

Biological Modeling

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BOSC Review for the
National Center for Computational Toxicology
April 24/25, 2005

RESEARCH &
DEVELOPMENT

*Building a
scientific
foundation
for sound
environmental
decisions*

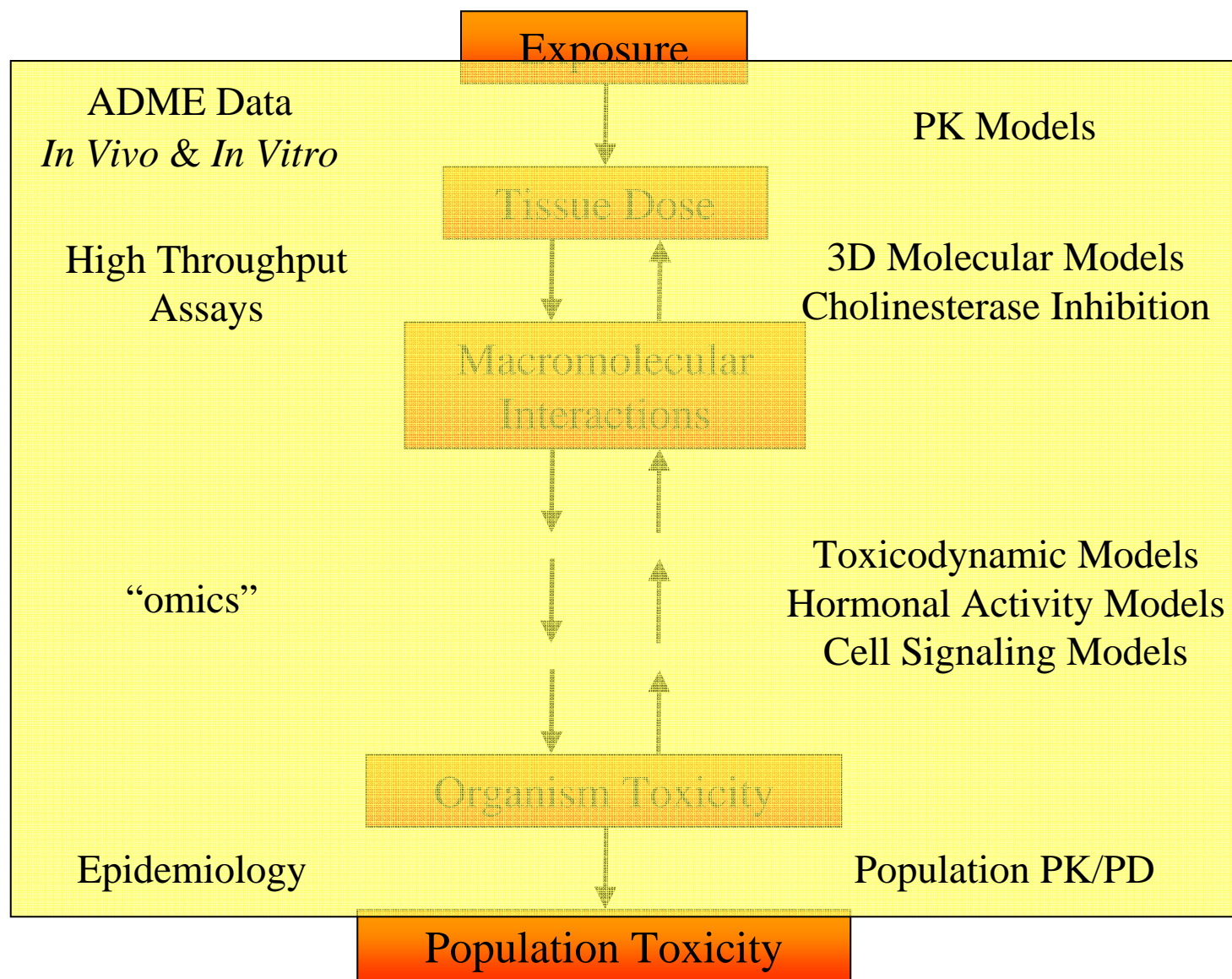
UNITED STATES ENVIRONMENTAL PROTECTION AGENCY



Biological Modeling: Now and the Future

1. Vision of Integrated Quantitative Systems Biology: Biologically Based Dose-Response Modeling
2. Computational Systems Biology
3. Research Plans: Ongoing and Future

The Vision



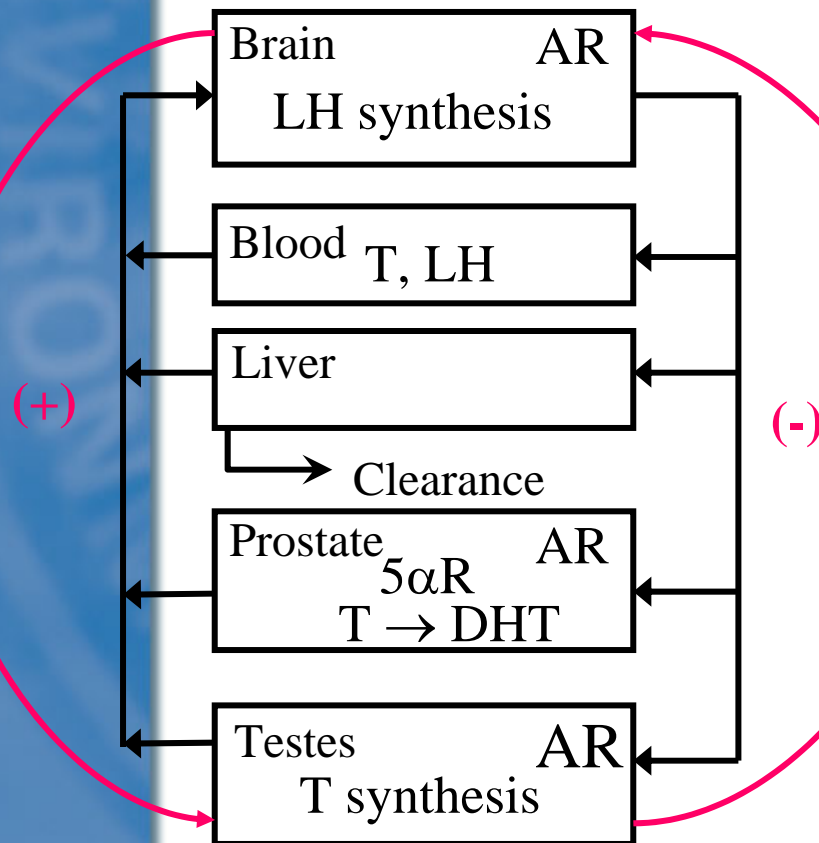
1. Vision Example: Antiandrogens and Prostate Dose-Response

