Selection of Patient Specific Dosing Schemes for Procedures of Short Duration and Moderate Stimulation Utilizing Multiobjective Optimization Techniques

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Abstract- **Modern anesthesia practice uses a combination of drugs to manage pain and sedation. There are often adverse or negative side effects that arise due to the same combination. A control system will be designed that optimizes the delivery of intravenous sedatives and analgesics to allow esophageal instrumentation while minimizing respiratory compromise and loss of responsiveness in spontaneously breathing patients. A cost functional will be developed to combine the multiple optimization goals into a single objective optimization problem. It is not possible to simultaneously optimize all criteria. A compromise solution must be selected. After selecting weighting coefficients, simulations were run and evaluated by the optimization function. The top five were plotted. The peaks for the five selected doses look reasonable. The maintenance infusions are probably too low for someone to tolerate a placed probe. Additional work is needed to investigate this. These results show promise for the development of a multiobjective optimization approach to patient-specific selection of dosing schemes.**

I. Introduction

Modern anesthesia practice uses a combination of drugs to manage pain and sedation. Two fast acting drugs – propofol (sedative) and remifentanil (opioid) – are becoming increasingly popular because of their rapid onset of effect, ease of dose titration, and rapid elimination. Combining a sedative and hypnotic drug often enhances the beneficial or positive effects of both drugs. However, there are often adverse or negative side effects that arise due to the same combination. These include the cessation of spontaneous breathing due to obstruction of the airway and/or loss of respiratory drive (respiratory compromise) and loss of the ability to communicate with the patient (loss of responsiveness).

While anesthesiologists are trained to handle such complications, these drugs are increasingly being used by non-anesthesiologists in settings where the training and equipment necessary to deal with these complications do not exist. Procedures performed in these settings increase patient risk. This paper will focus primarily on a common GI procedure – placement of an ultrasound probe in the mid-esophagus (esophageal instrumentation).

Because most GI clinics do not have anesthesiologists administering the drug(s), a system will be developed to advise the clinician of an optimal dosing scheme that has been adjusted specifically for each patient. A control system will be designed that optimizes the delivery of intravenous sedatives and analgesics to allow esophageal instrumentation while minimizing respiratory compromise and loss of responsiveness in spontaneously breathing patients. The control system will (i) minimize the time between the start of administration of these intravenous anesthetics and when there is sufficient analgesia to blunt a response to esophageal instrumentation, (ii) minimize the duration of respiratory compromise, (iii) minimize the duration of unresponsiveness, and (iv) minimize the time required for full recovery once the intravenous anesthetics are terminated.

The optimization process will account for (i) the pharmacokinetic behavior (distribution) of each drug, (ii) the synergistic interaction between sedatives and analgesics, (iii) the analgesic and sedative requirements for esophageal instrumentation, (iv) the respiratory effects caused by these drugs and (v) the mechanical capabilities and limitations of the infusion pump delivery systems. A cost functional will be developed to combine (scalarize) the multiple optimization goals into a single objective optimization problem.

II. Background

Pharmacokinetics and pharmacodynamics

Both propofol and remifentanil have well established population pharmacokinetic[1, 2]. Both models use a 3-compartment model structure to predict plasma drug concentrations over time. A fourth compartment is added to account for the time lag between plasma and brain (effect site) concentration. With these models, computers can simulate the concentration versus time profile that results from any combination of boluses and continuous infusions. They also can account for differences in age and weight.

Pharmacodynamic models have been constructed to describe the relationship between effect site levels and drug effect. This process for a single drug is characterized graphically using a sigmoidal concentration-effect curve (Figure 1). The most important part of this curve is the steep section that represents the dynamic range of drug effect. This part charts the concentration-effect relationship from baseline to maximal effect. Small changes in drug concentration lead to large changes in drug effect within this range. Similar changes made above or below this region only produce minimal change in effect. These models can therefore help avoid giving more drug than is needed to achieve the desired effect.

