Preprint

Modeling Approaches for Hepatic Spatial Heterogeneity in Pharmacokinetic Simulations

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Abstract

The metabolization and excretion of drugs in the liver are spatially heterogeneous processes. This is due to the spatial variability of physiological processes at different length scales of biological organization in healthy individuals, while many liver diseases further contribute to the heterogeneity. Classical, well-stirred pharmacokinetic models do not represent this heterogeneity, and various modeling approaches capable of representing heterogeneity have been developed recently. These approaches range from mechanistic and physio-geometrically realistic models focusing on specific spatial scales, via continuum models using homogenized physiological and metabolic properties, to integrative multiscale models. Such models could become essential research tools for simulations involving drugs with notable first-pass effects, fast-acting drugs or tracers, and diseased livers.

Keywords: physiologically based pharmacokinetic simulations, spatial heterogeneity, liver diseases, drug metabolism

1. Introduction

Drug transit through the body is a heterogeneous process [1]. The liver plays a pivotal role in the metabolization and excretion of drugs and contributes to this heterogeneity: Besides inter-individual physiological variability, cellular metabolic capability varies between different locations in the liver due to different cellular enzymatic setups. Furthermore, many diseases manifest themselves in spatially heterogeneous ways.

Pharmacokinetic (PK) models are generally used to describe drug concentration profiles within the blood plasma or in specific tissues. Models including spatial resolution and thus being capable of representing heterogeneity have been developed during the last four decades [2]. Such models are relevant for fast-acting drugs where first-pass effects play a role and where the presence of drugs does not equilibrate instantaneously. Spatial resolution is crucial in case of spatially heterogeneous diseases and if individualized models are envisioned.

Important advances have been made in multiscale liver modeling in the past ten years [3, 4, 5]. The purpose of the present article is to give an overview of recent developments in liver models with spatial heterogeneity.

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2. Physiologically Based Pharmacokinetic Simulations

PK models describe the fate of a drug in the body by means of mathematical equations. Levels of detail range from rather phenomenological gross plasma clearance at the whole-body level to specific enzyme-catalyzed molecular pathways at a cellular scale.

In compartmental PK models, model parameters have no strict physiological or anatomic basis; hence, these models are rather descriptive. In contrast, physiologically based PK (PBPK) modeling allows mechanisms underlying drug pharmacokinetics to be described at a high level of physiological detail. In brief, PBPK models are based on three types of building blocks:

1. The physiology of the organism including, e.g., organ volumes or blood flow rates
2. The physicochemistry of compounds used to calculate tissue-plasma partition coefficients
3. The dosing scheme of a specific therapy [6]

PBPK models explicitly include those organs in the body of an organism which are most relevant in terms of drug absorption, distribution, metabolism and excretion. This involves, amongst others, the gastrointestinal tract, lung, kidney, or liver. Tissue composition in terms of lipid, water, or protein content is frequently included as prior knowledge in PBPK modeling, with parameters representing standardized individuals. The large amount of prior physiological information considered in the basic PBPK model structure also includes specific biological processes such as the mixing of blood from the portal vein and the hepatic artery at the liver inflow.

Importantly, PBPK modeling enables simulating drug concentration profiles in different tissues [7]. This allows, e.g., simultaneously quantifying on-target and off-target drug exposure to optimize risk-benefit profiles [8]. Further applications for PBPK modeling include simulating virtual populations for design and analyzing clinical trials [9], cross-species-extrapolation [10] or investigating of drug-drug interactions.

PBPK models are presently well accepted by regulatory agencies and in pharmaceutical development programs, because such models support the prospective design of clinical trials, particularly for specific populations, and posterior analysis of trial data in terms of inter-individual variability. PBPK models may, therefore, significantly contribute to a mechanistic understanding of processes governing drug pharmacokinetics. Hence, differences in therapeutic outcomes or occurrence of adverse, drug-induced effects may be analyzed in more detail. Such analyses may also involve integrating models and data from different scales of biological information. This allows, e.g., considering results generated at the cellular scale in a whole-body context.

Many PK models assume a net clearance capacity homogeneously distributed across the organs, which implicitly assumes fast equilibration of concentrations between the between plasma and the surrounding tissue. However, for fast-acting drugs such as intravenous anesthetics or tracers, more advanced approaches are required to explicitly cover spatial heterogeneity within the liver.

