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(54) **Title:** METHODS AND SYSTEMS FOR CLOSED-LOOP CONTROL OF DRUG ADMINISTRATION

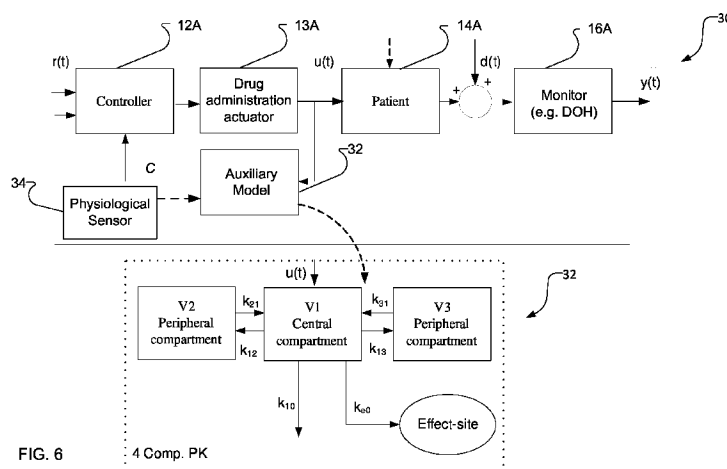


FIG. 6

(57) **Abstract:** A control system for administration of a drug comprises a drug administration actuator for administering the drug to a patient at a controllable dosage; a monitor for measuring an effect of the drug on the patient; and a controller configured to determine a control signal to the drug administration actuator; wherein the controller is configured to implement a closed loop model- predictive control scheme comprising, for each of a series of time steps, minimizing a cost function subject to one or more constraints to determine the control signal, the cost function based at least in part on a reference level and the monitor measurement; wherein the control signal is used as an input to an auxiliary model to estimate at least one concentration level of the drug in the patient; and wherein the constraints comprise at least one constraint on the estimate of the concentration level of the drug.

METHODS AND SYSTEMS FOR CLOSED-LOOP CONTROL OF DRUG ADMINISTRATION

Reference to Related Applications

- 5 [0001] This application claims priority from United States Application No. 62/258,656 filed on 23 November 2015 and entitled PHYSIOLOGICALLY SAFE CLOSED-LOOP CONTROL OF ANESTHESIA VIA MPC. For purposes of the United States, this application claims the benefit under 35 U.S.C. §119 of United States Application No. 62/258,656 filed on 23 November 2015 and entitled PHYSIOLOGICALLY SAFE CLOSED-LOOP CONTROL OF ANESTHESIA VIA
10 MPC which is hereby incorporated herein by reference for all purposes.

Technical Field

[0002] This technology relates to systems and methods to control the infusion of agents administered into the body. Particular embodiments relate to closed-loop control of anesthesia infusion.

15 Background

- [0003] Total intravenous anesthesia typically involves continuous infusion of at least two carefully titrated drugs: one to suppress consciousness (a hypnotic, such as propofol) and one to suppress response to painful stimuli (an analgesic, such as remifentanyl). Typically these drugs are infused by syringe pumps which are manually programmed to deliver a fixed drug infusion
20 rate based on patient body weight, among other factors. However, individual patient response to these drugs varies highly across patients, situations (e.g., extreme bleeding), and changes with prolonged infusion. Anesthesiologists typically manually adjust dosing to account for this variability, based on their observations of feedback from physiological measures. Effective and safe manual anesthesia requires considerable clinical experience and thorough understanding of
25 the transport, metabolism and temporal effects of the drugs.

[0004] Automatic control of anesthesia can assist the anesthesiologist by administering the appropriate drug dosage to keep the patient at an adequate level of anesthesia, reducing the effect of patient variability and providing fast rejection of surgical stimuli (as described, for example, in Gentilini, A., M. Rossoni-Gerosa, *et al.* (2001), "*Modeling and closed-loop control of*

hypnosis by means of bispectral index (BIS) with isoflurane", Biomedical Engineering, IEEE Transactions on 48(8): 874-889; Struys, M. D. P. D. Michel M. R. F., M. S. T. De Smet, *et al.* (2001), "*Comparison of Closed-loop Controlled Administration of Propofol Using Bispectral Index as the Controlled Variable versus 'Standard Practice' Controlled Administration*", The

5 Journal of the American Society of Anesthesiologists 95(1): 6-17; and Dumont, G. A., Martinez, A., Ansermino, J.M. (2008), "*Robust control of depth of anesthesia*", Int. J. Adapt. control Signal Process 23: 435-454 ("Dumont 2008"). Closed-loop control of anesthesia uses a physiological measure of the effect of drug infusion as feedback to continuously adjust drug infusion rates, resulting in individualized drug infusion constantly optimized to clinical circumstance.

10 Experimental systems have shown that closed-loop control of anesthesia has the potential to improve patient safety by reducing variability in the desired drug effect, overall drug quantities required, and instances of overdose. Furthermore, such systems may reduce variation in clinical practice, offering the opportunity to improve clinical outcomes (see Kheterpal, M. D. M. B. A. S. (2012), "*Random Clinical Decisions Identifying Variation in Perioperative Care*", The Journal

15 of the American Society of Anesthesiologists 116(1): 3-5; and Mackey, M. D. David C. (2012), "*Can We Finally Conquer the Problem of Medical Quality? The Systems-based Opportunities of Data Registries and Medical Teamwork*", The Journal of the American Society of Anesthesiologists 117(2): 225-226. A significant difficulty in the design of controllers for closed-loop control of anesthesia is the significant intra- and inter-patient variability that is

20 observed in response to a standard dose of drug. This has led to concern about the safety of closed-loop control systems in anesthesia (as discussed for example in Bibian, S., C. R. Ries, *et al.* (2005), "*Introduction to Automated Drug Delivery in Clinical Anesthesia*", European Journal of Control 11(6): 535-557).

[0005] It is desirable that closed-loop control systems for anesthesia incorporate safety

25 constraints on estimated drug concentrations and magnitude of infusion rates. The constraints can be due the physical hard constraints on the system and/or may be defined based on the therapeutic window of the anesthesia drug (see K. van Heusden, N. W., A. Umedaly, J. M. Ansermino, R. N. Merchant, and G. A. Dumont (2014), "Safety, constraints and anti-windup in closed-loop anesthesia", 19th IFAC World Congress: 6569–6574 ("van Heusden *et al.* 2014")).

30 During surgical procedures, a combination of hypnotic anesthetic drugs and opioid (analgesic) drugs is typically administered by an anesthesiologist to induce hypnosis and to attenuate the

natural response to injury. Consequently, there is a desire to control anesthesia by controlling both hypnosis and analgesia with safety constraints incorporated in the controller design.

[0006] Model Predictive Controller (MPC) control strategy offers solutions for the regulation of constrained linear or nonlinear systems, as discussed for example in Maciejowski, J. M. (2002),
5 "*Predictive control with restraints*", Prentice Hall ("Maciejowski 2002"). MPC control strategy has the inherent ability to handle multivariable control problems and to allow constraints to be imposed on both the controlled and manipulated variables. MPC has been successfully implemented in many applications in the chemical industry (see, for example, Qin, S. J., Badgwell, T. A (1997), "*An overview of industrial models predictive control technology*",
10 *Automatica* 93(316): 232-256) and use of MPC has been proposed for the control of blood glucose (see Cobelli, C., C. D. Man, *et al.* (2009), "*Diabetes: Models, Signals, and Control*" *IEEE reviews in biomedical engineering* 2: 54-96) and anesthesia drugs (see Ionescu, C. M., R. De Keyser, *et al.* (2008), "*Robust Predictive Control Strategy Applied for Propofol Dosing Using BIS as a Controlled Variable During Anesthesia*", *Biomedical Engineering, IEEE Transactions on* 55(9): 2161-2170 ("Ionescu, De Keyser *et al.* 2008"); Sawaguchi, Y., E. Furutani, *et al.* (2008), "*A Model-Predictive Hypnosis Control System Under Total Intravenous Anesthesia*", *Biomedical Engineering, IEEE Transactions on* 55(3): 874-887 ("Sawaguchi, Furutani *et al.* 2008"); and Niño, J., R. De Keyser, *et al.* (2009), "*EPSAC-controlled anesthesia with online gain adaptation*," *International Journal of Adaptive Control and Signal Processing*
20 23(5): 455-471 ("Niño, De Keyser, *et al.* 2009")). In the field of anesthesia, an advantage of MPC is that it provides the ability to control both hypnosis and analgesia, with constraints on drug infusion rates and predicted drug concentrations. Closed-loop control of hypnosis using MPC in adults has been evaluated in simulation (in Ionescu, De Keyser, *et al.*, 2008, and Niño, Keyser, *et al.* 2009) as well as in a clinical study (in Sawaguchi, Furutani, *et al.* 2008). A control
25 system using an individualized MPC controller augmented by a "risk control" supervisory system was evaluated in 79 clinical cases in Sawaguchi, Furutani *et al.*, 2008. Induction of anesthesia was manually controlled and the measured response was used to identify model parameters for the individualized MPC controller. The proposed controller was evaluated in simulation prior to the study, where plant-model mismatches were introduced. However,
30 formulation of robust stability and performance guarantees for this adaptive approach is technically challenging. An extended prediction self-adaptive control algorithm (EPSAC) was

compared to an adaptive controller in simulation (see Ionescu, De Keyser *et al.* 2008). The dynamics of the models do not take the inter-patient variability observed in pharmacokinetic-pharmacodynamic (PKPD) studies into account, and the uncertainty description used in this study possibly underestimates the variability observed in practice.

- 5 [0007] Safety bounds on estimated drug concentrations and magnitude of infusion rates have been included in a number of experimental systems for closed-loop control of anesthesia (see, for example, Sawaguchi, Furutani *et al.* 2008; van Heusden *et al.* 2014). Van Heusden *et al.* investigated a number of scenarios encountered in anesthesia practice where there is an obvious need for safety. The constraints were defined based on the therapeutic window of propofol and
10 were implemented in a PID closed-loop system with anti-windup (see van Heusden *et al.* 2014). A control system using an individualized model predictive control (MPC) controller plus a “risk control” supervisory system was employed by Sawaguchi, Furutani *et al.* during a study of closed-loop control of hypnosis. Sawaguchi, Furutani *et al.* implemented the supervisory system to imitate counter measures taken by anesthesiologists for undesirable states such as
15 intraoperative arousal, hypotension (low blood pressure), and bradycardia (heart rate under 60 beats per minute) (see Sawaguchi, Furutani *et al.* 2008).

- [0008] Significant challenges in closed-loop control of the delivery of liquid agents or medications that are administered into the patient’s body (e.g. intravenously, by inhalation, or otherwise) arise from the inter-patient uncertainty in the patient’s response to the agent. There is
20 a general desire for technology including an MPC based on robust control principles that addresses and/or ameliorates at least some of the aforementioned problems and/or improves the physiological safety of patients and efficacy of the delivery of anesthesia and other agents.

- [0009] The foregoing examples of the related art and limitations related thereto are intended to be illustrative and not exclusive. Other limitations of the related art will become apparent to
25 those of skill in the art upon a reading of the specification and a study of the drawings.

Summary

- [0010] The following embodiments and aspects thereof are described and illustrated in conjunction with systems, tools and methods which are meant to be exemplary and illustrative, not limiting in scope. In various embodiments, one or more of the above-described problems
30 have been reduced or eliminated, while other embodiments are directed to other improvements.

[0011] One aspect of the technology relates to robust and constrained MPC controllers for closed-loop control of infusion of agents in adults and children. The MPC is based on a nominal model and integrates one or more auxiliary models (such as a population-based PKPD model of a physiological characteristic) that is used to handle constraints on the drug concentration level within a patient or the one or more physiological characteristics on which the model is based. Minimization of an MPC performance index can be performed subject to constraints on the drug infusion rate (which may be a hard physical constraint based on the maximum infusion rate of the syringe pump, or a patient safety constraint that is based on the therapeutic window of the particular drug being delivered), the estimated drug plasma concentration and/or the estimated effect site concentration (which may be derived from the auxiliary model), and/or measurable physiological pressures (such as systolic blood pressure), and/or combined with constraints provided by the one or more auxiliary models to determine the optimized drug infusion rate. The technology has particular application for the control of infusion of anesthetic agents, including hypnotics and analgesics, which are delivered to a patient through intravenous injection, inhalation or other means. Other embodiments can be applied to control infusion of other types of agents, including for example, neuromuscular-blocking agents (which can be used in conjunction with anesthesia to prevent involuntary movement), hemodynamic medications, antihypertensive agents, analgesic adjuvants, neuroprotective drugs, anti-inflammatory agents and/or the like. In some embodiments, the MPC controller is a multivariable MPC controller that controls the infusion of more than one agent administered into the body.

[0012] Another aspect of the technology provides for the use of auxiliary models in a closed-loop control system to model the effect of an infused drug on a physiological characteristic within a patient, and project certain constraints back into the input space of the robust MPC controller when performing the MPC optimization. In some embodiments, the physiological characteristic may comprise one or more of: depth of hypnosis, blood pressure, cardiac output, heart rate variability, end tidal CO₂, respiratory rate, minute ventilation, end-tidal anesthetic agent monitoring and/or the like. The auxiliary model may be linear or nonlinear, and may have the form of a transfer function, state-space model or any form of data-driven model. The auxiliary model may comprise a PKPD model, a population-based PKPD model, a patient-specific PKPD model (e.g. based on the patient's history), a multi-compartment PKPD model, a Kalman filter, and/or the like.

[0013] A further aspect of the technology relates to the use of an actual measurement of a measurable physiological characteristic of the patient. The auxiliary model is modified such that a Kalman filter, a state observer or similar method is used to estimate the next prediction of the physiological characteristic to provide the constraint to the MPC to find the optimized drug infusion rate.

[0014] In addition to the exemplary aspects and embodiments described above, further aspects and embodiments will become apparent by reference to the drawings and by study of the following detailed descriptions.

Brief Description of the Drawings

[0015] Exemplary embodiments are illustrated in referenced figures of the drawings. It is intended that the embodiments and figures disclosed herein are to be considered illustrative rather than restrictive.

[0016] FIG. 1 is a block diagram of a closed loop system for controlling the delivery of a drug.

[0017] FIG. 2 illustrates the relative errors and uncertainty for samples of adults (A) and children (B).

[0018] FIG. 3 illustrates a closed-loop sensitivity and complementary sensitivity analysis for the nominal system for samples of adults (A) and children (B).

[0019] FIG. 4 illustrates a closed-loop MPC_{adult} control response of 44 patient models using WAV_{CNS} index wherein a hypothetical surgical stimulus is fixed to start 20 minutes after the beginning of the simulation (shown as the dotted line).

[0020] FIG. 5 illustrates a closed-loop MPC_{child} control response of 47 patient models using WAV_{CNS} index wherein a hypothetical surgical stimulus is fixed to start 20 minutes after the beginning of the simulation (shown as the dotted line).

[0021] FIG. 6 illustrates a closed-loop system with a parallel 4-compartment PKPD model according to one embodiment wherein k_{10} is the elimination rate, k_{ij} is the distribution rate constant from compartment i to j , k_{e0} is the plasma and effect-site equilibrium constant, V_i is the volume of the compartment i .

[0022] FIG. 7A illustrates the infusion rate and FIG. 7B illustrates the predicted plasma concentration and effect-site concentration for a patient chosen for the study in the presence of

disturbance from minutes 20 to 45.

[0023] FIG. 8 illustrates a closed-loop MPC response of 44 patients with unconstrained MPC.

[0024] FIG. 9 illustrates a closed-loop MPC response of 44 patients using constrained MPC.

5 [0025] FIG 10 illustrates a closed-loop constrained MPC response of 880 Monte Carlo simulated patients.

[0026] FIG. 11 illustrates a closed-loop MPC response for a patient in the study where a conflict between constraints resulted in a compromised solution.

10 [0027] FIG. 12A illustrates closed-loop MPC response of 44 patients with systolic blood pressure (SBP) limit of 50%. The percent SBP drop in from baseline to 80mmHg are shown for a constrained system (FIG. 12B) and an unconstrained system (FIG. 12C).

[0028] FIG. 13 is a flowchart of a method of closed-loop MPC control for the delivery of a drug, subject to constraints, according to one embodiment.

[0029] FIG. 14 is a flowchart showing a specific implementation of closed-loop MPC control for the delivery of a drug, subject to constraints, according to one embodiment.

15 **Description**

[0030] Throughout the following description specific details are set forth in order to provide a more thorough understanding to persons skilled in the art. However, well known elements may not have been shown or described in detail to avoid unnecessarily obscuring the disclosure. Accordingly, the description and drawings are to be regarded in an illustrative, rather than a
20 restrictive, sense.

[0031] Model Predictive Control (MPC) is a type of control technique used for process control applications. An advantage of MPC is that it allows control under constraints. In addition to handling constraints on the control signal, MPC can be used in a state-space form to handle constraints on state variables that do or do not have a physical meaning. In particular
25 embodiments, closed-loop control of the administration of anesthesia using MPC is based on a pharmacokinetic-pharmacodynamic (PKPD) model in which the controller states represent various concentrations (e.g. the plasma and/or effect site concentrations of the drug), and the closed-loop control is subject to safety-driven constraints on these concentrations.

[0032] Significant inter-patient uncertainty (resulting from the variability in patients' response to the delivered drug(s)) presents challenges in designing a closed-loop controller for delivery of anesthesia drug infusion. To address these challenges, robust control principles may be applied to the design of an MPC for control of anesthesia infusion. To robustly tune a MPC controller based on an existing bank of representative patient models, one may first derive a nominal model and characterize the uncertainty of this model due to inter-patient variability. Then a controller may be designed to meet performance requirements for the defined uncertainty around the nominal model. A challenge associated with this methodology is that the nominal model loses the PKPD structure and the controller states no longer represent concentrations. The inventors of the present application have addressed this problem by integrating, in an MPC controller, an auxiliary model (such as a population-based PKPD model) to compute concentrations and project concentration constraints back into the input space of the controller. The auxiliary models can also be used to describe impacts on physiological characteristics such as blood pressure. Aspects of the invention facilitate both robust control and constrained control as a solution to the problem of providing effective and physiologically safe control for systems under significant inter-patient uncertainty.

[0033] An MPC controller incorporating an auxiliary model was presented for control of depth of hypnosis in adults and children. A first step involves designing an MPC controller. The control strategy associated with the MPC controller may be designed to overcome the large inter-patient variability in response to a standardized anesthetic drug infusion using robust control principles. First, a nominal model may be constructed from individual frequency responses of patient models. To reduce the uncertainty due to inter-patient variability, the parameters of the nominal model may be tuned by minimizing the difference between the nominal and individual patient models in the frequency domain. The uncertainty with respect to this nominal model may then be quantified. The effect of the tunable controller parameters on stability and performance may be investigated by using sensitivity functions. For each population, the performance of the MPC controller on a set of models may be assessed in simulation during induction and maintenance of anesthesia including surgical stimulation. Evaluation of the MPC controller showed that the MPC controller meets desired design specifications and achieves the required robustness against patient uncertainty.

[0034] Evaluations on the MPC controller according to the embodiments described herein were

conducted for adults and children assuming that no constraints are active. The objectives of the evaluations were: (1) to design an MPC controller for adults (MPC_{adult}) that provides adequate propofol infusion for the complete study population, (2) to compare the MPC_{adult} with previously published robust designs and check the feasibility of achieving similar performance with the new MPC controller, that can be extended to constrained and multivariable control, (3) to define a nominal model and uncertainty description in children, and (4) to design a robust MPC controller for children (MPC_{child}) that can meet clinical criteria.

[0035] Evaluations were also conducted on an MPC-based controller with the imposition of additional constraints on drug concentrations and/or physiological characteristics for closed-loop control of anesthesia drugs (such as propofol). An auxiliary model was used to estimate or determine the drug concentration levels within a patient which were projected into the input space of the MPC controller when performing the MPC optimization. The objectives of the evaluations were: (1) to explore the importance of constraints in closed-loop control of hypnosis, (2) to add constraints to the previously designed and evaluated MPC controller, and (3) to assess the consequences of the constraints on the performance of the closed-loop control system in simulation. The MPC controller and methods described herein may incorporate constraints based on physiological characteristics, such as systolic blood pressure, and/or the like. The MPC-based systems and methods described herein may additionally or alternatively incorporate constraints based on other physiological characteristics.

[0036] An MPC controller according to various embodiments of the invention are discussed below as applied to closed-loop control of propofol (a hypnotic), with reference to the steps in designing, developing and evaluating the controller. As discussed below, a nominal model was first derived to model patients' response to propofol based on a measured or predicted output (for example, in this case, output from a depth of hypnosis (DOH) monitor which is indicative of a patient's depth of sedation or anesthesia). The uncertainty of the model, due to inter-patient variability, was then quantified with respect to the nominal patient model. An MPC controller was designed around the nominal model and its uncertainty. An auxiliary model was incorporated into the MPC controller to constrain the MPC controller based on drug concentration levels and/or physiological characteristics. Minimization of an MPC index was performed subject to these constraints. The physiological characteristics that are used to constrain the system may be determined from an auxiliary model, which may comprise a PKPD

model, a population-based PKPD model, a patient-specific PKPD model (e.g. based on the patient's history), a multi-compartment PKPD model, a Kalman filter, and/or the like.

[0037] An auxiliary model may also be used to describe impacts of the propofol on other physiological characteristics such as blood pressure. In some embodiments, certain physiological characteristics (such as systolic blood pressure) may be measured from the patient and these measured physiological characteristics may be used with an auxiliary model to refine other physiological characteristics (such as drug concentration levels or the like) which are used to constrain the system. In other embodiments, an auxiliary model may be used to estimate values for physiological characteristics such as blood pressure and these values may then be used to predict drug concentration levels and/or other physiological characteristics which are used to constrain the system.

[0038] Particular embodiments of the MPC-based system and methods described herein may be used to control the delivery of anesthesia drugs to a patient during a clinical and/or surgical procedure. "Anesthesia drugs" (or equivalent terms), as used herein, may refer to any drug that may be used for the purposes of sedating the patient and/or temporarily inducing in the patient a state of anesthesia (which may incorporate one or more of analgesia, paralysis, amnesia and/or unconsciousness), and may comprise, among other drugs, analgesics, hypnotics, neuromuscular blocking agents, and/or the like.

