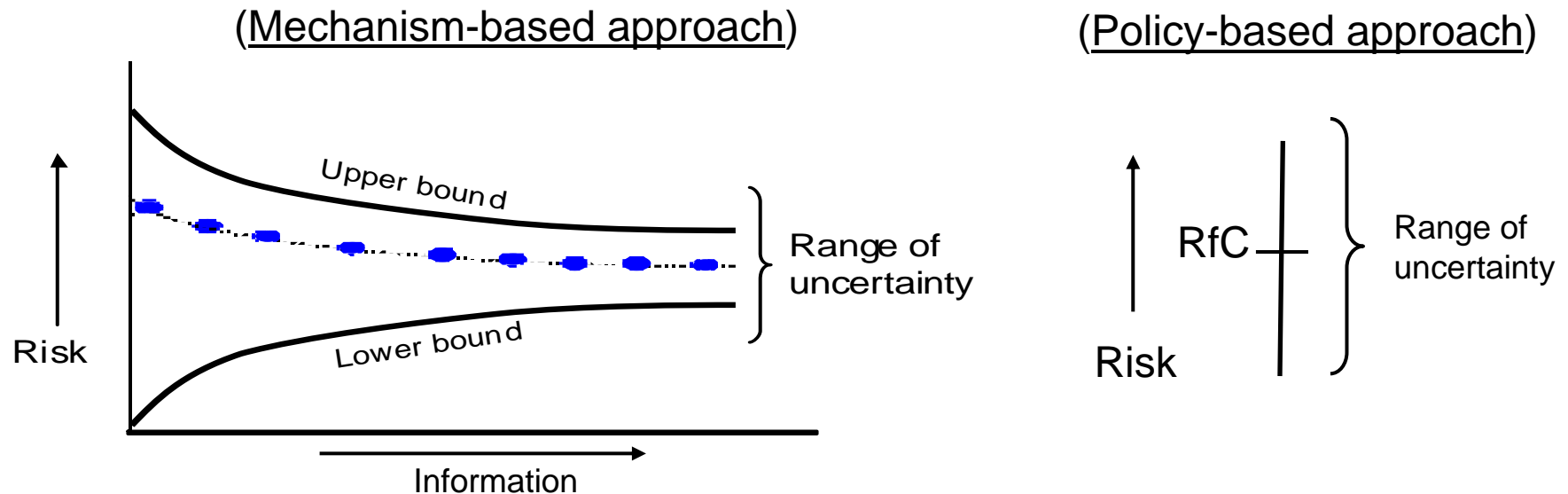


Computational Modeling of the Liver

Rory Conolly, Jerry Blancato, et al.

*NCCT BOSC Review
June 19-20, 2006*

A new project that will reduce uncertainty in risk assessment



Outline

- What?
- Why?
- How?
- Who?



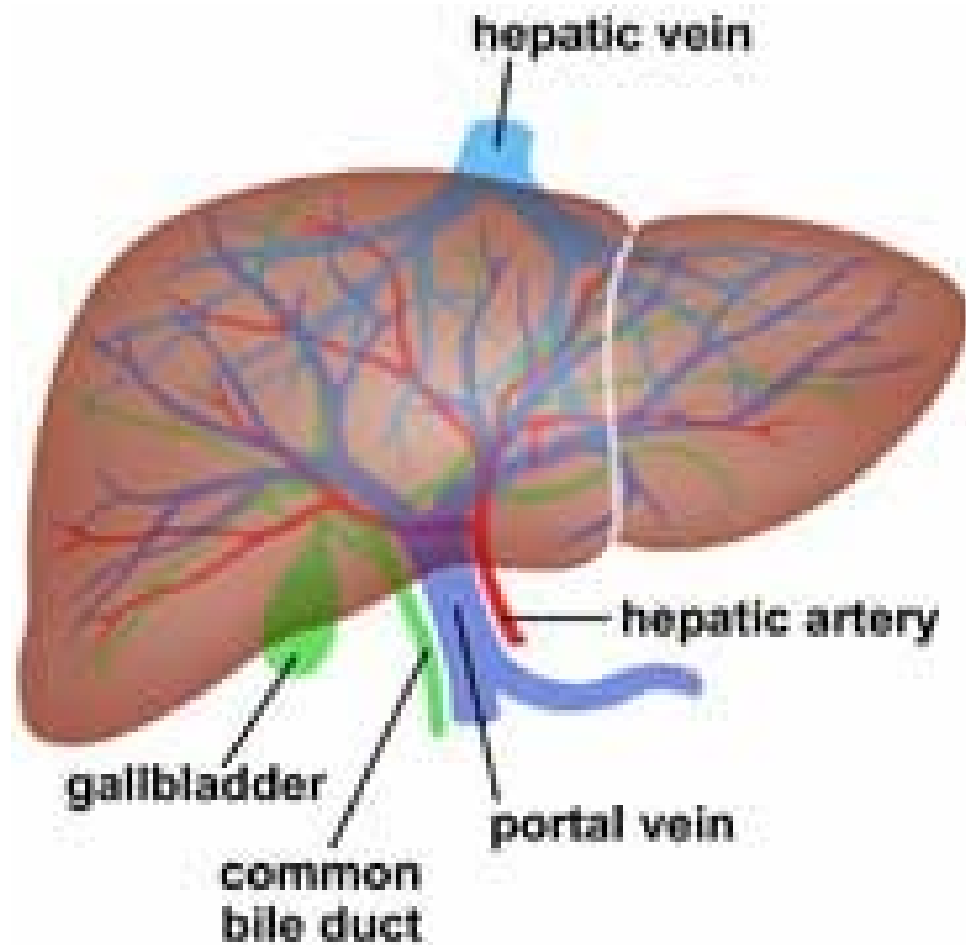
What?



