Absolute Robustness in Deterministic and Stochastic Chemical Reaction Networks

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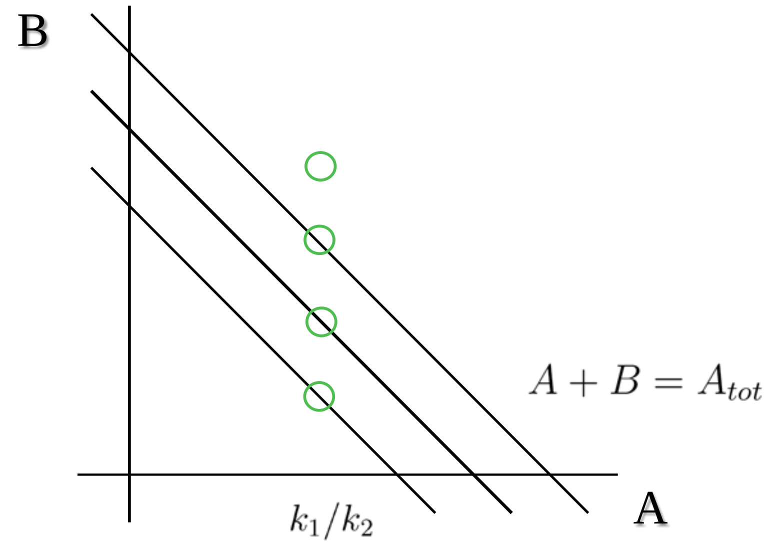
Absolute robustness: Toy model

$$A + B \xrightarrow{k_1} 2B$$
$$B \xrightarrow{k_2} A$$



ODE:

$$A' = -k_1 AB + k_2 B$$
$$B' = k_1 AB - k_2 B$$

Mass conservation:

$$A + B = A_{tot}$$

At steady state:

$$k_1 AB = k_2 B$$

$$\boxed{A = k_1/k_2}$$
$$(B \neq 0)$$

- The steady state concentration of A is *absolutely robust* to changes in the total protein concentration Atot
- If A is the active version of the protein, then this system is robust to protein fluctuations at steady state

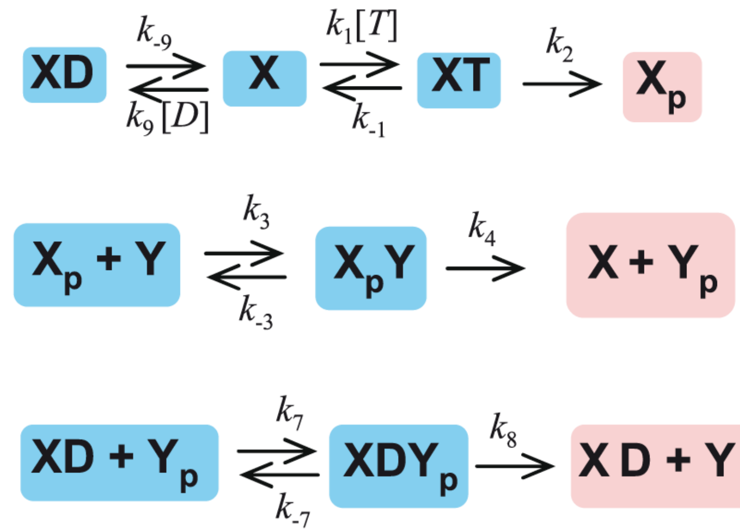
Absolute robustness: General result

Deficiency:

$$\delta := \mathcal{C} - \ell - \operatorname{rank}\Gamma$$

nodes (aka complexes)

connected components



nonterminal node

terminal node

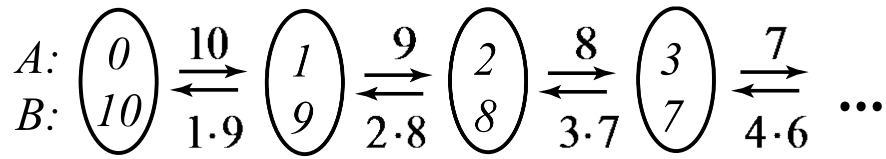
THEOREM: Suppose that δ=1 and that there exist two nonterminal nodes that differ by a single variable A. Then A is absolutely robust.

