ANESTHESIA OUTCOME PREDICTION

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Abstract

This paper studies the problem of outcome prediction in anesthesia procedures. Anesthesia depth and blood pressures are used as typical outcomes in this study. Traditional diagnosis and control in anesthesia focus on a one-drug-one-outcome scenario. It is well understood, however, that consideration of multiple outcomes is necessary and beneficial for anesthesia managements. This paper introduces a method of modeling that significantly reduces the complexity of the problem and yet retains model accuracy. Utility of the modeling method is demonstrated in the areas of anesthesia outcome prediction and decision assistance.

Introduction

Real-time anesthesia decisions are exemplified by general anesthesia for attaining an adequate anesthetic depth (consciousness level of a patient), ventilation control, etc. One of the most critical requirements in this decision process is to predict the impact of the inputs (drug infusion rates, fluid flow rates, etc.) on the outcomes (consciousness levels, blood pressures, heart rates, etc.). This prediction capability can be used for control, display, warning, predictive diagnosis, decision analysis, outcome comparison, etc. The core function of this prediction capability is embedded in establishing a reliable model that relates the drug or procedure inputs to the outcomes. Typically, an anesthesia drug influences more than one patient outcomes. For monitoring, diagnosis, and control, it becomes essential that the impact of anesthesia drugs on multiple outcomes be taken into consideration. Several researchers have considered the multivariate models[5,6,7], mostly off-line and population based models. Since each patient responses to drug inputs with very different dynamics, it is necessary to establish models in real-time and for individual patients. This paper introduces a method to significantly reduce the number of parameters contained in the model.

This paper is organized as follows. Section 2 presents procedures and systems for clinical data collection. Section 3 concentrates on patient modeling. It shows that a Wiener model structure can be used to simplify model structures quite significantly, subjecting only to minor loss of accuracy. When this approach is applied to multi-input-multi-output (MIMO) systems, one may use physiological insights to combine submodels to reduce model complexity. The models are used in Section 4 for anesthesia output prediction and decision assistance. Finally, Section 5 highlights findings of this paper and also points out some important related issues that are not covered in this paper.

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Data Acquisition

The patient population age group is between 20 and 70 years old. These patients are undergoing upper extremity arterio-venous fistula placement or thrombectomy, under intravenous unconscious sedation. Anesthesia is administered by an experienced anesthesiologist or registered nurse anesthetist. The patient is seen, examined and evaluated in the pre-operative holding area by an anesthesiologist. The anesthesiologist makes sure that the patient is ready for the surgery. Labs are checked in the pre-operative holding area and 1 mg of Midazolam IV is administered to the patient, after receiving full consent for the surgery and the participation in this study. All risks and benefits are thoroughly explained to the patient while obtaining consent.

The patient is, then, taken to the operating room, placed on the OR table, started on face mask oxygen at a rate of 8 liters/min, hooked to the electrocardiogram monitor, noninvasive blood pressure cuff is placed on the contralateral arm, and the cuff cycle is set to measure blood pressure every three minutes. A pulse oximeter is hooked on the patient's contralateral index.

The patient consciousness levels during anesthesia are measured by a BIS (bi-spectrum) monitor by Aspect Medical Devices, Inc[8,10]. The monitor provides continuously an index in the range of [0, 100] such that the lower the index value, the deeper the anesthesia state. Hence, an index value 0 will indicate "brain dead" and 100 will be "awake". A bispectral (BIS) electrode is placed on the patient's forehead before administering anesthesia to the patient. The electrode is connected to the BIS monitor, which in turn is connected to a special computer system to allow continuous recording and saving of the BIS values.

