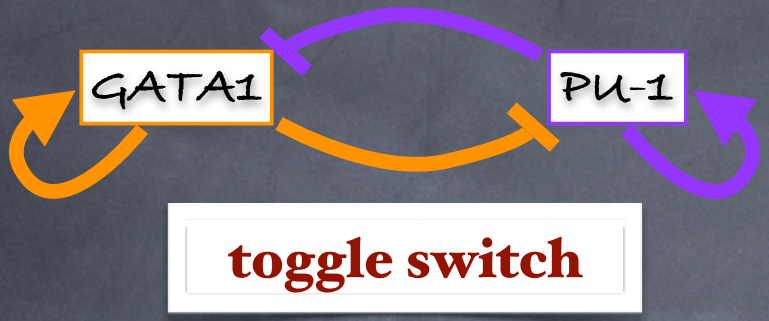
5. Regulatory Models that Mimic Phenotype and Dynamics, Part I

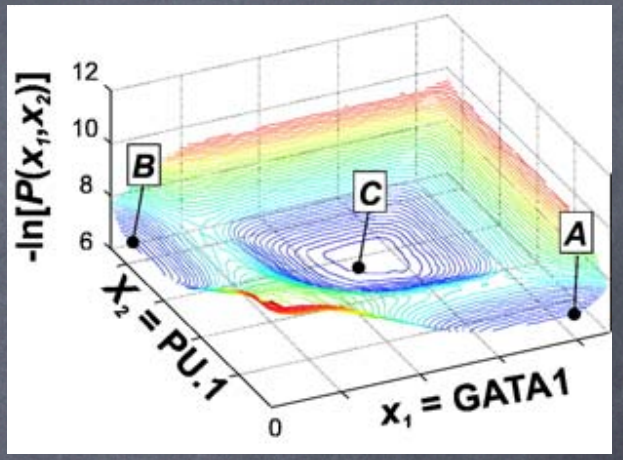
Warning: Statistical Physics.
It only works on average.

http://regan.med.edu/CVRB-course.php

Multi-stable circuits



- The simplest "developmental" type circuit
- Bistable

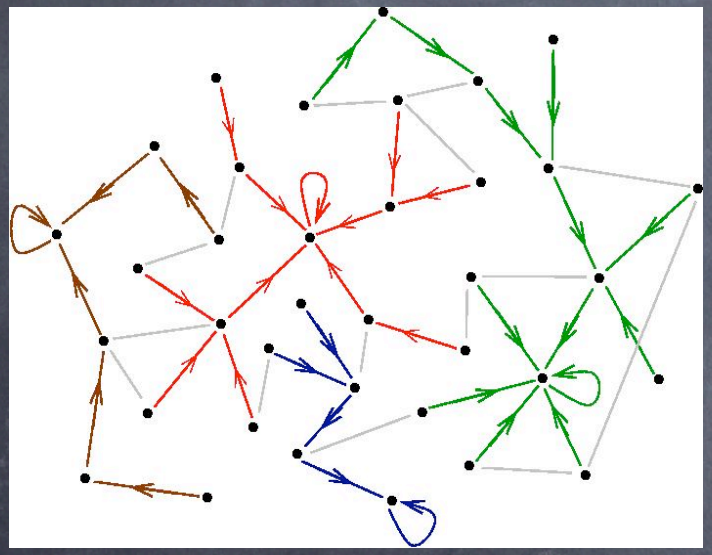


- Modeling
  - ➡ differential equations
  - ➡ Gillespie stochastic dynamics
  - ➡ Thermodynamic models of binding and transcription
    - ➡ concentration dependence
    - ➡ precise dynamics of switching
- Boolean dynamics
  - ➡ logic gates
  - ➡ discrete time
  - ➡ captures broad-scale features

GATA1	PU-1	GATA1	PU-1
ON	ON	OFF	OFF
ON	OFF	ON	OFF
OFF	ON	OFF	ON
OFF	OFF	ON	ON

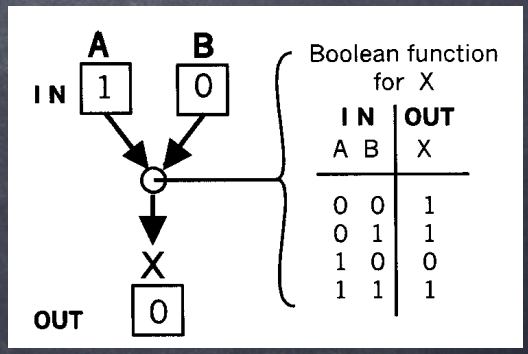
Boolean networks

Kauffman, S, **Homeostasis and differentiation in random genetic control networks**
Nature 224, pp 177, 1969



- Random network
- State of the system, or gene activ
  profile: (0,1,1,0,0,1,1,1,0,....,0)
- Random Boolean rules
  ➡ p - prob. output value 1

