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(54) TIME-OF-FLIGHT MASS SPECTROMETER

(57) The invention discloses a time-of-flight mass spectrometer, comprising a vacuum chamber, a vacuum generation device, an ion flight cavity, an ion source device, a laser excitation device, a chip exchange device, a sample processing device, an excitation sequence device, a signal acquisition device, a high-voltage control device and an operation control device. The vacuum chamber, the vacuum generation device and the ion flight cavity are assembled into a vacuum system. The ion source device is installed in the vacuum system. The laser excitation device provides energy for ion excitation. The excitation sequence device, the high-voltage control device and the ion source device are electrically connected in sequence. The signal acquisition device is electrically connected to the ion flight cavity. According to the invention, by introducing a time-of-flight mass spectrometry detection technology into the field of gene detection, the time-of-flight mass spectrometer has high signal-to-noise ratio, mass resolution and repetition rate. The time-of-flight mass spectrometer is integrated with a sample preparation module, thereby conveniently and quickly completing a mass spectrometry detection process. The time-of-flight mass spectrometer has high operation efficiency, is not prone to failure, and also solves the problems such as sample contamination.

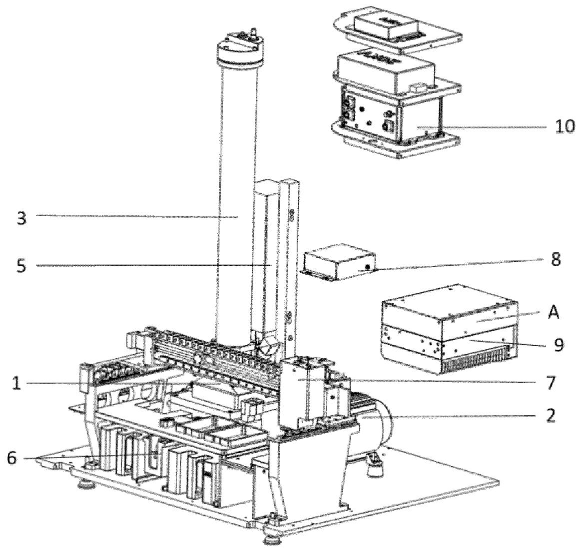

FIG. 1

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Description

TECHNICAL FIELD

[0001] The present invention relates to the field of mass spectrometry detection of biological macromolecules and in particular to a molecular time-of-flight detection mass spectrometry technology and equipment.

BACKGROUND ART

[0002] The time-of-flight mass spectrometry detection technology refers to an instrument that uses an electrostatic field to accelerate ions and then analyzes the mass of ions based on the difference in arrival time caused by the difference in flight velocity of ions In time-of-flight mass spectrometers, linear mass analyzers have been widely used due to their simple structure, wide analysis range, and high mass resolution ability. For example, CN101601119B discloses a time-of-flight mass spectrometer, which mainly includes a mass spectrometry chip, an ion source, an ion focusing tube, an ion detector, a flight drift tube, a vacuum chamber, a vacuum generation device and a supporting control circuit. The mass spectrometry chip is prepared by another instrument and then placed in a mass analyzer. Under the action of the ion source, ions with a certain velocity and charge are generated. After being focused by the focusing tube, the ions arrive at the ion detector via the flight drift tube. Ions of different masses obtain different velocities in the ion source, so the time they arrive at the ion detector is different. By analyzing the difference in the arrival time of the ions, the masses of the ions can be obtained.

[0003] The excitation, flight, and detection processes of ions are affected by many factors, and ion signals detected are not ideal. The quality of ion signals is evaluated mainly on the basis of three main parameters, i.e., signal-to-noise ratio, mass resolution, and repetition rate. Currently practical time-of-flight mass analyzers generally use repeated sampling superposition technology to improve the signal-to-noise ratio, thereby obtaining high signal quality. However, it is also affected by factors such as the repetition rate of ion signals and sample quality, and there is an upper limit for the number of repeated samplings. Mass resolution is the most important evaluation parameter for time-of-flight mass analyzers. Linear mass analyzers have low mass resolution due to limitation of their own structures. Limited by the above factors, currently practical time-of-flight mass analyzers are generally used for the analysis of low-mass molecules such as small molecules, polysaccharides, or proteins. Few time-of-flight mass analyzers are available for nucleic acid mass spectrometry analysis in China.

SUMMARY

[0004] An objective of the present invention is to address the problems in the prior art and provides a time-of-flight mass spectrometer which has high signal-to-noise ratio, mass resolution and repetition rate. The time-of-flight mass spectrometer is integrated with a sample preparation module, thereby conveniently and quickly completing a mass spectrometry detection process. To achieve the above objective, the present invention provides a time-of-flight mass spectrometer, including, but not limited to, a vacuum chamber, a vacuum generation device, an ion flight cavity, an ion source device, a laser excitation device, a chip exchange device, a sample processing device, an excitation sequence device, a signal acquisition device, a high-voltage control device and an operation control device, wherein the vacuum chamber, the vacuum generation device and the ion flight cavity are assembled into a vacuum system, the ion source device is installed in the vacuum system, the laser excitation device provides energy for ion excitation, and the excitation sequence device, the high-voltage control device and the ion source device are electrically connected in sequence; after the ion source device generates ions, the excitation timing device sends a control signal to the high-voltage control device, and the high-voltage control device controls the ion source device to guide the ions into the ion flight cavity; after receiving the ions, the ion flight cavity outputs a signal to the signal acquisition device, and the signal acquisition device processes and store the signal in the operation control device; the chip exchange device and the sample processing device constitute a mass spectrometry pre-processing system; a liquid sample is first processed by the sample processing device and then fed into the vacuum chamber via the chip exchange device.

[0005] In a preferred embodiment, the vacuum chamber includes a lower vacuum chamber base, an upper vacuum chamber cover plate, an ion interface, an XY movement assembly, a transfer window, a camera assembly, a illumination assembly, and a high-voltage connector, the upper vacuum chamber cover plate is installed on the lower vacuum chamber base, the ion interface is provided on the upper vacuum chamber cover plate, the ion source device is installed at one end of the ion interface and the ion flight cavity is installed at the other end of the ion interface; the XY movement assembly is installed in the lower vacuum chamber base, the transfer window is provided on the lower vacuum chamber base, and the camera assembly, the illumination assembly, and the high-voltage connector are installed on the upper vacuum chamber cover plate; the camera assembly includes a telecentric lens and a CCD camera, and an axis of the telecentric lens coincides with an axis of the CCD camera; the illumination assembly includes an LED lamp bead and a focusing lens, and an axis of the LED lamp bead coincides with an axis of the focusing lens.

[0006] In a preferred embodiment, the vacuum generation device includes a secondary vacuum pump, a primary vacuum pump, a vacuum gauge and a solenoid valve assembly, the secondary vacuum pump is installed on the lower vacuum chamber base, and the secondary vacuum pump is configured as a turbo molecular pump or an ultra-high vacuum combination pump; the solenoid valve assembly is provided between the secondary vacuum pump and the primary vacuum pump, and the vacuum gauge is installed in the vacuum chamber.

[0007] In a preferred embodiment, the ion flight cavity includes a flight tube, an end cover, an ion detector and an ion mesh assembly, the flight tube is a hollow tube with annular surfaces at two ends, the length of the flight tube is between 0.5 m and 1.5 m, one end of the flight tube is installed on the ion interface of the vacuum chamber, the other end of the flight tube is provided with an end cover, and the ion detector and the ion mesh assembly are both installed on the end cover; the vacuum chamber, the flight tube, the end cover, and the ion mesh assembly are electrically connected and have a same ground voltage.

[0008] In a preferred embodiment, the ion source device includes an extraction electrode, an accelerating electrode, a focusing ring, and a fixed frame, the focusing ring is installed in the fixed frame, and the extraction electrode and the accelerating electrode are installed on one side of the fixed frame.

[0009] In a preferred embodiment, the extraction electrode includes an electrode base plate, adjustment threads, an electrode plate and a mass spectrometry chip, the electrode base plate is rectangular, three adjustment threads distributed in an isosceles triangle are installed in a groove of the electrode base plate, the electrode plate is placed on the adjustment threads in the groove; there is also another groove in the center of the electrode plate, the mass spectrometry chip is placed in the groove, and an upper plane of the mass spectrometry chip is flush with an upper plane of the electrode plate; the accelerating electrode includes an upper electrode, an upper ion mesh, an insulating mounting ring, a lower ion mesh, and a lower electrode, the upper electrode is configured as a ring with a hole in the center, the upper ion mesh is fixed on the upper electrode, the lower electrode is also a ring with a hole in the center, the lower ion mesh is fixed on the lower electrode, the insulating mounting ring has a hole in the center and two mounting grooves, and the upper electrode and the lower electrode are respectively fixed in the two mounting grooves of the insulating mounting ring; the focusing ring includes an upper ground ring, a high-voltage ring, a lower ground ring and an insulating support, the upper ground ring, the high-voltage ring and the lower ground ring are all installed in the insulating support, and axes of the upper ground ring, the high-voltage ring, the lower ground ring and the insulating support coincide with each other.

[0010] In a preferred embodiment, the laser excitation device includes a laser device, a first reflector assembly, a second reflector assembly, and a focusing lens assembly, the laser device is configured as an ultraviolet-band laser device, the first reflector assembly and the second reflector assembly are each composed of a laser reflector and an adjustment base, and a laser beam is emitted from the laser device, is reflected by the first reflector and the second reflector, and then enters the focusing lens assembly.

[0011] In a preferred embodiment, the chip exchange device includes an exchange chamber cover, a driving device, a heating device, and an exchange solenoid valve device, the exchange chamber cover is installed on the driving device and driven by the driving device to move forward and backward, and the heating device and the exchange chamber cover are linked with the driving device; when the exchange chamber cover moves toward the lower vacuum chamber base, the heating device and the exchange chamber cover simultaneously descend to a bottom of the exchange chamber cover.

[0012] In a preferred embodiment, the exchange solenoid valve device includes a solenoid valve body, an air solenoid valve and a vacuum solenoid valve, the air solenoid valve and the vacuum solenoid valve are installed in the solenoid valve body, the solenoid valve body is provided with an exchange air passage, an air passage and a vacuum passage, two upper ports of the exchange air passage are respectively connected with air inlets of the air solenoid valve and the vacuum solenoid valve, an air outlet of the air solenoid valve is connected with the air passage, and an air outlet of the vacuum solenoid valve is connected with the vacuum passage of the solenoid valve body.

[0013] In a preferred embodiment, the sample processing device includes a mobile platform, a sample adding device, a liquid pump, an image recognition device, a sample carrier, a microplate carrier, a tip box carrier, a pure water tank, and a waste box; the mobile platform can move independently in X-axis and Y-axis directions; the sample adding device and the image recognition device are installed on the mobile platform; the sample adding device and the image recognition device can move in a Z-axis direction; the sample adding device is connected with the liquid pump; the sample carrier and the microplate carrier can carry biological reagents or samples; the liquid pump and the pure water tank are connected by a one-way valve and a pipeline, and the waste box is provided below the sample adding device.

[0014] The beneficial effect of the invention: According to the present invention, by introducing a time-of-flight mass spectrometry detection technology into the field of gene detection and based on a reasonable structural design, the time-of-flight mass spectrometer has high signal-to-noise ratio, mass resolution and repetition rate. The time-of-flight mass spectrometer is integrated with a sample preparation module, thereby conveniently and quickly completing a mass spectrometry detection process. The time-of-flight mass spectrometer has high operation efficiency, is not prone to failure, and also solves the problems such as sample contamination.

[0015] The features and advantages of the present invention will be described in detail by way of embodiments in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016]

FIG. 1 is a schematic structural diagram of a time-of-flight mass spectrometer according to the present invention;
FIG. 2 is a schematic structural diagram of a vacuum chamber in the time-of-flight mass spectrometer according to the present invention;
FIG. 3 is a schematic structural diagram of a transfer window in the time-of-flight mass spectrometer according to the present invention;
FIG. 4 is a schematic structural diagram of a camera assembly and a illumination assembly in the time-of-flight mass spectrometer according to the present invention;
FIG. 5 is a schematic structural diagram of a vacuum generation device in the time-of-flight mass spectrometer according to the present invention;
FIG. 6 is a schematic diagram of pipeline connection of the vacuum generation device in the time-of-flight mass spectrometer according to the present invention;
FIG. 7 is a schematic installation diagram of an ion flight cavity and an ion source device in the time-of-flight mass spectrometer according to the present invention;
FIG. 8 is a schematic structural diagram of an extraction electrode in the time-of-flight mass spectrometer according to the present invention;
FIG. 9 is a schematic structural diagram of an accelerating electrode and a focusing ring in the time-of-flight mass spectrometer according to the present invention;
FIG. 10 is a schematic diagram of an ion flight process of the time-of-flight mass spectrometer according to the present invention;
FIG. 11 is a schematic structural diagram of a laser excitation device in the time-of-flight mass spectrometer according to the present invention;
FIG. 12 is a schematic structural diagram of a chip exchange device in the time-of-flight mass spectrometer according to the present invention;
FIG. 13 is a schematic structural diagram of an exchange solenoid valve in the time-of-flight mass spectrometer according to the present invention;
FIG. 14 is a schematic diagram of different states of an exchange chamber in the time-of-flight mass spectrometer according to the present invention;
FIG. 15 is a schematic structural diagram of a sample processing device in the time-of-flight mass spectrometer according to the present invention;
FIG. 16 is a schematic diagram of an excitation timing device in the time-of-flight mass spectrometer according to the present invention;
FIG. 17 is a schematic diagram of a signal acquisition device in the time-of-flight mass spectrometer according to the present invention;
FIG. 18 is a schematic diagram of a high-voltage control device in the time-of-flight mass spectrometer according to the present invention; and
FIG. 19 is a schematic diagram of an operation control device in the time-of-flight mass spectrometer according to the present invention.

