A PRELIMINARY STUDY OF MODELING AND SIMULATION IN INDVIDUALIZED DRUG DOSAGE – AZATHIOPRINE ON INFLAMMATORY BOWEL DISEASE

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Abstract: Individualized drug dosage based on population pharmacokinetic/dynamic models is an important future technology used to reduce or eliminate side effects of certain drugs, e.g. cancer drugs. In this paper we report preliminary results from work-in-progress: a simplified linear model of the metabolism of a cancer treatment drug was estimated from experimental data. The model was then validated against the same data as a test of the adequacy of the model structure. From this investigation it became apparent that the model structure could not be used due to its inability to recreate the dynamic properties of the system.

Keywords: azathioprine, inflammatory bowel disease, pharmacokinetic.

1 WHY INDIVIDUALIZED DRUG DOSAGE?

Drug dosage is usually optimized for, and adapted to, average adult white male persons. People who do not belong to that group, e.g. females, children, certain minority groups of people, very often get problems from drugs due to incorrect dosage.

Although there are usually different dosage recommendations for children, and sometimes for females, the dosage is still incorrect in many cases. In fact, there exist a vast number of parameters influencing the decomposition and ingestion of a medical substance in a patient's body, as well as the reactions caused by the substances. At present though, the most common personalization factors that may influence the dosage are whether you are a child or not, and sometimes your sex.

Additionally, incorrect dosage usually leads to over consumption of drugs. The prescription from the doctor is often too much, to be on the “safe” side. This leads to increased costs for society and increased environmental pollution from chemical substances, not to mention the often hazardous treatment the patient has to endure, with possible side-effects and the like.

In order to avoid over consumption of drugs, as well as side effects caused by incorrect dosages, it would be very advantageous if it were possible to adapt drug dosage individually. However, due to the enormous complexity of biological systems, and the difficulty in predicting cellular and subcellular processes, it has not yet been possible to develop concepts for personalized drug dosage.

2 MODELING AND SIMULATION FOR INDIVIDUALIZED DRUG DOSAGE

The main idea of this work is to be able to give each person a personal dosage based on advanced computer simulation and a precise measured biochemical profile of the patient who is about to receive the treatment, as well as known properties of the used drug. This is very important in order to reduce or eliminate side-effects of certain drugs, e.g. cancer drugs such as cytotoxins.

Fig. 1. The metabolism of thiopurines

The specific properties of the drug that are used for computing an optimal personalized dosage are e.g. the effect of the drug on metabolic pathways. Such information may be obtained from existing public data bases, from drug manufacturers, or by experimental measurements from the patient.

3 AZATHIOPRINE AND INFLAMMATORY BOWEL DISEASE

In order to test these ideas, we need a disease and a corresponding drug for which accurate dosage is very important. We selected the disease inflammatory bowel disease (IBD) and the drug 6-mercaptopurine (6-MP) and its derivative azathioprine (AZA).

Inflammatory bowel disease is a serious illness with a number of symptoms in the bowel. Approximately 70000 to 110000 new cases occur annually in Europe (Lindqvist, 2005).

The drug 6-MP/AZA belongs to a special group of drugs, thiopurines, i.e., cytotoxins, see Fig. 1. Drugs within this group are also used for cancer treatment, e.g. treating leukemia for children, and to prevent rejection of transplanted organs (Duley *et al.*, 2005).

During the 60th and the 70th, before treatment by cytotoxins had started, the only way to treat inflammatory bowel disease was to surgically remove part of the small intestine. After a number of such operations, not much remained. Instead, more recently treatment by thiopurines has been introduced with very good effects. Unfortunately, certain patients are very sensitive to the dosage level; very strong side-effects (even deaths) have occurred. Thus, it is very important to be able to reliably predict a suitable individualized dosage level for a specific patient.

