Functional analysis of biochemical signaling pathways mediating the acute inflammatory response

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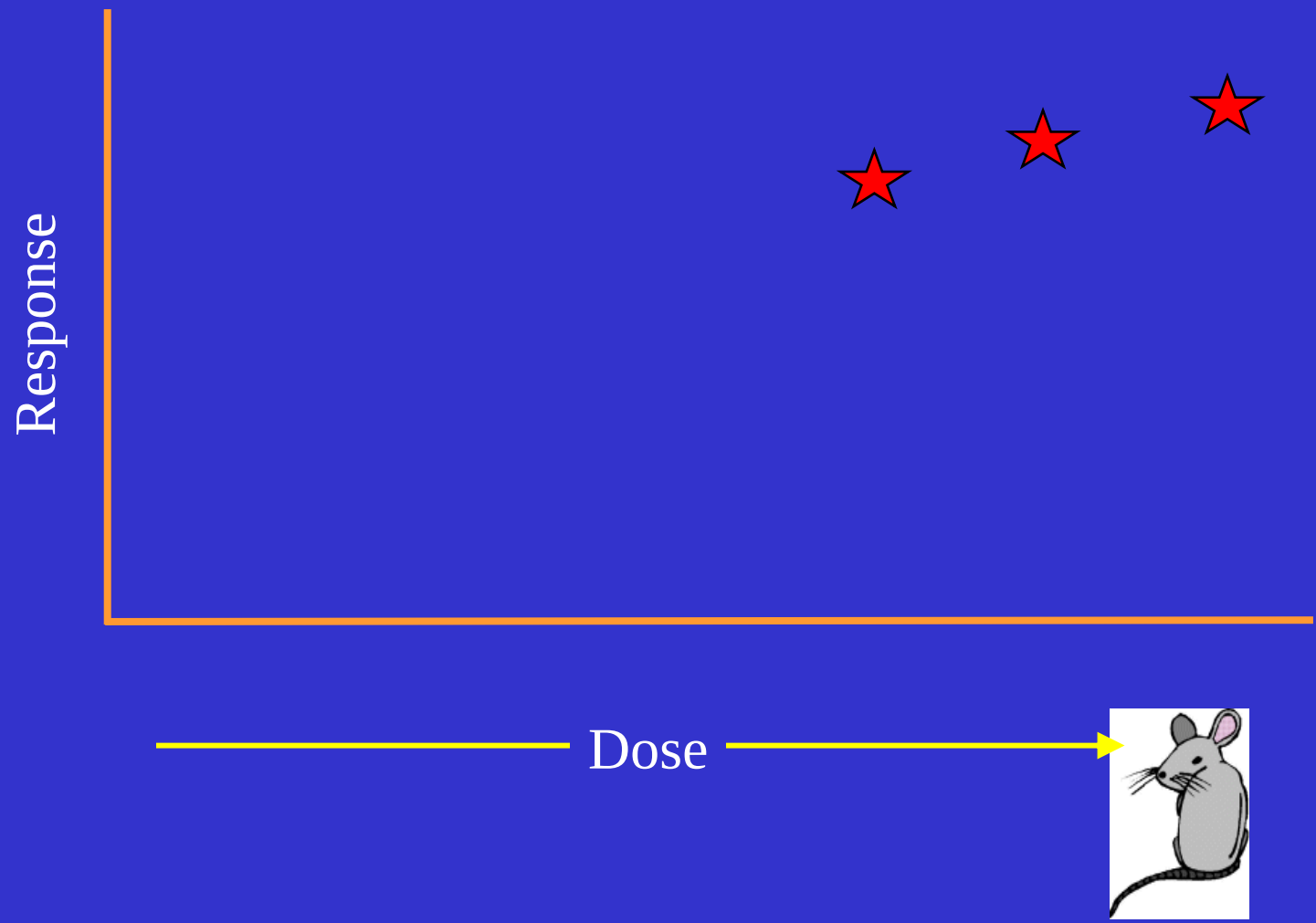
July 31, 2006

Outline

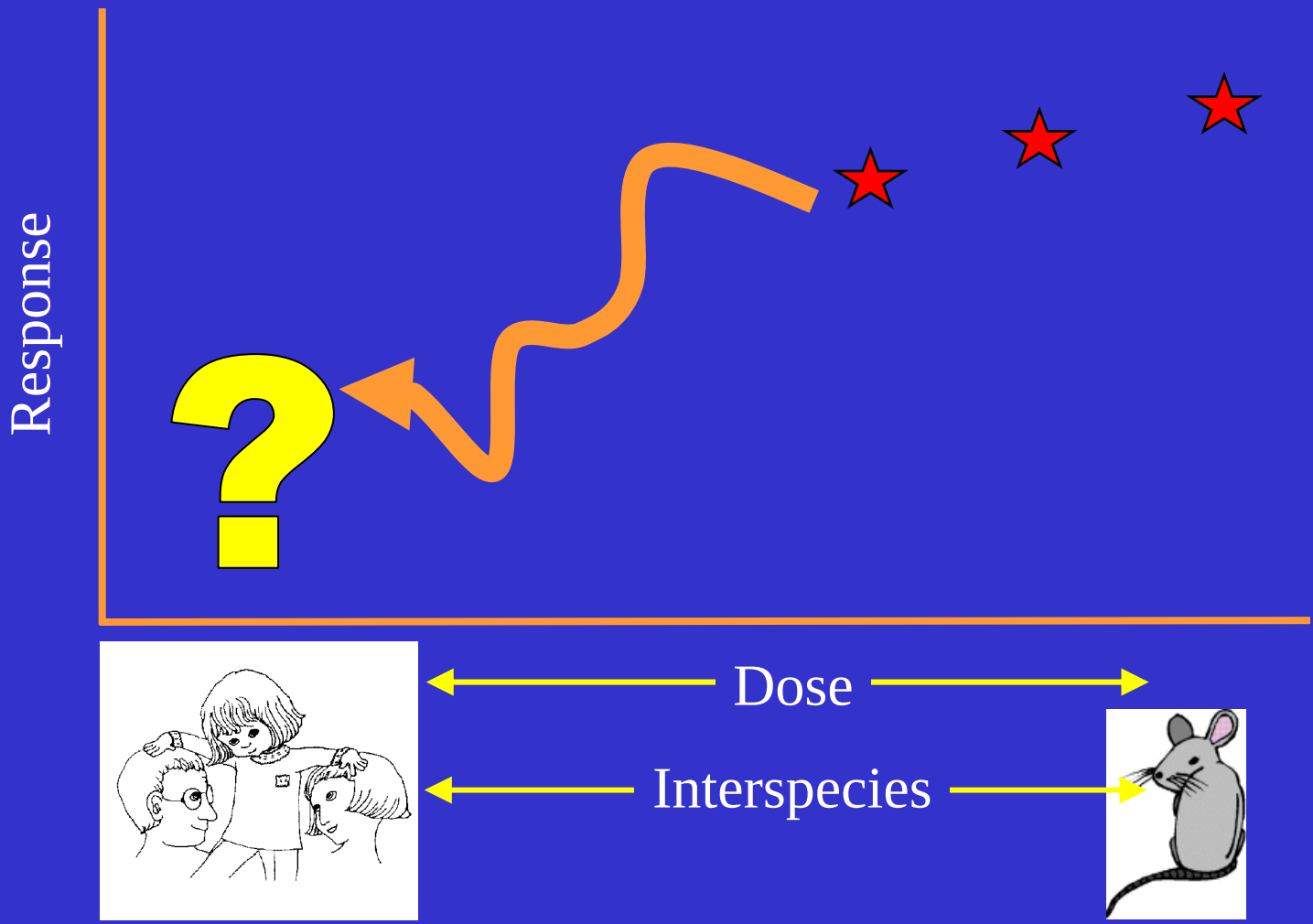
- Dose-response, time-course, and risk assessment
- Nonlinearities in cell signaling
- Analysis of IL-1α-mediated signaling in acute inflammation
- What's needed to develop a computational model

Predicting health risks: Dose-response and exposure assessments

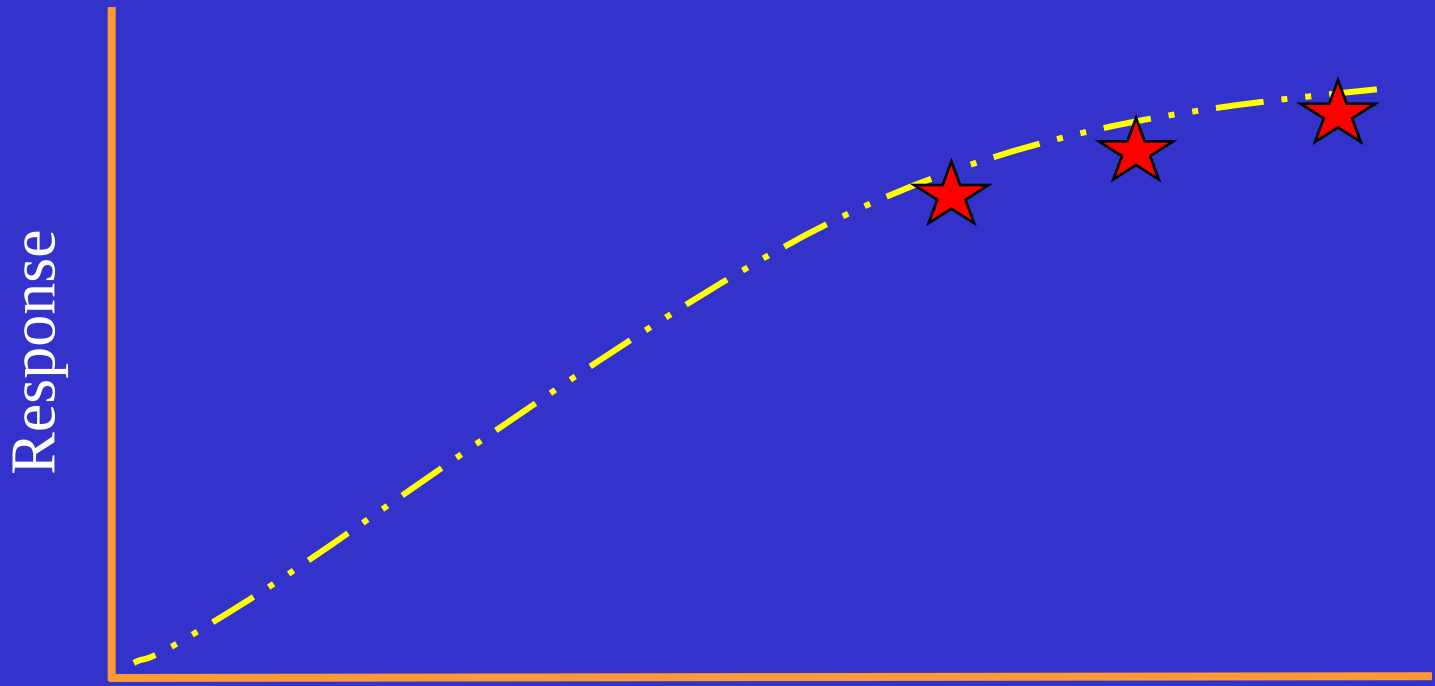
Typical high dose rodent data – what do they tell us?

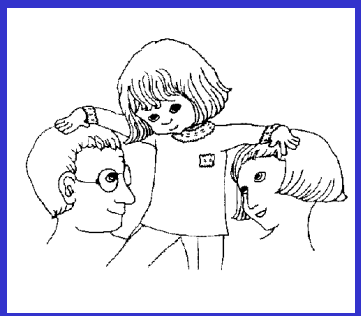


Not much!



