



(51) International Patent Classification:
A61M 16/00 (2006.01)

(21) International Application Number:
PCT/US2015/035731

(22) International Filing Date:
15 June 2015 (15.06.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/011,912 13 June 2014 (13.06.2014) US

(71) Applicant: **THE REGENT OF THE UNIVERSITY OF MICHIGAN** [US/US]; Office of Technology Transfer, 1600 Huron Parkway, 2nd Floor, Ann Arbor, MI 48109-2590 (US).

(72) Inventors; and

(71) Applicants : **WARD, Kenvin, R.** [US/US]; 6730 Fleming Creek Dr., Superior Township, MI 48198 (US). **BLUM, James, M.** [US/US]; 3477 Wagner Woods Court, Ann Arbor, MI 48103 (US). **NAJARIAN, Kayvan** [US/US]; 46710 Merion Circle, Northville, MI 48109 (US).

(74) Agent: **KRIEGEL, Jeremy, R.**; Marshall, Gerstein & Borun LLP, 233 S. Wacker Drive, 6300 Wills Tower, Chicago, IL 60606-6357 (US).

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

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

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

(54) Title: SYSTEMS WITH CONTROL MECHANISM FOR NEGATIVE PRESSURE AND POSITIVE PRESSURE FOR OPTIMIZATION OF VENTILATION, CENTRAL HEMODYNAMICS, AND VITAL ORGAN PERFUSION

(57) Abstract: An intelligent control system for controlling a patient ventilation apparatus having at least negative end expiratory pressure ventilation (NEEP) system. The controller accepts signals from one or more physiological parameter sensors, compares data received from those sensors to target values stored in a memory, and either recommends changes to the NEEP or signals the NEEP to change or maintain certain settings, such as level and frequency. A positive end pressure ventilation system may be further employed with the intelligent control system, such that, based on data received from the physiological sensors, the intelligent control system can be used to deliver optimal levels of negative pressure ventilation and positive pressure ventilation, and promote weaning of a patient off the ventilators. The intelligent control system may also be used with an external pressure oscillatory device.



**SYSTEMS WITH CONTROL MECHANISM FOR NEGATIVE PRESSURE AND
POSITIVE PRESSURE FOR OPTIMIZATION OF VENTILATION, CENTRAL
HEMODYNAMICS, AND VITAL ORGAN PERFUSION**

Reference to Related Applications

[0001] This is a non-provisional of, and claims the benefit of the filing date of, US Provisional Application No. 62/011,912, filed June 13, 2014, the entirety of which is hereby incorporated by reference.

Field of the Disclosure

[0002] The present disclosure relates generally to respiratory ventilation systems and, more specifically, to the regulation and optimization of negative pressure ventilation and positive pressure ventilation in patient respiratory ventilation systems which in turn are used to optimize ventilation, central hemodynamics, and vital organ perfusion.

Background

[0003] Ventilators are machines designed to mechanically move breathable air into and out of the lungs, to provide the mechanism of breathing for a patient who is physically unable to breathe, or breathing insufficiently. Monitoring various physiological parameters provides raw data to clinicians to help them assess how therapy is proceeding. However, these parameters tell them very little about how to adjust the ventilator settings. Clinicians regularly monitor patients' ability to cope with a given support level and then decide whether support should be further reduced, maintained or increased based on their experience and knowledge. An intelligent system which is aimed to assist, rather than replace, the clinician would therefore result in improved patient comfort and safety. Intelligent systems can also play a vital role in weaning patients from ventilators. Currently, weaning tends to be undertaken in a somewhat ad hoc manner, and the clinician, once more, must rely on his or her experience and knowledge. However, there is evidence that weaning may proceed more efficiently if directed according to some specified protocol.

[0004] Negative pressure ventilation (NPV) was once the primary mode of assisted mechanical ventilation in the setting of respiratory failure. However, during the Copenhagen

polio epidemic in the 1950's when insufficient resources were available, the use of positive pressure ventilation through an endotracheal tube was necessary. Since that time, NPV has fallen out of favor and is now used only in niche markets of cystic fibrosis, chest wall deformities, and other relatively rare disorders, which make long term normal ventilation difficult. In these settings, NPV has been utilized using a chest cuirass. A common NPV device of these is the Hayek RTX respirator device, available from United Hayek Industries (Medical) of London, UK, which employs what Hayek refers to a biphasic cuirass ventilation technique.

[0005] Despite the dominance of positive pressure mechanical ventilation (PPV) in the field of critical care, PPV is not without problems. PPV produces physiology opposite of the intrathoracic negative pressure mechanism that humans use to breath normally. The elevated intrathoracic and lung pressure that PPV produces can result in lung injury through excessive stretch of lung tissue. In addition, elevated intrathoracic pressure can result in decreases in venous return and other consequences which can worsen central cardiovascular hemodynamics and intracranial pressure. This can result in decreases in vital organ perfusion, for example to the brain and splanchnic bed.

[0006] Given little progress in the treatment of critical illness and injury ranging from the treatment of acute lung injury, respiratory failure, cardiogenic shock, sepsis, traumatic brain injury, and others, there is a need to re-engineer NPV and other negative pressure modalities to improve the effectiveness of mechanical ventilation, improve central and peripheral hemodynamics and perfusion and improve cerebral physiology. Such methods would also greatly improve therapeutic drug delivery to the lung.

[0007] In order to better leverage NPV and other negative pressure modalities (external negative abdominal and external negative neck pressure), control and feedback mechanisms will be necessary so that these negative pressure modalities work in concert with both current invasive and noninvasive mechanical PPV methods as well as various invasive and noninvasive monitoring technologies of the cardiopulmonary, cerebrovascular, and peripheral vascular and organ systems.

Summary of the Disclosure

[0008] The present disclosure includes an intelligent monitoring/controller system that interfaces with a ventilator and patient, to optimize the use of negative pressure ventilation (NPV) and its various parameters such as negative end expiratory pressure ventilation (NEEP) modalities, as well as positive pressure ventilation (PPV) including its parameters such as positive end expiratory pressure (PEEP) modalities. The intelligent monitoring/controller system may manipulate the rate, frequency, and force of these measures to achieve desired endpoints.

