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How predictive quantitative modelling of tissue organisation can inform liver disease pathogenesis

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Summary

From the more than 100 liver diseases described, many of those with high incidence rates manifest themselves by histopathological changes, such as hepatitis, alcoholic liver disease, fatty liver disease, fibrosis, and, in its later stages, cirrhosis, hepatocellular carcinoma, primary biliary cirrhosis and other disorders. Studies of disease pathogeneses are largely based on integrating -omics data pooled from cells at different locations with spatial information from stained liver structures in animal models. Even though this has led to significant insights, the complexity of interactions as well as the involvement of processes at many different time and length scales constrains the possibility to condense disease processes in illustrations, schemes and tables. The combination of modern imaging modalities with image processing and analysis, and mathematical models opens up a promising new approach towards a quantitative understanding of pathologies and of disease processes. This strategy is discussed for two examples, ammonia metabolism after drug-induced acute liver damage, and the recovery of liver mass as well as architecture during the subsequent regeneration process. This interdisciplinary approach permits integration of biological mechanisms and models of processes contributing to disease progression at various scales into mathematical models. These can be used to perform *in silico* simulations to promote unravelling the relation between architecture and function as below illustrated for liver regeneration, and bridging from the *in vitro* situation and animal models to humans. In the near future novel mechanisms will usually not be directly elucidated by modelling. However, models will falsify hypotheses and guide towards the most informative experimental design.

Keywords: Systems medicine; Virtual liver; Liver regeneration; Spatial-temporal modelling; Imaging; Image quantification; Liver sinusoidal endothelial cells; Hepatotoxicity; Ammonia; Metabolism; Carbon tetrachloride; Agent-based modelling.

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Abbreviations: CCl_4, Carbon tetrachloride; APAP, Acetaminophen; STM, Spatial-temporal model; HAS, Hepatocyte-sinusoid alignment; LSEC, Sinusoidal endothelial cells; Ang2, Angiopoietin-2; MM, Metabolic model; IMM, Integrated metabolic model.

Introduction (Fig. 1)

While recent developments have significantly increased our capability to collect information at multiple spatial and temporal scales, research in disease pathogenesis is largely hampered by the difficulty to orchestrate the individual components and mechanisms inferred by traditional ways of analysis into a consistent picture and to infer a complex interplay of components by pure reasoning. Here, mathematical models can play an important role as they formalise relations between components, quantify components and mechanisms, and test their interplay in a virtual setting defined by the modeller, thus, avoiding possible perturbations by unknown influences that can rarely be excluded in a real biological system. Mathematical models addressing liver pathology or drug effects increasingly integrate different levels of organisation [1]. Extra-hepatic contributions are usually addressed by compartment models [2,3], material transport (blood, lymph, bile) in liver or individual lobules by perfusion models considering local averages of concentrations, volume fractions and flow speed [4–7], Poiseuille-like flow [8] or spatial compartment models [9,10]. Hepatocytes, stellate cells, sinusoidal endothelial cells or other cell types may be included as cell compartments or as individual entities in space [8,11–13]. Metabolism, signal transduction or gene expression is usually modelled by systems of ordinary differential equations [9,14,15]. Model parameters, components or mechanisms can readily be modified, suppressed or added and the impact of such changes can be studied on different system observables. However, mathematical models remain abstractions of their biological counterpart. The aim is not an '*in silico* duplicate' of the 'real biological system' as this would have the same complexity as the original system. The choice of model components, horizontally on the same scale as vertically spanning several scales, should be guided by a scientific question.

Ideally all model parameters would be measured simultaneously but we are currently far from such an ideal situation. Therefore, the model parameters shall represent measurable

