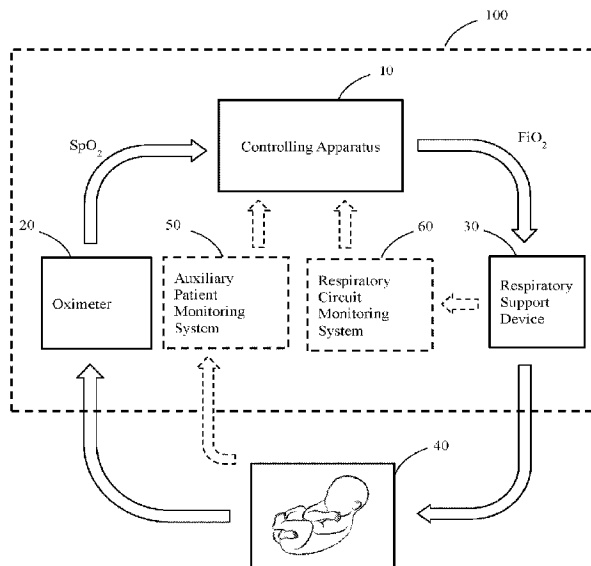




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(54) Titre : PROCEDE, APPAREIL ET SYSTEME POUR COMMANDER AUTOMATIQUEMENT LA DISTRIBUTION D'OXYGENE INSPIRE
(54) Title: METHOD, APPARATUS AND SYSTEM FOR AUTOMATICALLY CONTROLLING INSPIRED OXYGEN DELIVERY



(57) **Abrégé/Abstract:**

Provided herein is a method for automatically controlling inspired oxygen delivery, including: receiving signals representing a plurality of input oxygen saturation (SpO_2) values for a patient; generating control values based on the input SpO_2 values and a target SpO_2 value; and generating output inspired oxygen concentration (FiO_2) values based on the control values and reference inspired oxygen concentration ($rFiO_2$) values; wherein the control values include: immediate control values, generated based on the input SpO_2 values, the target SpO_2 value, and an immediate gain coefficient; accumulation control values, generated based on the input SpO_2 values, the target SpO_2 value, and an accumulation gain coefficient; and predictive control values, generated based on the input SpO_2 values, the target SpO_2 value, and a predictive gain coefficient; wherein the immediate gain coefficient is determined based on the $rFiO_2$ value; and wherein a non-linear compensation weighting is applied to the accumulation control value based on a predetermined non-linear relationship between partial pressure of arterial oxygen (PaO_2) and SpO_2 .

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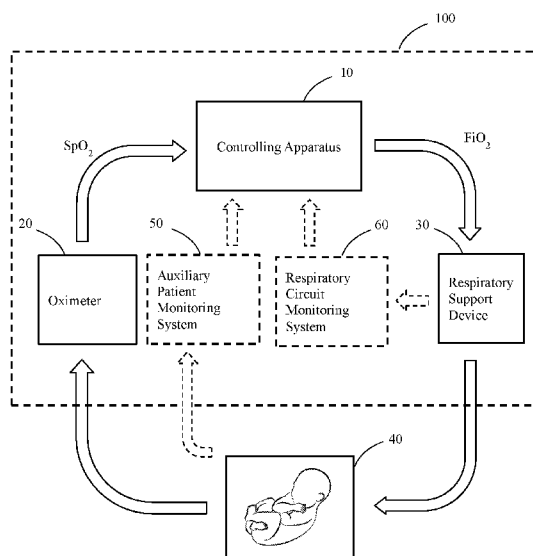


Fig. 1

(57) Abstract: Provided herein is a method for automatically controlling inspired oxygen delivery, including: receiving signals representing a plurality of input oxygen saturation (SpO_2) values for a patient; generating control values based on the input SpO_2 values and a target SpO_2 value; and generating output inspired oxygen concentration (FiO_2) values based on the control values and reference inspired oxygen concentration ($rFiO_2$) values; wherein the control values include: immediate control values, generated based on the input SpO_2 values, the target SpO_2 value, and an immediate gain coefficient; accumulation control values, generated based on the input SpO_2 values, the target SpO_2 value, and an accumulation gain coefficient; and predictive control values, generated based on the input SpO_2 values, the target SpO_2 value, and a predictive gain coefficient; wherein the immediate gain coefficient is determined based on the $rFiO_2$ value; and wherein a non-linear compensation weighting is applied to the accumulation control value based on a predetermined non-linear relationship between partial pressure of arterial oxygen (PaO_2) and SpO_2 .

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METHOD, APPARATUS AND SYSTEM FOR AUTOMATICALLY CONTROLLING INSPIRED OXYGEN DELIVERY

TECHNICAL FIELD

[001] The present invention generally relates to a method, an apparatus and a system for automatically controlling inspired oxygen delivery, e.g., a method, an apparatus and a system for automatically controlling inspired oxygen concentration to maintain oxygen saturation in a target range.

BACKGROUND

[002] Supplemental oxygen therapy can be used for a variety of purposes in both chronic and acute patient care. For example, it plays a pivotal role in management of newborn infants with respiratory dysfunction. For preterm infants, studies have shown that there is a connection between unremitting hypoxia and an increase in mortality. Further, it has also been observed that excess oxygen delivery is associated with adverse outcomes, in particular retinopathy of prematurity. Hence, there is a need to continuously adjust the fraction of inspired oxygen (FiO_2) to maintain oxygen saturation (SpO_2) in an acceptable target range so as to avoid the extremes of oxygenation. The response of SpO_2 to changes in FiO_2 is referred to as “system gain”, where the “system” is the patient.

[003] Currently, striking a balance in delivering oxygen to preterm infants is largely in the hands of bedside caregivers, who manually adjust FiO_2 in an effort to maintain oxygen saturation SpO_2 in a target range. Unfortunately such manual control of FiO_2 is imprecise, with infants spending a considerable amount of time with SpO_2 outside the target ranges.

[004] Automated adjustment of FiO_2 may afford more time in the target range than manual control, and considerably reduce the proportion of iatrogenic hyperoxia and severe

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hypoxia. However, there are significant challenges in applying automation of oxygen delivery to preterm infants with lung dysfunction. A first challenge is to improve the effectiveness in SpO_2 targeting and to avoid time in and episodes of, hypoxia and hyperoxia. A second challenge for automated control of oxygen delivery is that the main determinants of oxygenation are intermingled with endless variety in premature infants, and contribute fundamentally different responses to changes in FiO_2 , thus an automated controller with a uniform and unchanging response to a given SpO_2 perturbation may be incapable of serving the needs of all individuals. A third challenge is that system gain may change over time.

[005] It is desired to address or ameliorate one or more disadvantages or limitations associated with the prior art, or to at least provide a useful alternative.

[006] The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

SUMMARY

[007] In accordance with an aspect of the present invention there is provided a method for automatically controlling inspired oxygen delivery, including:

- receiving signals representing a plurality of input oxygen saturation (SpO_2) values for a patient;

- generating control values based on the input SpO_2 values and a target SpO_2 value; and

- generating output inspired oxygen concentration (FiO_2) values based on the control values and reference inspired oxygen concentration (rFiO_2) values;

- wherein the control values include:

- immediate control values, generated based on the input SpO_2 values, the target SpO_2 value, and an immediate gain coefficient;

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accumulation control values, generated based on the input SpO_2 values, the target SpO_2 value, and an accumulation gain coefficient; and

predictive control values, generated based on the input SpO_2 values, the target SpO_2 value, and a predictive gain coefficient;

wherein the immediate control valves are determined based on the rFiO_2 value; and

wherein a non-linear compensation weighting is applied to the accumulation control value based on a predetermined non-linear relationship between partial pressure of arterial oxygen (PaO_2) and SpO_2 .

[008] In accordance with another aspect of the present invention there is provided an apparatus for automatically controlling inspired oxygen delivery, including:

an input unit, receiving signals representing a plurality of input oxygen saturation (SpO_2) values for a patient;

a memory, recording the received input SpO_2 values;

a controller, determining output inspired oxygen concentration (FiO_2) values based on the input SpO_2 values; and

an output unit, outputting the determined output FiO_2 values;

wherein the controller:

generates control values based on the input SpO_2 values and a target SpO_2 value; and

generates the output inspired oxygen concentration (FiO_2) values based on the control values and reference inspired oxygen concentration (rFiO_2) values;

wherein the control values include:

immediate control values, generated based on the input SpO_2 values, the target SpO_2

value, and an immediate gain coefficient;

accumulation control values, generated based on the input SpO_2 values, the target SpO_2 value, and an accumulation gain coefficient; and

predictive control values, generated based on the input SpO_2 values, the target SpO_2 value, and a predictive gain coefficient;

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wherein the immediate control valves are determined based on the $r\text{FiO}_2$ value; and

wherein a non-linear compensation weighting is applied to the accumulation control value based on a predetermined non-linear relationship between partial pressure of arterial oxygen (PaO_2) and SpO_2 .

[009] In accordance with another aspect of the present invention there is provided a system for automatically controlling inspired oxygen delivery, including:

one or a plurality of oxygen saturation monitoring devices, and one or a plurality of inspired oxygen control devices;

a controlling device; and

a network, enabling communication between the one or a plurality of oxygen saturation monitoring devices and the controlling device, and communication between the one or a plurality of inspired oxygen control devices and the controlling device,

wherein the controlling device controls inspired oxygen delivery by:

receiving signals representing a plurality of input oxygen saturation (SpO_2) values for a patient from each of the one or a plurality of oxygen saturation monitoring devices through the network;

generating control values based on the input SpO_2 values and a target SpO_2 value;

generating output inspired oxygen concentration (FiO_2) values based on the control values and reference inspired oxygen concentration ($r\text{FiO}_2$) values;

sending the determined output FiO_2 values to a corresponding inspired oxygen control device through the network;

wherein the control values include:

immediate control values, generated based on the input SpO_2 values, the target SpO_2 value, and an immediate gain coefficient;

accumulation control values, generated based on the input SpO_2 values, the target SpO_2 value, and an accumulation gain coefficient; and

predictive control values, generated based on the input SpO_2 values, the target SpO_2 value, and a predictive gain coefficient;

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wherein the immediate control valves are determined based on the $r\text{FiO}_2$ value; and

wherein a non-linear compensation weighting is applied to the accumulation control value based on a predetermined non-linear relationship between partial pressure of arterial oxygen (PaO_2) and SpO_2 .

[010] In accordance with an aspect of the present invention there is provided a method for automatically controlling inspired oxygen delivery, including:

receiving signals representing a plurality of input oxygen saturation (SpO_2) values for a patient;

generating control values based on the input SpO_2 values and a target SpO_2 value; and

generating output inspired oxygen concentration (FiO_2) values based on the control values and reference inspired oxygen concentration ($r\text{FiO}_2$) values;

wherein the control values include:

immediate control values, generated based on the input SpO_2 values, the target SpO_2 value, and an immediate gain coefficient;

accumulation control values, generated based on the input SpO_2 values, the target SpO_2 value, and an accumulation gain coefficient; and

predictive control values, generated based on the input SpO_2 values, the target SpO_2 value, and a predictive gain coefficient.

BRIEF DESCRIPTION OF THE DRAWINGS

[011] Some embodiments of the present invention are hereinafter described, by way of example only, with reference to the accompanying drawings, in which:

[012] Fig. 1 is a block diagram of an inspired oxygen delivery system;

[013] Fig. 2 is a block diagram of components in the inspired oxygen delivery system;

[014] Fig. 3 is a flow chart depicting a process of generating PID terms, i.e., generating the proportional term, the integral term and the derivative term;

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[015] Fig. 4 is a flow chart depicting a process of modifying K_p based on the performance evaluation result;

[016] Fig. 5 is a flow chart depicting a process of modifying the value of $rFiO_2$;

[017] Fig. 6 is a flow chart depicting a process of determining the perfusion index value;

[018] Fig. 7 is a flow chart depicting a process of the hierarchical SpO_2 validation procedure;

[019] Fig. 8 is a flow chart depicting a process of determining the output FiO_2 value based on the validity of SpO_2 ;

[020] Fig. 9 is a flow chart depicting a process of switching between the manual mode and the automatic control mode;

[021] Fig. 10 is a flow chart depicting a process of controlling and resetting alarms;

[022] Fig. 11 is a diagram of a user interface of the oxygen delivery system apparatus;

[023] Fig. 12 is a flow chart depicting a general control process of the method for automatically controlling inspired oxygen delivery;

[024] Fig. 13 is a flow chart depicting a process of processing inputs;

[025] Fig. 14 is a flow chart depicting a process of reading inputs;

[026] Fig. 15 is a flow chart depicting a process of validating inputs;

[027] Fig. 16 is a flow chart depicting a process of validation of input bounds;

[028] Fig. 17 is a flow chart depicting a process of the automated control;

[029] Fig. 18 is a flow chart depicting a periodic adaptive process;

[030] Fig. 19 is a graph of a relationship between PaO_2 error and unitary SpO_2 error;

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[031] Fig. 20 is a block diagram of an inspired oxygen delivery system used in the second exemplary experiment;

[032] Figs. 21A and 21B are graphs of two hour recordings from the same infant during manual and automated control recorded in the second exemplary experiment;

[033] Fig. 22 is a graph of frequency histograms of pooled SpO₂ data according to the results of the second exemplary experiment; and

[034] Fig. 23 is a graph comparing best manual control epoch with automated control according to the results of the second exemplary experiment.

DETAILED DESCRIPTION

[035] Described herein is an inspired oxygen delivery system 100 which performs a method of automatically controlling inspired oxygen delivery to a patient (e.g., a human infant).

[036] The described system (and method) may provide one or more advantages compared to pre-existing systems and methods. First, the described system may efficiently target the desired SpO₂ range and avoid the extremes of oxygenation. Second, the described system may respond rapidly to SpO₂ deviations, e.g., due to vicissitudes of the V/Q ratio and shunt within the lung. Third, the described system may compensate for non-linearities in the PaO₂-SpO₂ relationship (where PaO₂ means partial pressure of arterial oxygen—e.g., PaO₂ changing by only 1-2 mm Hg for each 1% step change in SpO₂ on the linear portion of the sigmoid curve, but by more than 20 mm Hg further towards the asymptote). Fourth, the described system can respond differently for different individuals to compensate for individuals' variable SpO₂ responses to FiO₂ adjustments, corresponding to different individuals' mixes of shift in the FiO₂-SpO₂ curve (where a rightward shift corresponds to a decreasing ventilation-perfusion (V/Q) ratio) and shunt (the proportion or fraction of blood pumped to the body without any oxygen added to it within the lungs). Fifth, the described system may adjust its gain based on performance metrics.

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[037] As shown in Fig. 1, the system 100 includes a controlling apparatus 10, an oximeter 20 and a respiratory support device 30.

[038] The controlling apparatus 10 is configured for automatically controlling inspired oxygen delivery.

[039] The oximeter 20 measures arterial oxygen saturation (SpO_2) of a patient 40, and sends an output signal representing SpO_2 values to the controlling apparatus 10. The SpO_2 value represented by the output signal of the oximeter 20 is also referred to as an “input SpO_2 value” from the perspective of the controlling apparatus 10.

[040] The oximeter 20 can have an analogue or digital data output.

[041] Based on the input SpO_2 values from the oximeter 20, the controlling apparatus 10 determines an output inspired oxygen concentration (FiO_2) value, and outputs a FiO_2 signal representing the determined output FiO_2 value.

[042] The output FiO_2 signal from the controlling apparatus 10 is transmitted to the respiratory support device 30. The respiratory support device 30 is a system capable of responding to an FiO_2 input, i.e., the respiratory support system can receive and execute a desired value of FiO_2 . The respiratory support device 30 can be in the form of an air-oxygen blender, a mechanical ventilator, a continuous positive airway pressure (CPAP) driver, or a flow generator for high flow nasal cannula support or low flow oxygen delivery.

[043] The respiratory support device 30 delivers the blended gas (the fractionally inspired oxygen with the determined FiO_2) to the patient 40. The inspired oxygen delivery system 100 may further include an auxiliary patient monitoring system 50, and a respiratory circuit monitoring system 60.

[044] The auxiliary patient monitoring system 50 monitors the patient 40 and outputs signals representing the patient's condition. The auxiliary patient monitoring system 50 may include monitoring devices in the form of a cardiorespiratory monitor or a respiration monitor.

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[045] The respiratory circuit monitoring system 60 monitors the output of the respiratory support device 30, i.e., the fraction of inspired oxygen to be delivered to the patient. It outputs signals representing the monitoring results. The respiratory circuit monitoring system 60 may include devices in the form of an oxygen analyser and additionally a pressure transducer.

[046] The outputs from the auxiliary patient monitoring system 50 and the respiratory circuit monitoring system 60 are transmitted to the controlling apparatus 10. The controlling apparatus 10 may determine the output FiO_2 value based on the input SpO_2 and the signals transmitted from the auxiliary patient monitoring system 50 and the respiratory circuit monitoring system 60.

[047] As shown in Fig.2, the controlling apparatus 10 may be a stand-alone device. The controlling apparatus 10 may include: a controller 11, which determines the output FiO_2 value based on the input SpO_2 values; and an input/output interface 12, which receives signals representing input SpO_2 values and outputs signals representing the determined output FiO_2 values. The input/output interface 12 may also received inputs from the auxiliary patient monitoring system 50 and/or the respiratory circuit monitoring system 60.

[048] The controller 11 is in the form of an electronic control apparatus, including one or more digital microcontrollers or microprocessors that perform or execute steps of the method described herein. The controller 11 may include one or more application-specific integrated circuits and/or field-programmable gate arrays that are configured to perform the method steps.

[049] The controlling apparatus 10 may further include a memory 13 which records the received input SpO_2 values. The memory 13 may store machine-readable instructions that define the method steps described herein, and are read and executed by the controller 11 to perform one or more of the method steps.

[050] The controlling apparatus 10 may also include a user-interface display 14, which displays a user interface showing various information to a user (e.g., a bedside

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caregiver) and receives instructions inputted by the user through the user-interface. The received user inputs are transmitted to the controller 11.

[051] The controlling apparatus 10 may further include a data acquisition device (DAQ) 15, which acquires signals/data transmitted from other components of the system 100.

[052] The oximeter 20 may include a pulse oximeter 21. The pulse oximeter 21 measures SpO₂ of a patient 40, and sends an output signal representing SpO₂ values to the controlling apparatus 10. The pulse oximeter 21 may further measure: (1) a perfusion index, being a metric of oximetry waveform pulsatility, with low values potentially associated with spurious SpO₂ values; and (2) a SpO₂ plethysmographic waveform (“Pleth”). An output signal representing the perfusion index and an output signal representing a SpO₂ plethysmographic waveform are sent to the controlling apparatus 10 from the pulse oximeter 21. The pulse oximeter 21 may further measure a heart rate derived from the SpO₂ plethysmographic waveform (HR_{pleth}) and send it to the controlling apparatus 10.

[053] The respiratory support device 30 may include an air-oxygen blender 31. From the controlling apparatus 10, a signal representing the determined output FiO₂ value may be routed to a servomotor 32 custom-mounted on the air-oxygen blender 31, which allows automatic rotation of the blender FiO₂ selection dial via a ringed gearing mechanism. The servomotor 32 and the gearing system may have sufficient torque and precision to allow small adjustments to FiO₂ (e.g., minimum $\pm 0.5\%$) to be made accurately and repeatedly. The servomotor 32 may also have a low holding torque such that the blender dial can still be turned manually; such manual intervention may be detected by a position sensor and resulted in a switch to a manual mode in which FiO₂ was no longer under automated control.

[054] At the beginning of the automatic control of FiO₂, the servomotor calibration may be checked and if necessary altered. The servomotor calibration may also be checked and/or altered periodically during prolonged usage if necessary.

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[055] The controlling apparatus 10 may confirm that changes in the output FiO_2 value are executed correctly by the servomotor 32, using feedback signals from the servomotor 32 of the position of the FiO_2 selector dial (servo FiO_2).

[056] As shown in Fig.2, the auxiliary patient monitoring system 50 may include a respiration monitor 51 and a cardiorespiratory monitor 52. The respiration monitor 51 monitors the respiration of the patient 40 and outputs a signal representing a respiration rate of the patient 40. The cardiorespiratory monitor 52 monitors the electrocardiogram (ECG) of the patient 40 and outputs a signal representing a heart rate of the patient 40 derived from the electrocardiographic monitoring (HR_{ecg}). Outputs from the respiration monitor 51 and the cardiorespiratory monitor 52 are transmitted to the controlling apparatus 10.

[057] The respiratory circuit monitoring system 60 may include an oxygen analyser 61 and a pressure transducer 62. The oxygen analyser 61 monitors the output of the air-oxygen blender 31, i.e., the blended gas to be delivered to the patient 40, and outputs a signal representing the measured FiO_2 to the controlling apparatus 10. The pressure transducer 62 transduces a pressure in the inspiratory limb of the CPAP circuit, and outputs a signal representing the CPAP circuit pressure to the controlling apparatus 10.

[058] Confirmation that changes in the output FiO_2 value sent from the controlling apparatus 10 are executed correctly by the automated air-oxygen blender 31 may also be based on measurement of output FiO_2 from the air-oxygen blender 31, using the oxygen analyser 61. Information from the oxygen analyser 61 (measured FiO_2) may be digitised from an analogue signal, and may further be offset by a selected flow-time delay (which can be 5 seconds or any other suitable values, and can be selected or determined at the time of system set-up) to compensate for the time for gas flow and equilibration downstream from the blender.

[059] Based on these input signals from the oximeter 20, the auxiliary patient monitoring system 50 and the inspired oxygen monitoring system 60, the controlling apparatus 10 determines the output FiO_2 value.

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[060] Inputs from the oximeter 20, the auxiliary patient monitoring system 50 and the respiratory circuit monitoring system 60 other than the input SpO_2 are referred to as “additional inputs”. As described hereinbefore, the additional inputs may include measured FiO_2 , CPAP circuit pressure, respiration rate, perfusion index, pleth waveform, HR_{pleth} , and HR_{ecg} .

[061] The controlling apparatus 10 may further include an alarm unit, controlled by the controller 11, for triggering an audible and/or visible alarm. For example, in the event of either servo FiO_2 or measured FiO_2 deviating from the output FiO_2 value beyond tolerance limits (1 and 2%, respectively), an alarm may be triggered. In one example, a high level alarm and a change to manual mode may occur for deviations of 5 and 10%, respectively.

[062] Further, alternatively, the controlling apparatus 10 may not be a stand-alone device, but mounted or integrated in another device. For example, the controlling apparatus 10 may be integrated in the oximeter 20, or integrated in the respiratory support device 30.

