Biomimetic In Silico Devices

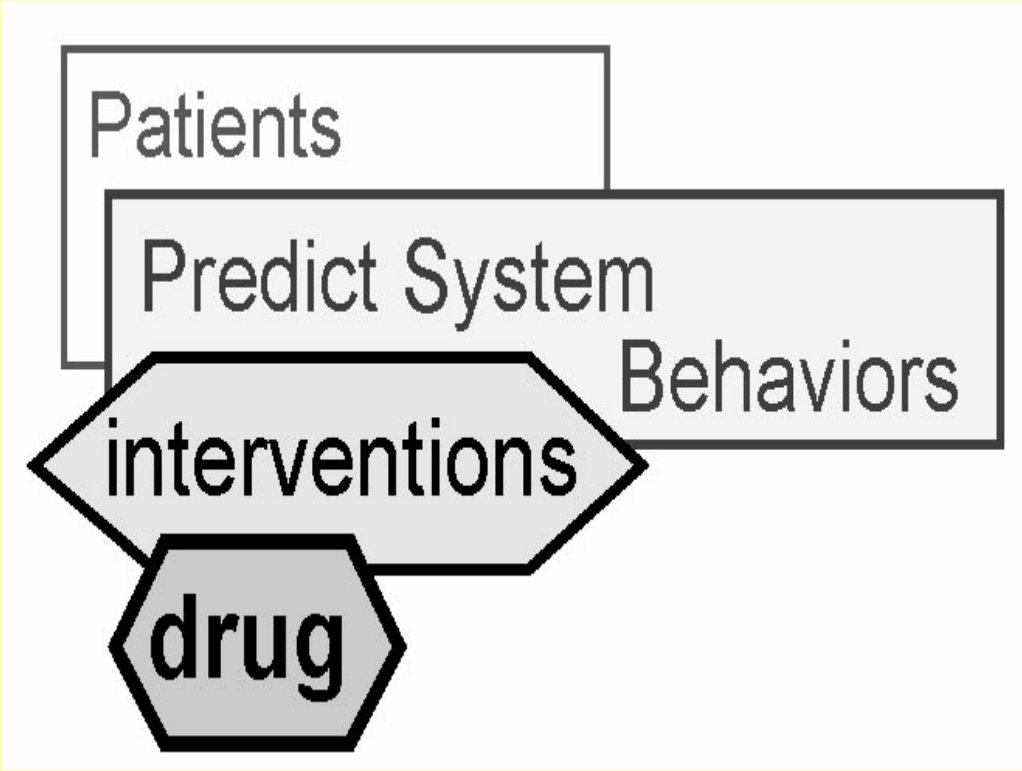
M&Snet Workshop, 2004, San Jose

July 25, 2004

C. Anthony Hunt Presenting

Our Domain of Interest

Our long term interests:



Specific Questions of Interest

- How does an organ – the liver in this case – behave when presented with therapeutic interventions?
- …when intervention = new drug?

In this presentation I …

- Make a case for using a **constructive approach** to build hierarchical, biological system models…

  …to answer the preceding questions
- Make the case for ***not*** using either a top-down or bottom-up (reductionist) approach to modeling systems within organisms
- Present biomimetic in silico devices – models of hepatic **functional units** – that are capable of predicting the metabolism & disposition a new drug…
- … capable of predicting differences in behavior between normal & diseased liver (at different stages of disease)

Overarching Goals

- Develop and use models where model components **map** logically to biological components…

  … & the models are suitable for experimentation
- Better understand **how** biological systems function as they do
- Better understand biological components & their interactions

  … at different levels of organization

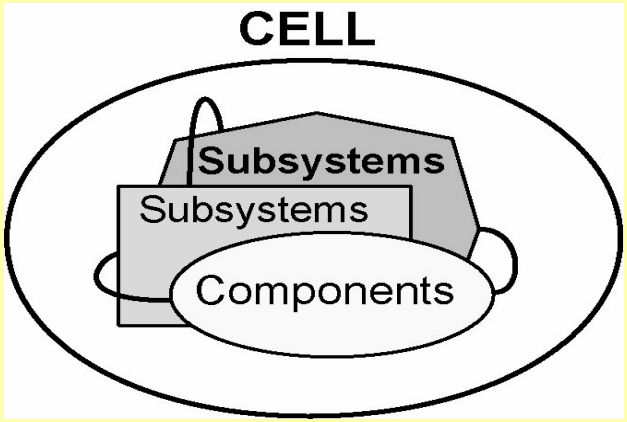
  … in healthy, diseased, damaged & aged states

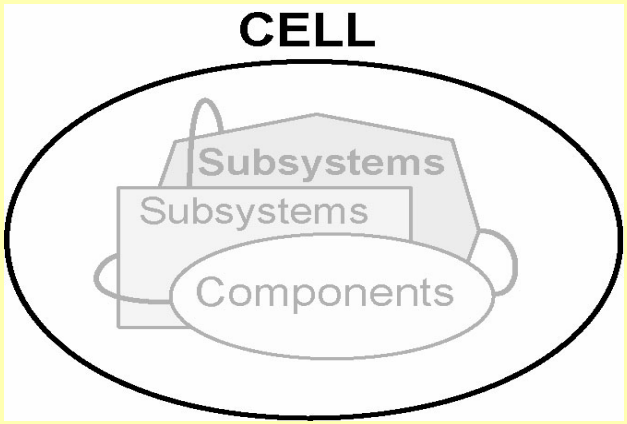
Functional Unit Approach

- Within humans, organ systems are composed of essentially identical **functional units**
- There is important communication within & between functional units
- In most case, e.g., the heart, lung, intestine, liver, the functional unit is an organized collection of cells (more on this later)
- In other cases, the functional unit is a cell

Functional Unit Approach

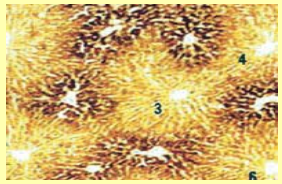
- Within cells there is one level of communication between components…
- …and a different level of communication between cells or between functional units;
- When cells communicate most subsystem details are essentially invisible, and that suggests some modeling options

