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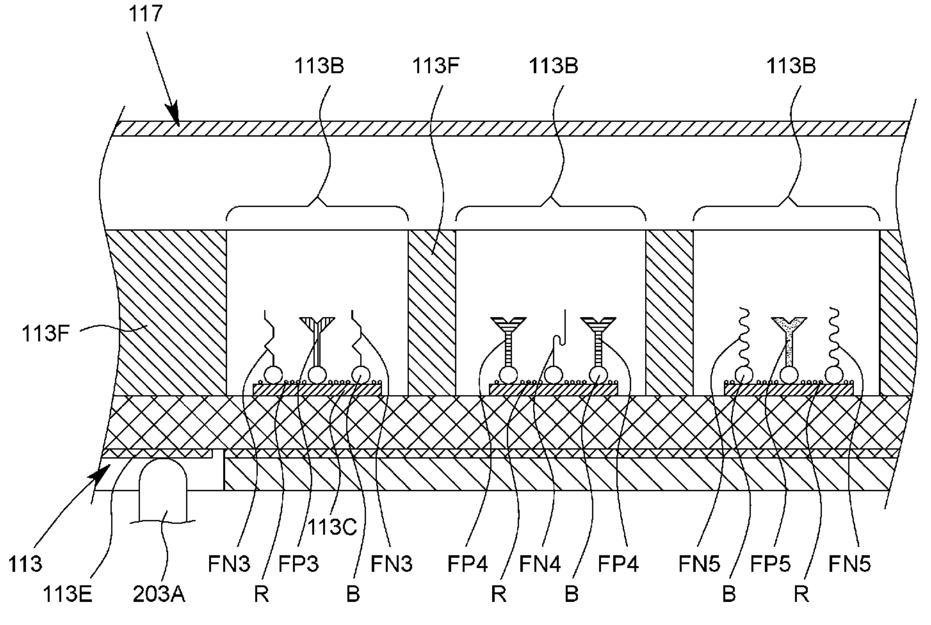

Fig. 7

(57) Abstract: An analysis system and a method for testing a biological sample is proposed, wherein a plurality of assays selected from at least two assays from a group consisting of a protein assay for detecting a target protein, a nucleic-acid assay for detecting a target nucleic-acid sequence and/or an aptamer assay for detecting another target analyte are carried out preferably simultaneously in a common sensor array by means of a sensor apparatus.

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Analysis system and method for testing a sample

The present invention relates to an analysis system according to the preamble of claim 1, to a method according to the preamble of claim 18 and to the use of claim 30.

Preferably, the present invention deals with analysing and testing a sample, in particular from a human or animal, particularly preferably for analytics and diagnostics, for example with regard to the presence of diseases and/or pathogens and/or for determining blood counts, antibodies, hormones, steroids or the like. Therefore, the present invention is in particular within the field of bioanalytics. A food sample, environmental sample or another sample may optionally also be tested, in particular for environmental analytics or food safety and/or for detecting other substances.

Preferably, by means of the present invention, at least one analyte (target analyte) of a sample can be identified, determined or detected. In particular, the sample can be tested for qualitatively or quantitatively determining at least one analyte, for example in order for it to be possible to detect or identify a disease and/or pathogen.

Within the meaning of the present invention, analytes are in particular nucleic-acid sequences, in particular DNA sequences and/or RNA sequences, or proteins, in particular antigens and/or antibodies, or other analytes, in particular hormones, low-molecular substances, steroids, organophosphates or the like. In particular, by means of the present invention, nucleic-acid sequences can be determined or detected as analytes of a sample, proteins can be determined or detected as analytes of the sample, or other analytes of the sample can be determined or detected. More particularly preferably, the present invention deals with systems, devices and other apparatuses for carrying out a nucleic-acid assay for detecting a nucleic-acid sequence, a protein assay for detecting a protein, or an aptamer assay for detecting a protein, a low-molecular substance, a steroid, an organophosphate or other target analytes.

The present invention deals in particular with what are known as point-of-care systems, i.e. in particular with mobile systems, devices and other apparatuses, and deals with methods for carrying out tests on a sample at the sampling site and/or separately or away from a central laboratory or the like. Preferably, point-of-care systems can be operated autonomously or independently of a mains network for supplying electrical power.

US 5,096,669 discloses a point-of-care system for testing a biological sample, in particular a blood sample. The system comprises a single-use cartridge and an analysis device. Once the sample has been received, the cartridge is inserted into the analysis device in order to carry out the test. The cartridge comprises a microfluidic system and a sensor apparatus comprising electrodes, which apparatus is calibrated by means of a calibration liquid and is then used to test the sample.

Furthermore, WO 2006/125767 A1 discloses a point-of-care system for integrated and automated DNA or protein analysis, comprising a single-use cartridge and an analysis device for fully automatically processing and evaluating molecular-diagnostic analyses using the single-use cartridge. The cartridge is designed to receive a sample, in particular blood, and in particular allows cell disruption, PCR and detection of PCR amplification products, which are bonded to capture molecules and provided with a label enzyme, in order for it to be possible to detect bonded PCR amplification products or nucleic-acid sequences as target analytes in what is known as a redox cycling process.

US 2014/0377852 A1 discloses a microfluidic device for performing protein assays and/or nucleic acid assays, wherein glass nano-reactors formed by functionalised micro-length tubes are used for optical detection. The glass nano-reactors can be made with captures strands complementary to a sequence of interest. Multiple different populations of glass nano-reactors, specific for different DNA target populations can be used.

Furthermore, the scientific publication "Isothermal Amplification and Quantification of Nucleic Acids and its Use in Microsystems" according to Tröger et al., published in Journal of Nanomedicine & Nanotechnology, 2015, vol. 6, issue 3, relates to microfluidic platforms and lab-on-a chip devices and particularly to isothermal amplification methods and their implementation in micro systems in relation to quantification of nucleic acids.

Likewise, the scientific publication "Point-of-care-testing of nucleic acids by microfluidics" according to Zhang et al., published in Trends in Analytical Chemistry, 2017, vol. 94, pages 106 to 116, gives an overview on microfluidics-based point of care testing of nucleic acids, particular in connection with diagnosing pathogen infection and monitoring disease treatment.

The scientific publication "Microfluidic devices for sample preparation and rapid detection of foodborne pathogens" according to Kant at al., published in Biotechnology Advances, 2013, vol. 36, pages 1003 to 1024, relates to the detection of foodborne pathogens via microfluidic devices and lab-on chip technology.

WO 2018/065104 A1 discloses an analysis system and a method for testing a biological sample, wherein a plurality of assays selected from at least two assays from a group consisting of a protein assay for detecting target protein, a nucleic-assay for detecting a target nucleic-acid sequence and/or an aptamer assay for detecting another target analyte are carried out sequentially in a common sensor array by means of a sensor apparatus. However, due to the high temperatures, which are necessary for the amplification of the target nucleic-acids, the analysis system and method require a spatial and temporal separation of the amplification of target nucleic-acids from the capture proteins and capture aptamers and from the protein and/or aptamer assay.

Overall, point-of-care systems and microfluidic devices according to the prior art are linked with several disadvantages. Point-of-care systems as known in the prior art often require the application of high temperatures of about 90 °C, particularly when an amplification of target DNA by PCR is necessary. The application of high temperatures, particularly thermal cycling reactions like the PCR, are highly energy and time consuming. Furthermore, in case of a simultaneous or sequential detection of antigens, antibodies, hormones and the like, the high temperatures lead to a denaturation of the proteins. Furthermore, high temperature of some reactions, particularly of amplification reactions, require a spatial and temporal separation of such reaction, which leads to longer run-times of testing samples.

Therefore, the problem addressed by the present invention is to provide an improved analysis system and an improved method for testing a sample, a simple and/or compact construction or design of the analysis system and/or comprehensive, efficient, rapid, reliable, energy-efficient and/or precise testing of the sample, in particular at a high sample throughput, preferably being made possible or facilitated thereby. Furthermore, an improved or simplified use of the reagents necessary for testing the sample is desired.

The above problem is solved by an analysis system according to claim 1 or by a method according to claim 18 or by a use according to claim 30. Advantageous developments are the subject of the dependent claims.

The proposed analysis system for testing an in particular biological sample preferably comprises a sensor arrangement/apparatus for identifying or detecting – preferably multiple different – analytes of the sample.

The analysis system preferably comprises a fluid system having a plurality of channels.

The sensor arrangement/apparatus preferably comprises a sensor array.

The sensor arrangement/apparatus, in particular the sensor array, preferably comprises a plurality of sensor fields and/or electrodes.

Particularly, the analysis system preferably comprises a cartridge having the fluid system and the sensor arrangement/apparatus, the cartridge and/or sensor arrangement/apparatus preferably being provided with at least one reagent for an amplification of target nucleic acid sequences and furthermore with capture molecules for capturing and/or bonding the analytes.

Particularly preferably, the analysis system, its cartridge or fluid system comprises a sensor compartment, with the sensor apparatus or a sensor array thereof being arranged within the sensor apparatus.

One aspect of the present invention is that the analysis system or sensor apparatus comprises at least one reagent and/or reaction mix for isothermal DNA amplification of at least one analyte or multiple/different analytes in the sensor compartment. In other words, according to the present invention at least one reagent and/or reaction mix for isothermal DNA amplification are used for an DNA amplification of one or more analytes of the sample in a sensor compartment of the analysis system, particularly of a sensor apparatus or sensor arrangement of the analysis system or the cartridge.

In particular, it is an aspect of the present invention that the sensor arrangement/apparatus, particularly the sensor array and/or (some or all) sensor fields and/or electrodes of the sensor arrangement/apparatus, comprises/comprise capture nucleic acid sequences and at least one reagent for carrying out an amplification reaction of target nucleic acid sequences as analytes from the sample in the sensor array of the sensor arrangement/apparatus. Particularly, the analysis system of the present invention is designed to allow an amplification of target analytes, in particular target nucleic acid sequences, in/on and/or by means of the (same) sensor arrangement/apparatus, in particular the (same) sensor array, the (same) sensor fields and/or the (same) electrodes.

Contrary to point-of-care systems known in the prior art, according to the present invention a spatial and/or temporal separation of amplification reactions from the detection and measurement of analytes in the analysis system is not intended. Instead, the analysis system, in particular the sensor arrangement/apparatus, is designed to allow an amplification of target analytes, particularly target nucleic acid sequences, on the one hand, and bonding of analytes, particularly target molecules, in a sample to capture molecules and detection and/or measurement of bonded analytes, particularly target molecules, on the other hand, in/on and/or by means of the (common) sensor arrangement/apparatus, preferably the (same) sensor fields and/or the (same) electrodes.

One further aspect of the present invention according to a particularly preferred embodiment is that the sensor arrangement/apparatus – preferably the sensor array, (some or all) sensor fields and/or electrodes thereof – comprises capture nucleic acid sequences and at least one more type of capture molecules selected from capture proteins and/or capture aptamers, in particular in order to bond target analytes, preferably target nucleic acid sequences which correspond to the capture nucleic acid sequences, target proteins and/or target hormones, which correspond to the capture proteins and/or target proteins, low-molecular substances, steroids, organophosphates or other target analytes, which correspond to the capture aptamers. Furthermore, the sensor arrangement/apparatus, preferably the sensor array, (some or all) sensor fields and/or electrodes thereof, comprises at least one reagent for carrying out an amplification reaction of analytes on the basis of target nucleic acid sequences.

In other words, the analysis system of the present invention allows an amplification of target nucleic acid sequences as well as bonding of (different) analytes and the bonding and/or hybridisation of analytes to capture molecules and detection assays, particularly the detection of nucleic acids, proteins, hormones etc., in a common reaction room on the basis of the sensor arrangement/apparatus. Therefore, the present invention provides an analysis system which overcomes the often necessary spatial and temporal separation of amplification reactions from the detection assays.

The analysis system is linked with several advantages, in particular a higher throughput and shorter run-times for analysing a sample.

According to a preferred embodiment of the present invention, target nucleic acid sequences are amplified at constant and relatively low temperatures of preferably less than 45 °C by means of the sensor arrangement/apparatus.

Due to the constant and lower amplification temperature, the analysis system according to the present invention is not only energy efficient but also prevents proteins on or in the sensor arrangement/apparatus, either in the form of capture proteins or in the form of target proteins, from being denatured, in particular during amplification of the target nucleic acid sequences. On this basis, target proteins can be bonded to the corresponding capture molecules simultaneously with or after amplification and bonding of the target nucleic acid sequences.

Overall, the analysis system according to the present invention allows comprehensive, efficient, rapid, reliable, energy-efficient and/or precise testing of the sample, in particular detection of the analytes, and a high sample throughput.

According to a first embodiment, the sensor arrangement/apparatus, in particular (some or all) sensor fields and/or electrodes, comprise/comprises both capture nucleic acid sequences as well as capture proteins as capture molecules, preferably in order to bond target analytes, in particular target proteins and/or target hormones, which correspond to the capture proteins, and to bond target analytes, in particular target nucleic acid sequences, which correspond to the capture nucleic acid sequences.

According to another embodiment, the sensor arrangement/apparatus, in particular (some or all) sensor fields and/or electrodes, comprise/comprises both capture nucleic acid sequences and capture aptamers as capture molecules, in particular in order to bond target analytes, in particular target proteins, low-molecular substances, steroids, organophosphates or other target analytes, which correspond to the capture aptamers, and to bond target analytes, in particular target nucleic acid sequences which correspond to the capture nucleic acid sequences.

According to a further embodiment, the sensor arrangement/apparatus, in particular (some or all) sensor fields and/or electrodes, comprise/comprises besides capture nucleic acid sequences capture proteins as well as capture aptamers as capture molecules, in particular in order to target analytes, in particular target nucleic acid sequences, which correspond to the capture nucleic acid sequences, target proteins, which correspond to the capture proteins, and/or low molecular substances, steroids, organophosphates or other target analytes, which correspond to the capture aptamers.

According to another aspect of the present invention, the analysis system and/or the cartridge, particularly the sensor arrangement/apparatus, is designed to carry out an amplification of target nucleic acid sequences from the sample.

In order to allow an amplification of target nucleic acid sequences, it is particularly preferred that the sensor arrangement/apparatus, in particular (some or all) sensor fields and/or electrodes, comprise/comprises at least one reagent for the amplification, preferably a reaction mix.

According to a particularly preferred embodiment, the sensor arrangement/apparatus, in particular (some or all) sensor fields and/or electrodes, comprise/comprises the at least one reagent and/or a reaction mix in the form of a dry reagent.

The at least one reagent preferably includes reagents which are necessary for the amplification of target nucleic acid sequences, particularly under constant temperatures of preferably less than 45 °C. It is particularly preferred when the at least one reagent is selected from enzymes, particularly enzymes for a preferably isothermal DNA amplification, NTPs, dNTPs, preferably pathogen specific primers, sugar molecules and/or salts.

The at least one reagent, particularly the enzyme(s), are adapted to the respective isothermal amplification technique. According to the present invention, any known isothermal amplification technique can be used.

According to a preferred embodiment of the present invention, the at least one reagent is selected from enzymes for a recombinase polymerase amplification, particularly DNA polymerases with strand displacement activity, recombinases and/or single strand binding proteins.

In order to allow a detection of the target nucleic acid sequences, it is preferred when the at least one reagent is selected from preferably pathogen-specific primers, particularly wherein a portion of the primers comprises a detectable label.

According to a particularly preferred embodiment, the sensor arrangement/apparatus, in particular (some or all) sensor fields and/or electrodes, comprise/comprises a reaction mix for amplifying target nucleic acid sequences, particularly wherein the reaction mix comprises enzymes, particularly enzymes for a preferably isothermal DNA amplification, NTPs, dNTPs, preferably pathogen specific primers, sugar molecules and/or salts.

Preferably, the at least one reagent and/or the reaction mix are immobilized and/or fixed into or onto the sensor arrangement/apparatus. It is particularly preferred, when the at least one reagent or the reaction mix are immobilized and/or fixed onto the surface of the sensor fields and/or the electrodes of the sensor arrangement/apparatus.

When using the analysis system, particularly in a method according to the present invention, the at least one reagent and/or the reaction mix is rehydrated and/or solubilized. The rehydrated and/or solubilized reagents preferably contain reagents for the amplification of target nucleic acid sequences. Furthermore, the rehydrated and/or solubilized reagents can stabilize the capture and/or target proteins and/or the detection of target analytes. Particularly sugar molecules have a stabilizing effect on capture and/or target proteins and/or the detection of target analytes.

Sugar molecules can be selected from the group of monosaccharides, disaccharides, oligosaccharides, polysaccharides and combinations thereof, preferably monosaccharides and/or disaccharides. In particular, the sugar molecules are selected from glucose, mannose, galactose, lactose, sucrose, fructose, isomalt, isomaltulose, maltulose, trehalose, oligofructose, inulin, starch, dextrin, cyclodextrin and combinations thereof.

Furthermore, according to another aspect of the present invention it is preferred, when the analysis system and/or the cartridge and/or the sensor arrangement/apparatus is designed to allow a detection and/or measurement of bonded target molecules.

Particularly, the analysis system and/or the cartridge and/or the sensor arrangement/apparatus is designed to carry out a plurality of (different) assays, the assays preferably being selected from the selection group consisting of a nucleic acid assay for detecting a target analyte, in particular a target nucleic acid sequence, particularly preferably by means of a capture nucleic acid sequence, and/or a protein assay for detecting a target analyte, in particular a target protein, particularly preferably by means of a capture protein, and/or in aptamer assays for detecting a target analyte, in particular a target protein or another target analyte that is preferably different from the target protein, particularly preferably by means of a capture aptamer.

The sensor arrangement/apparatus or its sensor array preferably comprises a plurality of sensor fields and/or electrodes, in particular electrode pairs, which each permit independent measurement and/or detection. Furthermore, the sensor arrangement/apparatus or its sensor array permits an amplification of target nucleic acid sequences.

Preferably, the – in particular some or all – sensor fields and/or electrode pairs or individual electrodes are each provided with capture nucleic acid sequences and at least one more type of capture molecules selected from capture proteins and/or capture aptamers. A plurality of different assays and/or detection processes can thus be carried out in succession or simultaneously, preferably simultaneously, using the same sensor fields and/or electrode pairs. This allows a simple, compact and/or cost-effective construction and allows testing and/or detection of many different target analytes.

Particularly preferably, the sensor fields and/or electrode pairs or individual electrodes are each provided with both capture nucleic acid sequences and capture proteins. In this way, a protein assay and a nucleic acid assay can be carried out.

According to another preferred embodiment of the present invention, a first portion of the sensor fields and/or electrode pairs or individual electrodes are each provided with capture nucleic acid sequences and at least one further portion of the sensor fields and/or electrode pairs or individual electrodes are each provided with at least one more type of capture molecules selected from capture proteins and/or capture aptamers, preferably capture proteins.

Furthermore, the sensor fields and/or electrode pairs and/or individual electrodes can be further provided with spacer molecules, preferably selected from non-nucleotide spacer molecules and/or nucleotide spacer molecules, in particular nucleotide spacer molecules. According to a particularly preferred embodiment of the present invention, the spacer molecules are oligonucleotides, preferably oligonucleotides having at least 5 or 10 bases and/or at most 70 or 80 bases, especially 10 to 50 bases, particularly preferably 12 to 20 bases. Preferably, the spacer molecules are based on thymine bases. Likewise, spacers can be based on any other nucleobase, particularly adenine, guanine, cytosine and/or combinations thereof.

According to a particularly preferred embodiment, the at least one reagent and/or the reaction mix comprise reagents for an isothermal DNA amplification and a stabilization of the capture molecules and the at least one reagent and/or the reaction mix are immobilized and/or fixed onto or into the sensor arrangement/apparatus.

Furthermore, it is preferred when the sensor arrangement/apparatus comprise capture nucleic acid sequences and at least one more type of capture molecules selected from capture proteins and/or capture aptamers and when the at least one reagent and the reaction mix is immobilized and/or fixed onto or into the sensor arrangement/apparatus.

According to another aspect of the present invention, the analysis system and/or analysis device of the analysis system comprises a temperature-control apparatus for temperature-controlling the sensor arrangement/apparatus and/or the cartridge and/or a fluid contained therein. Particularly, the temperature-control apparatus is designed to control the temperature of the sensor arrangement/apparatus in order to activate and/or support the amplification of the target nucleic acid sequences, in particular by regulating and/or heating the sensor arrangement/apparatus, preferably the sensor array and/or sensor fields of the sensor arrangement/apparatus, to a temperature less than 45 °C, even more preferred less than 43 °C and/or less than the denaturing temperatures of proteins, particularly capture proteins and/or target proteins.

According to another aspect of the present invention, which can also be implemented independently, the amplification of target nucleic acid sequences as well as their bonding to capture nucleic acid sequences and the bonding of at least one more type of target nucleic acid sequences, preferably selected from target proteins and/or target analytes corresponding to capture aptamers, and preferably a plurality of (different) assays are carried out, in particular simultaneously, preferably in one sensor arrangement/apparatus, in particular in a common or the same sensor array and/or sensor field of the sensor arrangement/apparatus.

Particularly preferably, a plurality of assays is carried out, selected from at least two assays from the selection group consisting of a nucleic acid sequence assay for detecting a target analyte, in particular a target nucleic acid sequence, a protein assay for detecting a target analyte, in particular a target protein or target hormone, and/or an aptamer assay for detecting a target analyte, in particular target proteins, low molecular substances, steroids, organophosphates or other target analytes, which correspond to the capture aptamers, wherein the assays are carried out simultaneously or sequentially to the amplification of the target nucleic acid sequences to the capture nucleic acid sequences. This makes comprehensive, rapid and/or precise and furthermore energy-efficient testing of the sample possible.

Furthermore, according to the proposed invention it is preferred when the capture molecules, particularly the capture proteins, and/or the target analytes, particularly the target proteins, are stabilized by sugar molecules, especially during amplification of target nucleic acid sequences and/or bonding of target analytes. For this purpose, it is preferred when the at least one reagent and/or the reaction mix comprises sugar molecules. Likewise, a buffer, particularly a reaction buffer, which contains sugar molecules, can be used during amplification and/or bonding of target analytes.

Sugar molecules can be selected from the group of monosaccharides, disaccharides, oligosaccharides, polysaccharides and combinations thereof, preferably monosaccharides and/or disaccharides. In particular, the sugar molecules are selected from glucose, mannose, galactose, lactose, sucrose, fructose, isomalt, isomaltulose, maltulose, trehalose, oligofructose, inulin, starch, dextrin, cyclodextrin and combinations thereof.

According to a particularly preferred embodiment of the present invention, the sensor arrangement/apparatus, in particular (some or all) sensor fields and/or electrodes, comprise/comprises capture nucleic acid sequences as well as capture proteins, wherein target nucleic acid sequences are amplified preferably by means of isothermal amplification and bonded to the capture nucleic acid sequences in/on and/or by means of the (common) sensor arrangement/apparatus, in particular the (same) sensor fields and/or electrodes, and wherein target proteins are bonded to the capture proteins and wherein a nucleic acid assay and a protein assay are carried out in/on and/or by means of the (common) sensor arrangement/apparatus and/or sensor array, in particular the (same) sensor fields and/or electrodes, in order to detect and/or measure the target analytes.

