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CLINICAL DECISION SUPPORT AND CLOSED-LOOP CONTROL FOR INTENSIVE CARE UNIT SEDATION

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ABSTRACT

Critical care patients undergoing surgery require drug administration to regulate physiological variables such as blood pressure, cardiac output, heart rate, and degree of consciousness. The rate of infusion of each administered drug is critical, requiring constant monitoring and frequent adjustments. Patients in the intensive care unit who require mechanical ventilation due to acute respiratory failure also frequently require the administration of sedative agents. Open-loop control (manual control) by clinical personnel can be tedious, imprecise, time-consuming, and sometimes of poor quality, depending on the skills and judgment of the clinician. Dynamical system pharmacokinetic and pharmacodynamic modeling and closed-loop control system design methodologies can significantly advance our understanding of the wide effects of pharmacological agents and anesthetics, as well as advance the state-of-the-art in active control of drug delivery systems for clinical pharmacology. In this paper, we discuss the challenges and opportunities of clinical decision support and closed-loop control for intensive care unit sedation.

Key Words: Automated sedation, adaptive control, mechanical ventilation, optimal control, expert systems, clinical decision support.

I. INTRODUCTION

Modern control technology is having a revolutionary impact in modern medicine through medical robotics (stereotactical brain surgery, implant fitting, and coronary procedures), electrophysiological systems (pacemakers and automatic implantable defibrillators), life support (ventilators and artificial hearts), and medical imaging (image-guided surgery and therapy). An additional area of medicine that can benefit enormously from systems and control oriented ideas is clinical pharmacology, in which mathematical modeling plays a prominent role [1–5]. This is particularly true when dealing with critically ill patients in the intensive care unit (ICU) or in the operating room. These patients often require administration of drugs to regulate key physiological variables, such as level of consciousness, heart rate, blood pressure, ventilatory drive, *etc.*, within desired targets. The rate of administration of these drugs is critical, requiring constant monitoring and frequent adjustments. Open-loop control by clinical personnel can be tedious, imprecise, time-consuming, and sometimes of poor quality. Hence, the need for closed-loop control (active control) in medical drug delivery systems is significant, with the potential for improving the quality of medical care as well as curtailing the increasing cost of health care.

One of the main drawbacks in developing active control-based drug delivery systems is the lack of accurate mathematical models for characterizing the dynamic behavior of drugs on physiological variables. System nonlinearities, model parameter variations from patient to patient, as well as parameter variations within the same patient under different conditions make it very challenging to develop models and effective control law architectures for active drug delivery systems. Standard data-driven system identification techniques may not be applicable to complex biological system modeling involving *in situ* diagnostics.

Patients in the intensive care unit who require mechanical ventilation due to acute respiratory failure also frequently require the administration of sedative agents. The need for sedation arises from patient anxiety due to the loss of personal control and the unfamiliar and intrusive environment of the intensive care unit. In addition, pain or other variants of noxious stimuli frequently require administration of anxiolytic and analgesic drugs for patient comfort. In particular, the interface between the patient and the ventilator is typically an endotracheal tube passing through the oropharynx and into the trachea. Due to the powerful gag reflex, this tube is very noxious. Without sedation patients can become dangerously agitated, risking dislodgement of life support devices in the

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worst case and, in any case, resulting in stress that is ethically unacceptable and also physiologically unacceptable due to deleterious increases in heart rate, blood pressure, and work of breathing.

Sedation of mechanically ventilated patients in the intensive care unit is an important and challenging problem with ethical, clinical, and financial implications. At the ethical level, we have a self-evident moral imperative to provide adequate anxiolysis and analgesia for patients in the intensive care unit. From the clinical perspective, it is important that this be done without either overdosage or underdosage as either may have undesirable clinical effects. At the financial level, sedation of patients in the intensive care unit requires large investments of health care provider time, with a commensurate financial cost, while inefficient titration of sedation and analgesia may prolong intensive care unit length of stay.

While physicians select the agent(s) used for sedation, the actual administration of these agents is the responsibility of the nursing staff. The intensive care unit nurse has one of the most task-laden jobs in medicine, and titration of the sedative drug dose to achieve the optimal levels of sedation can be a difficult and time consuming task. If clinical decision support systems and closed-loop control systems could be developed for critical care monitoring and the administration of sedation, the intensive care unit nurse could be released from the intense monitoring of sedation, allowing her/him to focus on other critical tasks.

In clinical practice the dose of sedative agent is varied, or titrated, to achieve the desired level of sedation. The level of sedation is currently based on clinical scoring systems. One example is the Motor Activity Assessment Score (MAAS) [6] in which patients are given an integer score of 0–6 as follows: 0, unresponsive; 1, responsive only to noxious stimuli; 2, responsive to touch or name; 3, calm and cooperative; 4, restless and cooperative; 5, agitated; and 6, dangerously agitated. Other examples of well known clinical scoring sedation scales include the Richmond Agitation Sedation Scale (RASS) [7] and the modified Ramsay sedation scale (MRSS) [8].

To implement closed-loop control in an acute environment, control of cardiovascular function needs also to be addressed along with sedation since hemodynamic management and control of consciousness are interrelated. For example, a major side effect of cardiac surgery is that patients can become hypertensive [9], requiring treatment to prevent cardiac dysfunction, pulmonary edema, myocardial ischemia, stroke, and bleeding from fragile sutures. Although drugs are available for treating postoperative hypertension, titration of these drugs to regulate blood pressure is often difficult. Underdosing leaves the patient hypertensive, whereas overdosing can reduce the blood pressure to levels associated with shock.

Although blood pressure control is important, cardiovascular function involves several other important variables, all of which are interrelated [9]. The intensive care unit clinician must ensure not only that blood pressure is within appropriate limits but also that cardiac output (*i.e.*, the amount of blood pumped by the heart per minute) is acceptable and that the heart rate is within reasonable limits. Mean arterial blood pressure is proportional to cardiac output, with the proportionality constant denoting the systemic vascular resistance, in analogy with Ohm's law. Cardiac output is equal to the product of heart rate and stroke volume, the volume of blood pumped with each beat of the heart. Stroke volume, in turn, is a function of contractility, the intrinsic strength of the cardiac contraction; preload, the volume of blood in the heart at the beginning of the contraction; and afterload, the impedance to ejection by the heart.

The intensive care unit clinician must balance all of these variables. Inotropic agent drugs, that is, drugs that increase the strength of contraction of the heart, also have variable effects on heart rate and afterload. There are also vasopressor drugs, which increase afterload, and vasodilator drugs, which decrease afterload. Finally, stroke volume can be improved by giving the patient intravenous fluids and increasing preload. However, too much fluid can potentially be deleterious by impairing pulmonary function as fluid builds up in the lungs. The fact that closed-loop control of blood pressure has not been widely adopted by clinicians is not surprising when one considers the complex interrelationships among hemodynamic variables.

Since cardiovascular and central nervous system functions are critical in the acute care environment, technologies have evolved for their measurements. The challenge for extending feedback control technology to the problem of sedation of critically ill patients, however, is finding the appropriate performance variable for control. Hence, the first step in the development of closed-loop control of sedation is the discovery of an objective, continuously-measurable parameter that correlates with clinician assessment of the level of sedation. Once such a parameter is discovered and validated, it then becomes necessary to use the measure of sedation for the titration of drug dose. In this paper, we discuss the challenges and opportunities of clinical decision support and closed-loop control for intensive care unit sedation. Several closed-loop control paradigms are investigated including adaptive control, neuroadaptive control, expert systems, controlled active vision, optimal control, and hybrid adaptive control for clinical decision support and intensive care unit sedation.

II. CLOSED-LOOP CONTROL FOR HYPNOSIS AND SEDATION

2.1 Overview, background, and significance

Critically ill patients, especially those supported with mechanical ventilation, frequently require administration of sedative drugs [10–12]. The magnitude of the clinical

indication for sedation of critically ill patients is evident in the estimate that over one billion dollars are spent in the United States annually on drugs used for this purpose [13]. Sedation is indicated for two compelling reasons. The first of these is ethical. It is estimated that up to 70% of patients experience clinically significant anxiety [14]. This is understandable since the patients will undoubtedly have some awareness of the critical nature of their illness and they will find themselves in an unfamiliar and intrusive environment. Many procedures performed in the intensive care unit, including mechanical ventilation, are uncomfortable and in many cases painful, requiring anxiolytic and analgesic drugs for patient comfort.

In addition to these ethical considerations, sedation is indicated for therapeutic reasons. Agitated patients can do physical harm to themselves by dislodging vital life support and monitoring devices with excessive musculoskeletal activity. Agitation due to anxiety or pain can result in excessive metabolic and cardiopulmonary demands. Oxygen delivery to vital organs (heart, brain, kidneys, mesentery) can be enhanced in patients with limited cardiopulmonary reserve if ventilatory effort and excessive musculoskeletal activity due to agitation are minimized. In patients with acute respiratory distress syndrome (ARDS) current evidence-based practices of mechanical ventilation [15,16] using low tidal volumes often result in profound dyspnea, requiring deep sedation to prevent patients "fighting the ventilator." In severe cases, muscle paralysis is needed to improve oxygenation. In this case, sedation approximates general anesthesia to avoid having a paralyzed patient who is aware.

