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(54) SENSING AND INTERACTIVE DRUG DELIVERY

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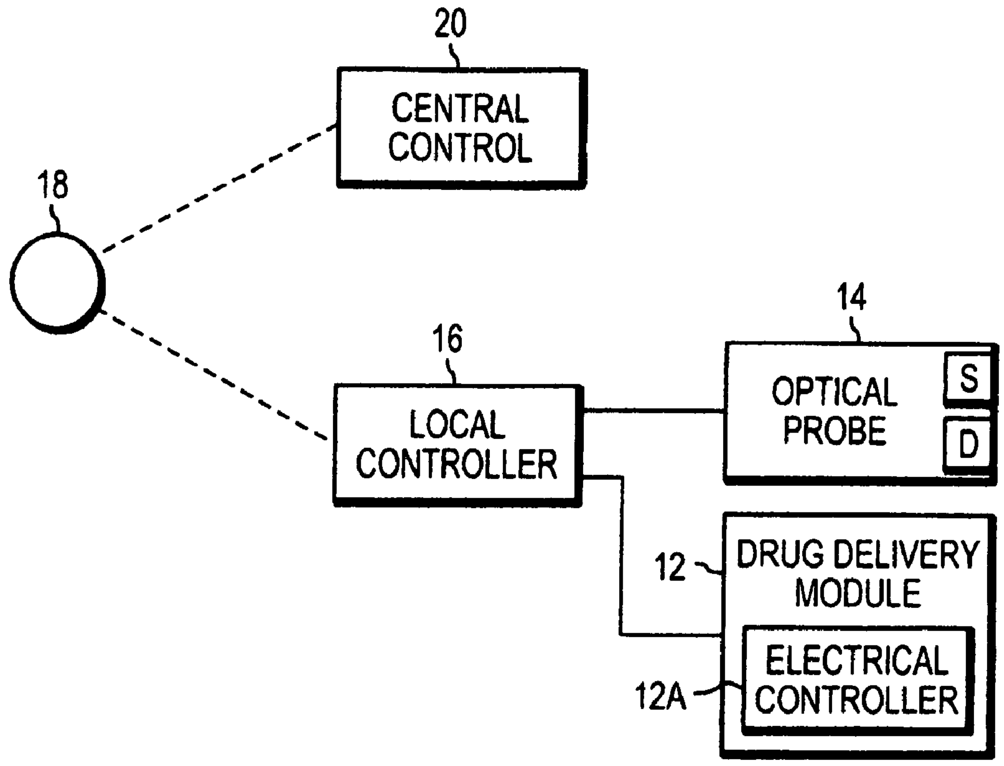
(57) **ABSTRACT**

An interactive drug delivery system includes a drug delivery module, an optical probe, a local controller, and an optional central controller. The drug delivery module is constructed and arranged to deliver selected amounts of a drug into a subject. The optical probe is constructed and arranged to detect in a selected tissue region of the subject a manifestation caused by the delivered drug. The local controller is constructed and arranged to receive data from or transmit data to the optical probe and the drug delivery module. The local controller is arranged to correlate optical data, received from the optical probe, to selected data and provide signals to the drug delivery module for adjusting the amounts of the drug to be delivered into the subject.



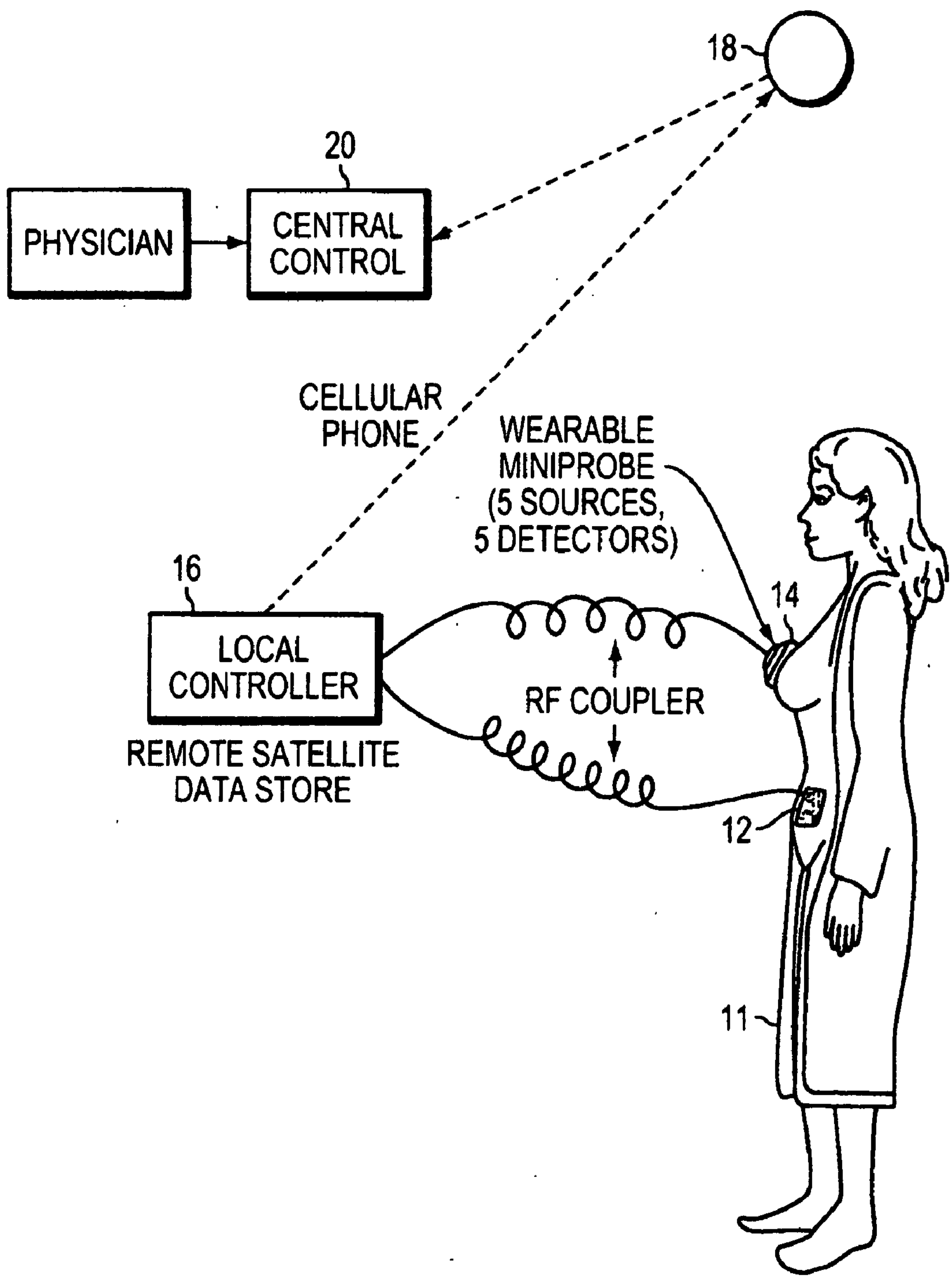

18
20
PHYSICIAN
CENTRAL CONTROL
CELLULAR PHONE
WEARABLE MINIPROBE (5 SOURCES, 5 DETECTORS)
16
LOCAL CONTROLLER
14
RF COUPLER
REMOTE SATELLITE DATA STORE
12
11