The sensor arrangement/apparatus is preferably designed for electrochemical and/or fluorescence detection of analytes bonded to the capture molecules.

The sensor arrangement preferably comprises the sensor apparatus. In particular, the sensor apparatus forms part of the sensor arrangement.

The sensor arrangement preferably comprises a sensor cover for the sensor apparatus, a sensor compartment, an inlet into the sensor compartment and/or an outlet out of the sensor compartment, preferably wherein the sensor apparatus and the sensor cover define or delimit the sensor compartment, preferably on the flat sides, and/or wherein the sensor compartment is arranged (directly) between the sensor apparatus and the sensor cover.

Mostly preferred, the sensor arrangement comprises exactly one sensor compartment, exactly one inlet into the sensor compartment and/or exactly one outlet out of the sensor compartment.

Preferably, the sensor compartment is coherent/contiguous and/or not sectioned/segmented/subdivided.

The sensor arrangement/apparatus preferably comprises a plurality of sensor fields and/or electrodes (electrode pairs) and/or (exactly) one sensor array having a plurality of sensor fields and/or electrodes (electrode pairs), preferably wherein some or all sensor fields and/or electrodes (electrode pairs) are each provided with capture molecules and/or wherein some or all sensor field and/or electrodes (electrode pairs) face the sensor compartment and/or protrude into the sensor compartment and/or are fluidically (directly) connected to one another by means of the sensor compartment.

Within the meaning of the present invention, capture molecules are in particular nucleic-acid sequences, in particular DNA sequences, RNA sequences and/or aptamers, and/or proteins, in particular antigens and/or antibodies. In particular, capture molecules are designed to bond and/or immobilise corresponding analytes of the sample.

Within the meaning of the present invention, capture nucleic acid sequences are in particular capture molecules based on long (single-stranded) nucleic acid sequences, in particular DNA sequences and/or RNA sequences, particularly preferably having more than 70 or 80 bases and/or fewer than 5000 or 1000 bases. In particular, capture nucleic-acid sequences are designed to bond corresponding target nucleic-acid sequences, in particular target DNA sequences and/or target RNA sequences, which are particularly preferably at least substantially of the same length. Particularly, nucleic acid sequences are based on pathogen-specific oligonucleotides. Furthermore, as delineated in detail in relation to the amplification of target nucleic acid sequences, the capture nucleic acid sequences are capable of bonding amplification products and/or to function as primers in the amplification reaction.

Within the meaning of the present invention, capture proteins are preferably antibodies or antigens that specifically bind analytes on the basis of the corresponding antigens or antibodies, respectively, from the sample.

Within the meaning of the present invention, capture aptamers are in particular capture molecules based on short (single-stranded) nucleic-acid sequences, particularly preferably having at least 10 or 20 bases and/or at most 70 or 80 bases. Particularly preferably, capture aptamers are shorter than capture nucleic-acid sequences and/or capture aptamers have fewer bases than capture nucleic-acid sequences. Capture aptamers are preferably designed to bond target proteins, low-molecular substances, steroids, organophosphates and/or other target analytes. In particular, within the meaning of the present invention, capture aptamers are DNA oligonucleotides and/or RNA oligonucleotides and/or peptides.

Capture aptamers are preferably produced synthetically and generally do not (yet) have a three-dimensional structure (immediately) after being produced. Against this background, it may be necessary for capture aptamers to first be thermally activated before being used and/or in order to bond target analytes, and/or it may be necessary for the hydrogen bridge bonds to be opened by the effect of heat and formed by subsequent cooling (folding). The capture aptamers thus assume a three-dimensional structure which makes target analyte bonding possible. The temperature for activating and/or folding the capture aptamers (threshold temperature) is preferably greater than 70 °C or 80 °C, in particular greater than 90 °C or 95

°C. The capture molecules are in particular applied to and immobilised on and/or bonded to the sensor array, in particular the sensor fields and/or electrodes, in a process known as spotting.

According to a preferred embodiment of the present invention, the sensor fields and/or electrodes each comprise besides the at least one reagent and/or a reaction mix for the amplification of target nucleic acid sequences from the sample capture nucleic acid sequences and at least one more type of capture molecules selected from capture proteins, in particular in the form of antibodies and/or antigenes, and/or capture aptamers. For this purpose, in a preferred manner, the capture nucleic acid sequences, capture proteins and/or capture aptamers are immobilized on the sensor arrangement/apparatus, in particular on the sensor array and/or the sensor fields and/or the electrodes. The capture nucleic acid sequences, capture proteins and/or capture aptamers can bond and/or immobilize analytes based on target nucleic acid sequences, target proteins and/or other target analytes. The immobilized analytes can be identified or detected by means of subsequent electrochemical measurement and/or redox cycling and/or fluorescence measurement.

According to the proposed invention, the analysis system and/or the cartridge and/or the sensor arrangement/apparatus allows a time efficient and comprehensive testing of the sample, as amplification of target nucleic acid sequences, bonding of analytes to the capture molecules as well as detection and/or measurements of bonded analytes are carried out in a common sensor arrangement/apparatus instead of spatially separated reaction cavities. Thus, a particularly large number of preferably different tests can advantageously by carried out on the sample and/or a plurality of diseases and/or pathogens can be detected or identified in the sample in a relatively short time period.

The analysis system is preferably portable, mobile and/or is a point-of-care system and/or can be used in particular at the sampling site and/or away from a central laboratory and/or can be operated autonomously and/or independently of the mains, in particular independently of a mains power supply, for example by accumulators, batteries and/or other power storage means.

The analysis system preferably comprises an analysis device and a cartridge for testing the sample, the cartridge preferably being designed for receiving the sample and the analysis device preferably being designed for receiving the cartridge.

The term "analysis device" is preferably understood to mean an instrument which is in particular mobile and/or can be used on site, and/or which is designed to chemically, biologically and/or physically test and/or analyse a sample or a component thereof, preferably in and/or by means of a cartridge. In particular, the analysis device controls the pretreatment and/or testing of the sample in the cartridge.

Particularly preferably, the analysis device is designed to receive the cartridge or to connect said cartridge electrically, thermally, mechanically and/or pneumatically.

The term "cartridge" is preferably understood to mean a structural apparatus or unit designed to receive, to store, to physically, chemically and/or biologically treat and/or prepare and/or to measure a sample, preferably in order to make it possible to detect, identify or determine at least one analyte, in particular a protein, a nucleic-acid sequence and/or another analyte, of the sample.

A cartridge within the meaning of the present invention preferably comprises a fluid system having a plurality of channels, cavities and/or valves for controlling the flow through the channels and/or cavities.

In particular, within the meaning of the present invention, a cartridge is designed to be at least substantially planar and/or card-like, in particular is designed as a (micro)fluidic card and/or is designed as a main body or container that can preferably be closed and/or said cartridge can be inserted and/or plugged into a proposed analysis device when it contains the sample.

The term "assay" is preferably understood to mean an in particular molecular-biological test for detecting or identifying at least one analyte in a sample. In particular, at least one analyte in a sample can be qualitatively and/or quantitatively detected or identified by means of an assay or by carrying out an assay. A plurality of method steps is preferably required to (fully) carry out an assay. Preferably, within the meaning of the present invention, when carrying out an assay, a sample is pretreated with one or more reagents and the pretreated sample is tested, in particular at least one analyte in the sample being detected or identified.

An assay within the meaning of the present invention is in particular an immunoassay and/or protein assay for detecting a target hormone and/or target protein, in particular a target antigen and/or target antibody, particularly preferably by bonding to corresponding capture proteins, a nucleic-acid assay for detecting a target nucleic-acid sequence, in particular a target DNA sequence and/or target RNA sequence, particularly preferably by bonding to corresponding capture nucleic-acid sequences, and/or an aptamer assay for detecting a target protein and/or other target analytes, particularly preferably by bonding to corresponding capture aptamers.

The assays thus differ in particular in terms of the capture molecules used. In the protein assay, preferably capture proteins are used as the capture molecules, in particular in order for it to be possible to bond and/or detect or identify target analytes corresponding to the capture proteins. In the nucleic-acid assay, preferably capture nucleic-acid sequences are used as the capture molecules, in particular in order for it to be possible to bond and/or detect or identify target analytes corresponding to the capture nucleic-acid sequences. Furthermore, the nucleic acid assay preferably comprises an amplification of the target nucleic acid sequences ZN. In the aptamer assay, preferably capture aptamers are used as the capture molecules, in particular in order for it to be possible to bond and/or detect or identify target analytes corresponding to the capture aptamers.

The above-mentioned aspects and features of the present invention and the aspects and features of the present invention that will become apparent from the claims and the following description can in principle be implemented independently from one another, but also in any combination or order.

Other aspects, advantages, features and properties of the present invention will become apparent from the claims and the following description of a preferred embodiment with reference to the drawings, in which:

Fig. 1	is a schematic view of a proposed analysis system comprising a proposed analysis device and a proposed cartridge received in the analysis device;
Fig. 2	is a schematic view of the cartridge;
Fig. 3	is a schematic front view of a sensor apparatus of the analysis system and/or cartridge;
Fig. 4	is an enlarged detail from Fig. 3 illustrating a sensor field of the sensor apparatus;

Fig. 5	is a schematic rear view of the sensor apparatus;
Fig. 6	is a schematic sectional view of a first preferred sensor arrangement of the analysis system and/or cartridge comprising the sensor apparatus and a sensor cover that has been moved away;
Fig. 7	is a schematic sectional view of another preferred sensor arrangement of the analysis system and/or cartridge comprising the sensor apparatus and a sensor cover that has been moved away;
Fig. 8	is a schematic representation of the preferably isothermal amplification of target nucleic acid sequences;
Fig. 9	is a schematic sectional view of the sensor arrangement after the amplification of target nucleic acid sequences and bonding of target analytes has been carried out;
Fig. 10	is a schematic sectional view of the sensor arrangement after label and detector molecules and substrate have been added;
Fig. 11	is a schematic sectional view of the sensor arrangement while a nucleic acid and a protein assay are being carried out simultaneously;
Fig. 12	are graphical representations of the results of electrochemical measurements of the sensor array;

In the Figures, which are only schematic and not necessarily to scale, the same reference signs are used for the same or similar parts and components, corresponding or comparable properties and advantages being achieved even if these are not repeatedly described.

Fig. 1 is a highly schematic view of a proposed analysis system 1 and analysis device 200 for testing an particular biological sample P, preferably by means of or in an apparatus or cartridge 100.

Fig. 2 is a schematic view of a preferred embodiment of the proposed apparatus or cartridge 100 for testing the sample P. The apparatus or cartridge 100 in particular forms a handheld unit, and in the following is merely referred to as a cartridge 100.

The term "sample" is preferably understood to mean the sample material to be tested, which is in particular taken from a human or animal. In particular, within the meaning of the present invention, a sample is a fluid, such as saliva, blood, urine or another liquid, preferably from a human or animal, or a component thereof. Within the meaning of the present invention, a sample may be pretreated or prepared if necessary, or may come directly from a human or animal or the like, for example. A food sample, environmental sample or another sample may optionally also be tested, in particular for environmental analytics, food safety and/or for detecting other substances, preferably natural substances, but also biological or chemical warfare agents, poisons or the like.

A sample within the meaning of the present invention preferably contains one or more analytes, it preferably being possible for the analytes to be identified or detected, in particular qualitatively and/or quantitatively determined. Particularly preferably, within the meaning of the present invention, a sample has target nucleic-acid sequences as the analytes, in particular target DNA sequences and/or target RNA sequences, target proteins as the analytes, in particular target antigens and/or target antibodies, and/or other target analytes, such as hormones, low-molecular substances, steroids, organophosphates, etc. Particularly preferably, at least one disease, pathogen and/or other substances can be detected or identified in the sample P by qualitatively and/or quantitatively determining the analytes.

Preferably, the analysis system 1 or analysis device 200 controls the testing of the sample P in particular in or on the cartridge 100 and/or is used to evaluate the testing or the collection, processing and/or storage of measured values from the test.

By means of the proposed analysis system 1, analysis device 200, and/or the cartridge 100 and/or using the proposed method for testing the sample P, preferably an analyte of the sample P, in particular a (certain) nucleic-acid sequence or target nucleic-acid sequence ZN, a (certain) protein or target protein ZP, and/or another target analyte, can be determined, identified or detected. Particularly preferably, a plurality of analytes of the sample P, in particular a plurality of different target nucleic-acid sequences ZN, different target proteins ZP and/or different other target analytes, can be determined, identified or detected, in particular on a cartridge 100, preferably simultaneously. Said analytes are in particular detected, identified and/or measured not only qualitatively, but, alternatively or additionally, particularly preferably also quantitatively.

Therefore, the sample P can in particular be tested for qualitatively and/or quantitatively determining at least one analyte, for example in order for it to be possible to detect or identify a disease and/or pathogen or to determine other values or substances, which are important for diagnostics, for example.

Particularly preferably, a molecular biological test is made possible by means of the analysis system 1 and/or analysis device 200 and/or by means of the cartridge 100.

Particularly, the sample P or individual components of the sample P or analytes are amplified, in particular by means of an amplification reaction at constant temperatures, particularly a temperature less than the denaturing temperature of proteins, and can be tested, identified and/or detected in the analysis system 1 or analysis device 200 or in the cartridge 100. Preferably, amplification products or amplicons of the analyte or analytes are thus produced.

Particularly preferably, a nucleic-acid assay for detecting or identifying a target nucleic acid sequence ZN, in particular a target DNA sequence and/or target RNA sequence, a protein assay for detecting or identifying a target protein ZP, in particular a target antigen and/or target antibody, and/or an aptamer assay for detecting or identifying a target protein ZP and/or other target analytes, are made possible and/or carried out.

In the following, further details are first given on a preferred construction of the cartridge 100, with features of the cartridge 100 preferably also directly representing features of the analysis system 1, in particular even without any further explicit explanation.

The cartridge 100 is preferably at least substantially planar, flat, plate-shaped and/or card-like.

The cartridge 100 preferably comprises an in particular at least substantially planar, flat, plate-shaped and/or card-like main body or support 101, the main body or support 101 in particular being made of and/or injection-moulded from plastics material, particularly preferably polypropylene.

The cartridge 100 preferably comprises at least one film or cover 102 for covering the main body 101 and/or cavities and/or channels formed therein at least in part, in particular on the front, and/or for forming valves or the like, as shown by dashed lines in Fig. 2.

The analysis system 1 or cartridge 100 or the main body 101 thereof, in particular together with the cover 102, preferably forms and/or comprises a fluidic system 103, referred to in the following as the fluid system 103.

The cartridge 100, the main body 101 and/or the fluid system 103 are preferably at least substantially vertically oriented in the operating position and/or during the test, in particular in the analysis device 200, as shown schematically in Fig. 1. In particular, the main plane or surface extension of the cartridge 100 thus extends at least substantially vertically in the operating position.

The cartridge 100 and/or the fluid system 103 preferably comprises a plurality of cavities, in particular at least one receiving cavity 104, at least one metering cavity 105, at least one intermediate cavity 106, at least one mixing cavity 107, at least one storage cavity 108, at least one reaction cavity 109, at least one intermediate temperature-control cavity 110 and/or at least one collection cavity 111, a plurality of cavities preferably being fluidically interconnected in particular by a plurality of channels 114.

Within the meaning of the present invention, channels are preferably elongate forms for conducting a fluid in a main flow direction, the forms preferably being closed transversely, in particular perpendicularly, to the main flow direction and/or longitudinal extension, preferably on all sides.

In particular, the support 101 comprises elongate notches, recesses, depressions or the like, which are closed at the sides by the cover 102 and form channels within the meaning of the present invention.

Within the meaning of the present invention, cavities or chambers are preferably formed by recesses, depressions or the like in the cartridge 100 or support 101, which are closed or covered by the cover 102, in particular at the sides. The space enclosed by each cavity is preferably fluidically linked by means of channels.

In particular, within the meaning of the present invention, a cavity comprises at least two openings for the inflow and/or outflow of fluids.

Within the meaning of the present invention, cavities preferably have a larger diameter and/or flow cross section than channels, preferably by at least a factor of 2, 3 or 4. In principle, however, cavities may in some cases also be elongate, in a similar manner to channels.

The cartridge 100 and/or the fluid system 103 also preferably comprises at least one pump apparatus 112 and/or at least one sensor arrangement or sensor apparatus 113. In particular, the sensor apparatus 113 forms part of a sensor arrangement, as shown in Fig. 6 to 11.

In the example shown, the cartridge 100 or the fluid system 103 preferably comprises two metering cavities 105A and 105B, a plurality of intermediate cavities 106A to 106G, a plurality of storage cavities 108A to 108E and/or a plurality of reaction cavities 109, which can preferably be loaded separately from one another, in particular a first reaction cavity 109A, a second reaction cavity 109B and an optional third reaction cavity 109C, as can be seen in Fig. 2.

The metering cavities 105 are preferably designed to receive, to temporarily store and/or to meter the sample P, and/or to pass on said sample in a metered manner. Particularly preferably, the metering cavities 105 have a diameter which is larger than that of the (adjacent) channels.

In the initial state of the cartridge 100 or when at the factory, the storage cavities 108 are preferably filled at least in part, in particular with a liquid such as a reagent, solvent or wash buffer.

The collection cavity 111 is preferably designed to receive larger quantities of fluids that are in particular used for the test, such as sample residues or the like. Preferably, in the initial state or when at the factory, the collection cavity 111 is empty or filled with gas, in particular air. The volume of the collection cavity 111 corresponds to or preferably exceeds the (cumulative) volume of the storage cavity/cavities 108 or the liquid content thereof and/or the volume of the receiving cavity 104 or the sample P received.

The reaction cavity/cavities 109 is/are preferably designed to allow a substance located in the reaction cavity 109 to react when an assay is being carried out, for example by being linked or coupled thermally, electrically, mechanically and/or pneumatically to apparatuses or modules of the analysis device 200. Particularly, pretreatments of the sample P can be carried out in the reaction cavity 109.

The sensor arrangement or sensor apparatus 113 is used in particular for an amplification of target analytes, particularly target nucleic acid sequences, on the one hand, and for detecting, particularly preferably qualitatively and/or quantitatively determining, the analyte or analytes of the sample P, in this case particularly preferably the target nucleic-acid sequences ZN and/or target proteins ZP or further analytes as the analytes, on the other hand. Alternatively or additionally, however, other values may also be collected and/or determined.

Particularly, the sensor arrangement or the sensor apparatus 113 are used for carrying out a nucleic acid assay, a protein assay and/or an aptamer assay.

Furthermore, it is preferred when at least one reagent and/or a reaction mix R is immobilized and/or fixed to the sensor apparatus 113, preferably the sensor fields 113B and/or the electrodes 113C of the sensor array 113A and/or the sensor compartment 118.

Preferably, the at least one reagent R is selected from enzymes, particularly enzymes for a preferably isothermal DNA amplification, NTPs, dNTPs, preferably pathogen-specific amplification primers, sugar molecules and/or salts, Likewise, the reaction mix R can comprise enzymes, particularly enzymes for a preferably isothermal DNA amplification, NTPs, dNTPs, preferably pathogen-specific amplification primers, sugar molecules and/or salts.

Sugar molecules are preferably selected from the group of monosaccharides, disaccharides, oligosaccharides, polysaccharides and combinations thereof, preferably monosaccharides and/or disaccharides. In particular, the sugar molecules are selected from glucose, mannose, galactose, lactose, sucrose, fructose, isomalt, isomaltulose, maltulose, trehalose, oligofructose, inulin, starch, dextrin, cyclodextrin and combinations thereof.

In particular, target nucleic acid sequences ZN as analytes of the sample P are amplified in the sensor apparatus 113, preferably in the sensor array 113A, even more preferred in the sensor fields 113B, of the sensor apparatus 113 or the sensor arrangement, in particular in order to produce amplification products for the subsequent detection in the sensor arrangement or sensor apparatus 113.

Within the meaning of the present invention, amplification reactions are in particular molecular-biological reactions in which an analyte, in particular a target nucleic-acid sequence ZN, is amplified and/or copied and/or in which amplification products or amplicons, in particular nucleic-acid products, of an analyte are produced. Amplification preferably takes place with participation of enzymes, preferably of at least one enzyme with strand displacement activity. Particularly preferably, amplification reactions with constant reaction temperatures of particularly less than 45 °C, even more preferred less than 43 °C, and/or less than the denaturing temperature of proteins and/or isothermal DNA amplifications are amplification reactions within the meaning of the present invention.

For the amplification, marker primers are preferably used, i.e. primers which (additionally) produce a marker or a label L, in particular biotin and/or a fluorescent label, on the amplified analyte or analytes or amplification product. This allows or facilitates detection. Preferably, the primers used are biotinylated and/or comprise in particular covalently bonded a biotin marker as the label L. According to a particularly preferred embodiment, the primers comprise a label which differs from the label for the detection of target proteins ZP. Alternatively, the primers used are fluorescently labelled and/or comprise in particular covalently bonded fluorescence marker as the label L. Furthermore, the primers used for amplification preferably comprise a pathogen-specific nucleotide sequence. According to a particularly preferred embodiment of the present invention, the primers are the at least one reagent on or in the sensor apparatus for the amplification. Likewise, the primers can be part of the reaction mix for carrying out the amplification.

In particular, the pump apparatus 112 comprises or forms a tube-like or bead-like raised portion, in particular by means of the film or cover 102, particularly preferably on the back of the cartridge 100, as shown schematically in Fig. 1.

The cartridge 100, the main body 101 and/or the fluid system 103 preferably comprise a plurality of channels 114 and/or valves 115, as shown in Fig. 2.

By means of the channels 114 and/or valves 115, the cavities 104 to 111, the pump apparatus 112 and/or the sensor arrangement or sensor apparatus 113 can be temporarily and/or permanently fluidically interconnected and/or fluidically separated from one another, as required and/or optionally or selectively, in particular such that they are controlled by the analysis system 1 or the analysis device 200.

The cavities 104 to 111 are preferably each fluidically linked or interconnected by a plurality of channels 114. Particularly preferably, each cavity is linked or connected by at least two associated channels 114, in order to make it possible for fluid to fill, flow through and/or drain from the respective cavities as required.

The fluid transport or the fluid system 103 is preferably not based on capillary forces, or is not exclusively based on said forces, but in particular is essentially based on the effects of gravity and/or pumping forces and/or compressive forces and/or suction forces that arise, which are particularly preferably generated by the pump or pump apparatus 112. In this case, the flows of fluid or the fluid transport and the metering are controlled by accordingly opening and closing the valves 115 and/or by accordingly operating the pump or pump apparatus 112, in particular by means of a pump drive 202 of the analysis device 200.

Preferably, each of the cavities 104 to 110 has an inlet at the top and an outlet at the bottom in the operating position. Therefore, if required, only liquid from the respective cavities can be removed via the outlet.

In the operating position, the liquids from the respective cavities are preferably removed, in particular drawn out, via the outlet that is at the bottom in each case, it preferably being possible for gas or air to flow and/or be pumped into the respective cavities via the inlet that is in particular at the top. In particular, relevant vacuums in the cavities can thus be prevented or at least minimised when conveying the liquids.

In particular, the cavities, particularly preferably the storage cavity/cavities 108, the mixing cavity 107 and/or the receiving cavity 104, are each dimensioned and/or oriented in the normal operating position such that, when said cavities are filled with liquid, bubbles of gas or air that may potentially form rise upwards in the operating position, such that the liquid collects above the outlet without bubbles. However, other solutions are also possible here.

