Table of Contents

Suite Manual

Version 7.0

Publication date February 2017

Internet:

- http://www.systems-biology.com
- http://www.pk-sim.com
- https://github.com/Open-Systems-Pharmacology

Email:

- support@systems-biology.com (for technical support)
- info@systems-biology.com (for general information)

About this Manual

This manual describes the Open Systems Pharmacology Suite. This includes technical descriptions of the different software elements together with examples and brief introductions to relevant scientific aspects including references for further reading. Naturally, the science described is selected based on our experience and judgment of relevance in the given context. Further, our “philosophy” is largely reflected in the software platform, and, vice versa, the software platform influences how we work and think.

The handbook is divided into the following parts:

Part I: “*Mechanistic modeling of pharmacokinetics and -dynamics*” provides a brief general introduction to the science of computational systems biology with a strong focus on mechanistic modeling of pharmacokinetics and –dynamics.

Part II: “*Open Systems Pharmacology Suite*” provides a brief overview of our software platform, its scope, and puts it into context with the science.

Thereafter, a technical description of the different software elements is presented starting with *PK-Sim*® focusing on physiologically-based pharmacokinetics in **Part III**: “*Working with PK-Sim*®”, followed by *MoBi*® focusing on model customization and extension as well as on pharmacodynamics in **Part IV**, “*Working with MoBi*®”.

Tools shared between *PK-Sim*® and *MoBi*® and some workflow examples are presented in **Part V**, “*Shared Tools and Example Workflows*” . After that, the interfaces to the common computing environments *Matlab*® and *R* are described in **Part VI**, “*Working with Matlab*® *and R*” and Section 44.1, “*R Toolbox for MoBi*®”, respectively.

PBPK Modeling - Systems Biology

Systems biology is a multidisciplinary and not clearly defined field of research. From an abstract point of view it is about understanding and investigating biology from a systems perspective. That is to say, the focus is not on isolated parts or processes, but on their interaction by which a certain behavior is generated or a certain task is fulfilled.

In modern science and engineering, systems are often studied using mathematical models for example in order to aggregate, integrate, formalize and challenge distributed existing knowledge, systematically analyse system behavior, develop and test hypotheses, and plan next experimental steps. Of course, the idea of using mathematical models also to investigate biology is not new. However, the more widespread use has strongly developed in the last decade as well as the increasing recognition and appreciation that mathematical models are needed besides, e.g. experimental and graphical models that have traditionally been used in biology, in order to cope with the ever increasing amount of data and information that are generated in life sciences. Considering the molecular complexity that forms the basis of life, it is clear that system boundaries and level of detail of any kind of model are limited. While experiments are and will remain an essential part of biological (and systems biological) research, in line with many "sytems biologists", we consider mathematical models as the core discipline of systems biology distinguishing it from other research approaches. Consequently, in this manual we mean mathematical models, if we speak simply of models and indicate, if we mean another form of model.

As stated in About this Manual, the content of this manual naturally is selected and biased. While systems biology includes biological diversity, we will focus on organisms and topics of broader relevance in pharmaceutical research and development, i.e. systems pharmacology, even though large parts of this software platform can also be used to address questions way beyond. But if we consider biochemical reactions or networks, for example, we often do that in a whole-body context to address the interaction of an active substance with an organism - this is where the software platform has unique capabilities and strengths.

While the very early phases of drug development do not involve work on whole organisms (animals or humans), the late preclinical phase includes animal experiments, mainly in mammals such as mice, rats, dogs, or monkeys before entering the clinical phase where the focus is on trials on humans as outlined in Figure 1.1. Different modeling approaches have been developed to support investigations on different scales [39]. As outlined above, we will focus on systems pharmacology, which can be viewed as a mechanistic approach to study pharmacodynamics and pharmacokinetics as illustrated in Figure 7.1.

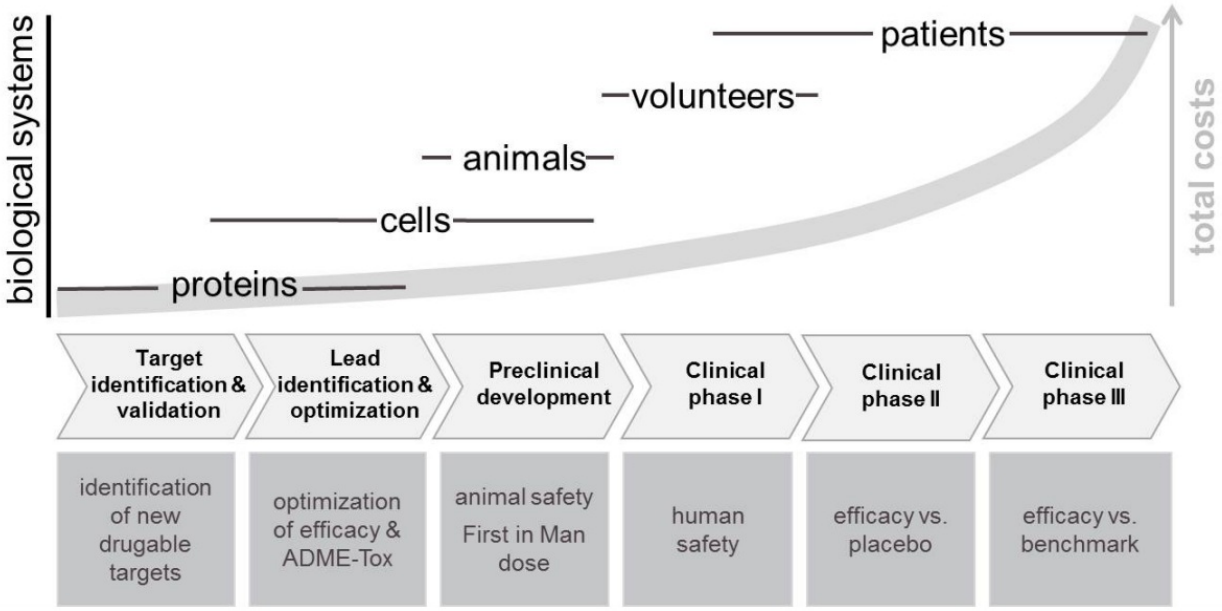

Figure 1.1. Phases, costs, and biological systems used in drug development (taken from [39]).

