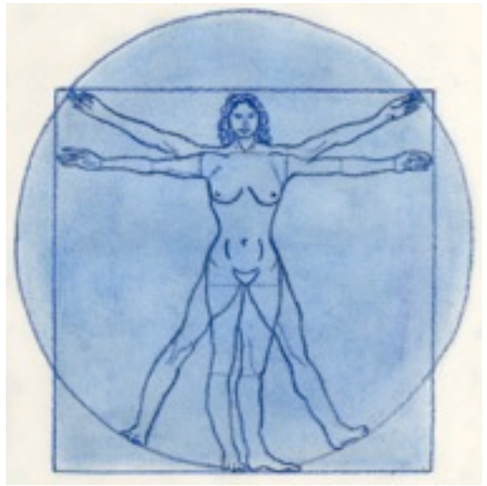
Delayed Bifurcations in Gene-regulating Decision Making Networks



Alexey Zaikin

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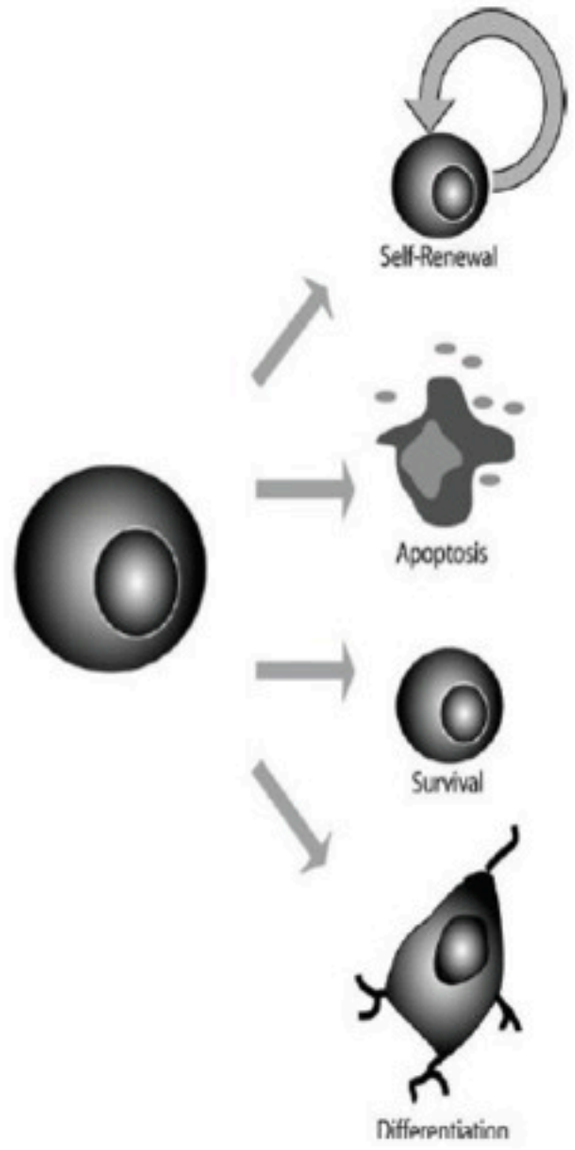
University College London
www.zaikinlab.com

Epigenetic decision making

- It is a stochastic process that helps cells to decide between different and functionally important fates.
- It is controlled by **genetic networks**.



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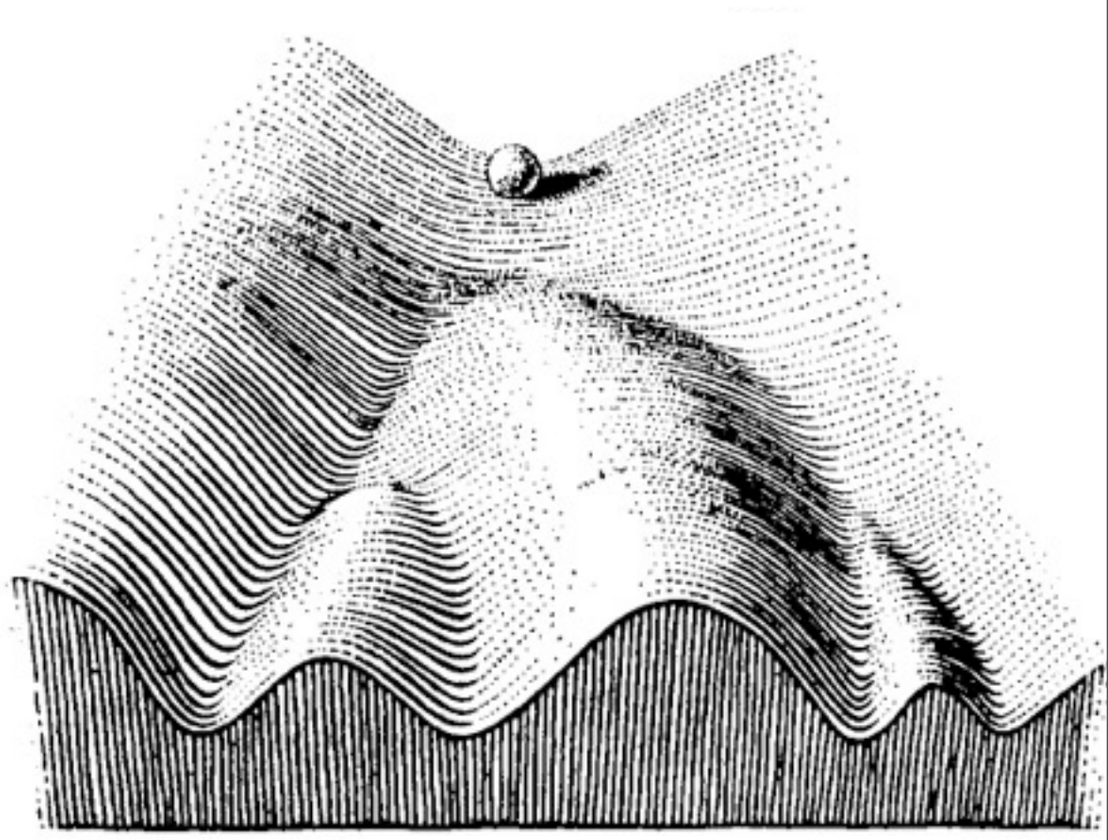
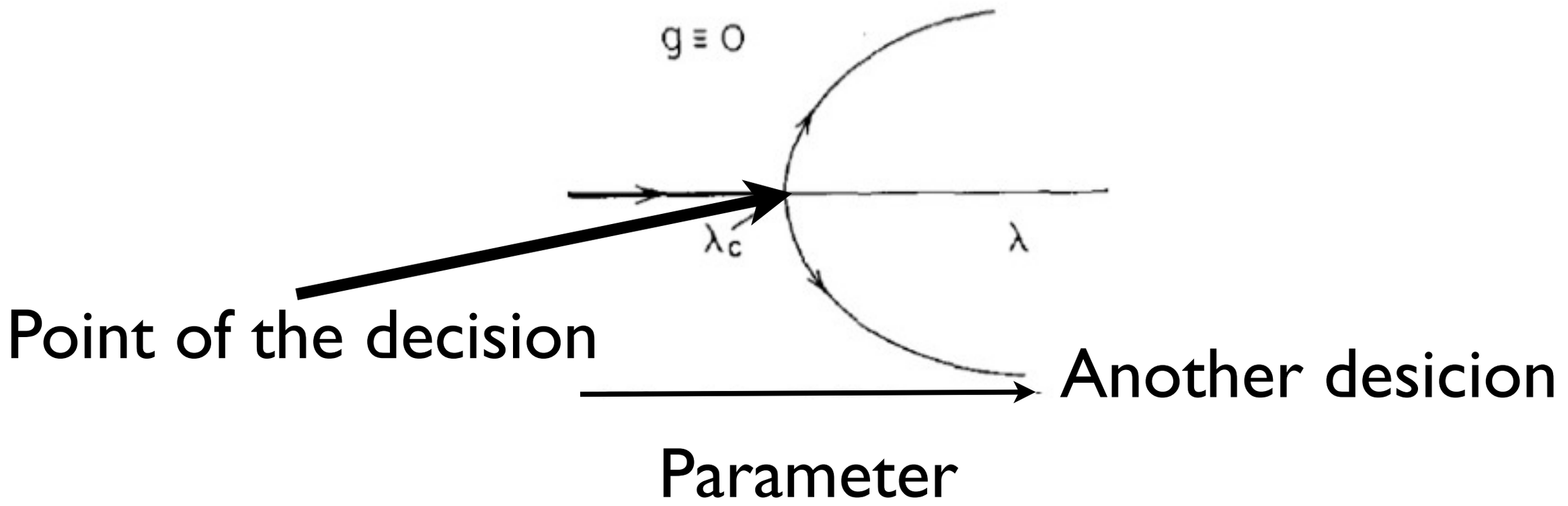


One decision



Epigenetic decision making

Timing matters!

- It is a stochastic process that helps cells to decide between different and functionally important fates.
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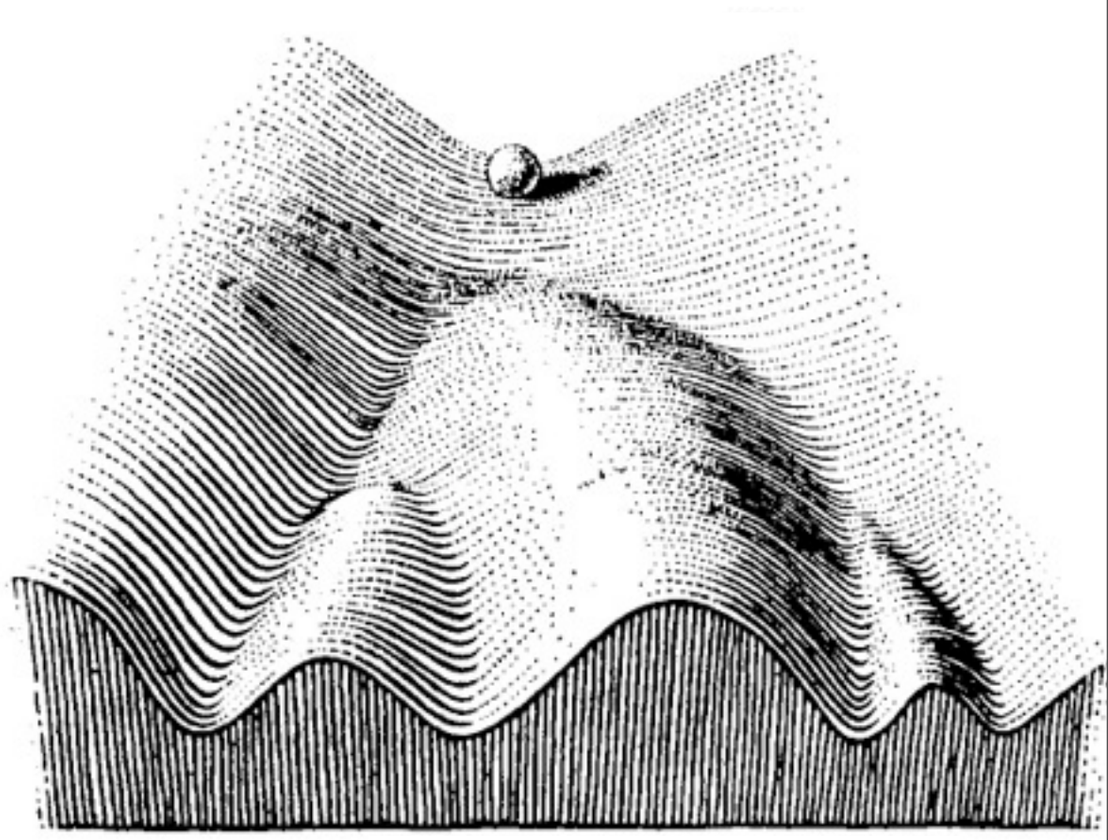

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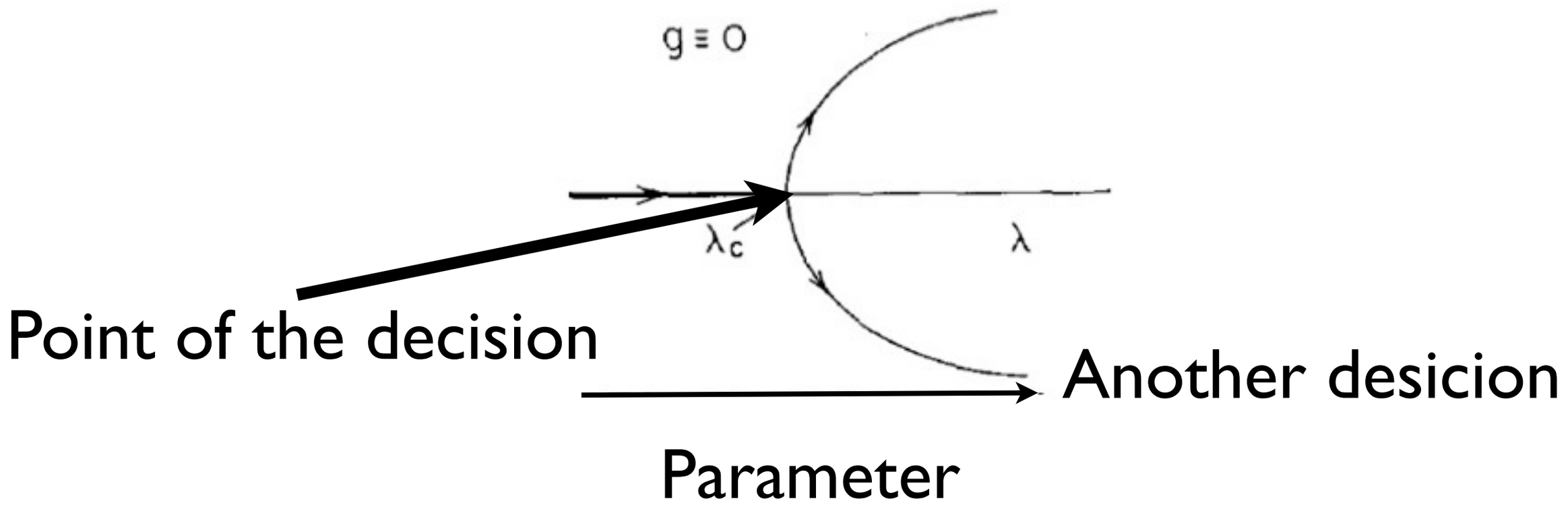


Epigenetic decision making Timing matters!

- Where important? Main idea.
- Paradigmatic genetic switch - Speed dependent cellular decision making
- Another form of signalling
- Genetic switch regulating differentiation of immune cells
- Multidimensional genetic switch
- Conclusions and Open questions
- Example of timing regulated by quorum-sensing

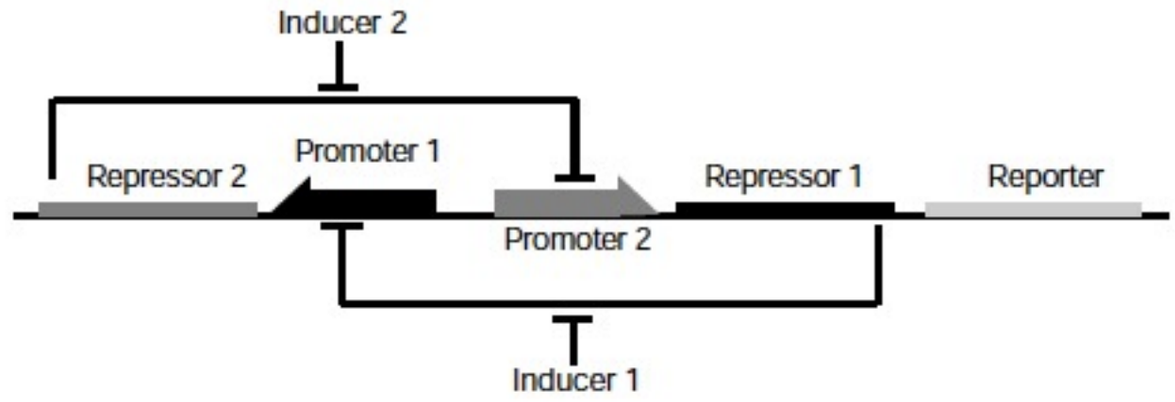
Epigenetic genetic decision. Where important:

- In synthetic genetic switches and logical circuits

Construction of a genetic toggle switch in *Escherichia coli*

Timothy S. Gardner*†, Charles R. Cantor* & James J. Collins*†

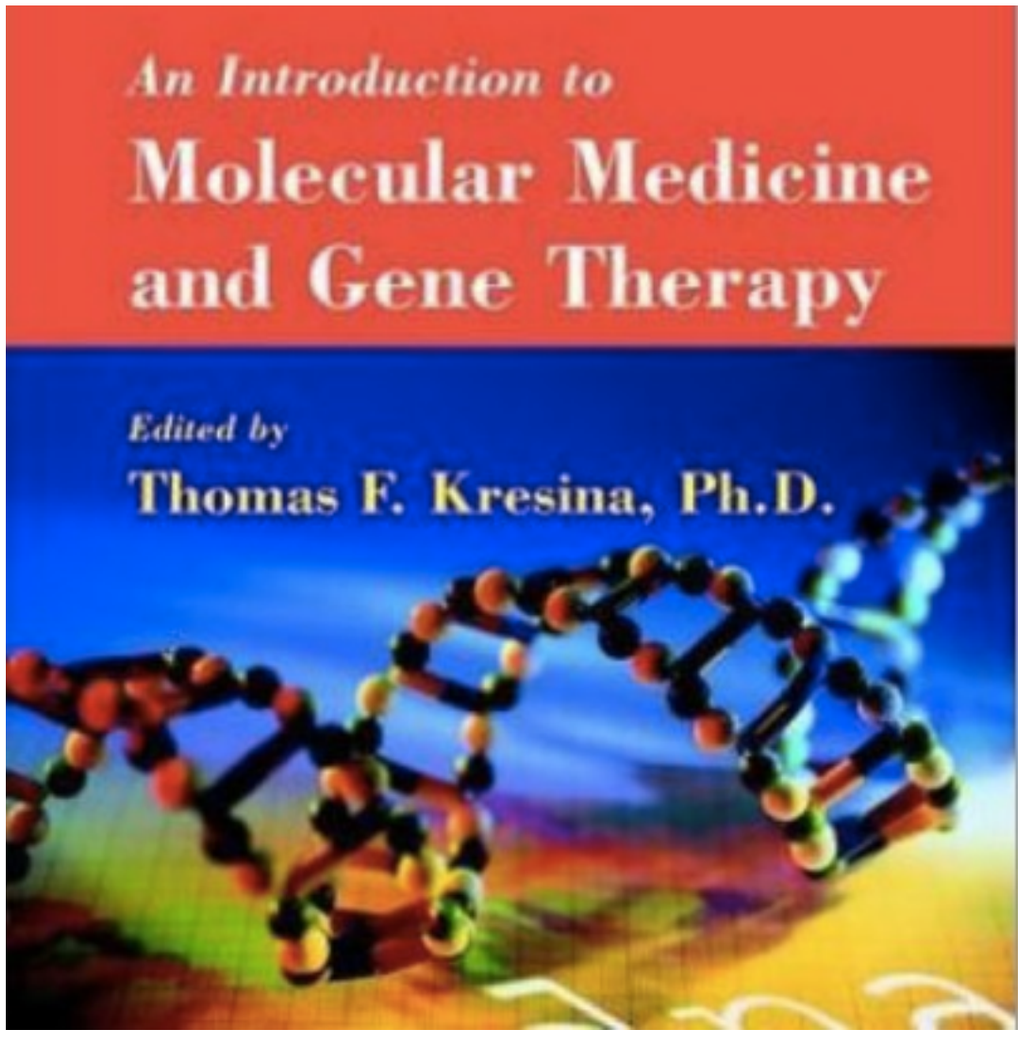
NATURE | VOL 403 | 20 JANUARY 2000 |



- artificial genetic modules
- consist of a limited number of genes
- designed to operate isolated from the rest of the cellular machinery
- test system for special functions of natural gene networks
- greatly reduced complexity of natural networks

