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Closed-loop control for intensive care unit sedation☆

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The potential clinical applications of 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. Nonnegative and compartmental models provide a broad framework for biological and physiological systems, including clinical pharmacology, and are well suited for developing models for closed-loop control for drug administration. These models are derived from mass and energy balance considerations that involve dynamic states whose values are nonnegative and are characterized by conservation laws (e.g., mass, energy, fluid, etc.) capturing the exchange of material between kinetically homogenous entities called compartments. Compartmental models have been particularly important for understanding pharmacokinetics and pharmacodynamics. One of the basic motivations for pharmacokinetic/pharmacodynamic research is to improve drug delivery. 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. Open-loop control (manual control) by clinical personnel can be tedious, imprecise, time-consuming, and sometimes of poor quality, depending on the skills and judgement of the clinician. Closed-loop control based on appropriate dynamical systems models merits investigation as a means of improving drug delivery in the intensive care unit. In this article, we discuss the challenges and opportunities of feedback control using nonnegative and compartmental system theory for the

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specific problem of closed-loop control of intensive care unit sedation. Several closed-loop control paradigms are investigated including adaptive control, neural network adaptive control, optimal control, and hybrid adaptive control algorithms for intensive care unit sedation.

Introduction

Acute respiratory failure due to infection, trauma, and major surgery is one of the most common problems encountered in intensive care units (ICU) and mechanical ventilation is the mainstay of supportive therapy for such patients. In particular, mechanical ventilation of a patient with respiratory failure is a critical life-saving procedure performed in the intensive care unit. However, mechanical ventilation is physically uncomfortable due to the noxious interface between the ventilator and patient, and mechanical ventilation evokes substantial anxiety on the part of the patient. This will often be manifested by the patient "fighting the ventilator." In this situation, there is dyssynchrony between the ventilatory effort of the patient and the ventilator. The patient will attempt to exhale at the time the ventilator is trying to expand the lungs or the patient will try to inhale when the ventilator is decreasing airway pressure to allow an exhalation. When patient-ventilator dyssynchrony occurs, at the very least there is excessive work of breathing with subsequent ventilatory muscle fatigue and in the worst case, elevated airway pressures that can actually rupture lung tissue. In this case, it is a common clinical practice to sedate patients to minimize "fighting the ventilator." Sedative-hypnotic agents act on the central nervous system to ameliorate the anxiety and discomfort associated with mechanical ventilation and facilitate patient-ventilator synchrony.

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. In this article, we discuss potential advantages and challenges of feedback control technology to this important clinical problem.

Overview, background, and significance

Advanced control methodologies have been and are being extensively developed for highly complex engineering systems.[1] Specifically, robust and adaptive control systems have been developed that ensure system stability and performance in the face of system modeling uncertainty, system disturbances, and system nonlinearities. These control systems have facilitated many of the technological advances of recent years. In particular, control-system technology forms the underpinning of technological advances in fields as diverse as aerospace, chemical, power, manufacturing, electronic, communications, transportation, and network engineering. However, modern active control technology has received far less consideration in medical systems.

One of the main reasons for this state of affairs is the steep barriers to communication between mathematics/control engineering and medicine. However, this is slowly changing and there is no doubt that control-system technology has a great deal to offer medicine.[2–7] This is particularly true when dealing with critically ill patients in the intensive care unit 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 (manual control) by clinical personnel can be tedious, imprecise, time-consuming,

and sometimes of poor quality. Hence, the need for active control (closed-loop control) in medical 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 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. Even though control strategies based on fixed-gain linear control laws[8], adaptive linear control laws[9], and rule-based (fuzzy logic) control laws[10] have been proposed in the literature, the complex and highly uncertain nature of patient response to multiple drugs renders such strategies deficient in the face of large system variations and system nonlinearities.

Critically ill patients, especially those supported with mechanical ventilation, frequently require administration of sedative drugs.[11–13] The magnitude of the clinical indication for sedation of critically ill patients is evident in the estimate that approximately one billion dollars are spent in the United States annually on drugs used for this purpose.[14] Sedation is indicated for two compelling reasons. The first of these is ethical. It has been estimated that up to 70% of patients experience clinically significant anxiety.[15] 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 commonly performed in the intensive care, including mechanical ventilation, are uncomfortable and in many cases painful. Both anxiolytic and analgesic drugs are required for patient comfort.

In addition to these ethical considerations, sedation is indicated for therapeutic reasons. Agitated patients may do physical harm to themselves by dislodging vital life support and monitoring devices with excessive musculoskeletal activity. Agitation due to anxiety or pain can also result in excessive metabolic and cardiopulmonary demands. Oxygen delivery to vital organs (heart, brain, kidneys, mesentery) may be enhanced in the patient with limited cardiopulmonary reserve if we minimize ventilatory effort and excessive musculoskeletal activity due to agitation. In patients with acute respiratory distress syndrome (ARDS) current evidence-based practices of mechanical ventilation[16,17] using low tidal volumes often result in profound dyspnea, requiring deep sedation to prevent "fighting the ventilator." In the most severe cases, muscle paralysis is needed to improve oxygenation. In this case, sedation must approximate 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 because of a diminished level of consciousness and respiratory depression from sedative drugs.

The clinical relevance of this problem is made clear by a study by Kress et al.[14] These investigators demonstrated 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 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 to 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.

Closed-loop control of intensive care unit sedation is virtually undeveloped in the literature. However, control algorithms have been developed, simulated, and implemented for the related problem of closed-loop control of general anesthesia. The first of these have focused on the control of inhalation anesthesia and several adaptive control algorithms have been developed.[18–24] 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 far more interested in drug effect than concentration. Much 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.

Building on the pioneering work by Bickford[25], Schwilden and his colleagues[9] developed and clinically tested a closed-loop, model-based adaptive controller for the delivery of intravenous anesthesia using the median frequency of the EEG power spectrum as the control variable. Their model assumed a two-compartment pharmacokinetic model for which the concentration of drug $C(t)$ as a function of time t after a single bolus dose was given by

$$C(t) = Ae^{-\alpha t} + Be^{-\beta t}, \ t \geq 0, \tag{1}$$

where A, B, $\alpha > 0$, $\beta > 0$ are patient-specific pharmacokinetic parameters. It was also assumed that the control variable, median EEG frequency (denoted by E), was related to the drug concentration by the *Hill equation*[26]

$$E = E_0 - E_{\max}\left[C^{\gamma}/\left(C^{\gamma} + C_{50}^{\gamma}\right)\right], \tag{2}$$

where E_0 is the baseline signal, $E_{\max}$ is the maximum decrease in signal with increasing drug concentration, C_{50} is the drug concentration associated with 50% of the maximum effect, and γ is a parameter describing the steepness of the concentration-effect curve. From Eq. (2) it can be seen that the drug effect is a function of the pharmacokinetic parameters A, B, α, and β as well as the pharmacodynamic parameters E_0, $E_{\max}$, C_{50}, and γ. If these parameters are known, calculation of the dose regimen needed to achieve the target EEG signal is straightforward. However, these parameters are not known for individual patients.

The algorithm developed by Schwilden and his colleagues[9] assumes that each of the pharmacodynamic parameters E_0, $E_{\max}$, C_{50}, and γ and the pharmacokinetic parameters α and β were equal to the mean values reported in prior studies. Using the mean population values of the pharmacokinetic parameters A and B as starting values, estimates of these parameters were refined by analysis of the difference between the target and observed EEG signal (ΔE). Linearizing ΔE with respect to A and B yields

$$\Delta E = \frac{\partial E}{\partial A}\delta A + \frac{\partial E}{\partial B}\delta B, \tag{3}$$

where δA and δB represent the updates to the values of A and B in the adaptive control algorithm. In conjunction with minimization of $(\delta A)^2 + (\delta B)^2$, this equation was used to solve for δA and δB. It is important to note that this algorithm was only partially adaptive in that the only parameters of the model that were updated were A and B. This algorithm was implemented for the intravenous anesthetic agents methohexital and propofol but did not appear to offer great advantage over standard manual control.[9,27] This may have been due to the approximations of the algorithm or due to the deficiencies of the median EEG frequency as a measure of the depth of anesthesia.

