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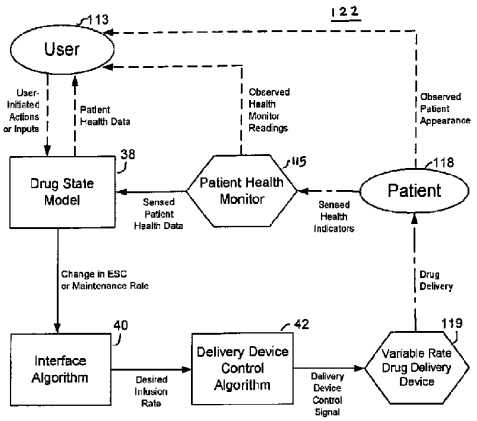

(57) Abstract: A method and apparatus for reducing the workload of titrating drug to effect while leaving clinician users in control of a related procedure is described. A drug delivery device (122) is controlled to achieve a target drug concentration at a selected site in the patient or a predetermined infusion rate waveform. The time profile of the target drug concentration or a predetermined infusion rate waveform is controlled by a drug state model (38) that uses clinical heuristics to implement safe, pre-defined changes in the target drug concentration or infusion rate and usercommanded changes in target drug concentration or infusion rate. The invention allows time to assess the response of the patient to changes in drug level by making small incremental and conservative changes in drug level over time.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

APPARATUSES AND METHODS FOR TITRATING DRUG DELIVERY

This application claims priority under 35 U.S.C. §119(e) to U.S. Patent Application Serial Number 60/308,591filed July 31, 2001, which is incorporated herein in its entirety by reference.

FIELD OF THE INVENTION

This invention relates generally to apparatuses and methods for altering the drug delivery rate, time profile and/or effect site concentration to a patient in response to certain events. In particular, the invention electronically integrates, through conservative and safety-biased software that forms part of a drug state model, the titration of one or more drugs (which may be, for example, sedatives, analgesics, or amnestics) in response to electronic monitoring signals of one or more patient physiological conditions and/or user observation and input.

BACKGROUND OF THE INVENTION

Titration of a drug is commonly used by clinicians to achieve a desired effect. In general, variability in patient response to titrated drugs may be expected because an identical amount of drug may produce widely dissimilar effects in different patients. During a typical titration, therefore, clinicians may give an initial dose of a drug and observe a patient's reaction. If the desired effect is not achieved within an expected time frame (e.g., if a dose is too weak), additional increments of the drug may be administered. Each additional administration may be followed by an observation period until the desired effect is ultimately achieved. The natural variability of patient response to drugs has maintained titration as a time-honored process in the armamentarium of the clinician. The traditional titration process, however, is time-consuming and labor-intensive and may be vulnerable to human error.

When a clinician performs a painful procedure for a patient, administration and careful monitoring, or supervision of administration, of sedative and/or analgesic agents may be required. Thus, the clinician may often be physically and/or cognitively multi-tasked, thereby potentially increasing the risks of mistakes.

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The traditional manual titration process may be multi-stepped and may generally be summarized as follows: (a) selecting an initial, conservative bolus dose of a given drug, based on, among others, the patient's demographic data such as age, gender, weight, height, from, among others, personal memory, a manual and drug insert, (b) delivering an initial bolus of a given drug, (c) waiting a certain time period before assessing an effect or effects of the administered drug, (d) assessing the effect or effects of the drug (possibly in the absence of equipment to objectively and consistently monitor the patient's physiological or clinical parameter(s) affected by the drug), (e) if required, selecting the size of a supplemental bolus to deliver, (f) manually delivering the supplemental bolus of given drug and (g) repeating steps (c) to (f) as required.

On the other hand, computer-controlled drug delivery systems may essentially take clinicians out of the "cognitive loop" of decision making with regard to drug administration. This "all or nothing" aspect of entirely computer-controlled drug delivery systems has hindered the acceptance of these systems by clinicians.

Rate controlled infusion (RCI) describes an infusion mode whereby clinicians define an infusion in terms of volume or mass of drug per unit time or, when normalized to patient weight, in terms of volume or mass of drug per patient weight per unit time. Generally, when using RCI, clinicians will give a loading dose infusion at a higher infusion rate to rapidly attain a desired drug level within the patient's body for a short period of time and then lower the infusion rate so that the desired drug level is maintained.

Target controlled infusion (TCI) allows clinicians to work in terms of target or effect site concentrations (ESC) instead of actual infusion rates. TCI algorithms use a pharmacokinetic (PK) model to predict target or effect site concentrations of a given drug at a given site in a patient with given demographic data such as weight, height, age and gender. Therefore, the infusion rate time profile or waveform in a TCI infusion is not constant as in RCI but generally varies with time to attain a desired target concentration.

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Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

SUMMARY OF THE INVENTION

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

The invention provides apparatuses and methods for providing computer-assisted titration of the level of sedative, amnestic and/or analgesic drugs in a controlled and transparent fashion that allows time for manual and/or automatic assessment of the patient's response to changing drug levels. The invention further provides computer-assisted

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reduction of the clinical workload without clinicians surrendering control of the administration of potent anesthetics to a computer and/or pharmacokinetic (PK) model. The invention additionally provides a means for increasing the safety of administering sedative, anesthetic or analgesic drugs to patients and enhancing the effectiveness of relieving fear and pain for patients.

In one aspect, the present invention provides a system for providing drug delivery to a patient, wherein said system comprises:

a user interface for accepting input from a user;

a drug delivery device that delivers an amount of drug to a patient;

two or more patient health monitors adapted so as to be coupled to a patient and generate a signal reflecting at least one health condition of the patient; and

a processor that integrates the user interface, drug delivery device, and patient health monitors according to a hierarchy of software algorithms such that the amount of drug delivered to the patient by the delivery device is modulated based on an input from the user and based on a signal generated by the patient health monitors without further user input, and wherein automated actions initiated by said processor will not increase overall drug levels automatically without an explicit request for a drug level by said user.

The system among other things, provides a gradual change in the effect site concentration (ESC) in a patient to achieve a particular target ESC in a manner that provides a safe and effective means of changing drug levels while evaluating the patient's response to changes in drug concentration. The present invention also provides a system that allows time for an assessment of patient status as the ESC is gradually increased where, for example, in a default mode the rate of change of ESC could be deliberately slowed down over a programmable period of time.

The present invention comprises a drug delivery device that administers sedative, amnestic and/or analgesic drugs to a patient. Computer software manages the rate of drug administration and may utilize, among other things, algorithms incorporating a pharmacokinetic model. The invention includes apparatuses and methods of assessing the patient's physiological reaction and response to changing drug levels and altering, as a function of the patient's physiological reaction and response at least one from the group including, among others, the rate of change of drug level, the targeted drug level, the time profile of the infusion rate, the rate of change of ESC, the time profile of the change in ESC, the targeted ESC and the total volume to be infused over a period of time.

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The invention adopts a "clinician knows best" design philosophy because the course of sedative, analgesic and/or amnestic drug action is in general both complex and influenced by many inter-related factors that may not be predictable or pre-programmable.

Simultaneously, the invention automates tedious tasks, such as titrating a drug to effect, allowing clinicians to have more time to perform other tasks such as monitoring patients more closely.

The invention incorporates input from multiple sensors (both of patient and/or machine state parameters) because using the input from multiple and redundant sensors may provide a more robust system design than reliance on a single sensor. Suitable sensors can include, but are not necessarily limited to heart rate, pulse rate, respiratory rate, arterial oxygen saturation, and blood pressure monitors, and a patient responsiveness monitor.

Sensors can also include monitors of machine states such as alarms status. Further, the invention implements, in general, a gradual change in target drug concentrations or infusion rate time profiles in such a way that there is time for assessment of drug effect, in objective terms and by the user, during transitions from one infusion mode, regime, profile, bolus, drug state or target to the next. The invention evaluates the responsiveness of patients (the ability of a patient to respond to a stimulus or query) directly, without requiring constant interaction and/or interpretation of a clinician. Additionally, the invention optionally alters the rate of assessment of responsiveness when infusion modes, regimes, profiles, boluses, drug states or targets are being changed or during instances when more frequent updates of responsiveness are desired such as, among others, deteriorating physiological parameters.

The invention also applies gradual titration to increase patient safety. A further objective is to "free up" clinicians' time while still leaving clinicians in charge of drug delivery and maintaining the benefits of a safe, conservative and incremental administration of potent medications.

The fields of use of the present invention include, but are not limited to, fear and/or pain management, administration of sedative, analgesic and/or amnestic drugs, anesthesia, monitored anesthesia care, deep sedation, and sedation and analgesia. Users can include clinicians, anesthesiologists, CRNAs, non-anesthesiologist physicians, nurses, technicians, and patients (self-administration). The environment of use includes all environments where sedative, analgesic or amnestic drugs are administered, (including but not limited to operating rooms, catheterization labs and hospital floors among others), patient controlled analgesia on ward floors for post-operative pain, and home use for chronic pain conditions.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic diagram depicting the interaction of a drug state model, an interface algorithm, and drug delivery control software with a patient and a user according to embodiments of the present invention.

FIG. 2 is a schematic representation of a relationship between three hierarchical layers of drug administration algorithms.

FIG. 3 is a plot of a typical rate of infusion of Propofol over time for a particular rate of increase of ESC.

FIG. 4 is a time plot of ESC for a step input and a ramp input of ESC both with the same target and both showing respective ESC trajectories when infusion is interrupted.

FIG. 5 is a block diagram depicting a particular embodiment of a drug delivery system for use with the drug state model of the present invention.

FIG. 6 shows a schematic representation of a drug state model for a RAMP UP drug state in accord with embodiments of the present invention.

FIG. 7 shows a schematic representation of a drug state model for a RAMP DOWN drug state in accord with embodiments of the present invention.

FIG. 8 shows a schematic representation of a drug state model for a STAT UP drug state in accord with embodiments of the present invention.

FIG. 9 shows a schematic representation of a drug state model for a STAT DOWN drug state in accord with embodiments of the present invention.

FIG. 10 shows a schematic representation of a drug state model for a REDUCTION drug state in accord with embodiments of the present invention.

FIG. 11 shows a schematic representation of a drug state model for a LEVEL drug state in accord with embodiments of the present invention.

FIG. 12 shows a schematic representation of a drug state model for an OFF drug state in accord with embodiments of the present invention.

FIG. 13 shows a schematic representation of an alternative drug state model for a LEVEL drug state in accord with embodiments of the present invention.

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DETAILED DESCRIPTION OF THE INVENTION

To accomplish a "clinician knows best" paradigm and thus allow clinician users to always remain in charge while computers perform repetitive and labor-intensive tasks, the present invention utilizes computer-assisted drug delivery as opposed to computer-controlled drug delivery. The systems and methods for computer-assisted drug delivery according to the present invention can initiate well-defined, pre-programmed actions, based on clinical heuristics, without clinician input, if the automated action (e.g., drug level reduction) will, in general, produce a safe effect. The pre-programmed actions, based on clinical heuristics, can be implemented as a transparent, finite-state algorithm wherein well-defined events (such as certain caution or warning alarms (based on the patient's physiological reaction or on the state of the drug delivery apparatus), user input, or impending loss of responsiveness to stimulation) trigger the system to transition from one drug delivery state (or "drug state") to another drug delivery state thus providing a complete drug state model. Automated actions initiated by the computer and/or software to decrease the workload of clinicians are in general limited to inherently "safe" actions, such as maintaining or decreasing drug level. In particular embodiments of the present invention, the system's controller software will, in general, not increase drug levels automatically without an explicit user (clinician, physician, nurse, etc.) or patient request for a higher drug level. The computer assisted drug delivery system of the present invention further allows users to override the pre-programmed software and automated actions, including the above-described "safe automated actions," thereby maintaining clinician control of drug delivery.

