

# Optimization Methods to Minimize Emergence Time While Maintaining Adequate Post-Operative Analgesia

Carl Tams BS, Noah Syroid MS, Ken B. Johnson MD,  
Talmage D. Egan MD, Dwayne Westenskow PhD

## ABSTRACT

A rapid emergence from anesthesia combined with an extended duration of adequate analgesia is desired. Difficulties arise when trying to achieve a rapid emergence and provide adequate analgesia for procedures associated with moderate post operative pain. We propose to use pharmacokinetic (PK) and pharmacodynamic (PD) models with optimization techniques to determine anesthetic drugs ratios to improve post-anesthetic outcomes of emergence and analgesia. We hypothesize that optimized propofol, remifentanyl, and fentanyl administrations will shorten emergence time and extend the period of adequate analgesia during patient recovery. Anesthesiologists administered a general anesthetic to 21 patients for laparoscopic procedures with propofol, remifentanyl, and fentanyl according to their standard practice. The theoretical improvement provided by the optimization was measured by comparing the time differences between the control predictions and the optimized prediction of the  $T_{ROR}$  time and  $T_{RON}$  time. In the control group the  $T_{ROR}$  was 10.2+-5.8 minutes (mean +- SD) and  $T_{RON}$  was 3.5+-5.0 minutes after emergence. In the optimized group the  $T_{ROR}$  was 7.5+-2.2 minutes or 26% faster ( $p < .001$ , paired t-test) and the  $T_{RON}$  was 7.4 +-2.4 minutes or 88% longer ( $p < .00001$ , t-test). Optimized administrations of propofol, remifentanyl, and fentanyl resulted in a theoretically shorter emergence time and a longer period of adequate postoperative analgesia. The optimization algorithm shows potential for real-time clinical guidance in drug management.

## INTRODUCTION

In anesthesia, a rapid emergence time and an adequate period of analgesia are both desired.<sup>11</sup> Pharmacokinetic (PK) and pharmacodynamic (PD) modeling and simulation can be used to predict the anesthetic drug's effect site concentration ( $C_e$ ) and the expected probability of response to stimuli.<sup>1-6</sup> PK/PD optimization methods take advantage of unique drug characteristics in order to effectively achieve preferred anesthetic goals. PK model optimization capitalizes on a drug's time course and accumulation within the body. PD model optimization utilizes the synergistic interaction between sedatives (e.g., propofol) and opioids (e.g., remifentanyl or fentanyl), which can predict a single probability of effect given a range of concentrations for the drug combination. For example, the same PD drug effect can be achieved by decreasing the sedative and increasing the opioid  $C_e$ , or vice versa. Combined PK and PD simulation allows one to explore differing combinations of sedative and opioid  $C_e$  and to choose an optimal combination that best achieves anesthetic goals.

Optimization via PK and PD modeling and simulation has been used in prior research that was intended to prevent response to surgical stimulation, yet provide an optimal time to emergence upon termination of the anesthetic.<sup>7</sup> Limited infusion durations of 15, 60, 300, and 600 minutes for propofol and 4 different opioids were explored. Optimal target concentrations identified were largely dependent on the PD effect and also on the infusion length. Shafer et al. also found the optimal concentrations are dependent on the infusion history.<sup>8</sup> Emergence time was shown to be minimized, but post-operative pain management requirements were not considered as part of the optimization.

Our motivation was to expand upon prior optimization research by considering both a rapid wake up and prolonged post-operative analgesia. In some cases, anesthetic goals may compete with one another (i.e. a rapid emergence versus maintaining adequate analgesia after surgery). The aim of this study was to develop a cost functional that identifies the best dose of opioids and propofol to meet each goal while minimizing unwanted prolonged emergence and inadequate analgesia. We hypothesize that

our optimization algorithm will find optimal infusion rates of propofol, remifentanyl, and fentanyl which will decrease the  $T_{\text{ROR}}$  and extend the  $T_{\text{RON}}$  without respiratory depression.

## METHODS

### Overview

The method for optimization was designed as a real time algorithm for anesthesiologists administering propofol and remifentanyl during general anesthesia. The algorithm, without a reduction of the desired level of sedation and analgesia, suggested changes to propofol and remifentanyl infusion rates that resulted in a more rapid recovery of responsiveness and an increased period of adequate post-operative analgesia. This was accomplished via pharmacokinetic (PK) simulation to calculate effect site concentration ( $C_e$ ), and the use of response surface pharmacodynamic (PD) models, which gave a range of concentration pairs for propofol and opioids maintaining the desired level of effect, see figure 1.