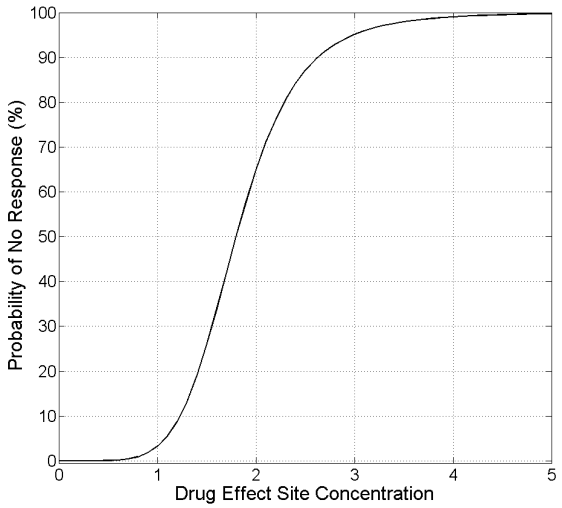

Figure 1. An example of a single-drug pharmacodynamic model, loss of responsiveness caused by propofol. This curve predicts the probability of a given patient drawn from the sample population losing responsiveness at a given propofol effect site concentration.

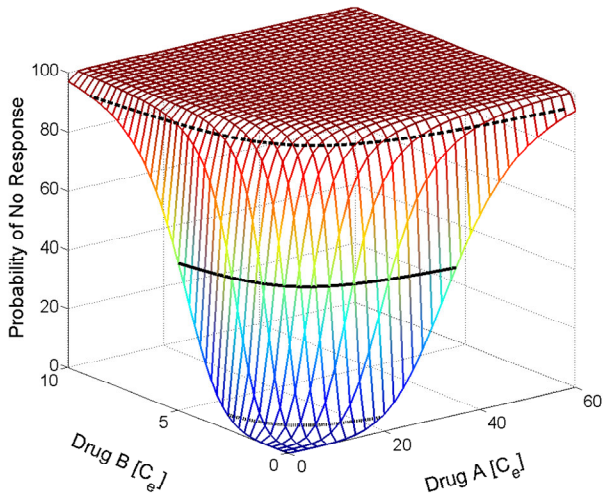

Figure 2. This surface shows rapid loss of responsiveness as propofol is increased. Sevoflurane does not have as profound an effect on sedation, shown by the very slow rise of the surface along the sevo axis. The solid line about halfway up the surface slope represents the C50 isobol, or the combination of drugs that would result in LOR in 50% of the population.

When two drugs are administered, their concentration-effect curves can be combined into a 3D response surface model. Response surface models consist of a set of parameters that estimate the extent of drug interaction (synergistic, antagonistic, or linear), the surface "slope", and the concentration of each drug alone that is required to achieve a 50% probability of maximal effect.

Response surface models provide a three dimensional visualization of combined drug effects (Fig 2) across various dosing schemes. Response surfaces may be a useful tool in identifying ideal concentration pairs that meet patient analgesic needs yet avoid adverse effects, thereby improving patient safety.

Control theory and drug delivery

Control systems often need to consider multiple conflicting objectives in the pursuit of a real world optimal solution. This can be expressed mathematically by the simultaneous minimization of a set of objective functions, ϕ_k and k=1,2,..,n where "n" is the number of objectives. (equation 1).

$$\min_{p \in U} (\phi_1(p), \phi_2(p), \ldots, \phi_n(p)) \qquad (1)$$

Variable vector "p" represents all simulated dosing schemes and $\phi_k(p)$ the objective value to be optimized. The control system attempts to simultaneously minimize all the objective functions. Objectives of interest for drug delivery during endoscopic procedures include:

(i) minimize the time between the start of administration of anesthetics and when there is sufficient analgesia to blunt a response to esophageal instrumentation,
(ii) minimize the duration of respiratory compromise,
(iii) minimize the duration of unresponsiveness, and
(iv) minimize the time required for full recovery once the anesthetics are terminated.

For this study, the anesthetics are propofol and remifentanil. The variable vector for each the four objectives include the amount of each drug that is delivered as a bolus and as an infusion. Time is the variable to be minimized in each objective.

