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A Model Predictive Control Approach for Optimal Drug Administration

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The barriers between systems engineering and medicine are slowly eroding as recently it has become evident that medicine has a lot to gain by systems technology. In particular, the drug administration problem can be cast as a control engineering problem, where the objective is to keep the drug concentration at certain organs in the body close to desired set-points. A number of constraints render the problem rather challenging. For example, hard constraints may be posed on the drug concentration in blood, because a higher than a certain limit concentration may render the drug effects adverse and toxic. In this paper we show that a popular method for tackling chemical engineering control problems can be used for determining the optimal drug administration. Specifically, the Model Predictive Control (MPC) technology is used for taking optimal decisions regarding regulation of drug concentration in the human body, while incorporating constraints on both drug concentration and drug infusion rate.

1. Introduction

Pharmacokinetics is the study of the drug/xenobiotic-organism interaction, in particular the investigation of absorption, distribution, metabolism, excretion and toxicological (ADMETox) processes. In pharmacokinetics, mathematical modeling has historically played a vital role. A mathematical model in pharmacokinetics is a set of mathematical equations, which can be used to characterize with reproducibility, the behaviour and fate of a drug in a biological system when it is given by a certain route of administration and in a particular dosage form. Several types of mathematical models have been used in the field, including non-compartment models, compartment models and physiologically-based models (Shargel et al., 2004).

The barriers between systems engineering and medicine are slowly eroding as recently it has become evident that medicine has a lot to gain by systems technology. A family of models that are very popular and have been used with success in many engineering disciplines are the so-called black box models, i.e. models that describe the effect of system inputs on system outputs, and are mainly developed using input-output data, i.e. no fundamental equations are involved in the development of this particular type of

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models. These models range from simple-structured linear models to more complicated models, which are based on computational intelligence technologies, such as neural networks and fuzzy logic. Process control is an important engineering discipline that deals with architectures, mechanisms, and algorithms for controlling the output of a specific process.

The black-box modelling and the process control concepts can be easily applied to pharmacokinetics, by considering the body as a system, where drug administration is the input to the system, while drug concentrations in blood and/or specific organs of interest are the system outputs (Gaweda et al., 2003; Bailey and Haddad, 2005). The input-output data which are required in order to build black-box models are often available in the form of concentration-time profiles, i.e. plots of concentrations as functions of time, following the administration of the organism with a drug dose. Concentration-time profiles can be considered as surrogates of the complex processes involved in the processes of absorption, distribution, metabolism and excretion of the drug. Additionally, the drug administration problem can be cast as a control engineering problem, where the objective is to keep the drug concentration at certain organs in the body close to desired set-points. A number of constraints render the problem rather challenging. For example, hard constraints may be posed on the drug concentration in blood, because a higher than a certain limit concentration may render the drug effects adverse and toxic.

In this paper, we show how linear Finite Impulse Response (FIR) black-box models can be developed using available experimental concentration-time profiles. The procedure resembles the popular step response or pulse-response methods for developing dynamic models for conventional engineering systems (Maciejowski, 2002). Then, the FIR models are incorporated in the formulation and solution of a control problem which aims at determining the optimal drug administration. Specifically, the Model Predictive Control (MPC) technology (Pannocchia and Brambilla, 2006) is used for taking optimal decisions regarding regulation of drug concentration in the human body, while incorporating constraints on both drug concentration and drug infusion rate. The MPC methodology is based on the formulation and solution of an optimization problem where the objective function contains the deviation of the predicted controlled variable from a desired set point over a prediction horizon and the control effort over a control horizon. Several MPC formulations can take into account the system limitations, by formulating and incorporating appropriate mathematical constraints.

2. Development of finite impulse response model

As mentioned in the introduction, for many drugs concentration-time profiles are available, which show drug concentration responses after the administration of an organism with a drug dose. These data are often population data, i.e. they include concentration-time responses for several individuals, describing in this way the differences in concentration responses between patients. The method described in this paper is generic and can be used to any particular case where the necessary data are available, after adjusting appropriately the time and magnitude scales. The method will be based on the population concentration-time profiles depicted in Figure 1, which

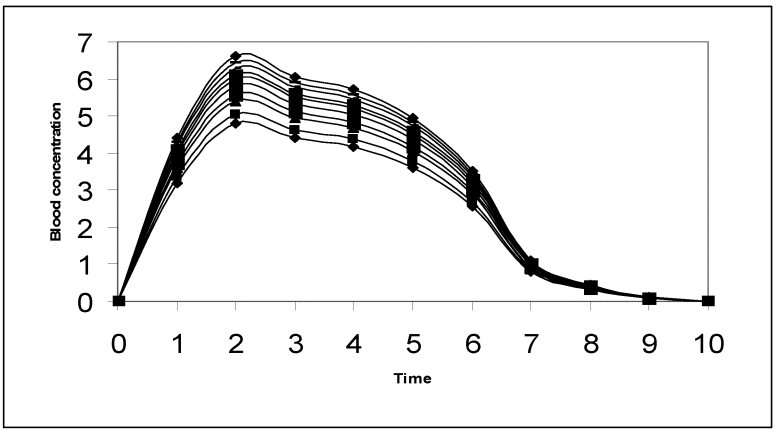

Figure 1. Concentration-time profiles.

