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(54) DEVICE FOR DETECTING A MEDICAL CONDITION OR DISEASE

VORRICHTUNG ZUR ERKENNUNG EINES MEDIZINISCHEN LEIDENS ODER EINER KRANKHEIT

DISPOSITIF POUR DÉTECTER UN ÉTAT PATHOLOGIQUE OU UNE MALADIE

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Description

Technical field

[0001] The invention relates to a device for detecting a medical condition or disease in a subject.

Background of the invention

[0002] Medical knowledge on detecting and influencing disease processes have increased significantly in the last decennia. Advancing diagnostic technologies increasingly allow for earlier diagnosis and provide options for earlier and theoretically more effective treatment. Although most of the new advanced diagnostic methods are very useful to confirm a diagnosis in high risk individuals, they are, unfortunately, often still too costly and/or invasive and/or inconvenient and/or not specific enough (leading to false positive results, medicalization and increased healthcare costs) to provide to the general average risk population for early diagnostic and screening purposes. Therefore, new methods that can simplify the diagnostic procedure while maintaining high levels of sensitivity, specificity, minimal false-positive results and not being too costly are increasingly demanded. Furthermore, too improve the feasibility of diagnostic tests in a screening setting (to select those individuals for whom further (and more invasive) testing will be useful) they need to be as client/patient friendly, cheap and easy to use as possible. Each barrier, such as visiting a laboratory or medical centre, to have the test performed will influence the participation rate and is (cost-)inefficient. Empowerment of the individual with a trustworthy device that can be easily and safely used at home and that will only signal the subject if further action is needed, would be useful and efficient.

[0003] WO-A-2007/113838 discloses a swallowable device for detecting in vivo the presence of a condition. The device comprises a nanocontainer wherein a small amount of dye is received. As a direct result of detecting the condition, the small content of nanocontainers is released and a local colouring can be observed.

[0004] EP1695662 discloses a device for detecting a medical condition or disease in a subject, wherein the device is capable of entering the subject and comprises a detector which is able to specifically react in situ in a body fluid or biomaterial of the subject and detect a marker associated with the medical condition or disease. The device comprises a chamber wherein a visualisable substance is received and further has a signalling unit arranged and constructed to emit the visualisable substance from the chamber upon detection of the marker into the bodily fluid.

Detailed description of the invention

[0005] The inventors came to the idea to combine different techniques reported over the last twenty years to detect and indicate the presence of a medical condition or disease in a subject using an automated miniature analysis system, also called a lab-on-a-chip (LOC) system or "smart pill" combined with a signalling method to notify a subject if a test result is "positive" (i.e. abnormal). The combination results in an "In Situ Lab On a Chip Signalling (ISLOCS) device". The ISLOCS device is small enough to be safely put internally into contact in a subject (gastrointestinal or vaginal contact for example), automatically analyzes samples *in situ* and notifies a subject if a "positive" result has been detected. The invention is set out in the appended claims.

General definitions

[0006] A device as described herein is small enough to be safely put into a subject. Preferred dimensions of the device depends on the type of device used. For example, for an ingested device, preferred dimensions are comparable with the dimensions of a pill. More preferably, an ingested device has dimensions which range between approximately 5 mm and approximately 20 mm as illustrated in figure 2. More preferably, an ingested device has dimensions which range between 1 and 30 mm, more specifically between 5 mm and 20 mm. Also described herein, when a device is introduced into the vagina, dimensions may comprise between approximately 20 mm and approximately 50 mm. More preferably, when a device is introduced into the vagina, dimensions may comprise between 20 mm and 50 mm. In this application the device could for example be linked to a tampon which colorizes (i.e. blue) if the test result is "positive".

[0007] As used herein, "detecting" a medical condition or disease preferably relates to diagnosing, staging, monitoring, prognosticating or determining predisposition to a medical condition or disease.

[0008] As used herein, a subject is preferably a human or an animal. More preferably, a subject is a human. As used herein, *"in situ",* means in a subject or *in vivo.*

Device

[0009] The description provides a device for detecting a medical condition or disease in a subject. The device is capable of entering the subject. The device comprises a detector which is able to specifically react *in situ* in a subject and to detect a marker associated with said medical condition or disease. The detection is executed under the condition of having entered the body of a subject. The detector is arranged and constructed to detect a marker after the device entering the body of a subject. The device will be received in a body fluid or biomaterial of a subject. At that location the detector will start 'searching' the marker, and will detect the marker if present. The device preferably comprises a signalling unit for emitting a visible substance, such as a coloured dye. The ejection of a sufficient amount of visible substance will colour a body fluid and will allow observation of the detection of

the marker outside the body, when the bodily fluid exits the body.

[0010] The signalling unit will after detection of the marker emit the visible substance. The visible substance can be a colouring agent that colours a body fluid, said colouring being visible to the user or subject if the body fluid leaves the body. The detection is visualised by colouring e.g. a tested body fluid or biomaterial (for example faeces, urine or saliva) or the device itself, to notify the subject. The visualisation is visible for outsiders as the visible substance will leave the subject. The test results of the in situ detection will be visible from outside the subject. The visible substance can be a substance transportable by a body fluid and/or biomaterial.

The visible substance can be a coloured dye. The dye can be released upon detection of the marker. The device can have one, two or multiple chambers for receiving one or more dyes of different colours. The colours can correspond with predetermined markers. The dye corresponding with the detected marker is released upon detection. This allows detection of different markers using a single device.

[0011] As also described herein, the device may comprise a chamber or reservoir for a visualisable substance of at least 1 microlitre to 100 micro litre. Such a small amount suffices to be visible outside a subject.

[0012] As also described herein, the signalling device may comprise a nanopump connected to the chamber and arranged for ejecting the visible substance from the chamber. A suitable nanopump system is known from Böhm, S., et al. (2000).

[0013] The device is described more extensively below and a most preferred device is also described (for detecting colorectal cancer).

[0014] In a first aspect, there is provided a device for detecting a medical condition or disease in a subject, wherein said device comprises a detector which is able to specifically react *in situ* in a body fluid or biomaterial of a subject and detect a marker associated with said medical condition or disease. The detector can send an actuation signal to a signalling unit. The signalling unit will upon receipt of the actuation signal emit and preferably eject the visualisable signal. The signalling unit can be arranged and constructed to emit a visible substance such as a dye having a predetermined colour. The detector can send a (detection) signal, preferably an electronic signal, to the signalling device upon detection. The detector and signalling device are electronically connected. By providing the detector or multiple detectors separate from the signalling unit, the signalling unit can be activated as a result of one or more conditions or e.g. with a delay after detection. Further multiple detections can be made and signal is only emitted after detection of a certain amount or combination of conditions.

[0015] As described herein, the visible substance may comprise a representation of the detected marker. Also described herein isa device capable of detection multiple different markers. Detection of a specific marker leads to emitting of a specific visible substance. The emitted colour then represents the detected data. Multiple colours can be available. This allows the specific detection to be observed, visualised, outside the subject. The device can comprise multiple chambers wherein different visualisable substance are received, having different optical properties. Upon detection of a specific marker, a specific visualisable substance is released.