[0039] Agents that may be administered to a patient in a controllable manner using the systems and methods described herein may be administered in any of a variety of known routes.

Examples of methods that may be suitable for the administration of a drug agent or compound include intravenous, inhalation, intramuscular, subcutaneous, intraperitoneal and intrathecal delivery methods and the like. As a general reference, see for example, Remington, The Science and Practice of Pharmacy, Edited by Allen, Loyd V., Jr, 22nd edition, 2012, Pharmaceutical Press.

STEPS FOR DESIGNING, DEVELOPING AND EVALUATING A CLOSED-LOOP CONTROL SYSTEM FOR ANASTHESIA DELIVERY

Step 1: Model Set used for the Controller Design and Simulation

[0040] Hypnotic state can be measured or estimated using depth of hypnosis (DOH) monitors

such as the bispectral index (BIS) or the wavelet-based index (WAV_{CNS}) (see Johansen, M. D. P. D. Jay W. and M. B. B. S. P. D. M. B. A. Peter S. Sebel (2000), “*Development and Clinical Application of Electroencephalographic Bispectrum Monitoring*”, The Journal of the American Society of Anesthesiologists 93(5): 1336-1344). The WAV_{CNS} index provided by the

5 NeuroSENSE monitor (NeuroWave Systems, Cleveland Heights, USA) is used as a monitor for DOH in currently preferred embodiments. The NeuroSENSE monitor was developed specifically for closed-loop control; the dynamic behavior of this monitor is time-invariant and does not add additional computational delays (Zikov, T., S. Bibian, *et al.* (2006), “*Quantifying cortical activity during general anesthesia using wavelet analysis*”, Biomedical Engineering, IEEE

10 Transactions on 53(4): 617-632 (“Zikov, Bibian *et al.* 2006”). As known by those skilled in the art, the NeuroSENSE monitor measures physiological characteristics of a patient and returns a WAV_{CNS} value in a range of [1,100] with 100 being fully alert and 1 being the opposite of fully alert. Optimal hypnosis levels during stable state of general anesthesia are typically between WAV_{CNS} index of 40-60 (Agrawal, G., Bibian, S., Zikov, T. (2010), “*Recommended clinical*

15 *range for wavCNS*”, Society for Technology in Anesthesia Annual Meeting).

Patient Model - Pharmacological modeling

[0041] One commonly used intravenous hypnotic is propofol, which produces a sedative-hypnotic effect in the central nervous system. The effect of propofol is traditionally modeled using pharmacokinetic (PK) and pharmacodynamic (PD) models. In the evaluation conducted by

20 the inventors, the model set described by Dumont *et al.* (Dumont 2008) and the model set identified by van Heusden *et al.* (van Heusden, K., J. M. Ansermino, *et al.* (2013), “*Quantification of the Variability in Response to Propofol Administration in Children*”, Biomedical Engineering, IEEE Transactions on 60(9): 2521-2529 (van Heusden, Ansermino *et al.* 2013) were used for adults and children respectively. The adult model set includes 44 models,

25 identified from data from 18-60 year old adults with an American Society of Anesthesiologists (ASA) status of I or II. The mean (SD) age and weights were 36(12) years and 80(14) kg. The model set for children is identified from data from 47 children age 6-16 years, ASA I-II, requiring general anesthesia. The mean (SD) age and weights were 12(3) years and 44(16) kg. The adult models use the 3-compartment PK model of Schüttler (Schüttler, M. D. J. and M. S. H.

30 Ihmsen (2000), “*Population Pharmacokinetics of Propofol: A Multicenter Study*”, The Journal of the American Society of Anesthesiologists 92(3): 727-738 (“Schüttler and Ihmsen 2000”) and

pediatric models use the Paedfusor PK model (Absalom, A. and G. Kenny (2005), “‘Paedfusor’ pharmacokinetic data set,” British Journal of Anaesthesia 95(1): 110) to predict the propofol plasma concentration (C_p) as a function of the infusion rate (u):

$$\begin{bmatrix} \dot{C}_1 \\ \dot{C}_2 \\ \dot{C}_3 \end{bmatrix} = \begin{bmatrix} -(k_{10} + k_{12} + k_{13}) & k_{21} & k_{31} \\ k_{12} & -k_{21} & 0 \\ k_{13} & 0 & -k_{31} \end{bmatrix} \begin{bmatrix} C_1 \\ C_2 \\ C_3 \end{bmatrix} + \begin{bmatrix} 1/V_1 \\ 0 \\ 0 \end{bmatrix} \cdot u(t) \quad C_p(t) = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix} \cdot \begin{bmatrix} C_1 \\ C_2 \\ C_3 \end{bmatrix} \quad (1)$$

where C_1 is the central compartment and C_2 and C_3 are the peripheral compartments, k_{10} is the central compartment elimination rate constant and k_{12} , k_{13} , k_{21} and k_{31} are the inter-compartmental rate constants and V_1 is the central compartment volume (Schüttler and Ihmsen 2000). The pharmacodynamics of propofol is represented by a linear time invariant (LTI) transfer function and a non-linear function. The relationship between the plasma site concentration ($C_p(s)$) and the propofol concentration at the effect site ($C_e(s)$) may be described in the Laplace domain by:

$$C_e(s) = \frac{k_d}{s + k_d} e^{-T_d s} C_p(s) \quad (2)$$

where T_d is a transport delay and k_d is the rate of propofol distribution from the central compartment to the effect site compartment.

[0042] The relation between the $C_e(s)$ and the clinical effect (E) is described by a sigmoidal function known as the Hill function:

$$E = \frac{C_e^\gamma}{EC_{50} + C_e^\gamma} \quad (3)$$

where EC_{50} is the steady state propofol concentration associated with 50% of the full clinical effect and γ is a Hill function parameter which determines the steepness of the curve.

[0043] The linearized PD model for induction phase of anesthesia may then be expressed as:

$$PD(s) = e^{-T_d s} \frac{k_d}{s + k_d} \cdot \frac{1}{2 \cdot EC_{50}} \quad (4)$$

Patient Model - Dose-response model

[0044] The drug-response relationship of propofol can be expressed by combining the PK and

PD models. The PK model in (1) can be rewritten as a zero-pole-gain transfer function:

$$PK(s) = K_{PK} \frac{(s + z_1)(s + z_2)}{(s + p_1)(s + p_2)(s + p_3)} \quad (5)$$

where K_{PK} is a constant gain, and p and z represent the poles and zeros, respectively.

The linearized PKPD model may be obtained by combining the PK and PD: (4), (5).

$$PKPD(s) = e^{-T_d s} K \frac{(s + z_1)(s + z_2)}{(s + p_1)(s + p_2)(s + p_3)(s + p_4)} \quad (6)$$

where K is the overall PKPD(s) gain.

Patient Model - Nominal Model

[0045] MPC typically involves the use of a process model to predict the future output values.

The performance of MPC is dependent on the quality of this process model and hence it is

important to define the model and quantify the uncertainty around it. Following the approach presented by Dumont *et al.* (in Dumont 2008), the nominal model $PKPD_o(T_{do}, K_o, z_{o1}, z_{o2}, p_{o1}, p_{o2}, p_{o3}, p_{o4})$ may be constructed from the individual frequency responses of all patients in the study based on equation (6). A summary of the nominal parameters is presented in Table 1. To minimize the uncertainty, the parameters of $PKPD_o$ are tuned by minimizing the difference between the patients and the nominal frequency response using:

$$\begin{aligned} \min_{PKPD_o} \sum_{p=1}^n |PKPD_p(j\omega) - PKPD_o(j\omega)|, \\ s.t. \quad lb \leq \theta \leq ub \end{aligned} \quad (7)$$

where n is the number of patients in the group and $\theta = (T_{do}, K_o, z_{1o}, z_{2o}, p_{1o}, p_{2o}, p_{3o}, p_{4o})$ represents the optimum parameters of the nominal model and $lb = \min(T_d, K, z_1, z_2, p_1, p_2, p_3, p_4)$ and $ub = \max(T_d, K, z_1, z_2, p_1, p_2, p_3, p_4)$ are the lower and upper bounds of θ respectively.

[0046] Table 1: Optimum identified nominal model parameters

	T_d	K	z_{1o}	z_{2o}	p_{1o}	p_{2o}	p_{3o}	p_{4o}
	s	$10^{-4}/\text{mg}\cdot\text{s}^{-1}$	10^{-3}	10^{-5}	10^{-2}	10^{-3}	10^{-4}	10^{-5}
Adult	17	1.8	1.5	3.7	2.5	6.7	2.7	1.9

Child	48	1.3	0.9	5.2	2.0	5.0	4.9	3.9
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Step 2: Controller Design

[0047] The nominal model obtained after discretization can be represented as a state-space model, which is one type of non-limiting MPC formulation often used in the research literature (see Bemporad, A. and M. Morari (1999), *Robust model predictive control: A survey. Robustness in identification and control*, A. Garulli and A. Tesi, Springer London. 245: 207-226). Maciejowski *et al.* showed that for every transfer function formulation of an MPC there is an equivalent state-space formulation (see Maciejowski 2002):

$$\begin{aligned} x(k+1) &= Ax(k) + Bu(k) \\ y(k) &= Cx(k) \end{aligned} \quad (8)$$

[0048] In the evaluation conducted by the inventors, the disturbance is assumed to act on the output and $\eta(k)$ was defined as the disturbed output and $y(k)$ represents the actual measured output (see Maciejowski 2002). The setup for closed-loop control system **10** for anesthesia delivery to a patient is shown as a block diagram in FIG. 1. The system **10** comprises a controller **12** for controlling the delivery of anesthesia drugs to a patient **14** and a DOH monitor **16** for monitoring the patient **14**'s depth of hypnosis. Controller **12** is an MPC controller connected to an infusion pump **13** which controls the pump to deliver the drug at a particular infusion rate into patient **14** to take the patient to a desired depth of hypnosis (DOH). In the setup, $r(t)$ is the desired or reference DOH set by the anesthesiologist, $u(t)$ is the infusion rate calculated by the controller **12**, $d(t)$ represent a disturbance, such as a stimulation from the surgical procedure being performed on the patient, and $y(t)$ is the DOH output from the DOH monitor **16**. To obtain offset-free tracking, the equation (8) MPC state space formulation was augmented by defining a new state vector, $z(k)$ and an augmented state space formulation:

$$\begin{aligned} z &= \begin{bmatrix} \Delta x(k+1) \\ \eta(k+1) \end{bmatrix} = \overbrace{\begin{bmatrix} A & 0 \\ CA & 1 \end{bmatrix}}^{A_z} \begin{bmatrix} \Delta x(k) \\ \eta(k) \end{bmatrix} + \overbrace{\begin{bmatrix} B \\ CB \end{bmatrix}}^{B_z} \Delta u(k) + \begin{bmatrix} 0 \\ 1 \end{bmatrix} w(k) \\ y(k) &= \underbrace{\begin{bmatrix} 0 & 1 \end{bmatrix}}_{C_z} \begin{bmatrix} \Delta x(k) \\ \eta(k) \end{bmatrix} + v(k) \end{aligned} \quad (9)$$

where (A_s, B_s, C_s) are the state-space matrices of the augmented formulation, G_s of the augmented model, $w(k)$ and $v(k)$ are the output disturbance and white measurement noises.

- [0049] The augmented state vector z cannot be measured and, consequently, in some embodiments, is estimated, using the one-step ahead steady-state Kalman filter. From the
 5 estimated state z , the predicted output $y(k)$ is calculated. The output in a compact matrix form is

$$Y = F\hat{z}(k_i) + \Phi\Delta U \quad (10)$$

where $\hat{z}$ is the estimated state, ΔU , Y and F and matrix Φ are defined as follow:

$$\Delta U = \begin{bmatrix} \Delta u(k) & \Delta u(k+1) & \dots & \Delta u(k+n_c-1) \end{bmatrix}^T$$

$$Y = \begin{bmatrix} y(k+1) & \dots & y(k+n_p | k_i) \end{bmatrix}^T$$

$$F = \begin{bmatrix} C_s A_s \\ C_s A_s^2 \\ \vdots \\ C_s A_s^{n_p} \end{bmatrix} \quad \Phi = \begin{bmatrix} C_s B_s & \dots & 0 \\ C_s A_s B_s & s & \dots & 0 \\ \vdots & & & \\ C_s A_s^{n_p-1} B_s & s & \dots & C_s A_s^{n_p-n_c} B_s \end{bmatrix}$$

- 10 where n_c , the control horizon, is the number of samples used to capture the future control trajectory and n_p , the prediction horizon is the length of the optimization window.

- [0050] The control objective is to minimize a performance index (cost function) involving the difference between the given set-point DOH signal $r(k)$ and the measured (e.g. WAV_{CNS}) DOH $y(k)$ within a prediction horizon (see equations (11) below). In these evaluations, a constraint
 15 which may be used is on the amplitude of the drug (e.g. propofol) infusion rate or control variable $u(k)$:

$$\min_{\Delta u(k)} \left[\sum_i^{n_p} \|y(k) - r(k)\|_Q^2 + \sum_0^{n_c-1} \|\Delta u(k)\|_R^2 \right] \quad (11A)$$

$$s.t. \quad u_{\min} \leq u(k) \leq u_{\max} \quad (11B)$$

where Q and R are weights of output error and changes to the infusion rate respectively.

Step 3: Determining the Robust Stability and Nominal Performance

Uncertainty model

[0051] Robustness may be defined with respect to PKPD model uncertainty and a fixed linear controller. Factors resulting in uncertainty in PKPD models include: age, weight, height, and medical history and/or the like, as individuals with different ages, weight, height, medical history, etc. may respond differently to the drug. This uncertainty in the frequency domain may be represented by multiplicative uncertainty, where the magnitude of the multiplicative uncertainty ($l_I(\omega)$) may be expressed as:

$$l_I(\omega) = \max_{G_p \in \Pi} \left| \frac{G_p(j\omega) - G_o(j\omega)}{G_o(j\omega)} \right| \quad \forall \omega \quad (12)$$

where G_o is the nominal patient model with no uncertainty, G_p is a particular patient model and Π is the set of all patient models.

Sensitivity Functions

[0052] Robustness to model uncertainties is reflected in the sensitivity function and the complementary sensitivity function based on the loop transfer function of the feedback system, L . The sensitivity functions are defined as:

$$\begin{aligned} \text{Sensitivity function: } S &= (I + L)^{-1} \\ \text{Complementary Sensitivity function: } T &= L(I + L)^{-1} \end{aligned} \quad (13)$$

[0053] Robust Stability (RS) and Nominal Performance (NP) are guaranteed if:

$$\left\{ \begin{array}{l} RS \Leftrightarrow |T(j\omega)| < 1/|w_I| \quad \forall \omega \\ NP \Leftrightarrow |S(j\omega)| < 1/|w_P| \quad \forall \omega \end{array} \right. \quad (14)$$

where w_I is the multiplicative uncertainty weight and w_P is the performance weight.

[0054] The requirement of robust stability with multiplicative uncertainty gives an upper bound on T . To represent unmodelled dynamics, w_I may be determined by (Skogestad, S., Postlethwaite, I. (2005), “*Multivariable feedback control: Analysis and Design*,” 2nd edition Wiley-Interscience (“Skogestad 2005”)):

$$w_I(s) = \frac{\tau s + r_0}{(\tau / r_\infty)s + 1}$$

$$s.t. \quad |w_I(j\omega)| \geq l_I(\omega) \quad \forall \omega \quad (15)$$

where r_0 is the relative uncertainty at steady state, $1/\tau$ is approximately the frequency at which the relative uncertainty reaches 100%, and r_∞ is the magnitude of the weight at high frequency (Skogestad 2005). FIG. 2 shows the relative errors for a sample of 44 adults (denoted as plot **25A**) and 47 children (denoted as plot **25B**) in solid lines **20** and the uncertainty, $l_I(\omega)$ (denoted by curve **22**) and w_I (denoted by curve **24**) derived using the nominal model identified earlier.

[0055] To provide a clinically acceptable response, the system may be designed to have an overshoot of less than 15% and an initial rise time of less than 5 minutes. To meet the overshoot specification, the maximum value of the sensitivity function, M_s , may be limited to < 2 (Astrom, K. J., Hagglund, T. (2006), Advanced PID Control ; Research Triangle Park, NC ISA-The Instrumentation, Systems, and Automation Society). The weight w_P is defined as an upper bound on the sensitivity S , based on ω_m , the minimum bandwidth frequency, E_s the maximum steady and M_s state error and M_s (Skogestad 2005):

$$w_P(s) = \frac{s / M_s + \omega_m}{s + \omega_m E_s},$$

$$\text{where } M_s = \max_{\omega} |S(j\omega)| \quad (16)$$

[0056] The robust control theory considered here assumes that no constraints are active, so that evaluations can be conducted on the MPC controller operating in its unconstrained mode (i.e. as a linear controller), which is the case during most of the procedure (Maciejowski 2002), since even a constrained system should not hit its constraints too often when it is properly tuned and designed for its application.

Step 4: Robust Tuning of the Controller

[0057] Different tuning methods and formulations are available for designing a robust MPC (Mayne, D. Q., M. M. Seron, *et al.* (2005), “Robust model predictive control of constrained linear systems with bounded disturbances,” *Automatica* 41(2): 219-224). An objective of the evaluation performed by the inventors was to determine an appropriate MPC tuning for automatic control of hypnosis.

[0058] The tuning parameters of the MPC controller n_p , n_c , and R , as well as the parameters for the Kalman filter may be tuned in a systematic way to meet the specifications defined in equation (14). In a first step, the Kalman filter parameters, R_w and R_v may be tuned. This is achieved with a preliminary tuned MPC controller. The covariance of NeuroSENSE measurement noise is set to $R_v=9.0$ as described by Soltesz *et al.* (Soltesz, K., Van Heusden, K., Dumont, G.A., Hagglund, T., Petersen, C.L., West, N., Ansermino, J.M (2012), “*Closed-Loop Anesthesia in Children using a PID Controller: A Pilot Study*,” IFAC conference on advances in PID control). Based on this particular R_v value, the covariance R_w may be identified to optimize the output predictive capability of the Kalman filter by minimizing the difference between the observed output from NeuroSENSE, Y_{obs} and the predicted output from Kalman filter Y_{est} such that robust stability and nominal performance holds:

$$\min_{R_w} \sum |y_{obs} - y_{est}| \quad (17)$$

[0059] In a second step, the MPC parameters may be tuned. Increasing n_c , increases the degree of freedom in calculating the control move. A longer control horizon, results in a faster system response at the cost of the system being less robust. Penalizing Δu with R , results in a more robust controller at the price of the controller being sluggish (Varvel, J. R., D. L. Donoho, *et al.* (1992), “*Measuring the predictive performance of computer-controlled infusion pumps*”, J Pharmacokinet Biopharm 20(1): 63-94 (“Varvel *et al.* 1992”). Altering n_p concerns a trade-off between the rise-time and the overshoot upon induction of anesthesia. Increasing n_p has a stabilizing effect but also increase the computational effort. The parameters were tuned to optimize performance while meeting the robustness criteria, according to the following algorithm (“MPC Tuning Algorithm”):

- initialize the preliminary MPC parameters
- fix R_v value, and select R_w by minimizing the difference between Y_{obs} and Y_{est} using Equation (17)
- for MPC parameter: { n_c , R , N_p }:
- while conditions for Equation (14) are satisfied:
 - evaluate time-domain performance by calculating rise-time and overshoot values
 - evaluate M_s
 - select the parameter which results in lowest M_s value when rise-time and overshoot specifications (Robust Stability and Nominal Performance

Sensitivity Functions) are met

- end

- end .

5 **[0060]** For the example preliminary tuned controller developed by the inventors, the prediction horizon was fixed to $n_p=60$ samples, corresponding to the 5 minutes induction time with sampling time of $t_s=5$ seconds. The remaining MPC parameters were chosen as $n_c = 1$, and $R=1$. Minimization for Kalman filter tuning was performed with R_w values in the range 0.01-10, where predictability of the filter improved with increasing value of R_w . With R_v values fixed to 9.0,
10 increasing R_w , increased the observer gain meaning that for a noisy output, the gain will amplify the noise in the output. R_w was set to 1 to provide accurate predictions, while keeping the observer gain small.

[0061] MPC parameter tuning started with n_c . Increasing the control horizon to $n_c = 2$ resulted in a faster rise-time. The system remained stable and the added computational cost was negligible.
15 For n_c values greater than 2, the nominal system was unstable. The effect of changing R was examined for values between 0.1-1. The controller attained robust stability and nominal performance with all the values in the range. For R value 0.3, the system achieved a fast induction with no initial overshoot. With $n_c = 2$, $R_w = 1$, $R_v = 9$, $R = 0.3$, n_p values between 40 to 100 were considered. The controller achieved robust stability and nominal performance for all n_p
20 values in the specified range. The prediction horizon, n_p was fixed at 70, as the system achieves the smallest M_s value with that tuning parameter. This manually tuned controller satisfies the robust stability requirement and the nominal performance requirement as shown in FIG. 3A

[0062] Following the MPC Tuning Algorithm and the same tuning guideline described for adults, the MPC controller for children is tuned with parameters set to $n_c = 2$, $R_w = 0.01$, $R_v=9$,
25 $R=0.3$, $n_p=50$. The robust stability and nominal performance conditions and the sensitivity plots are presented in FIG. 3B.

Step 5: Closed-Loop Simulations

Simulation Set-up

[0063] For each (e.g. adult and children) controller, a 60 minute surgical procedure was
30 simulated for the complete set of models assuming an infusion rate of 10 mg/ml propofol.

Simulations were performed using nonlinear patient models. The target DOH was set to a WAV_{CNS} 50 for the duration of the procedure. For all patients, a hypothetical surgical stimulus was fixed to start 20 minutes after the beginning of the simulation. This stimulus profile was adapted from Dumont 2008. The infusion rate in this study is constrained between $u_{\min}=0$ and $u_{\max}=1200\text{ml/hr}$ which is the maximum infusion rate of the propofol pump.