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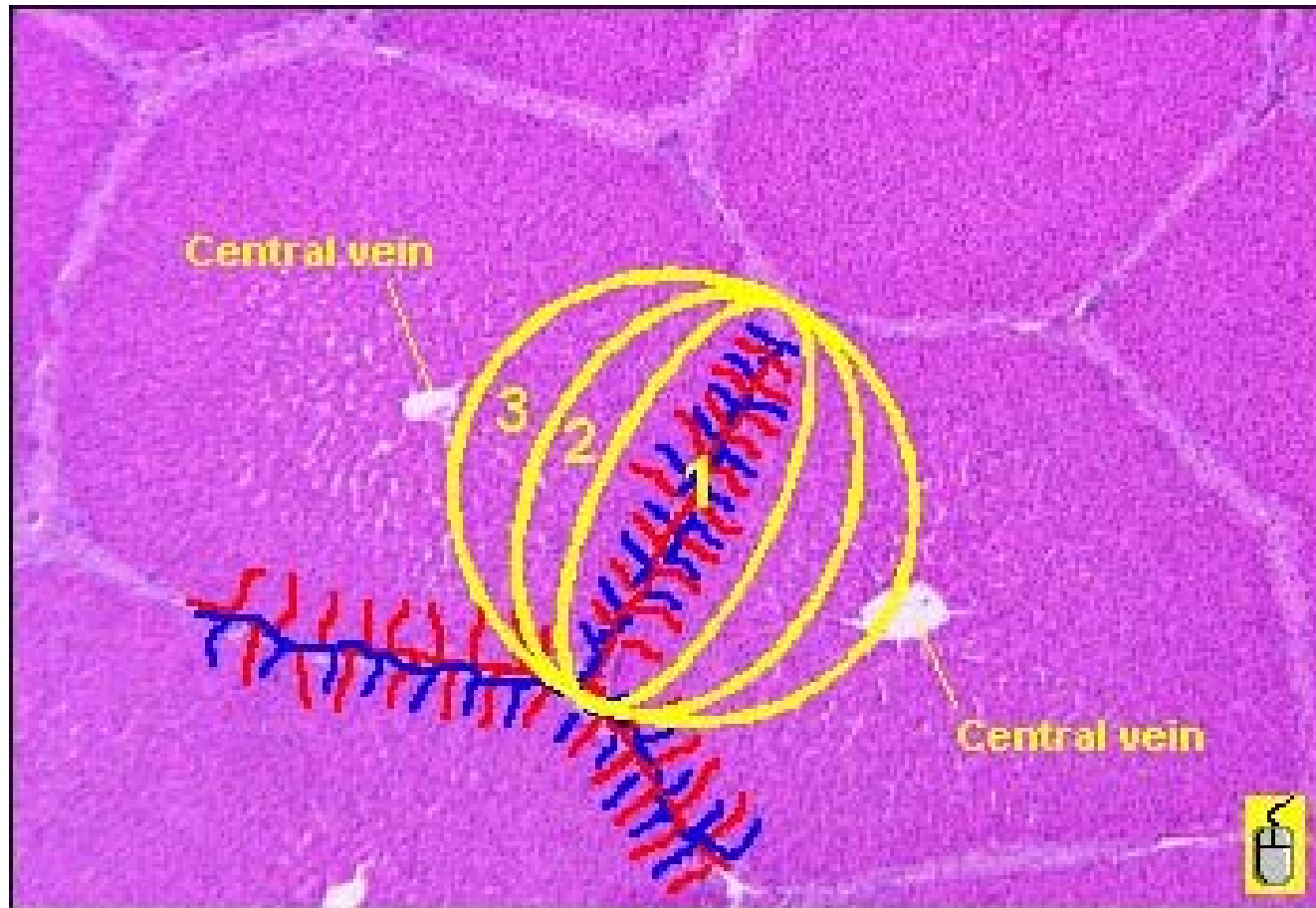
Multiscale, computational model of the liver



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Starting point: 2-D hepatic acinus



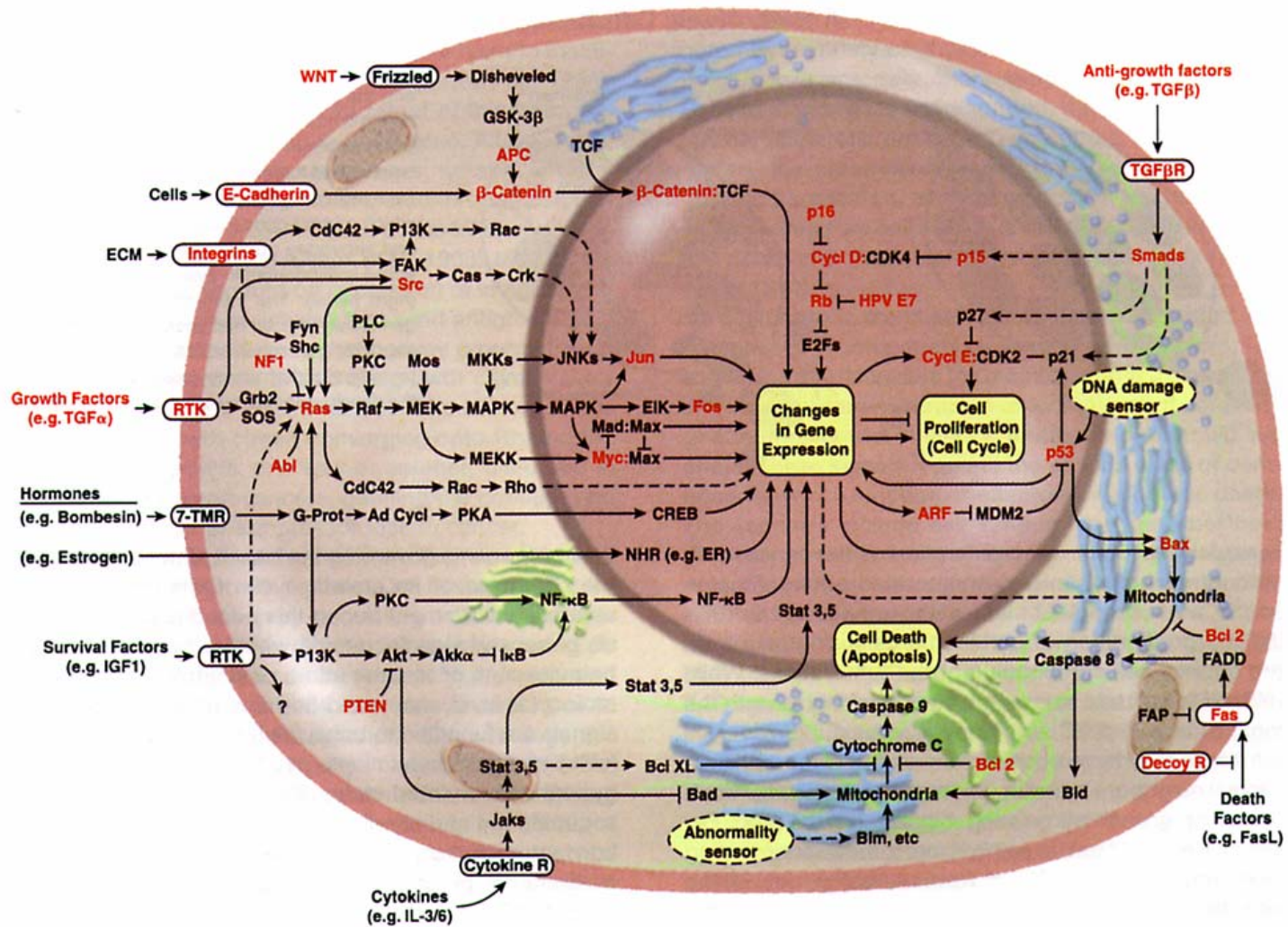
http://www.klinik.uni-mainz.de/Zentrallabor/Lab-Web/Hypertextbook/histo_acinus.jpg



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Molecular Circuitry



Hanahan and Weinberg, *Hallmarks of Cancer*, Cell, 100, 57-70, 2000.

