Addressing New and Emerging Science and Data

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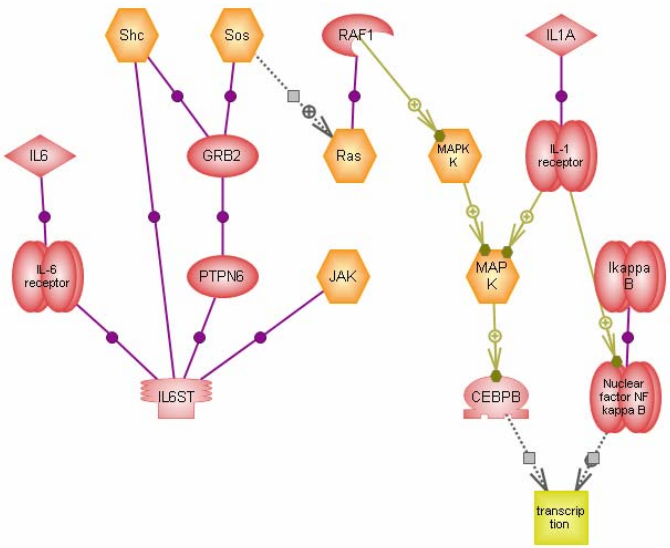
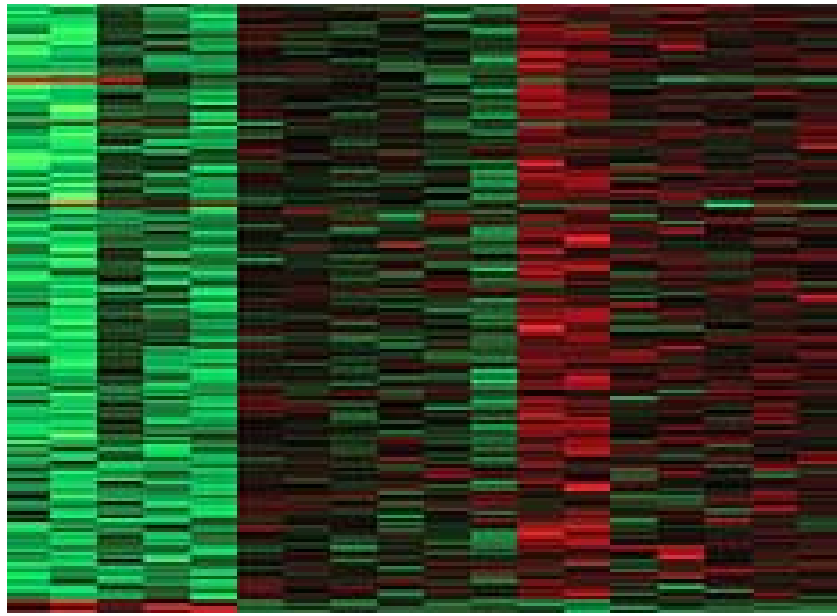
"New Biology" or "Omics"

- Come from Greek root Ome meaning all, every, or complete:
  - Genomics
    - Genes and their function
  - Proteomics
    - Full set of proteins encoded by a genome
  - Metabolomics/Metabonomics
    - Study of total metabolite pool

"Omics" biomarker data



Protein interaction network (stressed vs. control)



Gene array "heat map" (stressed vs, control)

Issue

- How can the new “omics” technologies be used to improve exposure science?

