

Computational systems biology:

The integration of data across multiple levels of biological organization to understand how perturbations of normal biology become adverse health effects

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Disclaimer

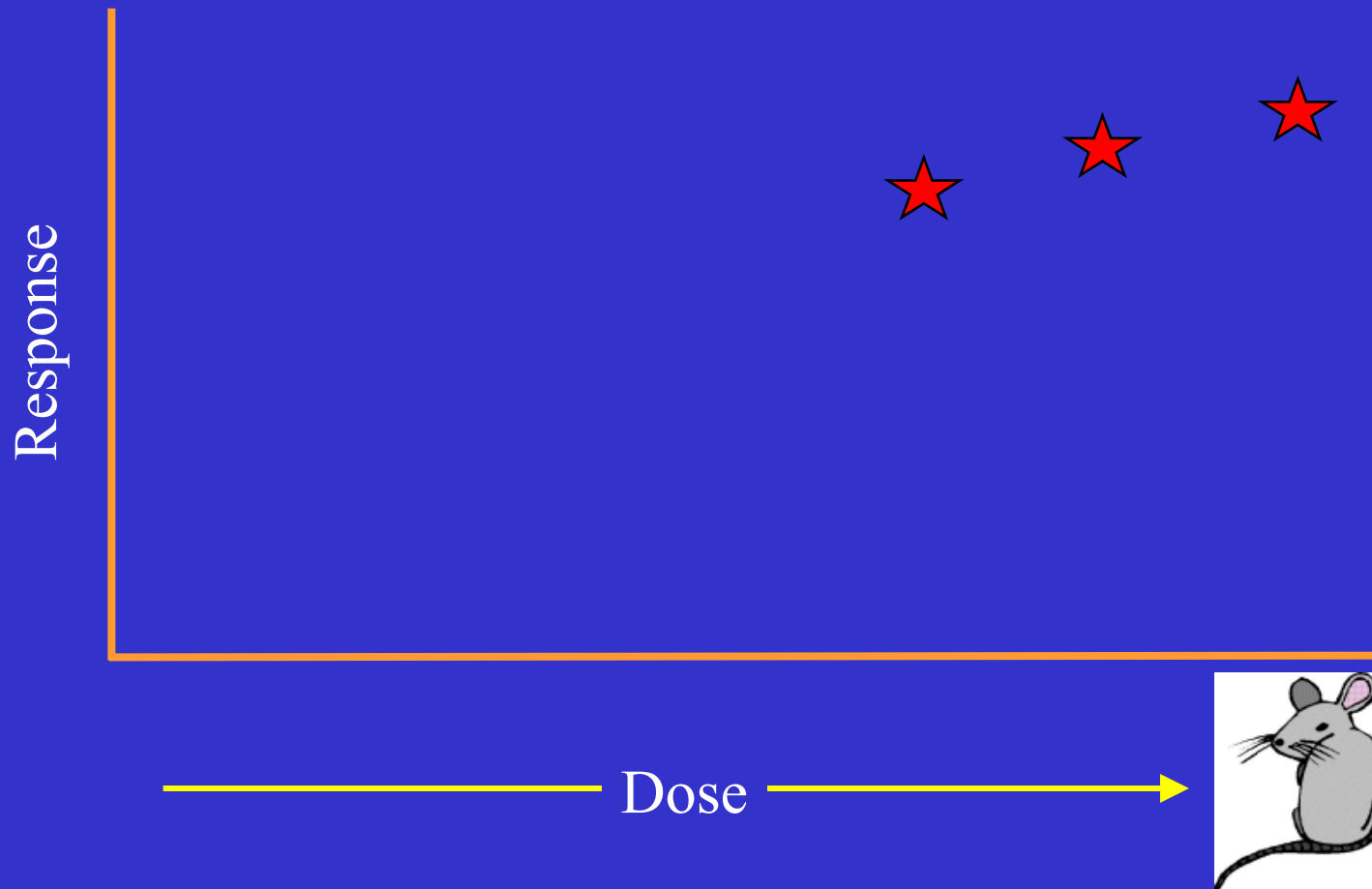
- This presentation may not reflect official policy of the US. EPA.

Outline

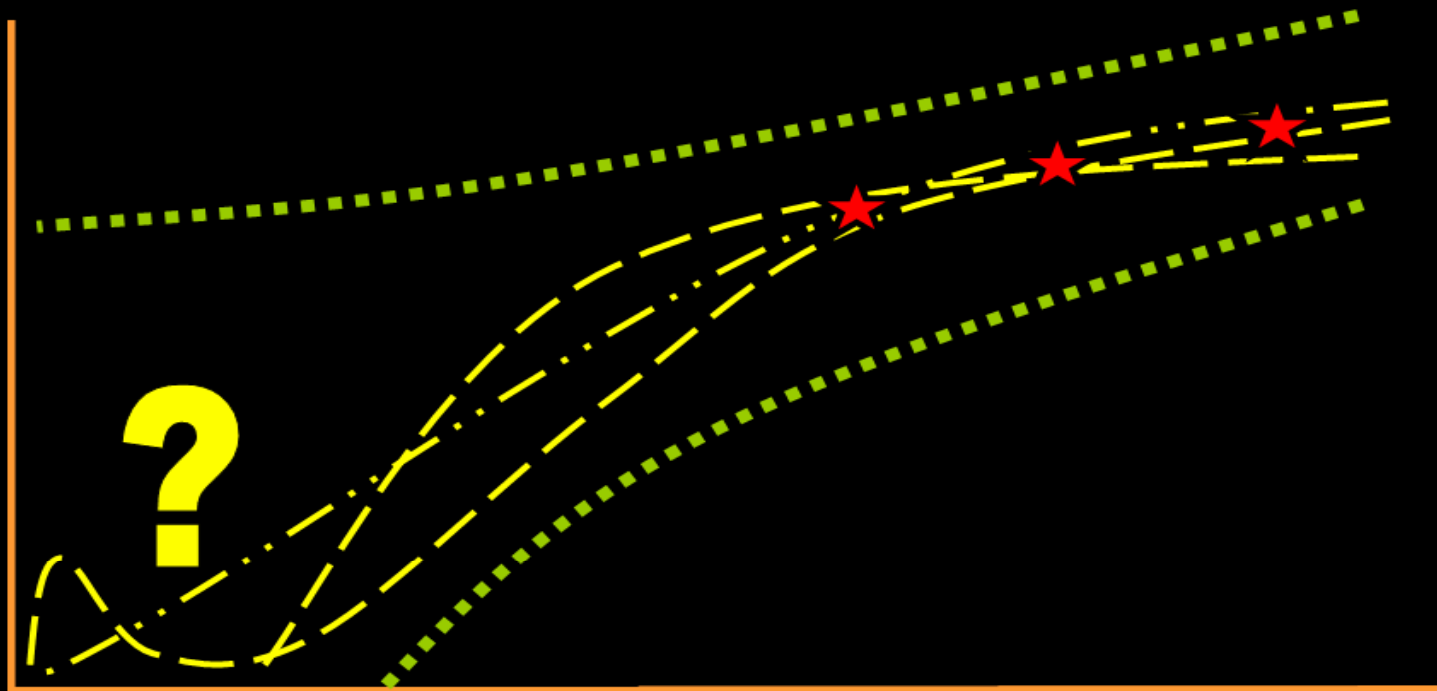
- Biological mechanisms of dose-response and risk assessment
- Computational systems biology
- Example and technical challenges
- Regulatory acceptance

*Biological mechanisms of dose-response
and risk assessment*

Typical high dose rodent data – what do they tell us?