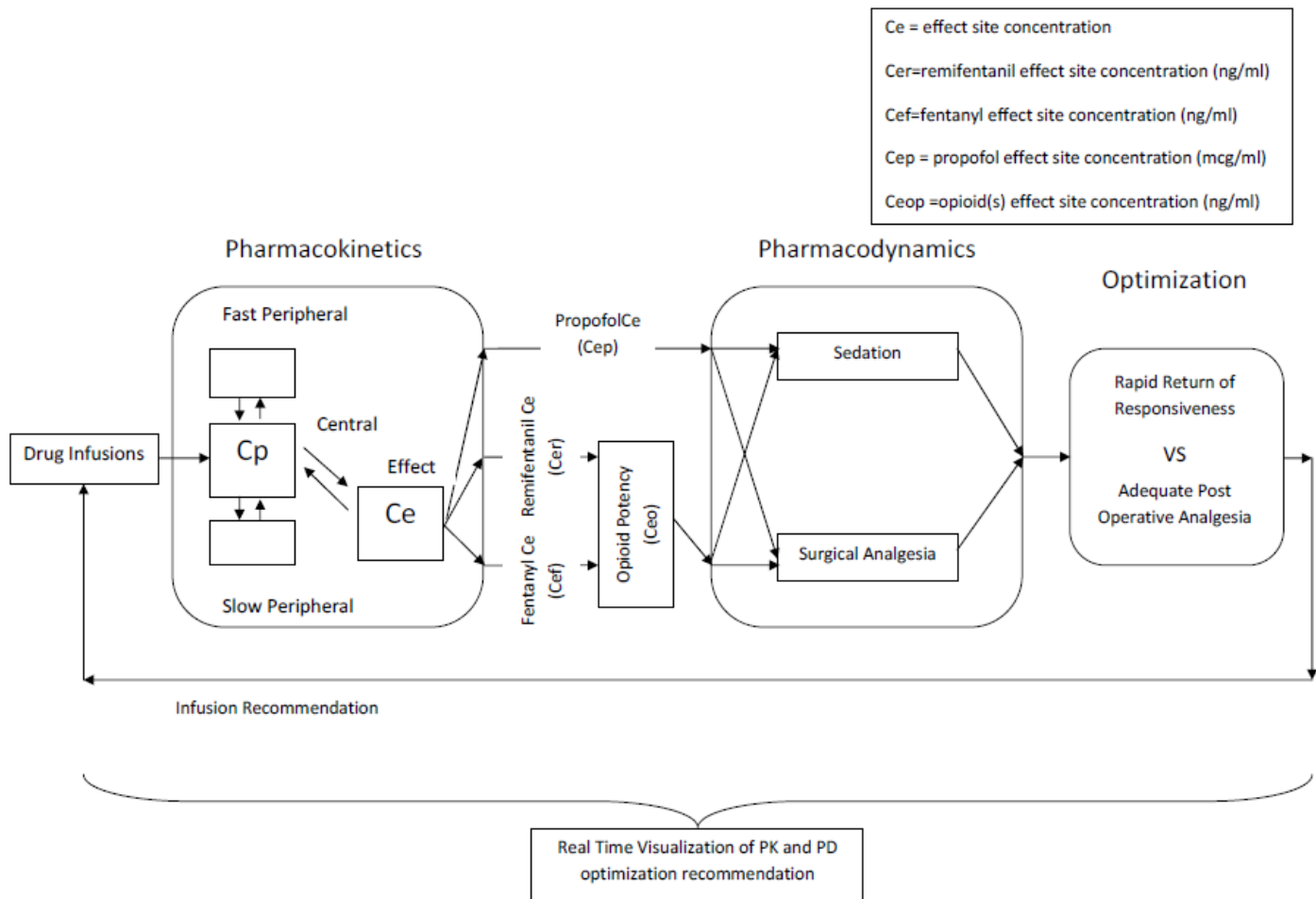


Figure 1 – Algorithm overview

Using a within study design, the potential utility of the optimization algorithm was assessed using previously collected drug administration data from 21 anesthetics using propofol and remifentanyl.<sup>6</sup> To evaluate the algorithm, PK and PD simulation were performed twice, once without optimization (control group) and once with optimization (experimental group). During optimization simulations, PD effects were maintained at the same level as in each of the control simulations; however propofol and remifentanyl infusion rates were adjusted to achieve a rapid ROR and increased time until RON.