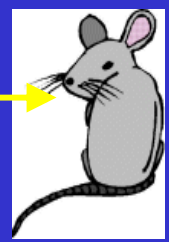
Possibilities





Dose

Interspecies



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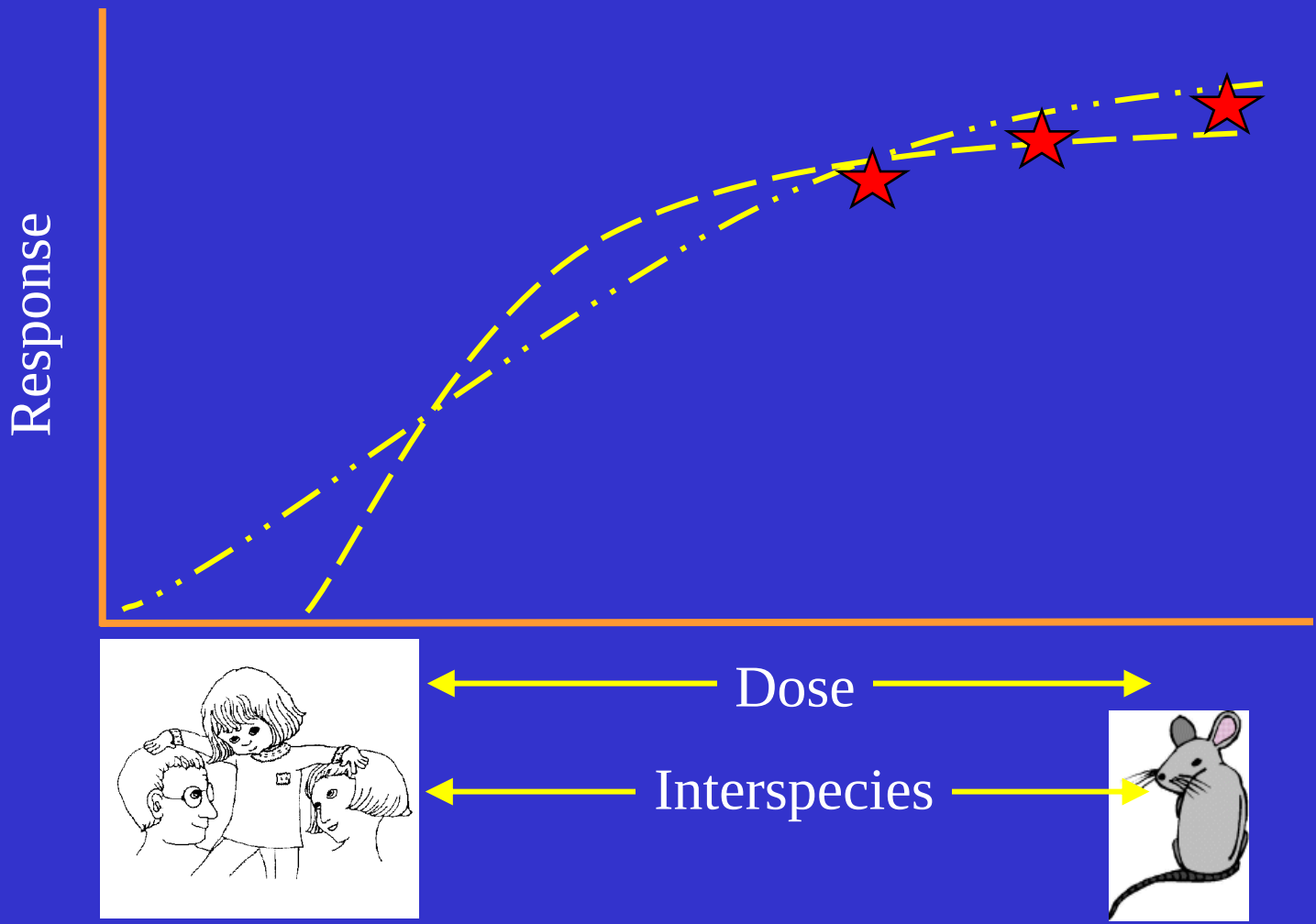
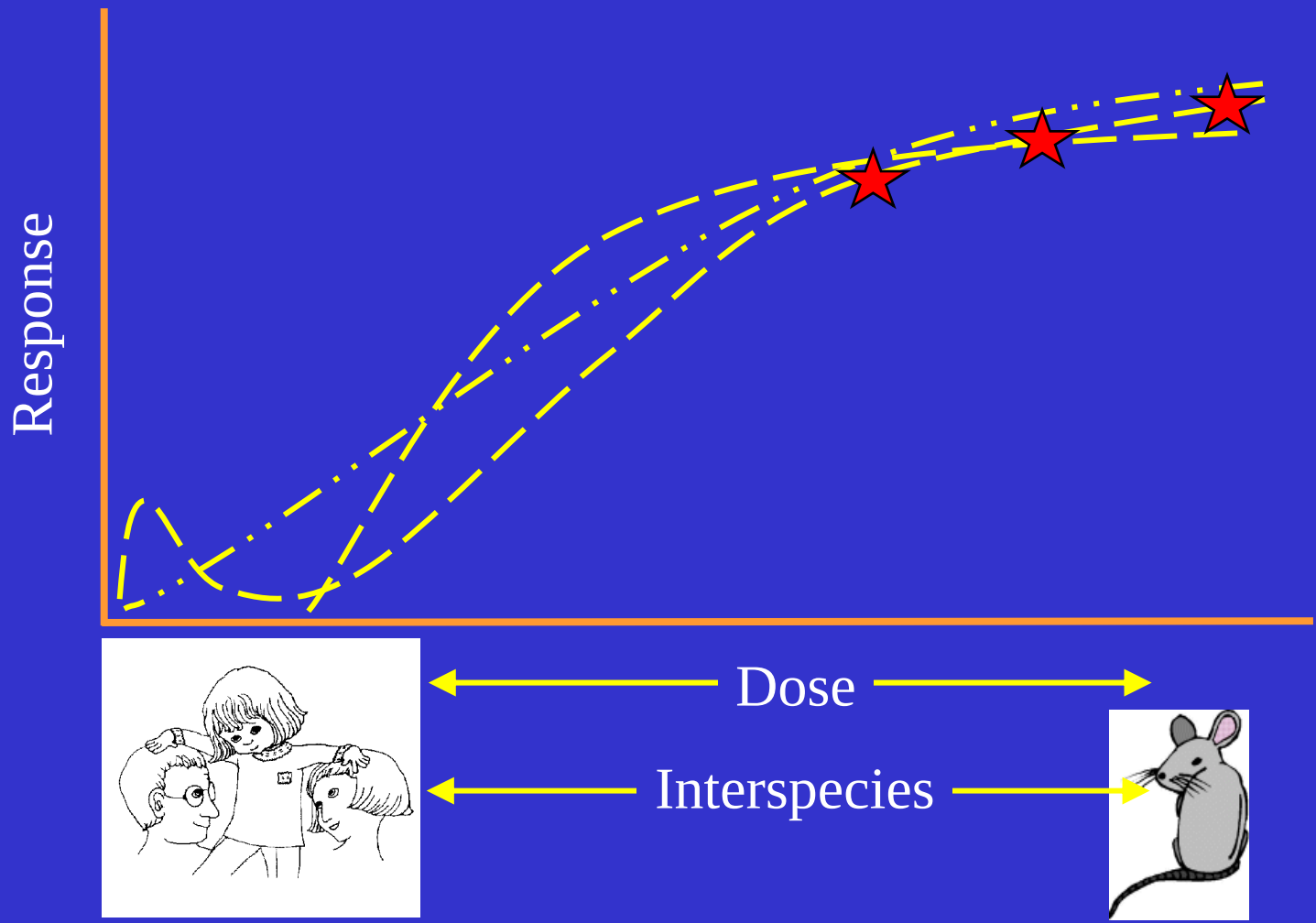


