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(54) Title: IMPLANTABLE DISSOLVED OXYGEN SENSOR AND METHODS OF USE

(57) Abstract: A sensor is provided for measuring a dissolved oxygen concentration *in vivo* when implanted at a tissue site and in ex vivo applications. The sensor includes an article comprising a sensing medium retained within the implantable article by an oxygen- permeable material. The sensing medium comprises an MR contrast agent for oxygen. The sensor is configured to indicate the dissolved oxygen concentration of a fluid, *e.g., in vivo* at the tissue site, when subjected to an MR-based method.

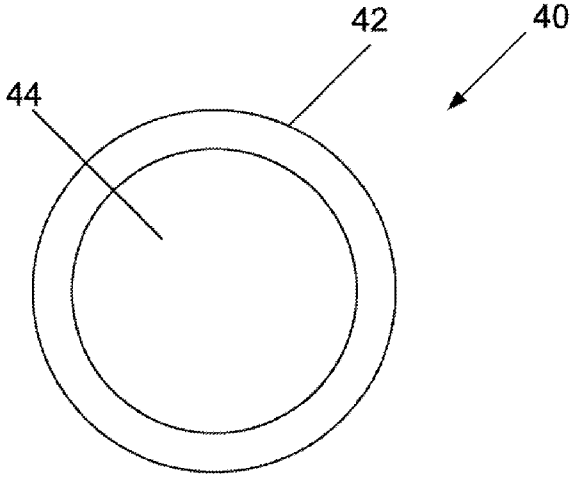


FIG. 7

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**Declarations under Rule 4.17**:

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# IMPLANTABLE DISSOLVED OXYGEN SENSOR AND METHODS OF USE

## REFERENCES TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/331,236, filed on May 4, 2010, which is incorporated by reference herein in its entirety.

## STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with U.S. government support under Contract No. 5-U54-CA119349-02, awarded by the National Cancer Institute. The U.S. government has certain rights in the invention.

## BACKGROUND

The present invention is generally in the field of sensor devices. More particularly, the present invention relates to a sensor device that may be used to detect or measure the presence of oxygen in a fluid, such as a gas or liquid.

The concentration of dissolved oxygen within biological fluids may provide important information about biological systems. As an essential nutrient and metabolite, the concentration of dissolved oxygen in microenvironments is influenced by a number of factors, such as cellular activity, and can possibly be used to evaluate disease states. It is well known, for example, that the hypoxic state of a tumor negatively affects the efficacy of non-surgical therapies, especially with radiotherapy. Strategies to mitigate hypoxia in tumors before therapy are thought to result in improved outcomes for patients. Real-time knowledge of intratumoral dissolved oxygen would allow a physician to schedule therapy at the most opportune moment to improve outcome. Dissolved oxygen can, for example, be used to estimate the required dose of radiation or the appropriate regimen of chemotherapy. In addition, dissolved oxygen measurements can be used to assess the stage of compartment syndrome in trauma patients.

Current standard methods to measure intratumoral dissolved oxygen in patients are invasive, as they rely on probes directly linked to the measuring instruments. These instruments are not suited for repeated measurements or measurement of non-superficial tumors. The current standard for hypoxia measurement in tumors is $pO_2$ histography. This technique uses a polarographic needle electrode to obtain an Eppendorf histograph, a

frequency distribution of oxygen partial pressures measured at several points along a tumor. The needle is guided by computed tomography fluoroscopy to allow physicians to visualize its location in real time. This technique is limited to superficial tumors or metastatic lymph nodes because of the invasiveness of the needle, and results in significant patient discomfort. A number of non-invasive methods have been developed to circumvent the limitations of $pO_2$ histography, based on electron paramagnetic resonance (EPR) oximetry, positron emission tomography (PET), single photon emission computed tomography (SPECT) and MRI. However, improved methods are needed. For example, some of these methods rely on the administration of a contrast agent. The distribution of the contrast agent within the tumor is not precisely known which limits the ability to interpret the results.

It therefore would be desirable to provide a sensor that provides the ability to take repeated measurements at the same location over extended periods. This can be particularly valuable where continual monitoring of *in vivo* dissolved oxygen levels is required or beneficial.

## SUMMARY

In one aspect, a sensor is provided for measuring a dissolved oxygen concentration *in vivo* when implanted at a tissue site. The sensor comprises an implantable article comprising a sensing medium retained within the implantable article by an oxygen-permeable material. The sensing medium comprises an MR contrast agent for oxygen. The sensor is configured to indicate the dissolved oxygen concentration *in vivo* at the tissue site when subjected to an MR-based method. In one embodiment, an implantable sensor includes a container having a reservoir and a reservoir opening; an oxygen-permeable membrane covering the reservoir opening; and a sensing medium contained in the reservoir, the sensing medium comprising an MR contrast agent for oxygen. The sensor is configured to indicate the dissolved oxygen concentration of the fluid when subjected to an MR-based method. In another embodiment, the implantable sensor includes one or more beads or microspheres which comprise an agent having an MR relaxivity that is sensitive to oxygen. The one or more beads or microspheres may be injectable, for example in a fluid suspending media, and possess a volume of the agent

effective to indicate the dissolved oxygen concentration of the tissue site *in vivo* when subjected to an MR-based method.

In another aspect, a method is provided for measuring a dissolved oxygen concentration *in vivo* of a tissue site of a patient. The method includes deploying a sensor at the tissue site in the patient, the sensor comprising a sensing medium, the sensing medium comprising an MR contrast agent for oxygen; and thereafter subjecting the tissue site to electromagnetic radiation and employing an MR-based spectroscopy or other method to analyze the dissolved oxygen concentration *in vivo* at the tissue site.

In yet another aspect, uses for a dissolved oxygen sensor are provided. For example, the sensor may be used to evaluate the state of a tumor, to determine the presence of hypoxia, to evaluate the effectiveness of a treatment strategy on a patient, to schedule therapies at an opportune time to achieve an improved patient outcome, to monitor metabolic activities in specific regions or organs of the body.

In still another aspect, sensor devices and methods for *ex vivo* applications are provided for measuring oxygen concentration. The method may include placing a sensor at a location, e.g., in a process stream, in which the sensor is exposed to a fluid to be analyzed, the sensor comprising a sensing medium, the sensing medium comprising an MR contrast agent for oxygen; and thereafter subjecting the sensor to electromagnetic radiation and analyzing the dissolved oxygen concentration by measuring a change in relaxivity of the sensing medium while the sensor is exposed to the fluid to be analyzed.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is an exploded perspective view, illustrating an embodiment of a sensor having a reservoir for containing an MR contrast agent for oxygen.

FIG. 2 is a perspective view, illustrating the embodiment of FIG. 1 in an assembled state.

FIG. 3 is a chart, illustrating spin lattice relaxation time (T1) as a function of oxygen concentration for HMDSO.

FIG. 4 is a chart, illustrating a sensor's response to an oxygenated environment over time.

FIG. 5 is a chart, illustrating spin lattice relaxation time (T1) as a function of oxygen concentration in a sensor comprising a DDMPS / PDMS composite body.

FIG. 6 is a perspective view, illustrating a sensor having a composite polymeric body.

FIG. 7 is a section view, illustrating one embodiment of a sensor in a bead form.

