Modelling paradigms for gene regulatory networks

Erik Plahte
Centre for Integrative Genetics (CIGENE)
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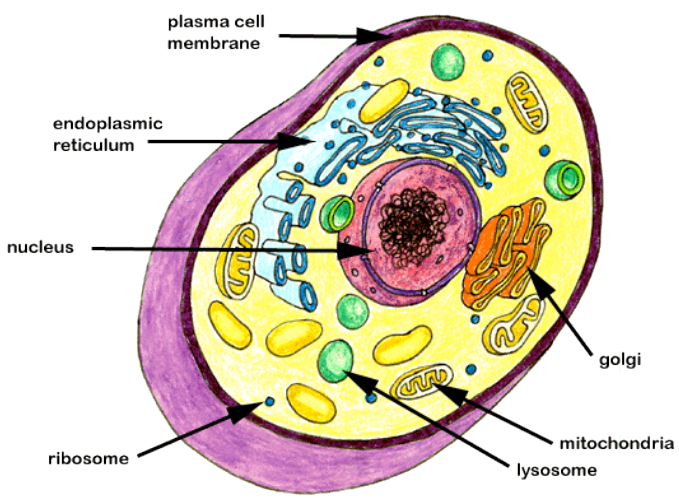
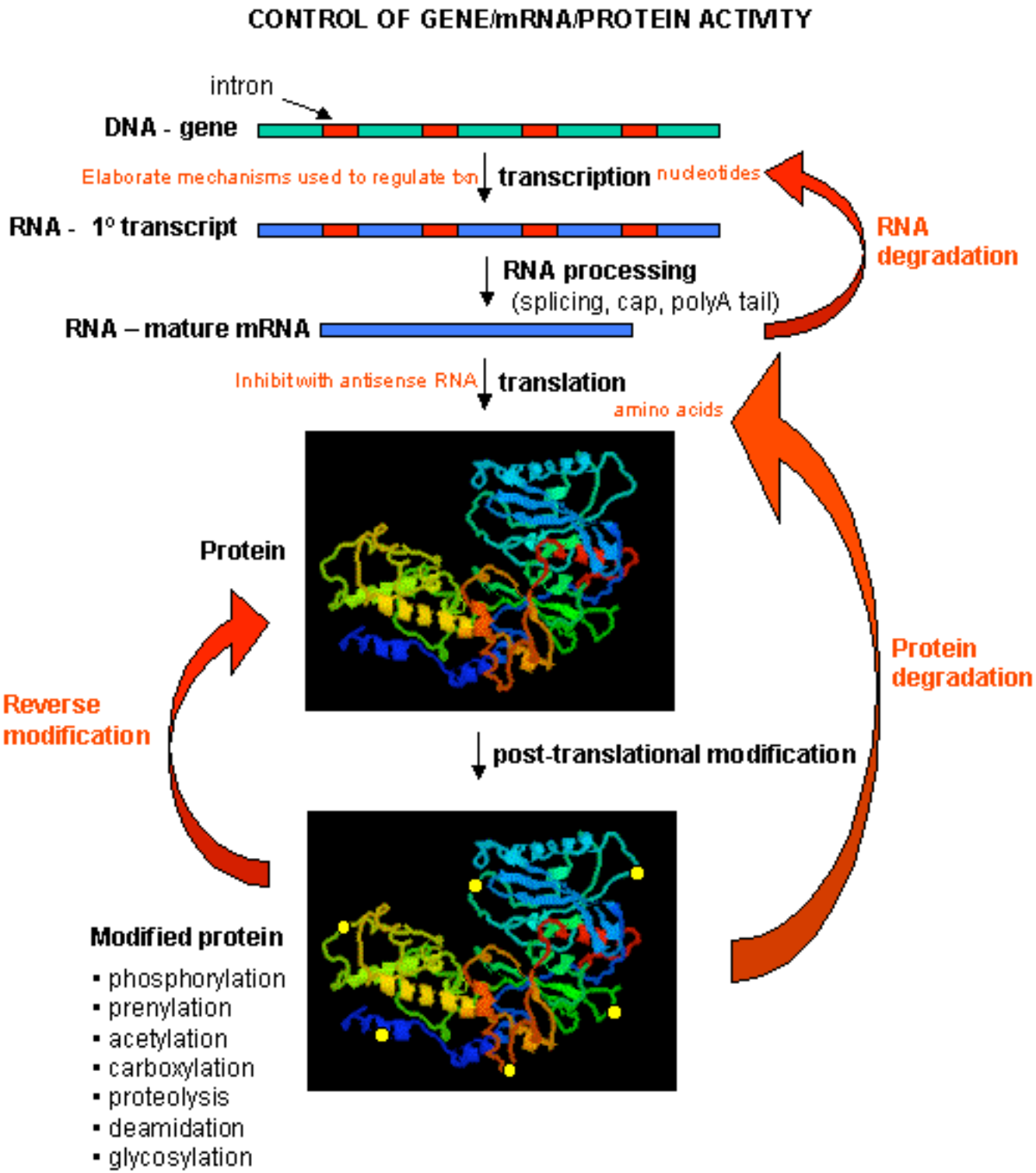
Bioinformatics for molecular biology
UiO, 16. Sept. 2009