Epigenetic genetic decision. Where important:

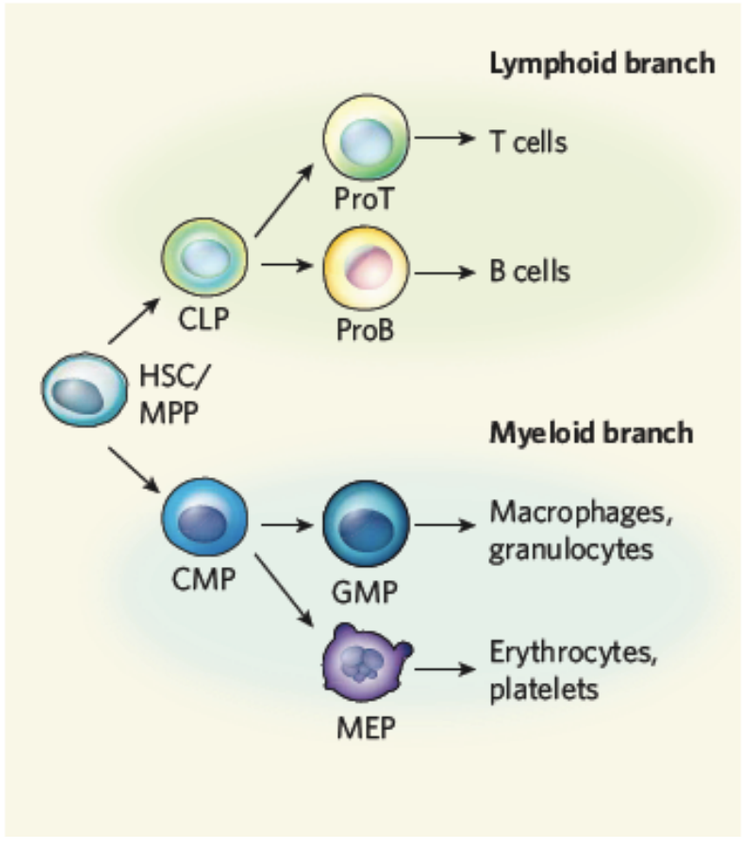
- In the design of genetic therapies



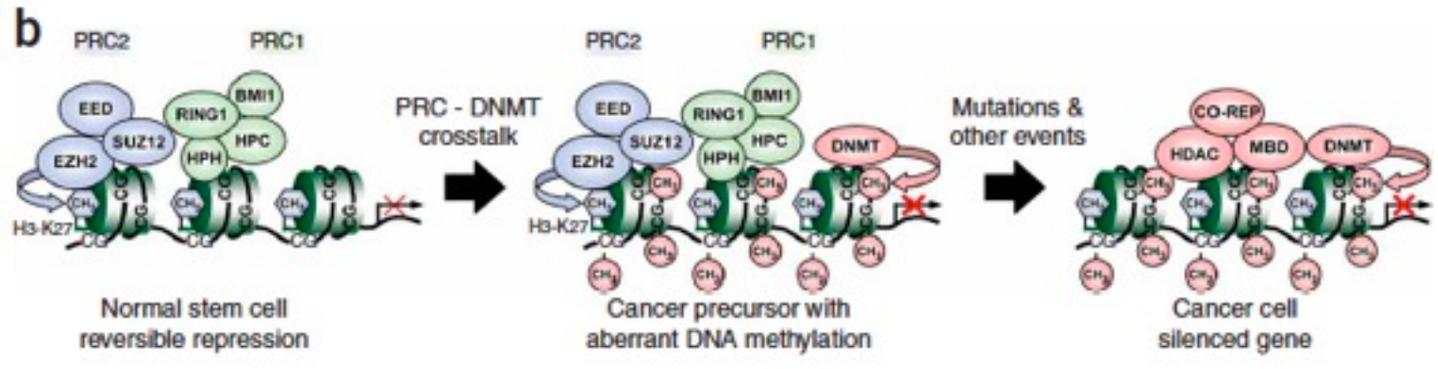
Where important:

Understanding of natural cell differentiation circuits

Differentiation of progenitors in immune systems (Graf 2008)

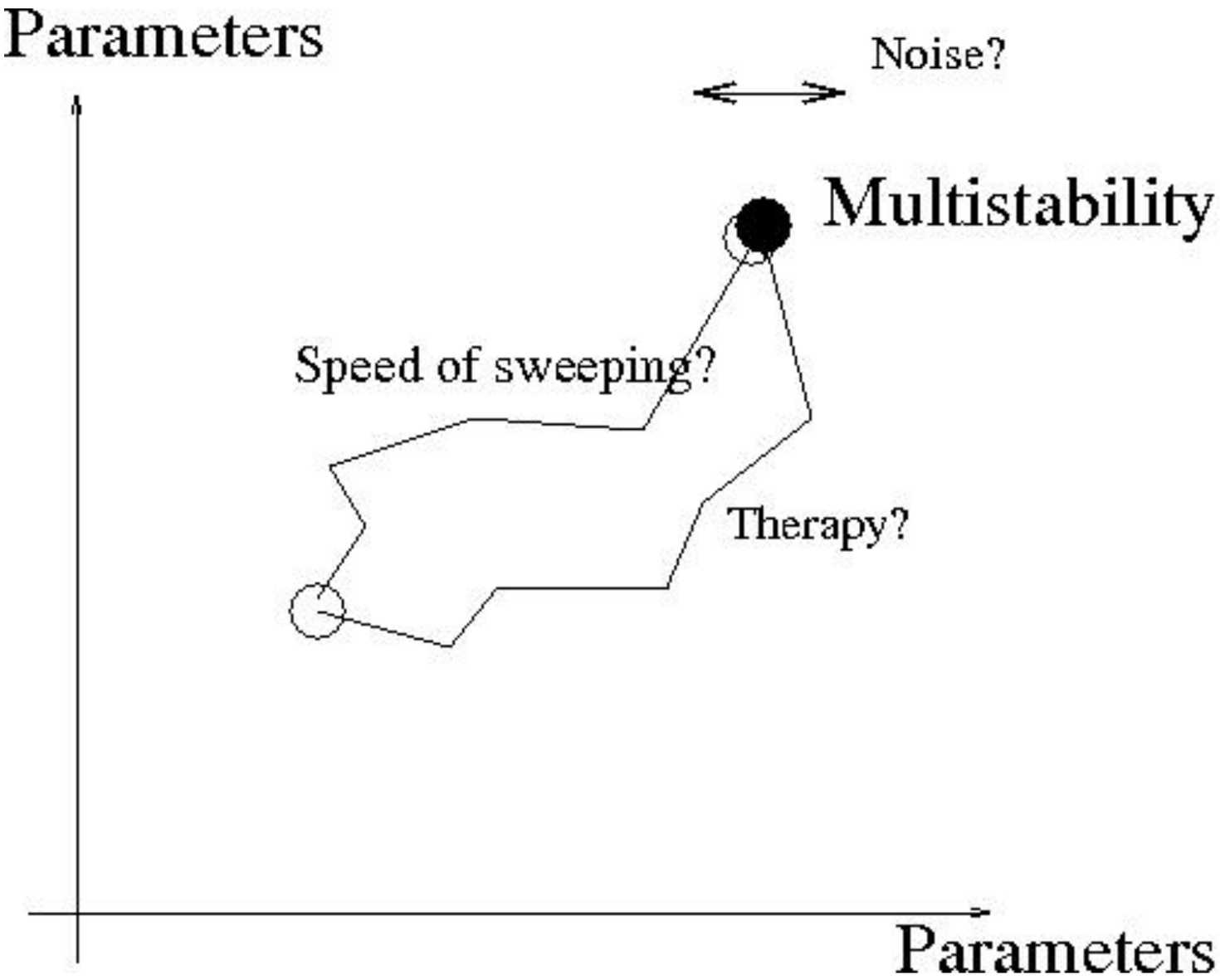


- DNA Methylation signature is different in cancer in networks responsible for stem cell differentiation



From M. Widschwendter et al, Nature Genetics (2006)

Design of therapies:



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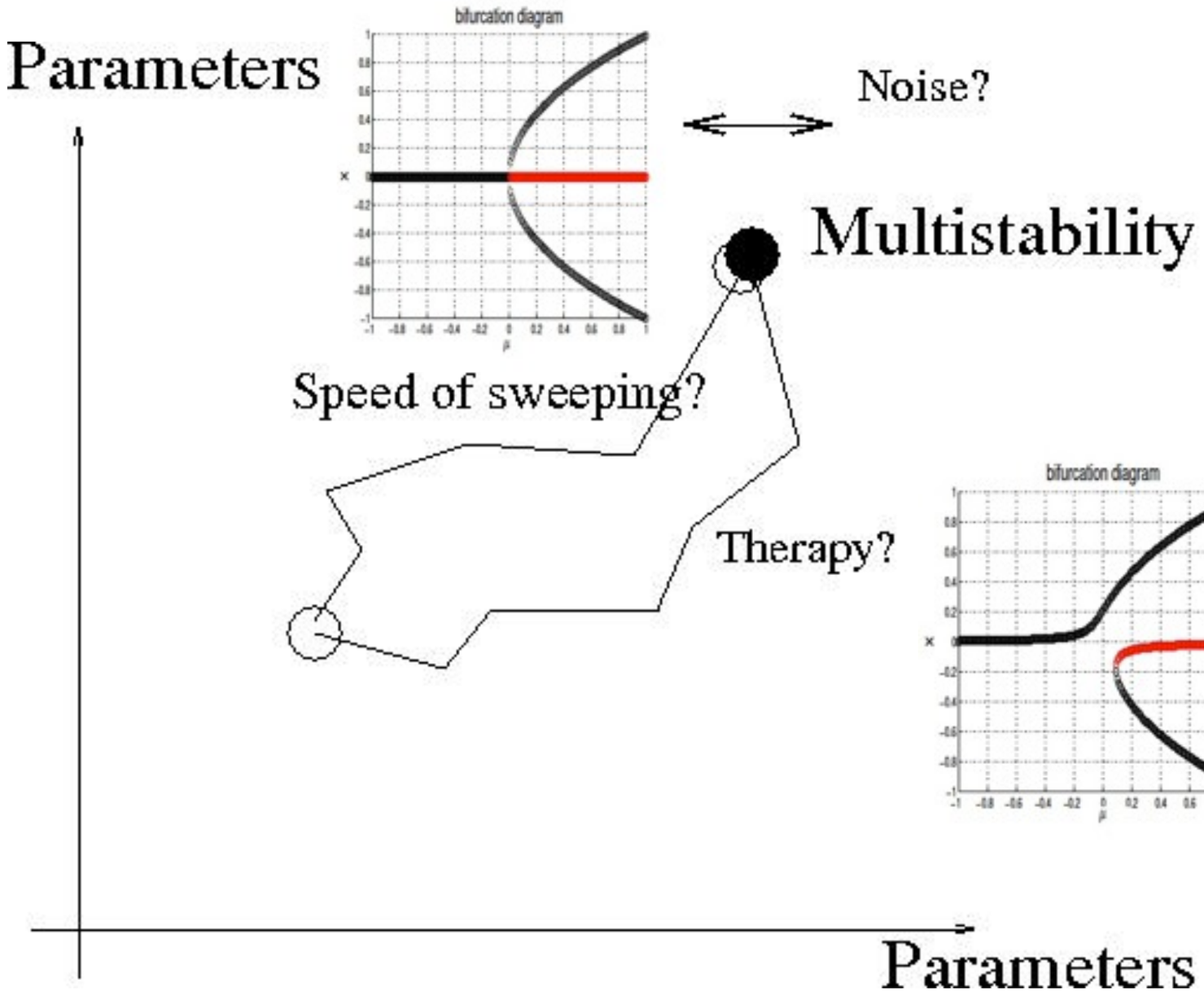
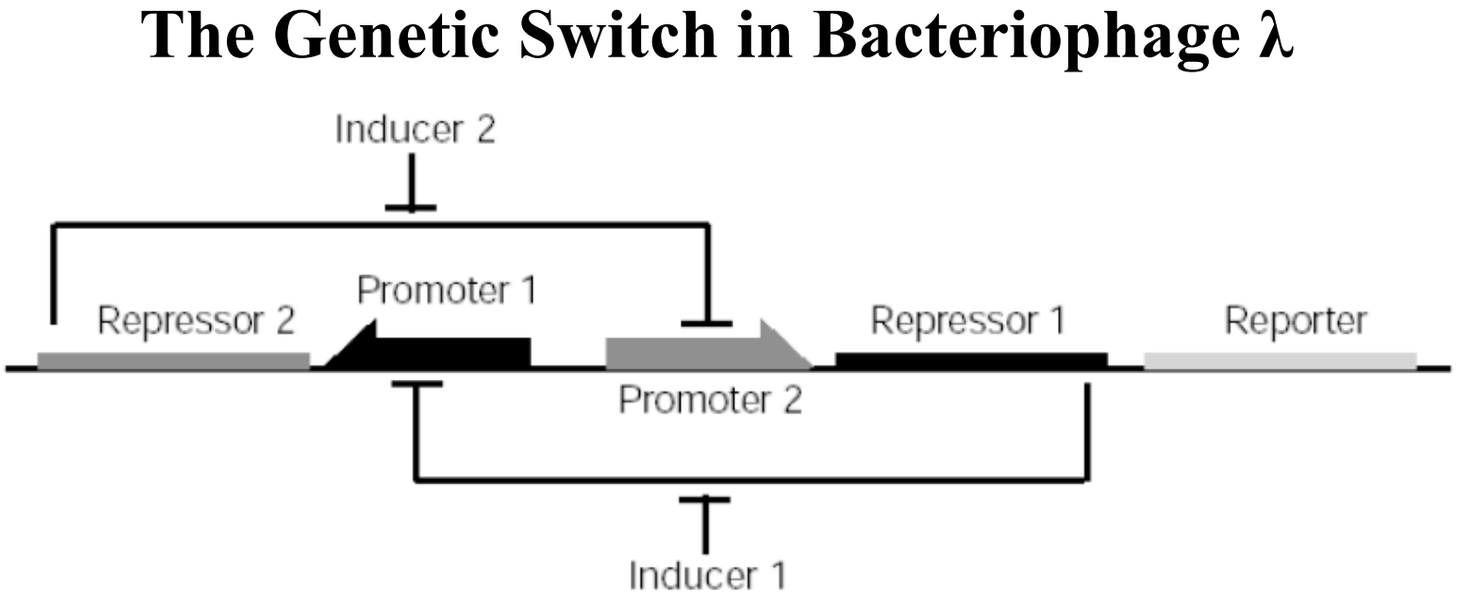
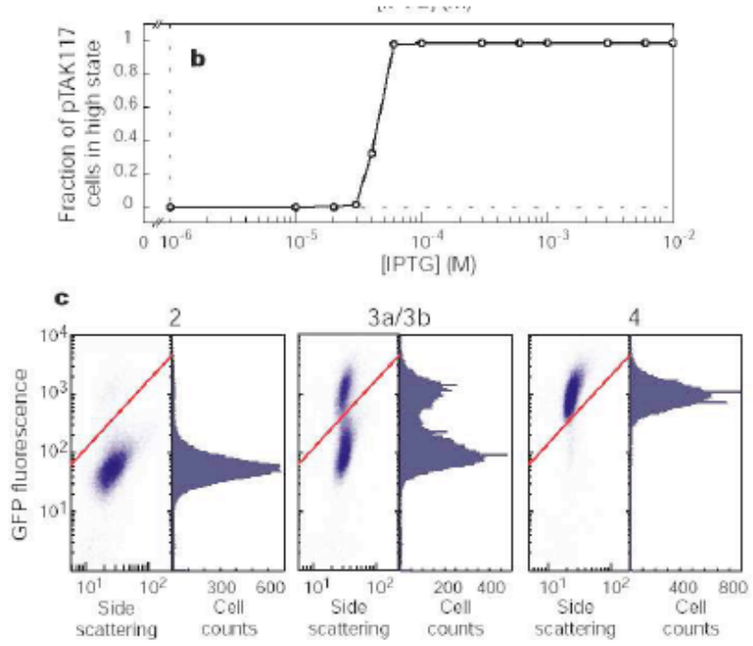


