ORIGINAL ARTICLE

Infusions of Potent Vasoactive Drugs using Computational Therapeutic Models in Critical Care Setups - A Modeling and Simulation Study

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Abstract

Aim: The maintenance of mean arterial pressure (MAP) is a critical parameter which needs to be continuously maintained in patients in trauma or recuperating from surgery. The effective means of maintaining it is through intravenous infusions like potent vasoactive drugs like sodium nitroprusside (SNP) and nitro glycerine (NTG). **Materials and Methods:** Maintenance of MAP is critical, and to keep it control many drug delivery and control strategies powered by fuzzy logic, artificial neural network, and internal model control are used. In this work a modeling and simulation study was attempted to develop and validate a viable computational therapeutic model of the patient infused with the drug. **Results and Discussion:** The model developed helps us to study and predict the patient's response to the drug during simulation stages. This work considers the modeling of patients based on based on an open source dataset of MAP in response to the drug administered (NTG) collected from a critical care unit. **Conclusion:** The data obtained was used to develop a therapeutic model based the first order–dead time using the linear time domain system identification method. The obtained models were classified into fast responders, normal responders and slow responders based on the model parameters.

Key words: Computational therapeutics, critical care, drug infusions, modeling

INTRODUCTION

The intravenous (IV) infusion of the drug is a viable and efficient means of eliciting a therapeutic response. Despite this advantage, the IV infusion needs to be administered with caution and is a highly manual and guess prone process of administration.[1] One specific case is the infusion of vasoactive drugs such as sodium nitroprusside (SNP) and nitroglycerine (NTG) to lower blood pressure in patients who are recuperating from surgery or trauma. There are two methods for administering the drug. The first one is a bolus injection that rapidly lowers blood pressure but has the disadvantage of rapidly diminishing effect, and that it can only be applied periodically to avoid cyanide poisoning. The second method is the continuously controlled release of the drug, which has the advantage of achieving lower blood pressures over long periods of time. This problem can be solved by developing a control system to find the correct dose which quickly lowers the blood pressure to the desired level, while avoiding a drug overdose. A computational model for the patient's response to the administered drug has been developed by Slate and Sheppard (1982) and Slate *et al*. (1980) and has been subsequently used by several workers to develop a controller design for programmed control of drug infusion in drug infusion pumps. The model propounded is a linear single-input-single-output (SISO) model which considers the intrasubject variability in physiological parameters found in different patients to the drug.[2] Slate *et al*. (1980) have performed extensive studies on the patients to find a model that relates the change in blood

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pressure to the infusion rate of the vasoactive drug. They used correlation analysis with a pseudorandom binary signal to derive the transfer function which helps to infuse the drug shown in Equation (1).

$$\frac{\Delta P_d(s)}{I(s)} = \frac{Ke^{-T_i s}(1+\alpha e^{-T_c s})}{\tau s+1} \quad (1)$$

where, ΔP_d (s) refers to the change in the mean arterial pressure (MAP) in units of mmHg and the I(s) is the infusion rate of the drug in mlh^{-1}, K is the sensitivity of the patient to the drug in mmHg $(mlh^{-1})^{-1}$, α is the dimensionless recirculation coefficient, T_i is the initial transport delay in s, T_c is there circulation transport delay in s, and τ is a lag time constant in s. Slater *et al*. had reported no average value for the recirculation component but noted that the steady-state gain has a high degree of intrasubject variability as high as 36 folds.[3] Due to this inherently high intrasubject variability in the subject the researchers adopt a PBRS which mimics the output similar to a random sequence which is statistically consistent.

In this work, the response of MAP to NTG was studied for 10 different patients and similar first-order dead time models are developed. The model feasibility was studied through input-output plots and presented in the results and discussion.

METHODOLOGY

Clinical patient data for the study

Data were obtained from a published thesis obtained from the public domain. As per the data, 10 patients were collected who were recuperating from surgery.[2,6] This dataset entails MAP of the patients was monitored, and NTG dosage was administered to control any fluctuation. The MAP and NTG rates were observed and recorded at an interval of 5 min for the duration of 1 h. Thus, the time synchronized records of input and output data of MAP change and drug rate were generated for modeling.

Modeling and simulation platform

Matlab® version 2017a with Model Predictive Control toolbox was used for modeling purpose, and Simulink® was used to simulate the runs of the model developed.

