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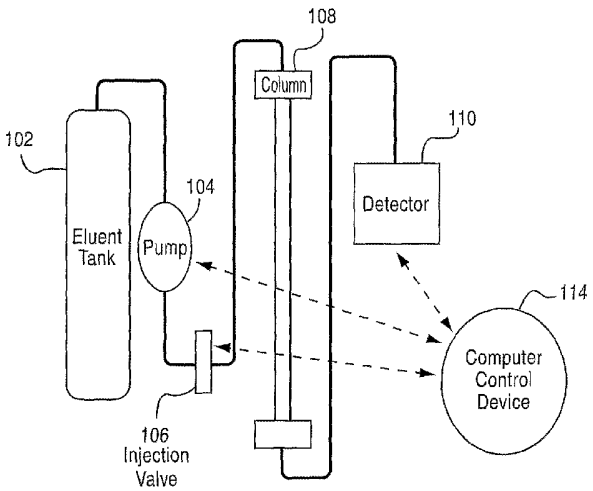
(54) **Title:** AUTOMATED EVALUATION OF TARGET SAMPLES IN A HIGH PERFORMANCE ANALYSIS SYSTEM



(57) **Abstract:** A high performance analysis system for automated evaluation of target samples includes an automated liquid handler having one or more probes for aspirating and dispensing one or more target samples. The system also includes multi-port valve stations each having a plurality of ports, at least one of the ports mating in a direct manner with a corresponding probe to receive one of the target samples dispensed from the probe. A detector is included for detecting the target samples in a mobile phase of the system.

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AUTOMATED EVALUATION OF TARGET SAMPLES IN A HIGH PERFORMANCE ANALYSIS SYSTEM

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BACKGROUND OF THE INVENTION

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FIELD OF THE INVENTION

The present invention relates generally to the field of high throughput sample analysis. In particular, the invention relates to the application of high performance liquid chromatography coupled with novel sample introduction techniques.

RELATED ART

High performance analysis system, such as High Performance Liquid Chromatography (HPLC), is generally directed to a separation and analysis technique. Substances or chemical constituents under analysis, called analytes, are separated and detected based on their relative affinities for chemical phases. The components of a sample mixture are carried through a solid stationary phase by the flow of a liquid mobile phase, which is pumped under specifically controlled conditions.

HPLC applications are wide ranging, from industrial preparation to trace level detection. This is due to the ability of HPLC to separate a tremendous variety of analytes, including biomaterials, organics and inorganics with varying molecular properties. For instance, separation can be accomplished for varying degrees of analyte acidity, polarity, ionization, and hydrophobicity. Advanced HPLC systems

bear heightened sensitivity, enabling scientists to detect mutations in DNA fragments and separate isotopes.

HPLC is currently used for performing the greater part of environmental and biomedical analyses. In particular, HPLC has become the separation and analysis technique of choice for the pharmaceutical industry, where it is used in every phase of drug discovery and development, including quality control. Important parameters for first-rate analysis are system sensitivity, resolution, accuracy, precision, reproducibility, and analysis time/method/robustness.

In an HPLC system, a pump delivers the eluent, or mobile phase, through an injection valve. The analyte containing sample is injected into the valve. The injection valve controls the dissemination of the mobile phase and analyte onto the column.

Separation occurs within the stationary phase in the column of the HPLC. The column is packed with such materials as a bed of finely divided particles, to retain and differentially retard the migration of analytes through it. This permits the individual analytes that comprise a mixture to be gradually separated from each other. The components exit the column at predictable time differentials during an HPLC run, and the elution is detected by the HPLC detector.

Notably, detection techniques with extensively available sensitivity and specificity have contributed to the widespread employment of HPLC. Such detection techniques include refractive index, ultraviolet (fixed wavelength, variable wavelength, full spectrum), fluorescence, radiochemical, conductivity, mass spectrometric (LC/MS), and evaporative light scattering techniques.

There are also techniques which include automatic, or microprocessor based control of injection of the analyte into the valve. These devices, called autosamplers, can sufficiently speed up and render an efficient chromatography process.

Unfortunately, commercially available autosamplers are generally produced to handle a single analyte sample at a time. Although versatile, these autosamplers lack the speed and capacity to handle the workflow in a high throughput environment. Many of today's HPLC systems are configured in parallel to require the introduction of multiple samples in a given time interval.

Autosamplers configured to handle multiple analyte samples offer the ability to introduce multiple samples in a given time interval at the expense of system

versatility. Such autosamplers are difficult or impossible to individually adjust for such parameters as probe washing (to prevent contamination between samples), minimum sample volume, valve speed, sample plate density, displacement parameters for each probe, and sample capacity. The foregoing autosamplers also cannot be individually or independently adjusted to select multiple analyte samples.

There are additional constraints in using existing autosamplers as well. In pharmaceutical applications, a pharmaceutical developer or manufacturer performs numerous high-throughput screening biological assays to determine whether small molecules have an established affect upon pathogens, proteins or gene sequences. Such a positive effect is known as a "hitting a target" or simply as a "hit." These high throughput screening analyses are typically performed by biological assay robots, colloquially called "screening systems."

The pharmaceutical researcher generally needs to determine whether the target samples deemed to be "hit" by small molecules are pure samples, or else the results of the "hit" can be meaningless or misleading. For this reason, researchers use HPLC based systems, for example HPLC in combination with mass spectrometry detection (LC/MS), to determine the integrity of the "hit".

Speed is an essential element of the hit-pick and integrity analysis dynamics. With technological and financial constraints, pharmaceutical researchers are able to process in the hundreds of thousands to millions of samples on a given day, but can only process a mere fraction of the hits for further analysis. This inefficiency renders a bottleneck in the drug discovery and development system.

Researchers have used autosamplers for sample injection to streamline the system. However, as noted commercially available autosamplers lack the ability to handle multiple samples and require difficult or impossible adjustments for realizable implementation. Moreover, existing autosamplers do not replace the actual human element bottleneck, which is the requirement that a person transmit a plate (containing hundreds of wells, each bearing a sample) from the hit-picker robot to the HPLC analysis system. What is also required is the ability to streamline sample injection and detection in a way that integrates with other controller based systems, such as the hit-picker robot in the aforementioned example.

SUMMARY OF THE INVENTION

In a number of embodiments, the present invention discloses a high performance analysis system for automated evaluation of target samples. The system includes an automated liquid handler, one or more multi-port valve stations, and a detector. The automated liquid handler has one or more probes for aspirating and dispensing one or more target samples. The multi-port valve stations each have a plurality of ports. At least one of the ports mates in a direct manner with a corresponding probe to receive one of the target samples dispensed from the probe. The detector detects the target samples in a mobile phase of the system.

The liquid handler includes, in an embodiment, a support arm by which the probes are mounted, with each of the probes being freely movable in three dimensional space. Each of the probes can have a tip portion with a first diameter and a holding portion with a second diameter, with the first diameter being smaller than the second diameter. In one example, the tip portion of the probe is designed to have a fixed length (L) and a fixed diameter (D) in a proportion to a port.

In one embodiment, each valve station can include: at least two ports connected by one or more tubes for holding one of the target samples; one port as an inlet port for receiving a mobile fluid; one port as a first outlet port for transporting the aforementioned target sample via mobile fluid; and one port as a second outlet port for overflow control of the valve station.

In another embodiment, each valve station can include: an embedded valve of a fixed volume for holding the target samples; one port as an inlet port for receiving a mobile fluid; one port as a first outlet port for transporting the aforementioned target sample via mobile fluid; and one port as a second outlet port for overflow control of the valve station.

The system is designed in an embodiment so that a portion of the probe descends directly into a port during the dispensing step. The system can also be a parallel system comprising at least two or more of the aforementioned valve stations wherein the probes synchronously or serially mate with the valve stations. Here, during the aspirating and dispensing steps the probes can function independently of one another.