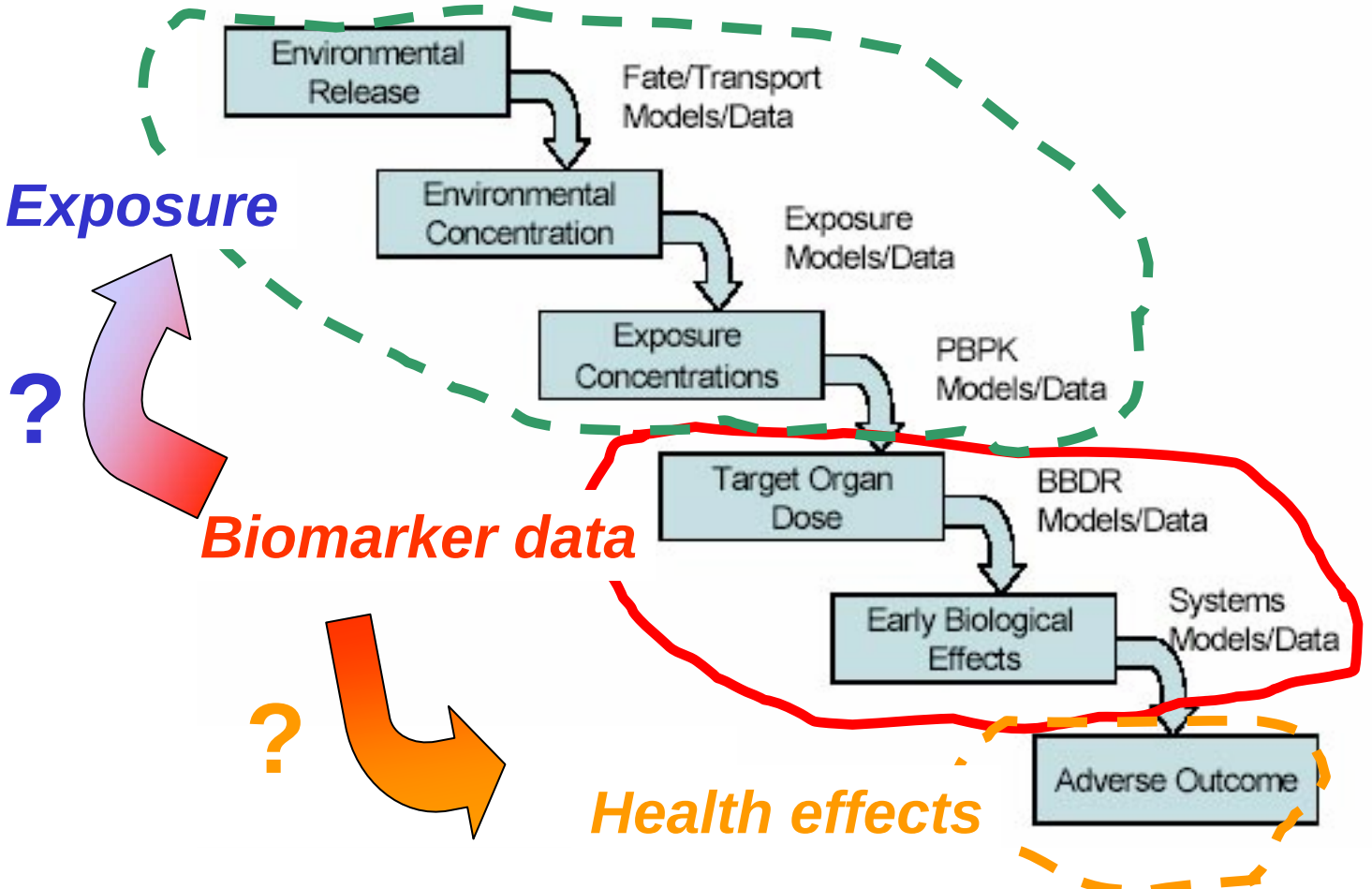
Potential Uses of Omics Data

- As biomarkers of exposure
  - But can the exposure be characterized?
- As biomarkers of effect
  - But can the effect be characterized?

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

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



What do biomarker data tell us about exposures and effects?

