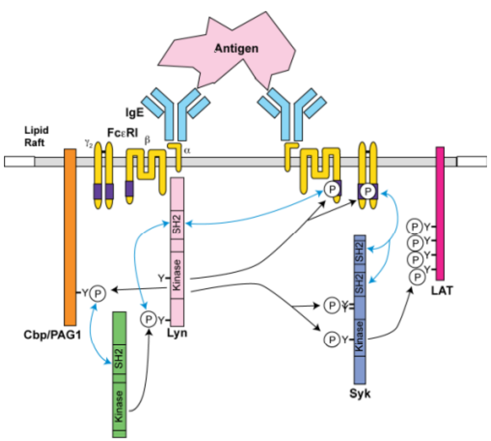
Model Checking Cell Decision Processes

Jim Faeder

Department of Computational and Systems Biology

University of Pittsburgh

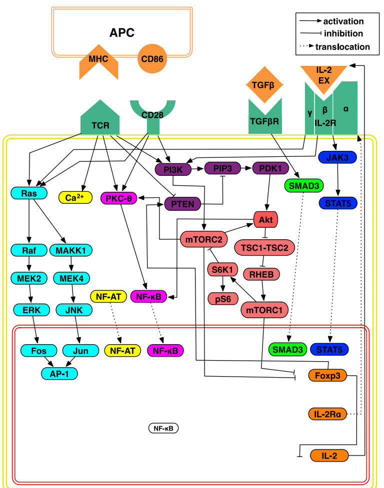


EMC 2014 Symposium

Carnegie Mellon University

Pittsburgh, PA

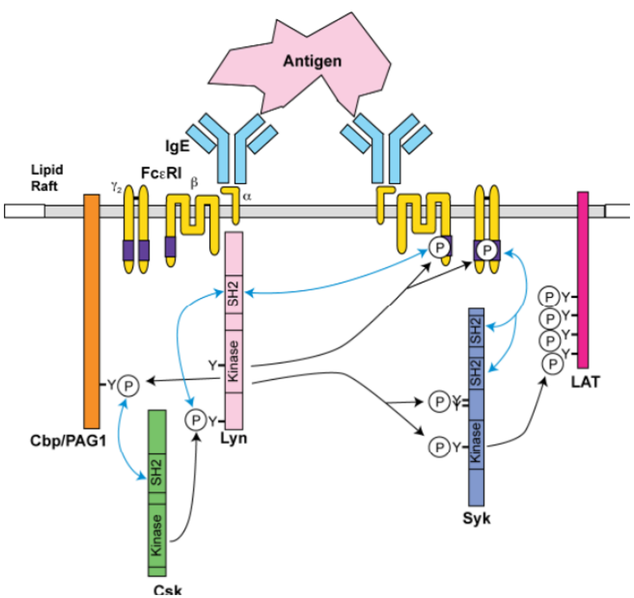
September 20, 2014



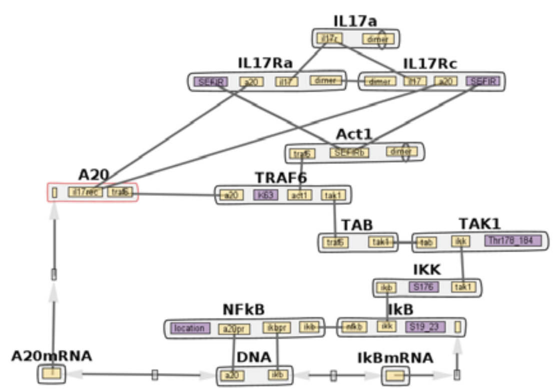
Goals for Mechanistic Modeling

- Understand
- Control
- Treat

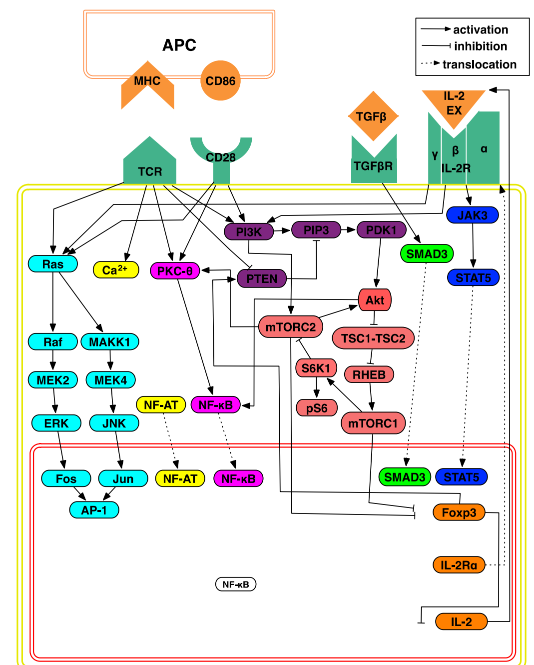
Molecular mechanisms of cellular decisions