Since the early work by Schwilden et al.[27], other 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 that appears to be closely related to the level of consciousness.[29] Recently, Struys and his colleagues[30] have described 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 that of Schwilden and his colleagues[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 by Schwilden et al.[27] relating the BIS signal to concentration. However, in contrast to Schwilden and his colleagues[27], Struys et al.[30] assume that the pharmacokinetic parameters are always correct and that any variability in individual patient response is due to pharmacodynamic variability.

More specifically, with induction they calculated a predicted concentration using the pharmacokinetic model and then constructed a BIS-concentration relationship using the observed BIS during induction and the predicted propofol concentration. With 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. This algorithm is also only partially adaptive in the sense that there is no adaptive updating of pharmacokinetic parameters.

Using this algorithm, Struys et al.[30] demonstrated excellent performance as measured by the difference between the target and observed BIS signals. However, as pointed out by Glass and Rampil[31], the excellent performance of the system may have been because the system was not fully stressed. In their study, Struys et al.[30] administered a relatively high fixed dose of the opioid remifentanil, a neurotransmitter inhibitor resulting in significant analgesic effect, in conjunction with propofol. Consequently, central nervous system excitation due to surgical stimulus was blunted, and hence, 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 these model-based adaptive controllers, Absalom et al.[8] have developed a proportional-integral-derivative (PID) controller using the BIS signal as the variable to control the infusion of propofol. The median absolute performance error (the median value of the absolute value of $\Delta E/E_{\text{target}}$) of this system was good (8.0%) but in 3 out of 10 patients oscillations of the BIS signal around the set-point were observed and anesthesia was deemed clinically inadequate in 1 of the 10 patients. This same system has also been used with an auditory evoked potential as the control variable.[32] 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.[10] This system has had only very minimal clinical testing. More recently, Ref. 33 considers 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.

Closed-loop control of 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. 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.[34–39] 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.[39] High BIS scores have been observed in patients who were comatose. A good deal of 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 because of the potential for outside interference to produce an unfavorable signal-to-noise ratio yielding spurious results.[40]

Nonphysiologic artifactual signals may be generated from sources external to the patient that include lights, electric cautery devices, ventilators, pacemakers, patient warming systems, and electrical noise related to the many different kinds of monitors normally found in an operating room or ICU. Physiologic movements such as eye movements, myogenic activity, perspiration, and ventilation can produce artifactual increases in the BIS score. In particular, it is apparent that electromyographic (EMG) activity can spuriously increases the BIS score.[40]

The latest version of the Bispectral Index monitor has been designed to filter EMG noise but it remains to be seen whether this improves the correlation between clinician assessment of sedation and the BIS score. The biggest obstacle to the use of the processed EEG for sedation assessment could well be that our 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."[38] While this may yet prove to be the case, we believe it is worthwhile to investigate closed-loop control of sedation using the processed EEG as the performance variable for control. Our motivation is two-fold.

First, 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 an adaptive control algorithm.

Second, 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.[16] However, low tidal volume ventilation is uncomfortable, creating a sense of dyspnea and requiring deep sedation. We would prefer that patients being ventilated in this manner be unconscious, especially if they also require muscle paralysis to maintain oxygenation. The processed EEG is a plausible control variable in this situation. However, it will be important to develop more powerful robust and adaptive control algorithms for ICU sedation than the model-dependent algorithms developed for operative anesthesia given that the ICU is an unfriendly environment for EEG signal analysis due to several sources of noise.

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. It is generally believed that excessive work of breathing is deleterious to patient outcome and a very common 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.[41,42] Patient-ventilator dyssynchrony can also be identified using pressure and flow waveforms in the graphics available on almost all ventilators.[43] A novel approach to sedation of mechanically ventilated patients can use measures of dyssynchrony, either work of breathing or patient breath rate, as performance variables for closed-loop control. However, this will require development of optimal control algorithms.

Optimal control is a branch of modern control theory that deals with designing controllers for dynamical systems by minimizing a performance measure that depends on the system variables.[44] The performance measure 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.[45–48] For example, the motor activity and assessment scale (MAAS) system evaluates level of sedation on a score of 0-6 as follows[49]:

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.

Feedback control algorithms using this 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 could significantly improve the outcome for drug administration in the ICU. See the subsection on "Hybrid Control for Sedation."

Mathematical modeling and control for clinical pharmacology

Closed-loop control algorithms for operative anesthesia have been largely based on fixed pharmacokinetic or fixed pharmacodynamic models. Such algorithms are dependent on the accuracy of the system models. Given the complex and highly uncertain nature of patient responses, it is vital to develop parameter-independent control algorithms. Furthermore, given the wide variability in patient response to sedative drugs, adaptive controllers seem most appropriate.

An adaptive controller is a controller whose parameters are continuously adjusted to account for changes in system dynamics and system disturbances. Controller parameters can be adjusted directly or indirectly via estimation of system parameters. Specifically, adaptive controllers utilize the system output, observed in response to a given input, as the means to adjust, or adapt, the controller parameters in order to achieve the desired output in the face of system uncertainty.[50–52] As a concrete example, if a controller administers a dose of sedative drug in response to a BIS signal of 80 that results in decrease in the BIS score to an unacceptably low value of 10, the adaptive control algorithm uses this information to adapt the controller parameters (i.e., controller gains) so that the next dose in response to a BIS signal of 80 is smaller. The algorithm adapts to the different dose-response relationships among different patients.

Schwilden et al.[27] and Struys et al.[30] developed (partial) adaptive algorithms based on very specific low-order pharmacokinetic models. It is possible to develop adaptive control algorithms with much less restrictive assumptions utilizing nonnegative and compartmental dynamical system theory.[3,53–62] Nonnegative and compartmental dynamical systems are comprised of homogeneous interconnected subsystems (or compartments) which exchange variable nonnegative quantities of material with conservation laws describing transfer, accumulation, and elimination between the compartments and the environment. Hence, nonnegative systems theory is particularly appealing for clinical pharmacology since we sedate patients by controlling an intrinsically nonnegative variable, namely, the amount of drug present in various tissues. Furthermore, there is abundant literature to support the assumption that the disposition of drug in various tissues may be described by compartmental models.[3,53–55,57–60,62] Thus, adaptive control algorithms can be developed using compartmental systems theory without any assumptions about the number of compartments or their (possibly nonlinear) interconnections.

While adaptive control algorithms are ideal for dealing with the problem of interpatient variability, optimal control theory may also have an important role in developing controllers for intensive care unit sedation. As noted in the section on "Closed-Loop Control of Sedation," optimal control theory seeks to find control algorithms that minimize a given performance measure subject to satisfying system constraints. For example, one might seek to develop a control algorithm that minimizes the deviation of the BIS score from target while at the same time maintaining the infusion rate of the sedative drug below a given upper threshold. Optimal control theory may be particularly important in a clinician's efforts to use respiratory parameters as a performance variable for closed-loop control.

One of the most basic and central issues in control system analysis and design is *stability* of the closed-loop system (i.e., the controlled system). System stability is characterized by analyzing the

response of a controlled system to small perturbations in the system states (e.g., consciousness, drug concentration in the blood, BIS target, etc.). Specifically, an equilibrium state (i.e., set point or operating point) of a controlled dynamical system is said to be *stable* if, for sufficiently small values of initial disturbances in the system state, the perturbed state of the closed-loop system remains in an arbitrarily prescribed small region of the state space (i.e., operating space). If, in addition, all solutions of the controlled system (i.e., closed-loop states) approach the equilibrium state (or the desired set point) for large values of time, then the equilibrium state is said to be *asymptotically stable*.

The most complete contribution to the stability analysis of nonlinear dynamical systems was developed in the late nineteenth century by Lyapunov.[63] Lyapunov's main result provides a powerful framework for analyzing the stability of controlled dynamical systems as well as designing feedback controllers which *guarantee* closed-loop system stability. Lyapunov's main result states that if a positive-definite function (or *Lyapunov function*—see Fig. 1a) of the states of a given dynamical system can be constructed for which its time rate of change due to perturbations in a neighborhood of the system's equilibrium is always negative or zero, then the system's equilibrium state is guaranteed to be stable or, equivalently, *Lyapunov stable*. Alternatively, if the time rate of change of the Lyapunov function is strictly negative, then the system's equilibrium state is asymptotically stable.