In one embodiment, the system is designed to include a robot processor and a liquid handling processor. The robot processor retrieves identification information relating to one or more plates and one or more wells each located within a plate, where the target sample is aspirated from one of the wells. The liquid handling processor communicates with the robot processor to determine the identity of a well within the plate from which the target sample has been aspirated, and controls dispensing of the target sample from the well.

In a number of embodiments, the present invention discloses a method for performing high performance analysis for automated evaluation of target samples. The method includes aspirating and dispensing target samples via probes of an automated liquid handler. A corresponding probe of a multi-port valve station is mated in a direct manner to receive one of the target samples dispensed from the probe. The target samples are detected in a mobile phase of the system.

Each of the probes is freely movable in three dimensional space in an embodiment. The probes can be produced such that the diameter of a tip portion thereof is smaller than the diameter of a holding portion thereof. In one example, a tip portion of the probe is produced to have a fixed length (L) and a fixed diameter (D) in a proportion to a port.

In one embodiment, the function of each valve station includes: holding one of the target samples via one or more tubes connected between at least two ports thereof; receiving a mobile fluid via an inlet port; transporting the target sample via mobile fluid via an outlet port; and controlling overflow of the valve station via an outlet port.

In another embodiment, the function of each valve station includes: holding a target sample via an embedded valve of a fixed volume; receiving a mobile fluid via an inlet port; transporting the target sample via mobile fluid via an outlet port; and controlling overflow of the valve station via an outlet port.

The method includes, in an embodiment, descending directly into a port a portion of a probe during the dispensing step. The method can include using a parallel system having additional valve stations wherein the probes synchronously or serially mate with the valve stations. Here, during the dispensing step the probes can function independently of one another.

In one embodiment, the system is designed to include two additional steps. In the first step, identification information is retrieved relating to one or more plates and one or more wells each located within a plate, where the target sample is aspirated from one of the wells. In the second step, the identity of a well within the plate from which the target sample has been aspirated is determined, and dispensing of the target sample from the well is controlled.

Further features and advantages of the invention, as well as the structure and operation of various embodiments of the invention, are described in detail below with reference to the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other features and advantages of the invention will be apparent from the following, more particular description of a preferred embodiment of the invention, as illustrated in the accompanying drawings wherein like reference numbers generally indicate identical, functionally similar, and/or structurally similar elements. The left most digits in the corresponding reference number indicate the drawing in which an element first appears.

FIG. 1 is a block diagram illustrating an exemplary analysis system;

FIGS. 2A and 2B are schematic representations illustrating an exemplary injection valve;

FIGS. 2C and 2D are schematic representations illustrating another exemplary injection valve;

FIG. 3 illustrates an implementation of valve assemblies mounted on a robot;

FIG. 4 illustrates an implementation of probes (syringes) mounted on a robotic manipulator arm;

FIG. 5 illustrates an implementation of valve assemblies and probes mounted on a robotic manipulator arm;

FIG. 6 is a schematic illustration of a complete environment implementing the present invention; and

FIG. 7 illustrates an exemplary embodiment of a computer control device used in the present invention.

DETAILED DESCRIPTION OF AN EXEMPLARY EMBODIMENT OF THE PRESENT INVENTION

I. EXEMPLARY EMBODIMENT

While specific exemplary examples, environments and embodiments are discussed below, it should be understood that this is done for illustration purposes only. A person skilled in the relevant art will recognize that other components and configurations can be used without parting from the spirit and scope of the invention. In fact, after reading the following description, it will become apparent to a person skilled in the relevant art how to implement the invention in alternative examples, environments and embodiments.

II. HIGH PERFORMANCE ANALYSIS SYSTEM AND METHOD

FIG. 1 is a block diagram illustrating an exemplary high performance analysis system. FIG. 1 includes eluent tank 102, pump 104, injection valve 106, column 108, detector 110, and computer control device 114.

The mobile phase is pumped by pump 104 from eluent tank 102 into injection valve 106. The mobile phase refers to the solvent continuously applied from pump 104 to detector 110.

In this regard, the mobile phase serves as a carrier for the sample analyte solution. As the sample solution flows through column 108 with the mobile phase, the components thereof travel according to the interactions of the compound with the stationary phase of the column. In fact, chemical or physical interactions of the mobile phase and sample, with the column, determine the degree of migration and separation of components contained in the sample. Samples having greater interactions with the mobile phase than with the stationary phase elute from column 108 more quickly. Such samples have shorter retention times, and the opposite is true for samples with fewer interactions.

The mobile phase can be adjusted by researchers and to effect varying interactions of the sample and column 108. As skilled artisans will contemplate, exemplary mobile phases used in accordance with the present invention include, but are not limited to, isocratic, gradient, and polytyptic types of mobile phases.

Skilled artisans will recognize there are several types of pumps 104 that can be used in accordance with the present invention. Exemplary pumps 104 include reciprocating piston pumps, syringe type pumps, and constant pressure pumps.

The reciprocating piston pump includes a small motor driven piston that quickly moves in a hydraulic chamber. The chamber can vary in volume. During the forward stroke, pump 104 pushes solvent out to the column from eluent tank 102. During the back stroke, the piston pulls in solvent from the eluent tank 102. Altering the piston stroke volume or the stroke frequency during a given cycle permits a wide range of flow rates. Dual and triple head pumps can be used, comprising identical piston-chamber units operating 120 or 180 degrees out of phase to coordinate a continuous flow.

The syringe type pump has a volume defined by the size of the syringe employed. It operates by a motorized lead screw delivering the mobile phase to column 108 at constant rate. The solvent delivery rate can be controlled by changing the voltage on the motor.

The constant pressure pump permits the mobile phase to travel through it using pressure from a gas cylinder. The valve assembly used permits rapid refill of the eluent tank 102. The constant pressure provides for continuous movement of the mobile phase.

As noted, column 108 is also referred to as the stationary phase of the system of FIG. 1. To be more precise, the term stationary phase refers to the solid support material packed in column 108, over which the mobile phase continuously flows.

The sample solution is injected into the mobile phase through the injector port. As the sample solution flows with the mobile phase through the stationary phase, the components of that solution will migrate according to the interactions of the compounds with the stationary phase.

As recognized by skilled persons, any type of stationary phase can be used with the present invention. Exemplary stationary phases include affinity, ion-exchange, liquid-liquid, liquid-solid, normal phase, reversed phase and size exclusion stationary phases. Table 1 provides a more detailed view of such exemplary stationary phases.

Stationary Phase Types	Description (Table 1)
Affinity	Affinity operates by using immobilized biochemicals that have a specific affinity to the compound of interest. Separation occurs as the mobile phase and sample pass over the stationary phase. The sample compound or compounds of interest are retained as the rest of the impurities and mobile phase pass through. The compounds are then eluted by changing the mobile phase conditions.
Ion-Exchange	This stationary phase functions based selective exchange of ions in the sample with counterions in the stationary phase. Ion exchange occurs via columns having charge-bearing functional groups attached to a polymer matrix, with the functional ions being permanently bonded to the column with each having an attached counterion. Sample elution is performed by changing the mobile phase properties so that the mobile phase displaces sample ions from the stationary phase.
Liquid-Liquid	This stationary phase functions the same way as a liquid-solid stationary phase, but is better adapted for samples having medium polarity soluble in weakly polar to polar organic solvents. The polarities of the sample and stationary phase are matched and a mobile phase having different polarity is used to effect non-electrolyte separation.
Liquid-Solid	This stationary phase functions on the basis of compound polarity. Compounds with functional groups having stronger hydrogen bonding adhere more tightly to the stationary phase than less polar compounds, rendering their elution from the stationary phase slower.
Normal Phase	This stationary phase functions based on hydrophilicity and lipophilicity by using a polar stationary phase and a less polar mobile phase. Hydrophobic compounds elute faster than hydrophilic compounds.
Reversed Phase	This stationary phase functions based on hydrophilicity and lipophilicity by using a polar stationary phase and a less polar mobile phase. Hydrophilic compounds elute faster than hydrophobic compounds.
Size Exclusion	This stationary phase functions based on the molecular size of compounds under analysis. The stationary phase comprises porous beads, with larger compounds being excluded from the interior of the bead and therefore eluting before smaller compounds. The column can be designed as silica or non-silica based.