Mast cell degranulation



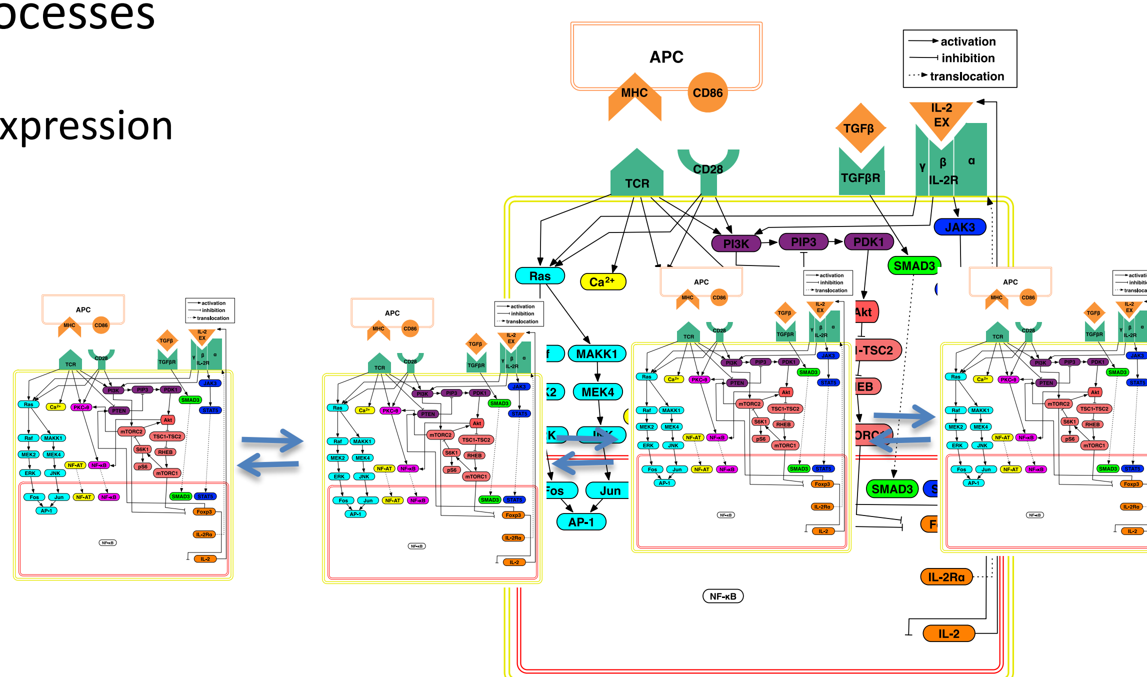
IL-17 signaling



T cell differentiation

Challenges for Modeling
(both mental and computational)

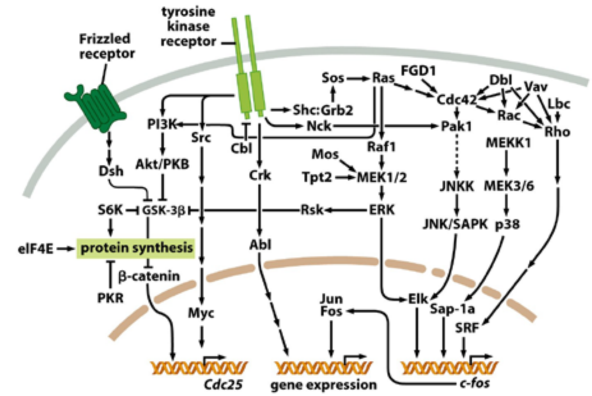
- Large number of components and interactions
- Rapidly evolving list of important components and interactions
- Feedback and feedforward loops
- Involvement of multiple processes
  - Signaling
  - Gene regulation / protein expression
  - Metabolism
  - Cell processes
    - Growth
    - Proliferation
    - Death
    - …
- Cell populations
  - Heterogeneity
  - Multi-scale integration



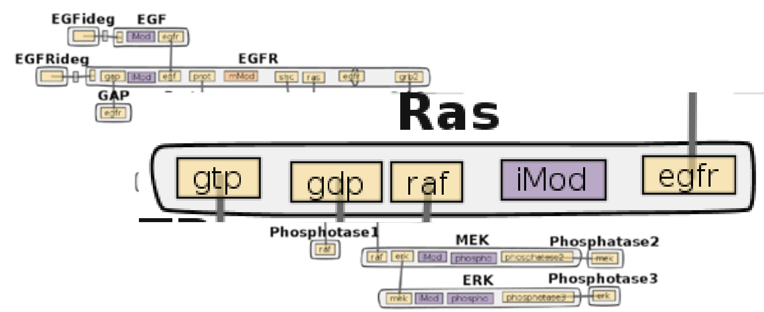
Rule-Based Modeling: An Intermediate Level Abstraction for Systems Biology

abstraction level

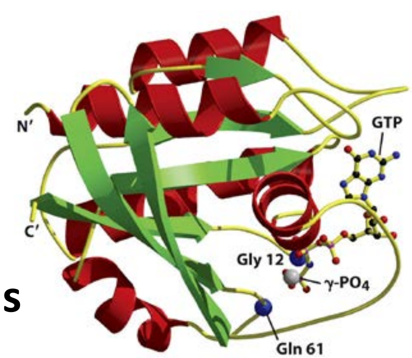
Reaction Networks



Site Dynamics
(Rule-Based Modeling)



