

Simulating Hepatic Tissue Lesions as Virtual Cellular Systems

v-Liver™ The Virtual Liver Project

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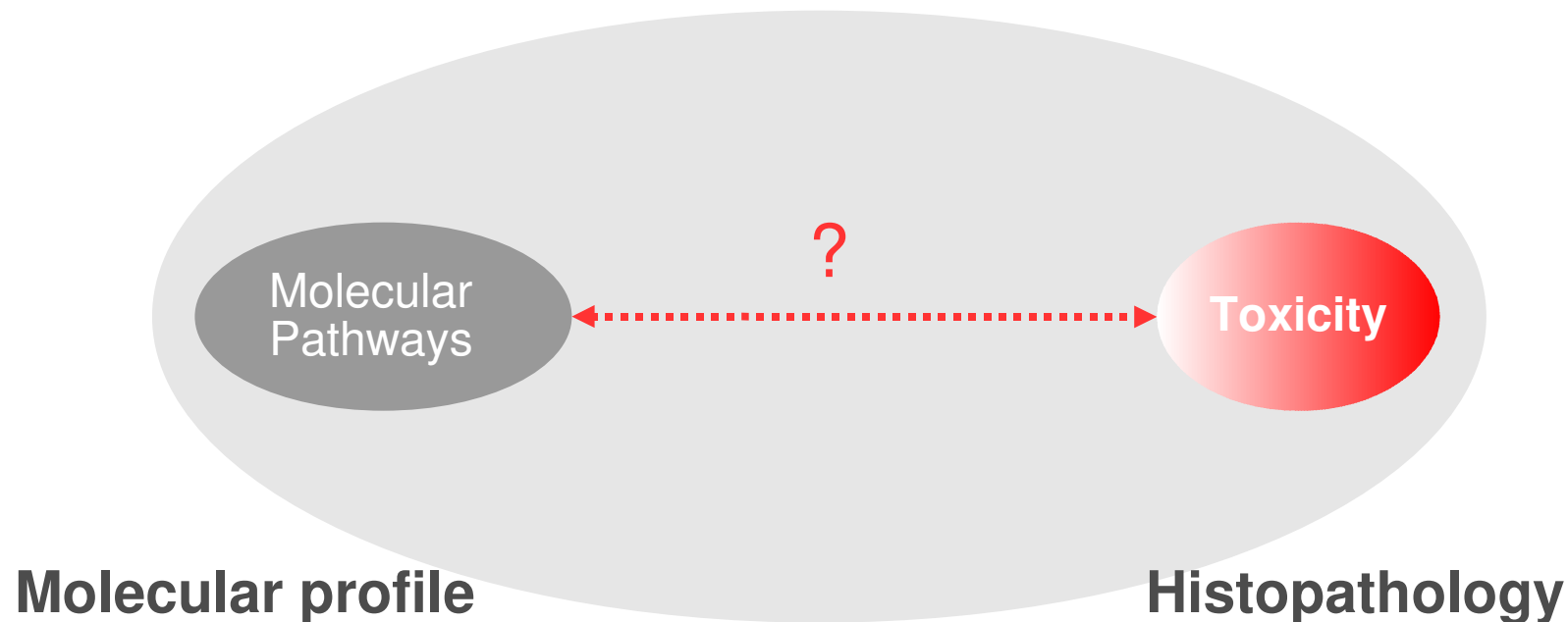
UNITED STATES ENVIRONMENTAL PROTECTION AGENCY



This work was reviewed by EPA and approved for publication but does not necessarily reflect official agency policy.

- ~10,000 HPV chemicals - little/no biological data !
- Animal testing infeasible / uncertain value
- 2007 NRC - Toxicity Testing 21st Century
- 2008 EPA - Strategic Plan for Evaluating Chemical Toxicity
- Liver injury frequent adverse effect
- Develop *in vitro-in silico* proof of concept
- Evaluate using environmental chemicals

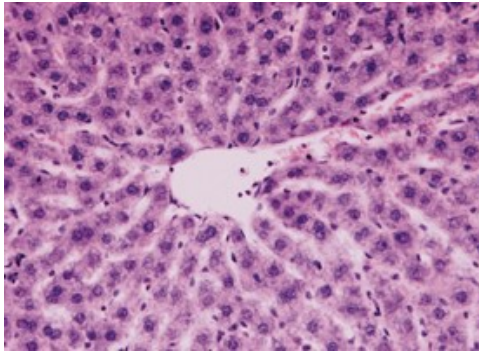
How to Predict Liver Toxicity ?



