(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 January 2017 (05.01.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/001495 A1

(51) International Patent Classification:
G06F 19/00 (2011.01)

(21) International Application Number:
PCT/EP2016/065170

(22) International Filing Date:
29 June 2016 (29.06.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/185880 29 June 2015 (29.06.2015) US

(71) Applicant: **KONINKLIJKE PHILIPS N.V.** [NL/NL]; High Tech Campus 5, 5656 AE Eindhoven (NL).

(72) Inventors: **CHENG, Limei**; High Tech Campus 5, 5656 AE Eindhoven (NL). **CHBAT, Nicolas, Wadih**; High Tech Campus 5, 5656 AE Eindhoven (NL).

(74) Agents: **FREEKE, Arnold, Jan** et al.; Philips International B.V. – Intellectual Property & Standards, High Tech Campus 5, 5656 AE Eindhoven (NL).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,

[Continued on next page]

(54) Title: OPTIMAL DRUG DOSING BASED ON CURRENT ANESTHESIA PRACTICE

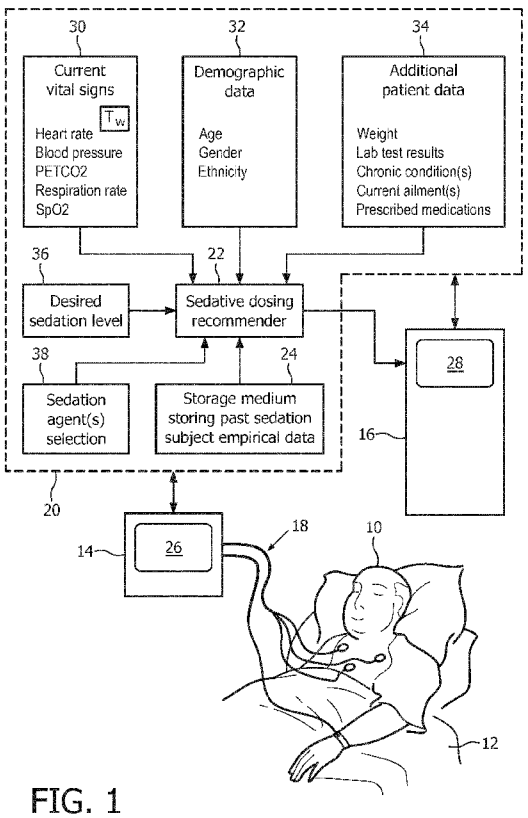

FIG. 1

(57) Abstract: Prior to initiating sedation of a subject (10), current values (30) of physiological parameters are measured for the subject using a sedation monitoring device (14, 16), including at least heart rate, a blood pressure, and a capnography parameter. A sedation dosing recommendation to achieve a desired level of sedation (36) is computed using the current values of the physiological parameters and past sedation subject data retrieve from a storage medium (24). The sedation dosing recommendation may be displayed on a display component (26, 28) or used as a default sedation dosing of an anesthesia machine (16). The past sedation subject data may comprise trained neural network parameters and the computing uses the trained neural network (22_{NN}). The past sedation subject data may comprise trained Bayesian inference model parameters and the computing uses the trained Bayesian inference model (22_{BC}).

WO 2017/001495 A1

LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

OPTIMAL DRUG DOSING BASED ON CURRENT ANESTHESIA PRACTICE

FIELD

The following relates generally to the medical sedation arts, anesthesia arts, surgical arts, and related arts.

BACKGROUND

Sedatives are used in various settings, such as in critical care units and during surgery. In an intensive care unit (ICU), cardiac care unit (CCU), or other critical care unit, sedatives such as morphine are administered to enhance patient comfort and reduce pain. Such sedatives are generally not intended to render the patient unconscious, but rather to reduce pain sensitivity and produce a calming effect. During surgery, anesthetics such as Propofol or sevoflurane are administered to render the patient unconscious, or to relax the patient and reduce anxiety (sometimes called "twilight" anesthesia). The term "sedation" and like phraseology as used herein is intended to encompass twilight or general anesthesia (but not local anesthesia which does not impact cognition or mental activity).

The depth of sedation achieved by a sedative can vary from induction, through various clinically useful stages (e.g. anxiolysis, unconsciousness) through to overdose. Too little sedation may be clinically ineffective (for example, leaving a patient with some consciousness during surgery, or heightened anxiety in the case of a twilight anesthetic) while too much sedation can be detrimental or even lethal to the patient. In view of its importance, in U.S. medical practice a dedicated and specially trained anesthesiologist or nurse anesthetist may be assigned to administer anesthesia during surgery and monitor the patient's sedation state. In a critical care setting, the patient's physician usually prescribes the sedative(s), which is (are) administered and continuously monitored by nursing staff of the critical care unit.

However, it is surprisingly difficult to actually measure the depth of sedation. One approach is the Bispectral Index™ (BIS™), a proprietary method requiring the use of electroencephalography (EEG) monitoring equipment. In the absence of an EEG, an observational approach relying upon a sedation classification scheme such as Guedel's classification may be employed. For example, in the Guedel classification scheme surgical anesthesia is classified as Stage III, and is assessed by observable features of the patient such as eyeball movement reduction, relaxation of specific muscles, and cessation of certain autonomous reflexes.

BIS™ or Guedel classification techniques are useful to assess and monitor the level of sedation during the administration of anesthesia, and the anesthetic dose may be adjusted in real-time based on such observations. However, they are not generally useful to choose the initial (or target) anesthesia dose, since the dose is chosen before beginning administration of the anesthetic. For this purpose, the physician or anesthesiologist usually chooses a combination of anesthetic agents based on applicable medical guidelines and professional experience. Depending on the situation, a low anesthetic dosage may allow the patient to experience intraoperative recall, while a large anesthetic dosage may pose risk to the patient such as decreased organ perfusion possibly leading to delayed awakening – an undesired outcome. The anesthetic dosing is chosen to provide a balance among multiple anesthetic goals while keeping patient safe and comfortable. Such goals may include, for example: suppressing consciousness and intraoperative awareness; optimizing quality of recovery; maintaining optimal hemodynamics; avoiding post-operative neurocognitive dysfunction; and so forth.

Choosing the dosage of anesthetic agent(s) based on medical guidelines and professional experience has certain disadvantages. Patient information known to the physician or anesthesiologist may be limited, e.g. based on information gleaned from the patient's medical record and recent laboratory test results, electrocardiogram (ECG), and other recorded patient vital signs, along with knowledge of the surgical procedure to be conducted, current medical ailment leading to admission to the critical care unit, or so forth. These data may be out-of-date by the time the sedative is administered. For example, a patient's heart rate and blood pressure may be different from the last readings in the medical record (e.g. higher due to anxiety just prior to undergoing surgery; or falling due to ongoing progression of a current medical ailment). Medical guidelines also tend to be static, and may not be updated in a timely fashion to reflect the most current medical literature or current best medical practices. Additionally, hospitals and other medical institutions sometimes change anesthetic agents based on current availability, pricing, and other factors, and the available medical guidelines and institutional professional experience may provide a limited basis for prescribing sedative dosing in such circumstances. Choosing the dosage of anesthetic is even more challenging when there are time constraints, such as sedating for emergency surgery.

To some degree, non-optimal sedative dosing may be corrected in real-time using BIS™ or Guedel classification techniques or other real-time sedation monitoring. However, initial under-sedation can lead to patient discomfort or suffering before the dosage

is corrected based on the sedation monitoring. Even more serious is initial over-sedation, which may lead to irreversible detriment before correction can be made.