## DETAILED DESCRIPTION

In one aspect, an implantable sensor is provided for measuring the dissolved oxygen concentration of a fluid *in vivo*. The implantable sensor may be wholly deployable and implantable within a patient and may include a sensing material that is a magnetic resonance (MR) contrast agent for oxygen. The term "implantable" as used herein refers to a device that is configured for implantation. That is, the device is to be introduced into a subject's body by a surgical or medical procedure and remain there after the procedure. The term "wholly deployable" or "wholly deployed" and "wholly implanted" or "wholly implantable" means that there is not a portion of the sensor device that extends out of the patient transcutaneously or from an anatomical orifice. For example, the device may be sized and shaped to be wholly deployed in the body of a human or animal and to remain deployed for a period of time, such as 30 days or more. The device also may have suitable sterility, biocompatibility, and physical and/or chemical integrity to be implanted and remain implanted over the intended duration of use of the device.

Advantageously, in some embodiments, the sensor may be wholly deployed *in vivo* and subjected to repeated measurements thereby overcoming the problems associated with repetitive invasive measurement procedures. Moreover, in some embodiments, the sensor may be wholly deployed to a specific target tissue site of interest to allow for site-specific measurement and analysis. Furthermore, the sensor, which comprises an MR contrast agent for oxygen, may provide a higher degree of measurement sensitivity, accuracy, and precision with respect to oxygen concentration than other measurement techniques. The sensor may be employed in various patients or subjects including human or other mammals.

In one embodiment, the implantable sensor may include a container having a reservoir and a reservoir opening, an oxygen-permeable membrane covering the reservoir opening, and a sensing medium contained in the reservoir. The sensing medium may comprise a MR contrast agent for oxygen, and the sensor may be configured to indicate the dissolved oxygen concentration of the fluid when subjected to MR-based methods. In

another embodiment, the implantable sensor may comprise a solid polymeric article that has an MR contrast agent for oxygen integrated with the polymeric structure of the article. In certain embodiments, the implantable sensor may be in the form of beads or microspheres which have an MR contrast agent for oxygen incorporated within the bead or microsphere.

In another aspect, a method is provided for measuring a dissolved oxygen concentration of a fluid *in vivo*. The method may include deploying a sensor at a tissue site, and thereafter subjecting the tissue site to electromagnetic radiation and employing MR-based methods to analyze the dissolved oxygen concentration of the fluid. The sensor may comprise a sensing medium that comprises an MR contrast agent for oxygen. The MR contrast agent may be contained in a reservoir provided with the sensor. Sensing media is prevented from escaping the device with the use of an impermeable membrane (impermeable to the sensing media, but permeable to dissolved oxygen).

In other aspects, sensors and methods are provided for measuring oxygen concentrations in *ex vivo* environments. Such sensors and methods may utilize the direct measurement of the NMR relaxivity of a sensing medium in contact with the liquid or gas of interest. The oxygen sensors may have advantages over conventional oxygen sensors that are based on a surface reaction such as the automotive oxygen sensor which requires oxygen to react at a precious metal electrode in contact with a solid electrolyte. The present sensors may absorb oxygen throughout the bulk of the material and may therefore be less sensitive to contamination.

Sensors

Implantable sensors are provided for measuring the dissolved oxygen concentration of a fluid *in vivo*. Advantageously, the sensors may be wholly implanted at a tissue site and may be used to take repeated measurements of dissolved oxygen levels at the tissue site without the need for repeated invasive measurement procedures. Specifically, the sensors may be configured to be utilized with standard MR-based spectroscopy. As used herein, the terms "MR-based spectroscopy" and "MR-based methods" broadly refer to analytical and measurement techniques in which a material, such as a material present at a tissue site, is subjected to electromagnetic radiation for purposes of characterization. In particular, the term encompasses analytical techniques in which a magnetic field is applied to a material and the effect of the applied magnetic field

on the material is measured or observed such as H1 NMR (hydrogen-1 nuclear magnetic resonance), Flourine-19 NMR, and MRI (magnetic resonance imaging). Although not limited to H1 NMR based techniques, this is a convenient approach because of the ready access to equipment, appropriate pulse sequences, and software.

One embodiment of an implantable sensor **10** is illustrated in FIG. 1. The implantable sensor **10** may include a container **14** having a reservoir **30** that contains a sensing medium. The container **14** may include a mouth portion **22** and a base portion **28**. The container **14** may further include a reservoir opening **24** within the mouth portion **22** above the reservoir **30**. An oxygen-permeable membrane **16** may be in register with the reservoir opening **24** so as to allow oxygen to diffuse through the membrane **16** and the reservoir opening **24**. For example, the membrane **16** may be attached to the container **14** across the reservoir opening **24**. The implantable sensor **10** may further include a cap **12** that may be attached to the mouth portion **22** of the container **28** to secure the membrane **16** to the implantable sensor **10** in a position over the reservoir **30**. The cap **12** may include a cap opening **18** that is completely or at least partially aligned with the reservoir opening **24** of the container **14** when the cap **12** is secured to the container **14**. The cap opening **18** need not occupy the entire width of the cap but may be adjusted to a size sufficient to allow chemical diffusion of oxygen into and out of the reservoir. Alternatively, there may be a plurality of smaller openings on the cap to insure mechanical stability of the device.

The mouth portion **22** of the container **14** may include an external flange **26** which engages a partial internal flange **20** of the cap **12** when the cap **12** is pressed over the mouth portion **22** of the container **14**, thereby securing the cap **12** to the container **14** and securing the membrane **16** in place over the reservoir **30**. Alternatively, other fastening features may be used for attaching the cap **12** to the container **14**, e.g., male and female threading, tabs, snap fingers, quarter-turn fastening structures and the like. In other embodiments, the membrane **16** may be secured over the reservoir **30** with an adhesive. It is possible that the oxygen permeable membrane **16** may be replaced entirely by a fully solid cap which is thin enough to allow permeability of oxygen into and out of the reservoir. In one embodiment, for example, the cap could achieve the necessary thin cross section by having one or a plurality of blind holes or dimples in its surface.

The implantable sensor **10** of FIG. 1 is shown in an assembled state in FIG. 2. When assembled, the implantable sensor **10** may assume a low-profile shape suitable for wholly deploying at a tissue site of a patient. The oxygen-permeable membrane **16** is exposed to fluids at the tissue site via the cap opening **18** of the cap **12**. As such, oxygen dissolved in the biological fluid at the tissue site may pass through the oxygen-permeable membrane **16** into the sensing medium.

Although the implantable sensor **10** is shown as being substantially cylindrical in shape in FIGs. 1 and 2, the implantable sensor **10** may be formed into many different shapes. Advantageously, the implantable sensor **10** may be shaped and dimensioned for minimally invasive implantation, for example through a needle or trocar. In some embodiments, the implantable sensor **10** may have a diameter, or width in the plane of the membrane **16**, of about 10 mm or less, or more preferably about 1 mm to about 5 mm. In certain embodiments, the implantable sensor **10** may have a diameter less than about 1 mm in diameter. In some embodiments, the implantable sensor **10** may have a depth, measured in a direction substantially perpendicular to the plane of the membrane **16** of about 0.5 mm to about 3 mm, or more preferably about 0.5 mm to about 1 mm. In certain embodiments, the implantable sensor **10** may have a depth less than about 0.5 mm. Other convenient dimensions are those compatible with biopsy tools such as a needle biopsy device.

The container **14** and the cap **12** can be made of various biocompatible materials. The container 14 and the cap **12** may comprise the same material or they may comprise different materials. Preferably, the container **14** and the cap **12** comprise a biocompatible polymeric material, such as a polyethylene polymeric blend, that does not interfere with the detection of dissolved oxygen in the sensing medium. In some embodiments, the container **14** and/or the cap **12** comprise a material that contrasts with the surrounding tissue when subjected to MR-based spectroscopy.

