



(19) **United States**

(12) **Patent Application Publication**  
**Deck et al.**

(10) **Pub. No.: US 2019/0336050 A1**  
(43) **Pub. Date: Nov. 7, 2019**

(54) **IMPLANTABLE SENSOR AND METHOD FOR DETECTING AT LEAST ONE ANALYTE IN A BODY FLUID**

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(21) Appl. No.: **16/515,984**

(22) Filed: **Jul. 18, 2019**

**Related U.S. Application Data**

(63) Continuation of application No. PCT/EP2018/051405, filed on Jan. 22, 2018.

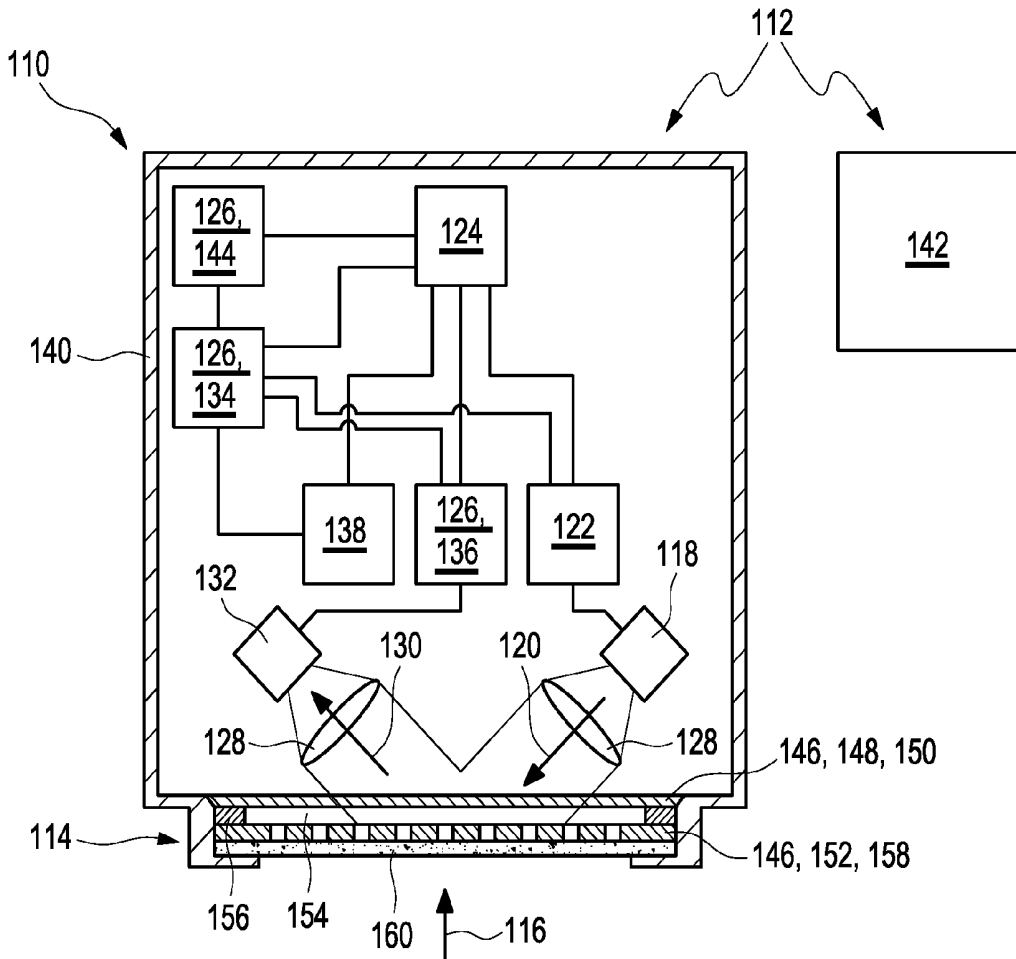
**Foreign Application Priority Data**

Jan. 23, 2017 (EP) ..... 17 152 684.1

**Publication Classification**

(51) **Int. Cl.**  
*A61B 5/1459* (2006.01)  
*A61B 5/145* (2006.01)  
*A61B 5/00* (2006.01)  
(52) **U.S. Cl.**  
CPC ..... *A61B 5/1459* (2013.01); *A61B 5/14546* (2013.01); *A61B 2560/0223* (2013.01); *A61B 2560/0214* (2013.01); *A61B 5/686* (2013.01)

(57) **ABSTRACT**  
Disclosed is a fully implantable sensor for detecting at least one analyte in a sample of body fluid. The sensor has a measurement chamber plate that receives the sample of bodily fluid and a quantum cascade laser illumination source that generates an illumination light beam in the spectral range and transmits it to the measurement chamber plate. The illumination light beam at least partially illuminates the measurement chamber plate and the measurement chamber plate generates a reflection light beam in response to the illumination by the illumination light beam. The reflection light beam at least partially illuminates the sample of body fluid within the measurement chamber plate. An optical detector detects at least one property of the reflection light beam and generates a sensor signal dependent on the presence of the analyte. A controlled evaluates the sensor signal. A method using an inventive fully implantable sensor is also disclosed.