- Questions raised about dose-response properties for endocrine disruption.
- Prostate is sensitive endpoint for antiandrogenic effects in pubertal rat assays
- Major human tissue for noncancer and cancer diseases in adults
- Environmental antiandrogens: vinclozolin & a few other pesticides, phthalates

Developing a Biological Model for Tissue Dosimetry and Dose- Response

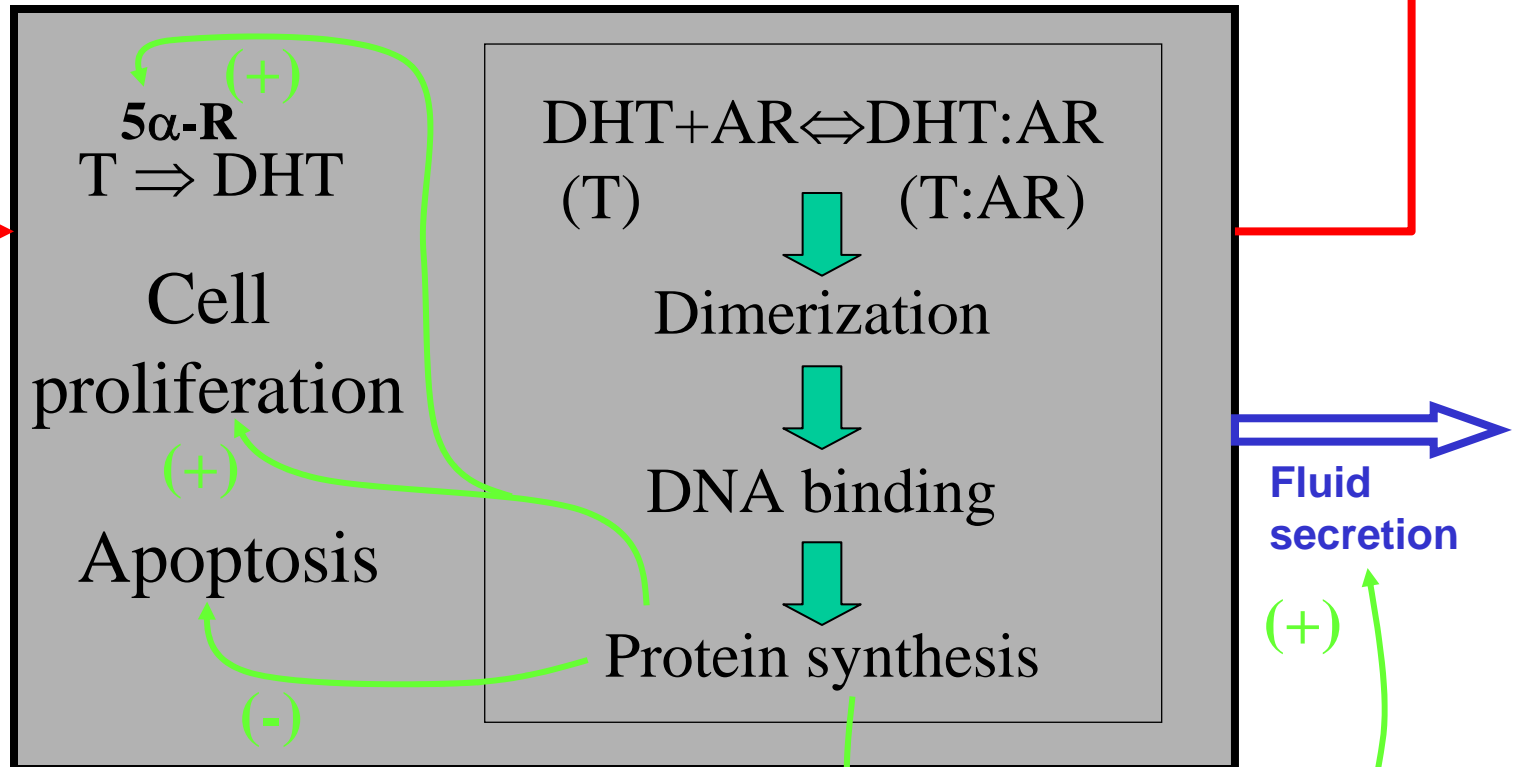
Combined Pharmacokinetic and Pharmacodynamic Modeling (PK/PD) – Adult Rat Model

- Endogenous hormones:
Pharmacokinetics &
Feedback regulation
- Antiandrogen:
Pharmacokinetics &
Interaction of antiandrogen
with targets in regulated
system (e.g. androgen
receptor or hormone
synthesis enzymes)
- Response tissue (e.g.
prostate) and androgen
regulated responses



