

Modelling Physiological Systems: Trends and Challenges

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With some notable exceptions (as for instance Guyton's model for the cardiovascular system) mathematical modelling in the past was mainly concerned with describing and explaining basic mechanisms using comparatively simple models. This situation has distinctively changed in recent years. We see a trend to realistic and integrative models for physiological subsystems of the human body and not just for a few more or less isolated mechanisms. In many cases several time scales and levels of functionality are considered. This trend towards complex models is driven by the necessity to base the development of diagnostic and therapeutic procedures on mathematical models. Related to these requirements is that the development of decision support systems for clinicians needs also extensive mathematical modelling. The large number of parameters of the underlying complex models and their large dimension pose challenging problems for model validation. Model validation becomes even more challenging in case of clinical applications, because these usually require individualization of the models. Because of the difficulty to obtain reliable data by non-invasive or slightly invasive techniques, the validation process in general is even more demanding. This poses the challenge to develop new technologies for non-invasive data collection.

In the future the success of mathematical modelling of physiological systems will depend to a large degree on progress in the following areas:

- *Sensitivity analysis and parameter estimation.* Since it is hopeless and also not feasible to identify all parameters of a complex model for an individual person, there is a need for methods in sensitivity analysis which allow determining systematically those parameters in a model which have the largest influence on the dynamics of the model. Those parameters are the ones which should be adapted to individual persons. Even if the number of these parameters is much smaller than the number of all parameters it is still necessary to develop new powerful methods for parameters estimation. A fundamental problem which will need far more attention is the problem of identifiability.
- *Sensitivity analysis and design of experiments.* Methods of sensitivity analysis (classical and generalized sensitivities) will play a major role for the design of experiments. Since the number of tests and the number of measurements taken during one test usually are limited, we want to take measurements such that as much information on parameters as possible is provided.
- *Stochastic and statistical methods.* The importance of stochastic and statistical methods for mathematical modelling will certainly increase. This is rather obvious for parameter identification and experimental design, where we need to take into account the stochastic components of data. But it will also be necessary to include stochastic components into models even if initially one is aiming at deterministic models. It may be necessary to consider stochastic perturbations acting on a system or it may be feasible to describe parts of the dynamics of the real system by a stochastic process.
- *Time series and deterministic models.* Diagnostic procedures frequently are based on the analysis of time series, which originate as the output of a physiological system (for instance the time series of the RR-intervals of heart

beats which describes heart rate variability). It is a challenging problem for future research to develop techniques to generate time series with a deterministic model which resemble time series obtained from the real system. This possibly would allow the identification of physiologically meaningful parameters from characteristic features of the observed time series.

- *Micro level vs. macro level.* One of the most challenging problems, not only in modelling of physiological system but in general, is to develop techniques which link mechanisms at the micro level of a system (e.g. at the molecular level) with the behaviour of the system at the macro level. Here certainly new ideas are necessary, because a step by step approach from one level to the next level in many cases is not tractable.