In some embodiments, the sensor **10** comprises a sensing medium in the reservoir **30** that comprises an MR contrast agent for oxygen. The term "MR contrast agent for oxygen" as used herein refers to material suitable for indicating the dissolved oxygen concentration within the material when employing MR-based spectroscopy by enhancing the desired signal beyond that which is provided by background molecules (i.e., molecules naturally present at the site of implantation), such as water molecules. For example, the

MR contrast agent for oxygen may comprise a material having a spin-lattice relaxation time (T1) that is dependent on dissolved oxygen concentration. In certain embodiments, the sensing medium may exhibit sufficient sensitivity to resolve oxygen concentration at low oxygen concentrations, particularly between about 0% and 2% oxygen. These sensing mediums include certain liquid or solid compounds having MR properties that are sensitive to oxygen concentration. Particulate suspensions or emulsions of such materials are contemplated.

Proton spins can be flipped into different planes and axis of rotation when protons are irradiated with a radio frequency (RF) pulse. This change in rotation is temporary and the direction in magnetic moment eventually returns to the original configuration. In particular, the restoration of magnetic moments to the original axis can be characterized by T1. As T1 is a material property, it can provide a reliable source of contrast in MRI images; T1 maps are frequently used in imaging applications to distinguish between different anatomical structures. Paramagnetic molecules or particulates that decrease the relaxation time of surrounding molecules can be used to enhance contrast of T1 maps. They can also provide a mechanism for sensing. For example, dissolved oxygen molecules are paramagnetic and can decrease the T1 relaxation time of water protons (or other spin bearing atoms) surrounding it. Thus, the T1 value of these mixtures would depend on the concentration of dissolved oxygen and thus dissolved oxygen concentration can be determined by averaging the T1 of the area.

Instead of using water protons, other materials can also be read using MR-based spectroscopy (e.g., H1 NMR, F119 NMR, or MRI) and some of these materials are more sensitive to concentrations of dissolved oxygen. Indeed, using materials other than water has the advantage that the sensing medium can give a different MR signature and can be more easily distinguished from the background water molecules inside the body. Siloxanes may be particularly useful in sensors as MR contrast agents for oxygen. One particularly useful siloxane is hexamethyldisiloxane (HMDSO), which is a highly hydrophobic and non-polar molecule. This molecule has a high solubility for oxygen, and has a single peak for hydrogen NMR. FIG. 3 illustrates the dissolved oxygen dependent T1 relaxation of HMDSO as measured with a Bruker Minispec. Other potentially useful siloxanes include octamethyltrisiloxane, decamethyltetrasiloxane, dodecamethylpentasiloxane,

hexamethylcyclotrisiloxane, octamethylcyclotetrasilane, decamethylcyclopentasiloxane, dodecamethylcyclohexasiloxane, and PDMS.

FIG. 4 illustrates magnetic relaxation properties of HMDSO loaded in an implantable sensor. The T1 measurements were taken using a single sided magnet (a modified version of an NMRMouse™). The data demonstrates that the sensor is capable of distinguishing between different concentrations of dissolved oxygen in a surrounding environment of aqueous solution. In these measurements, T1 of devices are measured before and after complete deoxygenation of the surrounding environments, and can be seen to reflect increasing levels of oxygen in the surrounding medium. FIG. 4 illustrates the sensor's response to changes in oxygenation conditions. The "closed" data series represent a device that has been left in the deoxygenated environment, whereas the "open" data series represent a device that has been exposed to atmospheric air after the first data point. The sensors may be fully reversible, which would allow for repeated sampling of the same area with changing oxygen content over time.

Other potentially useful materials that may be employed in sensors as a sensing medium include, but are not limited to, compounds that have a high oxygen solubility. For example, perfluorocarbons, a class of highly fluorinated and inert organic compounds, may be used in place of siloxanes as oxygen sensitive agents for use in Fluorine-19 MR systems. Exemplary perfluorocarbons include perfluoro-15-crown-5-ether, hexafluorobenzene, and perfluorotributylamine.

In another embodiment, the implantable sensor may be in the form of a solid polymeric article that has an MR contrast agent for oxygen integrated with the polymeric structure of the article, e.g., by the direct incorporation of MR-readable, oxygen sensitive materials into a polymeric matrix. In a certain embodiment, the implantable sensor may be a cured composite article comprising an MR contrast agent for oxygen dispersed throughout a polymeric matrix. The polymeric matrix material may be permeable to oxygen and may be configured to prevent the diffusion of MR contrast agent for oxygen from the structure at least over the period the sensor device is deployed *in vivo*, e.g., 1 to 6 months. An exemplary polymeric matrix material is polydimethylsiloxane ("PDMS"). Other polymers that can serve as the matrix material include various UV-curable epoxies and silicones.

An exemplary polymeric composite sensor **30** is illustrated in FIG. 6. The sensor **30** is formed of a cured polymeric body **32** that may be substantially uniform in composition throughout the body **32**. The cured polymeric body **32** may be in the form of a polymeric matrix having an MR contrast agent for oxygen dispersed throughout the body **32**. In some embodiments, the MR contrast agent for oxygen is dispersed substantially uniformly throughout the body **32**. The MR contrast agent for oxygen may be, for example, a siloxane such as HDMSO or dodecamethylpentasiloxane (DDMPS). In the present example, the body **32** includes corner or portions **34**, which may be used as attachment points for securing the sensor **32** to a specific tissue site or otherwise facilitate the embedding of the sensor **32** at the specific tissue site. The body **32** may be formed in any regular or irregular shape as desired.

To fabricate such sensors, an MR contrast agent for oxygen, such as a siloxane, may be added to an uncured liquid polymer base, such as SYLGARD® 184 elastomer base from Dow Corning, and mixed thoroughly. An appropriate curing agent may then may be added, and the mixture/solution may be cured, e.g., with heat treatment, to form a solid composite article. These solid composite articles may be directly used in oxygen sensing applications without further modification or can be coated with other materials to enhance biocompatibility, stability, and/or containment of the MR contrast agent for oxygen. For example, the polymeric body may further include PDMS or another oxygen permeable material that is completely or substantially impermeable to the MR contrast agent for oxygen.

Polymeric composite sensors may be made in various shapes and sizes. In certain embodiments, the sensor is about 1 mm or more in size. Such a size is suitable for imaging based on the resolution of most clinical scans. The shape of devices may be negative impressions of the mold forms in which they are cured. The mold forms and sensor shapes can be designed in shapes that facilitate implantation. They can also be designed to impact particular features on molded devices, such as anchor points for attaching the device to implantation site.

In another embodiment, the implantable sensor may be in the form of a beads or microspheres. For example, in one embodiment, the sensor is composed of a single or a plurality of fine beads or microspheres each containing an agent whose MR relaxivity is sensitive to oxygen. The beads or microspheres may consist of a core of the MR contrast

agent encapsulated by the oxygen permeable material. The beads may be spherical or non-spherical (e.g., elongated, like grains of rice). One advantage of such an embodiment is that the sensor(s) may be injected through a conventional hypodermic needle/syringe into one or more tissue sites in the patient, providing a minimally invasive route to deploy the sensor into the patient's body. In some embodiments, the beads or microspheres may have a volume average diameter of about 100 microns or less. In certain embodiments, the beads or microsperes may have a volume average diameter of about 20 microns or less. The beads or microsperes may be provided in an injectable formulation, for example, as a colloidal or other suspension with pharmaceutically acceptable liquid known in the art.

