Functional analysis of biochemical signaling pathways mediating the acute inflammatory response

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Workshop on Systems Biology and the Human Health Risks of Environmental Chemicals
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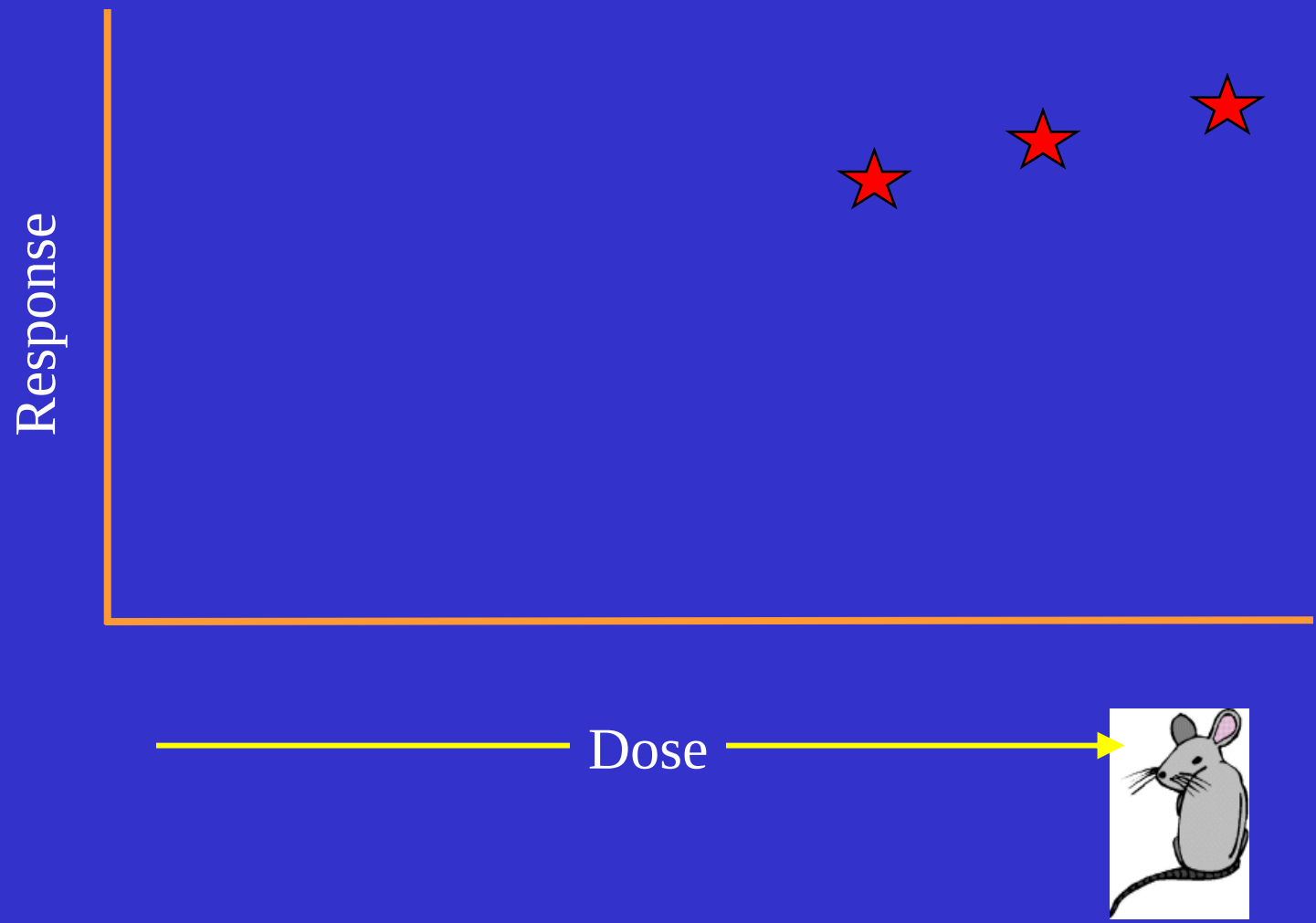
Outline

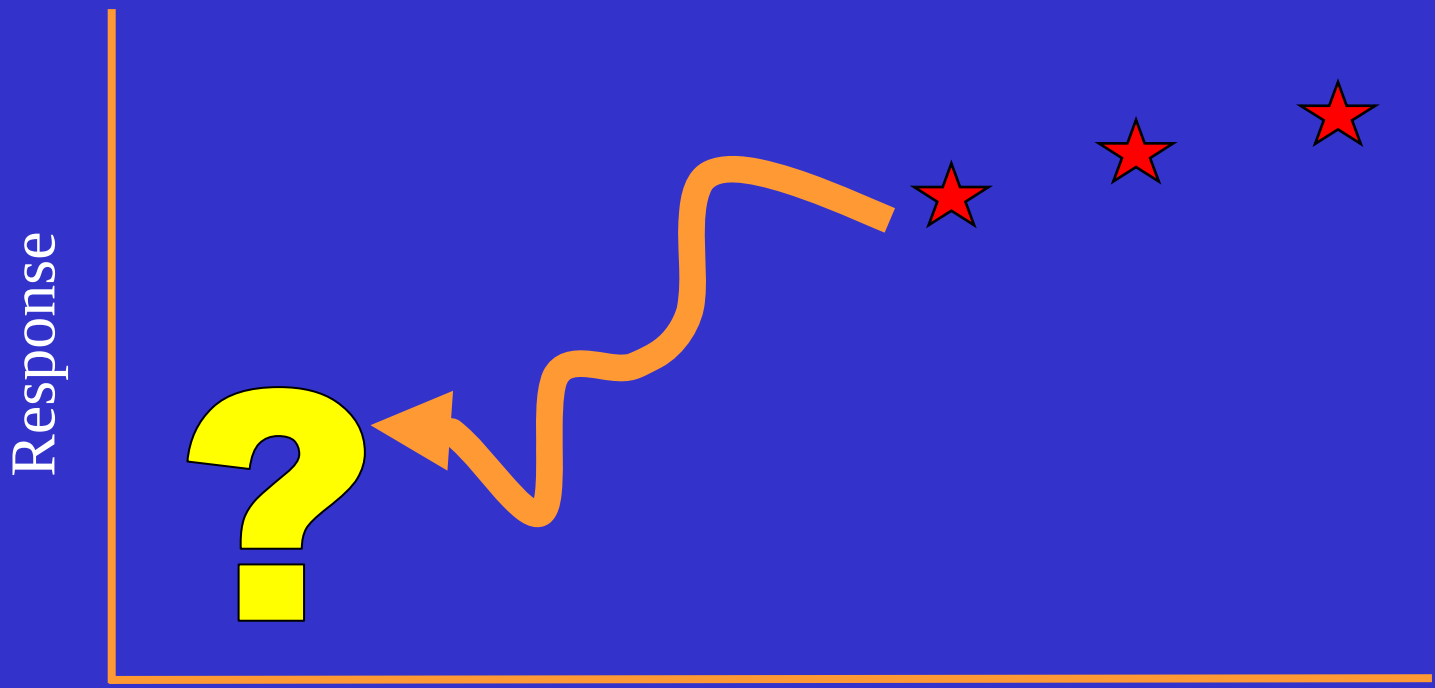
- Dose-response, time-course, and risk assessment
- Nonlinearities in cell signaling
- Issues in developing computational models of signaling networks
- Analysis of IL-1α-mediated signaling in acute inflammation

Predicting health risks: Dose-response and exposure assessments

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

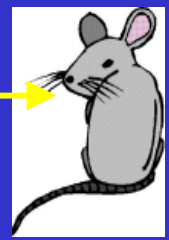


Not much!

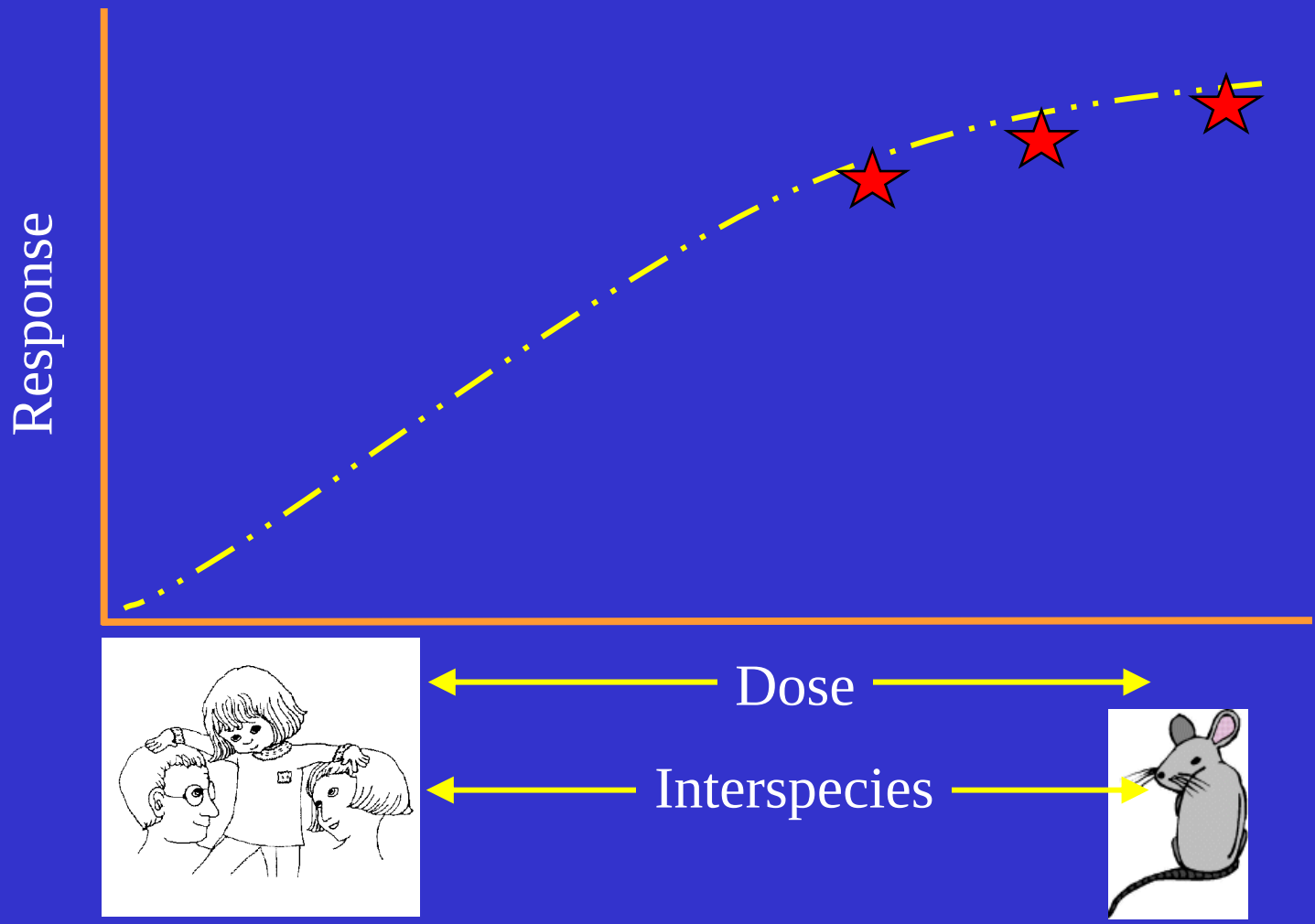


Dose

Interspecies



Possibilities



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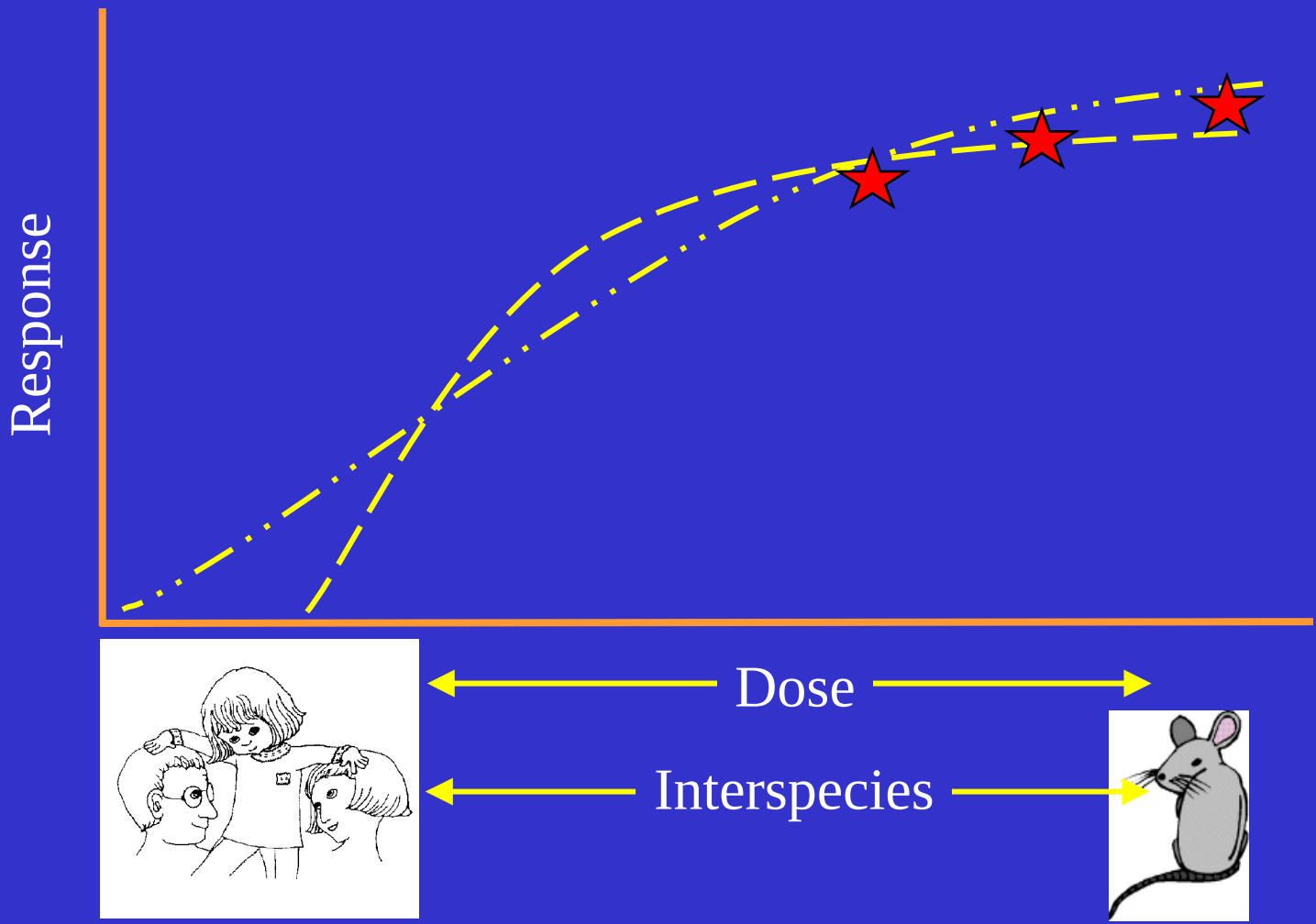

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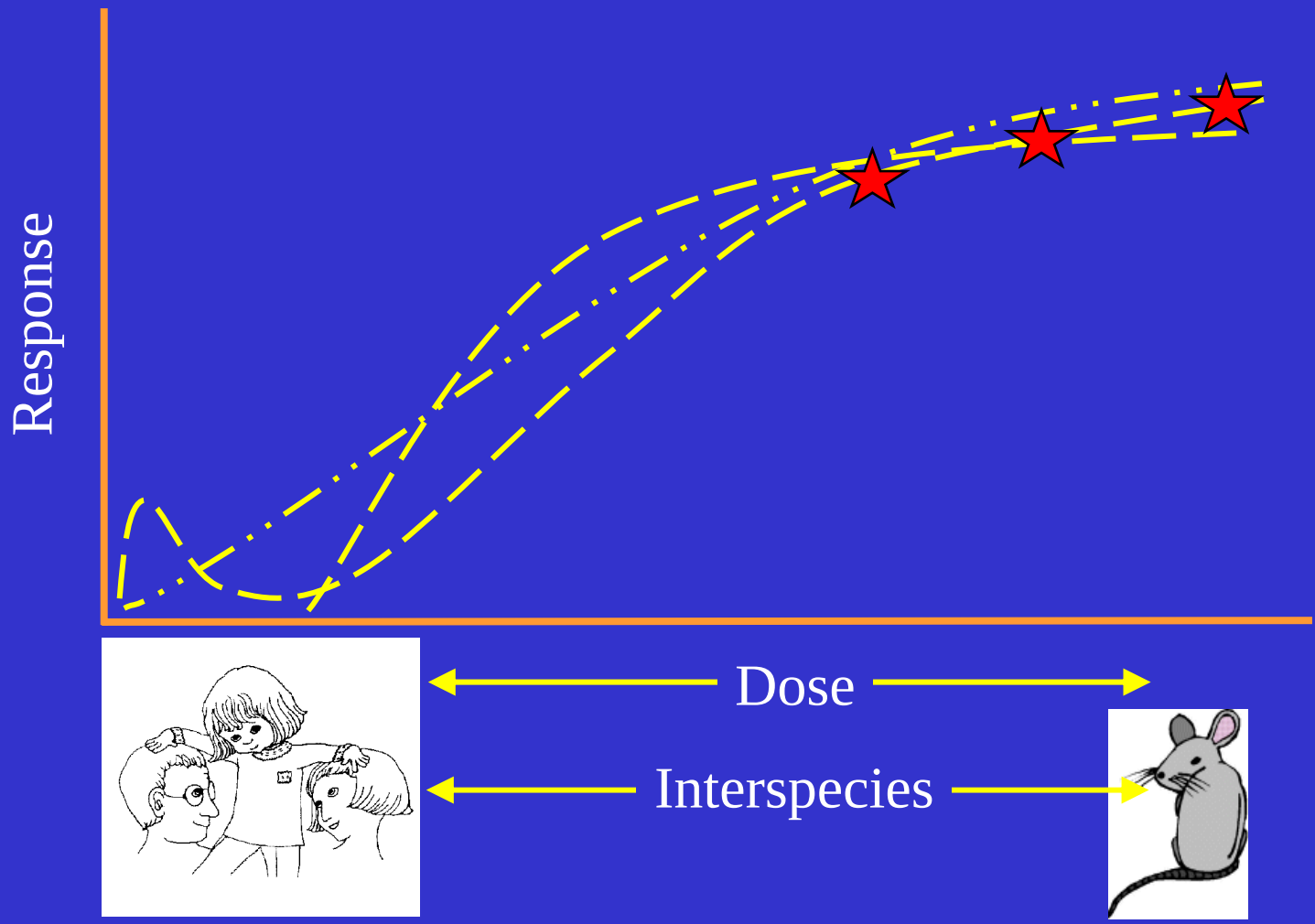