While clinicians are well aware of the need for sedation in critically ill patients, the challenge is how to provide adequate sedation without oversedation. This is particularly problematic in patients requiring mechanical ventilation due to pulmonary or respiratory insufficiency. Sedation is required for mechanical ventilation for the causes cited above. However, once the cause of pulmonary insufficiency has been corrected it is important to wean the patient from mechanical ventilation in as timely a fashion as is safe, since prolonged ventilation is expensive and is associated with known risks, such as inadvertent extubation, laryngo-tracheal trauma, and, most significantly, ventilator-associated pneumonia. If the patient is oversedated at this point, liberation from mechanical ventilation and endotracheal extubation may not be possible due to a diminished level of consciousness and respiratory depression from sedative drugs.

The clinical relevance of this problem is elucidated by a study published in [13]. The investigators in [13] demonstrate that daily interruption of sedation with reinstitution when patients were considered "awake" significantly decreased the duration of mechanical ventilation and intensive care unit stay. Daily interruption of sedation is necessary because continuous constant rate infusions lead to accumulation of sedative drugs as peripheral compartments saturate with the agent over time. The problem is exacerbated by the fact that sedation is most often administered to patients undergoing mechanical ventilation and the most common manifestation of overdosing with modern sedative agents is respiratory depression. Given that the patient is typically being mechanically ventilated, it is easy to fail to detect overdosing. While daily interruption of sedation was shown to be effective in shortening the duration of mechanical ventilation, many clinicians balk at the necessity of "waking" patients, given the compelling reasons for sedation in the first place. By using a more objective measure of sedation and then controlling the appropriate level of sedation, this problem may be greatly ameliorated. The development of efficient algorithms for closed-loop sedation control can obviate the need to prevent oversedation by a daily interruption of sedation.

2.2 Closed-loop control for operating room hypnosis

Unlike closed-loop control of intensive care unit sedation, which is virtually undeveloped in the literature, closed-loop control algorithms for intraoperative anesthesia have been developed, simulated, and implemented. The first of these have focused on the control of inhalation anesthesia and several adaptive control algorithms have been developed [17–23]. These algorithms have been shown to provide superior control of general inhalation anesthesia in simulations and animal studies. However, they are not directly relevant to the specific problem of ICU sedation since the controlled variable is end-tidal anesthetic concentration. It is not possible with current technology to rapidly measure the plasma concentration of the intravenously-administered drugs commonly used for ICU sedation. Thus, drug concentration is not a viable control variable. Furthermore, drug concentration, even if it could be measured rapidly, is not the best control variable. We are more interested in drug effect than drug concentration. Far more relevant to the problem of ICU sedation are several recently developed algorithms for the control of intravenous anesthesia using a processed electroencephalograph (EEG) or auditory evoked response (AER) signal as the measurement variable for control.

EEG-based closed-loop control of anesthesia was first proposed in [24]. Subsequently, a closed-loop, model-based adaptive controller was developed and clinically tested in [25] for delivering intravenous anesthesia using the median frequency of the EEG power spectrum as the control variable. The model used in [25] assumes a two-compartment pharmacokinetic model involving a set of patient-specific pharmacokinetic parameters and describes the concentration of drug as a function of time after a single bolus dose was given. It is also assumed that the control variable, median EEG frequency is related to the drug concentration by the Hill equation [26]. Using this relationship it can be seen that the drug

effect is a function of the pharmacokinetic as well as the pharmacodynamic parameters. If these parameters are known, it is straightforward to calculate the dose regimen needed to achieve the target EEG signal. However, these parameters are not known for individual patients, with variability estimates for some parameters being as high as 100%.

The algorithm developed in [25] assumes that the pharmacodynamic and pharmacokinetic parameters were equal to the mean values reported in prior studies. Using the mean values of the pharmacokinetic parameters from prior studies as starting values, estimates of these parameters were refined by analyzing the difference between the target and observed EEG signal. This algorithm was implemented for the intravenous anesthetic agents methohexital and propofol but did not appear to offer great advantage over standard manual control [25,27]. The observed performance might have been due to the approximations of the algorithm or the deficiencies of the median EEG frequency as a measure of the depth of anesthesia.

Since the work of [27], alternative EEG measures of depth of anesthesia have been developed. Possibly the most notable of these is the bispectral index or BIS [28]. The BIS is a single-composite EEG measure, which appears to be closely related to the level of consciousness [29]. In [30] the authors present a closed-loop controller of the delivery of the intravenous anesthetic propofol using a model-based adaptive control algorithm with the BIS as the measurement and performance variable. The algorithm is similar to the one developed in [27] in that it is based on a pharmacokinetic model predicting the drug concentration as a function of infusion rate and time, and a pharmacodynamic model analogous to that used in [27] relating the BIS signal to concentration. However, in contrast to [27], it is assumed in [30] that the pharmacokinetic parameters are always correct and that any variability in individual patient response is due to pharmacodynamic variability.

More specifically, the approach of [30] predicts the anesthetic concentration using the pharmacokinetic model and then constructs a BIS-concentration curve using the observed BIS during induction and the predicted propofol concentration. During each time epoch, the difference between the target BIS signal and the observed BIS signal is used to update the pharmacodynamic parameters relating concentration and BIS signal for the individual patient. However, this algorithm is also only partially adaptive in the sense that it does not update the pharmacokinetic parameters.

The results in [30] demonstrated excellent performance as measured by the difference between the target and observed BIS signals. However, as pointed out in [31], the excellent performance of the system may have been because the system was not fully stressed. In [30], a high dose of the opioid remifentanil, a neurotransmitter inhibitor resulting in significant analgesic effect, was administered in conjunction with propofol. Consequently, central nervous system excitation due to surgical stimulus was blunted and, thus, the need to adjust the propofol dose as surgical stimulus varied was diminished. It is unknown whether the control system would have been effective in the absence of deep narcotization.

In contrast to the model-based adaptive controllers in [25,27,30], a proportional-integral-derivative (PID) controller using the BIS signal as the variable to control the infusion of propofol is considered in [32]. The median absolute performance error of this system was good (8.0%), although in three out of ten patients, oscillations of the BIS signal around the set point were observed, and anesthesia was deemed clinically inadequate in one of the ten patients. The same system was used in [33], with an auditory evoked potential as the control variable. Intravenous propofol anesthesia has also been delivered by a closed-loop controller that uses both auditory evoked responses and cardiovascular responses as the control variables with a fuzzy-logic algorithm in [34]. This system has had only very minimal clinical testing. More recently, the authors in [35] consider model-based controllers for inhalation anesthetic agents that attempt to control the BIS signal or mean arterial blood pressure, while keeping end-tidal anesthetic concentrations within prespecified limits.

To address the uncertainties in the pharmacokinetic and pharmacodynamic parameters due to interpatient variability, the authors in [36–38] developed and clinically tested adaptive controllers that can be implemented using the processed EEG as a performance variable. Using compartmental models, a Lyapunov-based direct adaptive control framework was developed in [36,37] that guarantees partial asymptotic setpoint stability of the closed-loop system, that is, asymptotic setpoint stability with respect to part of the closed-loop system states associated with the physiological state variables. Furthermore, the remaining states associated with the adaptive controller gains are shown to be bounded. In addition, the adaptive controllers, which are constructed without requiring knowledge of the system pharmacokinetic and pharmacodynamic parameters, provide a nonnegative control input for stabilization with respect to a given setpoint in the nonnegative orthant of the state space. Clinical evaluation trials of these controllers are reported in [3,39,40].

In [39], the authors present a neural network adaptive control framework that accounts for combined interpatient pharmacokinetic and pharmacodynamic variability. In particular, a framework for adaptive setpoint regulation of nonlinear uncertain compartmental systems is developed. The formulation in [39] addresses adaptive output feedback controllers for nonlinear compartmental systems with unmodeled dynamics of unknown order while guaranteeing ultimate boundedness of the error signals corresponding to the physical system states, as well as the neural network weighting gains. Extensions of adaptive and neuroadaptive controllers for drug delivery systems with actuator saturation constraints,

measurement noise, and system time delays are discussed in [41–45].

2.3 Closed-loop control for ICU sedation

The challenge for extending feedback control technology to the problem of sedation of critically ill patients, in contrast to the control of intraoperative anesthesia, is finding the appropriate performance variable for control. While there is a considerable body of literature demonstrating that the processed EEG can be a viable measure of the level of consciousness, the goal in the sedation of critically ill patients is not necessarily depression of consciousness. As discussed in the Introduction, sedation is typically assessed using subjective ordinal scales that distinguish between patients who are unresponsive or responsive only to noxious stimuli and those who respond to voice and are calm and cooperative in this response.

There have been a number of investigations of processed EEG monitoring (all using the BIS monitor) of intensive care unit patients and the results have been inconsistent [46–51]. Considerable variability in BIS scores in patients with the same apparent degree of sedation (by subjective scoring systems) has been observed, although there appears to be more consistency in deeply sedated patients [51]. High BIS scores have been observed in patients who were comatose. This discrepancy may be attributed to the "noisy" environment of the intensive care unit. It is widely appreciated that BIS monitoring, or for that matter, any EEG monitoring, can be fraught with error due to the potential for outside interference to produce an unfavorable signal-to-noise ratio yielding spurious results [52]. Nonphysiologic artifactual signals can be generated from sources external to the patient that include lights, electric cautery devices, ventilators, pacemakers, patient warming devices, and electrical noise related to the many different kinds of monitors normally found in an operating room or an ICU. Physiologic movements such as eye movements, myogenic activity, perspiration, and ventilation can also produce artifactual increases in the BIS score. In particular, it is apparent that electromyographic (EMG) activity can spuriously increases the BIS score [52].