The receiving cavity 104 preferably comprises a connection 104A for introducing the sample P. In particular, the sample P may for example be introduced into the receiving cavity 104 and/or cartridge 100 via the connection 104A by means of a pipette, syringe or other instrument.

The receiving cavity 104 preferably comprises an inlet 104B, an outlet 104C and an optional intermediate connection 104D, it preferably being possible for the sample P or a portion thereof to be removed and/or conveyed further via the outlet 104C and/or the optional intermediate connection 104D. Gas, air or another fluid can flow in and/or be pumped in via the inlet 104B, as already explained.

Preferably, the sample P or a portion thereof can be removed via the outlet 104C or the optional intermediate connection 104D of the receiving cavity 104. In particular, a supernatant of the sample P, such as blood plasma or blood serum, can be conducted away, discharged or removed via the optional intermediate connection 104D.

Preferably, at least one valve 115 is assigned to each cavity and/or storage cavity 108, the receiving cavity 104, the pump apparatus 112 and/or the sensor apparatus 113 and/or is arranged upstream of the respective inlets and/or downstream of the respective outlets.

Preferably, the cavities 104 to 111 or sequences of cavities 104 to 111, through which fluid flows in series or in succession for example, can be selectively released and/or fluid can selectively flow therethrough by the assigned valves 115 being actuated, and/or said cavities can be fluidically connected to the fluid system 103 and/or to other cavities.

In particular, the valves 115 are formed by the main body 101 and the film or cover 102 and/or are formed therewith and/or are formed in another manner, for example by or having additional layers, depressions or the like.

Particularly preferably, one or more valves 115A are provided which are preferably tightly closed initially or in the storage state, particularly preferably in order to seal liquids or liquid reagents F, located in the storage cavities 108, and/or the fluid system 103 from the open receiving cavity 104 in a storage-stable manner.

Preferably, an initially closed valve 115A is arranged upstream and downstream of each storage cavity 108. Said valves are preferably only opened, in particular automatically, when the cartridge 100 is actually being used and/or during or after inserting the cartridge 100 into the analysis device 200 and/or for carrying out the assay.

A plurality of valves 115A, in particular three valves in this case, are preferably assigned to the receiving cavity 104, in particular if the intermediate connection 104D is provided in addition to the inlet 104B and the outlet 104C. Depending on the use, in addition to the valve 115A on the inlet 104B, then preferably only the valve 115A either at the outlet 104C or at the intermediate connection 104D is opened.

The valves 115A assigned to the receiving cavity 104 seal the fluid system 103 and/or the cartridge 100 in particular fluidically and/or in a gas-tight manner, preferably until the sample P is inserted and/or the receiving cavity 104 or the connection 104A of the receiving cavity 104 is closed.

As an alternative or in addition to the valves 115A (which are initially closed), one or more valves 115B are preferably provided which are not closed in a storage-stable manner and/or which are open initially or in an inoperative position, in an initial state or when the cartridge 100 is not inserted into the analysis device 200, and/or which can be closed by actuation. These valves 115B are used in particular to control the flows of fluid during the test.

The cartridge 100 is preferably designed as a microfluidic card and/or the fluid system 103 is preferably designed as a microfluidic system. In the present invention, the term "microfluidic" is preferably understood to mean that the respective volumes of individual cavities, some of the cavities or all of the cavities 104 to 111 and/or channels 114 are, separately or cumulatively, less than 5 ml or 2 ml, particularly preferably less than 1 ml or 800 µl, in particular less than 600 µl or 300 µl, more particularly preferably less than 200 µl or 100 µl.

Particularly preferably, a sample P having a maximum volume of 5 ml, 2 ml or 1 ml can be introduced into the cartridge 100 and/or the fluid system 103, in particular the receiving cavity 104.

According to a preferred embodiment, the analysis system 1 can comprise – additionally to the at least one reagent and/or the reaction mix R in the sensor apparatus 113 – further reagents and liquids which are preferably introduced or provided before the test in liquid form as liquids or liquid reagents F and/or in dry form as dry reagents S, as indicated in the schematic view according to Fig. 2 by reference signs F1 to F5 and S1 to S10.

Other reagents, preferably other liquids F, are preferably selected from solubilization and/or rehydration buffers, reaction buffers or wash buffers, solvent for dry reagents S and/or a substrate SU.

Particularly, the other reagents can include a solubilization and/or rehydration buffer for the amplification of target nucleic acid sequences ZN. The solubilization and/or rehydration buffer preferably functions as a solvent for the at least one reagent and/or the reaction mix R. The solubilization and/or rehydration buffer is preferably selected from water and/or TRIS buffer.

According to another embodiment, the other reagents can include a reaction buffer particularly wherein the reaction buffer contains sugar molecules. A reaction buffer with sugar molecules is preferred, when the at least one reagent and/or the at least one reagent and/or the reaction mix R does not include sugar molecules. A sugar containing buffer for carrying out the preferably isothermal amplification is linked with the advantage of a stabilizing effect on capture molecules, in particular capture proteins FP and/or capture aptamers FA, and target molecules, in particular target proteins ZP and target analytes corresponding to capture aptamers.

Sugar molecules are preferably selected from the group of monosaccharides, disaccharides, oligosaccharides, polysaccharides and combinations thereof, preferably monosaccharides and/or disaccharides. In particular, the sugar molecules are selected from glucose, mannose, galactose, lactose, sucrose, fructose, isomalt, isomaltulose, maltulose, trehalose, oligofructose, inulin, starch, dextrin, cyclodextrin and combinations thereof.

Furthermore, the other reagents can include reagents which are required for the detection process, particularly for the detection assays for bonded target analytes, for example in order to form detection molecules D and/or a redox system.

Preferably, other reagents, in particular other liquids F and/or dry reagents S and/or substrate SU, are provided in the cartridge 100, i.e. are likewise introduced before use, in particular before delivery. At some points in the following, a distinction is not made between liquid reagents and other liquids, and therefore the respective explanations are accordingly also mutually applicable.

The analysis system 1 or the cartridge 100 preferably contains all the reagents and liquids required for pretreating the sample P and/or for carrying out the test or assay. In particular, the analysis system 1 or the cartridge 100 preferably contain further reagents and/or liquids, especially liquids, for carrying out one or more amplification reactions, particularly amplification reactions at constant temperatures, and therefore, particularly preferably, it is only necessary to receive the optionally pretreated sample P.

The cartridge 100 or the fluid system 103 preferably comprises a bypass 114A that can optionally be used, in order for it to be possible, if necessary, to conduct or convey the sample P or components thereof past the reaction cavities 109 and/or, by bypassing the optional intermediate temperature-control cavity 110, also directly to the sensor apparatus 113.

The cartridge 100 or the fluid system 103 or the channels 114 preferably comprise sensor portions 116 or other apparatuses for detecting liquid fronts and/or flows of fluid.

It is noted that various components, such as the channels 114, the valves 115, in particular the valves 115A that are initially closed and the valves 115B that are initially open, and the sensor portions 116 in Fig. 2 are, for reasons of clarity, only labelled in some cases, but the same symbols are used in Fig. 2 for each of these components.

The collection cavity 111 is preferably used for receiving excess or used reagents and liquids and volumes of the sample, and/or for providing gas or air in order to empty individual cavities and/or channels. In the initial state, the collection cavity 111 is preferably filled solely with gas, in particular air.

In particular, the collection cavity 111 can optionally be connected to individual cavities and channels or other apparatuses fluidically in order to remove reagents and liquids from said cavities, channels or other apparatuses and/or to replace said reagents and liquids with gas or air. The collection cavity 111 is preferably given appropriate (large) dimensions.

Once the sample P has been introduced into the receiving cavity 104 and the connection 104A has been closed, the cartridge 100 can be inserted into and/or received in the proposed analysis device 200 in order to test the sample P, as shown in Fig. 1. Alternatively, the sample P could also be fed in later.

Fig. 1 shows the analysis system 1 in a ready-to-use state for carrying out a test or assay on the sample P received in the cartridge 100. In this state, the cartridge 100 is therefore linked to, received by and/or inserted into the analysis device 200.

In the following, some features and aspects of the analysis device 200 are first explained in greater detail, in particular on the basis of Fig. 1. The features and aspects relating to said device are preferably also directly features and aspects of the proposed analysis system 1, in particular even without any further explicit explanation.

The analysis system 1 or analysis device 200 preferably comprises a mount or receptacle 201 for mounting and/or receiving the cartridge 100.

Preferably, the cartridge 100 is fluidically, in particular hydraulically, separated or isolated from the analysis device 200. In particular, the cartridge 100 forms a preferably independent and in particular closed or sealed fluidic or hydraulic system 103 for the sample P and the reagents and other liquids. In this way, the analysis device 200 does not come into direct contact with the sample P and can in particular be reused for another test without being disinfected and/or cleaned first.

It is however provided to connect or couple the analysis device 200 mechanically, electrically, thermally and/or pneumatically to the cartridge 100.

In particular, the analysis device 200 is designed to have a mechanical effect, in particular for actuating the pump apparatus 112 and/or the valves 115, and/or to have a thermal effect, in particular for temperature-controlling the reaction cavity/cavities 109 and/or the intermediate temperature-control cavity 110 and/or the sensor apparatus 113.

In addition, the analysis device 200 can preferably be pneumatically connected to the cartridge 100, in particular in order to actuate individual apparatuses, and/or can be electrically connected to the cartridge 100, in particular in order to collect and/or transmit measured values, for example from the sensor apparatus 113 and/or sensor portions 116.

The analysis system 1 or analysis device 200 preferably comprises a pump drive 202, the pump drive 202 in particular being designed for mechanically actuating the pump apparatus 112.

Preferably, a head of the pump drive 202 can be rotated in order to rotationally axially depress the preferably bead-like raised portion of the pump apparatus 112. Particularly preferably, the pump drive 202 and pump apparatus 112 together form a pump, in particular in the manner of a hose pump or peristaltic pump and/or a metering pump, for the fluid system 103 and/or the cartridge 100.

Particularly preferably, the pump is constructed as described in DE 10 2011 015 184 B4. However, other structural solutions are also possible.

Preferably, the capacity and/or discharge rate of the pump can be controlled and/or the conveying direction of the pump and/or pump drive 202 can be switched. Preferably, fluid can thus be pumped forwards or backwards as desired.

The analysis system 1 or analysis device 200 preferably comprises a connection apparatus 203 for in particular electrically and/or thermally connecting the cartridge 100 and/or the sensor arrangement and/or sensor apparatus 113.

As shown in Fig. 1, the connection apparatus 203 preferably comprises a plurality of electrical contact elements 203A, the cartridge 100, in particular the sensor arrangement or sensor apparatus 113, preferably being electrically connected or connectable to the analysis device 200 by the contact elements 203A. The contact elements 203A are preferably contact springs; however, they may also be spring-loaded connection pins or the like.

The analysis system 1 or analysis device 200 preferably comprises one or more temperature-control apparatuses 204 for temperature-controlling the cartridge 100 and/or having a thermal effect on the cartridge, in particular for heating and/or cooling, the temperature-control apparatus(es) 204 (each) preferably comprising or being formed by a heating resistor or a Peltier element.

Individual temperature-control apparatuses 204, some of these apparatuses or all of these apparatuses can preferably be positioned against the cartridge 100, the main body 101, the cover 102, the sensor arrangement, sensor apparatus 113 and/or individual cavities and/or can be thermally coupled thereto and/or can be integrated therein and/or in particular can be operated or controlled electrically by the analysis device 200. In the example shown, in particular the temperature-control apparatuses 204A, 204B and/or 204C are provided.

Preferably, the temperature-control apparatus 204A, referred to in the following as the reaction temperature-control apparatus 204A, is assigned to the reaction cavity 109 or to a plurality of reaction cavities 109, in particular in order for it to be possible to carry out one or more amplification reactions therein.

When the cartridge 100 is inserted, the reaction temperature-control apparatus 204A preferably abuts the cartridge 100 in the region of the reaction cavity/cavities 109, and therefore a fluid located in said cartridge, in particular the sample P, can be heated and/or cooled.

The temperature-control apparatus 204B, referred to in the following as the intermediate temperature-control apparatus 204B, is preferably assigned to the intermediate temperature-control cavity 110 and/or is designed to (actively) temperature-control or heat the intermediate temperature-control cavity 110 or a fluid located therein.

The intermediate temperature-control cavity 110 and/or intermediate temperature-control apparatus 204B is preferably arranged upstream of or (immediately) before the sensor arrangement or sensor apparatus 113, in particular in order for it to be possible to temperature-control or preheat, in a desired manner, fluids to be fed to the sensor arrangement or sensor apparatus 113.

Additionally or alternatively, the intermediate temperature-control cavity 110 and/or intermediate temperature-control apparatus 204B is designed or provided to thermally activate and/or fold the capture aptamers FA, in particular such that said aptamers FA can bond corresponding target proteins ZP and/or other target analytes, as already explained at the outset.

Preferably, the analysis system 1, analysis device 200 and/or the cartridge 100 and/or one or each temperature-control apparatus 204 comprise/comprises a temperature detector and/or temperature sensor (not shown), in particular in order to make it possible to control and/or feedback control temperature.

One or more temperature sensors may for example be assigned to the sensor portions 116 and/or to individual channel portions or cavities, i.e. may be thermally coupled thereto.

The temperature-control apparatus 204C, referred to in the following as the sensor temperature-control apparatus 204C, is in particular assigned to the sensor apparatus 113 and/or is designed to (actively) temperature-control, cool or heat fluids located in or on the sensor arrangement or sensor apparatus 113, in particular analytes or target proteins ZP or target nucleic acid sequences ZN, in a desired manner, in particular in order to support the amplification and/or the assays.

According to a preferred embodiment, the temperature-control apparatus 204C is designed or provided to evenly heat or cool the sensor apparatus 113 and/or the sensor compartment 118 and/or to set a uniform and/or even temperature in the sensor apparatus 113 and/or the sensor compartment 118.

Particularly, the sensor temperature-control apparatus 204C is designed or provided to thermally activate and/or support the amplification of the target nucleic acid sequences ZN, particularly to activate and/or support an amplification under constant temperatures, preferably temperatures of less than 45 °C, even more preferred less than 43 °C, and/or temperatures less than the denaturing temperature of proteins and/or to activate and/or support an isothermal DNA amplification.

Furthermore, the sensor temperature-control apparatus 204C is designed or provided to thermally inactivate and/or denature the capture proteins FP and/or target proteins ZP.

Additionally or alternatively, the sensor temperature-control apparatus 204C is designed or provided to thermally activate and/or fold the capture aptamers FA, in particular such that said aptamers FA can bond corresponding target proteins ZP and/or other target analytes, as already explained at the outset.

The sensor temperature-control apparatus 204C is preferably planar and/or has a contact surface which is preferably rectangular and/or corresponds to the dimensions of the sensor arrangement or sensor apparatus 113, the contact surface allowing for heat transfer between the sensor temperature-control apparatus 204C and the sensor apparatus 113.

Preferably, the analysis device 200 comprises the sensor temperature-control apparatus 204C. However, other structural solutions are also possible in which the sensor temperature-control apparatus 204C is integrated in the cartridge 100, in particular the sensor arrangement or sensor apparatus 113.

Particularly preferably, the connection apparatus 203 comprises the sensor temperature-control apparatus 204C, and/or the connection apparatus 203 together with the sensor temperature-control apparatus 204C can be linked to, in particular pressed against, the cartridge 100, in particular the sensor arrangement or sensor apparatus 113.

More particularly preferably, the connection apparatus 203 and the sensor temperature-control apparatus 204C (together) can be moved towards and/or relative to the cartridge 100, in particular the sensor arrangement or sensor apparatus 113, and/or can be positioned against or abutted on said cartridge, preferably in order to both electrically and thermally couple the analysis device 200 to the cartridge 100, in particular the sensor arrangement or sensor apparatus 113 or the support 113D thereof.

Preferably, the sensor temperature-control apparatus 204C is arranged centrally on the connection apparatus 203 or a support thereof and/or is arranged between the contact elements 203A.

In particular, the contact elements 203A are arranged in an edge region of the connection apparatus 203 or a support thereof or are arranged around the sensor temperature-control apparatus 204C, preferably such that the connection apparatus 203 is connected or connectable to the sensor apparatus 113 thermally in the centre and electrically on the outside or in the edge region. However, other solutions are also possible here.

The analysis system 1 or analysis device 200 preferably comprises one or more actuators 205 for actuating the valves 115. Particularly preferably, different (types or groups of) actuators 205A and 205B are provided which are assigned to the different (types or groups of) valves 115A and 115B for actuating each of said valves, respectively.

The analysis system 1 or analysis device 200 preferably comprises one or more sensors 206. In particular, fluid sensors 206A are assigned to the sensor portions 116 and/or are designed or intended to detect liquid fronts and/or flows of fluid in the fluid system 103.

Particularly preferably, the fluid sensors 206A are designed to measure or detect, in particular in a contact-free manner, for example optically and/or capacitively, a liquid front, flow of fluid and/or the presence, the speed, the mass flow rate/volume flow rate, the temperature and/or another value of a fluid in a channel and/or a cavity, in particular in a respectively assigned sensor portion 116, which is in particular formed by a planar and/or widened channel portion of the fluid system 103.

Particularly preferably, the sensor portions 116 are each oriented and/or incorporated in the fluid system 103 and/or fluid flows against or through the sensor portions 116 such that, in the operating position of the cartridge 100, fluid flows through the sensor portions 116 in the vertical direction and/or from the bottom to the top, or vice versa, in particular in order to make it possible or easier to accurately detect liquid.

Alternatively or additionally, the analysis device 200 preferably comprises (other or additional) sensors 206B for detecting the ambient temperature, internal temperature, atmospheric humidity, position, and/or alignment, for example by means of a GPS sensor, and/or the orientation and/or inclination of the analysis device 200 and/or the cartridge 100.

The analysis system 1 or analysis device 200 preferably comprises a control apparatus 207, in particular comprising an internal clock or time base for controlling the sequence of a test or assay and/or for collecting, evaluating and/or outputting or providing measured values in particular from the sensor apparatus 113, and/or from test results and/or other data or values.

The control apparatus 207 preferably controls or feedback controls the pump drive 202, the temperature-control apparatuses 204 and/or actuators 205, in particular taking into account or depending on the desired test and/or measured values from the sensor arrangement or sensor apparatus 113 and/or sensors 206.

The flows of fluid are controlled in particular by accordingly activating the pump or pump apparatus 112 and actuating the valves 115.

Particularly preferably, the pump drive 202 comprises a servomotor, stepper motor, or a drive calibrated in another way or a drive having a rotational speed and/or number of (partial) revolutions that can be controlled or feedback controlled, such that desired metering can be achieved, at least in principle, by means of appropriate activation.

Additionally or alternatively, the fluid sensors 206A are used to detect liquid fronts or flows of fluid, in particular in cooperation with the assigned sensor portions 116, in order to achieve the desired fluidic sequence and the desired metering by accordingly controlling the pump or pump apparatus 112 and accordingly activating the valves 115.

Optionally, the analysis system 1 or analysis device 200 comprises an input apparatus 208, such as a keyboard, a touch screen or the like, and/or a display apparatus 209, such as a screen.

The analysis system 1 or analysis device 200 preferably comprises at least one interface 210, for example for controlling, for communicating and/or for outputting measured data or test results and/or for linking to other devices, such as a printer, an external power supply or the like. This may in particular be a wired or wireless interface 210.

The analysis system 1 or analysis device 200 preferably comprises a power supply 211 for providing electrical power, preferably a battery or an accumulator, which is in particular integrated and/or externally connected or connectable.

Preferably, an integrated accumulator is provided as a power supply 211 and is (re)charged by an external charging device (not shown) via a connection 211A and/or is interchangeable.

The analysis system 1 or analysis device 200 preferably comprises a housing 212, all the components and/or some or all of the apparatuses preferably being integrated in the housing 212. Particularly preferably, the cartridge 100 can be inserted or slid into the housing 212, and/or can be received by the analysis device 200, through an opening 213 which can in particular be closed, such as a slot or the like.

The analysis system 1 or analysis device 200 is preferably portable or mobile. Particularly preferably, the analysis device 200 weighs less than 25 kg or 20 kg, particularly preferably less than 15 kg or 10 kg, in particular less than 9 kg or 6 kg.

As already explained, the analysis device 200 can preferably be pneumatically linked to the cartridge 100, in particular to the sensor arrangement and/or to the pump apparatus 112.

Particularly preferably, the analysis device 200 is designed to supply the cartridge 100, in particular the sensor arrangement and/or the pump apparatus 112, with a working medium, in particular gas or air.

Preferably, the working medium can be compressed and/or pressurised in the analysis device 200 or by means of the analysis device 200.

Preferably, the analysis device 200 comprises a pressurised gas supply 214, in particular a pressure generator or compressor, preferably in order to compress, condense and/or pressurise the working medium.

The pressurised gas supply 214 is preferably integrated in the analysis device 200 or the housing 212 and/or can be controlled or feedback controlled by means of the control apparatus 207.

Preferably, the pressurised gas supply 214 is electrically operated or can be operated by electrical power. In particular, the pressurised gas supply 214 can be supplied with electrical power by means of the power supply 211.

Preferably, air can be drawn in, in particular from the surroundings, as the working medium by means of the analysis device 200 or pressurised gas supply 214.

The analysis device 200 or pressurised gas supply 214 preferably comprises a connection element 214A, in particular in order to pneumatically connect the analysis device 200 or pressurised gas supply 214 to the cartridge 100.

In the following, further details are given on a preferred construction and the preferred mode of operation of the analysis system 1 and/or the cartridge 100 or the sensor arrangement, with reference to Fig. 3 to Fig. 11. The features of the sensor apparatus 113 and/or of the sensor arrangement formed thereby are preferably also directly features of the analysis system and/or of the cartridge 100, in particular even without any further explicit indication.

The sensor arrangement preferably comprises the sensor apparatus 113, especially the sensor apparatus 113 with the sensor array 113A, a sensor cover 117 for the sensor apparatus 113, a (common) sensor compartment 118, an inlet 119 into the sensor compartment 118 and/or an outlet 120 out of the sensor compartment 118, as shown in Fig. 2 and 6 to 11.

The sensor arrangement, in particular the sensor apparatus 113, especially the sensor array 113A, is preferably designed for amplifying analytes, particularly target nucleic acid sequences ZN, and for electrochemically and/or fluorescence measuring or detecting analytes of the sample P, in particular in the common/same sensor compartment 118.

In particular, the sensor arrangement or sensor apparatus 113, especially the sensor array 113A, is designed to amplify target nucleic acid sequences at constant temperatures, particularly temperatures less than 45 °C, even more preferred less than 43 °C, and/or temperatures less than the denaturing temperature of proteins and to identify, to detect and/or to determine (identical or different) analytes bonded to capture molecules or products derived therefrom, in particular amplification products of the analyte or different analytes.

Particularly, the sensor arrangement or sensor apparatus 113, especially the sensor array 113A of the sensor apparatus 113, is designed for carrying out a nucleic acid assay, a protein assay and/or an aptamer assay, either sequentially or simultaneously, preferably simultaneously.