Intuitively, a Lyapunov function can be regarded as a generalized *energy function* for the controlled system. In particular, viewing the *Lyapunov surfaces*[63] of a given Lyapunov function as constant energy surfaces covering a neighborhood of an equilibrium state of a controlled dynamical system, it follows from Lyapunov's result that requiring the Lyapunov derivative to be negative, the controlled system trajectories move from one energy surface to an inner, or lower, energy surface. In this case, the controlled system trajectories will approach the system equilibrium state and remain within a neighborhood of the equilibrium state for any system initial condition lying inside a Lyapunov surface contained in that neighborhood. Alternatively, if the Lyapunov derivative is strictly negative, then the controlled system's energy surfaces shrink to equilibrium state guaranteeing that the controlled system trajectories approach the equilibrium state asymptotically (i.e., as time progresses). See Fig. 1b. Since exogenous disturbances and system uncertainty are always present in every actual system, stability plays a central role in control system design. Most of the existing closed-loop control algorithms for clinical pharmacology developed in the literature do not ensure stability in the face of unmodeled system dynamics, system uncertainty, and system nonlinearities. Designing drug dosing control algorithms using Lyapunov methods, eliminates the risk of encountering unstable cases, while providing regulatory review boards with mathematical proofs for stability guarantees.

In many applications, especially in active control of drug dosing, wherein it is often necessary to regulate the drug concentration in the central compartment comprised of the intervascular blood volume and the highly perfused organs, *partial stability*, that is, stability with respect to part of the

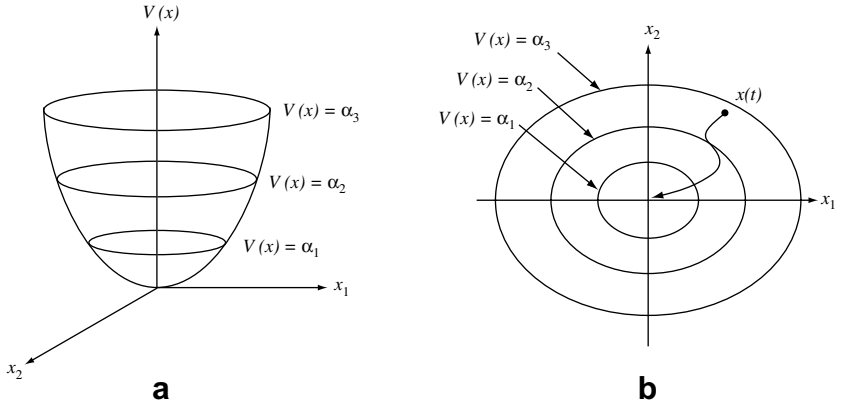

Fig. 1. (a) Typical Lyapunov function candidate $V(x)$. (b) Constant Lyapunov energy surfaces with system trajectory $x(t)$, $t \geq 0$, moving from one energy surface to an inner energy surface. For both figures $\alpha_1 < \alpha_2 < \alpha_3$.

(closed-loop) system's states, is often necessary. Perhaps the most common application where partial stabilization is necessary is adaptive control, wherein asymptotic stability with respect to part of the closed-loop system states associated with the physiological state variables is guaranteed without necessarily achieving controller parameter error convergence. Alteratively, in certain applications, it may be more natural to ascertain whether for every system initial condition in a neighborhood of an equilibrium state, the controlled system trajectories (or possibly the controlled partial system trajectories) are bounded. This notion is known as *ultimate boundedness*.[63]

Viable control algorithms for clinical pharmacology need to *guarantee* closed-loop asymptotic stability, partial asymptotic stability, or ultimate boundedness in the face of system uncertainty, system disturbances, and system nonlinearity. Such controllers can guarantee that the output of the controlled dynamical system is "well behaved" in some sense when the input (disturbance) to the system is well behaved. To make this notion of *input-output stability* precise, one needs to quantify the dependence of the output (typically via norms) on the input applied to the system.[63] For the active drug dosing control problem this essentially translates to a feedback controller guaranteeing that the deviation of the BIS score from the target value of a controlled system is within an *a priori* fixed range in the face of system uncertainties.

Previously developed closed-loop control algorithms reported in the literature for intraoperative anesthesia have not formally considered stability, partial stability, or ultimate boundedness. Rather, it has been assumed that stability follows from the pharmacokinetic/pharmacodynamic model. However, this is not the case since these controllers do not account for full model uncertainty, unmodeled dynamics, exogenous disturbances, and system nonlinearities. Since drug kinetic and dynamic models involve conservation laws describing transfer, accumulation, and elimination between compartments, it is obvious that any realistic model of drug effect, incorporating both pharmacokinetics and pharmacodynamics, will be a nonlinear, nonnegative compartmental dynamical system (see Fig. 2). Hence, nonnegative and compartmental dynamical system theory[64] provides the framework to develop and analyze the stability of adaptive, hybrid adaptive, and optimal control algorithms for clinical pharmacology.

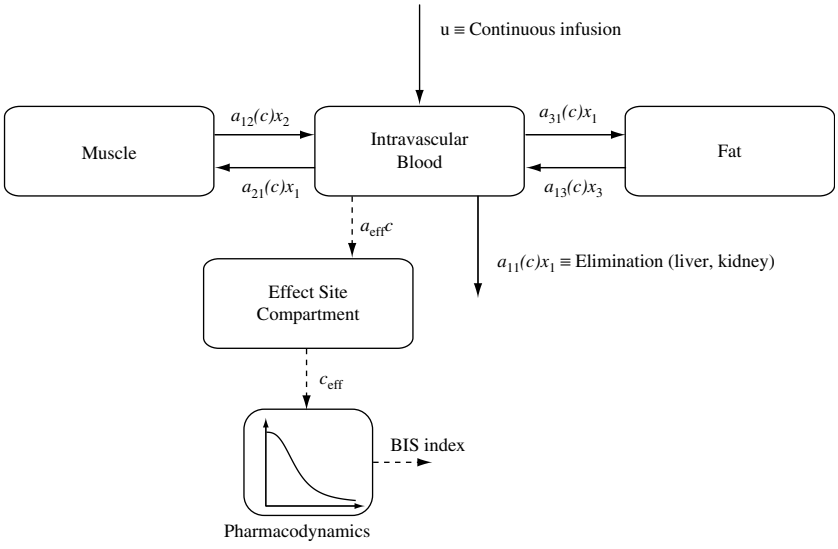

Fig. 2. Typical compartmental model for drug distribution. The central compartment, which is the site for drug administration, is comprised of the intravascular blood volume as well as the highly perfused organs. The two peripheral compartments comprised of muscle and fat receive a small portion of the cardiac output. The effect-site compartment is introduced to account for finite equilibration time between the central compartment concentration and the central nervous system concentration.

Control design paradigms and methods

The purpose of feedback control is to achieve desirable system performance in the face of system uncertainty. Although system identification for estimating mean pharmacokinetic parameters for a population of patients can reduce uncertainty to some extent, residual modeling discrepancies for individual patients always remain. For example, modeling uncertainty in compartmental systems for the disposition of sedatives for ICU sedation arise in the system transfer coefficients due to patient gender, weight, pre-existing disease, age, and concomitant medication. Controllers must therefore achieve desired disturbance rejection and/or tracking performance requirements in the face of such modeling uncertainty. The goal of adaptive control is to achieve system performance without excessive reliance on system models (see Fig. 3). In this section, we discuss several paradigms and methods for active control of clinical pharmacology.

Adaptive control for clinical pharmacology

The complex and hostile environment of surgery as well as the intensive care unit places stringent performance requirements for closed-loop regulation of physiological variables. In light of the complex and highly uncertain nature of system (patient) response characteristics requiring controls, it is not surprising that reliable system models for many high performance drug delivery systems are unavailable. In the face of such high levels of system uncertainty, robust controllers may unnecessarily sacrifice system performance, whereas adaptive controllers are clearly appropriate since they can tolerate far greater system uncertainty levels to improve system performance.[50–52]

In contrast to fixed-gain robust controllers, which maintain specified constants within the feedback control law to *sustain* robust performance, adaptive controllers directly or indirectly adjust feedback gains to maintain closed-loop stability and *improve* performance in the face of system uncertainties. Specifically, indirect adaptive controllers utilize parameter update laws to identify unknown system parameters and adjust feedback gains to account for system variation, while direct adaptive controllers directly adjust the controller gains in response to system variations.