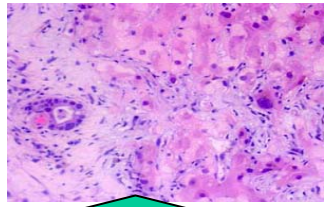
- Biomarker data tell us that exposure has occurred
  - But they do not, by themselves, characterize the exposure
- Biomarker data identify a toxic hazard
  - They do not, by themselves, characterize health risk

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)

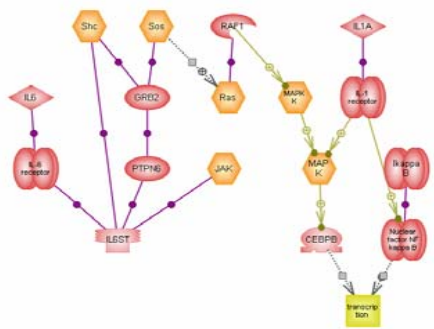
Systems Models: series of linked sub-models

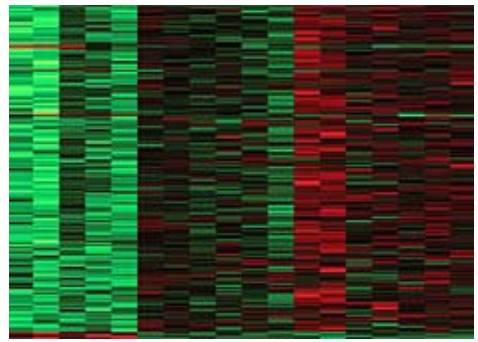


Cellular Toxicity

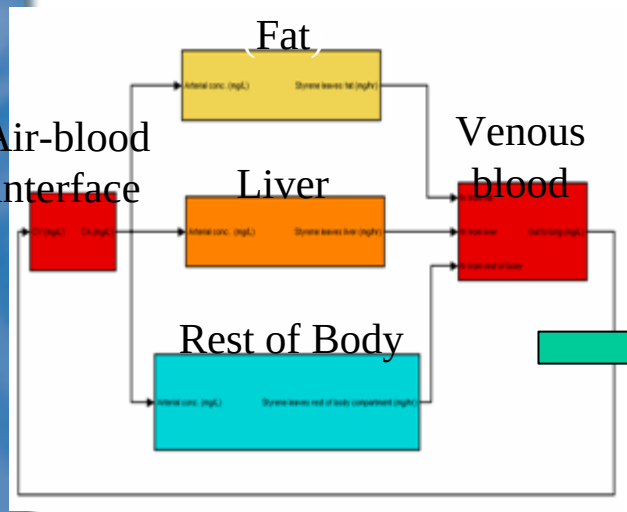
CMAQ

SHEDS

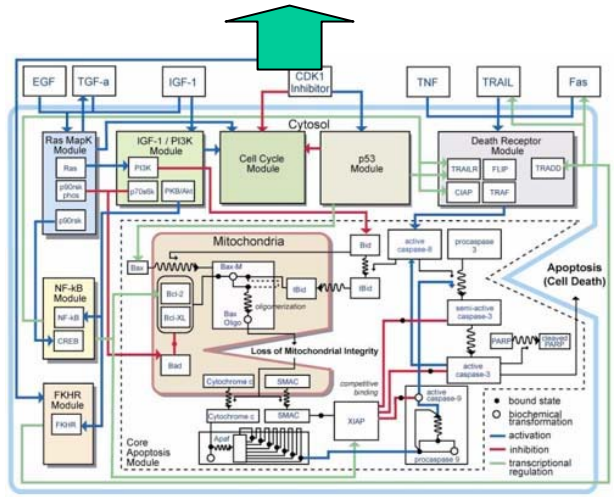




"Omics" data



PBPK model



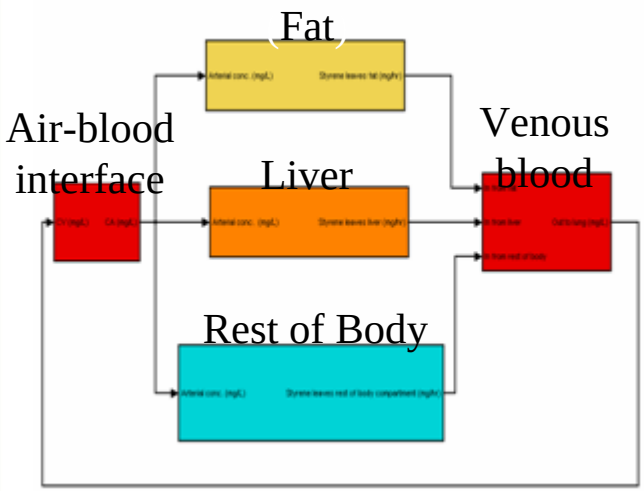
PBPD and/or Cell biology model

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