[0009] The system of the present disclosure uses physiological signals specific to a disease or condition of the patient, such as such as esophageal pressure, intracranial pressure, intra-abdominal pressure, bladder pressure, arterial blood pressures, central venous and pulmonary artery pressure, arterial and venous oxygenation, tissue oxygenation, electrical activity of the heart (as is measured by an electrocardiogram), impedance, cerebral blood flow, cardiac output, stroke volume variation, pulse pressure variation, and others, to determine how ventilation should be optimized. Using machine learning methods, the system then determines, based on the physiological signals, what kind of ventilation is best suited to the particular condition, when to stop ventilation, when to resume ventilation, and facilitates gradually weaning the patient off the ventilator so that the patient may resume normal breathing.

[0010] The control system of the present disclosure optimizes the use of negative pressure modalities, alone or together with for a variety of clinical applications. The control system of the present disclosure also optimizes treatment of acute lung injury, acute respiratory failure, cardiogenic and other shock states, traumatic brain injury and other cerebrovascular catastrophes. The system can decrease incidence of abdominal compartment syndrome, enhances weaning from mechanical ventilation and resumption of normal breathing, and can be used to improve delivery of therapeutic agents to the lung.

[0011] The patient monitoring data collected by the control system of the present disclosure may be easily integrated with electronic medical records. The control system may also be configured to interface with communication systems so as to deliver alerts to medical professionals, thereby enabling the transmission of ventilator alarms to a clinician's pager, computer monitor, tablet, public address system, two-way radio, watch, and/or smartphone device to enable fast response without clinician being in earshot of ventilator or patient.

[0012] The system is capable of leveraging other negative pressure devices such as a negative pressure collar capable of producing fluctuating or continuous levels of positive or negative pressure, which can be helpful for relieving intracranial pressure following, for example, a traumatic brain injury. Abdominal curiass's which either span the abdomen or abdomen and chest are also envisioned to have utility with the system allowing for production of continuous levels of positive or negative pressure working with the system in conjunction with the aforementioned ventilation systems and physiologic signals to optimize ventilation as well as central hemodynamics and vital organ perfusion.

[0013] By taking data from nonlinear sources, namely sensor data indicative of physiologic parameters such as cardiac output, tissue oxygenation, lung pressures, arterial blood pressure (ABP), cerebral pressure perfusion, esophageal pressure, intraabdominal pressure, bladder pressure, arterial blood pressures, central venous pressure, pulmonary artery pressure, arterial oxygenation, venous oxygenation, tissue oxygenation, electric activity of the heart, impedance, cerebral blood flow, cardiac output, stroke volume variation, intracranial pressure, and pulse pressure variation, and based on that data, controlling the delivery of positive or negative pressure, therapeutic results can be achieved with great precision and efficiency. A controller that is programmed to make certain adjustments or recommendations for adjustments to positive and negative pressure delivery based on physiologic parameter data essentially works in concert with the body's cardiovascular and neurological systems.

[0014] Examples of the manner in which the system of the present disclosure may be configured are shown schematically in the drawings, as described below.

Brief description of the Several Views of the Drawings

[0015] Fig. 1 is a schematic diagram of a first embodiment of a control system of the present disclosure, in which negative end expiratory pressure ventilation (NEEP) and positive end expiratory pressure ventilation (PEEP) are employed simultaneously, and the control system is configured to ensure an optimal setting for each of the NEEP and PEEP devices at any given time based on a patient's physiological data. The control system may be used for oscillatory negative and positive pressure ventilation as well;

[0016] Fig. 2 is a schematic diagram of a second embodiment of a control system of the present disclosure, in which only NEEP is utilized, and NEEP may be used for oscillatory negative pressure, constant negative pressure, or both; and

[0017] Fig. 3 is a schematic diagram of a third embodiment of a control system of the present disclosure, in which external pressure oscillatory devices such as a neck collar or abdominal curiass is used either alone or in conjunction with positive pressure and negative pressure ventilation to further effect and optimize ventilatory, hemodynamics, or vital organ perfusion response.

Detailed Description of the Preferred Embodiments

[0018] With reference to Figure 1, a controller in the form of an intelligent control system 10 of the present disclosure for use in controlling ventilation systems receives a set of desired or target values for the physiological signals of interests, which may be provided according to a database that is stored in a memory 12 of the intelligent control system 10. The memory 12 may be a local memory, or, as indicated by the dash-dotted line between the intelligent control system and the memory 12 in Figure 1, the memory 12 may be provided or updated remotely, enabling the set of desired or target values to be updated from time to time in accordance with, for instance, updated research as to best practices for target values for various physiological parameters as indicators for stages or goals in a patient's ventilation therapy.

[0019] The intelligent control system 10 of this first embodiment is in controlling communication with a positive end expiratory pressure ventilation (PEEP) system 14 and a negative end expiratory pressure ventilation (NEEP) system 16, which are in communication with a breathing tube for a patient P. One or more patient physiological parameter measuring devices 18 that are in communication with at least the intelligent control system 10 are applied to the patient P, and provide the intelligent control system 10 with physiological signals specific to a disease or condition of the patient, such as such as esophageal, intracranial, arterial blood pressures, oxygenation, and/or blood flow.

[0020] The intelligent control system 10 is in further communication with a logic control that constantly, or at periodic intervals, compares one or more of the physiological signals received from the patient physiological parameter measuring devices 18 to a desired or target value for the

physiological parameter associated with that that one or more physiological signal from the memory 12, and sends appropriate control signals to the NEEP 16 and/or PEEP 14 based on those comparisons in accordance with the programmed logic control. The intelligent control system 10 may be programmed to make certain adjustments to the NEEP and/or PEEP automatically based on the comparisons, and with regard to other adjustments, not implement the adjustment until after a recommendation has been sent to a clinician, such as via a display 20, and that clinician has approved the adjustment to be made. The intelligent control system 10 may be further programmed to accept a manually-entered command to effect an adjustment to one or more of the NEEP 14 and PEEP 16 ventilators other than that which is recommended from the programmed logic control. The display 20 may be in communication with the intelligent control system 10, as well as neither, one, or both of the NEEP 14 and the PEEP 16.