Response

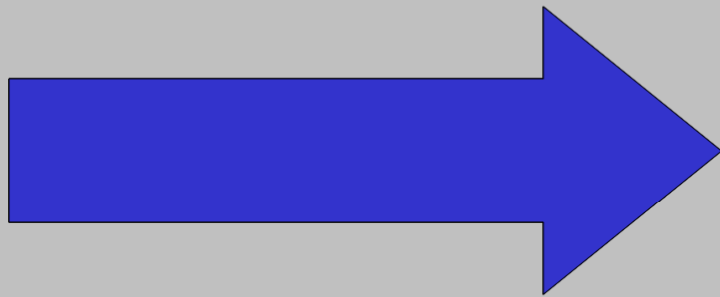


Dose

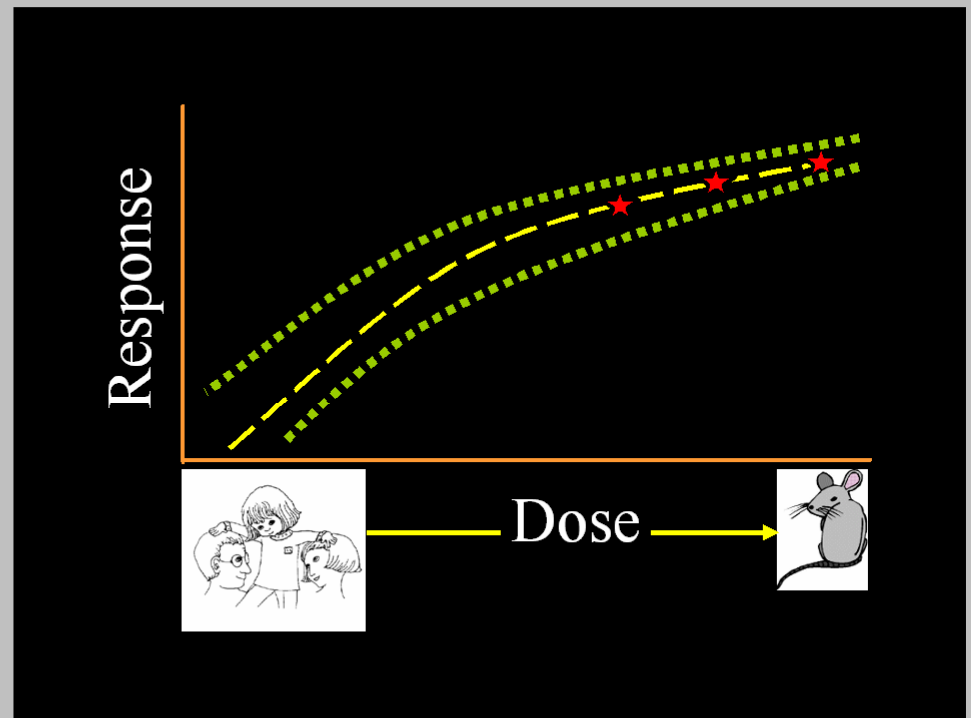


The problem

Mode-of-action analysis

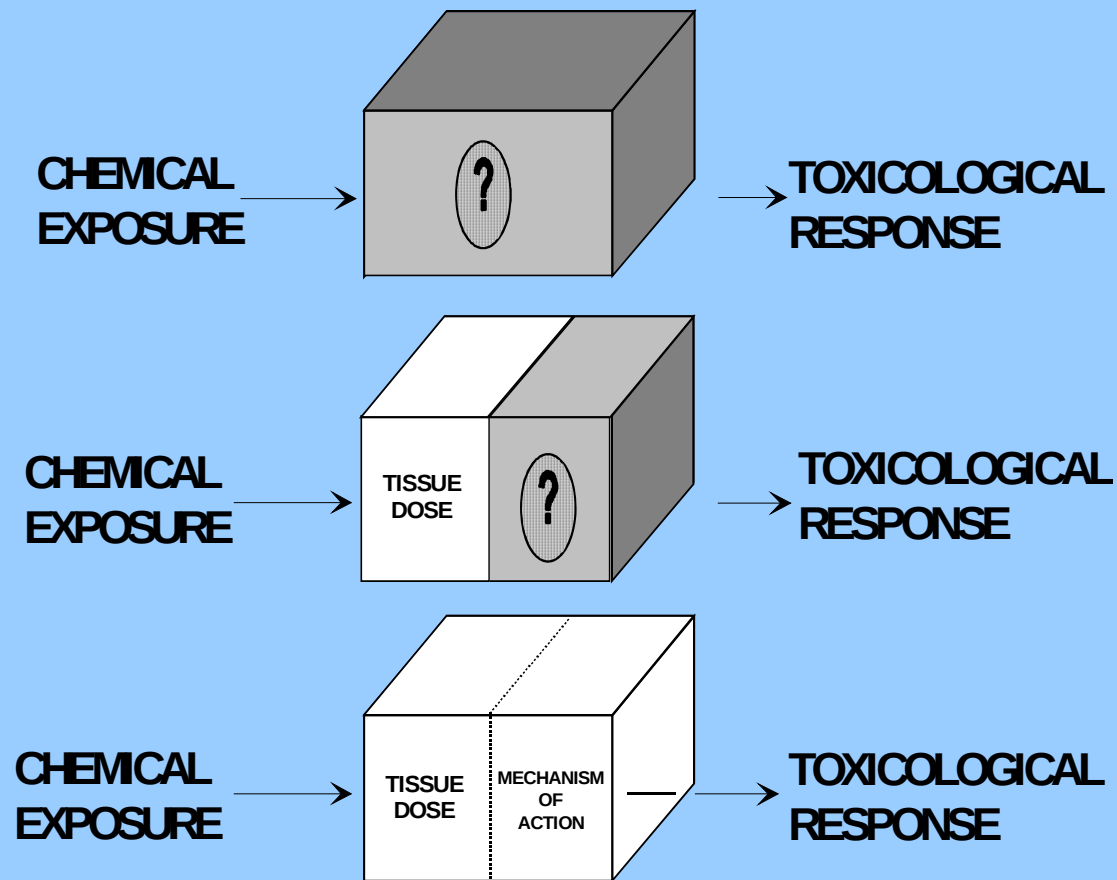


Biologically-based
computational modeling



The solution

Partition the problem into manageable parts



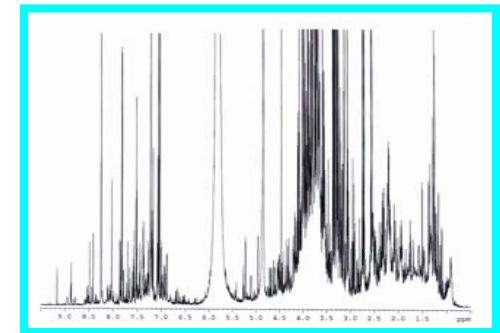
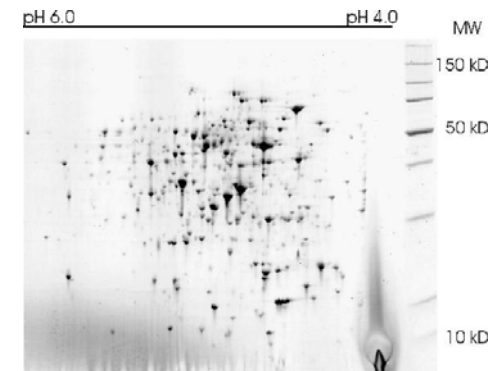
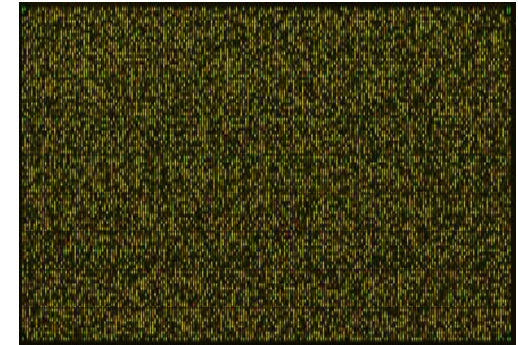
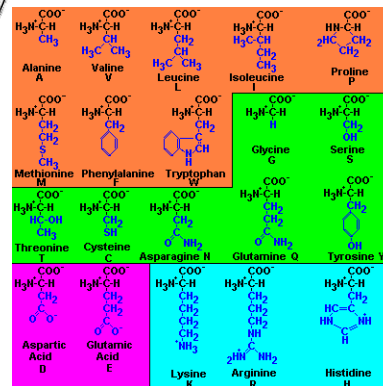
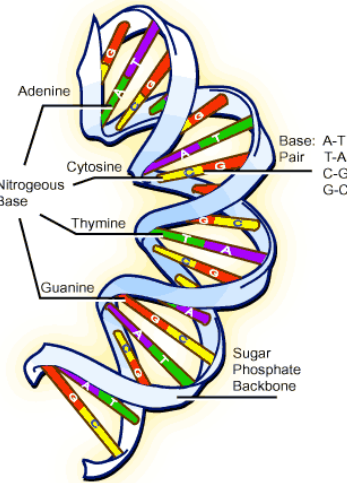
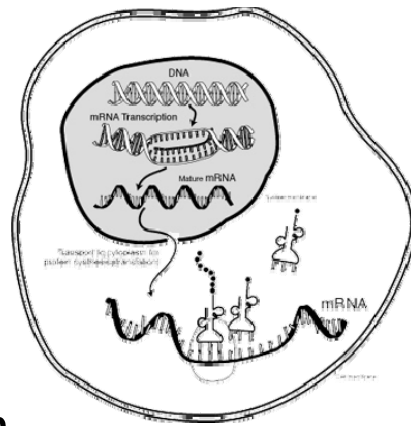
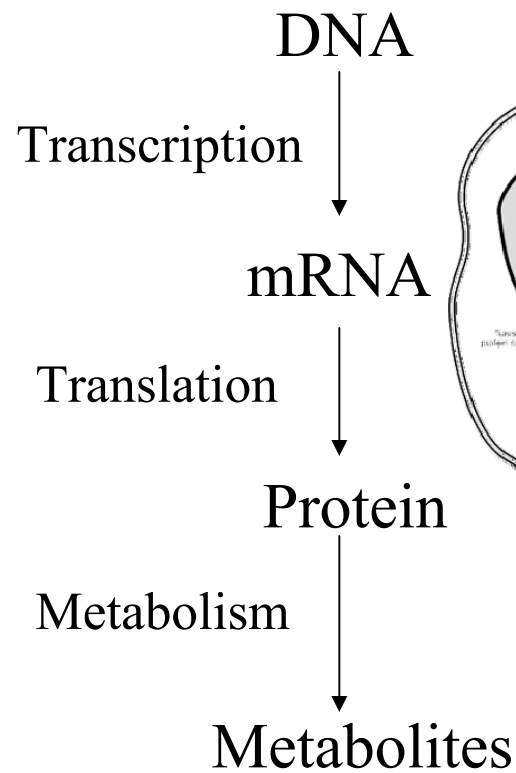
Motivations

- Widespread recognition that chemical-specific high-to-low dose extrapolation may differ from default approaches.
- Concern that some high dose mechanisms may not be relevant.
- Need to protect the public health.
- Need to avoid unnecessary loss of access to useful materials.
- Need to do *good science* in support of human health risk assessment.

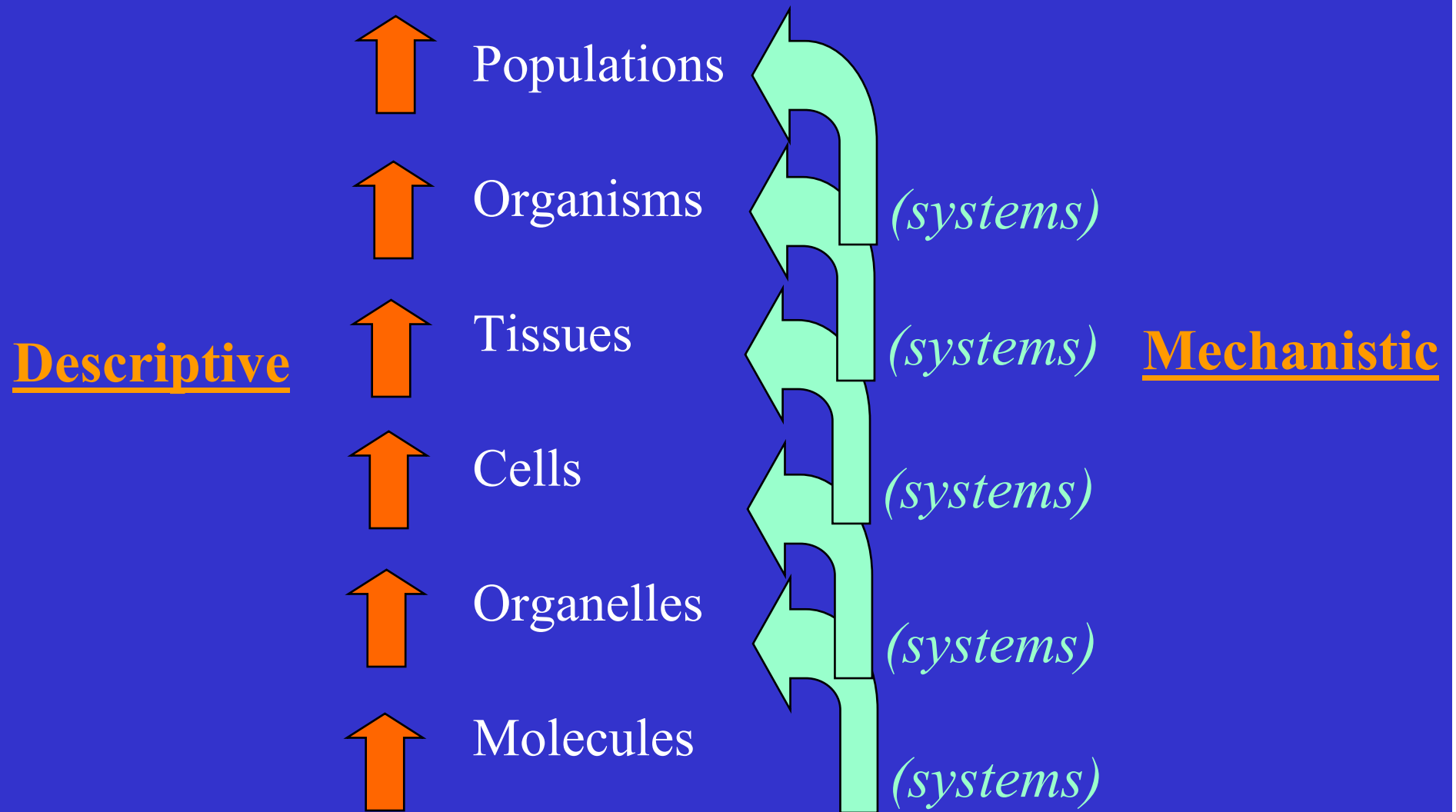
Computational systems biology

Enabling (“Omic”) Technologies

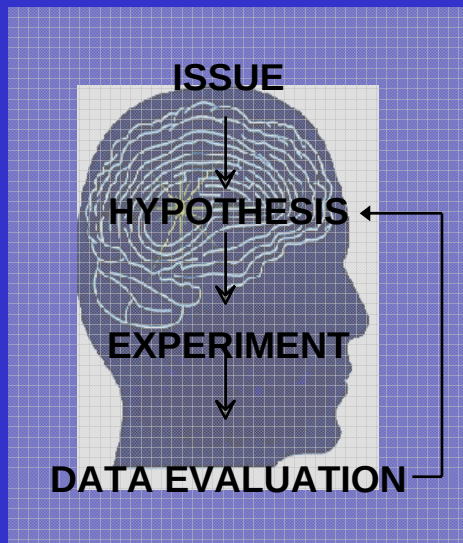
Cell Biology



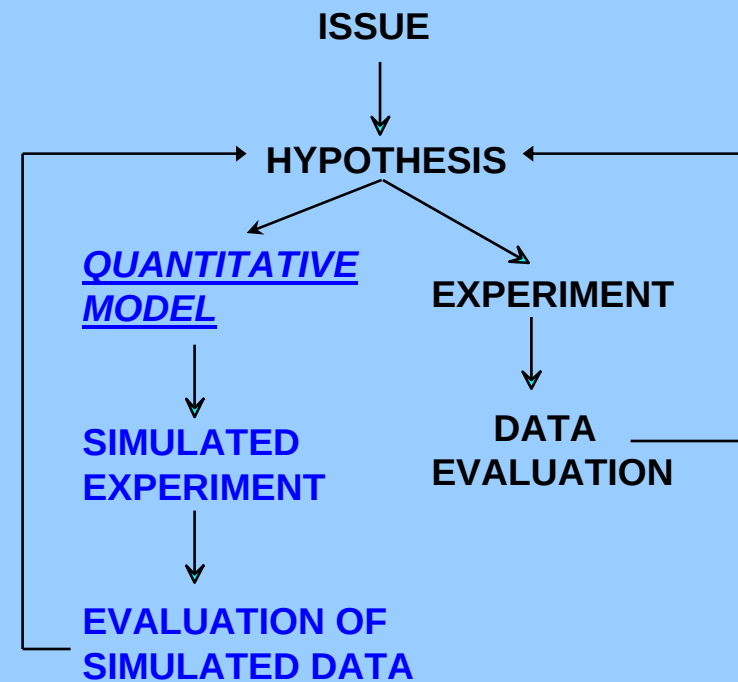
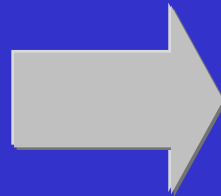
Systems biology



Computational modeling as an adjunct to laboratory research

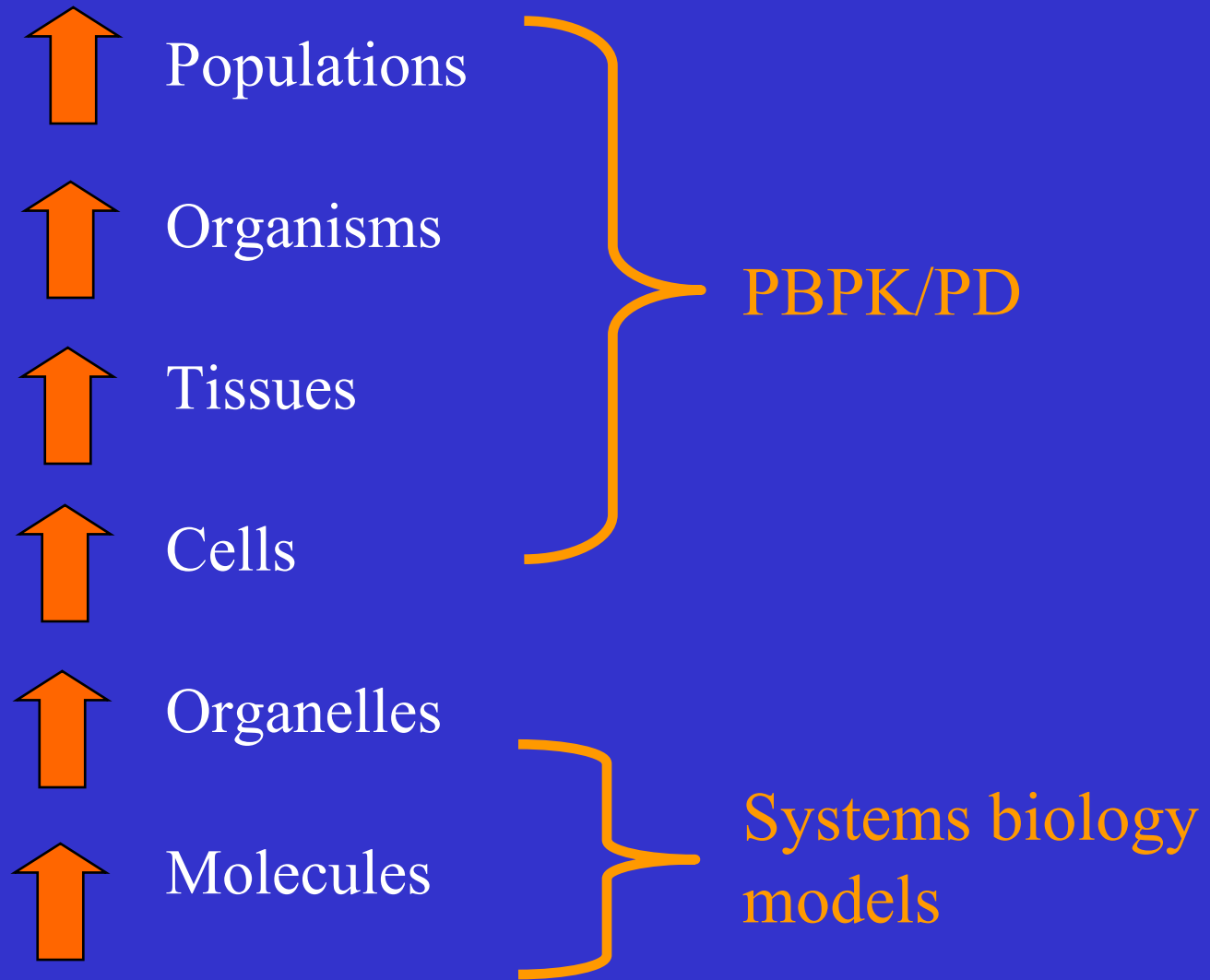


(Intuitive modeling)