Molecular Dynamics

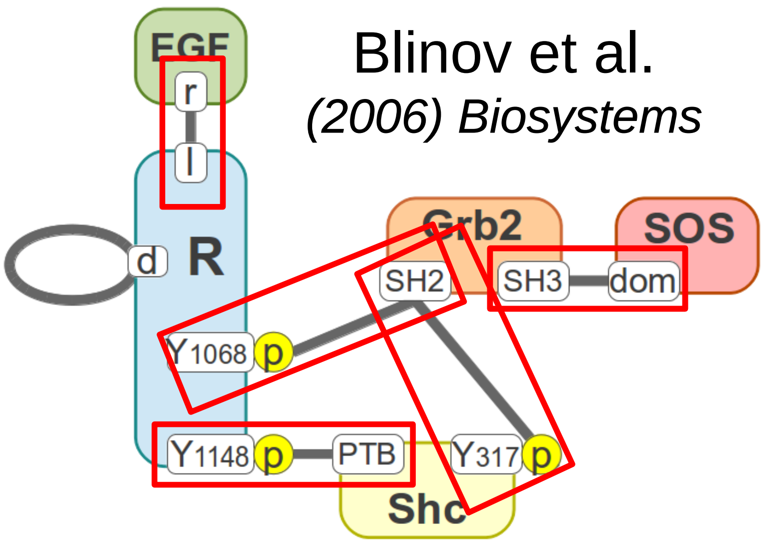


Ras

Combinatorial Complexity

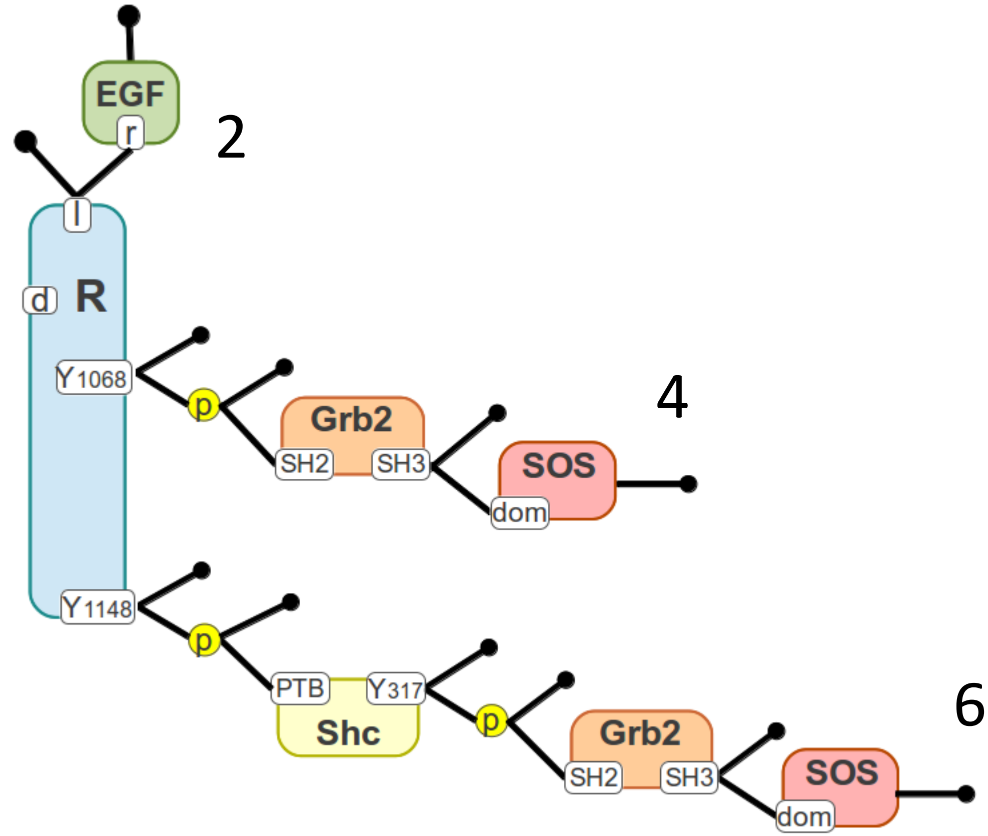
a simple model can produce many species and reactions

Blinov et al.
(2006) Biosystems



Contact Map

- Protein Domain Structure
- Site Modifications
- Protein-Protein contacts



$$N_{\mathrm{R}} = 2 \times 4 \times 6 = 48$$

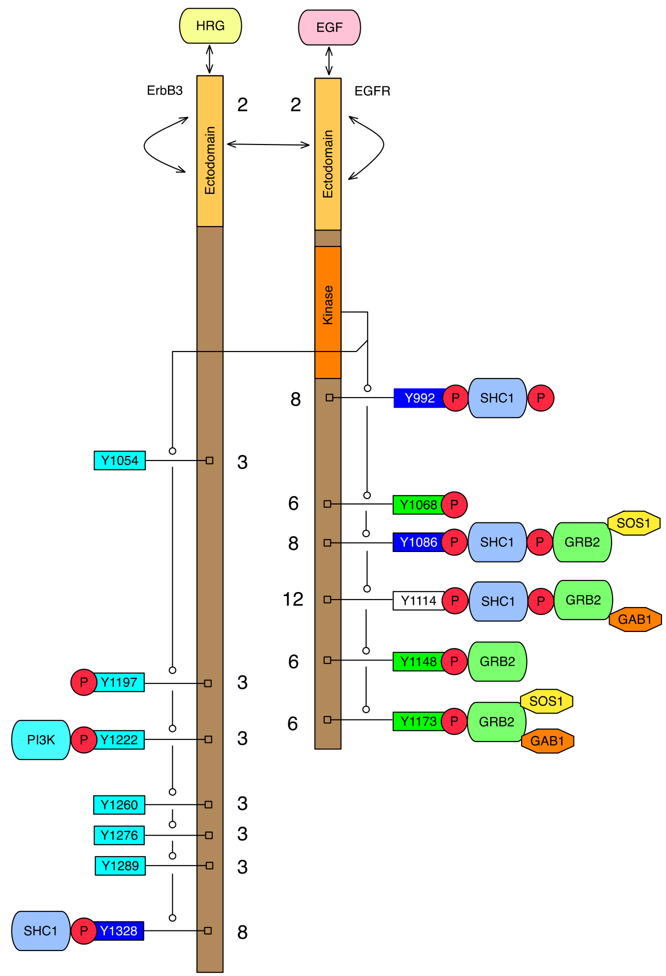
$$N_{\mathrm{RR}} = N_{\mathrm{R}}(N_{\mathrm{R}}+1)/2 = 1176$$

