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Systems Toxicology at US EPA

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ebCTC workshop
SYSTEMS TOXICOLOGY:
Multiscale Modeling of
Environmental Impacts on Bionetworks
Piscattaway, New Jersey

Office of Research and Development
National Center for Computational Toxicology

April 26, 2007

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What Do We Mean by Systems Modeling?

- In today's world –
  - "the application of mathematical modeling and reasoning to the understanding of biological systems and the explanation of biological phenomena"

    (http://www.epa.gov/comptox/comptoxfactsheet.html#computationaldisciplines)

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But yet, is this really new?

- Probably not….
  - Frank-Starling Law of the Heart for Example
    - First published in early 1900s
  - Even older examples
    - Descartes description of the human body in the 1600s
    - Harvey also in the 1600s
      - *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* (An Anatomical Exercise on the Motion of the Heart and Blood in Animals)
    - Ibn Nafis – Muslim Medical Scientist
      - Principles of circulation in the 1300s
    - Numerous other examples going back to Galen but Harvey may have been the first to study the circulation quantitatively

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Let's Start by Seeing What a System is

- An organized entity that survives the demands of a changing environment by being adaptable and at the same time maintaining a status quo – or maintain life
- The system is defined by the level of organization being described
  - The whole organism is the typical system
  - Could be a system within the organism
  - Could be a system within a tissue or even within a cell
- The key is that the components of the system are interrelated or networked – each component is influenced by other components and each component influences other components – these influences are both direct and indirect

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Models

- Model is a conceptual representation of a phenomenon or process
  - Contain logical and often quantitative relationships between the components
    - So then we can model a system
- Models are constructed to enable reasoning within the framework described
- Models have certain assumptions built in
  - Often the assumptions are knowingly wrong or incomplete
    - These assumptions are allowed because they result in a model simplified for practicality and yet in acceptable solutions for the problem at hand
    - Yet in many cases the simplifications prevent a thorough understanding of the underlying process
  - A delicate balance between simplification and thorough description is necessary

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Some Types or Approaches To Modeling

- Scale models
  - Different sized copies of target systems
- Idealized models
  - Deliberately simplified models of complicated processes to make the descriptive model more tractable
- Analogical models
  - Relevant similarities or shared properties make two things analogous.
    - Thus one can serve as the model for the other
- Phenomenological models
  - Incorporate principles and laws associated with theories
- Models of data

Above concepts adapted from: On-line Stanford Encyclopedia of Philosophy (http://plato.stanford.edu/entries/models-science/)

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Biological Models

- Probably combinations of various types of models
  - Predominantly
    - Phenomenological models
    - Idealized models
    - Models of data

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Some Uses for Models

- Describe past observations
- Predict future observations
- Control or regulate events
- Help us learn about the underlying phenomenon
  - "Model laboratories"

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System Models

- Model biological phenomena
  - Not in isolation
  - System represents a network of interconnected and interlaced regulatory and communication pathways
    - Pathways are interconnected to regulate and maintain the normal function of the system

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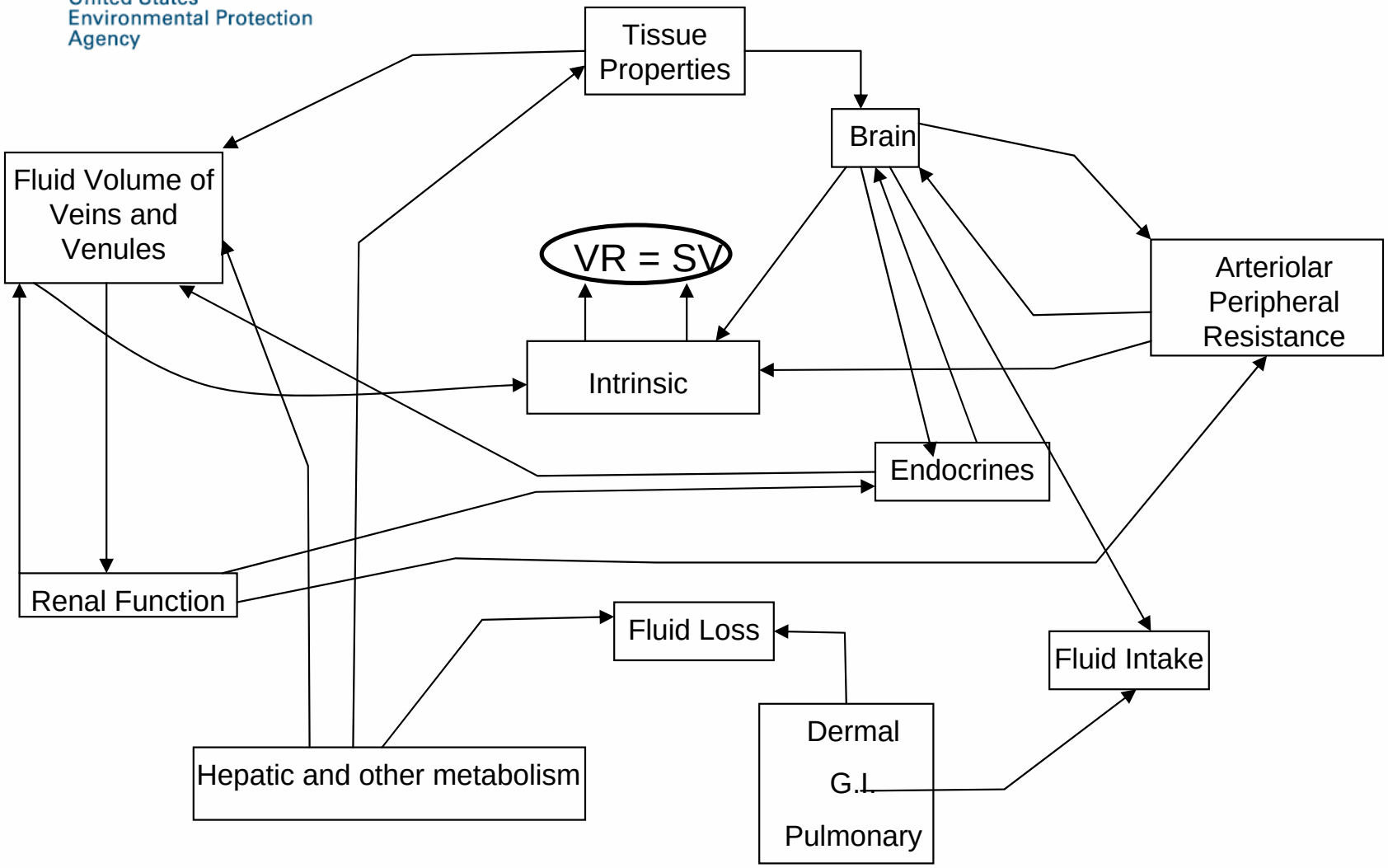
Frank-Starling Law of the Heart