The latest version of the Bispectral Index monitor has been designed to filter EMG noise; however, it remains to be seen whether this improves the correlation between clinician assessment of sedation and the BIS score. The key obstacle to the use of the processed EEG for sedation assessment could well be that the goal for the critically ill patient is not simply depression of level of consciousness. It has been suggested that "the anesthetized patient in the operating room is a different creature from that of the critically ill and injured" [50]. While this may yet prove to be the case, it is worthwhile to investigate closed-loop control of sedation using the processed EEG as the performance variable for control.

The latest version of the BIS monitor, which more effectively filters EMG noise, has not yet been fully investigated as a tool for intensive care unit sedation. While there are other sources of electrical noise in the intensive care unit, EMG signals are an important noise source. Furthermore, spurious but time-limited BIS values that may contribute to the poor correlation between the BIS score and clinician-generated sedation scores may have minimal effect on the titration of sedation using adaptive and neuroadaptive control algorithms.

In a subset of critically ill patients a deeper level of sedation, more closely approximating general anesthesia is appropriate. Patients with acute respiratory distress syndrome who are ventilated with low tidal volumes rather than large tidal volumes have a lower mortality [15]. However, low tidal volume ventilation is uncomfortable, creating a sense of dyspnea and requiring deep sedation. Patients being ventilated in this manner should be unconscious, especially if they also require muscle paralysis to maintain oxygenation. The processed EEG is a plausible control variable for ICU sedation in this situation.

An alternative performance variable for closed-loop control of sedation involves respiratory parameters. As mentioned in the Introduction, one of the most common reasons for administering sedation is to facilitate mechanical ventilation, and patient discomfort or anxiety is often manifested as fighting the ventilator or patient-ventilator dyssynchrony. Excessive work of breathing is deleterious to patient outcome and a key scenario is the administration of sedation to prevent fighting the ventilator. Patient-ventilator dyssynchrony is clinically identified as use of accessory muscles, nasal flaring, active expiration, and tachypnea. However, dyssynchrony can be quantified by measuring patient work of breathing using an esophageal balloon [53,54]. Patient-ventilator dyssynchrony can also be identified using pressure and flow waveforms in the graphics available on almost all ventilators [55]. A novel approach to sedation of mechanically ventilated patients can involve measures of dyssynchrony, either work of breathing or patient breath rate, as performance variables for closed-loop control. This will necessitate the development of optimal control algorithms for clinical pharmacology.

The performance measure for an optimal drug dosing control algorithm can include a measure of the system operating error, a measure of the control effort, or any other characteristic that is important to the clinician using the control system. For example, propofol can be used to induce general anesthesia with concomitant apnea, and hence, eliminate ventilator-patient dysynchrony. However, the price may be excessive hemodynamic compromise or a totally unresponsive and oversedated patient. Hence, optimal control algorithms can maximize patient-ventilator synchrony while preserving acceptable hemodynamic function.

While advances in understanding sedation, and its appropriate measure, are inevitable, it remains a fact that currently the clinical standard is an ordinal scoring system [56–59]. Feedback control algorithms using the sedation score as a partial performance variable for control would require simultaneously exhibiting continuous-time dynamics as well as logic commands, discrete events, and resetting events. We envision a system in which the clinician (nurse or physician) evaluates the patient, enters the score into the controller, which then adjusts the dosing regimen to maintain sedation at the desired score. The unique characteristics of this problem are noteworthy. The performance variable is discontinuous in the sense that clinical evaluation of sedation is done intermittently. Thus, issues of embedded control architectures become paramount and the development of an efficient hierarchical hybrid control algorithm [60] could significantly improve the outcome for drug administration in the ICU [4].

III. MEASUREMENT SENSORS FOR CLINICAL PHARMACOLOGY

The sensors used in the intensive care unit to monitor patient status include those that measure hemodynamic status, respiratory status, renal function, and central nervous function. Hemodynamic status is most typically assessed by continuous monitoring of heart rate and electrocardiograph (ECG). The ECG measures the electrical potential difference between skin electrodes placed at various sites on the torso and limbs, and can be analyzed to provide continuous heart rate measurement as well as identify signs of cardiac dysfunction. Hemodynamic function is also assessed using blood pressure measurements. While this may be done using non-invasive methods, it is most typically done by placing a small plastic catheter directly into an artery (most often the radial artery as it passed through the underside of the wrist) and then using a pressure transducer to convert the pulse pressure wave into an electrical signal.

In a similar fashion, catheters are also often placed into large central veins (such as the internal jugular vein) so that their tips are situated close to the entry of the main veins (superior vena cava or inferior vena cava) returning blood to the heart. Pressure waves in these veins are then transduced into electrical signals to provide the central venous pressure. This gives an indirect measure of the volume of blood in the heart which is a major determinant of cardiac output, the volume of blood pumped by the heart per minute.

In some situations in which there is more profound cardiac dysfunction, a pulmonary artery catheter is placed. This is a catheter that runs through the heart into the pulmonary artery (*i.e.*, the artery going from the heart to the lungs) and can measure pressures in the pulmonary artery (another indirect measure of volume in the heart) as well as directly measure cardiac output. Finally, it is important to monitor the adequacy of blood flow to the various tissues of the body. One common technique is to measure the amount of oxygen in venous blood. If the delivery of oxygen to tissue decreases, then there will be a greater relative extraction of oxygen from the delivered blood by the tissue, and hence, the venous blood returning to the heart will have less oxygen in it. This is most typically measured as the percentage of hemoglobin molecules (the primary carrier of oxygen in the blood) that are bound to oxygen (referred to as the venous saturation).

The purpose of respiration is to eliminate carbon dioxide from, and deliver oxygen to, the blood. Hence, the most important monitors of respiratory function are measures of carbon dioxide and oxygen in the blood. With the most commonly used sensor technologies these are not directly measurable; however, it is possible to continuously measure hemoglobin oxygen saturation, the percentage of hemoglobin in arterial blood that is bound to oxygen, using absorbance spectroscopy and light emitting diode technology. In addition, many intensive care units use continuous analysis of gas exhaled from the lungs to measure end-tidal carbon dioxide concentration, an indirect and approximate measure of blood carbon dioxide concentrations. Furthermore, modern mechanical ventilators are equipped to measure the pressure used to expand the lungs when the patient is undergoing mechanical ventilation, as well as respiratory rate.

Assessment of renal function is not as sophisticated as either hemodynamic or respiratory monitoring. Currently renal function is most typically assessed by the continuous measurement of urine output. Sensors for assessment of central nervous system function are currently in their infancy, at least as far as routine clinical use is concerned.

IV. PAIN, AGITATION, AND SEDATION ASSESSMENT AND CONTROL USING DIGITAL IMAGING

Pain assessment in patients who are unable to verbally communicate with the medical staff is a challenging problem in patient critical care. This problem is most prominently encountered in sedated patients in the ICU recovering from trauma and major surgery, as well as infant patients and patients with brain injuries [61–63]. Current practice in the ICU requires the nursing staff to assess the pain and agitation experienced by the patient, and take appropriate action to ameliorate the patient's anxiety and discomfort.

The fundamental limitations in sedation and pain assessment in the ICU stem from subjective assessment criteria, rather than quantifiable, measurable data for ICU sedation. This often results in poor quality and inconsistent treatment of patient agitation from nurse to nurse. Recent

advances in computer vision techniques can assist the medical staff in assessing sedation and pain by constantly monitoring the patient and providing the clinician with quantifiable data for ICU sedation. An automatic pain assessment system can be used within a decision support system which can also provide automated sedation and analgesia in the ICU [4]. In order to achieve closed-loop sedation control in the ICU, a quantifiable feedback signal is required that reflects some measure of the patient's agitation. A non-subjective agitation assessment algorithm can be a key component in developing closed-loop control algorithms for ICU sedation.

Individuals in pain manifest their condition through "pain behavior" [64], which includes facial expressions. Clinicians regard the patient's facial expression as a valid indicator for pain and pain intensity [65]. Hence, correct interpretation of the facial expressions of the patient and its correlation with pain is a fundamental step in designing an automated pain assessment system. Of course, other pain behaviors including head movement and the movement of other body parts, along with physiological indicators of pain, such as heart rate, blood pressure, and respiratory rate responses should also be included in such a system.

As discussed in the Introduction, the current clinical standard in the ICU for assessing the level of sedation is an ordinal scoring system, such as the motor activity and assessment scale (MAAS) [6] or the Richmond agitation-sedation scale (RASS) [7], which includes the assessment of the level of agitation of the patient as well as the level of consciousness. Assessment of the level of sedation of a patient is, therefore, subjective and limited in accuracy and resolution, and hence, prone to error which in turn can lead to oversedation. In particular, oversedation increases risk to the patient since liberation from mechanical ventilation may not be possible due to a diminished level of consciousness and respiratory depression from sedative drugs resulting in prolonged length of stay in the ICU. Prolonged ventilation is expensive and is associated with known risks, such as inadvertent extubation, laryngo-tracheal trauma, and ventilator-associated pneumonia. Alternatively, undersedation leads to agitation and can result in dangerous situations for both the patient and the intensivist. Specifically, agitated patients can do physical harm to themselves by dislodging their endotracheal tube which can potentially endanger their life. In addition, an intensivist who must restrain a dangerously agitated patient has less time for providing care to other patients, making their work more difficult.