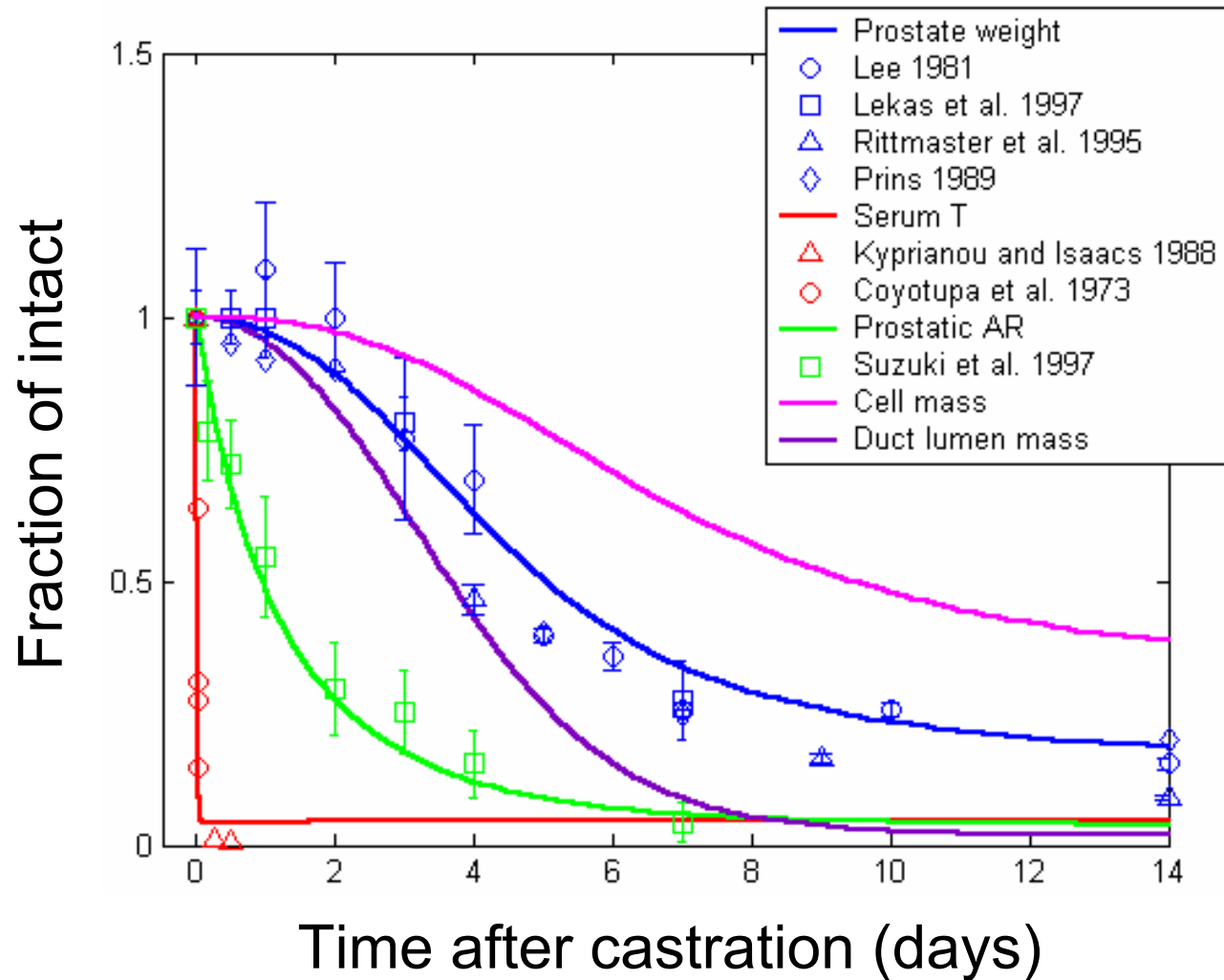
Prostate: Gene to Tissue Response

Blood flow



Ventral Prostate

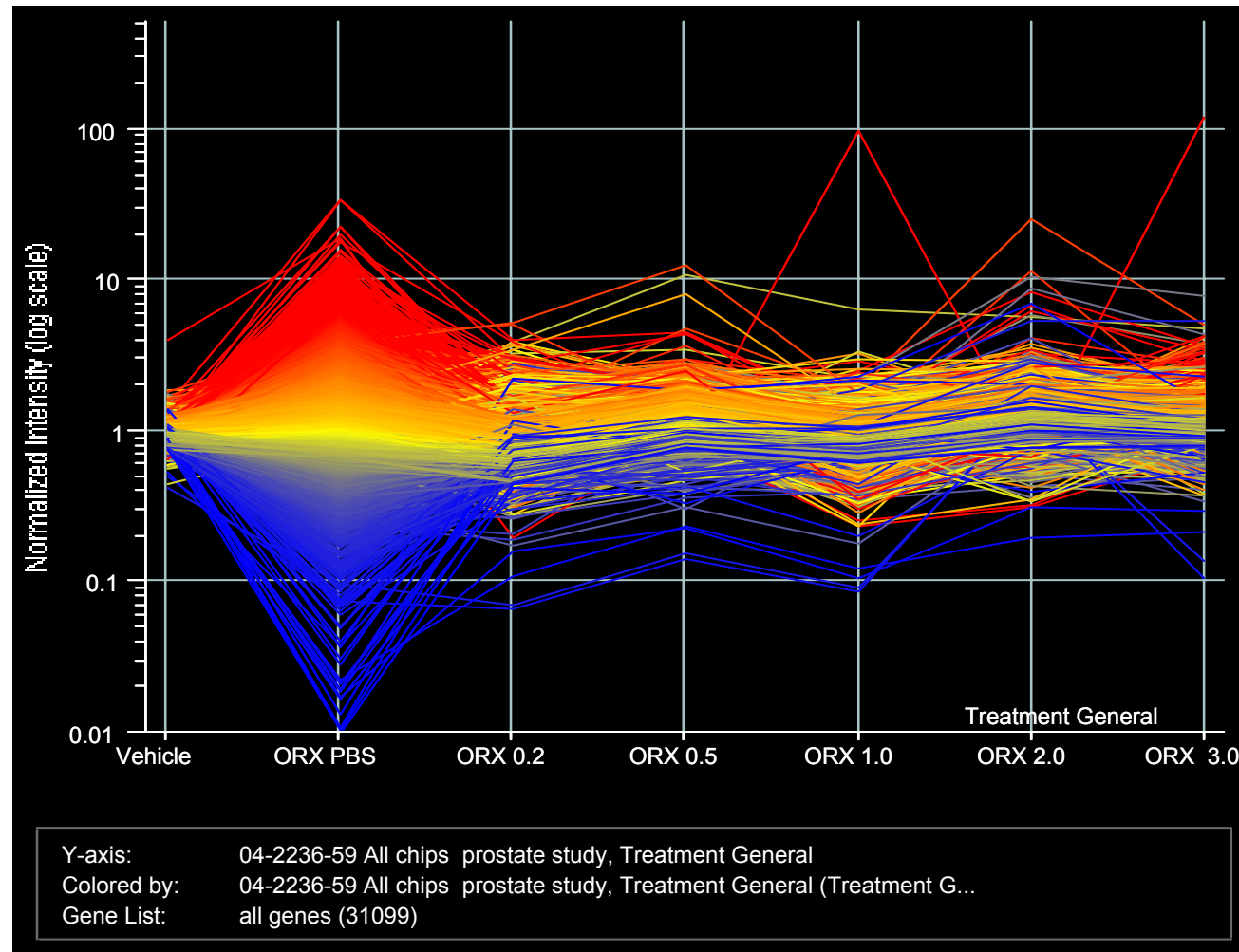
Timing of events after castration



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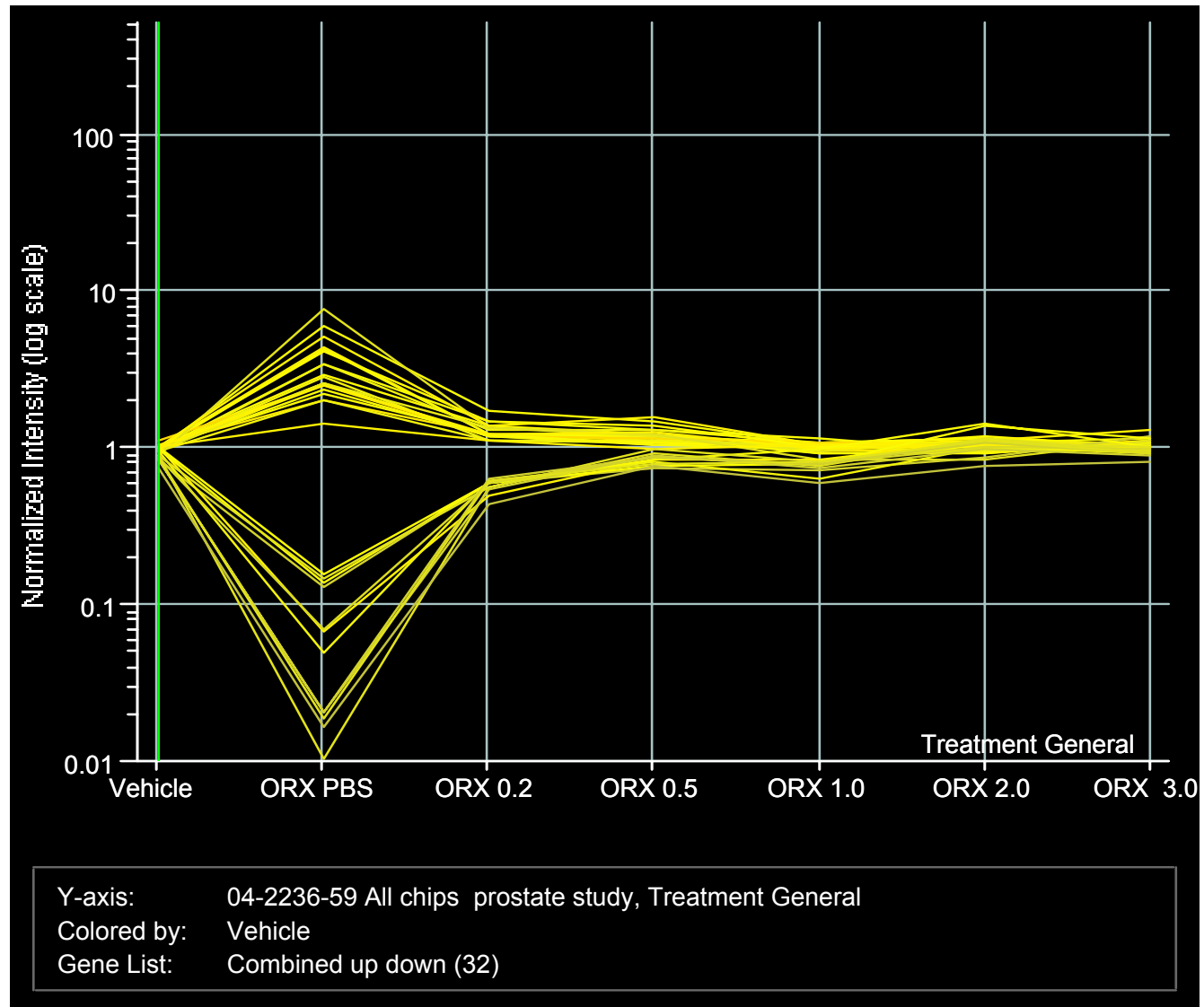
