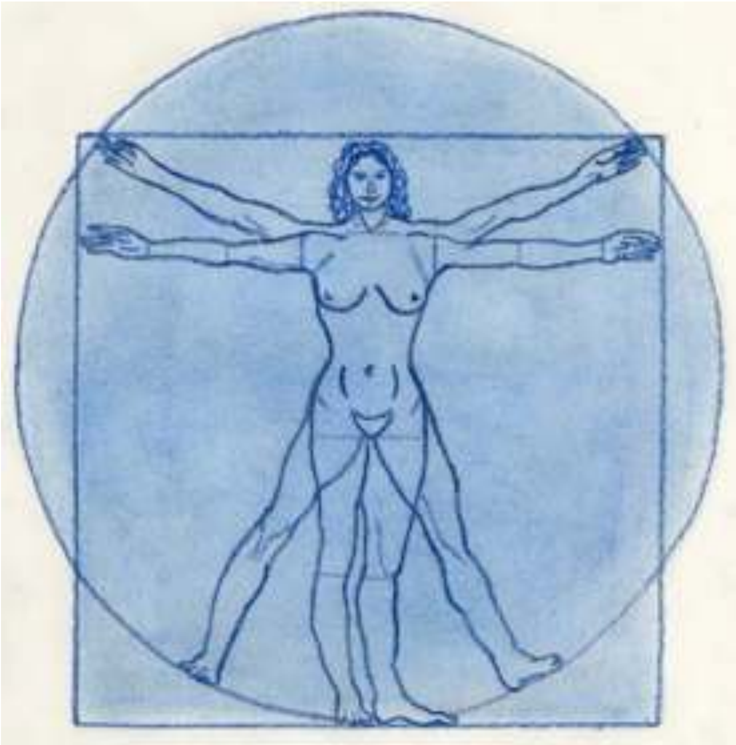
Unexpected effects in genetic regulatory networks: understanding complex dynamics



Alexey Zaikin

Institute for Women's Health and Department of Mathematics

University College London

www.zaikinlab.com

People: O. Blyuss, I. Morino, T. Bartlett, Y. Borg, R. Heussen, R. Bates

Zaikin Group on Systems Medicine
Systems Science, Integrative Interdisciplinary Interfaculty Research

Alumni: R. Bilal, E. Long, N. Nene, S. Alt

1. Medicine
Clinical Data Analysis

1.1 Proteomics
J. Timms, U. Menon, O. Blyuss

1.2 Hormones, RANKL, Endometrium Thickness
E. Fourkala, M. Widschwendter, U. Menon, A. Rosenthal

1.3 Epigenetics(DNAm)
T. Bartlett, I. Krylov, M. Widschwenter

1.4 Fetal Medicine
O. Blyuss, N. Kositzina, K. Nicolaides, A. David, D. Peeble, N. Wessel (HU Berlin)

1.5 iPhone App.
Anna Lanceley

1.6 Ultra S. (Ov. thick.)
Usha Menon

2. Biology
Modelling wet experiments

2.1 Neural Stem Cells
S. Pollard, S. Hadjur(Cancer Inst), A.Koseska

2.2 Genetic Pattern Form.
Buzz Baum (LMCB)

2.3 Chronobiology
R. Heussen, D. Whitmore (Cell & Dev.Biol.)

2.4 Synthetic Biology
Y. Borg, D. Nesbeth, N. Szita(Biochem. Eng.), M. Romano, Y. Saka(Aberdeen), L. Tsimring(SanDiego)

2.5 Systems Immunology
Neil Dalchau, P. Coveney, P.M. Kloetzel (Charite, Berlin)

3. Mathematics
Theory of gene expression

3.1 Cybernetics
Intracellular artificial Intelligency

R. Bates, O. Blyuss, M. Ivanchenko, O. Kanakov M. Romano, J. Kurths

3.2 Theory of Gene Expression (Speed, Differentiation)
S. Balta, I. Morino, Nuno Nene (Imperial), A. Zakcharova (TU Berlin), A. Afnan

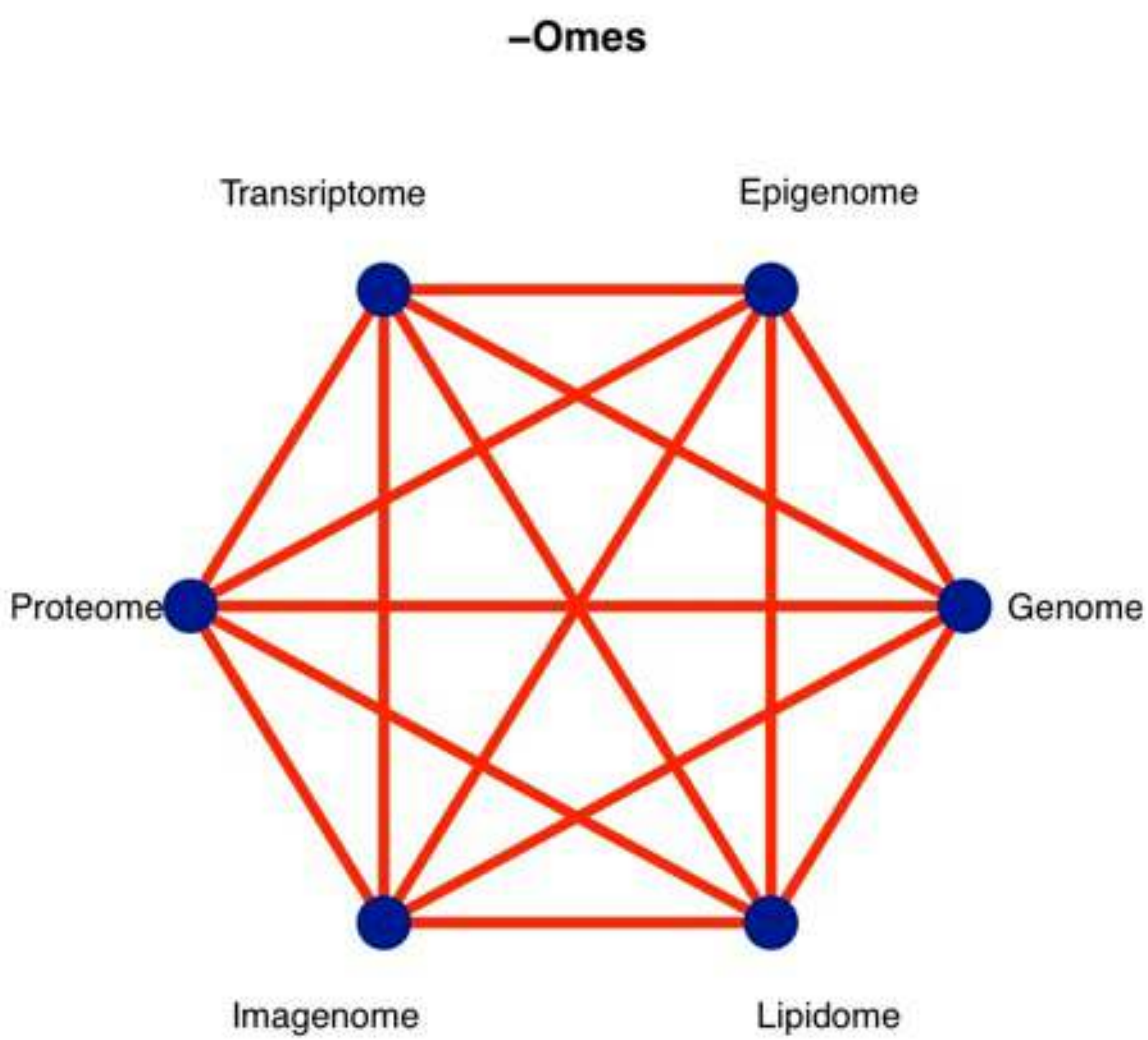
3.3 New Methods in Statistics
ABC MCMC vs SMC

Sofia Olhede (Statistical Science)

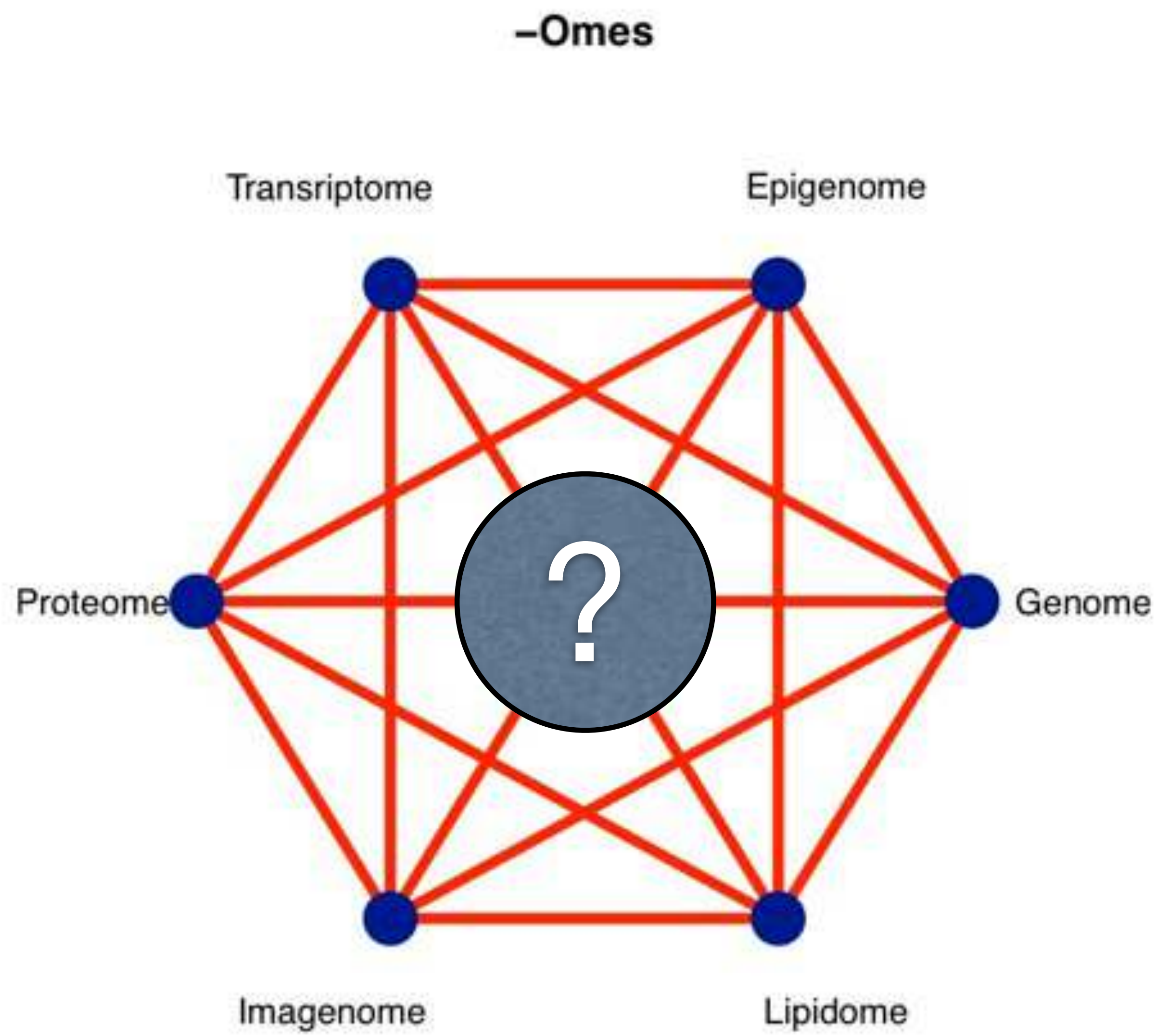
O. Blyuss, T. Bartlett, I. Morino, S. Boccaletti, M. Zanin

3.4 Network Analysis
O. Blyuss, T. Bartlett, I. Morino, S. Boccaletti, M. Zanin

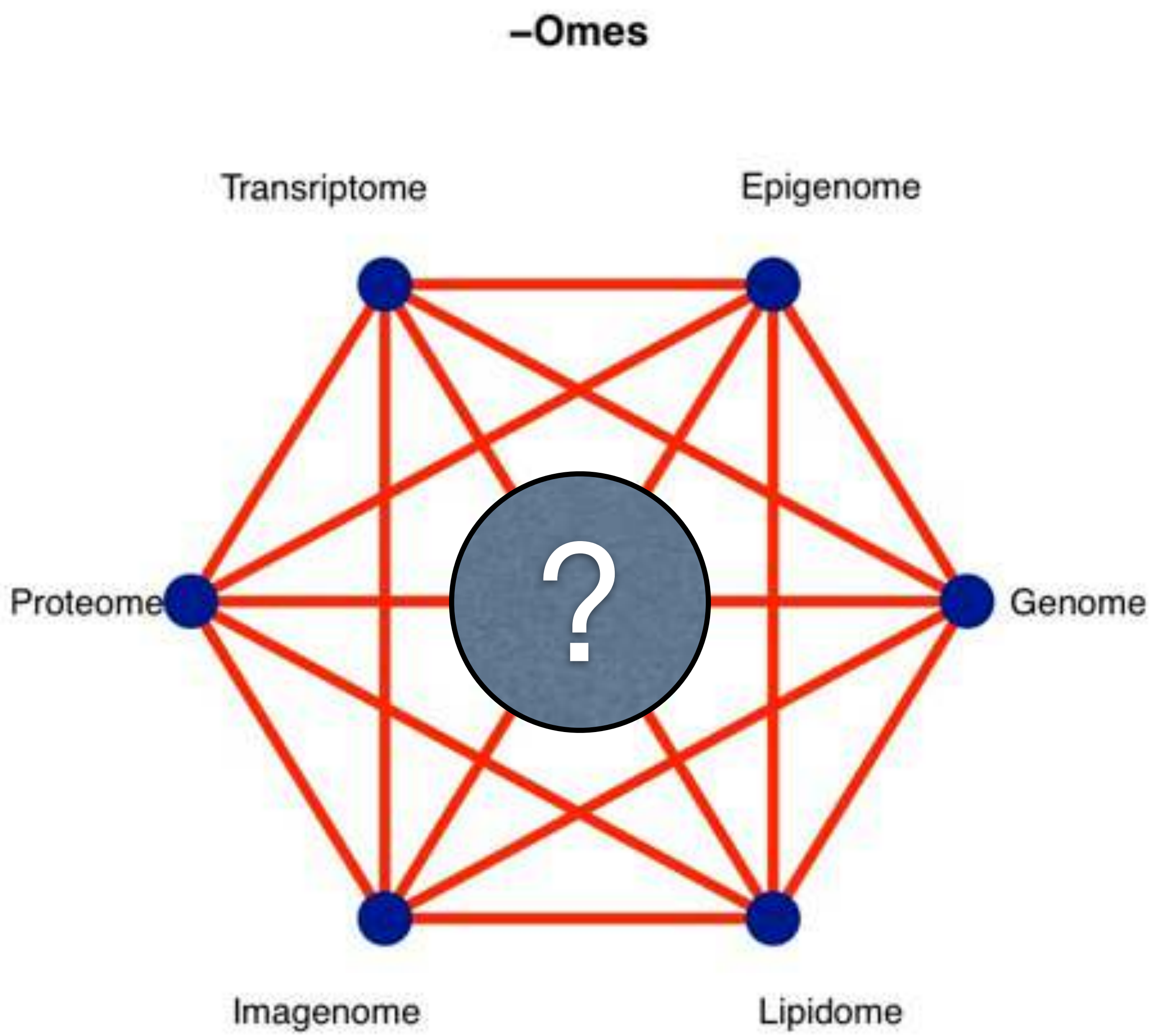
Challenge of Systems Medicine: combination of -omes vs disease

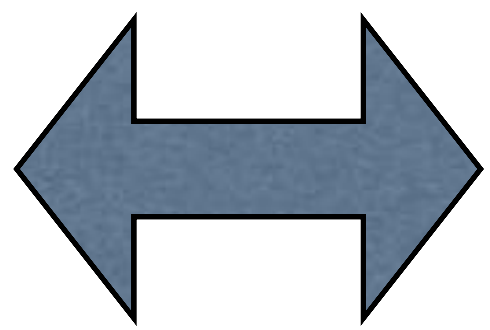


Challenge of Systems Medicine: combination of -omes vs disease



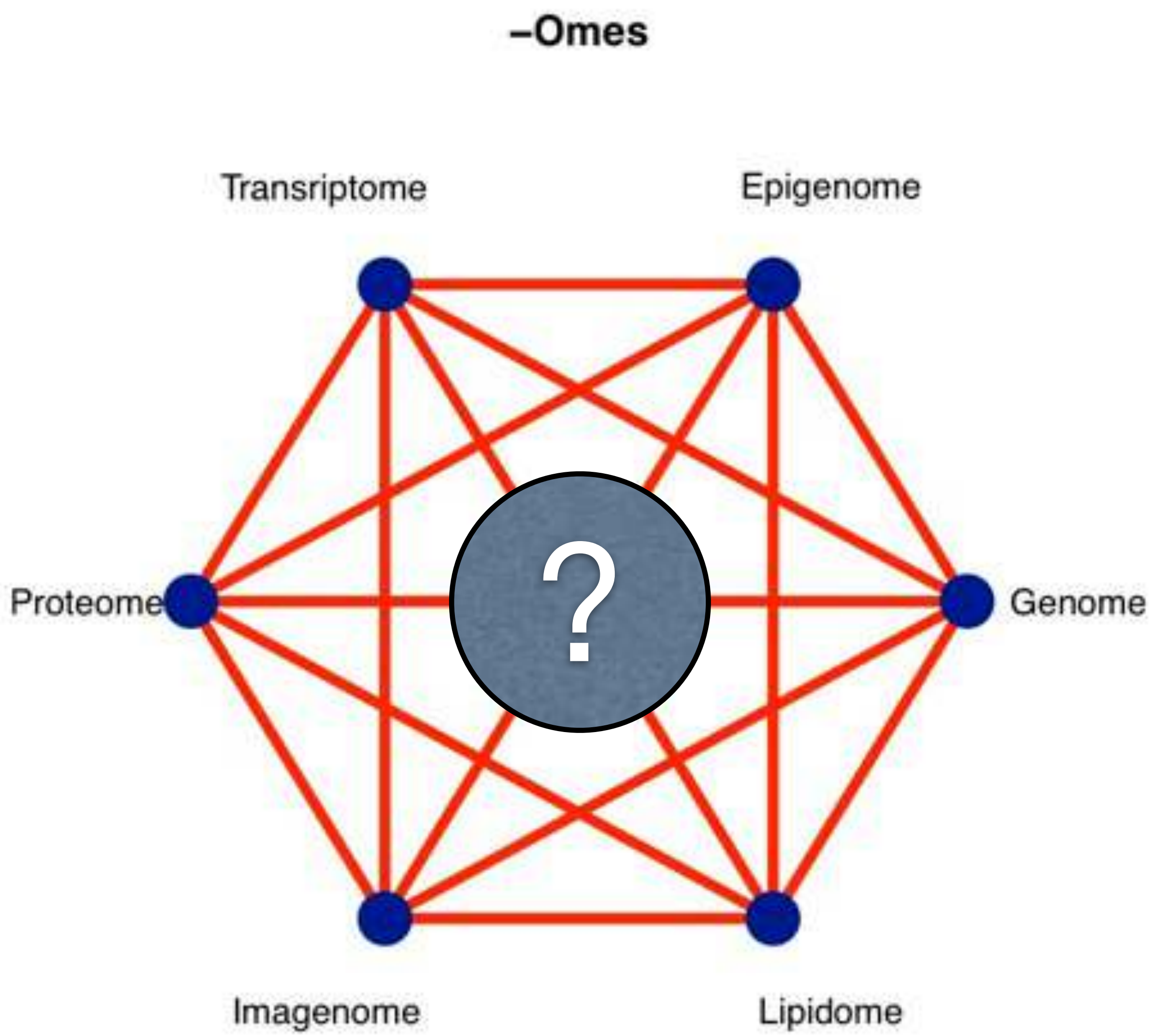
Challenge of Systems Medicine: combination of -omes vs disease

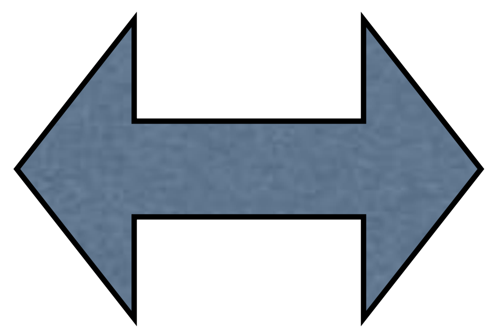




e.g. Ovarian cancer
Breast cancer
Pancreatic cancer

Challenge of Systems Medicine: combination of -omes vs disease

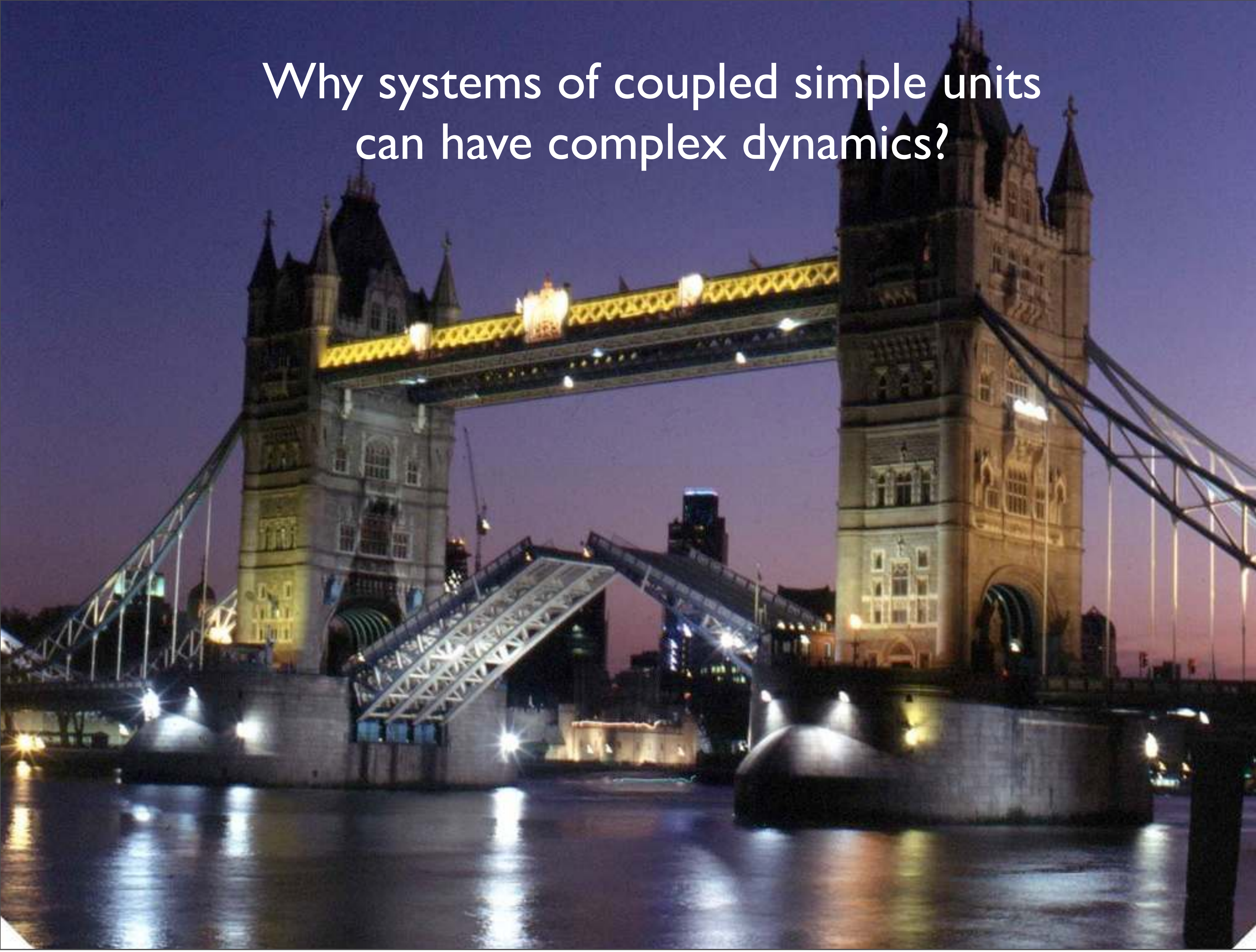


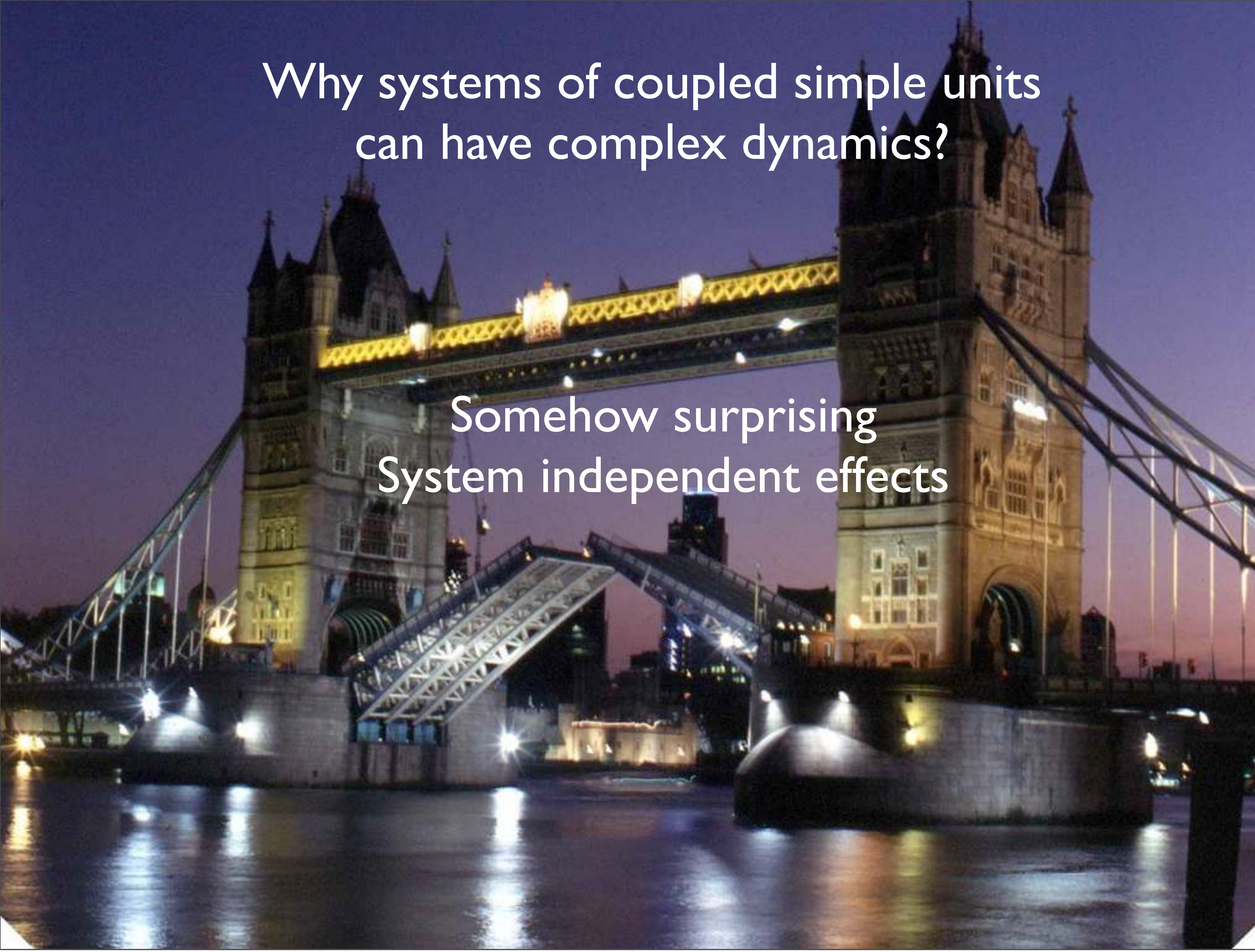


e.g. Ovarian cancer
Breast cancer
Pancreatic cancer

Understanding of dynamics?

Why systems of coupled simple units can have complex dynamics?




Why systems of coupled simple units
can have complex dynamics?
Somehow surprising
System independent effects

1. Pioneering experiments and basic elements in synthetic biology.
2. Suprising dynamics in:
   1. **Intercell communication**:
      Synchronization vs Desynchronization
   2. **Decision making**
   3. **Cellular intelligence**
3. Summary

Synthetic Biology

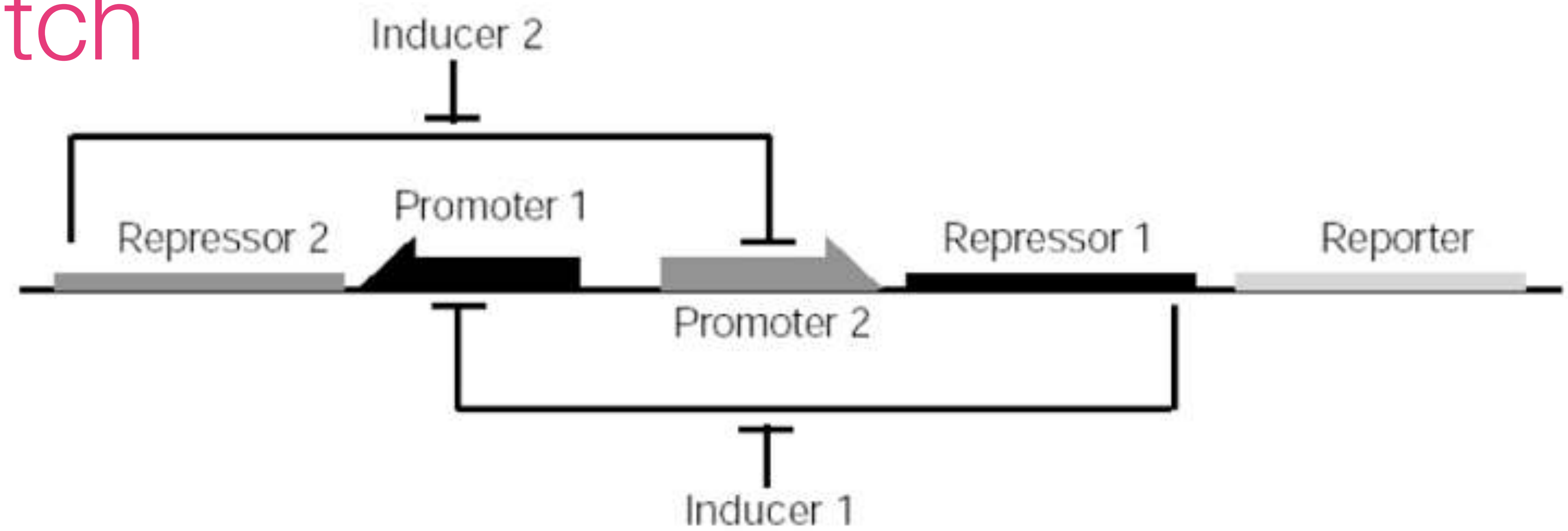
Research spectrum:

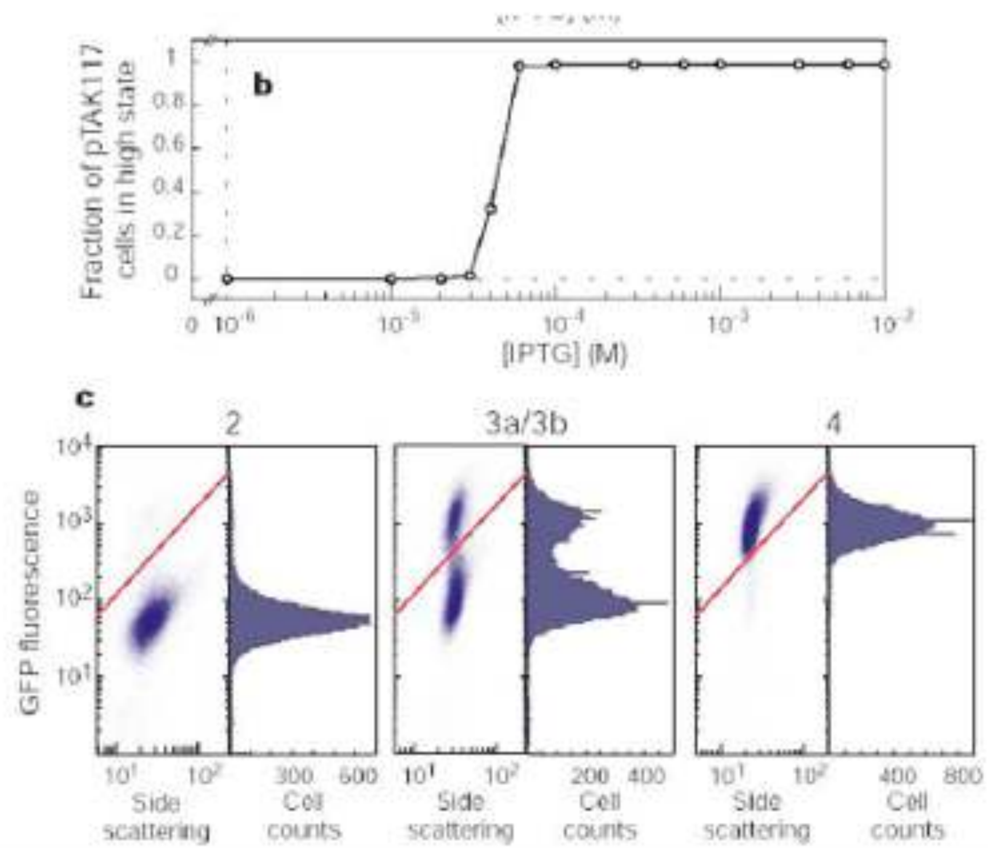
Idea of reduced complexity:
construction of simple biological models which mimic more complex natural systems.

Nanorobots to be "downloaded" into cells to perform elaborated functions.
Intelligent drugs. Programmed chips.

Synthetic biology: combines science and engineering to design novel biological systems

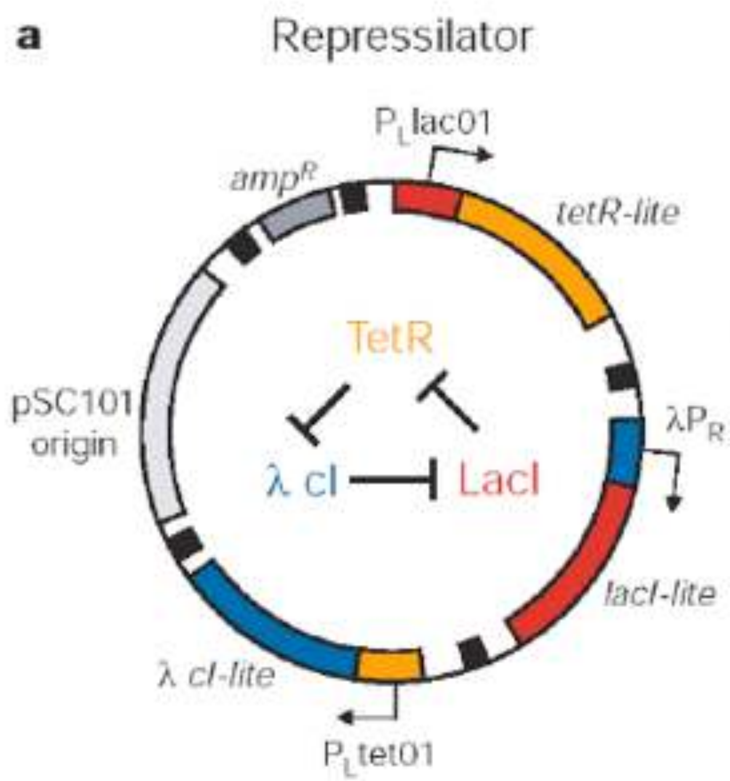
Switch

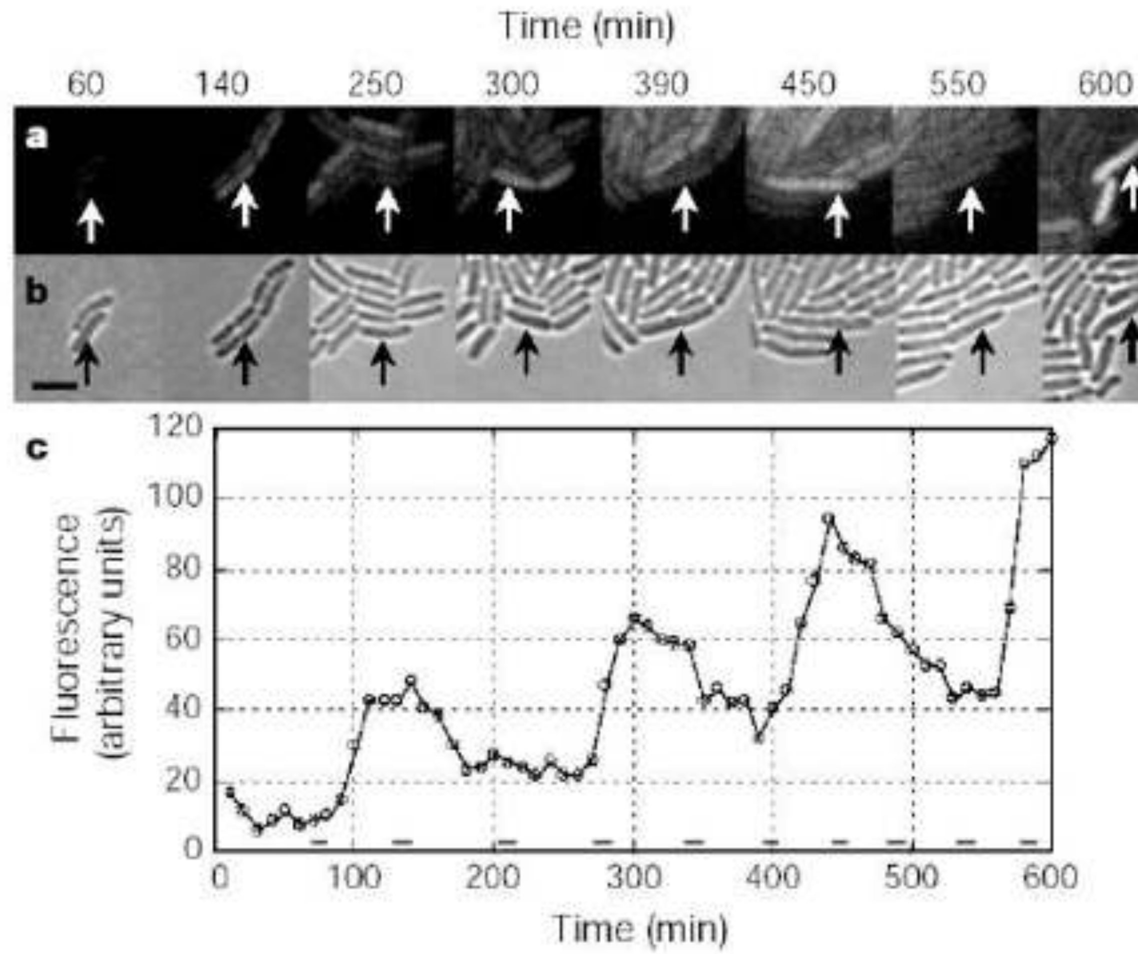




T. Gardner, C. Cantor, J.J. Collins , ”Construction of a genetic toggle switch in Escherechia coli”, Nature, 2000.

Repressilator





$$\frac{dm_i}{dt} = -m_i + \frac{\alpha}{(1 + p_j^n)} + \alpha_0$$

$$\frac{dp_i}{dt} = -\beta(p_i - m_i)$$

$$\begin{pmatrix} i = lacI, tetR, cI \\ j = cI, lacI, tetR \end{pmatrix}$$

M. Elowitz, S. Leibler, "A synthetic oscillatory network of transcriptional regulators", Nature, 2000.

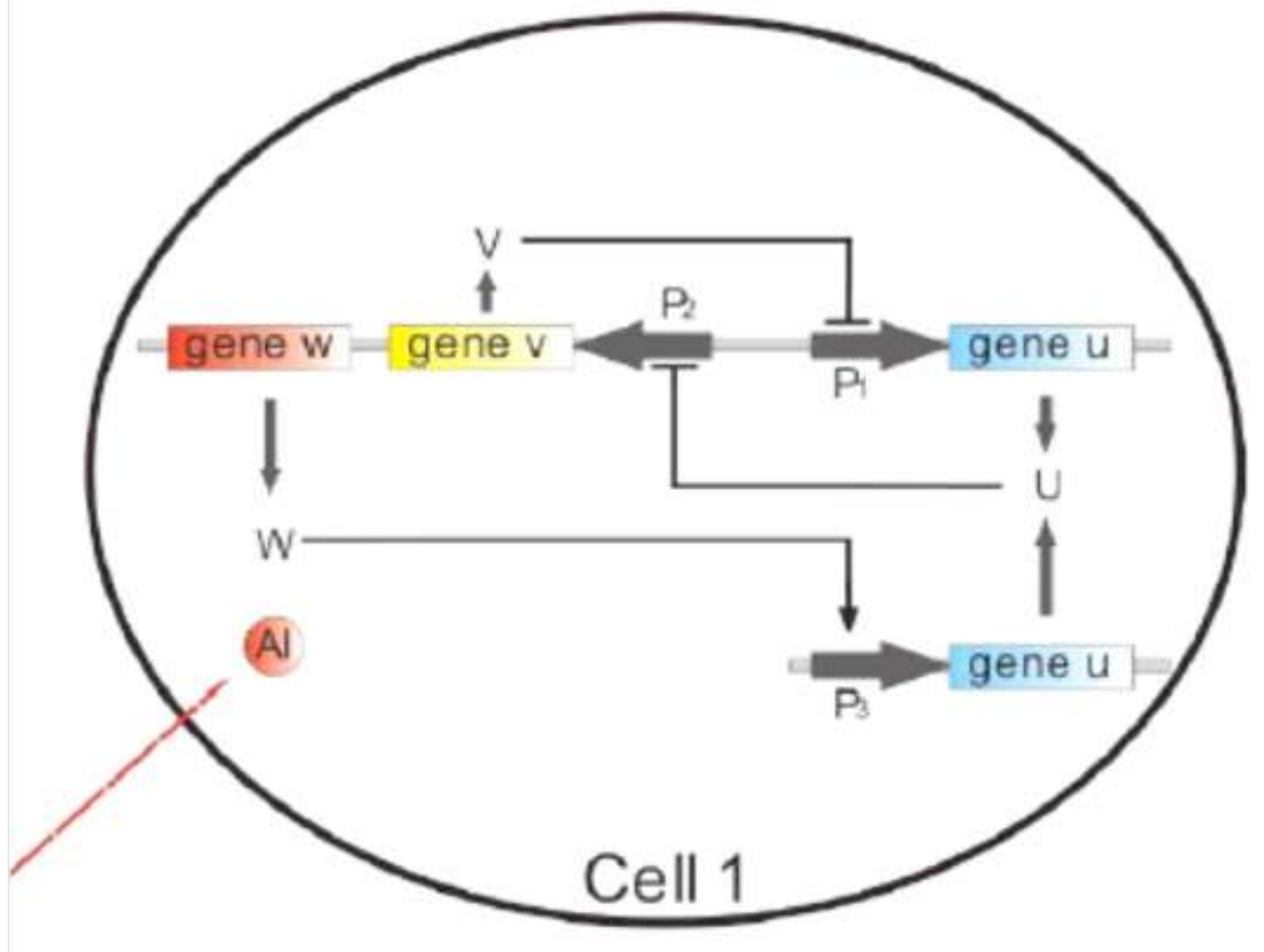
Cell, Vol. 113, 597–607, May 30, 2003, Copyright ©2003 by Cell Press