Detector 110 emits a response in accordance with the eluting sample compound's ability to signal a response. Adjustment controls permit tuning the relative bandwidth and height of the response. Sensitivity parameters can also be controlled on the detector system 110.

Skilled artisans will recognize there are several types of detectors 110 that can be used in accordance with the present invention. Exemplary detectors 110 include refractive index (RI), ultra-violet (UV), fluorescent, radiochemical, electrochemical, mass spectrometry (MS) and light scattering (LS). Table 2 provides a more detailed view of such exemplary stationary phases.

Detector Types	Description (Table 2)
Refractive Index	Measure the ability of sample molecules to bend or refract light.
Ultraviolet (UV)	Measure the ability of sample to absorb light. Includes fixed wavelength; variable wavelength; and full spectrum.
Fluorescent	Measure the ability of a compound to absorb and then re-emit light at given wavelengths.
Radiochemical	Uses radiolabeled material, usually tritium (3H) or carbon-14 (14C). Operates by detecting fluorescence associated with beta-particle ionization. Includes homogeneous and heterogeneous types.
Electrochemical	Measure compounds undergoing oxidation or reduction reactions.
Mass Spectroscopy (MS)	Sample is ionized, passed through a mass analyzer, and the ion current is detected.
Light-Scattering (LS) Detectors	Measures light reflected, absorbed, transmitted, or scattered.

The samples are injected into an injection port of injection valve 106. The injection valve of the system comprises an injection port and the sample loop. The sample is aspirated into a probe and dispensed into the system via the injection valve 106. Rotation of the valve rotor accomplishes injection of the sample into the stream of the mobile phase.

FIGS. 2A and 2B are schematic representations illustrating exemplary injection valve assembly 106, specifically the stator phase and stator phase assembly thereof. FIG. 2A includes sample injection port 201, sample loop ports 202, 205, column port 203, pump port 204, and drain port 206. FIG. 2A specifically illustrates the positioning of the valve assembly ports during an "inject" phase of the valve assembly. During the injection phase, the connection between sample injection port 201 and drain port 206 are active, whereas the connection between column port 203, sample loop ports 202, 205, and pump port 204 are active. In the injection phase, the sample contained in the sample loop, between sample loop ports 202, 205, is fed to column port 203. This action is caused by the pumping action of the mobile phase from pump 104 into pump port 204. During this inject phase, the sample is fed from sample injection port 201 through drain port 206.

FIG. 2B illustrates the same valve assembly 106 having the foregoing ports, with the positioning of the valve assembly ports illustrated during a "load" phase of the valve assembly. During the "load" phase, the connection between sample injection port 201, sample loop ports 202, 205, and drain port 206 are active, whereas the connection between column port 203 and pump port 204 is active. In the "load" phase, the sample is fed to the sample loop port 202 by introduction from sample injection port 201. Volume in excess of the volume of the sample loop is fed through sample loop port 205 to drain port 206. Meanwhile, the mobile phase is pumped by pump 104 to column 108, by a direct connection between pump port 204 and column port 203.

The valve assembly 106 toggles between the "load" phase and the "inject" phase. In this manner, the system pumps toggles between pumping the mobile phase from pump 104 into the stationary phase of column 108, and pumping the sample from valve 106 into the stationary phase of column 108.

FIGS. 2A, 2B illustrate a 2-position, 6-port motorized valve assembly. However, as skilled artisans will contemplate, any type of valve assembly can be used in accordance with the teachings of the present invention.

In one or more embodiments, synchronization and control of introduction of sample into injection valve 106, pumping of the mobile phase from eluent tank 102 through injection valve 106 onto column 108, and detection at the detector 110 are

effected by a computer control device 114. As skilled persons will recognize, the computer control device 114 can include the functions and features described in the computer hardware and software environments below.

In one or more exemplary embodiments, computer control device 114 performs the following functions: (i) adjusts introduction of samples into the injection valve; (ii) adjusts the position of the valve at a given time to deliver sample downstream; (iii) determines the arrival of the sample at the detector 110 in real-time; (iv) collects and calculates pressure readings over time from pump 104; (v) adjusts the composition and rate of the flow from eluent tank 102 into pump 104.

In one or more embodiments, sample injection into sample injection port 201 is actuated automatically via an autosampler, which can work independently of the computer control device 114 through its own processor-based control, or can be integrated with the computer control device 114.

In one or more embodiments, the external sample loop in an injection valve assembly 106 connecting ports 202 and 205 is replaced by an internal sample loop. FIGS. 2C and 2D illustrate such embodiment of valve assembly 106'. The internal sample loop (not shown) holds a maximum volume as dictated by the size of the tube or reservoir connecting the ports. For instance, the external sample loop generally has a minimum volume requirement of, e.g., 2 microliters, whereas the internal sample loop allows the injection valve assembly 106' to efficiently operate at a lower volume of, e.g., 0.5 microliters. Also, because the distance between ports 202 and 205 is such that any modifications to the diameter of the external sample loop would be impractical because such would render the diameter of the loop prohibitively small in view of the predetermined volume and length. Accordingly, by using the internal sample loop, different injection volumes can be realized by changing the inscribed volume of the injection valve assembly 106'. Other aspects of fluid control operate in a same manner as the valve configurations depicted in FIGS. 2A and 2B.

Commercially available autosamplers, including for example the Gilson 215 Autosampler model, can be used for sample dispense to the sample injection port 201 of valve assembly 106. Numerous other autosampler models are available for suitable adaptation to the present invention as recognized by skilled artisans.

It has been found that commercially available autosamplers are often produced to handle a single analyte sample at a time, not multiple samples, and are often difficult to individually adjust for intensive, time-sensitive applications, where probe washing (to prevent contamination between samples), minimum required sample volume, valve speed, sample plate density, displacement parameters for each probe, and sample capacity are important parametric constraints.

In addition, existing autosamplers do not replace the need for human intervention in a systems environment. One such environment is in the pharmaceutical research and development, where once a robot that handles high-throughput screening of biological assays has determined a small molecule has had an affect on a pathogen, protein or gene sequence (a "hit"). These "hits" form a subset of the company collection in which the analysis is often performed to determine whether the sample is indeed of sufficient purity to validate the result. Integration of the hit-picking with purity analysis would represent an important efficiency producer, cost per analysis and time saver.

For this reason, in one or more embodiments, specialized robot handlers are specially adapted for performing the autosampling function. In particular, in one or more embodiments, a liquid handling robot is adapted to perform autosampling by mounting thereon valve assemblies 106 and specially adapting the probes (syringes) to aspirate the samples and dispense the samples into the valve assemblies 106 during the loading phase of the valve assemblies.

In one embodiment, Robotic Sample Processors (RSPs) liquid handling robots available from Genesis are specially adapted in accord with the present teachings. Exemplary models adapted for use herewith include RSP 100, RSP 150 and RSP 200, having varying worktable sizes, depending upon commercial utility and cost constraints.

Though the following description details special adaptation of a liquid handling robot to perform the autosampling function, after reading the description, it will be apparent to persons skilled in the relevant art how to implement the invention using any other robotic based systems.

FIG. 3 illustrates an implementation of valve assemblies mounted on a liquid handling station 200. Included are valve assembly 106, and additional valve

assemblies 302, 304, 306 mounted parallel to valve assembly 106. Shown on valve assembly 106 are the sample port 201, sample loop ports 202, 205, column port 203, pump port 204, and drain port 206. As illustrated, parallel valve assemblies 302-306 include the same ports as valve assembly 106, namely sample injection port 201, sample loop ports 202, 205, column port 203, pump port 204 and drain port 206.

FIG. 4 illustrates an implementation of probes (syringes) mounted on a robotic manipulator arm. Specifically, probes 402/403 and 404/405 are mounted on the robotic manipulator arms 401 of the robot.