[063] As described in further detail hereinafter, the controller 11 may include a core component in the form of a feedback controller that is adapted and configured for automated oxygen control for the preterm infant. The feedback controller includes mechanical, digital and/or electronic circuits to generate output control signals based on input control signals, and internal control values (also referred to as “terms”) in the feedback controller. The internal control values may include a summation of:

- (a) an immediate control value that adjusts the output based on the current value of the input;
- (b) an accumulation control value that adjusts the output based on previous or past values of the input; and
- (c) a predictive control value that adjusts the output based on predicted future values of the input.

[064] The method for automatically controlling inspired oxygen delivery includes:

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- (a) receiving signals representing a plurality of input oxygen saturation (SpO_2) values for a patient;
- (b) generating control values based on the input SpO_2 values and a target SpO_2 value; and
- (c) generating output inspired oxygen concentration (FiO_2) values based on the control values and reference inspired oxygen concentration (rFiO_2) values.

[065] The control value may include an immediate control value associated with a comparison of the current input SpO_2 value and the target SpO_2 value. The immediate control value may be generated based on the input SpO_2 values, the target SpO_2 value, and an immediate gain coefficient.

[066] The control value may further include an accumulation control value generated based on an accumulation relationship between the input SpO_2 values and the target SpO_2 value. The accumulation relationship between the input SpO_2 values and the target SpO_2 value may be an accumulation of differences between the input SpO_2 values and the target SpO_2 value. The accumulation control value may be generated based on the input SpO_2 values, the target SpO_2 value, and adjusted by an accumulation gain coefficient.

[067] The control value may further include generating a predictive control value generated based on a predictive relationship between the input SpO_2 values and the target SpO_2 value. The predictive relationship may be a time derivative of differences between the input SpO_2 values and the target SpO_2 value. The predictive control value may be generated based on the input SpO_2 values, the target SpO_2 value, and a predictive gain coefficient.

[068] The feedback controller generates the control value based on the immediate control value, the accumulation control value and the predictive control value, and the rFiO_2 value, and determines the output FiO_2 value.

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[069] In the feedback controller, an error (e) is defined as the deviation of the process signal from a set-point. The feedback controller may be a proportional-integral-derivative (PID) controller.

[070] The PID feedback controller may be enhanced by a number of methods. A measure of severity of lung dysfunction may be obtained periodically by automated assessment of current oxygen requirements. The enhancements of the immediate control value may include modulation based on severity of lung dysfunction, error attenuation while within the target range and error capping during hypoxia. The enhancements of the accumulation control value may include integrand magnitude capping, compensation for the non-linear PaO_2 - SpO_2 relationship, and inhibition of integrand increase in room air.

[071] For the PID feedback controller, the value of the manipulated signal output at each moment is proportional to the error, its integral and its derivative, with a different multiplying coefficient in each case, i.e., the immediate gain coefficient, the accumulation gain coefficient, and the predictive gain coefficient (referred to as K_p , K_i , K_d respectively). For the PID feedback controller, the immediate control value may also be referred to as a “proportional term”; the accumulation control value may also be referred to as an “integral term”; and the predictive control value may also be referred to as a “derivative term”, the three of which may be referred to as “PID terms”.

[072] In the method for automatically controlling inspired oxygen delivery as described herein, the immediate control value may be generated by multiplying an error value associated with the difference between the current input SpO_2 value and the target SpO_2 value) by an immediate gain coefficient. The error value may be the error (e), i.e., generated by determining the difference between the current input SpO_2 value and the target SpO_2 value. Alternatively, the error value may be generated by other suitable mathematical methods that compare the current input SpO_2 value with the target SpO_2 value.

[073] For the PID controller, the numerical difference between the incoming value for SpO_2 (assuming a valid signal) and the midpoint of the selected target range (e.g., target range 91-95%, mid-point 93%) may be used as the error (e).

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[074] Further, the accumulation control value may be generated by multiplying the accumulation of differences between the input SpO_2 values and the target SpO_2 values by an accumulation gain coefficient. For example, the accumulation control value may be generated by multiplying a summation of the error values by the accumulation gain coefficient for digital signals, or by multiplying an integral of the error values by the accumulation gain coefficient for analog signals. Alternatively, the accumulation control value may be generated by other suitable mathematical methods that result in the accumulation relationship between the input SpO_2 values and the target SpO_2 value.

[075] For the PID controller, the integrand ($\int e \, d\tau$) may be the sum or integral of all errors (subject to constraints outlined hereinafter); the integral term in PID control lends the advantage of overcoming steady state error.

[076] Further, the predictive control value may be generated by multiplying the difference divided by the time between successive error values (for digital signals) or derivative (for analog signals) of the error values (i.e., differences between the input SpO_2 values and the target SpO_2 values) by a predictive gain coefficient. Alternatively, the predictive control value may be generated by other suitable mathematical methods that result in the predictive relationship between the input SpO_2 values and the target SpO_2 value.

[077] For the PID controller, the derivative ($\frac{de}{dt}$) may be the SpO_2 slope by linear regression over the previous 5 seconds, and in PID control gives a prediction of future error.

[078] For example, the sum of each of the PID terms may be represented as ΔFiO_2 (as shown in the Equation 1 hereinafter).

[079] As previously described, the output FiO_2 value (the FiO_2 to be delivered to the patient) may be determined based on the control value and a reference inspired oxygen concentration (rFiO_2) value.

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[080] In some embodiments, the output FiO_2 values may be the sum of the corresponding control value and the corresponding rFiO_2 value, i.e., as shown in Equation 2.

[081] For example, FiO_2 may be the sum of ΔFiO_2 and rFiO_2 (as shown in the Equation 2 hereinafter). In addition, FiO_2 may be rounded to $\pm 0.5\%$ and coerced to a value between 21 and 100%, i.e., any value under 21% is rounded up to 21% and any value over 100% is rounded down to 100%.

$$[082] \quad \Delta\text{FiO}_2 = K_p \cdot e + K_i \cdot \int e \, d\tau + K_d \cdot \frac{de}{dt} \quad (\text{Equation 1})$$

$$[083] \quad \text{Set } \text{FiO}_2 = \Delta\text{FiO}_2 + \text{rFiO}_2 \quad (\text{Equation 2})$$

[084] The rFiO_2 value may represent the current baseline oxygen requirement, which indicates the severity of lung dysfunction of the patient. It may be a predetermined value or a value range, or may be selected by user's input. For example, the rFiO_2 value may be predetermined as a number between 21% and 60%, or any other suitable number up to 100%. The rFiO_2 value may have an initial value and be modified repeatedly over time, as described in further detail hereinafter. The time period for repeating the determination may be fixed (e.g., any period from 30 minutes to 2 hours) or may alternatively be indefinite. In this way, it is possible to detect and respond to the gradual changes in basal oxygen requirement that occur in subjects with respiratory dysfunction.

[085] In some embodiments, the immediate gain coefficient has an initial value selected to be between -2 and -0.2, e.g., -1.

[086] In some embodiments, the accumulation gain coefficient has an initial value selected to be between -0.25 and -0.005, e.g., -0.0125.

[087] In some embodiments, the predictive gain coefficient has an initial value selected to be between -2 and -0.25, e.g., -1.

[088] Each of the values of K_p , K_i and K_d may be determined based on predetermined reference values or a value range. For example, K_p , K_i and K_d may be determined based on reference values or value ranges derived from simulation studies

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using data from preterm infants. Values for each of the coefficients may be negative, meaning that the PID terms act in concert to correct the error. Exemplary value ranges for the coefficients may be: K_p -2 to -0.2; K_i -0.25 to -0.005; K_d -2 to -0.25, for example, $K_p = -1$, $K_i = -0.0125$, and $K_d = -1$. As described in further detail hereinafter, the standing value for K_p may be modified depending on the severity of lung dysfunction, and may further be refined through a self-tuning process during the automatic control, e.g., refined once every 30 to 60 minutes (or any other suitable time period which is sufficient for a proper assessment, e.g., more than 10 minutes and less than 120 minutes).

[089] In some embodiments, the immediate control values may be modified.

[090] In some embodiments, the method may further include:

determining the target SpO_2 value based on a target SpO_2 range;

wherein when the current input SpO_2 value is within the target SpO_2 range, an attenuator is applied to the immediate gain coefficient, and

wherein the attenuator is generated based on the current input SpO_2 value and a midpoint of the target SpO_2 range.

[091] The attenuator may be a fractional multiplier that is proportional to difference between the current input SpO_2 value and the midpoint of the target SpO_2 range.

[092] Further, when the current input SpO_2 value is lower than the target SpO_2 value, the error value associated with the difference between the current input SpO_2 value and the target SpO_2 value may be capped at a selected maximum difference.

[093] For the PID control, the determination of the proportional term may be modified when the input SpO_2 value is within the target SpO_2 range.

[094] The system 100 may target the mid-point of the target range, defining any deviation from this value as an error (e). In recognition that SpO_2 values elsewhere within the target range are acceptable, errors related to deviation from the mid-point of the target range may be reduced with a fractional multiplier K_{pfm} proportional to the distance from the mid-point (target range attenuation). For example, for a target range with a span of ± 2

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value									
Error multiplier	1.2	1.4	1.7	2.2	2.9	4.4	7.9	20.1	50

[102] The error multipliers may have the effect of rapidly increasing negative integrand back towards zero, and thus mitigating overshoot.

[103] Further, in some embodiments, generating the accumulation control values may include:

inhibiting increases in the accumulation control values when: (i) a current output FiO_2 value is at room air level, and (ii) a current input SpO_2 value is above the target SpO_2 value.

[104] Once the integrand is positive (i.e., tending to reduce ΔFiO_2), further positive errors may be added to the integrand only while set FiO_2 remains above room air (21%). When in room air (i.e., $\text{FiO}_2=21\%$), sequential values of SpO_2 above the target range may no longer be considered to represent unremitting hyperoxia, and the positive errors may not be added to the integrand, i.e., these positive error values are nulled or zeroed. This may avoid a build-up of positive integrand that would delay an appropriate response from the integral term to the next episode of hypoxia.

[105] In some embodiments, the predictive control values may be modified.

[106] In some embodiments, the predictive control values may be nullified if the input SpO_2 values have been above a selected SpO_2 threshold for the entirety of the negative SpO_2 slope determination period.

[107] For the PID control, the derivative term may be modified. For example, the derivative term may be modified during hyperoxia.

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[108] In some embodiments, negative SpO₂ slope may be nullified (e.g., rendered = 0) if all of the latest 5 SpO₂ values are above the set-point (a hyperoxia event). Upward pressure on ΔFiO₂ by the derivative term may thus be avoided in hyperoxia.

[109] Fig. 3 illustrates a process 300 performed by the controller 11 of generating the proportional term, the integral term and the derivative term, including the modifications as described hereinbefore.

[110] As shown in Fig. 3, in S302, a value of the error (e) is determined as the numerical difference between an input SpO₂ value and a target SpO₂ value (e.g., the midpoint of the selected target range), as shown in Equation 3 below.

[111]
$$e = \text{SpO}_2 - \text{SpO}_2 \text{ target} \quad (\text{Equation 3})$$

[112] Next, in S304, the proportional term is modified, using the following steps:

(a) Select a value for the fractional multiplier K_{pfm} based on the value of the error:

If $|e| \leq 1$ (i.e., the error is smaller than or equal to 25% of the target range, and thus the input SpO₂ value is within the target range and close to the target SpO₂ value), $K_{\text{pfm}} = 0.25$;

else if $|e| \leq 2$ (i.e., the error is bigger than 25% of the target range but smaller than or equal to 50% of the target range, and thus the input SpO₂ value is within the target range while not close to the target SpO₂ value), $K_{\text{pfm}} = 0.5$;

else (i.e., the error is bigger than 50% of the target range, and thus the input SpO₂ value is outside the target range) $K_{\text{pfm}} = 1$.

(b) Adjusting K_{pfm} based on CPAP Circuit Pressure and respiratory rate:

If (CPAP Circuit Pressure = low), $K_{\text{pfm}} = 2 * K_{\text{pfm}}$ (i.e., reduction in circuit pressure leads to doubling of K_{pfm});

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else if (respiratory pause for 5 to 15 sec), $K_{\text{pfm}} = 2 * K_{\text{pfm}}$ for 30 seconds (i.e., a respiratory pause results in a doubling of K_{pfm} for 30 seconds).

(c) Apply proportional term error capping during hypoxia:

If $e > -15\%$ (i.e., the patient is in hypoxia), the proportional error $e_p = -15\%$ (i.e., cap the proportional term error);

else $e_p = e$.

(d) Calculate the proportional term:

$$\text{Proportional Term} = P(t) = K_{\text{pfm}} * K_p * e_p.$$

[113] After the modification of the proportional term, the logic moves to S306 to modify the integral term, using the following steps:

(a) Determination of a non-linear compensation multiplier (K_s) based on a non-linear, predetermined relationship, which can be predetermined using known relationships between blood oxygen level and high values of SpO_2 : (including those described by the Severinghaus equation):

If the previous integral term $I(t-1) < 0$ (i.e., the integrand remained negative) and $e > 0$ (i.e., SpO_2 is above the target range),

then

if $\text{SpO}_2 = 92$, $K_s = 1.2$;

else if $\text{SpO}_2 = 93$, $K_s = 1.4$;

else if $\text{SpO}_2 = 94$, $K_s = 1.7$;

else if $\text{SpO}_2 = 95$, $K_s = 2.2$;

else if $\text{SpO}_2 = 96$, $K_s = 2.9$;

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else if $SpO_2 = 97$, $K_s = 4.4$;

else if $SpO_2 = 98$, $K_s = 7.9$;

else if $SpO_2 = 99$, $K_s = 20.1$;

else if $SpO_2 = 100$, $K_s = 50$;

else $K_s = 1$

(i.e., apply the non-linear compensation multiplier to positive errors proportional to relevant ΔPaO_2 values).

(b) Inhibition of integrand increase in room air:

If $FiO_2 = 21\%$ (i.e., in room air) and $e > 0$, $dI = 0$ (i.e., further positive error is not added to the integrand);

else $dI = K_i * K_s * e$.

(c) Determine the value of integral term:

$$\text{Integral Term} = I(t) = I(t-1) + dI.$$

(d) Integrand magnitude capping:

$$\text{If } |I(t)| > |\Delta FiO_{2\max} / K_i|, I(t) = (\text{sign}) * (\Delta FiO_{2\max} / K_i)$$

(i.e., cap the value of integral term based on selected $\Delta FiO_{2\max}$ value).

[114] After the modification of the integral term, the derivative term is then modified in S308 using the following steps:

(a) Evaluate Derivative Term:

Derivative Term = $D(t) = K_d * de/dt$, where de/dt is determined by linear regression over 5 seconds.

(b) Nullify for negative slope and hyperoxia:

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If $de/dt < 0$ and $(SpO_2(t) > SpO_2 \text{ target})$ and
 $(SpO_2(t-1) > SpO_2 \text{ target})$ $(SpO_2(t-2) > SpO_2 \text{ target})$ and
 $(SpO_2(t-3) > SpO_2 \text{ target})$ and $(SpO_2(t-4) > SpO_2 \text{ target})$
 (i.e., all of the latest 5 SpO_2 values are above the set-point),
 $D(t) = 0$ (i.e., negative SpO_2 slope is nullified).

[115] Further, the control value may be generated further based on the $rFiO_2$ value.

[116] In some embodiments, the immediate control value (the proportional term) is determined further based on the $rFiO_2$ value.

[117] The immediate control value (the proportional term) is modified by a modification value determined from the $rFiO_2$ value. The modification value may be determined using a monotonic relationship with $rFiO_2$, i.e., based on a monotonic function. For example, K_p may be modified from a predetermined initial reference value or from its current value by a value determined from the $rFiO_2$ value. This modification value increases the effective value of the immediate control value for increasing $rFiO_2$, e.g., with a scaling factor proportional to the severity of lung dysfunction as indicated by the current $rFiO_2$. For example, the standing value of K_p may be multiplied by a factor in the range 0.5 to 1.5 for $rFiO_2$ in a corresponding range 21% to 60% (e.g., for $rFiO_2$ 21%, scaling factor may be 0.5, for $rFiO_2$ 40%, the scaling factor may be 1.0, and the scaling factor can vary linearly from 0.5 to 1.5 proportional to the $rFiO_2$ varying from 21% to 60%). Alternatively, the scaling factor can be implemented as an equivalent modification value that modifies the immediate control value. Adaptation of K_p in this way may compensate for an inverse proportional relationship between gain and severity of lung disease.

[118] Further, the method may further include:

receiving the signals representing the plurality of input SpO_2 values during a performance analysis time period;

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generating a performance evaluation result based on the input SpO_2 values received during the performance analysis time period; and

generating the control value based on the performance evaluation result.

[119] Further, the immediate gain coefficient is modified based on a performance evaluation result.

[120] In some embodiments, the value of K_p may be modified repeatedly during automated control of inspired oxygen delivery: an analysis of the performance of the automatic control of inspired oxygen delivery may be carried out periodically, based on the input SpO_2 values received over a performance analysis time period and generating a performance evaluation result, and the value of K_p may be modified based on the performance evaluation result.

[121] In some embodiments, the performance evaluation result may be generated based on at least one of: a hypoxic time duration in which the input SpO_2 values in the performance analysis time period were in a hypoxic range, and a hyperoxic time duration in which the input SpO_2 values in the performance analysis time period were in a hyperoxic range.

[122] Further, in some embodiments, the performance evaluation result is generated based on a ratio of the hyperoxic time duration to the hypoxic time duration.

[123] Further, in some embodiments, the method may further include:

determining the target SpO_2 value based on a target SpO_2 range;

wherein the performance evaluation result is generated based on at least one of:

a target time duration in which the input SpO_2 values in the performance analysis time period were in the target SpO_2 range, and

an eupoxic time duration in which the input SpO_2 values in the performance analysis time period were in an eupoxic range, wherein the

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eupoxic range is a range in which the input SpO₂ values were in the target SpO₂ range, or above the target SpO₂ range in room air.

[124] The performance analysis time period may be a fixed time period, e.g., predetermined or set by the user. The performance analysis time period may be 60 minutes, such that the analysis is performed based on the SpO₂ data recorded in the last 60 minutes before the analysis. Alternatively, the performance analysis time period may be a variable time period (e.g., any time period between 30 minutes and 2 hours), based on the result of the analysis, or instructions inputted by the user.

[125] The analysis may be performed on a regular basis. For example, the analysis may be performed once every 30 minutes. The analysis may also be performed continuously, or performed once after each of a certain interval, which may be any suitable time period up to 2 hours. The frequency of the analysis may also be set by the user.

[126] The analysis may be based on the response to all hypoxic events in the time window, starting at hypoxia onset (SpO₂ <85%), and continuing for a certain period (any selected suitable time period between 2 and 10 minutes) beyond its resolution.

[127] The total time of hypoxia (SpO₂ 80-84%) and severe hypoxia (SpO₂ <80%), as well as the duration of subsequent SpO₂ overshoot into hyperoxia (97-98%) and severe hyperoxia (99-100%) when receiving oxygen, may be quantified, as described hereinafter with reference to Fig. 4.

[128] From these data, a weighted performance coefficient may be derived as the ratio of time in hyperoxia to time in hypoxia, value of which <1 and >1 may indicate an underpowered and overpowered K_p, respectively. The current value of K_p may be altered by up to ±10% each 30 min as a result of this analysis.

[129] Further, proportions of time in which SpO₂ was in the target range and in an eupoxic range (SpO₂ in target range, or above target range in room air) may be calculated, as well as the occurrence of hypoxia and hyperoxia in oxygen.

[130] In some embodiments, an alarm may be triggered when the performance evaluation result fails to meet certain conditions, including the controller output is

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substantially below the minimum requirement for proportion of eupoxia, which can be adjusted by the user, and set in the range 50 to 80%.

[131] Fig. 4 illustrates a process 400 performed by the controller 11 of modifying K_p based on the performance evaluation result as described hereinbefore.

[132] As shown in Fig. 4, in S402, the process 400 determines whether 30 minutes have elapsed since outset of automated control or previous Performance Analysis.

[133] If the result of determination is no, the process 400 ends. If it is determined that 30 minutes have elapsed, the process 400 moves to S404 to execute a performance analysis based on the performance of the control over previous 60 minute time window, using the following steps:

(a) Calculate proportion of time in eupoxic, hypoxic and hyperoxic ranges:

$t_{\text{severe hypoxia}}$: $\text{SpO}_2 < 80\%$.

t_{hypoxia} : $80\% \leq \text{SpO}_2 \leq 84\%$.

t_{eupoxia} : SpO_2 in target range, or above with $\text{FiO}_2 = 21\%$.

$t_{\text{hyperoxia}}$: $97\% \leq \text{SpO}_2 < 99\%$ when receiving oxygen.

$t_{\text{severe hypoxia}}$: $\text{SpO}_2 \geq 99\%$ when receiving oxygen

(i.e., quantify the total time of hypoxia, severe hypoxia, hyperoxia, severe hyperoxia and eupoxia).

(b) Calculate weighted performance coefficient:

$$C_{\text{performance}} = (t_{\text{severe hyperoxia}} + t_{\text{hyperoxia}}) / (t_{\text{hypoxia}} + t_{\text{severe hypoxia}})$$

(i.e., the ratio of time in hyperoxia including severe hyperoxia to time in hypoxia including severe hypoxia, indicating an underpowered and overpowered K_p).

(c) Calculate new K_p :

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If $C_{\text{performance}} \leq 0.7$, $K_p = K_p * 1.1$.

If $0.7 < C_{\text{performance}} \leq 0.85$, $K_p = K_p * 1.05$.

If $1.15 \leq C_{\text{performance}} < 1.3$, $K_p = K_p * 0.95$.

If $C_{\text{performance}} \geq 1.3$, $K_p = K_p * 0.9$.

(i.e., alter the value of K_p based on the ratio of time)

(d) Calculate eupoxia time:

$\text{eupoxia time} = (t_{\text{eupoxia}} \times 100) / t_{\text{total}}$.

(i.e., proportion of time in which SpO_2 was in an eupoxic range)

If eupoxia time < target range adherence goal,

alarm: “target range adherence” = true

(i.e., an alarm is triggered if the automatic control was below the minimum requirement).

[134] Further, the method for automatically controlling inspired oxygen delivery may further include:

- (a) generating an rFiO_2 evaluation result based on the input SpO_2 values and the respective output FiO_2 values over an rFiO_2 evaluation time period; and
- (b) modifying the rFiO_2 value based on the rFiO_2 evaluation result.

[135] The rFiO_2 value may have an initial value and may be modified repeatedly over time.