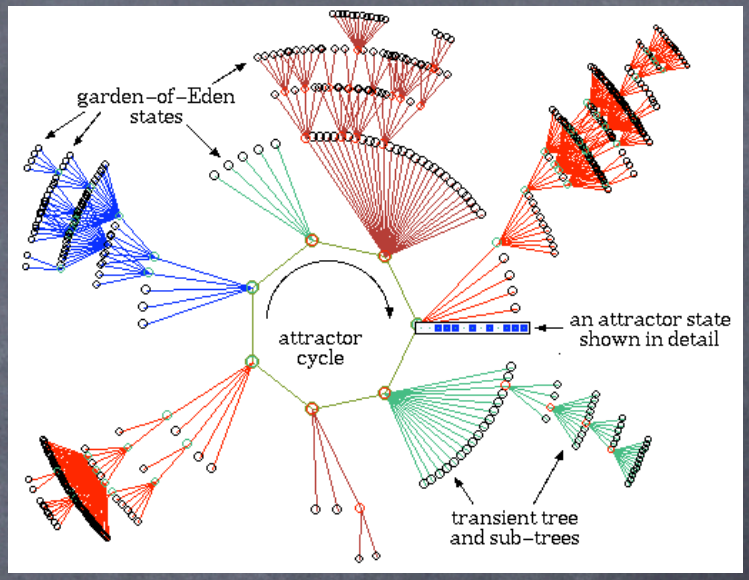
(NOT A) OR B



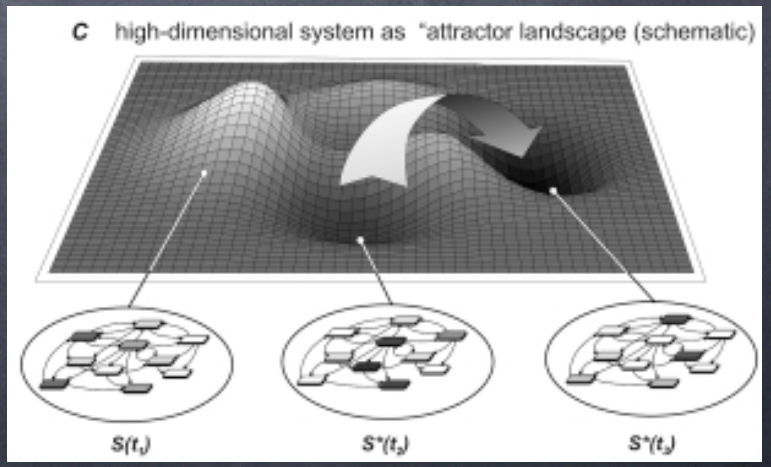
- State changes in time: trajectory in nD space
- **Structure** of state space determines all possible **dynamics**

Random Boolean networks have an ordered regime

- Only a small fraction of all cell states are **stable**
- The system does not visit all possible states

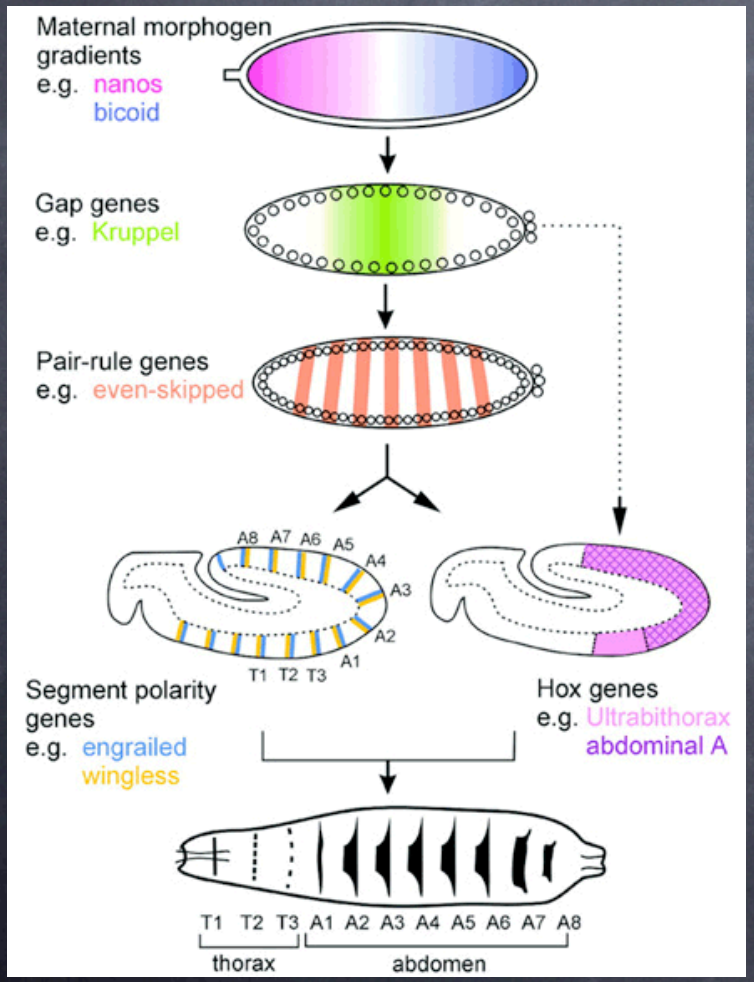


- **Attractors**:
  - Fixed points: a state in which all Boolean rules are satisfied
  - Limit cycles: a finite number of states through which the system cycles
- **Attractor basins**