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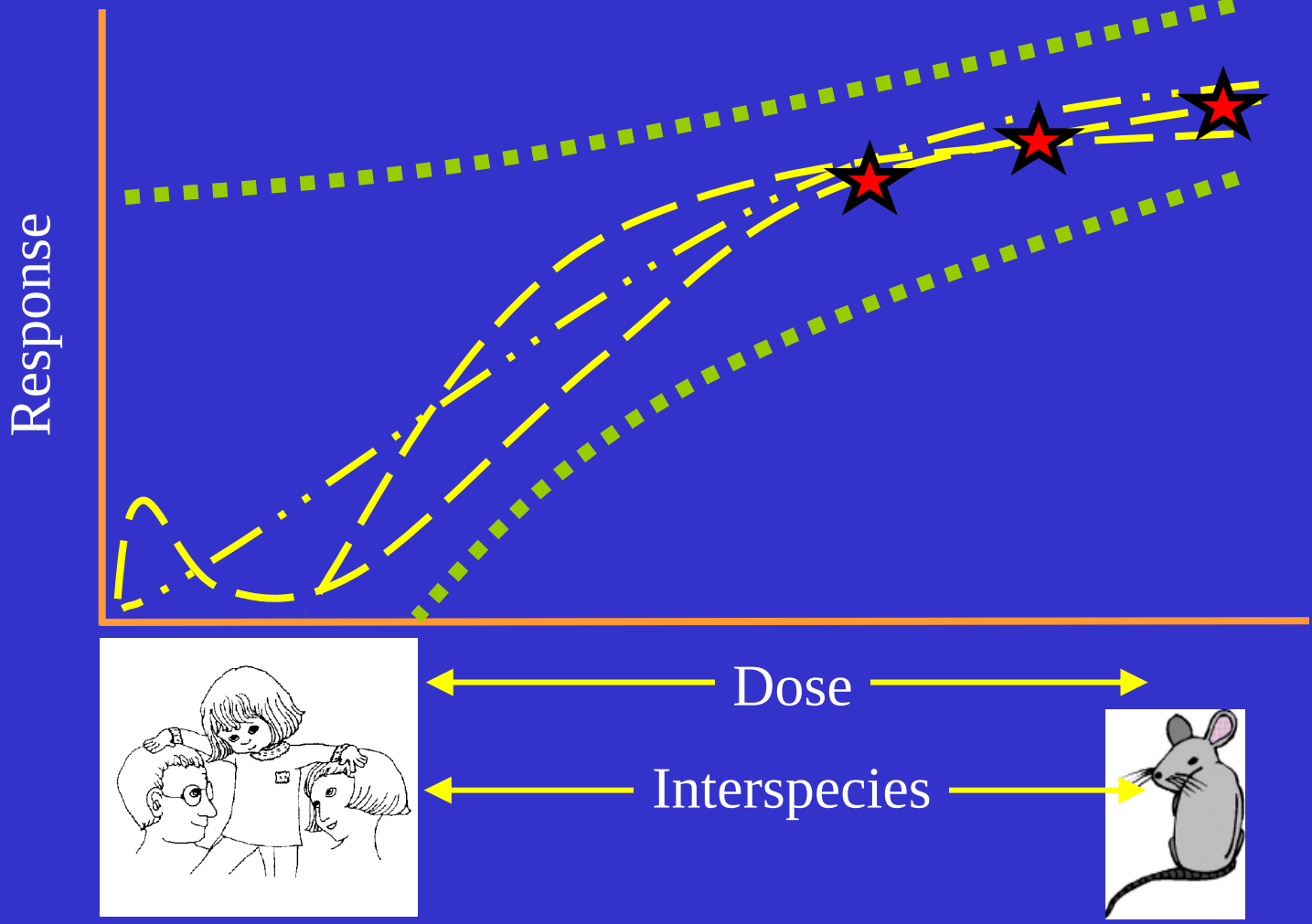
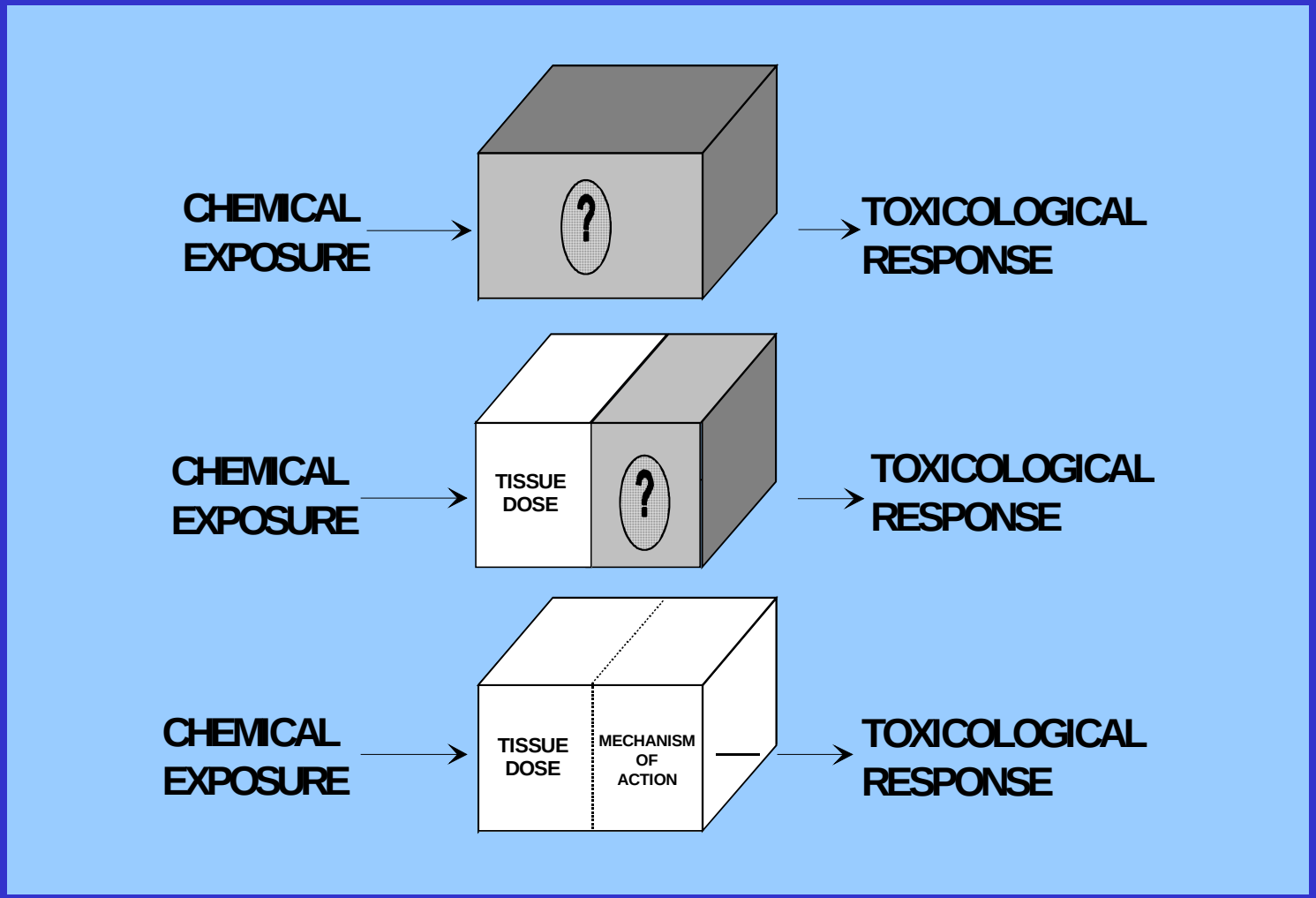
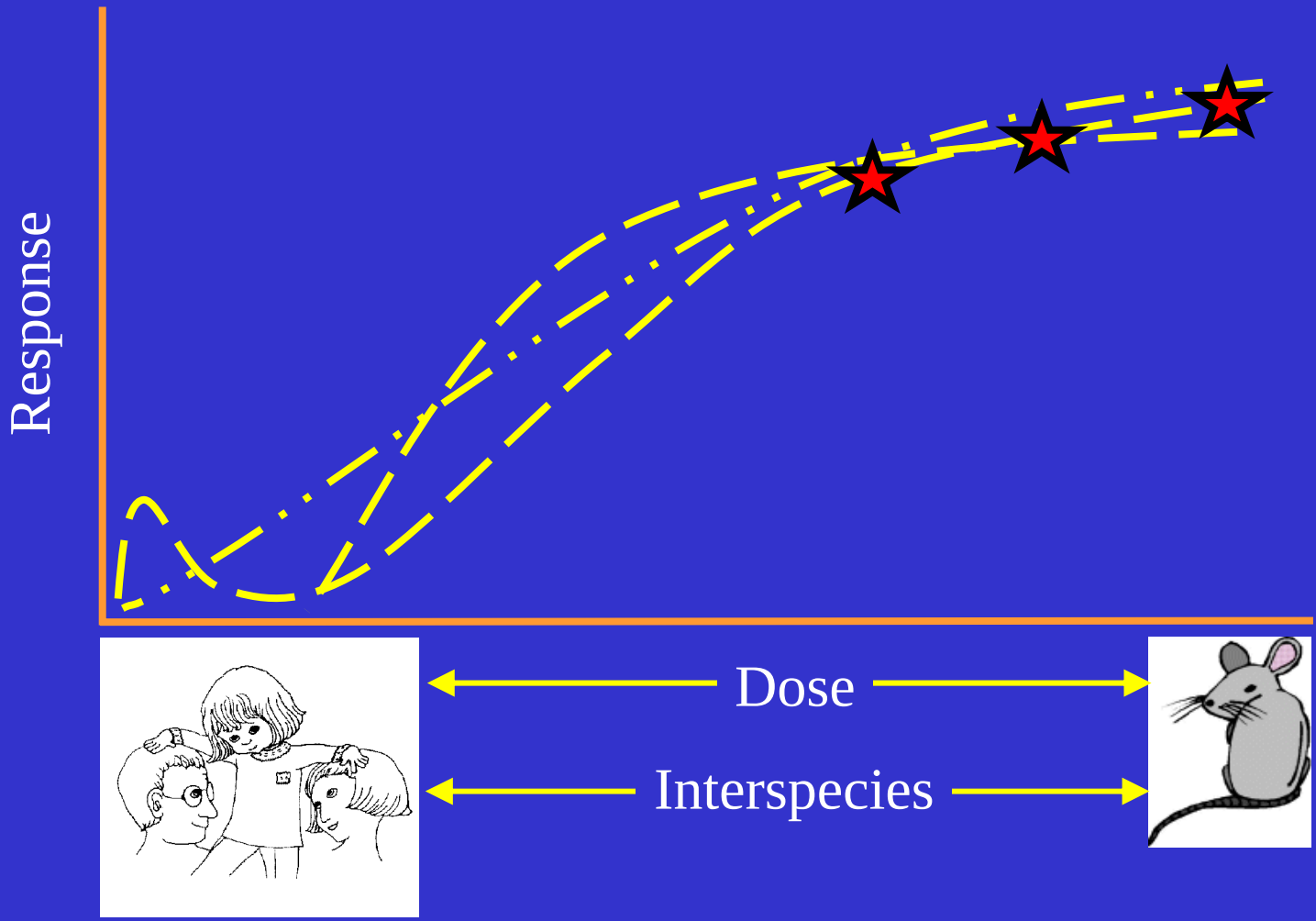


Biological mechanisms determine dose-response



Refining the description with research on mechanisms



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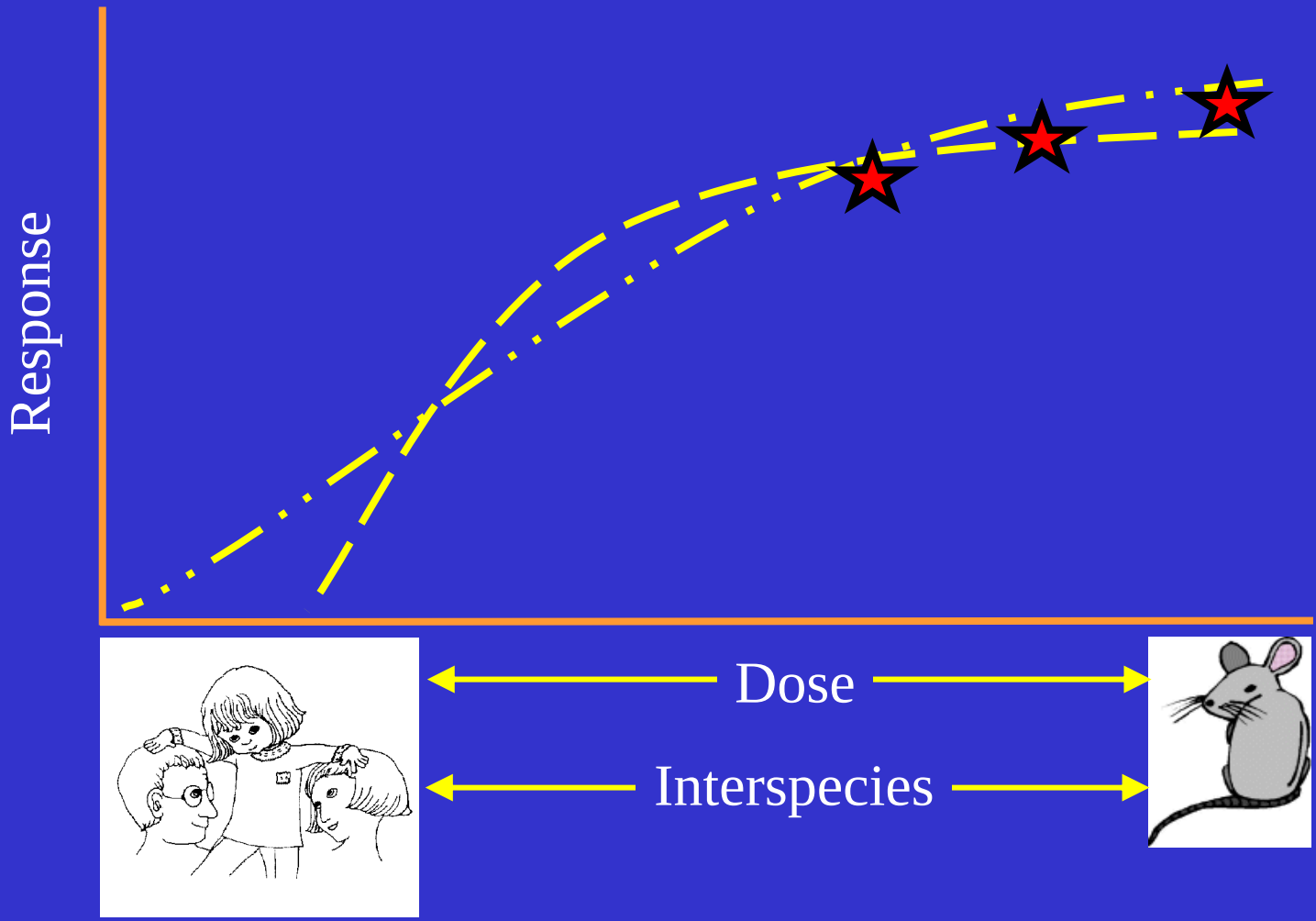

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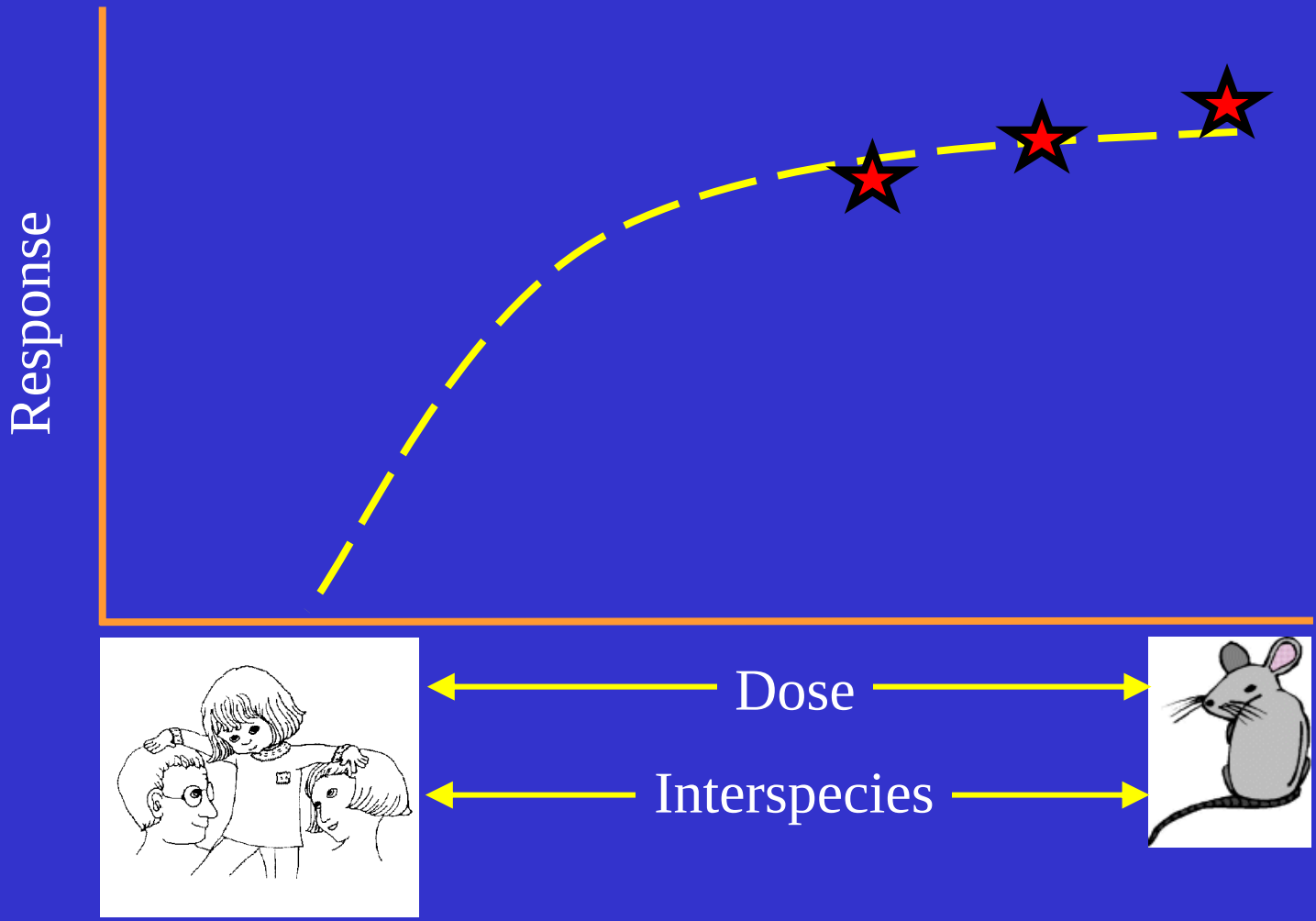

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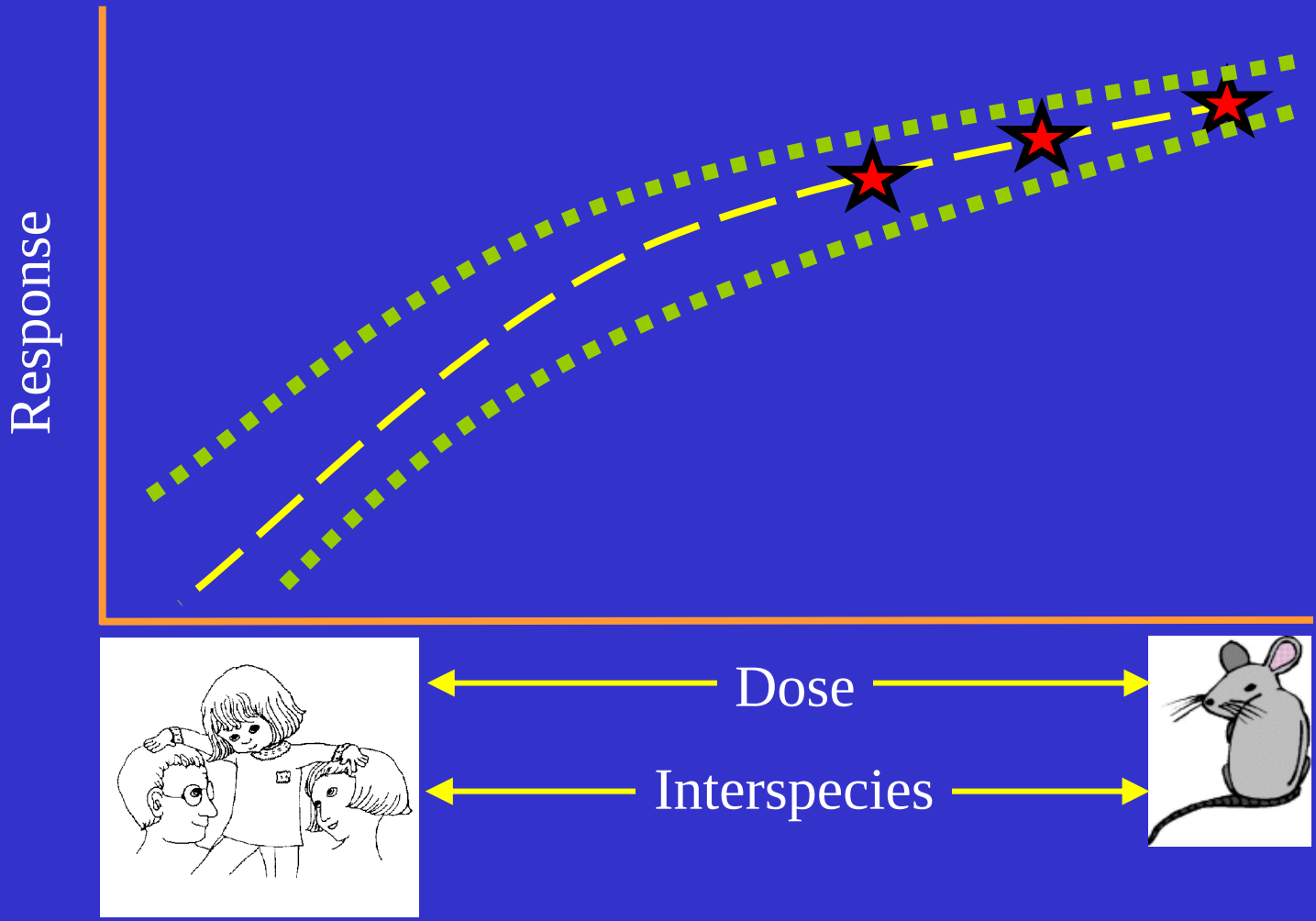
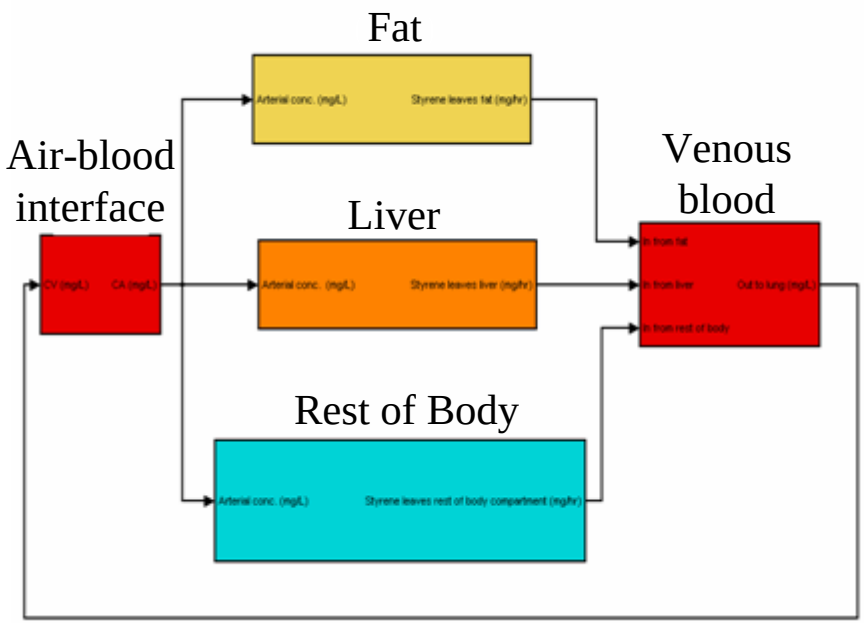
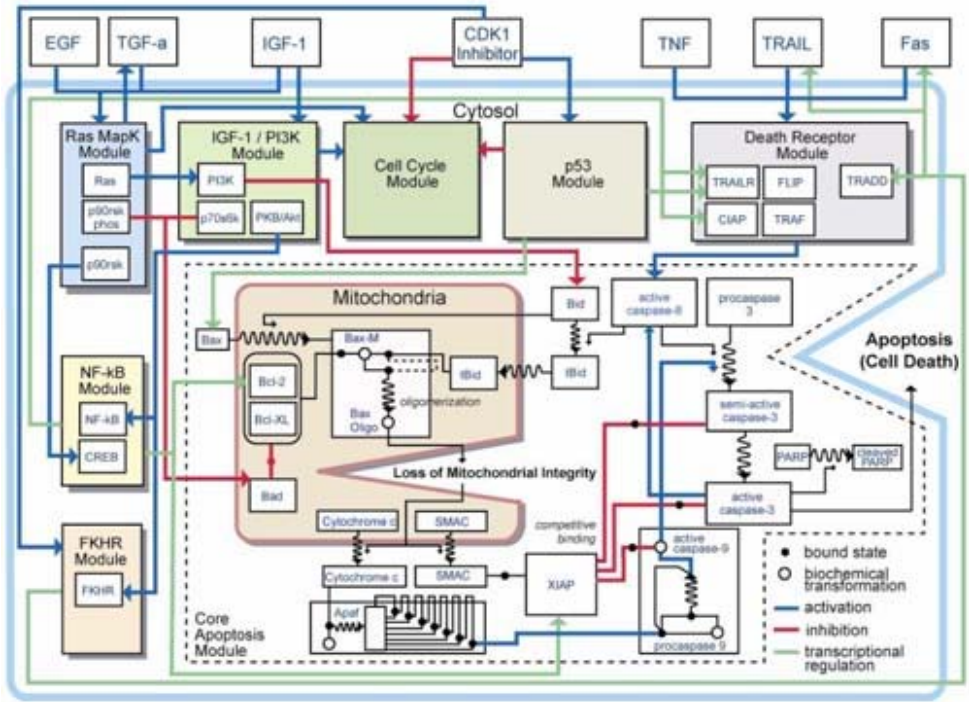
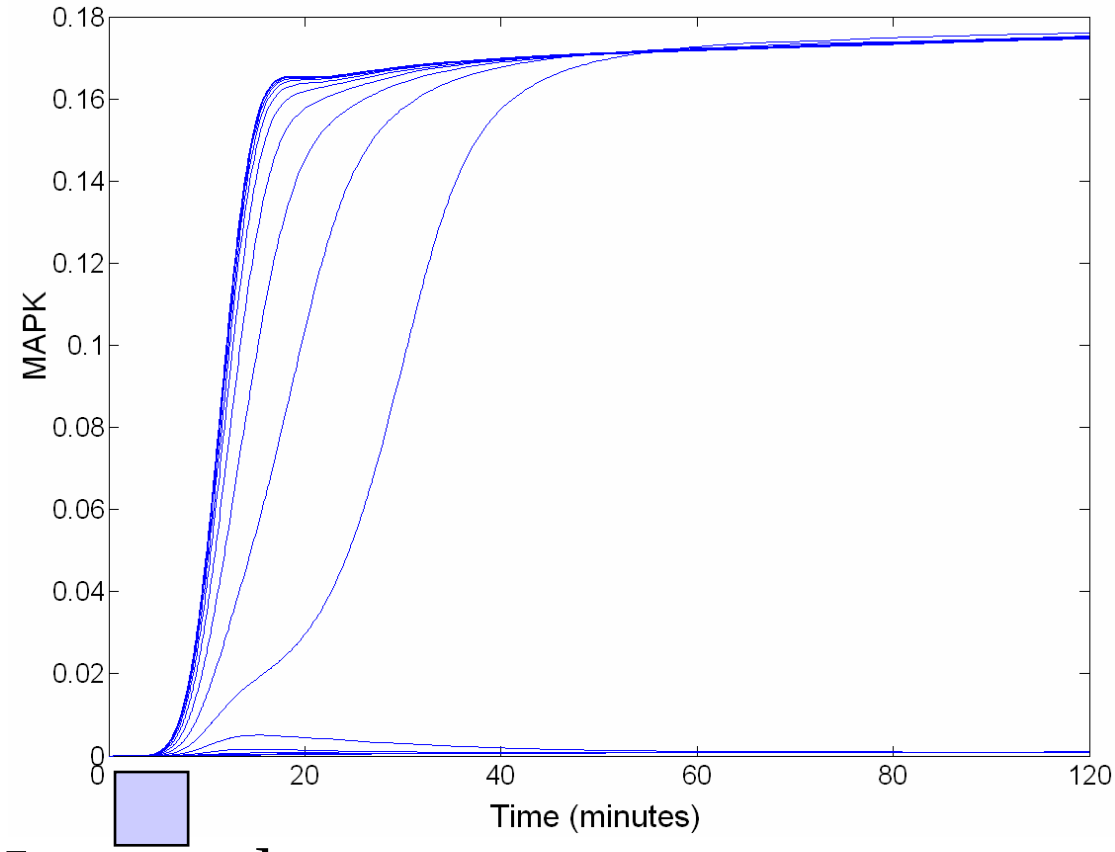