3. Hepatic Spatial Heterogeneity

A detailed representation of spatial heterogeneity in PK models requires an accurate description of physiological and temporal mechanisms at different scales of biological organization. Some examples of heterogeneity are shown in Figure 1.

Physiological Heterogeneity. Livers are organized in lobules, small functional units of a few 100 µm radius. Blood is supplied by portal fields in the periphery, flows through sinusoids, and is drained by a central vein [19]. Along the sinusoids, the blood is in contact with liver cells (mainly hepatocytes), which metabolize pharmaceutical and certain other compounds in the blood. More precisely, different families of enzymes in the cells metabolize different pharmaceutical compounds. Specific enzymes may only be present in one fraction of the hepatocytes, thus metabolic properties of the cells along a sinusoid differ, often in a zonated way [20]. Furthermore, substances such as oxygen and drugs decay or increase in the blood along the sinusoids, i.e., form concentration gradients, in particular in case of dominant first-pass elimination [21].

Pathological Heterogeneity. Liver diseases also occur in spatially heterogeneous form. Zonation at the lobular length scale is one relevant length scale for pathological conditions such as steatosis [22] or necrosis after carbon tetrachloride intoxication [23] as a model for acetaminophen overdose. A second relevant length scale is heterogeneity across the entire organ (between lobules), e.g., in case of steatosis [24], fibrosis [25], carcinoma [26], or regeneration after resection [13]. Additionally, drugs may be applied non-uniformly by targeted drug delivery [27] or catheter injection [28].

Time Scales. Spatial heterogeneity in terms of mixing effects at different scales of biological organization ultimately affect drug PK at the whole-body level. In particular, this involves different temporal scales. If compounds do not instantaneously equilibrate in the body, first-pass effects [29] need to be resolved. This corresponds to a time scale of seconds to minutes. Faster time scales are typically not considered in PK modeling. In contrast, changes in hepatic heterogeneity due to diseases typically change on a time scale of days to weeks. Thus, a separation of time scales, i.e., keeping diseased states constant during consecutive PK simulations, may be possible when the influence of the drug on the diseased state, therapeutic or toxic, can be neglected.