Simple yet elegant description of a very complex system

- The more the ventricle is filled with blood during diastole (venous return), the greater the volume of ejected blood will be during the resulting systolic contraction (stroke volume)
  - In mathematical terms:
    - VR = SV
- This the underlying description of the mechanism of healthy, well functioning heart and cardio-vascular system
- When this underlying principle is violated the system goes into failure


Tissue Properties
Brain
Fluid Volume of Veins and Venules
VR = SV
Arteriolar Peripheral Resistance
Intrinsic
Endocrines
Renal Function
Fluid Loss
Fluid Intake
Dermal
G.I.
Pulmonary
Hepatic and other metabolism

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"An important outcome…is the realization that genes do not act alone but are participants in extensive networks of activity within cells. Any change in the functioning of one gene can therefore be accompanied by changes in the workings of multiple genes and proteins involved in the cells' self-maintenance."

--Renato Dulbecco, President Emeritus, Salk Institute

(From Scientific American, March, 2007)

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PBPK and PBPD Models

- Help us understand and analyze internal events, including the relationship with exposure
- Help us predict the impact of those events

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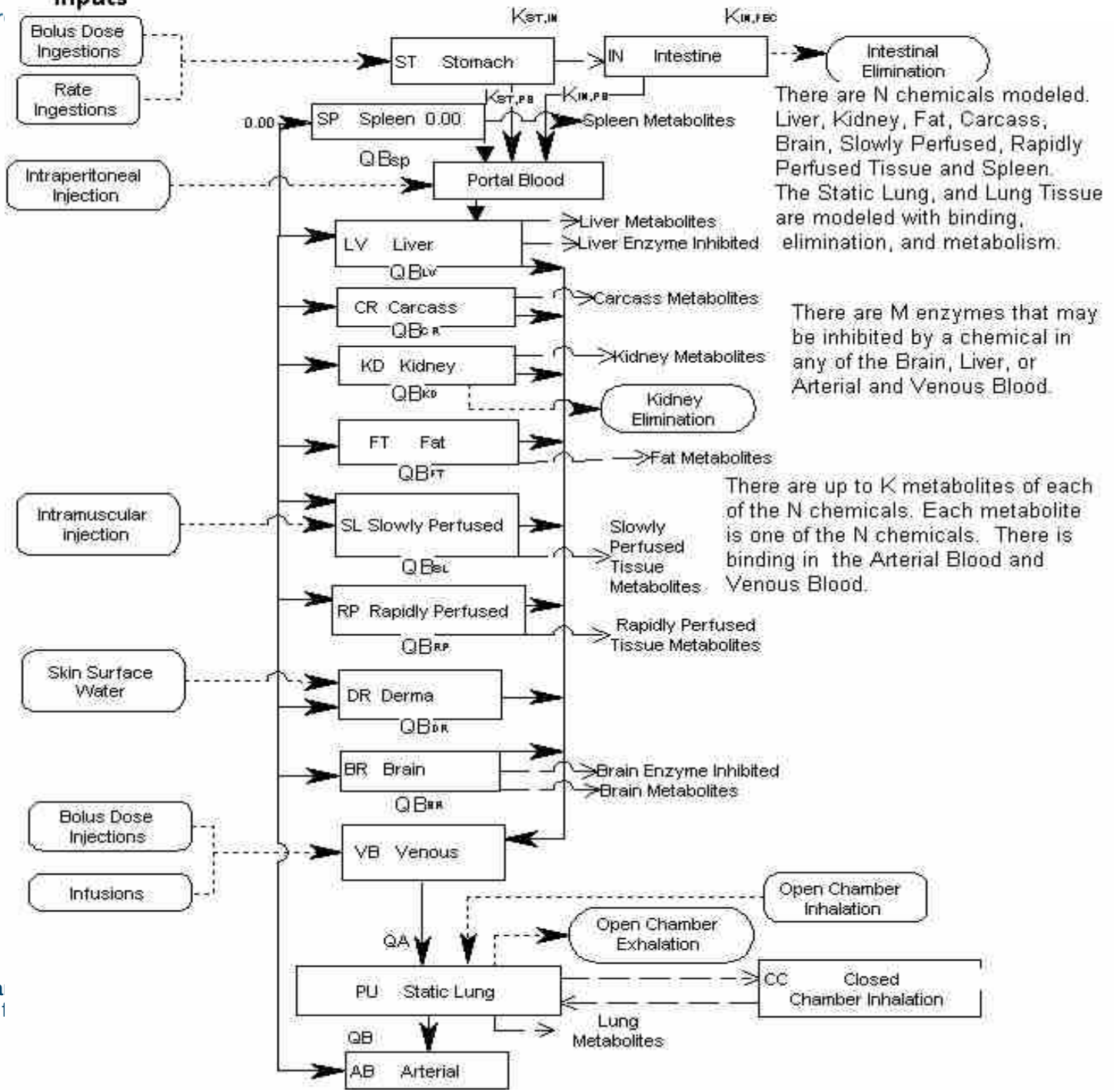
PBPK Models

