Virtual Organ Models

For Drug Transport and Metabolism

Rebeccah Marsh, MITACS

Canada-China Workshop on Industrial Mathematics
August 7, 2007
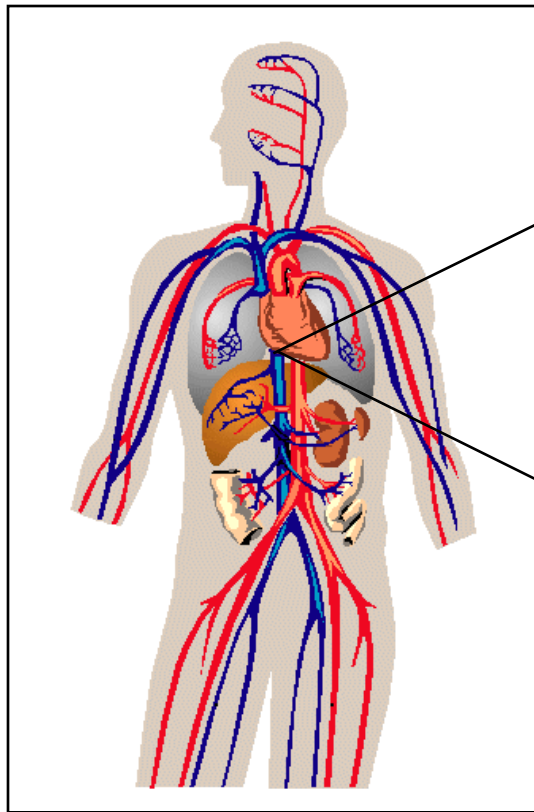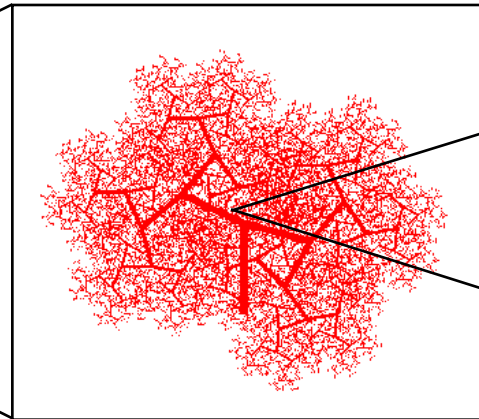
Overview

I.

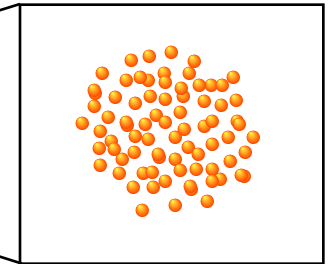## Pharmacokinetic Modeling

# Pharmacokinetics

the medium

the interaction matrix

the ensemble of drug molecules

Challenges

- ***Effectiveness of a drug relies on:***
  - Transport processes
  - Reaction processes

- ***Body tissues are highly heterogeneous***

- ***Physiological processes typically involve many complex chains of reactions***

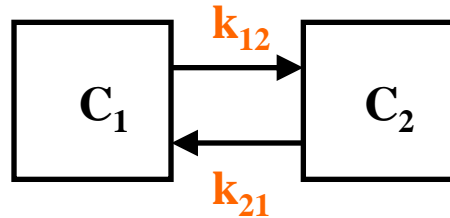- ***Lab experiments and clinical trials are time-consuming, costly, and potentially harmful.***

Compartmental Modeling

$$\mathbf{k_{12}}$$

| $\mathbf{C_1}$ | $\mathbf{C_2}$ |

$$\mathbf{k_{21}}$$
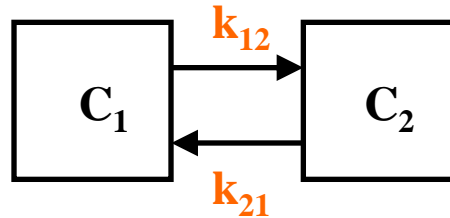
k = kinetic rate coefficient

	Conditions	
	Homogeneous	Heterogeneous
Linear reaction	$\dot{C} = kC$	
Enzyme-mediated reaction	$\dot{C} = \dfrac{v_{\max} C}{K_M + C}$	

Compartmental Modeling

k = kinetic rate coefficient

	Conditions		
	Homogeneous	**Heterogeneous**	
Linear reaction	$\dot{C} = kC$	$\dot{C} = k_0 t^{-h} C$	
Enzyme-mediated reaction	$\dot{C} = \dfrac{v_{\max} C}{K_M + C}$	$\dot{C} = \dfrac{v_{\max} C^X}{K_M + C^X}$	

FRACTAL KINETICS

Objectives of "Virtual Models"

- **Develop physiologically-accurate models**

- **Investigate the behaviour at different scales**
  - Both spatial and temporal scaling

- **Test compartmental predictions**

- **Develop a simulation platform and a visualization tool**

- **Start with the liver: main site of drug metabolism**

II.

Methods

STARS (Computer Modelling Group Ltd.)

- ***Advanced process simulator***

- ***Models the flow of multi-phase, multi-component fluid in porous media***

- ***Employs:***
  - Mass and energy conservation
  - Equations of state
  - Poiseuille flow
  - Darcy's Law

- ***Pressure differences can be due to thermal, mechanical, or chemical processes***
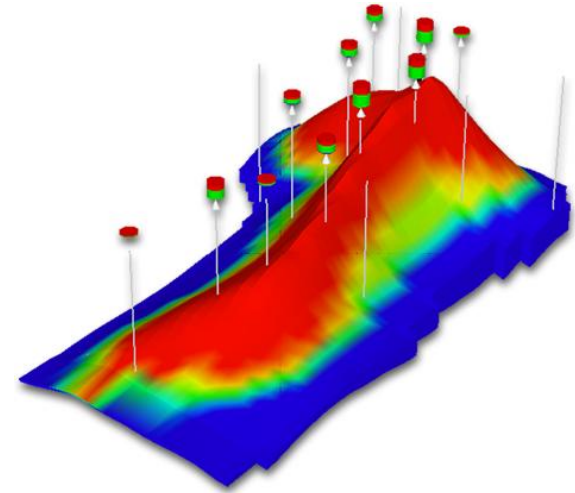
Example: Simulation of Oil Extraction
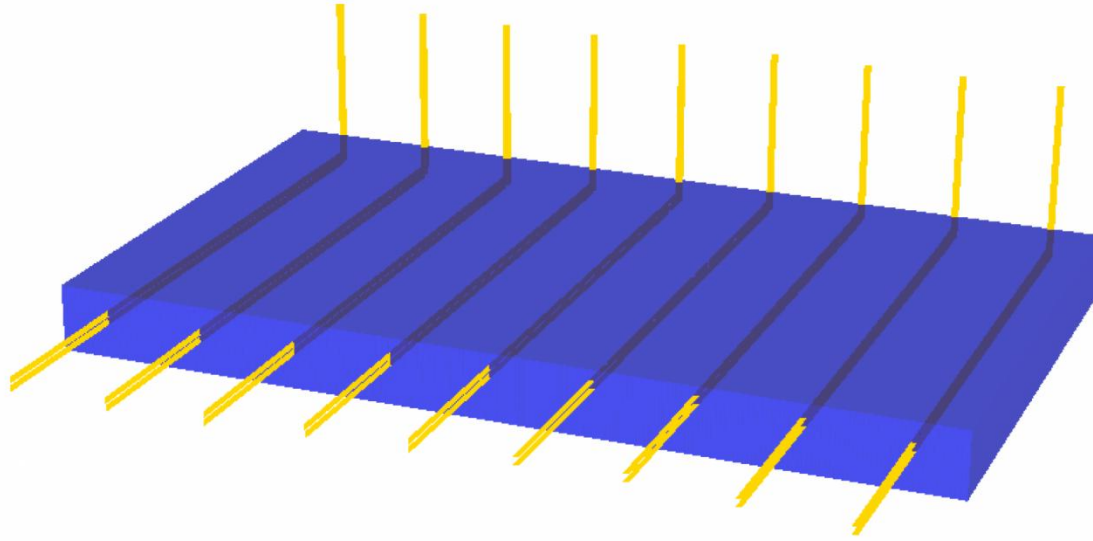
Model Components

