molecular systems biology

NEWS AND VIEWS

Towards whole-body systems physiology

Lars Kuepfer*

Competence Center Systems Biology and Computational Solutions, Bayer Technology Services, Leverkusen, Germany
* Corresponding author. Competence Center Systems Biology and Computational Solutions, Bayer Technology Services, Building 9115, Leverkusen 51368, Germany.
Tel.: + 49 214 30 22745; Fax: +49 214 30 64801; E-mail: lars.kuepfer@bayertechnology.com

The liver executes a multitude of functions in human physiology such as detoxification or hormone synthesis. Consequently, hepatic dysfunction, be it inborn or acquired, can lead to diverse pathological manifestations as for instance argininemia or hypercholesterolemia. To analyze liver function at the cellular scale and to investigate underlying genotype–phenotype relationships, a growing number of high-throughput data has been generated in recent years. However, mechanistic computational models are equally important in order to interpret and contextualize this data and to obtain a holistic understanding of human liver functionality *per se*.

In a first attempt to capture human metabolism in a rigorous quantitative sense, two generic stoichiometric models at genome scale have been developed recently (Duarte *et al*, 2007; Ma *et al*, 2007). They correlate pathway information with gene annotation thereby describing basic metabolic biochemistry. These models successfully identified selected drug targets, whereas investigation of tissue-specific metabolism was only possible by additionally considering gene-expression measurements, which revealed flux activity of disease-related enzymes in different organs (Shlomi *et al*, 2008). This approach, however, cannot compensate for the lacking tissue-specific metabolic networks, which are essential to analyze modes of drug action by probing strategies of structural network intervention *in silico*.

Now two research groups have overcome this limitation and independently developed genome-scale stoichiometric models of human liver metabolism, thus allowing in-depth mechanistic insights into hepatic functioning (Gille *et al*, 2010; Jerby *et al*, 2010). Interestingly, the approaches for network reconstruction chosen by the respective groups are fairly different even though both have started from the same generic metabolic models. Gille *et al* performed a large-scale analysis of bibliomic data and subsequently reconciled the network named HepatoNet1 by hand. In comparison, Jerby *et al* used a model-building algorithm (MBA) for network reconstruction, which has a broad applicability to generic models in general. Regarding the resulting compartmentalization, both models consider cytosol, mitochondria, lysosome, endoplasmatic reticulum and nucleus, but peroxisome, bile canaliculus and sinusoidal space are unique to HepatoNet1, whereas the MBA-based model includes a generic extracellular space. This divergence in overall model structure is also reflected in the total number of network reactions, which is higher for HepatoNet1 (2539 versus 1827 reactions), albeit a direct comparison of both models is difficult due to different exchange reactions and compound names. In this respect, development of a consensus network such as previously undertaken for yeast (Herrgard *et al*, 2008) will be a rewarding endeavor for the future.

Both models were subsequently tested for an accurate description of both gluconeogenesis and detoxification of ammonia, two central functions of liver metabolism. In addition, Gille *et al* show the accuracy of their model by validating the fulfillment of 442 metabolic tasks of various degrees of complexity. These can be considered as hepatic equivalents to simpler cellular objective functions identified in microbial cells (Schuetz *et al*, 2007). Jerby *et al* implicitly account for similar information, though presumably to a lesser extent, by structural inclusion of tissue-specific 'omics' data and additionally evaluate the validity of their model by predicting hepatic flux distributions and metabolic biomarkers. Finally, both groups compare the predictive performance of their hepatic models to the earlier generic models of human metabolism and demonstrate a considerable improvement in both cases. The newly developed models therefore represent promising platforms for further mechanistic studies of liver function.

With human metabolic models coming of age, medical, diagnostic and pharmaceutical applications are now becoming feasible. Network models offer a structural scaffold onto which high-throughput data sets can be mapped in order to analyze experimental findings mechanistically. Hence, the impact of structural network modifications and interventions by genetic variation or drug administration can be investigated by simulating the resulting effect on metabolic states. Potential diagnostic applications are, for instance, model-based identification of specific biomarkers with altered levels in biofluids (Shlomi *et al*, 2009) or mapping of disease networks to human metabolism (Lee *et al*, 2008).

