

*Computational Modeling in
Concert with Laboratory Studies:
Application to B Cell
Differentiation*

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Office of Research and Development
U.S. EPA

Dioxin Toxicity: Mechanisms, Models, & Potential Health Risks, Michigan State University Superfund Program Workshop
MSU Kellogg Center Lincoln Room, October 20-21, 2008

Outline

1. Risk assessment motivation
2. Biological determinants of dose-response
3. The role of computational models
4. Work-in-progress example: irreversible biochemical switches in the differentiation of B cells

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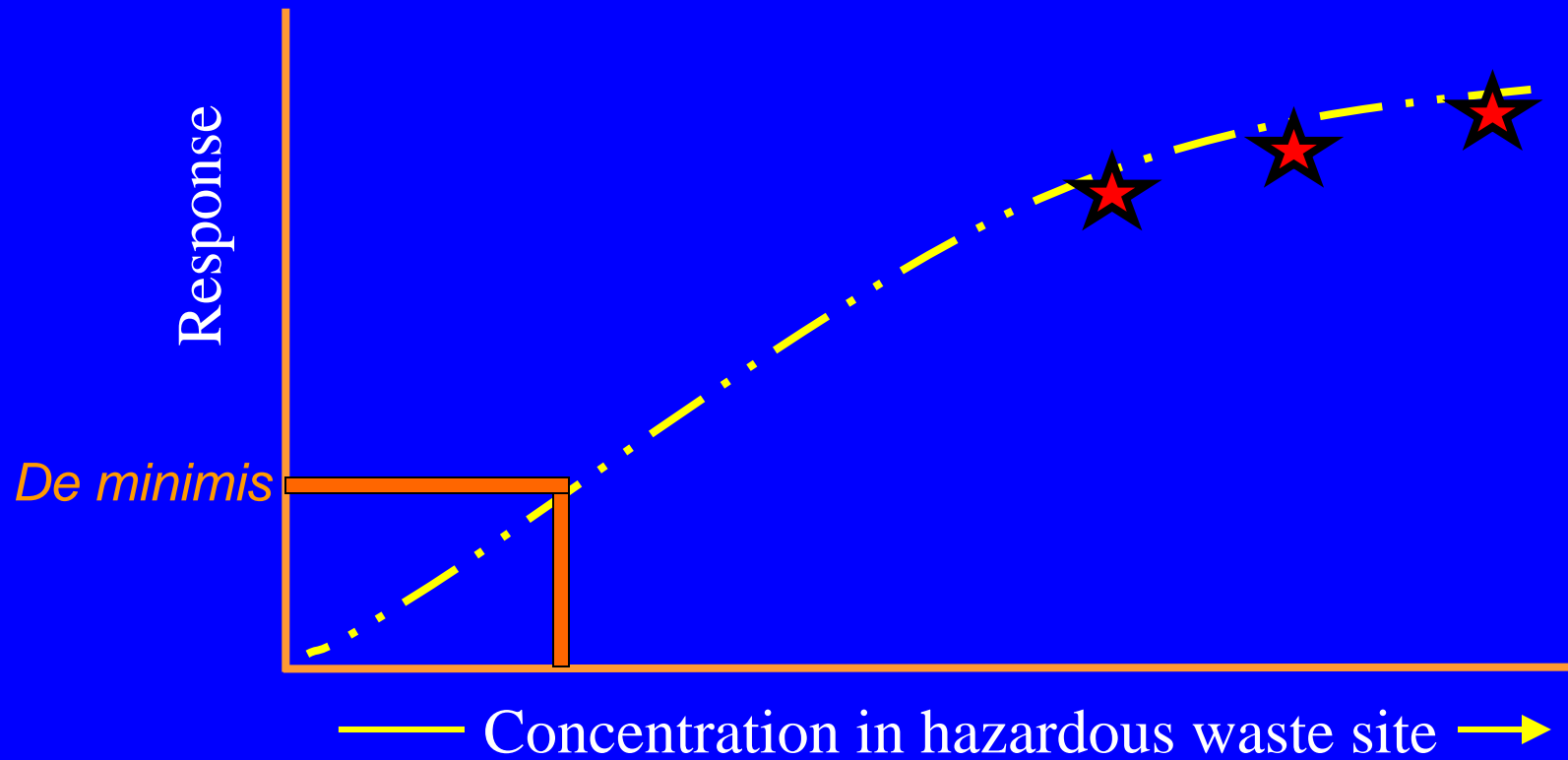


Scar tissue. A crisscross of roads and pits scars the surface of a former gold mine in Summitville, Colorado, while underground workings and tunnels allow acidic waste to drain into nearby watersheds. The Superfund site has cost more than \$150 million in remediation efforts and remains incomplete. (*Scott Fields, EHP 111, 154-161, 2003*)

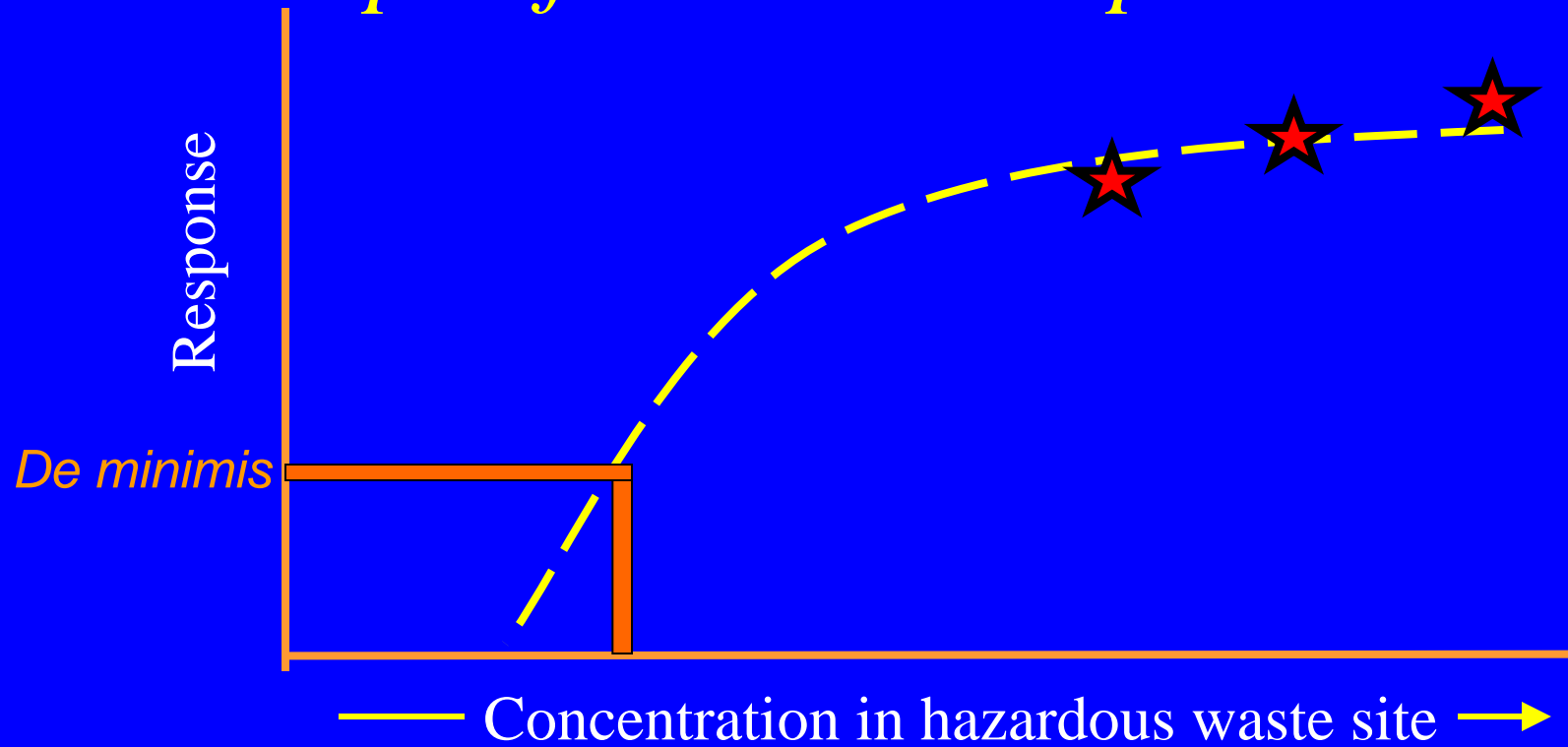
Although there is no good estimate of the cost to clean up abandoned mines, experts agree that in the United States alone the price tag reads tens of billions of dollars.

(Scott Fields, EHP 111, 154-161, 2003)

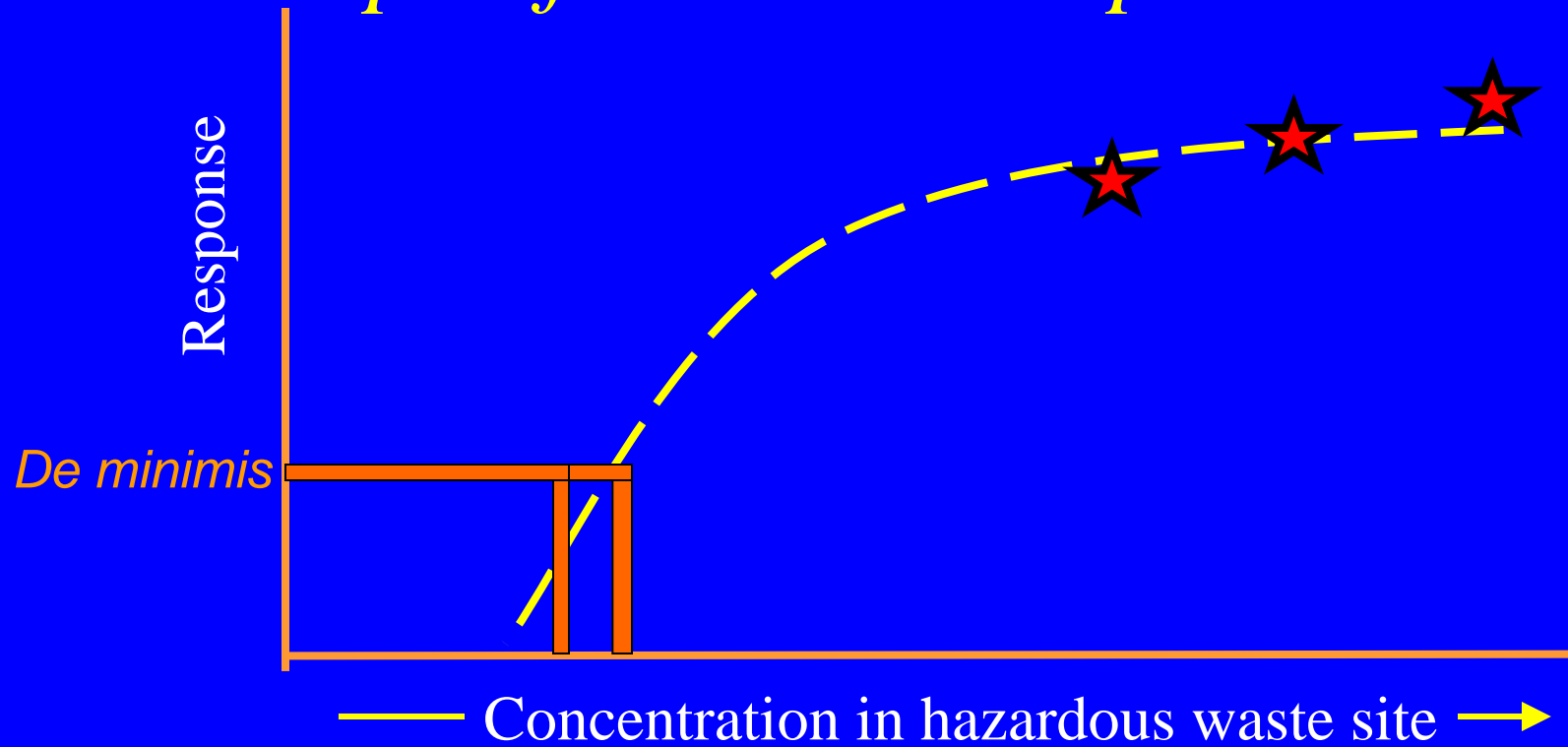
Cost of cleanup is a function of the shape of the dose-response curve



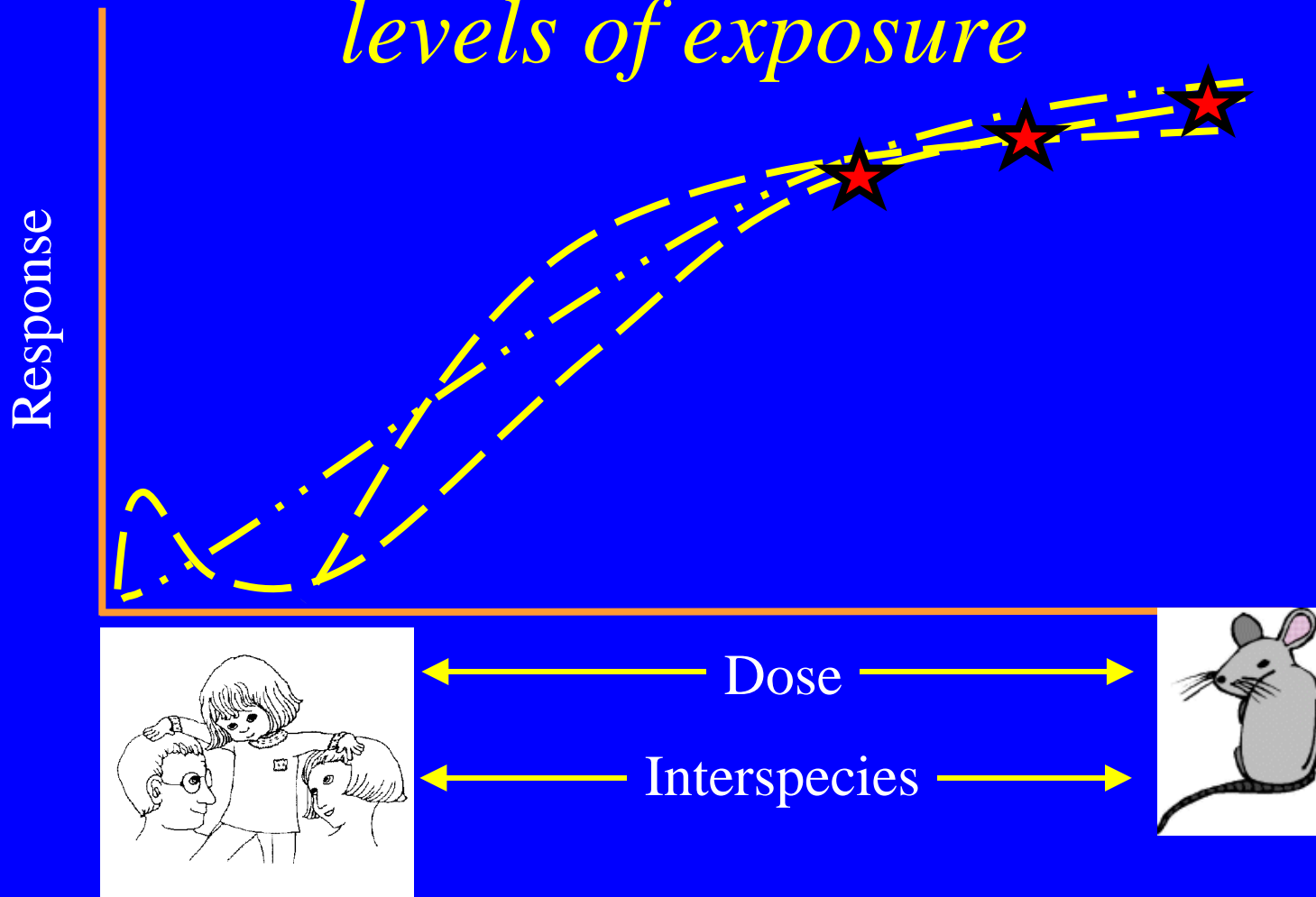
Cost of cleanup is a function of the shape of the dose-response curve