Let us consider paradigmatic genetic switch





T. Gardner, C. Cantor, J.J. Collins , "Construction of a genetic toggle switch in Escherechia coli", Nature, 2000.

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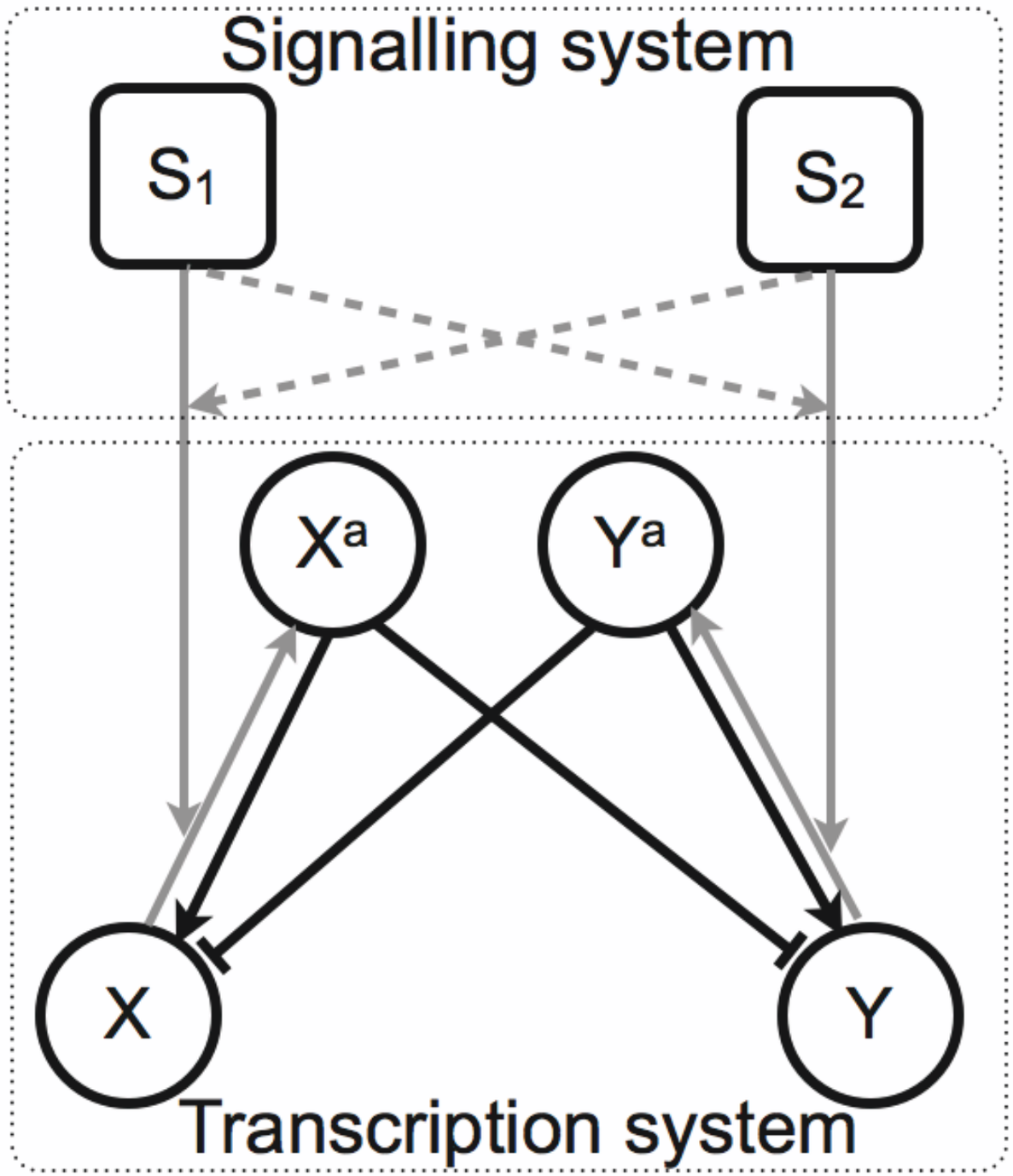
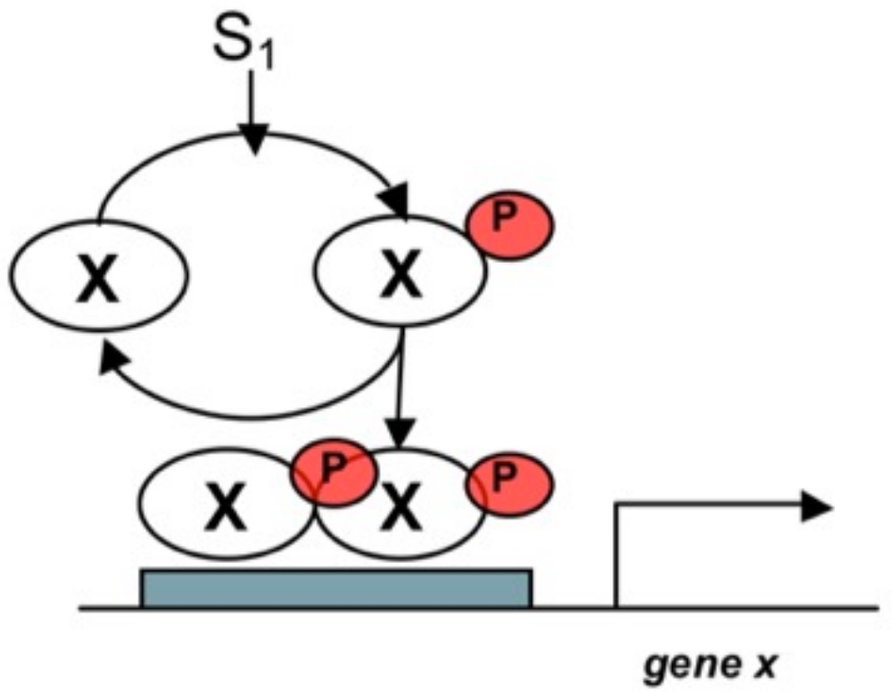
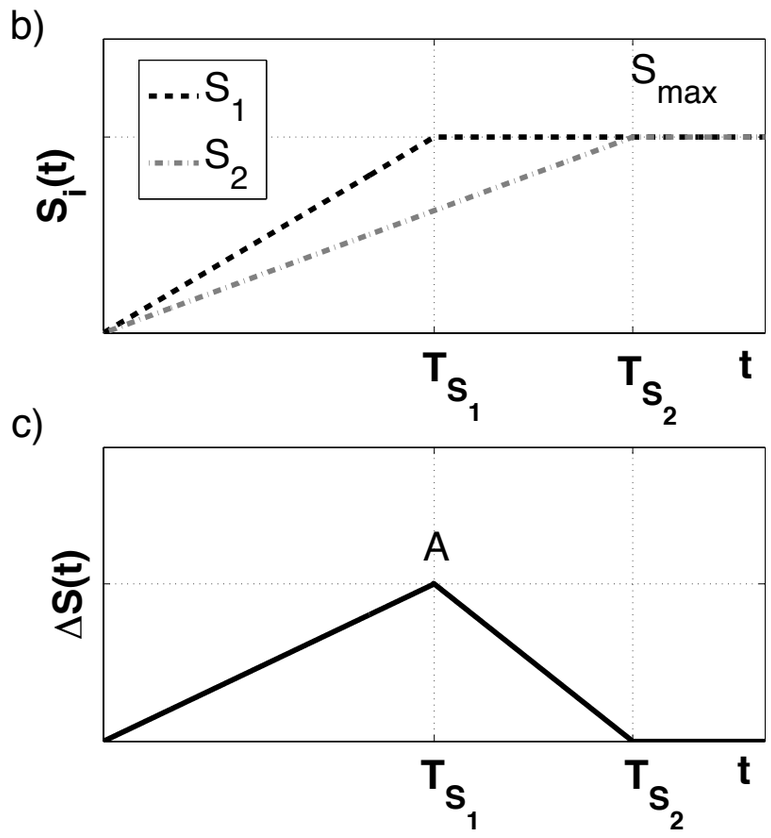






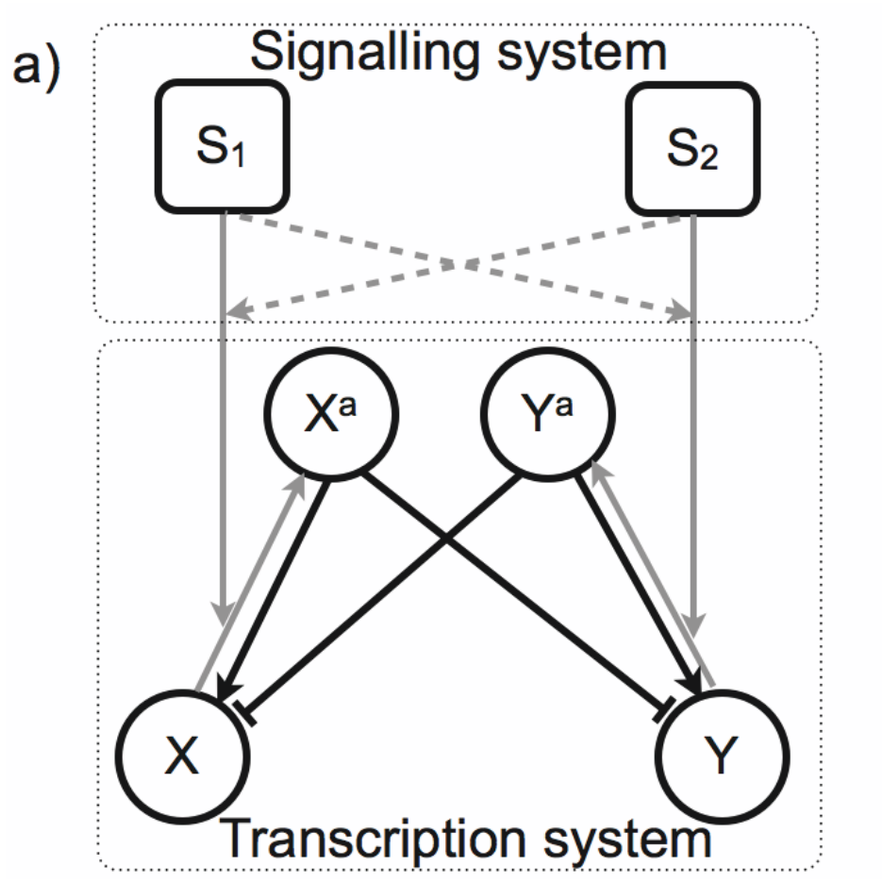
Mathematical model:

Activation or inhibition:

$$G(X^a, Y^a) = \eta_X \frac{1 + c_X b_X X^{a2}}{1 + b_X X^{a2} + b_Y Y^{a2}}.$$

Phosporylation by external signals

$$F_X(S_1, S_2) = \alpha_X + k_{1,X} S_1 + k_{2,X} S_2$$



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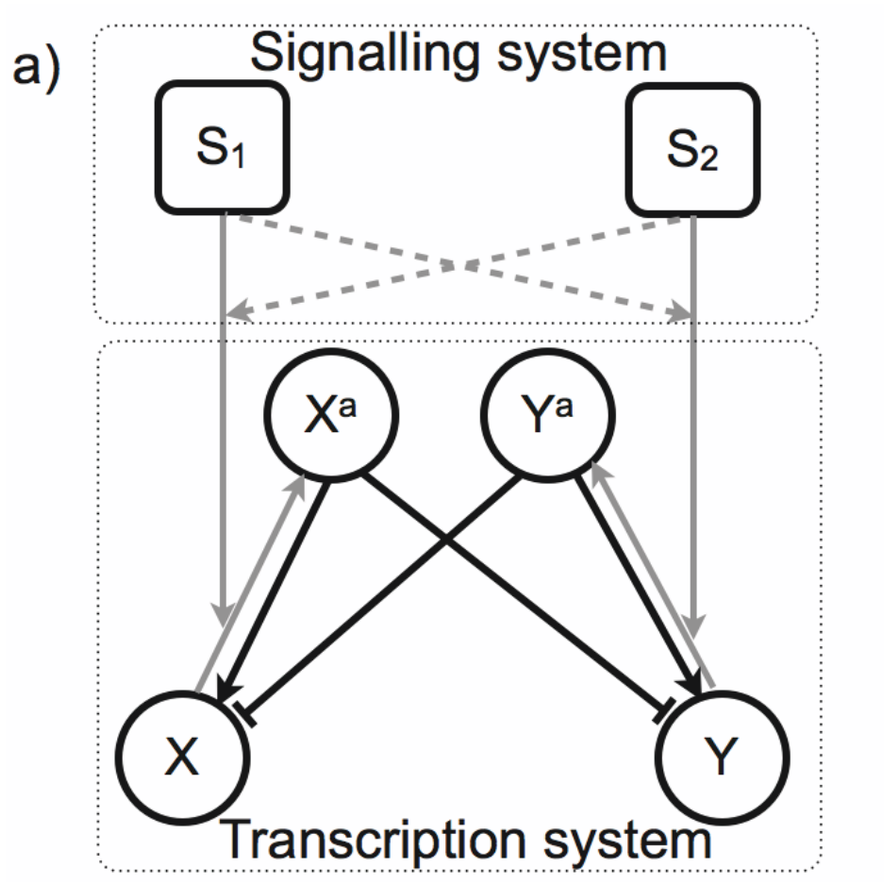

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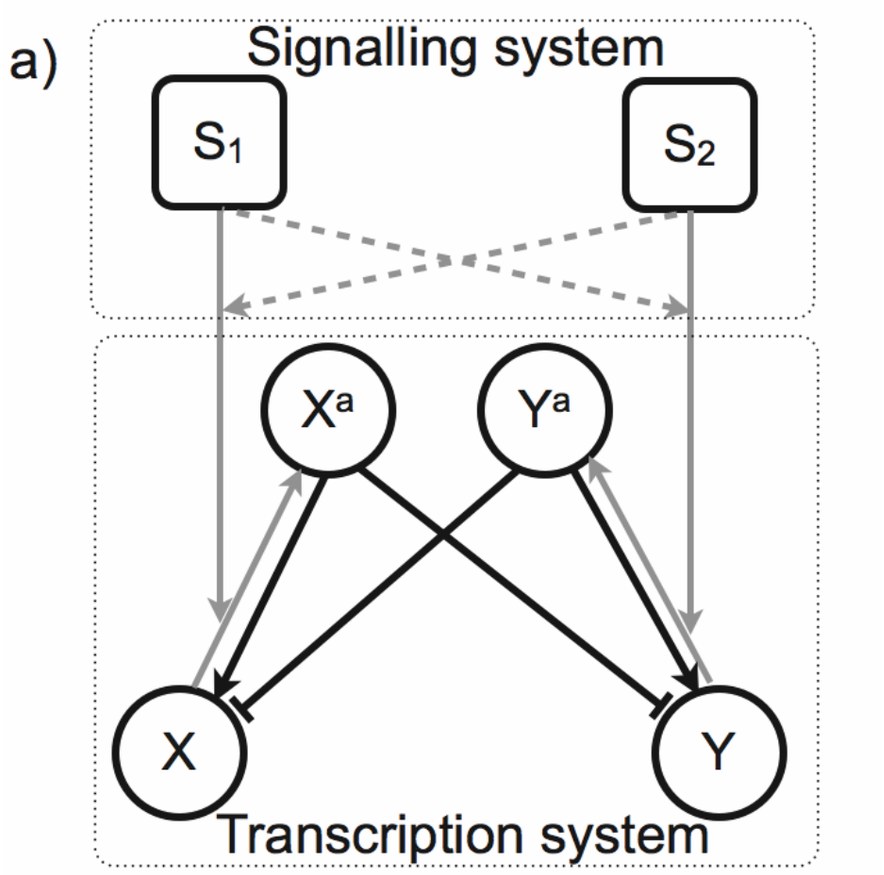

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Dephosporylation

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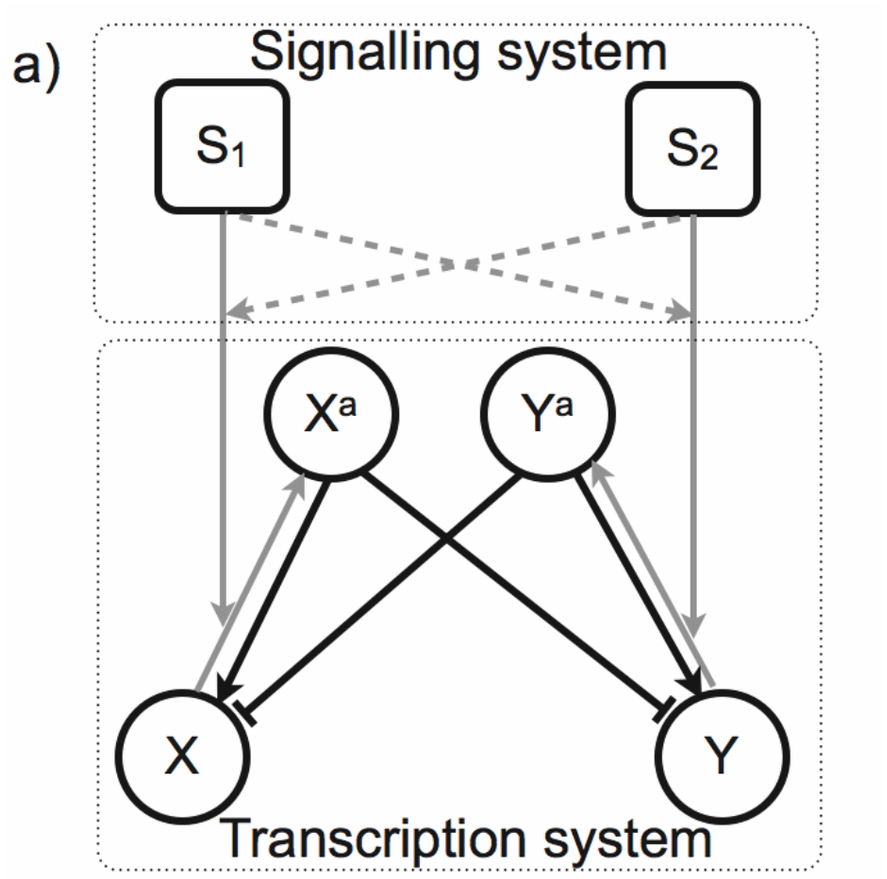
Mutual Inhibition:



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It's a noisy business!

Genetic regulation at the nanomolar scale

H.H. McAdams, A. Arkin 1999

SCIENCE VOL 297 16 AUGUST 2002

Stochastic Gene Expression in a Single Cell

Michael B. Elowitz,[1,2]* Arnold J. Levine,[1] Eric D. Siggia,[2] Peter S. Swain[2]

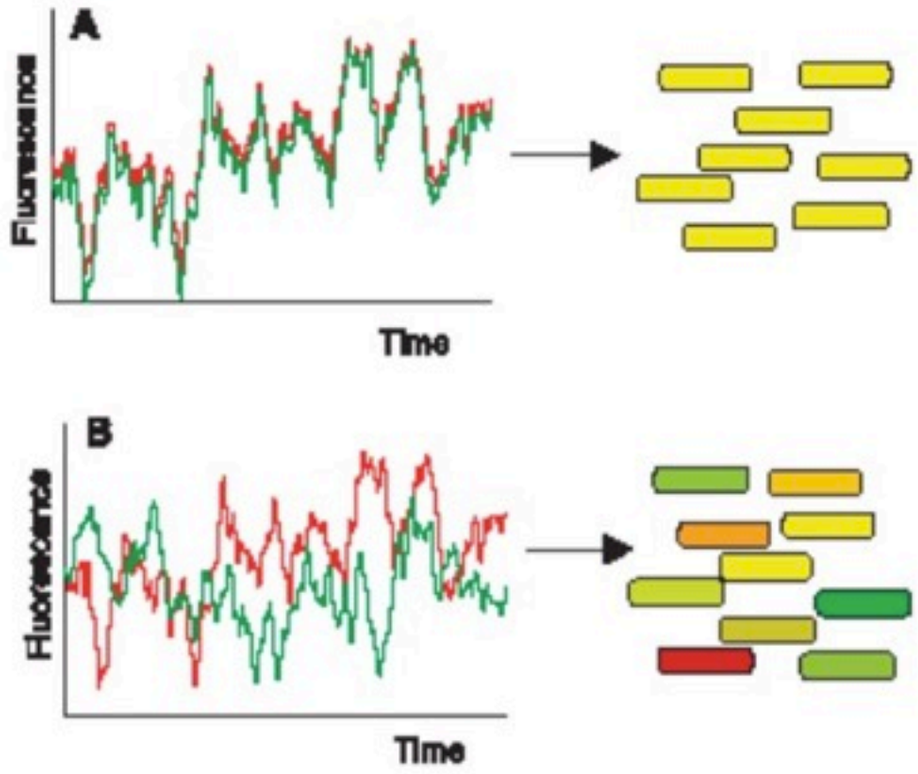

Fig. 1. Intrinsic and extrinsic noise can be measured and distinguished with two genes (*cfp*, shown in green; *yfp*, shown in red) controlled by identical regulatory sequences. Cells with the same amount of each protein appear yellow, whereas cells expressing more of one fluorescent protein than the other appear red or green. (A) In the absence of intrinsic noise, the two fluorescent proteins fluctuate in a correlated fashion over time in a single cell (left). Thus, in a population, each cell will have the same amount of both proteins, although that amount will differ from cell to cell because of extrinsic noise (right). (B) Expression of the two genes may become uncorrelated in individual cells because of intrinsic noise (left), giving rise to a population in which some cells express more of one fluorescent protein than the other.