[0016] As disclosed herein, the visible substance can colour the device or part thereof, which will be visible once the device has left the body. As also disclosed herein, the coloured substance may colour a body fluid or biomaterial that can leave the subject.

[0017] The device as described herein may comprise a house for entering a subject. This will allow the detector to react in situ for detecting a marker. Further such a house will allow the activation of the unit for visualising the detection of a marker. The house can be a capsule.

[0018] Preferably the device comprises a house for leaving a subject. This will allow the recovery of the device. There could also be a unit for visualisation located on the device that will indicate whether a marker was detected.

[0019] The device can comprise an electronic circuit. The device can be miniaturized. The device can be fabricated using methods commonly applied for the manufacture of integrated circuits, such as photolithography, reactive ion etching or electron beam evaporation.

[0020] As described herein, the detector for detecting the marker may comprise nanowires. As a result of detecting a marker, an electrical property, such as impedance, of a nanowire can change. The nanowires can be connected to a control circuitry, having an electrical power source. The nanowires and control circuitry form part of the detector of the device. The control circuitry can determine an electrical property of the nanowires, such as the impedance or resistance. The control circuitry is arranged to output an actuation signal at detection.

[0021] In a laboratory environment, nanowires can be calibrated by determining a threshold value that is an indication for detecting a targeted DNA molecule. This threshold value can be programmed in the control circuitry, e.g. in a memory. If during operation the threshold value is measured, the control circuitry can provide, output, an actuation signal.

[0022] As used herein, a medical condition or disease may refer to any disease or medical condition known to occur within a given subject, for which a specific detection system may be developed and incorporated into a LOC and for which said disease or medical condition is detectable *in situ* where a device has been introduced. Preferred diseases are cancer, for example gastrointestinal -, mouth/throat/salivary glands -, urogenital cancer, or Human Papilloma Virus infection, which may be a cervical infection and intestinal infections. It is preferred, especially when an ingestible device is used, that a medical condition or disease is a medical condition or disease of the digestive tract and/or detectable in the digestive tract.

More preferably, medical conditions or diseases of the digestive tract are, amongst others, gastric- and duodenal ulcers with or without *H. pylori* infection, stomach cancer and colorectal cancer.

It is also preferred that a medical condition or disease is a medical condition or disease of the vaginal tract and/or detectable in the vagina. Such medical condition or disease of the vaginal tract is preferably a cancer, preferably a HPV cancer and/or infection, orother infectious disease.

[0023] A device is first introduced in the mouth/swallowed or put internally into contact with a body fluid or biomaterial of a subject. A device may be an ingestible device like a pill. A device may also be ingested into a gastrointestinal tract of a subject and a detector of the device is able to specifically react in the digestive tract of a subject. Also disclosed herein is a device designed to be safely introduced into the vagina of a subject. As disclosed herein, a detector present in a device is able to specifically react in the vaginal tract of a subject. As also disclosed herein, a device may be designed to be safely introduced into the anal tract, the mouth, the nose, the ear, or the eye of a subject. An example of a disease that may diagnosed via the mouth is mouth cancer, leukoplakie, caries or paradontitis. An example of a disease that may be diagnosed via the nose is nasopharyngeal carcinoma. Also for example the presence of *Staphylococcus Aureus* could be detected and visualized. A device as described herein is quite attractive since it does not necessitate the presence of a physician to carry out the detection of the medical disease or condition. The device is quite simple to use, may be used at home by a subject. There is no need to go to the doctor or to the hospital as long as the test result is normal.

[0024] Once the device is internally in contact with a subject, it may be needed that a device is resistant against degradation that could occur *in situ.* Preferably, when the device is an ingestible device, the device is resistant against degradation that could occur within the digestive tract. For example, said device may be resistant against stomach acid pH. Several enteric coating are already known and used in the formulation of medicaments. Examples of an enteric coating that may be present on a device may comprise gelatin and/or starch and/or cellulose and/or carrageenans and/or a polymer. Modified forms of starch and/or cellulose may also be used. Examples of polymers are impermeable hard polymers such as polypropylene and/or teflon.

[0025] A device as disclosed herein comprises: a] an extraction unit and/or a purification unit for extracting and/or purifying a marker or a component present within a subject, b] a detector and c] means to transmit a signal to the outside world, e.g. comprising an emitter. The detected signal can be converted into a visualisable signal by ejecting a coloured substance. The ejected coloured substance, held in a reservoir in the device, will be mixed and dispersed in a bodily fluid, which bodily fluid can exit the body and will allow observation thereof outside the body. Each of these elements of the device are extensively described below.

comprises device as disclosed herein may comprise means to extract and/or purify a marker or a component present within a subject and whose detection will indicate that a medical condition or disease has been diagnosed. It is preferred in this case that the means to extract and/or purify are present in a compartment of the device. A compartment indicates that this element is physically separated from other elements of the device. This may be realized by the use of an inert membrane. A preferred component to be extracted and/or purified is DNA. More preferred means to extract and/or purify among others DNA include a pump, mixing means, a liquid to be mixed with a sample extracted from a subject, an extracting column and/or a second distinct liquid. A preferred pump is a micromachined electrochemically driven pump capable of dosing precise nanoliter amounts of a liquid sample from a subject. Such pump consists of a micromachined channel structure realized in silicon by reactive ion etching (16). A liquid may facilitate the extraction and/or purification of a marker and/or component to be tested. A preferred liquid is a high salt solution. High preferably means about approximately 5 to 6 M salt solution. High preferably means between 5 and 6 M salt solution. More preferably, the salt is a chaotropic salt such as sodium iodide, sodium perchlorate and guanidine thiocyanate. A compound or marker present in a sample extracted from a subject may be diluted with a liquid present in a device as described herein. Subsequently, a purification may be carried out by passing a diluted sample from a subject on to an extraction column. An extraction column micro machined in glass or silicon is preferably a column designed to retain a marker and/or component to be detected. A retained marker and/or component may be subsequently released from a column by using a distinct second liquid. This second liquid may have a lower salt concentration than the one of the first liquid used. A released marker and/or component is preferably directed from the extraction column directly into a detector. It is even more preferredif the intestinal fluid is to be sampled, diluted and all free DNA is to be denatured in an initial step. The purification is then to be done based on the fact that DNA will bind to silica in the presence of high concentrations (about approximately 5 and 6M, or between 5 and 6 M) of chaotropic salt solutions, such as sodium iodide, sodium perchlorate and guanidine thiocyanate. These chaotropic salts are then washed away from the columns and system. The attached DNA is then released, or eluted, from the columns using a 10mM-100mM salt containing buffer solution or water. A preferred column is a silica column. Such columns are commercially available by Promega Corporation.

A centrifugation method may further be used to separate a marker from denatured proteins. The obtained supernatant may be subsequently delivered to an extraction column as defined herein. Ethanol precipitation may also be used as part of the extraction method.