[136] In some embodiments, the analysis may be performed on a regular basis. For example, the analysis may be performed once every 30 minutes, which may be referred to the evaluation time frequency. The analysis may also be performed once after each of a certain interval, which may be any suitable time between 30 minutes and 2 hours. At the

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evaluation time frequency, an analysis of the relationship between set FiO_2 and SpO_2 in a shifting time window (an “evaluation time period”) may be undertaken, with the assumption that a fixed V/Q ratio, along with a variable shunt, caused the oxygenation disturbances. The time window may be 60 minutes, or any suitable time period (any selected period from 30 minutes to 2 hours). A value for V/Q ratio may then be derived, e.g., using known ways and formulae for calculating V/Q ratio, and from it the rFiO_2 value may be modified for overcoming its effect on oxygenation. This may become the new value for rFiO_2 , which may be coerced to within $\pm 10\%$ of the previous value. Rapid changes in rFiO_2 may thus be avoided.

[137] Fig. 5 illustrates a process 500 performed by the controller 11 of modifying the value of rFiO_2 .

[138] As shown in Fig. 5, in S502, the process 500 determines whether it is outset of automated control or 30 minutes have elapsed since last time reference FiO_2 (rFiO_2) was updated.

[139] If the result of determination is no, the process 500 ends. If it is determined that it is outset of automated control or 30 minutes have elapsed, the process 500 moves to S504 to update the value of rFiO_2 , using the following steps:

(a) Sliding-window analysis

Perform 60 minute sliding-window analysis of FiO_2 and SpO_2 to obtain V/Q ratio, and obtain rFiO_2 from V/Q ratio.

(b) Coerce rFiO_2 to within $\pm 10\%$ of the previous value

If $(\text{rFiO}_2 - \text{previous rFiO}_2) / (\text{previous rFiO}_2) > 0.1$,

$$\text{rFiO}_2 = \text{previous rFiO}_2 + \text{sign}(\text{rFiO}_2 - \text{previous rFiO}_2) * 0.1 * \text{previous rFiO}_2$$

(i.e., determine the new value of rFiO_2 , coerced to within $\pm 10\%$ of the previous value; rapid changes in rFiO_2 may thus be avoided).

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- (c) At the outset of automated control, use the current value for FiO_2 or a value input by the user as the starting value for rFiO_2 .

[140] In addition, the method for automatically controlling inspired oxygen delivery may further include:

- (a) generating a SpO_2 validation result based on a current input SpO_2 value by classifying a current input SpO_2 value into one of multiple validity levels in a hierarchical validation procedure; and
- (b) determining the output FiO_2 value based on the SpO_2 validation result..

[141] The following hierarchical validation levels may be adopted:

- (a) “Level I”, corresponding to the SpO_2 input “missing”, if the SpO_2 input meets a first condition;
- (b) “Level II”, corresponding to the SpO_2 input being “suspect”, if the SpO_2 input meets a second condition; and
- (c) “Level III”, correspond to the SpO_2 input being “invalid”, if the SpO_2 input meets a third condition.

[142] Further, in some embodiments, the method may further include:

receiving at least one of:

a signal representing a heart rate derived from a SpO_2 plethysmographic waveform;

a signal representing a heart rate derived from electrocardiographic monitoring; and

a signal representing a perfusion index;

wherein the validity of the current input SpO_2 value is determined based on at least one of:

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the received heart rate derived from a SpO₂ plethysmographic waveform;

the received heart rate derived from electrocardiographic monitoring; and

the received perfusion index.

[143] For validation of the SpO₂ signal, some or all of the following ancillary inputs may be sourced as digital signals:

- (a) a heart rate derived from the SpO₂ plethysmographic waveform (HR_{pleth});
- (b) a heart rate derived from electrocardiographic monitoring (HR_{ecg}); and
- (c) perfusion index, this being a metric of oximetry waveform pulsatility, with low values potentially associated with spurious SpO₂ values.

[144] At the outset of automated control, and then each 24 hours (the “perfusion check period”), a perfusion index value representing optimum perfusion may be recorded at a time when the plethysmographic waveform is stable and the signal is strong. The perfusion check period may be any suitable time period, including any selected time period from 6 hours to 2 days.

[145] Fig. 6 illustrates a process 600 performed by the controller 11 of determining the perfusion index value.

[146] As shown in Fig. 6, in S602, the process 600 determines whether it is outset of automated control or 24 hours have elapsed since last perfusion index review.

If the result of determination is no, the process 600 ends. If it is determined that it is outset of automated control or 24 hours have elapsed, the process 600 moves to S604 to enter a new optimal perfusion index value, e.g., being the 95th centile over the last 24 hours.

[147] The plethysmographic waveform, which can be recorded over the preceding 10 seconds (or any suitable time period, including any selected time period from 5 seconds to

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20 seconds) may also be input as an analogue signal that was digitised with the aid of an analogue-digital converter. Digital and analogue signals may be acquired using a data acquisition device.

[148] Waveform analysis validates the SpO₂ by analysing the plethysmographic signal from the pulse oximeter to confirm it is conformant to the properties expected from a valid plethysmographic signal. Assessment methods include, either individually or in combination, analysis of statistical properties of the signal (such as mean and variance), classic signal processing techniques (such as autocorrelation), logical algorithms (including fuzzy logic) and pattern recognition techniques (including neural networks).

[149] For example, one exemplary process for carrying out the SpO₂ plethysmographic waveform analysis includes the following steps:

- (a) periodically obtaining a valid “representative” plethysmographic tracing from the individual patient;
- (b) normalising the current input SpO₂ plethysmographic signal in two axes, so that so that both the periodicity and the peak and trough amplitudes correspond with the ‘representative’ plethysmographic tracing;
- (c) comparing the two signals by multiple linear regression, with the mean-squared error giving an indication of the departure of the current signal from the ‘representative’ SpO₂ plethysmographic waveform.

[150] Alternatively, the two signals may be compared by other methods, for example pattern recognition, such as linear discriminant analysis or artificial neural networks. Using these methods, a pre-recorded database of recordings of plethysmographic waveform signals with SpO₂ classified as valid or invalid may be used for training and validation of the pattern recognition such that it may be used to classify the monitored SpO₂ signal as valid or invalid.

[151] With these additional inputs, the following hierarchical validation procedure may be adopted:

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- (a) Level I: if the SpO_2 value is zero or non-numeric;
- (b) Level II: if, after normalisation in both axes, the waveform does not conform with a generic plethysmographic waveform; and
- (c) Level III: if:
 - i. perfusion index is $<30\%$ (or any other suitable value, e.g., any value between 10% and 50%) of the optimum value *and* the waveform is “suspect”, or
 - ii. absolute value of $\text{HR}_{\text{ecg}} - \text{HR}_{\text{pleth}} > 30$ bpm (or any other suitable value, e.g., any value between 20 bpm and 50 bpm) *and* the waveform is “suspect”, or
 - iii. there is a precipitous fall in SpO_2 (e.g., $>15\%$ in 5 seconds, or any other suitable value representing a sudden and deep drop in SpO_2 , where the drop needs to last for a certain time period, e.g., 5 seconds, since sometimes a sudden drop in SpO_2 may be a spurious reading.), along with any of: “suspect” waveform, heart rate discrepancy or perfusion index discrepancy (suggesting spurious hypoxia).

[152] Fig. 7 depicts an example of the hierarchical validation process (700) performed by the controller 11.

[153] As shown in Fig.7, first, it is determined in S702 whether the input SpO_2 value is zero or non-numeric. If yes, a flag “Level 1” is set as true (S704) and the process 700 ends.

[154] If the input SpO_2 value is not zero or non-numeric, the flag “Level 1” is set as false (S706) and a further determination is performed in S708 to test the input SpO_2 signal’s conformant to plethysmographic waveform. If it is determined that, after normalisation in both axes, the waveform of the input SpO_2 signal does not conform with a generic plethysmographic waveform, a flag “Level 2” is set as true (S712), i.e., the SpO_2

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input is “suspect”. If the waveform of the input SpO₂ signal conforms to a generic plethysmographic waveform, the flag “Level 2” is set as false.

[155] Next, the logic moves to S714 to determine whether the perfusion index is <30% of the optimum, and sets a flag “PI mismatch” as true if the perfusion index is <30% of the optimum (S716), or sets the flag “PI mismatch” as false if not (S718).

[156] Next, a test is performed in S724 to determine whether the absolute value of $HR_{ecg} - HR_{pleth} > 30$ bpm in S720. If yes, a flag “HR mismatch” is set as true (S722); and if not, the flag “HR mismatch” is set as false (S724);

[157] Further, it is determined in S726 that whether a “Level III” condition is satisfied, i.e., whether the SpO₂ input is “invalid”, e.g., by using the following logic:

(“PI Mismatch” and “Level 2”) or (“HR mismatch” and “Level 2”) or

((SpO₂ reduced >15% in 5 seconds) and (“Level 2” or PI mismatch” or “HR mismatch”))

If the result is positive, a “Level III” flag is set as true (S728), i.e., the SpO₂ input is “invalid”; if not, the “Level III” flag is set as false (S730).

[158] In some embodiments, when the input SpO₂ value is determined as being invalid (e.g., in the event of missing or invalid signal), the FiO₂ may be set to hold the output FiO₂ value at the current value, i.e., the previously recorded FiO₂ value. In the event of prolonged missing or invalid signal, beyond the triggering of alarms described hereinafter, the output FiO₂ value may be trended towards the rFiO₂.

[159] Fig. 8 illustrates a process 800 performed by the controller 11 for determining the output FiO₂ value based on the validity of SpO₂.

[160] As shown in Fig. 8, a test is carried out in S802 to decide whether the input SpO₂ value is “Missing” or “Invalid”. If it is determined that the input SpO₂ value is “Missing” or “Invalid”, the output FiO₂ value is set the same as the previous output FiO₂ value in S806. If in S802 it is held that the input SpO₂ value is not “Missing” or “Invalid”,

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the logic moves to S804, where an output FiO_2 value is determined based on the input SpO_2 value, e.g., using the following steps:

- (a) Calculate ΔFiO_2 : $\Delta\text{FiO}_2 = \text{P}(t) + \text{I}(t) + \text{D}(t)$.
 - (b) Calculate output FiO_2 value: $\text{FiO}_2 = \Delta\text{FiO}_2 + \text{rFiO}_2$.
 - (c) If apnoea >15 sec, alter output FiO_2 value up by 5% for 30 sec beyond apnoea cessation.
 - (d) Round “output FiO_2 value” to $\pm 0.5\%$.
 - (e) If $\text{FiO}_2 < 21\%$, output FiO_2 value = 21%.
- If $\text{FiO}_2 > 100\%$, output FiO_2 value = 100%.

[161] In some embodiments, an alarm (e.g., an audible and/or a visible alarm) may be activated when the SpO_2 is determined as having been invalid for a certain time period (e.g., 30 seconds, or any other suitable time period which can prevent continuously missing out a signal from a baby who has been having a low SpO_2). For example, the alarm may be an audible alarm, and the volume of the alarm may increase every few minutes (e.g., 2 minutes) when the alarm is being activated, with an error message to check the oximeter probe and connections.

[162] In some embodiments, the alarm may be terminated and determination of the output FiO_2 value based on the immediate control value, the accumulation control value, the predictive control value and the reference inspired oxygen concentration may resume as soon as a valid SpO_2 is detected.

[163] In addition, the method for automatically controlling inspired oxygen delivery may further include:

- (a) receiving a signal representing a respiratory rate;
- (b) wherein the immediate control value is generated further based on the respiratory rate.

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[164] In some embodiments, respiratory rate may be recorded with an abdominal capsule linked to a respiration monitor, from which with every detected spontaneous breath a digital pulse may be routed to the automatic controller via an analogue-digital converter.

[165] Episodes of respiratory pause (e.g., 5 to 15 seconds of breathing cessation, or a breathing cessation for any suitable time period sufficient for predicting a likely hypoxic event) and apnoea (e.g., longer than 15 seconds or longer than any suitable time period sufficient for predicting a likely hypoxic event) may be identified.

[166] The value of K_p may be modified based on this additional input.

[167] For example, a respiratory pause may result in a doubling of K_p for a certain time period (e.g., 30 seconds, or any suitable time period) beyond the cessation of breathing. Through this adjustment, the automatic controller is more sensitive in its response to a hypoxic event if one occurs. If the respiratory pause continues into frank apnoea, the FiO_2 may also be transiently increased 2 to 8% in proportion to the underlying K_p value.

[168] In addition, the method for automatically controlling inspired oxygen delivery may further include:

- (a) receiving a signal representing a circuit pressure;
- (b) wherein the immediate control value is generated further based on the circuit pressure.

[169] For infants on continuous positive airway pressure (CPAP) respiratory support, the pressure in the inspiratory limb of the CPAP circuit may be transduced, and input as a digital signal.

[170] For example, reduction in circuit pressure to levels below a certain proportion (including any selected value between 20% and 50%) of the plateau value may lead to doubling of K_p , and, after 30 seconds, triggering of an alarm representing a circuit pressure reduction. Complete loss of circuit pressure (< 1 cm H_2O , i.e., when there is essentially no

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pressure being delivered) may trigger a higher level alarm representing circuit pressure loss.

[171] In some embodiments, the method may further include:

receiving an manual override input;

determining the output FiO_2 value based on the manual override input instead of the control values.

[172] Further, the controlling apparatus 10 may have an automatic control mode and a manual control mode, and the automatic control mode can be switched to the manual control mode under certain user inputs (i.e., the manual override inputs), and subsequently reverted back to automatic mode if desired.

[173] For example, a user (e.g., bedside staff) may switch the controlling apparatus 10 into a manual control mode, such that the controller 11 no longer produced changes in the output FiO_2 value, and oxygenation is entirely under manual control.

[174] Manual control mode may be selected through a manual override input in the user interface displayed on the user-interface display 14. It may be either as a temporary halt (e.g., 30 seconds duration) in the function of the controller producing changes in FiO_2 , or as continuous manual operation until deselected.

[175] The manual control mode may be also be selected by rotating the FiO_2 selection dial on the automated air-oxygen blender, i.e., providing a manual override input to trigger a halt to automated control (e.g., a halt of 30 second or any selected suitable time period).

[176] In the first iteration after the halt, i.e., returning from manual control mode, the integrand may be adjusted such that the output FiO_2 value is set equal to the current (i.e., user-selected) value of servo FiO_2 , with automated control resumed thereafter.

[177] Fig. 9 illustrates a process 900 performed by the controller 11 for switching between the manual mode and the automatic control mode.

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[178] As shown in Fig. 9, first, a test is carried out in S902 to determine whether the servo FiO_2 input has been changed manually, i.e., a manual override input received. If yes, a manual override mode is started in S904. If the servo FiO_2 input has not been changed manually, the logic moves to S906 to determine whether the manual mode time limited has expired. If the manual mode time limited has expired, the controlling apparatus 10 is then set to return to automatic control mode in S908. If the manual mode time limited has not expired, the process 900 ends.

[179] Further, one or more alarms may be triggered under certain condition during the automatic control.

[180] For example, alarms (e.g., audible and/or visible alarms) may be included in the controlling apparatus 10, alerting bedside staff to rapidly rising FiO_2 , achievement of maximum ΔFiO_2 , missing or invalid SpO_2 signal for >30 sec and >2 min, prolonged apnoea or circuit pressure loss, and system malfunction. These alarms may be added to, integrated with, or supplant, the alarms set within standard bedside monitors in the NICU.

[181] Fig. 10 illustrates a process 1000 performed by the controller 11 of controlling alarms based on by monitoring various signals described hereinbefore.

[182] As shown in Fig. 10, in S1002 a process of activating alarms is performed, using the following steps:

- (a) If alarm: "missing signal" = true, activate missing signal alarm.
- (b) If alarm: "hypoxia" = true, activate hypoxia alarm.
- (c) If alarm: "circuit pressure reduction" = true, activate circuit pressure reduction alarm.
- (d) If alarm: "circuit pressure loss" = true, activate circuit pressure loss alarm.
- (e) If alarm: "servo FiO_2 mismatch" = true, activate servo FiO_2 mismatch alarm.
- (f) If alarm: "servo FiO_2 error" = true, activate servo FiO_2 error alarm.

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- (g) If alarm: "measured FiO₂ mismatch" = true, activate measured FiO₂ mismatch alarm.
- (h) If alarm: "measured FiO₂ error" = true, activate measured FiO₂ error alarm.
- (i) If alarm: "target range adherence"=true, activate target range adherence alarm.

[183] Next, the process 1000 moves to S1004, where alarms are reset using the following steps:

- (a) If missing signal alarm reset, alarm ("missing signal ") = false.
- (b) If hypoxia alarm reset, alarm ("hypoxia") = false.
- (c) If circuit pressure reduction alarm reset, alarm ("circuit pressure reduction") = false.
- (d) If circuit pressure loss alarm reset, alarm ("circuit pressure loss") = false.
- (e) If servo FiO₂ alarm reset, alarm ("servo FiO₂ mismatch ") = false.
- (f) If servo FiO₂ alarm high reset, alarm ("servo FiO₂ error") = false.
- (g) If measured FiO₂ alarm reset, alarm ("measured FiO₂ mismatch ") = false.
- (h) If measured FiO₂ high alarm reset, alarm ("measured FiO₂ error ") = false.
- (i) If target range adherence alarm reset, alarm ("target range adherence") = false.

[184] After finishing S1004, the process 1000 ends.

[185] Further, as described hereinbefore, the controlling apparatus 10 may further include a user-interface display 14, which displays a user interface showing various information to a user (e.g., a bedside caregiver) and receiving instructions inputted by the user based on the user-interface. The received user inputs are then transmitted to the controller 11.

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[186] One example of a user interface 200 displayed on the user-interface display 14 is illustrated in Fig. 11. The user interface 200 may include:

- (a) a numerical $\text{SpO}_2/\text{FiO}_2$ display area A01, displaying the latest input SpO_2 value and the latest output FiO_2 value;
- (b) a graphical $\text{SpO}_2/\text{FiO}_2$ display area A02, graphically displaying the trend of input SpO_2 values and the output FiO_2 values;
- (c) an oximeter type choosing area A03, for a user to choose the type of oximeter used for generating the SpO_2 signal;
- (d) a SpO_2 target range setting area A04, for displaying and allowing a user to alter the target SpO_2 range in real-time;
- (e) a maximum ΔFiO_2 setting area A05, for indicating and allowing a user to alter a limitation for the value of ΔFiO_2 in real-time;
- (f) a manual control mode button B06, by pressing which the controlling apparatus 10 can be switched between an automatic control mode and a manual control mode;
- (g) an on/off button B07, by pressing which the controlling apparatus 10 can be turned on or turned off;
- (h) a status display area A08, displaying the working status of the controlling apparatus 10, which may include displaying visible alarm information under certain conditions;
- (i) a reference FiO_2 display area A09, displaying the most recent values for rFiO_2 ;
- (j) an eupoxia time display area A10, displaying the proportion of time in eupoxia;

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- (k) FiO₂ feedback indicating area A11, indicating whether the servo FiO₂ or measured FiO₂ matches the output FiO₂ value, e.g., by a light indicator;
- (l) valid SpO₂ indicating area A12, indicating whether the input SpO₂ value is valid, e.g., by a light indicator; and
- (m) additional inputs indicating areas A13 and A14, indicating respectively whether signals representing a respiratory rate and a respiratory circuit pressure have been inputted into the controlling apparatus 10, e.g., by light indicators.

[187] A general control process of the method for automatically controlling inspired oxygen delivery performed by the controller 11 according to some embodiments is depicted by the flow chart in Fig. 12.

[188] As shown in Fig. 12, when the control process has started, inputs to the controlling apparatus 10 are processed in S1202.

[189] Fig. 13 depicts exemplary steps (1300) of processing inputs in S1202: the inputs are read from the input unit (S1302), and then validated (S1304). After the validation of the inputs, a manual override assessment is performed (S1306).

[190] Exemplary steps of reading inputs in S1302 are as illustrated in Fig. 14. As shown in Fig. 14, in S1402, input signals including signals representing a plurality of input oxygen saturation (SpO₂) values for a patient are received. The input signals may include: SpO₂, HR_{pleth}, Perfusion Index, Pleth waveform, HR_{ecg}, Respiration Rate, CPAP Circuit Pressure, Servo FiO₂, Measured FiO₂, ΔFiO₂max, SpO₂ target, Target range adherence goal.

[191] Exemplary steps of the validation of the inputs in S1304 are as illustrated in Fig. 15. First, validation of input bounds is performed in S1502, after which the perfusion index status is updated in S1504. A hierarchical validation of SpO₂ is then performed in S1506. Further, alarms may be triggered based on the result of the hierarchical validation of SpO₂ and based on whether servo FiO₂ or measured FiO₂ deviating from set FiO₂ beyond tolerance limits (1 and 2%, respectively) in S1508.

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[192] Activating alarms in S1508 may adopt the following steps:

(a) If SpO₂ signal is Level 1 or Level 3 for > 30 sec,

alarm: "missing signal" = true.

If SpO₂ signal is Level 1 or Level 3 for > 2 min,

increase volume of alarm: "missing signal"

error message to check the oximeter probe and connections

(b) If $|(set\ FiO_2 - servo\ FiO_2)/(set\ FiO_2)| > 1\%$,

alarm: "servo FiO₂ mismatch" = true.

If $|(set\ FiO_2 - servo\ FiO_2)/(set\ FiO_2)| > 5\%$,

alarm: "servo FiO₂ error" = true, and ManualMode = true;

(c) If $|(set\ FiO_2 - measured\ FiO_2)/(set\ FiO_2)| > 2\%$,

alarm: "measured FiO₂ mismatch" = true.

If $|(set\ FiO_2 - measured\ FiO_2)/(set\ FiO_2)| > 10\%$,

alarm: "measured FiO₂ error" = true, and ManualMode = true.

[193] Further, Fig. 16 illustrates exemplary steps of validation of input bounds in S1502.

[194] As shown in Fig. 16, first, valid input bounds are set in S1602. For example, valid input bounds for IB(1) – IB(9) may be set as the following:

IB(1)	SpO ₂ :	$0 \leq SpO_2 \leq 100\%$
IB(2)	HR _{pleth} :	$0 \leq HR_{pleth} \leq 300\text{ bpm}$
IB(3)	Perfusion Index :	$0 \leq \text{Perfusion Index} \leq 10$
IB(4)	Pleth waveform :	$0 \leq \text{Pleth waveform} \leq 5V$

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IB(5)	HR _{ecg} :	$0 \leq \text{HR}_{\text{ecg}} \leq 300 \text{ bpm}$
IB(6)	Respiration Rate :	$0 \leq \text{Respiration Rate} \leq 150/\text{min}$
IB(7)	CPAP Circuit Pressure:	$0 \leq \text{CPAP Circuit Pressure} \leq 20 \text{ cm H}_2\text{O}$
IB(8)	Servo FiO ₂ :	$21\% \leq \text{Servo FiO}_2 \leq 100\%$
IB(9)	Measured FiO ₂ :	$21\% \leq \text{Measured FiO}_2 \leq 100\%$

[195] Next, through the loop in S1604, S1608 and S1616, a determination is made to decide whether the input value of each IB(i) is outside the valid input bound. If not, the loop proceeds to determine the next IB(i). If yes, the logic moves to S1610, where last valid value for IB(i) is used instead of the current IB(i). After S1610, a test is carried out to determine whether an excessive timeout has occurred (S1612). If yes, an input timeout flag ITO(i) is set (S1614), and the logic proceed to S1616 to process the next IB(i) or finish the input bounds assessment.

