relevant interindividual variability. The predictive performance for subjects' responses to meals and challenges even after several months was very good demonstrating the robustness of the representation and its dynamic behavior. With its size of several hundred ODEs, the model is exemplary for the level of biological detail state-of-the-art modeling approaches are able to capture.

4 Applications of Modeling and Simulation to Situations with Limited Mechanistic Understanding

In pharmaceutical R&D, the knowledge of molecular, physiological, and pharmacological mechanisms is usually limited and important processes may have been identified empirically only. While even intended drug effects are not necessarily fully understood in a mechanistic sense and at all biological scales, the canonical area for knowledge gaps is the field of drug safety. Although toxicological and safety pharmacological testing and monitoring accompany each and every step of drug development and pharmacovigilance continues to detect, collect, and assess safety events after marketing authorization, the causal chain leading to empirically observed but relatively rare adverse drug events is often only understood after intense research and with significant time delays. The importance of drug safety makes it an obvious application area for M&S. In a previously published case study on statin-related myopathy risks (Lippert et al. 2012), it was demonstrated how challenges resulting from knowledge gaps can be overcome by the systematic application of M&S to bridge between existing information linked to drug safety issues.

Statins are generally well-tolerated 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors. They are widely used as lipid-lowering treatments with more than 30 million patients worldwide. Mild cases of myopathy occur in around 1–5% of statin-treated patients but only 0.001% develop rhabdomyolysis with a more than tenfold increase in creatine kinase and potentially fatal consequences. Due to the extent of use, hundreds of patients are at risk for severe forms of myopathy, and in genome-wide association studies (GWAS), a single-nucleotide polymorphism (SNP; c.521T → C, p.Val174Ala) in the SLCO1B1 gene encoding the organic anion-transporting polypeptide OATP1B1 has been linked to an increased risk of myopathy after simvastatin treatment. It is also known that myopathy risk is lower at smaller doses or with other statins such as pravastatin.

For drugs such as statins that are substrates of OATP1B1, hepatic uptake by the transport protein can have significant impact on the PK and PBPK models that are able to represent the role of OATP1B1 (Fig. 7).

Once adjusted to simvastatin and pravastatin PK data from subjects with a homozygous OATP1B1 genotype (Fig. 8), the models are able to quantitatively predict the PK in subjects with a heterozygous genotype, a nontrivial task since PK depends on OATP1B1 in a nonlinear fashion (Fig. 8, blue line).

Using prior information about the variability of anatomical (e.g., body weight and organ volumes and composition) and physiological parameters (e.g., blood flow