Each robot manipulator arm is movable in three dimensional space, namely in the X (width), Y (length) and Z (height) directions, with motion based on such parameters as step-function variation and gradient variations. This permits three dimensional motion of probes 402-405. Computer control device 114 effects motion of the robot manipulator arm 401 through preprogrammed or real-time programmable algorithms.

The probes respectively have holding portions 402, 404 connected to the robot manipulator arm 401. The probes also respectively have tip portions 403, 405 connected to the robot manipulator arm 401. In one or more embodiments, the probes function independently of one another.

Probe 404/405 shows a typical design which includes a longer tip portion 405, and correspondingly shorter holding portion 404. The diameter of the tip portion 405 is noticeably smaller than the diameter of the holding portion. This adaptation has been provided to enable descending of probe tip portion 405 directly into sample ports 201 of valve assemblies 106, and 302-304. In one or more embodiments, the tip portion of probe 404/405 has a fixed length (L) and a fixed diameter (D), each in a predetermined proportion to the valve sample injection port 201.

The foregoing function occurs during dispensation of sample into valve assemblies 106, and 302-304. The function should not be confused with injection and loading phases of the valve assembly 106 as described above. Dispensation here, in reference to manipulation of the manipulator robot arm 401, refers to placing the tip portion 405 into the valve assembly at sample port 201, to dispense the target sample compound. Injection and loading phases of the valve assembly refer to pumping of sample, or alternatively mobile phase, into column 108.

FIG. 5 illustrates an implementation of valve assemblies and probes mounted on a robotic manipulator arm. Valve assemblies 106, 302-305 are mounted on the robot. Probes are mounted on manipulator robot arm 401. Additionally, a test plate 501 is illustrated. Test plate 501 including hundreds of sample compounds located in discrete locations (wells) of the plate. During an aspiration phase of the system, the manipulator robot arm 401 descends an exemplary probe 404/405 into a well of the plate, to retrieve one or more target sample compounds. The manipulator robot arms 401 function independently, permitting aspiration (or dispense) by the probes 404/405 independently of one another.

FIG. 6 is a schematic illustration of a complete environment implementing the present invention. Although illustrated separately, the sample plates 501, manipulator robot arms 401, and valve assemblies 106, 302-306 are mounted on one or more liquid handling stations, as illustrated in FIG. 5. Pumps 104 feed the mobile phase into pump ports 204 of valve assemblies 106, 302-306. Columns 108 are detected by a detector 110, which in an exemplary embodiment is a 4-channel 2488 UV detection system produced by Waters. In this embodiment, detector 110 is also connected to a multiplexed 5-channel MUX mass spectrometer source denoted as detector 608.

In this embodiment, computer control device 114 comprises three independent processors, namely robot processor 602, liquid handling processor 604, and LC/MS processor 606, together communicating through one or more protocols recognized by skilled persons.

In an embodiment, the robot processor 602 retrieves a plate and provides such to the liquid handling processor 604. The robot processor 602 also passes the wells that the liquid handling processor 604 needs to aspirate. Subsequently the liquid handling processor 604 loads the valves and probes the status of the LC/MS processor 606.

More specifically, the robot processor 602 retrieves the plate identification from a barcode scanner to a program that will identify a worklist of the samples. The processor queries a database for the plate, retrieves a mapping of the plate, formats the worklist into a required protocol and communicates this information to the liquid handling processor 604 and/or LC/MS processor 606.

The liquid handling processor 604 communicates with robot processor 602 to determine the well locations on a sample plate, of the samples to be dispensed. In another embodiment, the robot processor 602 is implemented to issue commands directly to liquid handling processor 604, eliminating the need for an extra "handshake" between the systems prior to dispensation. Once a current plate is processed, liquid handling processor 604 informs robot processor 602 of this condition, to elicit the next plate. The sample is also queued to the LC/MS processor 606 from robot processor 604, with acquisition start and complete messages used to determine the beginning and completion of detections.

Skilled persons will recognize the present invention permits a plurality of ways to inventory and track samples, and queue up appropriate sample wells for aspirating/dispensing and detection.

III. COMPUTER HARDWARE AND SOFTWARE ENVIRONMENTS

In one or more embodiments, (a) the steps of the present invention; and (b) the functional steps performed by computer control device 114, are embodied in machine-executable instructions. The instructions can be used to cause a processing device, for example a general-purpose or special-purpose processor, which is programmed with the instructions, to perform the steps of the present invention.

Alternatively, the aforementioned steps can be performed by specific hardware components that contain hardwired logic for performing the steps, or by any combination of programmed computer components and custom hardware components.

For example, the aforementioned steps of the present invention can be provided as a computer program product. In this environment, the invention can include a machine-readable medium having instructions stored on it. The instructions can be used to program any processor (or other electronic devices) to perform a process according to the present invention.

The machine-readable medium can include, for example, floppy diskettes, optical disks, CD-ROMs, and magneto-optical disks, ROMs, RAMs, EPROMs, EEPROMs, magnet or optical cards, or other type of media/machine-readable medium suitable for storing electronic instructions, but is not limited to the foregoing.

In addition, the aforementioned steps of the present invention can also be downloaded as a computer program product. Here, the program can be transferred from a remote computer (e.g., a server) to a requesting computer (e.g., a client) by way of data signals embodied in a carrier wave or other propagation medium via a communication link (e.g., a modem or network connection).

In one exemplary embodiment, illustrated in FIG. 7, computer control device 114 is a computer system 700. Computer system 700 includes bus 702, processor 704 (including graphics subsystem 703), display interface 705, display 706, main memory 708, secondary memory 710 (including hard disk drive 712, removable storage drive 714, and interface 720), removable storage units 718, 722, graphical user-interface 730, peripheral devices 732 and communications interface 724. Computer system 700 is also connected via communications path 726 to external networks. Various embodiments are described in terms of this example computer system. After reading this description, it will be apparent to a person skilled in the relevant art how to implement the invention using other computer systems and/or computer architectures.

Processor 704, which can represent multiple processors, is connected to a communications bus 702. Graphics subsystem 703, shown as associated with processor 704, can be implemented as one or more processor chips. In fact, graphics subsystem 703 can be included as part of processor 704 as shown in FIG. 7 or as a separate graphics engine or processor. Graphics data is output from the graphics subsystem 703 to the bus 702.

Display interface 705 forwards graphics data from the bus 702 for display on the display unit 706. This graphics data includes graphics data for the screen displays described herein.

Main memory 708 can be a random access memory (RAM), and can also include a secondary memory 710. In the present invention the secondary memory 710 can include, for example, a hard disk drive 712 and/or a removable storage drive 714, representing a floppy disk drive, a magnetic tape drive, an optical disk drive, etc. The removable storage drive 714 reads from and/or writes to a removable storage unit 718 in a well known manner. Removable storage unit 718 represents a floppy disk, magnetic tape, optical disk, etc., which is read by and written to by removable storage

drive 714. As will be appreciated, the removable storage unit 718 includes a computer usable storage medium having stored therein computer software and/or data.

In alternative embodiments, secondary memory 710 can include other similar means for allowing computer programs or other instructions to be loaded into computer system 700. Such means can include, for example, a removable storage unit 722 and an interface 720. In the present invention examples can also include a program cartridge and cartridge interface (such as that found in video game devices), a removable memory chip (such as an EPROM, or PROM) and associated socket, and other removable storage units 722 and interfaces 720 which allow software and data to be transferred from the removable storage unit 722 to computer system 700.

Graphical user interface module 730 transfers user inputs from peripheral devices 732 to bus 706. These peripheral devices 732 can be a mouse, keyboard, touch screen, microphone, joystick, stylus, light pen, or any other type of peripheral unit.

Computer system 700 can also include a communications interface 724. Communications interface 724 allows software and data to be transferred between computer system 700 and external devices via communications path 726. Examples of communications interface 724 that can be used with the present invention include a standard or cable modem, a DSL connection, a network interface (such as an Ethernet card), a communications port, a LAN connection, a WAN connection, etc. Computer programs and data transferred via communications interface 724 are in the form of signals which can be electronic, electromagnetic, optical or other signals capable of being received by communications interface 724, via communications path 726. Note that communications interface 724 provides a means by which computer system 700 can interface to a network such as the Internet.