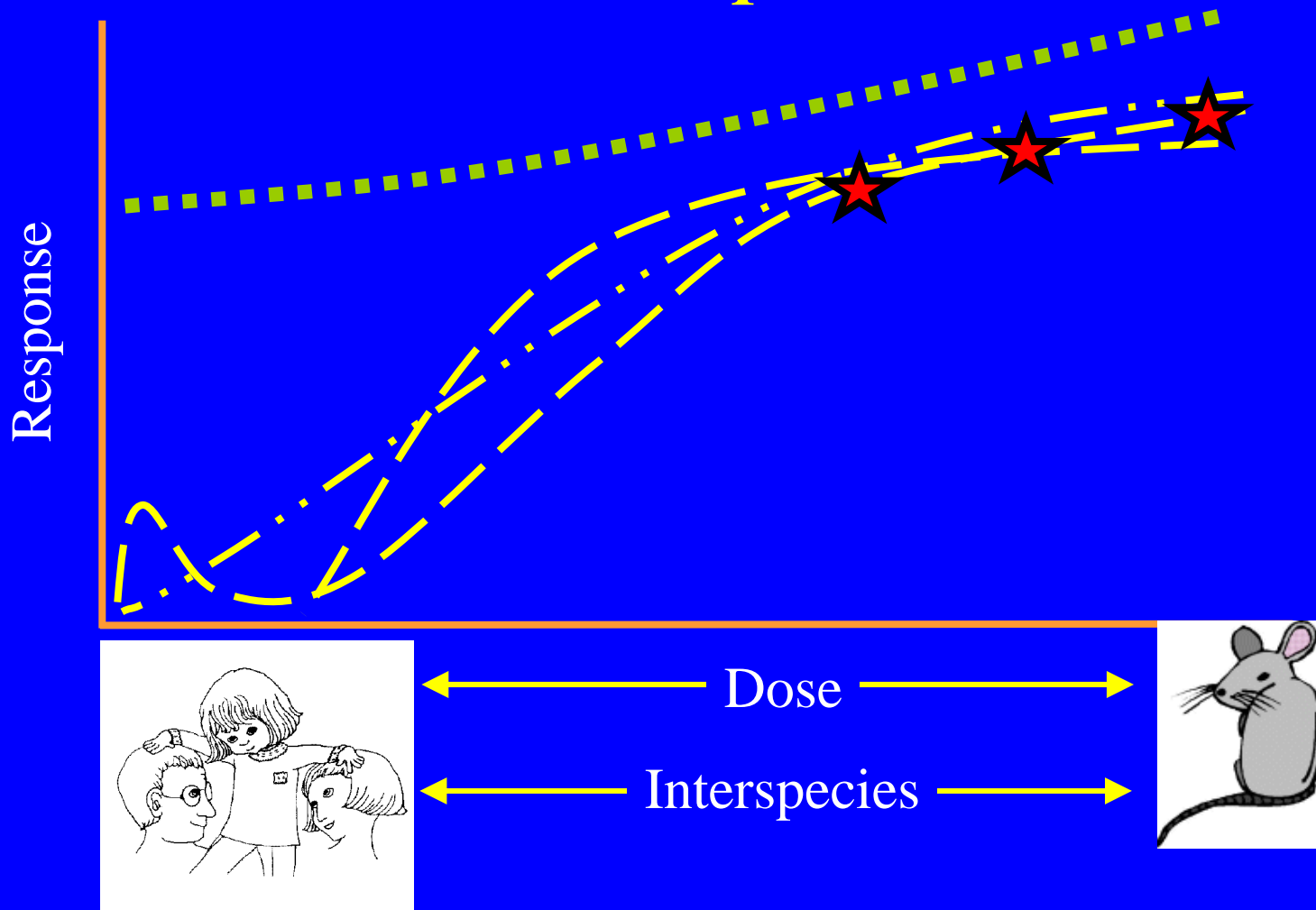
Cost of cleanup is a function of the shape of the dose-response curve



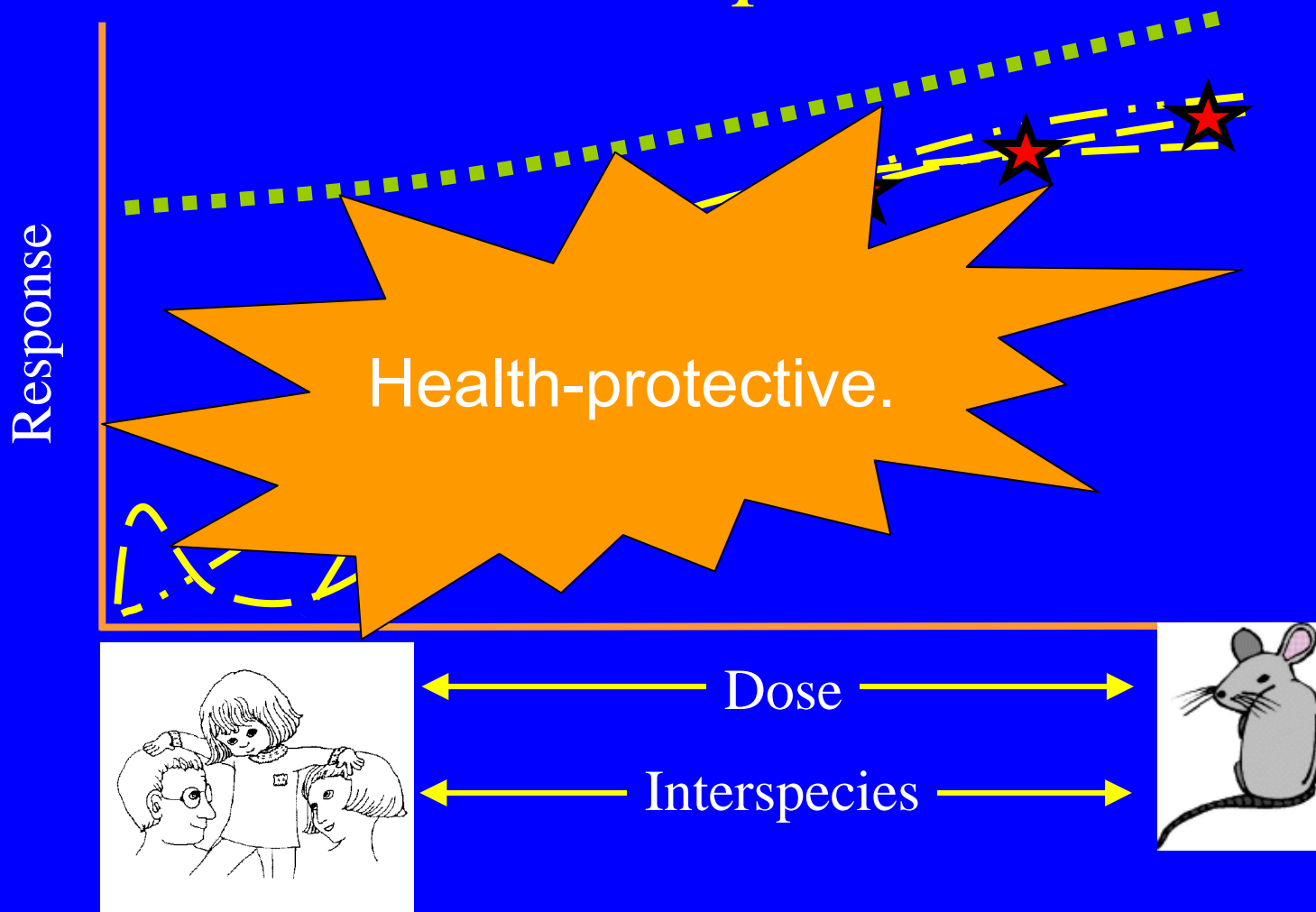
Available data don't constrain the dose-response curve at relevant levels of exposure



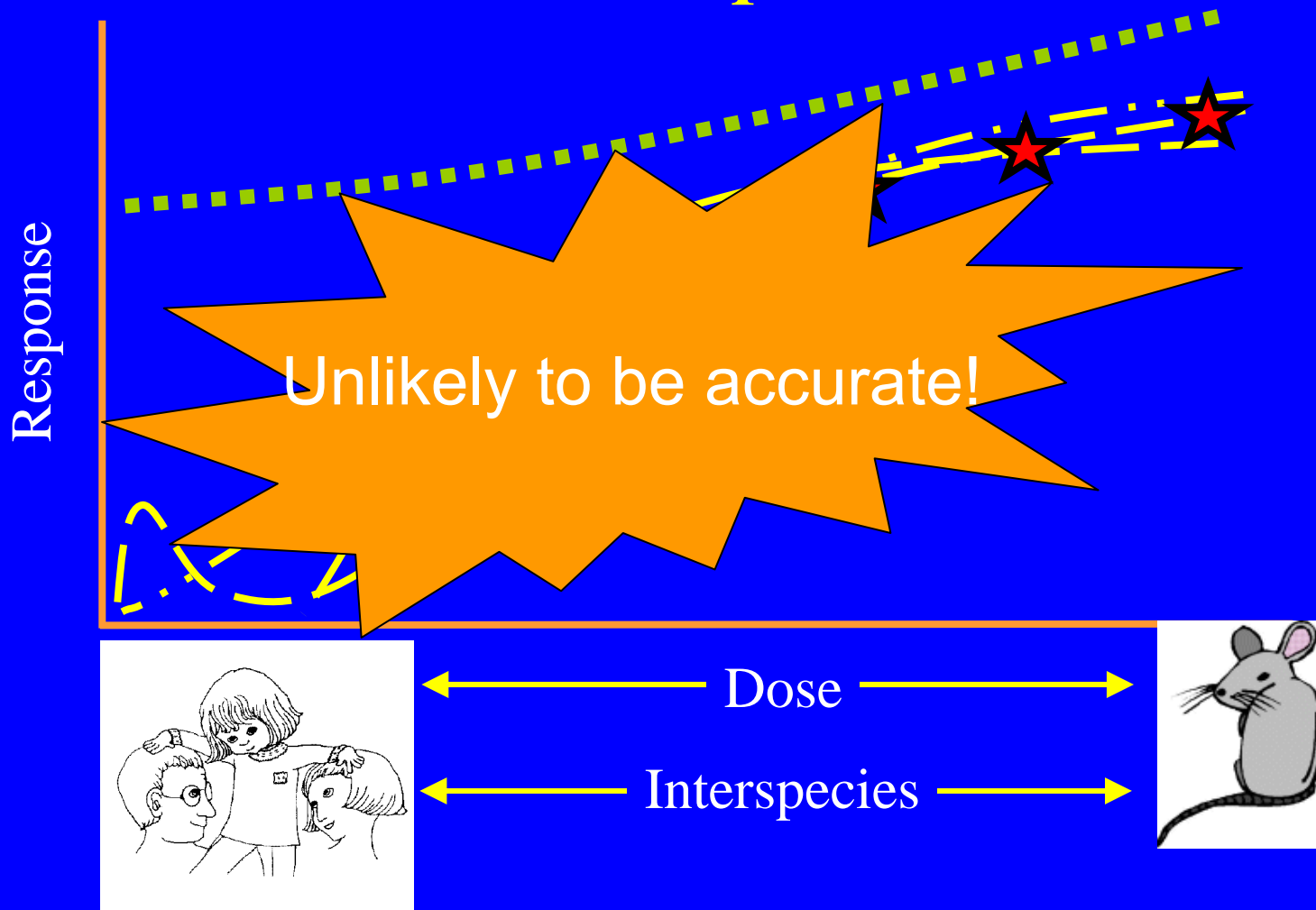
Default-based treatment of dose-response



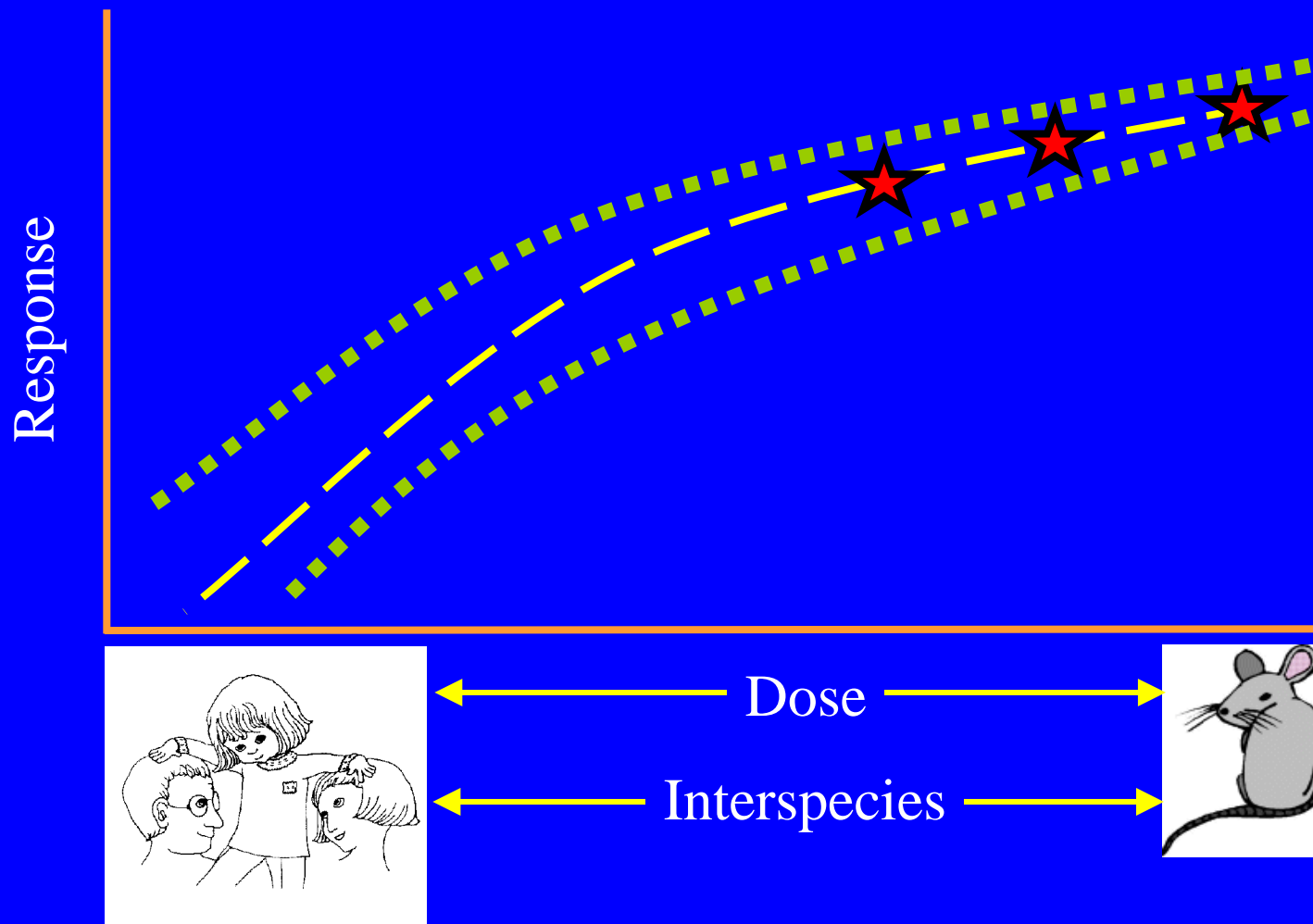
Default-based treatment of dose-response



Default-based treatment of dose-response



Accuracy

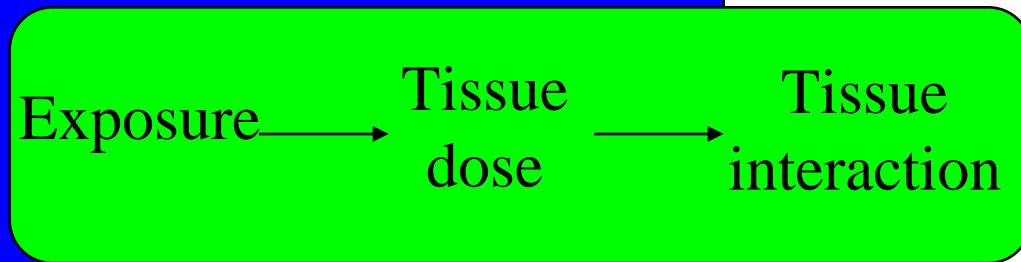


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Biological mechanisms determine dose-response

Pharmacokinetics



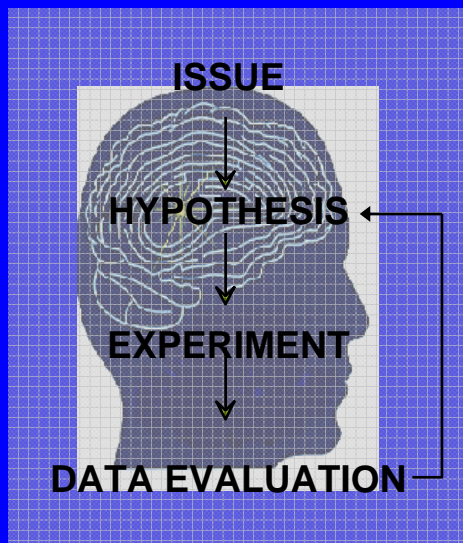
```
graph LR; A[Tissue interaction] --> B[Early tissue response]; B --> C[Irreversible pathology];
```

A horizontal flowchart within an orange rounded rectangle. It starts with the words 'Tissue interaction', followed by a right-pointing arrow to the words 'Early tissue response', followed by another right-pointing arrow to the words 'Irreversible pathology'.