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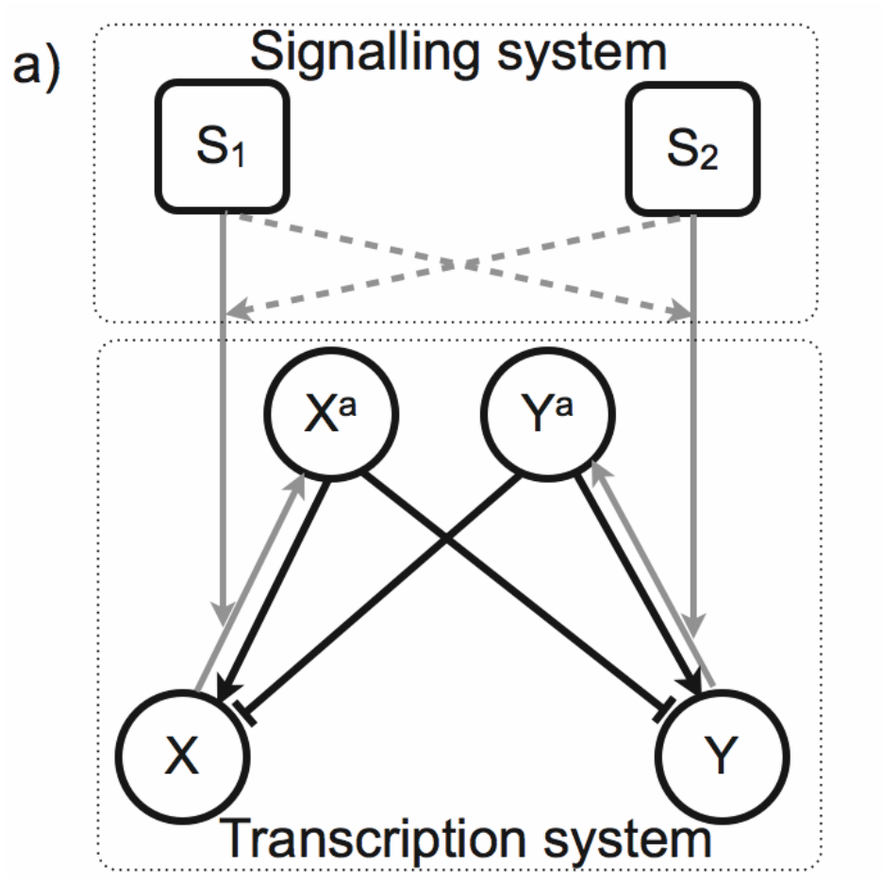

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Noise:

Mathematical model:

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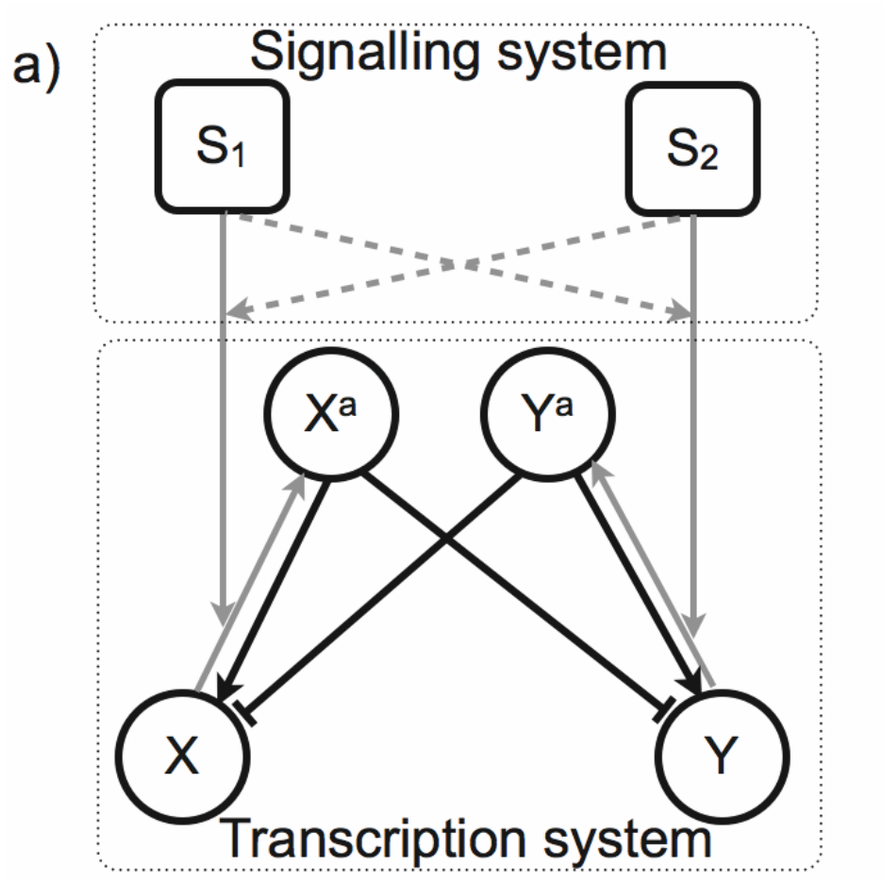

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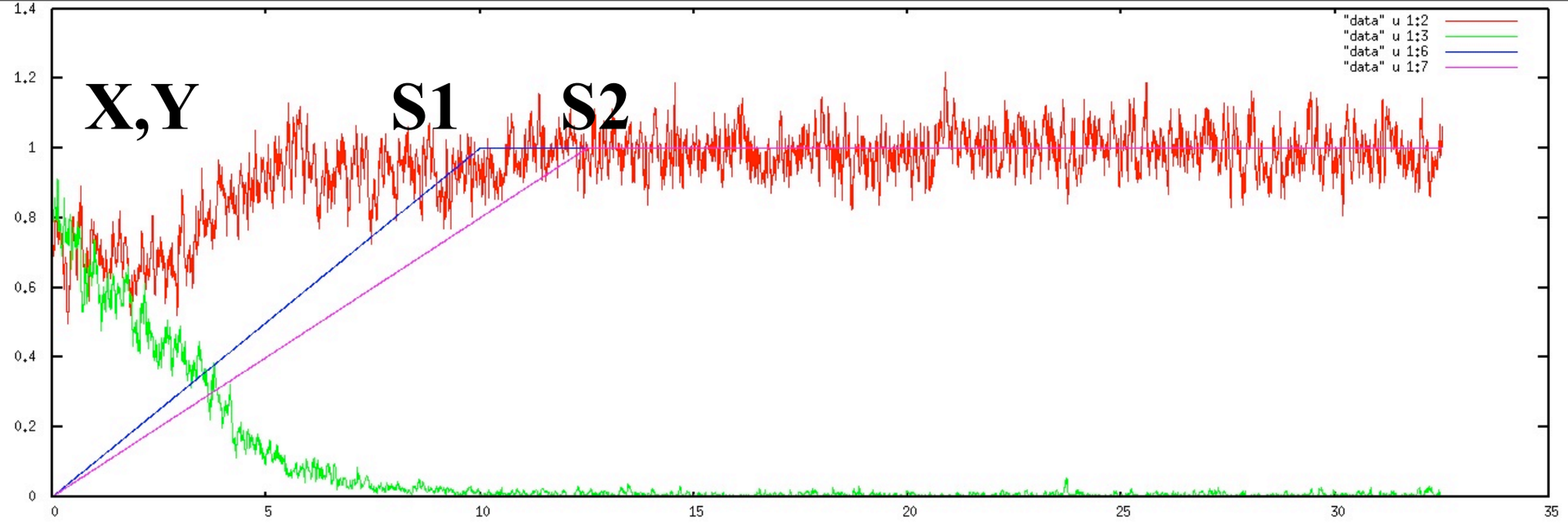
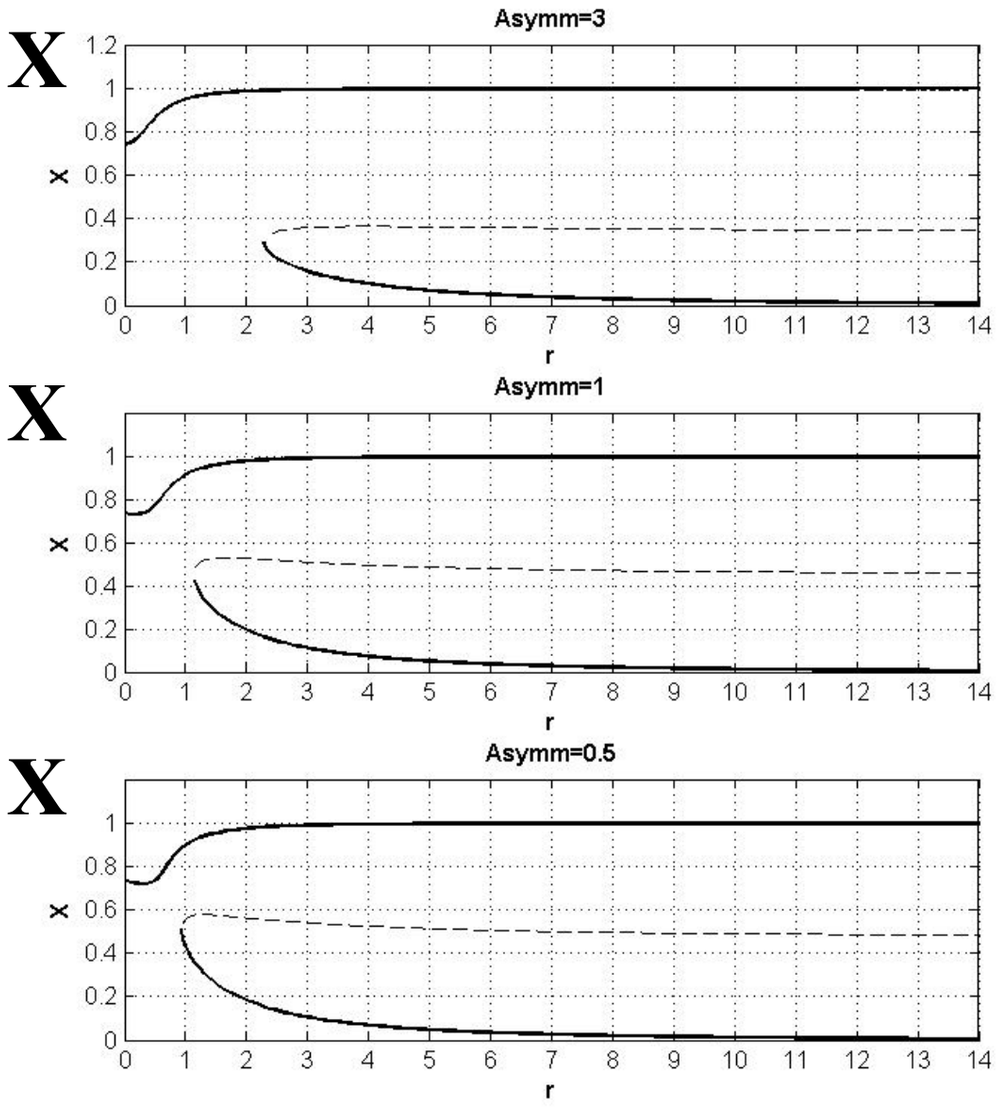
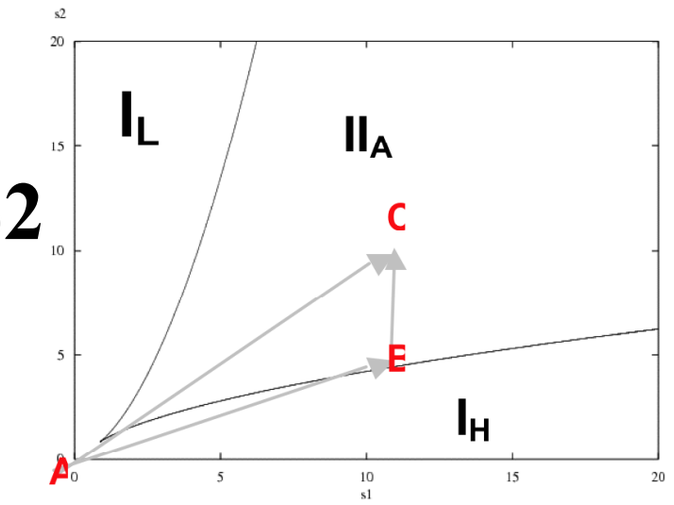
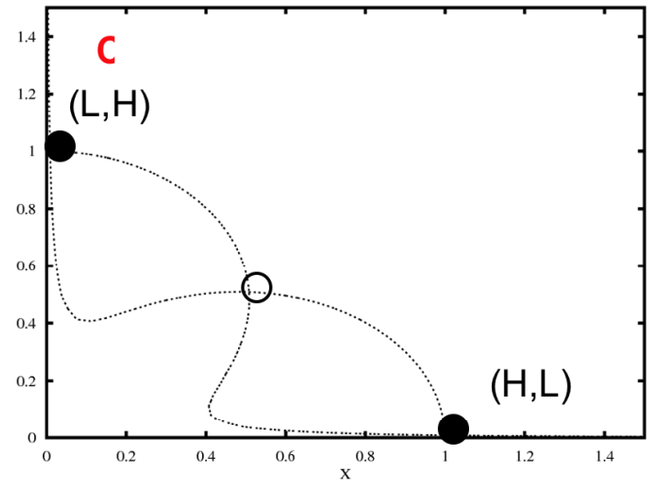
Noise:

Degradation

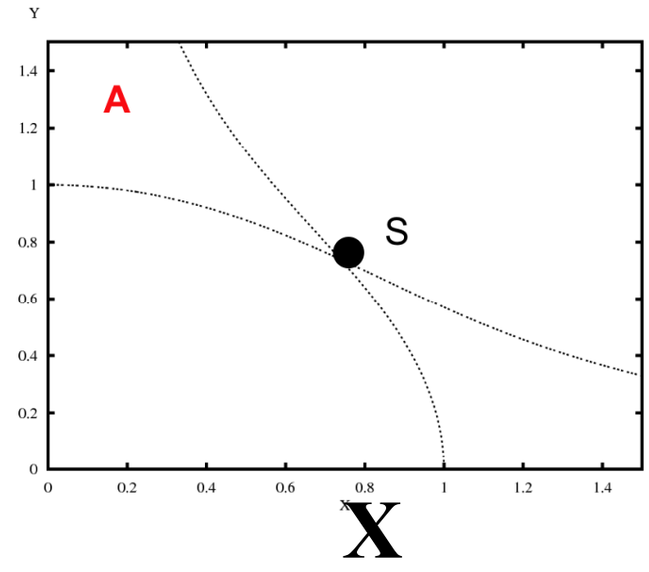

X,Y
S1
S2
"data" u 1:2
"data" u 1:3
"data" u 1:6
"data" u 1:7


X
Asymm=3
Asymm=1
Asymm=0.5
x
r

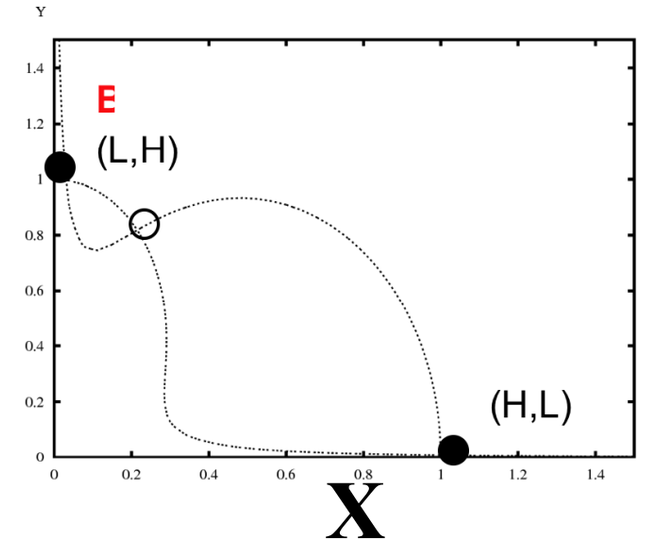

S2
I_L
II_A
C
E
I_H
A
s2
s1


C
(L,H)
(H,L)
Y
X

C


S1
A
S
X
Y

D


X
E
(L,H)
(H,L)
Y

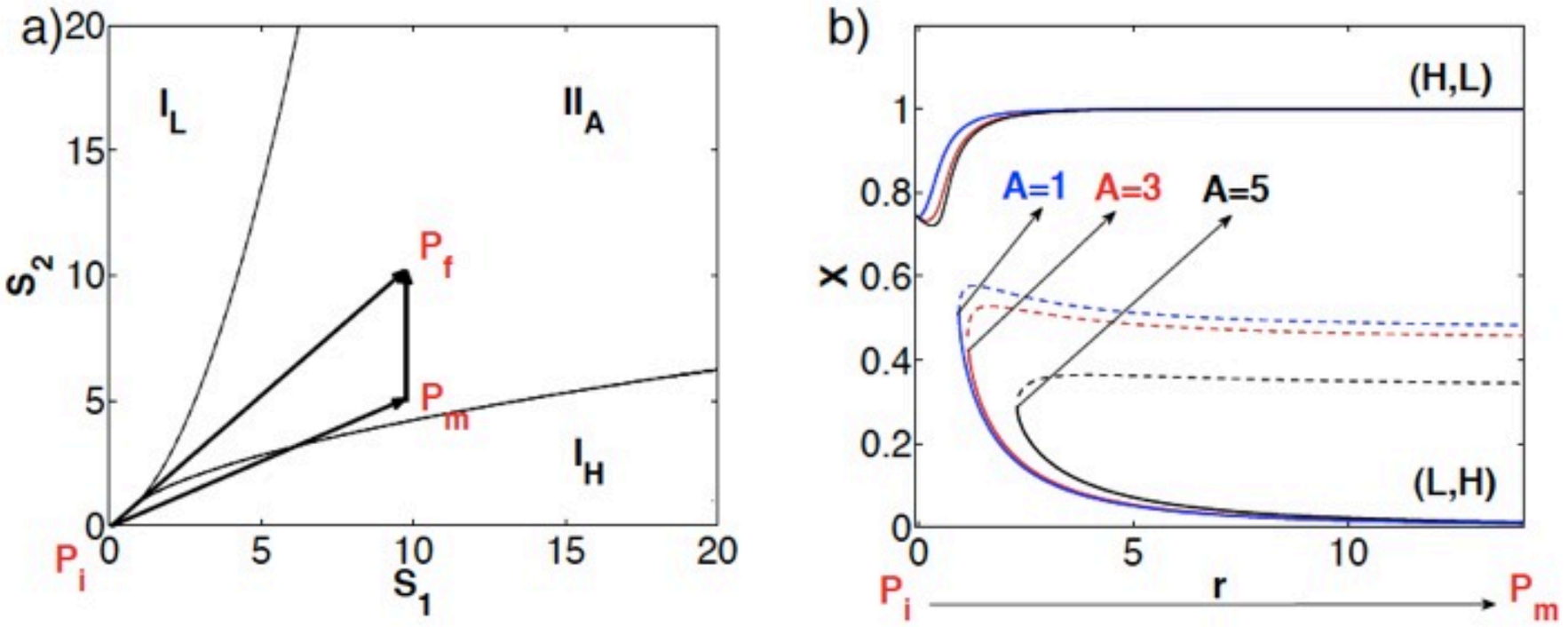


FIG. 2: Parameter analysis of the decision genetic switch with external stimulation. a) Phase diagram for X in space