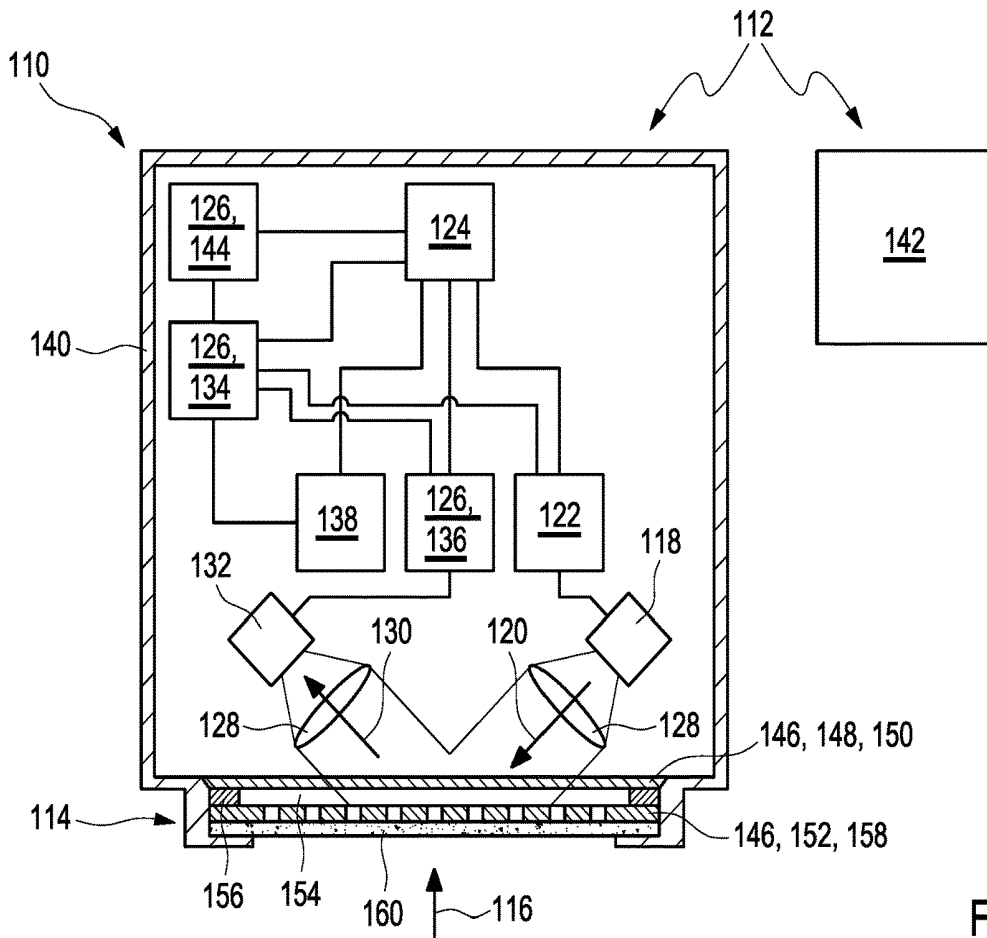


Fig. 1

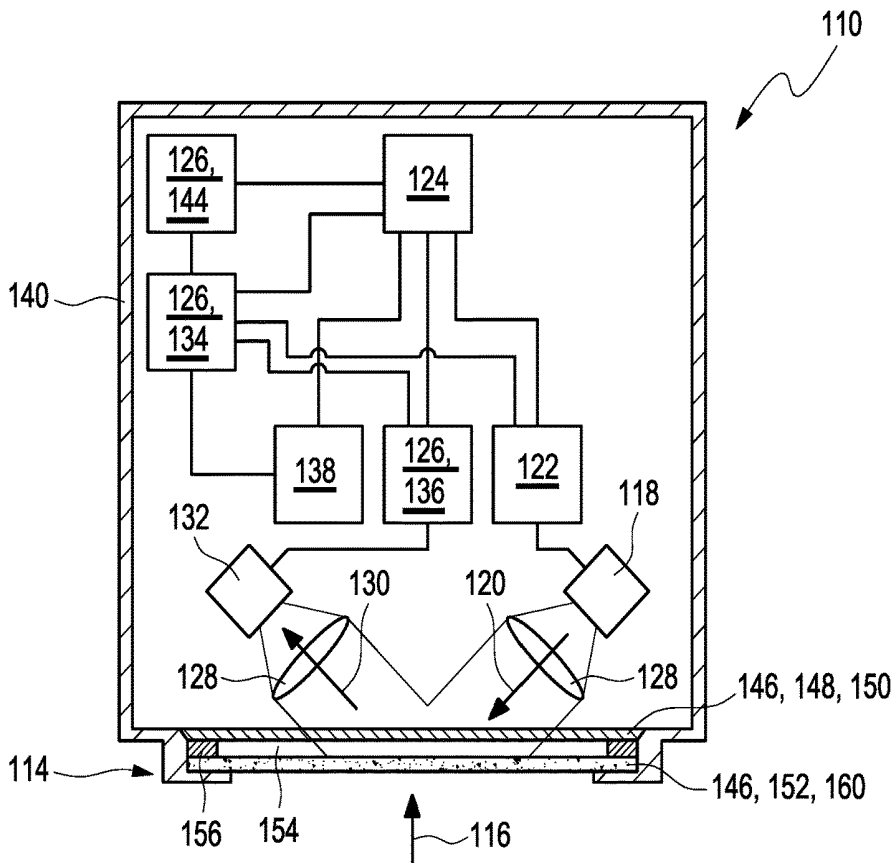


Fig. 2

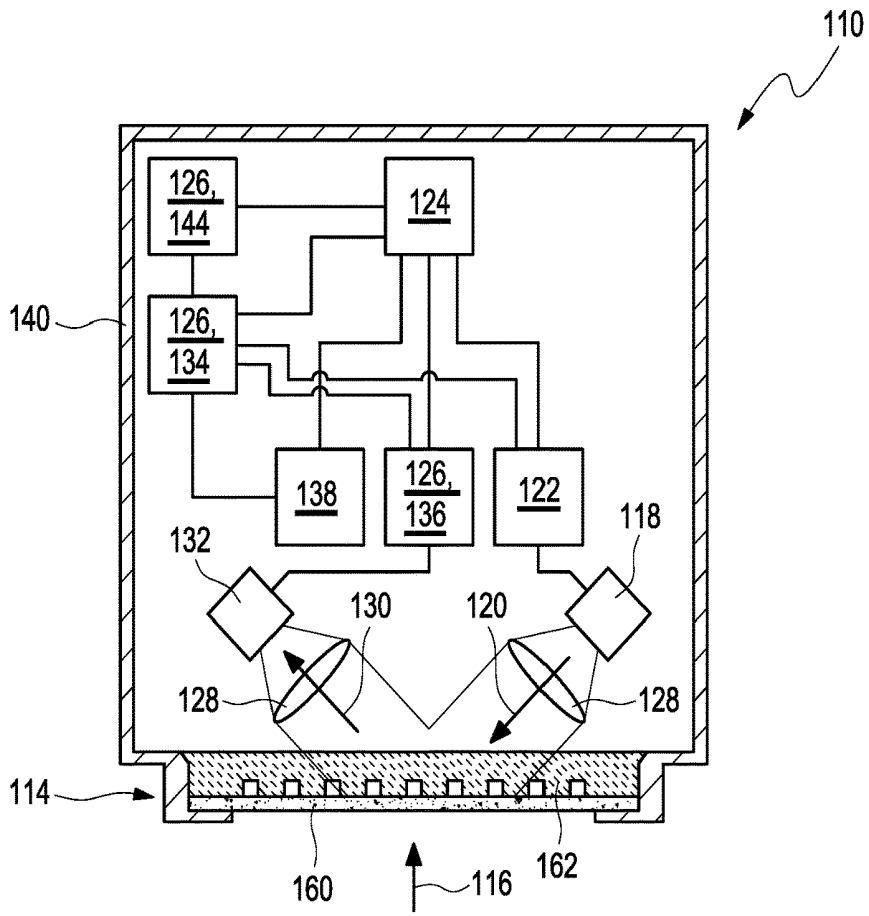


Fig. 3

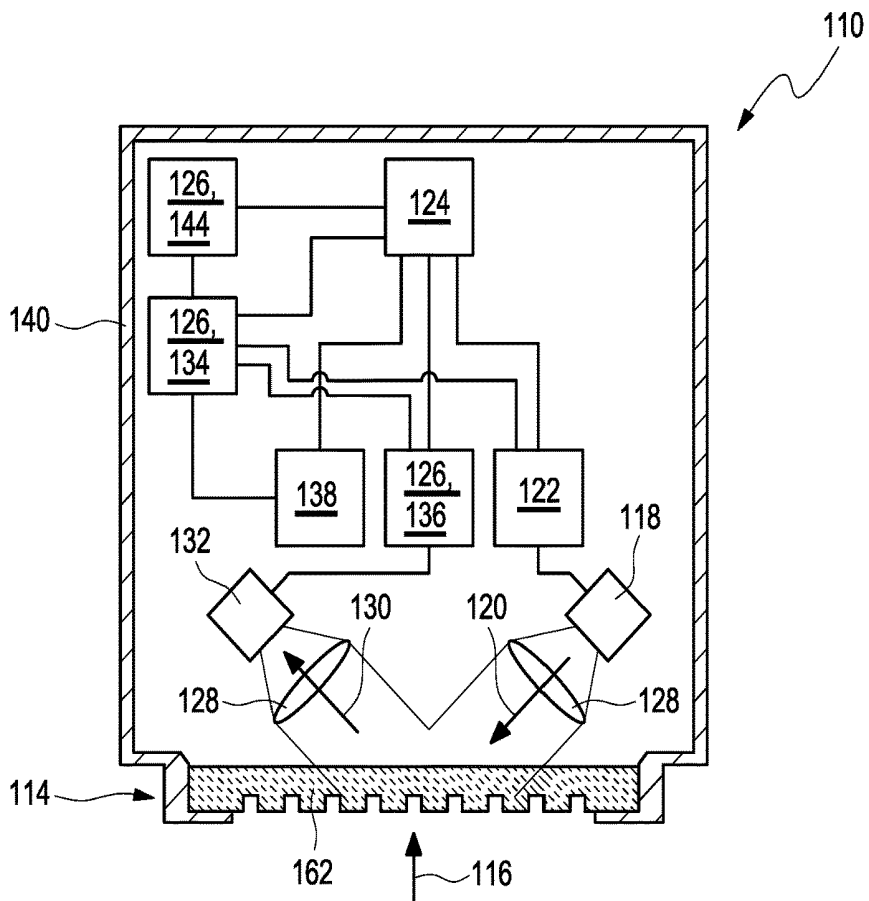


Fig. 4

**IMPLANTABLE SENSOR AND METHOD  
FOR DETECTING AT LEAST ONE ANALYTE  
IN A BODY FLUID**

RELATED APPLICATIONS

**[0001]** This application is a continuation of PCT/EP2018/051405, filed Jan. 22, 2018, which claims priority to EP 17 152 684.1, filed Jan. 23, 2017, the entire disclosures of each of which are hereby incorporated herein by reference.

BACKGROUND

**[0002]** This disclosure relates to an implantable sensor element and a kit for detecting at least one analyte in a body fluid as well as to a method for detecting at least one analyte. The devices and methods according to this disclosure may mainly be used for long-term monitoring of an analyte concentration in a body fluid, such as for long-term monitoring of a glucose level or of the concentration of one or more other types of analytes in a body fluid. This disclosure may both be applied in the field of home care and in the field of professional care, such as in hospitals. Other applications are feasible.

**[0003]** Monitoring certain body functions, more particularly monitoring one or more concentrations of at least one metabolite concentration in a body fluid plays an important role in the prevention and treatment of various diseases. Such metabolites can include by way of example, but not exclusively, blood glucose, lactate, cholesterol or other types of analytes and metabolites. Without restricting further possible applications, this disclosure will be described in the following text with reference to blood-glucose monitoring. However, additionally or alternatively, this disclosure can also be applied to other types of analytes.

**[0004]** Conventional devices for determining analyte concentrations are in many cases based on generating a sample of a body fluid, for example a drop of blood, which is then tested with respect to its analyte content. Continuous surveillance of the body's glucose concentration can significantly improve the treatment and precaution of long-term complications of diabetes patients. Typically devices for continuous glucose monitoring are meant for minimally-invasive short-term use, for example shorter than 14 days, and are based on an electrochemical detection scheme, in particular on the enzymatic digestion of glucose. Transcutaneous sensor systems typically imply a large number of technical challenges. Thus, a first challenge resides in the fact that the lifetime of a sensor is limited. A sensor is generally worn for approximately one week. After that, influences such as enzymes being used up and/or a sealing off in the body generally reduce the sensitivity of the sensor, or it is expected that the sensor fails. However, long-term continuous glucose monitoring, for example for terms of around one year, is desirable for several applications. Sensors for long-term monitoring based on optical systems are an area of current research.

**[0005]** Optical systems generally use at least one sensor material which changes at least one optically measurable property in the presence of one or more specific analytes. Alternatively absorption methods may be used. For example, U.S. Publication No. 2007/0004974 describes an apparatus for assaying an analyte in a body comprising: at least one light source implanted in the body controllable to illuminate a tissue region in the body with light at least

one wavelength that is absorbed by the analyte and as a result generates photoacoustic waves in the tissue region; at least one acoustic sensing transducer coupled to the body that receives acoustic energy from the photoacoustic waves and generates signals responsive thereto; and a processor that receives the signals and processes them to determine a concentration of the analyte in the illuminated tissue region.

**[0006]** In principle, sensors based on mid-infrared technology may be used for long-term continuous glucose monitoring. Mid-infrared radiation can be used for excitation of fundamental oscillation modes of biomolecules, such as for quantitative determination of glucose. Beside spectroscopic detection of glucose using photoacoustic and photothermal methods, quantitative determination of glucose may be performed via absorption spectroscopy. However, for in vivo measurements using mid-infrared radiation absorption spectroscopy skin heterogeneity and, because typically relative change of absorption spectrum due to glucose concentration is small, high absorption coefficient of water are major challenges.

**[0007]** Quantum cascade lasers (QCLs) are known as mid-IR radiation source with uniquely high spectral power density. Because of high spectral power density of QCLs the high absorption coefficient of water can be overcome by using QCLs and, thus, allowing quantitative determination of glucose. For example, C. Vrančić et al., "Continuous glucose monitoring by means of mid-infrared transmission laser spectroscopy in vitro", *Analyst*, 2011, 136, 1192-1198 and C. Vrančić et al., "A Quantitative Look Inside the Body: Minimally Invasive Infrared Analysis in Vivo", *Anal. Chem.*, 2014, 86 1836-1845 describe implantable fiber-based sensors using mid-infrared laser spectroscopy. Such fiber-based sensors comprise a fiber transmitting light in the mid-infrared spectral range and having a central cavity as measurement volume. Molecules of interstitial fluid are transported via diffusion into the measurement volume and can be determined quantitatively via an absorption measurement.

**[0008]** U.S. Pat. No. 8,040,526 B2 describes an implantable product which includes an optical cavity structure with first and second parts, each of which can operate as an optical cavity. The first part includes a container with at least one opening through which bodily fluid can transfer between the container's interior and exterior when the product is implanted in a body. The second part includes a container that is closed and contains a reference fluid. The implantable product can also include one or both of a light source component and a photosensing component. Photosensed quantities from the first part's output light can be adjusted based on photosensed quantities from the second part's output light. Both parts can have their light interface surfaces aligned so that they both receive input light from a light source component and both provide output light to a photosensing component.

**[0009]** U.S. Publication No. 2012/059232 A1 describes an apparatus including a support configured to be implanted within a body of a subject and a sampling region coupled to the support. The apparatus is configured to passively allow passage through the sampling region of at least a portion of fluid from the subject. The apparatus also includes an optical measuring device in optical communication with the sampling region. The optical measuring device comprises at least one light source configured to transmit light through at

least a portion of the fluid, and at least one sensor configured to measure a parameter of the fluid by detecting light passing through the fluid.

**[0010]** U.S. Publication No. 2008/231857 A1 describes a sensor system for detection of a gaseous chemical substance, which includes an optical sampling cell holding a sampling chamber of a volume of at most 20 mm<sup>3</sup>, a light emitter and a light receiver. The sampling cell is adapted for free-space, single monomodal propagation of the light beam.

**[0011]** U.S. Publication No. 2010/121163 A1 describes optical microneedles which are adapted for near-infrared or mid-infrared in vivo spectroscopic sensing; and provide a MEMS-based spectrometer for continuous lactate and glucose monitoring by means of a near-infrared or mid-infrared optical microneedle array in a transdermal patch.

**[0012]** However, despite the advantages of such known fiber-based sensors, fiber-based sensors have considerable disadvantages in practice. Optical fibers in practice have considerable sensitivity to mechanical influences, for example due to mechanical loads during implantation and/or removal and during wearing and monitoring in the body. Furthermore, sensor design of known fiber-based sensors leads to at least two permanent injuries of the skin for implantation which may limit wearing comfort and may permit ingress of contaminations. In addition, known fiber-based sensors require filtration of interstitial fluid for quantitative determination of glucose via infrared absorption spectroscopy in order to ensure functionality of the sensor. The measurement volume has to be membrane shielded and protected from macromolecules, for example by using a semipermeable membrane. However, implementation of such a membrane into the sensor design of known fiber-based sensors is difficult without increasing diffusion course and thus worsening response behavior of the sensor. Further, availability of such membranes is limited. Furthermore, known infrared fibers such as chalcogenide fibers, coated hollow fibers and silver halide fibers are cytotoxic and require a, e.g., polyethylene coating in order to be used in the body.

#### SUMMARY

**[0013]** This disclosure provides an implantable sensor element and methods for determining at least one analyte in a sample of body fluid, which avoid the above-described disadvantages of known sensors and methods. In particular, the implantable sensor element should permit reliable reagent-free continuous monitoring of glucose in a sample of body fluid and mechanical stability such as enhanced wearing comfort and reduced ingress of contaminations.

**[0014]** As used in the following, the terms “have,” “comprise” or “include” or any arbitrary grammatical variations thereof are used in a non-exclusive way. Thus, these terms may both refer to a situation in which, besides the feature introduced by these terms, no further features are present in the entity described in this context and to a situation in which one or more further features are present. As an example, the expressions “A has B,” “A comprises B” and “A includes B” may both refer to a situation in which, besides B, no other element is present in A (i.e., a situation in which A solely and exclusively consists of B) and to a situation in which, besides B, one or more further elements are present in entity A, such as element C, elements C and D or even further elements.

**[0015]** Further, as used in the following, the terms “preferably,” “more preferably,” “particularly,” “more particularly,” “specifically,” “more specifically” or similar terms are used in conjunction with optional features, without restricting alternative possibilities. Thus, features introduced by these terms are optional features and are not intended to restrict the scope of the claims in any way. The invention may, as the skilled person will recognize, be performed by using alternative features. Similarly, features introduced by “in an embodiment of the invention” or similar expressions are intended to be optional features, without any restriction regarding alternative embodiments of the invention, without any restrictions regarding the scope of the invention and without any restriction regarding the possibility of combining the features introduced in such way with other optional or non-optional features of the invention.

**[0016]** It shall be understood for purposes of this disclosure and appended claims that, regardless of whether the phrases “one or more” or “at least one” precede an element or feature appearing in this disclosure or claims, such element or feature shall not receive a singular interpretation unless it is made explicit herein. By way of non-limiting example, the terms “measurement chamber plate,” “illumination source” and “reflection light beam,” to name just a few, should be interpreted wherever they appear in this disclosure and claims to mean “at least one” or “one or more” regardless of whether they are introduced with the expressions “at least one” or “one or more.” All other terms used herein should be similarly interpreted unless it is made explicit that a singular interpretation is intended.

**[0017]** In a first aspect of this disclosure, an implantable sensor element for detecting at least one analyte in a sample of body fluid is disclosed.

**[0018]** The sensor element comprises at least one measurement chamber plate adapted to receive the sample of bodily fluid. The sensor element comprises at least one illumination source designed to generate at least one illumination light beam in at least one spectral range and to transmit the illumination light beam to the measurement chamber plate such that the illumination light beam at least partially illuminates the measurement chamber plate. The measurement chamber plate is designed to generate at least one reflection light beam in response to the illumination by the illumination light beam such that the reflection light beam at least partially illuminates the sample of body fluid within the measurement chamber plate. Preferably, the sample of body fluid may be illuminated at least twice within the measurement chamber plate. The sample may be illuminated, firstly, by the illumination light beam, for example in a first direction, and, subsequently, by the reflection light beam, for example, in a second direction.

**[0019]** The sensor element comprises at least one optical detector designed to detect at least one property of the reflection light beam and to generate at least one sensor signal dependent on the presence of the analyte. The sensor element furthermore comprises at least one control unit (also referred to as a “controller”) designed to evaluate the sensor signal.

**[0020]** As used herein, the term “implantable” refers to the fact that the sensor element is adapted to have appropriate dimensions to be inserted into the body tissue of the user, such as into subcutaneous tissue, and, further, that the sensor element is biocompatible in order to remain in the body tissue for an elongated time period, such as for several days

or even several weeks or several months. Thus, as an example, the sensor element may have a biocompatible coating and/or may be biocompatible. The term “implant” refers to the fact that the sensor element may be inserted fully or partially into the body tissue. Thus, in the following, the terms “implant” and “insert” will be used as synonyms. The sensor element is a fully implantable sensor element. The term “fully implantable” further refers to that the sensor element may be designed such that all parts of the sensor element can be fully implanted into the body tissue, in particular without any part of the sensor element protruding through the skin of the user, i.e., a full subcutaneous implantation. Generally, during implantation and/or during use of the sensor element, the sensor element may fully or partially penetrate the skin of the user. Thus, the sensor element preferably may be embodied as a fully implantable transcutaneous sensor element.