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Gene Responses to Castration and Hormone Supplement



Data courtesy of R. Chapin, Pfizer

Gene Responses to Castration and Hormone Supplement: Filtered



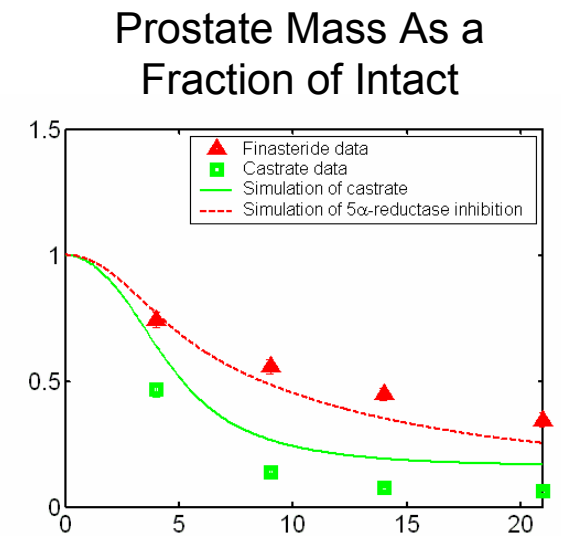
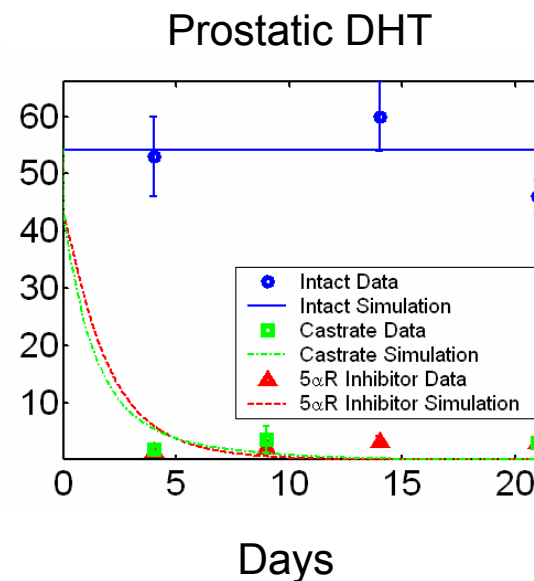
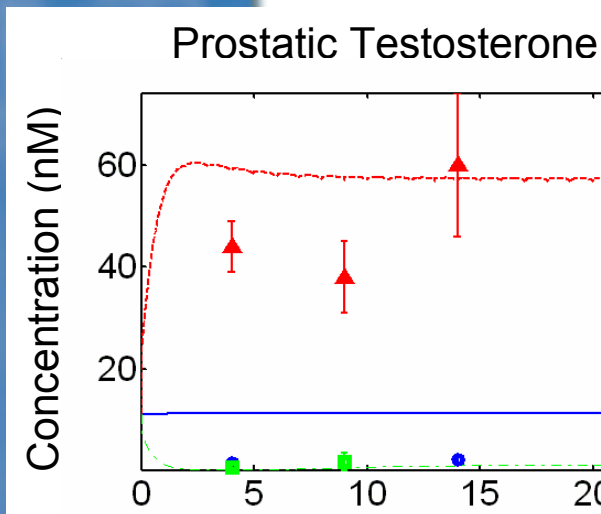
Data courtesy of R. Chapin, Pfizer