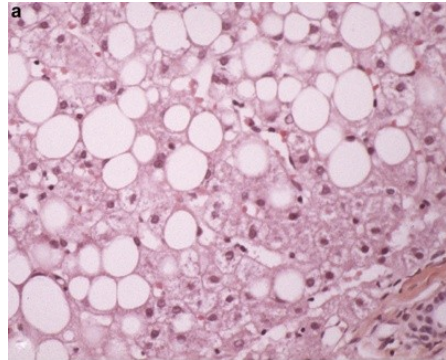
Phenotypic anchoring valuable for prioritization
Difficult to elucidate mode-of-action / dose-response

Toxicity: Cell Alteration

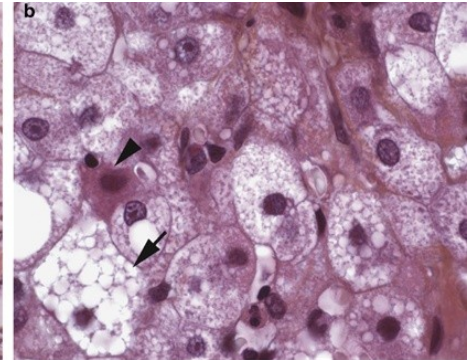
Swelling



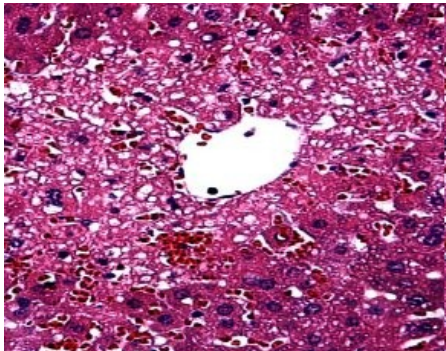
Steatosis, Macroves.



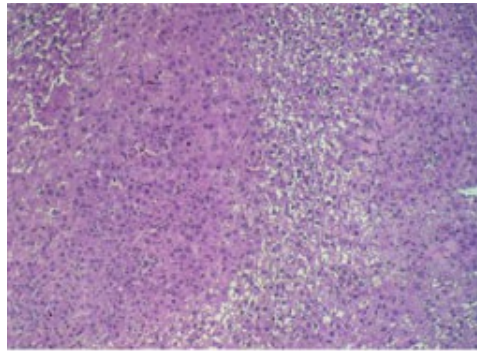
Steatosis, Microves.