[0021] In case of adult respiratory distress syndrome, it is often the case that the objective of ventilation is to achieve and maintain a certain desired level for esophageal pressure, which in this control scheme is referred to as r_d . Considering r_d and the actual values of all relevant measured/estimated physiological signals, the intelligent control system 10 first decides whether to use only PEEP 14, only NEEP 16, or some combination of the two for ventilation. In other words, at any time, by analyzing the physiological signals the intelligent control system 10 will decide to operate in one of the following four modes of operations:

[0022] I. Constant NEEP without PEEP: The intelligent control system 10 can recommend, based on the analysis of one or more physiological signals received from the patient physiological parameter measuring devices 18, and comparison of the physiological signals to a desired or target value for the physiological parameter associated with that that one or more physiological signal from the memory 12, that it would be beneficial to only use a constant NEEP and remove PEEP. In this case, the intelligent control system 10 will calculate the optimal level of negative pressure within any given time window, signal the NEEP 14 to deliver that level of negative pressure, and update the calculation based on patient's physiological changes.

[0023] II. Constant NEEP with oscillating PEEP: In this mode, in each time window, the intelligent control system 10 will calculate the optimal values for the constant level of NEEP, the frequency of PEEP as well as the level (magnitude) of PEEP.

[0024] Note that the possible mode of applying PEEP without constant NEEP is equivalent to having PEEP with almost zero level of constant NEEP which is a special case of mode II and is automatically generated by the intelligent control system 10. Another function of the intelligent control system 10 is to recommend which mode of operation discussed above is needed, or if the entire ventilation is no longer needed.

[0025] Specifically, a task of the controller is to form a recommendation (to care givers), based on the analysis of physiological signals at previous time windows, to gradually stop ventilation and allow patient to breathe normally. The controller will also recommend if ventilation, at a specific mode of operation, has to be resumed / started.

[0026] In each of the above mentioned modes of operation, the patient P receives PEEP and/or NEEP ventilation with the optimal levels and frequency at any given time. Physiological parameter measuring devices 18 measure all relevant physiological signals which are provided to the intelligent control system 10 for decision making and control analysis. For instance, in case of ARDS, these signals can include: esophageal pressure (the signal to be controlled), intrathoracic pressure and inspiratory pressure.

[0027] Structure 2:

[0028] The second structure, shown in Figure 2, deals with applications where only NEEP 116 is available or used. In such cases, NEEP can be used for oscillatory negative pressure, constant negative pressure or both. The system would also allow the curiass producing NEEP to produce positive pressure to assist with expiration in an active manner to ensure more complete along the emptying which may be necessary in such disease states as asthma which produce bronchospasm. As in the arrangement illustrated in Figure 1 and discussed above, the intelligent control system 110 of this embodiment receives a desired level for the targeted physiological signals from a memory 112, as well as the actual values of these and other physiological signals which are continuously monitored by physiological parameter measuring devices 118 in communication with the intelligent control system 110.

[0029] As example of this in treatment of traumatic brain injury patients (TBI) is controlling the level of intracranial pressure, ICP, at or below a certain level. In such an application, ICP as well as other signals including arterial blood pressure (ABP) and cerebral pressure perfusion are

measured and provided to the intelligent control system 110. Values associated with one or more of these physiological parameter signals are compared by the intelligent control system 110 to a respective desired or target value for the physiological parameter from the memory 112, and the intelligent control system 110 sends appropriate control signals to the NEEP 116 based on those comparisons in accordance with the programmed logic control, or sends a recommendation, such as to a display 120 in communication with the intelligent control system 110, to make an appropriate adjustment to, or maintain a particular level and/or frequency of, the negative pressure delivered by the NEEP. For instance, based on the comparison of signals received from each of the one or more physiological parameter sensors to a respective one of the target values included in the memory, the controller generates one of a recommendation that the NPV should be set to deliver an oscillatory magnitude and a recommendation that the NPV should be set to deliver an oscillatory frequency of negative pressures. In this manner, NPV is utilized effectively for therapeutic effects. NPV is controlled in a manner that enhances cerebral blood flow. Use of such a system would bring even greater value to the victim of multisystem trauma. Multisystem trauma patients regularly have multiple injuries including TBI, lung injury and cardiovascular shock. By using the system described above, the enhancement of cerebral blood flow can occur simultaneously to reducing PPV inspiratory pressures that might otherwise be injurious to the lung. Increases in cerebral blood occur as a result of both reductions in intracranial pressure and also enhancements of cardiac output through the actions of NPV increasing venous return to the heart, all while countering the injurious effects of PPV on lung injury.

[0030] Another example would be to utilize the system as a countermeasure to patients who have septic shock and adult respiratory distress syndrome (ARDS). ARDS can be associated with significant decreases in lung compliance where lung injury is exacerbated by increasing PPV but where increases in PPV via PEEP may be needed to provide adequate oxygenation. This scenario is further complicated by the fact that sepsis can result in myocardial depression and reductions in cardiac output which exacerbate systemic tissue hypoxia. Use of PPV can further reduce cardiac output and tissue blood flow. The use of the system described previously would greatly improve the physiology of such a complex patient. Through incorporation of physiologic signals such as arterial blood pressure, cardiac output, airway pressure, tissue oxygenation, central venous pressure, tissue impedance, and others, the optimal combination of

NPV and PPV can be found which optimizes cardiac output and tissue oxygenation while simultaneously enhancing arterial blood oxygen and carbon dioxide at the lowest airway pressure. Continuous use of such as system becomes extremely critical during the transition of patients off the use of vasopressors and as weaning from mechanical ventilation occurs.

[0031] As in Structure 1, in the structure of this embodiment, the intelligent control system 110 can function in one of the following functional modes:

[0032] I. Constant NEEP without oscillating NEEP: The operation of the intelligent control system 110 to achieve this mode would be the same as mode I of Structure 1.

