embodiment of an ion source 210 depicted in Figure 2B features two separate ionization volumes 211, 212. The flow from the sample 2 is split, such that a part of the sample 2 is transmitted to the first volume 211, whereas another part of the sample 2 is transmitted to the second volume 212. In the first volume 211 a hard ionization method such as electron-impact ionization (EI) is applied to the particles to be analyzed. In the second volume 212 a soft ionization method such as single photon ionization (PI) is applied to the particles to be analyzed.

[0144] The ions generated in both volumes 211, 212 are further transmitted to the mass spectrometer 220. For that purpose a first ion optics is coupled to the first ionization volume 211, and a second ion optics is coupled to the second ionization volume 212.

[0145] EI may be used in a continuous manner, such that it is active in all sequence element types. Or, EI is pulsed by leaving the electron-generating filament on and varying the acceleration energies of the electrons into the ionization volume. PI may be as well used in a pulsed or continuous manner.

[0146] In the embodiment according to Figure 2B with two separate ionization volumes 211, 212, a gate may be arranged in between at least one of the volumes 211, 212 and the mass analyzer 220, whereas the gate may be operated in a pulsed manner. This eliminates the need for operating ionization methods in a pulsed manner.

[0147] As an alternative to electron ionization other hard ionization methods such as field ionization may be employed.

[0148] As an alternative to single photon ionization other soft ionization methods such as Penning ionization may be employed.

[0149] The Figure 3 is a schematic representation of a first embodiment of an inventive apparatus. The apparatus 100 comprises an ion source 110 with an ionization volume 111 into which a sample flow 102 is directed. Adjacent to the ionization volume 111, a light source 113 for generating UV radiation and a related optics 114 for directing the radiation into the ionization volume 111 are arranged. Furthermore, adjacent to the ionization volume 111, an electron source 115 is arranged comprising a hot filament made of, e.g., tungsten. The generated electrons are accelerated into the ionization volume 111 by an electrostatic potential.

[0150] Within the ionization volume 111 particles of the sample flow 102 are ionized. The created ions are accelerated into a reflectron-type time-of-flight mass spectrometer TOFMS 120 using ion optics 150 surrounding an opening constituting the entrance of the mass spectrometer 120. In an extraction chamber 121 the ions are orthogonally extracted from the primary ion beam. Accelerated by grids 122 the ions traverse the TOFMS 120, passing a reflector 123, and finally hit a detector 124. The detector 124 is connected to analog-to-digital converter (ADC 30) for acquisition of the signals generated by TOFMS 120 and further to a control computer (PC 40), cf. Figure 1.

[0151] The desired pressure within the ionization volume 111 and the TOFMS 120 is adjusted using a 2-stage split flow turbo pump 160, which evacuates the ionization volume 111 to a first pressure p_I, and the analysis chamber of the TOFMS 120 to a second pressure p_T, whereas $p_T < p_I$.

[0152] The Figure 4 is a schematic representation of a second embodiment of an inventive apparatus. The apparatus 200 comprises an ion source 210 with a first ionization volume 211 into which a sample flow 202 is directed. Adjacent to the first ionization volume 211, a light source 213 for generating UV radiation and a related optics 214 for directing the radiation into the ionization volume 211 are arranged. Behind the first ionization volume 211 in the direction of the sample flow 202 a second ionization volume 212 is situated. Adjacent to the second ionization volume, diametrically opposite two electron sources 215, 216 are arranged comprising hot filaments made of, e.g., tungsten. The generated electrons are accelerated into the ionization volume 212 by electrostatic potentials.

[0153] During times when the light source 213 is turned on, in the first ionization volume 211 particles of the sample flow 202 are ionized. The created ions are accelerated and pass through the second ionization volume 212 into a reflectron-type time-of-flight mass spectrometer TOFMS 220 using ion optics 250 surrounding an opening constituting the entrance of the mass spectrometer 220. In an extraction chamber 221 the ions are orthogonally extracted from the primary ion beam. Accelerated by grids 222 the ions traverse the TOFMS 220, passing a reflector 223, and finally hit a detector 224. The detector 224 is connected to analog-to-digital converter (ADC 30) for acquisition of the signals generated by TOFMS 220 and further to a control computer (PC 40), cf. Figure 1.

[0154] Both ionization volumes 211, 212 are arranged in a common chamber, at equal pressure. The desired pressure within the ionization volumes 211, 212 and the TOFMS 220 is adjusted using a 2-stage split flow turbo pump 260, which evacuates the ionization volumes 211, 212 to a first pressure p_I, and the analysis chamber of the TOFMS 220 to a second pressure p_T, whereas $p_T < p_I$.

[0155] The Figure 5 is a schematic representation of a third embodiment of an inventive apparatus. The apparatus 300 comprises an ion source 310 with a first ionization volume 311 into which a sample flow 302 is directed. Adjacent to the first ionization volume 311, a light source 313 for generating UV radiation and a related optics 314 for directing the radiation into the ionization volume 311 are arranged. Behind the first ionization volume 311 in the direction of the sample flow 302 a second ionization volume 312 is situated. The two ionization volumes 311, 312 are arranged in separate chambers connected by a pressure interface 361. Adjacent to the second ionization volume, diametrically opposite two electron sources 315, 316 are arranged comprising hot filaments made of, e.g., tungsten. The generated electrons are accelerated into the ionization volume 312 by electrostatic potentials.

[0156] During times when the light source 313 is turned on, in the first ionization volume 311 particles of the sample flow 302 are ionized. The created ions are accelerated and pass through the second ionization volume 312 into a reflectron-type time-of-flight mass spectrometer TOFMS 320 using ion optics 350 surrounding an opening constituting the entrance of the mass spectrometer 320. In an extraction chamber 321 the ions are orthogonally extracted from the primary ion beam. Accelerated by grids 322 the ions traverse the TOFMS 320, passing a reflector 323, and finally hit a detector 324. The detector 324 is connected to analog-to-digital converter (ADC 30) for acquisition of the signals generated by TOFMS 320 and further to a control computer (PC 40), cf. Figure 1.

[0157] Both ionization volumes 311, 312 being arranged in different chambers, they may be held at different pressures.

The desired pressure within the ionization volumes 311, 312 and the TOFMS 320 is adjusted by differential pumping, using a 3-stage split flow turbo pump 360, which evacuates the first ionization volume 311 to a first pressure p_{I1}, the second ionization volume 312 to a second pressure P_{I2} and the analysis chamber of the TOFMS 320 to a third pressure p_T, whereas $p_T < p_{I2} < p_{I1}$.

[0158] The Figure 6 shows a block diagram representing the structure of a segmented memory of an inventive apparatus. The memory 31 is provided within the ADC 30. It is user managed and configured to store a plurality of segments 32.1, 32.2, 32.3...32.n. The segments have a dimension that is appropriate to store data generated within the ADC 30, namely in the form of peak lists, peak pictures, or peak waveforms. Different element types (see below) are assigned to different segments 32.1...32.n. In the shown example, the first three segments 32.1, 32.2, 32.3 store data relating to different element types, denoted by different hatchings. The last segment 32.n stores data that relates to the same element type as the data stored in the first segment 32.1.