- In the example above, the variable Yp is absolutely robust, i.e. its concentration at steady state is independent of total protein concentrations Xtot and Ytot
- Absolute robustness is a consequence of the structure of the network, not of specific parameter values

G. Shinar and M. Feinberg, Structural sources of robustness in biochemical reaction networks, Science 327(12):1389-1391, 2010

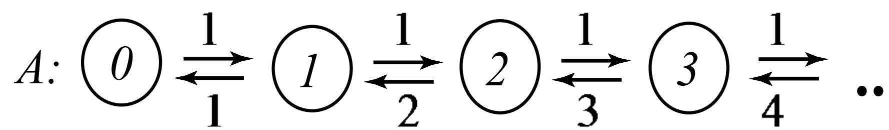
Stochasticity and absolute robustness: toy model

$$A + B \xrightarrow{k_1} 2B$$
$$B \xrightarrow{k_2} A$$



Notice the similarity with

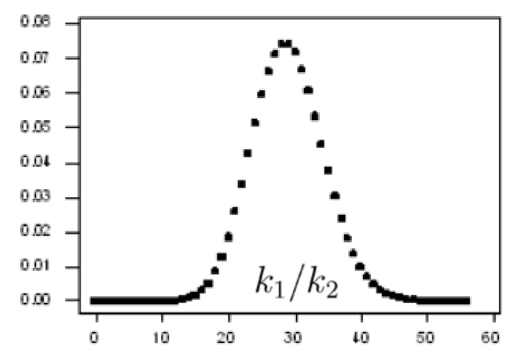
$$A \xrightarrow{k_1} \phi$$
$$\phi \xrightarrow{k_2} A$$



which has Poisson distribution

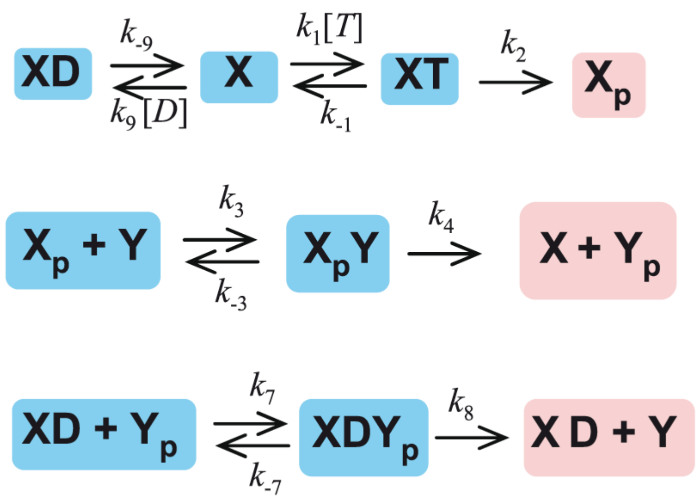
$$P(A = k) = \frac{\lambda^k}{k!} e^{-\lambda}$$

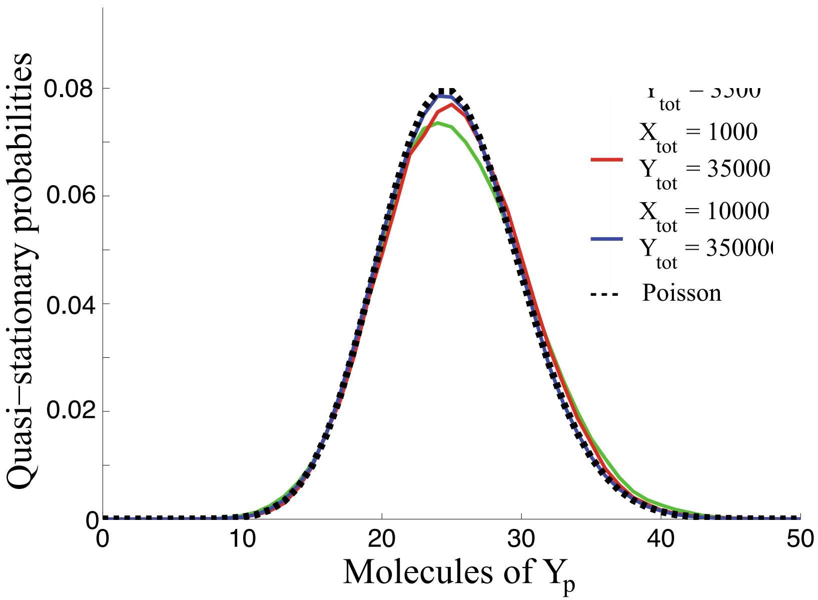
$$\lambda = k_2/k_1$$
$$E(A) = \lambda$$
$$\sigma^2(A) = \lambda$$