## Modeling

Four compartment pharmacokinetic (PK) models were used to predict the propofol, remifentanyl and fentanyl Ce during the anesthetic. Three response surface pharmacodynamic (PD) models were used during the optimization process: (I) probability of unconsciousness to assess the level of sedation during and after the anesthetic ( $E_S$ ), (II) probability of no response to laryngoscopy as a surrogate for analgesic effect during surgery ( $E_L$ ), and (III) probability of no response to tibial pressure algometry as a surrogate for analgesia effect during post-operative recovery ( $E_A$ ).<sup>5, 6, 9-13</sup> The pharmacodynamic response model input is  $Ce_R$  and  $Ce_P$ . Fentanyl Ce ( $Ce_F$ ) was converted to  $Ce_R$  using the equivalence potency ratio of 1:1.2.<sup>6</sup>

The response surface models are characterized by the following equation:

$$E = \frac{E_{MAX} * \left( \frac{Ce_P}{C_{50P}} + \frac{Ce_R}{C_{50R}} + \alpha * \frac{Ce_P}{C_{50P}} * \frac{Ce_R}{C_{50R}} \right)^\gamma}{\left( \frac{Ce_P}{C_{50P}} + \frac{Ce_R}{C_{50R}} + \alpha * \frac{Ce_P}{C_{50P}} * \frac{Ce_R}{C_{50R}} \right)^\gamma + 1}$$

*Equation 1 – Greco Pharmacodynamic response surface model*

Where E is the probability to effect,  $E_{MAX}$  is the maximal possible effect.  $Ce_P$  and  $Ce_R$  are the effect site propofol and remifentanyl concentrations,  $C_{50P}$  and  $C_{50R}$  are the individual effect site concentrations that produce 50% of the maximal effect,  $\alpha$  is the synergistic interaction between propofol and remifentanyl, and  $\gamma$  is the slope of the response surface curve. E ranges from 0 (0% probability of no response) to 1 (100 % probability of no response). Because these models have been evaluated in a clinical setting, the models are expressed in terms of the clinically relevant goals: the probability of unconsciousness, probability of adequate surgical analgesia, and the probability of adequate post-operative analgesia.

## Optimization Algorithm

The algorithm behaves as follows:

1. Estimate the remaining time of surgery.
  - A. To mimic the estimation a clinician would have the algorithm assumed the remaining surgical time is actual remaining time rounded to the nearest 30 minutes with 20% error.
  - B. Every 60 minutes during the simulation the algorithm re-evaluates the remaining time of surgery.
  - C. 15 minutes prior to the end of surgery the algorithm re-estimates the end of surgery with 20% error for one last optimization iteration.
2. Estimate the Ce of all anesthetics using the respective PK models.
3. Calculate an opioid  $Ce_O$  (in terms of remifentanyl), combining the remifentanyl ( $Ce_R$ ) and fentanyl ( $Ce_F$ ) effect site concentrations using relative opioid potency relationships ( $Ce_O = Ce_R + 1.2 * Ce_F$ )
4. Calculate the PD drug effects using the Ce for propofol and opioids, in terms of the probability of unconsciousness ( $E_S$ ), probability of no response to laryngoscopy ( $E_L$ ), and the probability of adequate post-operative analgesia ( $E_A$ ).
5. Starting after induction three different infusions of fentanyl were simulated targeted to 0, 1.5, and 2.5 ng/ml for long term analgesia. In locales where a fentanyl infusion pump is unavailable (e.g., the U.S.A.), the algorithm suggests alternative dosing intervals of 50 mcg boluses of fentanyl over time to maintain the fentanyl Ce within 20% of the target.

