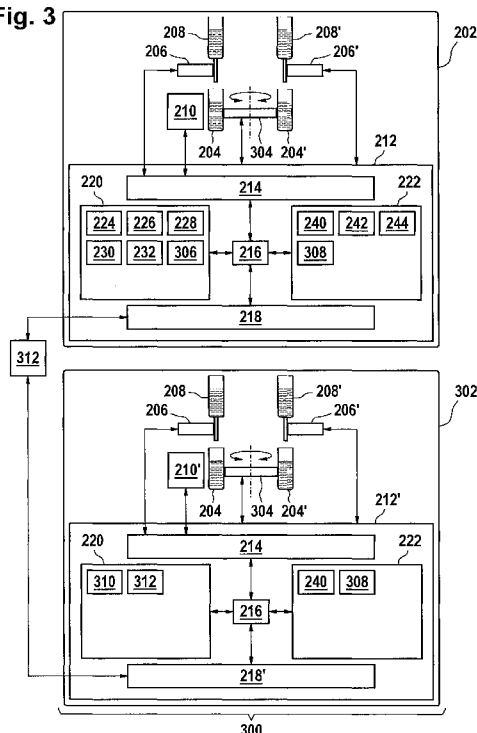




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[Continued on next page]

(54) **Title:** CALIBRATION METHOD FOR PHOTOMETRY**Fig. 3**

(57) **Abstract:** The invention provides for a method of determine a physical property of a biological sample. The method comprises the steps of: acquiring (100) a set of preliminary calibration signals (306) of a first lot (208') of a reagent using an automatic analyzer (202) with a first photometry module (210); acquiring (102) a reference set of signals (310) of the first lot of the reagent using a calibration analyzer (302) with a second photometry module (210'); determining (104) a set of module specific components (224) by subtracting the reference set of signals from the preliminary calibration signals; acquiring (106) a lot specific set of signals (226) of a second lot of the reagent using the second photometry module; determining (108) a lot calibration (228) for the first photometry module using the set of module specific components and the lot specific set of signals; and acquiring (110) a measurement signal (230) of the biological sample using the first photometry module and the second lot of the reagent; and determining (112) a physical property (232) of the biological sample using the measurement signal (230) and the lot calibration (228).

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Calibration method for photometry

Description

Field of the invention

The invention relates to a method of calibrating photometric measurements of a biological sample with a reagent.

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Background and related art

One way of analyzing a biological sample is to use photometry. Typically the spectra of scattered light or the transmission at certain wavelengths is measured. Not all

molecules have a scattering or transmission spectra which is useful. Solutions containing a reagent may be mixed into the biological sample to alter its spectral properties. Different reagents may be selected which exhibit changes in spectral properties depending upon a physical property such as the concentration of a particular molecule or analyte. In order to make these measurements useful the changes in the spectral properties as a function of the physical property should be calibrated.

Summary

The invention provides for a method and an analysis system in the independent claims. Embodiments are given in the dependent claims.

The term 'analyzer' refers to a device being operable to execute one or multiple analyses on biological samples such as blood, urine, saliva, or other sample types.

An analyzer is operable to determine via various chemical, biological, physical, optical or other technical procedures a parameter of the sample or a component thereof, the parameter in the following being referred to as 'measurement value'. An analyzer is operable to measure said parameter of the sample or of at least one reagent and return the obtained measurement value. The list of possible analysis results returned by the analyzer comprises, without limitation, concentrations of the reagent in the sample, a digital (yes or no) result indicating the existence of the reagent in the sample (corresponding to a concentration above the detection level), optical parameters, DNA or RNA sequences, data obtained from mass spectroscopy of proteins or metabolites and physical or chemical parameters of various type.

As will be appreciated by one skilled in the art, aspects of the present invention may be embodied as a apparatus, method or computer program product. Accordingly, aspects of the present invention may take the form of an entirely hardware embodiment, an entirely software embodiment (including firmware, resident software, micro-code, etc.) or an embodiment combining software and hardware aspects that may all generally be referred to herein as a "circuit," "module" or "system." Furthermore, aspects of the present invention may take the form of a computer program product embodied in one or more computer readable medium(s) having computer executable code embodied thereon.

Any combination of one or more computer readable medium(s) may be utilized. The computer readable medium may be a computer readable signal medium or a computer readable storage medium. A 'computer-readable storage medium' as
5 used herein encompasses any tangible storage medium which may store instructions which are executable by a processor of a computing device. The computer-readable storage medium may be referred to as a computer-readable non-transitory storage medium. The computer-readable storage medium may also be referred to as a tangible computer readable medium. In some embodiments, a
10 computer-readable storage medium may also be able to store data which is able to be accessed by the processor of the computing device. Examples of computer-readable storage media include, but are not limited to: a floppy disk, a magnetic hard disk drive, a solid state hard disk, flash memory, a USB thumb drive, Random Access Memory (RAM), Read Only Memory (ROM), an optical disk, a magneto-
15 optical disk, and the register file of the processor. Examples of optical disks include Compact Disks (CD) and Digital Versatile Disks (DVD), for example CD-ROM, CD-RW, CD-R, DVD-ROM, DVD-RW, or DVD-R disks. The term computer readable-storage medium also refers to various types of recording media capable of being accessed by the computer device via a network or communication link. For example
20 a data may be retrieved over a modem, over the internet, or over a local area network. Computer executable code embodied on a computer readable medium may be transmitted using any appropriate medium, including but not limited to wireless, wireline, optical fiber cable, RF, etc., or any suitable combination of the foregoing.

25 A computer readable signal medium may include a propagated data signal with computer executable code embodied therein, for example, in baseband or as part of a carrier wave. Such a propagated signal may take any of a variety of forms, including, but not limited to, electro-magnetic, optical, or any suitable combination
30 thereof. A computer readable signal medium may be any computer readable medium that is not a computer readable storage medium and that can communicate, propagate, or transport a program for use by or in connection with an instruction execution system, apparatus, or device.

'Computer memory' or 'memory' is an example of a computer-readable storage medium. Computer memory is any memory which is directly accessible to a processor. 'Computer storage' or 'storage' is a further example of a computer-readable storage medium. Computer storage is any non-volatile computer-readable storage medium. In some embodiments computer storage may also be computer memory or vice versa.

A 'processor' as used herein encompasses an electronic component which is able to execute a program or machine executable instruction or computer executable code. References to the computing device comprising "a processor" should be interpreted as possibly containing more than one processor or processing core. The processor may for instance be a multi-core processor. A processor may also refer to a collection of processors within a single computer system or distributed amongst multiple computer systems. The term computing device should also be interpreted to possibly refer to a collection or network of computing devices each comprising a processor or processors. The computer executable code may be executed by multiple processors that may be within the same computing device or which may even be distributed across multiple computing devices.

Computer executable code or machine executable instructions may comprise machine executable instructions or a program which causes a processor to perform an aspect of the present invention. Computer executable code for carrying out operations for aspects of the present invention may be written in any combination of one or more programming languages, including an object oriented programming language such as Java, Smalltalk, C++ or the like and conventional procedural programming languages, such as the "C" programming language or similar programming languages and compiled into machine executable instructions. In some instances the computer executable code may be in the form of a high level language or in a pre-compiled form and be used in conjunction with an interpreter which generates the machine executable instructions on the fly.

The machine executable instructions may execute entirely on the user's computer, partly on the user's computer, as a stand-alone software package, partly on the user's computer and partly on a remote computer or entirely on the remote

computer or server. In the latter scenario, the remote computer may be connected to the user's computer through any type of network, including a local area network (LAN) or a wide area network (WAN), or the connection may be made to an external computer (for example, through the Internet using an Internet Service Provider).

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Aspects of the present invention are described with reference to flowchart illustrations and/or block diagrams of methods, apparatus (systems) and computer program products according to embodiments of the invention. It will be understood that each block or a portion of the blocks of the flowchart, illustrations, and/or block diagrams, can be implemented by computer program instructions in form of computer executable code when applicable. It is further understood that, when not mutually exclusive, combinations of blocks in different flowcharts, illustrations, and/or block diagrams may be combined. These computer program instructions may be provided to a processor of a general purpose computer, special purpose

10 computer, or other programmable data processing apparatus to produce a machine, such that the instructions, which execute via the processor of the computer or other programmable data processing apparatus, create means for implementing the functions/acts specified in the flowchart and/or block diagram block or blocks.

15

20 These computer program instructions may also be stored in a computer readable medium that can direct a computer, other programmable data processing apparatus, or other devices to function in a particular manner, such that the instructions stored in the computer readable medium produce an article of manufacture including instructions which implement the function/act specified in the flowchart and/or block

25 diagram block or blocks.

25

The computer program instructions may also be loaded onto a computer, other programmable data processing apparatus, or other devices to cause a series of operational steps to be performed on the computer, other programmable apparatus

30 or other devices to produce a computer implemented process such that the instructions which execute on the computer or other programmable apparatus provide processes for implementing the functions/acts specified in the flowchart and/or block diagram block or blocks.

30

A 'hardware interface' as used herein encompasses a interface which enables the processor of a computer system to interact with and/or control an external computing device and/or apparatus. A hardware interface may allow a processor to send control signals or instructions to an external computing device and/or apparatus. A hardware interface may also enable a processor to exchange data with an external computing device and/or apparatus. Examples of a hardware interface include, but are not limited to: a universal serial bus, IEEE 1394 port, parallel port, IEEE 1284 port, serial port, RS-232 port, IEEE-488 port, Bluetooth connection, Wireless local area network connection, TCP/IP connection, Ethernet connection, control voltage interface, MIDI interface, analog input interface, and digital input interface.

In one aspect the invention provides for a method of determining a physical property of a biological sample. A physical property as used herein encompasses a property of the biological sample which may be measured. In particular the physical property may also be an intensive property of the biological sample. This for instance may be the presence or concentration of a particular molecule within the biological sample. A biological sample as used herein encompasses a sample which comprises material generated by a biological system. A biological system may include parts or products of a living organism or chemicals or materials derived or replicated from an organism. For instance DNA or RNA may be copied by a PCR process although the material is not directly generated by an organism it was derived originally from a biological system or organism.

The method comprises the step of acquiring a set of preliminary calibration signals of a first lot of a reagent using an automatic analyzer according to a calibration protocol. The automatic analyzer acquires the preliminary calibration signals using a first photometry module. Essentially the set of preliminary calibration signals are a set of photometric measurements. A first lot as used herein is simply a lot of reagent that is referred to as a first lot. The terminology 'first lot' is intended to be a label for identifying a particular lot. For instance the term 'first lot' could be replaced with 'a first lot of a reagent' instead. An automatic analyzer as used herein encompasses a system for automatically performing a measurement or processing of a biological sample.