includes blood concentration-time profiles for 10 different patients, following the oral administration with a drug dose of magnitude 1 (for example a tea-spoon dose). The data are artificial, but typical of concentration-time profiles for different individuals.
The FIR model is of the following form:

$$C_p(k) = H_1 u(k-1) + H_2 u(k-2) + \cdots + H_N u(k-N) = \sum_{i=1}^{N} H_i u(k-i) \quad (1)$$

where $C_p(k)$ is blood concentration at time instance *k*, $u(k-1)$ is drug administration at time instance *k-i* and $H_i,\ i = 1,...N$ are the FIR model coefficients. The method for obtaining the model coefficients assuming a linear model is standard and is briefly described next:
If the model is applied on one concentration-time profile of figure 1, this corresponds to a drug administration where $u(0) = 1$ and $u(l) = 0,$ for any $l \neq 0$. Therefore, using the model (1) it holds that $H_i = C_p(i),\ H_i, i = 1,...N$, where $C_p(i)$ is blood concentration at time instance *i* on the particular concentration-time profile of figure 1. The fact that after sufficient time, the blood concentration becomes zero indicates a stable system and that *N* is finite. One additional important note is the following: Since multiple concentration time-profiles are available, there are multiple $C_p(i)$ values at each time instance. If we denote as $C_{p,\max}(i), C_{p,\min}(i)$ the maximum and minimum values at time instance *i,* H_i is finally obtained as the average (i.e. $H_i = (C_{p,\max}(i) + C_{p,\min}(i))/2$. In addition, the maximum modelling error for coefficient H_i is defined as $E_i = C_{p,\max}(i) - (C_{p,\max}(i) + C_{p,\min}(i))/2 = C_{p,\max}(i) - H_i$. It should be mentioned that the FIR modelling methodology is adequate for this study for two reasons: Firstly, the

produced model is linear and thus, the MPC problem that will be formulated in the next section is quadratic, and thus, tractable. Secondly, it needs only a limited set of data as opposed to other black-box modelling techniques (for example neural networks), where larger data sets are necessary.

3. Model predictive control for optimal drug administration

Model Predictive Control has emerged over the last decade as a very attractive scheme for controlling complex systems due to its capability to handle modeling errors and process constraints. The major attraction of MPC algorithms lies on the long range predictive horizon and the fact that the control law is not fixed, but it is based on on-line optimization. This makes it possible to deal with:

- Multivariable systems;
- Constraints on the manipulated or controlled variables;
- Model uncertainty. The objective of an MPC system design should be robust performance, i.e. the controller should be designed so that the closed loop performance specifications are met despite the system/model mismatch.

The main idea behind MPC-type control is the following: At sampling time *k*, a set of *m* future manipulated variable moves (control horizon) are selected, so that the predicted response over a finite horizon *p* (prediction horizon) has certain desirable characteristics. This is achieved by minimizing an objective function based on the deviation of the future controlled variables from a desired trajectory over the prediction horizon *p*. The MPC optimization is performed for a sequence of hypothetical future control moves over the control horizon and only the first move is implemented. The problem is solved again at time *k*+1 with the measured output $C_p(k+i)$ as the new starting point. Model uncertainty and unmeasured process disturbances are handled by calculating an additive disturbance as the difference between the process measurement and the model prediction at the current time step. For the measured disturbances it is assumed that the future values will be equal to the current value.
The exact MPC formulation is the following:

$$J(k)=\sum_{i=1}^{p}\Theta\left(\hat{C}_p(k+i\,|\,k)-C_p^{sp}\right)^2+\sum_{i=1}^{m}\left(R_i^{1/2}\Delta v(k+i)\right)^2 \tag{2}$$

subject to the following constraints:

Model-based prediction: $$\hat{C}_p(k+i\,|\,k)=d(k\,|\,k)+\sum_{j=1}^{i}H_i u\left(k+i-j\right)+\sum_{j=i+1}^{N}H_i v\left(k+i-j\right) \tag{3}$$

Disturbance estimation: $$d(k\,|\,k)=C_p(k)-\hat{C}_p(k\,|\,k)=C_p(k)-\sum_{j=1}^{N}H_i u\left(k-j\right) \tag{4}$$

Input move constraints: $$-\Delta u_{\max}\le\Delta v(k+i)\le\Delta u_{\max},\quad 0\le i\le m \tag{5}$$