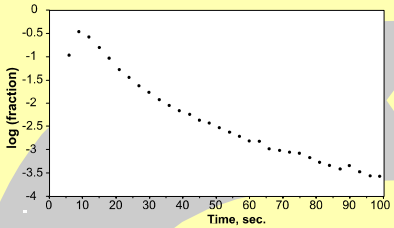




Constructive Modeling Approach

Experimental Data

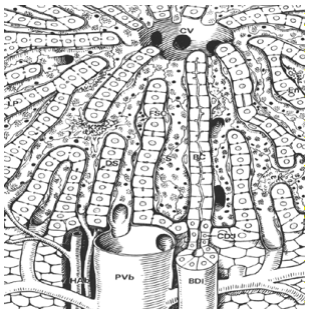




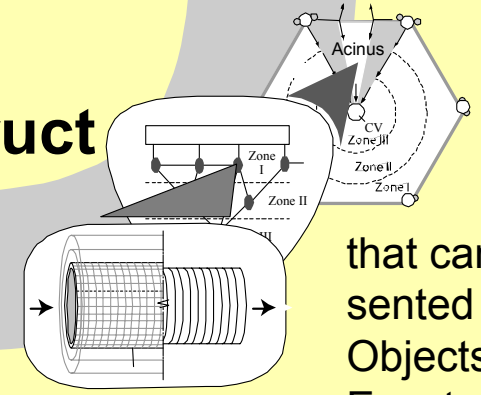
Reverse Engineer

Decompose

Mental Model

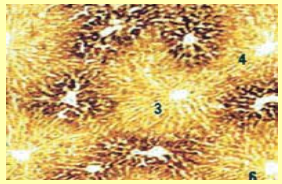


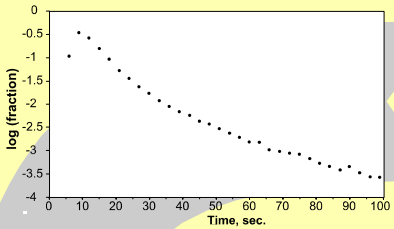
Deconstruct

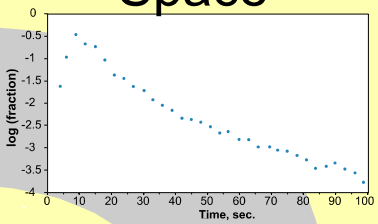


Components & processes that can be repre-sented as Software Objects & Agents & Events

Cover Behavior Space







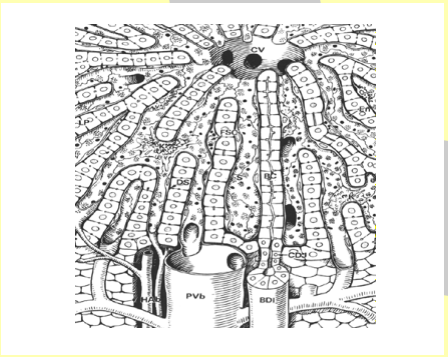
Biomimetic Behavior

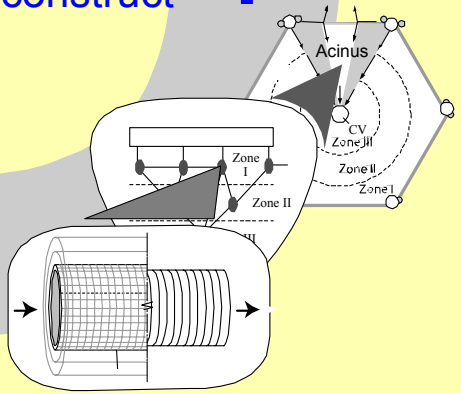
Software Device

Synthesize

Reconstruct

Mental Model

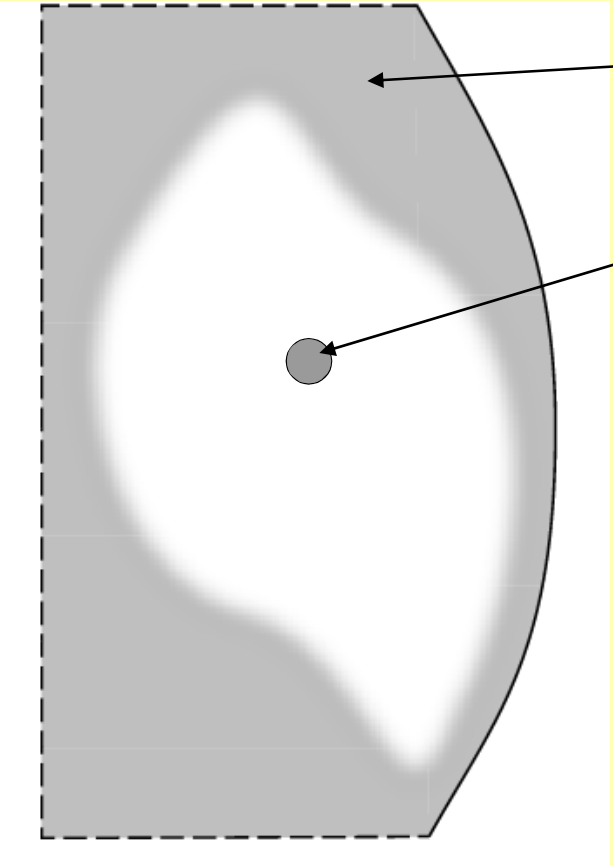




Why Use a Constructive Approach Rather Than a Traditional Modeling Approach?

Problems

(encountered by traditional approaches)



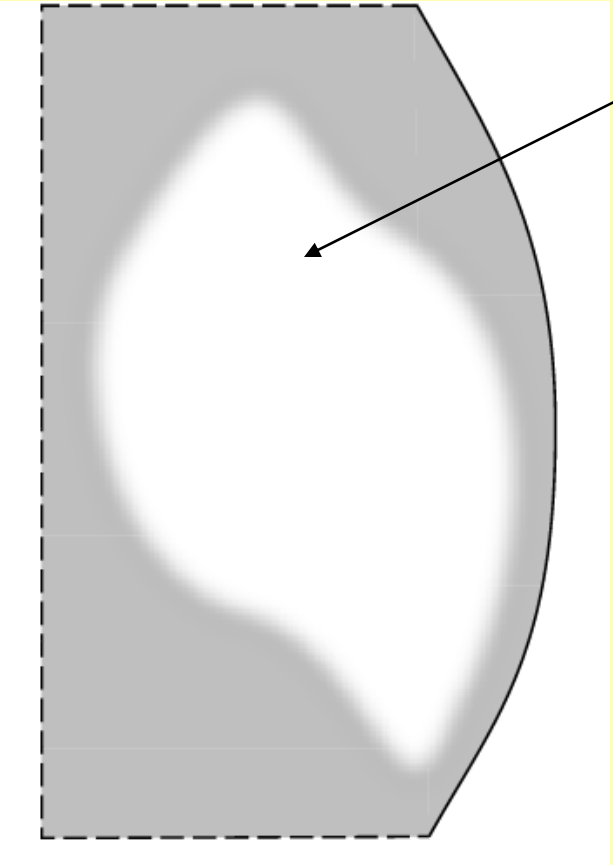
Biological systems have huge behavior spaces