The following discloses improvements which overcome various foregoing deficiencies and others.

5

SUMMARY

In accordance with one illustrative example, an apparatus is disclosed for monitoring sedation. A sedation monitoring device has a display component, and may for example include one or both of a medical patient monitor and an anesthesia machine. The sedation monitoring device is configured to measure values of a plurality of physiological parameters including at least heart rate, a blood pressure, and a capnography parameter. A non-transitory storage medium stores past sedation subject data comprising or generated from data including at least sedation dosing for past sedation subjects and values of the plurality of physiological parameters measured for past sedation subjects prior to initiation of sedation. In some illustrative examples, the past sedation subject data is stored as trained parameters of a neural network trained on past sedation subject data. In other illustrative examples, the past sedation subject data is stored as trained model parameters of a Bayesian inference model trained on past sedation subject data. The apparatus further includes an electronic processor programmed to (prior to initiating sedation of the subject): receive from the sedation monitoring device current values of the plurality of physiological parameters measured for a subject; receive a desired level of sedation of the subject; compute a sedation dosing recommendation to achieve the desired level of sedation of the subject using at least the current values of the plurality of physiological parameters measured for the subject prior to initiating sedation of the subject and the past sedation subject data stored in the non-transitory storage medium; and display, on the display component of the sedation monitoring device, the computed sedation dosing recommendation. In some embodiments the computing operation employs the trained neural network or Bayesian inference model.

In accordance with another illustrative example, a method is disclosed for monitoring a subject undergoing sedation. In this method, prior to initiating sedation of the subject, current values are measured for the subject of a plurality of physiological parameters including at least heart rate, a blood pressure, and a capnography parameter, and a sedation dosing recommendation to achieve a desired level of sedation of the subject is computed using at least: (i) the current values of the plurality of physiological parameters measured for the subject prior to initiating sedation of the subject; and (ii) past sedation subject data

comprising or generated from data including at least sedation dosing for past sedation subjects and values of the plurality of physiological parameters measured for past sedation subjects prior to initiation of sedation. The sedation dosing recommendation is displayed on a display component, and/or a default sedation dosing of an anesthesia machine is set to the sedation dosing recommendation. In some embodiments, the past sedation subject data comprise trained parameters of a neural network trained on past sedation subject data, and the computing comprises processing input data including at least the current values of the physiological parameters measured for the subject using the trained neural network. In some embodiments, the past sedation subject data comprise trained model parameters of a Bayesian inference model trained on past sedation subject data, and the computing comprises processing input data including at least the current values of the physiological parameters measured for the subject using the trained Bayesian inference model.

One advantage resides in providing a more efficient sedation system.

Another advantage resides in providing an improved human-machine interface for an anesthesia machine or for a patient monitor.

Another advantage resides in providing an improved sedation method with advantages including reduced likelihood of underdosing or overdosing.

Still further advantages of the present invention will be appreciated to those of ordinary skill in the art upon reading and understand the following detailed description. It is to be appreciated that none, one, two, or more of these advantages may be achieved by a particular embodiment.

BRIEF DESCRIPTION OF THE DRAWINGS

The disclosure may take form in various components and arrangements of components, and in various steps and arrangement of steps. The drawings are only for purposes of illustrating the preferred embodiments and are not to be construed as limiting the invention.

FIGURE 1 illustrates a sedation system including a patient monitor, an anesthesia machine, and a sedative dosing recommender that may be suitably integrated with the patient monitor and/or the anesthesia machine.

FIGURE 2 illustrates a block diagram of a neural network embodiment of the sedative dosing recommender.

FIGURE 3 illustrates a block diagram of a Bayesian inference embodiment of the sedative dosing recommender.

DETAILED DESCRIPTION

In approaches disclosed herein, real-time assessment of optimal anesthetic dosing for a patient (or, more generally, subject) is computed using the patient's current vitals (i.e. physiological parameter values), demographics information (e.g. age, gender, ethnicity), and/or other patient information such as weight, chronic condition(s), current ailment(s), and the desired level of sedation (which in some cases may be provided as an indication of the reason for sedation). This assists anesthesiologists in providing the optimal dosage of anesthetic agents.

With reference to FIGURE 1, a subject **10** is to undergo sedation. This can occur in various medical situations. In one example, the subject **10** is a hospital patient (in-patient or out-patient) who is to undergo surgery. In this case the sedation may be general anesthesia in which the patient is to be rendered unconscious, or may be a lower level of sedation (i.e. less sedated) such as twilight sedation in which the patient is to be placed into a relaxed, tranquil, but still conscious, state. The sedative agent or agents in this case may include anesthetics such as Propofol or sevoflurane. In another example, the subject **10** is a patient in a critical care unit who is to be administered a sedative such as morphine to relieve anxiety and relax the patient. (Morphine also has an analgesic effect, i.e. provides relief from pain, which is commonly beneficial for critical care patients.) While sedation is commonly used for patients in hospital settings, it is also contemplated that the subject **10** may be other than a hospital in-patient or outpatient – for example, the subject **10** may be a nursing home resident, a chronically ill person being sedated at home, or so forth.

Conventionally, the sedation dosing for sedating the subject **10** is prescribed by a physician, an anesthesiologist, or other authorized medical person in advance of initiating the sedation. This decision is typically made based on medical guidelines and professional experience of the physician or other medical person who chooses the dosing. Moreover, the sedation dosing is commonly chosen well in advance of the actual initiation of sedation – for example, a surgeon may make the dosing decision for anesthetizing a patient during surgery at the same time a surgical procedure is scheduled. Similarly, in the case of sedating a patient in a critical care unit, the dosage is usually prescribed by the patient's physician when he or she visits the patient during hospital rounds, or even may be decided in consultation with nursing staff of the critical care unit via telephone, with the actual sedation being initiated some time later. Outside of a hospital setting, the sedation dosing decision may be made even earlier, for example being prescribed by a physician during an office visit.

Such approaches for choosing the sedation dosing can lead to underdose (and consequent discomfort, anxiety, fear, and/or pain for the subject) or overdose which can lead to delayed recovery, increased post-operative neurocognitive dysfunction, reduced organ perfusion or other adverse hemodynamic effects, or even death.

As recognized herein, improved sedation dosing can be achieved by a synergistic combination of (1) choosing the sedation dosing close to the time of initiating the sedation, and (2) leveraging current values of physiological parameters measured for the subject prior to initiating sedation of the subject. In some embodiments, the current values of the physiological parameters are measured for the subject **10** in a time window extending no greater than one hour into the past, although time windows of different sizes are contemplated. It is further recognized herein that there is (at least as of year 2015) a limited understanding of the linkage between sedation dosing and the sedation level. This limited understanding is reflected in the empirical nature of depth of sedation monitoring techniques such the Bispectral Index™ (BIS™) or Guedel's classification. Accordingly, sedation dosing recommendation devices disclosed herein employ a solely or primarily empirical approach for computing a sedation dosing recommendation to achieve the desired level of sedation of the subject **10** which relies solely or primarily on (1) the current values of physiological parameters measured for the subject **10** prior to initiating sedation of the subject (e.g. measured within one hour of computing the dosing recommendation) and (2) past sedation subject data used to relate information including the current physiological parameter values to the dosing chosen for those past patients. By contrast, physiological modeling such as a pharmacokinetic (PK) model relating dosing and blood serum dose or a pharmacodynamic (PD) model relating blood serum dose and values of physiological parameters is relied upon less heavily. For example, a combined PK-PD model component may be used to provide prior information for computing sedative dosing using a Bayesian inference model.