DETAILED DESCRIPTION

[0017] In order to make the objectives, technical solutions and advantages of the present invention more clear, the present invention will be further described in detail below with reference to the accompanying drawings and embodiments. However, it should be understood that the specific embodiments described herein are only used to explain the present invention, and not to limit the scope of the present invention. In addition, in the following description, descriptions of well-known structures and technologies are omitted to avoid unnecessarily obscuring the concept of the present invention.

[0018] Referring to FIG. 1, a time-of-flight mass spectrometer includes a vacuum chamber 1, a vacuum generation device 2, an ion flight cavity 3, an ion source device 4, a laser excitation device 5, a chip exchange device 6, a sample processing device 7, an excitation timing device 8, a signal acquisition device 9, a high-voltage control device 10 and an operation control device A, wherein the vacuum chamber 1, the vacuum generation device 2 and the ion flight cavity 3 are assembled into a vacuum system, the ion source device 4 must work in the vacuum system, and the laser excitation device 5 provides energy for ion excitation; after ions are generated in the ion source device 4, the excitation timing device 8 sends a control signal to the high-voltage control device 10, and the high-voltage control device 10 controls the ion source device 4 to extract and accelerate the ions into the ion flight cavity 3; after receiving the ions, the ion flight cavity 3 outputs a signal to the signal acquisition device 9, and the signal acquisition device 9 processes and store the signal in the operation control device A; the chip exchange device 6 and the sample processing device 7 constitute a mass spectrometry pre-processing system; a liquid sample is first processed by the sample processing device 7 and then fed into the vacuum chamber 1 via the chip exchange device 6. The operation control device A can control the operation of the vacuum chamber 1, the vacuum generation device 2, the ion flight cavity 3, the ion source device 4, the laser excitation device 5, the chip exchange device 6, the sample processing device 7, the excitation timing device 8, the signal acquisition device 9, and the high-voltage control device 10.

[0019] Referring to FIG. 2, the vacuum chamber 1 includes but is not limited to a lower vacuum chamber base 11, an upper vacuum chamber cover plate 12, an ion interface 13, an XY movement assembly 14, a transfer window 15, a camera assembly 16, a illumination assembly 17, and a high-voltage connector 18. The lower vacuum chamber base 11 serves as an installation basis of the entire vacuum chamber 1. The lower vacuum chamber base 11 is provided with a positioning pin (not shown) and a sealing ring (not shown). To install the upper vacuum chamber cover plate 12 on the lower vacuum chamber base 11, precise positioning can be achieved through the cooperation of the positioning hole and the positioning pin, and at the same time, vacuum sealing can be completed by allowing a smooth bottom surface to press the sealing ring tightly, where the sealing ring is fixed in a groove on the lower vacuum chamber base 11. The number of sealing rings is preferably 1, and it may be increased to 2 when sealing needs to be strengthened.

[0020] The ion interface 13 is provided on the upper vacuum chamber cover plate 12 and configured into a set of precision coaxial cylindrical surfaces perpendicular to the bottom surface of the upper vacuum chamber cover plate 12. The ion source device 4 may be provided at one end of the ion interface 13 and the ion flight cavity 3 may be provided on the other end of the ion interface 13. By virtue of the ion interface 13, the ion source device 4 and the ion flight cavity 3, the alignment accuracy of the axes is guaranteed, thereby ensuring that the flight path of ion do not deviate.

[0021] Referring to FIGS. 2 and 3, the transfer window 15 is configured into a set of through holes located on the lower vacuum chamber base 11, where a chip transfer window 151 is configured as a square cross-section through hole that vertically penetrates the lower vacuum chamber base 11, and an air transfer window 152 is configured as a circular cross-section through hole that is perpendicular to the lower vacuum chamber base 11 and the chip transfer window 151.

[0022] Referring to FIG. 4, the camera assembly 16 is composed of a telecentric lens 161 and a CCD camera 162, the axes of which are coincident, and the telecentric lens can only pass parallel light to the CCD camera; the illumination assembly 17 is composed of an LED lamp bead 171 and a focusing lens 172, the axes of which are also coincident; divergent light emitted by the LED lamp bead 171 passes through the focusing lens 172 and becomes parallel light for emission. As shown in FIG. 4, an angle between an axis of the camera assembly 16 and an axis of the ion interface 13 and an angle between an axis of the illumination assembly 17 and the axis of the ion interface 13 are equal and located in a same plane, and the three axes intersect at one point, which is called convergence point. The convergence point is in an upper plane of a mass spectrometry chip 414, and the focus of the telecentric lens is also located at the convergence point. An upper surface of the mass spectrometry chip 414 is configured as a mirror surface and is perpendicular to the axis of the ion interface 13, so the parallel light emitted by the illumination assembly 17 can be reflected into the camera assembly 17, but light reflected by other objects is not parallel to the axis of the camera assembly 16 and cannot be received by the camera assembly 16. In this way, the camera assembly 16 can only capture the upper surface of the mass spectrometry chip 414, and due to the shallow depth of field of the telecentric lens, when the camera assembly 16 can clearly capture all samples on the mass spectrometry chip 414, it means that all sample points on the mass spectrometry chip 414 coincide with the convergence point. When some points are not captured clearly, the position deviation of the mass spectrometry chip 414 can be automatically determined by an algorithm to remind a user of making timely adjustments, thereby avoiding inaccurate test results.

[0023] Referring to FIGS. 12 and 14, the XY movement assembly 14 includes an action structure 141 and an insulating sealing support 142; the XY movement assembly 14 is installed in the lower vacuum chamber base 11 and has a two-axis motion mechanism which is driven to move by a linear motor and guide rails; the guide rails in X and Y directions are accurately adjusted to be parallel to installation planes of the lower vacuum chamber base 11 and the upper vacuum chamber cover plate 12; an extraction electrode 41 of the ion source device 4 may be installed on the XY movement assembly 14; the extraction electrode includes the mass spectrometry chip 414 which can be adjusted to be parallel to an XY guide rail plane. When the XY movement mechanism drives the mass spectrometry chip 414 to move, the upper surface of the mass spectrometry chip 414 can coincide with the intersection of axes of the camera assembly 16 and the illumination assembly 17 at any point, ensuring that the upper surface of the mass spectrometry chip 414 can be clearly captured by the camera assembly 16 at any point.

[0024] Referring to FIGS. 5 and 6, the vacuum generation device 2 includes but is not limited to a secondary vacuum pump 21, a primary vacuum pump 22, a vacuum gauge 23 and a solenoid valve assembly 24, and the secondary vacuum pump 21 is directly installed on a shell of the lower vacuum chamber base 11. The secondary vacuum pump 21 functions to pump gas out of the vacuum chamber at a very high pumping speed to form an ultra-high vacuum environment in the vacuum chamber. The secondary vacuum pump 21 being directly installed on the shell of the lower vacuum chamber base 11 can reduce the impact of a molecular flow of the pipeline on the pumping speed. A turbo molecular pump is preferred for the secondary vacuum pump, and other types of ultra-high vacuum combination pumps may also be used. The secondary vacuum pump 21 needs an initial working vacuum environment. The primary vacuum pump 22 is required to pump air out of the secondary vacuum pump 21 and the vacuum chamber to form an initial working vacuum degree which is between 1 hpa and 10 hpa, so the primary vacuum pump 22 may be connected to the vacuum chamber 1 and the secondary vacuum pump 21 by flexible vacuum pipelines. The installation position of the primary vacuum pump 22 can be flexibly arranged, which can facilitate maintenance and increase shock absorption and ventilation measures. A diaphragm pump, a rotary vane pump, or a Roots pump may be used as the primary vacuum pump 22. The vacuum gauge 23 is configured to measure the vacuum degree in the vacuum chamber 1. Generally, a Pirani/cold cathode combined vacuum gauge or a cold cathode vacuum gauge is used. In order to detect the vacuum degree in the vacuum chamber 1 in real time, the vacuum gauge 23 is directly installed vertically on a shell of the upper vacuum chamber cover plate 12, so that changes in the vacuum degree in the vacuum chamber 1 can be detected more rapidly, thereby avoiding delay.

[0025] Referring to FIG. 6, the solenoid valve assembly 24 is composed of a two-position two-way normally closed solenoid valve and two hose connectors. Reference is made to FIG. 6 for its pipeline connection. A pumping port of the primary vacuum pump 22 is connected to one of the hose connectors of the solenoid valve assembly 24 by a pipeline, and the connector is also connected to an exchange chamber solenoid valve assembly; an air outlet of the secondary vacuum pump 21 is connected to the other hose connector of the solenoid valve assembly 24 by a pipeline. Only after the solenoid valve is powered on, can the secondary vacuum pump 21 be connected to the primary vacuum pump 22, and when the solenoid valve is powered off, the secondary vacuum pump 21 and the primary vacuum pump 22 are disconnected. This can avoid the problem that, when the whole instrument is suddenly powered off, the primary vacuum pump lost sealing and the secondary vacuum pump 21 rapidly loses its vacuum degree, causing the secondary vacuum pump 21 to wear out. In addition, the holding time of the vacuum degree in the vacuum chamber 1 can also be increased to avoid excessive vacuum re-establishment time caused by loss of vacuum degree after the instrument has been stored for too long.

[0026] Referring to FIG. 7, the ion flight cavity 3 includes a flight tube 31, an end cover 32, an ion detector 33 and an ion mesh assembly 34, where the flight tube 31 is a hollow tube with precision-fitting annular surfaces at two ends. The precision-fitting annular surfaces are configured for ensuring that the two ends of the flight tube are consistent with the axis of the ion interface 13. The length of the flight tube 31 is between 0.5 m and 1.5m. One end of the flight tube 31 is installed on the ion interface 13 of the vacuum chamber 1, the other end of the flight tube 31 is provided with the end cover 32, and the end cover 32 is also kept coaxial with the flight tube 31 by means of the precision-fitting annular surfaces. The ion detector 33 is installed on the end cover 32. A microchannel plate (ETP) or an electron multiplier (CEM) is generally used as the ion detector. The ion mesh assembly 34 is also installed on the end cover 32. The vacuum chamber 1, the flight tube 31, the end cover 32, and the ion mesh assembly 34 are electrically connected and have the same ground voltage. The ion mesh assembly 34 includes an ion mesh mounting ring 341 and an ion mesh 342. The ion mesh mounting ring 341 has a precisely machined annular surface and a precisely machined flat surface, and the annular surface cooperates with the end cover to ensure coaxiality. In this way, the ion mesh assembly 34 can be kept coaxial with the ion interface 13. The precisely machined flat surface is configured to fix the ion mesh 342 and also to ensure the flatness of the ion mesh 342. In order to ensure that ions can pass through the center of the ion mesh assembly 34 to the maximum extent, a hole is formed in the center of the flat surface of the ion mesh mounting ring. A perforated metal mesh grid is used as the ion mesh 342 and is made of a material including but not limited to conductive materials such as gold, silver, copper, nickel, and stainless steel. A nickel mesh grid is preferred. The transmittance of the grid is between 50% and 99%, preferably between 95% and 99%. L1 in FIG. 7 is the same as L1 in FIG. 10, both represent a free flight distance of ions after acceleration.

[0027] Referring to FIGS. 7 and 8, the ion source device 4 includes an extraction electrode 41, an accelerating electrode 42, a focusing ring 43, and a fixed frame 44; the extraction electrode 41 includes an electrode base plate 411, adjustment threads 412, an electrode plate 413, and a mass spectrometry chip 414; the electrode base plate 411 is rectangular; three adjustment threads 412 distributed in an isosceles triangle are installed in a groove of the electrode base plate 411, the electrode plate 413 is placed on the adjustment threads 412 in the groove and supported by upper planes of the threads, and the angle of the upper plane of the electrode plate 413 can be adjusted by adjusting the heights of the three adjustment threads 412; there is also another groove in the center of the electrode plate 413, the mass spectrometry chip 414 is placed in the groove, and the upper plane of the mass spectrometry chip 414 is flush with the upper plane of the electrode plate 413; the electrode base plate 411, the adjustment threads 412, and the electrode plate 413 are made of a metal with good electrical conductivity; and the mass spectrometry chip 414 is made of a semiconductor silicon wafer. The components of the entire extraction electrode 41 are electrically connected, an even electric field is formed near the extraction electrode to ensure that ions generated at different locations are affected by the same electric field. The upper plane of the mass spectrometry chip 414 is subjected to special surface treatment and can adsorb matrix sample liquid on its surface.

[0028] Referring to FIG. 9, the accelerating electrode 42 is composed of an upper electrode 421, an upper ion mesh 422, an insulating mounting ring 423, a lower ion mesh 424, and a lower electrode 425. The upper electrode 421 is configured as a precise ring with a hole in the center, and the upper ion mesh 422 is fixed on the upper electrode 421. Similarly, the lower electrode 425 is also configured as a precise ring with a hole in the center, and the lower ion mesh 424 is fixed on the lower electrode 425. The insulating mounting ring 423 has a hole in the center and two mounting grooves, and the upper electrode 421 and the lower electrode 425 are fixed in the mounting grooves of the insulating mounting ring 423.

The grooves of the insulating mounting ring 423 are precisely machined to ensure that the axes of the upper electrode 421, the lower electrode 425 and the insulating mounting ring 423 are on the same axis. In this way, the upper electrode 421 and the lower electrode 425 are parallel to each other, and electric field lines formed are parallel to the axis and the flight direction of the ions, thus preventing non-parallel electric fields from deflecting the flight direction of the ions. The upper electrode 421 and the lower electrode 425 are made of a metal with good electrical conductivity. The upper ion mesh 422 and the lower ion mesh 424 are made of the same material as the ion mesh 342. The insulating mounting ring 423 is made of a material with good insulation to ensure that the upper electrode 421 and the upper ion mesh 422 are completely electrically isolated from the lower electrode 425 and the lower ion mesh 424.

