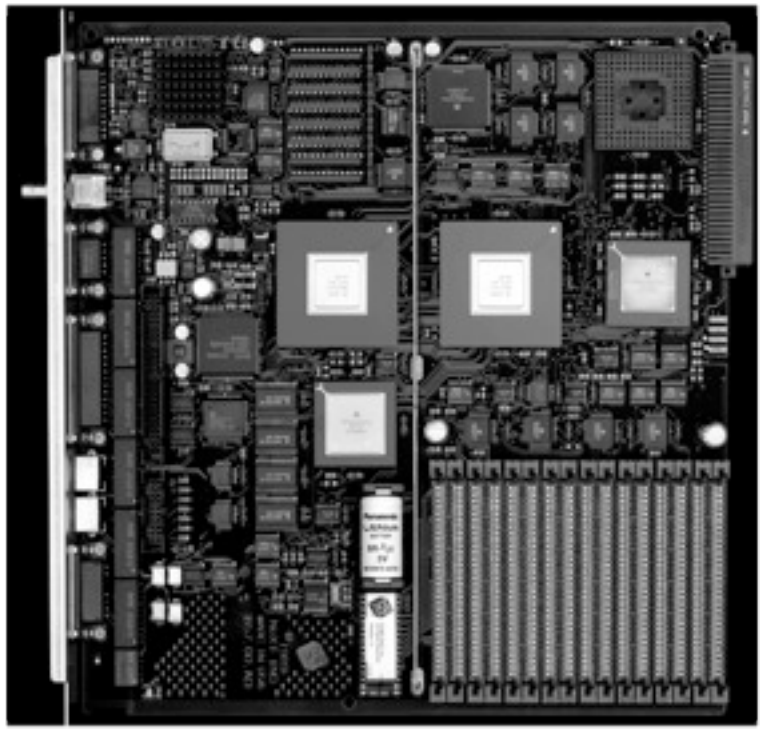
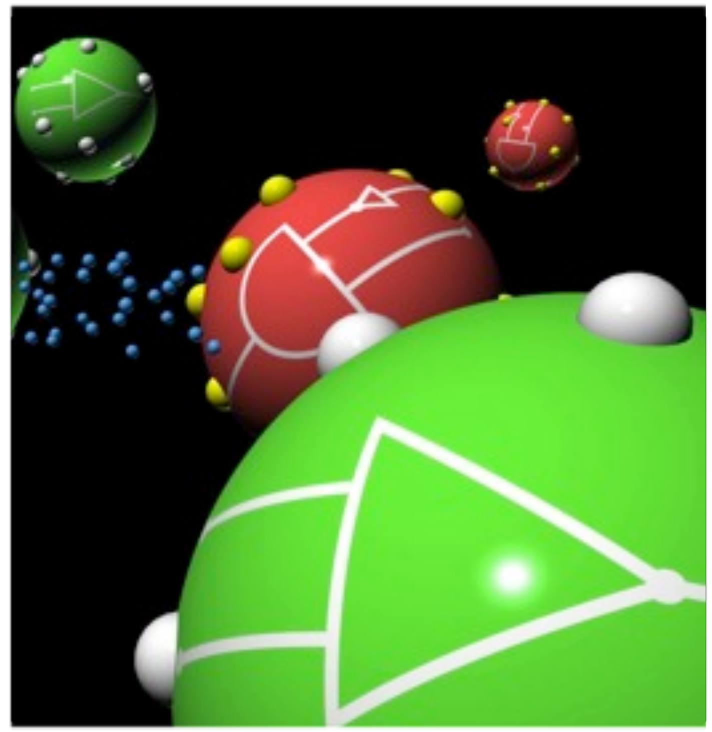
Synthetic biological computers: new design principles?

RoSBNet Workshop, Oxford, July 2011





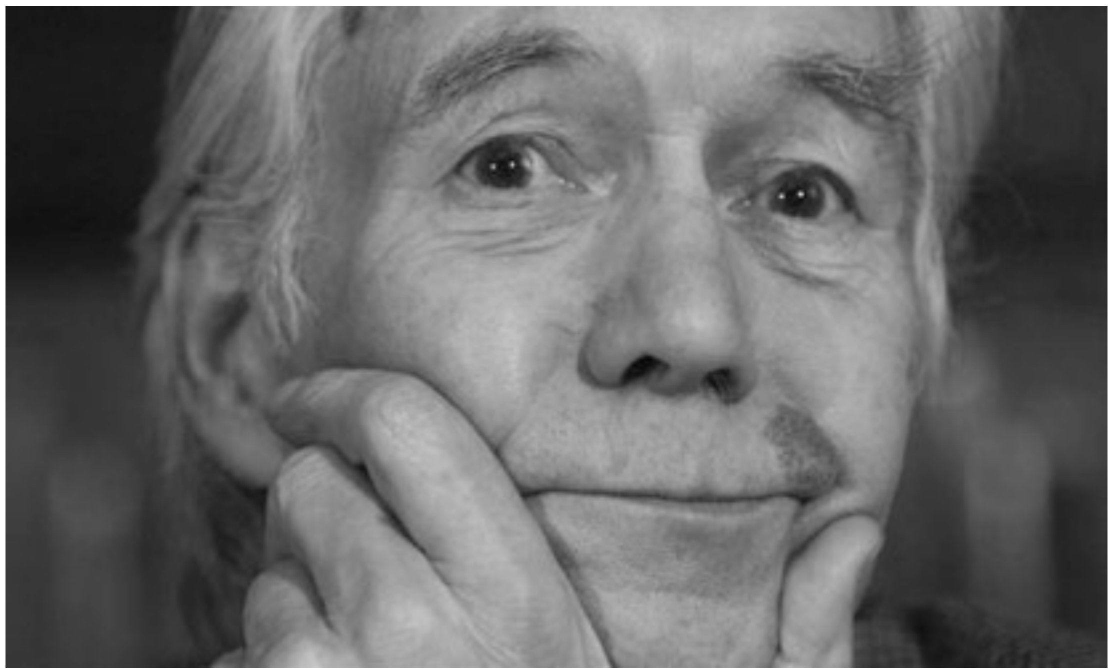
Ricard Solé
ICREA-Complex Systems Lab, Universitat Pompeu Fabra
Santa Fe Institute, New Mexico

icrea Institució Catalana de Recerca i Estudis Avançats

UNIVERSITAT POMPEU FABRA

Fundación Marcelino Botín

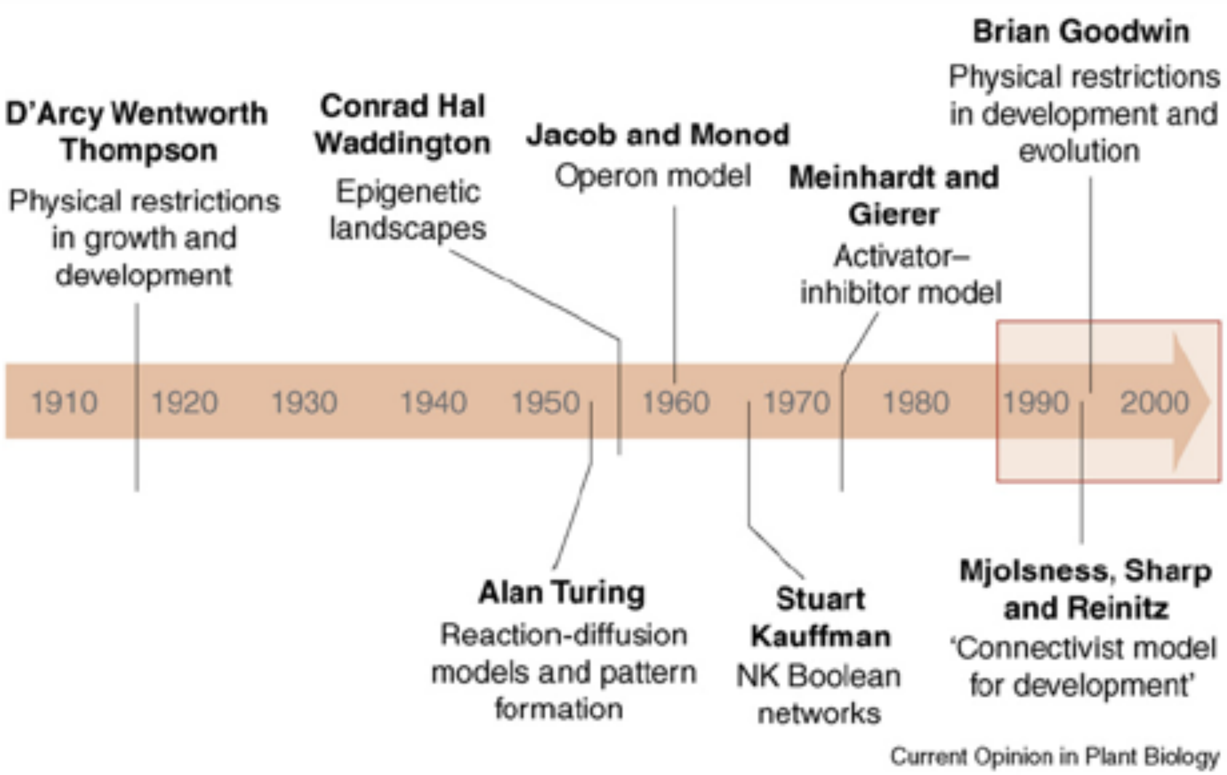
Brian Goodwin on networks and evolution

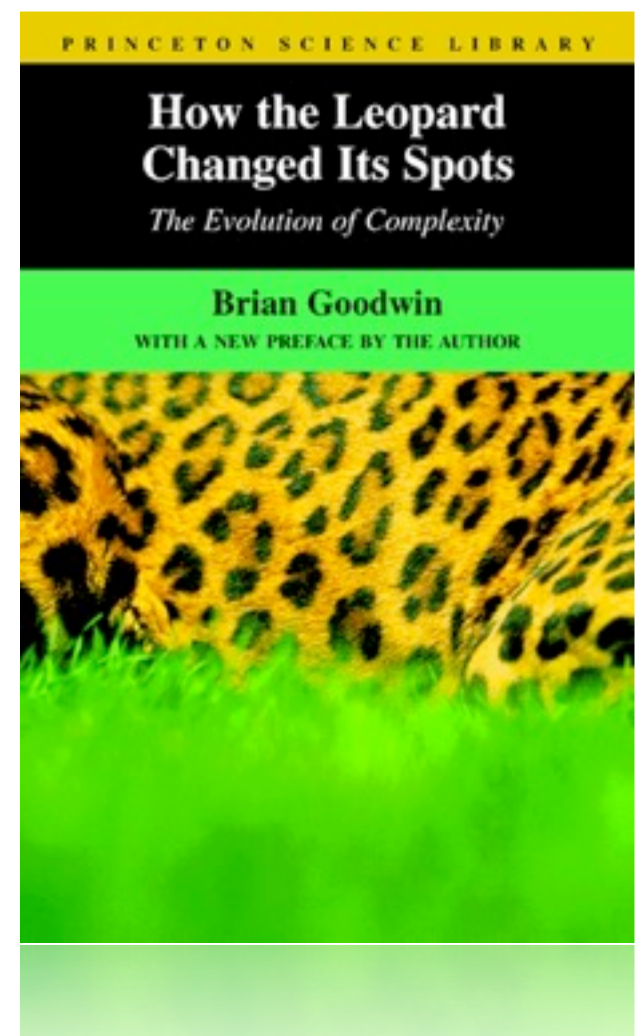


First model of gene regulation
First model of oscillatory genetic circuit
Theory of gene networks

Form and Transformation: Generative and Relational Principles in Biology,
Cambridge Univ Press, 1996.

How the Leopard Changed its Spots: The Evolution of Complexity,
Scribner, 1994





Where does network complexity come from?

Selection, Tinkering, and Emergence in Complex Networks

RICARD V. SOLÉ,[1,2] RAMON FERRER-CANCHO,[1] JOSE M. MONTOYA,[1,3] AND SERGI VALVERDE[1]
[1]*ICREA-Complex Systems Lab, GRIB-UPF, Barcelona, Spain*
[2]*Sante Fe Institute, Santa Fe, NM 87501*
[3]*Department of Ecology, University of Alcalá, Madrid, Spain*

Complexity, 2003

Summary of the Basic Features that Relate and Distinguish Different Types of Complex Networks, Both Natural and Artificial

Property	Proteomics	Ecology	Language	Technology
Tinkering	Gene duplication and recruitation	Local assemblages from regional species pools and priority effects	Creation of words from already established ones	Reutilization of modules and components
Hubs	Cellular signaling genes (e.g., p53)	Omnivorous and most abundant species	Function words	Most used components
What can be optimized?	Communication speed and linking cost	Unclear	Communication speed with restrictions	Minimize development effort within constraints
Failures	Small phenotypic effect of random mutations	Loss of only a few species-specific functions	Maintenance of expression and communication	Loss of functionality
Attacks	Large alterations of cell-cycle and apoptosis (e.g., cancer)	Many coextinctions and loss of several ecosystems functions	Agrammatism (i.e., great difficulties for building complex sentences)	Avalanches of changes and large development costs
Redundancy and degeneracy	Redundant genes rapidly lost	R minimized and D restricted to non-keystone species	Great D	Certain degree of R but no D

Here different characteristic features of complex nets, as well as their behavior under different sources of perturbation, are considered.

What is the role of tinkering?

"Natural selection does not work as an engineer but as a tinkerer, limited by the constraints present at all levels of biological organization"

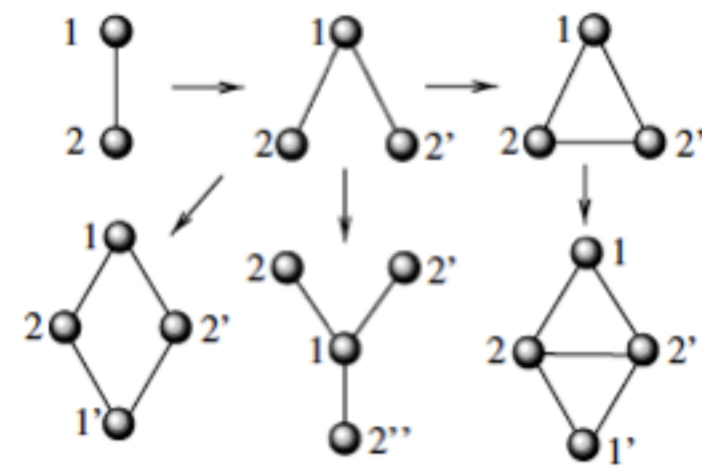
François Jacob

Science 196: 1161-1166 (1976)

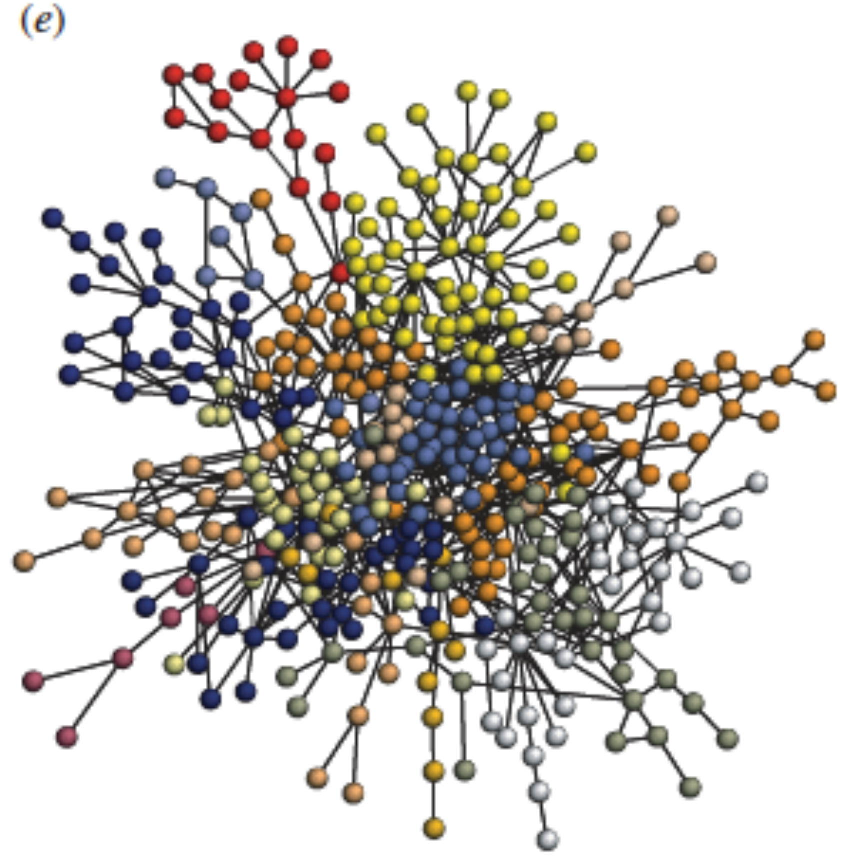
Are network motifs the spandrels of cellular complexity?

Ricard V. Solé[1,2] and Sergi Valverde[1]

[1] ICREA-Complex Systems Lab, Universitat Pompeu Fabra, Dr. Aiguader 80, 08003 Barcelona, Spain
[2] Santa Fe Institute, 1399 Hyde Park Road, Santa Fe, NM 87501, USA



(e)



JOURNAL OF THE ROYAL SOCIETY Interface

J. R. Soc. Interface (2008) 5, 129–133
doi:10.1098/rsif.2007.1108
Published online 11 July 2007

REPORT

Spontaneous emergence of modularity in cellular networks

Ricard V. Solé[1,2,*] and Sergi Valverde[1,2]

Tinkering is widespread, even in Tech

PHYSICAL REVIEW E 72, 026107 (2005)

Network motifs in computational graphs: A case study in software architecture

Sergi Valverde[1] and Ricard V. Solé[1,2]

EUROPHYSICS LETTERS

Europhys. Lett., **72** (5), pp. 858–864 (2005)

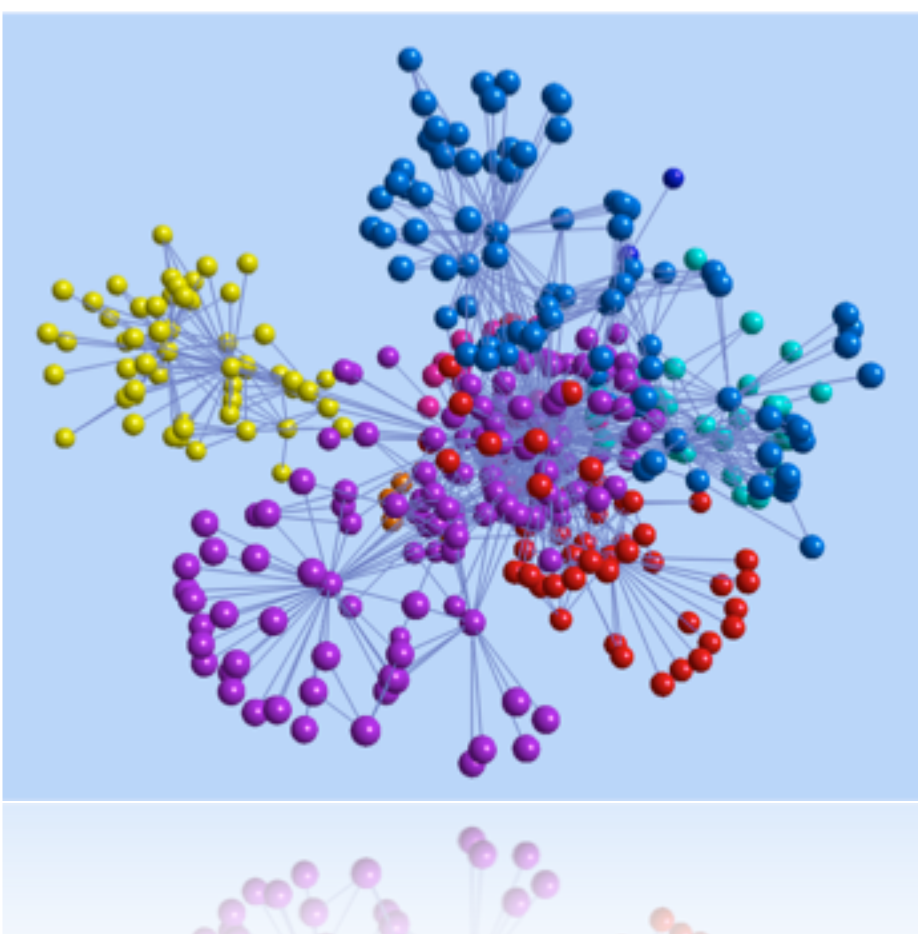
DOI: 10.1209/epl/i2005-10314-9

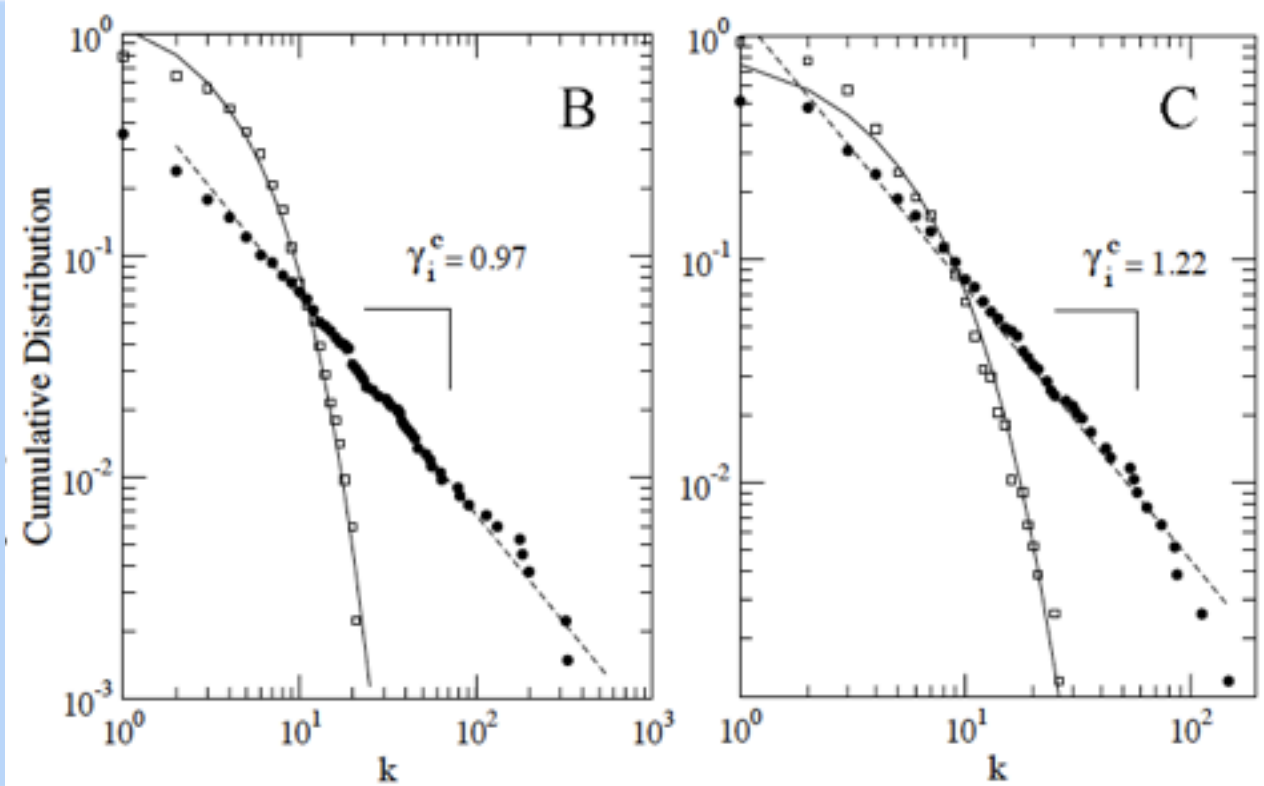
Logarithmic growth dynamics in software networks

S. Valverde[1] and R. V. Solé[1,2]

$$\frac{\mathrm{d}L}{\mathrm{d}t} = \left[mp + mq \frac{L}{\Phi(t)} \right] \dot{\Phi}^{-1}$$

$$L(t) = e^{mq \int (\Phi\dot{\Phi})^{-1} \mathrm{d}t} \left[mp \int e^{-mq \int (\Phi\dot{\Phi})^{-1} dt} \dot{\Phi}^{-1} \mathrm{d}t + \Gamma \right]$$

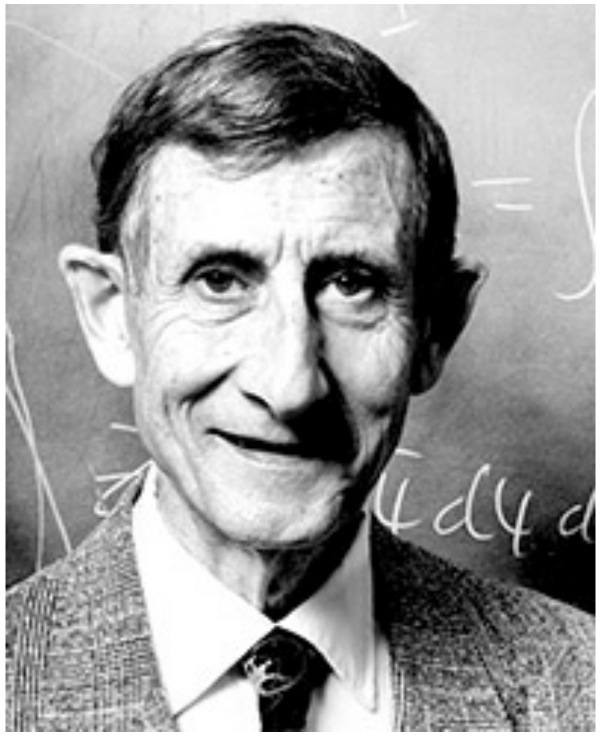




SynBio, evolution, functionality and design

With rare exceptions, Darwinian evolution requires established species to become extinct so that new species can replace them.