**[0021]** As used herein, the term “sensor element” generally refers to a unit, which may be handled as one entity, comprising the at least one measurement chamber plate, at least one illumination source, at least one optical detector and at least one control unit. The sensor element may be adapted to perform at least one absorption measurement.

**[0022]** As used herein, the term “detecting” refers to a quantitative and/or qualitative determination of an analyte concentration, i.e., a determination of the amount and/or concentration of the analyte in the body fluid and/or the response to the question of whether the analyte is present in the body fluid. As further used herein, the term “analyte” may refer to an arbitrary element, component or compound which may be present in a body fluid and the concentration of which may be of interest for a user. Preferably, the analyte may be or may comprise an arbitrary chemical substance or chemical compound which may take part in the metabolism of the user, such as at least one metabolite. As an example, the at least one analyte may be selected from the group consisting of glucose, cholesterol, triglycerides, lactate. Additionally or alternatively, however, other types of analytes may be used and/or any combination of analytes may be determined. As generally used within this disclosure, the term “user” may refer to a human being or an animal, independent from the fact that the human being or animal, respectively, may be in a healthy condition or may suffer from one or more diseases. As an example, the user may be a human being or an animal suffering from diabetes. However, additionally or alternatively, this disclosure may be applied to other types of users.

**[0023]** Generally, an arbitrary type of body fluid may be used. (The terms “body fluid” and “bodily fluid” are used synonymously herein.) Preferably, the body fluid is a body fluid which is present in a body tissue of the user, such as in the interstitial tissue. Thus, as an example, the body fluid may be selected from the group consisting of blood and interstitial fluid. However, additionally or alternatively, one or more other types of body fluids may be used. The body fluid generally may be contained in a body tissue. Thus, generally, the detection of the at least one analyte in the body fluid may preferably be determined in vivo.

**[0024]** The sensor element comprises at least one measurement chamber plate adapted to receive the sample of bodily fluid. As used herein, the term “measurement chamber plate” refers to an element adapted to receive the sample of body fluid having a sheet or plate-like geometry. The measurement chamber plate may have a flat geometry. The

measurement chamber plate may comprise a monolithic or a multi-plate setup. The sheet or plate-like structure geometry may enhance mechanical stability and thus robustness of a measurement signal. As further used herein, the term “receive” the sample of body fluid refers to the fact that the measurement chamber plate is adapted to one or more of permitting ingress of body fluid, contacting with body fluid and being in exchange with the body fluid. The measurement chamber plate may be designed such that the analyte concentration within the measurement chamber is adjusted and/or adapted, for example by diffusion processes, to the analyte concentration of the ambient body fluid. The measurement chamber plate may receive the sample of body fluid via diffusion processes. Filling the sample via diffusion processes may ensure maintenance-free operation of the implanted sensor element. The measurement chamber plate may comprise at least one hydrogel as diffusion permeable material.

**[0025]** The measurement chamber plate is designed to generate at least one reflection light beam in response to the illumination by the illumination light beam such that the reflection light beam at least partially illuminates the sample of body fluid within the measurement chamber plate. Preferably, the sample of body fluid is illuminated by the illumination light beam before the sample of body fluid is illuminated by the reflection light beam. The reflection light beam may be adapted to illuminate the sample of body fluid. The reflection light beam may illuminate a volume of the sample of body fluid. As used herein, the term “reflection light beam” refers to at least one light beam reflected by the measurement chamber plate. The measurement chamber plate may comprise at least one reflector element and/or may comprise a reflective material such as a reflective coating. The measurement chamber plate may be adapted to at least partially reflect the illumination light beam. The term “at least partially reflect” refers to a complete or partial reflection of the illumination light beam. For example, the measurement chamber plate, in particular at least one reflector of the measurement chamber, may be adapted to reflect more than 20% of the illumination light beam, preferably more than 50% of the illumination light beam, most preferably more than 80% of the illumination light beam. As further used herein, the term “at least partially illuminates the sample of body fluid” refers to the fact that the reflection light beam may completely or partially illuminate the sample of body fluid. For example, the reflection light beam may illuminate more than 5% of the sample of body fluid, preferably more than 10%, more preferably more than 25% of the sample of body fluid. However, other embodiments are feasible. The measurement chamber plate may be designed such that the reflection light beam illuminates a volume of the sample as large as possible.

**[0026]** The measurement chamber plate may comprise at least one membrane element. The membrane element may be adapted to protect the measurement chamber plate from penetration of particles above a certain size such as large sized molecules like proteins and/or cells like leukocytes.

**[0027]** The measurement chamber plate may comprise at least one chamber wall, wherein the chamber wall is adapted to receive the sample of body fluid. The sensor element may be adapted to perform at least one measurement based on absorption spectroscopic techniques using a miniaturized fluid cell. The measurement chamber plate may be adapted to receive a sample size of body fluid such that a reliable

absorption measurement can be performed. For example, a layer thickness of body fluid in the measurement chamber plate may be between 1  $\mu\text{m}$  and 100  $\mu\text{m}$ , preferably between 5  $\mu\text{m}$  and 50  $\mu\text{m}$ , more preferably the layer thickness may be between 8  $\mu\text{m}$  and 15  $\mu\text{m}$ . For example, the layer thickness may be 10  $\mu\text{m}$  in order to ensure high sensitivity to detect glucose in aqueous solution. The chamber wall may be adapted to have a first side at least partially permeable to light, for example in the infrared spectral range, and a second side at least partially permeable to the sample of body fluid. As used herein, "permeable to light" refers to at least partially permit a light beam, for example the illumination light beam and/or the reflection light beam, to pass through. Thus, the first side of the chamber wall may be at least partially transparent. As used herein, "permeable to the sample of body fluid" refers to at least partial permit ingress into and/or permit pass through the sample of body fluid into the measurement chamber wall. The chamber wall may be arranged such that the side permeable to the sample of body fluid faces an exterior of the sensor element.

**[0028]** For example, the measurement chamber plate may comprise at least one first chamber wall adapted to be at least partially transparent to the illumination light beam. The first chamber wall may be designed as at least one at least partially transparent first infrared window. The first chamber wall may be arranged facing an interior of the sensor element such as an interior surrounded by a housing of the sensor element. The first chamber wall may face the illumination light beam. The first infrared window may be designed to let at least partially the illumination light beam through the infrared window to the sample of body fluid. For example, the infrared window may be designed to let at least partially the illumination light beam pass through the infrared window into the measurement chamber plate. The first chamber wall may be designed as transmission window. The first chamber wall may be a light-permeable inner plate. The first chamber wall may be biocompatible. The first chamber wall may comprise and/or may be produced from at least one biocompatible material. The first chamber wall may consist fully of biocompatible material, for example a biocompatible material comprising at least one synthetic diamond or silicon. The first chamber wall may comprise at least one anti-reflective coating adapted to minimize reflections from a surface of the first chamber wall to the optical detector and/or reflections of the reflected beam back into the measurement chamber plate for example in order to minimize interference effects on the signal. The first chamber wall may comprise at least one micro-structured surface, e.g., roughened surface adapted to minimize reflections from a surface of the first chamber wall to the optical detector and/or reflections of the reflected beam back into the measurement chamber plate for example in order to minimize interference effects on the signal.

**[0029]** The measurement chamber plate may comprise at least one second chamber wall adapted to at least partially receive the sample of body fluid. The second chamber wall may be a fluid-permeable outer plate. The measurement chamber plate may comprise at least one capillary element arranged between the first chamber wall and the second chamber wall. The capillary element may be adapted to receive the sample of body fluid. As used herein, the term "capillary element" generally refers to an element which forms at least a part of a cuvette, cell or cavity for receiving and/or storage of the sample of body fluid. The receiving of

the sample of body fluid may be supported by capillary forces. The first and the second chamber walls may be arranged at opposing sides of a capillary element and form a measurement cuvette. The capillary element may be designed to receive an amount of body fluid required for reliable determination of the analyte. In order to obtain a maximum sensitivity of glucose in aqueous solution the capillary element may be designed to receive a fluid layer thickness between 1 to 100  $\mu\text{m}$ , preferably between 5  $\mu\text{m}$  and 50  $\mu\text{m}$ , more preferably between 8  $\mu\text{m}$  and 15  $\mu\text{m}$ . For example, the capillary element may be designed to receive a fluid layer thickness of 10  $\mu\text{m}$ . The capillary element may receive the sample of body fluid via diffusion processes. In order to ensure suitable sensor response behavior, the capillary element may be designed such that diffusion distances are as short as possible, preferably around 100  $\mu\text{m}$ .

**[0030]** The measurement chamber plate may comprise at least one spacer element arranged between the first chamber wall and the second chamber wall. As used herein, the term "spacer element" refers to an arbitrary shaped element adapted to adjust a distance between the first and second chamber walls. The spacer element may have an arbitrary shape, for example the spacer element may be at least one ring. The spacer element may have a thickness between 1 and 100  $\mu\text{m}$ . The spacer element may be a cut polyester film. Additionally or alternatively, one of the first and the second chamber walls may comprise at least one cavity and/or recess, for example produced by photolithographic methods, adapted to form a capillary element.

**[0031]** The second chamber wall may be designed to be rigid against mechanical influence, for example, during assembling of the sensor element, such that a constant measurement volume can be ensured. The second chamber wall may be designed to be permeable to the analyte, for example, to glucose, such that the analyte can reach the measurement chamber plate. The second chamber wall may be designed to prevent large-sized molecules and/or cells to penetrate into the measurement chamber plate.

**[0032]** The second chamber wall may be designed as at least one at least partially reflective second infrared window. The second infrared window may comprise at least one reflective layer, for example a gold layer. The reflective layer may be arranged on at least one side of the second infrared window facing the illumination light beam in order to enhance reflection of the illumination light beam. The second infrared window may be designed to permit transport, for example by diffusion, of the analyte into the capillary element. The second infrared window may be a fluid-permeable outer plate. The second infrared window may comprise a plurality of holes. The second infrared window may comprise a plurality of micro fluid channels. For example, the holes may be drilled micro holes having diameter less than 100  $\mu\text{m}$ , preferably less than 20  $\mu\text{m}$ , more preferably less than 10  $\mu\text{m}$ . An average distance between two holes may be less than 500  $\mu\text{m}$ , preferably less than 200  $\mu\text{m}$ , more preferably less than 100  $\mu\text{m}$ . A thickness of the second infrared window may be less than 1000  $\mu\text{m}$ , preferably less than 500  $\mu\text{m}$ . Such dimensions may ensure short diffusion times of glucose from interstitial fluid into the capillary element. The holes may have other shapes as for example slits or bendings. The holes may be produced using laser processing techniques or other methods known in the art, for example wet etching. The second infrared window may be or may comprise a silicon plate having a plurality of

holes. Such a design can ensure proper rigidity. The silicon plate may be sputtered with a gold layer in order to enhance reflectivity. The second chamber wall may have a hydrophilic surface structure on one side and/or on the other side and/or in the holes of the wall adapted to have better fluidic properties. This hydrophilic surface may be made by a microfabricated surface for example by photolithographic or wet etching methods.

**[0033]** The measurement chamber plate may comprise further membrane elements such as flat membrane elements. The flat plate design of the measurement chamber plate may allow simple mounting of the flat membrane element. In case of using the flat membrane element, the diffusion distance may be enhanced only slightly by the thickness of the flat membrane. The further membrane element may be arranged on the side of the second infrared window and/or of the membrane element receiving the sample of body fluid. The further membrane element may be an ultra filtration membrane. The further membrane element may be adapted to reduce influence from proteins on the absorption measurement. Additionally or alternatively to a further membrane element, the holes of the second infrared window may be designed such that the second infrared window functions as membrane such that no additional membrane element is required.

**[0034]** The second chamber wall may comprise the at least one membrane element. The second chamber wall may be designed as membrane element. Additionally or instead of the second infrared window, the second chamber wall may be or may comprise the at least one membrane element. The membrane element may have reflective properties. For example, the membrane element may comprise at least one sintered metal. The membrane element may be sputtered with a reflective layer such as a gold, silver or aluminum layer to enhance reflectivity. For example, the membrane element may be selected from the group consisting of a track-etched membrane comprising polycarbonate; an Anodisc membrane comprising aluminum oxide; a membrane having a supporting structure such as a polymeric microporous membrane available from Precision Membranes, LLC; a high-aspect-ratio membrane comprising silicon and/or carbon available from Precision Membranes, LLC; a porous membrane comprising sintered metal. In one embodiment, the membrane element may be a membrane having a supporting structure such as a polymeric microporous membrane available from Precision Membranes, LLC. The supporting structure may be adapted to provide rigidity to the measurement chamber plate. The membrane element having a supporting structure may have a thickness of several 10  $\mu\text{m}$  such that the membrane element can be used as spacer element. In a further embodiment, the membrane element may be a high-aspect-ratio membrane comprising silicon and/or carbon available from Precision Membranes, LLC. The high-aspect-ratio membrane may have a reflective coating, for example the membrane element may be sputtered with a gold layer. The membrane element may have a reflective coating, for example, the membrane element may be sputtered with a gold layer. However, embodiments are feasible, without a reflective coating, e.g., a porous membrane comprising sintered metal has reflective properties in the infrared spectral range.