System identification

System identification is the procedure of developing or improving the mathematical representation of a biological or a physical system using an experimental dataset. The model parameters are computed from the system matrices obtained from real-time data. System identification is required to create models of dynamic systems that cannot be modeled from first principles or specifications. In this work, the patient is construed as plant/model. Drug disposition among patients is extremely complex with high intra subject variability . The parameter values of a human model changes with respect to several intrinsic or extrinsic factors and the modeling cannot be carried out with first parameter mathematical modeling techniques.[4] Hence, to address this, complex higher order human patient system is represented as a first-order system with dead time as shown in Equation (1). It has been observed from clinical studies that the recirculation coefficient α in Equation (1) can be approximated to zero without any deviation in the MAP response. Literature studies have shown that this system, shown in Equation 2, very closely approximates the real-time patient as the dead time accounts for all the response and recirculation delay encountered in an actual patient, hence closely matching a real response.[5,6]

$$\frac{\Delta P_d(s)}{\Delta I(s)} = o\frac{Ke^{-Tds}}{\tau s+1} \quad (2)$$

The estimation of the system model is carried out using the constrained black-box modeling. Black-box models are formulated based on experimental datasets. A purely black-box model is not reliable when the process or the system exhibits significant nonlinear behavior when moving into new operating conditions, which may result from configuration changes, new operating practices, or external factors.[7] In this work, the black-box modeling is used in conjunction with the semi-physical modeling using the a - priori knowledge of the model's physical structure in Equation (2) to estimate the parameters of the black-box model.[8]

System identification on MATLAB

System identification is implemented in MATLAB (for the data modeling) using the System Identification Toolbox. This toolbox uses time-domain and frequency-domain input-output data to identify and modulate continuous-time and discrete-time transfer functions - in this case, the drug infusion volumes, process models, and state-space models.[9] The toolbox performs gray-box system, rather than a binary input, identification for estimating the parameters of a user-defined model. The identified model is used for predicting the system response plant modeling in the Simulink.

System Identification Toolbox enables the estimation of multi-input multi-output continuous or discrete-time transfer functions with a specified number of poles and zeros.[10,11] In cases where a low-order continuous-time model in pole-zero form is required, the toolbox estimates the process models, which are simple transfer functions involving three or fewer poles, and optionally, a zero, a time-delay, and an integrator.[12]

System process modeling: Procedure

The input and output matrices for each data set are first obtained using the data. For modeling using system identification, the matrices generate a unique data-object for each patient.[13] This is carried out using the MATLAB keyword id data, as shown in Equation (3).

$$data = id\ data\ (y,u,T_s) \quad (3)$$

This creates an id data object containing the time-domain output signal y and input signal u, respectively. T_s specifies the sampling interval of the experimental data. Figure 1 shows the data object so obtained that is imported to the System Identification Toolbox.

In the System Identification Tool graphical user interface, working data refer to estimation data. Similarly, validation data refers to the data set used to validate a model.[14,15] Residual analysis is performed using the validation data. The working data are then used to estimate the process model shown in Figure 2. The estimation is carried out using one of the numerical methods such as the Gauss-Newton, Adaptive Gauss-Newton, Levenberg-Marquardt, Trust Region Reflective Newton or Gradient Search, depending on the type and nature of the data.[16,17]

The system then computes and estimates the values of gain K, time constant T_{p1} and the time delay T_d, as shown in Figure 3. The output MAP for the same set of input NTG is also computed for the estimated patient model using time plots, the MAP output simulated from the estimated first-order dead time patient model closely follows the MAP measured from the patient during the conventional administration.[18,19] This proves that the model obtained using system identification considers the recirculation delay, initial delay, and disturbances that affect the patient's response to the drug in a real-time scenario.[20,21]

MODELS OBTAINED FROM CLINICAL STUDY DATA

This study aims at modeling the response of the patient MAP to the vasodilator drug NTG. Clinical data were used to derive the mathematical representation of the model, called data-driven model. Through this process, an accurate model can be constructed quickly, and the model can be well trusted because the data obtained from the actual system are used to derive it. To find the SISO model parameters, the previously described system identification algorithm based on the black-box step response modeling has been used. Table 1 gives the estimated values of K, T_d, and τ for all patients.