[0159] Depending on implementation, data for passes of like element type can be accumulated in a single segment or in multiple different segments.

[0160] As an example, suppose an ion source enables two ionization methods, A and B. Method A is continuous and method B can be modulated between active and inactive states.

- In one implementation of the disclosed multiplexing method, the multiplexing sequence has two element types that record data for the same m/Q values but have different ionization method combinations: [A] and [A + B].
    - o The multiplexing sequence has a length equal to the total number of passes to be acquired pseudo-simultaneously, and contains at least one element of type [A + B]
    - o Method A is constantly active.
    - o Method B is in an inactive state during passes corresponding to elements of type [A] and active during passes of type [A + B]
    - o The acquisition of passes is synchronized with the multiplexing sequence, such that the modulation of method B between active and inactive states occurs at the start of passes.
    - o The accumulation memory is divided into two segments of equal dimension (because the two sequence element types monitor the same m/Q values).
    - o The data from passes associated with the sequence elements using only ionization method A are recorded into one of the segments; waveforms including ions generated during the simultaneous application of methods A and B are accumulated in the second segment.

[0161] For any multiplexing scheme, the nature of the accumulated waveforms representing combinations of ionization methods will depend on the combination of methods and the sample.

- In the most straightforward case, the accumulated spectrum in any segment will be the sum of the mass spectra of the sample when ionized by each of the active ionization methods.
    - o For instance, in the previous example, the spectrum associated with methods [A + B] would be the sum of the spectrum associated with method [A] and the spectrum associated with method [B].
- In other cases, ion generation may be dominated by one of the active methods, and the spectrum will have features strongly resembling of the spectrum generated by that ionization method.
    - o For instance, if method [B] is dominant, the accumulated spectrum the accumulated spectrum [A + B] will strongly resemble the spectrum that would be acquired if data were collected with only method B active.
- In other cases, the ionization mechanisms may interact, producing a mass spectrum with features that are not present in any of the spectra generated by the individual methods.

[0162] Depending on the nature of the resultant data, different analysis methods can be applied to memory segments generated by the multiplexing of methods. For instance, it may be possible to deconstruct spectra generated by multiple methods into the spectra associated with individual methods. Or, it may be possible to treat combinations of ionization

methods as unique methods.

[0163] Importantly, the accumulated data in any segment will always be a mass spectrum of the sample. Multiplexing of ionization methods does not create spectral artifacts nor does interpretation of the accumulated data by standard mass spectral methods depend on any mathematical deconvolution of the accumulated waveforms.

[0164] The Figure 7 is a schematic representation of a sample train of TOF extraction start pulses and the synchronization with ADC acquisition.

[0165] The ADC 30 is able to sample the TOF detector output at an adjustable frequency, F, which is typically greater than or equal to 1 GHz. In a preferred mode of operation, Fis constant for all sequence element types. The ADC begins sampling the TOF detector output for each pass, beginning a user-defined delay 71 (ADC data delay) after each extraction start pulse 72. This timing is outlined in Figure 7. In the preferred embodiment, the data delay is constant for all sequence element types.

[0166] In the preferred embodiment, the user defines how many data samples, *s*, the ADC should record following each TOF extraction (block 73). In the preferred embodiment, *s* is constant for all sequence element types.

[0167] As a consequence of constant F, data delay, and s, in the preferred embodiment, the selected range of m/Q values is constant for all sequence element types applied in a given sequence.

[0168] The TOFMS extraction frequency, which defines the TOF extraction period 74, is user adjustable and is constant for all element types within the applied sequence. This value is typically between 10 kHz and 100 kHz. The ADC acqusition time 75 is the interval starting after the ADC data delay 71 up to the next TOF extraction start pulse 72. In the preferred embodiment, data are stored and saved as peak waveforms having length s.

[0169] The Figure 8 is a schematic representation of sequence elements and sequence segments of a possible multiplexing sequence.

[0170] A sequence segment 82 comprises a certain number of passes 81, whereas each pass 81 relates to a single mass spectrum. Acquisition of a pass involves generation of ions, dispersion of the generated ions according to their mass-to-charge ratios, and recording of the MS data into memory. As mentioned before, data from a pass may be stored as either a peak waveform, peak picture, or peak list.

[0171] For a filtering mass spectrometer (FMS), a pass includes one measurement at each preselected mass-to-charge ratio. For example, a pass using a quadrupole mass spectrometer might record ions of a single mass-to-charge (single ion monitoring), a list of selection mass-to-charge ratios, or at all mass-to-charge ratios in a broad range.

[0172] For a dispersive mass spectrometer (DMS) a pass includes one simultaneous measurement of the entire range of mass-to-charge ratios, as preselected by the mass spectrometer user. For example, if a TOFMS is used a pass corresponds to one TOFMS extraction, with mass-to-charge range determined by the extraction frequency, TOFMS geometry and voltages, and acquisition electronic configuration.

[0173] Averaging of passes increases the efficiency of the analyzer by reducing dead times associated with saving and reduces the total quantity of data saved to hard disk (bytes).

[0174] The passes 81 constituting a sequence segment 82 relate to the same ionization method or to the same combination of ionization methods, respectively. A plurality of sequence segments 82 follow one another, all of them constituting a sequence block 83. A sequence block 83 may comprise a plurality of sequence segments 82 relating to the same type of ionization. In the shown example, the first three sequence segments 82 relate to three different types of ionization whereas the last sequence segment 82 relates again to the same type of ionization as the first sequence segment 82.

[0175] All segments within a sequence are of the same length, n elements. (Note that n may equal 1). The multiplexing sequence follows a cyclical sequence of segments. It is the pattern of segments that is repeated that is called the sequence block 83.

[0176] Usually, it is advantageous to divide the ADC memory (as shown in Figure 6) into a number of memory segments equal to the number of sequence segments.

[0177] The Figure 9 is a schematic representation of sequence blocks of the multiplexing sequence. A succession of sequence blocks 83.1, 83.2, ..., 83.m constitute the multiplexing sequence 84. The multiplexing sequence is a succession of elements. We refer to a unique combination of (i) active ionization method(s) and (ii) monitored mass-to-charge ratios as an element type. Elements within the sequence can have the same type. The abundances of element types within the sequence do not need to be equal. In the disclosed method, application of the multiplexing sequence is synchronized with passes, such that transitions between elements occurs between passes. The multiplexing sequence is non-random, such that the sequence element type that is active during any pass is always known.

[0178] In the disclosed method, successive passes are acquired for a single sample while multiplexing the applied ionization methods. During any pass, one or more ionization methods are active. A disadvantage of alternating multiple ionization methods is the reduced duty cycle of each ionization method (i.e., fraction of sampling time when the method is active) relative to single-method operation. The disclosed multiplexing scheme can increase the duty cycle of each ionization method, relative to sequential alternation schemes. Furthermore, depending on the ionization methods used it may be possible to increase the intensity in order to uphold the total power. For example, when using photon ionization

or field ionization an increase of the intensity may compensate the reduction of the duty cycle to a large extent.

[0179] Whereas it is well known from other fields of chemical analysis that implementation of such multiplexing decreases detection limits, here, by simultaneously acquiring complimentary data, it also leads to more comprehensive analysis.