A baseline BIS value of at least 90 is recorded before the administration of anesthesia. The patient is given 1-2 mcg/kg of bolus IV Fentanyl at the beginning of the surgery and 1 mcg/kg bolus during the surgery, as needed. The patient is started on intravenous Propofol pump at a rate of 50 mcg/kg/min and titrated as needed during the surgery. All measured heart rates, blood pressures and pulse oximetry values are entered and saved manually into the computer every three minutes and following any bolus administration. The Propofol rate, any changes made to the Propofol rate, and any Propofol or Fentanyl bolus given are transmitted to the computer monitoring system automatically and continuously at the sampling rate of 1 Hz (one sample per second). Towards the end of the procedure, and after making sure no more surgical stimuli are applied to the patient, all anesthetics are turned off and the patient is awakened with the BIS value of more than 75. The patient is then taken to the recovery room on oxygen tank for a period of two hours of observation.

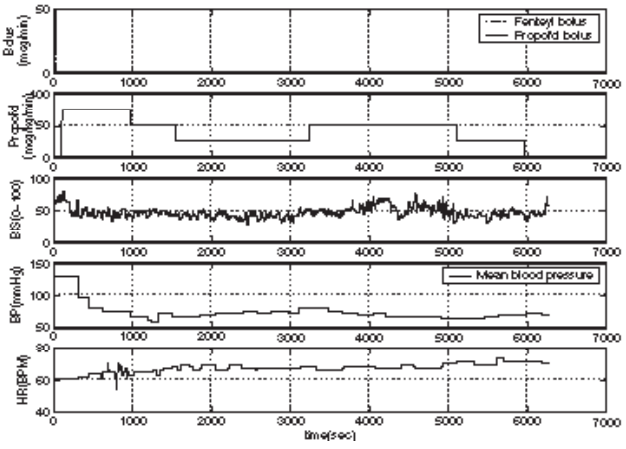
Typically, an anesthesia drug influences more than one patient outcomes. Fig. 1 shows a typical recording of a patient's response to propofol and fentanyl titration and bolus injections. For this patient, the anesthesia drugs not only control the anesthesia depth but also influence significantly blood pressures. For outcome prediction and decision assistance, it becomes essential that the impact of anesthesia drugs on both anesthesia depth and blood pressures be taken into consideration.

MIMO Patient Modeling for Anesthesia Monitoring and Control

A basic information-oriented model structure (a special case of Wiener models), for patient anesthesia depth responses to propofol infusion as an SISO system was introduced in 2002[11,12,13]. This model can also be applied to relate other patient outcomes, such as blood pressure and heart rate, to input drugs. Its basic idea is summarized below.

The patient dynamics is a nonlinear system. Although the actual physiological and pathological

Fig. 1
Drug inputs influence many patient outcomes



features of the patient require models of high complexity, for prediction or control purposes it is not only convenient but essential to use simple models as long as they are sufficiently rich to represent the most important properties of the patient response. Understanding the information used by anesthesiologists in infusion control, we characterize the patient response to propofol titration with three basic components: (1) Initial time delay τ_p after drug infusion: During this time interval after a change of the infusion rate, the BIS value does not change due to time required for drugs to reach the target tissues, to complete volume distribution. (2) Dynamic reaction: This reflects how fast the BIS value will change once it starts to respond, and is modeled by a transfer function $G_p(s)$. (3) A nonlinear static function for sensitivity of the patient to a drug dosage at steady state: This is represented by a function or a look-up table f. The meaning of these system blocks is illustrated in Fig. 2. Combined with infusion pump and monitor models, this model structure for titration response is a special case of the Wiener models shown in Fig. 3.

