Markov and mixed models with applications

This thesis deals with mathematical and statistical models with focus on applications in pharmacokinetic and pharmacodynamic (PK/PD) modelling. These models are today an important aspect of the drug development in the pharmaceutical industry and continued research in statistical methodology within these areas are thus important. PK models are concerned with describing the concentration profile of a drug in both humans and animals after drug intake whereas PD models are used to describe the effect of a drug in relation to the drug concentration. PK models for an individual are usually described as a deterministic mean value using ordinary differential equations to which a random error is added. This thesis explores methods based on stochastic differential equations (SDEs) to extend the models to more adequately describe both true random biological variations and also variations due to unknown or uncontrollable factors in an individual. Modelling using SDEs also provides new tools for estimation of unknown inputs to a system and is illustrated with an application to estimation of insulin secretion rates in diabetic patients. Models for the effect of a drug is a broader area since drugs may affect the individual in almost any thinkable way. This project focuses on measuring the effects on sleep in both humans and animals. The sleep process is usually analyzed by categorizing small time segments into a number of sleep states and this can be modelled using a Markov process. For this purpose new methods for non-parametric estimation of Markov processes are proposed to give a detailed description of the sleep process during the night. Statistically the Markov models considered for sleep states are closely related to the PK models based on SDEs as both models share the Markov property. When the models are applied to clinical data there will often be a large variation between individuals and this can be included in both types of models using the mixed modelling approach. Estimation in these models is discussed with emphasis on data with a more complex grouping structure.

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