[0180] The Figure 10 depicts signals representative for the timing of a first multiplexed sequence. For illustration purposes it shows a sequence block 183 comprising three segments 182.1, 182.2, 182.3. Each of the segments is constituted by two passes 181.1, 181.2, 181.3, respectively. Each pass is initiated by a TOF extraction start pulse 172 as described above, in connection with Figure 7. Therefore, TOFMS extractions are synchronized with the multiplexing sequence, such that transitions between sequence element types occur between TOF extractions.

[0181] A signal 191 controls the operation of the electron ionization (EI). If the signal 191 is in the ON state electron ionization takes place, if it is in the OFF state electron ionization is switched off. During the passes 181.1 of the first segment 182.1 as well as during the passes 181.3 of the third segment 182.3 the signal 191 is in the ON state, i. e. the analyte is ionized using electron impact ionization during these passes.

[0182] A further signal 192 controls the operation of the single photon ionization (PI). If the signal 192 is in the ON state single photon ionization takes place, if it is in the OFF state single photon ionization is switched off. During the passes 181.2 of the second segment 182.2 as well as during the passes 181.3 of the third segment 182.3 the signal 192 is in the ON state, i. e. the analyte is ionized using single photon ionization during these passes.

[0183] Correspondingly, the sequence block 183 is constituted by three segments 182.1...182.3 that have different types: EI only (182.1), PI only (182.2) and EI/PI combined (182.3). TOFMS extraction frequency, ADC sampling rate, ADC data delay, and the number of samples recorded by the ADC are constant for the three element types. As an example, the three types may be characterized as follows:

Parameter		Type 1 (182.1)	Type 2 (182.2)	Type 3 (182.3)
TOF	Extraction	50 kHz	50 kHz	50 kHz
Ionization	EI	Active	Inactive	Active
	PI	Inactive	Active	Active
ADC	Sampling	1 GHz	1 GHz	1 GHz
	Data Delay	1 μs	1 μs	1 μs
	Samples	12,000	12,000	12,000

[0184] Data relating to the first sequence segment 182.1 are written to a first ADC memory segment 32.1, data relating to the second sequence segment 182.2 are written to a second ADC memory segment 32.2, and data relating to the third sequence segment 182.3 are written to a third ADC memory segment 32.3 (cf. Fig. 6).

[0185] The Fig. 11 depicts signals representative for the timing of a second multiplexed sequence. For illustration purposes it shows a sequence block 283 comprising six segments 282.1...282.6. Each of the segments is constituted by a single pass 281.1...281.6, respectively. Each pass is initiated by a TOF extraction start pulse 272 as described above, in connection with Figure 7. Therefore, TOFMS extractions are synchronized with the multiplexing sequence, such that transitions between sequence element types occur between TOF extractions.

[0186] A signal 291 controls the operation of the electron ionization (EI). If the signal 291 is in the ON state electron ionization takes place, if it is in the OFF state electron ionization is switched off. During the pass 281.1 of the first segment 282.1 as well as during the pass 281.6 of the sixth segment 282.6 the signal 291 is in the ON state, i. e. the analyte is ionized using electron impact ionization during these passes.

[0187] A further signal 292 controls the operation of the single photon ionization (PI). If the signal 292 is in the ON state single photon ionization takes place, if it is in the OFF state single photon ionization is switched off. During the passes 281.2...281.6 of the second to sixth segments 282.2...282.6 the signal 292 is in the ON state, i. e. the analyte is ionized using single photon ionization during these passes.

[0188] Correspondingly, the sequence block 283 is constituted by six segments 282.1...282.6 of three different types: 1 segment EI only (282.1), four segments PI only (282.2...282.5) and one segment EI/PI combined (282.6). TOFMS extraction frequency, ADC sampling rate, ADC data delay, and the number of samples recorded by the ADC are constant for the three element types. The data of the six sequence segments 282.1...282.6 are written to six different ADC memory segments 32.1...32.6.

[0189] The Figure 12 depicts signals representative for the timing of a third multiplexed sequence. For illustration purposes it shows a sequence block 383 comprising three segments 382.1, 382.2, 382.3. Each of the segments is constituted by two passes 381.1, 381.2, 381.3, respectively. Each pass is initiated by a TOF extraction start pulse 372

as described above, in connection with Figure 7. Therefore, TOFMS extractions are synchronized with the multiplexing sequence, such that transitions between sequence element types occur between TOF extractions.

[0190] A signal 391 controls the operation of the electron ionization (EI). If the signal 391 is in the ON state electron ionization takes place, if it is in the OFF state electron ionization is switched off. During the passes 381.1, 381.2 of the first and second segments 382.1, 382.2 the signal 391 is in the ON state, i. e. the analyte is ionized using electron impact ionization during these passes. The single photon ionization (PI) is continuous, i. e. during all segments 382.1...382.3 the analyte is ionized using single photon ionization.

[0191] Correspondingly, the sequence block 383 is constituted by six segments 382.1...382.6 of two different types: two segments EI/PI (382.1...382.2) and one segment PI only (382.3). TOFMS extraction frequency, ADC sampling rate, ADC data delay, and the number of samples recorded by the ADC are constant for the three element types. The data of the three sequence segments 382.1...382.3 are written to three different ADC memory segments 32.1, 32.2, 32.3.

[0192] In the following, data processing of an embodiment of the invention is described. Data are written to the memory segments in a sequential manner. Data from passes within the same sequence segment are averaged in the same memory segment.

[0193] In the following, the process of writing sequential passes to the same memory segment is called "co-adding". During each block, n sequential passes are co-added in each memory segment. For instance, data from passes in Block 1 /Segment 1 are averaged in memory segment 1. Then data from Block 1 /Segment 2 are averaged in Segment 2. And so on. At the completion of Block 1, averaging returns to Memory segment 1. Data from passes in Block 2/Segment 1 are averaged in memory segment 1, with the data from Block 1. And so on. This process of writing sequential blocks to the same segments is called round robin averaging. For any multiplexing sequence, m blocks are round robin averaged.

[0194] The relative duty cycle of each element type is determined by the relative number of segments of that type in the block. For instance, Figure 10 shows a sequence that is equal parts Element Types 1, 2, and 3. Figure 11 shows a sequence that is 75% Element Type 2.

[0195] The invention is not limited to the embodiments described above. In particular, the employed ionization methods, the type of mass detector and the parameters of the multiplexing sequence may be widely varied. The data processing may be effected in a different way as well. Depending on the data rate delivered by the detector as well as on connection throughput and memory availability, on-line averaging and/or discrete memory segments may not be required.

Claims

1. A method for chemical analysis, comprising the steps of

a) ionizing a first group of particles of a sample of interest using a first ionization method for generating a first group of ions;
b) ionizing a second group of particles of the sample of interest using a second ionization method which is different from the first ionization method for generating a second group of ions;
c) analyzing the first group of ions and the second group of ions in a mass analyzer;
whereas
d) ions of the first group and ions of the second group are detected using a same detector of the mass analyzer;
e) at least one of the ionization methods is operated in a pulsed manner and/or the ionized particles of at least one of the groups is transmitted to the mass analyzer in a pulsed manner;
f) at least in a time interval the first ionization method and the second ionization method are operated simultaneously and ions of the first group and ions of the second group are both transmitted to the mass analyzer.