Possibilities



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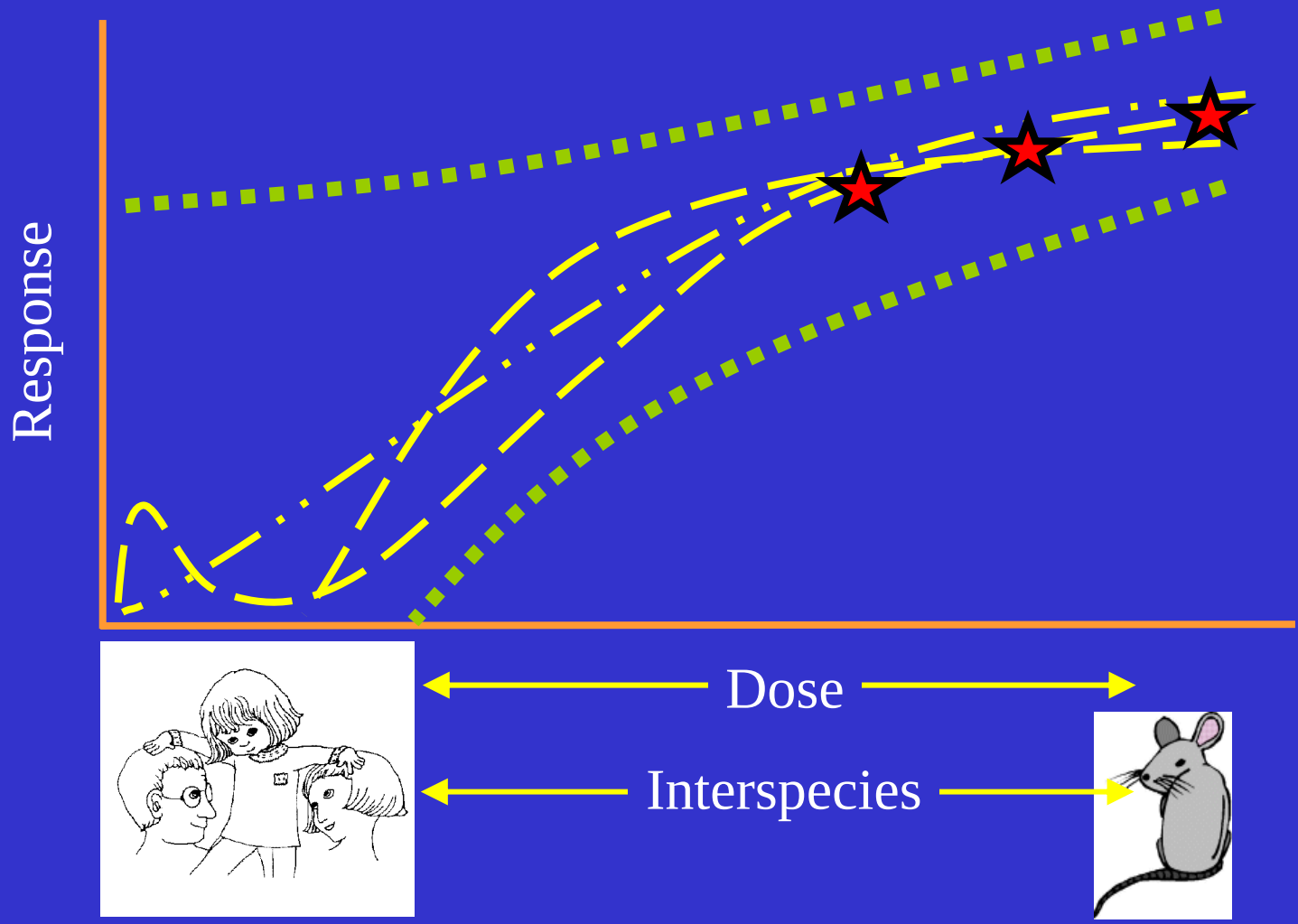
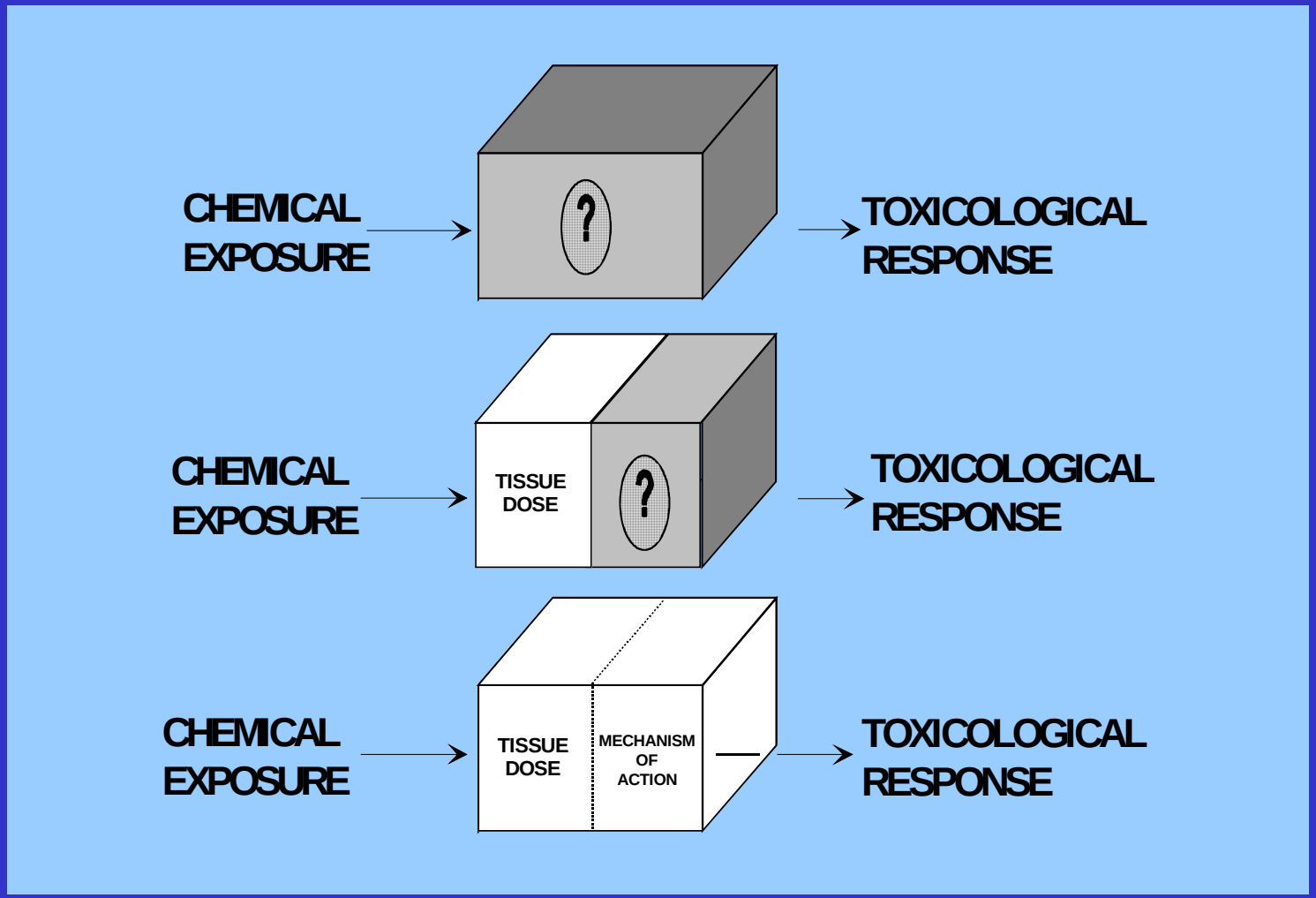
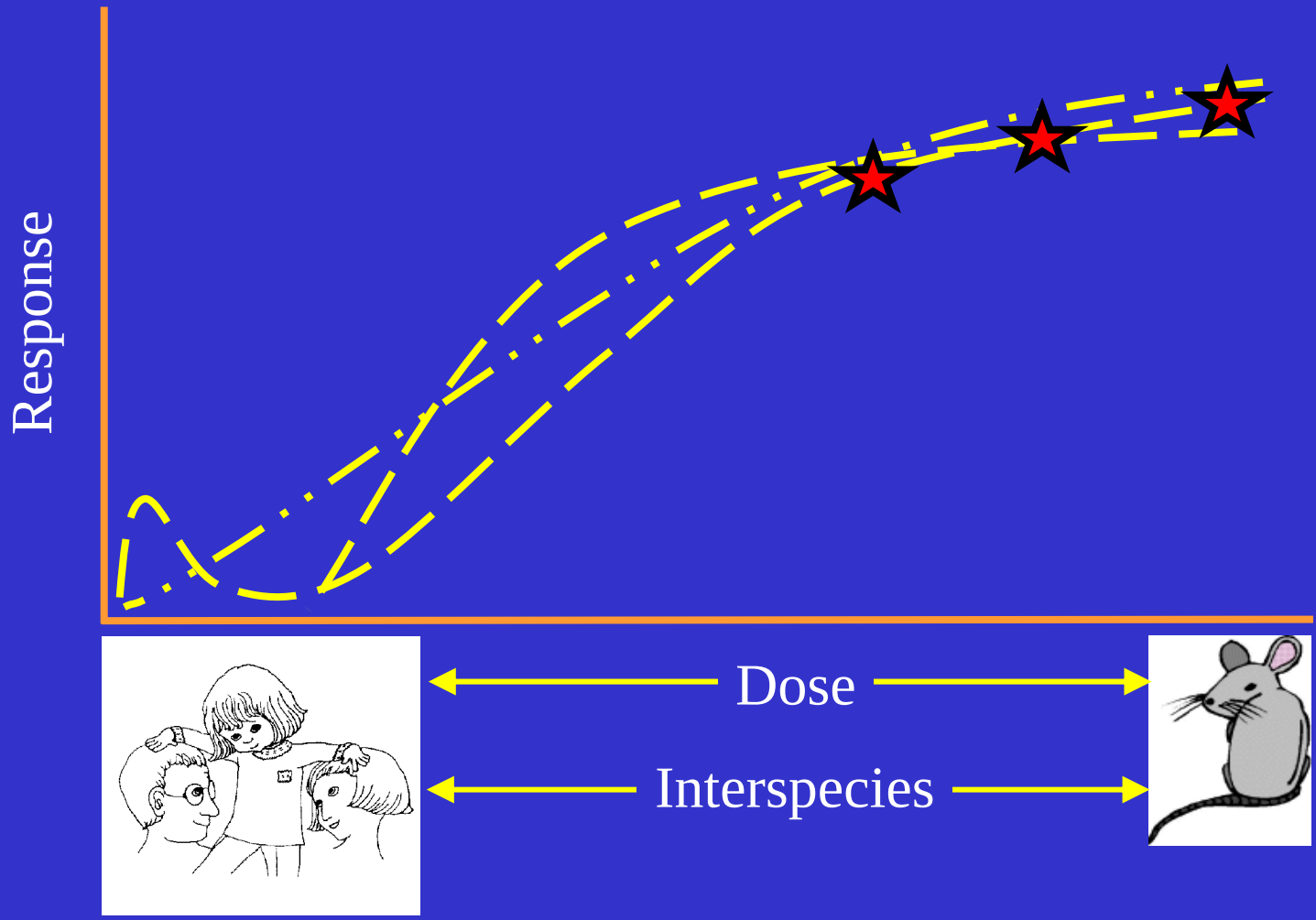


Biological mechanisms determine dose-response



Refining the description with research on mechanisms



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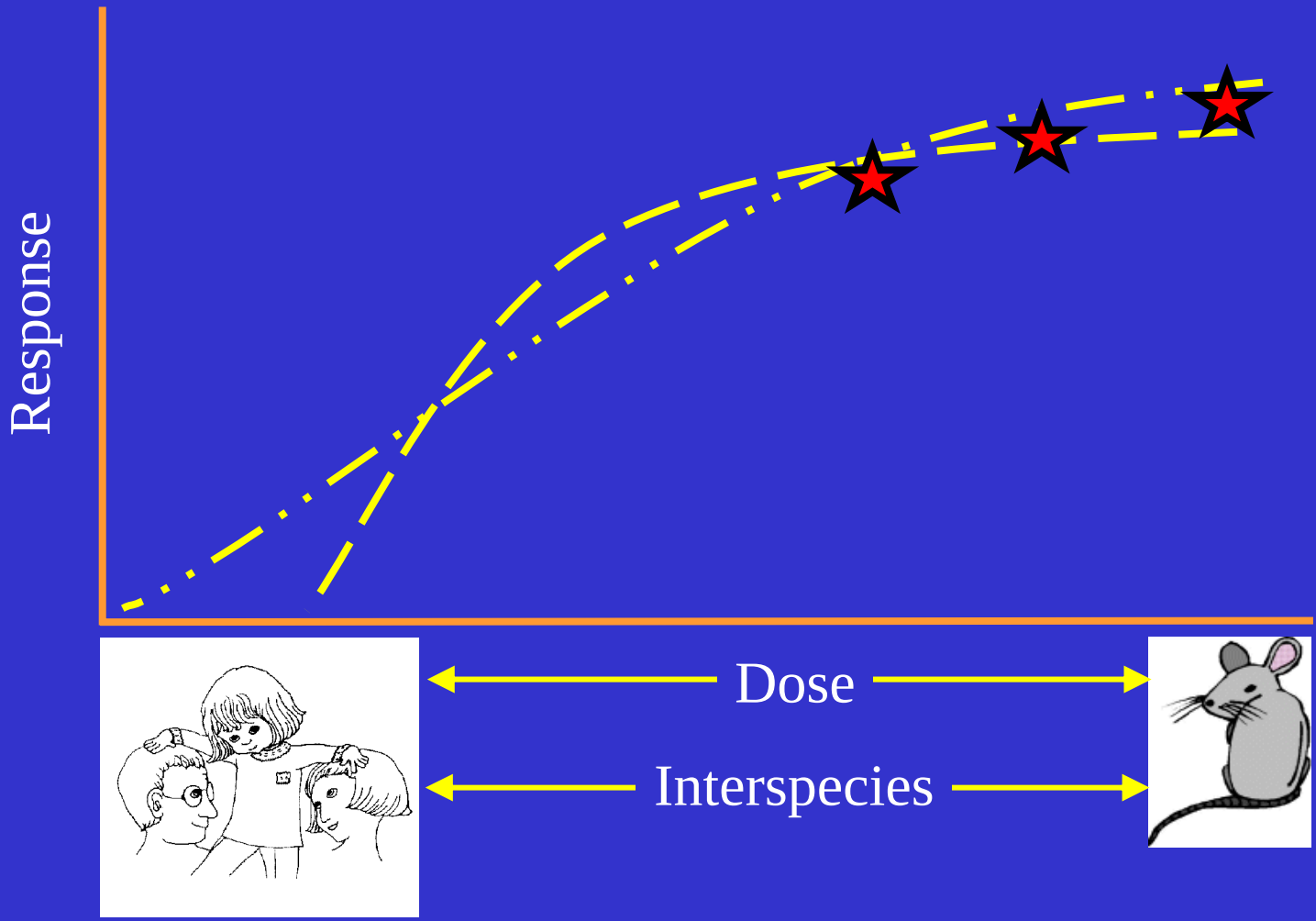