- Simulations show that the toy model has transient steady state distributions that are very similar to a Poisson distribution and centered around the deterministic mean

Stochasticity and absolute robustness: General simulations





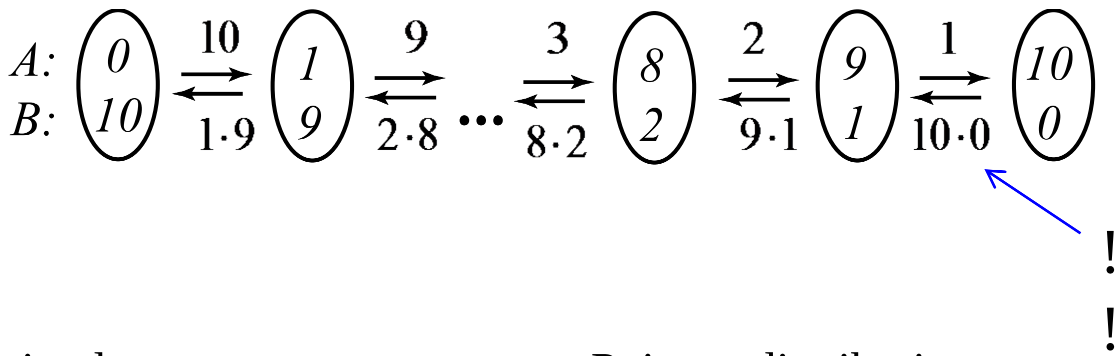
- Gillespie simulations were carried out with more complex systems such as the Envz/OmpR osmoregulation model (above)
- After simulating absolutely robust systems for some time, they *appear* to converge towards the same Poisson distribution regardless of total concentrations
- Mean of the distribution corresponds to the steady state of deterministic system

D. Anderson, G. Enciso, M. Johnston, Stochastic analysis of biochemical reaction networks with absolute concentration robustness, Journal of the Royal Society Interface 11(93), doi: 10.1098/rsif.2013.0943, 2014.

Stochastic extinction: Toy model

$$A + B \xrightarrow{k_1} 2B$$

$$B \xrightarrow{k_2} A$$



- Although this system transiently seems to converge to a Poisson distribution, when the system reaches the state (10,0) it gets stuck at the boundary (!)
- This extinction event cannot happen in the deterministic system, but in the stochastic case it happens with probability 1 given enough time
- Simple example of a significant qualitative difference between a continuous chemical reaction model and its corresponding stochastic system

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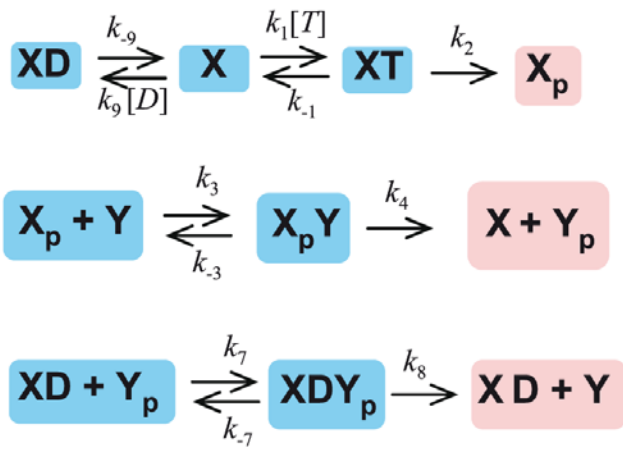
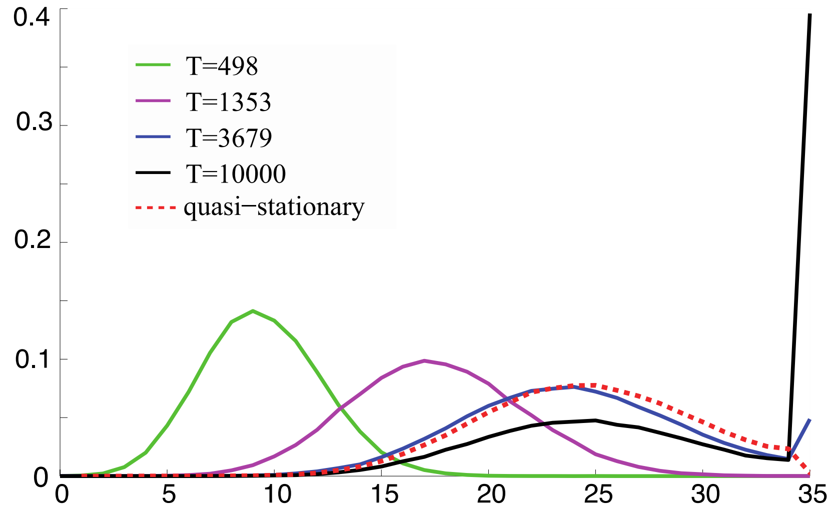
Stochastic extinction: General result