Closed loop Responses

[0064] For assessment of the adult MPC controller, results were compared to the results from the controller by Hahn *et al.* (Jin-Oh, H., G. A. Dumont, *et al.* (2010), Robust closed-loop control of propofol administration using WAVCNS index as the controlled variable, Engineering in Medicine and Biology Society (EMBC), 2010 Annual International Conference of the IEEE (“Hahn, Dumont, *et al.* 2010”). The nominal model in both designs was constructed from the PK model by Schüttler and characteristic data and PD parameters from Dumont 2008. For Hahn *et al.*, the controller was also fixed for all patients and the patient models were divided into four age groups (Gr 1:18-30 yr, Gr 2:31-40 yr, Gr 3: 41-50 yr, and Gr 4:51-60 yr) to also investigate the effect of age as a covariate.

[0065] Results from the MPC controller for children were compared with the results from the clinical evaluation of a PID controller in van Heusden *et al.* 2014. The controller in both designs use the Paedfusor PK model and PD parameters from van Heusden, Ansermino *et al.* 2013. In the van Heusden *et al.* study, anesthesia was closed-loop controlled in 102 children ASA I-II where median (range) age and weights were 12.5(6-17) yr and 48(19-75) kg. The study was conducted in two stages. The originally tuned PID controller was evaluated in 31 cases.

[0066] The acquired results were used to fine tune the final controller which was evaluated in 71 cases. The controller performance at induction ($0\text{min} < \text{time} < 20\text{min}$) of anesthesia was evaluated based on overshoot, S_{os} and with rise-time, T_{ind} . During maintenance ($20\text{min} < \text{time} < 60\text{min}$) of anesthesia, the performance of the MPC controller was assessed in terms of percentage error (PE)-based metrics commonly used in anesthesia closed-loop control systems (Varvel *et al.* 1992). The median PE (MDPE), median absolute PE (MDAPE), divergence and wobble were calculated using the maintenance portion of the procedure and are presented in Table 2 and Table 3 respectively. The sign of MDPE represents the direction of the PE, where a negative value indicates that the controller tends to overdose the patient, leading to DOH levels

below target, whereas a positive value shows the tendency of a light anesthesia. MDAPE indicates the expected size of the error between the systems output and the set-point. Wobble measures the intra-patient variability in performance errors and divergence reflects the possible time-related trend of the output in relation to the set point. (PE)-based metrics were introduced to assess the performance of target controlled infusion (TCI) systems. These metrics are argued to be inadequate for evaluating EEG-guided automatic control of depth of hypnosis (Soltesz, K., G. A. Dumont, *et al.* (2013), Assessing control performance in closed-loop anesthesia, Control & Automation (MED), 2013 21st Mediterranean Conference on) and were only employed in these preliminary evaluations to provide a comparison of current results and those obtained in Hahn, Dumont *et al.* 2010 and in van Heusden *et al.* 2014.

[0067] Table 2: Performance of the MPC and the Hahn *et al.* controller (Hahn, Dumont *et al.* 2010) during induction and maintenance of simulated surgery in adults.

Group[age interval]: 1: [18-30] yr, 2: [31-40] yr, 3: [41-50] yr, 4: [51-60] yr.

Group	Number	Controller	S_{os} [%]	T_{ind}		MDPE [%]	MDAPE [%]	Divergence [%/min]	Wobble [%]
				WAV _{CNS}					
				<55					
				[min]					
All	44	MPC _{adult}	3.7±7.5	4.1±2.1	-	0.9±0.8	-0.02±0.01	0.9±0.8	
1	15	MPC	7.6±10.5	3.4±1.2	-	0.6±0.6	-0.02±0.01	0.5±0.5	
		Hahn	14.3±9.8	5.2 ±	0.1±0.4	2.9±1.1	-0.26±0.10	2.9±1.1	
2	12	MPC	2.6±6.3	3.7±1.3	-	0.7±0.3	-0.02±0.01	0.6±0.2	
		Hahn	13.7±12.8	2.4±0.3	1.2±0.2	1.6±0.3	-0.09±0.03	0.6±0.2	
3	8	MPC	0.61±1.72	5.3±2.3	-	1.5±1.4	-0.02±0.01	1.5±1.5	
		Hahn	15.1±4.3	2.8±0.2	0.9±0.2	1.5±0.3	-0.10±0.03	1.0±0.3	
4	9	MPC	1.4±3.1	4.7±2.1	-	1.2±0.8	-0.02±0.01	1.1±0.8	
		Hahn	2.0±5.0	5.3±1.3	0.5±0.3	2.6±0.7	-0.28±0.08	2.8±0.7	

[0068] Table 3: Performance of the MPC and the van Heusden *et al.* controller (van Heusden *et al.* 2014) during induction and maintenance of simulated surgery in children.

Number	Controller	S_{os} [%]	S_{os} 3min after T_{ind} [index]	T_{ind} WAV_{CNS} <60 [min]	MDPE [%]	MDAPE [%]	Divergence [%/min]	Wobble [%]
47	MPC _{child}	7.3±7.8	50±5	5.0±1.8	-3.6±1.3	5.3±1.7	-0.04±0.1	4.0±1.4
31	van Heusden	N/A	40±5	4.5±1.5	-8.7±7.8	11.5±6.3	N/A	6.2±3.5
71	van Heusden	N/A	42±5	3.7±1.2	-6.2±5.3	8.8±4.2	N/A	6.0±2.4

[0069] These evaluations determined that the example MPC controllers described herein met the overshoot specification. WAV_{CNS} values below 40 are associated with occurrence of apnea making the overshoot value a significant performance factor, especially for the cases where spontaneous breathing is required. Pain on injection of propofol is another common concern particularly for pediatric anesthesiologists, making the rise-time another important aspect in performance evaluation for closed-loop control of anesthesia. In the field of anesthesia, rise-time is commonly defined as the time that takes for DOH index to fall below 60 and for the patient to be in a moderate hypnotic state. A WAV_{CNS} index of 60 was reached with the MPC_{adult} and MPC_{child} controllers within an average of 4.1 min and 5min respectively. The trade-off to guarantee stability given the large inter-patient variability is the slower than desired rise-time for insensitive patients.

[0070] FIGS. 4 and 5 show the MPC closed-loop simulations for the 44 adult patients and 47 pediatric patients respectively. The results show that despite the large inter-patient variability in adults and especially in children, stability and performance was achieved. Evaluation of the proposed MPC controllers during simulated induction and maintenance of anesthesia show that the design specifications are met and that the desired robustness against patient uncertainty was achieved.

Step 6: Addition of safety constraints to the MPC controller using an auxiliary model

[0071] Constraints on the amplitude of the control variable u , which, in the examples described

herein, is the propofol infusion rate, may arise from the hard physical constraints on the system.

By way of non-limiting example, such hard physical constraints may include that the infusion rate cannot be negative, and the infusion rate must be less than the maximum rate that can be provided by the infusion pump. In addition to or in the alternative to hard physical constraints,

constraints can also be applied on other criteria (e.g. patient safety and/or the like). For example, in the control of propofol administration, constraints can be enforced to minimize hemodynamic changes which tend to follow propofol delivery to the patient. Bilotta *et al.* showed in a study in which patients were randomly assigned to receive propofol at two different infusion rates

(10mg/s vs 2mg/s), that the higher infusion rate induced a larger drop in mean arterial pressure

than the lower infusion rate (Bilotta, F., L. Fiorani, *et al.* (2001), “*Cardiovascular effects of intravenous propofol administered at two infusion rates: a transthoracic echocardiographic study*,” *Anaesthesia* 56(3): 266-271). Having constraints on the magnitude of u may give the

option to limit the maximum infusion rate. The infusion rate in the example evaluations

conducted by the inventors was constrained between 0 and 600 ml/hr, whereas the infusion pump

is capable of 1200ml/hr.

$$0 \leq u(t) \leq 600 \text{ ml/hr} \quad (18)$$

[0072] One of the main effects of propofol on the cardiovascular system is a decrease in arterial blood pressure due to a drop in systemic vascular resistance. Reductions in systolic blood pressure (SBP) greater than 25% have been reported during induction of anesthesia with

propofol (Kazama, T., K. Ikeda, *et al.* (1999), “*Comparison of the effect-site $k(eO)$ s of propofol for blood pressure and EEG bispectral index in elderly and younger patients*,” *Anesthesiology* 90(6): 1517-1527 (“Kazama, Ikeda *et al.* 1999”).

West *et al.* (West, N. V. H., K., Görges, M., Petersen, C.L., Umedaly, A., Dumont, G.A., Ansermino, J.M. and Merchant, R.N (2014), “*Blood pressure changes during closed-loop control of anesthesia*,” Proceedings of the Canadian

Anesthesiologists Society Annual Meeting) evaluated the intraoperative blood pressure measurements for 35 adults age 64.5 [38-81] yr, ASA I-III where propofol was closed-loop controlled and remifentanyl was administered by target controlled infusion. Hypotension was treated in 7 (19%) subjects during the period between start of propofol infusion and incision.

Kazama *et al.*, investigated the effect of age on SBP change with propofol in patients aged 20-

85yr. Their results showed that at high plasma concentrations ($>10 \mu\text{g/ml}$), propofol may

significantly decrease SBP, an effect more evident in elderly (> 70 yr) patients (Kazama, Ikeda *et al.* 1999).

[0073] Another effect of propofol at high concentration is a reduction of cerebral electrical activity as confirmed by an electroencephalography (EEG) Burst Suppression (BS) pattern with significant periods of isoelectric activity (Illievich, U. M., W. Petricek, *et al.* (1993), “*Electroencephalographic burst suppression by propofol infusion in humans: hemodynamic consequences*,” *Anesth Analg* 77(1): 155-160 (“Illievich, Petricek *et al.* 1993”). Besch *et al.* reported that the occurrence of isoelectric periods is more frequent with increasing hypnotic drug concentration, suggesting that BS may indicate too deep anesthesia (Besch, G., N. Liu, *et al.* (2011), “*Occurrence of and risk factors for electroencephalogram burst suppression during propofol-remifentanyl anaesthesia*,” *Br J Anaesth* 107(5): 749-756). Their study concluded that the main independent factors linked with BS were advanced age, medical history of coronary disease and male gender. BS onset has been reported with effect-site concentrations higher than 8 µg/ml (Illievich, Petricek *et al.* 1993) without opioids and 7.3 µg/ml with an opioid (remifentanyl 30 µg/kg/min).

[0074] The lower bound on the propofol concentration may be generally defined by concentrations which admit patient awakening. Light anesthesia is a result of low propofol concentration and is associated with an increased possibility of awareness during surgery (Ghoneim, M. M., R. I. Block, *et al.* (2009), “*Awareness during anesthesia: risk factors, causes and sequelae: a review of reported cases in the literature*,” *Anesth Analg* 108(2): 527-535.). Propofol concentrations less than 1.6µg/ml (when administered with fentanyl) (Kazama, Ikeda *et al.* 1999) and 1.8 µg/ml (Iwakiri, H., N. Nishihara, *et al.* (2005), “*Individual effect-site concentrations of propofol are similar at loss of consciousness and at awakening*,” *Anesth Analg* 100(1): 107-110) without opioids are associated with awakening from anesthesia.

[0075] To place safety bounds or constraints on the dosage of the drug, values with respect to a therapeutic window of the drug may be used to define drug concentration levels in the patient’s body, and side effects may be minimized or reduced by staying within the therapeutic window. Thus, safety bounds on the estimated propofol plasma concentration (C_p) and estimated effect-site concentration (C_e) can be defined using the therapeutic window for propofol as constraints on measured physiological characteristics explained above. In particular embodiments, the following bounds may be used in the controller design:

$$1.6 \leq C_p \leq 10 \mu g / ml \quad (19)$$

$$1.6 \leq C_e \leq 7 \mu g / ml \quad (20)$$

[0076] It should be noted that the concentrations expressed in equations (19) and (20) are based on an open-loop population-based PKPD model and thus may not be an optimal indication of the actual concentrations for a particular patient. This reinforces the desirability of incorporating constraints on measured physiological characteristics.

Patient Model

[0077] The effect of propofol is traditionally modelled using pharmacokinetic (PK) and pharmacodynamics (PD) models. PK models are used to estimate the plasma drug concentration profile of a drug in response to its administration. The plasma concentration of a drug in a patient may be referred to as C_p . PD models can be employed to estimate the drug concentration at a hypothetical effect-site (often referred to as C_e) with an equilibrium constant (k_{e0}) describing the dynamic delay associated with the distribution of the drug between the plasma and the effect-site. PD models may also describe the relationship between the concentration of the drug at the effect-site and the clinical effect of the drug.

[0078] In some embodiments, the dose-response relationship of propofol could be expressed by using a PKPD model. However, in currently preferred embodiments, a nominal model, G_o , is employed. G_o is based on a model set described by Dumont *et al.* (Dumont 2008). The set includes 44 models, identified from 18-60 year old adults with an American Society of Anaesthesiologist (ASA) status of I or II. The mean (SD) age and weights were 36(12) years old and 80(14) kg. In some embodiments, the nominal model G_o , in state-space formulation, may be used in the controller.

$$\begin{aligned} x(k+1) &= Ax(k) + Bu(k) \\ y(k) &= Cx(k) \end{aligned} \quad (21)$$

Controller Set-up Based on Nominal Model

[0079] FIG. 1B shows a closed-loop control system **10** for delivery of a drug (in this example embodiment, an anesthesia drug, in particular, propofol) to a patient according to a particular example embodiment. It will be appreciated from the description that follows that

control system **10** and its components could be suitably modified to controllably deliver other drugs. Control system **10** and in particular controller **12** are based on an MPC control scheme based on a nominal model G_o . System **10** comprises an MPC controller **12** for controlling the delivery of an anesthesia drug (e.g. propofol) to patient **14** and a DOH monitor **16** for monitoring the depth of hypnosis (DOH) of patient **14**. DOH monitor **16** may comprise an electroencephalogram (EEG) monitor, wherein physiological EEG data from sensors placed on the forehead may be used to assess the patient's DOH. The DOH output from the monitor **16** can be represented, for example, as a WAV_{CNS} index ranging from 0 for iso-electric EEG to 90-100 for full consciousness. It will be appreciated that DOH monitor **16** is an example of a monitor that is useful for sensing the physiological characteristics of patient **14** and determining therefrom a monitor measurement that is useful for the cases where the drug being administered is propofol and/or some other anesthetic drug. In general, however, where control system **10** is used for different types of drugs, monitor **16** need not be a DOH monitor. Instead, monitor **16** may generally comprise any suitable device which senses one or more monitorable physiological characteristics of patient **14** and which determines therefrom one or more monitor measurements indicative of the effect of the drug being administered on the patient. In system **10**, controller **12** comprises a computer or a control and processing unit which is connected to a source of the drug to be administered (not shown in Figure 1) and to a controllable drug administration actuator **13**. In the case of the illustrated embodiments, drug administration actuator **13** comprises a controllable infusion pump or infusion syringe **13**.

[0080] Controller **12** is configured to determine one or more control variables $u(t)$, also referred to as control signal $u(t)$ and/or manipulated variables $u(t)$, which may in turn be used to control drug administration actuator **13**. In the particular case where drug administration actuator **13** comprises an infusion pump, control signal $u(t)$ may be considered to comprise or be otherwise correlated with an infusion rate $u(t)$ of the drug being administered. In the case of the example embodiment of FIG. 1, controller **12** determines a control variable which is used to generate a control signal which in turn is used to control syringe pump **13** to deliver propofol at a particular infusion rate. In the exemplary control system 10 of FIG. 1, $r(t)$ is a desired or reference level (also referred to as a set point) for the monitor measurement. For example, in the exemplary embodiment where the drug being administered is propofol and monitor **16** is a DOH monitor, $r(t)$ may be a reference DOH level, which may be set by an anesthesiologist, for

example. When the drug is administered to patient **14** via drug administration actuator **13**, the response of patient **14** is monitored by monitor 16 (DOH monitor **16**, in the case of the FIG. 1 example embodiment) and monitor **16** generates a corresponding monitor measurement $y(t)$. The monitor measurement $y(t)$ may be referred to as the controlled variable. Control system 10, an in particular controller **12** uses reference level $r(t)$ and the monitor measurement $y(t)$ from monitor **16** to calculate a control signal $u(t)$ which will cause monitor measurement $y(t)$ to track reference level $r(t)$. Where controller **12** implements a digital MPC based control scheme (as is the case in the illustrated embodiment), controller **12** may determine a control signal $u(t)$ in each of a series of time steps by minimizing a corresponding cost function (also referred to as optimizing a corresponding performance index) in each time step. The control signal $u(t)$ determined by the optimization in each time step may be applied to drug administration actuator **13** in a subsequent time step.

[0081] To obtain offset-free tracking for the case of the example FIG. 1 embodiment, controller **12** of the exemplary FIG. 1 embodiment may incorporate the nominal model G_o in the augmented formulation (van Heusden *et al.* 2014) described above, where $\eta(k)$ is defined as the disturbed output and $y(k)$ represents the actual monitor measurement output (Maciejowski 2002). In a discrete-time state-space formulation, this augmented controller formulation may be described by

$$\begin{aligned} \begin{bmatrix} \Delta x(k+1) \\ \eta(k+1) \end{bmatrix} &= \begin{bmatrix} \overbrace{A}^{A_s} & 0 \\ CA & 1 \end{bmatrix} \begin{bmatrix} \Delta x(k) \\ \eta(k) \end{bmatrix} + \begin{bmatrix} \overbrace{B}^{B_s} \\ CB \end{bmatrix} \Delta u(k) + \begin{bmatrix} 0 \\ 1 \end{bmatrix} w(k) \\ y(k) &= \underbrace{\begin{bmatrix} 0 & 1 \end{bmatrix}}_{C_s} \begin{bmatrix} \Delta x(k) \\ \eta(k) \end{bmatrix} + v(k) \end{aligned} \quad (22)$$

where (A_s, B_s, C_s) is the state-space representation of the augmented model, $w(k)$ and $v(k)$ are the output disturbance and white measurement noises respectively.

[0082] The augmented state vector $\begin{bmatrix} \Delta x(k) \\ \eta(k) \end{bmatrix}$ of the augmented nominal model cannot be measured and may therefore be estimated, using, for example, the one-step ahead steady-state Kalman filter.

Addition of Constraints Based on Auxiliary Model

[0083] As discussed above, the nominal model, G_o used for the FIG. 1 control system **10** was

constructed from individual frequency responses of a set comprising 44 subjects. Because of the frequency domain technique used in the construction of G_o , the states of the resulting controller do not represent hypothetical PK compartments. In particular, a nominal model constructed according to the above-described frequency domain techniques loses its PKPD structure and the states no longer represent drug concentrations. According to particular embodiments of the invention, an auxiliary model is added to the FIG. 1 control system **10**, wherein the auxiliary model takes into account the control signal $u(t)$ and estimates, based on the control signal $u(t)$, at least one concentration level of the drug in the patient. FIG. 6 shows a control system **30** for closed loop control of administration of a drug (in the exemplary case, an anesthesia drug, particularly propofol) wherein an auxiliary model **32** is added to the FIG. 1 control system **10**. In control system **30** shown in FIG. 6, drug administration actuator **13A** and monitor **16A** may be substantially similar to drug administrator actuator **13** and monitor **16** described herein in connection with control system **10** (FIG. 1). Except where otherwise indicated herein, controller **12A** of the FIG. 6 control system **30** may be similar to controller **12** of the FIG. 1 control system **10**.

[0084] As can be seen from FIG. 6, auxiliary model **32** receives control signal $u(t)$ as input and uses control signal $u(t)$ to estimate at least one concentration C of the drug in the body of patient **14**. In some embodiments, the at least one concentration C comprises a plasma concentration C_p of the drug. In some embodiments, other concentrations such as a notional effect site concentration C_e may be additionally or alternatively estimated by auxiliary model **32**.

[0085] Controller **12A** may implement a MPC control scheme which involves, for each of a series of time steps, minimizing a cost function (optimizing a performance index) which yields the control signal $u(t)$ for the next time step. When auxiliary model **32** is incorporated into control system **30**, the minimization performed by controller **12A** at each time step may be subject to one or more constraints, wherein at least one such constraint is based on a concentration C estimated by auxiliary model **32**. In some embodiments, as described in more detail below, auxiliary model **32** models the effect of the drug being administered on a physiological characteristic of the patient and may be used to map a constraint on the physiological characteristic into a corresponding constraint on an estimated concentration C that is output by auxiliary model **32** and provided to controller **12A**.

[0086] In accordance with the particular example control system embodiment **30** shown in FIG.

6, auxiliary model **32** comprises a multiple-compartment PKPD model, e.g. a 4-compartment PKPD model (a 3-compartment PK model plus an effect-site compartment). As discussed above, auxiliary model **32** of the FIG. 6 example embodiment estimates the propofol concentration in a central compartment (referred to as a plasma concentration C_p) and an effective concentration at the effect-site (referred to as an effect site concentration C_e). The 4-compartment PKPD model **32** of the FIG. 6 example embodiment may be represented in state-space as follows:

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_4 \end{bmatrix} = \underbrace{\begin{bmatrix} -(k_{10} + k_{12} + k_{13} + k_{e0}) & k_{12} & k_{13} & k_{e0} \\ k_{21} & -k_{21} & 0 & 0 \\ k_{31} & 0 & -k_{31} & 0 \\ k_{e0} & 0 & 0 & -k_{e0} \end{bmatrix}}_A \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix} + \underbrace{\begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \end{bmatrix}}_B u \quad (23)$$

where k_{10} is the elimination rate, k_{ij} is a distribution rate constant from compartment i to compartment j , x_1 represents the amount of drug in the central compartment, C_p , and x_4 represents the amount of drug in the effect-site compartment, C_e . By adding an auxiliary model **32** such as the 4-compartment PKPD model of equation (23) to an MPC controller, values for the concentrations C_p , C_e can be determined and minimization of the MPC cost function can be carried out subject to constraints on these concentrations C_p , C_e .