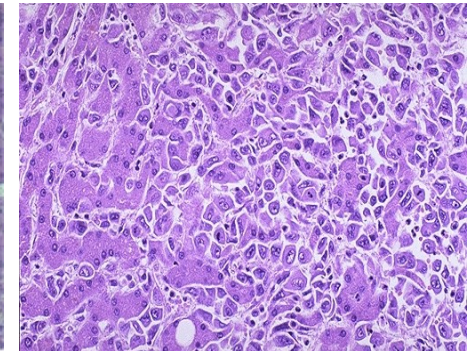
Necrosis



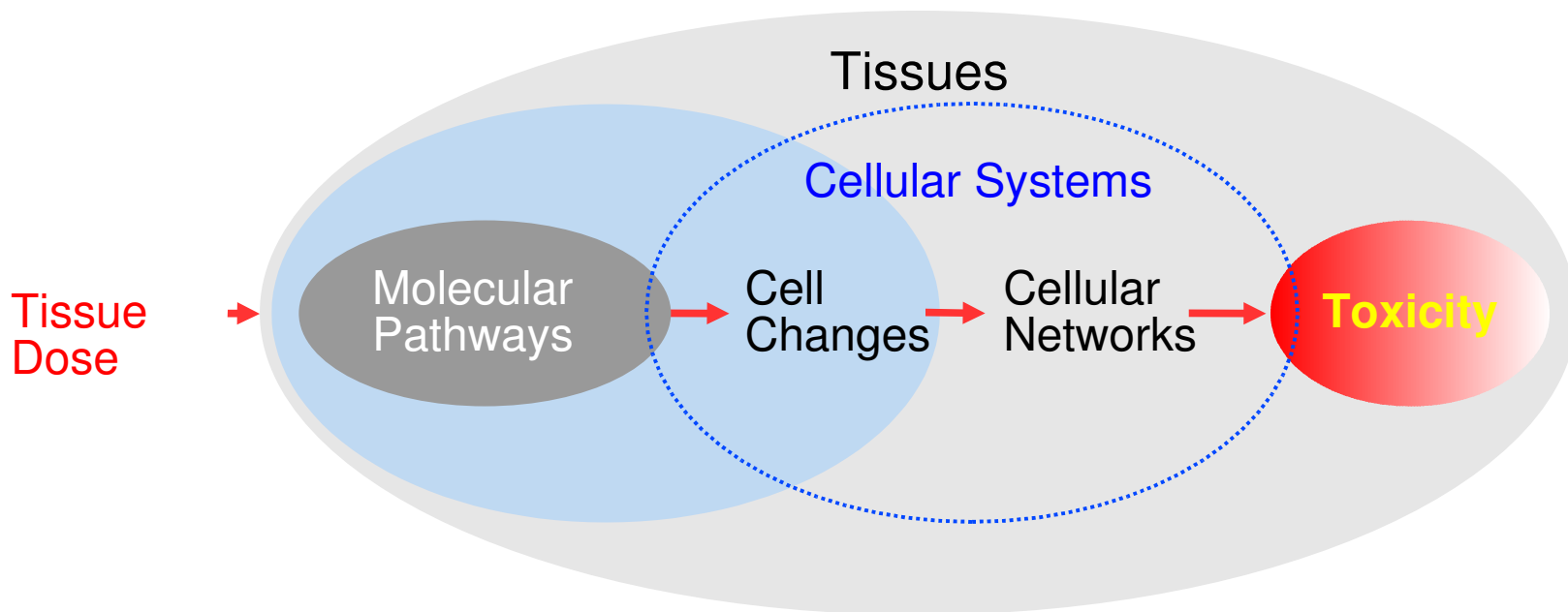
Hyperplasia



Carcinoma



Toxicity: Cross-Scale Phenomena



Tissue lesions propagated by dynamic cellular networks

Cell changes are caused by molecular pathways

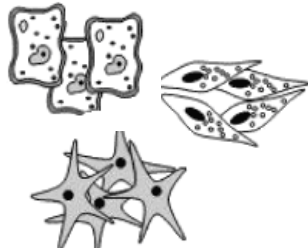
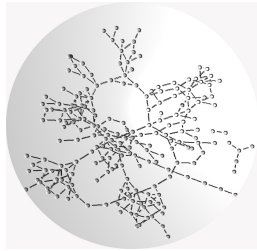
Use a cell-oriented view to deal with complexity ...