The path from gene activation to an active protein molecule is long and intricate





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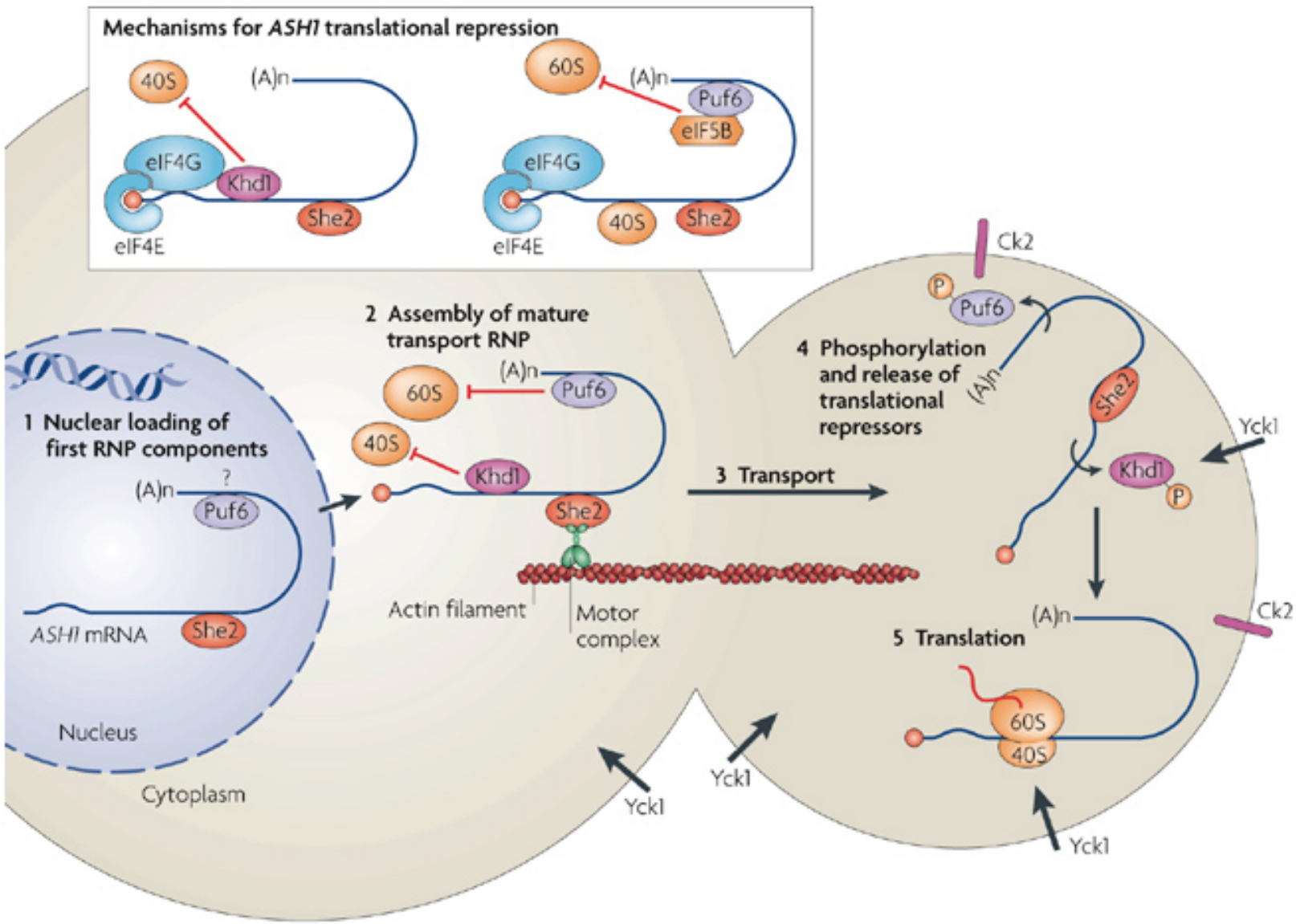
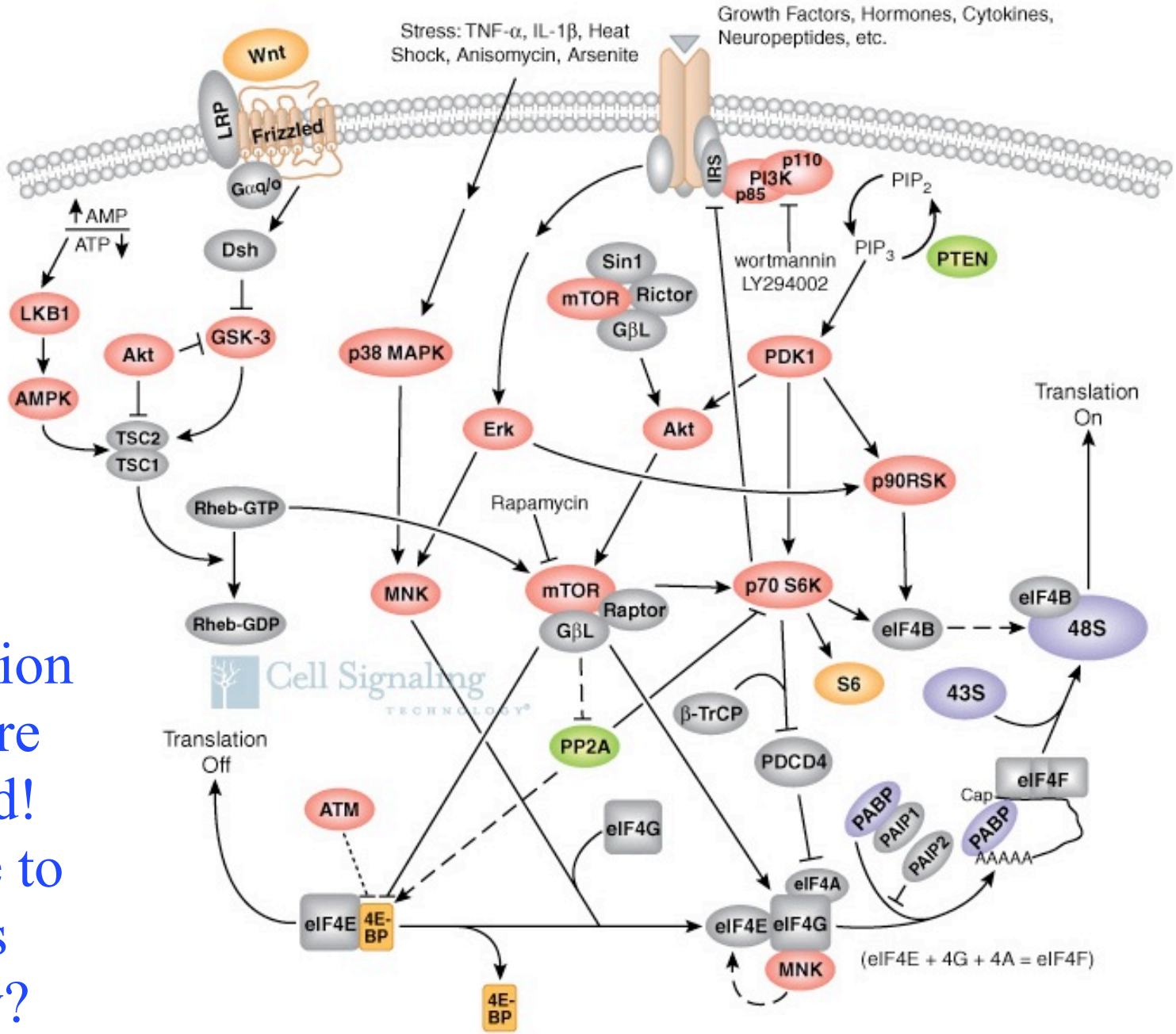


