Numerical Modeling of Drug Delivery in Organs: From CT Scans to FE Model

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Abstract. Mass transport within an organ is complex process which occurs through two different domains: networks of blood vessels and surrounding tissue. Consequently, development of a comprehensive transport model remains a challenge. In this paper we showed an application of a recently introduced multi-scale transport model [1, 2], where larger vessels are modeled by simple 1D finite elements. This model couples convective and diffusive transport within complex system consisted of capillaries and tissue, where connection between these fluid (capillaries) and solid (tissue) domains is accomplished by using fictitious 1D elements. In order to apply the developed model, a reconstruction procedure, consisted of: segmentation, skeletonization using augmented FMM method, and diameter recognition within indoor software, is processed. At the end, numerical simulations are performed in order to get the pressure and concentration distribution in the vessel network and surrounding tissue, showed by examples presented in the paper.

Keywords: Segmentation · Skeletonization · Finite element method
Pipe finite element · Pancreas model · Liver model

1 Introduction

Patient specific numerical modeling of drug transport in tumor and organs requires a long way from CT images to representative FE model. Models of tumor and organs are very complex due to heterogeneity of capillary network, tissue cells, etc. In order to have an accurate drug transport model, one would suggest that representation of complex capillary network should be done using either detailed 2D or 3D finite elements. But, it would be very demanding since the number of equations will increase rapidly, and process will soon become very inefficient.

We recently introduced a transport model which can be applied to large vascular systems [1, 2]. This model uses 1D finite element for larger vessels and equivalent continuum FEs for capillary beds. Additionally, the model incorporates blood vessel wall properties with respect to hydraulic and diffusive transport.

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In our drug transport model [2], we considered that transport occurs from the arteries into tissue, and back - from tissue to the veins. First transport region is fluid domain consisting of blood, which is coupled with second region: solid (tissue) domain. We assume that transport of molecules, for both capillary and tissue domains, occurs by both convection and diffusion, by assumption that tissue is treated as a porous solid.

The most important part of generating realistic and accurate models for simulation of drug transport is to have appropriate tools. In order to create realistic model, a number of sub-steps have to be taken - from CT images to FE model. Our first step was the 3D segmentation from CT images using indoor CAD software. Next step was skeletonization of capillary objects, so capillaries can be used as 1D elements in the simulation. Skeletonization procedure is done using Augmented Fast Marching Method (FMM) [3, 4]. The reconstructed 1D trees of capillaries and the volumetric 3D model are then employed in numerical simulations of drug transport using the finite element method.

In Sect. 2 we summarize all methodologies implemented in our reconstruction process and modeling. In Sect. 3 we briefly formulate our computational model. At the end, in Sect. 4, we present results for two different examples: mouse pancreas and human liver models.

2 Reconstruction of the 3D Tissue and Capillary Network

The task of organ modeling, with detailed vasculature, can be divided in few sub-problems. First of all, geometry of larger vascular structures has to be identified from data obtained by CT scans.

Images are taken from CT scans, and reconstruction process is done using our CAD-Dicom software for 3D reconstruction. CAD-Dicom software is used for semi-automatic segmentation and generation of 3D meshes from dicom files (Fig. 1a). Graphical user interface of CAD-Dicom is build up using Visual Studio MFC classes. Meshes are then voxelised through a binvox application [3].

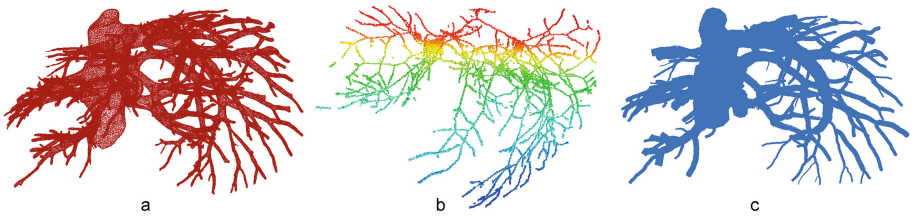

Fig. 1. (a) Segmentation process of liver model – 3D reconstruction of capillaries from CT images - mesh of outer faces; (b) Skeletonization of voxelized capillary network using SkeletonSandbox interface software [3]. (c) Diameter recognition of skeletonized lines using indoor CAD-Darcy graphical interface, according to voxelized capillary network.

In order to abstract from the voxel shape, various shape descriptors have been proposed. In 1967, Blum introduced the skeleton, which transforms a shape into

another one that is of a lower dimensionality than the shape it describes [3]. Skeletons and medial axes can be produced in the three main ways: Morphological thinning, Geometric methods, and Distance transform (DT). A third class of methods computes the distance transform (DT) of the object's boundary. Recent approaches for computing the DT use the robust and simple implementation of Fast Marching Method (FMM) for evolution of boundaries in normal direction with constant speed.

In our model we used Skeleton sandbox software [3], and also algorithms based on Fast Marching Methods [4]. Skeleton Sandbox software uses a simple and robust method for computing skeletons for arbitrary planar objects and centerlines for 3D objects - Augmented FMM. Another algorithm based on FMM is available as open source Matlab code [4]. The resulting parameter field was then thresholded to produce the skeleton branches created by boundary features of a given size (Fig. 1b).