**[0035]** The measurement chamber plate may comprise at least one attenuated total reflection element. The attenuated total reflection element may comprise at least one ATR-

crystal, for example an ATR-crystal available from ATR Elements. The ATR-crystal may comprise a structured surface. The ATR-crystal may comprise at least one microstructure adapted to receive the sample of body fluid. The microstructure may enhance amplification of the sensor signal compared to ATR-crystals without microstructures. The microstructure may be adapted as capillary, wherein the receiving of the sample of body fluid may be supported by capillary forces. The microstructure may have hydrophilic properties such that the microstructure is adapted to draw out the body fluid when in contact with the interstitial fluid. Thereby a transition layer may be formed having a fixed thickness in which the reflection measurement can be performed. The ATR-crystal may be arranged such that the illumination light beam is at least reflected once. Preferably, the illumination light beam may be reflected several times within the ATR-crystal. The illumination light beam may be collimated by the at least one transfer device, and may impinge on the ATR-crystal. The ATR-crystal may be designed such that the illumination light beam is reflected by an area of the ATR-crystal comprising the body fluid. The ATR-crystal may be biocompatible. The ATR-crystal may comprise or may be produced from biocompatible material, for example silicon or diamond. The ATR-crystal may be adapted to reflect the light beam such that it illuminates the optical detector, for example after being collimated by at least one further transfer device. At least one ultra filtration membrane element may be arranged on the ATR-crystal.

**[0036]** The sensor element comprises at least one illumination source designed to generate at least one illumination light beam in at least one spectral range and to transmit the illumination light beam to the measurement chamber plate such that the illumination light beam at least partially illuminates the measurement chamber plate. As used herein, the term "light" generally refers to electromagnetic radiation in one or more of the visible spectral range, the ultraviolet spectral range and the infrared spectral range. The term visible spectral range generally refers to a spectral range of 380 nm to 780 nm. The term infrared (IR) spectral range generally refers to electromagnetic radiation in the range of 780 nm to 1000  $\mu\text{m}$ , wherein the range of 780 nm to 2.5  $\mu\text{m}$  is usually denominated as the near-infrared (NIR) spectral range, and the range from 2.5  $\mu\text{m}$  to 1000  $\mu\text{m}$  as the far-infrared (FIR) spectral range. The term mid-infrared (MIR) spectral range refers to the range from 2.5 to 25  $\mu\text{m}$ . Preferably, light as used within this disclosure is light in the mid-infrared spectral range. As used herein, the term "light beam" generally refers to an amount of light emitted into a specific direction. Thus, the light beam may be a bundle of the light rays having a predetermined extension in a direction perpendicular to a direction of propagation of the light beam.

**[0037]** As further used herein, the term "illumination source" refers to at least one device adapted to generate at least one light beam. As used herein, the term "illumination light beam" refers to a light beam generated by the illumination source.

**[0038]** The illumination source may comprise at least one light source. The illumination source may be a mid-IR radiation source. The illumination source may have a high spectral power density. The illumination source may be adapted for quantitative determination of glucose in an aqueous solution. The illumination source comprises at least one quantum cascade laser. For example, the illumination

source may comprise at least one quantum cascade laser chip. The quantum cascade laser may be a miniaturized quantum cascade laser. The quantum cascade laser may be selected from the group consisting of: at least one fixed-frequency Fabry-Pérot quantum cascade laser; at least one tunable external cavity quantum cascade laser; at least one distributed feedback quantum cascade laser. For example, the illumination source may comprise at least one array of quantum cascade lasers. The illumination source may be designed to be operated in pulsed or continuous mode. The sensor element may comprise at least one pulser device adapted to operate the illumination in the pulsed mode. The control unit may be adapted to control the pulser device. The sensor element may comprise at least one rechargeable energy storage device, for example at least one lithium-ion battery, adapted to supply energy to the quantum cascade laser. The quantum cascade laser may have a low power consumption such that power supply by lithium-ion battery is possible.

**[0039]** The illumination light beam may have a wavelength in the infrared spectral range, preferably in mid-infrared spectral range. The illumination source may be adapted to generate broadband illumination light or illumination light having a narrow bandwidth. The illumination source may be adapted to change the wavelength continuously over time. The illumination source may be adapted to generate a plurality of illumination light beams, wherein each of the illumination light beams has a different wavelength. The control unit may be adapted to one or more of assign, adjust or select the wavelength of the illumination light beams. For example, the illumination source may comprise at least one tunable distributed feedback quantum cascade laser and/or at least one tunable external cavity quantum cascade laser having a narrow bandwidth. The control unit may be adapted to change the wavelength continuously or non-continuously, for example within the mid-infrared spectral range. The control unit may be adapted to adjust and/or select wavelengths suitable for identification of glucose and/or distinction of glucose from further substances in the sample of body fluid, for example substances present even after filtration such as maltose. Additionally or alternatively, a broadband spectral range is used. For example, the illumination source may comprise at least one Fabry-Pérot quantum cascade laser. In order to permit absorption measurements with a broadband illumination source, the sensor element may comprise several optical detectors and suitable spectral bandpass filters or at least one tunable optical detector having at least one tunable, spectral bandpass filter. The control unit may be adapted to rapidly switch between several different illumination light beams and/or several detectors to probe different spectral regions.

**[0040]** As used herein, the term “at least partially illuminates the measurement chamber plate” refers to the fact that the illumination light beam may completely or partially illuminate the measurement chamber plate. The illumination light beam may, preferably, at least partially illuminate the sample of body fluid within the measurement chamber plate. For example, the illumination light beam may illuminate more than 5% of the measurement chamber plate, preferably more than 10% of the measurement chamber plate, more preferably more than 25% of the measurement chamber plate. However, embodiments are feasible. The illumination light beam may illuminate the measurement chamber plate under an illumination angle between  $0^\circ$  and  $85^\circ$ , preferably

between  $20^\circ$  and  $60^\circ$ , more preferably between  $30^\circ$  and  $50^\circ$ . For example, the illumination angle may be  $45^\circ$ . The term “illumination angle” refers to an angle between an axis of incidence, i.e., a line perpendicular to a surface on which the illumination light beam impinges, and the illumination light beam.

**[0041]** The sensor element may comprise at least one modulation device for modulating the illumination light beam. The term “modulating of the illumination” should be understood to mean a process in which a total power of the illumination is varied, for example, with one or a plurality of modulation frequencies. For example, the modulation device may be designed for a periodic modulation, for example a periodic beam interrupting device. The modulation can be effected for example in a beam path between the illumination source and the measurement chamber plate. For example the at least one modulation device may be arranged in said beam path. The modulation device may be based on an electro-optical effect. The at least one modulation device may comprise, for example, a mechanical shutter and/or a beam chopper or some other type of beam interrupting device. Alternatively or additionally, however, it is also possible to use one or a plurality of different types of modulation devices. The modulation device may comprise at least one filter element, for example at least one polarizer. In one embodiment, the illumination source itself can also be designed to generate a modulated illumination. For example, the illumination source may be embodied as a pulsed illumination source, for example as a pulsed laser. Thus, by way of example, the at least one modulation device can also be wholly or partly integrated into the illumination source.

**[0042]** The sensor element may comprise at least one transfer device. The transfer device may be adapted to collimate the illumination light beam and/or the reflection light beam. The transfer device may comprise at least one optical lens, such as one or more convex lenses, one or more refractive lenses, one or more collimating lenses. For example, the transfer device may be arranged such that the illumination light beam travels first through the at least one transfer device and thereafter to the measurement chamber plate. The sensor element may comprise at least one further transfer which may be arranged such that the reflected light beam travels from the measurement chamber plate to the further transfer device until it may finally impinge on the optical detector. As used herein, the term “transfer device” refers to an optical element which may be configured to transfer the illumination light beam from the illumination source to the measurement chamber plate and/or from the measurement chamber plate to the optical detector.

**[0043]** The sensor element comprises at least one optical detector designed to detect at least one property of the reflection light beam and to generate at least one sensor signal dependent on the presence of the analyte. As used herein, the term “optical detector” refers to a device which is adapted for detecting at least one property of a light beam. As used herein, the term “sensor signal” generally refers to an arbitrary signal indicative of the presence of the analyte. As an example, the sensor signal may be or may comprise a digital and/or an analog signal. As an example, the sensor signal may be or may comprise a voltage signal and/or a current signal. Additionally or alternatively, the sensor signal may be or may comprise digital data. The sensor signal may comprise a single signal value and/or a series of signal values. The sensor signal may further comprise an arbitrary

signal which is derived by combining two or more individual signals, such as by averaging two or more signals and/or by forming a quotient of two or more signals. The optical detector may comprise at least one photodetector. The optical detector may comprise at least one pyroelectric detector. The optical detector may comprise at least one spectrometric setting, for example at least one Fabry-Pérot interferometer. The optical detector may comprise at least one analog and/or digital amplifier and/or filter in order to for example amplify at least one property of the reflection light beam and/or reduce noise. As used herein, the term “at least one property of the reflection light beam” refers to one or more of intensity, absorbance, attenuation, transmission, reflection, wavelength and frequency of the reflection light beam. The at least one property of the reflection light beam, for example the intensity, may change due to the presence of the analyte and/or other substances in the sample of body fluid. The optical detector may be adapted to determine a change in intensity, for example due to the presence of the analyte and/or other substances in the sample of body fluid. The sensor element may be adapted to perform one or more of at least one reflection measurement, at least one absorption measurement, at least one attenuated total reflectance measurement. The optical detector may be adapted to determine at least one absorption information and/or attenuation information as a function of wavelength and/or frequency of the reflection light beam. The optical detector may be adapted to determine at least one spectrum, for example at least one absorbance spectrum, of the reflection light beam.

**[0044]** The sensor element furthermore comprises at least one control unit designed to evaluate the sensor signal. As used herein, the term “control unit” generally refers to an arbitrary element which is adapted to evaluate the sensor signal. The control unit may be adapted for one or more of processing, analyzing, and storing of the sensor signal. The control unit may be a central control unit. The term “data” or “measurement data” refers to both raw sensor signal and processed sensor signal. As further used within this disclosure, the term “measurement data” refers to arbitrary data acquired by using the sensor element, indicative of the analyte concentration. The data may specifically comprise a plurality of measurement values acquired at subsequent points in time, such as over a time period of several hours, several days, several weeks or even several months. The data preferably may be acquired in an analogue or digital electronic format. The data further may be processed or pre-processed within the control unit, such as by applying at least one evaluation or pre-evaluation algorithm to the data. Thus, as an example, at least one algorithm may be applied to the data, wherein the at least one algorithm transforms primary data acquired by using the optical detector into secondary data indicating the concentration of the analyte in the body fluid, such as by applying a known or predetermined relationship between the primary data and the analyte concentration to the primary data, thereby generating secondary data. Here and in the following, no difference will be made between primary data and secondary data. The control unit may comprise at least one evaluation device designed to evaluate the sensor signal. The evaluation device may be designed to generate at least one information on the analyte by evaluating the sensor signal. As an example, the evaluation device may be or may comprise one or more integrated circuits, such as one or more application-specific integrated circuits (ASICs), and/or one or more data processing

devices, such as one or more computers, preferably one or more microcomputers and/or microcontrollers. Additional components may be comprised, such as one or more pre-processing devices and/or data acquisition devices, such as one or more devices for receiving and/or preprocessing of the sensor signals, such as one or more AD-converters and/or one or more filters. Further, the evaluation device may comprise one or more data storage devices. Further, the evaluation device may comprise one or more interfaces, such as one or more wireless interfaces and/or one or more wire-bound interfaces. As used herein, the term “at least one information on the analyte” refers to quantitative and/or qualitative information on the analyte. For example, the evaluation device may be adapted to determine at least one spectral information of the reflection light beam from the sensor signal. The spectral information may be at least one absorption spectrum or at least one attenuation spectrum. For example, spectra may be acquired by continuously changing the laser’s wavelength over time and measuring the sensor signal on the optical detector. The difference in absorbance  $\Delta A$  can be calculated using water as a reference,  $I_{ref}$  by

$$\Delta A = -\log[(I_{meas})/(I_{ref})],$$

with  $I_{meas}$  being the sensor signal seen.

**[0045]** The evaluation device may be adapted to determine the analyte concentration by evaluating the spectral information. The evaluation device may be designed to identify characteristic spectral signature of molecules in the mid-infrared spectral range. The evaluation device may be adapted to compare the measured spectral information with predetermined or theoretical spectral information stored, for example, in an electronic table such as in at least one look-up table. The evaluation device may be adapted to determine from the spectral information the at least one information on the analyte by using uni- or multivariate data analysis, e.g., principle component regression (PCR) and partial least square regression (PLS). The evaluation device may be adapted to detect and potentially quantify a variety of biomolecules using uni- or multivariate data analysis. For example, the evaluation device may be adapted to determine the presence and/or concentration of glucose. The evaluation device may be adapted to identify and/or determine a relevant signal or signal component, for example a signal referring to glucose, and to distinguish the relevant signal from signals of interfering molecules. The evaluation device may be adapted to distinguish the relevant signal from other signal influences such as from signal influences due system changes such as temperature.