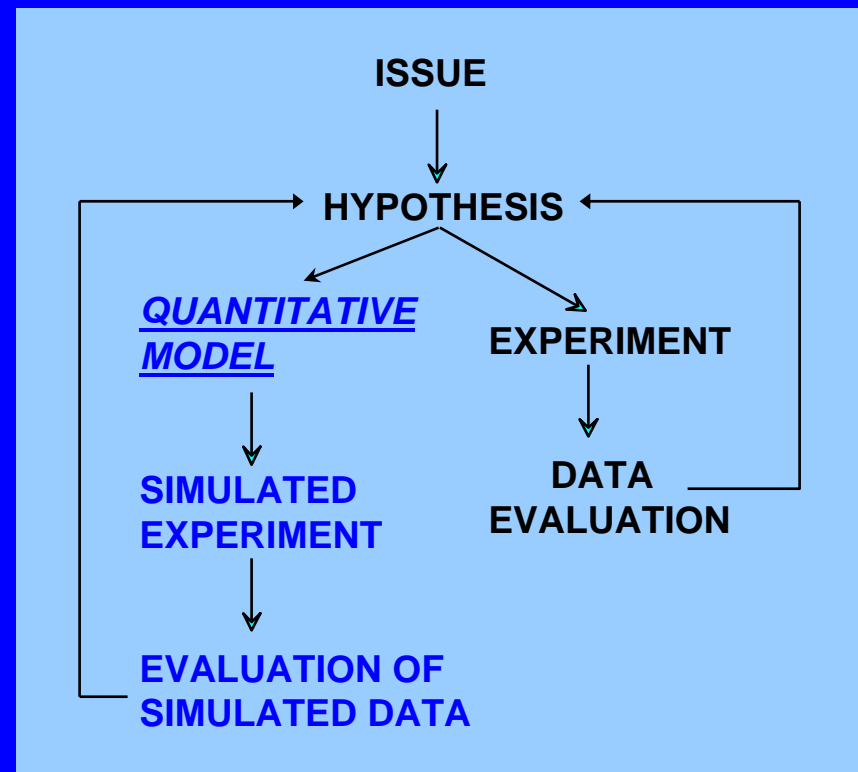
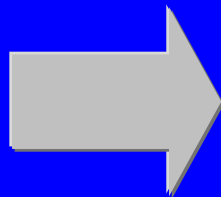
Pharmacodynamics

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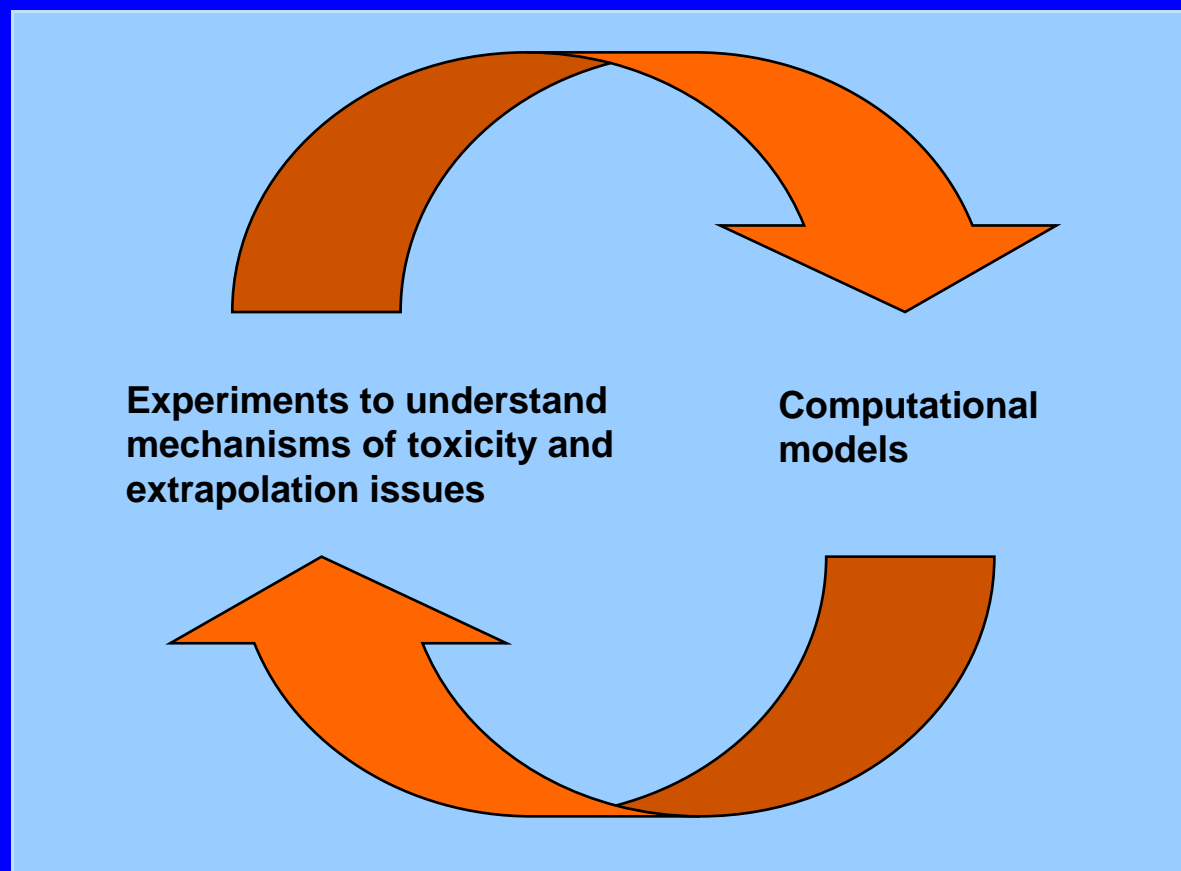


(Intuitive modeling)



(Formal + intuitive modeling)

Computational modeling and lab experiments



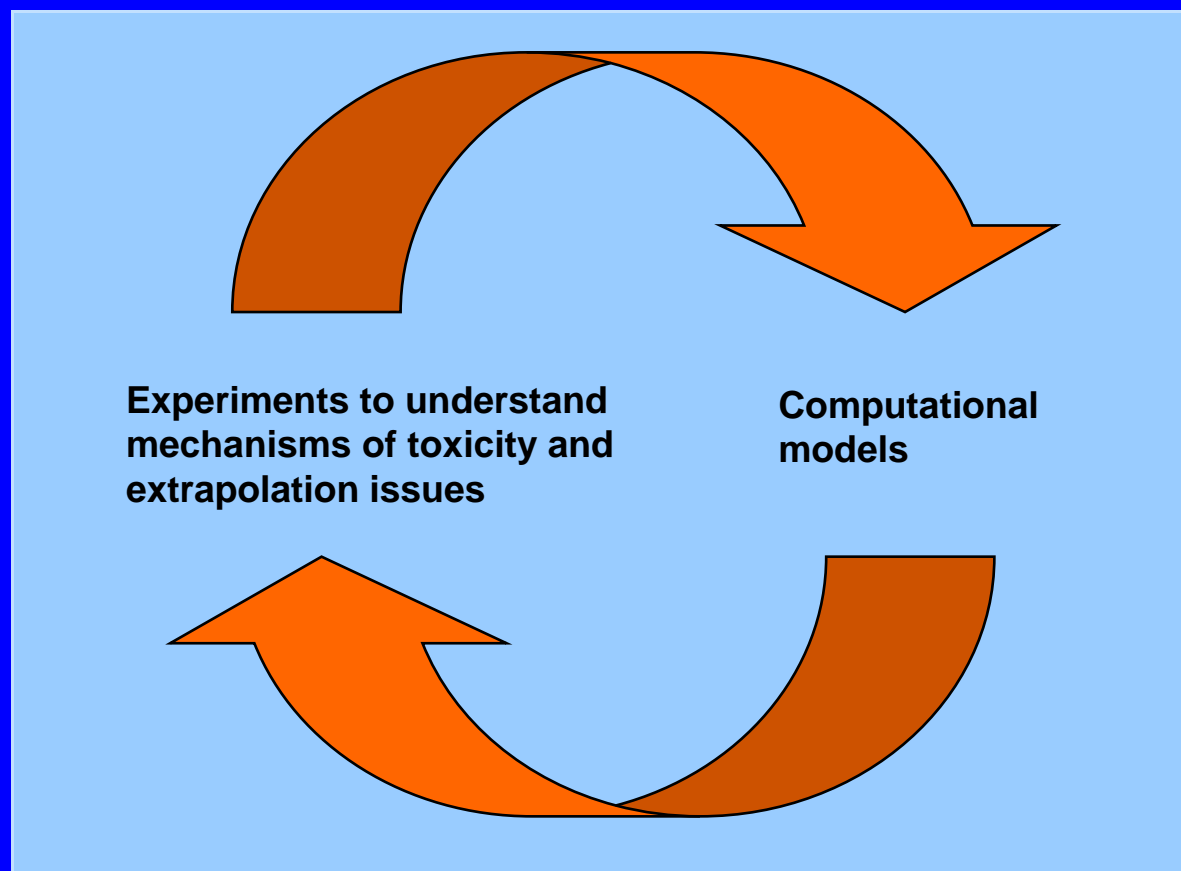
Projects Supported by Core C

Project 1: Characterization of the pathways linking Ah receptor activation with altered B cell differentiation using an integrated experimental and computational modeling approach (**Norb Kaminski**).

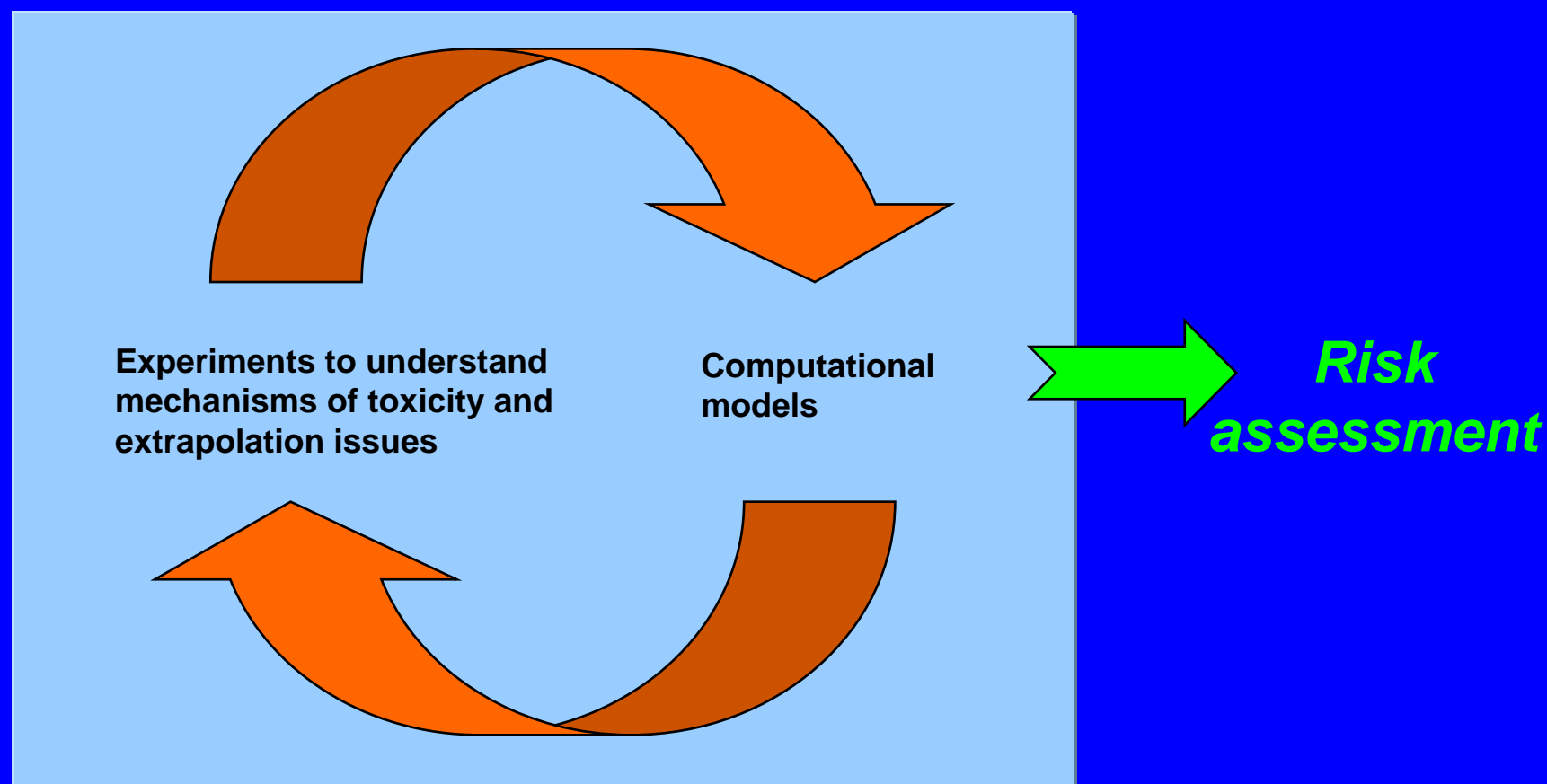
Project 2: Dissecting the signaling network for Ah receptor-mediated B cell toxicity (**Rusty Thomas**).

Project 4: Influence of Ah receptor ligands on inflammatory responses: consequences for tissue injury and gene expression (**Patty Ganey**).

Computational modeling and lab experiments



Bridging to risk assessment



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Inhibition by TCDD of LPS-induced IgM

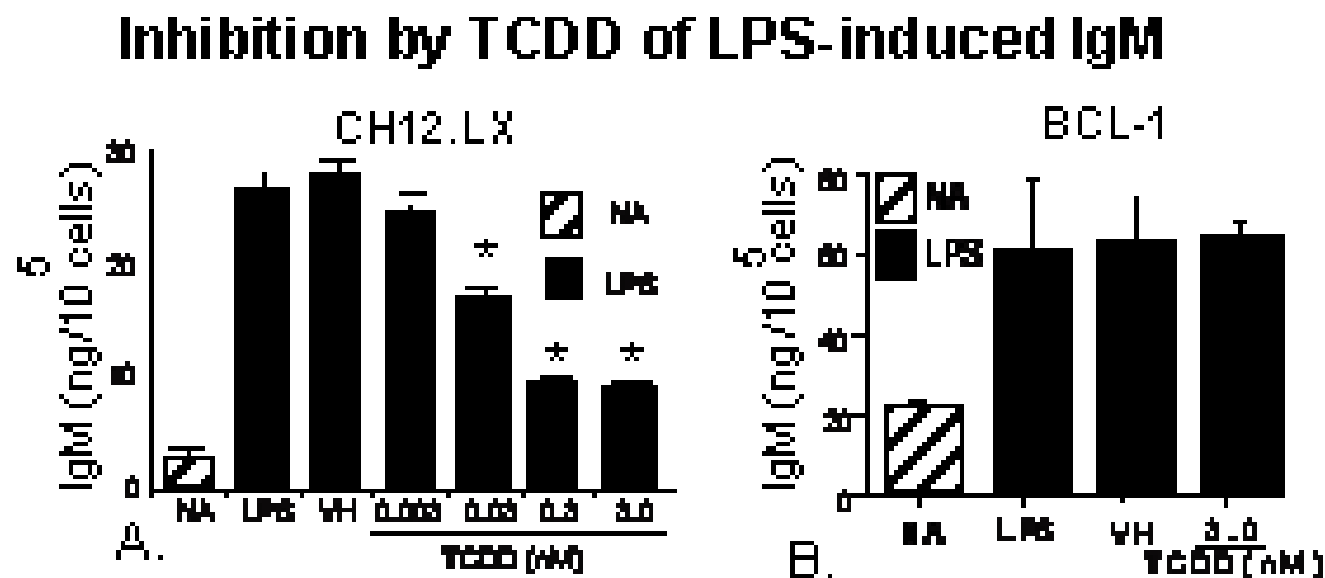
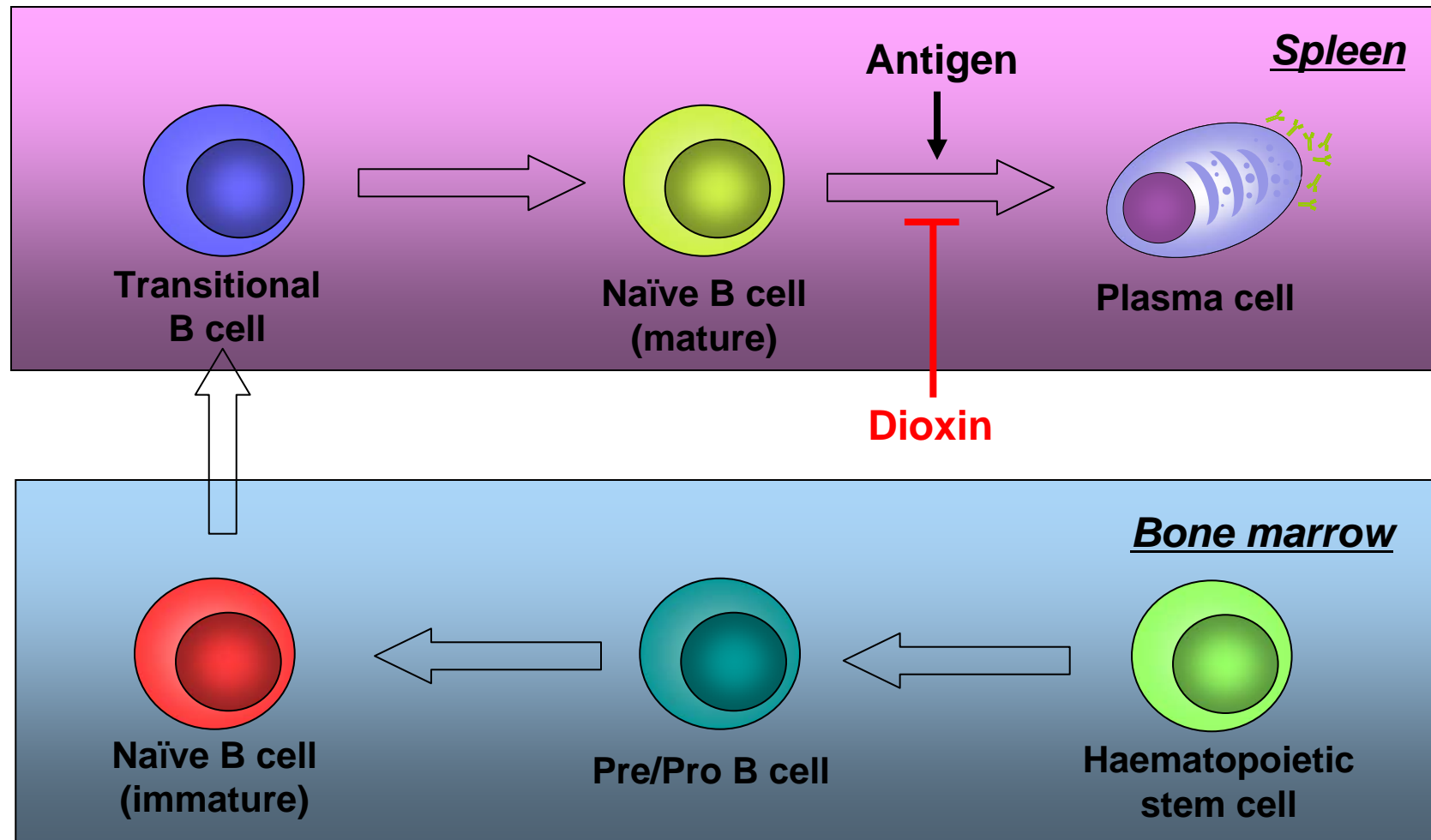


Fig1 (A) CH12.LX or (B) BCL-1 cells treated at time 0 with TCDD or vehicle (VH:0.01% DMSO) plus LPS (5 μ g/ml). Supernatant IgM assayed by ELISA at 48 h. * - significantly different at $p < 0.05$ from VH control $n = 4$ treatment group.