2. The method as recited in claim 1, whereas the first ionization method is a hard ionization method, whereas the second ionization method is a soft ionization method and whereas the first ionization method is operated in a pulsed manner.

3. The method as recited in claim 2, whereas the first ionization method is electron-impact ionization.

4. The method as recited in claim 2, whereas the first ionization method is field ionization.

5. The method as recited in claim 3 or 4, whereas the second ionization method is single photon ionization.

6. The method as recited in claim 3 or 4, whereas the second ionization method is Penning ionization.

7. The method as recited in claim 3 or 4, whereas the second ionization method is chemical ionization.

8. The method as recited in one of claims 1 to 7, whereas the mass analyzer is a time-of-flight mass spectrometer.

9. The method as recited in one of claims 1 to 8, whereas an acquisition of data from the mass analyzer is synchronized with the operation of the ionization methods such that an origin of ions in a data set from the different ionization methods is always known.

10. The method as recited in one of claims 1 to 9, whereas the first ionization method and the second ionization method operate in a same ionization volume.

11. The method as recited in one of claims 1 to 10, whereas the first ionization method and the second ionization method operate in different ionization volumes.

12. The method as recited in claim 11, whereas

a) a first pressure in a first of the ionization volumes is higher than a second pressure in a second of the ionization volumes,
b) a soft ionization method is used in the first ionization volume,
c) a hard ionization method is used in the second ionization volume, whereas the hard ionization method is operated in a pulsed manner,
d) ions generated in the first ionization volume are accelerated and transmitted to the second ionization volume in such a way that they traverse the second ionization volume and arrive at the mass analyzer essentially unaffected by the second ionization method.

13. The method as recited in one of claims 1 to 12, further comprising the step of storing data relating to unique ionization methods and/or unique combinations of ionization methods in multiple discrete memory segments, whereas storing is synchronized with the operation of the ionization methods.

14. The method as recited in claim 13, comprising the further step of averaging data for ions originating from multiple ionization methods in at least one of the memory segments prior to save to a mass storage.

15. An apparatus for chemical analysis, in particular for carrying out the method as recited in one of claims 1 to 14, comprising

a) at least one ionization source being capable of ionizing a first group of particles using a first ionization method for generating a first group of ions and of ionizing a second group of particles using a second ionization method which is different from the first ionization method for generating a second group of ions;
b) a mass analyzer;
c) a modulator for modulating at least one of the ionization methods and/or a transmission of the ionized particles of at least one of the groups to the mass analyzer between active and inactive states;
whereas
d) the mass analyzer is coupled to the at least one ionization source such that ions of the first group and ions of the second group may be simultaneously analyzed by the mass analyzer, whereas ions of the first group and ions of the second group are detected using a same detector of the mass analyzer;
e) the modulator is capable of modulating the at least one of the ionization methods in a manner synchronized with the acquisition of successive mass spectra;
f) at least in a time interval the at least one ionization source is operable to carry out the first ionization method and the second ionization method simultaneously and to transmit ions of the first group and ions of the second group simultaneously to the mass analyzer.

16. The apparatus as recited in claim 15, whereas the mass analyzer is a time-of-flight mass spectrometer.

17. The apparatus as recited in claim 15 or 16, further comprising data acquisition electronics comprising a user-manageable memory that is dividable into segments for recording and averaging ion data relating to unique ionization methods and/or unique combinations of ionization methods in multiple discrete memory segments.

18. The apparatus as recited in claim 17, the data acquisition electronics comprising a time-to-digital converter or an analog-to-digital converter and a main computing unit, whereas the user-manageable memory is comprised by the time-to-digital converter, the analog-to-digital converter and/or the main computing unit.