In one example, each bead is composed of a shell that has a primary purpose of providing mechanical stability and permeability to oxygen and an interior volume in which the MR sensitive material resides. The shell and interior volume materials may be very similar to one another in their chemistry, but they may differ in their mechanical properties. The interior may, for example, be a low molecular weight or liquid silicone derived material but the shell may be a high molecular weight or cross linked silicone material in such a way that it provides sufficient strength to the bead. In another example, the core and the shell are comprised of the same material and substantially indistinguishable.

An exemplary embodiment of a bead sensor **40** is illustrated in FIG. 7. The sensor **40** includes an oxygen permeable shell **42** that surrounds a sensing medium core **44**. The sensing medium core **44** more comprise an MR contrast agent for oxygen, such as a siloxane.

In another embodiment, the beads may be in the form of composite polymeric particles comprising an MR contrast agent for oxygen dispersed throughout a polymeric matrix. For example, the particles may comprise a PDMS matrix and a siloxane, such as DDMPS or HMDSO, dispersed throughout the polymeric matrix. In some embodiments, no shell is provided around the composite polymeric particles. In other embodiments, an oxygen-permeable shell material may be provided around each of the beads for improved biocompatibility or stability.

The beads may be formulated into an injectable suspension using one or more liquid vehicles or pharmaceutically-acceptable excipients known in the art. In a particular

embodiment, it may be advantageous to incorporate a gel in the formulation of such beads so that they remain in one location within the body after injection, e.g., proximate to the injection site. Suitable gels and gelling materials for parenteral use are known in the art. The volume of the formulation (and beads) administered in a given injection is adjustable. Thus, one may insure that the total volume of oxygen sensitive material is sufficient to image in any given MRI instrument.

The sensor may be packaged for shipping and storage. It may be sterilized before or after packaging. For example, sterilization may be achieved by ionizing radiation (gamma or electron beam) or ethylene oxide (EtO) as known in the art. In one embodiment, the container is made from a gamma-irradiation stable, biocompatible polymer known in the art.

Methods of Use

In another aspect, a method is provided for measuring the dissolved oxygen concentration of the extracellular environment *in vivo*. The method may include deploying a sensor at a tissue site, and thereafter subjecting the tissue site to electromagnetic radiation and employing MR-based spectroscopy to analyze the dissolved oxygen concentration of the fluid. The sensor may comprise a sensing medium that comprises an MR contrast agent for oxygen contained in a reservoir.

In some embodiments, the implanted device may be used to analyze the dissolved oxygen concentration of a tissue site at the same location(s) over time. Because of the non-invasive nature of the "sampling" analysis, the "sampling" may advantageously be performed more frequently or over a shorter sampling interval. Compared to the injection of HMDSO directly into tissue, the implantable devices may also offer the advantage of confining the molecules to a known space and also keeping the amount of HMDSO sampled constant. In injection methods, it may be difficult to ascertain a specific amount of contrast agent in a specific area; as the contrast agent is cleared from the body, the exact amount of contrast agent remaining can also be difficult to determine. The use of the sensor devices may alleviate these problems, as the molecules are prevented from escaping by the oxygen permeable membrane.

In some embodiments, one or more sensors are implanted in a patient. For example, the sensors may be placed at or adjacent to or within an organ or tissue site of interest in the patient, such as the brain, the heart, or other vital organ. The sensors may

also be placed at or around the site of a tumor. The sensors may be subjected to MR-based spectroscopy for analysis or imaging. In some embodiments, the sensors and tissue site may be analyzed by measuring T1 relaxation times using MRI. These measurements may be taken repeatedly, such as over the course of a patient's treatment for a disease.

In some embodiments, one or more sensors are used to monitor hypoxia within solid tumors. The one or more sensors may be implanted in or around the tumor tissue. For example, the one or more sensors may be implanted during a resection surgery or a biopsy procedure. Thereafter, the tumor site may be analyzed or imaged using MR-based spectroscopy, such as H1 NMR or MRI. The measurements may be repeated regularly and non-invasively as needed. A physician or other health care professional may use the dissolved oxygen data obtained from the sensors to manage the treatment of the patient. For example, the physician or health care professional may used the dissolved oxygen data from the sensor to evaluate the state of the tumor, to identify hypoxia conditions in tumors, to evaluate the effectiveness of a treatment strategy on the patient, and to schedule therapies, such as radiotherapy, at the most opportune times to achieve improved outcomes.

Other applications for measurement of dissolved oxygen include the monitoring of metabolic activities in specific regions or organs of the body. One highly investigated area is the use of MRI techniques to probe oxygen usage in the brain in functional MRI studies. Biologists studying neural activities can glean information on the functions of those areas by monitoring the usage of oxygen in different regions of the brain. Oxygen depletion in parts of the body can be detected with implanted sensors, specifically, detecting oxygen depletion in vital organs such as the heart or brain can potentially inform physicians of problems (e.g., minor myocardial infarction or stroke) that can otherwise go unnoticed.

Another application is the staging of compartment syndrome in trauma patients and whether a fasciotomy is indicated. The swelling that occurs in an injured limb of a trauma patient can dramatically reduce blood flow to the limb which can ultimately lead to necrosis of the tissue. A surgical procedure where the fascia is cut to reduce such pressure (a fasciotomy) is called for when there is insufficient circulation in the limb. One indicator of that circulation is interstitial dissolved oxygen. An oxygen sensitive device placed in the limb and monitored over time will be very helpful in quantitative assessment of the level of compartment circulation.

These sensor devices may be used in other clinical and research applications. The sensor devices may provide physicians and researchers unprecedented access to real-time $pO_2$ data without affecting patients' quality of life.

These sensor devices may also be employed in *ex vivo* applications. For example, the sensors may be used in *ex vivo* applications in which it is desirable to determine the oxygen concentration of a fluid, such as a liquid or a gas. In some embodiments, an electromagnet, such as an electromagnet comprising a coil and a rare-earth magnet, may be used to measure the relaxivity of a sensing medium when it is in contact with the fluid. The sensing medium may be an MR contrast agent for oxygen. As the oxygen content of the fluid changes, the relaxivity of the sensor medium will also change, and the change in the relaxivity of the sensing material may be detected by a sensing circuit that is electrically connected to the electromagnet. The sensing circuit may be calibrated to detect changes in the relaxivity of the sensor material that are of significance to the particular sensing application. For example, in sensing application in which a 1% change in oxygen concentration from a set point of 10 volume percent oxygen concentration would be of significance, the sensor may be calibrated by employing the appropriate amount of sensing medium with an appropriately-sized electromagnet and an appropriately-calibrated sensing circuit to detect changes of the magnitude of concern in the sensing application. Of course, the foregoing percentages are only intended to be illustrative, and one of ordinary skill in the art will appreciate that, consistent with the present disclosure, the actual control set points and degree of change in concentration that is of significance may vary depending on the particular application and the disclosed sensors and methods may be calibrated to the particular application.

In a certain embodiment, the sensor may be employed in an automobile to determine oxygen concentration in an exhaust stream. For example, a sensor may be placed in the exhaust stream flow path, such as downstream and/or upstream of a catalytic converter in a location in the exhaust stream flow path that exposes the sensing medium to the exhaust stream. The sensing medium may be positioned and arranged with respect to an electromagnet such that changes in the relaxivity of the sensing medium may be detected by a sensing circuit that is electrically coupled to the electromagnet. The sensing circuit may detect the oxygen concentration of the exhaust gas at the location of the sensor. The oxygen concentration may be an absolute oxygen concentration or it may be

change in concentration from a pre-designated control set point. The sensor may communicate with a controller, e.g., via an electrical connection between the sensor and controller or via telemetry. The controller may then control an actuation function when the measured oxygen concentration meets, exceeds, or is less than a set point. For example, the controller may control the actuation of a change in fuel injection, e.g., by injector pulse-width modulation or by altering pulse frequency, to achieve a desired air-fuel ratio, such a stoichiometric air-fuel ratio.