Hypothesis: Suppression of the primary humoral immune response by AhR agonists is mediated through changes in the B cell differentiation program

– Norb Kaminski

Dioxin and B Lymphocyte Differentiation

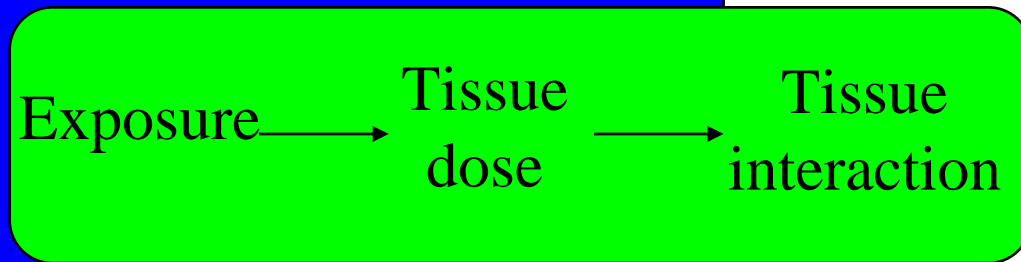


Approach

1. Adapt an existing PBPK model
2. Develop a new computational model of key aspects of the molecular mechanism of B cell differentiation
3. In the model, describe how AhR agonists interfere with the process
4. Iterate model refinement with laboratory experiments
5. Use the computational model to predict dose-response

Exposure-response continuum

Pharmacokinetics

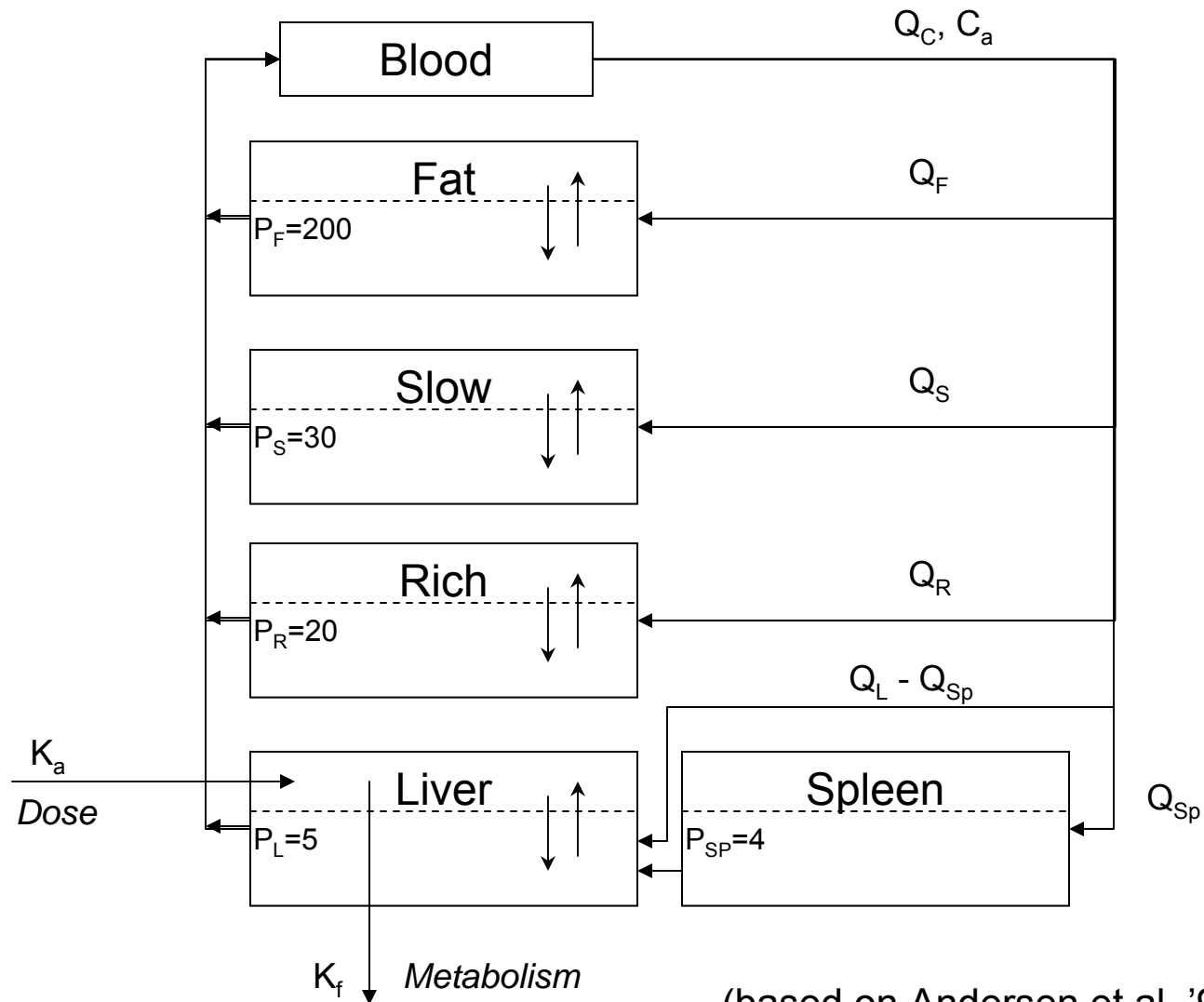


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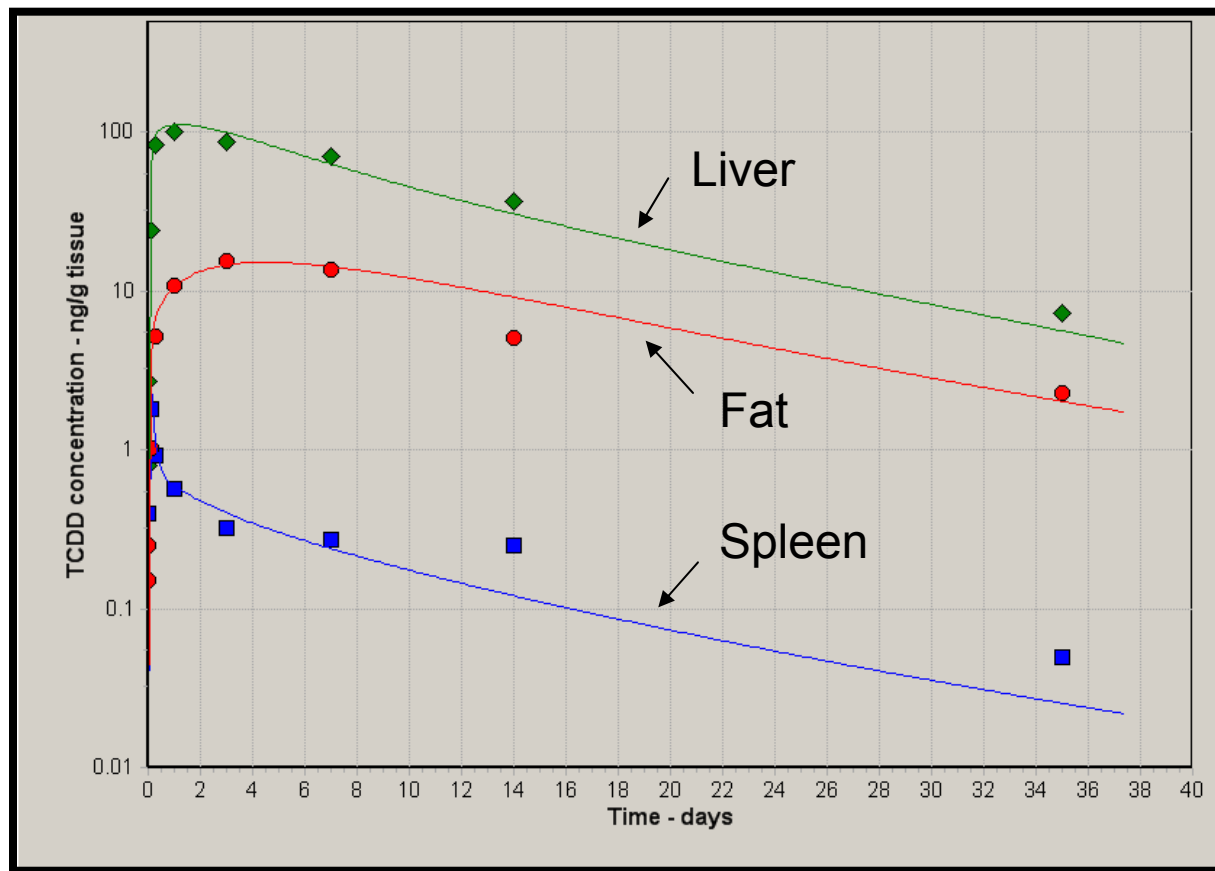
Pharmacodynamics

Dioxin PBPK Model with Spleen



(based on Andersen et al. '93, Wang et al. '97)

Dioxin PBPK Model with Spleen - Fitting long time-course rat data

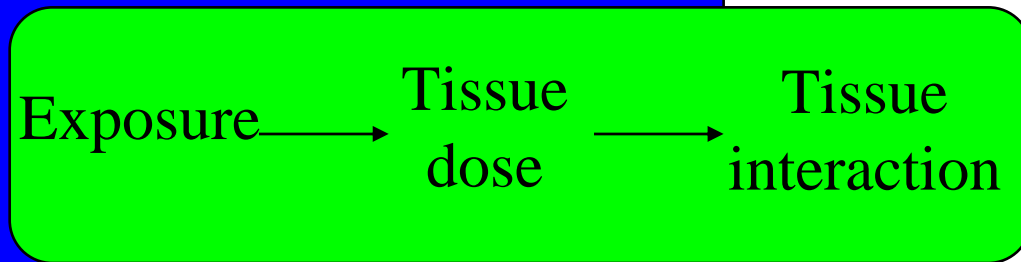


Oral dose: 10 $\mu\text{g/kg}$

(Wang et al. '97)