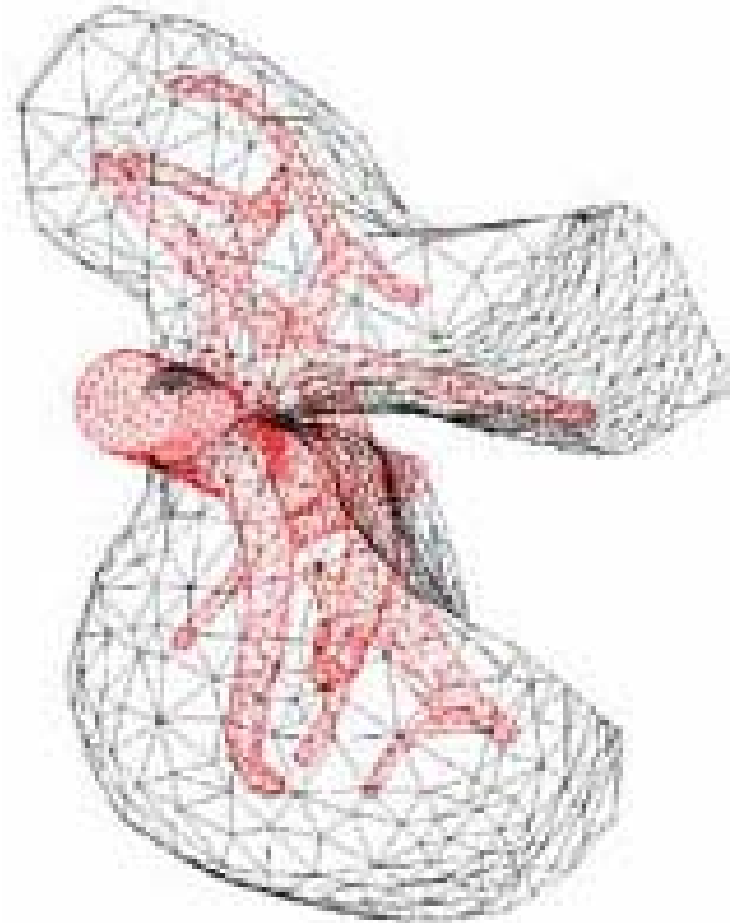


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Longer-term

- Multi-scale 3-D model
 - Vasculature
 - Spatial relationships of cells



http://bme.pe.u-tokyo.ac.jp/research/liver/liver_model_en.html



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Why?



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Why liver?

Pub Med hits

Liver	44,857
Kidney	23,010
Lung	23,903
Neuro	29,649
Developmental	5,369



Ongoing, relevant research (I)

- Conazole toxicogenomics
- Aging project
 - Microsomes, gene-protein activity
- PPAR-regulated gene expression
- Nuclear receptors
- Profiles from diabetic rats
- Profiles for isolated Kupfer cells



Ongoing, relevant research (II)

- HESI
 - 500 Affy array data files
 - Control rat liver
- XME expression
 - life stages, interspecies
 - F344 rats, C57 black mice
- Metabolic simulator (Athens)
- Star grant on OP metabolism
- Fish liver



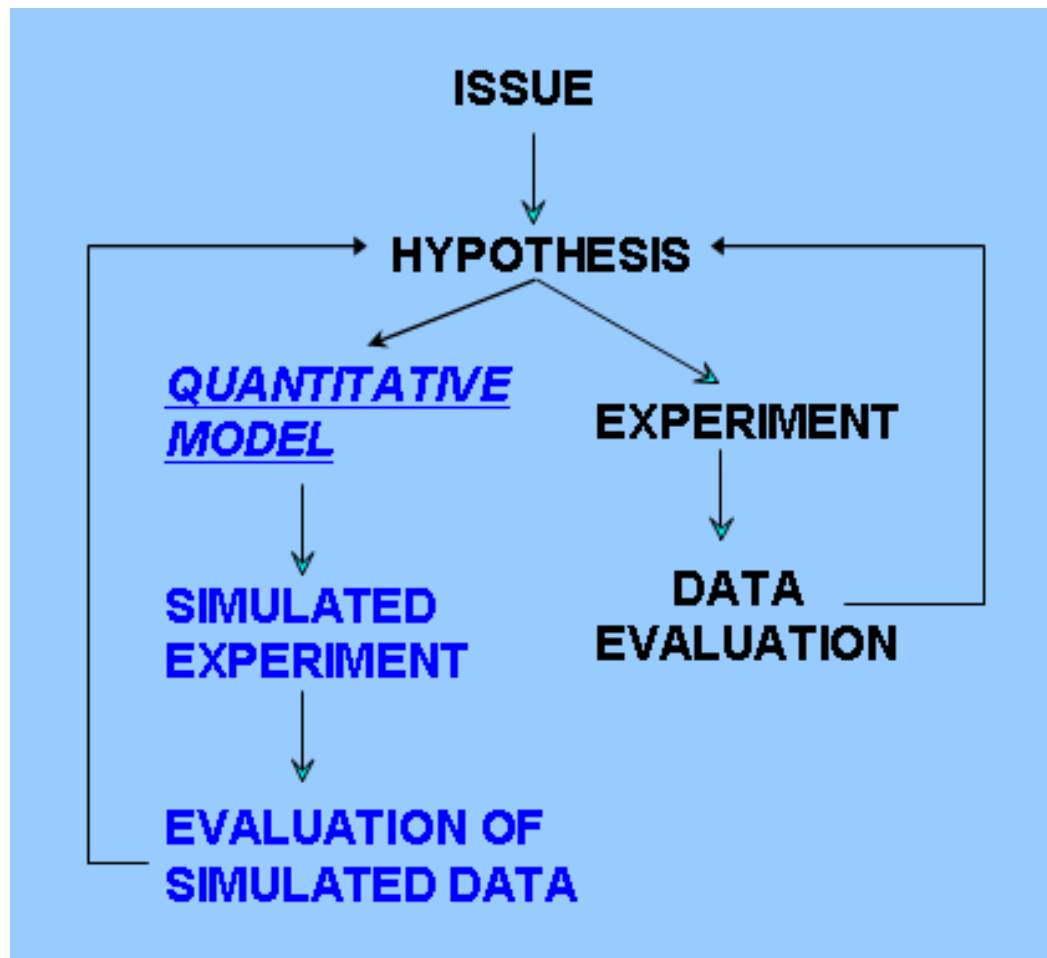
Why a computational model?



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Computational biology/toxicology



Uses of computational models

- Logical framework for available information.
- Identify data gaps.
- Obtain non-intuitive insights.
- Biomarkers of exposure and of response may be identified.
- Predictions for science-based risk assessment.



Why a multi-scale, spatial model of the liver?



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Babylonian model of sheeps liver, 19th century BC



Used in divination and for instruction in the temple.