A photometry module as used herein encompasses a scientific instrument which illuminates the biological sample with light and then uses a spectrometer to measure the scattered light and/or the light which is transmitted through the biological sample. For instance a particular reagent may combine with a biological molecule or analyte and may have certain spectroscopic properties which allow the identification of the biological molecule or even the concentration present of the biological molecule within the biological sample. The first and second photometry modules may be, but are not limited to: transmission photometry modules for performing transmission photometric measurements or scattered light photometry modules for measuring scattered light.

The biological sample also encompasses biological material which has been diluted or processed in several ways. For instance the biological sample may be diluted with a solvent or it may be processed physically such as being placed in a centrifuge or subjected to some other chemical processing. The automatic analyzer may be operable for performing any or all of these operations and also may be operable for adding the reagent to the biological sample automatically.

In another step the method further comprises the step of acquiring a reference set of signals of the first lot of the reagent using a calibration analyzer according to the calibration protocol. The calibration protocol as used herein encompasses a set of particular measurements which are used to calibrate the photometric measurements of the first lot. For instance it may involve adding a certain amount of the first lot of the reagent to biological samples which have particular concentrations of biological molecules. The calibration analyzer acquires reference sets of signals using a second photometry module. The calibration analyzer may also be an automatic analyzer or it also may be a manually or partially manually operated analyzer also. The term 'calibration analyzer' is intended to be a label to distinguish it from the automatic analyzer previously described. The method is performed using two distinct analyzers.

The method further comprises the step of determining a set of module specific components by subtracting the reference set of signals from each of the preliminary calibration signals. The set of preliminary calibration signals and the reference set of signals are both photometric measurements that have been measured according to

the calibration protocol. As such the individual measurements in both the preliminary calibration signals and the reference set of signals can be paired and the reference set of signals are subtracted from the preliminary calibration signals. The calibration protocol may specify measuring the photometric measurement and a particular wavelength band. Intensity or number of counts detected in this wavelength band is the quantity which is processed. Measurements taken by the first photometry module and the second photometry module are largely determined by how the photometry module is constructed. A diffraction grating may be used to break the spectrum into components and then some type of optical detector is used to make a measurement on the light. For instance a slit could be used to determine the bandwidth of the measurement and a detector such as a photodiode, CCD array, or a photomultiplier tube could be used. In other embodiments the diffraction grating shines the light onto an array of photo detectors and the width of the detector in a specific design of the diffraction grating determines the bandwidth.

The method further comprises the step of acquiring a lot-specific set of signals of a second lot of the reagent using the second photometry module according to the calibration protocol. The term 'second lot of the reagent' is a label which is intended to distinguish a second lot or a further lot of the reagent from the first lot of the reagent which is referred to as the first lot. The term 'lot-specific set of signals' is also intended as a label for the specific photometric measurements that are made on the second lot of the reagent.

The method further comprises the step of determining a lot calibration for the first photometry module using the set of module-specific components and the lot-specific set of signals. In other words, the lot calibration is calculate at least partially using the module specific components and the lot specific set of signals. The method further comprises the step of acquiring a measurement signal of the biological sample using the first photometry module. The method further comprises the step of determining a physical property of the biological sample using the measurement signal and the lot calibration.

This embodiment may be valuable because it may enable the automatic analyzer to use a lot of a reagent without performing a calibration. In this method the automatic

analyzer and the calibration analyzer first both make photometric measurements according to the calibration protocol on the first lot. This determines a set of module-specific components. The module-specific components are calculated from the photometric measurements on the first lot. Next a set of photometric measurements referred to as the lot-specific set of signals were measured on a second lot using the second photometry module of the calibration analyzer. For instance when a manufacturer produces a lot of the reagent the manufacturer could use the calibration analyzer to then acquire the lot-specific set of signals. The lot calibration is then calculated using the lot-specific set of signals and the module-specific components. This enables acquiring the measurement signal and determining the physical property using the first photometry module and the second lot of the reagent.

The measurements needed to provide the valid calibration were done using the calibration analyzer and not the automatic analyzer. For instance the reagent could be incorporated into a cartridge which contains either the module-specific components or the lot calibration already calculated for the automatic analyzer. The calibration may be performed by a manufacturer or at a different location. The laboratory making the biological sample does not need to perform the calibration protocol in order to use the second lot of the reagent. For instance it may enable more samples to be performed and increase the throughput of the laboratory.

In another embodiment the photometry module is configured for measuring the absorbance of the biological sample. The signals are photometric absorbance measurements.

In another embodiment the physical property is the concentration of an analyte.

In another embodiment the analyte is any one of the following, but is not limited to: a enzyme, a substrate, a protein, an indicator of drug abuse, an indicator for therapeutic drug monitoring, and other analytes.

In another embodiment the analyte is a substrates. The analyte may be any one of the following, but is not limited to: Alumin (BCP+BCG) , Ammonia, Bicarbonate,

Bilirubin-direct, Bilirubin-total, Calcium, Cholesterol, HDL Cholesterol, LDL Cholesterol, Creatinine enz., Creatinine Jaffé, Fructosamine, Glucose, Iron, Lactate, Magnesium, Phosphorus, Total Protein, Total Protein U / CSF, Triglycerides, Triglycerides GB, UIBC, Urea / BUN, and Uric Acid. Reagents for testing for these
5 analytes by measuring the absorbance of light are well known and are commercially available. For example they may be purchased from Roche Diagnostics Ltd., CH-6343 Rotkreuz, Switzerland.

In another embodiment the analyte is an enzyme. The analyte may be any one of
10 the following, but is not limited to: ACP, ALP, ALT / GPT, Amylase-tot., Amylase-pancr., AST / GOT, Cholinesterase Acetyl, Cholinesterase Butyryl, Cholinesterase Dibucain, CK, CK-MB, GGT, GLDH, HBDH, LDH, and Lipase. Reagents for testing for these analytes by measuring the absorbance of light are well known and are commercially available. For example they may be purchased from Roche
15 Diagnostics Ltd., CH-6343 Rotkreuz, Switzerland.

In another embodiment the analyte is an Electrolytes (ISE) The analyte may be any one of the following, but is not limited to: Chloride, Potassium, and Sodium. Reagents for testing for these analytes by measuring the absorbance of light are
20 well known and are commercially available. For example they may be purchased from Roche Diagnostics Ltd., CH-6343 Rotkreuz, Switzerland.

In another embodiment the analyte is a Protein. The analyte may be any one of the following, but is not limited to: α 1-Acid Glycoprotein, α 1-Antitrypsin, α 1-Microglobulin, β -Microglobulin, Albumin (immuno.), APO A1, APO B, ASLO, C3c, C4, Ceruloplasmin, CRP, CRP High Sensitivity, Cystatin C, Ferritin, Haptoglobin, HbA1c (whole blood + hemolysate), Homocysteine, IgA, IgG, IgM, Kappa Light chains, Freelite™ Human Lambda Free, Lambda Light chains, Lipoprotein (a), Myoglobin, Prealbumin, RF, Soluble Transferrin Receptor, and Transferrin.
25 Reagents for testing for these analytes by measuring the absorbance of light are well known and are commercially available. For example they may be purchased from Roche Diagnostics Ltd., CH-6343 Rotkreuz, Switzerland.
30

In another embodiment the analyte is an indicator of drugs of abuse. The analyte may be for testing the abuse of any one of the following drugs, but is not limited to: Amphetamines, Barbiturates, Benzodiazepines, Cannabinoids, Cocaine, LSD, Ethanol, Methadone, Methadone Methabolite (EDDP), Methaqualone, Opiates, Oxycodone, Phencyclidine, and Propoxyphene. Reagents for testing for these analytes by measuring the absorbance of light are well known and are commercially available. For example they may be purchased from Roche Diagnostics Ltd., CH-6343 Rotkreuz, Switzerland.

In another embodiment the analyte for therapeutic drug monitoring (TDM) The analyte may be any one of the following, but is not limited to: Acetaminophen, Amikacin, Carbamazepine, Digitoxin, Digoxin, Gentamicin, Lidocaine, Lithium, MPA-T, NAPA, Phenobarbital, Phenytoin, Procainamide, Quinidine, Salicylate, Theophylline, Tobramycin, Valproic Acid, and Vancomycin. Reagents for testing for these analytes by measuring the absorbance of light are well known and are commercially available. For example they may be purchased from Roche Diagnostics Ltd., CH-6343 Rotkreuz, Switzerland.

The analyte may be any one of the following, but is not limited to: D-Dimer and Anti-Thrombin III. Reagents for testing for these analytes by measuring the absorbance of light are well known and are commercially available. For example they may be purchased from Roche Diagnostics Ltd., CH-6343 Rotkreuz, Switzerland.

In another embodiment the method further comprises the step of acquiring at least one additional calibration signal of the second lot of the reagent using the first photometry module. The method further comprises the step of adjusting the calibration using the at least one additional calibration signal. Some reagents may change over time. For instance the second lot of the reagent could be manufactured and then the reference set of signals is acquired. The second lot of the reagent then may for instance be shipped to a different location or it may sit unused for a period of time. The measurement of at least one calibration signal may allow for this change in the reagent over time. For many reagents one or two additional measurements is all that is necessary. Although some calibration measurements are performed this may be less than performing a full calibration. This may be

advantageous because it reduces the amount of calibration that needs to be performed before the automatic analyzer uses the second lot of the reagent to determine the physical property of the biological sample.

- 5 In another embodiment the measurement of the at least one additional calibration signal and the adjusting of the calibration using the at least one additional calibration signal is repeated after a predetermined duration. The predetermined duration may for instance be preprogrammed into the analyzer controller or may be given as input by an operator. In some embodiments the predetermined duration may be adjusted.

10

If the reagent which properties change over time is not used up within the predetermined duration the calibration may have shifted. In this case it may be beneficial to repeat the measurement of the at least one additional calibration signals.

15

In another embodiment the step of determining the lot calibration for the first photometry module comprises adding the set of module specific components to the lot specific set of signals

- 20 In another embodiment the method further comprises the step of calculating a calibration constant by dividing the set of module-specific components by the reference set of signals. Determination of the lot calibration from the first photometry module is determined by multiplying the quantity $1 + \text{the calibration constant}$ by the lot-specific set of signals. The first photometry module and the second photometry
- 25 module are of course optical instruments. In principle the measurements should be identical; however the optical alignment of various components or the efficiency of a particular photo detector may vary from instrument to instrument. For instance this time it may be reflected in different intensities being measured. Measurements in the preliminary calibration signal and the reference set of signals which correspond
- 30 to each other will be roughly constant when divided by each other. It may provide for a more efficient means of calculating the lot calibration.

In another embodiment the method further comprises the step of calculating the linear fit between the module-specific components and the reference set of signals.

The linear fit comprises a calibration constant and an offset constant wherein the determination of the lot calibration for the first photometry module is determined by adding the offset constant to the product of the calibration constant and the lot-specific set of signals. This embodiment is similar to the previous embodiment except there is some non-linearity in the calibration constant. For instance photo detectors may have different response curves at different wavelengths of light. Or for different wavelengths the optical alignment may be slightly different. This embodiment is able to compensate for these differences also.