Hlavacek, Faeder, et al., *Biotechnol. Bioeng.* (2003)

Combinatorial complexity in a more realistic model of EGFR signaling

ErbB3:ErbB1 has > 3.8×10^{9} states

ErbB1:ErbB1 has > 5.5×10^{10} states

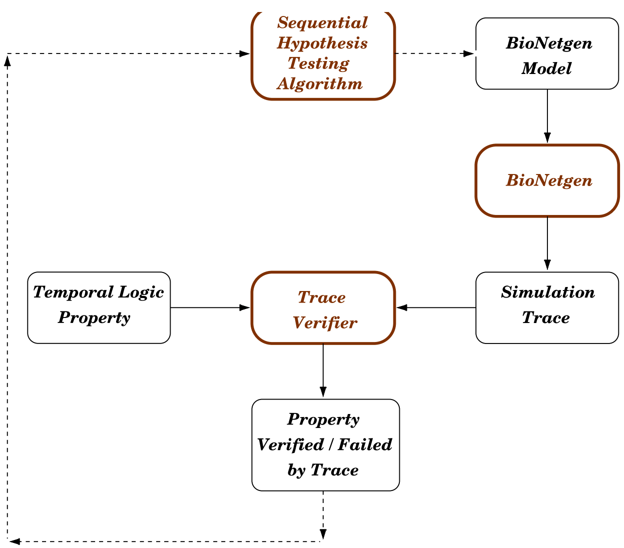


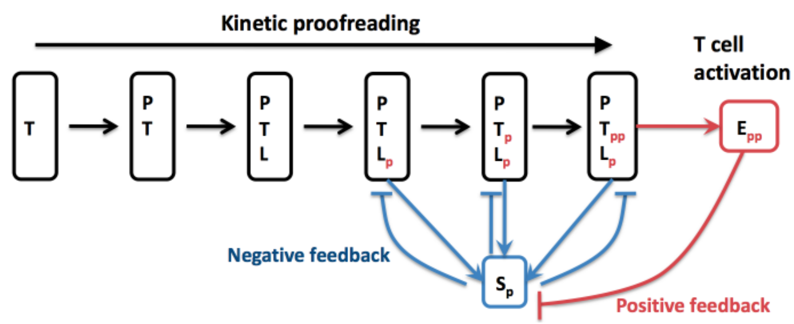
Creamer et al. (2012) *BMC Syst. Biol.* [TGen group]

Statistical Model Checking in *BioLab* : Applications to the automated analysis of T-Cell Receptor Signaling Pathway ⋆

Edmund M. Clarke[1], James R. Faeder[2], Christopher J. Langmead[1], Leonard A. Harris[2], Sumit Kumar Jha[1], and Axel Legay[1]

[1] Computer Science Department, Carnegie Mellon University, Pittsburgh PA
[2] Department of Computational Biology , University of Pittsburgh School of Medicine, Pittsburgh PA





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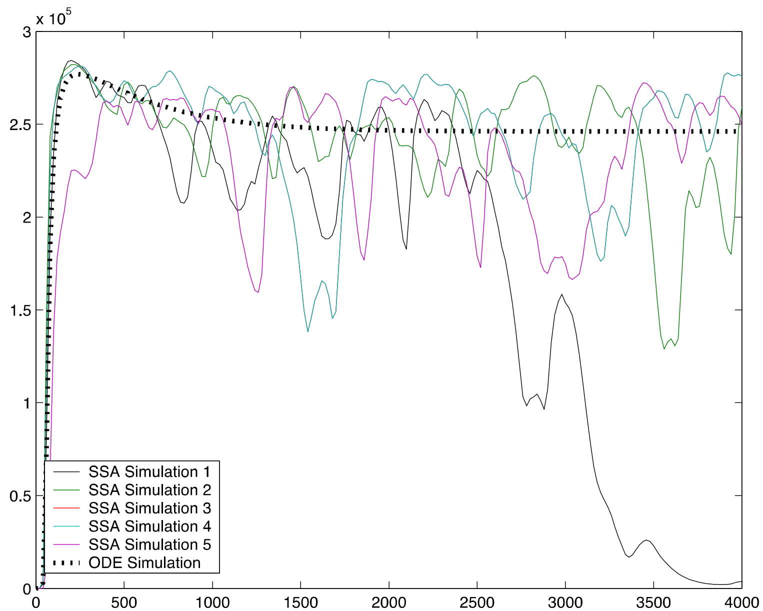


Property 2 In our second experiment, we were interested in the truth of the hypothesis that the system can go from the inactive state to the active state. We verified the following property with various values of the probability p.