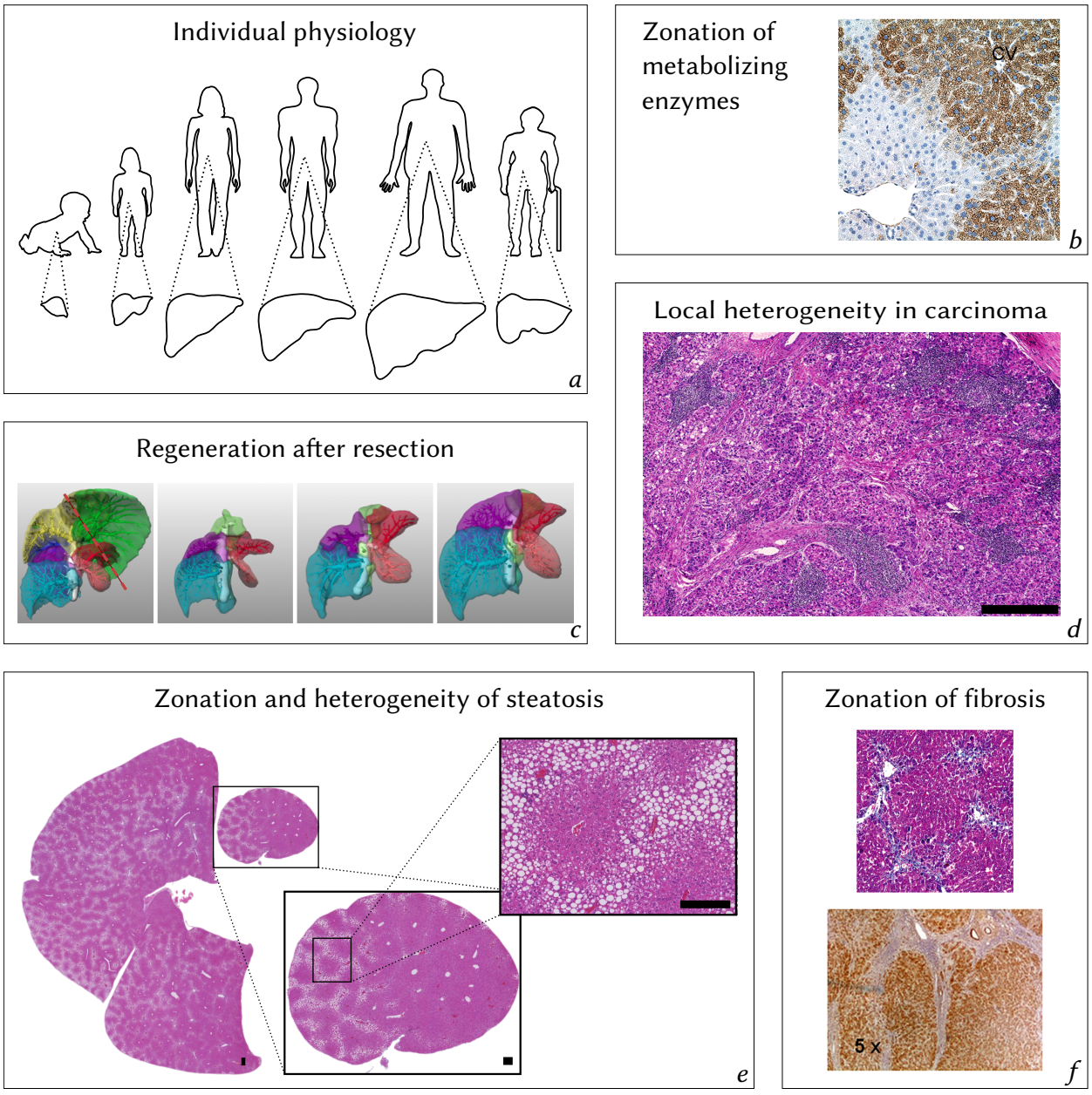


Figure 1: Examples of spatially heterogeneous physiological and pathological phenomena at different length scales of biological organization. Scale bars (where present) indicate 200 µm.

Image credits: (a) human outlines partly adapted from [11] (subject to public domain license), *(b)* enzyme staining images* (in mice) adapted from [12, Fig. 3] *(c)* regeneration image* (in mice) adapted from [13, Fig. 2], *(d)* carcinoma image* (human) adapted from [14, Fig. 1A], *(e)* steatosis image (mouse) shows data from [15], *(f)* fibrosis images* adapted from [16, Fig. 1] (top; mouse) and [17, Fig. 8] (bottom; human), (* subject to CC-BY license [18]).

4. Modeling Approaches for Spatial Heterogeneity

The aforementioned physiological and temporal mechanisms within the liver can be described by different mathematical modeling formalisms at different scales of biological organization. Throughout this section and in Tables 1 and 2, we provide an overview of recent modeling approaches including spatial heterogeneity, assigned to one spatial scale even though there is no strict separation for all the approaches mentioned. This is, however, not an exhaustive overview of models from the last decades.

4.1. Cell Scale

Hepatocytes form the majority of parenchymal liver cells and perform the actual hepatic metabolism. Cellular metabolism is typically modeled via highly complex metabolic networks [34]. For integration in larger-scale PK models, metabolic networks can be reduced to non-spatial ODE models [30]. Because certain involved molecules are only present in part of the cell, e.g., in the mitochondrion, such ODEs distinguish intracellular substructures [32, 35, 33]. These substructures are typically not resolved geometrically, but assumed to be well-stirred, as high variability and fast intracellular diffusion at the cellular length scale can be expected.

Alternatively, ODE models for the cellular scale are parametrized directly, e.g., [43] and models based thereon [31, 40, 36]. The surrounding interstitial/extracellular extravascular space can be associated to the cell [46, 47, 37].

4.2. Lobule Scale: Zonation

Different cells in a lobule may be equipped with different enzymatic setups and thus have different metabolic properties. Cells at different locations are typically exposed to different compound concentrations in the blood flowing past. Such zonation or continuous gradients are represented in approaches using two main techniques: sinusoid models involving individual cells and continuum models focusing on the cells' effective behavior in the tissue.