Relaxator

Development of Genetic Circuitry Exhibiting Toggle Switch or Oscillatory Behavior in *Escherichia coli*

Mariette R. Atkinson,[1] Michael A. Savageau,[2,4]
Jesse T. Myers,[2,3] and Alexander J. Ninfa[1,*]

(Gardner et al., 2000; Elowitz and
toggle switch, consisting of two re



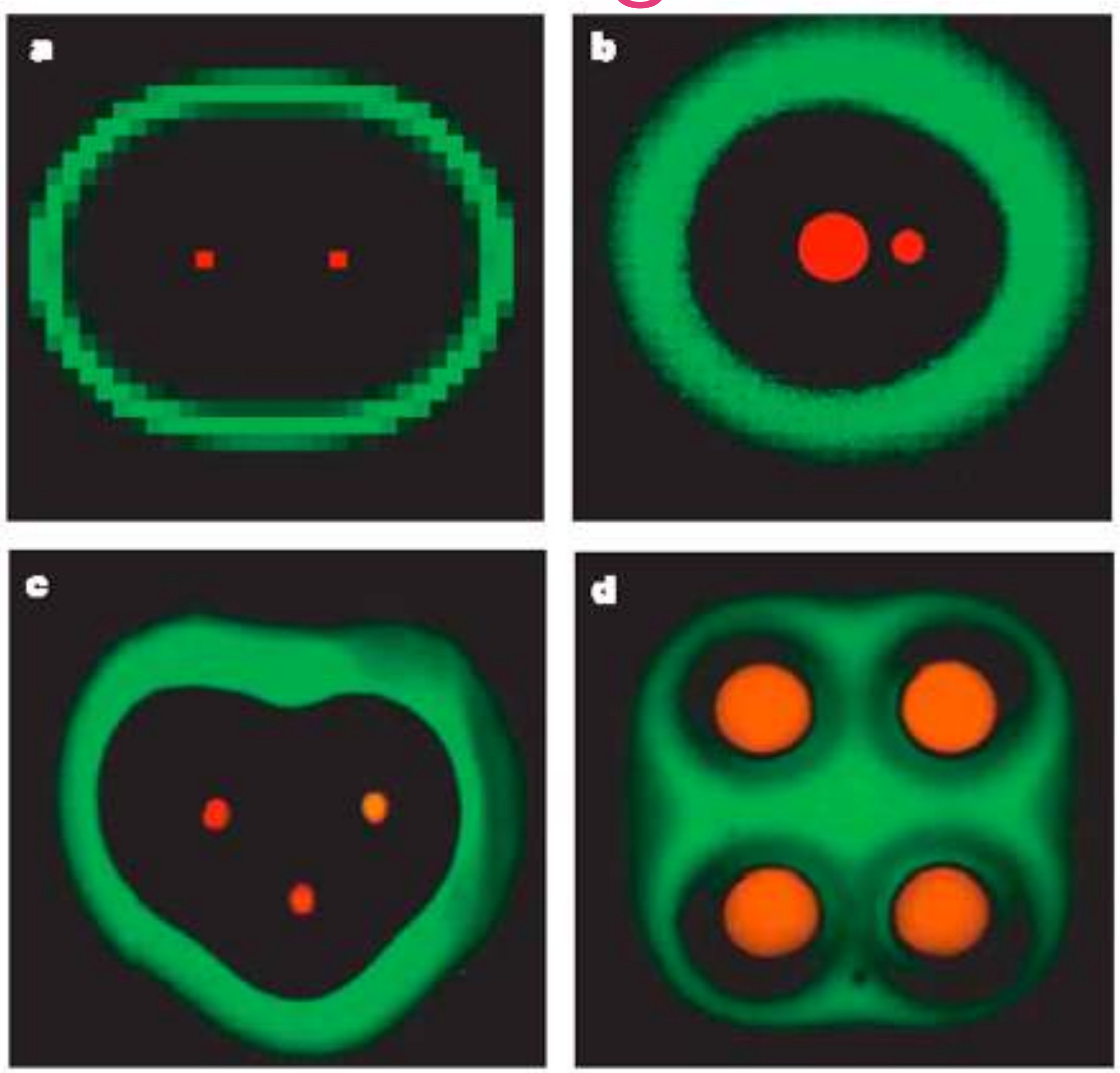
A synthetic multicellular system for programmed pattern formation

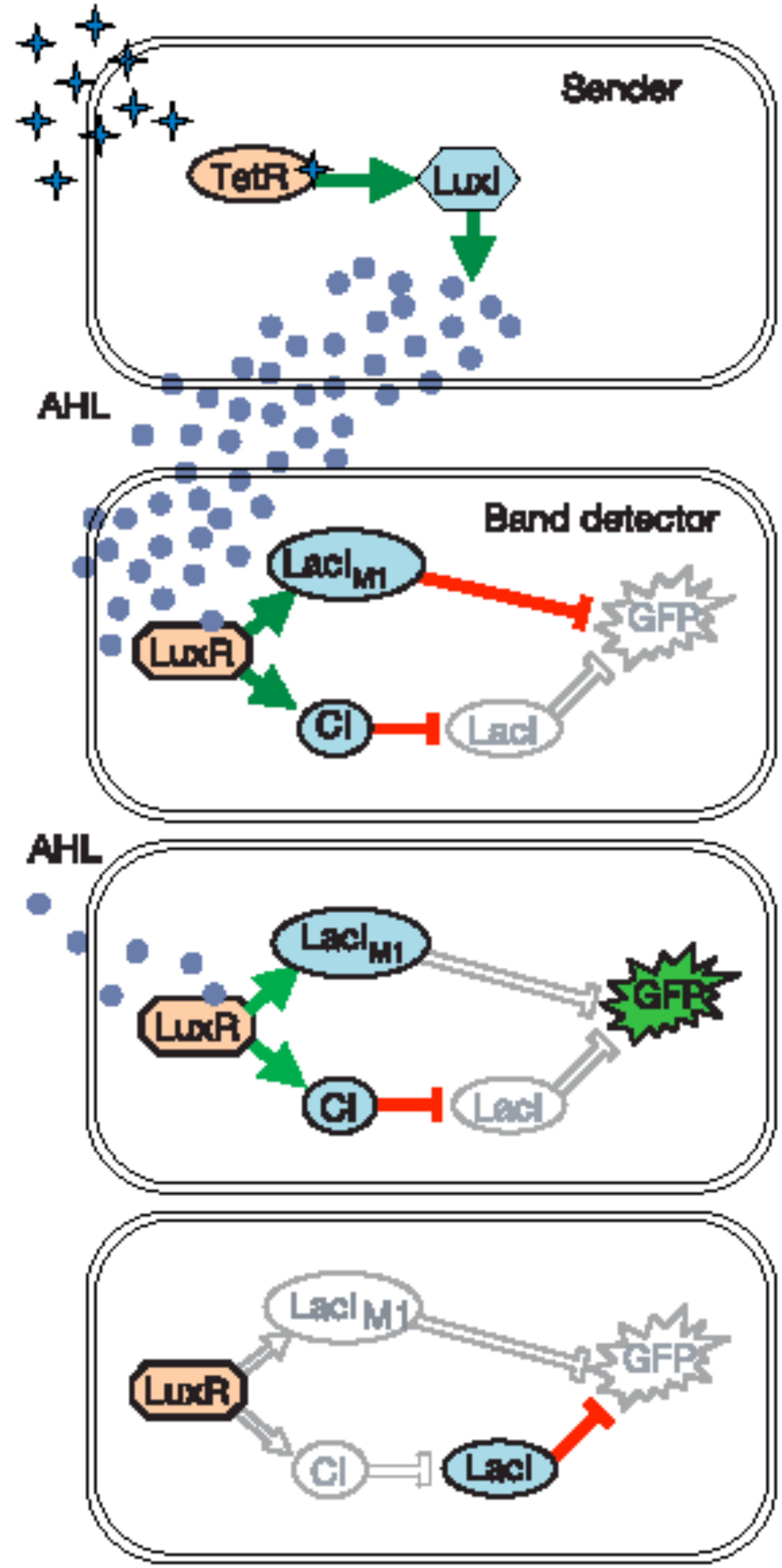
Subhayu Basu[1], Yoram Gerchman[1], Cynthia H. Collins[3], Frances H. Arnold[3] & Ron Weiss[1,2]

NATURE | VOL 434 | 28 APRIL 2005 |

Repression activity of CI is significantly larger than of LACI

Quorum-sensing





1.Logical devices

nature biotechnology

NATURE BIOTECHNOLOGY VOLUME 25 NUMBER 7 JULY 2007

A universal RNAi-based logic evaluator that operates in mammalian cells

Keller Rinaudo[1,4], Leonidas Bleris[1,4], Rohan Maddamsetti[1], Sairam Subramanian[2,3], Ron Weiss[2,3] & Yaakov Benenson[1]

Synthetic Gene Networks That Count

Ari E. Friedland,[1*] Timothy K. Lu,[1,2*] Xiao Wang,[1] David Shi,[1] George Church,[2,3] James J. Collins[1]†

Synthetic gene networks can be constructed to emulate digital circuits and devices, giving one the ability to program and design cells with some of the principles of modern computing, such as counting. A cellular counter would enable complex synthetic programming and a variety of biotechnology applications. Here, we report two complementary synthetic genetic counters in *Escherichia coli* that can count up to three induction events: the first, a riboregulated transcriptional cascade, and the second, a recombinase-based cascade of memory units. These modular devices permit counting of varied user-defined inputs over a range of frequencies and can be expanded to count higher numbers.

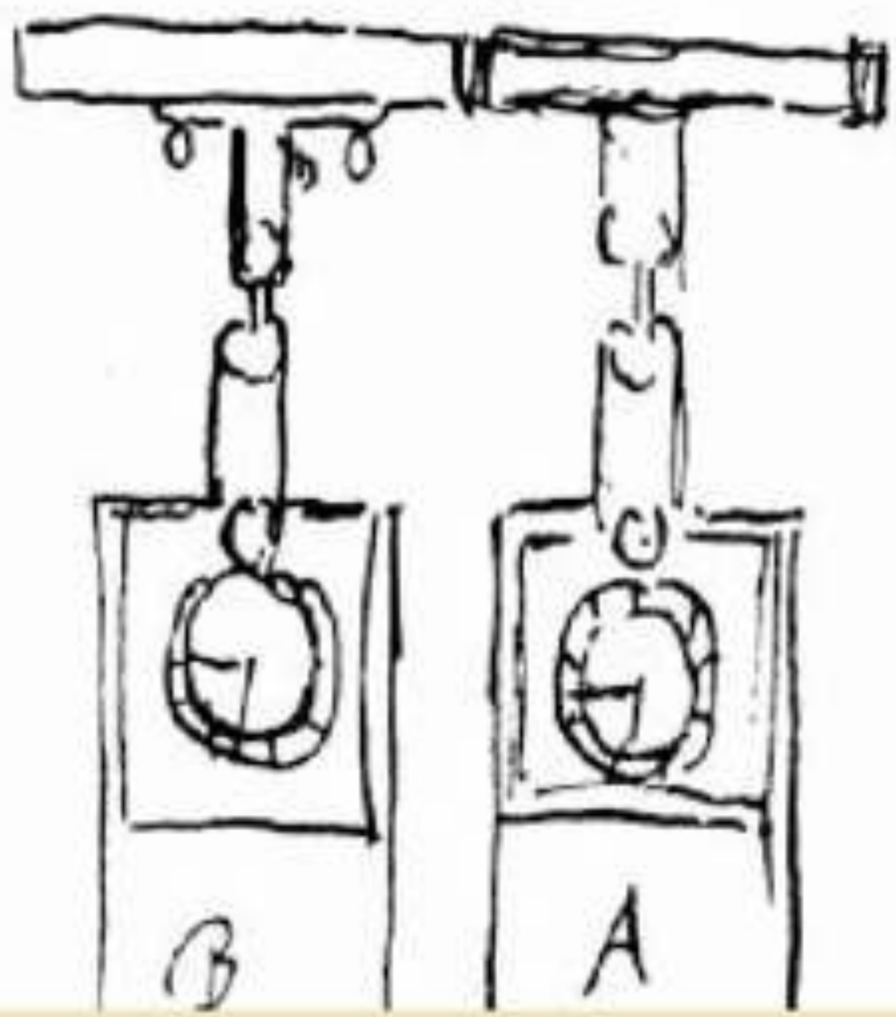
SCIENCE VOL 324 29 MAY 2009

Synchronization vs Desynchronization

huygens' V.[1] **clocks**

1665.

[Fig. 75.][2]



22 febr. 1665.

Diebus 4 aut 5 horologiorum duorum novorum in quibus catenulæ [Fig. 75], miram concordiam obſervaveram, ita ut ne minimo quidem exceſſu alterum ab altero ſuperaretur. ſed conſonarent ſemper reciprocationes utriusque perpendiculi. unde cum parvo ſpatio inter ſe horologia diſtarent, ſympathiæ quandam [3]) quasi alterum ab altero afficeretur ſuſpicari cœpi. ut experimentum caperem turbavi alterius penduli reditus ne ſimul incederent ſed quadrante horæ poſt vel ſemihora rurſus concordare inveni.

For example, repressilator equations:

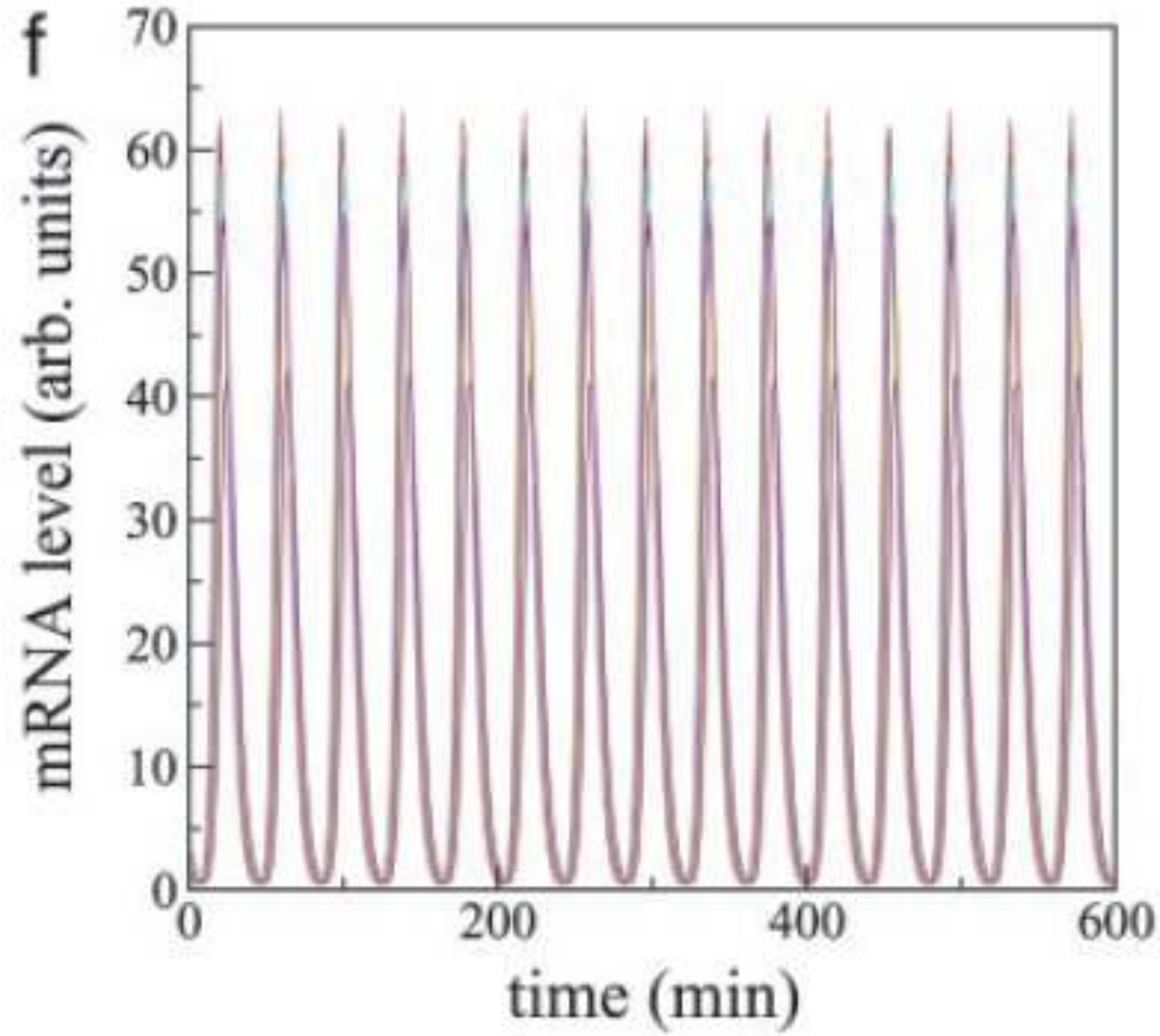
$$\frac{da_i}{dt} = -a_i + \frac{\alpha}{1 + C_i^n}$$

$$\frac{db_i}{dt} = -b_i + \frac{\alpha}{1 + A_i^n}$$

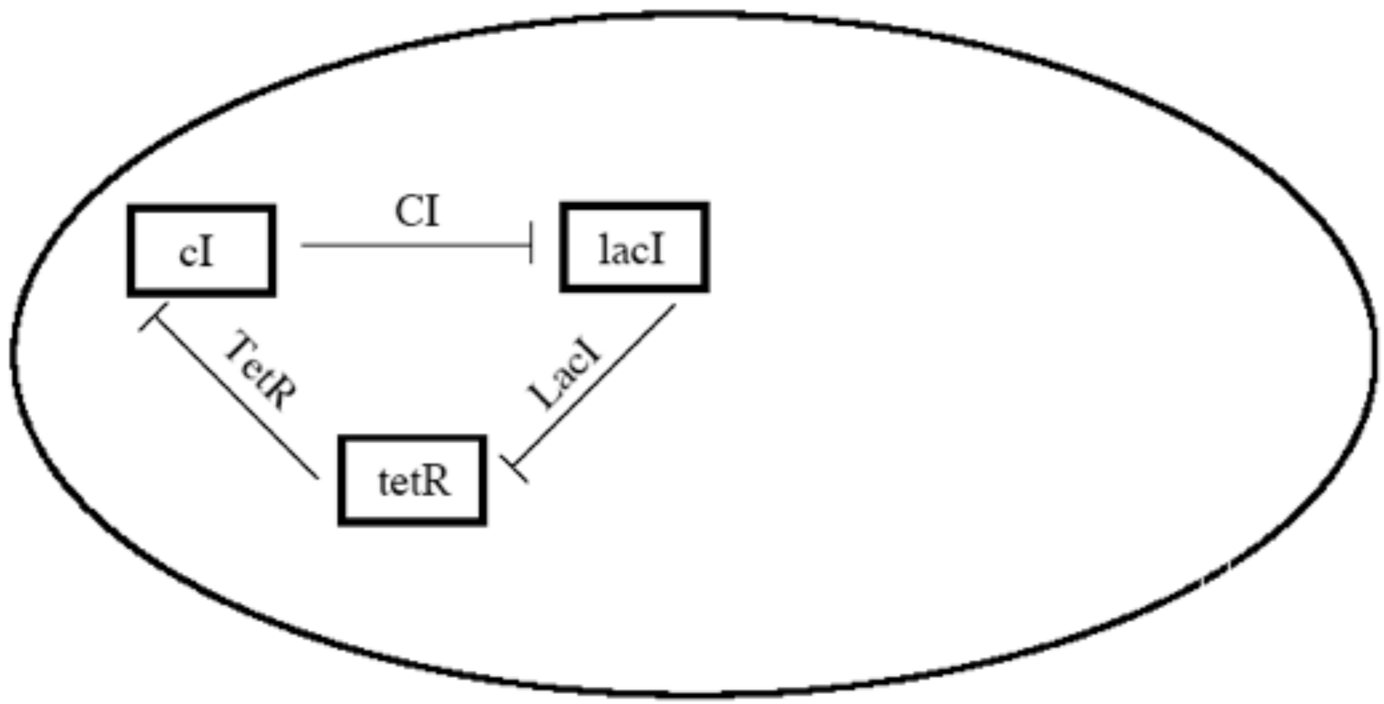
$$\frac{dc_i}{dt} = -c_i + \frac{\alpha}{1 + B_i^n}$$

The protein dynamics is given by

$$\frac{dA_i}{dt} = \beta(a_i - A_i),$$



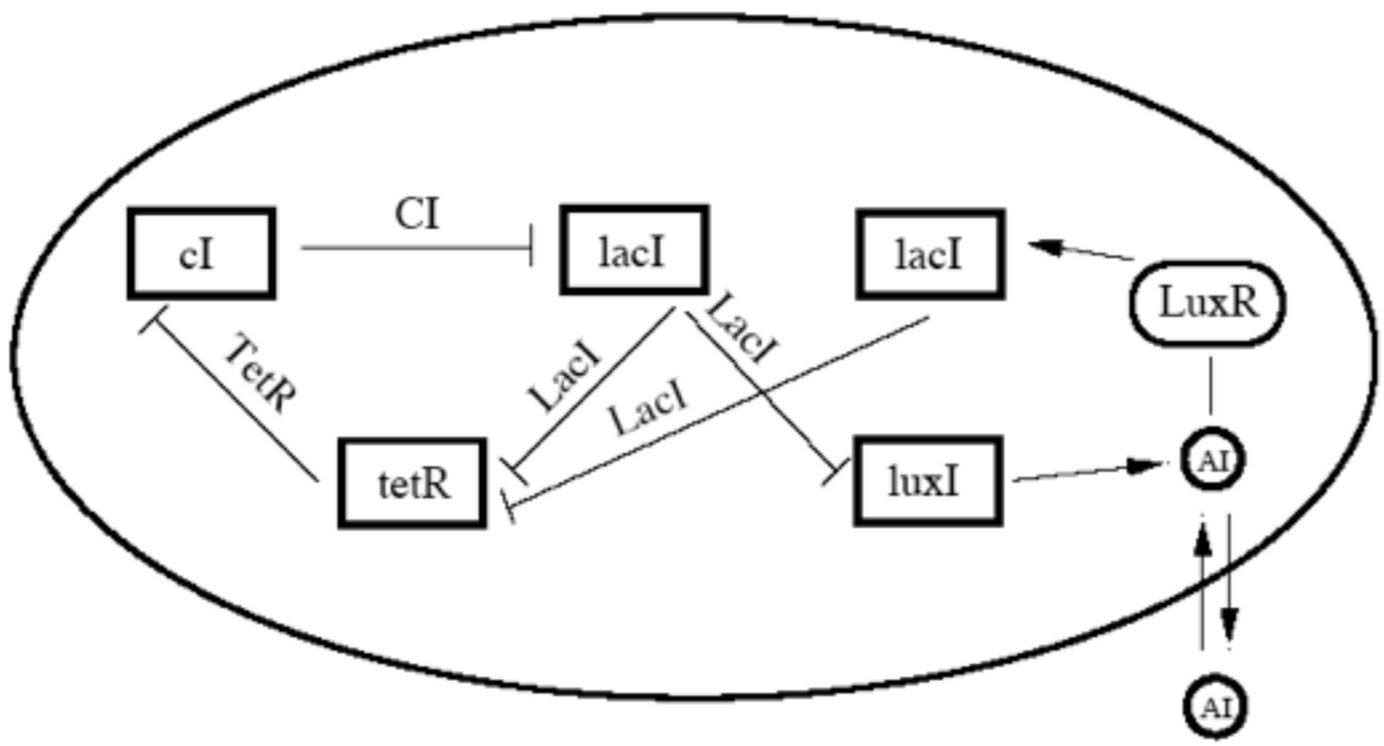
The repressilator with quorum sensing



M.B. Elowitz and S Leibner, *Nature* **405**, p. 335, 2000.

J. García-Ojalvo, M.B. Elowitz and S.H. Strogatz, *PNAS* **101**, p. 10955, 2004.

The repressilator with quorum sensing



M.B. Elowitz and S Leibner, *Nature* **405**, p. 335, 2000.

J. García-Ojalvo, M.B. Elowitz and S.H. Strogatz, *PNAS* **101**, p. 10955, 2004.

Modeling a synthetic multicellular clock: Repressilators coupled by quorum sensing

Jordi Garcia-Ojalvo*†, Michael B. Elowitz‡, and Steven H. Strogatz*§¶

$$\frac{da_i}{dt} = -a_i + \frac{\alpha}{1 + C_i^n},$$

$$\frac{db_i}{dt} = -b_i + \frac{\alpha}{1 + A_i^n},$$

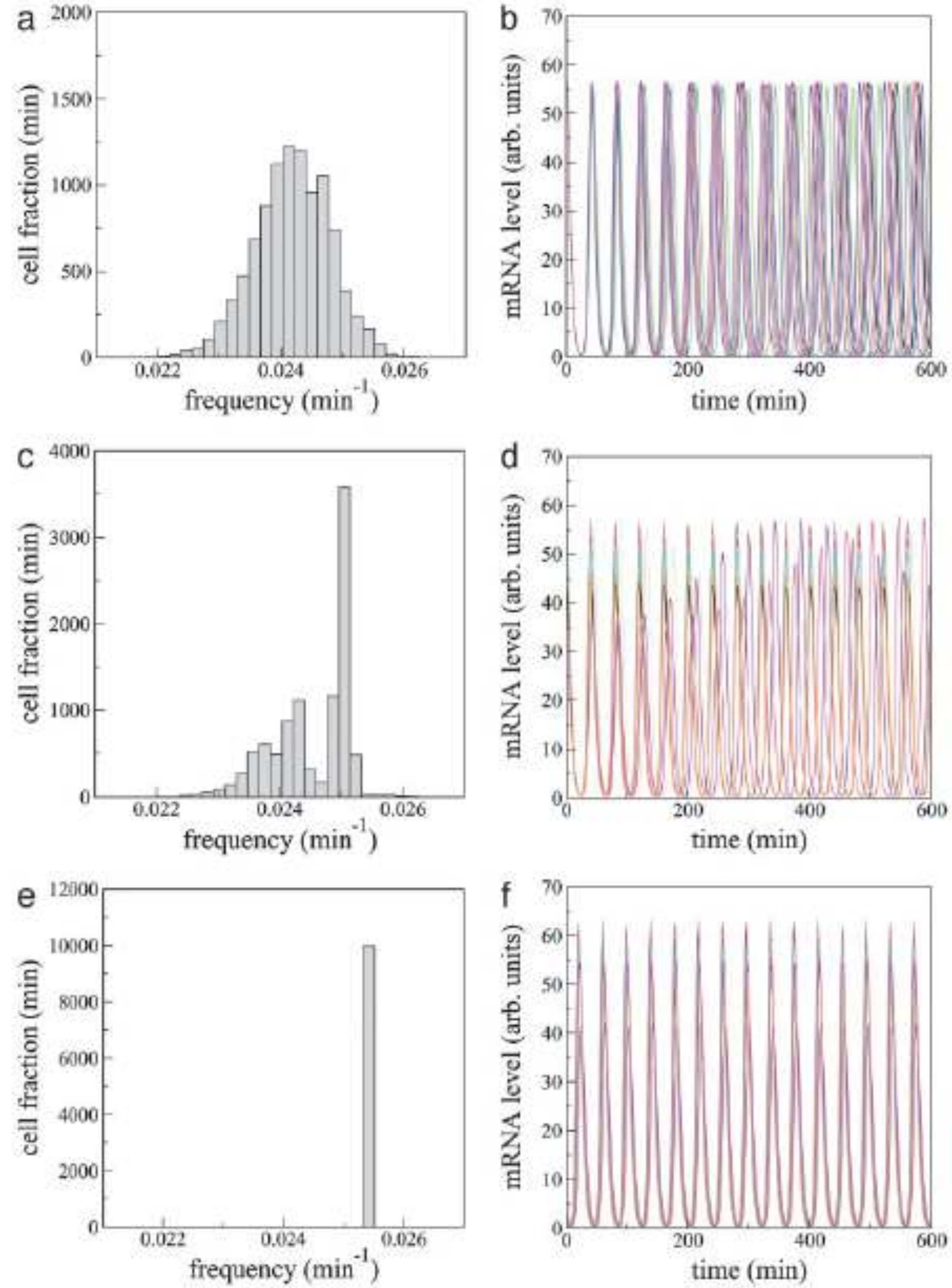
$$\frac{dc_i}{dt} = -c_i + \frac{\alpha}{1 + B_i^n} + \frac{\kappa S_i}{1 + S_i}.$$

The protein dynamics is given by

$$\frac{dA_i}{dt} = \beta(a_i - A_i),$$

$$\frac{dS_i}{dt} = -k_{s0}S_i + k_{s1}A_i - \eta(S_i - S_e),$$

$$S_e = \frac{k_{\text{diff}}}{k_{\text{se}} + k_{\text{diff}}}\bar{S} = Q\bar{S}.$$



1. Experimentally implemented synchronization of synthetic genetic networks.

nature Vol 463 | 21 January 2010 | doi:10.1038/nature08753

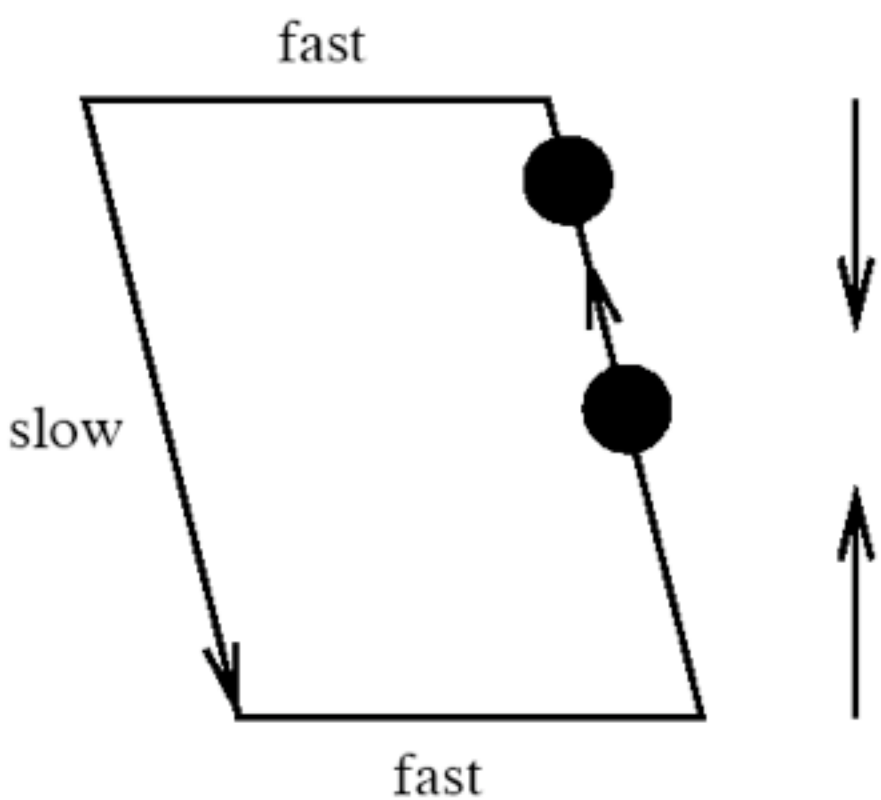
ARTICLES

A synchronized quorum of genetic clocks

Tal Danino[1]*, Octavio Mondragón-Palomino[1]*, Lev Tsimring[2] & Jeff Hasty[1,2,3]

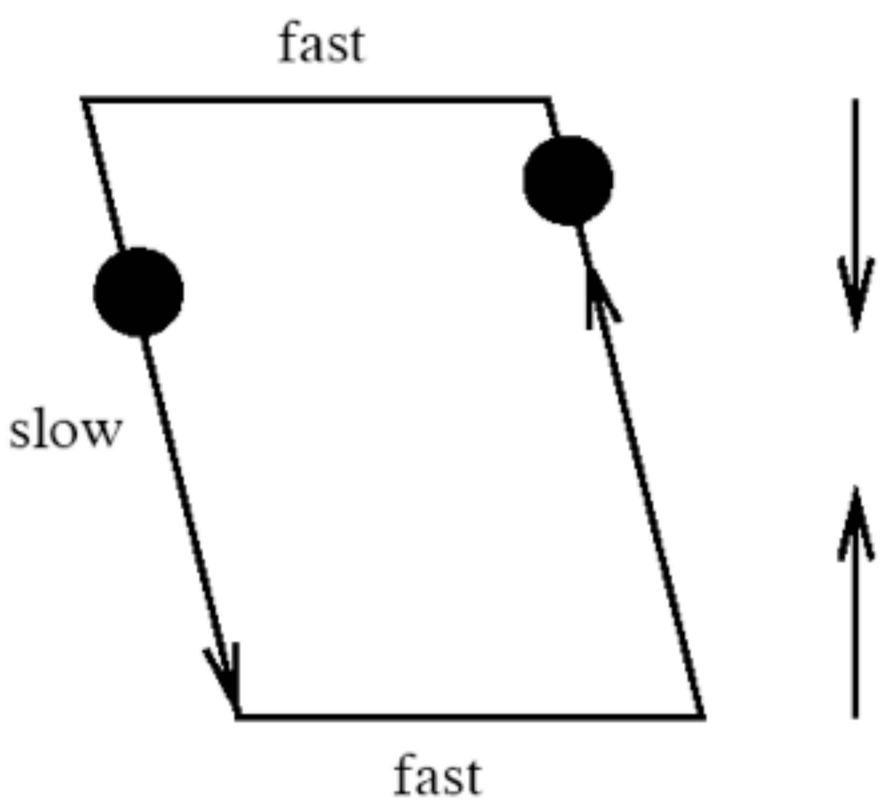
Desynchronization

Autoinducer coupling - Phase repulsive coupling



- Autoinducer coupling - slow timescale in a system with fast and slow dynamics
- Hence: phase-repulsive or inhibitory coupling
- Immanent multistability, multirhythmicity or clustering, found in: logistic and circle maps (K. Kaneko 1990), biological oscillators (K. Tsaneva-Atanasova, et.al. 2006, V. In, et al. 2003), phase identical oscillators (K. Okuda 1993, D. Colomb et al 1992), also experimentally in salt-water (K. Miyaakawa et al 2001) and electrochemical oscillators (J.L. Hudson et al 2001).
- Not reported for concrete genetic networks
- Multistability and clustering in synthetical genetic oscillators?

Autoinducer coupling - Phase repulsive coupling



- Autoinducer coupling - slow timescale in a system with fast and slow dynamics
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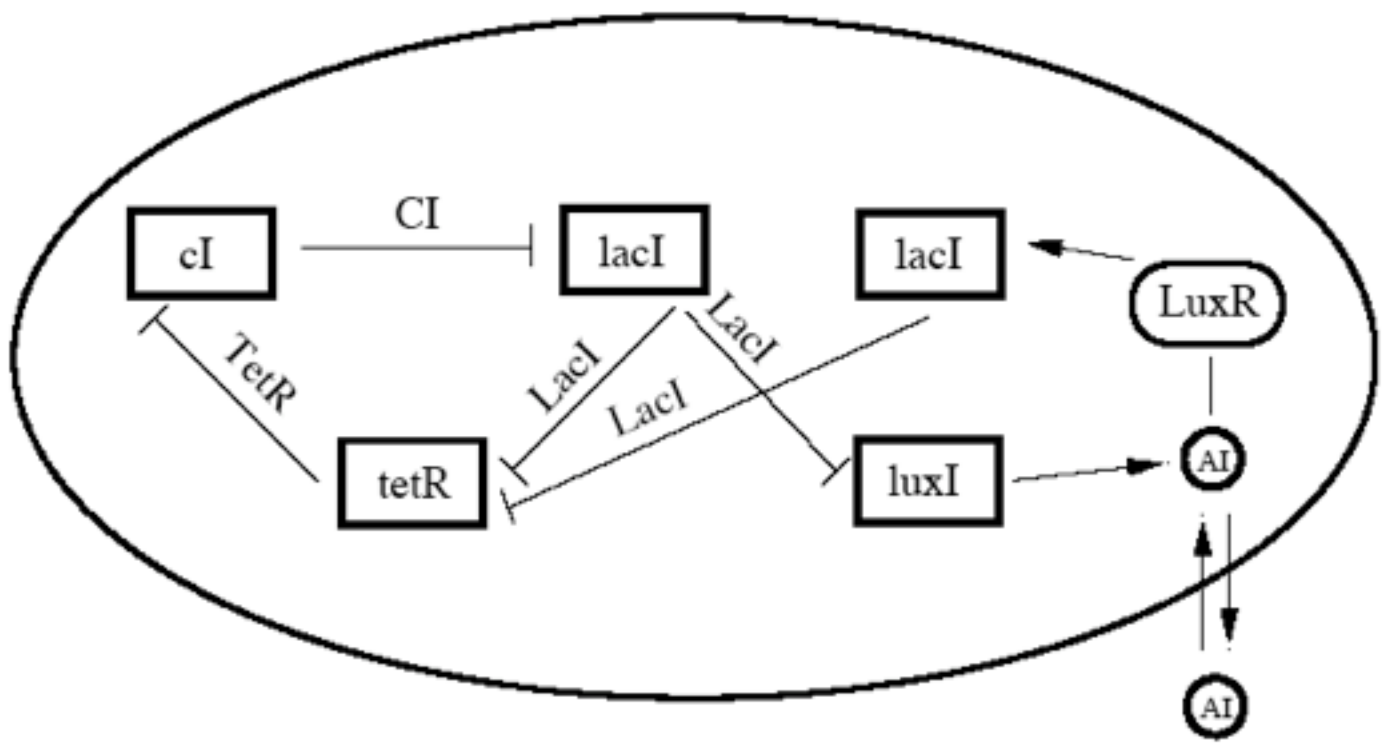
- Not reported for concrete genetic networks
- Multistability and clustering in synthetical genetic oscillators?

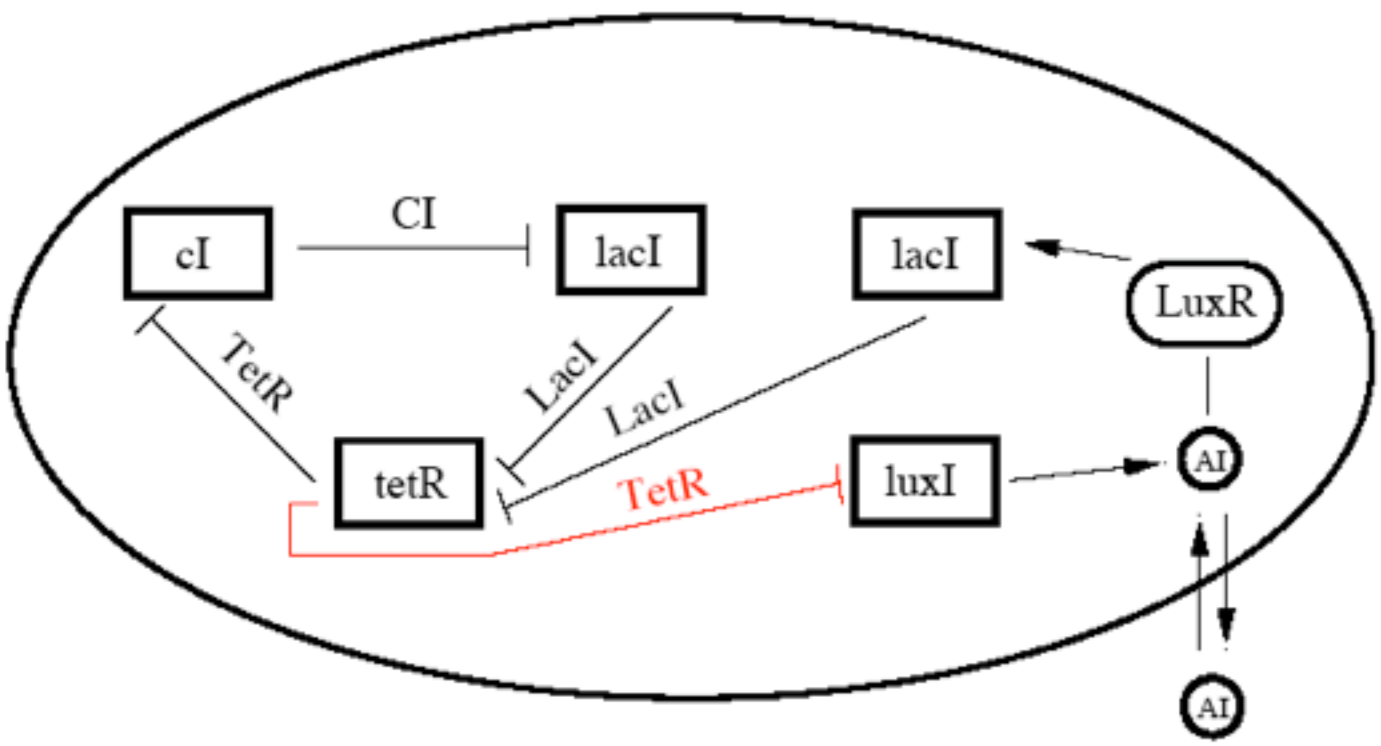
The repressilator with quorum sensing



M.B. Elowitz and S Leibner, *Nature* **405**, p. 335, 2000.