Virtual Liver: v-Liver™

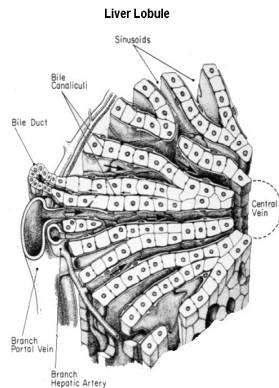
Agent-Based Cellular Systems Model

Tissues

Key events
in cell
response



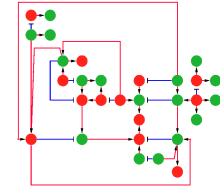
Cell
Signaling



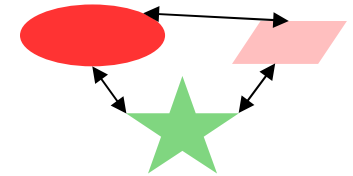
Blood
Flow

Virtual Tissues

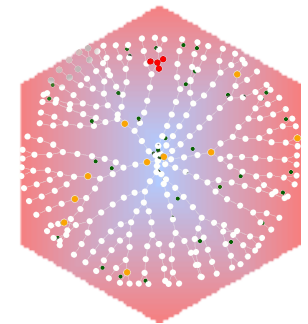
Molecular Logic
Cell Changes



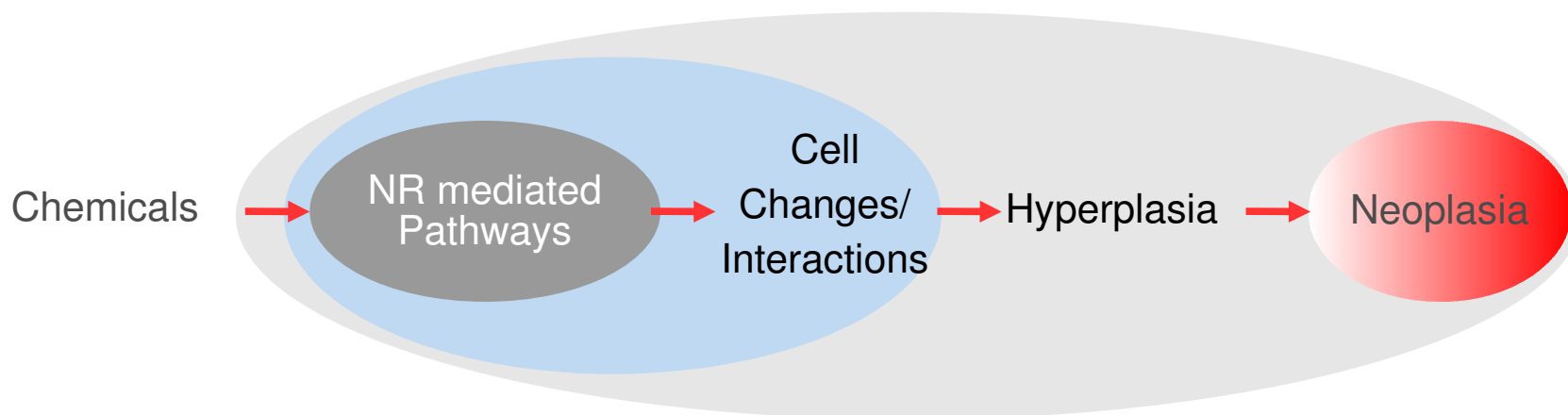
Cell
Interactions



Spatial
Cellular
System



v-Liver™: Proof of Concept

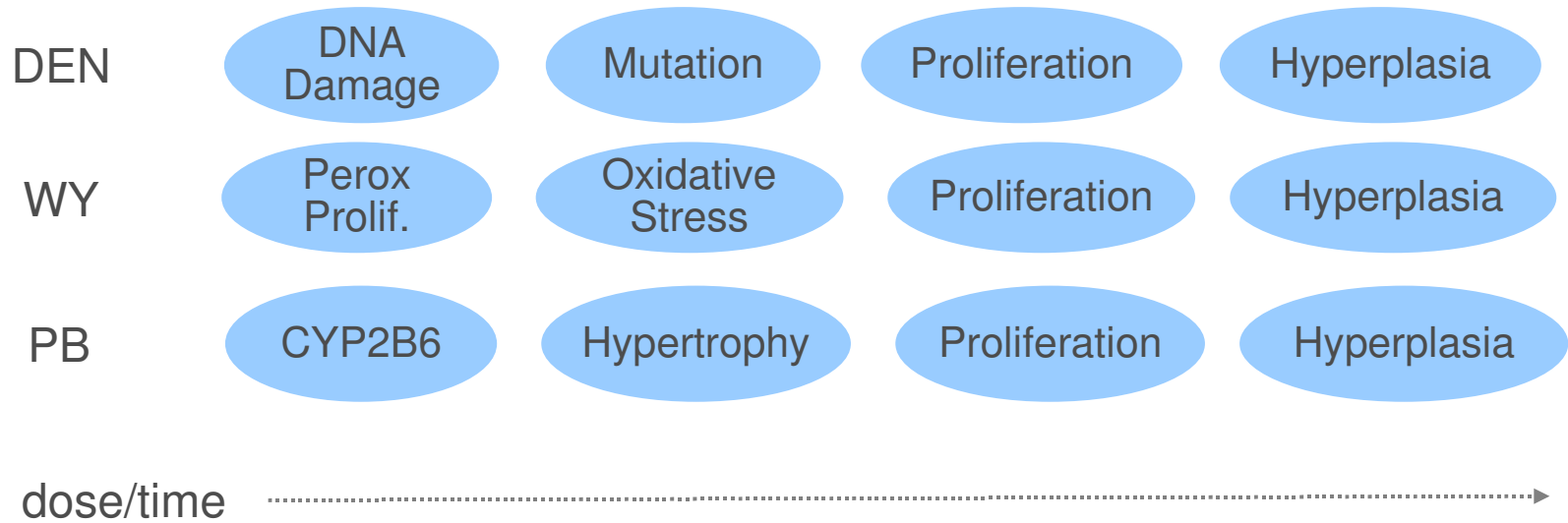


Goal: Simulate dose-dependent events in nuclear receptor-mediated hyperplasia

Modes-of-Action: Regenerative proliferation, Mitogen, DNA Damage

Approach: Cross-scale Cellular Systems Model

Carcinogenesis: Key Events



Which molecular pathways lead to cell death / division ?

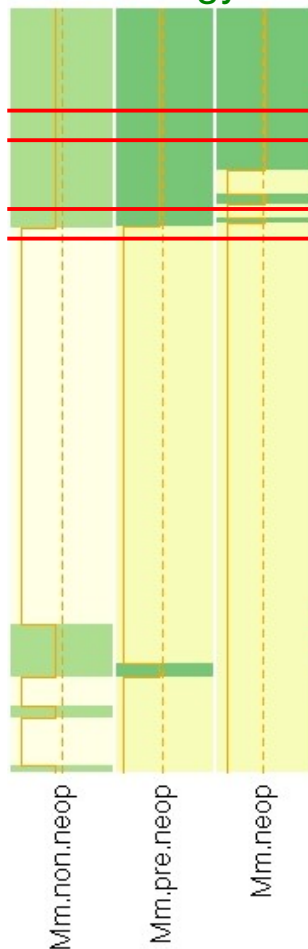
Which cellular interactions/events propagate proliferative lesions ?