Realistic sinusoidal networks for 2D slices through lobules [38] or for 3D model lobules [39, 33] have been used, where blood flow through the sinusoids and an exchange of compounds with surrounding cells has been modeled. As a stronger simplification, lobules have been represented by single sinusoids [51, 37, 36] or networks of sinusoids [57]. Sinusoidal blood flow is actually an intermittent corpuscular flow on variable and complex geometries [58, Video S1]. The blood flow model is typically simplified to constant [38, 37] or radially symmetric [51] velocity profiles. More complex fluid dynamics models [59] exist, but the value of this level of complexity in PK simulations is unclear.

Continuum models involve multi-phase flow, diffusion, and metabolization in porous media. Such models have been used for 2D slices through lobules [40, 60] or 3D model lobules [41, 42].

4.3. Organ Scale: Liver

There are various classical PK approaches representing livers as a well-stirred compartment, single tube (sinusoid), series of tubes (zonated sinusoid), and parallel tubes (capturing heterogeneity between different hepatic regions, e.g., Couinaud segments [61] or diseased regions). We refer to [62, 63, 44, 2] for reviews of these approaches and references to the respective original publications.

Similar to the lobule scale, two main techniques are used to represent heterogeneity at the organ scale: multiscale models and continuum models. Multiscale models treat the liver as the combination of multiple lobules (with different properties/parameters). This approach is conceivable for all the approaches above, and may require suitable quantitative parameters describing the heterogeneity. Examples include an investigation of boundary effects [60] and models using simulated intralobular heterogeneity [45, 37]. Examples of organ-scale continuum models include [48], [47] with simulated heterogeneous disease data, and [27, 46]. The latter demonstrates that continuum models permit combining PK with other processes, in this case, externally induced thermal release of bound drugs and cell damage.

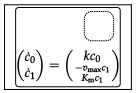
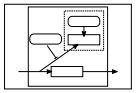
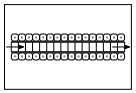
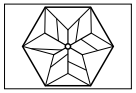
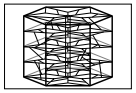
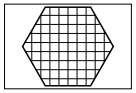
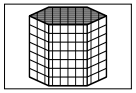
Scale	Modeling Approach		Heterogeneity	Example Models/Compounds
Cell		ODE	cellular substructure	glucose metabolism [30] fatty acid uptake, triacylglycerol storage [31] ammonia detoxification [32, 33]
		metabolic network	cellular substructure, metabolic pathways	glycochenodeoxycholate synthesis, ammonia detoxification [34]
Lobule		1D sinusoid	zonation	fatty acid metabolism [35] acetaminophen ADME [36] midazolam, caffeine, and insulin clearance [37]
		2D sinusoidal network	zonation + lobule	(generic) [38]
		3D sinusoidal network	zonation + lobule	ammonia detoxification [32, 33] (tissue structure) [39]
		2D continuum (porous medium)	zonation + lobule	glucose and lactate metabolism [40]
		3D continuum (porous medium)	zonation + lobule	(blood flow and pressure) [41] paclitaxel metabolism, oxygen distribution [42]

Table 1: Overview of modeling approaches capable of dealing with physiological heterogeneity at different length scales, cell and lobule, of biological organization. (ADME: absorption, distribution, metabolization, and excretion)

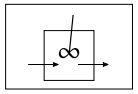
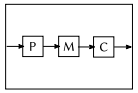
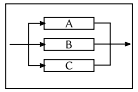
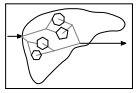
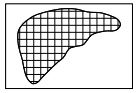
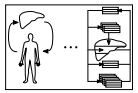
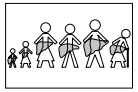
Scale	Modeling Approach		Heterogeneity	Examples
Organ		well stirred	none	(generic) [43]
		zonated organ (similar to 1D sinusoid)	constant zonation	(generic) [44, 2]
		parallel sinusoids	organ+zonation	midazolam, caffeine, and insulin clearance [37]
		multiple lobules	organ+zonation	sucrose and antipyrine elimination [45]
		continuum (porous medium)	organ	doxorubicin delivery from temperature-sensitive liposomes [46, 27] carboxyfluorescein diacetate succinimidyl ester distribution, midazolam, and spiramycin clearance [47] paclitaxel clearance [48]
Whole-Body		spectrum between organ compartments and lumped organs	inter-organ	(generic) [43, 38, 49] indocyanine green clearance. [50] cilostazol absorption [**?**] acetaminophen metabolism [51] ciprofloxacin ADME [6] acetaminophen ADME [36]
Population		adjusted model parameters	inter-individual	ciprofloxacin and paclitaxel clearance [52] atorvastatin metabolism [53] indocyanine green and rocuronium distribution [54] pravastatin ADME [55] furosemide and morphine distribution and elimination [56]