In addition to automotive sensing applications, other *ex vivo* applications are envisioned for the present sensors. For example, the sensors may be used to measure dissolved oxygen in bodies of water such as lakes, rivers, and oceans. In such applications, the sensing medium may be submerged into the body of water, and a sensing circuit that is coupled to an electromagnet may detect changes in relaxivity of the sensing medium as the concentration of dissolved oxygen around the sensor changes.

## EXAMPLE

Three composite sensors having different concentrations of contrast agent in a matrix material were produced. Each sensor was produced by adding dodecamethylpentasiloxane (DDMPS) to SYLGARD® 184 elastomer base from Dow Corning. The liquid mixture was then mixing thoroughly, poured into a mold, and then cured to produce solid composite sensors. The three samples were 75% DDMPS, 50% DDMPS, and 25% DDMPS (percentages expressed in volume percent).

Spin-lattice relaxation time (T1) data has been collected for each device. Each of the three molded PDMS/siloxane devices were placed in a 10mm NMR tube and then inserted into a Bruker Minispec TD-NMR system for measurements. Gas composition in the tube was altered with the use of a gas mixer that outputs gas mixtures at different oxygen concentrations. The T1 data for three samples is illustrated in FIG. 5. The numbers at the top of the graph indicate the oxygen concentration around the sample when measurements were taken. As shown in FIG. 5, the measured T1 for each sample correlate strongly with oxygen concentration and therefore provide a good indicator for dissolved oxygen concentration.

While the present invention may be embodied in many different forms, disclosed herein are specific illustrative embodiments thereof that exemplify the principles of the

invention. It should be emphasized that the present invention is not limited to the specific embodiments illustrated.

We claim:

1. A sensor for measuring a dissolved oxygen concentration *in vivo* when implanted at a tissue site, comprising:

an implantable article comprising a sensing medium retained within the implantable article by an oxygen-permeable material, the sensing medium comprising an MR contrast agent for oxygen;

wherein the sensor is configured to indicate the dissolved oxygen concentration *in vivo* at the tissue site when subjected to an MR-based method.

2. The sensor of claim 1, wherein the oxygen-permeable material is a polymeric matrix and the sensing medium is dispersed throughout the polymeric matrix.

3. The sensor of claim 2, wherein the polymeric matrix comprises PDMS.

4. The sensor of claim 1, wherein the oxygen-permeable material is a membrane covering a reservoir containing the sensing medium.

5. The sensor of claim 1, wherein the sensor is in the form of a bead, and the oxygen-permeable material is a shell covering a core comprising the sensing medium.

6. The sensor of claim 1, wherein the sensor is in the form of a bead, and the oxygen-permeable material is a polymeric matrix and the sensing medium is dispersed throughout the polymeric matrix.

7. The implantable sensor of any one of claims 1-6, wherein the sensing medium has a spin-lattice relaxation time that is dependent on dissolved oxygen concentration.

8. The implantable sensor of any one of claims 1-7, wherein the sensing medium comprises a siloxane or a perfluorochemical.

9. An implantable sensor for measuring a dissolved oxygen concentration *in vivo* when implanted at a tissue site, comprising:

one or more beads or microspheres which comprise an agent having an MR relaxivity that is sensitive to oxygen,

wherein the one or more beads or microspheres are injectable and possess a volume of the agent effective to indicate the dissolved oxygen concentration of the tissue site *in vivo* when subjected to an MR-based method.

10. The implantable sensor of claim 9, wherein the one or more beads or microspheres comprises silicone.

11. The implantable sensor of claim 9 or 10, wherein the bead or microsphere of the one or more beads or microspheres comprises a shell and an interior volume, the shell being oxygen permeable and containing the agent in the interior volume.

12. The implantable sensor of claim 11, wherein the shell comprises a high molecular weight or crosslinked silicone and the interior volume comprises a low molecular weight or liquid silicone derived material.

13. The implantable sensor of any one of claims 9 to 12, further comprising a pharmaceutically acceptable liquid vehicle in which the one or more beads or microspheres are dispersed.

14. The implantable sensor of claim 13, wherein the liquid vehicle comprises a gel or gelling material effective to retain the one or more beads or microspheres substantially at a site of injection of the sensor within a patient.

15. An implantable sensor for measuring a dissolved oxygen concentration of a fluid *in vivo* when implanted at a tissue site, comprising:

a container having a reservoir and a reservoir opening;

an oxygen-permeable membrane covering the reservoir opening; and

a sensing medium contained in the reservoir, the sensing medium comprising an MR contrast agent for oxygen;

wherein the sensor is configured to indicate the dissolved oxygen concentration of the fluid when subjected to an MR-based method.

16. The implantable sensor of claim 15, wherein the sensing medium has a spin-lattice relaxation time that is dependent on dissolved oxygen concentration.

17. The implantable sensor of claim 15 or 16, wherein the sensing medium comprises a siloxane or perfluorocarbon.

18. The implantable sensor of any one of claims 15 to 17, wherein the oxygen-permeable membrane is impermeable to the sensing medium.

19. The implantable sensor of any one of claims 15 to 18, wherein the container comprises a material that contrasts with the tissue site when subjected to MR-based spectroscopy.

20. A method of measuring oxygen concentration, comprising:

placing a sensor at a location in which the sensor is exposed to a fluid to be analyzed, the sensor comprising a sensing medium, the sensing medium comprising an MR contrast agent for oxygen; and thereafter

subjecting the sensor to electromagnetic radiation and analyzing the dissolved oxygen concentration by measuring a change in relaxivity of the sensing medium while the sensor is exposed to the fluid to be analyzed.

21. A method of measuring a dissolved oxygen concentration *in vivo* of a tissue site of a patient, comprising:

(a) deploying a sensor at the tissue site in the patient, the sensor comprising a sensing medium, the sensing medium comprising an MR contrast agent for oxygen; and thereafter

(b) subjecting the tissue site to electromagnetic radiation and employing an MR-based spectroscopy or other method to analyze the dissolved oxygen concentration *in vivo* at the tissue site.

22. The method of claim 20 or 21, wherein the sensor comprises a reservoir containing the sensing medium.

23. The method of claim 21, wherein the tissue site comprises a tumor.

24. The method of claim 23, wherein the dissolved oxygen concentration of the tissue site is analyzed to evaluate the state of the tumor.

25. The method of claim 21, wherein the dissolved oxygen concentration of the tissue site is analyzed to determine the presence of hypoxia.

26. The method of claim 21, wherein the dissolved oxygen concentration of the tissue site is analyzed to evaluate the effectiveness of a treatment strategy on the patient.

27. The method of claim 21, wherein the dissolved oxygen concentration of the tissue site is analyzed to schedule a therapy on the patient.

28. The method of claim 21, wherein the tissue site is the brain of the patient.

29. The method of claim 28, wherein the dissolved oxygen concentration of the tissue site is analyzed in conjunction with a functional MRI study.

30. The method of claim 21, wherein the dissolved oxygen concentration of the tissue site is analyzed to monitor metabolic activities in specific regions or organs of the body of the patient.