At the end, using our CAD-Darcy interface software, and algorithms for diameter recognition, we calculate diameters for each of pipe segments (Fig. 1c).

3 Fundamental FE Equations

In our recently introduced multi-scale transport model [1, 2] larger vessels are modeled by simple 1D finite elements, while capillary bed is modeled by equivalent 3D continuum finite elements. Introduced model couples convective–diffusive transport within fluid (capillaries) and solid (tissue) domain, where coupling is done using fictitious 1D finite element. Blood flow at lower hierarchies within tissue is modeled as parallel flows in a 3D porous media governed by the Darcy equation.

Blood vessel can be described as deformable pipe through which blood flows. In our paper [1] we formulated a 2-node finite element with deformable cross-section. In general, nodal variables can be pressures and nodal fluxes. From the continuity equation and the equation of the balance of linear momentum, the Navier-Stokes equation can be transformed into incremental-iterative FE balance equation, which can further be expressed for a time step Δt and iteration i, as [5]:

$$\left(\mathbf{M}^{p(i-1)} + \mathbf{K}^{p(i-1)}\right)\Delta\mathbf{P}^{(i)} = \mathbf{F}^{(i-1)} - \left(\mathbf{M}^{p(i-1)} + \mathbf{K}^{p(i-1)}\right)\mathbf{P}^{(i-1)} + \mathbf{M}^{p(i-1)}\mathbf{P}^{t} \tag{1}$$

where the matrix components $M_{IJ}^{p(i-1)}$, $K_{IJ}^{p(i-1)}$ and $F_{I}^{(i-1)}$ are given in [2] in details, and $\mathbf{P}^{t}$ is nodal pressure at start of time step.

If we assume that blood can be considered as homogenous fluid, convective-diffusive transport within blood vessels will have mathematically very simplified form. In case of diffusion transport, in addition to (1) we will have another system of equations following from the balance equation of diffusion [2]:

$$\left(\frac{1}{\Delta t}\mathbf{M}^{c} + \mathbf{K}^{c} + \mathbf{K}^{cv}\right)^{(i-1)}\Delta\mathbf{C}^{(i)} = \mathbf{Q}_{c}^{ext} + \mathbf{Q}_{c}^{V} - \frac{1}{\Delta t}\mathbf{M}^{c(i-1)}\left(\mathbf{C}^{(i-1)} - \mathbf{C}^{t}\right) - \left(\mathbf{K}^{c} + \mathbf{K}^{cv}\right)^{(i-1)}\mathbf{C}^{(i-1)} \tag{2}$$

where the matrices M_{IJ}^{c}, K_{IJ}^{c}, K_{IJ}^{cv} and the source vector $\mathbf{Q}_{c}^{V}$ are given in [2], and $\mathbf{C}^{(i-1)}$ and $\mathbf{C}^{t}$ are nodal concentrations at the iteration $(i - 1)$ and start of time step, respectively; $\mathbf{Q}_{c}^{ext}$ is the external nodal flux vector, and $\mathbf{K}^{cv}$ is matrix which couples convection and diffusion within the pipe.

The boundary between fluid and tissue domain is represented by blood vessel walls. As was extensively investigated in the past, particulate transport through the wall is very complex due to various physical and biological effects. In order to overcome those challenges, we in [2] introduced 2-node 1D fictitious elements which can connect these two domains. For each of those domains, in practical applications, we select continuum nodes which are connected to the 1D pipe elements. Introduced 1D fictitious element includes all wall transport properties, regarding diffusion and convection transport. Additional details regarding the implementation of fictitious 1D elements and connection between domains are given in [2].

4 Results

In following two examples we present applications of our numerical model for large systems consisted of blood vessels and tissue: one for a mouse pancreas and the other for a human liver. Data were obtained by CT imaging at Huston Methodist Research Institute, and at MD Anderson Cancer Center, Houston, USA. The computational models were generated at the R&D Center for Bioengineering, Kragujevac, Serbia and implemented into our FE code PAK [6].