Laboratory experiments cover only tiny aspects of a system's (full) behavior

Mathematical models over focus on such behavior

- often ignore the **essential spatial organization of components**
- they lack flexibility to adapt
- & to represent more of the behavior space

What is Needed?



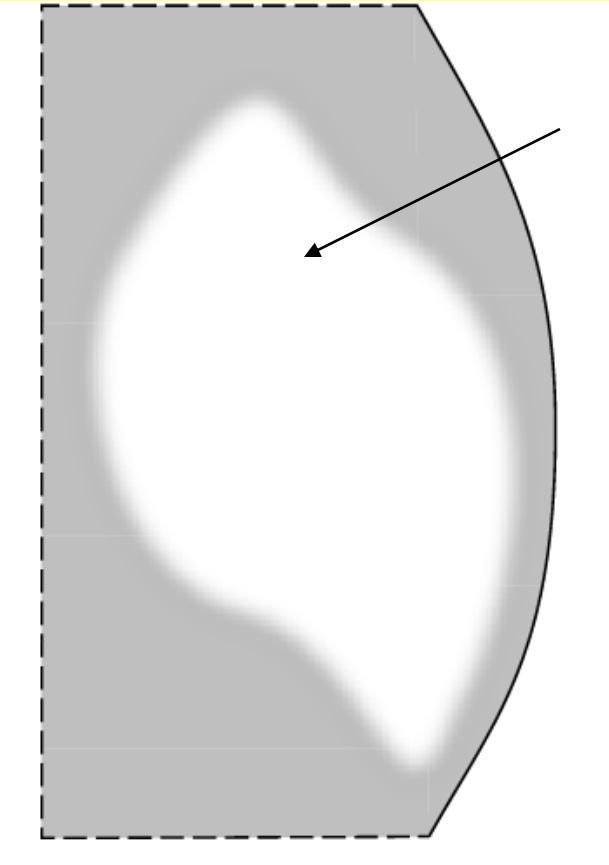
- New modeling and simulation methods that are sufficiently flexible and adaptable to cover much larger portions of the behavior space…

  … multiple levels of organization

  … where components of the models ***map logically to components in the referent***

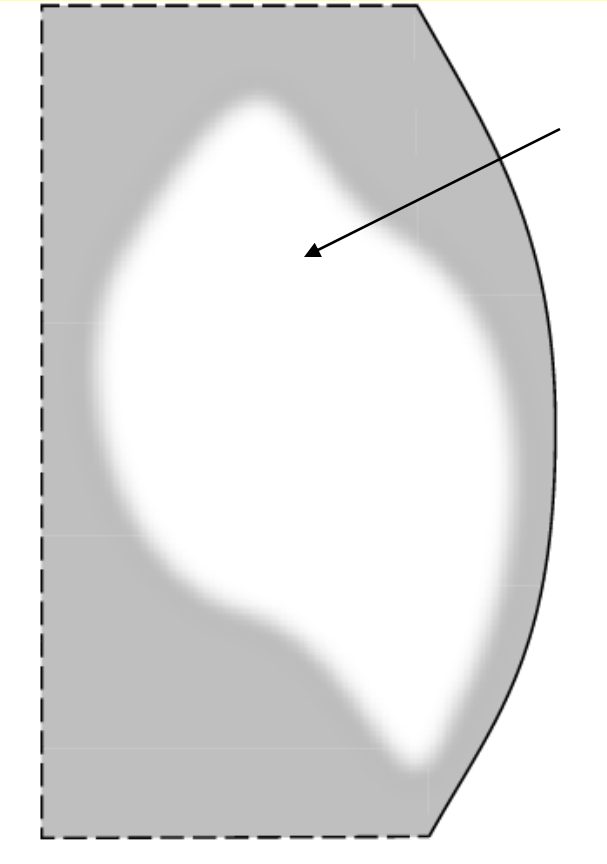
  … within biologically recognizable spaces
- This will require merging multiple modeling methods in novel ways
- ***…Hybrid System Models***

Essential Properties of New Models



- They can be easily revised…
  - … to represent a different perspective
  - … or to bring into focus different aspects of the system…
  - … (done by) by adding or removing components
  - … or by changing the level of resolution of components

Additional Essential Properties



- They need to function as a platform for in silico experimentation …

  … in much the same way as real *in* vitro or *in* vivo experimental systems

- They need to be able to function in different experimental contexts

… Biomimetic In Silico Devices

- **We work within the Swarm Framework**

… must also be capable of spanning multiple levels of organization …

… as needed by the problem at hand

- Genes … RNAs / Proteins …
- Molecular Parts … multimolecular modules
- Cellular subsystems … Cells …
- **Primary Functional Units** … 2nd Units …
- Organs … Organ Systems
- Patients

Biomimetic In Silico Devices
– Design Strategy –

- Design from the middle out, starting at the level of ***functional units***
  - As Denis Noble has observed

    the type of simulation models that we need can not be built from bottom up, starting at the molecular level
  - Nor can they be built from the top down, from the organism level

    or from the level of a physiological system

    Why?