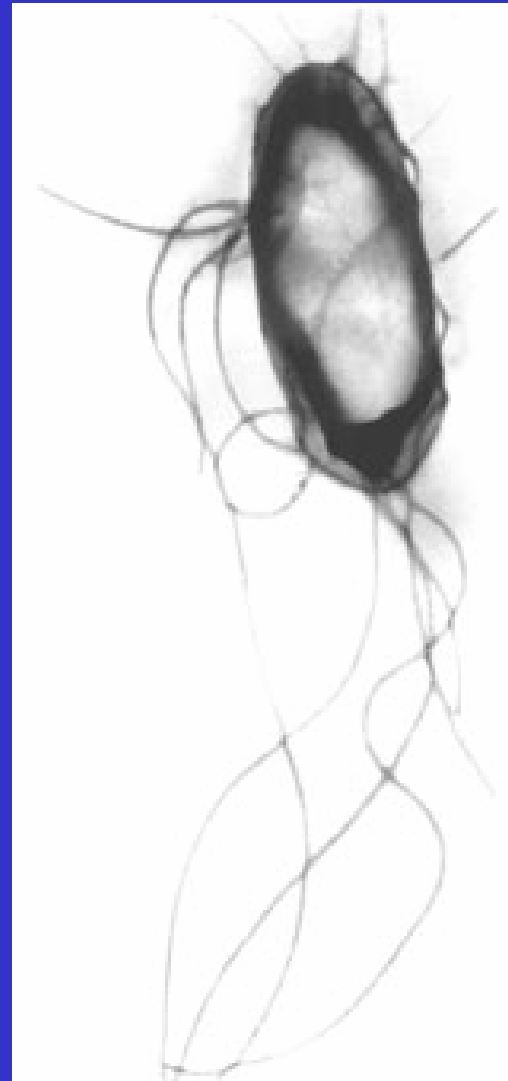
(Formal + intuitive modeling)

The state-of-the-art



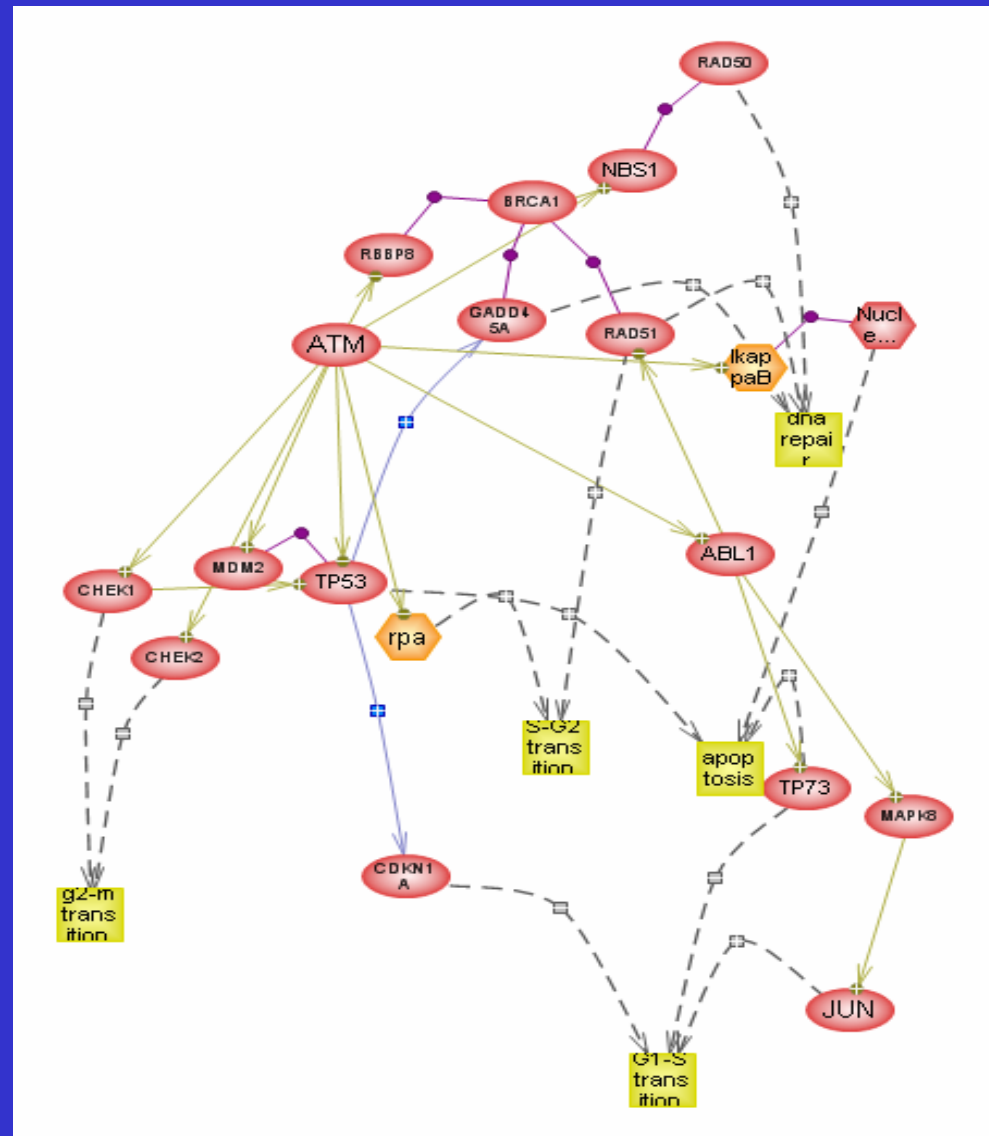
International e. coli Alliance

- Goal is to develop a molecular-level computational model of *e. coli*.