[0087] At the start of a propofol infusion, after an increase in the infusion rate and/or after an administration of bolus, the concentration C_p of drug in the plasma of patient **14A** rises first. After a small delay, the concentration C_e at the effect-site compartment increases until a maximum effect-site drug concentration is reached. When simulating this process, C_p should be allowed to have a greater early stage (e.g. initial) concentration limit (constraint) than C_e . After C_e has reached its steady-state concentration, the maximum constraint $C_{p_{max}}$ may be set equal to the maximum constraint $C_{e_{max}}$. Accordingly, after the initial spike in the plasma concentration C_p , the plasma concentration constraint may be modified (e.g. reduced) as the effect site concentration C_e increases. This is shown in FIG. 7, which illustrates the administration of a propofol bolus, shown by an increase in infusion rate (top panel), the response of the plasma concentration C_p (lower panel, solid line) and the effect site concentration C_e (lower panel, dashed line). When the infusion is stopped or the infusion rate is reduced, the plasma propofol concentration C_p falls first, the minimum concentration reached by C_p may be lower than C_e . This effect is also shown in FIG. 7.

1) Effect-site Concentration (k_{e0} of EEG Monitor)

[0088] The effect site concentration C_e parameter is representative of a drug concentration in the body of a patient which may correspond with a particular physiological characteristic. A PD model may provide a relationship between an effect site concentration C_e of a particular drug and a level of characteristics in its corresponding physiological characteristic. In some embodiments, the effect site concentration C_e estimated by auxiliary model **32** may correspond to the monitor **16A** of system **30**. In the case of the FIG. 6 embodiment, monitor **16A** is a EEG monitor which provides a DOH monitor measurement. (In other particular embodiments, one or more monitors may be provided as monitor **16A** in order to monitor multiple physiological characteristics). To predict C_e in accordance with some such embodiments, equation (23) may be evaluated as explained in Schnider, T. W., C. F. Minto, *et al.* (1998), “*The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers,*” Anesthesiology 88(5): 1170-1182 (“Schnider, Minto *et al.* 1998”), with k_{e0} (18-60yr:0.456 min⁻¹). A C_e constraint is written as shown in equation (24A) as follows:

$$C_{e_{\min}} \leq C_e \leq C_{e_{\max}} \quad (24A)$$

$$C_{e_{\min}} \leq \underbrace{[0 \quad 0 \quad 0 \quad 1]}_{C_{effect}} \cdot (Ax[k] + Bu[k]) \leq C_{e_{\max}} \quad (24B)$$

where the effect site concentration C_e may be estimated by auxiliary model **32** according to equation (24B) for the particular case of the 4-compartment PKPD model of equation (23).

[0089] To be compatible with the control algorithm (21), the constraints are rearranged in terms of Δu :

$$\begin{aligned} C_e &\leq C_{e_{\max}} \\ \Rightarrow C_{effect} \cdot B\Delta u[k] &\leq C_{e_{\max}} - \underbrace{(C_{effect} \cdot (Ax[k] + B(u[k-1])))}_{\Delta C_e} \\ C_{\min} &\leq C_e \\ \Rightarrow C_{e_{\min}} - \underbrace{(C_{effect} \cdot (Ax[k] + B(u[k-1])))}_{\Delta C_e} &\leq C_{effect} \cdot B\Delta u[k] \end{aligned} \quad (25)$$

2) Plasma Concentration

Following the same guidelines as those explained for C_e , in equations (24) and (25) the constraints for C_p can be written as follows:

$$Cp_{\min} \leq \underbrace{[1 \ 0 \ 0 \ 0]}_{C_{plasma}} \cdot (Ax[k] + Bu[k]) \leq Cp_{\max} \quad (26)$$

[0090] As explained above, the maximum and minimum limits for C_p can change. From the values suggested in equations (19) and (20), some suitable constraints for C_p may be as follows:

$$Cp_{\max} = \text{Min} \left\{ \begin{array}{l} 10 \\ 7 + (7 - \Delta Ce) \end{array} \right.$$

$$Cp_{\min} = \text{Max} \left\{ \begin{array}{l} 1.6 \\ 1.6 + (1.6 - \Delta Ce) \end{array} \right. \quad (27)$$

3) Blood Pressure (K_{e0} of SBP)

[0091] As seen in FIG. 6, system **30** optionally includes one or more additional sensors **34** for monitoring an additional measurable physiological characteristic of the patient (e.g. in addition to the physiological characteristic that corresponds to the controlled variable and is sensed by monitor **16A** (e.g. DOH, in the case of the illustrated FIG. 6 embodiment)). For example, in some embodiments, sensor **34** comprises a blood pressure sensor, and a physiological characteristic of patient **14A** which may be measured during hypnosis is the systolic blood pressure (SBP) of the patient. The SBP values can themselves be used as constraints on the optimizations performed by controller **12A** and/or they can be used to generate or refine the C_p , C_e values determined by auxiliary model **32**. An optional constraint to be considered in closed-loop control of hypnosis is the maximum drop in SBP during induction. This maximum drop in SBP may be particularly important for certain patients who are at higher risk of experiencing adverse side effects from anesthesia due to a change in SBP. Kazama *et al.* showed that the effect of propofol on the BIS DOH monitor (Aspect Medical Systems Inc. Norwood, MA, USA) occurs relatively rapidly compared with the effect of propofol on SBP (Kazama, Ikeda *et al.* 1999). To predict the effect site propofol concentration corresponding to the SBP, C_{eBP} , equation (23) may be calculated using the PK model (Schnider, Minto *et al.* 1998) in parallel with the patient model and k_{e0} (20-39yr: 0.1232 min^{-1} , 40-59yr: 0.1182 min^{-1} and 60-69yr: 0.0778 min^{-1}) identified in Kazama, Ikeda *et al.* 1999. Kazama *et al.* expressed the effect of propofol on SBP as a percentage SBP decrease, SBP %, from baseline, SBP_{base} , to 80mmHg as follows:

$$SBP_{\%} = \frac{SBP - 80}{SBP_{base} - 80} \cdot 100 = 100 - 100 \cdot \frac{Ce_{BP}[k]^{\gamma}}{EC50^{\gamma} + Ce_{BP}[k]^{\gamma}} \quad (28)$$

where $EC50$ is the propofol concentration associated with the 50% of maximum effect and γ is the Hill coefficient.

- 5 **[0092]** For an optimization with respect to Δu performed by controller **12A** and subject to a lower bound (constraint) on SBP, it may be computationally efficient to establish a linear relationship between SBP and the effect-site propofol concentration Ce_{BP} corresponding to SBP. In some embodiments, the Hill equation (28) may be linearized around the point at which the SBP decreases from the baseline to the 50% point (i.e. a 50% decrease from baseline to
- 10 80mmHg) with a constant slope of unity.

$$SBP_{\%} = 100 \cdot \frac{Ce_{BP}[k]}{2EC50} \quad (29)$$

Hypotension may be defined as a SBP drop of 50% from the baseline to 80mmHg.

Optimization Steps Subject to the Constraints

- [0093]** The control objective of the FIG. 6 control system **30** is to minimize a performance index
- 15 (cost function), J involving the difference between the desired DOH reference level $r(k)$ and monitor measurement $y(k)$ (e.g. the DOH WAV_{CNS} measurement in the case of the illustrated embodiment) over a prediction horizon. This minimization may be performed at each time step k to determine the next control signal $u(k)$. In particular embodiments, the minimization is performed subject to various constraints. As discussed elsewhere herein, the constraints may
- 20 comprise one or more constraints on the concentrations estimated by auxiliary model **32**. Auxiliary model **32** may model a physiological characteristic (e.g. SBP and/or the like) of patient **14A** and auxiliary model **32** may map constraints on such physiological characteristics into corresponding constraints on the concentrations estimated by auxiliary model **32**. The constraints on the optimization performed by controller **12A** are not limited to constraints on concentrations
- 25 estimated by auxiliary model **32**. In some embodiments, controller **12A** may additionally incorporate constraints based on other safety considerations for patient **14A** and/or physical constraints on drug administrator actuator **13A** and/or monitor **16A**. In one particular non-

limiting embodiment, optimization problem performed by controller **12A** to minimize a cost function, J , has the form:

$$J = \sum_i^{n_p} \|y(k) - r(k)\|_Q^2 + \sum_0^{n_c-1} \|\Delta u(k)\|_R^2$$

$$s.t \begin{cases} 0 \leq u(k) \leq 600 \text{ mL/hr} \\ 1.6 \leq C_p(k) \leq 10 \mu\text{g/mL} \\ 1.6 \leq C_e(k) \leq 7 \mu\text{g/mL} \quad \text{or} \quad SBP_{\%} \leq 50 \end{cases} \quad (30)$$

5 where n_c , the control horizon, is the number of samples used to capture the future control trajectory and n_p , the prediction horizon is the length of the optimization window, while Q and R are weights on the output error and incremental input respectively. In particular embodiments, the values for the estimated propofol plasma concentration (C_p) and estimated effect-site concentration (C_e) are estimated by auxiliary model **32**. As discussed elsewhere herein, auxiliary
 10 model **32** may comprise a PKPD model (e.g. a population-based PKPD model, a patient-specific PKPD model based on the patient's personal history with the drug or some other type of PKPD model). In some embodiments, the concentrations (e.g. C_e and C_p) estimated by auxiliary model **32** are related to physiological characteristics (e.g. like the DOH measured by monitor **16A**, SBP measured by sensor **34** and/or the like). In this manner, auxiliary model **32** may be used to
 15 estimate values for evaluating physiological constraints which are projected back into the input space (e.g. concentration) of controller **12A** when performing MPC optimization. In addition to or in the alternative to the foregoing, additional physiological characteristics (such as SBP and/or the like) may be measured from patient **14A** and auxiliary model **32** may map these additional measured physiological characteristics and constraints based on these physiological
 20 characteristics into corresponding concentrations and constraints based on these corresponding concentrations. Additional constraints (not specifically related to auxiliary model **32**) may be incorporated into the MPC optimizations performed by controller **12A**. Such constraints may be related to safety considerations for patient **14A** and/or physical limitations of hardware such as drug administration actuator **13A** and/or monitor **16A**, for example. For example, in the equation
 25 (30) optimization, a constraint limits the infusion rate, u between zero (as it is not possible to deliver a negative infusion rate) and a maximum infusion rate which is considered safe for the therapeutic window of the drug being administered (i.e. 600 mL/hr in the above example).

[0094] The function J and the constraints (30) can be rewritten in the following form:

$$\begin{aligned} J &= \min_{\Delta U} \frac{1}{2} \Delta U^T H \Delta U + \Delta U^T f \\ M \Delta U &\leq \Gamma \end{aligned} \quad (31)$$

where M represents the constraints. The number of rows in the matrix M is equal to the number of constraints and the number of columns is equal to the dimension of ΔU .

- 5 [0095] The inequality constraints may consist of active constraints and inactive constraints. The Kuhn-Tucker conditions define the active and inactive constraints in term of the Lagrange multipliers, λ . For an active constraint, the resultant λ is positive and for a non-active constraint, λ equals zero (Wang, L. (2009), “*Model Predictive Control System Design and Implementation Using MATLAB®*”, London, Springer London). Some embodiments may make use of the dual
- 10 active method, Hildreth’s quadratic programming procedure (Hildreth, C. (1957), “*A quadratic programming procedure*,” *Naval Research Logistics Quarterly* 4(1): 79-85) to systematically identify the constraints that are not active. The dual problem to the original quadratic problem may be expressed by:

$$\begin{aligned} J &= \frac{1}{2} \lambda^T H \lambda + \lambda^T K + \frac{1}{2} \gamma^T E^{-1} \gamma \\ s.t. \lambda &\geq 0 \end{aligned} \quad (32)$$

- 15 where $H = ME^{-1}M$ and $K = \gamma + ME^{-1}F$.

[0096] Let the optimal solution of this quadratic program be given by λ^* . Using Hildreth’s algorithm, λ^* can be obtained with successive optimization of each element of λ separately:

$$\begin{aligned} \lambda_i^{m+1} &= \max(0, \omega_i^{m+1}) \\ \omega_i^{m+1} &= -\frac{1}{h_{ii}} \left[k_i + \sum_{j=1}^{i-1} h_{ij} \lambda_j^{m+1} + \sum_{j=i+1}^n h_{ij} \lambda_j^m \right], \end{aligned} \quad (33)$$

where h_{ij} is the ij th element in H and k_i is the i th element in K .

- 20 [0097] An advantage of using Hildreth’s algorithm is that it does not involve matrix inversion. In the event of conflict between constraints, the algorithm will deliver a compromise without terminating.

[0098] Tuning parameters of a typical MPC include n_p , n_c , R and Q . For the current system, the

Kalman filter parameters, R_w and R_v , may also be considered. For the unconstrained controller, the parameters were manually tuned for robustness with $n_p = 60$, $n_c = 2$, $R_w = 1$, $R_v = 9$, $R = 0.8$.

[0099] FIG. 13 is a flowchart of a method **50** for performing closed loop control of administration of at least one drug to a patient, to determine a control signal that can be provided to a drug administration actuator to controllably administer the drug to the patient. Method **50** can be performed with the use of an MPC control system, such as system **30** shown in FIG. 6. Method **50** comprises setting a reference level for one or more monitorable physiological characteristics (e.g. such as a depth of hypnosis obtained from a DOH monitor **16A**), at block **52**. In some embodiments, block 52 may comprise setting a reference trajectory which describes how a reference level changes over time. Method **50** further comprises providing a drug administration actuator (such as a controllable infusion pump or infusion syringe **13**, a controllable drug inhalation device and/or the like), at block **54**. Method **50** proceeds to block **56** by sensing the one or more monitored physiological characteristics of the patient and determining a monitor measurement indicative of an effect of the drug on the patient (e.g. in the case of administration of propofol or other hypnotic drug, block 56 may involve monitoring DOH of the patient). At block **58**, method **50** comprises determining a control signal for the drug administration actuator and supplying the control signal to the drug administration actuator to cause the drug administration actuator to administer the drug to the patient at a drug dosage rate which causes the monitor measurement to track the block 52 reference level.

[0100] One example method **55** for determining a control signal at block **58** is shown in FIG. 13 (i.e. at blocks **62**, **64** and **66**). Method **55** comprises implementing a closed loop model-predictive control scheme which comprises, for each of the series of time steps, minimizing a cost function (performance index) subject to one or more constraints to thereby determine the control signal. The cost function is based at least in part on the reference level and the monitor measurement. In the illustrated embodiment, method **55** comprises using the control signal as an input to an auxiliary model (block **62**); using the auxiliary model and the control signal to estimate at least one concentration level of the drug in the patient (block **64**); and minimizing the cost function (performance index) subject to one or more constraints to determine the control signal (block **66**). The constraints may comprise at least one constraint on the estimate of a concentration level of the drug as determined using the auxiliary model in block 64.

[0101] FIG. 14 is a flowchart of a method **100** of performing closed-loop MPC control for

delivery of a drug, subject to constraints on physiological characteristics and/or other parameters, according to one example embodiment. Method **100** can be performed by an MPC control system, such as system **30** shown in FIG. 6. Method **100** may be performed at least once in respect of each finite horizon T of the MPC controller. The output of method **100** is a control signal **38** (e.g. $u(k)$) provided to drug administrator actuator **13A** to controllably administer a drug to the patient in accordance with the control signal **38**. Method **100** begins by receiving a control signal **38** (e.g. an initialization value or the output of the previous iteration of method **100**). For example, control signal **38** may be an infusion rate $u(k)$ which is provided to a drug administration actuator **13A** (e.g. syringe pump) of the FIG. 6 system **30**. The control signal $u(k)$ (including, optionally, its historical values) is input to an auxiliary model (e.g. auxiliary model **32** of the FIG. 6 system **30**) at block **102**, and using the auxiliary model together with the control signal $u(k)$, the control system estimates, at block **103**, values **37** for drug concentration levels in the patient. Drug concentration values **37** estimated by the auxiliary model may comprise estimates for the plasma concentration C_p of a drug being administered, an effect site concentration C_e corresponding to a monitored physiological characteristic **16A** associated with the drug being administered (e.g. DOH) and/or an effect site concentration C_e corresponding to some additional physiological characteristic of patient **14A** that may be impacted by the drug being administered. The auxiliary model **32** that is used to determine these values may comprise one or more of: a population-based model; a PKPD model; a population-based PKPD model; a multiple-compartment PKpd model; a multiple-compartment PKPD model, a patient-specific PKPD model, and/or the like. The auxiliary model **32** may comprise a model of any physiological characteristic that can be monitored, such as, for example, depth of hypnosis, blood pressure, cardiac output, heart rate variability, end tidal CO_2 , respiratory rate, minute ventilation, end-tidal anesthetic agent monitoring and/or the like and may relate such physiological characteristics to corresponding drug concentrations (e.g. C_p , C_e). The auxiliary model **32** may make use of its one or more inputs (such as the control signal **38** ($u(k)$) in the illustrated embodiment of FIG. 14) and its model corresponding to this physiological characteristic, which may then be used to determine drug concentration levels (or other characteristic that can be used to constrain the MPC controller **12A** at block **106**). In certain embodiments, the auxiliary model **32** may comprise a model of a depth of hypnosis (DOH) of the patient, and based on the input to the auxiliary model (i.e. control signal **38** ($u(k)$), the model

may be used to determine values for plasma concentration C_p and effect site concentration C_e for the drug based on the DOH model. Further, user-configurable constraints expressed in terms of DOH may be converted by auxiliary model to 32 to constraints expressed in terms of these concentrations C_p and/or C_e . In some embodiments, the auxiliary model **32** may comprise a

5 model of systolic blood pressure (SBP) of the patient, and based on the input to the auxiliary model (i.e. control signal **38** ($u(k)$)), the model may be used to determine values for plasma concentration C_p and effect site concentration C_e for the drug based on the SBP model. Further, user-configurable constraints expressed in terms of SBP may be converted by auxiliary model to 32 to constraints expressed in terms of these concentrations C_p and/or C_e .

10 **[0102]** In addition (or in the alternative) to the steps at block **102**, method **100** comprises providing one or more sensors (such as sensor **34** of the FIG. 6 system **30**) for measuring an additional physiological characteristic of the patient and taking actual readings of measured sensor values **35A** for the additional physiological characteristic at block **104A**. These measured sensor values **35A** can be input to an auxiliary model at block **105** and used at block **103A** to

15 refine the drug concentration values predicted by auxiliary model 32 to produce refined concentration values **37A**. For example, auxiliary model 32 may comprise a Kalan filter or a state observer and/or the like. Additionally or alternatively, auxiliary model 32 may refine the drug concentration values previously obtained at block **103**. In one particular example embodiment, the physiological characteristic that is measured by a sensor at block **104A** is the

20 systolic blood pressure (SBP) of the patient. The measured SBP values **35A** can be input to an auxiliary model, comprising a Kalman filter for example, at block **105**, to generate refined values **37A** for C_e and C_p .

[0103] Method **100** proceeds to block **106** which involves using estimated concentration values **37** for C_e and C_p (and/or refined values **37A** for C_e and C_p), which are now expressed in the input

25 space for the MPC controller **12A**, along with the output **40** of a monitor for measuring the response of the patient (e.g. DOH $y(k)$) and a reference level **41** set by the operator (e.g. DOH $r(k)$) to implement constrained MPC control. At block **106**, the MPC controller **12A** performs MPC minimization subject to constraints on the drug concentration levels in the patient and/or physiological characteristics and other parameters as described above with reference to equation

30 (30). In the illustrated embodiment, the drug concentration values that are used to constrain the block 106 MPC minimization comprise the values **37** for C_e and C_p (or refined values **37A** for C_e

and C_p). In addition, physical constraints and/or safety constraints **39** such as constraints on the infusion rate can be applied in the minimization step performed at block **106**. The output **38** of method **100**, determined as a result of performing the MPC optimization step at block **106**, is a calculated control variable or infusion rate $u(k)$ of the infusion pump.

5 **[0104]** Method **100** then repeats itself in considering the next finite horizon T and performing again the method steps starting at block **102** by using the auxiliary model to determine new predicted values **37** for C_e and C_p . Method **100** may be repeated for subsequent time steps for the duration that closed-loop MPC control is required for controlling the delivery of propofol to the patient. One or more of the steps indicated through dotted flow lines (e.g. the steps performed at
10 blocks **103A** and **105**) may be omitted in certain embodiments. For example, some embodiments of the method for closed-loop MPC control may not use measured SBP values, and may rely on the estimated concentration values **37** obtained through the auxiliary model at block **102** to provide constraints to the MPC cost minimization step at block **106**.

[0105] The steps of method **100** may be implemented in software running on a suitable
15 processor, in hardware incorporated in or accessible to a suitable processor, or in a mix of software and hardware. In particular embodiments, method **100** is implemented as software contained in a program memory accessible to a suitable processor. The processor implements the method by executing software instructions provided by the software. Such a processor may be integrated with other parts of a computer system or it may be implemented as a distinct
20 component or system. Such processor, hardware and/or software may implement controller **12A** and auxiliary model **32** of the FIG. 6 system **30**.

[0106] The MPC-based systems and methods described herein including the FIG. 6 system **30** and the methods **50**, **100** of FIGS. **13**, **14** may be adapted for closed-loop MPC control of other substances that are administered into a body, such as other hypnotics, or analgesics,
25 neuromuscular-blocking agents, hemodynamic medications, antihypertensive agents, analgesic adjuvants, neuroprotective drugs, anti-inflammatory agents, and/or the like. In such cases the concentration values and/or physiological characteristics that are obtained at blocks **103** and **104A** and that are projected into the input space of the MPC controller to constrain the system at block **106** may be different, since for each type of drug, the evaluation of certain parameters may
30 be more useful than others.