- ***Grid***
  - Geometry and dimensions
  - Permeability and porosity of each grid cell

- ***"Rock and fluid" properties***
  - "water" and "oil" components
  - Density, chemical composition, viscosity, melting point, etc.
  - Relative permeabilities

- ***Reactions***

- ***Initial conditions***
  - Distribution of components in the grid cells

- ***Wells - injectors and producers***
  - Location on grid
  - Upper pressure boundary and/or flow rate

- ***Times at which to record data***

III.

Angiogenesis and Vascular Networks

Angiogenesis

Lenormand experiment on immiscible displ
Viscosity in Oil Phase(ARC_O) (cp)   52.00 min   K layer: 1
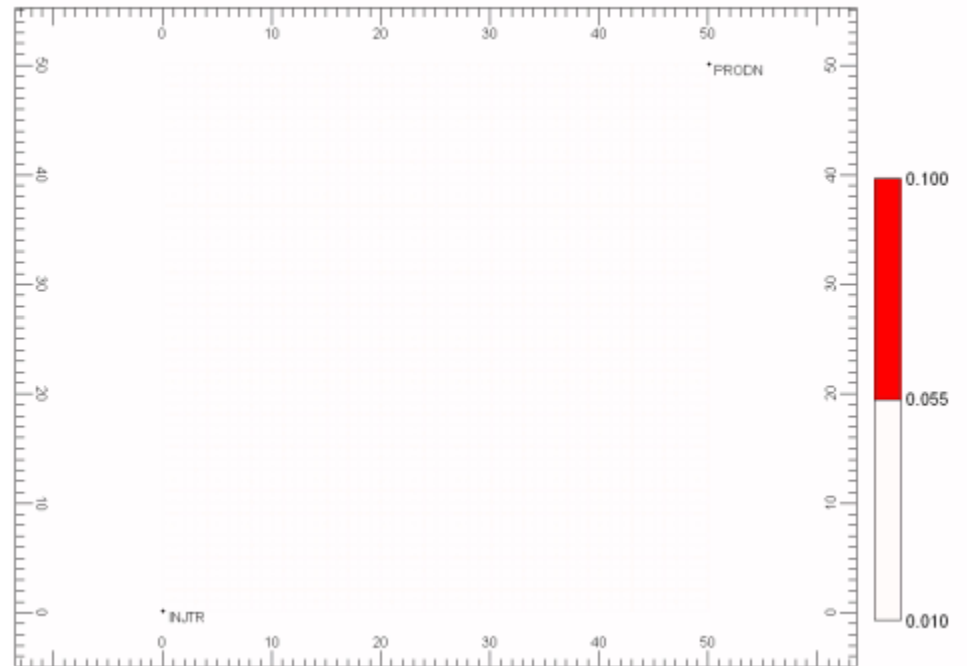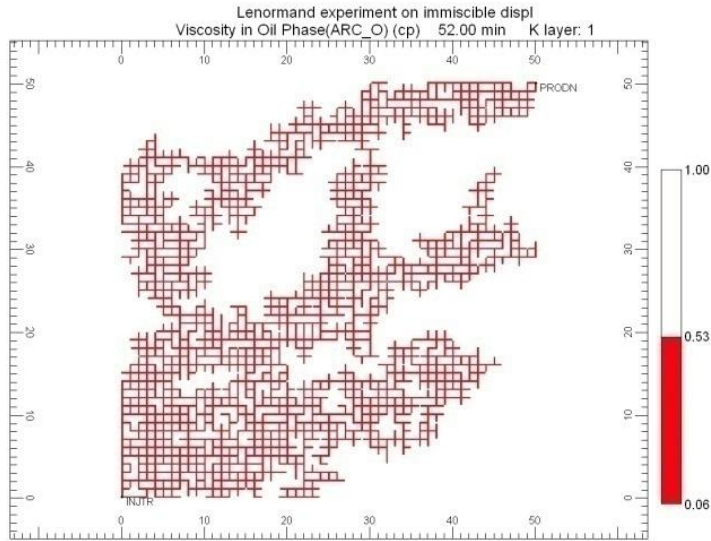
Movement of Glucose Through the Vessels
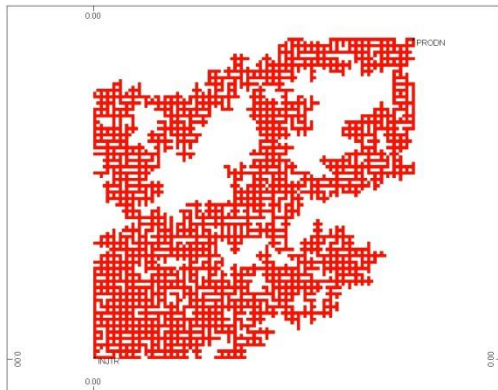
t = 0 min
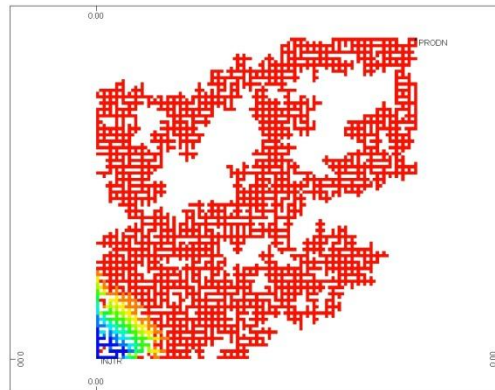
t = 0.02 min
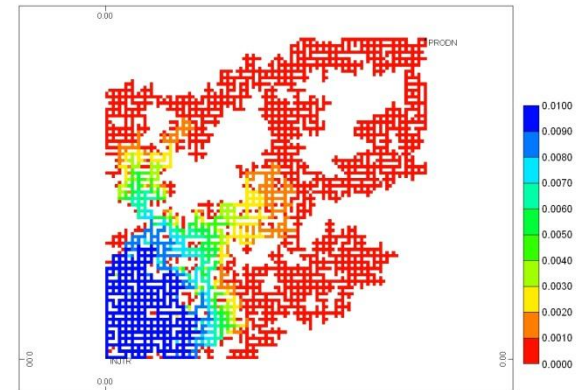
t = 0.14 min
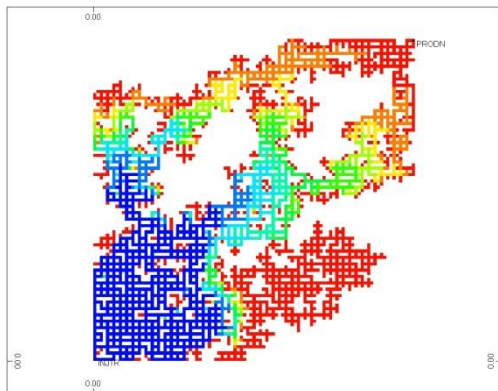
t = 0.25 min
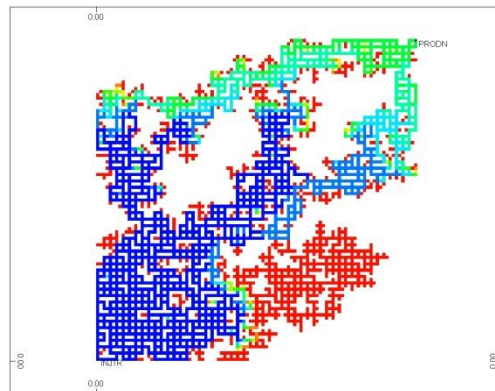
t = 0.4 min
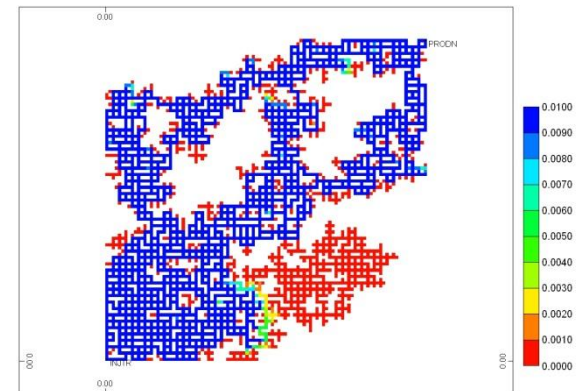
t = 0.61 min