[0029] Referring to FIG. 9, the focusing ring 43 is composed of an upper ground ring 431, a high-voltage ring 432, a lower ground ring 433 and an insulating support 434, where the upper ground ring 431, the high-voltage ring 432 and the lower ground ring 433 are precisely machined smooth conductive hollow cylinders with the same inner and outer diameters and are all installed in the insulating support 434 made of an insulating material, so as to be insulated from each other. By virtue of the precisely machined cylindrical fitting surfaces, the axes of the upper ground ring 431, the high-voltage ring 432, the lower ground ring 433 and insulating support 434 coincide with each other. In this way, an electric field formed among the upper ground ring 431, the high-voltage ring 432 and the lower ground ring 433 will form an axisymmetrically distributed focusing electric field, and this focusing electric field can focus the ions to a smaller diameter or a more parallel orientation. The fixed frame 44 is made of a material with good electrical conductivity and is fixed on the ion interface 13. By virtue of precisely machined mounting fitting surfaces, the fixed frame 44 coincides with the axis of the ion interface 13. In the meanwhile, the accelerating electrode 42 and the focusing ring 43 are installed on the fixed frame 44. Similarly, by virtue of precisely machined mounting fitting surfaces, common axes of the accelerating electrode 42 and the focusing ring 43 coincide with an axis of the fixed frame 44.

[0030] Based on the structural design and installation method described above, all electrical parts included in the ion mesh assembly 34, the accelerating electrode 42, the focusing ring 43, and the ion detector 33 are accurately installed on a same axis 1. By virtue of the adjustment threads 412, the common upper plane of the electrode plate 413 and the mass spectrometry chip 414 is adjusted to be completely parallel to the lower ion mesh 414 of the accelerating electrode 42 and in the meanwhile, the upper plane of the mass spectrometry chip 414 coincides with the intersection of axes (i.e., the convergence point in FIG. 4) of the camera assembly 16 and the illumination assembly 17.

[0031] The entire extraction electrode 41 is installed in the insulating sealing support 142 of the XY movement assembly 14 and can move with the XY movement assembly 14. When a sample point on the mass spectrometry chip 414 moves to the center of the field of view of the camera assembly 16, the sample point coincides with the axis 1 on which the mass spectrometry chip 414 is installed. The flight process of ions is shown in FIG. 10. After a pulse laser beam irradiates the sample point on the mass spectrometry chip 414, the sample will generate a certain amount of charged ions. The charged ions have a certain initial velocity and basically move along the axis 1 from the extraction electrode 41 to the accelerating electrode 42, where the extraction electrode 41 is connected to high voltage HV1, the lower ion mesh 424 of the accelerating electrode is connected to pulse high voltage HV2, the upper ion mesh 422 is grounded, the voltage of HV1 is constant and between 15 KV and 30 KV, preferably 20KV, and the voltage of HV2 is pulse voltage and is the same as HV1 most of the time. After laser irradiation, HV2 will have a pulse voltage pulled down. The drop amplitude of the pulse voltage is between 1 KV and 3 KV, the drop time of the pulse voltage is within 200 ns, and the recovery time of the voltage HV2 is within 100 ms. When the voltage of HV2 is pulled down, the voltage HV1 is greater than HV2, and a potential difference is formed between the extraction electrode 41 and the lower ion mesh 424. Under the action of the potential difference, the ions accelerate to pass through the lower ion mesh 424 and enter an accelerating electric field area formed by the lower ion mesh 424 and the upper ion mesh 422, where the upper ion mesh 422 and the ion mesh assembly 34 are both grounded, so the ions pass through the accelerating electric field area formed by HV2 and the ground voltage and then enter an even electric field area with no potential difference to fly freely, and finally pass through the ion mesh assembly 34 and enter the ion detector 33.

[0032] Coinciding the axes of all electrical parts has the following effects: 1. After ions are generated on the upper plane of the mass spectrometry chip 414, extraction and acceleration electric fields they pass through are completely parallel, and the velocity direction that the ions obtain is parallel to the axis 1. There is no non-parallel electric field causing the flight velocity direction of ions to disperse. Moreover, after the ions are accelerated, ions with the same velocity enter and fly out of the even electric field flight area at the same time and are received by the ion detector at the same time, which reduces the pulse width of ion signals received by the ion detector and increases the resolution. 2. The axis of the focusing ring 43 coincides with the axis 1, so that ions of which the direction farther deviates from axis 1 are subject to a stronger focusing correction effect, thereby focusing most of divergent ion beams into the ion detector 33.

[0033] The ion flight process described above occurs in an ideal situation. In fact, the initial velocity of ions generated by the sample has a certain difference in velocity and direction. In order to compensate for the velocity difference of ions, after the ions are generated by laser irradiation, HV2 will not be immediately pulled down to extract ions, but will be set with a certain delay time t for the purpose that ions with different velocities can fly to the lower ion mesh 424 for a period of time in an even electric field. Ions which fly faster travel longer distances than slower ions. In this way, when HV2 is pulled low, the slower ions obtain more acceleration potential energy than the faster ions, thus achieving the purpose of compensating for the velocity difference. The initial flight direction of the ions is not strictly along the axis 1, which produces a radial velocity component perpendicular to the axis 1, so the ions will spread to a very large area after flying for a period of time and cannot all be received by the ion detector 33, and this weakens ion signals. In order to ensure that most ions are received by the ion detector 33, the instrument of the present invention is designed with the focusing ring 43. The upper ground ring 431 and the lower ground ring 433 of the focusing ring 43 are grounded and the high-voltage ring 432 is connected to the high voltage HV3. In this way, an uneven electric field is formed in gaps L2 among the upper ground ring 431, the lower ground ring 433 and the high-voltage ring 432. When ions pass through this electric field, the radial acceleration effect on the ions due to the uneven electric field distribution will reduce and eliminate the radial velocity component of the ions, resulting in the effect of focusing the ions, just like an optical lens. By adjusting the voltage HV3 carefully, most of the ions can be brought into the ion detector 33, thereby improving the signal level. Arranging the ground rings 431 and 433 at two ends of the high-voltage ring 432 can prevent the electric field of the high-voltage ring 432 from interfering with the even electric field area between the upper ion mesh 422 and the ion mesh assembly 34. The ions first pass through the accelerating electrode 42 and then through the focusing ring 43 arranged. Because the accelerated ions are faster, even if the gaps L2 among the upper ground ring 431, the lower ground ring 433 and the high-voltage ring 432 are designed to be large, the time that ions stay in the uneven electric field of the gaps is still very short, and the radial acceleration that the ions obtain is also small, which can just compensate for a very small initial radial component of the ions. If the focusing ring 43 is installed in front of the accelerating electrode 42, the velocity of the ions is very slow at this time. In order to just compensate for the very small initial radial component of the ions, the gaps L2 must be designed to be very small, which does not satisfy the insulation requirement of the upper ground ring 431, the lower ground ring 433 and the high-voltage ring 432.

[0034] Referring to FIG. 10, L1 is the free flight distance of ions after acceleration. Because ions of different masses obtain different velocities, the longer the distance of L1, the longer the time interval for ions with different velocities to arrive at the ion detector, and the easier it is for the ion detector to distinguish ions of different masses. Therefore, the longer the distance of L1, the better in theory. However, due to limitations in process and device, the distance of L1 is between 800 mm and 1500mm. The distance of L2 should meet the insulation requirement of the ground ring and the high-voltage ring, and the needs of ion focusing should also be considered. The distance of L2 is generally between 1 mm and 8 mm. For L3, the insulation requirement of the upper ion mesh 422 and the lower ion mesh 424 is mainly considered, and the distance of L3 is generally between 3 mm and 10 mm. For L4, there is no need to consider insulation and functional requirements, and the gap only needs to meet the tolerance margin and is generally between 1 mm and 5 mm. For L5, the insulation, extraction function and the outer dimensions of the insulating sealing support 142 are mainly considered, and the distance of L5 is generally between 4 mm and 10 mm.

[0035] Referring to FIG. 11, the laser excitation device 5 mainly includes a laser device 51, a first reflector assembly 52, a second reflector assembly 53, and a focusing lens assembly 54. The laser device 51 is configured as an ultraviolet-band laser device. When the laser device 51 works in a pulse mode, the pulse width is between 2 ns and 10 ns. The wavelength of the pulse laser device may be one of 248 nm, 266 nm, 275 nm, 337 nm, and 355 nm. A 337nm nitrogen molecule laser device is preferred. The first reflector assembly 52 and the second reflector assembly 53 are each composed of a laser reflector and an adjustment base. The reflectivity of the laser reflector to a laser beam is greater than 95%. The adjustment base can adjust the tilt angle of the laser reflector. An angle between the tilt angle adjustment directions of the laser reflectors in the first reflector assembly 52 and the second reflector assembly is 90°. That is, the first reflector assembly 52 can adjust a pitch angle of the laser beam, and the second reflector assembly 53 can adjust a horizontal angle of the laser beam. By adjusting the angles of the first reflector 52 and the second reflector 53, the laser beam can be irradiated to any point in a plane. The focusing lens assembly 54 is composed of a laser focusing lens and a focusing base. A laser beam is emitted from the laser device, and after being reflected by the first reflector 52 and the second reflector 53, enters the focusing lens assembly 54, and then is concentrated by the laser focusing lens. By virtue of the first reflector assembly 52 and the second reflector assembly 53 for angle adjustment and the focusing lens assembly for adjusting the focus position of the laser beam, the focus of the laser beam is located in the upper plane of the mass spectrometry chip 414 of the extraction electrode 41. When the instrument of the present invention collects mass spectrometry, the focus of the camera assembly 16, the focus of the laser beam, and the sample point of the mass spectrometry chip 414 coincide with each other and are on the axis 1. As shown in FIG. 11, the laser beam concentrated by the focusing lens assembly 54 passes through the gap between the accelerating electrode 42 and the focusing ring 43, penetrates the upper ion mesh 422 and the lower ion mesh 424, and finally irradiates the mass spectrometry chip 414. This arrangement can minimize the angle between the laser beam and the axis 1, avoid uneven distribution of spot energy irradiated on the mass spectrometry chip 414, and it also can avoid the flight path of ions, thereby preventing laser parts from interfering with ion flight.

[0036] Referring to FIG. 12, the chip exchange device 6 includes but is not limited to an exchange chamber cover 61, a driving device 62, a heating device 63, and an exchange solenoid valve device 64. The exchange chamber cover 61 is designed as a square cavity with one end open, and a sealing ring is installed at the open end of the cavity. The exchange chamber cover 61 can be driven by the driving device 62 to move forward and backward. The heating device 63 is linked with the exchange chamber cover 61 and the driving device 62. When the exchange chamber cover moves toward the lower vacuum chamber base 11, the heating device 63 synchronously descends to the bottom of the exchange chamber cover 61. Otherwise, the heating device 63 rises to contact the lower plane of the accelerating electrode 41.

[0037] Referring to FIG. 13, the exchange solenoid valve device 64 is composed of a solenoid valve body 641, an air solenoid valve 642 and a vacuum solenoid valve 643. The air solenoid valve 642 and the vacuum solenoid valve 643 are installed at one end of an exchange air passage 644 in the solenoid valve body 641 and are connected with the air transfer window 152. The other end of the exchange air passage 644 is divided into two ports, which are connected to air inlets of the air solenoid valve 642 and the vacuum solenoid valve 643, respectively. An air outlet of the air solenoid valve 642 is connected to an air passage 645 of the solenoid valve body 641, and an air outlet of the vacuum solenoid valve is connected to a vacuum passage 646 of the solenoid valve body 641. The air passage 645 of the solenoid valve body 641 is equipped with an air filter and is connected to the atmosphere. The vacuum passage 646 of the solenoid valve body 641 is connected to the pumping port of the primary vacuum pump 22 by virtue of a pipeline.

[0038] Referring to FIG. 14, state 1 indicates the detection working state of the instrument of the present invention. The accelerating electrode 41 is in the vacuum chamber. The exchange chamber cover 61 is tightly fitted to the lower vacuum chamber base 11 to seal one end of the chip transfer window 151 and at the same time, the air solenoid valve 642 and the vacuum solenoid valve 643 are switched off to seal one end of the air transfer window 152, and then the vacuum chamber 1 is in a sealed state. When the mass spectrometry chip 414 in the accelerating electrode 41 needs to be replaced after the detection is completed, the mass spectrometry chip 414 needs to be transferred out of the vacuum chamber. In this case, the state 1 of the instrument needs to be changed to state 2. That is, the accelerating electrode is driven by the insulating sealing support 142 to pass through the chip transfer window 151 and enter the cavity of the exchange chamber cover 61, and at the same time, the insulating sealing support 142 seals the other end of the chip transfer window 151. In this case, the two ends of the chip transfer window 151 are sealed by the exchange chamber cover 61 and the insulating sealing support 142 respectively, forming a sealed space together with the air transfer window 152. This space is still in a vacuum state, and at this time, the exchange chamber cover 61 cannot be opened due to the effect of atmospheric pressure. Therefore, the air solenoid valve 642 needs to be switched on to connect the air transfer window 152 to the atmosphere and release the vacuum in the sealed space. After state 2 is completed, the mass spectrometer can be changed to state 3. The exchange chamber cover 61 is operated to break away from the contact with the lower vacuum chamber base 11 and moves backward. Then, the air solenoid valve 642 is switched off to disconnect the air transfer window from the atmosphere, and the mass spectrometry chip 414 on the accelerating electrode 41 is exposed outside the vacuum chamber, and then the chip replacement operation can be performed. After the mass spectrometry chip 414 is replaced, the sample processing device 7 can be used to transfer the amplified liquid sample to a corresponding matrix point of the mass spectrometry chip 414. At this time, the mass spectrometry chip 414 is heated to a predetermined temperature by the heating device 63 and the liquid transferred to the mass spectrometry chip 414 can be dried quickly. After the liquid is dried, the mass spectrometry chip 414 needs to be fed into the vacuum chamber 1 again for detection and analysis, the instrument changes from state 3 to state 2, and the exchange chamber cover 61 moves forward and tightly fits the lower vacuum chamber base 11 to seal the chip transfer window 151. At this time, the chip transfer window 151 and the air transfer window 152 form a sealed space again, and the air pressure in the sealed space is consistent with the atmospheric pressure. In this case, if the insulating sealing support 142 is moved to release the sealed gas, a large amount of gas will impact the secondary vacuum pump and cause the vacuum degree in the vacuum chamber 1 to rise sharply. So, before the insulating sealing support 142 is moved, the vacuum solenoid valve 643 needs to be switched on to connect the air transfer window 152 to the primary vacuum pump 22. The primary vacuum pump 22 will pump most of the gas out of the sealed space to form a vacuum degree of 0.01-5 hpa, and then the vacuum solenoid valve 643 is switched off. In this case, the instrument can be changed to state 1, and the insulating sealing support 142 drives the extraction electrode 41 to move into the vacuum chamber 1, and finally moves to a working position to start detection.