Digital imaging and computer vision can be used to quantify agitation in sedated ICU patients [66–70]. In particular, digital video image processing and computer vision can be used to develop objective agitation measurements from patient motion. In the case of paraplegic patients, whole body movement is not available, and hence, digital imaging of whole body motion is not a viable sensor. In this case, measuring head motion and facial grimacing for quantifying patient agitation in critical care can be a viable alternative.

Although there is a vast potential for using computer vision for agitation and pain assessment, there are very few articles in the computer vision literature addressing this issue. The authors in [71] have used computer vision for pain assessment in demented elderly patients. In [67], an agitation assessment scheme is proposed for patients in the ICU. The approach of [67] is based on the hypothesis that facial grimacing induced by pain results in additional "wrinkles" (equivalent to edges in the processed image) on the face of the patient, and this is the only factor they use in assessing pain. Although this approach is computationally inexpensive and especially appealing for a real-time decision support system, it can be limiting since it does not account for other facial actions (*e.g.*, smiling, crying, *etc.*), which may not necessarily correspond to pain. The authors in [63,72–74] use various face classification techniques including support vector machines (SVM) and neural networks (NN) to classify facial expressions in neonates into "pain" and "non-pain" classes. Such classification techniques were shown to have reasonable accuracy.

In [75] and [76], the authors extend the classification technique addressed in [63,72–74] to distinguish pain from non-pain as well as assess pain intensity using a relevance vector machine (RVM) classification technique [77]. The RVM classification technique is a Bayesian extension of SVM which achieves comparable performance to SVM while providing posterior probabilities for class memberships and a sparser model. In a Bayesian interpretation of probability, as opposed to the classical interpretation, the probability of an event is an indication of the uncertainty associated with the event rather than its frequency [78]. If data classes represent "pure" facial expressions, that is, extreme expressions that an observer can identify with a high degree of confidence, the posterior probability of the membership of some intermediate facial expression to a class can provide an estimate of the intensity of such an expression. This, along with other pain behaviors, can be translated into one of the scoring systems currently being used for assessing sedation (*e.g.*, MAAS or RASS).

Pain and agitation assessment using digital imaging involves tracking the patient through a video sequence, observing the patient behavior, and inferring the patient's pain and agitation levels. Particle filters are ideal in processing video information for real-time detection, tracking, and recognition [79,80]. Due to the temporal nature of the data involved in pain and agitation detection, filtering theory (*e.g.*, Kalman and nonlinear filtering) becomes very relevant. Specifically, filtering theory is concerned with recovering information given a time sequence of noise corrupted data. However, traditional filtering techniques apply to rather idealized situations. Given the nonlinear and uncertain nature of

the observations for pain and sedation assessment, continuous state hidden Markov models (HMM) [81,82] are needed to model the uncertain dynamics (*i.e.*, patient behavior) from a video sequence. It is important to emphasize that even in the presence of linear dynamics, which is certainly not the case for the problem at hand, a nonlinear filtering procedure is required. This is due to the fact that the image at a given time forms the observation and a series of data extraction techniques need to be employed before the information is fed to the filter. Particle filters are then used to track the HMM, that is, estimate the hidden state given the observations.

Another important problem in critical care monitoring is abnormality detection. Alarm algorithms can greatly benefit from reliable frameworks for detecting abnormality in the ICU patient. Particle filtering methods also apply to identification as well as change and abnormality detection. In this case, problems arise from the presence of clutter, noise, and occlusions, as well as the classification and correlation of relevant information. Significant changes can be easily detected using the increase in tracking error or the negative log of the observation likelihood. However, slow changes usually get missed. Particle filters can be used to estimate the posterior probability distribution of the state at a given time given the observations up to that time. As in [83], one can use a simple statistic, namely the expected log-likelihood, to detect slow changes. Furthermore, since the particle filter can be used as the basis for a simultaneous tracking/recognition system, it is ideal for the data association problem as well [84]. In addition, since particle filtering is used in a Bayesian framework [79,80] for tracking, identification, and detection, it fits into the Bayesian learning framework discussed above.

Finally, since critical care monitoring, and in particular, agitation and sedation assessment involves the use of multiple sensors, efficient data fusion frameworks can also be developed for automatic agitation and sedation assessment. Multisensor data fusion is concerned with combining information from multiple sources in order to improve the accuracy of information provided by individual sensors [85,86]. Specifically, multi-sensor data fusion frameworks can combine patient data obtained from different sensors (*e.g.*, EEG, digital imaging, *etc.*) and provide the clinician with an objective measure of agitation and sedation. Clearly, such frameworks are inherently more robust to error and failure as compared to single-sensor based assessments.

V. CLOSED-LOOP CONTROL DESIGN PARADIGMS AND METHODS

In this section, we discuss several paradigms and methods for cardiopulmonary management, sedation control, active mechanical ventilation control, and drug dosing in the ICU.

5.1 Feedback control using expert systems

A closed-loop expert system is composed of the controller, the plant (patient), and the plant output measurement block (*i.e.*, sedation assessment block). Within a sedation control framework, the plant (patient) is a dynamical system with unknown dynamics, where the input is the sedative drug dose and the output is the patient behavior. Patient behavior refers to patient's level of sedation and analgesia, manifested through facial expression, gross motor movement, pain, agitation, blood pressure, heart rate, *etc.* The goal of the sedation assessment feedback block is to monitor the patient's behavior, and objectively assess the sedation level based on one of the clinical scoring systems (*e.g.*, MAAS). The input to the controller is the desired level of sedation, and the objective assessment of sedation provided by the sedation assessment block. The closed-loop system is shown in Fig. 1. The current clinical practice in the ICU involves human expert assessment of patient's level of sedation (corresponding to the sedation assessment block), and titration of the correct dose of sedatives (corresponding to the controller).

One approach to closed-loop control of sedation is to design a system that processes the information currently used by the medical staff and mimics the human process of decision making for ICU sedation [87,88]. Such a system can be equipped with various sensors, including the bispectral index monitor [28,29], actigraph (accelerometer for measuring hand and leg movement) [89,90], and digital imaging (for measuring facial expression and gross motor movement) [4,66,67]. In a recent study, machine learning methods have been used to assess the level of pain in patients using facial expressions and analyze the correlation between computer and human expert pain intensity assessments [75,76]. With measurements provided by different viable sensors, an expert system can be designed which mimics expert human actions and follows a similar decision making process.

In [87] and [88], a knowledge-based system, and, in particular, an expert system is considered for clinical decision support and closed-loop control for cardiopulmonary management and intensive care unit sedation. A knowledge-based system is a computer program that is capable of making

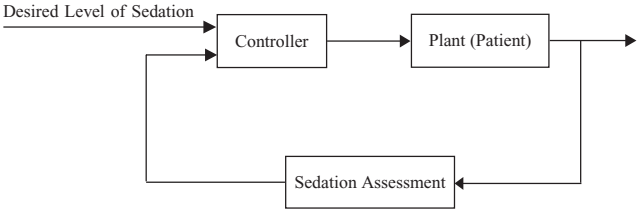

Fig. 1. Closed-loop sedation control architecture.

deductions based on the information provided by the user and the information stored in its knowledge base. In other words, a knowledge-based system is a system which applies a "rules of thumb" approach to a symbolic representation of knowledge [91]. The main characteristic that distinguishes a knowledge-based system from a conventional computer program is its structure [92]. In conventional computer programs, the knowledge and the computational/analytical components of the program are coupled. Knowledge-based systems, however, have two main independent components; namely, the knowledge base, which stores the information, and the inference engine, which makes assertions based on the available knowledge. Expert systems are a subclass of knowledge-based systems, where their objective is to emulate the human expert behavior [92,93].

Expert systems in general deal with two different types of problems: deterministic versus stochastic. As a result, expert systems belong to one of the two general classes of: (i) deterministic expert systems; and (ii) stochastic expert systems. Deterministic expert systems are also referred to as rule-based expert systems due to the fact that in such systems the deduction process is based on a series of rules [93]. A more challenging set of problems is that involving uncertainty in knowledge and in the problem variables. Stochastic expert systems specifically deal with such problems and different frameworks exist to address uncertainty including certainty factors [94], fuzzy logic [95], theory of evidence [96], and, more recently, probability theory [93]. In the probabilistic approach, a joint probability distribution function over the set of variables is defined and the inference is based on probability rules. Such expert systems are referred to as probabilistic expert systems.

5.1.1 A rule-based expert system for cardiopulmonary management and ICU sedation control

In [87] and [88], the authors introduce a simple rule-based expert system for cardiopulmonary management and ICU sedation control. They assume a sedation protocol with the drugs propofol (as the primary agent) and fentanyl (as the secondary agent) with sedation assessment using the MAAS scale to illustrate a rule-based system for control of ICU sedation. Propofol, or 2,6-diisopropylphenol, is an intravenous hypnotic agent that in low doses can produce anxiolysis and in higher doses, hypnosis (*i.e.*, lack of responsiveness and lack of consciousness). Propofol is widely used for ICU sedation because of this spectrum of pharmacodynamic effects and also because of its pharmacokinetics. It is typically administered as a continuous infusion and it is a short acting drug that can be readily titrated, that is, if the infusion rate is increased the blood level increases relatively quickly. Hence, the pharmacological effect of the drug can be quickly varied by varying the infusion rate.