Modeling Antiandrogens: 5 α - Reductase Inhibitors

- Finasteride – therapeutic drug administered for benign prostatic hyperplasia
- Compartmental PK model implemented from published literature for tissue dose estimations
- 5 α -reductase (5 α R) has 2 known isoforms
- Isoform 1 (5 α R1): high concentrations in liver, low concentrations in prostate
 - Finasteride competes competitively with testosterone for 5 α R1
 - Reversible enzyme inhibition
- Isoform 2 (5 α R2): High concentrations in prostate, low concentrations in most other tissues
 - Finasteride exhibits time-dependent inhibition of 5 α R2
 - Very slow off rate renders enzyme effectively useless

Kinetic and Dynamic Effects of a Finasteride Challenge

- Data: R.S. Rittmaster *et al.*, Endocrinology 136 (1995) 741-748
- Experimental Conditions: 40 mg/kg Finasteride daily for 21 d
- Hormone concentrations and prostate mass for intact, finasteride treated and castrated rats at days 4, 9, 14, 21



1. Vision Summary

- Mathematical/statistical dose-response relationships can be quantitatively explained by underlying biology
- Toxicity results from excesses or deficiencies that perturb biological pathways at critical times and may lead to a range of dose-response behaviors

2. Computational Systems Biology

- Organize and integrate data from disparate sources
- Hypothesis Testing and Generation
 - Are model predictions consistent with existing data?
 - What would happen if ... ? or Under what conditions would ... ?
- Prediction and Extrapolation
 - Qualitative: dose-response shape
 - Quantitative: predict and extrapolation tissue

3. Research Plans: Ongoing & Future

Modeling Methods/Technology Development

- Statistical analyses of biologically based models
- Model portability, linking, archiving

Modeling Applications

- c. PBPK Modeling Across Lifestages
- d. Systems Modeling

Statistical Analyses of Biological Systems Models

- Quantify uncertainty about:
 - Estimated parameters
 - Model predictions
 - Extrapolations using the model: route of exposure, cross-species
- Formally compare alternative model formulations, given data.
- Use formal experimental design methods.

Some Problems

- Problems of meta-analysis:
Several to many datasets from heterogeneous experimental designs, as well as computational methods, may contribute to estimates of parameter values

Some Problems (cont.)

- Models are highly parameterized; often some parameters are not identifiable → extrapolation and fitting methods adversely affected, e.g.
 - Metabolic rate constants, V_{max} and K_m , confounded (only able to estimate V_{max}/K_m) if internal concentrations too low;
 - Parameters in a multi-compartment GI tract
 - Including all parameters in a PBPK model (e.g., physiological parameters, partition coefficients, metabolic rate constants, absorption and elimination parameters) in a likelihood expression can lead to highly singular likelihood. “Solved” by:
 - setting physiological values to nominal values (but the animals in the studies surely differed);
 - using informative priors for physiological values, maybe even hierarchical or population models;
 - more data

Some Problems (cont.)

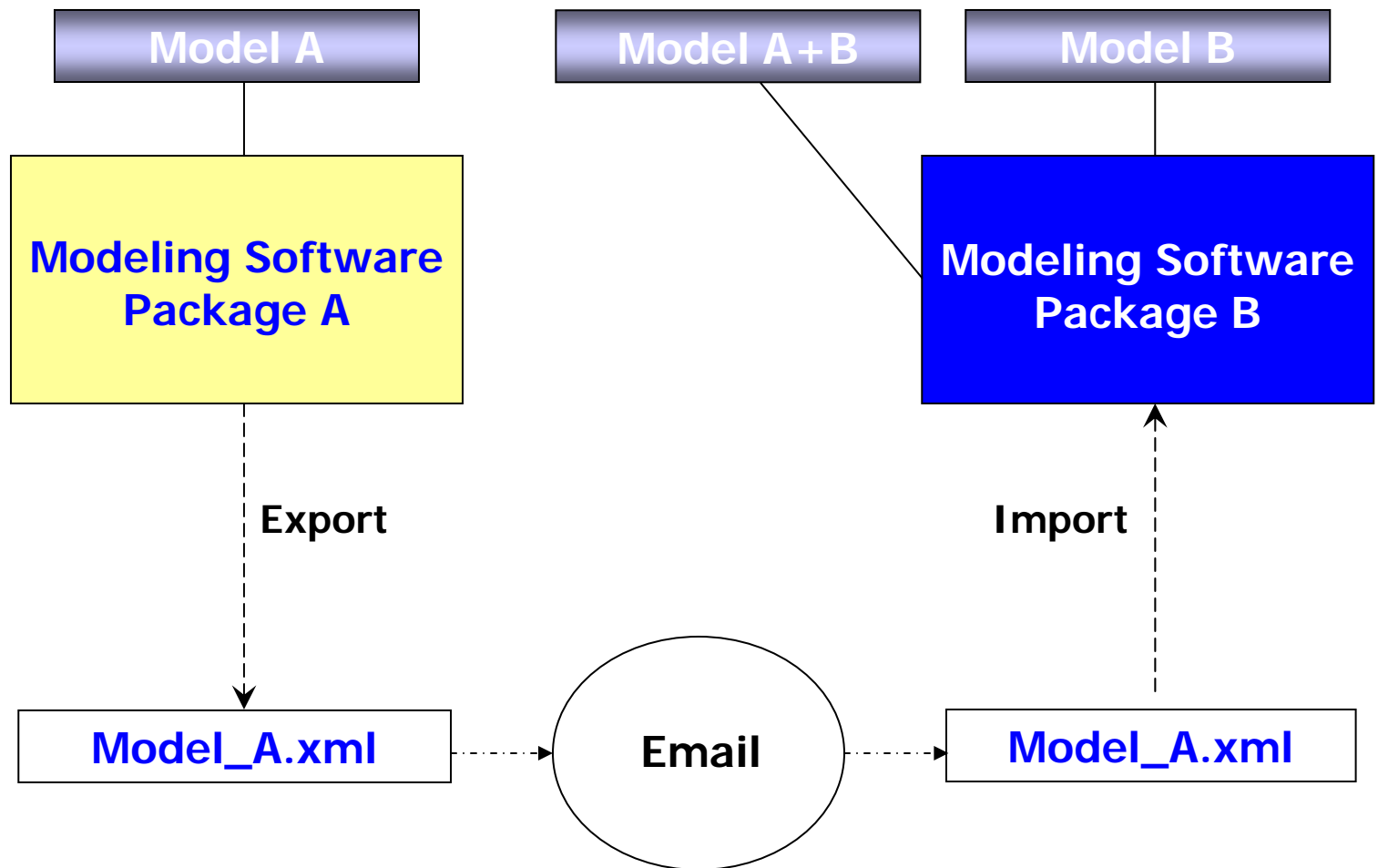
- Models typically cover a wide dynamic range: model misspecification is likely (can interact with multiple data sets and identifiability problems)
- Error/Variance models are likely to be complex
- Numerical issues from numerical solutions to systems of ODEs, PDEs, DAEs.