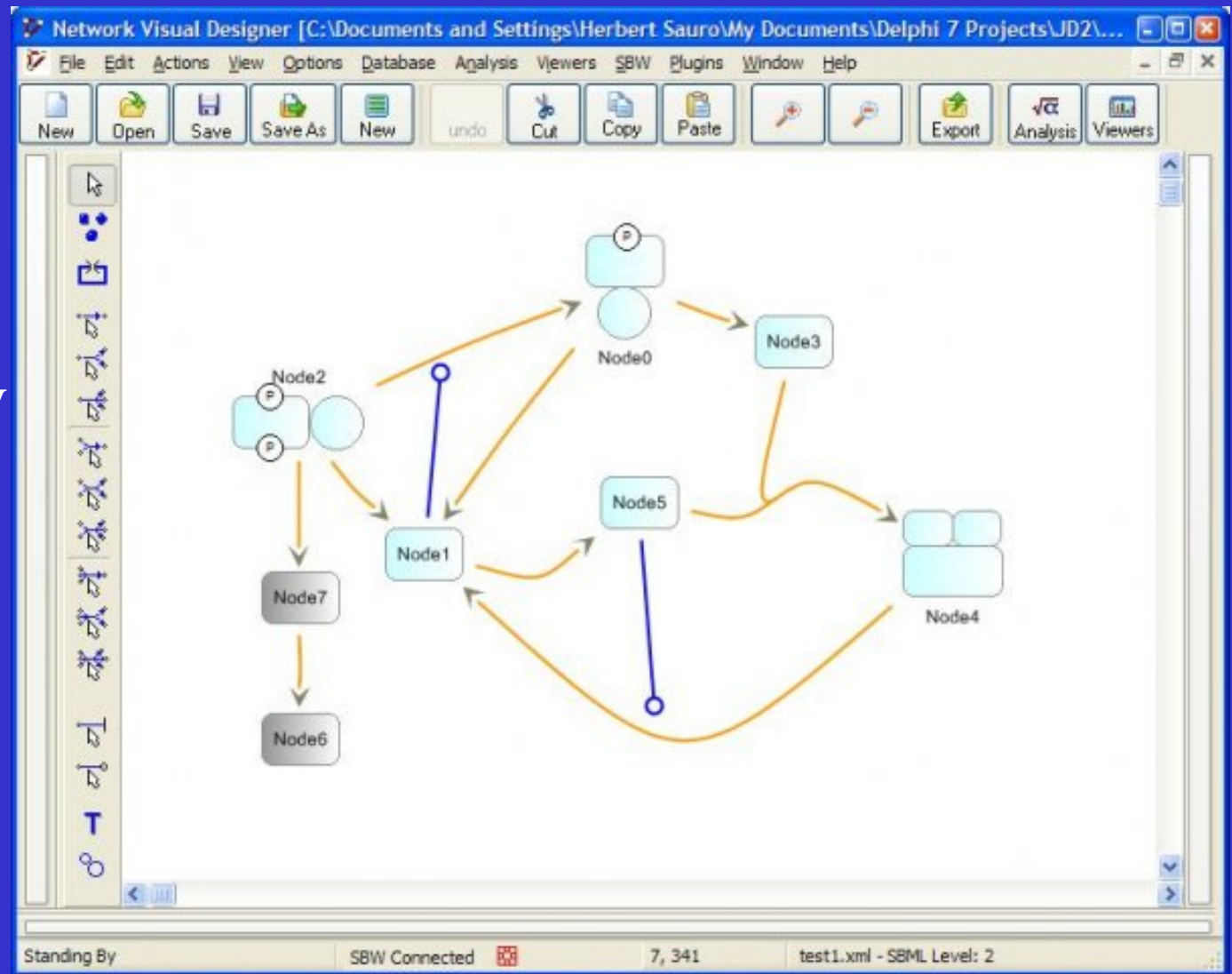
Computational tools

ATM curated
Pathway from
Pathway Assist®



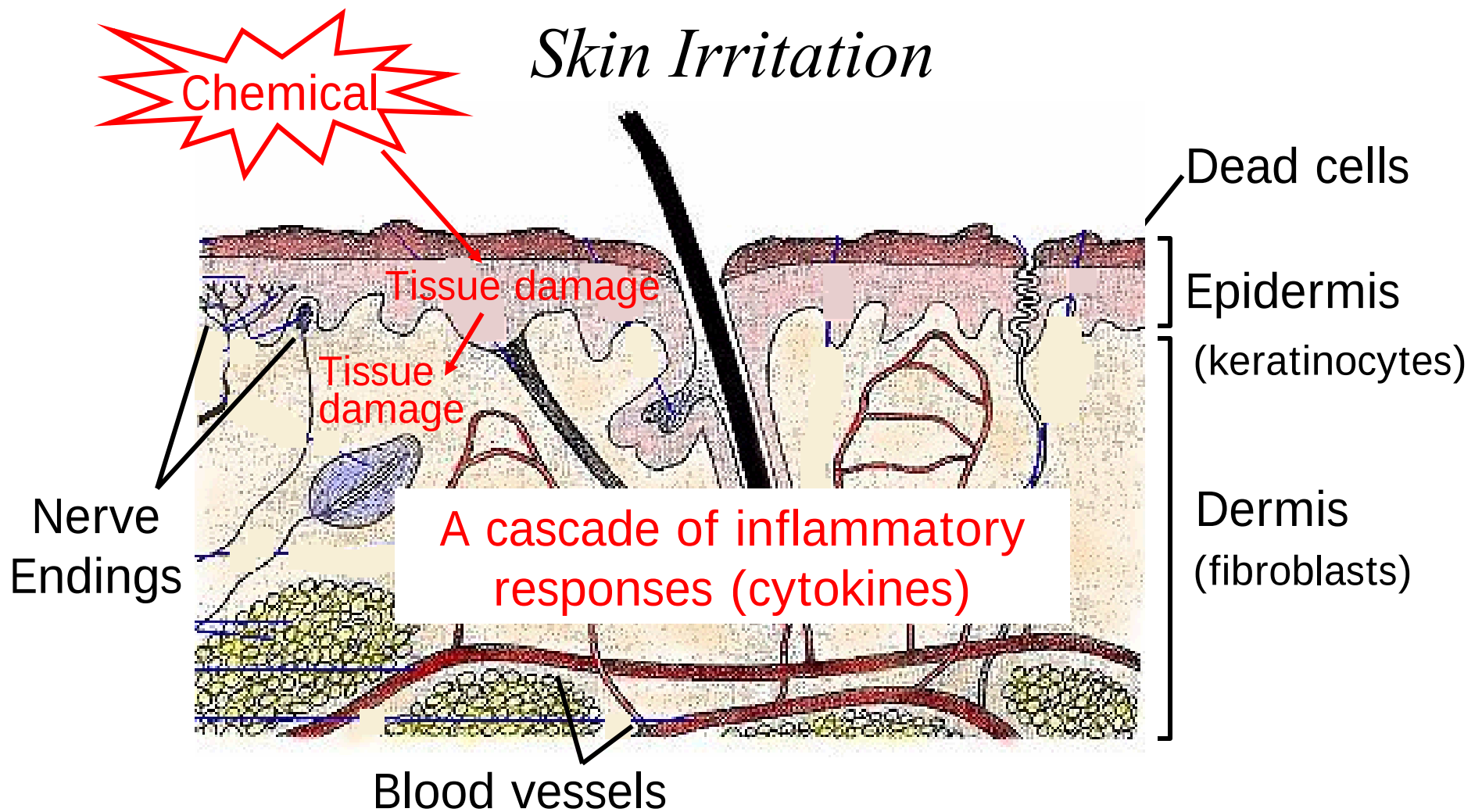
Computational tools

Systems biology
workbench

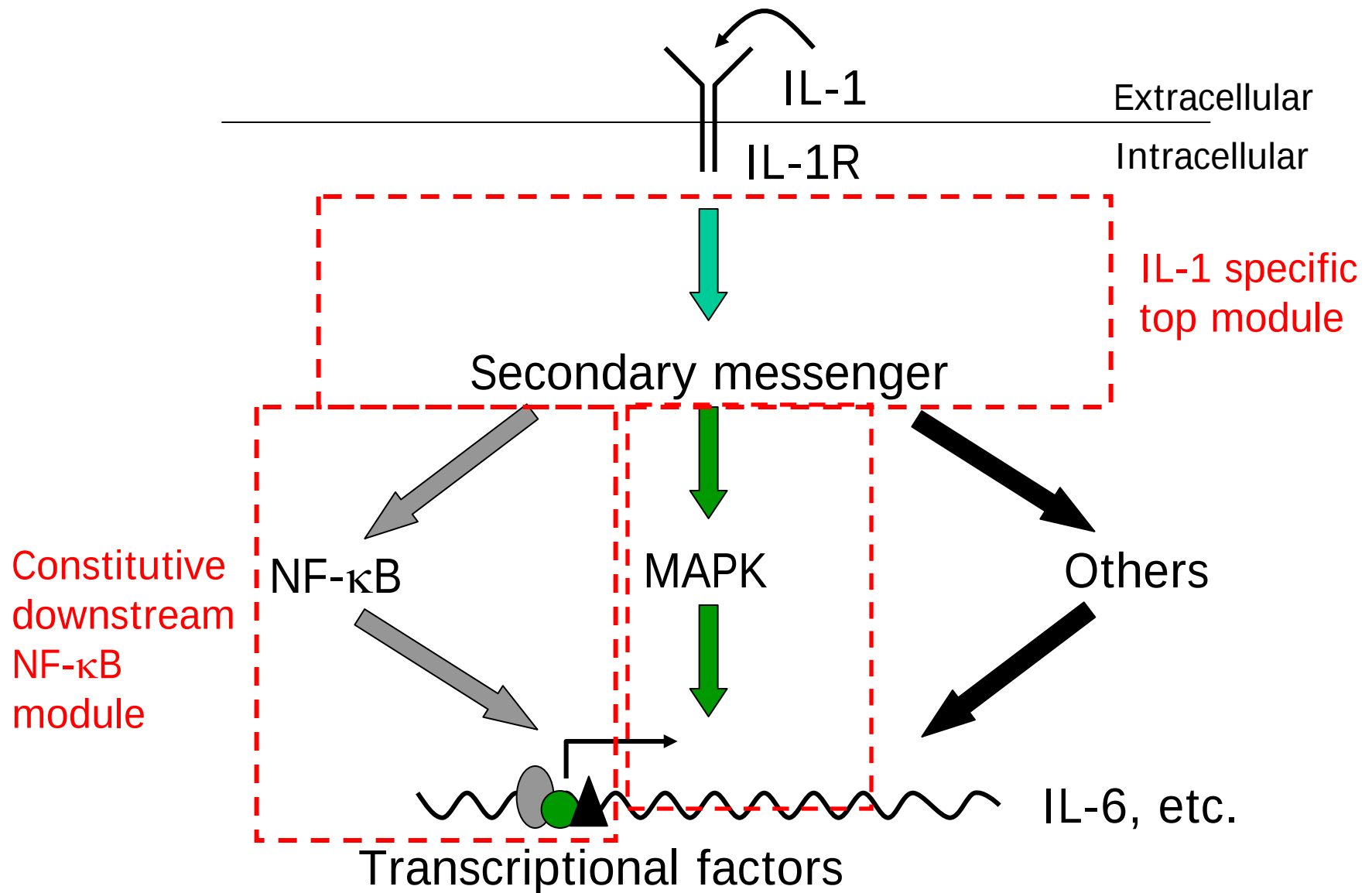


Example and technical challenges

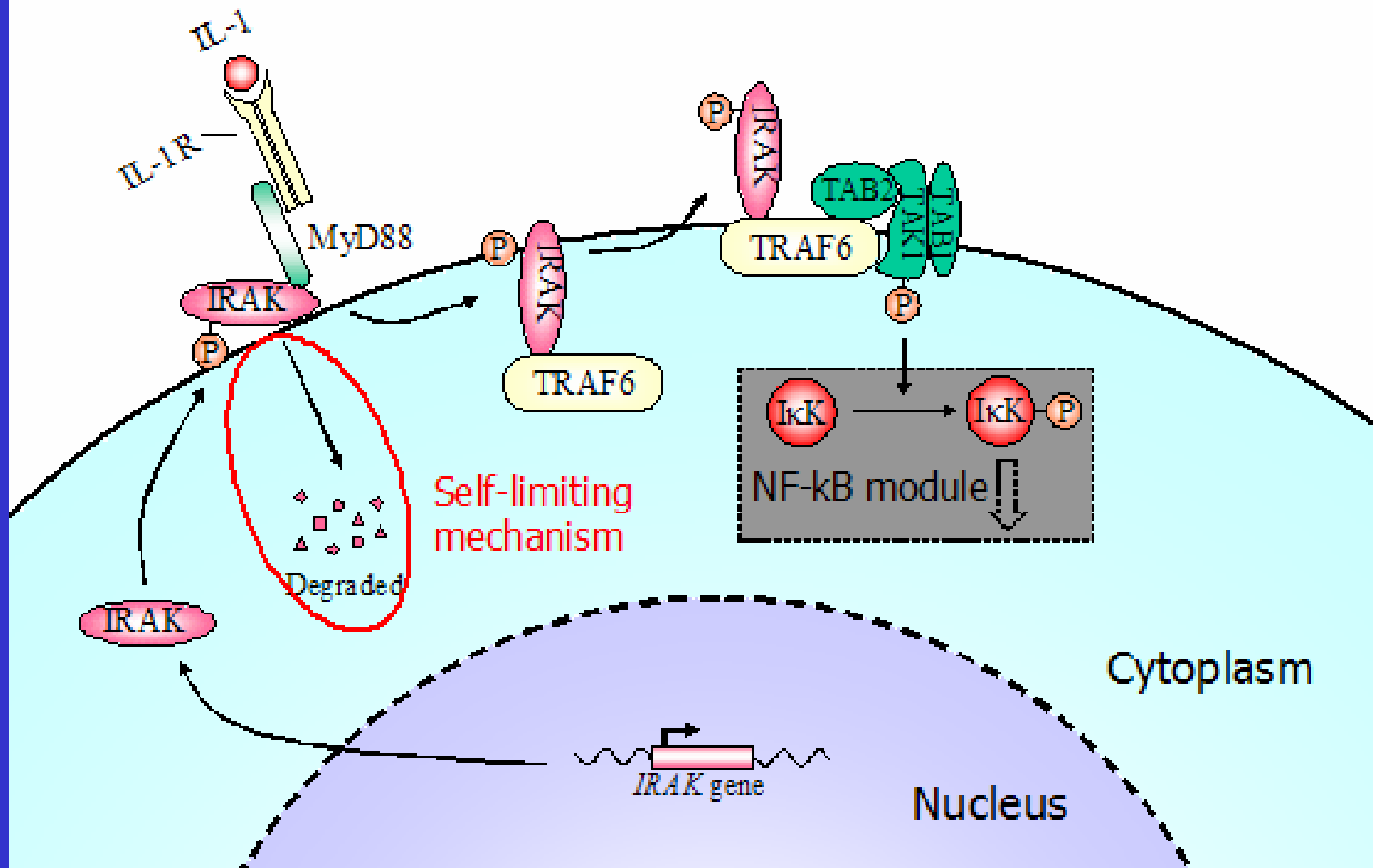
- Skin irritation
 - MAPK, IL-1a, and NF-kB computational “modules”
 - High throughput overexpression data to characterize IL-1a – MAPK interaction with respect to NF-kB