Nature Reviews | Molecular Cell Biology

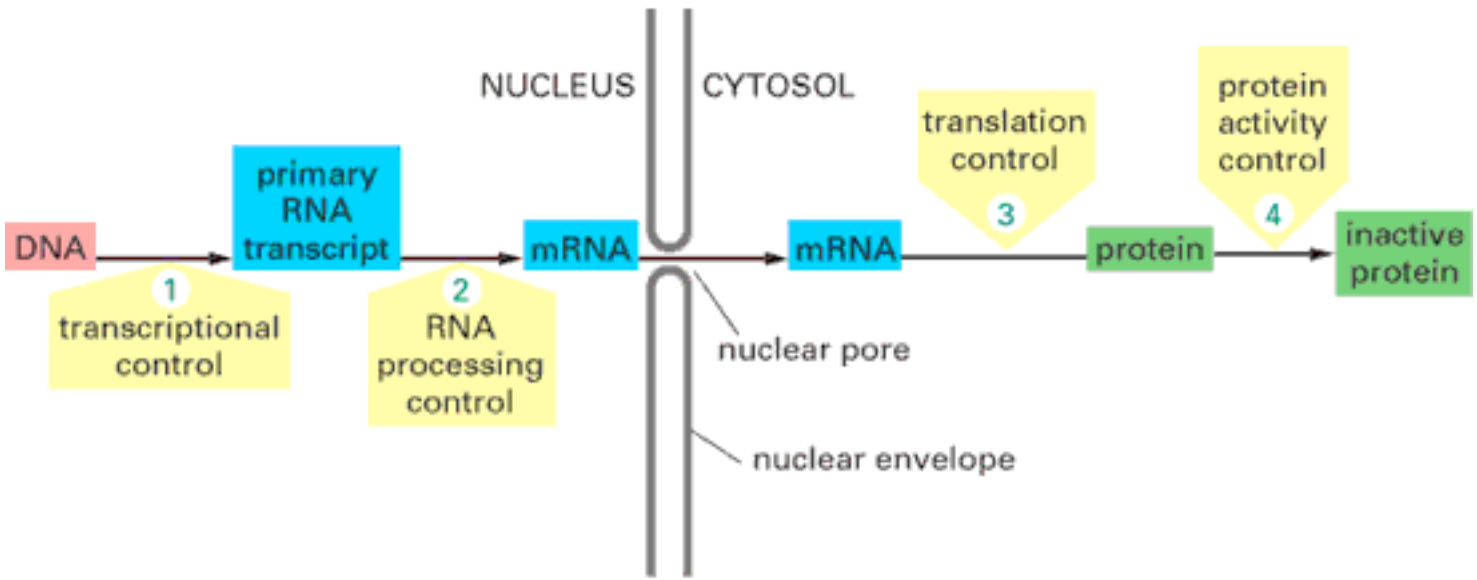
3

Gene regulation processes are complicated! Is it possible to model this complexity?