While propofol has primary pharmacodynamic and pharmacokinetic effects that suit it well for ICU sedation, there are some serious side effects that may limit its usefulness. Specifically, it causes dilation of both arteries and veins, as well as mild depressant effects on the heart, that can cause in turn excessive drops in blood pressure. Furthermore, it does not have analgesic effects, and thus, is ineffective in treating pain. Since pain often results in increases in heart rate and blood pressure, propofol can be paradoxically associated with either hypotension (at excessive doses) or hypertension (when the patient has untreated pain).

Because of the hypotensive effects of propofol, and since it does not treat pain-induced hypertension, the rule-based expert system proposed in [88] also uses fentanyl as a secondary agent for sedation. Fentanyl is a synthetic opioid and potent analgesic. It can be quite effective in the treatment of pain-induced hypertension. At the same time, it has mild sedative effects (although even in high doses it does not reliably produce hypnosis). Since it does not have the pronounced hypotensive effects of propofol, it can be used for its sedative effects in hypotensive patients. While it can be employed as a primary agent for sedation, the authors in [88] illustrate their rule-based expert system by assuming it is a second-line agent. This is motivated largely by the fact that it is not quite as fast-acting as propofol and not as easily titrated.

The rule base of a simple ICU sedation control expert system is summarized in Table I. The desired level of sedation corresponds to an MAAS score of 3. The premise of each rule involves the current (M) and previous (M') MAAS scores, blood pressure (BP), and heart rate (HR). The conclusion of each rule consists of primary action and secondary action. The required dose of drugs, denoted by primary action in the table, is given in the first part of the conclusion of each rule. The symbols "$\uparrow$" and "$\downarrow$" denote increase and decrease in the infusion rate of the drug, respectively. Furthermore, "+/$\uparrow$ fentanyl" stands for "if the patient is already on fentanyl, then increase the fentanyl infusion rate by 1 mcg/kg/hr after a 2 mcg/kg bolus dose and, if not, then start fentanyl at 1 mcg/kg/hr after a 2 mcg/kn bolus dose." Finally, the authors in [88] assume that, for a given MAAS score, the previous MAAS score is within its ± 1 range. This is not a limiting assumption if the sedation assessment is performed frequently so that we capture the dynamics of the MAAS score.

The second part of the conclusion of each rule, denoted by secondary action, involves activating a secondary expert system, namely, the hemodynamic control expert system (HDCES). Depending on the blood pressure and the heart rate of the patient, the ICU sedation control expert system can activate the hemodynamic control expert system to regulate patient cardiovascular function. The rule base of a hemodynamic control expert system is summarized in Table II.

The most obvious monitor of cardiovascular function in the intensive care unit is blood pressure, and treatment of

Table I. The rule base of a simple ICU sedation control expert system, which involves the current MAAS score (M), previous MAAS score (M'), and patient's blood pressure (BP) and heart rate (HR).

M	M'	BP/HR	Primary Action	Secondary Action
0 & 1	—	BP ≥ 150 or HR ≥ 120	discontinue fentanyl & propofol	activate HDCES
		90 < BP < 150	discontinue fentanyl & propofol	—
		BP ≤ 90	discontinue fentanyl & propofol	activate HDCES
2	1	BP ≥ 150 or HR ≥ 120	+/↑ fentanyl	if on fentanyl activate HDCES
		90 < BP < 150	—	—
		BP ≤ 90	25% ↓ propofol	—
	2	BP ≥ 150 or HR ≥ 120	25% ↓ propofol, +/↑ fentanyl	if on fentanyl activate HDCES
		90 < BP < 150	25% ↓ propofol	—
		BP ≤ 90	25% ↓ propofol	—
	3	BP ≥ 150 or HR ≥ 120	25% ↓ propofol, +/↑ fentanyl	if on fentanyl activate HDCES
		90 < BP < 150	25% ↓ propofol	—
		BP ≤ 90	50% ↓ propofol	—
3	2	BP ≥ 150 or HR ≥ 120	+/↑ fentanyl	—
		90 < BP < 150	—	—
		BP ≤ 90	—	activate HDCES
	3	BP ≥ 150 or HR ≥ 120	+/↑ fentanyl	—
		90 < BP < 150	—	—
		BP ≤ 90	—	activate HDCES
	4	BP ≥ 150 or HR ≥ 120	+/↑ fentanyl	—
		90 < BP < 150	—	—
		BP ≤ 90	—	activate HDCES
4	3	BP ≥ 150 or HR ≥ 120	50% ↑ propofol	—
		90 < BP < 150	25% ↑ propofol	—
		BP ≤ 90	25% ↓ propofol, +/↑ fentanyl	—
	4	BP ≥ 150 or HR ≥ 120	50% ↑ propofol	—
		90 < BP < 150	25% ↑ propofol	—
		BP ≤ 90	25% ↓ propofol, +/↑ fentanyl	—
	5	BP ≥ 150 or HR ≥ 120	+/↑ fentanyl	—
		90 < BP < 150	—	—
		BP ≤ 90	—	activate HDCES
5	4	BP ≥ 150 or HR ≥ 120	50% ↑ propofol, +/↑ fentanyl	—
		90 < BP < 150	50% ↑ propofol	—
		BP ≤ 90	+/↑ fentanyl	activate HDCES
	5	BP ≥ 150 or HR ≥ 120	50% ↑ propofol, +/↑ fentanyl	—
		90 < BP < 150	50% ↑ propofol	—
		BP ≤ 90	+/↑ fentanyl	activate HDCES
	6	BP ≥ 150 or HR ≥ 120	25% ↑ propofol, +/↑ fentanyl	—
		90 < BP < 150	25% ↑ propofol	—
		BP ≤ 90	+/↑ fentanyl	activate HDCES
6	—	BP ≥ 150 or HR ≥ 120	100% ↑ propofol, +/↑ fentanyl	—
		90 < BP < 150	100% ↑ propofol	—
		BP ≤ 90	+/↑ fentanyl	activate HDCES

blood pressure is a very common activity in the intensive care unit. The hemodynamic expert system presented in [88] is based on the treatment of blood pressure. To a first approximation, the circulation can be described as a very simple direct-current system conforming with a hemodynamic version of Ohm's law. Specifically, the relationship between mean arterial blood pressure (the hemodynamic equivalent of voltage) and cardiac output (the hemodynamic equivalent of current) can be described by [97]

$$\mathrm{MAP}(t) = \mathrm{CO}(t) \times \mathrm{SVR}(t) + \mathrm{CVP}(t), \quad t \geq 0, \tag{1}$$

where $\mathrm{MAP}(t)$ is mean arterial blood pressure, $\mathrm{CO}(t)$ is cardiac output (the volume of blood the heart pumps per minute), $\mathrm{SVR}(t)$ systemic vascular resistance (an index of arteriolar compliance or constriction throughout the body), and $\mathrm{CVP}(t)$ is central venous pressure (the venous pressure of the right atrium of the heart). Since $\mathrm{CVP}(t)$ is typically much less significant than $\mathrm{CO}(t) \times \mathrm{SVR}(t)$, we can see that any

Table II. The rule base of a simple hemodynamics control expert system, which involves the patient's blood pressure (BP) and heart rate (HR).

BP	HR	Action
BP ≥ 150	HR ≥ 110	Beta-Blocker
	HR < 110	Vasodilator
90 < BP < 150	HR ≥ 110	Beta-Blocker
	HR < 110	—
BP < 90	—	See Hypotension Protocol

analysis of blood pressure perturbation should focus on whether the change in blood pressure is due to a change in cardiac output or a change in systemic vascular resistance.

For hypotensive patients (systolic blood pressure < 90 mm Hg or mean blood pressure < 60 mm Hg) the expert system algorithm first entails an evaluation of cardiac output. This can be done by direct measurement or by indirect means. There are a number of technologies for the measurement of cardiac output, including thermodilution, lithium dilution, and analysis of the contour of the arterial pulse wave. Since these technologies are not that frequently employed, the adequacy of cardiac output is often assessed by measurement of central venous hemoglobin oxygen saturation as described in Section III. In some situations it is necessary to assess the adequacy of cardiac output using clinical findings such as poor peripheral circulation, acidosis, or poor urine output.

It follows from the basic equation for hemodynamics given by (1) that if cardiac output is inadequate, then efforts to correct hypotension should be directed toward improving cardiac output. Cardiac output equals stroke volume (*i.e.*, the amount of blood pumped by the heart each time it beats) multiplied by heart rate. If the heart rate is exceptionally low, then one can administer drugs to speed up the heart. More frequently, the focus is on increasing stroke volume. Stroke volume is determined by preload, the term used in the hemodynamic literature to refer to the amount of blood volume in the heart at the onset of each contraction, contractility, the strength of the contraction, and, to a lesser degree, afterload, roughly the load the heart faces in order to pump blood. The first step is to ensure adequate preload. This is evaluated by consideration of the central venous pressure, or pulmonary artery wedge pressure if a pulmonary artery catheter is in place, or by analysis of how the peak systolic arterial pressure changes with inspiration if the patient is undergoing mechanical ventilation, by using echocardiography to visualize the heart, or by simply giving the patient a bolus of intravenous fluids and observing the blood pressure response. If preload is adequate but stroke volume is assessed as inadequate, then the only recourse is to administer drugs (positive inotropes) that increase the contractility of the heart.