Systems Modeling





Nonlinearity in MAPK signaling

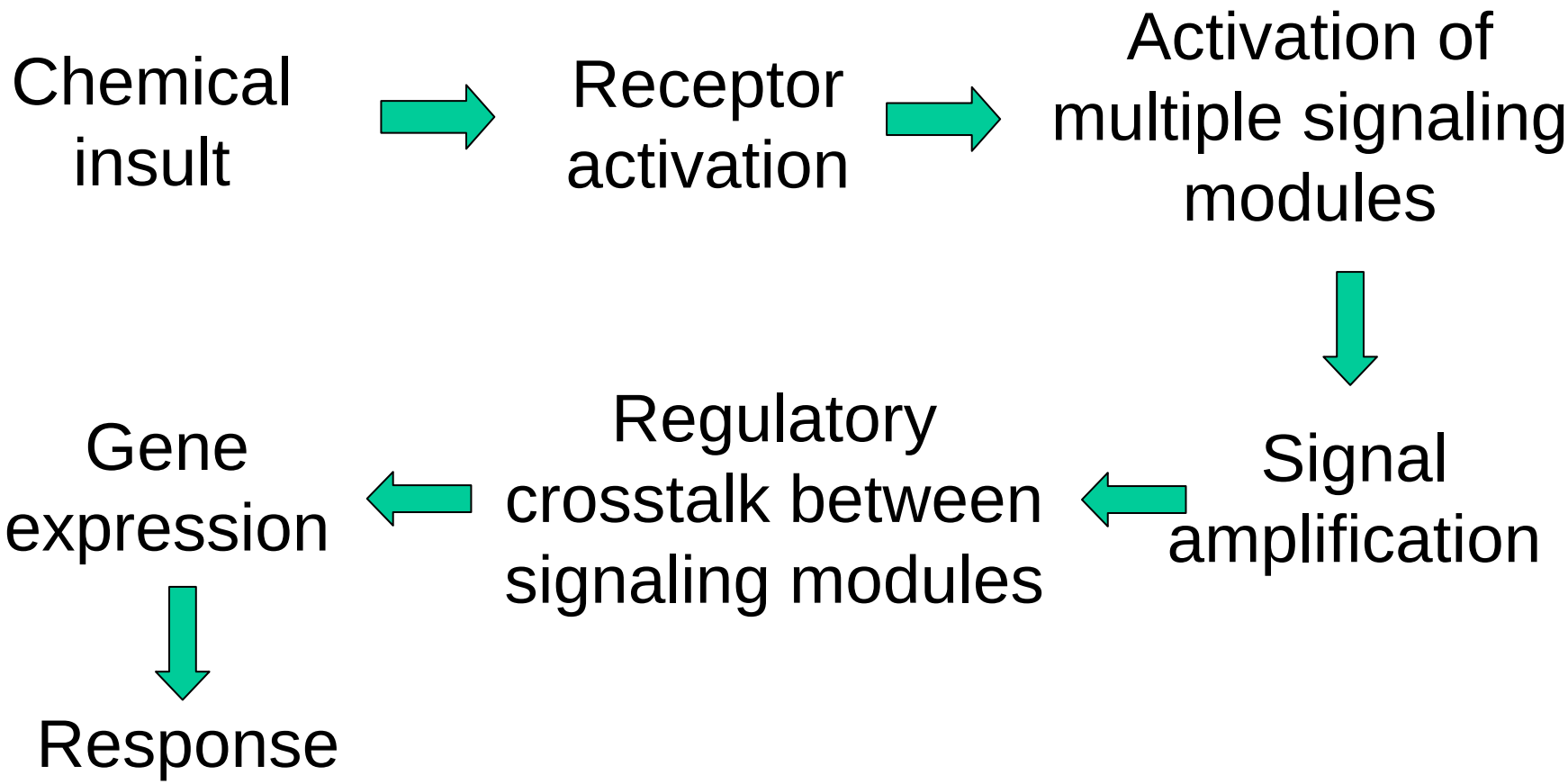


Input pulse

Hypothesis

- Intracellular signaling can introduce nonlinearities into dose-response behaviors

Generic scheme for signaling



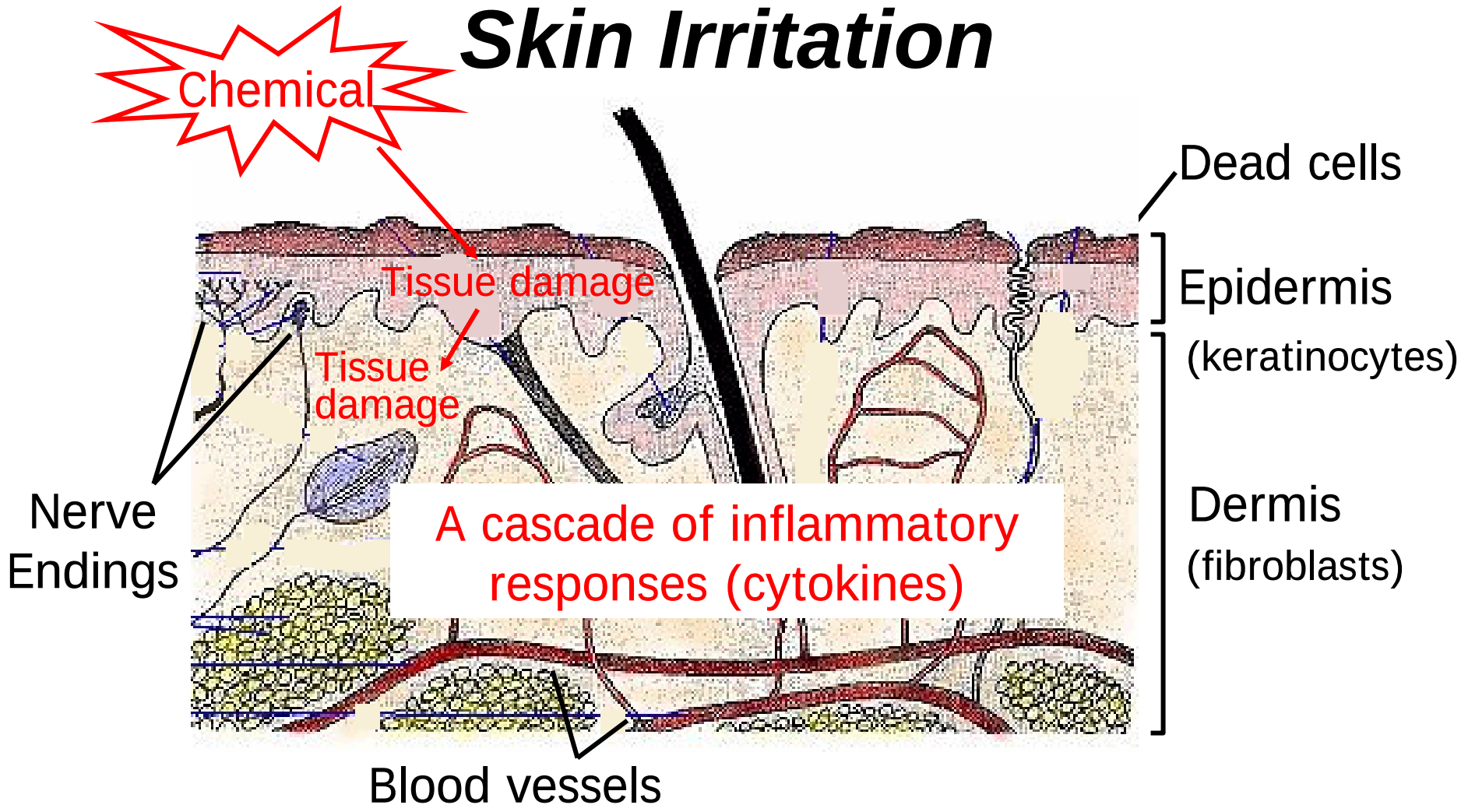
Characteristics of cellular signaling

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

Illustrating concepts by working through an example involving the acute dermal inflammatory reaction

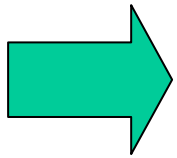
- Collaboration with James MacDougal, Wright State University, Ohio, USA

Skin Irritation



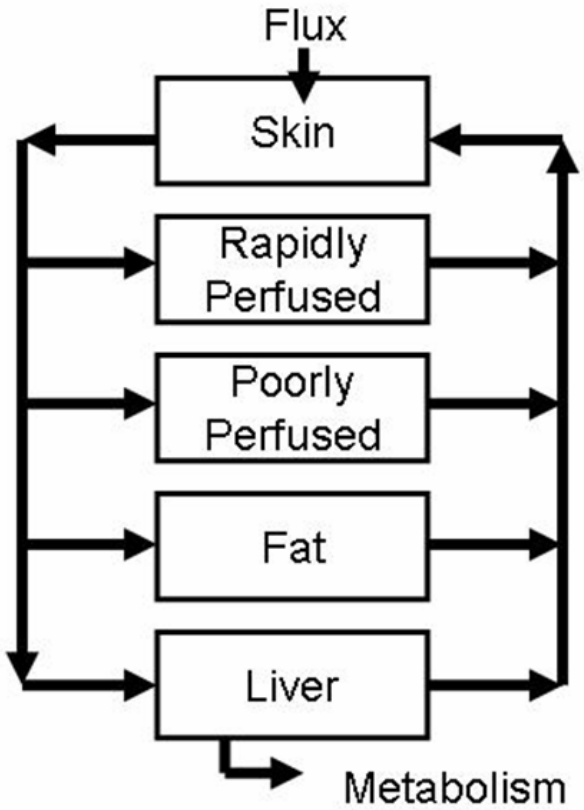
Apical scheme (model)

Chemical irritant

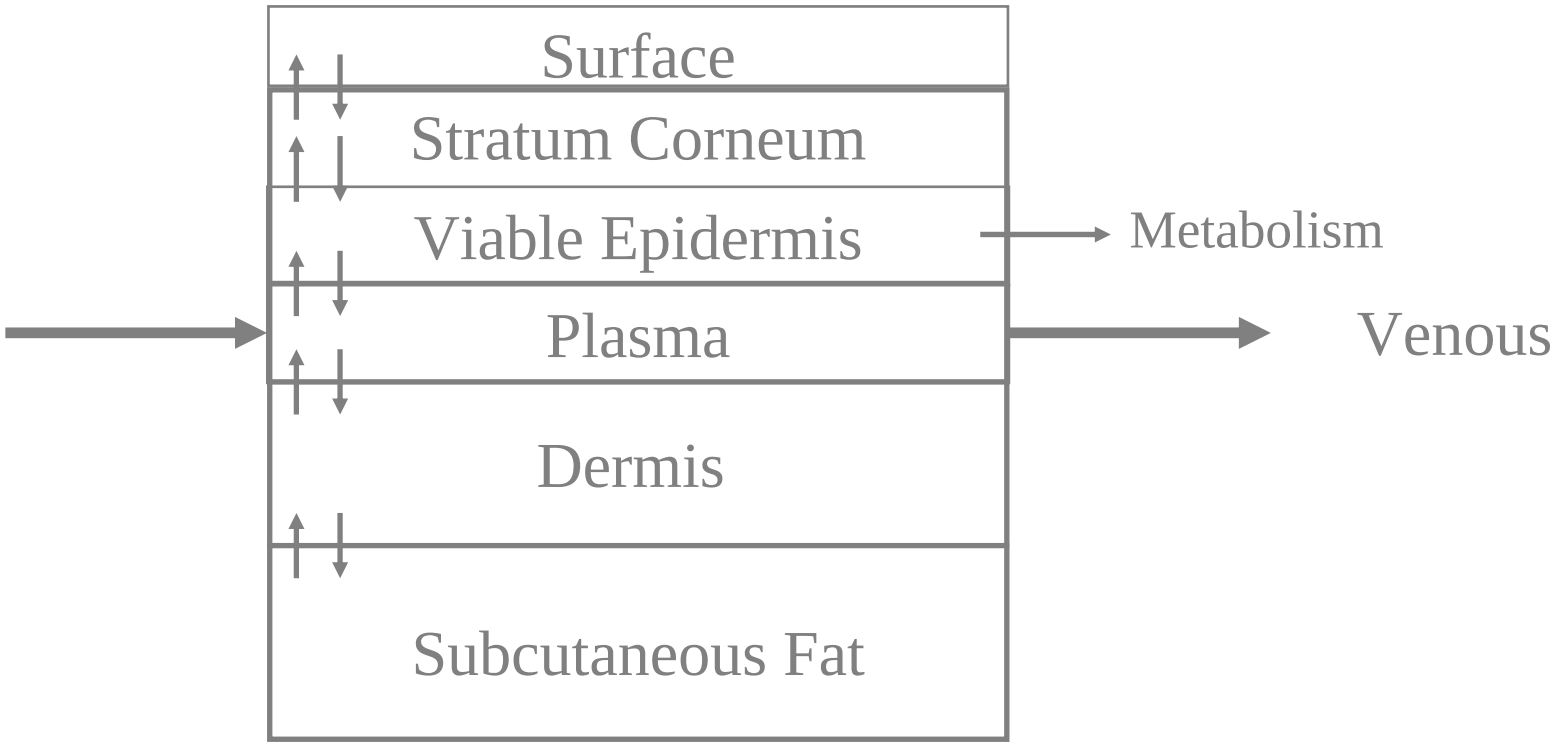


Skin inflammation

First, define the dose to cells in the skin: Biologically-based PK model



Enhanced model of skin

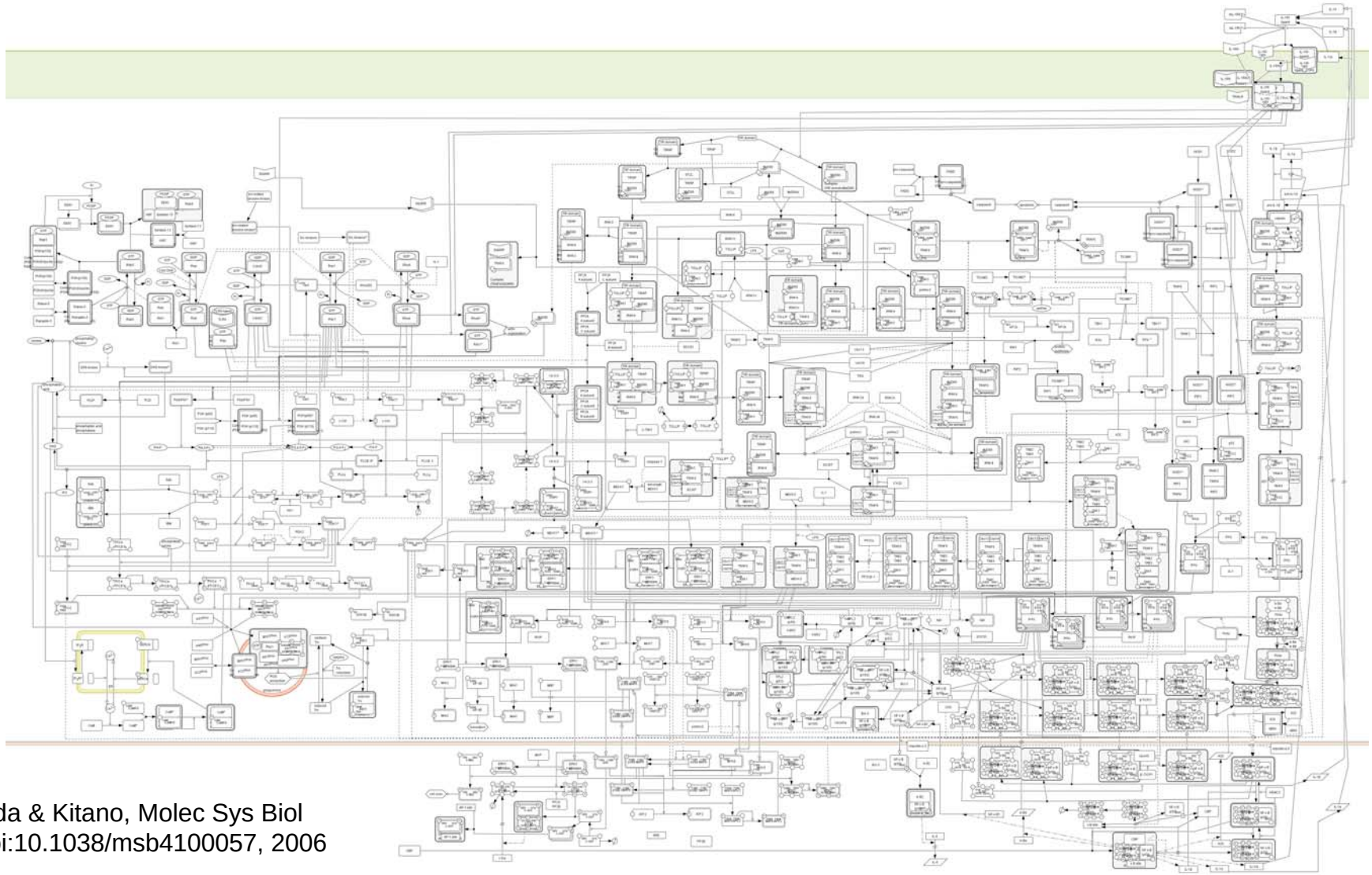


Scheme including pharmacokinetic modeling

Chemical irritant → Dose at target site → Skin inflammation

Having defined the dose, work on a description of how the tissue responds

Molecular-level scheme



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

Functional analysis

- How do we capture the essential dynamic features of a signaling network without describing every molecular interaction?
  - Ideal vs. practical

Available online at www.sciencedirect.com
SCIENCE DIRECT
Biology of the Cell 96 (2004) 355–362
Biology of the Cell
www.elsevier.com/locate/biocell