Exposure-response continuum

Pharmacokinetics

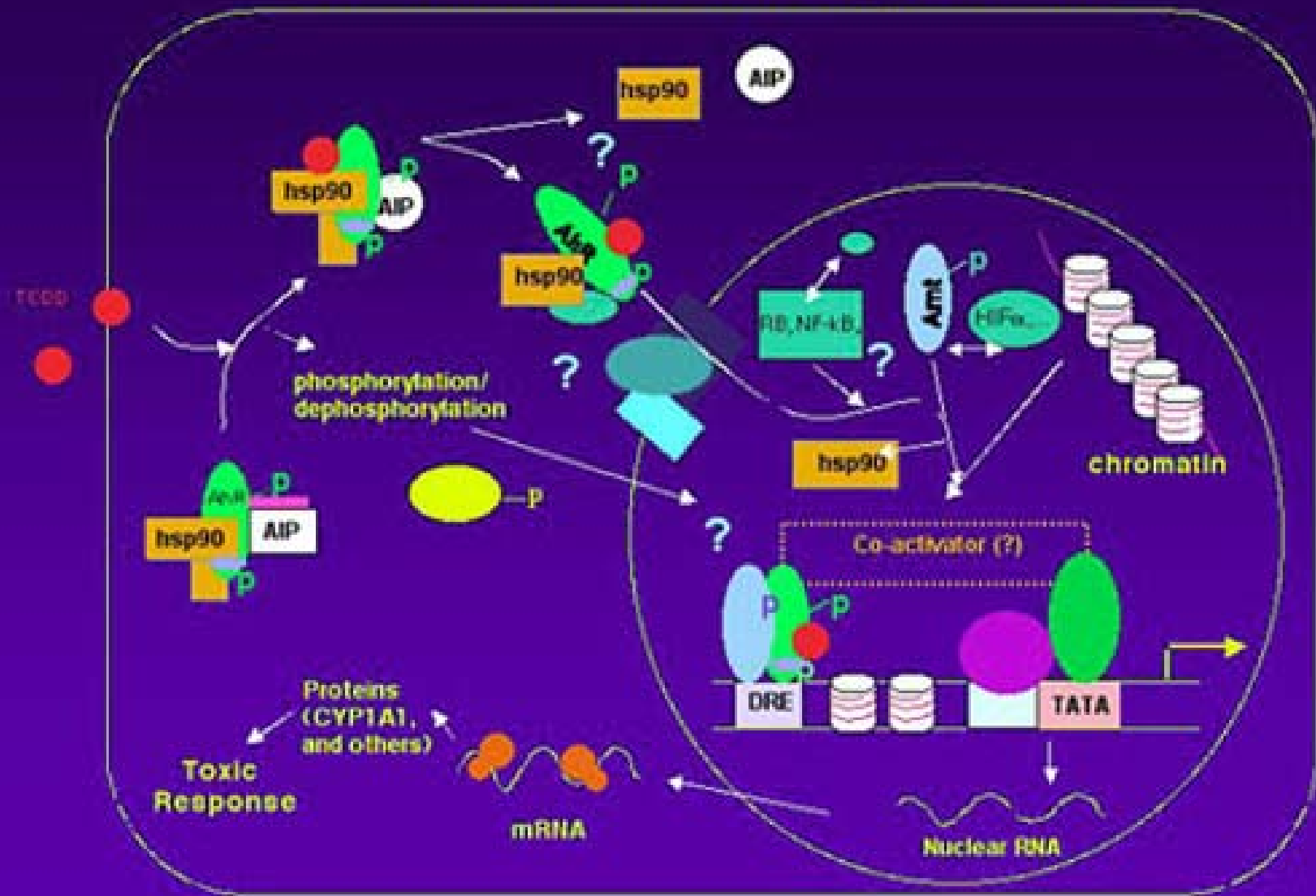


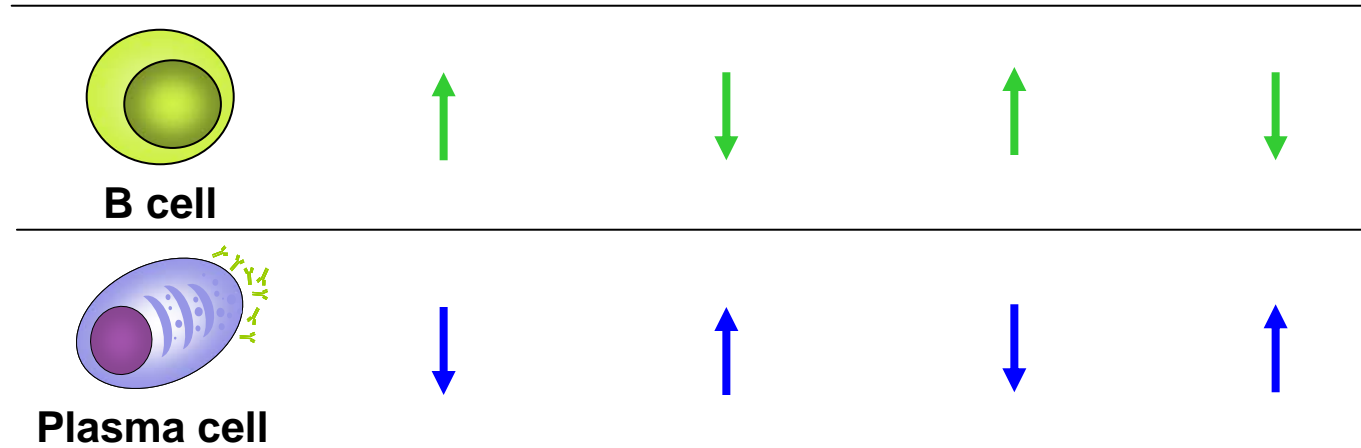
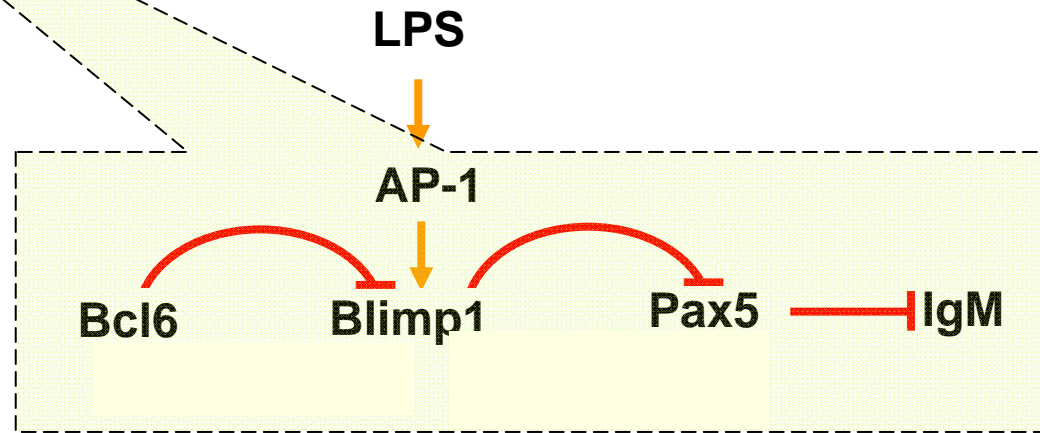
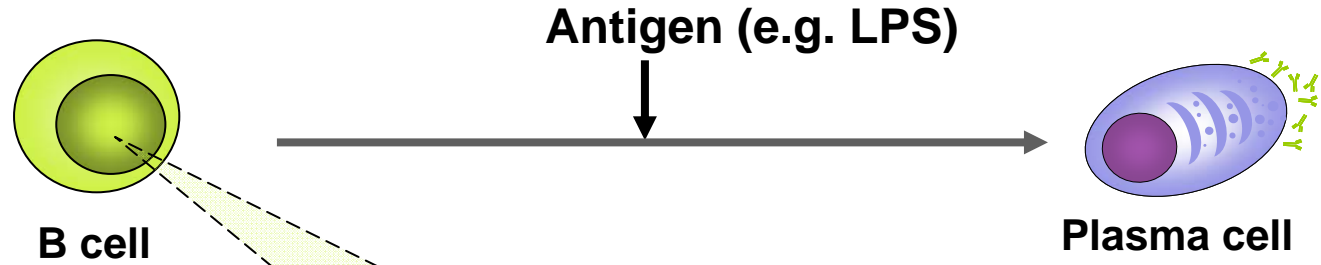
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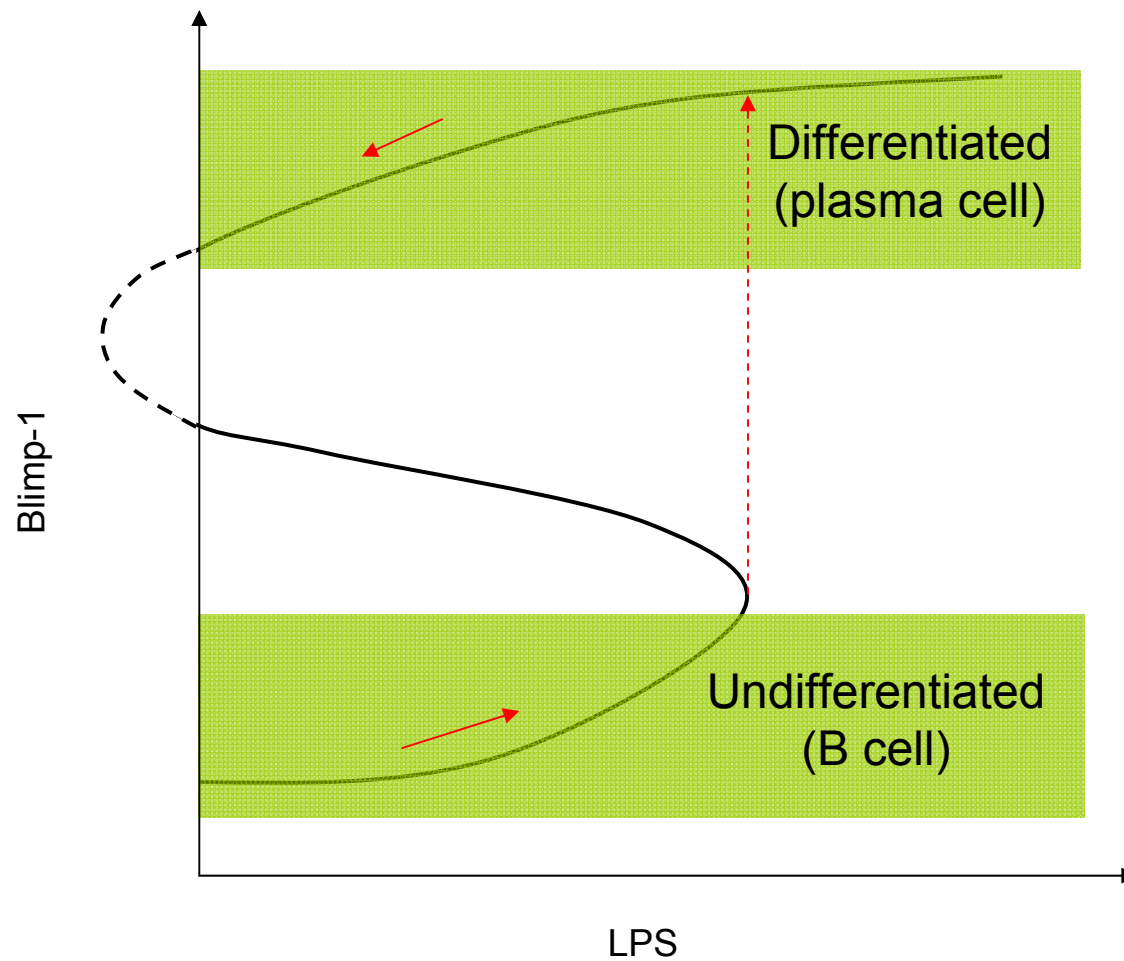
Pharmacodynamics

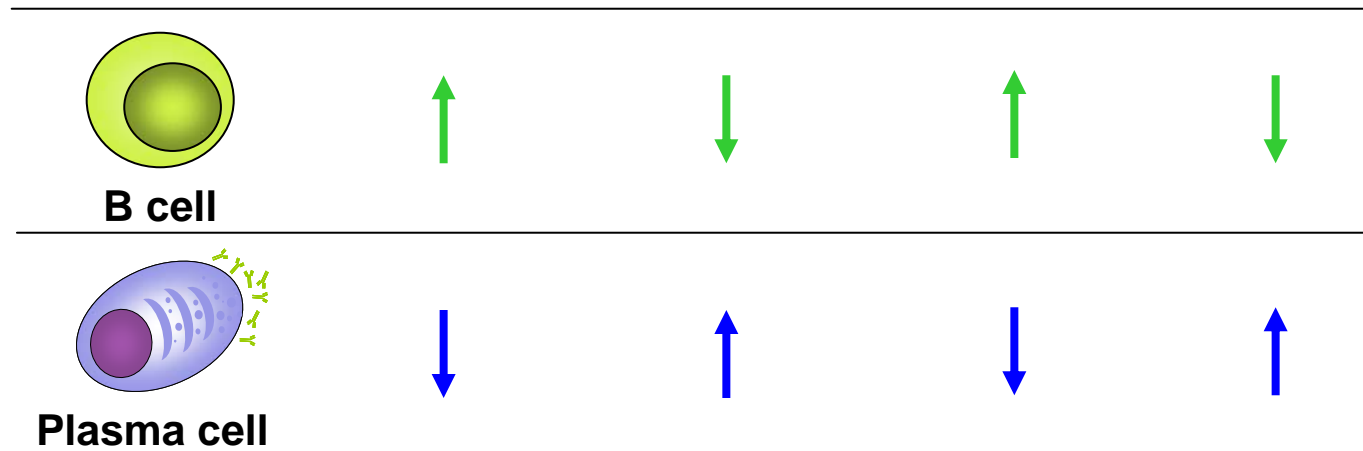
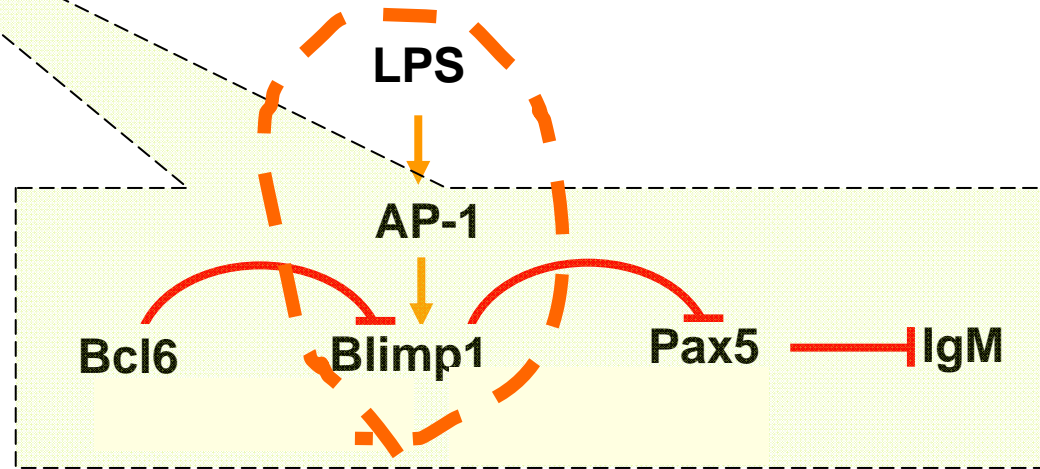
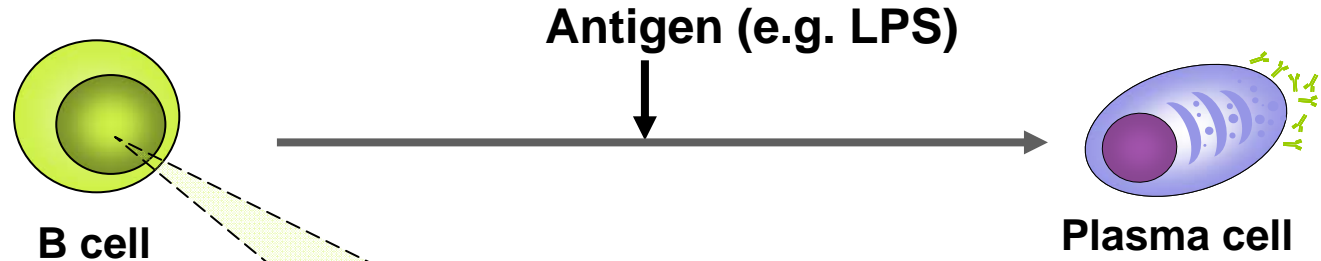
Cellular Mechanisms for Ah Receptor Action