PK and PD modeling

Pharmacokinetics (PK) may be defined as what the body does to the drug, as opposed to pharmacodynamics (PD) which may be defined as what the drug does to the body [4].

The site of action of a pharmacological substance might be restricted to certain tissues or cells, which is why a quantitative estimate of the amount of administered substance that is available at the site of action is required. This question is the subject of pharmacokinetics and different modeling techniques are wellestablished in pharmaceutical research to support its investigation. So far, the most widely used approach is to establish descriptive and comparatively simple compartmental PK models that can be well identified based on available data (Figure 2.1-A). Often these models are applied to population PK data using nonlinear mixed-effect techniques (NLME), e.g. to quantify sources of population variability or covariate effects. Besides PK, such models may also include a description of a compound's effects (PD), for example, in the form of a simple hyperbolic or sigmoid concentration-effect relation (Michaelis-Menten, Hill, or Emax type).

Thus, in classical pharmacokinetic modeling, the aim is to fit a comparatively simple model to experimental data in order to determine pharmacokinetic parameters from the fitted concentration-time-course. These parameters are then used to characterize and quantify the behavior of the investigated substance in general or in a certain clinical trial and, potentially, to make extrapolations to situations that have not been already investigated.

In contrast to the rather phenomenological consideration of drug PK in compartmental models, physiologically–based pharmacokinetic (PBPK) models aim for a detailed representation of physiological processes (Figure 2.1-B) as will be summarized in the following. Consequently, PBPK-modeling is based on the mathematical description of physical and physiological processes and in the framework of PBPK modeling a genuine simulation of the pharmacokinetic behavior using this description is performed. Also, the pharmacodynamics can be represented in more mechanistic detail as briefly discussed in Chapter 6, Modeling Concepts - PD and Reaction Network Modeling. A good starting point for further reading can be found in [65].

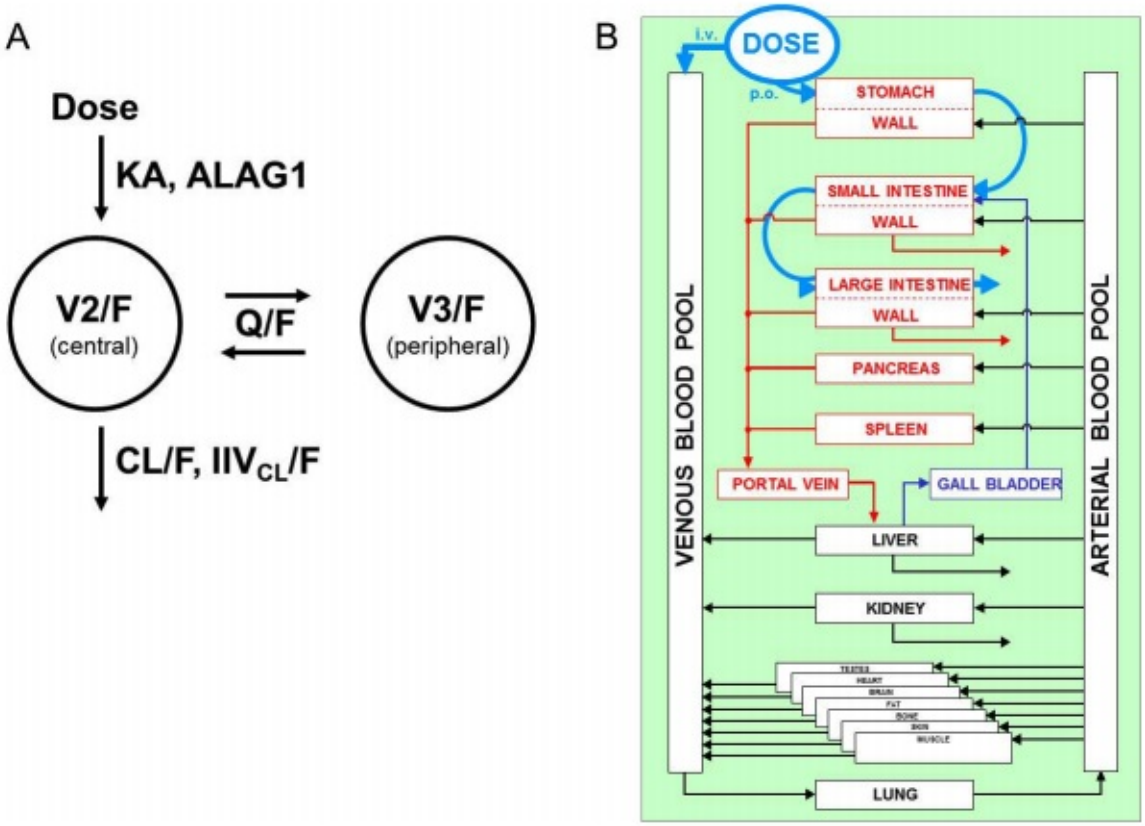

Figure 2.1. Structure of compartmental PK model (A) and PBPK model (B) (taken from [39] and [92]).