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Modeling Liver Physiology: Combining Fractals, Imaging and Animation

Debbie W. Lin, Scott Johnson, C. Anthony Hunt
Department of Biological and Medical Informatics, University of California San Francisco, CA 94143 USA

Abstract-- **Physiological modeling of vascular and microvascular networks in several key human organ systems is critical for a deeper understanding of pharmacology and the effect of pharmacotherapies on disease. Like the lung and the kidney, the morphology of its vascular and microvascular system plays a major role in its functional capability. To understand liver function in absorption and metabolism of food and drugs, one must examine the morphology and physiology at both higher and lower level liver function. We have developed validated virtualized dynamic three dimensional (3D) models of liver secondary units and primary units by combining a number of different methods: three-dimensional rendering, fractals, and animation. We have simulated particle dynamics in the liver secondary unit. The resulting models are suitable for use in helping researchers easily visualize and gain intuition on results of in silico liver experiments.**

*Keywor*ds-- **Agent-based modeling, simulation, visualization, organ physiology, liver, vascular, drug transport, visualization**

I. INTRODUCTION

A full understanding of pharmacological effects of drugs on major organs is often difficult to obtain from traditional pharmacological analysis of experimental data. It is well known that the number and size of independent portal segments and hepatic venous sectors and their distribution on the liver surface show great anatomical variations. The variation in vascular architecture influences how xenobiotics influence clearance and distribution. Patients with cirrhotic livers often undergo liver resection. For example, in experimentally induced biliary cirrhosis, anatomical modifications of the hepatic vascular structures have been documented with most investigators observing predominantly neovascularization of arterial branches. Rearrangement of portal venous branches has also been found under the same conditions, although scientists have not agreed as to the cause of these changes.

Scientists must have methods to estimate the minimum amount of liver volume needed to guarantee sufficient liver function and to gain insight on drug dynamics due to vascular rearrangements[1]. The liver and its major venous and arterial branches can be viewed using standard CT, MRI and PET imaging methods; however, due to the low resolution of imaging output, viewing the number and distribution of liver segments remains difficult. Due to the current status of imaging technology, the visualization and complete prediction of interaction between drugs and functional liver parenchyma remains elusive. Moreover, with the increasing application of in silico experimentation in biological and pharmacological research, it is apparent that scientists with computer-based experimental platforms for testing hypotheses will need a means for better visualizing the results of experimental simulations.

We have developed validated dynamic 3-dimensional models of virtualized liver secondary units, primary units and their vasculature by combining a number of different methods: three dimensional rendering, fractals, animation, and imaging. We aim to provide the visual capabilities to help scientists analyze the effect of pharmacological interactions with the liver under varying vascular structure arrangements: different number, size and arrangement of liver branches.

To represent liver physiology in silico, an agent-based model of isolated perfused rat liver experiments (IS-IPRL) has been developed by the Biosystems Group at UCSF. IPRL provides scientists with the capability to test experimental hypotheses on an isolated perfused rat experiment simulator [2]. An interactive platform to visualize IPRL results is our goal. The majority of organ visualization projects focus on visualization of drug dynamics in the liver by developing 3D image reconstructions and accompanying algorithms for modeling vasculature of an organ from the results of one actual study. Kitaoka calls these 'virtualized organ' models. 'Virtual organs' however are models where the virtual images are created entirely by the computer [3]. We have developed a method for dynamically visualizing 3D virtual rat liver secondary units, liver vasculature and liver drug interactions from isolated perfused rat liver (IS-IPRL) simulation results.

II. METHDOLOGY

A. Liver Physiology

The functional unit of the liver is the lobule [4]. Anatomically, each liver lobe contains hundreds of lobules. A lobule is roughly, a hexagonal arrangement of plates of hepatocytes radiating outward from a central vein (CV) in the center. At the vertices of the lobule are regularly distributed portal triads (also known as portal tracts). Perfusion studies demonstrated that each lobule contains several acini that include terminal afferent vessels (final branches of portal vein and hepatic artery as well as the bile duct, called portal triad). The acinus is comprised of a network of sinusoids

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that separate one-cell thick hepatocyte formations. The acinus consists of an irregular shaped, roughly ellipsoidal mass of hepatocytes aligned around the hepatic arterioles and portal venules just as they anastomose into sinusoids. Several hundred lobules form eight liver secondary units defined by the branching pattern of the portal vein and the localization of the hepatic veins [5]. The liver is composed of the assembly of these eight secondary units.

The liver has a dual vascular blood supply through the portal and hepatic arterial veins. All of the blood which passes through the intestine and spleen is delivered to the liver by the hepatic portal vein. There are three main hepatic veins. They drain the lobules through the sinusoids and start as intralobular veins. The liver also receives arterial blood, carrying oxygen, from the hepatic artery. The bile duct leading to the intestine collects bile. Hepatocytes form linear cords, within which a network of bile canaliculi provides passage through intercellular channels to the nearest branches of the bile duct.