Physiological Homeostasis Depends on Communication Among *Functional Units*

- Within organisms, what is important for cells is *location,* ***location***, ***location***

  and we do not have either an understanding for directed & managed

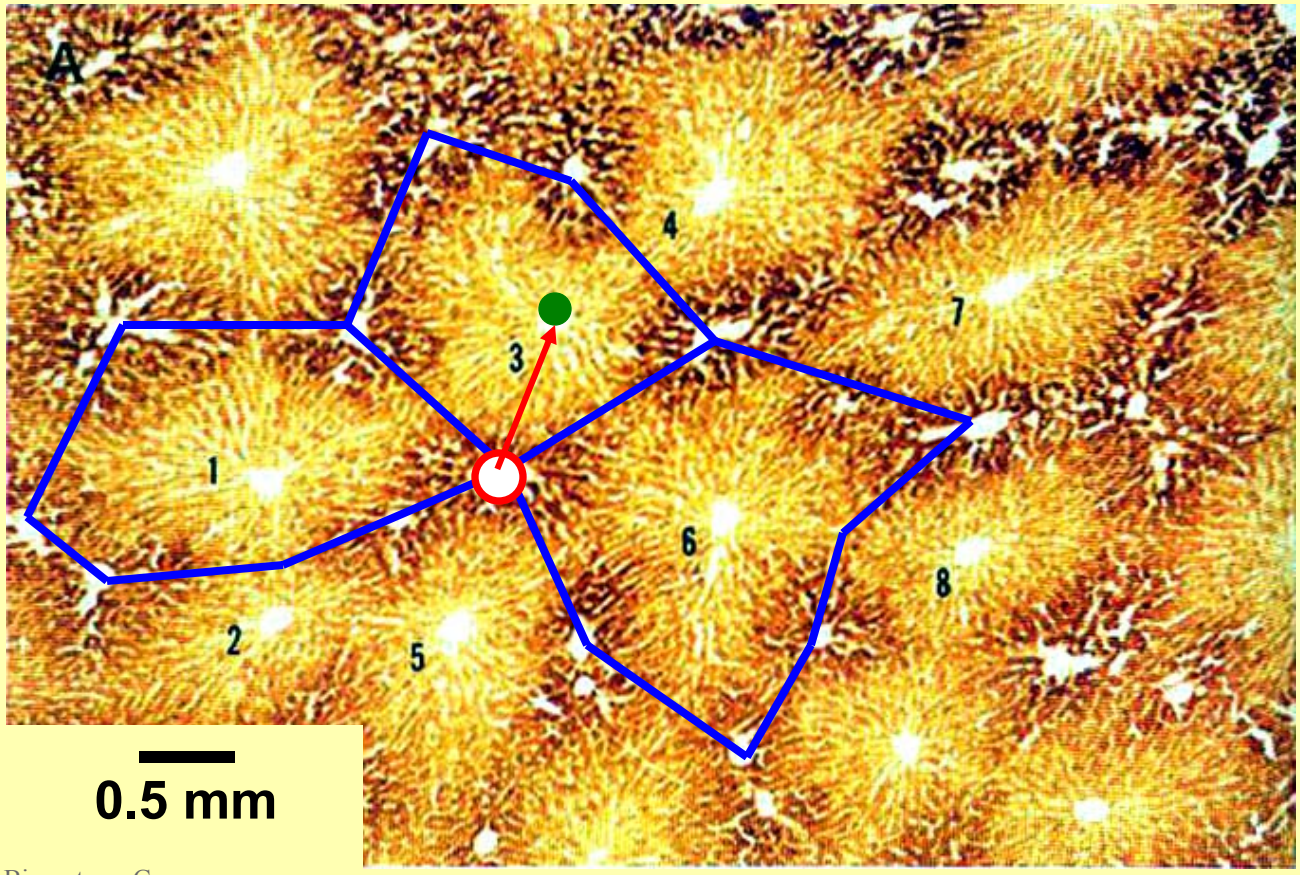
- Cells are organized in specialized primary functional units that are replicated & connected together to form various tissues and organs

- Within functional units, cells of the same type **have different phenotypes**

The Liver Example

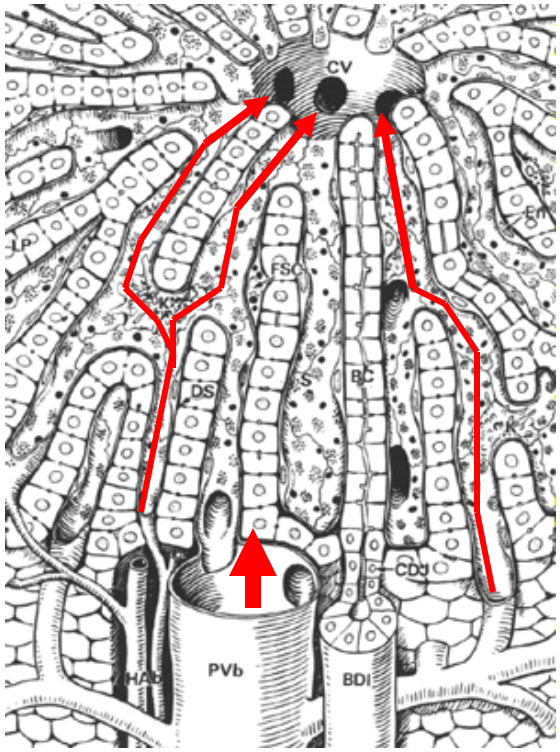
Lobules are the primary functional units of the liver