[0026] A detector is a further element present in a device. A detector is able to specifically react *in situ* in a subject to detect a marker or component present in a sample extracted and/or purified from a subject. A detector has to be specifically designed depending on the medical condition or disease to be detected. A marker detected by a detector is known to be associated with said medical condition or disease. For example, when a cancer is to be detected, the presence or absence of a specific gene product associated with this cancer may be detected: for example the presence of an oncogene and/or the absence of a gene known to be a suppressor of tumour. Such a detector may comprise a probe or primer that is specifically able to recognize or hybridize with such a gene product such as mRNA, or protein. More preferably, a detector is able to specifically detect several types of diseases or medical conditions. Even more preferably, a detector is able to specifically detect several types of cancer. It is also preferred that the detector is able to specifically detect a specific state of DNA. A preferred specific state of DNA in this context is hypermethylated DNA. Gene promoter hypermethylation is a specific marker for the development of several cancers ((9) till (15)). For detecting the presence of hypermethylated DNA, a detector preferably comprises a miniature silica extraction column with high surface area. "High surface area" refers to the fact that a porous structure is made in the glass material. This may be developed using conventional glass or silicon etching solutions. Such columns are commercially available as earlier defined herein.

[0027] In particular, the detector can comprise a control circuitry for analysis by comparison of detection results. The control circuitry may measure and compare electric properties of the probe or primer, and if the property has a predefined value, determine that the marker is detected and outputs a actuation or detection signal to the signalling unit.

[0028] A device as described herein may stay inside a subject during a certain period of time. The duration of the period of time should be long enough to allow the extraction and/or purification and detection steps to take place. This period depends on the *in situ* localisation wherein a device has been introduced and the condition for which the device is used. For example, if a device has been introduced into the gastrointestinal tract by ingestion, the device will stay approximately one to three days *in situ* till it may be exported into the faeces. In this case, a device leaves a subject via his or her anal tract. For any other types of device for example intravaginal, the period of time may be much shorter and may be ranged between several minutes to a couple of hours. For this type of device, a subject will introduce the device and will take it out himself/herself. The duration of the period of time should be long enough to allow the extraction and/or purification and detection steps to take place.

[0029] Once a detection step has taken place, a signalling unit is actuated. As described herein, means to convert a detection signal produced by the detector into a visualisable signal may be present as a further element of a device. A signalling unit is arranged and constructed to emit a visible substance. Upon detection of hypermethylated DNA the visible substance can be released. The conversion from detection to visualisable signal may be direct, i.e. in one single step. However, it is preferred that the conversion is realized in two steps or more by the presence of an electronic interface, which may translate a detection signal into an electronic signal which in its turn may be translated into a visualisable signal. A visualisable signal may be a colouring of the tested body fluid or biomaterial,for example faeces, urine or saliva or a colouring of the device itself, that can be detected by a human eye. The colouring of the tested body fluid or biomaterial is preferred due to practical and hygienic reasons. For example, a dye may be pulled out of a reservoir by a signal generated by the electronic signal emanating from an electronic interphase in response to a detection of a marker and/or compound. A visualisable signal may only be visualised once the device, body fluid or biomaterial has left a subject. This is not mandatory. The visualisable signal may already be theoretically visualised while the device is still *in situ* in a subject. However, this will generally not occur, since the visualisation with a human eye will only be possible once the device has left the subject. This language has been added to clarify that a device as described herein is not an imaging device.

[0030] It is preferred that a device is such that a detection is made without adding any other substance to a device once it has left a subject.

[0031] The disclosure also provides a device for detecting a medical condition or disease in a subject. The device is capable of entering the subject. The device comprises a detector which is able to specifically react *in situ* in a subject and to detect a marker associated with said medical condition or disease. The detection is executed under the condition of having entered the body of the subject. The detector is arranged and constructed to detect a marker after the device entering the body of a subject. The device will be received in a body fluid or biomaterial of a subject. At that location the detector will start 'searching' the marker, and will detect the marker if present. The device preferably comprises a signalling unit for transmitting the detected data in some form to the outside world, such as via acoustic, optical, or radio frequency signals or a coloured dye.

[0032] There is also provided a device for detecting a medical condition or disease in a subject, wherein the device comprises a detector which is able to specifically react *in situ* in a body fluid or biomaterial of a subject and detect a marker associated with said medical condition or disease. The detector comprises a control circuitry. As a result of detection, an electrical property, in particular the impedance or resistance of an element of the detector changes. The control circuitry can detect the change. The control circuitry can compare a change with a threshold value, e.g. available from a memory that is connected to the control circuitry. In dependence of the

comparison of threshold value and electrical property, the control circuitry can provide an actuation signal for signalling that the marker is detected. As described herein, an actuation signal is formed due to the detection of a change in an electrical property of the detector. Preferably the detector comprises suitable nanowires.

[0033] A signalling unit is connected to the detector and specifically to the control circuitry. The signalling unit is arranged and constructed to emit a detectable signal, such as an acoustic, optical or RF signal, or a visible substance such as a dye having a predetermined colour, such that the detection is visualised outside the subject. The RF signal can be detected by an external receiver, or e.g. a cell phone and may be automatically transmitted to the expert's office. The acoustic signal, optical signal or visible substance may be observable once the device has left the body. It is also envisaged that the coloured substance colours a body fluid or biomaterial that can leave the subject.

[0034] The nanowires may be calibrated for detection of targeted DNA molecules. Calibrated nanowires can be connected to a control circuitry, said control circuitry having a memory with a parameter representing a threshold value for an impedance value of the nanowire. If the impedance of the nanowires changes and reaches said impedance during operation, this is a measure for identification of the targeted DNA molecules. Comparing the threshold value with the measured impedance in the nanowires using the control circuitry is advantageous for detecting a marker.

[0035] The control circuitry may be connected to a signaling device comprising a sound emitting unit for emitting sound after receiving an actuation signal from the control circuitry indicating detection of the targeted DNA molecule with the nanowire.

[0036] The signaling unit connected to the control circuitry may comprise an electromagnetic radiation source, preferably an optical radiation source such as a visible light radiation source, that is operated to emit electromagnetic radiation as a result of receiving an actuation signal from the control circuitry. The electromagnetic emitter can be a radio frequency emitter for transmitting a detection signal through the body. Said signal can be received in a receiver outside the body. The signaling device may comprise an ultrasonic sound emission unit.

[0037] A collection of differently calibrated nanowires may be received in the capsule for detecting different DNA molecules. Detection of a DNA molecule results in an impedance/resistance change.

[0038] The emitted signal can comprise a code for identification of the targeted DNA molecule. The control circuitry sends an actuation signal representative for the detected marker/DNA molecule. The signaling device emits a signal comprising a code representative for the detected marker/DNA molecule. An operator is able to determine which targeted DNA molecule was detected. This allows detecting multiple different DNA molecules in a single "run".

[0039] A nanowire for detecting a targeted DNA molecule can be part of a microchip on the device. Such a microchip is known from Vrouwe (2005).

A preferred ISLOCS device for detecting colorectal cancer

[0040] The situation of the diagnosis of colorectal cancer is representative for several relevant diseases in the western world, e.g. cardiovascular diseases, diabetes, kidney disease and various other cancers and is therefore exemplified below. Colorectal cancer is one of the most common malignancies that will be developed by at least 5 % of the western population, and is considered one of the leading causes of cancer related death (1). Fortunately, it is a disorder with a relatively long latent premalignant stage. This pathophysiology offers a clear 'window of opportunity' for early detection and effective treatment of the disease in an early phase. Colonoscopy is considered as the most effective method to detect the premalignant stage of colorectal cancer. This procedure, however, has several disadvantages, such as the large patient inconvenience, the possibility of serious complications and the high costs involved. There is, therefore, a broad consensus that colonoscopy should only be offered to individuals with an increased risk for colorectal cancer.