FIG. 1

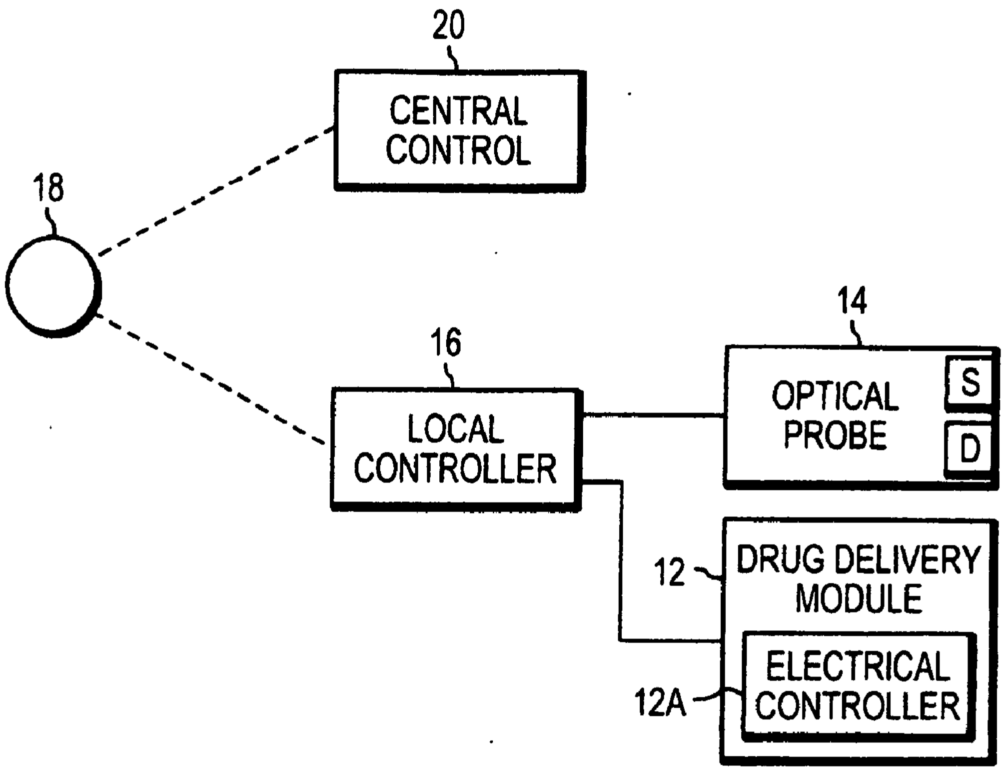

20
CENTRAL CONTROL
18
16
LOCAL CONTROLLER
14
OPTICAL PROBE
S
D
12
DRUG DELIVERY MODULE
12A
ELECTRICAL CONTROLLER

FIG. 2

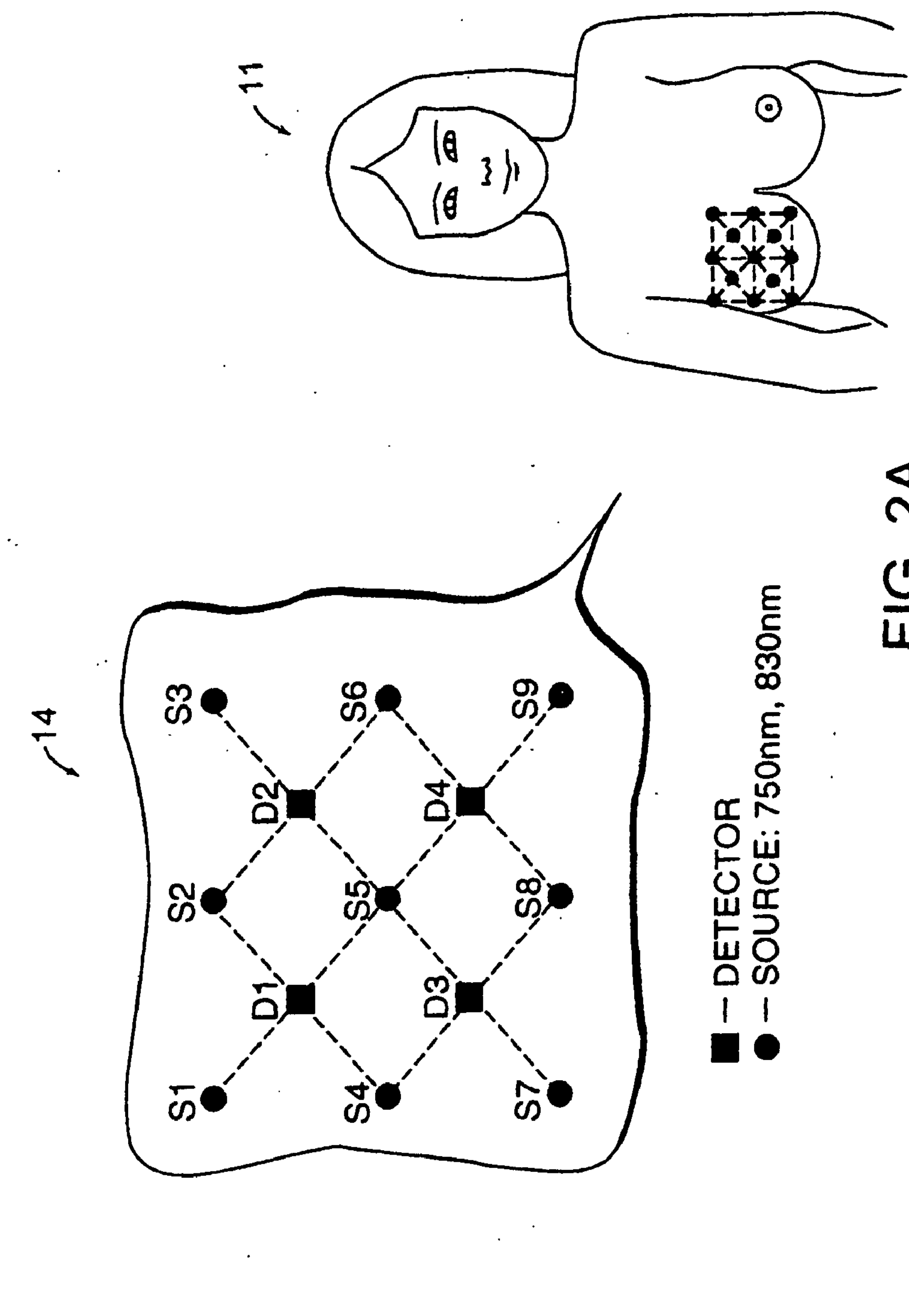
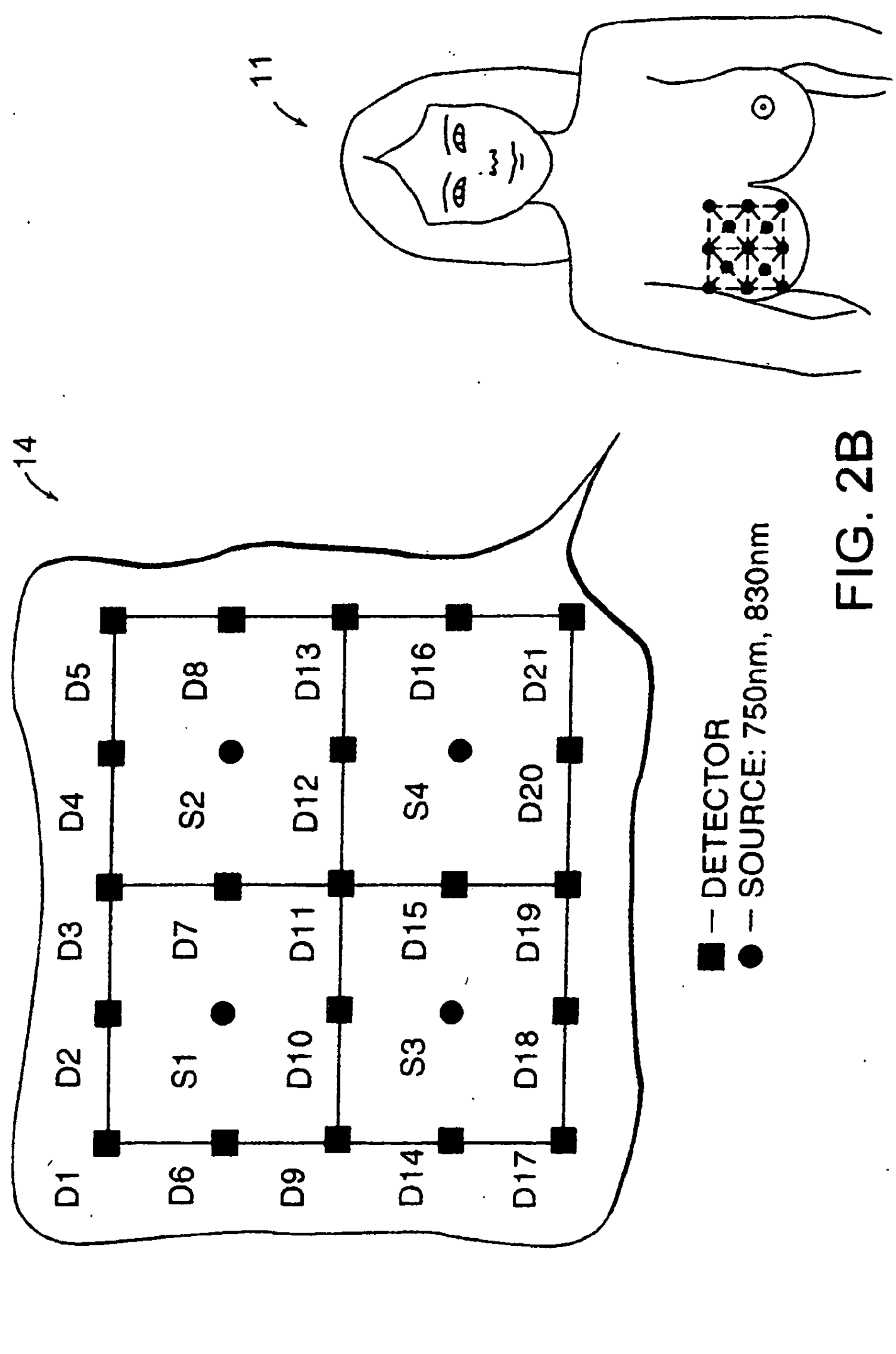