Definition: A chemical reaction network is *conservative* if every species is included in some mass conservation relation.

Definition: Given a state *c*, we say that a node in the network graph is *off* if at least one of the species in the complex is equal to zero.

Theorem: Suppose that δ=1, there exist two nonterminal nodes that differ by a single variable A, and the system is conservative. Then for every solution of the stochastic system, every nonterminal node eventually turns (and stays) off.

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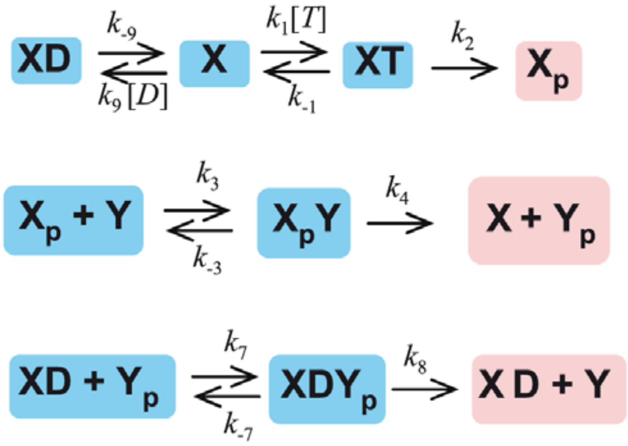
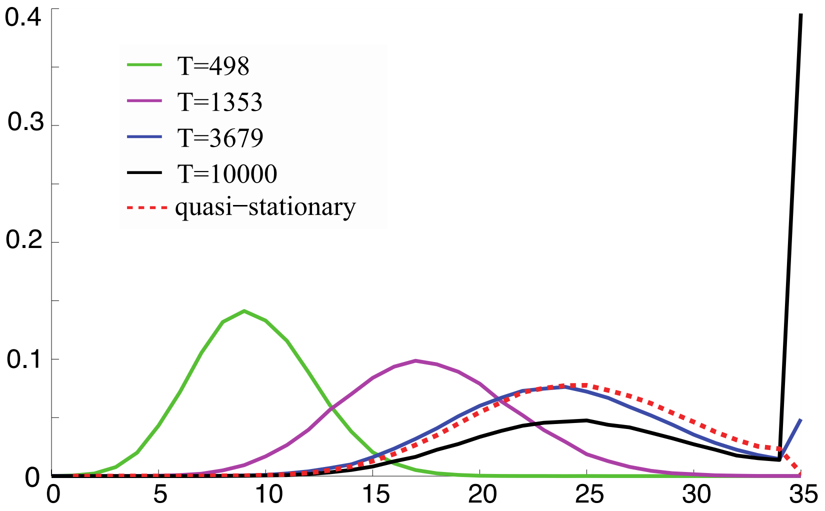
Stochastic extinction: General result





- In the particular example above, eventually the variables XD, X, XT, XpY, XDYp must vanish, since they are the only variables in their respective nodes. Therefore Xp=Xtot in the long run, since all other forms of X vanish
- Since XD=0 in the long run, the only reaction that can destroy Yp can never take place. Also, since Xp+Y is eventually off, it must eventually hold Y=0. We conclude that Yp=Ytot in this system after sufficiently long time.
- A similar result holds for conservative systems under the same assumptions as in Shinar et al.