Literature study, it was found that the steadystate gain was found highly variable and can differ as much as 36 fold

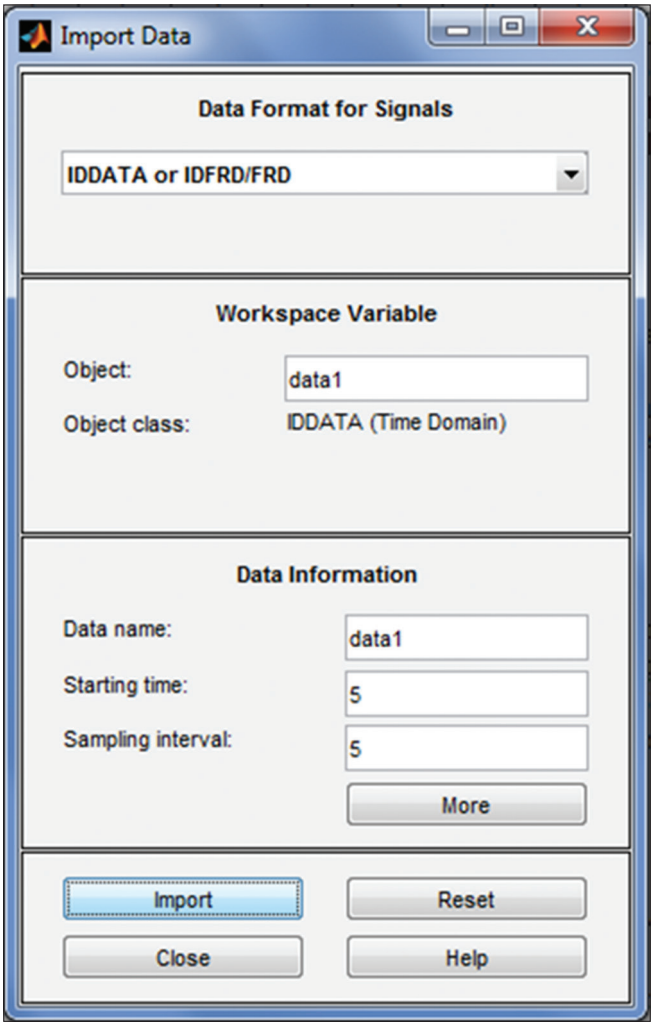

Figure 1: Import of data object for system identification

Table 1: Estimated model parameters for patients

Patient No.	K mmHg $(mlh^{-1})^{-1}$	τ (s)	T_d (s)
1	−3.81704	285.66	29.675
2	−0.5876	0.0067	6.9843
3	−0.63	32.67	120.98
4	−2.2323	11.8345	0.00132
5	−2.276	5.9766	9.978
6	−4.675	0.002	143.87
7	−6.4367	2.8856	102.54
8	−15.564	31.39	4.9875
9	−187.87	2.9976	1.1786
10	−340.78	58.567	148.2

from one subject to another.[2] Based on the obtained model parameter values, the patients can be classified as "slow responders", "normal responders" and "fast responders." This classification has been arrived at after studying the sensitivity, time constant, and the time delay of each patient. The patient models with large values of delay time and low magnitude of sensitivity were found to be less

Table 2: Classification of patients based on the estimated models

Parameter	Slow responders	Normal responders	Fast responders
K Steady-state gain mmHg $(mlh^{-1})^{-1}$	−2.17	−7.23	−64.35
T time constant (s)	160.60	9.98	4.45
T_d time delay (s)	76.42	64.82	2.60