10 In another aspect the invention provides for an analysis system comprising an automatic analyzer for analyzing a biological sample. The automatic analyzer further comprises a dispenser for dispensing the reagent into the biological sample. The automatic analyzer comprises a first photometric module for acquiring the measurement signal of the biological sample. The analysis system comprises a
15 memory for storing machine-executable instructions. The automatic analyzer comprises an analyzer controller for controlling the automatic analyzer. Execution of the machine-executable instructions causes the analyzer controller to receive a set of module-specific components. The set of module-specific components is analogous to the set of module-specific components as described previously with
20 respect to the method. Execution of the machine-executable instructions causes the analyzer controller to further receive a lot-specific set of signals. The lot-specific set of signals is also analogous to the lot-specific set of signals that was previously with respect to the method. There are a variety of ways in which the set of module-specific components and the lot-specific set of signals may be received. For
25 instance they may both be transmitted to the automatic analyzer via a network connection. The second lot of a reagent may also have a cartridge with a storage device such as an RFID chip or other memory which may store the set of module-specific components or also even the lot-specific set of signals. In some embodiments the set of module-specific components may be stored locally in the
30 memory of the automatic analyzer.

Execution of the machine-executable instructions further cause the analyzer controller to determine a lot calibration according to a calibration protocol for an second lot of an reagent using the set of module-specific components and the lot-

specific set of signals. Execution of the machine-executable instructions further cause the analyzer controller to add an reagent from the second lot of reagents to the biological sample using the dispenser. In other words, the machine executable instructions cause the dispenser to dispense a portion of the second lot of reagent into the biological sample. Execution of the machine-executable instructions further cause the analyzer controller to acquire the measurement signal of the biological sample using the photometry module. Execution of the machine-executable instructions further cause the analyzer controller to determine a physical property of the biological sample using the measurement signal and the lot calibration. This embodiment is an implementation of the previously described method of determining a physical property. In this embodiment the steps performed by just the automatic analyzer are described. It is advantageous because it describes components and functions of the apparatus that would be installed within a laboratory to measure the physical property of the biological sample.

In another embodiment the analysis system further comprises a calibration analyzer with a second photometry module. The analysis system further comprises a calibration controller. Execution of the instructions causes the analyzer controller to acquire the set of preliminary calibration signals of a first lot of an reagent using the automatic analyzer according to a calibration protocol. The automatic analyzer is operable to acquire the preliminary calibration signals using the first photometry module. Execution of the machine-executable instructions further cause the calibration controller to acquire a set of reference set of signals of the first lot of the reagent using the calibration analyzer according to the calibration protocol. The calibration analyzer acquires the reference set of signals using the second photometry module. The analysis system is operable to determine the set of module-specific components by subtracting the reference set of signals from the preliminary calibration signals.

Execution of the machine-executable instructions cause the calibration controller to acquire the lot-specific set of signals of a second lot of the reagent using the second photometry module according to the calibration protocol. The analysis system is operable to determine the lot calibration for the first photometry module using the set of module-specific components and the lot-specific set of signals. The analyzer

controller is operable to receive the calibration correction components from the analysis system. In this embodiment the analysis system comprises both the automatic analyzer and the calibration analyzer as described previously with respect to the method.

5

In another embodiment execution of the machine-executable instructions causes the analyzer controller to acquire at least one additional calibration signal of the second lot of the reagent using the first photometry module.

10 In another embodiment execution of the machine-executable instructions causes the analyzer controller to acquire at least one additional calibration signal of the second lot of the reagent using the first photometry module. Execution of the machine-executable instructions causes the analyzer controller to adjust the calibration using the at least one additional calibration signal.

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In another embodiment execution of the machine-executable instructions further causes the analyzer controller to repeat the acquisition of the at least one additional calibration signal and the adjusting of the calibration using the at least one additional calibration signal after a predetermined duration.

20

In another embodiment the analysis system is further operable for determining the lot calibration for the first photometry module comprises adding the set of module specific components to the lot specific set of signals. This may be implemented for instance by programming machine-executable instructions into the analyzer
25 controller.

In another embodiment the analysis system is further operable for calculating the calibration constant by dividing the set of module-specific components by the reference set of signals. The determination of the lot calibration for the first
30 photometry module is determined by multiplying the quantity $1 +$ the calibration constant by the lot-specific set of signals. This may be implemented for instance by programming machine-executable instructions into the analyzer controller.

In another embodiment the analysis system is further operable for calculating a linear fit between the module-specific components and the reference set of signals. The linear fit comprises a calibration constant and an offset constant. The determination of the lot calibration for the first photometry module is determined by adding the offset constant to the product of the calibration constant and the lot-specific set of signals. This may be implemented for instance by programming machine-executable instructions into the analyzer controller.

In another embodiment the analysis system further comprises a server for transferring any one of the following to the measurement system via a computer network: the set of calibration correction components, the lot-specific set of signals and combinations thereof.

In another embodiment the analysis system further comprises a reagent cartridge at least partially filled with the second lot of the reagent. The dispenser is operable for dispensing the reagent from the reagent cartridge.

It is understood that one or more of the aforementioned embodiments of the invention may be combined as long as the combined embodiments are not mutually exclusive.

Brief description of the drawings

In the following embodiments of the invention are explained in greater detail, by way of example only, making reference to the drawings in which:

Fig. 1 shows a flow chart which illustrates a method,

Fig. 2 illustrates an example of an analysis system,

Fig. 3 illustrates a further example of an analysis system,

Fig. 4 illustrated calculating the set of module specific components,

Fig. 5 shows a flow chart which illustrates a further method,

Fig. 6 shows an example of a simple linear two point calibration,

Fig. 7 illustrates two calibration curves for the Roche IGA-2 reagent used on a Roche Cobas c system,

Fig. 8 plots the percent difference between the calibration curves in Fig. 7,

Fig. 9 plots the difference between calibration curves in Fig. 7 in absolute terms,

Fig. 10 illustrates two alternative calibration curves for the Roche IGA-2 reagent used on a Roche Cobas c system using the same data as was used in Fig. 7, and

Fig. 11 plots the percent difference between the calibration curves in Fig. 10.

5

Detailed Description

Like numbered elements in these figures are either equivalent elements or perform the same function. Elements which have been discussed previously will not necessarily be discussed in later figures if the function is equivalent.

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Fig. 1 shows a flow diagram which illustrates a method of determining a physical property of a biological sample. First in step 100 a set of preliminary calibration signals is acquired from a first lot of a reagent using an automatic analyzer according to a calibration protocol. The automatic analyzer acquires the preliminary calibration signals using a first photometry module. Next in step 102 a reference set of signals of the first lot of the reagent is acquired using a calibration analyzer according to the calibration protocol. The calibration analyzer acquires the reference set of signals using a second photometry module. In step 104 a set of module-specific components is determined by subtracting the reference set of signals from the preliminary calibration signals. Next in step 106 a lot-specific set of signals of a second lot of the reagent is acquired using the second photometry module according to the calibration protocol. Next in step 108 a lot calibration for the first photometry module is acquired by adding the set of module-specific components to the lot-specific set of signals. Next in step 110 a measurement signal of the biological sample is acquired using the first photometry module and the second lot of the reagent. Finally in step 112 a physical property of the biological sample is determined using the measurement signal and the lot calibration.

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Fig. 2 shows an example of an analysis system 200. The analysis system comprises an automatic analyzer 202. The automatic analyzer 202 is operable for analyzing a biological sample 204. There is a dispenser 206 which is operable for dispensing a second lot of reagent 208 into the biological sample 204. The second lot of reagent 208 may for instance be located within a cartridge. Although not shown in this Fig. the automatic analyzer 202 may have an apparatus for positioning multiple

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biological samples 204 for dispensing the reagent and also for being analyzed by a first photometric module 210. The dispenser 206 and the first photometric module 210 are connected to a hardware interface 214 of a computer system 212. The computer system 212 is one example of an analyzer controller. The computer 212 further comprises a processor 216 which is in connection with the hardware interface 214, a network interface 218, computer storage 220 and computer memory 222. The computer storage 220 is shown as containing a set of module-specific components 224. The computer storage is further shown as containing a lot-specific set of signals 226. The computer storage 220 is further shown as containing a lot calibration. The computer storage 220 is further shown as containing a measurement signal 230. The computer storage 220 is further shown as containing a value of a physical property. The value representing the physical property 232 can be considered to be a measurement of the physical property of the biological sample 204. In some embodiments only the lot calibration 228 is received. In other examples the set of module-specific components 224, and the lot-specific set of signals are received. These for instance may be received by the network interface 218.

The computer memory 222 is shown as containing a control module 240. The control module 240 contains computer-executable code which enables the processor 216 to control the operation and function of the automatic analyzer 202. For instance this may control the dispenser 206 to dispense the reagent into the biological sample 204. The control module 240 may also contain instructions which cause the processor 216 to control the first photometry module 210 to acquire the measurement signal 230. The computer storage 222 is further shown as containing a calibration calculation module 242. The calibration calculation module 242 is an optional module present in some examples which contains code which enables the processor 216 to calculate the lot calibration 228 using the set of module-specific components 224 and the lot-specific set of signals 226. The computer memory 222 is further shown as containing a measurement calculation module 244 which enables the processor 216 to calculate the value representing the physical property 232 from the measurement signal 230 and the lot calibration 228.

Fig. 3 shows a further example of an analysis system 300. The analysis system 300 comprises an automatic analyzer 202 similar to that shown in Fig. 2, a calibration analyzer 302, and a server 312. The automatic analyzer 202 additionally contains a sample movement system 304 which is able to move multiple biological samples 204, 204' into position for measurement of a first photometric module 210 and/or between different dispensers 206, 206'. The automatic analyzer 202 may comprise multiple dispensers 206, 206'. In this example there are two dispensers 206, 206' for dispensing a second lot of the reagent 208 and a first lot of the reagent 208'. In practical use the first lot 208 would have been used for measurements in the automatic analyzer 202 at a point in the future of when the second lot of the reagent 208 is used. Both are shown in this figure to illustrate the measurements taken on the second lot of the reagent 208 and the first lot of the reagent 208'.

The computer storage 220 is additionally shown as containing preliminary calibration signals 306. The preliminary calibration signals 306 were measured using the first lot of the reagent 208' according to a calibration protocol 308. The computer memory is additionally shown as containing a calibration protocol module 308 which enables the processor 216 to follow a calibration protocol. This would likely involve measuring biological samples with known concentrations of a particular molecule that reacts with the reagent. The calibration analyzer 302 is shown as having a configuration nearly identical to the automatic analyzer 202 shown in Fig. 3. The computer 212' contains many of the same components and has the same functionality as the computer 212. The calibration analyzer 302 comprises a computer 212' which functions as the calibration controller. The computer storage 220 of the calibration analyzer 302 contains reference set of signals 310 measured from the first lot of the reagent 208' and a lot-specific set of signals 312 measured from the second lot of the reagent 208 according to the calibration protocol 308. The set of module-specific components 24 can be determined by subtracting the reference set of signals 310 from the preliminary calibration signals 306. This could be performed by the automatic analyzer 202, the calibration analyzer 302 or the server 312. There is a server 312 which serves to exchange data between the automatic analyzer 202 and the calibration analyzer 302.