Transient Fractal Kinetics in the Outflow
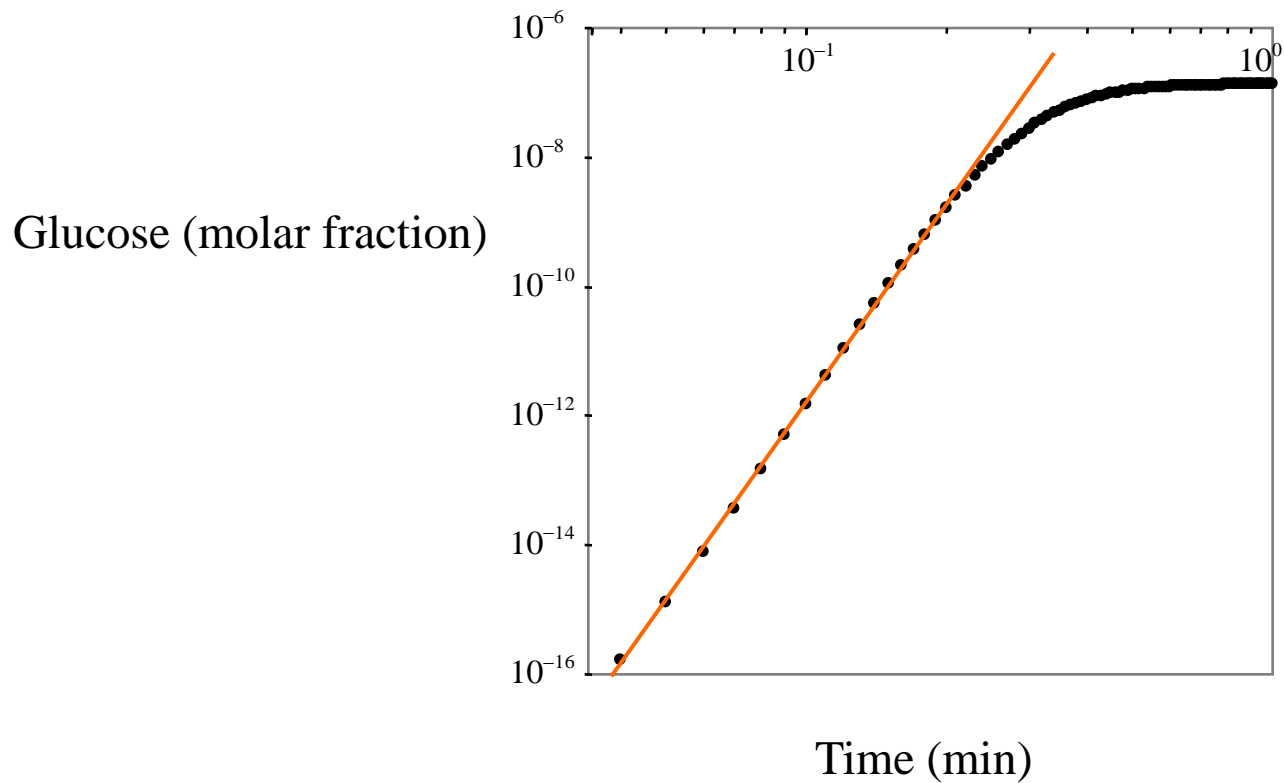
IV.