- Describe the time course mass balances of chemicals entering the body.
  - Mathematically account for both the physiologic and biochemical processes within the body that affect the disposition of the chemicals entering the body and their products of biotransformation.
  - These models estimate and predict the time course of the internal doses within the body especially at sites relevant to toxicity.

Figure 1 SYSTEM FLOW CHART With Static Lung/Stomach/Intestine



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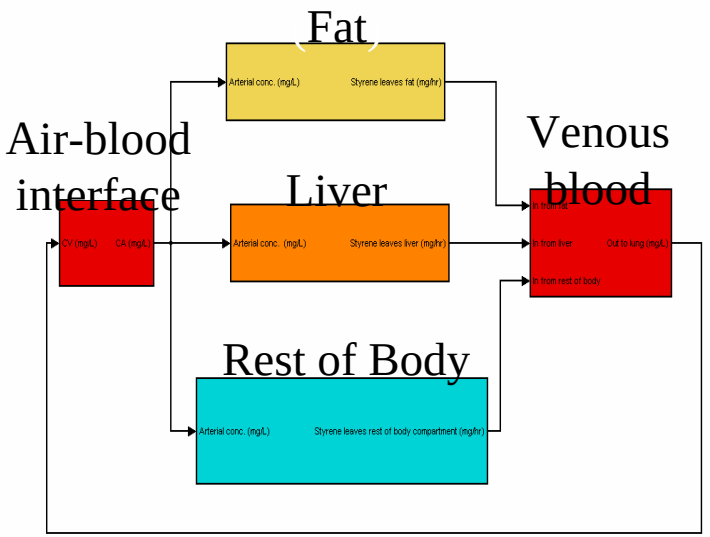
More Simplified or Idealistic Case