Describing and Quantifying Processes

- Probably the greatest progress in the field of computational toxicology to date has been in characterizing and quantifying relevant internal doses
  - PBPK models

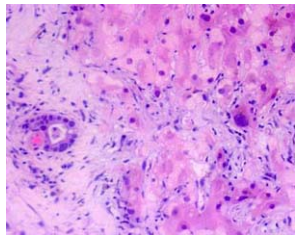


PPK model

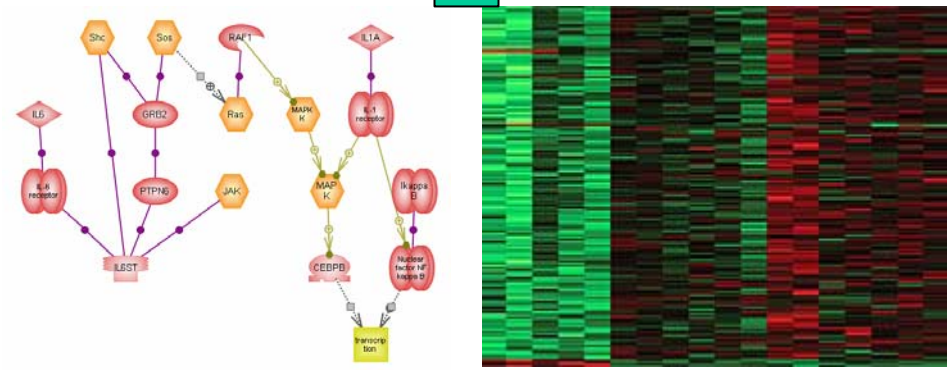
PBPK Models

- 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.

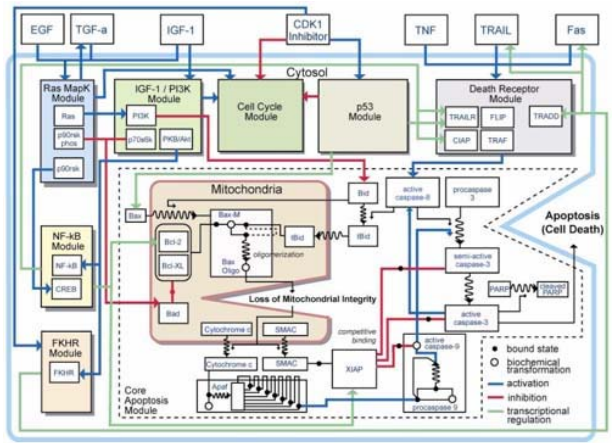
PD and Cell Level Models



cellular toxicity

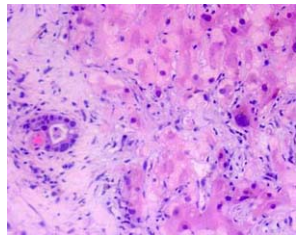


"Omics" data



PBPD and/or Cell biology model

Modeling in "Reverse"



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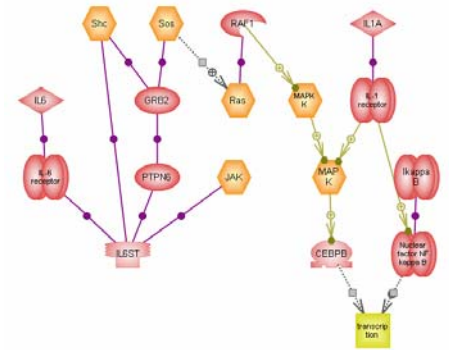