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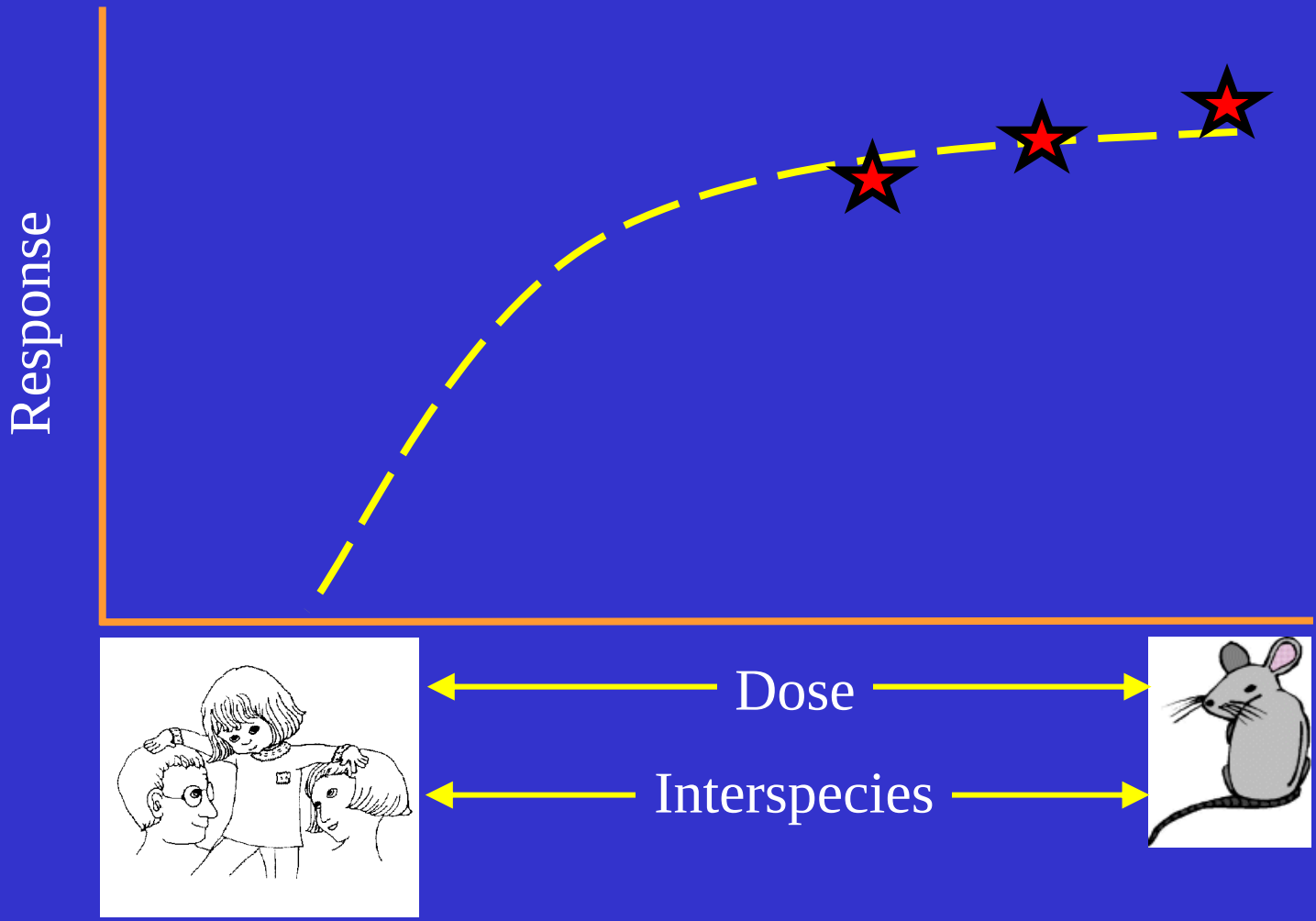

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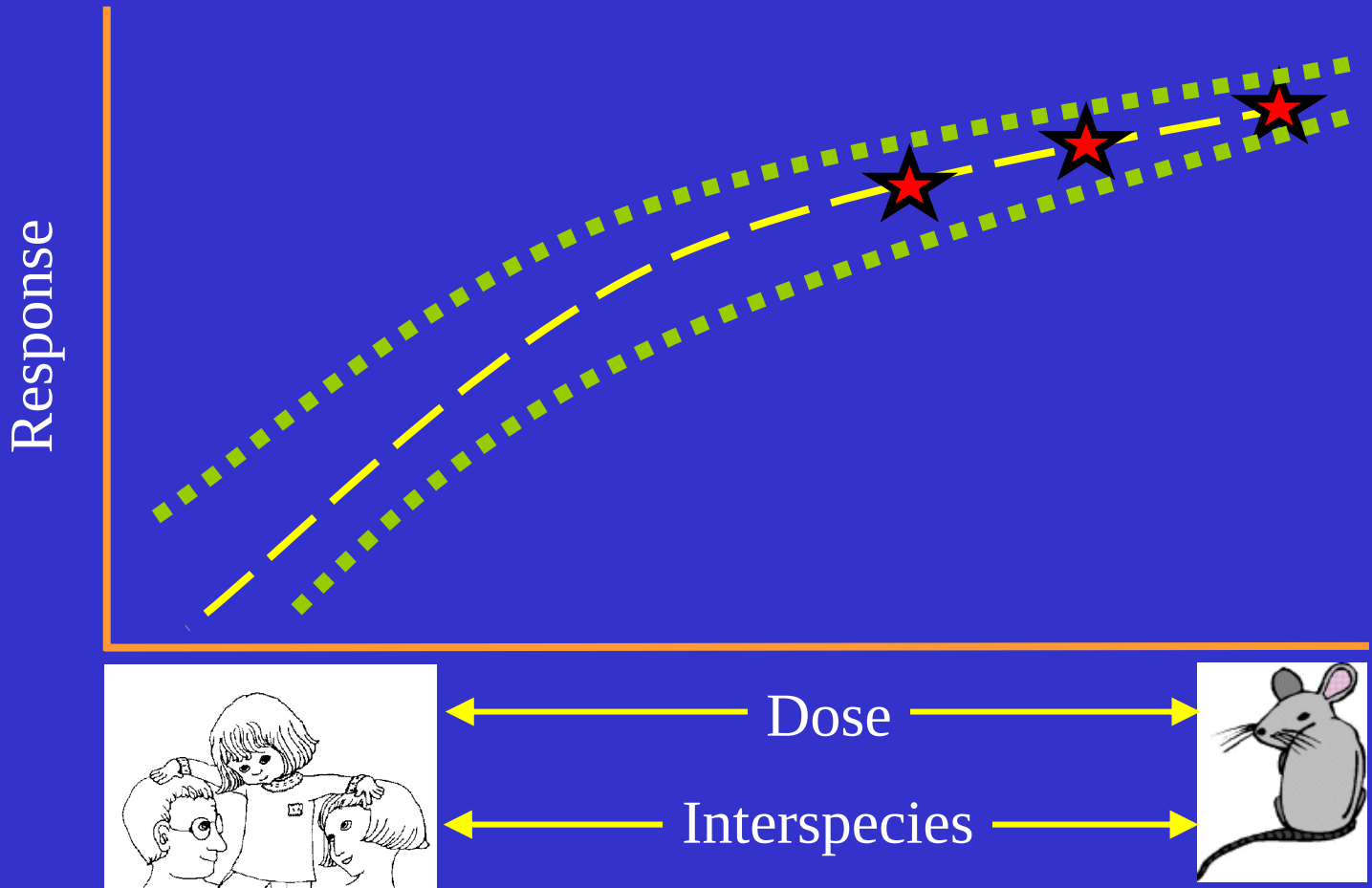
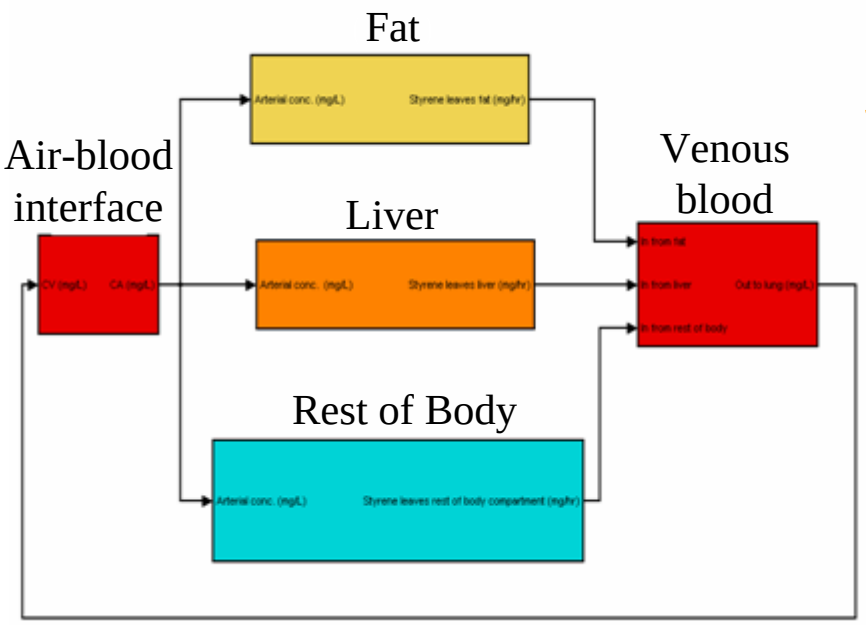
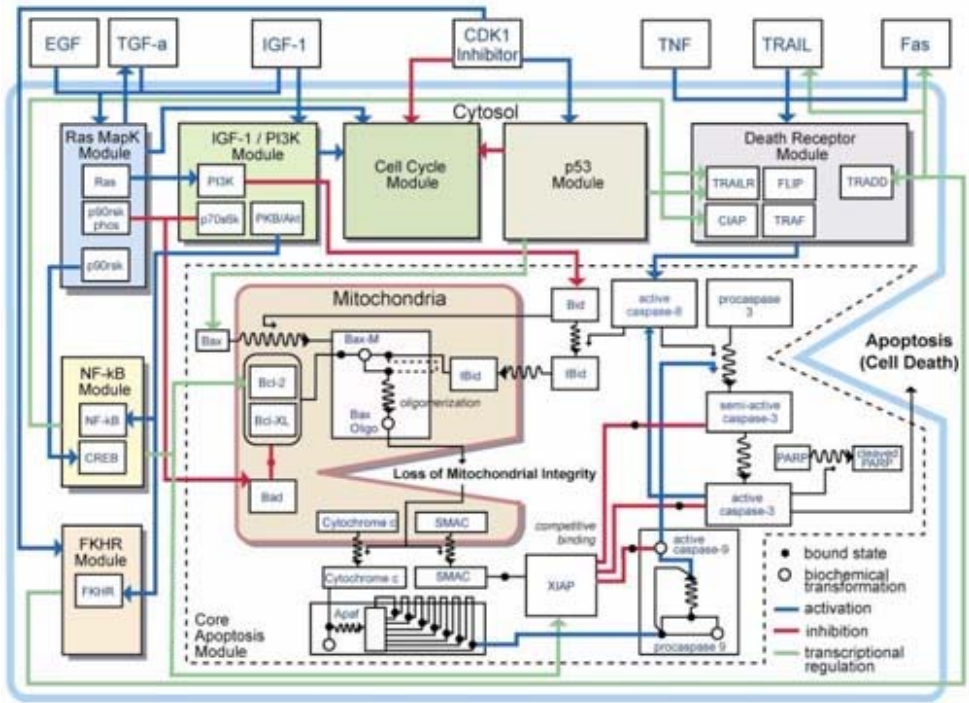
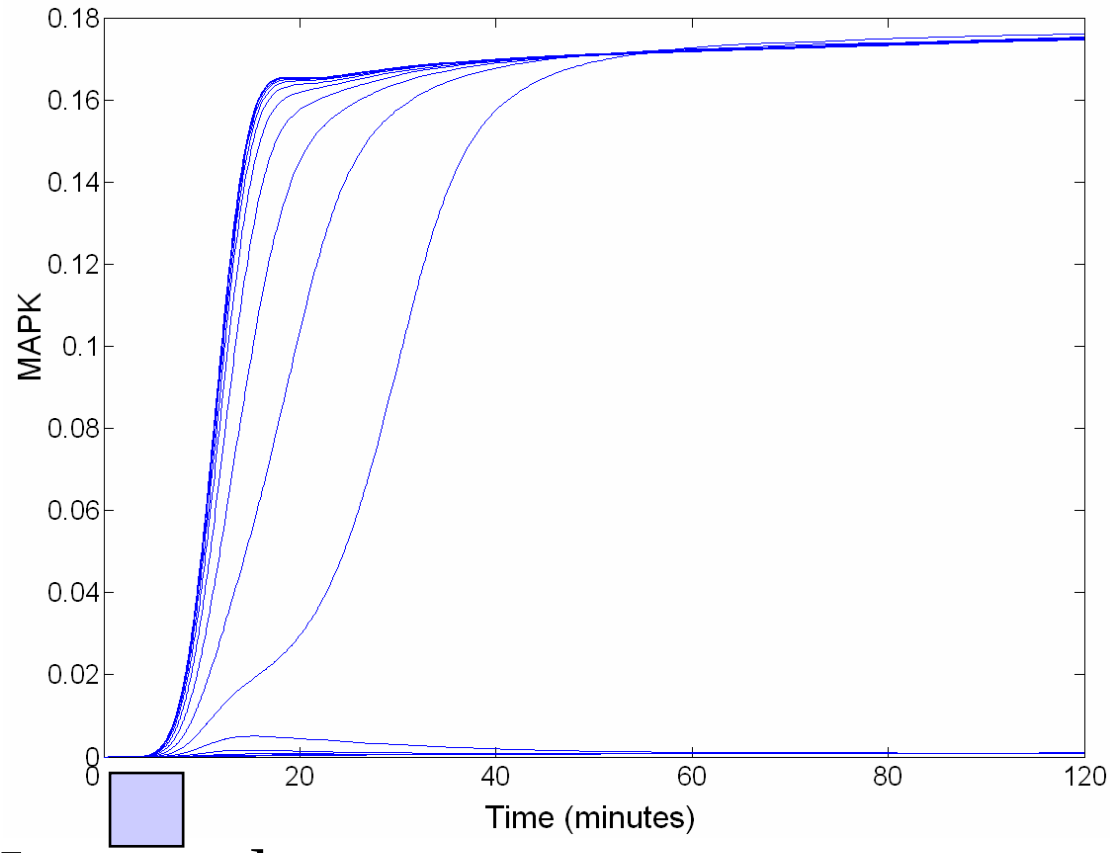