Now, after three billion years, the Darwinian interlude is over.



Our Biotech future

Freeman Dyson

http://www.nybooks.com/articles/archives/2007/jul/19/our-biotech-future/

A common description of functionality

All biological systems perform some kind of computation. Computation is inherent to adaptive systems and makes biology different from physics.

John Hopfield

Physics, computation and why biology looks so different.

J. Theor. Biol. 171, 53-60 (1994)

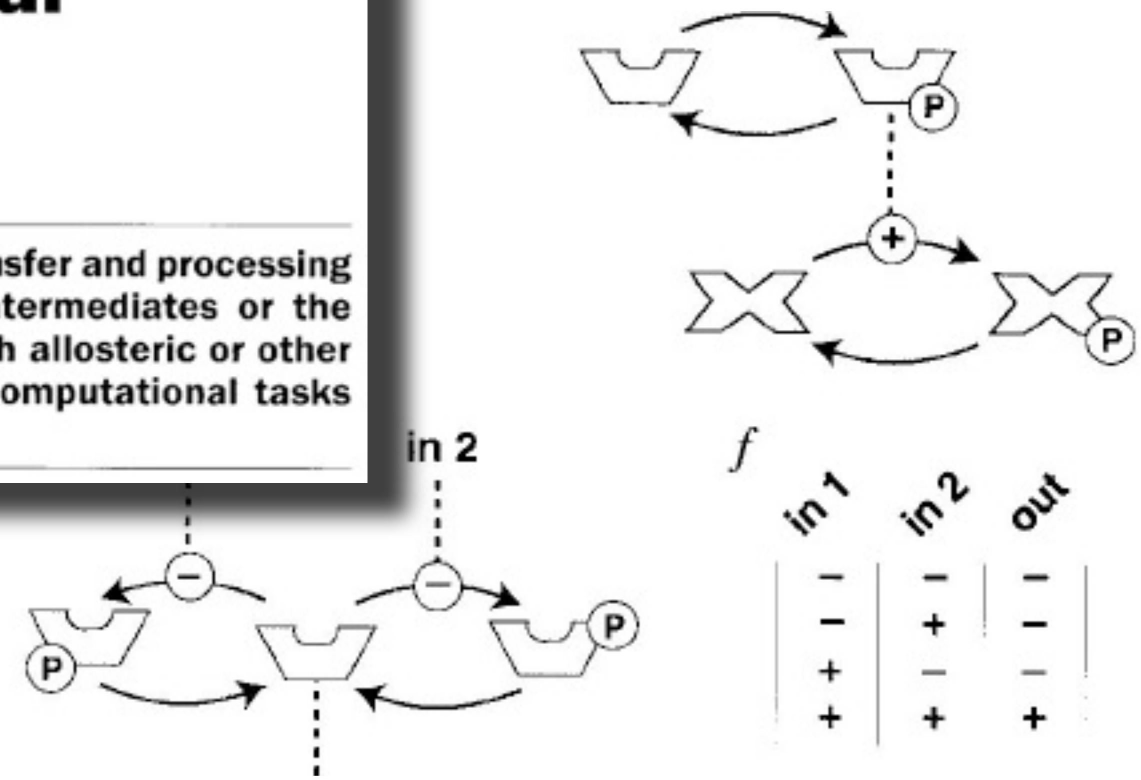
Cells and molecules as computers

REVIEW ARTICLE

Protein molecules as computational elements in living cells

Dennis Bray

Many proteins in living cells appear to have as their primary function the transfer and processing of information, rather than the chemical transformation of metabolic intermediates or the building of cellular structures. Such proteins are functionally linked through allosteric or other mechanisms into biochemical 'circuits' that perform a variety of simple computational tasks including amplification, integration and information storage.

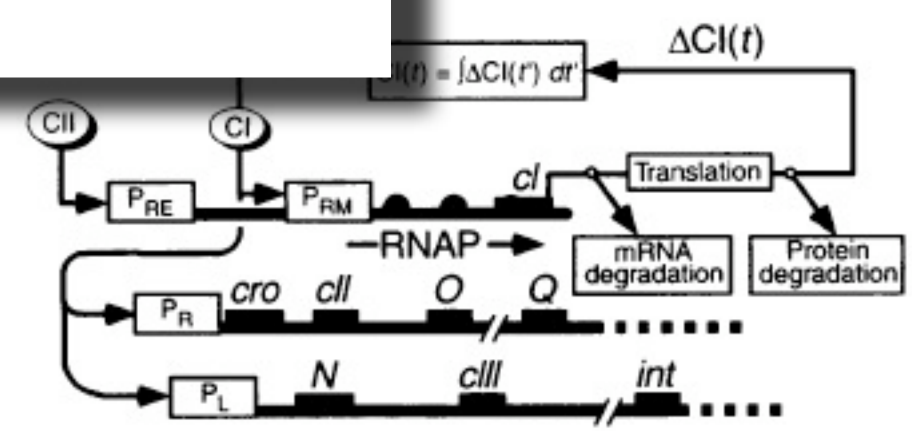


Nature 1995

ARTICLE

Circuit Simulation of Genetic Networks

Harley H. McAdams and Lucy Shapiro



Science 1995

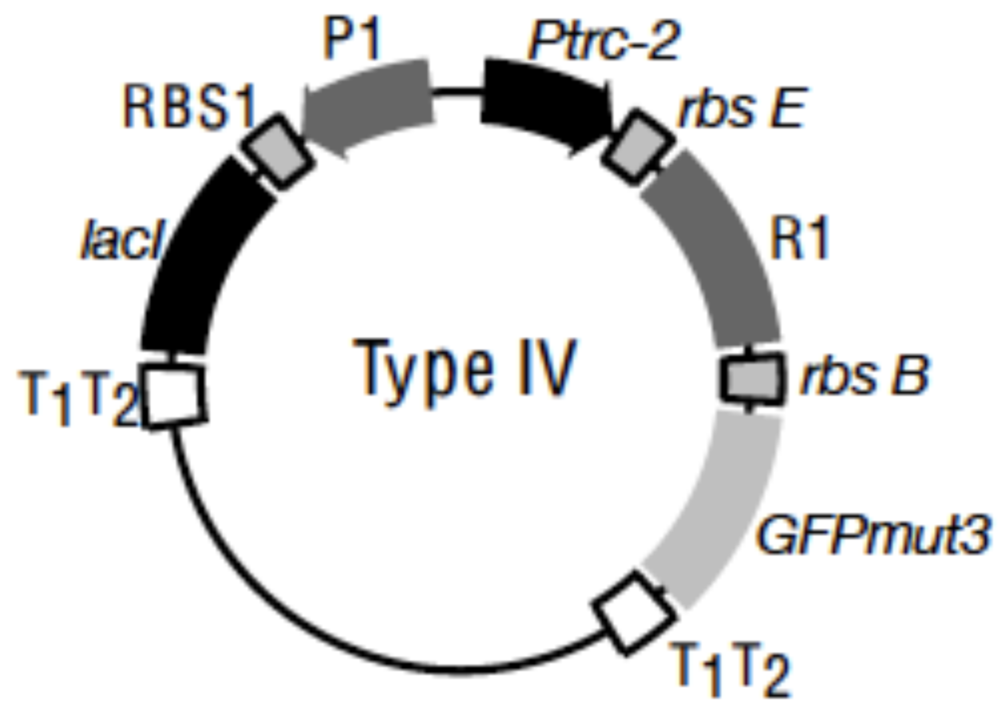
Synthetic biology: milestones

letters to nature

Construction of a genetic toggle switch in *Escherichia coli*

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

** Department of Biomedical Engineering, † Center for BioDynamics and ‡ Center for Advanced Biotechnology, Boston University, 44 Cummington Street, Boston, Massachusetts 02215, USA*



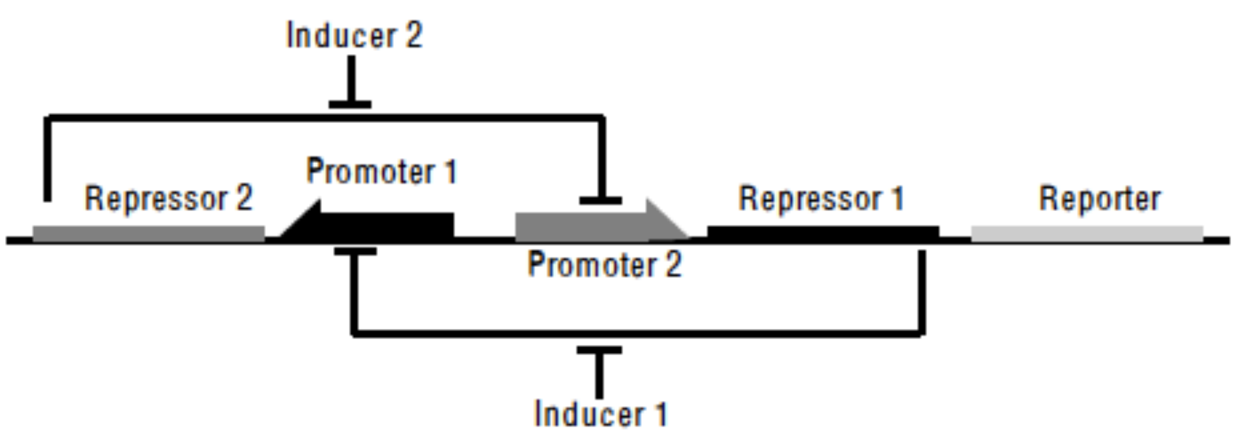
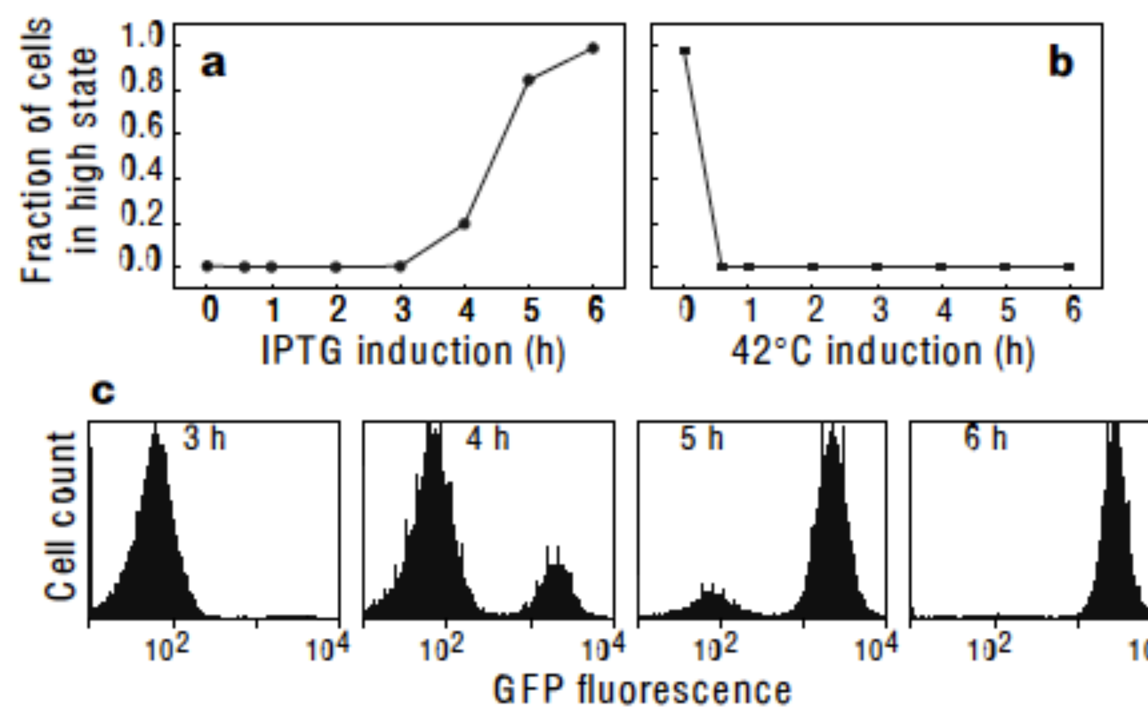
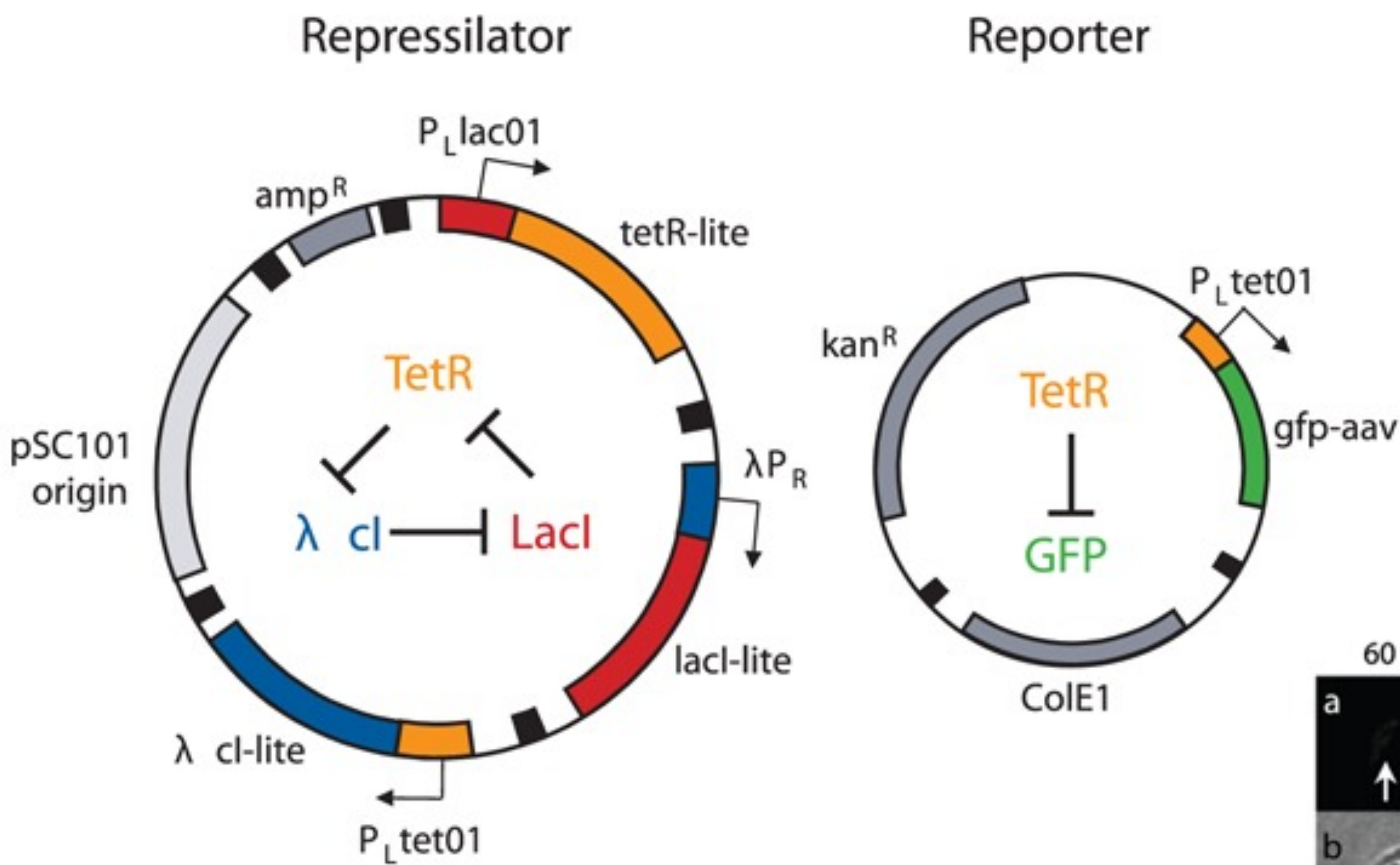


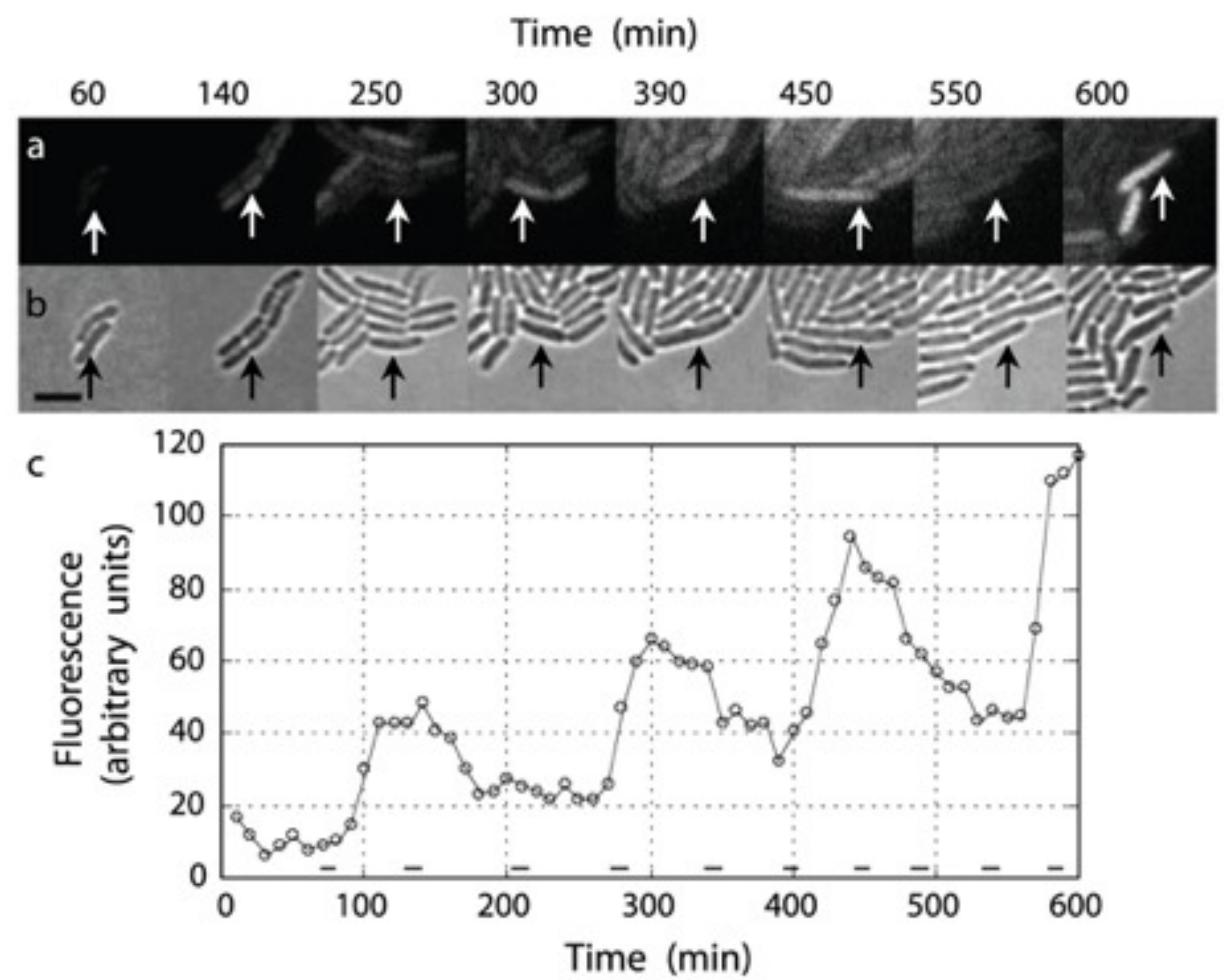
Figure 1 Toggle switch design. Repressor 1 inhibits transcription from Promoter 1 and is induced by Inducer 1. Repressor 2 inhibits transcription from Promoter 2 and is induced by Inducer 2.