[0039] Referring to FIG. 15, the sample processing device 7 includes but is not limited to a mobile platform 71, a sample adding device 72, a liquid pump 73, an image recognition device 74, a sample carrier 75, a microplate carrier 76, a tip box carrier 77, a pure water tank 78, and a waste box 79. The mobile platform 71 can move independently in X-axis and Y-axis directions. The sample adding device 72 and the image recognition device 74 are installed on the mobile platform 71. The sample adding device 72 and the image recognition device 74 may be but not necessarily driven by a same motor. The sample adding device 72 and the image recognition device 74 can move in a Z-axis direction to complete suction, installation, and injection operations at different heights and photograph objects of different heights. The sample adding device 72 includes but is not limited to 1/6/24/48/96 pipette heads. Each of 1/6/24/48/96 pipette heads is connected to the liquid pump 73 by virtue of a pipeline. The pipette head may be loaded with various types of disposable pipetting tips. Before a pipetting operation, the sample adding device 72 takes the tips from a tip box, and after the pipetting operation is completed, the sample adding device 72 detaches the tips. The detached tips are collected into the waste box 79 to prevent the sample liquid remaining in the tips from contaminating the interior of the instrument. Every time a liquid handling procedure is completed, a new disposable pipetting tip needs to be replaced to completely avoid cross-contamination problems caused by reusing tips.

[0040] The liquid pump 73 is preferably a quantitative syringe pump, including 1/6/24/48/96 independently controlled liquid paths. Each liquid path is controlled by a reversible solenoid valve. The number of liquid syringes of the liquid pump 73 is consistent with the number of pipette heads of the sampling device 72. That is, the liquid path of each pipette head is independent, which can avoid inconsistent injection volume of the pipette heads when multiple pipette heads share one syringe. The liquid pump 73 and the pure water tank 78 are connected by virtue of a one-way valve and a pipeline to ensure that the liquid pump 73 can only pump water from the pure water tank 78, thereby avoiding the problem that the pure water tank is contaminated due to backflow of liquid in the pipeline.

[0041] The image recognition device 74 includes a CCD camera, an optical lens and a light source, and can recognize, including but not limited to, images of objects and barcodes. The barcodes here include but are not limited to one-dimensional barcodes and/or two-dimensional barcodes. The optical lens is preferably a telecentric lens. Because of very stable magnification, the telecentric lens can be used to measure the size of an object being photographed.

[0042] The sample carrier 75 and the microplate carrier 76 are configured to carry various biological reagents and samples. In order to keep biological reagents and samples effective for a long time, a temperature control device is preferably installed at the bottom of the sample carrier 75 or/and the microplate carrier 76. According to the storage requirements of different biological reagents and samples, the temperature control device can maintain the temperature at a set temperature between 0 °C and room temperature.

[0043] The tip box carrier 77 is used to carry disposable boxed tips. The tip box carrier 77 includes a horizontal adjustment structure and a tip box clamping structure. Through horizontal adjustment and clamping, it is ensured that the sample adding device can accurately and stably take the tip every time.

[0044] The liquid handling procedure of the sample processing device 7 is roughly as follows: After the program is started, the X, Y, and Z axes of the sample processing device 7 are reset, and then the image recognition device 74 is moved to the mass spectrometry chip 414 to recognize and archive the two-dimensional barcode of the mass spectrometry chip 414. Then, the sample adding device 72 moves to the tip box carrier 77 to load the disposable pipetting tips. The sample adding device 72 then drives the disposable pipetting tips to move to the microplate carrier 76 to pipet liquid processing consumables. The sample adding device 72 then moves to the sample carrier 75 and injects the consumables into a sample solution placed at the sample carrier 7. After the sample solution is processed, the disposable pipetting tips pipet a certain amount of the sample solution. Then, the sample adding device 72 moves to the mass spectrometry chip 414, and the sample solution pipetted by the disposable pipetting tips is injected into the matrix point of the mass spectrometry chip 414. Finally, the sample adding device 72 moves to the waste box 79 and discards the used disposable pipetting tips into the waste box 79, and then a round of liquid handling procedure is finished. If a larger amount of liquid needs to be processed, this procedure can be repeated. The sample carrier 75, the microplate carrier 76, the tip box carrier 77 and the mass spectrometry chip 414 are closely arranged in a same area, which can reduce the moving distance of the sample adding device 72 between the locations of the devices mentioned above, thereby reducing the time of the liquid handling procedure and improving the working efficiency of the instrument. The waste box 79 is installed at a position far away from the pure water tank 78, the sample carrier 75, the microplate carrier 76, and the tip box carrier 77, thereby preventing waste liquid and discarded tips from contaminating the samples at the locations of the devices mentioned above.

[0045] Referring to FIGS. 16 and 17, the excitation timing device 8 receives a synchronization signal output by the ultraviolet-band laser device 11 and outputs two tunable pulses P1 and P2. P1 is a delayed extraction pulse, which is composed of T1+T2 timing sequence. T1 is pulse delayed extraction time, and T2 is delayed extraction pulse width. P2 is a delayed acquisition pulse, which is composed of T3+T4 timing sequence. T3 is the pulse delayed acquisition time, and T4 is the delayed acquisition pulse width.

[0046] Referring to FIG. 16, the excitation timing device 8 is composed of a voltage type conversion circuit A1, an excitation pulse identification circuit A2, a pulse shaping delay circuit A3, a sequential logic circuit A4, a storage circuit A5, and an interface circuit A6. The voltage type conversion circuit A1 outputs five different voltages to provide working power for the internal circuits of the excitation sequence device. These five different voltages respectively provide power to the excitation pulse identification circuit A2, the pulse shaping delay circuit A3, the sequential logic circuit A4, the storage circuit A5, and the interface circuit A6. The excitation pulse identification circuit A2 receives the synchronization signal output by the pulse laser device 11, identifies non-square wave pulses, shapes and delays the non-square wave pulses, and fed the pulses into the sequential logic circuit A4. The sequential logic circuit A4 reads set parameters of T1, T2, T3, and T4 pre-stored by the storage circuit A5 and according to the parameters, outputs two pulse signals of P1 and P2 based on the synchronization signal from the pulse laser device 11. The interface circuit A6 is responsible for the setting and storage of pulse time parameters

[0047] Referring to FIG. 17, the signal acquisition device 9 includes an ion signal interface B 1, a sampling pulse interface B2, and a data exchange interface B3. The ion signal interface B1 is configured to receive an analog voltage signal from the ion detector. Configuration parameters of ion acquisition are set by virtue of the data exchange interface B3. The sampling pulse interface B2 receives the delayed acquisition pulse P2 output by the excitation timing device A and then starts to acquire an ion signal, and then obtains the data of the original curve of the ion about the relationship between time and voltage.

[0048] Referring to FIG. 18, the main function of the high-voltage control device 10 is to provide a necessary high-voltage power supply and high-voltage timing sequence for the extraction, acceleration, flight, and detection of ions after the laser desorption ionization cocrystallization. The high-voltage control device C includes but is not limited to a high-voltage control enable HV-EN, a high-voltage trigger input C1, high-voltage inputs HV1-IN and HV2-IN, high-voltage outputs HV1-OUT and HV2-OUT, and a working power interface C2, as shown in FIG. 18. The HV1-IN is connected to a +10 kV to +50 kV high-voltage power supply 1, the HV2-IN is connected to a +3 kV to +10 kV high-voltage power supply 2, the HV1-OUT is connected to the accelerating electrode 23, and the HV2-OUT is connected to the extraction electrode 21.

[0049] When the HV-EN is invalid, the control function of the high-voltage control device 10 is disabled and the HV1-OUT and the HV2-OUT are disabled.

[0050] When the HV-EN is valid, the control function of the high-voltage control device 10 is valid, and the output of HV2-OUT is equal to the voltage of HV1-IN. After the high-voltage trigger input C1 receives the delayed extraction pulse P1 output by the excitation timing device A, the output voltage of HV2-OUT is a voltage difference between the high-voltage power supply 1 and the high-voltage power supply 2, because the voltage difference of the high-voltage power supplies cannot suddenly change. The high-voltage control timing sequence of the high-voltage control device 10 is shown in FIG. 18.

[0051] Referring to FIG. 19, the operation control device 11 includes but is not limited to an operation control unit D1, a data exchange interface D2, a data storage unit D3, a power management unit D4, an operation display device D5, and a working power supply D6. By control signals, the operation control device 11 is respectively connected to, including but not limited to, the laser device 51, the vacuum chamber 1, the exchange chamber 6, the vacuum generation device 2, the sample processing device 7, the excitation timing device 8, the signal acquisition device 9, and the high-voltage control device 10. The complete and orderly operation of the time-of-flight mass spectrometer is coordinated and controlled by the operation control device 11. The working sequence of the operation control device 11 in the time-of-flight mass spectrometer is shown in FIG. 19.

[0052] The above embodiments are illustrative of the present invention, not limitations of the invention. Any simple transformation of the present invention falls within the scope of the invention.

Claims

1. A time-of-flight mass spectrometer, **characterized by** comprising: a vacuum chamber (1), a vacuum generation device (2), an ion flight cavity (3), an ion source device (4), a laser excitation device (5), a chip exchange device (6), a sample processing device (7), an excitation timing device (8), a signal acquisition device (9), a high-voltage control device (10) and an operation control device (A), wherein the vacuum chamber (1), the vacuum generation device (2) and the ion flight cavity (3) are assembled into a vacuum system, the ion source device (4) is installed in the vacuum system, the laser excitation device (5) provides energy for ion excitation, and the excitation timing device (8), the high-voltage control device (10) and the ion source device (4) are electrically connected in sequence, and the signal acquisition device ((9) is electrically connected to the ion flight cavity (3); after the ion source device (4) generates ions, the excitation timing device (8) sends a control signal to the high-voltage control device (10), and the high-voltage control device (10) controls the ion source device (4) to guide the ions into the ion flight cavity (3); after receiving the ions, the ion flight cavity (3) outputs a signal to the signal acquisition device (9), and the signal acquisition device (9) processes the signal and store the signal in the operation control device (A); the chip exchange device (6) and the sample processing device (7) form a mass spectrometry pre-processing system; a liquid sample is first processed by the sample processing device (7) and then fed into the vacuum chamber (1) via the chip