[196] When all IB(i) have been validated, the logic moves to S1618 to determine whether a alarm should be activated based on the current value of CPAP circuit pressure, e.g., using the following steps:

a. Valid Circuit Pressure is in-range:

if CPAP Circuit Pressure < 50% of the plateau value,

CPAP Circuit Pressure = low

(i.e., if the circuit pressure is below 50% of the plateau value,
determine that the circuit pressure as low);

if CPAP Circuit Pressure < 1 cm H₂O,

CPAP Circuit Pressure = loss.

(i.e., if the circuit pressure is below 1cm H₂O of the plateau value,
determine that the circuit pressure is completely lost);

b. Activate CPAP Circuit Pressure alarms:

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if CPAP Circuit Pressure low for > 30 seconds,

activate alarm: "circuit pressure reduction"

(i.e., the circuit pressure has been below 50% for more than 30 seconds, trigger an alarm).

[197] Updating the perfusion index status in S1504 may adopt the process illustrated in Fig. 6 as described before.

[198] The hierarchical validation of SpO₂ in S1506 may adopt the process illustrated in Fig. 7 as described before.

[199] Manual override assessment in S1306 may adopt the process illustrated in Fig. 9 as described before.

[200] After processing inputs in S1202, an automated control is performed (S1204), determining the FiO₂ values based on the input SpO₂ values.

[201] Fig. 17 depicts the exemplary steps of the automated control in S1204. As shown in Fig. 17, once the automated control starts, a periodic adaptive process is first performed (S1702).

[202] Exemplary steps of the periodic adaptive process in S1702 are depicted by the flow chart in Fig. 18. As illustrated in Fig. 18, the periodic adaptive process may include updating the reference FiO₂ (S1802) and performance analysis (S1804), which may adopt the exemplary process as illustrated in Fig. 5 and Fig. 4 (as described hereinbefore) respectively.

[203] After the periodic adaptive process in S1702, the PID terms are generated in S1704. The exemplary process as illustrated in Fig. 3 as described before may be adopted by S1704.

[204] In S1706, an output FiO₂ value is determined based on the PID terms, a rFiO₂ value and the validity of the input SpO₂ value. The exemplary process as illustrated in Fig. 8 as described before may be adopted for determining the output FiO₂ value in S1706.

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[205] In S1708, whether the device has been switched into a manual mode is detected. If it is detected that the device has been switched into a manual mode, the output FiO_2 value is set to be equal to the FiO_2 value selected by a user (e.g., a bedside staff).

[206] In S1710, the control process determines whether one or a plurality of alarms need to be triggered, and controls the alarm(s) accordingly. The exemplary process as illustrated in Fig. 10 (as described before) may be adopted by S1710.

[207] In Fig. 12, after S1204, the determined FiO_2 value is then set as the output and sent to the output unit (S1206), and the control process updates the display to reflect the updated data (S1208), e.g., displaying data including the received input SpO_2 and the updated outputs.

[208] After updating the display, the control process detects whether a user input has been detected which instructs exiting the automated control (S1210). If not, the control process proceeds to S1202 again to repeat the steps S1202 to S1210. If a user input has been detected instructing exiting the automated control, the control process ends.

[209] Further, although the method of automatically controlling inspired oxygen delivery in some embodiments as described hereinbefore is performed by a controlling apparatus 10, the method can also be performed in the form of software; hardware; firmware; some combination of software, hardware, and/or firmware; and/or other mechanisms. For example, the method can be performed by a computer or microcomputer executing steps in machine-readable code, e.g., generated using coding tools. The software may also be integrated or installed in a controlling device, an oximeter, or a respiratory support device. The signals described herein are electronic signals, and the stored values are stored in non-transient electronically accessible storage.

[210] Described herein is an apparatus for automatically controlling inspired oxygen delivery.

[211] The apparatus includes: an input unit, receiving signals representing a plurality of input oxygen saturation (SpO_2) values for a patient; a memory, recording the received input SpO_2 values; a controller, determining output inspired oxygen concentration (FiO_2)

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values based on the input SpO_2 values; and an output unit, outputting the determined output FiO_2 values.

[212] The controller generates control values based on the input SpO_2 values and a target SpO_2 value; and generates the output FiO_2 values based on the control values and reference inspired oxygen concentration (rFiO_2) values. As previously described, the control values include: immediate control values, generated based on the input SpO_2 values, the target SpO_2 value, and an immediate gain coefficient; accumulation control values, generated based on the input SpO_2 values, the target SpO_2 value, and an accumulation gain coefficient; and predictive control values, generated based on the input SpO_2 values, the target SpO_2 value, and a predictive gain coefficient; wherein the immediate gain coefficient is determined based on the rFiO_2 value; and wherein a non-linear compensation weighting is applied to the accumulation control value based on a predetermined non-linear relationship between partial pressure of arterial oxygen (PaO_2) and SpO_2 .

[213] For example, the apparatus may have a configuration as the controlling apparatus 10, as shown in Fig. 2.

[214] Described herein is a system for automatically controlling inspired oxygen delivery. The system includes: one or a plurality of oxygen saturation monitoring devices, and one or a plurality of inspired oxygen control devices; a controlling device; and a network, enabling communication between the one or a plurality of oxygen saturation monitoring devices and the controlling device, and communication between the one or a plurality of inspired oxygen control devices and the controlling device.

[215] The controlling device controls inspired oxygen delivery by: receiving signals representing a plurality of input oxygen saturation (SpO_2) values for a patient from each of the one or a plurality of oxygen saturation monitoring devices through the network; generating control values based on the input SpO_2 values and a target SpO_2 value; generating output inspired oxygen concentration (FiO_2) values based on the control values and reference inspired oxygen concentration (rFiO_2) values; and sending the determined output FiO_2 values to a corresponding inspired oxygen control device through the network.

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As previously described, the control values include: immediate control values, generated based on the input SpO_2 values, the target SpO_2 value, and an immediate gain coefficient; accumulation control values, generated based on the input SpO_2 values, the target SpO_2 value, and an accumulation gain coefficient; and predictive control values, generated based on the input SpO_2 values, the target SpO_2 value, and a predictive gain coefficient; wherein the immediate gain coefficient is determined based on the rFiO_2 value; and wherein a non-linear compensation weighting is applied to the accumulation control value based on a predetermined non-linear relationship between partial pressure of arterial oxygen (PaO_2) and SpO_2 .

[216] In this way, the controlling device may be used in a network with one or more pairs of oxygen saturation monitoring devices and inspired oxygen control devices connected to the network. This may allow real-time automatic control of performance at remote sites, and may allow collection of data on a large scale. A centralised controlling device may also simplify the adjustment or modification of the controlling process.

EXAMPLES

[217] Described below are exemplary experiments involving methods for automatically controlling inspired oxygen delivery, and the corresponding experimental results.

First Example

Method

[218] In a first example, a proportional-integral-derivative (PID) controller was enhanced by (i) compensation for the non-linear SpO_2 - PaO_2 relationship, (ii) adaptation to the severity of lung dysfunction, and (iii) error attenuation within the target range.

[219] The oxygen controller method was embodied in a stand-alone device consisting of a processing platform (laptop computer), device inputs and outputs, a servo-controlled air-oxygen blender and a user-interface displayed on the computer screen. The controlling instructions were written in a graphical programming language (LabVIEW

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2010, National Instruments, Austin, USA) and uploaded in the laptop computer as machine-readable instructions.

[220] The instructions provided a proportional-integral-derivative (PID) controller. For PID control, an error is defined as the deviation of the process signal from the set-point, and the value of the manipulated signal output at each moment is proportional to the error, its integral and its derivative, with a different multiplying coefficient in each case (K_p , K_i , K_d). In this case the error (e) was the numerical difference between the incoming value for SpO_2 (assuming a valid signal) and the midpoint of the selected target range (e.g. target range 91-95%, mid-point 93%). The integrand ($\int e d\tau$) was the sum of all errors (subject to constraints outlined below); the integral term in PID control lends the advantage of overcoming steady state error. The derivative ($\frac{de}{dt}$) was the SpO_2 slope by linear regression over the previous 5 seconds, and in PID control gives a prediction of future error. The output of the process at each iteration was ΔFiO_2 , being the sum of each of the PID terms (Equation 4). The FiO_2 to be delivered (set FiO_2) was the sum of ΔFiO_2 and a reference FiO_2 value ($rFiO_2$), a representation of the current baseline oxygen requirement (Equation 5). Set FiO_2 was rounded to $\pm 0.5\%$ and coerced to a value between 21 and 100%.

$$\Delta FiO_2 = K_p \cdot e + K_i \cdot \int e d\tau + K_d \cdot \frac{de}{dt} \quad (\text{Equation 4})$$

$$\text{Set } FiO_2 = \Delta FiO_2 + rFiO_2 \quad (\text{Equation 5})$$

[221] The PID controlling process was within a loop iterating each second, allowing FiO_2 alterations to be made at 1 second intervals if necessary. Value ranges for K_p , K_i and K_d were derived from extensive simulation studies. The values of K_p , K_i and K_d used in the example were: K_p -1; K_i -0.0125; K_d -1. The value of K_p could be adapted to the severity of lung dysfunction, within the range between -0.5 and -1 (see below).

[222] Modifications of the PID controller were applied to accommodate some idiosyncrasies of the system under control. The error related to SpO_2 values within the target range was reduced by applying a fractional multiplier proportional to distance from the mid-point of the target range (target range attenuation). Further, given the relative

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imprecision of SpO₂ monitoring at values less than 80%, negative error was capped at 13%. These error adjustments were applied to calculation of the proportional term only.

[223] Some modifications to handling of the integral term were also implemented. In recognition that the integral term progressively increments FiO₂ in the event of unremitting hypoxia, its magnitude was capped so as to limit the maximum ΔFiO_2 to 40% above rFiO₂. In hyperoxia (SpO₂ above target range when in supplemental oxygen), which can follow a hypoxic event as an “overshoot”, the error at high SpO₂ values is not proportional to the likely deviation of PaO₂ from an acceptable value (Fig. 19).

[224] To overcome this, Severinghaus compensation was adopted, whereby during hyperoxia, for as long as the integral term remained positive (i.e., tending to increase ΔFiO_2), an error multiplier was applied to incoming positive errors (see Table 2 below). In determination of the integral term, the error multiplier was applied to positive SpO₂ errors until the integral term was reduced to zero. Values for the error multiplier were derived from the Severinghaus equation. When in room air, sequential values of SpO₂ above the target range were no longer considered to represent unremitting hyperoxia, and the integral term was not altered.

[225] Table 2. Error multiplier for positive SpO₂ errors

SpO ₂ value	92%	93%	94%	95%	96%	97%	98%	99%	100%
Error multiplier	1.2	1.4	1.7	2.2	2.9	4.4	7.9	20.1	50

[226] The derivative term calculation was also modified in hyperoxia, such that negative SpO₂ slope was nullified (i.e. rendered = 0) if all of the latest 5 SpO₂ values were above the set-point. Upward pressure on ΔFiO_2 by the derivative term was thus avoided in hyperoxia.

[227] An adaptive approach was investigated in which K_p was modified according to the severity of lung dysfunction by applying a scaling factor proportional to current rFiO₂. The K_p modification was by multiplication of the standing value of K_p by a factor in the range 0.5 to 1.0 for rFiO₂ in the corresponding range 21% to 40%. Adaptation of K_p in this

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way acknowledges the inverse proportional relationship between gain and severity of lung disease that has been observed in this population.

[228] The primary input to the controlling process, SpO_2 , can be sourced from any oximeter having an analogue or digital data output. For the pre-clinical testing, SpO_2 was derived from a simulation of oxygenation in the preterm infant. The output from the controlling process can be transmitted to any device that can receive and execute a desired value of FiO_2 , including air-oxygen blenders and mechanical ventilators. For pre-clinical testing, the output FiO_2 was linked to the oxygenation simulator.

Preclinical testing

[229] The contribution of three enhancing features was investigated. The performance of all permutations of the PID control with a) Severinghaus compensation, b) K_p adaptation and c) target range attenuation was evaluated using a simulation of oxygenation. A 1 Hz recording of FiO_2 and SpO_2 (~24h duration) from each of 16 preterm infants on continuous positive airway pressure was converted to a series of values for ventilation-perfusion ($\dot{V}/Q$) ratio and shunt. SpO_2 averaging time of the original recordings was 2-4 seconds, and was not averaged further during the data abstraction and simulation. The $\dot{V}/Q$ and shunt series was then linked to the controller under test within the automated oxygen controller, allowing a sequence of unique values for SpO_2 to be generated. The SpO_2 target range was set at 91-95%. Function of the controller without an integral term (i.e., proportional-derivative, PD), and of the fully-enhanced controller with a 30 sec lockout after an FiO_2 adjustment, were also examined. For these latter analyses, multiple permutations of PID coefficients were trialled in an attempt to optimise performance.

[230] For each of the 16 SpO_2 sequences generated during simulation, proportions of time in the following oxygenation states were calculated: SpO_2 in target range, eupoxia (SpO_2 in target range, or above target range when in room air), $\text{SpO}_2 < 80\%$, $< 85\%$, below and above target range, $> 96\%$ in oxygen, and $> 98\%$ in oxygen. Frequency of prolonged episodes of hypoxia ($\text{SpO}_2 < 85\%$) and hyperoxia ($\text{SpO}_2 > 96\%$ in oxygen) were identified, as was frequency of SpO_2 overshoot, defined as SpO_2 readings above the target range for at least 60 sec over the 2 minutes following a hypoxic event with $\text{SpO}_2 < 85\%$. SpO_2

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instability was evaluated using SpO₂ coefficient of variation (CV), and frequency and mean duration of episodes outside the target range. These data were summarised as median and interquartile range (IQR), other than for SpO₂ overshoot, where data were pooled and expressed as a single value for each controlling process. Controlling performance was evaluated by comparison of medians using Friedman non-parametric repeated measures ANOVA with Dunn's *post hoc* test). For simplicity the comparisons were limited to the following groupings: a) PID with or without one enhancing factor (Severinghaus compensation/ K_p adaptation / target range attenuation); b) enhanced PID with or without subtraction of one enhancing factor; c) comparison of PID/enhanced PID/PID with 30 sec lockout/PD. Summary data regarding SpO₂ targeting by manual control from the original recordings were also generated, but statistical comparisons not made given the different SpO₂ target range (88-92%).

Results

[231] The recordings using in the simulation came from 16 preterm infants of median gestation at birth 30.5 weeks (IQR 27.5-31 weeks), birth weight 1320 (910-1860) grams and post-natal age 2.0 (0-5.3) days. The infants had a considerable degree of SpO₂ instability, with hypoxic episodes (SpO₂ <80) occurring with a frequency of 3.1 (1.6-9.9) episodes per 4 hours. At the time of the recording, CPAP pressure level was 7.0 (6.5-8.0) cm H₂O and baseline FiO₂ 0.28 (0.25-0.31), with a baseline FiO₂ range of 0.21 to 0.61. After removal of missing SpO₂ data, the recordings were of duration 22 (20-26) hours.

[232] In simulation testing, the complementary function of the different components of the PID controller was evident. Separate addition of K_p adaptation and target range attenuation to the PID controller improved eupoxia time, whereas addition of Severinghaus compensation decreased episodes of hyperoxia (Table 3 and 4). Overall, the performance of the PID controller with all 3 enhancements was superior to other combinations. Without target range attenuation, eupoxia time trended higher than for fully enhanced PID (Table 3). Hypoxic and hyperoxic episodes were most effectively eliminated without K_p adaptation (Table 4). Removal of Severinghaus compensation from the enhanced controller minimised hypoxia, but predictably led to more time in, and episodes of, hyperoxia (Tables 3 and 4). The enhanced controller performed better in all respects than an controller with a

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30 second lockout period after each FiO_2 alteration, and considerably better than a PD controller (Tables 3 and 4).

[233] Stability of the SpO_2 recording also varied considerably with different permutations of enhancing features (Table 5). The SpO_2 CV values in the recordings overall reflected the instability seen in individual examples (e.g., with K_p adaptation removed from the enhanced controller). SpO_2 CV was minimised with the enhanced controller (and several other combinations) suggesting relative stability under these circumstances. Both PID control with a 30 second lockout and PD control resulted in less SpO_2 stability, with longer-lasting episodes above and below the target range (Table 5).

[234] Separate addition of each enhancing feature to the PID controller showed a benefit. The enhanced controller had better all-round performance than PID controller with fewer enhancements, with an optimal combination of time in the desired SpO_2 range and avoidance of hypoxia and hyperoxia. This controller performed better than one with a 30 second lockout, and considerably better than PD control.

[235] The enhanced PID controller was able to respond rapidly to SpO_2 deviations, adjusting FiO_2 up to once per second if necessary. The initial response to a hypoxic or hyperoxic event was largely the domain of the proportional and derivative terms, with further and more tempered FiO_2 adjustments dictated by the integral term until normoxia was restored.

[236] At least in simulation, the enhanced PID controller was very effective in mitigation of episodes of prolonged hypoxia and hyperoxia. The addition of Severinghaus compensation to the PID controller was instrumental in overcoming hyperoxic events (including overshoot), and removing it from the enhanced controller resulted in their reappearance.

[237] To sum up, in the above preclinical testing using an oxygenation simulation, the enhanced controller was very effective in targeting the desired SpO_2 range and avoiding the extremes of oxygenation.

[238] Table 3. SpO₂ targeting

	SpO ₂ in target range	Eupoxia	SpO ₂ <80%	SpO ₂ <85%	SpO ₂ below target range	SpO ₂ above target range	SpO ₂ >96% in oxygen	SpO ₂ >98% in oxygen
Manual control (original recordings)	49.2 (39.3-54.1)	55.6 (51.3-65.1)	0.60 (0.13-2.0)	3.0 (2.0-6.4)	10 (7.2-17)	38 (32-54)	3.3 (2.3-4.6)	0.30 (0.16-0.83)
Core PID	91.1 (83.1-92.6) ^{a,i}	92.6 (90.9-94.0) ^{a,h,i}	0.059 (0.022-0.12) ^g	0.22 (0.13-0.43) ^g	3.7 (3.1-4.2) ^{a,i}	4.8 (3.9-13) ^{a,f}	1.73 (1.0-2.1) ^h	0.070 (0.030-0.12) ^g
Core PID + SC	82.9 (78.3-89.8) ^c	90.0 (83.9-92.9) ^a	0.56 (0.15-2.6) ^a	1.2 (0.55-4.2) ^a	6.2 (4.5-10) ^c	6.9 (4.5-13)	1.5 (0.63-3.0)	0.10 (0.016-0.51)
Core PID + adaptive Kp	92.2 (85.3-95.1) ^{b,d}	94.7 (92.2-95.7) ^b	0.040 (0.014-0.12) ^b	0.20 (0.088-0.26) ^b	2.6 (2.0-3.8) ^{b,d}	4.4 (2.6-12) ^b	1.1 (0.87-1.8)	0.089 (0.0077-0.19)
Core PID + TRA	91.7 (85.1-94.5) ^d	93.8 (91.8-95.5) ^b	0.049 (0.019-0.11) ^b	0.20 (0.10-0.30) ^b	2.9 (2.0-3.9) ^d	4.6 (2.8-13)	1.2 (0.87-1.7)	0.047 (0.019-0.11)
Enhanced PID – SC	91.7 (84.4-94.9) ^e	94.3 (91.7-95.5) ^d	0.037 (0.017-0.11) ^c	0.20 (0.091-0.26) ^c	2.8 (2.1-4.1) ^e	4.6 (2.7-12) ^e	1.1 (0.88-1.8) ^e	0.092 (0.011-0.20) ^{d,f}
Enhanced PID – adaptive Kp	88.1 (82.3-92.2) ^g	92.5 (89.5-95.2) ^d	0.43 (0.076-1.3) ^d	0.75 (0.23-1.8) ^d	5.1 (3.5-6.9) ^{f,g}	4.9 (3.1-12) ^e	1.2 (0.51-1.7)	0.088 (0.014-0.23) ^d
Enhanced PID – TRA	91.4 (86.2-95.6) ^{f,h}	95.5 (93.3-95.9) ^c	0.094 (0.028-0.25) ^d	0.28 (0.18-0.66)	3.6 (2.8-4.9) ^h	3.0 (1.3-12) ^d	0.44 (0.25-0.63) ^d	0.013 (0-0.042) ^e
Enhanced PID	91.2 (85.3-95.5) ^{h,i}	95.1 (92.9-96.5) ^g	0.088 (0.024-0.18) ^{d,g}	0.24 (0.094-0.43) ^g	3.8 (2.6-5.0) ^{f,i}	3.2 (1.2-12) ^{d,e}	0.31 (0.22-0.56) ^{d,g}	0.013 (0-0.042) ^{e,h}
Enhanced PID 30 sec lockout	87.9 (81.3-93.3) ^{i,k}	92.5 (90.1-94.0) ^{h,i}	0.21 (0.13-0.40) ^h	0.51 (0.30-0.73) ^h	5.5 (4.1-6.8) ^j	4.8 (1.9-12)	0.76 (0.45-1.2) ^h	0.024 (0-0.11)
PD control	52.7 (38.6-55.5) ^{j,l}	52.8 (38.6-59.1) ^{h,j}	1.6 (0.24-8.4) ^h	4.4 (0.67-17) ^h	20 (6.3-44) ^j	12 (4.2-39) ^f	2.5 (0.51-20) ^h	0 (0-0.037) ^h

Comparison of proportion of time (% of total time) within pre-specified SpO₂ ranges. Median (interquartile range). Within-column statistical comparisons (Friedman ANOVA with Dunn's *post hoc* test): ^aDiffers from b, P<0.05, ^cDiffers from d; ^eDiffers from f; ^gDiffers from h; ⁱDiffers from j; ^kDiffers from l. PID: proportional-integral-derivative; Kp: proportional coefficient; SC: Severinghaus compensation, TRA: target range attenuation.