The present invention can be implemented using computer programs (i.e., "software," or "computer control logic") running on Processor 704. The software can be originally stored as a "computer program product" on removable storage device 718 or hard disk drive 712. Therefore, computer program product refers to means for providing software to computer system 700.

Computer programs can also be stored in main memory 708 and/or secondary memory 710. Computer programs can also be received via communications interface

724. Such computer programs, when executed, enable the computer system 700 to perform the features of the present invention as discussed herein. In particular, the computer programs, when executed, enable the processor 704 to perform the features of the present invention.

In another embodiment, the invention is implemented primarily in firmware and/or hardware using, for example, hardware components such as application specific integrated circuits (ASICs). Implementation of a hardware state machine so as to perform the functions described herein will be apparent to persons skilled in the relevant arts.

In the example environment shown, communication interface 724 provides a two-way data communication coupling via a communications path 726 to a local network 736. For example, if communication interface 724 is an integrated services digital network (ISDN) card or a modem, communication interface 724 provides a data communication connection to the corresponding type of telephone line, which comprises part of communications path 726. If communication interface 724 is a local area network (LAN) card, or connects to a LAN 736, then it can provide a data communication connection via communications path 726 to a compatible LAN. Wireless links are also possible. In any such implementation, communication interface 724 sends and receives electrical, electromagnetic or optical signals which carry digital data streams representing various types of information.

Communications path 726 typically provides data communication through one or more networks to other data devices. For example, in the present invention communications path 726 can provide a connection through local network 736 to host computer 734 or to data equipment operated by an Internet Service Provider (ISP) 738. In turn, ISP 738 provides data communication services through the worldwide packet data communication network now commonly called the "Internet" 740, described in detail in other embodiments.

Local network 736 and Internet 740 both use electrical, electromagnetic or optical signals that carry digital data streams. The signals through the various networks and the signals on communications path 726 and through communication interface 724, which carry the digital data to and from computer 700, are exemplary forms of carrier waves transporting the information.

Computer system 700 can send messages and receive data, as well as computer programs, through the network or networks, communications path 726, and communication interface 724. If the network used is the Internet, server 742 can transmit a requested code for an application program through Internet 740, ISP 738, local network 736 and communications path 726. Examples of such applications are the application programs run by application servers and database servers, as described in detail below.

IV. CONCLUSION

Skilled persons will also understand that the use of any terms throughout the specification depicting particular mechanical elements, hardware, software, or combinations thereof, are provided by way of example, not limitation, and that the present invention can be utilized and implemented by any systems and methods presently known or possible without escaping from the features and functions disclosed herein.

While various embodiments of the present invention have been described above, it should be understood that they have been presented by way of example only, and not limitation. Thus, the breadth and scope of the present invention should not be limited by any of the above-described exemplary embodiments, but should instead be defined only in accordance with the following claims and their equivalents.

What Is Claimed Is:

1. A high performance analysis system for automated evaluation of target samples comprising:

an automated liquid handler having one or more probes for aspirating and dispensing one or more target samples;

one or more multi-port valve stations each having a plurality of ports, at least one of said ports mating in a direct manner with the corresponding probe thereof to receive one of said target samples dispensed from said probe; and

a detector for detecting said target samples in a mobile phase of the system.

2. The system of claim 1, wherein said liquid handler comprises a support arm by which said probes are mounted thereon, each of said probes being freely movable in three dimensional space.

3. The system of claim 1, wherein each of said probes has a tip portion with a first diameter and a holding portion with a second diameter, said first diameter being smaller than said second diameter.

4. The system of claim 1, wherein a tip portion of a said probe has a fixed length (L) and a fixed diameter (D) each in proportion to a said port.

5. The system of claim 1, wherein each said valve stations comprises any one of:

at least two ports thereof being connected by one or more tubes for holding one of the target samples;

at least one port thereof being an inlet port for receiving a mobile fluid;

at least one port thereof being a first outlet port for transporting mobile fluid; and

at least one port thereof being a second outlet port for overflow control of a said valve station.

6. The system of claim 1, wherein each said valve station comprises any one of:

an embedded valve of a fixed volume for holding a said target sample;

at least one port thereof being an inlet port for receiving a mobile fluid;

at least one port thereof being a first outlet port for transporting mobile fluid; and

at least one port thereof being a second outlet port for overflow control of the valve station.

7. The system of claim 1, wherein a portion of a said probe descends directly into said at least one port during said dispensing step.

8. The system of claim 1, wherein the system is a parallel system comprising at least two or more of said valve stations, and said probes synchronously or serially mating with said valve stations.

9. The system of claim 8, wherein during any one of said aspirating and said dispensing steps said probes function independently of one another.

10. The system of claim 1, further comprising:

a robot processor retrieving identification information relating to one or more plates and one or more wells each located within a said plate, wherein a said target sample is aspirated from a said well; and

a liquid handling processor communicating with said robot processor to determine the identity of a said well within a said plate from which said target sample has been aspirated, and for controlling dispensing of said target sample from said well.

11. A method for performing high performance analysis for automated evaluation of target samples, comprising:

aspirating and dispensing one or more target samples via one or more probes of an automated liquid handler;

mating in a direct manner a corresponding probe of a multi-port valve station to receive one of said target samples dispensed from the probe; and

detecting said target samples in a mobile phase of the system.

12. The method of claim 11, wherein each of said probes is freely movable in three dimensional space.

13. The method of claim 11, wherein a said probe is produced such that the diameter of a tip portion thereof is smaller than the diameter of a holding portion thereof.

14. The method of claim 11, wherein a tip portion of a said probe is produced to have a fixed length (L) and a fixed diameter (D) in proportion to a said port.

15. The method of claim 11, wherein a function of a said valve station comprises any one of:

holding one of the target samples via one or more tubes connected between at least two ports thereof;

receiving a mobile fluid via an inlet port thereof;

transporting a said mobile fluid via an outlet port thereof; and

controlling overflow of a said valve station via an outlet port thereof.

16. The method of claim 11, wherein a function of a said valve station comprises any one of:

holding a said target sample via an embedded valve of a fixed volume;

receiving a mobile fluid via an inlet port thereof;

transporting a mobile fluid via an outlet port thereof; and

controlling overflow of a said valve station via an outlet port thereof.

17. The method of claim 11, comprising descending directly into said at least one port a portion of a said probe during said dispensing step.

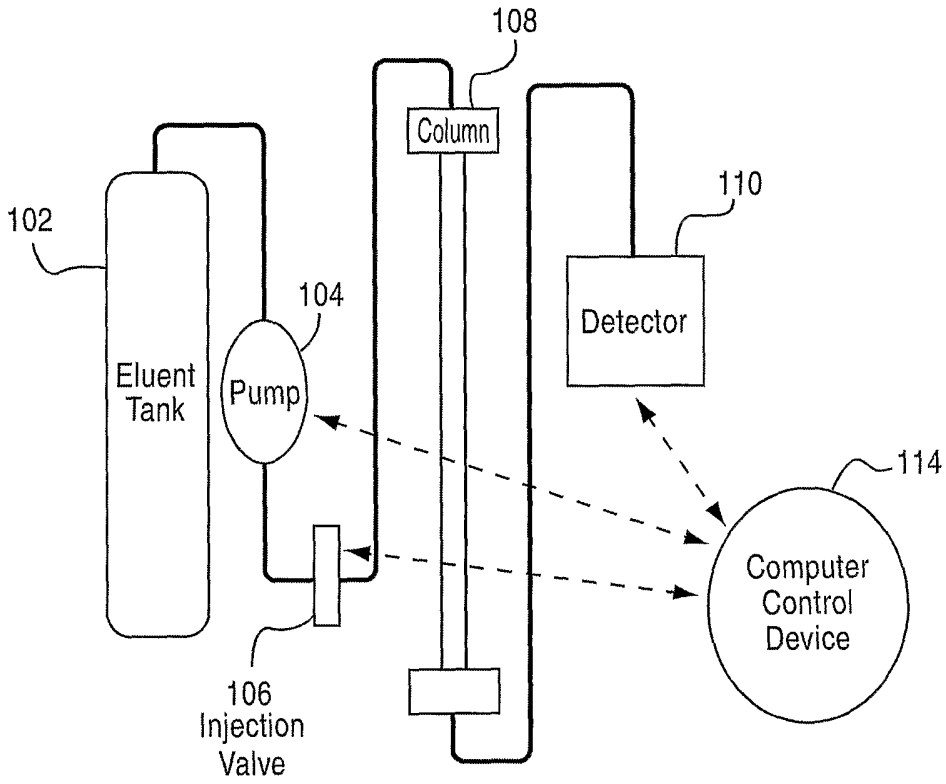
18. The method of claim 11, comprising using a parallel system having one or more additional valve stations, and said probes synchronously or serially mating with said valve stations.