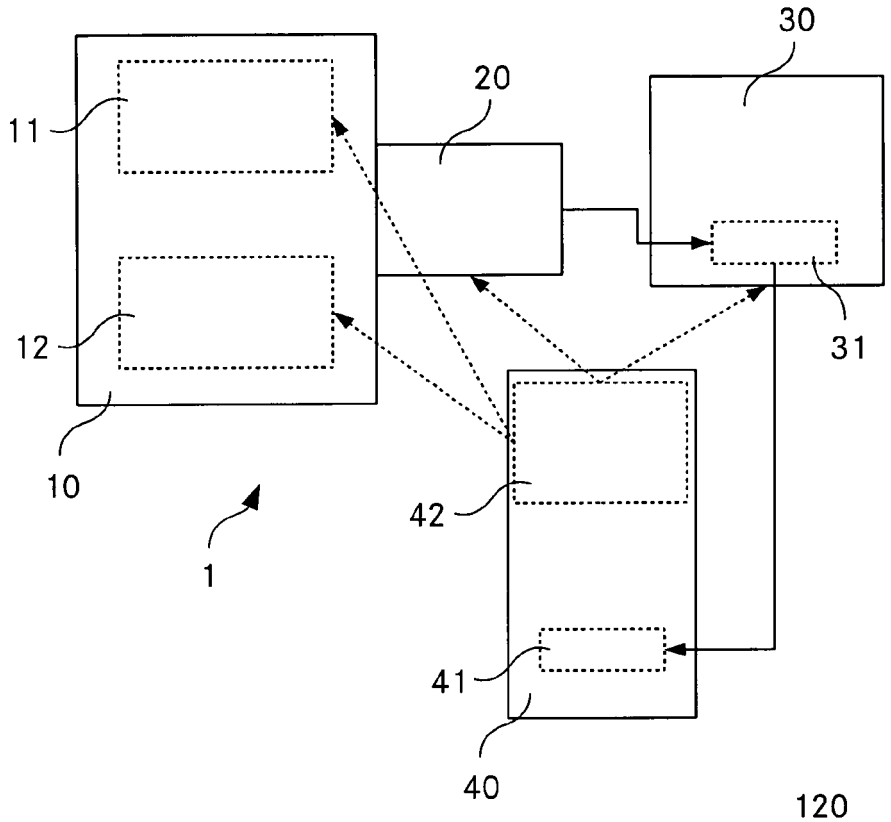

Fig. 1

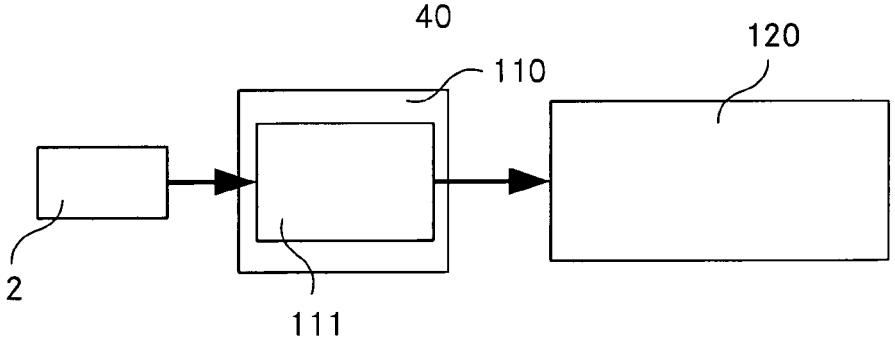

Fig. 2A

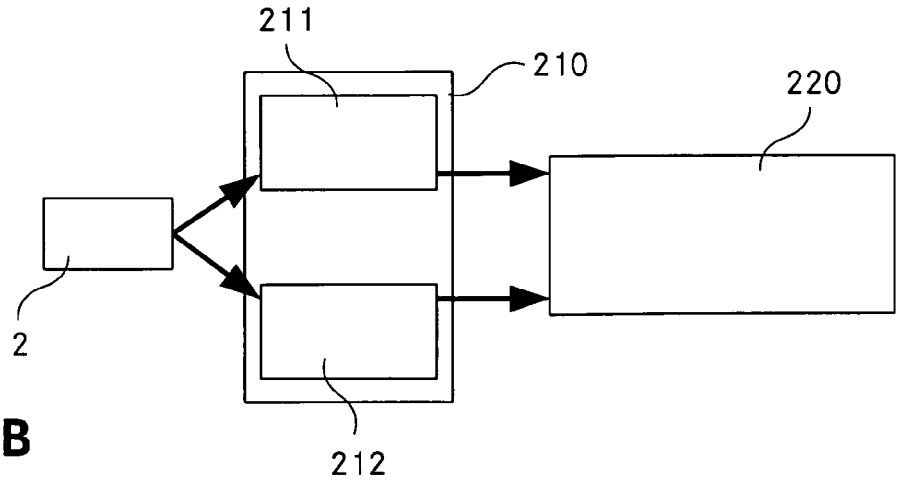

Fig. 2B

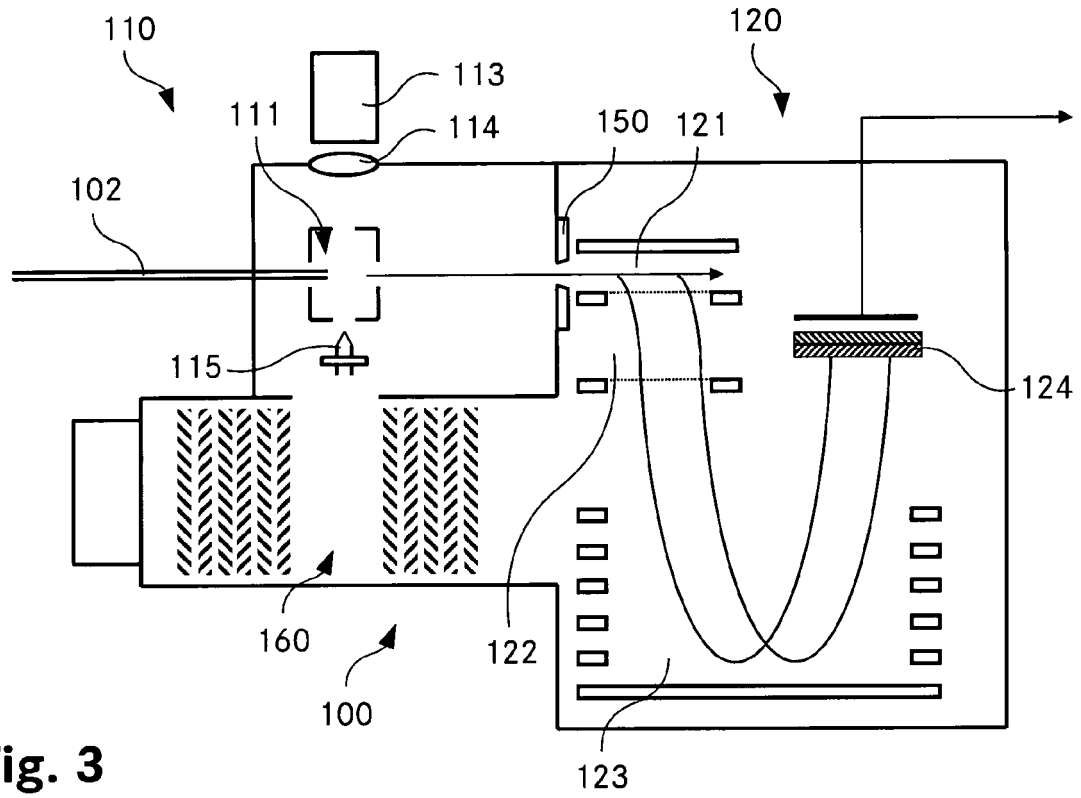
110
120
113
111
114
150
121
102
115
124
160
122
100
123

Fig. 3

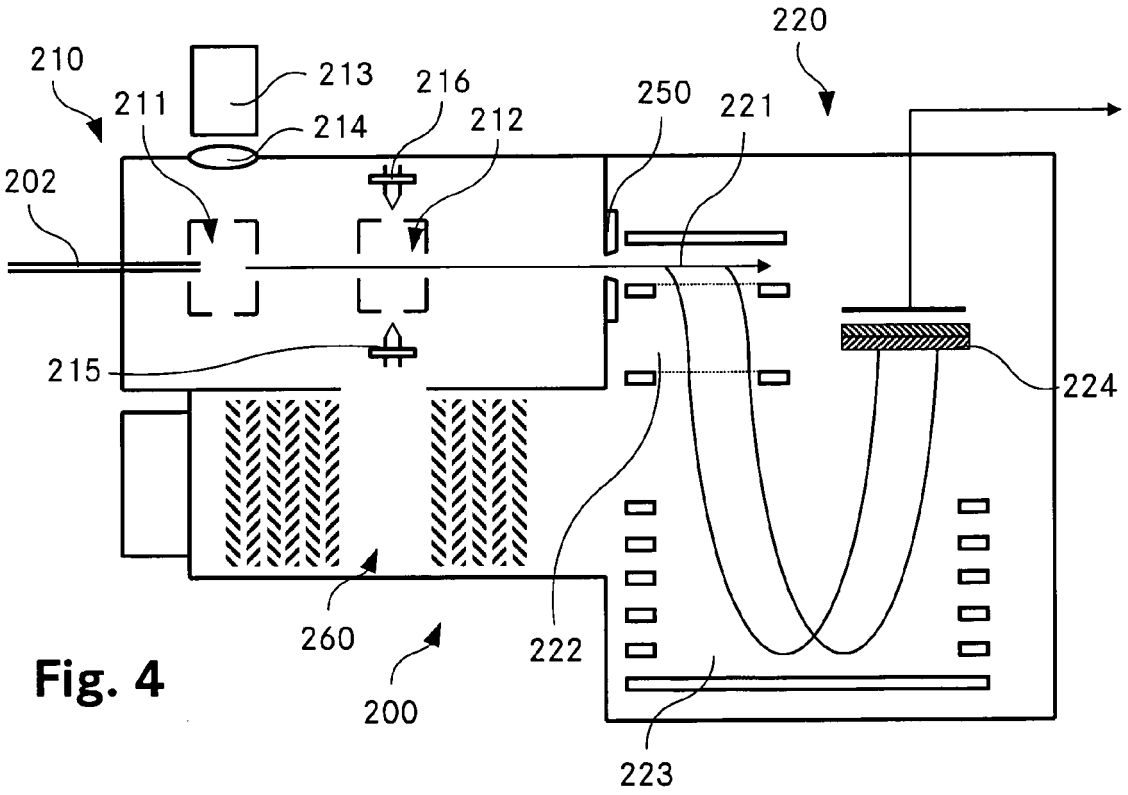
220
210
213
216
211
214
212
250
221
202
215
224
260
222
200
223