Liver Functional Unit

The Lobule

Liver Lobule

Detail of Lobule

Hepatic venule

Branch of hepatic artery

Hepatocytes

Sinusoids

Bile duct

Branch of hepatic portal vein
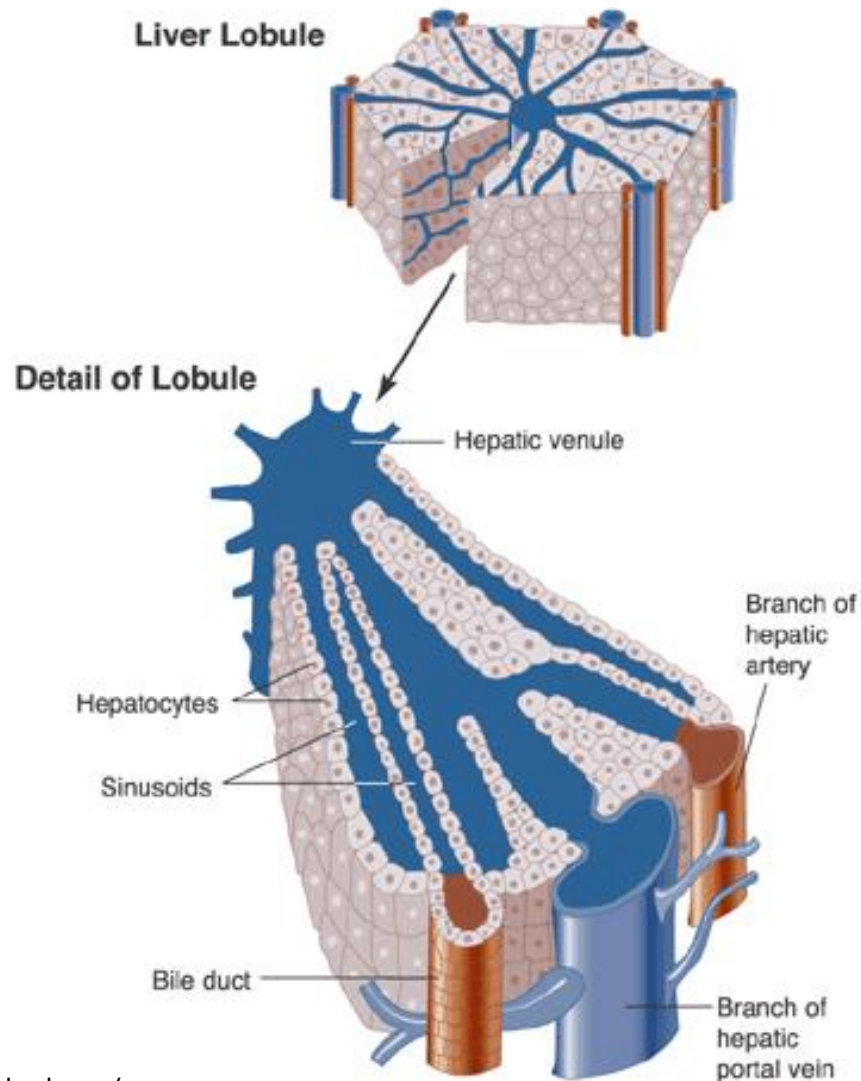
Physiologically-Based Network Model

Vasculature

Hepatocytes

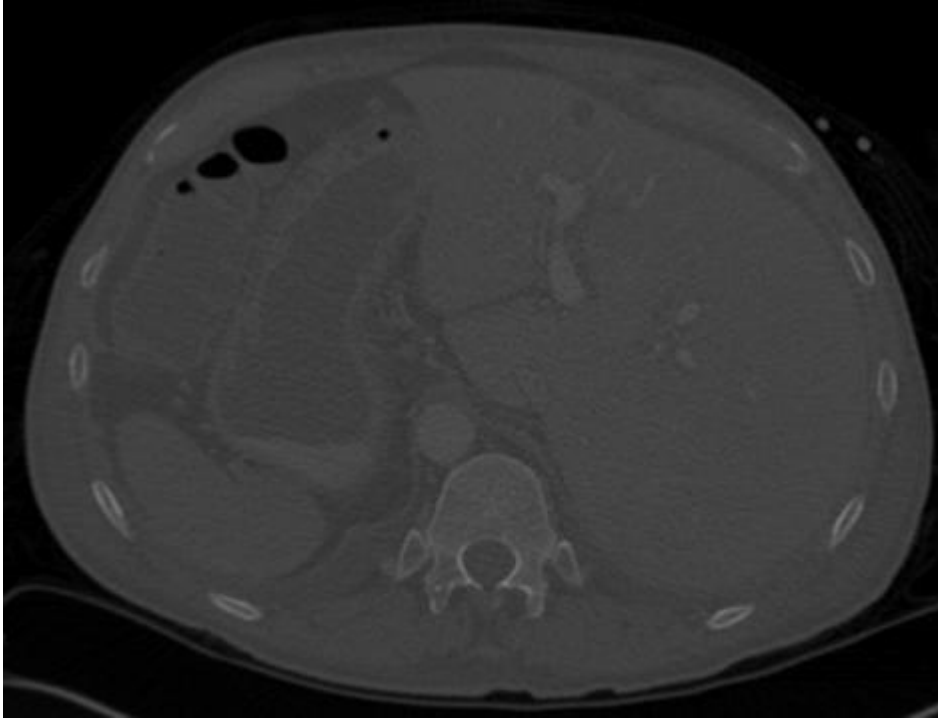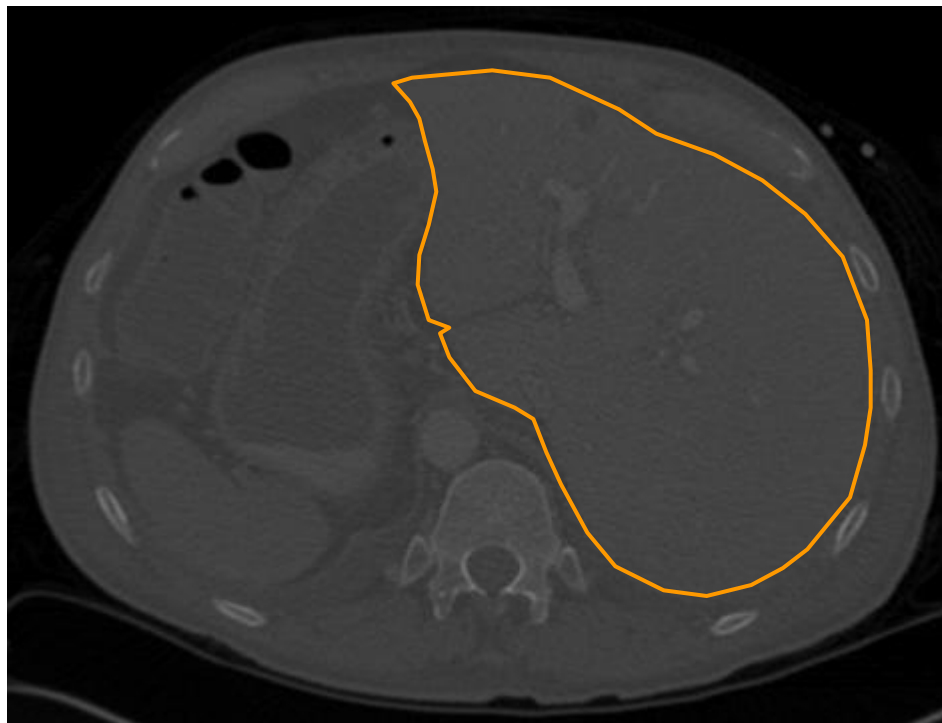# Image-Based Model