PPK model

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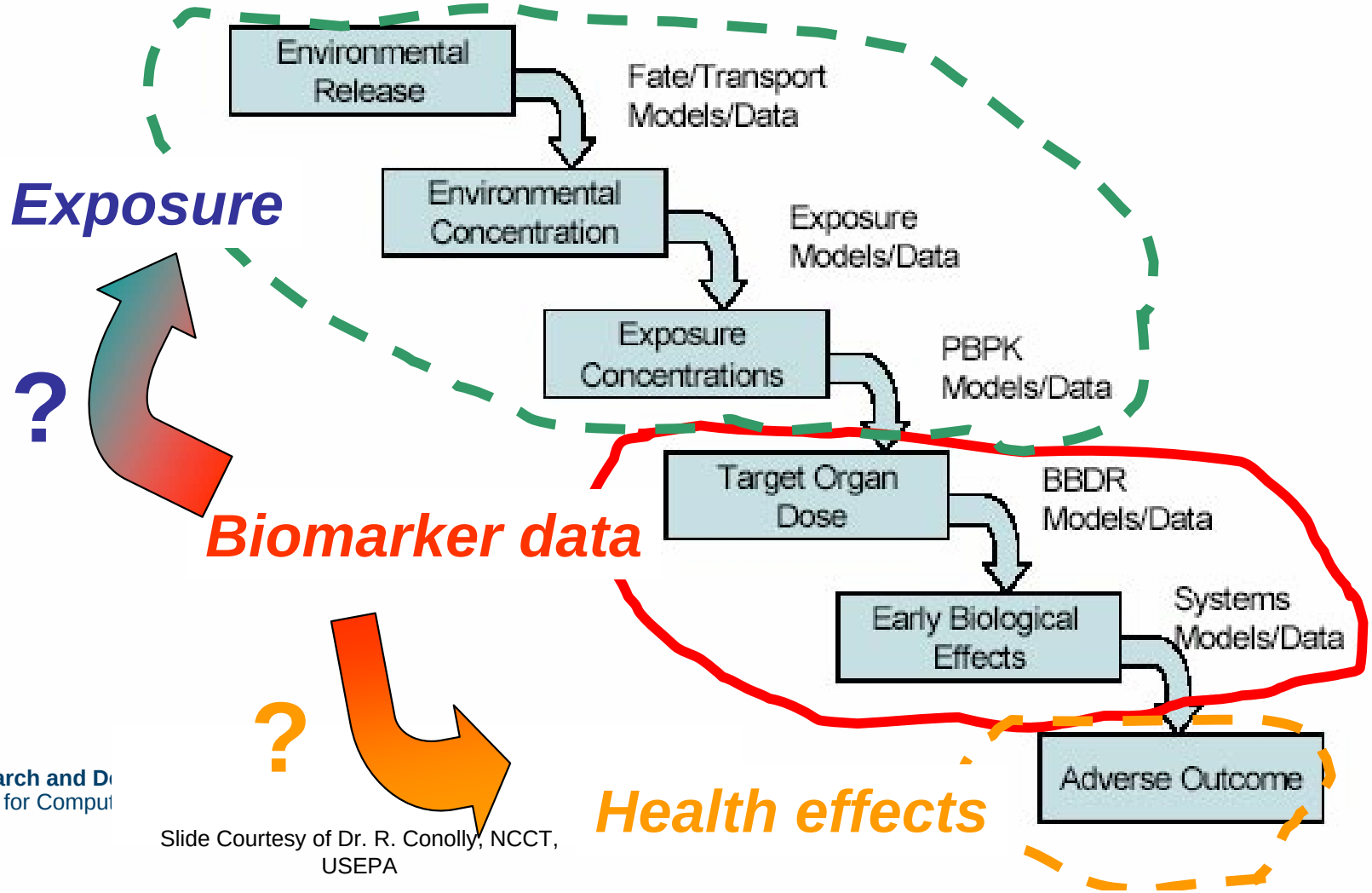
Characterizing the relationships between exposures, health risks, and biomarker data



Slide Courtesy of Dr. R. Conolly, NCCT, USEPA

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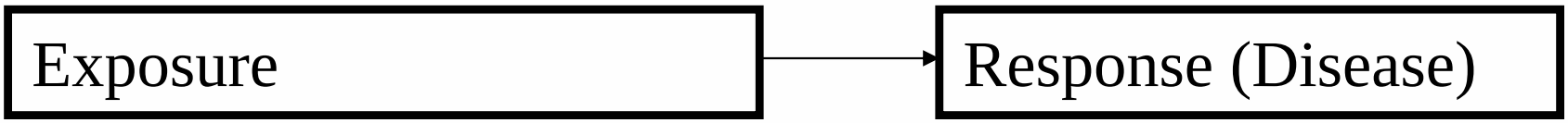
Risk Assessment: Classical Era



Exposure was used instead of the dose normally used in classic dose-response models