4 DETERMINING INDIVIDUALIZED DRUG DOSAGE

Fig. 2 shows the steps needed to obtain/compute an individualized drug dosage:

1. Knowledge from earlier experiments makes it possible to determine the biochemical pathways that describes the most important model equations that determines how 6-MP/AZA is metabolized by the body. If this knowledge is not complete enough, system identification methods may be used for determining the missing model information. In the simplified biochemical path after (1) the substrate A can be viewed as input signal and the metabolite C or the enzyme E4 as an output signal
2. The metabolic pathway is equivalent to a system of differential equations. This can be formulated in various ways, including an explicit state-space formulation where u represents the input signals and y the output signal(s). The state variables are represented by the vector x, whereas the functions f and h are functions relating the variables.
3. The model can be graphically described as a biochemical pathway or as en explicit system of equations.
4. A biological sample from the patient gives the personal biochemical profile that is the basis for computing the individualized dosage. This is typically a blood sample, from which the genotypes for different enzymes can be determined. It can also be used measure the concentration of TPMT, IMPDH, HGPRT, and the metabolites that are created (e.g. TGN and

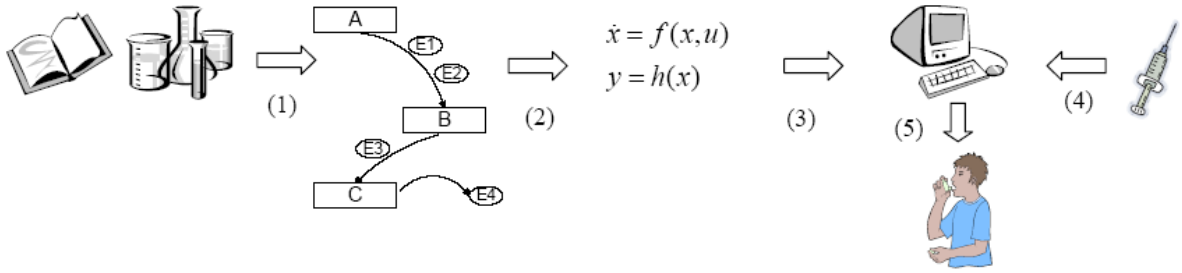


Fig. 2. Flow chart for individualized drug dosage.

5. meTIMP). Also input parameters such as sex, age, and health status influence the biochemical profile.
6. When the biochemical pathway model has been adjusted according to the individual biological sample, i.e., adapted to that individual, it can be used to simulate the effect of different dosage levels and determine a suitable dosage for that patient. Alternatively, a suitable dosage of azathioprine can be directly determined if an exact criterion for the desired treatment effect can be formulated.

5 EXPERIMENTAL DATA

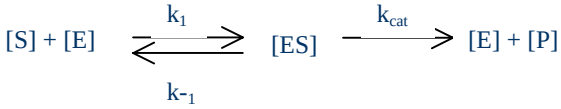
A group of 60 IBD-patients were observed during 20 weeks. Of these, 27 patients completed the study. Measurements were made once a week.

6 PATHWAY MODEL AND A SIMPLIFIED COMMON-SENSE MODEL

Here we present two models of the thiopurine metabolism: a straight-forward mechanistic pathway model, with many unknown parameters, and a simplified "common sense" model based on reasoning about the basic system properties.

6.1 Pathway Model of the System

The following is a pathway model approximately the same as the one in Fig. 3. An arrow in the above pathway means an enzymatic reaction, approximately as follows:



The pathway model contains a number of state variables, corresponding to concentrations of the various metabolites according to (1.1).

$$
\begin{aligned}
x_1 &= [\text{6-MP}] \\
x_2 &= [\text{XO/6-MP}] \\
x_3 &= [\text{TUA}] \\
x_4 &= [\text{TPMT/6-MP}] \\
x_5 &= [\text{meMP}] \\
x_6 &= [\text{HGPRT/6-MP}] \\
x_7 &= [\text{TIMP}] \\
x_8 &= [\text{TGN}] \\
x_9 &= [\text{TPMT/TIMP}] \\
x_{10} &= [\text{meTIMP}]
\end{aligned}
\tag{1.1}
$$

The model, translated to explicit form, would look approximately as (1.2).