Synthetic biology: repressilator



A molecular clock out of three mutually inhibiting regulations

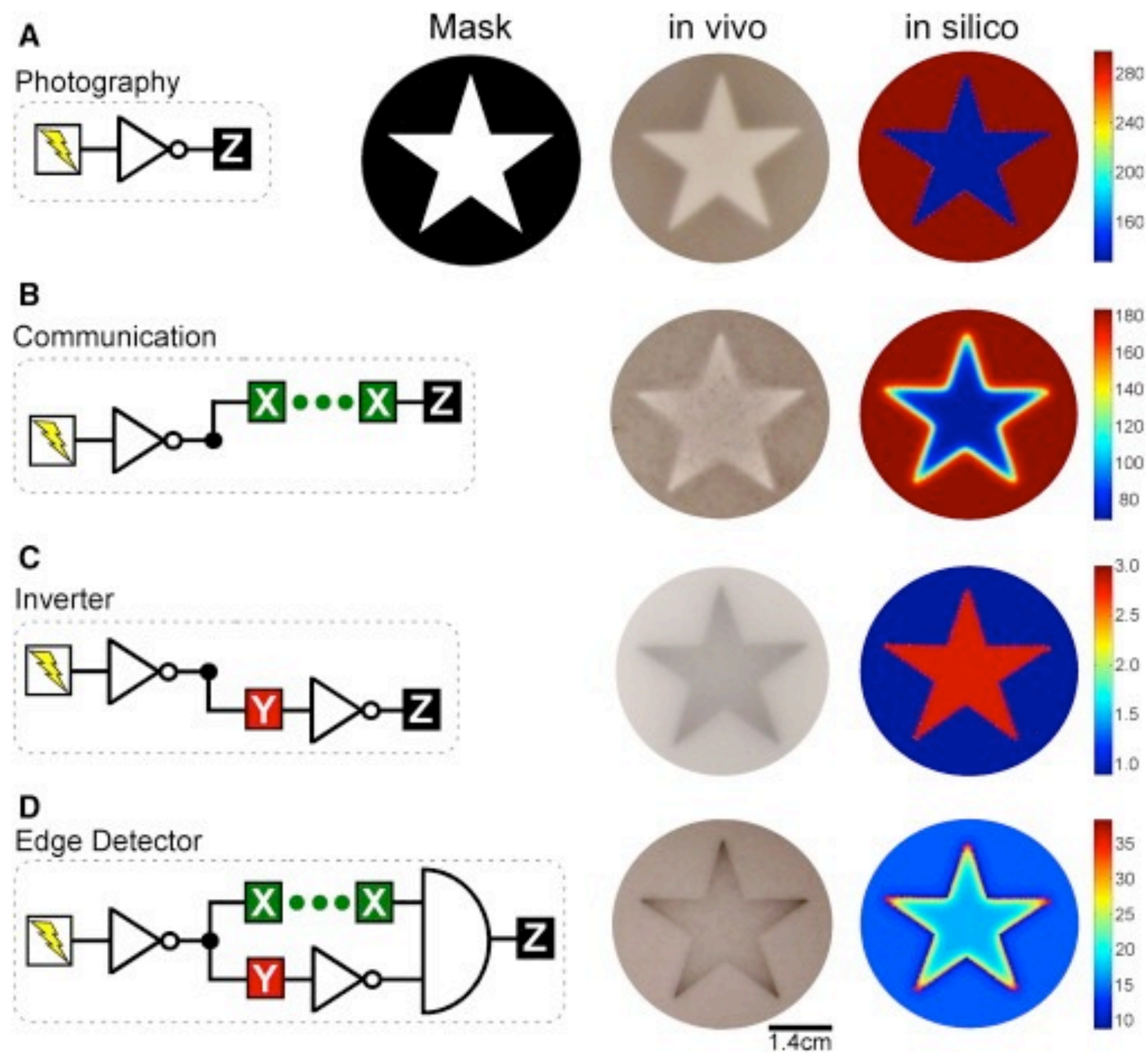


$$\frac{dm_i}{dt} = -m_i + \frac{\alpha}{(1+p_j^n)} + \alpha_0$$

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

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

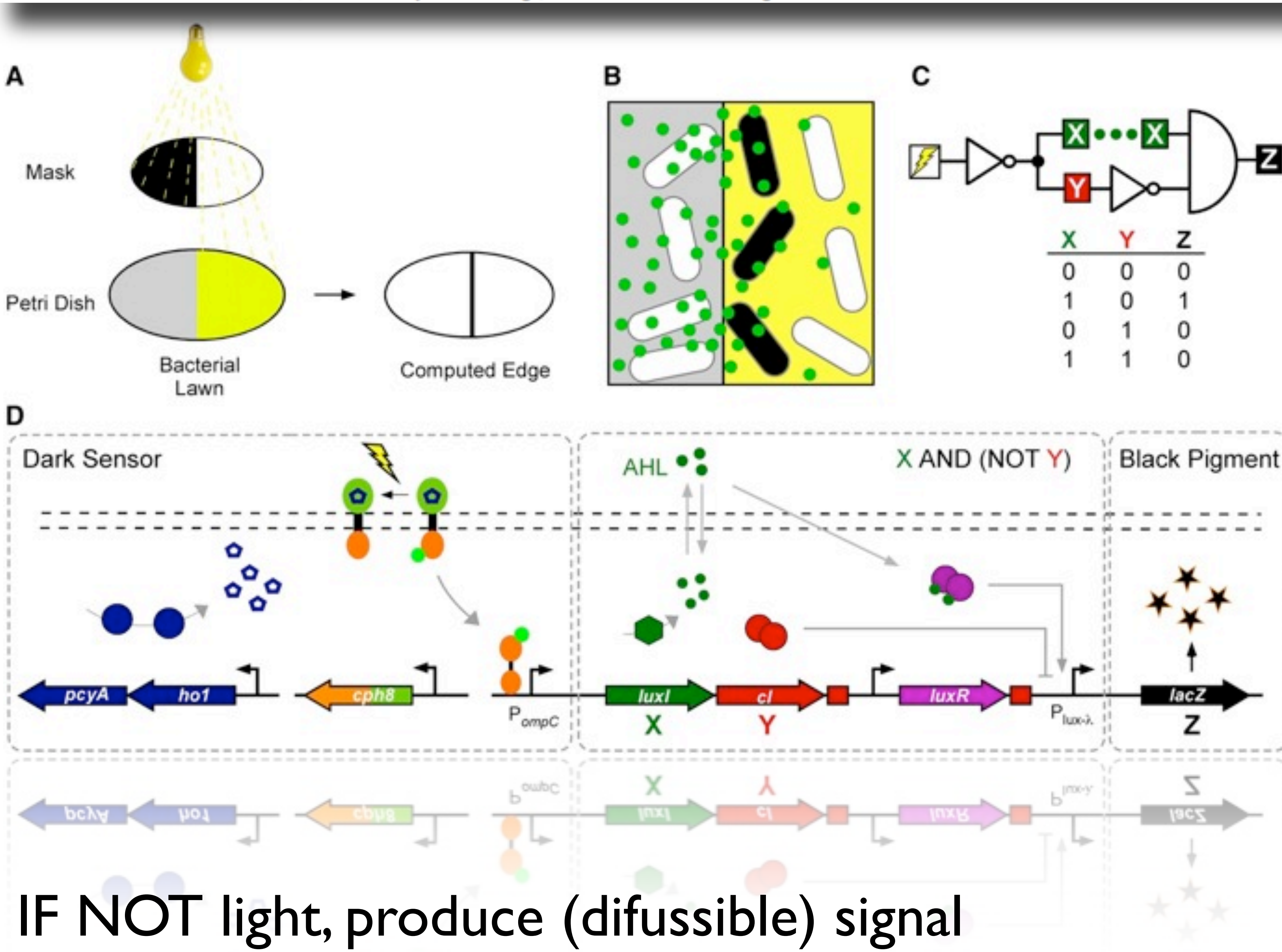
Synthetic biology: edge detector



Synthetic biology: edge detector

A Synthetic Genetic Edge Detection Program

Jeffrey J. Tabor,[1] Howard M. Salis,[1] Zachary Booth Simpson,[2,3] Aaron A. Chevalier,[2,3] Anselm Levskaya,[1]
Edward M. Marcotte,[2,3,4] Christopher A. Voigt,[1,*] and Andrew D. Ellington[2,3,4]



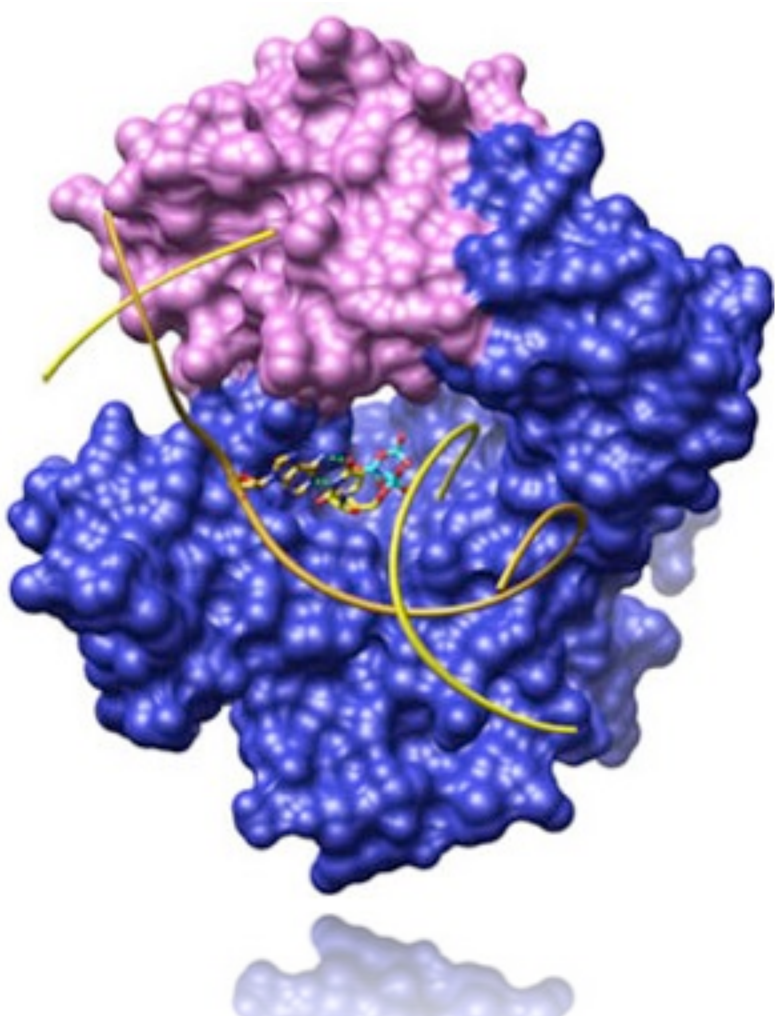
IF NOT light, produce (difussible) signal
IF signal and NOT (NOT light) produce pigment

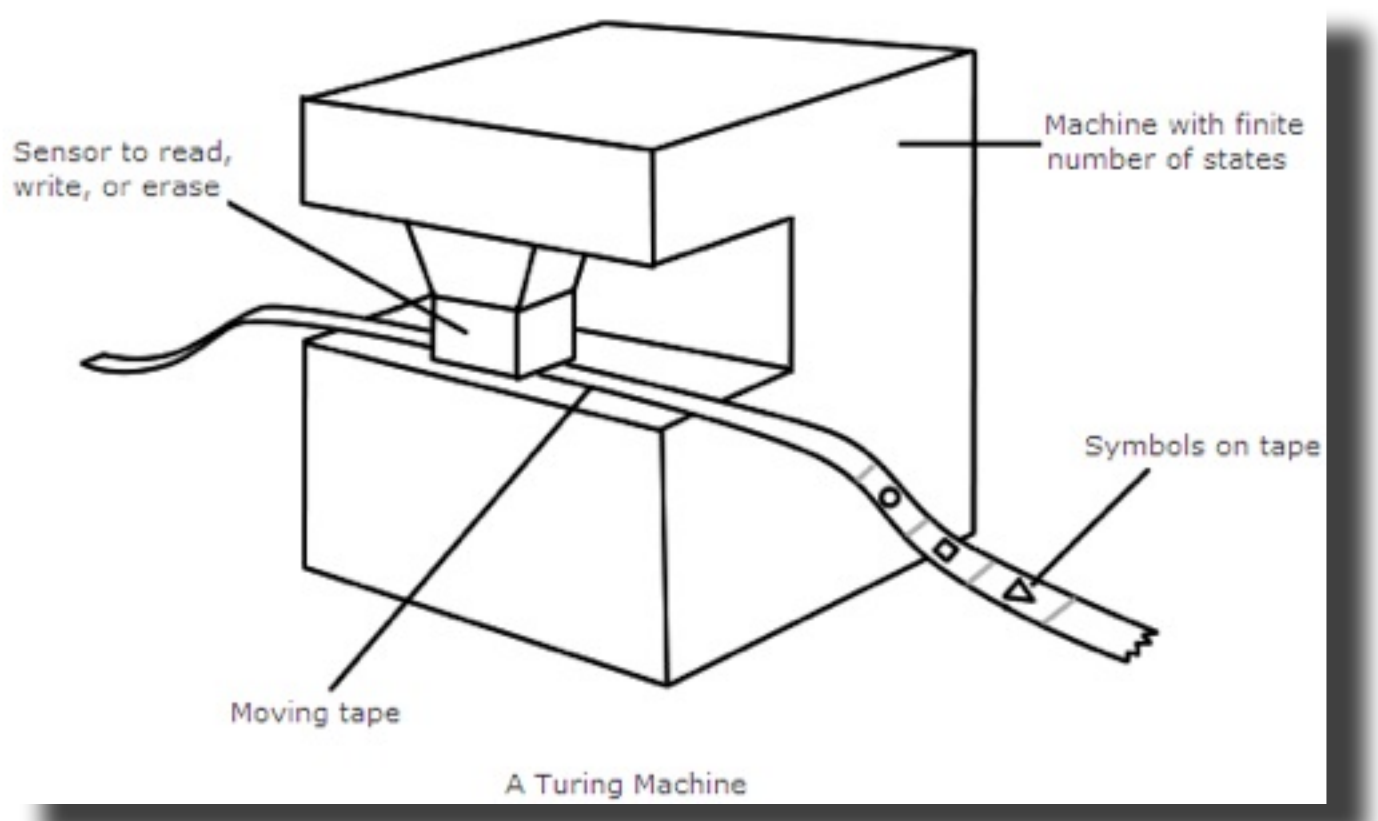
Theoretical models of computation

Turing, A. M. "On Computable Numbers, with an Application to the Entscheidungsproblem."

Proc. London Math. Soc. Ser. 2 **42**, 230-265, 1937.

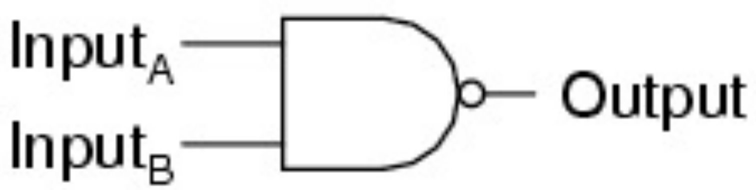
Turing machines





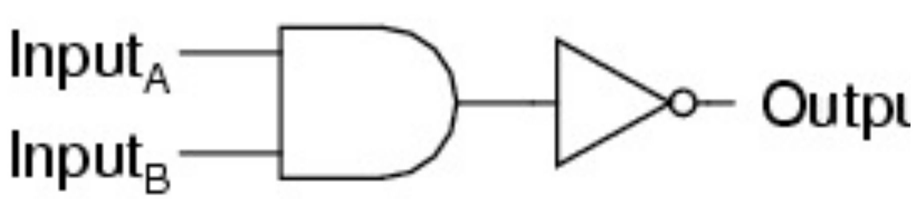
Universal gates: NAND and NOR

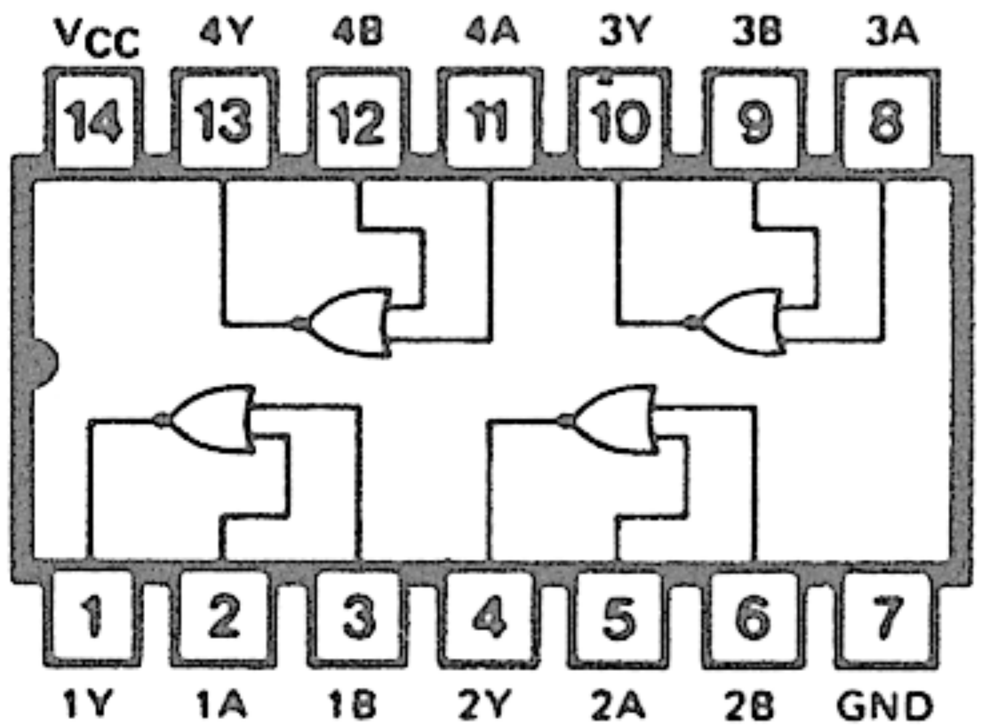
2-input NAND gate

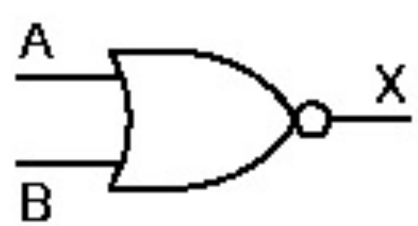


A	B	Output
0	0	1
0	1	1
1	0	1
1	1	0

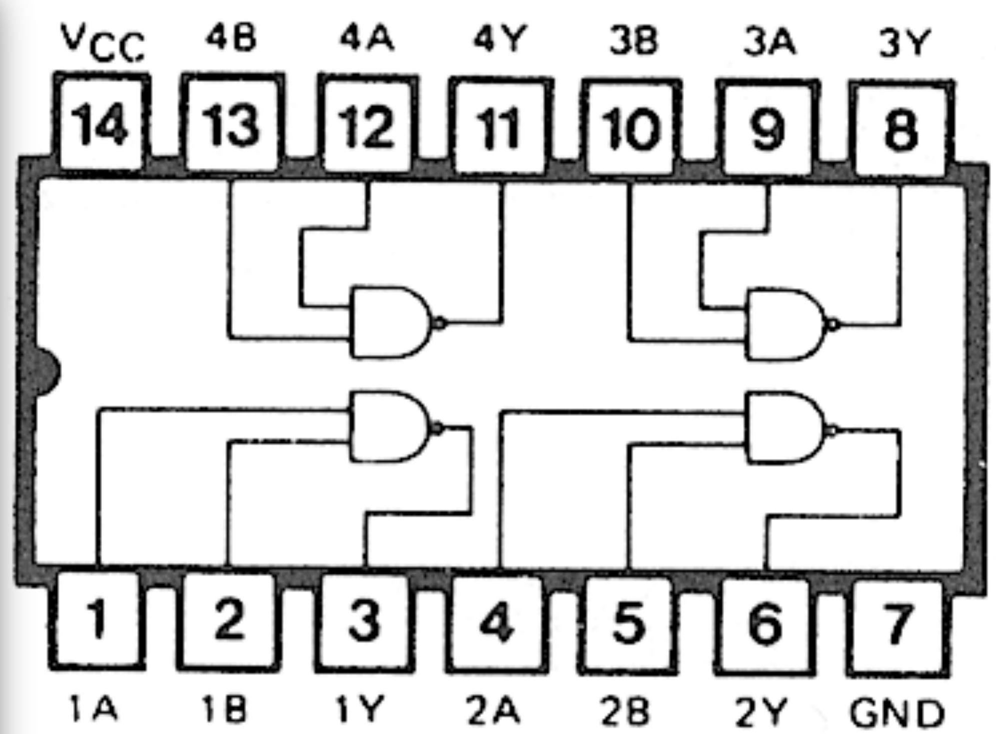
Equivalent gate circuit



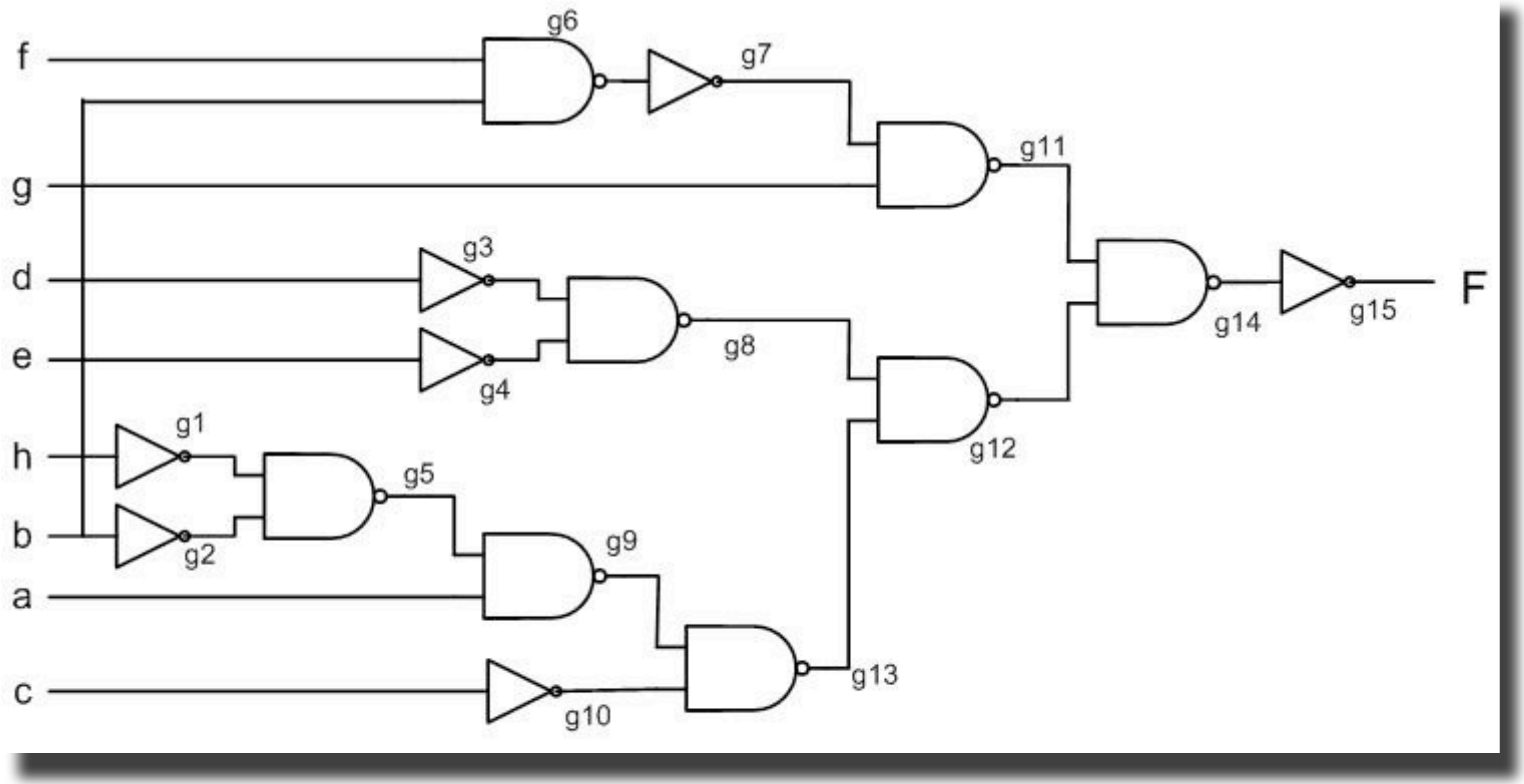




A	B	X
0	0	1
0	1	0
1	0	0
1	1	0



Combining logic circuits



Combining multiple small gates we obtain more complex circuits. The output is located at some given subset of elements

Can we get solutions from engineering?