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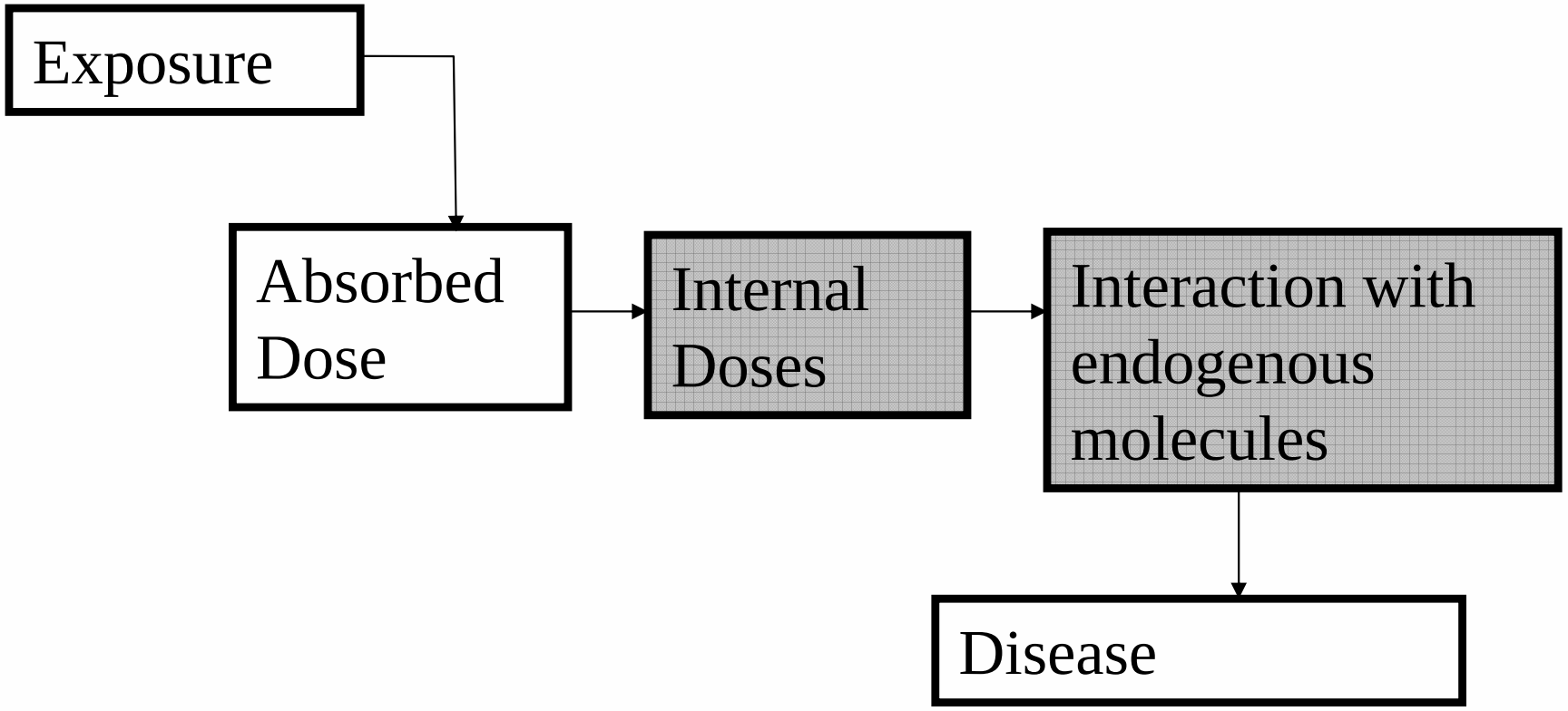
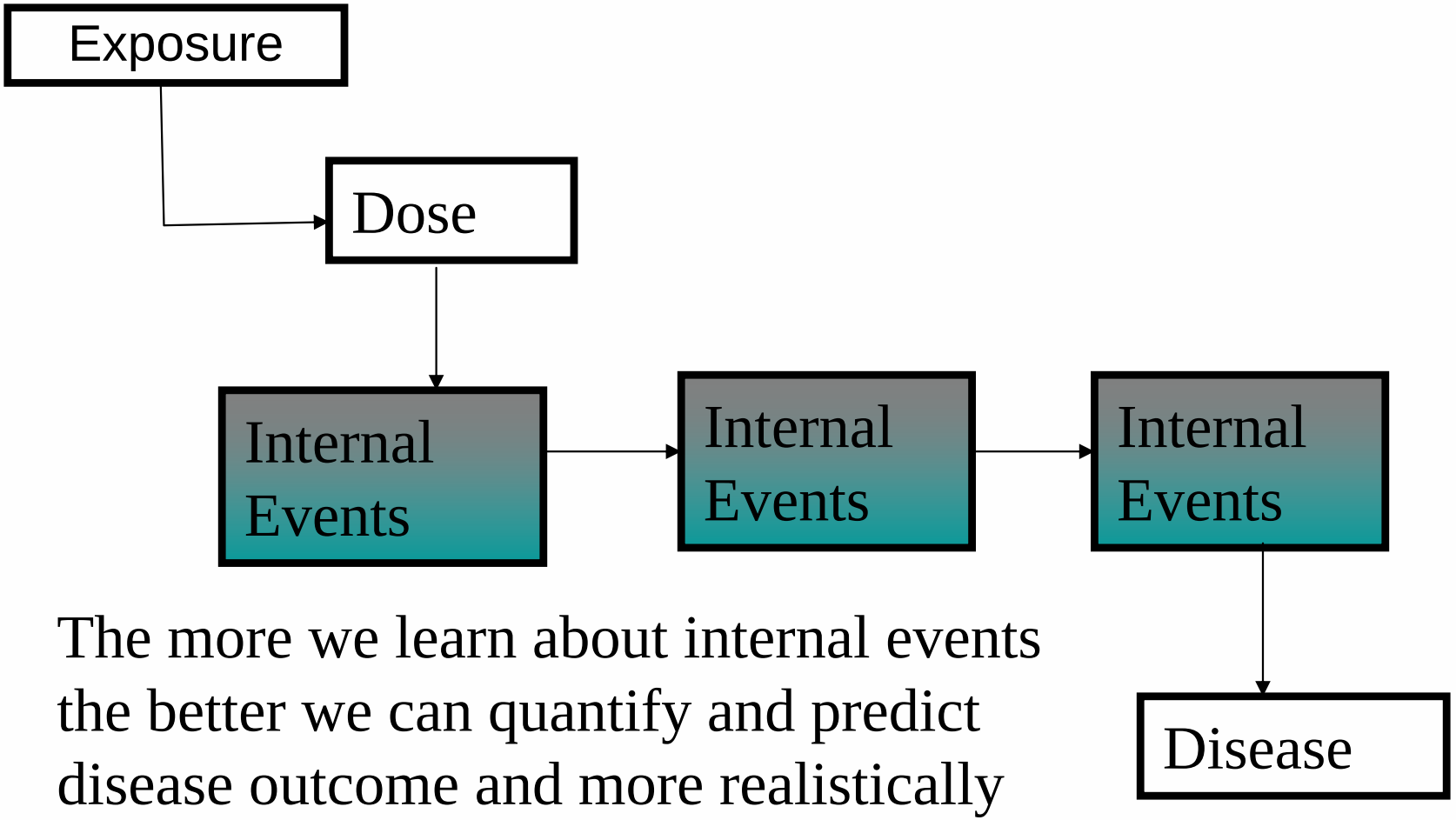
Actually, a Series of Steps or Boxes – Neoclassic Era or Where We are Now