FIG. 1 is a schematic diagram of a drug delivery system **122** showing processes used by a user **113** of a drug delivery system, and the controller of the variable rate drug delivery device **119** to manage the delivery of drugs to patient **118** according to user observation of patient appearance and data supplied by at least one patient health monitor **115** and hierarchical control algorithms **38**, **40**, and **42**.

FIG. 2 shows three hierarchical layers of software algorithms that a drug delivery system **122** may use to control the delivery of drugs to a patient. These layers include a Delivery Device Control or Flow Control algorithm **42** as the most basic central layer, a Drug State Model (DSM) **38** as the highest layer, and an Interface or translation algorithm **40** as an intermediate layer. The software algorithms interact with their neighboring

algorithm layers so as to achieve a desired result such, as among others, a concentration of drug at an effect site compartment in the patient, i.e., an effect site concentration (ESC). The algorithms can hold the ESC as close as possible to a current value, the "current" ESC, or they can modulate the ESC towards a target value by a variable rate of change.

At the lowest level of this hierarchy, a computer manages the delivery device **122** with a flow control algorithm **42** so that the device accurately delivers a drug at a requested infusion rate. For example, the flow control algorithm, when provided with a requested infusion rate of 10 mg/kg/hr may, for example, (a) factor the size of a syringe or other drug delivery means, the drug's concentration, and the patient's weight, (b) perform particular calculations based on those factors, and (c) control the delivery mechanism so that an infusion rate as close as possible to 10 mg/kg/hr is delivered.

At the middle level of the hierarchy, an interface or translation algorithm **40** monitors certain conditions of the drug delivery process, interprets the requests from, and status of, the high level drug state model **38** layer and translates these high level, generally clinical, commands into infusion rate time profiles or waveforms that modulate over time the infusion rate requested of the flow control algorithm. This interface or translation algorithm **40** may be, among other things, a rate controlled infusion (RCI) algorithm, or a target controlled infusion (TCI) algorithm based on a pharmacokinetic model. The invention also contemplates translation layers **40** that do not use models or models running in real time but instead may use, among others, pre-programmed infusion rate templates that are adjusted via patient demographics, the total volume to be infused over a time period and drug labeling recommendations. The interface layer may also use other processes to modulate the infusion rate requested of the flow control algorithm.

An example of an RCI based algorithm uses a controller to automatically convert a user-entered loading dose and a user entered maintenance infusion rate from the units selected by the user into units for the flow control algorithm **42** to utilize. For example, a user may enter a loading dose of 5 mg of Propofol, and the translation layer **40** using RCI could automatically calculate or convert that dose into units such as cc or mg/kg, among others. The user may also enter the patient's weight via the user interface for the RCI model to calculate the loading dose in mg/kg. Similarly, the user may enter a maintenance rate of 10 mg/kg/hr, and the translation layer **40** using RCI could automatically calculate or convert that requested infusion rate into units such as mg/hr or cc/hr, among others. Once the user

enters the loading dose and maintenance rate, and the translation layer **40** performs its calculation or conversion, the drug delivery system **122** may then deliver the drug accordingly so as to keep track of the total amount of infusate delivered to the patient, including that from both the initial loading dose and from the maintenance infusion.

An example of a TCI-based algorithm uses a pharmacokinetic model and a controller, preferably a proportional integral derivative ("PID") controller, for open loop, model-based control of the delivery system's pump. This PID controller may calculate a drug delivery rate error and use that error data to control the target drug levels. Based on the predictions of a pharmacokinetic model appropriately selected or modified from one or more of numerous available models, a TCI algorithm modulates the desired infusion rate requested of the delivery device in an effort to achieve a desired target concentration of a given drug at a given target or effect site within given times or time periods. A TCI software algorithm, as one embodiment of an interface or translation layer, can operate effectively on the drug delivery device computer directly or on an external computer.

According to a particular embodiment, a target-controlled infusion (TCI) algorithm comprising a controller and a pharmacokinetic model using, for example, the Schnider parameter set for propofol, may be used to control the ESC of propofol at the brain, by modulating the infusion rate of propofol. Different control algorithms can be used such as, among others, proportional (P), proportional integral (PI), and proportional integral derivative (PID) in digital or analog form, and various mathematical models such as fuzzy logic and/or neural networks. The TCI algorithm can be any suitable TCI algorithm containing an appropriate pharmacokinetic model, such as the commercially available Diprifusor® TCI module.

FIG. 3 shows an example time plot of the actual rate of infusion of propofol for an 18 year-old, 90 kg, 140 cm tall female using an infusion pump with a 200 mg/min pumping limit set to reach a 2.0 μg/ml ESC target at a 0.5 μg/ml/min ramp-up of ESC according to one of these models. The software algorithm predicting the drug concentration at a target site and defining the rate of drug administration can employ many different pharmacokinetic models (for example, 2, 3, 4 or n compartments) now known or yet to be developed. Target and/or monitoring sites include the blood plasma, brain, central nervous system, neuromuscular junction, alveolar space, kidney, liver, pancreas, hypothalamus, heart tissue, baroreceptors and any other drug receptor laden sites or spaces in or on the body. The PK

model-based software algorithm predicting the drug concentration at a target or effect site may be omitted in certain embodiments of the invention.

The interface algorithm **40** controlling the rate of change of the drug concentration can produce different time profiles of the target drug concentration at different effect sites. The time profiles can be a linear ramp from target concentration A to B or a nonlinear increase or waveform. Nonlinear drug level increases can be controlled by several variables including the starting point (target concentration A) and the initial patient response during the initiation of a drug level change.

FIG. 4 shows curves for the ESC over time in a patient for, by way of example, a TCI step input of 2.0 μg/ml **10** of drug as well as a TCI ramp input of 0.5 μg/ml/min **14** of drug that is targeted to reach an ESC of 2.0 μg/ml. Assuming that the patient loses consciousness when the ESC is 1.5 μg/ml and that it is immediately detected by the drug infusion system and the infusion rate is immediately set to 0, the actual ESC may overshoot the target by 0.6 μg/ml for the step input **12** compared to 0.1 μg/ml for the ramp input **16**. Also, the patient may be unconscious (ESC > 1.5 μg/ml) for 2.25 min for the step input **12** compared to 1 minute for the ramp input **16**. In other words, the loss of consciousness may be more profound (i.e. occur at higher drug levels) and last more than twice as long with the step input compared to the ramp input. Thus, a ramp-up or other gradual means of increasing drug concentration or delivery may reduce the risk of unintended overdose or loss of consciousness. Accordingly, the drug state model **38** of the present invention utilizes a ramp-up state as a default mode for increasing drug levels to a patient.

At the highest level of the hierarchy, software representing a drug state model **38** modulates the target ESC based on certain well-defined events such as patient response, monitored physiological parameters, alarm status, and user input. The highest level layer may, in general, accept inputs that are clinical in nature, thus facilitating use by clinicians.

FIG. 5 is a block diagram depicting a particular embodiment of drug delivery system **122**, in accordance with the present invention, having user interface **112**, controller **114**, peripherals **115**, power supply **116**, external communications **110**, patient interface **117**, and drug delivery device **119**, where drug delivery system **122** is operated by user **113** in order to provide sedation and/or analgesia to patient **118**. As with the interface algorithm software **40**, the drug state model software **38** can operate on the controller of drug delivery device **119**, on controller **114** of an integrated system comprising drug delivery device **119** or an

external computer. In alternative embodiments, the invention features other hierarchical systems of control algorithms such as one with a hierarchy of only two layers where the drug state model controls the flow directly without an interface algorithm.

The drug delivery device **119** can be a syringe pump, volumetric pump, roller pump, peristaltic pump, piston pump, positive displacement pump, vane pump, gear pump, gas vaporizer and other means of controlling gas concentration or IV drug concentration. The drug administered can be a sedative, amnestic or analgesic such as propofol, remifentanil, dexmedetomidine, intravenous xenon (xenon dissolved in a lipid emulsion) and other narcotics and hypnotics. Additionally, the rate of drug infusion may be managed by computer and/or by both digital and analog circuitry. An example of such a drug delivery system **122** is disclosed and enabled by United States Patent Application Serial No. 09/324,759, filed June 3, 1999 which is herein incorporated by reference in its entirety.

The sedation and analgesia system of Application No. 09/324,759 includes at least one patient health monitor device (which can be a pulse oximeter, NIBP, capnometer, EEG, EKG, and others) adapted so as to be coupled to a patient and generate a signal reflecting at least one physiological condition of the patient; a drug delivery controller supplying one or more drugs to the patient; a memory device storing a safety data set reflecting safe and undesirable parameters of at least one monitored patient physiological condition; and an electronic controller interconnected between the patient health monitor, the drug delivery controller, and the memory device storing the safety data set; wherein said electronic controller receives said signals and in response manages the application of the drugs partly in accord with the safety data set. Again, the health monitor device may include any one or more monitors for NIBP, arterial line, respiratory monitoring (among others, capnometry, transthoracic impedance plethysmography, pulse oximeter plethysmogram, the Optovent device, airway pressure, acoustical analysis), ECG assessment of heart rate, pulse oximeter assessment of heart rate and oxygen saturation and other similar tests. More than one patient-response monitor may help increase the sensitivity and specificity of the assessment and the robustness of the design.

These patient health monitor devices or patient interface **117** may generate signals reflecting physiological conditions of the patient that reflect certain warning or caution levels. These warning or caution events may be communicated to the user as alarms (e.g., caution or warning) via the user interface **112**. Embodiments of user interface **112** and such

alarms are disclosed and enabled by United States Patent Application Serial No. 60/330,853, filed November 1, 2001 which is herein incorporated by reference in its entirety.

A further patient monitor may be provided with the drug delivery system **122** to track a patient's responsiveness during drug delivery. An automated responsiveness test (ART) monitor may be used to provide a sensory stimulus such as, among others, an audible and/or tactile stimulus to the patient. Patients are instructed to respond to such stimuli by initiating a response means, e.g., pressing an electromechanical button, every time they receive the stimulus. The time interval between the stimuli and the patient response is called "latency" or the latent response time. In one embodiment of ART, a latency exceeding, for example, 14 seconds may be considered a "failed" ART test. A response time between, for example, 5.3 and 14 seconds may be considered a "late" response and a response time less than, for example, 5.3 s may be considered "successful". The rate at which the ART monitor queries the patient can be varied between particular settings, such as NORMAL (a query cycle every three minutes, for example), FAST (a query cycle every 15 seconds, for example), and SEARCHING (for example, a query cycle every 15 seconds until 3 consecutive response times each less than 14 seconds occur whereupon the query cycle rate is switched to NORMAL). The NORMAL setting may be a default setting and may have a user selectable delay between query cycles of, for example, 1 to 3 minutes with a default value of 3 minutes. The user may interact with the ART settings and patient response to ART information via the user interface **112** in a manner described in the Application Serial No. 60/330,853. Particular embodiments of ART in accordance with the above description and certain alternative embodiments of the features of ART are disclosed and enabled by United States Patent Application Serial No. 60/342,773, filed December 28, 2001 which is herein incorporated by reference in its entirety. The means of assessing the patient's responsiveness can alternatively include any one or more of BIS, EEG analysis, manual assessment of consciousness using different scoring systems (e.g., OAA/S – Observer's Assessment of Alertness/Sedation, Ramsay, Glasgow coma scale, etc.), or other means of consciousness or responsiveness assessment (math quiz, finger games, video games, musical note playing, etc.).