[239] Table 4. Hypoxic and hyperoxic episodes and overshoot

	Hypoxia SpO ₂ <85%		Hyperoxia SpO ₂ >96% in oxygen		Post-hypoxia overshoot
	30 sec episodes per 24h	60 sec episodes per 24h	30 sec episodes per 24h	60 sec episodes per 24h	Episodes per 24h*
Manual control (original recordings)	30 (12-55)	8.0 (5.7-18)	23 (17-30)	10 (6.5-14)	0.71
Core PID	0 (0-1.2) ^b	0 (0-0.82)	5.0 (3.1-6.8) ^{b,c,h}	2.2 (0.84-3.4) ^{b,h}	0.90
Core PID + SC	0 (0-1.2)	0 (0-0.21)	0 (0-0.62) ^a	0 (0-0) ^a	0.19
Core PID + adaptive K_p	0 (0-1.4)	0 (0-0)	6.5 (5.5-11) ^{b,d}	2.7 (1.7-5.4) ^b	0.90
Core PID + TRA	0 (0-1.2)	0 (0-0.20)	5.5 (3.1-6.2) ^b	1.7 (0.84-3.4) ^b	0.84
Enhanced PID – SC	0 (0-1.9)	0 (0-0)	6.5 (5.5-11) ^e	2.3 (1.7-5.4) ^e	1.0
Enhanced PID – adaptive K_p	0 (0-0.053)	0 (0-0.0086)	0 (0-0.026) ^f	0 (0-0) ^f	0.19
Enhanced PID – TRA	0 (0-2.1)	0 (0-0)	1.1 (0.62-1.2) ^f	0 (0-0) ^f	0.13
Enhanced PID	0 (0-1.9) ^h	0 (0-0) ^h	1.0 (0-1.6) ^{f,g}	0 (0-0) ^{f,g}	0.19
Enhanced PID 30 sec lockout*	0.47 (0-2.2)	0 (0-0) ^h	2.4 (1.8-5.6)	0 (0-0.14) ^g	0.45
PD control*	4.8 (2.2-17) ^g	2 (0-4.2) ^g	12 (0-110) ^h	5.5 (0-54) ^h	0.13

Comparison of frequency of continuous hypoxic and hyperoxic episodes (≥ 30 and ≥ 60 sec duration) and of overshoot. Within-column statistical comparisons (Friedman ANOVA with Dunn's *post hoc* test): ^aDiffers from b, P<0.05, ^cDiffers from d; ^eDiffers from f; ^gDiffers from h; *data for overshoot episodes pooled for all 16 recordings. Abbreviations as per Table 3; see Methods hereinbefore for definition of overshoot.

[240] Table 5. SpO₂ instability

	SpO ₂ coefficient of variation (%)	SpO ₂ <91 % (episodes/h)	SpO ₂ <91 % (episode duration, sec)	SpO ₂ >95 % (episodes/h)	SpO ₂ >95 % (episode duration, sec)
Manual control (original recordings)	4.2 (3.3-4.8)	n.a.	n.a.	n.a.	n.a.
Core PID	1.8 (1.7-2.3) ^g	16 (14-19) ^{a,h}	7.9 (7.2-8.8) ^{a,c}	17 (14-28) ^{a,i}	11 (9.4-21) ^{a,g}
Core PID + SC	2.9 (2.3-5.4) ^a	24 (19-40) ^c	9.1 (8.2-9.3)	27 (18-30) ^c	9.2 (8.6-20) ^c
Core PID + adaptive Kp	1.7 (1.5-2.1) ^b	10 (7.7-12) ^{b,d}	9.2 (8.7-11) ^b	13 (7.1-17) ^{b,d}	16 (13-25) ^{b,d}
Core PID + TRA	1.7 (1.6-2.2) ^b	13 (9.6-14) ^d	8.9 (8.2-9.6) ^b	15 (9.5-24) ^d	13 (11-25) ^d
Enhanced PID – SC	1.7 (1.5-2.1)	11 (8.0-13) ^e	9.7 (9.0-11) ^d	13 (7.3-18) ^g	15 (13-26) ^e
Enhanced PID – adaptive Kp	2.7 (1.8-3.8) ^c	18 (15-25) ^f	9.4 (8.9-10)	17 (13-25) ^e	9.7 (8.7-23) ^f
Enhanced PID – TRA	1.8 (1.6-2.4) ^d	13 (11-16) ^f	9.2 (8.7-10) ^c	11 (5.3-17) ^f	9.3 (8.3-24) ^f
Enhanced PID	1.7 (1.6-2.3) ^g	13 (11-15) ^{f,g}	9.7 (9.0-11) ^{d,g}	12 (5.2-15) ^{f,h,j}	9.7 (8.6-26) ^{f,g}
Enhanced PID 30 sec lockout	2.2 (2.0-2.8) ^b	15 (12-17)	13 (12-15) ^{f,h}	13 (5.8-16) ^j	14 (12-29) ^h
PD control	4.5 (3.0-7.4) ^h	27 (14-56) ^h	21 (17-27) ^{f,h}	15 (7.1-36)	28 (11-42) ^h

Indices of SpO₂ instability. Median (interquartile range). Within-column statistical comparisons (Friedman ANOVA with Dunn's *post hoc* test): ^aDiffers from b, P<0.05, ^cDiffers from d; ^eDiffers from f; ^gDiffers from h; ⁱDiffers from j. PID: proportional-integral-derivative; Kp: proportional coefficient; SC: Severinghaus compensation, TRA: target range attenuation.

Second Example

Method

[241] In a second example, the enhanced PID controller of Example 1 was incorporated in an oxygen control device, and tested by clinical evaluation.

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[242] As illustrated in Fig. 20, the device incorporating the method for automated oxygen control was a standalone instrument consisting of a laptop computer, an automated air-oxygen blender and a data input/output device (USB-6008, National Instruments, Austin, USA) incorporating an analogue-digital (AD) converter. The controller received digital inputs from a standard cardiorespiratory monitor (Dräger Infinity, Dräger Medical Systems Inc, Notting Hill, Australia), including SpO₂ (Masimo oximetry probe, Masimo Corp, Irvine, California), heart rate determined from the electrocardiographic signal (HR_{ecg}), and plethysmographic heart rate (HR_{pleth}). SpO₂ averaging was set at fast (2-4 sec). FiO₂ was measured via a sensor in the proximal limb of the respiratory circuit (Teledyne), and input to the device via the AD converter. The desired value for FiO₂ derived from the controller was routed to a servomotor (model HS-322HD, Hitec RCD USA, Poway, USA) custom-mounted on an air-oxygen blender (Bird Ultrablender, Carefusion, Seven Hills, NSW), which allowed automatic rotation of the blender FiO₂ selection dial via a ringed gearing mechanism. The servomotor and gearing system had sufficient torque and precision to allow small adjustments to FiO₂ (minimum $\pm 0.5\%$) to be made accurately and repeatedly. The servomotor also had a low holding torque such that the blender dial could still be turned manually; such manual intervention was detected by a position sensor and resulted in a switch to a manual mode in which FiO₂ was no longer under automated control (see below). At the beginning of each study, the servomotor calibration was checked and if necessary altered.

[243] The automated control method consisted of a PID controlling process with enhancements in the determination of the proportional, integral and derivative terms to suit application of PID control to automated oxygen control in the preterm infant. The enhancements of the proportional term included modulation based on severity of lung dysfunction, error attenuation while within the target range and error capping during hypoxia. Integral term enhancements included integrand magnitude capping, compensation for the non-linear PaO₂-SpO₂ relationship, and inhibition of integrand increase in room air.

[244] The PID controlling process was within a loop iterating each second. The method was thus designed to detect and respond to the rapid changes in oxygenation that are all-too-frequent in preterm infants. Value ranges for the PID coefficients were derived from extensive simulation studies using data from preterm infants, allowing multiple

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permutations of different values for all coefficients to be examined. The values of K_p , K_i and K_d used in the example were: K_p -1; K_i -0.0125; K_d -1. The value of K_p could be adapted to the severity of lung dysfunction, within the range between -0.5 and -1.

[245] Non-numeric SpO_2 values were treated as missing, as were SpO_2 values in which the values of HRecg and HRpleth differed by >30 bpm. In the event of missing SpO_2 values, the FiO_2 was held at the current value. Full function of the controller resumed as soon as a valid signal was recovered.

[246] During automated control, bedside staff could over-ride the control device by manually turning the blender FiO_2 dial. This signalled manual over-ride through the detection of a discrepancy between the set FiO_2 and the FiO_2 value detected by the position sensor within the servomotor. Once in manual over-ride, automated control resumed at the user-selected FiO_2 30 seconds after the last manual alteration to FiO_2 . The device could also be locked in manual control mode by the research team on instruction from bedside staff if deemed necessary.

Clinical Testing

[247] The study was conducted in the Neonatal and Paediatric Intensive Care Unit at the Royal Hobart Hospital. The Unit provides care for ~70 preterm infants <32 weeks gestation per year, and has an ethos of using non-invasive respiratory support whenever possible for this patient group, including continuous positive airway pressure (CPAP) and high flow nasal cannulae (HFNC). The SpO_2 target range for titration of oxygen therapy has been revised to 90-94%, having previously been 88-92%.

[248] Preterm infants <37 weeks gestation and < 4 months of age were eligible for study if on non-invasive respiratory support (CPAP or HFNC) and receiving supplemental oxygen at the outset of the study period. Infants with acute instability or congenital abnormalities (including cardiac malformations other than patent ductus arteriosus) were excluded.

[249] This was a prospective interventional study of a 4 hour period of automated oxygen control, which was compared with two flanking periods of standard manual control

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totalling 8 hours (4 hours before and after automated control). There was a 15 min interval between study periods to avoid carryover effects. Study personnel were in attendance for the duration of the automated control period, but were not to interact with bedside clinical staff unless there was a critical system malfunction. During automated control, caregivers could over-ride the control device output to the customised air-oxygen blender used in the study by turning the blender dial. During the recordings of manual control, bedside caregivers were instructed to use their usual approach to SpO₂ targeting, with the standard SpO₂ target range (90-94%). Based on previous studies, it was expected that with manual control the upper end of this range would be preferentially targeted. Given that the automated controller targets the mid-point of the SpO₂ range, during automated control the target range was set at 91-95%, with the expectation that the manual and automated SpO₂ histograms would overlap, with a similar median SpO₂. For both manual and automated study epochs, the SpO₂ alarm settings were identical – lower limit 89%, upper limit 96%.

[250] Prior to the study the oximetry probe was placed in a post-ductal position, and not moved during the 3 study epochs unless there was a clinical need or a consistently poor SpO₂ signal. Care times were scheduled to fall outside the data recording periods where possible. For automated control a constant value for reference FiO₂ (rFiO₂) was selected in each infant based on most recent basal supplemental oxygen requirements.

[251] Relevant demographic and clinical data were recorded for each infant, including gestation, birth weight, and details of clinical state and level of respiratory support at the time of the study. SpO₂ and FiO₂ were recorded at 1 Hz during both manual and automated control. Analysis of these recordings allowed evaluation of SpO₂ instability in each infant, assessed by SpO₂ coefficient of variation, and number and mean duration of episodes outside the target range. Further, the proportion of time in each of the following oxygenation states was ascertained: SpO₂ in target range, eupoxia (SpO₂ in target range, or above target range in room air), SpO₂ in alarm range (89-96%), and SpO₂ <80%, 80-84%, 85-88%, 97-98% in oxygen, and >98% in oxygen. For calculation of these values the denominator was usable time after exclusion of data during periods of missing SpO₂ signal. Frequency of prolonged episodes of hypoxia and hyperoxia were identified, as was frequency of SpO₂ overshoot, defined as SpO₂ readings above the target range for at least 60 sec over the 2 minutes following a hypoxic event with SpO₂ <85%. The number of FiO₂

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adjustments (change in measured FiO_2 by 1% or greater) during manual and automated recordings was determined, as was the average oxygen exposure (mean FiO_2) in each case.

[252] Data were expressed as median and interquartile range (IQR) unless otherwise stated. Comparisons were made between automated and manual control epochs using Wilcoxon matched pairs test. For these analyses data from both manual control epochs were pooled, but additionally the best manual control epoch for each infant (i.e., the manual recording of duration $\geq 2\text{h}$ with the greatest proportion of time in eupoxia) was also used as the comparator. The primary outcome was proportion of time in eupoxia. The chosen sample size for the study (20 infants) was primarily based around need to gain an initial clinical experience of controller performance and safety in a sufficient number of subjects. In a previous study of 45 infants we found proportion of time in the target range when in oxygen to be $30 \pm 15\%$ (mean $\pm$ SD). Assuming a similar standard deviation for the differences between paired automated and manual control values in the present study, a sample of 20 infants thus allowed detection of a 10% difference in eupoxia time between automated and manual epochs with 80% power and alpha error 0.05.

Results

[253] The study was conducted from May to December 2015. Enrolled infants (n=20) were of median gestational age at birth 27.5 weeks (IQR 26-30 weeks) and birth weight 1130 (940-1400) gm. 15 of the 20 infants were male (75%). The infants were studied at a post-natal age of 8.0 (1.8-34) days, corrected gestational age of 31 (29-33) post-menstrual weeks, and body weight of 1400 (1120-1960) g. For infants studied on CPAP (n=13) the pressure level at the start of recording was 6 (5-8) cm H_2O ; for those studied on HFNC (n=7), starting flow rate was 6 (5.5-6.5) L/min. Nurse:patient ratio was 1:2 in all cases.

[254] Data from two flanking periods of manual control were available in 18 infants, with data logging failure and need for intubation immediately after automated control being the reasons for unavailability of a second manual control data recording (one case each). The proportion of missing signal was 2.9 (0.5-5.4)%, 1.7 (0.7-3.4)% and 1.5 (0.8-

7.1)% in the first manual, automated and second manual recordings, respectively, leaving 3.8 (3.7-4.0), 3.8 (3.7-3.9) and 4.0 (3.8-4.0) hours of usable time for analysis.

[255] Figs. 21A and 21B show two hour recordings from the same infant during manual and automated control, including sample recordings of SpO₂ (solid line, Y-axis: % saturation) and FiO₂ (dashed line, Y-axis: % oxygen) of:

(A) Infant 5 born at 27 weeks gestation, studied on day 40, on high flow nasal cannulae (HFNC) 6 L/min, manual control, eupoxia time 59% (shown in Fig. 21A); and

(B) Infant 5, automated control, eupoxia time 79%, with automated control with rFiO₂ set at 29% throughout, eupoxia time 82% (shown in Fig. 21B).

[256] Figs. 21A and 21B reveal the typical variability of SpO₂ during manual control of FiO₂ (Fig. 21A), which was less prominent during automated control (Fig. 21B). The exemplary data shown in Figs. 21A and 21B demonstrate the rapid responses in FiO₂ made by the controller and the increase in time in the target range (as shown by the grey band).

[257] As shown in Fig. 22 (black bars: manual control; white bars: automated control, T=SpO₂ values within target range, the target range being 90% - 94% for manual control, 91% - 95% for automated control), frequency histograms of pooled SpO₂ data show a substantial increase in proportion of time within the target range with automated control, with both hypoxic and hyperoxic values under-represented compared with manual control. The SpO₂ targeting profile during manual control appeared having the peak of the curve at the upper end of the targeted range. By contrast, and as expected, automated control targeted the mid-point of the set target range (i.e. SpO₂ 93%). When receiving supplemental oxygen, median SpO₂ in pooled data was 93% for both manual and automated control.

[258] Oxygenation was considerably more stable during automated control, with fewer SpO₂ deviations below target range and below 80%, and a shorter duration of all episodes outside target range compared with manual control. The SpO₂ coefficient of

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variation also differed considerably (manual: 3.8 (3.2-4.7)%, automated: 2.3 (1.8-3.0)%, $P < 0.0001$).

[259] Compared with both manual control epochs combined, automated control resulted in 23% and 25% more time in the target and eupoxic ranges, respectively (Table 6). Time spent within the alarm range (89-96%) was also higher. Automated control considerably diminished time at both extremes of oxygenation, virtually eliminating hypoxia with $\text{SpO}_2 < 80\%$ and hyperoxia in oxygen with $\text{SpO}_2 > 98\%$. Time spent in the lesser ranges of hypoxia and hyperoxia was also reduced.

[260] These findings were mirrored in the analysis of prolonged episodes of hypoxia and iatrogenic hyperoxia, both of which occurred with modest frequency during manual control (Table 7), but were distinctly uncommon during automated control. No overshoot episodes were identified in any of the automated control recordings.

[261] As shown in Fig. 23 (individual paired values of time in eupoxia for the best manual control epoch compared with automated control; Horizontal bar=median; Eupoxia= SpO_2 in target range, or above target range when in room air), when measured against the best of the two manual control epochs, the apparent benefit of automated control persisted, with time in the eupoxic range being 60 (50-72)% and 81 (76-90)% for best manual and automated control, respectively ($P < 0.001$). Moreover, automated control was associated with better SpO_2 targeting in each individual studied, with the relative improvement in eupoxia time ranging from 2.2 to 55% (Fig. 23).

[262] During manual control epochs, FiO_2 adjustments of at least 1% were made 2.3 (1.3-3.4) times per hour by bedside staff. During automated control, the minimum alteration to FiO_2 of 0.5% was being actuated by the servomotor frequently (9.9 alterations/min overall), and changes to measured FiO_2 of at least 1% occurred at a frequency of 64 (49-98) per h. When in automated control, a total of 18 manual adjustments were made in all 20 recordings (0.24 adjustments/h), a reduction by 90% from the rate of manual adjustments observed during manual control (2.3/h). The maximum number of manual adjustments in an individual subject during automated control was 4 in a 4 hour recording (i.e. 1/h). No critical system malfunctions occurred.

[263] Median values for oxygen requirement (average FiO_2) were 27 (25-30)%, 27 (25-30)% and 26 (24-31)% for first manual, automated and second manual recordings, respectively. Oxygen requirements did not differ between automated and either manual recording ($P>0.05$, Wilcoxon matched pairs test).

[264] In summary, the enhanced PID controller was considerably more effective in SpO_2 targeting than routine manual control, with 25% more time in the desired SpO_2 range. The extremes of oxygenation were largely avoided, and prolonged episodes of hypoxia and hyperoxia were virtually eliminated. Effective oxygen control was achieved with very few manual fraction of inspired oxygen adjustments, and similar exposure to oxygen.

[265] Table 6. Oxygen saturation (SpO_2) targeting

	Manual control	Automated control	P value*
SpO_2 in target range	55 (46-60)%	78 (75-87)%	0.0001
SpO_2 below target range	19 (12-27)%	14 (7.8-19)%	0.0027
SpO_2 above target range	25 (23-35)%	5.1 (3.-6.9)%	0.0003
Eupoxia	56 (48-63)%	81 (76-90)%	<0.0001
SpO_2 in alarm range (89-96%)	81 (70-83)%	93 (90-98)%	0.0006
SpO_2 in alarm range or higher when in air	81 (73-83)%	95 (92-98)%	<0.0001
$\text{SpO}_2 < 80\%$	0.7 (0.10-1.3)%	0 (0-0.17)%	0.0006
SpO_2 80-84%	2.6 (1.2-3.2)%	0.39 (0.10-0.67)%	0.0001
SpO_2 85-88%	10 (6.8-15)%	3.5 (1.1-5.8)%	0.0002
SpO_2 97-98% when in oxygen	5.0 (3.2-7.9)%	0.71 (0.28-1.5)%	0.0001
SpO_2 99-100% when in oxygen	0.46 (0.22-1.4)%	0 (0-0.12)%	0.0010

Comparison of proportion of time (% of total usable time) within pre-specified SpO_2 ranges for manual and automated control. Manual control data pooled from two flanking periods. Median (interquartile range).

*Wilcoxon matched pairs test.

[266] Table 7. Hypoxic and hyperoxic episodes

	30 second episodes			60 second episodes		
	Manual control	Automated control	P value*	Manual control	Automated control	P value*
Hypoxia SpO₂ <80%, episodes/4h	1.0 (0-3.2)	0 (0-0)	0.0001	0.51 (0-0.76)	0 (0-0)	0.0010
Hypoxia SpO₂ <85%, episodes/4h	5.6 (2.4-7.5)	0 (0-1.1)	<0.0001	1.9 (0.62-2.6)	0 (0-0)	0.0001
Hyperoxia SpO₂ >96% in oxygen, episodes/4h	8.5 (4.9-14)	0 (0-0.25)	0.0001	1.9 (1.0-3.7)	0 (0-0)	0.0001
Hyperoxia SpO₂ >98% in oxygen, episodes/4h	0.55 (0.37-2.4)	0 (0-0)	0.0021	0 (0-1.0)	0 (0-0)	0.049

Comparison of frequency of continuous hypoxic and hyperoxic episodes (30 and 60 sec duration) between manual and automated control. Manual control data pooled from two flanking periods. Median (interquartile range). *Wilcoxon matched pairs test.

[267] Many modifications will be apparent to those skilled in the art without departing from the scope of the present invention as hereinbefore described with reference to the accompanying drawings.

CLAIMS:

1. A control method for an apparatus for automatically controlling inspired oxygen delivery, including:

receiving signals representing a plurality of input oxygen saturation (SpO_2) values for a patient;

generating control values based on the input SpO_2 values and a target SpO_2 value; and

generating output inspired oxygen concentration (FiO_2) values based on the control values and reference inspired oxygen concentration (rFiO_2) values;

wherein the control values include:

immediate control values, generated based on the input SpO_2 values, the target SpO_2 value, and an immediate gain coefficient;

accumulation control values, generated based on the input SpO_2 values, the target SpO_2 value, and an accumulation gain coefficient; and

predictive control values, generated based on the input SpO_2 values, the target SpO_2 value, and a predictive gain coefficient;

wherein the immediate control values are determined based on the rFiO_2 value; and

wherein a non-linear compensation weighting is applied to the accumulation control value based on a predetermined non-linear relationship between partial pressure of arterial oxygen (PaO_2) and SpO_2 .

2. The method of claim 1, wherein:

the immediate control values are generated by multiplying error values by the immediate gain coefficient, wherein the error values are associated with differences between the input SpO_2 values and the target SpO_2 value;

the accumulation control values are generated by multiplying summation or integrals of the error values by the accumulation gain coefficient,

the predictive control values are generated by multiplying differences or derivatives of the error values by the predictive gain coefficient.

3. The method of claim 1 or 2, further including:

determining a target SpO_2 range, wherein the target SpO_2 is within the target SpO_2 range;

wherein, when a current input SpO₂ value is within the target SpO₂ range, an attenuator is applied to the immediate control value, the attenuator being generated based on the current input SpO₂ value and a midpoint of the target SpO₂ range.

4. The method of any one of claims 1 to 3, wherein, when a current input SpO₂ value is lower than the target SpO₂ value, an error value associated with a difference between the current input SpO₂ value and the target SpO₂ value is capped at a selected maximum error value.