With continuing reference to FIGURE 1, the subject **10** is suitably positioned to be safely sedated, for example being disposed in an illustrative bed **12**, or on a hospital gurney, imaging system couch, or the like. The subject **10** is monitored by a sedation monitoring device, such a medical patient monitor **14** or an anesthesia machine **16**, or both. The patient monitor **14** may, for example, be a bedside monitor of the type ubiquitously found in hospital rooms and critical care units, and suitably measures values of a plurality of physiological parameters usually including at least heart rate, respiration rate, and one or more types of blood pressure (e.g., systolic blood pressure, diastolic blood pressure, and/or mean arterial pressure). Other physiological parameters that may be measured include

peripheral capillary oxygen saturation (SpO_2, e.g. measured by a pulse oximeter), and at least one capnography parameter (for example $PETCO_2$ which is the end-tidal partial pressure of carbon dioxide). These are merely illustrative examples, and additional, fewer, or other physiological parameters may be measured by the medical patient monitor **14**. The anesthesia machine **16** may be provided in addition to or in substitution for the patient monitor **14**, and typically includes tubing, connections, flow meters, or so forth for supplying controlled oxygen, air, anesthetic gas (e.g. nitrous oxide) or so forth to the subject **10**, a vaporizer for supplying volatile anesthetics such as sevoflurane, and sensors for monitoring patient parameters such as heart rate, blood pressure, respiration rate, SpO_2, capnography parameter(s), and so forth. The anesthesia machine **16** may, for example, be an IntelliSave AX700 anesthesia machine (available from Koninklijke Philips N.V., Eindhoven, the Netherlands). It will be appreciated that the anesthesia machine **16** will generally not be provided when administering sedatives intravenously, orally, or by some other non-respiratory pathway; moreover, some sedatives may be administered via a respiratory pathway without the use of a dedicated anesthesia machine. It is also noted that diagrammatic FIGURE 1 illustrates the patient monitor **14** connected with the subject **10** by sensor leads **18** or the like (although wireless connections are also contemplated) while the anesthesia machine **16** is shown unconnected to the subject **10**; but the anesthesia machine **16** may additionally or alternatively be connected with the subject to acquire current values for physiological parameters.

The sedation monitoring device includes an electronic processor **20** which is programmed to implement a sedative dosing recommender **22** that computes, prior to initiating sedation of the subject **10**, a sedation dosing recommendation to achieve the desired level of sedation of the subject **10**. This computation uses at least (1) current values of a plurality of physiological parameters measured for the subject **10** prior to initiating sedation of the subject and (2) past sedation subject data stored in a non-transitory storage medium **24** which is included with (as illustrated) or accessed by the electronic processor **20**. The non-transitory storage medium **24** may, by way of non-limiting illustrative example, comprise one or more of: a hard disk drive or other magnetic storage medium; an optical disk or other optical storage medium; an electronically programmable read-only memory (EPROM), flash memory, or other electronic storage medium; or so forth.

In some embodiments, the electronic processor **20** is a component of the medical patient monitor **14** and is further programmed to control the medical patient monitor **14**. In some embodiments, the electronic processor **20** is a component of the anesthesia

machine **16** and is further programmed to control the anesthesia machine **16**. In such embodiments in which the electronic processor **20** is a component of a sedation monitoring device **14**, **16**, the electronic processor **20** may receive data used in computing the dosing recommendation including current physiological parameter measurements acquired by the sedation monitoring device (e.g. patient monitor **14** or anesthesia machine **16**) of which it is a component. In yet other embodiments, the electronic processor **20** is separate from both the medical patient monitor **14** and the anesthesia machine **16**, for example being embodied as a standalone computer (not shown), and receives data used in computing the dosing recommendation including current physiological parameter measurements from the sedation monitoring device (e.g. patient monitor **14** or anesthesia machine **16**) via suitable wired or wireless communication.

The computed sedation dosing recommendation to achieve the desired level of sedation of the subject **10** may be variously utilized. Because the sedative dosing recommender **22** employs a solely or primarily empirical approach, the sedation dosing recommendation is preferably not used as a direct control input for the anesthesia machine **16** or any other medical therapy delivery apparatus. In some embodiments, the dosing recommendation is displayed on a display of the sedation monitoring device (e.g., on a display **26** of the patient monitor **14** and/or on a display **28** of the anesthesia machine **16**). In embodiments in which the sedation monitoring device includes the anesthesia machine **16**, the anesthesia machine **16** may optionally be programmed to set its default sedation dosing setting to the sedation dosing recommendation computed by the electronic processor **20**. (Such an "automatic default" setting approach is more easily implemented in embodiments in which the electronic processor **20** is a component of the anesthesia machine **16** and is further programmed to control the anesthesia machine, but can also be implemented in other embodiments by connecting the electronic processor **20** to communicate the dosing recommendation to the anesthesia machine). In such "automatic default" embodiments, the sedation dosing recommendation is the default dosing, but this default dosing can be overridden by the anesthesia machine operator, for example in order to input a different dosing setting chosen by the physician or anesthesiologist.

With continuing reference to FIGURE 1, the inputs to the sedative dosing recommender **22** include current vital signs **30** of the subject **10** (that is, current values of a plurality of physiological parameters measured for the subject **10** prior to initiating sedation of the subject). The plurality of physiological parameters constituting the current vital signs **30** does not necessarily include all vital signs that are measured by the sedation monitoring

device **14**, **16** – rather, the current vital signs **30** of the subject **10** which are used by the sedative dosing recommender **22** in computing the dosage recommendation may be some sub-set of the total set of measured vital signs. Typically, the current vital signs **30** will include values for heart rate, a blood pressure (e.g., one or more of systolic blood pressure, diastolic blood pressure, and mean arterial pressure), and a capnography parameter (e.g., end-tidal partial pressure of carbon dioxide, that is, $PETCO_2$), as these are expected to have significant effect on the sedation level achieved by a given dose of a sedative. Other contemplated vital sign inputs include respiration rate, SpO_2, and so forth. The current vital signs **30** are "current" in the sense that they are acquired shortly before initiation of sedation of the subject **10**. For example, in some embodiments, the current values **30** (i.e. current vital signs) of the plurality of physiological parameters are measured for the subject **10** in a time window (denoted T_W in FIGURE 1) extending no greater than one hour before the computing of the sedation dosing recommendation (although larger values for this window T_W are contemplated). In some embodiments, the sedative dosing recommendation computation is repeated iteratively, e.g. every two minutes, with the current vitals time window T_W being a sliding window that moves in real-time.

The sedative dosing recommender **22** may optionally employ additional inputs besides the current vital signs **30**. For example, demographic information **32** such as the age, gender, or ethnicity of the subject **10** may be additional inputs. Additional patient data **34** may include patient weight, lab test results, or indications of various chronic conditions, current ailments, or medications prescribed to the subject **10**. Patient weight is generally needed insofar as the dosage is expected to scale with patient weight (i.e. dosage may be preferably expressed in a "per unit mass" form). However, it is contemplated that this scaling may not be a linear relationship. Patient laboratory results differ from current vital signs **30** in that the laboratory results are typically not generated within the current time window T_W due to the delayed nature of these data. (For example, arterial blood gas test results, or a complete blood panel, require drawing a blood sample which is sent to the appropriate laboratory for processing and analysis – such data are unlikely to be acquired in a time window T_W of, for example, one hour or less.) The indication of prescribed medications may be limited to medications known to interact with the sedative agent(s), and likewise the indication of chronic conditions and current ailments may be limited to those known to have a significant impact on the level of sedation attained by a given dose of the sedative agent(s).