The drug state model **38** of the present invention is preferably a finite state algorithm that codifies, via clinical heuristics, safety-biased, pre-defined actions that result from, among others, patient response, monitored data, alarm conditions and user input. The drug

state model according to the present invention may include a plurality of individual drug states that define heuristics for administering a drug to a patient safely under a variety of situations as well as heuristics for transitioning between the individual drug states based on certain well-defined events. These events may include, among others, a patient's ART response, Caution and Warning alarms (from patient physiological reactions to the drug administration and/or the machine states of the delivery apparatus itself), and user requests. Seven drug states and their associated heuristics are described below, though more may be implemented within the drug state model of the present invention.

These seven states include RAMP UP, RAMP DOWN, STAT UP, STAT DOWN, REDUCTION, LEVEL, and OFF. When the system initiates the "RAMP UP" drug state, it generates a gradual, linear increase in drug ESC at a predefined rate (e.g., 0.5 or 1.0 μg/ml/min) to reach a particular target ESC. When the system initiates the "RAMP DOWN" drug state, it generates a gradual linear decrease in drug ESC at a predefined rate (e.g., -0.01 or -0.3 □g/ml/min) to reach a particular target ESC. The "STAT UP" drug state generates a step increase to a target ESC as fast as possible. In certain implementations, the ESC is increased rapidly while allowing no more than a certain overshoot (e.g., 15%) of the target ESC. When the system initiates the "STAT DOWN" drug state, it immediately and completely discontinues drug administration until a new target ESC is reached, for example, via an exponential decay curve which may be the most rapid possible decrease to a new target ESC. When the system initiates the "REDUCTION" drug state, it decreases the current ESC to a new target, which is some fraction (e.g., 80%) of that initial level, as fast as possible via an exponential decay. When the system initiates the "LEVEL" drug state, it maintains the current ESC as close as possible to a constant value. When the system initiates the "OFF" drug state, it immediately and completely discontinues drug administration and ESC may drop, for example, via an exponential decay curve which may be the most rapid possible decrease to zero ESC. These states of drug delivery will be explained below in more detail.

FIG. 6 shows a graphical chart of the transitions to and from the RAMP UP drug state that the drug state model may initiate based on certain defined events. When the system initiates the "RAMP UP" drug state, it generates a gradual, linear increase in drug ESC at a predefined rate (e.g., 0.5 or 1.0 μg/ml/min) to reach a particular target ESC. Whenever users enter a new target ESC which is greater than the current ESC and do not

select the STAT UP delivery mode, the system will enter the RAMP UP drug state. During the RAMP UP drug state, the ART query cycle frequency is set to FAST. If, while in the RAMP UP drug state, there are three consecutive "late" ART responses, the system transitions to the LEVEL drug state and sets the ART query cycle frequency to NORMAL. This transition is based on trends and/or the symptoms that the RAMP UP target ESC is higher than the ESC threshold at which the patient starts to become unresponsive. If, while in the RAMP UP drug state, the current ESC reaches a level that is within 95% of the target ESC, the system transitions to the LEVEL drug state and sets the ART query cycle frequency to SEARCHING.

Table 1a shows possible transitions away from a current drug state of RAMP UP that are possible according to the drug state model of the present invention as based on the occurrence of certain well-defined events. The transitions depicted are those from the current RAMP UP drug state to a new drug state and from the current ART query cycle frequency to a new frequency. **Table 1b** shows possible transitions to the RAMP UP drug state from the various other drug states and the events that would lead to those transitions according to the drug state model of the present invention.

Table 1a. Transitions away from RAMP UP to other drug states

Event	New drug state	New ART frequency
Target reached (ESC within 95% of target)	LEVEL at target	SEARCHING
User enters new target:		
> current ESC and selects Stat	STAT UP to new target	Unchanged
--which is > current ESC but does **not** select Stat	RAMP UP to new target	Unchanged
--which is < current ESC but > 0	STAT DOWN to new target	NORMAL
--which = 0	OFF	NORMAL
3 consecutive "late" ARTs	LEVEL at current ESC*	NORMAL
"Failed" ART	RAMP DOWN to 0	SEARCHING
Caution Alarm	REDUCTION to 80% of current ESC; start 4 min. timer	SEARCHING
Warning Alarm	OFF	SEARCHING

*Transition **22 (FIG. 6)** of the Example run described below

Table 1b. Transitions leading to RAMP UP from other drug states

Previous Drug State	Event
	User enters target which is > current ESC but does not select Stat
STAT UP	User enters target which is > current ESC but does not select Stat
RAMP UP	User enters target which is > current ESC but does not select Stat
LEVEL	User enters target which is > current ESC but does not select Stat
LEVEL	Target Lost (ESC drops below 95% of target ESC)
STAT DOWN	User enters target which is > current ESC but does not select Stat
STAT DOWN	Target Lost (ESC drops below 95% of target ESC)
RAMP DOWN	User enters target which is > current ESC but does not select Stat
REDUCTION	User enters target which is > current ESC but does not select Stat

FIG. 7 shows a graphical chart of transitions to and from the RAMP DOWN drug state that the system may initiate based on certain well-defined events. When the system initiates the "RAMP DOWN" drug state, it generates a gradual linear decrease in drug ESC at a predefined rate (e.g., -0.01 or -0.3 □g/ml/min) to reach a particular target ESC. Whenever users enter a new target ESC which is less than the current ESC and do not select the STAT DOWN delivery mode, the system will enter the RAMP DOWN drug state. If, while in the RAMP DOWN drug state, there are three consecutive "successful" ART responses, the system transitions to the LEVEL drug state and sets the ART frequency to NORMAL. If the RAMP DOWN target is zero and that target is reached during the RAMP DOWN mode, the system transitions to the OFF drug state. If a patient becomes non-responsive, as indicated by a failed ART, during either the LEVEL or RAMP UP drug states, the system may transition to the RAMP DOWN drug state with a target ESC of zero and an ART frequency set to SEARCHING such that if the patient's responsiveness returned during RAMP DOWN, as indicated by ART success, the system would transition to LEVEL at the ESC current as of when responsiveness returned.

Table 2a shows possible transitions away from a current drug state of RAMP DOWN that are possible according to the drug state model of the present invention as based on the occurrence of certain well-defined events. The transitions depicted are those from the current RAMP DOWN drug state to a new drug state and from the current ART query cycle frequency to a new frequency. **Table 2b** shows possible transitions to the RAMP DOWN drug state from the various other drug states and the events that would lead to those transitions according to the drug state model of the present invention.

Table 2a. Transitions away from RAMP DOWN to other drug states

Event	**New drug state**	**New ART frequency**
Target reached (when target = 0)	OFF	unchanged
User enters new target:		
--which is > current ESC and selects Stat	STAT UP to new target	FAST
--which is > current ESC but does **not** select Stat	RAMP UP to new target	FAST
--which is < current ESC but > 0	STAT DOWN to new target	unchanged
--which = 0	OFF	unchanged
Caution Alarm	REDUCTION of target to 80% of current ESC; start 4 min. timer	SEARCHING
Warning Alarm	OFF	SEARCHING
ART Success (3 consecutive responses < 14 s)	LEVEL at current ESC*	NORMAL

*Transition **26** (**FIG. 7**) of the Example run described below

Table 2b. Transitions leading to RAMP DOWN from other drug states

Previous Drug State	**Event**
RAMP UP	Failed ART
LEVEL	Failed ART

FIG. 8 shows a graphical chart of transitions to and from the STAT UP drug state that the system may initiate based on certain well-defined events. The "STAT UP" drug state generates a step increase to a target ESC as fast as possible. In certain implementations, the ESC is increased rapidly while allowing no more than a certain overshoot (e.g., 15%) of the target ESC. Whenever users enter a target ESC which is greater than the current ESC and select STAT delivery via the user interface, the STAT UP drug state will be initiated by the system. If the current drug state is OFF and the user enters any target ESC which is greater than 0 and chooses STAT delivery via the user interface, the STAT UP drug state will be initiated by the system to achieve that target ESC quickly. In either case, if the user does not choose the STAT delivery mode, the system will enter the RAMP UP drug state. ART query cycle frequency is set to FAST during the STAT UP drug state. If, while in the STAT UP drug state, the current ESC reaches a level that is within 95% of the STAT UP target ESC, the system transitions to the LEVEL drug state and sets the ART frequency to SEARCHING.

The invention contemplates that clinicians deliberately choose "stat up" for appropriate clinical indications which should not be over-ridden by the automated system. Therefore, in particular embodiments of the present invention, the system will not initiate a transition to the "off" drug state or set the ART frequency to "searching" upon a Warning alarm if it is in the STAT UP drug state.

Table 3a shows possible transitions away from a current drug state of STAT UP that are possible according to the drug state model of the present invention as based on the occurrence of certain well-defined events. The transitions depicted are those from the current STAT UP drug state to a new drug state and from the current ART query cycle frequency to a new frequency. **Table 3b** shows possible transitions to the STAT UP drug state from the various other drug states and the events that would lead to those transitions according to the drug state model of the present invention.

Table 3a. Transitions away from STAT UP to other drug states

Event	**New drug state**	**New ART frequency**
Target reached (ESC within 95% of target)	LEVEL at target*	SEARCHING
User enters new target:		
--which is > current ESC and selects Stat	STAT UP to new target	Unchanged
--which is > current ESC but does **not** select Stat	RAMP UP to new target	Unchanged
--which is < current ESC but > 0	STAT DOWN to new target	SEARCHING
--which = 0	OFF	SEARCHING

*Transition **29** (**FIG. 8**) of the Example run described below

Table 3b. Transitions leading to STAT UP from other drug states

Previous Drug State	Event
OFF	User enters target which is > current ESC and selects Stat
STAT UP	User enters new target which is > current ESC and selects Stat
RAMP UP	User enters new target which is > current ESC and selects Stat
LEVEL	User enters new target which is > current ESC and selects Stat
STAT DOWN	User enters new target which is > current ESC and selects Stat
RAMP DOWN	User enters new target which is > current ESC and selects Stat
REDUCTION	User enters new target which is > current ESC and selects Stat

FIG. 9 shows a graphical chart of transitions to and from the STAT DOWN drug state that the system may initiate based on certain well-defined events. When the system initiates the "STAT DOWN" drug state, it immediately and completely discontinues drug administration until a new target ESC is reached, for example, via an exponential decay curve which may be the most rapid possible decrease to a new target ESC. Whenever users enter a new target ESC which is less than the current ESC and is greater than zero while in any of the other drug states, the STAT DOWN drug state may be initiated by the system. If users enter a new target ESC which is less than a current STAT DOWN target and is greater than zero, then the system may continue in the STAT DOWN drug state towards the new target ESC. If, while in the STAT DOWN drug state, the current ESC reaches a level that is within 95% of the STAT DOWN target ESC, the system transitions to the LEVEL drug state. If the ESC target is "lost" (i.e., the current ESC drops to below 95% of the target ESC; this may happen, for example, during an interruption in drug delivery to change a drug container) while in the STAT DOWN drug state, the system transitions to the RAMP UP drug state to reacquire the target ESC and the ART query cycle frequency is set to FAST.

Table 4a shows possible transitions away from a current drug state of STAT DOWN that are possible according to the drug state model of the present invention as based on the occurrence of certain well-defined events. The transitions depicted are those from the current STAT DOWN drug state to a new drug state and from the current ART query cycle frequency to a new frequency. **Table 4b** shows possible transitions to the STAT DOWN drug state from the various other drug states and the events that would lead to those transitions according to the drug state model of the present invention.