5. The method of any one of claims 1 to 4, further including:
modifying the accumulation control values to cap the control values at a selected maximum control value.

6. The method of claim 5, wherein each of the output FiO₂ values is the sum of the corresponding control value and the corresponding rFiO₂ value.

7. The method of any one of claims 1 to 6, wherein generating the accumulation control values includes:

inhibiting increases in the accumulation control values when: (i) a current output FiO₂ value is at room air level, and (ii) a current input SpO₂ value is above the target SpO₂ value.

8. The method of any one of claims 1 to 7, wherein the predictive control values are nullified if the input SpO₂ values have been above a selected SpO₂ threshold for a SpO₂ slope determination period.

9. The method of any one of claims 1 to 8, further including:
generating an rFiO₂ evaluation result based on the input SpO₂ values and the respective output FiO₂ values over an rFiO₂ evaluation time period; and
modifying the rFiO₂ value based on the rFiO₂ evaluation result.

10. The method of any one of claims 1 to 9, further including:

generating a SpO₂ validation result based on a current input SpO₂ value by classifying the current input SpO₂ value into one of multiple validity levels in a hierarchical validation procedure; and

determining the output FiO₂ value based on the SpO₂ validation result.

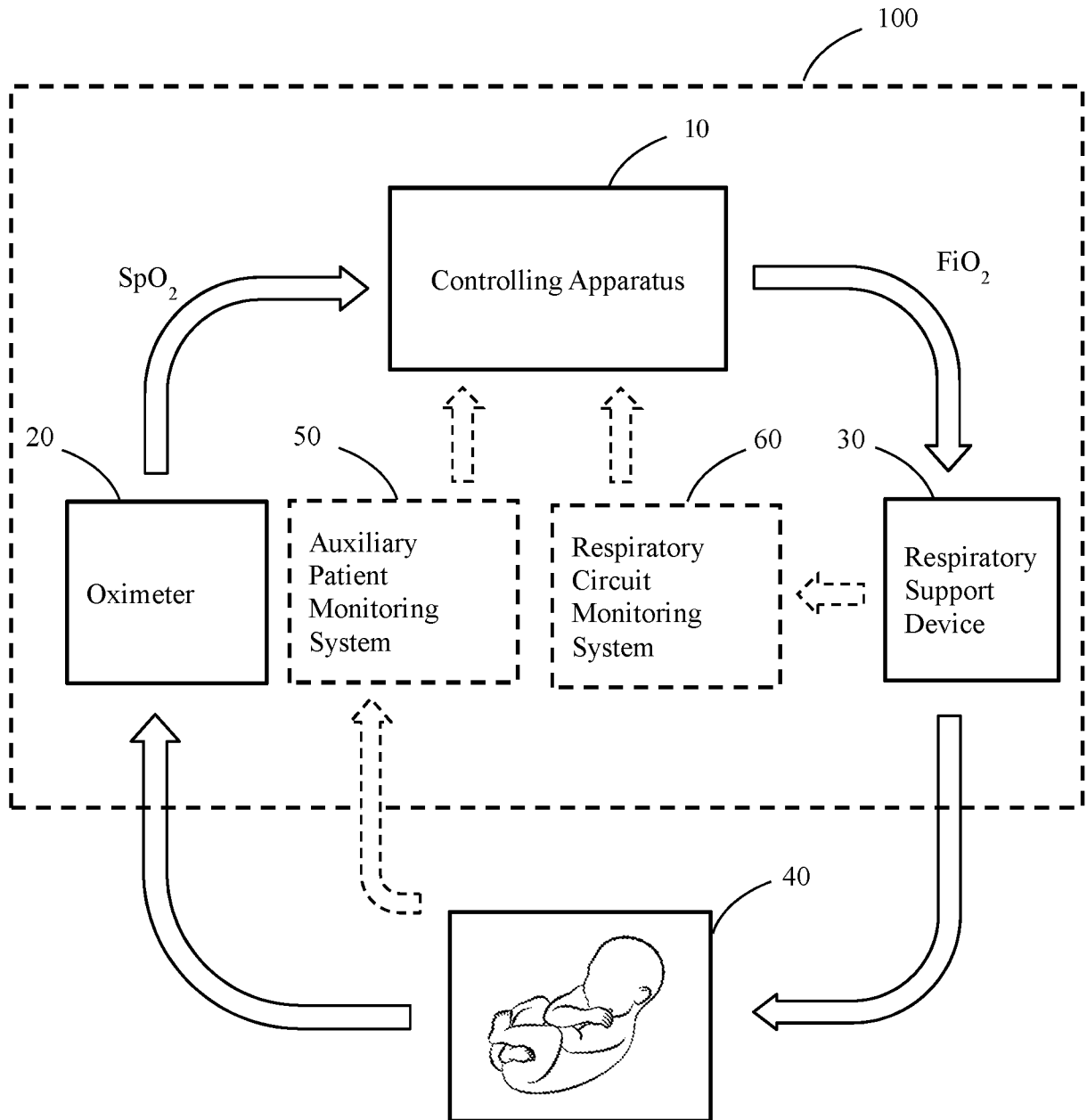
11. The method of any one of claims 1 to 10, further including:
receiving an manual override input;
determining the output FiO₂ value based on the manual override input instead of the control values.
12. The method of any one of claims 1 to 11, wherein the immediate gain coefficient has an initial value being:
 - (i) a selected value between -2 and -0.2; or
 - (ii) -1.
13. The method of any one of claims 1 to 12, wherein the accumulation gain coefficient has an initial value being:
 - (i) a selected value between -0.25 and -0.005; or
 - (ii) -0.0125.
14. The method of any one of claims 1 to 13, wherein the predictive gain coefficient has an initial value being:
 - (i) a selected value between -2 and -0.25; or
 - (ii) -1.
15. The method of any one of claims 1 to 14, wherein the immediate gain coefficient is modified based on a performance evaluation result.
16. The method of claim 15, wherein the performance evaluation result is generated based on at least one of:
a hypoxic time duration, in which the input SpO₂ values in the performance analysis time period were in a hypoxic range; and

a hyperoxic time duration, in which the input SpO_2 values in the performance analysis time period were in a hyperoxic range.

17. The method of claim 15 or 16, further including:
 - determining a target SpO_2 range, wherein the target SpO_2 is within the SpO_2 range;
 - wherein the performance evaluation result is generated based on at least one of:
 - a target time duration, in which the input SpO_2 values in the performance analysis time period were in the target SpO_2 range; and
 - an eupoxic time duration, in which the input SpO_2 values in the performance analysis time period were in the target SpO_2 range, or above the target SpO_2 range in room air.
18. An apparatus for automatically controlling inspired oxygen delivery, including:
 - an input unit, receiving signals representing a plurality of input oxygen saturation (SpO_2) values for a patient;
 - a memory, recording the received input SpO_2 values;
 - a controller, determining output inspired oxygen concentration (FiO_2) values based on the input SpO_2 values; and
 - an output unit, outputting the determined output FiO_2 values;wherein the controller:
 - generates control values based on the input SpO_2 values and a target SpO_2 value;
 - and
 - generates the output inspired oxygen concentration (FiO_2) values based on the control values and reference inspired oxygen concentration (rFiO_2) values;wherein the control values include:
 - immediate control values, generated based on the input SpO_2 values, the target SpO_2 value, and an immediate gain coefficient;
 - accumulation control values, generated based on the input SpO_2 values, the target SpO_2 value, and an accumulation gain coefficient; and
 - predictive control values, generated based on the input SpO_2 values, the target SpO_2 value, and a predictive gain coefficient;wherein the immediate control values are determined based on the rFiO_2 value; and

wherein a non-linear compensation weighting is applied to the accumulation control value based on a predetermined non-linear relationship between partial pressure of arterial oxygen (PaO_2) and SpO_2 .

19. A system for automatically controlling inspired oxygen delivery, including:
- one or a plurality of oxygen saturation monitoring devices, and one or a plurality of inspired oxygen control devices;
 - a controlling device; and
 - a network, enabling communication between the one or a plurality of oxygen saturation monitoring devices and the controlling device, and communication between the one or a plurality of inspired oxygen control devices and the controlling device,
- wherein the controlling device controls inspired oxygen delivery by:
- receiving signals representing a plurality of input oxygen saturation (SpO_2) values for a patient from each of the one or a plurality of oxygen saturation monitoring devices through the network;
 - generating control values based on the input SpO_2 values and a target SpO_2 value;
 - generating output inspired oxygen concentration (FiO_2) values based on the control values and reference inspired oxygen concentration (rFiO_2) values;
 - sending the determined output FiO_2 values to a corresponding inspired oxygen control device through the network;
- wherein the control values include:
- immediate control values, generated based on the input SpO_2 values, the target SpO_2 value, and an immediate gain coefficient;
 - accumulation control values, generated based on the input SpO_2 values, the target SpO_2 value, and an accumulation gain coefficient; and
 - predictive control values, generated based on the input SpO_2 values, the target SpO_2 value, and a predictive gain coefficient;
- wherein the immediate control values are determined based on the rFiO_2 value; and
- wherein a non-linear compensation weighting is applied to the accumulation control value based on a predetermined non-linear relationship between partial pressure of arterial oxygen (PaO_2) and SpO_2 .

**Fig. 1**

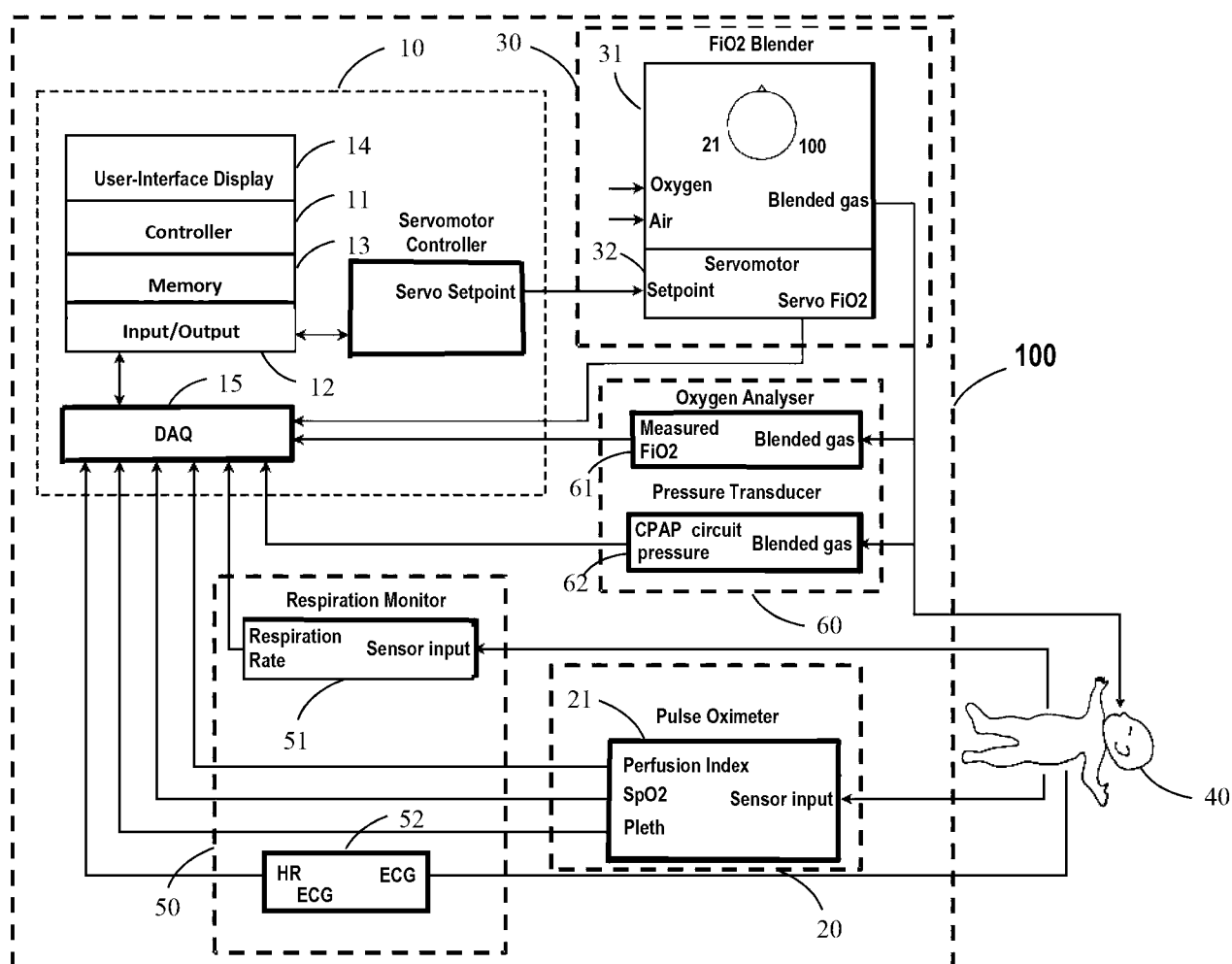
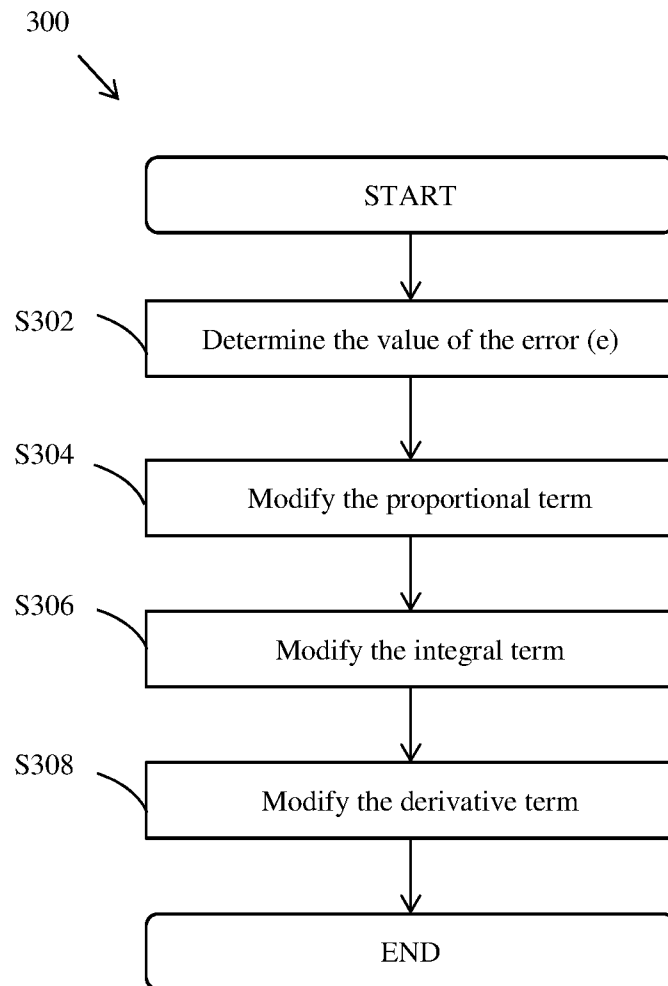
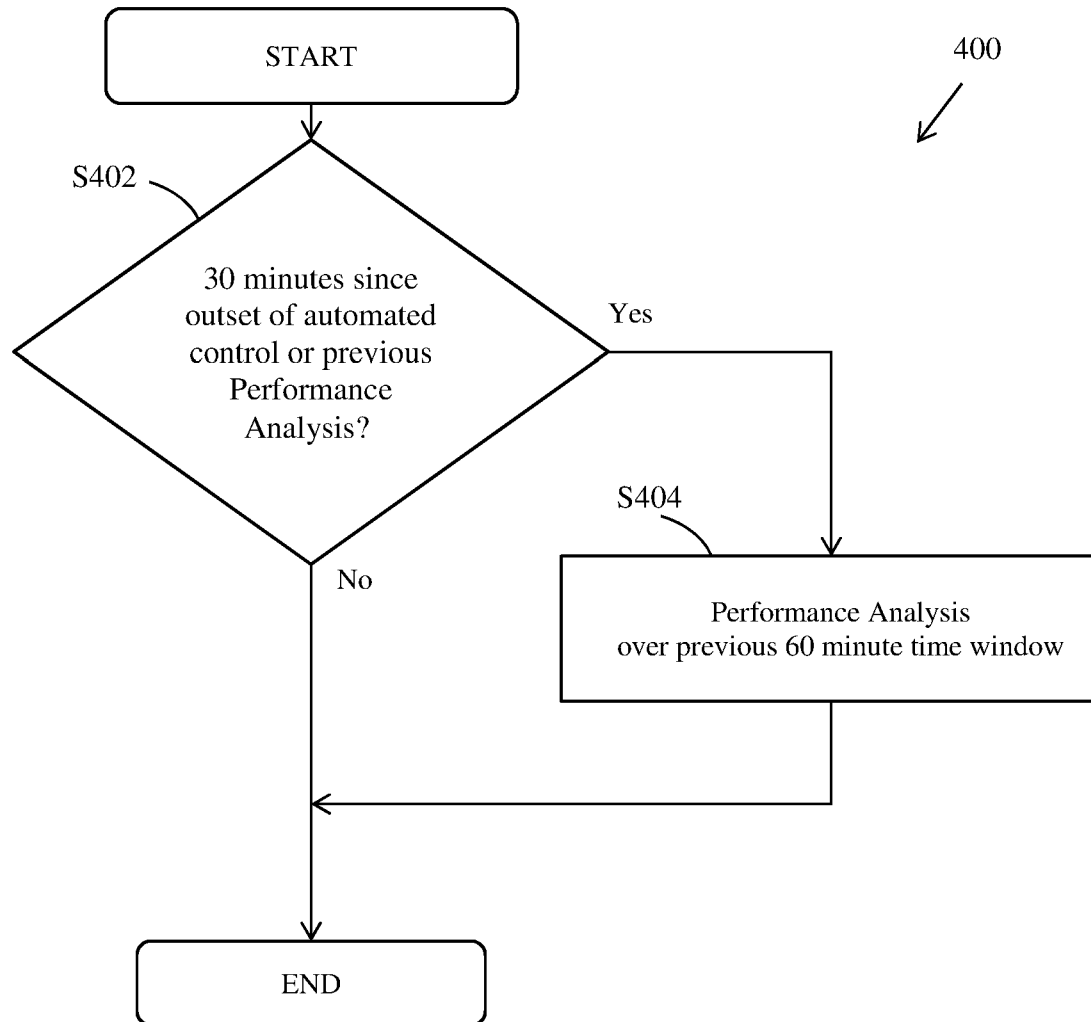


Fig. 2

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**Fig. 3**

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**Fig. 4**

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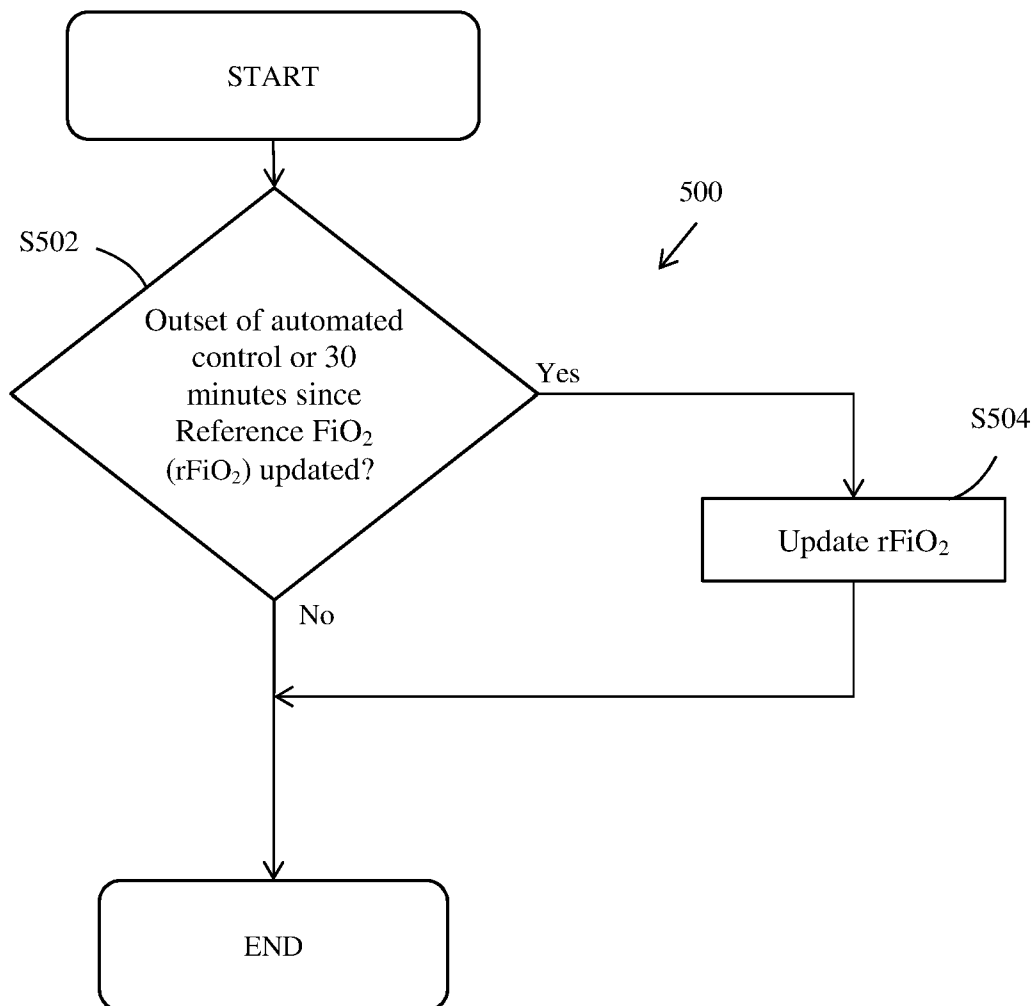
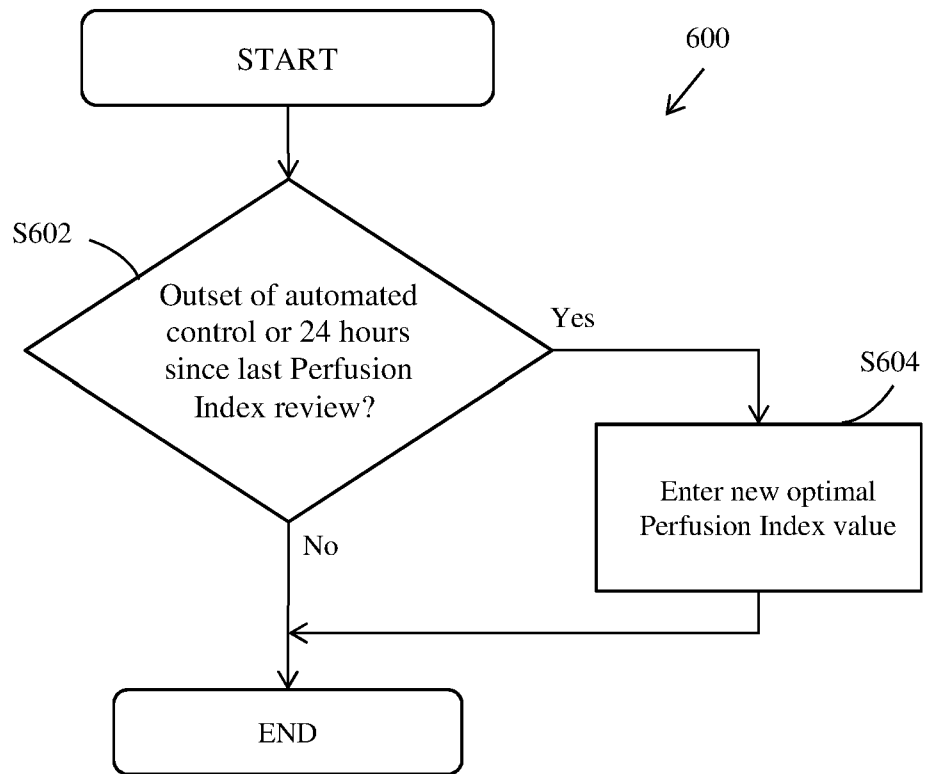