Chemicals: Activities & Toxicity

ToxCast:
309 Chemicals
600 Assays
Chronic Pathology

ToxRefDB
in vivo

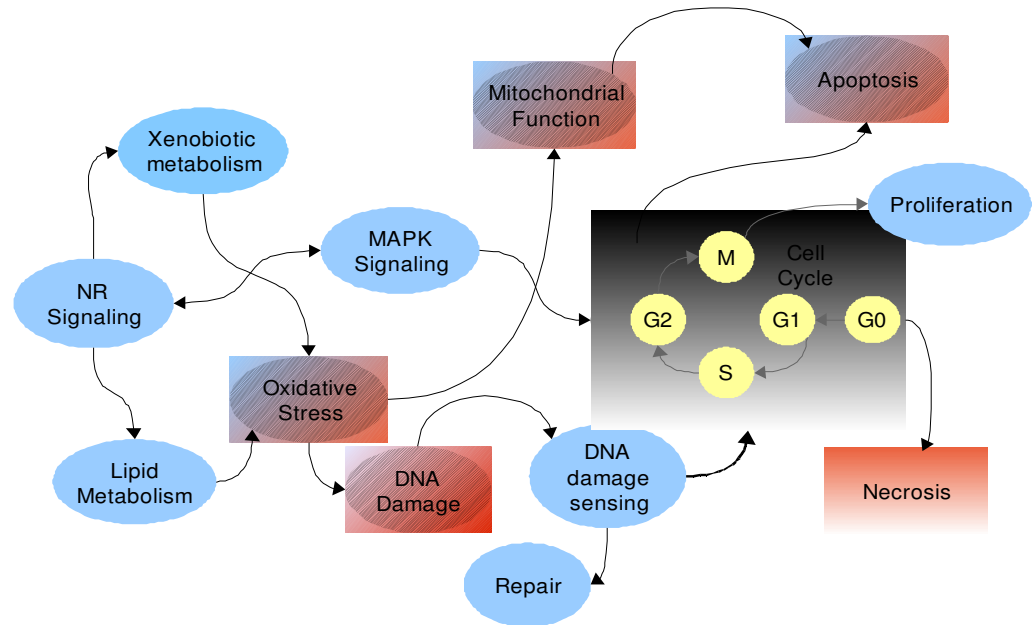
Mouse Chronic
Pathology



Cellular Pathways & Outcomes

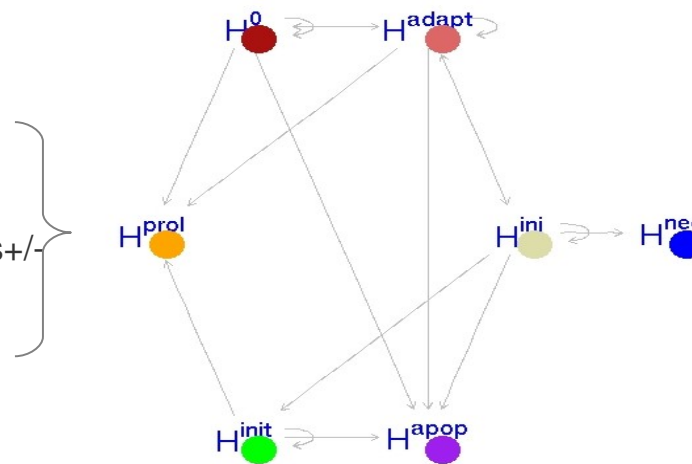
Mine literature,
DBs and prior data

(a) Cellular
pathways &
interactions
involved in
death / division



(b) Agent **inputs**,
states
and **state**
transitions

Xenobiotic
Nutrients
Growth Factors+/
Cell-contacts

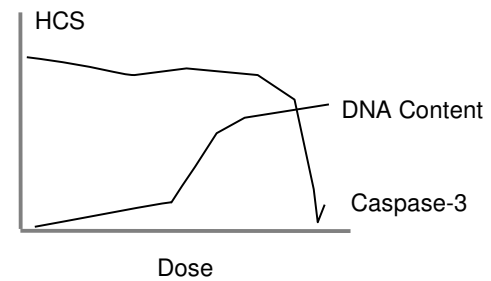
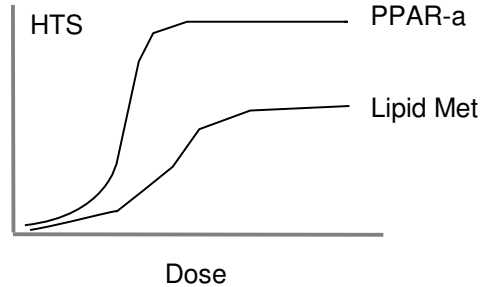