Hepatic Cross Section – G6Pase Staining

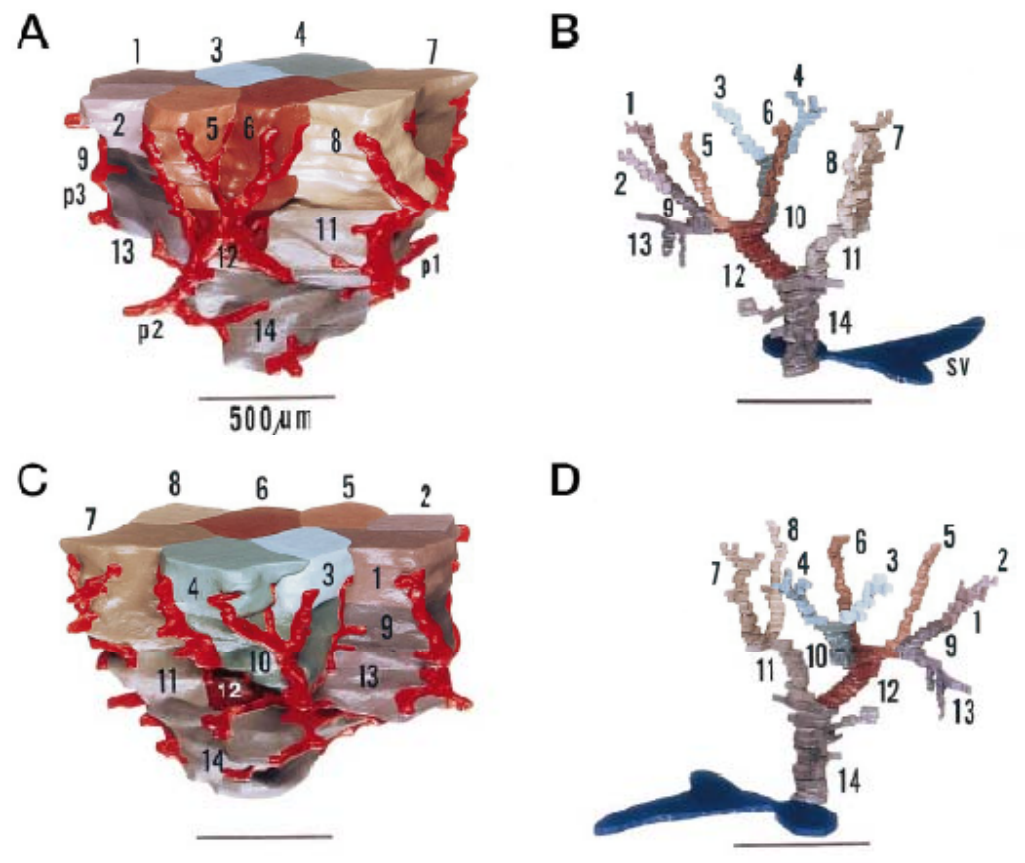


From: Teutsch, et al., *Hepatology* **29**, 495, '99

Illustration of Sinusoids Within Lobules



Secondary Hepatic Unit:
A cluster or network of lobules



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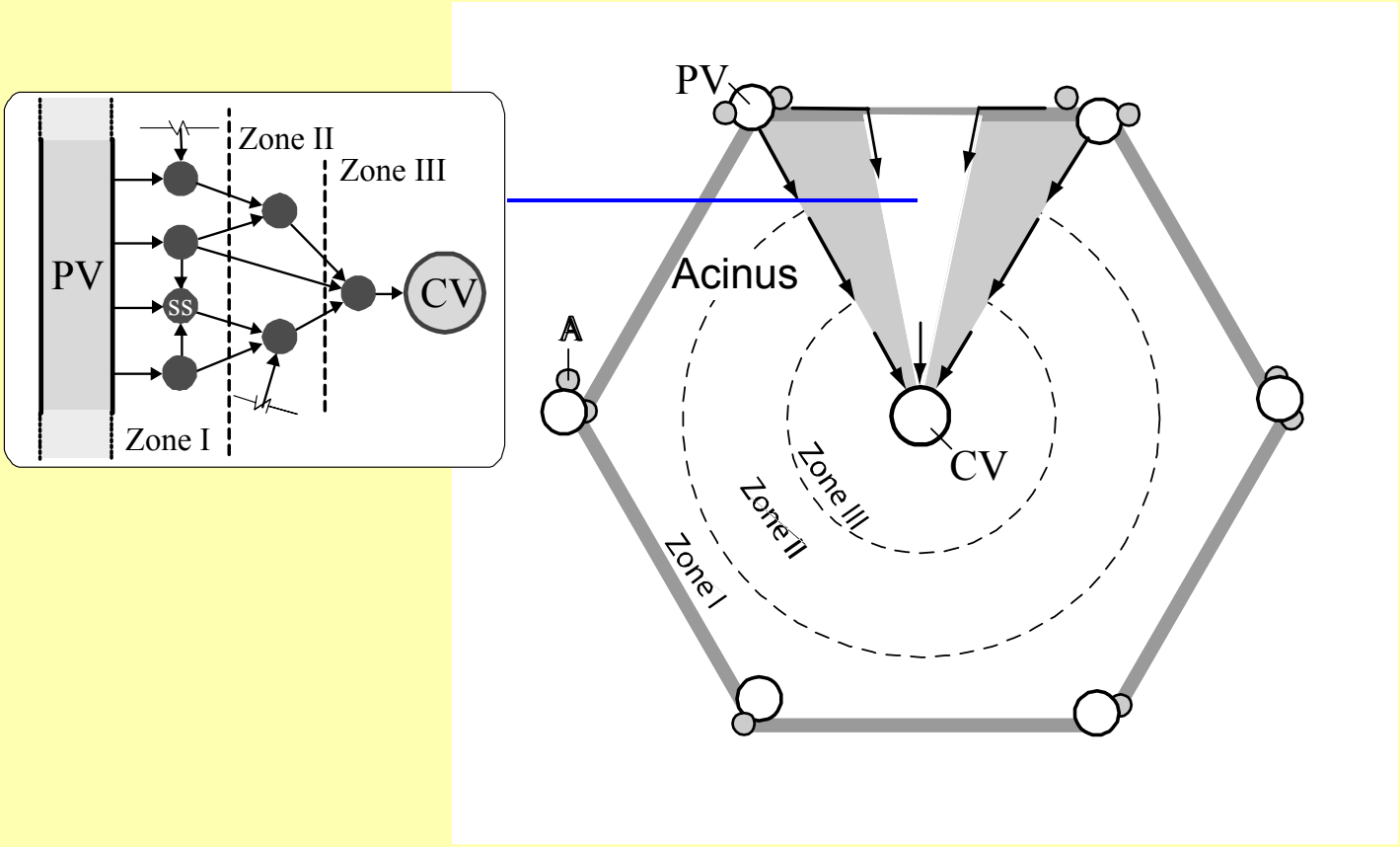
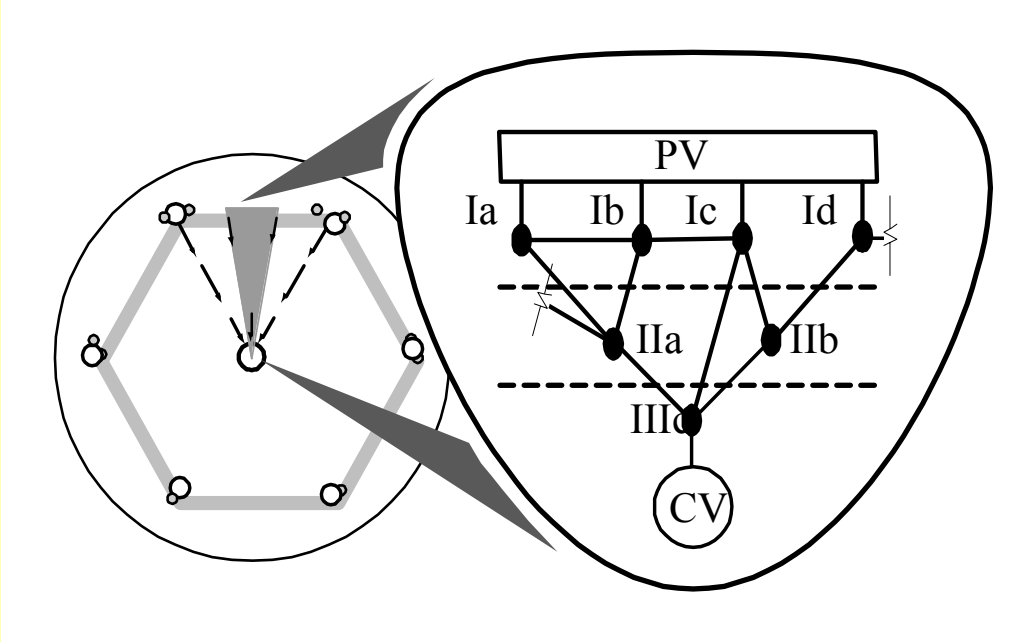
Graphs and Networks Play Key Roles in Device Design & Construction