J. García-Ojalvo, M.B. Elowitz and S.H. Strogatz, *PNAS* **101**, p. 10955, 2004.

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



PRL 99, 148103 (2007) PHYSICAL REVIEW LETTERS week ending 5 OCTOBER 2007

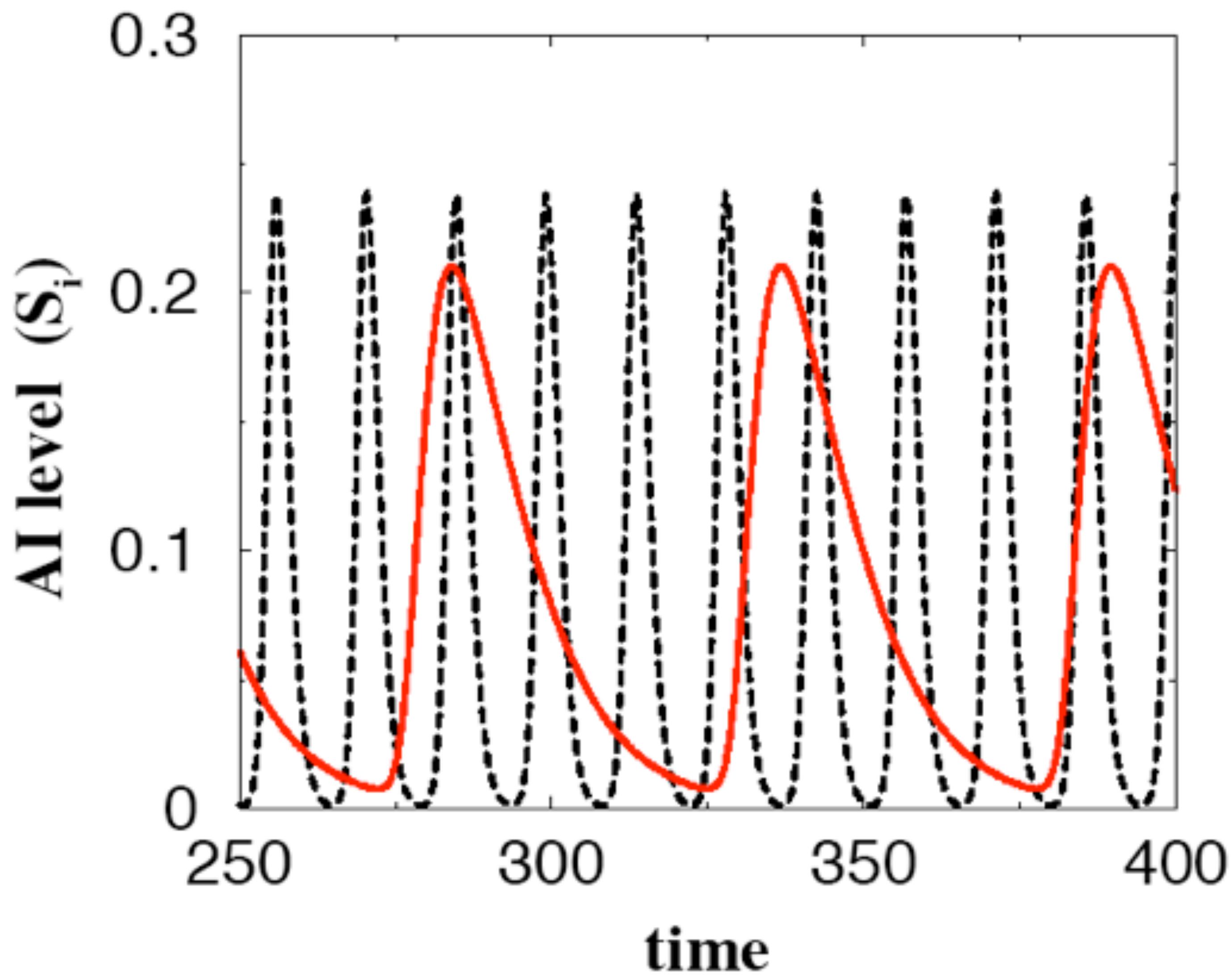
Multistability and Clustering in a Population of Synthetic Genetic Oscillators via Phase-Repulsive Cell-to-Cell Communication

Ekkehard Ullner,[1] Alexei Zaikin,[2] Evgenii I. Volkov,[3] and Jordi García-Ojalvo[1]
[1]*Departament de Física i Enginyeria Nuclear, Universitat Politècnica de Catalunya, Colom 11, E-08222 Terrassa, Spain*
[2]*Department of Mathematics, University of Essex, Wivenhoe Park, Colchester CO4 3SQ, United Kingdom*
[3]*Department of Theoretical Physics, Lebedev Physical Institute, Leninskii 53, Moscow, Russia*
(Received 16 April 2007; published 2 October 2007)

The modified repressilator model

$$
\begin{aligned}
\dot{a}_i &= -a_i + \frac{\alpha}{1+C_i^n} && tetR \\
\dot{b}_i &= -b_i + \frac{\alpha}{1+A_i^n} && cI \\
\dot{c}_i &= -c_i + \frac{\alpha}{1+B_i^n} + \kappa \frac{S_i}{1+S_i} && lacI \\
\dot{A}_i &= \beta_a (a_i - A_i) && TetR \\
\dot{B}_i &= \beta_b (b_i - B_i) && CI \\
\dot{C}_i &= \beta_c (c_i - C_i) && LacI \\
\dot{S}_i &= -k_{s0} S_i + k_{s1} B_i - \eta (S_i - Q\bar{S}) && \text{auto inducer}
\end{aligned}
$$

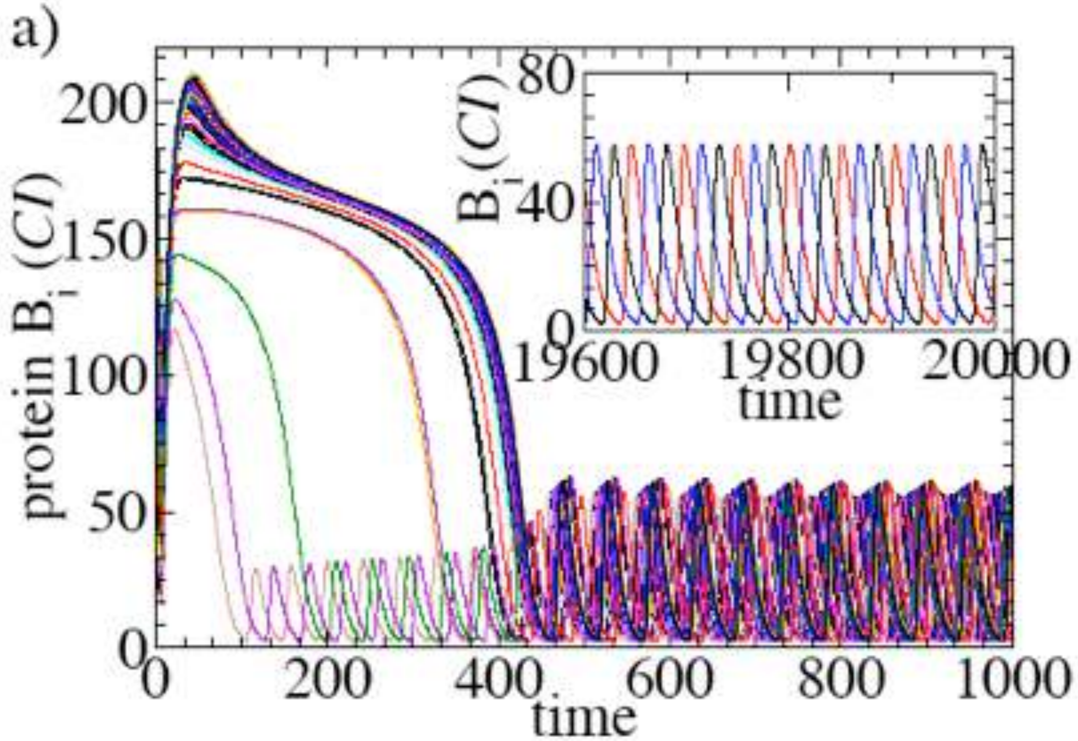
The new time series with the slow-fast dynamics



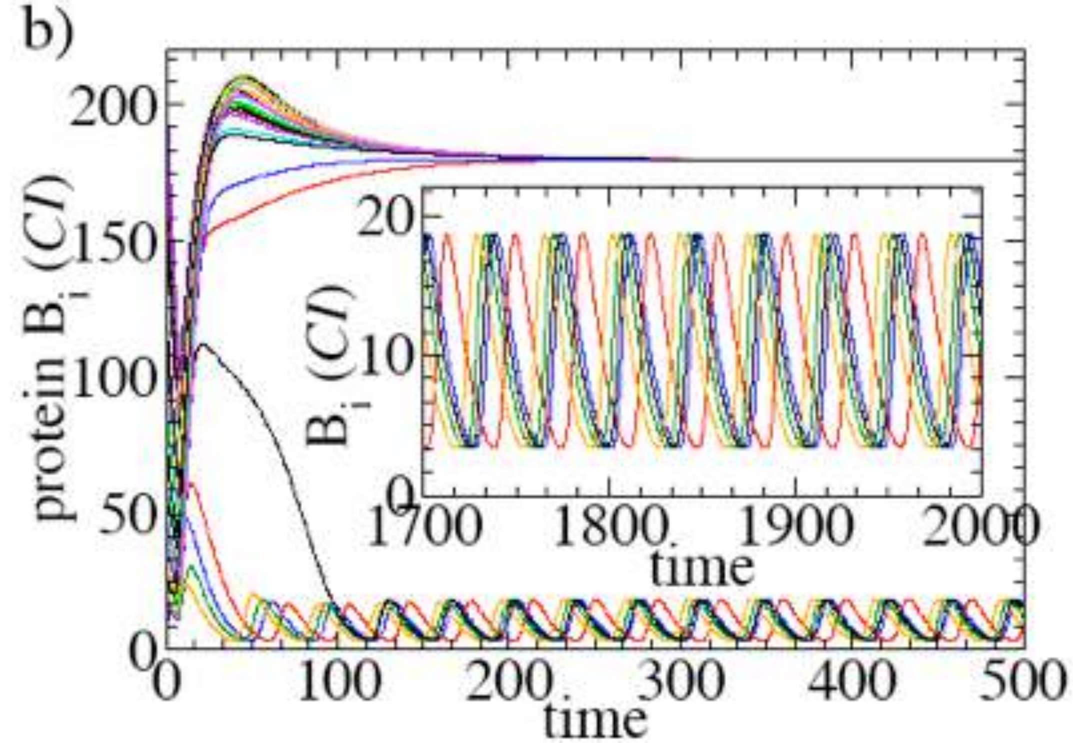
Two time scales in the AI dynamics

The stable dynamic regimes

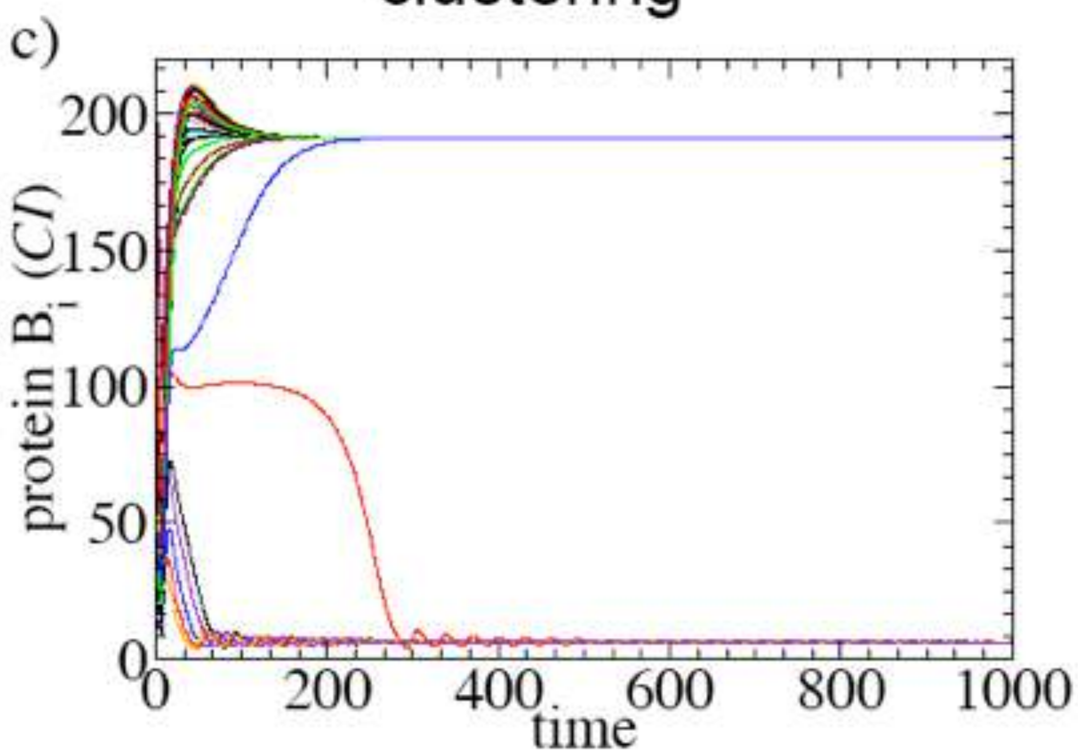
oscillatory



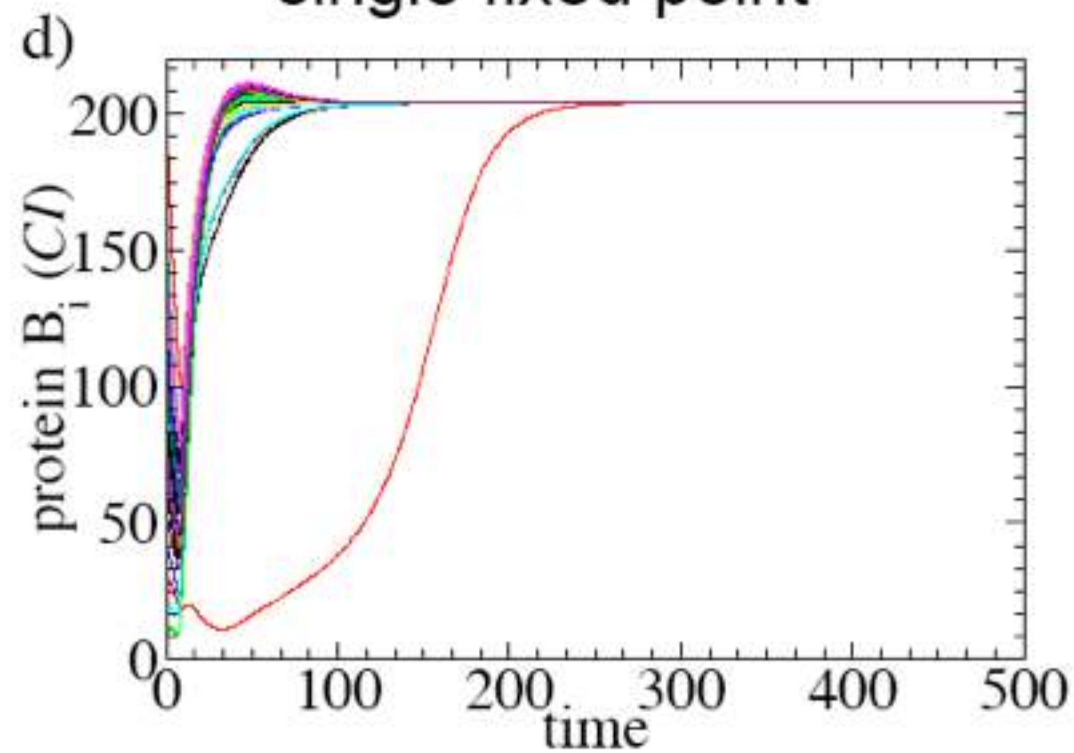
inhomogen limit cycle



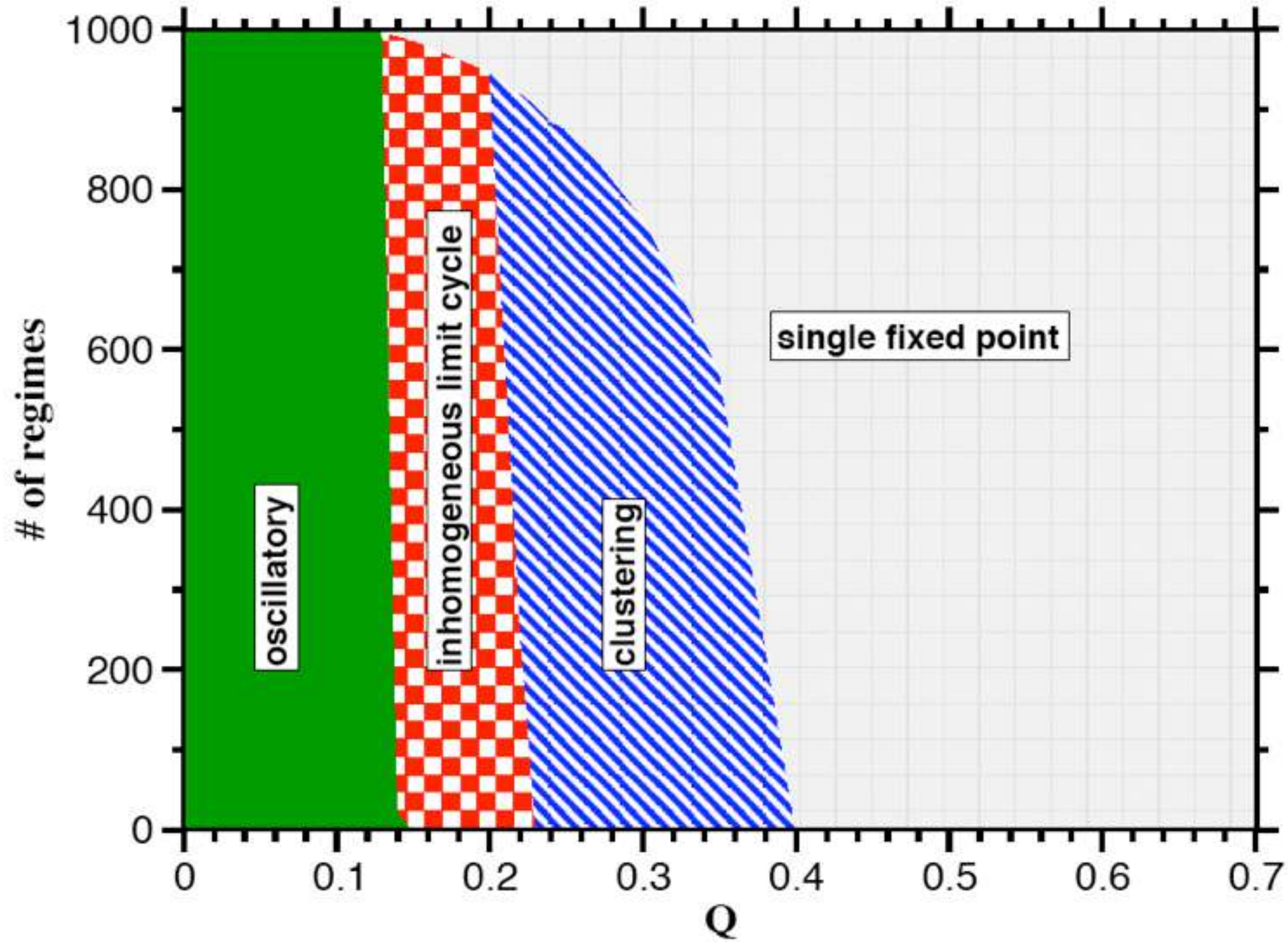
clustering



single fixed point

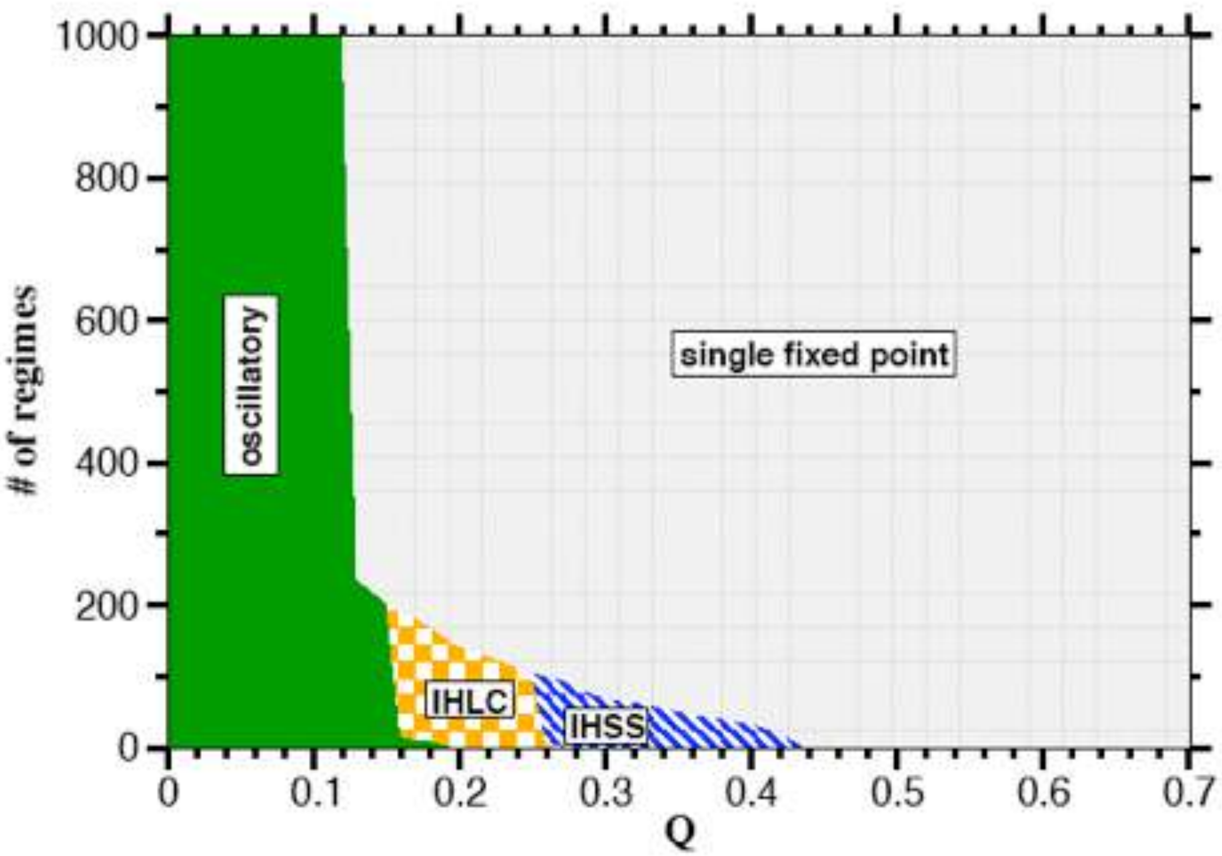


Multistability by varying cell density

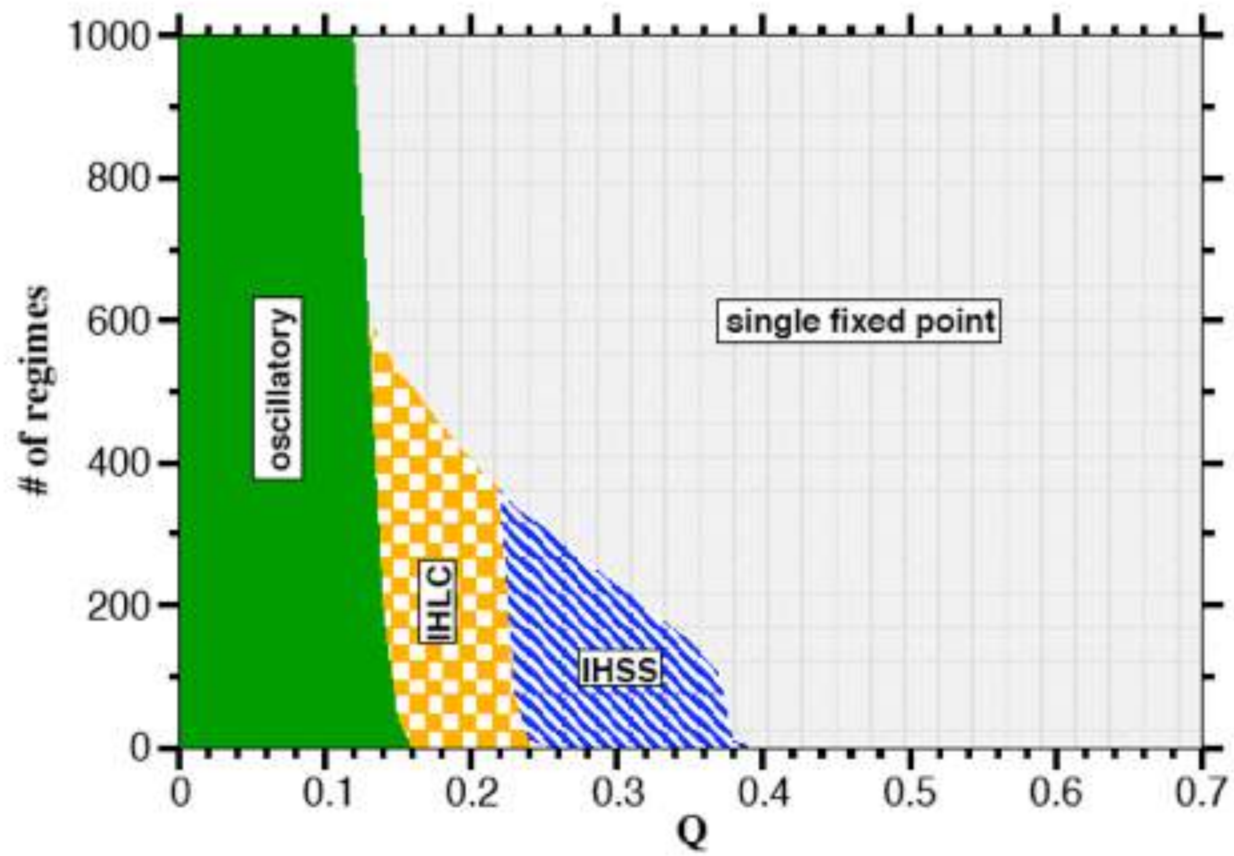


The system size effect

N=5



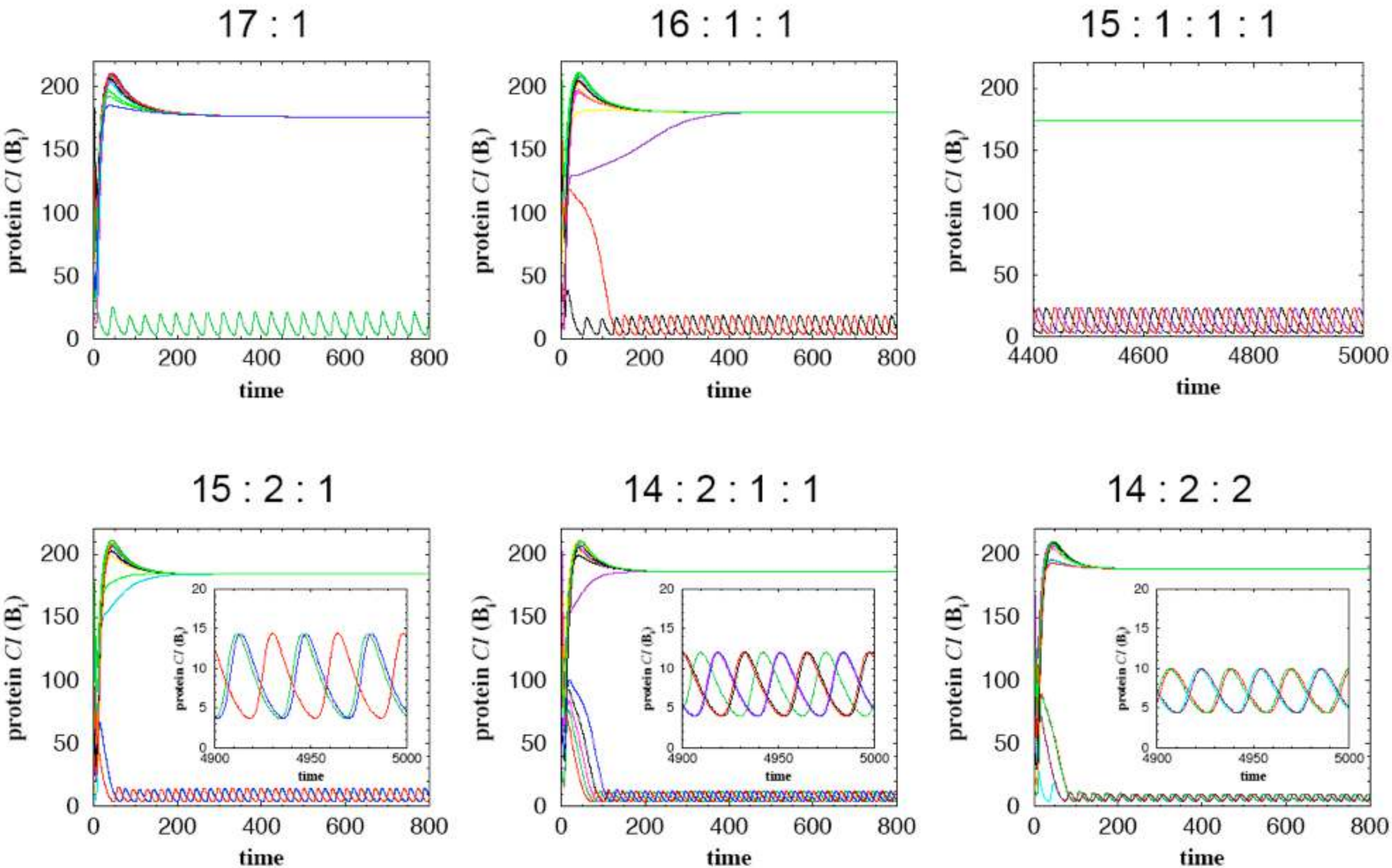
N=18



The artificial differentiation (IHLC, IHSS) becomes more likely in large ensembles

The system size influences the position of IHLC and IHSS

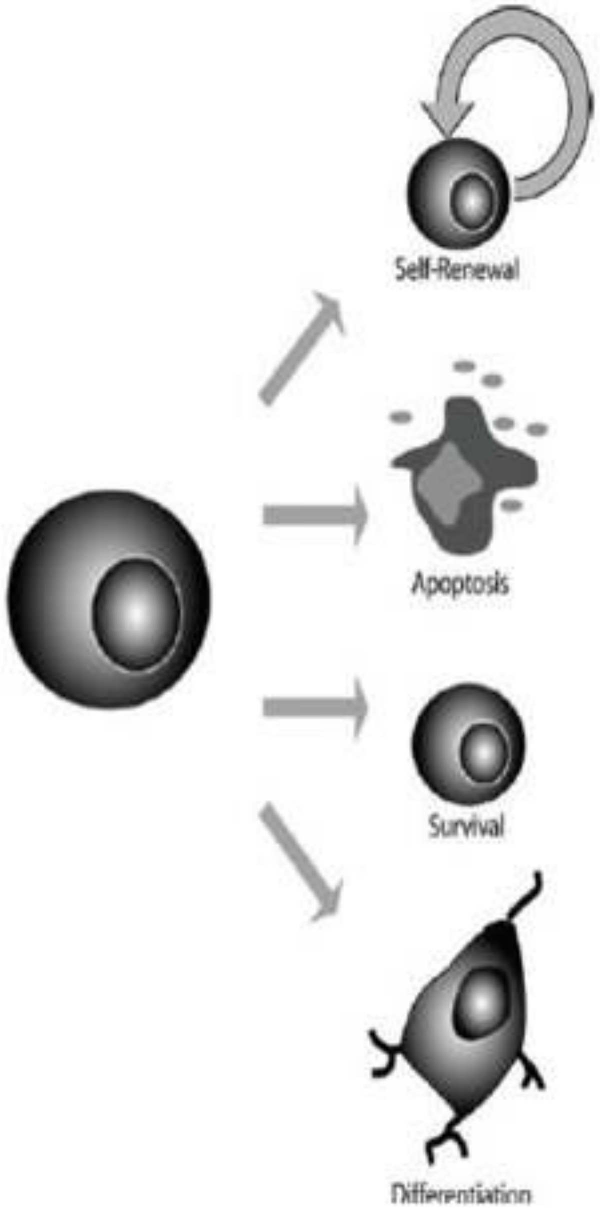
Some details of the differentiation



Making decision:
Speed dependent effects
in noisy switches

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**.



Epigenetic decision making

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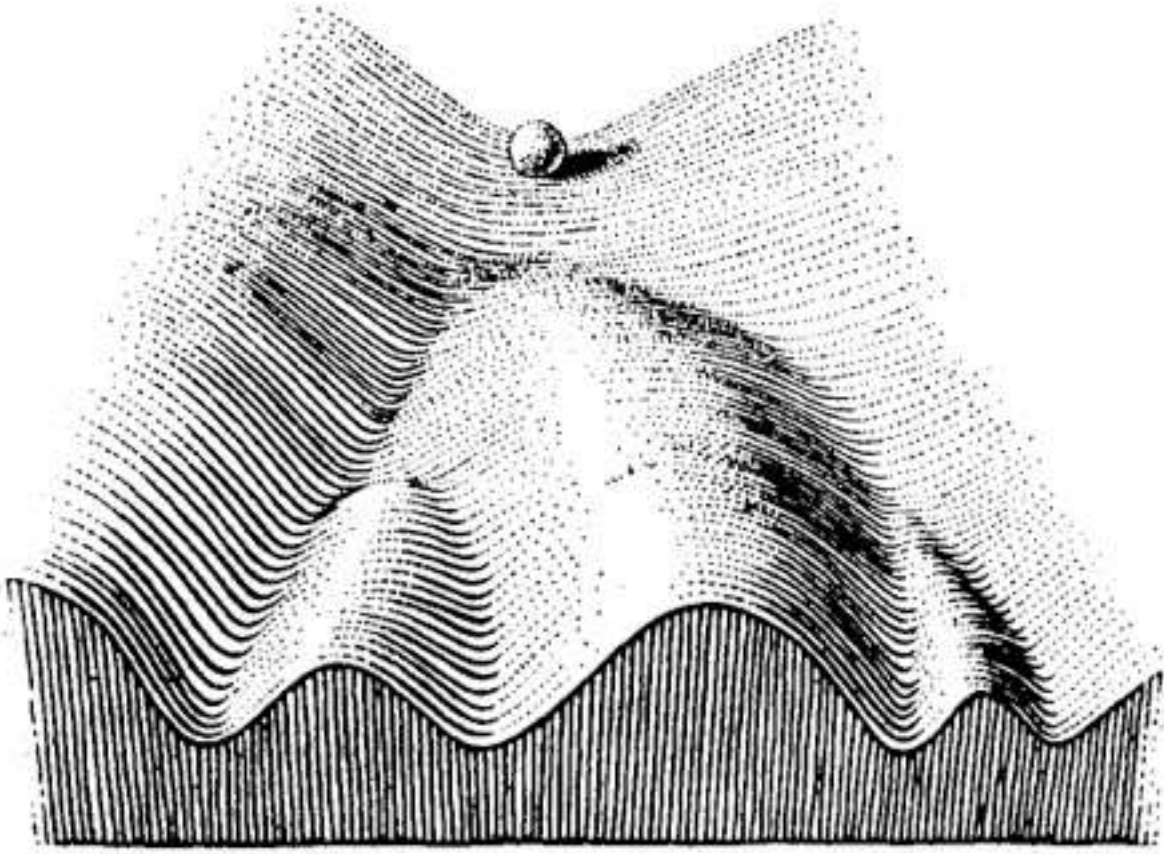
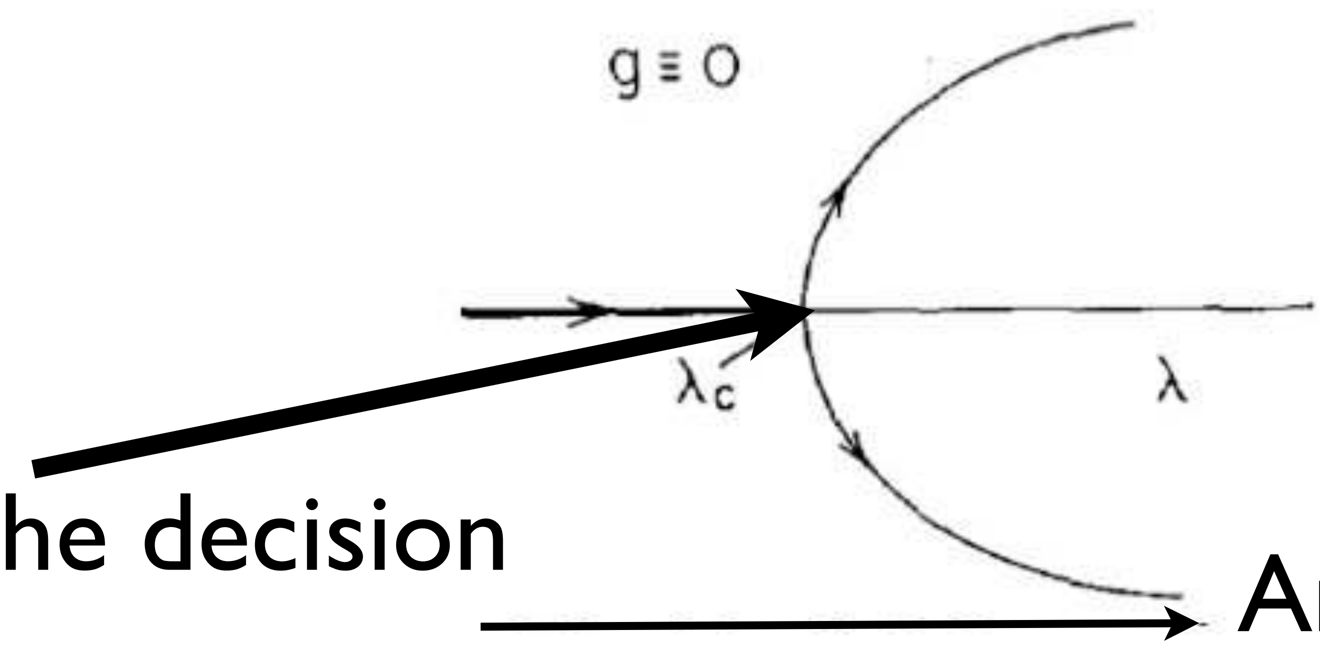


One decision



Point of the decision

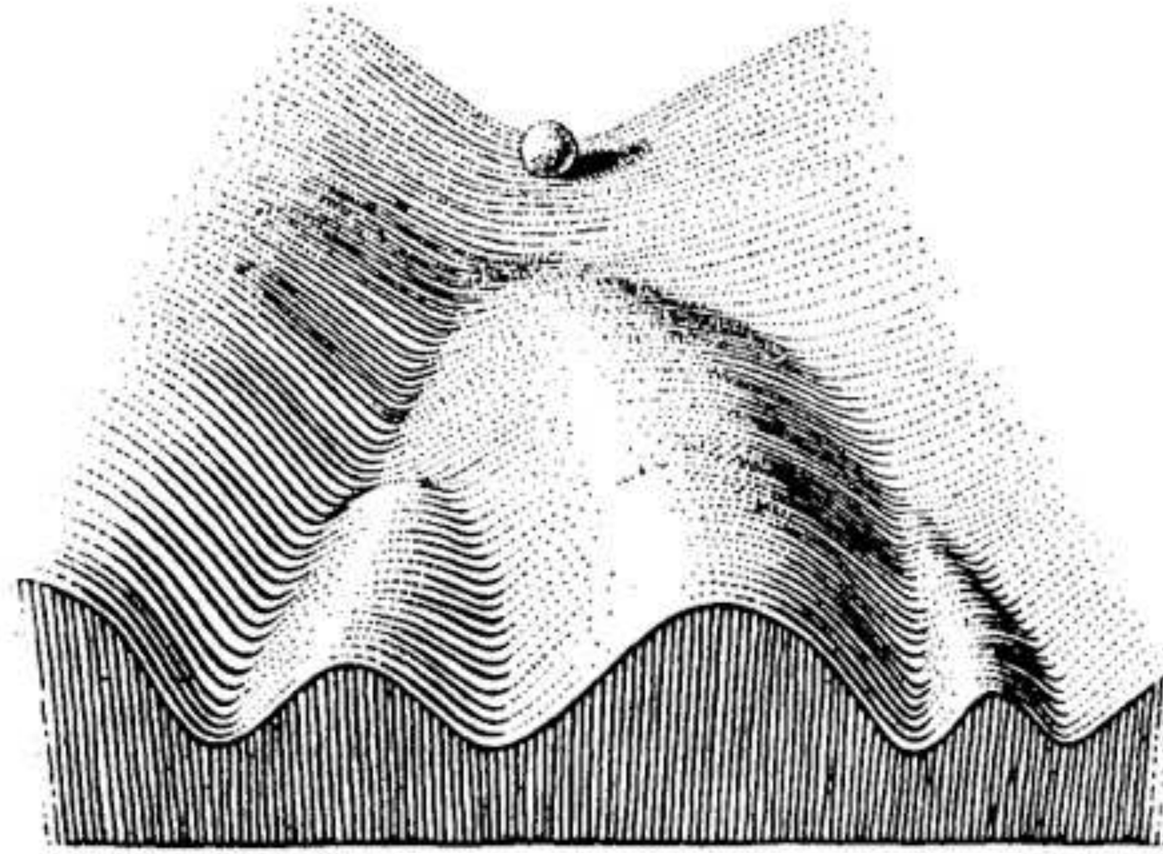
Another desicion

Parameter

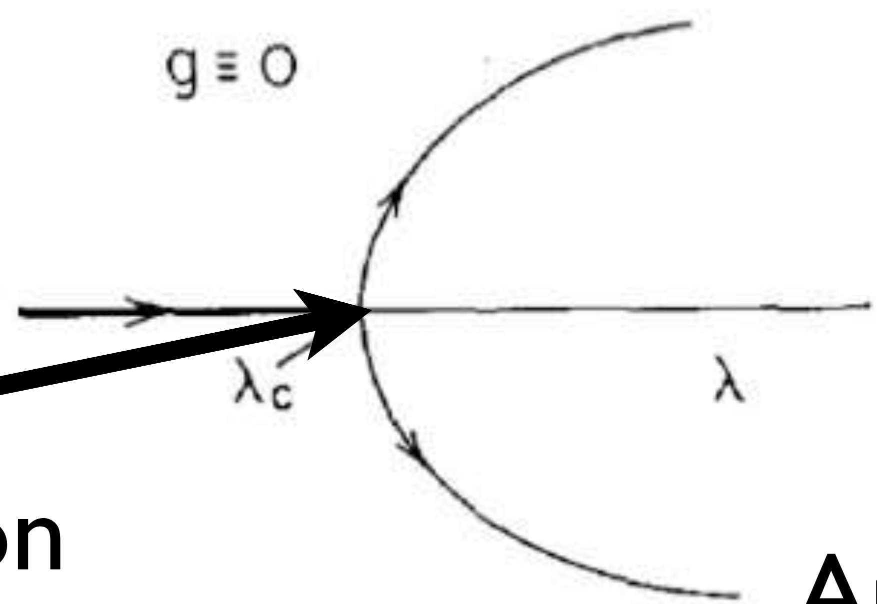
Epigenetic decision making

Timing matters!