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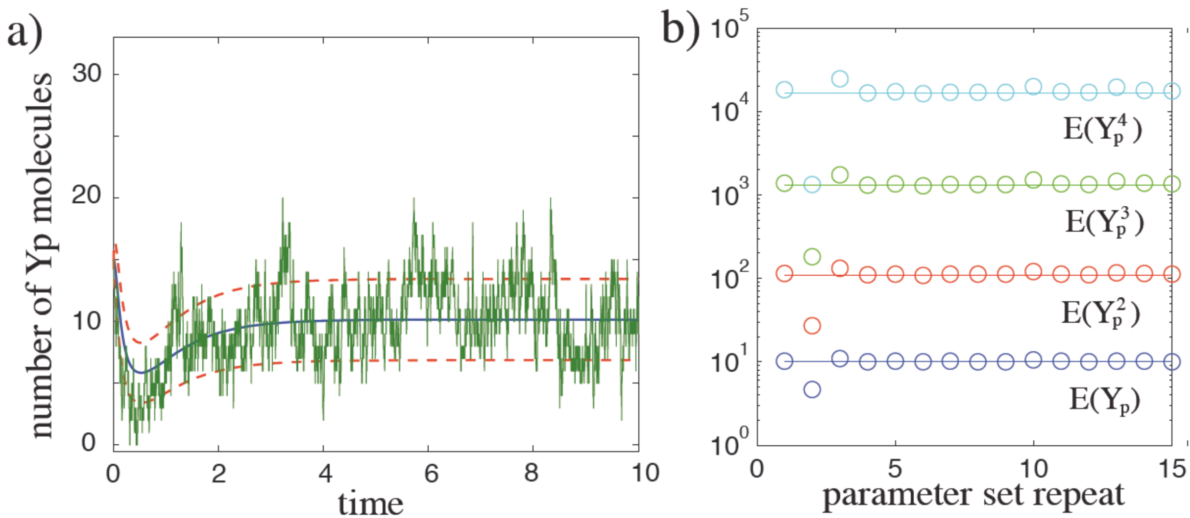
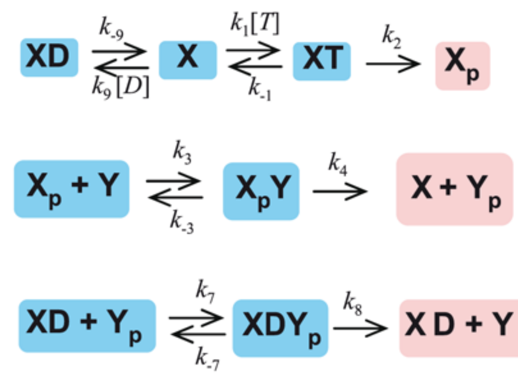
Transient Behavior: Computational Results



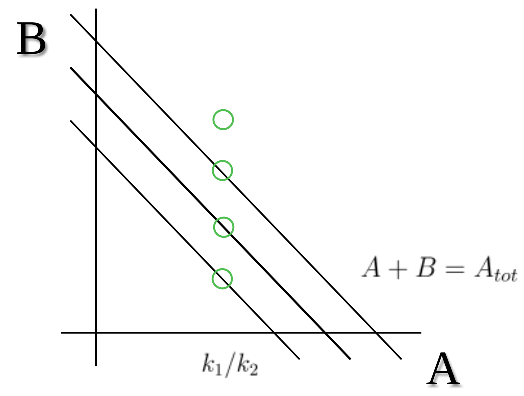


- Moment closure analysis to estimate mean, variance and higher moments of Yp in quasistationary distribution, using Joao Hepanha's StochDynTools software for Matlab
- Randomized each parameter value over six orders of magnitude, and compared E(Yp^k) with the moments of the Poisson distribution

Transient Behavior: Mathematical Analysis

$$\begin{array}{ccc} A + B & \xrightarrow{k_1} & 2B \\ B & \xrightarrow{k_2} & A \end{array}$$

$$A + B = n$$



Factorial moments:

$$y_1 = E(A),\ y_2 = E(A(A-1)),\ y_m = E(A(A-1)\ldots(A-m+1)),\ m \geq 0$$

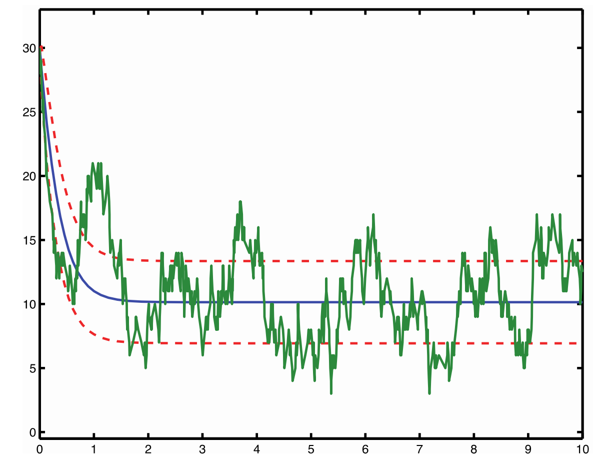
One can calculate for this system:

$$y'_m = mk_2(n-m+1)y_{m-1} - mk_2 y_m - mk_1(n-m)y_m + mk_1 y_{m+1},\ m \geq 1$$

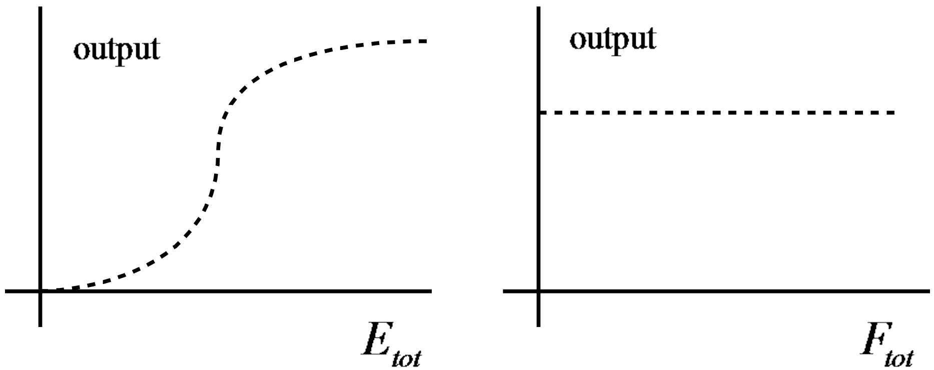
For large n, setting $y_{m'} = 0$ and dividing by n:

$$mk_2 y_{m-1} = mk_1 y_m \qquad y_m = \frac{k_2}{k_1} y_{m-1} = \lambda y_{m-1}$$