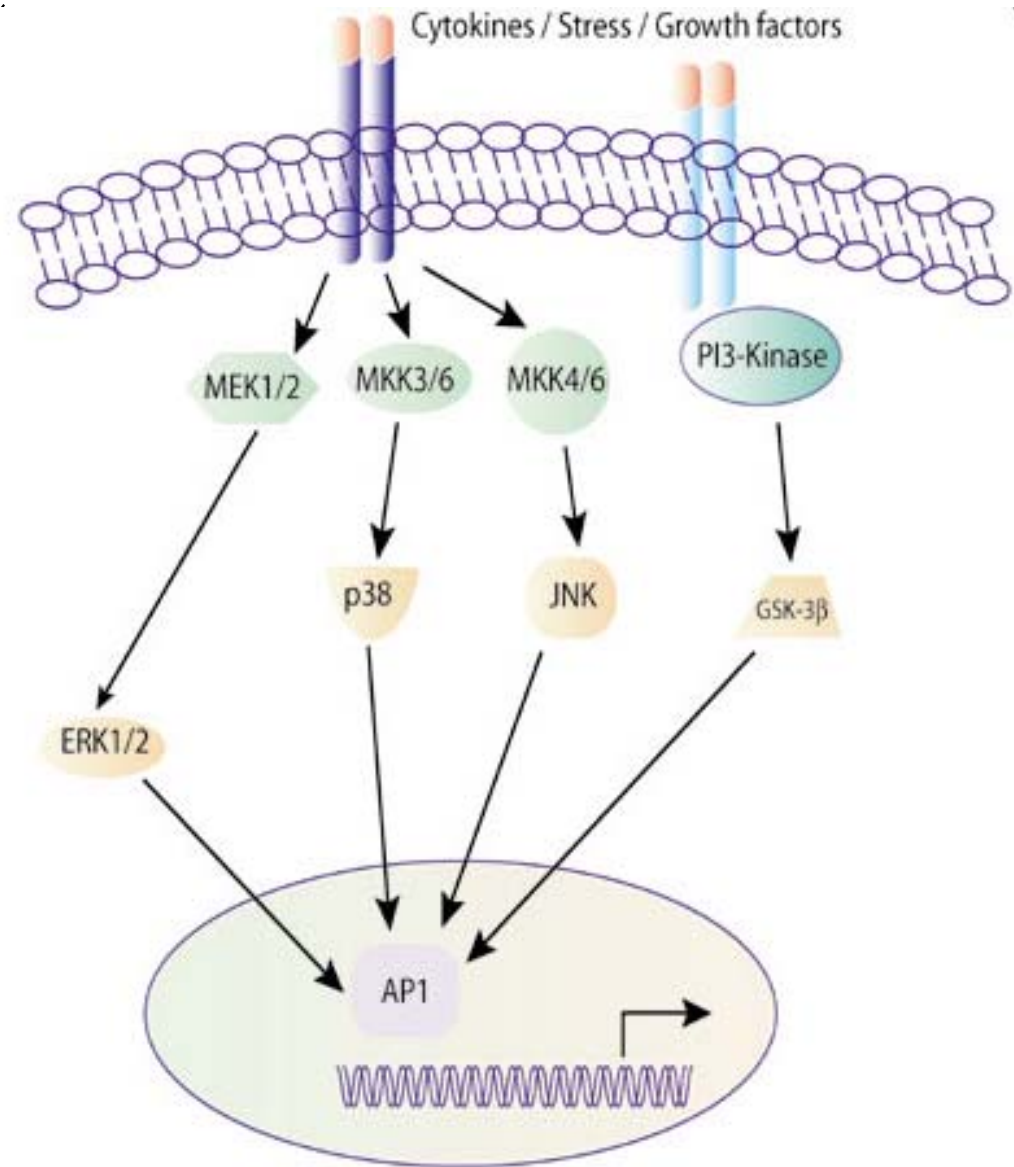


An irreversible switch: hysteresis and memory





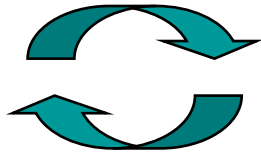
AP-1 activation



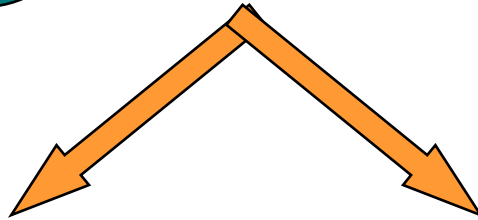
INPUT



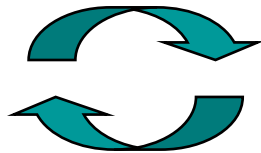
MAPKKK



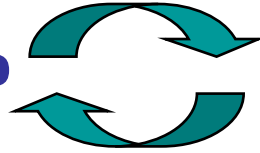
MAPKKK*



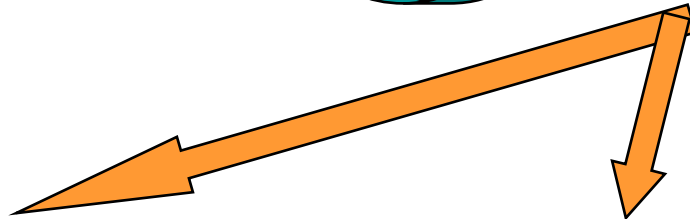
MAPKK



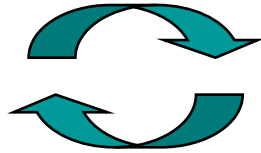
MAPKK-P



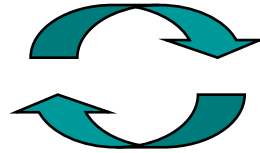
MAPKK-PP



MAPK



MAPK-P

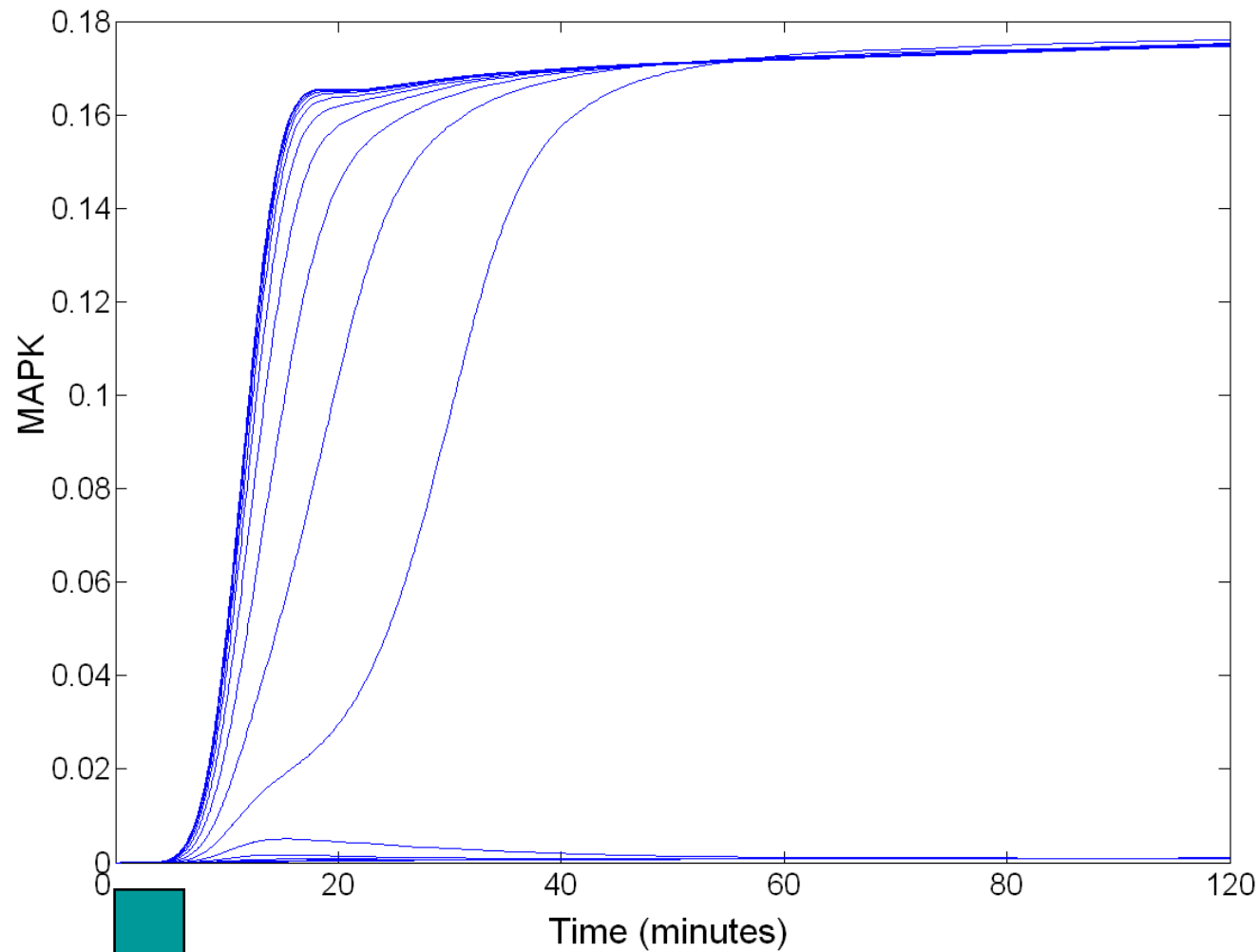


MAPK-PP



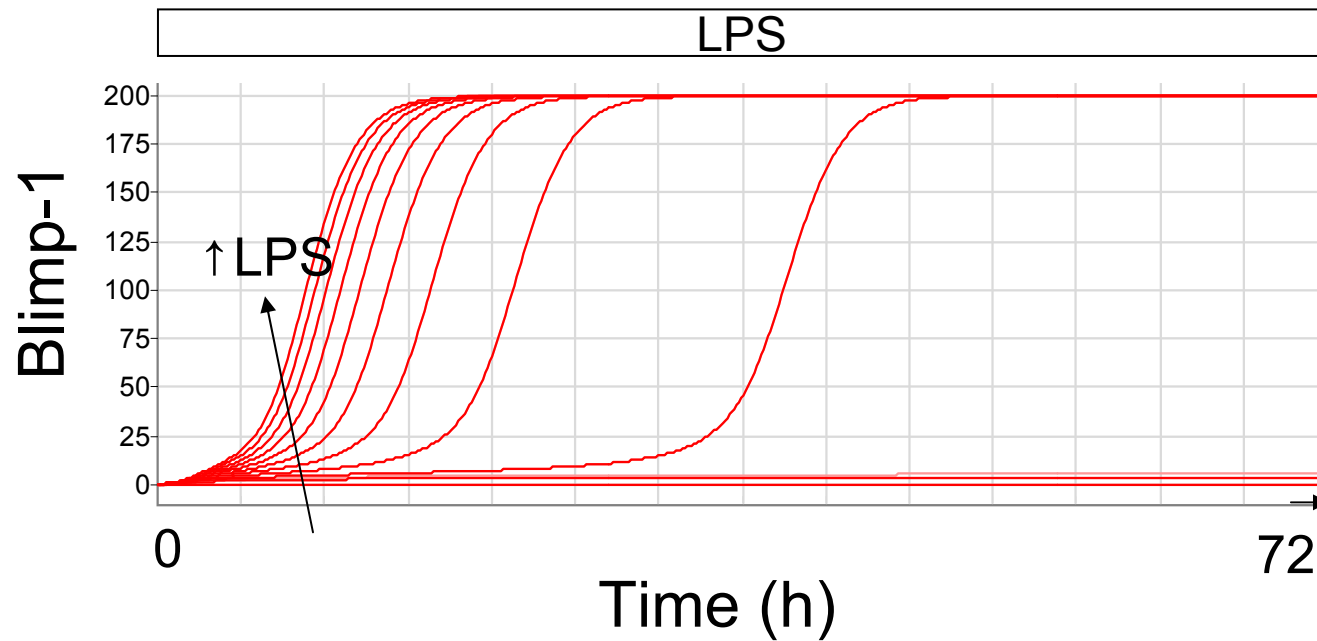
OUTPUT

MAPK time-course and bifurcation after a short pulse of PDGF

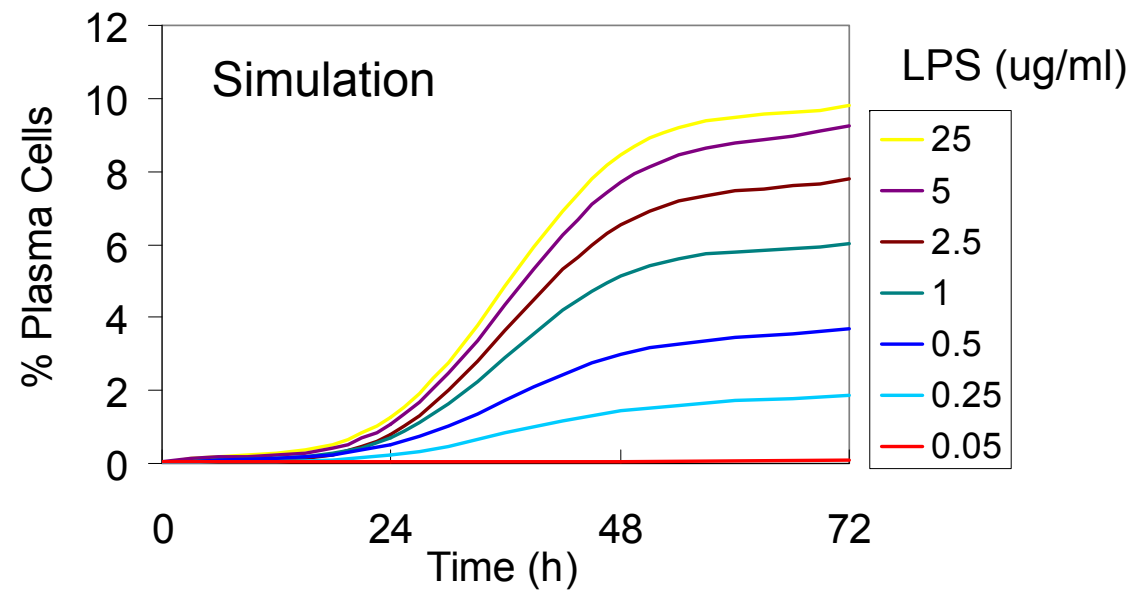
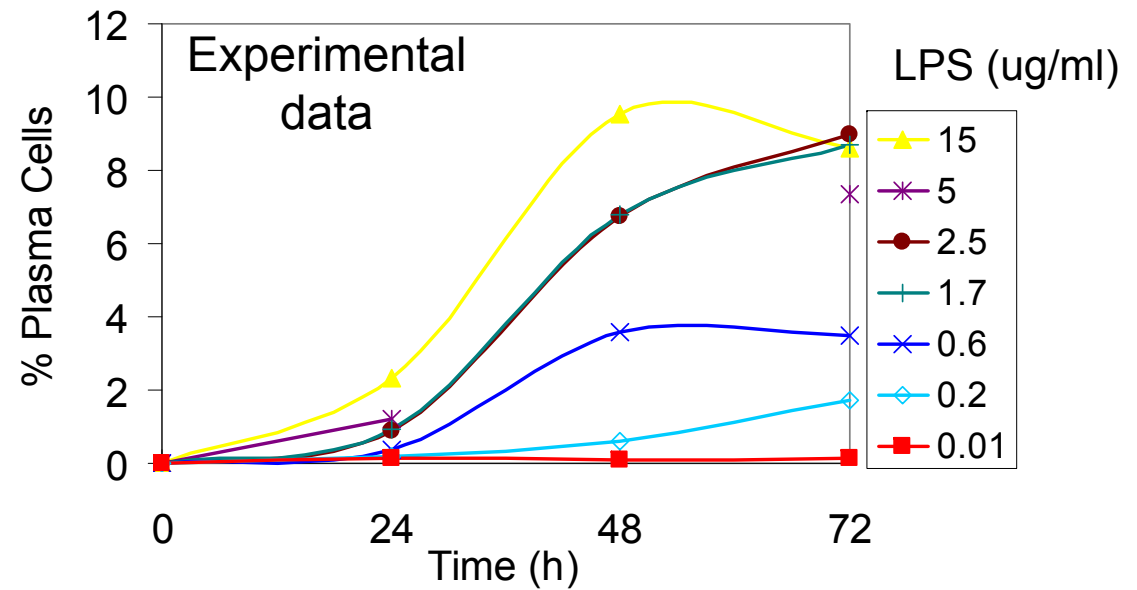


Input pulse

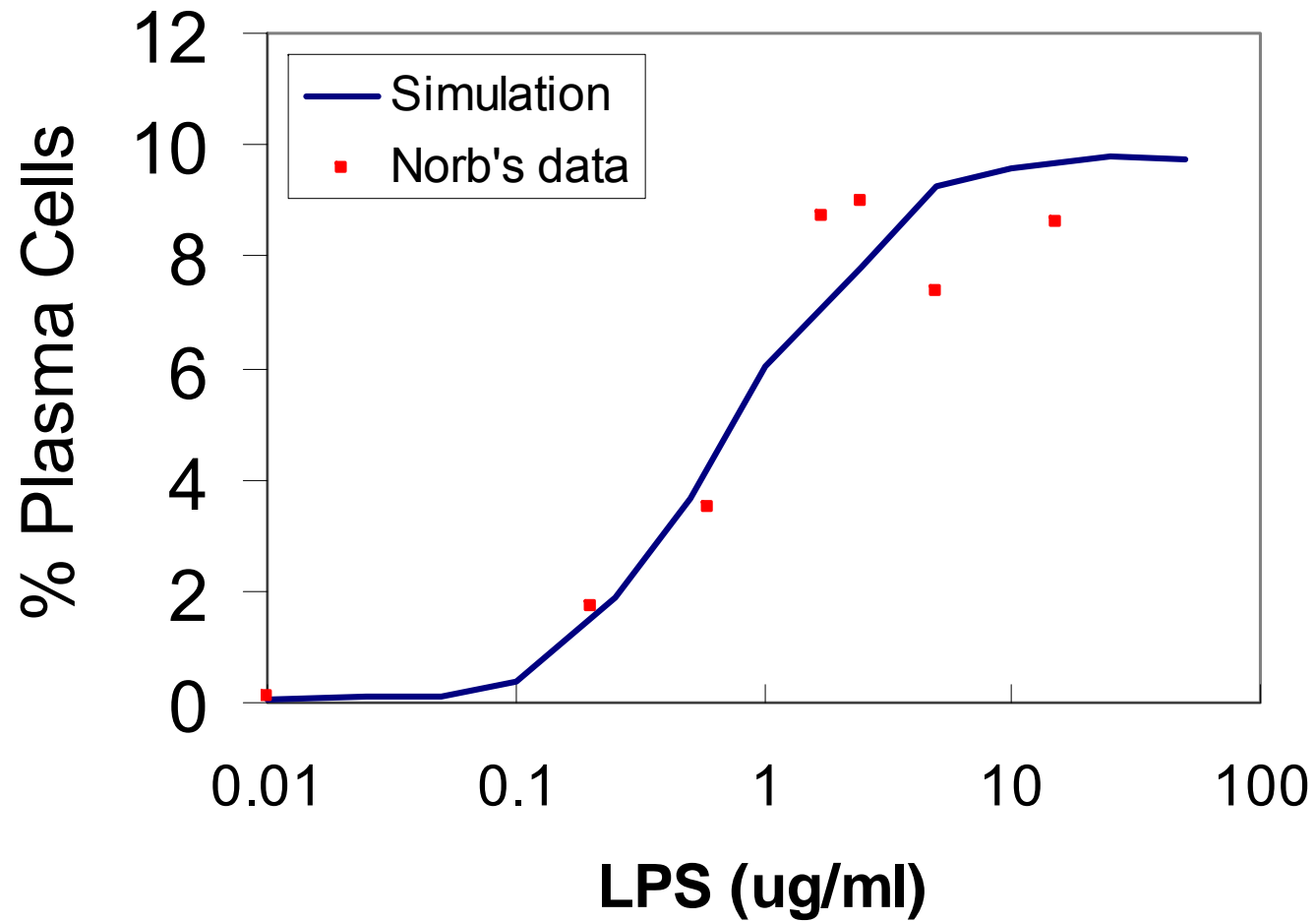
Prediction: LPS activates Bcl6-Blimp1-Pax5 switch with a threshold dose



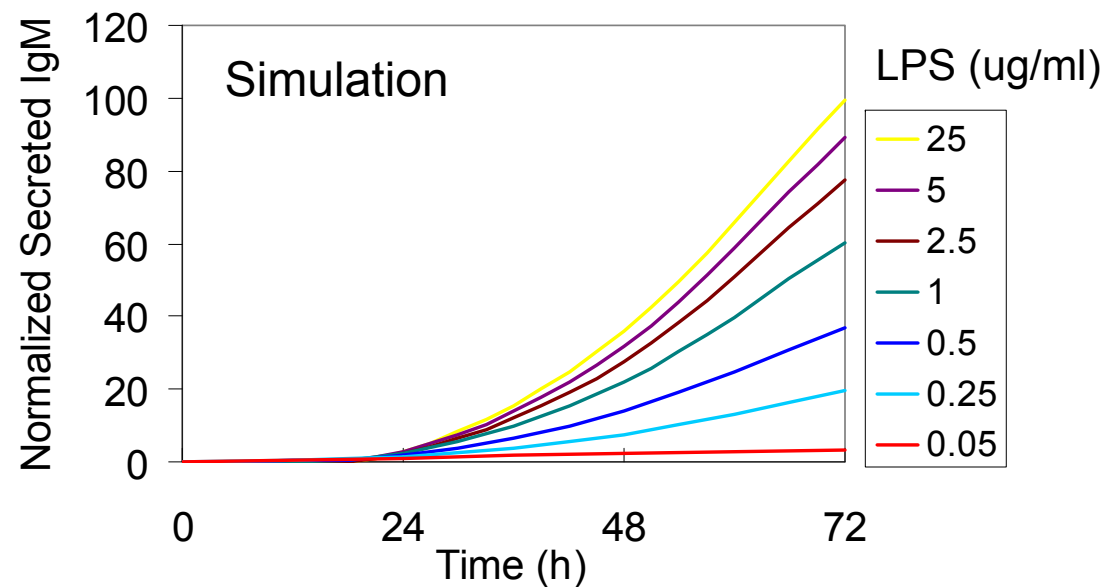
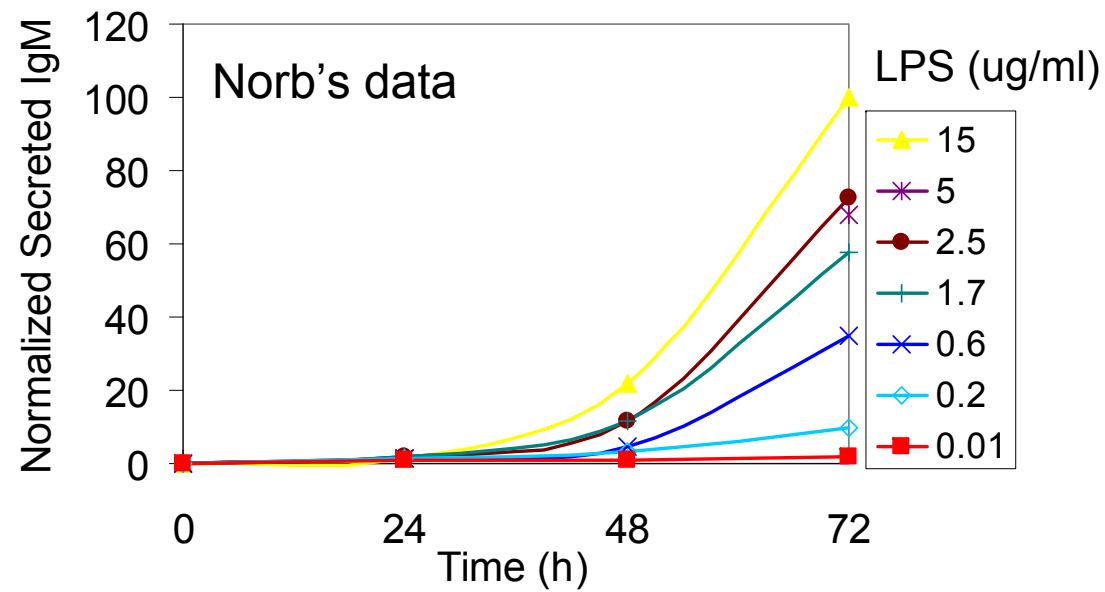
Percentage LPS-activated Plasma Cells Over Time