So we have bifurcation, noise and asymmetry

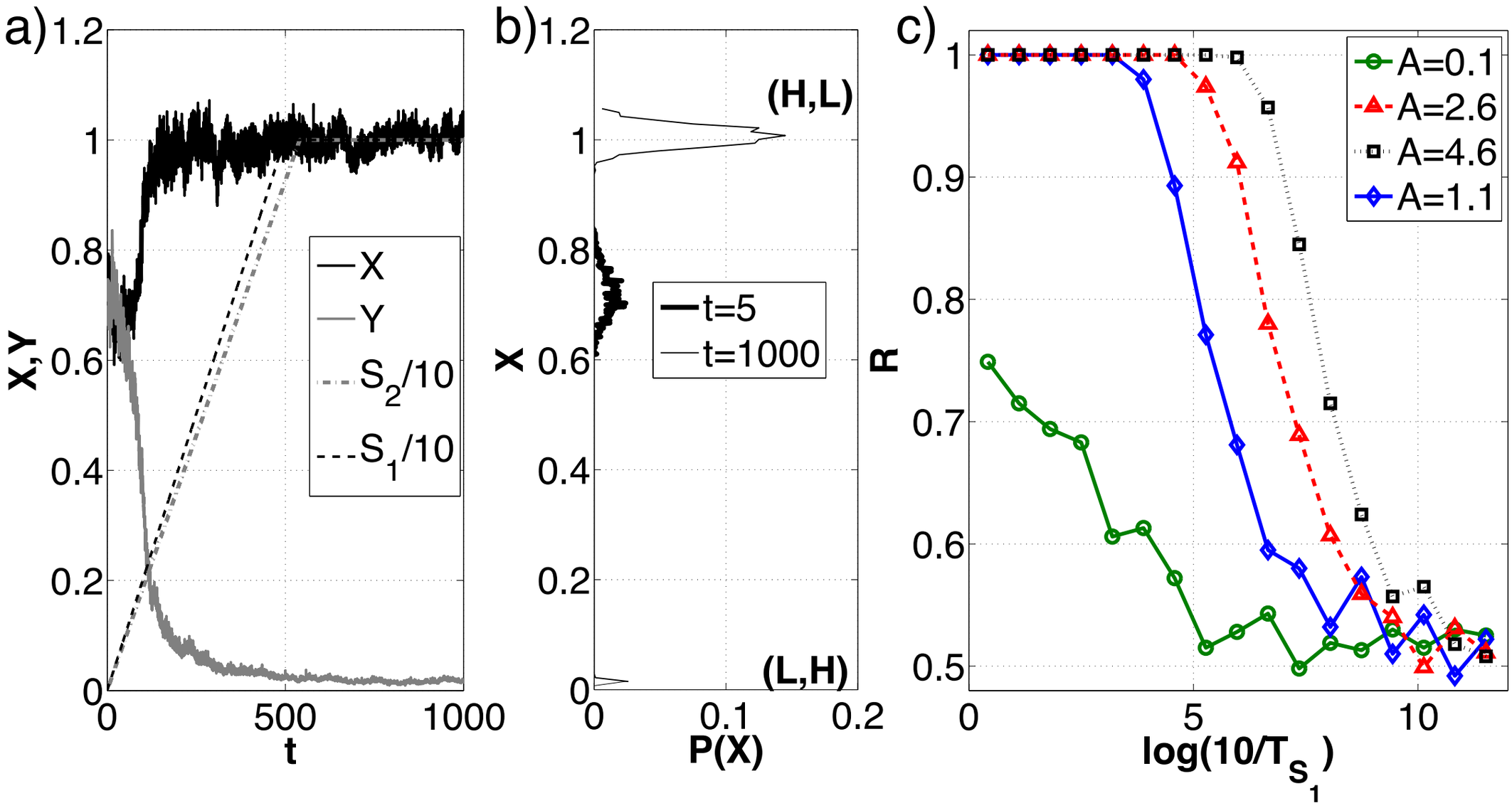
What is known from statistical physics?

Chiral Symmetry Breaking in Nonequilibrium Systems

D. K. Kondepudi and G. W. Nelson

Center for Studies in Statistical Mechanics, University of Texas at Austin, Austin, Texas 78712

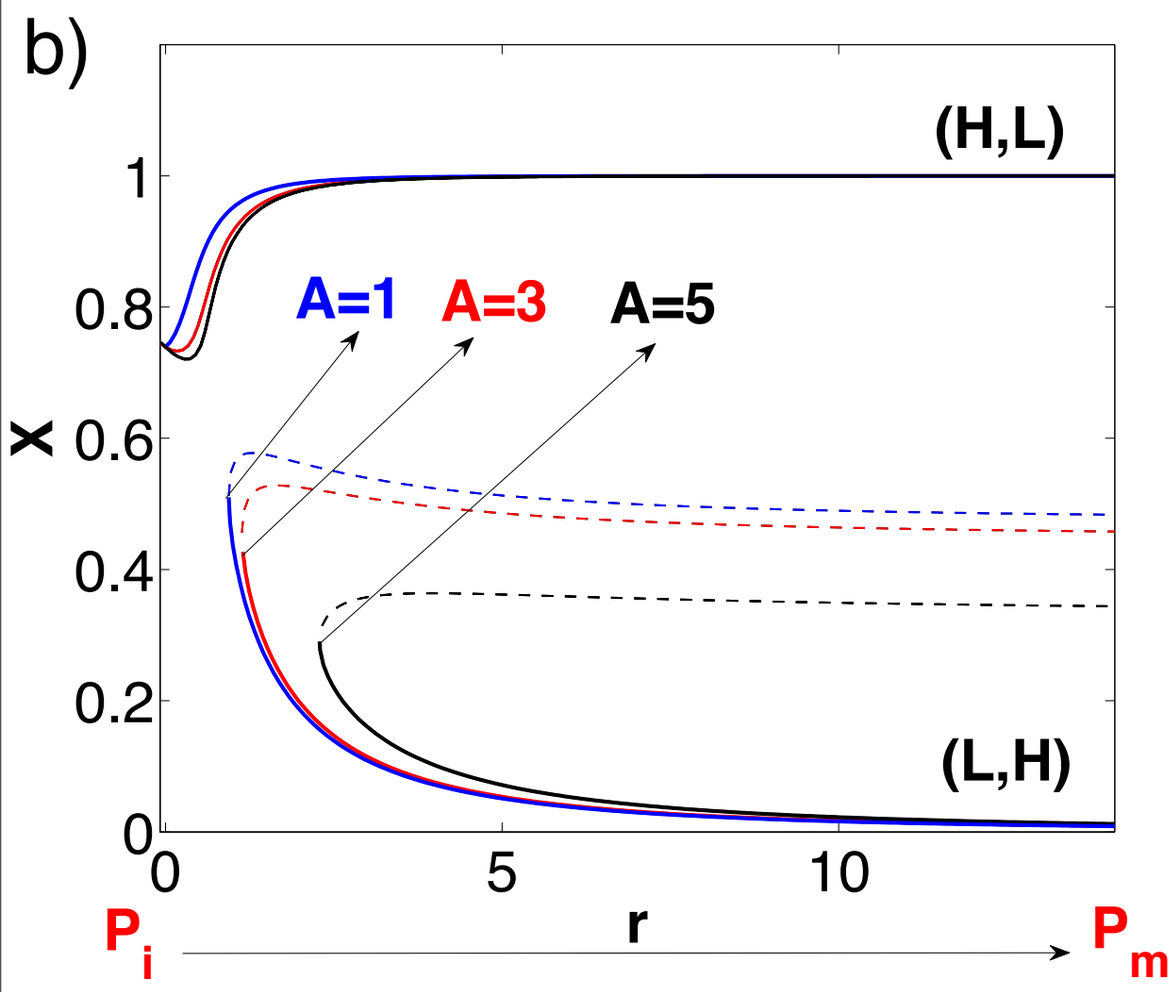
(Received 14 June 1982)

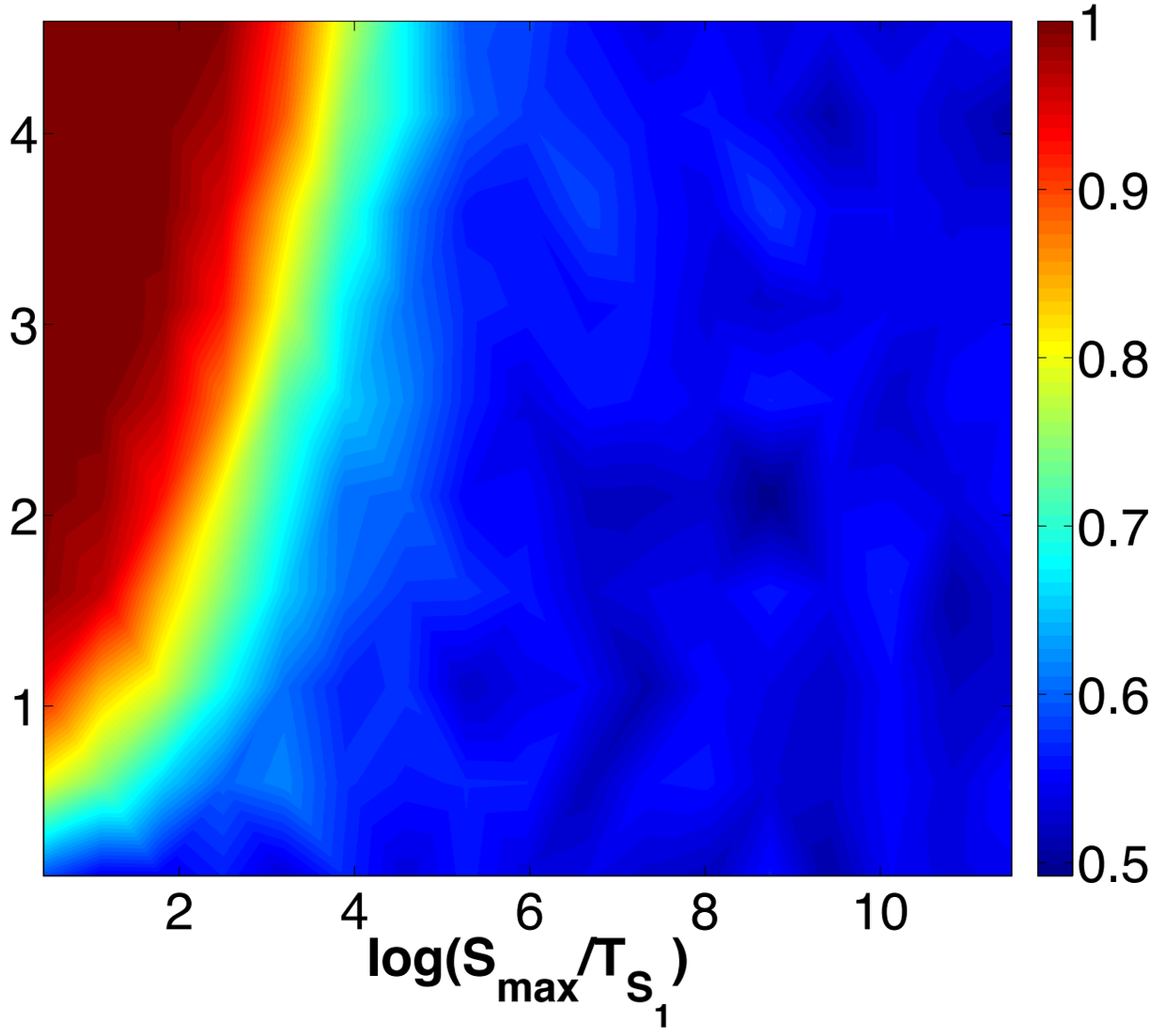


R is the ratio Ph/(Ph+Pl) where Ph is the probability to choose the upper branch, Pl - the lower one.

Speed- dependent Cellular decision making

Asymmetry Ratio



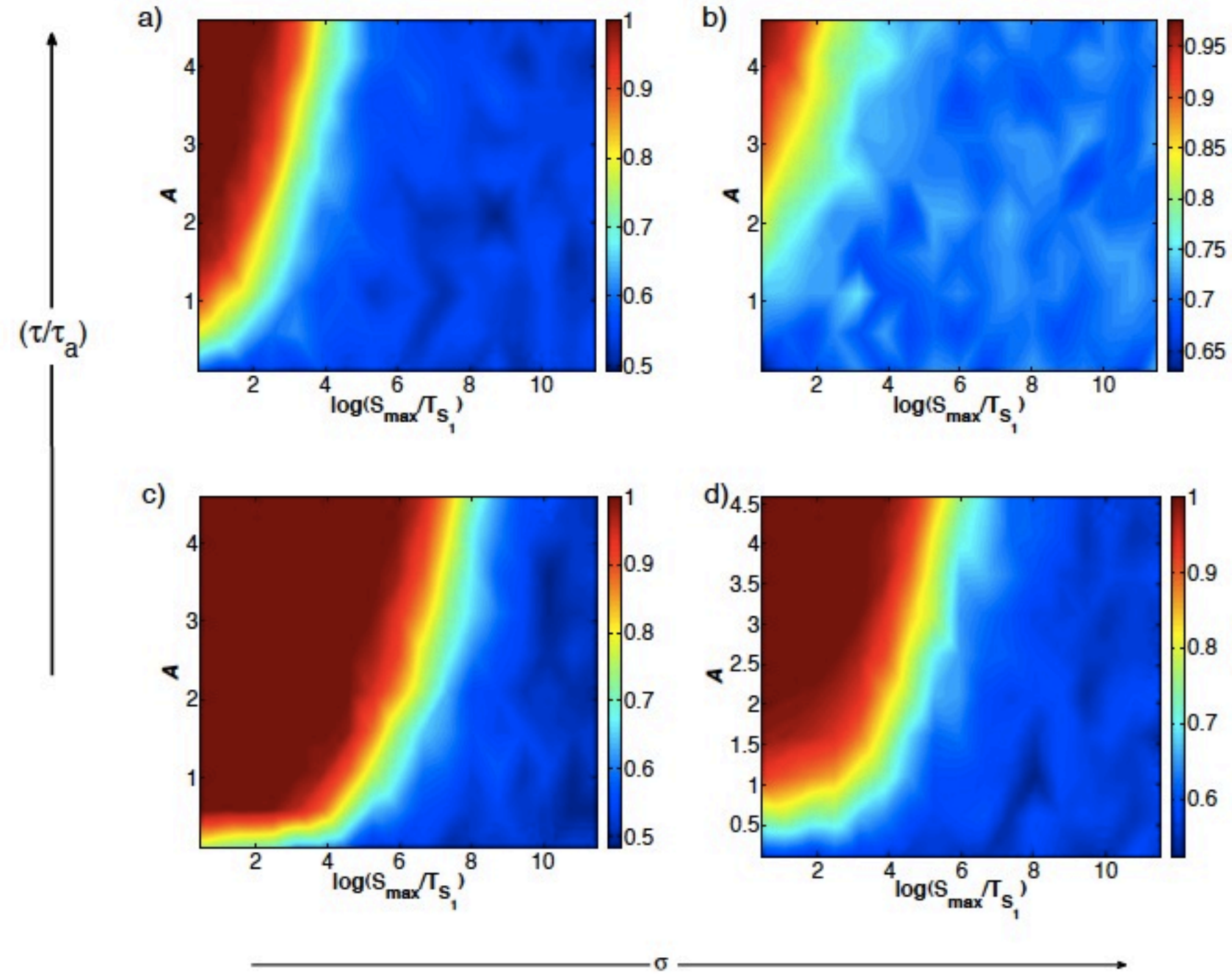


Speed

Speed- dependent Cellular decision making

Asymmetry

Ratio

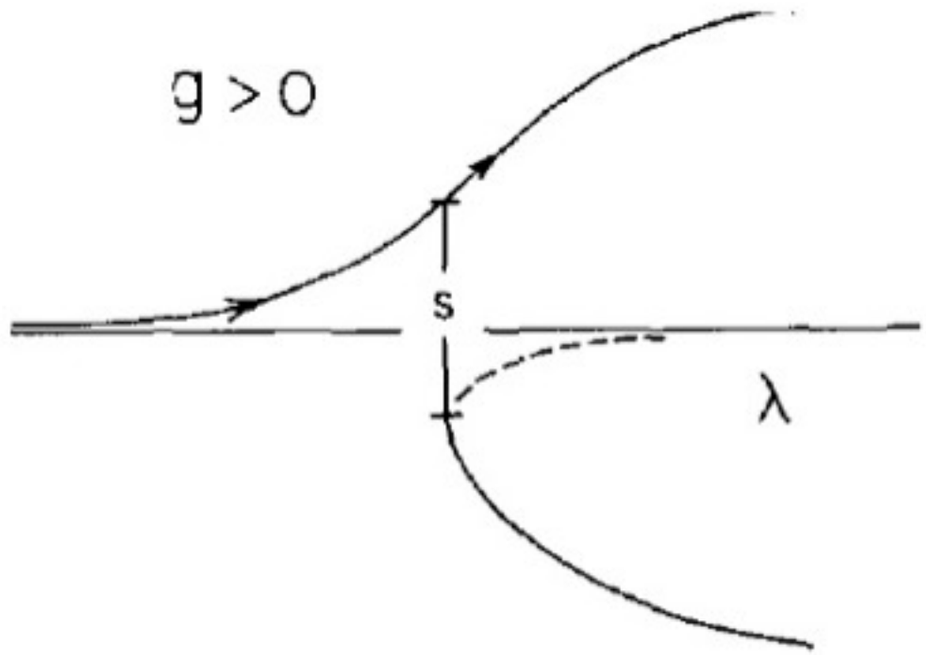


Speed

FIG. 4: Effect of timescale differences and noise on SdCDM.