These are the factorial moments of the Poisson distribution

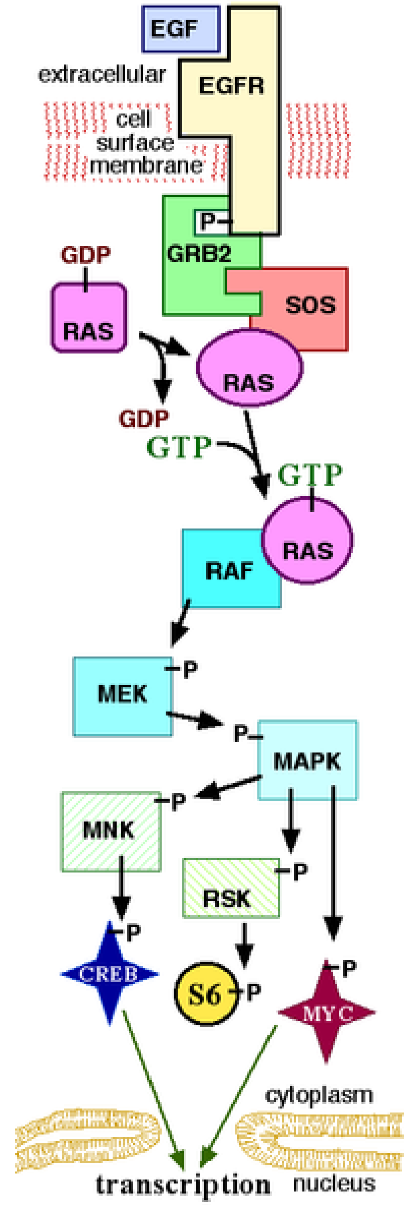


Absolutely robust dose responses

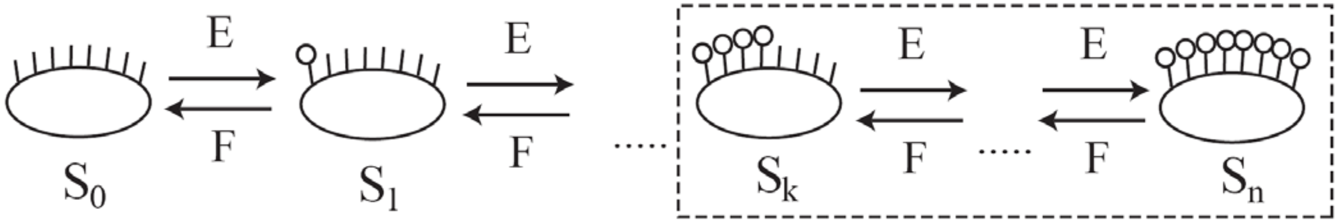


QUESTION: Can a system be absolutely robust to *some* total protein concentrations, but not *others*?

- This behavior can lead to robustness in signal transduction, where systems respond selectively to certain environmental signals while suppressing others
- Since such partial absolute robustness is a weaker statement than full absolute robustness, one can expect that weaker assumptions can lead to it



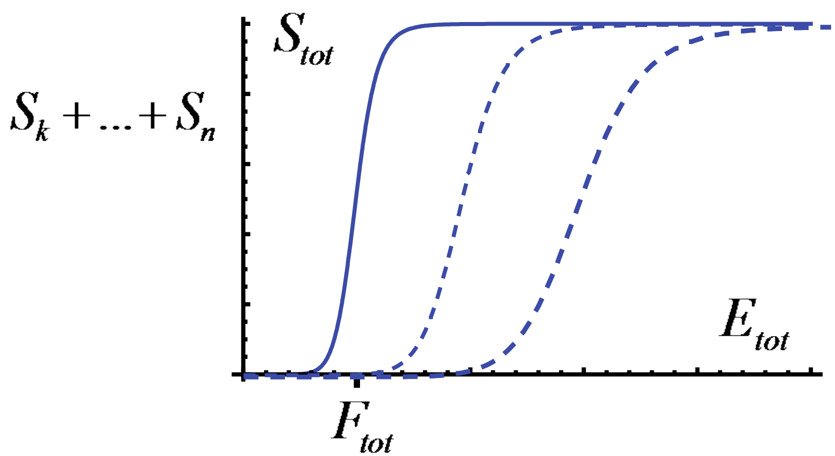
Example: Multisite phosphorylation



$$S_0 + S_1 + \ldots + S_n = S_{tot}$$

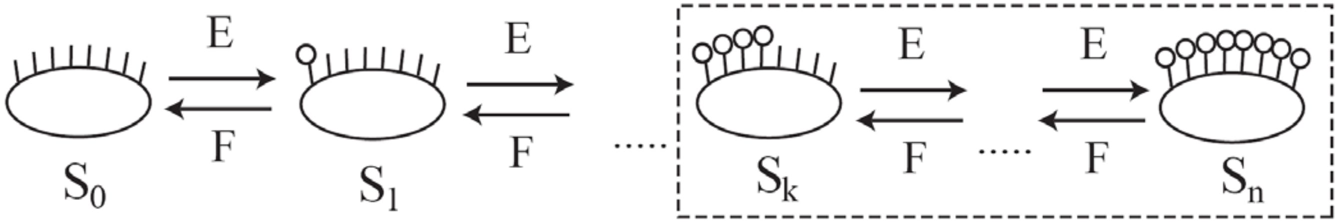
$$E = E_{tot}$$

$$F = F_{tot}$$



- In this model the active substrate concentration is an ultrasensitive function of the kinase E=Etot
- However, the system is highly dependent on small changes of the total phosphatase Ftot as well as Stot

Example: Multisite phosphorylation



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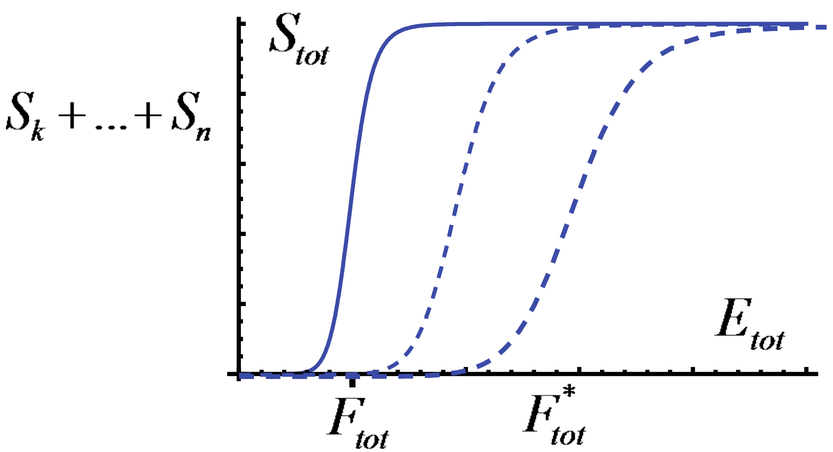