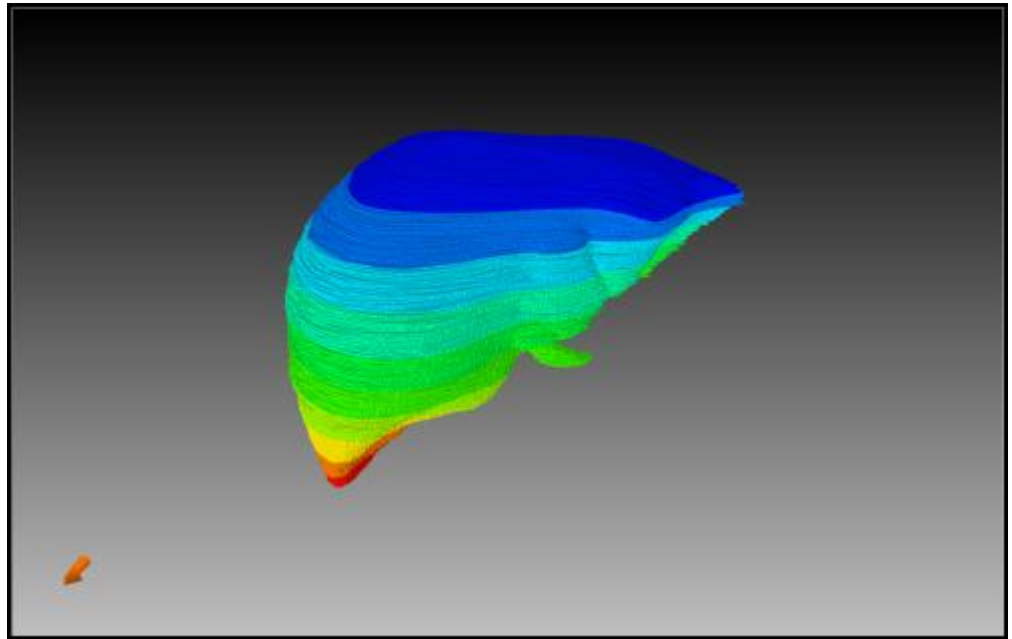Courtesy of Prof. Eddie Wisse
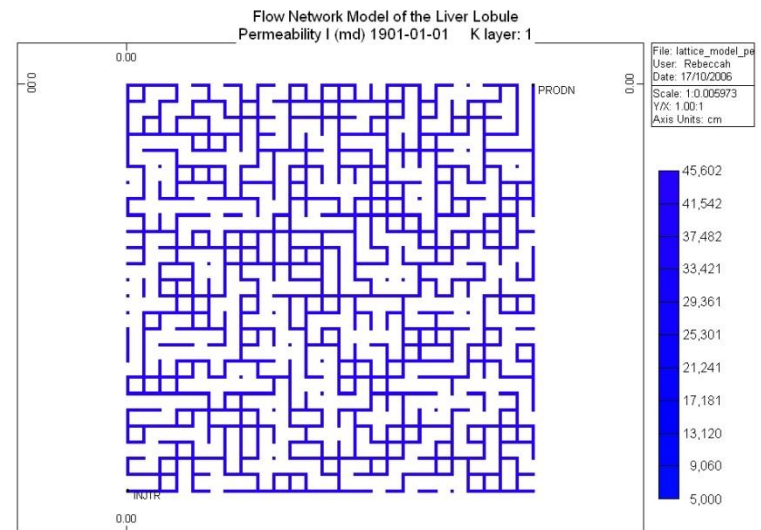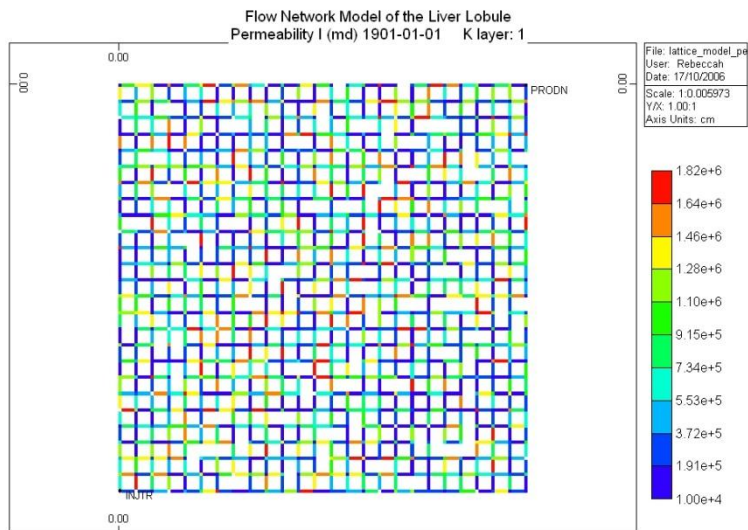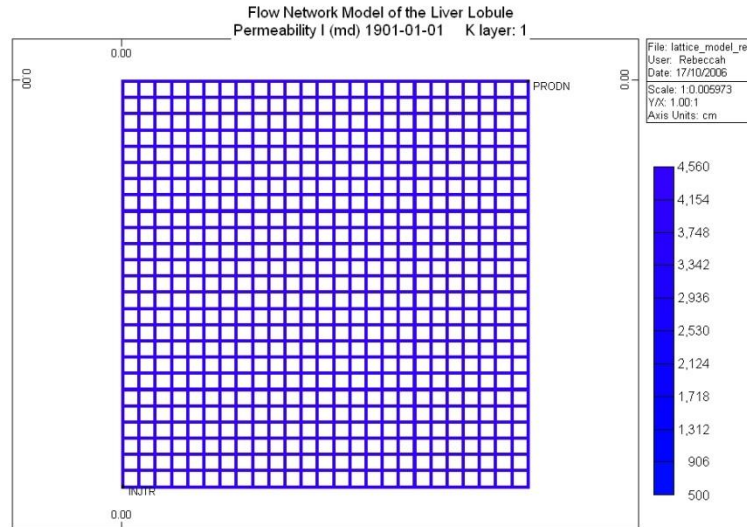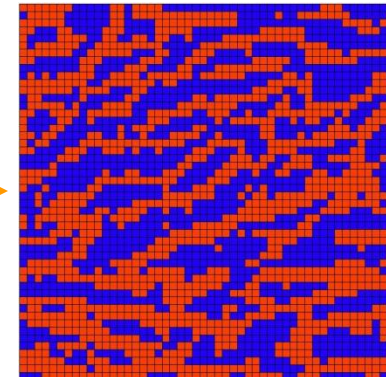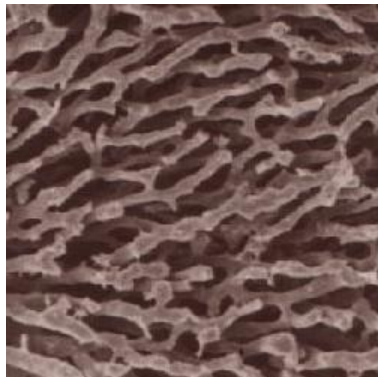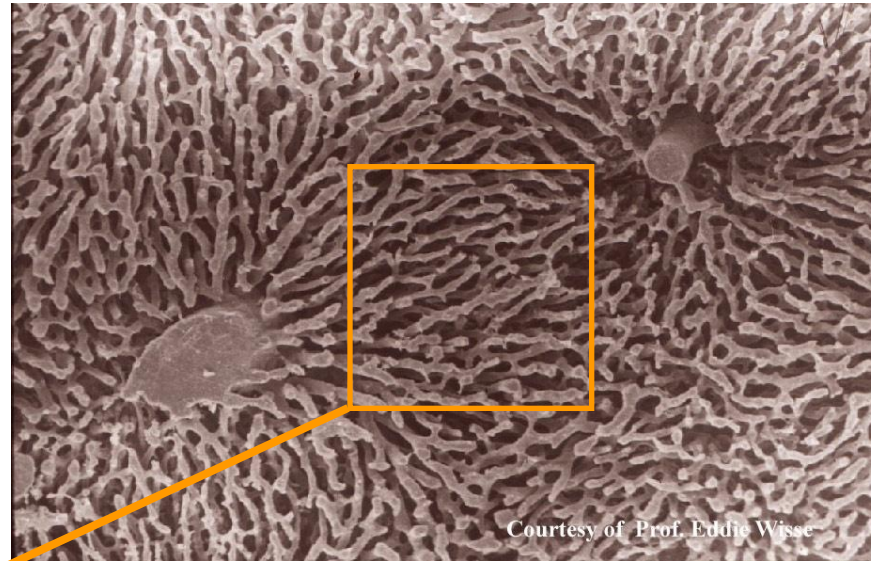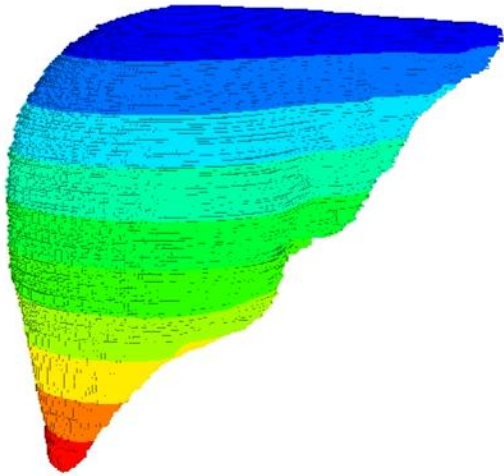