Input constraints: $u_{\min} \le v(k+i) \le u_{\max}, \quad 0 \le i \le m$ (6)

Output constraints: $\hat{C}_p(k+i \mid k) \le C_{p,\max}, \quad 0 \le i \le p$ (7)

End condition: $v(k+m+i) = \left(1 \Big/ \sum_{i=1}^{N} H_i\right)\left(C_p^{sp} - d(k \mid k)\right), \quad i \ge 0$ (8)

where Δ is the backward difference operator, i.e. $\Delta v(k+i) = v(k+i) - v(k+i-1)$; $\hat{C}_p(k+i \mid k)$ is the FIR model prediction generated at time point *k*, for the value of blood concentration at time point *k*+*i*; C_p^{sp} is the desired drug concentration in blood; $d(k \mid k)$ is the current disturbance defined as the difference between the actual drug concentration in blood and the FIR model prediction; $u(k-1), u(k-1), \ldots, u(k-N)$ are the drug doses at time points *k*-1, …, *k*-*N*; $v(k), v(k+1), \ldots, v(k-m)$ and $\Delta v(k), \Delta v(k+1), \ldots, \Delta v(k-m)$ are decision variables; $u_{\max}$ and $u_{\min}$ are the upper and lower values on $v(k+i), \quad 0 \le i \le m$ respectively; $\Delta u_{\max}$ is the upper bound on the absolute value $\Delta v(k+i), 0 \le i \le m$; $C_{p,\max}$ is an upper bound on the predicted levels of drug concentration in blood; Θ is the weight for the output deviation term in *J*(*k*); $R_i \quad 0 \le i \le m$ are the input move suppression coefficients in *J*(*k*).

4. Results

The simulation presented in this paper assumes that the MPC methodology, where the FIR model has been developed as shown in section 3, is applied on the individual patient corresponding to the concentration-time response with the highest concentration peak (i.e. the highest modeling error is assumed). The objective is to achieve a drug concentration in blood as close to C_p^{sp}=10 as possible.

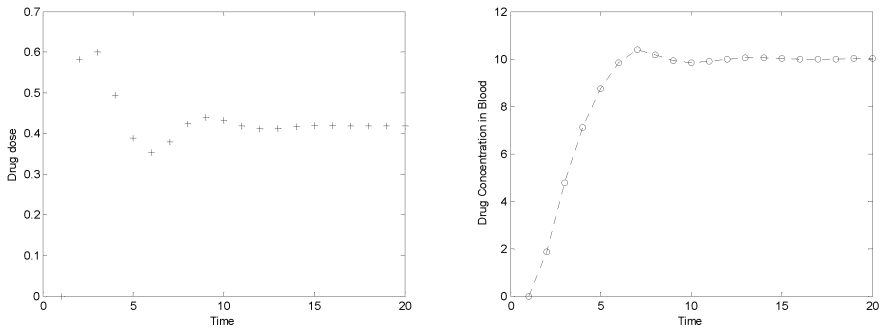

Figure 2. Optimal drug administration and drug-concentration time profile.

The following bounds were used: $u_{\min} = 0$, $u_{\max} = 0.6$, $\Delta u_{\max} = 0.2$, $C_{p,\max}$=12 . Weights Θ and R_i were calculated using the method described in Vuthandam et al., 2005, which guarantees robust stability and performance, even in the presence of the highest modeling error, computed in section 2. The prediction and control horizons were set to 15 and 10 respectively. Due to the linear nature of the FIR model the quadratic programming MPC problem is solved with small computational effort (less than 1 s is needed using MATLAB in a PC with a Dual Core 2.4Ghz processor), while convergence is guaranteed. The linear nature of the FIR model becomes even more important when the manipulated variable (drug dose) is limited to take discrete values from a finite set. In this case the resulting MPC optimization problem is formulated as a Mixed Integer Quadratic Programming (MIQP) problem, which is more computationally intensive, but still tractable. If a nonlinear model is used, the resulting Mixed Integer NonLinear Programming (MINLP) problem is difficult to solve. The concentration response and the optimal drug administration are shown in figure 2, which illustrates the efficiency of the method. It is clear that regardless of the modeling error that was introduced, the control strategy performs with success all the control tasks: the drug concentration settles to the desired set-point and is kept below the upper bound of 12 during the entire simulation, the drug doses do not exceed the maximum bound of 0.6 and two consecutive drug doses do not differ by more than 0.2.

5. Conclusions

In this paper, it has been shown that powerful tools, such as black-box modeling and process control, which are popular in systems engineering, can be used in pharmacokinetics for developing dynamic concentration-time models and for determining the drug administration. The method is successful even in the presence of modeling errors, i.e. it can be used for a wide range of individuals. The method is currently extended to address the cases where drug doses are not continuous variables, but discrete (for example multiple of a minimum dose, such as a pill).

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