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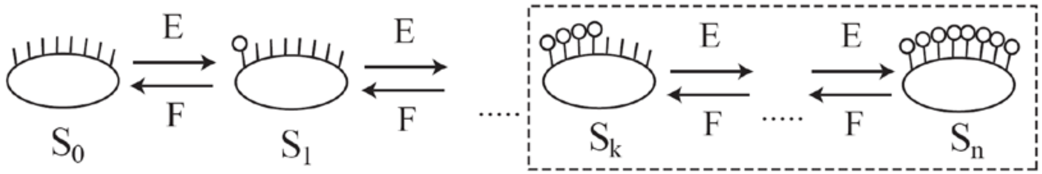


$$F + B \xrightarrow{k_1} 2B$$

$$B \xrightarrow{k_2} F$$

$$S_0 + S_1 + \ldots + S_n = S_{tot}$$

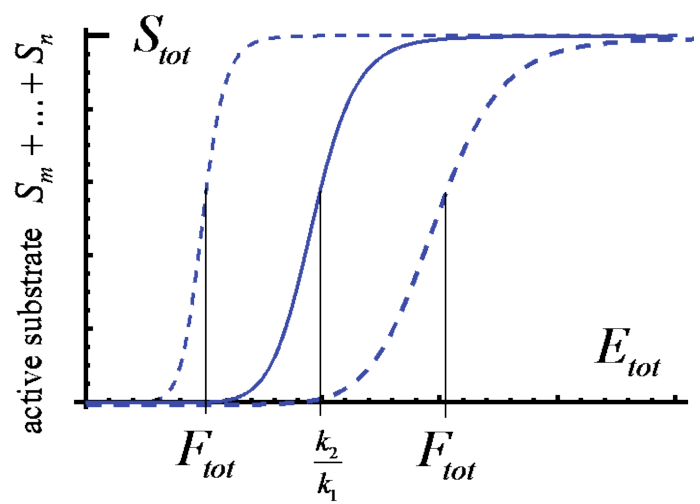
$$E = E_{tot}$$

$$F + B = F_{tot}$$

at steady state:

$$B' = k_1 F B - k_2 B = 0$$

$$\Rightarrow \quad F = k_2 / k_1 \quad (B \neq 0)$$



- In this new system the dose response is not dependent on Ftot, but only on the rate parameters
- A similar change can be implemented to create (approximated) independence from Stot

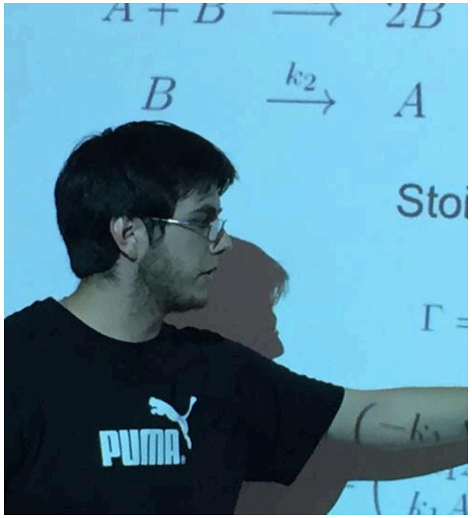
Conclusions

- Absolute robustness is a structural property that enables independence from protein variability for a steady state output
- After sufficient time, an extinction event leads to a significantly different dynamics from the deterministic case, and absolute robustness is lost
- Computational and analytical evidence shows that the absolutely robust variable has Poisson quasistationary distribution

Future work

- Investigate which chemical reactions can give rise to absolutely robust dose responses
- Prove that transient behavior of stochastic systems approximates a Poisson distribution
- Find experimental evidence for this mechanism in signal transduction in bifunctional proteins, such as in two component signaling, olfactory receptor selection, etc

Thanks!



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Questions?

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