**[0046]** The control unit, for example the evaluation device, may comprise at least one or more of amplifier circuits adapted to amplify the sensor signal and/or to transform the sensor signal into an electrical current or voltage; at least one analog-/digital converter adapted to digitalize the sensor signal, for example the amplified sensor signal; at least one digital filter adapted to optimize a signal-to-noise ratio such as at least one Lock-In amplifier and/or at least one Boxcar integrator; at least one analog filter adapted to filter the sensor signal, for example before digitalization; at least one memory unit adapted to store the sensor signal, for example the raw sensor signal and/or the evaluated, for example digitalized and/or amplified, sensor signal. As used herein, a “memory unit” generally may refer to an arbitrary device adapted for collecting and preferably

storing data such as measurement data. Thus, the memory unit generally may comprise at least one data storage device such as at least one volatile and/or at least one non-volatile data storage element. The components listed above may be designed as separate components within a housing of the sensor element. Alternatively, two or more of the components as listed above may be integrated into one component. For example, the optical detector may comprise an integrated amplifier circuit and/or one or more signal filters. Additionally or alternatively, one or more of these components may be provided in a further device situated outside the body of the user. The sensor element can be adapted to transfer data, such as the raw sensor signal and/or the evaluated sensor signal, automatically and/or upon request to the further device for evaluation and data storing. The control unit can be designed to receive instructions and/or data, for example from the further device, contactless, for example via the inductive connection. The sensor element and the further device may be adapted to communicate, i.e., transfer data and instructions, wirelessly such as by an inductive connection. Other ways of data transfer, however, are feasible. The control unit may comprise at least one communication unit for wireless communication. Read-out of the measurement data from the sensor element may be performed wireless such that wearing comfort and freedom of movement is enhanced.

**[0047]** The evaluation device may be adapted to perform a temperature correction. The sensor signal may be influenced due to temperature changes such that drifts in signal may occur. The evaluation device may be adapted to distinguish signal drift due to temperature change from signal drift due to changes in analyte concentration by using spectral information. The temperature influence may be corrected using calibration data from a prior temperature calibration measurement. Additionally or alternatively, the sensor element may comprise at least one temperature sensor as for example a platinum resistance thermometer. The temperature sensor may be arranged in close proximity to the measurement chamber plate. The temperature influence may be corrected using calibration data from a prior temperature calibration measurement and the measured temperature of the temperature sensor.

**[0048]** The sensor element may comprise at least one housing adapted to encapsulate the further components of the sensor element such as the illumination source, the control unit and the optical detector. The housing may allow complete or at least partial implantation of the sensor element within the body of the user. Thus, the housing may prevent permanent open skin barrier and thus, the housing may prevent penetration of bacteria and other contaminations in the body. The housing may be designed to prevent contamination of the sensor element, for example with dirt and moisture. The housing may be biocompatible in order to reduce and/or minimize specific immune reactions. The housing may comprise and/or is produced from biocompatible material. For example, the biocompatible material may comprise titanium alloy.

**[0049]** The sensor element may comprise at least one rechargeable energy storage device. The rechargeable energy storage device may be adapted to supply voltage for one or more of the sensor element such as to illumination source, the control unit, in particular the amplifier circuit, and the optical detector, pulser device etc. The control unit may be adapted to control power supply to the components

of the sensor element. For example, the control unit may be adapted to control power supply to one or more of the optical detector such as to the amplifier circuit, the illumination source such as the pulser device. The rechargeable energy storage device may be adapted to be charged in a contactless fashion. For example, the rechargeable energy source may be adapted to be charged wirelessly such as by an inductive connection. Other ways of recharging, however, are feasible. Charging in a contactless fashion may allow long-term operation without surgical interventions. The rechargeable energy storage device may comprise at least one lithium-ion battery. The rechargeable energy storage device may be charged by using the further device situated outside the body of the user such as by using a docking station or the like. For example, the further device may be designed to be worn by the user. The further device may comprise at least one further rechargeable energy storage device. The further rechargeable energy storage device may be adapted to be charged using at least one cable. The further device may be adapted to bring a demand for recharging the rechargeable energy storage device of the sensor element to a user's attention, such as in one or more of a visual fashion, an acoustic fashion or a vibrational fashion. Thus, as an example, the further device may be adapted to provide at least one of a visual indication, such as a display of an appropriate message, and/or an acoustic indication, such as a warning sound or a voice message, and/or a vibrational indication, such as a vibrational alarm, to a user, in order to indicate to the user that a recharging of the rechargeable energy storage device is required. As used herein, a "demand for recharging" generally may be or may comprise an arbitrary item of information regarding one or both of a status of charge of the at least one rechargeable energy storage and/or an information indicating that a recharging of the rechargeable energy storage device is necessary in order to maintain an operation of the sensor element. A "demand", as used in the context of this disclosure, thus generally may refer to an arbitrary item of information from which a necessity for recharging the rechargeable energy storage device may be deduced.

**[0050]** The sensor element may comprise at least one measurement channel and at least one reference channel. The measurement channel may be designed to determine the concentration of the analyte. Thus, the measurement channel may comprise at least the measurement chamber plate adapted to receive the sample of body fluid. The reference channel may be designed to determine at least one correction information. The reference channel may comprise at least one reference measurement chamber adapted to receive at least one reference sample, for example water. The reference measurement chamber may not be permeable to fluids. The reference measurement chamber may be designed to prevent ingress of the sample of body fluid into the reference measurement chamber. The reference channel may have known or pre-determined beam path of reference illumination light beam and/or reference reflection light beam. The beam paths of the reference illumination light beam and/or reference reflection light beam may be identical or similar to beam path of illumination light beam and/or reflection light beam. The reference measurement chamber may have known or pre-determined layer thickness. The reference measurement chamber may have identical or similar layer setup and/or thickness compared to the measurement chamber plate. The at least one correction information may be

determined simultaneously or independent from the determination of the analyte. The correction information may comprise at least one information about a drift correction and/or temperature correction. The evaluation device may be adapted to correct the measurement data dependent on the correction information.

**[0051]** In a further aspect of this disclosure, a kit for detecting at least one analyte in a sample of body fluid is disclosed. The kit comprises at least one implantable sensor element according to this disclosure and at least one further device. The further device is adapted to provide energy to at least one rechargeable energy storage device. For further details concerning this aspect of this disclosure, reference may be made to the description of the other aspects of the implantable sensor element as provided above and/or below.

**[0052]** As used herein, a “kit” is an assembly of a plurality of components, wherein the components each may function and may be handled independently from each other, wherein the components of the kit may interact to perform a common function. Thus, the kit may comprise a plurality of components, wherein each component may be handled individually, independent from the other components and may perform at least one function independently, wherein, further, all components or groups of components comprising at least two of the components may be combined, such as by physically connecting these components, in order to perform a common function implying functionality from the connected components. The kit comprises the above-mentioned components, i.e., the at least one implantable sensor element and the at least one further device. As used herein, the term “further device” generally may refer to an arbitrary module of the kit which may be handled independently from the sensor element. The further device may be adapted to fulfill at least one function, such as an analytical function and/or an electrical function and/or a medical function and/or computational function. The components of the kit may be handled independently from each other, i.e., each of the components may have at least one state in which the respective component is not mechanically connected to any other component. Further, each of the components of the kit may have an individual function, such as a measurement function, a data storage function and a data transmission function, which may be exerted independently from the presence of other components. The further device may be situated outside the body of the user, for example the further device may rest on the skin of the user or may be worn by the user. The further device may be adapted to be placed on a skin or an out-of-body surface of the user. Thus, the further device may be an external, extracorporeal device. With respect to the definitions and embodiments of the further device reference is described to definitions and embodiments of the further device described with respect to the first aspect of this disclosure.

**[0053]** The at least one further device may be adapted to provide electrical energy to the rechargeable energy storage device in a contactless fashion, for example via the inductive connection. Other ways of recharging, however, are feasible. The sensor element and the kit may be adapted to provide a concept of recharging on-demand for the rechargeable energy storage device and thus, allowing long-term operation.

**[0054]** The at least one further device may comprise at least one portable data management device. The portable data management device may be adapted to directly or

indirectly receive the measurement data and to at least partially display data on at least one display. The term “data management device,” as used herein, refers to a device adapted to handle measurement data, such as by storing the measurement data and/or subjecting the measurement data to at least one data evaluation algorithm. Thus, as an example, the data management device may have at least one algorithm for displaying the measurement data, such as by displaying the measurement data on a display device, thereby displaying one or more measurement curves. Additionally or alternatively, averaging algorithms may be applied to the measurement data and/or one or more algorithms adapted to give medical advice to the user. Further, the portable data management device may comprise one or more databases, such as for storing and/or comparing measurement data.

**[0055]** The at least one further device may comprise at least one data reader module adapted to receive measurement data transmitted by the implantable sensor element via wireless communication. The data reader module may comprise at least one data storage device and may be adapted to store the measurement data.

**[0056]** In a further aspect of this disclosure, a method for determining a concentration of at least one analyte in a body fluid of a user is disclosed. The method comprises the following method steps:

**[0057]** receiving the sample of body fluid in at least one measurement chamber plate,

**[0058]** generating at least one illumination light beam in at least one spectral range by using at least one illumination source and transmitting the illumination light beam to the measurement chamber plate;

**[0059]** at least partially illuminating the measurement chamber plate with the illumination light beam;

**[0060]** generating at least one reflection light beam in response to the illumination by the illumination light beam;

**[0061]** at least partially illuminating the sample of body fluid within the measurement chamber plate with the reflection light beam;

**[0062]** detecting at least one property of the reflection light beam and generating at least one sensor signal dependent on the presence of the analyte by using at least one optical detector,

**[0063]** evaluating the sensor signal by using at least one control unit.

**[0064]** The method steps may be performed in the given order or in a different order. Further, one or more or even all of the method steps may be performed once or more than once or even repeatedly. The method may further comprise additional method steps which are not listed. In the evaluation step, at least one information on the analyte may be generated by evaluating the sensor signal.

**[0065]** The method comprises the use of one or both of the sensor element according to this disclosure, such as according to one or more of the embodiments disclosed above or disclosed in further detail below, and/or of the kit according to this disclosure, such as according to one or more of the embodiments disclosed above or disclosed in further detail below. For further optional details, reference may be made to the disclosure of the sensor element and/or the kit as given above and/or as given in further detail below.

**[0066]** The sensor element, the kit and the method according to this disclosure provide a large number of advantages

over known devices for detecting at least one analyte in body fluid, such as continuous monitoring glucose sensors. The sensor element is a fully implantable sensor element. The sensor element is based on optical measurements and allows reagent-free analyte monitoring. All components as described above can be miniaturized allowing production of very small sensor elements. The sheet or plate-like geometry ensures mechanical robustness with respect to mechanical influences and thus may ensure signal stability and reliability of measurement data. Further, usage of biocompatible material such as silicon or diamond allows producing an implantable sensor element without additional coatings. Further, using a concept of recharging the rechargeable energy storage device of the sensor element may allow long-term operation of the sensor element. Thus, the sensor element may be embodied as a very small and robust module allowing reagent-free and long-term analyte monitoring.

[0067] Summarizing the findings of this disclosure, the following embodiments are preferred. Still, other embodiments are feasible.

#### Embodiment 1

[0068] Implantable sensor element for detecting at least one analyte in a sample of body fluid, wherein the sensor element comprises at least one measurement chamber plate adapted to receive the sample of bodily fluid, wherein the sensor element comprises at least one illumination source designed to generate at least one illumination light beam in at least one spectral range and to transmit the illumination light beam to the measurement chamber plate such that the illumination light beam at least partially illuminates the measurement chamber plate, wherein the measurement chamber plate is designed to generate at least one reflection light beam in response to the illumination by the illumination light beam such that the reflection light beam at least partially illuminates the sample of body fluid within the measurement chamber plate, wherein the sensor element comprises at least one optical detector designed to detect at least one property of the reflection light beam and to generate at least one sensor signal dependent on the presence of the analyte, wherein the sensor element furthermore comprises at least one control unit designed to evaluate the sensor signal.

#### Embodiment 2

[0069] Implantable sensor element according to the preceding embodiment, wherein the illumination source comprises at least one quantum cascade laser.

#### Embodiment 3

[0070] Implantable sensor element according to the preceding embodiment, wherein the illumination source comprises at least one quantum cascade laser chip.

#### Embodiment 4

[0071] Implantable sensor element according to any one of the two preceding embodiments, wherein the quantum cascade laser is selected from the group consisting of: at least one fixed-frequency Fabry-Pérot quantum cascade laser; at least one tunable external cavity quantum cascade laser; at least one distributed feedback quantum cascade laser.

#### Embodiment 5

[0072] Implantable sensor element according to any one of the preceding embodiments, wherein the illumination source is designed to be operated in pulsed or continuous mode.

#### Embodiment 6

[0073] Implantable sensor element according to the preceding embodiment, wherein the sensor element comprises at least one pulser device adapted to operate the illumination in the pulse mode, wherein the control unit is adapted to control the pulser device.

#### Embodiment 7

[0074] Implantable sensor element according to any one of the preceding embodiment, wherein the illumination light beam has a wavelength in the infrared spectral range.

#### Embodiment 8

[0075] Implantable sensor element according to the preceding embodiment, wherein the illumination light beam has a wavelength in the mid-infrared spectral range.

#### Embodiment 9

[0076] Implantable sensor element according to any one of the preceding embodiments, wherein the illumination source is adapted to change the wavelength continuously over time.

#### Embodiment 10

[0077] Implantable sensor element according to any one of the preceding embodiments, wherein the illumination source is adapted to generate a plurality of illumination light beams, wherein each of the illumination light beams has a different wavelength.

#### Embodiment 11

[0078] Implantable sensor element according to the preceding embodiment, wherein the control unit is adapted to one or more of assign, adjust or select the wavelength of the illumination light beams.

#### Embodiment 12

[0079] Implantable sensor element according to any one of the preceding embodiments, wherein the measurement chamber plate comprises at least one membrane element.

#### Embodiment 13

[0080] Implantable sensor element according to the any one of the preceding embodiments, wherein the measurement chamber plate comprises at least one chamber wall, wherein the chamber wall is adapted to receive the sample of body fluid.

#### Embodiment 14

[0081] Implantable sensor element according to the preceding embodiment, wherein the measurement chamber plate comprises at least one first chamber wall adapted to be at least partially transparent to the illumination light beam, wherein the first chamber wall is designed as at least one at least partially transparent first infrared window.