Systems Modeling



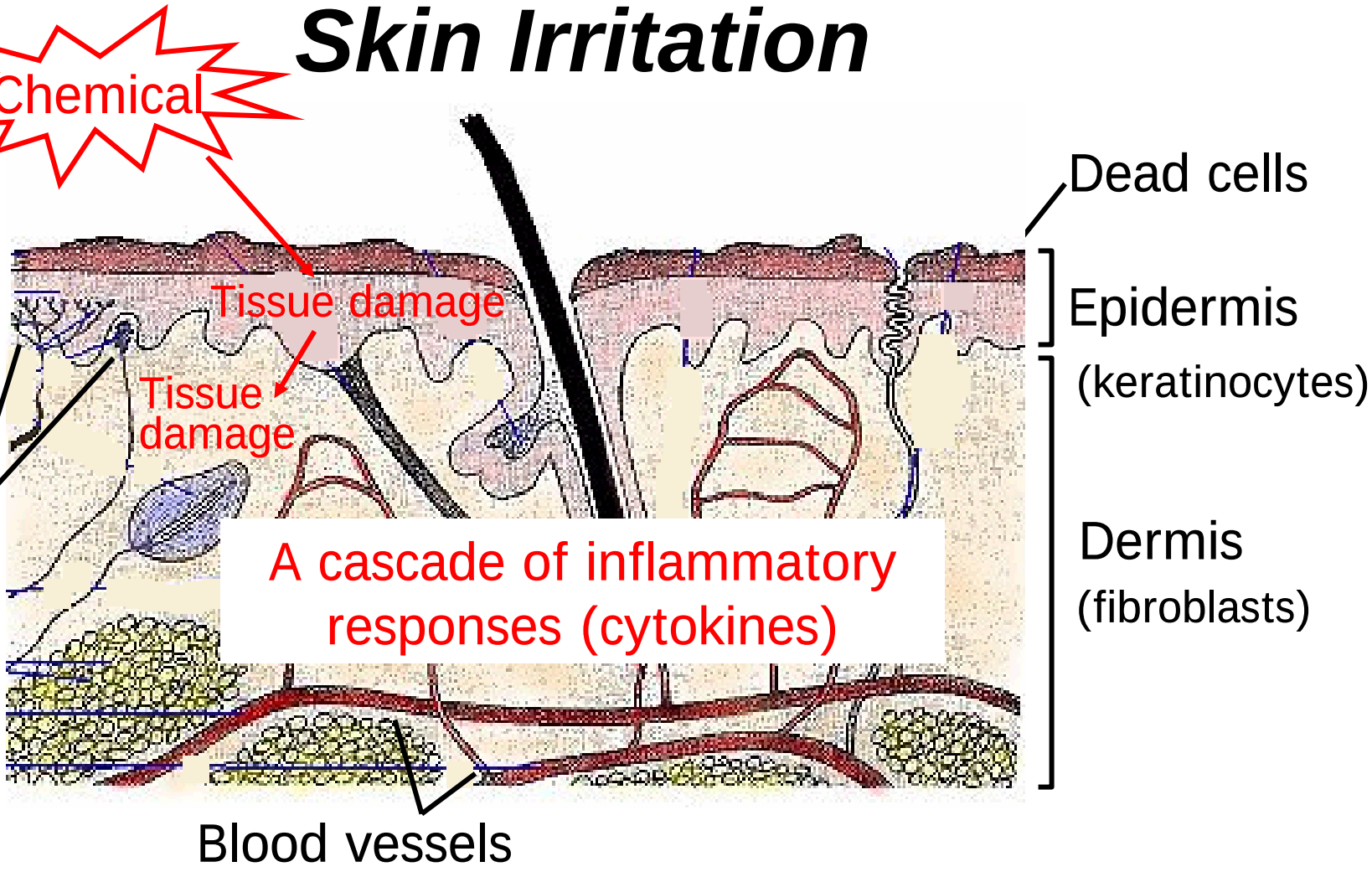


How might signaling behaviors modulate dose-response? MAPK

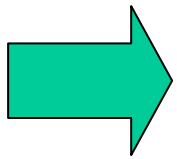


Input pulse

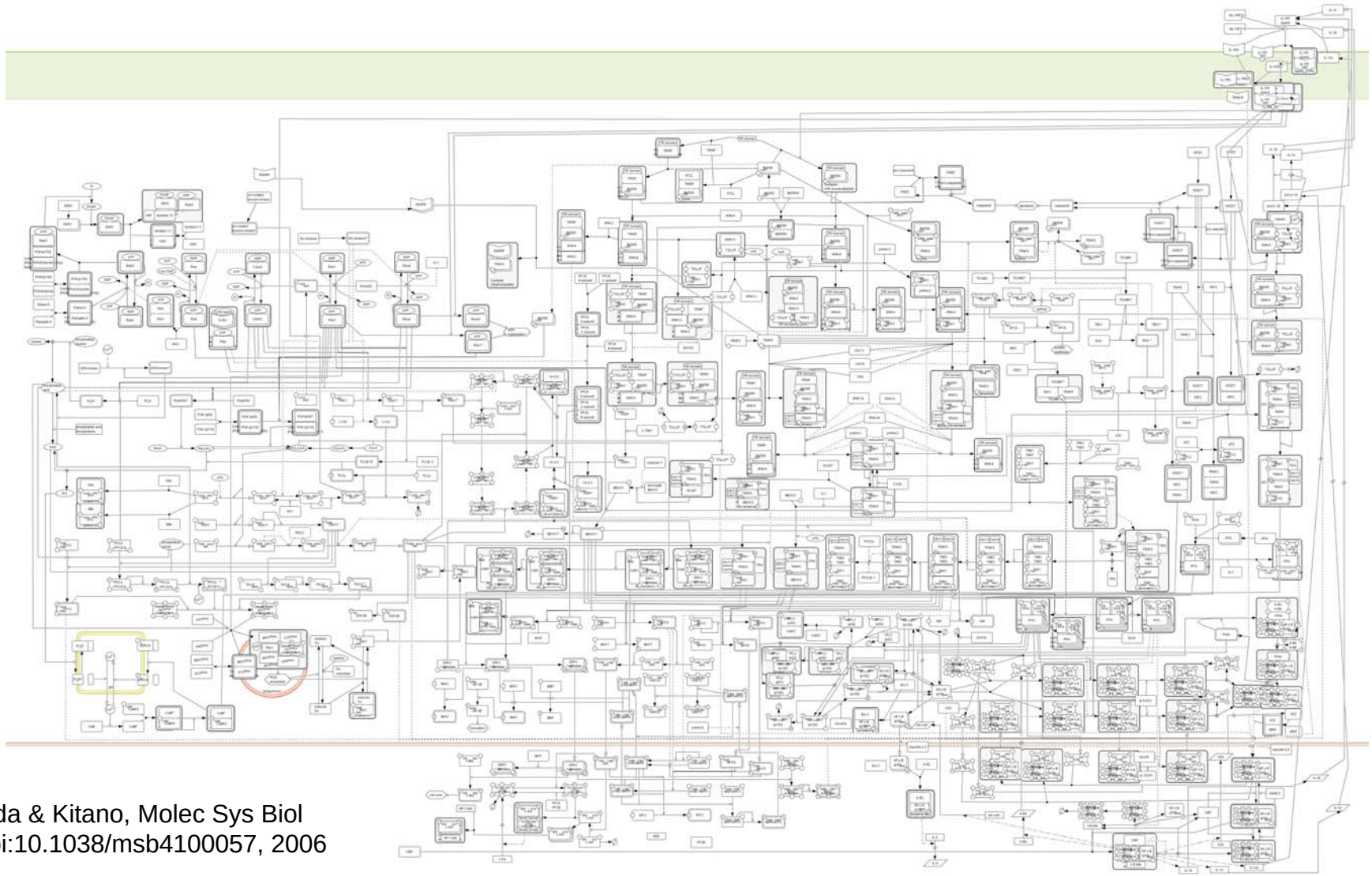
Skin Irritation



Apical scheme

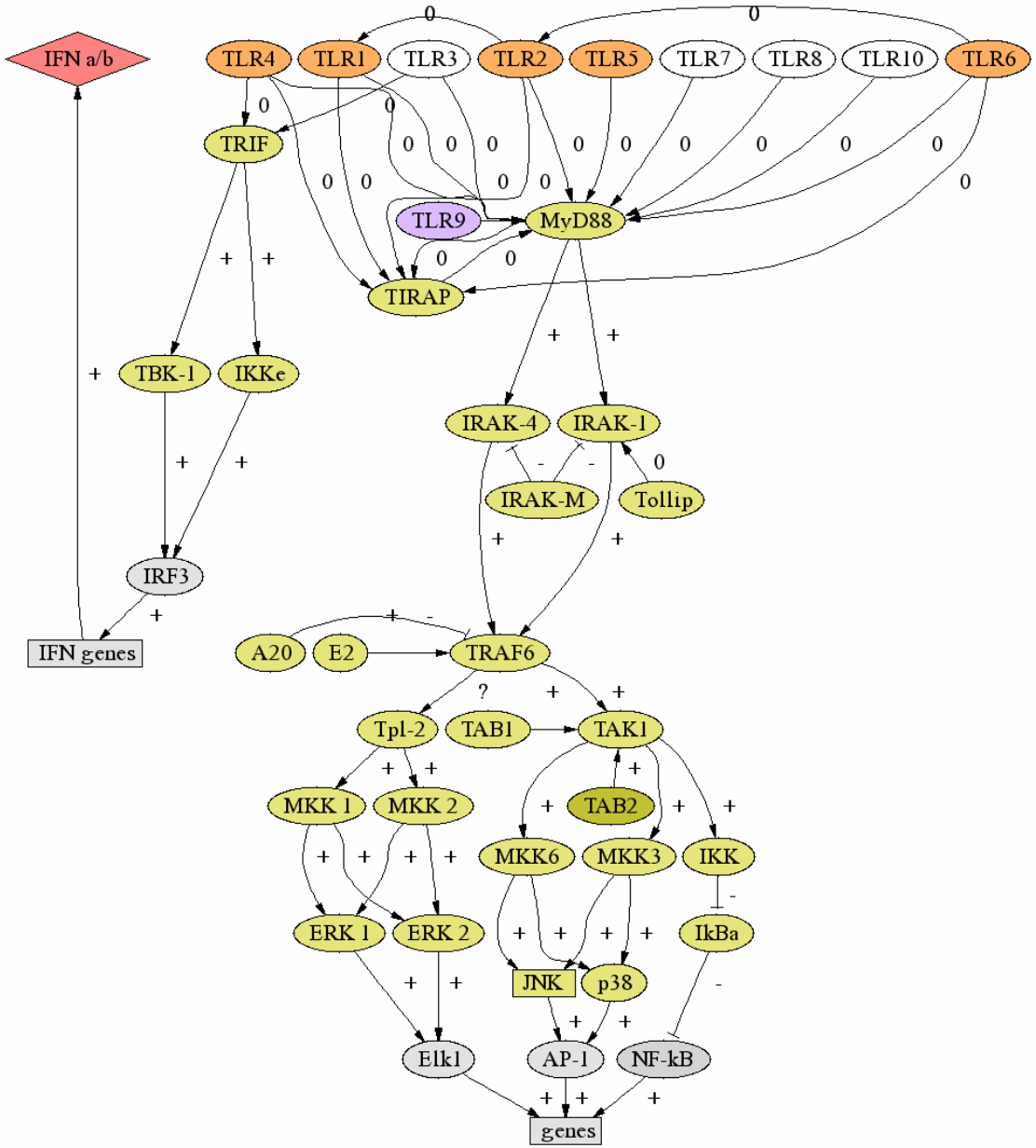
Chemical irritant  Skin inflammation

Molecular-level scheme



Oda & Kitano, Molec Sys Biol
doi:10.1038/msb4100057, 2006

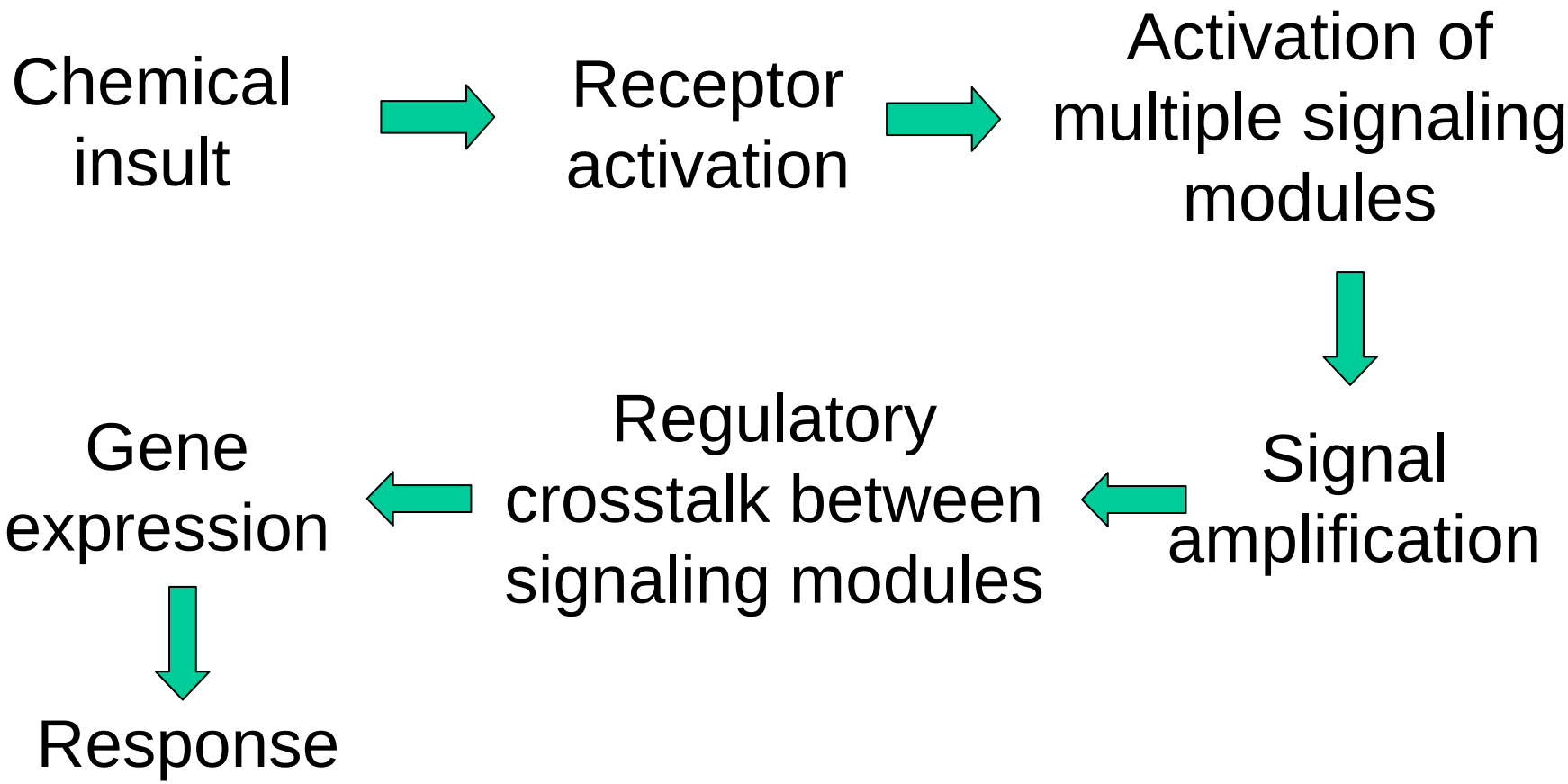