6. Without reducing the current effects  $E_L$  or  $E_S$ , 50 new  $Ce_R$  and  $Ce_P$  pairs are generated for each of the three fentanyl administrations. This is achieved by choosing a new  $Ce_P$  ranging from 1.5 mcg/ml to 10 mcg/ml and solving Equation 1 for  $Ce_R$ . To avoid respiratory depression, if the  $Ce_R$  was greater than 10 ng/ml within 10 minutes of the end of surgery it was removed from the 50 test  $Ce$  pairs.
7. Simulate an effect-site target controlled infusion from the original  $Ce_P$  and  $Ce_R$  to the  $Ce$  values targeted in step 6 for the remainder of the surgery. Simulate the three fentanyl infusions.
8. Terminate infusions at the end of surgery
9. Calculate the return of responsiveness time ( $T_{ROR}$ ) and return of nociception time ( $T_{RON}$ ) times for the simulated infusions.
  - a. The  $T_{ROR}$  is the time difference between the time when the infusions are terminated and the expected emergence.
    - i. The expected emergence time is determined by the PD probability of unconsciousness ( $E_S$ ). The average patient emerges at  $E_S = 50\%$ .  $E_S^*$  is the  $E_S$  value at the observed ROR during the surgical procedure.
  - b. The RON time is found by subtracting the time of expected emergence from the time when the  $E_A$  falls below 25%.
10. Repeat steps 7-9, targeting a new combination of  $Ce_R$  and  $Ce_P$  values.
11. Given the set of simulated  $T_{ROR}$  and  $T_{RON}$ , use the weighting function with appropriate weights, equation 2, to determine the best remifentanyl and propofol  $Ce$  pair (i.e., best return of responsiveness time given the constraint of adequate analgesia).
  - a. The weights represent the anesthesiologist priority on sedation and analgesia. After repeated simulations of this data we found for this data set  $W_{ROR} = 0.85$  and  $W_{RON} = .15$  are the best weights.
12. Recommend to the anesthesiologist an infusion rate or a TCI target for remifentanyl and propofol.
13. If the end of surgery has not been reached after 10 minutes, repeat steps 1-12

$$f(Ce_P, Ce_F, Ce_R) = W_{ROR} \cdot T_{ROR}(Ce_P, Ce_F, Ce_R) - W_{RON} \cdot T_{RON}(Ce_P, Ce_F, Ce_R)$$

Equation 2 – Optimizing weight function

The optimizing weight function is used in step 11. The weighting function minimum determines the optimal  $Ce_P$  and  $Ce_R$  with the given priorities on sedation and post-operative analgesia.  $W_{ROR}$  and  $W_{RON}$  are percentages of priority given to sedation and analgesia; however they are kept as variables to indicate the possibility of altering the priority given to sedation and analgesia.  $T_{ROR}$  is the forecasted time until the expected return of responsiveness and  $T_{RON}$  is the forecasted time for the expected return of nociception. The weights  $W_{ROR}$  and  $W_{RON}$  are percentages between 0 and 100 %, the sum of  $W_{ROR}$  and  $W_{RON}$  are set to 100 %.

## **Algorithm Assessment**

### ***Overview***

The potential utility of the optimization algorithm was assessed using a PK/PD simulation study that was based upon clinical data collected from 21 total intravenous general anesthetics using propofol, remifentanyl, and fentanyl using a within-subjects study design.<sup>6</sup> The control condition was based upon model predictions of the anesthetic dosing without any PK/PD optimization. The experimental conditions were based upon an optimized anesthetic, where the optimization algorithm suggested changes to propofol and remifentanyl infusions were implemented every 10 minutes. A conceptual “virtual anesthesiologist” always complied with the algorithm’s recommendations. Metrics for comparison were the  $T_{ROR}$  and  $T_{RON}$

### ***Clinical Data Set***

Data was used from a previous study, where anesthesiologists gave total intravenous general anesthesia to 21 patients for laparoscopic procedures administering propofol, remifentanyl, and fentanyl.<sup>6</sup> In addition, as part of the standard anesthetic technique, a small dose of midazolam was given pre-operatively. A muscle relaxant (rocuronium) was also administered during induction of anesthesia and as needed during surgical maintenance. A study investigator was present to record the patients’ demographics, time and amount of drug administrations, and the time of surgical and anesthetic events including loss of responsiveness, tracheal intubation, incisions, end of surgery, return of responsiveness, tracheal extubation, and the start of post-operative care. More patient demographic information is in table 3, for more details about the procedures we refer you to the work by Johnson et al.<sup>6</sup>

### ***Control simulations***

For the control simulations, PK and PD simulations on the anesthetics’ dosing scheme were performed to predict the  $C_{eR}$ ,  $C_{eP}$ ,  $E_S$ ,  $E_L$ , and  $E_A$  during and after the anesthetic. The patient’s PD level of sedation,  $E_S^*$ , was set to the  $E_S$  value at the observed ROR.  $E_S^*$  was calculated in the control group and used in the experimental group to predict the individual patient’s ROR.  $E_R$  values were also calculated for times after surgery.

