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Algorithmically generated rodent hepatic vascular trees in arbitrary detail

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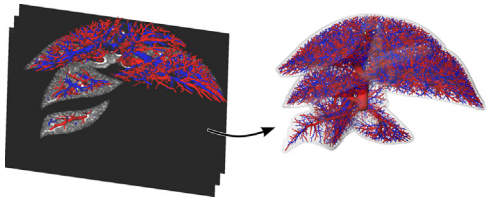
HIGHLIGHTS

- We refine geometric models of vascular systems in livers of mice and rats.
- Constrained constructive optimization provides an initial refinement.
- We calibrate a postprocessing to obtain geometrically realistic vascular structues.

GRAPHICAL ABSTRACT



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ABSTRACT

Physiologically realistic geometric models of the vasculature in the liver are indispensable for modelling hepatic blood flow, the main connection between the liver and the organism. Current in vivo imaging techniques do not provide sufficiently detailed vascular trees for many simulation applications, so it is necessary to use algorithmic refinement methods.

The method of Constrained Constructive Optimization (CCO) (Schreiner et al., 2006) is well suited for this purpose. Its results after calibration have been previously compared to experimentally acquired human vascular trees (Schwen and Preusser, 2012). The goal of this paper is to extend this calibration to the case of rodents (mice and rats), the most commonly used animal models in liver research. Based on in vivo and ex vivo micro-CT scans of rodent livers and their vasculature, we performed an analysis of various geometric features of the vascular trees. Starting from pruned versions of the original vascular trees, we applied the CCO procedure and compared these algorithmic results to the original vascular trees using a suitable similarity measure.

The calibration of the postprocessing improved the algorithmic results compared to those obtained using standard CCO. In terms of angular features, the average similarity increased from 0.27 to 0.61, improving the total similarity from 0.28 to 0.40. Finally, we applied the calibrated algorithm to refine measured vascular trees to the (higher) level of detail desired for specific applications. Having successfully adapted the CCO algorithm to the rodent model organism, the resulting individual-specific refined hepatic vascular trees can now be used for advanced modeling involving, e.g., detailed blood flow simulations.

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1. Introduction

The liver is a central organ for the mammalian metabolism as well as for clearance of xenobiotic substances from the blood plasma. The liver is connected to the organism via four vascular systems: blood is supplied by the portal vein (PV) and the hepatic artery (HA), the liver is drained by the hepatic vein (HV), and the bile ducts (BD). The PV, providing about 75% of the hepatic blood flow, distributes venous blood rich in nutrients as it comes from the digestive system. The HA, providing the remaining hepatic blood supply and largely running in parallel with the PV, supplies the liver with arterial blood rich in oxygen. The HV drains the venous blood from the liver into the inferior vena cava. The BD drain the bile produced inside the liver (Kuntz and Kuntz, 2008). The actual hepatic metabolization and elimination/clearance of compounds take place in the liver cells (hepatocytes), which are spatially organized in lobuli. Here a sinusoidal network permits an exchange of compounds between blood flowing through the network and hepatocytes adjacent to the sinusoids. The vascular trees of the liver thus provide the link between the organism and the functional units of the liver. Inter-individual variations of hepatic elimination are observed already for healthy livers, but in particular also in case of diseases (Atkinson and Kushner, 1979).

1.1. Geometric liver models

Modeling and simulation of biophysical processes have become powerful tools for analyzing and understanding the behavior of dynamical biological systems as well as predicting their future states. Its impact lies, on the one hand, in basic science such as understanding how living organisms work, and on the other hand in applications such as improving surgical interventions and pharmaceutical developments.