Fluid transported to the lobules is distributed at the portal triad into the surrounding parenchyma. Zahlten et al. focus on the correspondence between the region where fluid is supplied by a third order portal vein branch and the human liver secondary units. They use CT image 3D reconstruction of the portal vein and a symbolic tree algorithm to analyze the tree-like branching pattern of third order portal veins [6]. Masyuk et al. examined the effect of alpha-naphthylisothiocyanate (ANIT), a compound that causes selective proliferation of epithelial cells that line the bile ducts, by using tracing images and performing a 3D reconstruction of the biliary tree and accompanying major vasculature [7].

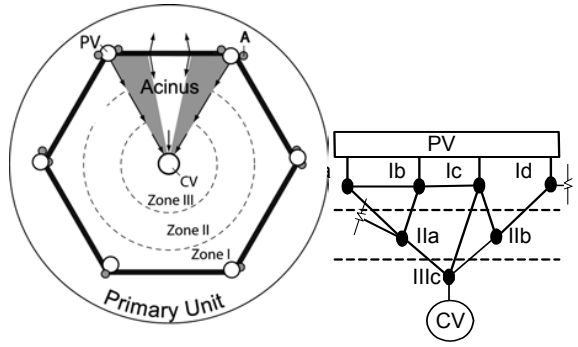

Fig. 1a **Fig. 1b**

Fig. 1a Figure of a primary unit of a liver including the acinus which is composed of the portal vein-PV, the central vein-CV, the bile duct-A **Fig. 1b.** A 2 dimensional illustration of a possible sinusoid-al network structure connecting *one* Zone III node to the CV.

B. *In silico IPRL*

To represent such a system, we use the FURM-IS-IPRL a model developed by the UCSF Biosystems Group to simulate drug dynamics in the liver lobule. The group is developing a new class of computer models that use object-oriented (OO), agent-based models (ABMs). The computer models are being used to run simulated experiments on isolated perfused rat livers (IPRLs). As a system, it captures liver function as an organized assembly of sub-organ microstructures, (i.e. sinusoids, acini, lobules). Here, we visualize the data output from IS-IPRL. The IS-IPRL project is ongoing and currently independent of this project. [1] Liver lobule ABMs are designed to account for data from multiple sources, but specifically drug disposition and metabolism data obtained from experiments on isolated perfused rat livers (IPRLs).

C. Fractals and Physiology

The branching structures of vascular systems have been attributed with having fractal architectures, most commonly in the lung, in blood arteries, and the kidney [8,9]. Fractal properties of arterial trees are characterized by their fractal dimension. They are defined as a power law progression of a functional or geometrical property (flow rate, velocity, branch length or diameter) along the tree. Because of this, fractal systems are most suitable for modeling vascular systems where the functional units of the organs are set in a fairly symmetric and uniform manner. However, the systemic arterial system and the system of vessels within each organ have fractal character but non-symmetric and non-uniform distributions of vessels that function to distribute the blood supply. Parametric L-Systems have been adapted to model arterial systems that have the theoretical properties of open tree structures with both fractal character and physiological branching properties [9]. We have adopted an algorithm that allows us to model the major and first and second order branches of the liver as a fractal-like tree structure with physiological branching properties including non-symmetry. The methodology we have used to determine the branching angle is similar to Kitaoka's algorithm for the three-dimensional modeling of the human airway tree [10]. Kitaoka outlines two major design principles to inform the branching system of the liver vascular system. The branching structure of the liver must account for fluid transport capabilities and space constraints. The larger the angle of branching, the slower the rate of fluid transport; however, without considerable space, optimal branching angles for all bifurcations cannot be attained. There exists a tradeoff between efficiency of fluid transport and availability of organ space; thus the liver vascular system

[1] See FURM-IPRL
http://biosystems.ucsf.edu/Researc/furm/index.html

must optimize its branching according to space division. The first principle states that the amount of fluid delivery through the branches is proportional to the volume of the region of drug distribution. The second design principle assumes that given optimal branching angle and diameter size, the liver modulates the geometry of the respective branches according to its fluid transport needs [11]. A third principle applies specifically to our model. While Kitaoka's lung model assumes homogenous terminal branches and uniform branching, our model accounts for the non-uniform branching and fractal nature of the vascular system in the liver. We account for all these design principles in our model. For the 1st and 2nd order branches of the liver, our system allows the liver to generate its branching structure taking into account directionality, the spatial constraints of the region where the parent branch bifurcates and non-uniformity of branching for each simulation.