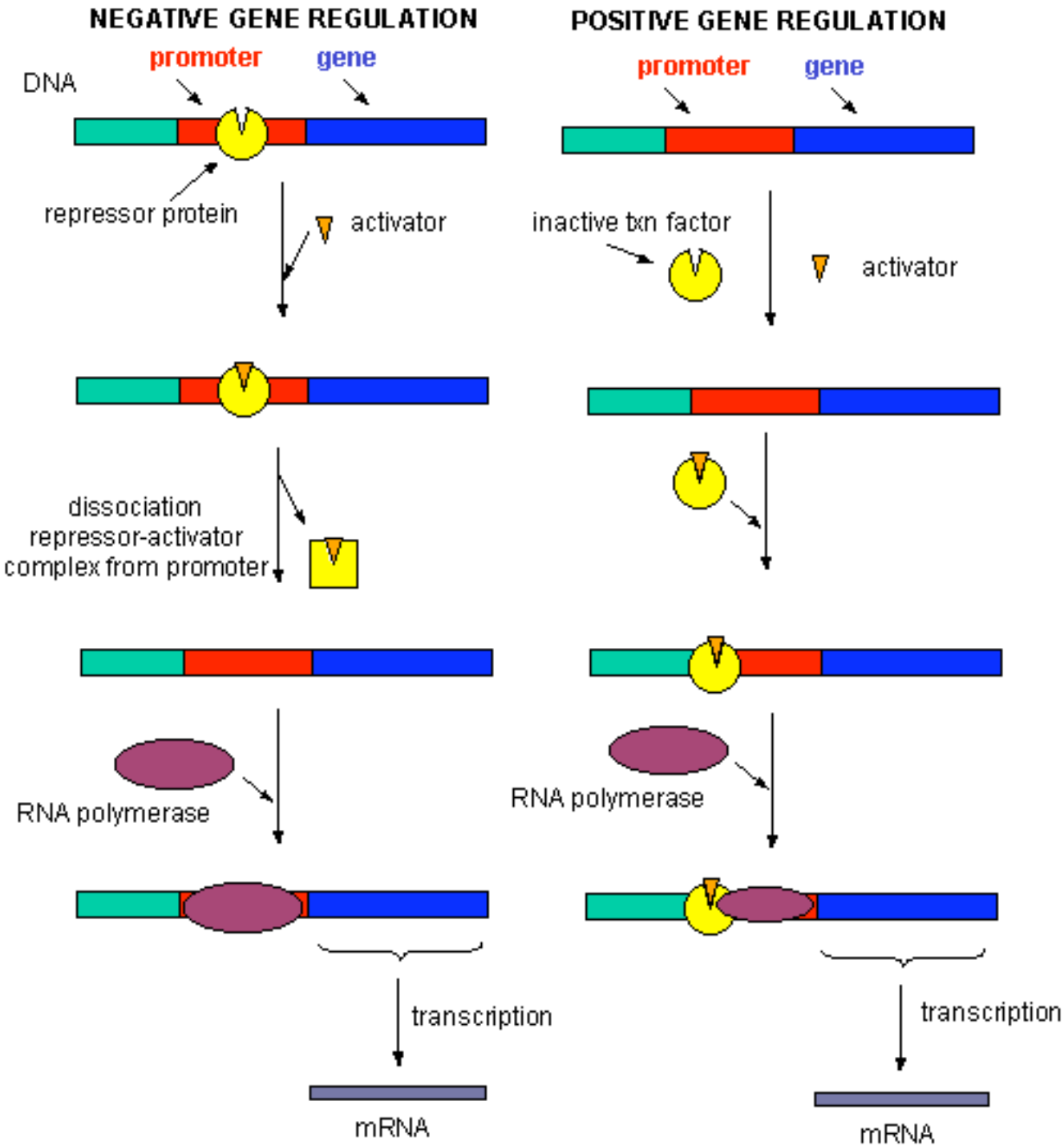
4

Controlling the process from DNA to protein



5

A (too) simple picture of transcription

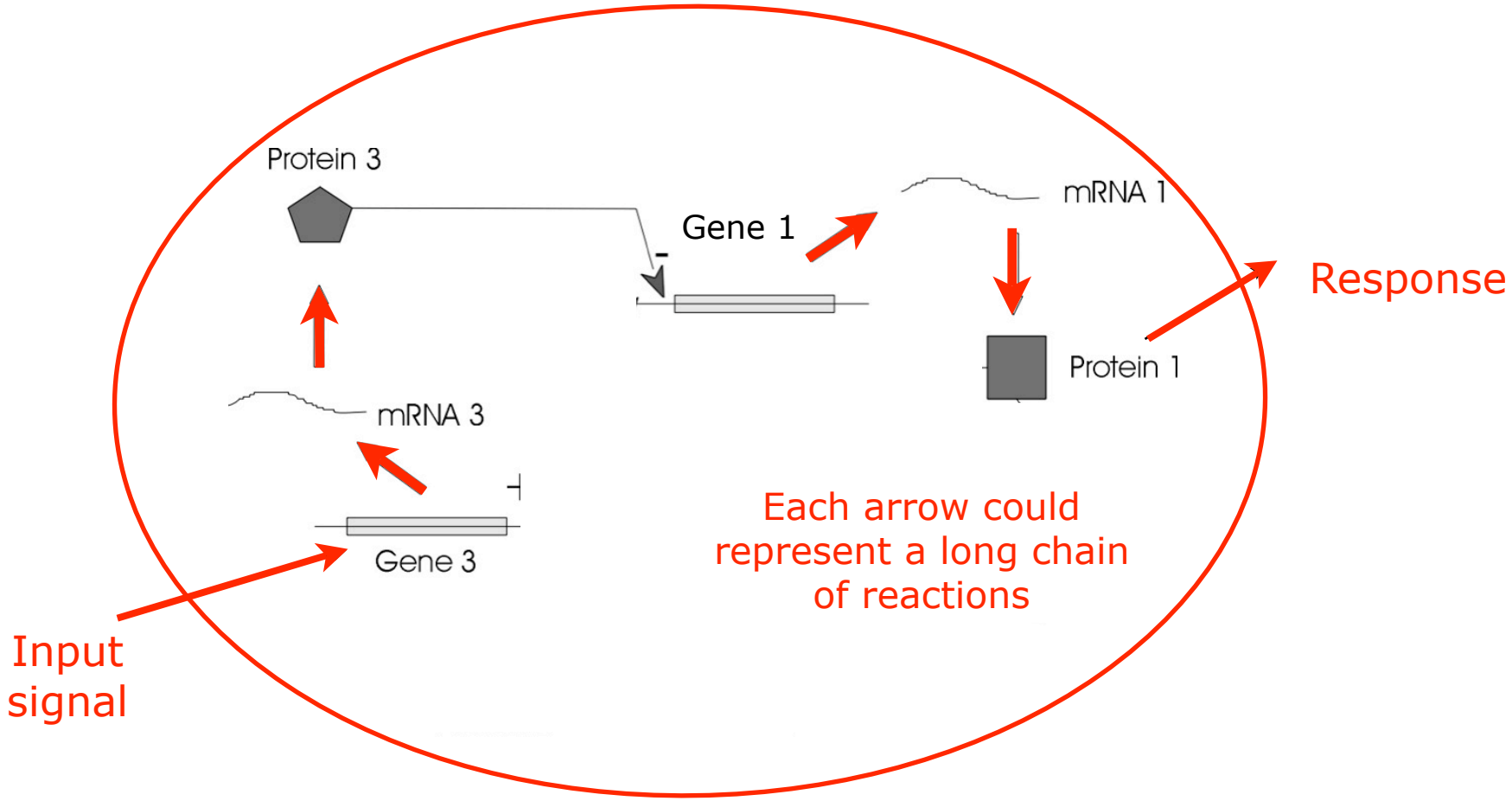


I will talk about

- Feedback as a regulatory mechanism
- Gene transcription
- Modelling philosophy
- Transcription regulation
- Boolean variables and functions: a little bit of mathematics
- Simple frameworks for modelling gene regulatory networks

7

How does a cell ensure the right response to an incoming signal?