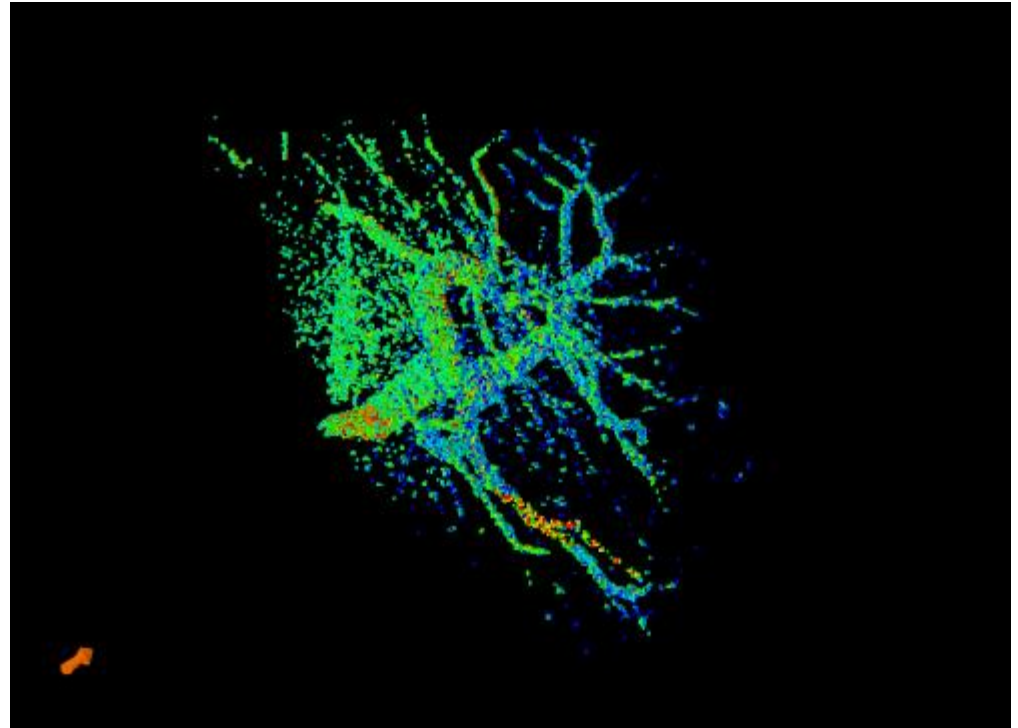
Simulation of Drug Metabolism
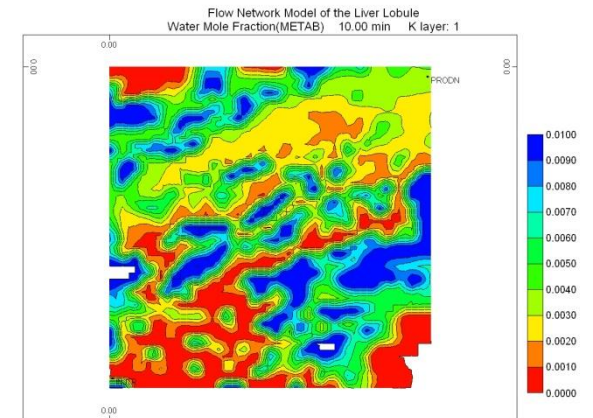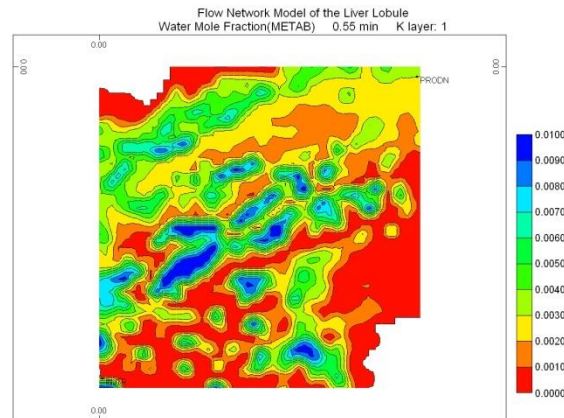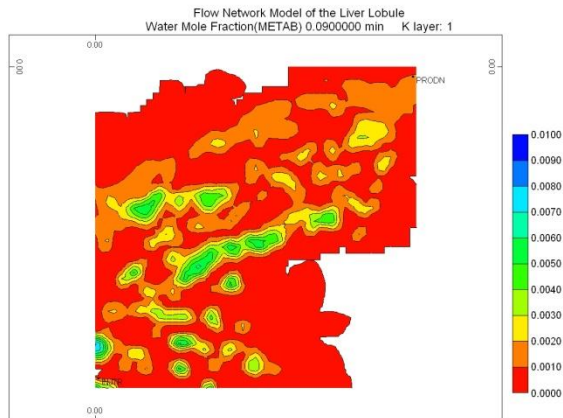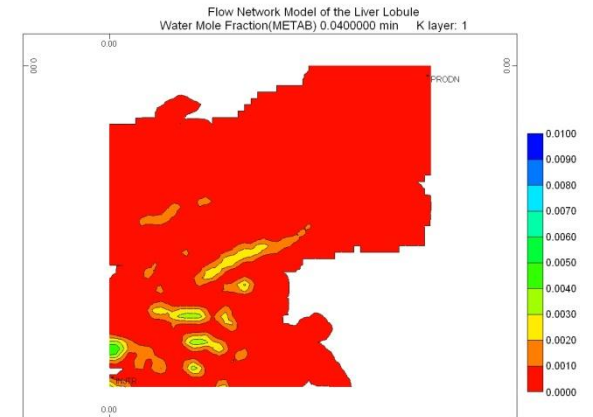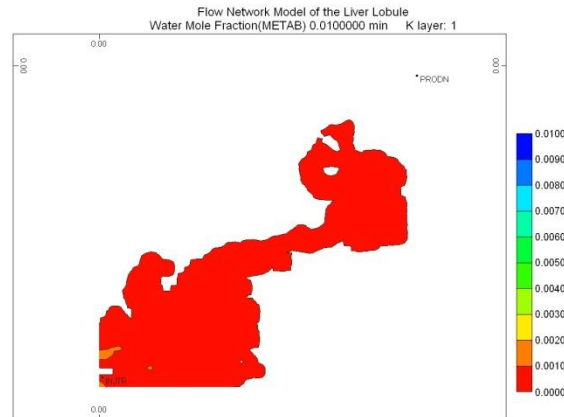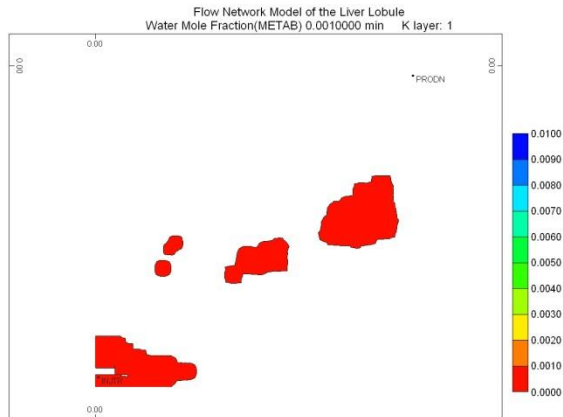
V.