Review

Modeling Cell Signaling Networks

Narat J. Eungdamrong, Ravi Iyengar *

Department of Pharmacology and Biological Chemistry Mount Sinai School of Medicine New York NY 10029 USA

Received 24 October 2003; accepted 11 March 2004

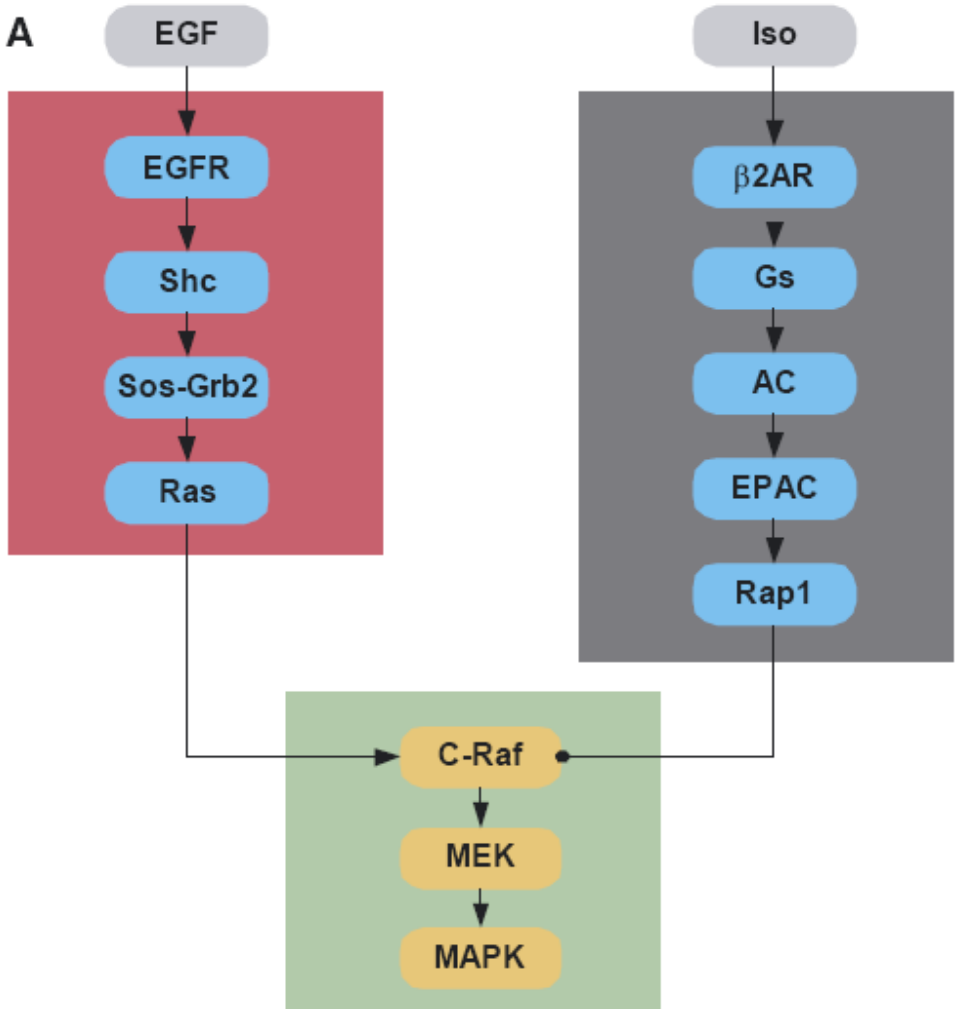
Available online 28 April 2004

Eungdamrong & Iyengar

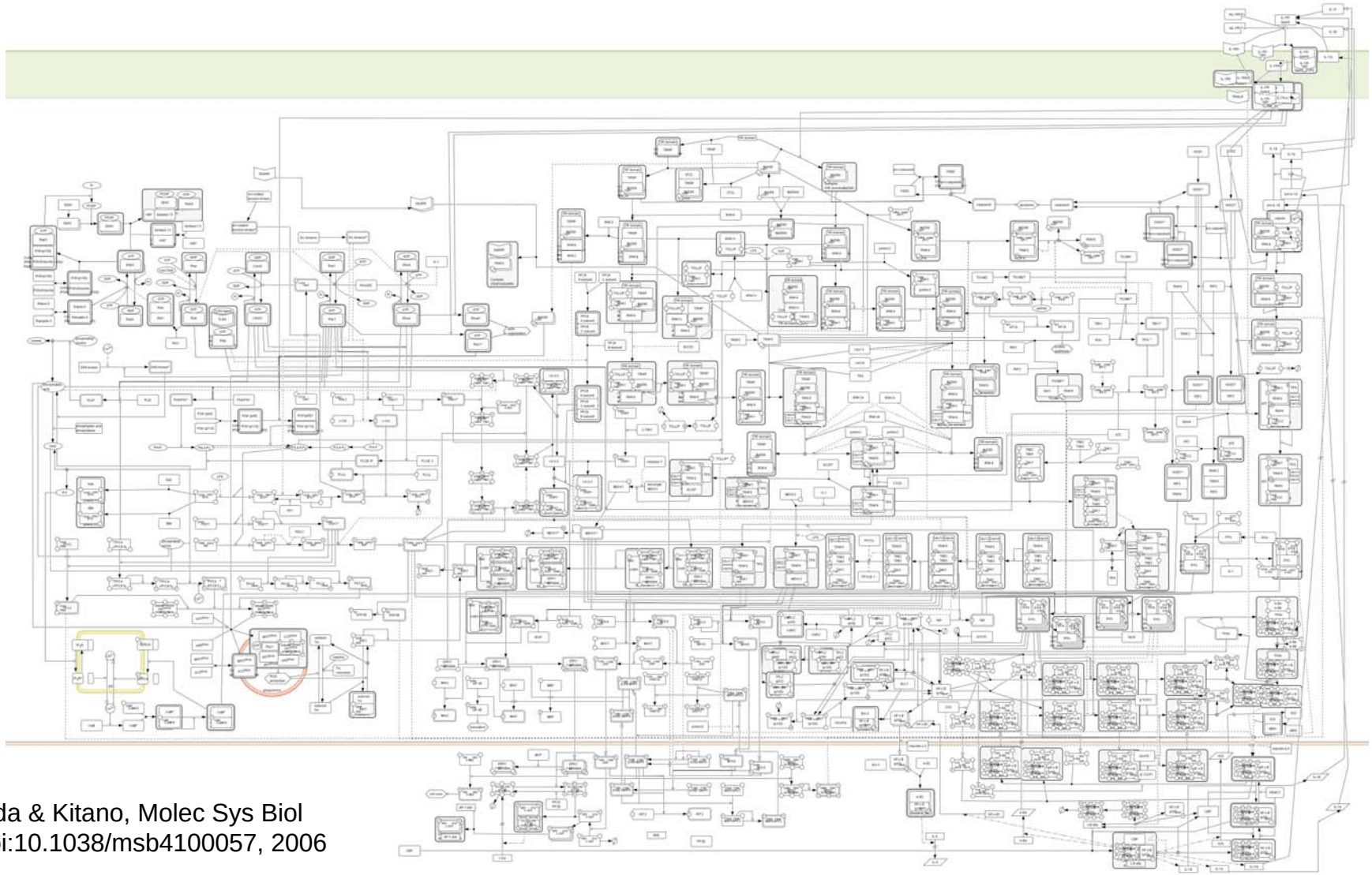
- …the first step is to identify the “connection map”…
- …then to organize the connection into modules that can be constrained by experimental data and analyzed computationally…

Eungdamrong & Iyengar

Modules that could be used to describe interactions between the growth factor and b-adrenergic receptor pathways. The growth factor signaling pathway is divided into two modules (the red box and the green box). Such modularity divides this pathway by their location within different subcellular regions. All members of the red box are functional at the plasma membrane while the members of the green box are cytoplasmic. At a functional level, the reactions in the red box specify how EGF binding to its receptor regulates activation of Ras while the reactions in the green box specify how the activated Ras regulates MAPK phosphorylation. The gray box provides a counter point to the organizational logic of the red and green boxes. Here the module spans reactions from the membrane to the cytoplasm, from the b-adrenergic receptor agonist isoproternol to the small G protein Rap1 in the cytoplasm. This modular arrangement provides a facile way of understanding how b-adrenergic receptor stimulation could inhibit or augment EGF activation of MAP-kinase.



Molecular-level scheme



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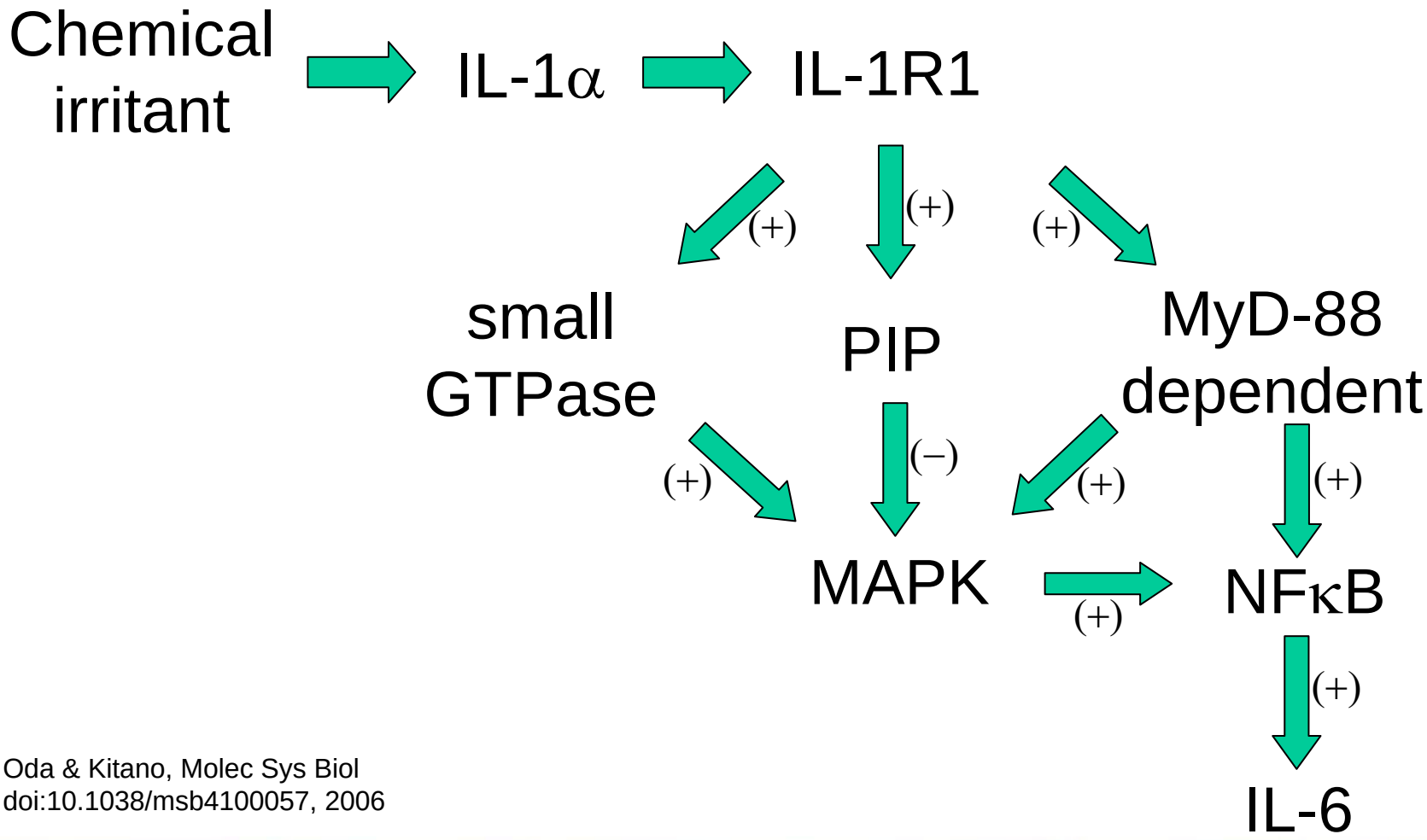
Modular scheme for IL-1α-mediated irritant response



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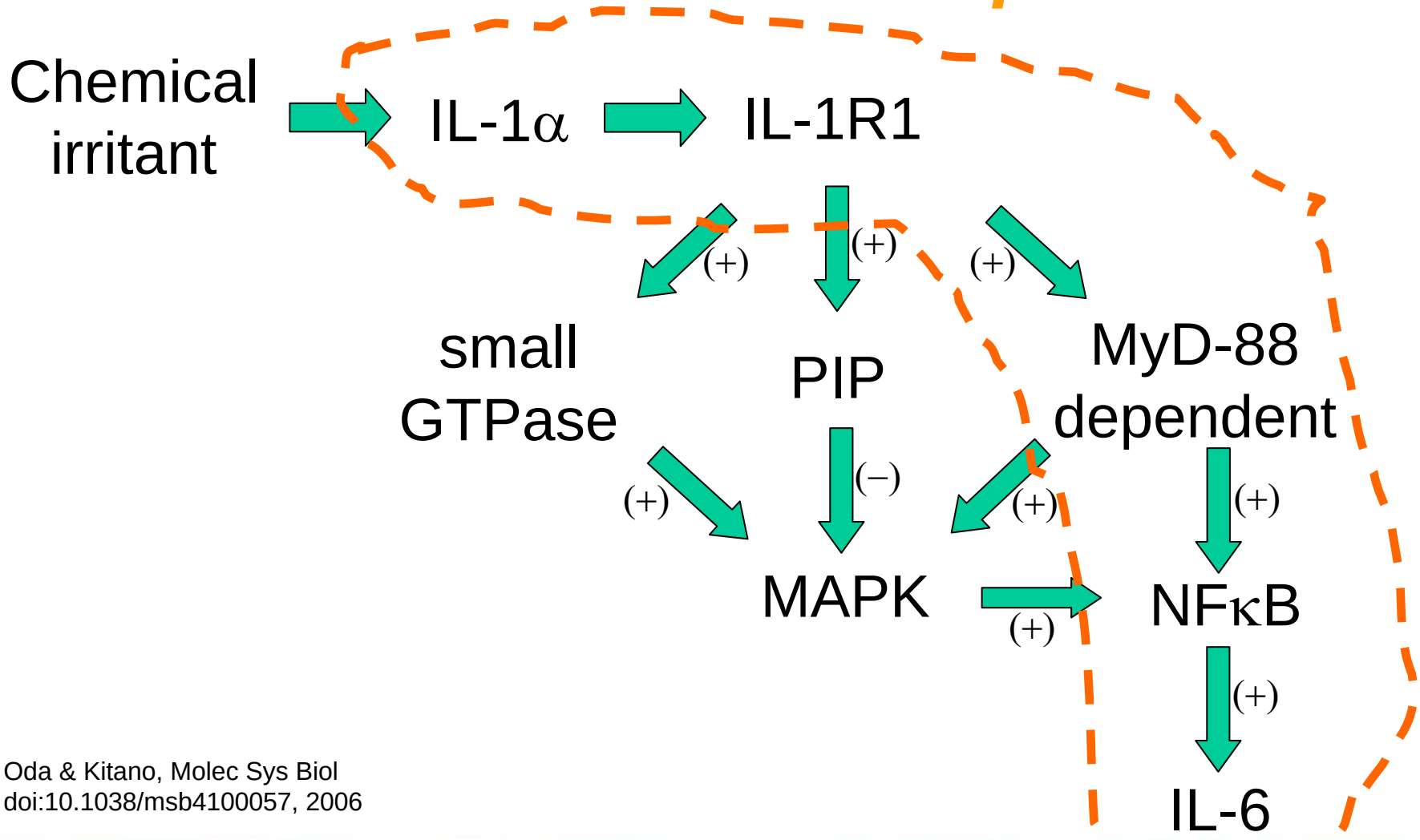
What do we know about these modules?

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

Computational modeling of IL1α signaling through NFκB to IL6

Modular scheme for IL-1α-mediated irritant response



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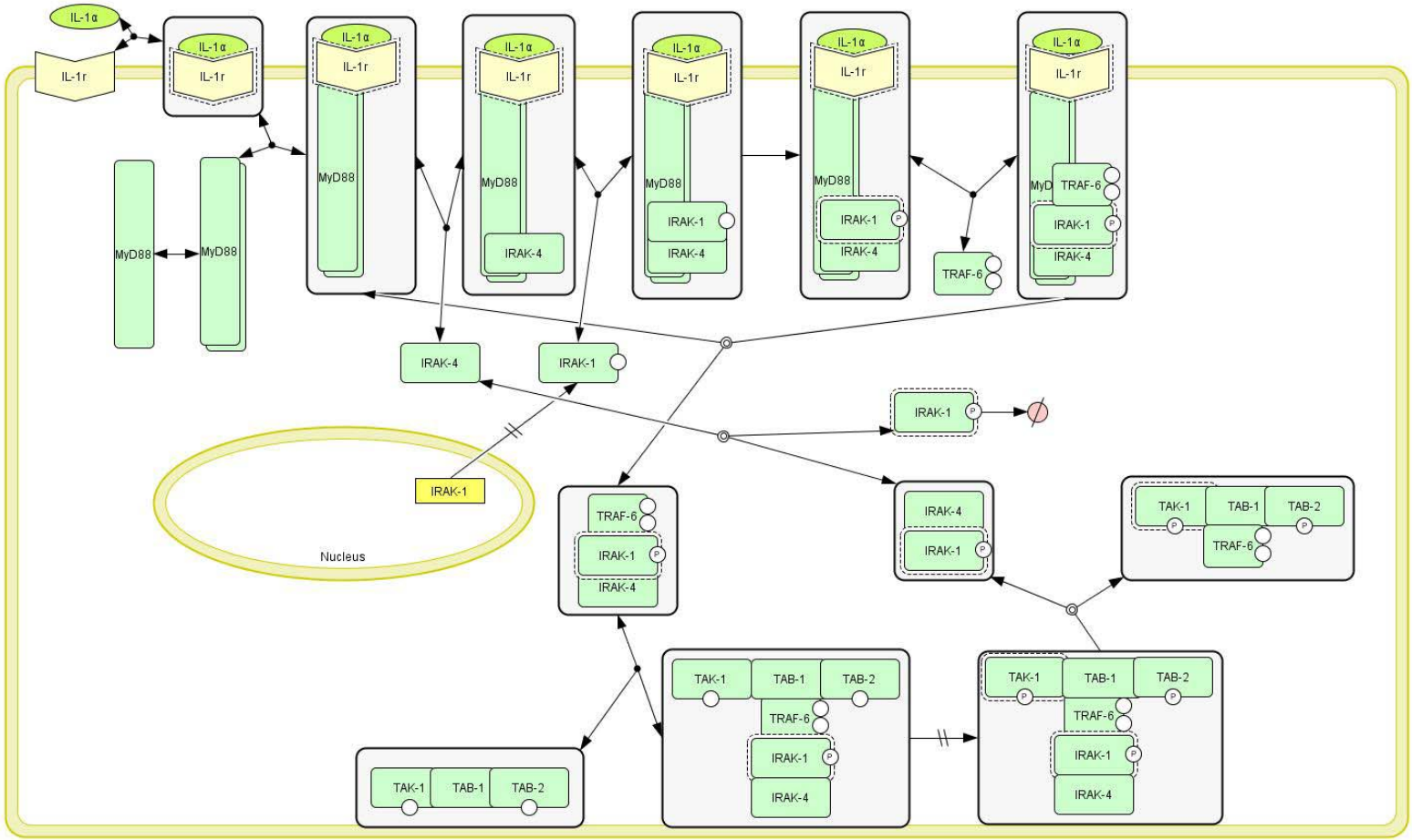
Types of models

- 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

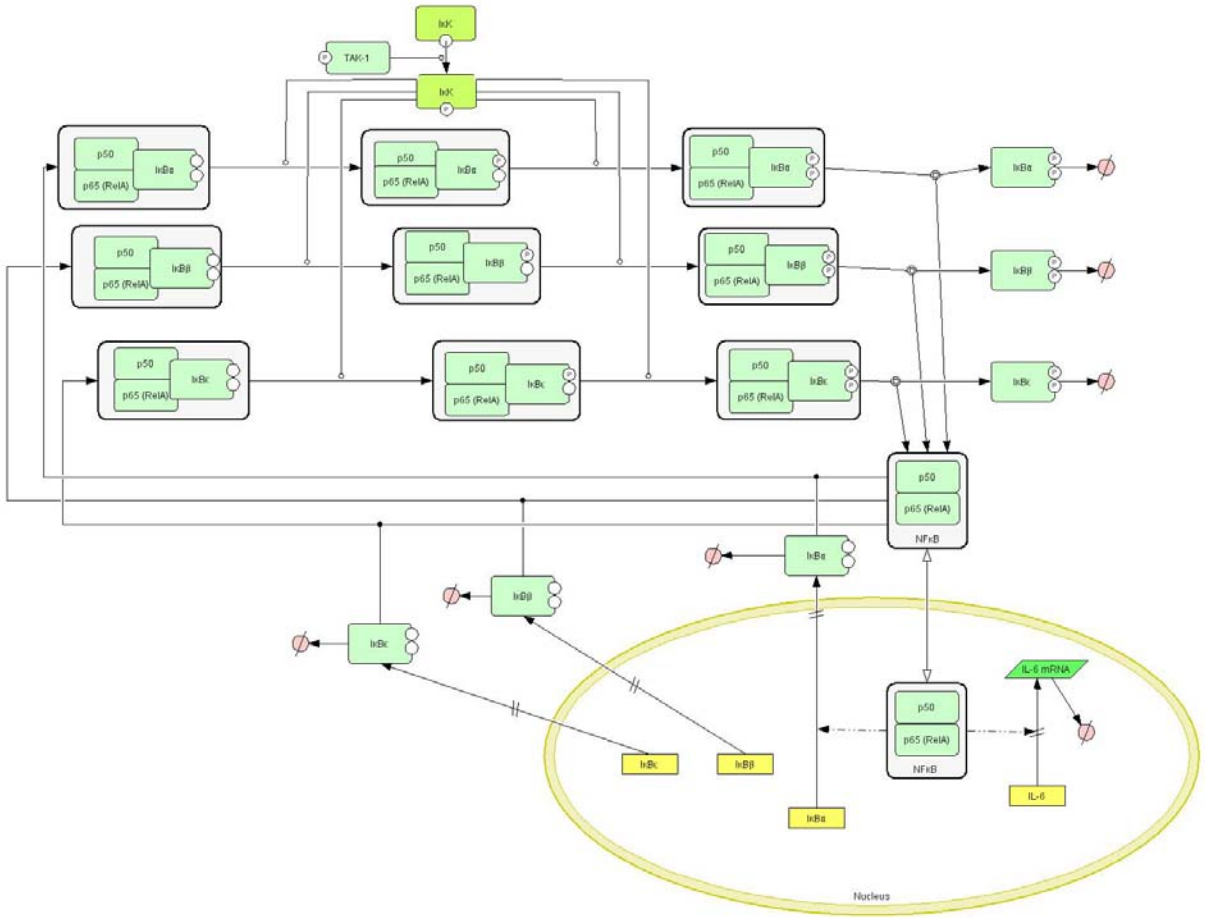
Software

- CellDesigner
- MATLAB/Simulink

IL1α signaling through MyD88 to TAK1



Signaling from TAK1 through NFκB to IL6



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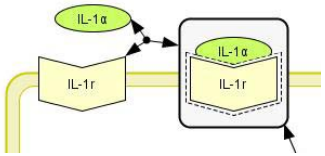