Long Term Goals

- Identify and address unsolved statistical methodological problems.
- Develop systematic framework or handbook for statistical analysis; both likelihood- and Bayesian-based.
- Develop freely distributable software tools (perhaps based on R)
- Collaboration (so far) w/UNC Dept. of Biostatistics, NHEERL, NERL, CIIT, NCEA, NIEHS/NTP

Modeling Technology Development

Creating Portability in Biological Models:



Solving a Long-Standing Problem

- PBPK model community: Numerous software packages that are significantly incompatible
 - Model obsolescence due to discontinued software support
 - Difficulty in transcribing a model from one software pack to another
 - Difficult to link models, including linking PBPK models to other models covering the source-to-outcome continuum
 - No PBPK model databases or standard protocols for documenting model development and implementation
- Possible solution: Systems Biology Markup Language (SBML)
 - Standardized XML-based markup language enabling portability of biological pathway models across platforms and software packs
 - Objective: Develop an extension for SBML allowing it to be used for PBPK models
- Benefits:
 - Eliminate the risk of losing models to software obsolescence and/or discontinued support
 - Curated databases and archiving protocols for PBPK models
 - Model linking becomes simple - PBPK models easily linked to biological pathway models already existing in SBML format

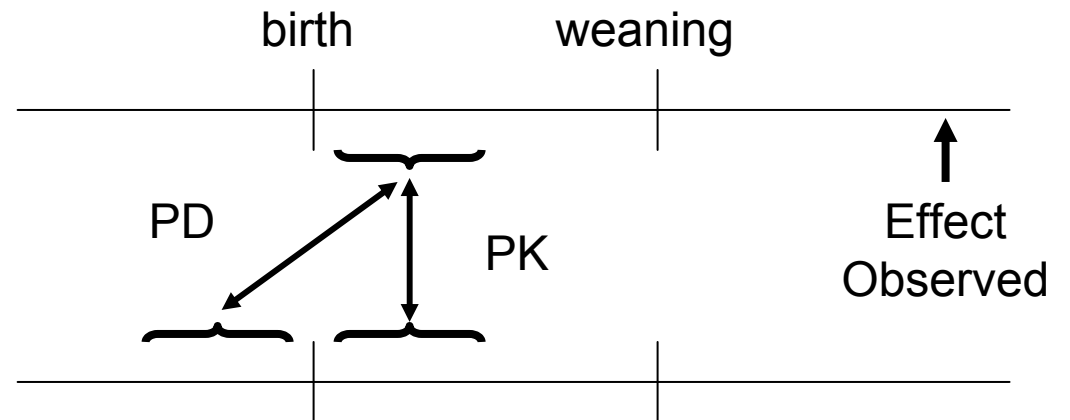
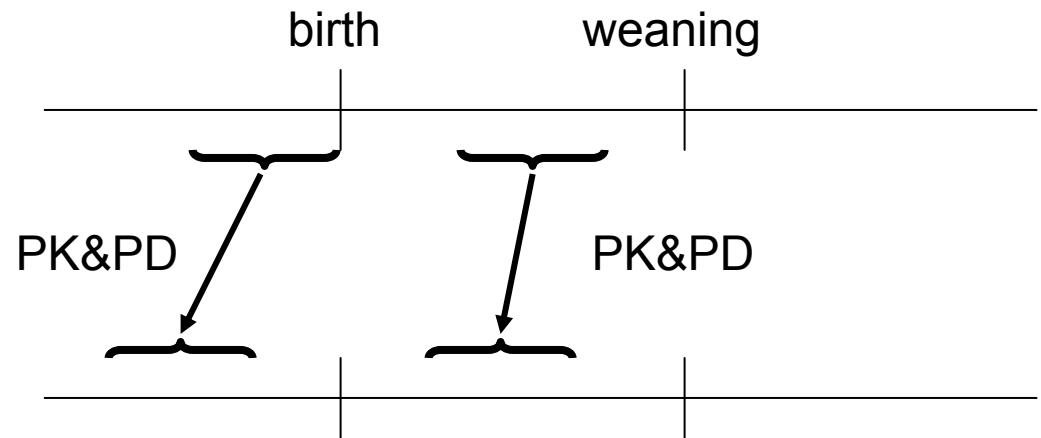
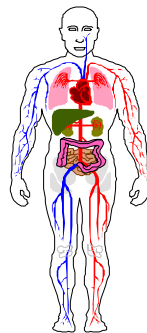
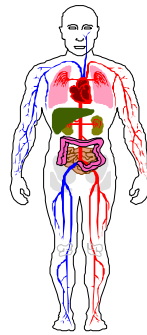
Strategy for Software Development

- Collaboration with [Lockheed Martin](#) through EPA Office of Environmental Information and the NCCT
 - Identify limitations of current SBML version for use in PBPK modeling;
 - Develop an XML extension (schema) to be used in tandem with SBML
- Collaboration with [SBML authors \(Caltech\)](#)
- Contingency plans
 - Substantial changes to SBML or complete rewriting of language using appropriate SBML attributes as templates for design
 - Look for an entirely different XML markup language to use as a guide in writing the PBPK language

PBPK Modeling Across Lifestages

- Improving dose-response analysis for 1- and 2-generation studies involving in utero, lactational, and early post-weaning exposures
 - Current default analyses use exposure dose/concentration to mother
- Extrapolation of PK across lifestages with awareness of developmental windows

Mapping Cross-species



PBPK Modeling Across Lifestages

- Database of physiological parameters for developing rats, mice, and humans (collaborations with NCEA and ILSI)
- Experimental PK and modeling for conazoles in collaboration with Human Health Research Mode of Action developmental studies (NHEERL collaboration)
- Perfluorinated chemicals (e.g., PFOA) PK modeling (NTP collaboration)