$$
\begin{aligned}
\frac{d}{dt}x_1 &= -k_{1,\text{TUA}}(C_1 - x_2)x_1 + k_{-1,\text{TUA}}x_2 \\
&\quad - k_{1,\text{meMP}}(C_2 - x_4 - x_9)x_1 + k_{-1,\text{meMP}}x_4 \\
&\quad - k_{1,\text{TIMP}}(C_3 - x_6)x_1 + k_{-1,\text{TIMP}}x_6 \\
\frac{d}{dt}x_2 &= k_{1,\text{TUA}}(C_1 - x_2)x_1 - k_{-1,\text{TUA}}x_2 - k_{cat,\text{TUA}}x_2 \\
\frac{d}{dt}x_3 &= k_{cat,\text{TUA}}x_2 \\
\frac{d}{dt}x_4 &= k_{1,\text{meMP}}(C_2 - x_4 - x_9)x_1 - k_{-1,\text{meMP}}x_4 \\
&\quad - k_{cat,\text{meMP}}x_4 \\
\frac{d}{dt}x_5 &= k_{cat,\text{meMP}}x_4 \\
\frac{d}{dt}x_6 &= k_{1,\text{TIMP}}(C_3 - x_6)x_1 - k_{-1,\text{TIMP}}x_6 - k_{cat,\text{TIMP}}x_6 \\
\frac{d}{dt}x_7 &= k_{cat,\text{TIMP}}x_6 - k_{1,\text{meTIMP}}(C_2 - x_4 - x_9)x_7 \\
&\quad + k_{-1,\text{meTIMP}}x_9 - f(x_8) \\
\frac{d}{dt}x_8 &= \ldots \\
\frac{d}{dt}x_9 &= \ldots \\
\frac{d}{dt}x_{10} &= \ldots
\end{aligned}
\tag{1.2}
$$

However, there are far too many unknown coefficients in this model, compared to the few data points available. We will need to create a model with fewer parameters in order to make progress.

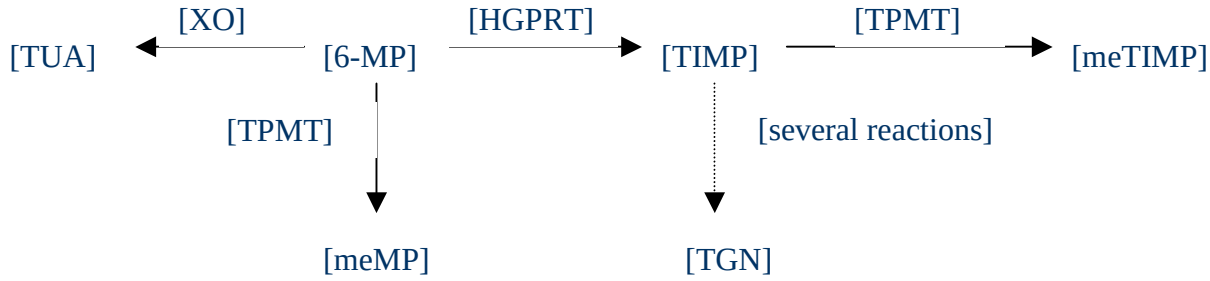


Fig. 3. A pathway model of the thiopurine metabolism.

6.2 *Simplified "Common-Sense" Model*

As already mentioned, the pathway model has far too many unknown parameters to estimate from the scarce data. Instead we create the following simplified common sense model with only 7 unknown parameters to estimate:

$$\begin{aligned}&[meTIMP]_{t+1}\\&= -k_{meT}[meTIMP]_t + k_{meT,AccD}AccD_t\end{aligned}$$

$$\begin{aligned}&[TGN]_{t+1}\\&= -k_{TGN}[TGN]_t + k_{TGN,AccD}AccD_t\end{aligned} \qquad (1.3)$$

$$\begin{aligned}&[WBC]_{t+1}\\&= -k_{WBC,meT}[meTIMP]_t - k_{WBC,TGN}[TGN]_t\\&\quad + k_{WBC}(WBC_0 - [WBC]_t)\end{aligned}$$

Here AccD = the accumulated weekly dosage (i.e. total dosage during one week), RBC means Read Blood Cell, WBC means White Blood Cell, and WBC0 = WBC during week 0, which is assumed to be the normal body concentration in blood of the quantity in question.

7 SYSTEM IDENTIFICATION OF MISSING PARAMETER VALUES

In order to use the above model for simulation of drug concentration effects, we need to estimate the seven unknown parameters from the patient data.

This is done using a grey-box model, where the system identification process and the limitations for the specific problem are shown in Fig. 4.

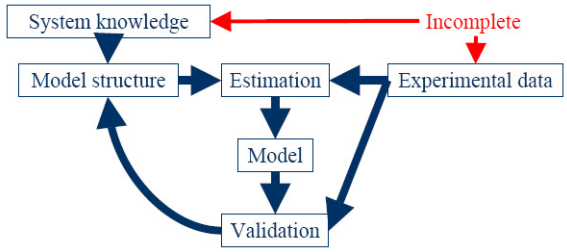


Fig. 4. The grey-box identification process

We use the linear grey-box model (1.4) for identification.