14
11
S1
S2
S3
D1
D2
S4
S5
S6
D3
D4
S7
S8
S9
— DETECTOR
— SOURCE: 750nm, 830nm

FIG. 2A



11
14
D1
D2
D3
D4
D5
D6
S1
D7
S2
D8
D9
D10
D11
D12
D13
D14
S3
D15
S4
D16
D17
D18
D19
D20
D21
■ – DETECTOR
● – SOURCE: 750nm, 830nm

FIG. 2B

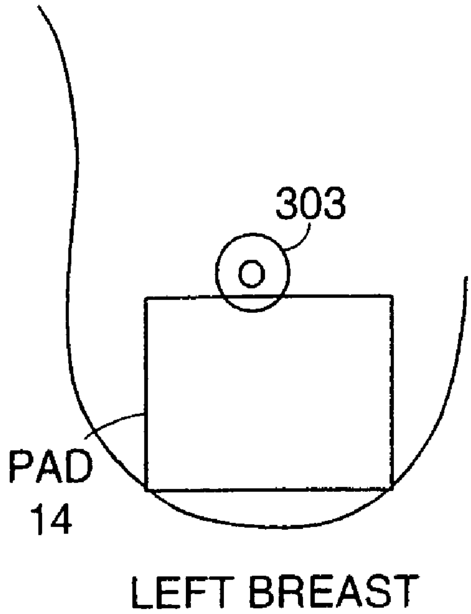

303
PAD
14
LEFT BREAST

FIG. 3A

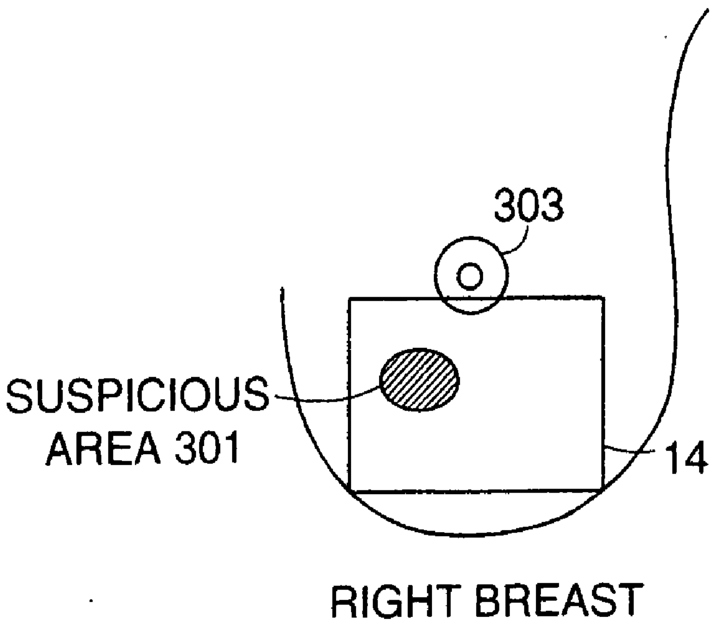

303
SUSPICIOUS
AREA 301
14
RIGHT BREAST

FIG. 3B

SENSING AND INTERACTIVE DRUG DELIVERY

[0001] This application is a continuation U.S. application Ser. No. 12/459,279, filed on Jun. 29, 2009, which is a continuation of U.S. application Ser. No. 11/234,016 filed on Sep. 24, 2005, which is a continuation of U.S. application Ser. No. 09/383,476, filed on Aug. 26, 1999, now U.S. Pat. No. 6,949,081, which claims priority from U.S. Provisional Application 60/098,017, filed on Aug. 26, 1998, all of which are incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to interactive drug delivery systems and methods.