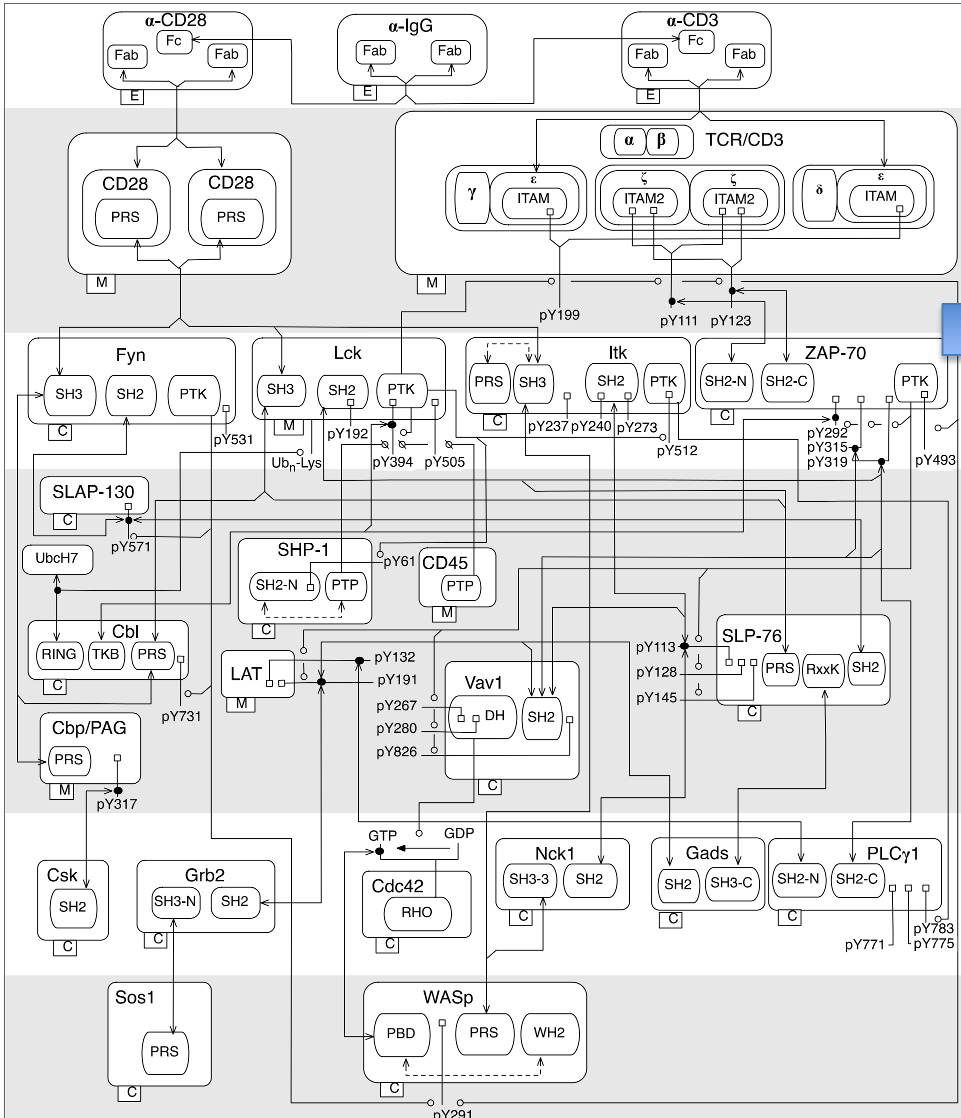
$$Pr_{\geq p}(\mathbf{F^{300}}(ppERK/totalERK{<}0.1 \wedge \mathbf{F^{300}}\ (ppERK/totalERK{>}0.5)))$$

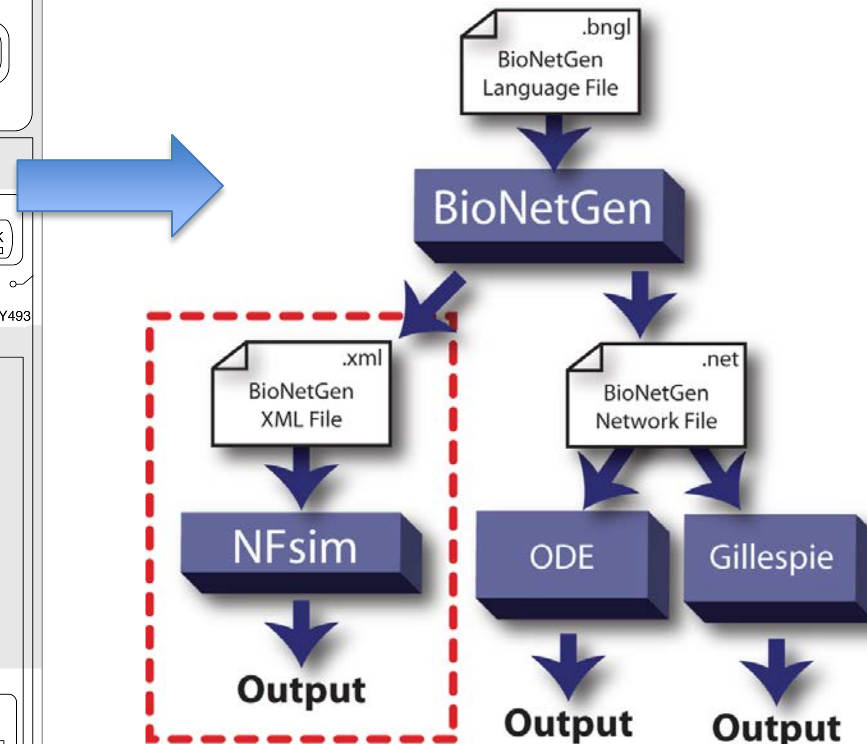
Our first model started with 100 molecules of agonist pMHC (with dissociation constant 1/20 per second) while antagonist pMHC was assumed to be absent in the initial state. The results are presented in Table 5.