Toll-like receptor signaling (Science STKE)



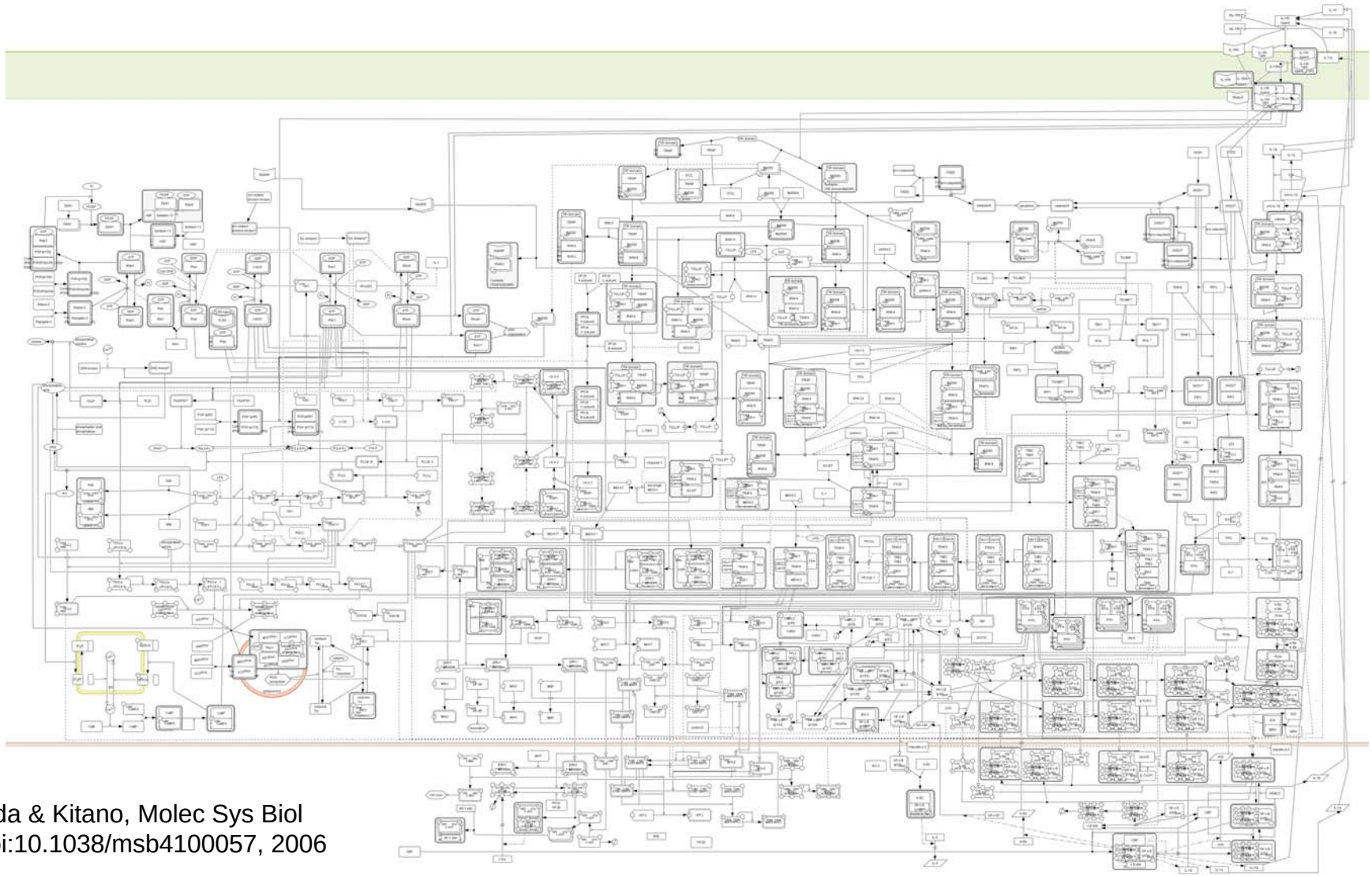
Expected characteristics of cellular signaling

- Signal transduction
- Amplification (ultrasensitivity)
- Switch-like response to input
- Regulatory crosstalk
- Self-limiting after signal cutoff
- Redundancy
- Timeliness

Generic scheme



Molecular-level scheme



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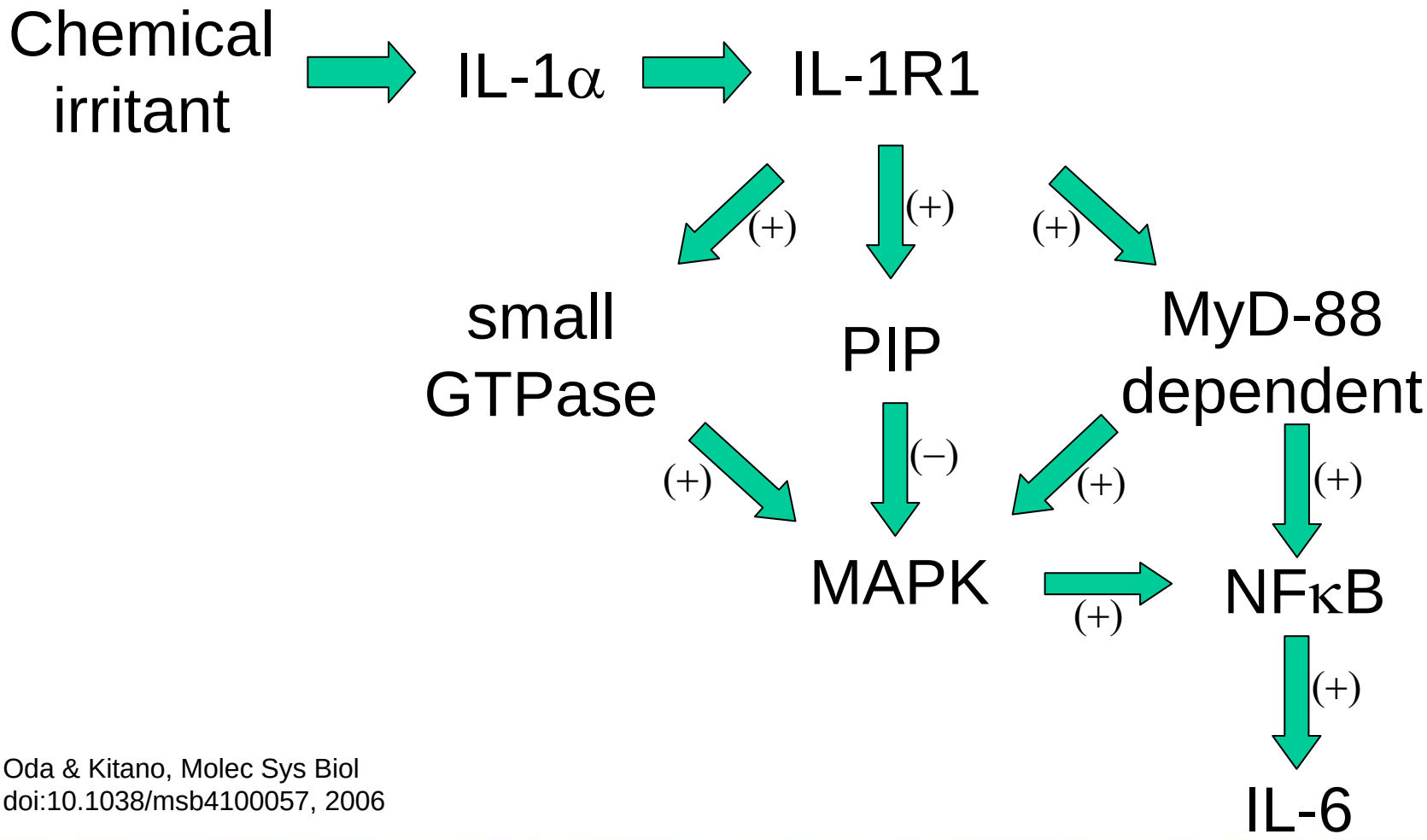
Modular scheme for IL-1α-mediated irritant response