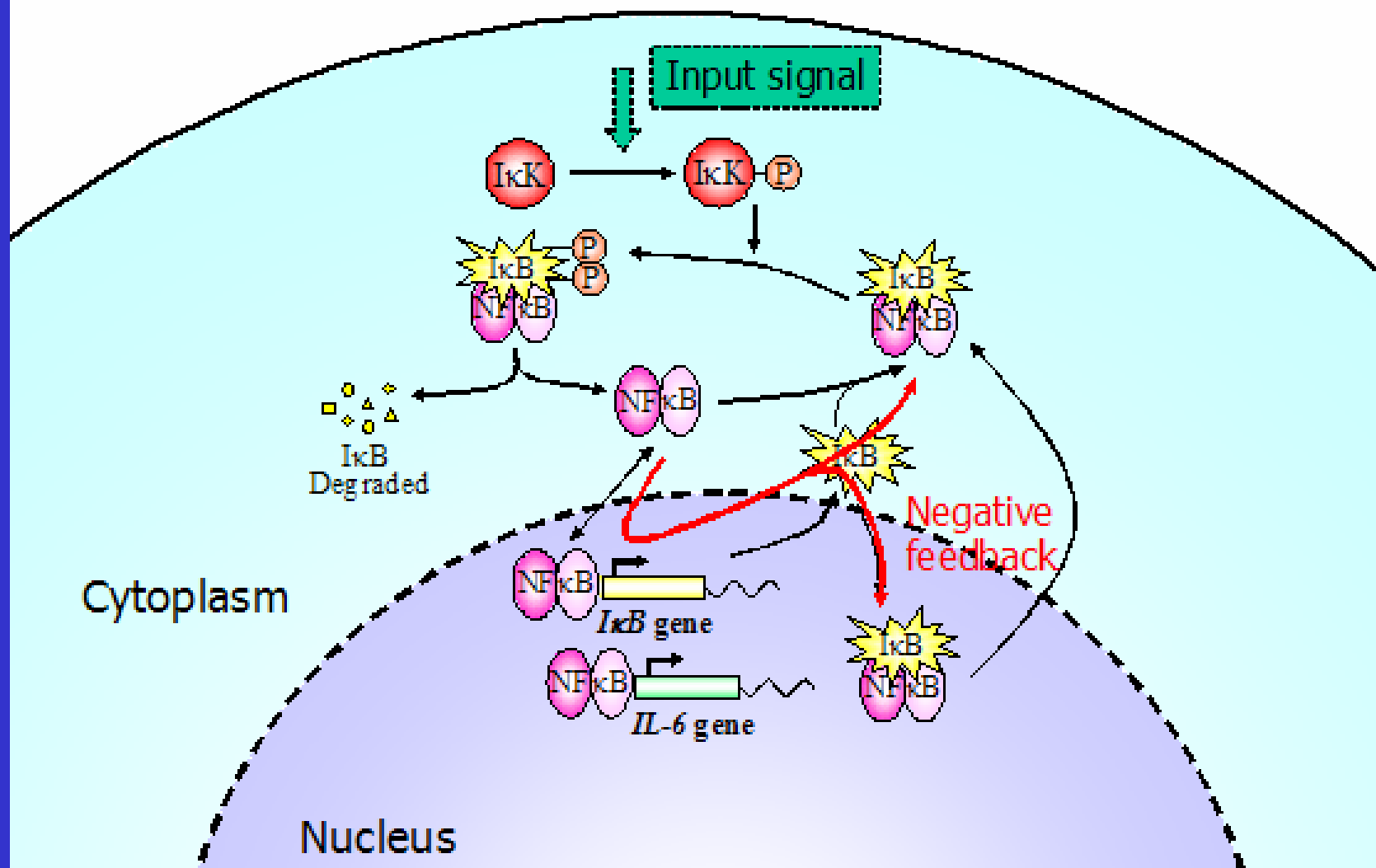
Modular Composition of IL-1 Signaling



Top IL-1 Signaling Module

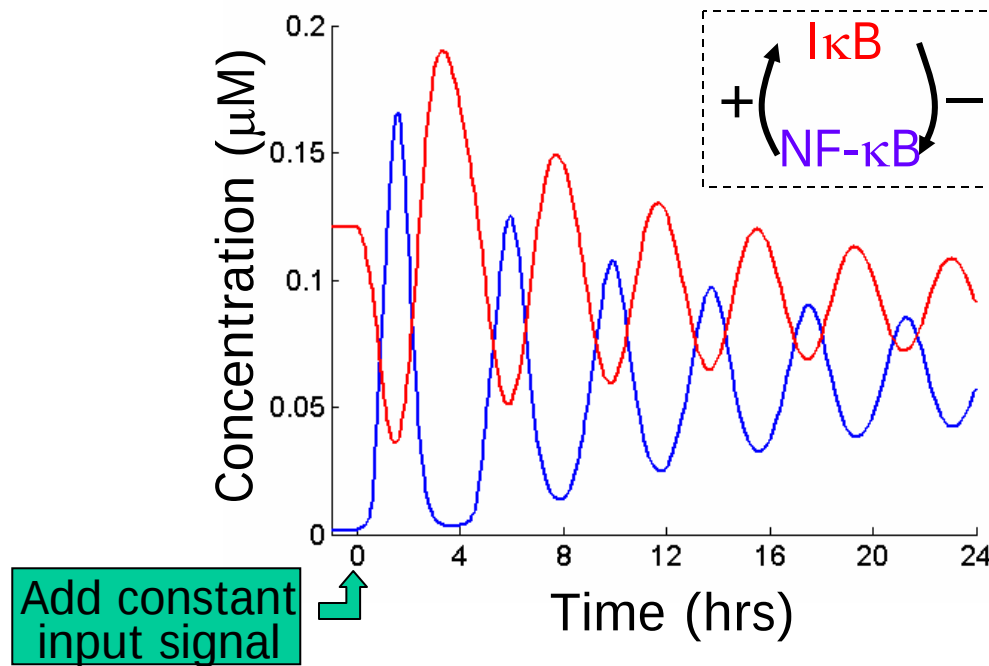


Constitutive NF- κ B Signaling Module



NF- κ B Module Simulation

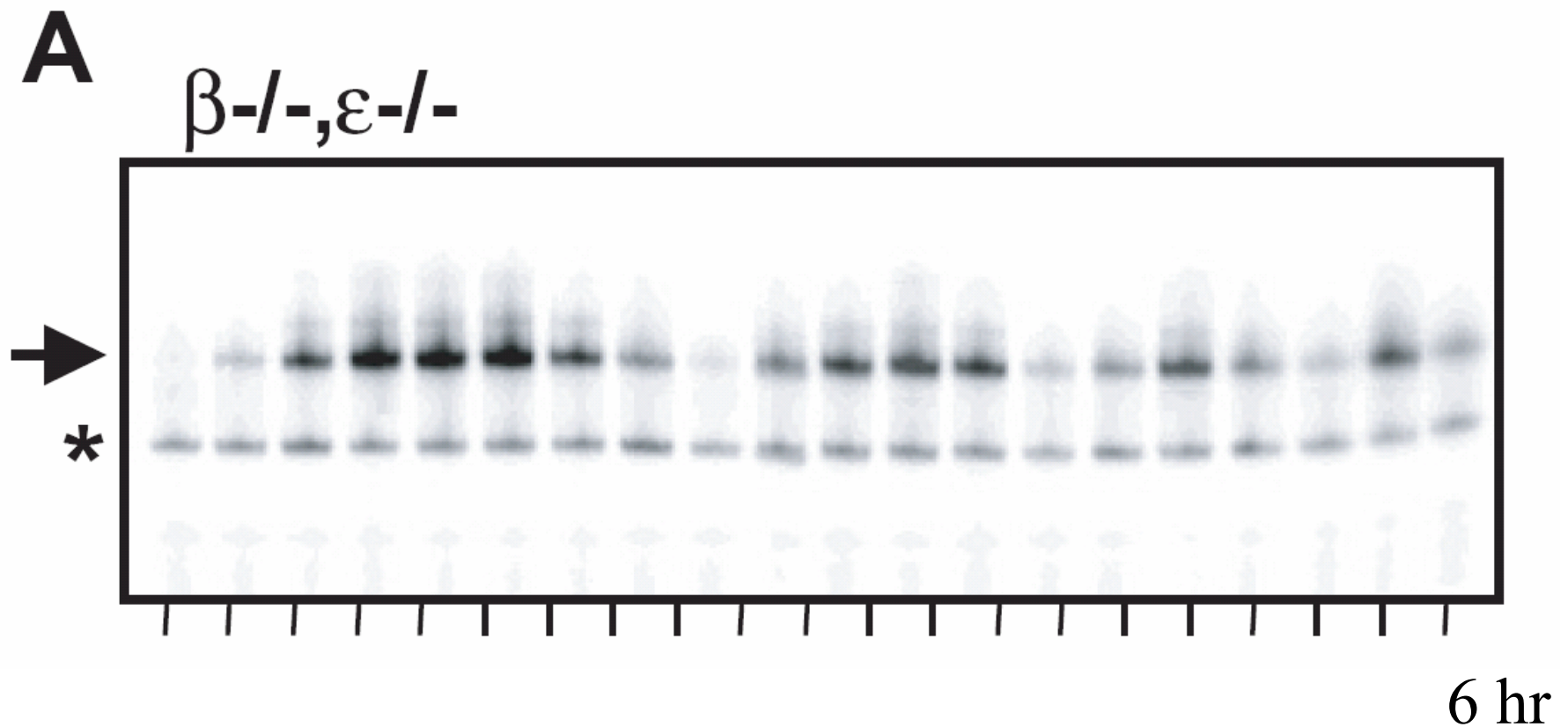
- Parameters from existing NF- κ B model (Hoffmann et al., 2002) and refined to fit experimental data in literature



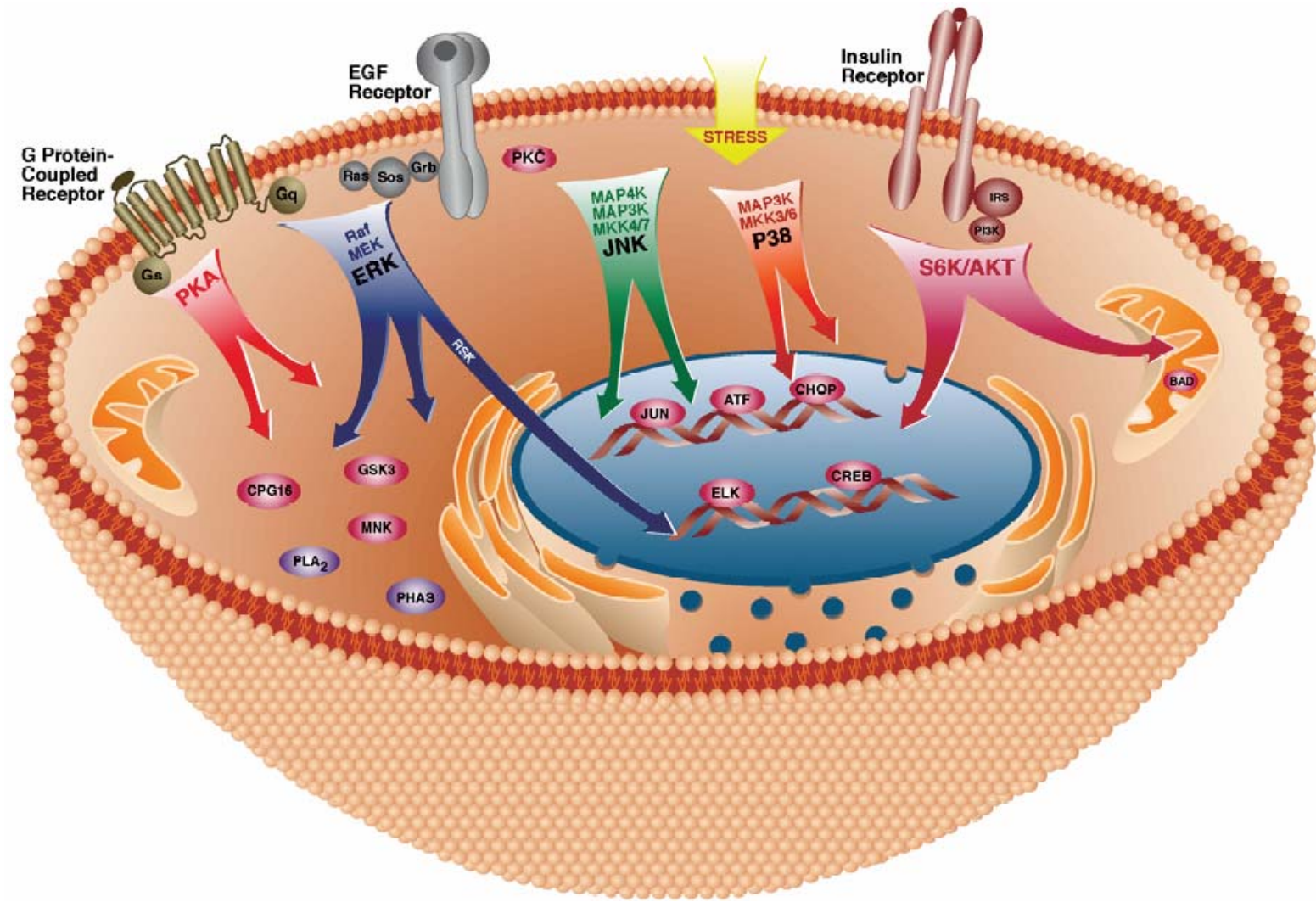
The IB–NF- κ B Signaling Module: Temporal Control and Selective Gene Activation