19. The method of claim 18, wherein during said dispensing step said probes function independently of one another.

20. The method of claim 11, further comprising:

retrieving identification information relating to one or more plates and one or more wells each located within a said plate, wherein a said target sample is aspirated from a said well; and

determining the identity of a said well within a said plate from which said target sample has been aspirated, and for controlling dispensing of said target sample from said well.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110
102
Detector
104
Eluent
Tank
Pump
114
Computer
Control
Device
106
Injection
Valve

FIG.1

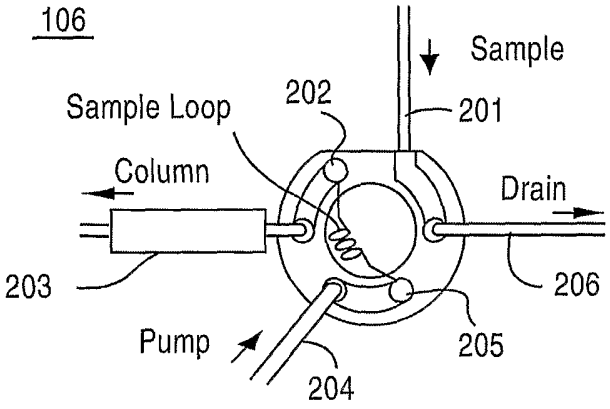
106
Sample
Sample Loop
202
201
Column
Drain
203
206
Pump
205
204

FIG.2A

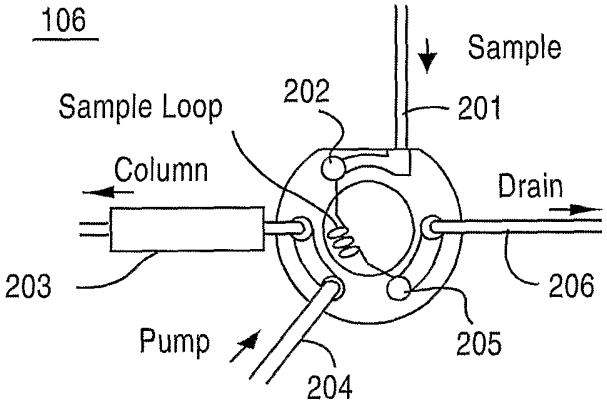
106
Sample
Sample Loop
202
201
Column
Drain
203
206
Pump
205
204