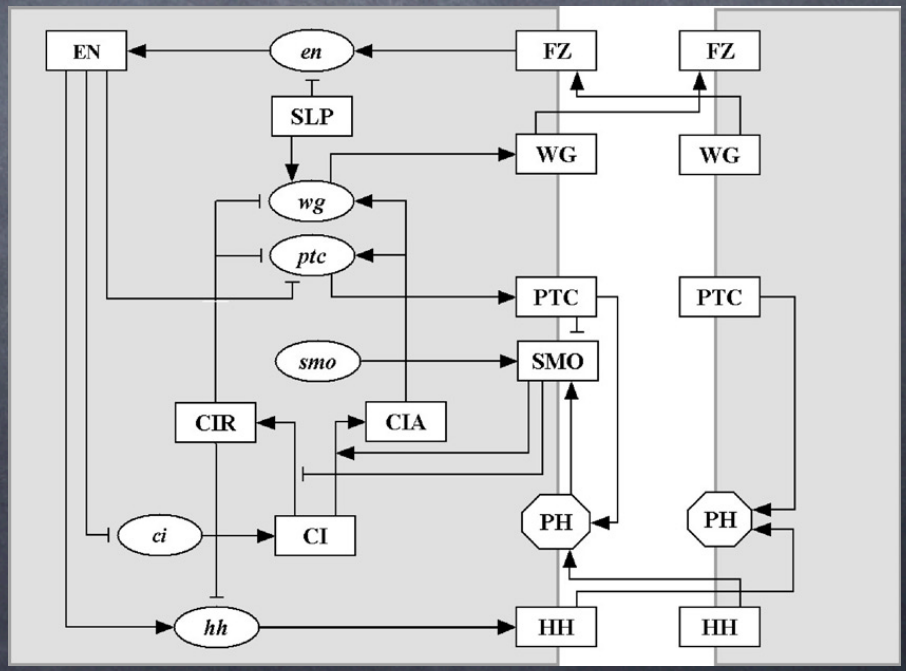
Physicists love this. Biology... not so much

"Random" is not a good interdisciplinary word.



Reka Albert & Hans G. Othmer

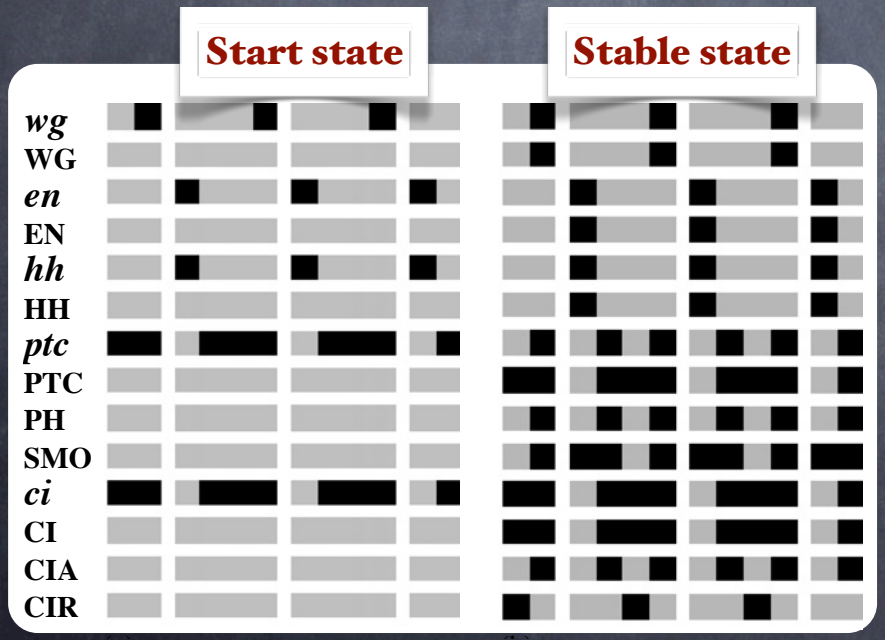
Drosophila segment polarity network

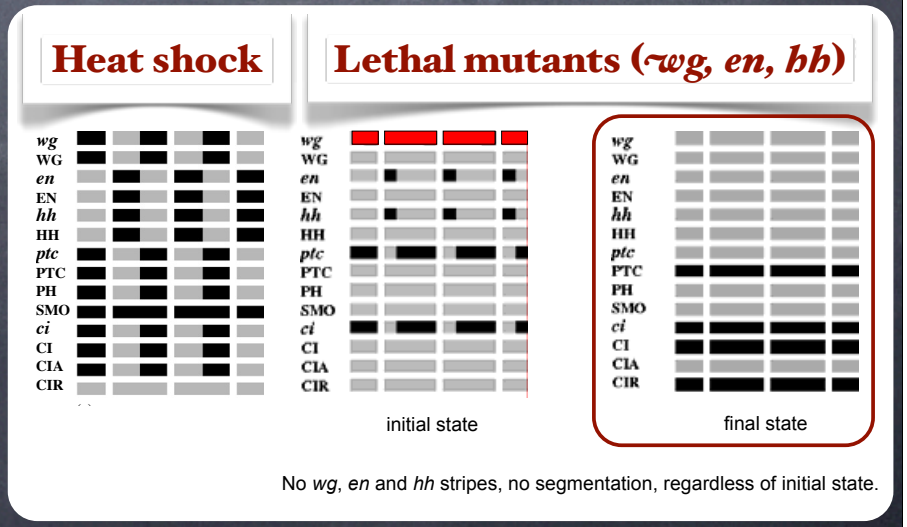


Boolean rules and correct topology are sufficient!

- The network topology was know, most Boolean rules could be inferred from literature
- Small enough system for exact enumeration!