Table 2: Overview of modeling approaches capable of dealing with physiological heterogeneity at different length scales, organ to population, of biological organization. (ADME: absorption, distribution, metabolization, and excretion)

Image credits: stick figures adapted from clip art from [11] (subject to public domain license).

4.4. Whole-Body Scale

In addition to the liver, other organs and their heterogeneity also play roles in the processes from absorption to excretion of drugs and their metabolites. This is, e.g., represented in sub-structured small intestine model for drug absorption [64, 49]. Focusing on the liver, we will confine the discussion of the organism to a 'hepatic point of view'.

For research purposes, isolated perfused livers are commonly considered. For such models [57, 32, 47, 48], different liver inflow and outflow profiles can be considered [40], but there is no organism present in the model.

The complexity and level of detail of the whole-body representation form a spectrum ranging from strongly simplified models to those considering sub-compartments for each individual organ. In a model for hyperthermia-induced targeted drug delivery [27], only body tissue and body plasma compartments have been considered. Pulmonary and remaining systemic circulation besides gut/liver have been discriminated in a simulation of indocyanine green clearance [50]. A generic microdosimetry model [38] further distinguishes a handful of organs (lung, gut), one compartment each for the rest of the body, and the arterial and the venous blood. The kidney is involved in the clearance of many drugs and has thus been included explicitly in PK models [36].

Structuring can also be based on properties of organs relevant for the specific application, e.g., in a blood reservoir plus highly and poorly perfused tissue [49] or, additionally, adipose tissue [51]. In contrast, the structure in [43**?** , 6] and models based thereon [52, 37, 56] are examples of generic and detailed whole-body models in which organs are represented by their plasma, erythrocyte, interstitial, and cellular subcompartments. To reduce model complexity, lumping [65, 66] can be applied to reduce the number of compartments. To avoid unphysiologically fast equilibration, delays can be introduced between compartments [67].

4.5. Population Scale: Inter-Individual Differences

Inter-individual differences in PK can be due to age, gender, body weight, ethnicity, individual organ function or disease state, etc. These differences can be represented by variability in PBPK model parameters [52], but also in compartmental models [54]. Inter-individual variability has been investigated for assessing patient safety in drug development and for subgroup stratification [55]. With a growing elderly population, modeling the influence of age [56] is particularly important.

Adapting PK models to differences in patient groups or building individualized models is, in principle, possible for models focusing on any scale. Individualizing models may involve adapting numerical physiology parameters [55, 68, 56], organ geometries [47, 69], disease models [32, 37, 33] at the lobular scale, or cellular properties [53], etc. from literature or public databases.

4.6. Multi-Scale Modeling Approaches

Despite mainly focusing on heterogeneity at one spatial scale, the described approaches can be integrated in multi-scale models. Possible approaches are actual multi-scale integration and model reduction to obtain effective model behavior.

Actual multi-scale integration involves using multiple instances of a model at a fine scale with different parametrizations reflecting heterogeneity. Examples include using different cellular models in a sinusoid [35, 37, 36], lobule [39, 32, 40, 33], organ [46, 47], or whole-body model [70]; lobule models with different properties in an organ [45, 37], and different whole-body models in a population [52, 54, 68, 55, 56].

Model reduction is useful in multi-scale models to reduce the computational workload. Additionally, continuum models typically require homogenized properties from finer spatial scales, e.g., flow and metabolization in porous medium models at the lobule [40] or organ scale [47].