[0033] II. Constant NEEP with oscillating NEEP: In this mode, in each time window, the intelligent control system 110 will calculate the optimal values for the constant level of NEEP, the frequency of NEEP as well as the level (magnitude) of NEEP.

[0034] Again note that the possible mode of applying oscillating NEEP without constant NEEP is equivalent to having NEEP with almost zero level of constant NEEP which is a special case of mode II and is automatically generated by the intelligent control system 110.

[0035] Again, also note that the potential for application of other external negative and positive pressure devices such as a neck collar or abdominal curiass is anticipated to be used with or without the systems above to improve ventilation, central hemodynamics and vital organ perfusion. While NPV can be controlled to enhance cerebral blood flow, for example, PPV can be controlled to modulate cerebral blood flow, aiding in therapy for traumatic brain injury patients.

[0036] In addition, as in Structure 1, another function of the intelligent control system 110 is to recommend which mode of operation discussed above is needed, or if the entire ventilation is no longer needed. Or if manipulation of central hemodynamics or vital organ perfusion is no longer needed. Specifically, a task of the intelligent control system 110 is to form a recommendation (to care givers), based on the analysis of physiological signals at previous time windows, to gradually stop ventilation and allow patient to breathe normally. The intelligent control system 110 will also recommend if ventilation, at a specific mode of operation, has to be resumed / started.

[0037] The systems of the present disclosure are intended to be used in constant or oscillating conditions of combined positive pressure ventilation and negative pressure ventilation to improve lung function, reduce lung injury associated with PPV, enhance central and peripheral hemodynamics and organ function, improve cerebral perfusion pressure, improve delivery of therapeutic agents to the lung given via inhalation methods, and assist in weaning from mechanical ventilation. A significant example of this would be to use the combination of NPV and PPV to enhance the delivery and distribution of such lung therapeutic agents as surfactants to injured lung areas. Delivery of surfactants has only been done via PPV which has not been demonstrated to be helpful due to the probability that natural negative inspiratory pressure cannot be leveraged in this mode. Through the use of surfactants coupled with NPV, enhanced distribution of surfactants coupled with the PPV alleviating effects of NPV on lung tissue, reductions in acute lung injury resulting in improved oxygenation and ventilation can occur. This same approach could be used for improved delivery of other beneficial lung agents such as bronchodilators and even intrapulmonary antibiotics.

[0038] Application of any therapeutic agent (intrapulmonary, intravascular, etc.) may result in changes in lung compliance, central hemodynamics, or both that then require dynamic and automatic altering and recalibrating of the PPV and NPV parameters that continue optimization of the patients respiratory, cardiovascular, and cerebrovascular physiology.

[0039] Also as indicated the use of other external negative or positive pressure producing devices may be used as adjuncts to improve lung function, reduce lung injury associated with PPV, enhance central and peripheral hemodynamics and organ function, improve cerebral perfusion pressure, improve delivery of therapeutic agents to the lung given via inhalation methods, and assist in weaning from mechanical ventilation.

[0040] The intelligent control systems 10, 110 described above include three major components:

[0041] I. A signal processing component to filter, estimate, predict and transform the measured signals physiological and extract features from them. This can be realized using a combination of a variety of methods including discrete wavelet transform (DWT), discrete Fourier transform (DFT), and discrete cosine transform (DCT).

[0042] II. A machine learning component to analyze extracted features and predict when to stop, resume or start ventilation at each specific mode of operation. This can be implemented using Random Forest, support vector machines (SVM), neural networks (NN), deep learning, error-correcting output codes (ECOC), and other machine learning and artificial intelligence techniques.

[0043] III. A Feedback control mechanism to create the optimal levels and frequencies for PEEP and NEEP. This can be implemented using one or more of PID control, model-based control, neural control, optimal control, neuro-fuzzy control, and robust control.

[0044] Turning to Figure 3, a schematic diagram of a third embodiment of a control system 210 of the present disclosure is illustrated, in which external pressure oscillatory devices such as a neck collar or abdominal curiass 213 (illustrated in broken lines) is used either alone or in conjunction with positive pressure and negative pressure ventilation 214, 216 to further effect and optimized ventilatory, hemodynamics, or vital organ perfusion response. As in the first and second embodiments, one or more physiologic measuring devices 218 is provided on the patient, which communicates physiological signals to the controller 210. The controller 210 performs a comparison of the physiological signals to a desired or target value for the physiological parameter associated with that that one or more physiological signal from the memory 212. The memory 212 may either integral with, or as indicated by dash-dotted line, remote from, the control system 210.

[0045] While various embodiments have been disclosed, it will be appreciated that variations may be made thereto that are still considered within the scope of the appended claims.

CLAIMS

What is claimed is:

1. A system for controlling at least one of patient ventilation, central hemodynamics, and organ perfusion, comprising:

a controller;

a memory in communication with the controller, the memory including a target value for one or more physiological parameters;

one or more physiological parameter sensors in communication with the controller and a patient; and

a negative pressure ventilation (NPV) and negative end expiratory pressure ventilation (NEEP) system (NPV/NEEP system) in communication with the controller, the controller including a programmed logic control that, based on a comparison of signals received from each of the one or more physiological parameter sensors to a respective one of the target values included in the memory, generates one of a recommendation that an adjustment should be made to negative pressure provided by the NPV/NEEP system, or a signal to the NPV/NEEP system to make an adjustment to negative pressure provided by the NPV/NEEP system.

2. The system of claim 1, further comprising a positive pressure ventilation (PPV) and positive end expiratory pressure ventilation (PEEP) system (PPV/PEEP system) in communication with the controller, the programmed logic control of the controller, based on the comparison of signals received from each of the one or more physiological parameter sensors to a respective one of the target values included in the memory, further generating one of a recommendation that an adjustment should be made to positive pressure provided by the PPV/PEEP system, or a signal to the PPV/PEEP system to make an adjustment to positive pressure provided by the PPV/PEEP system.