One item of information that is generally needed by the sedative dosing recommender **22** in order to compute the sedation dosing recommendation is the desired level

of sedation **36** of the subject. This information can be provided in various ways. For example, the desired level of sedation **36** of the subject may be indicated by a provided reason for sedation, since the reason for sedation often dictates the desired level of sedation. For example, certain types of surgery require general anesthesia, while less aggressive surgeries may be performed using twilight anesthesia. This is only an illustrative example, and the desired level of sedation may be provided in some other format, such as a BIS™ number, a Guedel classification stage, or so forth. The sedative dosing recommender **22** may in some embodiments compute the desired level of sedation of the subject from multiple pieces of provided data – for example, a combination of the type of surgery and the patient's age and/or general physical condition may collectively constitute the received desired level of sedation **36**, which is automatically determined from this information. This is feasible because the number of possible levels of sedation is typically relatively small. For example, some Guedel classification schemes employ four stages with Surgical Stage III being sub-divided into four further sub-stages or planes. The BIS™ number ranges from 0 to 100, but these may be binned to create a smaller number of sedation levels for defining the desired level of sedation **36**. In view of the typically small number of possible sedation levels, it is feasible to provide a look-up table associating levels of sedation characterized using different metrics (e.g. BIS™ number, Guedel classification) and various reasons for sedation and other data (e.g. patient age).

With continuing reference to FIGURE 1, further data optionally input to the sedative dosing recommender **22** is an indication of the sedation agent (or agents) selection **38**. In some embodiments, these are an input to the sedative dosing recommender **22**; while, in other embodiments it is contemplated for the sedative dosing recommender **22** to automatically choose the optimal sedation agent or combination of sedation agents to achieve the desired level of sedation for the subject **10**. Since the number of different sedative agents and sedative agent combinations used at a given medical institution is likely to be relatively limited, this again may be suitably implemented as a look-up table, e.g. it may be standard to use a particular combination of sedative agents to achieve general anesthesia (with certain possible differences depending upon specific items of the patient information **32**, **34**).

It will be appreciated that the sedation dosing recommendation to achieve the desired level of sedation of the subject **10** may be expressed in various formats. For example, the sedation dosing recommendation may be expressed in terms of a flow rate of the sedative agent, or a vaporizer concentration in the case of a volatile anesthetic, or so forth. In some embodiments, the desired level of sedation may further include a dosing schedule, e.g. a

ramp-up of the flow rate or other sedative concentration, or a switchover from one sedative agent to another during the procedure, or so forth. In embodiments in which the sedative dosing recommender **22** determines the optimal sedative agent(s) to use, the sedation dosing recommendation further includes an identification of the sedative agent(s).

Having provided an overview of an illustrative sedation system including a sedative dosing recommender **22** for providing a sedation dosing recommendation to achieve the desired level of sedation of the subject **10**, some illustrative implementations of the sedative dosing recommender **22** implemented by the electronic processor **20** including or accessing the storage medium **24** are next described.

With reference to FIGURE 2, in some embodiments the sedative dosing recommender **22** is implemented as a neural network **22**$_{NN}$. In these implementations, the non-transitory storage medium **24** suitably stores trained parameters of a neural network trained on past sedation subject data to process input data including at least values of the plurality of physiological parameters to generate a sedation dosing recommendation. By way of non-limiting illustration, the neural network-based dosing recommender **22** receives as inputs current values of the following physiological parameters: heart rate (HR); respiration rate (RR); arterial blood pressure (ABP) from which systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial blood pressure (MAP); SpO_2; and $PETCO_2$; and additional patient data including: patient weight; an indication of chronic conditions; and an indication of reason for admission to the hospital.

The neural network **22**$_{NN}$ is assumed to be trained for a specific sedative agent (or combination of agents) under consideration, and maps the foregoing inputs to the output, namely the sedation dosing recommendation for the specific sedative agent under consideration. In a training (or "development") phase the neural network is designed to provide the dosage recommendation, while the deployment phase the neural network is used to provide dosage recommendations for specific subjects (e.g. the subject **10**).

During the development phase, past subject data are obtained. For each past subject (i.e. each "training" subject), these data include current measurements for the physiological parameters and other data that serve as the inputs to the neural network **22**$_{NN}$. For each subject, the actually administered sedative dosage is also recorded. To provide useful dosage recommendations, the past subject data are preferably collected for past subjects for whom the sedation was effective – past patients for whom the administered sedative dosage was later determined to be an underdose or overdose are preferably omitted from the training set (since inclusion of these data would tend to train the neural network to

reproduce these "bad" results). Alternatively, these "bad" results may be included as negative examples for the neural network training. In one approach, the past subject data are collected over some period of time (e.g. a few months, or a year, or some other interval) for patients of physicians or anesthesiologists who are considered expertly trained in the anesthetic agent (or agent combination) for which the neural network is being trained, and for which current vital signs are recorded in the time window T_W. In creating the training data set, the expert physicians or anesthesiologists are preferably consulted to make an initial determination of which vital signs they consider important in choosing the sedative dosing, and these are recorded. Any conventional neural network training technique can be used to generate the trained parameters (e.g. weight coefficients and bias values) of the neural network **22**$_{NN}$. The past patient data may be divided into training and validation sets, and the validation data set is used to test the input to output mapping of the trained neural network. In one approach, a cross validation set, unseen to the neural network, is used to cross-validate the trained neural network and to compute estimation errors to be used as a metric of the efficacy of the trained neural network. The trained parameters are then stored in the non-transitory storage medium **24**, and effectively constitute the past sedation subject data stored in the non-transitory storage medium **24** which is then used by the sedative dosing recommender **22**. It should be noted that the neural network training is typically performed off-line, that is, not necessarily by the electronic processor **20** that is programmed to implement the sedative dosing recommender **22**.

During the deployment phase (which is represented in FIGURE 1, for the neural network embodiment, as the sedative dosing recommender **22** and in FIGURE 2 as the neural network **22**$_{NN}$) the stored trained neural network parameters are retrieved from the non-transitory storage medium **24** and the electronic processor **20** is programmed to compute the sedation dosing recommendation by processing the input data (left side of FIGURE 2) using the neural network with the trained parameters.

With reference to FIGURE 3, in other embodiments the sedative dosing recommender **22** is implemented as a "per-class" Bayesian inference engine **22**$_{BC}$. In these implementations, the non-transitory storage medium **24** suitably stores trained parameters of a Bayesian inference engine trained on past sedation subject data to process input data including at least values of the plurality of physiological parameters to generate a sedation dosing recommendation. By way of non-limiting illustration, the input data may be similar to the input data for the neural network **22**$_{NN}$ of FIGURE 2. A difference in the illustrative Bayesian dosing recommender **22**$_{BC}$ as compared with the illustrative neural network

embodiment of FIGURE 2 is that the Bayesian dosing recommender **22**$_{BC}$ is trained for a specific class of subjects, where the class is defined in terms of subject characteristics such as one or more demographic characteristics (age, gender, ethnicity), one or more chronic conditions, or so forth. This "per-class" approach can be useful for subject characteristics that strongly affect the optimal sedative dosing. For example, if men tend to have significantly different optimal sedative dosing for a particular sedative agent (or agent combination) as compared with women, then it may be more effective to train separate Bayesian inference engines for these two different classes (men and women), as compared with training a single Bayesian inference engine for both men and women.