BACKGROUND

[0003] X-ray or γ-ray radiation, optical radiation, ultrasound waves and magnetic fields have been used to examine and image biological tissue. X-rays or γ-rays propagate in the tissue on straight, ballistic lines; that is, their scattering is negligible. Thus, imaging is based on evaluation of the absorption levels of different tissue types. For example, in roentgenography the X-ray film contains darker and lighter spots. In more complicated systems, such as computerized tomography (CT), a cross-sectional picture of human organs is created by transmitting X-ray radiation through a section of the human body at different angles and by electronically detecting the variation in X-ray transmission. The detected intensity information is digitally stored in a computer that reconstructs the X-ray absorption of the tissue at a multiplicity of points located in one cross-sectional plane.

[0004] Near infrared radiation (NIR) has been used to study non-invasively biological tissue including oxygen metabolism in the brain, finger, or ear lobe, for example. The use of visible, NIR and infrared (IR) radiation for medical imaging may have several advantages. In the NIR or IR range the contrast factor between a tumor and a tissue is much larger than in the X-ray range. In addition, the visible to IR radiation is preferred over the X-ray radiation since it is non-ionizing and thus, potentially causes fewer side effects. However, the visible or IR radiation is strongly scattered and absorbed in biological tissue, and the migration path cannot be approximated by a straight line, making inapplicable certain aspects of cross-sectional imaging techniques.

[0005] Optical spectroscopy has been used to monitor and image tissue blood oxygenation and volume by measuring absorption of oxyhemoglobin and deoxyhemoglobin in the near infrared (NIR) wavelength region. Below 700 nm, light is strongly absorbed by hemoglobin, and above 900 nm, it is strongly absorbed by water. By making differential measurements at either side of the isosbestic point of oxy-hemoglobin and deoxy-hemoglobin absorbance (near 800 nm), it is possible to quantify the blood oxygenation and volume levels. Typically, these measurements are made at 750 nm and 830 nm.

[0006] NIR spectrometry adapted to the principles of computerized tomography has been used for in vivo imaging. This technique utilizes NIR radiation in an analogous way to the use of X-ray radiation in an X-ray CT. The X-ray source is replaced by several laser diodes emitting light in the NIR range. The NIR-CT uses a set of photodetectors that detect the light of the laser diodes transmitted through the imaged tissue. The detected data are manipulated by a computer in a fashion similar to that of the detected X-ray data in an X-ray CT. Different NIR-CT systems have recognized the scattering aspect of the non-ionizing radiation and have modified the X-ray CT algorithms accordingly.

[0007] The above-mentioned techniques have been used to detect a tissue tumor. The term "angiogenesis" refers to the generation of new blood vessels in a tissue or organ. Under normal physiological conditions humans or animals undergo angiogenesis only in very specific restricted situations. For example, angiogenesis is normally observed in wound healing, fetal and embryonic development and formation of the corpus luteum, endometrium and placenta.

[0008] Both controlled and uncontrolled angiogenesis are thought to proceed in a similar manner. Persistent, unregulated angiogenesis occurs in a multiplicity of disease states, such as tumor metastasis and abnormal growth by endothelial cells, and supports the pathological damage seen in these conditions. The diverse pathological disease states in which unregulated angiogenesis is present have been grouped together as angiogenesis dependent or angiogenesis associated diseases. The hypothesis that tumor growth is angiogenesis dependent was first proposed in 1971. (Folkman J., Tumor Angiogenesis: Therapeutic Implications. N. Engl. Jour. Med. 285: 1182-1186, 1971.) In its simplest terms it states: "Once tumor 'take' has occurred, every increase in tumor cell population must be preceded by an increase in new capillaries converging on the tumor." Tumor 'take' is understood to indicate a prevascular phase of tumor growth in which a population of tumor cells occupying a few cubic millimeters' volume and not exceeding a few million cells, can survive on existing host microvessels. Expansion of tumor volume beyond this phase requires the induction of new capillary blood vessels. This explanation was directly or indirectly observed and documented in numerous publications.

[0009] After a tumor is detected by X-ray mammography, ultrasound, computerized tomography or MRI, the patient undergoes surgery, radiation therapy and/or drug therapy that frequently has negative effects on other organs and tissue of the patient. Furthermore, different patients respond differently to the drug therapy.

SUMMARY

[0010] In one aspect, an interactive drug delivery system includes a drug delivery module, an optical probe, and a local controller. The drug delivery module delivers selected amounts of a drug into a subject undergoing drug therapy while the optical probe detects the delivered drug, or a manifestation caused by the delivered drug, in a selected tissue region of the subject. The local controller receives data from the optical probe and provides signals to the drug delivery module for adjusting the amounts of the drug to be delivered to the body.

[0011] According to another aspect, an interactive drug delivery system includes a drug delivery module, an optical probe, a local controller, and a central controller. The drug delivery module delivers selected amounts of a drug into a subject undergoing drug therapy while the optical probe monitors a manifestation caused by the delivered drug in a selected tissue region of the subject. The local controller receives optical data from the optical probe and transmits data to the central controller. The central controller correlates the

received data with control data and transmits data back to the local controller. The local controller provides signals to the drug delivery module for adjusting the amounts of the drug to be delivered to the body.

[0012] Preferred embodiments of these aspects include one or more of the following features:

[0013] The central controller includes a monitor for displaying the received data and suggested treatment data to a clinician. The central controller further includes an input device (e.g., a keyboard, a voice recognition system, a magnetic card reader) for entering control data to the central controller. The central controller further includes a data bank with various types of treatment data and optical data.

[0014] The interactive drug delivery system includes several drug delivery modules connected to the local controller. The interactive drug delivery system includes several additional probes, such as a temperature probe, an ultrasound probe, or an electrical probe including one or several electrodes that are implanted or attached to the skin. These probes are designed to monitor tissue properties, including the tissue metabolism, the heart rate, EKG, or the tissue temperature, and provide the measured data to the local controller. The system further includes a temperature probe coupled to the local controller. The temperature probe uses an infra-red beam to measure a local temperature of a tissue region.

[0015] The interactive drug delivery system enables continuous monitoring of a patient and adjusting interactively the drug delivery. Thus, the patient is able to move around the medical facility or leave the medical facility while undergoing drug therapy.

[0016] According to another aspect, an interactive drug delivery method includes delivering by a drug delivery module selected amounts of a drug into a subject; optically detecting in a selected tissue region of said subject a manifestation caused by the delivered drug by an optical probe; and receiving data from or transmitting data to said optical probe and said drug delivery module by a local controller. The method also includes correlating data received from said optical probe to selected data stored in said local controller; and providing signals to said drug delivery module for adjusting the amounts of the drug to be delivered into said subject.

[0017] The interactive drug delivery method includes regulating the rate of the delivered drug based on signals from said local controller.

[0018] According to another aspect, an interactive drug delivery system includes a drug delivery module, an optical probe, a local controller, and a central controller. As described in PCT Application PCT/US99/02953, the optical probe can employ one or several optical modules positioned on the right or left breast of a female patient placed in different positions. The patient may be sitting upright supporting the examined breast by the optical module, or may be lying face down with the breast on the optical module pad. Alternatively, the patient may be lying supine face up with the breast spread over the chest as evenly as possible. If a suspicious mass is detected, the technique can non-invasively characterize the mass by taking optical data at different wavelengths and by measuring one or several tissue specific characteristics related to the tissue metabolism (or hypermetabolism), biochemistry, pathophysiology (including angiogenesis) or another characteristic of a pathological tissue condition.