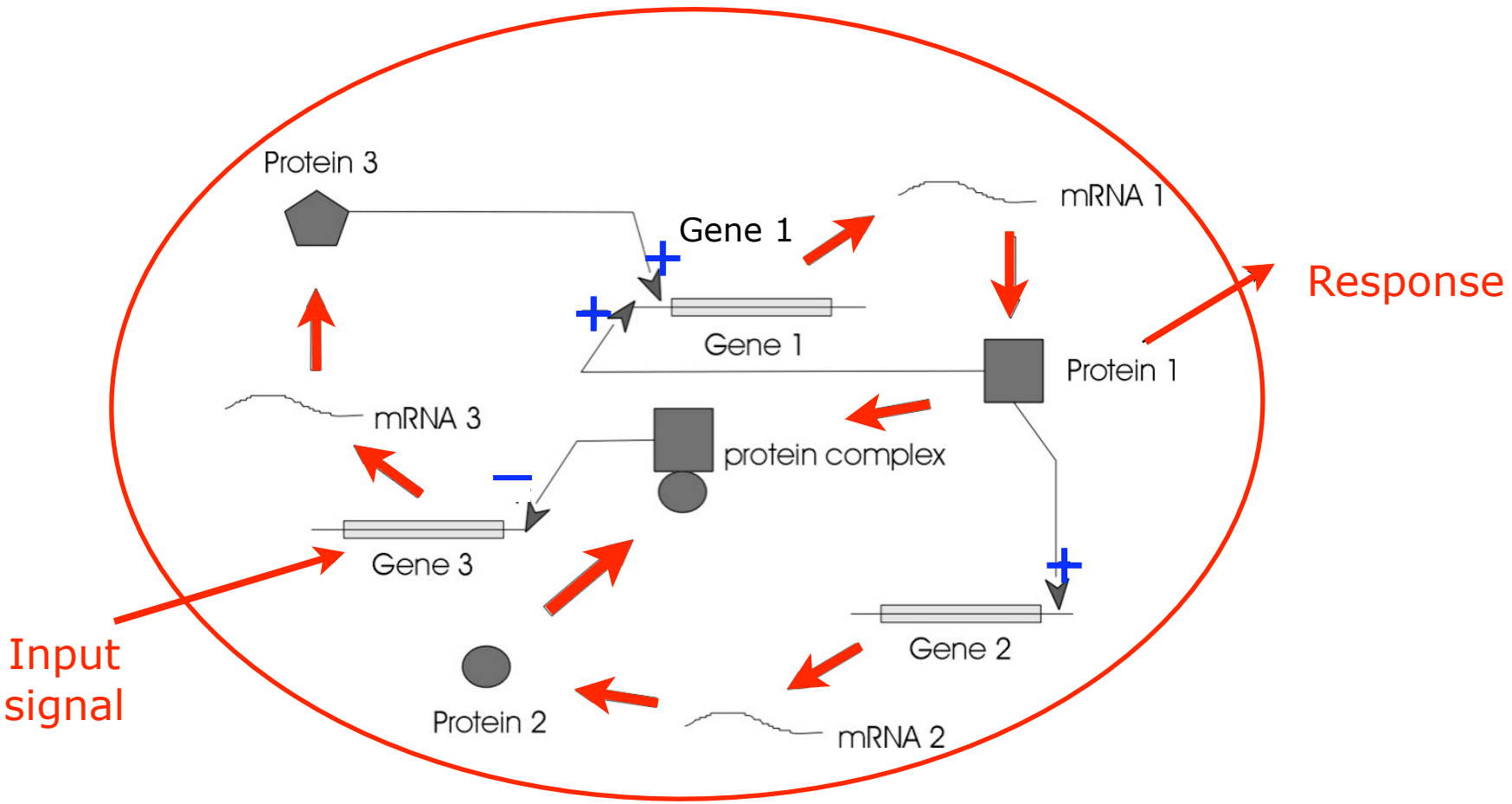


This simple scheme is not going to work:

- How to ensure not too high response, not to low?
- How could the gene know when the response is sufficient?
- How to sustain the response after the input signal has gone?

8

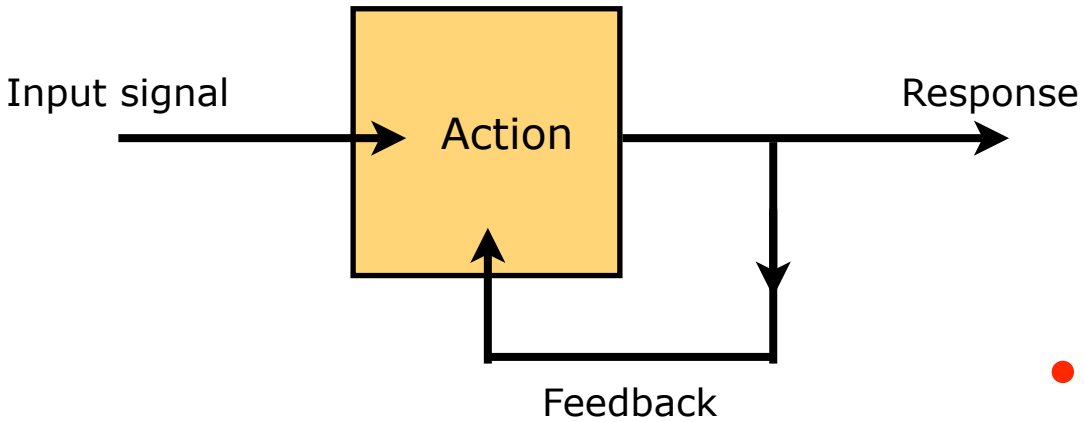
How does a cell ensure the right response to an incoming signal?



Generic mechanism: feedback regulation!
Feedback is a key concept.

9

Basics of feedback



Feedback is either positive or negative

- Positive feedback: the response is enhanced (stimulated).
- Negative feedback: the response is counteracted.

Advantages of positive feedback:

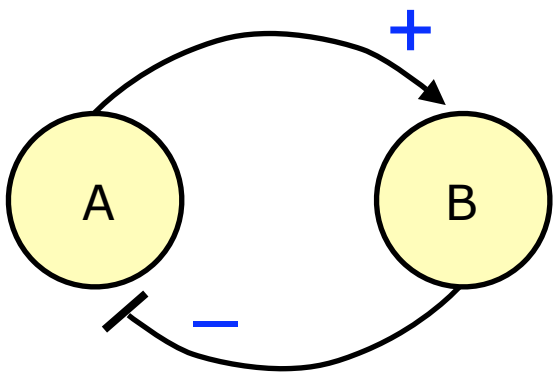
- Fast build-up of response level.
- Even if the input signal vanishes, the feedback may maintain the process.
- Without positive feedback the system can only have *one* steady state.