To address pharmacokinetic and pharmacodynamic variability, direct adaptive controllers for adaptive stabilization, disturbance rejection, and command following (i.e., set-point regulation) of *nonlinear* uncertain compartmental systems with exogenous disturbances need to be developed. In Refs. 65–67, a linear and nonlinear Lyapunov-based direct adaptive control framework was developed that guarantees partial asymptotic stability of the closed-loop system, that is, asymptotic stability with respect to part of the closed-loop system states associated with the physiological state variables. The nonlinear adaptive controllers in Refs. 66,67 are constructed *without* requiring knowledge of the system dynamics or the system disturbances while providing a nonnegative control (source) input for system stabilization. Clinical evaluation trials of these controllers are reported in Refs. 7,68,69.

With the notable exception of Ref. 67, exogenous system disturbances have not been addressed in drug dosing control. However, during stress (such as hemorrhage and transfusion) in an acute care environment (such as the operating room and the ICU) perfusion pressure falls and hypertonic saline solutions are typically intravenously administered to regulate hemodynamic effects and avoid

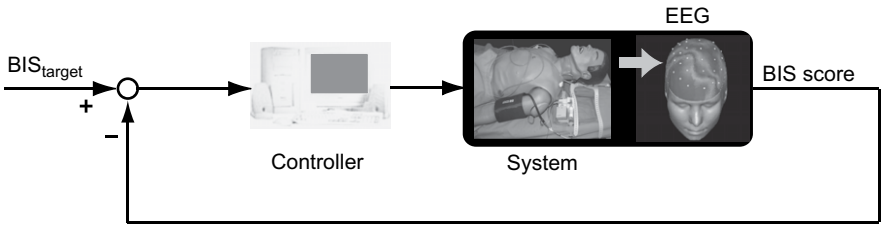

Fig. 3. Adaptive closed-loop control for drug administration. Active control can improve the medical care of patients requiring anesthesia or sedation in the operating room or intensive care unit.

hemorrhagic shock. Hemorrhage and *hemodilution*, that is, increase in fluid content of blood resulting in reduced concentration of red blood cells in the blood, can affect the concentration of a drug in the blood, and hence, the level of patient sedation.[70] Thus, it is of paramount importance that the adaptive controller be able to compensate for the effects of hemorrhage and hemodilution. These effects can be modeled as an exogenous system disturbance.[67] Adaptive controllers for nonlinear nonnegative dynamical systems with applications to general anesthesia are given in Refs. 65,66,68,71,72.

An implicit assumption inherent in most adaptive control frameworks for clinical pharmacology is that the adaptive control law is implemented without any regard to actuator amplitude and rate saturation constraints. Of course, any electromechanical control actuation device (e.g., infusion pump) is subject to amplitude and/or rate constraints leading to saturation nonlinearities enforcing limitations on control amplitudes and control rates. More importantly, in physiological applications, drug infusion rates can vary from patient to patient, and, to avoid overdosing, it is vital that the infusion rate does not exceed patient-specific threshold values. As a consequence, actuator constraints (e.g., infusion pump rate constraints) need to be accounted for in drug delivery systems.

Actuator nonlinearities arise frequently in practice and can severely degrade closed-loop system performance, and in some cases drive the system to instability, if not accounted for in the control design process. These effects are even more pronounced for adaptive controllers which continue to adapt when the feedback loop has been severed due to the presence of actuator saturation causing unstable controller modes to drift, which in turn leads to severe windup effects leading to unacceptable transients after saturation. Direct adaptive controllers for adaptive tracking of multivariable nonlinear uncertain compartmental systems with amplitude and rate saturation constraints need to be developed. Specifically, as outlined in Ref. 73, a reference (governor or supervisor) dynamical system can be constructed to address tracking and regulation in the face of actuator constraints by deriving adaptive update laws that guarantee that the error system dynamics (physiological set point error variables) are asymptotically stable and the adaptive controller gains are Lyapunov stable. In the case where the actuator amplitude and rate are limited, the adaptive control signal to the reference system can be modified to effectively robustify the error dynamics to the saturation constraints, and hence, guaranteeing asymptotic stability of the error states. Adaptive controllers for drug delivery systems with actuator saturation constraints are discussed in Ref. 74.

Another important issue not considered by most of the drug dosing control algorithms presented in the literature is sensor measurement noise. In particular, as discussed in the section on ''Closed-Loop Control of Sedation,'' EEG signals may have as much as 10% to 20% variation due to noise. The co-administration of neuromuscular blockade eliminates artifacts from muscle movement, which can be superimposed on the BIS score; and this undoubtedly contributes to the widespread use and value of the BIS device during surgery. However, to extend this technology to the ICU, or for that matter, to nonparalyzed patients in the operating room, further refinements are needed. In particular, adaptive set-point stabilization controllers for nonlinear nonnegative systems with sensor measurement noise need to be developed.[75] As indicated by preliminary clinical trials[68], this is clearly relevant for uncertain nonnegative systems with poorly modeled sensor disturbances which possess significant power within arbitrarily large bandwidths.

In many compartmental pharmacokinetic and pharmacodynamic models, transfers between compartments are assumed to be instantaneous, that is, the model does not account for material in transit. The assumption of instantaneous mixing between compartments is not valid. For example, if a bolus of drug is injected, there is a time lag before the drug is detected in the extracellular and intercellular space of an organ.[3,76–78] Phase lag due to mixing times can be approximated by including additional compartments in series. However, to accurately describe the distribution of pharmacological agents in the human body, it is necessary to include in any mathematical pharmacokinetic model some information of the past system states. In this case, the state of the system at any given time involves a *piece of trajectories* in the space of continuous functions defined on an interval in the nonnegative orthant of the state space. This of course leads to (infinite-dimensional) delay dynamical systems.[79–81] This extension necessitates the development of nonlinear adaptive control algorithms for compartmental systems with *unknown* time delay.[74,82,83]

Neural network adaptive control

Neural networks offer an ideal framework for on-line identification and control for many complex uncertain nonlinear dynamical systems.[84–89] Neural networks consist of a weighted interconnection of fundamental elements called *neurons*, which are functions consisting of a summing junction and a nonlinear operation involving an activation function (see Fig. 4). One of the primary reasons for the large interest in neural networks is their capability to approximate a large class of continuous nonlinear maps from the collective action of very simple, autonomous processing units interconnected in simple ways. In addition, neural networks have attracted attention due to their inherently parallel and highly redundant processing architecture that makes it possible to develop parallel weight update laws. This parallelism makes it possible to effectively update a neural network on line. These properties make neural networks a viable paradigm for adaptive control in clinical pharmacology.

Given the complexity, uncertainties, and nonlinearities inherent in pharmacokinetic and pharmacodynamic models needed to capture the wide effects of pharmacological agents in the human body, neural network adaptive control algorithms that account for combined interpatient and intrapatient pharmacokinetic and pharmacodynamic variability merit investigation for intensive care unit sedation and operating room hypnosis. In Ref. 68, we present a neural adaptive output feedback control framework for adaptive set-point regulation of nonlinear uncertain nonnegative and compartmental systems. The proposed neuroadaptive control framework is modular in the sense that if a nominal linear drug dosing controller is available, the neuroadaptive controller could be augmented to the nominal design to account for system nonlinearities and system uncertainty.

The formulation in Ref. 68 addresses adaptive output feedback (i.e., partial observation) controllers for nonlinear compartmental systems with unmodeled dynamics of unknown dimension while guaranteing ultimate boundedness of the error signals corresponding to the physical system states as well as the neural network weighting gains. Output feedback controllers are crucial in clinical pharmacology since key physiological (state) variables cannot be measured in practice or in real time. Preliminary clinical evaluation trials of the proposed neuroadaptive automated anesthesia controller demonstrate excellent regulation of unconsciousness and allow for a safe and effective administration of the anesthetic agent propofol.[68]

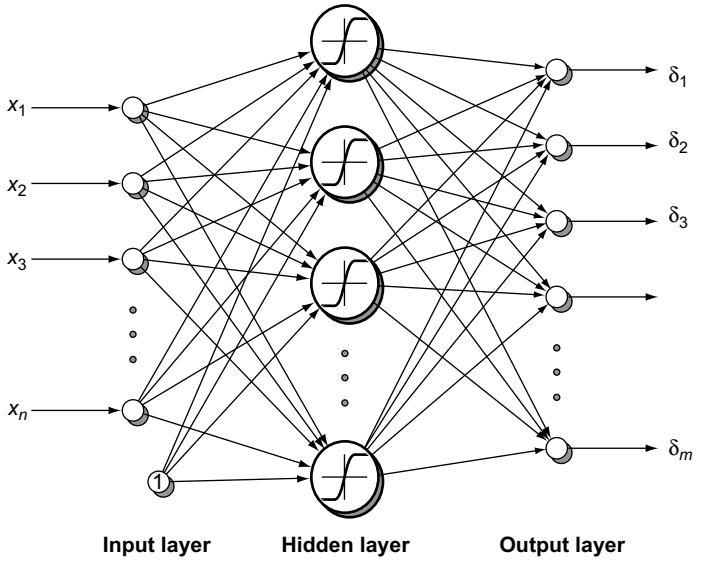

Fig. 4. A schematic representation of a two-layer neural network with sigmoidal activation functions.