exchange device (6); the vacuum chamber comprises a lower vacuum chamber base (11), an upper vacuum chamber cover plate (12), an ion interface (13), an XY movement assembly (14), a transfer window (15), a camera assembly (16), an illumination assembly (17), and a high-voltage connector (18), the upper vacuum chamber cover plate (12) is installed on the lower vacuum chamber base (11), the ion interface (13) is provided on the upper vacuum chamber cover plate (12), the ion source device (4) is installed at one end of the ion interface (13), and the ion flight cavity (3) is installed at the other end of the ion interface (13); the XY movement assembly (14) is installed in the lower vacuum chamber base (11), the transfer window (15) is provided on the lower vacuum chamber base (11), and the camera assembly (16), the illumination assembly (17), and the high-voltage connector (18) are installed on the upper vacuum chamber cover plate (12); the camera assembly (16) comprises a telecentric lens (161) and a CCD camera (162), and an axis of the telecentric lens (161) coincides with an axis of the CCD camera (162); the illumination assembly (17) comprises an LED lamp bead (171) and a focusing lens (172), and an axis of the LED lamp bead (171) coincides with an axis of the focusing lens (172); an angle between an axis of the camera assembly (16) and an axis of the ion interface (13) and an angle between an axis of the illumination assembly (17) and the axis of the ion interface (13) are equal and located in a same plane and the three axes intersect at one point defined as a convergence point; the convergence point is in an upper plane of a mass spectrometry chip (414); an upper surface of the mass spectrometry chip (414) is configured as a mirror surface and is perpendicular to the axis of the ion interface (13), so that parallel light emitted by the illumination assembly (17) is reflected into the camera assembly (17), but light reflected by other objects is not parallel to the axis of the camera assembly (16) and cannot be received by the camera assembly (16); the ion flight cavity (3) comprises a flight tube (31), an end cover (32), an ion detector (33) and an ion mesh assembly (34), the flight tube (31) is a hollow tube with annular surfaces at two ends, a length of the flight tube (31) is between 0.5 m and 1.5 m, one end of the flight tube (31) is installed on the ion interface (13) of the vacuum chamber (1), the other end of the flight tube (31) is provided with an end cover (32), and the ion detector (33) and the ion mesh assembly (34) are both installed on the end cover (32); the vacuum chamber (1), the flight tube (31), the end cover (32), and the ion mesh assembly (34) are electrically connected and have a same ground voltage; the ion source device (4) comprises an extraction electrode (41), an accelerating electrode (42), a focusing ring (43), and a fixed frame (44), the focusing ring (43) is installed in the fixed frame (44), and the extraction electrode (41) and the accelerating electrode (42) are installed on one side of the fixed frame (44); the extraction electrode comprises an electrode base plate (411), adjustment threads (412), an electrode plate (413) and a mass spectrometry chip (414), the electrode base plate (411) is rectangular, three adjustment threads (412) distributed in an isosceles triangle are installed in a groove of the electrode base plate (411), the electrode plate (413) is placed on the adjustment threads (412) in the groove; there is also another groove in the center of the electrode plate (413), the mass spectrometry chip (414) is placed in the groove of the electrode plate (413), and an upper plane of the mass spectrometry chip (414) is flush with an upper plane of the electrode plate (413); the accelerating electrode (42) comprises an upper electrode (421), an upper ion mesh (422), an insulating mounting ring (423), a lower ion mesh (424), and a lower electrode (425), the upper electrode (421) is configured as a ring with a hole in the center, the upper ion mesh (422) is fixed on the upper electrode (421), the lower electrode (425) is also a ring with a hole in the center, the lower ion mesh (424) is fixed on the lower electrode (425), the insulating mounting ring (423) has a hole in the center and two mounting grooves, and the upper electrode (421) and the lower electrode (425) are respectively fixed in the two mounting grooves of the insulating mounting ring (423); the focusing ring (43) comprises an upper ground ring (431), a high-voltage ring (432), a lower ground ring (433) and an insulating support (434), the upper ground ring (431), the high-voltage ring (432) and the lower ground ring (433) are all installed in the insulating support (434), and axes of the upper ground ring (431), the high-voltage ring (432), the lower ground ring (433) and the insulating support (434) coincide with each other; the chip exchange device (6) comprises an exchange chamber cover (61), a driving device (62), a heating device (63), and an exchange solenoid valve device (64), the exchange chamber cover (61) is installed on the driving device (62) and driven by the driving device (62) to move forward and backward, and the heating device (63) and the exchange chamber cover (61) are linked with the driving device (62); when the exchange chamber cover (61) is moved toward the lower vacuum chamber base (11), the heating device (62) and the exchange chamber cover (61) are synchronously lowered to a bottom of the exchange chamber cover (61); the sample processing device (7) comprises a mobile platform (71), a sample adding device (72), a liquid pump (73), an image recognition device (74), a sample carrier (75), a microplate carrier (76), a tip box carrier (77), a pure water tank (78), and a waste box (79); the mobile platform (71) is configured to be moved independently in X-axis and Y-axis directions; the sample adding device (72) and the image recognition device (74) are installed on the mobile platform (71); the sample adding device (72) and the image recognition device (74) is configured to be moved in a Z-axis direction; the sample adding device (72) is connected with the liquid pump (73); the sample carrier (75) and the microplate carrier (76) are configured for carrying a biological reagent or a sample; the liquid pump(75) and the pure water tank (78) are connected by a one-way valve and a pipeline, and the waste box (79) is provided below the sample adding device (72); and the liquid pump (73) is a quantitative syringe pump.

2. The time-of-flight mass spectrometer according to claim 1, **characterized in that**, the vacuum generation device (2) comprises a secondary vacuum pump (21), a primary vacuum pump (22), a vacuum gauge (23) and a solenoid valve assembly (24), wherein the secondary vacuum pump (21) is installed on the lower vacuum chamber base (11), and the secondary vacuum pump (21) is a turbo molecular pump; and the solenoid valve assembly (24) is provided between the secondary vacuum pump (21) and the primary vacuum pump (22), and the vacuum gauge (23) is installed in the vacuum chamber (1).

3. The time-of-flight mass spectrometer according to claim 1, **characterized in that**, the laser excitation device (5) comprises a laser device (51), a first reflector assembly (52), a second reflector assembly (53), and a focusing lens assembly (54), the laser device (51) is an ultraviolet-band laser device, the first reflector assembly (51) and the second reflector assembly (52) each comprise a laser reflector and an adjustment base, and a laser beam is emitted from the laser device and reflected by the first reflector and the second reflector, and then enters the focusing lens assembly (54).

4. The time-of-flight mass spectrometer according to claim 1, **characterized in that**, the exchange solenoid valve device (64) comprises a solenoid valve body (641), an air solenoid valve (642) and a vacuum solenoid valve (643), the air solenoid valve (642) and the vacuum solenoid valve (643) are installed in the solenoid valve body (641), the solenoid valve body (641) is provided with an exchange air passage (644), an air passage (645) and a vacuum passage (646), two upper ports of the exchange air passage (644) are respectively connected with air inlets of the air solenoid valve (642) and the vacuum solenoid valve (643), an air outlet of the air solenoid valve (642) is connected with the air passage (645), and an air outlet of the vacuum solenoid valve is connected with the vacuum passage (646) of the solenoid valve body (641).