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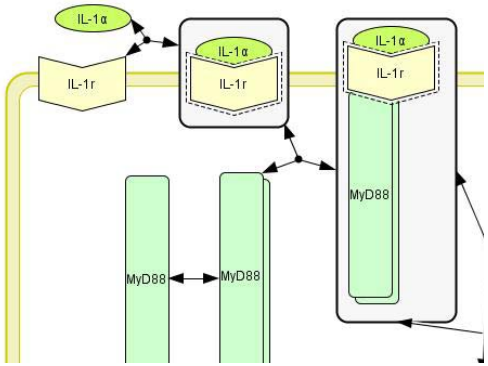

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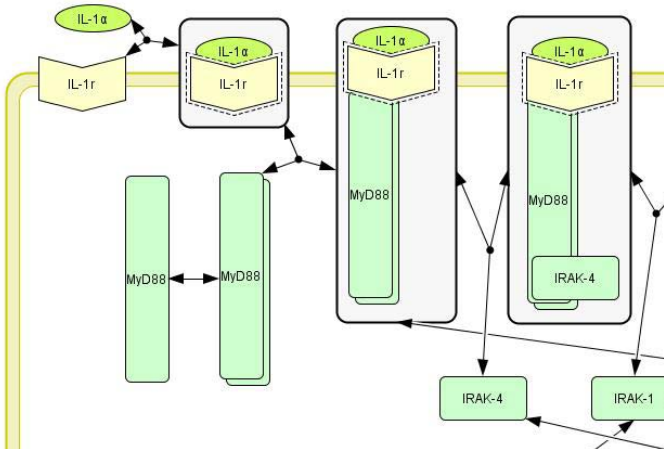

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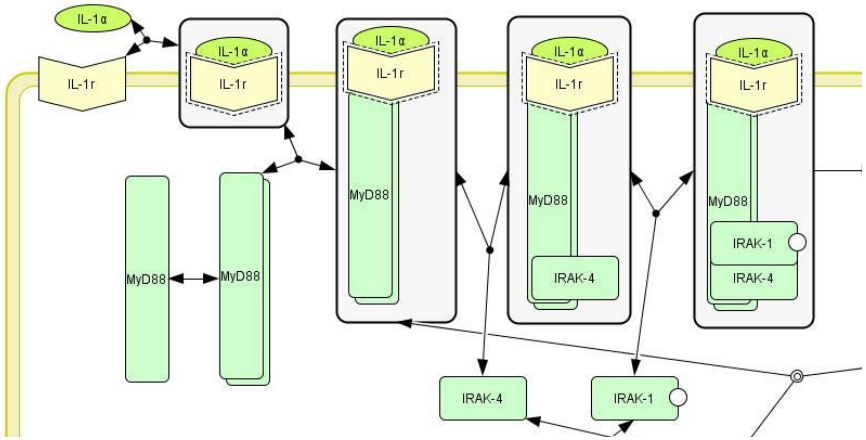

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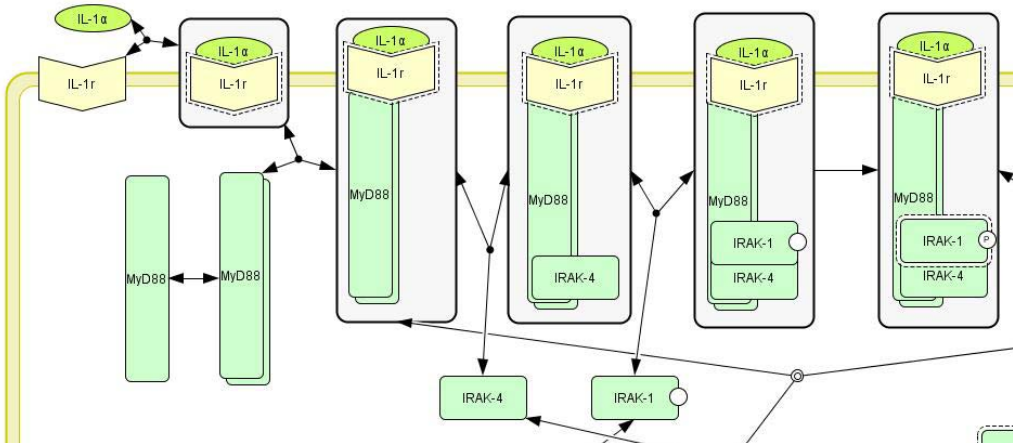

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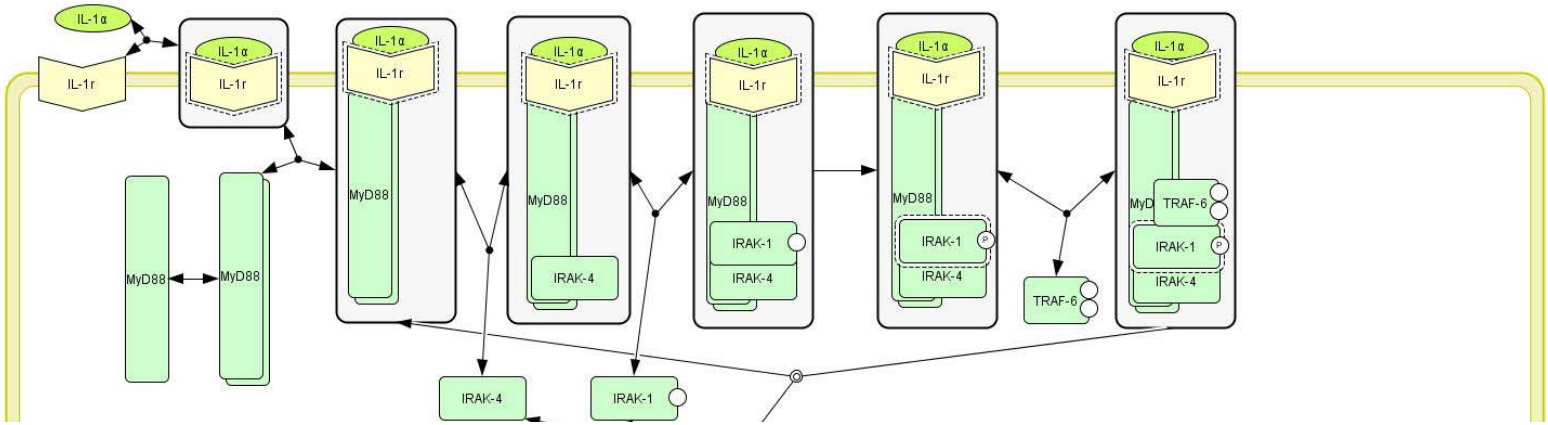

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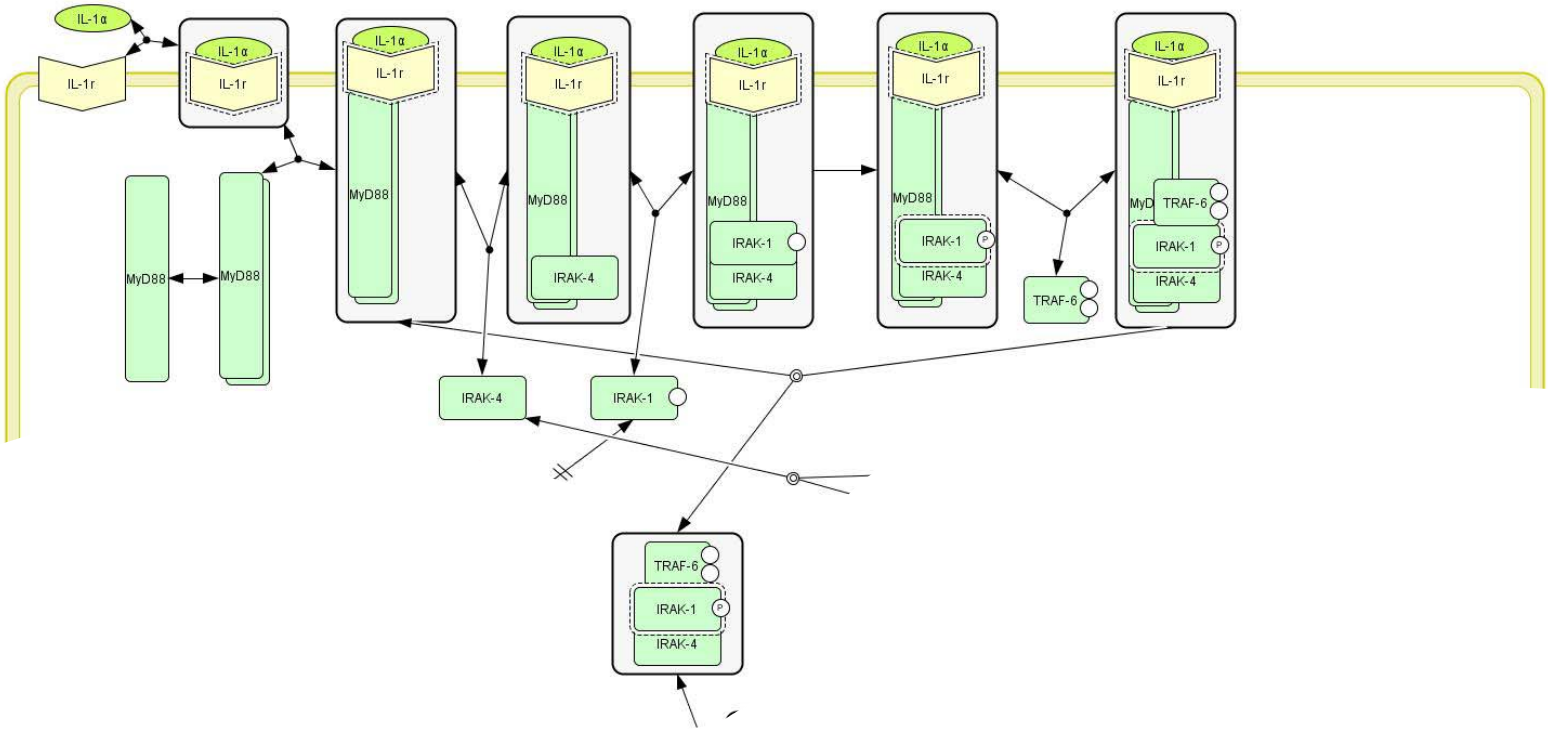

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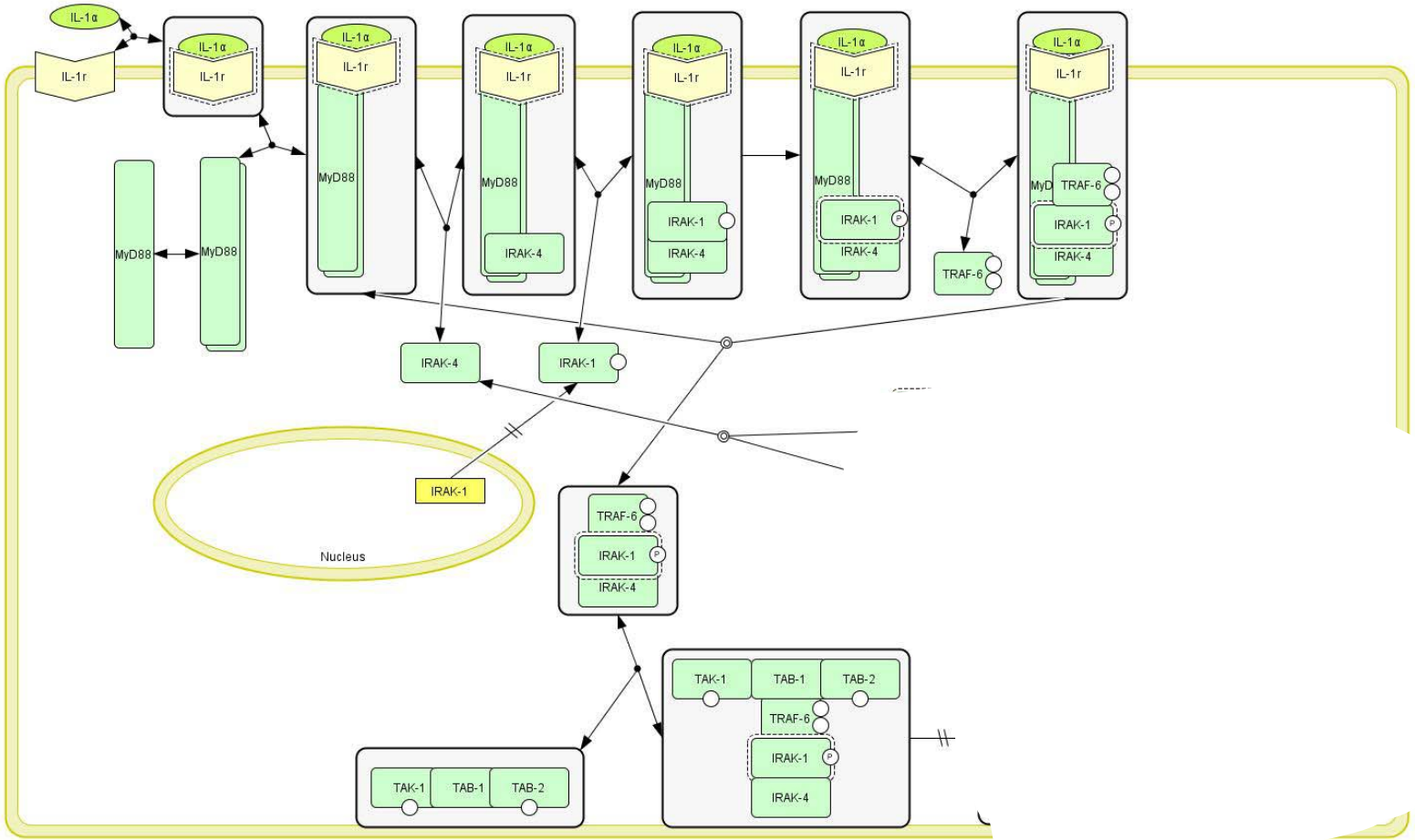

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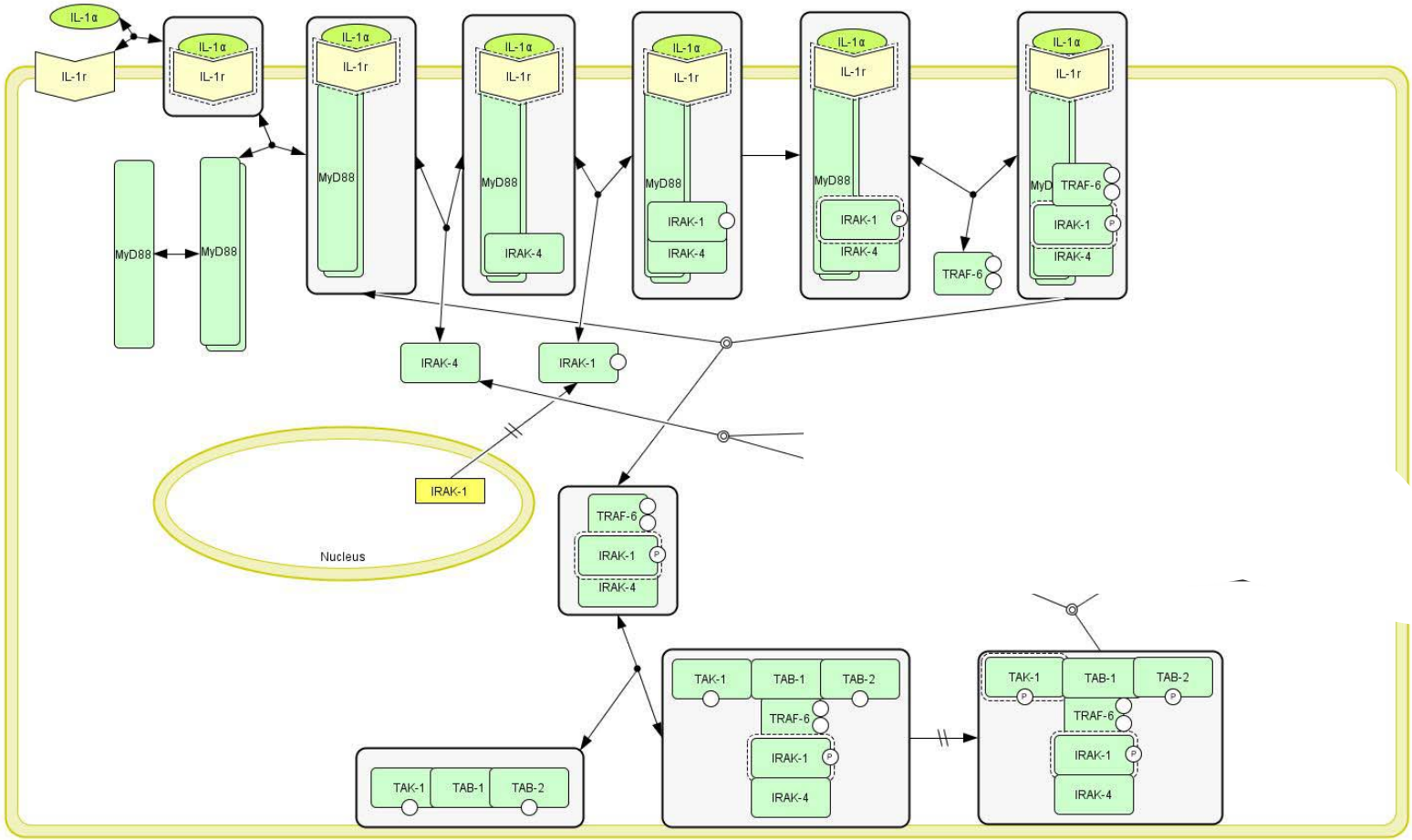