### ***Experimental simulations***

For the experimental simulations, PK and PD calculations were performed in a fashion similar to the control simulation. However, after tracheal intubation, the optimization algorithm was employed to recommend changes in the propofol and remifentanyl infusion rates every 10 minutes, yet would maintain the same anesthetic PD effects that were computed in the control condition. A conceptual “virtual anesthesiologist” complied with the suggested changes provided by the optimization algorithm.

While the optimization algorithm was active, the virtual anesthesiologist maintained  $W_{ROR}$  and  $W_{RON}$  constant at 0.85 and 0.15 respectively. A wide range of weights were experimented;  $W_{ROR} = 0$  to 1 with  $W_{RON} = 1$  to 0 both by increments of .05, only results for the combination  $W_{ROR} = 0.85$  and  $W_{RON} = 0.15$  will be presented. The other weights either increased  $T_{RON}$  or decreased  $T_{ROR}$  but were not significantly different.

Each patient’s optimized anesthetic was assumed to emerge at the same model predicted probability of ROR as the value observed in the control anesthetic,  $E_S^*$ . The  $C_{eR}$ ,  $C_{eP}$ ,  $E_S$ ,  $E_L$ , and  $E_A$  were calculated as the optimized experimental values during and after surgery. Note, the  $E_S$  and  $E_L$  are equal to or greater than the control  $E_S$  and  $E_L$ .

This research was to test the viability of an optimization of remifentanyl and propofol administrations; however the fentanyl contribution greatly changes the effect of analgesia. The control

simulations administered the fentanyl as boluses as administered by the anesthesiologists'. The fentanyl was administered starting after induction targeted to either 0, 1.5, or 2.5 ng/ml. The average fentanyl infusion  $C_e$  at the end of surgery from the control administered boluses was 1.5 ng/ml with a max at 4 ng/ml.

**Metrics and Statistical Analysis**

Two metrics were compared between the control and experimental conditions of this simulation study: the time difference between the end of surgery and the return of responsiveness ( $T_{ROR}$ ), and secondly, the time difference between the return of responsiveness and the point of inadequate post-operative analgesia as predicted by the PD postoperative analgesia models ( $T_{RON}$ ). A two-tailed, paired, student's t-test (Matlab version, R2008b, Mathworks Inc., MNatick, MA) was used to assess differences between groups. A p value of 0.05 was considered a statistically significant difference. However, a Bonferroni correction was applied due to the presence of multiple measures. The  $E_R$  was calculated for comparison between the control and experimental group.

**RESULTS**

Computer simulations were performed on the anesthetic administrations from elective surgeries for 21 patients. The observed times, patient's demographics, and the model predicted probability for sedation at ROR ( $E_s^*$ ) for the patients are shown in table 3. Figures 4 and 5 show the control and optimized simulation experiment for a selected patient #4. Figure 4 has the effect site concentrations and figure 5 has the model predictions for sedation and post-operative analgesia.