[0107] The methods and systems for constrained closed-loop MPC control may be expanded for use in controlling the simultaneous delivery of more than one drug to a patient. For example, in procedures conducted under anaesthesia, both a hypnotic (such as propofol as described in the above examples) and an analgesic (such as remifentanyl) may be injected into the patient simultaneously, using separate syringe pumps for each substance. In such cases, the MPC control system **30** of FIG. 6 may be adapted to accept multiple inputs useful for the MPC optimization with these two substances (hypnotic and analgesic). These inputs may include the inputs and constraints already described above, with reference to method **100** of FIG. 14, that are used for control of the infusion of propofol (e.g. DOH $y(k)$, reference DOH $r(k)$ and physiological and physical constraints which may be estimated or otherwise evaluated using auxiliary model 32 which may project such constraints back into the input space of controller 12A), along with any additional inputs and constraints that are used for control of the infusion of an analgesic such as remifentanyl. Such additional inputs and constraints for the administration of an analgesic may include, for example, the infusion rate $u(k)$ for the drug (as an input for the MPC controller optimization, and as inputs to an auxiliary model to determine drug concentration levels such as plasma drug concentration values C_p) and constraints on the estimated drug concentration values. Performing the MPC minimization step with these inputs and subject to these constraints, the system **30** produces multiple outputs or control variables, namely, a rate of infusion for propofol and a rate of infusion for remifentanyl.

Step 7: Monte Carlo Simulations and Results

[0108] Analytically proving the robustness of the FIG. 6 control system **30** in the presence of constraints provided by an auxiliary model may be complicated. For the purpose of evaluations conducted on the FIG. 6 control system **30**, Monte Carlo simulations were used to observe the controller's robustness. Eight hundred and eighty random models were created by applying $\pm 20\%$ perturbations to all the PK and PD parameters of the patients in the study and generating 20 random models for each of the 44 individuals. The number of samples was determined by trial and error. In the evaluation, 10, 20, and 30 Monte-Carlo models (for each of the 44 individuals) were employed in simulating surgery scenarios. The results using 20 and 30 Monte-Carlo models were very close to each other and consistent upon repeating the simulation. To minimize the computation time while keeping the reliability of the results, the evaluation used 20 Monte-Carlo models per individual.

[0109] Induction time was defined as the time between the start of the propofol infusion and the time the WAV_{CNS} first dropped below 60. Maintenance of anaesthesia was defined as the time between end of induction and the end of the propofol infusion. In controller tuning, a design specification is to minimize the time to induction and system overshoot during induction while improving response to stimulation without compromising patient safety. Simulated induction of anaesthesia was completed in an average (SD) of 3.4(2.0) minutes with reference level overshoot ($WAV_{cns} < 50$) of 2.7 % (6.1) for the constrained MPC. Comparing those results with the ones obtained with the unconstrained MPC, (induction time 2.9(0.9) minutes and overshoot of 3.7 % (7.5) demonstrates that safety constraints can be added to the control system for hypnosis without significantly increasing the rise time. Results obtained with an unconstrained MPC emphasize the benefits of incorporating the concentration constraints in the MPC controller, as they show that without these constraints, 39% of patients would reach $C_p > 10 \mu\text{g/ml}$ and 36% of patients would reach $C_e > 7 \mu\text{g/ml}$, (see FIGS. 8 and 9 which respectively show a closed-loop MPC response of 44 patients with unconstrained MPC and constrained MPC). These high concentrations may result in significant drops in SBP and may also increase the incidence of burst suppression (BS).

[0110] FIG. 10 shows the results of Monte Carlo simulations for 880 random patient models conducted on the constrained closed-loop MPS control system **30** of FIG. 6. The control system is shown to be robust with the $\pm 20\%$ uncertainties to the PK and PD parameters and in the presence of simulated disturbance. The $\pm 20\%$ uncertainties resulted in numerous patients which are far from the average population and are considered outliers. These were patients with very long delays, very slow or very fast clearance, etc. When coming across such cases, often identified during induction, anesthesiologists may modify referenced levels and/or constraint values, which in return should improve the performance.

[0111] Using Monte Carlo simulations, a few cases were encountered where due to conflict between constraints, Hildreth's quadratic programming technique was forced to deliver a compromised solution. A compromise on the infusion rate constraint may result in a value outside the physical limit of the pump. However, this may be avoided by incorporating a physical constraint on the infusion rate. FIG. 11 shows an example of this situation, in a closed-loop MPC response for a patient in the study where a conflict between constraints, $u < 600 \text{ ml/hr}$ and $C_p > 1.6$, resulted in a compromised solution. The resulting u around 37 minutes was

restrained with a physical constraint, namely, the maximum infusion rate allowable by the pump.

[0112] FIG. 12A shows the results of SBP constraint on the closed-loop MPC response of 44 patients with systolic blood pressure (SBP) limit of 50% with no disturbance. FIGS. 12B and 12C show the percent SBP drop from baseline to 80 mmHg with BSP constrained MPC and unconstrained MPC respectively. These results demonstrate that the implemented constraint was effective in controlling the SBP above the limit. These results were achieved at the expense of a slower induction as shown in Table 4.

TABLE 4

MPC Controller	Rise-Time [min]	Overshoot [%]
Unconstrained	2.9±0.9	3.7±7.5
Constrained	3.4±2.0	2.7±6.1

Rise-Times is defined as time in minutes required for WAV_{cns} to fall below 60 and Overshoot as the WAV_{cns} index below the set-point of 50.

[0113] Delivery of opioids to the patient may reduce the amount of propofol required, causing greater clinical effects than would be expected with propofol alone (Vuyk, J., M. J. Mertens, *et al.* (1997), “Propofol anesthesia and rational opioid selection: determination of optimal EC50-EC95 propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness,” *Anesthesiology* 87(6): 1549-1562). As appreciated by persons of skill in the art, in the presence of surgical stimuli, patients may tolerate higher propofol concentrations without experiencing serious cardiovascular side effects. Due to these influences, the values selected as safety bounds (constraints) in accordance with particular embodiments can be adjusted as needed to factor in age, ASA (American Society of Anesthesiologists) status, known medical history, opioids use, intensity of expected stimuli, and other considerations. As demonstrated by the evaluations conducted in respect of the present technology, there are benefits to imposing constraints in the application of closed-loop control of the administration of drugs to a patient and in particular in the implementation of a closed-loop MPC to control the delivery of anesthesia drugs. The present technology introduces the implementation of physiological constraints in closed-loop control of hypnosis using MPC with a parallel PKPD model. Evaluation of this MPC controller during simulated induction and maintenance of anesthesia

shows that the design specifications were satisfied. The constrained control strategy can potentially reduce the risk of under- or overdosing for most patients by providing controller enforced safety bounds.

Interpretation of Terms

5 [0114] Unless the context clearly requires otherwise, throughout the description and the claims:

- “comprise”, “comprising”, and the like are to be construed in an inclusive sense, as opposed to an exclusive or exhaustive sense; that is to say, in the sense of “including, but not limited to”;

- “herein”, “above”, “below”, and words of similar import, when used to describe this specification, shall refer to this specification as a whole, and not to any particular portions of this specification;

- “or”, in reference to a list of two or more items, covers all of the following interpretations of the word: any of the items in the list, all of the items in the list, and any combination of the items in the list;

- 15 • the singular forms “a”, “an”, and “the” also include the meaning of any appropriate plural forms.

[0115] Embodiments of the invention (including the control systems and/or methods described herein) may be implemented using specifically designed hardware, configurable hardware, programmable data processors configured by the provision of software (which may optionally
20 comprise “firmware”) capable of executing on the data processors, special purpose computers or data processors that are specifically programmed, configured, or constructed to perform one or more steps in a method as explained in detail herein and/or combinations of two or more of these. Examples of specifically designed hardware are: logic circuits, application-specific integrated circuits (“ASICs”), large scale integrated circuits (“LSIs”), very large scale integrated
25 circuits (“VLSIs”), and the like. Examples of configurable hardware are: one or more programmable logic devices such as programmable array logic (“PALs”), programmable logic arrays (“PLAs”), and field programmable gate arrays (“FPGAs”). Examples of programmable data processors are: microprocessors, digital signal processors (“DSPs”), embedded processors, graphics processors, math co-processors, general purpose computers, server computers, cloud

computers, mainframe computers, computer workstations, and the like. For example, one or more data processors in a computer system for a device may implement methods as described herein by executing software instructions in a program memory accessible to the processors.

[0116] Processing may be centralized or distributed. Where processing is distributed,

5 information including software and/or data may be kept centrally or distributed. Such information may be exchanged between different functional units by way of a communications network, such as a Local Area Network (LAN), Wide Area Network (WAN), or the Internet, wired or wireless data links, electromagnetic signals, or other data communication channel.

[0117] While processes or blocks are presented in a given order, alternative examples may

10 perform routines having steps, or employ systems having blocks, in a different order, and some processes or blocks may be deleted, moved, added, subdivided, combined, and/or modified to provide alternative or subcombinations. Each of these processes or blocks may be implemented in a variety of different ways. Also, while processes or blocks are at times shown as being performed in series, these processes or blocks may instead be performed in parallel, or may be
15 performed at different times.

[0118] In addition, while elements are at times shown as being performed sequentially, they may instead be performed simultaneously or in different sequences. It is therefore intended that the following claims are interpreted to include all such variations as are within their intended scope.

[0119] Embodiments of the invention may also be provided in the form of a program product.

20 The program product may comprise any non-transitory medium which carries a set of computer-readable instructions which, when executed by a data processor, cause the data processor to execute a method of the invention. Program products according to the invention may be in any of a wide variety of forms. The program product may comprise, for example, non-transitory media such as magnetic data storage media including floppy diskettes, hard disk drives, optical data
25 storage media including CD ROMs, DVDs, electronic data storage media including ROMs, flash RAM, EPROMs, hardwired or preprogrammed chips (e.g., EEPROM semiconductor chips), nanotechnology memory, or the like. The computer-readable signals on the program product may optionally be compressed or encrypted.

[0120] The invention may be implemented in software. For greater clarity, “software” includes

30 any instructions executed on a processor, and may include (but is not limited to) firmware,

resident software, microcode, and the like. Both processing hardware and software may be centralized or distributed (or a combination thereof), in whole or in part, as known to those skilled in the art. For example, software and other modules may be accessible via local memory, via a network, via a browser or other application in a distributed computing context, or via other means suitable for the purposes described above.

[0121] Where a component (e.g. a controller, software module, processor, server, client, device, etc.) is referred to above, unless otherwise indicated, reference to that component (including a reference to a “means”) should be interpreted as including as equivalents of that component any component which performs the function of the described component (i.e., that is functionally equivalent), including components which are not structurally equivalent to the disclosed structure which performs the function in the illustrated exemplary embodiments of the invention.

[0122] While a number of exemplary aspects and embodiments have been discussed above, those of skill in the art will recognize certain modifications, permutations, additions and sub-combinations thereof.

As such, the scope of the claims should not be limited by the preferred embodiments set forth in the examples, but should be given the broadest interpretation consistent with the description as a whole.

WHAT IS CLAIMED IS:

1. A control system for closed loop control of administration of at least one drug to a patient, the control system comprising:
 - 5 a drug administration actuator connectable to a source of the at least one drug and to a patient for administration of the at least one drug to the patient at a controllable drug dosage rate;
 - one or more monitors for sensing one or more monitored physiological characteristics of the patient and determining therefrom a monitor measurement indicative of an effect of the at least one drug on the patient; and
 - 10 a processor configured, for each of a series of time steps, to determine a control signal and supply the control signal to the drug administration actuator to thereby cause the drug administration actuator to administer the at least one drug to the patient at a drug dosage rate which causes the monitor measurement to track a reference level;
 - 15 wherein the processor is configured to implement a closed loop model-predictive control scheme which comprises, for each of the series of time steps, minimizing a cost function (performance index) subject to one or more constraints to thereby determine the control signal, the cost function based at least in part on the reference level and the monitor measurement;
 - 20 wherein the processor is configured to use the control signal as an input to an auxiliary model and to use the auxiliary model and the control signal to estimate at least one concentration level of the at least one drug in the patient; and
 - wherein the one or more constraints comprise at least one constraint on the estimate of the at least one concentration level of the at least one drug.
 - 25
2. A control system according to claim 1 or any other claim herein wherein the processor is configured to implement a robust model-predictive control scheme wherein the robust model-predictive control scheme causes the monitor measurement to track the reference level despite inter-patient variability within a population with respect to the effect of the
30 at least one drug.

3. A control system according to claim 2 or any other claim herein wherein processor is configured to implement the robust model-predictive control scheme by using a nominal model that has been tuned with respect to quantified inter-patient uncertainty.
- 5 4. A control system according to claim 3 or any other claim herein wherein the nominal model is based on a combination of models from the population, with each model representing an effect of the drug on a corresponding member of the population.
5. A control system according to claim 4 or any other claim herein wherein the combination
10 of models comprises an average of the models over the population.
6. A control system according to any one of claims 1 to 5 or any other claim herein wherein the drug administration actuator comprises a controllable drug injection device.
- 15 7. A control system according to claim 6 or any other claim herein wherein the processor is configured, for each of the series of time steps, to determine the control signal and supply the control signal to the controllable injection device to thereby cause the controllable injection device to administer the at least one drug to the patient at a drug infusion rate which causes the monitor measurement to track the reference level.
20
8. A control system according to any one of claims 1 to 5 or any other claim herein wherein the drug administration actuator comprises at least one of: a controllable drug inhalation device; a controllable intrathecal drug delivery device; and a controllable drug pump.
- 25 9. A control system according to any one of claims 1 to 8 or any other claim herein wherein the drug dosage rate which the processor causes the drug administration actuator to administer is effected by varying a volume and/or concentration of the drug in a liquid or gas.

10. A control system according to any one of claims 1 to 9 or any other claim herein wherein the at least one concentration level of the at least one drug in the patient comprises an estimated plasma concentration of the at least one drug in the patient.
- 5 11. A control system according to any one of claims 1 to 10 or any other claim herein wherein the at least one concentration level of the at least one drug in the patient comprises an estimated effect site concentration of the at least one drug in the patient.
- 10 12. A control system according to claim 11 or any other claim herein wherein the auxiliary model comprises at least one of: a model of a relationship between the estimated effect site concentration of the at least one drug and the one or more monitored physiological characteristics; and a model of a relationship between the estimated effect site concentration of the at least one drug and one or more additional physiological characteristics.
- 15 13. A control system according to any one of claims 1 to 12 or any other claim herein wherein the one or more constraints comprise one or more constraints on the drug dosage rate.
- 20 14. A control system according to any one of claims 1 to 13 or any other claim herein wherein the auxiliary model comprises a pharmacokinetic-pharmacodynamic (PKPD) model.
- 25 15. A control system according to claim 14 or any other claim herein wherein the PKPD model comprises a population-based PKPD model based at least in part on historical data related to the effect of the at least one drug on members of the population.
- 30 16. A control system according to any one of claims 14 to 15 or any other claim herein wherein the PKPD model comprises a patient-specific PKPD model based at least in part on historical data related to the effect of the at least one drug on the patient.

17. A control system according to any one of claims 1 to 13 or any other claim herein wherein the auxiliary model comprises a multiple-compartment pharmacokinetic model.
18. A control system according to claim 17 or any other claim herein wherein the multiple-compartment pharmacokinetic model comprises at least one central compartment in which blood is relatively highly perfused and at least one peripheral compartment in which blood is relatively less perfused.
19. A control system according to any one of claims 17 to 18 or any other claim herein wherein the multiple-compartment pharmacokinetic model comprises an effect site compartment.
20. A control system according to any one of claims 17 to 19 or any other claim herein wherein the multiple-compartment pharmacokinetic model comprises a population-based model based at least in part on historical data related to the effect of the at least one drug on members of the population.
21. A control system according to any one of claims 17 to 20 or any other claim herein wherein the multiple-compartment pharmacokinetic model comprises a patient-specific model based at least in part on historical data related to the effect of the at least one drug on the patient.
22. A control system according to any one of claims 1 to 13 or any other claim herein wherein the auxiliary model comprises a multiple-compartment pharmacokinetic-pharmacodynamic (PKPD) model.
23. A control system according to claim 22 or any other claim herein wherein the multiple-compartment PKPD model comprises a population-based model based at least in part on historical data related to the effect of the at least one drug on members of the population.

24. A control system according to any one of claims 22 to 23 or any other claim herein wherein the multiple-compartment PKPD model comprises a patient-specific model based at least in part on historical data related to the effect of the at least one drug on the patient.
- 5
25. A control system according to any one of claims 1 to 24 or any other claim herein wherein the auxiliary model models the effect of the at least one drug on the one or more monitored physiological characteristics of the patient.
- 10
26. A control system according to claim 25 or any other claim herein wherein the processor is configured to use the auxiliary model to map at least one constraint on the one or more monitored physiological characteristics into the at least one constraint on the estimate of the at least one concentration level of the at least one drug.
- 15
27. A control system according to any one of claims 25 to 26 or any other claim herein wherein the auxiliary model incorporates the monitor measurement into the estimate of the at least one concentration level of the at least one drug.
- 20
28. A control system according to any one of claims 1 to 27 or any other claim herein wherein the auxiliary model models the effect of the at least one drug on one or more additional physiological characteristics of the patient.
- 25
29. A control system according to claim 28 or any other claim herein wherein the processor is configured to use the auxiliary model to map at least one constraint on the one or more additional physiological characteristics into the at least one constraint on the estimate of the at least one concentration level of the at least one drug.
- 30
30. A control system according to any one of claims 28 to 29 or any other claim herein comprising one or more physiological sensors for sensing one or more measured values of the one or more additional physiological characteristics of the patient and wherein the auxiliary model incorporates the one or more measured values of the one or more

additional physiological characteristics into the estimate of the at least one concentration level of the at least one drug.

31. A control system according to claim 30 or any other claim herein wherein the auxiliary
5 model comprises a Kalman filter which incorporates the one or more measured values of the one or more additional physiological characteristics into the estimate of the at least one concentration level of the at least one drug.

32. A control system according to claim 30 or any other claim herein wherein the auxiliary
10 model comprises a state observer which incorporates the one or more measured values of the one or more additional physiological characteristics into the estimate of the at least one concentration level of the at least one drug.

33. A control system according to any one of claims 28 to 32 or any other claim herein
15 wherein the one or more additional physiological characteristics comprise one or more of: EEG characteristics, depth of hypnosis, blood pressure, cardiac output, heart rate variability, end tidal CO₂, respiratory rate and minute ventilation.

34. A control system according to any one of claims 1 to 33 wherein the one or more
20 monitored physiological characteristics of the patient comprise EEG characteristics and the monitor measurement comprises a depth of hypnosis index.

35. A control system according to any one of claims 1 to 34 or any other claim herein
25 wherein the drug comprises an anesthesia drug.

36. A control system according to claim 35 or any other claim herein wherein the drug is propofol.

37. A control system according to any one of claims 1 to 33 or any other claim herein
30 wherein the drug comprises one or more of: a hypnotic agent, an analgesic agent, a

neuromuscular blocking agent, a hemodynamic medication, an analgesic adjuvant, a neuroprotective agent and an anti-inflammatory agent.

- 5 38. A control system according to any one of claims 1 to 33 wherein the one or more monitored physiological characteristics of the patient comprise one or more of: blood pressure, cardiac output, heart rate variability, end tidal CO₂, respiratory rate and minute ventilation.
- 10 39. A control system according to any one of claims 1 to 38 or any other claim herein wherein the auxiliary model is non-linear.
40. A control system according to any one of claims 1 to 38 or any other claim herein wherein the auxiliary model is linear.
- 15 41. A control system according to any one of claims 1 to 40 or any other claim herein wherein the auxiliary model comprises a state-space model.
42. A control system according to any one of claims 1 to 40 or any other claim herein wherein the auxiliary model comprises a transfer function-based model.
- 20 43. A control system according to any one of claims 1 to 42 or any other claim herein where the model-predictive control scheme is a multivariable model-predictive control scheme that controls the administration of more than one drug.
- 25 44. A control system according to any one of claims 1 to 43 or any other claim herein wherein the control system is adjustable to accommodate additional manual administration of the at least one drug by an attending physician.
- 30 45. A control system according to any one or claims 1 to 44 or any other claim herein wherein the control system is adjustable to accommodate major intraoperative changes, such as liver resection or blood loss.

46. A method for implementing closed loop controlled administration of at least one drug to a patient, the method comprising:
- providing a drug administration actuator for administration of the at least one drug to the patient at a controllable drug dosage rate;
- sensing one or more physiological characteristics of the patient and determining therefrom a monitor measurement indicative of an effect of the at least one drug on the patient; and
- for each of a series of time steps, determining a control signal and supplying the control signal to the drug administration actuator to thereby cause the drug administration actuator to administer the at least one drug to the patient at a drug dosage rate which causes the monitor measurement to track a reference level;
- wherein determining the control signal comprises implementing a closed loop model-predictive control scheme which comprises, for each of the series of time steps, minimizing a cost function (performance index) subject to one or more constraints to thereby determine the control signal, the cost function based at least in part on the reference level and the monitor measurement;
- wherein determining the control signal comprises using the control signal as an input to an auxiliary model and using the auxiliary model and the control signal to estimate at least one concentration level of the at least one drug in the patient; and
- wherein the one or more constraints comprise at least one constraint on the estimate of the at least one concentration level of the at least one drug.
47. A method according to claim 46 or any other claim herein wherein implementing the closed loop model-predictive control scheme comprises implementing a robust model-predictive control scheme wherein the robust model-predictive control scheme causes the monitor measurement to track the reference level despite inter-patient variability within a population with respect to the effect of the at least one drug.

48. A method according to claim 47 or any other claim herein wherein implementing the robust model-predictive control scheme comprises using a nominal model that has been tuned with respect to quantified inter-patient uncertainty.
- 5 49. A method according to claim 48 or any other claim herein wherein the nominal model is based on a combination of models from the population, with each model representing an effect of the drug on a corresponding member of the population.
- 10 50. A method according to claim 49 or any other claim herein wherein the combination of models comprises an average of the models over the population.
51. A method according to any one of claims 46 to 50 or any other claim herein wherein the drug administration actuator comprises a controllable drug injection device.
- 15 52. A method according to claim 51 or any other claim herein comprising, for each of the series of time steps, determining the control signal and supplying the control signal to the controllable injection device to thereby cause the controllable injection device to administer the at least one drug to the patient at a drug infusion rate which causes the monitor measurement to track the reference level.
- 20 53. A method according to any one of claims 46 to 50 or any other claim herein wherein the drug administration actuator comprises at least one of: a controllable drug inhalation device; a controllable intrathecal drug delivery device; and a controllable drug pump.
- 25 54. A method according to any one of claims 46 to 53 or any other claim herein wherein the drug dosage rate administered by the drug administration actuator is effected by varying a volume and/or concentration of the drug in a liquid or gas.
- 30 55. A method according to any one of claims 46 to 54 or any other claim herein wherein the at least one concentration level of the at least one drug in the patient comprises an estimated plasma concentration of the at least one drug in the patient.