[0019] According to one aspect, the optical probe employs an optical system for in vivo non-invasive examination of a volume of biological tissue of a subject. The optical examination system includes an optical module, a local controller and a processor. The optical module includes an array of optical input ports and optical detection ports located in a selected geometrical pattern to provide a multiplicity of source-detector paths of photon migration inside the biological tissue. Each optical input port is constructed to introduce into the tissue volume visible or infrared light emitted from a light source. Each optical detection port is constructed to provide light from the tissue to a light detector. The local controller is constructed and arranged to activate one or several light sources and light detectors so that the light detector detects light that has migrated over at least one of the source-detector migration paths. The processor receives signals corresponding to the detected light and creates a defined spatial image of the examined tissue.

[0020] The optical examination system may generate single wavelength or multiple wavelength images of the examined tissue, wherein the employed wavelength is sensitive to absorption or scattering by a tissue constituent (e.g., an endogenous or exogenous pigment, tissue cells, chemical compounds) or is sensitive to structural changes in the tissue. The optical images may display tissue absorption, tissue scattering, or both. The optical imaging system may also generate blood volume hemoglobin oxygenation images and hemoglobin deoxygenation images (or images of any other tissue constituent) based on a single wavelength optical data or a multiple wavelength optical data. A processor may use different image processing and enhancing algorithms known in the art. The processor may correlate several images taken on the same tissue or taken on symmetrical tissue regions such as the left breast and the right breast, or the left arm and the right arm. Based on this correlation, the system detects a suspicious tissue mass and characterize the detected mass. The correlation includes determining congruency of the structures detected in different images. The processor may employ different types of combined scoring, based on several optical images alone or in combination with X-ray mammography, ultrasound examination, or fMRI, to characterize a suspicious tissue mass.

[0021] The optical imaging system may generate the above-described images by examining symmetrical tissue regions of the right breast and the left breast, or may generate images of both the entire right breast and the entire left breast. To identify and characterize a suspicious tissue mass, the processor may employ the different types of combined scoring by correlating the right breast image with the left breast image.

[0022] The optical imaging system may collect single wavelength or multiple wavelength data of a breast tissue model for calibration or for detection of background data. In the calibration procedure, the optical module is placed on the model, and the imaging system can collect a limited number of optical data or can collect optical data using the same sequences as used during the tissue examination. The system may either collect and store the model data for subsequent digital processing, or may adjust the source or detector gains to detect optical data according to a predetermined optical pattern. The imaging system may use different breast models having the same scattering coefficient and the same absorption coefficient as the normal breast tissue of a female, for example, below 40 years or above 40 years. Furthermore, the models may have different sizes and have a shape of a female breast during examination. For example, the model has a shape of the breast (or the breast and a portion of the chest) of a woman lying on her back during examination.

[0023] According to another aspect, the optical probe employs an optical system for in vivo, non-invasive examination of biological tissue of a subject. The optical system includes an optical module, a local controller, and a processor. The optical module includes an array of optical input ports and detection ports located in a selected geometrical pattern to provide a multiplicity of photon migration paths inside an examined region of the biological tissue. Each optical input port is constructed to introduce visible or infrared light emitted from a light source. Each optical detection port is constructed to receive photons of light that have migrated in the examined tissue region from at least one of the input ports and provide the received light to a light detector. The local controller is constructed and arranged to control operation of the light source and the light detector to detect light that has migrated over at least one of the photon migration paths. The processor is connected to receive signals from the detector and arranged to form at least two data sets, a first of the data sets representing blood volume in the examined tissue region and a second of the data sets representing blood oxygenation in the examined tissue region. The processor is arranged to correlate the first and second data sets to detect abnormal tissue in the examined tissue region.

[0024] Preferably, the second data set includes hemoglobin deoxygenation values. The processor may be arranged to form a third data set being collected by irradiating a reference tissue region.

[0025] According to another aspect, the optical probe employs an optical system for in vivo, non-invasive examination of biological tissue of a subject. The optical system includes an optical module, a local controller, and a processor. The optical module includes an array of optical input ports and detection ports located in a selected geometrical pattern to provide a multiplicity of photon migration paths inside an examined region of the biological tissue. Each optical input port is constructed to introduce visible or infrared light emitted from a light source. Each optical detection port is constructed to receive photons of light that have migrated in the tissue from at least one of the input ports and provide the received light to a light detector. The local controller is constructed and arranged to control operation of the light source and the light detector to detect light that has migrated over at least one of the photon migration paths. The processor is connected to receive signals from the detector and arranged to form at least two data sets, a first of the data sets being collected by irradiating an examined tissue region of interest and a second of the data sets being collected by irradiating a reference tissue region having similar light scattering and absorptive properties as the examined tissue region. The processor is arranged to correlate the first and second data sets to detect abnormal tissue in the examined tissue region.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] Various embodiments of the invention will now be described, by way of example, with reference to the accompanying drawings, in which:

[0027] FIG. **1** shows an interactive drug delivery system using an optical probe.

[0028] FIG. **2** shows a block diagram of the interactive drug delivery system of FIG. **1**.

[0029] FIGS. **2**A and **2**B show the optical probe of the interactive drug delivery system of FIG. **1**.

[0030] FIGS. **3**A and **3**B show respectively the left breast and the right breast during examination of a female patient lying supine face up.

DETAILED DESCRIPTION

[0031] With reference to FIG. **1**, an interactive drug delivery system **10** includes a drug delivery module **12**, an optical probe **14**, located on the surface of the subject and including a light source (S) and a light detector (D), a local controller **16**, and a central controller **20**. A human subject **11** (or an animal) undergoing a medical treatment wears local controller **16** interfaced with optical probe **14**, drug delivery module **12**, and optionally additional probes. Local controller **16** includes a processor, a memory and one or several interfaces including a wireless interface.

[0032] FIGS. **2**A and **2**B show the optical probe of the interactive drug delivery system of FIG. **1**, including light sources S**1**-S**9** and light detectors D**1**-D**21**. The laser diodes and PMTs are embedded in a pliable rubber-like material positioned in contact with the examined breast. There may be a Saran® wrap or similar material located between the laser diodes and the skin, and between the PMTs and the skin. Similarly, optical module **14** includes four laser diodes S**1**, S**2**, S**3**, S**4** and **21** silicon diode detectors D**1**, D**2**, . . . , D**21** embedded in a pliable rubber-like material. As described in the PCT Application PCT/US99/02953, the system may use two identical optical modules for imaging of the breast tissue. The optical modules have pairs of optical input ports symmetrically located (or equidistantly located) relative to an optical detection port, or have pairs of optical detection ports symmetrically located relative to an optical input port. In general, however, the ports do not have to be positioned symmetrically. The two optical modules may be located on the right breast and the left breast for lateralization, that is, comparative examination of the symmetric parts of the right breast and the left breast. For calibration, the optical module may also be placed on one or several breast models having the same scattering coefficient and the same absorption coefficient as the normal breast tissue of a female, for example, below 40 years and above 40 years, and having different sizes and geometries. Alternatively, the breast tissue models may have other selected values of the scattering and absorption coefficient.