More "Details" – Modern Era or Where We Would Like to Be



The more we learn about internal events the better we can quantify and predict disease outcome and more realistically relate it to actual exposures and characterize the uncertainty

Computational Toxicology Challenges

- Regulating an environmental chemical requires a **quantitative** assessment for **risk of an adverse outcome / toxicity in a living system**
- **Animal models are current standard for measuring risk of adverse outcome but extrapolating these to humans is difficult because ...**
  - **The mechanisms of chemical-induced toxicity are incompletely understood and it is difficult to apply findings to humans due to inter-species variation**
  - **Adverse outcomes are measured at high doses but extrapolating their risk to the very low environmental concentrations without mechanistic models is very difficult**

Slide Courtesy of Dr. I. Shah, NCCT, USEPA

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Newer Types of Molecular Data Such as “Omics”

- Help us characterize and quantify with more resolution those internal events or mechanisms
  - “shed light in the boxes”
- As biomarkers of exposure
- As biomarkers of effect

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How Can the Omics Help?

- May yield specific patterns that may be markers of potential disease and markers of exposure
- Help prioritize the truly important “cases”
  - identify truly sensitive populations
  - quantify variation in populations
  - shed light on the mechanisms of action
- Elucidate the gene-environment interaction
- Rely less on gross in-vivo studies and more on molecular level in-vitro and in-silico studies
- Aid in high to low dose and interspecies extrapolations

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But… Where Are We Now with Omics?

- They are frequently considered informative biomarkers of effect and possibly exposure
- Not a rigorous quantitative application within the risk assessment framework
- Great promise for the future – rapid, reduce reliance on long-term studies
- Models for interfacing will be required
- One key is the exposure-to dose interface and we already do extensive modeling in that arena

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For This We Need Better Models and Systems Biology

- "…systems biology attempts to harness the power of mathematics, engineering, and computer science to analyze and integrate data from all the 'omics' and ultimately create working models of entire biological systems" (Spivey, Environmental Health Perspectives, 2004)

Systems Models: series of linked sub-models

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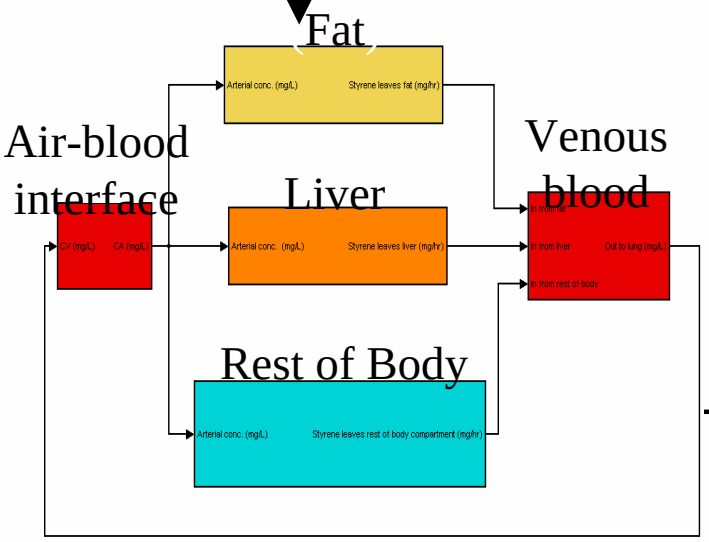
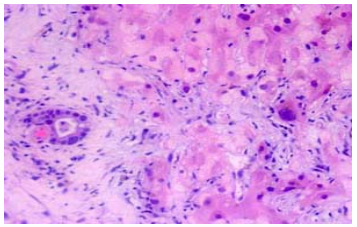
Env. Model