Based on current knowledge, Faeces Occult Blood Test (FOBT) is the most recognized method to select high risk individuals. Unfortunately, with FOBT a considerable percentage of the tumours in the screened group is missed. Consequently, there is need for further refinement of the selection methods preceding colonoscopy.

A new and exciting screening technique for colorectal cancer, as well as other types of cancers, is the detection of aberrant methylation, or hypermethylation, of normally unmethylated CpG islands of DNA (2,3). Methods for mapping methylated DNA regions have been demonstrated using Southern blotting hybridization assays (4), and methylation specific polymerase chain reaction (5). More recently, specific DNA methylation detection using microarray formats for sensitive, high throughput screening of patient samples has been reported (6).

Unfortunately, also these laboratory tests do not have a 100% accuracy. As a result they are preferably used as preselection method to select those individuals for whom further and usuallymore invasive testing will be useful. Especially in a screening setting the test need to be as client/patient friendly and easy to use as possible. Each barrier, such as visiting a laboratory or medical centre, to have the test performed will influence the participation rate and is (cost-)inefficient. A lab on a chip device that could be safely used at home and which only signals the user to go to the doctor if the test result is abnormal would be ideal in this setting.

[0041] Below we describe a device for detecting a colorectal cancer in the digestive tract of a subject. Upon ingestion, an ISLOCS device or smart pill travels to the

intestines, where intestinal fluid is delivered to the ISLOCS device, which automatically extracts and purifies a DNA as earlier defined herein. A purified DNA sample is subsequently transported to a detection system where it interacts with a probe oligonucleotide molecule, specific for a particular methylation abnormality as defined above, said probe being immobilized directly on a sensor surface. If a DNA sample hybridizes with a probe, indicating a positive result, such event is directly detected electronically, and a colour-intense dye is expelled from a device, which will cover and penetrate a biological fluid/biomaterial, which is visualized when a subject defecates. This type of early warning disease detection may revolutionize methylated-related cancer diagnosis, treatment and, if successful, will drastically reduce cancer causing fatalities. The concept ISLOCS device may comprise many interacting components, but may be described best by outlining the five main system components: i) sample extraction and purification, ii) DNA detection, iii) electronic interfacing, iv) dye dosing positive detection notification and v) electrical power supply. A more extensive description of each component is given in the example.

Method

[0042] The description provides a method for detecting a medical condition or disease in a subject wherein a device as defined in the previous section is used. The terms "detecting", "medical condition or disease" and "subject" have all been defined earlier herein. The method as defined herein is very attractive since it is a non-invasive method which could be carried out by a subject to be diagnosed. No collection or transport of the excreted biological fluid/biomaterial to a laboratory is required.

[0043] In this document and in its claims, the verb "to comprise" and its conjugations is used in its non-limiting sense to mean that items following the word are included, but combinations and/or items not specifically mentioned are not excluded.

In addition the verb "to consist" may be replaced by "to consist essentially of' meaning that a device, a part or a unit of said device or means present in said device as defined herein may comprise additional component(s) than the ones specifically identified, said additional component(s) not altering the unique characteristic of the device as described herein.

The word "about" or "approximately" when used in association with a numerical value (about 10) preferably means that the value may be the given value of 10 more or less 1% of the value.

[0044] In addition, reference to an element by the indefinite article "a" or "an" does not exclude the possibility that more than one of the element is present, unless the context clearly requires that there be one and only one of the elements. The indefinite article "a" or "an" thus usually means "at least one".

Brief description of the figures

[0045]

Figure 1. Schematic representation of a subject.
Figure 2. Schematic representation of a device as described herein.
Figure 3. Schematic representation of an output signal of a device according to figure 2.

[0046] Figure 1 shows a human subject 10. In the figure an exploded view of the human intestines 11 is shown. The subject 10 is ready to ingest an ISLOCS device.

[0047] Figure 2 shows a preferred device of the device 8 as described herein. The device 8 is a ISLOCS device. The device 8 comprises 1 a battery, a sample extraction and treatment part 2, a detection part 3, a dosing part 4 and an electronics part 5. The device is encapsulated in a house 6. The device 8 can be swallowed. The detection part 3 is connected to a micro fluidic system comprising a tubing 18 and a micro pump 19, allowing to extract small amounts of bodily fluid into the housing of the device and through or along the detector. The detection part 3 is connected to the electronic part 5, comprising a control circuitry for measuring an electrical property of the detection part and allowing comparing the measured value with a threshold value, e.g. contained in a memory, also present in the electronic part 5.

[0048] The sample extraction and treatment part 2, the detection part 3 and electronics part 5 cooperate in order to take samples and detect the presence of a possible marker relating to a specific medical condition.

[0049] Detection of the marker results in a change in an electrical property of the detector, comprising the sample and treatment part 2, detection part 3 and electronics part 5. The electronics part 5 may comprise a programmable memory and a compare module allowing comparing a current electrical property of the detection part, e.g. comprising nanowires, and a threshold value programmed in the memory. If the electrical property, such as the impedance of the detection part 3, reaches the threshold value, this is an indication for the fact that the marker is detected. Detection results in e.g. providing an actuation signal.

[0050] A detector may comprise 1-1000 nanowires. The detector can be a part of a micro fluidic system. Small amounts of bodily fluids are pumped through the system and along the detector and in particular the nanowires.

[0051] The dosing part 4 is an example of a signalling unit for signalling and in particular visualizing a detected condition. The dosing part 4 can comprise a chamber filled with a dye fluid. If the detection part 3 detects a marker, the electronic part 5 will send a actuation signal to the signalling unit to trigger the dosing part, comprising e.g. a micro pump, to release the dye fluid. The dye fluid may be released out of the housing 6 into the environment. If the device 8 is still inside the subject, the dye fluid will be released into a body fluid. The coloured body

fluid will be visible to the subject 10 e.g. if the subject 10 uses a bathroom. The dye may also be released into the housing 6, which will take over the dye colour. The coloured housing 6 will be visible when the housing leave the subject 10.

[0052] The signalling unit may comprise a device for emitting a signal to the outside world, other than a fluid release system. A RF signal may be sent after detection of the marker. The device 8 may comprises a (ultra)sound emitting source. The signalling device can be triggered by receiving the actuation signal from the detector.

[0053] The device 8 may also comprise a further housing part separate from the device. The device can be inserted in the human body using a separate insert e.g. for insertion into the vagina.