[0033] Drug delivery module **12** delivers selected amounts of a drug into the human body while optical probe **14** measures the concentration of the drug in a selected tissue region, or measures a selected response of a tissue region to the introduced drug, or measures changes in a selected tissue region, for example, a blood solute such as glucose, exogenous contrast agent or endogenous tissue pigment, and a tissue state such as blood volume or oxygenation of a tissue region, blood volume changes due to arterial pulse or the pulse rate.

[0034] Drug delivery module **12** and optical probe **14** provide data to local controller **16**, which stores the data and provides the data to central controller **20** via a network **18**, such as the cellular telephone network. The system **10** may include additional probes, such as a temperature probe, an ultrasound probe, or an electrical probe including one or several electrodes that are implanted or attached to the skin. These probes are designed to monitor tissue properties, including metabolism, the heart rate or EKG, temperature, perspiration, and provide data to local controller **16**. Interactive system **10** may also include several additional drug delivery modules, responsive to local controller **16**, for delivering several drugs according to a selected protocol.

[0035] Optical probe **14** is a non-invasive optical system that employs a CW spectrophotometer described in PCT application PCT/US95/15666, which is incorporated by reference. Alternatively, optical probe is a Time Resolved Spectroscopy (TRS) system as described in PCT applications PCT/US94/03518 or PCT/US94/07984 or U.S. Pat. No. 5,119,815 or U.S. Pat. No. 5,386,827, all of which are incorporated by reference. In another embodiment, optical probe **14** is a phase modulation system described in U.S. Pat. Nos. 4,972,331; 5,122,974; 5,187,672; 5,553,614 or 5,564,417, which are incorporated by reference. In another embodiment, optical probe **14** is a phased array, phase cancellation system described in PCT application PCT/US93/05868 or an amplitude cancellation system described in PCT application PCT/US95/15694, both of which are incorporated by reference as if fully set forth herein.

[0036] Optical probe **14** monitors directly a tissue constituent or a tissue region including an identified tumor during and after the drug delivery. Alternatively, optical probe **14** monitors a selected tissue organ to detect changes in the physiology of the tissue, or to monitor levels of a tissue solute attributable to the delivered drug. For example, optical probe **14** measures solute levels, such as glucose levels in the liver using the optical techniques described in the PCT Application PCT/US95/15666. In this process, optical probe **14** evaluates changes in the scattering coefficient associated with the measured solute levels.

[0037] Local controller **16** receives optical data from optical probe **14**. Furthermore, local controller **16** receives the temperature data, the EKG data, the heart rate data or the metabolism data. Local controller **16** compares the received data with stored data and stored instructions reflecting the expected treatment and the physiological changes caused by the delivered drug. After comparing the received data with the stored data, local controller **16** can provide control signals for adjusting or discontinuing the drug delivery performed by drug delivery module **12**. Furthermore, local controller **16** can transmit the detected optical data and the stored data to central controller **20**. Central controller **20** performs a data evaluation and provides the information to a physician. The physician evaluates the provided data and inputs dosing instructions into central controller **20**, which in turn transmits the dosing instructions to local controller **16** for adjusting the drug delivery by drug delivery module **12**. Local controller **16** further includes an input pad constructed and arranged for the human subject to input data including subjective condition of the human subject during the treatment. For example, the human subject can input information about fever, pain, nausea, vomiting, dizziness, or other symptoms.

[0038] Optical probe **14** is further constructed to measure the pulse rate of the subject during the drug delivery. Optical probe **14** detects increases in the pulse rate that may correspond to a sudden onset of tachycardia attributable, for example, to an anaphylactic reaction. The increase in the pulse rate may be accompanied with a temperature increase, corresponding to a drug related fever, or to an infection due to neutropenia or anemia caused by the delivered drug. The temperature probe measures the temperature of the subject and provides the temperature data automatically to local controller **16**.

[0039] In another embodiment, as shown in FIG. **1**, optical system **10** is used to monitor a breast tumor. Optical probe **14** detects a tumor as described in the PCT Application PCT/US99/02953, entitled "Examination and Imaging of Breast Tissue," filed on Feb. 11, 1999, incorporated by reference herein. FIGS. **3**A and **3**B show respectively the left breast and the right breast during examination with a patient lying supine face up. The right breast (FIG. **3**B) included a suspicious area **301** located below the nipple **303**. Back-projection images can be collected by an amplitude cancellation system described in the PCT Application PCT/US99/02953 employing optical module **14**. For normal breast tissue, the detectors detect light of the same intensity, and thus the differential signal is zero, i.e., the detected amplitude are canceled. The imaging system collects the differential data for a multiplicity of symmetric photon migration paths and generates an image of the examined tissue. The imaging system may collect optical data for several wavelengths and generate blood volume images and blood oxygenation images for the examined tissue. The imaging system may also use a second identical optical module **14** placed on the opposite breast. The blood volume or oxygenation images collected for the two breasts may be subtracted to provide a differential image, which will further emphasize a tissue abnormality located in one breast.

[0040] The images of the right breast and left breast can be corrected for the model data at 750 nm and 830 nm. A plot of a blood deoxygenation image of the right breast data minus the left breast data can be made. A plot of a blood volume image of the right breast minus the left breast data can also be made. These images have a high signal level and exhibit high congruence of the tumor, as described in the PCT Application PCT/US99/02953.

[0041] One or several drug delivery modules **12** deliver one or several drugs to the subject. For example, the drug treatment may include a combination regimen, such as CMF (Cyclophosphamide, Methotrexate and 5-Fluorouracil). Alternatively, drug delivery module 12 delivers a conjugated angiogenesis inhibitor for treatment of pathogenetic conditions, as described in U.S. Pat. No. 5,762,918 entitled "Methods of Using Steroid-Polyanionic Polymer-Based Conjugated Targeted to Vascular Endothelial Cells" or as described in U.S. Pat. No. 5,733,876 entitled "Method of Inhibiting Angiogenesis," both of which are incorporated by reference. Optical probe **14** measures the local blood volume and oxygenation of the tissue region including the detected tumor. Based on the measured blood volume and oxygenation, optical probe **14** monitors the growth and activity of the identified tumor. For example, optical probe **14** detects higher blood oxygenation. Based on this data, a local controller **16** provides signals to drug delivery module **12** for decreasing the drug amount (or vice versa). Furthermore, upon detecting a sudden onset of tachycardia, local controller **16** may direct drug delivery module **12** to reduce or eliminate the delivery of the drug.

[0042] In another embodiment, system **10** is used to monitor the liver during a combination regiment for treatment of carcinoma. The CMF regiment causes optically detectable changes of one or several solutes in the liver. By measuring changes in the scattering coefficient at the measured wavelength, optical probe **14** detects changes in the solute concentration and provides the data to local controller **16**, which adjusts the drug delivery. Alternatively, optical probe **14** is used to monitor drug delivery directly into the liver in treatment of hepatocellular carcinoma.