56. A method according to any one of claims 46 to 55 or any other claim herein wherein the at least one concentration level of the at least one drug in the patient comprises an estimated effect site concentration of the at least one drug in the patient.

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57. A method according to claim 56 or any other claim herein wherein the auxiliary model comprises at least one of: a model of a relationship between the estimated effect site concentration of the at least one drug and the one or more monitored physiological characteristics; and a model of a relationship between the estimated effect site concentration of the at least one drug and one or more additional physiological characteristics.

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58. A method according to any one of claims 46 to 57 or any other claim herein wherein the one or more constraints comprise one or more constraints on the drug dosage rate.

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59. A method according to any one of claims 46 to 58 or any other claim herein wherein the auxiliary model comprises a pharmacokinetic-pharmacodynamic (PKPD) model.

60. A method according to claim 59 or any other claim herein wherein the PKPD model comprises a population-based PKPD model based at least in part on historical data related to the effect of the at least one drug on members of the population.

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61. A method according to any one of claims 59 to 60 or any other claim herein wherein the PKPD model comprises a patient-specific PKPD model based at least in part on historical data related to the effect of the at least one drug on the patient.

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62. A method according to any one of claims 46 to 58 or any other claim herein wherein the auxiliary model comprises a multiple-compartment pharmacokinetic model.

63. A method according to claim 62 or any other claim herein wherein the multiple-compartment pharmacokinetic model comprises at least one central compartment in

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which blood is relatively highly perfused and at least one peripheral compartment in which blood is relatively less perfused.

5 64. A method according to any one of claims 62 to 63 or any other claim herein wherein the multiple-compartment pharmacokinetic model comprises an effect site compartment.

65. A method according to any one of claims 62 to 64 or any other claim herein wherein the multiple-compartment pharmacokinetic model comprises a population-based model based at least in part on historical data related to the effect of the at least one drug on members of the population.
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66. A method according to any one of claims 62 to 65 or any other claim herein wherein the multiple-compartment pharmacokinetic model comprises a patient-specific model based at least in part on historical data related to the effect of the at least one drug on the patient.
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67. A method according to any one of claims 46 to 58 or any other claim herein wherein the auxiliary model comprises a multiple-compartment pharmacokinetic-pharmacodynamic (PKPD) model.
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68. A method according to claim 67 or any other claim herein wherein the multiple-compartment PKPD model comprises a population-based model based at least in part on historical data related to the effect of the at least one drug on members of the population.

25 69. A method according to any one of claims 67 to 68 or any other claim herein wherein the multiple-compartment PKPD model comprises a patient-specific model based at least in part on historical data related to the effect of the at least one drug on the patient.

70. A method according to any one of claims 46 to 69 or any other claim herein wherein the auxiliary model models the effect of the at least one drug on the one or more monitored physiological characteristics of the patient.
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71. A method according to claim 70 or any other claim herein comprising using the auxiliary model to map at least one constraint on the one or more monitored physiological characteristics into the at least one constraint on the estimate of the at least one concentration level of the at least one drug.
72. A method according to any one of claims 70 to 71 or any other claim herein wherein the auxiliary model incorporates the monitor measurement into the estimate of the at least one concentration level of the at least one drug.
73. A method according to any one of claims 46 to 72 or any other claim herein wherein the auxiliary model models the effect of the at least one drug on one or more additional physiological characteristics of the patient.
74. A method according to claim 73 or any other claim herein comprising using the auxiliary model to map at least one constraint on the one or more additional physiological characteristics into the at least one constraint on the estimate of the at least one concentration level of the at least one drug.
75. A method according to any one of claims 73 to 74 or any other claim herein comprising providing one or more physiological sensors for sensing one or more measured values of the one or more additional physiological characteristics of the patient and wherein using the auxiliary model and the control signal to estimate the at least one concentration level of the at least one drug in the patient comprises incorporating the one or more measured values of the one or more additional physiological characteristics into the estimate of the at least one concentration level of the at least one drug.
76. A method according to claim 75 or any other claim herein wherein the auxiliary model comprises a Kalman filter which incorporates the one or more measured values of the one or more additional physiological characteristics into the estimate of the at least one concentration level of the at least one drug.

77. A method according to claim 75 or any other claim herein wherein the auxiliary model comprises a state observer which incorporates the one or more measured values of the one or more additional physiological characteristics into the estimate of the at least one concentration level of the at least one drug.

78. A method according to any one of claims 73 to 77 or any other claim herein wherein the one or more additional physiological characteristics comprise one or more of: EEG characteristics, depth of hypnosis, blood pressure, cardiac output, heart rate variability, end tidal CO₂, respiratory rate and minute ventilation.

79. A method according to any one of claims 46 to 78 wherein the one or more monitored physiological characteristics of the patient comprise EEG characteristics and the monitor measurement comprises a depth of hypnosis index.

80. A method according to any one of claims 46 to 79 or any other claim herein wherein the drug comprises an anesthesia drug.

81. A method according to claim 80 or any other claim herein wherein the drug is propofol.

82. A method according to any one of claims 46 to 78 or any other claim herein wherein the drug comprises one or more of: a hypnotic agent, an analgesic agent, a neuromuscular blocking agent, a hemodynamic medication, an analgesic adjuvant, a neuroprotective agent and an anti-inflammatory agent.

83. A method according to any one of claims 46 to 78 wherein the one or more monitored physiological characteristics of the patient comprise one or more of: blood pressure, cardiac output, heart rate variability, end tidal CO₂, respiratory rate and minute ventilation.

84. A method according to any one of claims 46 to 83 or any other claim herein wherein the auxiliary model is non-linear.
- 5 85. A method according to any one of claims 46 to 83 or any other claim herein wherein the auxiliary model is linear.
86. A method according to any one of claims 46 to 85 or any other claim herein wherein the auxiliary model comprises a state-space model.
- 10 87. A method according to any one of claims 46 to 85 or any other claim herein wherein the auxiliary model comprises a transfer function-based model.
88. A method according to any one of claims 46 to 87 or any other claim herein where the model-predictive control scheme is a multivariable model-predictive control scheme that controls the administration of more than one drug.
- 15 89. A method according to any one of claims 46 to 88 or any other claim herein wherein the method comprises adjusting to accommodate additional manual administration of the at least one drug by an attending physician.
- 20 90. A method according to any one or claims 46 to 89 or any other claim herein wherein the method comprises adjusting to accommodate major intraoperative changes, such as liver resection or blood loss.
- 25 91. Systems comprising any features, combinations of features or sub-combinations described herein and/or the accompanying drawings.
92. Methods comprising any features, combinations of features or sub-combinations described herein and/or the accompanying drawings.
- 30

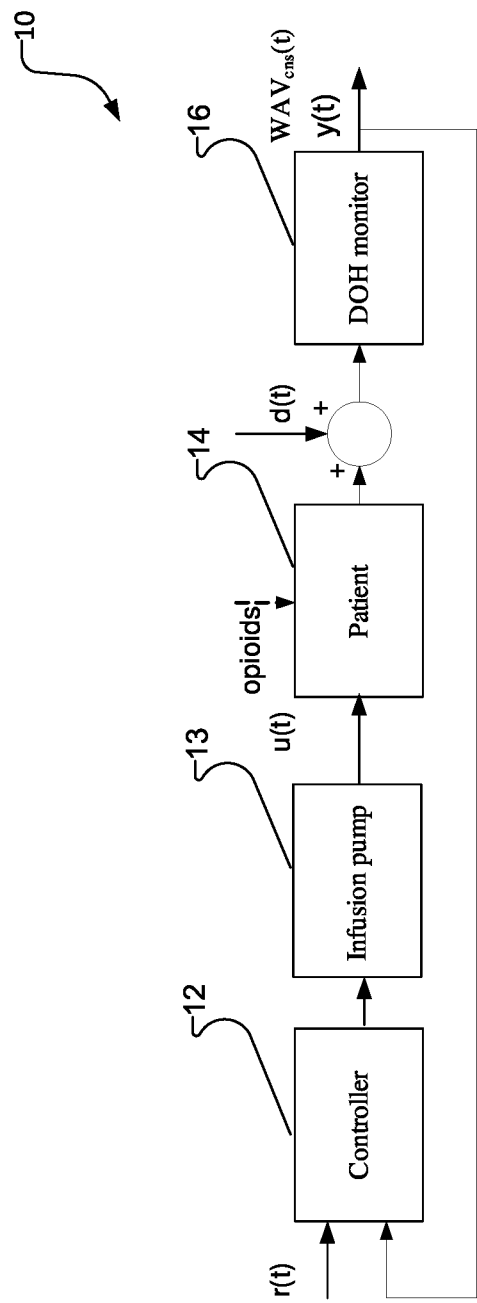


FIG. 1

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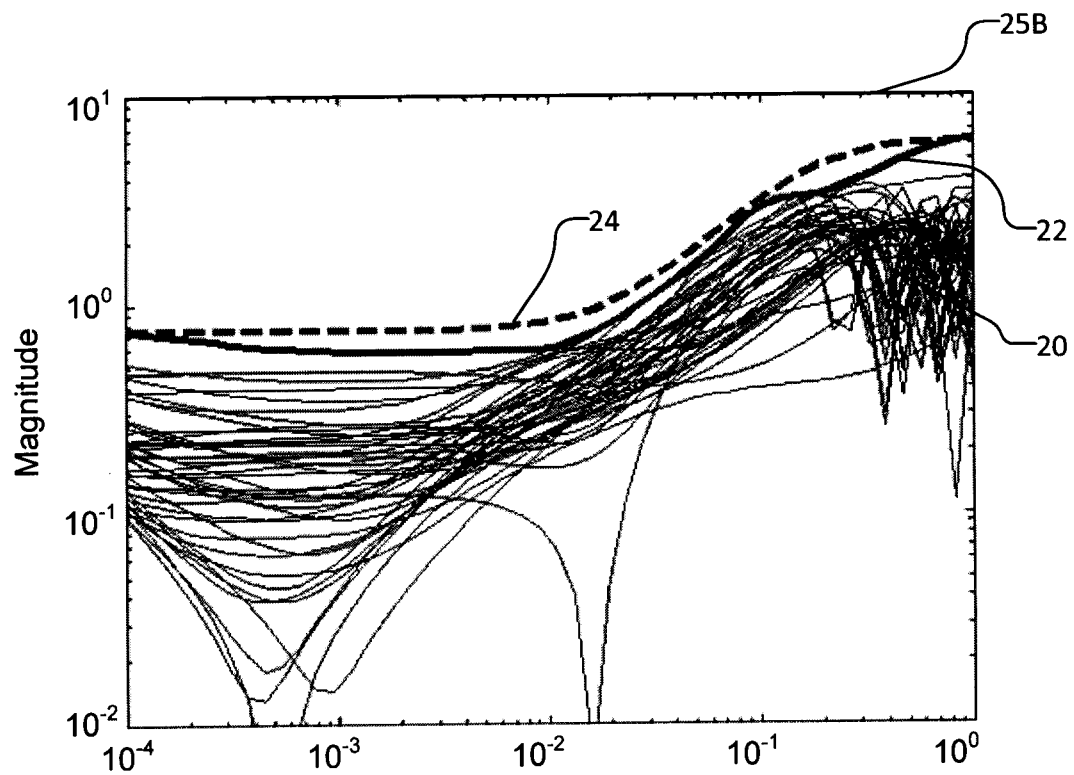
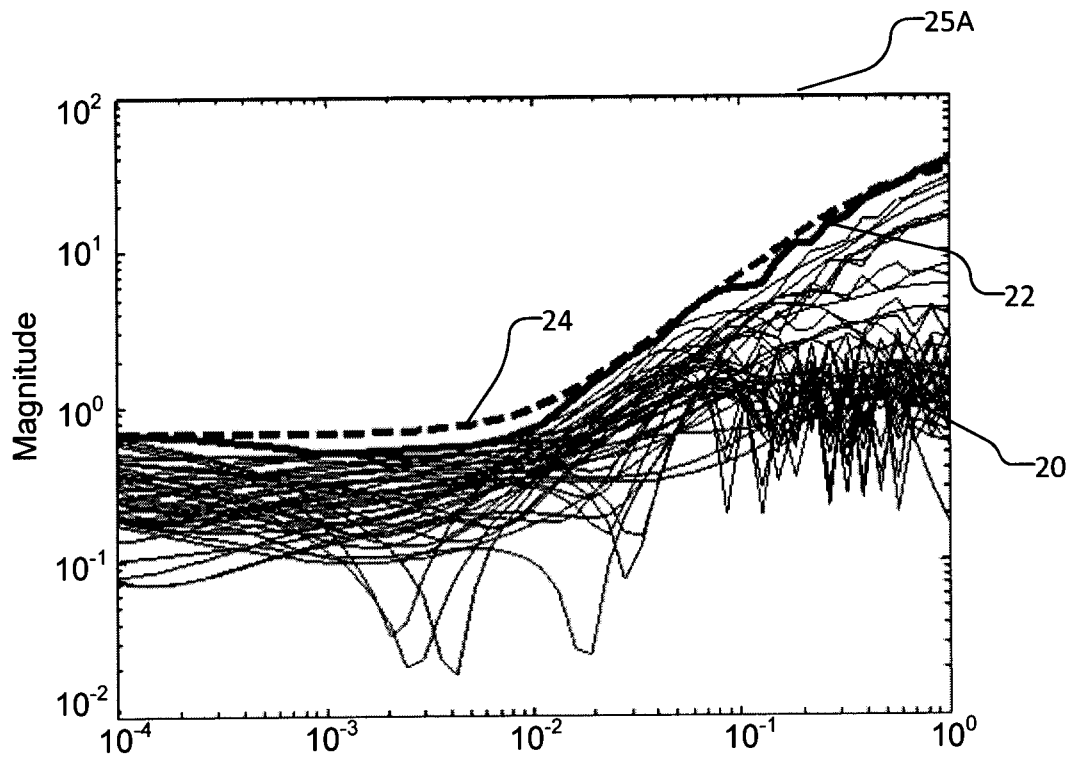