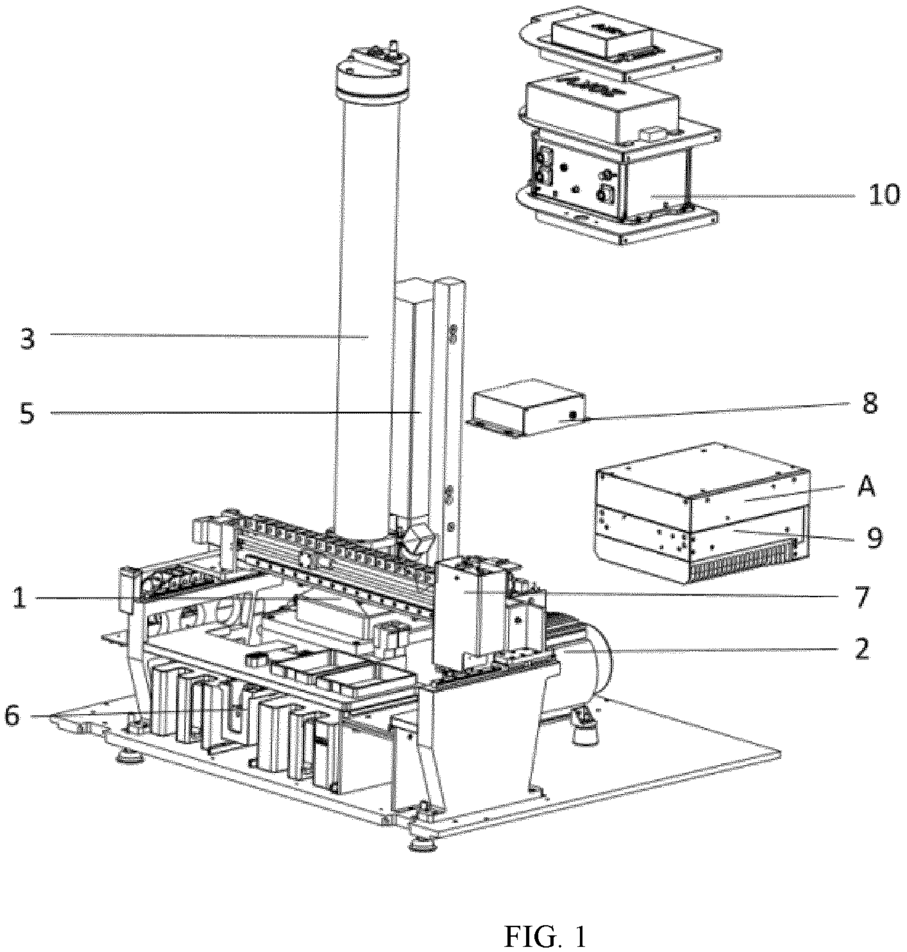

FIG. 1

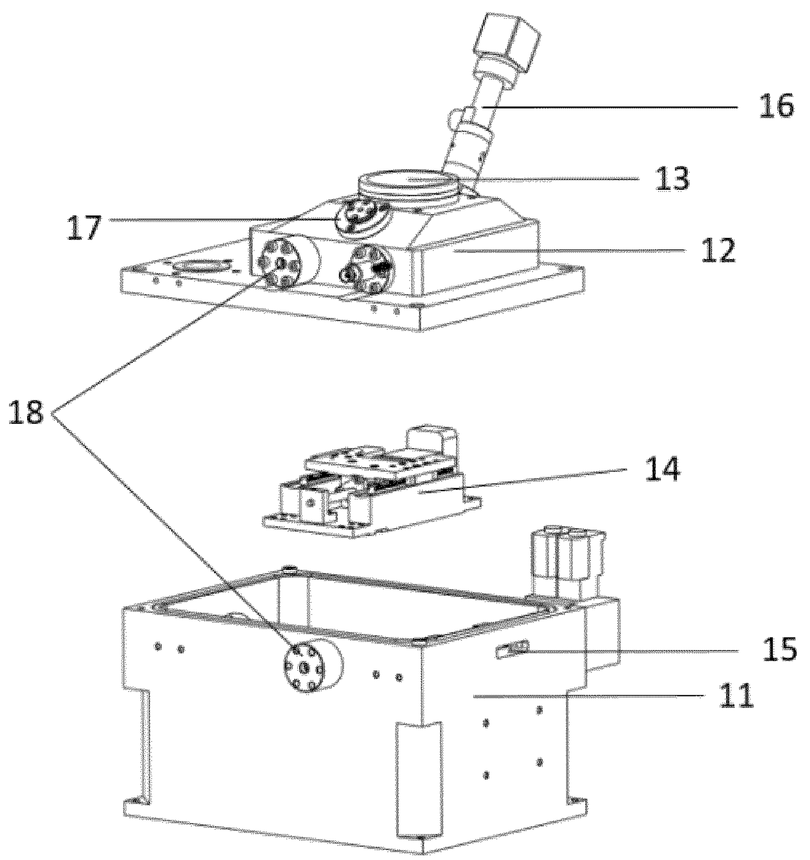

FIG. 2

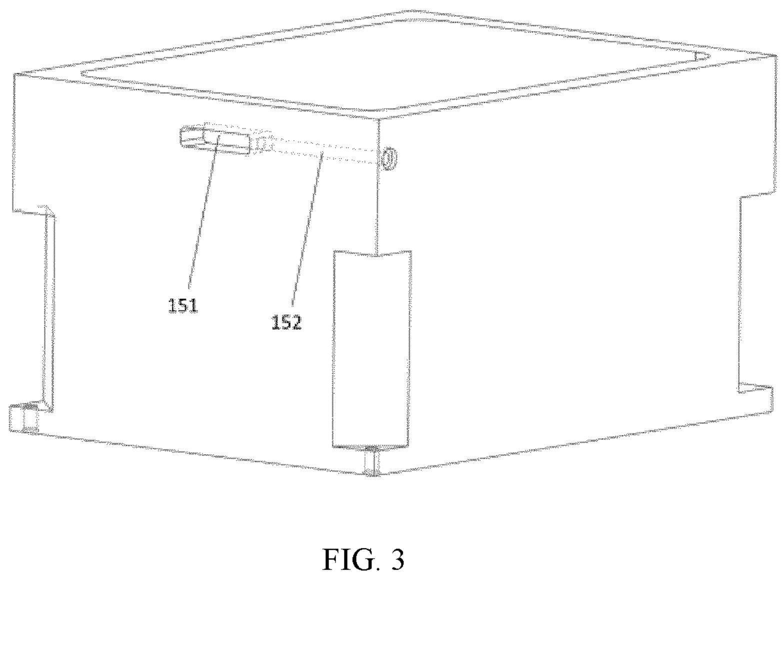

FIG. 3

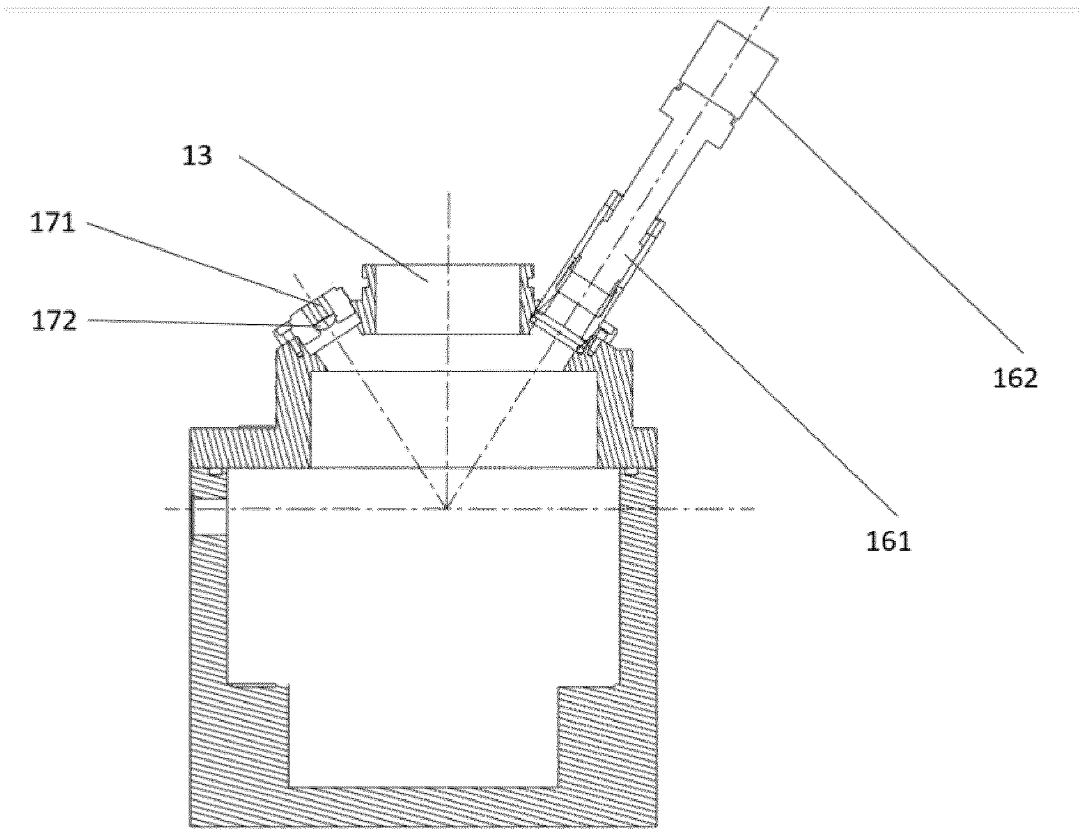

FIG. 4

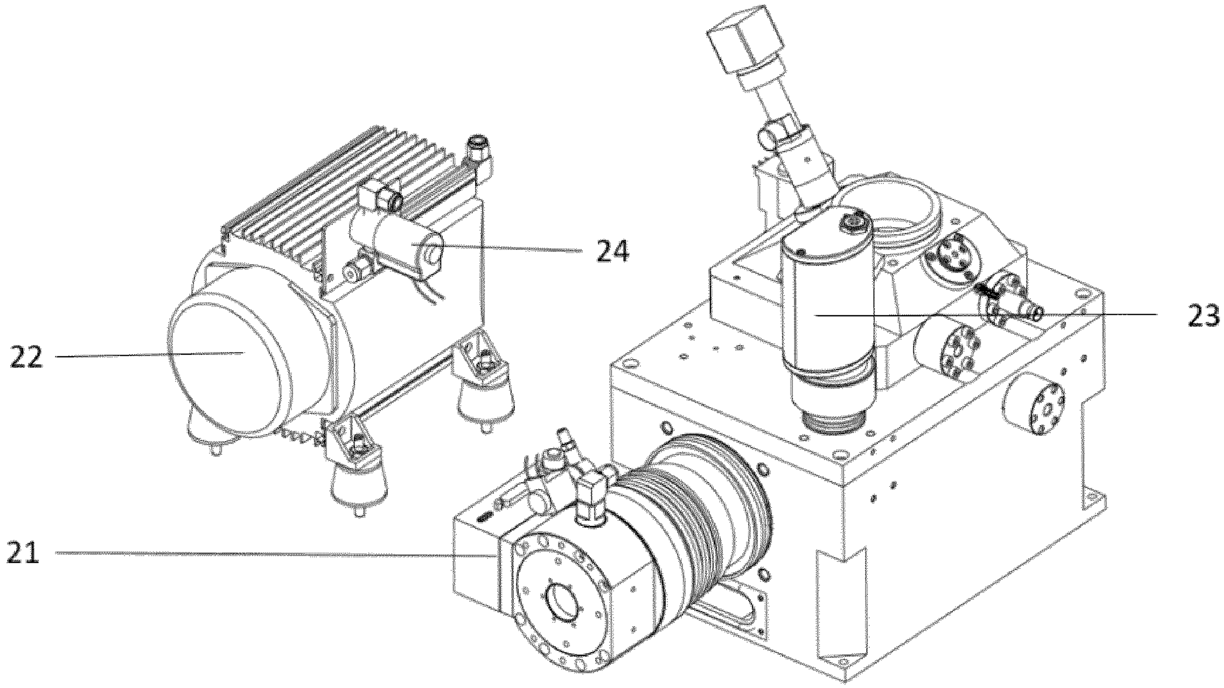

FIG. 5

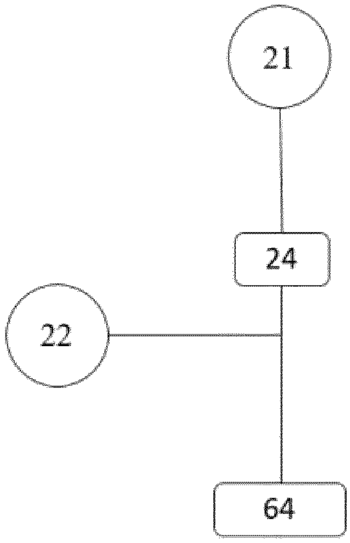

FIG. 6

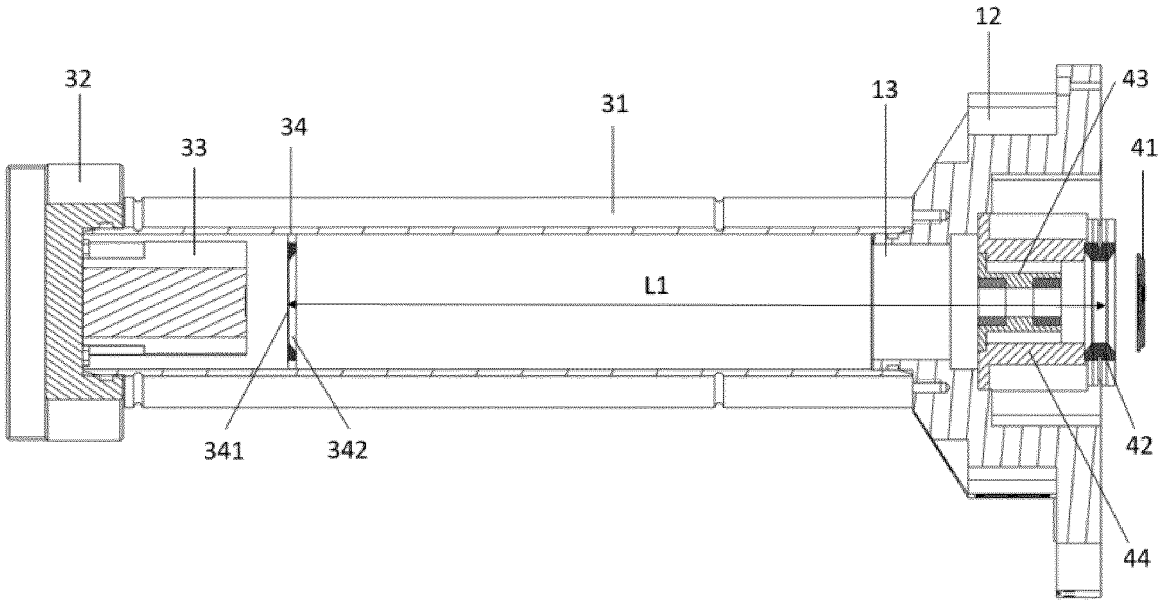

FIG. 7

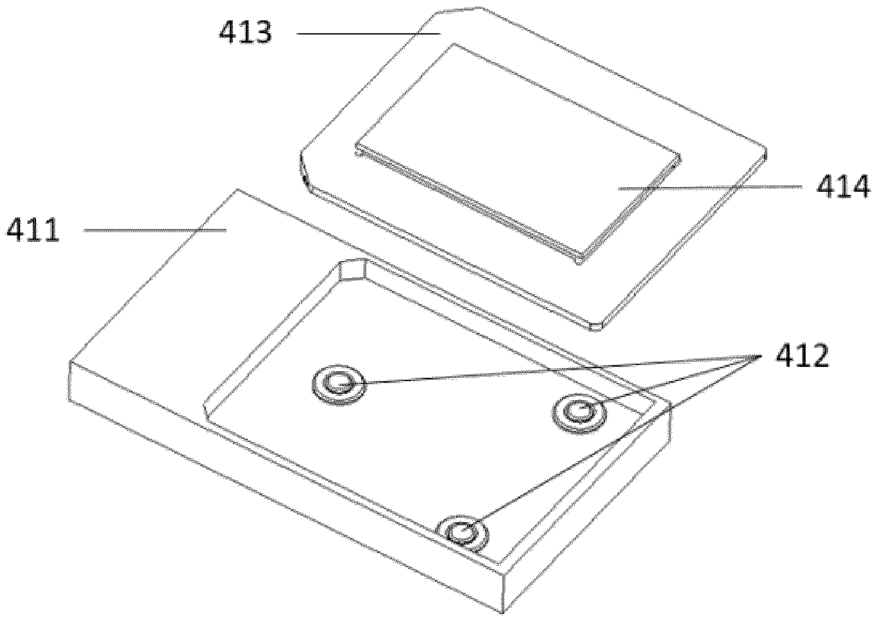

FIG. 8

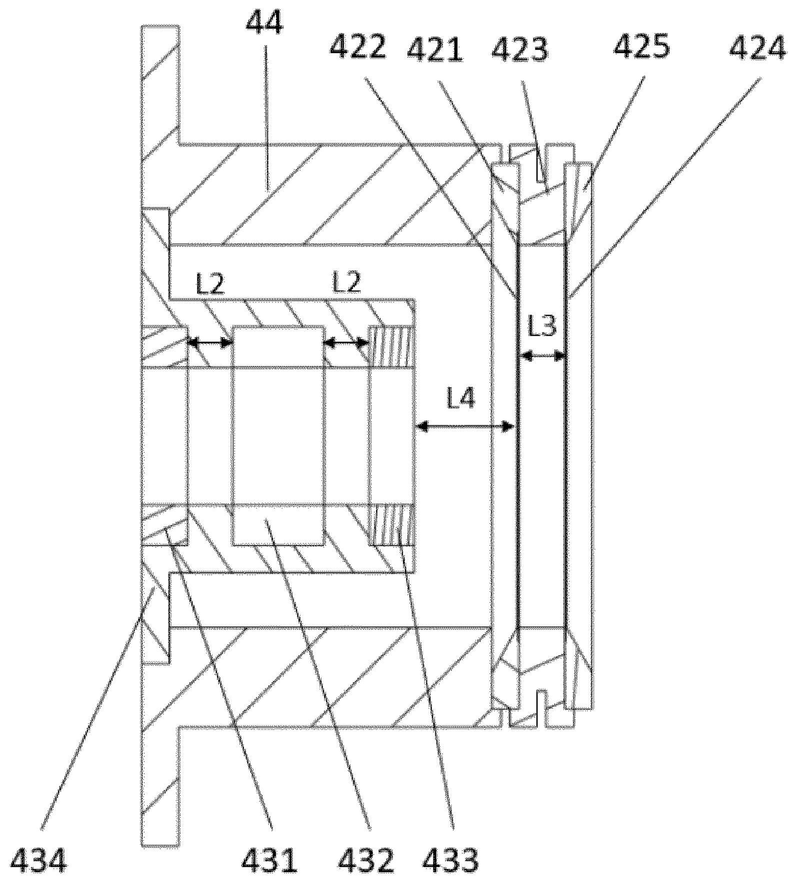

FIG. 9

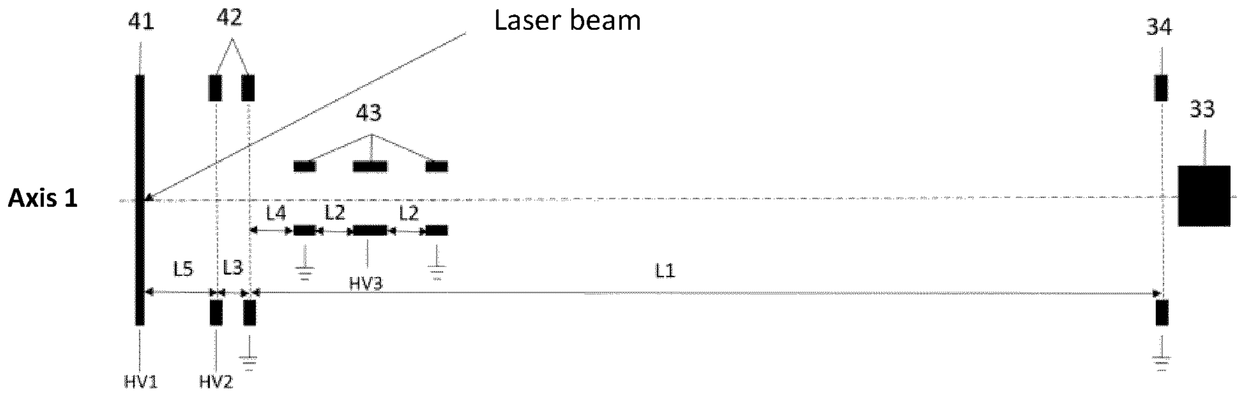
41
42
Laser beam
34
43
33
Axis 1
L4
L2
L2
L5
L3
HV3
L1
HV1
HV2