Normal
Adaptive/Injury
Necrosis
Apoptosis
Proliferation
Initiation

Cellular System: Agents

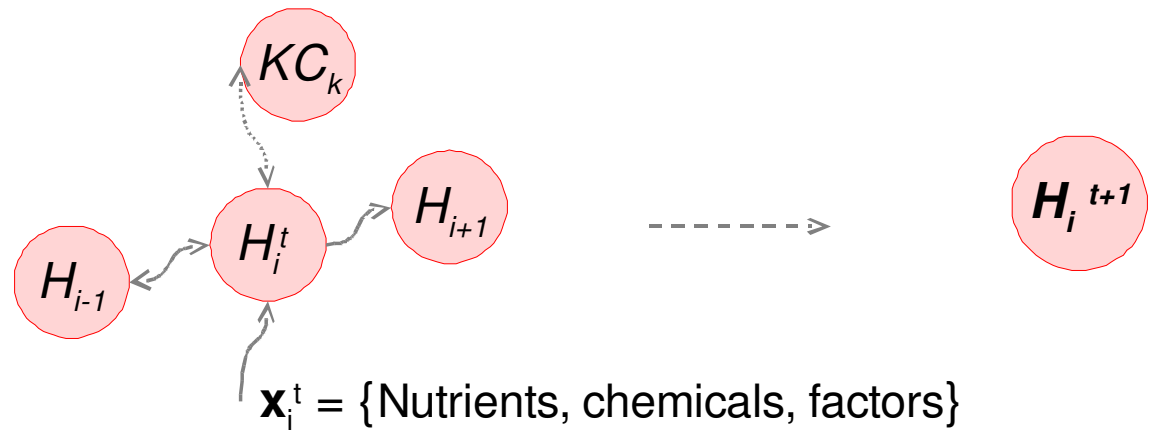
Data / Chemicals

Dose-response
data HTS, HCS:
Integrated response
from cell population



Dynamics

Data-driven dynamic probabilistic model
of cell-response
using **population data**

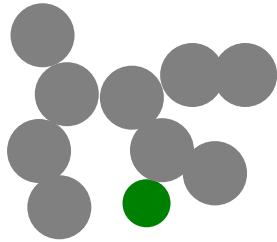


$$H_i^{t+1} = F(H_i^t, H_j^t, \mathbf{X}_i^{\text{in}})$$

$H_i^t = \text{Hepatocyte state at time } t$

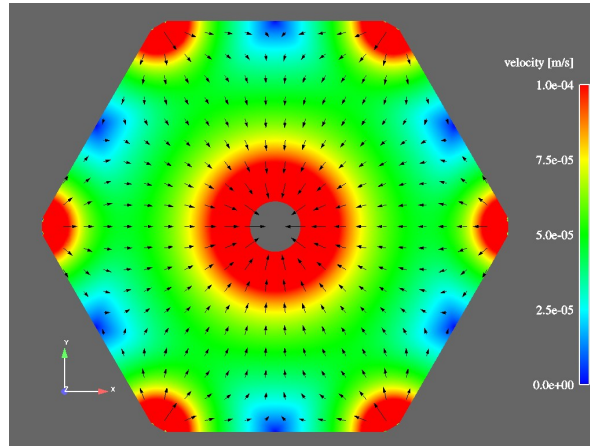
$H_j^t = \text{Hepatocyte neighbourhood at time } t$

“Virtual Cellular System”