[0054] Figure 3 shows a presentation of a signal from an ISLOCS device 8 according to figure 2. Figure 3 shows detecting the state of methylation of the DNA of a subject: a represents the signal given for hypermethylated DNA, b represents the signal given for hybridized DNA, c is the nanowire sensor whereupon DNA may hybridize, d is the electrical terminal and e represents the signal change which is induced by hybridization of DNA to the nanowire sensor. The signal change may be a change of nanowire resistance, measured through the current that is transported through the nanowire at a given applied potential. The applied potential may be a direct-current (DC) voltage, or an alternating current (AC) with frequency from 0-1 GHz. The signal may also be the cange in interfacial resistance between the nanowire surface and another electrode in contact with the DNA-sample solution. The resistance may be measured with DC or AC applied voltages, with a frequency range from 0-1 GHz. Fabrication of the nanowires is done using a combination of state of the art micro- and nanotechnologies, such as photolithography, E-beam lithography, laser-interference lithography, nanoimprint lithography, wet and dry etching, evaporation, sputtering, and e-beam implantation, to enable low price, high quality, low-contact resistance nanowire devices. After detection the signalling unit 4 is initiated to visualise the detection of the marker preferably by releasing the coloured substance/dye.

Example

Blue Bolus smart pill system

[0055] The Blue Bolus smart pill is an ideal ISLOCS application, as most of the required system components can be realized with conventional technological methods. The basic operation of the Blue Bolus (BB) smart pill begins with a subject swallowing a pill. When the smart pill reaches the lower intestine, the pill begins to sample the intestinal fluid. The sample fluid is mixed with a pre-stored salt solution that purifies a DNA sample, which is subsequently captured with a miniature extraction column. The captured DNA molecules are then eluted from a column and transported to the detection element, which contains a probe molecule attached to a sensor surface. When a positive detection event occurs, then an integrated electronic commands that a blue, pre-stored dye is pumped out of the pill into the bowel, which can be easily observed after defecation. The complete operation of the smart pill is automated and controlled by the "brains" of the system, the electronic control chip. The subject swallowing the pill should not have diarrhea, but should take a stool softener on the same day as the smart pill and onwards till the stools appear 24-72 hours after taking the Smart Pill. This is to guarantee soft stools during the next 3 days and adequate mixing of the dye, if pumped out of the pill. The five primary BB smart pill system concepts are shown schematically in figure 2. The main functions of the smart pill, including sample extraction and purification, hypermethylated DNA detection, electronic interfacing, dye dosing notification and electrical power supply. Each of these system components are now described in more detail.

Sample extraction and purification

[0056] The intestinal fluid is sampled from the external environment of the ingested smart pill. The sampling of the intestinal fluid is to be performed with an integrated pump system (for example the micromachined electrochemically driven pump as described in (16)) capable of withdrawing an adequate amount of intestinal fluid and mixing with a high-salt solution (about approximately 5 and 6M of chaotropic a salt solution, such as sodium iodide, sodium perchlorate and guanidine thiocyanate). The ISLOCS device contains a miniature silica extraction column (silica column from Promega) with high surface area to capture the DNA directly from the diluted sample. The captured DNA is then released by flowing another pre-stored low-salt solution (same salt as before in a concentration ranged between approximately 10mM-100mM) through the column and directly to the detection assay.

DNA detection

[0057] The purified DNA samples are transported directly to the detection system, which consists of an array of silicon nanowires (17) with oligonucleotide probe molecules attached to their surfaces. The probe molecules will be designed for a specific methylation abnormality, as has been reported for colorectal cancer (7), for example. Silicon nanowire sensors have been demonstrated to be highly sensitive to surface charge variations due to DNA/DNA hybridization and antibody/antigen binding. However, depending on the amount of hypermethylated DNA contained in the sample, then a preconcentration step or sample amplification step, using an integrated polymerase chain reactionsystem, will be required at the expense of increase complexity. Specific polymerase chain reaction system have already been designed to specifically detect colon cancer in human stool DNA (18,

19). Figure 3 shows a cartoon illustration of the DNA hybridization on the nanowire sensors and the resulting electrical output signal, which can be recorded directly by the integrated electronics. Silicon nanowires have recently been fabricated and electrically tested in the BIOS Group of the University of Twente (20). On the surface of the silicon nanowires the probe molecules will be immobilized using conventional silane linking chemistry. The probe molecules specific for a particular methylation abnormality will be tailored for this application.

Electronic interfacing

[0058] The front-end of the electronics circuitry performs the acquisition of the nanowire signals by means of conventional measurement techniques. A low-power microcontroller, the "brains" of the system, keeps track of various functions in the pill such as timing, functional checks of the subsystems and the actual data processing. The output electronics consist of the dosing interface that starts or inhibits the actual dye dosing, depending on the microcontrollers evaluation of the nanowire response. The nanowires can be connected to a control circuitry comprising a comparing unit. The comparing unit can compare an electrical property of the nanowire with a set threshold. If the electrical property change enough, beyond the set threshold, this is a signal for the fact that the marker was detected. The change in the electrical property is a result of a chemical reaction of the marker and the nanowire. The threshold value can be provided in the control circuitry in a programmable memory. The threshold value can be provided as a result of a calibration test performed beforehand. One or more different nanowires can be present for detecting different markers. Different threshold values can be provided for allowing detection of different markers. One or more detection signalling units can be present in the device 8, each actuated with a different actuation signal by the electronic part 6, sending the signal as a result of a specific detection.

Dye dosing notification

[0059] The dye dosing function will be performed using a low-power electrochemical actuation technique. In this system the dye is pulled out of a reservoir by pressure generated by the electrolysis of water, a proven technique developed in the BIOS group (8). The dye dosing unit can comprise a nanopump connected to an electric source. A limited amount of dye fluid is present in a dye chamber. The volume per chamber can be up to 1 ml. Multiple chambers filled with different dyes may be available.

Electrical power supply

[0060] The electrical power for sample extraction, transportation, detection, electronic processing and dye dosing will be supplied by a commercial high energy density battery, which can easily provide enough energy for all functions and operations.

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Claims

1. A device (8) for detecting a medical condition or disease in a subject (10), wherein the device is capable of entering the subject and comprises a detector (3) which is able to specifically react *in situ* in a body fluid or biomaterial of the subject and detect a marker associated with said medical condition or disease, the device comprising a chamber (14) comprising a visualisable substance, the device further having a signalling unit (4) arranged and constructed to emit the visualisable substance from the chamber upon detection of the marker into the body fluid or biomaterial wherein the device comprises an extraction and/or purification unit (2) for extracting and/or purifying the marker from the body fluid or biomaterial of the subject, **characterised in that** the visualisable substance is configured to disperse and mix, when emitted, in the body fluid or biomaterial that can exit the body and allow the substance to become visible outside the subject.

2. A device (8) according to claim 1, wherein the device comprises a swallowable housing (6) for entering a subject and leaving a subject (10).

3. A device (8) according to any one of the claims 1-2, wherein the detector (3) comprises an automated miniature analysis system.

4. A device (8) according to any one of the claims 1-3, wherein the signalling unit (4) comprises a release mechanism for releasing a substance upon detection, which has a predetermined colour or colouring effect corresponding with the detection of a specific marker.

5. A device (8) according to any of the claims 1-4, wherein said device additionally comprises a micropump or nanopump connected to the chamber (14) and arranged to eject the visualisable substance from the chamber upon detection of the marker into the body fluid.

6. A device (8) according to any one of claims 1 to 5, wherein the detection is made without adding any other substance to the device once it has left the subject (10).

7. A device (8) according to any one of claims 1 to 6, wherein the detector (3) is able to specifically react in the digestive tract (11) and/or in the vagina of a subject (10).