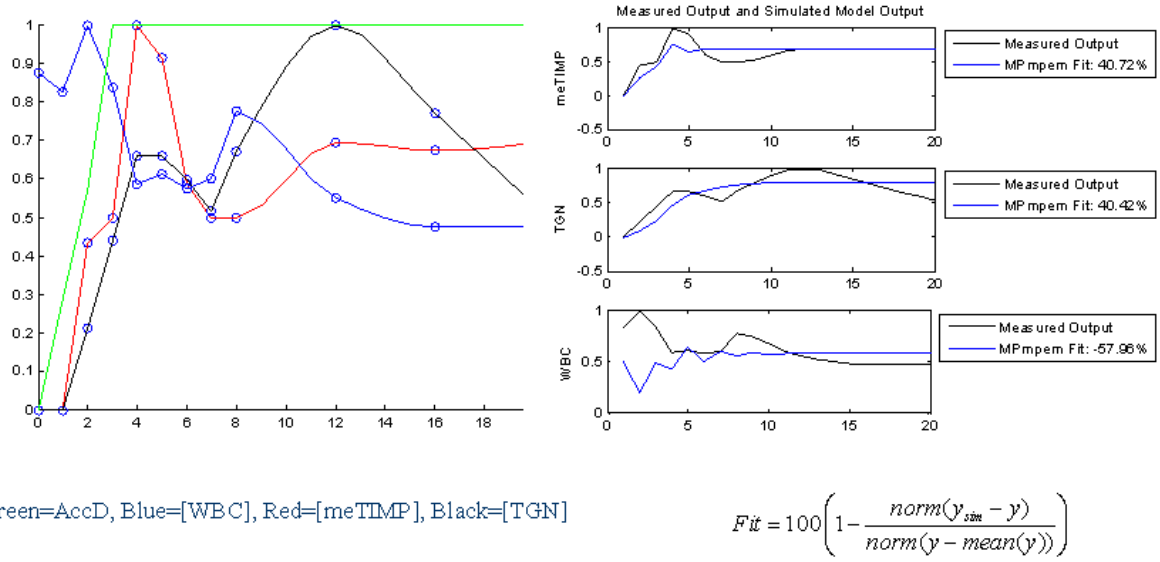
$$x(t+1) = Ax(t) + Bu(t)$$

$$A = \begin{pmatrix} -k_{meT} & 0 & 0 \\ 0 & -k_{TGN} & 0 \\ -k_{WBC,meT} & -k_{WBC,TGN} & -k_{WBC} \end{pmatrix} \qquad (1.4)$$

$$B = \begin{pmatrix} k_{meT,AccD} & 0 \\ k_{TGN,AccD} & 0 \\ 0 & k_{WBC} \end{pmatrix}$$

8 RESULTS

The parameters of the linear “common sense” model were estimated with patient measurements as output data and drug dosage as input data. The ability of the model to recreate the properties of the system, i.e., the curve fitting to patient data was evaluated for 8 patients. One such example is shown in Fig. 5. Parameter estimations were made in Matlab using the System Identification Toolbox. If the future nonlinear model (see below) proves to be a better choice, OpenModelica (Fritzson *et al.*, 2005), (Fritzson, 2004) will be used for simulation purposes.



$$Fit = 100\left(1 - \frac{norm(y_{sim} - y)}{norm(y - mean(y))}\right)$$

Fig. 5. The simplified model used to simulate the response for patient 19, compared to experimental data.

Ideally, the simple model would fit reasonably well to the measured output data and certainly capture the dynamics of the system, such as number of peaks. The model is able to capture some aspects, see Fig. 5, especially for the first two equations but there are still large deviations between the simulated and measured results. Thus, our model is apparently too simple. There are probably important nonlinear effects in the drug metabolism that are not part of this simple model. Another thing that should be taken into account is the frequency of the dose distribution that can have an effect on the blood concentrations (Bell *et al*., 2004).

9 CONCLUSION AND FUTURE WORK

We have done a preliminary study of modeling and simulation in individualized drug dosage, employing the drug 6-MP/AZA for treatment of IBD. An experimental study of a group of patients was made. The data was used to estimate unknown coefficients in a linear "common sense" model. Due to the simplicity of the model it was not able to recreate the measured output data used to estimate the parameters.

The next step will be to create a more complex model that can capture more of the possible nonlinear effects in the metabolism. A new experimental study will be needed to calibrate that model, i.e., to capture data on more of the detailed dynamics of the metabolism.

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