## Embodiment 15

[0082] Implantable sensor element according to the preceding embodiment, wherein the first chamber wall comprises at least one anti-reflective coating adapted to minimize reflections from a surface of the first chamber wall to the optical detector.

## Embodiment 16

[0083] Implantable sensor element according to any one of the two preceding embodiments, wherein the measurement chamber plate comprises at least one second chamber wall adapted to at least partially receive the sample of body fluid.

## Embodiment 17

[0084] Implantable sensor element according to the preceding embodiment, wherein the measurement chamber plate comprises at least one capillary element arranged between the first chamber wall and the second chamber wall, wherein the capillary element is adapted to receive the sample of body fluid.

## Embodiment 18

[0085] Implantable sensor element according to the preceding embodiment, wherein the measurement chamber plate comprises at least one spacer element arranged between the first chamber wall and the second chamber wall.

## Embodiment 19

[0086] Implantable sensor element according to any one of the two preceding embodiments, wherein the second chamber wall is designed as at least one at least partially reflective second infrared window.

## Embodiment 20

[0087] Implantable sensor element according to the preceding embodiment, wherein the second infrared window comprises at least one reflective layer, wherein the reflective layer is arranged on at least one side of the second infrared window facing the illumination light beam in order to enhance reflection of the illumination light beam.

## Embodiment 21

[0088] Implantable sensor element according to any one of the two preceding embodiments, wherein the second infrared window is designed to permit transport of the analyte into the capillary element.

## Embodiment 22

[0089] Implantable sensor element according to the preceding embodiment, wherein the second infrared window comprises at plurality of holes.

## Embodiment 23

[0090] Implantable sensor element according to any one of the eight preceding embodiments, wherein the second chamber wall comprises the at least one membrane element.

## Embodiment 24

[0091] Implantable sensor element according to the preceding embodiment, wherein the second chamber wall is designed as membrane element.

## Embodiment 25

[0092] Implantable sensor element according to any one of the preceding embodiments, wherein the measurement chamber plate comprises at least one attenuated total reflection element.

## Embodiment 26

[0093] Implantable sensor element according to the preceding embodiment, wherein the attenuated total reflection element comprises at least one ATR-crystal, wherein the ATR-crystal is arranged such that the illumination light beam is at least reflected once.

## Embodiment 27

[0094] Implantable sensor element according to the preceding embodiment, wherein the ATR-crystal comprises a structured surface.

## Embodiment 28

[0095] Implantable sensor element according to the preceding embodiment, wherein at least one ultra filtration membrane element is arranged on the ATR-crystal.

## Embodiment 29

[0096] Implantable sensor element according to any one of the preceding embodiments, wherein the sensor element comprises at least one transfer device, wherein the transfer device comprises at least one lens.

## Embodiment 30

[0097] Implantable sensor element according to any one of the preceding embodiments, wherein the optical detector comprises at least one photodetector.

## Embodiment 31

[0098] Implantable sensor element according to the preceding embodiment, wherein the optical detector comprises one or more of at least one pyroelectric detector; at least one Fabry-Pérot interferometer.

## Embodiment 32

[0099] Implantable sensor element according to any one of the preceding embodiments, wherein the control unit is adapted for one or more of processing, analyzing, and storing of the sensor signal.

## Embodiment 33

[0100] Implantable sensor element according to any one of the preceding embodiments, wherein the control unit comprises at least one evaluation device designed to evaluate the sensor signal, wherein the evaluation device is designed to generate at least one information on the analyte by evaluating the sensor signal.

## Embodiment 34

[0101] Implantable sensor element according to the preceding embodiment, wherein the evaluation device is adapted to determine at least one spectral information of the reflection light beam from the sensor signal.

## Embodiment 35

[0102] Implantable sensor element according to the preceding embodiment, wherein the evaluation device is adapted to determine from the spectral information the at least one information on the analyte by using uni- or multivariate data analysis, e.g., principle component regression (PCR) and partial least square regression (PLS).

## Embodiment 36

[0103] Implantable sensor element according to any one of the three preceding embodiments, wherein the evaluation device is adapted to perform a temperature correction.

## Embodiment 37

[0104] Implantable sensor element according to the preceding embodiments, wherein the control unit comprises at least one or more of amplifier circuit adapted to amplify the sensor signal and/or to transform the sensor signal into an electrical current or voltage; at least one analog-/digital converter adapted to digitalize the sensor signal; at least one digital filter adapted to optimize a signal-to-noise ratio such as at least one Lock-In amplifier and/or at least one Boxcar integrator; at least one analog filter adapted to filter the sensor signal; at least one memory unit adapted to store the sensor signal.

## Embodiment 38

[0105] Implantable sensor element according to the any one of the preceding embodiments, wherein the sensor element comprises at least one housing adapted to encapsulate further components of the sensor element.

## Embodiment 39

[0106] Implantable sensor element according to any one of the preceding embodiments, wherein the sensor element comprises at least one rechargeable energy storage device.

## Embodiment 40

[0107] Implantable sensor element according to the preceding claim, wherein the rechargeable energy source is adapted to be charged in a contactless fashion.

## Embodiment 41

[0108] A kit for detecting at least one analyte in a sample of body fluid, the kit comprising at least one implantable sensor element according to any one of the preceding embodiments, and at least one further device, wherein the further device is adapted to provide energy to at least one rechargeable energy storage device.

## Embodiment 42

[0109] The kit according to the preceding embodiment, wherein the at least one further device is adapted to provide electrical energy to the rechargeable energy storage device in a contactless fashion.

## Embodiment 43

[0110] The kit according to any one of the preceding embodiments referring to a kit, wherein the at least one further device comprises at least one data reader module adapted to receive measurement data transmitted by the implantable sensor element via wireless communication, wherein the data reader module comprises at least one data storage device and is adapted to store the measurement data.

## Embodiment 44

[0111] Method for detecting at least one analyte in a sample of body fluid comprising the following method steps:

[0112] receiving the sample of body fluid in at least one measurement chamber plate,

[0113] generating at least one illumination light beam in at least one spectral range by using at least one illumination source and transmitting the illumination light beam to the measurement chamber plate;

[0114] at least partially illuminating the measurement chamber plate with the illumination light beam;

[0115] generating at least one reflection light beam in response to the illumination by the illumination light beam;

[0116] at least partially illuminating the sample of body fluid within the measurement chamber plate with the reflection light beam;

[0117] detecting at least one property of the reflection light beam and generating at least one sensor signal dependent on the presence of the analyte by using at least one optical detector,

[0118] evaluating the sensor signal by using at least one control unit.

## Embodiment 45

[0119] Method according to the preceding embodiment, wherein the method comprises a use of one or both of at least one implantable sensor element according to any one of the preceding embodiments referring to an implantable sensor element or a kit according to any one of the preceding embodiments referring to a kit.

## BRIEF DESCRIPTION OF THE DRAWINGS

[0120] The above-mentioned aspects of exemplary embodiments will become more apparent and will be better understood by reference to the following description of the embodiments taken in conjunction with the accompanying drawings, wherein:

[0121] FIG. 1 shows an exemplary embodiment of an implantable sensor element and kit according to this disclosure;

[0122] FIG. 2 shows a further exemplary embodiment of the implantable sensor element;

[0123] FIG. 3 shows a further exemplary embodiment of the implantable sensor element; and

[0124] FIG. 4 shows a further exemplary embodiment of the fully implantable sensor element.

## DESCRIPTION

[0125] The embodiments described below are not intended to be exhaustive or to limit the invention to the precise forms disclosed in the following detailed description. Rather, the embodiments are chosen and described so that others skilled in the art may appreciate and understand the principles and practices of this disclosure.

[0126] In FIG. 1, an exemplary embodiment of an implantable sensor element 110 and a kit 112 for detecting at least one analyte in a body fluid is disclosed. The sensor element 110 may be designed to remain in the body tissue for an elongated time period, such as for several days or even several weeks or several months. The sensor element 110 is embodied as a fully implantable transcutaneous sensor element. Generally, an arbitrary type of body fluid may be used. Preferably, the body fluid is a body fluid which is present in a body tissue of the user, such as in the interstitial tissue. Thus, as an example, the body fluid may be selected from the group consisting of blood and interstitial fluid. However, additionally or alternatively, one or more other types of body fluids may be used. The body fluid generally may be contained in a body tissue. Thus, generally, the detection of the at least one analyte in the body fluid may preferably be determined in vivo.

[0127] The sensor element 110 comprises at least one measurement chamber plate 114 adapted to receive the sample of bodily fluid. The measurement chamber plate 114 may have a sheet or plate-like geometry. The measurement chamber plate 114 may have a flat geometry. The measurement chamber plate 114 may comprise a monolithic or a multi-plate setup. The measurement chamber plate 114 may receive the sample of body fluid via diffusion processes. In FIG. 1, a direction of diffusion of the body fluid is denoted with arrow 116. Filling the sample via diffusion processes may ensure maintenance-free operation of the implanted sensor element.

[0128] The sensor element 110 comprises at least one illumination source 118 designed to generate at least one illumination light beam 120 in at least one spectral range and to transmit the illumination light beam 120 to the measurement chamber plate 114 such that the illumination light beam 120 at least partially illuminates the measurement chamber plate 114.

[0129] The illumination source 118 may comprise at least one light source. The illumination source 118 comprises at least one quantum cascade laser. For example, the illumination source 118 may comprise at least one quantum cascade laser chip. The quantum cascade laser may be a miniaturized quantum cascade laser. The quantum cascade laser may be selected from the group consisting of: at least one fixed-frequency Fabry-Pérot quantum cascade laser; at least one tunable external cavity quantum cascade laser; at least one distributed feedback quantum cascade laser. For example, the illumination source 118 may comprise at least one array of quantum cascade lasers. The illumination source 118 may be designed to be operated in pulsed or continuous mode. The sensor element 110 may comprise at least one pulser device 122 adapted to operate the illumination in the pulsed mode. The sensor element 110 may comprise at least one rechargeable energy storage device 124, for example at least one lithium-ion battery, adapted to supply energy to the quantum cascade laser. The quantum cascade laser may have a low power consumption such that power supply by lithium-ion battery, is possible.

[0130] The illumination light beam 120 may have a wavelength in the infrared spectral range, preferably in mid-infrared spectral range. The illumination source 118 may be adapted to generate broadband illumination light or illumination light having a narrow bandwidth. The illumination source 118 may be adapted to change the wavelength continuously over time. The illumination source 118 may be adapted to generate a plurality of illumination light beams 120, wherein each of the illumination light beams has a different wavelength. The sensor element comprises at least one control unit 126, also referred to herein as a “controller.” The control unit 126 may be adapted to one or more of assign, adjust or select the wavelength of the illumination light beams. For example, the illumination source 118 may comprise at least one tunable distributed feedback quantum cascade laser and/or at least one tunable external cavity quantum cascade laser having a narrow bandwidth. The control unit 126 may be adapted to change the wavelength continuously or non-continuously, for example within the mid-infrared spectral range. The control unit 126 may be adapted to adjust and/or select wavelengths suitable for identification of glucose and/or distinction of glucose from further substances in the sample of body fluid, for example substances present even after filtration such as maltose. Additionally or alternatively, a broadband spectral range is used. For example, the illumination source 118 may comprise at least one Fabry-Pérot quantum cascade laser. In order to permit absorption measurements with a broadband illumination source, the sensor element 110 may comprise several optical detectors and suitable spectral bandpass filters or at least one tunable optical detector having at least one tunable, spectral bandpass filter.

[0131] The illumination light beam 120 may illuminate more than 5% of the measurement chamber plate 114, preferably more than 10% of the measurement chamber plate 114, more preferably more than 25% of the measurement chamber plate 114. However, embodiments are feasible. The illumination light beam 120 may illuminate the measurement chamber plate 114 under an illumination angle between 0° and 85°, preferably between 20° and 60°, more preferably between 30° and 50°. For example, the illumination angle may be 45°.

[0132] The sensor element 110 may comprise at least one transfer device 128 adapted to collimate the illumination light beam 120. The transfer device 128 may comprise at least one optical lens, such as one or more convex lenses, one or more refractive lenses. For example, the transfer device 128 may be arranged such that the illumination light beam 120 travels first through the at least one transfer device 128 and thereafter to the measurement chamber plate 114.

[0133] The measurement chamber plate 114 is designed to generate at least one reflection light beam 130 in response to the illumination by the illumination light beam 120 such that the reflection light beam 130 at least partially illuminates the sample of body fluid within the measurement chamber plate 114. Preferably, the sample of body fluid is illuminated by the illumination light beam 120 before the sample of body fluid is illuminated by the reflection light beam 130. Preferably, the sample of body fluid may be illuminated at least twice within the measurement chamber plate 114. The sample may be illuminated, firstly, by the illumination light beam 120, for example in a first direction, and, subsequently, by the reflection light beam 130, for example, in a second direction. The measurement chamber plate 114 may com-

prise at least one reflector element and/or may comprise a reflective material such as a reflective coating. The measurement chamber plate **114** may be adapted to at least partially reflect the illumination light beam **120**.