The sensor arrangement is preferably designed as a multiple-part module, the sensor apparatus 113 and the sensor cover 117 preferably each forming a component of the sensor arrangement or module.

Preferably, the sensor arrangement has a layered construction, the sensor apparatus 113 preferably forming a base of the sensor arrangement and the sensor cover 117 being directly connected to the sensor apparatus 113, at least at the edge, and/or resting thereon.

The sensor apparatus 113 and the sensor cover 117 define or delimit the sensor compartment 118, preferably on the flat sides. In particular, the sensor compartment 118 is formed or arranged (directly) between the sensor apparatus 113 and the sensor cover 117.

The sensor compartment 118 preferably has, in particular when the sensor cover 117 is not actuated or has been moved away, a volume of greater than 0.1 µl or 0.2 µl, particularly preferably greater than 0.5 µl or 1 µl, in particular greater than 2 µl, and/or less than 10 µl or 8 µl, particularly preferably less than 6 µl or 3 µl.

The sensor arrangement, in particular the sensor apparatus 113 and the sensor cover 117, is/are preferably planar, flat and/or plate-shaped. Preferably, the surface area of a flat side of the sensor apparatus 113 and/or sensor cover 117 is less than 400 mm^2 or 300 mm^2, particularly preferably less than 250 mm^2 or 150 mm^2, in particular less than 100 mm^2 or 50 mm^2, and/or greater than 0.01 mm^2 or 0.25 mm^2, particularly preferably greater than 1 mm^2 or 4 mm^2.

The sensor apparatus 113 preferably has a front side or measuring side and a rear side or connection side, the measuring side and the connection side each preferably forming one flat side of the in particular flat, planar and/or plate-shaped sensor apparatus 113.

The measuring side is preferably the side of the sensor apparatus 113 (directly) facing the fluid or the sample P or the analyte or the sensor compartment 118.

The connection side is preferably opposite the measuring side and/or is the side of the sensor apparatus 113 that faces away from the fluid or the sample P or the analyte or the sensor compartment 118.

Preferably, the sensor arrangement comprises precisely one sensor compartment 118, precisely one inlet 119 into the sensor compartment 118 and/or precisely one outlet 120 out of the sensor compartment 118.

Preferably, the sensor compartment 118 is coherent/contiguous and/or not sectioned/segmented/subdivided.

The sensor apparatus 113 preferably comprises (precisely) one sensor array 113A on the measuring side, having a plurality of sensor cavities and/or sensor fields 113B, the sensor fields 113B preferably being round, in particular circular, in a plan view of the sensor array 113A and/or being arranged so as to be spatially separated from one another and/or directly next to one another.

Fig. 3 is a plan view of the sensor array 113A or the measuring side of the sensor apparatus 113. Fig. 4 is an enlarged detail from Fig. 3. Fig. 5 shows the connection side of the sensor arrangement or the sensor apparatus 113. Fig. 6 to Fig. 11 are schematic sections through the sensor arrangement during different method steps.

Preferably, the sensor arrangement, in particular the sensor apparatus 113 or the sensor array 113A, comprises more than 10 or 20, particularly preferably more than 50 or 80, in particular more than 100 or 120 and/or less than 1000 or 800 sensor fields 113B.

Preferably, the sensor fields 113B are separated or spaced apart from one another, in particular by less than 100 µm or 10 µm and/or more than 10 nm or 100 nm. Particularly preferably, all the sensor fields 113B are arranged on a surface area of less than 100 mm^2 and/or greater than 1 mm^2 and/or the sensor array 113A has a surface area of less than 100 mm^2 and/or greater than 1 mm^2.

The sensor fields 113B are in particular spatially separated measuring regions of the sensor apparatus 113 and/or sensor array 113A that, independently from one another, allow an analyte to be amplified, detected, identified and/or measured. Different sensor fields 113B can thus amplify, detect and/or measure different analytes, respectively. However, a plurality of sensor fields 113B could also amplify and/or measure the same analytes, however, again independently from one another, depending on the capture molecules with which the sensor fields 113 are provided. Alternatively, individual sensor fields 113B can also be used for control purposes, i.e. may not be used for amplifying, measuring and/or detecting an analyte.

Preferably, the sensor apparatus 113 comprises barriers or partitions between each of the sensor fields 113B, which are preferably formed by an in particular hydrophobic layer 113F having corresponding recesses for the sensor fields 113B. However, other structural solutions are also possible.

Preferably, the sensor arrangement, in particular the sensor apparatus 113 or the sensor array 113A, comprises a plurality of electrodes 113C. Particularly preferably, at least two electrodes 113C are arranged in each sensor field 113B. In particular, at least or precisely two electrodes 113C corresponding to one another form one or each sensor field 113B.

Preferably, some or all sensor fields 113B and/or electrodes 113C face the sensor compartment 118 and/or protrude into the (common) sensor compartment 118 and/or are fluidically (directly) connected to one another by means of the (common) sensor compartment 118,

The electrodes 113C are preferably made of metal, preferably so as to be electrically conductive, in particular at least the surface thereof is made of noble metal, such as platinum or gold.

Preferably, the electrodes 113C are finger-like and/or engage in one another, as can be seen from the enlarged detail of a sensor field 113B according to Fig. 4. However, other structural solutions or arrangements are also possible.

Preferably, each electrode pair forms one sensor field 113B, or each sensor field 113B contains one electrode pair.

The electrodes 113C of a sensor field 113B preferably correspond to one another in terms of their shape and size.

The sensor apparatus 113 preferably comprises a support 113D, in particular a chip comprising an electronic or integrated circuit, and/or a semiconductor chip, the electrodes 113C preferably being arranged on the support 113D and/or being integrated in the support 113D.

The sensor apparatus 113, in particular the support 113D, preferably comprises at least one, preferably a plurality of, electronic or integrated circuits, the circuits in particular being designed to detect electrical currents or voltages that are preferably generated at the sensor fields 113B in accordance with the redox cycling principle.

Particularly preferably, the measurement signals from the different sensor fields 113B are separately collected or measured by the sensor apparatus 113 and/or the circuits.

Particularly preferably, the sensor apparatus 113 and/or the integrated circuits directly convert the measurement signals into digital signals or data, which can in particular be read out by or via the analysis device 200.

Particularly preferably, the sensor apparatus 113 and/or the support 113D is constructed as described in EP 1 636 599 B1.

The sensor apparatus 113, in particular the support 113D, preferably comprises a plurality of, in this case eight, electrical contacts or contact surfaces 113E, the contacts 113E preferably being arranged on the connection side and/or forming the connection side, as shown in Fig. 5.

Preferably, the sensor apparatus 113 can be electrically contacted on the connection side and/or by means of the contacts 113E and/or can be electrically connected to the analysis device 200. In particular, an electrical connection can be established between the cartridge 100, in particular the sensor apparatus 113, and the analysis device 200, in particular the control apparatus 207, by electrically connecting the contacts 113E to the contact elements 203A of the connection apparatus 203.

Preferably, the contacts 113E are arranged laterally, in the edge region and/or in a plan view or projection around the electrodes 113C and/or the sensor array 113A, and/or the contacts 113E extend as far as the edge region of the sensor apparatus 113, in particular such that the sensor apparatus 113 can be electrically contacted, preferably by means of the connection apparatus 203 or the contact elements 203A, laterally, in the edge region and/or around the sensor temperature-control apparatus 204C, which can preferably be positioned centrally or in the middle on the support 113D, as already explained.

As already explained, the sensor compartment 118 is preferably arranged between the sensor apparatus 113 and the sensor cover 117, the measurement side and/or the sensor array 113A of the sensor apparatus 113 preferably defining or delimiting the sensor compartment 118.

Preferably, the sensor fields 113B and/or the electrodes 113C are fluidically interconnected by the sensor compartment 118, in particular such that some or all sensor fields 113B and/or electrodes 113C can come into contact with a fluid, the sample P and/or the analytes via the (common) sensor compartment 118.

The sensor cover 117 can preferably be moved relative to the sensor apparatus 113. In particular, the sensor cover 117 can be lowered onto the sensor apparatus

113, in particular the sensor array 113A and/or the layer 113F, preferably such that the sensor fields 113B are closed and/or fluidically separated from one another.

In particular, the fluid can be displaced out of the sensor compartment 118 by means of the sensor cover 117, and/or by lowering the sensor cover 117 onto the sensor apparatus 113.

The sensor cover 117 is therefore designed to seal and/or fluidically separate the individual sensor fields 113B from one another for the actual measurement, preferably such that fluid cannot be exchanged (in a relevant manner) between the sensor fields 113B, at least when the measurement is being taken.

Fig. 6 and Fig. 7 are each a schematic section through a preferred embodiment of the sensor arrangement with the sensor cover 117 moved away and/or before use, particularly before amplification, bonding of analytes and measurement and/or detection.

At least when the sensor cover 117 is moved away, the sensor apparatus 113 or the sensor compartment 118 is fluidically linked to the fluid system 103, in particular to the reaction cavity/cavities 109, preferably by the inlet 119 and the outlet 120, in particular such that fluids, in particular the (pretreated) sample P or the analytes and/or reagents, can be admitted to the measurement side of the sensor apparatus 113 or sensor array 113A.

The sensor compartment 118 can thus be loaded with fluids and/or said fluids can flow therethrough, at least when the sensor cover 117 is raised or moved away from the sensor apparatus 113 or the sensor array 113A.

Preferably, fluid can flow through the sensor compartment 118 by means of the inlet 119 and the outlet 120. In particular, a fluid can flow into the sensor compartment 118 via the inlet 119 and can flow out of the sensor compartment 118 via the outlet 120. However, the flow direction can also be reversed. In particular, the inlet 119 can function or be used as the outlet, at least temporarily, and the outlet 120 can function or be used as the inlet, at least temporarily.

The inlet 119 and/or the outlet 120 is/are preferably formed by cut-outs, holes, openings, channels or the like in the main body 101, the sensor cover 117 and/or the sensor apparatus 113.

The sensor apparatus 113 preferably comprises a plurality of in particular different capture molecules for bonding the analytes, different capture molecules preferably being arranged and/or immobilised in or on different sensor fields 113B and/or being assigned to different sensor fields 113B.

Particularly preferably, the, in particular some or all, sensor fields 113B or electrodes 113C are provided with the capture molecules, in particular at the factory, and/or the capture molecules are immobilised or fixed in or on the sensor fields 113B or electrodes 113C, in particular at the factory.

As already explained at the outset, the capture molecules are preferably capture nucleic acid sequences FN, in particular capture DNA sequences, capture RNA sequences and/or capture oligonucleotides, and at least one more type of capture molecules selected from capture proteins FP, in particular capture antigens and/or capture antibodies, and/or capture aptamers. Particularly, the capture molecules are preferably capture nucleic acid sequences FN, in particular capture DNA sequences, capture RNA sequences and/or capture oligonucleotides, and capture proteins FP, in particular capture antigens and/or capture antibodies (shown in Figs. 6 to 11).

Preferably, the cartridge 100 and/or the sensor apparatus 113 comprises a first group of capture molecules, such as capture nucleic acid sequences FN for amplifying and bonding target nucleic acid sequences ZN, and in particular a second group of (different) capture molecules, such as capture proteins FP or capture aptamers FA, for bonding another type of target molecules and/or analytes.

It is proposed for the analysis system 1, the cartridge 100, the sensor apparatus 113 and/or the sensor array 113A to comprise both capture proteins FP and capture nucleic-acid sequences FN, which are provided and/or immobilised together or separately in sensor fields 113B.

It is thus possible and provided for both, a nucleic-acid assay for detecting a nucleic-acid sequence ZN, in particular a plurality of different nucleic-acid sequences ZN, and a protein assay for detecting a target protein ZP, in particular a plurality of different target proteins ZP, to be carried out using the analysis system 1 and/or by means of the cartridge 100 and/or sensor apparatus 113, in particular in and/or by means of the same cartridge 100.

Different capture nucleic acid sequences and/or different capture proteins are preferably provided for the different sensor fields 113B and/or the different electrode pairs and/or electrodes 113C, in order to specifically bond different analytes, in particular different target proteins, on the one hand and different target nucleic-acid sequences, on the other hand, in the sensor fields 113B.

Particularly preferably, the sensor apparatus 113 or sensor array 113A allows the analytes bonded in each sensor field 113B to be qualitatively and/or quantitatively determined.

Preferably, the capture molecules are bonded to the sensor apparatus 113, the sensor array 113A and/or the electrodes 113C by a bond B, in particular a thiol bond, and/or, optionally, by a so-called C6 spacer and/or elongated thymine primer with preferably 5 to 20 bases. The formation of structures that disrupt hybridisation, e.g. hairpin structures, can be prevented by the preferred bonding of the capture molecules by the bond B.

Preferred embodiments of the sensor apparatus 113, particularly the sensor array 113A, with respect to the functionalization of the sensor fields 113B are delineated in the following.

A first preferred embodiment is shown in Fig. 6, according to which a portion of the sensor fields 113B and/or electrodes 113C is provided with capture nucleic acid sequences FN, in particular in order to be able to detect or identify the target nucleic acid sequences ZN that correspond to the capture nucleic acid sequences FN, and another portion of the sensor fields 113B and/or electrodes 113C is provided with capture proteins FP, in particular in order to be able to detect or identify the target proteins ZP that correspond to the capture proteins FP.

In other words, capture nucleic acid sequences FN and capture proteins FP are applied to, fixed to and/or immobilised onto different sensor fields 113B of a common sensor arrangement and/or sensor apparatus 113 and/or sensor array 113A.

Such functionalization is linked with the advantage that no differentiation of detection signals produced by target nucleic acid sequences ZN, on the one hand, and target proteins ZP, on the other hand, is necessary. In other words, the same detection method and/or the same type of detection markers and/or detection labels L can be used for the detection of bonded target nucleic acid sequences ZN and target proteins ZP.

According to a preferred embodiment, some or all of the sensor fields 113B and/or electrodes 113C are additionally provided with spacer molecules SC, as shown in Fig. 6 for the second sensor field 113B (from the left).

Spacer molecules SC in the sense of the present invention are chemically inert molecules, which are not directly involved in amplification, bonding and measurement and/or detection of the analytes. Instead, spacer molecules SC reduce the steric hindrance for analytes, particularly target nucleic acid sequences, when bonded to capture molecules. Spacer molecules can have a positive effect on amplification and bonding of target nucleic acid sequences ZN as well as their detection and/or measurement. Preferably, spacer molecules are based on chemically inert substances.

According to a particularly preferred embodiment of the present invention, the spacer molecules SC are oligonucleotides, preferably oligonucleotides having at least 5 or 10 bases and/or at most 70 or 80 bases, especially 10 to 50 bases, particularly preferably 12 to 20 bases. Preferably, the spacer molecules SC are based on thymine bases. Likewise, spacers can be based on any other nucleobase, particularly adenine, guanine, cytosine and/or combinations thereof.

According to another, particularly preferred embodiment as shown in Fig. 7, preferably some or all of the sensor fields 113B and/or electrodes 113C are provided with both capture nucleic acid sequences FN and capture proteins FP, in particular in order to be able to detect or identify the target nucleic acid sequences ZN that correspond to the capture nucleic acid sequences FN and the target proteins ZP that correspond to the capture proteins FP by means of the sensor apparatus 113 and/or in the corresponding sensor fields 113B and/or on the corresponding electrodes 113C.

In other words, preferably both capture nucleic acid sequences FN and capture proteins FP are applied to, fixed to and/or immobilised in common sensor fields 113B and/or on common electrodes 113C and/or are applied, fixed and/or immobilised directly next to one another.

Preferably, one sensor field 113B is thus used not just for amplifying target nucleic acid sequences ZN and detecting at least one analyte, but rather for detecting and in particular measuring at least two analytes, specifically a target protein ZP on the one hand (in Fig. 7 e.g. ZP3 to ZP5) and a target nucleic-acid sequence ZN on the other hand (in Fig. 7 e.g. ZN3 to ZN5). The corresponding capture molecules, specifically capture proteins FP and capture nucleic-acid sequences FN, can in this case be arranged and/or immobilised together on each of the electrodes 113C of the sensor field 113B or, at least in theory, separately on the two electrodes 113C of the same sensor field 113B.

It is thus possible to carry out twice the number of detection processes and/or measurements of analytes using the same number of sensor fields 113B. Overall, a higher number of target molecules can be detected at once according to this embodiment.

As further shown in Fig. 6 and Fig. 7, preferably some or all of the sensor fields 113B and/or electrodes 113C, particularly all sensor fields 113B and/or electrodes 113C with capture nucleic acid sequences FN, comprise at least one reagent R for carrying out an amplification of target nucleic acid sequences ZN from the sample P.

According to a particularly preferred embodiment, some or all of the sensor fields 113B and/or electrodes 113C, particularly all sensor fields 113B and/or electrodes 113C with capture nucleic acid sequences FN, and/or the sensor compartment 118 comprise a reaction mix for carrying out an amplification of target nucleic acid sequences ZN from the sample P.

Preferably, the at least one reagent R and/or the reaction mix is immobilized and/or fixed, especially dried onto or into the, in particular some or all, sensor fields 113B and/or electrodes 113C, and/or the (common) sensor compartment 118.

According to a preferred embodiment of the present invention, the at least one reagent R is selected from enzymes, particularly enzymes for a DNA amplification, NTPs, dNTPs, primers, particularly wherein the primers comprise a pathogen-specific nucleotide sequence and/or wherein a portion of the primers comprises a detectable label, sugar molecules and/or salts.

According to a preferred embodiment, the reaction mix comprises enzymes, particularly enzymes for a DNA amplification, NTPs, dNTPs, primers, particularly wherein the primers comprise a pathogen-specific nucleotide sequence and/or wherein a portion of the primers comprises a detectable label, sugar molecules and/or salts.

One the one hand, it is preferred when the at least one reagent and/or the reaction mix R comprises reagents for the amplification of target nucleic acid sequences ZN. On the other hand, it is preferred when the at least one reagent and/or the reaction mix R comprises stabilizing substances for the amplification and/or proteins, particularly capture proteins FP and/or target proteins ZP, especially sugar molecules.

In particular, sugar molecules are selected from the group of monosaccharides, disaccharides, oligosaccharides, polysaccharides and combinations thereof, preferably monosaccharides and/or disaccharides. Especially, the sugar molecules are selected from glucose, mannose, galactose, lactose, sucrose, fructose, isomalt, isomaltulose, maltulose, trehalose, oligofructose, inulin, starch, dextrin, cyclodextrin and combinations thereof.

Preferably, all reagents for the amplification of target nucleic acid sequences ZN, in particular enzymes, primers, NTPs and/or dNTPs, are immobilized and/or fixed into or onto the sensor fields 113B and/or electrodes 113C. Alternatively, only a portion of the reagents for the amplification, particularly primers, NTPs and/or dNTPs, are immobilized and/or fixed to the sensor fields 113B and/or electrodes 113C.

According to a particularly preferred embodiment, the at least one reagent R and/or the reaction mix comprise reagents for an isothermal DNA amplification and a stabilization of the capture molecules and the at least one reagent R and/or the reaction mix are immobilized and/or fixed onto or into the sensor compartment 118 or the sensor array 113A, particularly onto the surface of sensor fields 113B and/or electrodes 113C of the senor array 113A.

Furthermore, it is advantageous when a senor array 113A of the sensor apparatus 113 comprises capture nucleic acid sequences FN and at least one more type of capture molecules selected from capture proteins FP and/or capture aptamers FA and when the at least one reagent R and/or the reaction mix are immobilized and/or fixed onto or into the sensor compartment 118 or sensor array 113A, particularly onto the surface of sensor fields 113B and/or electrodes 113C of the senor array 113A.

Particularly preferably, the analysis system 1 and/or the cartridge 100 is designed such that a nucleic acid assay, a protein assay and/or an aptamer assay can be carried out, particularly simultaneously.

During the nucleic-acid assay, the analytes and/or target nucleic-acid sequences ZN are amplified and bonded to the capture nucleic-acid sequences FN and then detection and/or measurement of bonded target nucleic acid sequences ZN is carried out. During the protein assay, the analytes and/or target proteins ZP are bonded to the capture proteins FP and then detection and/or measurement of bonded target proteins ZP is carried out. During the aptamer assay, analytes corresponding to the capture aptamers FA are bonded to the capture aptamers FA and then detection and/or measurement of the analytes is carried out.

Alternatively, the analysis system 1 and/or the cartridge 100 can be designed such that a nucleic acid assay, on the hand, and a protein assay and/or an aptamer assay, on the other hand, are carried out sequentially.

Preferably, particularly in case the protein assay is carried out before the nucleic acid assay and/or the aptamer assay, the capture proteins FP and/or target proteins ZP are denatured, in particular by a corresponding effect of heat, or degraded or blocked in another manner, after the protein assay has been carried out.

In the following, a preferred sequence of a test or analysis using the proposed analysis system 1 and/or analysis device 200 and/or the proposed cartridge 100 and/or in accordance with the proposed method is explained in greater detail by way of example.

The analysis system 1, the cartridge 100 and/or the analysis device 200 is preferably designed to carry out the proposed method.

The method may be used in particular in the field of medicine, in particular veterinary medicine, for example in order to detect or identify diseases and/or pathogens. Alternatively, the method may also be used for other purposes, for example for food safety, environmental analytics or the like.

The method of the present invention is particularly characterized in that amplification of target nucleic acid sequences ZN, bonding of target analytes and the plurality of assays in order to detect the bonded target analytes are carried out by means of the sensor apparatus 113 without a temporal and/or spatial separation.

Particularly, target nucleic acid sequences ZN are amplified as analytes from the sample, bonded to capture nucleic acid sequences FN and detected and/or measured, preferably on the basis of a nucleic acid assay, wherein amplification, bonding and detection and/or the nucleic acid assay are carried out in the sensor apparatus 113 of the analysis system 1 and/or the cartridge 100 and/or the analysis device 200.

Particularly preferably, amplification of target nucleic acid sequences ZN, bonding and detection of target analytes are carried out in a common sensor array 113A and/or in the same sensor fields 113B of the sensor apparatus 113 and/or in a common sensor compartment 118.

According to a particularly preferred embodiment of the proposed method, target nucleic acid sequences ZN are amplified from the sample and bonded to capture nucleic acid sequences FN and at least one more type of analytes selected from analytes that correspond to capture proteins FP and/or capture aptamers FA, preferably capture proteins FP, is bonded to capture proteins FP and/or capture aptamers FA in the sensor apparatus 113.

Preferably, a plurality of (different) assays for detecting or identifying (different) target analytes of the sample P are carried out by means of the sensor apparatus, wherein the assays are selected from at least two assays from the selection group of consisting of a protein assay, a nucleic acid assay and/or an aptamer assay.

Preferably, the amplification of target nucleic acid sequences ZN, bonding of target analytes and/or the plurality of assays are carried out in a common sensor array 113A and/or in the same sensor fields 113B of the sensor apparatus 113 and/or in a common sensor compartment 118.

The method of the present invention is particularly realized by amplifying the target nucleic acid sequences ZN at constant temperatures, particularly temperatures less than 45 °C, even more preferred less than 43 °C.

Likewise, it is preferred when the target nucleic acid sequences ZN are amplified at constant temperatures less than the denaturing temperature of proteins, particularly the denaturing temperature of capture proteins FP and/or target proteins ZP and/or target analytes that correspond to capture aptamers FA.