Fig. 4 shows an example of molecule concentration versus a measurement signal 402 for a calibration protocol. The points labeled 306 correspond to the preliminary calibration signals measured using the automatic analyzer. Each of these signals 306 can be broken into two components. The component corresponding to the reference set of signals and the module-specific components 224. The module-specific components 224 are calculated by subtracting each of the preliminary calibration signals 306 by its corresponding reference set of signals.

The observed signals can be abbreviated S_{obs} , and are the points 306 in Fig. 4. The 6 points 306 can be represented by the variables Sx_{obs} , where x is an index variable. The lots specific components 310 can be represented as Sx_{lot} , where x is again an index variable. The module specific components can be represented as Sx_{mod} , where x is again an index variable.

The relationship shown in 4 can be expressed as:

$$Sx_{obs} = Sx_{lot} + Sx_{mod}.$$

In some cases the ratio $Sx_{obs}/Sx_{lot} = const_{mod}$ is constant for each photometric module, in this case S_{obs} can be expressed as:

$$Sx_{obs} = Sx_{lot} + Sx_{lot} * const_{mod}.$$

An example of a workflow outlined for applying the method is first to derive module-specific values from reagents with known lot values. Next in step 2, lot-specific values of photometric absorbencies are provided as analytical files, for example from a server. Next in step 3 for new or following first lots the expected absorbency values can be calculated. Next in step 4 calculated signal values are used for calculation of the curve parameters as a lot calibration. It may be necessary to use water for S0 or zero concentration determination. Next in step 5, reagents with on-board timeout or cassette calibration should use system water and an S1 calibrator in case of non-linear calibration curves, also 1 or 2 point updates may be considered for on-board recalibration. Next in step 6 if there are many different cases which examples of the method can be applied to: the analyzer installation, a new lot of reagent being used by the automatic analyzer, and new first lot being used at the calibration analyzer are shown in Fig. 5.

Fig. 5 shows three different flowcharts. The first flowchart begins with step 500 wherein a new photometer is installed at a laboratory. Next in step 502 a calibration is performed with a calibrator. This makes measurements on the calibrator lot and first lot 504. Next in step 506 a calibration curve calculation is performed. This is done using calibration values 508. Next in step 510 module-specific values 510 are calculated using the first lot-specific values 512. The analyzer installation corresponds to step 500 and step 512.

The second flowchart begins with step 514, a new lot of reagent at a customer site is started. Next in step 516 signal values are calculated. This is done using the first lot in addition to the ABS + the module ABS 518. Finally in step 520 calibration curve calculation is done using calibration values 522.

The third flowchart begins at step 524, which shows an example of a new reagent lot being processed by a calibration analyzer. First in step 526 a calibration is performed with the calibrator for the first lot and the second lot 528. Next in step 530 a calibration curve calculation is performed using calibration value 532. And finally calculate lot-specific values in step 534 using the first lot and specific values 536.

Fig. 6 shows an example of a simple linear two point calibration. The X-axis 600 is the concentration and the Y-axis 602 the measured signal. This figure is used to illustrate the case where the lot calibration for the first photometry module is determined by adding the set of module specific components to the lot specific set of signals. Concentration C_0 is labeled 604. Concentration C_1 is labeled 606. Signal S_0 608 is the signal that corresponds to Concentration C_0 604. Signal S_1 610 is the signal that corresponds to concentration C_1 616.

In this example it is assumed that a simple linear two point calibration where S_0 608 is the signal with concentration C_0 604 and S_1 is the signal of concentration C_1 606. Then the calibration curve can be expressed as linear regression of $(C_0/S_0 \ C_1/S_1)$.

The Signals can also be expressed as $S_0 = S_{(mod)} + S_{0(lot)}$ and $S_1 = S_{(mod)} + S_{1(lot)}$. C_0 may be 0 and in this case S_0 may be derived from the second reagent lot– a signal measured for just the reagent or simply a blank signal.

- 5 Another way of performing the calibration is to calculate a calibration constant by dividing the set of module specific components by the reference set of signals. The determination of the lot calibration for the first photometry module is then determined by multiplying the quantity 1 plus the calibration constant by the lot specific set of signals.

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This technique is in general illustrated by Fig. 4 and the table below.

In the following example a non-linear calibration curves is made using six calibration points to build the calibration curve. The example is illustrated with the following table.

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Concentration	Signal(ABS)	S (from second module)	Factor
C_0	$S_0 = S_{0(lot)} * (1+x)$	$S_{0(lot)}$	x
C_1	$S_1 = S_{1(lot)} * (1+x)$	$S_{1(lot)}$	x
C_2	$S_2 = S_{2(lot)} * (1+x)$	$S_{2(lot)}$	x
C_3	$S_3 = S_{3(lot)} * (1+x)$	$S_{3(lot)}$	x
C_4	$S_4 = S_{4(lot)} * (1+x)$	$S_{4(lot)}$	x
C_5	$S_5 = S_{5(lot)} * (1+x)$	$S_{5(lot)}$	x

In this table the Factor "x" is the calibration constant and the values of S with the (lot) subscript are the lot specific set of signals. The module specific factor in this case "x" can be derived by least square regression during initial setup of the module. The lot specific set of signals are labeled 310 in Fig. 4.

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The effectiveness of this method of calibrating is demonstrated with a calibration for measuring the concentration of IgA in human serum.

Fig. 7 illustrates two calibration curves for the Roche IGA-2 reagent used on a Roche Cobas c system. This reagent is a test for IgA in human serum and uses two working solutions. A TRIS buffer is used for the first solution and Anti-human IgA antibody (goat) is used for the second solution. The X-axis 700 shows the concentration in g/L, The Y-axis 702 shows the measured signal for a bi chromatic calculation. The difference of absorption at two different wavelengths is used. In this particular case, for IGA-1, the signal is the different of the absorption at 340 nm minus the absorption at 700 nm. There are two calibration curves shown. One using a standard calibration 704 which was performed on the instrument making the measurements. The second calibration curve 706 was performed using a calibration as is illustrated in Fig. 4 and the above table. Comparing the two curves 704, 706 it can be seen that the difference is not visible in the plot.

Fig. 8 is used to illustrate the difference between the curves 704 and 706 in Fig. 7. The X-axis 700 is the concentration and Y-axis 800 shows the different between curves 706 and 704 in terms of the percent change. The percent error or change is shown to be below 1 percent for all but low concentrations.

Fig. 9 shows the difference between curves 704 And 706 in absolute terms. The X-axis 700 is the concentration and the Y-axis 900 is the measured signal. Again 1 corresponds to the entire signal be absorbed as is the axis 702 in Fig. 7. From this plot it can be seen that at low concentrations the difference or error between the two calibrations is small. Figs 8 and 9 together illustrate the effectiveness of the calibration.

The table below is used to illustrate an alternative where a linear fit is calculated between the module specific components and the reference set of signals. The linear fit comprises a calibration constant and an offset constant. The determination of the lot calibration for the first photometry module is then determined by adding the offset constant to the product of the calibration constant and the lot specific set of signals.

As with the previous example, the non-linear calibration curves is built up using six calibration points.

Concentration	Signal(ABS)	S (from second module)	Factor	constant
C ₀	$S_0 = S_{0 \text{ (lot)}} * (1+x) + b$	$S_{0 \text{ (lot)}}$	a	b
C ₁	$S_1 = S_{1 \text{ (lot)}} * (1+x) + b$	$S_{1 \text{ (lot)}}$	a	b
C ₂	$S_2 = S_{2 \text{ (lot)}} * (1+x) + b$	$S_{2 \text{ (lot)}}$	a	b
C ₃	$S_3 = S_{3 \text{ (lot)}} * (1+x) + b$	$S_{3 \text{ (lot)}}$	a	b
C ₄	$S_4 = S_{4 \text{ (lot)}} * (1+x) + b$	$S_{4 \text{ (lot)}}$	a	b
C ₅	$S_5 = S_{5 \text{ (lot)}} * (1+x) + b$	$S_{5 \text{ (lot)}}$	a	b

In this table the Factor "x" is the calibration constant, the values of S with the (lot) subscript are the lot specific set of signals, and b is the offset constant. The module specific factors "x" and "b" can be derived by least square regression during initial setup of the module.

Fig. 10 illustrates two calibration curves for the Roche IGA-2 reagent used on a Roche Cobas c system using the same data as was used in Fig. 7. There are also two calibration curves shown in Fig 10. One curve uses the standard calibration 704 which was performed on the instrument making the measurements. The second calibration curve 1000 was performed using a calibration as is illustrated in the above table with both the calibration constant and the offset constant. Comparing the two curves 704, 1000 it can be seen that the difference is not visible in the plot.

Fig. 11 is used to illustrate the difference between the curves 704 and 1000 in Fig. 10. The X-axis 700 is the concentration and Y-axis 800 shows the different between curves 1000 and 704 in terms of the percent change. The percent error or change is shown to be reduced when compared to the percentage error shown in Fig. 8.

List of reference numerals

	200	analysis system
5	202	automatic analyzer
	204	biological sample
	206	dispenser
	206'	dispenser
	208	second lot of reagent
10	208'	first lot of reagent
	210	first photometric module
	210'	second photometric module
	212	computer
	212'	computer
15	214	hardware interface
	216	processor
	218	network interface
	218'	network interface
	220	computer storage
20	222	computer memory
	224	set of module specific components
	226	lot specific set of signals
	228	lot calibration
	230	measurement signal
25	232	value representing a physical property
	240	control module
	242	calibration calculation module
	244	measurement calculation module
	300	analysis system
30	302	calibration analyzer
	304	sample movement system
	306	preliminary calibration signals
	308	calibration protocol module
	310	reference set of signals

	312	lot specific set of signals
	314	server
	400	concentration
	402	signal
5	600	X-axis (concentration)
	602	Y-axis (signal)
	604	concentration of analyte
	606	concentration of analyte
	608	signal
10	610	signal
	700	Y-axis (signal)
	704	calibration curve
	706	calibration curve
	800	Y-axis (percent change)
15	900	Y-axis (absolute difference)
	1000	calibration curve

C l a i m s

- 5 1. A method of determine a physical property of a biological sample, wherein the method comprises the steps of:
- acquiring (100) a set of preliminary calibration signals (306) of a first lot (208') of a reagent using an automatic analyzer (202) according to a calibration protocol (308), wherein the automatic analyzer acquires the preliminary calibration signals using a
 - 10 first photometry module (210);
 - acquiring (102) a reference set of signals (310) of the first lot of the reagent using a calibration analyzer (302) according to the calibration protocol, wherein the calibration analyzer acquires the reference set of signals using a second photometry module (210');
 - 15 - determining (104) a set of module specific components (224) by subtracting the reference set of signals from the preliminary calibration signals;
 - acquiring (106) a lot specific set of signals (226) of a second lot of the reagent using the second photometry module according to the calibration protocol;
 - determining (108) a lot calibration (228) for the first photometry module using the
 - 20 set of module specific components and the lot specific set of signals; and
 - acquiring (110) a measurement signal (230) of the biological sample using the first photometry module and the second lot of the reagent; and
 - determining (112) a physical property (232) of the biological sample using the measurement signal and the lot calibration.
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2. The method of claim 1, wherein the method further comprises the steps of:
- acquiring at least one additional calibration signal of the second lot of reagent using the first photometry module; and
 - adjusting the calibration using the at least one additional calibration signal.
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3. The method of claim 2, wherein the measurement of the at least one additional calibration signals and the adjusting of the calibration using the at least one additional calibration signal is repeated after a predetermined duration.