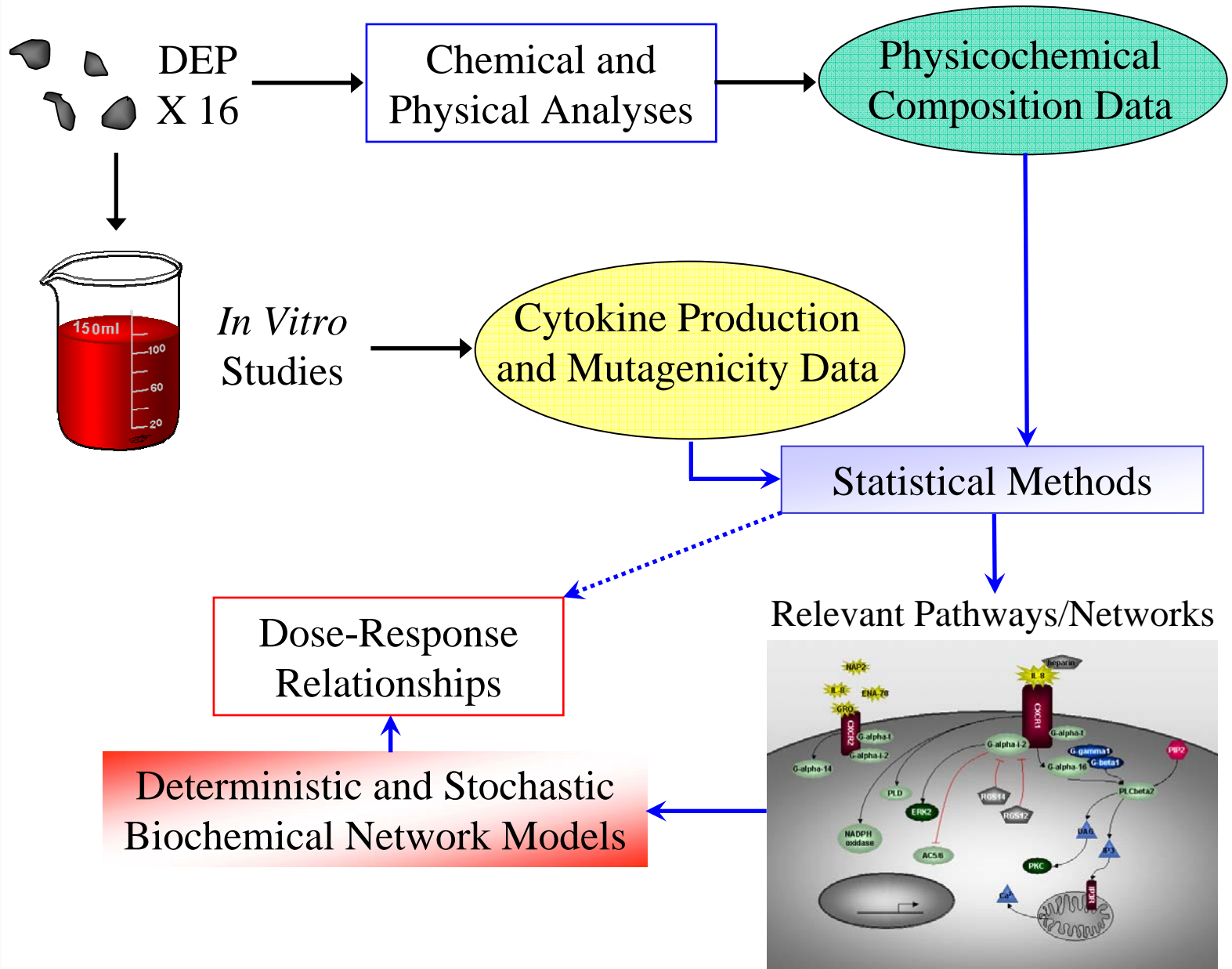
Systems Modeling

- Comp Tox New Start Program -
Systems approach to inflammogenic
and mutagenic effects of Diesel
Exhaust Particles (DEP)
- Application of SBML to Elaborate a
PBPK/PD model of Pyrethroid
Neurotoxicity

Risk Assessment of the Inflammogenic and Mutagenic Effects of DEP: a Systems Biology Approach

- Computational Toxicology New Start Program
 - **James Samet (lead)** HSD/NHEERL, **Ian Gilmour** ETD/NHEERL, **David DeMarini** ECD/NHEERL, **William Linak** APPCD/NRMRL, **William Reed** CEMALB/UNC-CH, **Hugh Barton** NCCT, and **Michael Zager** UNC-CH
- **Problem:** DEP cause respiratory inflammogenic and mutagenic effects but critical properties are unclear
- **Objective:** Develop biologically-based models describing the relationships between the physicochemical composition of DEP and the health effects.