In order to accurately simulate hepatic physiological processes, and thus avoid the need for performing actual experiments, single- or multi-scale models can be used. Pharmacokinetics models (Willmann et al., 2003; Eissing et al., 2011) considering the liver as a well-stirred compartment can provide phenomenologically correct descriptions of total liver clearance or metabolization. Such models can, however, not take into account zonation (Gebhardt, 1992) inside lobuli or heterogeneity on a larger length scale due to pathological conditions, such as steatosis (Karcaaltincaba and Akhan, 2007; Sun, 2011), fibrosis (Goldstein et al., 2005), cirrhosis (Hølund et al., 1980), or hepatitis (Rockey et al., 2009). Two-scale models considering multiple sinusoids (see Roberts and Rowland, 1986; Pang et al., 2007 and the references therein for an overview) permit sinusoidal zonation and can, in principle, also incorporate different sinusoids for different regions of the liver. The same can be achieved using a two-scale model Holzhütter et al. (2012) using lobuli as the fine scale (Saxena et al., 1999; Hoehme et al., 2010) rather than sinusoids. In both cases, only using realistic vascular trees and organ geometry allows a mechanistic and individual-specific model. This is particularly important if a spatially heterogeneous pathological state is to be considered (Schwen et al., 2014a) or the influence of specific surgical techniques is to be assessed in rodents as model organisms. Examples of such surgical techniques include, but are not limited to, vessel-oriented liver resection (Madrahimov et al., 2006) and their comparison to resections with mass ligation techniques (Dahmen et al., 2008).

Current contrast-enhanced radiological in vivo imaging provides sufficient resolution so that the main vascular trees can be reconstructed (Selle et al., 2002). In vivo computed tomography (CT) provides sufficiently detailed vascular trees for planning liver resection surgery in humans (Endo et al., 2007; Schenk et al., 2008). The level of detail may, however, be insufficient for modeling, depending on the spatial pattern of heterogeneity to be considered. In mouse livers, steady-state in vivo μCT protocols in combination with large molecular weight (long circulating) blood pool contrast agents can be used. These allow non-invasive imaging of hepatic blood vessels at 35 μm resolution (Ehling et al., 2014). Ex vivo imaging permits higher doses of radiation and thus better image quality. In either case, geometric parameters of the reconstructed vascular trees are subject to measurement and analysis errors (Drexl et al., 2004) as well as limitations of the image size that can be processed.

SDEE|4127In order to bridge the gap between the currently technically achievable vascular resolution and the one needed for accurate modeling (e.g., in Schwen et al., 2014a), algorithms for generating vascular trees can be applied, e.g., the method of constrained constructive optimization (CCO) (Schreiner, 2001). In Schwen and Preusser (2012), a procedure was presented to evaluate and calibrate a CCO implementation to algorithmically generate geometrically realistic vascular trees for human livers. The goal of the present paper is to transfer this algorithmic procedure to rodent hepatic vascular systems. For this purpose, we imaged vascular trees of rodents. We used 12 in vivo scans of mouse livers from a previous study focusing on tumor imaging (Ehling et al., 2014), and nine corrosion casts of rat livers. These species are frequently used as animal models for liver investigations.

In this paper, we describe two steps involving the algorithmic CCO procedure:

1. *Calibration*: First, we applied the algorithmic refinement procedure starting with substantially pruned versions of the experimentally acquired vascular trees. Comparing the results with experimentally acquired data, we could assess the quality of the algorithmic results and calibrate the algorithm to produce geometrically more realistic results.
2. *Application*: We then applied the algorithm to generate the desired level of detail in the vascular trees, this time starting from the full experimentally acquired vascular trees.

For the calibration step, we quantified similarity in terms of different geometric features using a statistics-based comparison described in Schwen and Preusser (2012). We performed two types of analyses addressing the following questions.

1. How similar are experimentally acquired mouse PVs to each other?
   ⇒ What should the algorithm reproduce?
2. How similar are algorithmically generated mouse PVs to experimentally acquired PVs?
   ⇒ How well does the algorithm perform?

Besides the mouse PVs, we also considered the other types of vascular trees (mouse HVs, rat PVs, and rat HVs). Similarity is quantified on a scale from 0 to 1 (no significant differences) individually for different geometric features and averaged over these as described in Schwen and Preusser (2012). In particular, we compare neither between PV and HV nor between species.

As for the application, we assume that the geometric properties determined in the experimentally acquired vascular trees also hold on finer geometric scales (self-similarity) so that our corresponding extrapolation is valid. Self-similarity is a plausible and partially verified assumption in this context, see, e.g., Van Beek et al. (1989), Zamir (2001), Mancardi et al. (2008).

The HA is not considered in this study. Its radii are generally smaller than those of the PV, making it more difficult to experimentally acquire HA vascular trees in appropriate quality. For many modeling applications, however, the HA can be assumed to geometrically lie parallel to the PV (Kuntz and Kuntz, 2008). The BDs are not considered here either since they are not part of the blood flow system on which we focus in this study.