Sl.	p_1	p_0	Result	Total Number of Samples	Number of Successful Samples	Time
1	0.90	0.95	Yes	160	160	412.25
2	0.70	0.75	Yes	120	120	309.58
3	0.50	0.55	Yes	80	80	214.74
4	0.20	0.25	Yes	40	40	88.32
5	0.10	0.15	Yes	40	40	98.84

Table 5. N_1 : 100, N_2 : 0 , Type-I and Type II error : 0.001

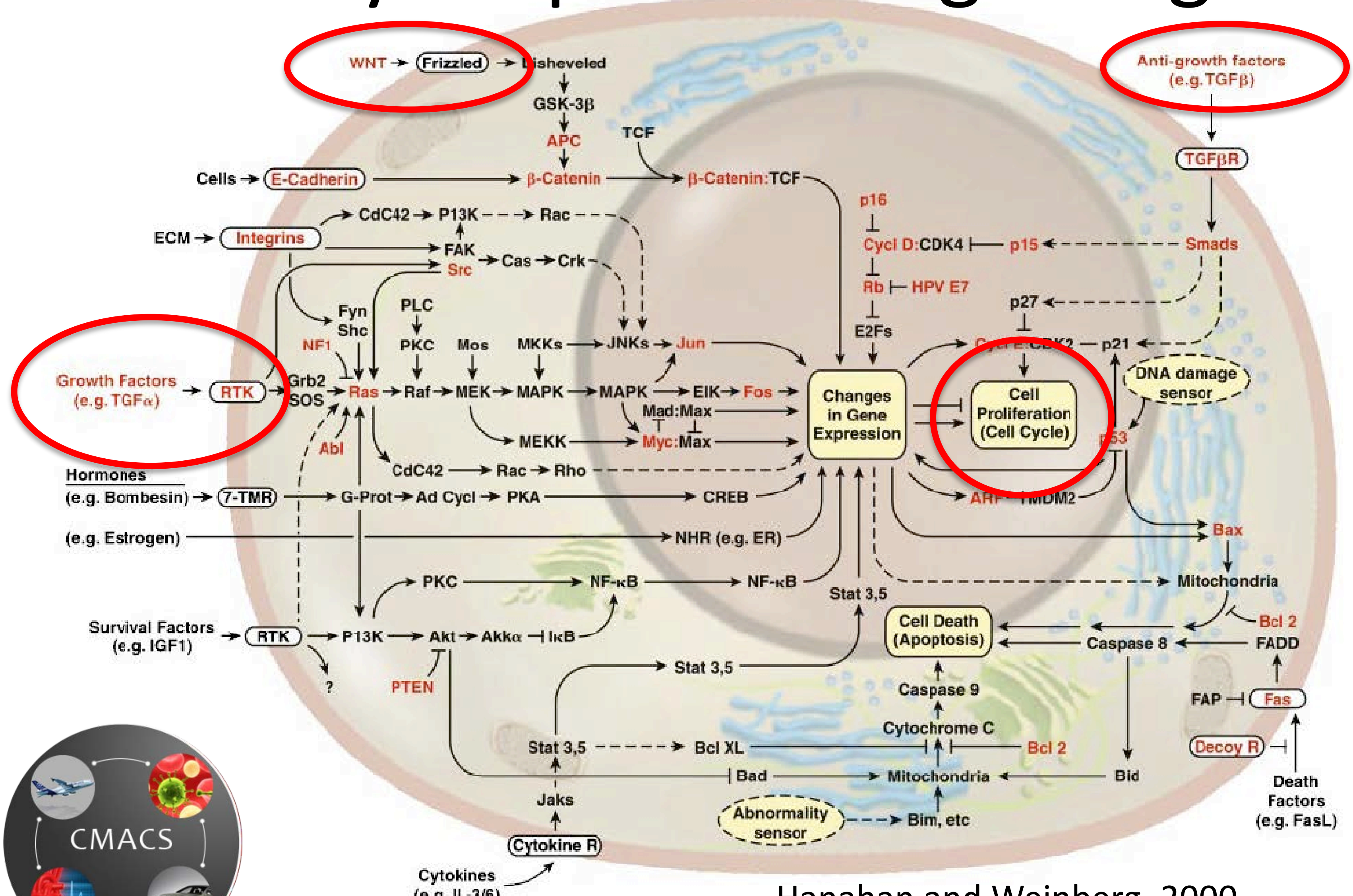
Large Scale TCR Signaling Model





Chylek, Hu, & Hlavacek

Subway Map of Cell Signaling



Hanahan and Weinberg, 2000

Logical model of peripheral T cell differentiation

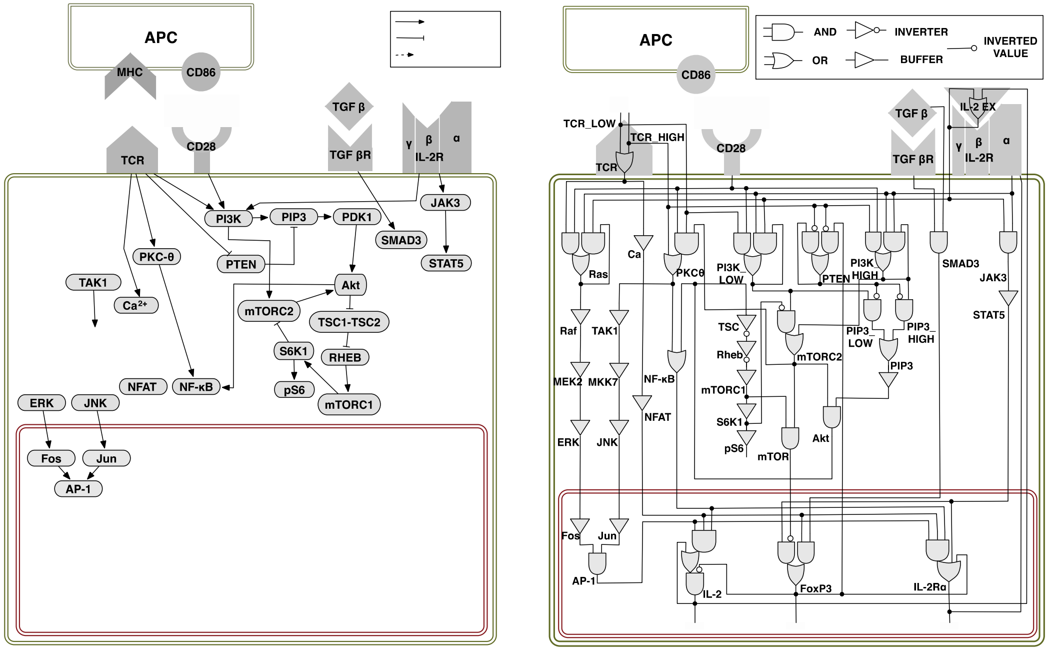
www.SCIENCESIGNALING.org 5 November 2013 Vol 6 Issue 300 ra97