8. A device (8) according to claim 7, wherein the device, if used in the digestive tract (11), is an ingestible device and/or is preferably resistant against degradation that occur within the digestive tract.

9. A device (8) according to any one of claims 1 to 8, wherein the medical condition or disease is a medical condition or disease of the digestive tract (11) and/or detectable in the digestive tract or of the vaginal tract and/or detectable in the vagina.

10. A device (8) according to any of the claims 1 to 9, wherein the device comprises two or more detectors (3) for different markers.

11. A device (8) according to any of the claims 1 to 10, wherein the device comprises two or more chambers (14), wherein different visualisable substances are received in said chambers.

12. A device (8) according to any of the claims 1-11, wherein the detector (3) comprises a control circuitry and a detecting element connected to the control circuitry, the detection element having an electrical property that changes if a marker is detected.

13. A device (8) according to claim 12, wherein the detecting element comprises nanowires and/or wherein the control circuitry comprises a memory for a parameter representing a threshold value for the changing electrical property and/or the electrical property is impendance.

14. A device (8) according to claim 1 wherein the detector (3) comprises a detection element which is able to specifically react *in situ* in a body fluid or biomaterial of the subject and detect a marker associated with said medical condition or disease by having a changing electrical property, wherein the detector comprises control circuitry connected to the detection element for measuring the electrical property.

15. A device (8) according to claim 14 in combination with any of claims 2-13 and/or wherein the chamber (14) comprises a dye fluid received therein and wherein the signalling unit is configured to emit the dye fluid into the bodily fluid upon detection.

Patentansprüche

1. Vorrichtung (8) zur Erkennung eines medizinischen Leidens oder einer Krankheit bei einem Testobjekt (10), wobei die Vorrichtung in das Testobjekt eindringen kann und einen Detektor (3) umfasst, der spezifisch *in situ* in einer Körperflüssigkeit oder im Biomaterial des Testobjekts reagieren kann und einen Marker erkennt, der mit dem medizinischen Leiden oder der Krankheit im Zusammenhang steht, wobei die Vorrichtung eine Kammer (14) umfasst, die eine visualisierbare Substanz enthält, die Vorrichtung ferner eine Meldeeinrichtung (4) aufweist, die so angeordnet und konstruiert ist, dass sie die visualisierbare Substanz aus der Kammer bei Erkennen des Markers in die Körperflüssigkeit oder das Biomaterial abgibt,
wobei die Vorrichtung eine Extraktions- und/oder Reinigungsanlage (2) zum Extrahieren und/oder Reinigen des Markers aus der Körperflüssigkeit oder dem Biomaterial des Testobjekts umfasst, **dadurch gekennzeichnet, dass** die visualisierbare Substanz so ausgelegt ist, dass sie sich bei Abgabe in der Körperflüssigkeit oder im Biomaterial dispergiert und vermischt, welche/s aus dem Körper austreten kann, und ermöglicht, dass die Substanz außerhalb des Testobjekts sichtbar wird.

2. Vorrichtung (8) nach Anspruch 1, wobei die Vorrichtung ein verschluckbares Gehäuse (6) zum Eindringen in ein Testobjekt und Verlassen eines Testobjekts (10) umfasst.

3. Vorrichtung (8) nach einem der Ansprüche 1 bis 2, wobei der Detektor (3) ein automatisches Miniatur-Analysesystem umfasst.

4. Vorrichtung (8) nach einem der Ansprüche 1 bis 3, wobei die Meldeeinrichtung (4) einen Freigabemechanismus zum Freigeben einer Substanz bei Erkennung umfasst, die eine vorgegebene Farbe oder einen Färbeeffekt aufweist, die/der mit dem Erkennen eines bestimmten Markers übereinstimmt.

5. Vorrichtung (8) nach einem der Ansprüche 1 bis 4, wobei die Vorrichtung zusätzlich eine Mikropumpe oder Nanopumpe umfasst, die mit der Kammer (14) verbunden ist und so angeordnet ist, dass sie die visualisierbare Substanz aus der Kammer bei Erkennen des Markers in die Körperflüssigkeit ausstößt.

6. Vorrichtung (8) nach einem der Ansprüche 1 bis 5, wobei die Erkennung ohne Zugabe einer anderen Substanz zur Vorrichtung erfolgt, sobald diese das Testobjekt (10) verlassen hat.

7. Vorrichtung (8) nach einem der Ansprüche 1 bis 6, wobei der Detektor (3) spezifisch im Verdauungstrakt (11) und/oder in der Vagina eines Testobjekts (10) reagieren kann.

8. Vorrichtung (8) nach Anspruch 7, wobei die Vorrichtung, wenn sie im Verdauungstrakt (11) eingesetzt wird, eine unverdauliche Vorrichtung ist und/oder vorzugsweise widerstandsfähig gegen die Zersetzung ist, die innerhalb des Verdauungstrakts auftritt.

9. Vorrichtung (8) nach einem der Ansprüche 1 bis 8, wobei das medizinische Leiden oder die Krankheit ein medizinisches Leiden oder eine Erkrankung des Verdauungstrakts (11) und/oder im Verdauungstrakt erkennbar ist oder im Vaginaltrakt und/oder in der

Vagina erkennbar ist.

10. Vorrichtung (8) nach einem der Ansprüche 1 bis 9, wobei die Vorrichtung zwei oder mehr Detektoren (3) für unterschiedliche Marker umfasst.

11. Vorrichtung (8) nach einem der Ansprüche 1 bis 10, wobei die Vorrichtung zwei oder mehr Kammern (14) umfasst, wobei unterschiedliche visualisierbare Substanzen in den Kammern aufgenommen werden.

12. Vorrichtung (8) nach einem der Ansprüche 1 bis 11, wobei der Detektor (3) einen Steuerschaltkreis und ein erkennendes Element, das mit dem Steuerschaltkreis verbunden ist, umfasst, wobei das Erkennungselement eine elektrische Eigenschaft aufweist, die sich verändert, wenn ein Marker erkannt wird.

13. Vorrichtung (8) nach Anspruch 12, wobei das erkennende Element Nanodrähte umfasst und/oder wobei der Steuerschaltkreis einen Speicher für einen Parameter umfasst, der einen Schwellenwert für die Änderung der elektrischen Eigenschaft darstellt und/oder die elektrische Eigenschaft die Impedanz ist.

14. Vorrichtung (8) nach Anspruch 1, wobei der Detektor (3) ein Erkennungselement umfasst, das spezifisch *in situ* in einer Körperflüssigkeit oder im Biomaterial des Testobjekts reagieren kann und einen Marker erkennt, der mit dem medizinischen Leiden oder der Krankheit im Zusammenhang steht, indem er die elektrische Eigenschaft ändert, wobei der Detektor einen Steuerschaltkreis umfasst, der mit dem Erkennungselement verbunden ist, um die elektrische Eigenschaft zu messen.

15. Vorrichtung (8) nach Anspruch 14 in Kombination mit einem der Ansprüche 2 bis 13 und/oder wobei die Kammer (14) eine Färbeflüssigkeit umfasst, die darin aufgenommen wird, und wobei die Meldeeinrichtung so ausgelegt ist, dass sie die Färbeflüssigkeit bei Erkennen in die Körperflüssigkeit abgibt.