In many situations, especially in patients with infections, the cardiac output is adequate or higher than normal but the blood pressure is still low. Referring again to the basic equation of hemodynamics (1), one must conclude that systemic vascular resistance is low. In this case, we administer drugs (vasopressors) that increase systemic vascular resistance. The hypotension protocol flow chart is given in Fig. 2.

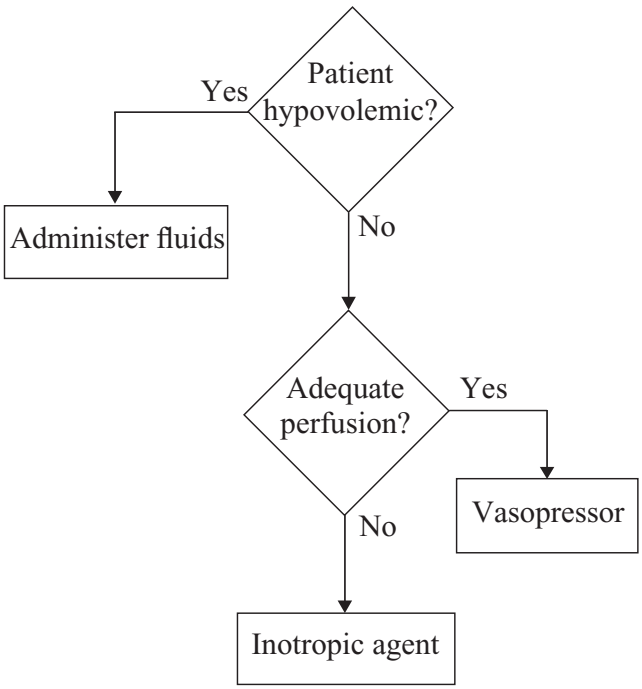

Fig. 2. Hypotension protocol flow chart.

The treatment of hyerptension (systolic blood pressure > 150 mm Hg) follows somewhat similar considerations. If the patient has an elevated heart rate as well as an elevated blood pressure, the usual cause is increased contractility. Since high heart rates potentially can cause myocardial ischemia (*i.e.*, inadequate matching of oxygen delivery to the heart to the demand) it is most appropriate to treat the patient with beta-blockers, that is, drugs that decrease both heart rate and contractility. However, if the heart rate is not elevated, then the most likely cause of the hypertension is elevated systemic vascular resistance and the best treatment would be vasodilaotors, that is, drugs that decrease systemic vascular resistance.

5.1.2 A rule-based expert system for ICU respiratory management

In [88], the authors additionally introduce a rule-based expert system for ICU respiratory management. The respiratory management expert system and the cardiopulmonary management and ICU sedation control expert system are two independent control systems running concurrently. In respiratory management, the goal is to control the arterial partial pressure of CO_2 (carbon dioxide) denoted by $P_aCO_2(t)$ and the

pH of arterial blood. The means to do this are embodied in two equations; one relating $P_aCO_2(t)$ to alveolar ventilation (*i.e.*, the volume of gas exchange in the lungs in a given unit of time), and the other, the Henderson-Hasselbalch equation [98], relating blood *pH* to $P_aCO_2(t)$ and the concentration of bicarbonate in the blood denoted by $[HCO_3^-](t)$.

The relationship between $P_aCO_2(t)$ and ventilation is given by [98]

$$P_aCO_2(t) = 0.863\frac{VCO_2}{V_a(t)}, \quad t \geq 0, \tag{2}$$

where VCO_2 is the total body production of CO_2 per minute and is approximately 259 ml/min in healthy subjects, 0.863 is a constant to reconcile units, and $V_a(t)$ is alveolar ventilation. In patients who are totally dependent on mechanical ventilation (and not taking any independent breaths) $V_a(t)$ is given by [98]

$$V_a(t) = (TV(t) - V_d)RR(t), \quad t \geq 0, \tag{3}$$

where $TV(t)$ denotes the volume of each breath set on the ventilator, $RR(t)$ denotes the respiratory rate set on the ventilator, and V_d denotes the dead space of the lungs. The product $TV(t)RR(t)$ is referred to as the minute ventilation [98] and V_d is approximately 1/3 of minute ventilation in healthy subjects. Changes in V_a and V_d are very gradual and these variables can be regarded as constants.

In actual practice, the clinical staff set the value of $TV(t) \equiv TV$ and $RR(t) \equiv RR$ on the ventilator and, using (3), we can see that these are the only variables that the clinician can manipulate to control $P_aCO_2(t)$. In modern critical care practice, *TV* is set to 6 ml/kg. As a result, the primary variable to control $P_aCO_2(t)$ is $RR(t)$. The other variables in the above equation (*i.e.*, V_d and VCO_2) are specific to the patient and her/his physiology, or rather, pathophysiology.

In addition to controlling $P_aCO_2(t)$, the clinician can control blood *pH* levels. In particular [98],

$$pH(t) = 6.1 + \log_e\left(\frac{[HCO_3^-](t)}{0.03P_aCO_2(t)}\right), \quad t \geq 0, \tag{4}$$

where $[HCO_3^-](t)$ is the bicarbonate ion concentration in arterial blood and 0.03 is a constant to reconcile units. This equation reflects the fact that dissolved carbon dioxide reacts with water to form carbonic acid, which will lower the *pH* of blood. Once the desired $P_aCO_2(t)$ is attained by manipulating $RR(t)$ (or, less commonly, $TV(t)$), control of the desired *pH* can only then be achieved by manipulating $[HCO_3^-](t)$. This is done by either administering bicarbonate in the case of acidosis or, less commonly, by administering an acidifying agent such as the drug *acetazolamide* or dilute hydrochloric acid. Since the deleterious effects of acidosis are more immediate and readily apparent than alkalosis, most clinicians administer acidifying agents only within specific clinical contexts.

The first step in respiratory management involves measuring the arterial gas. This is done intermittently by taking a small sample of blood from an artery and sending it to a laboratory where the partial pressure of carbon dioxide in the blood $P_aCO_2(t)$ is measured using electrochemical methods. In many clinical settings, the arterial $P_aCO_2(t)$ can be approximated by end-tidal CO_2, the concentration of CO_2 in exhaled gas at the end of expiration. This is conveniently measured using near infrared spectroscopy of exhaled gas collected by sampling from the endotracheal tube, the interface between the patient and the mechanical ventilator. This can be done on a breath-by-breath basis.

In most cases involving ventilation control the primary goal is to normalize *pH* so that $P_aCO_2(t)$ is controlled to facilitate achieving a normal *pH*. However, in the case of increased intracranial pressure it is important to maintain a normal carbon dioxide level as well as normal *pH* level. The brain is enclosed in a closed vault (*i.e.*, the skull). If the brain becomes edematous (*i.e.*, excessive accumulation of serous fluid), then this will increase the pressure (the intracranial pressure) inside this closed vault. If the intracranial pressure becomes too great, then the brain will be compressed and this can result in serious injury if not death. In cases of intracranial pathology (*e.g.*, brain tumors, traumatic injury to the brain, and bleeding in the brain) there will be increased edema, and hence, increased intracranial pressure. This is exacerbated by increased carbon dioxide as this increases blood flow to the brain and increases the edema fluid load.

On the other hand, a markedly decreased carbon dioxide can lower cerebral blood flow and, if severe, can result in cerebral ischemia (*i.e.*, inadequate blood flow to the brain). Hence, it is important to not only control $pH(t)$ but also $P_aCO_2(t)$ in patients with intracranial pathology who require mechanical ventilation. The rule base of a simple respiratory management expert system is summarized in Table III.

One of the limitations of the rule-based expert systems proposed in this section and Section 5.1.1 is their inability to deal with uncertainty. More specifically, the rule-based expert system in Section 5.1.1 assumes perfect accuracy in the measurement of present and previous MAAS scores, blood pressure, and heart rate. While current technology allows for high accuracy measurements of blood pressure and heart rate, the MAAS score, which quantifies the level of sedation and agitation of the patient, is subjective and can result in inconsistencies and variability in sedation administration. Moreover, in a rule-based expert system there is no uncertainty associated with the rules. A more general approach would allow for rules with multiple conclusions, where a different level of uncertainty is associated with each conclusion.

Table III. Rule base of a simple respiratory management expert system: (a) absence of intracranial pathology; (b) presence of intracranial pathology.