RESEARCH ARTICLE

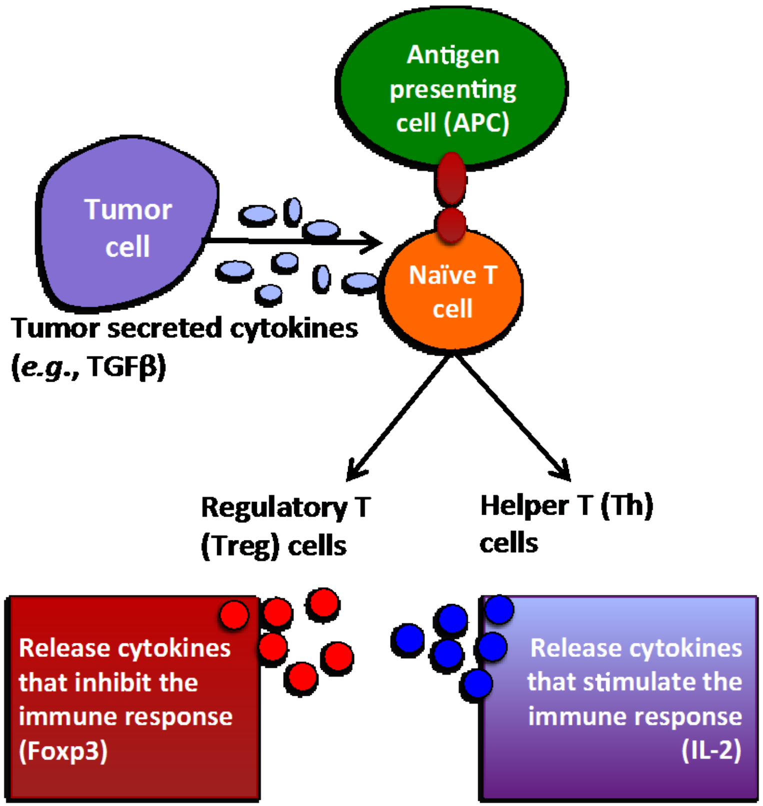
IMMUNOLOGY

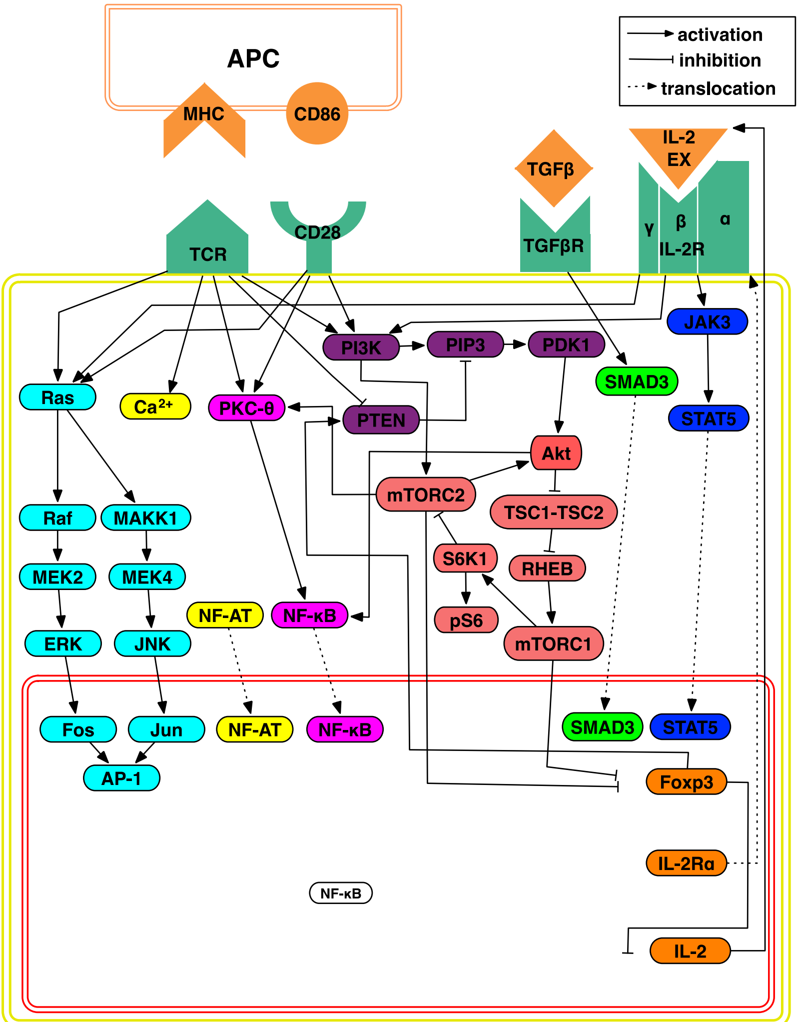
The Duration of T Cell Stimulation Is a Critical Determinant of Cell Fate and Plasticity

Natasa Miskov-Zivanov,[1] Michael S. Turner,[2*] Lawrence P. Kane,[2] Penelope A. Morel,[2†] James R. Faeder[1†]



Logical model of peripheral T cell differentiation





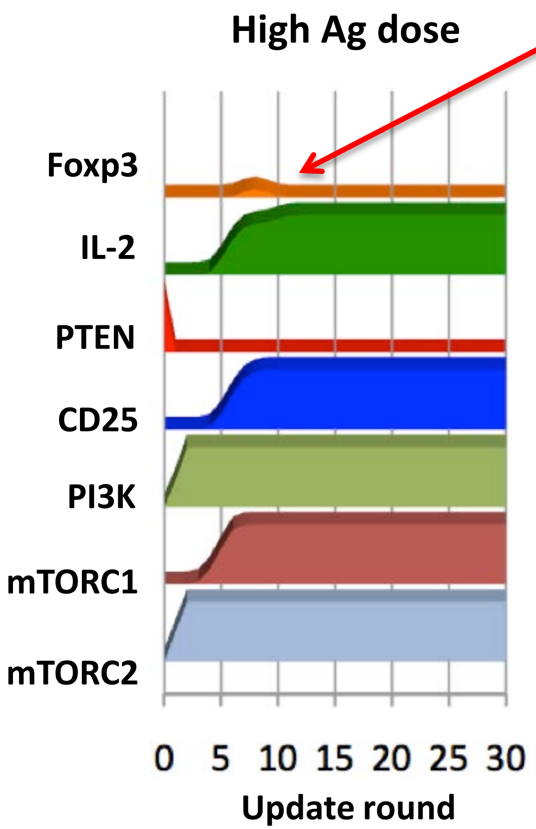
Model predicts timing of Ag stimulation key to the outcome

Model

Experiment

High antigen dose scenario

Simulation:
average element trajectories



Magnitude of transient is 0.1-0.15, which means that a maximum of 15% trajectories have Foxp3=1 in the same round.

How often Foxp3 increases to 1? How often it remains 0?

Probability of Foxp3 becoming 1 is higher than the peak value in simulations -> Foxp3 transiently increases on a larger number of trajectories.