TABLE 4a. Transitions away from STAT DOWN to other drug states

Event	New drug state	New ART frequency
Target reached (ESC within 95% of target)	LEVEL at target*	unchanged
User enters new target		
--which is > current ESC and selects Stat	STAT UP to new target	FAST
--which is > current ESC but does **not** select Stat	RAMP UP to new target	FAST
--which is < current stat down target but > 0	STAT DOWN to new target	unchanged
--which = 0	OFF	unchanged
Target lost (ESC drops below 95% of target ESC)	RAMP UP to original stat down target	FAST
Caution Alarm	REDUCTION of target to lesser of current stat down target or 80% of current ESC; start 4 min. timer	SEARCHING
Warning Alarm	OFF	SEARCHING

*Transition **32** (**FIG. 9**) of the Example run described below

Table 4b. Transitions leading to STAT DOWN from other drug states

Previous Drug State	Event
STAT UP	User enters new target which is < current ESC but > 0
RAMP UP	User enters new target which is < current ESC but > 0
LEVEL	User enters new target which is < current ESC but > 0
STAT DOWN	User enters new target which is < current stat down target but > 0
RAMP DOWN	User enters new target which is < current ESC but > 0
REDUCTION	User enters new target which is < current ESC but > 0
REDUCTION	4 minute timer associated with a Reduction drug state expires and no cautions exist

FIG. 10 shows a graphical chart of transitions to and from the REDUCTION drug state that the system may initiate based on certain well-defined events. When the system initiates the "REDUCTION" drug state, it decreases the current ESC to a new target, which is some fraction (e.g., 80%) of that initial level, as fast as possible via an exponential decay. The system may accomplish this by not administering any drug to the patient until the new lower REDUCTION target ESC is reached. The system generally transitions to the REDUCTION drug state from another drug state upon a Caution alarm. ART query cycle

frequency is generally set to SEARCHING upon the initiation of the REDUCTION drug state.

To prevent stacking of REDUCTION drug states due to successive Caution alarms and to allow time for drug reduction to take effect upon the initiation of the drug state, the system may start a timer upon transitioning to the REDUCTION drug state to establish a time window during which no additional drug reduction will be initiated due to a Caution alarm. The time window may be any suitable length, for example 4 minutes. Should a Warning alarm occur during the time window, the system may immediately transition to the OFF drug state regardless of the time remaining. The automatic transition to a REDUCTION drug state is consistent with the design principle that automation of drug delivery is only applied when biased towards safety. As a redundant safety measure, the system transitions from REDUCTION to STAT DOWN if the time window expires and no Caution alarms remain so as to achieve the REDUCTION target ESC in those cases that that new target had not been achieved during the time window. If at the end of the time window, no Caution alarms exist and the REDUCTION target ESC has been reached (or the current ESC is within 95% of that new target), the system will switch from REDUCTION to STAT DOWN and then immediately to LEVEL. If any Caution alarm (new or old) still exists at the end of the time window, the system sets the target ESC to the lesser of the REDUCTION target ESC or 80% of the ESC current at the expiration of the time window (i.e., a second reduction). The time window may be restarted if the target ESC is set to a second reduction level.

The system may follow the above general procedure when it transitions from the LEVEL, RAMP UP, or RAMP DOWN drug states to the REDUCTION state. When the system transitions from STAT DOWN to REDUCTION upon a Caution alarm, however, it may utilize an alternative transition procedure whereby the reduced target ESC is set to the lesser of the STAT DOWN target ESC or some fraction (e.g., 80%) of the current ESC (i.e., the ESC when the REDUCTION state is initiated). This alternative transition procedure ensures that if the target ESC set by users when selecting the STAT DOWN drug state is less than that fraction of the ESC prevailing upon the transition to REDUCTION, then the automated reduction will not override the judgment of the user. This is consistent with the "clinician knows best" philosophy. If the ESC target is "lost" (i.e., the current ESC drops to below 95% of the target ESC; this may happen, for example, during an interruption in drug

delivery to change a drug container) while in the REDUCTION drug state, the system resets the target ESC to the current ESC.

Preferably, the system does not automatically transition from STAT UP to REDUCTION upon a Caution alarm. This is also consistent with the "clinician knows best" design philosophy and the deliberate goal to trust and empower clinicians. The invention contemplates that clinicians deliberately choose "stat up" for appropriate clinical indications which should not be over-ridden by the automated system.

Table 5a shows possible transitions away from a current drug state of REDUCTION that are possible according to the drug state model of the present invention as based on the occurrence of certain well-defined events. The transitions depicted are those from the current REDUCTION drug state to a new drug state and from the current ART query cycle frequency to a new frequency. **Table 5b** shows possible transitions to the REDUCTION drug state from the various other drug states and the events that would lead to those transitions according to the drug state model of the present invention.

Table 5a. Transitions away from REDUCTION to other drug states

Event	New drug state	New ART frequency
User enters new target:		
--which is > current ESC and selects Stat	STAT UP to new target	FAST
--which is > current ESC but does **not** select Stat	RAMP UP to new target	FAST
--which is < current ESC but > 0	STAT DOWN to new target	unchanged
--which = 0	OFF*	unchanged
Target lost (ESC drops below 95% of target)	REDUCTION of target to current ESC	unchanged
When Reduction starts with 4 minute timer and:		
--4 minute timer expires and no cautions exist	STAT DOWN	unchanged
--4 minute timer expires and cautions do exist	REDUCTION of target to lesser of current target or 80% of current ESC; restart 4 minute timer	unchanged
--4 minute timer has not yet expired but cautions exist	Do nothing	unchanged
Warning Alarm	OFF	SEARCHING

*Transition **36** (**FIG. 10**) of the Example run described below

Table 5b. Transitions leading to REDUCTION from other drug states

Previous Drug State	Event
RAMP UP	Caution Alarm
LEVEL	Caution Alarm
STAT DOWN	Caution Alarm
RAMP DOWN	Caution Alarm
REDUCTION	Target lost (ESC drops below 95% of target)
REDUCTION	When Reduction starts with 4 minute timer that expires and cautions exist

FIG. 11 shows a graphical chart of transitions to and from the LEVEL drug state that the system may initiate based on certain well-defined events. When the system initiates the "LEVEL" drug state, it maintains the current ESC as close as possible to a constant value. The system may transition from another drug state to LEVEL whenever a target ESC is reached. A target ESC may be considered to have been reached by the system whenever

the current ESC is within 95%, or some other value, of the target ESC. ART query cycle frequency may be set to SEARCHING when the system transitions from another drug state to LEVEL based on a target ESC being reached and to NORMAL when the system transitions to LEVEL based on a "late" ART (i.e., three consecutive late responses) during RAMP UP or on a "successful" ART during RAMP DOWN. If the ESC target is "lost" (i.e., the current ESC drops to below 95% of the target ESC; this may happen, for example, during an interruption in drug delivery to change a drug container) while in the LEVEL drug state, the system transitions to the RAMP UP drug state to reacquire the target ESC and the ART query cycle frequency is set to FAST.

Table 6a shows possible transitions away from a current drug state of LEVEL that are possible according to the drug state model of the present invention as based on the occurrence of certain well-defined events. The transitions depicted are those from the current LEVEL drug state to a new drug state and from the current ART query cycle frequency to a new frequency. **Table 6b** shows possible transitions to the LEVEL drug state from the various other drug states and the events that would lead to those transitions according to the drug state model of the present invention.

Table 6a. Transitions away from LEVEL to other drug states

Event	**New drug state**	**New ART frequency**
User enters new target		
--which is > current ESC and selects Stat	STAT UP to new target*	FAST
--which is > current ESC but does **not** select Stat	RAMP UP to new target	FAST
--which is < current ESC but > 0	STAT DOWN to new target**	unchanged
--which = 0	OFF	unchanged
Target lost (ESC drops below 95% of target ESC)	RAMP UP to original target	FAST
Failed ART	RAMP DOWN to 0***	SEARCHING
Caution Alarm	REDUCTION to (80% of current ESC; start 4 min. timer****	SEARCHING
Warning Alarm	OFF	SEARCHING

*Transition **28** (**FIG. 11**) of the Example run described below
Transition **30 (**FIG. 11**) of the Example run described below
***Transition **24** (**FIG. 11**) of the Example run described below

****Transition **34** (**FIG. 11**) of the Example run described below

Table 6b. Transitions leading to LEVEL from other drug states

Previous Drug State	**Event**
STAT UP	Target Reached (when current ESC is within 95% of target; current ESC may overshoot target before coming down to within 95% of target)
RAMP UP	3 Consecutive "late" ARTs
RAMP UP	Target Reached (when current ESC is within 95% of target)
RAMP DOWN	ART "success"
STAT DOWN	Target Reached (when current ESC is within 95% of target)

FIG. 13 shows a graphical chart of transitions to and from an alternative embodiment of the LEVEL drug state that the system may initiate based on certain well-defined events. In a like manner, the other drug states of the present invention may be modified to provide alternative heuristics for achieving their functions. Transitions **44** and **46** are examples of alternative heuristic approaches the drug state model of the present invention may employ.

FIG. 12 shows a graphical chart of transitions to and from the OFF drug state that the system may initiate based on certain well-defined events. When the system initiates the "OFF" drug state, it immediately and completely discontinues drug administration and ESC may drop, for example, via an exponential decay curve which may be the most rapid possible decrease to zero ESC. The OFF drug state is generally triggered by a Warning alarm, but if users enter a target ESC of zero while in any of the other drug states, the system may transition to the OFF state. The OFF drug state may also be triggered whenever users press a "Stop Propofol" button or the like on the user interface of the system. The ART query cycle frequency may be set to SEARCHING or to NORMAL when the system transitions to OFF.

Table 7a shows possible transitions away from a current drug state of OFF that are possible according to the drug state model of the present invention as based on the occurrence of certain well-defined events. The transitions depicted are those from the current OFF drug state to a new drug state and from the current ART query frequency to a new frequency. **Table 7b** shows possible transitions to the OFF drug state from the various

other drug states and the events that would lead to those transitions according to the drug state model of the present invention.

Table 7a. Transitions away from OFF to other drug states

Event	New drug state	New ART frequency
User enters target which is > current ESC and selects Stat	STAT UP to target	FAST
User enters target which is > current ESC but does not select Stat	RAMP UP to target*	FAST
User enters target < current ESC and > 0	STAT DOWN to target	unchanged

*Transition **20 (FIG. 12)** of the Example run described below

Table 7b. Transitions leading to OFF from other drug states

Previous Drug State	Event
STAT UP	User enters new target which = 0
RAMP UP	User enters new target which = 0
RAMP UP	Warning Alarm
LEVEL	User enters new target which = 0
LEVEL	Warning Alarm
STAT DOWN	User enters new target which = 0
STAT DOWN	Warning Alarm
RAMP DOWN	User enters new target which = 0
RAMP DOWN	Warning Alarm
RAMP DOWN	Target reached where target was 0
REDUCTION	User enters new target which = 0
REDUCTION	Warning Alarm

A drug delivery Example Run will now be described in order to illustrate certain embodiments of the drug state transitions that are possible according to the present invention. Each of the particular features of the drug delivery system, the user interface (UI), the automated responsiveness test (ART), and the drug state model that are described in this Example Run are merely exemplary and many alternatives to such features are workable as part of the present invention. Initially, a clinician user enters the patient's demographic data such as, among others, weight, height, age, gender, and ethnicity via a UI of the system. The user then enters a conservative target ESC of propofol by pressing a "Propofol level"

button or the like on the UI. At an ensuing prompt, the user presses the button labeled "2.0" and then the "OK" button to actually administer propofol. The drug state model (DSM) then initiates a transition **20** from the OFF state to the RAMP UP drug state (see **FIG. 12** and **Table 7a** above). The rate of infusion in μg/min of propofol is modulated over time by the interface algorithm **40** to achieve a gradual increase in ESC at a constant rate of 0.5 μg/ml/min. This rate is determined by the delivery system according to an algorithm based on the entered demographic data of the patient. During the ramp-up of ESC, the automated responsiveness test (ART) query frequency is set to FAST and queries are initiated every 15 seconds.