FIG. 2

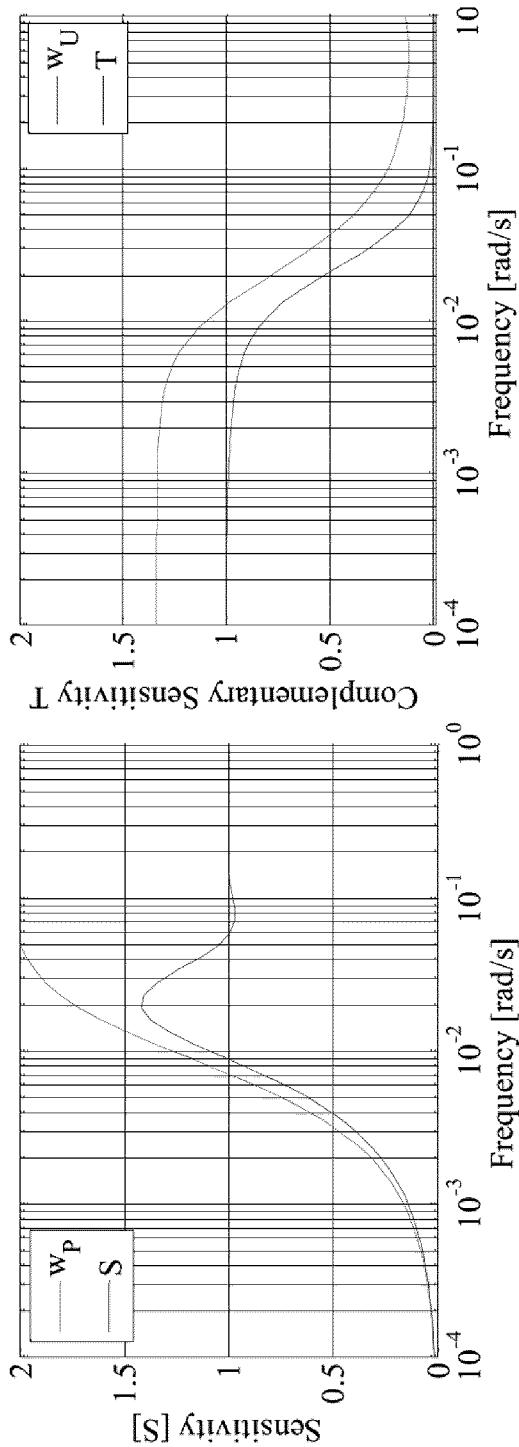


FIG. 3A

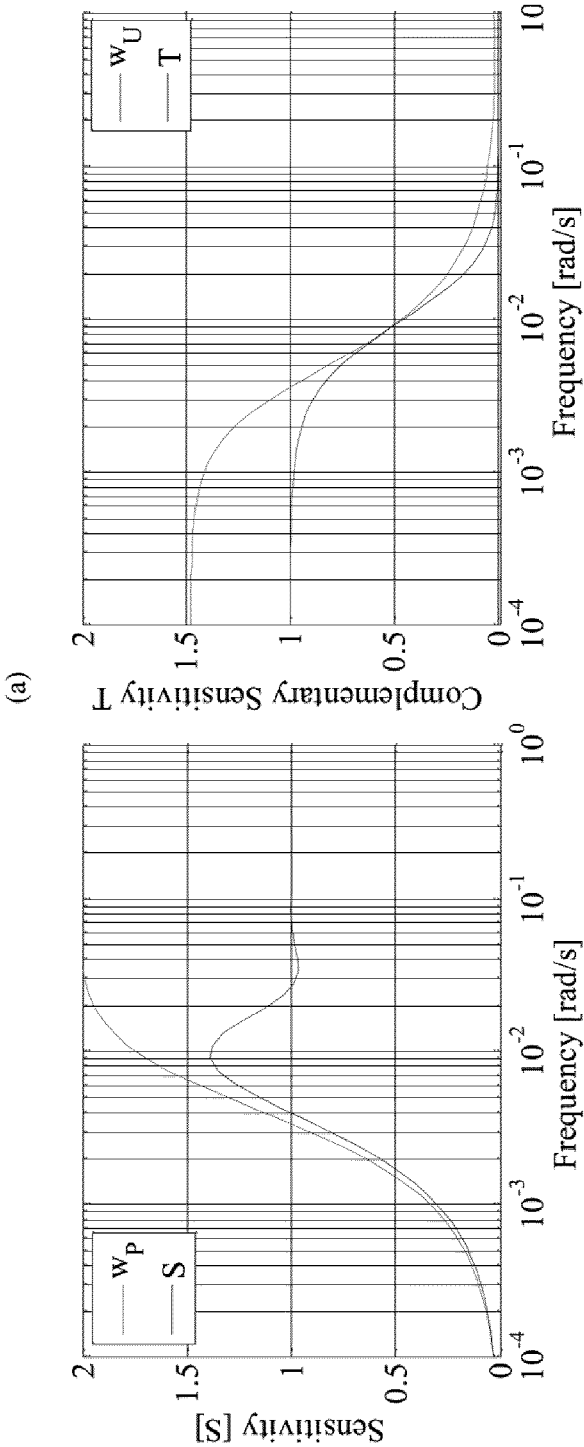


FIG. 3B

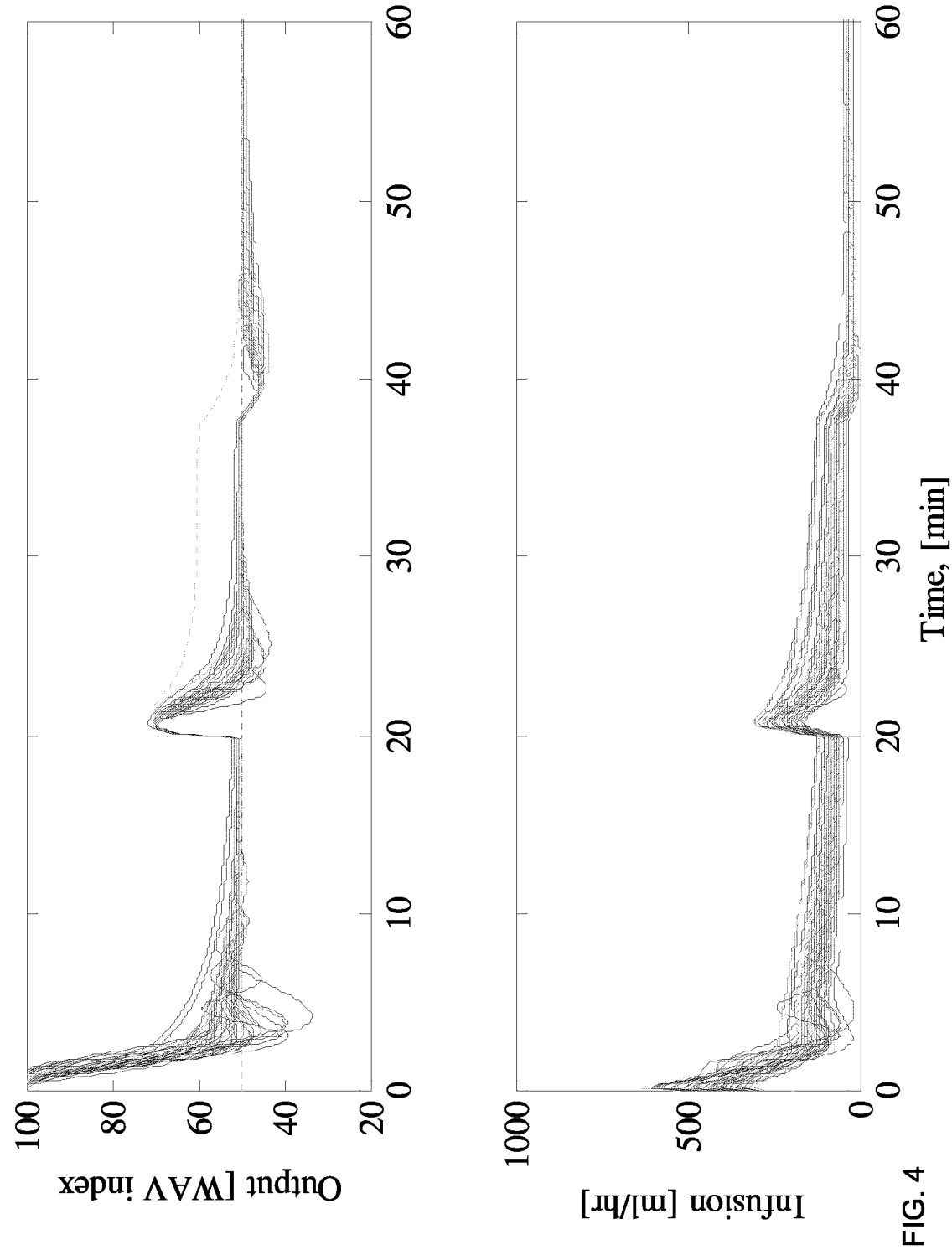


FIG. 4

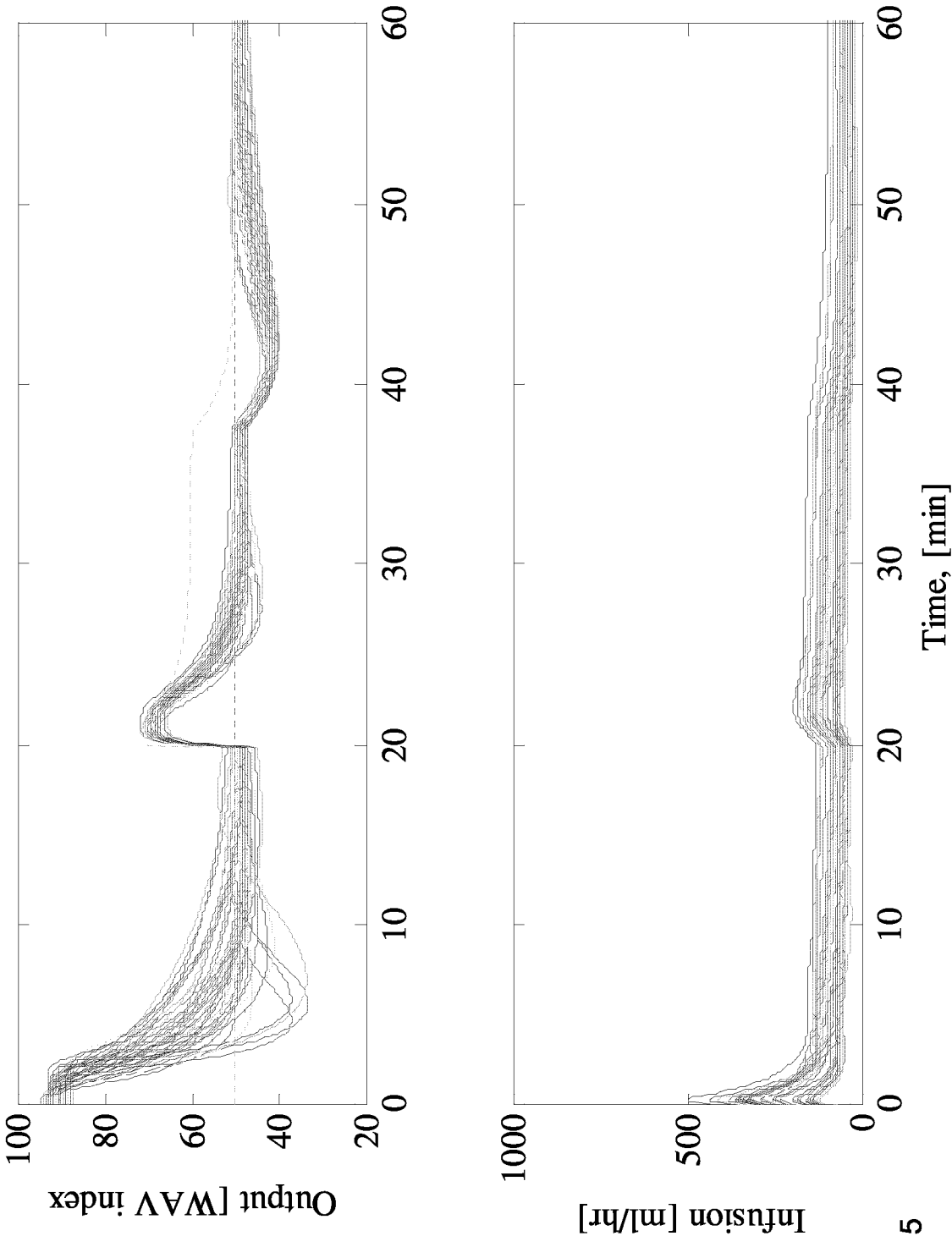


FIG. 5

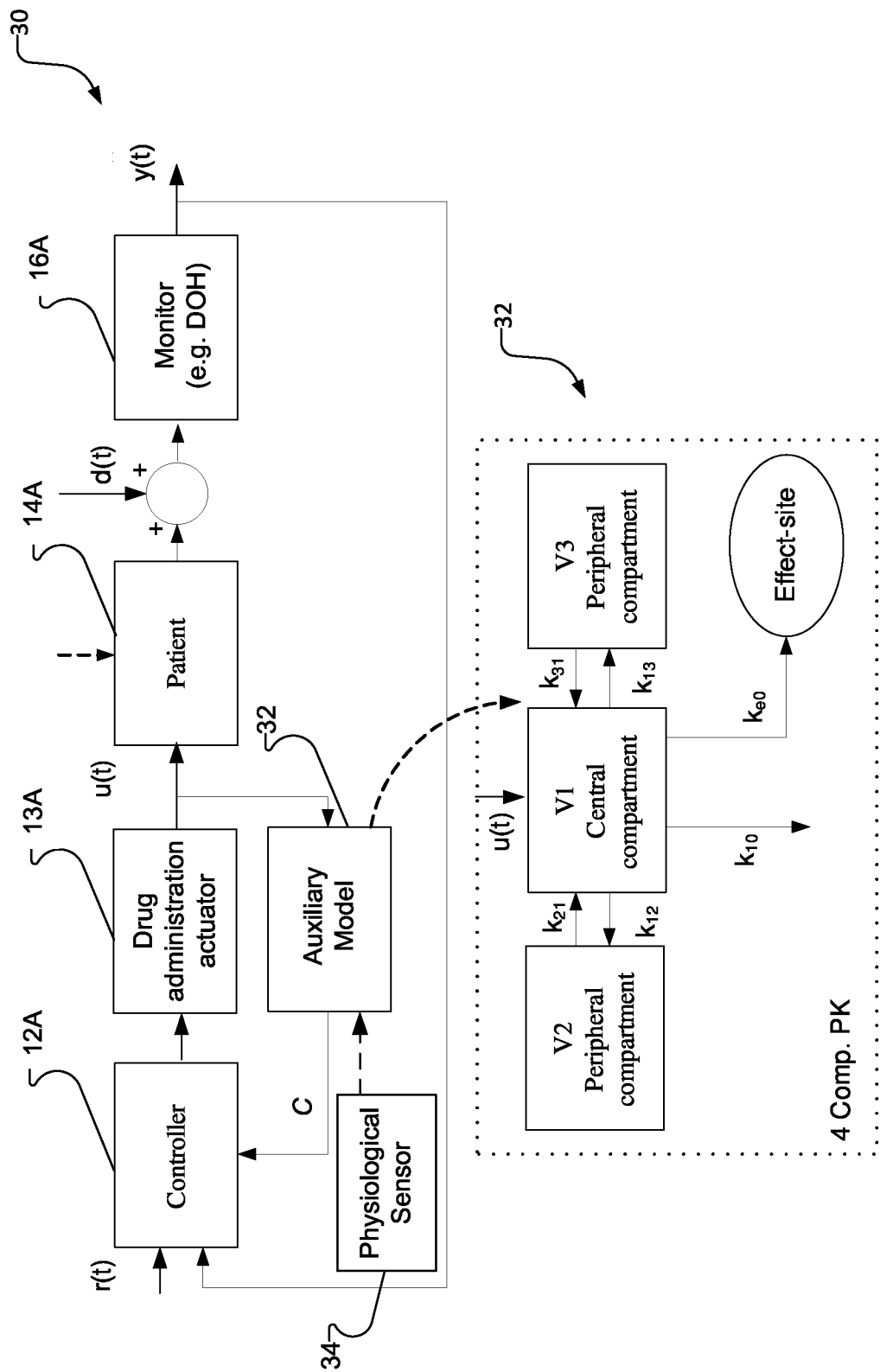


FIG. 6

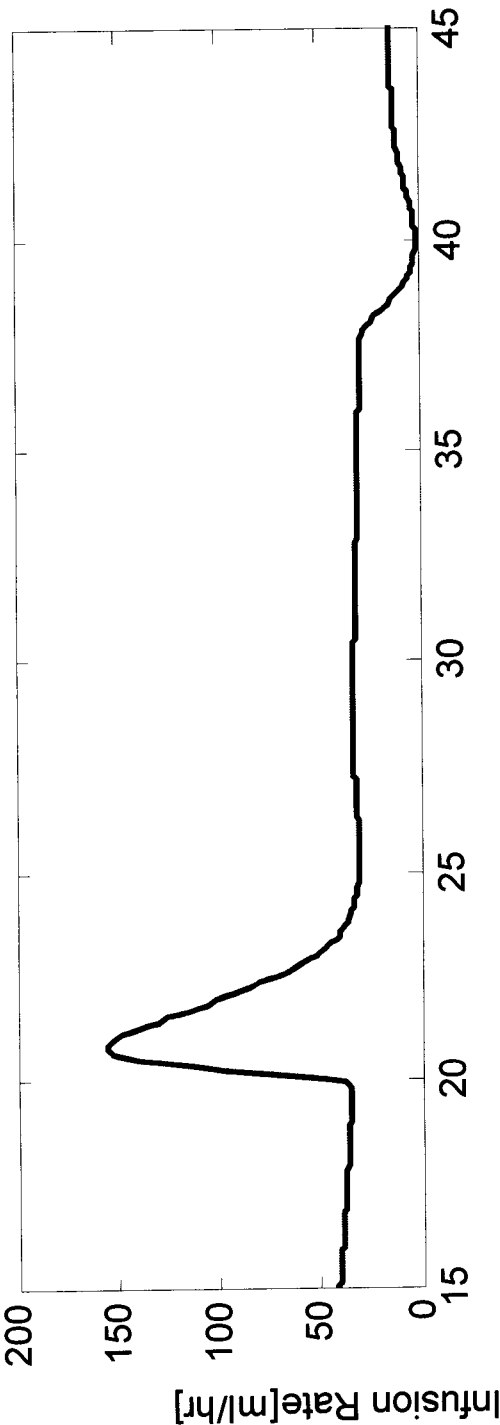


FIG. 7A

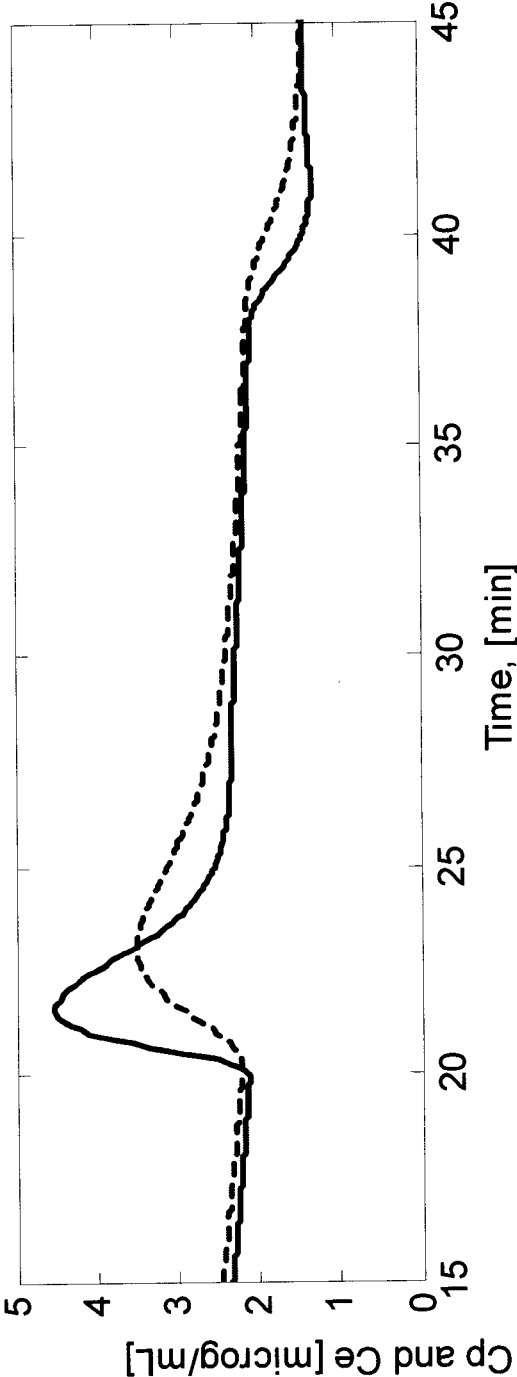


FIG. 7B

FIG. 7

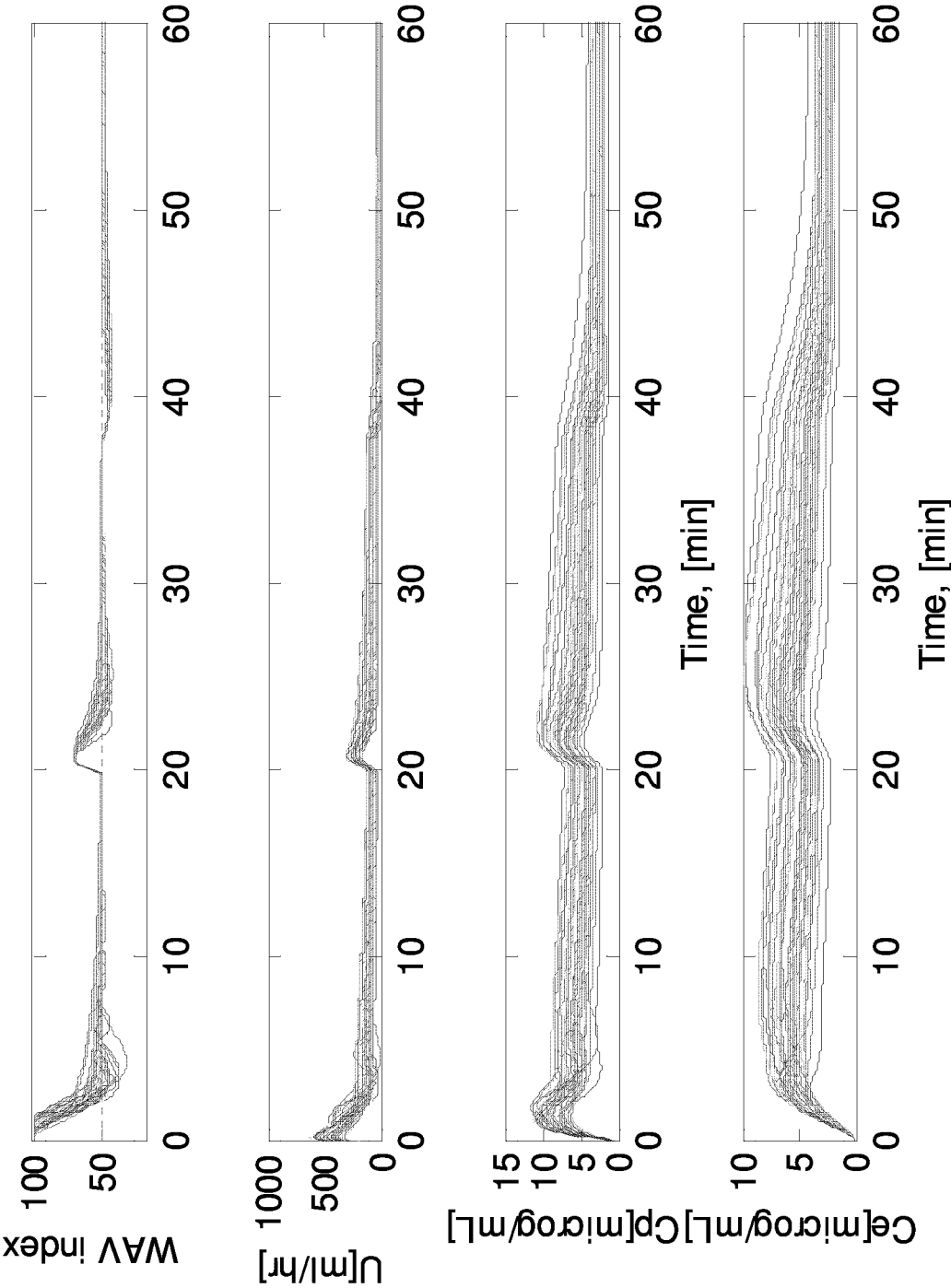


FIG. 8

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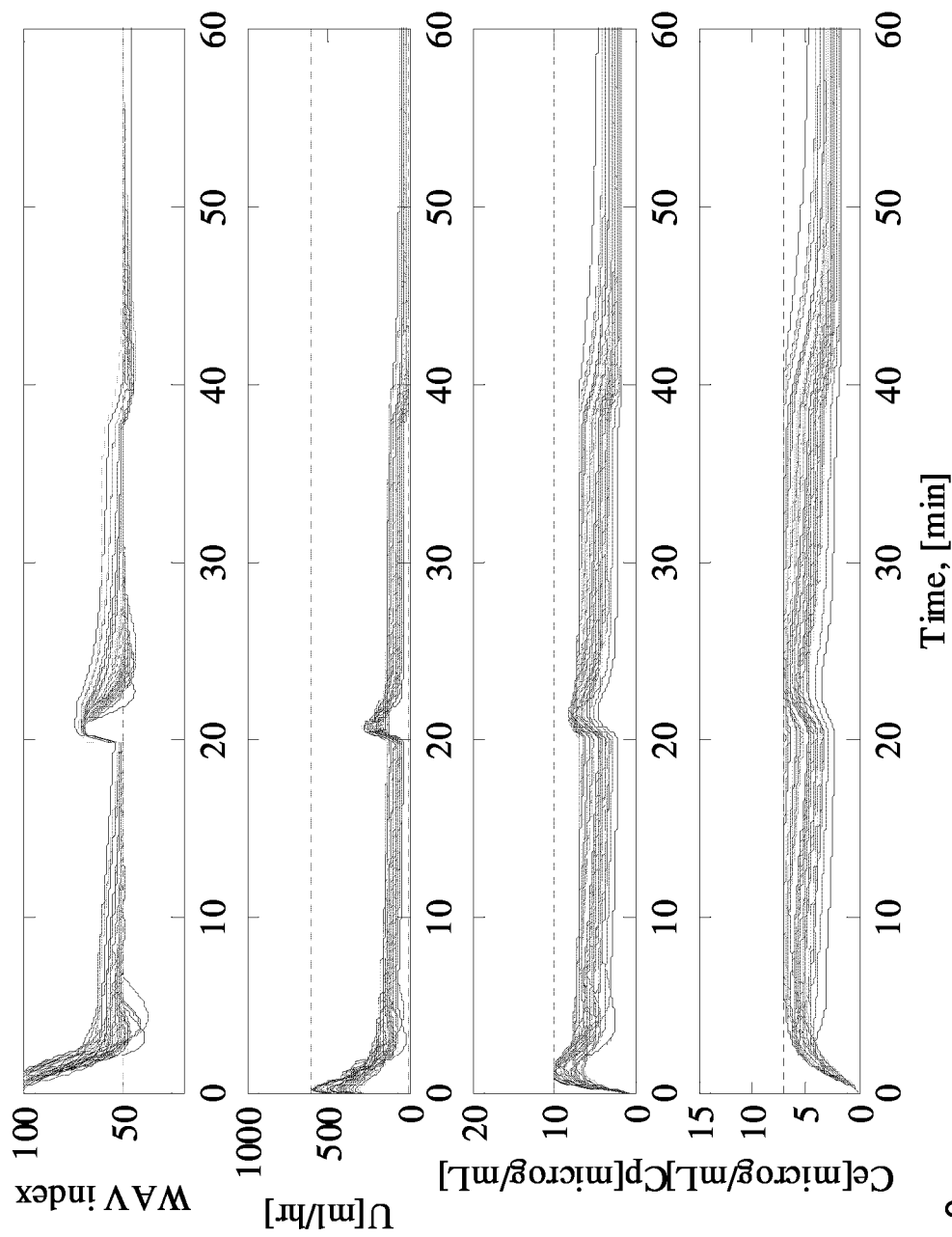


