2 Modeling and Simulation Approaches

Modeling and simulation concepts and techniques have developed independently in several areas of fundamental research in biology as well as in pharmaceutical research and development. Today's armory of M&S methods covers a highly diverse set of approaches from highly detailed representations of molecular-level interactions in signal transduction pathways or metabolic networks typically used for research purposes to abstract statistical models of population-level effects of ethnic, genetic, behavioral, and other covariates on drug exposure in clinical trials used in late-stage clinical development and in regulatory evaluations. While Hodgkin and Huxley (1952) already applied detailed mechanistic computational modeling to study the electric properties of nerve cell axons in the 1940s (a work for which they were awarded the Nobel Prize in medicine in 1963), the use of mechanistic modeling in pharmaceutical R&D is still rather young and developing. In 2011, Sorger and colleagues provided a concise overview of M&S approaches explicitly representing biology and pharmacology, nowadays often called systems pharmacology, in an NIH white paper (Sorger et al. 2011). By contrast, other approaches such as population pharmacokinetics (Ette and Williams 2004) have reached a significant level of maturity documented by industry guidelines from regulatory agencies (US Food and Drug Administration 1999; European Medicines Agency 2007) and recent publications (Romero et al. 2013; Schuck et al. 2015).

The main differences and similarities between mechanistic and abstract statistical M&S approaches can be illustrated by the different approaches to pharmacokinetics (PK), i.e., the concentration-time profiles of a drug in blood, blood plasma, or any other biological matrix resulting from its application to an animal or human volunteer or patient (Fig. 2).

The application of a drug via oral, intravenous, or any other administration route leads to a time-dependent drug concentration profile in the body and each of its compartments, e.g., blood plasma. The so-called PK of a drug depends both on drug properties (physicochemical such as solubility and lipophilicity and biological such as metabolic stability and affinity to protein-binding partners and transporter) and properties of a preclinical species, a volunteer, or a patient (body size and composition, cardiac output, expression levels of enzymes, drug transport, and drug-binding proteins). Classical, abstract approaches to the modeling of PK such as population modeling start when experimental data have been generated in clinical trials (or preclinical experiments) by blood or tissue sampling and analytical determination of drug concentrations. So-called compartmental models (ordinary differential equation (ODE) based) are identified that adequately describe the experimental data. The structures of the models, i.e., the number of compartments (representing parts of the body) and connections between them (representing blood flows, diffusion, and other exchange processes), are chosen in a trial and error manner, such that quantitative parameters can be found that lead to a statistically correct representation of the data. The drug and its properties and the organism are only represented in an abstract and indirect way.