31. The method of any one of claims 21 to 30, wherein the MR-based spectroscopy comprises H1 NMR, Fluorine-19 NMR or MRI.

32. The method of any one of claims 21 to 31, wherein the dissolved oxygen concentration of the tissue site is analyzed by measuring T1 relaxation.

33. The method of any one of claims 21 to 32, wherein step (b) is repeated multiple times over the course of a treatment.

34. The method of claim 20, wherein the sensor is disposed in contact with a combustion gas exhaust stream.

35. Use of a sensor comprising a sensing medium contained in a reservoir, the sensing medium comprising an MR contrast agent for oxygen as a dissolved oxygen sensor.

36. Use of a sensor comprising a sensing medium and an oxygen permeable material, the sensing medium comprising an MR contrast agent for oxygen in MR-based spectroscopy to analyze the dissolved oxygen concentration of the fluid, to evaluate the state of a tumor, to determine the presence of hypoxia, to evaluate the effectiveness of a treatment strategy on a patient, to schedule therapies for a patient, or to monitor metabolic activities in specific regions or organs of the body.

37. Use of a sensor comprising a sensing medium and an oxygen permeable material, the sensing medium comprising an MR contrast agent for oxygen in H1 NMR or MRI.

38. The use of any one of claims 36 to 37, wherein the oxygen permeable material is an oxygen-permeable membrane covering a reservoir.

39. A sensor for measuring oxygen concentration in a fluid *ex vivo*, comprising:

an article comprising a sensing medium retained within the article by an oxygen-permeable material, the sensing medium comprising an MR contrast agent for oxygen;

wherein the sensor is configured to contact the fluid and indicate the oxygen concentration in the fluid when the sensor is subjected to an MR-based method.

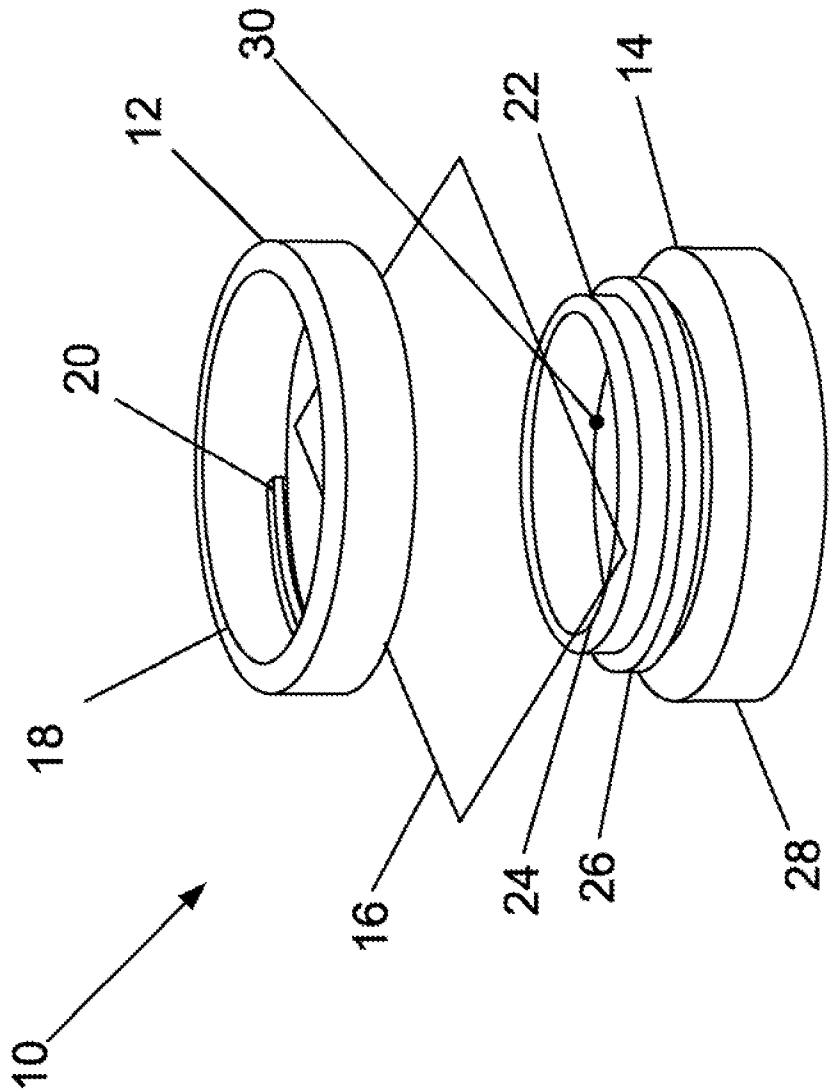



FIG. 1

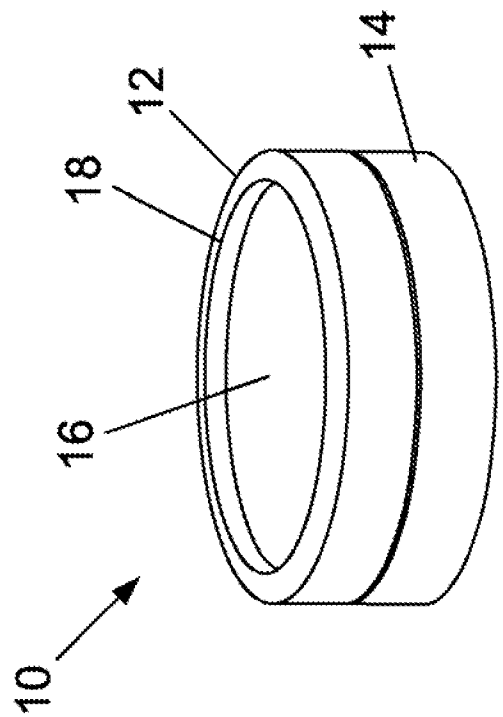
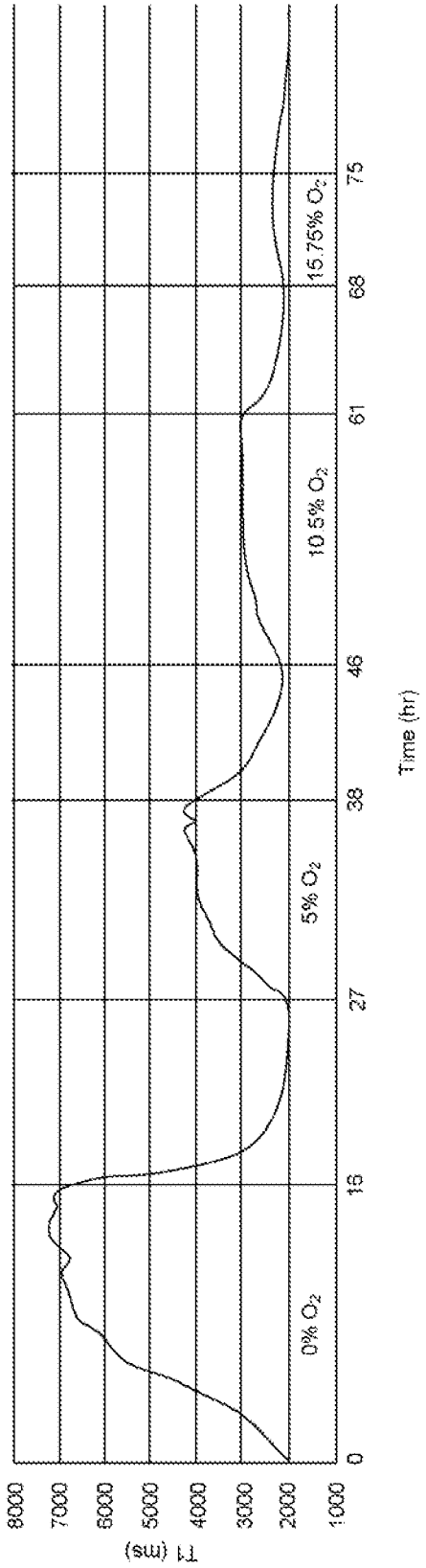