3. The system of claim 2, wherein, based on the comparison of signals received from each of the one or more physiological parameter sensors to a respective one of the target values included in the memory, the controller generates one of a recommendation that no positive

pressure be provided by the PPV/PEEP system, or a signal to the PPV/PEEP system not to deliver positive pressure.

4. The system of claim 2, and based on the comparison of signals received from each of the one or more physiological parameter sensors to a respective one of the target values included in the memory, the controller generates one of a recommendation that the NEEP should be set to deliver a constant level of NEEP at a particular value, a recommendation that the NEEP should be set to deliver a constant level of NEEP within a particular range of values, or a signal to the NEEP to deliver a constant level of negative pressure.

5. The system of claim 4, and based on the comparison of signals received from each of the one or more physiological parameter sensors to a respective one of the target values included in the memory, the controller further generates one of a recommendation that the PEEP be set to deliver positive pressure at a particular frequency and one of at a particular level of positive pressure or within a range of levels of positive pressure, or one or more signals to the PEEP to deliver positive pressure at a particular frequency and a particular level.

6. The system of claim 1, and based on the comparison of signals received from each of the one or more physiological parameter sensors to a respective one of the target values included in the memory, the controller generates one of a recommendation that the NEEP should be set to deliver a constant level of NEEP at a particular value, a recommendation that the NEEP should be set to deliver a constant level of NEEP within a particular range of values, or a signal to the NEEP to deliver a constant level of negative pressure.

7. The system of claim 1, the intelligent control system comprising:
a signal processing component to filter, estimate, predict and transform the measured signals physiological and extract features from them;

a machine learning component to analyze extracted features and predict when to stop, resume or start ventilation at each specific mode of operation; and . This can be implemented using Random Forest, support vector machines (SVM), neural network (NN), error-correcting output codes (ECOC), and other machine learning and artificial intelligence techniques; and

a feedback control mechanism to create the optimal levels and frequencies for PEEP and NEEP.

8. The system of claim 7, the signal processing component using a combination of two or more of a group including discrete wavelet transform (DWT), discrete Fourier transform (DFT), and discrete cosine transform (DCT).

9. The system of claim 7, the machine learning component using at least one of Random Forest, support vector machines (SVM), neural network (NN), error-correcting output codes (ECOC), and other machine learning and artificial intelligence techniques.

10. The system of claim 7, the feedback control mechanism using one or more of PID control, model-based control, optimal control, neuro-fuzzy control, neural control, and robust control.

11. The system of claim 1, further comprising a display in communication with the controller, the display displaying messages corresponding to recommendations generated by the controller.

12. The system of claim 1, further comprising an external pressure oscillatory device.

13. The system of claim 12, wherein the external pressure oscillatory device comprises at least one of a group of a neck collar and an abdominal curiass.

14. The system of claim 2, further comprising an external pressure oscillatory device.
15. The system of claim 14, wherein the external pressure oscillatory device comprises at least one of a group of a neck collar and an abdominal curiass.
16. The system of claim 1, wherein the one or more physiological parameter sensors are sensors to measure one or more of the group including: esophageal pressure, intraabdominal pressure, bladder pressure, arterial blood pressures, central venous pressure, pulmonary artery pressure, arterial oxygenation, venous oxygenation, tissue oxygenation, electric activity of the heart, impedance, cerebral blood flow, cardiac output, stroke volume variation, and pulse pressure variation.
17. The system of claim 4, and based on the comparison of signals received from each of the one or more physiological parameter sensors to a respective one of the target values included in the memory, the controller generates one of a recommendation that the NPV should be set to deliver an oscillatory magnitude of negative pressures and a recommendation that the NPV should be set to deliver an oscillatory frequency of negative pressures.
18. A system for optimizing the delivery of intrapulmonary therapeutic agents including at least one of surfactants, bronchodilators, mucolytics, and antibiotics, comprising:
- a controller;
 - a memory in communication with the controller, the memory including a target value for one or more physiological parameters;
 - one or more physiological parameter sensors in communication with the controller and a patient; and
 - a negative pressure ventilation (NPV) and negative end expiratory pressure ventilation (NEEP) system (NPV/NEEP system) in communication with the controller, the controller

including a programmed logic control that, based on a comparison of signals received from each of the one or more physiological parameter sensors to a respective one of the target values included in the memory, generates one of a recommendation that an adjustment should be made to negative pressure provided by the NPV/NEEP system, or a signal to the NPVNEEP system to make an adjustment to negative pressure provided by the NVP/NEEP system.

19. A method of controlling the level of intracranial pressure (ICP) in a patient, comprising:

measuring ICP of the patient;

providing signals indicative of the measured ICP to an intelligent control system;

performing, via the intelligent control system, a comparison of values associated with the signals to a respective desired or target value for the ICP from a memory; and

sending, via the intelligent control system, control signals to a negative end expiratory pressure ventilation (NEEP) system based on the comparison, or sending a recommendation that an adjustment be made, or no adjustment be made, to a particular level and/or frequency of, the negative pressure delivered by the NEEP.

20. The method of claim 19, further comprising measuring at least one additional physiologic parameter including at least one of a group including arterial blood pressure (ABP) and cerebral pressure perfusion, and providing signals indicative of the measured at least one additional physiologic parameter to the intelligent control system, and the comparison of values associated with the signals to a respective desired or target value for the ICP from a memory includes a comparison of values associated with the at least one additional physiologic parameter to a respective desired or target value for the additional physiologic parameter.

21. The method of claim 19 or 20, further comprising sending, via the intelligent control system, control signals to a positive end expiratory pressure ventilation (PEEP) system based on the comparison, or sending a recommendation that an adjustment be made, or no

adjustment be made, to a particular level and/or frequency of, the negative pressure delivered by the PEEP.