In genetic decision networks:

- natural noise and asymmetry
- decision depends on the scenario, choosing the branch and speed of the decision making



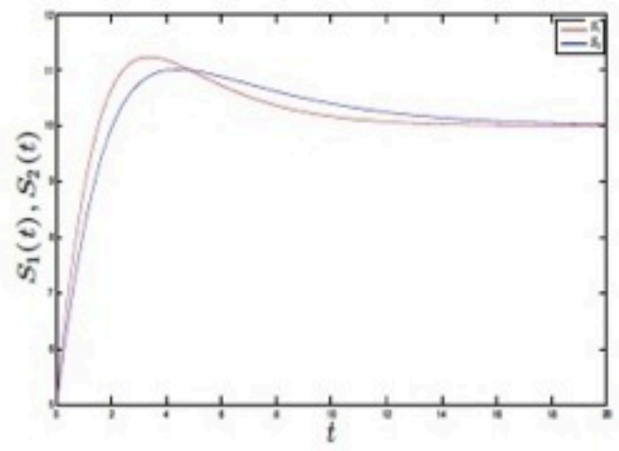
More realistic form of signals

- The signals take the following form

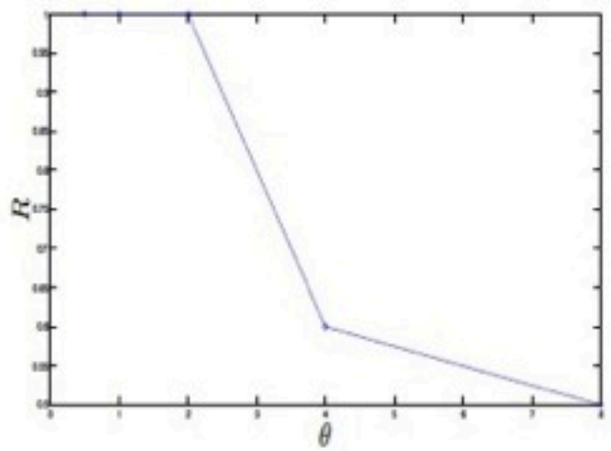
$$S_1(t) = \frac{a_1}{\theta_1^2} t e^{-\frac{t}{\theta_1}} + \frac{10}{1+e^{-t}} \tag{14}$$

$$S_2(t) = \frac{a_2}{\theta_2^2} t e^{-\frac{t}{\theta_2}} + \frac{10}{1+e^{-t}} \tag{15}$$

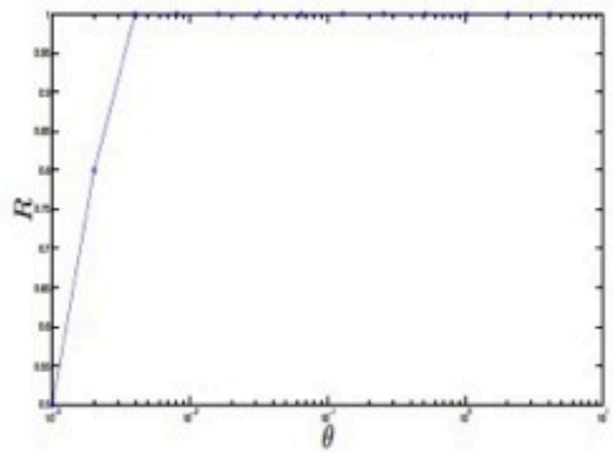
- θ is a parameter which determines the speed.
  - Increasing θ decreases the speed.



(k)



(l) θ_1=0.5-10



(m) θ_1=0.001-5

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Genomes & Developmental Control

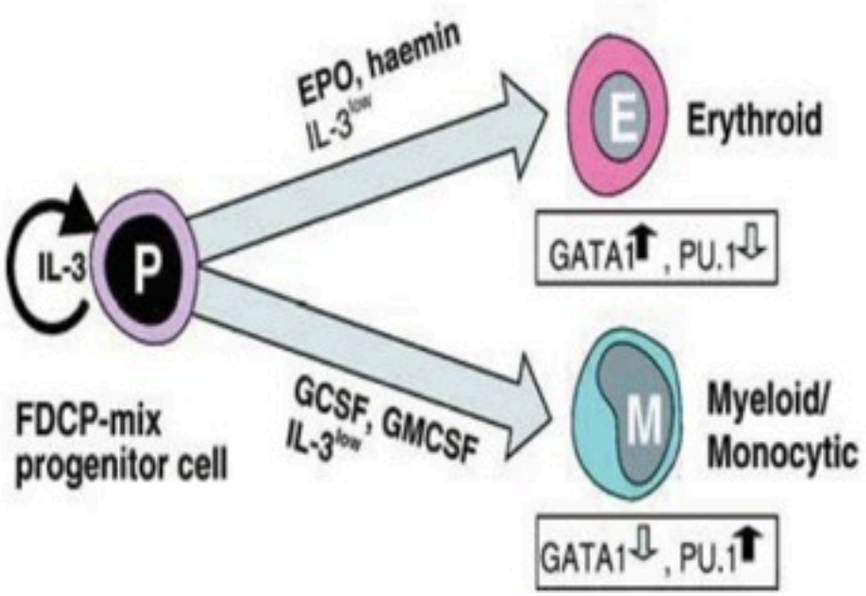
Bifurcation dynamics in lineage-commitment in bipotent progenitor cells

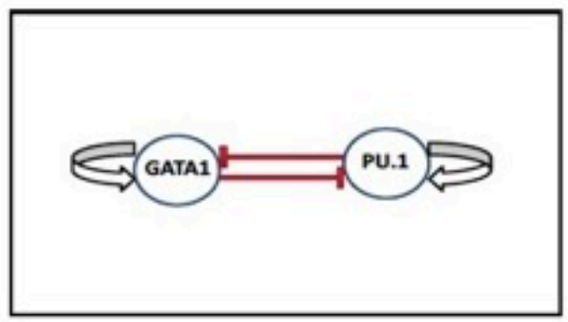
Sui Huang [a,*], Yan-Ping Guo [b], Gillian May [b], Tariq Enver [b]

The model of genetic switch has the following form

$$\frac{dX_1}{dt} = \frac{a_1 X_1^n}{r_{a_1}^n + X_1^n} + \frac{b_1 r_{b_1}^n}{r_{b_1}^n + X_2^n} - k_1 X_1 \qquad (16)$$

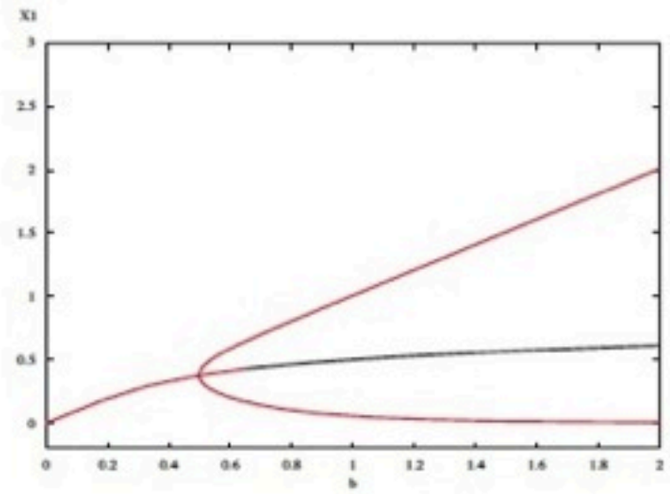
$$\frac{dX_2}{dt} = \frac{a_2 X_2^n}{r_{a_2}^n + X_2^n} + \frac{b_2 r_{b_2}^n}{r_{b_2}^n + X_1^n} - k_2 X_2 \qquad (17)$$



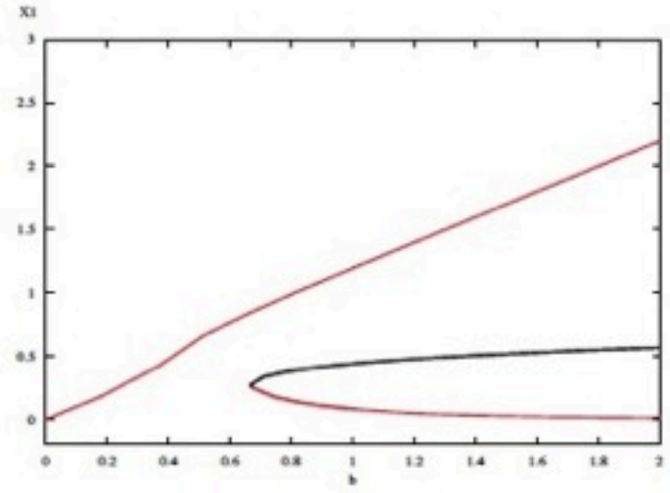


- Supercritical pitchfork bifurcation

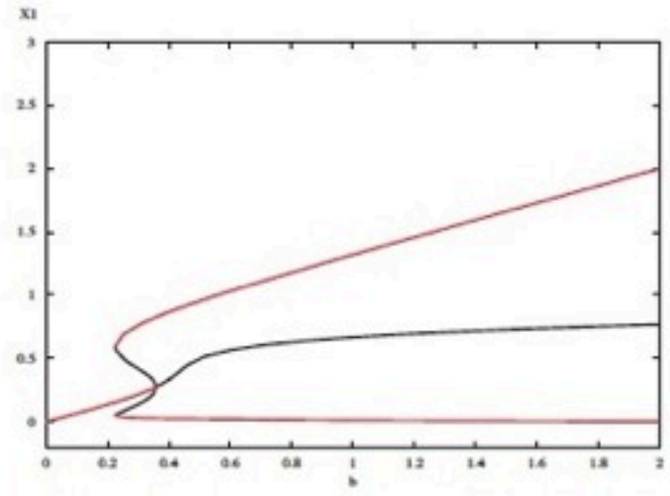
Symmetric case

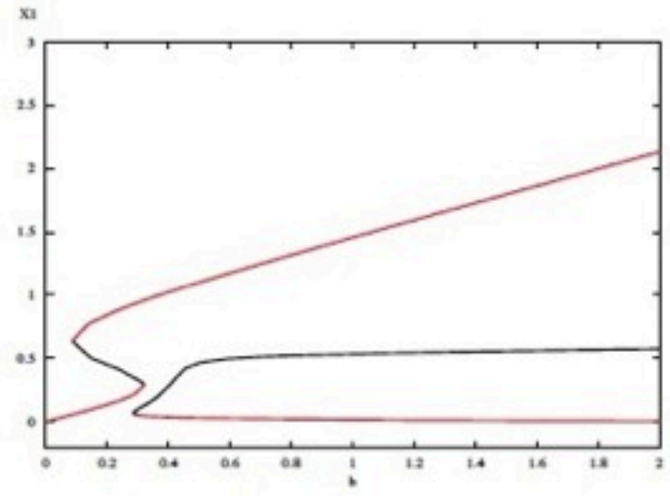


Asymmetric case



- Subcritical pitchfork bifurcation

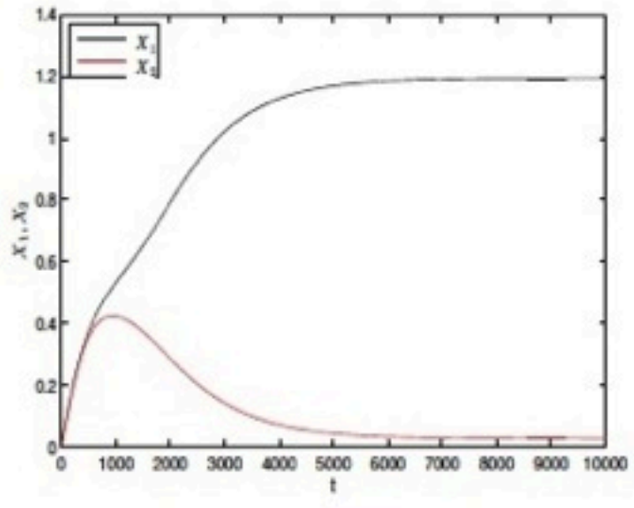




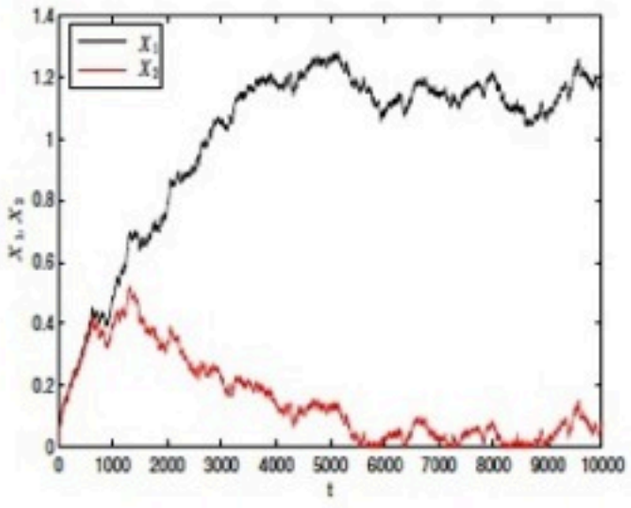
- To study the effect of noise, we put the equations in Langevin form.
- To study the effect of speed, we compute the ratio R.

$$\frac{dX_1}{dt} = \frac{a_1 X_1^n}{r_{a_1}^n + X_1^n} + \frac{b_1 r_{b_1}^n}{r_{b_1}^n + X_2^n} - k_1 X_1 + \sigma_1 \xi_1 \tag{18}$$

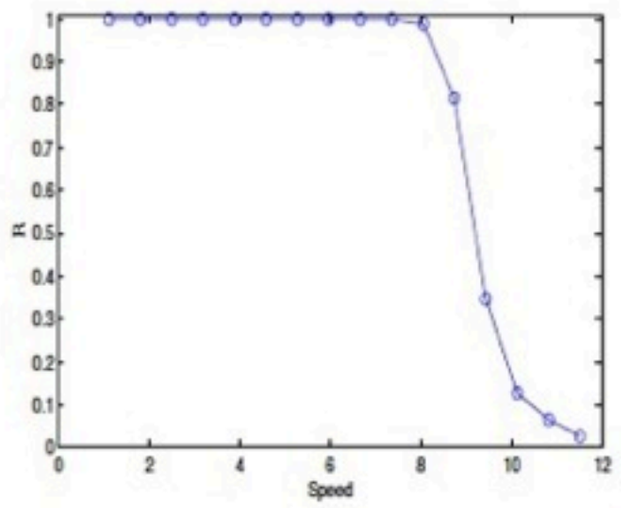
$$\frac{dX_2}{dt} = \frac{a_2 X_2^n}{r_{a_2}^n + X_2^n} + \frac{b_2 r_{b_2}^n}{r_{b_2}^n + X_1^n} - k_2 X_2 + \sigma_2 \xi_2 \tag{19}$$



(p)



(q) $\sigma^2 = 0.01$



(r)

Further research: multidimensional genetic switch

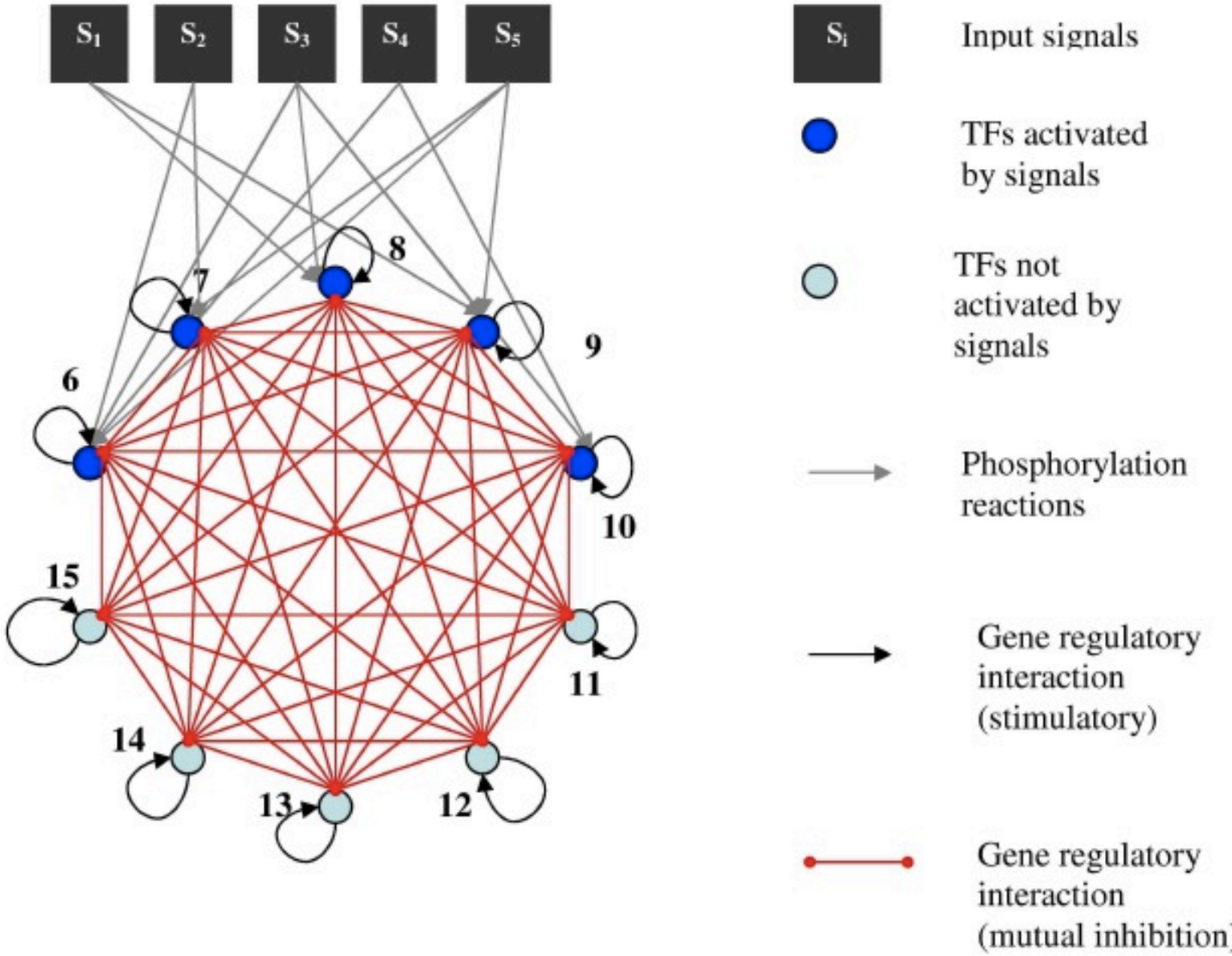


Figure 2. Representation of a highdimensional genetic decision switch with 10 transcription factors (nodes 6 to 15) and 5 input signals. Only nodes 6 to 10 need to be activated (phosphorylated) to act on any promoter region of the rest of the transcription factors in the network. Each transcription factor reinforces its own expression and represses all other nodes.