Fig. 4

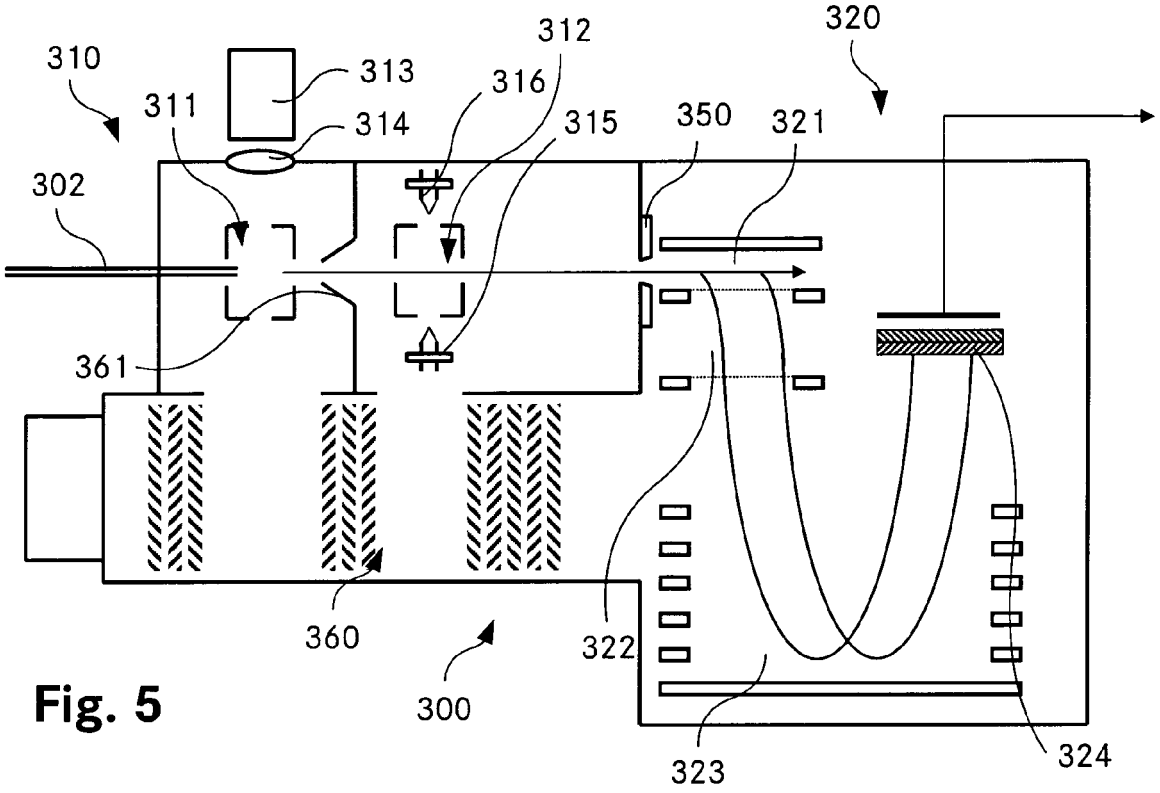
310
311
313
314
312
316
315
350
320
321
302
361
360
322
300
323
324