The Systems Approach



Expected Results and Benefits

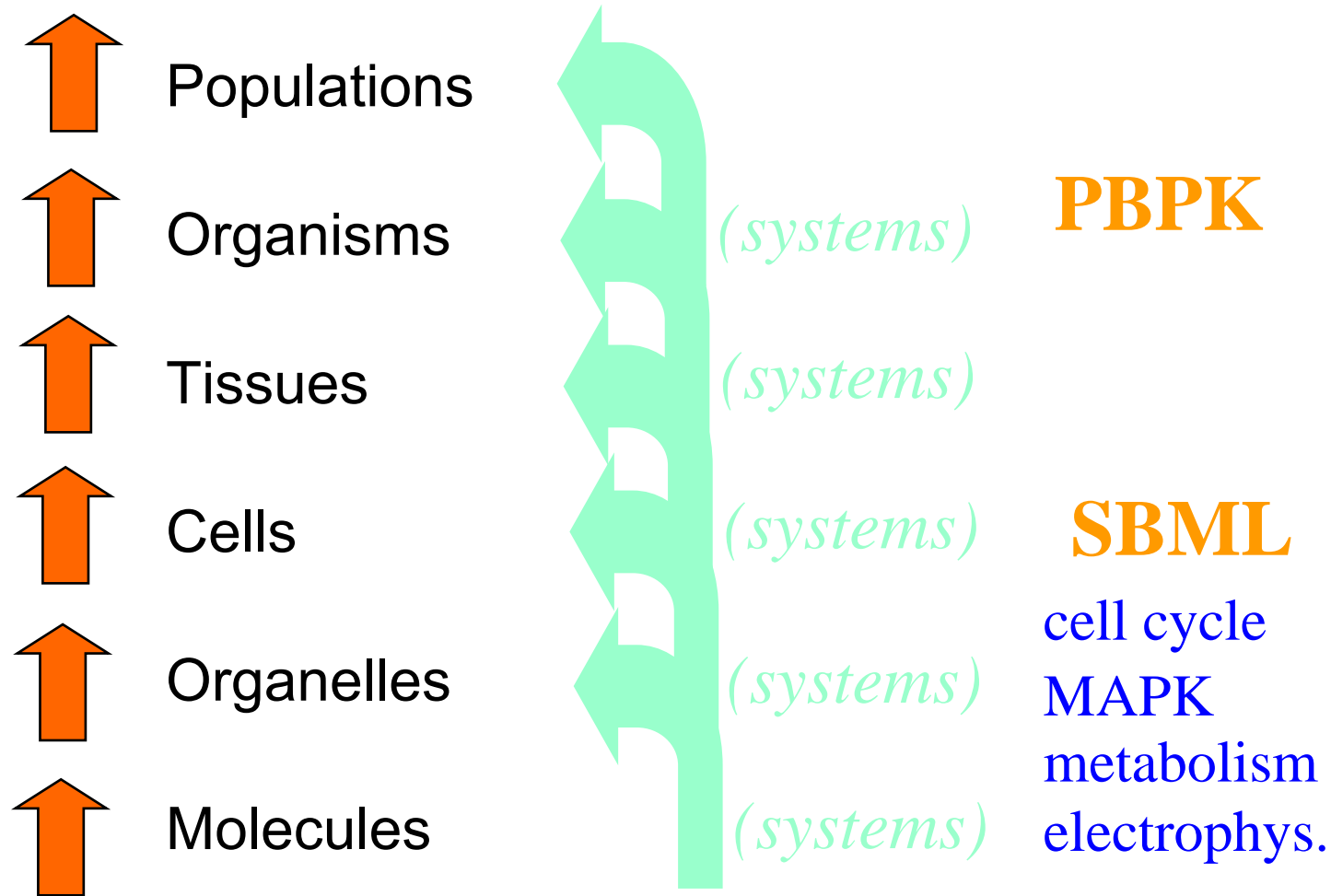
- Risk assessment aimed at mitigating health effects of DEP exposure
 - Quantitative and computational approaches
 - Cross-species extrapolation
 - Endpoint validation
- Directly responsive to priority research needs identified by **NCEA, Office of Air and Radiation** and **ORD PM Research Program**.
- State of the art facilities and technologies
 - Custom-designed diesel emissions sampling system
 - Leading edge genomics and proteomics technologies
 - Latest tools in bioinformatics and computational modeling software
- Generation of novel mechanistic data with specific intent of identifying and characterizing critical paths that lead from DEP exposure to toxicity.
 - Applicable to the study of other sources of particulate air pollution whose effects include mutagenesis or inflammatory responses.
- Adaptable to computational studies of exposure and toxicological effects of a broad range of environmental agents.

Application of SBML to Elaborate a PBPK/PD model of Pyrethroid Neurotoxicity

- ORD Pyrethroids Project, *pharmacodynamics*
 - **Kevin Crofton** NTD/NHEERL, **Marina Evans** ETD/NHEERL, **Mike DeVito** ETD/NHEERL, **Tim Shafer** NTD/NHEERL, **Mike Tornero** HEASD/NERL
- **Problem:** A pharmacodynamic model linking target tissue events (e.g., receptor activation, changes in ion channel function) to consequent biochemical, physiologic, or behavioral outcomes has not been elaborated.
- **Objective:** Employ tools of SBML, PBPK, and high-throughput technologies to link PK and PD.

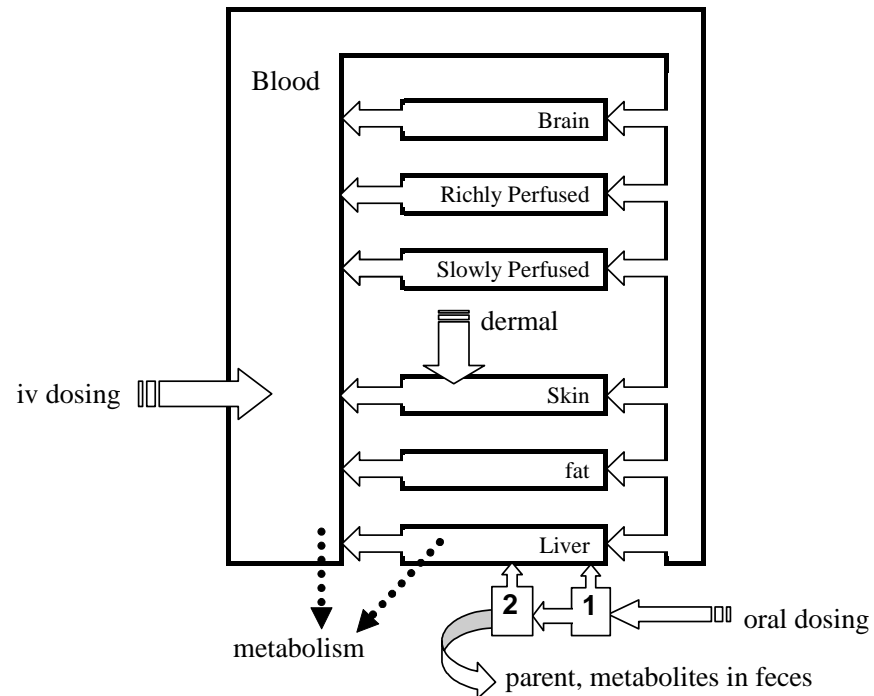
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Levels of biological organization

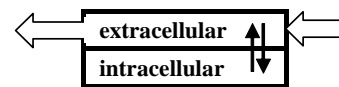


PBPK modeling of Pyrethroid Insecticides

(A) Flow-limited model



(B) Diffusion-limited model



Critical Components of SBML-Based Pharmacodynamic Model of Pyrethroid Acute Neurotoxicity

- PBPK Models of pyrethroid disposition (ORD-wide 'Cumulative Assessment')
- Mechanistic models of pyrethroid-induced membrane potential perturbations (Hodgkin-Huxley)
 - NEURON
 - SBML
- High-throughput data (neuronal membrane) to parameterize pharmacodynamic model
 - Membrane potential-sensitive dyes (96 well format)
 - Voltage-clamp screening (96 well format)

Research Plans: Summary

- Improving biologically-based modeling methods and technologies
- Developing novel applications linking PK and PD

Collaborations

- NHEERL, NERL, NCEA, Program Offices
- PNNL
- NCER Star RFA: Summer 2005
- NTP: PK collaboration