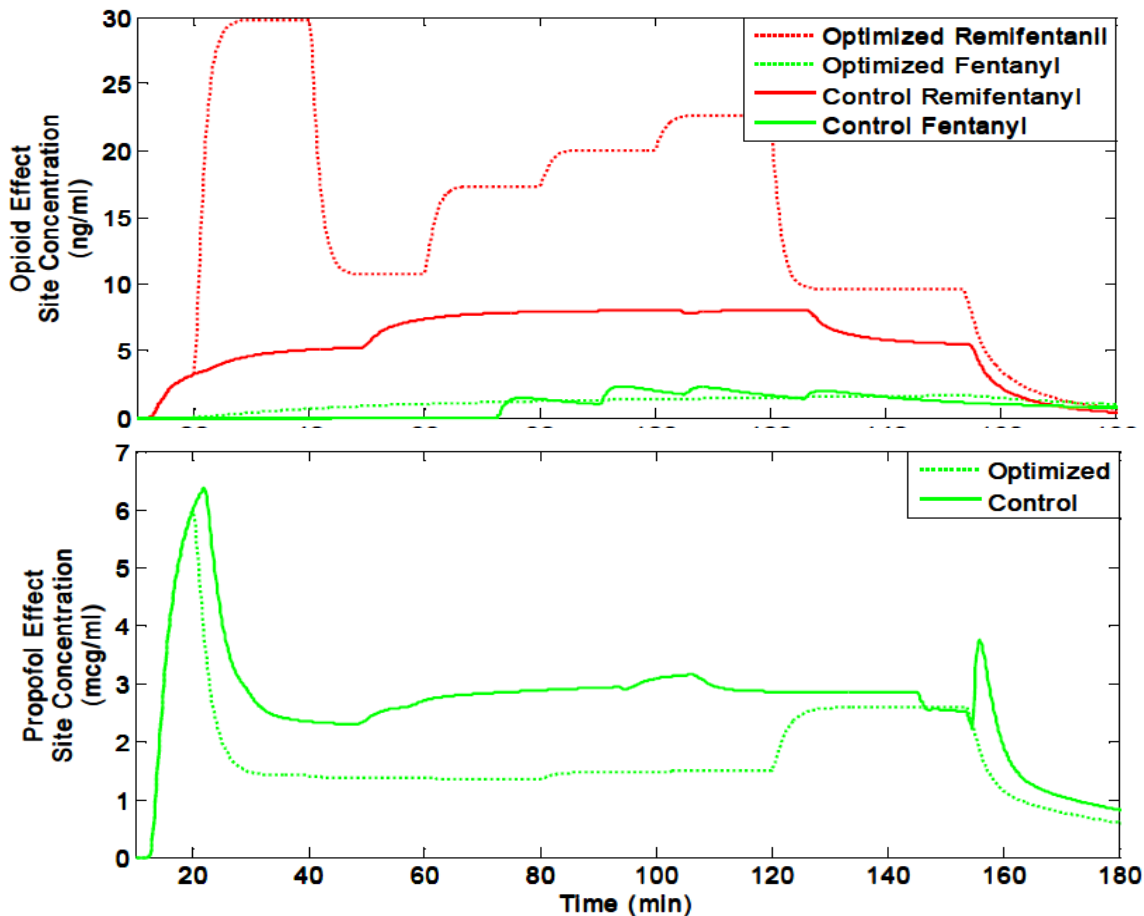


Figure 4 –The two panels show the effect site concentrations for the control and optimized simulations in solid and dotted lines respectively from patient #4. The top window shows the remifentanyl and fentanyl effect site concentrations while the bottom panel shows the propofol effect site concentration.

Figure 5 – Above is shown the expected PD model prediction for sedation and post-surgical analgesia for both control and optimized simulations in solid and dotted lines respectively from patient #4. After surgery, this patient was observed to regain consciousness when the probability of unconsciousness = 20.4%. The end of surgery, ROR, and RON times are displayed on the figure