Generally, no single solution exists that optimally satisfies all objectives simultaneously. However, a set of equally efficient (Pareto-optimal) solutions does exist. A decision process is used to select a suitable compromise solution from this set. The methods used to solve multiobjective optimization problems fall into three general classifications:

1. a priori – an aggregating function is used to combine all objectives to a single value (scalarization) using weighting coefficients, priorities or goals prior to optimization
2. a posteriori – the Pareto-optimal set is presented to a decision maker before any preference is made
3. progressive articulation – an iterative process between the decision maker and optimizer is used to approach a final solution.[3, 4]

III. METHODS

Clinical experience suggests that the depth of sedation and analgesia required to blunt the response to esophageal instrumentation through the oropharynx is significant and often leads to a loss of responsiveness[5]. With the response surface models for esophageal instrumentation, moderately painful stimuli, respiratory compromise and loss of responsiveness, we will explore through simulation the ability of various dosing schemes to blunt the response to esophageal instrumentation and once instrumented, be quickly titrated to provide adequate analgesia and sedation for a moderately painful stimulus while minimizing loss of responsiveness. We hypothesized that dosing schemes exists to meet these clinical goals.

An approach to establishing a clinically relevant weighting scheme for each objective is to consult a panel of experts (i.e. board certified anesthesiologists). In anesthesia, expert opinion has been used to develop a set of consensus statements that can be used to will be asked to develop consensus statements that prioritize the objectives using a modified Delphi technique. Weighting coefficients will be based on their objective prioritization.

Previous work has developed response surface models of propofol and remifentanil for loss of response to esophageal instrumentation[6], loss of responsiveness[7], sedation[8], respiratory compromise[9] and tibial pressure[8] (see Table 1 and equation 2). The iso-effect lines representing 95% probability of no response for each criterion, with the exception of respiratory compromise, which will use 50% probability, will be combined to identify ideal target remifentanil-propofol concentration pairs that allow esophageal instrumentation yet minimize unwanted respiratory compromise or loss of responsiveness. The response surface models will be used to define boundary conditions for a series of optimization targets. Clinical goals will be used to construct a cost functional.

A series of simulations will be conducted across a range of bolus sizes (Prop: 0-2.67 mg/kg, Remi: 0-6.67 mcg/kg) and infusion rates (Prop: 10-150 mcg/kg/min, Remi: 0-0.375 mcg/kg/min) to identify ideal dosing regimens and minimize the cost functional. All simulations will be run for a 55 year old, 75 kg, 175 cm male. Dosing regimens will be optimized in terms of the ratio of propofol to remifentanil, bolus dosing, and infusion rates, and time to reach or spent above each isobole.

$$P(E=1|C_P,C_R)=\frac{\left[\frac{C_R}{C_{50R}}+\frac{C_P}{C_{50P}}+\alpha\cdot\left(\frac{C_R}{C_{50R}}\cdot\frac{C_P}{C_{50P}}\right)\right]^n}{1+\left[\frac{C_R}{C_{50R}}+\frac{C_P}{C_{50P}}+\alpha\cdot\left(\frac{C_R}{C_{50R}}\cdot\frac{C_P}{C_{50P}}\right)\right]^n} \quad (2)$$

Table 1. Greco model parameters for pharmacodynamic effects used for optimizing dose selection. Remi C50 is in ng/mL while prop C50 is in mcg/mL. Alpha and n are unitless. These parameters can be combined with equation 2 to determine the probability of no response to the associated effect at a given remifentanil:propofol concentration pair.

Model	Remi C50	Prop C50	Alpha	n
Esophageal Instrumentation	27. 8	4.0	20.1	3.4
Loss of Responsiveness	33.1	2.2	3.6	5
Sedation	12.5	1.8	5.1	3.8
Respiratory Compromise	5.4	2.8	2.9	6.0
Analgesia (30 psi)	8.8	4.2	8.2	8.3

This study will follow the "a priori" approach to converge on an optimal dosing scheme for a given patient demographic. Weighting coefficients (w_k) will be used to adjust how much influence each objective has in the aggregate objective function (equation 3).

$$\min_{p\in U}\sum_{k=1}^{n} w_k\phi_k(p) \quad (3)$$

IV. RESULTS

It is not possible to simultaneously optimize all criteria. A compromise solution must be selected. For this paper we were not able to obtain weight coefficients (w_k) using the modified Delphi technique as mentioned in the methods. To obtain preliminary results, the weights listed in Table 2 were used.

In the first iteration, the objective function was selecting runs where the patient would not have tolerated esophageal instrumentation, evidenced by having negative times for criteria 1. Obviously, the procedure cannot occur if the probe is not inserted. Therefore, this target must be converted to a constraint – it absolutely must be reached.

