Framework and Tools: A Framework for Modelling, Optimization and Control of Biomedical Systems

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1.1 Mathematical Modelling of Drug Delivery Systems

Drug delivery can be defined as the process of administering a pharmaceutical agent in the human body, including the consequent effects of this agent on the tissues and organs. Mathematical modelling of drug delivery can be divided into two different yet complementary approaches, the pharmacokinetic and pharmacodynamic approaches. Pharmacokinetics describes the effect of the drug in the body, by capturing absorption, distribution, diffusion and elimination of the drug. Pharmacodynamics describes the effects of a drug in the body, which are expressed mathematically by relations of drug dose–body responses. Usually, modelling of the drug delivery system requires a pharmacokinetic part, a pharmacodynamics part and a link between the two (Figure 1.1).

1.1.1 Pharmacokinetic Modelling

Two approaches for pharmacokinetic models dominate the literature, the compartmental models and the physiologically based pharmacokinetic models.

1.1.1.1 Compartmental Models

The basic idea of compartmental modelling is to group organs with similar properties, such as the well-perfused organs, in one compartment and describe the uptake based on these tissues' properties (e.g. drug solubility and perfusion). The basic assumptions of compartmental modelling are: (a) homogeneity: uniform distribution and instant mixing within the compartment; (b) conservation of mass;

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Figure 1.1 Mathematical representation of a drug delivery system. *Source:* Ette and Williams (2007). Reproduced with permission of John Wiley and Sons.

(c) the intrinsic properties are constant (e.g. temperature and volume); (d) there are no time delays between compartments; and (e) all exiting fluxes are linearly proportional to the drug concentration in the compartment.

The simplest approach is to consider the whole body as one single compartment in which the drug is administered and also eliminated. Usually, this mathematical approach is used for the description of drugs that are intravenously injected and well diffused, the elimination of which follows first-order kinetics. Practically, within the human body, usually more than one compartment is considered due to the slow diffusion of the drug to the peripheral tissues (Figure 1.2).

There are several challenges related to compartmental model development, such as the correlation of the model parameters (e.g. transfer coefficients) to physiological parameters, as well as difficulties related to the determination of the appropriate number of compartments that should be used in order to represent the pharmacokinetics of a population. Furthermore, the ability of these models to give a valid estimation of the drug profile of a newly studied patient is rather questionable. The major source of model uncertainty is due to the fact that the values of the variables are based on the interpretation of the mean concentration profile of a group of patients. This *mean concentration profile* in most of the cases is not representative of the behaviour of patients in the group studied, let alone the whole patient population. These drawbacks are satisfied to a certain extent by the physiologically based pharmacokinetic models.

Figure 1.2 Schematic of a two-compartment pharmacokinetic model. *Source:* Saltzman (2001). Reproduced with permission of Oxford University Press.

1.1.1.2 Physiologically Based Pharmacokinetic Models

Physiological models are high compartmental models that use existing knowledge of the physiological mechanisms which regulate the drug action. These models capture the administration, diffusion and elimination of a drug in body organs that react with the drug. The drug mass balance for each organ can be described by Equation 1.1 (Saltzman, 2001):

$$V_i \frac{dC_i}{dt} = Flow_{in} - Flow_{out} - q_{el,i} V_i \quad (1.1)$$

where i is each specific organ/compartment, V_i is the organ volume, C_i is the drug concentration in the organ/compartment i , $q_{el,i}$ is the rate of drug metabolism in the organ/compartment i , and $Flow_{in}$ and $Flow_{out}$ are the inflow and outflow of the drug in the organ/compartment i .

A schematic overview of a physiological pharmacokinetic model, where each body organ is considered an independent compartment, is shown in Figure 1.3.

This modelling approach requires an in-depth understanding of the physiology, but it describes more accurately than empirical compartmental models the drug delivery system. The advantages of physiologically based models over empirical compartmental models lie in the ability to be extrapolated between different species and different drug dosages (Cashman *et al.*, 1996; Saltzman, 2001). The main drawback of physiologically based models is that, sometimes, certain parameters cannot be measured, and their values are difficult to be accurately predicted.

The description of one compartment itself in either of the previously mentioned approaches can be described by complex interactions and flows between, for example, blood cells, plasma, intestinal fluid, a rapid interactive pool and a slow interactive pool.