Fig. 5

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**Fig. 6**

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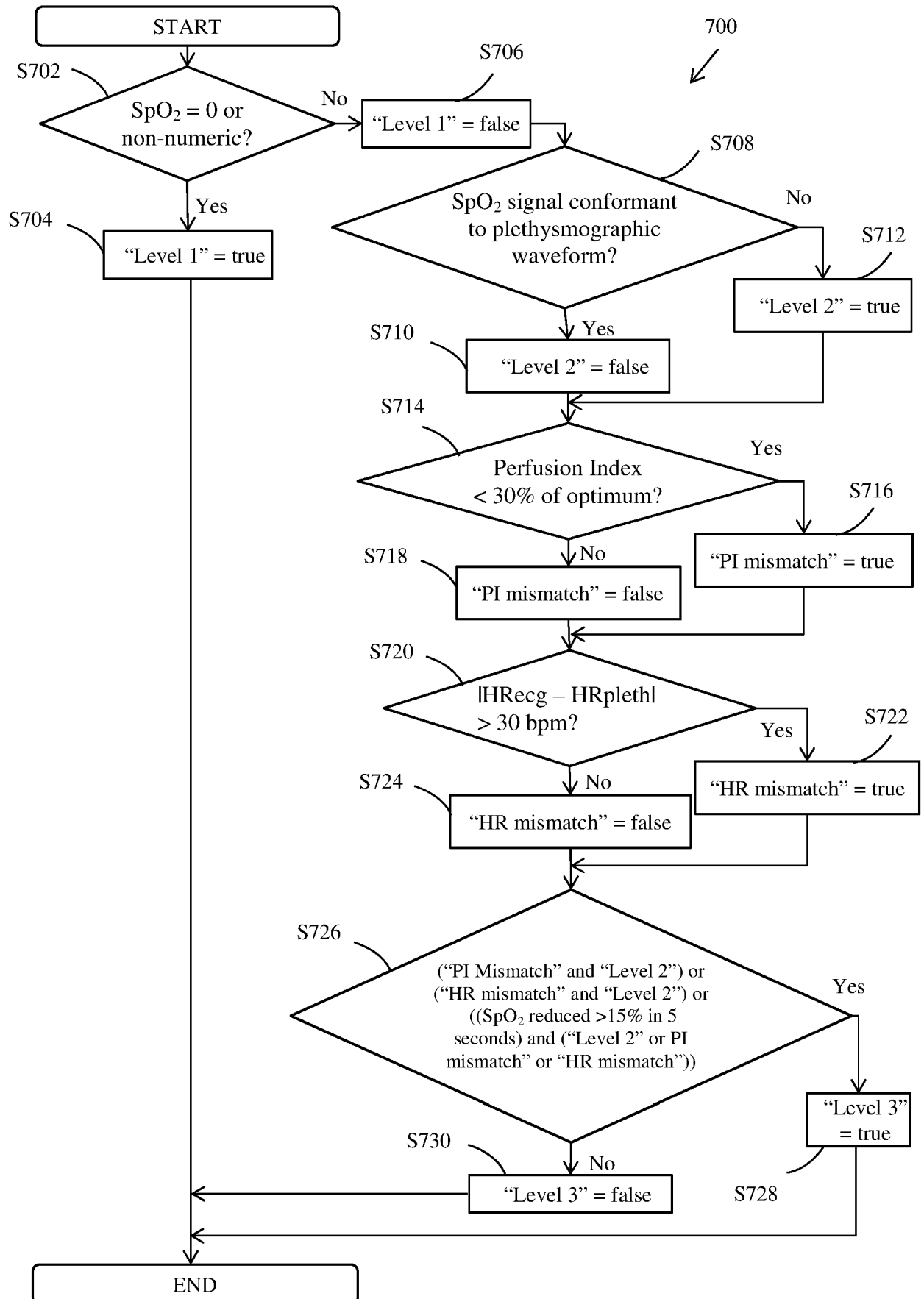


Fig. 7

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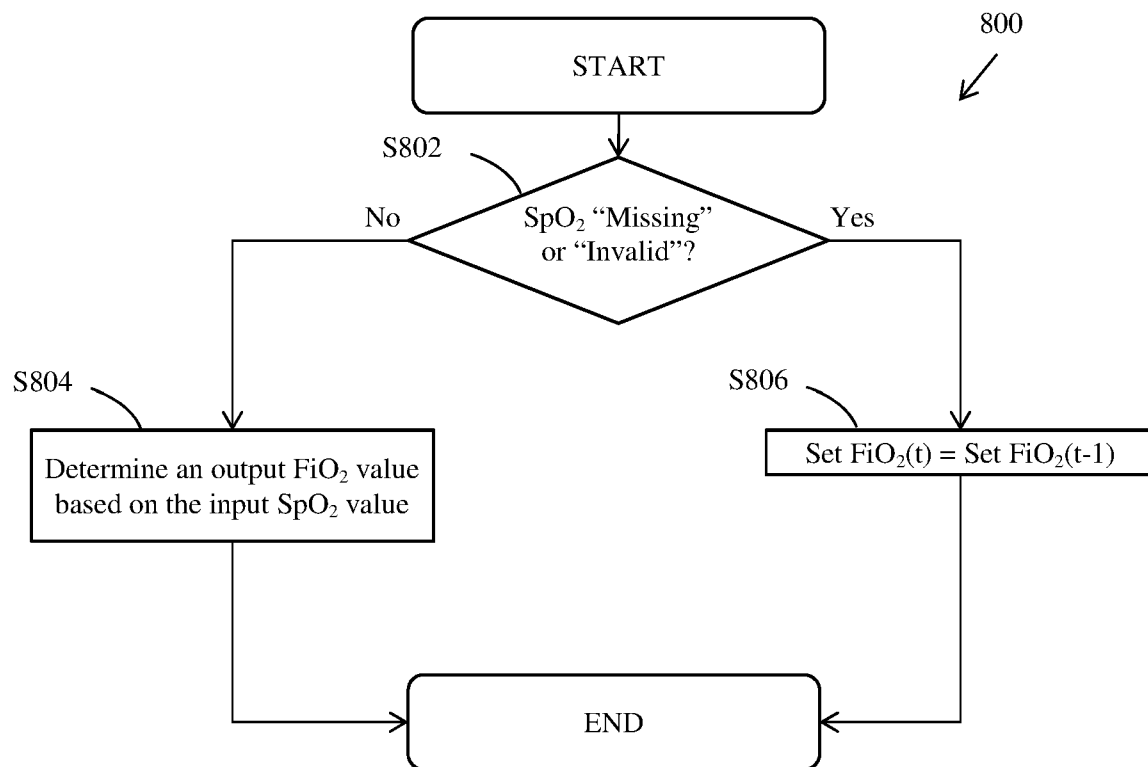
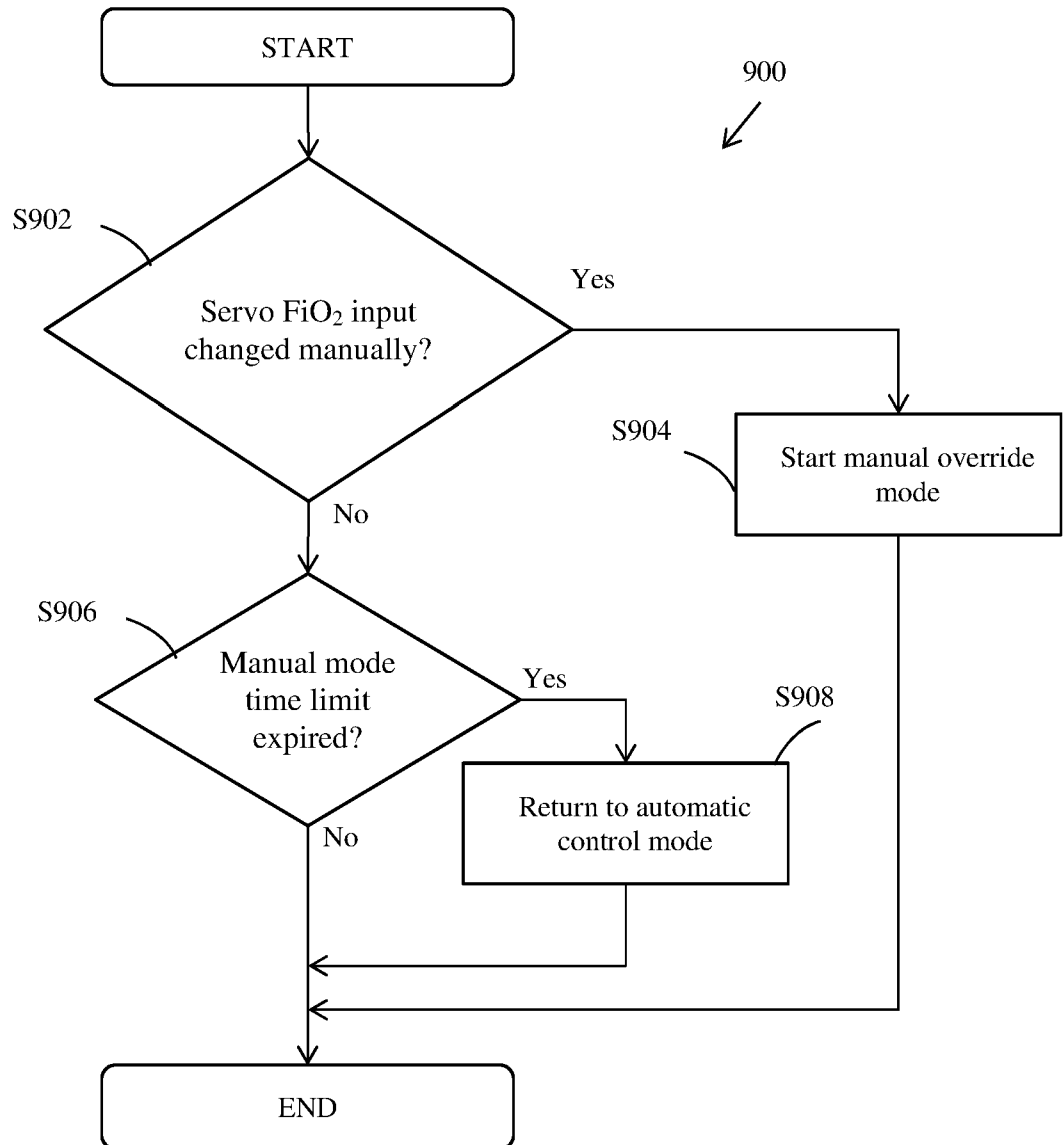
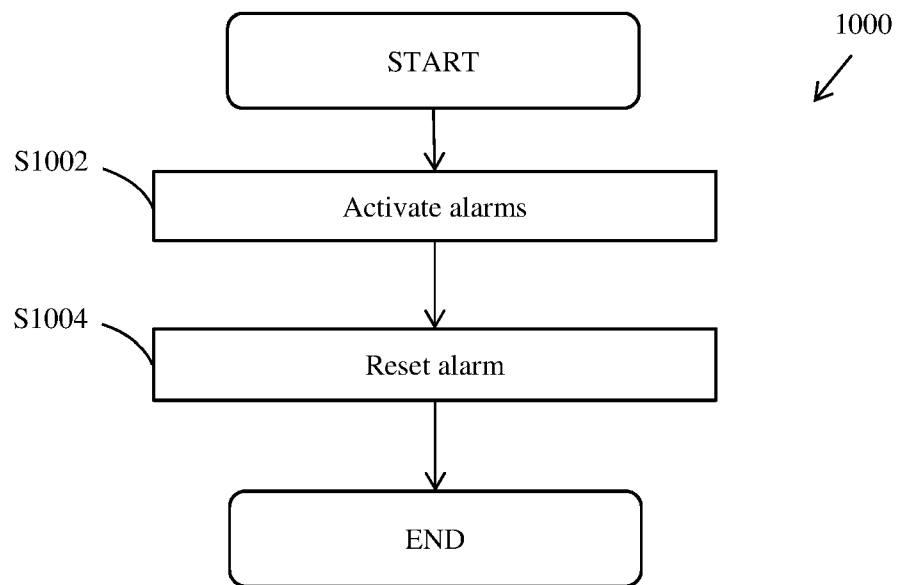


Fig. 8

**Fig. 9**

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**Fig. 10**

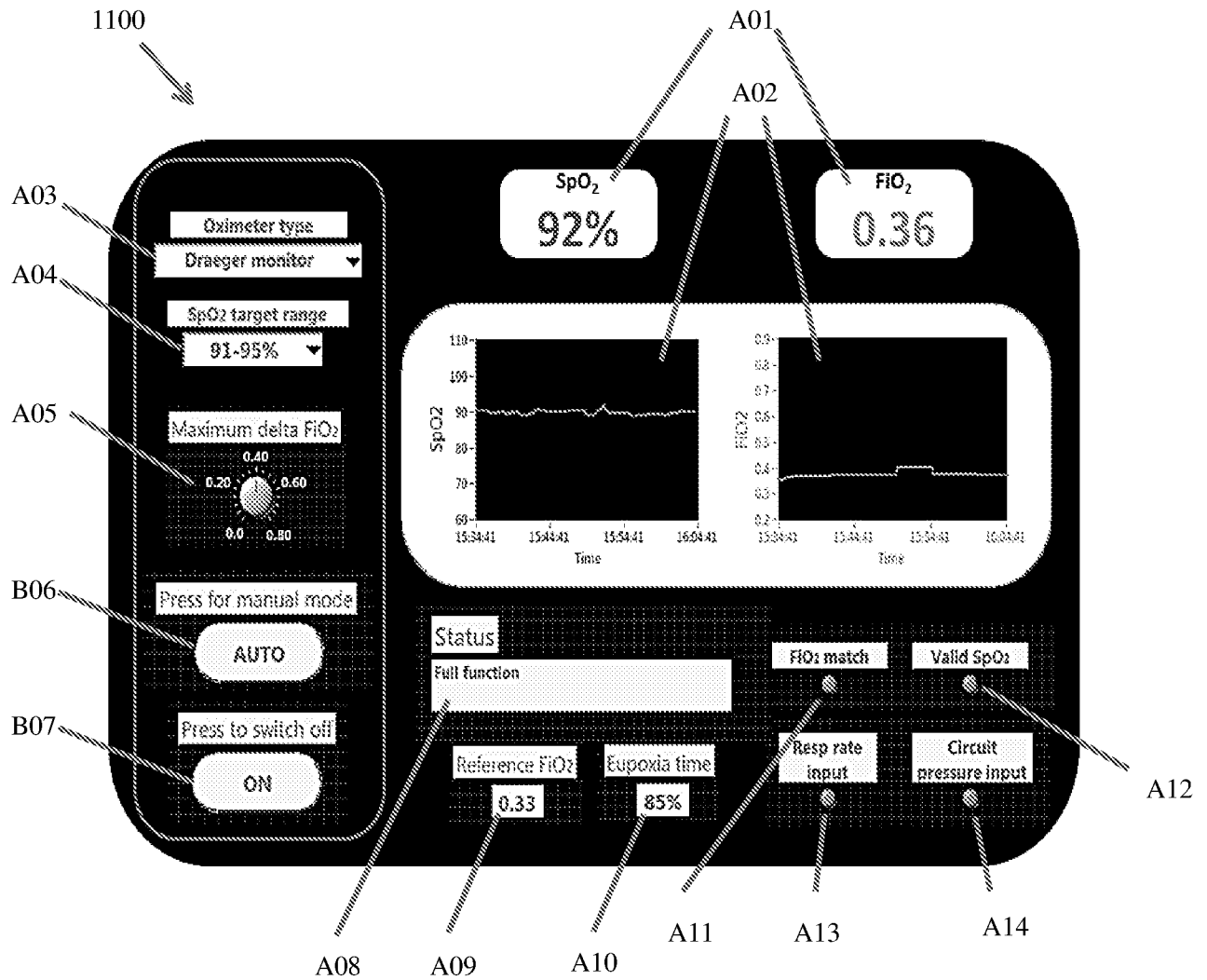
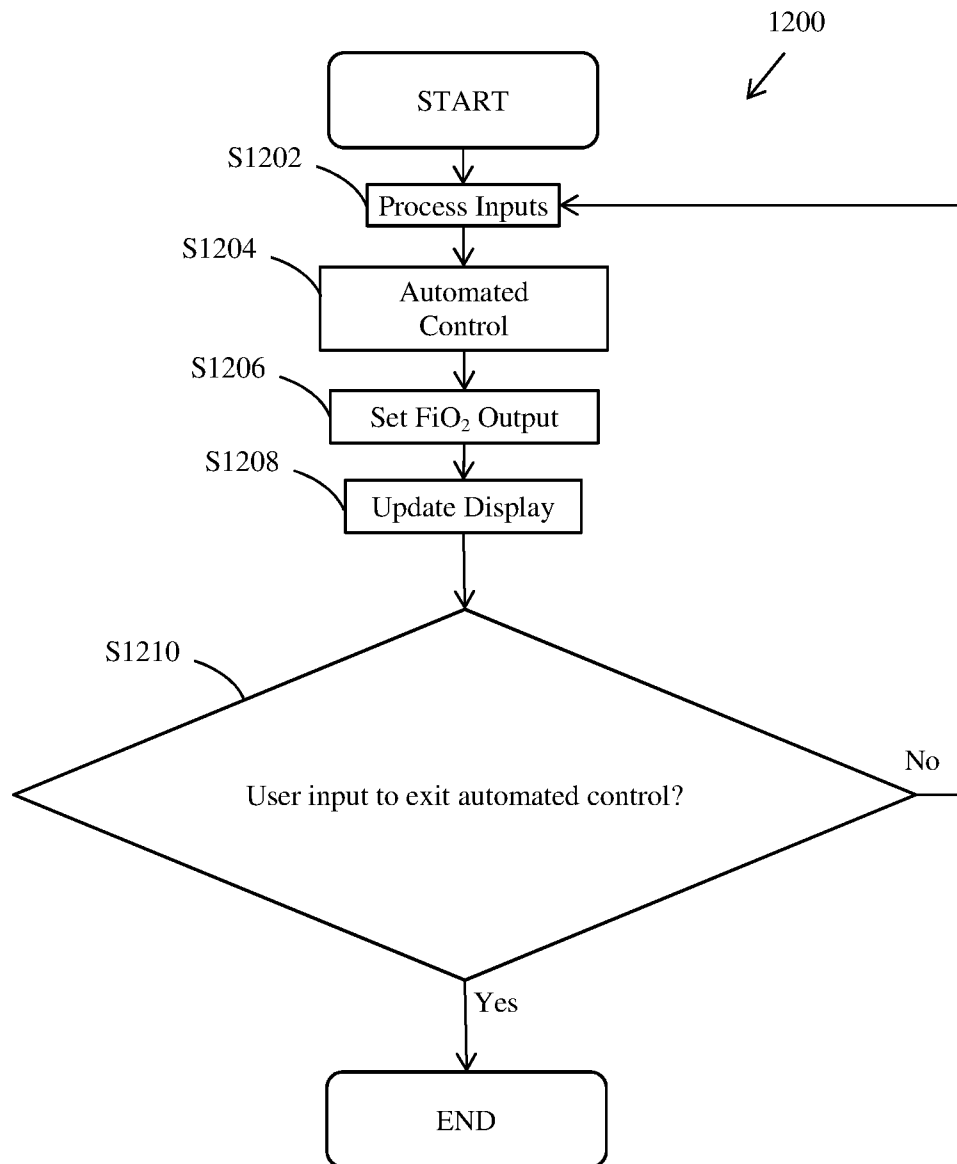
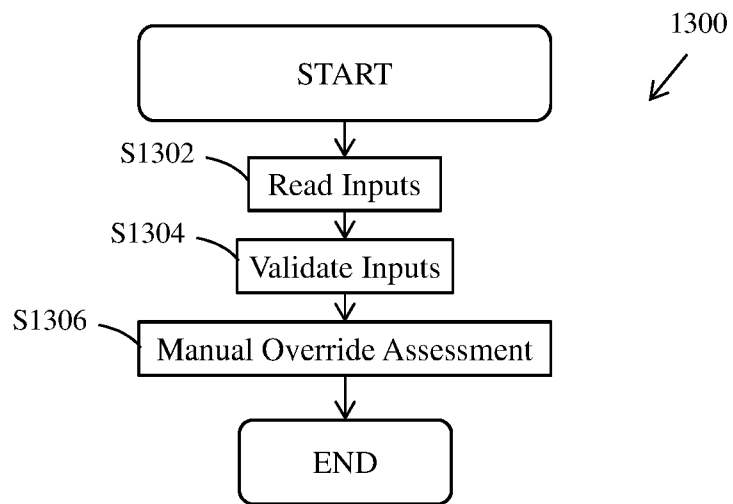