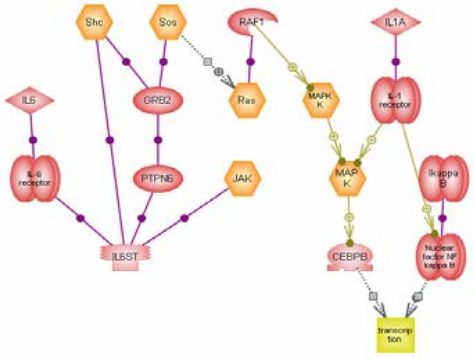
Exp. Model

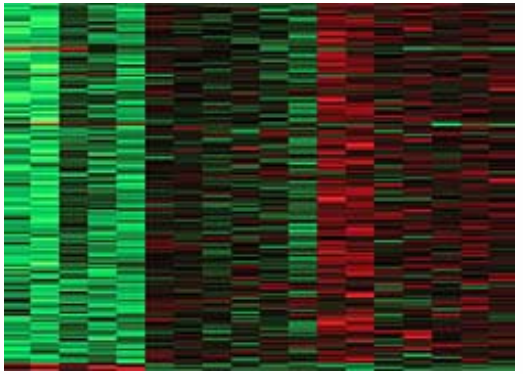


PBPK model

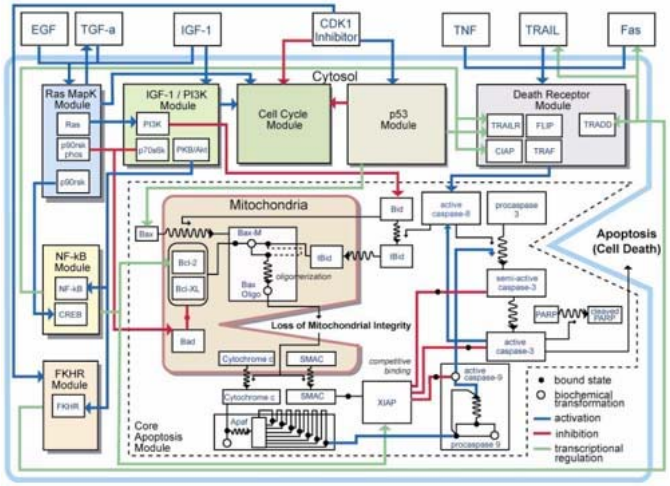


Cellular Toxicity





"Omics" data



PBPD and/or Cell biology model

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What is Nature of Such Models?

- Rely on data
  - Phenomenological and empirical
- Complexity or degree of idealization varies according to
  - Needs
  - Available data
- Models will need to be flexible
  - Generic yet adaptable
  - Change as more data become available
- Common frameworks are needed
  - Models are easily transferable and “portable”
  - Modular in nature

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Nature of the Data

- Much of it is high throughput across many domains
  - Genomic profiling
  - Gene family screening
  - Cellular endpoints – phenotypic
  - Proteomic
  - Metabolomics
  - Whole organisms
  - In-silico computationally based

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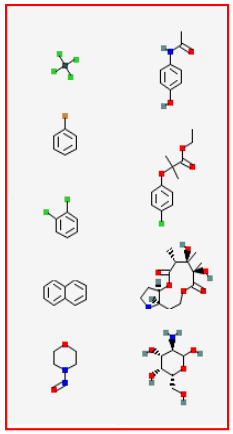
Assaying the *Global* State of a Living System: High-throughput Biology



Brain

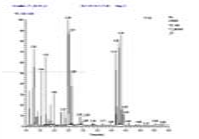
Blood

Liver

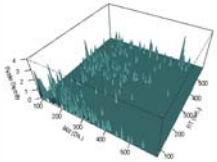
Kidneys

Urine

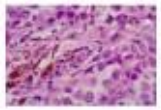
Gene-expression



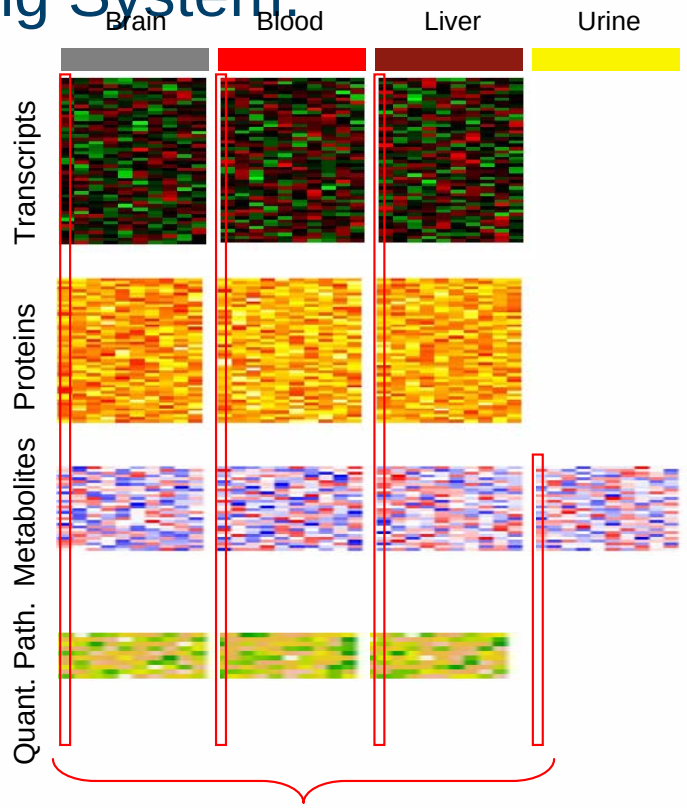
Proteomics



Metabolomics



Histomorphometry

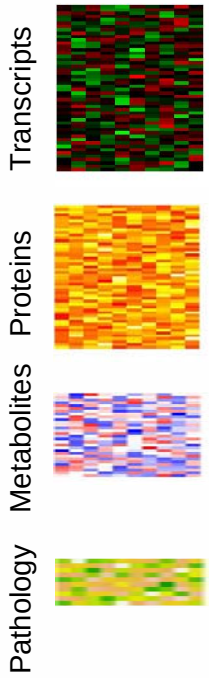


Large-scale profiles

Xenobiotics → Exposure Tissue/Dose/Time → *-omic* Data streams & Pathology end-points → Measures of "Global" response