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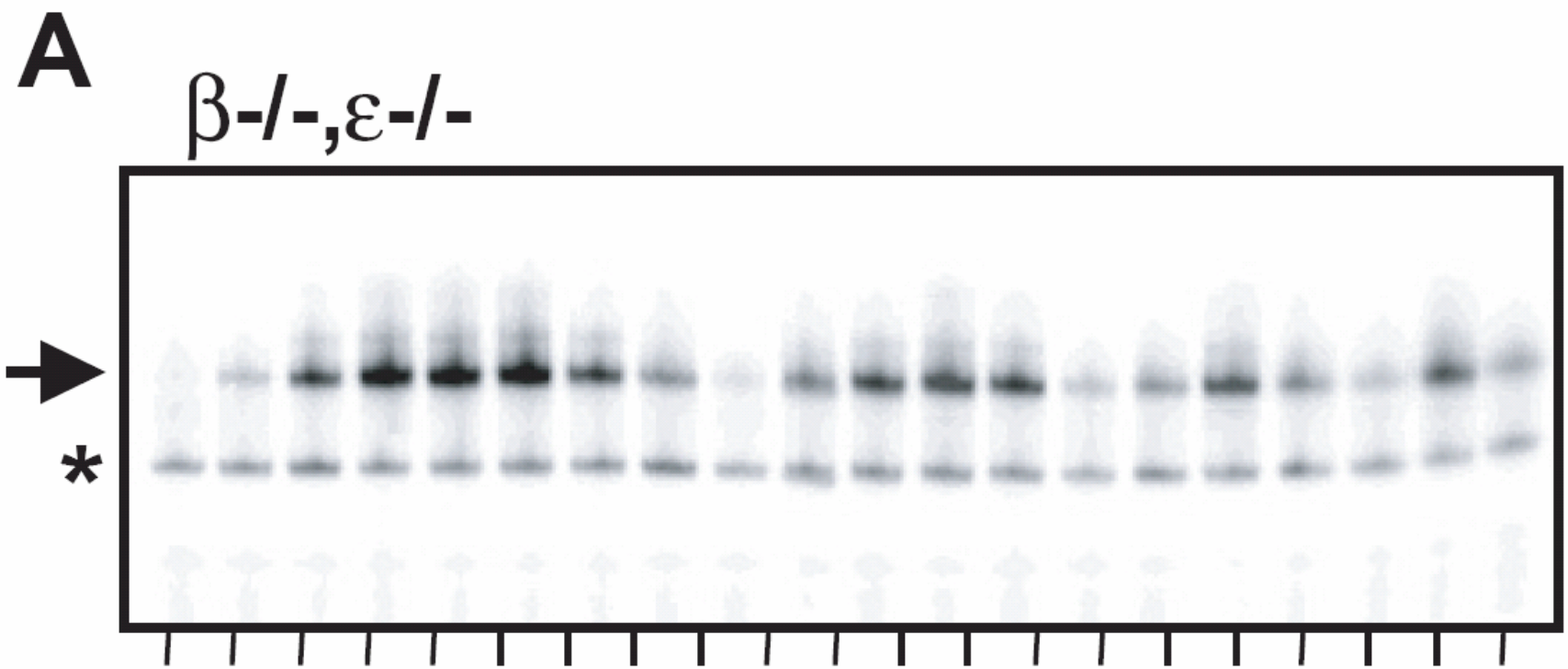
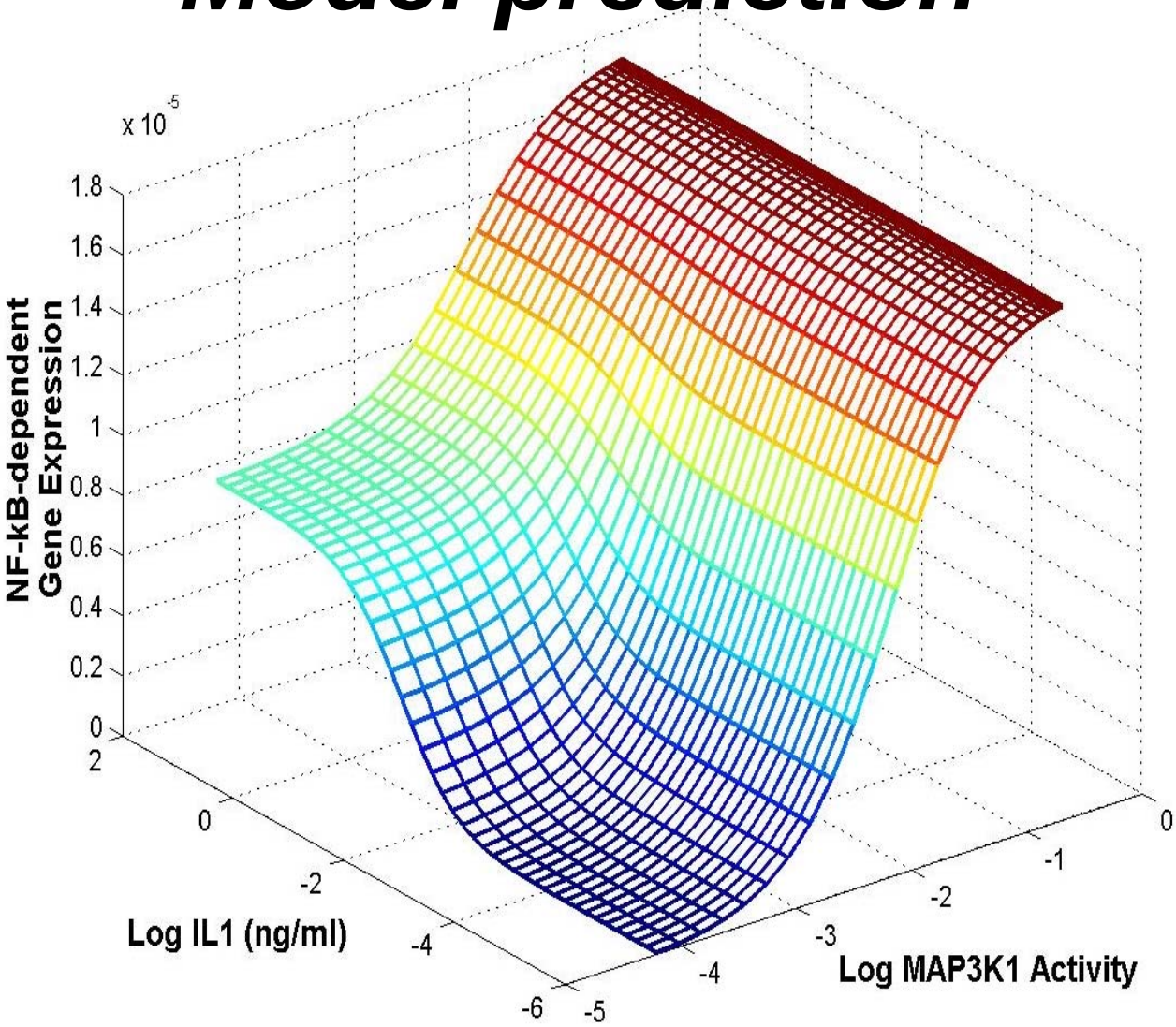
What do we know?

- IL-1α activates IL-1R1
- Small GTPases are switches
- MAPKs, amplifier and switch
- PIP, switch
- NFκB, oscillatory switch
- IL-6 mediates inflammatory response

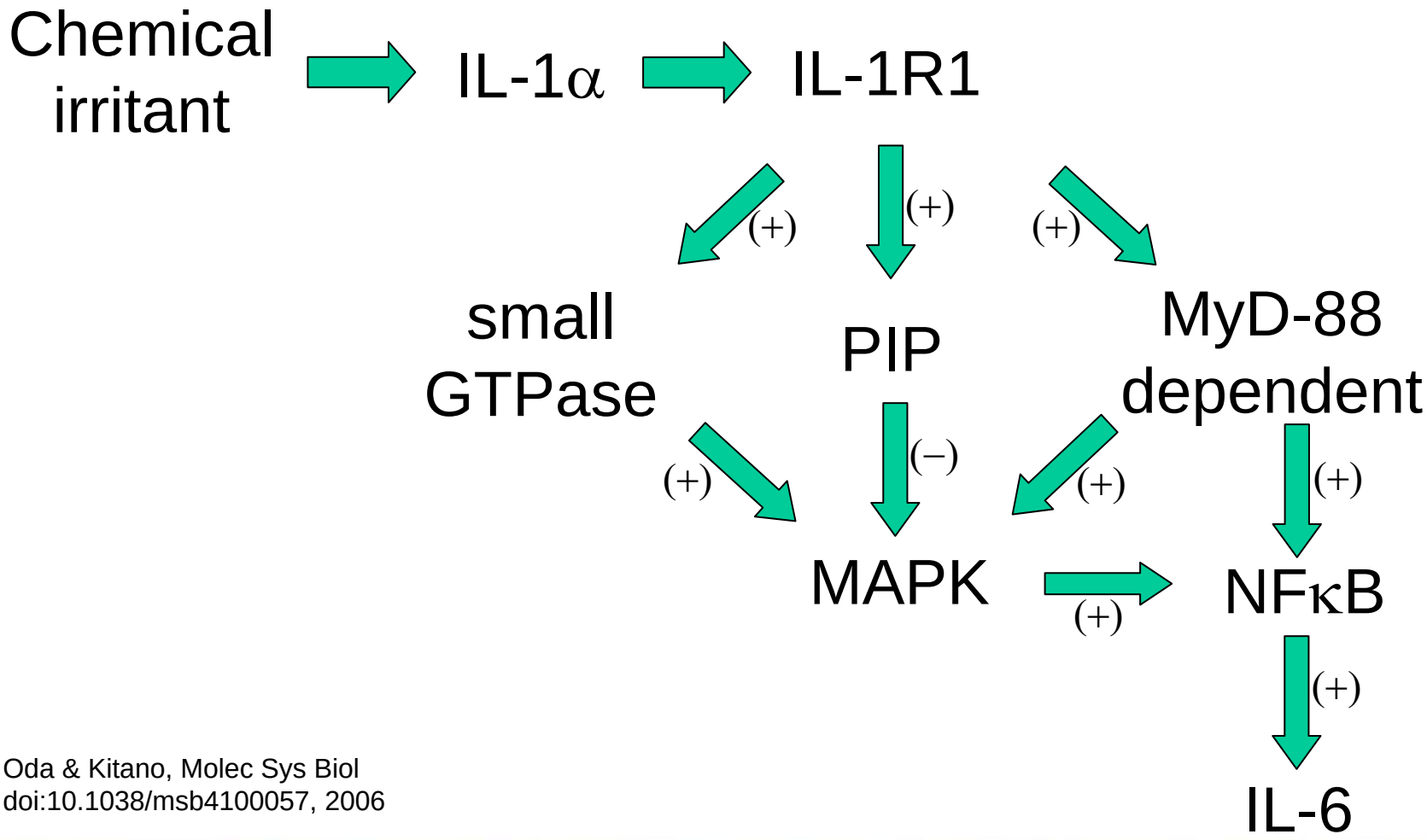
The IB–NF-B Signaling Module: Temporal Control and Selective Gene Activation
Alexander Hoffmann, Andre Levchenko, Martin L. Scott, David Baltimore
Science 298:1241 – 1245, 2002



Model prediction



Modular scheme for IL-1α-mediated irritant response



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Qualitative insights

- Signal is amplified but also terminated
- Parallel but convergent signaling
  - Redundancy?
  - Regulatory crosstalk?
- Positive and negative signals in the cross-talk
  - What determines who wins?
  - Or does this just sharpen the signal?