Amplification of target nucleic acid sequences ZN at temperatures less than 45 °C and/or temperatures less than the denaturing temperature of proteins allows the amplification of target nucleic acid sequences and the bonding of (different) target analytes, particularly target nucleic acid sequences ZN and target proteins ZP, to capture molecules as well as the detection assays to be carried out without a spatial and/or temporal separation.

According to a particularly preferred embodiment, the plurality of assays, especially the nucleic acid assay, the protein assay and/or the aptamer assay, are carried out at temperatures less than 45 °C, preferably less than 43 °C, and/or less than the denaturing temperature of proteins.

Preferably, target nucleic acid sequences ZN are amplified by means of isothermal DNA amplification and/or by using at least one enzyme, particularly a DNA polymerase, with strand displacement activity.

Amplification of target nucleic acid sequences ZN at constant temperatures, preferably temperatures less than 45 °C and/or temperatures less than the denaturing temperature of proteins, can be carried out according any established isothermal DNA amplification protocol, for example a multi-displacement amplification, an isothermal assembly, a recombinase polymerase amplification and the like.

Fig. 8 shows a schematic representation of a preferred isothermal amplification of target nucleic acid sequences, preferably on the basis of a recombinase amplification:

In a first step (Fig. 8A), labelled amplicons of target nucleic acid sequences ZN are generated from the sample P, particularly by using a pair of preferably pathogen-specific primers PR, wherein at least one primer comprises a detectable marker and/or label L. According to a preferred embodiment of the isothermal amplification, at least one primer comprises a nucleotide sequence which is homolog and/or identical to the nucleotide sequence of the capture nucleic acid sequences FN. Particularly, the pair of primers comprises one forward and one reverse primer.

In a further amplification step, preferably pathogen-specific capture nucleic acid sequences FN can function as further primers. Thereby, single strands of the amplicons hybridise to the capture nucleic acid sequences TN. Preferably, the capture nucleic acid sequences FN are elongated in the amplification process preferably to the length of the amplified target nucleic acid sequences ZN and/or the hybridised amplicons (Fig. 8B and 8C).

During and/or after amplification, the capture nucleic acid sequences FN can take various forms, depending on the elongation of the capture molecules. Particularly, the elongated single strand of a capture nucleic acid sequences FN can comprise a preferably labelled primer PR, as shown in Fig. 8C. Likewise, the capture nucleic acid sequences FN can be in a state as shown in Fig. 8D. Furthermore, intermediate states between the states shown in Figs. 8C and 8D are possible.

After amplification, the bonded and preferably labelled target nucleic acid sequences ZN can be detected and/or identified and/or measured.

A particularly preferred amplification method is described in Piepenburg et al.: "DNA Detection Using Recombination Proteins", published in Plos Biology, July 2006, Volume 4, Issue 7, e204

As already explained before, Fig. 8 shows only one preferred embodiment of a particularly suitable isothermal amplification reaction for target nucleic acid sequences ZN. Alternative amplification methods at constant temperatures, preferably temperatures less than 45 °C and/or less than the denaturing temperature of proteins can be used as well.

As delineated above, the method of the present invention allows a nucleic acid assay and at least one more type of assay, particularly a protein assay and/or an aptamer assay to be carried out in a common sensor array 113A and/or in the same sensor fields 113B of the sensor apparatus 113 and/or in a common sensor compartment 118.

Preferably, amplification and bonding of target nucleic acid sequences ZN to capture nucleic acid sequences FN are carried out simultaneously or sequentially, preferably simultaneously. According to a particularly preferred embodiment, bonding of target nucleic acid sequences ZN is performed within and/or in course with the amplification.

According to a further embodiment of the present invention, amplification and bonding of target nucleic acid sequences ZN to capture nucleic acid sequences FN and bonding of the at least one more type of analytes to capture proteins FP and/or capture aptamers FA are carried out simultaneously or sequentially, preferably simultaneously.

Particularly, the plurality of assays, especially the nucleic-acid assay, the protein assay and/or the aptamer assay, are carried out simultaneously or sequentially, preferably simultaneously.

Preferably, a nucleic-acid assay is carried out in order to amplify, bond, detect and/or identify and/or quantify a target nucleic-acid sequence ZN, in particular a target DNA sequence and/or target RNA sequence. Particularly preferably, target nucleic-acid sequences ZN are amplified and bonded to corresponding capture molecules, in particular capture nucleic-acid sequences FN, in the form of analytes of the sample P are detected.

Preferably, a protein assay, particularly in addition to the nucleic-acid assay, is carried out in order to detect or identify and/or quantify a target protein ZP, in particular a target antigen and/or target antibody. In particular, target proteins ZP are bonded to corresponding capture molecules, in particular capture proteins FP, in the form of analytes of the sample P are detected.

Optionally, an aptamer assay is carried out, in particular as an alternative to the protein assay, in order to detect or identify a target protein or another target analyte that is different from the target protein ZP.

According to a preferred embodiment, the bonded analytes, particularly bonded target nucleic acid sequences ZN, target proteins ZP and/or the target aptamers ZA, are identified or detected electrochemically and/or by redox cycling and/or by fluorescence measurement.

In case the sensor apparatus 113 comprises the capture nucleic acid sequences FN and the capture proteins FP in common sensor fields 113B, target nucleic acid sequences ZN and target proteins ZP are preferably detected and/or identified with different detection methods and/or different detection systems and/or different detection markers and/or labels L, preferably selected from the group of electrochemically detectable labels and/or fluorescence labels.

In case the sensor apparatus 113 comprises the capture nucleic acid sequences FN and the capture proteins FP in different sensor fields 113 B, target nucleic acid sequences ZN and target proteins ZP are preferably detected and/or identified with the same detection method and/or detection system and/or detection markers and/or labels L, preferably selected from the group of electrochemically detectable labels and/or fluorescence labels, particularly preferably electrochemically detectable labels.

In the following, however, a first, particularly preferred variant of the method is described first of all, in which both a protein assay and a nucleic-acid assay are carried out. However, any explanations relating to preparing and/or carrying out the respective assays apply correspondingly to other combinations from the selection group consisting of a protein assay, a nucleic-acid assay and/or an aptamer assay.

A particularly preferred conduct of the method is delineated in the following:

At the start of the proposed method, a sample P having at least one analyte, preferably a fluid or a liquid from the human or animal body, in particular blood, saliva or urine, is preferably first introduced into the receiving cavity 104 via the connection 104A, it being possible for the sample P to be pretreated, in particular filtered.

Once the sample P has been received, the receiving cavity 104 and/or the connection 104A thereof is fluidically closed, in particular in a liquid-tight and/or gas-tight manner.

Preferably, the cartridge 100 together with the sample P is then linked to the analysis device 200, in particular is inserted or slid into the analysis device 200 or the opening 213, particularly preferably from the top.

Particularly preferably, the cartridge 100 is received, at least substantially vertically, by the analysis device 200.

The method sequence, in particular the flow and conveying of the fluids, the mixing and the like, is controlled by the analysis device 200 or the control apparatus 207, in particular by accordingly activating and actuating the pump drive 202 or the pump apparatus 112 and/or the actuators 205 or valves 115.

Preferably, the sample P or a part or supernatant of the sample P is removed from the receiving cavity 104, in particular via the outlet 104C, and/or via the intermediate connection 104D, and is preferably fed to the mixing cavity 107 in a metered manner.

Preferably, the sample P or a portion thereof is removed, optionally via the outlet 104C or the intermediate connection 104D of the receiving cavity 104.

Preferably, the sample P or a portion thereof in the cartridge 100 is metered, in particular in or by means of the first metering cavity 105A and/or second metering cavity 105B, before being introduced into the mixing cavity 107. Here, in particular the upstream and/or downstream sensor portions 116 are used together with the assigned sensors 206 in order to make possible the desired metering. However, other solutions are also possible.

According to a preferred embodiment of the method, the sample P or a portion thereof is mixed in the mixing cavity 107 with a liquid F1, especially a rehydration and/or solubilization buffer and/or a reaction buffer, preferably a rehydration and/or solubilization buffer.

The rehydration and/or solubilization buffer for the proposed method is preferably selected from water and/or TRIS-buffer.

According to a specific embodiment, the liquid F1 and/or the buffer is suitable to stabilize the capture molecules, particularly the capture nucleic acids FN and/or the capture proteins FP and/or the capture aptamers FA, and/or the nucleic acid assay, the protein assay and/or the aptamer assay. In this context it is preferred when the sample P or a protein thereof is mixed with a reaction buffer containing sugar molecules and/or salts, particularly sugar molecules.

Nevertheless, addition and/or admixing of a liquid F1, particularly a rehydration and/or solubilization buffer and/or a reaction buffer, can likewise take place later, as delineated in the following.

Preferably, the sample P or a portion thereof is removed from the mixing cavity 107 and fed to the sensor arrangement and/or sensor apparatus 113, preferably directly, in particular via the bypass 114A and/or past the reaction cavities 109.

According to a specific embodiment of the method, the sample P or a portion thereof can, if required, be pretreated in the cartridge 100, or can be conducted to the sensor arrangement and/or sensor apparatus 113 without being pretreated. The latter case is possible in particular when, for example, a supernatant of the sample P is discharged via the intermediate connection 114D and conducted to the sensor arrangement or sensor apparatus 113 as a sample portion. However, other method sequences are also possible here.

For a pretreatment, the sample P or a portion thereof is preferably conducted through one or more of the reaction cavities 109.

According to a further preferred embodiment, once the sample P or a portion thereof has been conducted to the sensor arrangement and/or sensor apparatus 113, a liquid F1 and/or a rehydration and/or solubilization buffer and/or a reaction buffer, preferably a rehydration and/or solubilization buffer, is fed into the sensor arrangement and/or sensor apparatus 113.

The at least one reagent and/or the reaction mix R in the sensor apparatus 113 and/or the sensor array 113A and/or the sensor fields 113B and/or on the sensor electrodes 113C are solved and/or solubilized through the sample P and/or a portion thereof and/or a liquid F1, preferably the rehydration and/or solubilization buffer and/or the reaction buffer.

As delineated before, according to a particularly preferred embodiment the at least one reagent and/or the reaction mix R comprises sugar molecules and/or salts, particularly sugar molecules. After solubilization and/or solving of the at least one reagent and/or the reaction mix R, preferably through a rehydration and/or solubilization buffer, particularly preferably water and/or TRIS buffer, and/or the sample P, the solubilized and/or solved sugar molecules and/or salts, especially sugar molecules, stabilize not only the amplification reaction but also the capture and/or target proteins as well as the plurality of assays, in particular the nucleic acid assay and/or the protein assay.

According to another embodiment, the liquid F1 and/or the reaction buffer is suitable to stabilize the capture molecules, particularly the capture nucleic acids FN and/or the capture proteins FP and/or the capture aptamers FA, and/or the nucleic acid assay, the protein assay and/or the aptamer assay. According to a particularly preferred embodiment, a liquid F1 and/or a reaction buffer containing sugar and/or salts, particularly sugar, is fed into the sensor arrangement and/or the sensor apparatus 113.

Once the sample P or a portion thereof and/or a liquid F1 and/or a rehydration and/or solubilization buffer and/or a reaction buffer have been conducted to the sensor arrangement and/or sensor apparatus 113, the nucleic acid assay, the protein assay and/or the aptamer assay are carried out sequentially or simultaneously, preferably simultaneously.

According to a particularly preferred embodiment, amplification of the target nucleic acid sequences ZN and bonding of target nucleic acid sequences ZN, target proteins ZP and/or target molecules which correspond to the target aptamers ZA, preferably the bonding of target nucleic acid sequences ZN and target proteins ZP, to the corresponding capture nucleic acid sequences FN and/or capture proteins FP and/or capture aptamers FA are performed simultaneously or sequentially, preferably simultaneously.

Preferably, the nucleic acid assay and/or the protein assay and/or the aptamer assay, especially the protein assay and the nucleic acid assay, are carried out at temperatures less than 45 °C, preferably less than 43 °C, and/or temperatures less than the denaturing temperature of proteins.

Particularly preferably, the target nucleic acid sequences ZN are amplified from the sample at constant temperatures and/or by an isothermal amplification.

Particularly, target nucleic acid sequences ZP are produced with a detectable label L during amplification. Preferably, the label L is selected from electrochemically detectable labels and fluorescence labels. Nevertheless, the use of other detectable labels is likewise possible.

According to a particularly preferred embodiment, the nucleic acid assay and/or the amplification of the target nucleic acid sequences ZN is supported and/or activated by controlling the temperature of the sensor arrangement and/or sensor apparatus 113.

Preferably, the temperature of the sensor arrangement and/or sensor apparatus 113 is controlled by means of the sensor temperature-control apparatus 204C and/or by conducting a fluid that has been correspondingly preheated, preferably by means of the intermediate temperature-control apparatus 204B.

Particularly, the temperature of the sensor arrangement and/or the sensor apparatus is set to less than 45 °C, preferably less that 43 °C and/or less than the denaturing temperature of proteins, particularly of target proteins ZP and/or capture proteins FP and/or target analytes which correspond to target aptamers FA. Likewise, the temperature of the sensor arrangement and/or the sensor apparatus is set to a temperature in the range from 30 °C to 45 °C, preferably from 35 °C to 43 °C.

As delineated before, the protein assay and/or the aptamer assay, particularly the protein assay, are preferably carried out simultaneously to the nucleic acid assay.

Particularly, the at least one more analyte, particularly selected from target proteins FP and/or target analytes which correspond to target aptamers, bonds to the corresponding capture molecules simultaneously and/or in course with the nucleic acid assay and/or amplification and/or bonding of target nucleic acid sequences.

In order to stop amplification of target nucleic acid sequences ZN and/or bonding of target analytes, particularly preferably a washing and/or flushing process for the sensor arrangement or sensor apparatus 113 is carried out.

Following the bonding of the analytes, preferably an optional washing process takes place and/or additional reagents or liquids, in particular from the storage cavities 108B to 108E, are optionally fed in.

In particular, it may be provided that remnants of the sample P, sample residues, or unbonded analytes or amplification products, reagents and/or remnants from the amplification, and other substances that may disrupt the further method sequence, are in particular removed from the sensor compartment 118.

Preferably, a liquid, in particular a wash buffer, is conducted through the sensor compartment 118 and/or past the sensor apparatus 113, in particular in order to wash away or flush out unbonded analytes and/or excess reagents from the sensor compartment 118 and/or the region of the sensor apparatus 113. Preferably, the wash buffer itself does not comprise any analytes, and therefore the sensor compartment 118 is freed of substances that could prevent or distort a subsequent evaluation and/or measurement.

Washing or flushing may in particular take place using a liquid or reagent F2, in particular a wash buffer, particularly preferably a sodium-citrate buffer or SSC buffer, which is preferably contained in the storage cavity 108C. Unbonded analytes, amplification products and substances which could disrupt subsequent detection are preferably removed from the sensor compartment 118 and/or from the sensor apparatus 113 by the wash buffer and/or fed to the collection cavity 111.

Subsequently and/or after the washing process, in accordance with a preferred variant of the method, detection of the analytes and/or amplification products bonded to the capture molecules takes place.

According to a particularly preferred embodiment of the proposed method, the bonded target analytes, in particular the bonded target nucleic acid sequences ZN, the target proteins ZP and/or the target analytes corresponding to the capture aptamers FA, are identified and/or detected, in particular electrochemically and/or by redox cycling and/or by fluorescence measurement, in the sensor arrangement and/or sensor apparatus 113.

Detection of different analytes can be carried out either simultaneously or sequentially, preferably simultaneously.

Detection is preferably carried out by means of detection labels and/or markers, particularly a label L. In particular, a label L can be detected or a label L can be identified in a detection process, as explained in greater detail in the following.

In the method of the present invention, any molecular biological detection method and/or detection system and/or combination of detection labels in order to distinguish bonded target nucleic acid sequences ZN from target proteins ZP and vice versa can be used.

For the detection of target nucleic acid sequences, the label L is preferably produced directly and/or during the amplification reaction(s) (in each case) and/or is attached to the analytes, amplification products and/or target nucleic-acid sequences ZN. This is in particular achieved by using primers with a detectable label, for example biotinylated primers or fluorescently labelled primers.

In case the sensor apparatus 113 comprises capture nucleic acid sequences FN and capture proteins FP in common sensor fields 113B, it is preferred when target nucleic acid sequences ZN are produced with labels that are different from the labels used for target proteins ZP.

However, the label L can also be produced and/or bonded to the analytes, amplification products, target nucleic-acid sequences ZN and/or target proteins ZP separately or later. In particular with respect to target proteins ZP, a label L is only bonded to analytes and/or target proteins ZP after bonding of the analytes and/or target proteins ZP to the capture molecules.

Target nucleic acid sequences ZN and target proteins ZP can be detected by using identical or different detection labels.

With respect to embodiments where the sensor apparatus 113 and/or the sensor array 113A comprises capture nucleic acid sequences FN and at least one more type of capture molecules, particularly capture proteins FP, in common sensor fields 113B and/or on common sensor electrodes 113C, preferably different detection markers and/or detection labels L are used for target nucleic acid sequences ZN and target proteins ZP.

According to a particularly preferred embodiment of the method, target nucleic acid sequences ZN are produced with a fluorescence label and a label different therefrom, preferably a biotin marker, is bonded to the bonded target proteins ZP, especially after bonding of the target proteins ZP to the capture proteins FP.

Alternatively, the target nucleic acid sequences ZN are produced with a biotin label and a label different therefrom, preferably a fluorescence label, is bonded to the bonded target proteins ZP.

Nevertheless, any other combination of molecular biological detection molecules and/or detection labels or markers can be used for the detection and/or measurement of bonded analytes. The selection of a suitable detection system and/or detection labels belongs to the general knowledge of the person skilled in the art.

With respect to embodiments where the sensor apparatus 113 and/or the sensor array 113A comprises the capture nucleic acid sequences FN and at least one more type of capture molecules, particularly capture proteins FP, in different sensor fields 113B, preferably identical labels L are used for target nucleic acid sequences ZN and target proteins ZP, preferably electrochemically detectable labels, particularly preferably biotin.

Fig. 9 is a schematic sectional detail of the sensor arrangement when the sensor cover 117 is raised and/or not lowered after the amplification and bonding of target nucleic acid sequences ZN comprising a label L1 and bonding of target proteins ZP.

Fig. 10 is a schematic sectional view of the sensor arrangement after labels L2 for target proteins have been fed and before the detection and/or identification and/or measurement of the target analytes are carried out, wherein the sensor cover has been moved away.

As can be seen from Fig. 9, the target nucleic acid sequences ZN3, ZN4 and ZN5 are bonded to the capture nucleic acid sequences FN3, FN4 and FN5 and comprise a detectable marker and/or label L1. As explained before, the detectable labels L1 of the target nucleic acid sequences ZN have been produced during isothermal amplification.

According to a particularly preferred embodiment, the detectable marker and/or label L1 is an electrochemically detectable label and/or a fluorescence label, in this case a fluorescence label. Nevertheless, according to a likewise preferred embodiment, the label L1 for the target nucleic acid sequences can be an electrochemically detectable label.

Furthermore, the target proteins ZP3, ZP4 and ZP5 are bonded to the capture proteins FP3, FP4 and FP5. In contrast to the target nucleic acid sequences ZN3, ZN4 and ZN5, the bonded target proteins ZP3, ZP4 and ZP5 do not comprise a label yet.

Following the (respective) bonding of the analytes, the sensor arrangement and/or sensor apparatus 113 is prepared and/or pretreated for the detection of bonded target analytes.

According to a preferred embodiment, a washing and/or flushing process with a reagent and/or liquid F2, preferably a wash buffer, for the sensor arrangement or sensor apparatus 113, particularly for the sensor fields 113B is carried out, particularly to stop amplification and/or bonding of analytes.

Furthermore, particularly in order to allow a detection of the bonded target proteins ZP3, ZP4 and ZP5, a reagent and/or liquid F3, preferably a liquid comprising labels L2, are fed into the sensor arrangement or the sensor compartment 118, preferably from the storage cavity 108E. The labels L2 preferably bond to the bonded target proteins ZP3, ZP4 and ZP5 (cf. Fig. 10).

The labels L2 are preferably selected from electrochemically detectable labels and/or fluorescence labels, in the present case from electrochemically detectable labels, for example biotin. Likewise, the label L2 and/or the label for target proteins FP can be a fluorescence label.

Optionally, there is then another washing process.

Furthermore, a reagent or liquid F4 and/or detector molecules D, for example alkaline phosphatase/streptavidin, is/are fed to the sensor apparatus 113, preferably from the storage cavity 108D.

Within the meaning of the present invention, the term "detector molecules" is preferably understood to mean molecules that bond specifically to the marker or label L, in the present case only the label L2 of the bonded target proteins ZP and thus allow the detection thereof.

In particular, the detector molecules D may be enzyme conjugates and/or immunoconjugates, which bond specifically to the marker or label L, preferably the label L2, in particular biotin, and comprise a reporter enzyme for converting a substrate SU.

In the context of the present invention, the detector molecules D are preferably based on streptavidin, which has a high affinity for biotin, and/or alkaline phosphatase, which can convert non-reactive phosphate monoesters to electrochemically active molecules and phosphate.

Preferably, for the target proteins ZP a detection system is used, where the label L2 is based on biotin and where the detector molecules D are based on streptavidin/alkaline phosphatase. However, other detector molecules D can also be used.

The reagents F4 or detector molecules D can bond to the bonded target proteins ZP, in particular to the label L2 of the bonded analytes or proteins, particularly preferably to the biotin marker, as shown in Fig. 10.

Optionally, subsequently or after the reagents F4 and/or detector molecules D have bonded to the target proteins ZP or the labels L2, an (additional) washing process and/or flushing takes place, preferably by means of the fluid or reagent F2 or wash buffer, in particular in order to remove unbonded reagents F4 and/or detector molecules D from the sensor apparatus 113.

Preferably, a reagent S7 and/or S8 and/or substrate SU for the detection, in particular from the storage cavity 106D, is lastly fed to the sensor arrangement or sensor apparatus 113, preferably together with a liquid or reagent F1 or F2 (in particular a buffer), which is suitable for the substrate SU, particularly preferably for dissolving the reagent S7 and/or S8 and/or substrate SU. In particular, the reagent S7 and/or S8 can form or can comprise the substrate SU.

Preferably, p-aminophenyl phosphate (pAPP) is used as the substrate SU.

The substrate SU preferably reacts on and/or with the bonded analytes, particularly the bonded target proteins ZP, and/or detector molecules D and/or allows these to be electrochemically measured.

In order to carry out the detection or measurement of the bonded target analytes or after adding the substrate SU, the sensor cover 117 is preferably pneumatically actuated and/or lowered onto the sensor apparatus 113 (as shown in Fig. 11), in particular in order to fluidically separate the (individual) sensor fields 113B from one another, and/or to prevent or minimise the exchange of substances between the sensor fields 113B.

Actuating or lowering the sensor cover 117 in particular prevents a reaction and/or detection from being assigned to an incorrect or adjacent sensor field 113B, and in this way prevents measurement inaccuracies or errors from occurring. In particular, the sensor cover 117 increases the measurement accuracy of the method.