Virtual Liver

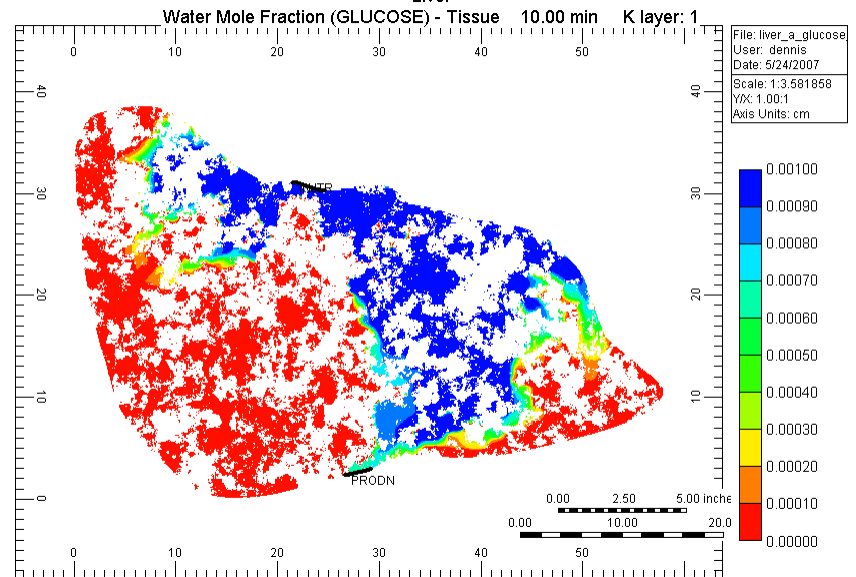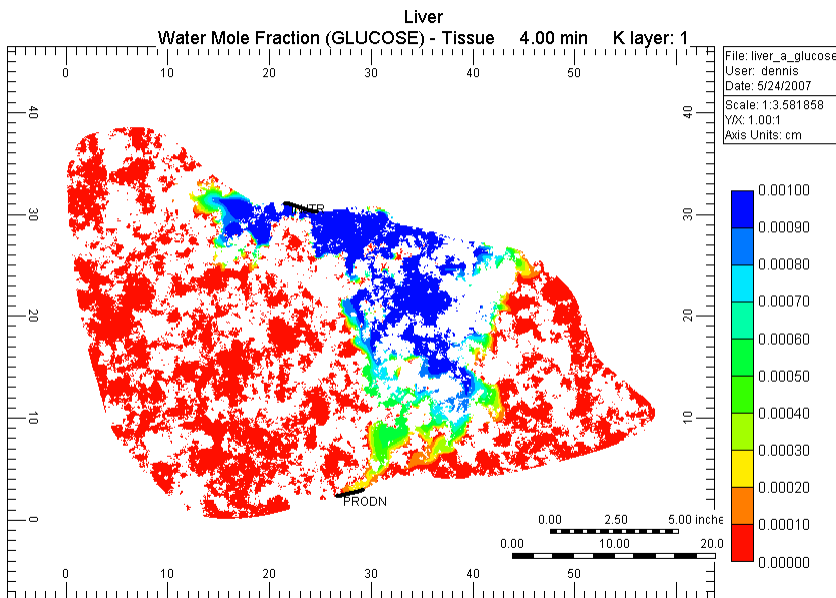# CT Scan of An Abdomen
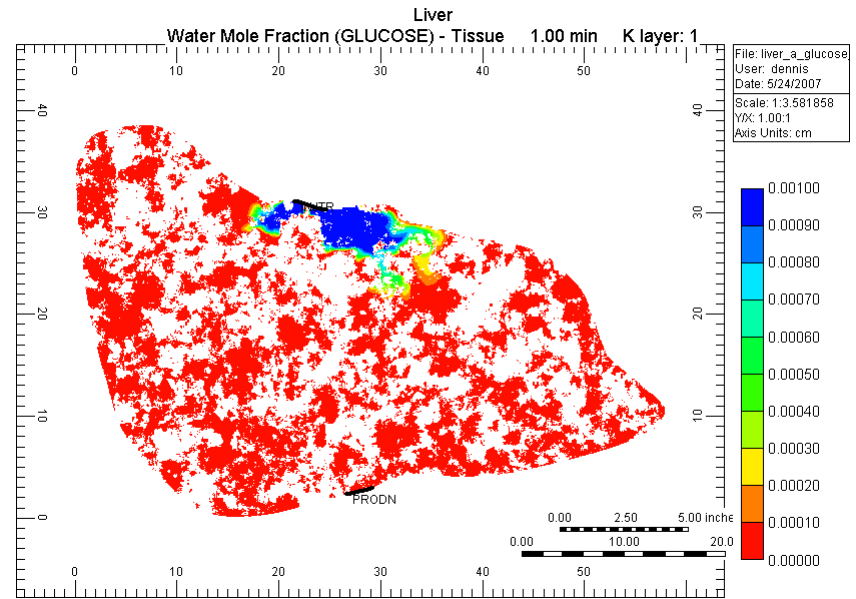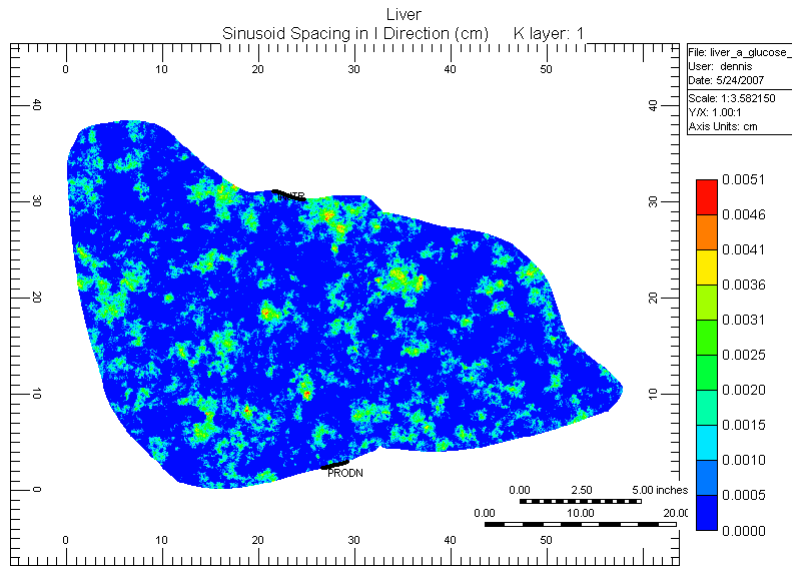
High-Resolution CT Scan