While such a "per-class" approach is not employed in the illustrative neural network-based approach of FIGURE 2, it will be appreciated that it can be used in neural network-based implementations as well (e.g., separate neural network recommenders can be trained for men and women). More generally, in the "per-class" approach the non-transitory storage medium **24** stores past sedation subject data grouped into different patient classes and the electronic processor **20** is programmed to compute the sedation dosing recommendation for the subject **10** using the past sedation subject data stored in the non-transitory storage medium for a patient class to which the subject belongs.

The Bayesian inference-based sedative dosing recommender **22**$_{BC}$ assumes a Bayesian relationship **50** between anesthetic dosage and the input data (called "$Vars$" in this example). This Bayesian relationship may be expressed as follows:

$$P(Dosage|Vars) = \frac{P(Vars|Dosage) \cdot P(Dosage)}{P(Vars)}$$

where $Vars$ represent the input data, including at least current values of the plurality of physiological parameters (e.g. heart rate, HR; SpO_2; blood pressure(s); respiratory rate, RR; $PETCO_2$; et cetera) and optionally including other subject data such as patient weight. These are the "evidence" in Bayesian inference phraseology; while, the Dosage for a given set of evidence (i.e. $P(Dosage|Vars)$) is the "hypothesis" to be determined (also called the a posteriori probability). The notation $P(\cdots)$ denotes a probability distribution. Thus, given the physiological parameter measurements, the Bayesian relationship is applied to obtain the dosage according to the conditional probability $P(Dosage|Vars)$ output by the Bayesian inference model. As diagrammatically illustrated in FIGURE 3, the probability distributions are suitably provided as histograms of the past sedation subject data. The distribution $P(Dosage)$ is suitably provided as a histogram **52** of dosage of the sedative agent (or as a set of histograms in the case of a combination of sedative agents). Similarly, the distribution

$P(Vars)$ is suitably provided as histograms **54** of current values of the various physiological parameters measured for past sedation patients prior to initiating sedation, with additional histograms representing other inputs of the past patients (e.g. patient weight). The distribution $P(Vars|Dosage)$ is suitably provided as histograms **56** of the variables for a specific sedative dosing actually administered to past subjects.

The various histograms **52**, **54**, **56** provide prior knowledge in the form of empirical data. An advantage of a Bayesian inference approach is that other sources of prior knowledge may be conveniently provided to the Bayesian relationship **50**. For example, prior probabilities for the variables given a dosage (that is, estimates for $P(Vars|Dosage)$) may be generated using a pharmacokinetic (PK) pharmacodynamic (PD) model (PK/PD model) **60** to estimate the optimal anesthetic dosing information. The PK model correlates given drug information (medication type, dosage, profile) with concentration of drug in the blood. The PD model relates estimated drug concentration from the PK model (along with other information such as demographics and chronic conditions) with the physiological parameters (i.e. vitals) such as blood pressures, RR, or so forth.

In another variant (not shown), the sedative dosing recommender **22** may be implemented non-empirically, for example employing the PK/PD model **60** with the PD component further designed to estimate the BIS number or other sedation level. In this example, the dosing input to the PK component of the PK-PD model **60** is adjusted until the PK-PD model **60** outputs the desired level of sedation of the subject.

With reference to any of the above illustrative embodiments of the sedative dosing recommender **22**, it will be appreciated that some or all input data values may optionally be discretized or otherwise pre-processed. For example, the current value of a physiological parameter may optionally be binned into a discrete number of bins N, e.g. in one example $N = 7$ and the seven discrete bins (or levels) may be semantically labeled as: "lowest", "lower", "low", "normal", "high", "higher" and "highest". The actual numerical current value of the physiological parameter is binned and the discrete level used as the input the neural network, Bayesian inference engine, or so forth.

It will also be appreciated that the illustrative examples of a neural network or Bayesian inference sedative dosing recommender are merely examples, and that other inference or mapping techniques may be employed to infer or map current values of the plurality of physiological parameters measured for the subject prior to initiating sedation of the subject, in view of past sedation subject data, to a sedation dosing recommendation to achieve a desired level of sedation of the subject.

It will be further appreciated that the disclosed techniques may be embodied as a non-transitory storage medium (not shown) storing instructions readable and executable by the electronic processor **20** to perform the disclosed operations including computing the sedative dosing recommendation. The non-transitory storage medium may, by way of non-limiting illustrative example, comprise one or more of: a hard disk drive or other magnetic storage medium; an optical disk or other optical storage medium; an electronically programmable read-only memory (EPROM), flash memory, or other electronic storage medium; or so forth.

The invention has been described with reference to the preferred embodiments. Modifications and alterations may occur to others upon reading and understanding the preceding detailed description. It is intended that the invention be constructed as including all such modifications and alterations insofar as they come within the scope of the appended claims or the equivalents thereof.

CLAIMS:

1. An apparatus for monitoring sedation, the apparatus comprising:

a sedation monitoring device with a display component (26, 28) and including at least one of a medical patient monitor (14) and anesthesia machine (16), the sedation monitoring device configured to measure values of a plurality of physiological parameters including at least heart rate, a blood pressure, and a capnography parameter;

a non-transitory storage medium (24) storing past sedation subject data comprising or generated from data including at least sedation dosing for past sedation subjects and values of the plurality of physiological parameters measured for past sedation subjects prior to initiation of sedation; and

an electronic processor (20) programmed to:

receive, from the sedation monitoring device, current values (30) of the plurality of physiological parameters measured for a subject (10) prior to initiating sedation of the subject;

receive, prior to initiating sedation of the subject, a desired level of sedation of the subject (36);

compute, prior to initiating sedation of the subject, a sedation dosing recommendation to achieve the desired level of sedation of the subject using at least the current values of the plurality of physiological parameters measured for the subject prior to initiating sedation of the subject and the past sedation subject data stored in the non-transitory storage medium; and

display, on the display component of the sedation monitoring device, the computed sedation dosing recommendation.

2. The apparatus of claim 1 wherein the desired level of sedation of the subject is received as an indication of a reason for initiating sedation of the subject.

3. The apparatus of any one of claims 1-2 wherein the electronic processor (20) is further programmed to:

receive, prior to initiating sedation of the subject, one or more of subject age, subject gender, subject ethnicity, subject weight, an indication of a chronic condition of the subject, and an indication of a current ailment of the subject, wherein the electronic processor is programmed to compute the sedation dosing recommendation to achieve the desired level of

sedation of the subject further using the received subject age, subject gender, subject ethnicity, subject weight, indication of a chronic condition of the subject, and indication of a current ailment of the subject.

4. The apparatus of any one of claims 1-3 wherein the plurality of physiological parameters further includes respiration rate and SpO_2.

5. The apparatus of any one of claims 1-4 wherein the plurality of physiological parameters includes at least one of: systolic blood pressure, diastolic blood pressure, and mean arterial pressure.