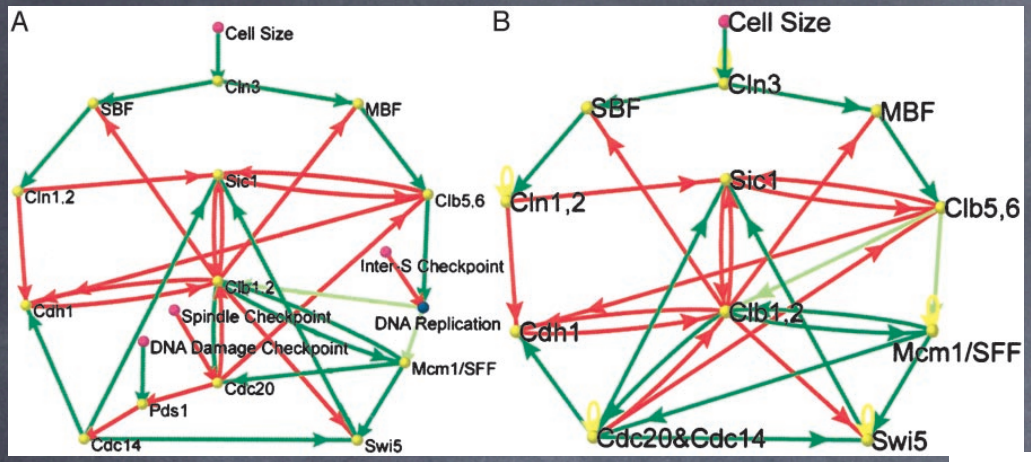
(i) the effect of transcriptional activators and inhibitors is never additive, but rather, inhibitors are dominant;
(ii) transcription and translation are ON/OFF functions of the state;
(iii) if transcription/translation is ON, mRNAs/proteins are synthesized in one time step;
(iv) mRNAs decay in one time step if not transcribed;
(v) transcription factors and proteins undergoing post-translational modification decay in one time step if their mRNA is not present.





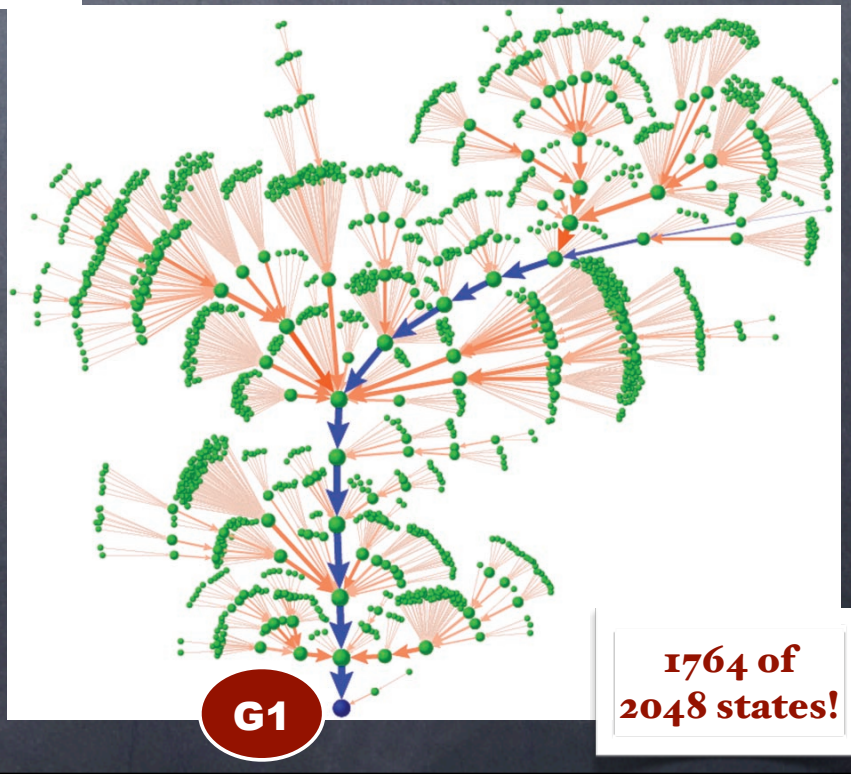
No *wg*, *en* and *hh* stripes, no segmentation, regardless of initial state.

The yeast cell cycle

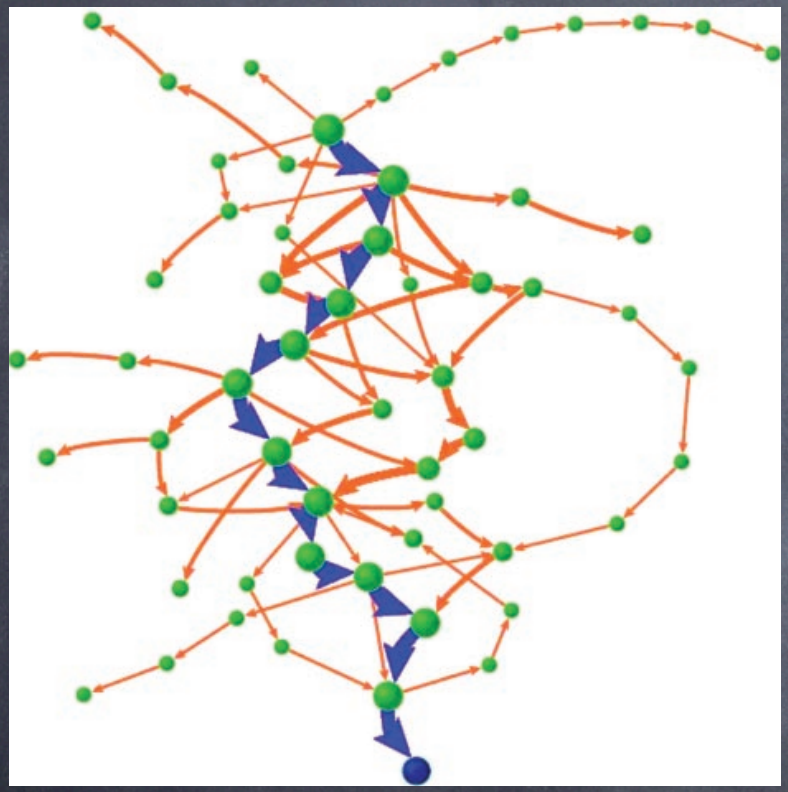


- The network topology is know
- NO Boolean rules, just activator/inhibitor relationships

$$S_i(t+1) = \begin{cases} 1, & \sum_j a_{ij} S_j(t) > 0 \\ 0, & \sum_j a_{ij} S_j(t) < 0 \\ S_i(t), & \sum_j a_{ij} S_j(t) = 0 \end{cases}$$