Optimal control for drug dosing

As discussed in the section on "Mathematical Modeling and Control for Clinical Pharmacology," nonnegative and compartmental dynamical systems are conceptually simple yet remarkably effective in describing the dynamical behavior of biological and physiological systems. Thus, it is not surprising that nonnegative and compartmental system analysis is frequently applied to pharmacokinetics to describe the exchanges of drugs between various (lumped) compartments in the human body. For therapeutic reasons in the ICU, it may be desirable to regulate (maintain) the amount of a drug in one compartment above a certain minimum threshold (dosage) level while maintaining the amount below a certain maximum level in another compartment. Furthermore, to minimize drug side effects, it is desirable to minimize the total amount (dosage) of drugs used.[4,90–97] Drug administration in clinics and hospitals do not generally satisfy the aforementioned conditions.

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 Ref. 98, we extend the optimal fixed-structure control framework of Refs. 99,100 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, we additionally characterize domains or regions of attraction contained in the nonnegative orthant for unconstrained optimal output feedback controllers[101] that guarantee nonnegativity of the closed-loop physiological system trajectories. Optimal controllers are particularly relevant for sedation control using respiratory parameters as the performance variable for control.

Hybrid control for sedation

Complex physiological systems typically possess a multiechelon hierarchical hybrid structure characterized by continuous-time dynamics at the lower-level units and logical decision-making units at the higher-level of the hierarchy[102]; see Fig. 5. The logical decision making units serve to coordinate and reconcile the (sometimes competing) actions of the lower-level units. Due to their multiechelon hierarchical structure, hybrid dynamical systems are capable of simultaneously exhibiting continuous-time dynamics, discrete-time dynamics, logic commands, discrete-events, and resetting events. Hence, *hybrid dynamical systems* involve an *interacting* countable collection of dynamical systems, wherein control actions are not independent of one another. In turn these systems contain mixtures of logic and discrete events, and continuous-variable dynamics. The continuous dynamics are typically characterized by differential equations while the discrete dynamics of a hybrid system is generally governed by a digital automaton with a countable number of states. The continuous and discrete dynamics interact at event or trigger times chosen by some higher process, such as a controller. *Switched systems* are a special case of hybrid dynamical systems and involve a family of continuous-time subsystems and a rule that orchestrates the switching between them.

Hybrid systems theory[102] is relevant for control of sedation using subjective ordinal scales (such as the MAAS system), as it necessitates hybrid control architectures to account for abstract decision-making units (nurse or physician) performing logical checks that identify system mode operation and specify the continuous-variable subcontroller to be activated. Specifically, the clinical standard for sedation is an ordinal scoring system, such as the MAAS score described earlier. For this reason, an important goal for any control design paradigm for ICU sedation should involve adaptive (or possibly

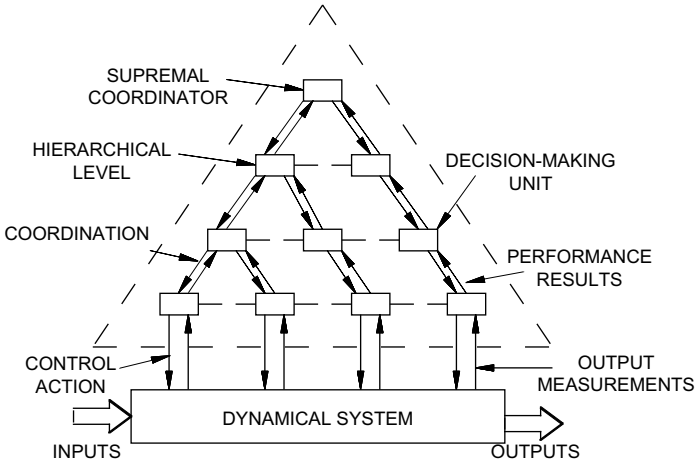

Fig. 5. Multiechelon hybrid control structure consisting of a number of subsystems situated in levels such that each one can coordinate lower-level units and be coordinated by a higher-level unit (see Ref. 102).

hybrid adaptive) control algorithms that allow clinicians to select a target sedation score and then control drug infusion by periodic evaluation and entry of observed scores.

The theoretical challenges of this endeavor are readily apparent. The problem is nonlinear since the relationship between sedation score and drug concentration is typically assumed to be

$$P(ss < x) = C^{\gamma(x)} \Big/ \left[C^{\gamma(x)} + C_{50,x}^{\gamma(x)}\right], \tag{4}$$

where $P(ss < x)$ is the probability of a sedation score less than x, $C_{50,\,x}$ is the drug concentration associated with $P(ss < x) = 0.5$, and $\gamma(x)$ is a factor determining the steepness of the concentration-effect relationship and is, in general, a nonlinear function of x. The nonlinearity of the problem greatly increases its complexity. Furthermore, the control variable is not evaluated continuously and the algorithm must of necessity assume that the desired sedation score is being maintained if there is no update of the score. Furthermore, the above relationship must be viewed as approximate. To begin with, the sedation score is evaluated subjectively. More importantly, the sedation score is a behavioral measure and, while there is clearly a relationship between drug concentration and this score, nevertheless, there are innumerable other influences on the behavior of critically ill patients. Thus, in order to develop an effective system for closed-loop control of ICU sedation using clinician input as the control variable, adaptive hybrid control algorithms have to be developed.

We envision a hybrid control system in which the clinician evaluates the patient using standard sedation scoring systems, enters the score into the controller, which then adjusts the dosing regimen to maintain sedation at the desired score. As noted above, this hybrid dynamical system would involve a switched system consisting of a *family* of continuous-time controllers. The resulting switched system would be described by a family of dynamical models parameterized by a finite index set with a piecewise constant switching signal. The basic control design problem entails finding conditions that guarantee that the switched system will be asymptotically stable for any switching signal.

Closed-loop control of sedation using respiratory parameters

Since sedation is often administered to prevent the patient from fighting the ventilator it seems plausible that we could 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[41], this could serve as a performance variable for closed-loop control of

sedation. Furthermore, patient-ventilator dyssynchrony may be identified by analysis of pressure/flow wave forms.[43]

Dyssynchrony can be divided into three major categories—trigger dyssynchrony, flow dyssynchrony, and cycle (breath termination) dyssynchrony. While there are a number of components of the pressure/flow wave forms that indicate dyssynchrony, possibly the simplest is the patient respiratory rate.[43] 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, one could simplistically target a spontaneous respiratory rate less than some threshold value. While speculative, this offers the possibility of closed-loop control using respiratory rate as the 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 to achieve a target performance value while still 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. As discussed in the section on "Optimal Control for Drug Dosing," 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 (adaptive) 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.[103–107] 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.[103,104,107]

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.[108–110] 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.[111] 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 Ref. 111, a model reference adaptive controller is proposed in Ref. 112. 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.

Closed-loop control of sedation using actigraphy and digital imaging

Current methods for assessing sedation are subjective and limited in accuracy and resolution, and hence, prone to error which in turn leads to oversedation, and increases health-care cost and length of stay in the ICU. In particular, oversedation increases risk to the patient since liberation from mechanical ventilation and endotracheal extubation 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.