Alexander Hoffmann, Andre Levchenko, Martin L. Scott, David Baltimore

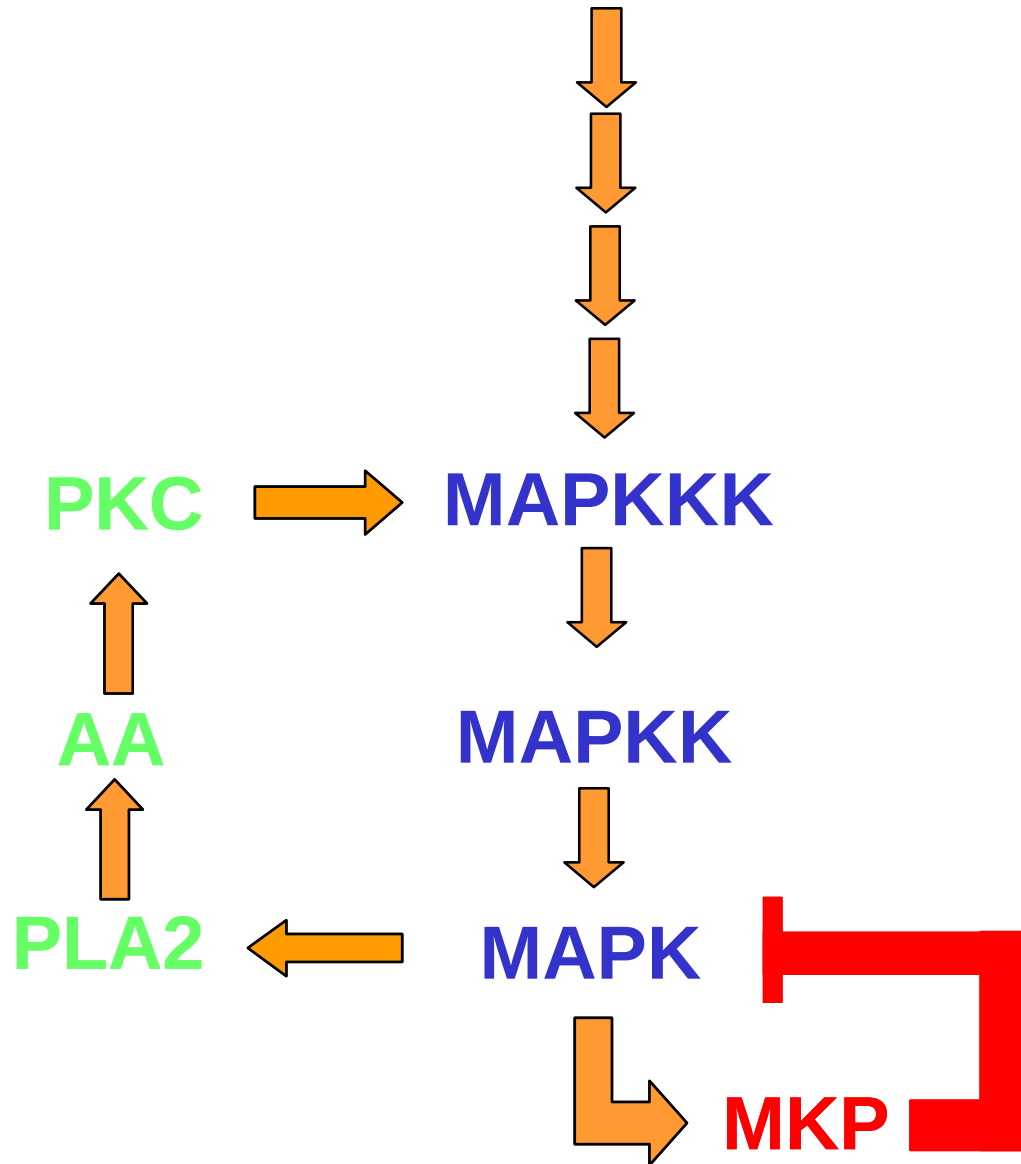
Science 298:1241 – 1245, 2002



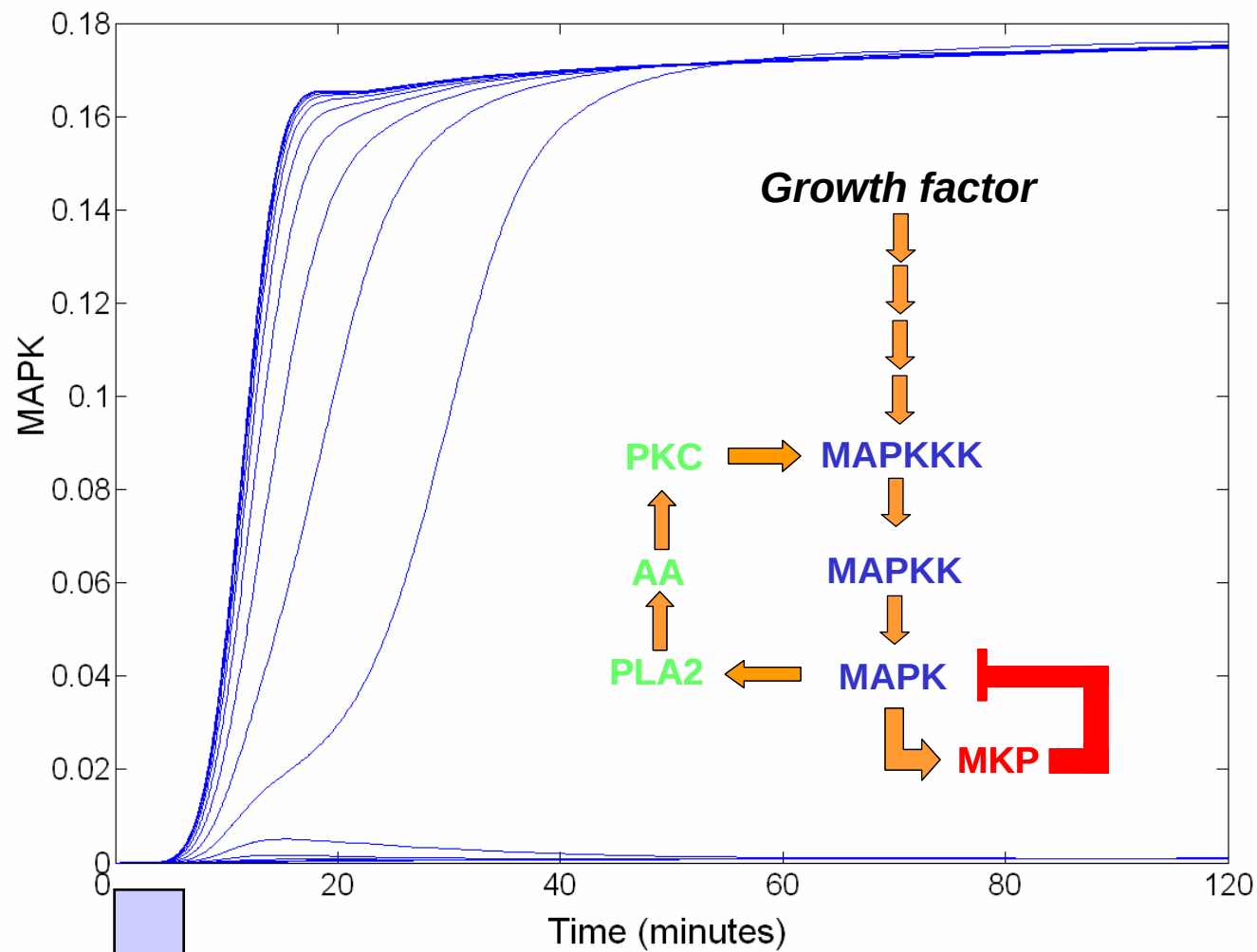
MAPK intracellular signaling cascades



Growth factor

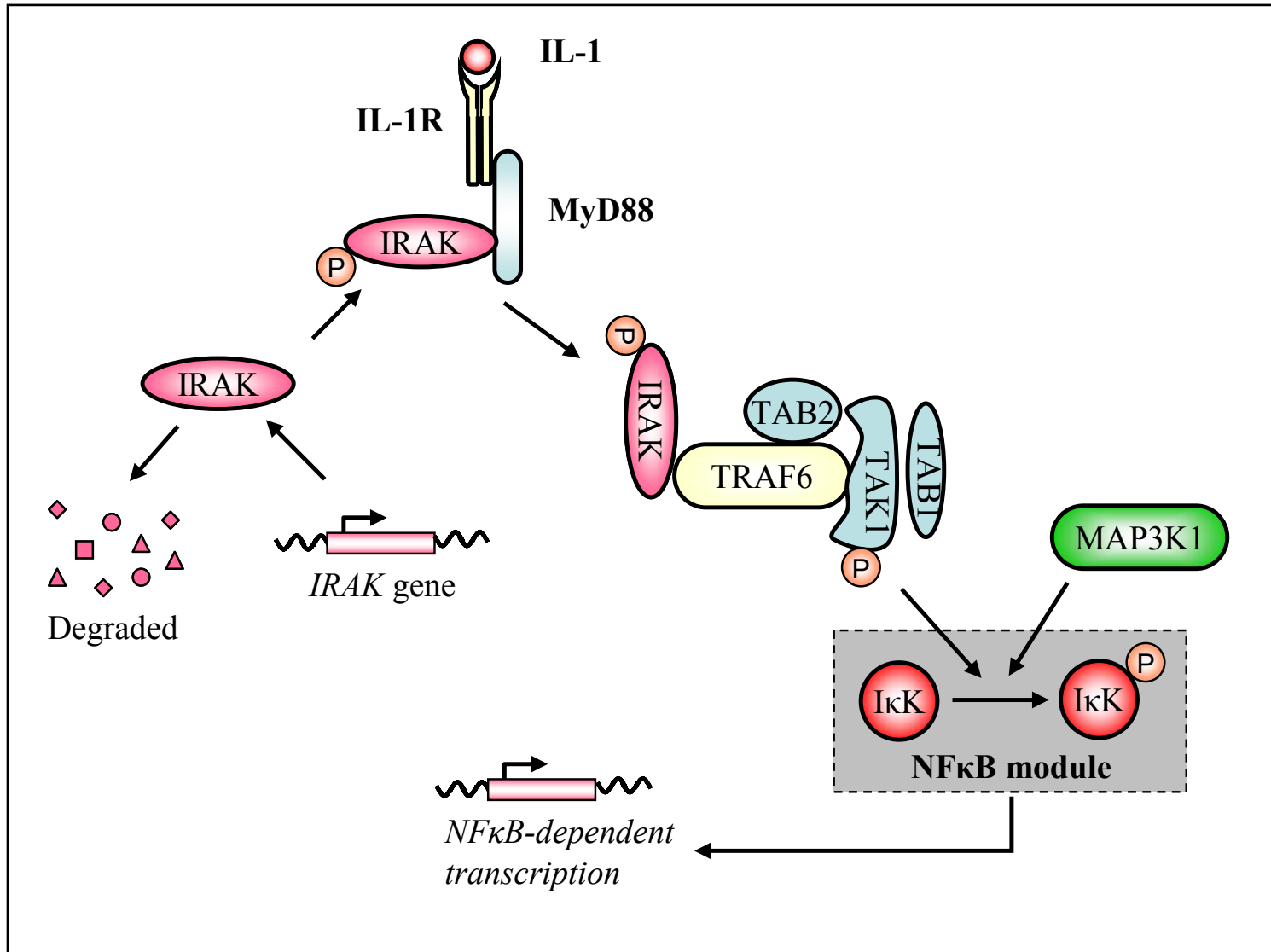


MAPK time-course and bifurcation after a short pulse of PDGF



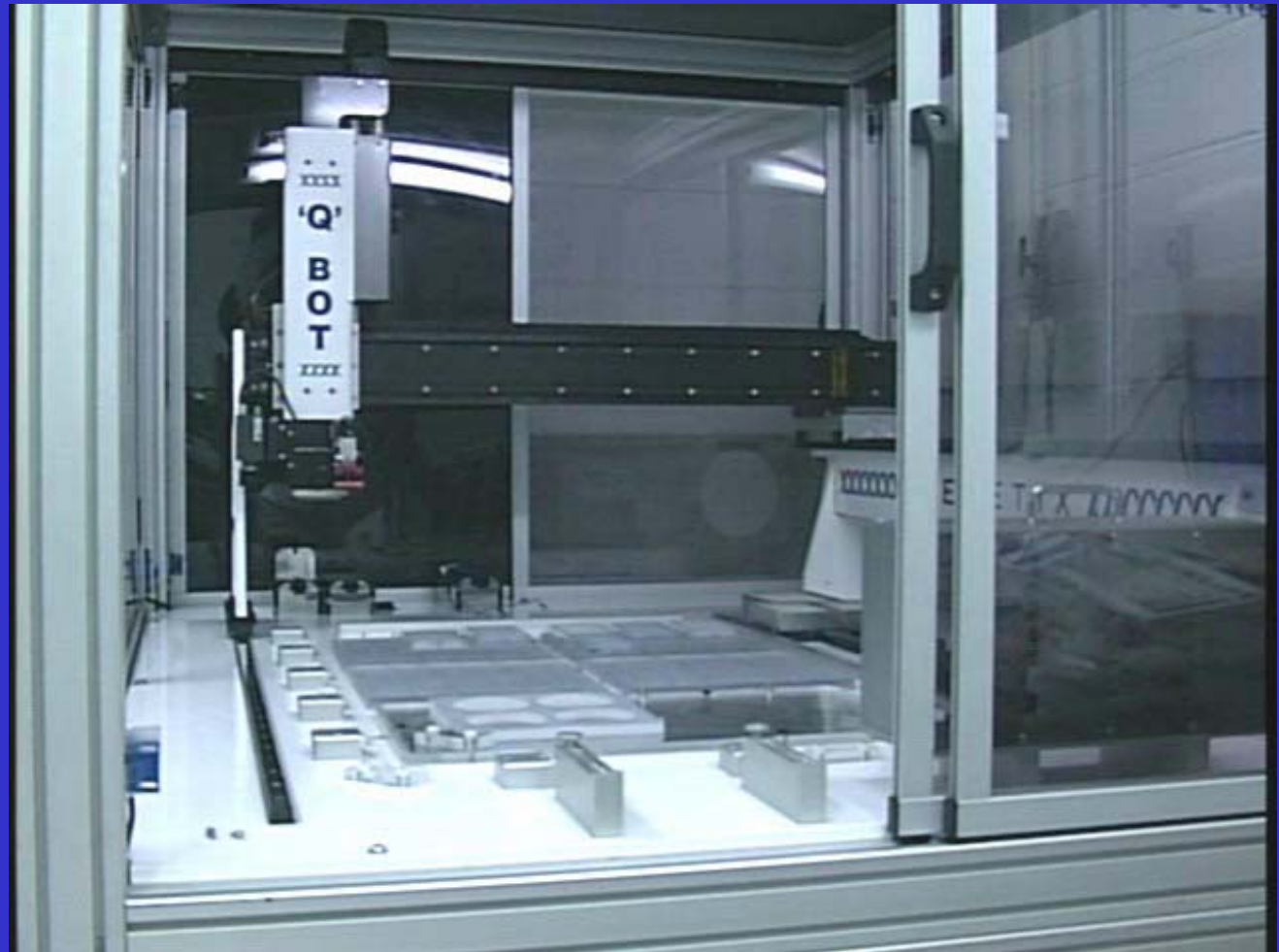
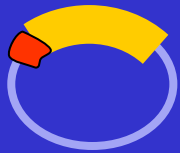
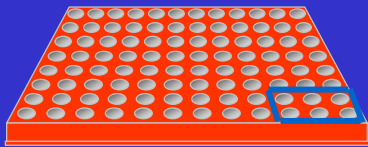
Input pulse