Fig. 2
Simplified patient model structure

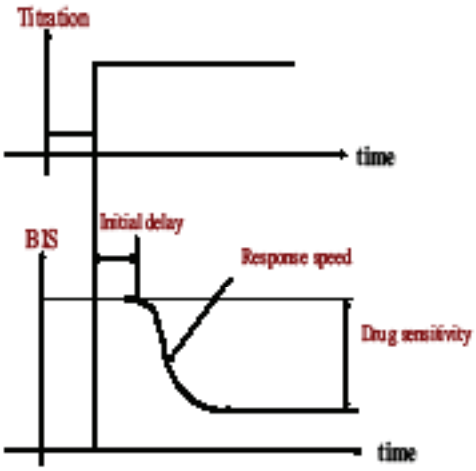


Fig. 3
Wiener model structure

The linear patient dynamics can be well approximated by a continuous-time system that consists of a pure time delay and a first-order dynamics, sampled with sampling interval T = 1 second. Let a continuous-time system be

$$P(s) = e^{-5s}\frac{0.93}{73s+1}.$$

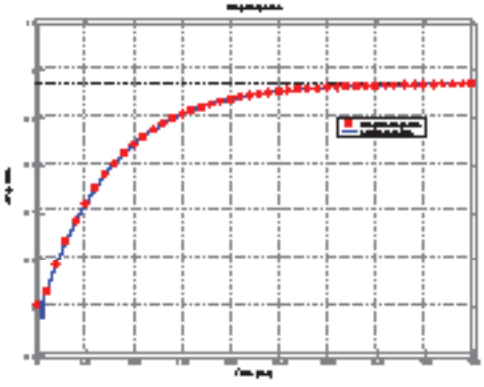
The step responses of the original system and the simplified system P(s) are shown in Figure 4. Since this model contains only three parameters, it is much easier to be identified in real time. It is also possible to use a simplified nonlinear function which has only three parameter r, α, b to represent the sensitivity function *f*:

$$y = r\left[u \pm \left(\frac{erf(au)}{erf(ab)} - u\right)\right].$$

Although in principle the above SISO method can be employed in MIMO models, by considering an m-input and n-output system as a collection of m × n subsystems, each of which represents one input and one outcome relationship. For example, if two drugs (propofol and fentanyl) are present and three outcomes (depth, blood pressures, and heart rates) are considered, we may view this as a collection of 6 subsystems, including propofol-to-depth, propofol-to-BP, propofol-to-HR, fentanyl-to-depth, fentanyl-to-BP, fentanyl-to-HR subsystems. This approach, however, involves many model parameters and encounters high system complexity in modeling processes. For example, if each submodel contains only L parameters, the over system will have 6L parameters that must be updated in real time, which is a substantial complexity in this application.

Fig. 4
Step responses of the original system and the simplified system

Modifications to the above approach are made to reduce modeling complexity by the following.



Modifications of the above approach are made to reduce by the following combination method. Since both propofol and fentanyl go through similar propagation and metabolism to influence blood pressure and heart rate, it is reasonable to use the same time delay and same dynamic response speed for both models. They, however, demonstrate very different sensitivity[15]. As a result, it is reasonable to use only one scaling factor to represent the difference between propofol and fentanyl in their impact on the blood pressure and heart rate. Furthermore, fentanyl does not have influence on BIS index[15]. This method reduces significantly the number of model parameters. These complexity reductions are substantial in making real-time MIMO modeling a feasible option in anesthesia applications which are not data rich.

Multi-Objective Anesthesia Predictive Diagnosis

Here, we consider a special case that involves two outcomes: the anesthesia depth y_B and and mean blood pressure y_P. The continuous control is provided by propofol titration whose rate is denoted by u. Propofol or Fentanyl bolus injections can be used when necessary to assist. Also, blood pressures may also be reduced by vasodilation agents or other means if necessary.

From a system viewpoint, we have a system with two types of control inputs: one main control variable u that is continuously managed, and another pulse types of control u that is used only when it is necessary. The system has two outputs y_B and y_P. The basic strategy is to use u to achieve control objectives as much as possible. When u alone cannot achieve certain control objectives, υ can be used to assist u to reach the goal.

This paper is focused only on predictive diagnosis, not feedback control design, aspects of the problem: (1) Given the current input u, what will be the outcomes in the near future? (2) If the input is changed to a new value, what will be the impact of this change? (3) If we want the outcomes to settle at a new level, will it be possible to achieve it with assistance from u?