The reliance on subjective assessment criteria, rather than quantifiable, measurable data for ICU sedation, results in inconsistencies and variability in sedation administration. In addition, due to large intrapatient and interpatient pharmacokinetic and pharmacodynamic variability to sedatives, the assessment and treatment of patient agitation is often of poor quality and inconsistent from nurse to nurse. Adaptive and neuroadaptive control algorithms based on appropriate dynamical system models and quantifiable observations for capturing patient agitation to eliminate oversedation as well as cycles between agitation and oversedation in the ICU can be developed using other measures of level of consciousness. Specifically, nonlinear adaptive controllers for sedation control can be developed using real-time actigraphic monitoring to fully automate ICU sedation. An actigraph has a piezoelectric sensor that continuously records movements to provide objective indications of changes in the depth of sedation and hence can be used for feedback control.[113] Recent studies in clinical anesthesia show that actigraphy captures reduced muscle activity in a patient's stress response well before heart rate, blood pressure, and respiratory rate responses are detected due to changing levels of sedation depth.[114] Feedback control for sedation using actigraphy can potentially revolutionize ICU sedation.

Alternatively, digital imaging can also be used to quantify agitation in sedated ICU patients.[115–119] 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 and actigraphy are not viable sensors. In this case, measuring head motion and facial grimacing for quantifying patient agitation in critical care can be a viable alternative. Vision-based control algorithms for automated ICU sedation have not been explored in the literature.

Conclusions

Control system technology has a great deal to offer pharmacology, anesthesia, and critical care medicine. Critical care patients, whether undergoing surgery or recovering in intensive care units, 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. Open-loop control by clinical personnel can be tedious, imprecise, time consuming, and sometimes of poor quality. Alternatively, closed-loop control can potentially achieve desirable system performance in the face of the highly uncertain and hostile environment of surgery and the intensive care unit. Since robust and adaptive controllers achieve system performance without excessive reliance on system models, robust and adaptive closed-loop control has the potential for improving the quality of medical care.

Closed-loop control for clinical pharmacology can significantly advance our understanding of the effects of pharmacological agents and anesthetics, as well as advance the state-of-the-art in drug delivery systems. Closed-loop control can be used for the administration of multiple drugs (anesthetics, opiods, and neuromuscular blocking agents) for critical care medicine. This would provide integrated control for hemodynamics and hypnosis in order to achieve automated anesthesia and analgesia. Such a methodology 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. Payoffs will arise from improvements in medical care, health care, reliability of drug dosing equipment, and reduced health-care costs.

Practice points

- Current methods of assessing the sedation of patients in the intensive care unit are subjective.
- Consequently patients are prone to either undersedation or oversedation.
- Use of a fixed rate infusion of sedative agents is particularly prone to oversedation barring daily interruption of the infusion.

Research highlights

- Processed EEG measurements (with appropriate filtering of EMG signals), measurement of ventilatory parameters that could assess "fighting the ventilator," actigraphy, or digital video image processing are potential methods of assessing sedation in a more objective fashion.
- Development of objective methods of assessing sedation will enable the application of modern control theory to clinical practice.
- Nonlinear adaptive control, neural network adaptive control, optimal control, and hybrid control algorithms have the potential to greatly improve the clinical practice of sedation.

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References

1. Murray RM (ed.). *Control in an information rich World*. Philadelphia, PA: SIAM, 2003.
2. Keener J & Sneyd J. *Mathematical physiology*. New York: Springer-Verlag, 1998.
*3. Jacquez JA. *Compartmental analysis in biology and medicine*. Ann Arbor, MI: University of Michigan Press, 1985.
4. Cherruault Y. *Mathematical modelling in biomedicine*. Dordrecht, Holland: Reidel, 1986.
5. Grodins FS. *Control theory and biological systems*. New York: Columbia University Press, 1963.
6. Riggs DS. *Control theory and physiological feedback mechanisms*. Baltimore, MD: Williams and Wilkins, 1970.
*7. Bailey JM & Haddad WM. Drug dosing control in clinical pharamacology: Paradigms, benefits, and challenges. *Control Systems Magazine* 2005; **25:** 35–51.
8. Absalom R, Sutcliffe N & Kenny GN. Closed-loop control of anesthesia using bispectral index: Performance assessment in patients undergoing major orthopedic surgery under combined general and regional anesthesia. *Anesthesiology* 2002; **96**(1)**:** 67–73.
9. Schwilden H, Schuttler J & Stoeckel H. Closed-loop feedback control of methohexital anesthesia by quantitative EEG analysis in humans. *Anesthesiology* 1987; **67**(3)**:** 341–347.
10. Linkens DA, Abbod MF & Peacock JE. Clinical implementation of advanced control in anaesthesia. *Transactions of the Institute of Measurement and Control* 2000; **22**(4)**:** 303–330.
11. Tung A & Rosenthal M. Patients requiring sedation. *Critical Care Clinics* 1995; vol. 11**:** 791–802.
12. Mazzeo J. Sedation for the mechanically ventilated patient. *Critical Care Clinics* 1995; **11:** 937–955.
13. Ostermann ME, Keenan SP, Seiferling RA & Sibbald WJ. Sedation in the intensive care unit: A systematic review. *JAMA: The Journal of the American Medical Association* 2000; **283:** 1451–1459.
14. Kress JP, Pohlman AS, O'Connor MF & Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing. *The New England Journal of Medicine* 2000; **342:** 1471–1477.
15. Strain J. Psychological reactions to acute medical illness and critical care. *Critical Care Clinics* 1978; **6:** 39–45.
16. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *The New England Journal of Medicine* 2000; **342:** 1301–1308.
17. Bidani A, Tzouanakis AE, Cardenas JVJ & Zwischenberger JB. Permissive hypercapnia in acute respiratory failure. *JAMA: The Journal of the American Medical Association* 1994; **272:** 957–962.
18. Hawes DW, Ross JA, White DC & Wloch RT. Servocontrol of closed circuit anesthesia. *British Journal of Anaesthesia* 1982; **54:** 229–230.
19. Hayes JK, Westenkow DR, East TD & Jordan WS. Computer controlled anesthesia delivery system. *Medical Instrumentation* 1984; **18:** 224–231.
20. Westenkow DR & Jordan WS. The Utah system: Computer controlled anesthesia delivery. *Future Anesthesia Delivery Systems* 1984; **8:** 221–233.
21. Ritchie RG, Ernst EA, Late BL et al. Closed-loop control of an anesthesia delivery system: Development and animal testing. *IEEE Transactions on Bio-medical Engineering* 1987; **34:** 437–443.
22. Spain JA, Janett TC & Ernst EA. The Alabama automated closed-circuit anesthesia project. *Future Anesthesia Delivery Systems* 1984; vol. 8**:** 177–183.
23. Vishnoi R & Roy RJ. Adaptive control of closed-circuit anesthesia. *IEEE Transactions on Bio-medical Engineering* 1991; **38**(1)**:** 39–47.
24. Jee GI & Roy RJ. Adaptive control of multiplexed closed-circuit anesthesia. *IEEE Transactions on Bio-medical Engineering* 1992; **39**(10)**:** 1071–1080.
25. Bickford RG. Automatic electroencephalographic control of anesthesia (servo-anesthesia). *Electroencephalography and Clinical Neurophysiology* 1951; **3:** 83–86.