Both compartmental and physiological models range from simple to more detailed models that are based on fewer assumptions. Simplifications in the previous scheme can be made, depending on the exact system which is studied. In Figure 1.3, organs which do not contain important amounts of the drug agent can be neglected (Saltzman, 2001). However, the level of detail added to the model depends on the data availability and the purpose of the model.

1.1.2 Pharmacodynamic Modelling

Pharmacodynamic models describe the effect of a drug in the body (i.e. the impact of a drug that enters the cell on the cellular function). Due to the high complexity of the drug mechanism of action that enables precise measurements of the drug effect, detailed pharmacodynamic models are not in use and empirical expressions which correlate the drug concentration with the drug effect are

Figure 1.3 Schematic of a physiological pharmacokinetic model. *Source:* Saltzman (2001). Reproduced with permission of Oxford University Press.

more preferable (Holford & Sheiner, 1982). Practically, the pharmacodynamic model is determined by testing potential models and estimating the parameters when a reference pharmacokinetic model is used, and the accuracy of the pharmacodynamic model is highly dependent on precision of the pharmacokinetic model. The usage of a pharmacokinetic model is essential for the valuable expression of a pharmacodynamic model, as the latter assumes that the concentration of the drug is in equilibrium with the effect site, which might be the case only in the steady state.

Table 1.1 The most common types of empirical pharmacodynamic models.

Model	Model equations	Description
Fixed-effect model	–	Effect: present (1) or absent (0), or degree of effect
Linear model	$E = S \cdot C + E_o$	E = drug effect, C = drug concentration, S = slope parameter, E_o = initial drug effect
Log-linear model	$E = S \cdot \log C + I$	E = drug effect, C = drug concentration, S = slope parameter, I = constant
$E_{\max}$ model	$E = E_o - \frac{E_{\max} \cdot C}{EC_{50} + C}$	E = drug effect, C = drug concentration, $E_{\max}$ = maximum drug effect, E_o = initial drug effect from previous application, EC_{50} = concentration producing half of the maximum drug effect
Sigmoid $E_{\max}$ model	$E = \frac{E_{\max} \cdot C^n}{EC_{50}^n + C^n}$	E = drug effect, C = drug concentration, $E_{\max}$ = maximum drug effect, E_o = initial drug effect from previous application, EC_{50} = concentration producing half of the maximum drug effect, n = constant affecting the shape of the drug effect–concentration curve

Source: Holford and Sheiner (1982). Reproduced with permission of Elsevier.

In general, pharmacodynamics is the study of dose–response relationships. For the development of pharmacodynamic models, target cells are exposed *in vitro* in different drug concentrations, and drug effect curves are obtained. These data are then used to fit empirical pharmacodynamic models (Table 1.1). An example of a common dose–response curve is presented in Figure 1.4. The drug effect curves are of crucial importance, especially for the early clinical trial phases, for the determination of maximal dose effect as well as for estimation of the effective drug dosing window.

1.2 Model analysis, Parameter Estimation and Approximation

Model analysis includes analysis of parameters and variables of the developed pharmacokinetic model, in order to define uncertainty of parameters. This uncertainty usually originates from inter-patient or experimental variability. In a consecutive step, the model is analysed towards its most influential parameters and variables. The methods that are usually used in order to obtain in-depth understanding of the model are global sensitivity analysis, variability analysis, parameter estimation and parameters correlation.

Figure 1.4 Illustration of a pharmacodynamic dose–response curve.

1.2.1 Global Sensitivity Analysis

Global sensitivity analysis allows the understanding and identification of crucial model parameters that affect the model output. In the case of mathematical models that describe biomedical systems, global sensitivity analysis enables the identification of the relative influence of parameters of the pharmacokinetic and/or pharmacodynamic part of the model, on the model output. Performance analysis is conducted in the graphical user interface/high-dimensional model representation (GUI-HDMR) software, which uses random sampling HDMR (RS-HDMR) to construct an expression for the output as a function of the parameters with orthogonal polynomials. This expression accounts for up to second-order interactions and corresponds to the ANOVA decomposition truncated to the second order. From the coefficients of the representation, the sensitivity index is derived. The sensitivity indices are calculated based on partial variances, which themselves are calculated from the approximation of the model by orthonormal polynomials (Li *et al.*, 2002; Ziehn and Tomlin, 2009).

