Building a Simplified Remifentanil Target Controlled Infusion System

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Introduction: The semi-synthetic opioid, Remifentanil, has been found to have versatile uses in the anesthetic practices that include induction for awake fiberoptic intubation [1] as well as the prevention of coughing during emergence [2]. While a target controlled infusion (TCI) system would simplify a quick titration to achieve a desired effect site concentration, this option does not presently exist in the United States. Consequently we demonstrate how to build a simplified bolus and infusion system, that can replicate a TCI pump from a zero initial state to a set final state, with simple arithmetic operations that can be performed with a basic spreadsheet. We then asses the performance of this system on several simulated patients.

Methods: The system design is conducted over a series of steps that are described in the appendix using the Minto Remifentanil model [3].

Using Matlab (R2016b) the above system was simulated with patients with the ages of 30, 50 and 70, weights between 50 and 110 kg in increments of 20 kg, heights of 120 and 210 cm in increments of 30 cm, as well as both genders. Patient with lean body mass (LBM) less than 20 kg were excluded from the analysis. The targeted concentration was 2.5 ng/mL. The normalized root-mean-squared error (NRMSE) was calculated to assess the system performance from 5 minutes to 30 minutes as a measure of the deviation from the target. This is calculated with the following formula:

$$NRMSE = \frac{\sqrt{\int_5^{30} \frac{(drug\_concentration(t) - target)^2}{30 - 5} dt}}{target}$$

Results: 96 simulated patients were simulated of which 9 had LBM < 20 kg and were excluded. Their effect site concentration over time is plotted in Figure 1. 4 patients are highlighted in Figure 1 and their characteristics are shown in Table 1. The mean NRMSE was 0.0423. The distribution of NRMSE is shown in Figure 2.

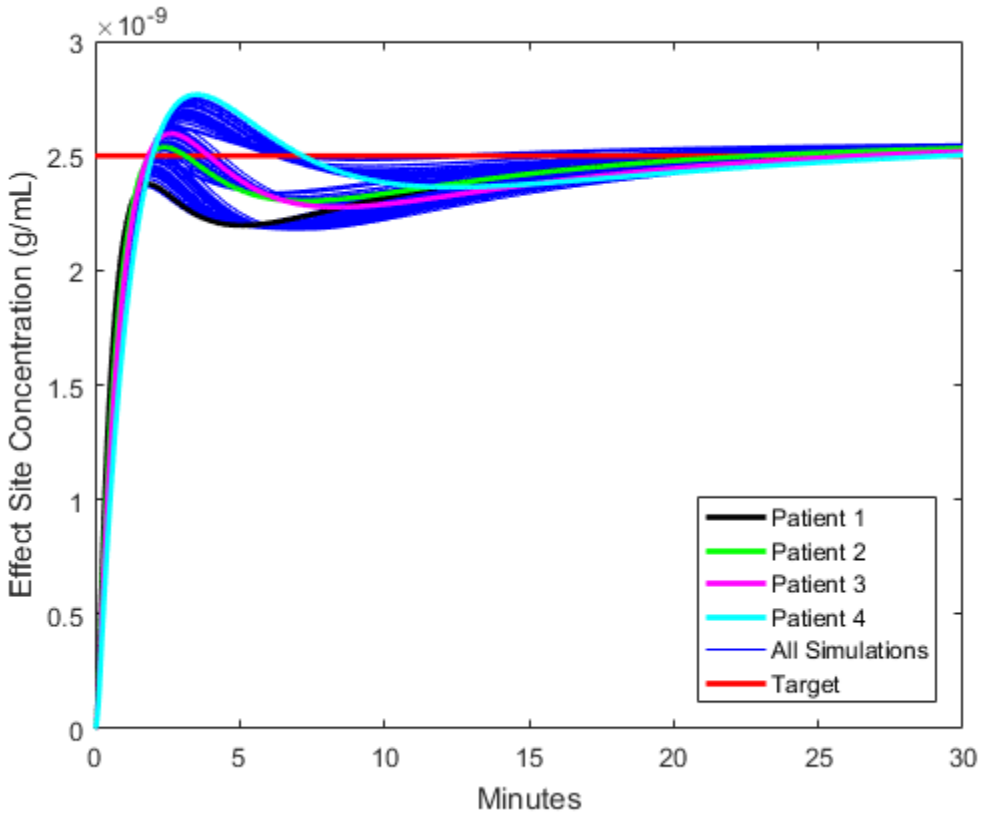
Conclusion: Using this technique one is able to quickly and effectively generate a bolus and infusion sequence that can mimic the performance of a simplified TCI system within a 7% error. This technique has been implemented on an online spreadsheet (http://bit.ly/2lXH0m8), but can equally be implemented in mobile apps as well as webpages. The clinical performance of the system has not yet been demonstrated.