6. The apparatus of any one of claims 1-5 wherein:

the non-transitory storage medium (24) stores trained parameters of a neural network (22_{NN}) trained on past sedation subject data to process input data including at least values of the plurality of physiological parameters to generate a sedation dosing recommendation; and

the electronic processor (20) is programmed to compute the sedation dosing recommendation to achieve the desired level of sedation by processing input data (30, 32, 34) including at least the current values (30) of the plurality of physiological parameters measured for the subject prior to initiating sedation of the subject using the neural network with the trained parameters stored in the non-transitory storage medium.

7. The apparatus of any one of claims 1-5 wherein:

the non-transitory storage medium (24) stores trained model parameters of a Bayesian inference model (22_{BC}) trained on past sedation subject data to process input data including at least values of the plurality of physiological parameters to generate a sedation dosing recommendation; and

the electronic processor (20) is programmed to compute the sedation dosing recommendation to achieve the desired level of sedation of the subject by processing input data (30, 32, 34) including at least the current values (30) of the plurality of physiological parameters measured for the subject prior to initiating sedation of the subject using the Bayesian inference model with the trained model parameters stored in the non-transitory storage medium.

8. The apparatus of claim 7 wherein the Bayesian inference model (22_{BC}) includes a pharmacokinetic pharmacodynamic (PK-PD) model component (60) that relates dosing to blood serum dose and that relates blood serum dose to values of the plurality of physiological parameters, the PK-PD model component providing prior information for the Bayesian inference model.

9. The apparatus of any one of claims 1-8 wherein the sedation monitoring device includes an anesthesia machine (16) and the anesthesia machine is programmed to set its default sedation dosing setting to the computed sedation dosing recommendation.

10. The apparatus of any one of claims 1-9 wherein the sedation monitoring device includes an anesthesia machine (16) and the electronic processor (20) is a component of the anesthesia machine and is further programmed to control the anesthesia machine.

11. The apparatus of any one of claims 1-9 wherein the sedation monitoring device includes a medical patient monitor (14) and the electronic processor (20) is a component of the medical patient monitor and is further programmed to control the medical patient monitor.

12. The apparatus of any one of claims 1-11 wherein the non-transitory storage medium (24) stores past sedation subject data grouped into different patient classes and the electronic processor (20) is programmed to compute the sedation dosing recommendation for the subject using the past sedation subject data stored in the non-transitory storage medium for a patient class to which the subject belongs.

13. The apparatus of any one of claims 1-12 wherein the electronic processor (20) is programmed to compute the sedation dosing recommendation for the subject using the current values of the plurality of physiological parameters measured for the subject in a time window (T_W) extending no greater than one hour before the computing of the sedation dosing recommendation.

14. A method for monitoring a subject undergoing sedation, the method comprising:

prior to initiating sedation of a subject (10), measuring current values (30) for the subject of a plurality of physiological parameters including at least heart rate, a blood pressure, and a capnography parameter;

prior to initiating sedation of a subject, computing a sedation dosing recommendation to achieve a desired level of sedation (36) of the subject using at least:

(i) the current values of the plurality of physiological parameters measured for the subject prior to initiating sedation of the subject, and

(ii) past sedation subject data comprising or generated from data including at least sedation dosing for past sedation subjects and values of the plurality of physiological parameters measured for past sedation subjects prior to initiation of sedation; and

at least one of (1) displaying the sedation dosing recommendation on a display component (26, 28) and (2) setting a default sedation dosing of an anesthesia machine (16) to the sedation dosing recommendation.

15. The method of claim 14 further comprising:

sedating the subject (10) in accordance with the sedation dosing recommendation.

16. The method of any one of claims 14-15 further comprising:

generating past sedation subject data as trained parameters of a neural network (22_{NN}) by training the neural network on past sedation subject data to process input data including at least values of the plurality of physiological parameters to generate a sedation dosing recommendation;

wherein the sedation dosing recommendation to achieve the desired level of sedation (36) of the subject (10) is computed by processing input data (30, 32, 34) including at least the current values (30) of the plurality of physiological parameters measured for the subject prior to initiating sedation of the subject using the neural network with the trained parameters.

17. The method of any one of claims 14-15 further comprising:

generating past sedation subject data as trained model parameters of a Bayesian inference model (22_{BC}) by training the Bayesian inference model on past sedation subject

data to process input data including at least values of the plurality of physiological parameters to generate a sedation dosing recommendation;

wherein the sedation dosing recommendation to achieve the desired level of sedation (36) of the subject (10) is computed by processing input data (30, 32, 34) including at least the current values (30) of the plurality of physiological parameters measured for the subject prior to initiating sedation of the subject using the Bayesian inference model with the trained model parameters.

18. The method of claim 17 wherein generating and the computing operations include generating prior information for the Bayesian inference model (22_{BC}) by:

relating dosing and blood serum dose; and

relating blood serum dose and values of the plurality of physiological parameters;

wherein the relating operations are performed using a pharmacokinetic pharmacodynamic (PK/PD) model (60).

19. The method of any one of claims 14-18 wherein the computing uses the current values (30) of the plurality of physiological parameters measured for the subject (10) over a current time interval (T_W) extending from the time of the computing backward in time an hour or less.

20. A non-transitory storage medium storing instructions readable and executable by an electronic processor (20) to perform operations including:

controlling an anesthesia machine (16) to initiate sedation of a subject (10) using one or more sedative agents; and

prior to initiating sedation of the subject, computing a sedation dosing recommendation for the one or more sedative agents to achieve a desired level of sedation (36) of the subject by applying a neural network (22_{NN}) or Bayesian inference model (22_{BC}) trained on sedation data for past sedation subjects to input data (30, 32, 34) including at least physiological parameters (30) measured for the subject over a time interval (T_W) of one hour or less before performing the computing;

wherein the controlling comprises controlling the anesthesia machine to initiate sedation of the subject at the sedation dosing recommendation.