22. A method of controlling the level of at least one physiologic parameter including cardiac output, tissue oxygenation, and lung pressures in a patient, comprising:

measuring physiologic parameters including at least one of cardiac output, tissue oxygenation, and lung pressures of the patient;

providing signals indicative of the measured physiologic parameters to an intelligent control system;

performing, via the intelligent control system, a comparison of values associated with the signals to a respective desired or target value for the physiologic parameters from a memory; and

sending, via the intelligent control system, control signals to a negative end expiratory pressure ventilation (NEEP) system based on the comparison, or sending a recommendation that an adjustment be made, or no adjustment be made, to a particular level and/or frequency of, the negative pressure delivered by the NEEP.

23 The method of claim 22, further comprising measuring at least one additional physiologic parameter including at least one of a group including arterial blood pressure (ABP) and cerebral pressure perfusion, and providing signals indicative of the measured at least one additional physiologic parameter to the intelligent control system, and the comparison of values associated with the signals to a respective desired or target value for the physiologic parameter including cardiac output, tissue oxygenation, or lung pressure from a memory includes a comparison of values associated with the at least one additional physiologic parameter to a respective desired or target value for the additional physiologic parameter.

24. The method of claim 22 or 23, further comprising sending, via the intelligent control system, control signals to a positive end expiratory pressure ventilation (PEEP) system based on the comparison, or sending a recommendation that an adjustment be made, or no

adjustment be made, to a particular level and/or frequency of, the negative pressure delivered by the PEEP.