- Messages and events characterize the medium of information flow in biology at all levels
- *Networks* – **coherent** nodes communicating over **quasi-stable** paths – can represent that flow
- In Silico Liver – everything is a network because everything happens via messages, from object to object, over a **medium that handles events**
- Objects can be identified as nodes in a graph with edges representing messages passing between them.

Lobule Cross Section



Design of Flow Pathways Within Lobules



Each in silico lobule is independently (& uniquely) modeled as an interconnected directed graph (based on the exp. data)

Within each lobule there are several dozen paths from PV to CV

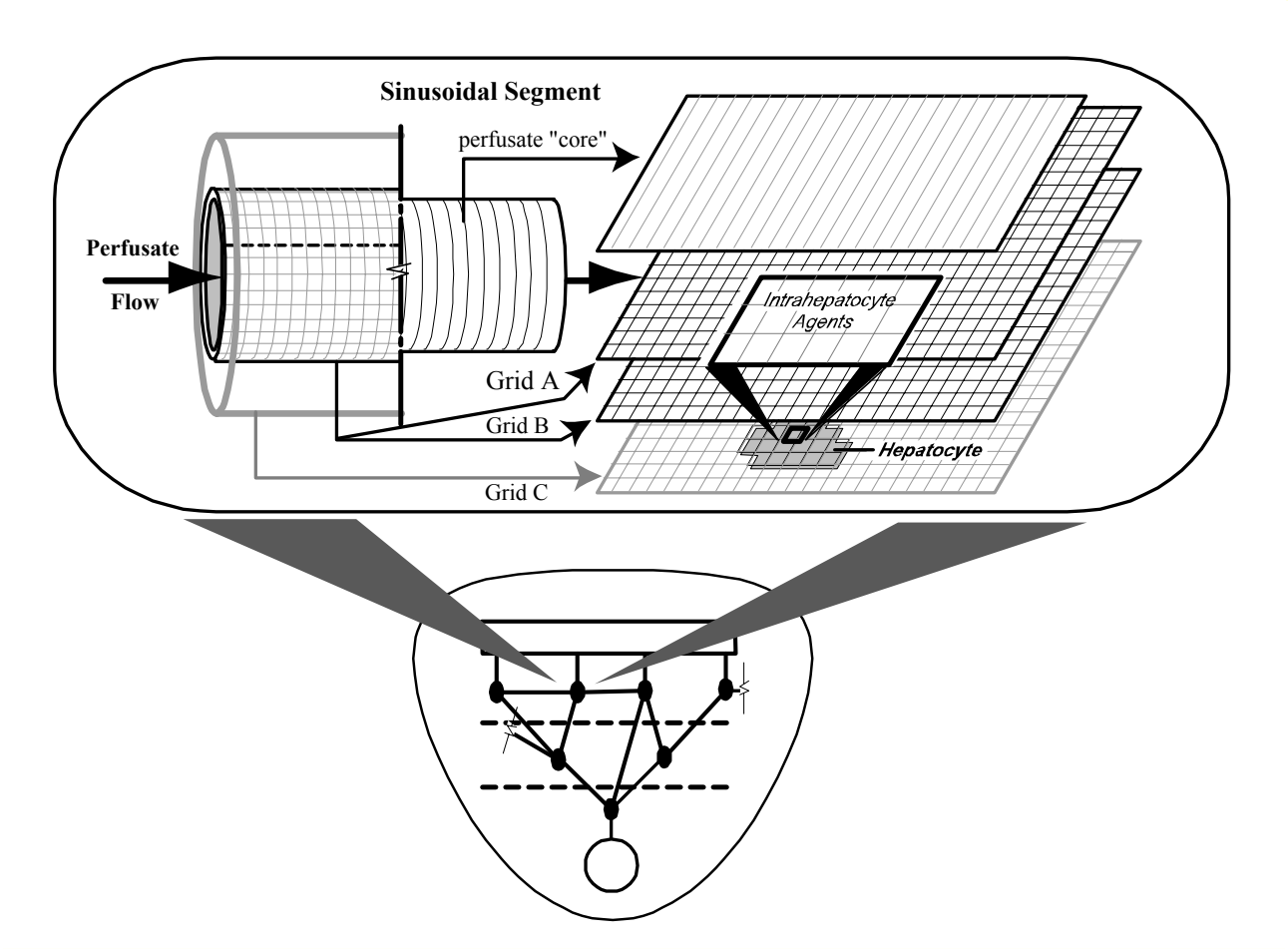
Each shortest path has either one, two, or three nodes

Allow cross connections between some adjacent nodes

We Account for Sinusoidal Heterogeneity

- *In vivo* there are differences in transit times, flows, topographic arrangements, and surface to volume ratios within the three zones (quantitative data)
- We place Sinusoidal Segments (SSs) at each graph node
- Two classes of SSs: one, S_A, has shorter path lengths and smaller surface-to-volume ratios
- Another, S_B, has longer path lengths and larger surface-to-volume ratios