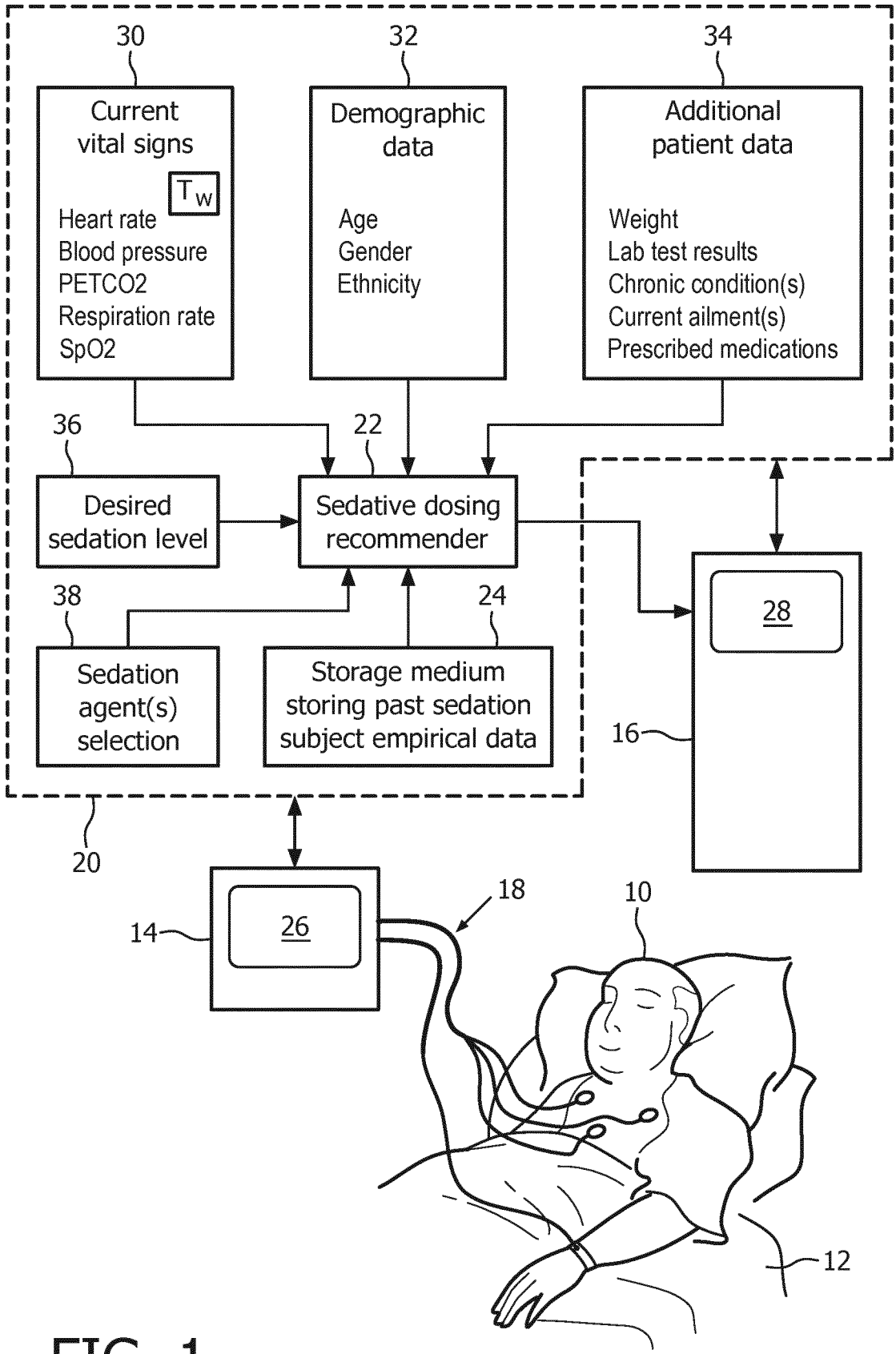
30
32
34
Current vital signs
T_W
Heart rate
Blood pressure
PETCO2
Respiration rate
SpO2
Demographic data
Age
Gender
Ethnicity
Additional patient data
Weight
Lab test results
Chronic condition(s)
Current ailment(s)
Prescribed medications
36
22
Desired sedation level
Sedative dosing recommender
38
24
Sedation agent(s) selection
Storage medium storing past sedation subject empirical data
28
16
20
26
14
18
10
12

FIG. 1

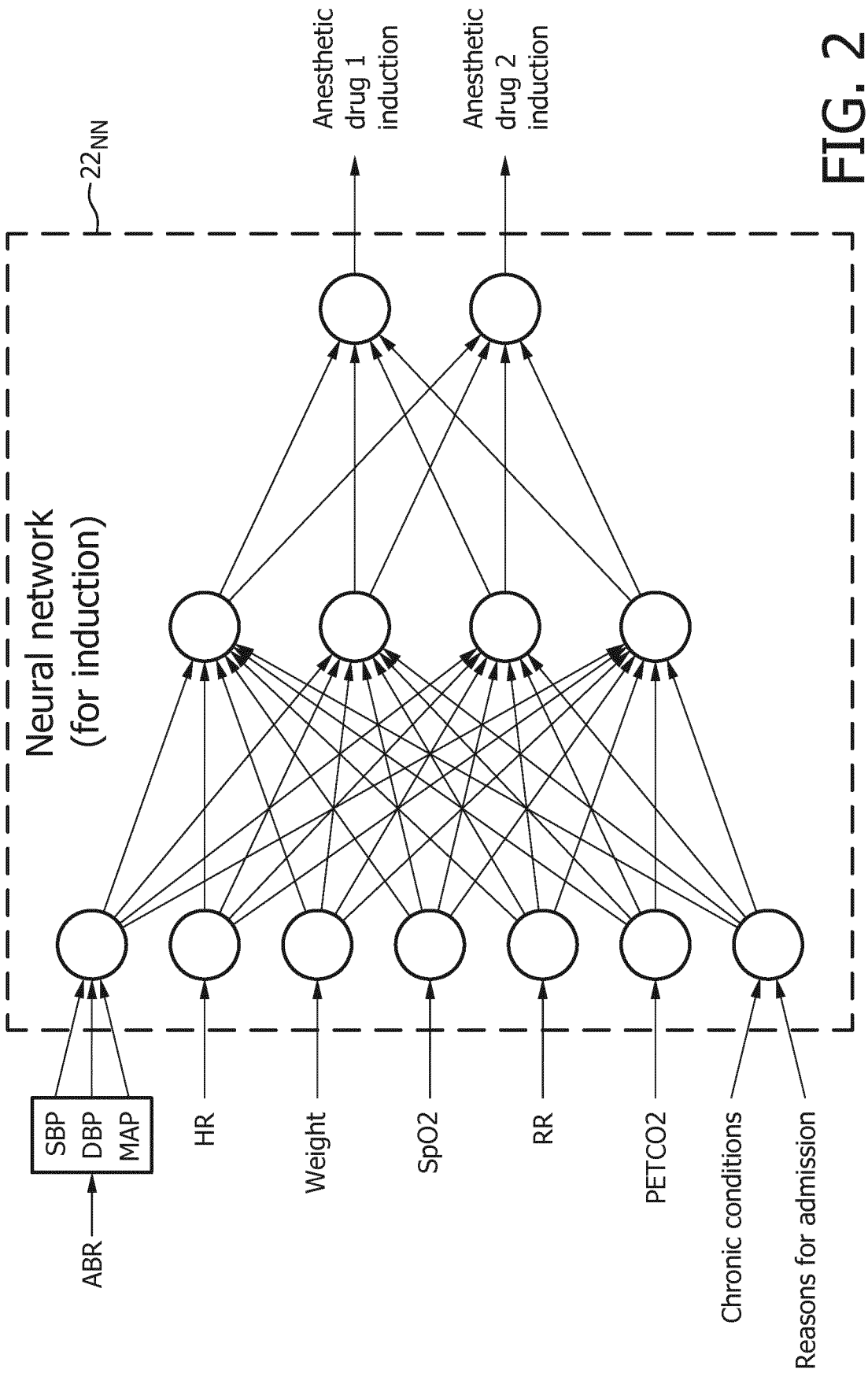
Neural network
(for induction)
22NN
Anesthetic drug 1 induction
Anesthetic drug 2 induction
ABR
SBP
DBP
MAP
HR
Weight
SpO2
RR
PETCO2
Chronic conditions
Reasons for admission