We first consider a generic simulated patient whose BIS response to propofol titration rate u (mcg/min)is modeled by

$$x_B = e^{-4s}\frac{2.2}{102s+1}U(s); \quad y_B = 100 - f_B(x_B(t)) + d_B$$

where f_B is a nonlinear sensitivity function, and d_B is an external disturbance to the BIS value; and whose mean blood pressure response to propofol titration is represented by the simplified delay model

$$x_P = e^{-4s}\frac{0.12}{65s+1}U(s); \quad y_P = 110 - f_P(x_P(t)) + d_P$$

where f_P is a nonlinear sensitivity function, and d_P is an external disturbance to the blood pressure.

We will use $w(t) = [y_B(t), y_P(t)]$ to represent the outputs. In real implementations of our prediction algorithms, the patient models will be generated in real-time, using actual input-output data. Here, for methodology description we use the above models to show how outcome prediction is performed.

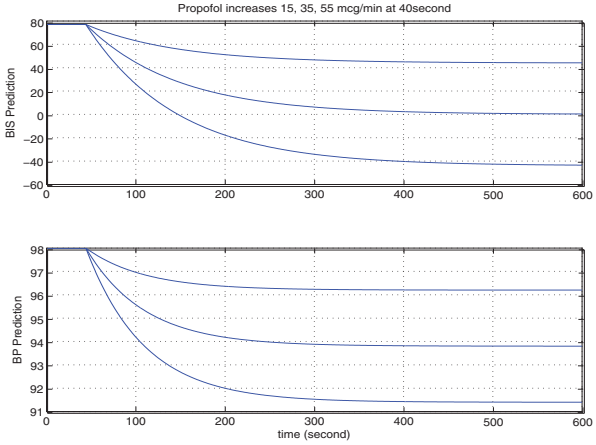
Suppose that the output vector $w(t)$ is initially at an equilibrium point with $w(t_0) = [y_B(t_0), y_P(t_0)]$ and input $u(t_0) = u_0$. When $u(t)$ is increased from u_0 to $u_0 + \Delta$, we may observe the outcome $w(t)$ starts to change due to this input jump. Outcome prediction shows how $w(t)$ will change in the near future and where it will settle to a new equilibrium. Drug impact prediction is an extension of outcome prediction. The outcome prediction provides future outcome trajectories when a drug decision is made and implemented. Drug impact prediction is an assessment of future outcomes when several drug decisions are being considered.

For example, if an anesthesiologist wants to consider possible decisions of increasing propofol rates by 15, 35, 55 starting at $t = 40$ second and compare their impacts, the models can be used to plot all possible trajectories related to these decisions. These impact predictions are plotted in Figure 5.

Suppose that the output vector $w(t)$ is initially at an equilibrium point $w(t_0) = w_0$. The question here is to determine if the propofol control alone is sufficient to achieve a designated target w_f. If the answer is affirmative, then assistance from v is not needed. Otherwise, v must be used such that after applying a bolus injection u, w_f becomes reachable.

For example, if the current outcomes are $y_B = 70$ and $y_P = 80$, then the reachable outcomes corresponding to different drug inputs are plotted in Figure 6.

Fig. 5
Drug impact prediction



From Figure 6, we can see that different designated targets can be achieved through applying different drug inputs. For example, if we want to depress the patient blood pressure without changing BIS values, then only Fentanyl bolus is needed. But, if we want to push the BIS value to some low levels without much fall of blood pressures (mean arterial pressure of 80 mmHg is usually the desired level during anesthesia), then the propofol bolus can be applied to achieve the goal. Figure 7 and 8 show the outcome time trajectories for different drug inputs.