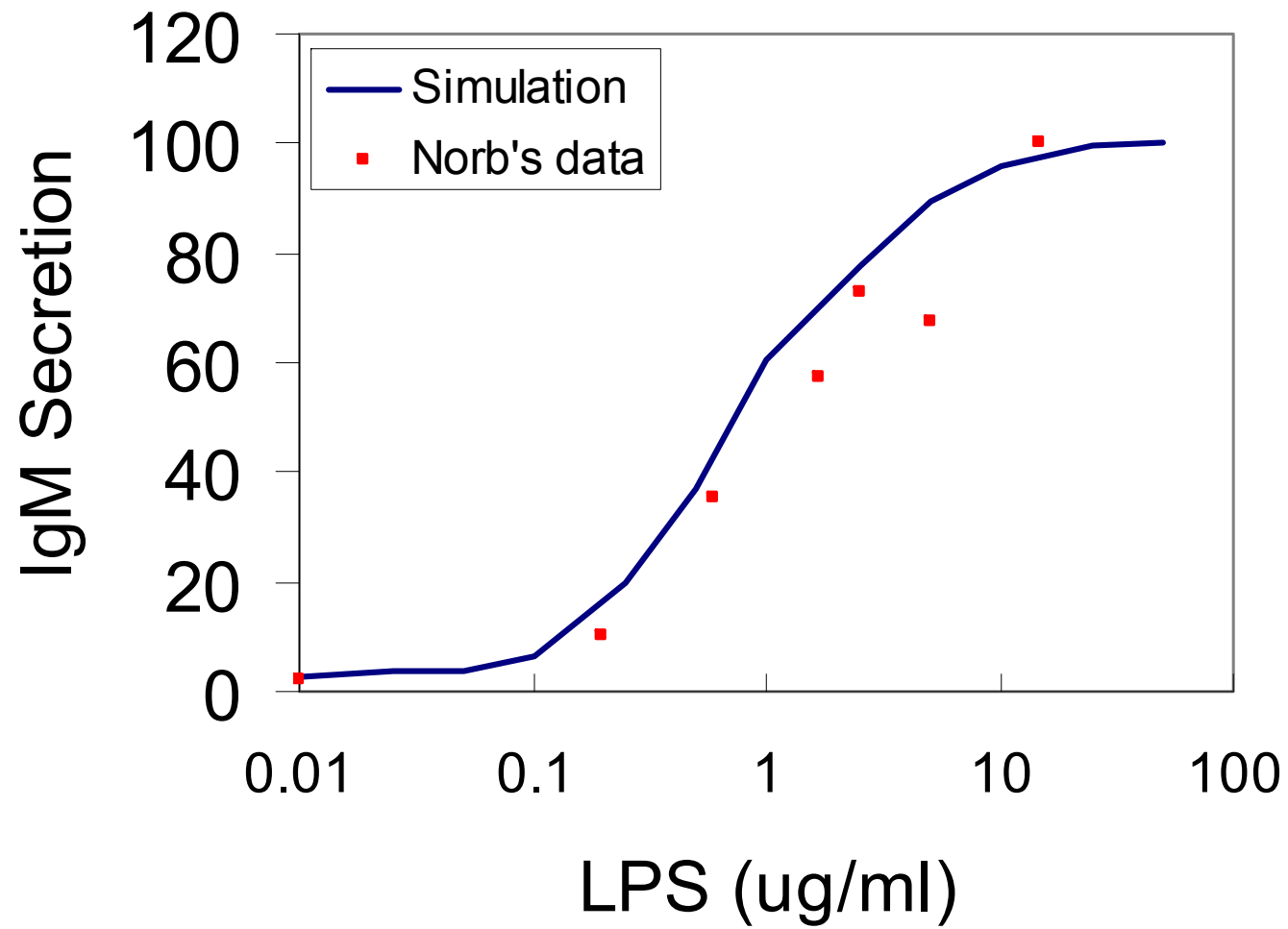
LPS Dose Response at 72 h



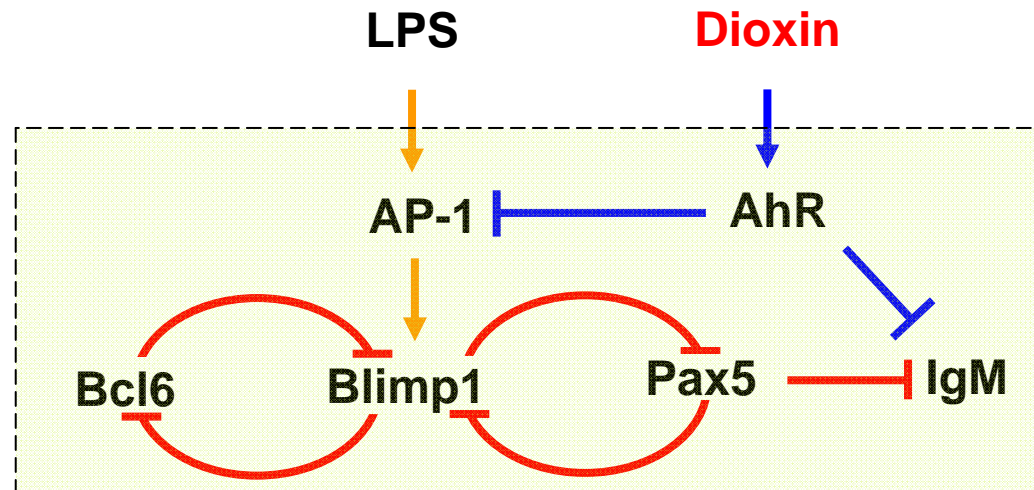
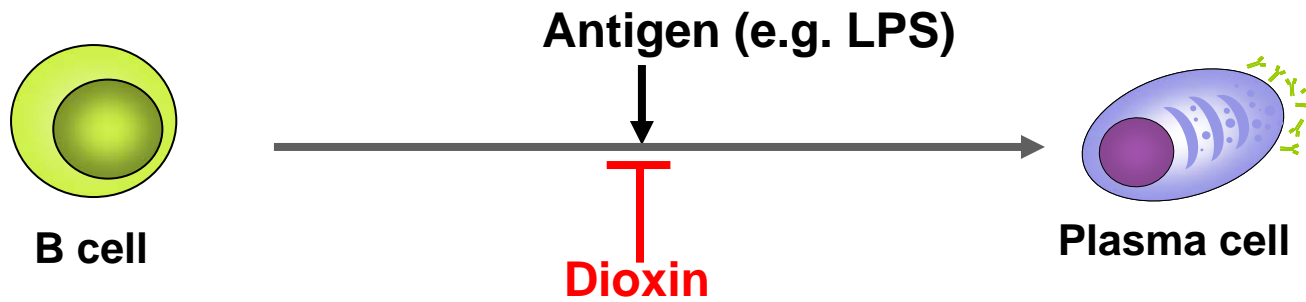
LPS-activated IgM Secretion Over Time