Virtual Liver
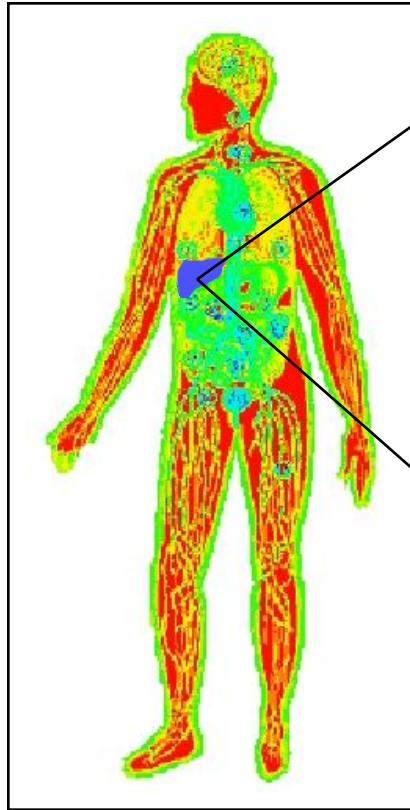
Liver vasculature
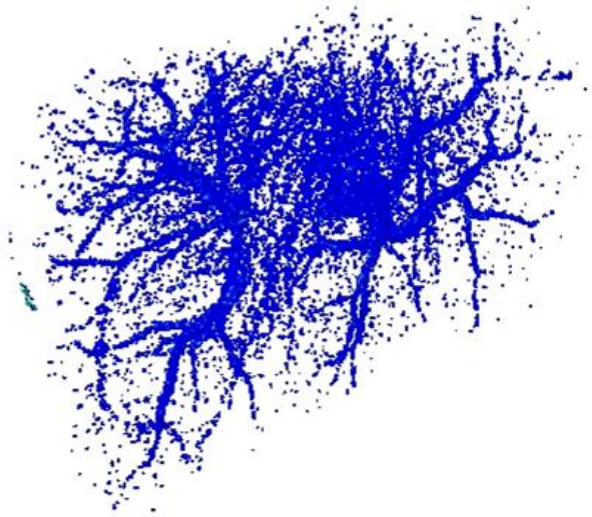
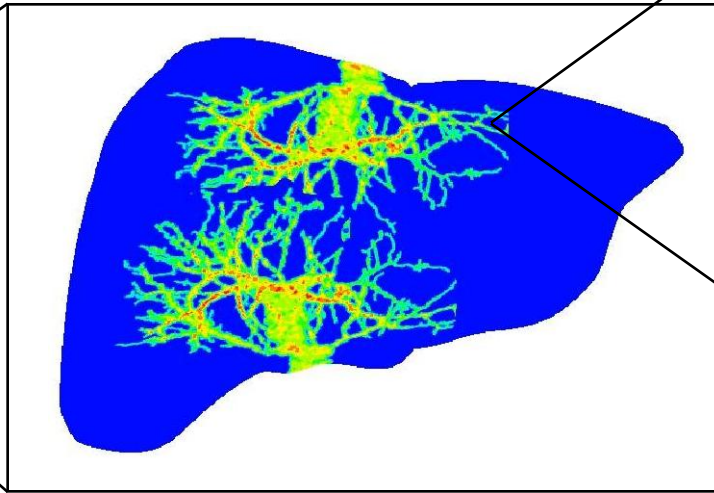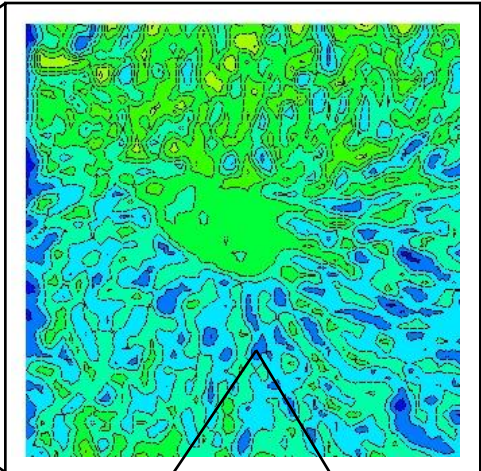# Glucose Transport Through the Liver

VI.

Future Directions

Multi-Scale Modeling

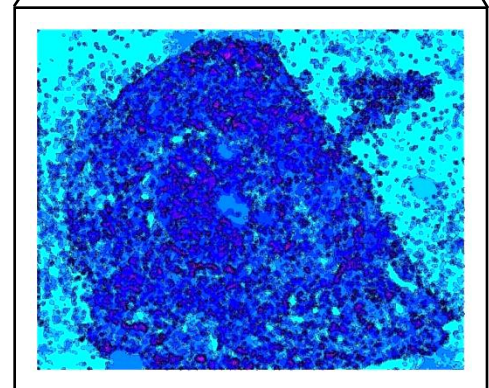whole body

liver

lobule

hepatocyte

Future Directions

- **Compare results with experimental data**

- **Model zonation of lobule**

- **Model other organs**
  - Kidney, GI tract, lung, brain, heart, gallbladder, etc.

- **Model tumours and their vasculature**

- **Model processes at the cellular or subcellular levels**

- **Connect organs into a virtual full-body model**