FIG. 2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5000
4000
3000
2000
1000
0
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Time (hr)
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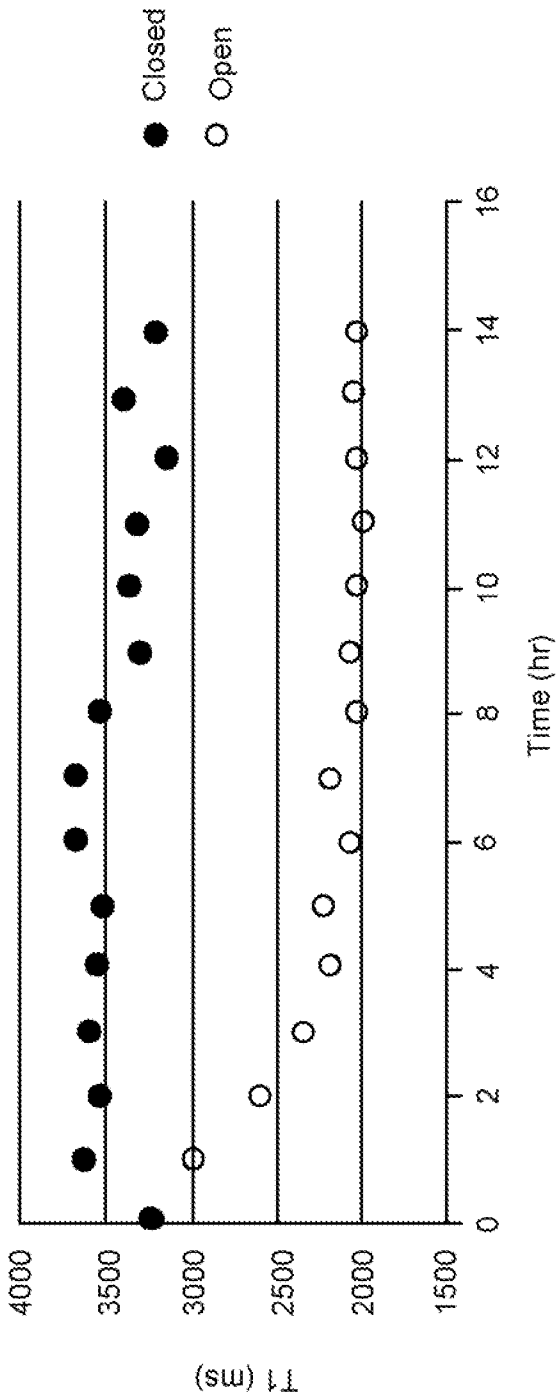
5% O2
10.5% O2
15.75% O2

FIG. 3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Open
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2500
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4
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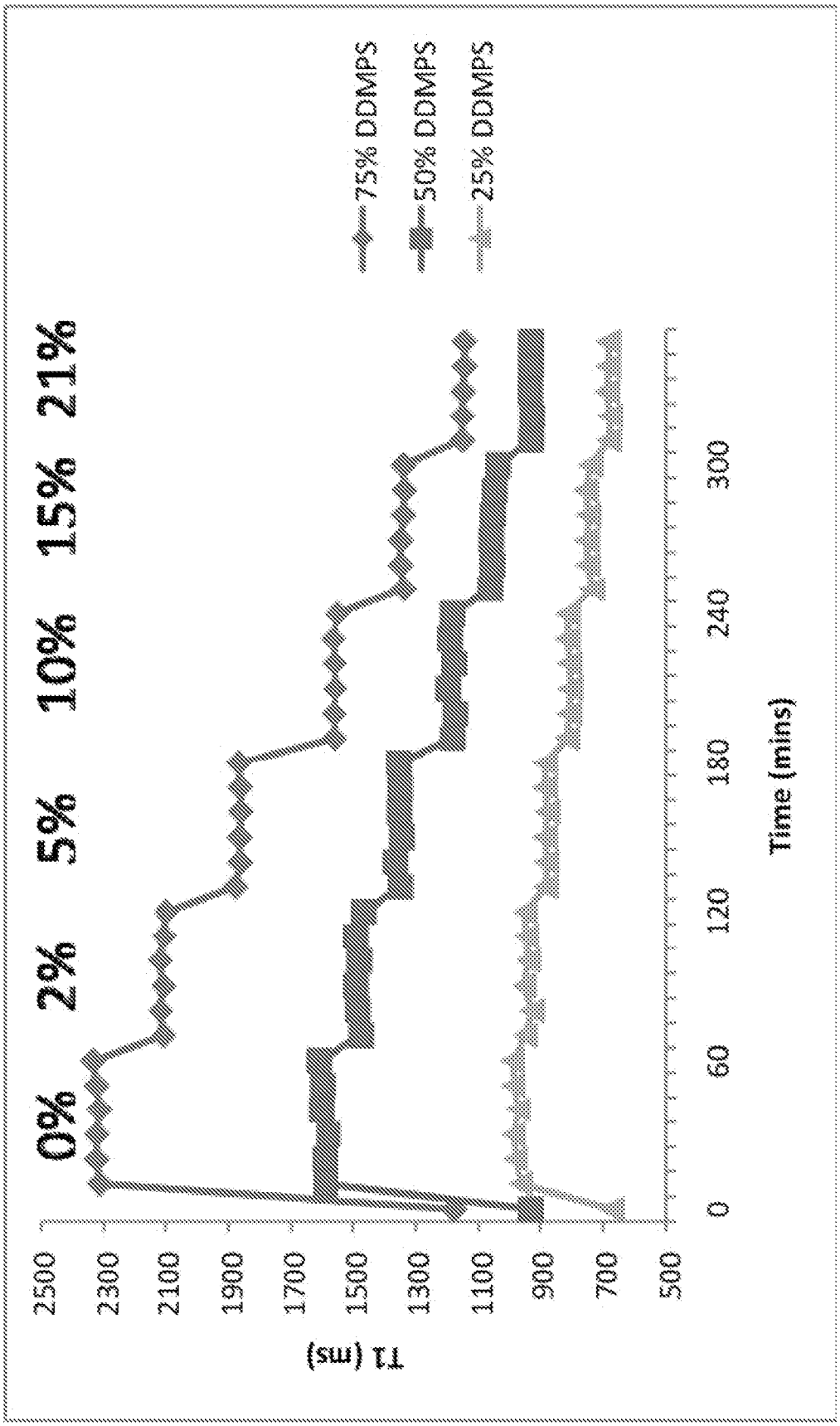
8
10
12
14
16
Time (hr)

FIG. 4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10%
15%
21%
75% DDMPS
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T1 (ms)
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1300
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900
700
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60
120
180
240
300
Time (mins)