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



One decision



Point of the decision

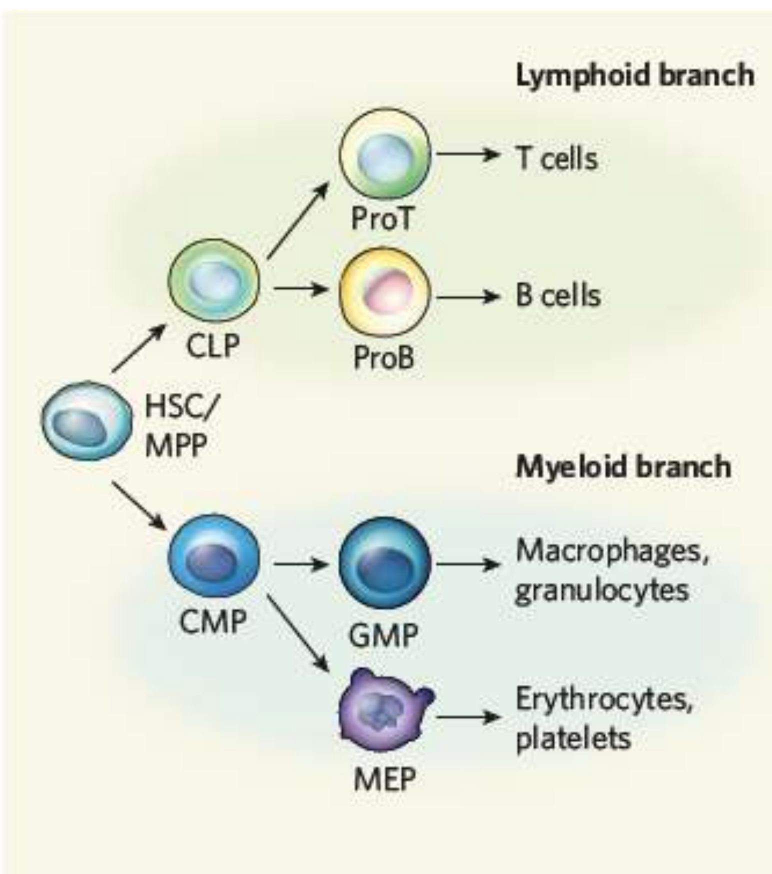
Another desicion

Parameter

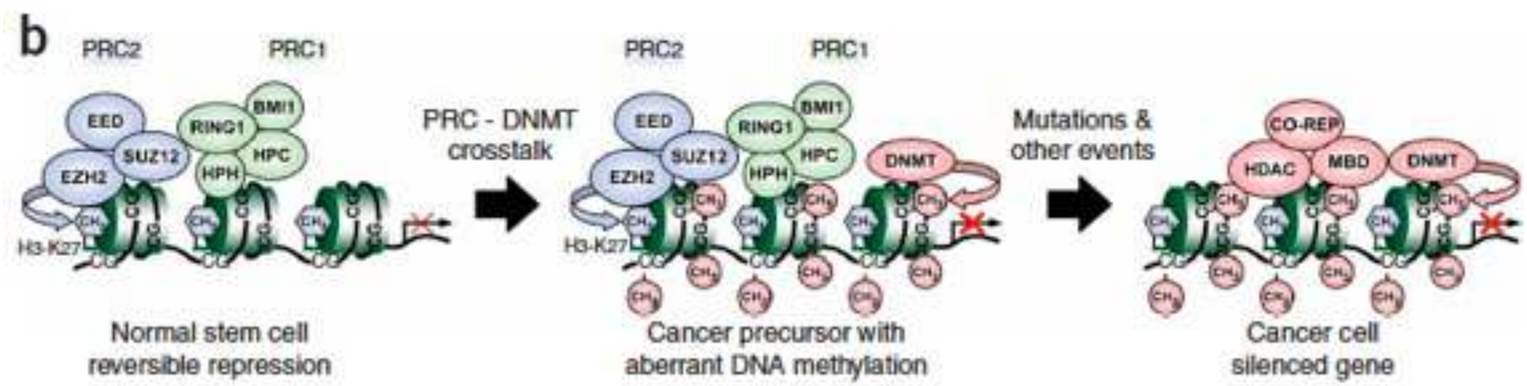
Where important:

Understanding of natural cell differentiation circuits

Differentiation of progenitors in immune systems (Graf 2008)

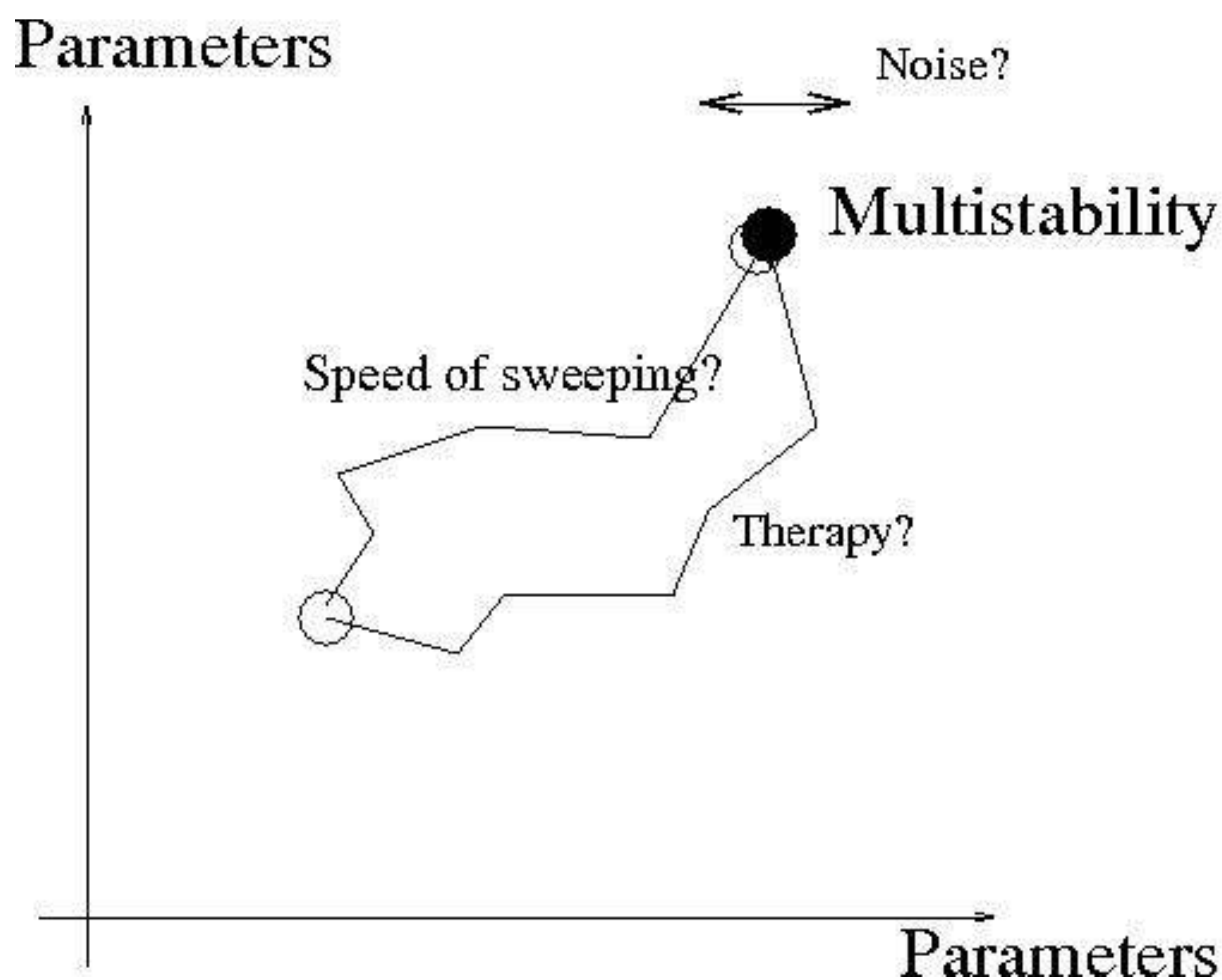


- DNA Methylation signature is different in cancer in networks responsible for stem cell differentiation

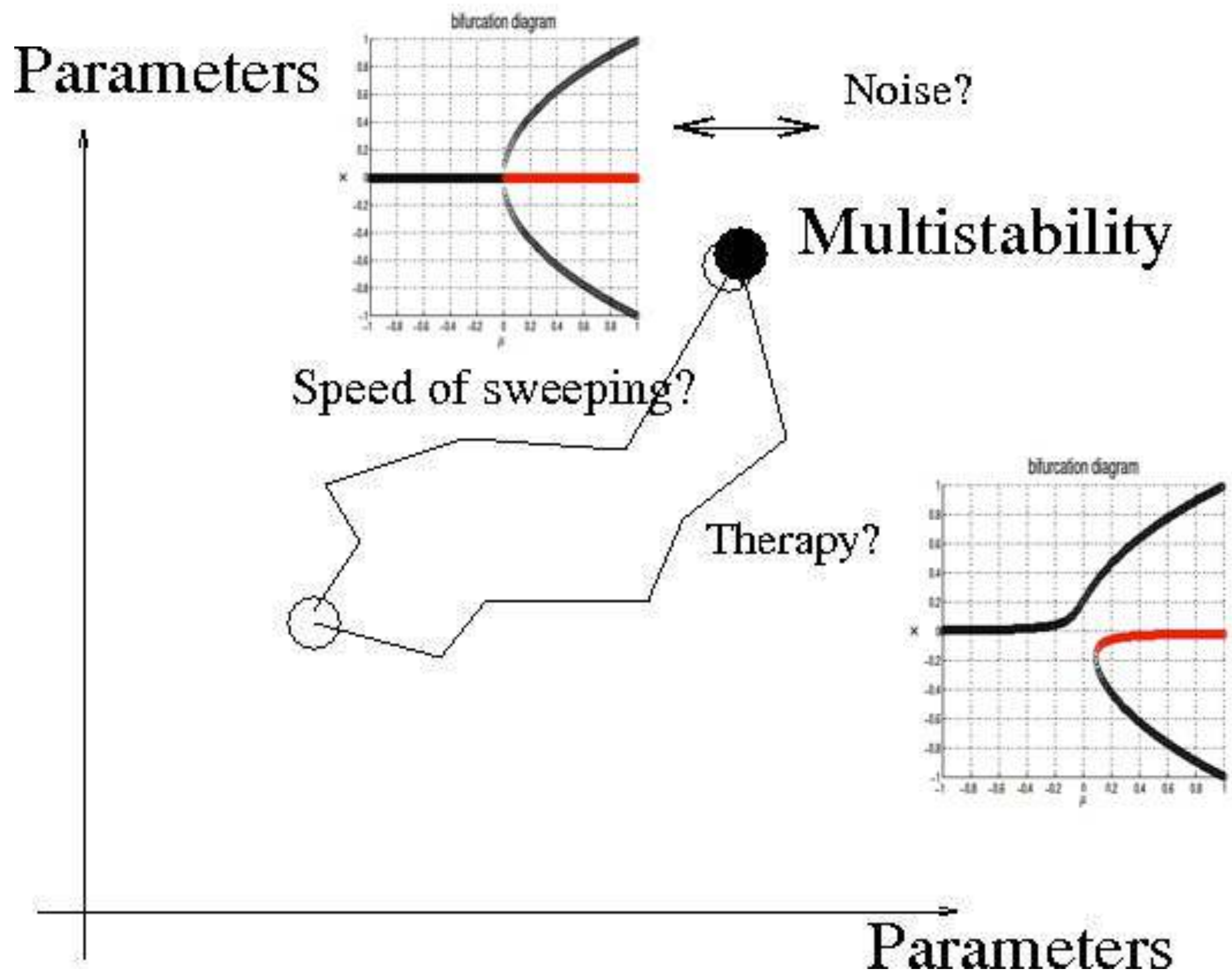


From M. Widschwendter et al, Nature Genetics (2006)

Design of therapies:

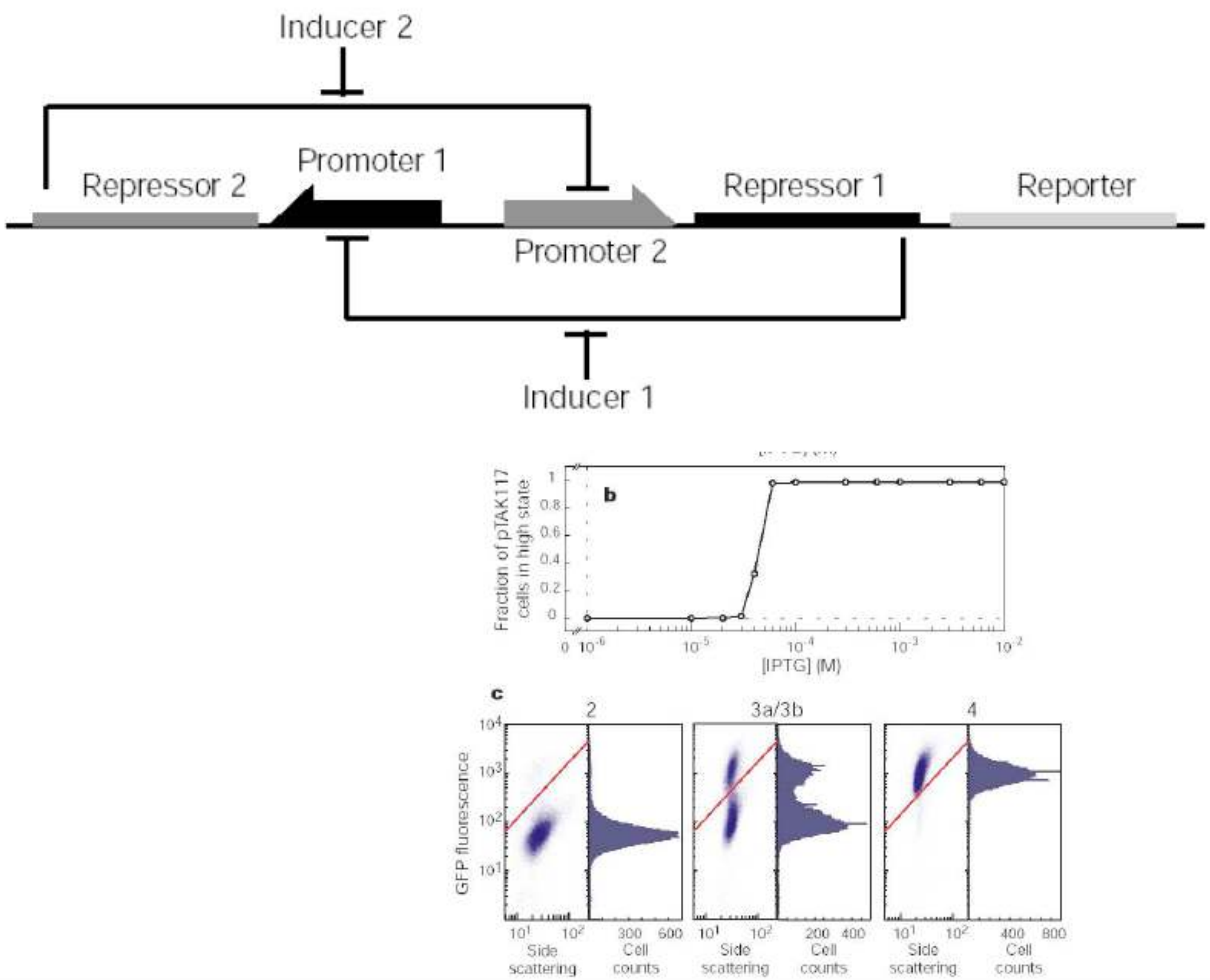


Design of therapies:



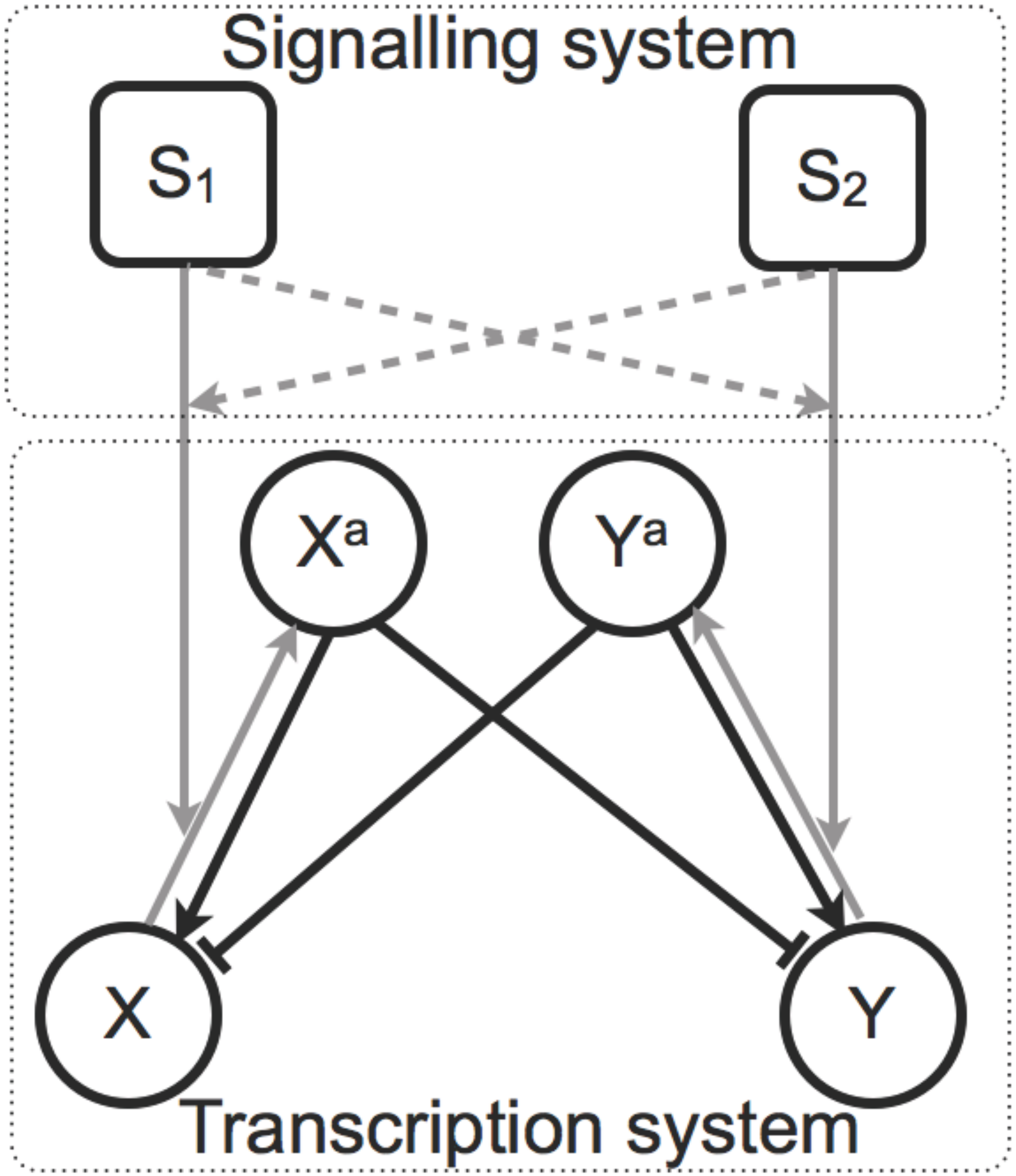
Let us consider paradigmatic genetic switch

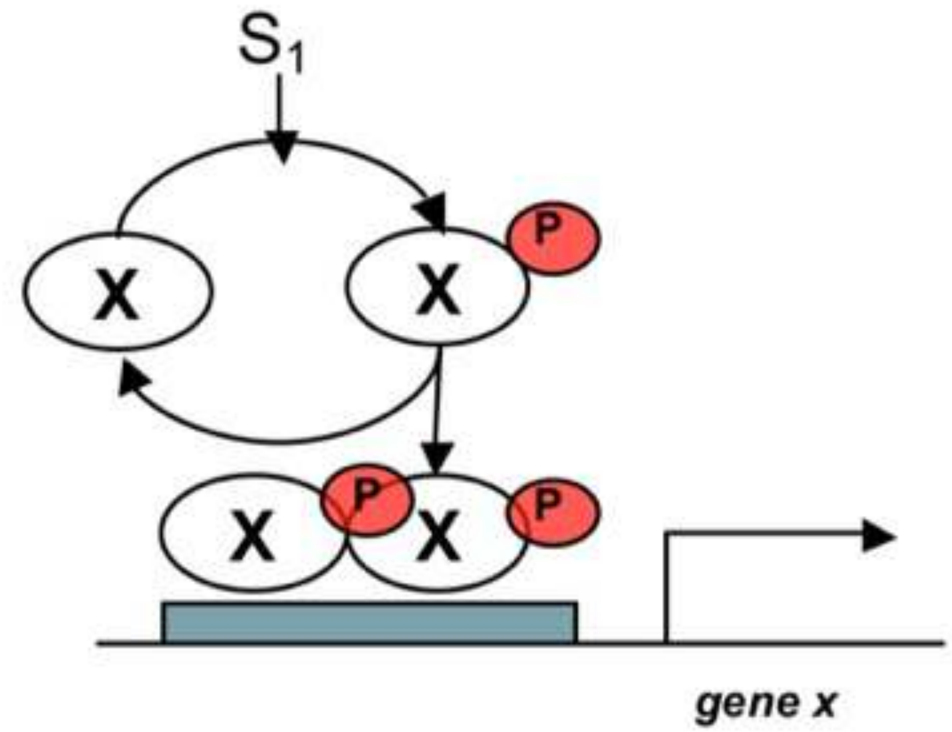
The Genetic Switch in Bacteriophage λ

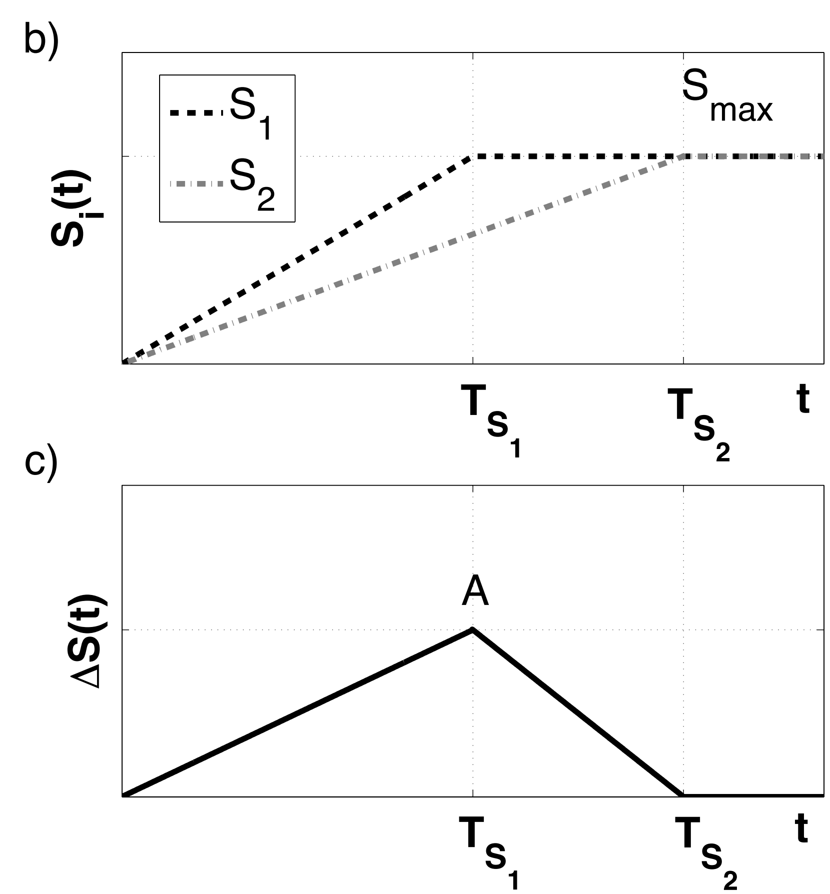


T. Gardner, C. Cantor, J.J. Collins , "Construction of a genetic toggle switch in Escherechia coli", Nature, 2000.

Let us consider the paradigmatic genetic switch:







Mathematical model:

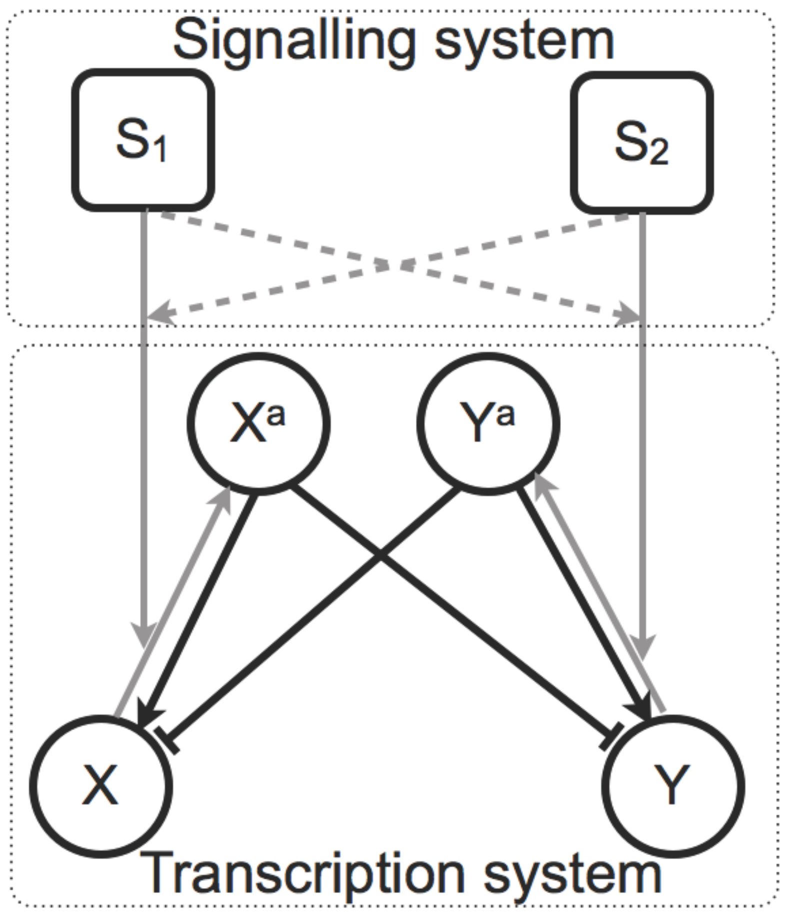
Activation or inhibition:

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

Phosporylation by external signals

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

a)



$$\begin{aligned}
\tau_a \dot{X^a} &= F_X(S_1, S_2) X - d_X X^a \\
\tau_a \dot{Y^a} &= F_Y(S_1, S_2) Y - d_Y Y^a \\
\dot{X} &= \frac{1}{\tau}(G(X^a, Y^a) - X) - \\
-\frac{1}{\tau_a} & \quad (F_X(S_1, S_2) X - d_X X^a) + \sigma_{X,Y} \xi_X(t) \\
\dot{Y} &= \frac{1}{\tau}(G(Y^a, X^a) - Y) - \\
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\end{aligned}$$

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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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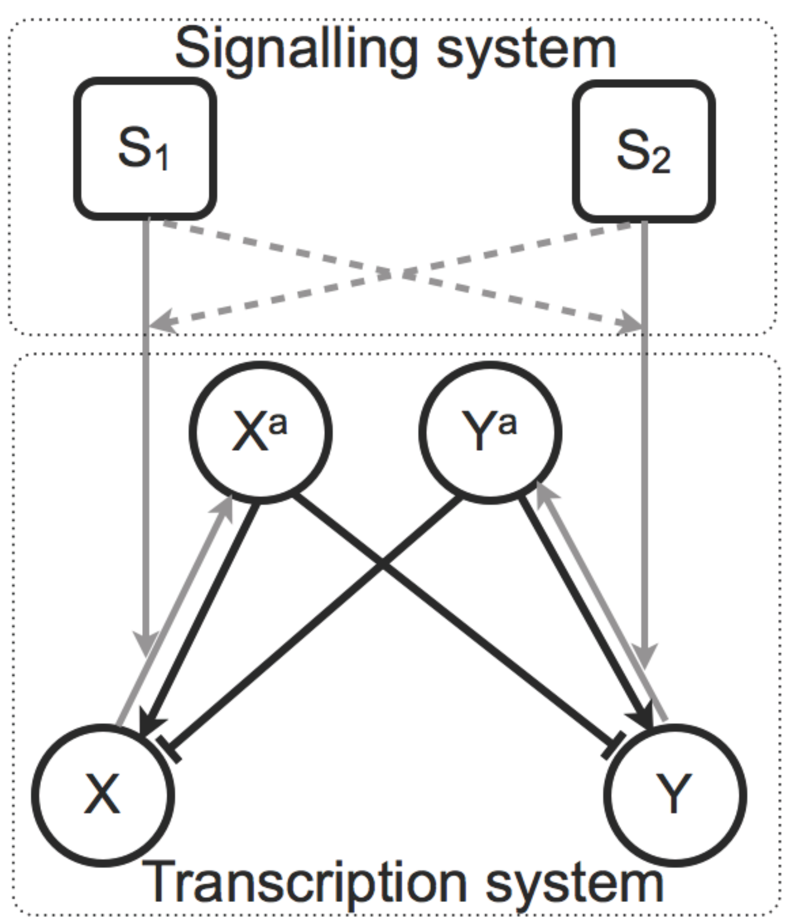

$$\tau_a \dot{X}^a = F_X(S_1, S_2) X - d_X X^a$$

$$\tau_a \dot{Y}^a = F_Y(S_1, S_2) Y - d_Y Y^a$$

$$\dot{X} = \frac{1}{\tau}(G(X^a, Y^a) - X) -$$

$$-\frac{1}{\tau_a} (F_X(S_1, S_2) X - d_X X^a) + \sigma_{X,Y} \xi_X(t)$$

$$\dot{Y} = \frac{1}{\tau}(G(Y^a, X^a) - Y) -$$

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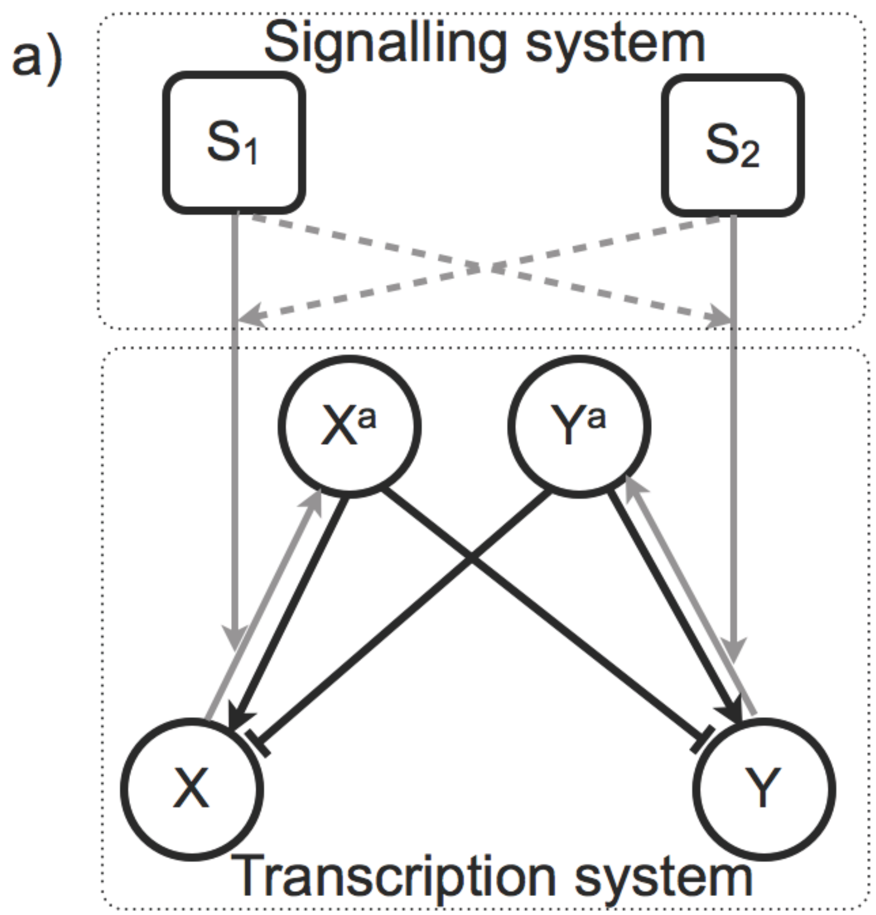

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Dephosporylation

Mathematical model:

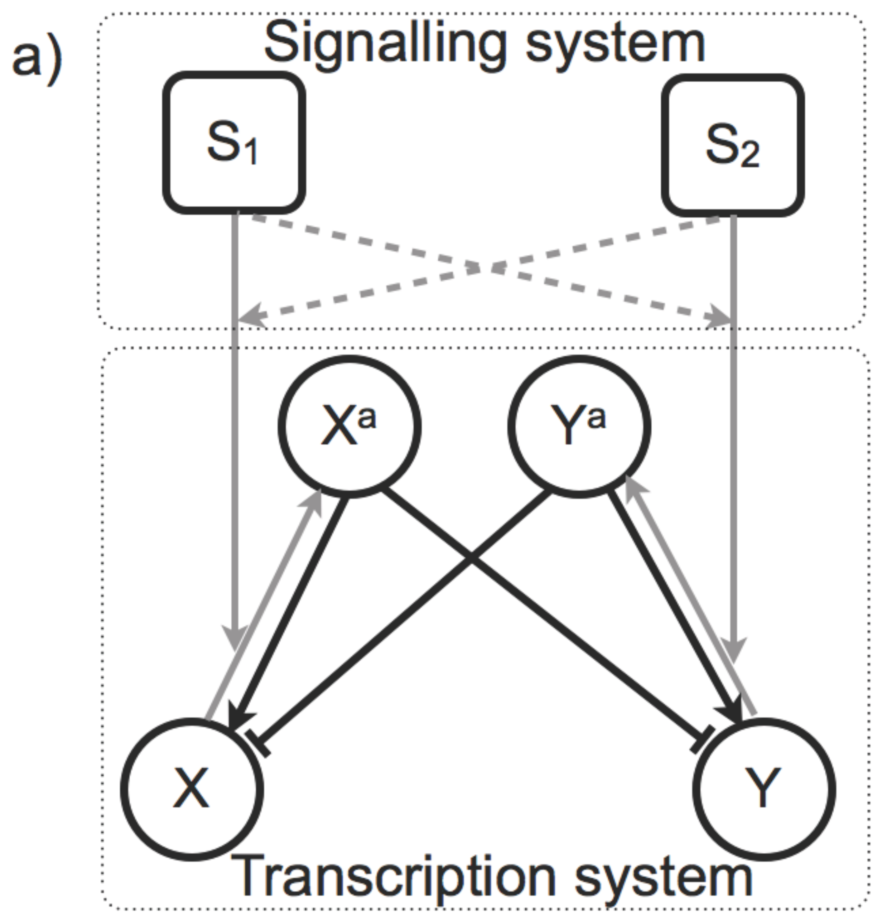
Activation or inhibition:

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

Phosporylation by external signals

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

Mutual Inhibition:



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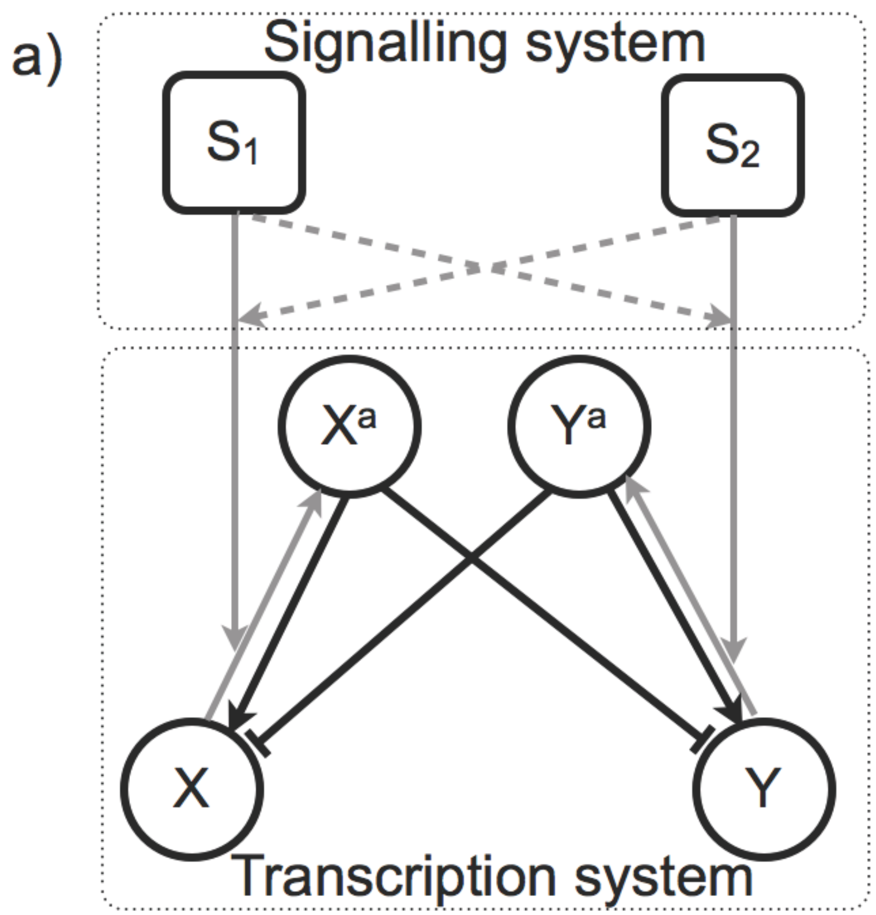

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-\frac{1}{\tau_a} & \quad (F_Y(S_1, S_2)Y + d_Y Y^a) + \sigma_{Y,X}\xi_Y(t),
\end{aligned}$$

Noise:

Mathematical model:

Activation or inhibition:

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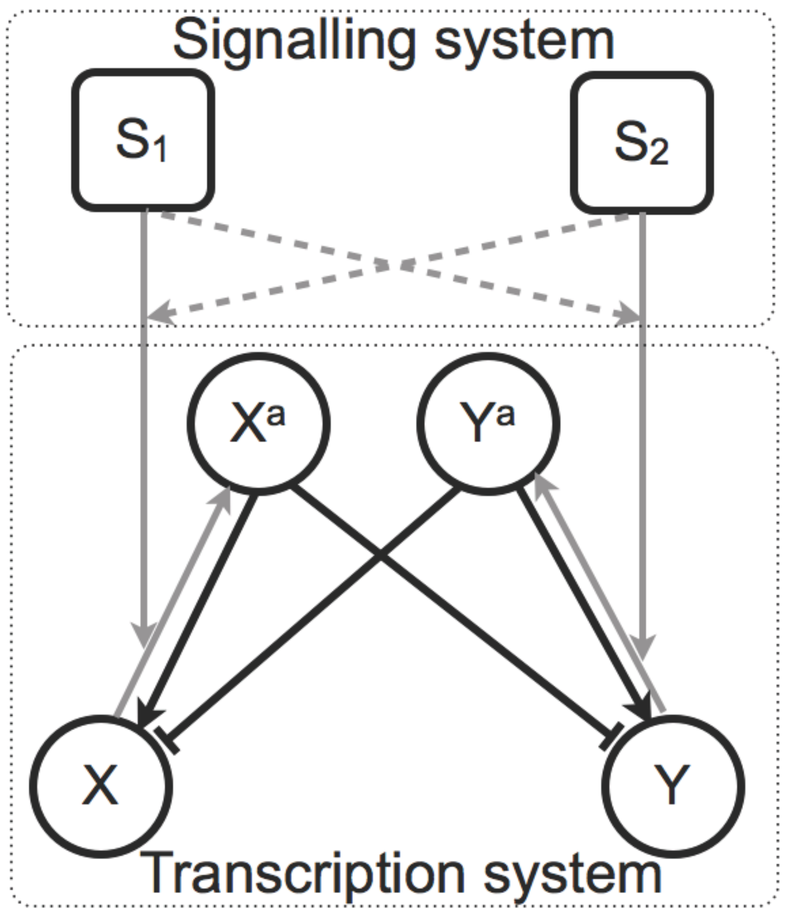