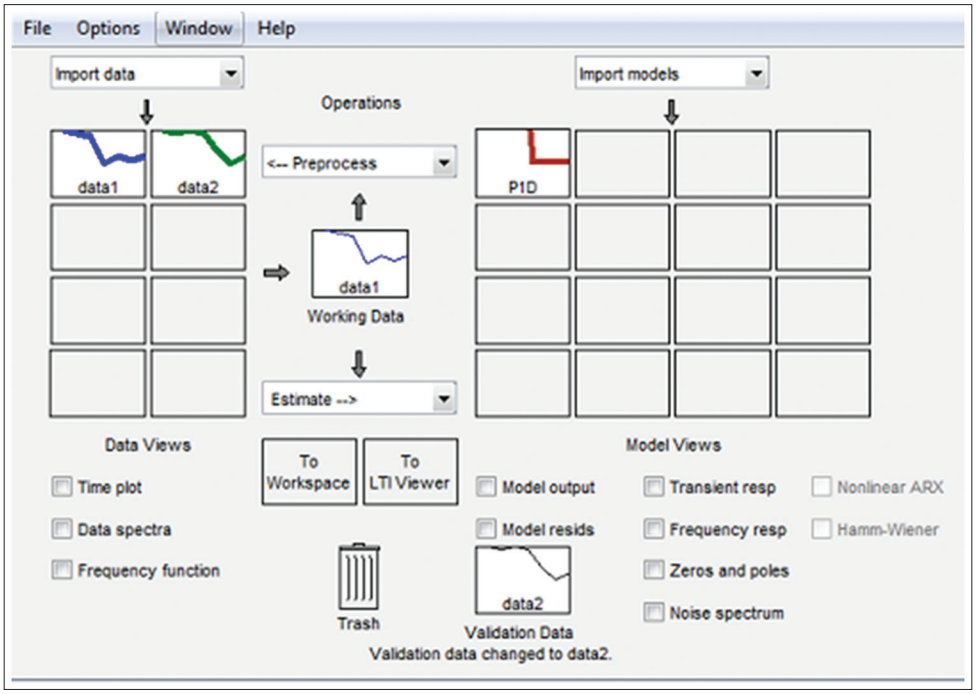

Figure 2: System Identification Toolbox graphical user interface and process modeling to estimate the unknown parameters

responsive to the drug NTG. On the other hand, patient models with a high magnitude of sensitivity value and low delay time were found to be highly responsive to the drug. In this study, the patients were in the age group of 30–55 years and were all diagnosed with hypersensitivity. The gender distribution was equal among the 10 patients. Thus, the entire study was carried out on patients with similar physiology and the obtained models very closely satisfied the properties of the actual patient.[12]

MODEL VALIDATION

The parameters obtained in Section III were used to model the patients, and a simulation experiment was carried out using Simulink, as shown in Figure 4. For each patient model, the simulation drug input was the same as the drug input measured during the measured response. Thus, the same drug dosage is given over the same period to the patient model. The simulation output is the patient MAP.

A plot of MAP (mmHg) versus Time (s) was obtained. The accuracy of the obtained SISO models was validated through the output. This illustrates the measured MAP of a patient and the MAP obtained from the patient model, respectively,

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Process model with transfer function:
                Kp
G(s) = ---------- * exp(-Td*s)
              1+Tp1*s
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Figure 3: Estimated model parameters

for the same set of drug input. From the graphical analysis of all sets of patient data, it was observed that the measured MAP of the patient and the MAP reading obtained from the simulation using the estimated patient model showed the same trend with a deviation of approximately 21%.

RESULTS AND DISCUSSION

The design of patient models as responsive, less responsive, and normal patients as discussed in the previous section was found to be similar to the general classification proposed by Slate *et al*. for the effect of SNP on MAP. At present, the use of SNP during anesthesia and surgery is controversial.[17] This is because it increases the risk of intrapulmonary shunting. This necessitates the use of additional blocking agents to minimize the undesired effects. Therefore, the SNP is being

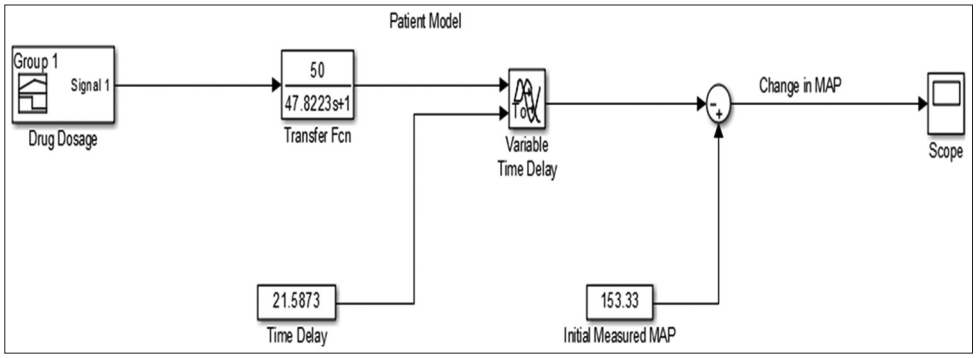

Figure 4: Simulation block diagram for model validation

replaced by NTG. With the use of NTG, there is significantly less blood loss and no ECG changes suggestive of myocardial ischemia. Thus, NTG is being successfully utilized worldwide to control mean arterial blood pressure.

CONCLUSION

In this paper, the effect of NTG on the MAP was studied through clinical observation of with similar physiological standing. The patient parameters obtained using the estimated models have been tabulated in Table 2. The table portrays the average value of each parameter for the three patient types. This classification makes it possible to standardize the patient model during the design phase for the control of MAP. Thus, standard models can be designed for each response, less responsive, and normal case and the gain values can be tuned to obtain the model that accurately describes each patient. The mathematical modeling of the patient's MAP response to the NTG, which has been derived in this paper, can be used in all types of linear control systems for software simulation. The models can also be converted suitably and used in embedded control systems to test and verify various control algorithms for the control of MAP.

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