In this example, the patient is hypersensitive to propofol and starts to lose responsiveness, as indicated by three consecutive late ART response times to the ART queries, at an ESC of 1.5 μg/ml. The DSM automatically initiates transition **22** from the RAMP UP drug state to the LEVEL drug state (see **FIG. 6** and **Table 1a** above). The DSM sets the ART query frequency to NORMAL. At this point, the procedure starts. Because the system was previously in RAMP UP mode to its user-selected set ESC of 2.0 μg/ml, the ESC concentration slightly overshoots past the ESC of 1.5 μg/ml in effect when the system transitioned to the LEVEL mode. During this temporary overshoot, the patient fails the ART.

The failed ART triggers transition **24** from the LEVEL state to the RAMP DOWN state (see **FIG. 11** and **Table 6a** above). The ESC is then decreased at a constant rate of -0.01 μg/ml/min towards a new target ESC of zero μg/ml. The ART frequency is set to SEARCHING. As the ESC is gradually decreased, the patient regains responsiveness.

Upon the patient's ART "success", the DSM triggers transition **26** from the RAMP DOWN drug state to the LEVEL drug state (see **FIG. 7** and **Table 2a** above). The ART frequency is set to NORMAL. The patient appears to be stable and comfortable. At this point, the patient starts to receive painful stimuli. The clinician user observes that the patient appears to be in pain and her clinical judgment is corroborated by a measured increase in blood pressure and heart rate. The clinician decides to increase the ESC in anticipation of even more painful stimuli yet to come during the procedure.

The clinician enters a higher target ESC by pressing the "Propofol level" button or the like on the UI. At the ensuing prompt, the user presses the button labeled "3.0" to select

an ESC of 3.0 μg/ml. Because of the imminence of the very painful stimuli, the user selects Stat delivery by pressing the "Target level stat" button or the like and on the ensuing screen presses "yes" to confirm that she really wants to do this. The DSM initiates transition **28** from the LEVEL state to the STAT UP drug state (see **FIG. 8** and **Table 3a** above) while the ART frequency is set to FAST.

During the "stat-up" drug state, the ESC is increased as fast as possible while allowing no more than, for example, a 15% overshoot past the 3.0 μg/ml target ESC. The patient fails the ART test during the STAT UP ESC increase and the failed ART test is noted on the UI of the medical device to inform the user. However, the DSM does not take any action upon ART failure, consistent with the "clinician knows best" design philosophy of the DSM and keeps on increasing the ESC until the user-selected target is reached. The target is considered to be reached when the ESC first enters within 5% of the 3.0 μg/ml target (i.e., $2.85 \leq ESC \leq 3.15$). Upon the target being reached, the DSM initiates transition **29** from STAT UP to the LEVEL drug state while the ART frequency is set to searching (see **FIG. 8** and **Table 3a** above). In the LEVEL drug state, the ESC is maintained at the 3.0 μg/ml target ESC with an accuracy of ±5%. In the subsequent vigorous stimulation of the patient caused by the procedure, ART success occurs thereby vindicating the user's experience that the painful stimulus may counter the deeper sedation. The ART success triggers the system to change the ART frequency from FAST to NORMAL.

Once the most painful part of the procedure is over and as the painful stimuli become less intense, the patient starts to have late ART responses but the DSM takes no action. The clinician resets the target ESC to a lower value of 2.0 μg/ml in anticipation that the ESC of 3.0 μg/ml may be too high now that the stimuli are not as painful. To do so, the clinician presses the "Propofol level" button on the UI. At the ensuing screen, the user presses the button labeled "2.0" to select an ESC of 2.0 μg/ml followed by the "yes" button to confirm that she really wants to do this. The DSM initiates transition **30** from LEVEL to the STAT DOWN drug state (see **FIG. 9** and **Table 4a** above) while the ART frequency is left unchanged from its setting prior to the transition, i.e., NORMAL. During the STAT DOWN drug state, the drug infusion rate is set to zero initially to reach the lower ESC set point as fast as possible. Subsequently, when the ESC first reaches the 2.0 μg/ml target ±5% (i.e., $1.9 \leq ESC \leq 2.1$), the DSM initiates transition **32** from STAT DOWN to the LEVEL drug

state (see **FIG. 9** and **Table 4a** above). The ESC is maintained within ±5% of the 2.0 μg/ml target while the ART frequency remains unchanged at NORMAL.

As the procedure begins to wind down, the clinician becomes slightly concerned about the slow heart rate of the patient and decides to administer some atropine. Distracted by her pager going off, she instead grabs a syringe containing fentanyl, a respiratory depressant, and injects it, without realizing her mistake. The patient's breathing rate starts to slow down and a capnometer detects the decrease in respiratory rate and triggers a caution alarm when the breathing rate falls below the caution alarm level.

The caution alarm generates an audible and visual alarm on the medical device to alert the user while the DSM initiates transition **34** from the LEVEL drug state to the REDUCTION drug state (see **FIG. 10** and **Table 5a** above). The audible alarm helps the user to realize her mistake and she immediately administers naloxone (Narcan) to reverse the effect of the inadvertent fentanyl. As a result of entering the REDUCTION drug state, the target ESC is set to 80% of the current 2.0 μg/ml ESC (i.e., to 1.6 μg/ml), a 4-minute timer is started, and the ART frequency is set to searching.

Before the 4-minute timer elapses, the procedure is over. The user then presses the "Stop propofol" button on the UI. This action is equivalent to setting the target ESC to zero μg/ml thereby causing a transition **36** from the REDUCTION drug state to the OFF drug state (see **FIG. 10** and **Table 5a** above).

The drug delivery system of this invention may also have a recognition function integrated into the software algorithms for controlling the rate of drug administration to assure that certified drugs (i.e. known concentration and purity) and supplies (i.e. known calibration and quality) are utilized as a part of the system. This recognition system "reads" the identification of the drug or supply that is attached to the system for use therewith. If a non-certified drug or supply is attached, the system will not initiate the administration of sedative or analgesic drugs. Additionally, in related alternative embodiments, it is also feasible and desirable to package these items along with other supplies in a kit that has integrated into it the ability to be recognized and "read" by the system as quality certified. The system may also have a writing function integrated into the software algorithms in order to avoid re-use and/or contamination problems. The writing function has the ability to "write" to a tagged supply article that it has been contaminated through use and "label" or "code" it appropriately. For multiple use articles susceptible to contamination, the system

can provide a "rewrite" function, enabling the article to only be used again after it has been properly cleaned and quality certified for re-use. Further, it is possible for the write function to store information regarding the number of cycles of use that the article has experienced and to compare this information to the certified life cycle limit. An alarm can sound when the limit is being approached and, once the limit is met, the invention will not recognize the device until it is replaced. Such tagging and verification can be accomplished through various means, including through electronic and physical tags such as are disclosed in U.S. Patent Application Serial No. 10/151,255 filed May 21, 2002 and Application Serial No. 60/324,043, filed September 24, 2001, the entirety of each of which are herein incorporated by reference.

2002322761 29 Jul 2008

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A system for providing drug delivery to a patient, wherein said system comprises:

a user interface for accepting input from a user;

a drug delivery device that delivers an amount of drug to a patient;

two or more patient health monitors adapted so as to be coupled to a patient and generate a signal reflecting at least one health condition of the patient; and

a processor that integrates the user interface, drug delivery device, and patient health monitors according to a hierarchy of software algorithms such that the amount of drug delivered to the patient by the delivery device is modulated based on an input from the user and based on a signal generated by the patient health monitors without further user input, and wherein automated actions initiated by said processor will not increase overall drug levels automatically without an explicit request for a drug level by said user.

2. The system for providing drug delivery of claim 1, wherein said hierarchy of software algorithms include a drug state model and a flow control algorithm.

3. The system for providing drug delivery of claim 1 or 2, wherein said hierarchy of software algorithms further include an interface algorithm.

4. The system for providing drug delivery of claim 3, wherein said interface algorithm is one of a rate controlled infusion algorithm and a target controlled infusion algorithm that run in real time.

5. The system for providing drug delivery of claim 3, wherein said interface algorithm employs a pre-programmed infusion rate template.

6. The system for providing drug delivery of claim 3, 4 or 5, wherein said drug is at least one of a sedative, amnestic and analgesic drug.

7. The system for providing drug delivery of any one of claims 3 to 6, wherein monitoring sites for said patient health monitors include at least one of said patient's blood plasma, brain, central nervous system, neuromuscular junction, alveolar space, kidney, liver, pancreas, hypothalamus, heart tissue and baroreceptors.

8. The system for providing drug delivery of claim 3, 4, 5, 6 or 7 wherein said interface algorithm can produce different time profiles of a target drug concentration at different effect sites.

9. The system for providing drug delivery of claim 1, wherein one of said two or more patient health monitors is a consciousness monitor.

10. The system for providing drug delivery of claim 9, wherein said consciousness monitor is an automated responsiveness test monitor.

11. The system for providing drug delivery of claim 10, wherein:

(a) said two or more patient health monitors further comprise at least one of a pulse oximeter and non-invasive blood pressure monitor; or

(b) said two or more patient health monitors further comprise at least one of a capnometer and ECG.

12. The system for providing drug delivery of claim 11(b), wherein said system determines a drug level limit based on automated responsiveness test data received during a gradual drug increase initiated by the user, and wherein said drug level limit does not exceed the initial user input level.

13. The system for providing drug delivery of claim 12, wherein said automated responsiveness test query cycle frequency is set to FAST during said gradual drug increase.

14. The system for providing drug delivery of claim 10, wherein a warning alarm indicates one or more failed response to said automated responsiveness test during a linear drug increase initiated by the user.

15. The system for providing drug delivery of claim 14, wherein said automated responsiveness test query cycle frequency is set to FAST during said linear drug increase.

16. The system for providing drug delivery of claim 10, wherein said system decreases a drug infusion rate upon receiving one or more failed responses to said automated responsiveness test.

17. The system for providing drug delivery of claim 16, wherein system maintains said drug infusion rate upon receiving one or more successful responses to said automated responsiveness test during said decrease of drug infusion rate.

18. The system for providing drug delivery of claim 10, wherein said system will prevent initiation of drug delivery if said signal reflecting at least one health condition of the patient is below acceptable values.

19. The system for providing drug delivery of claim 18, wherein said signal reflecting at least one health condition of the patient is an EEG signal to assess the patient's consciousness.

20. The system for providing drug delivery of claim 9, wherein said hierarchy of software algorithms includes a drug state model and wherein said drug state model includes the following states: RAMP UP; RAMP DOWN; LEVEL; and OFF.

21. The system for providing drug delivery of claim 20, wherein:

(a) said drug state model further comprises the following states: STAT UP; STAT DOWN; and REDUCTION; or

(b) said RAMP UP state is the default state whenever said user enters a new target ESC which is greater than the current ESC; or

(c) wherein said RAMP DOWN state is the default state whenever said user enters a new target ESC which is less than the current ESC.