[0134] The sensor element **110** comprises at least one optical detector **132** designed to detect at least one property of the reflection light beam **130** and to generate at least one sensor signal dependent on the presence of the analyte. The sensor signal may be or may comprise a digital and/or an analog signal. The sensor signal may be or may comprise a voltage signal and/or a current signal. Additionally or alternatively, the sensor signal may be or may comprise digital data. The sensor signal may comprise a single signal value and/or a series of signal values. The sensor signal may further comprise an arbitrary signal which is derived by combining two or more individual signals, such as by averaging two or more signals and/or by forming a quotient of two or more signals. The optical detector **132** may comprise at least one photodetector. The optical detector **132** may comprise at least one pyroelectric detector. The optical detector **132** may comprise at least one spectrometric setting, for example at least one Fabry-Pérot interferometer. The optical detector **132** may comprise at least one analog and/or digital amplifier and/or filter in order to for example amplify at least one property of the reflection light beam **130** and/or reduce noise. The optical detector **132** may be adapted to determine one or more of intensity, absorbance, attenuation, transmission, reflection, wavelength and frequency of the reflection light beam **130**. The at least one property of the reflection light beam **120**, for example the intensity, may change due to the presence of the analyte and/or other substances in the sample of body fluid. The optical detector **132** may be adapted to determine a change in intensity, for example due to the presence of the analyte and/or other substances in the sample of body fluid. The sensor element **110** may be adapted to perform one or more of at least one reflection measurement, at least one absorption measurement, at least one attenuated total reflectance measurement. The optical detector **132** may be adapted to determine at least one absorption information and/or attenuation information as a function of wavelength and/or frequency of the reflection light beam **130**. The optical detector **132** may be adapted to determine at least one spectrum, for example at least one absorbance spectrum, of the reflection light beam. The sensor element **110** may comprise at least one further transfer **128** which may be arranged such that the reflected light beam travels from the measurement chamber plate **114** to the further transfer device **128** until it may finally impinge on the optical detector **132**.

[0135] The sensor element furthermore comprises the at least one control unit **126** designed to evaluate the sensor signal. The control unit **126** may be adapted for one or more of processing, analyzing, and storing of the sensor signal. The control unit **126** may be a central control unit. The control unit **126** may comprise at least one evaluation device **134** designed to evaluate the sensor signal. The evaluation device **134** may be designed to generate at least one information on the analyte by evaluating the sensor signal. As an example, the evaluation device **134** may be or may comprise one or more integrated circuits, such as one or more application-specific integrated circuits (ASICs), and/or one or more data processing devices, such as one or more computers, preferably one or more microcomputers and/or microcontrollers. Additional components may be comprised, such

as one or more preprocessing devices and/or data acquisition devices, such as one or more devices for receiving and/or preprocessing of the sensor signals, such as one or more AD-converters and/or one or more filters. Further, the evaluation device **134** may comprise one or more data storage devices. Further, the evaluation device **134** may comprise one or more interfaces, such as one or more wireless interfaces and/or one or more wire-bound interfaces. The evaluation device **134** may be adapted to determine at least one spectral information of the reflection light beam from the sensor signal. The spectral information may be at least one absorption spectrum or at least one attenuation spectrum. For example, spectra may be acquired by continuously changing the laser's wavelength over time and measuring the sensor signal on the optical detector. The difference in absorbance  $\Delta A$  can be calculated using water as a reference,  $I_{ref}$  by

$$\Delta A = -\log[(I_{meas})/(I_{ref})],$$

with  $I_{meas}$  being the sensor signal seen.

[0136] The evaluation device **134** may be adapted to determine the analyte concentration by evaluating the spectral information. The evaluation device **134** may be designed to identify characteristic spectral signature of molecules in the mid-infrared spectral range. The evaluation device **134** may be adapted to compare the measured spectral information with predetermined or theoretical spectral information stored, for example, in an electronic table such as in at least one look-up table. The evaluation device **134** may be adapted to determine from the spectral information the at least one information on the analyte by using uni- or multivariate data analysis, e.g., principle component regression (PCR) and partial least square regression (PLS). The evaluation device **134** may be adapted to detect and potentially quantify a variety of biomolecules using uni- or multivariate data analysis. For example, the evaluation device **134** may be adapted to determine the presence and/or concentration of glucose. The evaluation device **134** may be adapted to identify and/or determine a relevant signal or signal component, for example a signal referring to glucose, and to distinguish the relevant signal from signals of interfering molecules. The evaluation device **134** may be adapted to distinguish the relevant signal from other signal influences such as from signal influences due to system changes such as temperature.

[0137] The control unit **126** may comprise at least one or more of amplifier circuits **136** adapted to amplify the sensor signal and/or to transform the sensor signal into an electrical current or voltage; at least one analog-/digital converter adapted to digitalized the sensor signal, for example the amplified sensor signal; at least one digital filter adapted to optimize a signal-to-noise ratio such as at least one Lock-In amplifier and/or at least one Boxcar integrator; at least one analog filter adapted to filter the sensor signal, for example before digitalization; at least one memory unit **138** adapted to store the sensor signal, for example the raw sensor signal and/or the evaluated, for example digitalized and/or amplified, sensor signal. The memory unit **138** generally may comprise at least one data storage device such as at least one volatile and/or at least one non-volatile data storage element. The components listed above may be designed as separate components within a housing **140** of the sensor element **110**. Alternatively, two or more of the components as listed above may be integrated into one component. For example, the

optical detector **132** may comprise an integrated amplifier circuit and/or one or more signal filters. Additionally or alternatively, one or more of these components may be provided in a further device **142** of the kit **112** situated outside the body of the user. The sensor element **110** can be adapted to transfer data, such as the raw sensor signal and/or the evaluated sensor signal, automatically and/or upon request to the further device **142** for evaluation and data storing. The control unit **126** can be designed to receive instructions and/or data, for example from the further device **142**, contactless, for example via the inductive connection. The sensor element and the further device may be adapted to communicate, i.e., transfer data and instructions, wirelessly such as by an inductive connection. Other ways of data transfer, however, are feasible. The control unit **126** may comprise at least one communication unit **144** for wireless communication. Read-out of the measurement data from the sensor element **110** may be performed wireless such that wearing comfort and freedom of movement is enhanced.

[0138] The evaluation device **134** may be adapted to perform a temperature correction. The sensor signal may be influenced due to temperature changes such that drifts in signal may occur. The evaluation device **134** may be adapted to distinguish signal drift due to temperature change from signal drift due to changes in analyte concentration by using spectral information. The temperature influence may be corrected using calibration data from a prior temperature calibration measurement. Additionally or alternatively, the sensor element **110** may comprise at least one temperature sensor as for example a platinum resistance thermometer. The temperature sensor may be arranged in close proximity to the measurement chamber plate **114**. The temperature influence may be corrected using calibration data from a prior temperature calibration measurement and the measured temperature of the temperature sensor.

[0139] In the embodiments shown in FIGS. 1 and 2, the measurement chamber plate **114** may comprise at least one chamber wall **146**, wherein the chamber wall **146** is adapted to receive the sample of body fluid. The sensor element **110** may be adapted to perform at least one measurement based on absorption spectroscopic techniques using a miniaturized fluid cell. The measurement chamber plate **114** may be adapted to receive a sample size of body fluid such that a reliable absorption measurement can be performed. For example, a layer thickness of body fluid in the measurement chamber plate **114** may be between 1  $\mu\text{m}$  and 100  $\mu\text{m}$ , preferably between 5  $\mu\text{m}$  and 50  $\mu\text{m}$ , more preferably the layer thickness may be between 8  $\mu\text{m}$  and 15  $\mu\text{m}$ . For example, the layer thickness may be 10  $\mu\text{m}$  in order to ensure high sensitivity to detect glucose in aqueous solution. The chamber wall **146** may be adapted to have a first side at least partially permeable to light, for example in the infrared spectral range, and a second side at least partially permeable to the sample of body fluid. The first side of the chamber wall **146** may be at least partially transparent. The chamber wall **146** may be arranged such that the side permeable to the sample of body fluid faces an exterior of the sensor element **110**.

[0140] In the embodiments depicted in FIGS. 1 and 2, the measurement chamber plate **114** may comprise at least one first chamber wall **148** adapted to be at least partially transparent to the illumination light beam **120**. The first chamber wall **148** may be designed as at least one at least

partially transparent first infrared window **150**. The first chamber wall **148** may be arranged facing an interior of the sensor element **110** such as an interior surrounded by the housing **140**. The first chamber wall **148** may face the illumination light beam **120**. The first infrared window **150** may be designed to let at least partially the illumination light beam **120** through the infrared window **150** to the sample of body fluid. For example, the infrared window **150** may be designed to let at least partially the illumination light beam pass **120** through the infrared window **150** into the measurement chamber plate **114**. The first chamber wall **148** may be designed as transmission window. The first chamber wall **148** may be a light-permeable inner plate. The first chamber wall **148** may be biocompatible. The first chamber wall **148** may comprise and/or may be produced from at least one biocompatible material. The first chamber wall **148** may consist fully of biocompatible material, for example a biocompatible material comprising at least one synthetic diamond or silicon. The first chamber wall **148** may comprise at least one anti-reflective coating adapted to minimize reflections from a surface of the first chamber wall **148** to the optical detector **132** and/or reflections of the reflected beam back into the measurement chamber plate **114**, for example in order to minimize interference effects on the signal. The first chamber wall **148** may comprise at least one micro-structured surface, e.g., roughened surface adapted to minimize reflections from a surface of the first chamber wall to the optical detector and/or reflections of the reflected beam back into the measurement chamber plate **114** for example in order to minimize interference effects on the signal.

[0141] The measurement chamber plate **114** may comprise at least one second chamber wall **152** adapted to at least partially receive the sample of body fluid. The second chamber wall **152** may be a fluid-permeable outer plate. The measurement chamber plate **114** may comprise at least one capillary element **154** arranged between the first chamber wall **148** and the second chamber wall **152**. The capillary element **154** may be adapted to receive the sample of body fluid. The receiving of the sample of body fluid may be supported by capillary forces. The first chamber wall **148** and the second chamber wall **152** may be arranged at opposing sides of a capillary element **154** and form a measurement cuvette. The capillary element **154** may be designed to receive an amount of body fluid required for reliable determination of the analyte. In order to obtain a maximum sensitivity of glucose in aqueous solution, the capillary element may be designed to receive a fluid layer thickness between 1 to 100  $\mu\text{m}$ , preferably between 5 and 50  $\mu\text{m}$ , more preferably between 8 and 15  $\mu\text{m}$ . For example, the capillary element **154** may be designed to receive a fluid layer thickness of 10  $\mu\text{m}$ . The capillary element **154** may receive the sample of body fluid via diffusion processes. In order to ensure suitable sensor response behavior, the capillary element **154** may be designed such that diffusion distances are as short as possible, preferably around 100  $\mu\text{m}$ .

[0142] The measurement chamber plate **114** may comprise at least one spacer element **156** arranged between the first chamber wall **148** and the second chamber wall **152**. The spacer element **156** may have an arbitrary shape, for example the spacer element may be at least one ring. The spacer element may have a thickness between 1 and 100  $\mu\text{m}$ . The spacer element **156** may be a cut polyester film. Additionally or alternatively, one of the first chamber wall **148** and the second chamber wall **152** may comprise at least

one cavity and/or recess, for example produced by photolithographic methods, adapted to form a capillary element 154.

[0143] The second chamber wall 152 may be designed to be rigid against mechanical influence, for example, during assembling of the sensor element 110, such that a constant measurement volume can be ensured. The second chamber wall 152 may be designed to be permeable to the analyte, for example, to glucose, such that the analyte can reach the measurement chamber plate. The second chamber wall 152 may be designed to prevent large-sized molecules and/or cells to penetrate into the measurement chamber plate 114.

[0144] In FIG. 1, the second chamber wall 152 may be designed as at least one at least partially reflective second infrared window 158. The second infrared window 158 may comprise at least one reflective layer, for example a gold layer. The reflective layer may be arranged on at least one side of the second infrared window 158 facing the illumination light beam 120 in order to enhance reflection of the illumination light beam 120. The second infrared window 158 may be designed to permit transport, for example by diffusion, of the analyte into the capillary element 154. The second infrared window 158 may be a fluid-permeable outer plate. The second infrared window 158 may comprise a plurality of holes. The second infrared window 158 may comprise a plurality of micro fluid channels. For example, the holes may be drilled micro holes having a diameter less than 100  $\mu\text{m}$ , preferably less than 20  $\mu\text{m}$ , more preferably less than 10  $\mu\text{m}$ . An average distance between two holes may be less than 500  $\mu\text{m}$ , preferably less than 200  $\mu\text{m}$ , more preferably less than 100  $\mu\text{m}$ . A thickness of the second infrared window may be less than 1000  $\mu\text{m}$ , preferably less than 500  $\mu\text{m}$ . Such dimensions may ensure short diffusion times of glucose from interstitial fluid into the capillary element. The holes may have other shapes as for example slits or bendings. The holes may be produced using laser processing techniques or other methods known in the art, for example wet etching. The second infrared window 158 may be or may comprise a silicon plate having a plurality of holes. Such a design can ensure proper rigidity. The silicon plate may be sputtered with a gold layer in order to enhance reflectivity. The second chamber wall 152 may have a hydrophilic surface structure on one side and/or on the other side and/or in the holes of the wall adapted to have better fluidic properties. This hydrophilic surface may be made by a microfabricated surface for example by photolithographic or wet etching methods.

[0145] The measurement chamber plate 114 may comprise at least one membrane element 160. The membrane element 160 may be adapted to protect the measurement chamber plate 114 from penetration of particles above a certain size such as large-sized molecules like proteins. In the embodiment of FIG. 1, the measurement chamber plate may comprise a flat membrane element 160. The flat plate design of the measurement chamber plate 114 may allow simple mounting of the flat membrane element 160. In case of using the flat membrane element 160, the diffusion distance may be enhanced only slightly by the thickness of the flat membrane. The membrane element 160 may be arranged on the side of the second infrared window 158. The membrane element 160 may be an ultra filtration membrane. The membrane element 160 may be adapted to reduce influence from proteins on the absorption measurement. Additionally or alternatively to the membrane element 160, the holes of

the second infrared window 158 may be designed such that the second infrared window functions as membrane such that no additional membrane element is required.