Table 2. A list of the multiple objectives the aggregating function is taking into consideration. Weighting coefficients are shown in the third column.

k	Criteria	w_k
1	Time to 95% Esophageal Instrumentation	0.3
2	Time above 95% Esophageal Instrumentation	0.05
3	[Time to 50% Respiratory Compromise]$^{-1}$	0.1
4	Time above 50% Respiratory Compromise	0.3
5	Time above 95% 30 psi	0.05
6	Time above 95% Loss of Responsiveness	0.1
7	Time to 5% Sedation	0.1

Table 3. Constraints added to multiobjective optimization to ensure the results will lead to successful procedures.

Criteria	Constraint
Time to 95% Esophageal Instrumentation	>0
Time to 5% Sedation	>1

In the second iteration it was noticed that the new "top" simulations were not keeping patients sufficiently anesthetized after probe insertion for them to tolerate the procedure. In other words, the patient would be able to tolerate placement of the probe but drug levels would soon drop, causing them to respond to the placed probe. This was evident by having negative times for criteria 7 (see Table 2). Correcting this required an additional constraint for wakeup time. Constraints are listed in Table 3.

Following these modifications, the 6,615 simulated dosing strategies were sorted by their aggregate objective function output (score). The top five results are shown in Table 4 as well as Figure 3.

Table 4a. Dosing information for the top 5 simulations selected by the aggregating objective function. (score).

Score	Propofol		Remifentanil	
	Bolus mg/kg	Infusion mcg/kg/min	Bolus mg/kg	Infusion mcg/kg/min
2.91	0.8	20	0.0125	0.5
2.98	0.93	20	0.01	0.47
2.99	0.67	20	0.02	0.67
3.06	0.8	20	0.015	0.6
3.12	0.67	20	0.0225	0.75

Table 4b. Times (in minutes) used by the aggregating objective function to determine a score for each simulation.

Score	Criteria # (from Table 2)						
	1	2	3	4	5	6	7
2.91	1.83	0.33	1.50	5.83	3.83	1.83	0.67
2.98	1.50	1.33	1.50	6.00	4.00	2.67	0.50
2.99	1.67	0.83	1.50	6.17	4.00	1.17	1.33
3.06	1.50	1.33	1.50	6.17	4.17	2.17	1.17
3.12	1.50	1.33	1.50	6.50	4.33	1.33	1.50

V. Discussion

The peaks for the five selected doses look reasonable. However, there might not be enough time above the esophageal instrumentation isobole (EI) to ensure the clinician has sufficient time to place the probe. This constraint can easily be modified to select just those doses that are above the 95% esophageal instrumentation isobole for some minimum amount of time.

A second concern is that the maintenance infusion (the effect site concentration that remains once the bolus effect has worn off) is still probably too low for someone to tolerate a placed probe. However, additional data collection

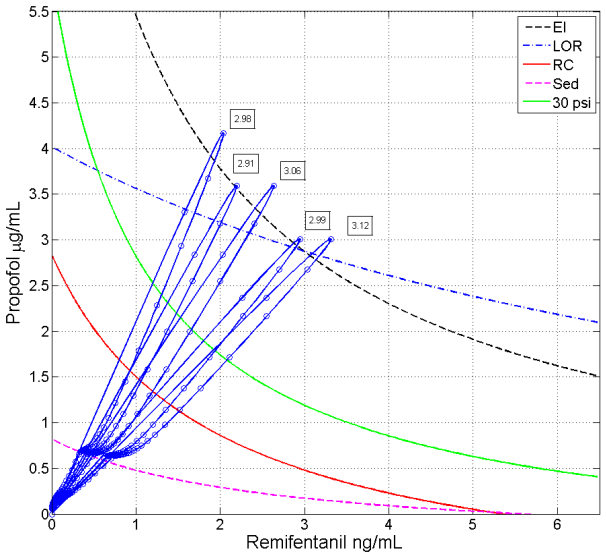

Figure 3. Plot showing the isoboles representing our optimization targets as well as plots of the top 5 dosing simulations as determined by the aggregating objective function. Markers represent whole minutes. The bolus dose causes the peak while the infusion holds the subject at a steady concentration for the duration of the procedure (dark lines just above Sed isobole). Text boxes show the score of the associated plot.

is necessary to determine what the minimum effect site concentration must be for patients to not respond to a placed probe. Once this isobole is built, an additional constraint can be added to the aggregating objective function, ensuring that the selected dosing schemes do not fall below this target.