Revendications

1. Dispositif (8) pour détecter une affection médicale ou une maladie chez un sujet (10), dans lequel le dispositif est capable de pénétrer dans le sujet et comprend un détecteur (3) qui est capable de réagir spécifiquement *in situ* dans un fluide corporel ou un biomatériau du sujet et de détecter un marqueur associé à ladite affection médicale ou à ladite maladie, le dispositif comprenant une chambre (14) comprenant une substance pouvant être visualisée, le dispositif ayant en outre une unité de signalisation (4) agencée et construite pour émettre la substance pouvant être visualisée à partir de la chambre lors de la détection du marqueur dans le fluide corporel ou le biomatériau
dans lequel le dispositif comprend une unité d'extraction et/ou de purification (2) pour extraire et/ou purifier le marqueur du fluide corporel ou du biomatériau du sujet, **caractérisé en ce que** la substance pouvant être visualisée est configurée pour se disperser et se mélanger, lorsqu'elle est émise, dans le fluide corporel ou le biomatériau qui peut sortir du corps et permettre à la substance de devenir visible à l'extérieur du sujet.

2. Dispositif (8) selon la revendication 1, dans lequel le dispositif comprend un boîtier pouvant être avalé (6) pour pénétrer dans un sujet et quitter un sujet (10).

3. Dispositif (8) selon l'une quelconque des revendications 1 et 2, dans lequel le détecteur (3) comprend un système d'analyse miniature automatisé.

4. Dispositif (8) selon l'une quelconque des revendications 1 à 3, dans lequel l'unité de signalisation (4) comprend un mécanisme de libération pour libérer une substance lors de la détection, qui a une couleur ou un effet de coloration prédéterminé(e) correspondant à la détection d'un marqueur spécifique.

5. Dispositif (8) selon l'une des revendications 1 à 4, dans lequel ledit dispositif comprend en outre une micropompe ou une nanopompe reliée à la chambre (14) et agencée pour éjecter la substance pouvant être visualisée de la chambre lors de la détection du marqueur dans le fluide corporel.

6. Dispositif (8) selon l'une quelconque des revendications 1 à 5, dans lequel la détection est effectuée sans ajouter aucune autre substance au dispositif une fois qu'il a quitté le sujet (10).

7. Dispositif (8) selon l'une quelconque des revendications 1 à 6, dans lequel le détecteur (3) est capable de réagir spécifiquement dans le tube digestif (11) et/ou dans le vagin d'un sujet (10).

8. Dispositif (8) selon la revendication 7, dans lequel le dispositif, s'il est utilisé dans le tube digestif (11), est un dispositif ingérable et/ou est de préférence résistant à la dégradation qui se produit dans le tube digestif.

9. Dispositif (8) selon l'une quelconque des revendications 1 à 8, dans lequel l'affection médicale ou la maladie est une affection médicale ou une maladie du tube digestif (11) et/ou est détectable dans le tube digestif ou du tractus vaginal et/ou est détectable

dans le vagin.

10. Dispositif (8) selon l'une des revendications 1 à 9, dans lequel le dispositif comprend deux détecteurs (3) ou plus pour différents marqueurs.

11. Dispositif (8) selon l'une des revendications 1 à 10, dans lequel le dispositif comprend deux chambres (14) ou plus, où différentes substances pouvant être visualisées sont reçues dans lesdites chambres.

12. Dispositif (8) selon l'une des revendications 1 à 11, dans lequel le détecteur (3) comprend des circuits de commande et un élément de détection relié aux circuits de commande, l'élément de détection ayant une propriété électrique qui change si un marqueur est détecté.

13. Dispositif (8) selon la revendication 12, dans lequel l'élément de détection comprend des nanofils et/ou dans lequel les circuits de commande comprennent une mémoire pour un paramètre représentant une valeur seuil pour la propriété électrique changeante et/ou la propriété électrique est une impédance.

14. Dispositif (8) selon la revendication 1, dans lequel le détecteur (3) comprend un élément de détection qui est capable de réagir spécifiquement *in situ* dans un fluide corporel ou un biomatériau du sujet et de détecter un marqueur associé à ladite affection médicale ou à ladite maladie en ayant une propriété électrique changeante, où le détecteur comprend des circuits de commande reliés à l'élément de détection pour mesurer la propriété électrique.

15. Dispositif (8) selon la revendication 14 en combinaison avec l'une des revendications 2 à 13 et/ou dans lequel la chambre (14) comprend un fluide colorant reçu dans celle-ci et dans lequel l'unité de signalisation est configurée pour émettre le fluide colorant dans le fluide corporel lors de la détection.