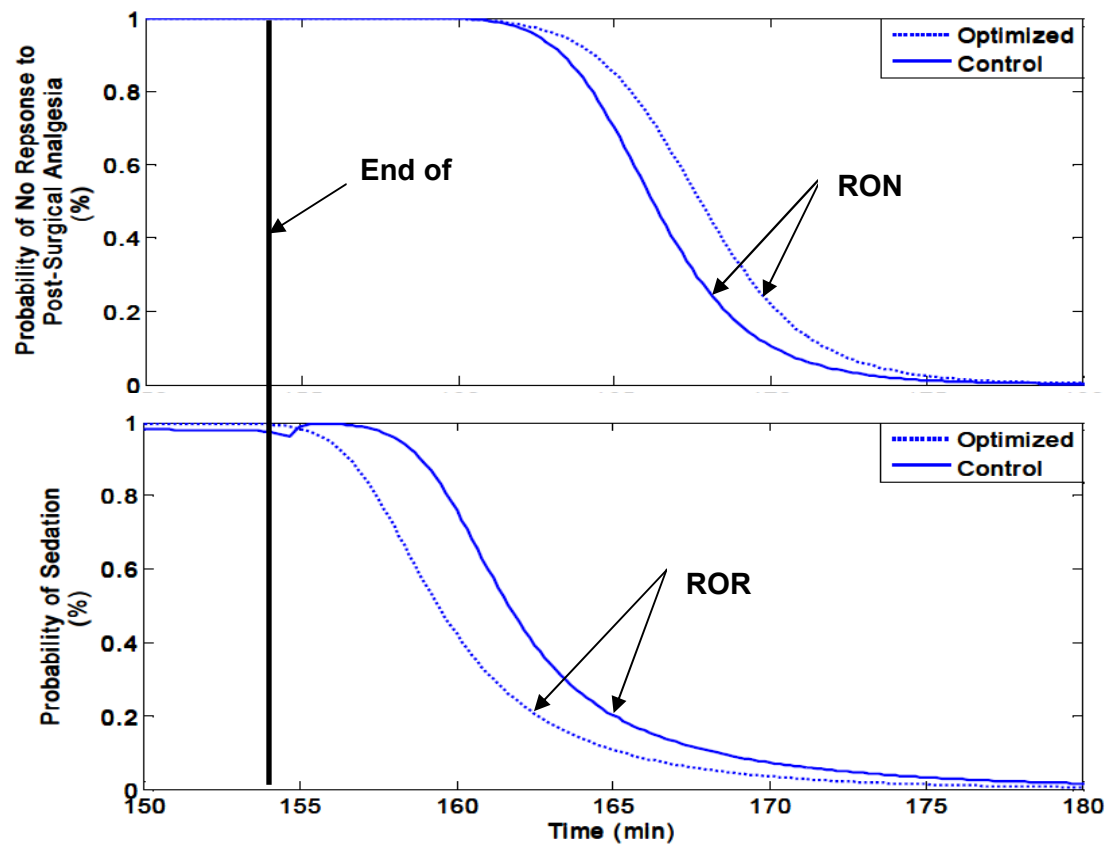


Figure 6 shows the difference in times between the control and optimized simulations with respect to ROR and RON. The control averages and standard deviation are green and the optimized are in blue. The standard deviations for ROR and RON in both simulations were decreased from the control simulations. Figure 6 shows the optimized simulation that administered the fentanyl infusion starting after induction. The standard deviations are decreased with the optimization algorithm, but the major change is in the average times. The standard deviations for the  $T_{ROR}$  from control simulations to optimized simulations were 5.6 minutes to 4.2 minutes and  $T_{RON}$  from control simulations to optimized simulations were 5.8 minutes to 3.4 minutes.

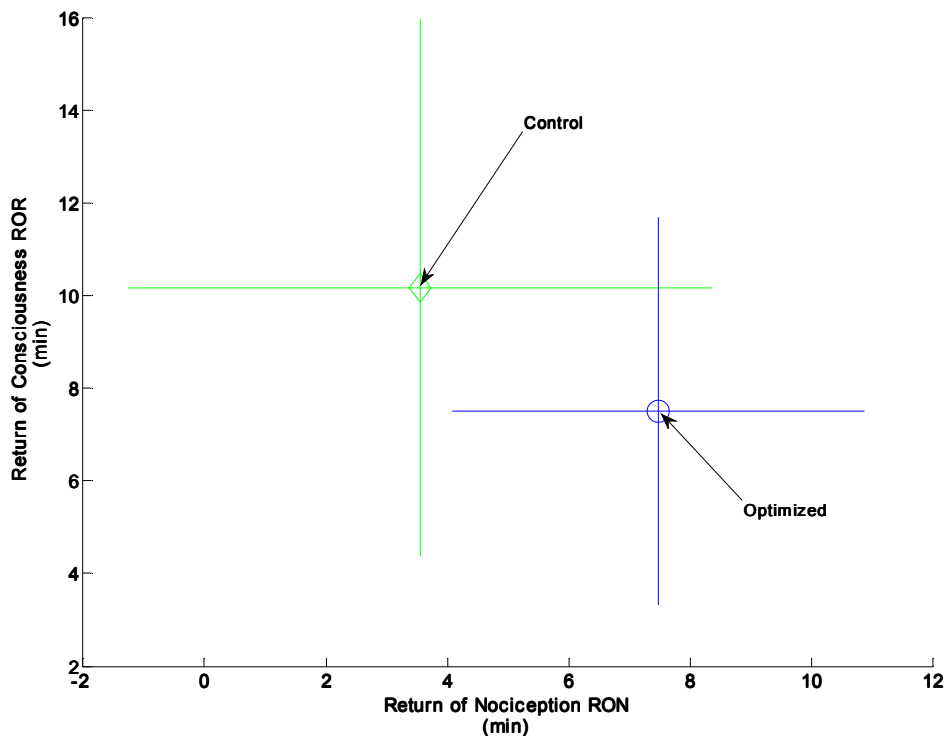


Figure 6 – The time to ROR and RON for the control (green) and the optimized (blue) groups. The average (ROR and RON) times are indicated by the circles; one standard deviation is shown by the lines.