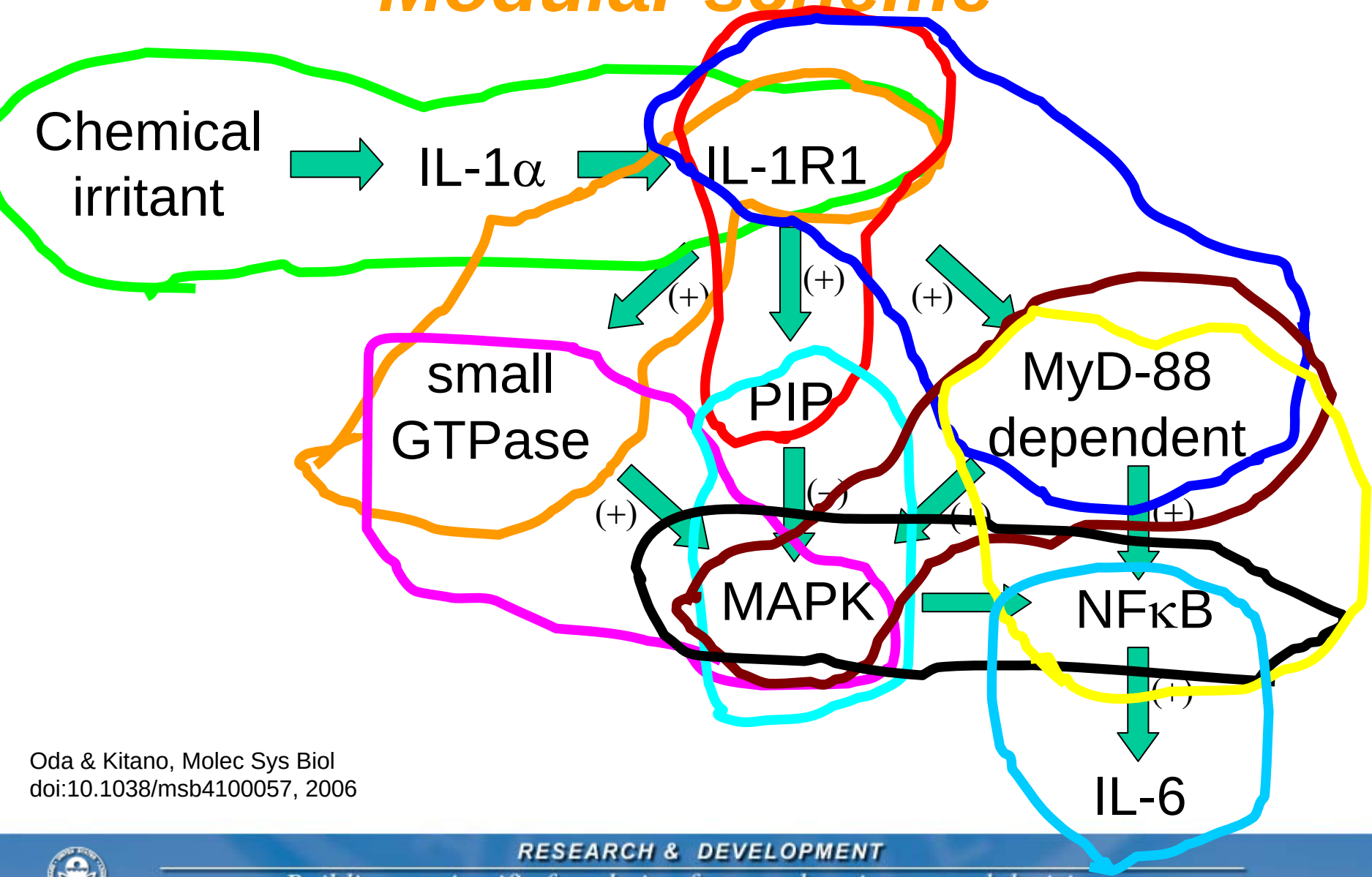
Actually, we know a lot…

- We know that activation of IL -1R1 leads to IL-6 upregulation.
- For a given duration of IL-1R1 activation, small GTPases, PIP, MyD-88 and MAPK determine the time-course and intensity (?) of IL-6 upregulation
- Overall signaling is self-limiting

How to move on to a quantitative model?

- Need dose-response and time-course data for each module
  - (Eungdamrong & Iyengar, Modeling Cell Signaling Networks, Biol. of the Cell, 355-362, 2004)

Modular scheme



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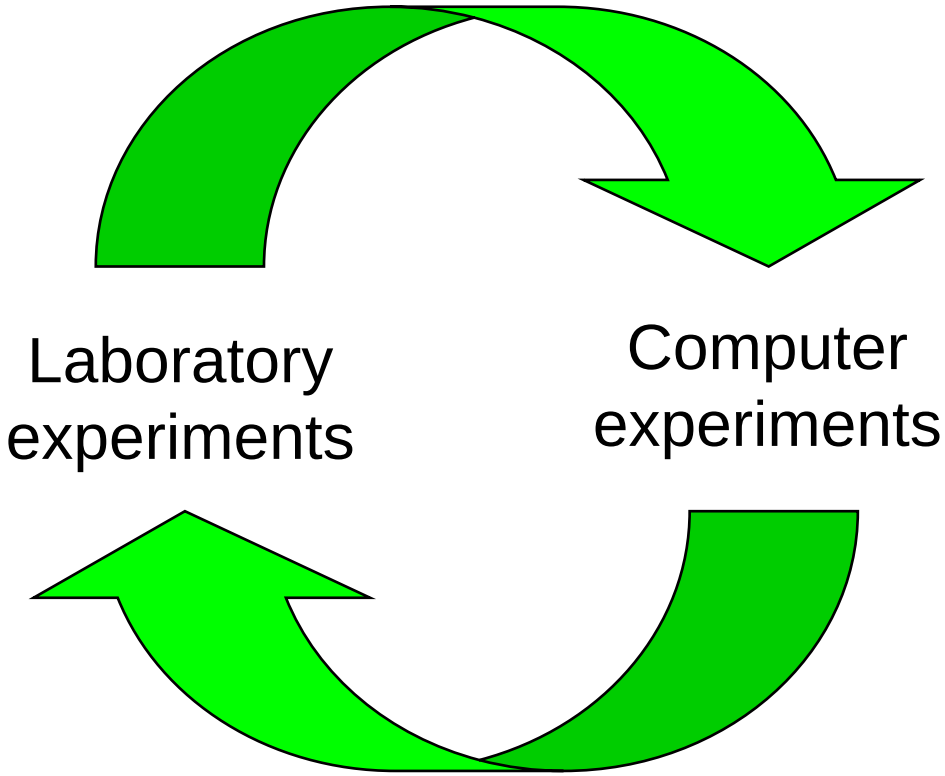
Types of models

- Qualitative
- Quantitative-1
  - Functional relationships not tested against data and parameter values not known
  - Hypothesis generation
- Quantitative-2
  - Data used to check functional relationships and parameter values
  - Prediction

Iteration of experiments in the laboratory and the computer



Questions

- Why should PIP be a negative regulator of the signaling?
  - Conditions under which the cell does not want to generate an inflammatory response?
  - Help to generate more switch-like transitions?

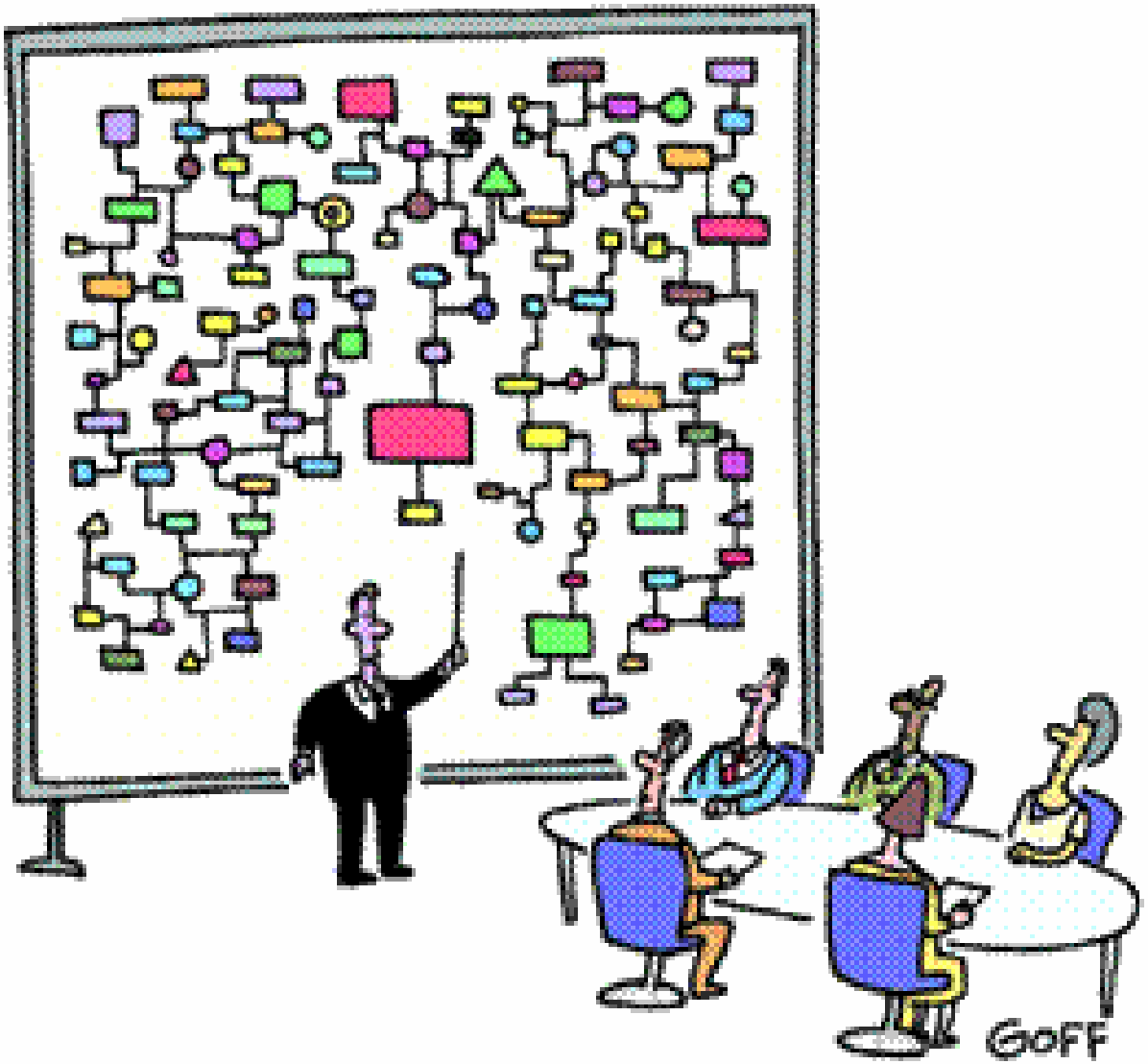
Summary

- Generic aspects of signal transduction pathways
- Qualitative analysis of existing literature suggests initial topology for computational model
- Targeted experimentation needed in support of computational model

Best time to think about signal transduction…

Acknowledgements

- Qiang Zhang
- Michael Breen
- Rusty Thomas
- Mel Andersen



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

End