As shown in particular in Fig. 11, the substrate SU is preferably split by the bonded detector molecules D, in particular the alkaline phosphatase of the bonded detector molecules D, preferably into a first substance SA, such as p-aminophenol, which is in particular electrochemically active and/or redox active, and a second substance SP, such as phosphate.

Preferably, the first or electrochemically active substance SA is detected in the sensor apparatus 113 or in the individual sensor fields 113B by electrochemical measurement and/or redox cycling.

Particularly preferably, by means of the first substance SA, a redox reaction takes place at the electrodes 113C, the first substance SA preferably discharging electrons to or receiving electrons from the electrodes 113C.

In particular, the presence of the first substance SA and/or the respective amounts in the respective sensor fields 113B is detected by the associated redox reactions. In this way, it can be determined qualitatively and in particular also quantitatively whether and how many analytes or amplification products are bonded to the capture molecules in the respective sensor fields 113B. This accordingly gives information on which analytes are or were present in the sample P, and in particular also gives information on the quantity of said analytes, particularly the target proteins ZP.

In particular, by means of the redox reaction with the first substance SA, an electrical signal is generated at the assigned electrodes 113C, the signal preferably being detected by means of an assigned electronic circuit.

Depending on the signal from the electrodes 113C that is generated in this way, it is determined whether and/or where hybridisation to the capture molecules has occurred.

According to a particularly preferred embodiment, simultaneously to electrochemical measurement and/or detection of target analytes, particularly target proteins ZP, a fluorescence measurement and/or fluorescence detection of target analytes, particularly target nucleic acid sequences ZN, is carried out.

Depending on the presence of a fluorescence signal FS, it is determined whether and/or where hybridisation to capture molecules has been occurred.

Furthermore, it is possible that electrochemical measurement and/or detection of target analytes and fluorescence measurement are carried out sequentially or with an overlap in time.

In the embodiment as shown in Fig. 11, target nucleic acid sequences ZN3, ZN4 and ZN5 are measured and/or detected by fluorescence measurement. Thereby, the fluorescence signal FS emitted from the fluorescence markers and/or the labels L1 are measured and/or recorded.

The above explanations in connection with Fig. 9 to 11 also apply for embodiments where the sensor arrangement, particularly the sensor apparatus 113 and/or the sensor compartment 118, comprises capture nucleic acid sequences FN and capture proteins FP in different or separated sensor fields of a common sensor apparatus 113 and/or a common sensor array 113A and/or a common sensor compartment 118 (cf. Fig. 6).

Nevertheless, in this context it is preferred to use the same type of detection labels L for the detection and/or measurement of all target analytes, particularly target nucleic acid sequences ZN and target proteins ZP. According to a particularly preferred embodiment, electrochemically detectable labels L are used for detection and/or measurement of target nucleic acid sequences ZN and target proteins ZP. In other words, target nucleic acid sequences ZN and target proteins ZP are preferably detected electrochemically and/or by redox cycling, in particularly simultaneously.

Overall, by means of the proposed method it is possible to bond and detect a plurality of, in particular also different, target proteins ZP, and a plurality of, in particular also different, target nucleic-acid sequences ZN, preferably simultaneously, in a common sensor array 113A and/or in common sensor fields 113B of the sensor apparatus 113 and/or of the sensor array 113A.

On account of the possible multiple occupancy of individual sensor fields 113B with capture molecules of different substance classes, a significantly larger number of samples P and/or analytes can thus be reliably detected using just one sensor apparatus 113, which is in turn associated with improved method efficiency and a reduction in costs.

As already mentioned, different groups of capture molecules are preferably used for bonding and/or detecting in particular different kinds and/or types of target molecules and/or target analytes.

Particularly, by means of the proposed method a nucleic acid assay and/or a protein assay and/or an aptamer assay can be carried out in a common sensor array 113A and/or in common sensor fields 113B of the sensor apparatus 113 and/or of the sensor array 113A and/or in a common sensor compartment 118, preferably simultaneously.

The test results or measurement results, in particular of both the protein assay and the nucleic-acid assay, are in particular electrically transmitted to the analysis device 200 or the control apparatus 207 thereof, preferably by means of the electrical connection apparatus 203 and/or sequentially or simultaneously, and are accordingly prepared, analysed, stored, displayed and/or output, in particular by the display apparatus 209 and/or interface 210.

After the test has been carried out, the cartridge 100 is disconnected from the analysis device 200 and/or is released or ejected therefrom, and is in particular disposed of.

Fig. 12 shows – as a non-limiting example – the results of electrochemical measurements of bonded target nucleic acid sequences ZN after isothermal amplification and bonding to capture nucleic acid sequences FN. Thereby, the effect of thymine-based spacer molecules of different length has been further analysed.

The biological sample P contained DNA of *Brachyspira hyodysenteriae* with 1,000 genome equivalents per µl. The bacterium causes dysentery in pigs.

The sensor array 113A contained 128 sensor fields 113B with the sensor fields 113B being arranged in eight rows and sixteen columns. 10 sensor fields 113B were used as negative control. 10 sensor fields 113B were used as positive controls. 108 sensor fields 113B were functionalized with capture nucleic acid sequences FN on the basis of *Brachyspira hyodysenteriae*-specific oligonucleotides. The capture nucleic acid sequences FN were fixed to the sensor fields 113B and/or the electrodes 113C of the sensor array 113A with a 15 thymine bases elongated 5' thiol-C6 linker. The sensor fields 113B additionally comprised spacer molecules on the basis of thymine bases, wherein 36 sensor fields 113B, respectively, comprised spacer molecules with a length of 15 thymine bases (T15 spacer), 30 thymine bases (T30 spacer) and 45 thymine bases (T45 spacer). The layout of the sensor array 113A is depicted in Fig. 12A.

Amplification of target nucleic acid sequences ZN and the nucleic acid assay, respectively, have been performed as delineated above.

Isothermal amplification has been performed on the basis of a recombinase polymerase amplification as delineated above. The amplicons and/or the target nucleic acid sequences ZN have been amplified and/or produced with a detectable label on the basis of biotin.

The electrochemical measurements were carried out in the manner already explained above.

The results of the electrochemical measurements are depicted in Figs. 12B and 12C.

As can be seen from Fig. 12B, the diagrams each show the sensor fields 113B arranged in eight rows (right-hand axis 1 to 8) and sixteen columns (top axis V1 to V16), and the current or power measurement curves resulting in each case (the bottom axis shows the time in sec, and the left-hand column shows the measured current or power in values proportional thereto).

An increase in the current or power and/or the signal intensity indicates splitting of the substrate p-aminophenyl phosphate to p-aminophenol, which is redox-active and thus leads to the increase in the measurement signal.

The highest substrate conversion could be measured in the sensor fields 113B with T15 spacer molecules. Nevertheless, also in sensor fields 113B with T30 spacer molecules T45 spacer molecules significant substrate conversion was measured. No relevant measurement signals could be detected in the sensor fields 113B that were used as a negative control.

In this context, reference is also made to Fig. 12C. Fig. 12C shows the results of electrochemical measurement on the basis of a boxplot. It can be seen that, on average, the highest substrate conversion was recorded in sensor fields 113B with T15 spacer molecules. In sensor fields 113B with T45 spacer molecules and T30 spacer molecules, substrate conversion was lower when compared with sensor fields 113B with T15 spacer molecules, but still higher than in sensor fields 113B used as positive controls.

Overall, the results show that target nucleic acid sequences ZN which have been amplified with isothermal amplification by means of the sensor apparatus 113, particularly in the sensor fields 113B of a sensor array 113A of the sensor apparatus 113, are capable of being detected in a nucleic acid assay.

Furthermore, the nucleic acid assay can be further supported by use of spacer molecules SP, particularly thymine spacers with a length of 10 to 50 bases.

Additionally, another aspect of the present invention is – as initially delineated – the use of one reagent R or a reaction mix for isothermal DNA amplification for testing an in particular biological sample P, wherein the DNA amplification of one or more analytes of the sample P is performed in a sensor compartment 118 with a sensor apparatus 113, wherein the sensor apparatus 113 comprises immobilized capture molecules for bonding the analyte(s).

In this context, it is further preferred when the DNA amplification is performed on and/or in a sensor array 113A of the sensor apparatus 113 or the sensor arrangement.

According to a particularly preferred embodiment, the reagent and/or reaction mix is used in an analysis system according to the present invention.

The use of the at least one reagent R or a reaction mix for isothermal DNA amplification for testing an in particular biological sample P with the DNA amplification being performed in a sensor compartment 118 of a sensor apparatus 113 and/or on and/or in a sensor array 113A of the sensor apparatus 113 allows relatively low amplification temperatures below the denaturing temperature of proteins, in particular capture proteins FP or protein-based analytes. With respect to the advantages of an amplification of target analytes in the sensor compartment 118 and/or in and/or on the sensor array 113A, reference is made to the respective explanations above. With respect to the use of at least one reagent and/or a reaction mix according to the present invention, reference is particularly made to the working examples described according to Figs. 12A to 12C.

For further details with respect to an isothermal DNA amplification in the sensor arrangement and/or the sensor apparatus 113, particularly in the sensor compartment 118 and/or in and/or on the sensor array 113A, and the use of the at least one reagent R and/or the reaction mix for the isothermal DNA amplification reference is made to the above and furthermore to the following explanations.

Individual aspects and features of the present invention and individual method steps and/or variants of the method and/or the use according to the present invention may be implemented independently from one another, but also in any desired combination and/or order.

List of reference signs:

1	analysis system
100	cartridge
101	main body
102	cover
103	fluid system
104	receiving cavity
104A	connection
104B	inlet
104C	outlet
104D	intermediate connection
105	metering cavity
105A	first metering cavity
105B	second metering cavity
106(A-G)	intermediate cavity
107	mixing cavity
108(A-E)	storage cavity
109	reaction cavity
109A	first reaction cavity
109B	second reaction cavity
109C	third reaction cavity
110	intermediate temperature-control cavity
110A	inlet
110B	outlet
111	collection cavity
112	pump apparatus
113	sensor apparatus
113A	sensor array
113B	sensor field
113C	electrode
113D	support
113E	contact
113F	layer
114	channel
114A	bypass
115	valve
115A	initially closed valve
115B	initially open valve
116	sensor portion
117	sensor cover
118	sensor compartment
119	inlet
120	outlet

200	analysis device
201	receptacle
202	pump drive
203	connection apparatus
203A	contact element
204	temperature-control apparatus
204A	reaction temperature-control apparatus
204B	intermediate tempera-ture-control apparatus
204C	sensor temperature-control apparatus
205	(valve) actuator
205A	(valve) actuator for 115A
205B	(valve) actuator for 115B
206	sensor
206A	fluid sensor
206B	other sensor
207	control apparatus
208	input apparatus
209	display apparatus
210	interface
211	power supply
211A	connection
212	housing
213	opening
214	pressurised gas supply
214A	connection element

B	bond
D	detector molecule
R	reagent / reagent mix
F(1-5)	liquid reagent
FA	capture aptamer
FP(1-5)	capture protein
FN(1-5)	capture nucleic-acid sequence
FS	fluorescence signal
L (1-2)	label
P	sample
S(1-10)	dry reagent
SA	first substance
SP	second substance
SC	spacer molecule
SU	substrate
ZP(1-5)	target protein
ZN(1-5)	target nucleic-acid sequence

Claims:

1. Analysis system (1) for testing an in particular biological sample (P),

the analysis system (1) comprising a fluid system (103) having a plurality of channels (114) and a sensor apparatus (113) comprising capture molecules for bonding analytes of the sample (P),

preferably wherein the analysis system (1) comprises a cartridge (100) with the fluid system (103) and with the sensor apparatus (113),

preferably wherein the analysis system (1), its cartridge (100) or fluid system (103) comprises a sensor compartment (118), with the sensor apparatus (113) or a sensor array (113A) thereof being arranged in the sensor compartment (118),

characterised

in that the analysis system (1) or sensor apparatus (113) comprises at least one reagent (R) and/or reaction mix for isothermal DNA amplification of at least one analyte or multiple/different analytes in the sensor compartment (118), and/or

in that the sensor apparatus (113) comprises capture nucleic acid sequences (FN) and at least one more type of capture molecules selected from capture proteins (FP) and/or capture aptamers (FA), and in that the sensor apparatus (113) comprises at least one reagent (R) and/or reaction mix for carrying out a reaction for amplifying target nucleic acid sequences (ZN) from the sample (P), preferably on a sensor compartment (118) thereof.

2. Analysis system according to claim 1, characterised in that the analysis system (1) comprises a sensor arrangement, wherein the sensor apparatus (113) forms part of the sensor arrangement.

3. Analysis system according to claim 2, characterised in that the sensor arrangement comprises a sensor cover (117), the sensor compartment (118), an inlet (119) into the sensor compartment (118) and/or an outlet (120) out of the sensor compartment (118).

4. Analysis system according to claim 2 or 3, characterised in that the sensor apparatus (113) and the sensor cover (117) define or delimit the sensor compartment (118).

5. Analysis system according to any of claims 2 to 4, characterised in that the sensor compartment (118) is arranged between the sensor apparatus (113) and the sensor cover (117).

6. Analysis system according to any of claims 2 to 5, characterised in that the sensor arrangement comprises exactly one sensor compartment (118), exactly one inlet (119) into the sensor compartment (118) and exactly one outlet (120) out of the sensor compartment (118).

7. Analysis system according to any of the preceding claims, characterised in that the sensor arrangement and/or the sensor apparatus (113) comprise one sensor array (113A) having a plurality of sensor fields (113B) and/or electrodes (113C), which permit independent measurement and/or detection of multiple analytes.

8. Analysis system according to claim 7, characterised in that some or all sensor fields (113B) and/or electrodes (113C) are provided with capture molecules.

9. Analysis system according to any of the preceding claims, characterised in that the analysis system (1) and/or the sensor apparatus (113) are designed for carrying out a protein assay, a nucleic-acid assay or an aptamer assay.

10. Analysis system according to any of the preceding claims, characterised in that the analysis system (1) and/or the sensor apparatus (113) are designed for carrying out a nucleic acid amplification reaction, in particular a nucleic acid amplification reaction under constant temperatures, preferably an isothermal DNA amplification.

11. Analysis system according to any of the preceding claims, characterised in that the reaction mix comprises reagents for a preferably isothermal DNA amplification and/or a stabilization of the capture molecules, in particular the capture proteins (FP).

12. Analysis system according to any of the preceding claims, characterised in that the at least one reagent (R) and/or the reaction mix comprise enzymes for a recombinase polymerase amplification, particularly a DNA polymerase with strand displacement activity, recombinases and/or single strand binding proteins.

13. Analysis system according to any of the preceding claims, characterised in that the at least one reagent (R) and/or the reaction mix comprise enzymes, particularly

enzymes for a preferably isothermal DNA amplification, NTPs, dNTPs, preferably pathogen-specific amplification primers, sugar molecules and/or salts.

14. Analysis system according to any of the preceding claims, characterised in that the at least one reagent (R) and/or the reaction mix are immobilized and/or fixed onto or into the sensor compartment (118), the sensor apparatus (113) and/or the sensor array (113A), particularly onto the surface of sensor fields (113B) and/or electrodes (113C) of a senor array (113A) and/or the sensor apparatus (113).

15. Analysis system according to any of the preceding claims, characterised in that the at least one reagent (R) and/or the reaction mix comprise reagents for an isothermal DNA amplification and a stabilization of the capture molecules and in that the at least one reagent (R) and/or the reaction mix is immobilized and/or fixed onto or into the sensor compartment (118) or the sensor array (113A), particularly onto the surface of sensor fields (113B) and/or electrodes (113C) of the senor array (113A).

16. Analysis system according to any of the preceding claims, characterised in that a senor array (113A) of the sensor apparatus (113) comprises capture nucleic acid sequences (FN) and at least one more type of capture molecules selected from capture proteins (FP) and/or capture aptamers (FA) and in that the at least one reagent (R) and/or the reaction mix is immobilized and/or fixed onto or into the sensor compartment (118) or sensor array (113A), particularly onto the surface of sensor fields (113B) and/or electrodes (113C) of the senor array (113A).

17. Analysis system according to any of the preceding claims, characterised in that the analysis system (1) comprises a temperature-control apparatus (204) for temperature-controlling the sensor apparatus (113), in particular wherein the analysis system (1) and/or the temperature-control apparatus are designed to activate and/or support the amplification of the target nucleic acid sequences (ZN) and/or the nucleic acid assay, preferably at a temperature less than 45 °C, even more preferred less than 43 °C, and/or at a temperature less than the denaturing temperature of proteins.

18. Method for testing an in particular biological sample (P),

analytes of the sample (P) being bonded to capture molecules of a sensor apparatus (113) and the bonded analytes being detected or identified by means of the sensor apparatus (113),

characterised

in that target nucleic acid sequences (ZN) are amplified as analytes from the sample (P) by means of and/or in the sensor apparatus (113), and

in that the target nucleic acid sequences (ZN) and at least one more type of analytes selected from analytes that correspond to capture proteins (FP) or capture aptamers (FA) are bonded to capture nucleic acid sequences (FN), capture proteins (FP) and/or capture aptamers (FA) in the sensor apparatus (113).

19. Method according to claim 18, characterised in that amplification of target nucleic acid sequences (ZN) and bonding of target analytes, in particular target nucleic acid sequences (ZN) and target analytes that correspond to capture proteins (FP) and/or capture aptamers (FA), to the capture molecules, in particular to capture nucleic acid sequences (FN), capture proteins (FP) and/or capture aptamers (FA), are carried out without spacial separation.

20. Method according to claim 18 or 19, characterised in that amplification of target nucleic acid sequences (ZN) and detection of target analytes, in particular target nucleic acid sequences (ZN) and target analytes that correspond to capture proteins (FP) and/or capture aptamers (FA), are carried out without spacial separation.

21. Method according to any of claims 18 to 20, characterised in that amplification of target nucleic acid sequences (ZN), bonding and detection of target analytes are carried out in a common sensor array (113A) and/or in same sensor fields (113B) of the sensor apparatus (113) and/or in a common sensor compartment (118).

22. Method according to claim 18 or 21, characterised in that target nucleic acid sequences (ZN) are amplified at constant temperatures, particularly temperatures of less than 45 °C, even more preferred less than 43 °C, and/or temperatures of less than the denaturing temperature of proteins.

23. Method according to any of claims 18 to 22, characterised in that target nucleic acid sequences (ZN) are amplified by means of isothermal DNA amplification

and/or in that target nucleic acid sequences (ZN) are amplified by using at least one enzyme, particularly a DNA polymerase, with strand displacement activity.

24. Method according to any of claims 18 to 23, characterised in that target nucleic acid sequences (ZN) are amplified from the sample (P) by using preferably pathogen-specific primers and/or characterised in that target nucleic acid sequences (ZN) are amplified and/or produced with a detectable label L.

25. Method according to any of claims 18 to 24, characterised in that amplification and bonding of target nucleic acid sequences (ZN) to capture nucleic acid sequences (FN) are carried out simultaneously or sequentially, preferably simultaneously.

26. Method according to any of claims 18 to 25, characterised in that amplification and bonding of target nucleic acid sequences (ZN) to capture nucleic acid sequences (FN) and bonding of the at least one more type of analytes to capture proteins (FP) and/or capture aptamers (FA) are carried out simultaneously or sequentially, preferably simultaneously.

27. Method according to any of claims 18 to 26, characterised in that the capture molecules, particularly the capture proteins (FP), and/or the target analytes, particularly the target proteins (ZP) are stabilized by sugar molecules.

28. Method according to any of claims 18 to 27, characterised in that amplification of target nucleic acid sequences (ZN), bonding and detection of target analytes are carried out simultaneously or sequentially, preferably simultaneously.

29. Method according to any of claims 18 to 28, characterised in that the bonded analytes, particularly bonded target nucleic acid sequences (ZN), target proteins (ZP) and/or the target aptamers (ZA), are identified or detected electrochemically and/or by redox cycling and/or by fluorescence measurement.

30. Use of one reagent (R) or a reaction mix for isothermal DNA amplification for testing an in particular biological sample (P), wherein the DNA amplification of one or more analytes of the sample (P) is performed in a sensor compartment (118) with a sensor apparatus (113), wherein the sensor apparatus (113) comprises immobilized capture molecules for bonding the analyte(s).