Fig 1

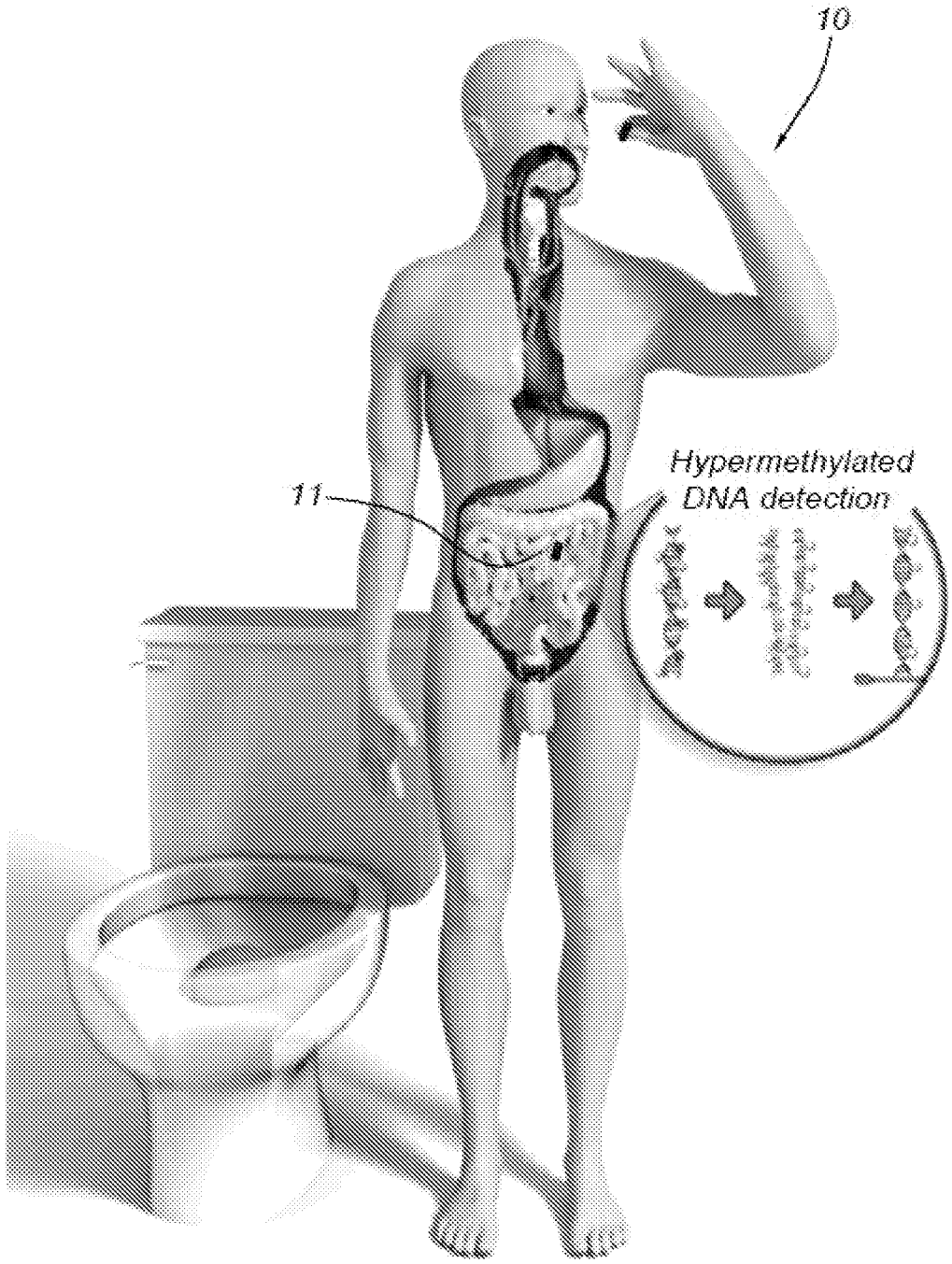


Fig 2

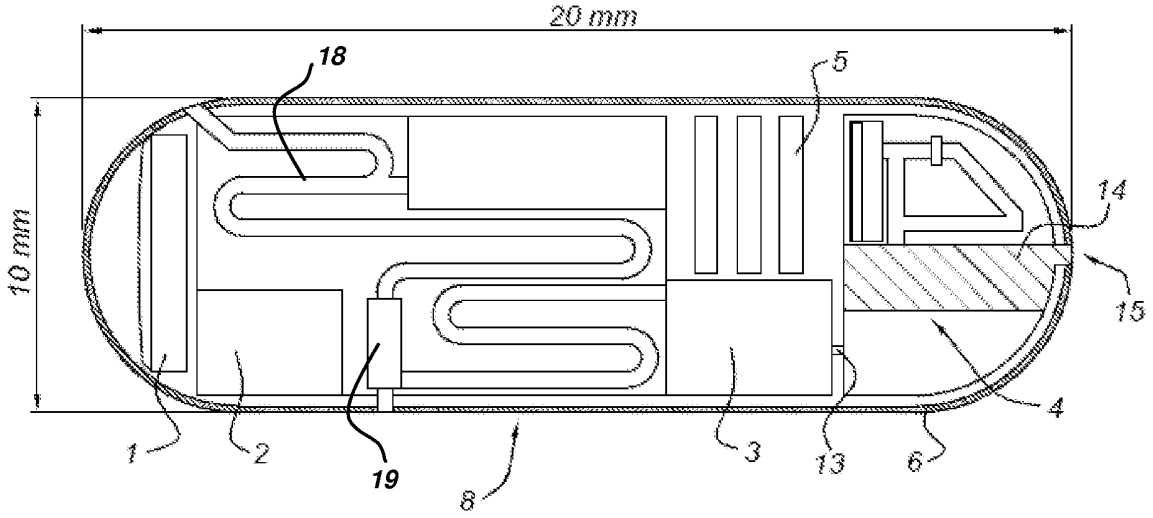
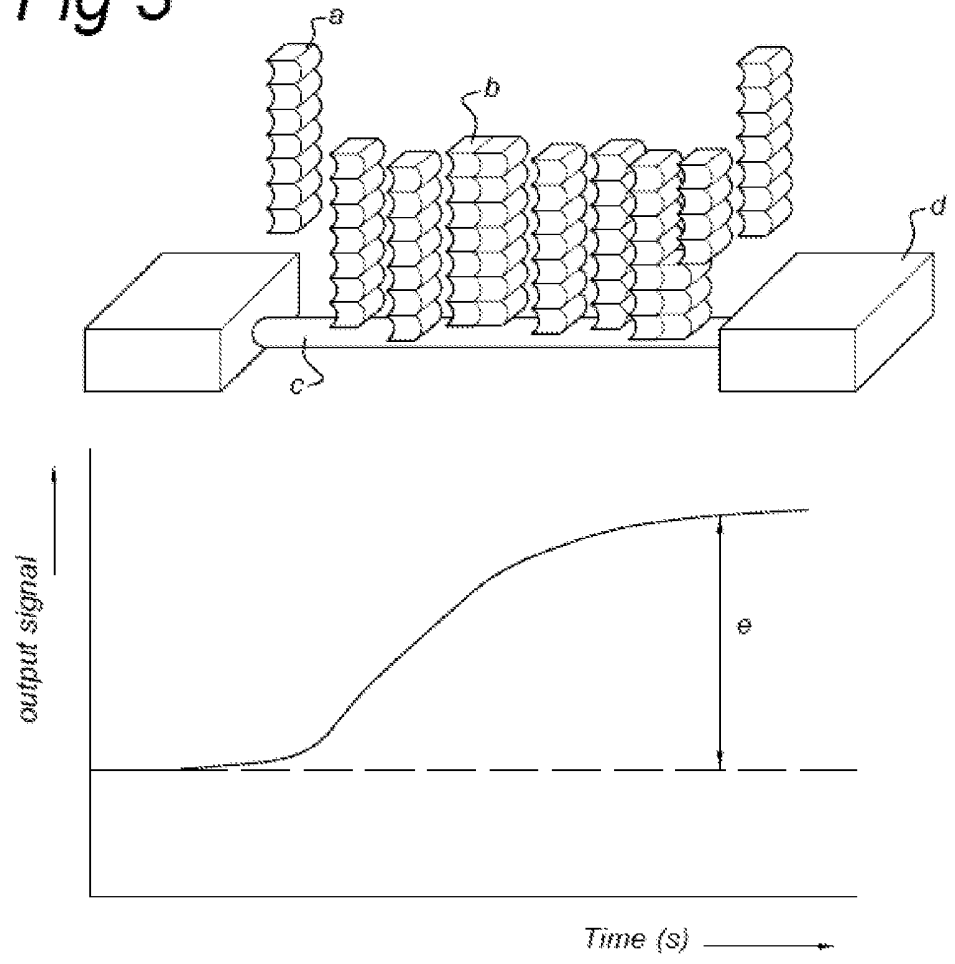


Fig 3



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专利名称(译)	用于检测医学病症或疾病的装置		
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摘要(译)

本发明涉及一种胶囊或芯片或传感器，其包括标记物/检测器和与医学病症/疾病的发展相关的信号装置/方法及其用途。该原位实验室芯片信号装置（ISLOGS装置）用于检测原位或体内（体内）的医学病症/疾病，例如通过将其吞咽以在消化道中进行测试或将其放入阴道，口腔或鼻子。所有反应都发生在体内，当测试结果为阳性时，设备将通过着色测试的体液或生物材料（例如粪便，尿液或唾液）或设备本身来通知受试者。当生物材料或ISLOCS装置离开身体时，在身体外部进行检测。

Fig 1