Robust in more than one way

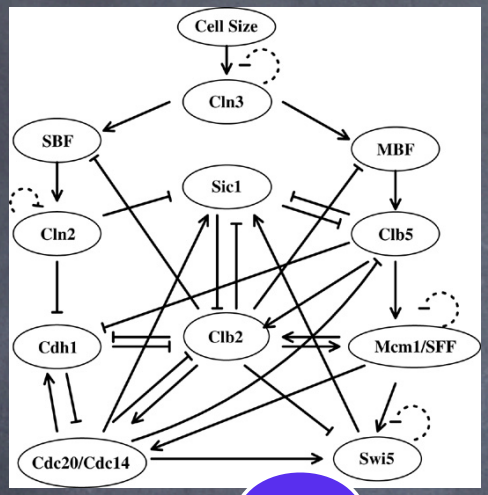


- Dynamics under perturbation
  - start dynamics from START
  - superimpose time-course for perturbed networks
    - ➡ 34 arrow deletions (41%)
    - ➡ 174 arrow additions (57%)
    - ➡ 29 activator/inhibitor switch (68%)

- Similar stable fixed point with
  - ➡ different dynamical rules
  - ➡ using other checkpoints

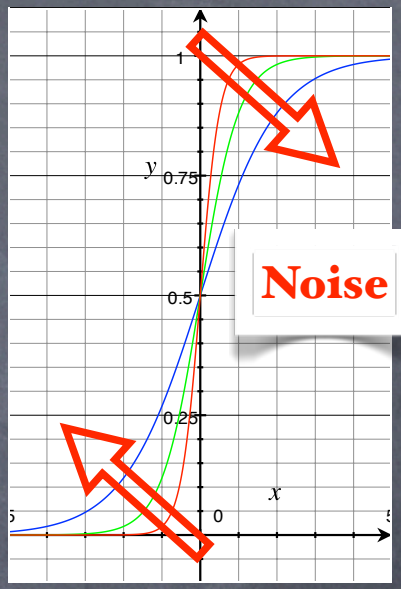
How about noise?

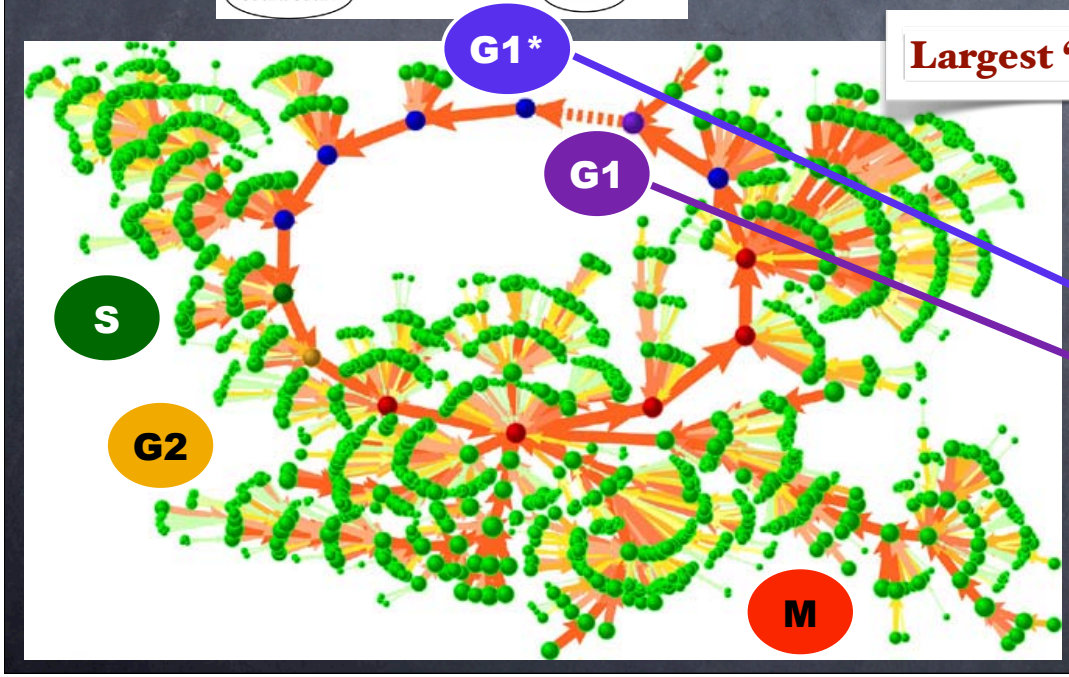
- Probabilistic cell cycle network



$$P_r(s_i(t+1)=\sigma_i \mid s_1(t),\ldots,s_{11}(t)) = \frac{\exp(\beta(2\sigma_i-1)T)}{\exp(\beta T)+\exp(-\beta T)},$$

