Chapter XI

Neural and Kernel Methods for Therapeutic Drug Monitoring

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Abstract

Recently, important advances in dosage formulations, therapeutic drug monitoring (TDM), and the emerging role of combined therapies have resulted in a substantial improvement in patients’ quality of life. Nevertheless, the increasing amounts of collected data and the non-linear nature of the underlying pharmacokinetic processes justify the development of mathematical models capable of predicting concentrations of a given administered drug and then adjusting the optimal dosage. Physical models of drug absorption and distribution and Bayesian forecasting have been used to predict blood concentrations, but their performance is not optimal and has given rise to the appearance of neural and kernel methods that could improve it. In this chapter, we present a complete review of neural
and kernel models for TDM. All presented methods are theoretically motivated, and illustrative examples in real clinical problems are included.

Introduction

In clinical practice, the collection of patient concentration-time data along with clinically relevant factors, such as anthropometrical, biochemical, or haematological parameters and the dosing history are routinely conducted as part of therapeutic monitoring for a variety of drugs. Over the last few years, numerous studies have shown that therapeutic drug monitoring (TDM) is an efficient tool for controlling the toxicity of therapeutic drugs. The adoption of a consistent, robust, and accurate TDM protocol has contributed, for example, to the improvement of cancer chemotherapy and the monitoring of transplant recipients and patients in periodic haemodialysis, in terms of the patient’s quality of life (QoL) and survival.

The administered dose is commonly adjusted individually using either a priori or a posteriori methods. A priori methods allow the computation of the first dose based on biometrical, biological, or clinical data. A posteriori methods use plasma drug concentrations to adjust the subsequent doses. In this context, nomograms allowing dose adjustment on the basis of blood concentrations are commonly used. Multiple regression models have also been developed to predict a single exposure variable, such as the area under the concentration-time curve (AUC) or blood concentrations. These models take advantage of a small number of plasma concentrations obtained at predetermined times after a standard dose. Bayesian estimation offers more flexibility in blood sampling times and accuracy. Unlike other a posteriori methods, Bayesian estimation is based on population pharmacokinetic (PK) studies. Pharmacokinetics (PK) defines the quantitative study of the concentration-time profile of the drug in the body including the absorption, distribution, metabolism, and excretion of the drug (Evans et al., 1992). Bayesian estimators can take into account the effects of different individual factors on the pharmacokinetics of the drug and have been widely used to determine maximum tolerated systemic exposure thresholds, as well as for the routine monitoring of drugs, which are characterized by high inter- and intra-individual pharmacokinetic variability. Recently, a number of population modeling programs have become available. Among these, the NONMEM program was the first developed and has been used most extensively in the analysis of actual clinical pharmacokinetic data. Building a population pharmacokinetic model requires understanding and selection of various mathematical/statistical submodels that include a pharmacokinetic structure model relating dose, sam-