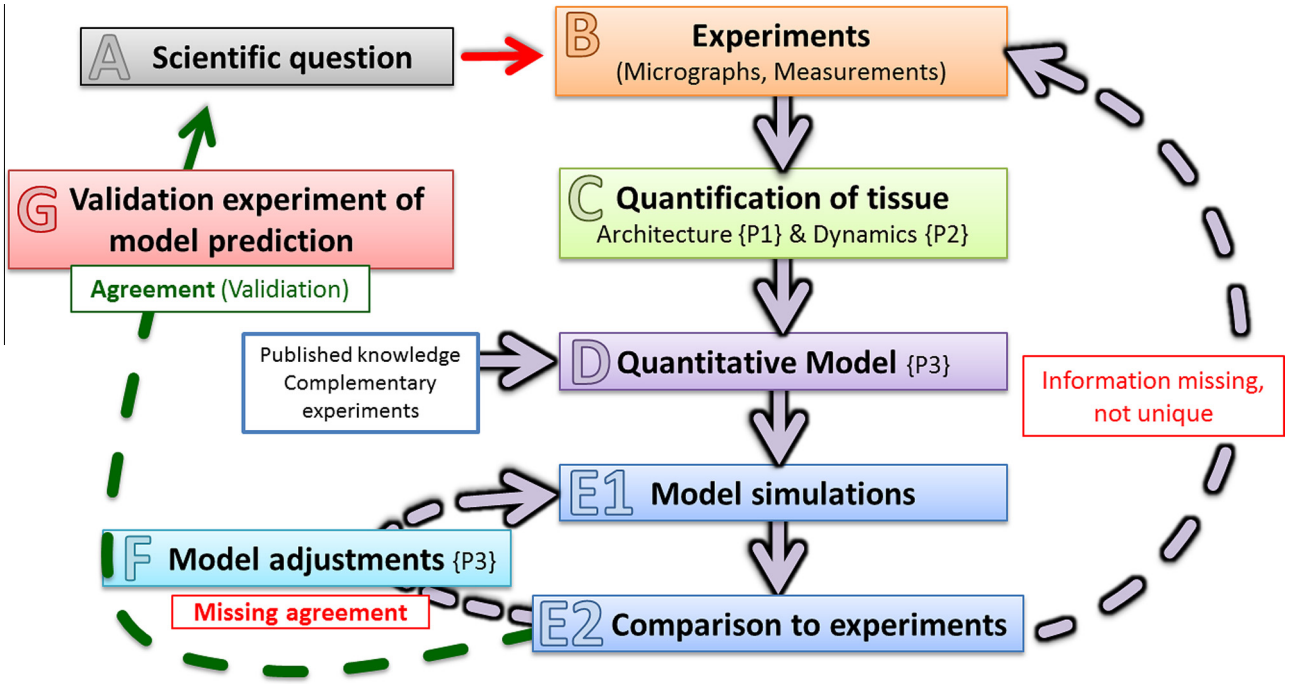

Fig. 1. Workflow from scientific question to possible answer. (A) Once the scientific question has been defined, hypothetical alternative mechanisms which could underlie the disease pathogenesis should be formulated. (B) In a next step, data has to be collected to inform the model quantitatively about initial conditions (the starting state), boundary conditions (values at the border of spatial domains, in/outflows etc.), and the condition(s) at which the model simulation should stop. Histopathology is characterised by the tissue composition (e.g., the cell types and extracellular matrix) and their architecture. It can be quantitatively described by a set {P1} of composition and architectural parameters (C) [12]. Such parameters can be inferred from a data analysis pipeline of imaging, image processing and analysis (C, [18]), serving as a starting state for the model simulations (E1). Both, data of a concrete individual tissue specimen or representative data obtained from the statistical distribution functions over the (architectural) parameters of many individuals can be used. Quantitative information about the disease process can be obtained from series of images in an equivalent way and leads to a second set of parameters {P2} (C). This parameter set must be explained by the model (D). The mathematical model should represent the hypothetical alternative mechanisms, and permit testing them *in silico* one by one. It introduces a third parameter set {P3}. If even after calibration of each model parameter within its range the model simulations (E1, E2) do not quantitatively capture the biologically observed behaviour, either important structures, mechanisms or processes that are required to correctly capture the specific *in vivo* situation are likely to be missing. In such situations the model needs to be adjusted (F) until finally agreement between model simulation results and experimental observations is achieved. It may occur that different mathematical models, each basing on another hypothetical mechanism, explain the same data quantitatively. In this case it is possible to use the mathematical model to search for an experimental situation in which the different hypothesis would predict different outcomes (G). Such an 'informative' experiment permits to select the correct out of several principally possible explanations.

quantities with a (known) direct physical or biological meaning and interpretation as this largely facilitates estimation of their range. Parameterization base on heuristics (experience-based techniques) should be avoided, as those parameter values are difficult to estimate. Each parameter that is not experimentally quantified introduces a degree of freedom that has to be explored by simulation, thereby increasing the search space of the model. For this reason, it is useful to construct a minimal model parameterised by the measurable quantities compatible with published knowledge.

As many liver diseases leave a signature in the composition and architecture of liver tissue in which case pathophysiology and histopathology are inherently linked the focus here is on quantitative (as opposed to qualitative) models involving liver mass and architecture. Fig. 1 sketches how a process chain consisting of experiment, data analysis and mathematical modelling can be iteratively applied to promote our understanding of liver disease pathogenesis.

In the next two sections we illustrate the workflow along two examples, the regeneration of liver mass and architecture after CCl_4-induced damage addressing the cell and tissue scale [12], and ammonia detoxification after CCl_4-induced damage addressing ammonia metabolism [10]. As our examples show, mechanisms can often only be ruled out if the model is quantitative.

A model on cell and tissue scale: Identification of key mechanisms of regeneration after drug-induced acute damage (Fig. 2)

Toxic doses of acetaminophen (APAP) can induce necrosis in the centre of the liver lobules [16] (Fig. 2A). A similar pericentral lesion is caused by the hepatotoxic model compound CCl_4. The extent of damage can amount to 30–40% of the total liver volume. In only approximately ten days livers of rodents not only regenerate their original cell numbers but also restore their functional tissue microarchitecture. This includes the process of reorganising the complex sinusoidal structure with endothelial cells and sheets of hepatocytes. The necessity of coordinating principles is obvious, since the starting situation of the regeneration process is a seemingly 'chaotic' dead cell mass. Much research has been done to understand the mechanisms controlling hepatocyte and non-parenchymal cell proliferation during regeneration [16,17]. However, only little is known how cells act coordinated to restore functional tissue microarchitecture. This question is of practical