Advantages of negative feedback:

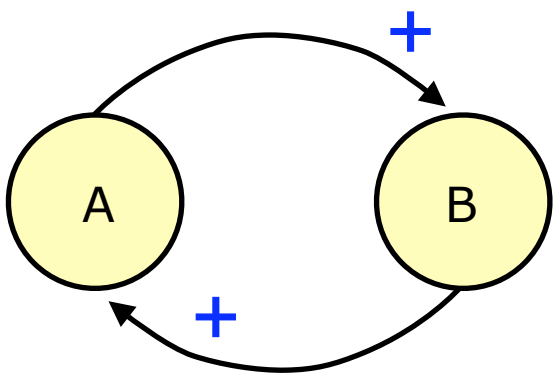
- The response is stabilised at the desired level (homeostasis).
- Disturbances are damped.

10

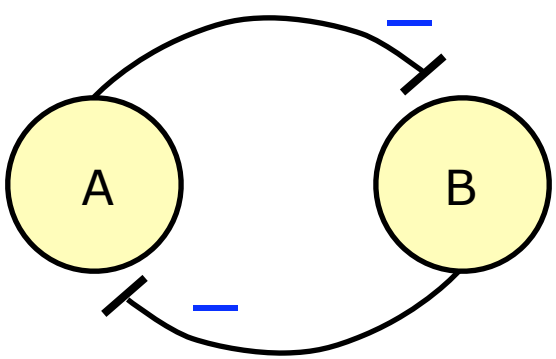
Positive and negative feedback between two agents



Negative feedback (+ –)
Homeostasis, periodicity.

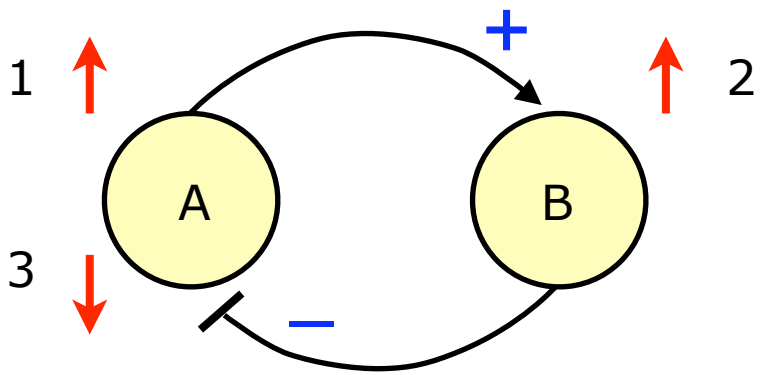


Positive feedback (+ +)
A and B deviate in the same direction after a perturbation.



Positive feedback (––)
A and B deviate in opposite directions after a perturbation.

Positive and negative feedback between two agents



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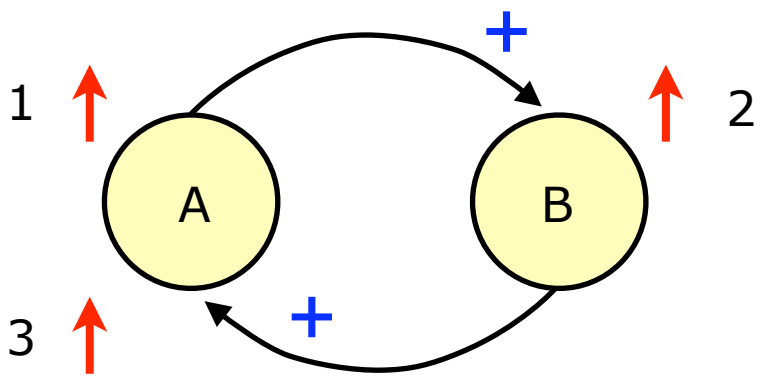

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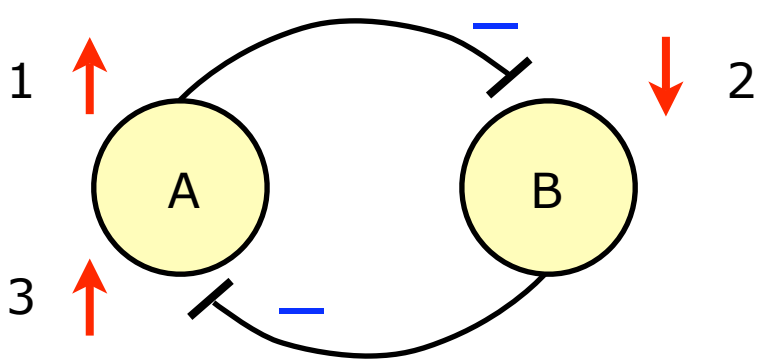
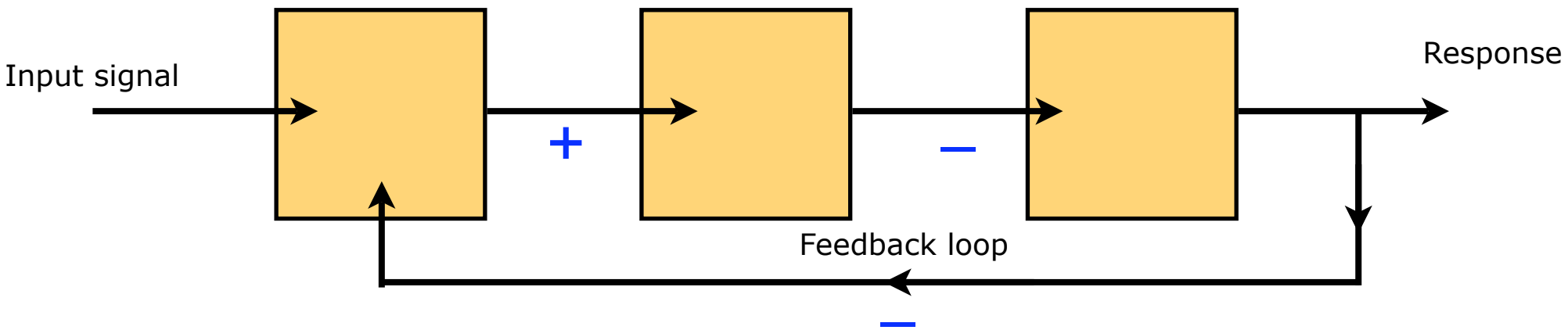