The contour of the organ and the position of the major vessels (hepatic artery, hepatic vein and bile duct) in the liver are fixed and approximated from 3D liver images. The morphology of major vessels in the liver is estimated from 3D reconstruction images. See Fig. 2 While the major vessels are static, 1st and 2nd order branches are dynamically generated by our algorithm based on fractals, on parametric L-systems and the three design principles specified above. Zahlten et al. reconstruct branching from CT image data and specify a "tree-like" vascular structure. Starting at the secondary unit, we implement a similar algorithm for branching up to the 2nd order bifurcations that takes into account both the fractal like nature of arterial systems and physiological space. After 2nd order branching, because the length of the microvascular and sinusoidal branching is on the order of less than a millimeter, specific localization to identify the characteristics of the vascular segment becomes irrelevant. Thus, any branching past the second order is modeled as random directed graphs. See Fig. 1b. We develop separate branching algorithms for the three different vessels in the portal triad: the hepatic artery, the portal vein and the bile duct. At each branch-point, the algorithm assesses the region for growth and optimizes the angle, diameter and length of branches based on the constraints. Approximations for arterial, biliary and venous tree segments were obtained from literature [12, 13, 14].

Each IPRL simulation produces drug concentration outflow curves based on setting a number of parameters: number of sinusoids, length of sinusoids, type of sinusoids, tortuosity of blood flow, among others. The inputs of the parameters will be used as further constraints to inform the visualization.

D. *Maya Rendering and Animation*

We use MAYA™ to visualize our virtual liver. MAYA™ is a rendering and animation software program that has its own scripting language and integrates C++ programming capabilities. We have written script to import data on parameter settings and IS-IPRL output into MAYA™ to generate each visualization. All algorithms are also written in MEL or C++ and run in MAYA™ . IS-IPRL also generates information about the nature of drug transport in the rat liver lobule. We have incorporated this information by using MAYA's particle dynamics capabilites in our virtual rat liver secondary unit.

III. RESULTS

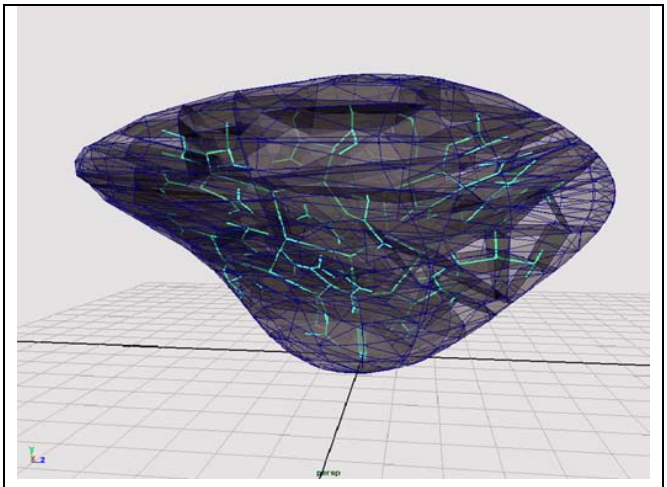

Fig. 2 Visualization of dynamic generation of rat liver secondary unit. The vasculature tree is generated by the algorithm, unit space is filled automatically.

We have developed an iterative replacement procedure for splitting vasculature graphs in the liver secondary unit that mimics the vasculature of physiological realistic liver secondary units. Node replacement based on L-systems and fractal segment substitution was used to generate the vascular branching. Our algorithm takes into account the organ space, fluid efficiency tradeoff Fig. 2 The branching algorithm begins from a major arterial vessel and forms 1st and 2nd order branches. Branches past the 2nd order are approximated using random directed graphs, which fill the remainder of the organ space of the liver secondary unit. Fig. 1b Localization of drugs can be depicted in the parenchyma by pinpointing the their location throughout the vasculature. Particle dynamics in MAYA™ were used to simulate fluid dynamics.

IV. DISCUSSION

The morpohological character of the vascular and microvascular system of the liver is fundamental to its functional capability. Therefore, any physiological model of

drug-liver dynamics must incorporate a morphological representation of the liver and its subunits. Visualizations of simulated liver dynamics will not only provide scientists with insights about how drugs interact with the liver and its vasculature, but also can give them a qualitative sense of how drugs are affected by morphological variation across different livers. These visualizations along with imaging data are tools that provide scientists with a more comprehensive understanding of drug dynamics in the rat liver.

This research is part of our goal to demonstrate the feasibility of developing an interactive, flexible and easily updateable system that links bio-simulation data with information visualization capabilities. Specifically, the system will generate dynamic 3D virtual tissue section images at the lobule and secondary unit level of the rat liver from bio-simulation data. We have developed a fractal algorithm for liver vasculature that physiologically mirrors rat liver secondary unit morphology. Algorithms are implemented in MAYA™. This allows dynamic rendering and visualization of liver morphology at many levels (lobule, secondary unit and whole liver) as well as the particle dynamics of liver-drug interactions. Simulations of drug interactions with the liver lobule are generated in IS-IPRL. Our system takes IS-IPRL output and visualizes liver-drug interactions for simulated isolated perfused rat liver experiments. This work is an implementation of one of several approaches we are considering in our aim to visualize liver morphology and drug-liver dynamics. In future work, we hope to develop an entire rat liver by recomposing secondary units. We hope to incorporate imaging information of healthy and diseased rat livers so that they can both validate and inform our visualizations and be provided alongside the 3D rat liver visualizations so that scientists are supported by more comprehensive visualization information.

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