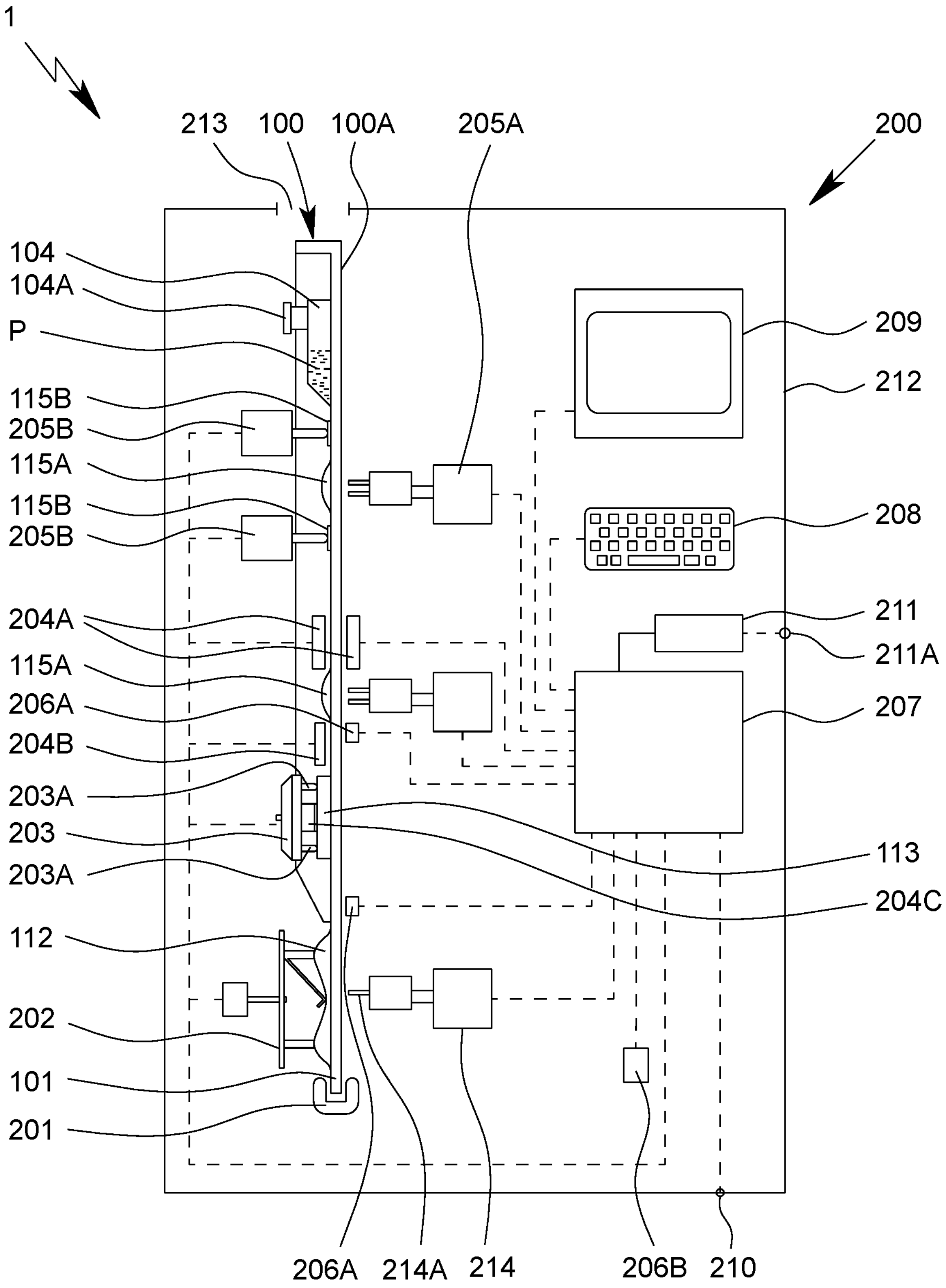
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Fig. 1

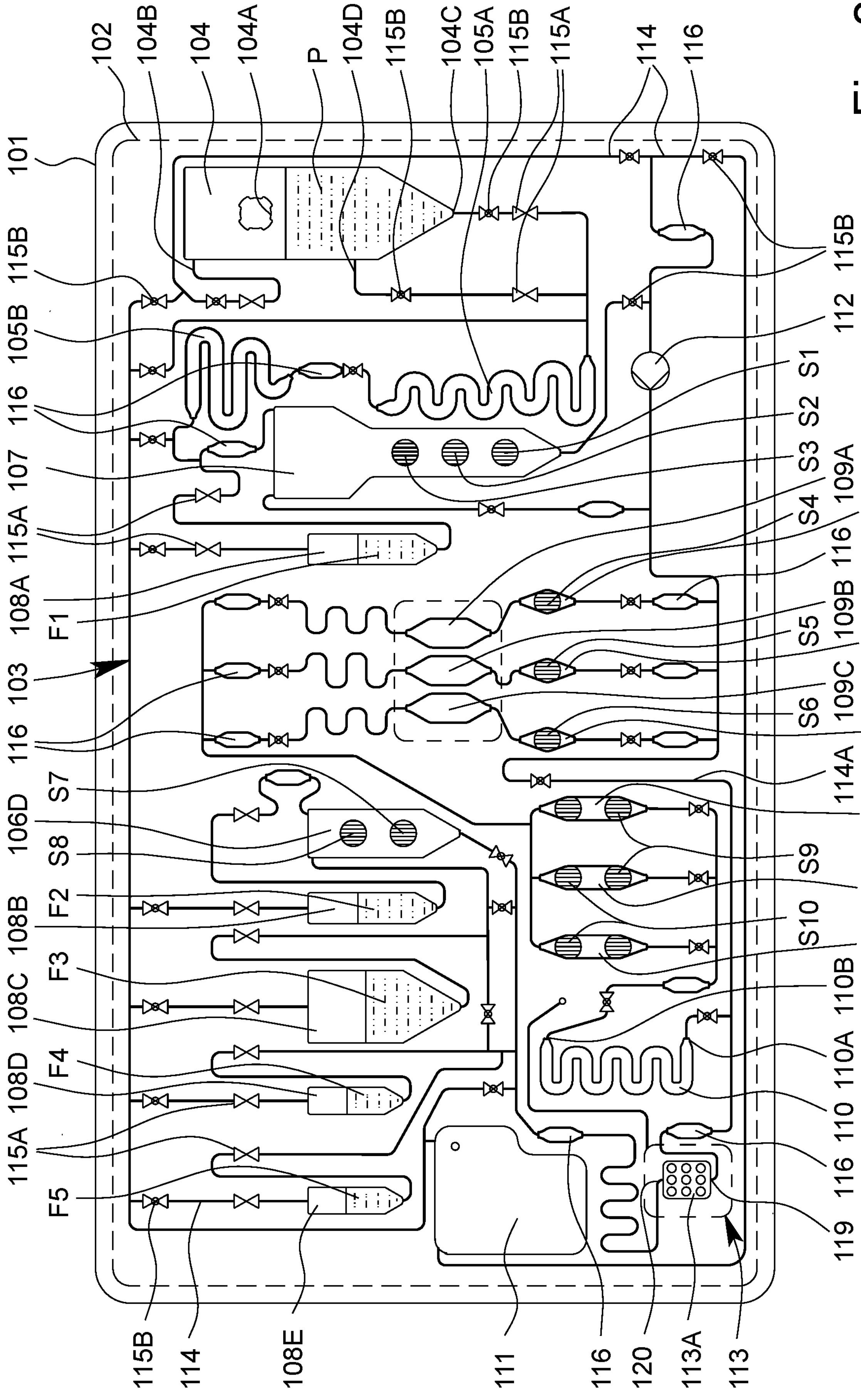
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Fig. 2

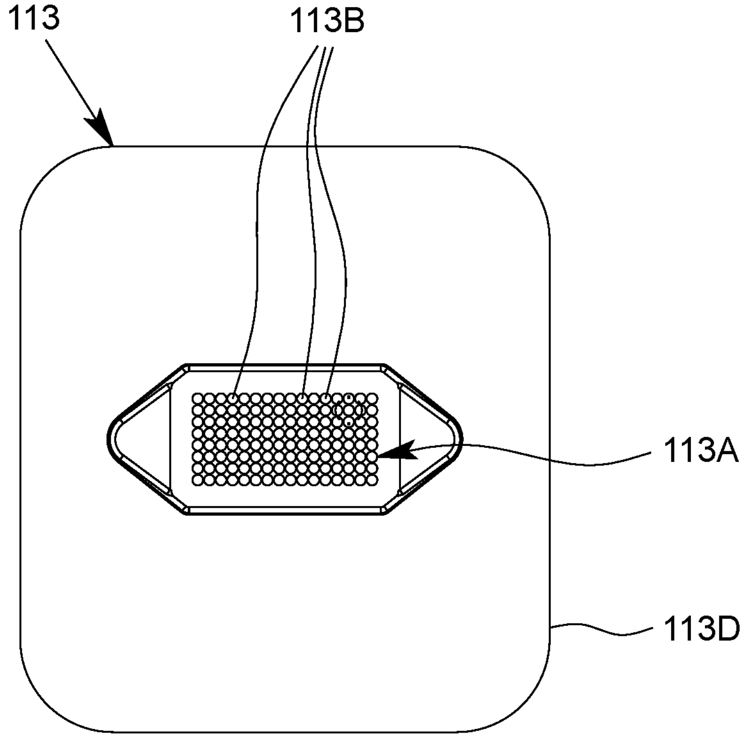


Fig. 3

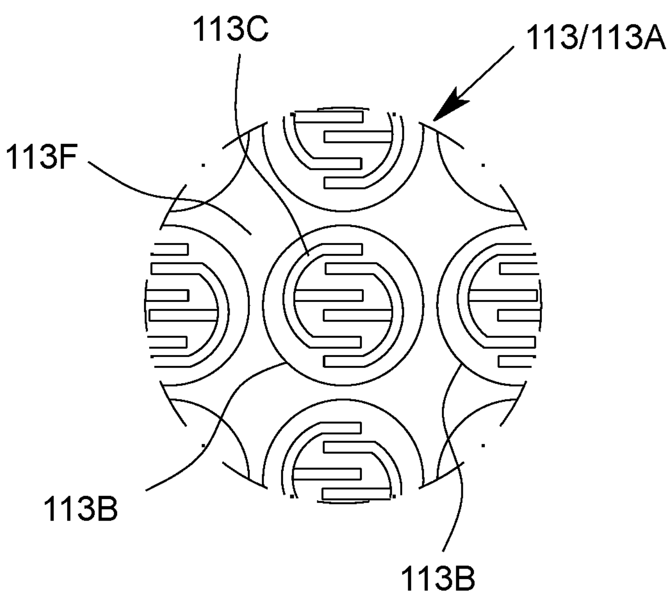


Fig. 4

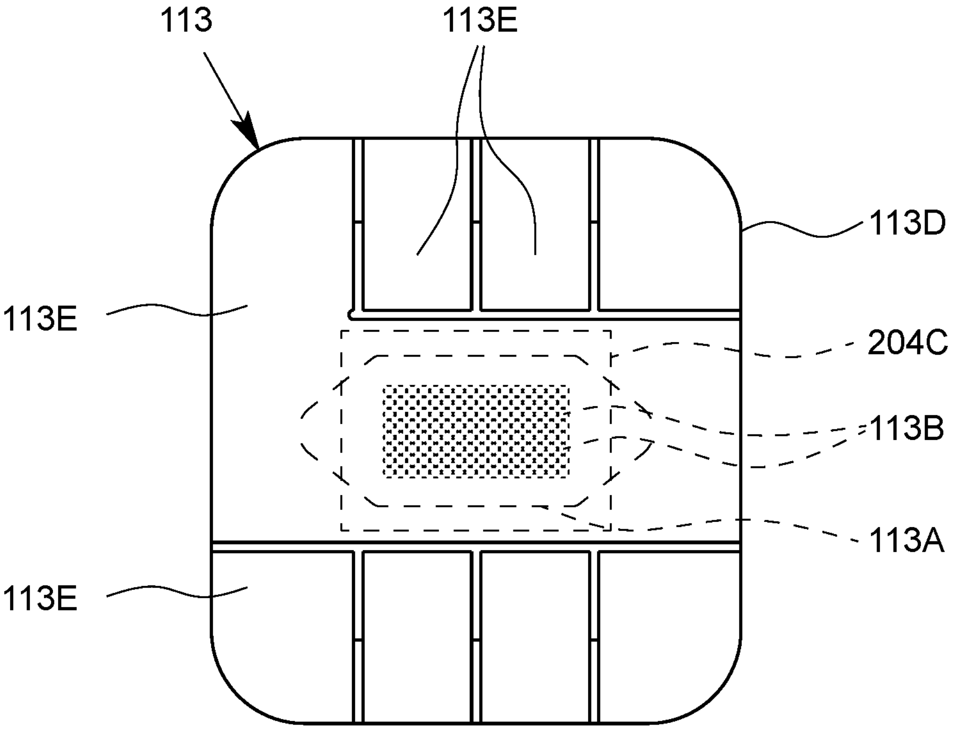
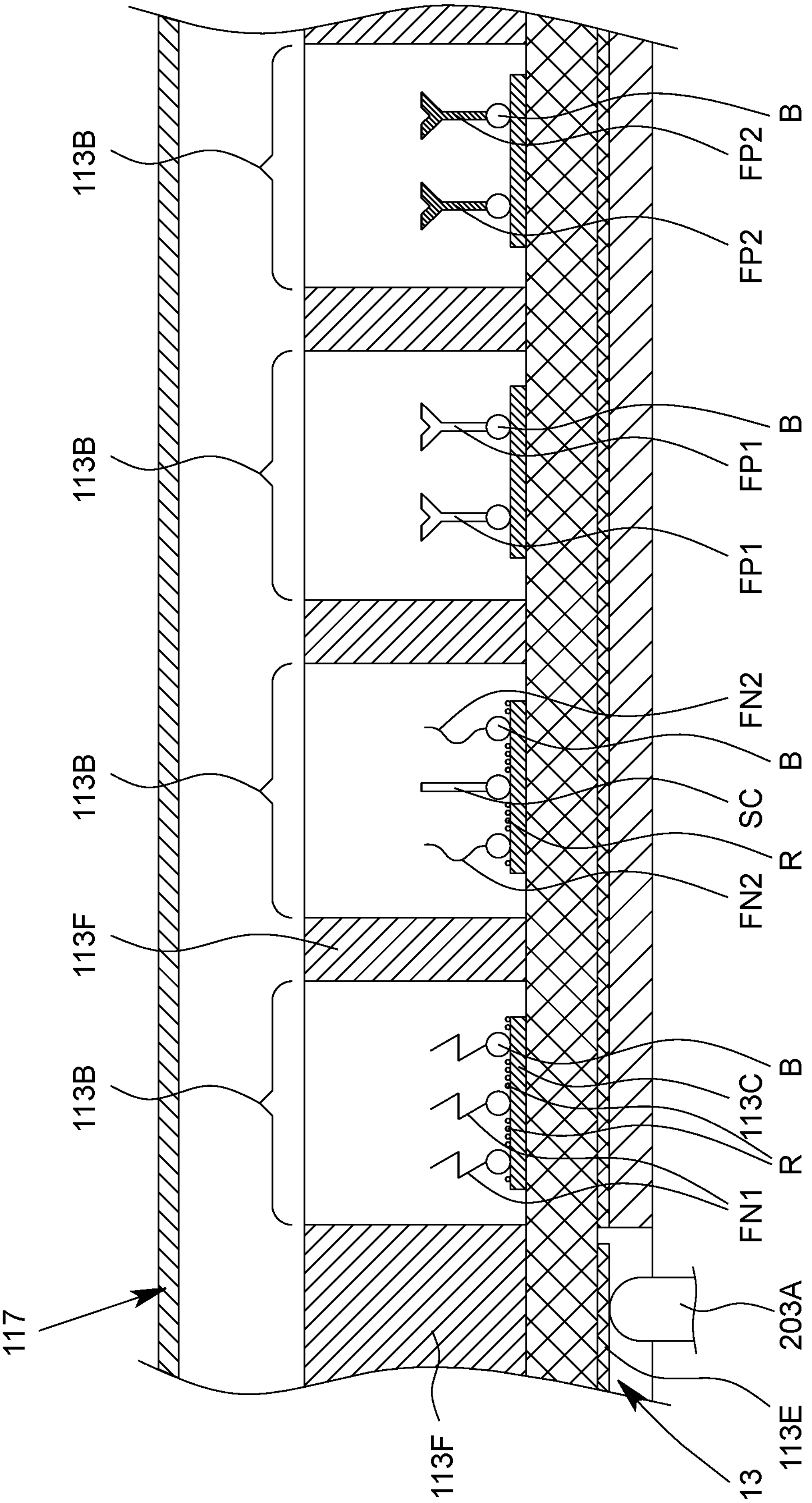


Fig. 5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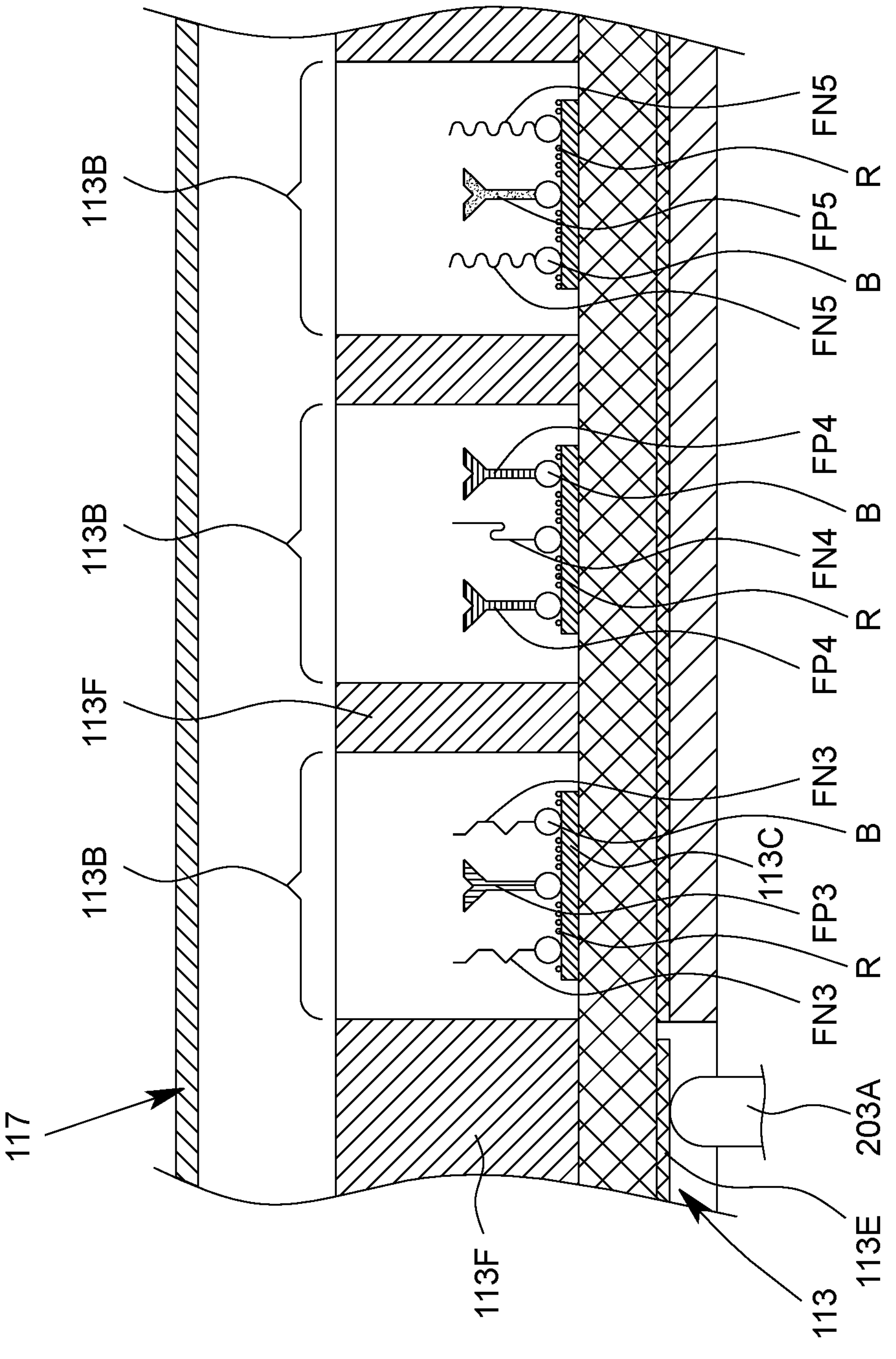
SC
R
FN2
B
113C
R
FN1

Fig. 6

Fig. 7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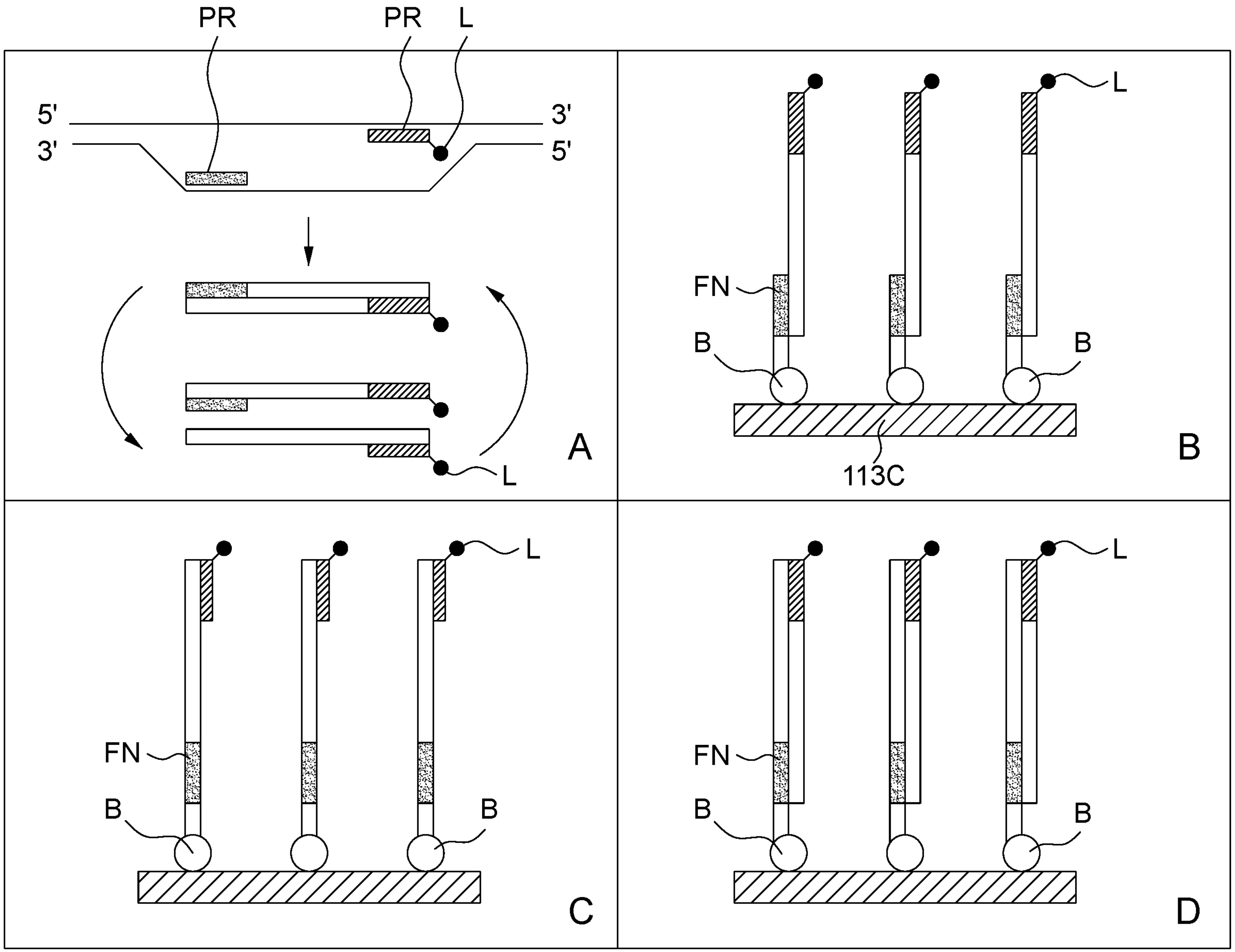
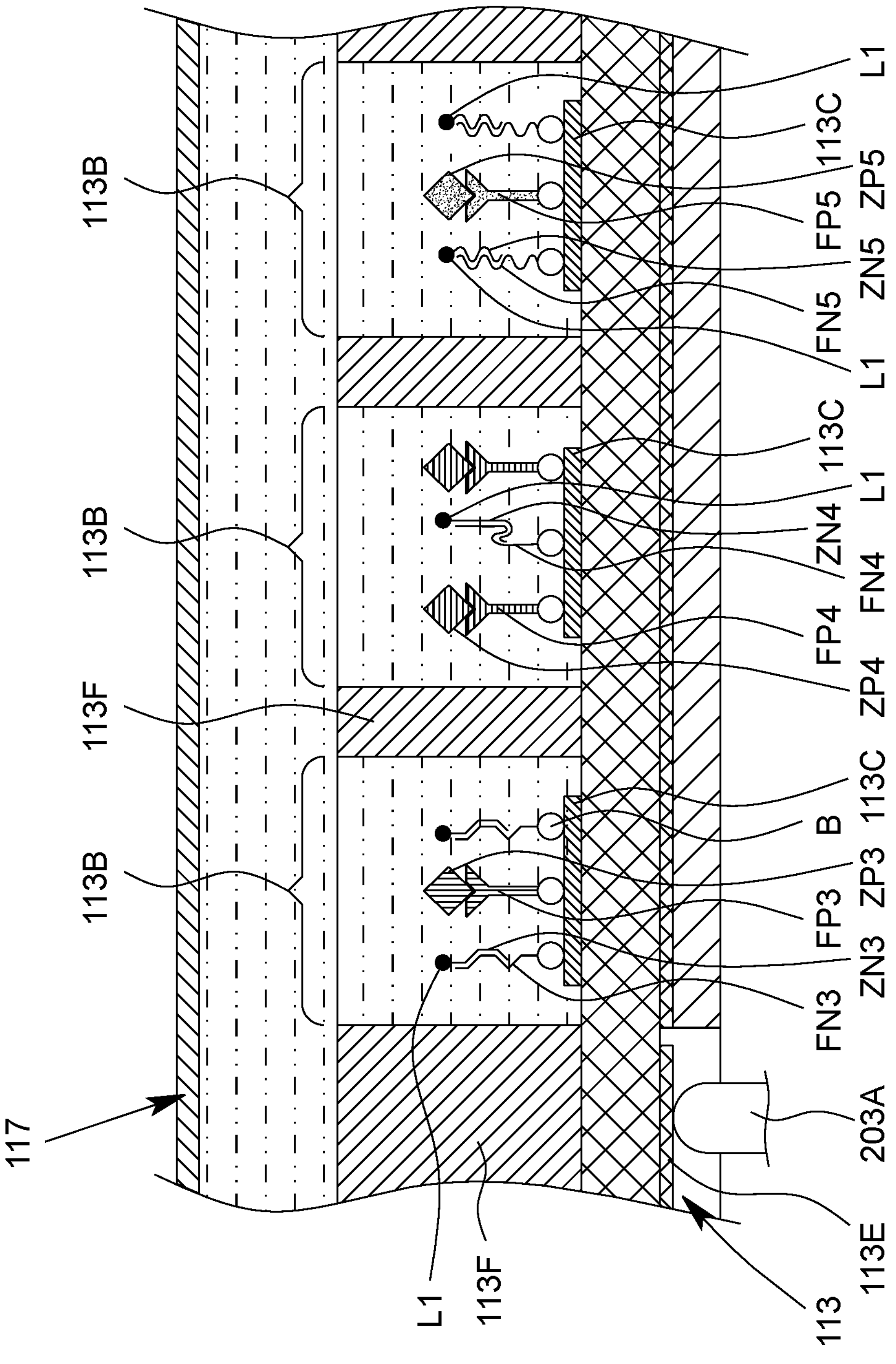


