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Title: Infusion Rate Control Algorithm for Target Control Infusion using Optimal Control

Introduction: Target Controlled Infusion (TCI) is a technique used in Total Intravenous Anaesthesia (TIVA) practice. TCI system allows the anaesthesiologist target a drug concentration in a specific site remotely commanding an infusion device. TCI system incorporates: Pharmacokinetic/Pharmacodynamic (PK/PD) Model to estimate the concentration at plasma and site-effect of the drug and; an Infusion Rate Control Algorithms (IRCA) to control the drug dose to be titrated by infusion pumps. The IRCA is based on BET (Bolus, Elimination and Transference) scheme [1] describe by a bolus and a vector of infusions. The bolus is a fast infusion to fill the central compartment followed by the vector of infusions to compensate the elimination between compartments and the transfer between peripheral compartments, aiming reach and maintain the target concentration. This work presents a new controller (NC) developed to control plasma concentration (Cp) and effect-site concentration (Ce), to be used in our TCI systems Anaesthesia Synchronization Software (ASYS) [2], as well an improvement of this NC using optimal control.

Method: The algorithm was developed in Matlab been implemented and test in simulation mode with ASYS implemented in LabView. This study is based on the analytical solution of Shafer and on the algorithm of Poucke. [3; 4] From the effect-site compartment only the k_{e0} rate constant was considered. The NC was develop, based on the continuous model, with a matrix based control rule:

$$\dot{X}(t) = A \cdot X(t) + B \cdot u(t), \qquad Y(t) = C \cdot X(t)$$

Where:

$$A = \begin{bmatrix} -(K10 + K12 + K13) & K21 & K31 & 0 \\ K12 & -K21 & 0 & 0 \\ K13 & 0 & -K31 & 0 \\ Ke0 & 0 & 0 & -Ke0 \end{bmatrix} \quad B = \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad C = [1 \quad 0 \quad 0 \quad 0]$$

Below the conversion of the continuous model in space states to discrete where Cp is the output and the input the dose (i). Equating the state space model in order to the input it is possible to know the exact value of the drug amount to obtain the next plasma concentration (Cpt):

$$Dose(i) = 0{,}36 \cdot (C \cdot A)^{-1} \cdot (C_{pt} \cdot 1000 \cdot V_1 - C \cdot A \cdot X),\ V_1 = \text{PatientWeight} \cdot V_c \quad [1]$$

Where kn and Vc are pharmacokinetic parameters. The NC, represented at diagram block figure 1, is mainly composed by equation 1 following the BET scheme automatically. The gain K, figure 1, was implemented to avoid the overshoot with optimal steeling time using the optimal control technique. The block diagram is represented by equation 2, as follow:

$$Cpt = K \cdot (((Cet - X(4)))/Vc)/1000 + Cet \quad [2]$$

To solve the problem using optimal control the mathematical model was wrote in AMPL (A Mathematical Programming Language) [5] allowing write a set of constraints and the cost function that is pretended minimize. Once KNITRO [6] solver supports AMPL was used to solve the optimal control problem.

To test the new controller (NC) a simulation protocol was implemented with Marsh's Pk model for propofol and 70kg male patient. The experimental protocol used was: an initial propofol target for Cp and Ce set at 3µg/ml and kept until steady state was reached at which point it was changed to 5µg/ml and kept until steady state was reached.

Results: The NC demonstrated a good response in stationary state, figure 1. However transitory phase for the target of effect-site concentration (Cet) at 3ug/ml shown an overshoot, not viewable for Cet=5ug/ml or Cpt. Aiming to eliminate the overshoot consecutively the drug toxicity and the overdose (plasma concentration), identified the optimal control technique was implemented in the NC. The NA using optimal control introduced a constraint Cplim, figure 1. The response obtained, figure 1, demonstrated the expected result.

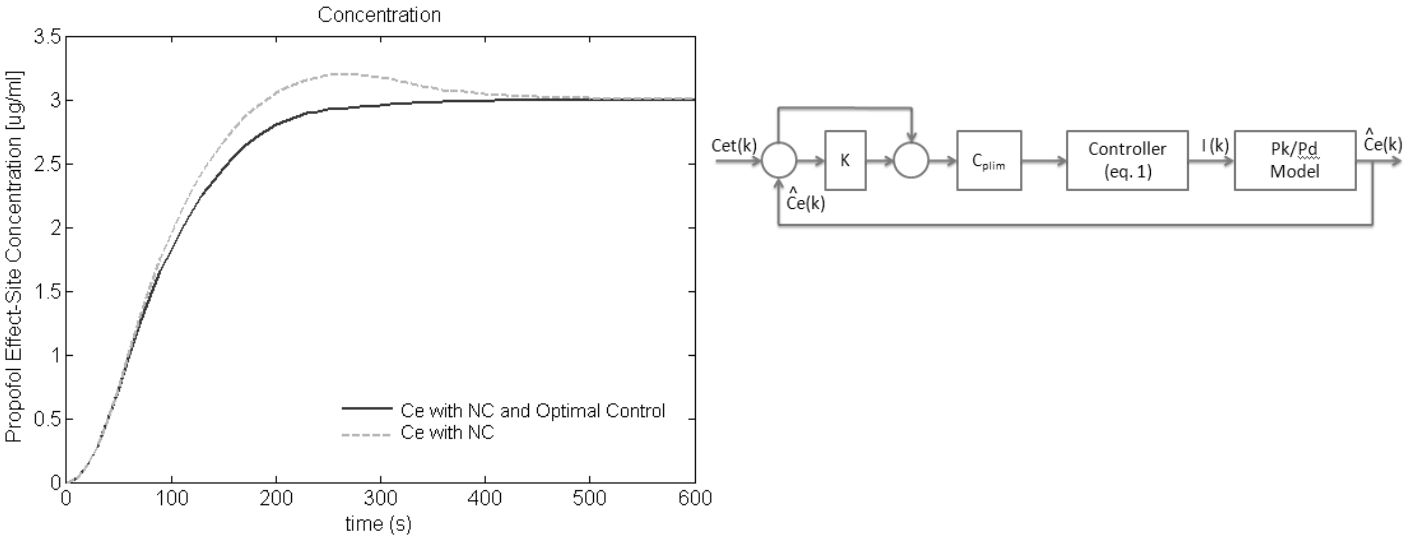

Figure 1 – Propofol Cet with Optimal Control and Block diagram with New Controller

Discussion: The results with the NC provide enough arguments of a robust and reliable IRCA. This study present an algorithm mathematically simpler than most of the existing algorithms and the results shown that it performance accurately. We believe that the fact it is simpler may offer advantages when used in the clinical setup to control infusion devices; more tests will be needed to fully assess it and a future work will present the optimal control using as tune the Lean Body Mass (LBM) and the target of effect-site.

Reference: [1] Schwilden H., European Journal of Clinical Pharmacology, vol. 20, 1981, pp 379:386.[2] N. Bressan et al, IEEE Transactions on Biomedical, 2008, pp 5543:47.[3] Shafer S.L., Journal of Pharmacokinetics and Biopharmaceutics, vol. 20, 1992, pp 147:169.[4] Poucke Van E.G., IEEE Transactions on Biomedical Engineering, vol. 51, no 11, November 2004.[5] Access at March/2010: http://www.ampl.com [6] Access at March/2010: http://www.ziena.com/knitro.html