4. The method of claim 1, 2, or 3, wherein the step of determining the lot calibration for the first photometry module comprises adding the set of module specific components to the lot specific set of signals

5. The method of claim 1, 2, or 3, wherein the method further comprises the step of: calculating an calibration constant by dividing the set of module specific components by the reference set of signals, wherein the determination of the lot calibration for the first photometry module is determined by multiplying the quantity 1 plus the calibration constant by the lot specific set of signals.

6. The method of claim 1, 2, or 3, wherein the method further comprises the step of: calculating a linear fit between the module specific components and the reference set of signals, wherein the linear fit comprises a calibration constant and an offset constant, wherein the determination of the lot calibration for the first photometry module is determined by adding the offset constant to the product of the calibration constant and the lot specific set of signals.

7. The method of any one of the preceding claims, wherein In another embodiment the photometry module is configured for measuring the absorbance of the biological sample.

8. The method of claim 7, wherein the the preliminary calibration signals, the reference set of signals, the lot specific set of signals, and the measurement signal are photometric absorbance measurements.

9. The method of any one of the preceding claims, wherein the physical property is the concentration of an analyte.

10. The method of claim 9, wherein the analyte is any one of the following: an enzyme, a substrate, a protein, an indicator of drug abuse, and an indicator for monitoring therapeutic drug use.

11. The method of claim 9, the analyte is any one of the following: Alumin (BCP+BCG) , Ammonia, Bicarbonate, Bilirubin-direct, Bilirubin-total, Calcium,

Cholesterol, HDL Cholesterol, LDL Cholesterol, Creatinine enz., Creatinine Jaffé ,
 Fructosamine, Glucose, Iron, Lactate, Magnesium, Phosphorus, Total Protein, Total
 Protein U / CSF, Triglycerides, Triglycerides GB, UIBC, Urea / BUN, Uric Acid, ACP,
 ALP, ALT / GPT, Amylase-tot., Amylase-pancr., AST / GOT, Cholinesterase Acetyl,
 5 Cholinesterase Butyryl, Cholinesterase Dibucain, CK, CK-MB, GGT, GLDH, HBDH,
 LDH, Lipase, Chloride, Potassium, Sodium, α 1-Acid Glycoprotein, α 1-Antitrypsin,
 α 1-Microglobulin, β -Microglobulin, Albumin (immuno.), APO A1, APO B, ASLO, C3c,
 C4, Ceruloplasmin, CRP, CRP High Sensitivity, Cystatin C, Ferritin, Haptoglobin,
 HbA1c (whole blood + hemolysate), Homocysteine, IgA, IgG, IgM, Kappa Light
 10 chains, Freelit Human Lambda Free, Lambda Light chains, Lipoprotein (a),
 Myoglobin, Prealbumin, RF, Soluble Transferrin Receptor, Transferrin, D-Dimer, and
 Anti-Thrombin III

12. The method of claim 9, wherein the analyte may be for testing the usage of
 15 any one of the following drugs: Amphetamines, Barbiturates, Benzodiazepines,
 Cannabinoids, Cocaine, LSD, Ethanol, Methadone, Methadone Methabolite
 (EDDP), Methaqualone, Opiates, Oxycodone, Phencyclidine, Propoxyphene,
 Acetaminophen, Amikacin, Carbamazepine, Digitoxin, Digoxin, Gentamicin,
 Lidocaine, Lithium, MPA-T, NAPA, Phenobarbital, Phenytoin, Procainamide,
 20 Quinidine, Salicylate, Theophylline, Tobramycin, Valproic Acid, and Vancomycin.

13. An analysis system (200, 300) comprising an automatic analyzer for
 analyzing a biological sample (204, 204'), wherein the automatic analyzer further
 comprises a dispenser (206, 206') for dispensing a reagent into the biological
 25 sample, wherein the automatic analyzer comprises a first photometric module (210)
 for acquiring a measurement signal (230) of the biological sample, wherein the
 analysis system comprises a memory (222) for storing machine executable
 instructions (240, 242, 244), wherein the automatic analyzer comprises an analyzer
 controller (212) for controlling the automatic analyzer, wherein execution of the
 30 machine executable instructions cause the analyzer controller to:
 - receive a set of module specific components (224);
 - receive a lot specific set of signals (312);

- determine a lot calibration (228) according to a calibration protocol for a second lot of a reagent using the set of module specific components and the lot specific set of signals;
- dispense a portion of the second lot of reagent into the biological sample using the dispenser;
- acquire (110) the measurement signal of the biological sample using the first photometry module; and
- determine (112) a physical property (232) of the biological sample using the measurement signal and the lot calibration.

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14. The analysis system of claim 13, wherein the analysis system further comprises a calibration analyzer (302) with a second photometry module (210'), wherein the analysis system further comprises a calibration controller (212'), wherein execution of the instructions cause the analyzer controller to acquire (100) a set of preliminary calibration signals (306) of a first lot of a reagent using the automatic analyzer according to a calibration protocol (308), wherein the automatic analyzer is operable to acquire the preliminary calibration signals using the first photometry module, wherein execution of the machine executable instructions cause the calibration controller to acquire (102) a reference set of signals (310) of the first lot of the reagent using the calibration analyzer according to the calibration protocol, wherein the calibration analyzer acquires the reference set of signals using the second photometry module, wherein the analysis system is operable to determine (104) the set of module specific components by subtracting the reference set of signals from the preliminary calibration signals, wherein execution of the machine executable instructions cause the calibration controller to acquire (106) the lot specific set of signals of a second lot of the reagent using the second photometry module according to the calibration protocol, and wherein the analyzer controller is operable to receive the calibration correction components from the analysis system.

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15. The analysis system of claim 13 or 14, wherein execution of the machine executable instructions causes the analyzer controller to:

- acquire at least one additional calibration signal of the second lot of reagent using the first photometry module; and
- adjust the calibration using the at least one additional calibration signal.

16. The analysis system of claim 15, wherein execution of the machine executable instructions causes the analyzer controller to repeat the acquisition of the at least one additional calibration signal and the adjusting of the calibration using the at least two additional calibrations signals after a predetermined duration.

17. The analysis system of any one of the claims 13 through 16, wherein analysis system is further operable for determining the lot calibration for the first photometry module comprises adding the set of module specific components to the lot specific set of signals.

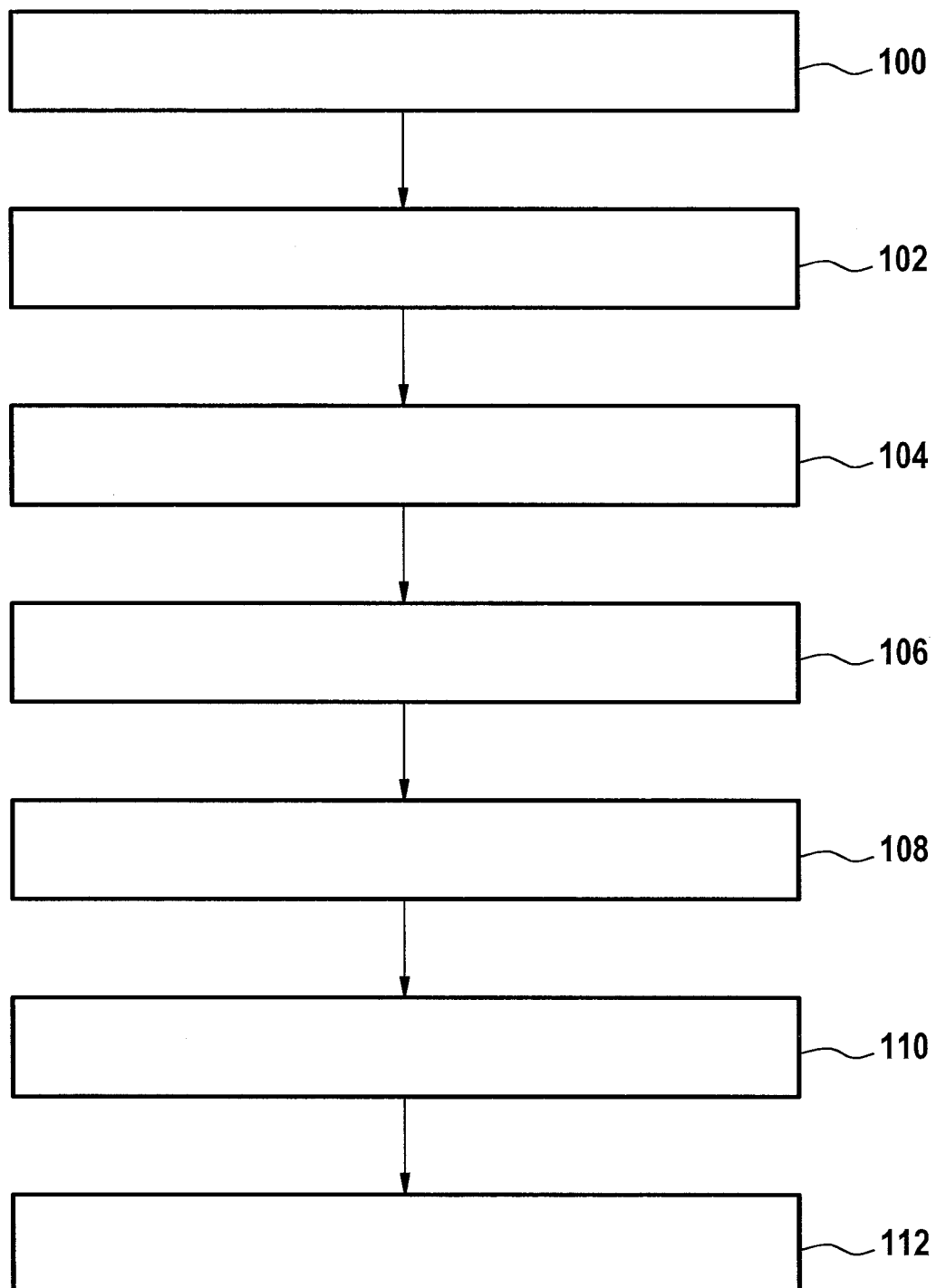
18. The analysis system of any one of the claims 13 through 16, wherein the analysis system is further operable for calculating an calibration constant by dividing the set of module specific components by the reference set of signals, wherein the determination of the lot calibration for the first photometry module is determined by multiplying the quantity 1 plus the calibration constant by the lot specific set of signals.