FIG. 10

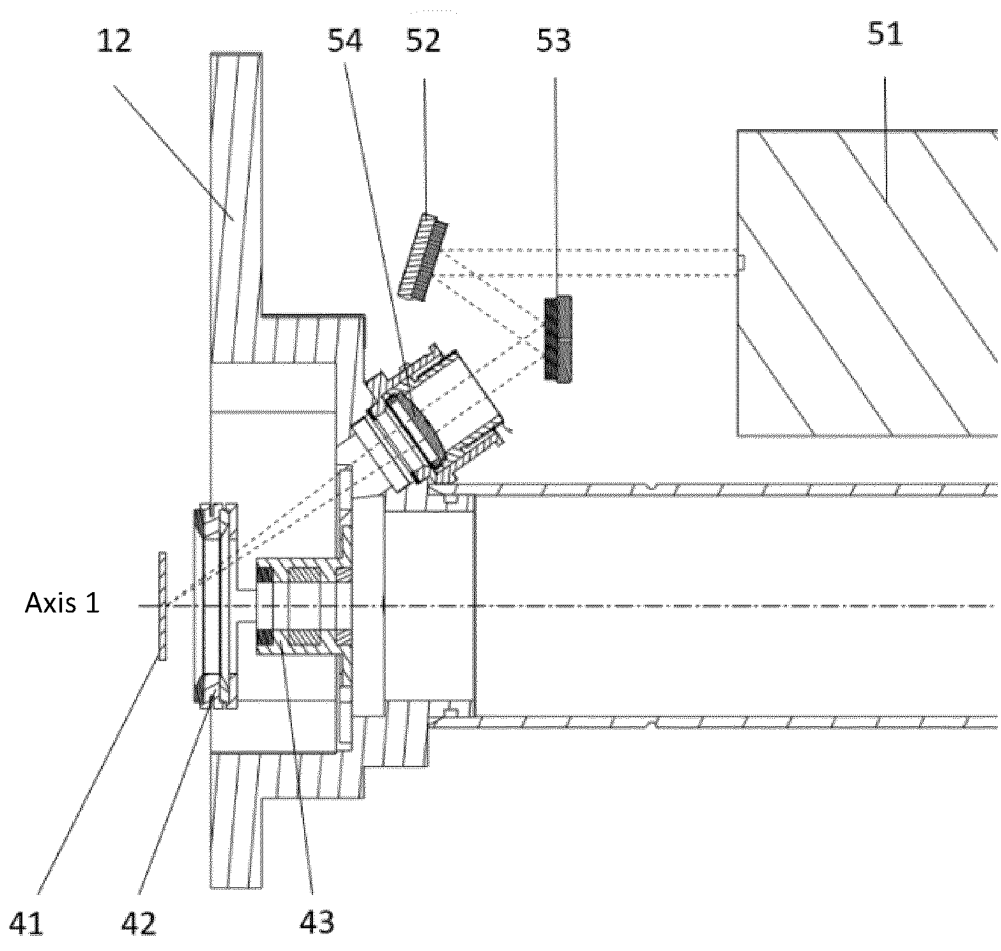
12
54
52
53
51
Axis 1
41
42
43

FIG. 11

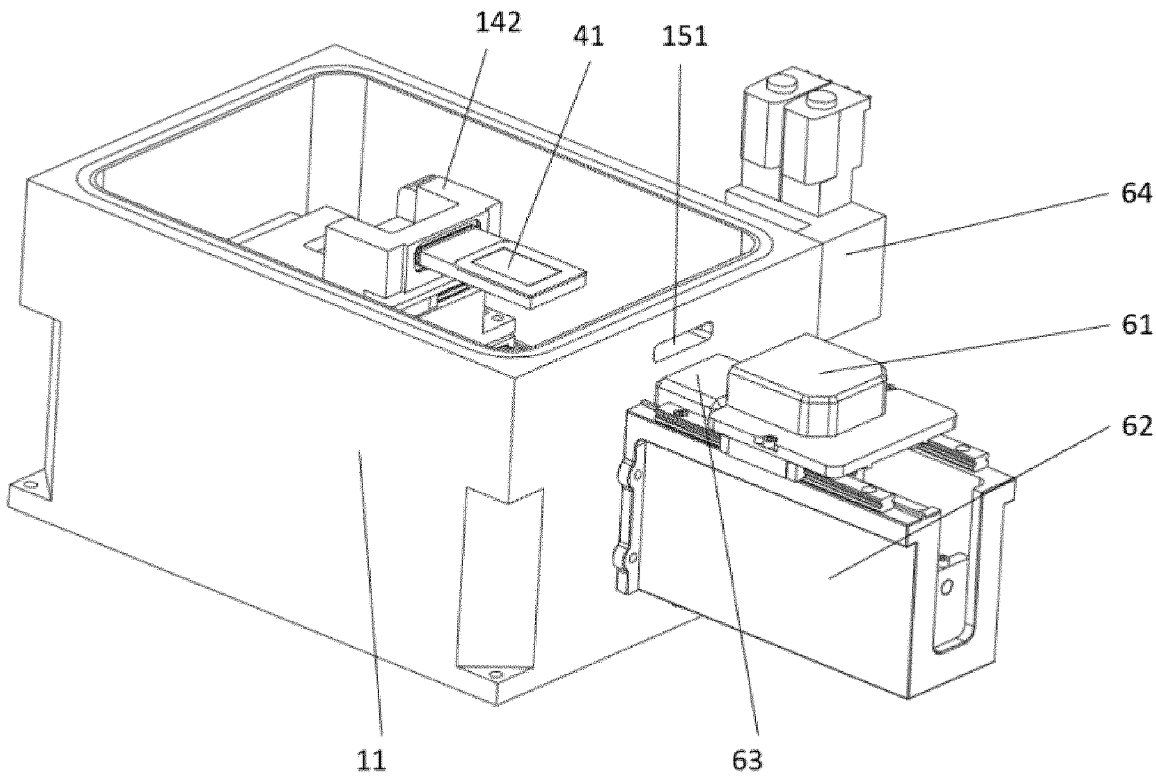

FIG. 12

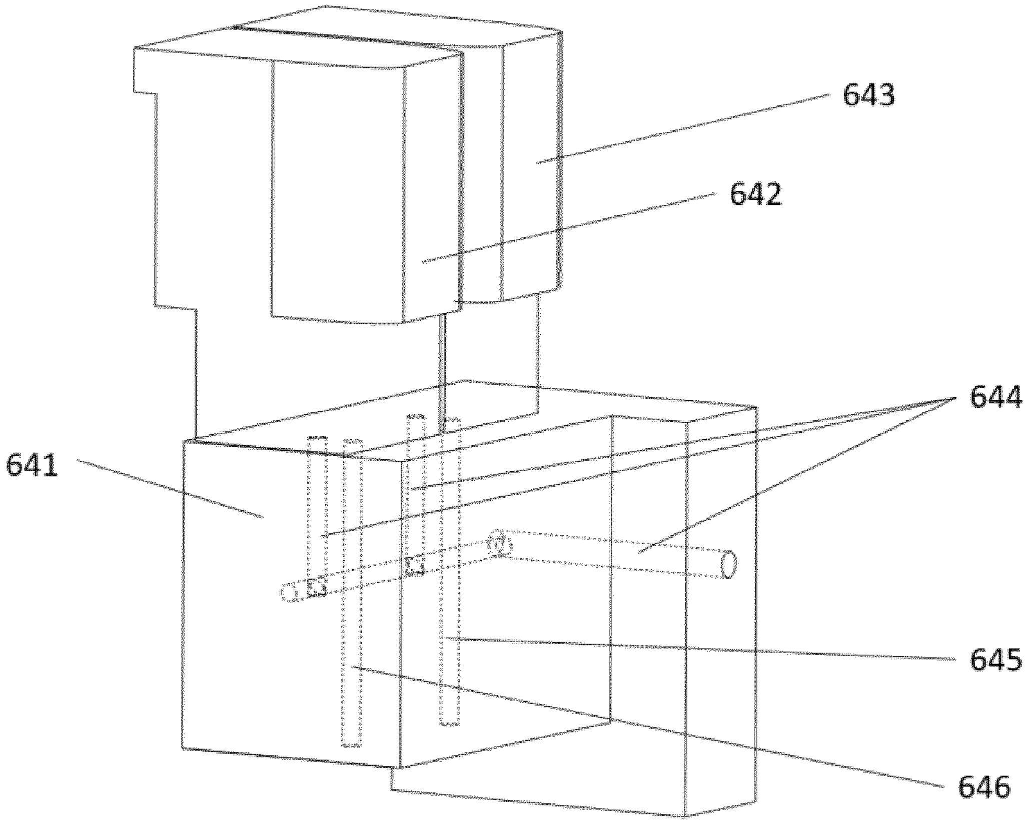
643
642
644
641
645
646

FIG. 13

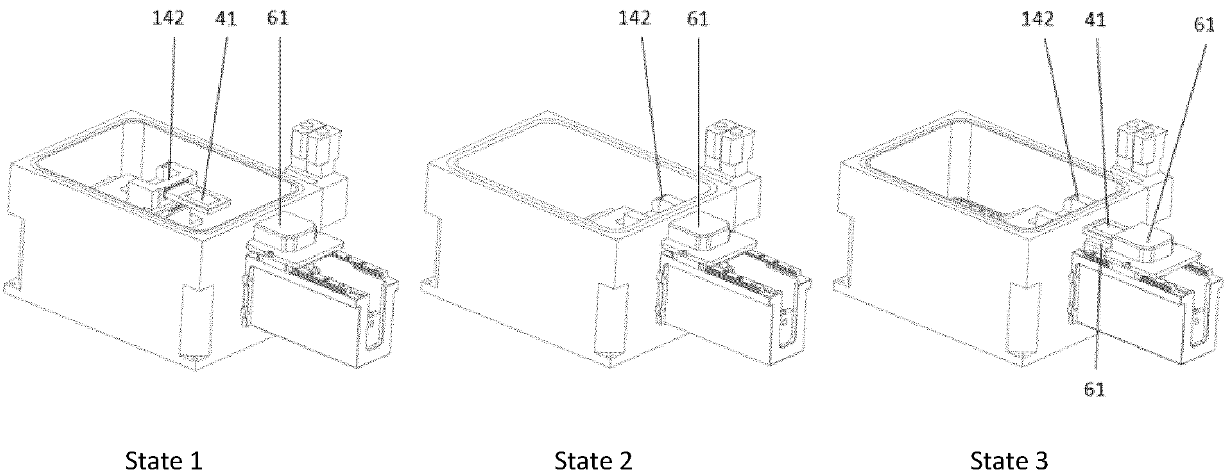
142
41
61
142
61
142
41
61
61
State 1
State 2
State 3