FIG. 9

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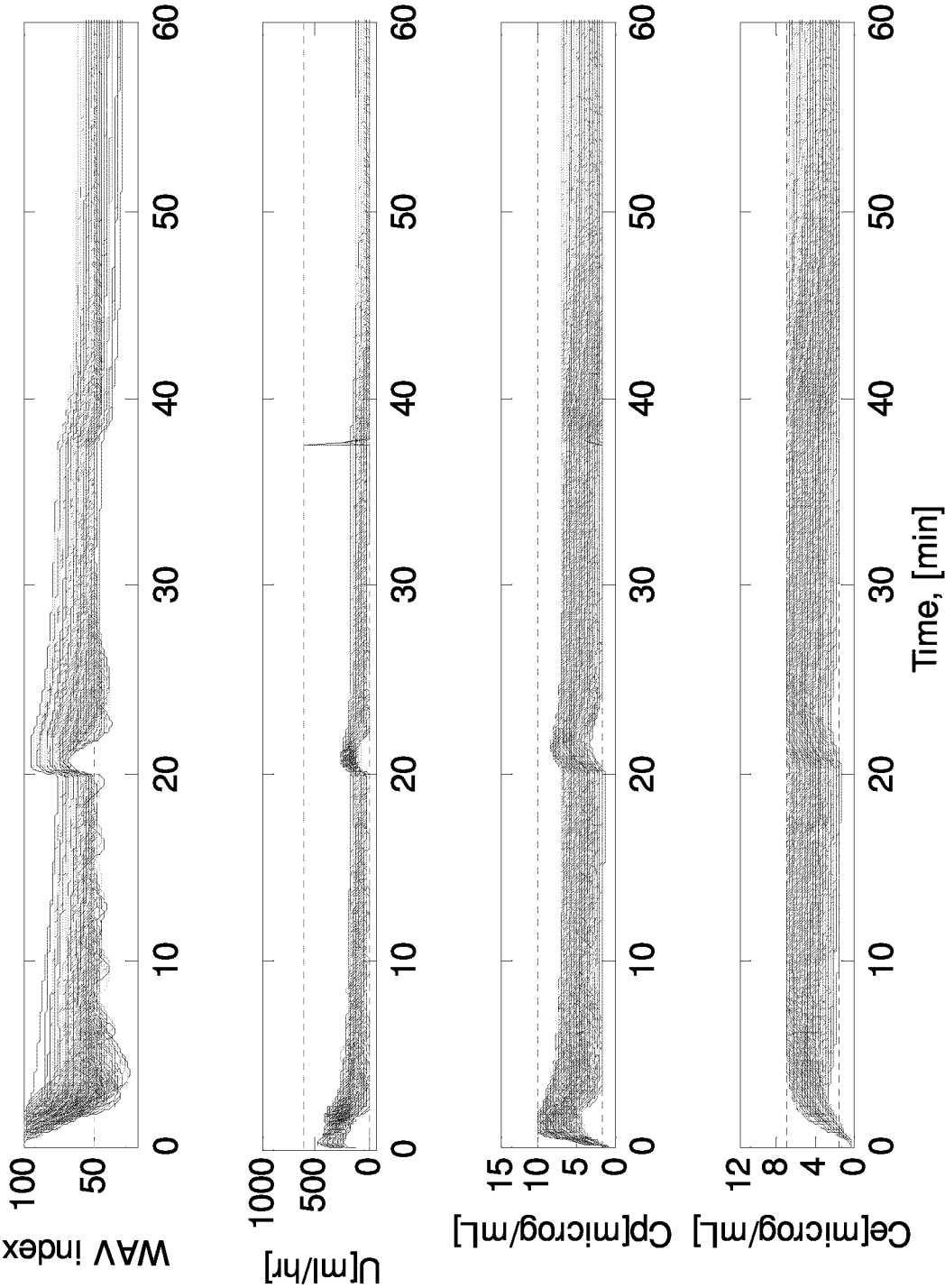


FIG. 10

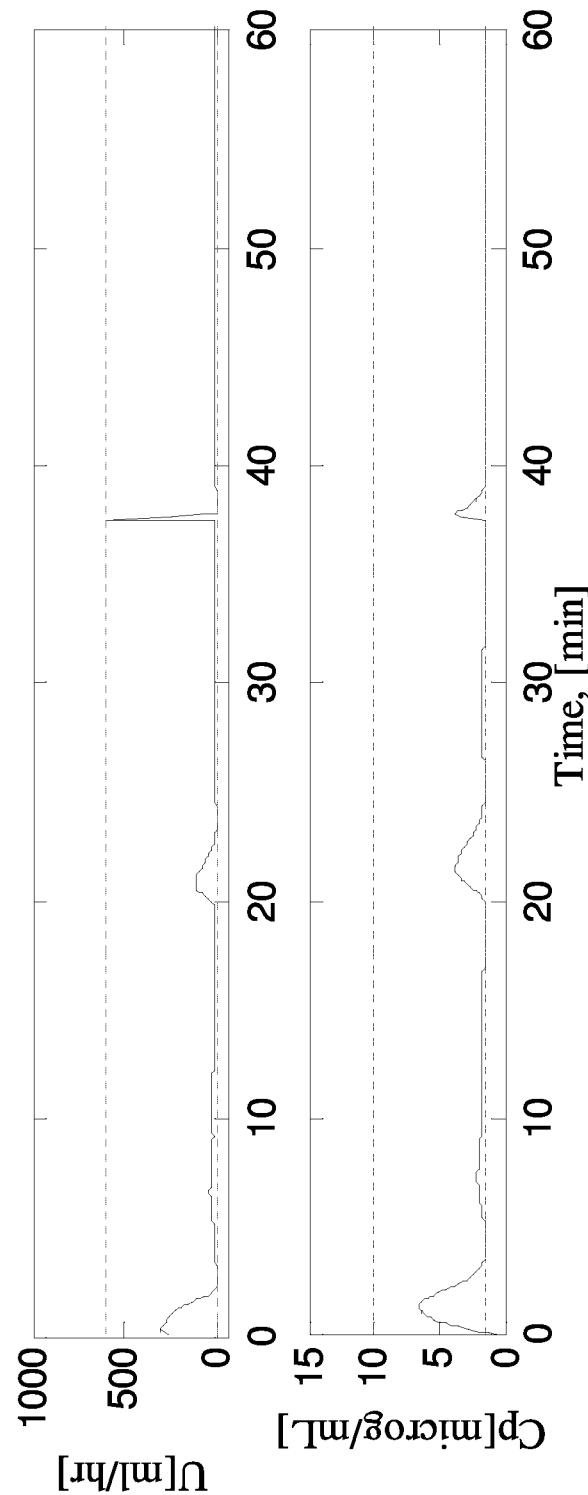


FIG. 11

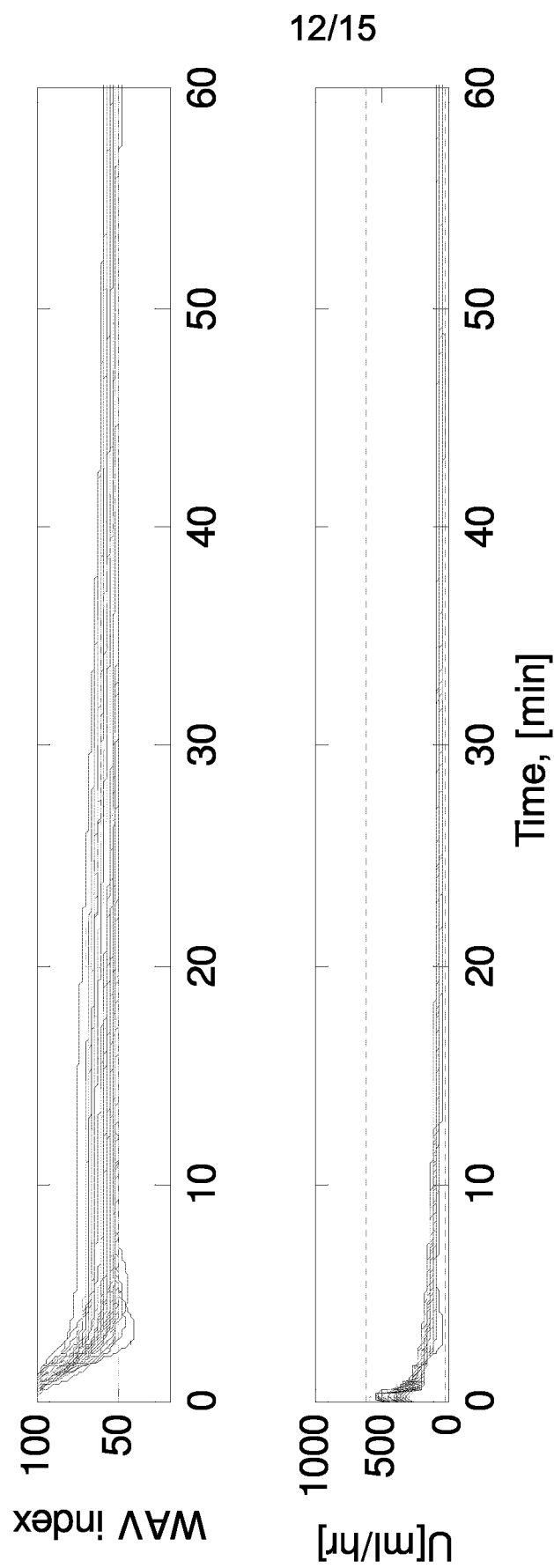


FIG. 12A

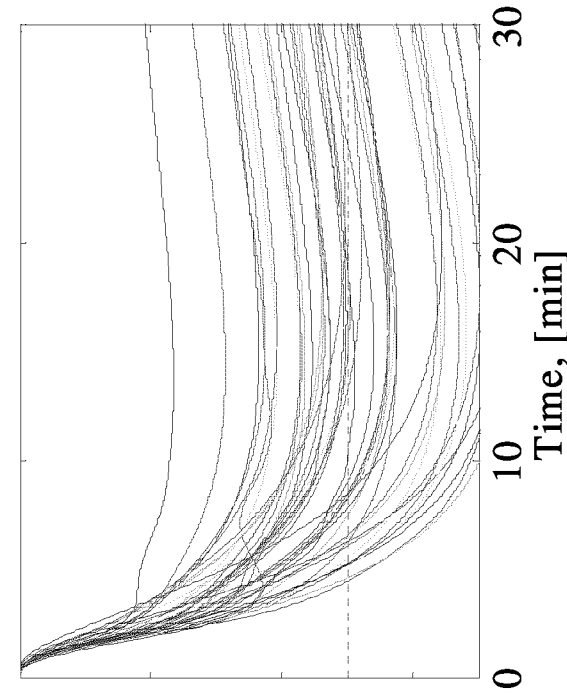


FIG. 12C

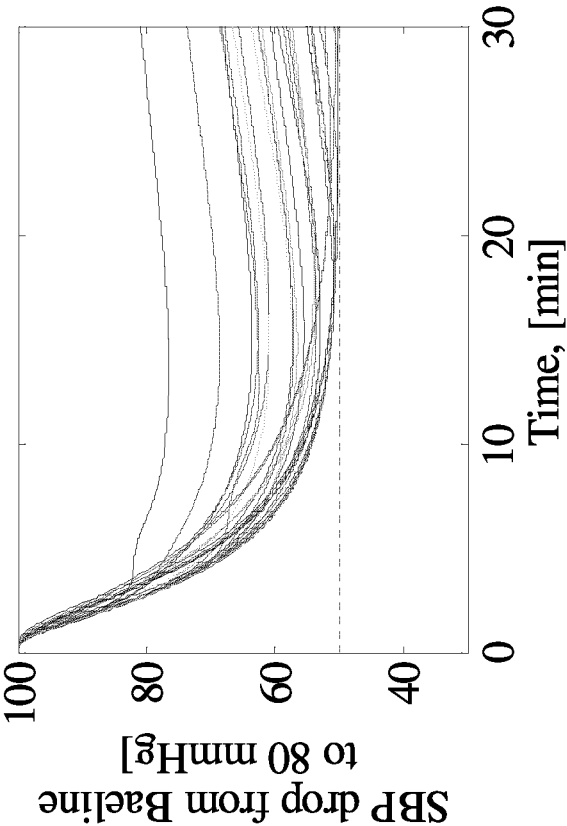


FIG. 12B

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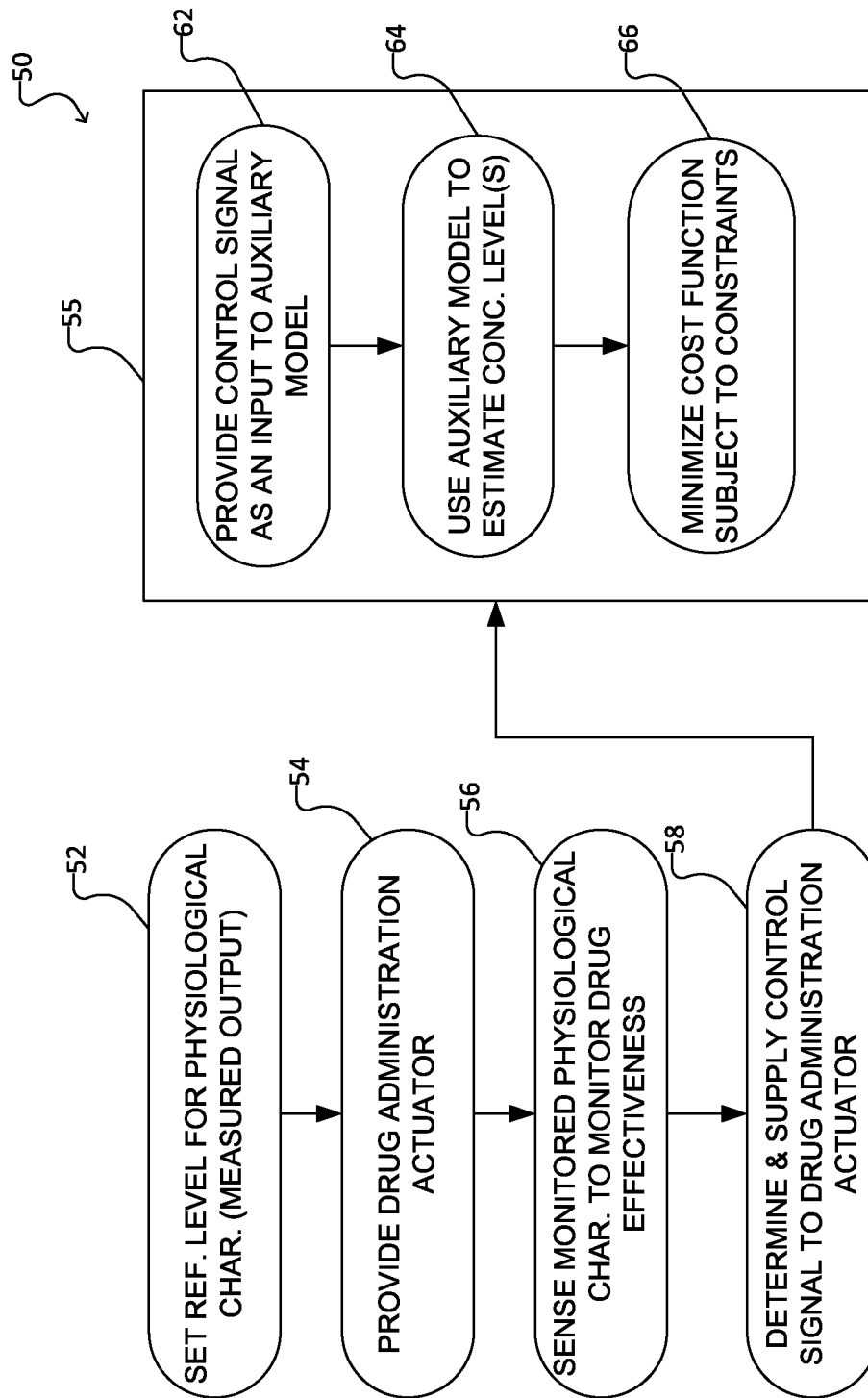


FIG. 13

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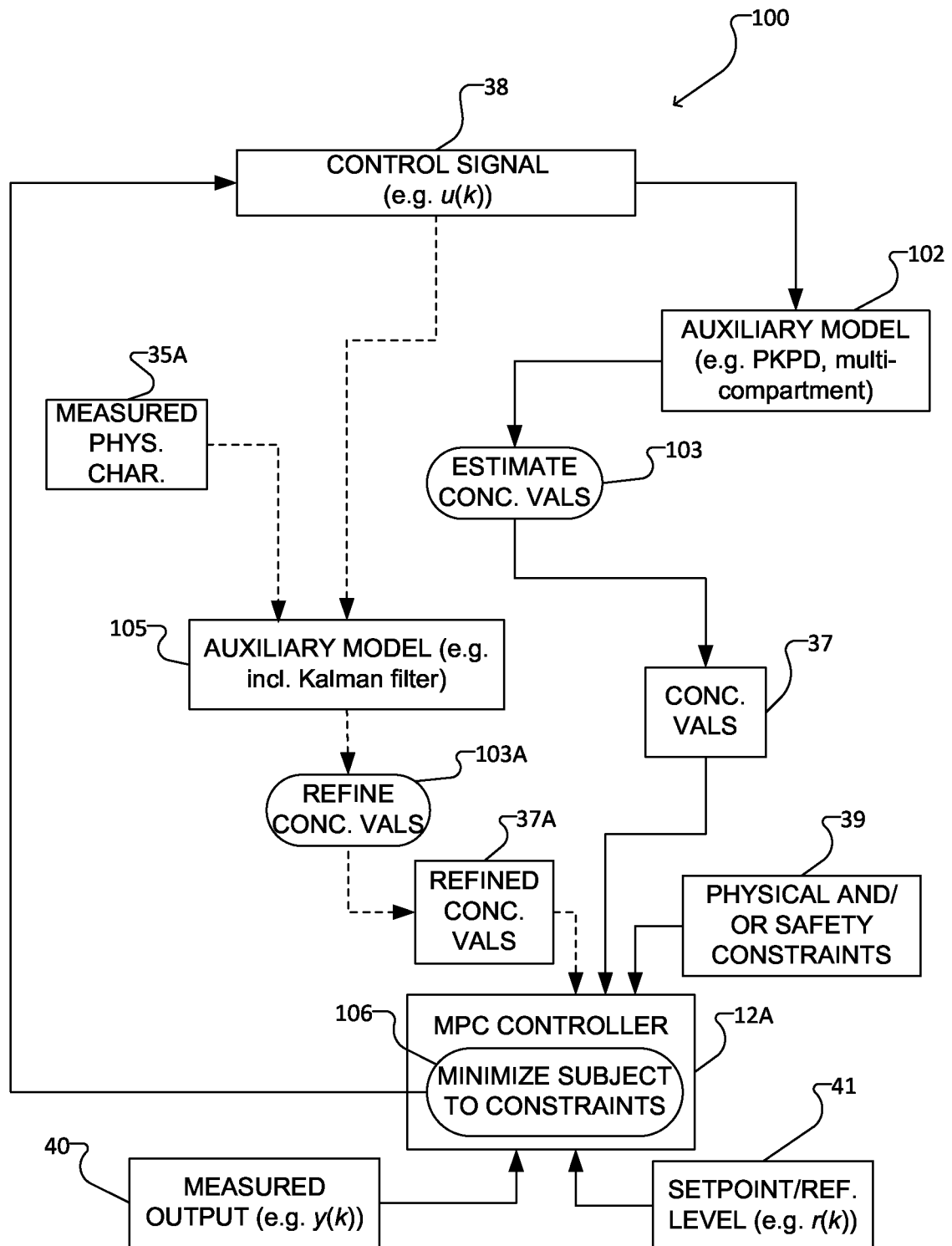


FIG. 14

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA2016/051375

A. CLASSIFICATION OF SUBJECT MATTER
IPC: **A61M 5/172** (2006.01) , **A61B 5/00** (2006.01)

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)
IPC: A61M 5/xx (2006.01) and A61B 5/xx (2006.01)

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Questel (FAMPAT), Intellect (Canadian Patents Database), Google (drug admin|+, controller+, closed-loop, risk control+, dos+, model+, nmc, hypno+ or ana+ or propofol)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SAWAGUCHI et al., "A Model-Predictive Hypnosis Control System Under Total Intravenous Anesthesia", IEEE Transactions on Biomedical Engineering Vol. 55 No. 3 March 2008 (pp.874-887)	1-44 and 46-89
A	VAN HEUSDEN et al., "Safety, constraints and anti-windup in closed-loop anesthesia" Proceedings of the 19 th World Congress, The International Federation of Automatic Control, Cape Town, South Africa, August 24-29, 2014	1-44 and 46-89

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* "A" "E" "L" "O" "P"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance earlier application or patent but published on or after the international filing date 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) document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed	"T" "X" "Y" "&"	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 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 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
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Date of the actual completion of the international search
21 February 2017 (21-02-2017)

Date of mailing of the international search report
13 March 2017 (13-03-2017)

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 819-953-2476

Authorized officer

Kristian MacKenzie (819) 639-7868

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA2016/051375**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)**

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

1. ☒ Claim Nos.: 89
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 89 is directed to a method for treatment of the human or animal body by surgery or therapy, which the International Searching Authority is not required to search under PCT Rule 39.1(iv). However, this Authority has carried out a search based on the alleged effect or purpose/use of the product defined in claim 89.

2. ☒ Claim Nos.: 45 and 90-92
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 91 and 92 encompass a product that is not defined in clear and concise terms as required under PCT Article 6. In the present case, the claims so lack clarity and/or support, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been established for the parts of the application which appear to be clear and/or supported.

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

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos.:

- Remark on Protest**
- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

专利名称(译)	用于药物施用的闭环控制的方法和系统		
公开(公告)号	EP3380133A4	公开(公告)日	2019-09-11
申请号	EP2016867484	申请日	2016-11-23
[标]申请(专利权)人(译)	英属哥伦比亚大学		
申请(专利权)人(译)	加拿大不列颠哥伦比亚大学		
当前申请(专利权)人(译)	加拿大不列颠哥伦比亚大学		
[标]发明人	DUMONT GUY ANSERMINO MARK KHOSRAVI SARA WEST NICHOLAS		
发明人	DUMONT, GUY ANSERMINO, MARK KHOSRAVI, SARA WEST, NICHOLAS		
IPC分类号	A61M5/172 A61B5/00		
CPC分类号	A61B5/0476 A61B5/4821 A61B5/4839 A61B5/725 A61M5/14 A61B5/00 A61M5/172 A61M5/1723 A61M2202/048 A61M2205/3303 A61M2205/50 A61M2230/06 A61M2230/10 A61M2230/30 A61M2230 /42 A61M2230/43 G16H20/13		
代理机构(译)	克罗宁, BRIAN HAROLD JOHN		
优先权	62/258656 2015-11-23 US		
其他公开文献	EP3380133A1		
外部链接	Espacenet		

摘要(译)

用于施用药物的控制系统包括药物施用致动器，用于以可控剂量向患者施用药物;用于测量药物对患者的影响的监测器;控制器，被配置为确定对药物管理致动器的控制信号;其中，控制器被配置为实现闭环模型预测控制方案，包括对于一系列时间步骤中的每一个，最小化受一个或多个约束限制的成本函数以确定控制信号，成本函数至少部分地基于在参考水平和监测测量;其中控制信号用作辅助模型的输入，以估计患者体内药物的至少一个浓度水平;并且其中约束包括对药物浓度水平估计的至少一个约束。