19. The analysis system of any one of claims 13 through 16. wherein the analysis system is further operable for calculating a linear fit between the module specific components and the reference set of signals, wherein the linear fit comprises a calibration constant and an offset constant, wherein the determination of the lot calibration for the first photometry module is determined by adding the offset constant to the product of the calibration constant and the lot specific set of signals.

20. The analysis system of any one of claims 13 to 19, wherein the analysis system further comprises a server for transferring any one of the following to the automatic analyzer via a computer network: the set of calibration correction components, the lot specific set of signals, and combinations thereof.

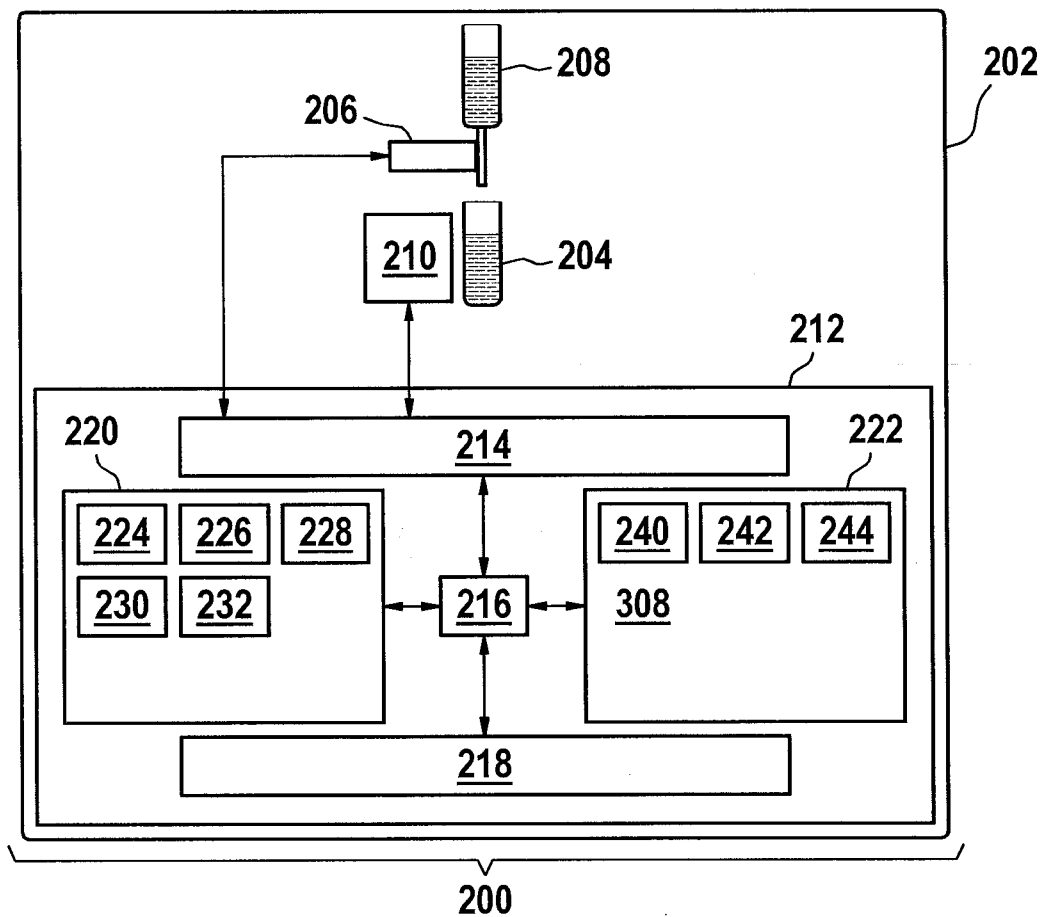
21. The analysis system of any one of claims 13 to 20, wherein the analysis system further comprises a reagent cartridge at least partially filled with the second lot of the reagent, and wherein the dispenser is operable for dispensing reagent from the reagent cartridge.

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Fig. 1

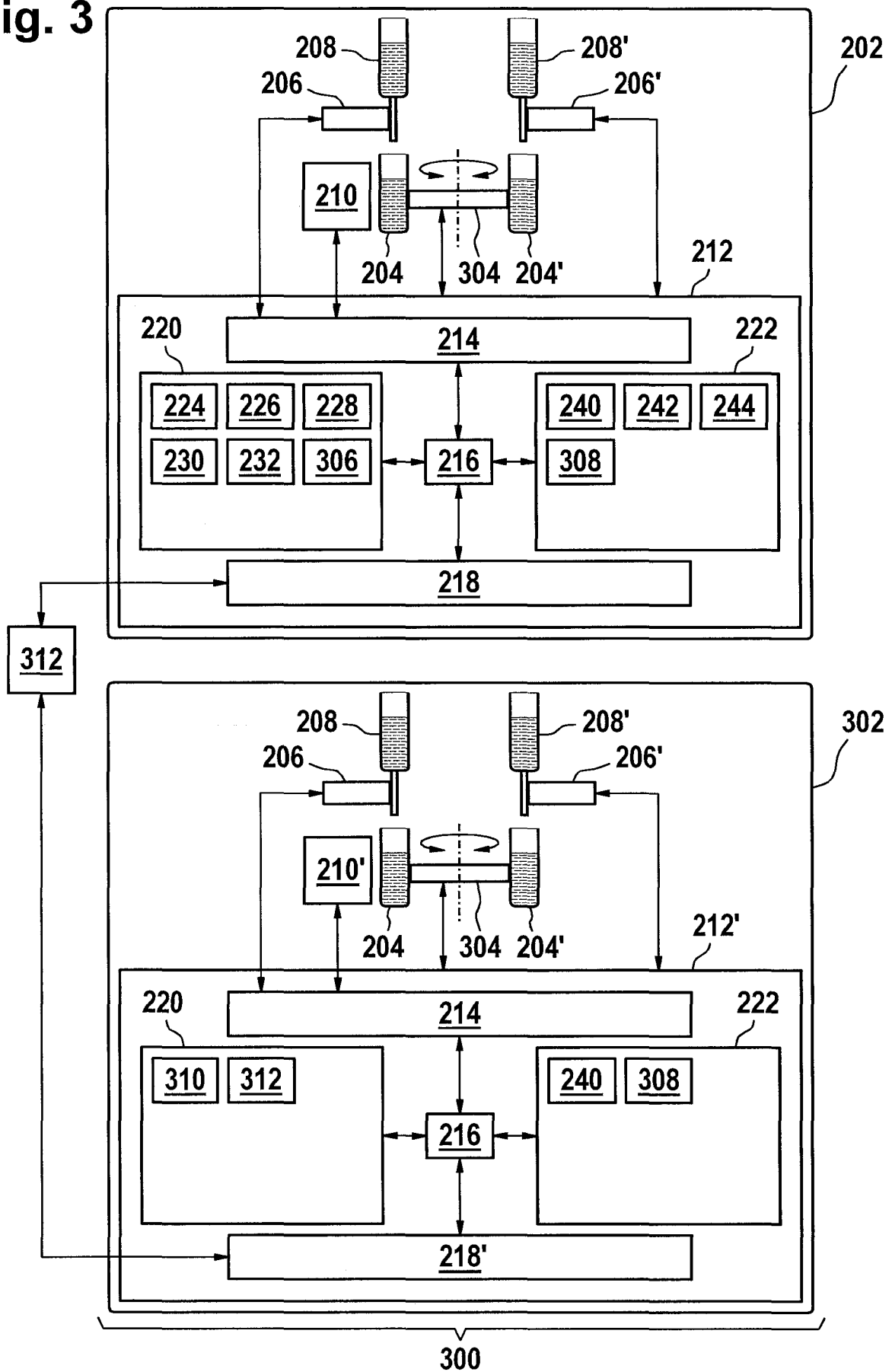
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Fig. 2



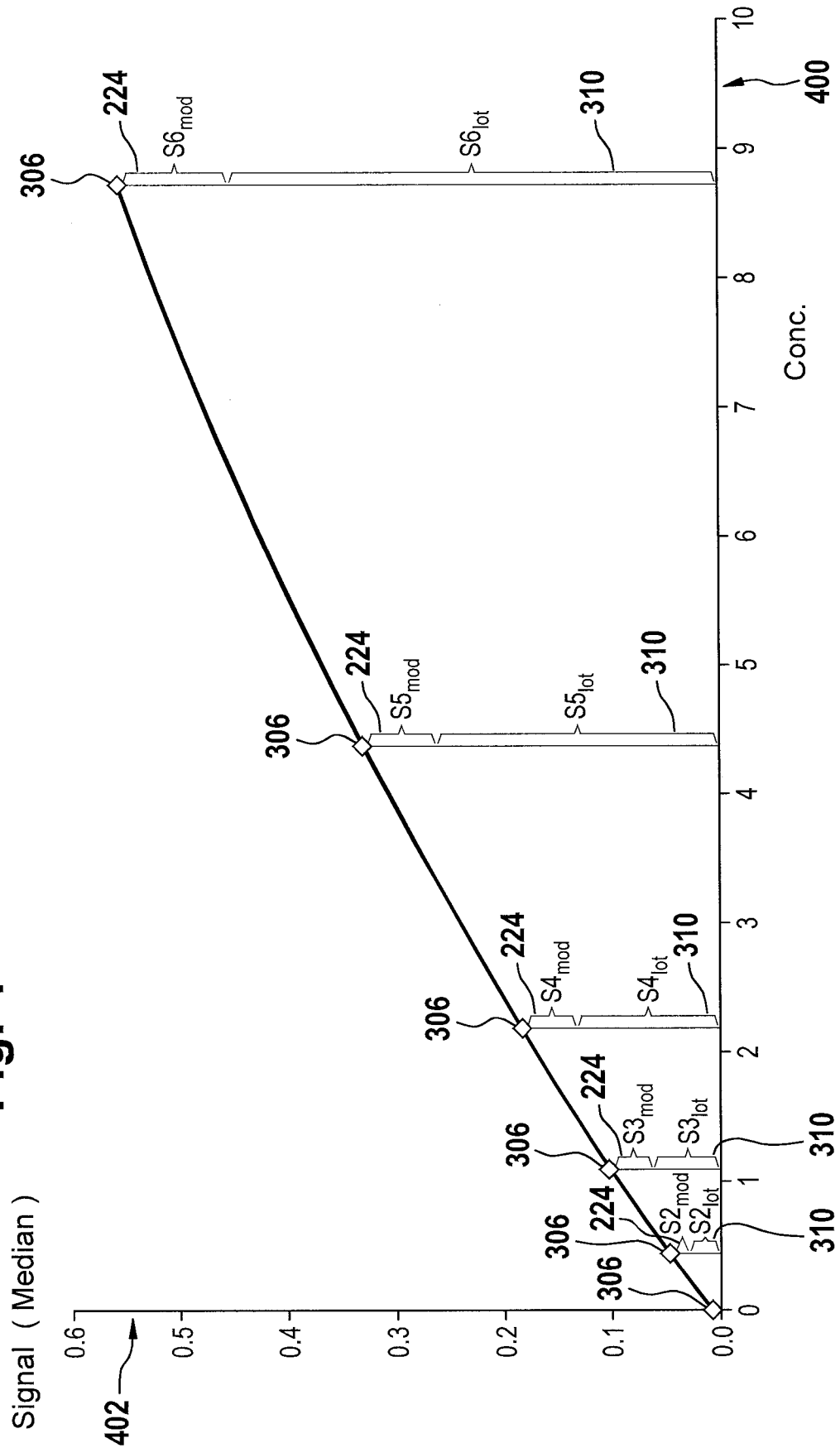
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Fig. 3