1.2.2 Variability Analysis

Variability analysis focuses on the identification of the influence of the individual parameters and variables on the model outputs. Global sensitivity analysis gives a measure of the relative influence of each parameter on the output. However, that approach does not incorporate whether a higher or lower

value of the parameter or variable of interest is increasing or decreasing the model output. Variability analysis enables the detection of the influence of each parameter and variable on the output, therefore facilitating the understanding of the actual physical influence of the pharmacokinetic and pharmacodynamic variables and parameters. In particular, when performing variability analysis, an investigation of whether an increase in the pharmacokinetic and/or pharmacodynamic variable or parameter increases or decreases the model output, y , takes place (Equation 1.2):

$$P_{\%,i} = \frac{y_{max,i} - y_{min,i}}{y_{nom}} \quad (1.2)$$

where $P_{\%,i}$ is the percentage of change due to an increase in variable or parameter i , $y_{max,i}$ is the upper bound model output, $y_{min,i}$ is the lower bound model output and y_{nom} is the calculated nominal model output.

1.2.3 Parameter Estimation and Correlation

Parameter estimation is the process of fitting the model parameters to clinical data. If the parameters are estimated with high precision, then the model's response is closer to reality. The parameter estimation problem is evaluated by the correlation matrix C of the estimated parameters. An entry in the off-diagonal elements of the correlation matrix C close to one ($|C_{ij}| \approx 1$) indicates a high correlation of the corresponding parameters i and j , whereas an entry of zero ($C_{ij} \approx 0$) indicates no correlation. The entries of the correlation matrix are calculated based on the variance–covariance matrix V , the variance of a parameter is given on the diagonal (V_{ii}) and the covariance of two parameters i and j is given on the off-diagonal elements (V_{ij}).

$$C_{i,j} = \frac{V_{i,j}}{\sqrt{V_{ii}V_{jj}}}, i \neq j \quad (1.3)$$

$$C_{ii} = 1 \quad (1.4)$$

1.3 Optimization and Control

Mathematical optimization and control of biomedical systems could lead to a better prediction of the optimal drug and/or therapy treatment for a specific disease. Advanced mathematical and computational techniques such as multiparametric predictive control, sensitivity analysis and model reduction are extensively discussed in Chapter 2. Moreover, those techniques are applied in a variety of diseases (i.e. anaesthesia, diabetes and leukaemia) that are further discussed in the following chapters.

Figure 1.5 Framework towards optimal drug delivery systems.

Anaesthesia (see Chapters 3 and 4) is a process which provides hypnosis, analgesia and muscle relaxation while maintaining the vital functions of a living organism. For efficient prediction and control of this bio-process, a model predictive controller (see Chapter 2) is required.

In *type 1 diabetes* (see Chapter 5), the goal is to maintain the blood's glucose concentration within normal levels. From a mathematical point of view, this can be formulated as a model predictive control problem.

In acute myeloid leukaemia (see Chapters 6, 7, and 8), the ultimate goal is to determine the optimal chemotherapy dose that would lead to minimization of the cancerous population while maintaining the normal/healthy population above a minimum acceptable level. From a computational point of view, this is a scheduling problem.

For all of these diseases, the overall framework for the design of optimal drug delivery systems is presented in Figure 1.5.

In order to move towards the design of optimal delivery systems, development of a high-fidelity model able to describe the biomedical problem for an individual patient has to take place. Identification of parameters that crucially affect the model output enables the model reduction and, at a second step, the predictive control of the drug dose, therefore leading to process optimization.

Especially in the case of acute myeloid leukaemia, we have developed an appropriate *in vitro* system which allows *ex vivo* experimentation of leukaemic patient cells for the more efficient understanding and further identification of parameters that crucially affect the model output (i.e. the drug dose determination). Moreover,

experimental data serve as an input for our mathematical model, allowing validation and improvement (Chapters 6, 7, and 8). Therefore, this *in vivo*–*in vitro*–*in silico* closed loop enables the accurate study and further determination of the optimal drug dose for an individual/specific patient (Velliou *et al.*, 2014).

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