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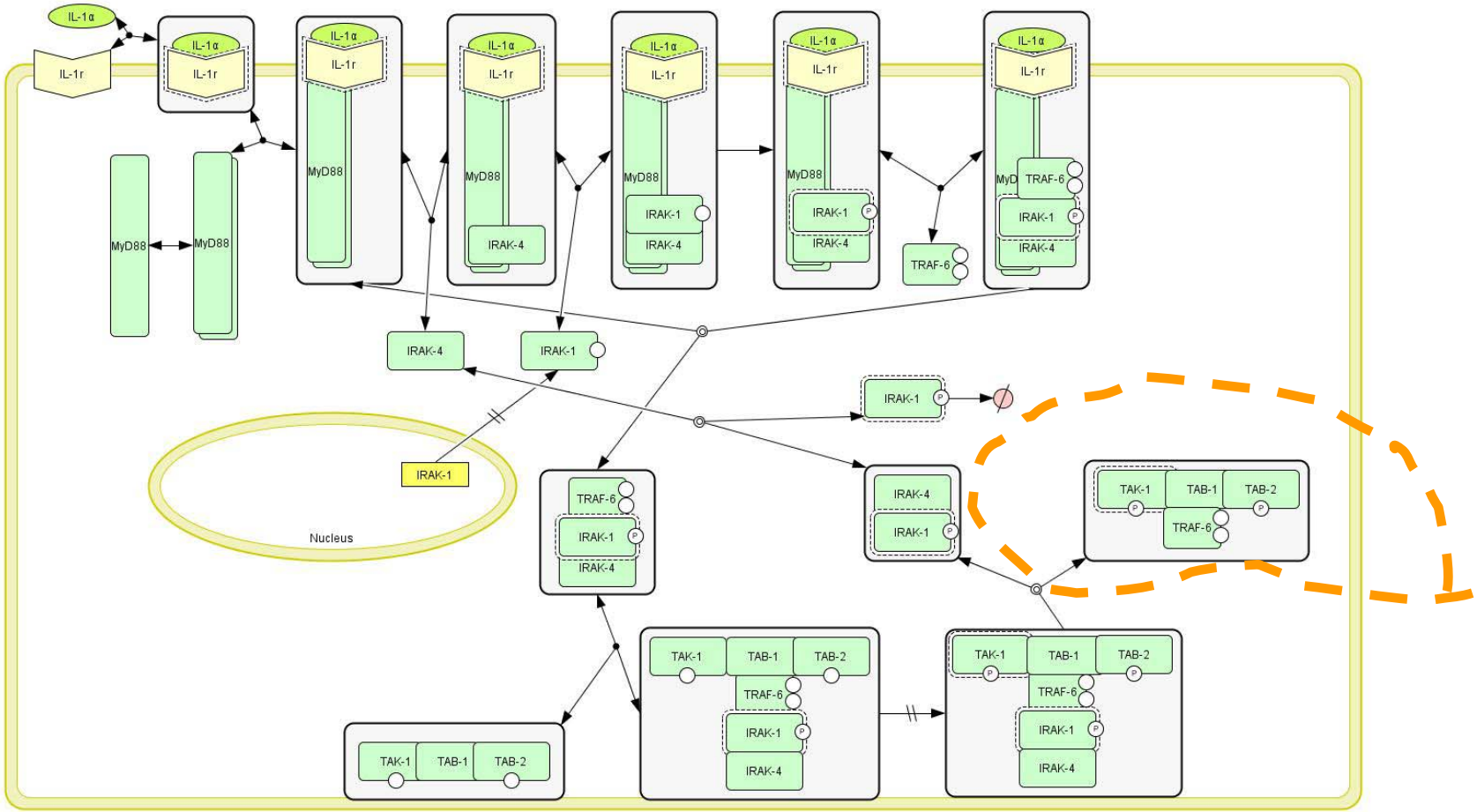
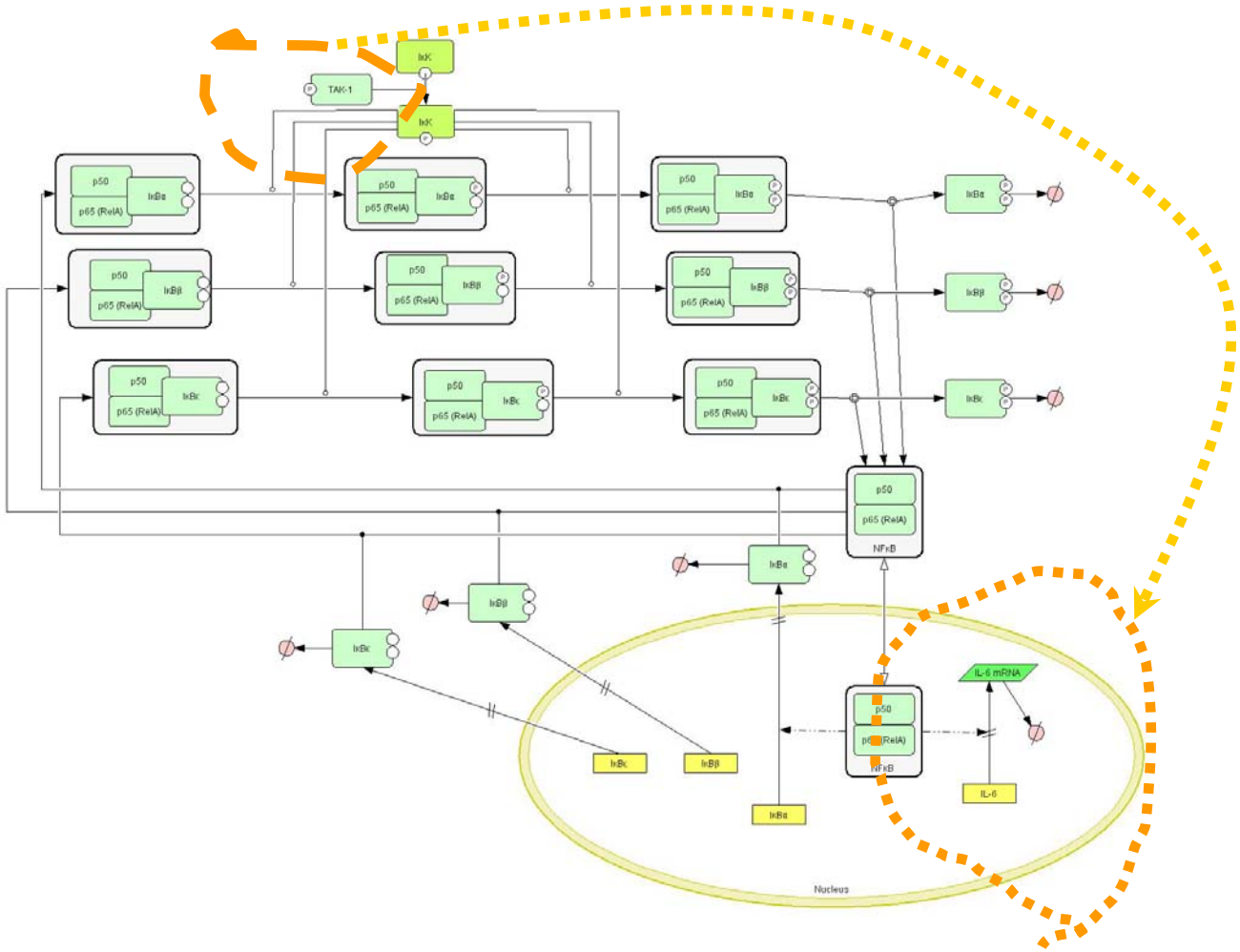
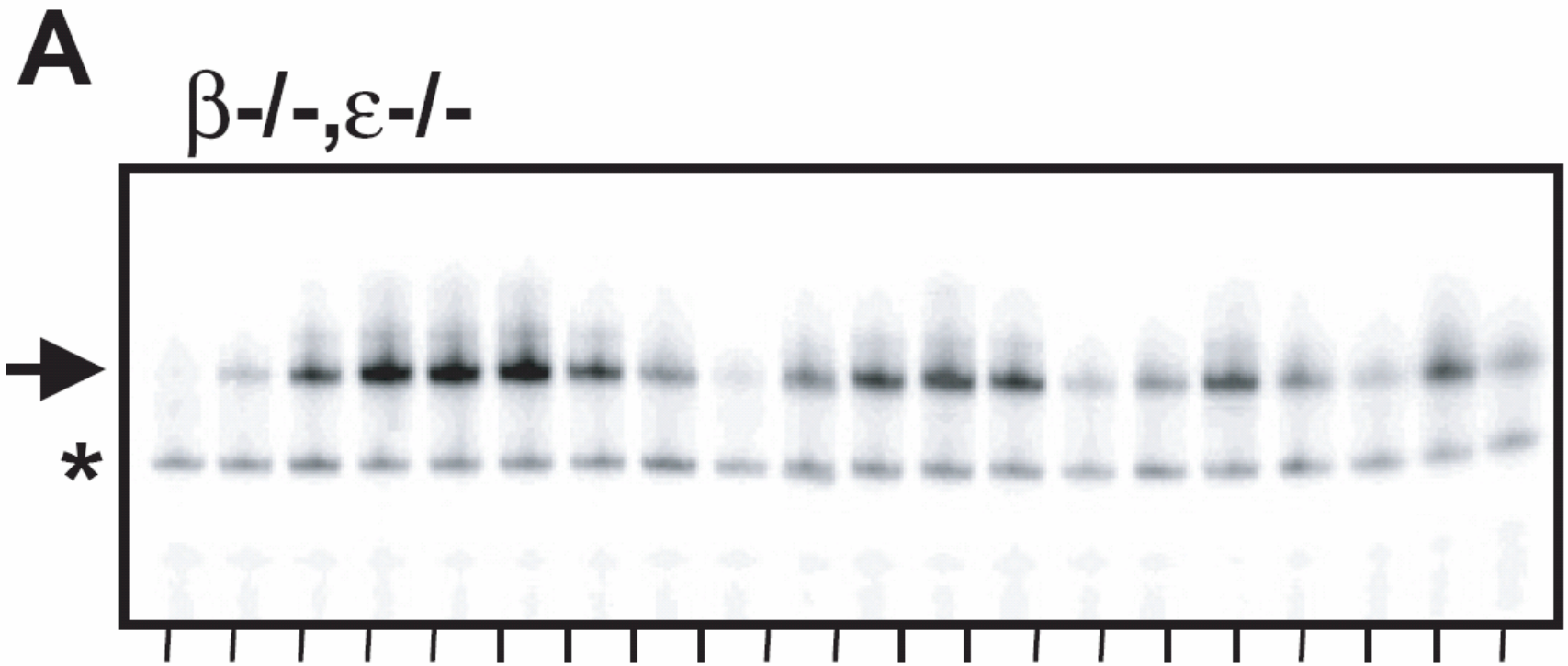


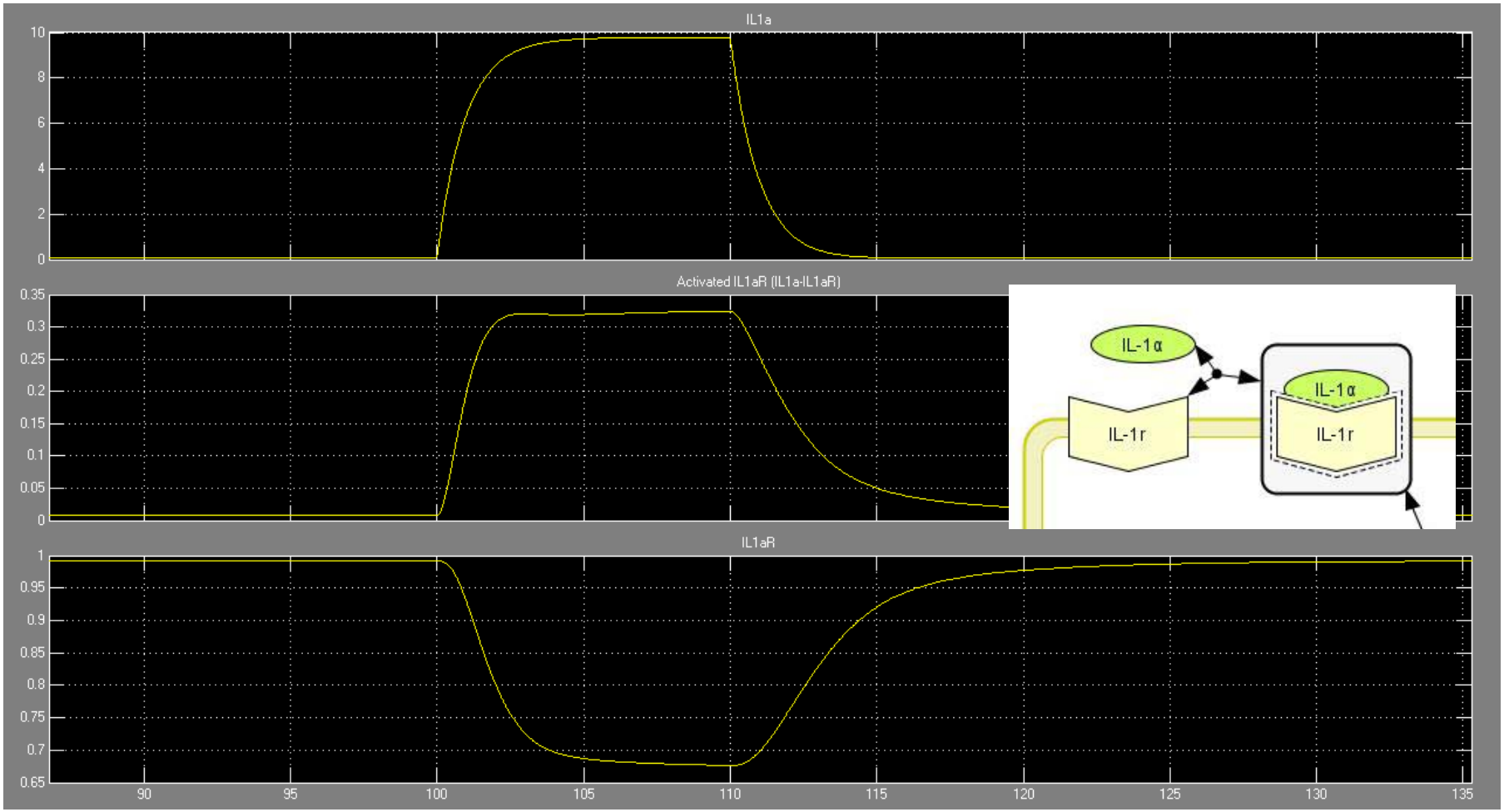
Signaling from TAK1 through NFκB to IL6



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



Hypothesis generation: IL1a-mediated signaling



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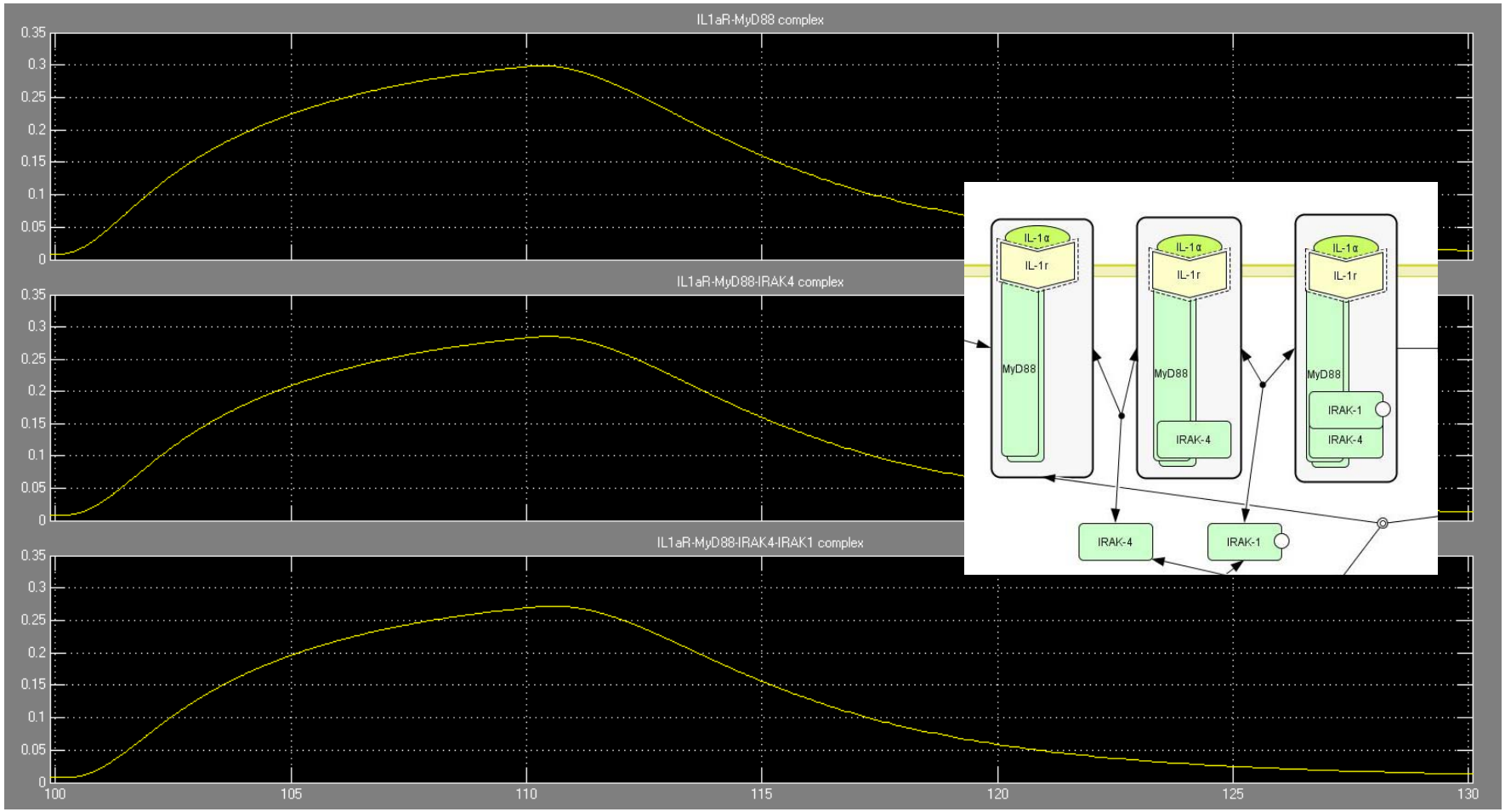

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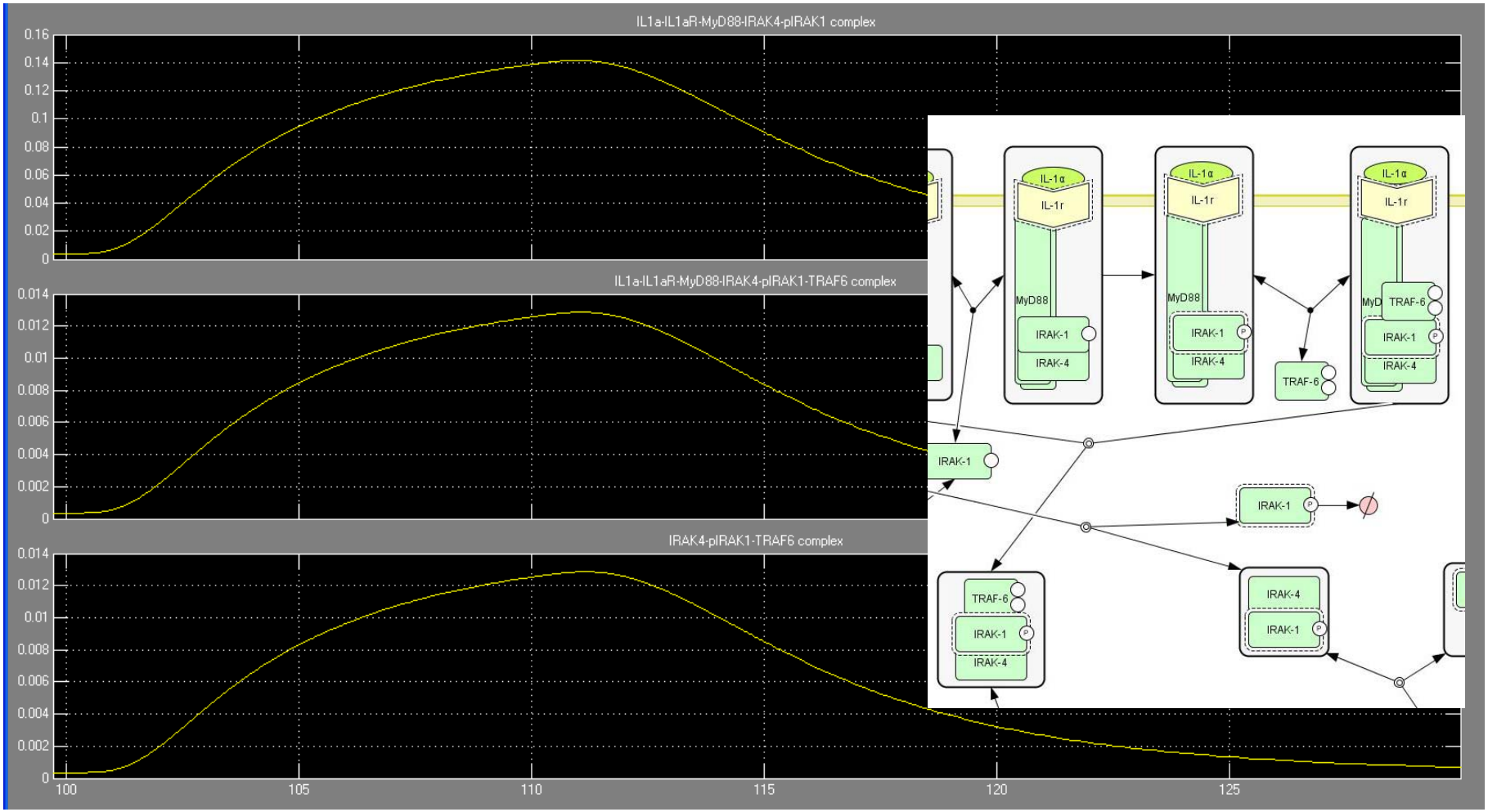