FIG. 14

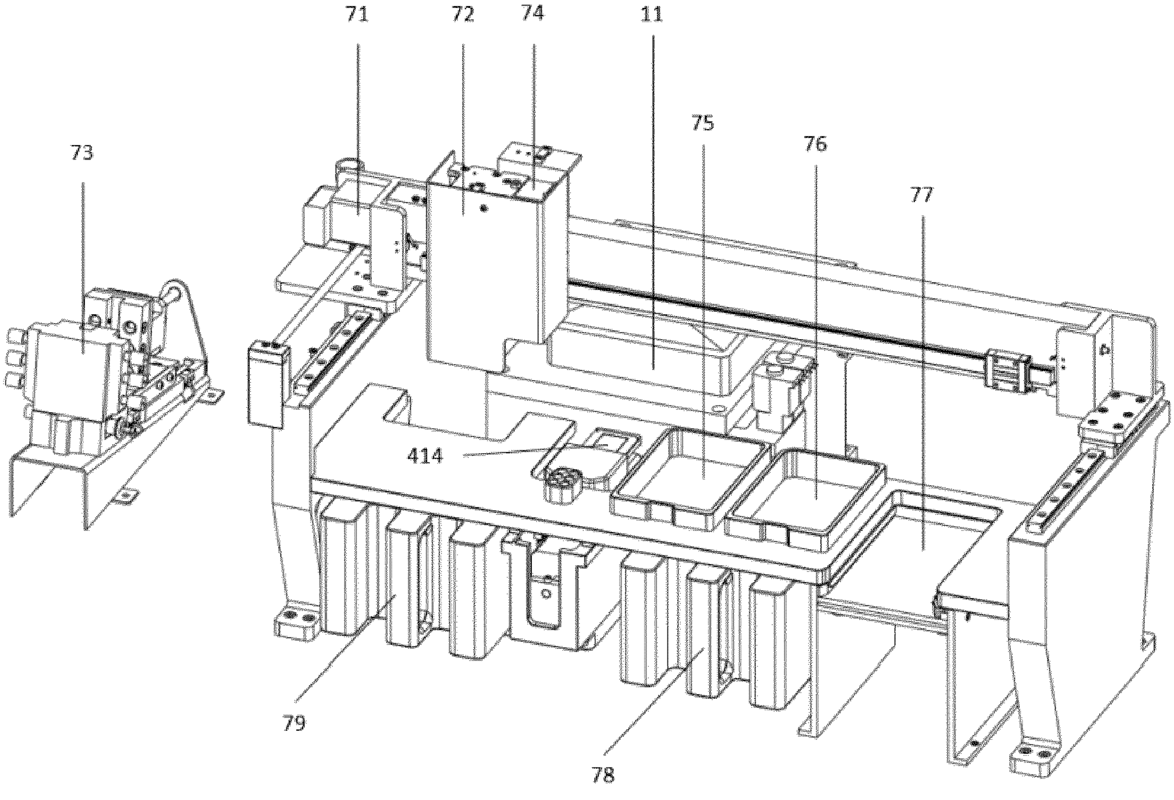

FIG. 15

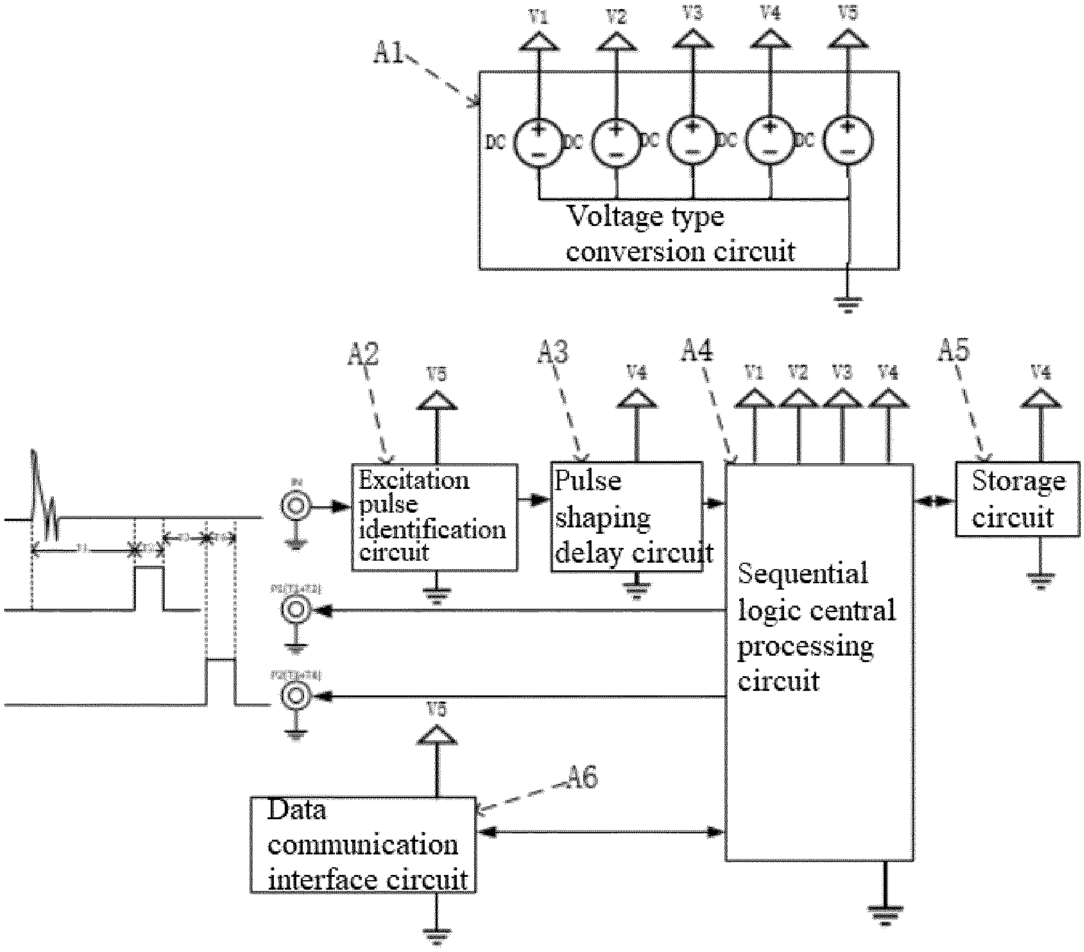
A1
V1
V2
V3
V4
V5
DC
Voltage type conversion circuit
A2
A3
A4
A5
Excitation pulse identification circuit
Pulse shaping delay circuit
Sequential logic central processing circuit
Storage circuit
Data communication interface circuit
A6

FIG. 16

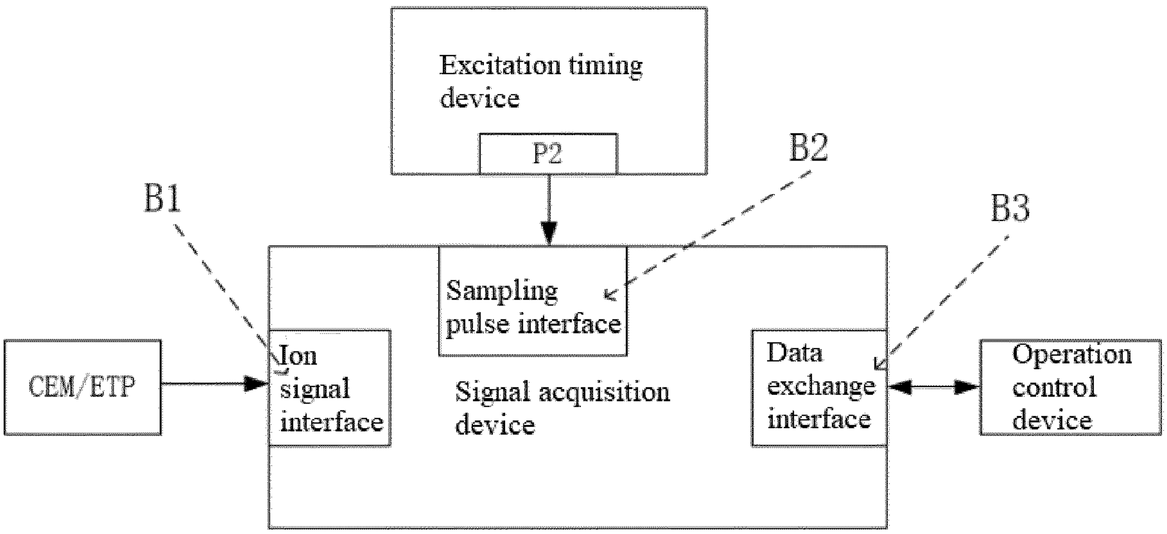
Excitation timing device
P2
B1
B2
B3
Sampling pulse interface
CEM/ETP
Ion signal interface
Signal acquisition device
Data exchange interface
Operation control device

FIG. 17

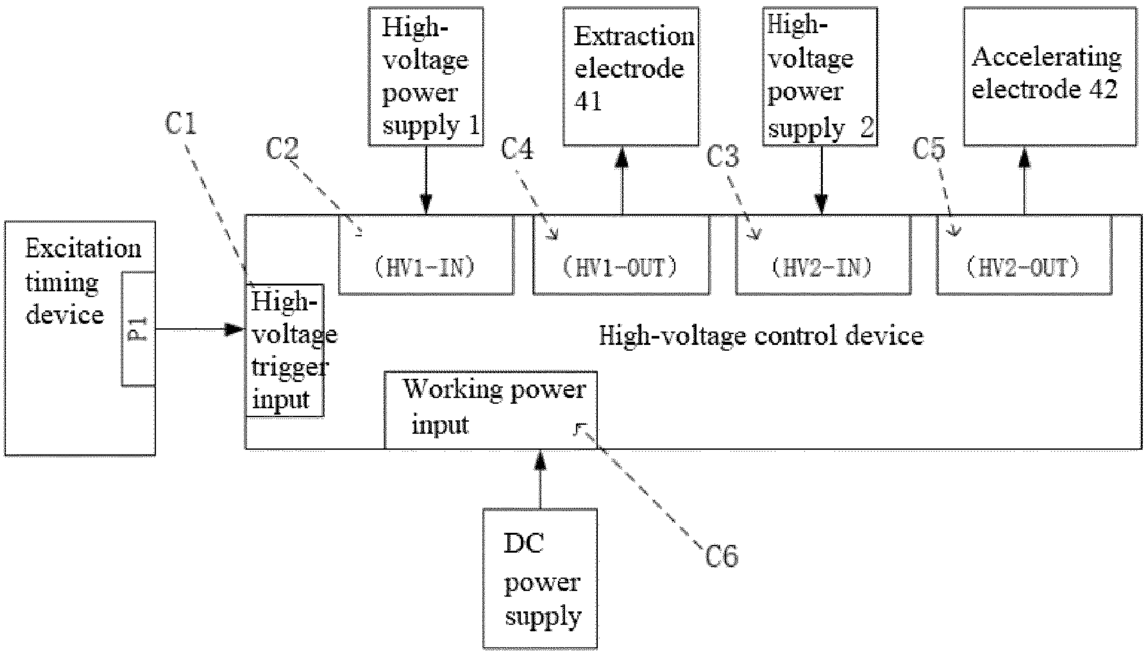
High-voltage power supply 1
Extraction electrode 41
High-voltage power supply 2
Accelerating electrode 42
C1
C2
C4
C3
C5
Excitation timing device
P1
High-voltage trigger input
(HV1-IN)
(HV1-OUT)
(HV2-IN)
(HV2-OUT)
High-voltage control device
Working power input
DC power supply
C6

FIG. 18

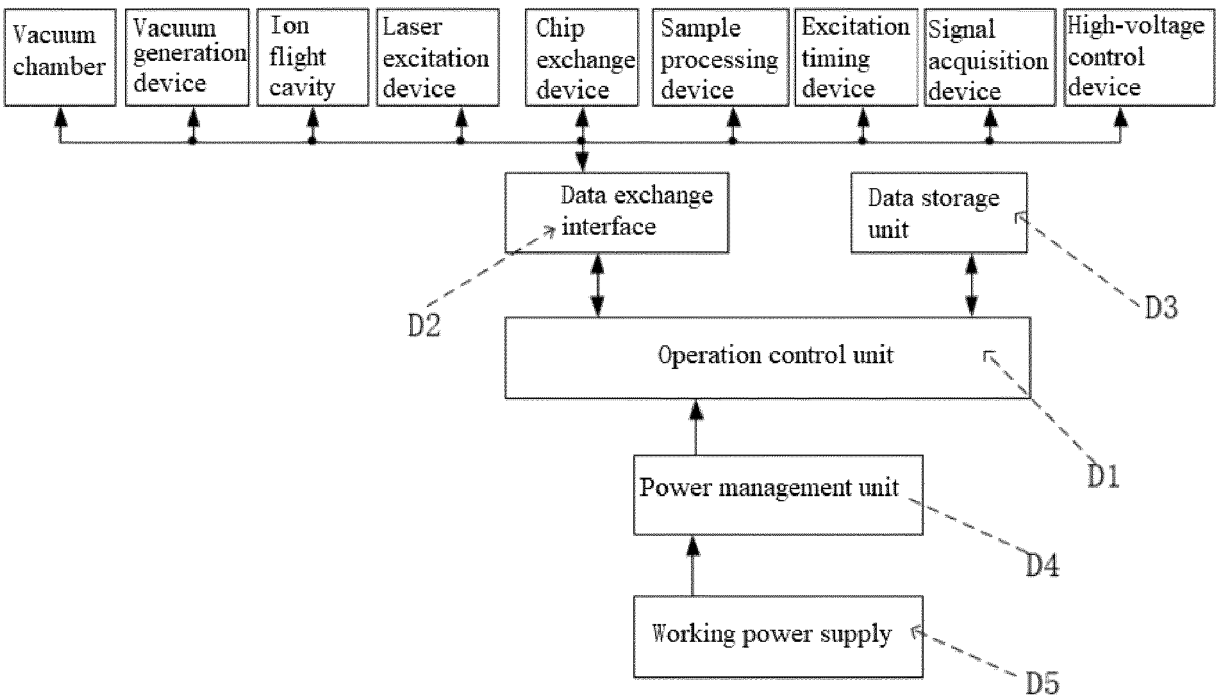
Vacuum chamber
Vacuum generation device
Ion flight cavity
Laser excitation device
Chip exchange device
Sample processing device
Excitation timing device
Signal acquisition device
High-voltage control device
Data exchange interface
Data storage unit
D2
D3
Operation control unit
D1
Power management unit
D4
Working power supply
D5

FIG. 19

TRANSLATION

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2023/122752

A. CLASSIFICATION OF SUBJECT MATTER

H01J49/04(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC:H01J

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

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

CNTXT, ENTXTC, WPABSC, DWPI, CJFD: 飞行时间, 质谱仪, 离子, 交换, 芯片, 点样, 激光, 图像, 摄像, 加热, 离子网, 栅网, 成像, 加速, 基因, 核酸; spectrometer, flight, vacuum, chip, chamber, heat???, laser, imag+, gene, sample s process+, accelerat+, exchange, ion

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	CN 116153761 A (ZHEJIANG DIGENA DIAGNOSTIC TECHNOLOGY CO., LTD.) 23 May 2023 (2023-05-23) description, paragraphs [0019]-[0051], and figures 1-19	1-4
A	CN 113745091 A (SHENZHEN TAILAI BIOSCIENCES CO., LTD. et al.) 03 December 2021 (2021-12-03) description, paragraphs [0002]-[0021] and [0028]-[0049], and figures 1-3	1-4
A	CN 211238162 U (XIAMEN HANKEZHEN APPARATUS CO., LTD.) 11 August 2020 (2020-08-11) description, paragraphs [0027]-[0036], and figures 1-4	1-4
A	CN 102492603 A (MA QINGWEI) 13 June 2012 (2012-06-13) description, paragraphs [0021]-[0030], and figures 1-10	1-4
A	CN 105304457 A (INSTITUTE OF NUCLEAR PHYSICS & CHEMISTRY, CHINA ACADEMY OF ENGINEERING PHYSICS) 03 February 2016 (2016-02-03) entire document	1-4

☑ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 December 2023	**19 December 2023**

Name and mailing address of the ISA/CN	Authorized officer
China National Intellectual Property Administration (ISA/CN) **China No. 6, Xitucheng Road, Jimenqiao, Haidian District, Beijing 100088**	Telephone No.

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INTERNATIONAL SEARCH REPORT

International application No. **PCT/CN2023/122752**

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN 107658205 A (ZHUHAI MEIHUA BIO-MEDICAL TECHNOLOGY CO., LTD.) 02 February 2018 (2018-02-02) entire document	1-4
A	CN 112103170 A (ZHUHAI MEIHUA BIO-MEDICAL TECHNOLOGY CO., LTD.) 18 December 2020 (2020-12-18) entire document	1-4
A	JP 2005025946 A (MITSUBISHI HEAVY INDUSTRIES, LTD.) 27 January 2005 (2005-01-27) entire document	1-4

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TRANSLATION

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2023/122752

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
CN	116153761	A	23 May 2023	None			
CN	113745091	A	03 December 2021	None			
CN	211238162	U	11 August 2020	None			
CN	102492603	A	13 June 2012	CN	102492603	B	01 May 2013
CN	105304457	A	03 February 2016	CN	105304457	B	29 March 2017
CN	107658205	A	02 February 2018	None			
CN	112103170	A	18 December 2020	None			
JP	2005025946	A	27 January 2005	None			

Form PCT/ISA/210 (patent family annex) (July 2022)

REFERENCES CITED IN THE DESCRIPTION

Patent documents cited in the description

- CN 101601119 B **[0002]**