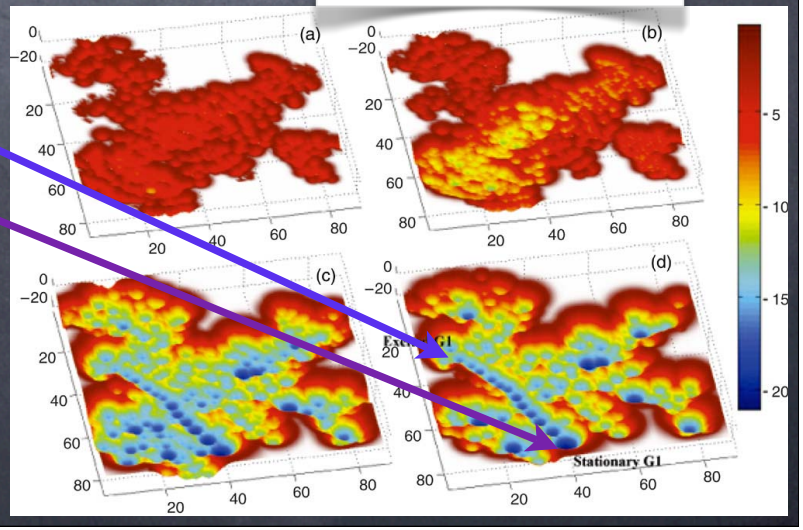
if $T=\sum_{j=1}^{11} a_{ij}s_j(t)\neq 0, \sigma_i \in \{0,1\}$;





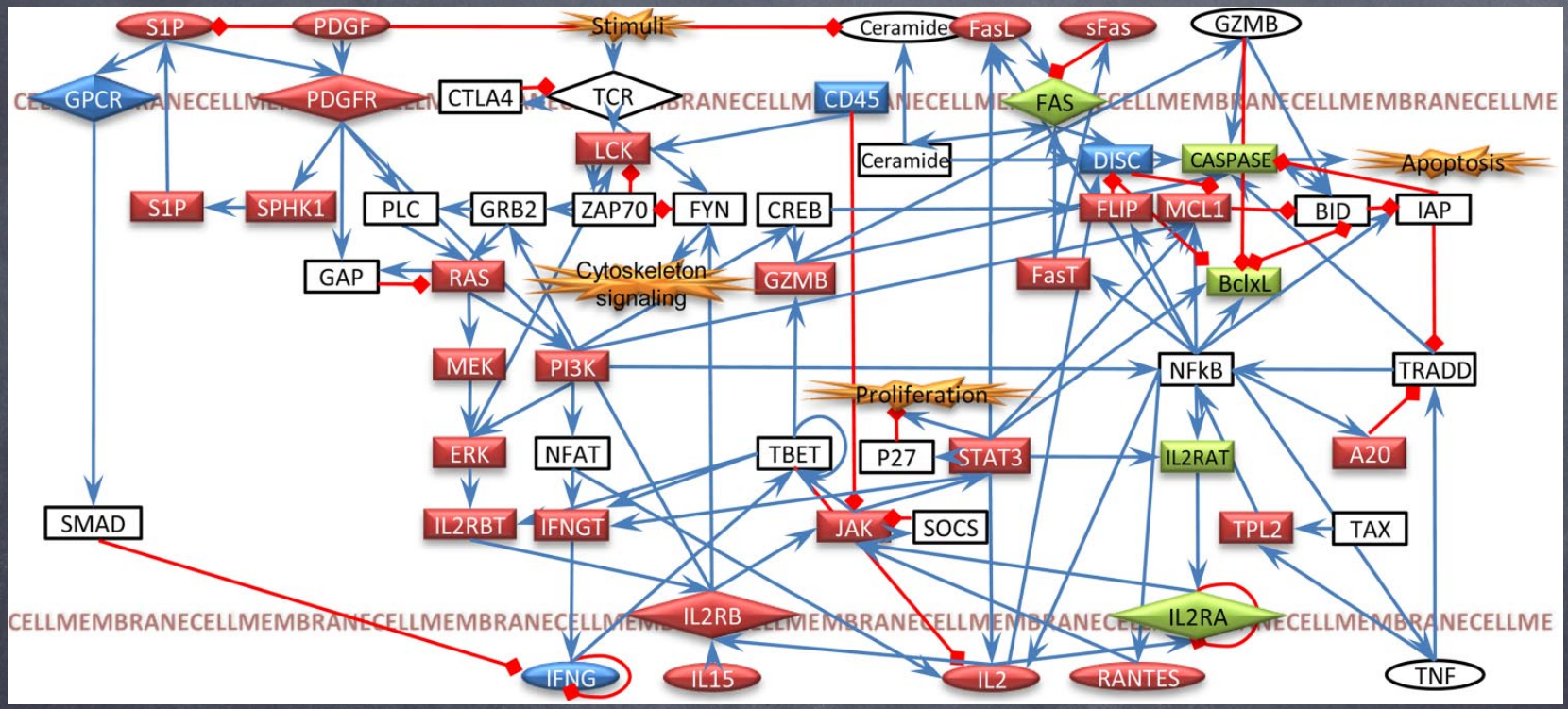
Largest "fluxes"