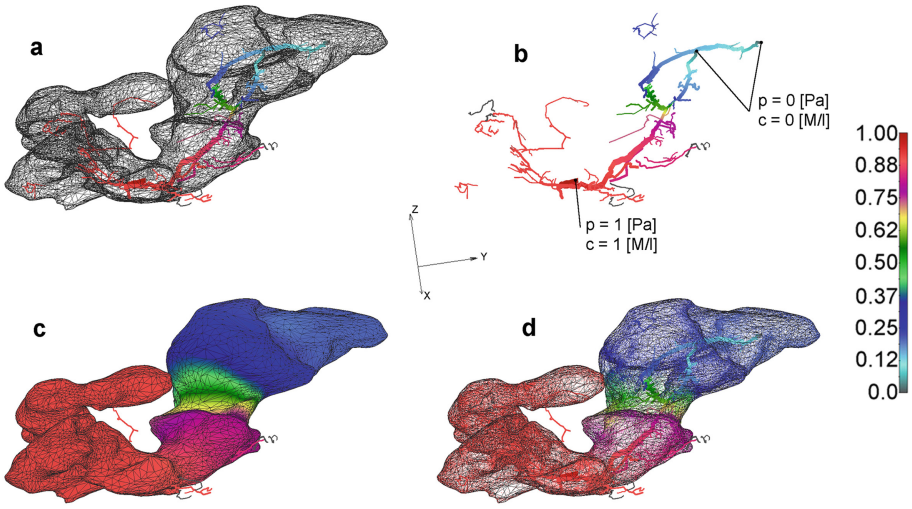

Fig. 2. Numerical model of pancreas vasculature and tissue. Pressure field for first (t = 2.5 s) time step of simulation. (a) 1D vascular network together with 3D mesh, (b) 1D mesh with prescribed values for pressures, (c) Full 3D mesh of tissue, (d) 1D vascular network together with 3D mesh – 3D results represented by dots.

Both models are composed of 1D finite elements representing blood vessels, fictitious elements to connect fluid and tissue domain, and 3D elements for tissue. Prescribed values for blood vessels are inlet/outlet pressures and inlet/outlet concentrations (Figs. 2b and 3c). Input parameters for both models are: Inlet pressure is 1 Pa, Outlet pressure is 0 Pa, Inlet concentration is 1 M/L, Outlet concentration is 0, Viscosity of fluid is 10^{-3} Pa s, Leakage coefficient of vessel wall is 10^{-11} mm/s (convection through vessel wall), Diffusion coefficient in vessels is 10^{4} mm^2/s, Diffusion coefficient in 3D tissue is 0.5 mm^2/s, and Darcy coefficient in 3D tissue is 10^{-15} mm^2/Pa s.

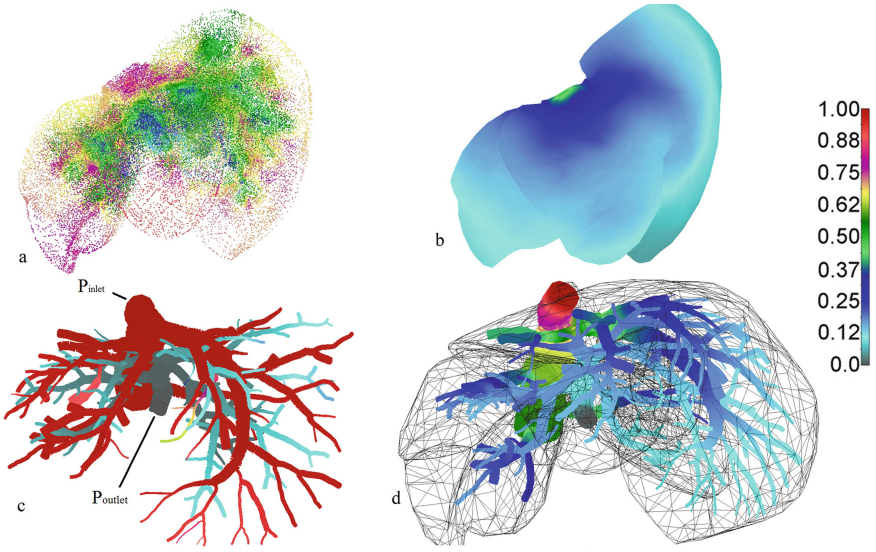

Fig. 3. Numerical model of human liver: (a) Pressure field for first (t = 2.5 s) time step of simulation - 1D vascular network together with 3D mesh (3D results represented by dots), (b) Concentration field for t = 2.5 s - full 3D mesh of tissue, (c) 1D mesh with prescribed values for pressures, (d) Concentration distribution - 1D vascular network with outer mesh of 3D model.

The pressure distribution within tissue and capillary network is shown in Fig. 2 for mouse pancreas model, and Fig. 3a and c for human liver, where the pressure changes from the inlet artery to the outlet vein. The concentration field is displayed in Figs. 3b and d, where concentration gradients are evident from the region of inlet artery to the region of outlet vein. The presented results for pressure and concentration fields show applicability of the presented model to other specific organs.

5 Conclusion

The goal of this study was to describe challenges in 3D reconstruction of complex geometries, such as tumors or human organs, and also in generating accurate computational model which is feasible for simulation of mass transport within those domains,

consisted of large blood vessel networks. We used recently formulated and computationally efficient 1D pipe finite element for blood vessels [1], which can take into account wall deformability in a simplified form. To couple transport between blood vessels and surrounding tissues we used recently introduced fictitious 1D finite element [2], which accounts for the hydraulic and diffusive properties of the vessel walls.

Presented computational methodology was implemented into our FE code PAK [6] - a research code developed over decades. The listed numerical concepts, which form the basis of our model, are implemented in two different examples: mouse pancreas and human liver model.

CT data were processed by the semi-automatic segmentation algorithms generating 1D structures for the vascular trees and a 3D volumetric model of the pancreas and liver tissue. Reconstruction procedure is done using third party software and source codes.

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