[0146] The sensor element 110 may comprise the at least one housing 140 adapted to encapsulate the further components of the sensor element 110 such as the illumination source 118, the control unit 126 and the optical detector 132. The housing 140 may allow complete or at least partial implantation of the sensor element 110 within the body of the user. Thus, the housing 140 may prevent permanent open skin barrier and thus, the housing 140 may prevent penetration of bacteria and other contaminations in the body. The housing 140 may be designed to prevent contamination of the sensor element, for example with dirt and moisture. The housing 140 may be biocompatible in order to reduce and/or minimize specific immune reactions. The housing 140 may comprise and/or is produced from biocompatible material. For example, the biocompatible material may comprise titanium alloy.

[0147] The sensor element 110 may comprise the at least one rechargeable energy storage device 124, e.g., a battery. The rechargeable energy storage device 124 may be adapted to supply voltage for one or more of the sensor element 110 such as to illumination source 118, the control unit 126, in particular the amplifier circuit, and the optical detector 132, pulser device 122 etc. The control unit 126 may be adapted to control power supply to the components of the sensor element 110. For example, the control unit 126 may be adapted to control power supply to one or more of the optical detector 132 such as to the amplifier circuit, the illumination source 118 such as the pulser device 122. The rechargeable energy source 124 may be adapted to be charged in a contactless fashion. For example, the rechargeable energy storage device 124 may be adapted to be charged wirelessly such as by an inductive connection. Other ways of recharging, however, are feasible. Charging in a contactless fashion may allow long-term operation without surgical interventions. The rechargeable energy storage device 124 may comprise at least one lithium-ion battery. The rechargeable energy storage device 124 may be charged by using the further device situated outside the body of the user such as by using a docking station or the like. For example, the further device 142 may be designed to be worn by the user. The further device 142 may comprise at least one further rechargeable energy storage device. The further rechargeable energy storage device may be adapted to be charged using at least one cable. The further device 142 may be adapted to bring a demand for recharging the rechargeable energy storage device 124 to a user's attention, such as in one or more of a visual fashion, an acoustic fashion or a vibrational fashion. Thus, as an example, the further device 142 may be adapted to provide at least one of a visual indication, such as a display of an appropriate message, and/or an acoustic indication, such as a warning sound or a voice message, and/or a vibrational indication, such as a vibrational alarm, to a user, in order to indicate to the user that a recharging of the rechargeable energy storage device 124 is required.

[0148] As shown in FIG. 1, the kit 112 comprises the at least one implantable sensor element 110 and the at least one further device 142. The further device 142 may be situated outside the body of the user, for example the further device 142 may rest on the skin of the user or may be worn by the user. The further device 142 may be adapted to be placed on

a skin or an out-of-body surface of the user. Thus, the further device **142** may be an external, extracorporeal device. As outlined above, the further device **142** is adapted to provide energy to at least one rechargeable energy storage device **124**. The at least one further device **142** may be adapted to provide electrical energy to the rechargeable energy storage device **124** in a contactless fashion, for example via the inductive connection. Other ways of recharging, however, are feasible. The sensor element **110** and the kit **112** may be adapted to provide a concept of recharging on-demand for the rechargeable energy storage device and thus, allowing long-term operation.

[0149] In the embodiment shown in FIG. 2, the second chamber wall **152** may be designed as membrane element **160**. With respect to further elements of the sensor element **110** shown in FIG. 2, reference is made to the description of FIG. 1 above. The membrane element **160** may have reflective properties. For example, the membrane element **160** may comprise at least one sintered metal. The membrane element **160** may be sputtered with a reflective layer such as a gold, silver or aluminum layer to enhance reflectivity. For example, the membrane element **160** may be selected from the group consisting of a track-etched membrane comprising polycarbonate; an Anodisc membrane comprising aluminum oxide; a membrane having a supporting structure such as a polymeric microporous membrane available from Precision Membranes, LLC; a high-aspect-ratio membrane comprising silicon and/or carbon available from Precision Membranes, LLC; a porous membrane comprising sintered metal. In one embodiment, the membrane element **160** may be a membrane having a supporting structure such as a polymeric microporous membrane available from Precision Membranes, LLC. The supporting structure may be adapted to provide rigidity to the measurement chamber plate. The membrane element **160** having a supporting structure may have a thickness of several 10  $\mu\text{m}$  such that the membrane element **160** can be used as spacer element **156**. In a further embodiment, the membrane element **160** may be a high-aspect-ratio membrane comprising silicon and/or carbon available from Precision Membranes, LLC. The high-aspect-ratio membrane may have a reflective coating, for example, the membrane element may be sputtered with a gold layer. However, embodiments are feasible, without a reflective coating, e.g., a porous membrane comprising sintered metal has reflective properties in the infrared spectral range.

[0150] In the embodiments shown in FIGS. 3 and 4, the measurement chamber plate **114** may comprise at least one attenuated total reflection element **162**. With respect to further elements of the sensor element **110** shown in FIGS. 3 and 4, reference is made to the description of FIGS. 1 and 2. The attenuated total reflection element **162** may comprise at least one ATR-crystal, for example an ATR-crystal available from ATR Elements. The ATR-crystal may comprise a structured surface. The ATR-crystal may comprise at least one microstructure adapted to receive the sample of body fluid. The microstructure may enhance amplification of the sensor signal compared to ATR-crystals without microstructures. The microstructure may be adapted as capillary, wherein the receiving of the sample of body fluid may be supported by capillary forces. The microstructure may have hydrophilic properties such that the microstructure is adapted to draw out the body fluid when in contact with the interstitial fluid. Thereby a transition layer may be formed

having a fixed thickness in which the reflection measurement can be performed. The ATR-crystal may be arranged such that the illumination light beam **120** is at least reflected once. Preferably, the illumination light beam **120** may be reflected several times within the ATR-crystal. The illumination light beam **120** may be collimated by the at least one transfer device **128**, and may impinge on the ATR-crystal. The ATR-crystal may be designed such that the illumination light beam **120** is reflected by an area of the ATR-crystal comprising the body fluid. The ATR-crystal may be biocompatible. The ATR-crystal may comprise or may be produced from biocompatible material, for example silicon or diamond. The ATR-crystal may be adapted to reflect the light beam such that it illuminates the optical detector **132**, for example after being collimated by at least one further transfer device **128**. In FIG. 3 an embodiment is shown wherein at least one ultra filtration membrane element **160** may be arranged on the ATR-crystal, wherein in FIG. 4 an embodiment without an additional membrane element **160** is shown.

[0151] While exemplary embodiments have been disclosed hereinabove, the present invention is not limited to the disclosed embodiments. Instead, this application is intended to cover any variations, uses, or adaptations of this disclosure using its general principles. Further, this application is intended to cover such departures from the present disclosure as come within known or customary practice in the art to which this invention pertains and which fall within the limits of the appended claims.

#### LIST OF REFERENCE NUMBERS

[0152]	<b>110</b> sensor element
[0153]	<b>112</b> kit
[0154]	<b>114</b> measurement chamber plate
[0155]	<b>116</b> direction of diffusion
[0156]	<b>118</b> illumination source
[0157]	<b>120</b> illumination light beam
[0158]	<b>122</b> pulser device
[0159]	<b>124</b> rechargeable energy storage device
[0160]	<b>126</b> control unit
[0161]	<b>128</b> transfer device
[0162]	<b>130</b> reflection light beam
[0163]	<b>132</b> optical detector
[0164]	<b>134</b> evaluation device
[0165]	<b>136</b> amplifier circuit
[0166]	<b>138</b> memory unit
[0167]	<b>140</b> housing
[0168]	<b>142</b> further device
[0169]	<b>144</b> communication unit
[0170]	<b>146</b> chamber wall
[0171]	<b>148</b> first chamber wall
[0172]	<b>150</b> first infrared window
[0173]	<b>152</b> second chamber wall
[0174]	<b>154</b> capillary element
[0175]	<b>156</b> spacer element
[0176]	<b>158</b> second infrared window
[0177]	<b>160</b> membrane element
[0178]	<b>162</b> attenuated total reflection element

What is claimed is:

1. A fully implantable sensor for detecting at least one analyte in a sample of body fluid, the sensor comprising:
  - a measurement chamber plate configured to receive the sample of bodily fluid;

- a quantum cascade laser illumination source configured to generate an illumination light beam in a spectral range and to transmit the illumination light beam to the measurement chamber plate, wherein:
- the illumination light beam is configured to at least partially illuminate the measurement chamber plate,
  - the measurement chamber plate is configured to generate a reflection light beam in response to the illumination by the illumination light beam, and
  - the reflection light beam is configured to at least partially illuminate the sample of body fluid within the measurement chamber plate;
- an optical detector configured to detect at least one property of the reflection light beam and to generate a sensor signal dependent on the presence of the analyte; and
- a controller configured to evaluate the sensor signal.
2. The fully implantable sensor according to claim 1, wherein the quantum cascade laser is selected from the group consisting of: a fixed-frequency Fabry-Pérot quantum cascade laser; a tunable external cavity quantum cascade laser; a distributed feedback quantum cascade laser.
  3. The fully implantable sensor according to claim 1, wherein the illumination light beam has a wavelength in the infrared spectral range.
  4. The fully implantable sensor according to claim 1, wherein measurement chamber plate comprises at least one membrane.
  5. The fully implantable sensor according to claim 1, wherein the measurement chamber plate comprises a first chamber wall configured to receive the sample of body fluid.
  6. The fully implantable sensor according to claim 5, wherein the first chamber wall is at least partially transparent to the illumination light beam and has an at least partially transparent first infrared window.
  7. The fully implantable sensor according to claim 6, wherein the measurement chamber plate comprises a second chamber wall adapted to at least partially receive the sample of body fluid.
  8. The fully implantable sensor according to claim 7, wherein the measurement chamber plate comprises a capillary arranged between the first chamber wall and the second chamber wall, wherein the capillary is adapted to receive the sample of body fluid.
  9. The fully implantable sensor according to claim 8, wherein the second chamber wall comprises an at least partially reflective second infrared window configured for transport of the analyte into the capillary.
  10. The fully implantable sensor according to claim 9, wherein the second chamber wall comprises a membrane.
  11. The fully implantable sensor according to claim 1, wherein the measurement chamber plate comprises at least one attenuated total reflection element having an ATR-crystal arranged to reflect the illumination light beam at least once.
  12. The fully implantable sensor according to claim 1, wherein the optical detector comprises a pyroelectric photodetector.
  13. The fully implantable sensor according to claim 1, wherein the controller is configured to generate information on the analyte by evaluating the sensor signal.
  14. The fully implantable sensor according to claim 13, wherein the controller is configured to perform a temperature correction.
  15. The fully implantable sensor according to claim 1, wherein the sensor comprises a rechargeable battery configured for contactless charging.
  16. A kit for detecting at least one analyte in a sample of body fluid, the kit comprising:
    - the fully implantable sensor according to claim 15; and
    - an energy source configured to provide energy to the battery.
  17. A method for detecting at least one analyte in a sample of body fluid, the method comprising:
    - receiving the sample of body fluid in a measurement chamber plate;
    - generating an illumination light beam in a spectral range and transmitting the illumination light beam to the measurement chamber plate;
    - at least partially illuminating the measurement chamber plate with the illumination light beam;
    - generating at least one reflection light beam in response to the illumination by the illumination light beam;
    - at least partially illuminating the sample of body fluid within the measurement chamber plate with the reflection light beam;
    - detecting at least one property of the reflection light beam and generating at least one sensor signal dependent on the presence of the analyte by using at least one optical detector; and
    - evaluating the sensor signal using a controller.
  18. The method according to claim 17, further comprising providing the illumination light beam using a quantum cascade laser.
  19. The method of claim 17, comprising providing the measurement chamber plate, a light source that generates the illumination light beam, the optical detector and the controller inside a housing for a fully implantable sensor.
  20. The method of claim 19, comprising providing the fully implantable sensor with a rechargeable battery.

\* \* \* \* \*

专利名称(译)	用于检测体液中至少一种分析物的可植入传感器和方法		
公开(公告)号	<a href="#">US20190336050A1</a>	公开(公告)日	2019-11-07
申请号	US16/515984	申请日	2019-07-18
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IPC分类号	A61B5/1459 A61B5/145 A61B5/00		
CPC分类号	A61B2560/0214 A61B2560/0223 A61B5/14546 A61B5/1459 A61B5/686 A61B5/14532 A61B5/1455		
优先权	2017152684 2017-01-23 EP		
外部链接	<a href="#">Espacenet</a> <a href="#">USPTO</a>		

摘要(译)

公开了一种用于检测体液样本中的至少一种分析物的完全可植入的传感器。该传感器具有一个用于接收体液样本的测量室板和一个量子级联激光照明源，该级联激光照明源在光谱范围内生成照明光束并将其传输到测量室板。照明光束至少部分地照亮测量室板，并且测量室板响应于照明光束的照明而产生反射光束。反射光束至少部分照射在测量腔室内的体液样本。光学检测器检测反射光束的至少一种特性，并根据分析物的存在产生传感器信号。控件会评估传感器信号。还公开了一种使用本发明的完全可植入传感器的方法。