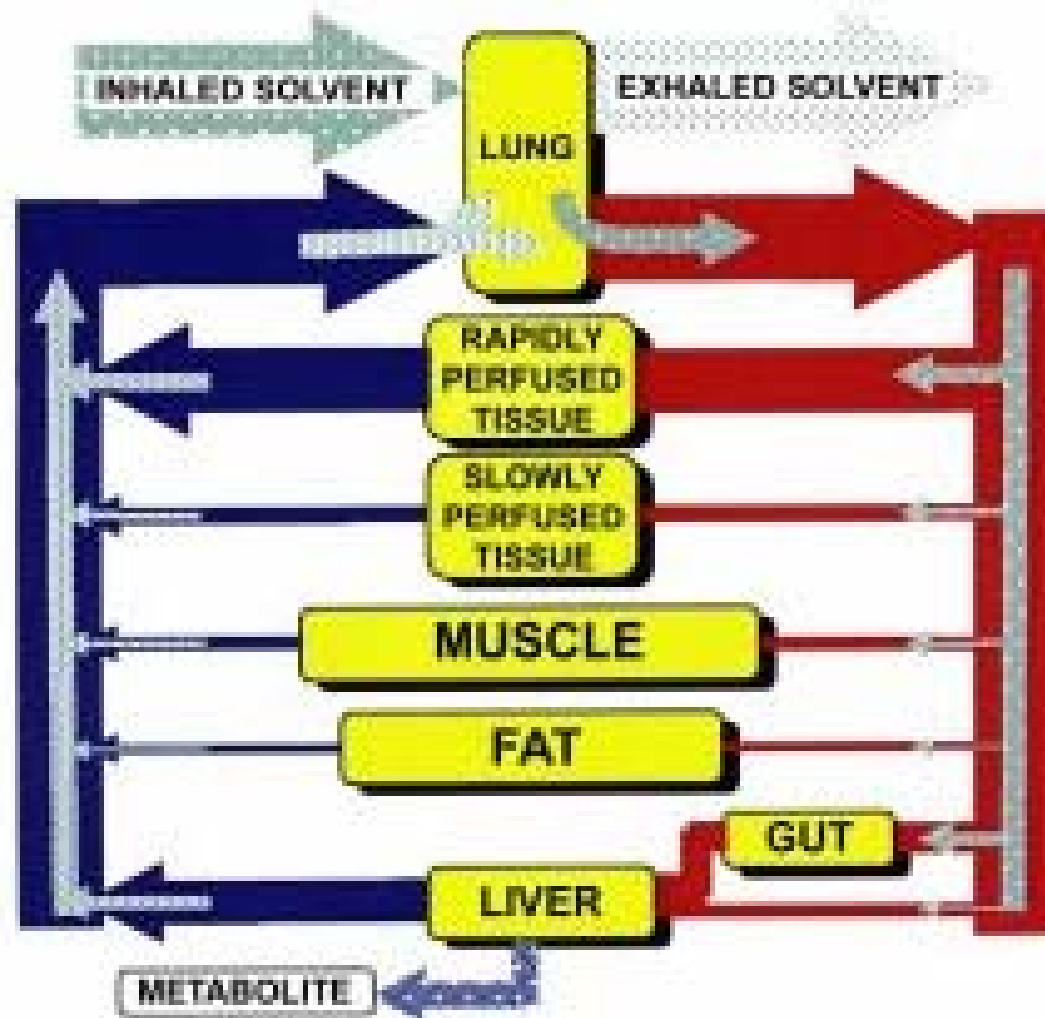
<http://www.umanitoba.ca/faculties/medicine/units/history/notes/anatomy/liver.html>



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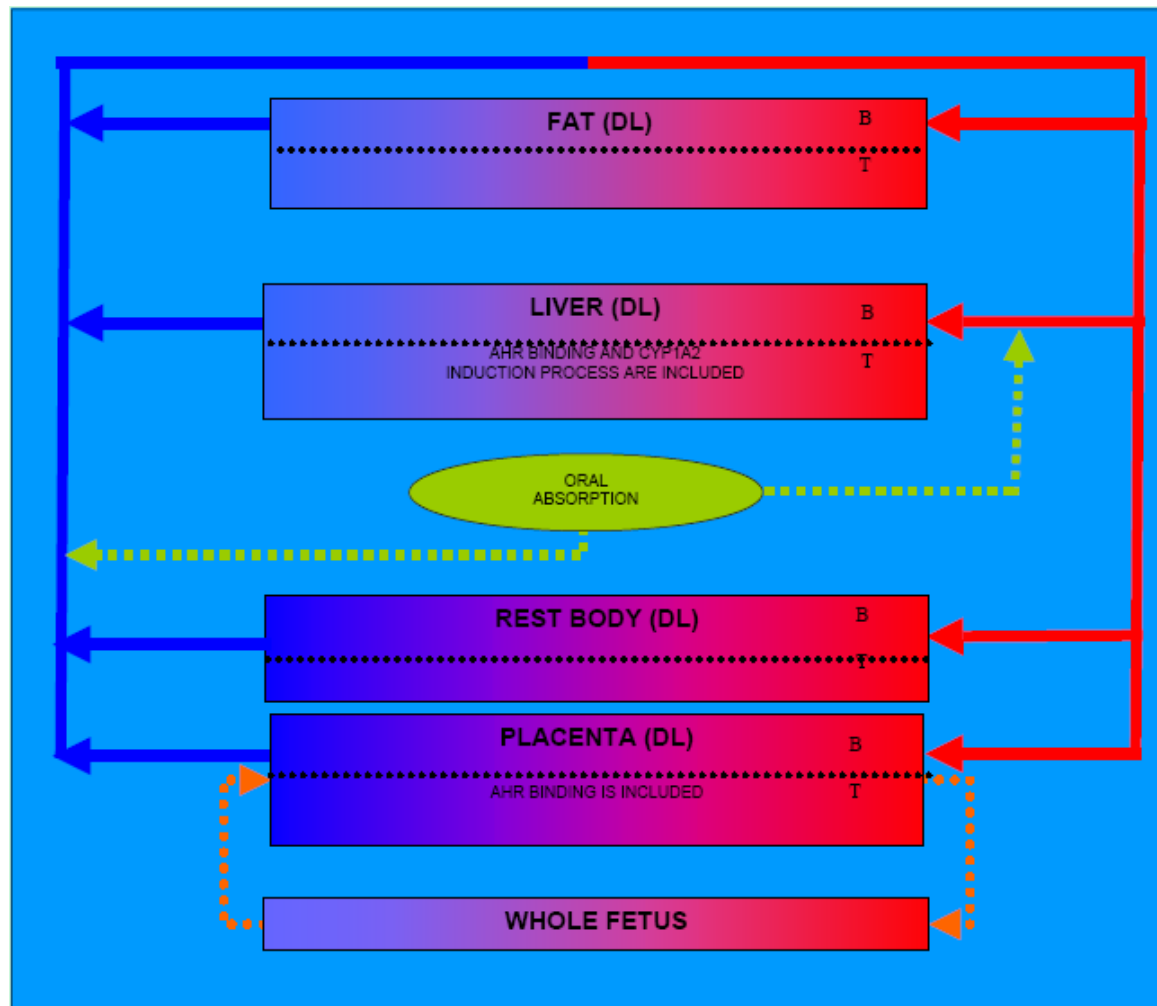
Flow-limited