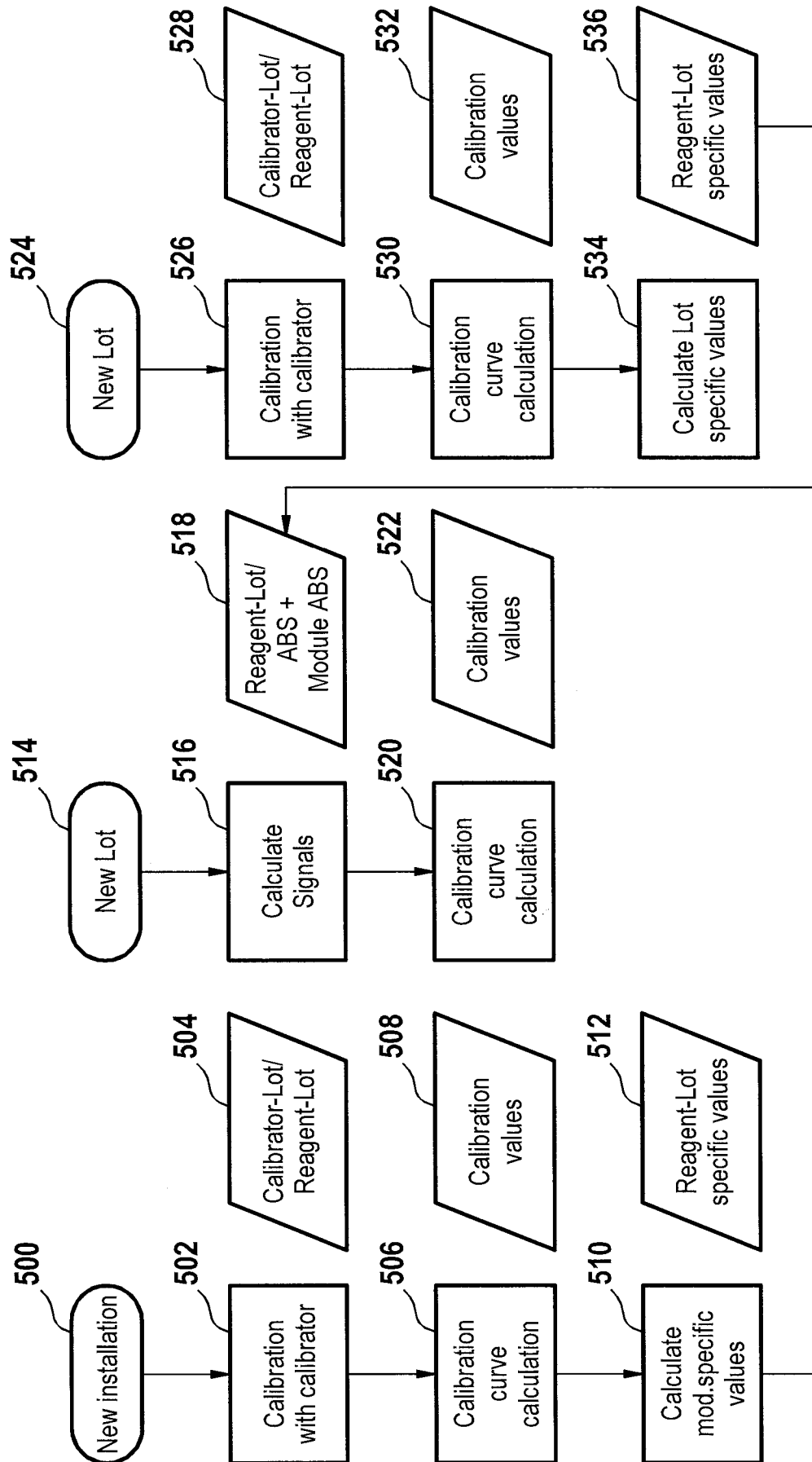
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Fig. 4

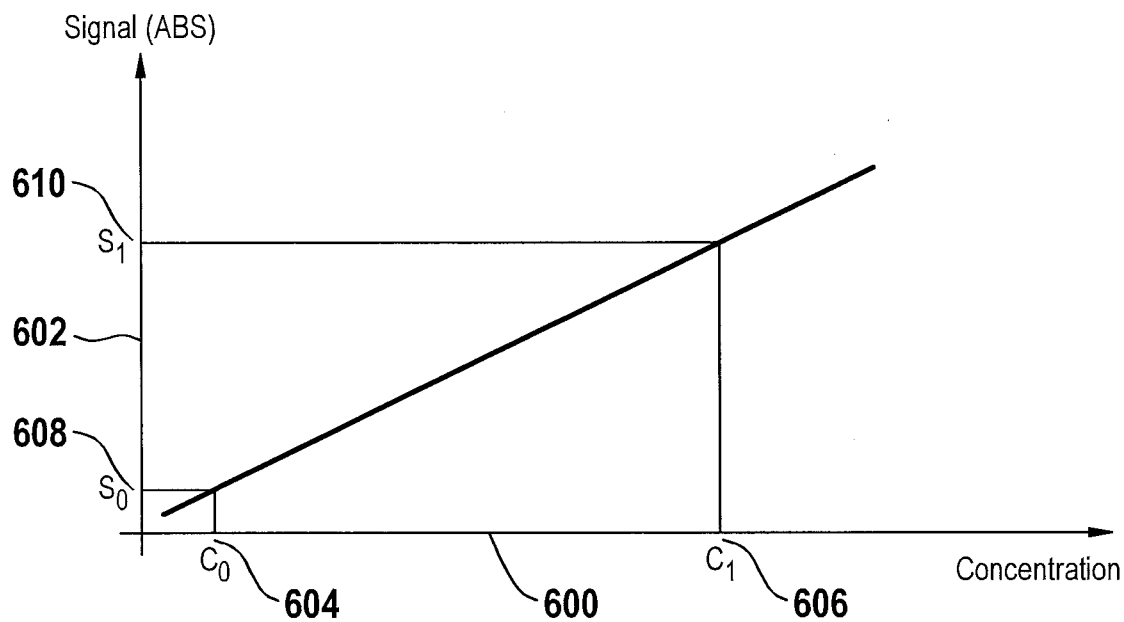
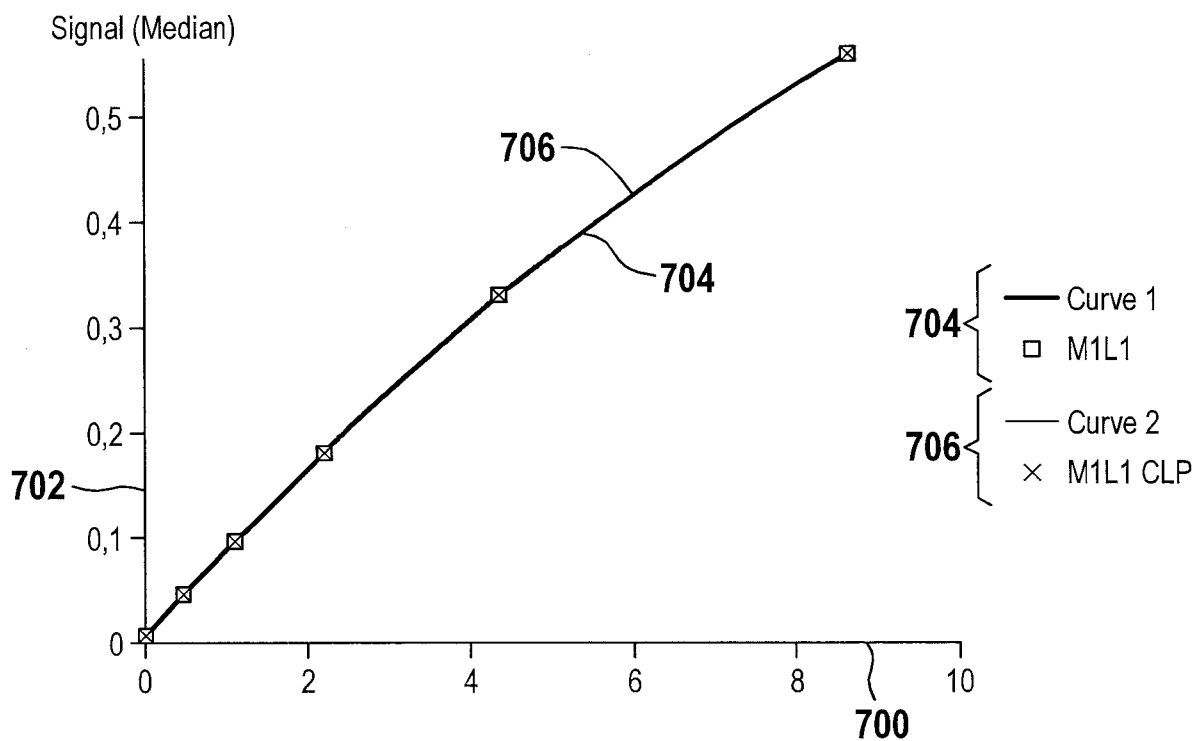