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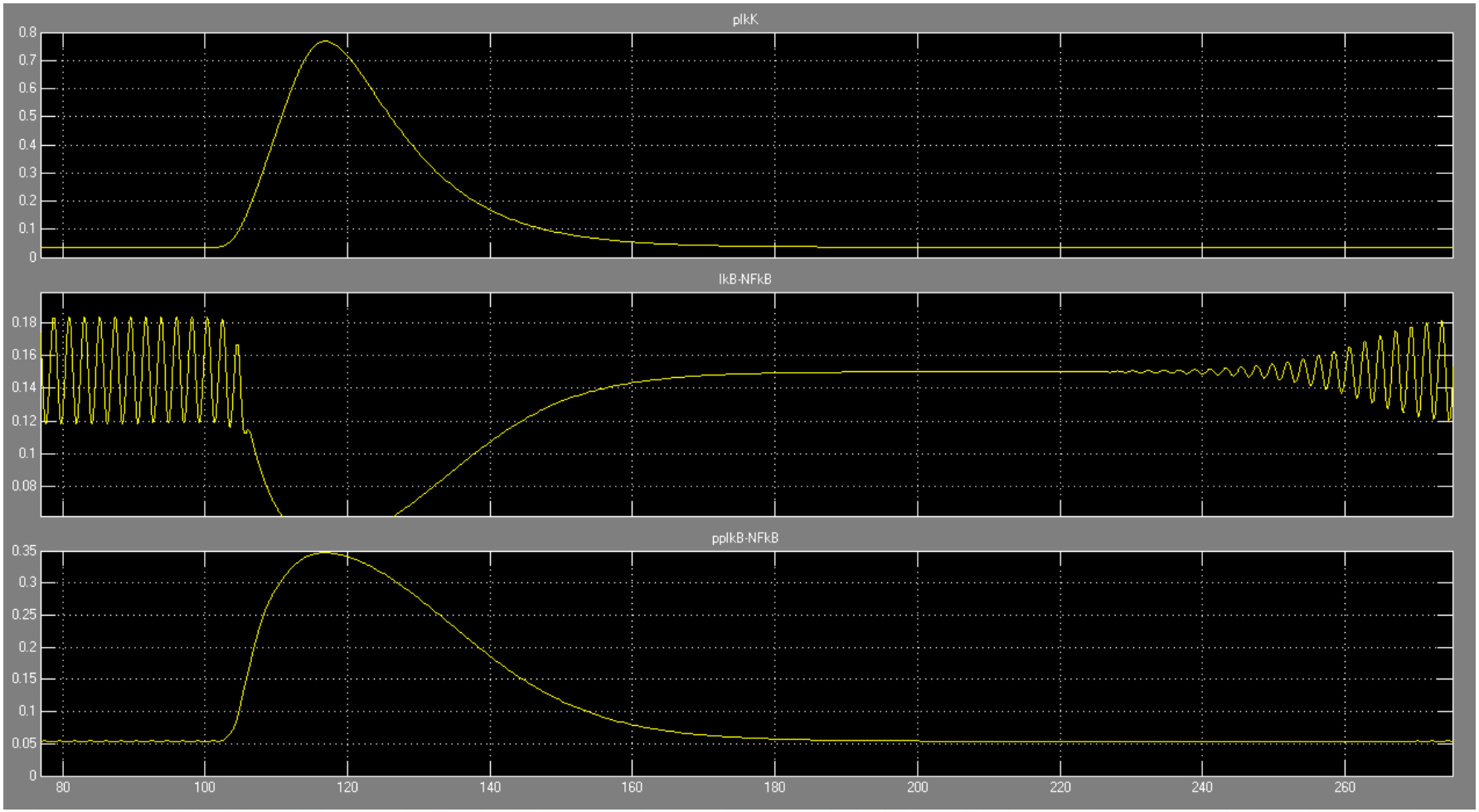
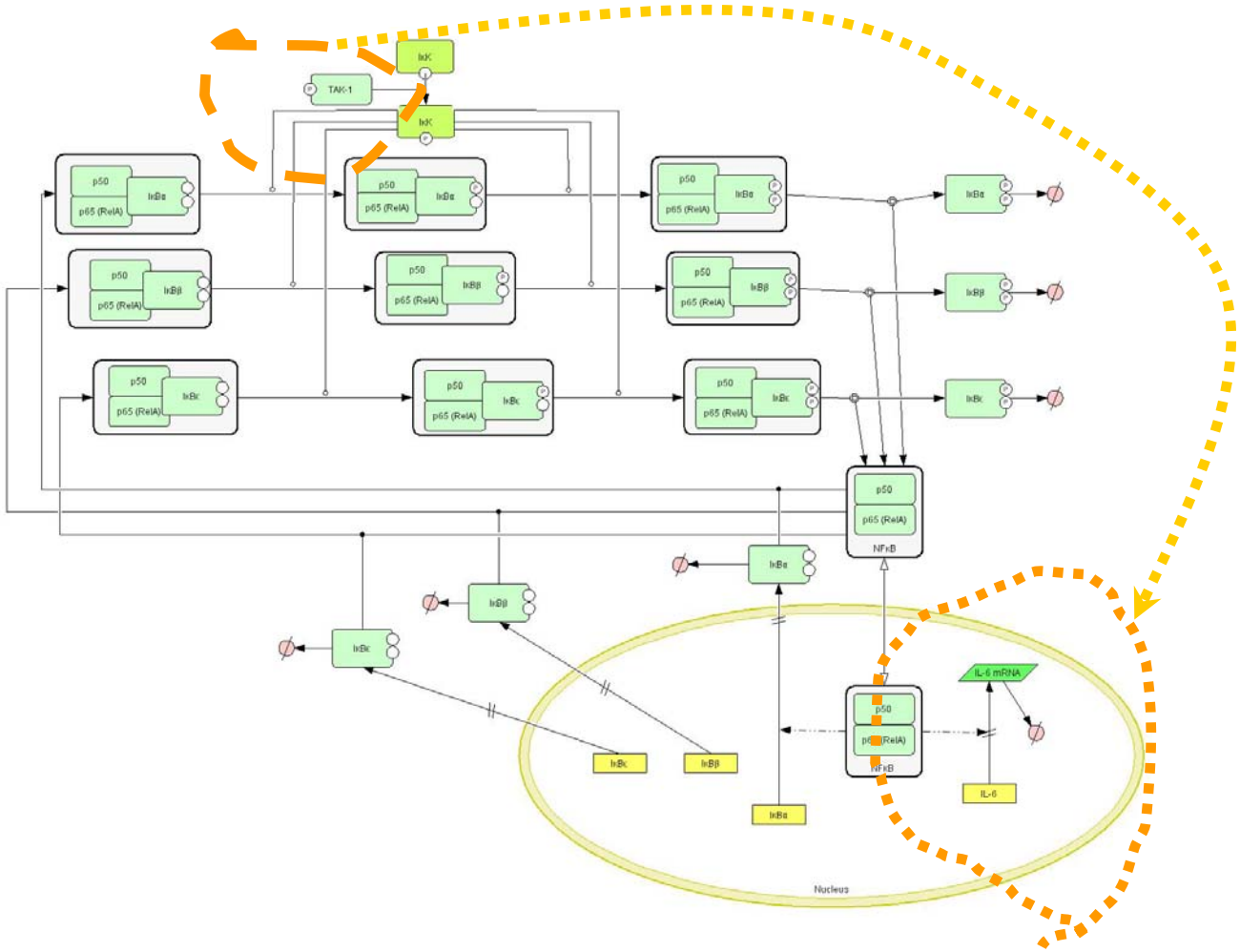
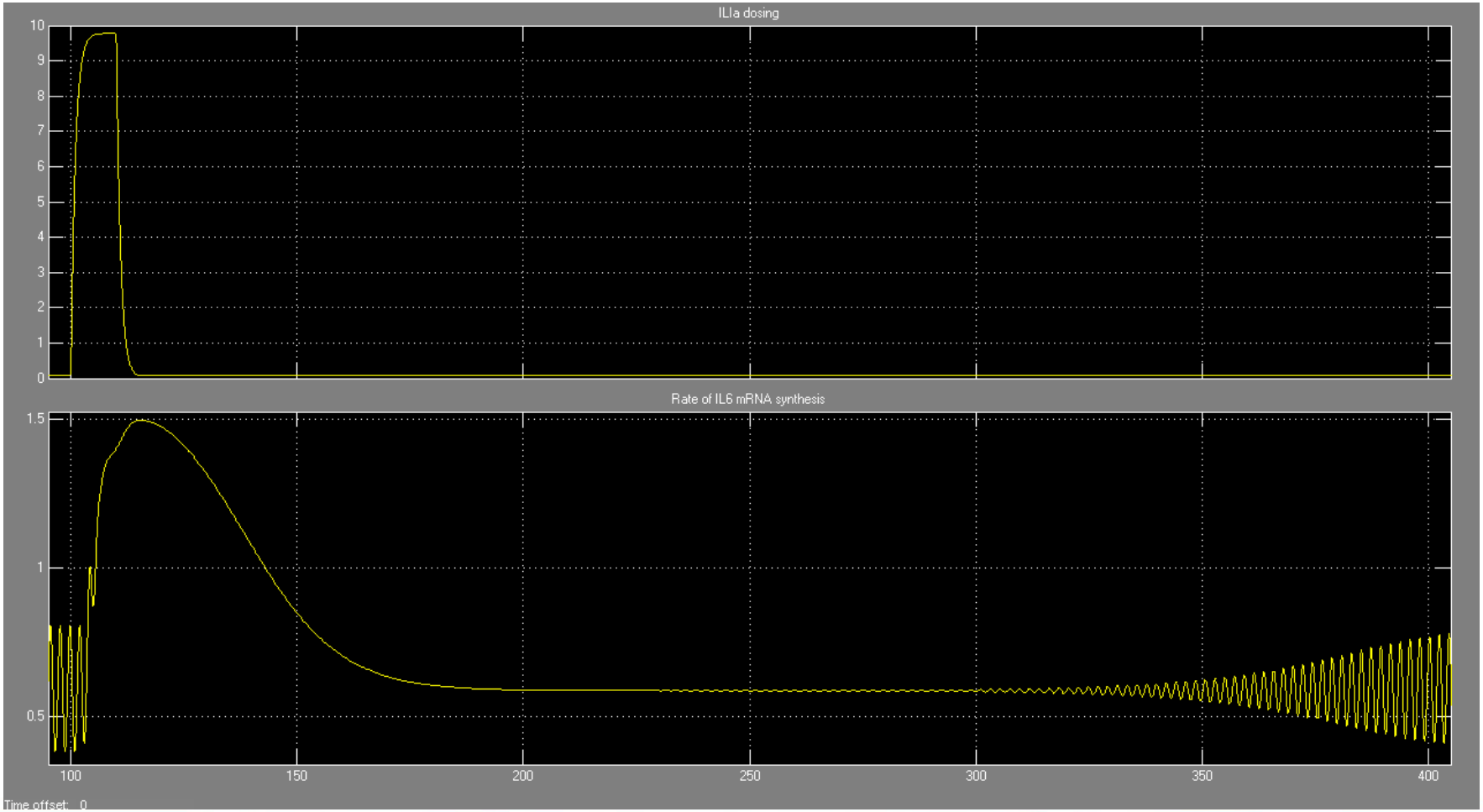


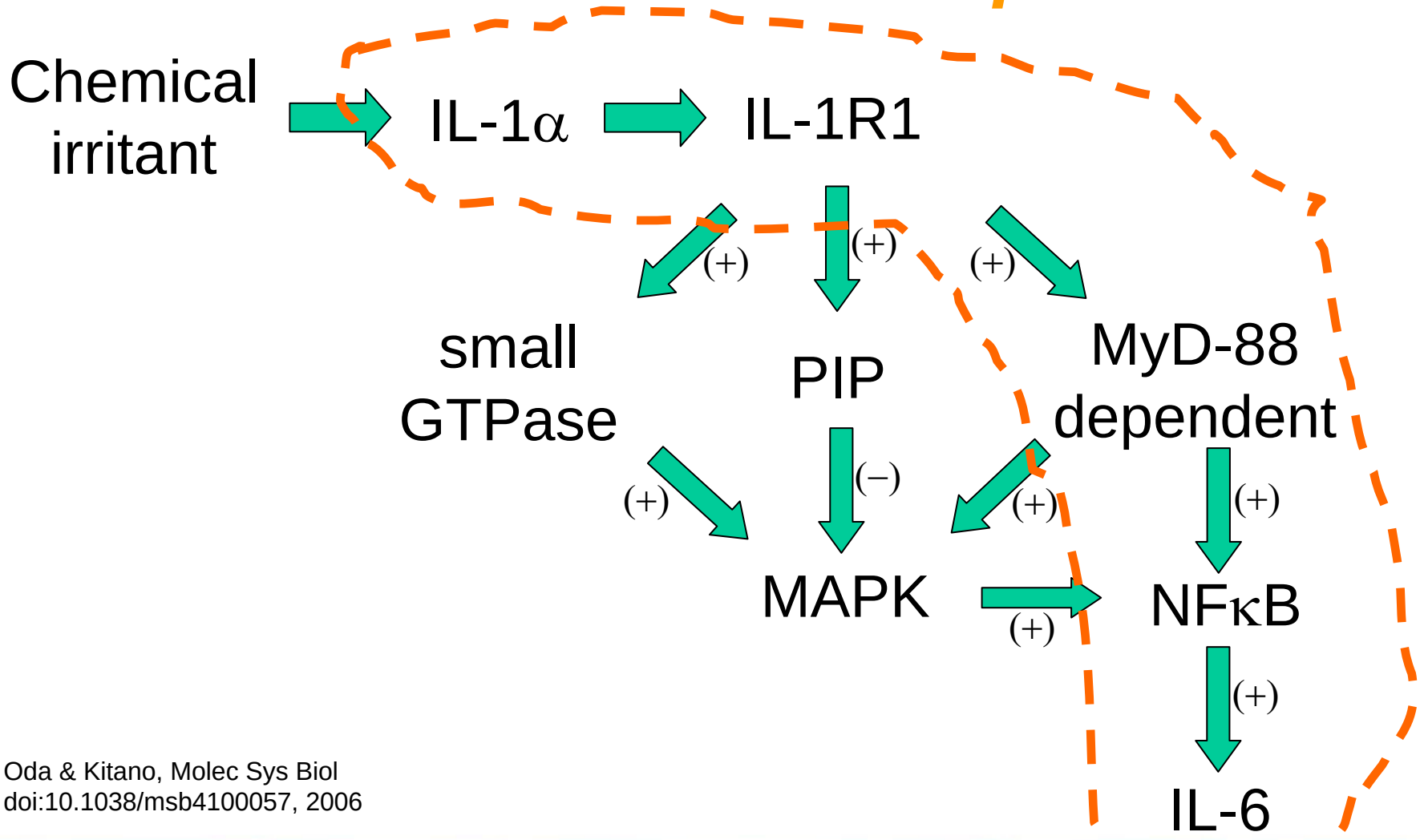
Signaling from TAK1 through NFκB to IL6



Hypothesis generation: IL1a pulse and NFkB-mediated IL6 production



Modular scheme for IL-1α-mediated irritant response



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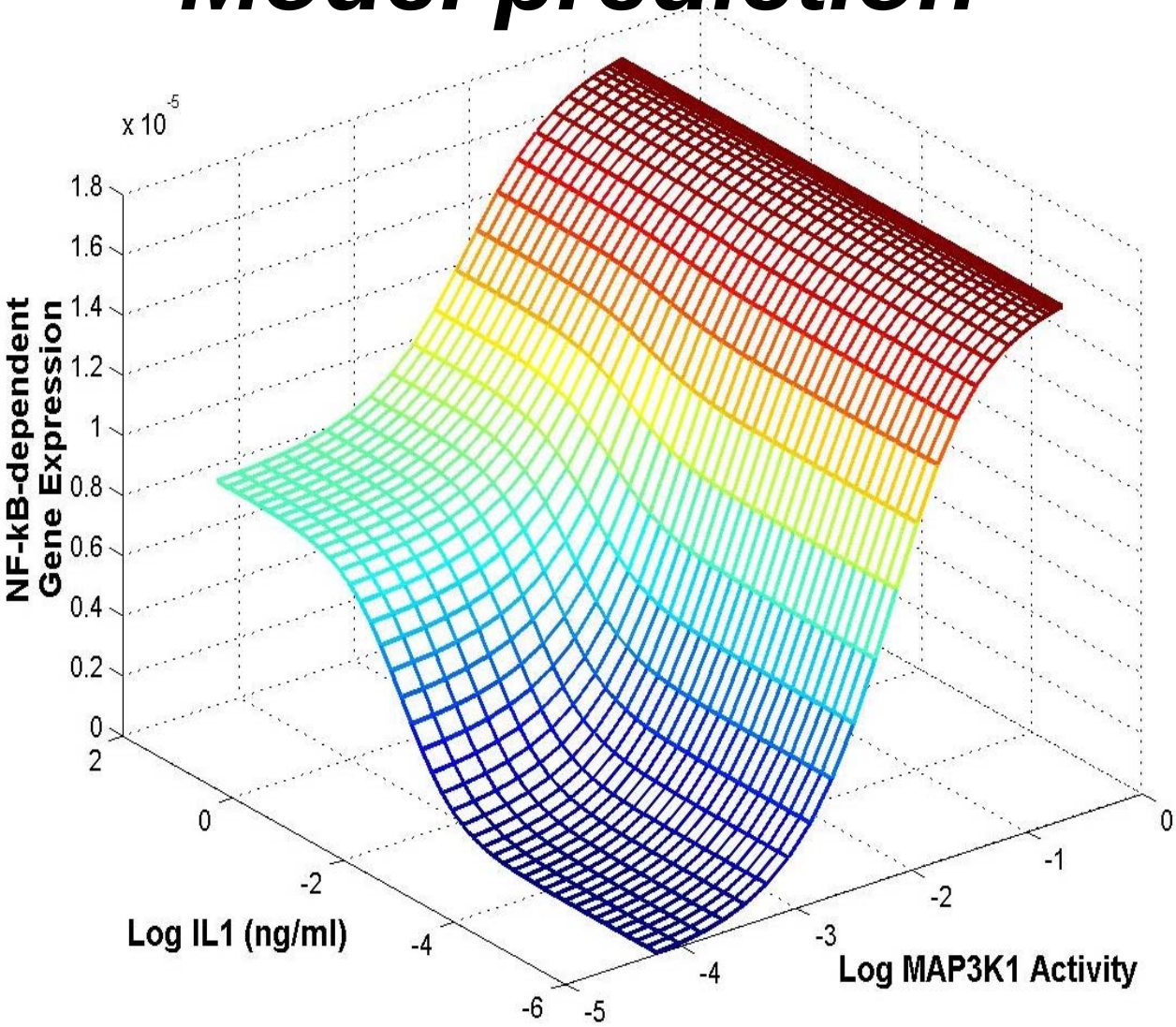
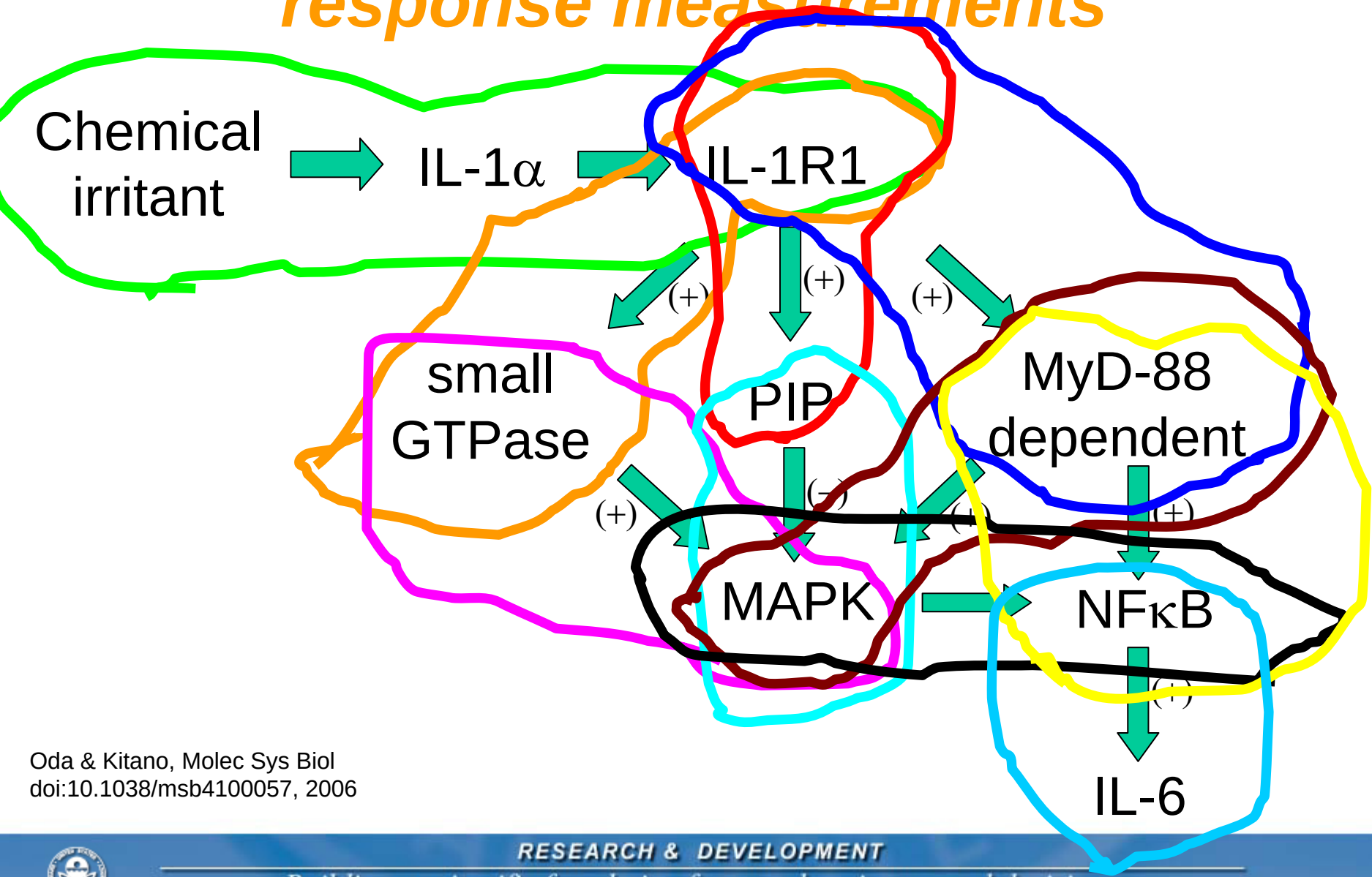
Model prediction



Potential time-course and dose-response measurements

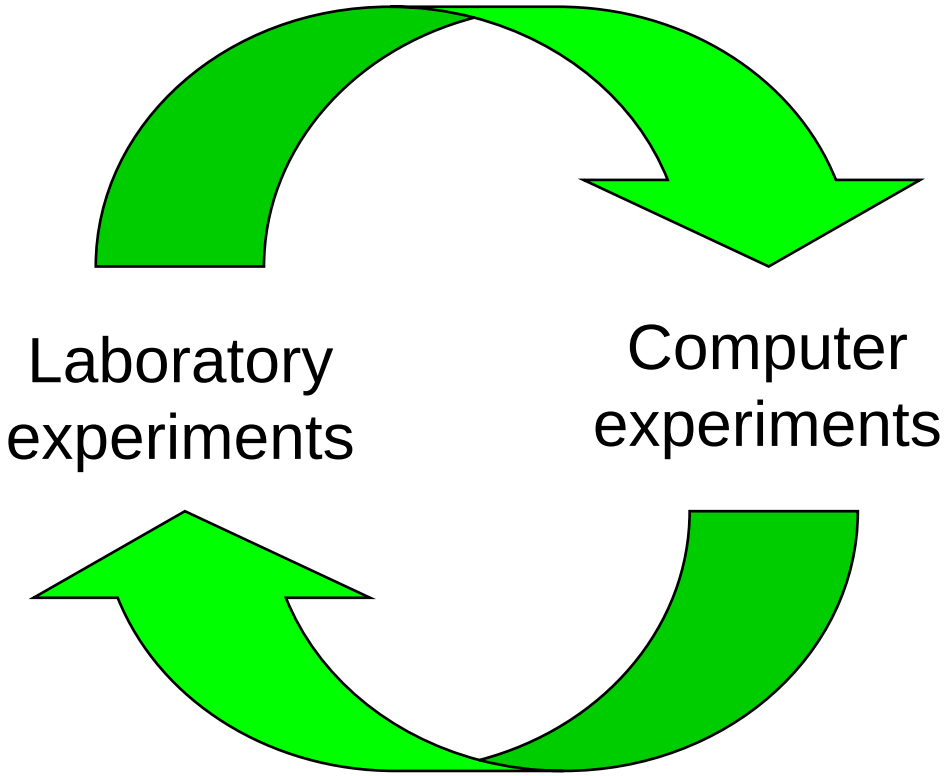


Oda & Kitano, Molec Sys Biol
doi:10.1038/msb4100057, 2006

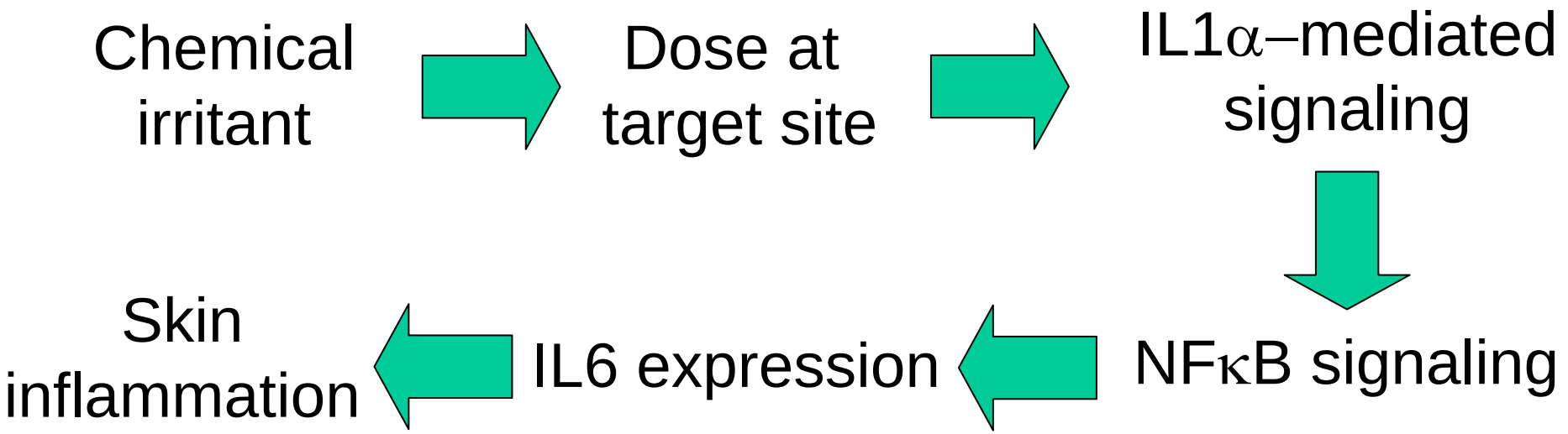
How to move on to a quantitative model?