Nucleic Acids Research, 2003, Vol. 31, No. 22 **6663–6673**
DOI: 10.1093/nar/gkg877

Molecular flip–flops formed by overlapping Fis sites

Paul N. Hengen, Ilya G. Lyakhov, Lisa E. Stewart[1] and Thomas D. Schneider[1,*]

Intramural Research Support Program, SAIC and [1]Laboratory of Experimental and Computational Biology, NCI Frederick, Frederick, MD, USA

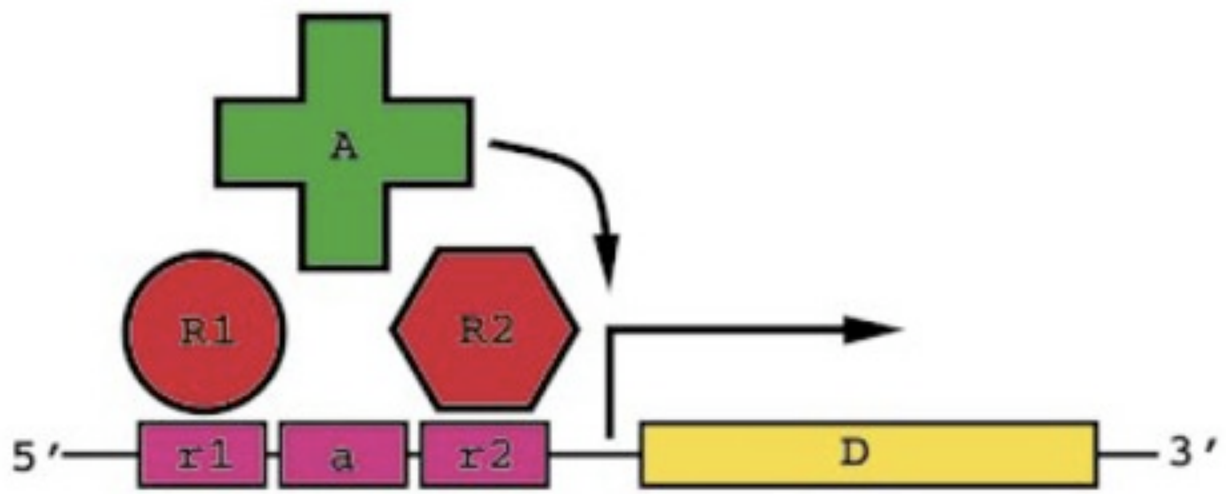
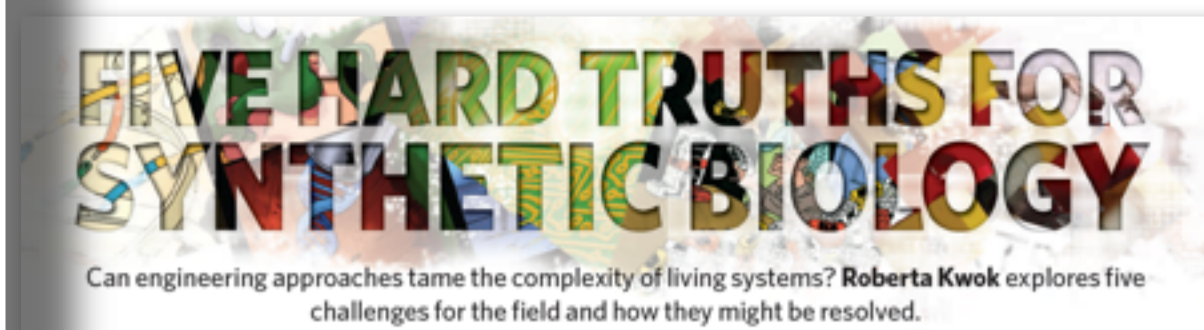
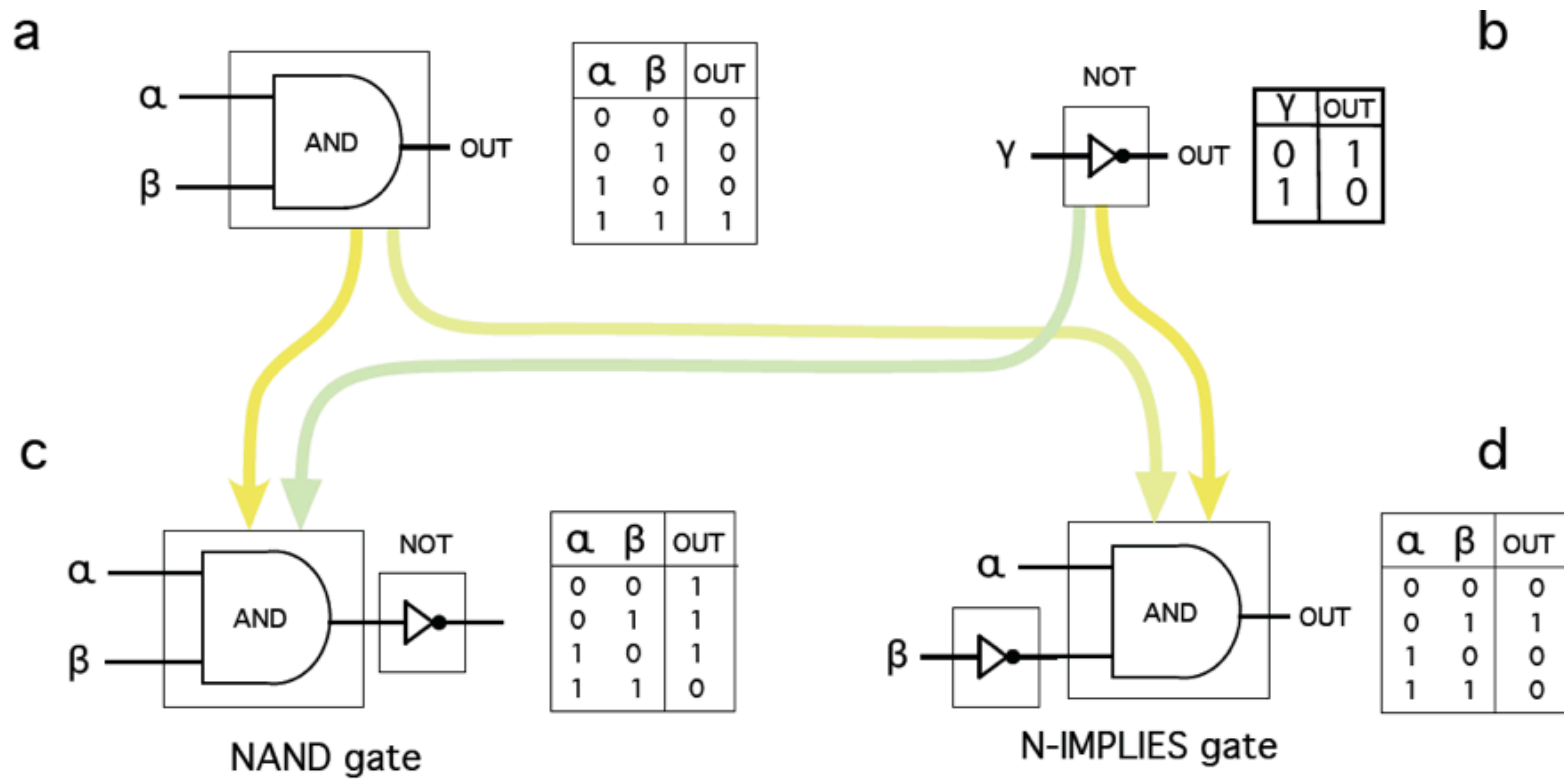


Figure 8. NOR gate molecular computer. An activator protein molecule **A** (green plus) binds to a DNA molecule at position **a**. When the activator binds, it turns on the promoter for gene D. Two repressor protein molecules **R1** and **R2** (red circle and red hexagon, respectively) bind to DNA at positions **r1** and **r2**. Binding to either **r1** or **r2** interferes with binding by **A**, so the activator can only bind when the two repressors are absent. Assigning the presence of a molecule as '1' or 'true' and the absence as '0' or 'false', then **D = R1 NOR R2**. By connecting such NOR gates together, any computer circuit can be built.

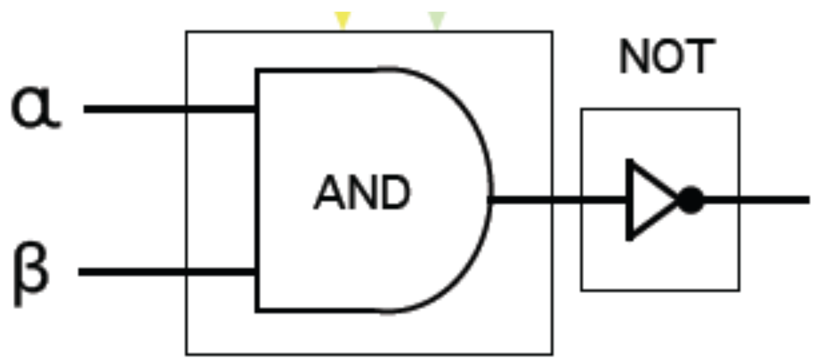


Problems: wiring and combinatorics

The wiring problem

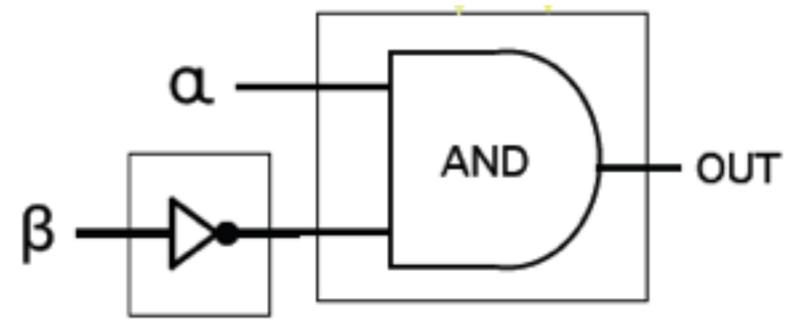


The wiring problem



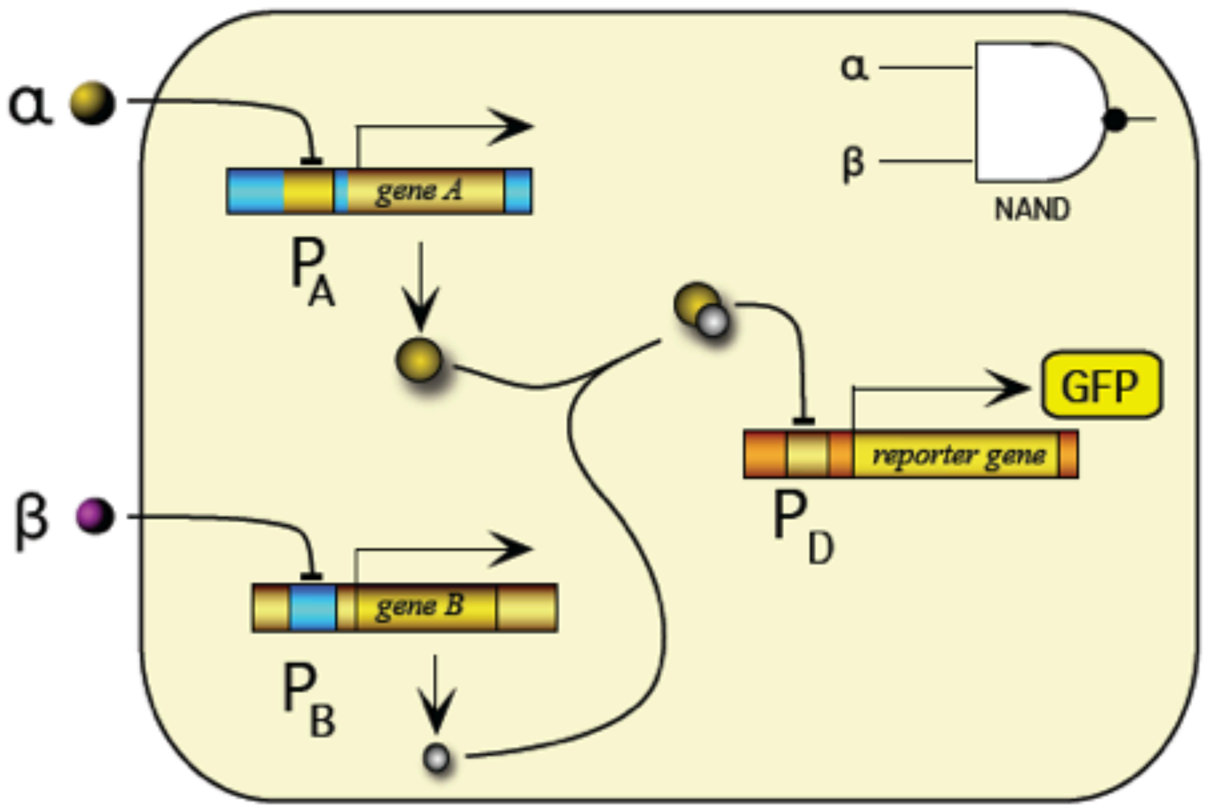
NAND gate

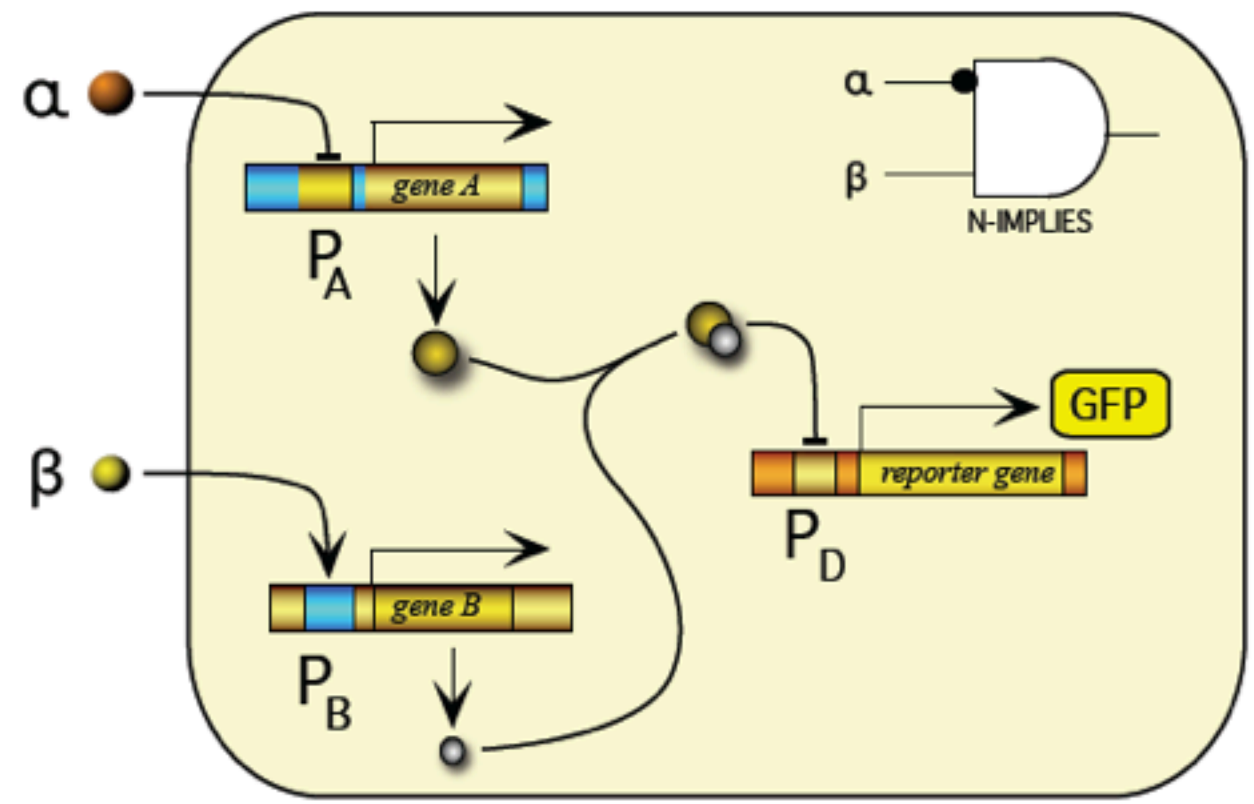
α	β	OUT
0	0	1
0	1	1
1	0	1
1	1	0



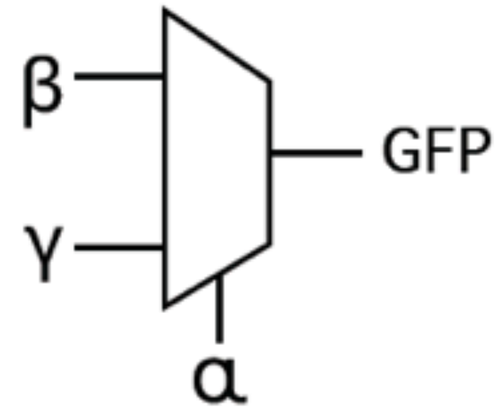
N-IMPLIES gate

α	β	OUT
0	0	0
0	1	1
1	0	0
1	1	0

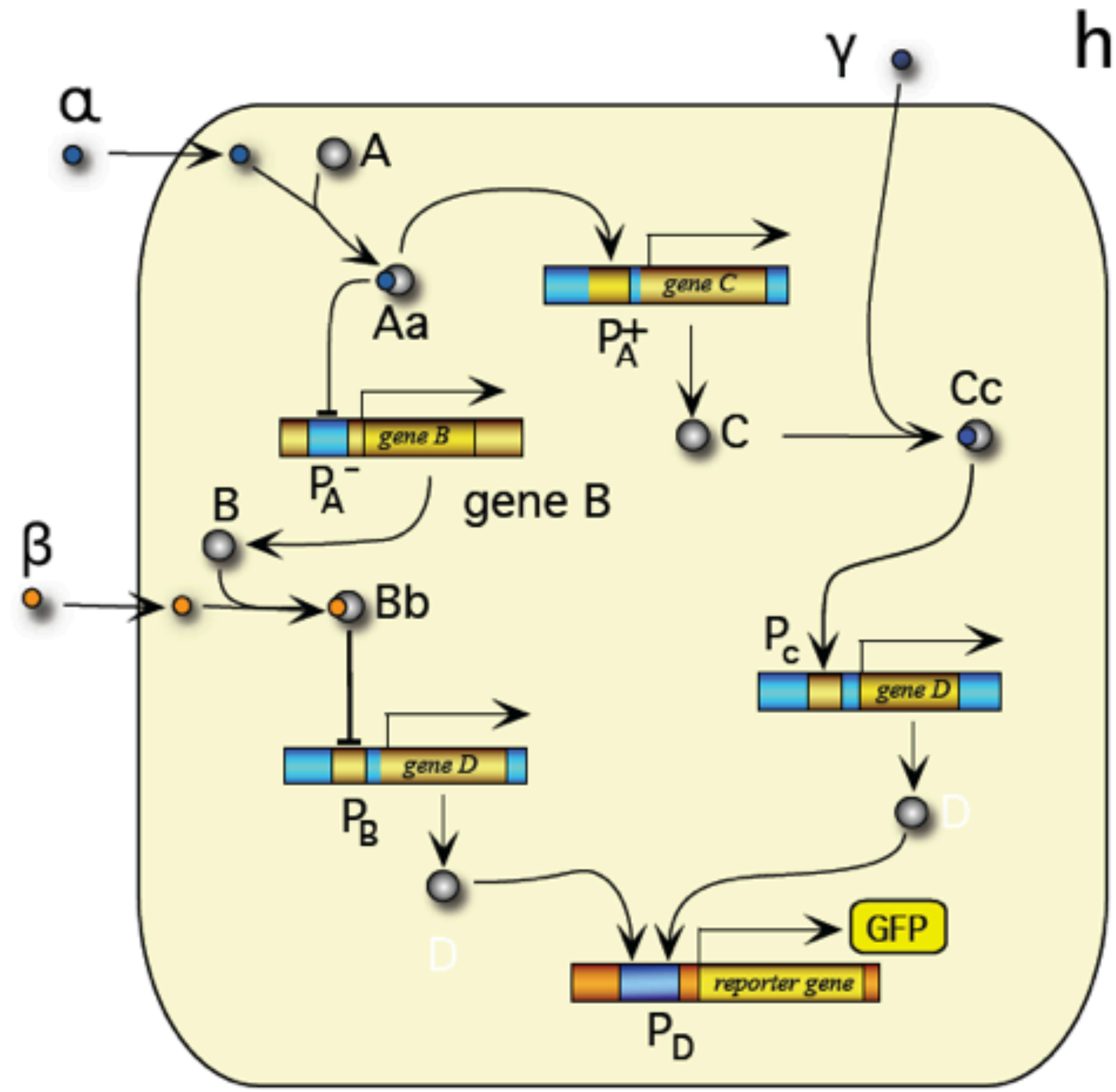




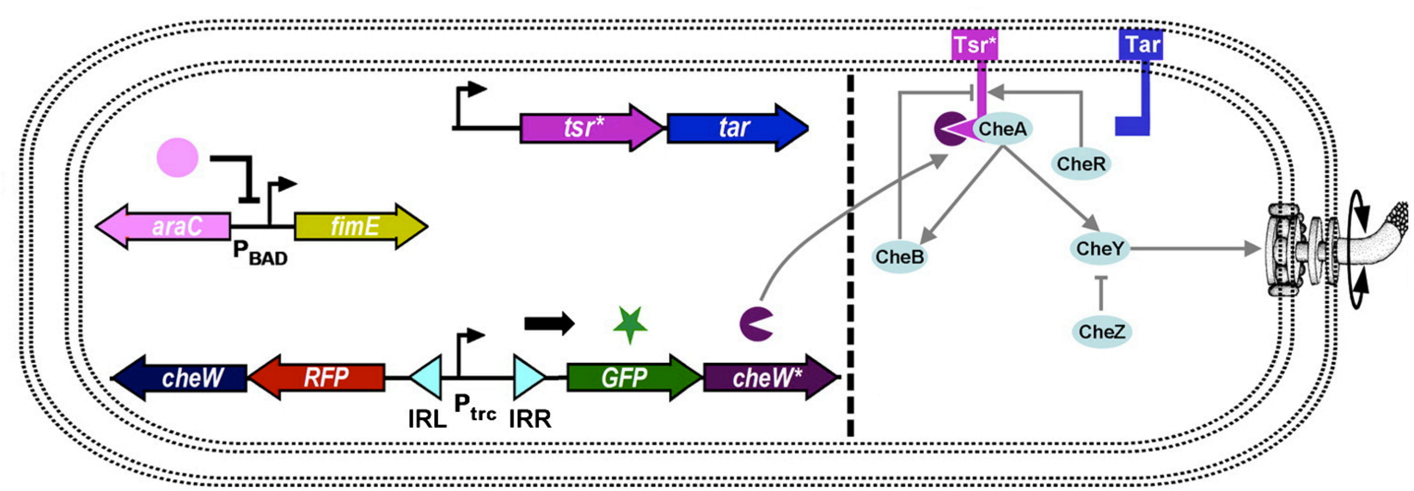
The wiring problem



α	β	γ	GFP
0	0	0	0
0	0	1	0
0	1	0	1
0	1	1	1
1	0	0	0
1	0	1	1
1	1	0	0
1	1	1	1



Wiring diversity increases with + Reuse strongly limited



SFI Complexity and computation




Proc. Natl. Acad. Sci. USA
Vol. 92, pp. 10742–10746, November 1995
Computer Sciences

The evolution of emergent computation

JAMES P. CRUTCHFIELD*† AND MELANIE MITCHELL‡

*Physics Department, University of California, Berkeley, CA 94720; and ‡Santa Fe Institute, 1399 Hyde Park Road, Santa Fe, NM 87501

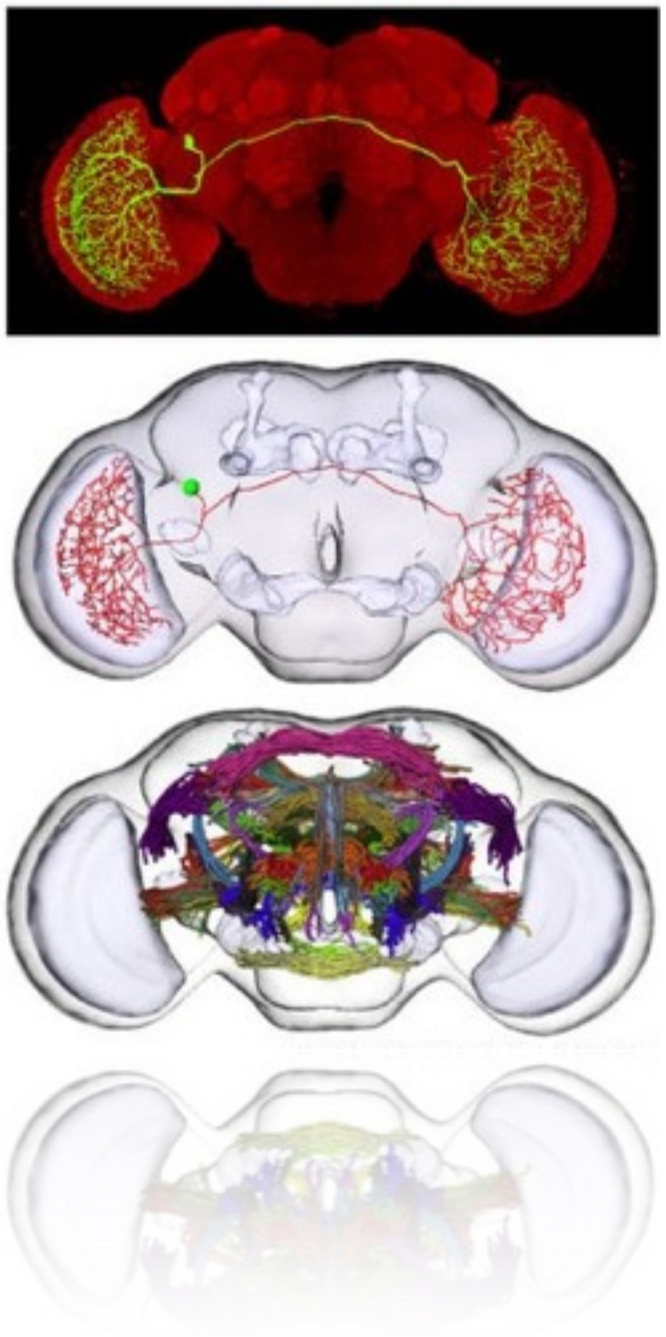
PHYSICAL REVIEW LETTERS

VOLUME 63 | 10 JULY 1989 | NUMBER 2

Inferring Statistical Complexity

James P. Crutchfield[a] and Karl Young[b]
Physics Department, University of California, Berkeley, California 94720
(Received 13 December 1988)