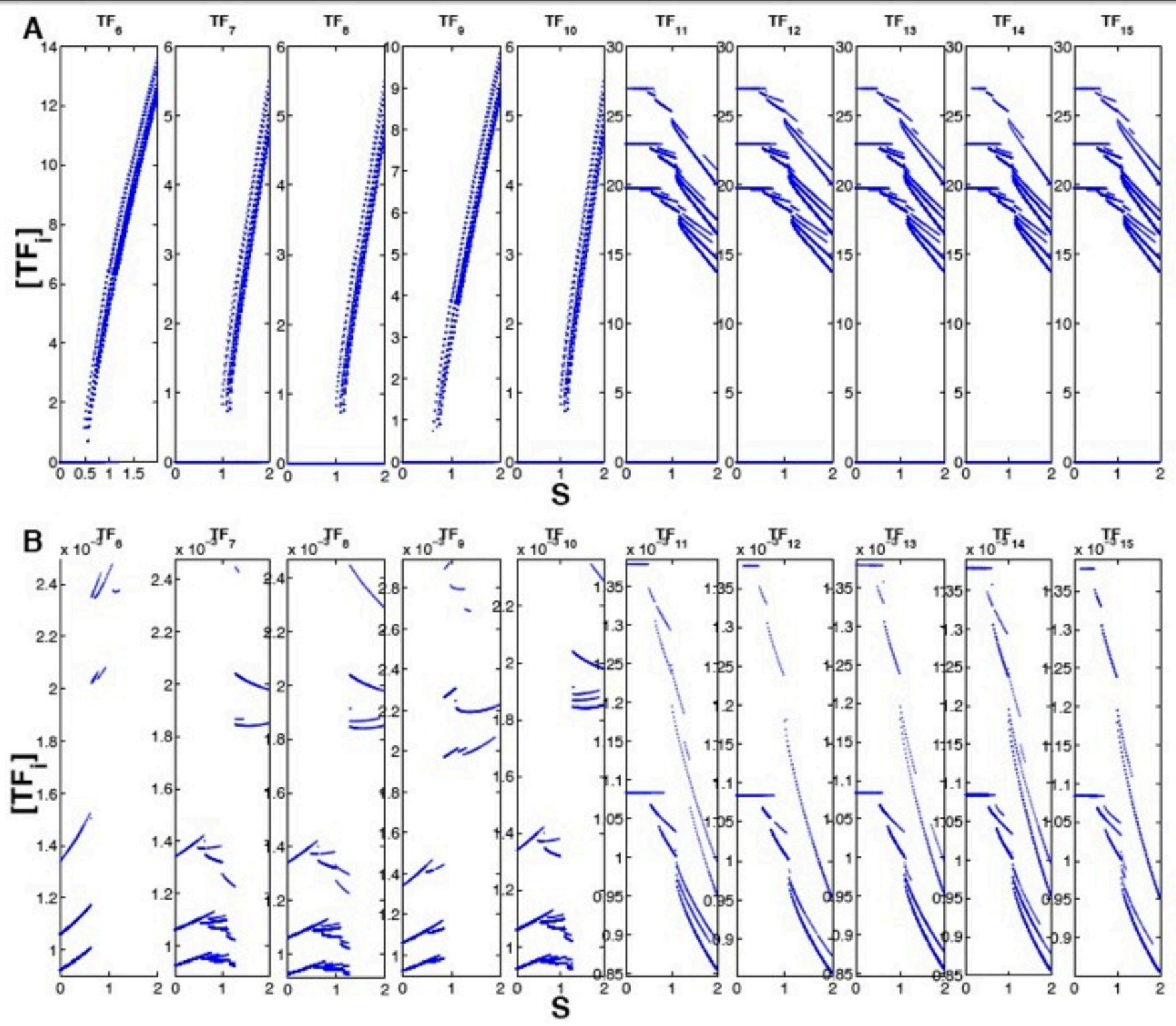


Figure 3. Bifurcation diagram for each of the transcription factors for $S = S_1 = S_2 = S_3 = S_4 = S_5$**.** (A) Complete bifurcation diagram. (B) Amplification of lower part of the bifurcation diagram represented in A. Parameters: $M = 2$, $\eta = 0.1$, $c_i^i = 20$, $k_i^i = 1$ (self-activation) and $k_j^i = 10$ (cross-repression), $\alpha = 0$, $d = 0.3$, $\tau^T/\tau^S = 1$, for $i, j = 6, ..., 15$ (see Methods). S is the horizontal axis for all the figures, from TF_6 to TF_{15}. In the construction of the bifurcation diagrams 100 initial consitions were randomly selected for each S and the long term trajectories recorded and plotted.

Correlation between matrices: C=0.12

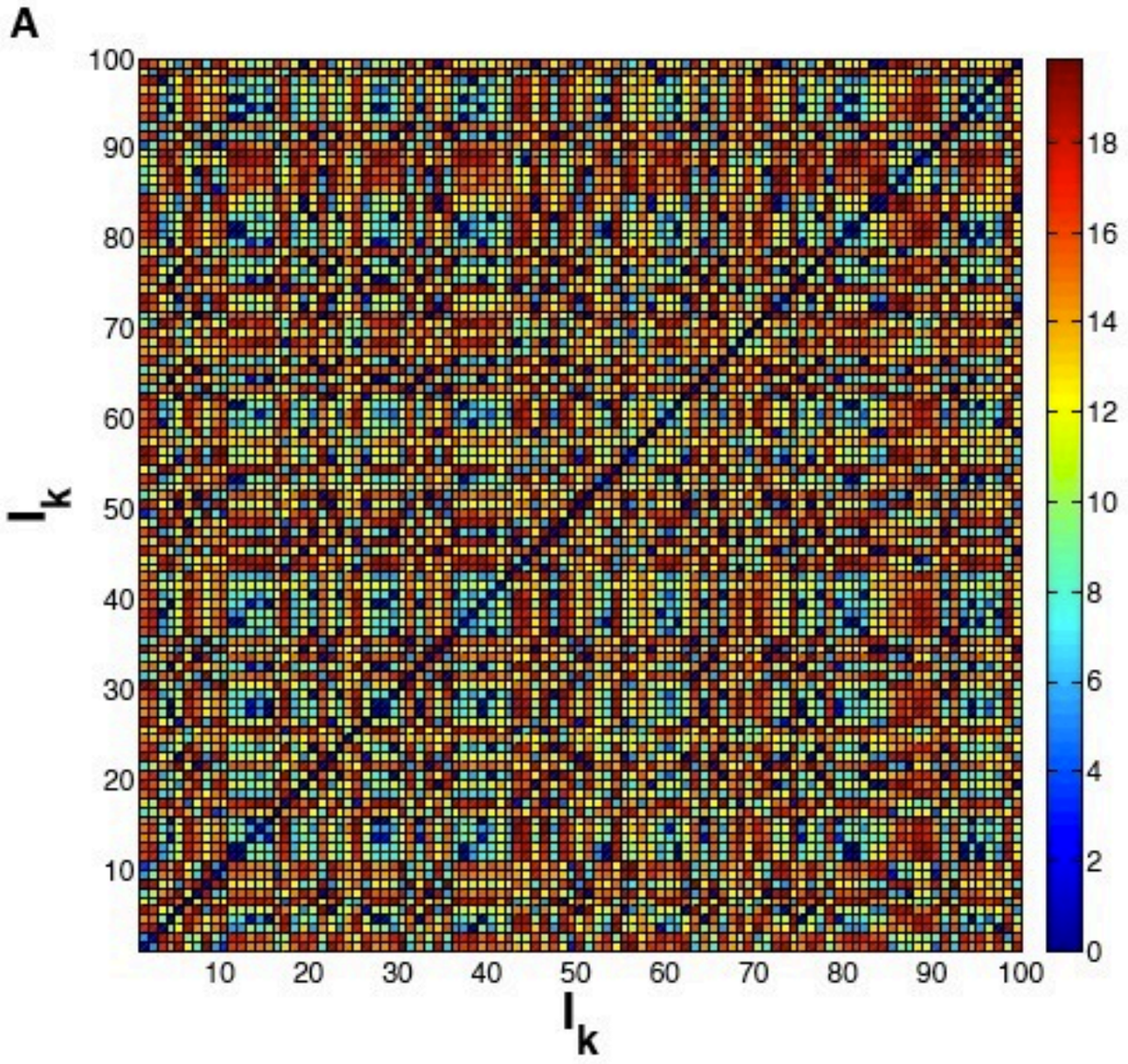


Figure 4. Pair-wise average distance over 100 runs (each corresponding to a different initial condition) between asymptotically stable states induced by input combinations. (A) Results for time-scale ratio $(\tau^T/\tau^S) = 1$ calculated through Eq. 2 . (B) Results for time-scale ratio $(\tau^T/\tau^S) = 10$ calculated through Eq. 2. (C) Distance between pairs of vectors $I_k = (S_1, ..., S_5)_k$, calculated through the distance metric $1 - r_{(I_k, I_{k'})}$, with $r_{(I_k, I_{k'})}$ being the Pearson coefficient of correlation between vectors I_k and $I_{k'}$. Parameters: $M = 2$, $\eta = 0.1$, $c_i^i = 20$, $k_i^i = 1$ (self-activation) and $k_j^i = 10$ (repression), $\alpha = 0$, $d_c = 0.3$ (see Methods), for $i, j = 6, ..., 15$.

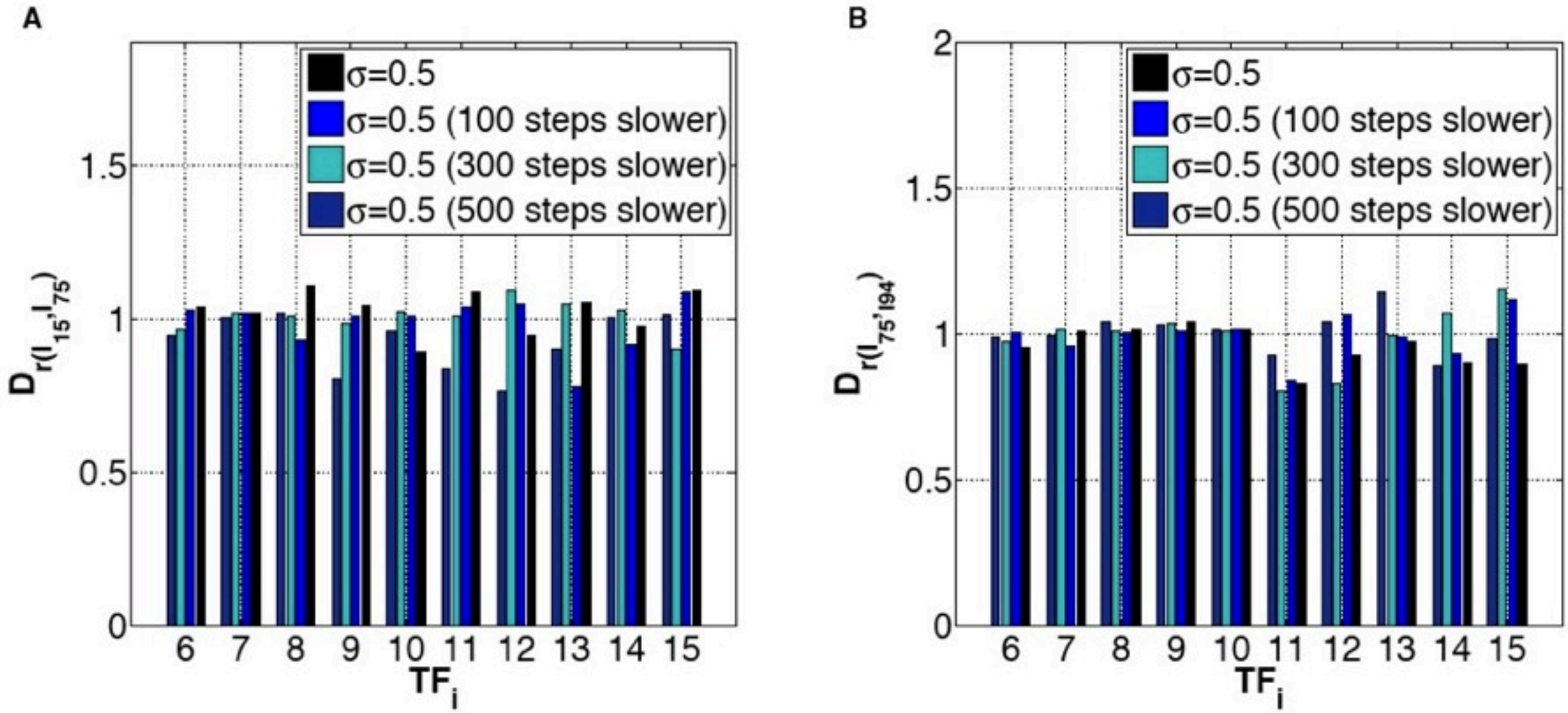


Figure 8. Inter-distribution distance dependence on sweeping speed. (A) Inter-distribution distance between the attractors induced by combination I_{15} and I_{75}. (B) Inter-distribution distance between the attractors induced by combination I_{75} and I_{94}. D_r stands for the distance metric based on the correlation between distributions (similar to Eq. 3). Parameters: M=2, $\eta = 0.1$, $c_i^i = 20$, $k_i^i = 1$ (self-activation) and $k_j^i = 10$ (repression), $\alpha = 0$, $d_c = 0.3$, $\tau^T/\tau^S = 1$ (see Methods), for i, j=6,...,15. σ stands for noise intensity (see Methods). On each figure each colour corresponds to different sweeping speeds obtained by increasing T_{S_i} by 100, 300, or 500 numerical integration time-steps (see Fig. 1B).

Summary

- All genetic decision switches naturally have asymmetry and noise.

- As a result we have speed dependent cellular decision making.

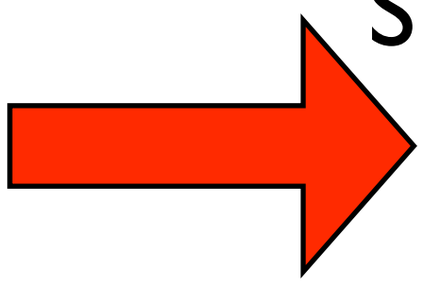
- In contrast to previous results on delayed bifurcations, here the asymmetry is *transient:* and potentially we have additional complexity due to the interplay between point of maximal asymmetry and point of the decision.

Summary

- All genetic decision switches naturally have asymmetry and noise.

- As a result we have speed dependent cellular decision making.

- In contrast to previous results on delayed bifurcations, here the asymmetry is *transient:* and potentially we have additional complexity due to the interplay between point of maximal asymmetry and point of the decision.



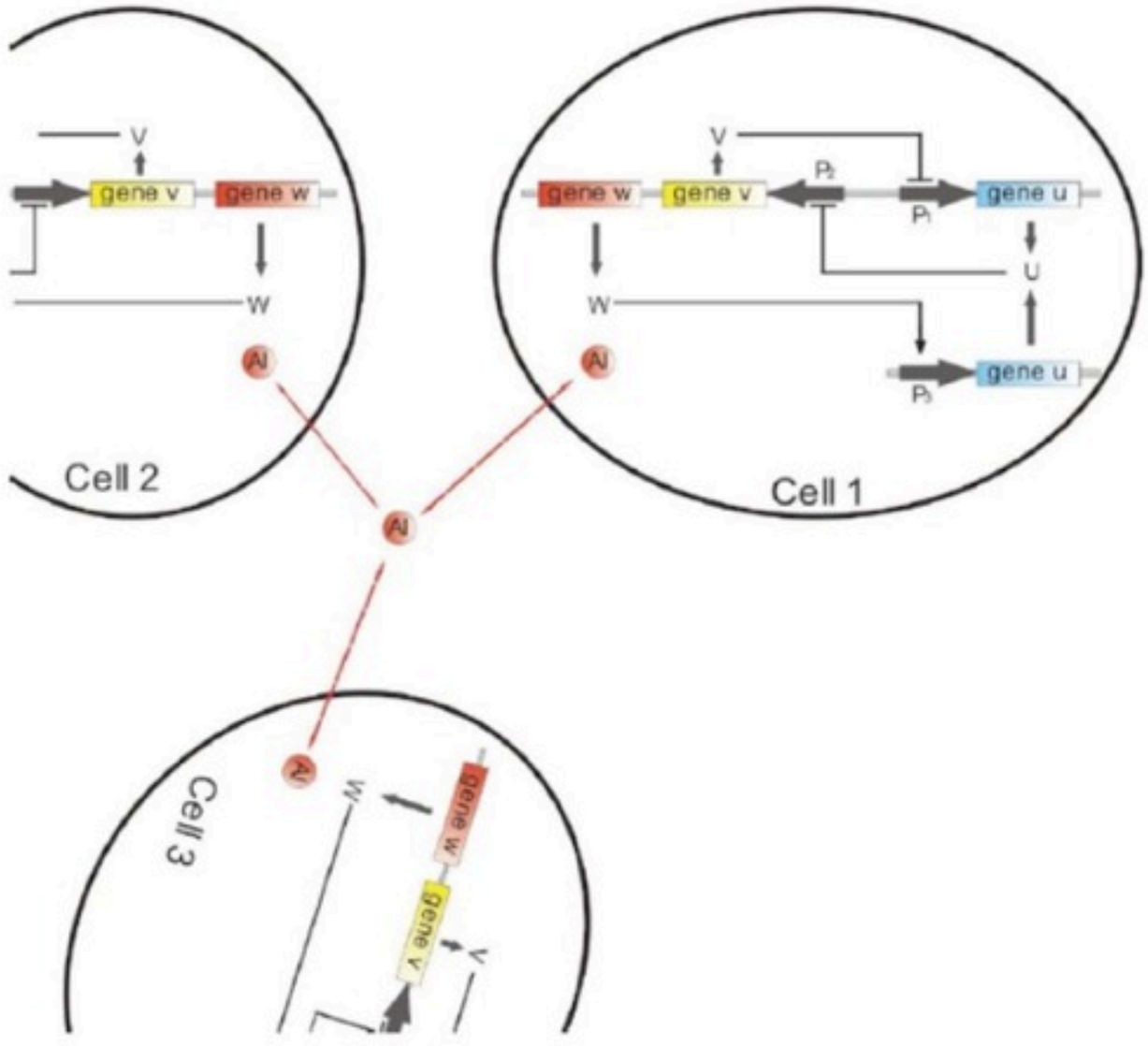
Such speed-dependent decision making should be taken account of in Biology, Synthetic Biology, Medicine

Open Q: Transition to coexisting dynamic attractors

PHYSICAL REVIEW E 75, 031916 (2007)

Inherent multistability in arrays of autoinducer coupled genetic oscillators

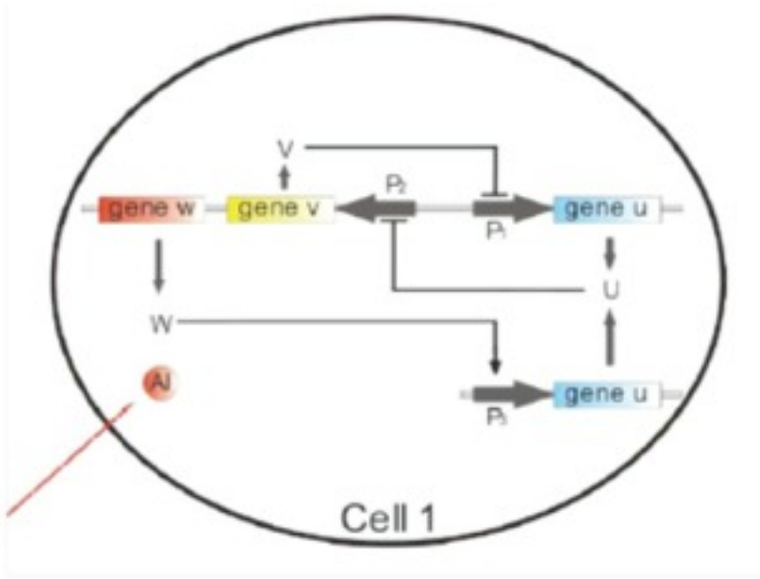
A. Koseska,[1] E. Volkov,[2] A. Zaikin,[1,3] and J. Kurths[1]
[1]*Institut für Physik, Potsdam Universität, Am Neuen Palais 10, D-14469 Potsdam, Germany*
[2]*Department Theoretical Physics, Lebedev Physical Institute, Leninskii 53, Russia*
[3]*Department of Mathematics, University of Essex, Wivenhoe Park, Colchester C04 3SQ, United Kingdom*
(Received 4 December 2006; published 30 March 2007)