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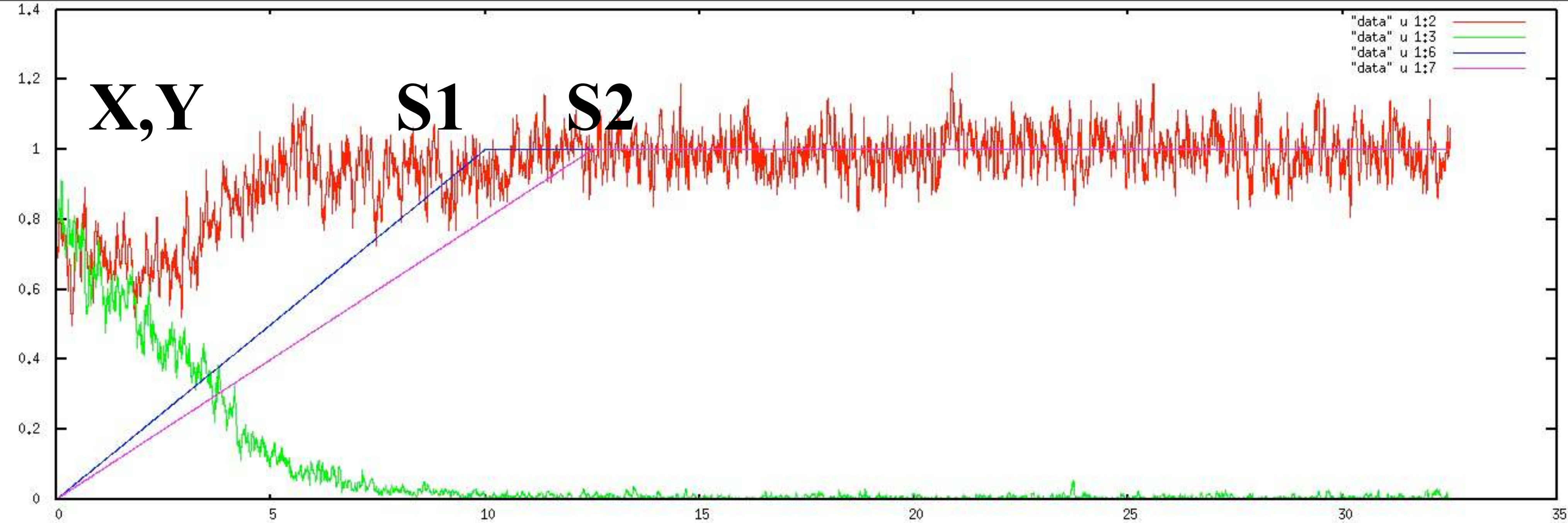
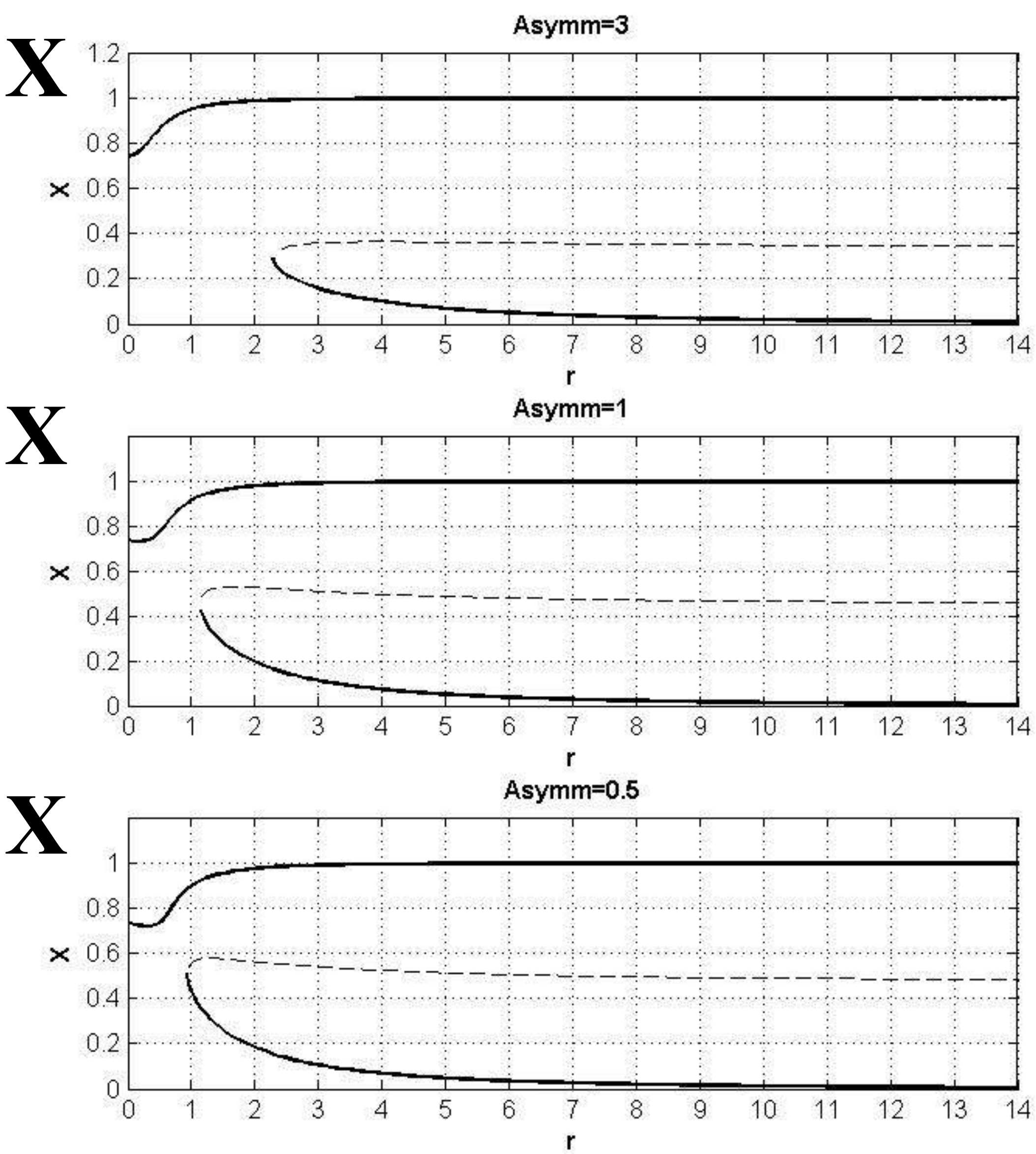
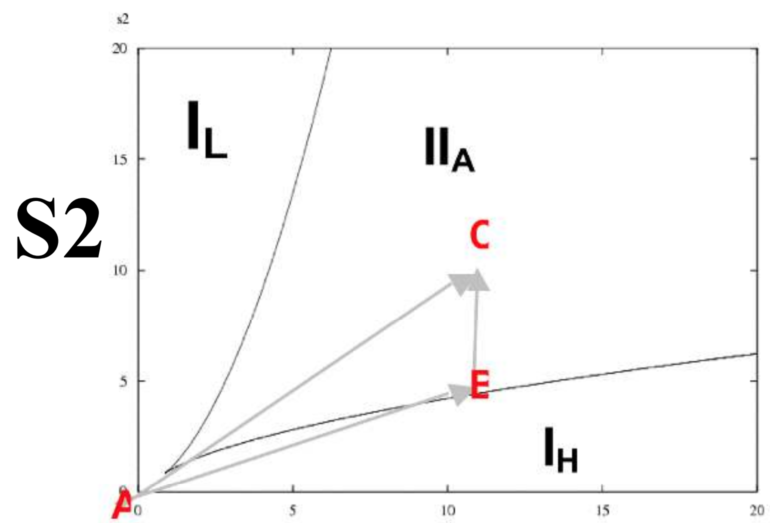
\end{aligned}$$

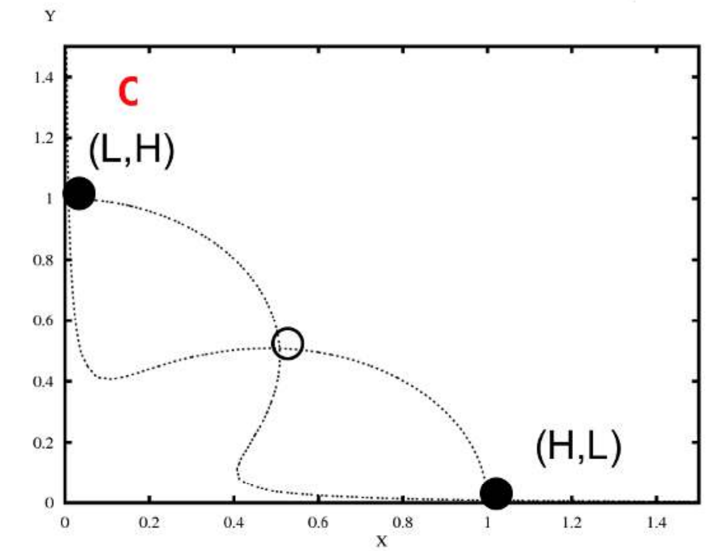
Noise:

Degradation


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


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


S2
I$_L$
II$_A$
C
E
I$_H$
A
s1
s2

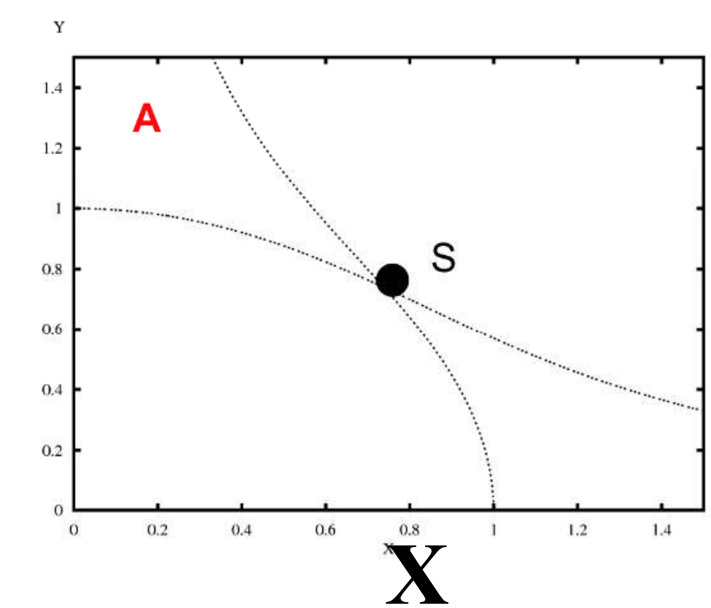

C
(L,H)
(H,L)
Y
X

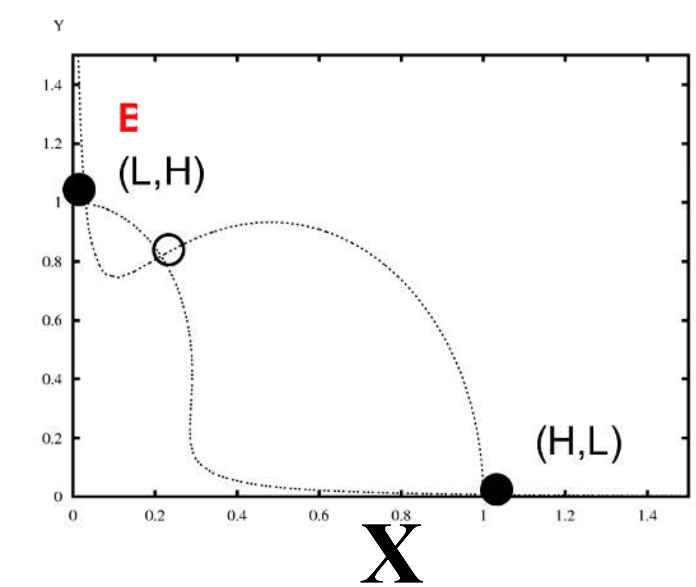
C

S1

D

X


A
S
Y
X


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

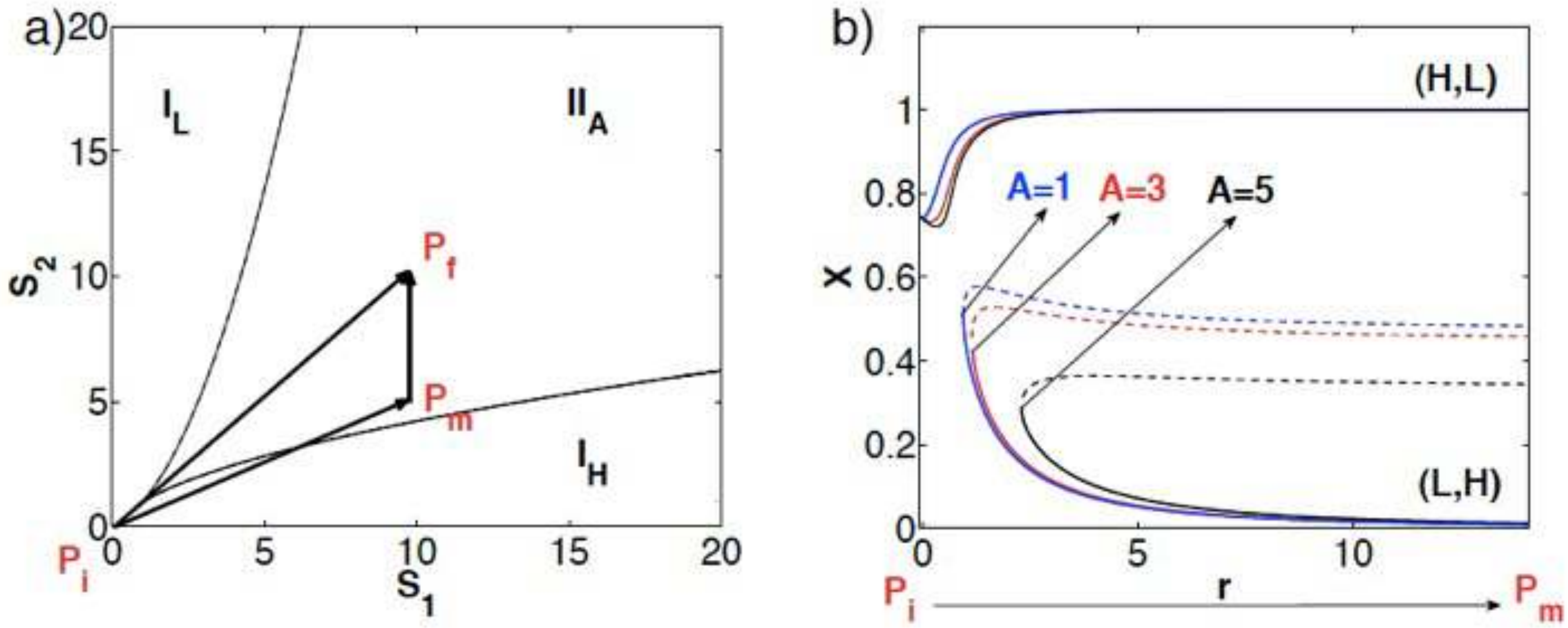


FIG. 2: Parameter analysis of the decision genetic switch with external stimulation. a) Phase diagram for X in space

So we have bifurcation, noise and asymmetry

What is known from statistical physics?

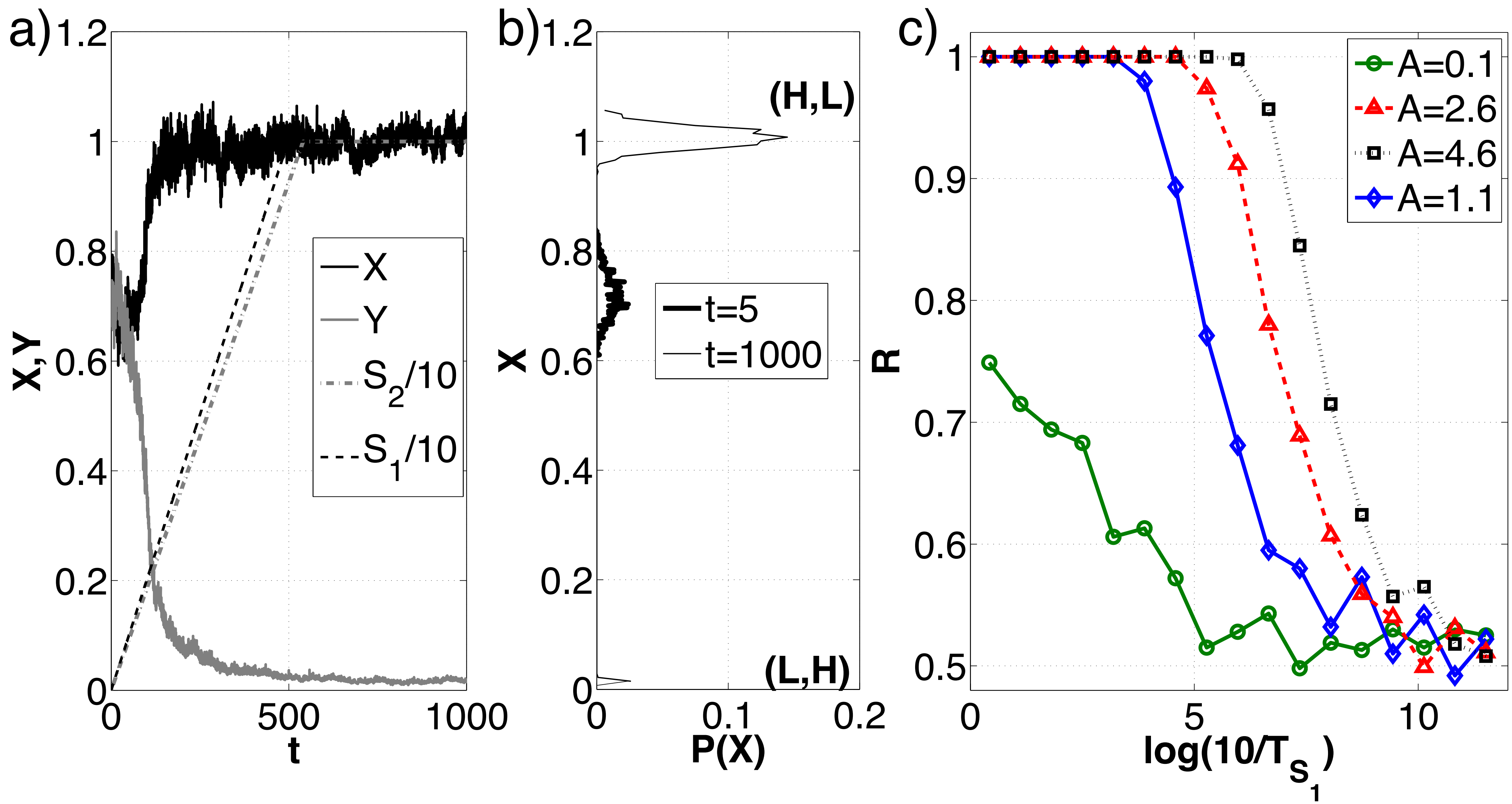
Delayed Bifurcation!

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)

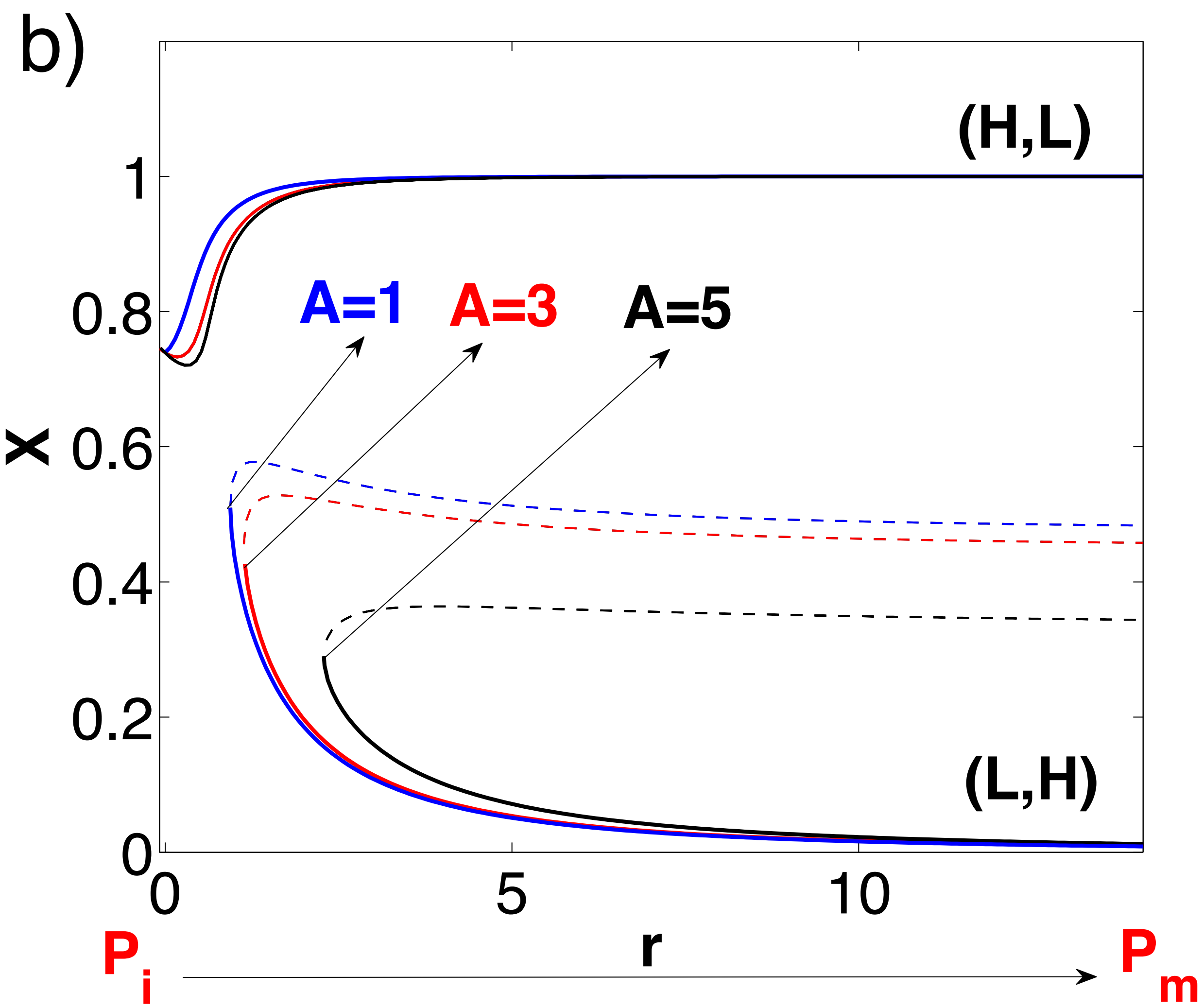


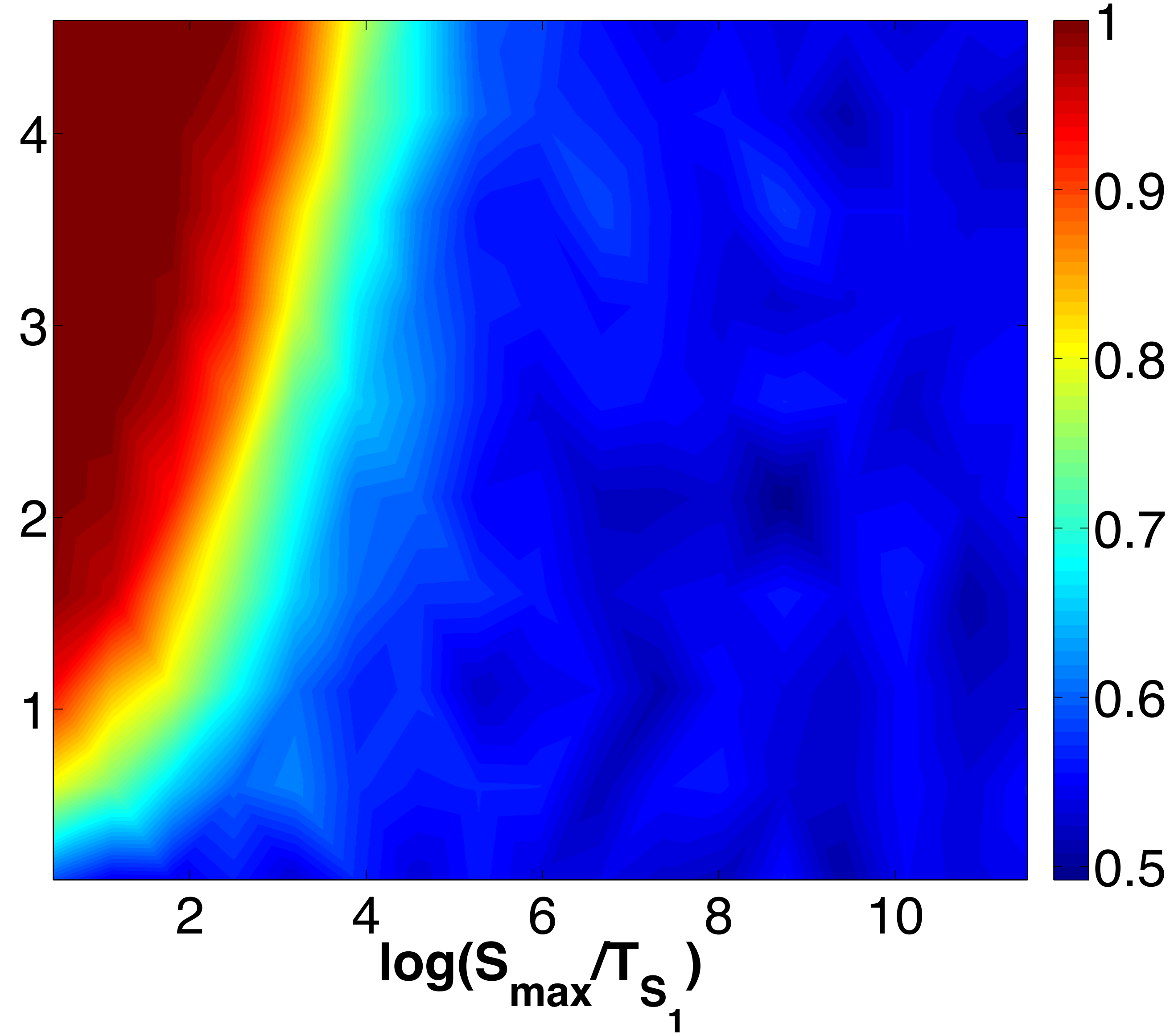
R is the ratio Ph/(Ph+Pl) where Ph is the probability to choose the upper branch, Pl - the lower one.

Speed- dependent Cellular decision making

Asymmetry

Ratio



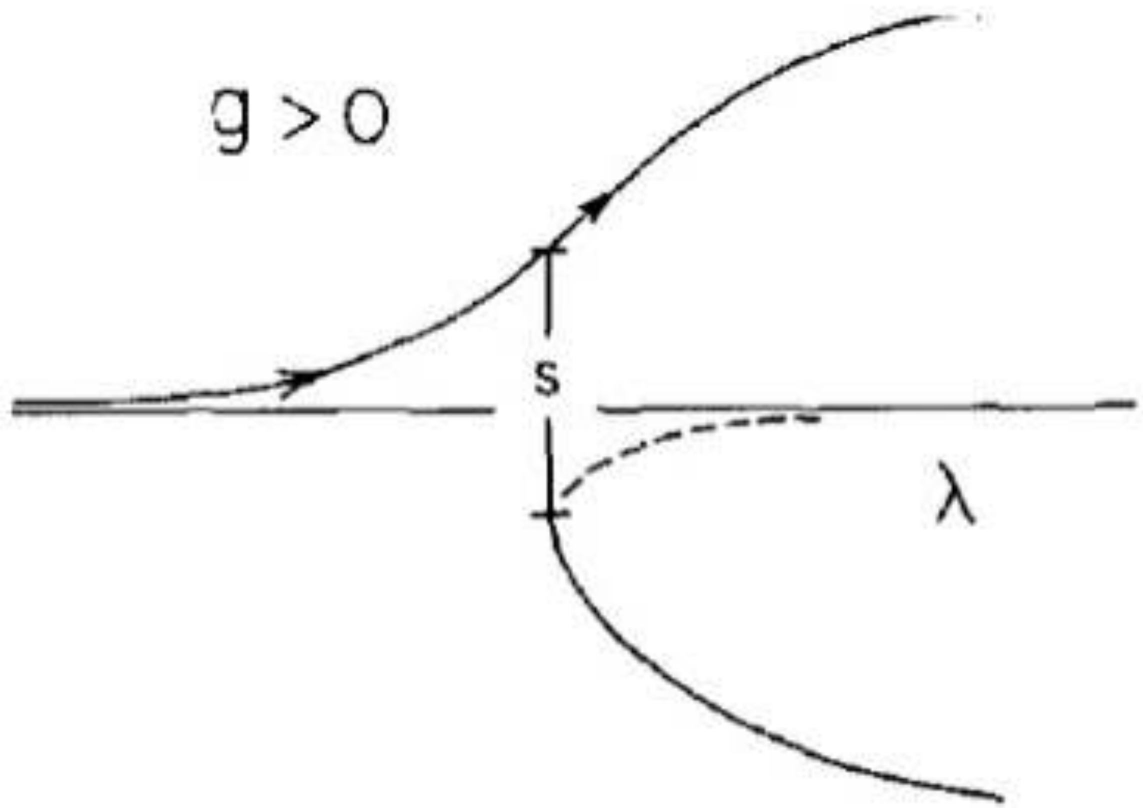


Speed

In genetic decision networks:

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

Mechanism:



In genetic decision networks:

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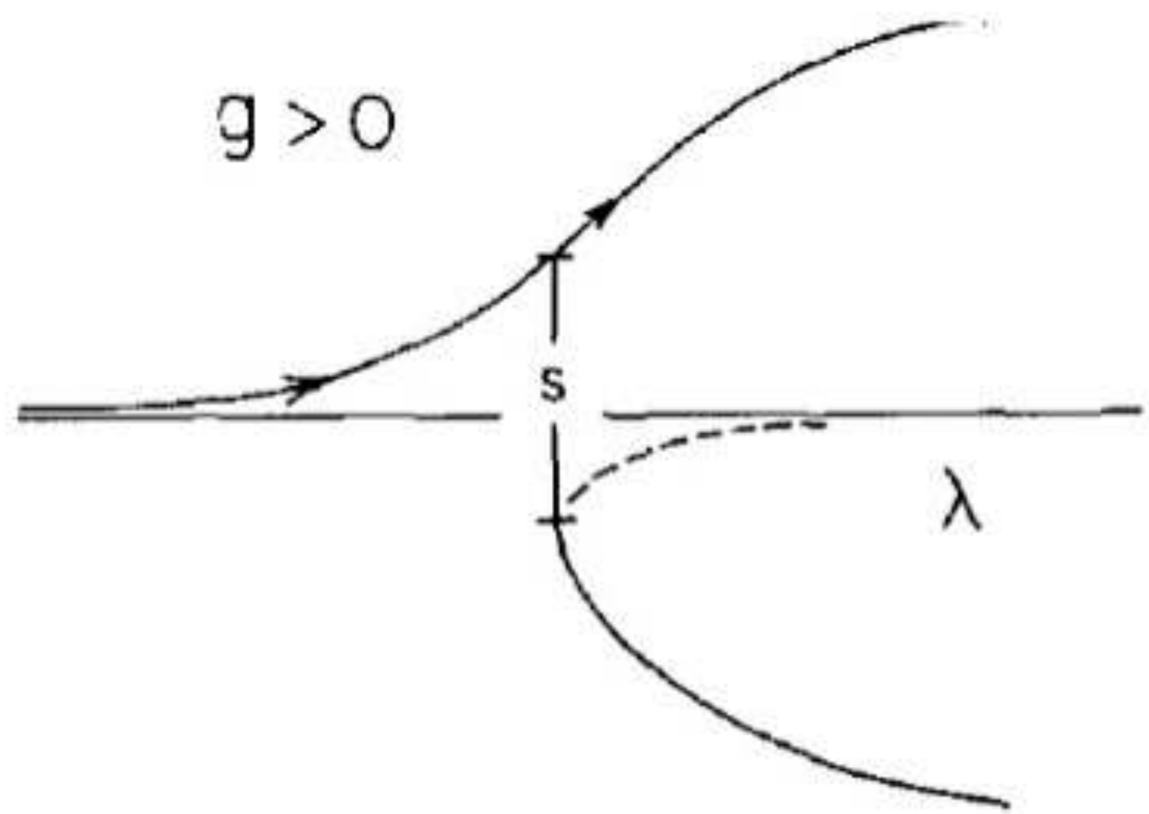


Biology, Synthetic Biology, Medicine

Further research: multidimensional genetic switch

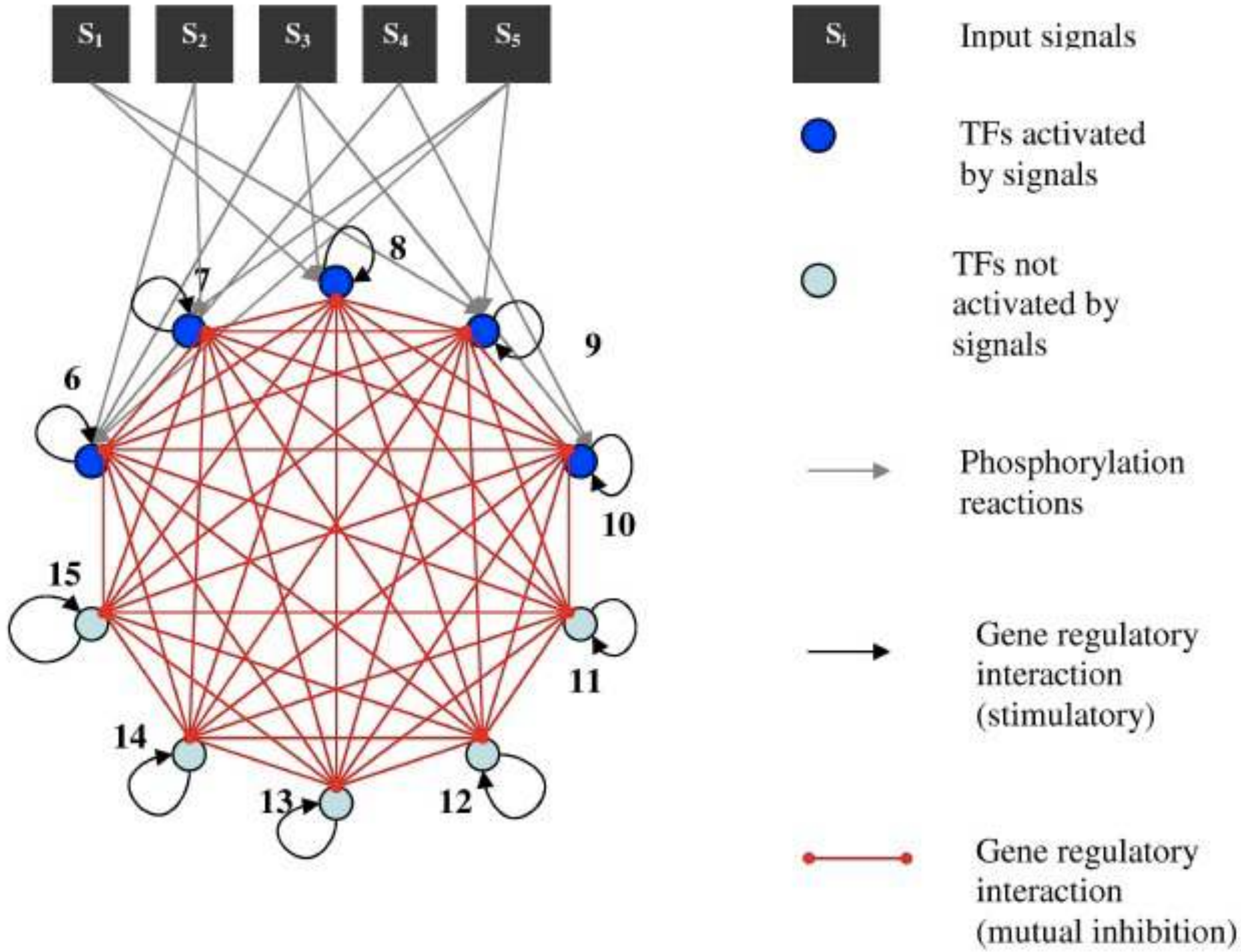


Figure 2. Representation of a highdimensional genetic decision switch with 10 transcription factors (nodes 6 to 15) and 5 input signals. Only nodes 6 to 10 need to be activated (phosphorylated) to act on any promoter region of the rest of the transcription factors in the network. Each transcription factor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

Cellular Intelligence

On

Genetic Level

and

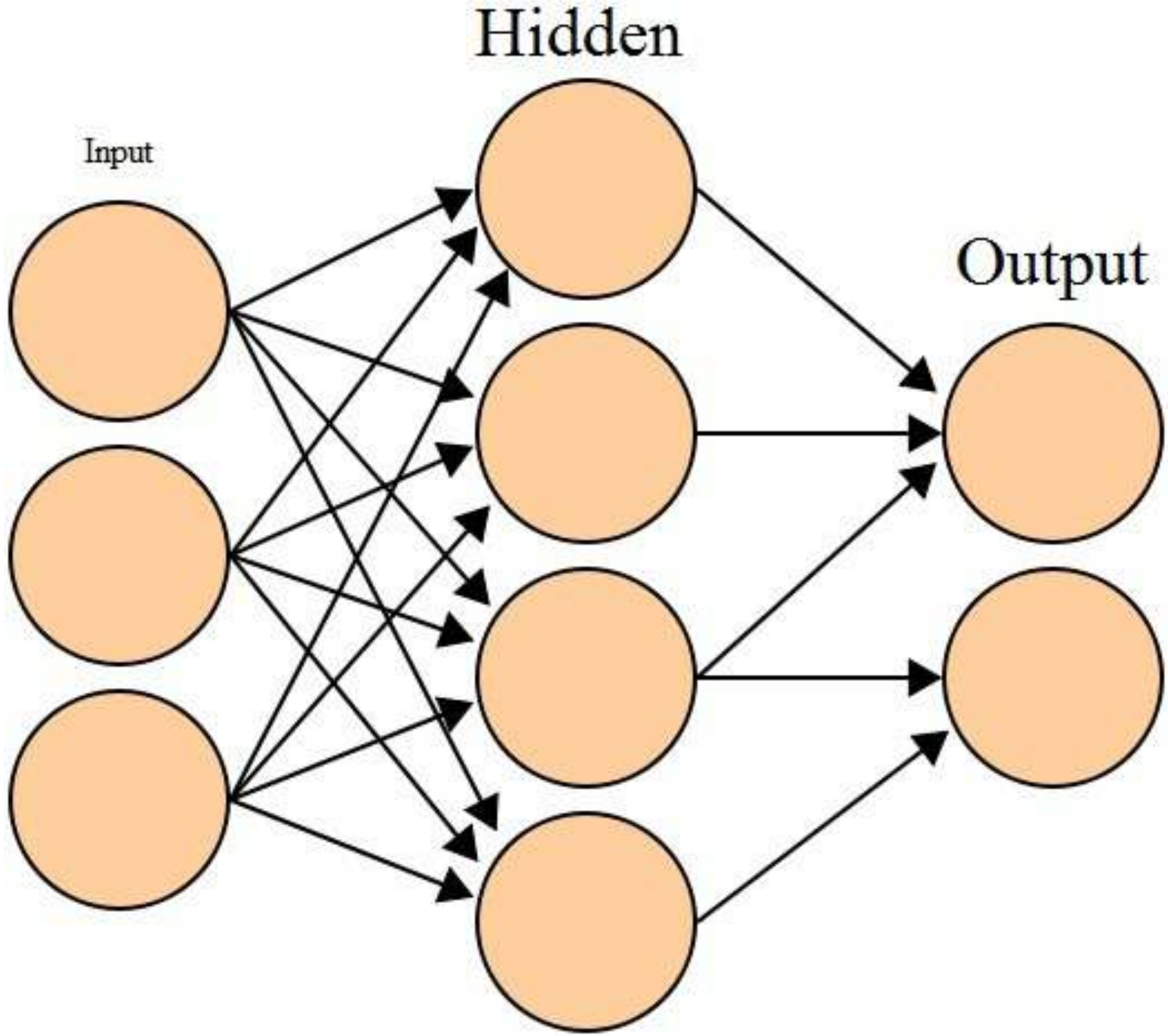
Noise

What is the difference?

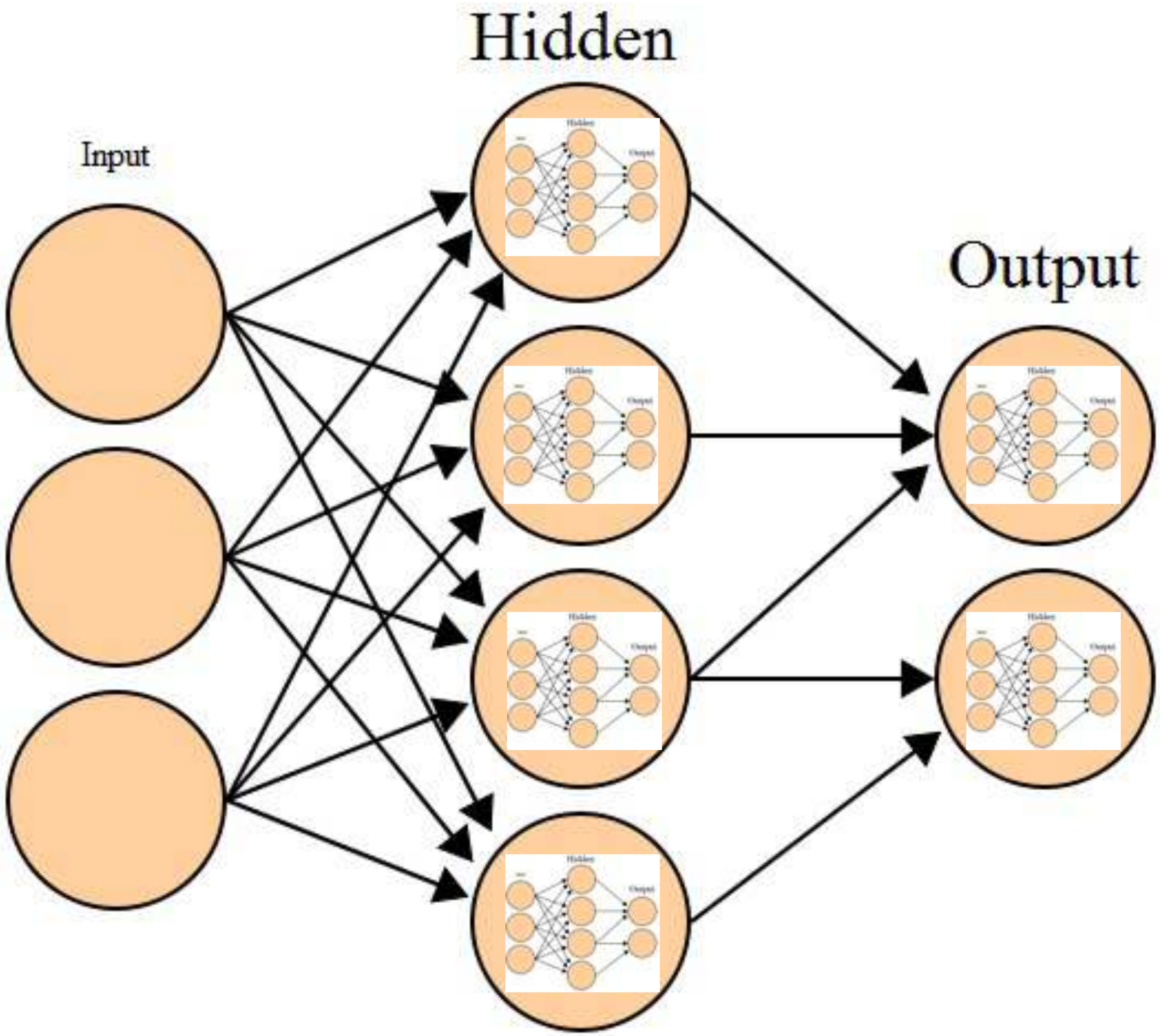
What is the difference?