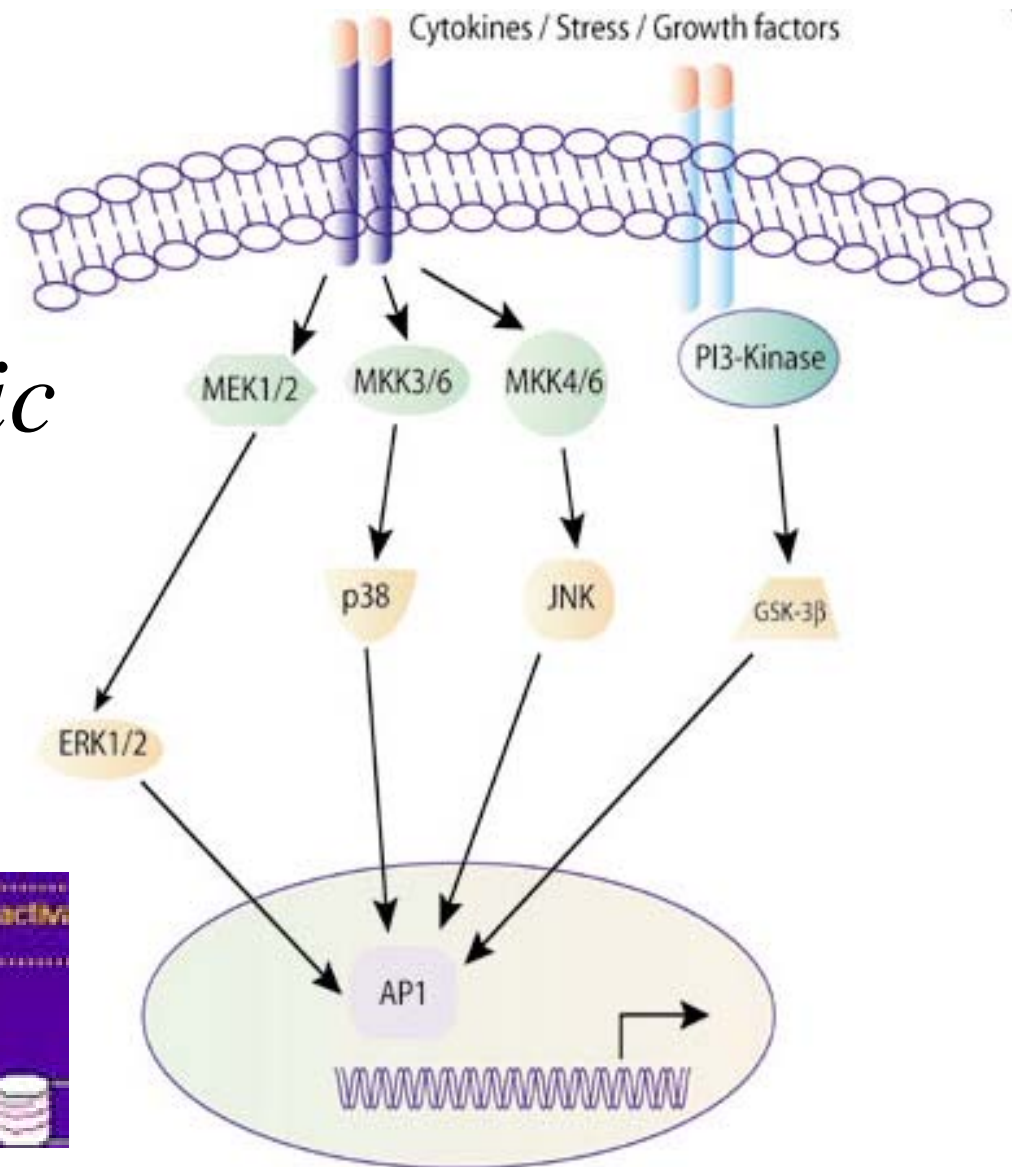
LPS Dose Response at 72 h



Dioxin Suppresses B Cell Terminal Differentiation

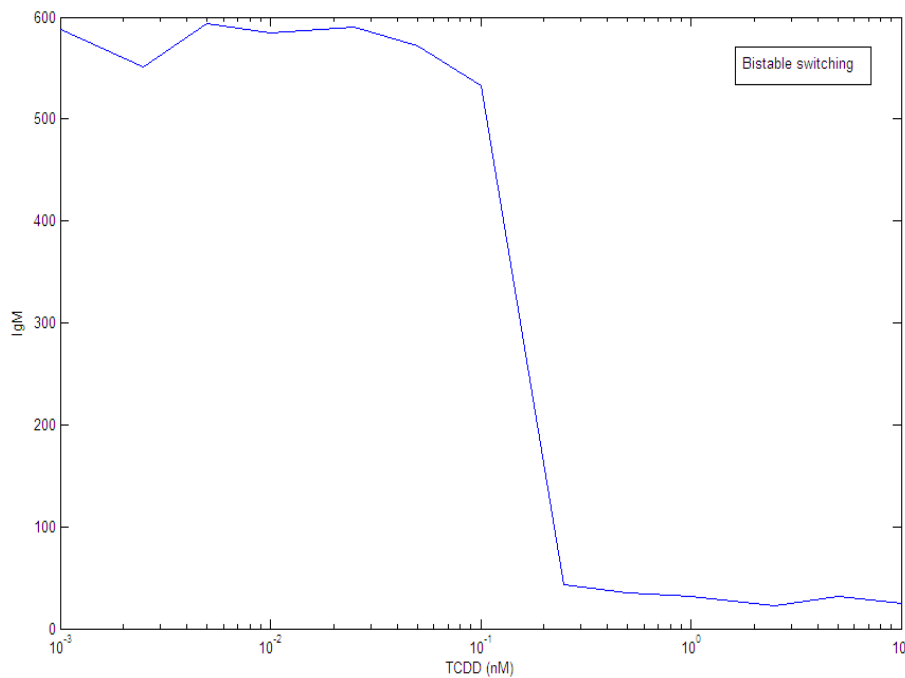


*TCDD and
AP-1 activation,
appropriate kinetic
description?*

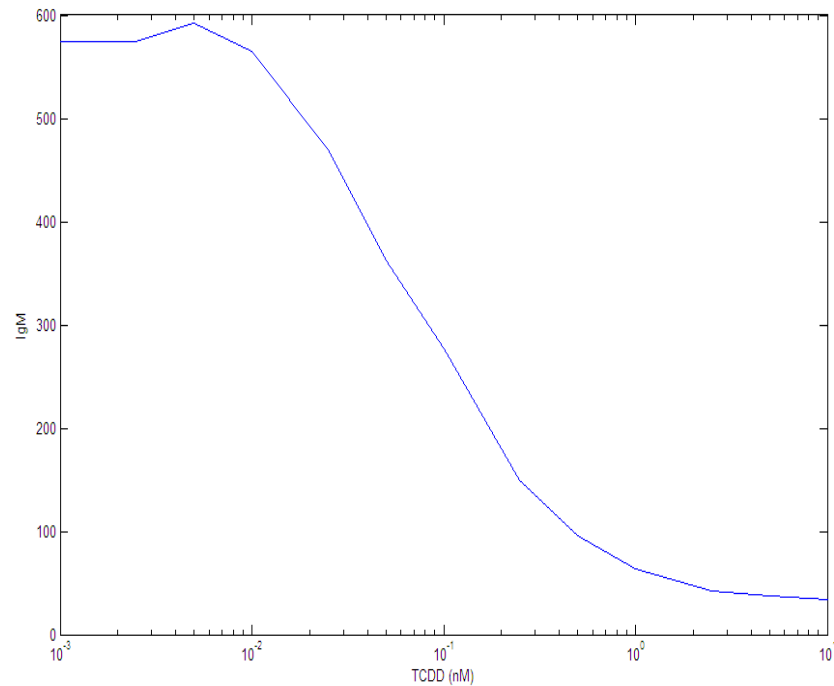


Implications of alternative kinetics for TCDD dose-response

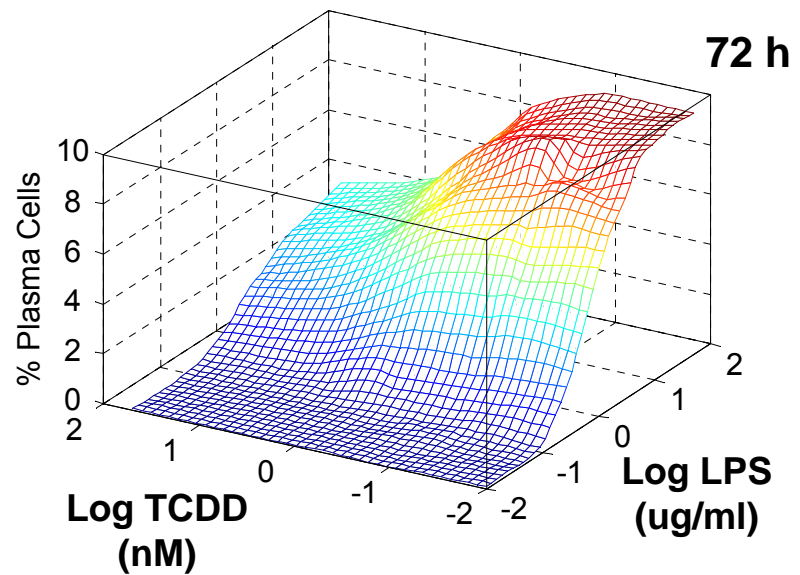
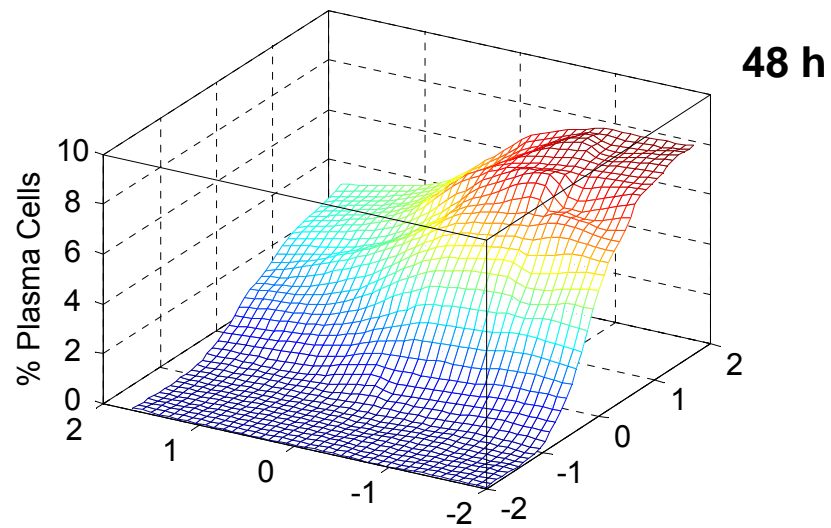
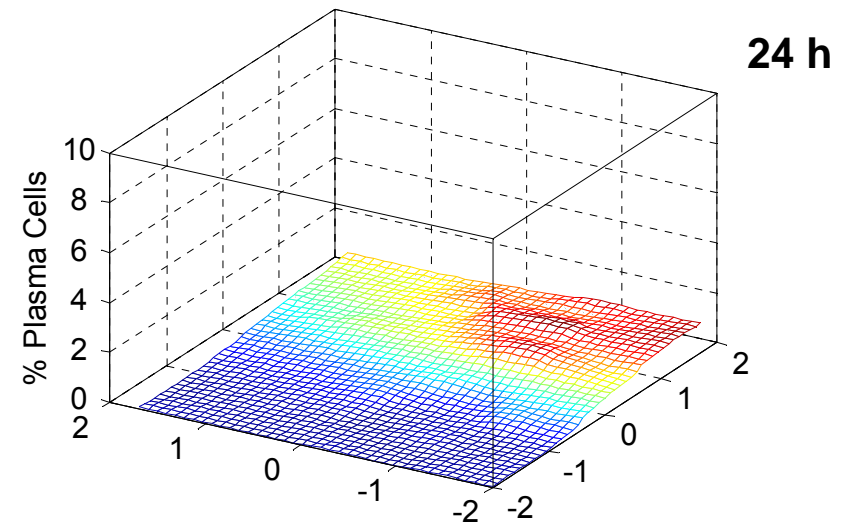
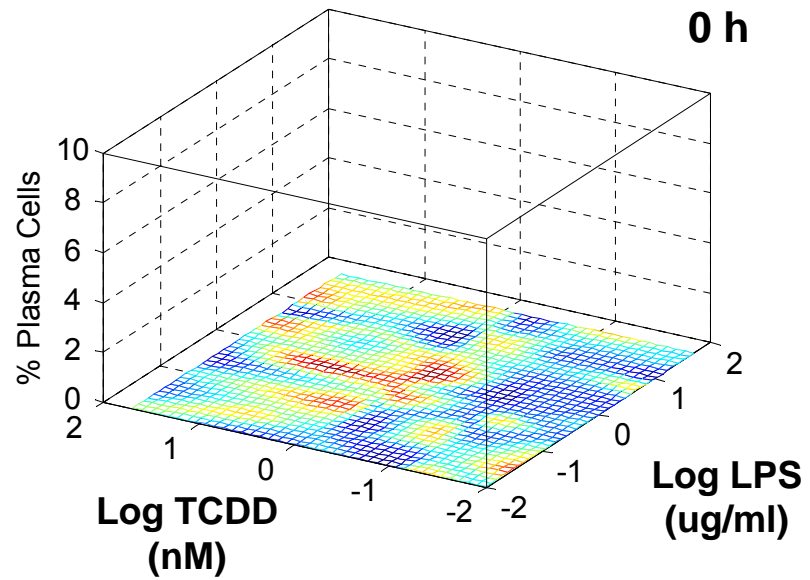
MAPK-like bifurcation
with noise



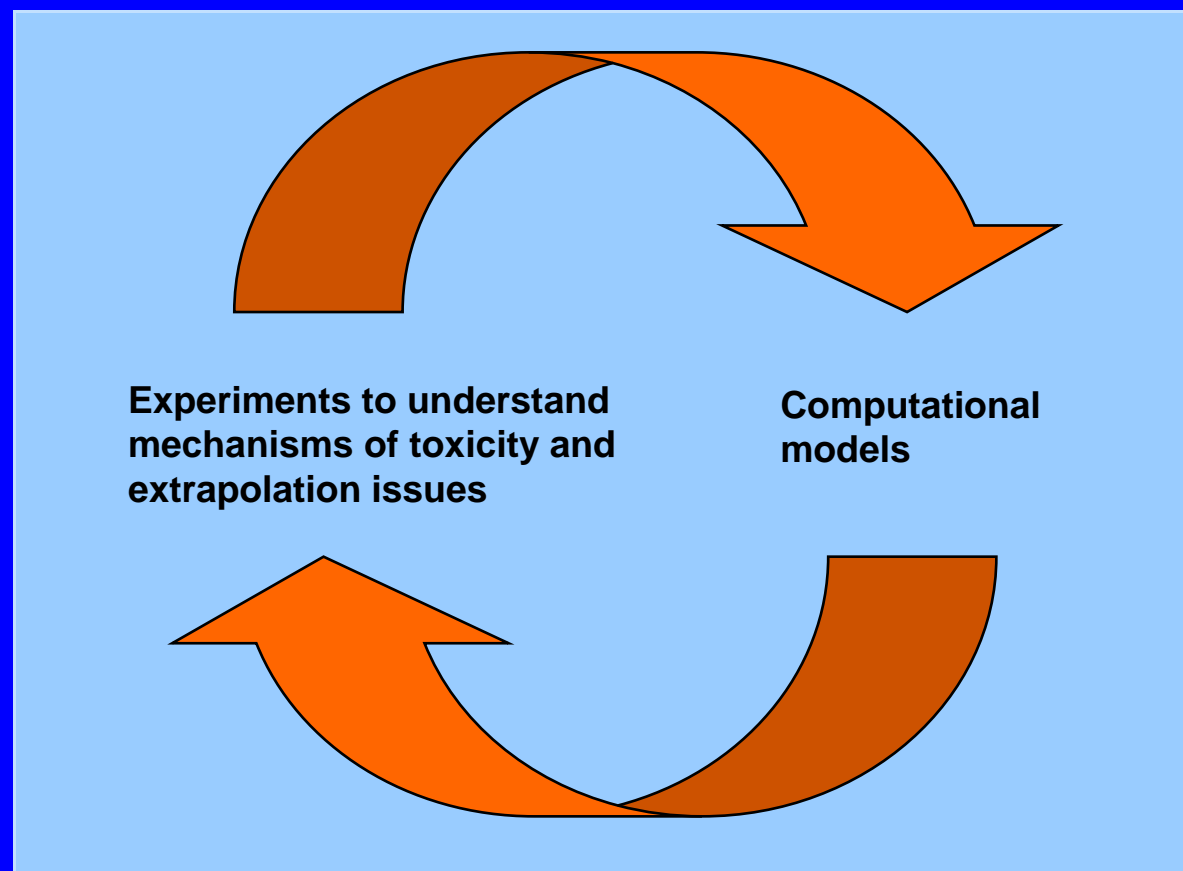
Continuous with noise



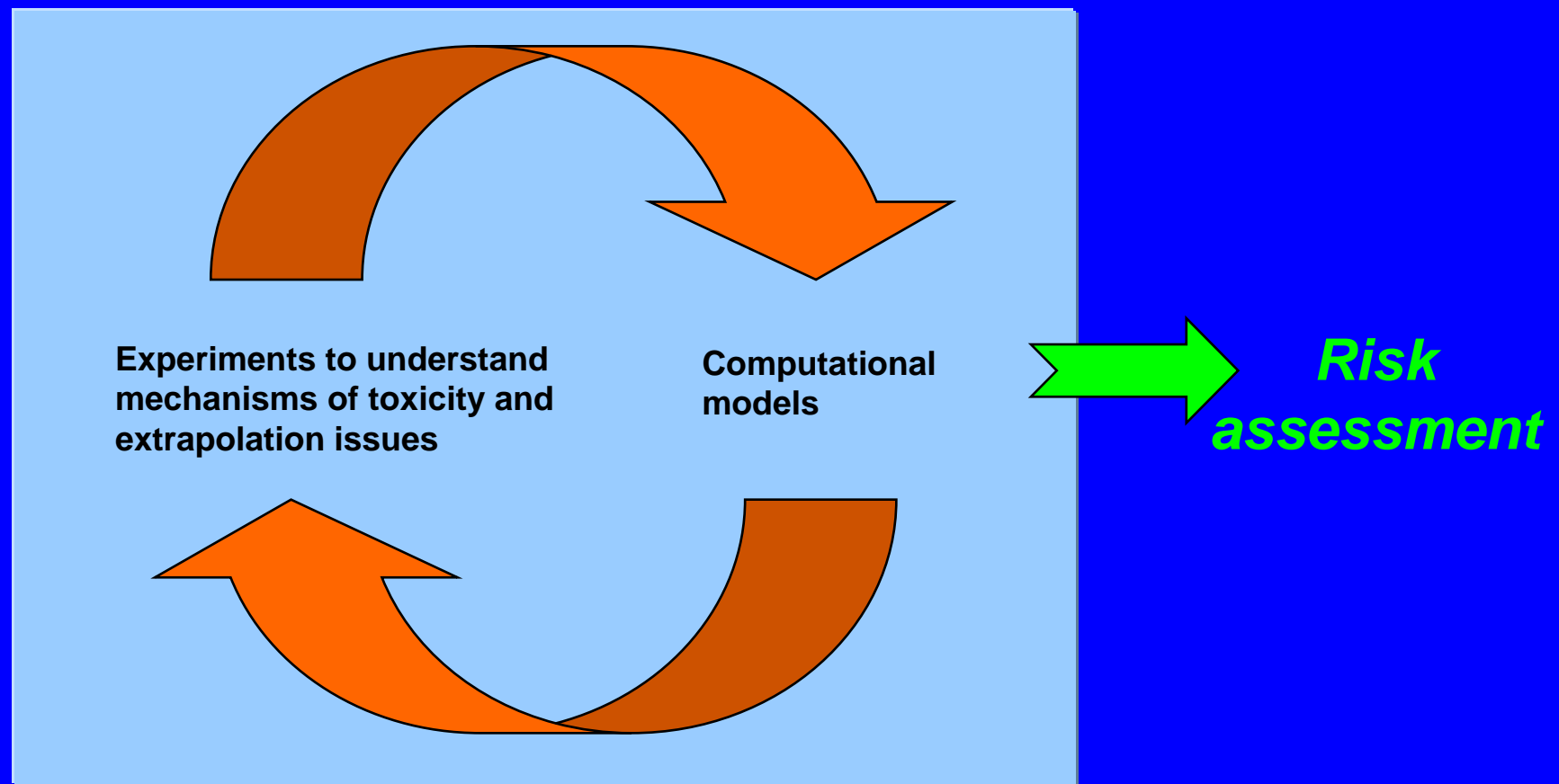
Predicted Dose Response Surfaces



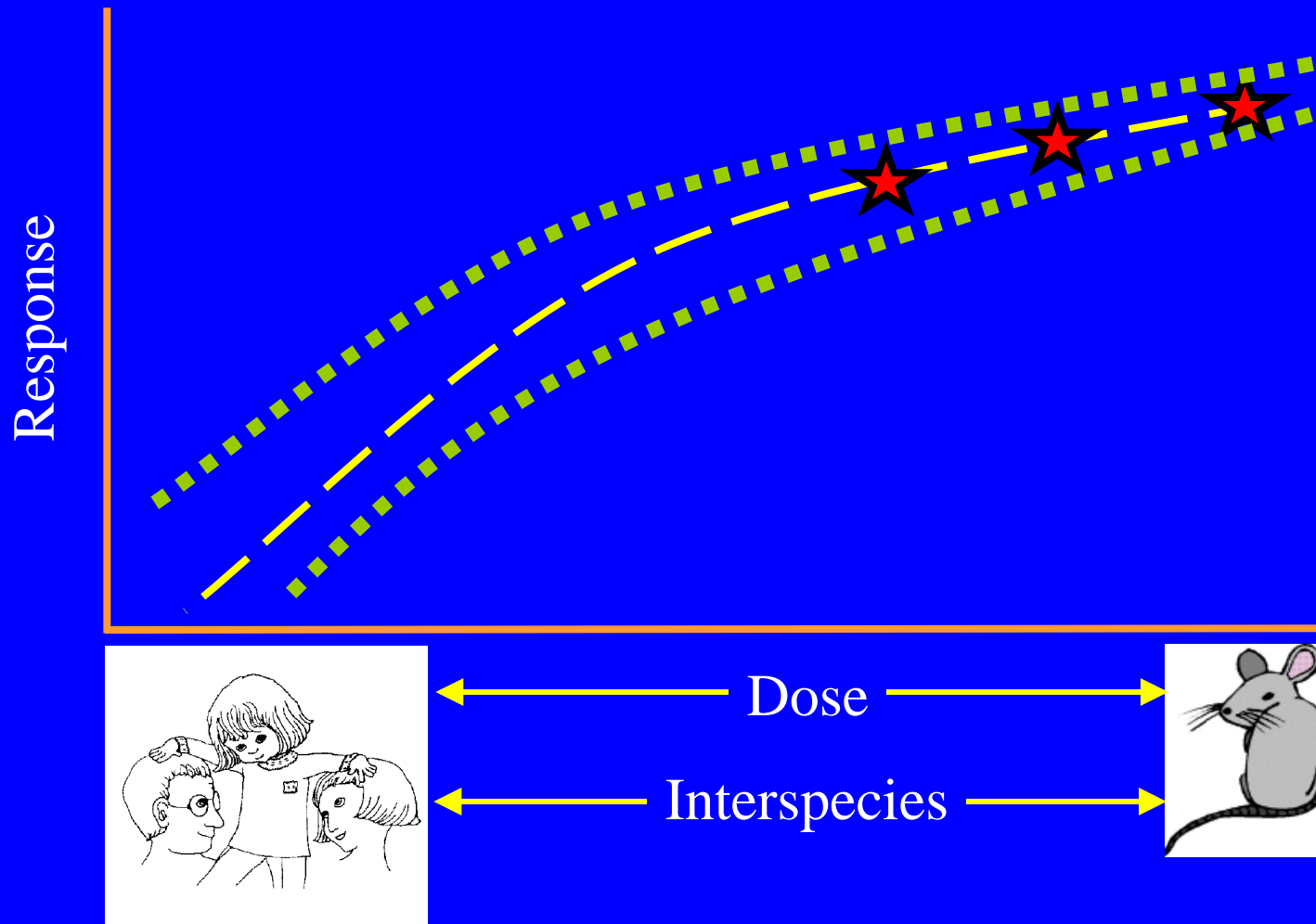
The computational model is a bridge from research and risk assessment



*The computational model is a bridge from
research and risk assessment*



Accuracy



Summary

- Remediation is expensive, so accurate prediction of dose-response is important to help control costs.
- Dose-response is a function of biological mechanisms.
- Computational models of these mechanisms improve the efficiency of research and provide the capability for prediction.
- Example: Prediction of dose-response for inhibition by AhR ligands of the terminal differentiation of B-cells.
- Need quantitative understanding of how TCDD-AhR interacts with AP-1 and other sites in the B cell differentiation program

*The Hamner Institutes for
Health Sciences*

Mel Andersen

*Michigan State
University*

Norb Kaminski



Qiang Zhang



Sudin Bhattacharya

End