Collective intelligence and computation



No central control

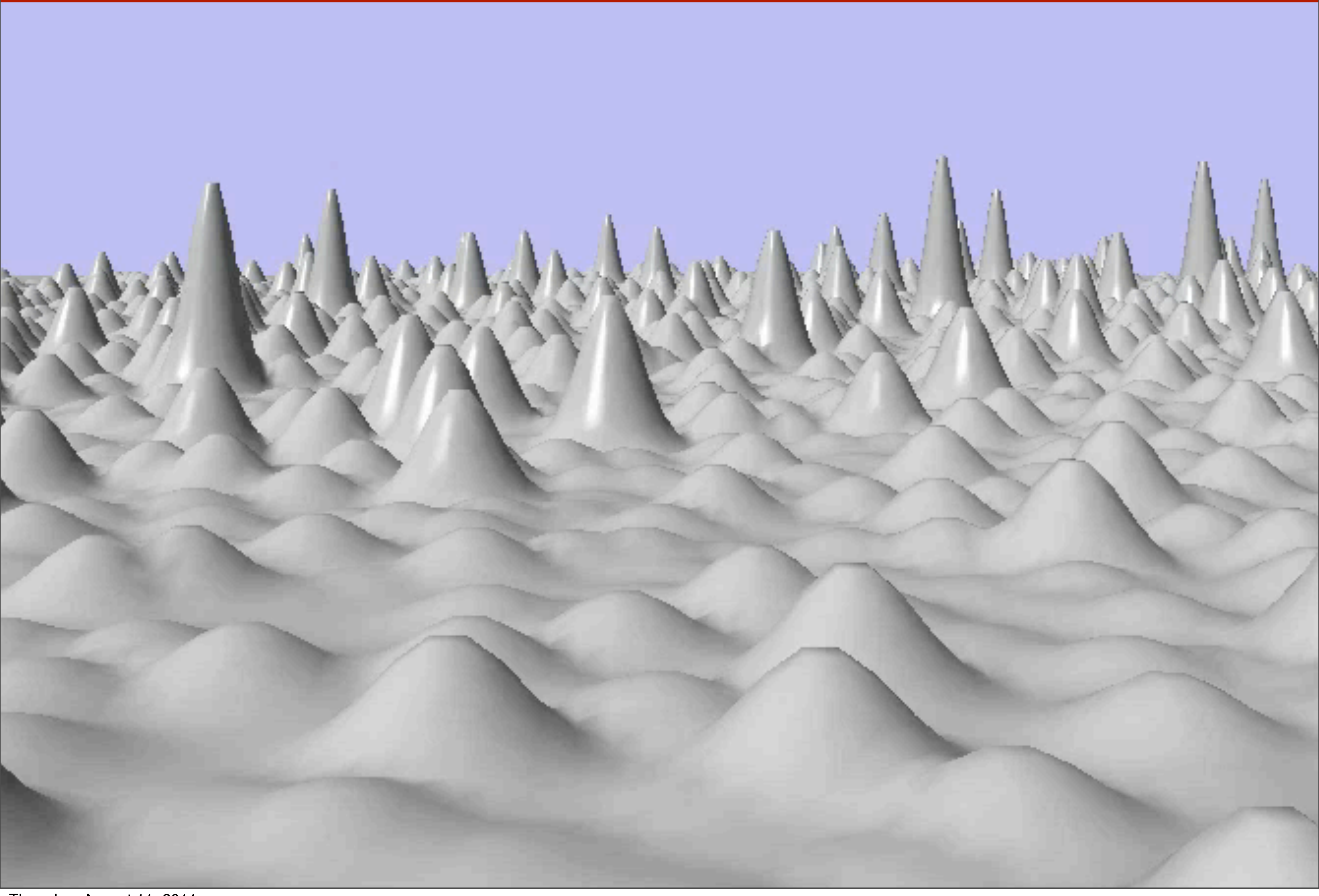
Distributed decisions
Simple individuals, complex CI

PHYSICAL REVIEW E VOLUME 55, NUMBER 3 MARCH 1997

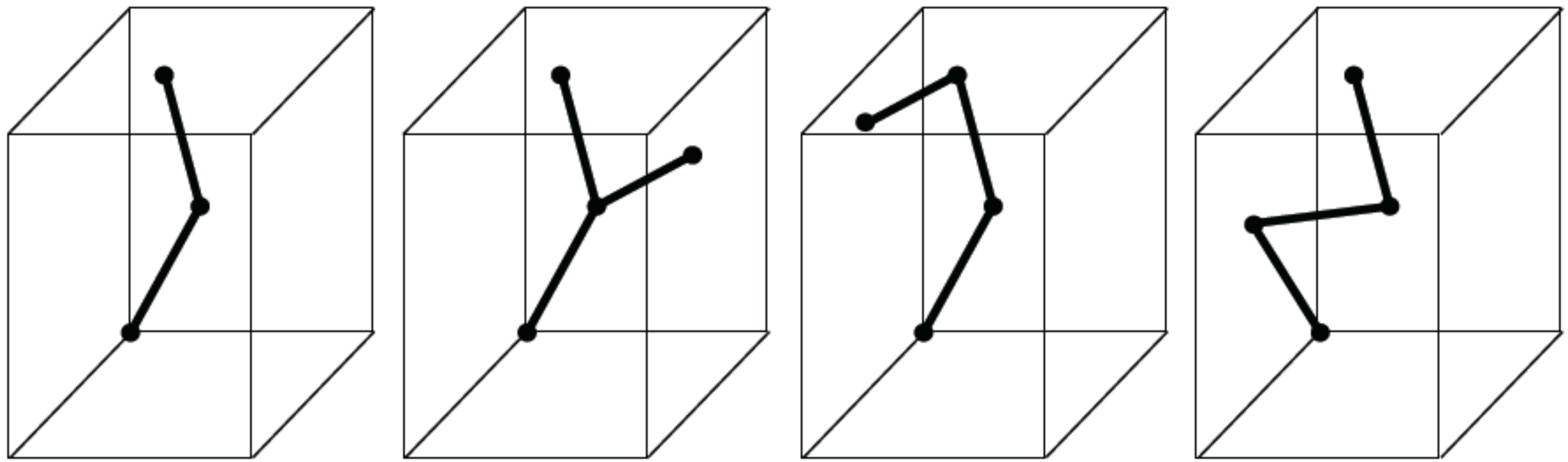
Collective-induced computation

Jordi Delgado[1,2,3] and Ricard V. Solé[2,3]
[1]*Departament de Llenguatges i Sistemes Informatics, Universitat Politecnica de Catalunya, Pau Gargallo 5, 08028 Barcelona, Spain*
[2]*Complex Systems Research Group, Departament de Física i Enginyeria Nuclear, Universitat Politècnica de Catalunya, Sor Eulàlia d'Anzizu s/n, Campus Nord, Mòdul B4, 08034 Barcelona, Spain*
[3]*Santa Fe Institute, 1399 Hyde Park Road, Santa Fe, New Mexico 87501*
(Received 26 August 1996)

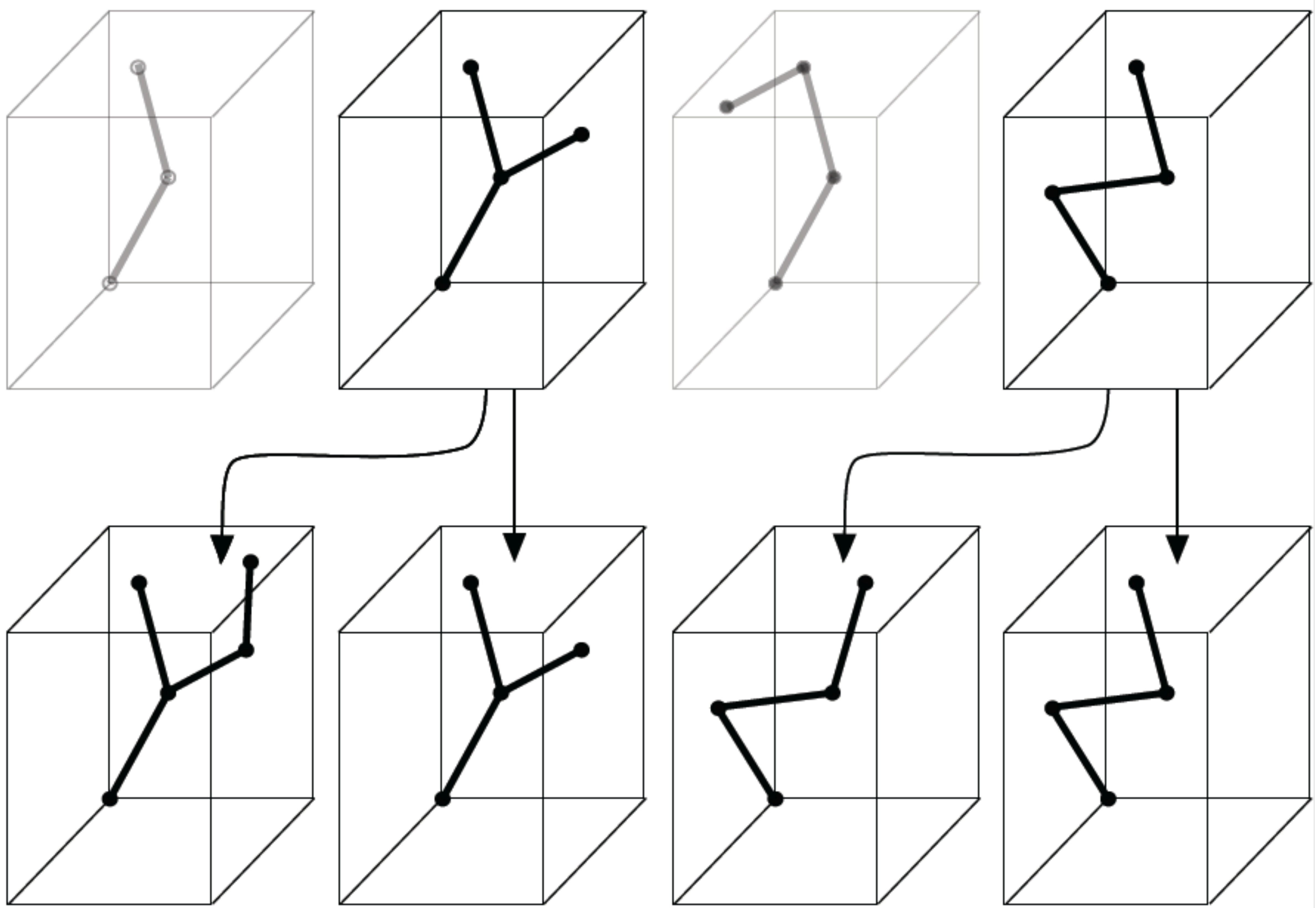
Design landscape



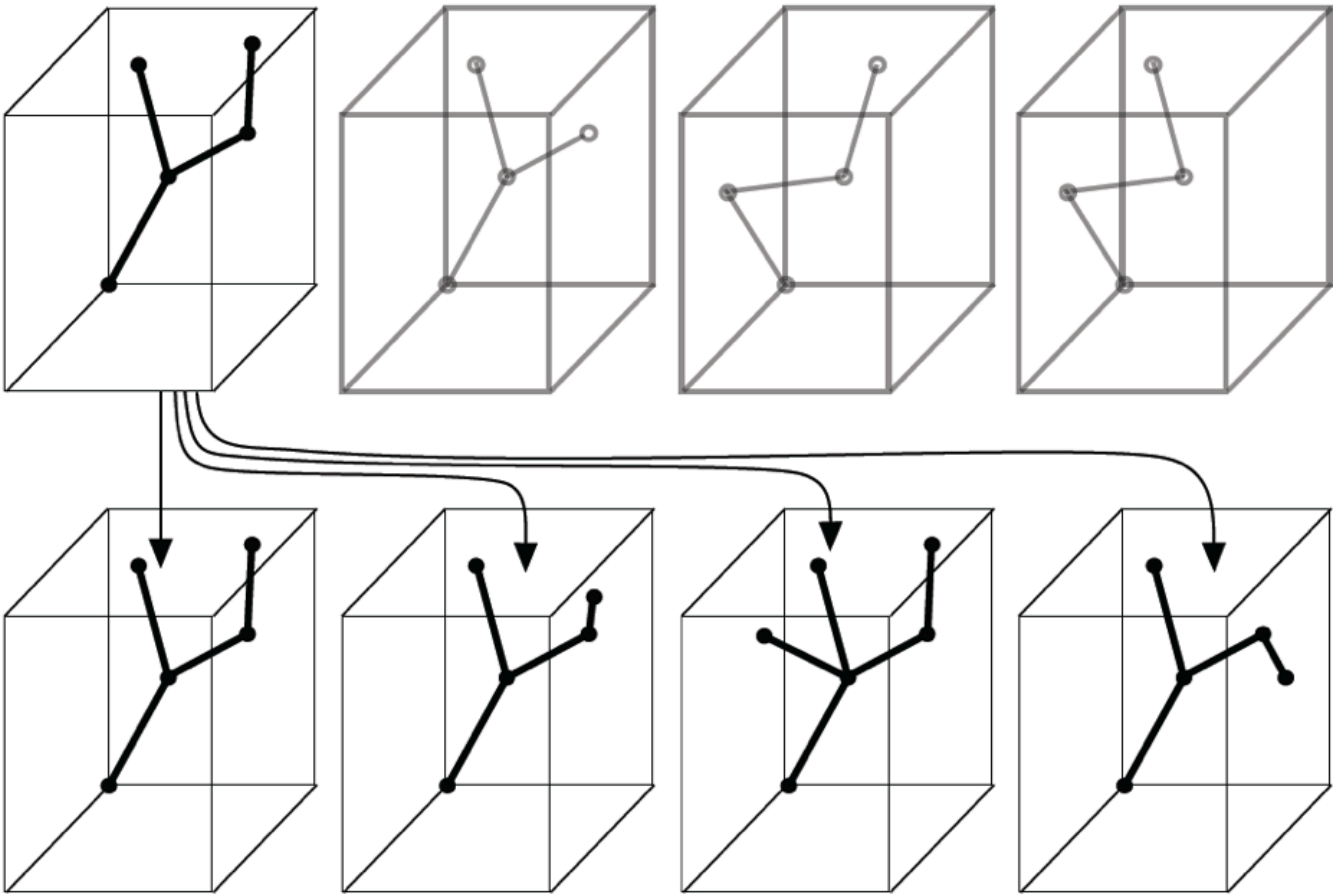
Evolved designs



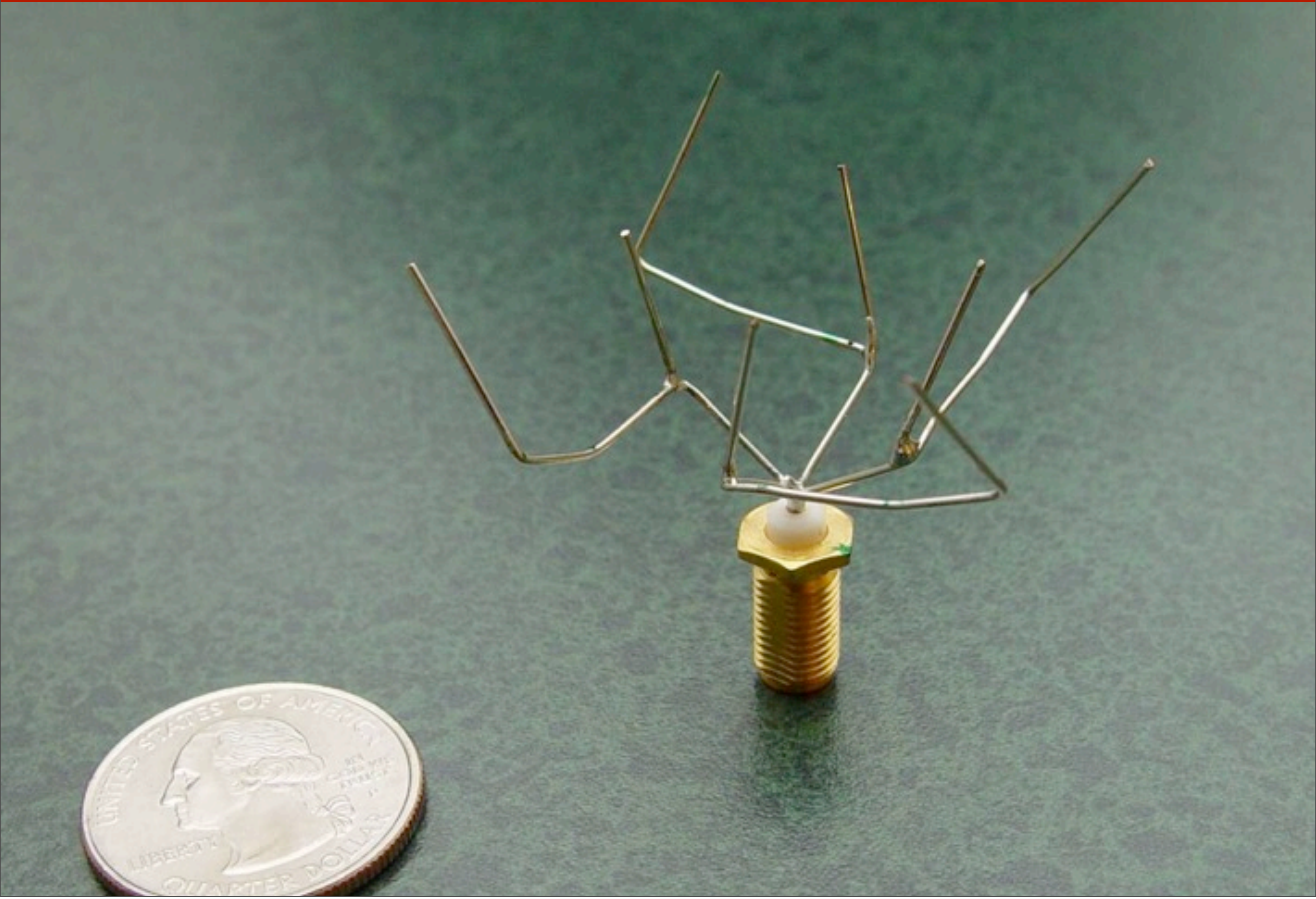
Evolved designs



Evolved designs



Evolved designs



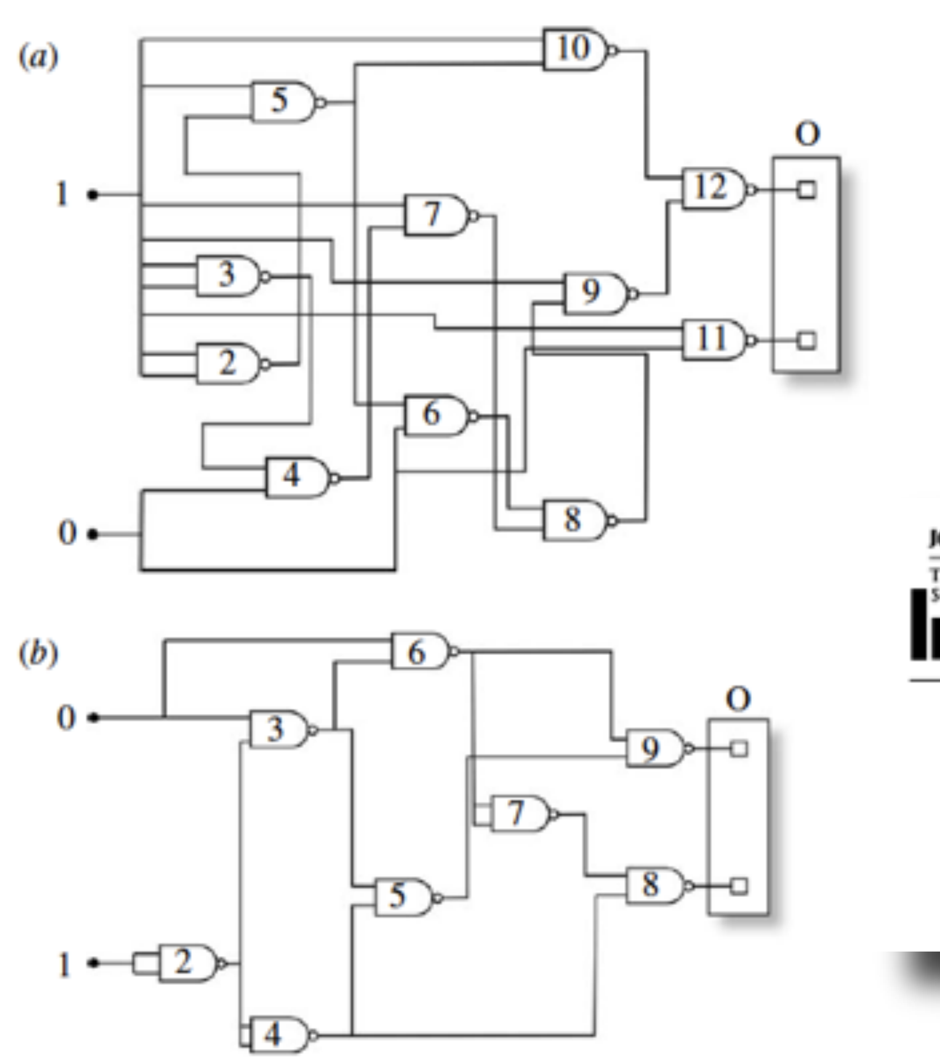
Robustness, redundancy and degeneracy

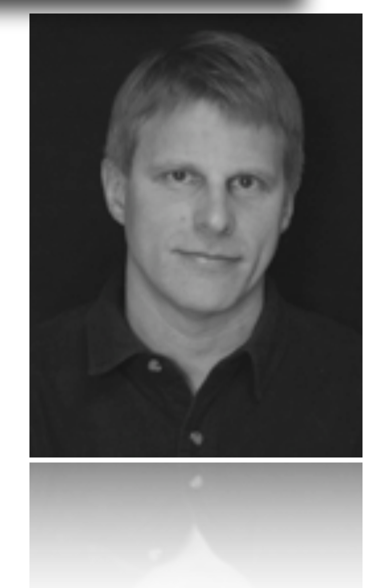
Proc. Natl. Acad. Sci. USA
Vol. 96, pp. 3257–3262, March 1999
Neurobiology

Measures of degeneracy and redundancy in biological networks

Giulio Tononi†, Olaf Sporns, and Gerald M. Edelman

The Neurosciences Institute, 10640 John J. Hopkins Drive, San Diego, CA 92121





JOURNAL OF THE ROYAL SOCIETY Interface

J. R. Soc. Interface (2009) **6**, 393–400
doi:10.1098/rsif.2008.0236
Published online 16 September 2008

Distributed robustness in cellular networks: insights from synthetic evolved circuits

Javier Macia[1] and Ricard V. Solé[1,2,*]

How to solve it?

In any field, find the strangest thing
and then explore it.