Intelligence and ability to learn

Multicellular intelligence



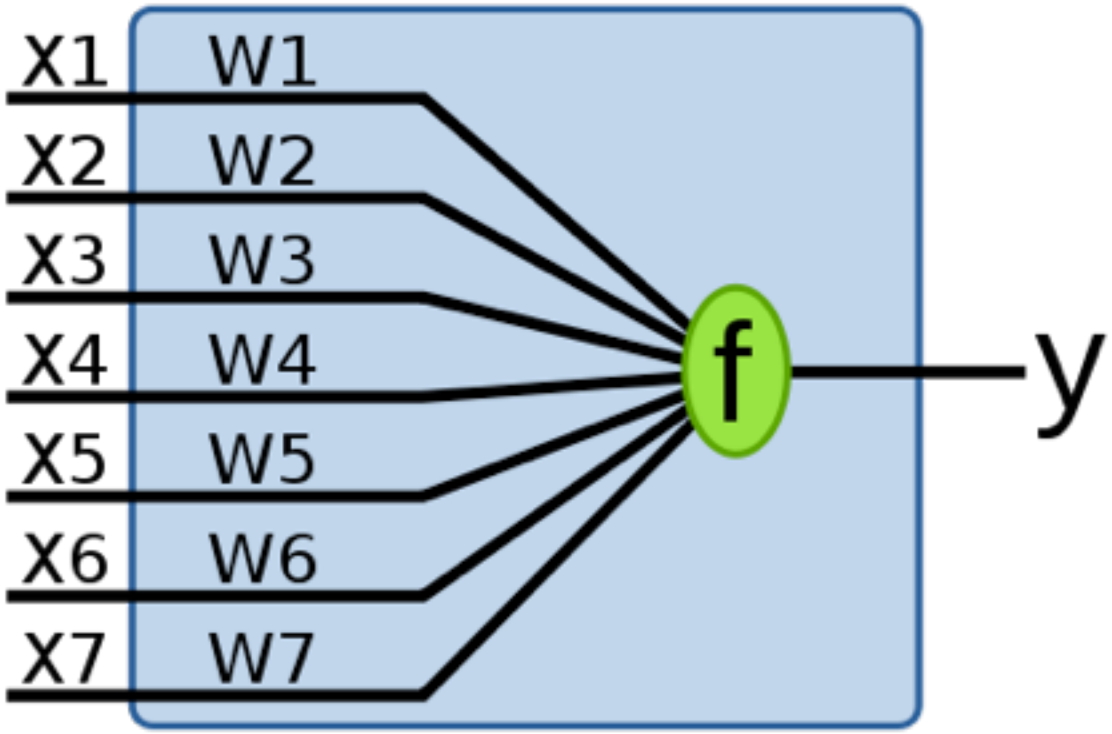
Intracellular intelligence



Content

- What is intelligence? (Artificial intelligence)
- Stochasticity in gene expression
- Stochasticity in intracellular intelligence?
  - Basic Rosenblatt's perceptron
  - Associative perceptron
- Summary

Perceptron- one layer feedforward neural network



$$f(x) = \begin{cases} 1 & \text{if } w \cdot x + b > 0 \\ 0 & \text{otherwise} \end{cases}$$

Learning algorithm(converges if linearly separable data):

1. Initialise weights and threshold. Note that weights may be initialised by setting each weight node $w_i(0)$ to 0 or to a small random value. In the example below, we choose the former.

2. For each sample j in our training set D, perform the following steps over the input $\mathbf{x}_j$ and desired output d_j:

   2a. Calculate the actual output:

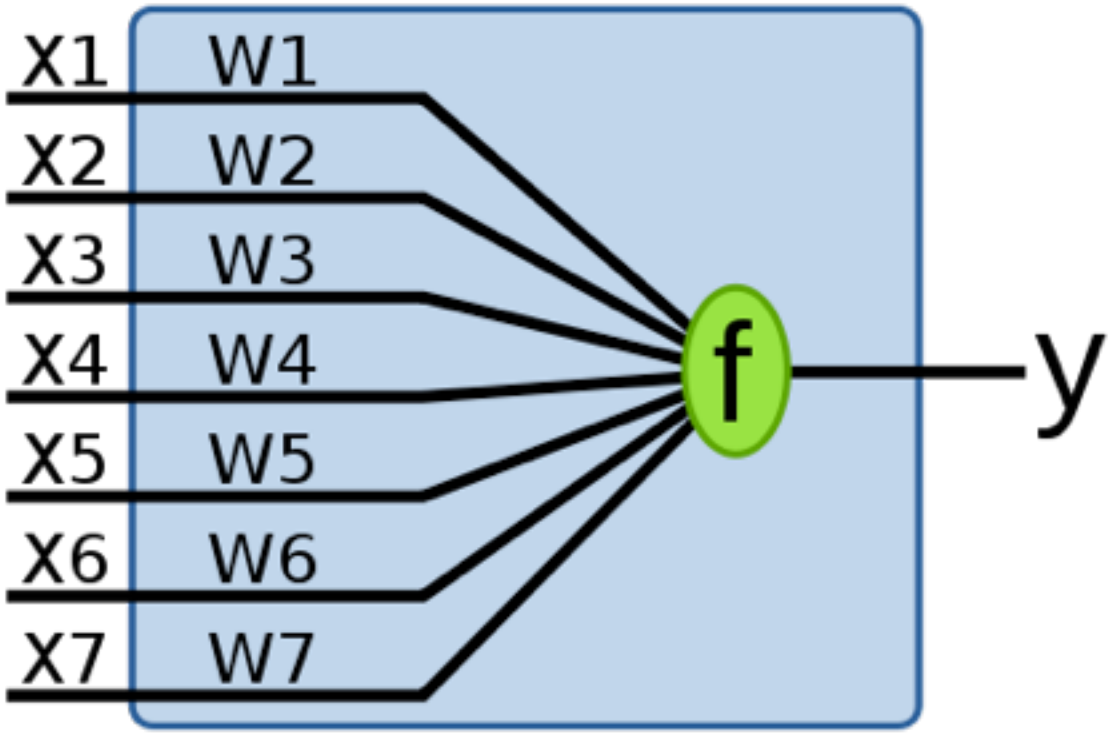
   $$y_j(t) = f[\mathbf{w}(t) \cdot \mathbf{x}_j] = f[w_0(t) + w_1(t)x_{j,1} + w_2(t)x_{j,2} + \cdots + w_n(t)x_{j,n}]$$

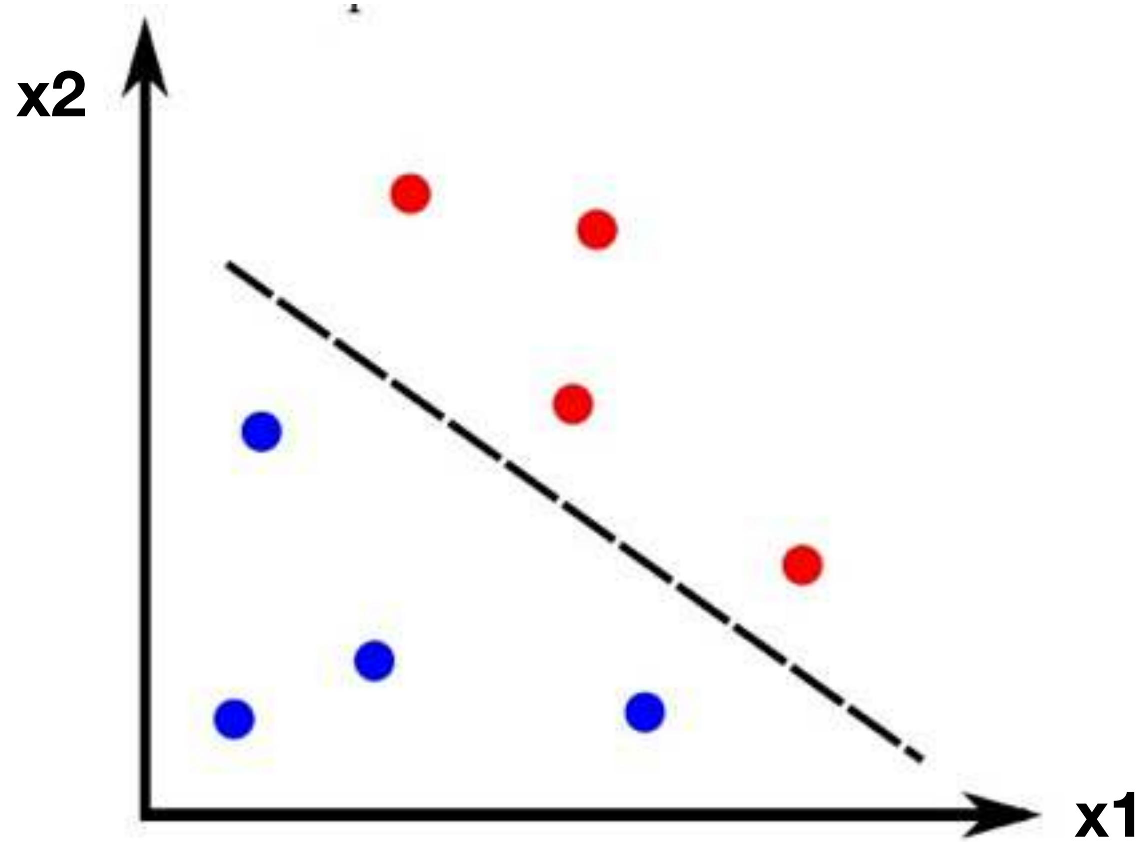
   2b. Adapt weights:

   $w_i(t+1) = w_i(t) + \alpha(d_j - y_j(t))x_{j,i}$, for all nodes $0 \le i \le n$.

Step 2 is repeated until the iteration error $d_j - y_j(t)$ is less than a user-specified error

Perceptron- one layer feedforward neural network





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Perceptron inside the cell??

Proc. Natl. Acad. Sci. USA
Vol. 88, pp. 10983–10987, December 1991
Chemistry

Chemical implementation of neural networks and Turing machines

ALLEN HJELMFELT[†], EDWARD D. WEINBERGER[†], AND JOHN ROSS[‡]

[†]Max-Planck-Institut für Biophysikalische Chemie, D-3400 Göttingen, Federal Republic of Germany; and [‡]Department of Chemistry, Stanford University, Stanford, CA 94305

972 Biophysical Journal Volume 66 April 1994 972–977

Computer Simulated Evolution of a Network of Cell-Signaling Molecules

Dennis Bray* and Steven Lay[†]
*Department of Zoology and [†]Department of Applied Mathematics and Theoretical Physics, University of Cambridge, Cambridge, United Kingdom

Journal of Theoretical Biology 249 (2007) 58–66
www.els

Associative learning in biochemical networks

Nikhil Gandhi[a], Gonen Ashkenasy[b,*], Emmanuel Tannenbaum[b,*]

[a]*College of Computing, Georgia Institute of Technology, Atlanta, GA 30332, USA*
[b]*Department of Chemistry, Ben-Gurion University of the Negev, Be'er-Sheva 84105, Israel*

PRL **100,** 018101 (2008) PHYSICAL REVIEW LETTERS week ending 11 JANUARY 2008

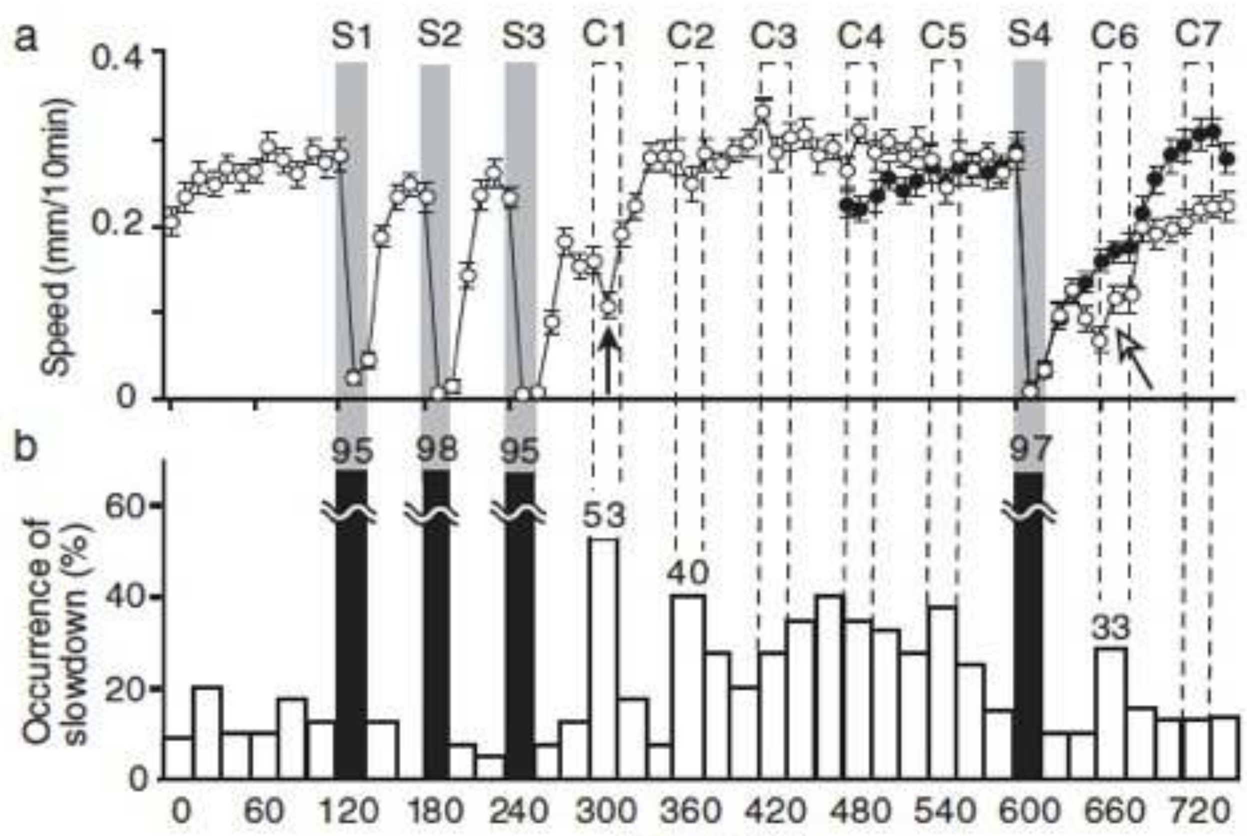
Amoebae Anticipate Periodic Events

Tetsu Saigusa
Graduate School of Engineering, Hokkaido University, N13 W8, Sapporo 060-8628, Japan

Atsushi Tero* and Toshiyuki Nakagaki†
Research Institute for Electronic Science, Hokkaido University, Sapporo, 060-0812, Japan

Yoshiki Kuramoto
Department of Nonlinear Science, ATR Wave Engineering Laboratories,
2-2-2 Hikaridai, Seika-Cho, Soraku-gun, Kyoto 619-0288, Japan
(Received 2 July 2007; published 3 January 2008)

When plasmodia of the true slime mold *Physarum* were exposed to unfavorable conditions presented as three consecutive pulses at constant intervals, they reduced their locomotive speed in response to each episode. When the plasmodia were subsequently subjected to favorable conditions, they spontaneously reduced their locomotive speed at the time when the next unfavorable episode would have occurred. This implied the anticipation of impending environmental change. We explored the mechanisms underlying these types of behavior from a dynamical systems perspective.



NATURE|Vol 451|24 January 2008

Cellular memory hints at the origins of intelligence

Learning and memory — abilities associated with a brain or, at the very least, neuronal activity — have been observed in protoplasmic slime, a unicellular organism with multiple nuclei.

The team found that when the mould experienced three episodes of dry air in regular succession an hour apart, it apparently came to expect more: it slowed down when a fourth pulse of dry air was due, even if none was actu-

LETTER

doi:10.1038/nature10262

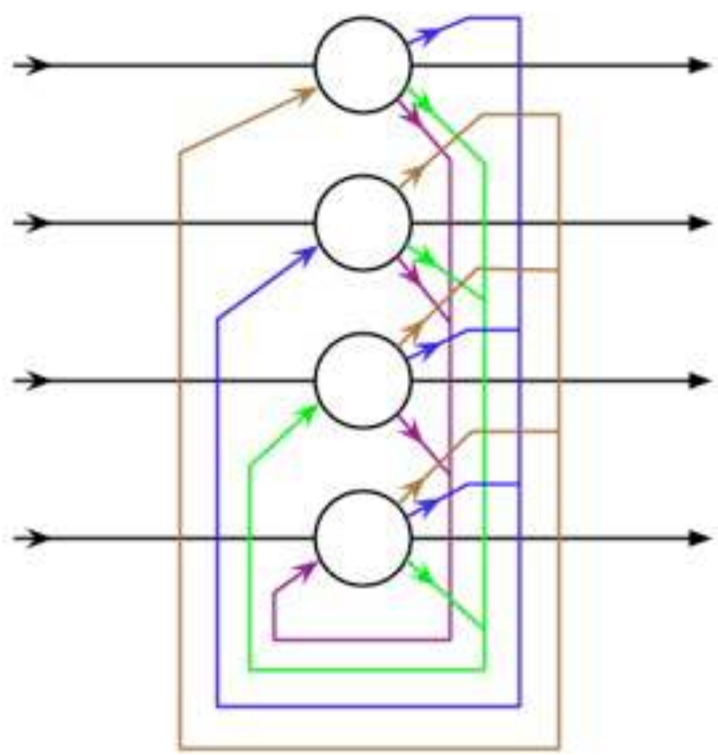
Neural network computation with DNA strand displacement cascades

368 | NATURE | VOL 475 | 21 JULY 2011

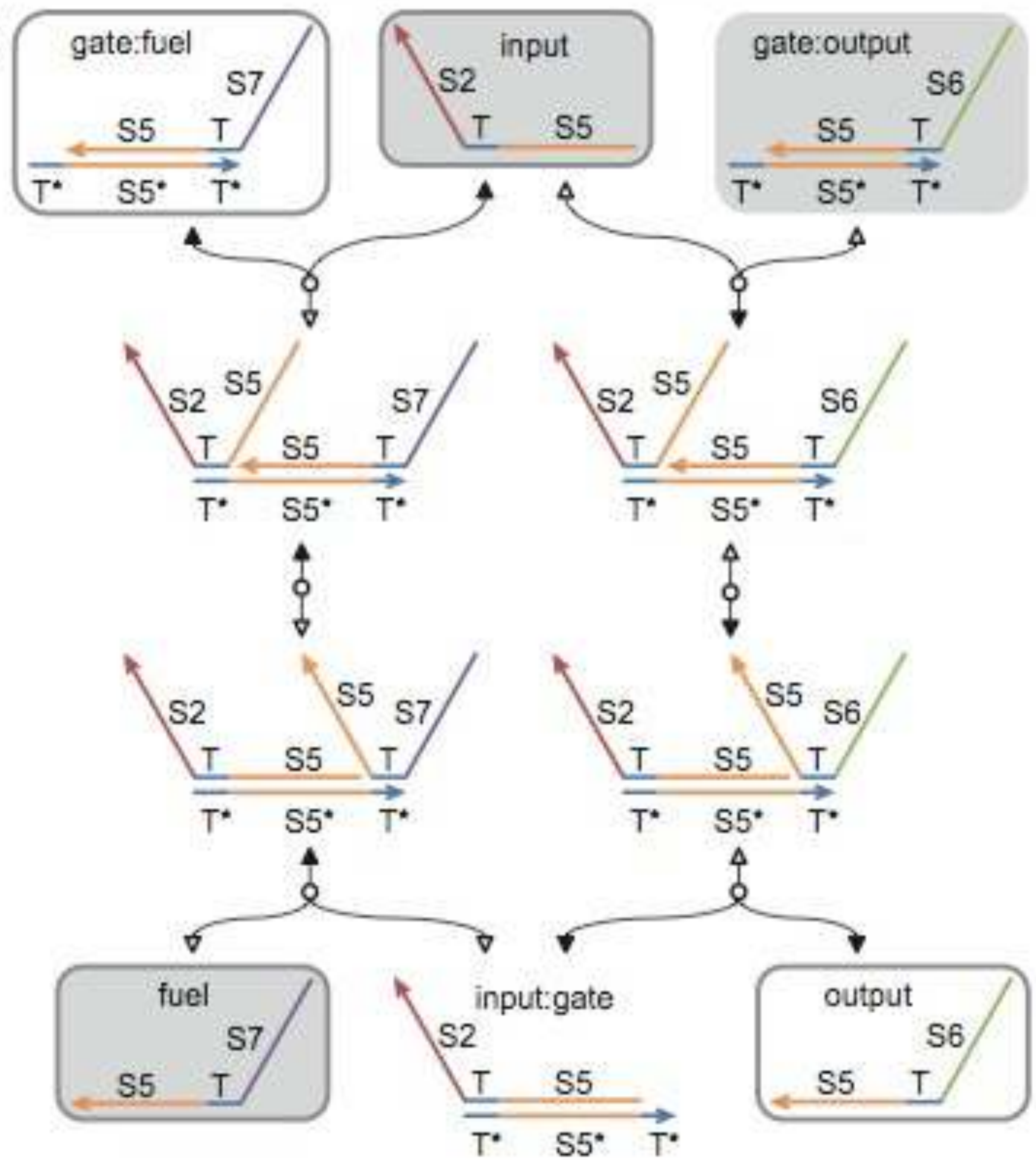
Lulu Qian[1], Erik Winfree[1,2,3] & Jehoshua Bruck[3,4]

A Hopfield network

In silico learning!



b



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]

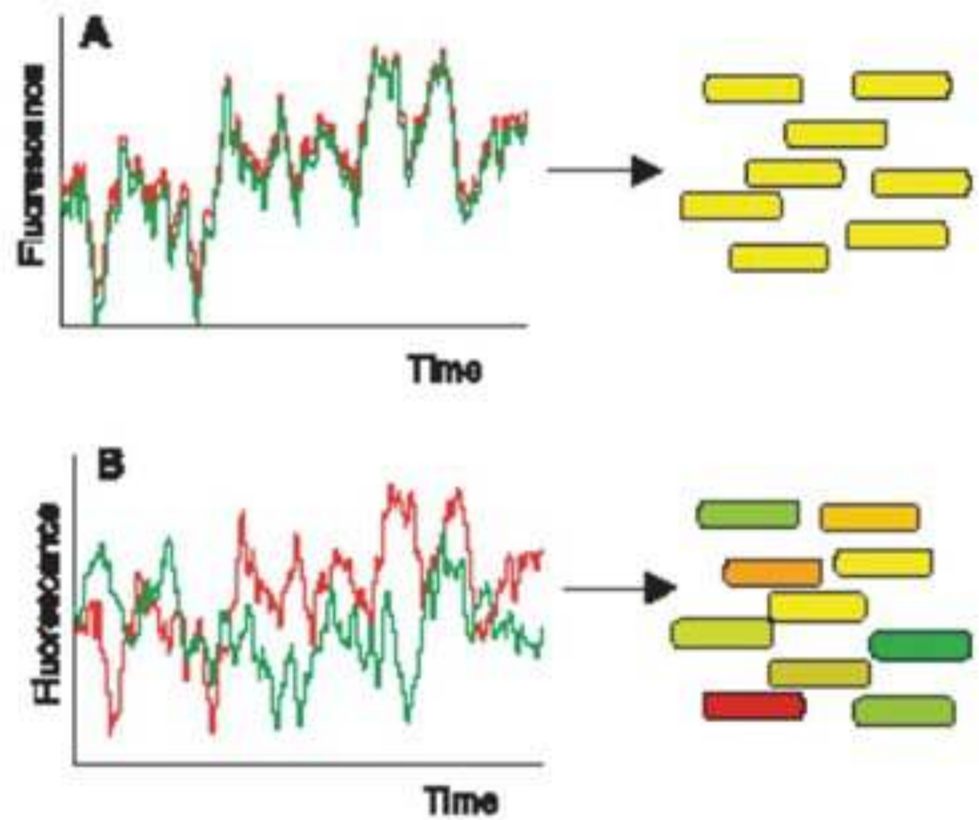
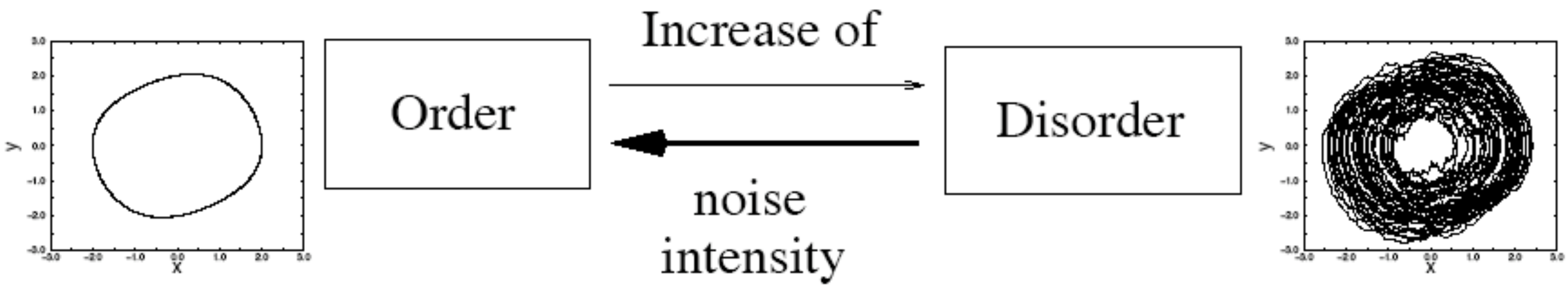


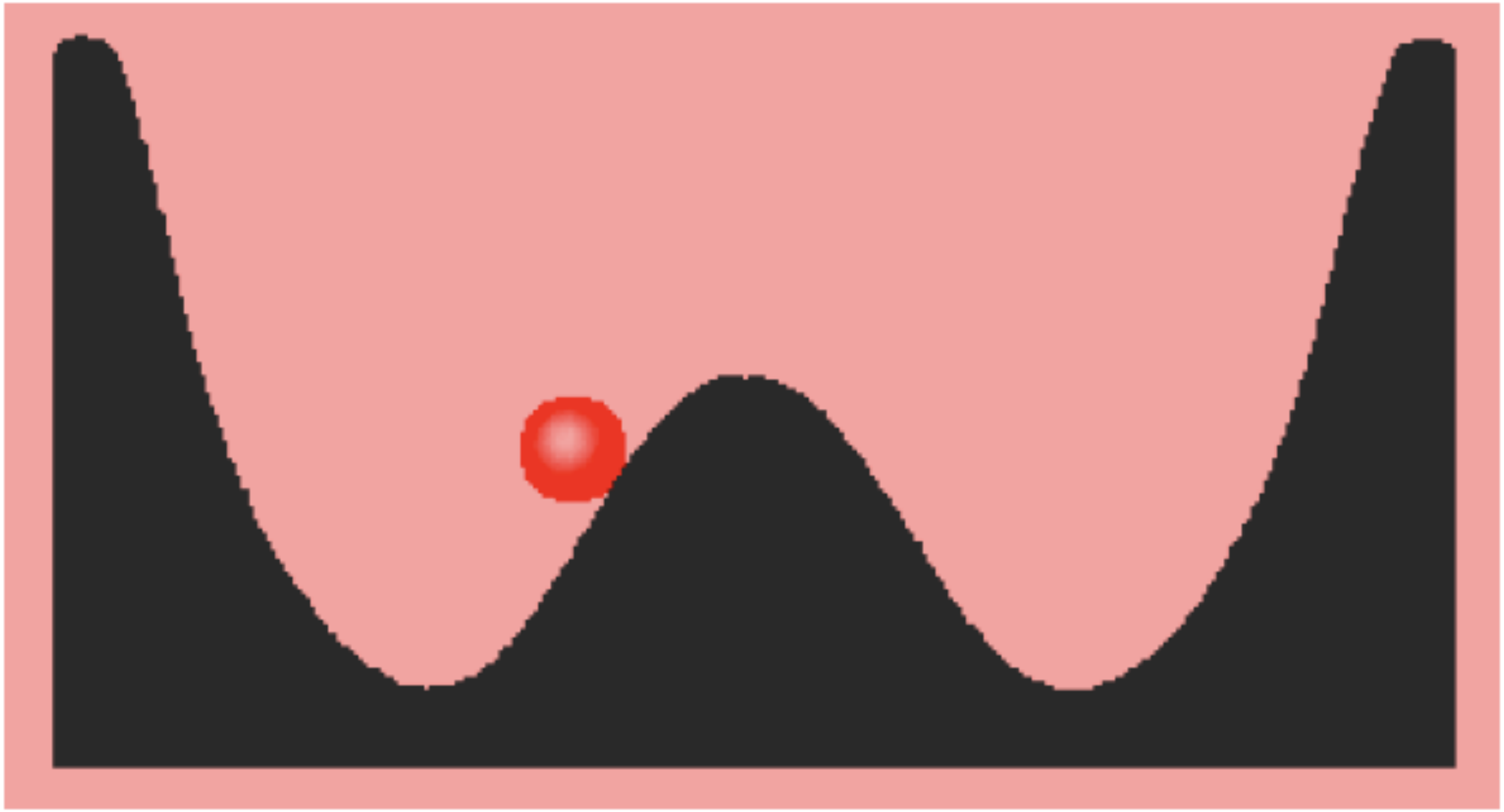
Fig. 1. Intrinsic and extrinsic noise can be measured and distinguished with two genes (*cfp*, shown in green; *yfp*, shown in red) controlled by identical regulatory sequences. Cells with the same amount of each protein appear yellow, whereas cells expressing more of one fluorescent protein than the 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.

Noise-induced Effects in Nonlinear Systems far from Equilibrium:

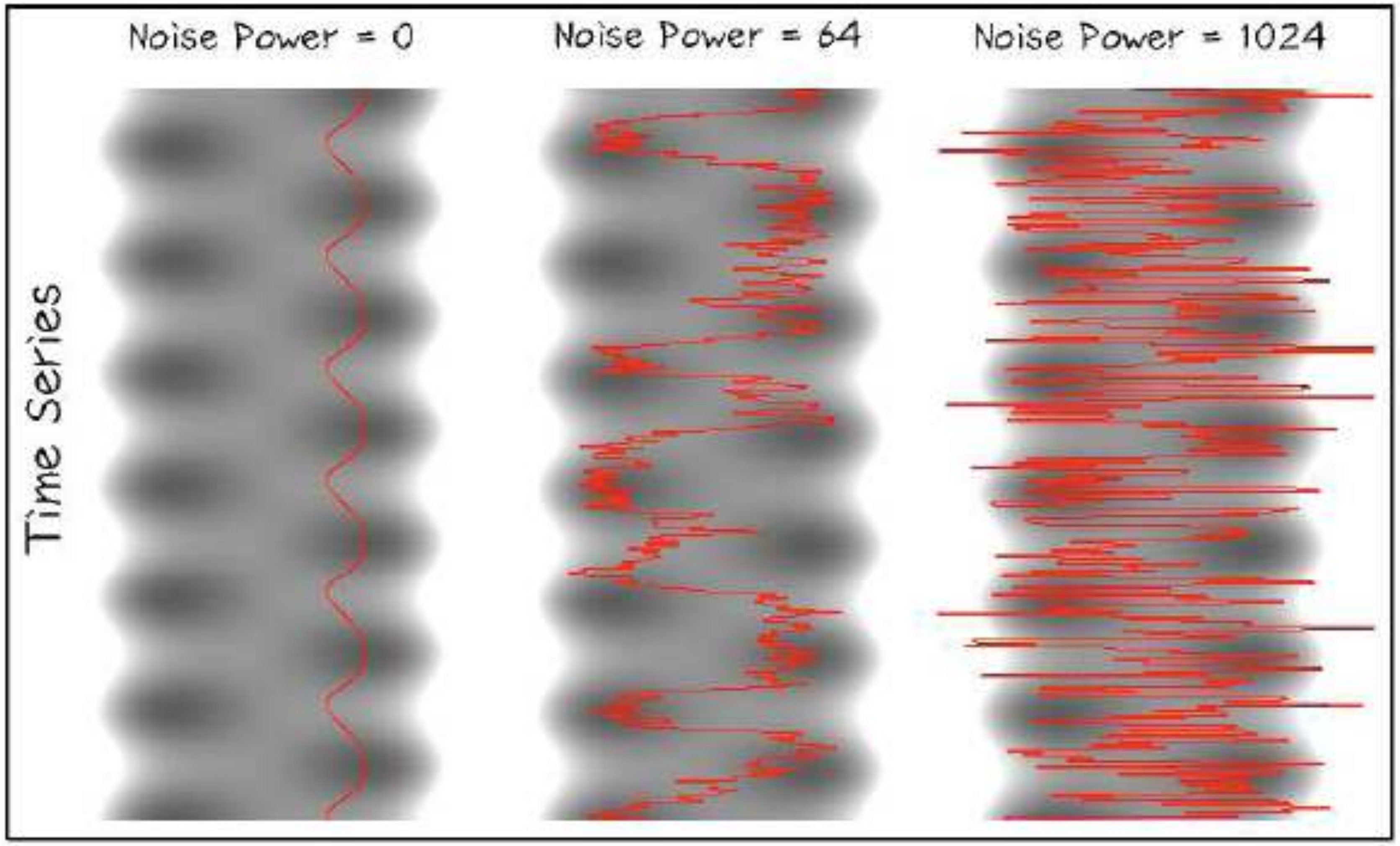


- Stochastic resonance and noise-induced propagation (since 80's)
- Noise-induced transitions (since 70's)
- Coherence resonance (since 90's)
- Noise-induced transport in ratchets (since 90's)
- Variations: noise-induced activation, formation of patterns, etc.

Another example - Stochastic Resonance

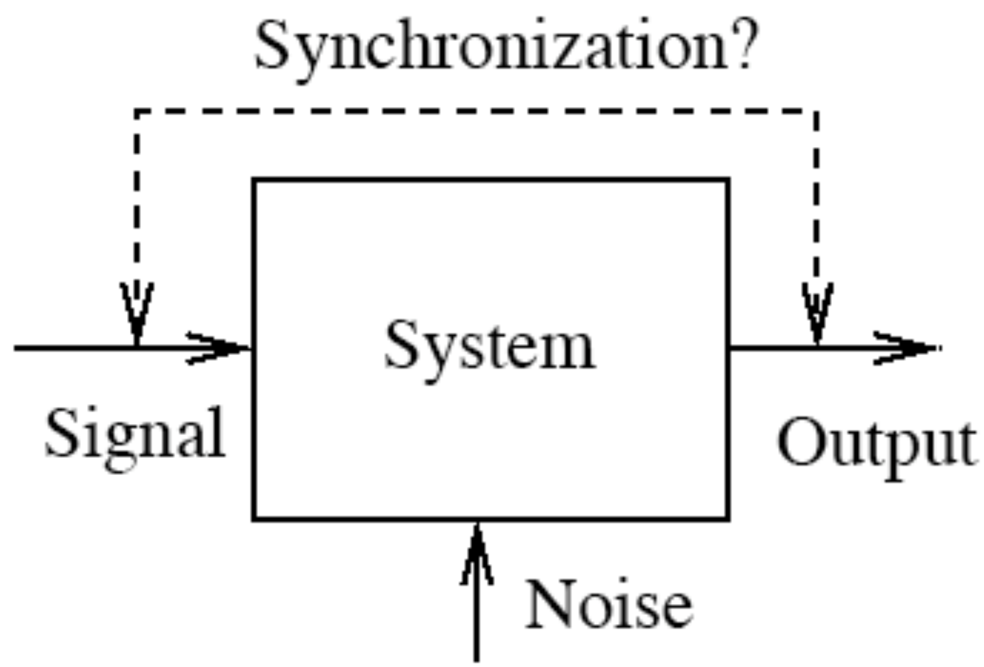


Another example - Stochastic Resonance

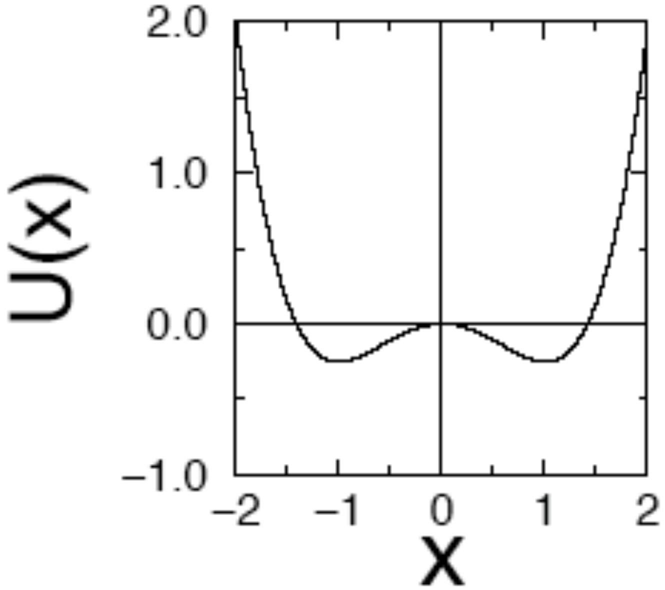


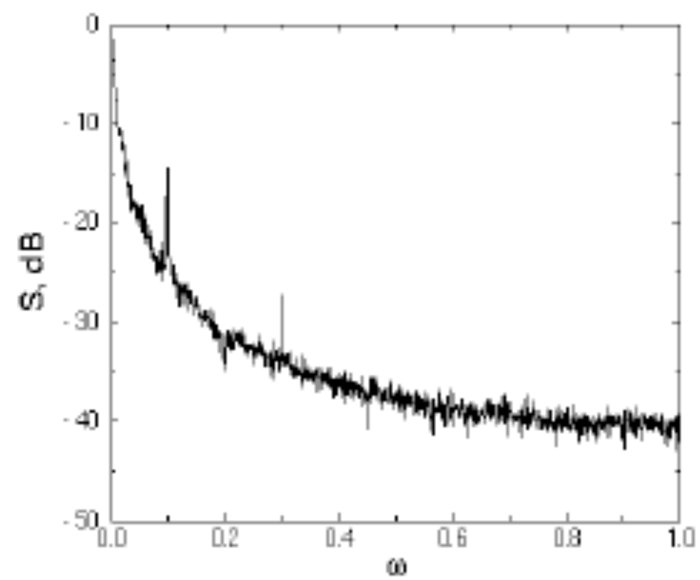
Stochastic Resonance:

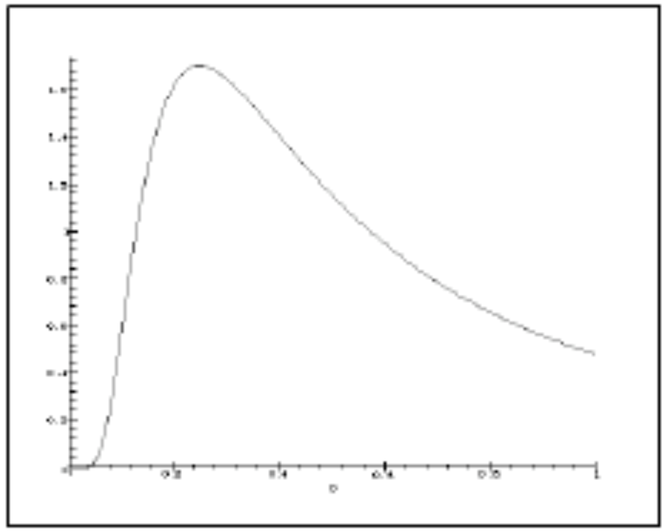
The conventional situation:



$$\dot{x}(t) = x - x^3 + A cos(w_s t + \varphi) + \xi(t)$$







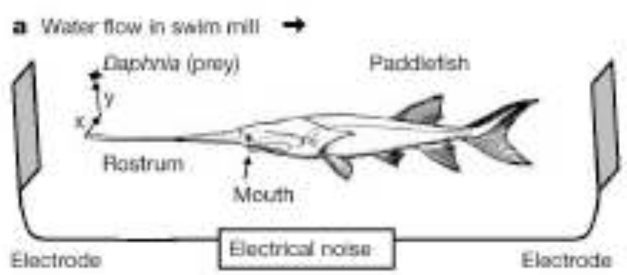
In addition, SR has been found in

- In large variety of systems: excitable, non-dynamical, thresholdless...
- With different signals: periodic, aperiodic, digital... • With different noise

Some examples - Living sciences:

In nature:

Behavioural stochastic resonance:



• D.F. Russel, L. A. Wilkens, and F. Moss, Nature (1999).

Noise-enhanced Human Balance Control:

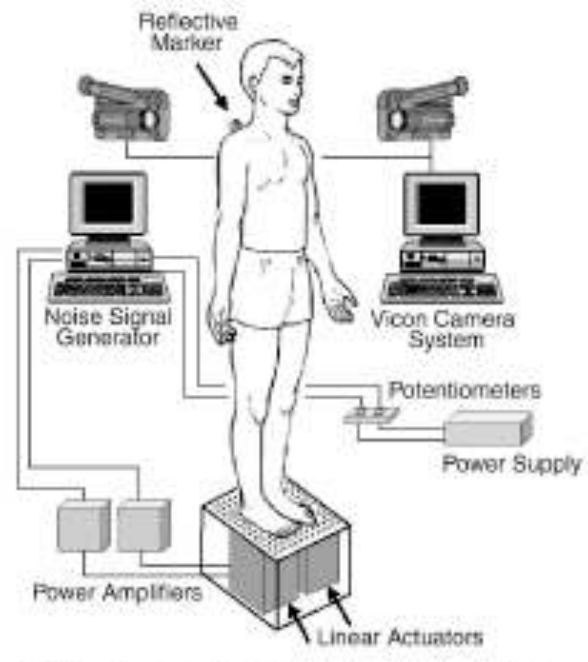
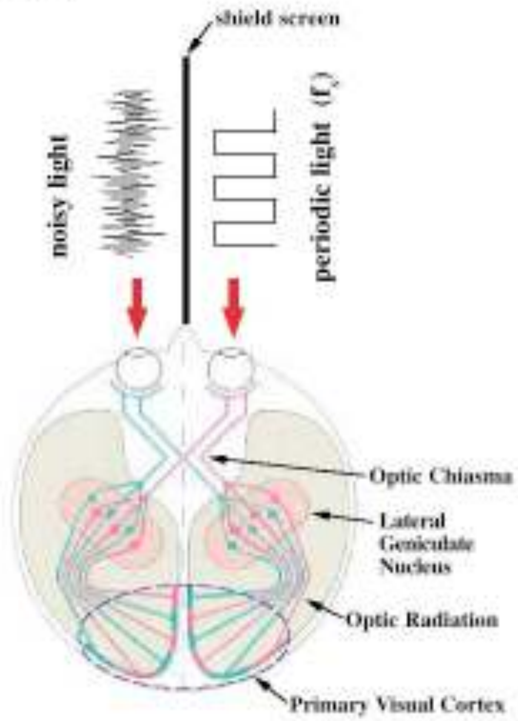


FIG. 1. A schematic diagram of the experimental setup.