FIG. 2

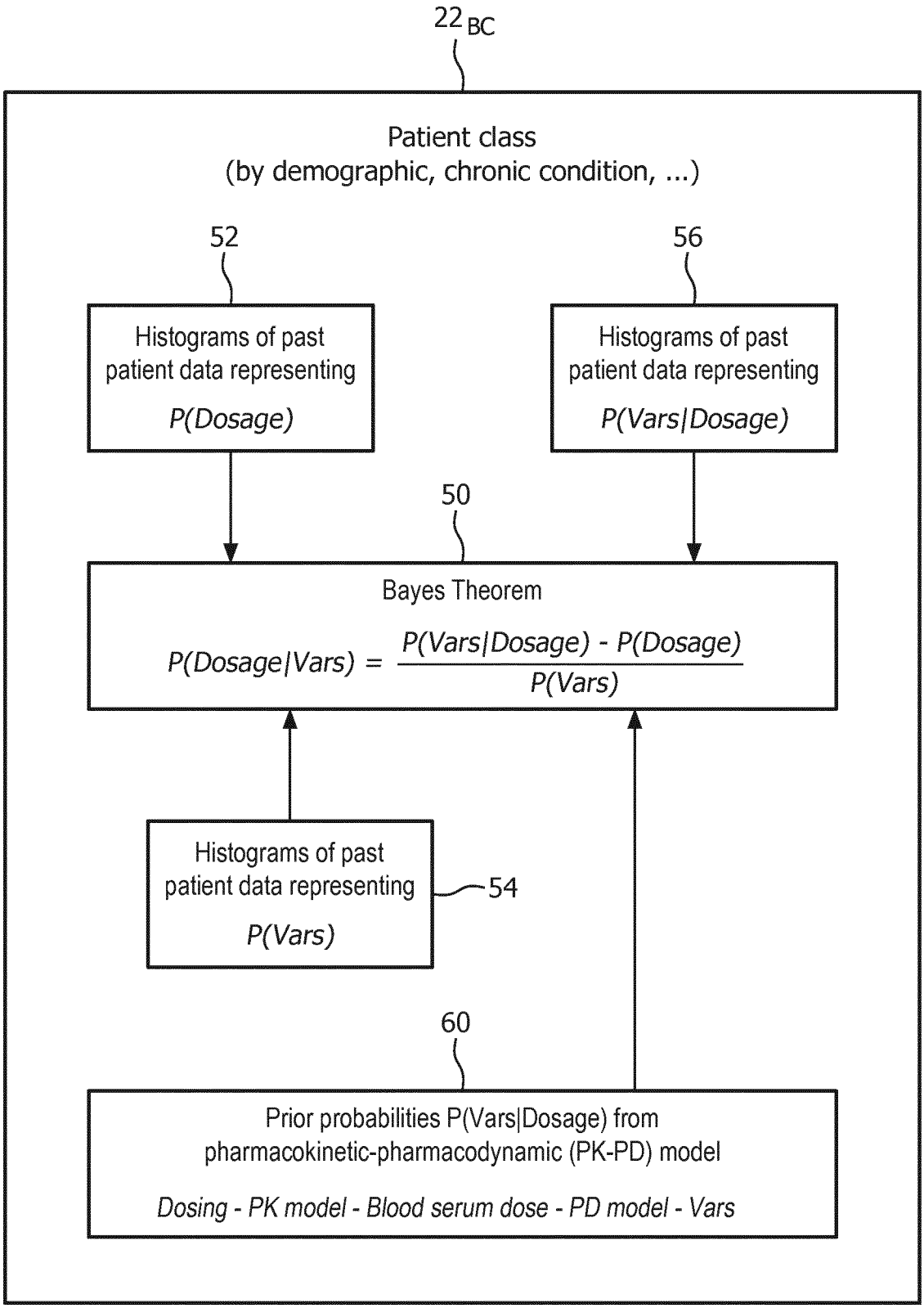
22 BC
Patient class
(by demographic, chronic condition, ...)
52
Histograms of past patient data representing
P(Dosage)
56
Histograms of past patient data representing
P(Vars|Dosage)
50
Bayes Theorem
P(Dosage|Vars) = P(Vars|Dosage) - P(Dosage) / P(Vars)
Histograms of past patient data representing
P(Vars)
54
60
Prior probabilities P(Vars|Dosage) from pharmacokinetic-pharmacodynamic (PK-PD) model
Dosing - PK model - Blood serum dose - PD model - Vars

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/065170

A. CLASSIFICATION OF SUBJECT MATTER
INV. G06F19/00
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)
G06F

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/079355 A1 (KONINKL PHILIPS NV [NL]) 4 June 2015 (2015-06-04)	1-5,7, 9-15,17, 19,20
Y	page 4, paragraphs 2, 6; figure 1 page 5, paragraph 3; figure 2 page 7, paragraph 2 page 8, paragraphs 3, 5-6 page 6, paragraph 1	6,8,16, 18
Y	WO 2013/179048 A1 (ISIS INNOVATION [GB]; MHUIRCHEARTAIGH ROISIN JUDITH NI [IE]; TRACEY IR) 5 December 2013 (2013-12-05) claim 8	8,18
Y	US 2003/176804 A1 (MELKER RICHARD J [US]) 18 September 2003 (2003-09-18) paragraphs [0016], [0017], [0037]	6,16

-/--

[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 application or patent but published on or after the international filing date

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 September 2016	13/09/2016

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/065170

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2006/042638 A1 (NIKLEWSKI PAUL J [US] ET AL) 2 March 2006 (2006-03-02) abstract -----	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/065170

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015079355 A1	04-06-2015	NONE	
WO 2013179048 A1	05-12-2013	AU 2013269331 A1	29-01-2015
		CN 104470425 A	25-03-2015
		EP 2854632 A1	08-04-2015
		JP 2015521076 A	27-07-2015
		US 2015148700 A1	28-05-2015
		WO 2013179048 A1	05-12-2013
US 2003176804 A1	18-09-2003	AU 2003241504 A1	06-01-2004
		EP 1519767 A2	06-04-2005
		JP 2005530553 A	13-10-2005
		US 2003176804 A1	18-09-2003
		WO 2004000400 A2	31-12-2003
US 2006042638 A1	02-03-2006	AU 2005280197 A1	09-03-2006
		BR PI0515134 A	08-07-2008
		CA 2579071 A1	09-03-2006
		CN 101905056 A	08-12-2010
		CN 101912655 A	15-12-2010
		CN 101912656 A	15-12-2010
		CN 101927049 A	29-12-2010
		CN 101954137 A	26-01-2011
		CN 101954138 A	26-01-2011
		CN 101961516 A	02-02-2011
		CN 101961519 A	02-02-2011
		CN 101961521 A	02-02-2011
		CN 101961522 A	02-02-2011
		CN 101961523 A	02-02-2011
		CR 9023 A	21-01-2010
		EP 1804872 A2	11-07-2007
		EP 2491969 A2	29-08-2012
		EP 2491970 A2	29-08-2012
		EP 2952223 A1	09-12-2015
		JP 4907534 B2	28-03-2012
		JP 2008511399 A	17-04-2008
		NZ 588352 A	25-05-2012
		US 2006042631 A1	02-03-2006
		US 2006042632 A1	02-03-2006
		US 2006042633 A1	02-03-2006
		US 2006042634 A1	02-03-2006
		US 2006042635 A1	02-03-2006
		US 2006042636 A1	02-03-2006
		US 2006042637 A1	02-03-2006
		US 2006042638 A1	02-03-2006
		US 2006081257 A1	20-04-2006
		US 2006081258 A1	20-04-2006
		US 2006081259 A1	20-04-2006
		US 2006106345 A1	18-05-2006
		US 2009133699 A1	28-05-2009
		US 2011245579 A1	06-10-2011
		WO 2006026335 A2	09-03-2006