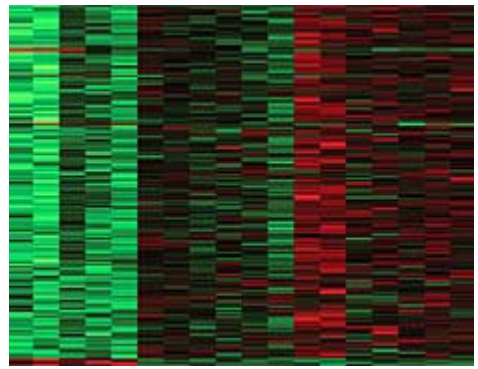

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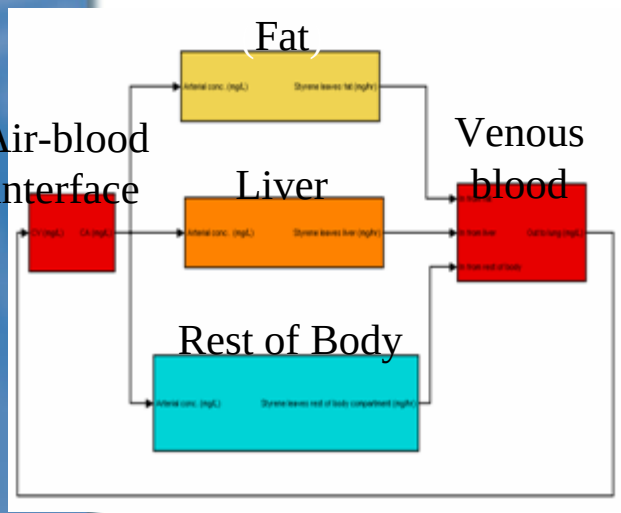
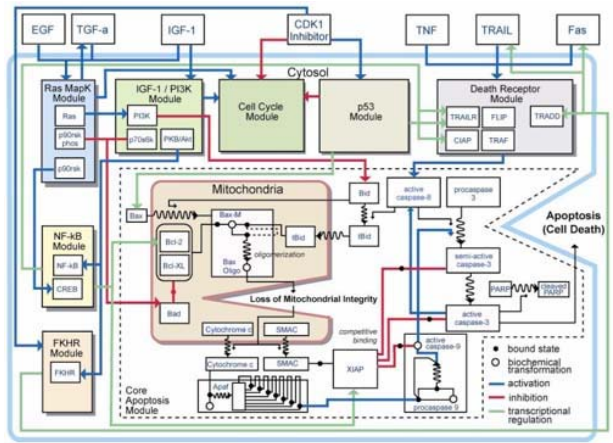


PBPK model



Cell biology model

"Reverse" modeling

- Given appropriate descriptions of PD, PK and environmental transport, we can work backwards to "characterize" exposure.

Uses

- Estimate doses resulting from different routes of entry into the body.
- Estimate equivalence between different exposure routes.

Uses

- Put bounds on exposure
- With statistical approaches determine the probable ranges of exposure in a population

Uses

- Describe the biologic relationship between entry into body and biomonitored data
- Help design rational, practical, and useful exposure studies

But…

- Not in a vacuum
  - The more that is known about the characteristics of the exposure the better the estimate of the exposure level
  - A single biomarker measurement is of little help for “reconstructing” the exposure

Areas for Development

- Microarray techniques for:
  - Identifying meaningful early biological response and exposure
  - Conducting assays in human blood samples to help determine variability and identify susceptible sub-populations

Areas for Development

- Use of PBPK models that can help ascertain measurement strategies for biomarkers

Areas for Development

- Development of computational methods to forecast speciation and fate of synthetic chemicals in complex matrices
- Computational techniques that will enable us to determine key metabolic pathways for foreign chemicals in living systems

Areas for Development

- Better computational methods to link the various models together:
  - Exposure models, fate and transport models and PK/PD models together into a systems approach

Areas for Development

- Design and conduct exposure studies that measure markers of the new biology – take omics out of the laboratory and into the field