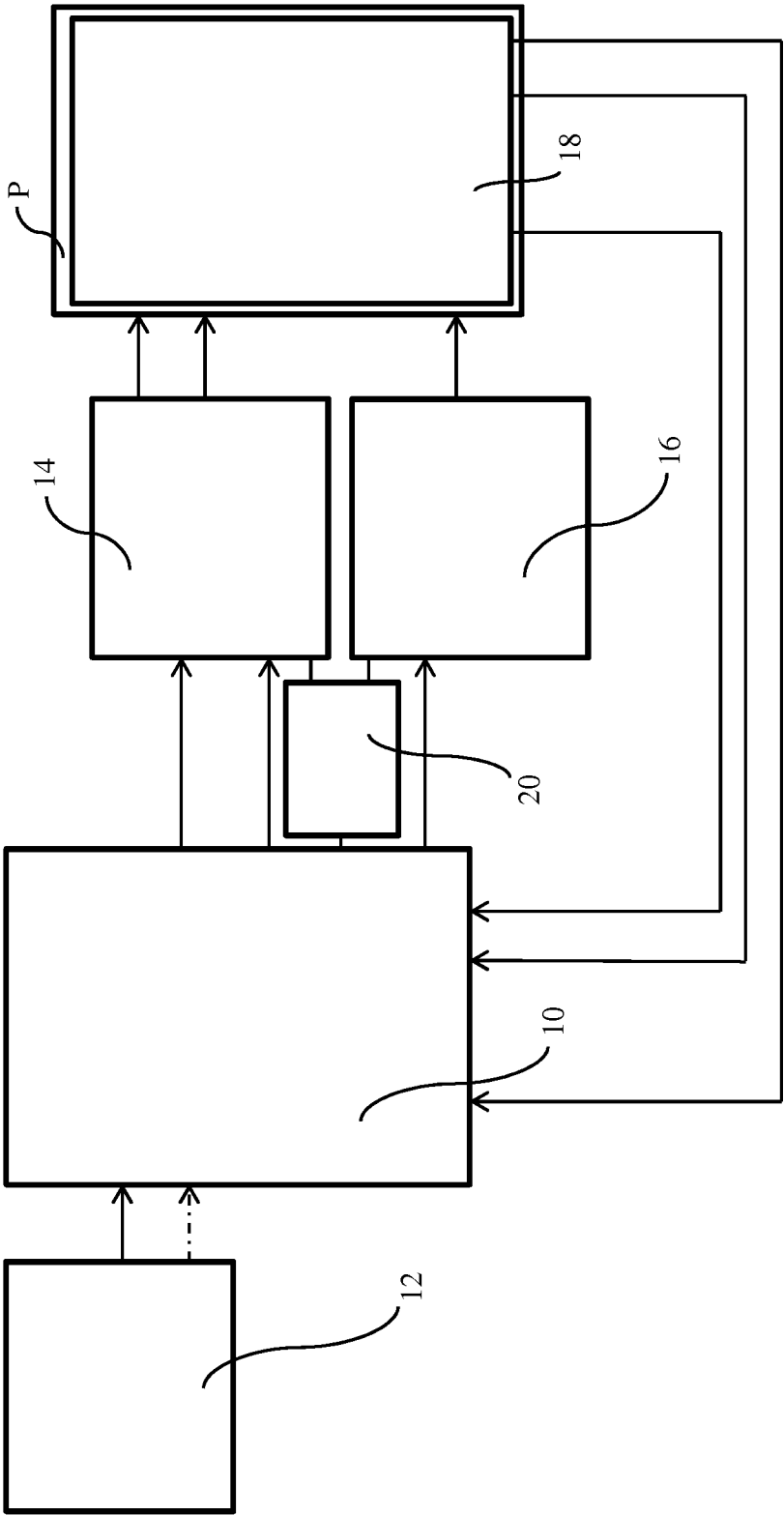


Fig. 1

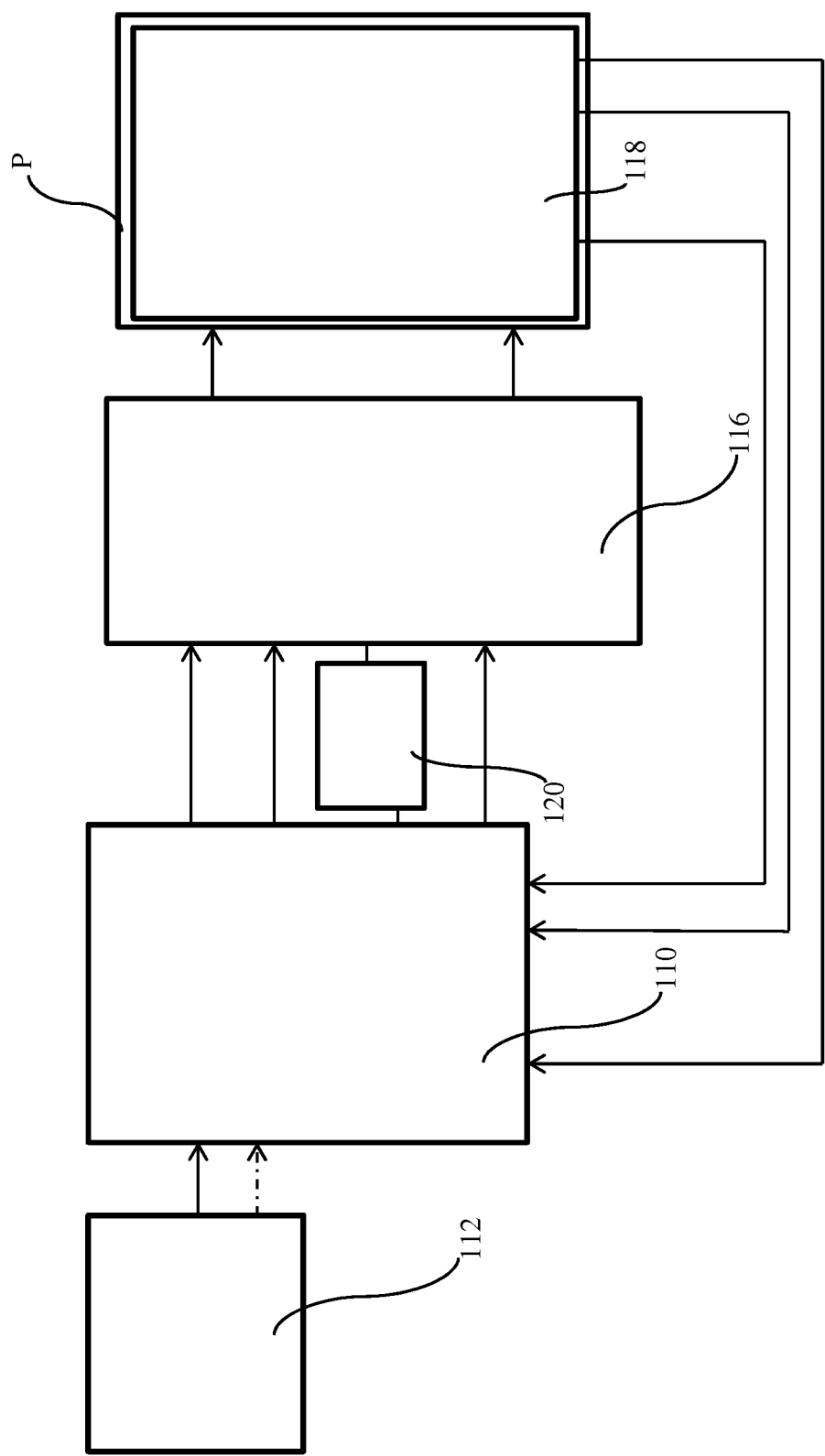


Fig. 2

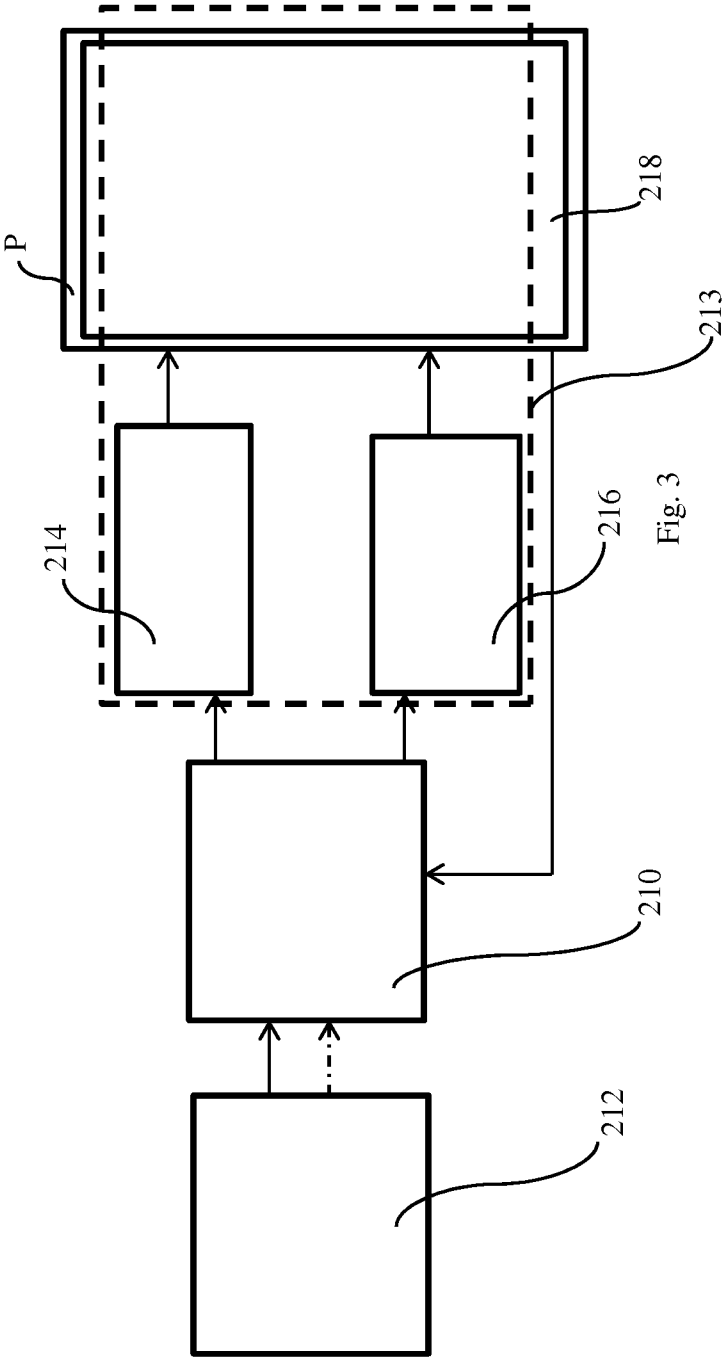


Fig. 3

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/US2015/035731**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