[0043] In another embodiment, interactive system **10** is used to monitor the drug delivery for treatment of diseases such as diabetes or cardiomyopathy. When treating diabetes, drug delivery module **12** includes an insulin pump, for providing controlled amounts of insulin to a patient. Optical probe **14** is located on the abdominal region near the liver so that the detected optical radiation passes through the liver. Optical probe **14** detects the level of glucose as described in the PCT Application PCT/US95/15666, which is incorporated by reference as if fully provided herein. Upon detecting a low glucose level by optical probe **14**, local controller **16** directs the insulin pump to reduce or discontinue the insulin delivery. The monitoring for hypoglycemia or hyperglycemia is also performed during the sleep of the patient to provide the data to local controller **16**, which not only reduces the insulin delivery, but also sends a message to central controller **20** and a clinician receiving information at central controller **20**. When treating cardiomyopathy, optical probe **14** measures the blood volume and saturation while drug delivery module **12** delivers the butamine, dopamine, or another drug.

[0044] Alternatively, optical probe **14** is a TRS system, a phase modulation system, a phased array, phase cancellation system, or an amplitude cancellation system for detecting fluorescent radiation. The principles of detecting fluorescent radiation were described by J. R. Lakowicz in "Principles of Fluorescence Spectroscopy," Plenum Press, N.Y., 1983. The delivered drug is "tagged" with an optically active contrast agent such as light absorbing contrast agent or a fluorescing contrast agent (e.g., ICG). Then, optical probe **14** uses a wavelength sensitive to the contrast agent, for example, a fluorescing contrast agent naturally occurring or delivered into the examined tissue.

[0045] For example, the delivered drug is "tagged" with a signal generator of high optical sensitivity and specificity, such as a molecular beacon. Molecular beacons are sense or antisense oligonucleotide probes that become fluorescent only in the presence of specific sequences of target nucleic acids. (Described by Tyagi, S. and Kramer, F. R., "Molecular beacons: probes that fluoresce upon hybridization," *Nature Biotech.* 14: 303-8 (1996).) They consist of hairpin shaped molecules containing a loop of specific sequence nucleotide that is complementary to the target nucleic acid.

[0046] In the loop, the 3'- and 5'-ends of this loop contain 5-8 nucleotide strands that are complementary to each other; upon hybridization they form a 'stem' which holds the ends of the loop together. Attached to one of the stem oligonucleotides is a short linker with a fluorophore at its end; attached to the other stem is a linker connected to a quencher. The linkers are designed to juxtapose the fluorophore and quencher. Since fluorescence energy transfer (FET) depends on the inverse sixth power of the donor-acceptor distance, the molecular beacon is non-fluorescent when the stem segments are hybridized to each other; the transferred energy is dissipated as heat. When the loop hybridizes with the target nucleic acid, the hydrogen bonds between the complementary stem nucleotides are broken (since there are many more hydrogen bonds formed between the loop and the target), separating the fluorophore and quencher and producing detectable fluorescence. The length of the loop is chosen to optimize the approximation of the fluorophore and the quencher.

[0047] Molecular beacons have been used to detect specific amino acids in homogeneous solution. (See Tyagi, S. and Kramer, F. R., "Molecular beacons: probes that fluoresce upon hybridization," *Nature Biotech.* 14: 303-8 (1996).) They are particularly useful for situations in which it is either not possible or desirable to isolate the probe-target hybrids, such as for real-time monitoring of polymerase chain reactions in sealed tubes or for detection of specific nucleic acids in cells. (See, Gao, W., Tyagi, S., Kramer, F. R. and Goldman, E., "Messenger RNA release from ribosomes during 5'-translational blockage by consecutive low-usage arginine but not leucine codons in *Eschericia coli," Mol. Microbiol.* 25: 707-716 (1997); and Matsuo, T., "In situ visualization of mRNA for basic fibroblast growth factor in living cells," *Biochim. Biophys. Acta* 1379: 178-84 (1998).) Molecular beacons have been used to detect specific RNAs in hamster fibroblasts and human leukemia cells. (See, Sokol, D. L., Zhang, X., Lu, P. and Gewirtz, A. M., "Real time detection of DNA/RNA hybridization in living cells," *Proc. Natl. Acad. Sc. USA* 95: 11538-43 (1998).) Here, the molecular beacons are active in the near-infrared region and contain sense or antisense oligonucleotides targeted at specific mRNAs of solid tumors in vivo. This type of near infra-red fluorescent probe can be delivered by a variety of vehicles, such as apoE-directed lipid vesicles for targeting tumor cells which overexpress low density lipoprotein (LDL) receptors, (see Rensen, P. C. N., Schiffelers, R. M., Versluis, J., Bijsterbosch, M. K., van Kuijk-Meuwissen, M. E. M. J. and van Berkel, T. J. C., "Human recombinant apolipoprotein E-enriched liposomes can mimic , low density lipoproteins as carriers for the site-specific delivery of antitumor agents," *Molec. Pharmacol.* 52: 445-455 (1997)), or such as B16 melanoma cells, (see de Smith, P. C. and van Berkel, T. J. C., "Prolonged serum half-life of antineoplastic drugs by incorporation into the low density lipoprotein," *Cancer Res.* 50: 7476082 (1990)) which will serve as a model tumor system for our study.

[0048] Optical probe **14** evaluates the tumor by evaluating the tissue and angiogenesis or by using enhanced fluorescent probe signaling cancer tissue based upon molecular abnormalities. A specific molecular beacon is used for detection of specific RNAs in specific tumors by targeting one or several enzymes. Several molecular beacons have been prepared with dyes detectable in the visible range of the optical spectrum, as described in Sokol, D. L., Zhang, X., Lu, P. and Gewirtz, A.M., "Real time detection of DNA/RNA hybridization in living cells," *Proc. Natl. Acad. Sci. USA* 95: 11538-43 (1998).

[0049] A molecular beacon has its natural fluorescence quenched by hybridization in a target sequence. When duplex formation occurs, the fluorophores become separated and quenching is no longer possible. A dual wavelength system is used for absorption measurements and fluorescent measurements, as described above. The measurements are used to detect intrinsic and angiogenesis (or deoxygenation) signals from the tumor. The two wavelengths are encoded with different radio frequencies. Depending on the optical characteristic of optical module **14**, ICG or Li-COR (manufactured by Li-Cor Company, Lincoln, Nebraska) is detected using the dual wavelength excitation measurement. For example, optical probe **14** is a dual wavelength phase cancellation system described in U.S. Pat. No. 5,807,263, which is incorporated by reference. The dual wavelength system uses laser diodes emitting light at 754 nm and 800 nm. The examined tissue is illuminated with either one of the wavelengths. These wavelengths excite fluorescence in ICG at 754 nm for low concentrations and at 800 nm for higher concentrations. The detected optical data is processed for phase detection or amplitude cancellation.

[0050] The dual wavelength system detects the sum of the detected optical signals at the two wavelengths to determine blood volume. The system also displays the difference of the two detected signals at the two wavelengths to determine the oxygenation of hemoglobin, or may display the individual detected optical signals obtained from the absorption measurement. The detected 800 nm signal reflects the absorption of ICG and other agent and its derivatives. The fluorescence of the ICG and other agents at 830 nm is measured with the 754 nm and 800 nm excitation. This system employs optical primary and secondary filters as described in the above-mentioned publication by J. R. Lakowicz.