26. Hill AV. The possible effects of the aggregation of the molecules of haemoglobin on its dissociation curves. *Journal of Physics* 1910; **40:** 4–7.
*27. Schwilden H, Stoeckel H & Schuttler J. Closed-loop feedback control of propofol anesthesia by quantitative EEG analysis in humans. *British Journal of Anaesthesia* 1989; **62**(3)**:** 290–296.
*28. Sebel PS, Lang E, Rampil IJ et al. A multicenter study of bispectral electroencephalogram analysis for monitoring anesthetic effect. *Anesthesia and Analgesia* 1997; **84**(4)**:** 891–899.
29. Glass PS, Bloom M, Kearse L et al. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in normal volunteers. *Anesthesiology* 1997; **86**(4)**:** 836–847.
*30. Struys MMRF, Smet TD, Versichelen LFM et al. Comparison of closed-loop controlled administration of propofol using bispectral index as the controlled variable versus "standard practice" controlled administration. *Anesthesiology* 2001; **95:** 6–17.
31. Glass PSA & Rampil IJ. Automated anesthesia: Fact or fantasy? *Anesthesiology* 2001; **95**(1)**:** 1–2.
32. Kenny GN & Mantzardis H. Closed-loop control of propofol anaesthesia. *British Journal of Anaesthesia* 1999; **83**(2)**:** 223–228.
33. Gentilini A, Rossoni-Gerosa M, Frei CW et al. Modeling and closed-loop control of hypnosis by means of bispectral index (BIS) with isoflurane. *IEEE Transactions on Bio-medical Engineering* 2001; **48**(8)**:** 874–889.
34. Simmons LE, Riker RR, Prato S & Fraser GL. Assessing sedation during intensive care unit mechanical ventilation with the bispectral index and the sedation-agitation scale. *Critical Care Medicine* 1999; **27:** 1499–1504.
35. Shapiro BA. Bispectral index: Better information for sedation in the intensive care unit? *Critical Care Medicine* 1999; **27**(6)**:** 1663–1664.
36. Riess ML, Graefe UA, Aken HV & Bone HG. Usefulness of bispectral index to assess the level of sedation in critically ill patients. *Critical Care Medicine* 1999; **27**(12)**:** A132.
37. Nasraway SA, Wu EC, Kelleher RM et al. How reliable in the bispectral index in critically ill patients? A prospective, comparative, single-blinded observer study. *Critical Care Medicine* 2002; **30**(7)**:** 1483–1487.
38. Nasraway SA. The bispectral index: Expanded performance for everyday use in the intensive care unit. *Critical Care Medicine* 2002; **33**(3)**:** 685–687.
39. Hijazi MN, Chaudhary A. The correlation between the bispectral index (bis) and motor activity assessment scale (maas) in sedated and mechanically ventilated patients, CHEST Meeting Abstracts; 2004. p. 897.
40. Johansen JW & Sebel PS. Development and clinical application of electroencephalographic bispectrum monitoring. *Anesthesiology* 2000; **93:** 1336–1340.
41. Kallet RH, Campbell AR, Dicker RA et al. Effects of tidal volume on work of breathing during lung-protective ventilation in patients with acute lung injury and acute respiratory distress syndrome. *Critical Care Medicine* 2006; **34**(1)**:** 8–14.
42. Hess DR & Thompson BT. Patient-ventilator dyssynchrony during lung protective ventilation: What's a clinician to do? *Critical Care Medicine* 2006; **34**(1)**:** 231–233.
43. Nilsestuen JO & Hargett KD. Using ventilator graphics to identify patient-ventilator asynchrony. *Respiratory Care* 2005; **50**(2)**:** 202–234.
44. Anderson BDO & Moore JB. *Optimal control: Linear quadratic methods*. Englewood Cliffs, New Jersey: Prentice-Hall, 1990.
45. Weinert CR, Chlan L & Gross C. Sedating critically ill patients: Factors affecting nurses' delivery of sedative therapy. *American Journal of Critical Care* 2001; **10**(3)**:** 156–167.
46. Gelinas C, Fortier M, Viens C et al. Pain assessment and management in critically ill intubated patients: A retroscpective study. *American Journal of Critical Care* 2004; **13**(2)**:** 126–135.
47. Sessler CN. Sedation scales in the ICU. *Chest* 2004; **126:** 1727–1730.
48. Jong MMJD, Burnes SM, Campbell ML et al. Development of the American Association of Critical-Care Nurses' sedation assessment scale for critically ill patients. *American Journal of Critical Care* 2005; **14**(6)**:** 531–544.
49. Devlin JW, Boleski G, Mlynarek M et al. Motor activity assessment scale: A valid and reliable sedation scale for use with mechanically ventilated patients in an adult surgical intensive care unit. *Critical Care Medicine* 1999; **27:** 1271–1275.
50. Åström KJ & Wittenmark B. *Adaptive control*. Reading, MA: Addison-Wesley, 1989.
51. Narendra KS & Annaswamy AM. *Stable adaptive systems*. Englewood Cliffs, NJ: Prentice-Hall, 1989.
52. Ioannou PA & Sun J. *Robust adaptive control*. Upper Saddle River, NJ: Prentice-Hall, 1996.
53. Rescigno A & Beck JS. Compartments. In Rosen R (ed.). *New York. Foundation of mathematical biology, ser. 5* 1972; vol. 2. NY: Academic Press, 1972, pp. 255–322.
54. Mohler RR. Biological modeling with variable compartmental structure. *IEEE Transactions on Automatic Control* 1974; **19:** 922–926.
55. Sandberg W. On the mathematical foundations of compartmental analysis in biology, medicine and ecology. *IEEE Transactions on Circuits and Systems* 1978; **25:** 273–279.
56. Brown RF. Compartmental system analysis: State of the art. *IEEE Transactions on Bio-medical Engineering* 1980; **27:** 1–11.
57. Anderson DH. *Compartmental modeling and tracer kinetics*. Berlin, New York: Springer-Verlag, 1983.
58. Godfrey K. *Compartmental models and their applications*. New York: Academic Press, 1983.
59. Jacquez J. Compartmental modeling. In: *IFAC Proceedings Series*; 1989. p. 31–37.
60. Hull CJ. How far can we go with compartmental models? *Anesthesiology* 1990; **72:** 399–402.
61. Jacquez JA & Simon CP. Qualitative theory of compartmental systems. *SIAM Review* 1993; **35:** 43–79.
62. Jacquez JA. *Modeling with compartments*. Ann Aarbor, MI: BioMedWare, 1999.
*63. Haddad WM & Chellaboina V. *Nonlinear dynamical systems and control: A Lyapunov-based approach*. Princeton, NJ: Princeton University Press, 2008.
*64. Haddad WM & Chellaboina V. Stability and dissipativity theory for nonnegative dynamical systems: A unified analysis framework for biological and physiological systems. *Nonlinear Analysis: Real World Applications* 2005; **6:** 35–65.
65. Haddad WM, Hayakawa T & Bailey JM. Adaptive control for nonnegative and compartmental dynamical systems with applications to general anesthesia. *International Journal of Adaptive Control and Signal Processing* 2003; **17:** 209–235.
*66. Haddad WM, Hayakawa T & Bailey JM. Adaptive control for nonlinear compartmental dynamical systems with applications to clinical pharmacology. *Systems & Control Letters* 2006**:** 62–70.

*67. Volyanskyy K, Haddad WM, Bailey JM. Adaptive disturbance rejection control for compartmental systems with applications to intraoperative anesthesia influenced by hemorrhage and hemodilution effects. *International Journal of Adaptive Control and Signal Processing*, in press.

*68. Haddad WM, Bailey JM, Hayakawa T & Hovakimyan N. Neural network adaptive output feedback control for intensive care uint sedation and intraoperative anesthesia. *IEEE Transactions on Neural Networks* 2007; **18**(4)**:** 1049–1066.

69. Bailey JM, Haddad WM., Im JJ, et al. Adaptive and neural network adaptive control of depth of anesthesia during surgery. In: *Proceedings of American Control Conference*. Minneapolis, MN; 2006. p. 3409–3414.

70. Kazama T, Kurita T, Morita K et al. Influence of hemorrhage on propofol pseudo-steady state concentration. *Anesthesiology* 2002; **97:** 1156–1161.

71. Haddad WM, Hayakawa T, Bailey JM. Nonlinear adaptive control for intensive care unit sedation and operating room hypnosis. In: *Proceedings of American Control Conference*. Denver, CO; June 2003. p. 1808–1813.

72. Volyansky K, Htaddad WM. Adaptive control for compartmental dynamical systems with disturbance rejection guarantees. In: *Proceedings of American Control Conference*. New York, NY; July 2007. p. 1215–1220.

73. Leonessa A, Haddad WM, Hayakawa T, Morel Y. Adaptive control for nonlinear uncertain systems with actuator amplitude and rate saturation constraints. International Journal of Adaptive Control and Signal Processing, in press.

74. Hui Q, Haddad WM, Chellaboina V & Hayakawa T. Adaptive control of mammillary drug delivery systems with actuator amplitude constraints and system time delays. *European Journal of Control* 2005; **11:** 586–600.

*75. Haddad WM, Volyanskyy KY, Bailey JM. Neuroadaptive output feedback control for automated anesthesia with noisy EEG measurements. In: Proceedings of American Control Conference. Seattle, WA; June 2008. p. 813–818.

76. Henthorn TK, Krejcie TC, Niemann CU et al. Ketamine distribution described by a recirculatory pharmacokinetic model is not stereo-selective. *Anesthesiology* 1999; **91**(6)**:** 1733–1743.

77. Gyori. Delay differential and integro-differential equations in biological compartment models. *Systems Science* 1982; **8**(2–3)**:** 167–187.