Fig. 8

Fig. 9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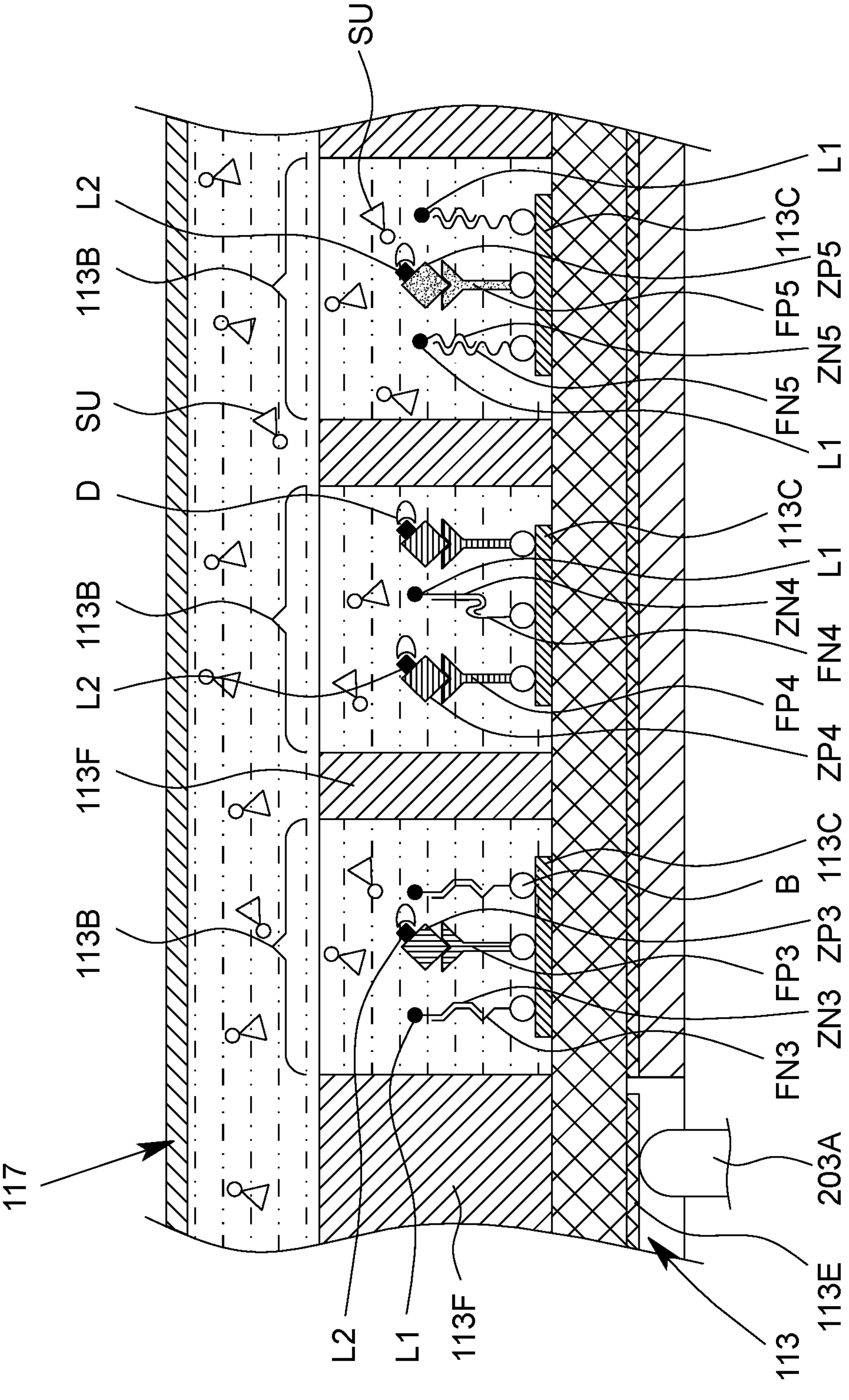
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FP3
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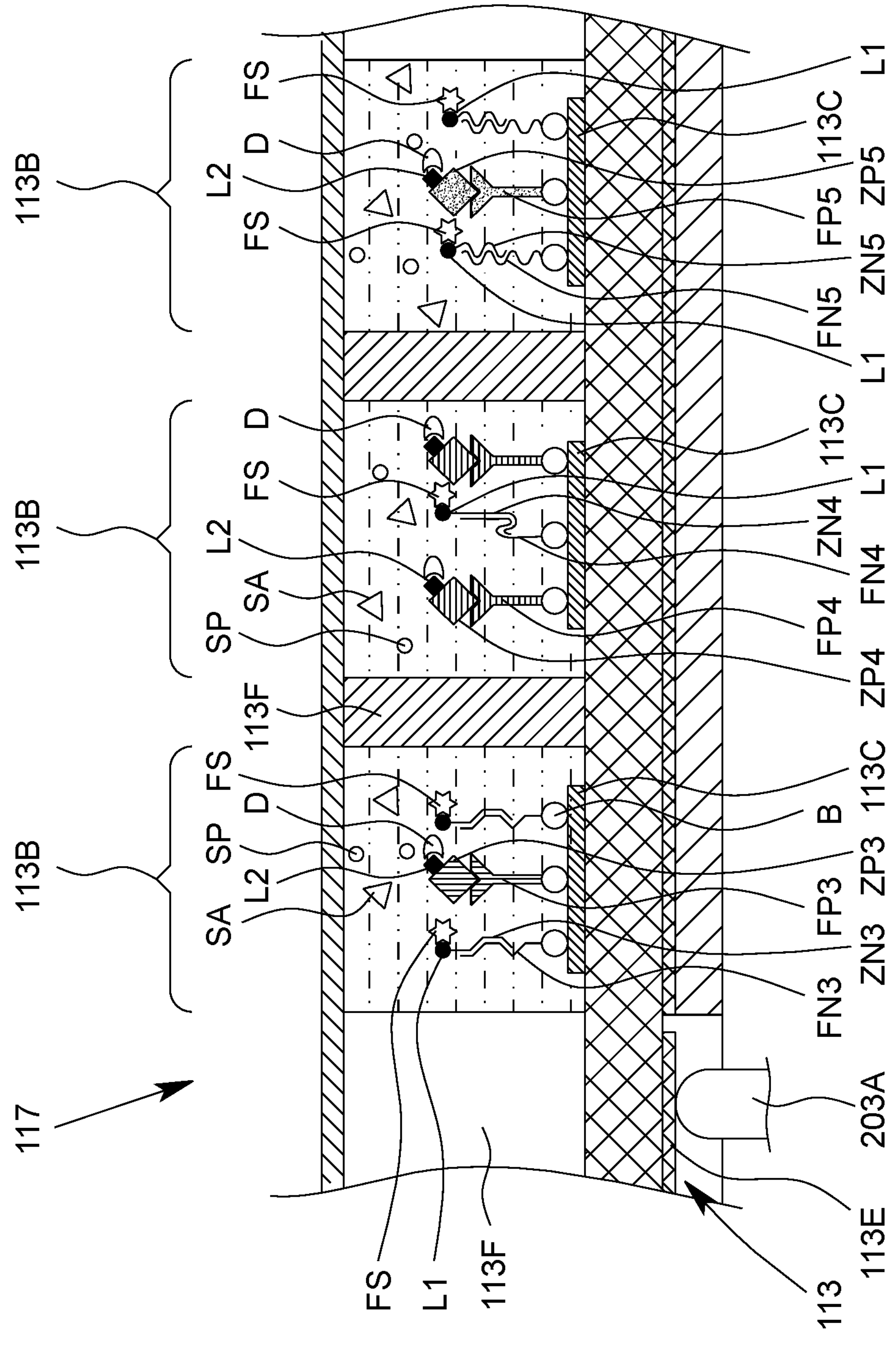
FN3

Fig. 10

Fig. 11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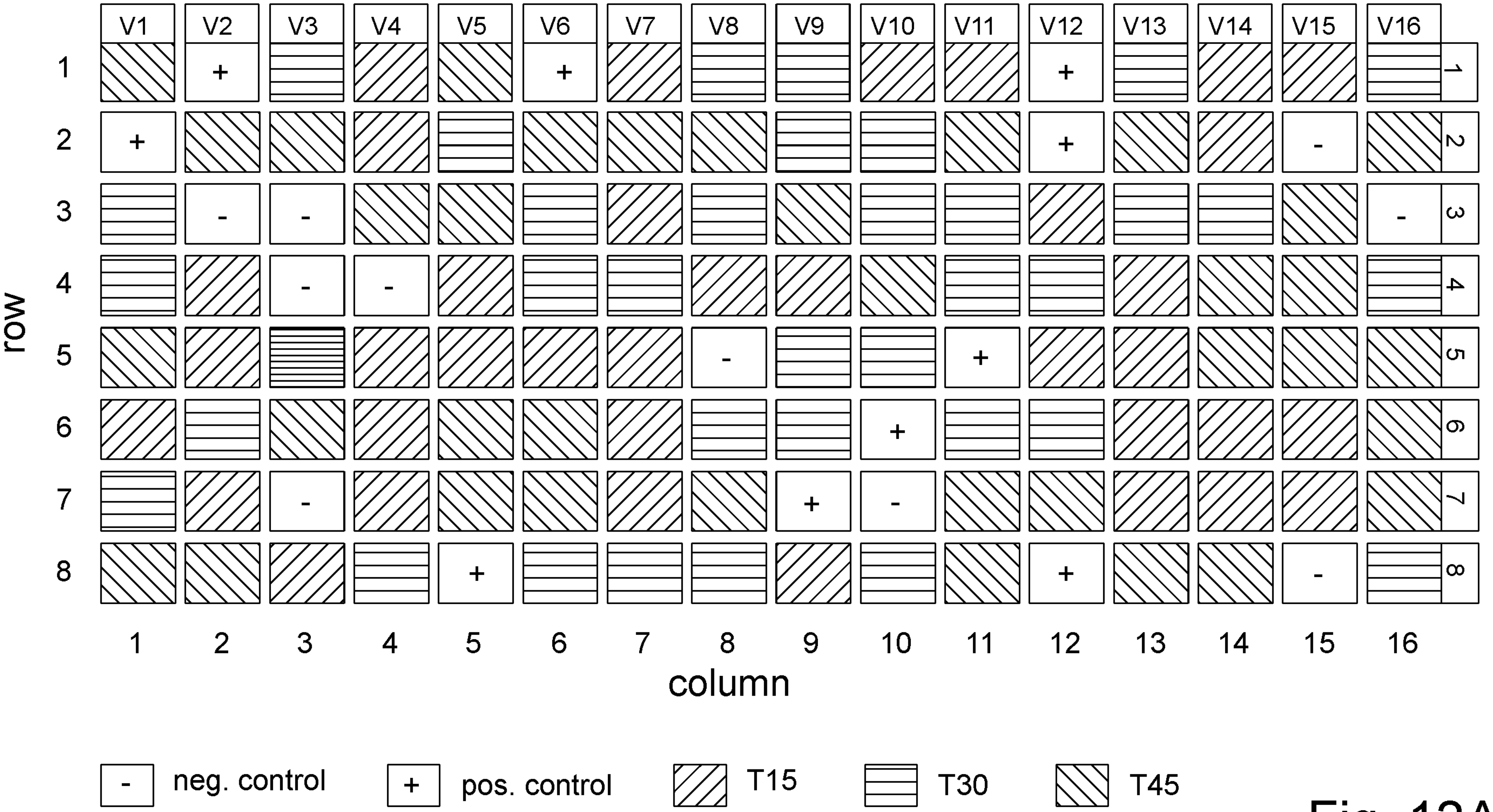
FN3
203A
113E
113



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3	▤	-	-	▧	▧	▤	▨	▤	▧	▤	▤	▨	▤	▤	▧	-	3
4	▤	▨	-	-	▨	▤	▤	▨	▨	▧	▤	▤	▨	▧	▧	▤	4
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+ pos. control
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▤ T30
▧ T45

Fig. 12A

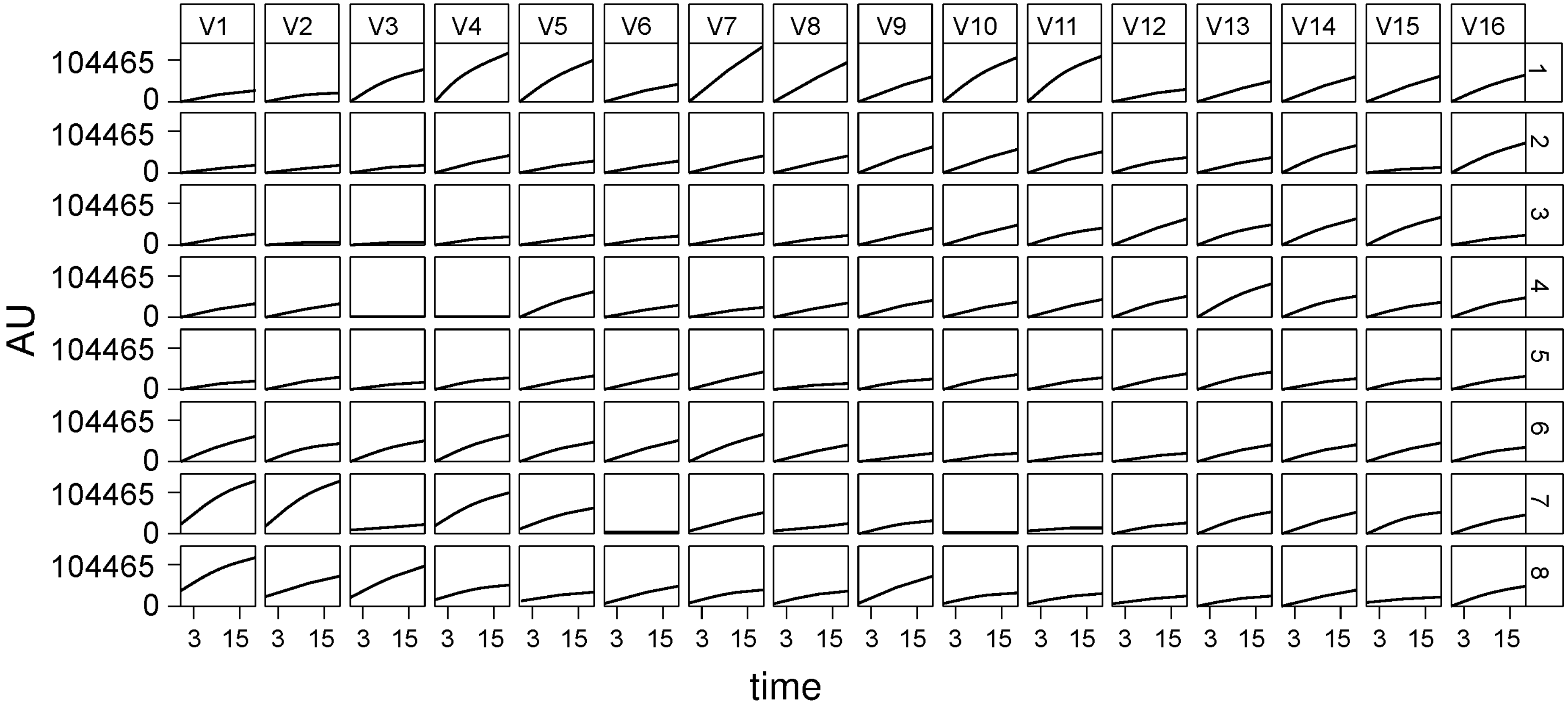
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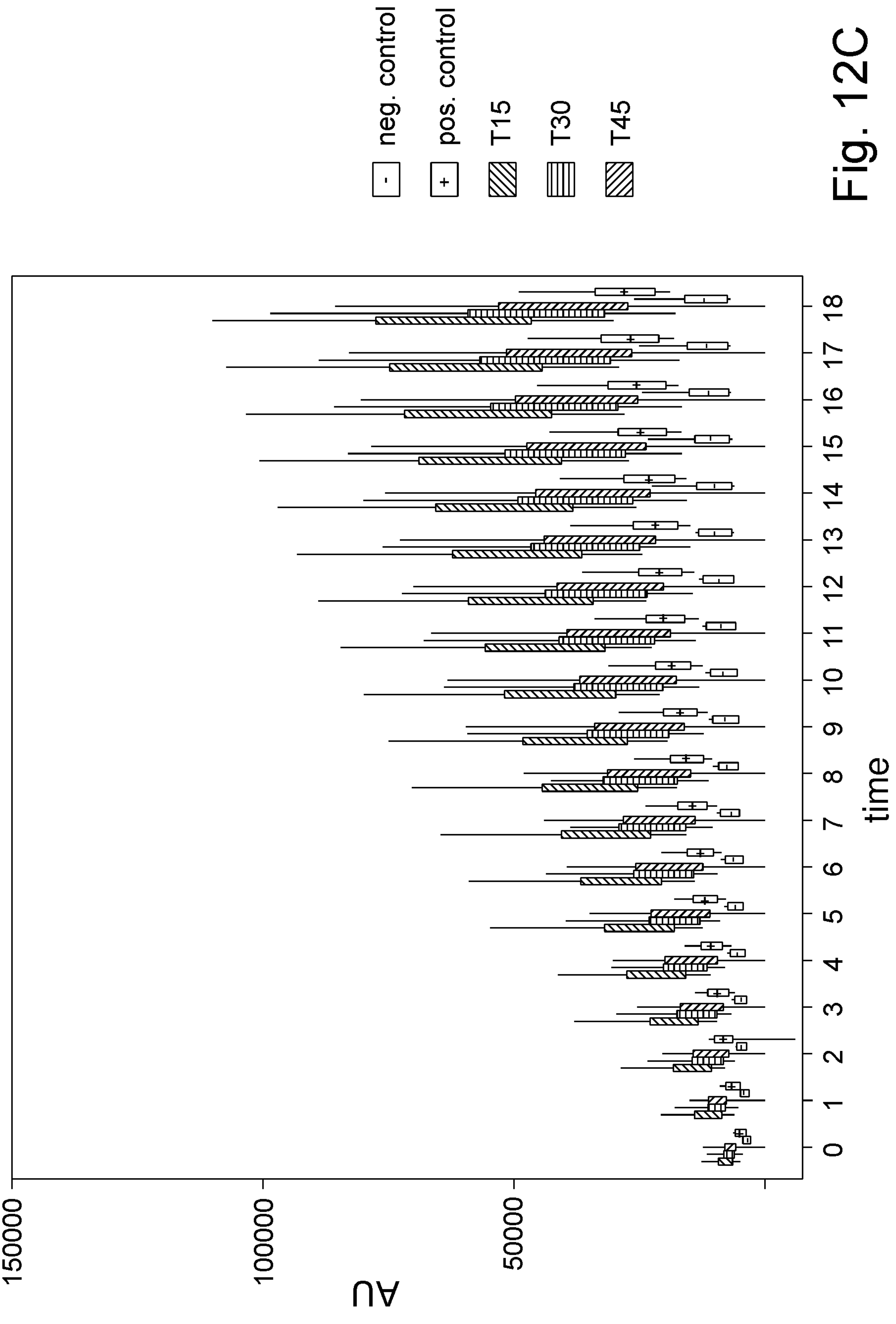
Fig. 12B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- neg. control
+ pos. control
T15
T30
T45

Fig. 12C

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/085490

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/6825 C12Q1/6837 C12Q1/689 B01L3/00 G01N33/53
G01N33/543
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 B01L C12Q

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, BIOSIS, Sequence Search, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2018/065104 A1 (BOEHRINGER INGELHEIM VETMEDICA GMBH [DE]) 12 April 2018 (2018-04-12) pages 1-6,10, pages 18,34,39; figures page 13 -----	1-30
X	KANT KRISHNA ET AL: "Microfluidic devices for sample preparation and rapid detection of foodborne pathogens", BIOTECHNOLOGY ADVANCES, ELSEVIER PUBLISHING, BARKING, GB, vol. 36, no. 4, 10 March 2018 (2018-03-10), pages 1003-1024, XP085400111, ISSN: 0734-9750, DOI: 10.1016/J.BIOTECHADV.2018.03.002 abstract; figure 1D page 1019 -----	30

-/--

☒ 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 18 March 2022	Date of mailing of the international search report 28/03/2022
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Reuter, Uwe

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ZHANG LU ET AL: "Point-of-care-testing of nucleic acids by microfluidics", TRAC TRENDS IN ANALYTICAL CHEMISTRY, vol. 94, 1 September 2017 (2017-09-01), pages 106-116, XP085166157, ISSN: 0165-9936, DOI: 10.1016/J.TRAC.2017.07.013 abstract; figure 1 pages 109,111 -----	1-30
A	VICKY TROGER KATJA NIEMANN: "Isothermal Amplification and Quantification of Nucleic Acids and its Use in Microsystems", JOURNAL OF NANOMEDICINE & NANOTECHNOLOGY, vol. 06, no. 03, 1 January 2015 (2015-01-01), XP055382264, DOI: 10.4172/2157-7439.1000282 abstract pages 2,6 -----	1-30
A	WO 2017/075649 A1 (MACDONALD JOANNE [AU]; LI JIA [AU]) 11 May 2017 (2017-05-11) claims 30-38 -----	1-30

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2021/085490

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2018065104 A1	12-04-2018	BR 112019007081 A2	09-07-2019
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		CN 110114145 A	09-08-2019
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