• A. Priplata et al. PRL (2002).

In human brain:

(brain's visual processing area):



• T. Mori, S. Kai, PRL (2002).

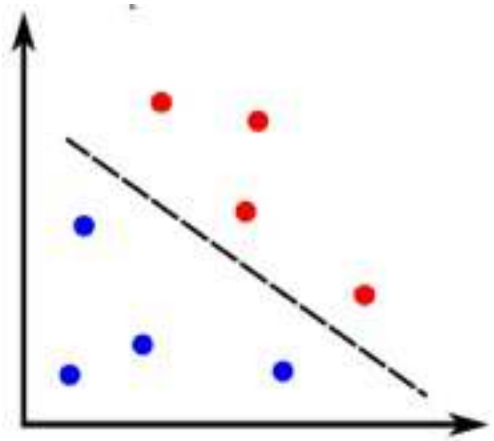
In human memory: Noise increases the speed of memory retrieval:

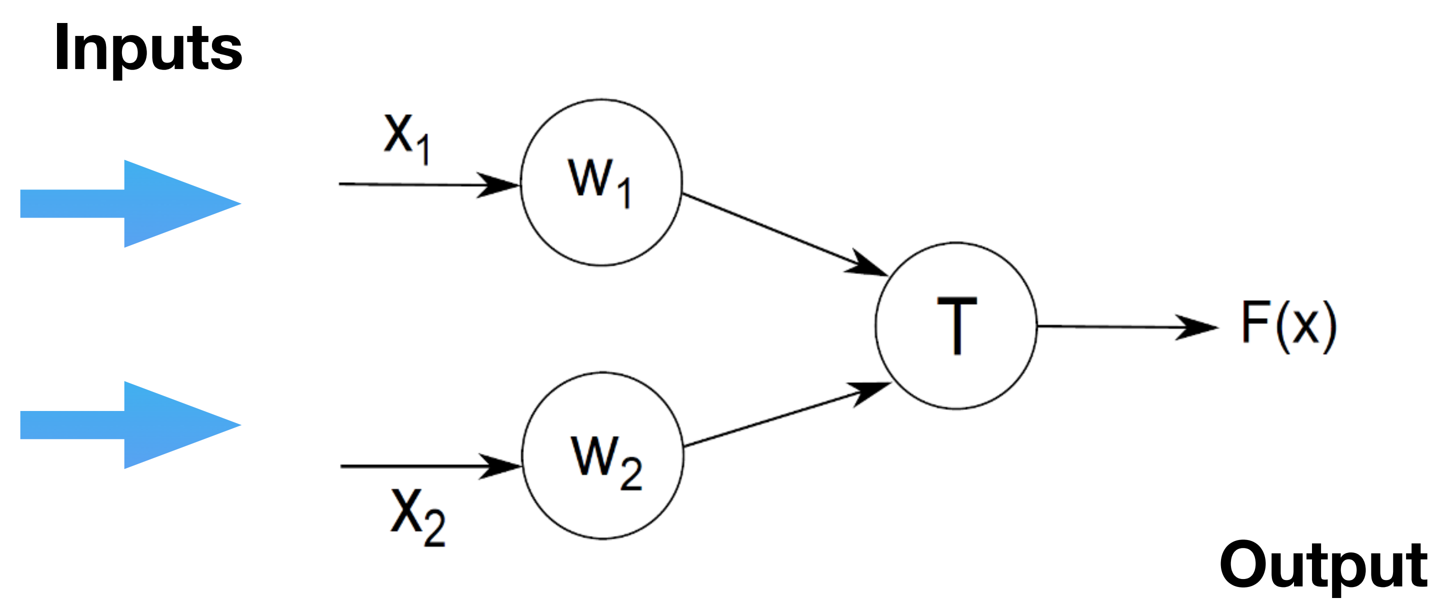
$$7 \times 8 = ?$$

M. Usher, M. Feingold, Biol. Cyber. (2000).

What is the effect of noise
in
intracellular intelligence?

Pseudo-genetic implementation of a linear classifier





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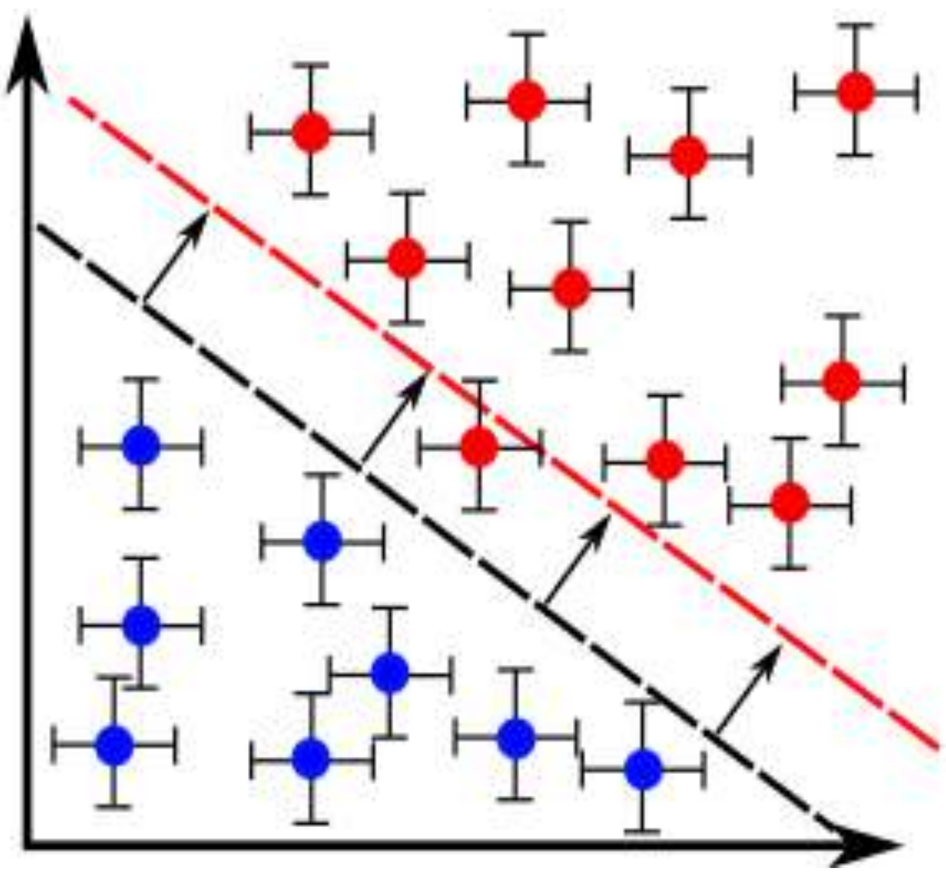
Oscillatory Protein Expression Dynamics Endows Stem Cells with Robust Differentiation Potential

Narito Suzuki[1], Chikara Furusawa[2,3], Kunihiko Kaneko[1]*

November 2011 | Volume 6 | Issue 11 | e27232

A Genetic Linear Classifier

Addition of Noise

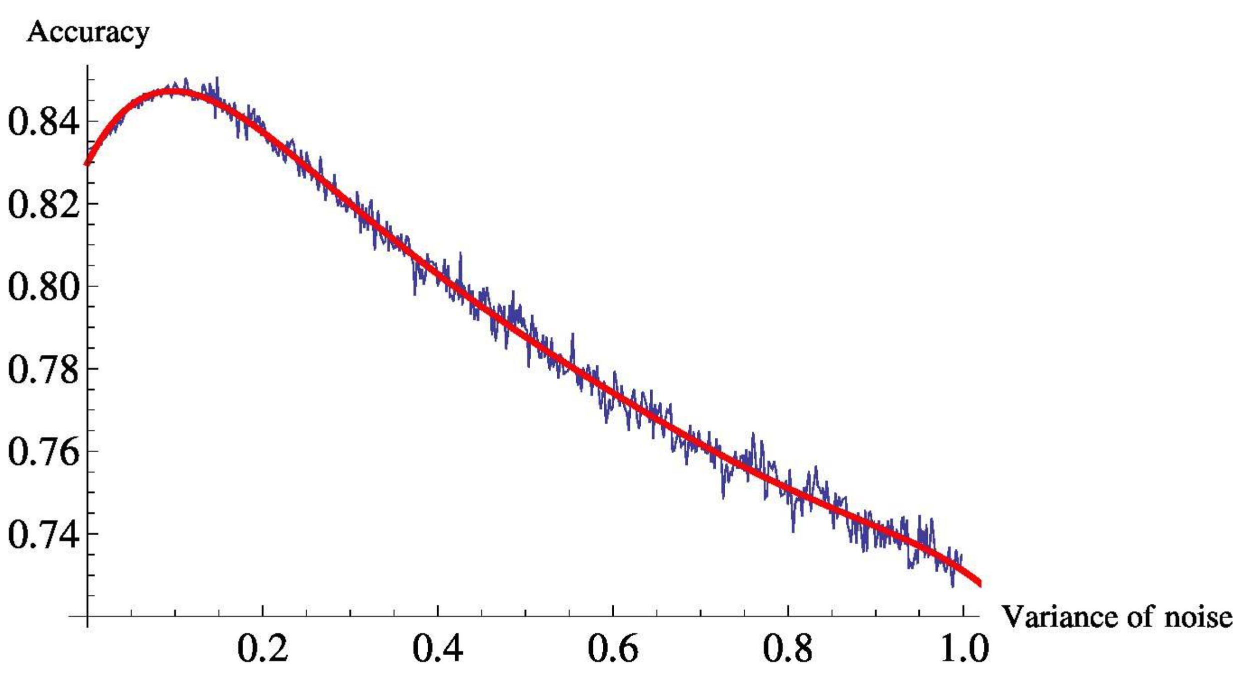


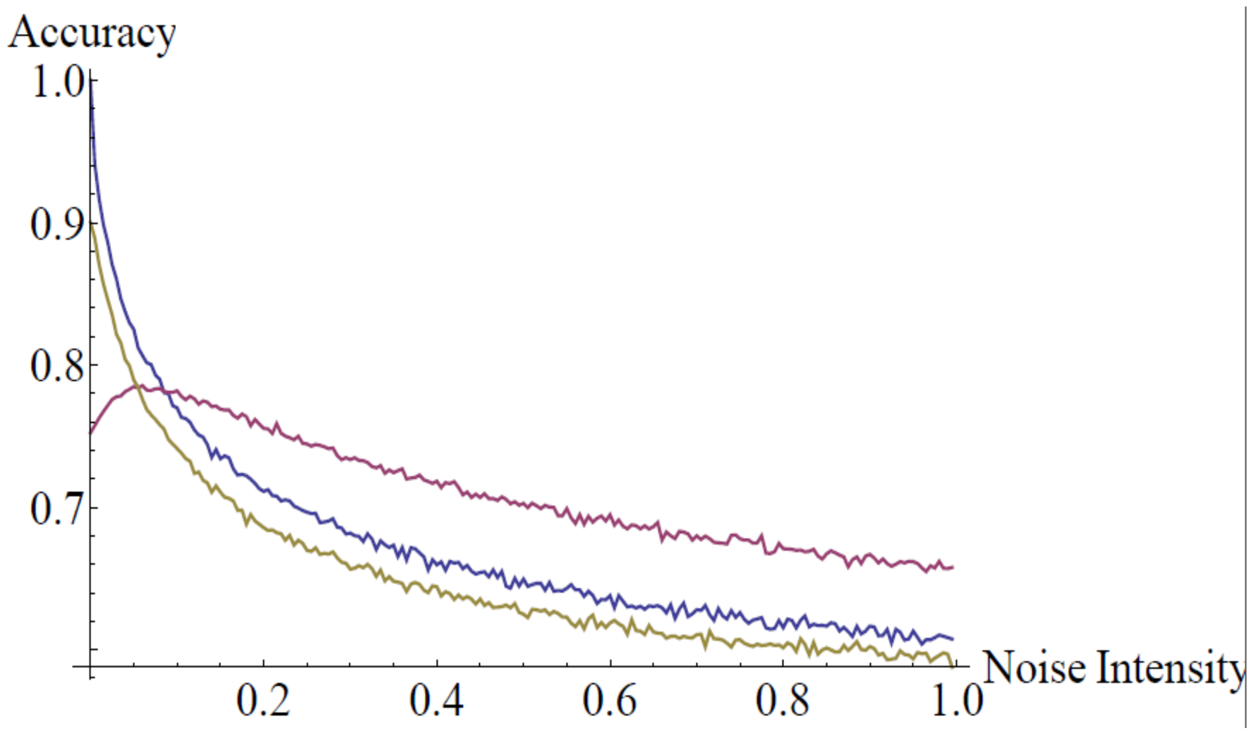
By adding noise to these points we essentially transform them into a distribution rather than a fixed point.

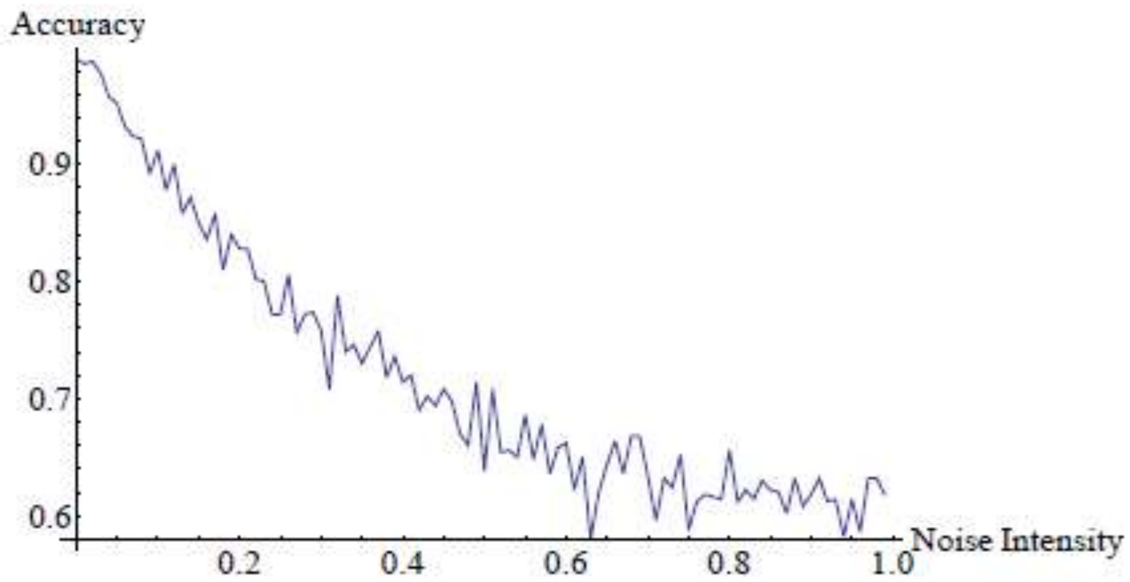
$$x_{i,n} = x_i + \mathcal{N}(0, \sigma^2)$$

A Genetic Linear Classifier

Monte Carlo Results

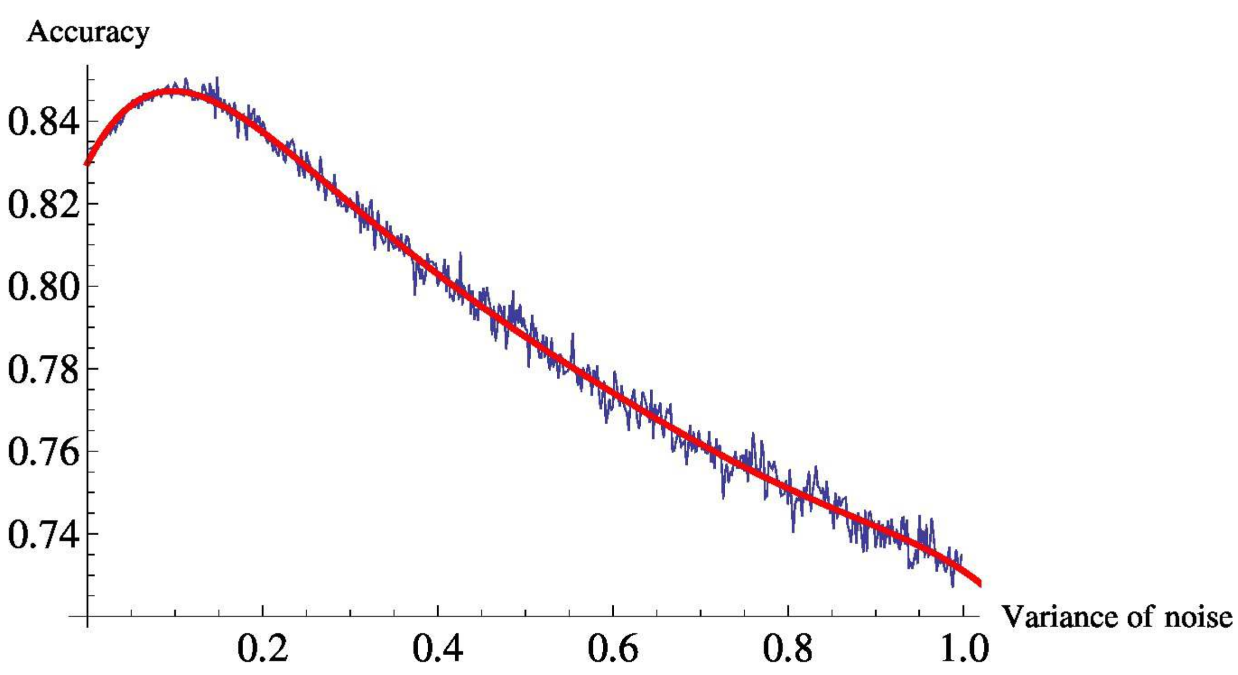


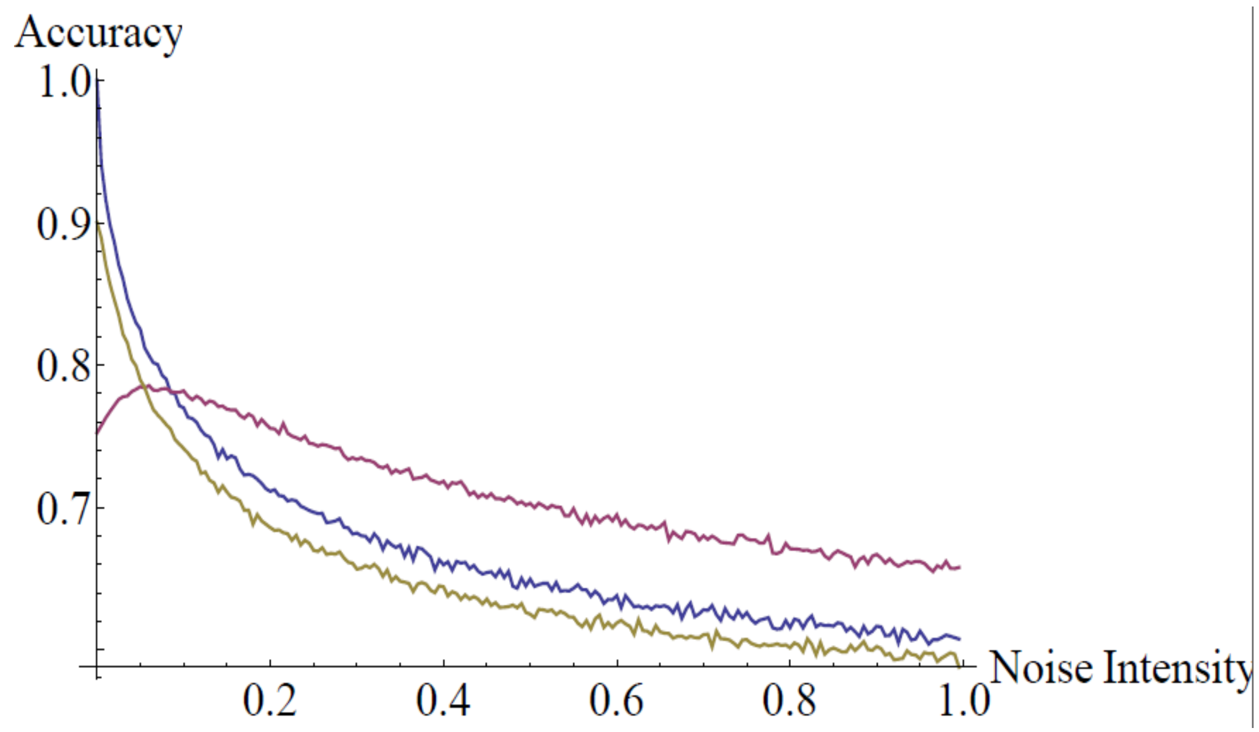


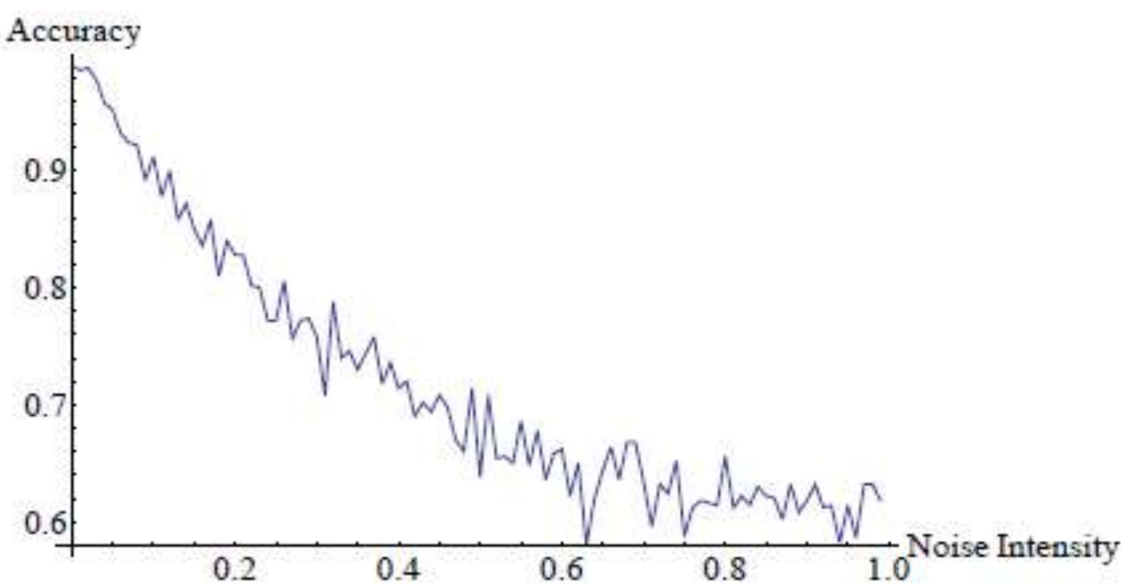


A Genetic Linear Classifier

Monte Carlo Results



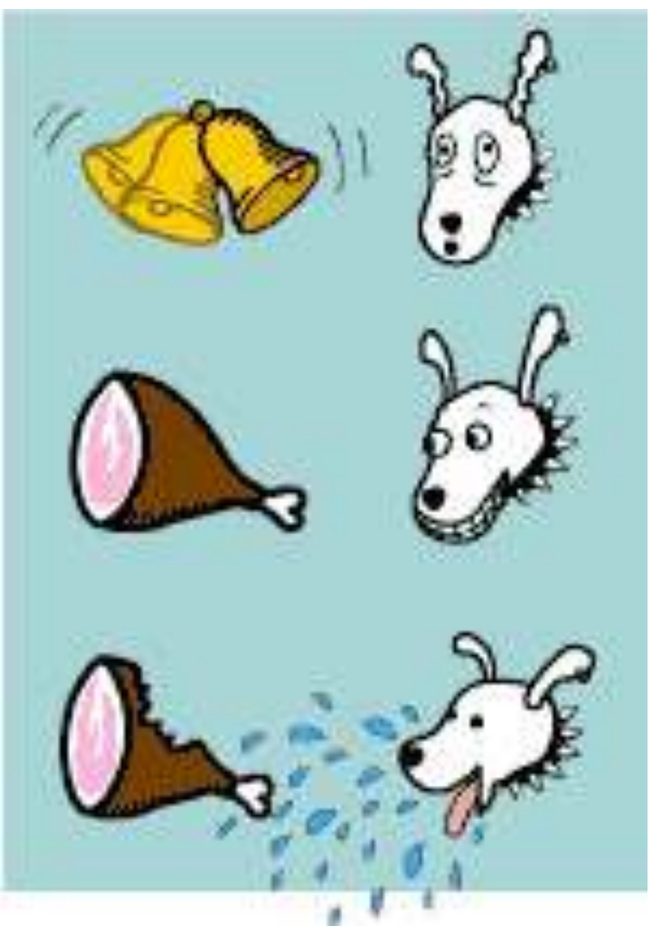


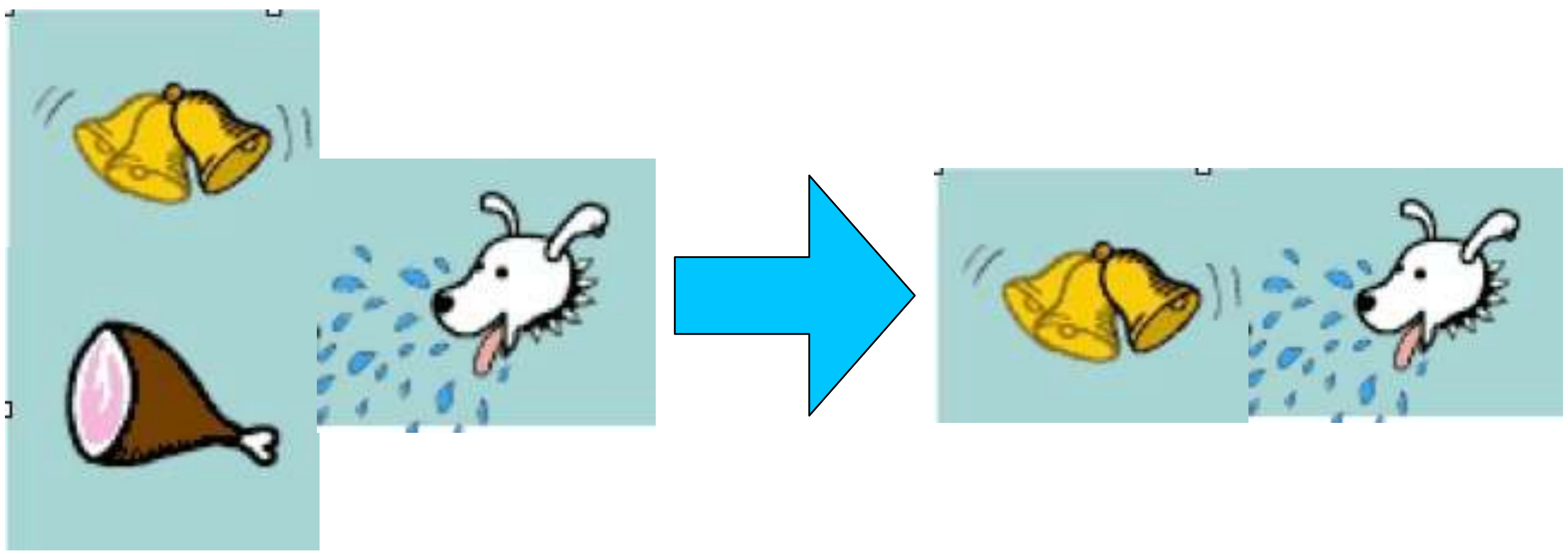


Stochastic Resonance in a Genetic Perceptron

What is Associative Learning?

Also known as classical/Pavlovian conditioning (Pavlov's dogs)

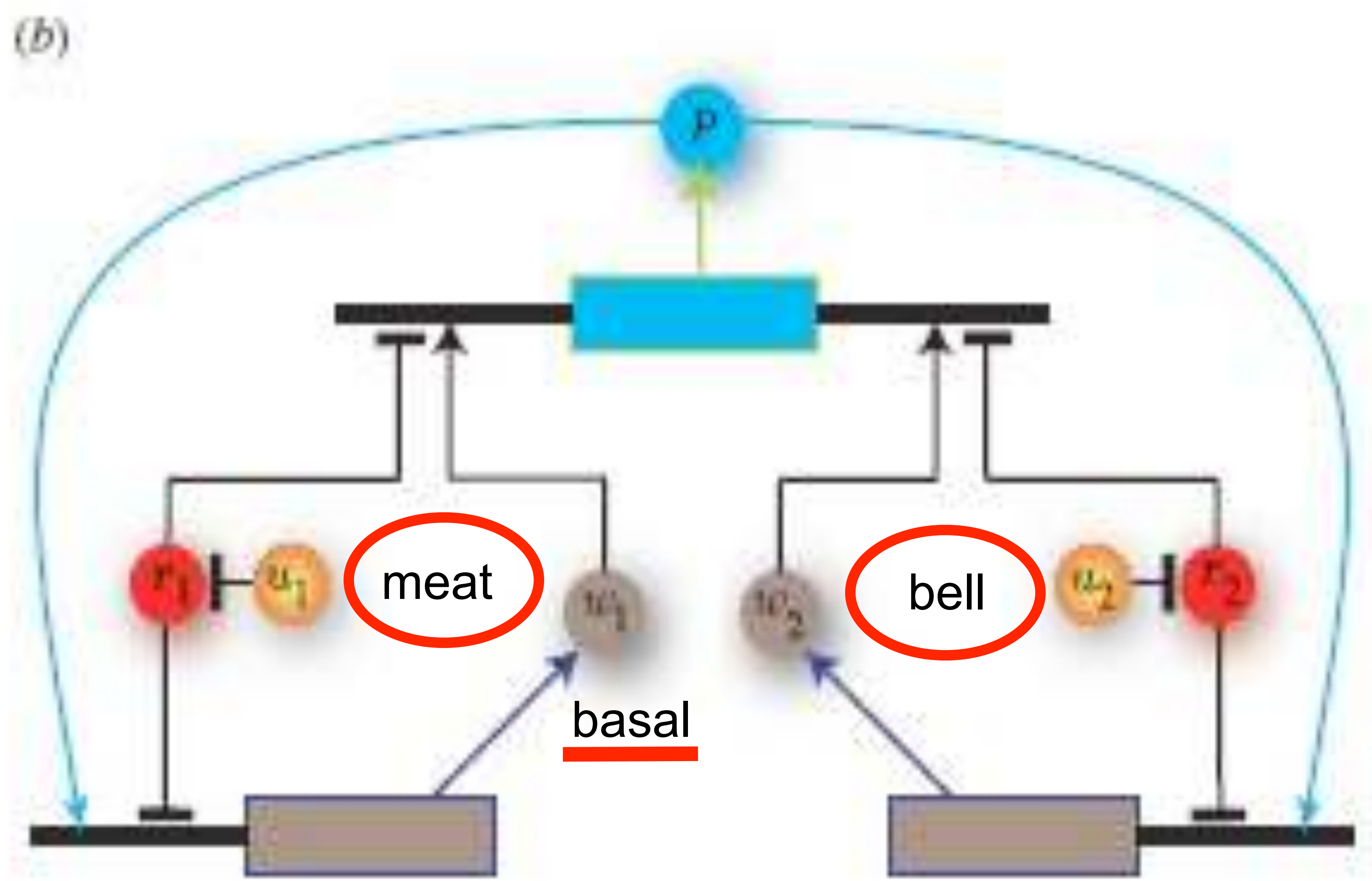




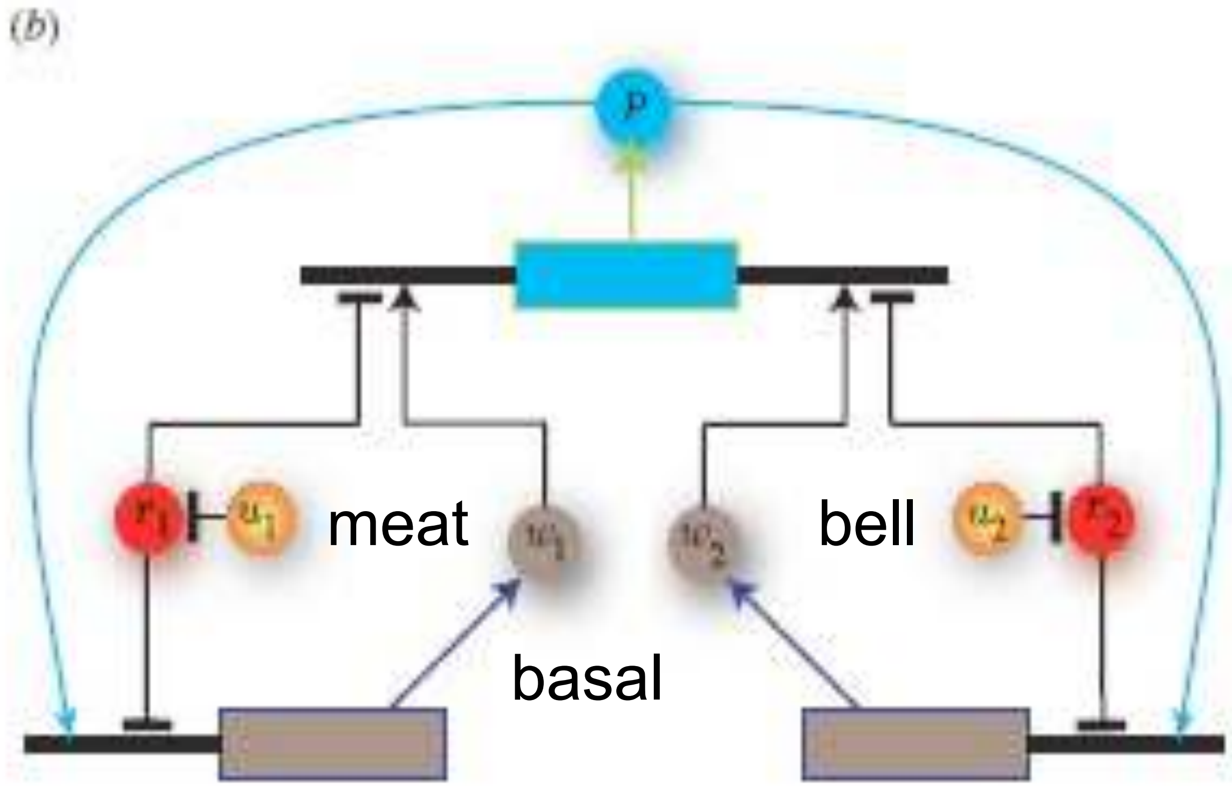
JOURNAL OF THE ROYAL SOCIETY Interface
FirstCite e-publishing
J. R. Soc. Interface
doi:10.1098/rsif.2008.0344
Published online

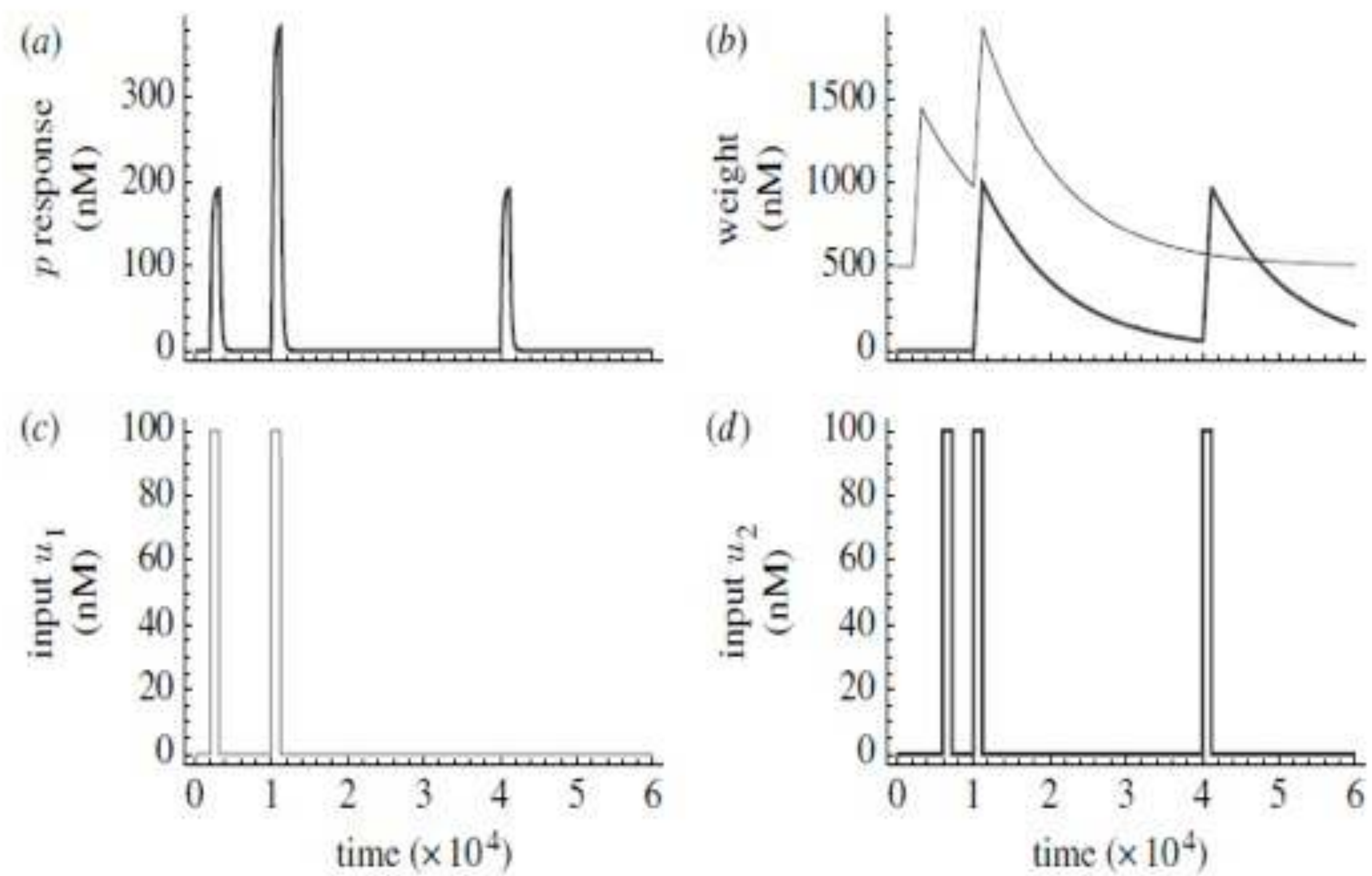
Molecular circuits for associative learning in single-celled organisms

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]



The Model Network

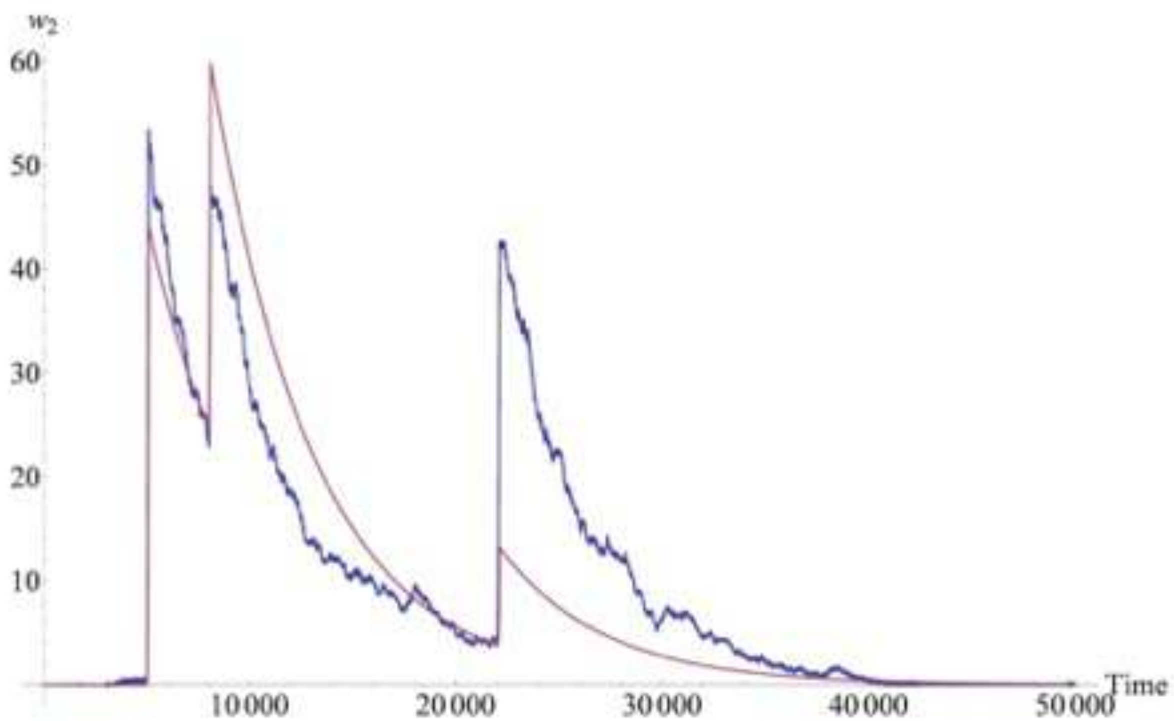




meat **bell**

In the first case where we are interested in eliciting simply a single response which lies out of range of the non-noisy system. We require that the output response p exceeds a threshold value of 40 but we also insist that in the 7000 seconds preceeding the pulse p does not exceed a lower threshold of 5.