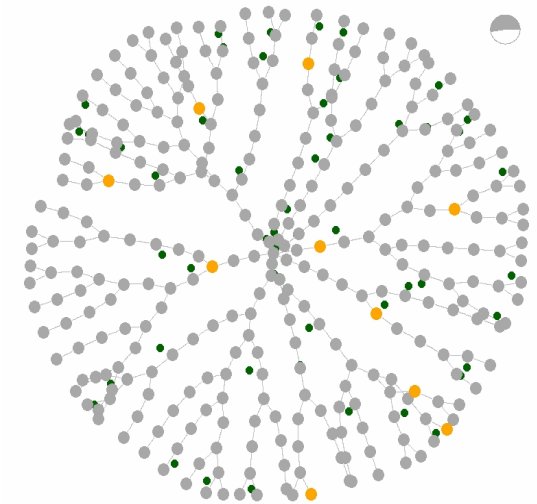


● Hepatocyte
● Kupffer cell

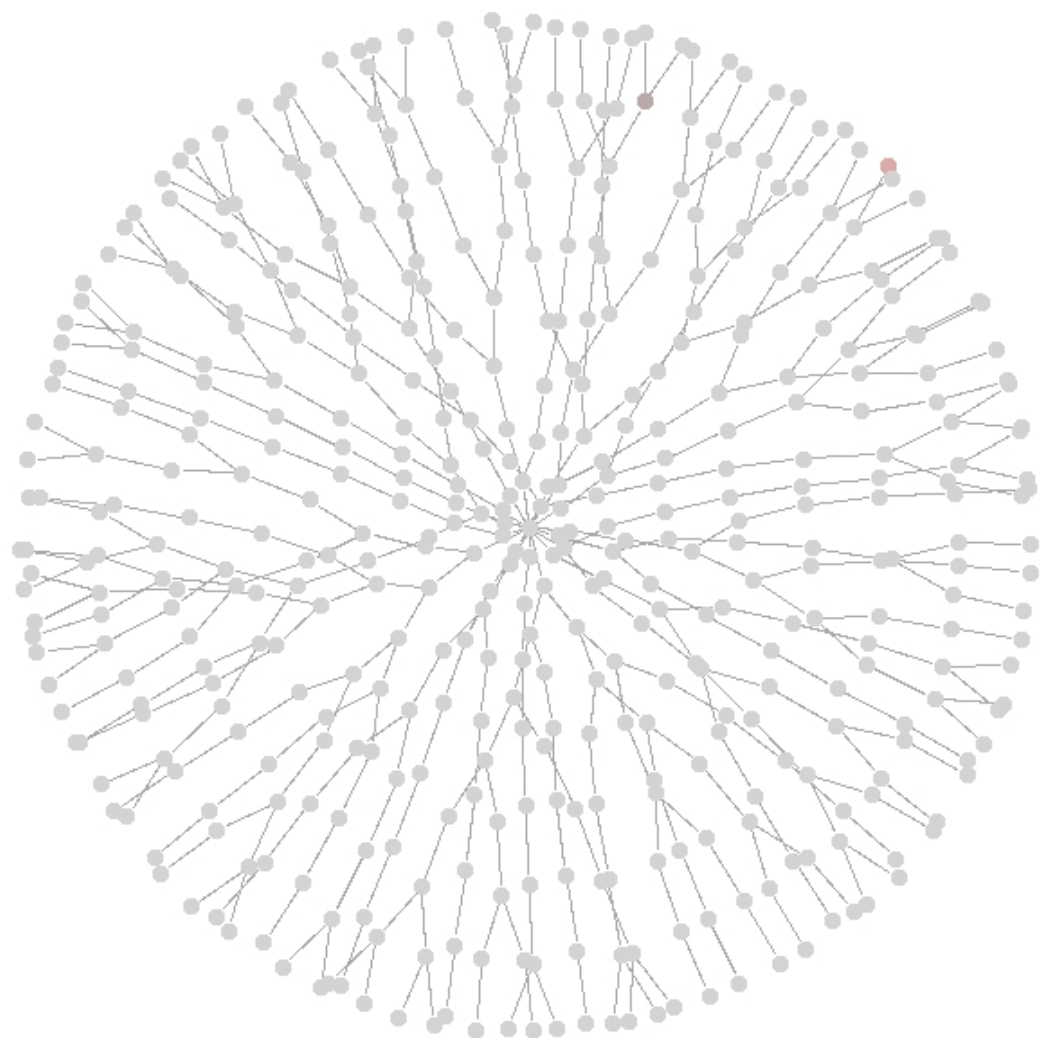
Multi-Agent
System



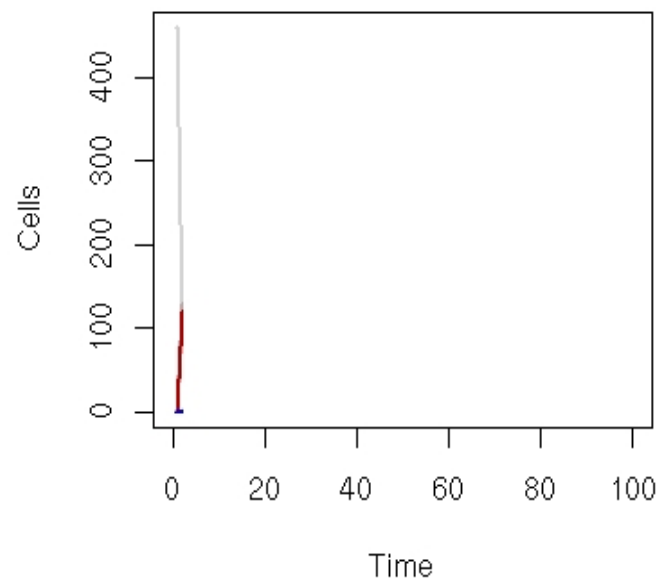
Blood
Flow



Virtual
Lobule



v-Liver Response



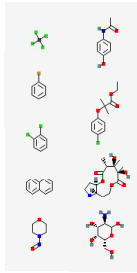
v-Liver™ Architecture

Assays

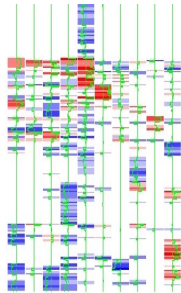
v-Liver
Knowledgebase

v-Liver
Simulator

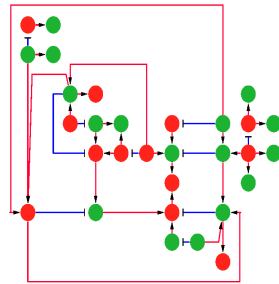
Outcomes



Env.
Chems



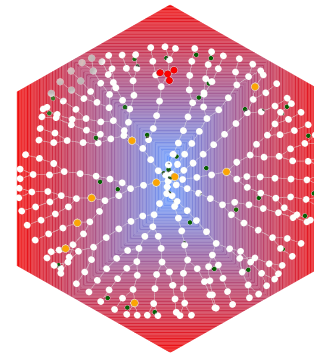
ToxCast
HTS, HCS
ex vivo



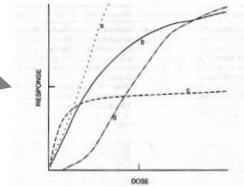
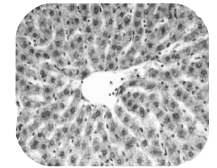
Molecular
Events



Cell-Cell