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Diffusion-limited



Compartmental

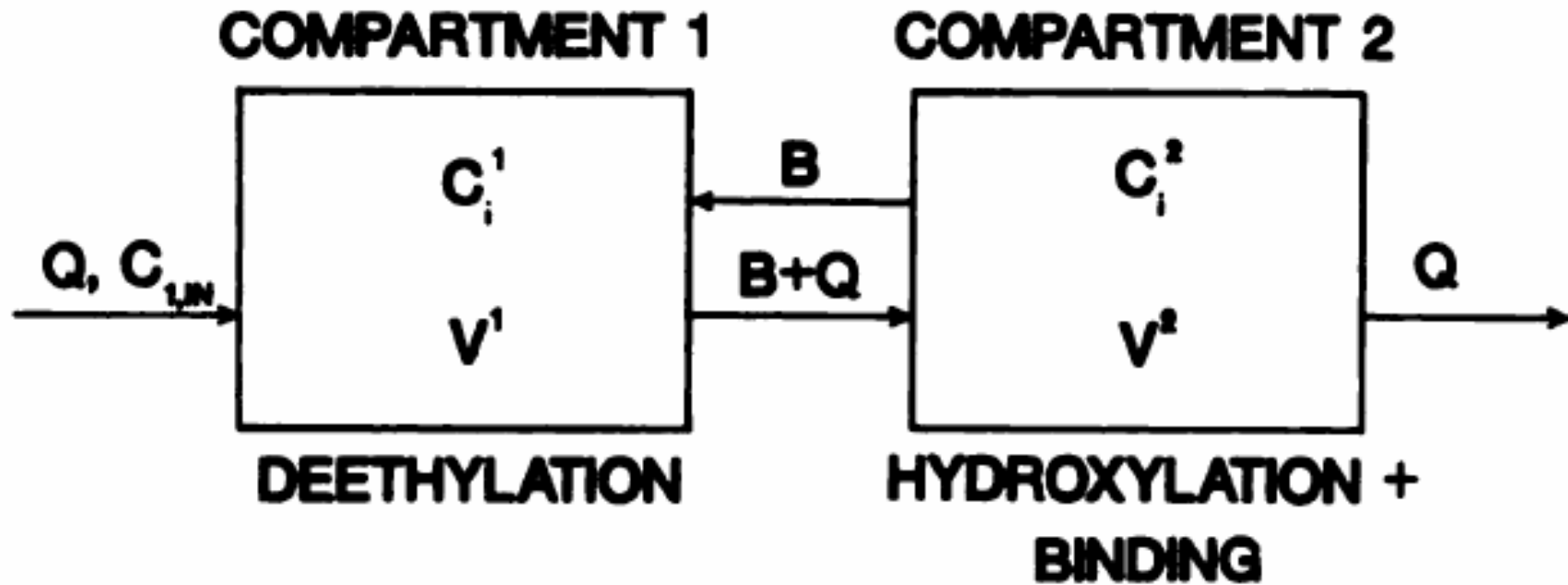
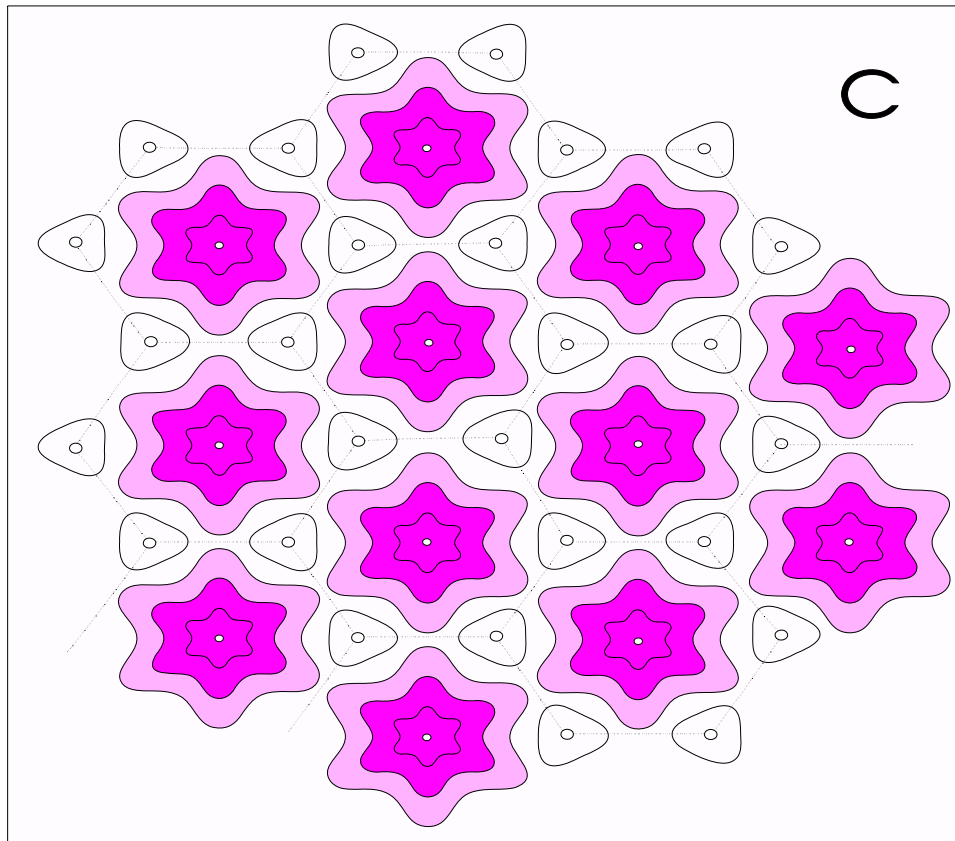


FIG. 1. *Two-compartment model for heterogeneous enzyme distribution in the liver.*



2-D spatial model of liver acini



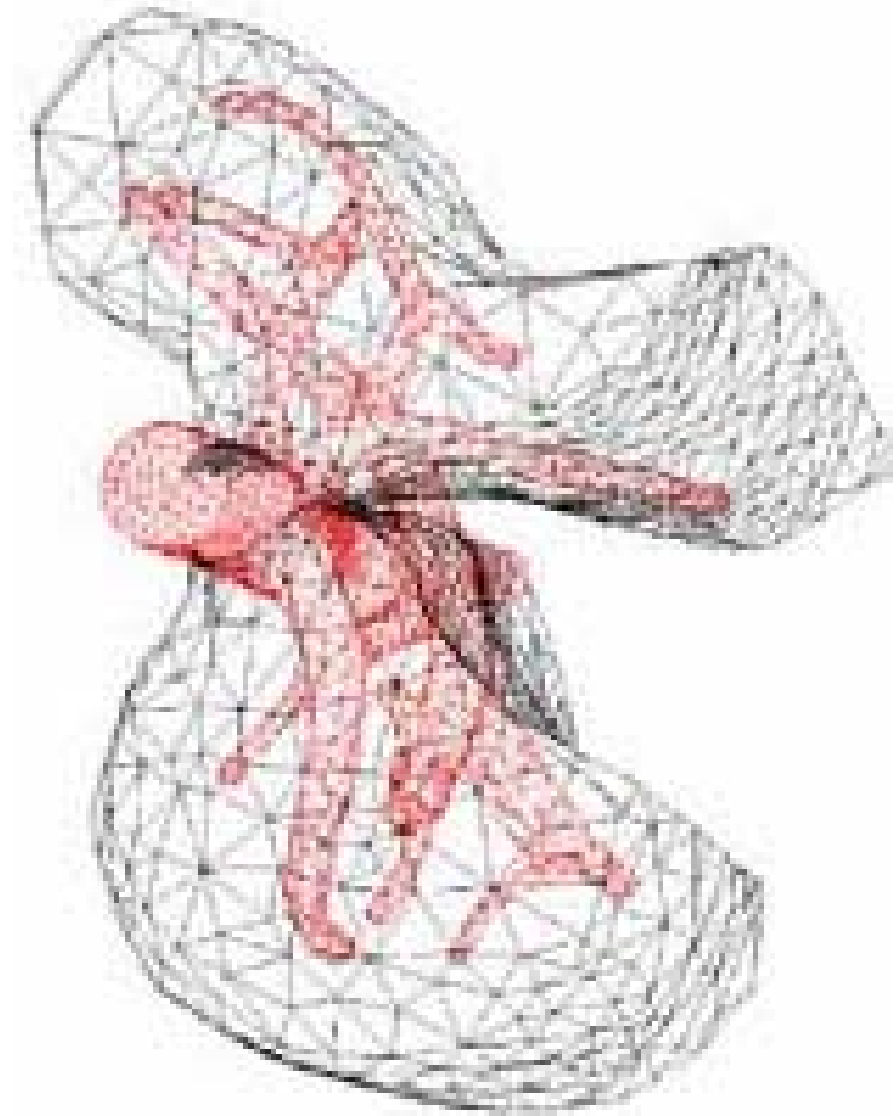
Protein induction visualized by painting the acinar structures according to extent of induction.