Fig. 5

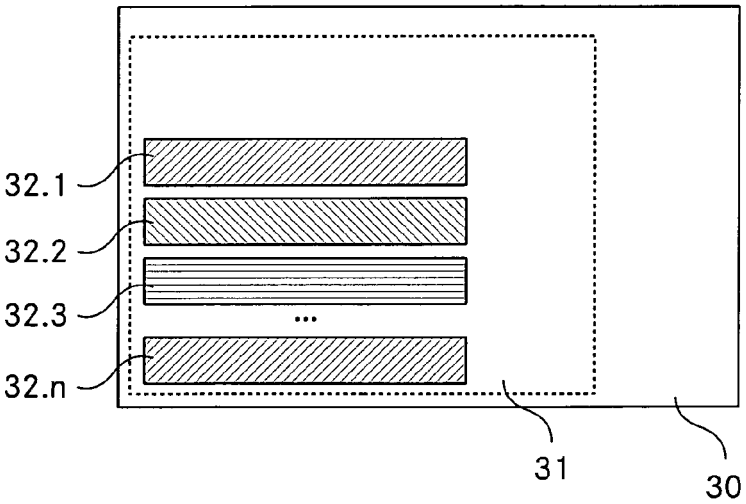
32.1
32.2
32.3
...
32.n
31
30

Fig. 6

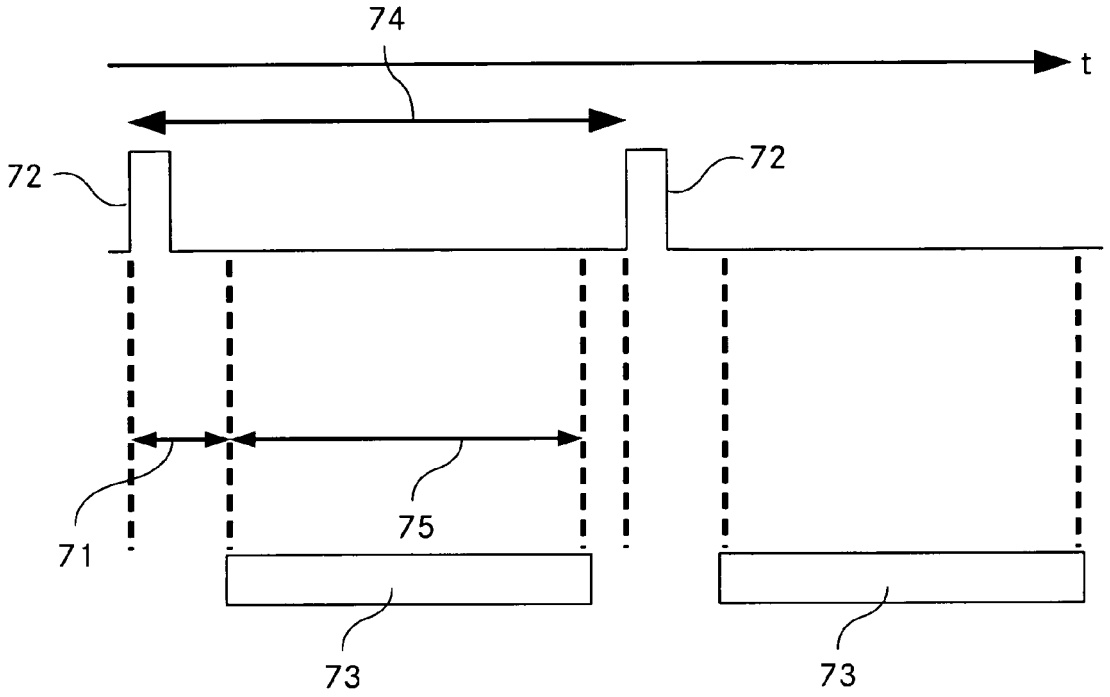

Fig. 7

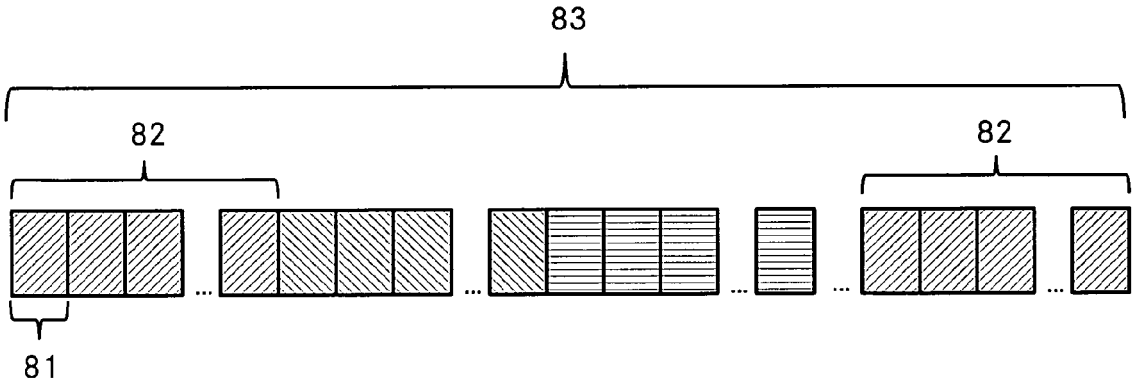

Fig. 8

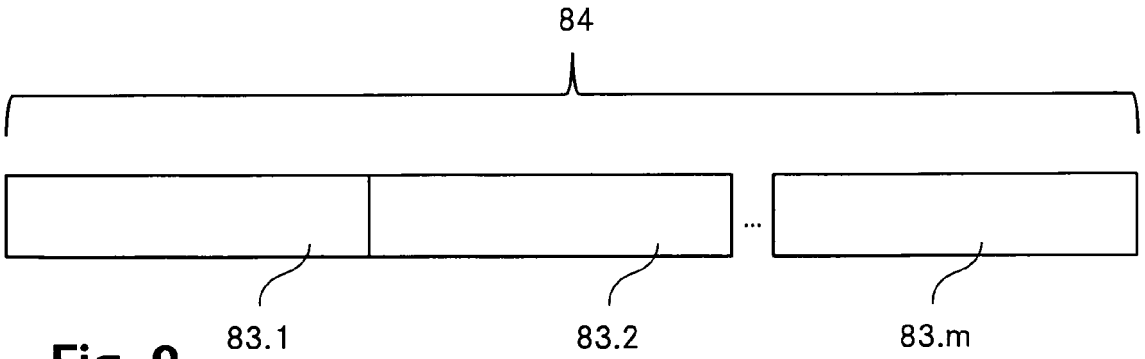

Fig. 9

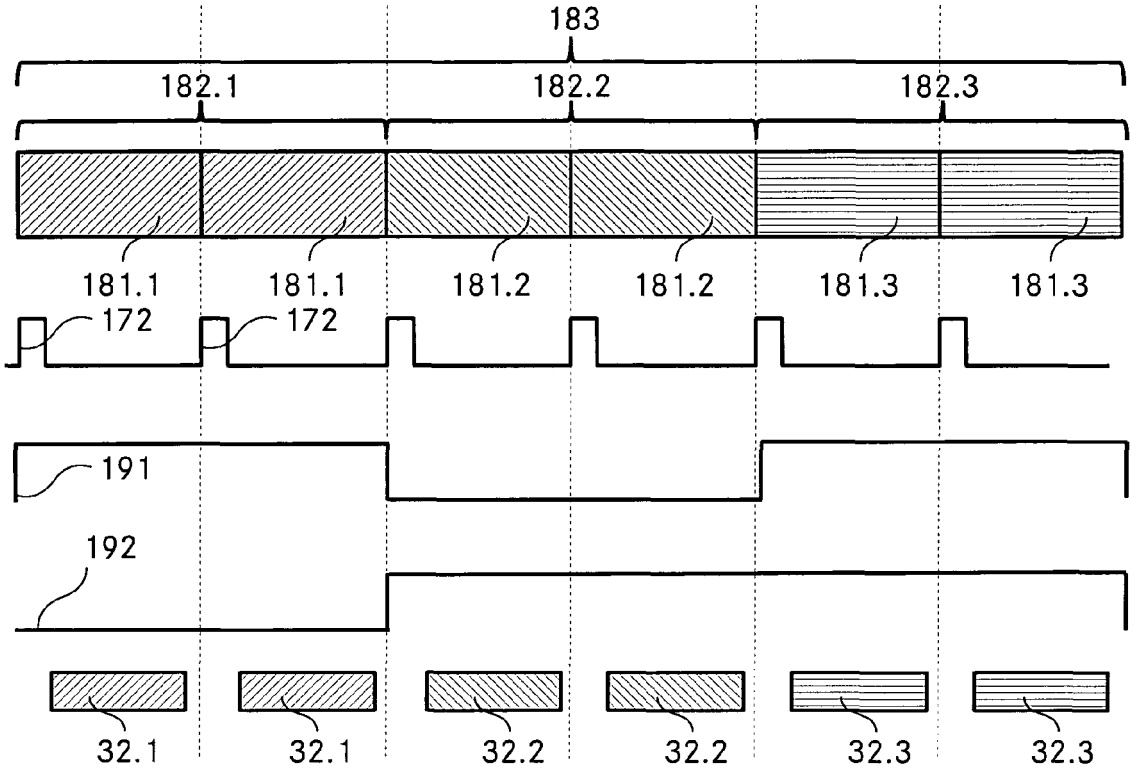
183
182.1
182.2
182.3
181.1
181.1
181.2
181.2
181.3
181.3
172
172
191
192
32.1
32.1
32.2
32.2
32.3
32.3