78. Maeda H, Kodama S & Konishi T. Stability theory and existence of periodic solutions of time delayed compartmental systems. *Electronics and Communications in Japan* 1982; **65**(1)**:** 1–8.

79. Haddad WM & Chellaboina V. Stability and dissipativity theory for nonnegative and compartmental dynamical systems with time delay. In Niculescu S-I & Gu K (eds.). *Advances in time-delay systems*. Springer, 2004, pp. 421–435.

80. Hale K & Verduyn lunel SM. *Introduction to functional differential equations*. New York, NY: Springer-Verlag, 1993.

81. Niculescu S-I. *Delay effects on stability: a robust control approach*. New York, NY: Springer, 2001.

82. Chellaboina V, Haddad WM, Ramakrishnan J, Hayakawa T. Direct adaptive control of nonnegative and compartmental dynamical systems with time delay. In: *Proceedings of American Control Conference*. Boston, MA; July 2004. p. 1235–1240.

83. Chellaboina V, Haddad W, Ramakrishnan J & Hui Q. Direct adaptive control of nonnegative and compartmental systems with time delay. In Queinnec I, Tarbouriech S, Garcia G & Niculescu S-I (eds.). *Biology and control theory: current challenges*. Springer, 2007, pp. 291–316.

84. Narendra S & Parthasarathy K. Identification and control of dynamical systems using neural networks. *IEEE Transactions on Neural Networks* 1990; **1:** 4–27.

85. Chen FC & Khalil HK. Adaptive control of nonlinear systems using neural networks. *International Journal of Control* 1992; **55**(6)**:** 1299–1317.

86. Hunt J, Sbarbaro D, Zbikowski R & Gawthrop PJ. Neural networks for control: A survey. *Automatica* 1992; **28:** 1083–1112.

87. Lewis FL, Yesildirek A & Liu K. Multilayer neural-net robot controller with guaranteed tracking performance. *IEEE Transactions on Neural Networks* 1996; **7**(2)**:** 388–399.

88. Lewis FL, Jagannathan S & Yesildirak A. *Neural network control of robot manipulators and nonlinear systems*. London, UK: Taylor & Francis, 1999.

89. Spooner J, Maggiore M, Ordonez R & Passino K. *Stable adaptive control and estimation for nonlinear systems: Neural and fuzzy approximator techniques*. New York, NY: John Wiley & Sons, 2002.

90. Buell J, Jelliffe R, Kalaba R & Sridhar R. Modern control theory and optimal drug regiments, I: The plateau effect. *Mathematical Biosciences* 1969; **5:** 285–296.

91. Buell J, Jelliffe R, Kalaba R & Sridhar R. Modern control theory and optimal drug regiments, II: Combination therapy. *Mathematical Biosciences* 1970; **6:** 67–74.

92. Soong TT. Pharmacokinetics with uncertainties in rate constants–II: Sensitivity analysis and optimal dosage control. *Mathematical Biosciences* 1972; **13:** 391–396.

93. Pierce JG & Schumitzky A. Optimal impulsive control of compartment models, I: Qualitative aspects. *Journal of Optimization Theory and Application* 1976; **18:** 537–554.

94. Kusuoka H, Kodama S, Hori M et al. Optimal control of drug administration. *Proceeding of International Conference Cybern Society* 1978; **1:** 63–68.

95. Pierce JG & Schumitzky A. Optimal control of compartment models, II: Algorithm. *Journal of Optimization Theory and Application* 1978; **26**(1)**:** 581–599.

96. Kusuoka H, Kodama S, Maeda H et al. Optimal control in compartmental systems and its application to drug administration. *Mathematical Biosciences* 1981; **53**(1–2)**:** 59–77.

97. Martin P & Ahuja AA. Optimal pharmacokinetic delivery of infused drugs: Application to the treatment of cardiac arrhythmias. *Journal of Biomedical Engineering* 1988; **10**(4)**:** 360–364.

98. Nersesov SG, Haddad WM & Chellaboina V. Optimal fixed-structure control for linear nonnegative dynamical systems. *International Journal of Robust and Nonlinear Control* 2004; **14:** 487–511.

99. Bernstein DS & Hyland DC. Optimal projection approach to robust, fixed-structure control design. In Junkins J (ed.). *Mechanics and control of space structures*. Washington, D.C.: AIAA, 1993.

100. Bernstein DS, Haddad WM, Nett CN. Minimal complexity control law synthesis, Part 2: Problem solution via H_2/H_∞ optimal static output feedback. In: *Proceedings of American Control Conference*. Pittsburgh, PA; 1989. p. 2506–2511.

101. Levine WS & Athans M. On the determination of the optimal output feedback gains for linear multivariable systems. *IEEE Transactions on Automatic Control* 1970; **15:** 44–48.

102. Haddad WM, Chellaboina V & Nersesov SG. *Impulsive and hybrid dynamical systems: Stability, dissipativity, and control*. Princeton, NJ: Princeton University Press, 2006.
103. Campbell D & Brown J. The electrical analog of the lung. *British Journal of Anaesthesia* 1963; **35:** 684–693.
104. Wald AA, Murphy TW & Mazzia VD. A theoretical study of controlled ventilation. *IEEE Transactions on Bio-medical Engineering* 1968; **15:** 237–248.
105. Epstein A & Epstein RA. Airway flow patterns during mechanical ventilation of infants: A mathematical model. *IEEE Transactions on Bio-medical Engineering* 1979; **26:** 299–306.
106. Barbini P. Nonlinear models of the mechanics of breathing applied to the use and design of ventilators. *Journal of Biomedical Engineering* 1982; **4:** 294–304.
107. Marini JJ & Crooke PS. A general mathematical model for respiratory dynamics relevant to the clinical setting. *American Review of Respiratory Disease* 1993; **147:** 14–24.
108. Hotchkiss JR, Crooke PS, Adams AB & Marini JJ. Implications of a biphasic two-compartment model of constant flow ventilation for the clinical setting. *Journal of Critical Care* 1994; **9:** 114–123.
109. Similowski T & Bates JH. Two-compartment modeling of respiratory system mechanics at low frequencies: Gas redistribution or tissue rheology. *European Respiratory Journal* 1991; **4:** 353–358.
110. Crooke PS, Head JD & Marini JJ. A general two-compartment model for mechanical ventilation. *Mathematical and Computer Modeling* 1996; **24:** 1–18.
111. Chellaboina V, Haddad WM, Bailey JM, Li H, Limit cycle stability analysis of a multi-compartment model for a pressure-limited respirator and lung mechanics system. In *Proceedings of American Control Conference*. New York, NY; 2007. p. 2411–2416.
112. Chellaboina V, Haddad WM, Li H, & Bailey JM. Direct adaptive control for a multi-compartment model of a pressure-limited respirator and lung mechanics systems. In: *Proceedings of IEEE Conference on Decision and Control*. Cancun, Mexico; 2008.
113. Grap J, Borchers T, Munro CL et al. Actigraphy in the critically ill: Correlation with acitivity, agition, and sedation. *American Journal of Critical Care* 2005; **14**(1)**:** 52–60.
114. Weinbroum A, Abraham RB, Ezri T & Zomer J. Wrist actigraphy in anesthesia. *Journal of Clinical Anesthesia* 2001; **13:** 455–460.
115. Chase JG, Agogue F, Starfinger C et al. Quantifying agitation in sedated ICU patients using digital imaging. *Computer Methods and Programs in Biomedicine* 2004; **76**(2)**:** 131–141.
116. Becouze CE, Hann JG, Chase & Shaw GM. Measuring facial grimacing for quantifying patient agitation in critical care. *Computer Methods and Programs in Biomedicine* 2007; **87**(2)**:** 134–147.
117. Ashraf AB, Lucey S, Cohn JF et al. The painful face: Pain expression recognition using active appearance models. In: *Proceedings of the 9th International Conference on Multimodal Interface*. Nagoya, Japan; 2007.
118. Brahnam S, Chuang C-F, Sexton RS & Shih FY. Machine assessment of neonatal facial expressions of acute pain. *Decision Support Systems* 2007; **43:** 1242–1254.
119. Monwar MM, Rezaei S & Prkachin K. Eigenimage based pain expression recongintion. *International Journal of Applied Mathematics* 2007; **36**(2).