(a)

pH	Action
$pH < 7.32$	$\uparrow$ *RR*, wait 30 min., repeat arterial blood gas measurement
$7.32 < pH < 7.45$	—
$pH > 7.45$	$\downarrow$ *RR*, wait 30 min., repeat arterial blood gas measurement

(b)

pH	P_aCO_2	Action
$pH < 7.32$	$P_aCO_2 > 40$	Increase RR, wait 30 min., repeat arterial blood gas measurement
	$30 \leq P_aCO_2 \leq 40$	Administer $[HCO_3^-]$ per base deficit
	$P_aCO_2 < 30$	$\downarrow$ *RR*, administer $[HCO_3^-]$
$7.32 \leq pH \leq 7.49$	$P_aCO_2 < 30$	$\downarrow$ *RR*, wait 30 min., repeat arterial blood gas measurement
	$30 < P_aCO_2 < 40$	No action
	$P_aCO_2 > 40$	$\uparrow$ *RR*, wait 30 min., repeat arterial blood gas measurement
$pH > 7.49$	$30 < P_aCO_2$	$\downarrow$ *RR*, repeat arterial blood gas measurement
	$30 < P_aCO_2 < 40$	consider acidifying agent, if given, repeat arterial blood gas measurement
	$P_aCO_2 > 40$	$\uparrow$ *RR*, consider acidifying agent

In [87], the authors use probability theory to quantify uncertainty to extend the rule-based expert system discussed in Section 5.1.1 to deal with more realistic situations. The rule-based respiratory management expert system discussed in Section 5.1.2 mainly uses P_aCO_2 and blood *pH* data for decision making. The same framework can be used to construct a probabilistic expert system for respiratory management. For details, see [87].

5.2 Closed-loop control for mechanical ventilation of critical care patients

The lungs are particularly vulnerable to acute, critical illness. Respiratory failure can result not only from primary lung pathology, such as pneumonia, but also as a secondary consequence of heart failure or inflammatory illness, such as sepsis or trauma. When this occurs it is essential to support patients while the fundamental disease process is addressed. For example, a patient with pneumonia may require mechanical ventilation while the pneumonia is being treated with antibiotics that will eventually effectively "cure" the disease. Since the lungs are vulnerable to critical illness, and respiratory failure is common, support of patients with mechanical ventilation is very common in the intensive care unit.

The goal of mechanical ventilation is to ensure adequate ventilation, which involves a magnitude of gas exchange that leads to the desired blood level of carbon dioxide, and adequate oxygenation, which involves a blood concentration of oxygen that will ensure organ function. Achieving these goals is complicated by the fact that mechanical ventilation can actually cause acute lung injury, either by inflating the lungs to excessive volumes or by using excessive pressures to inflate the lungs. The challenge to mechanical ventilation is to produce the desired blood levels of carbon dioxide and oxygen without causing further acute lung injury.

The earliest primary modes of ventilation can be classified, approximately, as volume-controlled or pressure-controlled [99]. In volume-controlled ventilation, the lungs are inflated (by the mechanical ventilator) to a specified volume and then allowed to passively deflate to the baseline volume. The mechanical ventilator controls the volume of each breath and the number of breaths per minute. In pressure-controlled ventilation, the lungs are inflated to a given peak pressure. The ventilator controls this peak pressure as well as the number of breaths per minute. In early ventilation technology negative pressure ventilation was employed, wherein a patient's thoracic area is enclosed in an airtight chamber and the volume of the chamber is expanded inflating the patient's lungs. Such ventilator devices include tank ventilators, jacket ventilators, and cuirassess [100].

The primary determinant of the level of carbon dioxide in the blood is minute ventilation, which is defined as the tidal volume (the volume of each breath) multiplied by the number of breaths per minute [101,102]. With volume-controlled ventilation both tidal volume and the number of breaths are determined by the machine (the ventilator) and typically the tidal volumes and breaths per minute are selected by the clinician caring for the patient. In pressure-controlled ventilation, the tidal volume is not directly controlled. The ventilator determines the pressure that inflates the lungs and the tidal volume is proportional to this driving pressure and the compliance, or "stiffness," of the lungs. Consequently, the minute ventilation is not directly controlled by the ventilator

and any change in lung compliance (such as improvement or deterioration in the underlying lung pathology) can result in changes in tidal volume, minute ventilation, and ultimately the blood concentration of carbon dioxide.

In respiratory management, the goal is to control arterial partial pressure of CO_2 (carbon dioxide) in the blood denoted by $P_aCO_2(t)$. The means to do this is reflected in the equation relating $P_aCO_2(t)$ to the volume of gas exchange in the lungs in a given unit of time, the alveolar ventilation. The relationship between $P_aCO_2(t)$ and ventilation is given by (2). In patients who are totally dependent on mechanical ventilation (and not taking any independent breaths) $V_a(t)$ is given by (3). During mechanical ventilation $TV(t) \in [400, 700]$ ml and $RR(t) \in [12,25]$. The tidal volume is the difference between the lung volume at the start of expiration and the lung volume at the end of expiration. Specifically, $TV = V(T_{in}) - V(T_{in} + T_{ex}) = V(T_{in}) - V(0)$, where $V(t)$ denotes the delivered air volume at time t, T_{in} is the inspiration time, and T_{ex} is the expiration time.

The concentration of oxygen in the blood is determined by the underlying lung pathology, the concentration of oxygen in the gas delivered by the mechanical ventilator, and also by the pressure that is used to inflate the lungs. In very general terms, oxygenation can be improved by higher mean pressures in the lungs, although higher peak pressures during the inflation-deflation cycle are associated with lung injury [103,104].

With the increasing availability of micro-chip technology, it has been possible to design mechanical ventilators that have control algorithms that are more sophisticated than simple volume or pressure control. Examples are proportional-assist ventilation [105,106], adaptive support ventilation [107], SmartCare ventilation [108], and neurally adjusted ventilation [109]. In proportional assist ventilation the ventilator measures the patient's volume and rate of inspiratory gas flow, and then applies pressure support in proportion to the patient's inspiratory effort [110]. In this mode of ventilation, inspired oxygen and positive end-expiratory pressure are manually adjusted by the clinician.

In adaptive support ventilation, tidal volume and respiratory rate is automatically adjusted [111]. In particular, minute ventilation ($TV(t)RR(t)$) is calculated from a %MinVol parameter and the patient's ideal body weight. The patient's respiratory pattern is measured point-wise in time and fed back to the controller to provide the required (target) tidal volume and patient respiratory rate. Adaptive support ventilation does not provide continuous control of minute ventilation, positive end-expiratory pressure, and inspired oxygen; these parameters need to be adjusted manually.

SmartCare ventilation monitors tidal volume, respiratory rate, and end-tidal pressure of carbon dioxide to maintain the patient in a respiratory "comfort" zone by automatically adjusting the level of pressure support [112,113]. SmartCare ventilators do not account for patient respiratory variations and do not generally guarantee adequate minute ventilation during weaning. In addition, positive end-expiratory pressure and inspired oxygen need to be manually adjusted.

Neurally adjusted ventilation is fundamentally different from the aforementioned automatic ventilation technologies in the sense that it uses the patient's respiratory neural drive as a measurement signal to the ventilator [114]. In this mode of ventilation, rather than controlling pressure, the patient's respiratory neural drive signal to the diaphragmatic electromyogram is controlled using electrodes placed on an oesophageal catheter [115]. Even though this approach has been shown to be effective in some recent clinical studies [116,117], its effectiveness is affected if the patient is highly sedated. In addition, as in the aforementioned ventilator technologies, positive end-expiratory pressure and inspired oxygen need to be manually controlled.

The common theme in modern ventilation control algorithms is the use of pressure-limited ventilation while also guaranteeing adequate minute ventilation. One of the challenges in the design of efficient control algorithms is that the fundamental physiological variables defining lung function, the resistance to gas flow and the compliance of the lung units, are not constant but rather vary with lung volume. This is particularly true for compliance, strictly defined as $\frac{dV}{dP}$, where V is the lung unit volume and P is the pressure driving inflation. More simply, lung volume is a nonlinear function of driving pressure. In addition, these physiological variables vary from patient to patient, as well as within the same patient under different conditions making it very challenging to develop models and effective control law architectures for active mechanical ventilation.

In [118], the authors develop an adaptive control architecture to control lung volume and minute ventilation with input pressure constraints that also accounts for spontaneous work-of-breathing by the patient. Specifically, a pressure- and work-limited neuroadaptive controller for mechanical ventilation is developed based on a nonlinear multi-compartmental lung model. The control framework does not rely on any averaged data and is designed to automatically adjust the input pressure to the patient's physiological characteristics capturing lung resistance and compliance modeling uncertainty. Moreover, the controller accounts for input pressure constraints as well as work-of-breathing constraints. Finally, the effect of spontaneous breathing is incorporated within the lung model and the control framework.

5.2.1 Closed-loop control of sedation using respiratory parameters

Since sedation is often administered to prevent the patient from fighting the ventilator it seems plausible to use

respiratory parameters as a performance variable for closed-loop control. Calculation of patient work of breathing requires measurement of a patient-generated pressure/volume loop or work of breathing. Since work of breathing can be measured using a commercially available esophageal balloon [53], work of breathing can serve as a performance variable for closed-loop control of sedation. Furthermore, patient-ventilator dyssynchrony can be identified by analysis of pressure/flow wave forms [55].

Dyssynchrony can be divided into three major categories—trigger dyssynchrony, flow dyssynchrony, and cycle (breath termination) dyssynchrony. Whereas there are several components of the pressure/flow wave forms that indicate dyssynchrony, possibly the simplest is the patient respiratory rate [55]. And it is certainly true that there is a correlation between patient work-of-breathing and patient-generated respiratory rate. If the goal of sedation is to reduce patient work of breathing, then one can target a spontaneous respiratory rate less than some threshold value. While speculative, this offers the possibility of closed-loop control using respiratory rate as a viable performance variable.