Fig. 10

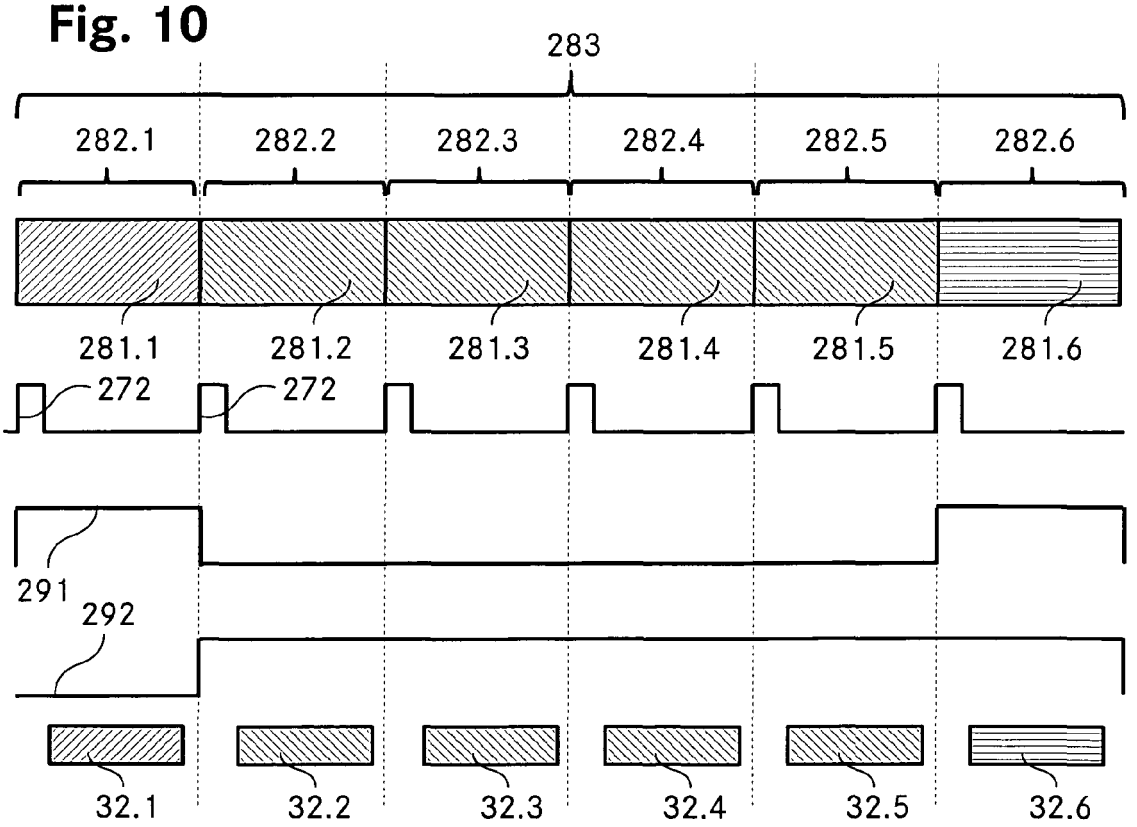
283
282.1
282.2
282.3
282.4
282.5
282.6
281.1
281.2
281.3
281.4
281.5
281.6
272
272
291
292
32.1
32.2
32.3
32.4
32.5
32.6

Fig. 11

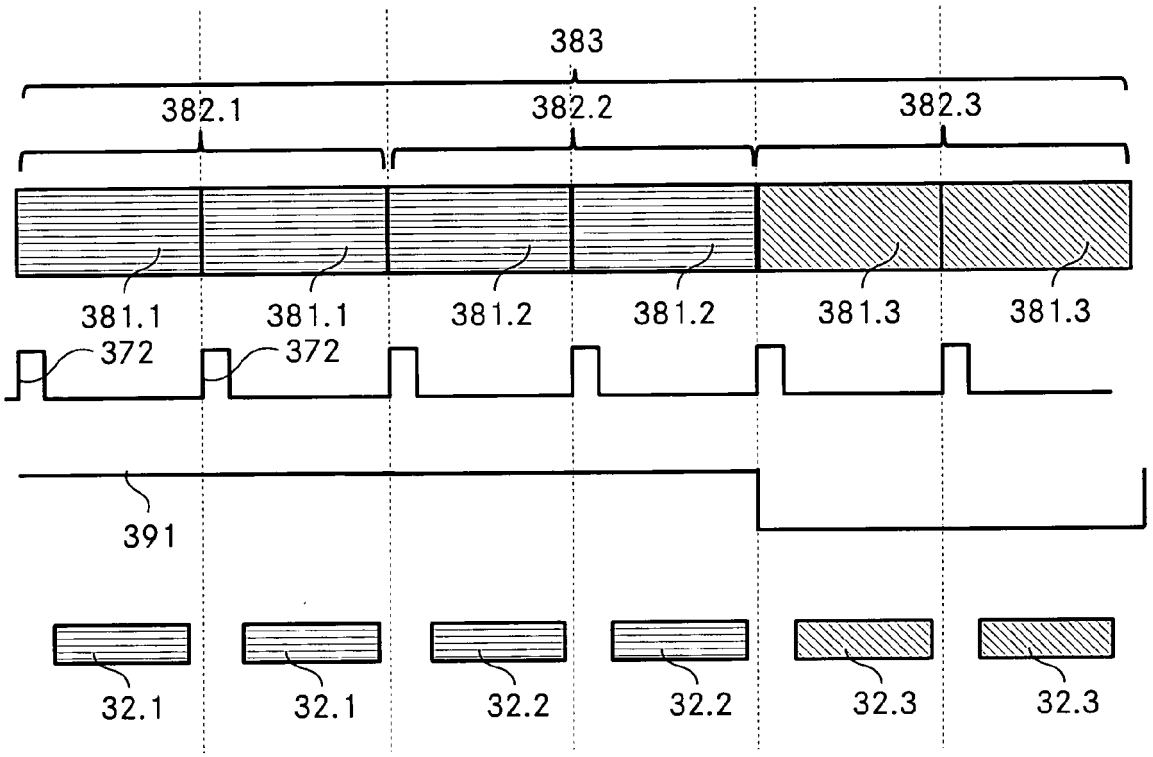
383
382.1
382.2
382.3
381.1
381.1
381.2
381.2
381.3
381.3
372
372
391
32.1
32.1
32.2
32.2
32.3
32.3

Fig. 12

Europäisches Patentamt
European Patent Office
Office européen des brevets

EUROPEAN SEARCH REPORT

Application Number
EP 10 40 5080

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	WO 2008/037073 A1 (MDS ANALYTICAL TECH BU MDS INC [CA]; APPLERA CORP [US]; SCHNEIDER BRAD) 3 April 2008 (2008-04-03) * paragraphs [0001] - [0038]; figures 1,2 *	1-18	INV. H01J49/10
X	US 2005/247871 A1 (BRYDEN WAYNE A [US] ET AL) 10 November 2005 (2005-11-10) * paragraphs [0030] - [0041]; figure 10 *	1-18	
X	US 2006/091308 A1 (BOYLE JAMES G [US] ET AL) 4 May 2006 (2006-05-04) * paragraphs [0018] - [0061]; claims 1-33; figure 1 *	1-18	
X	WO 2005/031306 A2 (SYAGEN TECHNOLOGY [US]; HANOLD KARL A [US]; SYAGE JACK A [US]) 7 April 2005 (2005-04-07) * the whole document *	1-18	

TECHNICAL FIELDS SEARCHED (IPC)
H01J

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	27 June 2011	Rutsch, Gerald

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

1 EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 10 40 5080

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

27-06-2011

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008037073 A1	03-04-2008	CA 2663698 A1	03-04-2008
		EP 2070102 A1	17-06-2009
		JP 2010504504 A	12-02-2010
		US 2008073502 A1	27-03-2008
US 2005247871 A1	10-11-2005	NONE	
US 2006091308 A1	04-05-2006	NONE	
WO 2005031306 A2	07-04-2005	CA 2538709 A1	07-04-2005
		EP 1665327 A2	07-06-2006

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US 6469297 B **[0064]**
- US 7294830 B **[0064]**