The optimized algorithm decreased ROR time by 2.7+- 2.2 min ( $p < 0.001$ ) and increased the RON time by 3.9+-2.4 min ( $p < 0.00001$ ). The post-anesthetic respiratory depression (RD) percentages are listed in table 5 for the control and optimized study conditions. On average the probability of RD increased from control to optimized anesthetics by a few percent at ROR and extubation times, but at 15 minutes after the end of surgery the RD probability was slightly decreased.

	Respiratory Depression		
Simulation	RD <sub>ROR</sub> (%)	RD Extubation (%)	RD EOS + 15 min (%)
Control	50.8+-25.5 (5.3 to 96.8)	33.6+- 21.3 (3.6 to 77.0)	23.8+- 17.2 (5.3 to 77.7)
Optimized	52.4+-27.7 (7.4 to 97.0)	34.6+- 24.2 (6.6 to 89.0)	21.8+- 10.0 (5.8 to 45.3)

Table 5 – Respiratory depression listed at the time of extubation as the average +- std dev (minimum value to maximum value) for the control simulations and the optimized simulations during three different post-anesthetic points; at the time of ROR, at the time of extubation, and 15 minutes after the end of surgery (EOS).

## DISCUSSION

Vuyk et al. found optimal infusions for a rapid return of consciousness. Analgesia was never addressed in the optimization, but is critical to anesthesia. Interpretation of the results from figure 6 indicates that changing infusions can decrease the  $T_{ROR}$  and increase the  $T_{RON}$ . The improvement of decreasing  $T_{ROR}$  is limited by the minimum propofol effect site concentration to maintain sedation intra-operatively and avoid PONV post-operatively.<sup>14</sup> The improvement in increasing  $T_{RON}$  is limited by the prohibition to administer sufentanil (a long lasting opioid), high levels of fentanyl, or opioids post-operatively. The results of the optimization did not significantly change the model predicted probability of respiratory depression.

The results indicate that increasing the remifentanil concentrations and decreasing the propofol concentrations will result in better post-anesthesia outcomes for both focuses of minimizing ROR and maximizing RON. The optimization algorithm tended towards higher remifentanil target  $C_e$  and lower propofol  $C_e$  because the remifentanil elimination kinetics are very rapid when compared with the propofol elimination kinetics. The algorithm is based on the PD response model thus the same effect for sedation and surgical analgesia can be obtained by lowering the propofol  $C_e$  and raising the remifentanil  $C_e$ . However adverse side effects may occur, increasing the remifentanil concentrations may induce respiratory depression<sup>13</sup> or decreasing propofol may increase the probability of PONV.<sup>15</sup>

For our simulation experimented algorithm, we used a single set of weights for  $W_{ROR} = 0.85$  and  $W_{RON} = 0.15$ . Real time clinical use of the algorithm might allow the clinician to choose a different weighting combination to allow for specification in focusing either on decreasing ROR or increasing RON.

In most of the control administrations the anesthesiologists terminated the propofol infusion at the end of surgery while continuing the remifentanil infusion for 2 to 8 more minutes. We assume this is to extend the  $T_{RON}$  because of the insufficient post-anesthetic analgesic effect. The algorithm was confined to terminate both infusions at the EOS.

### Assumptions

The algorithm is based on the assumption that the current levels of sedation and surgical analgesia were requisite for that patient during surgery and are respectively quantified by the response surface models with respect to sedation and laryngoscopy. The PD model is a population based average and will correctly predict events for very few patients. We do not assert the model prediction will correctly predict the events; ROR, RON, nor RD. We do assume that the elimination using optimal administration will be more beneficial to the patient and anesthesiologist. Other variability that was not



considered was: individual drug tolerance would change the actual  $C_{50}$  values and PD models and individual cardiac output and blood flow alter the rate constant  $k_{e0.16}$

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