Design of Interconnecting Sinusoidal Segment Agents



Fate of Drugs and Solutes

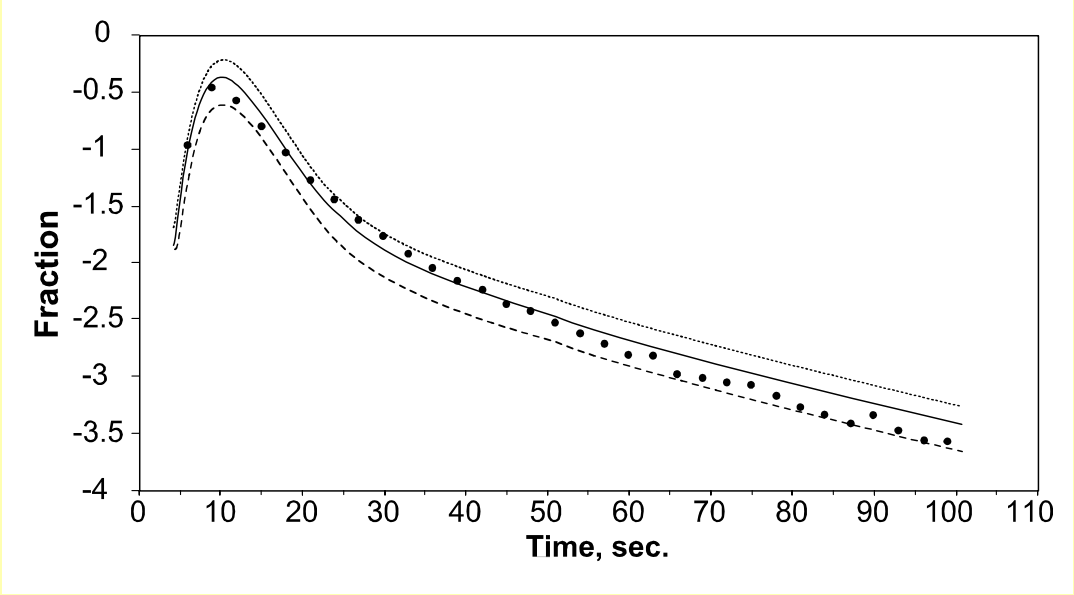
- Drugs, solutes and other **mobile objects** are subject to rules (& stochastic behaviors) at each grid point
- Solute behavior is dictated by rules specifying the relationships between solute type, grid location, and proximity to other objects and agents
- The rules can be specified to take into account the solute's **physicochemical properties**

Model Parameters

- Sinusoidal Segment (SS) circumference (min, max)
- SS length (α, β, γ)
- Solute Scale (molecules per solute "particle")
- Solute Dose (mass, constituents, timing)
- Turbo (effective solute flow pressure)
- Graph Structure (# SSs, connections between them)
- Fenestrations (size and prevalence)

… …

An Example of Results
A Sucrose Outflow Profile



- Atenolol, Antipyrine
- Prazosin, Labetalol, Propranolol, & Diltiazem

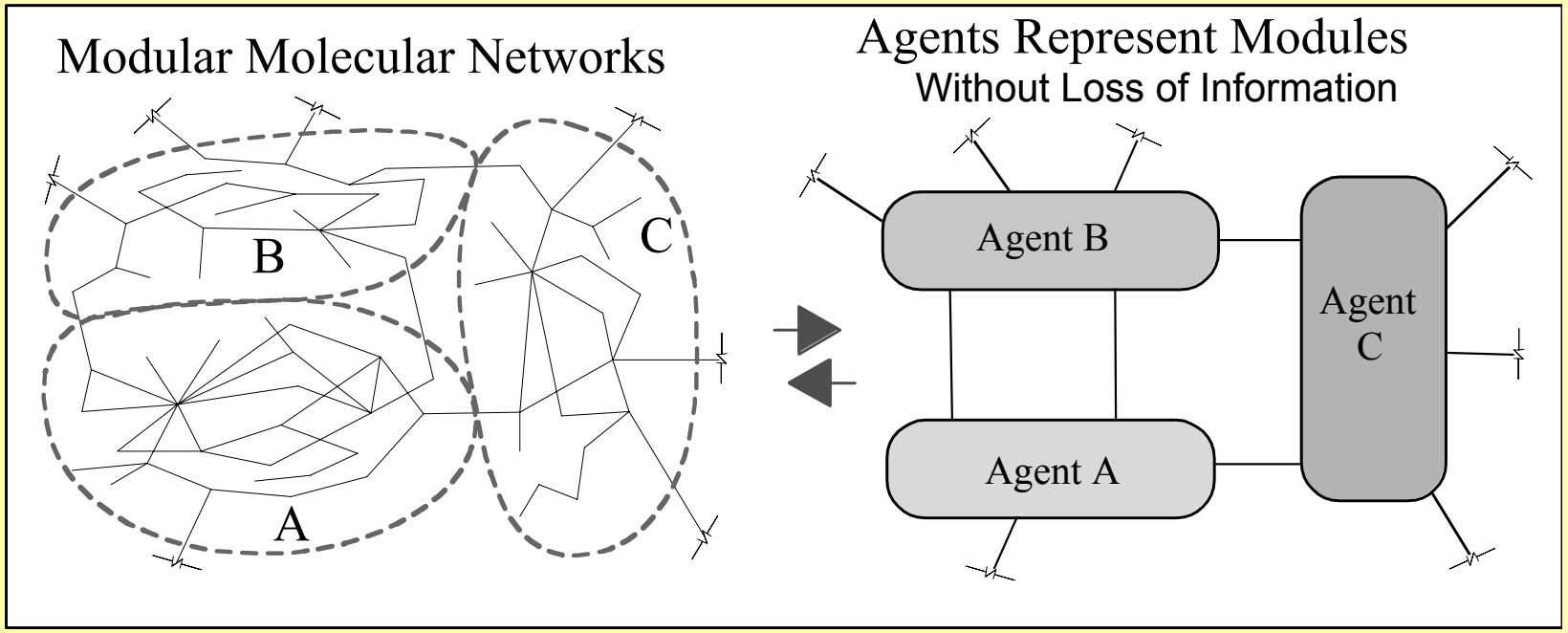
- The 3 curves represent the mean ± 1 std of exp. data
- Filled circles: in silico results 1 parameterization, mult. runs
- Nodes/Zone: 55, 24 and 3 for Zones I, II and III, respectively.
- Total edges: 60