John Wheeler

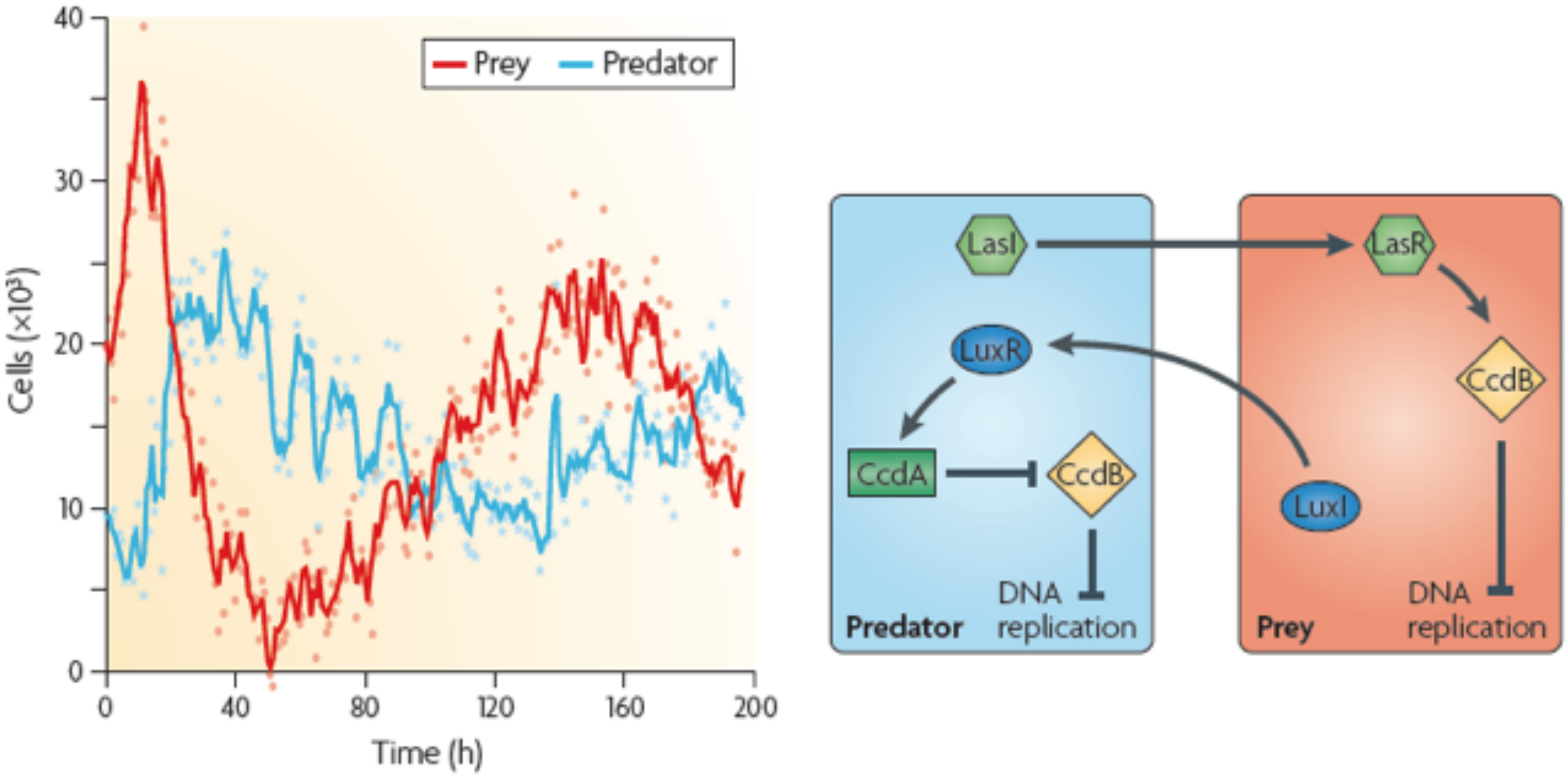
The wiring problem: first approach

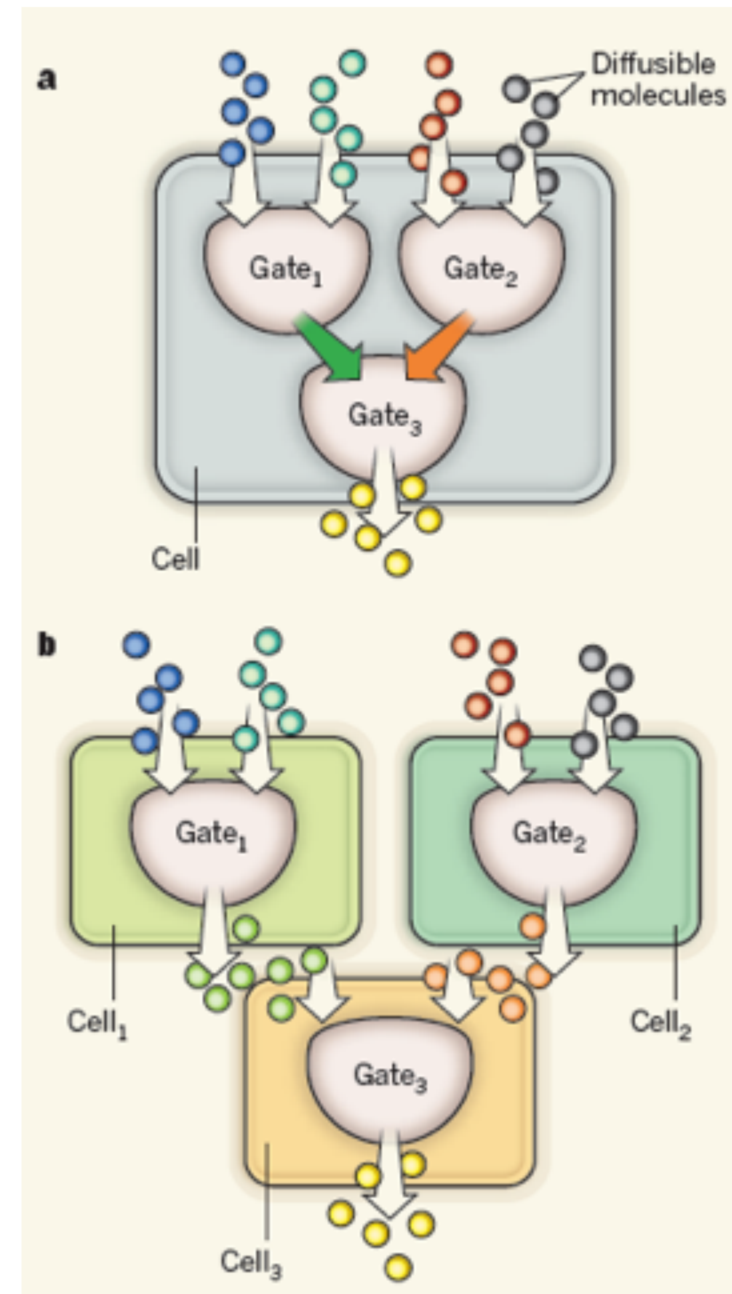
SYNTHETIC BIOLOGY

Division of logic labour

Cellular compartmentalization is an effective way to build gene circuits capable of complex logic operations, in which binary inputs are converted into binary outputs according to user-defined rules. SEE LETTERS P.207 & P.212