Hepatic metabolism closely interacts with whole-body physiology. Hence, the next step clearly requires moving from the cellular level to the organ scale, for example by consideration of hepatic zonation, and ultimately expansion to the organism level (Figure 1). With such fully integrated models, it will be possible to analyze hepatic metabolism in a clinical,
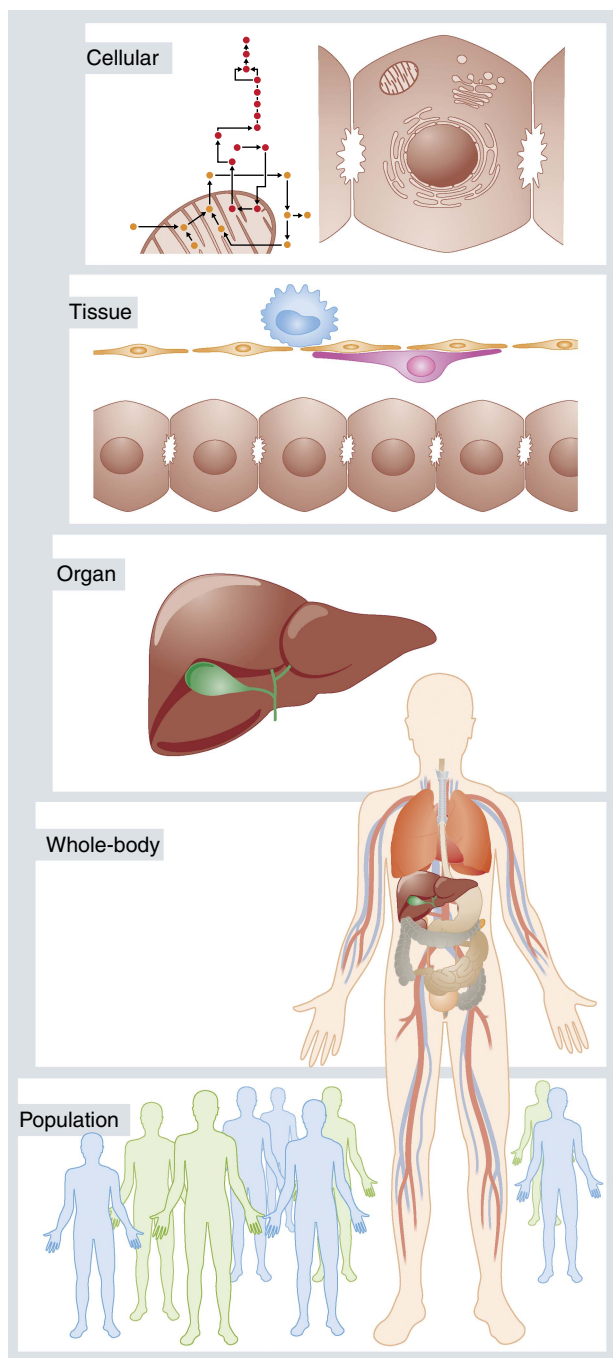
Figure 1 A multiscale representation of human physiology. Genome-scale models of human liver metabolism can be incorporated in organ models and may then be analyzed at a whole-body context. Specific phenotypes observed in population-wide studies (marked in blue and green) can thus be assigned mechanistically to a particular genotype.

computer-based models will greatly help to mechanistically explain pathophysiological states and support the development of targeted therapeutic strategies. With the genome-scale representations of hepatic metabolism by Gille *et al* and Jerby *et al* at hand, detailed models will become available, assigning a specific genetic background to an observed phenotype. Ultimately, such multiscale models will help to explain the complex interactions of the various networks in the human body from the cellular level up to the organism scale in an integrative way, thereby creating a comprehensive picture of whole-body physiology in its entirety.

Conflict of interest

The author declares that he has no conflict of interest.

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patient-level context and, for instance, simulate the impact of metabolic activity on pharmacokinetic drug distribution or, contrariwise, investigate changes in biomarker levels in response to external stimuli (de Graaf *et al*, 2009).

Population-wide genotype information regarding metabolic activity has already been used in whole-body models (Willmann *et al*, 2009). There is reasonable hope that, in future, such