FIG.2B

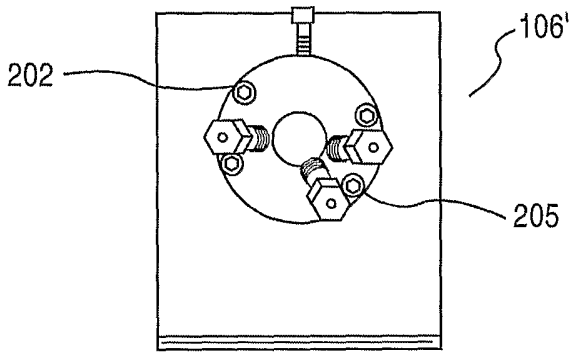

FIG.2C

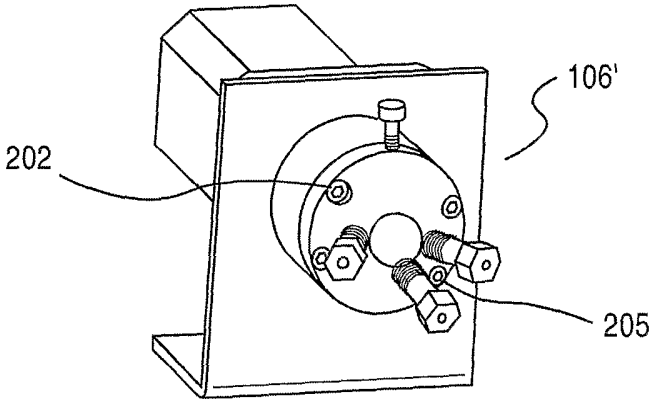

FIG.2D

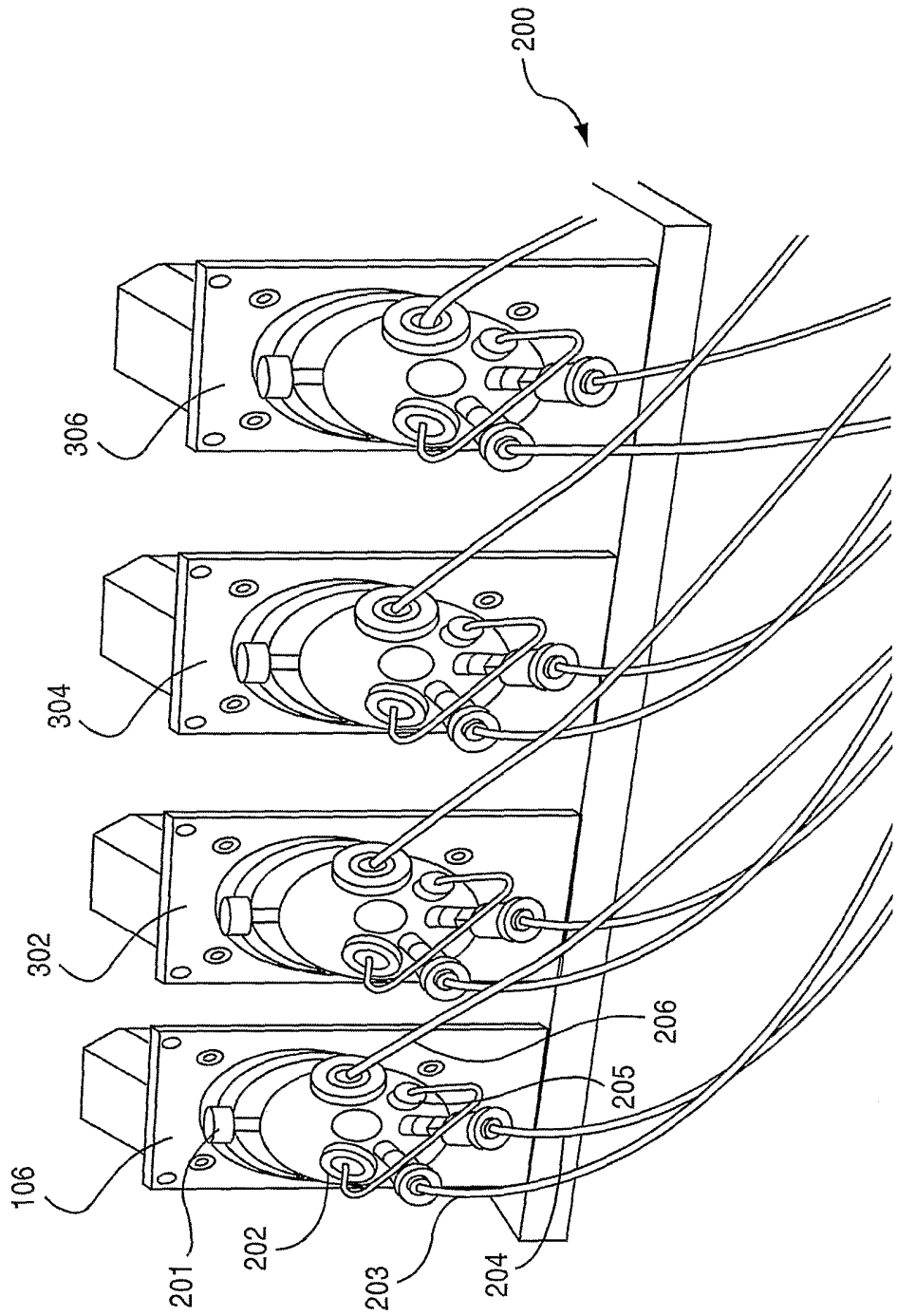

FIG.3

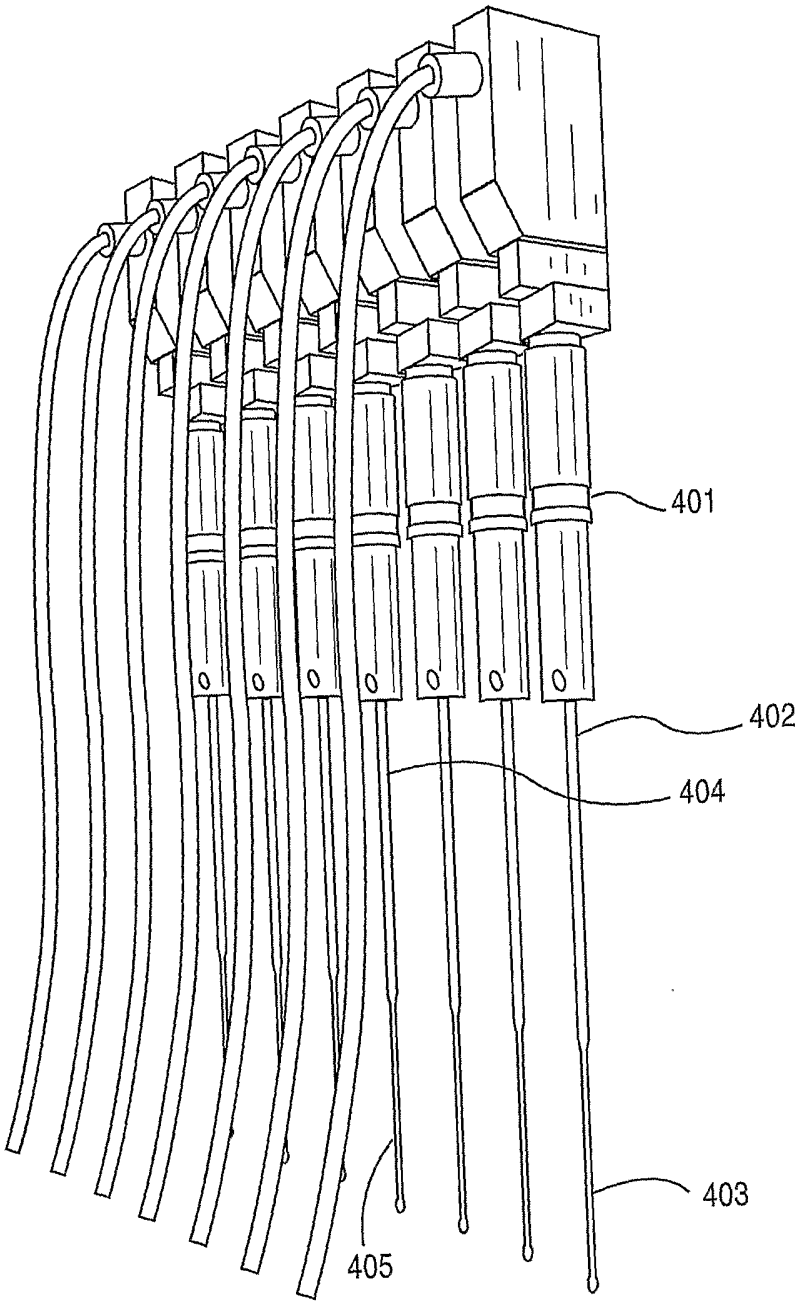

FIG.4

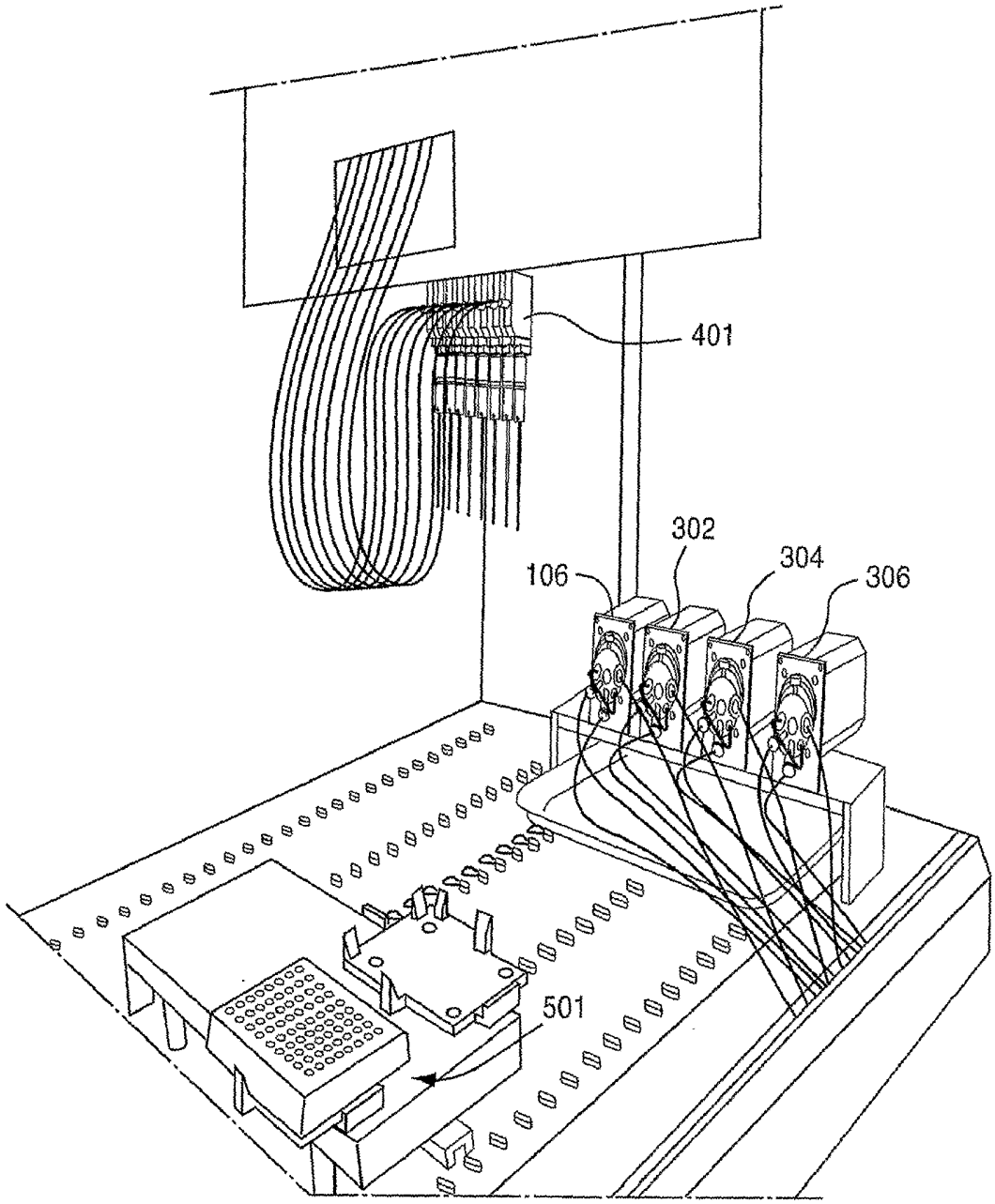

FIG.5

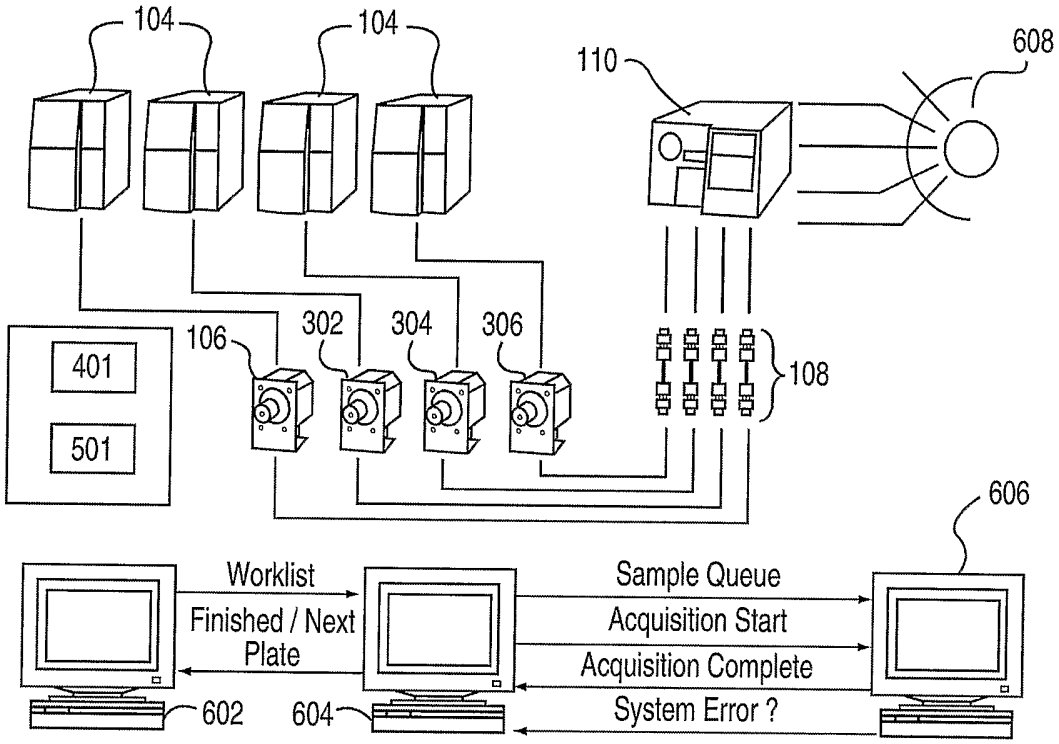
104
104
110
608
401
501
106
302
304
306
108
606
Worklist
Finished / Next Plate
Sample Queue
Acquisition Start
Acquisition Complete
System Error ?
602
604

FIG.6

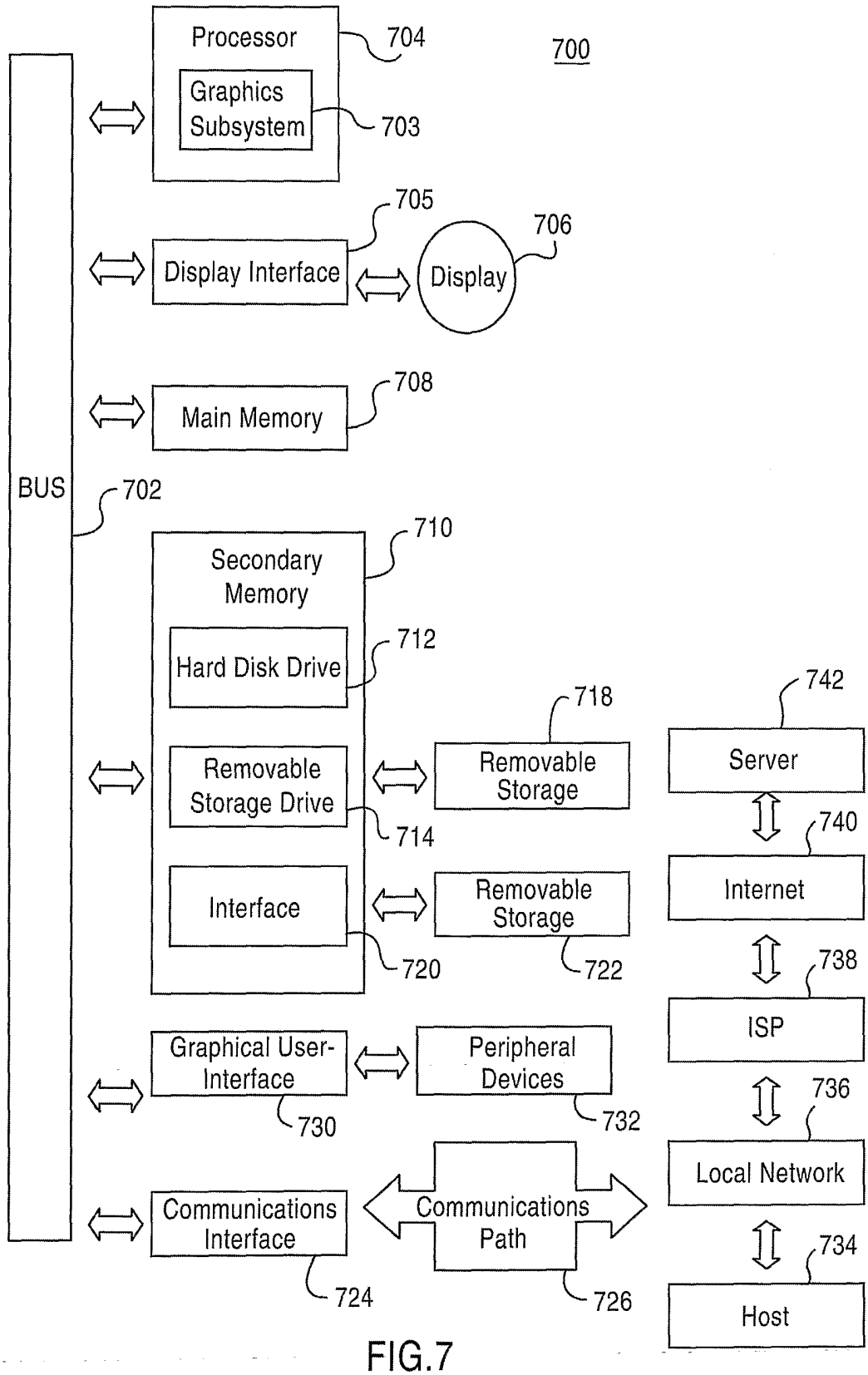
Processor
704
700
Graphics Subsystem
703
705
Display Interface
706
Display
708
Main Memory
BUS
702
710
Secondary Memory
712
Hard Disk Drive
718
Removable Storage Drive
Removable Storage
714
Interface
Removable Storage
720
722
742
Server
740
Internet
738
ISP
736
Local Network
734
Host
Graphical User-Interface
730
Peripheral Devices
732
Communications Interface
724
Communications Path
726

FIG.7

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/005608

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N30/24 G01N35/10

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)
G01N

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 practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/020670 A1 (PETRO MIROSLAV) 21 February 2002 (2002-02-21)	1,2, 4-12, 14-20
Y	the whole document	3,13
Y	VAN DER VLIS E ET AL: "Development of a needle device for on-line electroextraction-liquid chromatography" JOURNAL OF CHROMATOGRAPHY A, ELSEVIER, AMSTERDAM, NL, vol. 741, no. 1, 9 August 1996 (1996-08-09), pages 13-21, XP004020168 ISSN: 0021-9673 figure 1	3,13

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"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
22 May 2006	29/05/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bravin, M

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/005608

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002020670 A1	21-02-2002	NONE	