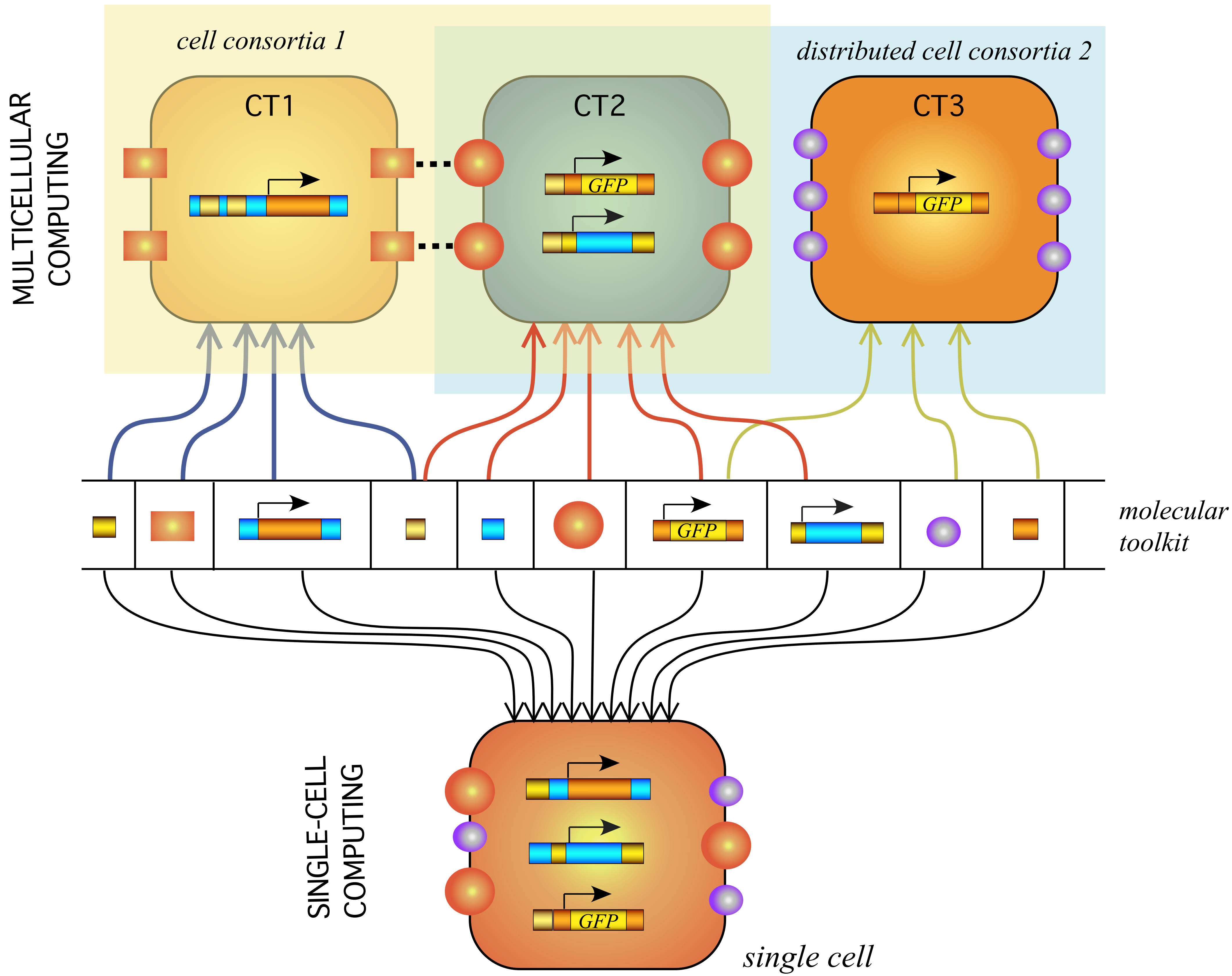
NEWS & VIEWS RESEARCH





Synthetic ecology: predator-prey, mutualistic, parasitic

Multicellular systems



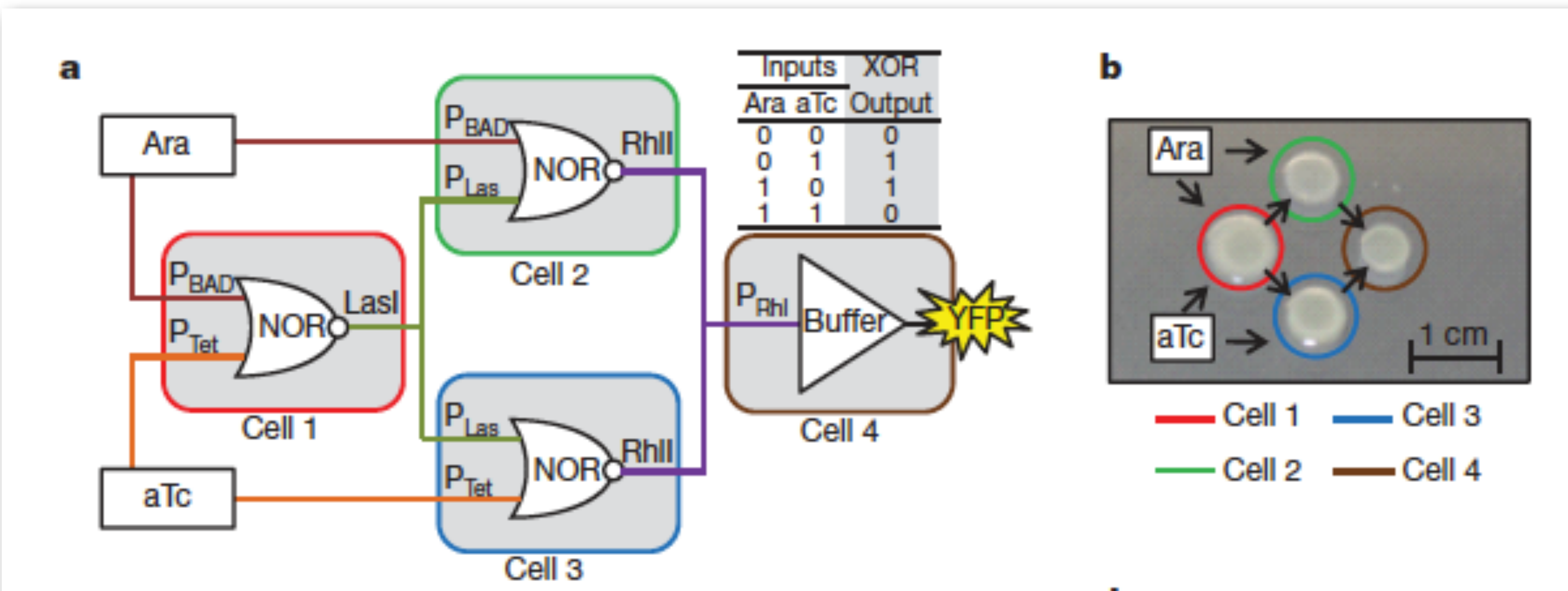
Multicellular computing

LETTER

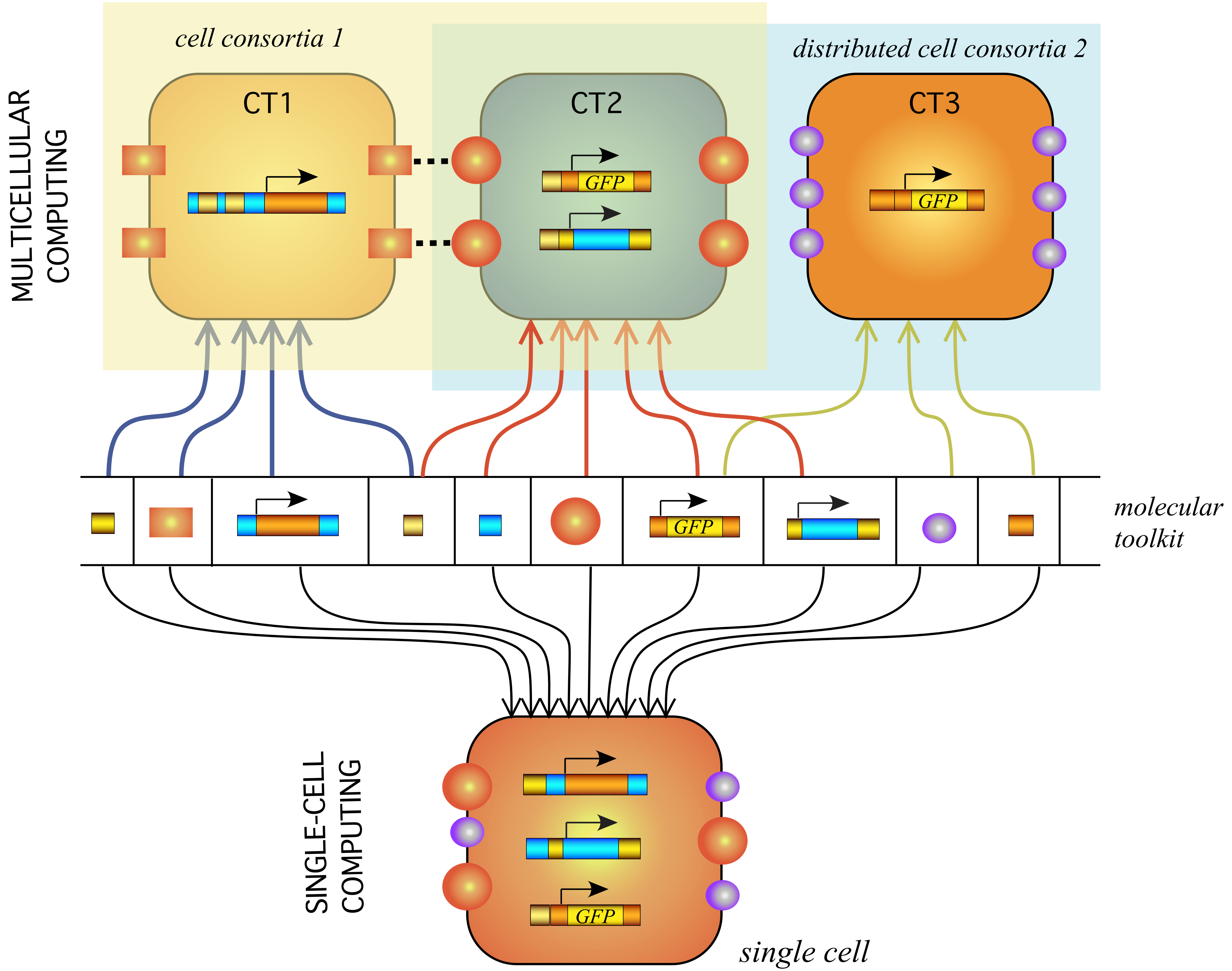
doi:10.1038/nature09565

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

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



Multicellular distributed computing



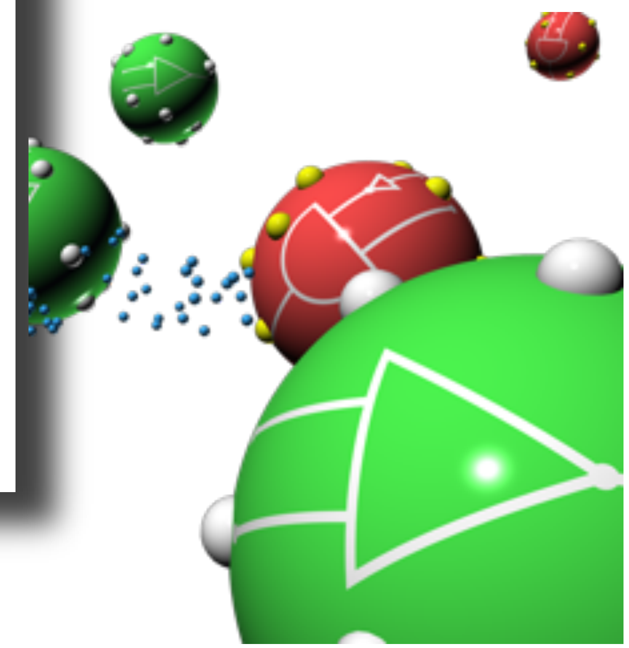
Multicellular distributed computing

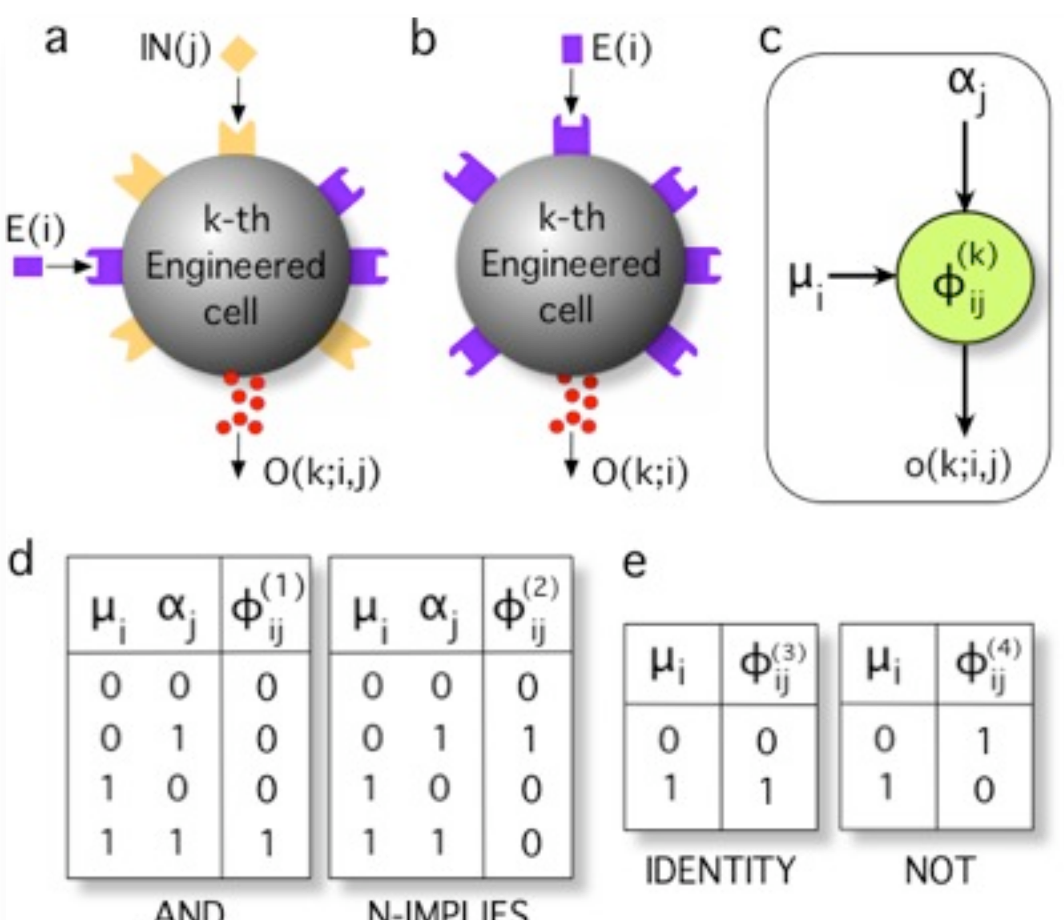
LETTER

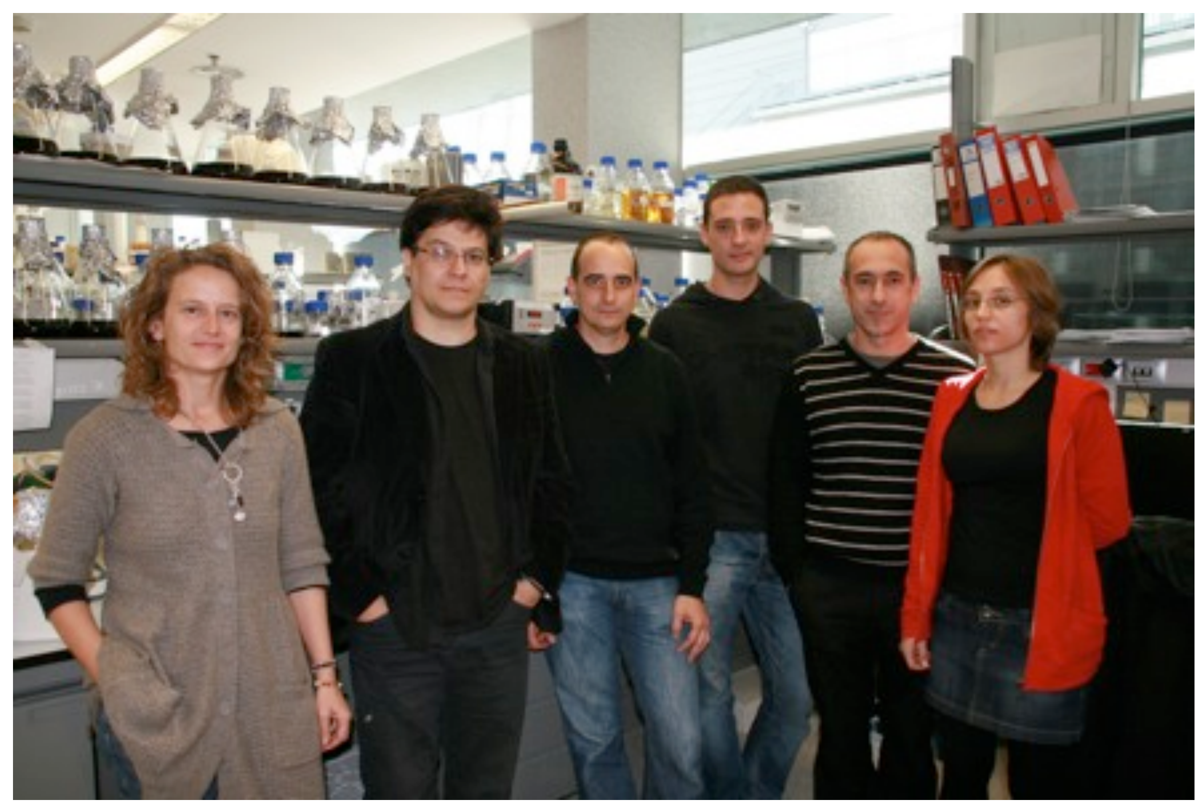
doi:10.1038/nature09679

Distributed biological computation with multicellular engineered networks

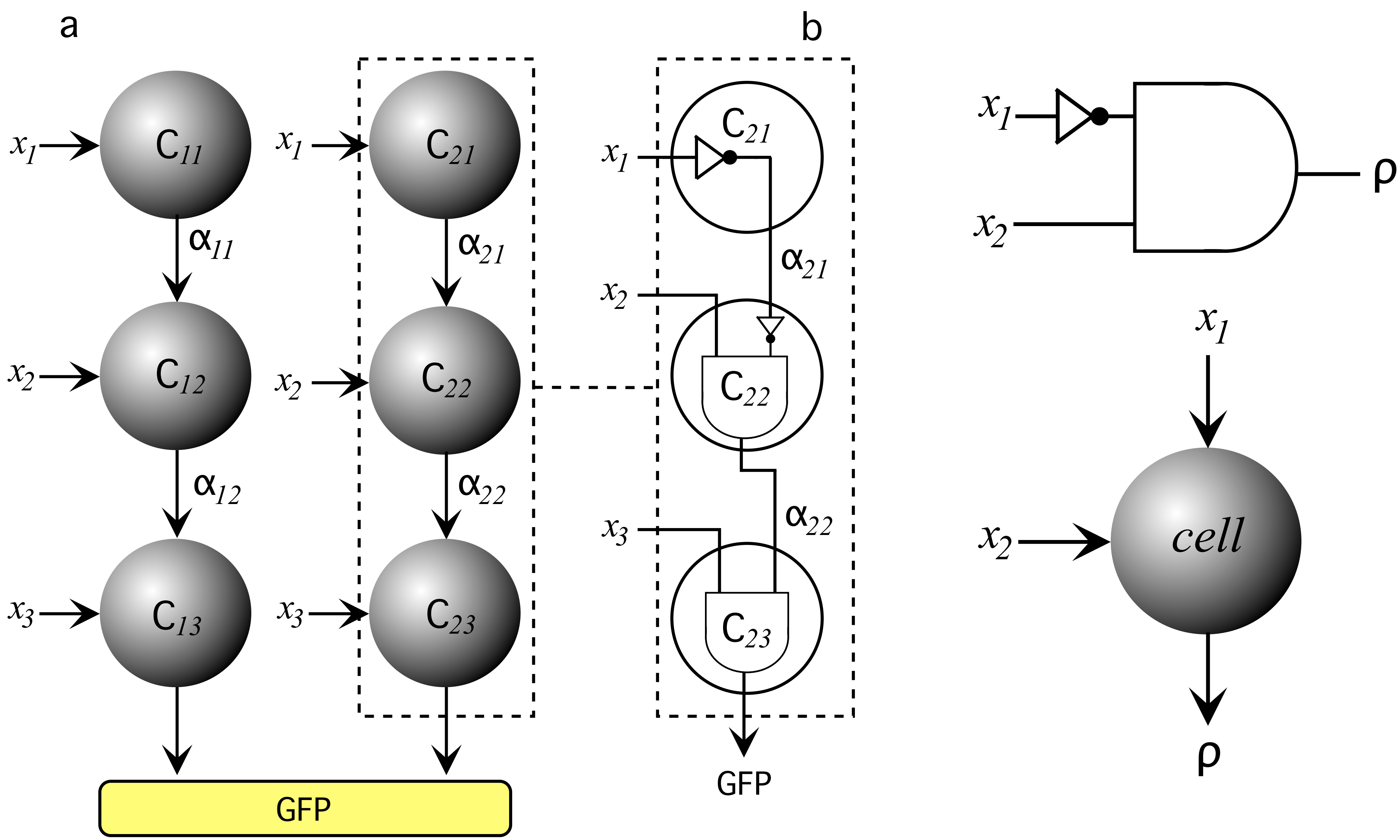
Sergi Regot[1]*, Javier Macia[2]*, Núria Conde[1,2], Kentaro Furukawa[3], Jimmy Kjellén[3], Tom Peeters[1], Stefan Hohmann[3], Eulàlia de Nadal[1], Francesc Posas[1] & Ricard Solé[2,4,5]





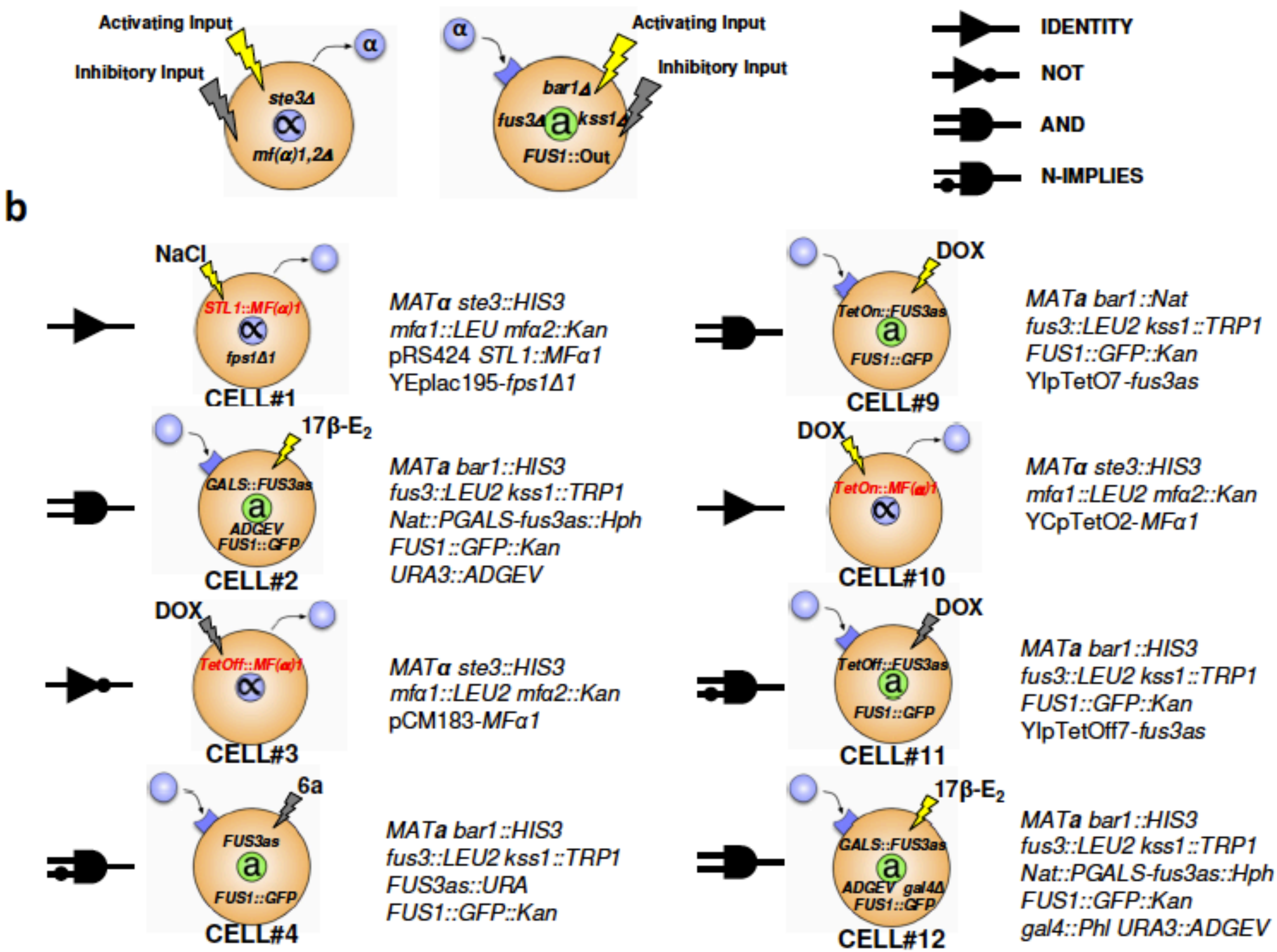


Multicellular distributed computing

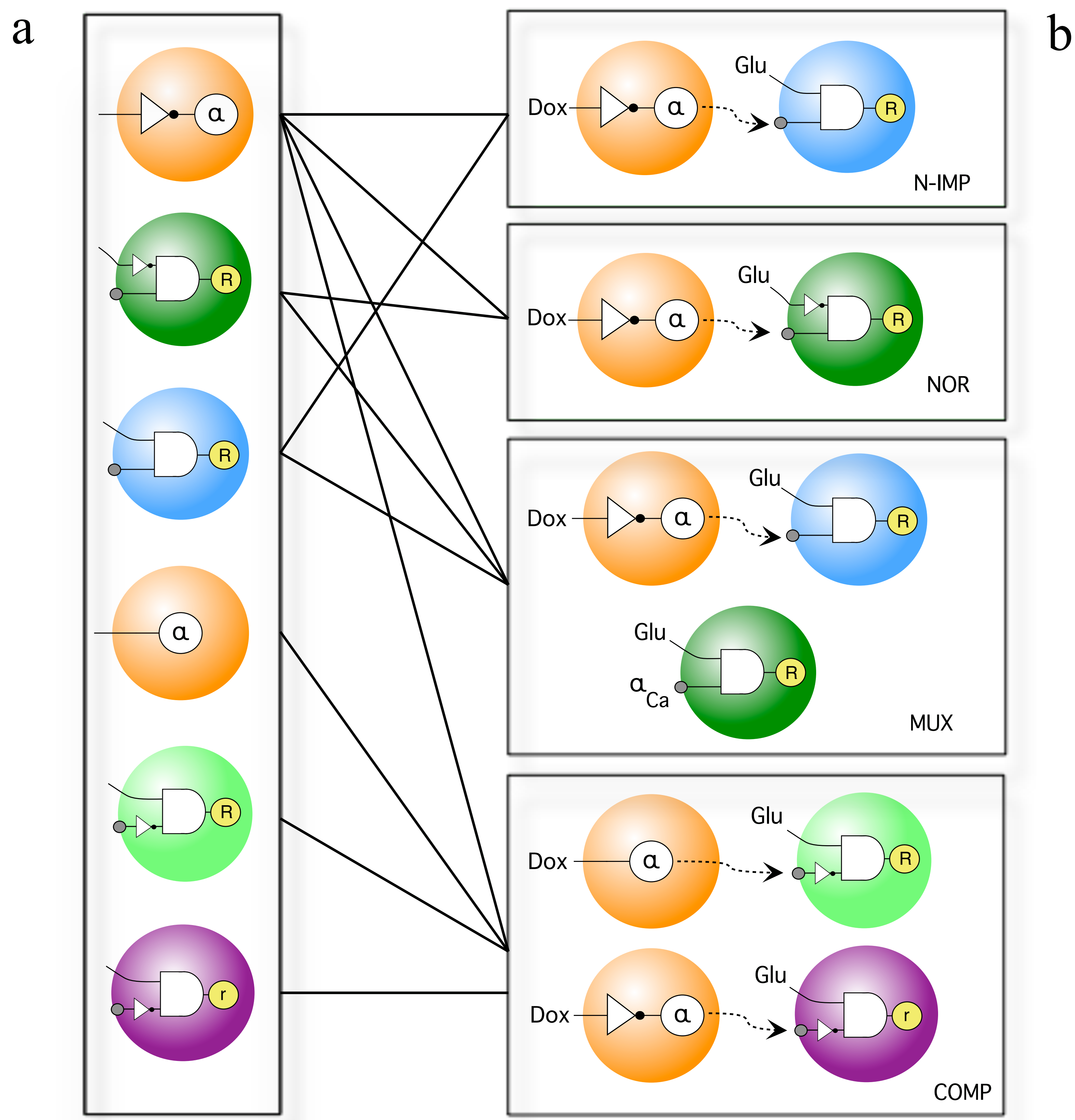


Several cells can provide the output

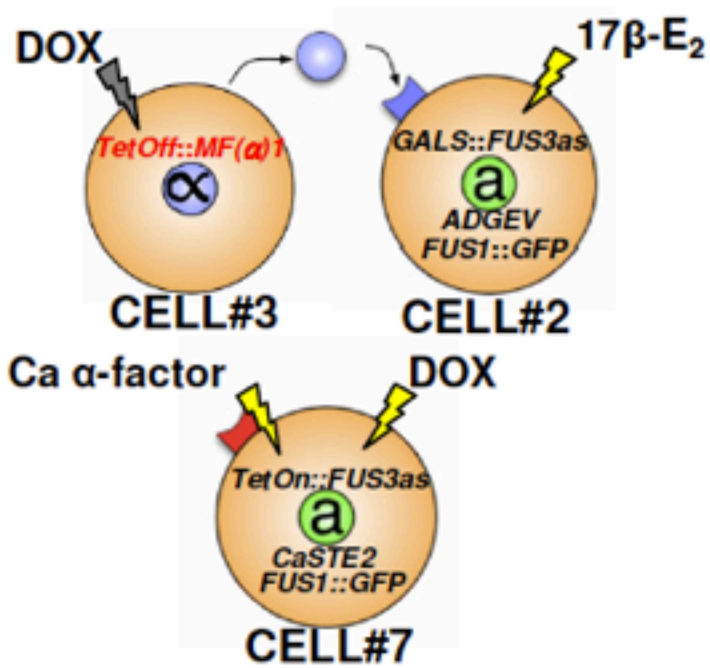
Multicellular distributed computing



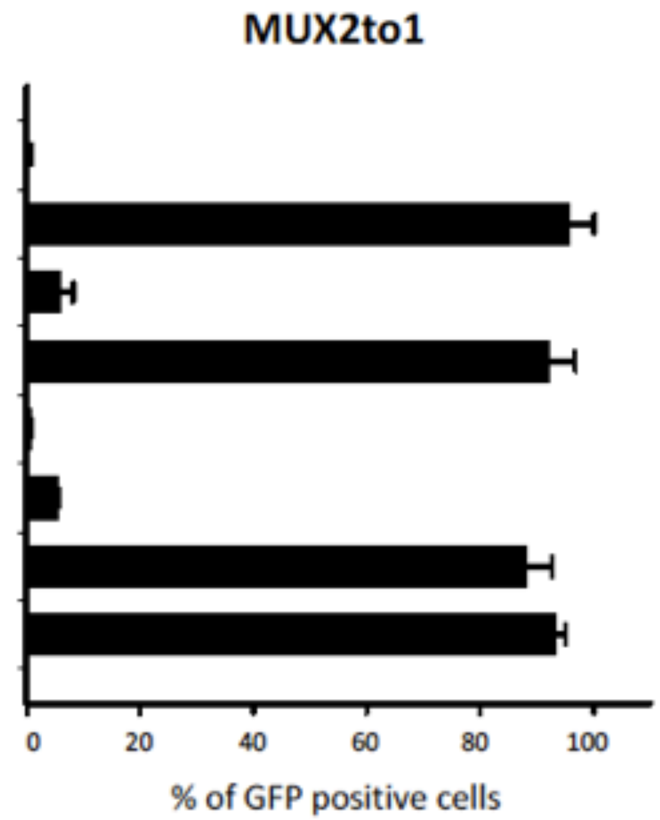
Multicellular distributed computing

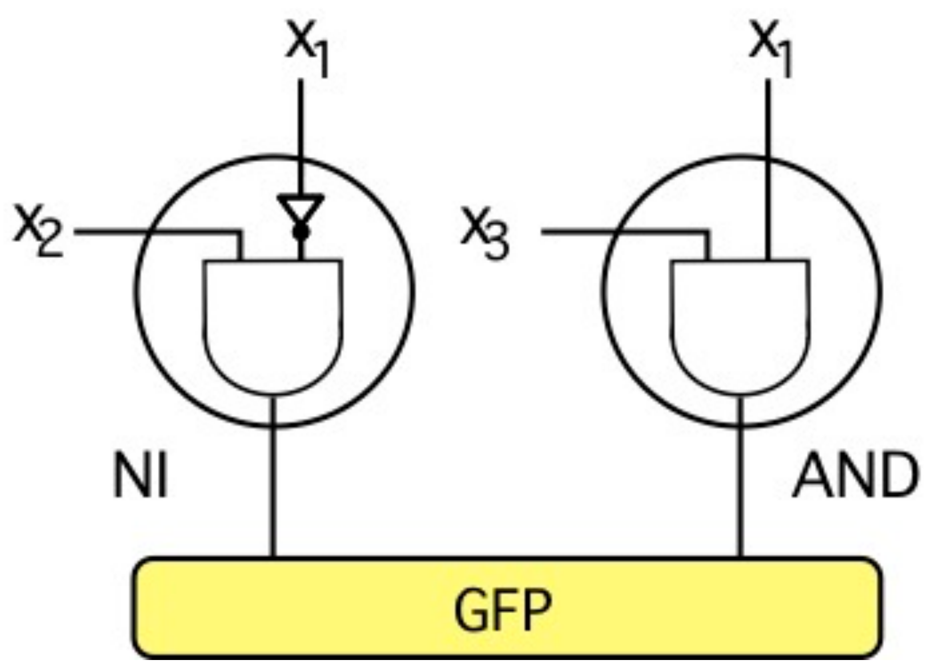


Distributed computation

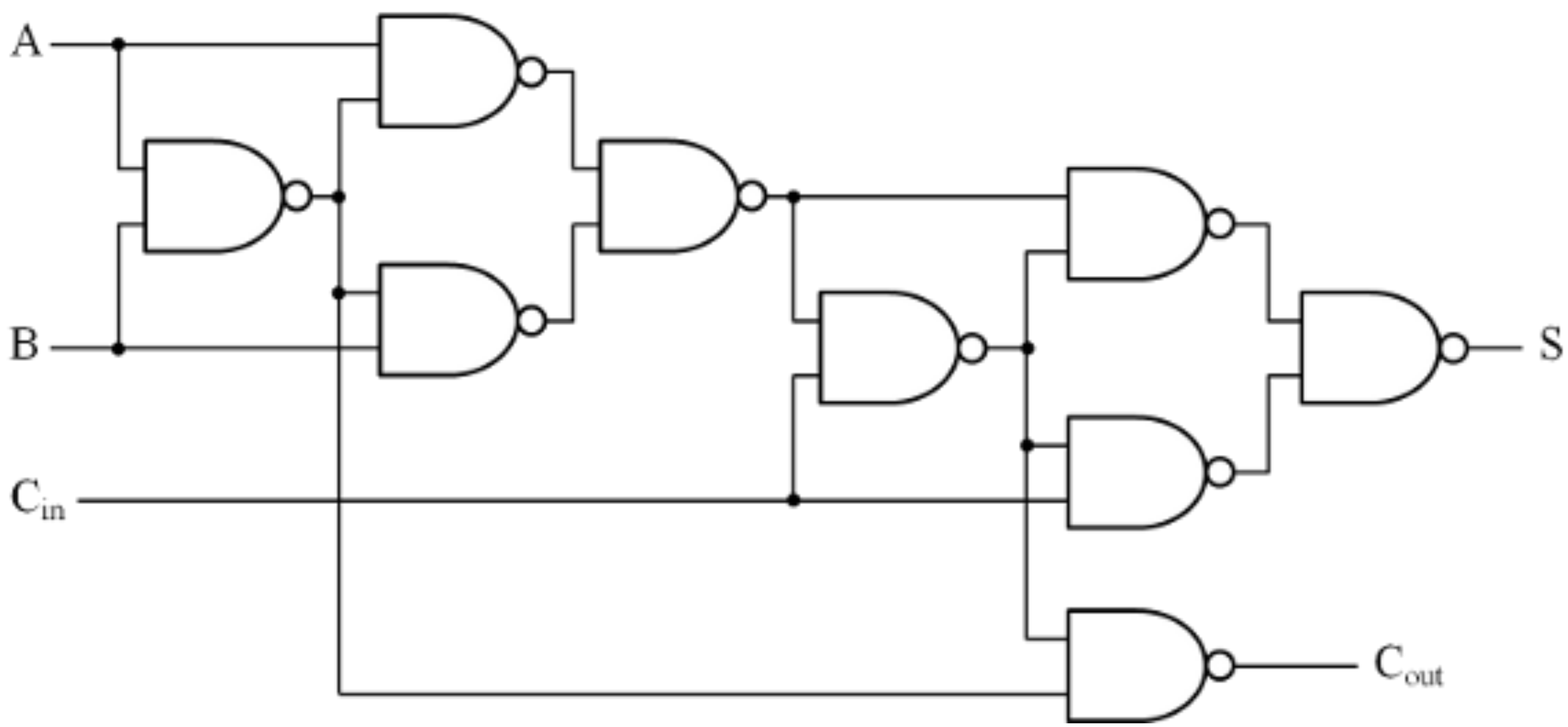


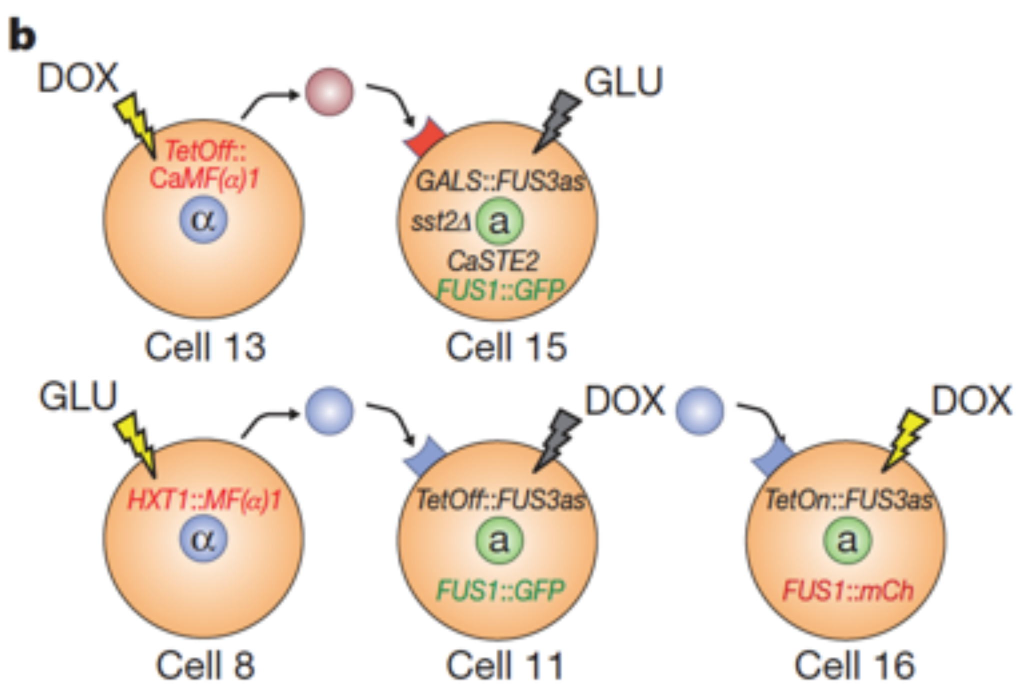
DOX	Ca α-factor	17β-E2	Output
0	0	0	0
0	0	1	1
0	1	0	0
0	1	1	1
1	0	0	0
1	0	1	0
1	1	0	1
1	1	1	1