22. The system for providing drug delivery of claim 2, wherein said flow control algorithm manages said delivery device so that the drug is accurately delivered at a requested infusion rate.

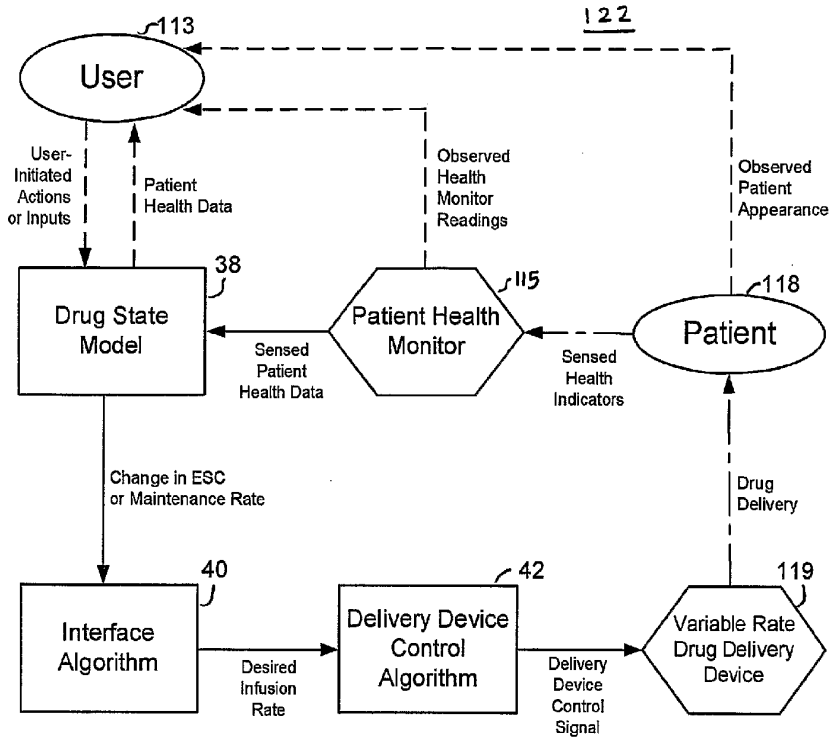
122
113
User
User-Initiated Actions or Inputs
Patient Health Data
Observed Health Monitor Readings
Observed Patient Appearance
38
Drug State Model
115
Patient Health Monitor
118
Patient
Sensed Patient Health Data
Sensed Health Indicators
Change in ESC or Maintenance Rate
Drug Delivery
40
Interface Algorithm
42
Delivery Device Control Algorithm
119
Variable Rate Drug Delivery Device
Desired Infusion Rate
Delivery Device Control Signal

FIG. 1

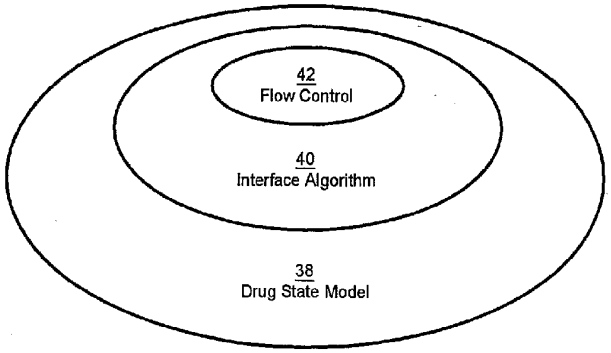
42
Flow Control
40
Interface Algorithm
38
Drug State Model

FIG. 2

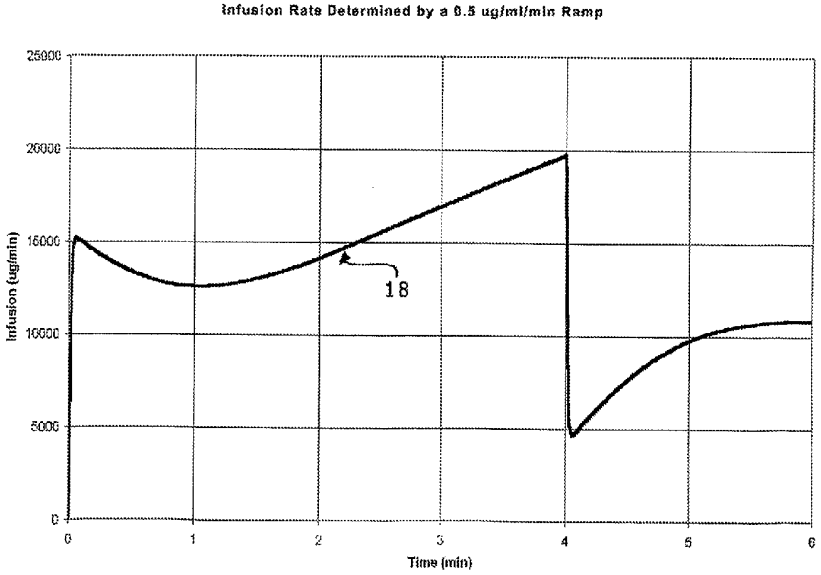
Infusion Rate Determined by a 0.5 ug/ml/min Ramp
25000
20000
15000
10000
5000
0
Infusion (ug/min)
18
0
1
2
3
4
5
6
Time (min)

FIG. 3

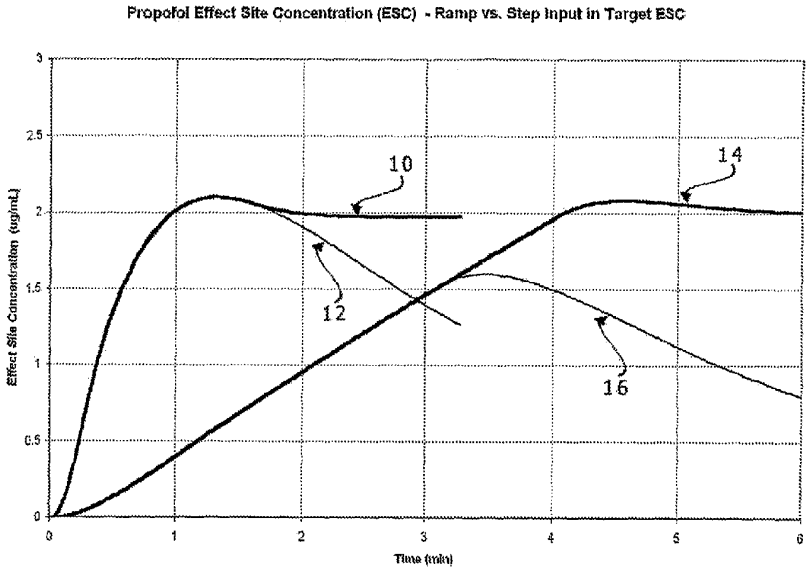
Propofol Effect Site Concentration (ESC) - Ramp vs. Step Input in Target ESC
Effect Site Concentration (ug/mL)
Time (min)
10
12
14
16
0
0.5
1
1.5
2
2.5
3
0
1
2
3
4
5
6

FIG. 4

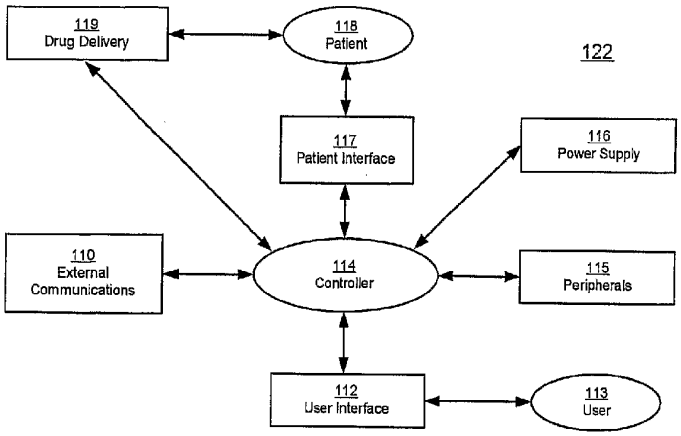
119
Drug Delivery
118
Patient
122
117
Patient Interface
116
Power Supply
110
External
Communications
114
Controller
115
Peripherals
112
User Interface
113
User

FIG. 5

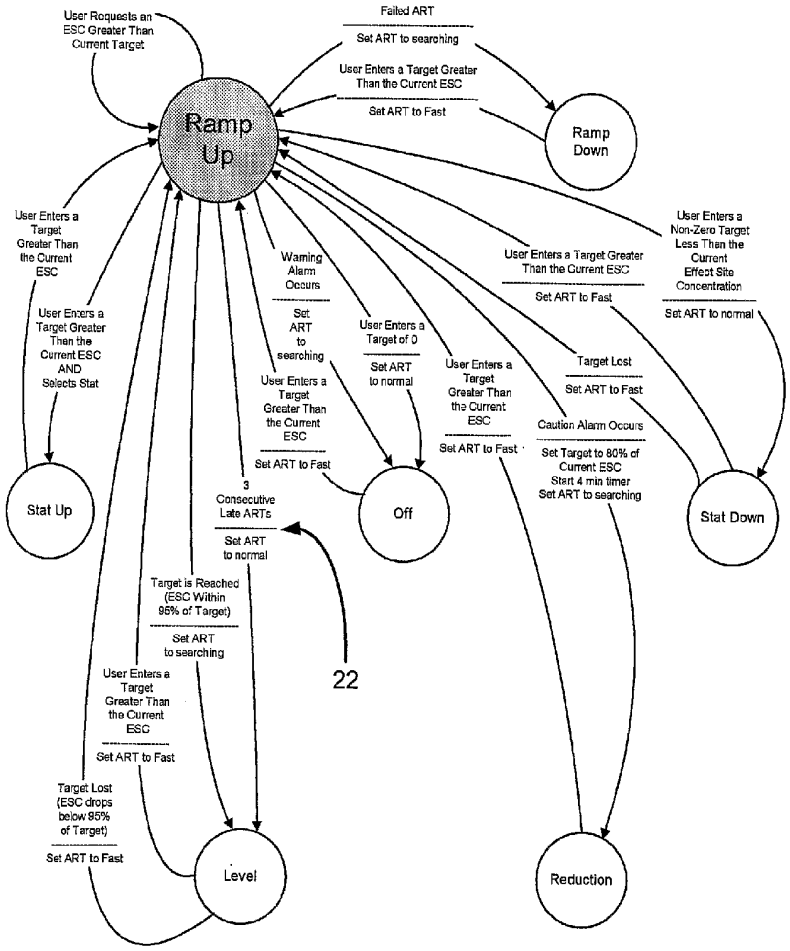
User Requests an ESC Greater Than Current Target
Failed ART
Set ART to searching
User Enters a Target Greater Than the Current ESC
Set ART to Fast
Ramp Up
Ramp Down
User Enters a Target Greater Than the Current ESC
Set ART to Fast
User Enters a Non-Zero Target Less Than the Current Effect Site Concentration
Set ART to normal
User Enters a Target Greater Than the Current ESC
Set ART to Fast
Warning Alarm Occurs
Set ART to searching
User Enters a Target of 0
Set ART to normal
Target Lost
Set ART to Fast
User Enters a Target Greater Than the Current ESC
Set ART to Fast
Caution Alarm Occurs
Set Target to 80% of Current ESC
Start 4 min timer
Set ART to searching
User Enters a Target Greater Than the Current ESC
Set ART to Fast
User Enters a Target Greater Than the Current ESC AND Selects Stat
Stat Up
User Enters a Target Greater Than the Current ESC
Set ART to Fast
Off
Stat Down
3 Consecutive Late ARTs
Set ART to normal
Target is Reached (ESC Within 95% of Target)
Set ART to searching
22
User Enters a Target Greater Than the Current ESC
Set ART to Fast
Target Lost (ESC drops below 95% of Target)
Set ART to Fast
Level
Reduction