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

1. ☒ Claims Nos.: 19-24
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 19-24 pertain to methods for treatment of the human body and thus relate to a subject-matter which this International Searching Authority is not required, under PCT Article 17(2)(a)(i) and PCT Rule 39.1(iv), to search.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

Remark on Protest

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/035731**A. CLASSIFICATION OF SUBJECT MATTER****A61M 16/00(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61M 16/00; A62B 9/02; A61M 31/00; A61M 15/00

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords: negative pressure ventilation (NPV), positive pressure ventilation (PPV), controller, sensor

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 7909034 B2 (SINDERBY, CHRISTER. et al.) 22 March 2011 See abstract; figures 2-8; column 3, line 1-column 6, line 56; claims 1-47.	1-6,12-17
Y		7-11,18
Y	WO 01-00265 A1 (UNIVERSITY OF FLORIDA) 4 January 2001 See abstract; page 15, line 1-page 25, line 30; claims 1-40.	7-11
Y	US 5707352 A (SEKINS, K. MICHAEL. et al.) 13 January 1998 See abstract; figures 1-6; column 12; claims 1-19.	18
A	US 7836881 B2 (LURIE, KEITH G. et al.) 23 November 2010 See abstract; figures 1-15B; column 5, line 30-column 6, line 53; claims 1-18.	1-18
A	WO 2008-008659 A2 (RIC INVESTMENTS, LLC) 17 January 2008 See abstract; figures 1-8; paragraphs [32]-[34]; claims 1-24.	1-18



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

14 September 2015 (14.09.2015)

Date of mailing of the international search report

21 September 2015 (21.09.2015)

Name and mailing address of the ISA/KR

International Application Division
Korean Intellectual Property Office
189 Cheongsu-ro, Seo-gu, Daejeon Metropolitan City, 35208,
Republic of Korea

Facsimile No. +82-42-472-7140

Authorized officer

Han, Inho

Telephone No. +82-42-481-3362



INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2015/035731

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 7909034 B2	22/03/2011	EP 1680167 A1	19/07/2006
		EP 1680167 A4	15/04/2009
		EP 1680167 B1	16/07/2014
		US 2008-0115786 A1	22/05/2008
		WO 2005-039679 A1	06/05/2005
WO 01-00265 A1	04/01/2001	EP 1189649 A1	27/03/2002
		EP 1189649 B1	15/06/2005
		EP 1586344 A2	19/10/2005
		EP 1586344 A3	05/07/2006
		EP 1586344 B1	06/10/2010
		US 2004-0003813 A1	08/01/2004
		US 2005-0098178 A1	12/05/2005
		US 2007-0028921 A1	08/02/2007
		US 6796305 B1	28/09/2004
		US 7066173 B2	27/06/2006
		US 7210478 B2	01/05/2007
		US 8122883 B2	28/02/2012
		WO 01-00264 A1	04/01/2001
US 5707352 A	13/01/1998	EP 0491685 A1	09/10/2002
		JP 05-503855 A	24/06/1993
		US 2002-0111386 A1	15/08/2002
		US 5158536 A	27/10/1992
		US 5562608 A	08/10/1996
		US 5788665 A	04/08/1998
		US 6166092 A	26/12/2000
		US 6242472 B1	05/06/2001
		WO 91-03267 A1	21/03/1991
US 7836881 B2	23/11/2010	EP 0728028 A1	08/01/2003
		EP 0728028 B1	21/05/2003
		EP 0739401 A1	18/12/2002
		EP 1337292 A2	27/08/2003
		EP 1387714 A1	11/02/2004
		EP 1617798 A2	25/01/2006
		JP 03-672922 B2	20/07/2005
		JP 09-508811 A	09/09/1997
		JP 10-507211 A	14/07/1998
		JP 2004-509654 A	02/04/2004
		JP 2004-532681 A	28/10/2004
		JP 2006-524543 A	02/11/2006
		US 2002-0069878 A1	13/06/2002
		US 2002-0170562 A1	21/11/2002
		US 2003-0037784 A1	27/02/2003
		US 2003-0192547 A1	16/10/2003
		US 2004-0200474 A1	14/10/2004
		US 2004-0211415 A1	28/10/2004
		US 2004-0211416 A1	28/10/2004

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2015/035731

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		US 2004-0211417 A1	28/10/2004
		US 2004-0231664 A1	25/11/2004
		US 2005-0165334 A1	28/07/2005
		US 2005-0199237 A1	15/09/2005
		US 2007-0277826 A1	06/12/2007
		US 2011-0098612 A1	28/04/2011
		US 5372095 A	13/12/1994
		US 5441658 A	15/08/1995
		US 5551420 A	03/09/1996
		US 5692498 A	02/12/1997
		US 6062219 A	16/05/2000
		US 6425393 B1	30/07/2002
		US 6526973 B1	04/03/2003
		US 6604523 B2	12/08/2003
		US 6986349 B2	17/01/2006
		US 7082945 B2	01/08/2006
		US 7174891 B2	13/02/2007
		US 7185649 B2	06/03/2007
		US 7195012 B2	27/03/2007
		US 7195013 B2	27/03/2007
		US 7204251 B2	17/04/2007
		US 7210480 B2	01/05/2007
		US 7766011 B2	03/08/2010
		US 8408204 B2	02/04/2013
		WO 2004-096109 A2	11/11/2004
		WO 2004-096109 A3	29/12/2005
		WO 95-13108 A1	18/05/1995
		WO 95-13334 A1	18/05/1995
		WO 96-28215 A1	19/09/1996
WO 2008-008659 A2	17/01/2008	EP 2043712 A2	08/04/2009
		JP 2009-543602 A	10/12/2009
		US 2008-0149099 A1	26/06/2008
		US 7594508 B2	29/09/2009
		WO 2008-008659 A3	13/11/2008