- Intra-zone connections: I = 10, II = 8, III = 0
- Inter-zone connections: I→II = 14, I→III = 4, II→III = 14
- SSs: 50% S_A and S_B
- Number of runs = 100

Higher Levels of Resolution

Genes → Protein Parts → Networks & Circuits

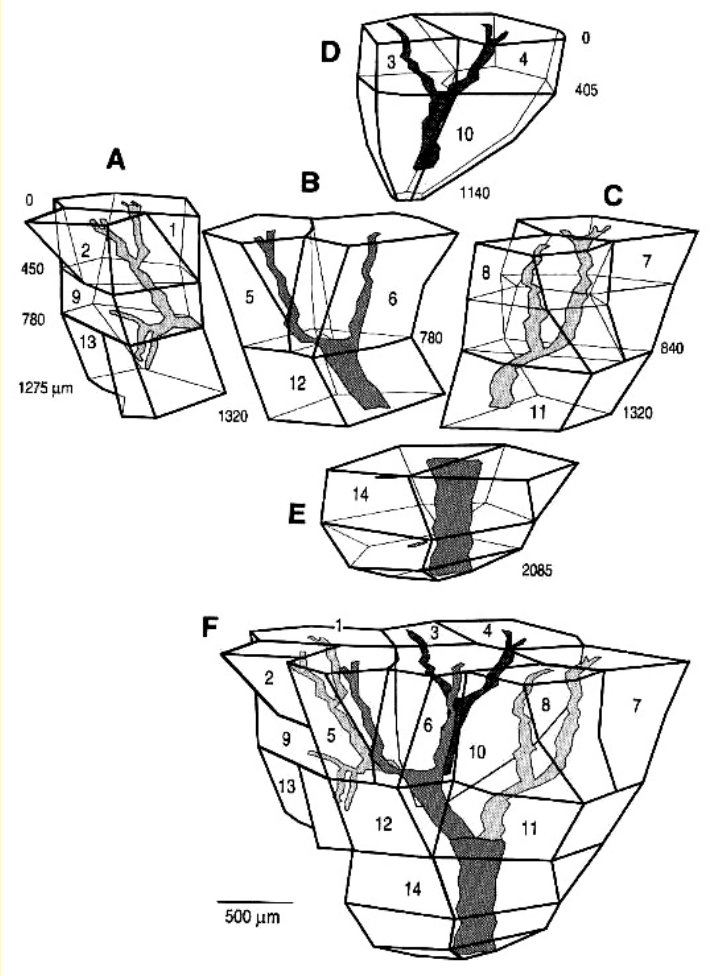
The fate solutes within “cells” within SSs depends on interactions with “macromolecules” and “molecular networks”



Higher Levels of Organization

Lobule → Secondary Unit → Lobe → Liver

Secondary Hepatic Unit



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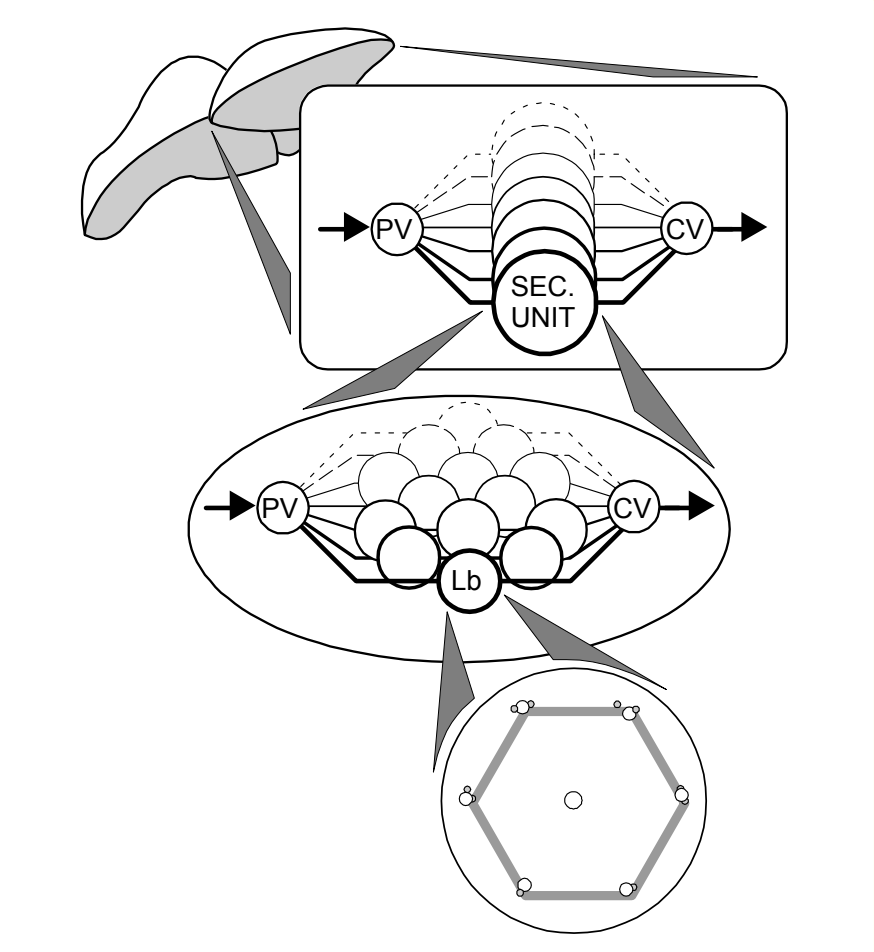
Higher Levels of Organization
Lobule → Secondary Unit → Lobe



Summary

- We see advantages in using a **constructive approach** to build hierarchical, biological system models
- We believe there are solid reasons for ***not*** using either a top-down or bottom-up (reductionist) approach to modeling & simulating systems within organisms
- Biomimetic in silico devices – simulation models of hepatic **functional units** – map logically to identifiable, spatially organized hepatic components
- They are capable of functioning at multiple levels of resolution, …
- …and they are capable of predicting the metabolism & disposition of drugs

Acknowledgements

Coauthors:

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