References:

1. Lee HM, et al.. Korean J Anesthesiol. 2013: 65(3):215-20.

2. Lee B et al. BJA 2009: 102(6):775-8.

3. Minto CF et al. Anesthesiology 1997: 86(1):10-23.



	Sex	Age	Weight (kg)	Height (cm)	Bolus (mcg)	Infusion (mcg/kg/min)	NRMSE
Patient 1	Female	30	50	120	25.6	0.117	0.052
Patient 2	Female	50	70	150	30.5	0.083	0.0411
Patient	Male	50	90	180	38.6	0.077	0.05

3							
Patient 4	Male	70	110	210	47.7	0.065	0.035

Figure 1: Effect site concentration over time plotted for 87 patient using method described in Appendix. 4 patients are highlighted in the figure whose characteristics are described in Table 1. Effect site goal is plotted as the thick red horizontal line

Table 1.Characteristic properties and bolus-infusion sequences of the four patients highlighted in Figure 1. The NRMSE is also calculated for those four cases

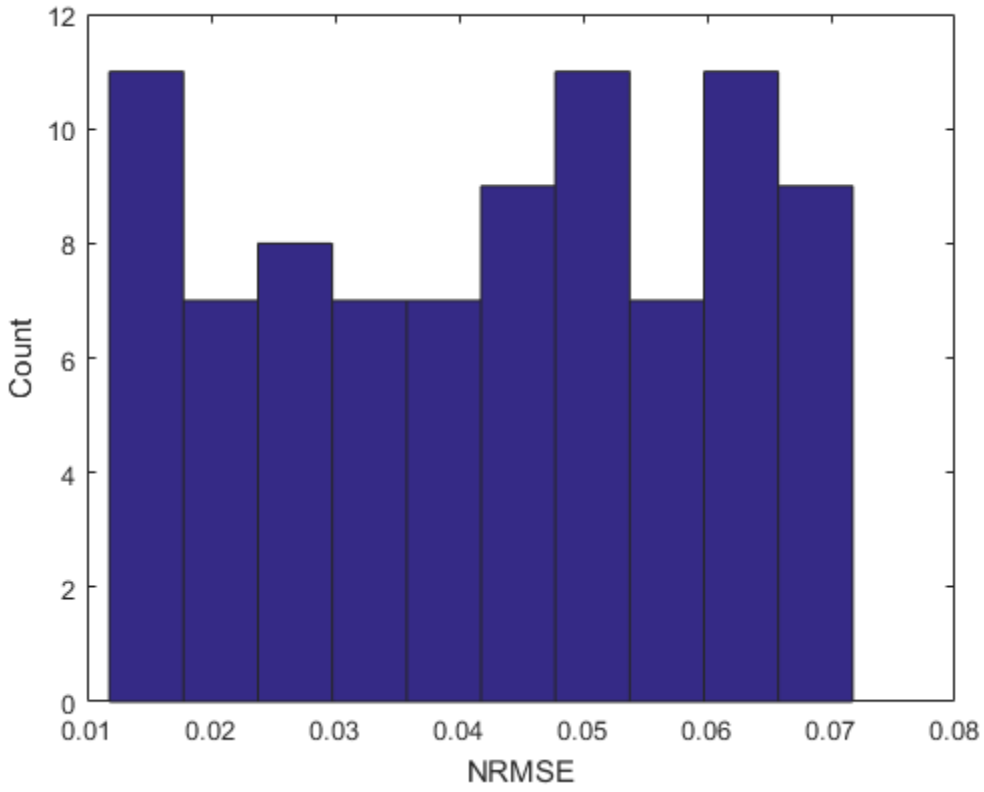


Figure 2: Distribution of the NRMSE for the performance of 87 simulated patients compared to a target.

Appendix:

1) Using the Minto model, calculate the patient's lean body mass, drug volumes, clearances and ke0.

2) Calculate the infusion rate by multiplying the desired effect site concentration by the metabolic clearance (Cl1). It is important to ensure proper unit conversions during this step

3) Calculate the bolus dose by multiplying the desired effect site concentration by the volume of distribution at peak effect. The latter can be determined by multiplying the primary compartment volume by the following ratio:

Ratio = 1.35 + 8.9/V1 - 0.669/Cl1 - 4.28/(V1*Cl1) – 0.154/Cl2 + 2.24/V2 - 1.22/LBM + 0.411/ke0

With LBM representing the lean body weight, V1 and V2, the volumes of the first and second compartments and Cl1, and Cl2, the clearance of the first and second compartments respectively. The derivation of this equation is described in another abstract.

4) Subtract from the bolus dose the amount of drug received during 1.5 minutes of the infusion

5) Multiply both the bolus and infusion rate by 1.045 to accelerate the pump's convergence to the desired target. This factor should be removed after 30 minutes.