Events



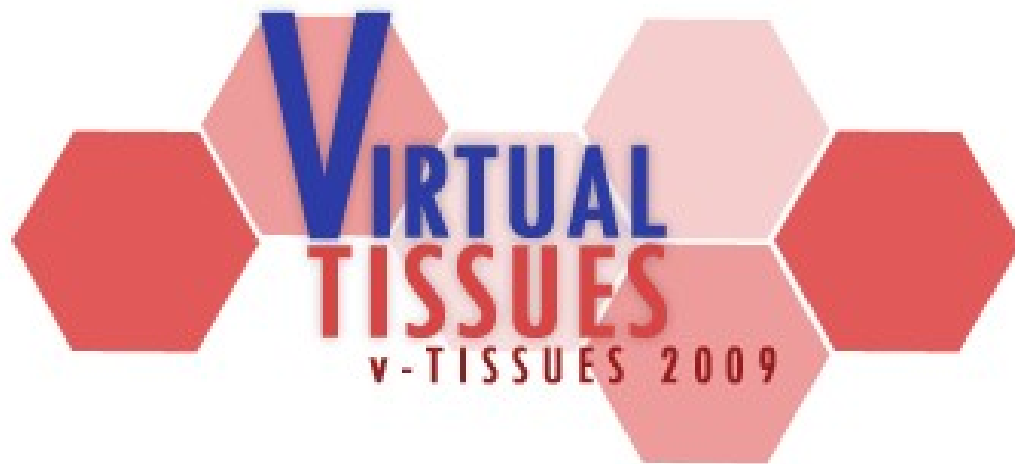
Cell Sys. &
Blood Flow



Cellular &
Tissue Effects

Summary

- Model tissues as “cellular systems”
- PoC: *in silico* platform to assess *in vivo* hepatic effects using *in vitro* data
- Focus on modeling lesions for ~20 +/- non-genotoxic carcinogens



Multi-disciplinary Team: Cross-EPA/ORD & External

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Jason Pirone
Mike DeVito
Nicholas Luke
Rory Conolly
Thomas Knudsen
David Dix
Matt Martin
Keith Houck
Richard Judson
David Reif
Woody Setzer
Amar Singh
Lockheed Marting

Risk Assessors:
Clients

ToxCast™
AcTOR
v-Embryo