#	Property	Probability estimate	Success count	Sample size	Elapsed time [s]
P1	F^{29} (FOXP3 == 1); F^{10} (FOXP3 == 1 & F^{19} (FOXP3 == 0))	0.237494	2857	12032	120
P2	F^{10} G^{2} (FOXP3 == 1)	0.0415313	10970	264160	2704
P3	F^{10} G^{1} (FOXP3 == 1)	0.119089	830	6976	73
P4	F^{20} G^{9} (FOXP3 == 0 & IL2 == 1 & PTEN == 0 & CD25 == 1 & PI3K == 1 & MTORC1 == 1 & MTORC2 == 1)	0.996124	256	256	2

Faeder Lab

current

John Sekar
Jose Juan Tapia
Robert Sheehan
Cihan Kaya

alumni

Dipak Barua
Qingyang Ding
Leonard Harris
Justin Hogg
Jintao Liu
Natasa Miskov-Zivanov
Yang Yang

Thierry Emonet
Michael Sneddon

Jason Haugh

Penelope Morel
Larry Kane
Michael Turner
William Hawse

Sarah Gaffen
Abhishek Garg

William Hlavacek
Lily Chylek

Byron Goldstein
Ambarish Nag
Michael Monine

Michael Blinov

Edmund Clarke
Haijun Gong
Paolo Zuliani

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Barbara Setlow
Xuan Yi

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