Closed-loop control algorithms can use either work-of-breathing as measured by an esophageal balloon or patient respiratory rate as a performance variable for closed-loop control of sedation. The need for optimal control algorithms is necessary for achieving a target performance value while satisfying certain constraints. For example, we could seek to design a control algorithm that seeks to minimize the patient respiratory rate (above the set ventilator rate) but which does not result in hypotension or which does not result in a MAAS score of 0 or 1. This requires the development of a constrained optimal control framework that seeks to minimize a given performance measure (*e.g.*, patient respiratory rate) within a class of fixed-architecture controllers satisfying internal controller constraints (*e.g.*, controller order, control signal nonnegativity, *etc.*) as well as system constraints (*e.g.*, blood pressure, system state nonnegativity, *etc.*).

To develop closed-loop feedback controllers for alleviating patient-ventilator dyssynchrony, mathematical models of pressure-limited respirator and lung mechanics system need to be developed. Numerous mathematical models of respiratory function have been developed in the hope of better understanding pulmonary function and the process of mechanical ventilation [119–123]. However, the models that have been presented in the medical and scientific literature have typically assumed homogenous lung function. For example, in analogy to a simple electrical circuit, the most common model has assumed that the lungs can be viewed as a single compartment characterized by its compliance (the ratio of compartment volume to pressure) and the resistance to air flow into the compartment [119,120,123].

While a few investigators have considered two-compartment models, reflecting the fact that there are two lungs (right and left), there has been little interest in more detailed models [124–126]. However, the lungs, especially diseased lungs, are heterogeneous, both functionally and anatomically, and are comprised of many subunits, or compartments, that differ in their capacities for gas exchange. Realistic models should take this heterogeneity into account. While more sophisticated models entail greater complexity, since the models are readily presented in the context of dynamical systems theory, sophisticated mathematical tools can be applied to their analysis [127]. Compartmental lung models are described by a state vector, whose components are the volumes of the individual compartments. Using the multi-compartment model of a pressure-limited respirator and a lung mechanics systems developed in [127], a model reference adaptive controller is also proposed in [127]. This adaptive feedback controller stabilizes a given limit cycle (*i.e.*, periodic signature) corresponding to a respiratory pattern identified by a clinician as a plausible breathing pattern in the face of full lung compliance and resistance uncertainty.

5.2.2 Optimal determination of respiratory airflow patterns

Early work on the optimality of respiratory control mechanisms using simple homogenous lung models dealt with the frequency of breathing. In particular, the authors in [128–130] predicted the frequency of breathing by using a minimum work-rate criterion. This work involves a static optimization problem and assumes that the airflow pattern is a fixed sinusoidal function. The authors in [130,131] developed optimality criteria for the prediction of the respiratory airflow pattern with fixed inspiratory and expiratory phases of a breathing cycle. These results were extended in [132] by considering a two-level hierarchical model for the control of breathing, in which the higher-level criterion determines values for the overall control variables of the optimal airflow pattern derived from the lower-level criteria, and the lower-level criteria determine the airflow pattern with the respiratory parameters chosen by minimizing the higher-level criterion.

Although the problem for identifying optimal respiratory patterns has been addressed in the literature (see [128–132] and the references therein), the models on which these respiratory control mechanisms have been identified are predicated on a single compartment lung model with constant respiratory parameters. However, as noted in Section 5.2.1, the lungs, especially diseased lungs, are heterogeneous, both functionally and anatomically, and are comprised of many subunits, or compartments, that differ in their capacities for gas exchange. Realistic models should take this heterogeneity into account. In addition, the resistance to gas flow and the compliance of the lung units are not constant but rather vary with lung volume. This requires the development of optimal respiratory airflow patterns predicated on nonlinear multi-compartment models for a lung-rib-cage system.

In [133], the authors extend the work of [130,131] to develop optimal respiratory airflow patterns using a nonlinear multi-compartment model for a lung-rib-cage system. Specifically, the linear multi-compartment lung model given in [127] is extended to address system model nonlinearities. Then, the performance functionals developed in [130,131] are extended for the inspiratory and expiratory breathing cycles to derive an optimal airflow pattern using classical calculus of variations techniques. In particular, the physiological interpretation of the optimality criteria involve the minimization of work-of-breathing and lung volume acceleration for the inspiratory breathing phase, and the minimization of the elastic potential energy and rapid airflow rate changes for the expiratory breathing phase. This model allows for the development of model reference adaptive control algorithms for fully automating mechanical ventilation to ensure adequate ventilation and oxygenation for critical care patients in intensive care units.

5.3 Optimal control for drug dosing

In clinical ICU practice sedative/analgesic agents are titrated to achieve a specific level of sedation. The goal of the clinician is to find the drug dose that maintains the patient at a moderately sedated state. This is typically done empirically, administering a drug dose that usually is in the effective range for most patients, observing the patient's response, and then adjusting the dose accordingly. Drug dosing can be made more precise by using pharmacokinetic and pharmacodynamic modeling [134]. Pharmacokinetics is the study of the concentration of drugs in tissue as a function of time and dose schedule, while pharmacodynamics is the study of the relationship between drug concentration and drug effect. By relating dose to resultant drug concentration (pharmacokinetics) and concentration to effect (pharmacodynamics), a model for drug dosing can be generated.

Pharmacokinetic compartmental models typically assume that the body is comprised of multiple compartments. Within each compartment the drug concentration is assumed to be uniform due to perfect, instantaneous mixing. Transport to other compartments and elimination from the body occur by metabolic processes. For simplicity, the transport rate is often assumed to be proportional to drug concentration. Although the assumption of instantaneous mixing is an idealization, it has little effect on the accuracy of the model as long as we do not try to predict drug concentrations immediately after the initial drug dose.

Although pharmacokinetics of sedative and anesthetic drugs can be adequately modeled by nonnegative and compartmental dynamical systems [5], the pharmacodynamics of these drugs are not well understood and drug effect predictions usually involve probabilities [4,135,136]. Specifically, when considering sedative agents, drug effect is closely related to patient sedation level. As discussed in [135,136], the corresponding sedation level of the ICU patient is related to drug concentration in the effect-site compartment using an empirical probabilistic model.

In [87] and [137], the authors model the pharmacokinetics and pharmacodynamics of a general sedative agent using a hybrid deterministic-stochastic model involving deterministic pharmacokinetics and stochastic pharmacodynamics. Then, using this hybrid model, the authors consider the sedative drug propofol and use nonnegative and compartmental modeling to model the drug pharmacokinetics and a stochastic process to represent the patient's sedation score and model the drug pharmacodynamics. The first-order distribution of the stochastic process is a function of the states of the compartmental dynamical system.

Finally, the aforementioned hybrid deterministic-stochastic model is used to develop an open-loop optimal control policy for ICU sedation. Specifically, first the optimal effect-site drug concentration corresponding to a high probability for the desired sedation score and a low probability for all other sedation scores is identified. Then, optimal control theory is used to drive the effect-site drug concentration to the optimal value found in the previous step while minimizing a given cost functional. The cost functional captures control effort constraints as well as probability constraints associated with different sedation scores.

Optimal control for drug administration (bolus and infusion) for nonnegative and compartmental dynamical systems for the specific problem of closed-loop control of intensive care unit sedation is critical. To address the specialized structure of compartmental and nonnegative systems, nonnegative state and control constraints need to be enforced. The optimal (nonnegative) control law needs to be designed as to maintain desired drug concentrations in the plasma dictated by therapeutic effects while minimizing drug dosage to reduce side effects.

In [138], the authors use an optimal fixed-structure control framework to develop optimal output feedback nonnegative controllers that guarantee that the trajectories of the closed-loop physiological system states remain in the nonnegative orthant of the state space for nonnegative initial conditions. The proposed optimal fixed-structure control framework is a constrained optimal control methodology that does not seek to optimize a performance measure per se, but rather seeks to optimize performance within a class of fixed-structure controllers satisfying internal controller constraints that guarantee the nonnegativity of the closed-loop plant physiological states. Furthermore, since unconstrained optimal controllers are globally optimal but may not guarantee nonnegativity of the closed-loop physiological system states, the authors additionally characterize domains or regions of attraction contained in the nonnegative orthant of the state space for unconstrained optimal output feedback

controllers that guarantee nonnegativity of the closed-loop physiological system trajectories.

VI. CONCLUSION

The potential clinical applications of clinical decision support and active control for pharmacology in general, and anesthesia and critical care unit medicine in particular, are clearly apparent. Specifically, monitoring and controlling the depth of anesthesia in surgery and the intensive care unit is of particular importance. In critical care medicine it is current clinical practice to administer potent drugs that profoundly influence levels of consciousness, respiratory, and cardiovascular function by manual control based on the clinician's experience and intuition.

In this paper, we discussed the challenges and opportunities of the specific problem of clinical decision support and closed-loop control for intensive care unit sedation. Such an integrated control design methodology for automating anesthesia and analgesia can significantly advance our understanding of a broad spectrum of problems in clinical pharmacology. In addition to delivering sedation to critically ill patients in an acute care environment, potential applications of closed-loop control include glucose, heart rate, and blood pressure regulation [139,140]. Payoffs will arise from improvements in medical care, health care, reliability of drug dosing equipment, and reduced health-care costs.

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