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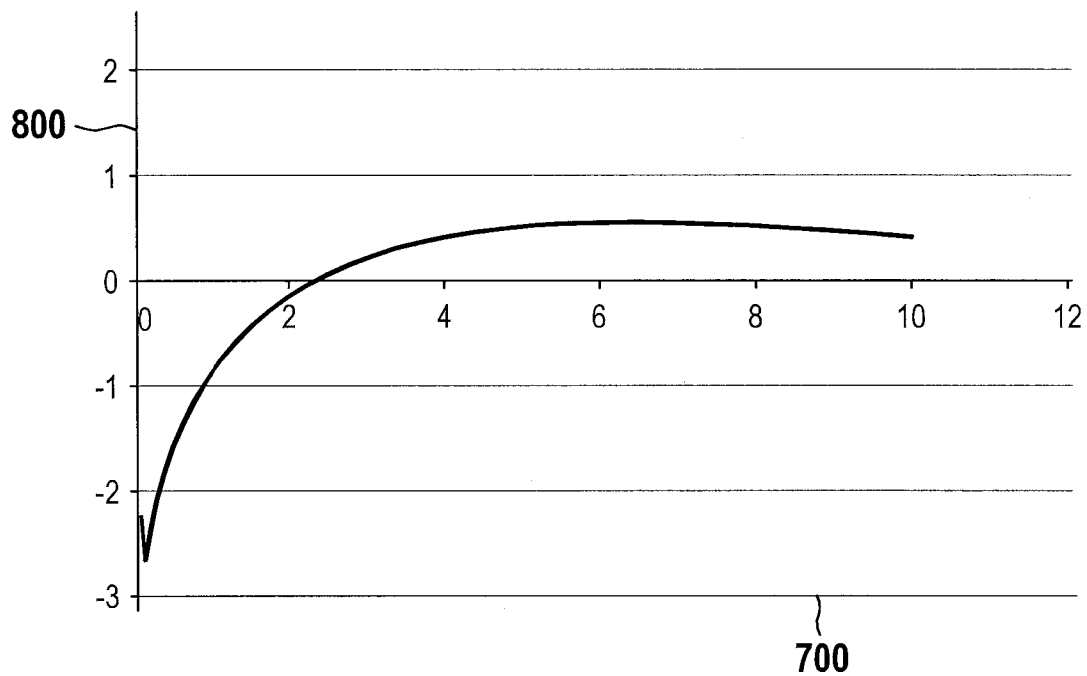
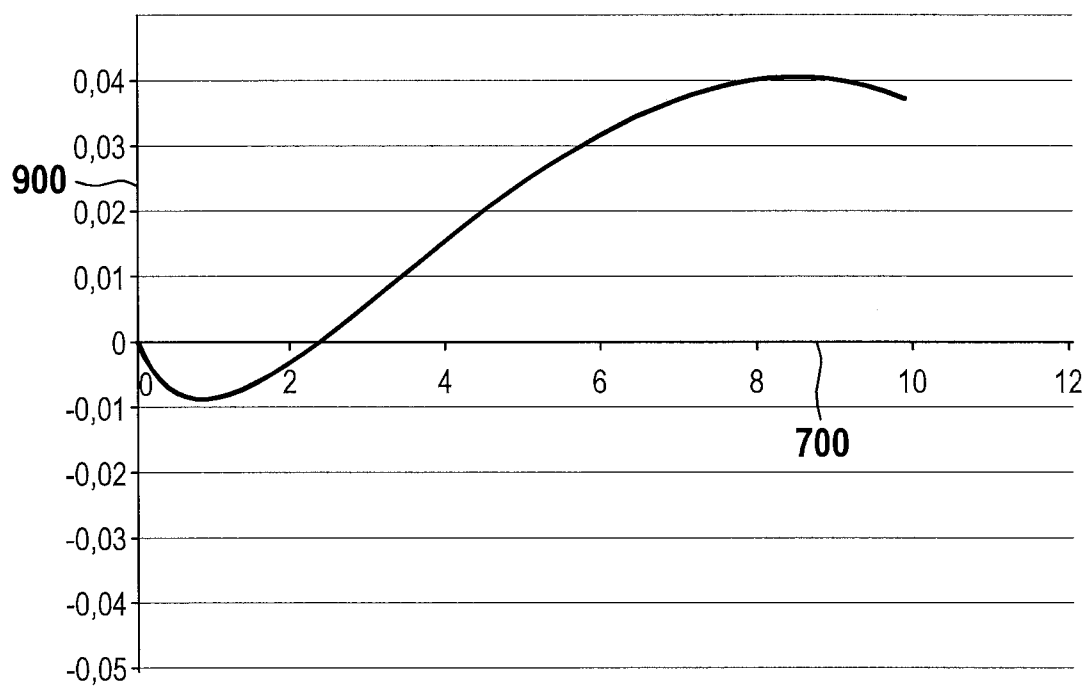
Fig. 5



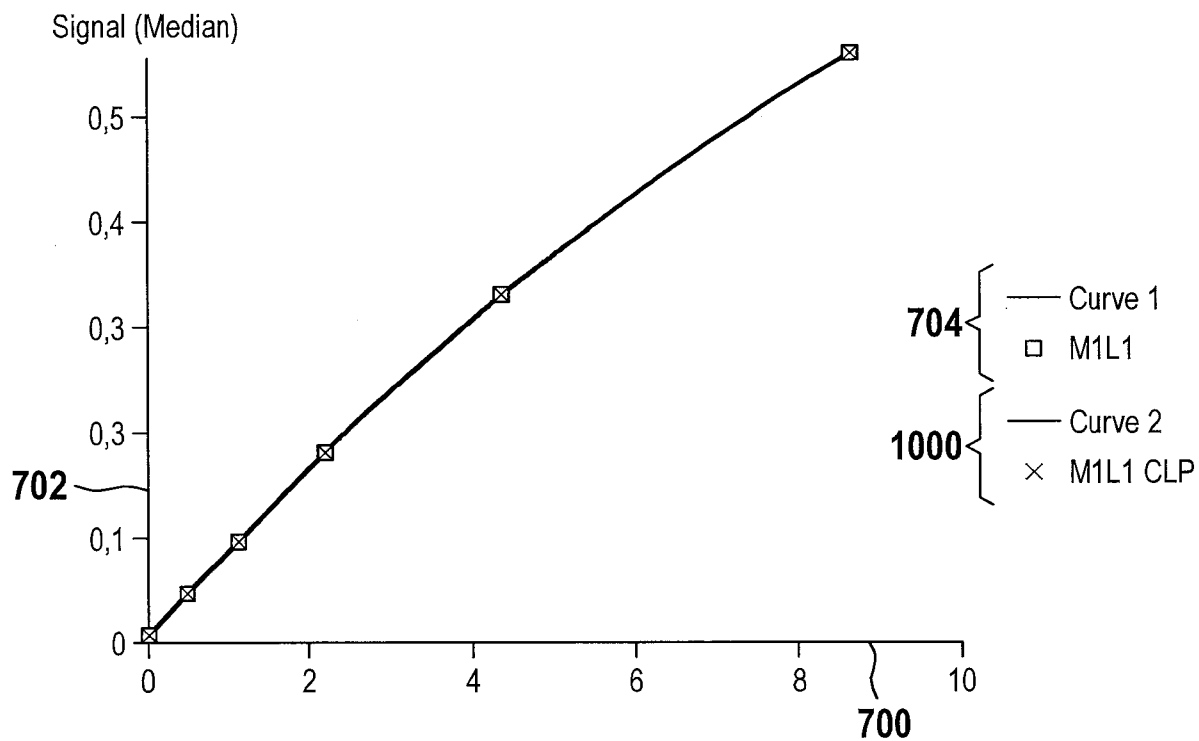
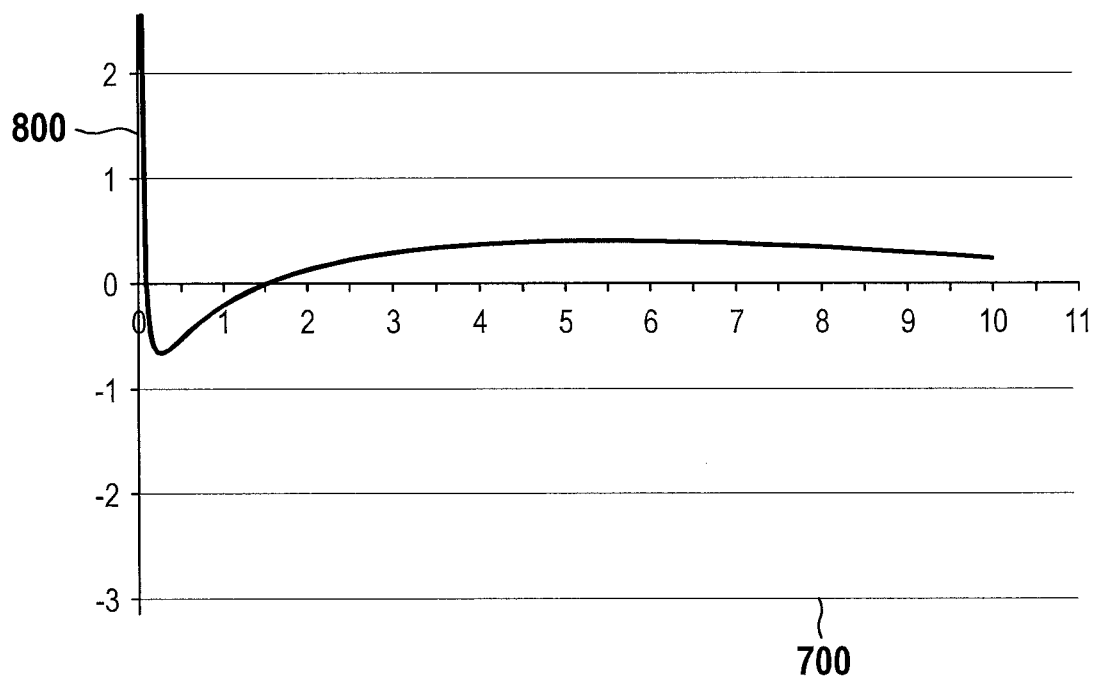
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Fig. 6**Fig. 7**

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Fig. 8**Fig. 9**

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Fig. 10**Fig. 11**

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/062015

A. CLASSIFICATION OF SUBJECT MATTER

INV. G01N21/25 G01N21/27 G01N35/00
ADD.

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 A61B

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)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 975 623 A2 (SYSMEX CORP [JP]) 1 October 2008 (2008-10-01) abstract; paragraphs [0002], [0004], [0015] - [0026], [0079] - [0090]; figures 4,16 -----	1-21
A	US 4 935 875 A (SHAH RAMESH M [US] ET AL) 19 June 1990 (1990-06-19) abstract; column 6, lines 5-18; column 13, lines 15-23 -----	1-21
A	US 2003/107738 A1 (CURTIS RICHARD H [US]) 12 June 2003 (2003-06-12) abstract; paragraphs [0064], [0066] ----- -/-	1-21



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

"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

2 September 2014

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