Noisy landscapes



A Mammalian Example

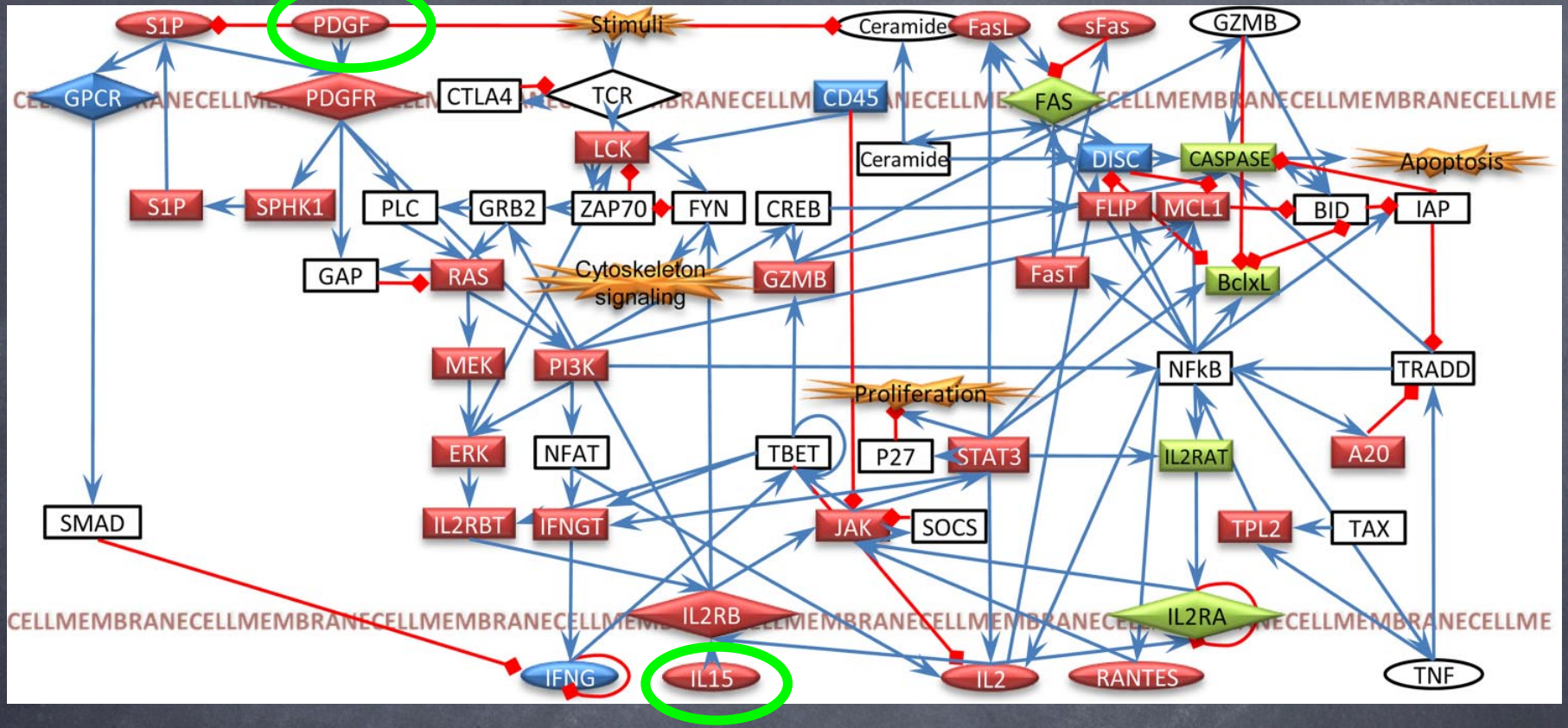
Survival signaling in Large Granular Lymphocyte Leukemia



- ➡ Extensive literature search of Activation induced Cell Death in cytotoxic T lymphocytes
- ➡ All know deregulation of the process
- ➡ Boolean rules from literature

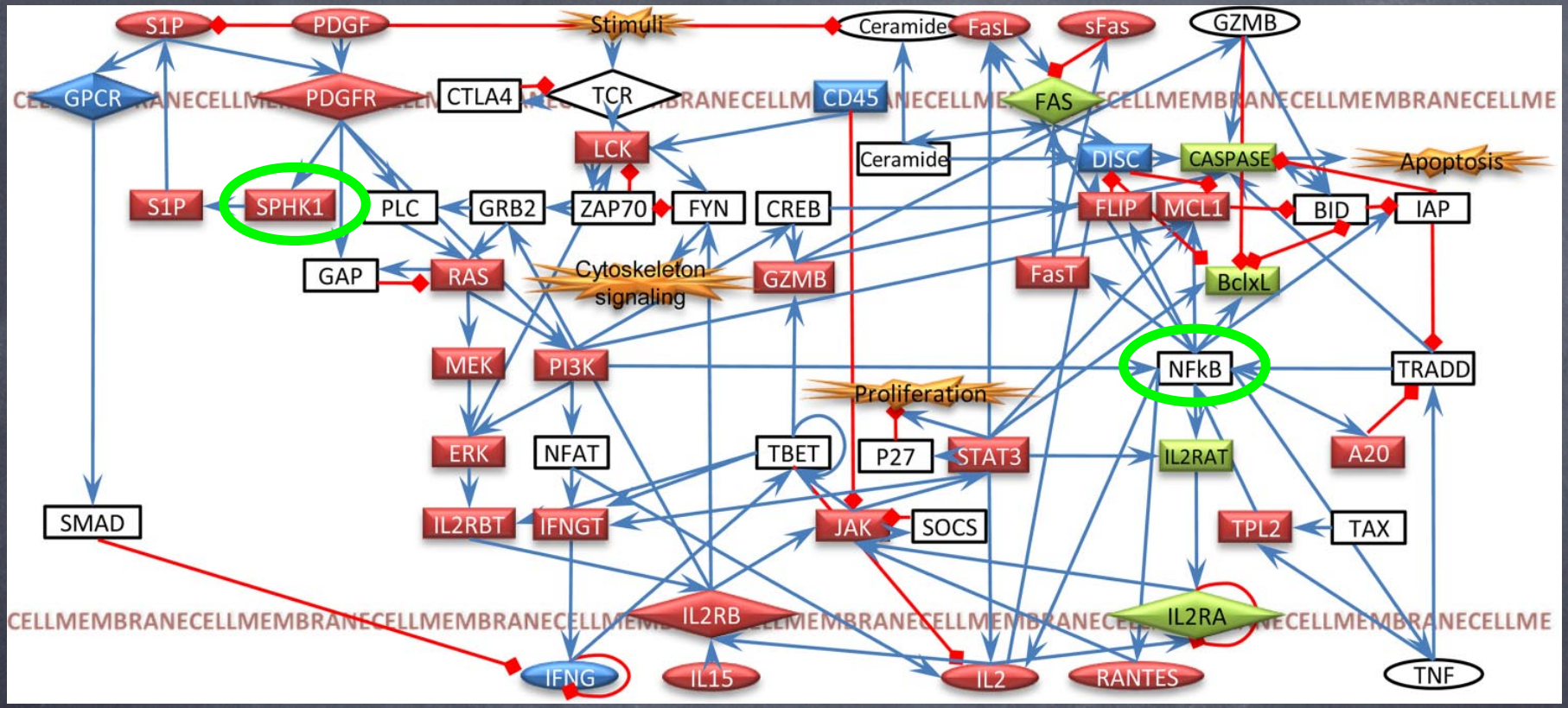
- Asynchronous update: a different way to model noise
- cell population response:
  - ➡ start from same initial state
  - ➡ different random update order