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3-D spatial model of human liver



http://bme.pe.u-tokyo.ac.jp/research/liver/liver_model_en.html



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Current practice

- The level of complexity in models developed to date has been defined by the available data.
 - Flow-limited
 - Diffusion limited
 - Compartmental
 - etc



Vision for the multi-scale liver project

- Analysis of data only one of the uses of the model
- Tool for integration
 - Diverse data
 - Research projects
- Model as a database
- Predictions for experimental design and risk assessment



Modeling in the post-genomic era

- As we are entering the post-genomic era, *models-of-data*, such as mining and filtering methods for gene sequences and microarrays and the clustering of co-expressed genes, must be complemented with *models-of-processes* that explain relationships between genomic information and phenomena at biochemical and physiological levels. (Voit, Math. Biosci.,80:263-274, 2002)



***MULTI-SCALE MODELING IN BIOMEDICAL,
BIOLOGICAL, AND BEHAVIORAL SYSTEMS NSF
04-607 RELEASE DATE: August 20, 2004***

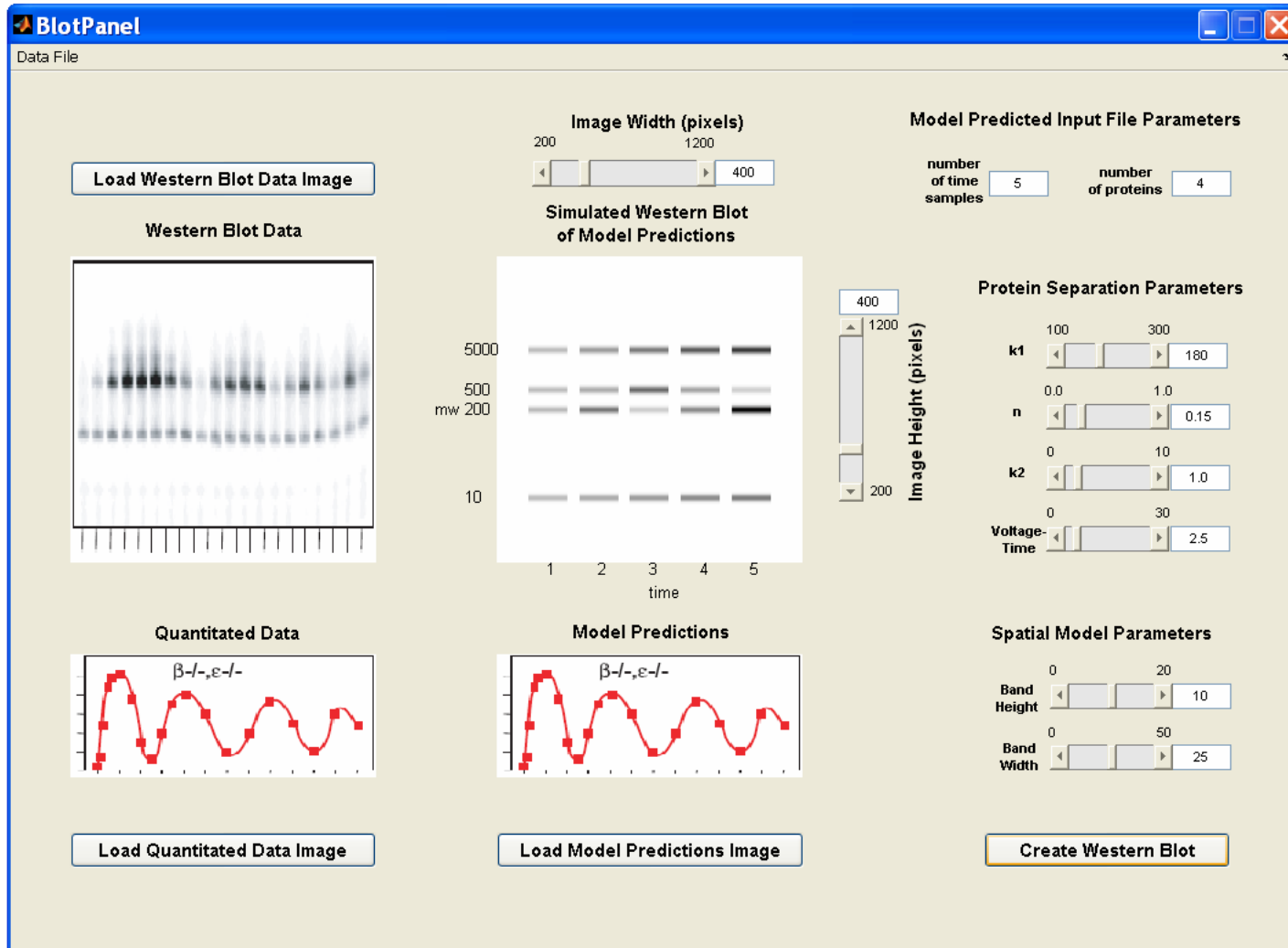
- National Science Foundation
- National Institute of Biomedical Imaging and Bioengineering
- National Cancer Institute
- National Institute of Child Health and Human Development
- National Institute on Drug Abuse
- National Institute of Environmental Health Sciences
- National Institute of General Medical Sciences
- National Institute of Neurological Disorders and Stroke
- National Library of Medicine
- National Aeronautics and Space Administration
- U.S. Dept. of Energy



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Visualization

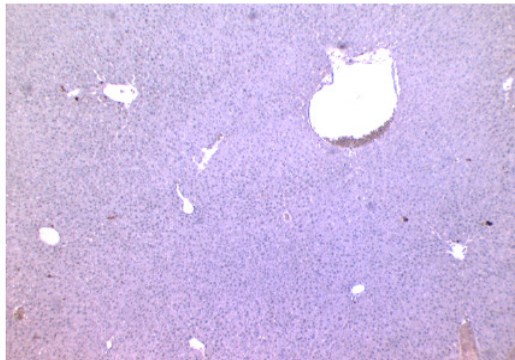


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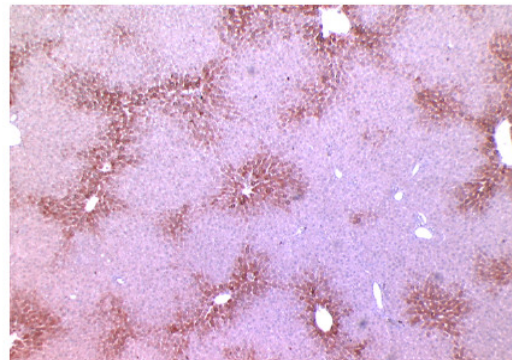
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Induction Occurs in Specific Regions of the Acinus

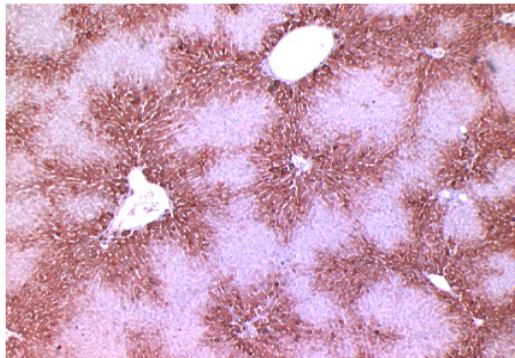
Corn Oil Control



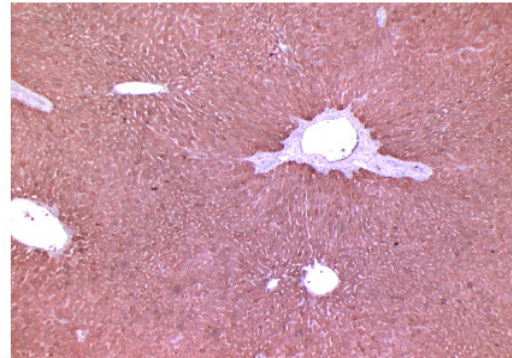
0.1 µg/kg PCB 126



1.0 µg/kg PCB 126



10 µg/kg PCB 126



(Mel Andersen)