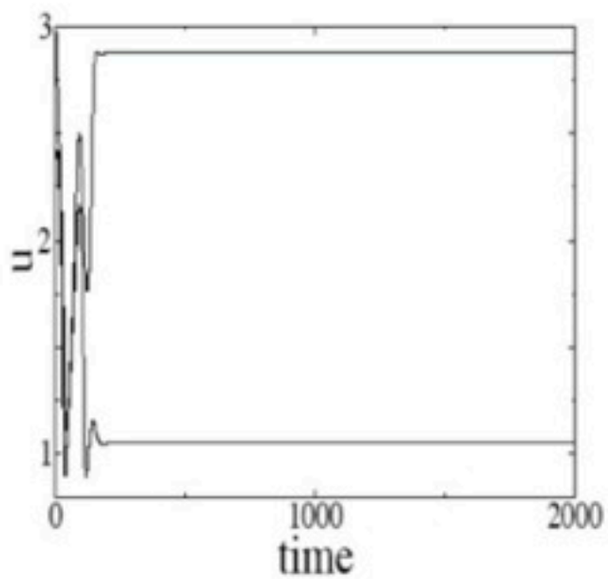
- the toggle switch is constructed from gene $u(lacI)$ and gene $v(cI587)$;
- AI is synthesized by the protein encoded by the gene $w(luxI)$ and drives the toggle switch;
- the extracellular AI will be represented by $\bar{\omega}_e$ and provides an intercell communication system

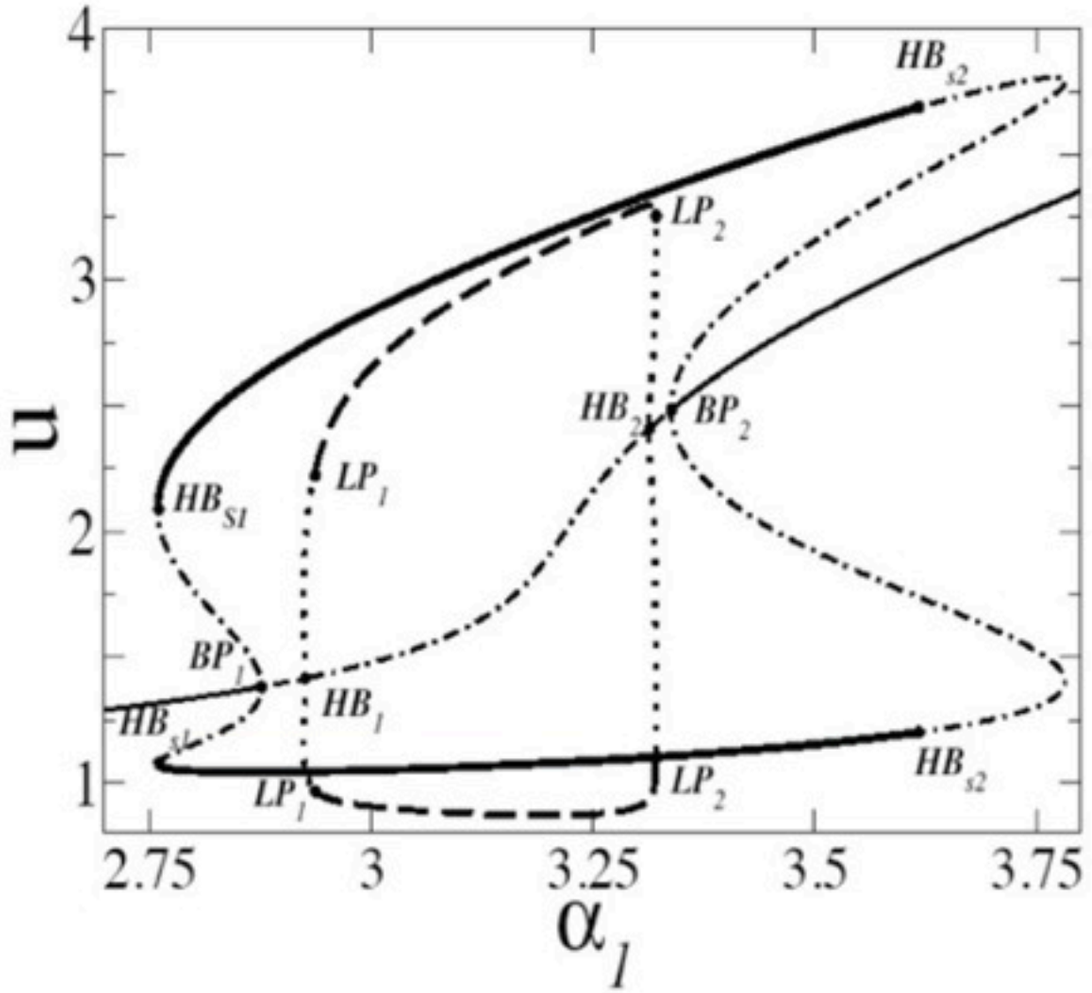
[Kuznetsov et al., SIAM J. APPL. MATH., 2005]

Open question: delayed bifurcations in transition to coexisting dynamic attractors



- **Oscillation death regime:** Increase of the coupling strength in the system entrains the oscillations and the oscillators distribute among steady state clusters.

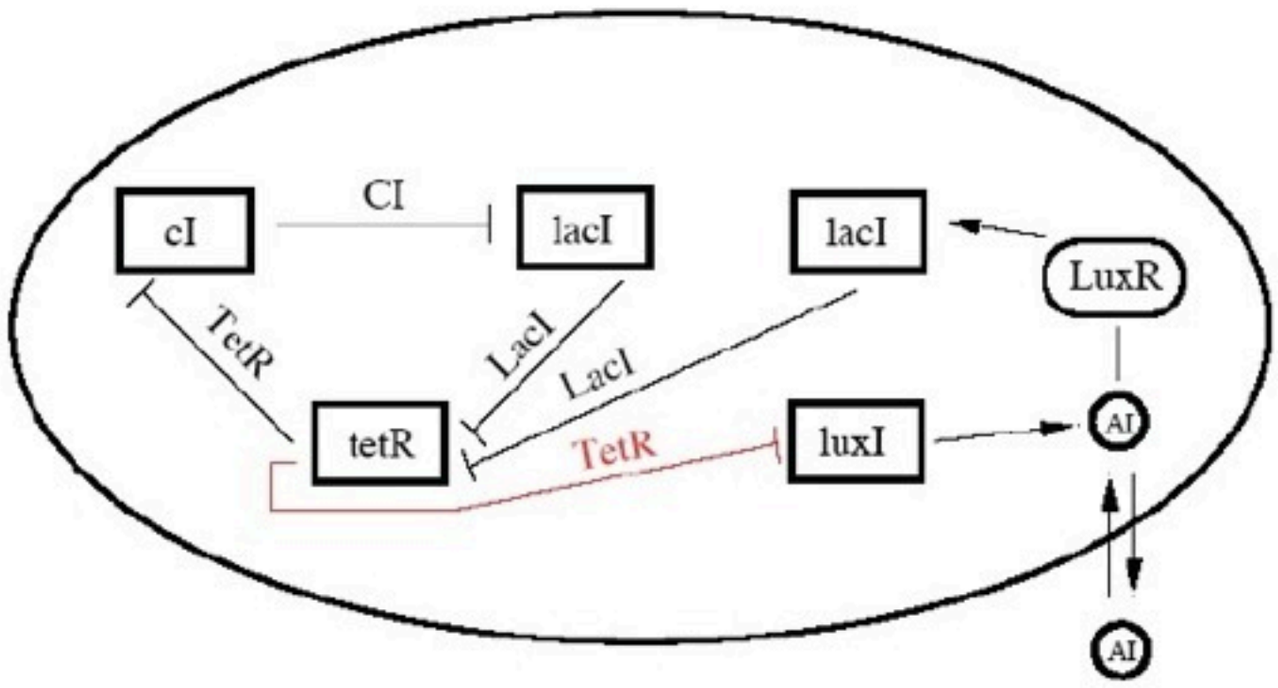




Multistability and Clustering in a Population of Synthetic Genetic Oscillators via Phase-Repulsive Cell-to-Cell Communication

Ekkehard Ullner,[1] Alexei Zaikin,[2] Evgenii I. Volkov,[3] and Jordi García-Ojalvo[1]

The repressilator with quorum sensing and repressive cell-to-cell communication



Open Question: Regulation of decision making in growing populations

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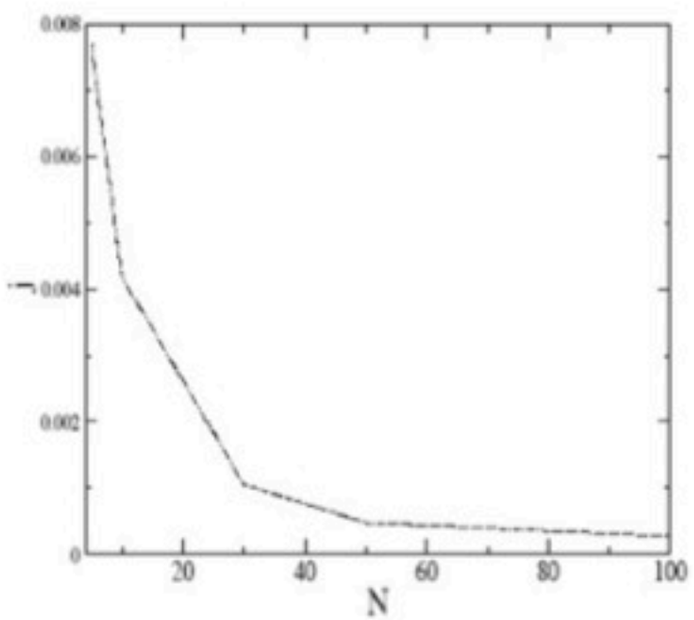
PLoS one

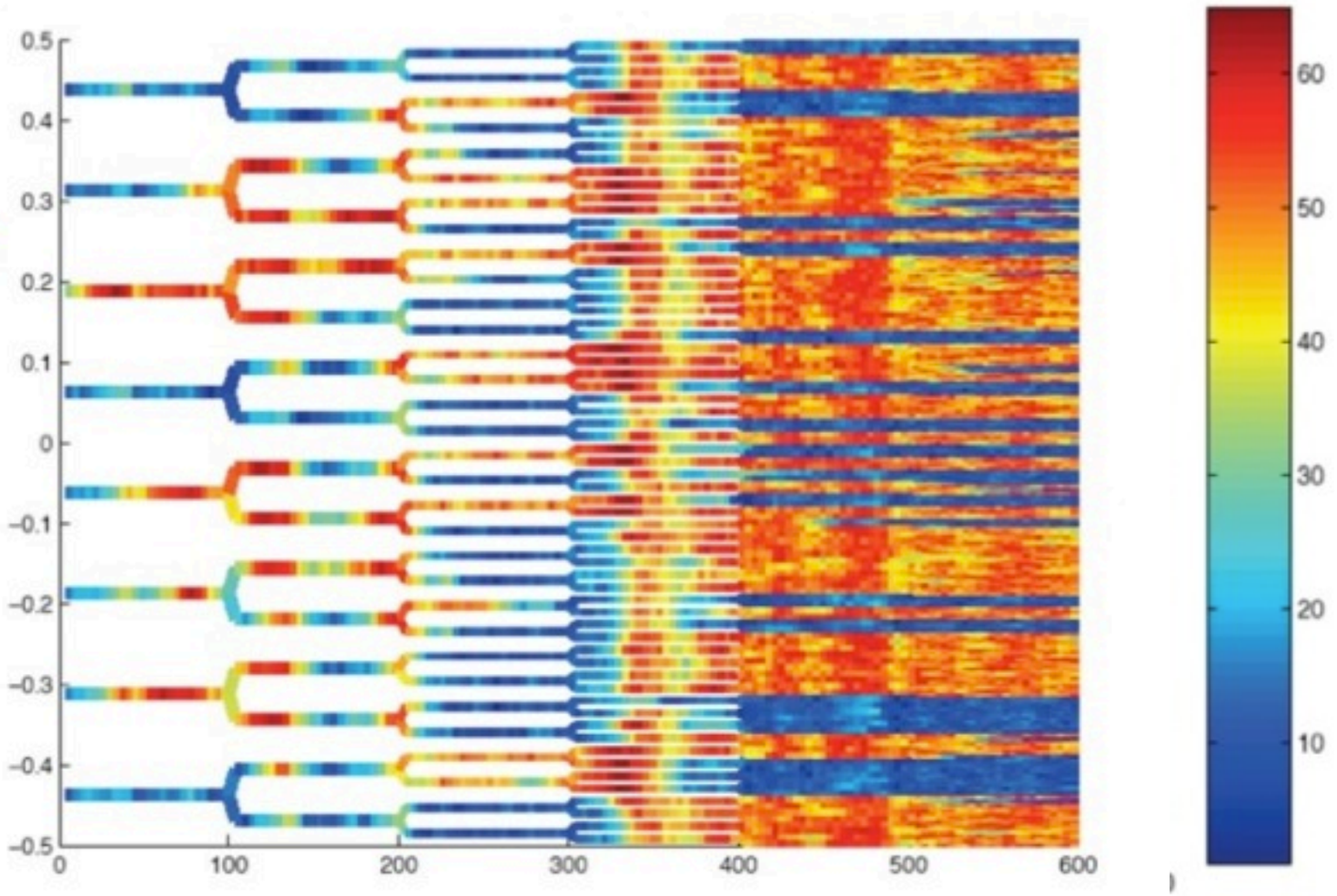
March 2009 | Volume 4 | Issue 3 | e4872

Timing Cellular Decision Making Under Noise via Cell–Cell Communication

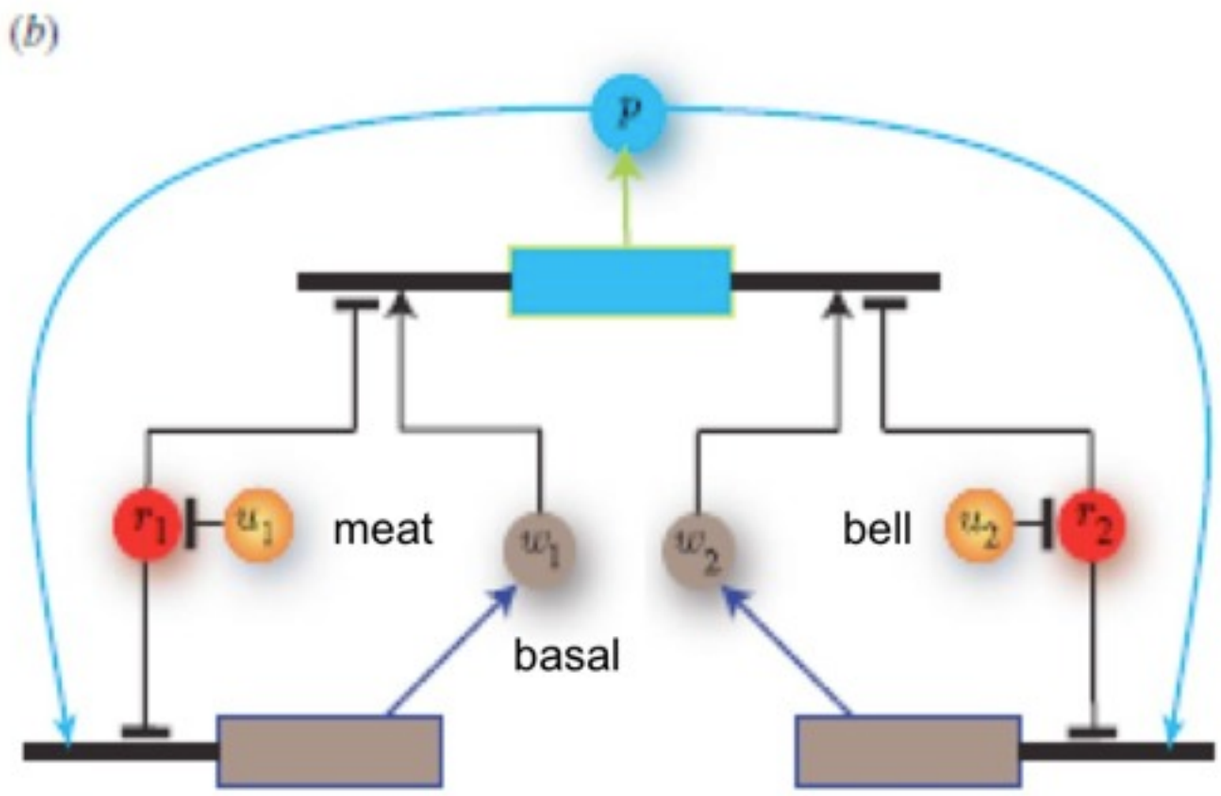
Aneta Koseska[1], Alexey Zaikin[2]*, Jürgen Kurths[1,3,4], Jordi García-Ojalvo[5]

- System Size Effect: Differentiation in noisy relaxator oscillators can be explained by the effective reduction of noise intensity?
- Programming cell differentiation?





Open Question: Cellular decisions in systems with cellular intelligency



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Molecular circuits for associative learning in single-celled organisms

Chrisantha T. Fernando[1,2,*], Anthony M. L. Liekens[3], Lewis E. H. Bingle[1], Christian Beck[4], Thorsten Lenser[4], Dov J. Stekel[1] and Jonathan E. Rowe[5]

Conclusions and thanks to my co-authors!!!

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Speed-Dependent Cellular Decision Making in Nonequilibrium Genetic Circuits

Nuno R. Nené[1]*, Jordi Garca-Ojalvo[2], Alexey Zaikin[3]

1 Department of Mathematics, Imperial College London, London, United Kingdom, 2 Departament de Fsica i Enginyeria Nuclear, Universitat Politècnica de Catalunya, Terrassa, Spain, 3 Institute for Women's Health and Department of Mathematics, University College London, London, United Kingdom

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Interplay between Path and Speed in Decision Making by High-Dimensional Stochastic Gene Regulatory Networks

Nuno R. Nené[1]*, Alexey Zaikin[2]

1 Department of Mathematics, Imperial College London, London, United Kingdom, 2 Institute for Women's Health and Department of Mathematics, University College London, London, United Kingdom

and to Afnan Alagha (KAZ University)

THANK YOU!!