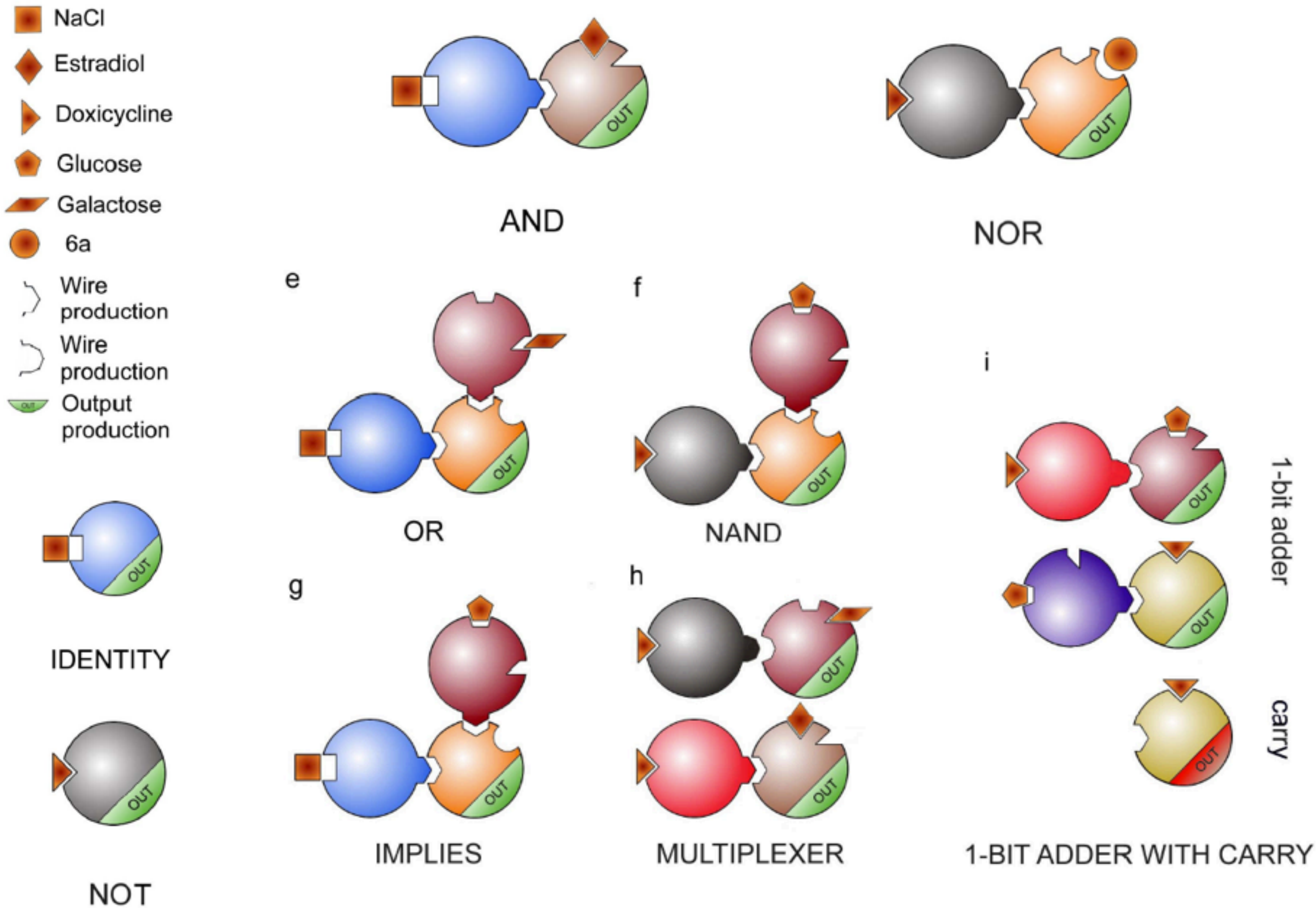


Distributed computation

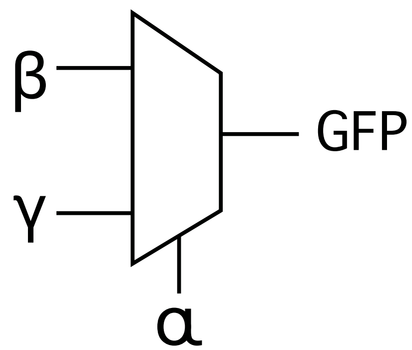




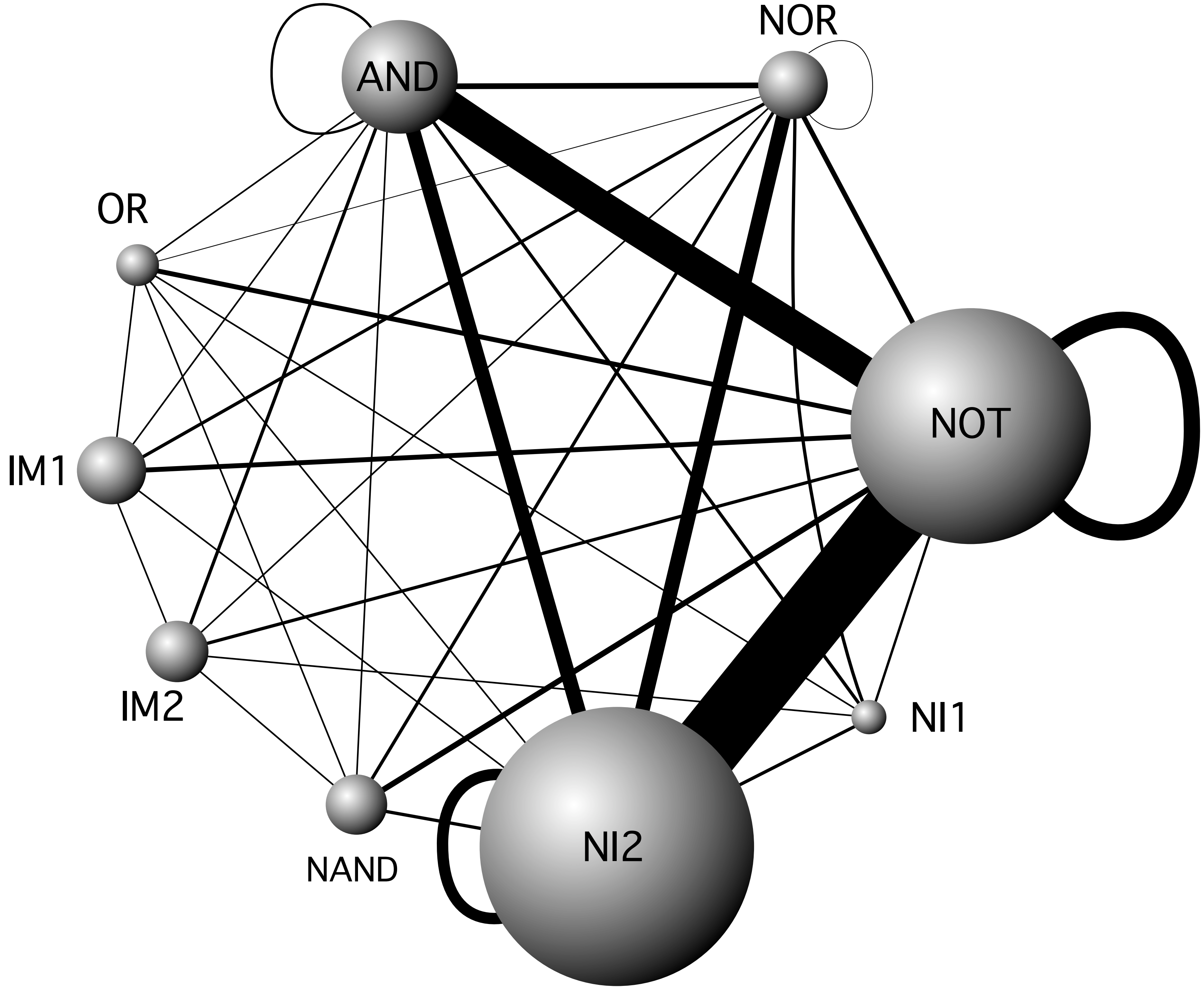
Distributed computation: LEGO-like



Non-standard combinatorial logic



α	β	γ	GFP
0	0	0	0
0	0	1	0
0	1	0	1
0	1	1	1
1	0	0	0
1	0	1	1
1	1	0	0
1	1	1	1



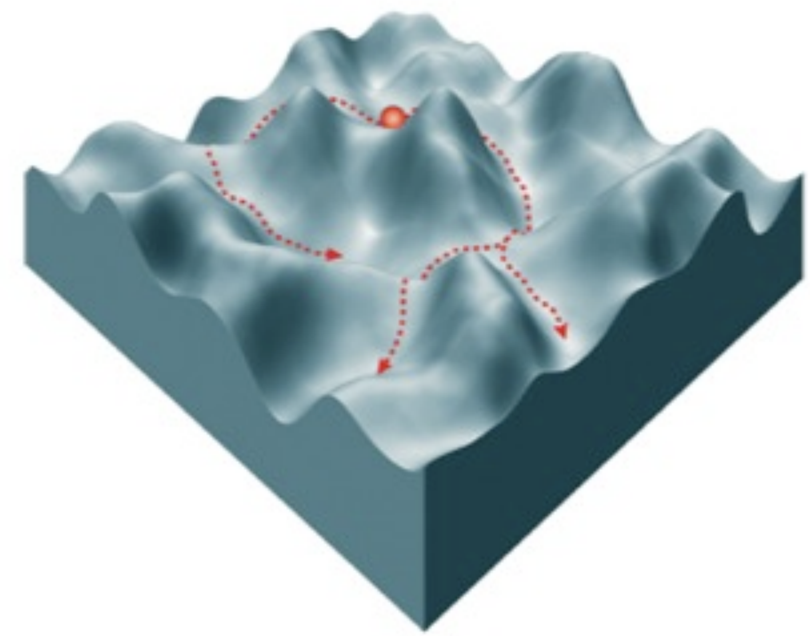
Evolved, optimal circuits reveal atypical combinations of gates

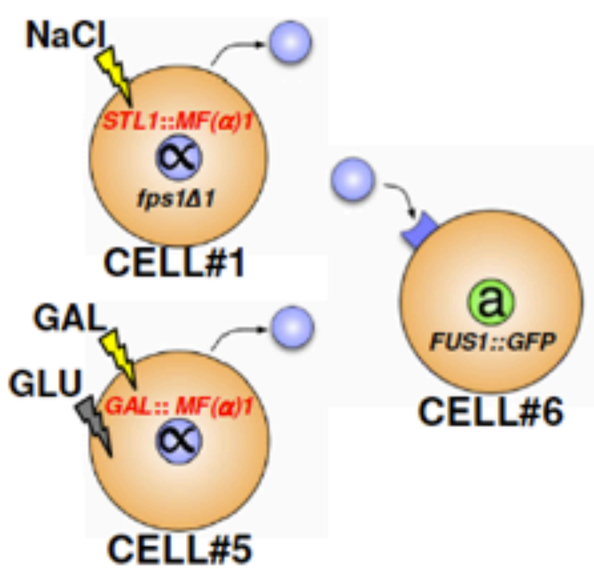
What's next? Reprogramming

STEM CELLS

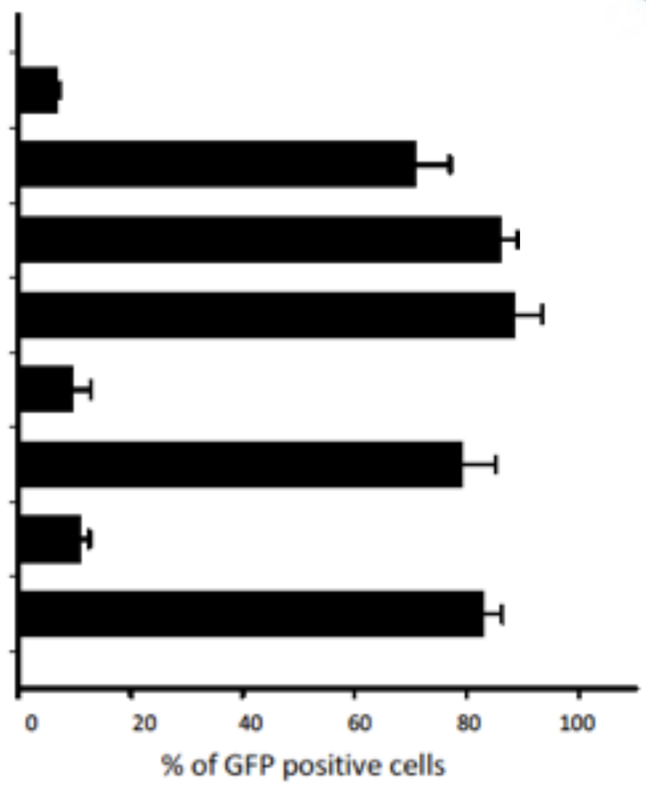
Systems biology of stem cell fate and cellular reprogramming

Ben D. MacArthur‡, Avi Ma'ayan‡ and Ihor R. Lemischka**

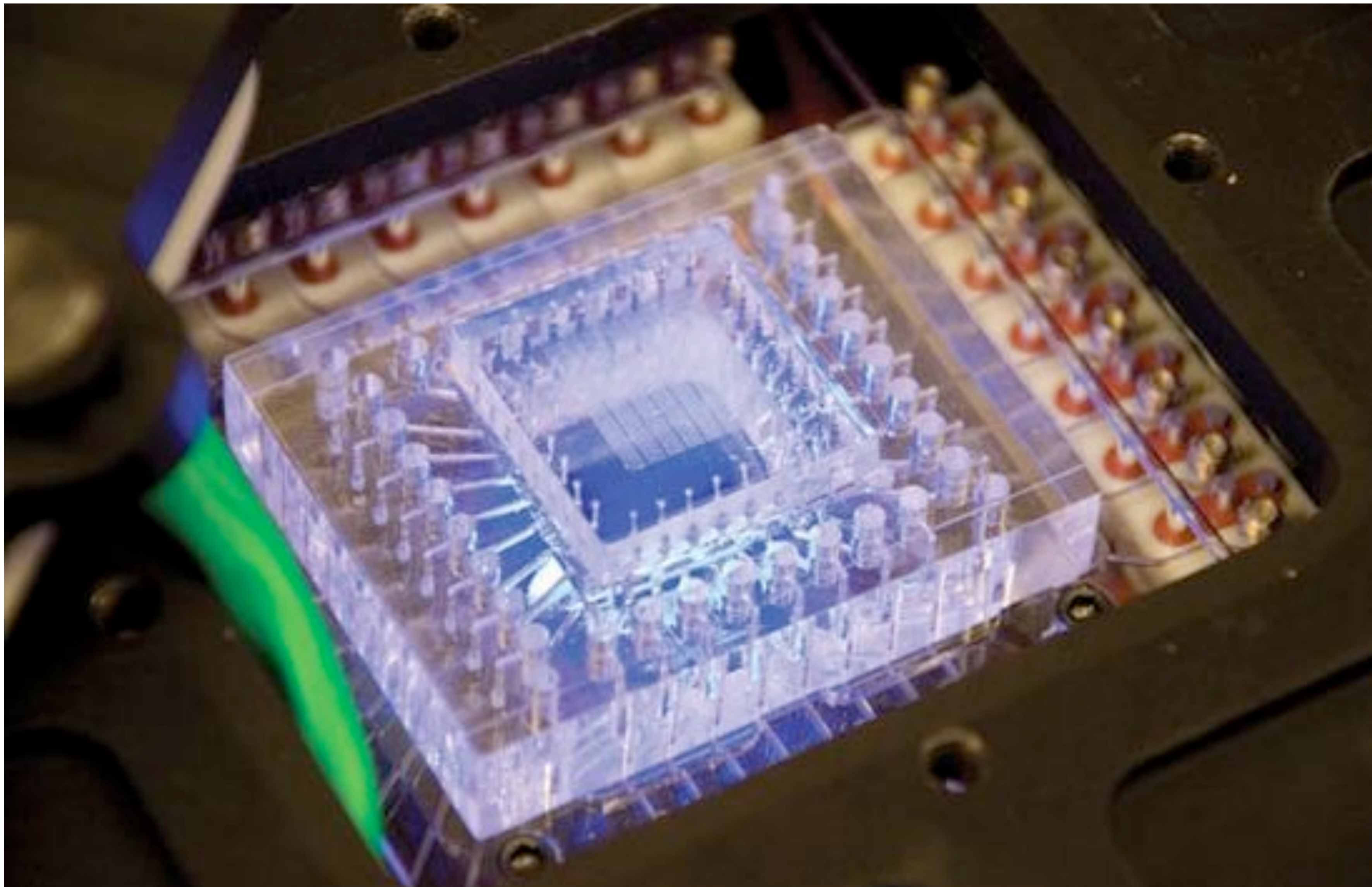




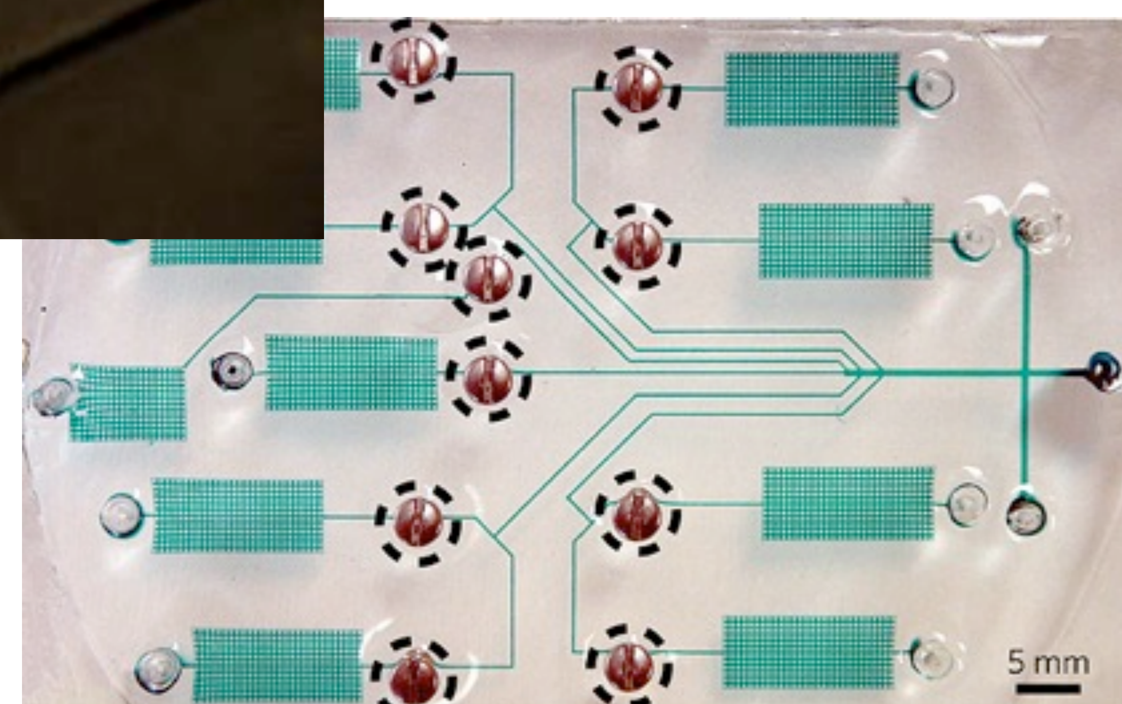
GAL	NaCl	GLU	Output
0	0	0	0
0	1	0	1
1	0	0	1
1	1	0	1
0	0	1	0
0	1	1	1
1	0	1	0
1	1	1	1



What's next? Microfluidic interface



Insight: Lab on a chip
Vol. 442, No. 7101 pp367-418

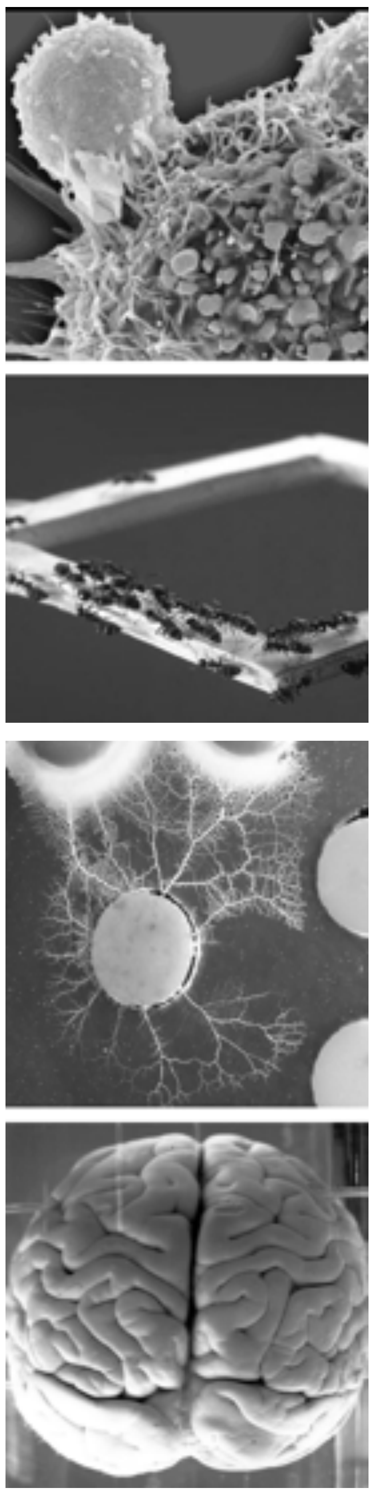


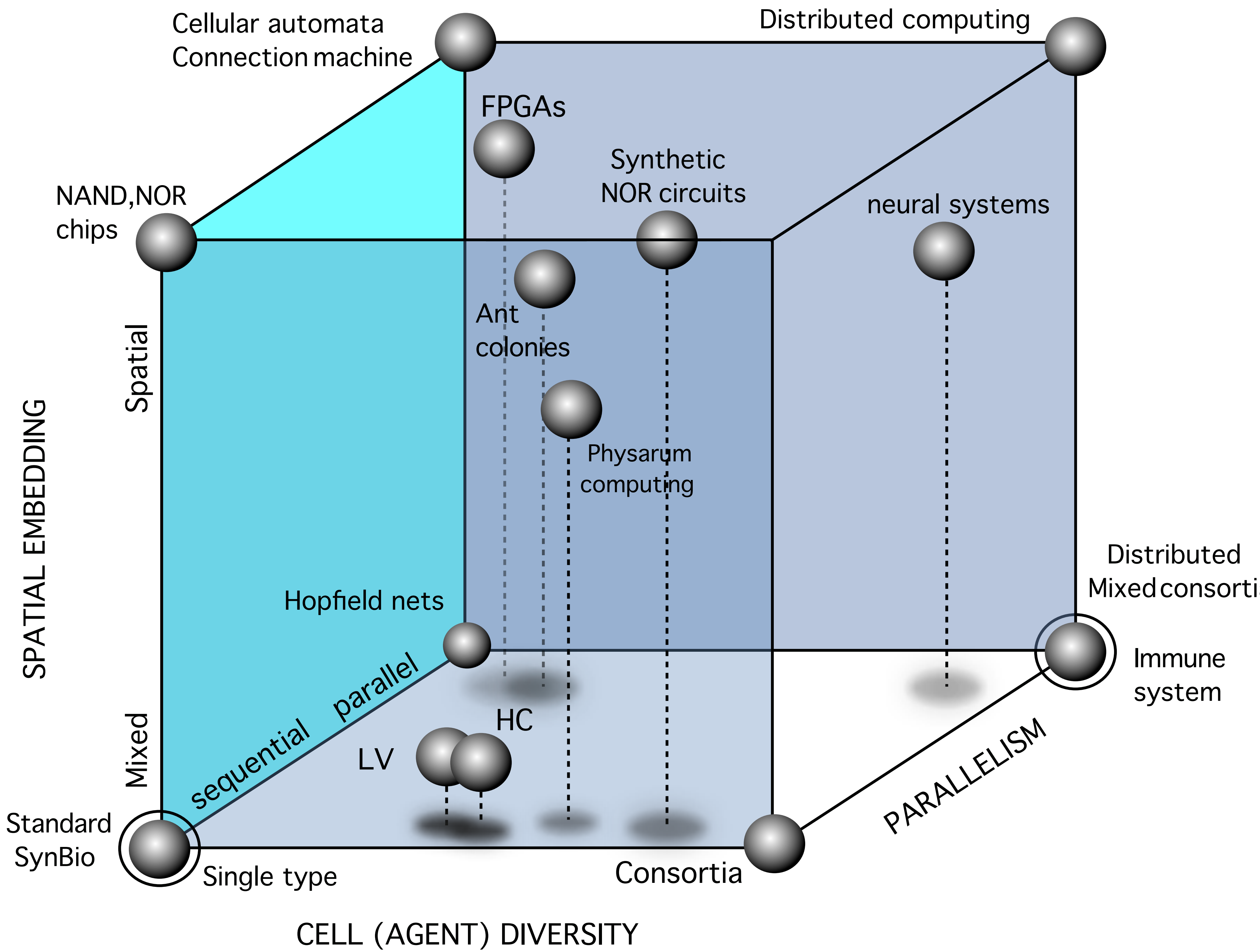
Spatial embodiment and/or increased wire diversity allows combinatorial explosion

Multicellularity and swarm intelligence

Multicellularity and swarm intelligence

Biological computation morphospace





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