- Extend preliminary modeling to PIP, MAPK, and small GTPase
- Obtain dose-response and time-course data for functional modules identified through preliminary modeling and literature review
  - Validate modular description
  - Demonstrate predictive capability

Iteration of experiments in the laboratory and the computer



Scheme with preliminary modeling of intracellular signaling



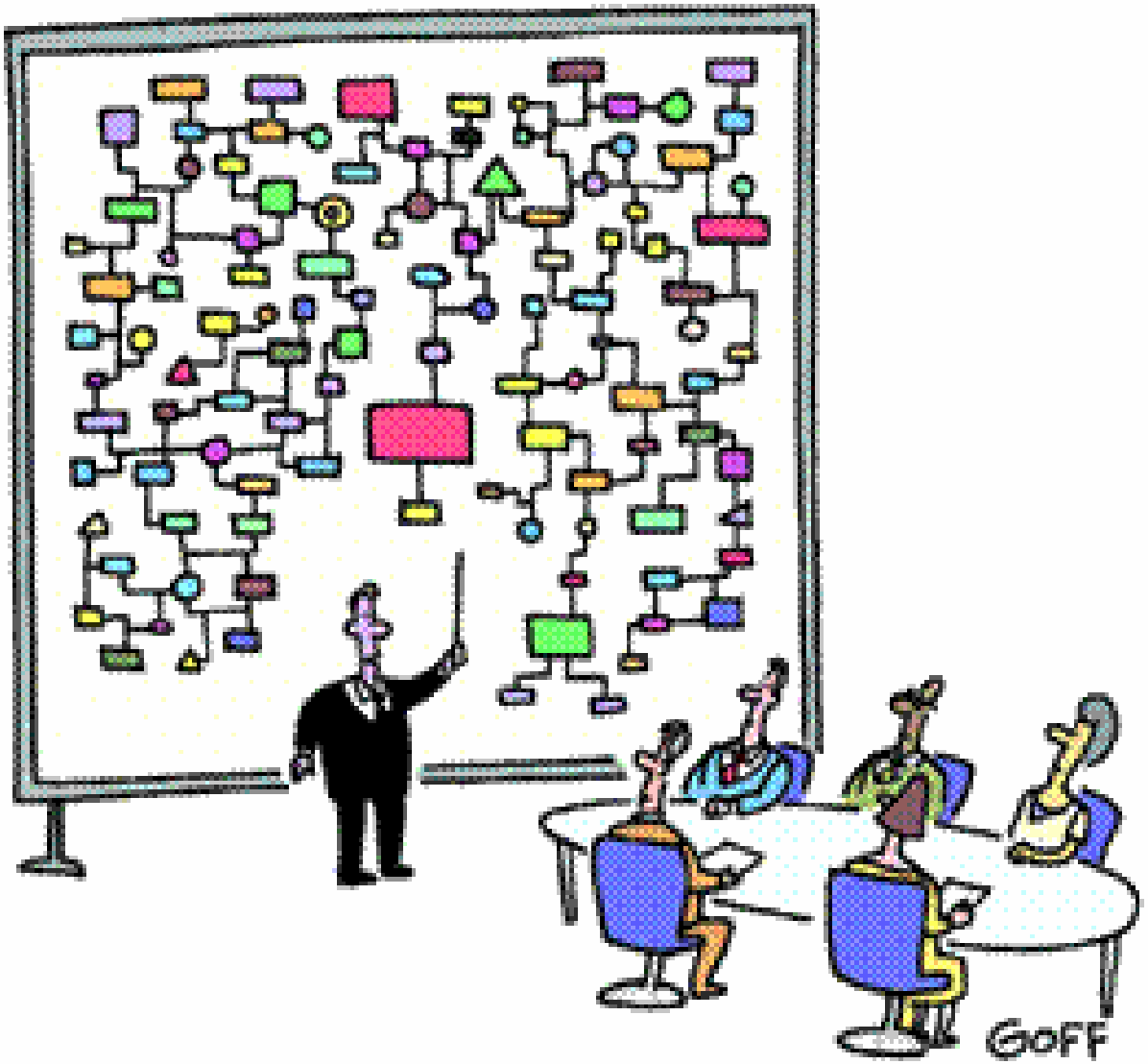
Summary

- Biological mechanisms of toxicants and risk assessment
- Interaction maps and modular descriptions
- Initial work on functional analysis of the acute dermal irritant response
- Progressively more sophisticated modeling as data become available

Best time to think about signal transduction…

Acknowledgements

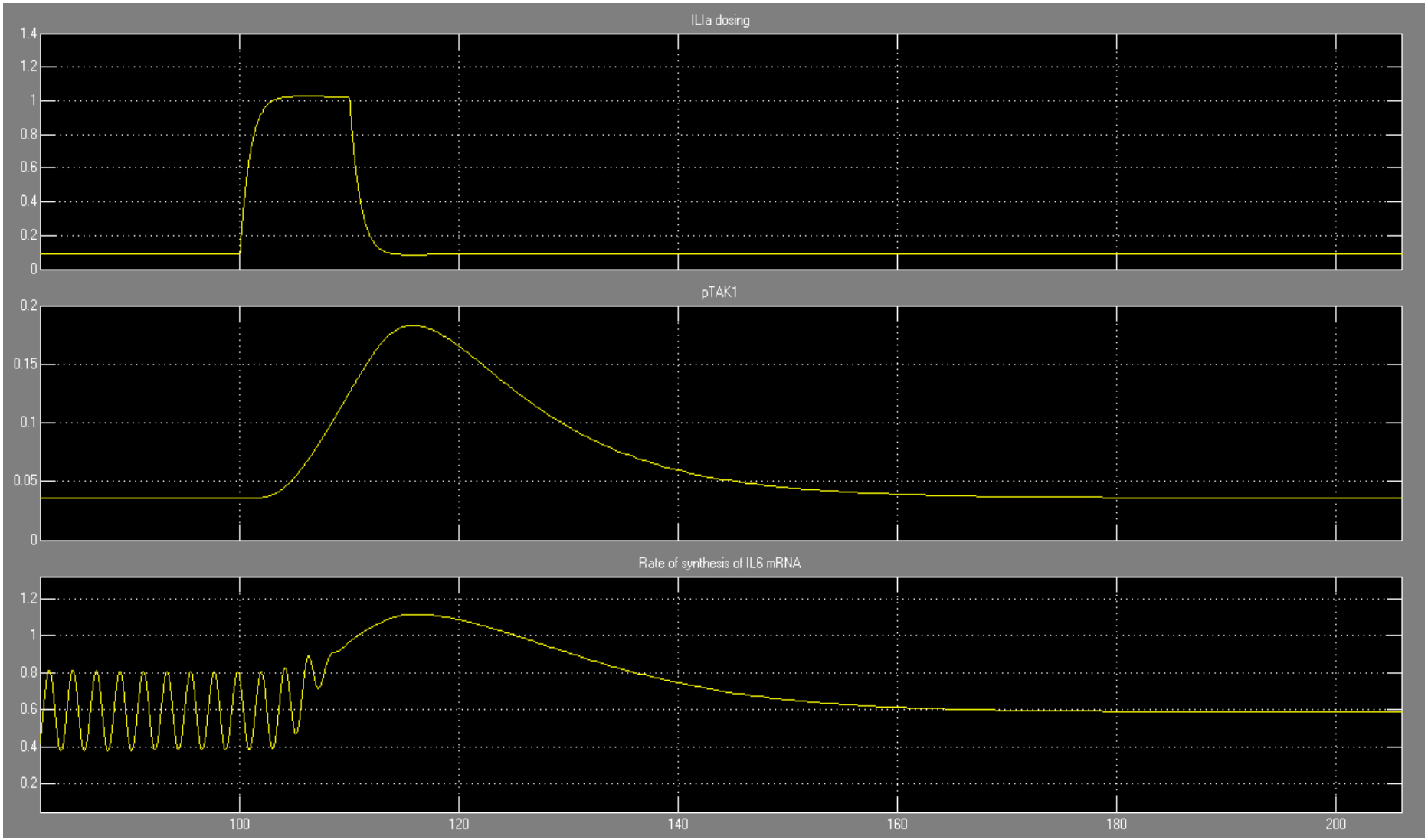
- Qiang Zhang
- Michael Breen
- Rusty Thomas
- Yanan Zheng



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

End

Pulse intensity = 1



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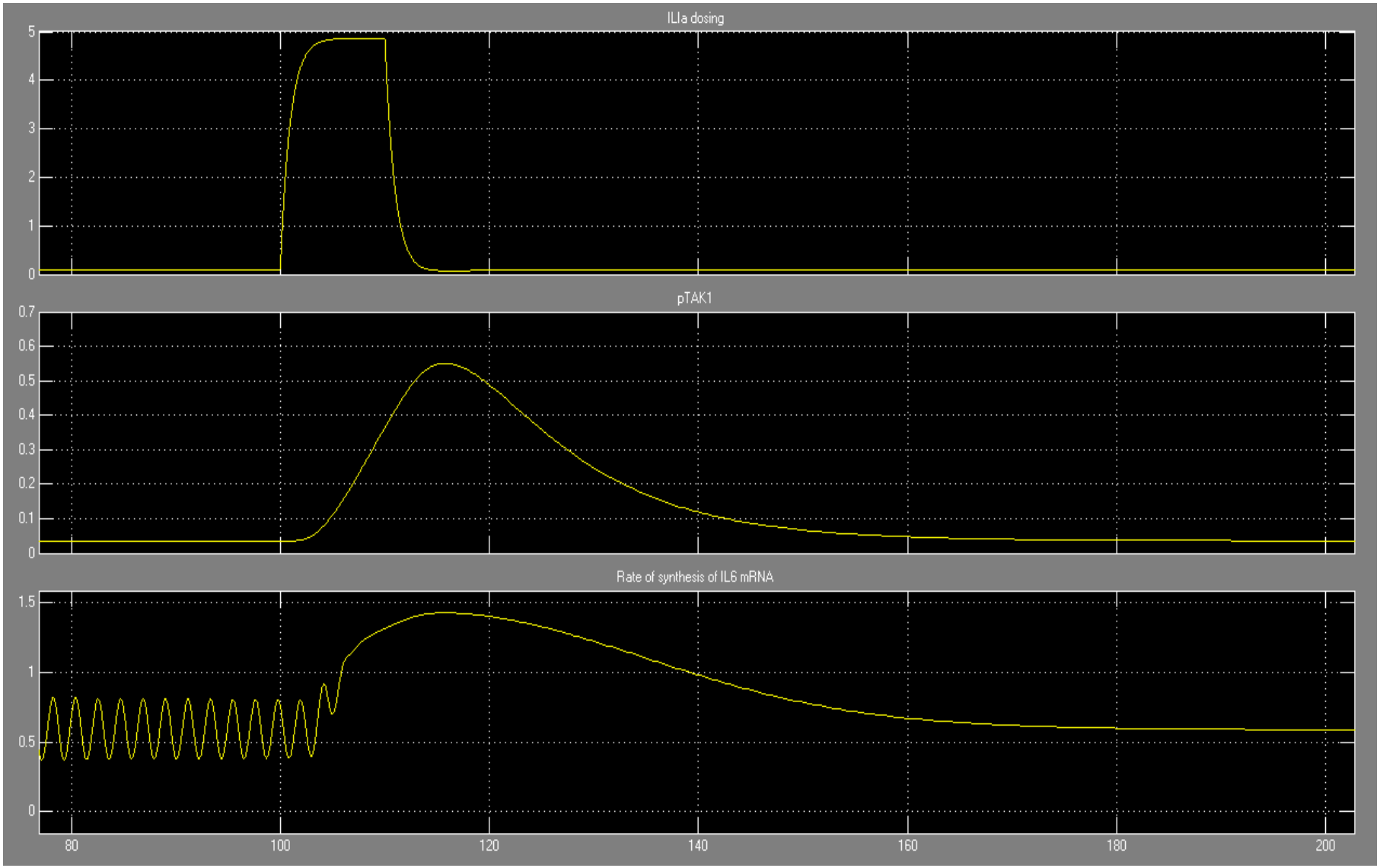

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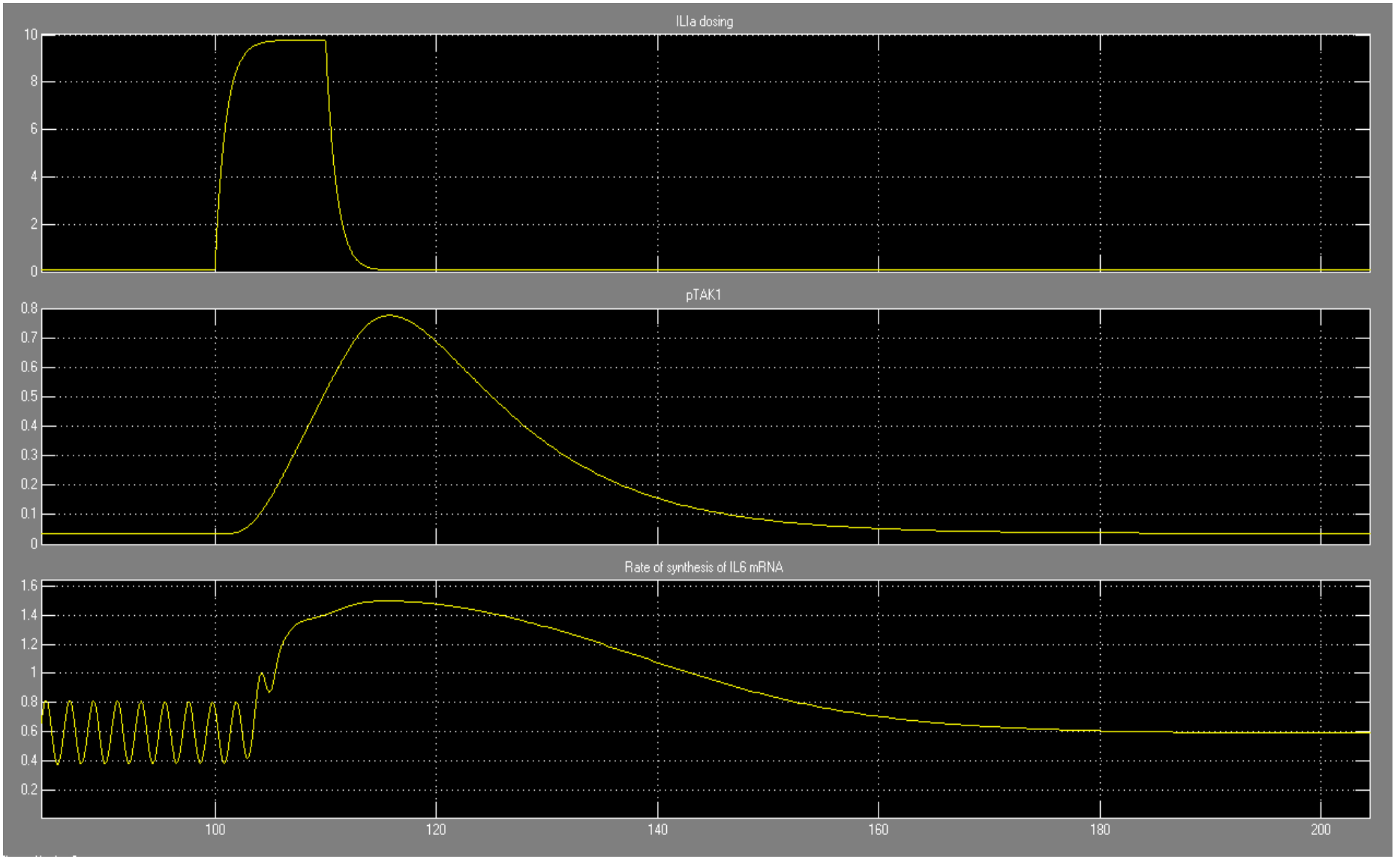
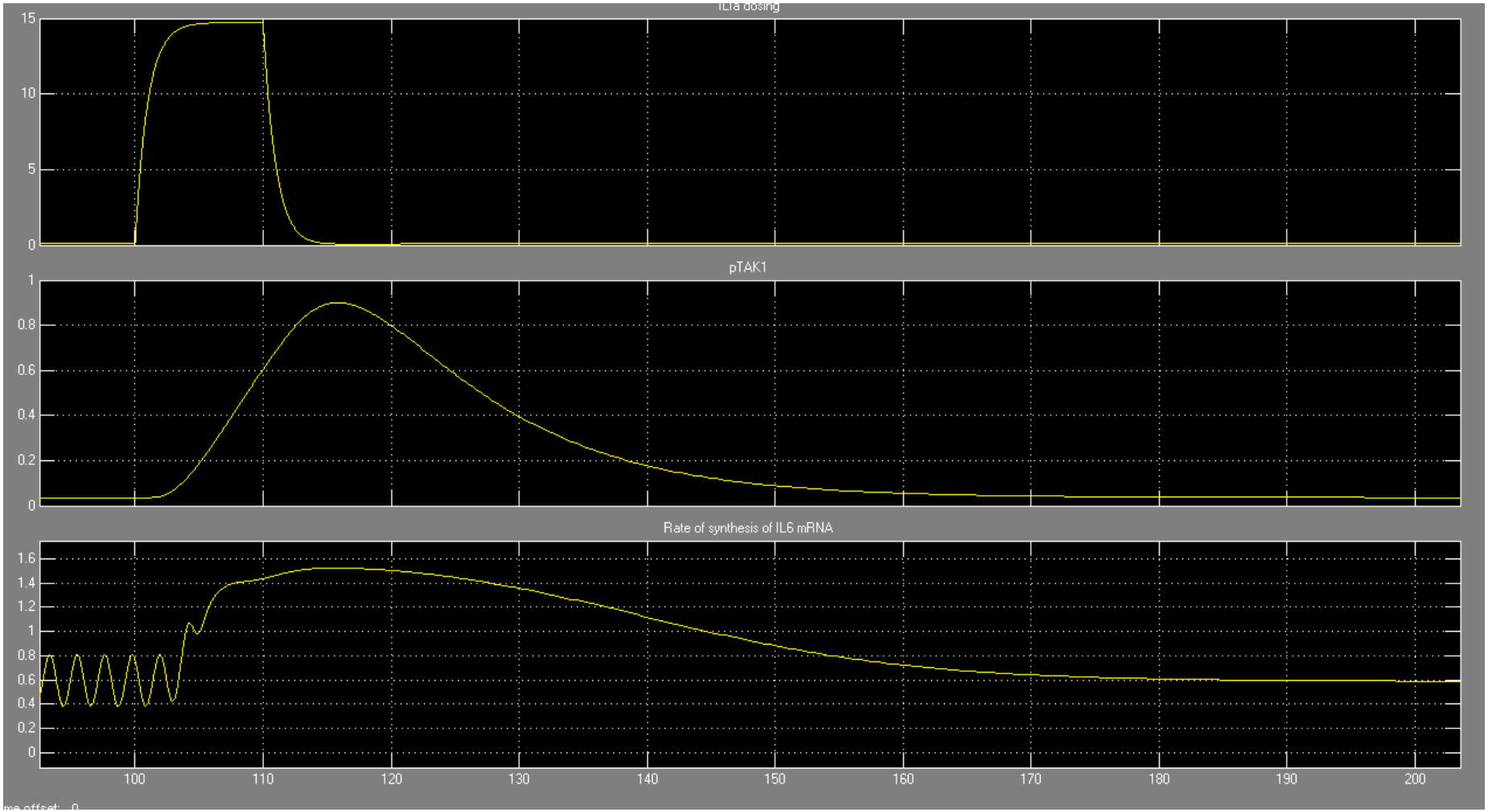


Pulse intensity = 15



Pulse intensity = 20