[0051] Interactive system **10** is constructed for using various drug delivery modules. Drug delivery module **12** may be based on electrotransport, such as iontophoresis that involves electrically induced transport of charged ions, or electroosmosis that involves the movement of the liquid through a biological membrane such as the skin, or electroporosis that involves the transport of an agent through transiently existing pores formed in a biological membrane under the influence of the electric field. The electrotransport-based module includes at least two electrodes in contact with a portion of the skin, mucous membrane, or another body surface, and at least one reservoir or source of the agent to be delivered to the body. The donor reservoir is connected to the donor electrode and positioned between the two electrodes to provide a renewable source of one or more agents or drugs. The drug delivery module **12** also includes an electrical controller **12**A designed to regulate the rate of the drug delivery based on the signals from local controller **16**.

[0052] Drug delivery module **12** may use different delivery devices described in U.S. Pat. No. 5,697,896, entitled "Electrotransport Delivery Device"; described in U.S. Pat. No. 5,445,609, entitled "Electrotransport Agent Delivery Device Having a Disposable Component and a Removable Liner"; described in U.S. Pat. No. 4,942,883, entitled "Drug Delivery Device"; described in U.S. Pat. No. 5,006,108, entitled "Apparatus for Iontophoretic Drug Delivery"; described in U.S. Pat. No. 4,474,570, entitled "Iontophoresis Device"; described in U.S. Pat. No. 5,013,293, entitled "Pulsating Transdermal Drug Delivery System"; described in U.S. Pat. No. 5,540,665, entitled "Gas Driven Dispensing Device and Gas Generating Engine Therefor"; or described in U.S. Pat. No. 5,057,318, entitled "Delivery System for Beneficial Agent Over a Broad Range of Rates," all of which are incorporated by reference.

[0053] Alternatively, drug delivery module **12** may use different devices described in U.S. Pat. No. 5,681,285, entitled "Infusion Pump with an Electronically Loadable Drug Library and a User Interface for Loading the Library"; described in U.S. Pat. No. 5,061,243, entitled "System and Apparatus for the Patient-Controlled Delivery of a Beneficial Agent, and set Therefor"; described in U.S. Pat. No. 5,464,392, entitled "Infusion System Having Plural Fluid Input Ports and at Least One Patient Output Port"; described in U.S. Pat. No. 4,468,222, entitled "Intravenous Liquid Pumping System and Method"; described in U.S. Pat. No. 5,785,688, entitled "Fluid Delivery apparatus and Method"; described in U.S. Pat. No. 4,828,545, entitled "Pressure Responsive Multiple Input Infusion system"; and also described in U.S. Pat. No. 5,100,380, entitled "Remotely Programmable Infusion System," all of which are incorporated by reference.

[0054] Additional embodiments are within the following claims:

1. An interactive drug delivery system comprising:
a drug delivery module constructed and arranged to deliver selected amounts of a drug into a subject;
an optical probe constructed and arranged to detect in vivo in two selected tissue regions of said subject a manifestation caused by the delivered drug, a first of said selected tissue region exhibiting normal tissue properties and a second of said selected tissue region exhibiting abnormal tissue properties; and
a local controller constructed and arranged to receive data from or transmit data to said optical probe and said drug delivery module; said local controller being arranged to correlate optical data received from said optical probe to selected data and provide signals to said drug delivery module for adjusting the amounts of the drug to be delivered into said subject.

2. The system of claim **1** further including a central controller remotely located from and in wireless communication with said local controller, central controller constructed and arranged to receive data from said local controller and provide to said local controller data for adjusting the amounts of said drug to be delivered into said subject.

3. The system of claim **1** further including a temperature probe coupled to said local controller.

4. The system of claim **3** wherein said temperature probe uses an infra-red beam to measure a local temperature of a tissue region.

5. The system of claim **1** further including an electrical probe coupled to said local controller.

6. The system of claim **1** wherein said optical probe is a time-resolved (TRS) system.

7. The system of claim **1** wherein said optical probe is a phase modulation system.

8. The system of claim **1** wherein said optical probe is a phased array.

9. The system of claim **1** wherein said optical probe is phase cancellation system.

10. The system of claim **1** wherein said optical probe is an amplitude cancellation system.

11. The system of claim **1** wherein said drug delivery module includes an electrical controller designed to regulate the rate of the delivered drug based on the signals from said local controller.

12. An interactive drug delivery method comprising:
delivering by a drug delivery module selected amounts of a drug into a subject;
optically detecting in vivo in two selected tissue regions of the subject a manifestation caused by the delivered drug by an optical probe, a first of said selected tissue region exhibiting normal tissue properties and a second of said selected tissue region exhibiting abnormal tissue properties;
receiving data from or transmitting data to said optical probe and said drug delivery module by a local controller;
correlating data received from said optical probe to selected data stored in said local controller; and

providing signals to said drug delivery module for adjusting the amounts of the drug to be delivered into said subject.

13. The interactive drug delivery method of claim **12** further including regulating the rate of the delivered drug based on signals from said local controller.

14. The interactive drug delivery method of claim **12** including measuring tissue temperature.

15. The interactive drug delivery method of claim **14** wherein said measuring temperature includes using an infrared beam for measuring a local temperature of a tissue region.

16. The interactive drug delivery method of claim **12** further including measuring electrical signals with an electrical probe.

17. An interactive drug delivery system comprising:

a drug delivery module constructed and arranged to deliver selected amounts of a drug into a subject;

an optical probe including a light source and a light detector constructed and arranged to examine in vivo in a selected biological tissue region of said subject during the operation of said drug delivery module, said optical probe being constructed to detect optical signal related to a manifestation in the examined biological tissue region caused by the delivered drug in the tissue region; and

a local controller constructed and arranged to communicate with said optical probe and said drug delivery module; said local controller being arranged to correlate data related to said manifestation with selected data and provide signals to said drug delivery module for adjusting the amounts of the drug to be delivered into said subject.

18. The system of claim **17** said optical probe includes an array of optical input ports optically coupled to several light sources and an array of detection ports optically coupled to several light detectors.

19. The system of claim **17** said optical probe is constructed to detect said optical signal including fluorescent light emitted as manifestation of said delivered drug.

20. The system of claim **17** further including a central controller remotely located from and in wireless communication with said local controller, central controller constructed and arranged to receive data from said local controller and provide to said local controller data for adjusting the amounts of said drug to be delivered by said drug delivery module into said subject.

21. The system of claim **17**, wherein said optical probe is further constructed to detect infra-red light to measure a local temperature of a tissue region.

22. The system of claim **17**, wherein said optical probe detects blood volume.

23. The system of claim **17**, wherein said optical probe detects blood oxygenation.

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专利名称(译)	感知和互动药物输送		
公开(公告)号	US20110270157A1	公开(公告)日	2011-11-03
申请号	US13/135473	申请日	2011-07-05
[标]申请(专利权)人(译)	CHANCE BRITTON		
申请(专利权)人(译)	CHANCE BRITTON		
当前申请(专利权)人(译)	CHANCE BRITTON		
[标]发明人	CHANCE BRITTON		
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摘要(译)

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