Chapter XLII
Model Development and Decomposition in Physiology

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ABSTRACT

In this chapter some model development concepts can be used for the mathematical modeling in physiology as well as a graph theoretical approach for a decomposition technique in order to simplify parameter estimation are presented. This is based on the human menstrual cycle. First some modeling fundamentals are introduced that are applied to the model development of the human menstrual cycle. Then it is shown how a complex mathematical model can be handled if a large number of parameters are used where the parameter values are not known for the most part. A method is presented to divide the model into smaller, disjoint model parts. At the same time, it is shown how this technique works in the case of the human menstrual cycle. The principles for model development and decomposition can be used for other physiological models as well.

INTRODUCTION

This chapter presents how a complex mathematical model of physiological processes (e.g. control systems in the human body) can be developed. Complexity makes successful parameter estimation difficult which is why a possibility to simplify this problem is shown.

In the first part of this chapter, *Background*, some modeling techniques are presented which are used in the second part, *Development of a Complex Mathematical Model for the Human Menstrual Cycle*. In the third part, *Decomposition of Complex Mathematical Models in Physiology*, it is demonstrated, how

complex mathematical models can be divided reasonably into smaller parts in order to simplify parameter estimation. This decomposition method is applied to the model for the human menstrual cycle.

BACKGROUND

First, some principle modeling concepts are introduced that could be useful in the modeling of physiological processes and that are used to construct the complex mathematical model of the human menstrual cycle. The concept of compartmentalization of the considered body parts and how the connections between the compartments can be modeled, for example, via receptor binding and feedback mechanisms, is described. If the biochemical mechanisms are known, simple reaction kinetics can be used and if enzymes catalyze the reaction, simple enzyme kinetics are applied. Taking into account the fact that the different elements of the system influence each other with a certain delay, delay differential equations instead of ordinary differential equations are used.

Compartmentalization of the Human Body

The human body is not a closed homogeneous system; it consists of organs and tissues etc. in which different processes take place. In order to reduce biological complexity, the body parts that are essential in the processes are extracted and divided into discrete body elements, referred to as *compartments* (Andersen, 1991) that are interconnected via the shared blood system (Luecke & Wosilait, 1979), here called *transport compartment*. The characteristics of compartments are that isolated processes take place, but at the same time they can interact with each other. The model formulating the relations between these compartments is called *compartmental model* (Takeuchi et al., 2007) and this process of organizing the human body in compartments is referred to as *compartmentalization* which is the concept of pharmacokinetic modeling (Andersen, 1991). More precisely, *physiological based compartments* are used in this context since the compartments are based on the actual anatomy and physiology (Andersen, 1991).

Interfaces between the Compartments

The compartments are non-closed systems and can influence each other. The question arises, how exactly the exchange takes place and what possibilities there are for interrelations between compartments. On the one hand, it is possible that only coarse interrelations such as inhibiting or stimulating effects are known. Then these feedback mechanisms can be modeled by Hill functions. On the other hand, it is possible to model on a biochemical basis via e.g. receptor binding.

Receptor Binding and Recycling

It is often the case that the hormone which is synthesized in one compartment reaches another compartment through the blood circulation and binds to its corresponding receptor. They form a complex and thereby the receptor becomes activated:

$$R_{activatable} + H \rightarrow (H\text{-}R_{activated})$$