FIG. 6

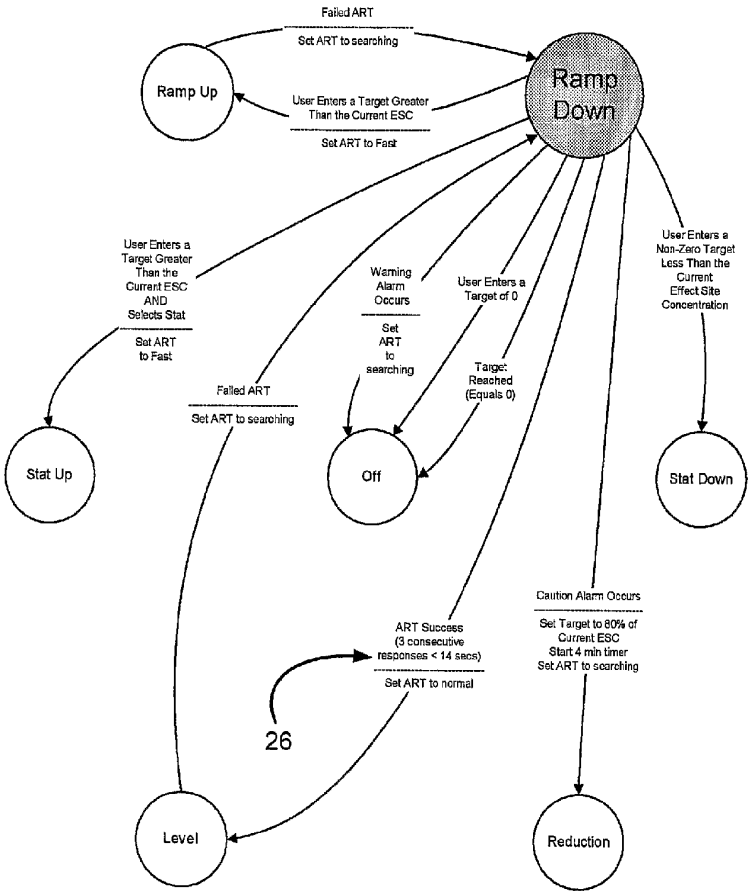
Failed ART
Set ART to searching
Ramp Up
User Enters a Target Greater Than the Current ESC
Set ART to Fast
Ramp Down
User Enters a Target Greater Than the Current ESC AND Selects Stat
Set ART to Fast
Warning Alarm Occurs
Set ART to searching
User Enters a Target of 0
Target Reached (Equals 0)
User Enters a Non-Zero Target Less Than the Current Effect Site Concentration
Failed ART
Set ART to searching
Stat Up
Off
Stat Down
Caution Alarm Occurs
Set Target to 80% of Current ESC
Start 4 min timer
Set ART to searching
ART Success (3 consecutive responses < 14 secs)
Set ART to normal
26
Level
Reduction

FIG. 7

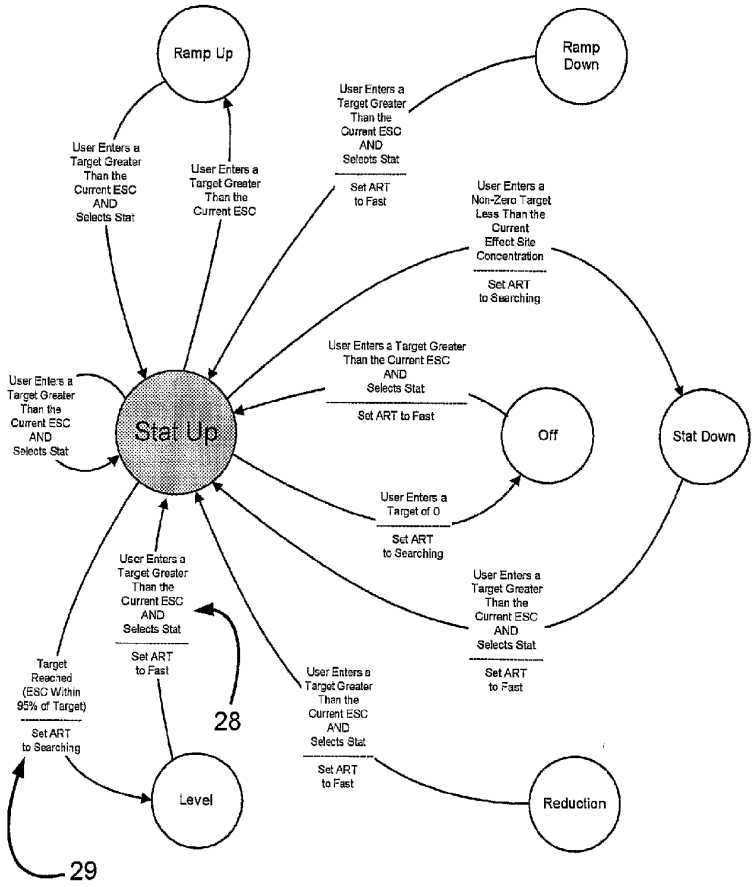
Ramp Up
Ramp Down
User Enters a Target Greater Than the Current ESC AND Selects Stat
Set ART to Fast
User Enters a Target Greater Than the Current ESC
User Enters a Target Greater Than the Current ESC AND Selects Stat
User Enters a Non-Zero Target Less Than the Current Effect Site Concentration
Set ART to Searching
User Enters a Target Greater Than the Current ESC AND Selects Stat
Set ART to Fast
Stat Up
Off
Stat Down
User Enters a Target of 0
Set ART to Searching
User Enters a Target Greater Than the Current ESC AND Selects Stat
Set ART to Fast
User Enters a Target Greater Than the Current ESC AND Selects Stat
Set ART to Fast
28
Target Reached (ESC Within 95% of Target)
Set ART to Searching
User Enters a Target Greater Than the Current ESC AND Selects Stat
Set ART to Fast
Level
Reduction
29

FIG. 8

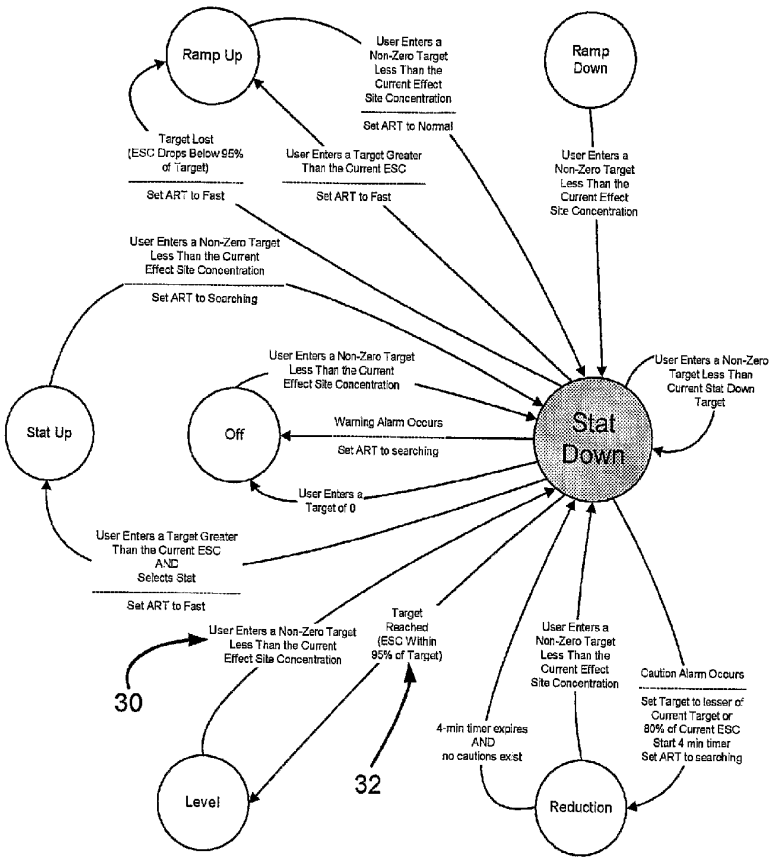
Ramp Up
User Enters a Non-Zero Target Less Than the Current Effect Site Concentration
Set ART to Normal
Ramp Down
Target Lost (ESC Drops Below 95% of Target)
Set ART to Fast
User Enters a Target Greater Than the Current ESC
Set ART to Fast
User Enters a Non-Zero Target Less Than the Current Effect Site Concentration
User Enters a Non-Zero Target Less Than the Current Effect Site Concentration
Set ART to Searching
User Enters a Non-Zero Target Less Than the Current Effect Site Concentration
User Enters a Non-Zero Target Less Than Current Stat Down Target
Stat Up
Off
Warning Alarm Occurs
Set ART to searching
Stat Down
User Enters a Target of 0
User Enters a Target Greater Than the Current ESC AND Selects Stat
Set ART to Fast
User Enters a Non-Zero Target Less Than the Current Effect Site Concentration
Target Reached (ESC Within 95% of Target)
User Enters a Non-Zero Target Less Than the Current Effect Site Concentration
Caution Alarm Occurs
Set Target to lesser of Current Target or 80% of Current ESC Start 4 min timer Set ART to searching
30
4-min timer expires AND no cautions exist
32
Level
Reduction

FIG. 9

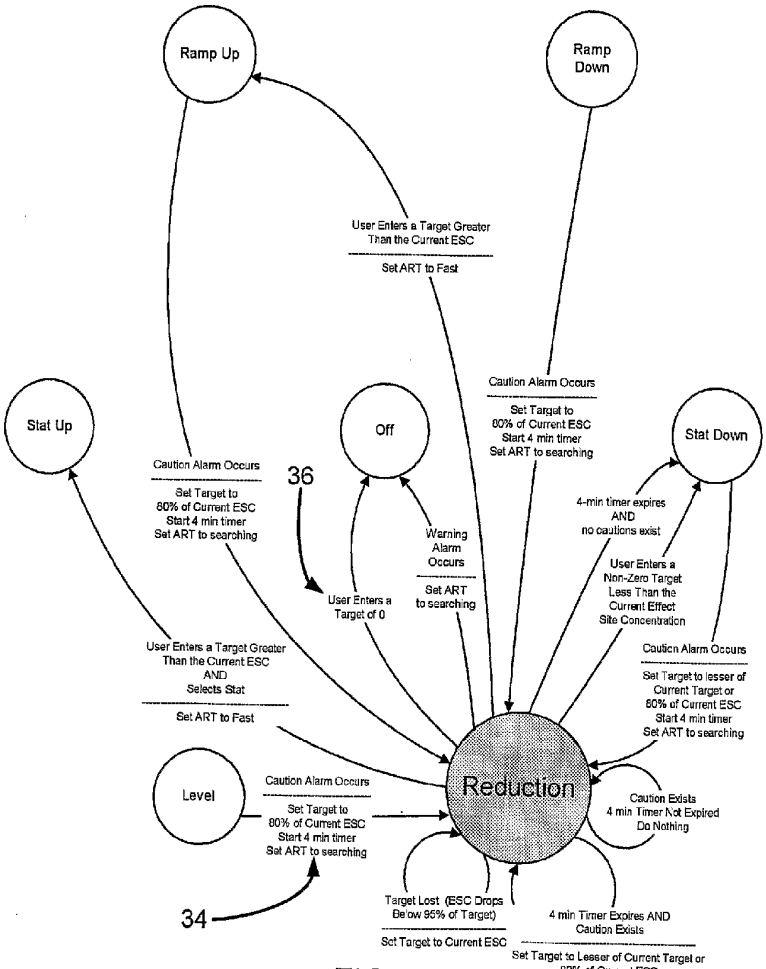
Ramp Up
Ramp Down
User Enters a Target Greater Than the Current ESC
Set ART to Fast
Caution Alarm Occurs
Set Target to 80% of Current ESC
Start 4 min timer
Set ART to searching
Stat Up
Off
Stat Down
Caution Alarm Occurs
Set Target to 80% of Current ESC
Start 4 min timer
Set ART to searching
36
4-min timer expires AND no cautions exist
Warning Alarm Occurs
Set ART to searching
User Enters a Target of 0
User Enters a Non-Zero Target Less Than the Current Effect Site Concentration
User Enters a Target Greater Than the Current ESC AND Selects Stat
Set ART to Fast
Caution Alarm Occurs
Set Target to lesser of Current Target or 80% of Current ESC
Start 4 min timer
Set ART to searching
Level
Caution Alarm Occurs
Set Target to 80% of Current ESC
Start 4 min timer
Set ART to searching
Reduction
Caution Exists 4 min Timer Not Expired Do Nothing
34
Target Lost (ESC Drops Below 95% of Target)
Set Target to Current ESC
4 min Timer Expires AND Caution Exists
Set Target to Lesser of Current Target or 80% of Current ESC
Restart 4 min timer