Results, 1



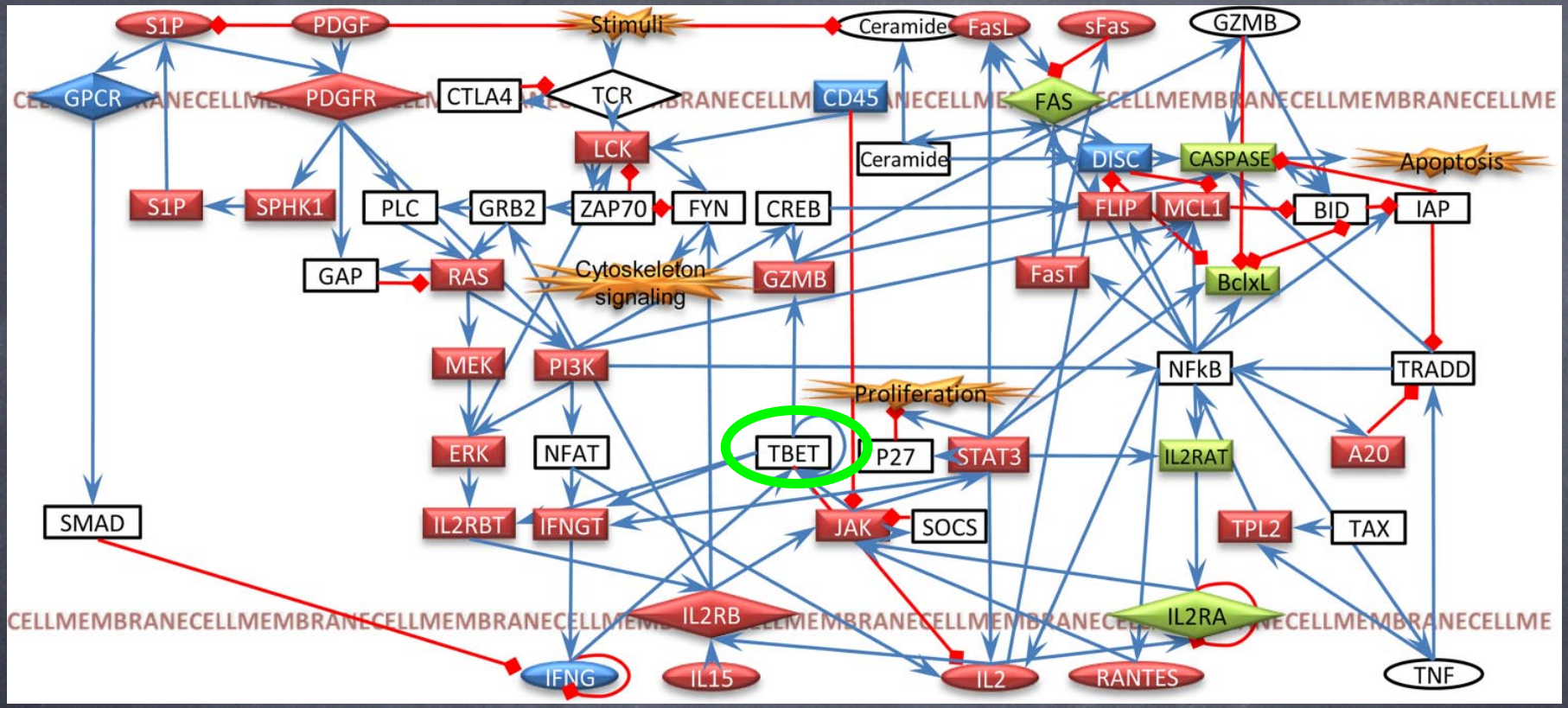
- Constitutive presence of IL15 AND PDGF reproduces all deregulation of apoptosis
  - experiment: increased PDFG in T-LGL sera
  - PDGF receptor inhibition makes T-LGL Peripheral Blood Mononuclear cells apoptotic, (normal ones do not mind!)

Results, 2



- Key mediators of activation and AICD decoupling: NFKB and SPHK1 (Sphingosine Kinase 1)
  - SPHK1 inhibition OR NFkB inhibiton makes T-LGL Peripheral Blood Mononuclear cells apoptotic, (normal ones do not mind!)

Results, 3



- TBET is predicted to be constitutively active in T-LGL
  - TBET levels Peripheral Blood Mononuclear cells is 3.3 fold higher than normal PBMCs

6. Regulatory Models that Mimic Phenotype and Dynamics, Part II

- Cycles and their stability -

June 8
12 PM