Another possible solution is to establish a minimum infusion rate. As seen in Table 4a, the doses currently being selected have a propofol infusion rate of 20 mcg/kg/min. Adding a constraint requiring a minimum of, for example, 50 mcg/kg/min could yield the same result without requiring additional data collection. It would still be necessary to determine the minimum rate necessary to ensure patients do not respond.

A preliminary look at this approach was taken. The results for the top five simulations selected by the aggregating objective function are shown in Table 5 and Figure 4. Immediately obvious is that the bolus sizes are larger, as are the propofol infusion rates. However, the remifentanil infusion rates are significantly lower. The times for criteria 6 and 7 are also higher than those listed in Table 4b. However, since higher infusion rates are used, it is expected that it will take longer for the drug effects to wear off.

In comparing Figures 3 and 4, it is interesting that this time the aggregating objective function selected dosings with significantly lower remifentanil concentrations as well as significantly higher bolus sizes. Additional work will investigate this, potentially modifying the weighting coefficients to place more emphasis on effects produced by remifentanil.

Table 5a. Dosing information for the top 5 simulations selected by the aggregating objective function (score) after a constraint has been added requiring a minimum propofol infusion rate of 50 mcg/kg/min. The bolus sizes are larger, as are the propofol infusion rates. However, the remifentanil infusion rates are significantly lower.

Score	Propofol		Remifentanil	
	Bolus mg/kg	Infusion mcg/kg/min	Bolus mg/kg	Infusion mcg/kg/min
4.19	1.2	50	0.3	0.0125
4.21	1.47	50	0.18	0.00625
4.36	1.6	50	0.2	0.00625
4.37	1.33	60	0.17	0.0075
4.39	1.2	50	0.3	0

Table 5b. Times (in minutes) used by the aggregating objective function to determine a score for each simulation. The times for criteria 6 and 7 are generally higher than those in Table 4b, a natural result of using higher infusion rates.

Score	Criteria # (from Table 2)						
	1	2	3	4	5	6	7
4.19	1.33	1.83	1.50	8.00	4.67	4.00	5.17
4.21	1.50	1.50	2.00	7.67	4.33	4.50	5.17
4.36	1.17	2.17	2.00	8.17	4.67	4.83	5.33
4.37	2.00	0.17	1.50	7.83	4.17	4.33	6.17
4.39	1.83	0.33	2.00	7.67	3.83	5.67	5.67

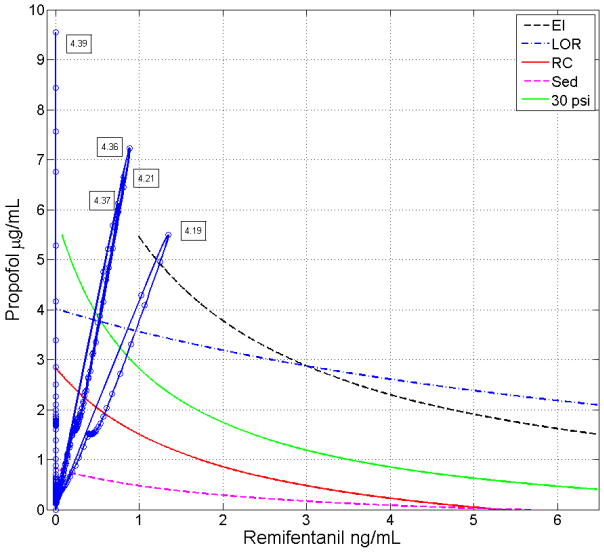

Figure 4. Plot showing the isoboles representing our optimization targets as well as plots of the top 5 dosing simulations as determined by the aggregating objective function once a constraint requiring a minimum propofol infusion rate of 50 mcg/kg/min has been added. Markers represent whole minutes. There are three simulations overlapping on the middle plot. Their peaks occur at the center of the text box showing their score. Notice the changed Y-axis scale as well.

VI. CONCLUSION

These results show promise for the development of a multiobjective optimization approach to patient-specific selection of dosing schemes. Additional work is needed to determine appropriate weighting coefficients and constraints.

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