Slide Courtesy of Dr. I. Shah, NCCT, USEPA

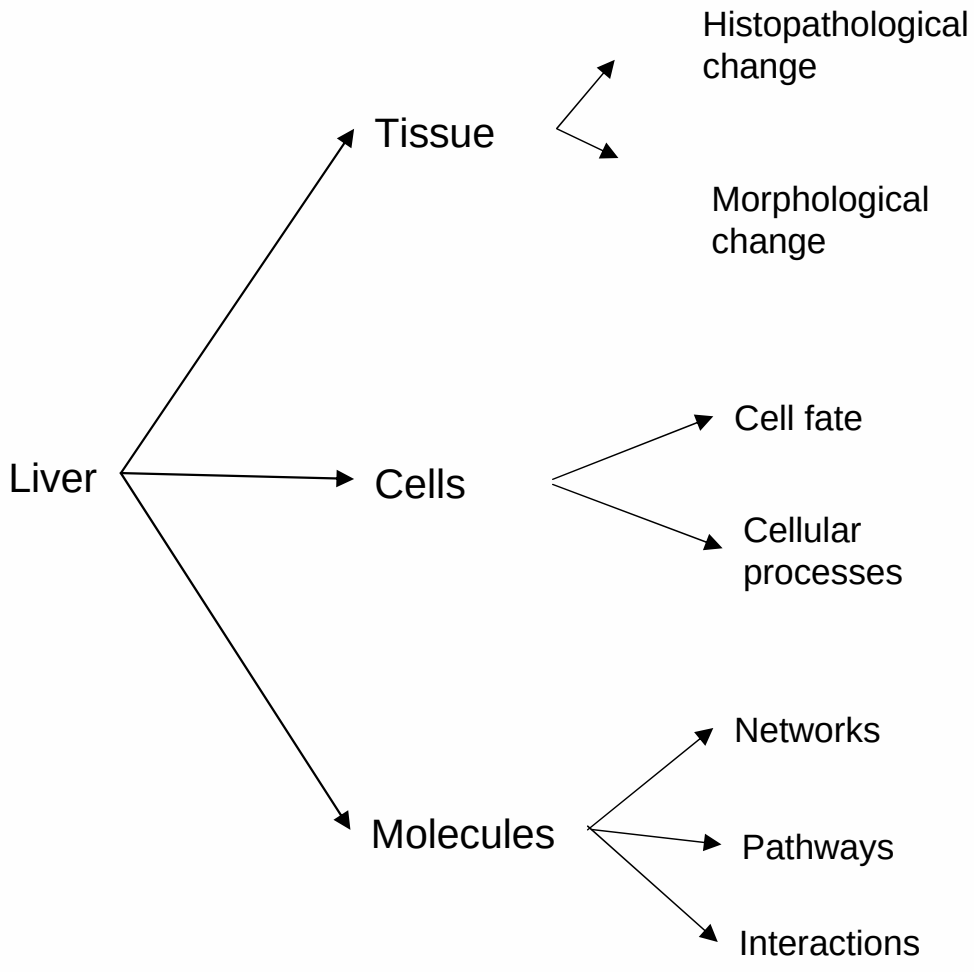
Data Processing and Analysis: Finding The Relevant Biology



Statistics	Significant entities: genes, proteins or metabolites
Machine Learning	Empirical models of toxicology end-points / Biomarkers
Functional Annotation	Functional categorization of significant changes
Pathway Analysis	Explain mechanistic context of perturbations

Large-scale Data sets → Statistical & Informatics methods → Biologically relevant results

Modeling Large-Scale Perturbations: Systems Biology



Morphological & HP changes on the way to cancer related to cell fate

Linkage between cell fate and morphological changes

Model cellular processes & fate generated by NR-signaling and Related to Cancer

Linkage between molecular networks and higher order cellular processes

Model of NR-signaling Interactions, pathways and network induced by ligands PPARa, CAR, PXR

Organ → Components → Perturbations → Mechanistic Systems Model

Slide Courtesy of Dr. I. Shah, NCCT, USEPA

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Elements of Model Building

- Data from literature and experiments
- Conceptual model from knowledge gained
- First may need to start with simple digital type approach corresponding to activated or deactivated molecule or gene
- Identify needed data for improved resolution to be obtained from literature or experiments (in-vivo, in-vitro, in-silico) – including HTS data.
- As more data become available change the model to a more mechanistic and stochastic model that has gradations of responses

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Some Computational Needs

- Knowledge representation, text-mining and inference
- Alternative systems modeling and simulation approaches
- Reverse-engineering biological networks from data
- Interactive 3D/2D multiscale visualization
- Data Storage capabilities
- Significant computational power

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Specific Related Projects at EPA

- DssTox
- ToxCast™
- Virtual Liver


To all, a good evening and thank you for your attention