any adjustment of parameters can only be based on correlations between independent properties such as body weight and PK, previously derived from experimental data. So-called covariate models are established that represent these correlations via regression models linking independent properties (e.g., body weight) with abstract model parameters (e.g., volumes of compartments and rate constants for drug clearance from the body). These regression models are then used to predict the model parameterization under the untested, to-be-predicted experimental conditions.

While population modeling is a generally accepted approach in pharmaceutical industry and regulatory agencies for almost two decades and nowadays a mandatory component in regulatory submission packages, PBPK modeling was considered difficult to implement and standardize and consequently limited to in-house and academic applications. This has changed over the last years. For prediction of drug–drug interactions (DDI), PBPK modeling has become a regulatory accepted standard (Wagner et al. 2015) and US FDA itself is using PBPK for applications such as pediatric scaling or translation to other understudied populations and for study design support (Geanacopoulos and Barratt 2015). This development has been largely driven by the availability of commercially available software solutions for PBPK modeling (e.g., PK-Sim®, http://www.systems-biology.com/products/pk-sim.html) that provide databases for prior information on organism properties for various preclinical species from mouse to monkey and important human populations in different geographic regions (Willmann et al. 2007).

3 Representation of Biological and Pharmacological Complexity

The availability of sophisticated M&S tools has enabled the integration of structural scientific knowledge and experimental information from multiple biological levels into unified computational representations that can simulate complex (patho)physiological phenotypes and pharmacological interventions. It is technically no longer a challenge to integrate a subcellular level model of a signal transduction pathway linked to cell proliferation in tumor cells (e.g., MAPK-PI3K pathway) with a model of cell division and apoptosis and to embed it into the affected organ in a whole-body PBPK model representing a drug parent and an active metabolite (Eissing et al. 2011). Limitations to mechanistic modeling result from the lack of available experimental data for quantitative properties of biological and pharmacological entities and processes at individual biological scales and our lack of understanding of the interplay between biological scales, i.e., the interaction between molecular (signaling) cascades and cellular dynamics, between cellular behavior and tissue, etc. In such cases, scientific assumptions need to substitute knowledge and data to enable the establishment of model-based representations. Very often several hypotheses and scenarios (i.e., model structures) are plausible and corresponding model versions have to be established to represent the different possible scenarios. One of the great strengths of M&S is that via simulation these model versions can