IL-1 MAPK crosstalk and NFκB activation

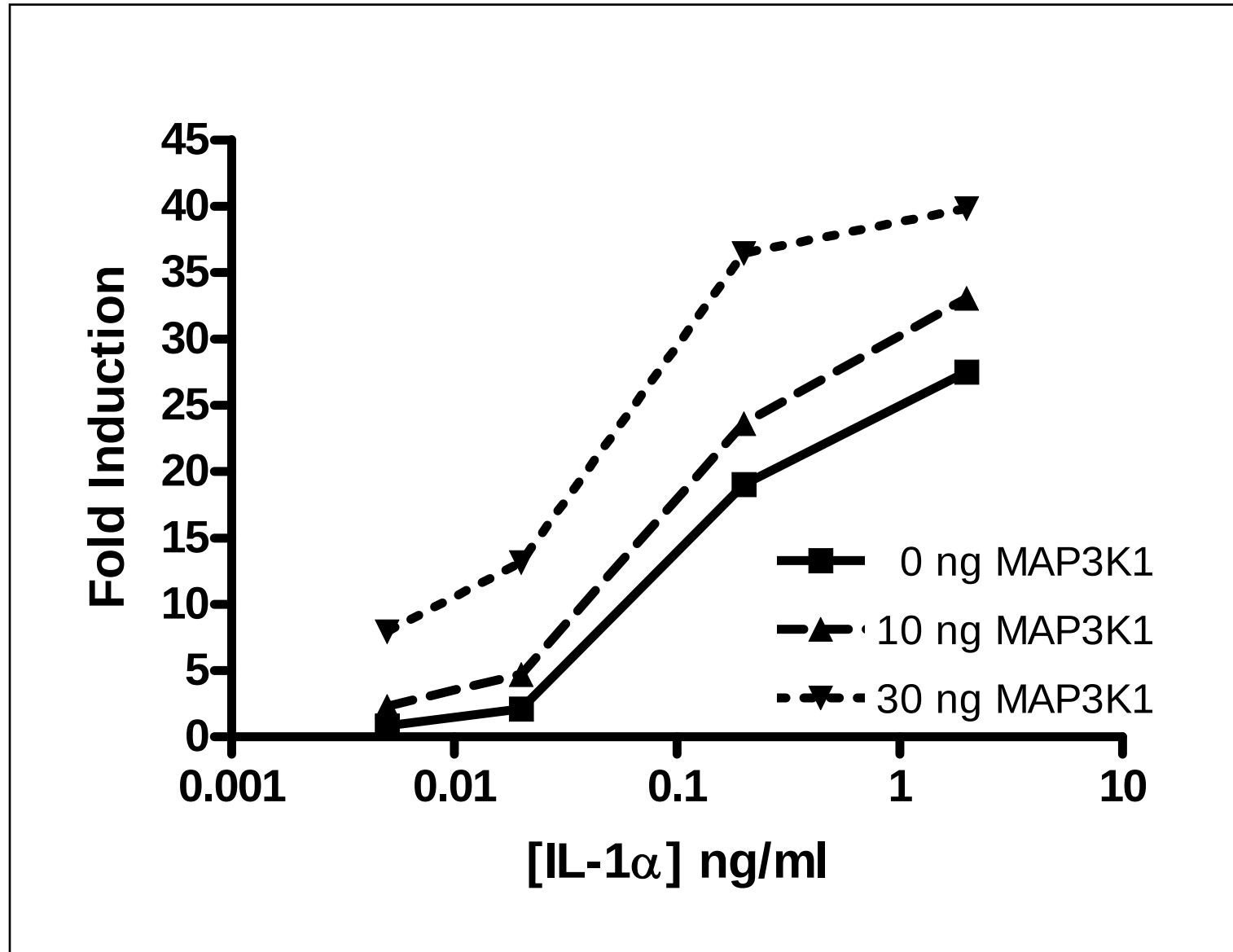


High throughput

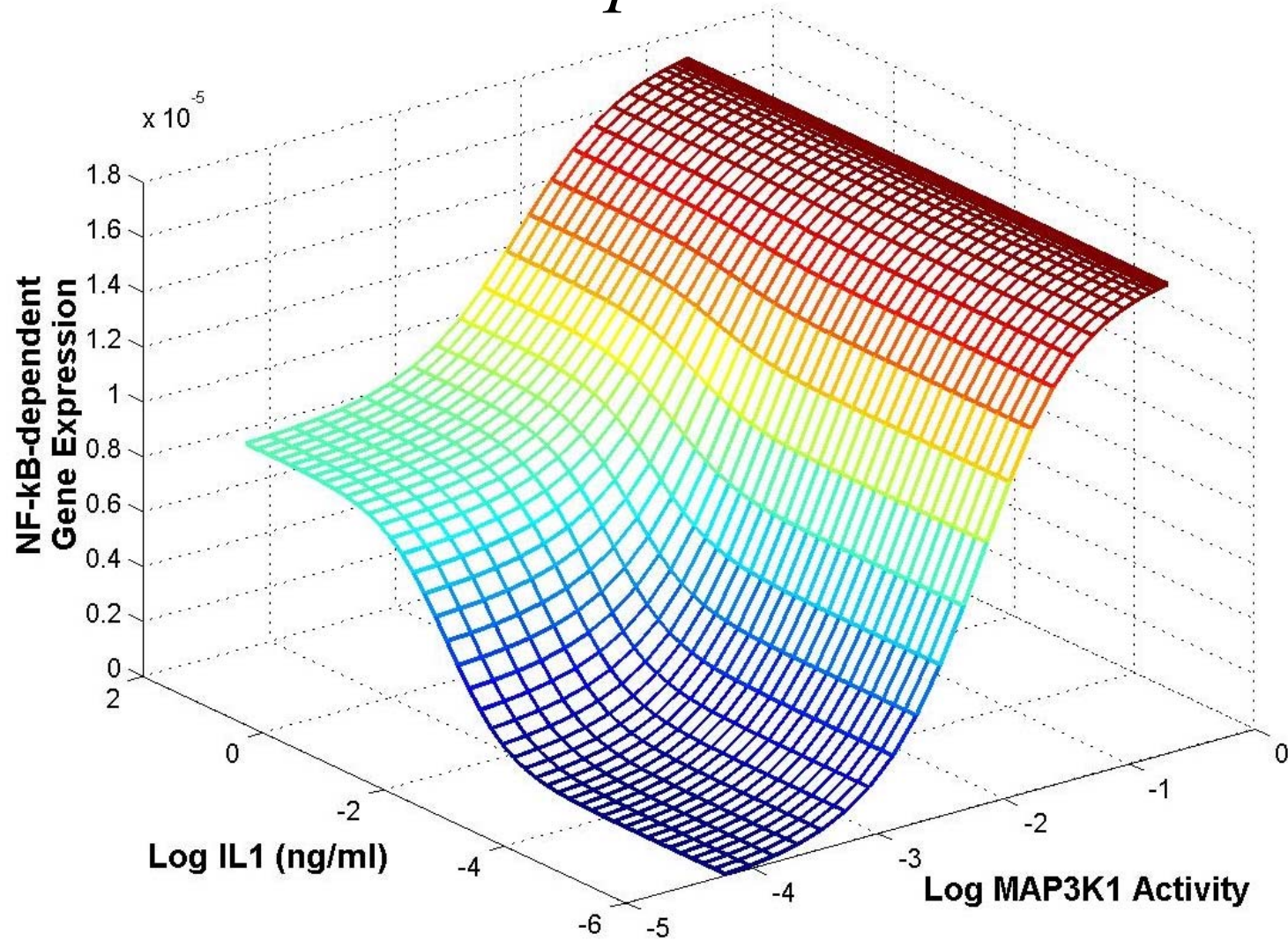
Arrayed, full-length genes
set in 384-well plates