Conclusions

This paper investigates the problem of real-time monitoring, diagnosing, and predicting multiple outcomes of anesthesia patients. For the enhanced anesthesia management, it is essential to view the

Fig. 6
Reachable outcomes from the current outcome with different drugs inputs

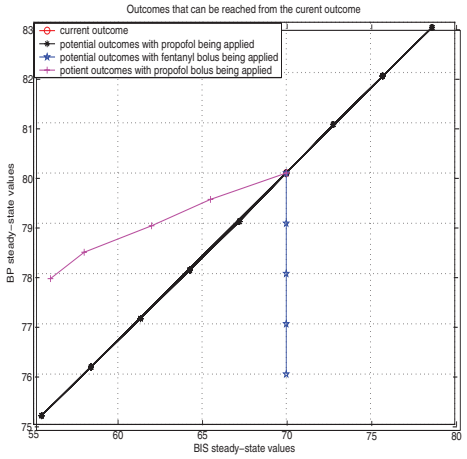


Fig. 7
BIS and mean blood pressure time trajectories with different inputs: propofol titration increased 30 mcg/min, 50 mcg

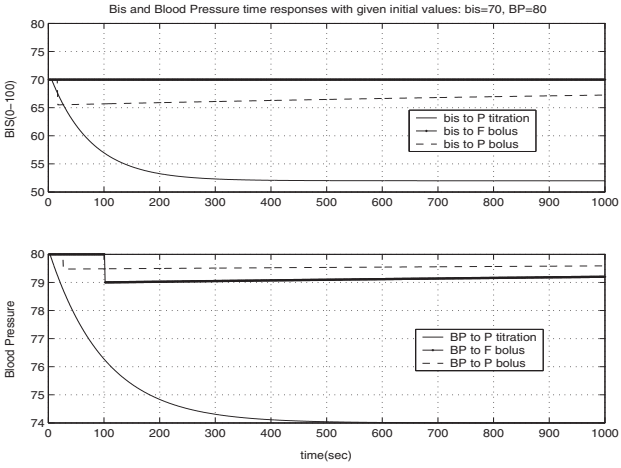
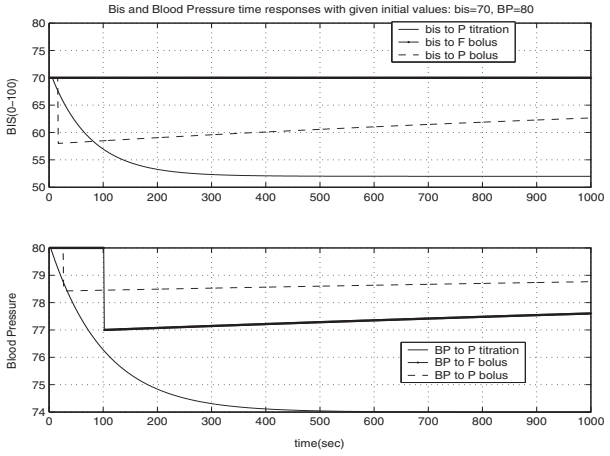


Fig. 8
BIS and mean blood pressure time trajectories with different inputs: propofol titration increased 30 mcg/min, 150 mcg propofol bolus, and 150 mcg fentanyl bolus



anesthesia patient dynamics as an multi-input and multi-output system. For the purpose of control, predictive diagnosis, outcome comparison, etc., a reliable model need to be established in real-time and in individual patient. An information-oriented model, Wiener model, is studied for its suitability in representing the patient responses to drug infusion. Furthermore, a method of consolidating submodels is introduced which can significantly reduce the total number of MIMO system parameters. Based on the constructed model, some new ideas and related simulations of prediction and control oriented multi-objective anesthesia diagnosis, such as outcome predictions, drug impact predictions and reachable sets, are demonstrated. In the future,

we will consider to develop this multivariable real-time patient model through Labview graphical programming software (National Instrument Inc.) and apply it in operating rooms for multi-outcome anesthesia diagnosis.

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