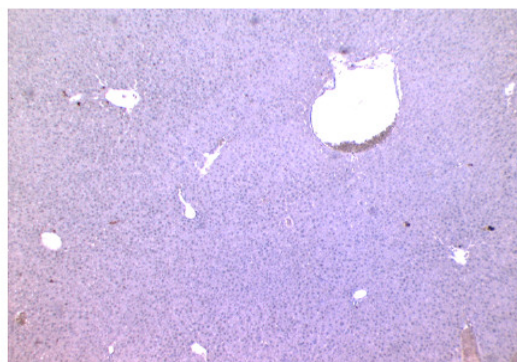


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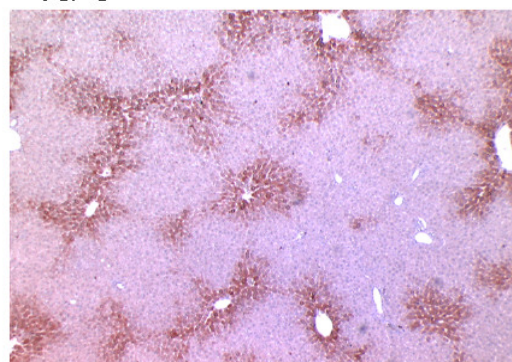
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Visualization...

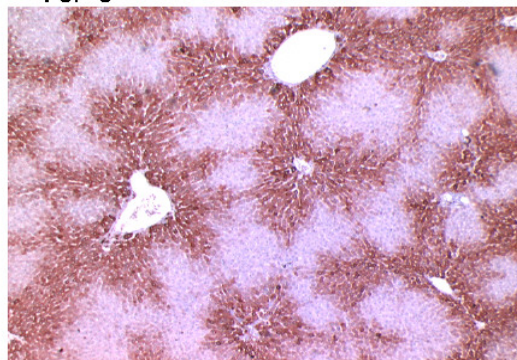
Corn Oil Control



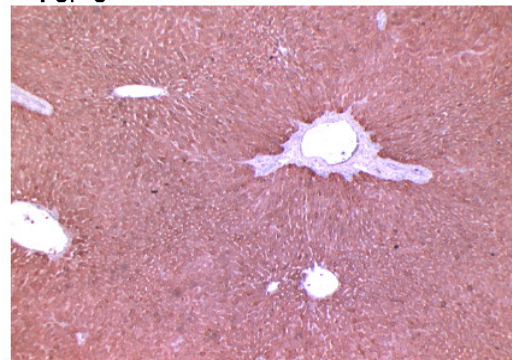
0.1 $\mu\text{g}/\text{kg}$ PCB 126



1.0 $\mu\text{g}/\text{kg}$ PCB 126



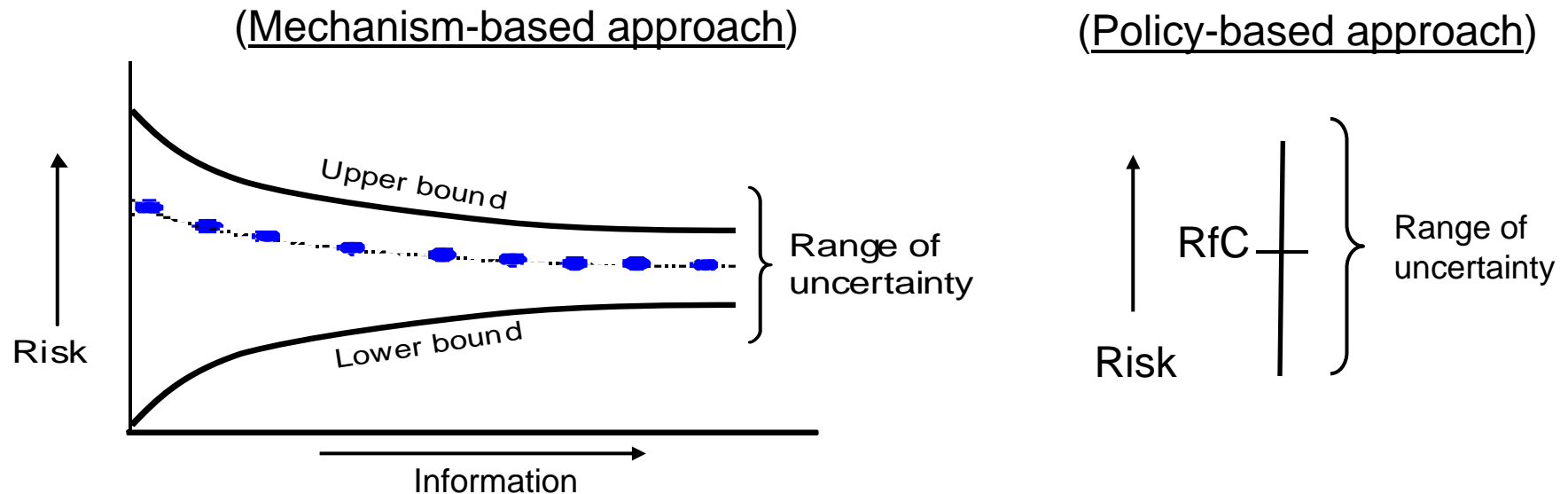
10 $\mu\text{g}/\text{kg}$ PCB 126



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Reduction of uncertainty in risk assessment



How?



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Planning meeting

- May 23-24 at EPA, RTP
- 18 investigators
- High level of enthusiasm



Initial steps

- Form project teams
 - commitment
- Define goals
 - Short-term
 - Longer term
- Will require integration of laboratory and computational modeling activities



Shorter-term goals

- More predictive PBPK models
- Empirical description of the regulation of XMEs
- Biology
 - Normal
 - Diseased



Longer-term goals

- Mechanistic description of regulation of XMEs
 - Age-dependence, interspecies
- 3-d reconstruction
 - Acinus or whole liver?
- Biology
 - Normal
 - Diseased
- Toxicological mechanisms most relevant to EPA