FIG. 5

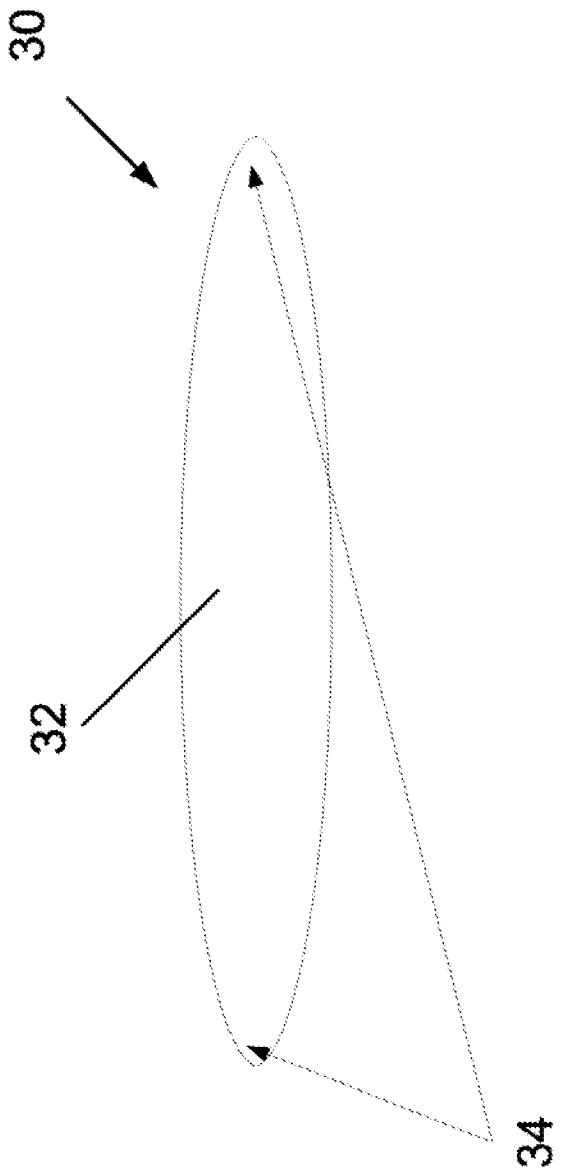


FIG. 6

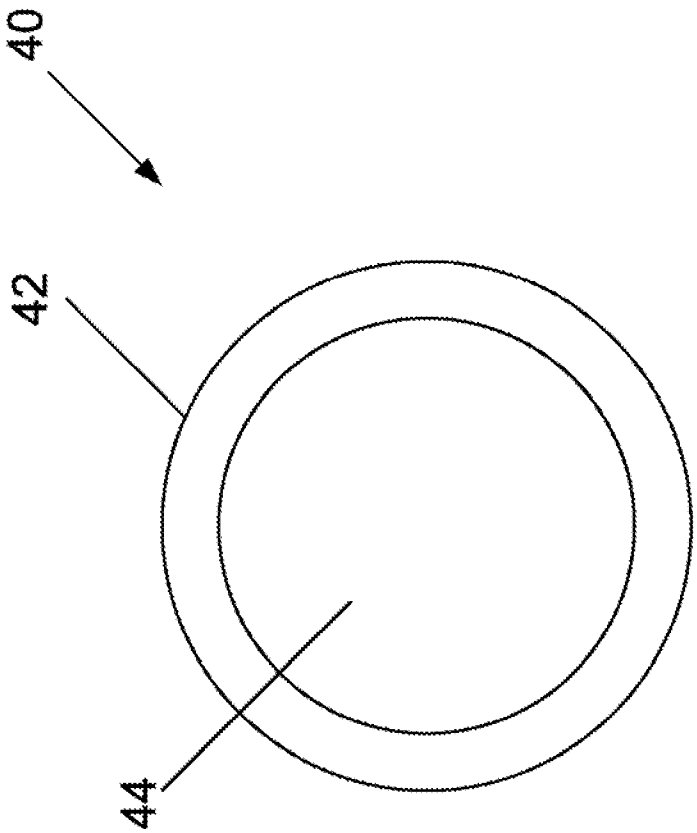


FIG. 7

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/035146

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/145 A61B5/055 A61K49/06
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, INSPEC, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | NOETH U ET AL: "19F-MRI IN VIVO DETERMINATION OF THE PARTIAL OXYGEN PRESSURE IN PERFLUOROCARBON-LOADED ALGINATE CAPSULES IMPLANTED INTO THE PERITONEAL CAVITY AND DIFFERENT TISSUES", MAGNETIC RESONANCE IN MEDICINE, ACADEMIC PRESS, DULUTH, MN, US, vol. 42, no. 6, 1 January 1999 (1999-01-01), pages 1039-1047, XP001162703, ISSN: 0740-3194, DOI: DOI:10.1002/(SICI)1522-2594(199912)42:6<1039::AID-MRM8>3.0.CO;2-N page 1039, left-hand column, paragraph 1 - page 1042, right-hand column, last paragraph<br>-----<br>-/-- | 1,4,5, 7-9, 11-14,39 |

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 11 August 2011 | 19/08/2011 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Völlinger, Martin |

3

Form PCT/ISA/210 (second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/035146

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 20-38
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 2005/097208 A2 (UNIV FLORIDA [US]; ROSS EDWARD ALLAN [US]; BATICH CHRISTOPHER DAVID [U) 20 October 2005 (2005-10-20)<br>claims 28-31<br>page 1, last paragraph - page 2, paragraph 2<br>page 13, paragraph 1 - paragraph 2<br>page 15, paragraph 2 - page 17, paragraph 1<br>page 22, paragraph 2<br>page 23, paragraph 2 - page 24, paragraph 1<br>page 31, paragraph 18 - page 32, paragraph 2 | 1,4,5, 7-9, 11-13,39 |
| X | US 5 498 421 A (GRINSTAFF MARK W [US] ET AL) 12 March 1996 (1996-03-12)<br>column 29, line 13 - line 42 | 1,4,5, 7-9, 11-13,39 |
| X | US 2003/199687 A1 (YALPANI MANSSUR [US]) 23 October 2003 (2003-10-23)<br>paragraph [0023] - paragraph [0024]<br>paragraph [0043]<br>paragraph [0157] - paragraph [0158]<br>paragraph [0002] | 1,2, 6-10,13, 39 |
| X | US 5 527 521 A (UNGER EVAN C [US]) 18 June 1996 (1996-06-18)<br>column 2, lines 7-13<br>column 2, line 36 - line 45 | 1-3, 6-10,13, 39 |
| X | WO 94/03210 A1 (CANCER RES INST [GB]; ROWLAND IAN JOHN [GB]; LEACH MARTIN OSMUND [GB];) 17 February 1994 (1994-02-17)<br>page 6, line 2 - line 6<br>page 14, line 2 - line 3<br>page 15, line 1 - line 18<br>page 17, line 19 - line 20<br>page 23, line 6<br>page 29, line 18 - line 20<br>page 30, line 2 - line 11 | 1-3, 6-10,13, 39 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/035146

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| US 2003199687 A1 | 23-10-2003 | US 2006235193 A1 | 19-10-2006 |
| US 5527521 A | 18-06-1996 | NONE | |
| WO 9403210 A1 | 17-02-1994 | NONE | |

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/** 210

Continuation of Box II.1

Claims Nos.: 20-38

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery Independent method claims 20 and 21 expressly claim the step of placing/deploying a sensor. According to the description, page 4, lines 10,11 this step is performed by a surgical procedure. Claims 22-34 are dependent on claims 20 and/or 21 and therefore also comprise the surgical step. The subject-matter of use claims 35-37 also comprise the use indicated on page 4, lines 10,11, i.e. a use which comprises a surgical step.