Out of range of non noisy system



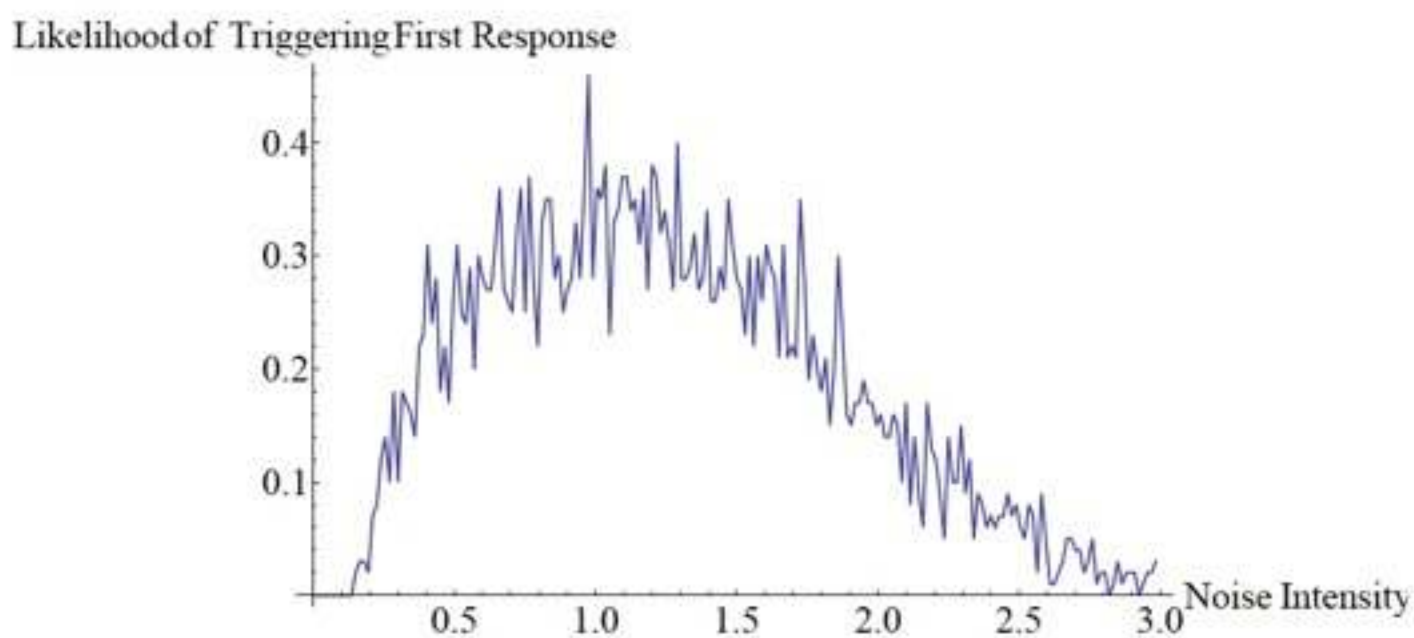
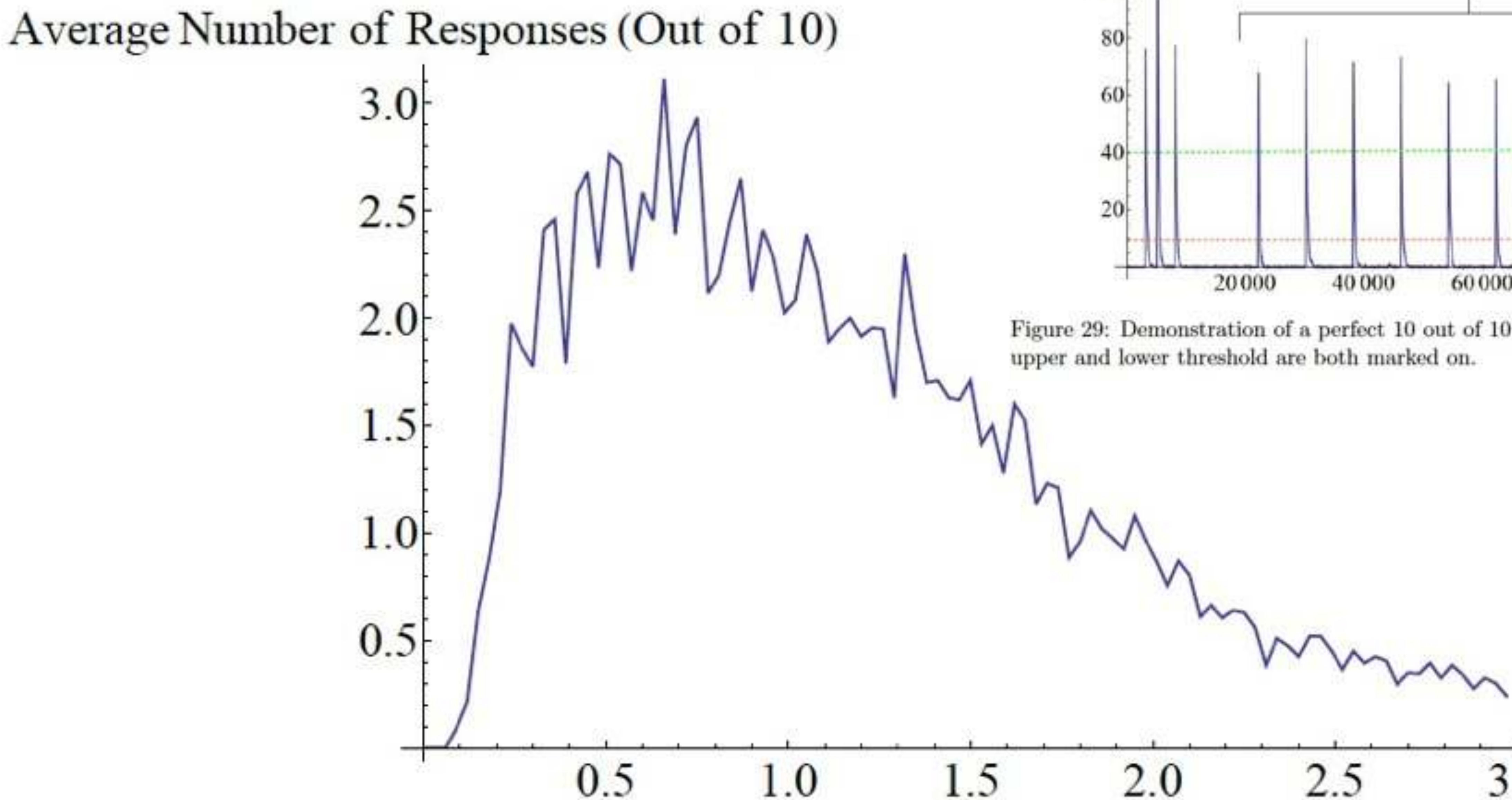


Figure 30

In the second case we present the system with a set of 10 evenly spaced input pulses, again the initial one is just out of range of the non-noisy system. Repeat simulations are performed and we can plot the expected number of responses against the intensity of noise added.



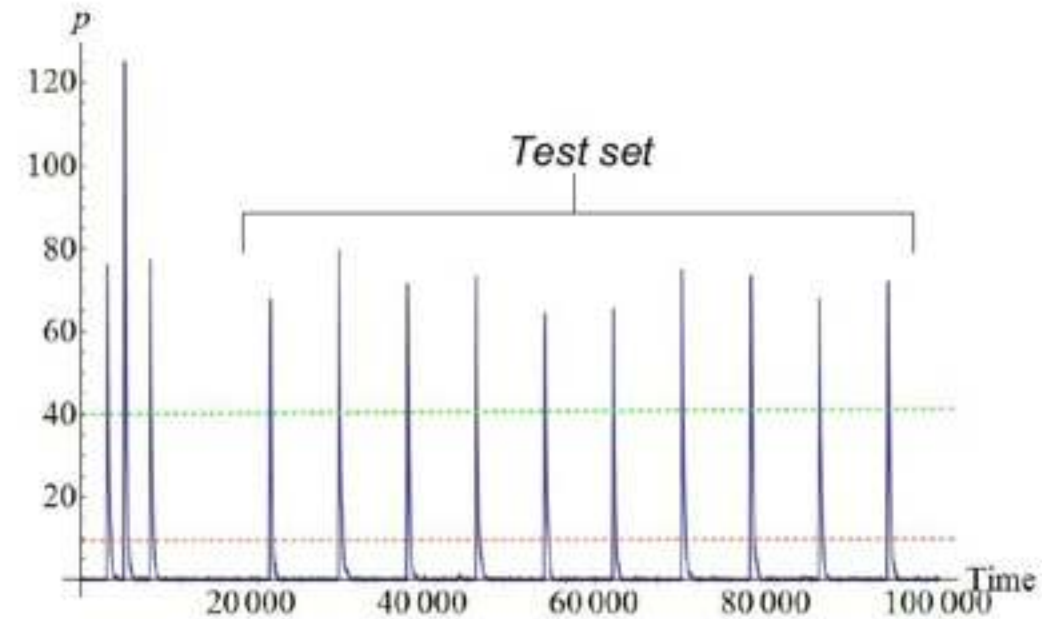


Figure 29: Demonstration of a perfect 10 out of 10 response to the series of inputs. An upper and lower threshold are both marked on.

Stochastic Resonance in a Genetic Perceptron

In the second case we present the system with a set of 10 evenly spaced input pulses, again the initial one is just out of range of the non-noisy system. Repeat simulations are performed and we can plot the expected number of responses against the intensity of noise added.

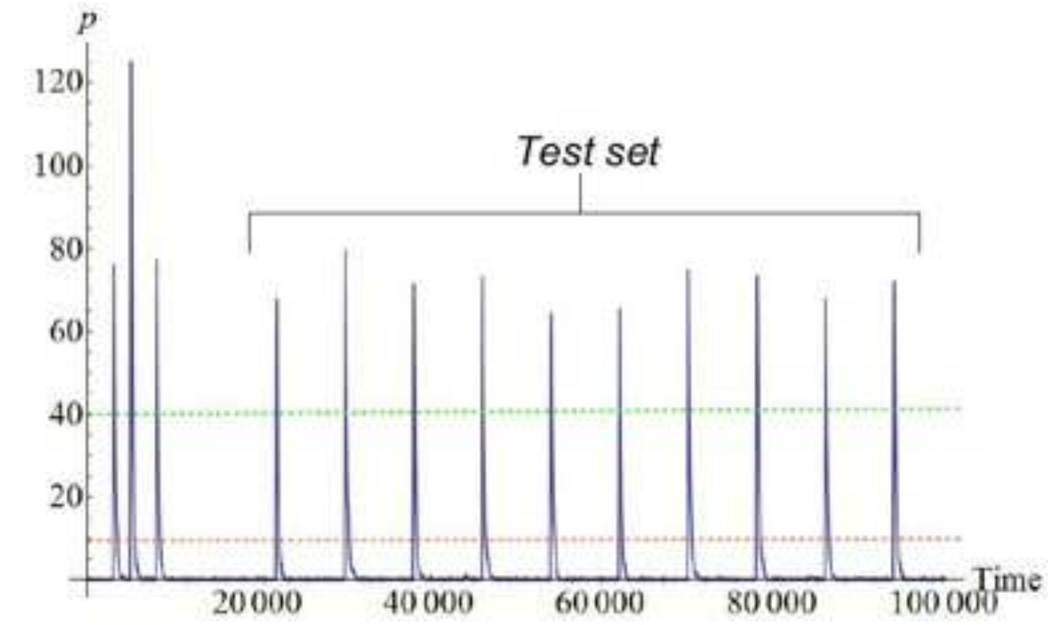
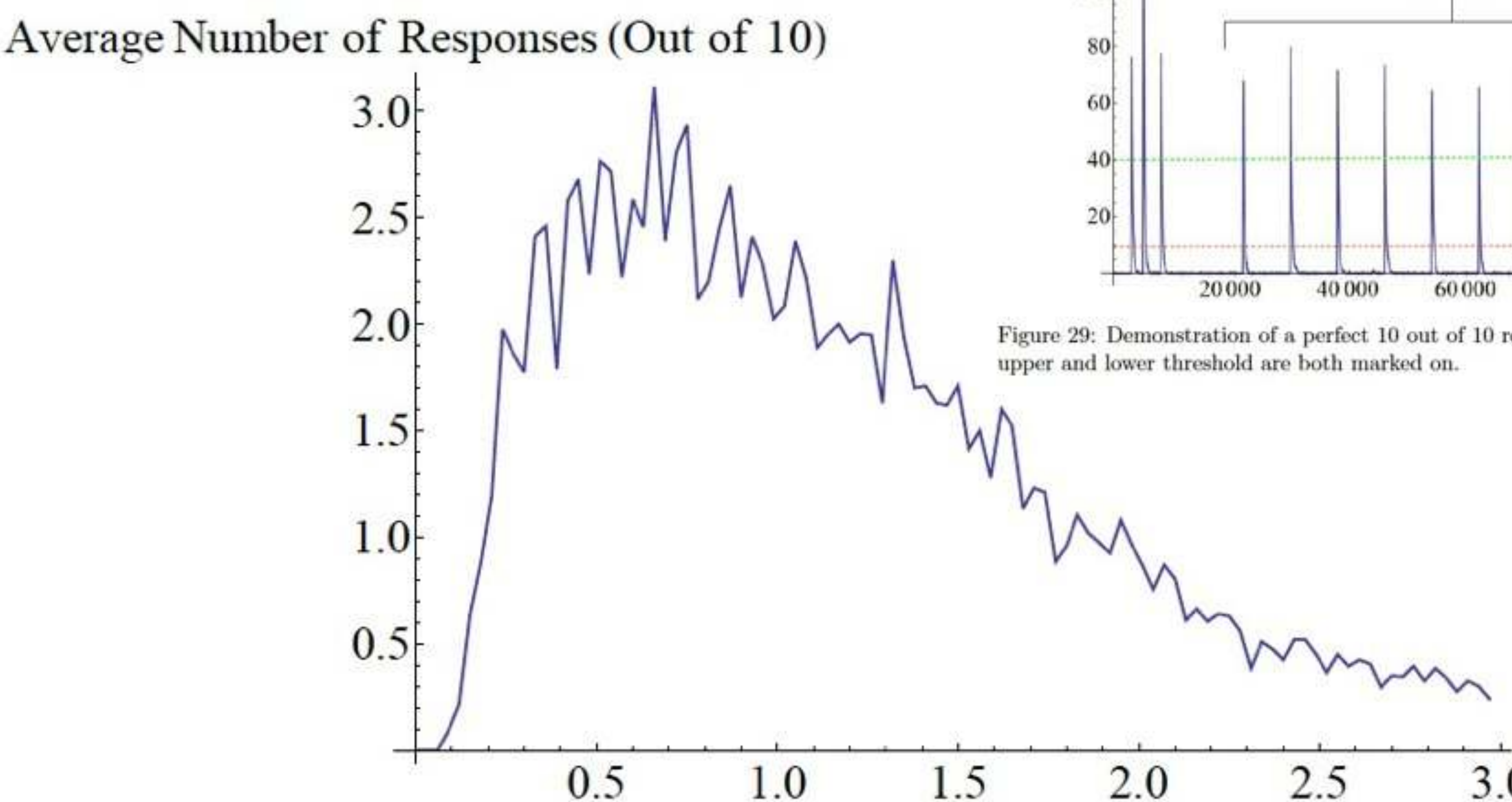


Figure 29: Demonstration of a perfect 10 out of 10 response to the series of inputs. An upper and lower threshold are both marked on.

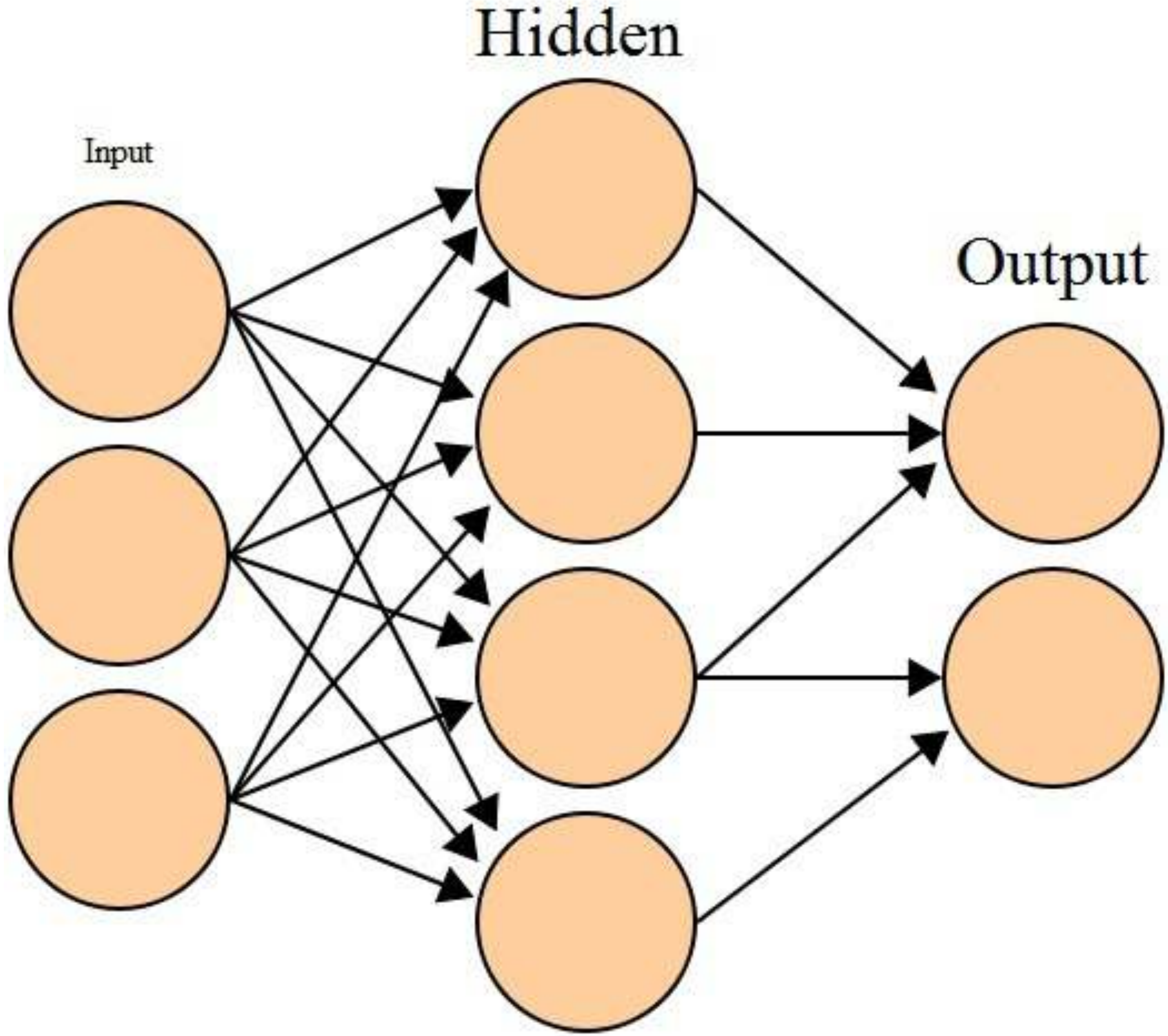


Summary

- Inside the cell we can have
  - basic perceptron
  - associative perceptron
- Surprisingly stochasticity (intrinsically present in gene expression) may improve the classification performed by intracellular perceptron

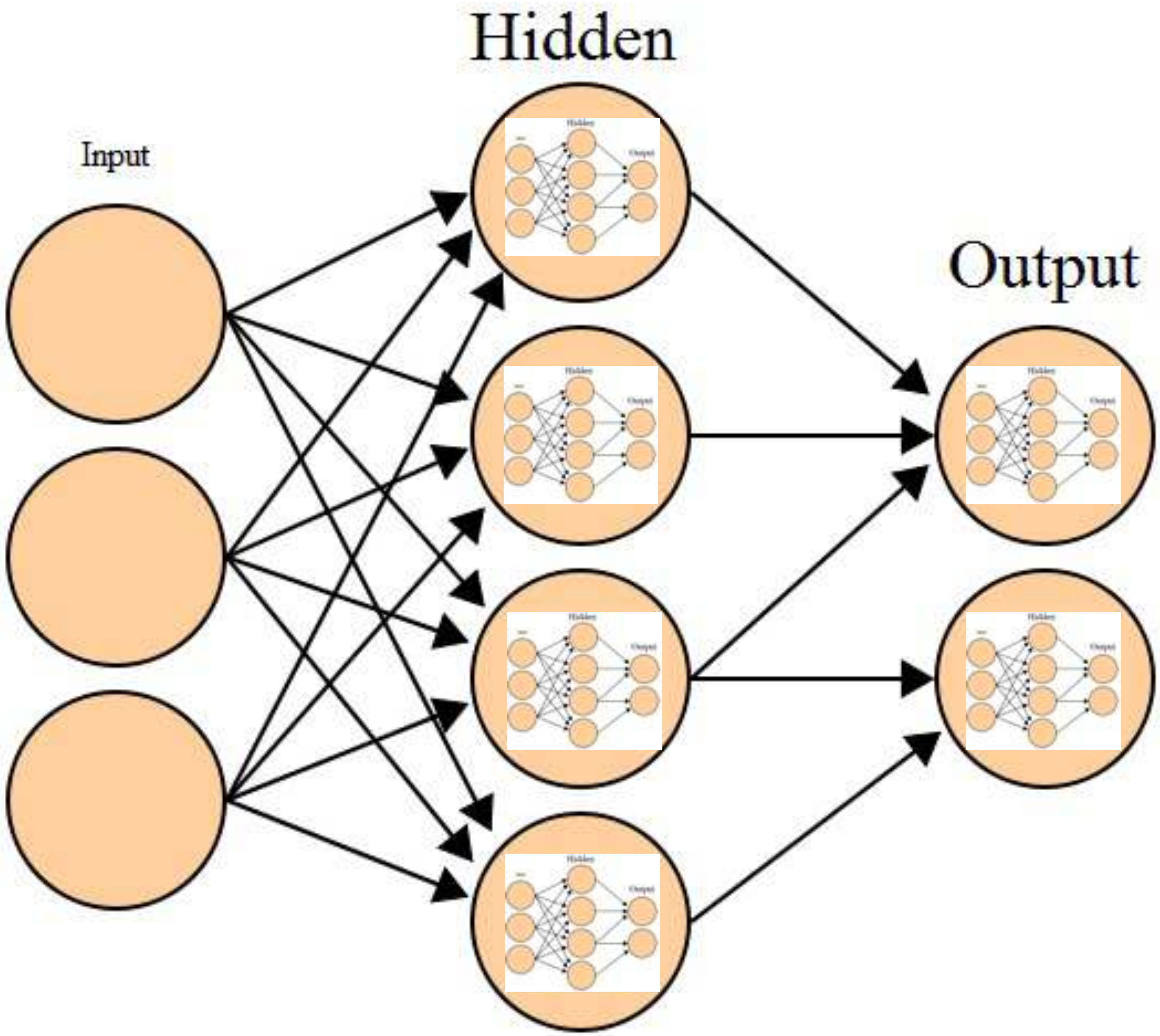
Open Questions

Brain as Network of Networks



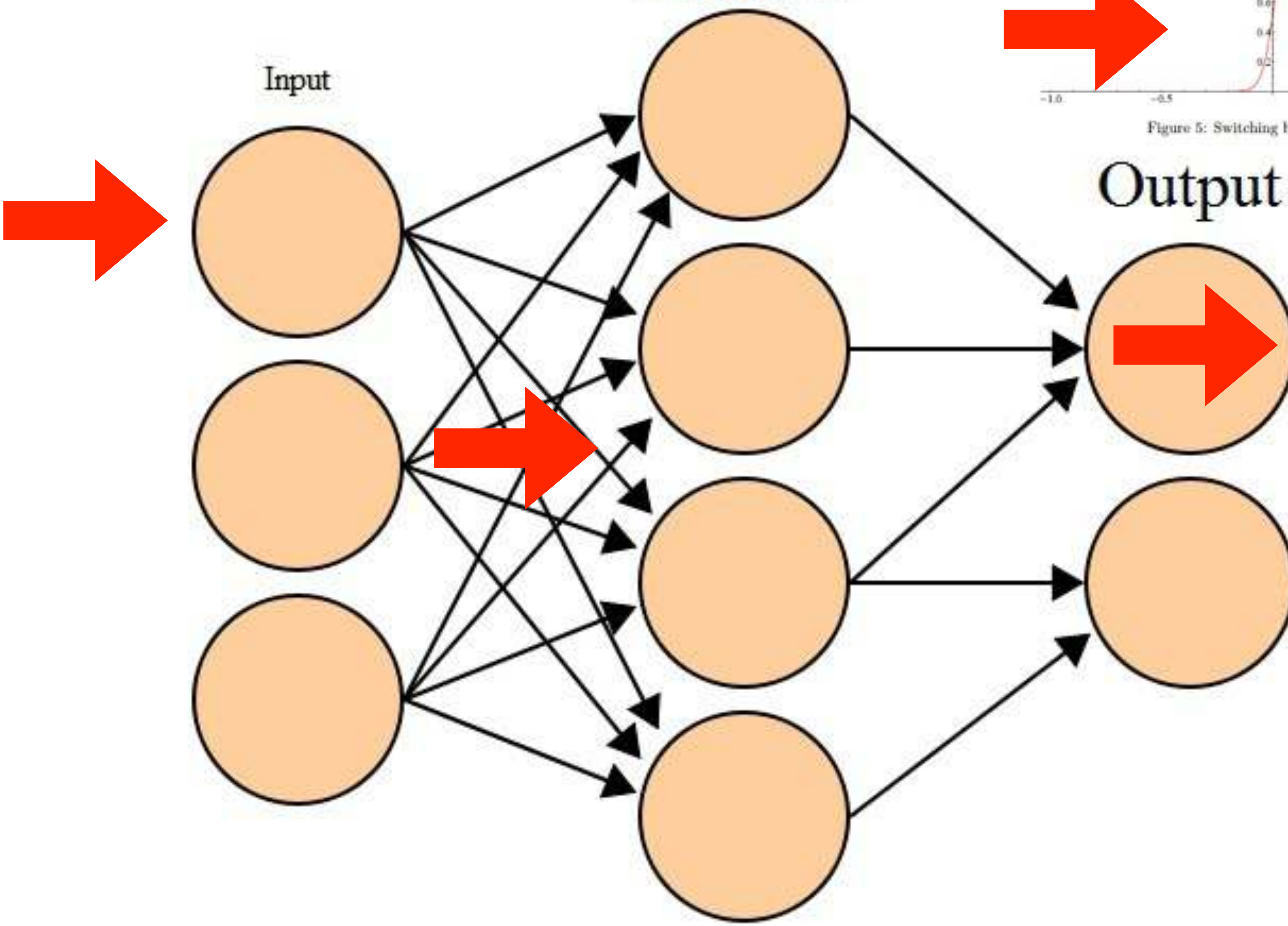
Open Questions

Brain as Network of Networks



Open Questions

Heterogeneity of Cancer



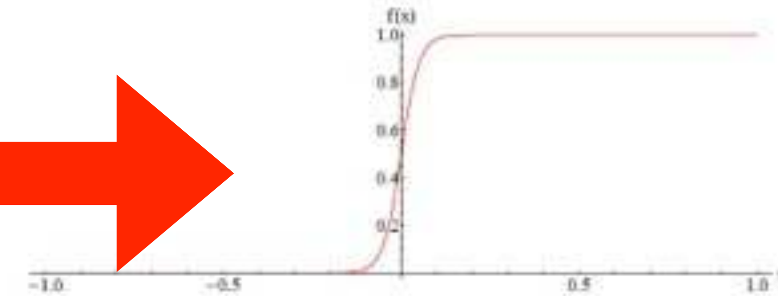


Figure 5: Switching behaviour of $f(x)$.

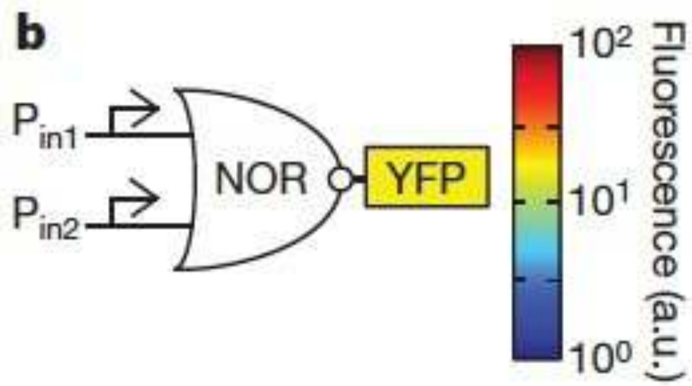
Open Questions   Perceptrons in Synthetic Biology

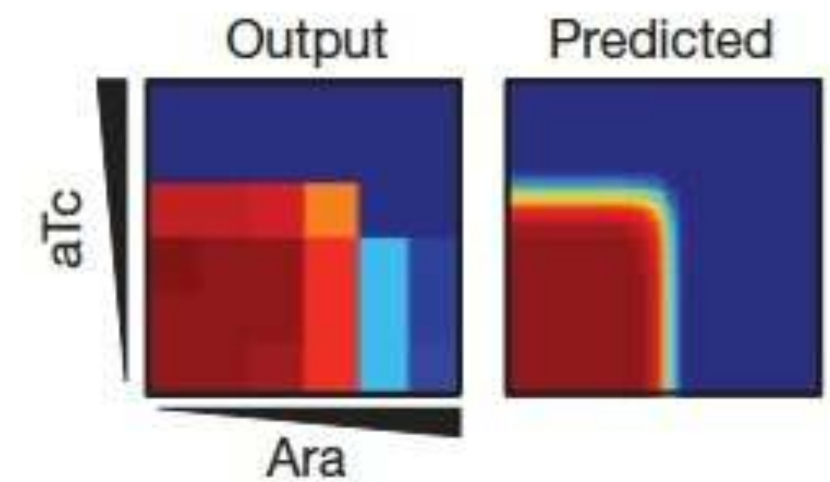
LETTER

doi:10.1038/nature09565

Robust multicellular computing using genetically encoded NOR gates and chemical 'wires'

Alvin Tamsir[1], Jeffrey J. Tabor[2] & Christopher A. Voigt[2]





Inputs		
in1	in2	Output
0	0	1
0	1	0
1	0	0
1	1	0

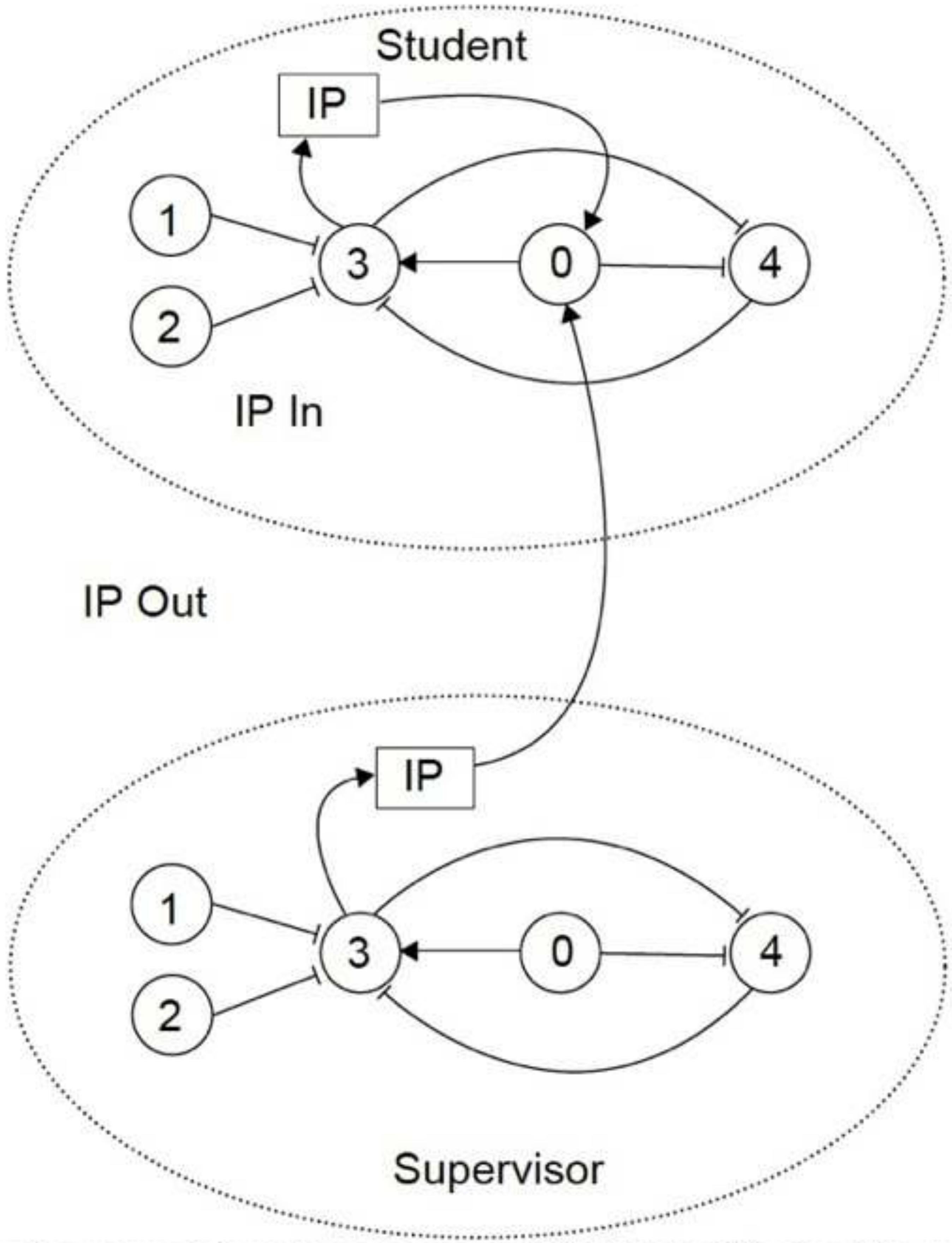
Figure 2 | Input modularity of the gates. a, Transfer functions for three OR gates (left) are compared with the predicted transfer function (right). The predicted transfer function is the simple sum of the transfer functions measured for the individual promoters (Supplementary Information). The Ara and aTc concentrations used are the same as in Fig. 1 and those for 3OC12-HSL are 0, 0.001, 0.01, 0.1, 1 and 10 μM (squares from bottom to top). **b,** Transfer functions for three NOR gates (left) are compared with the predicted transfer functions (right). The data represent means calculated from three experiments.

To be synthetically implemented:

Suprising dynamics in:

1. **Intercell communication**:
    1. Desynchronization, rhythm generation, memory
2. **Decision making**
3. **Cellular intelligence and effect of noise on this intelligence**

THANK YOU!!



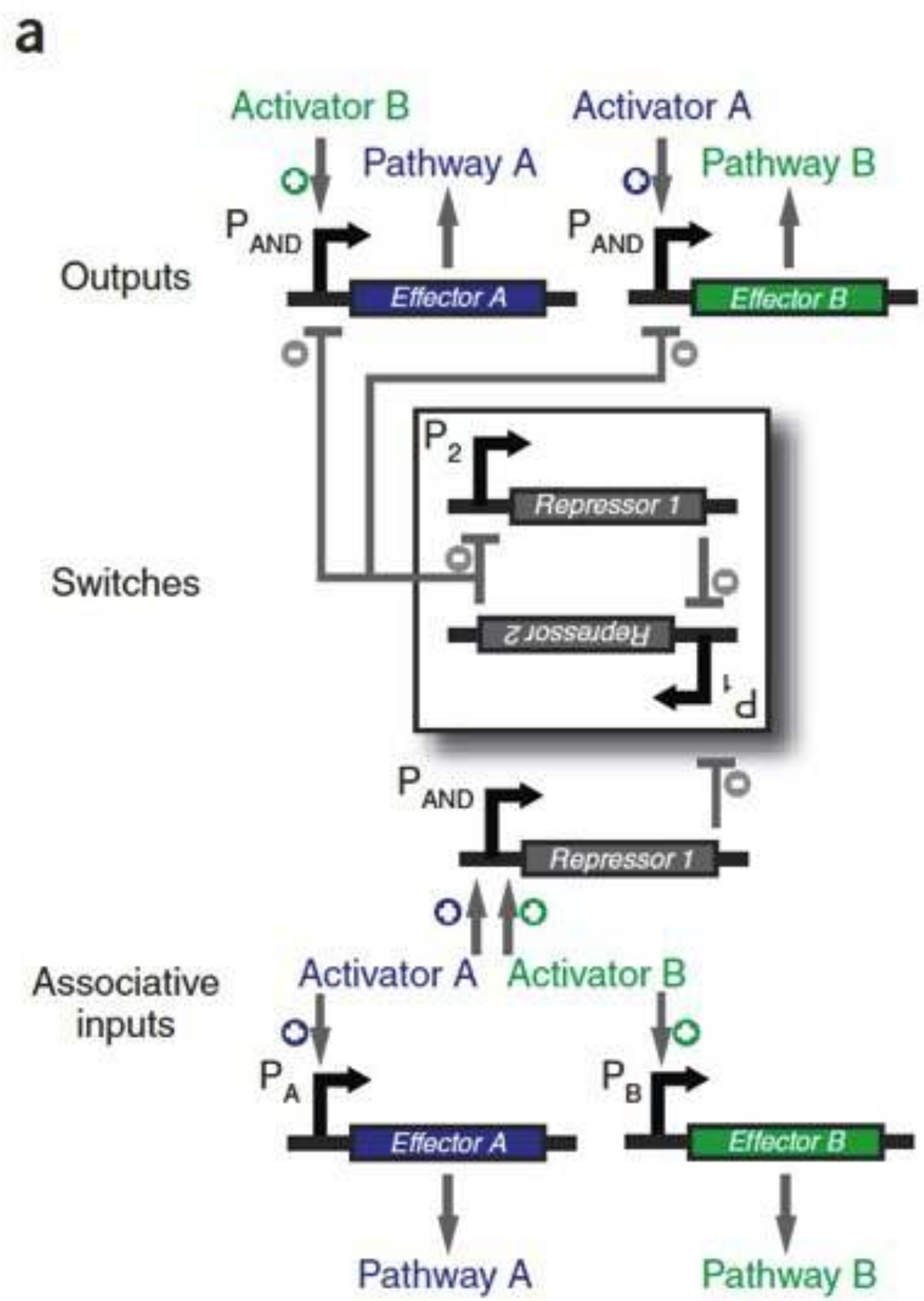
The scheme. Supervisor network is used as a memory of "ideal" classification. The student network will learn until it classifies input 1 and 2 correctly.

Next-generation synthetic gene networks

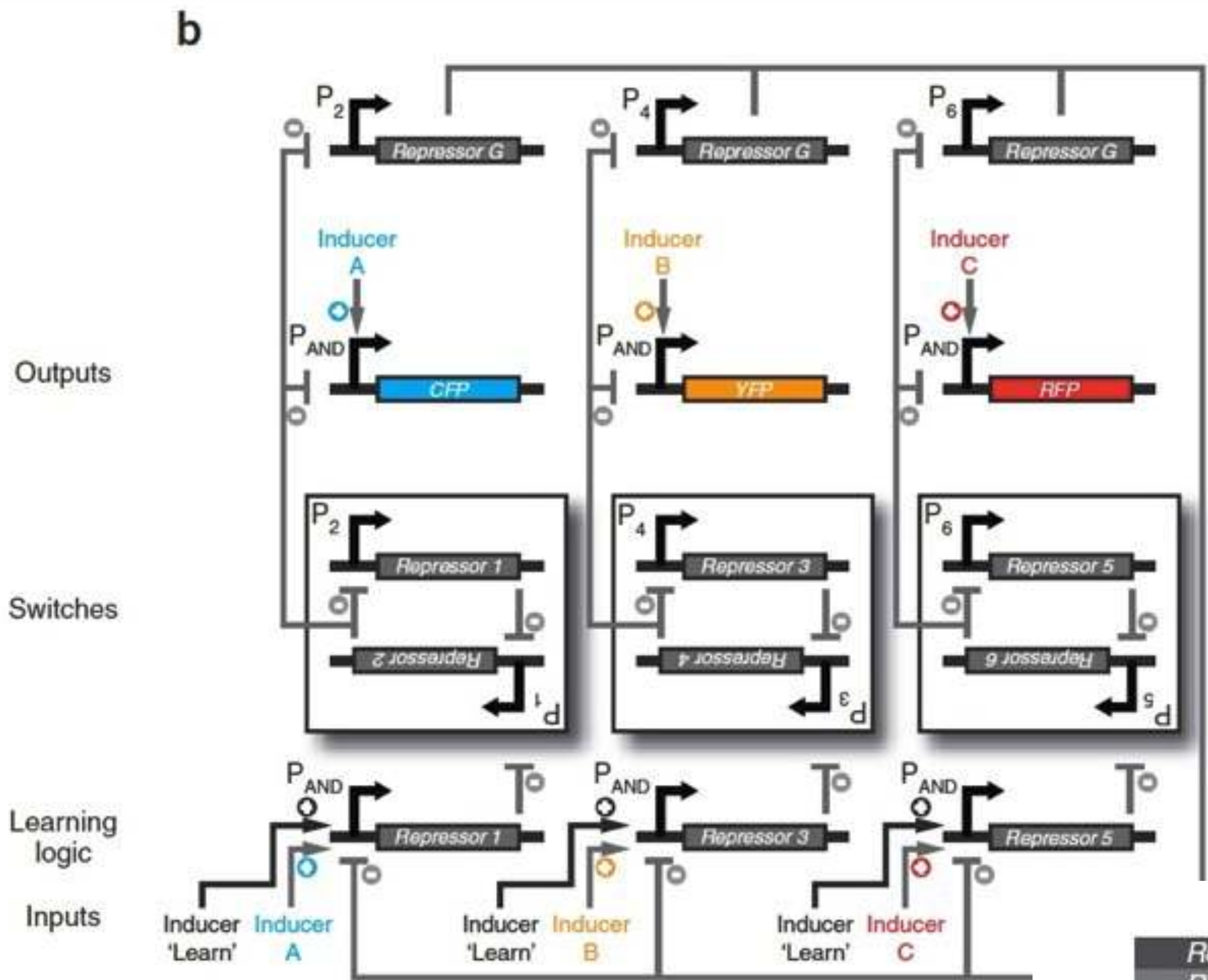
Timothy K Lu[1–3], Ahmad S Khalil[3] & James J Collins[3,4]

VOLUME 27 NUMBER 12 DECEMBER 2009 NATURE BIOTECHNOLOGY

a



Genes	*Repressor 1*	0	0	1	1
	Repressor 2	1	1	0	0
	Effector A	0	1	1	1
	Effector B	0	0	1	1
Proteins	Activator A	0	1	1	1
	Activator B	0	0	1	0
	Effector A	0	1	1	1
	Effector B	0	0	1	1
	Activator	A	A B	A	



Repressor 1	0	0	0
Repressor 2	1	1	1
Repressor 3	0	1	1
Repressor 4	1	0	0
Repressor 5	0	0	0
Repressor 6	1	1	1
Repressor G	0	1	1
CFP	0	0	0
YFP	0	0	1
RFP	0	0	0