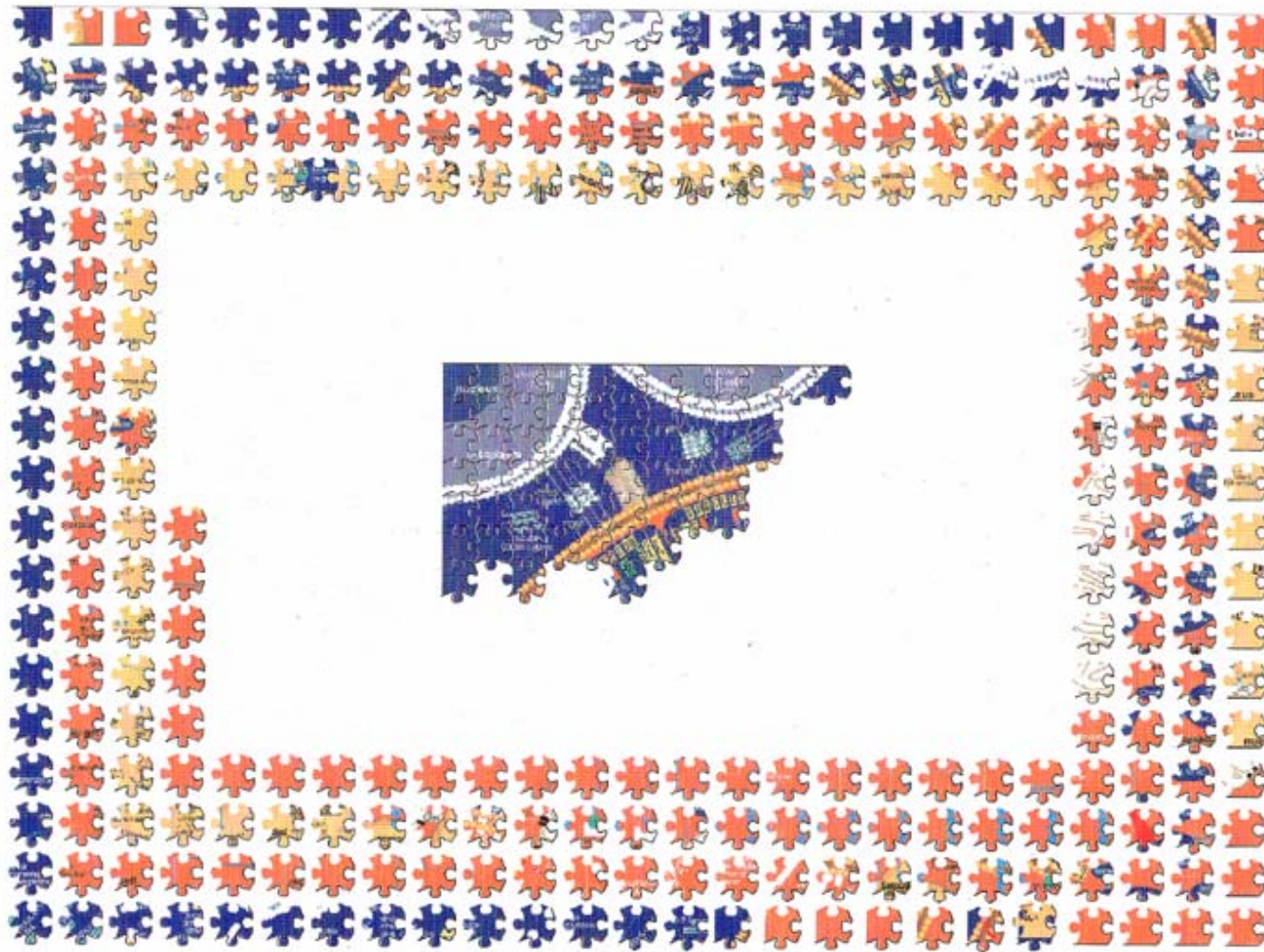


Modular, step-by-step approach

- Overall model will consist of portable modules
 - Only work with the part you need
- Coding standards

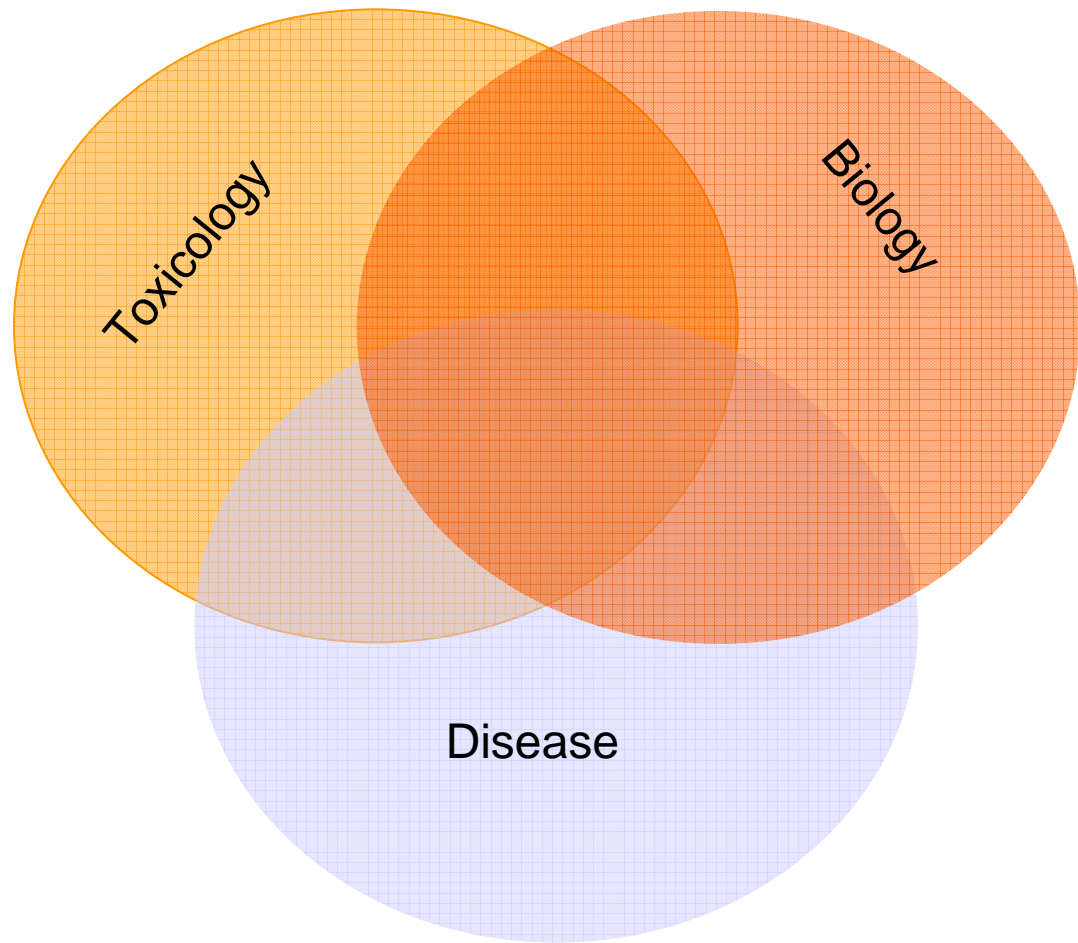


Begin assembly of pieces



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Who?



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A collaboration

- Development of computational models will require collaboration between experimentalists, statisticians, and computational modelers
- Model development requires expert input
 - biological and toxicological issues
 - Computational modeling issues
 - Bioinformatics and statistics



Project structure

- Steering committee
 - Conolly, Kavlock, Blancato, Preston, (NCEA)
- Modeling practice and QA
 - El-Masari, Schlosser, Conolly, Okino
- IT/databases/curation
 - Dix, Corton, Houck
- Intranet
 - Breen, Dewoskin



Potential external collaborators

- Entelos
- Genomatica
- Physiome project
- E-cell (Japan)
- V-cell (Connecticut)
- German hepatocyte project
- *e. Coli alliance*
- NIH multiscale modeling projects
- NJ Star Bioinformatics Center
- ISTC (Russia)
- Visualization lab



End



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