5. Discussion

The role of computational modeling is increasing in pharmaceutical development and medical research. Specific pathologies and inter-individual differences may necessitate multi-scale modeling approaches capable of dealing with spatial heterogeneity in PK modeling. A variety of sophisticated modeling approaches exists, mainly at a research stage, each with its own specific strengths. Considerations when choosing an approach adequate for a given specific application are mainly standard questions in modeling, such as

- Which model can capture the mechanisms and complexity at hand, but is not overly complex to avoid making unnecessary assumptions and to limit computational workload?
- How is the heterogeneity quantified and fed into the model?
- Is there suitable software available for the simulation?

5.1. Relevance and Applications

Spatially resolved PK simulations permit in-silico investigations of drug effects for which a diagnostic observation is difficult to impossible even via high-end imaging. Instead, a comprehensive mechanistic picture can be achieved by integrating modeling results from different scales of biological organization. One important application is the distribution of fast-acting drugs or tracers, for which the first few moments following drug administration are decisive [71, 2]. On this time scale, instantaneous mixing cannot be assumed, so that simple well-stirred PK models are not applicable, but spatially heterogeneous approaches are needed.

Computational models including liver zonation have been used together with targeted experimental measurements amongst other to investigate the impact of CCl_4 intoxication on ammonia detoxification or hepatic clearance capacity [72, 32]. Current clinical examples rather use effective parametrization of hepatic physiology, e.g., changes in liver perfusion and functional liver mass in cirrhotic patients [73] or alterations in ADME gene expression in steatotic patients [74]. In this regard, it is important for computational platforms to be structurally flexible enough for integrating physiological data at a sufficient level of physiological detail at all spatial scales. This allows, in particular, the differentiation between individuals of different age, gender, health state, or genotype (cf. Figure 1). A typical application of PBPK modeling using adapted whole-body physiologcial parameters is pediatric scaling, applied, e.g., to adapt bosentan dosage for children [75].

A suitable reduction of model complexity is necessary for translation to clinical applications since suitable techniques need to be available to quantify heterogeneity as model input parameters. Important model input is quantitative data describing pathophysiological states, as well as mechanistic descriptions of how diseases affect the local metabolic properties, so that PK simulations can provide accurate predictions for specific states and not only serve as descriptive models. As an example, zonation and heterogeneity of steatosis have been quantified histologically for an entire mouse liver in [15], but no comparable in-vivo or even clinically applicable approaches exist that could provide quantification in comparable detail: biopsies provide only very localized information, non-invasive imaging at the organ scale by ultrasound [76] or magnetic resonance imaging [77] only provides very coarse resolution.

Parenchymal perfusion heterogeneity across the organ is another crucial factor for pharmacokinetics, for which models in the heart [78] and in the liver [69] exist. It is, however, hard to measure parenchymal perfusion, discriminating it from vascular perfusion, in vivo and at sufficiently high resolution.

An example where spatially resolved PK simulations can possibly provide a valuable contribution is hepatic surgery planning [79], where liver function needs to be predicted prior to surgery. In this case, it is crucial to use individualized, geometrically accurate models that can consider both existing heterogeneity and the one introduced by the surgical procedure.

5.2. Perspective

Further development of spatially resolved PK modeling approaches would require several advancements. Implementations of the various approaches should be made available, ideally with open source for developers and as end-user tools. Models and parameters describing heterogeneity effects should also be made available. This (and possibly organized competitions/challenges [80]) could trigger a comparison of the strengths and weaknesses of different approaches. Ideally, this will also help develop a standard for describing multi-scale models (such as SBML for biochemical models) and data, even though the manifold phenomena involved in physiological heterogeneity and a mathematical formalization of the phenomena will present many challenges.

6. Conclusions

Promising advances have been made in spatially resolved PK modeling in the past decade. Recent developments in intravital imaging can be expected to contribute in two ways: obtaining model input parameters describing heterogeneity; and improving mechanistic knowledge about pathological heterogeneous alterations to physiological processes. Prospectively, spatially resolved PK simulations will thus considerably support the understanding of drug distribution in healthy and diseased livers and provide valuable techniques for pharmacological research.

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Conflicts of Interest

LK is employed by Bayer AG, the company developing the PBPK modeling tools PK-Sim and MoBi. LOS and TP have no conflicts of interest to declare.

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