Fig. 11

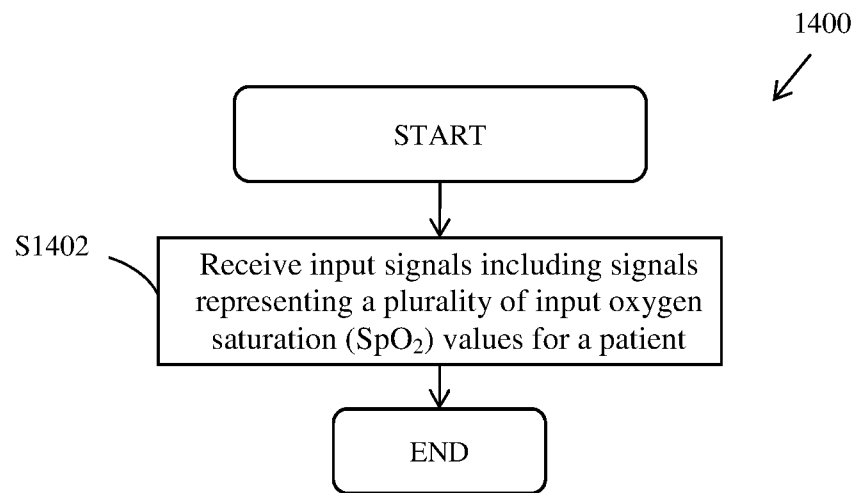
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**Fig. 12**

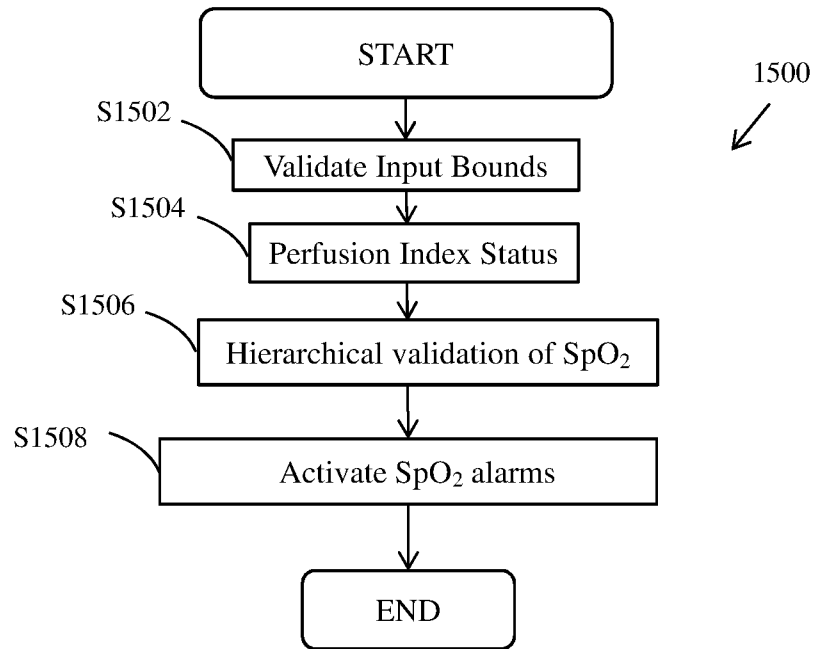
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**Fig. 13**

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**Fig. 14**

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**Fig. 15**

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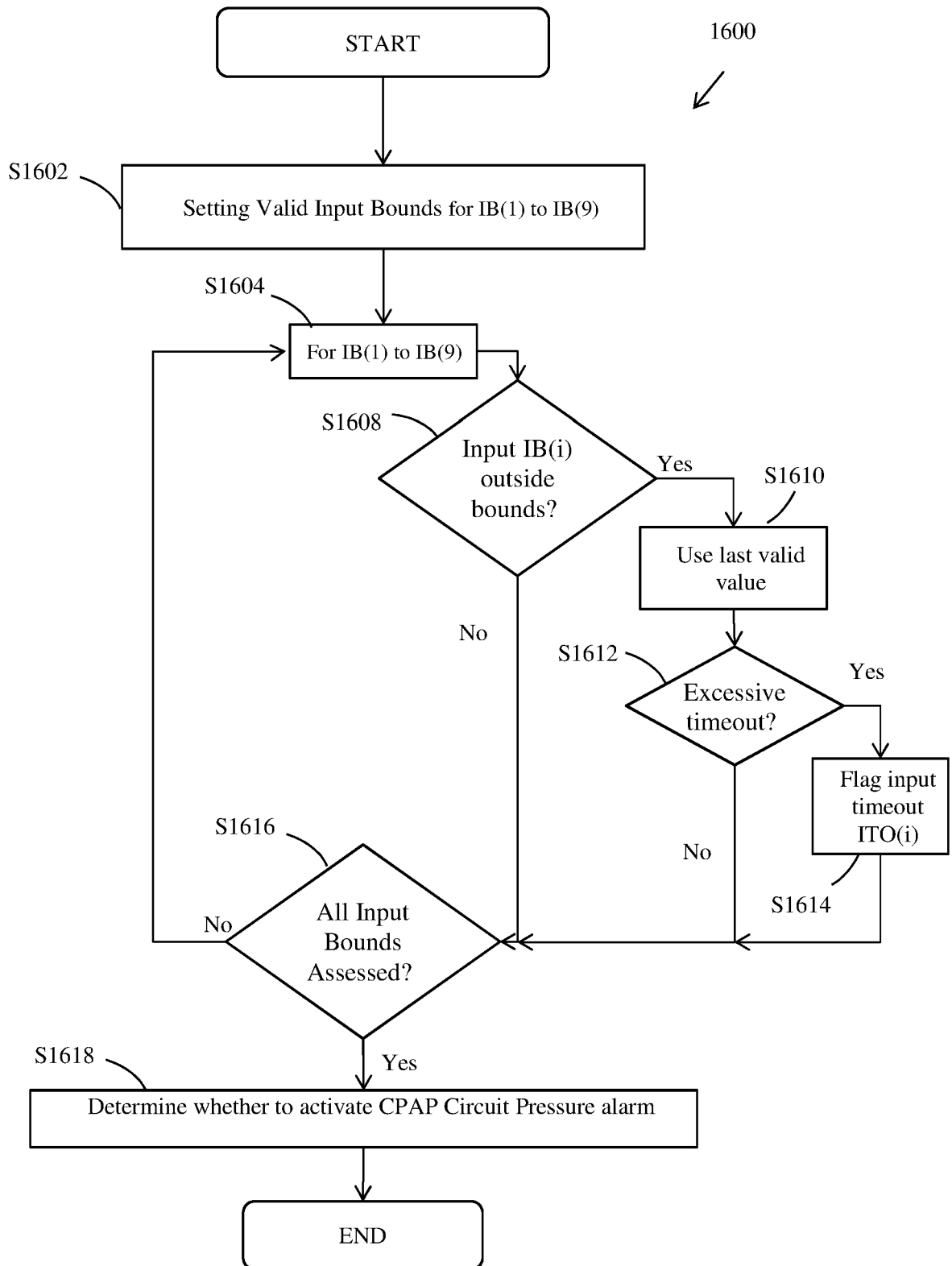
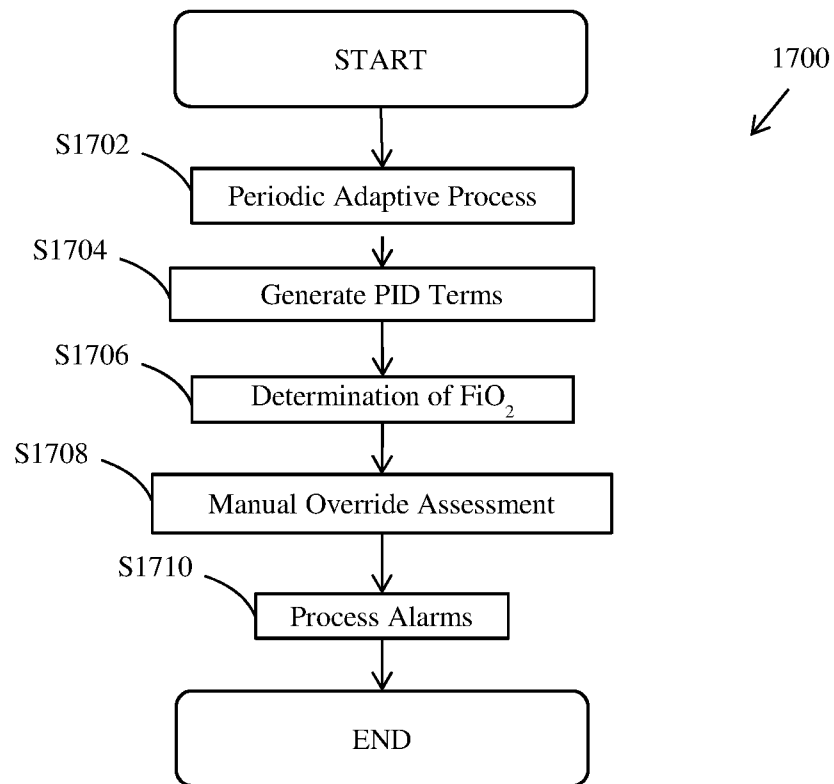
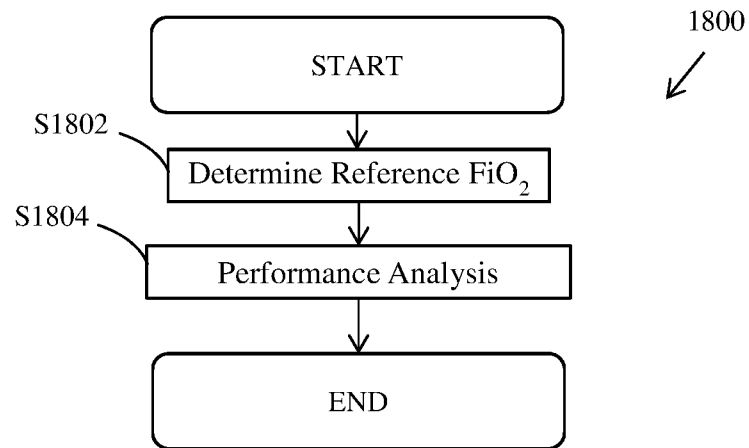


Fig. 16

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**Fig. 17**

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**Fig. 18**

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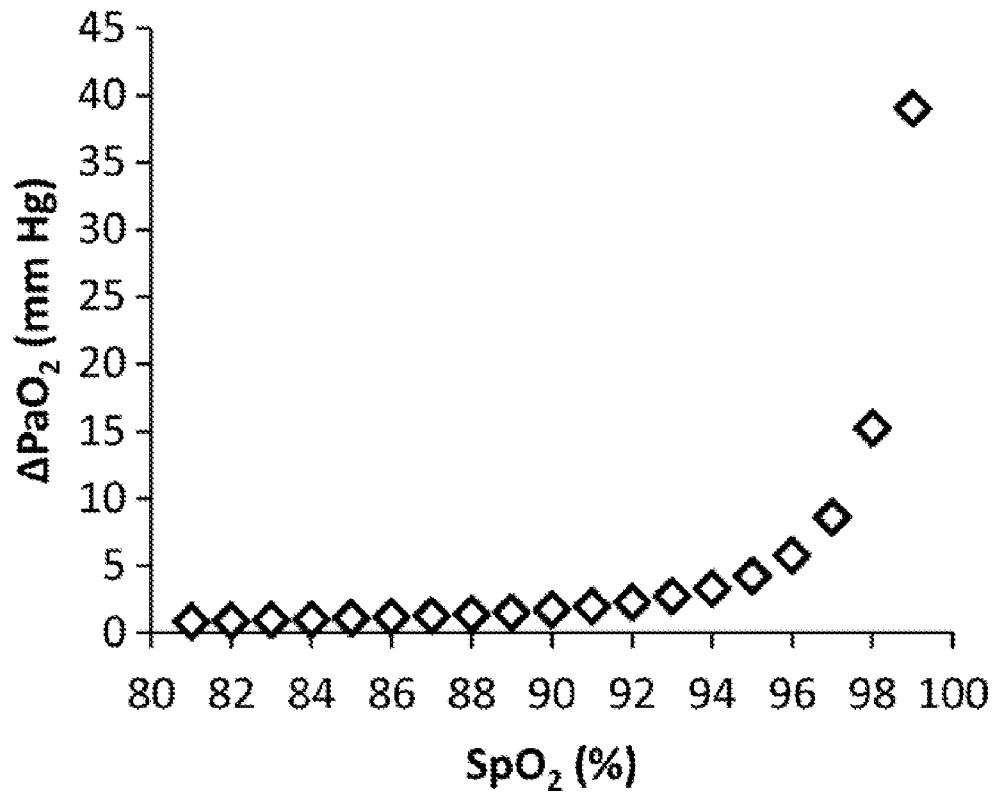


Fig. 19

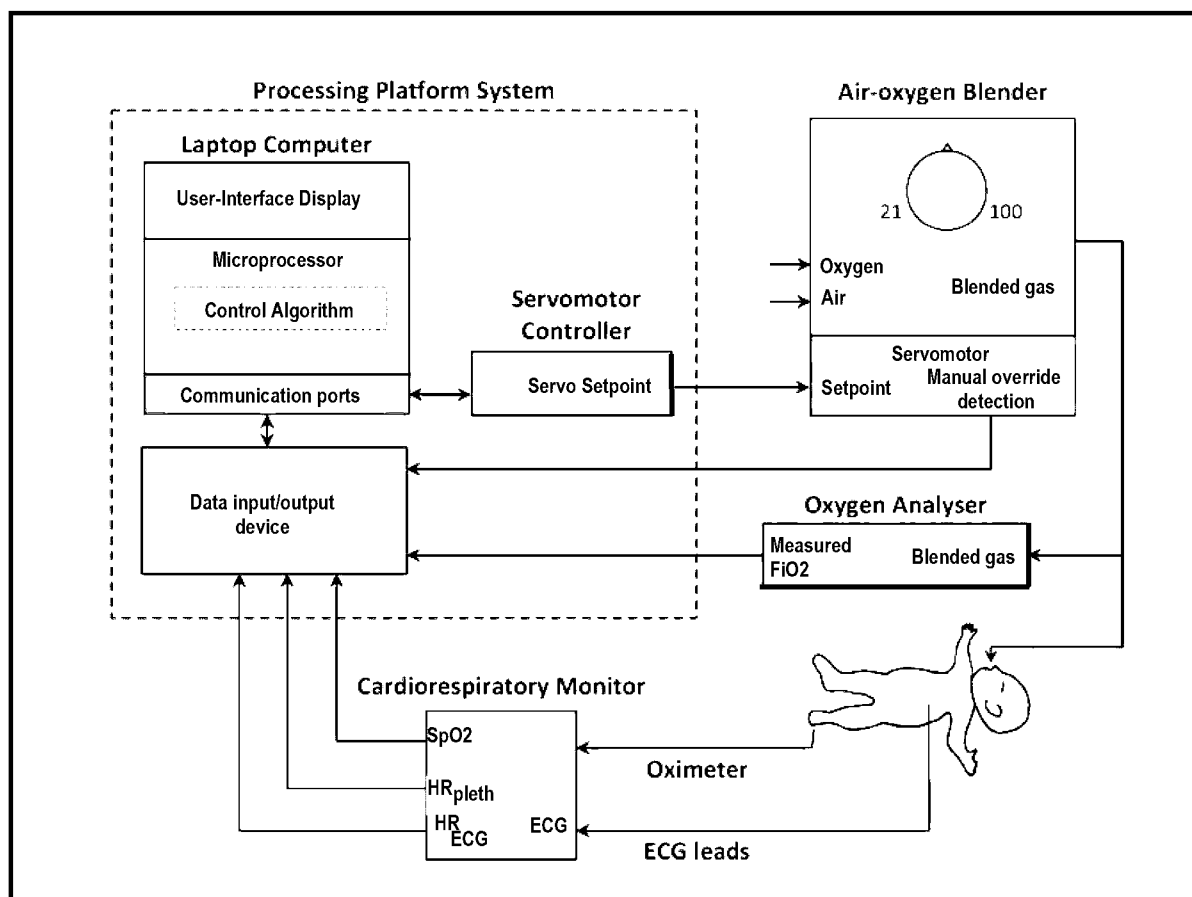


Fig. 20

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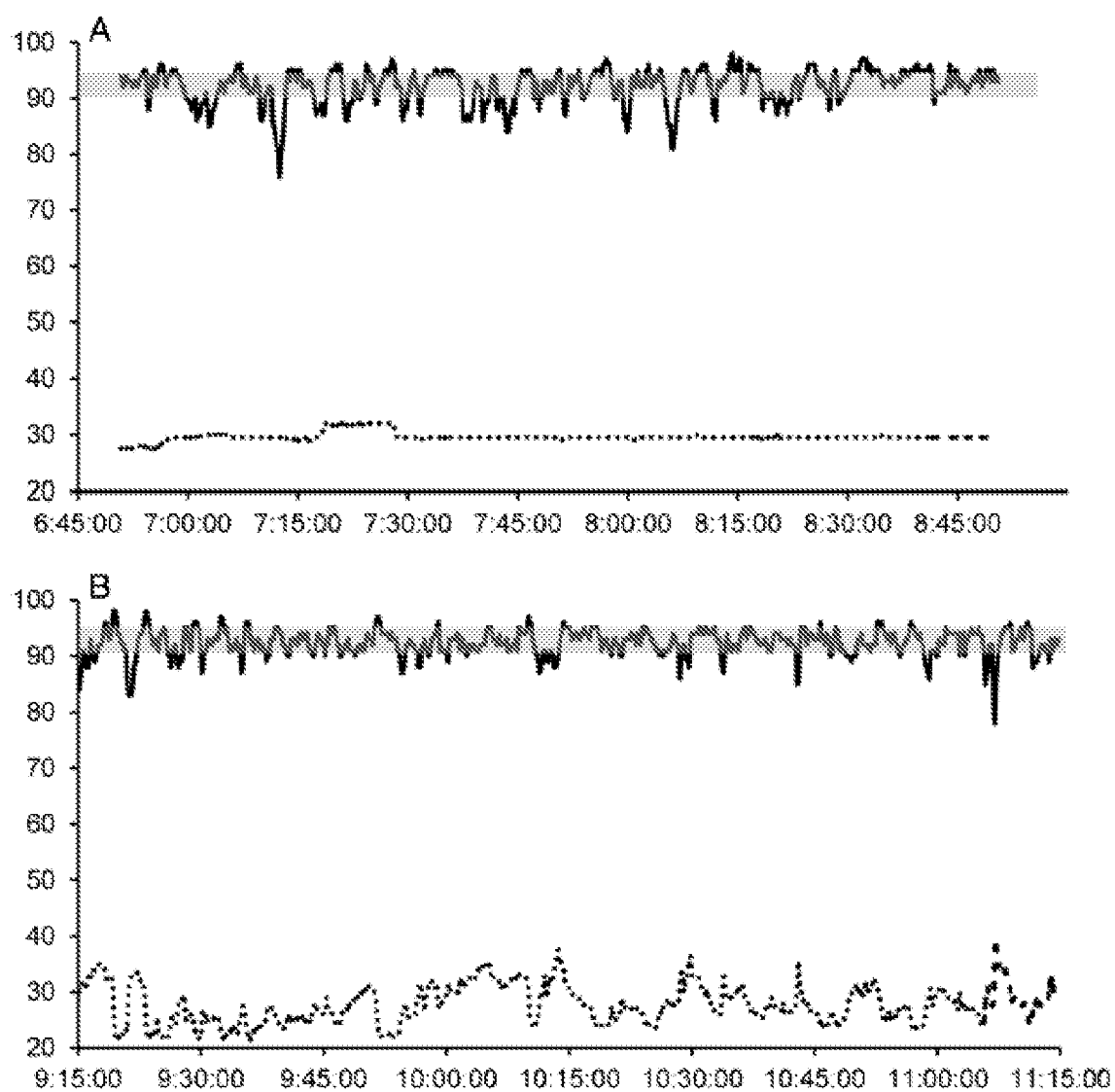


Fig. 21

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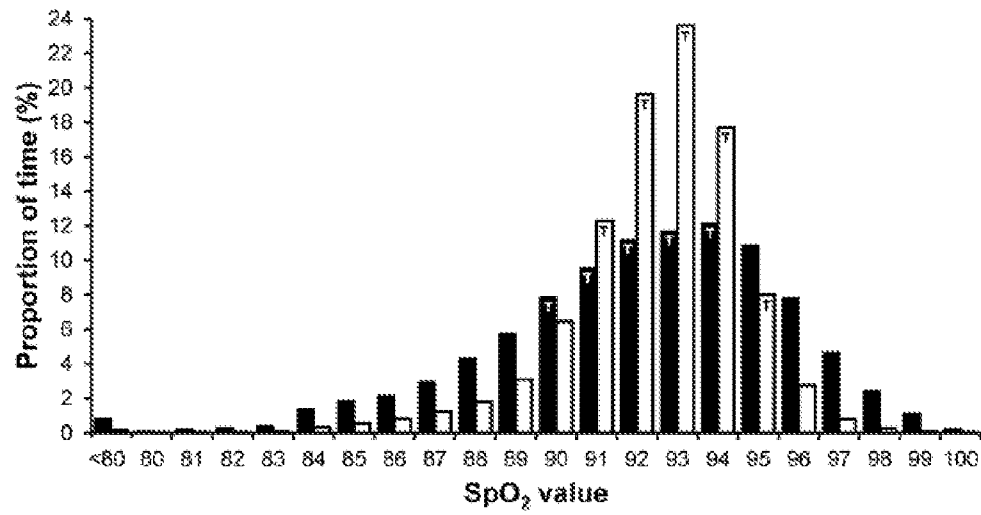


Fig. 22

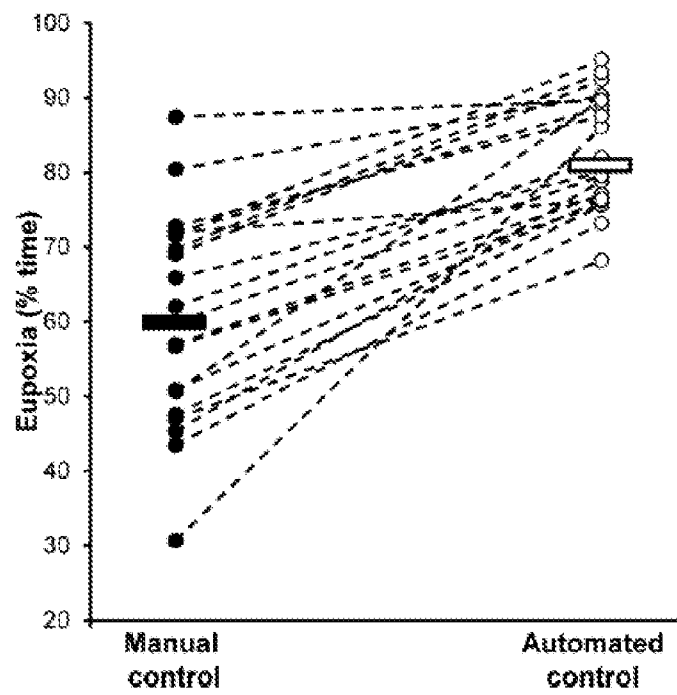


Fig. 23