FIG. 10

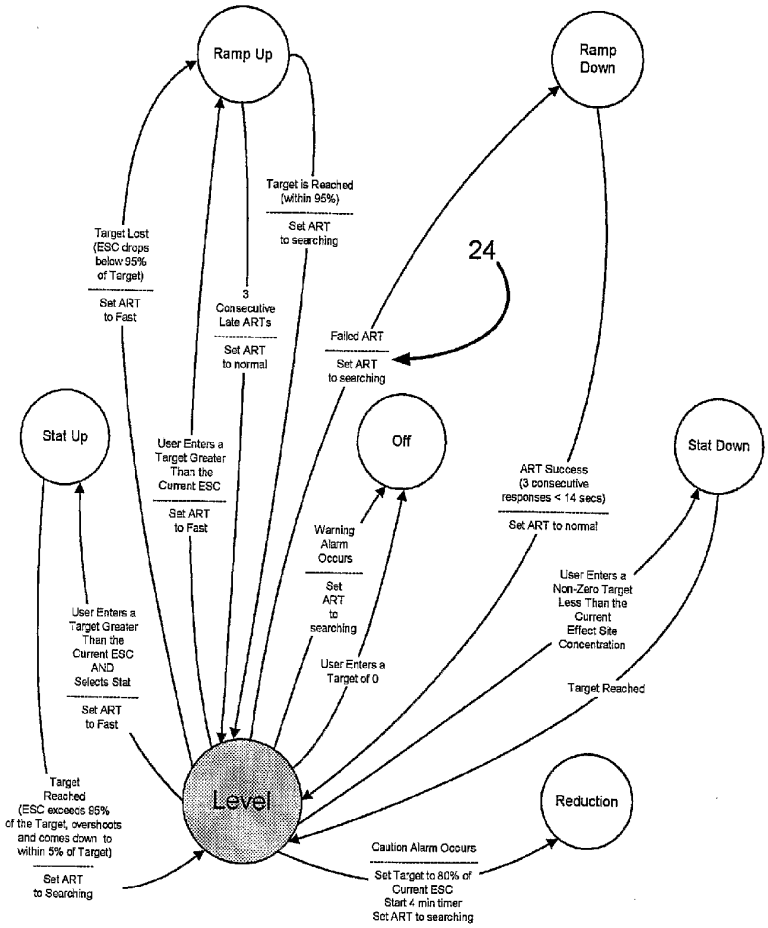
Ramp Up
Ramp Down
Target is Reached (within 95%)
Set ART to searching
Target Lost (ESC drops below 95% of Target)
Set ART to Fast
3 Consecutive Late ARTs
Set ART to normal
24
Failed ART
Set ART to searching
Stat Up
Off
Stat Down
User Enters a Target Greater Than the Current ESC
Set ART to Fast
ART Success (3 consecutive responses < 14 secs)
Set ART to normal
Warning Alarm Occurs
Set ART to searching
User Enters a Non-Zero Target Less Than the Current Effect Site Concentration
User Enters a Target Greater Than the Current ESC AND Selects Stat
Set ART to Fast
User Enters a Target of 0
Target Reached
Level
Reduction
Target Reached (ESC exceeds 95% of the Target, overshoots and comes down to within 5% of Target)
Set ART to Searching
Caution Alarm Occurs
Set Target to 80% of Current ESC
Start 4 min timer
Set ART to searching

FIG. 11

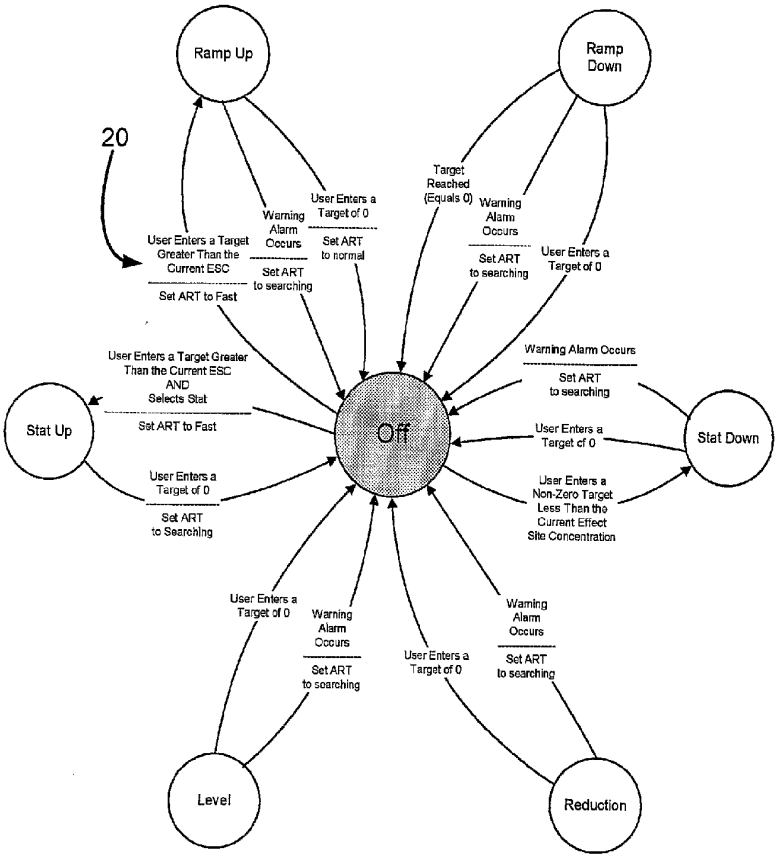
Ramp Up
Ramp Down
20
Target Reached (Equals 0)
Warning Alarm Occurs
Set ART to searching
User Enters a Target of 0
User Enters a Target of 0
Warning Alarm Occurs
Set ART to normal
User Enters a Target Greater Than the Current ESC
Set ART to Fast
Warning Alarm Occurs
Set ART to searching
User Enters a Target Greater Than the Current ESC AND Selects Stat
Set ART to Fast
Warning Alarm Occurs
Set ART to searching
Stat Up
Off
Stat Down
User Enters a Target of 0
User Enters a Target of 0
Set ART to Searching
User Enters a Non-Zero Target Less Than the Current Effect Site Concentration
User Enters a Target of 0
Warning Alarm Occurs
Set ART to searching
User Enters a Target of 0
Warning Alarm Occurs
Set ART to searching
Level
Reduction

FIG. 12

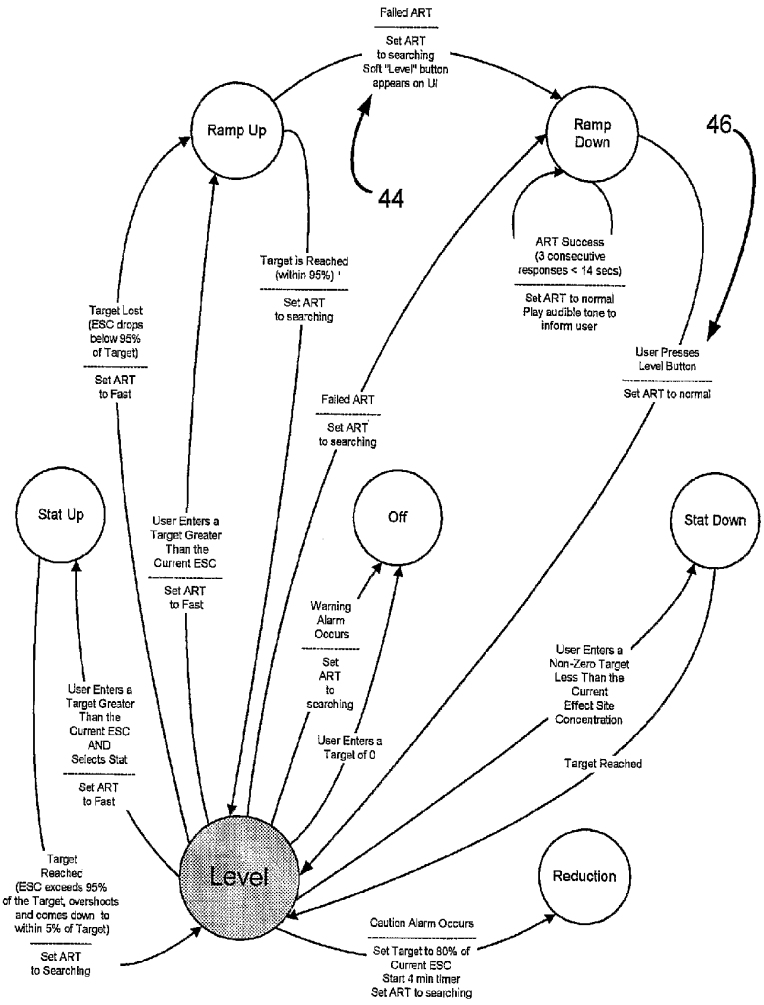
Failed ART
Set ART to searching
Soft "Level" button appears on UI
Ramp Up
Ramp Down
44
46
Target is Reached (within 95%) '
Set ART to searching
ART Success (3 consecutive responses < 14 secs)
Set ART to normal
Play audible tone to inform user
Target Lost (ESC drops below 95% of Target)
Set ART to Fast
User Presses Level Button
Set ART to normal
Failed ART
Set ART to searching
Stat Up
Off
Stat Down
User Enters a Target Greater Than the Current ESC
Set ART to Fast
Warning Alarm Occurs
Set ART to searching
User Enters a Non-Zero Target Less Than the Current Effect Site Concentration
User Enters a Target Greater Than the Current ESC AND Selects Stat
Set ART to Fast
User Enters a Target of 0
Target Reached
Level
Reduction
Target Reachec (ESC exceeds 95% of the Target, overshoots and comes down to within 5% of Target)
Set ART to Searching
Caution Alarm Occurs
Set Target to 80% of Current ESC
Start 4 min timer
Set ART to searching

FIG. 13