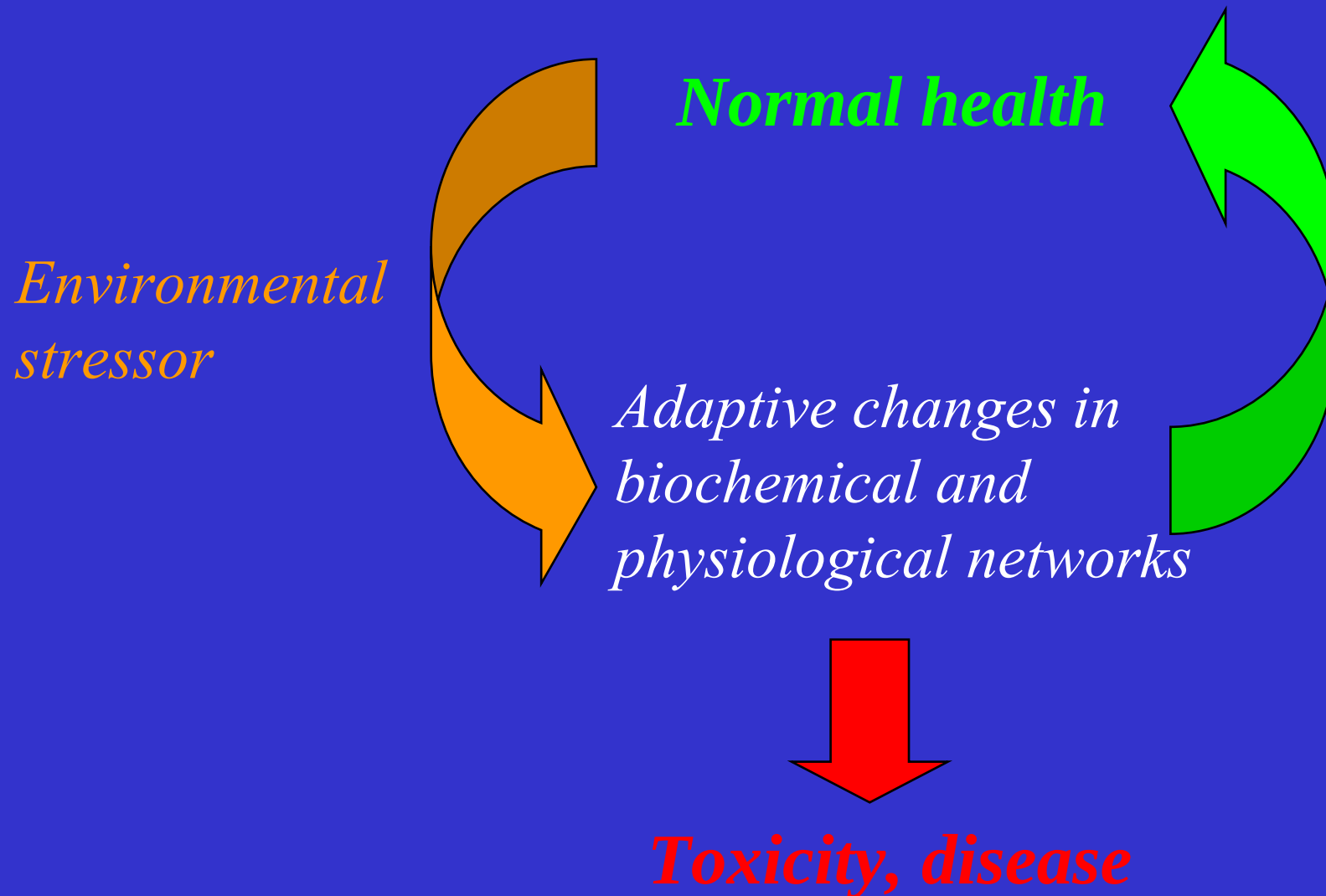
Gain-of-function screen



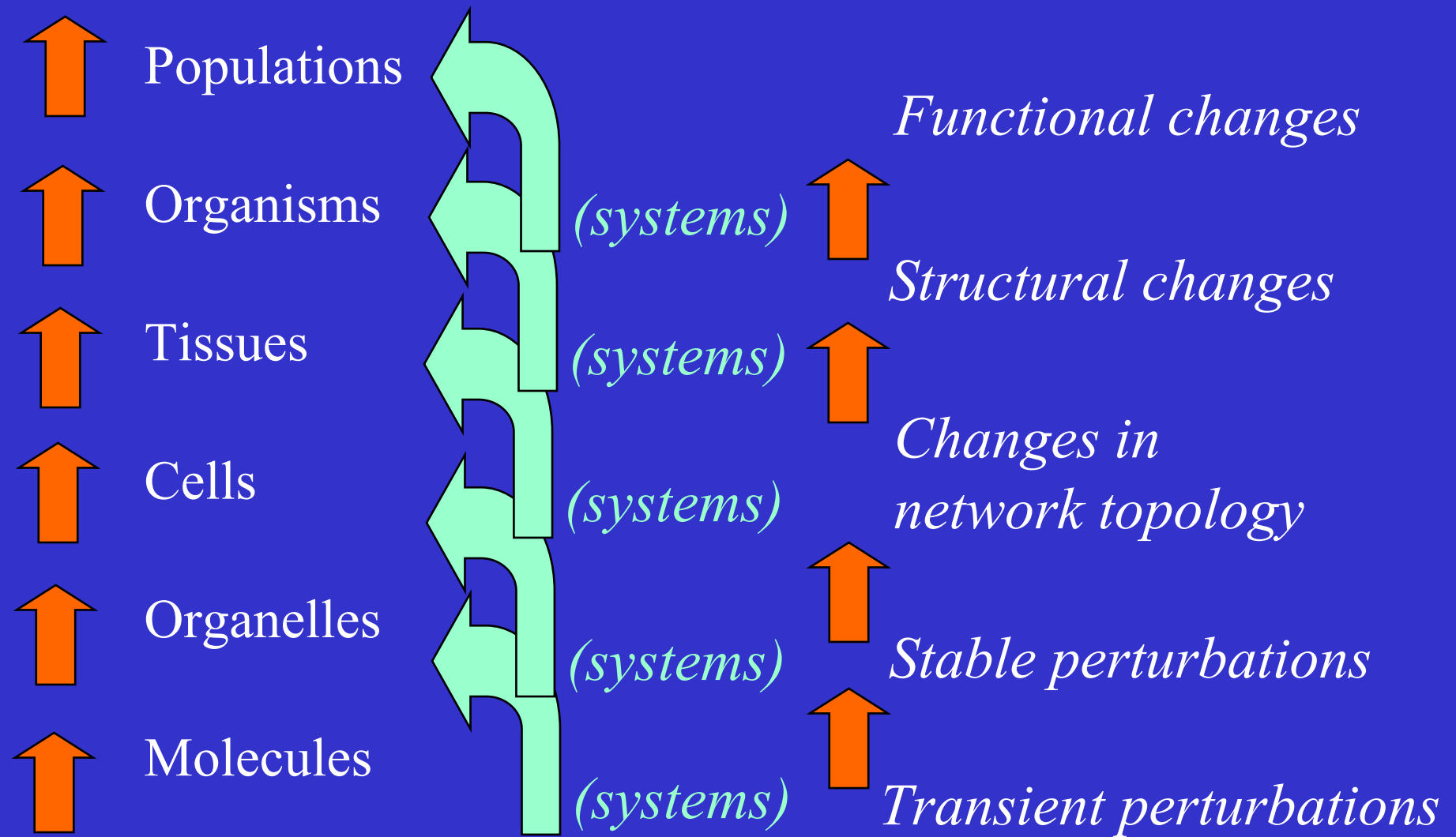
Model prediction



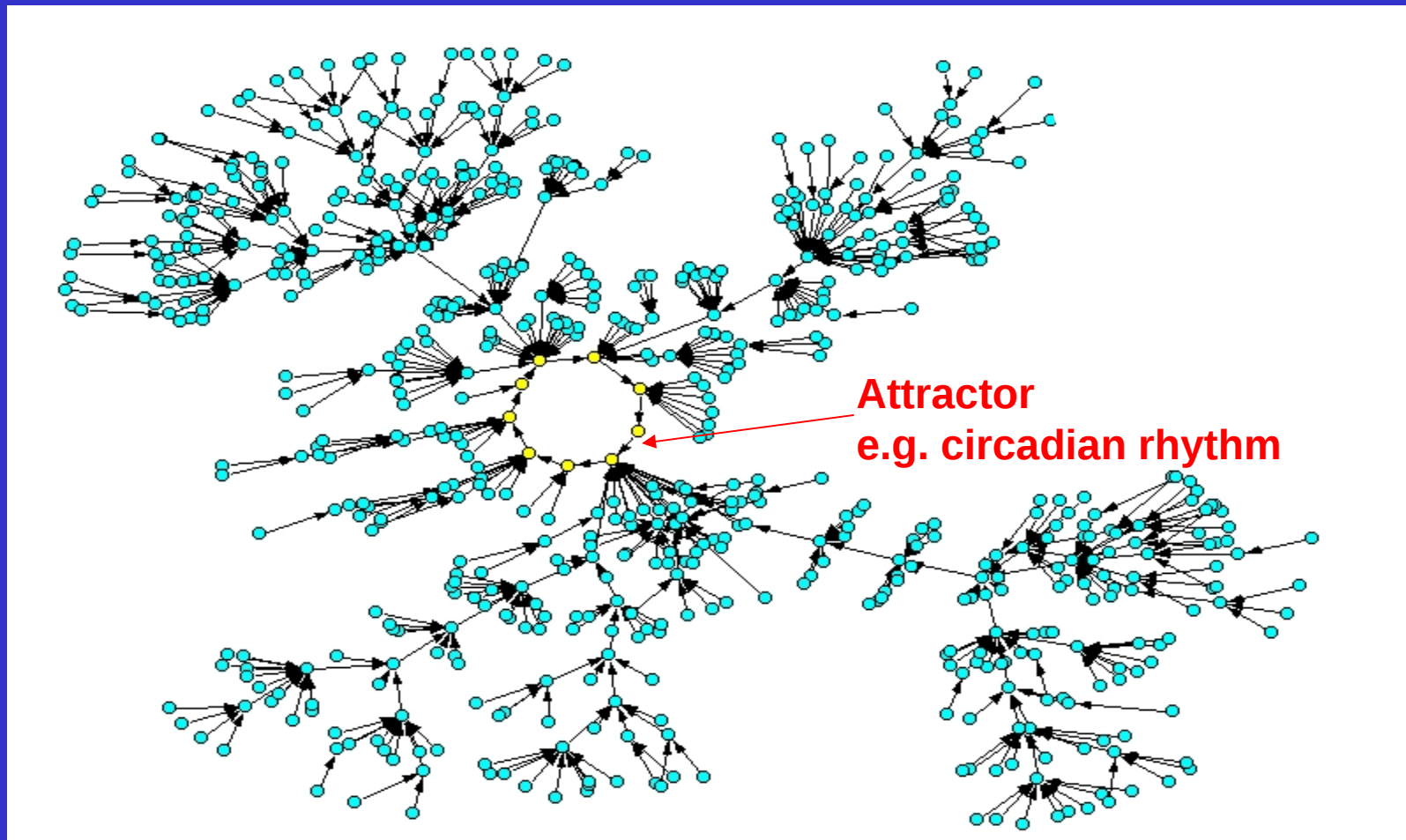
Homeostasis, health, and disease



Normal variation → frank toxicity

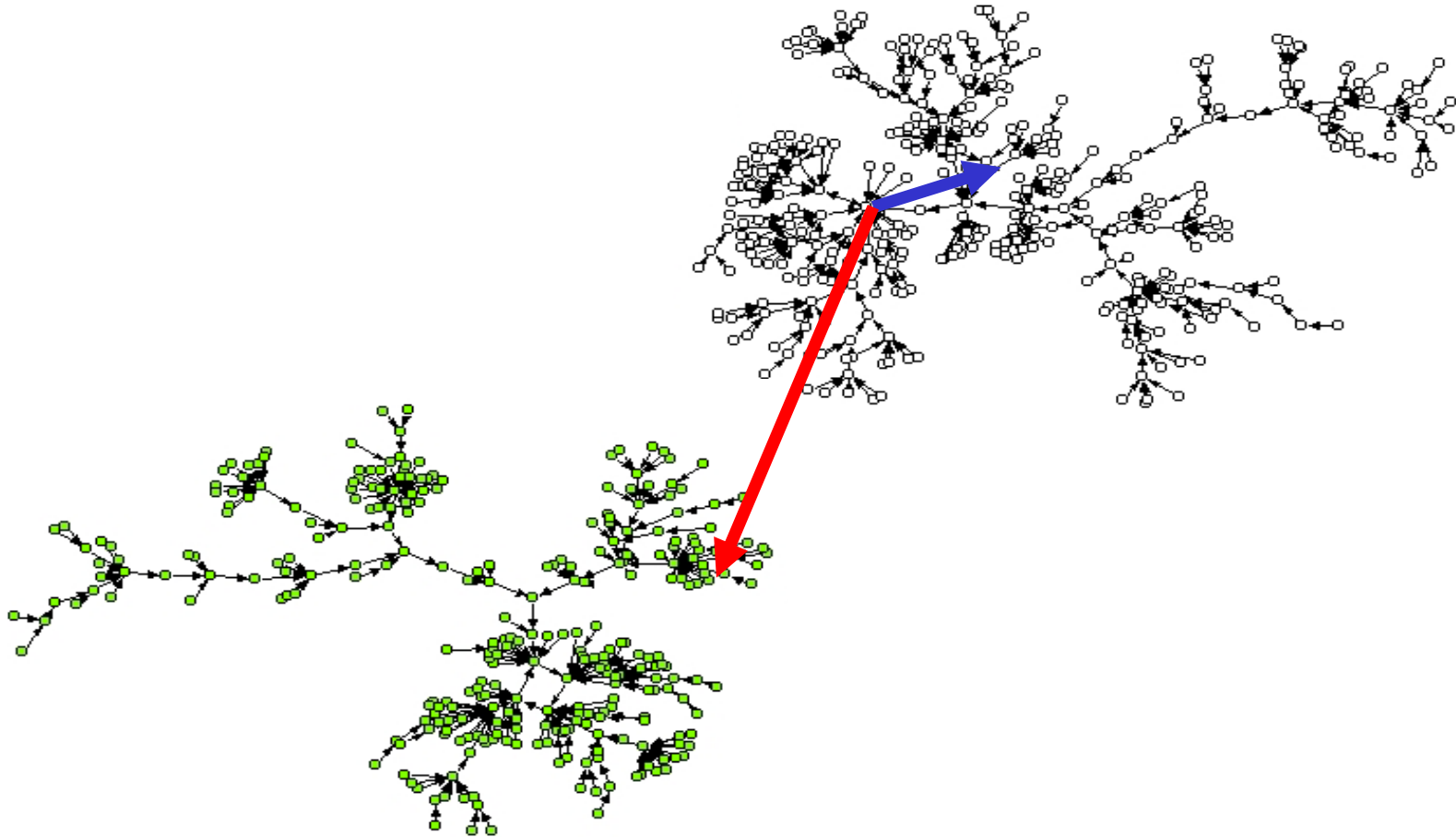


Attractors and biology



The critical feature of a regulatory network is that eventually it will reenter a state that it previously encountered and cycle repeatedly.³⁴

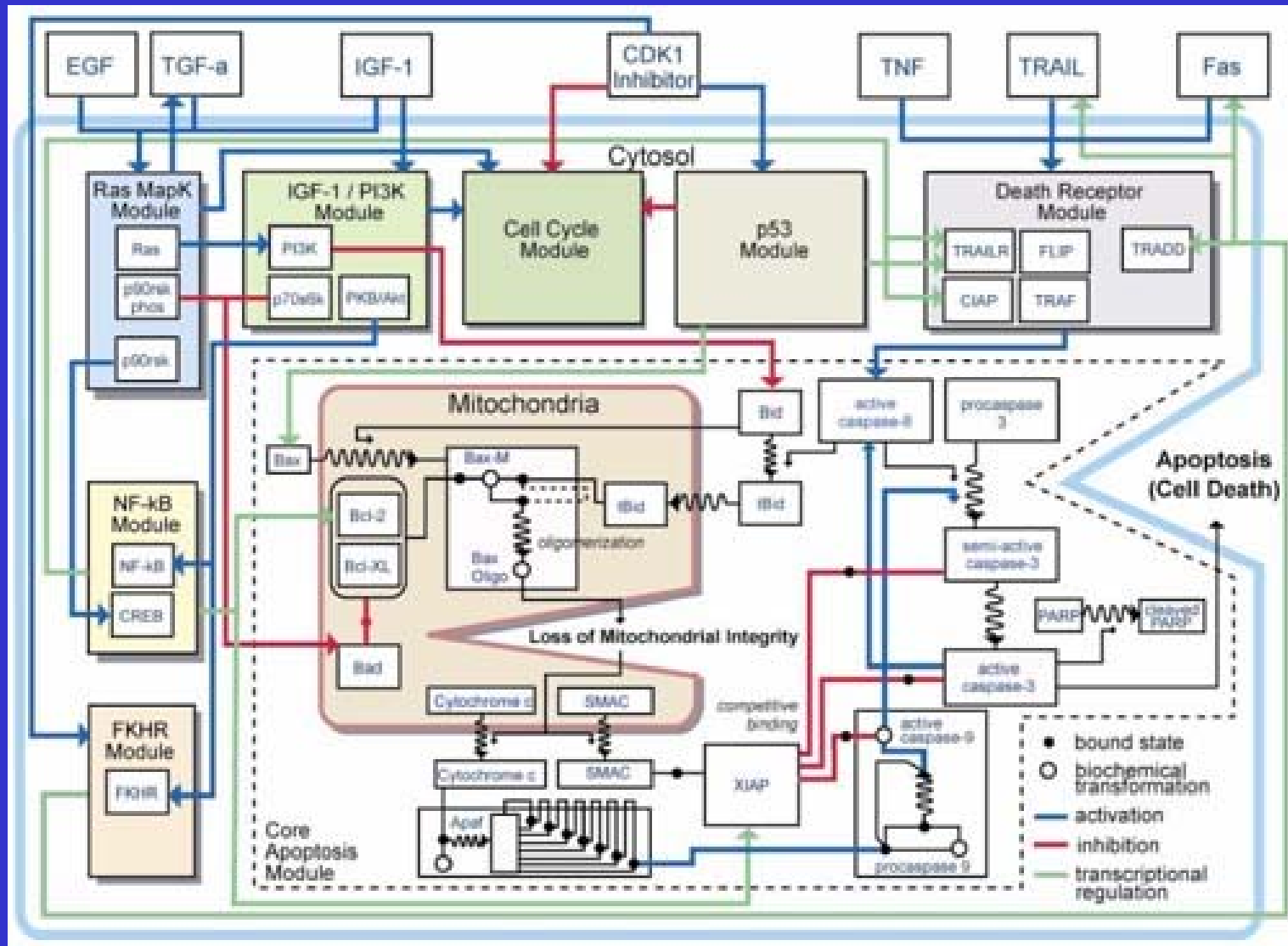
Health and disease



Practical and technical challenges

- Identification of network topology
- Parameter values
- Level of detail
 - Practical constraints
- Lumping
- “Functional modules”
 - MAPK amplifier
 - Cell cycle
 - Toolbox
- Coordination!!!!

Modular description of a cell



Regulatory acceptance

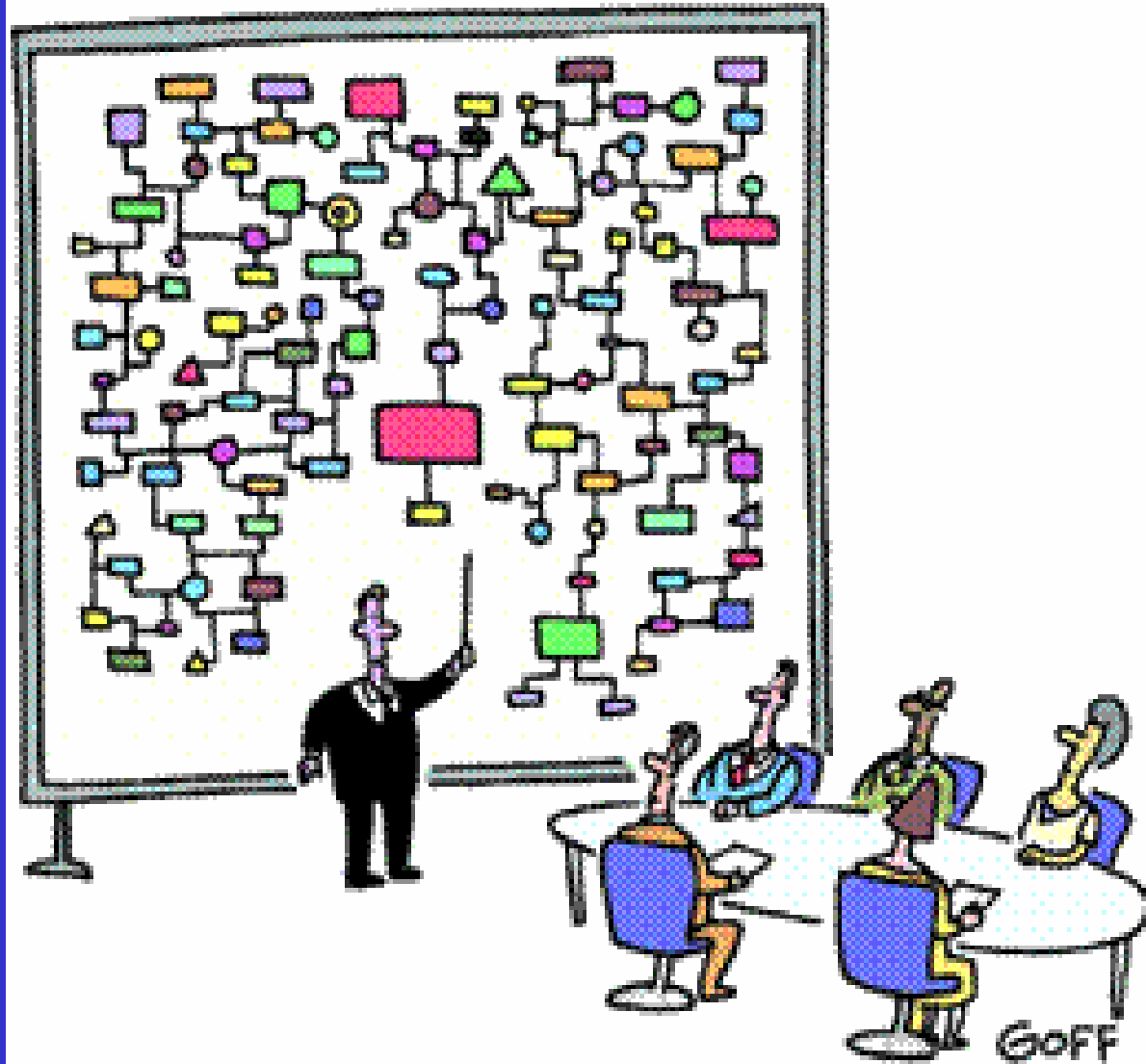


How compatible are research and risk assessment?

- Structurally complex models tend to illuminate sources of uncertainty
 - Models with hidden uncertainties may be preferred
- Large databases and associated models tend to identify questions for further research
 - Lose focus on what the existing data are telling us
- Sophisticated models require sophisticated evaluation
 - Ad hoc review groups
 - Balance interests rather than avoid real or perceived conflicts of interest

Acknowledgements

- *EPA NCCT*
 - Bob Kavlock, Jerry Blancato, Hugh Barton, Woody Setzer
- *CIIT Centers for Health Research*
 - Rusty Thomas, Mel Andersen
- *Purdue*
 - Yanan Zheng
- *Wright State University*
 - Jim McDougal



"And that's why we need a computer."

End