Positive feedback (––)
A and B deviate in opposite directions after a perturbation.

12

Feedback in a chain of reactions

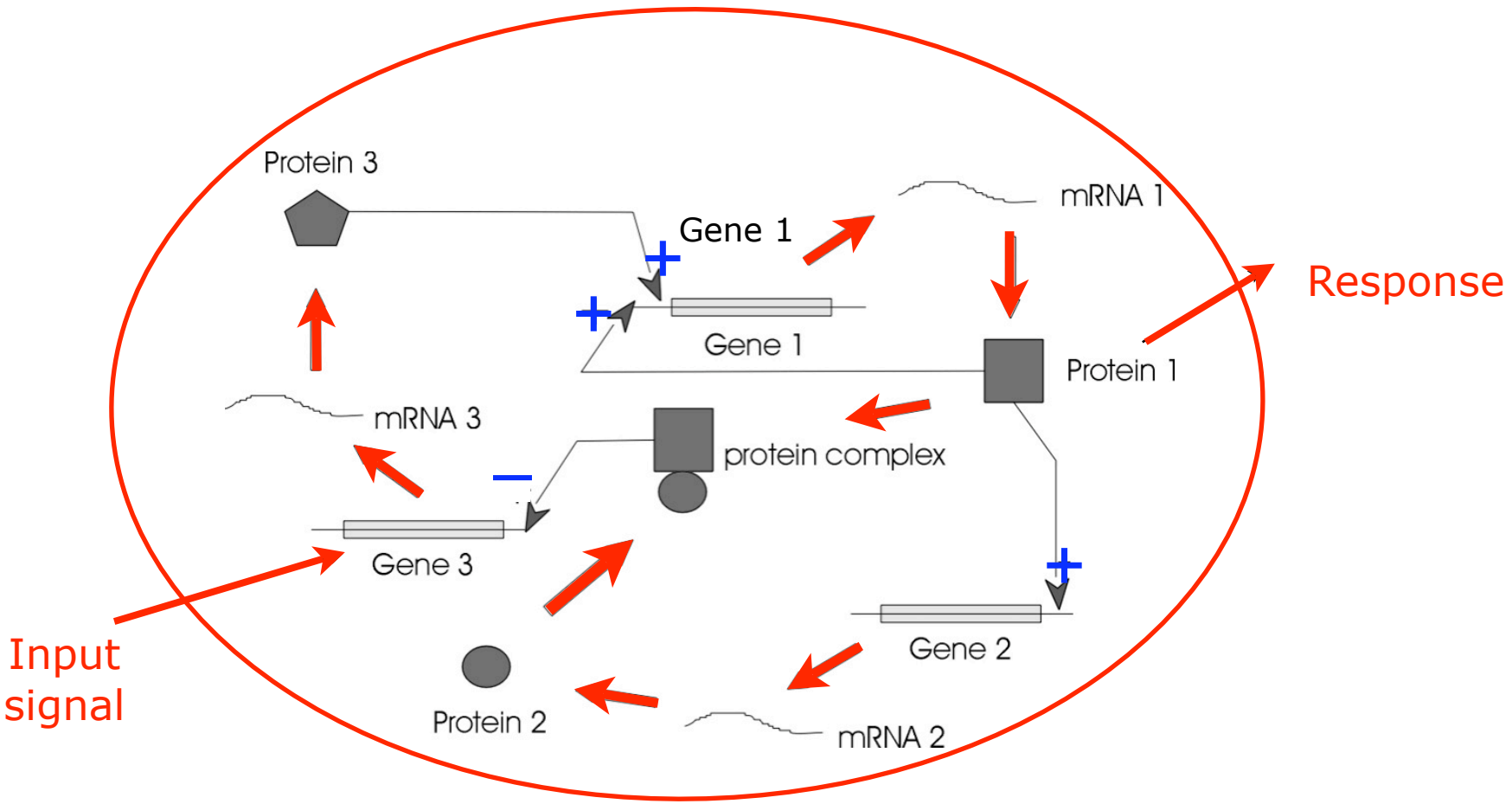


The signature of a feedback loop:

- If there is an odd number of negative (inhibitory) actions, the loop is negative (for all elements involved).
- If there is an even number of negative (inhibitory) actions, the loop is positive (for all elements involved).
- A negative loop generally leads to homeostasis.
- A positive loop may lead to multistationarity (no positive loop, no multistationarity).

13

How does a cell ensure the right response to an incoming signal?



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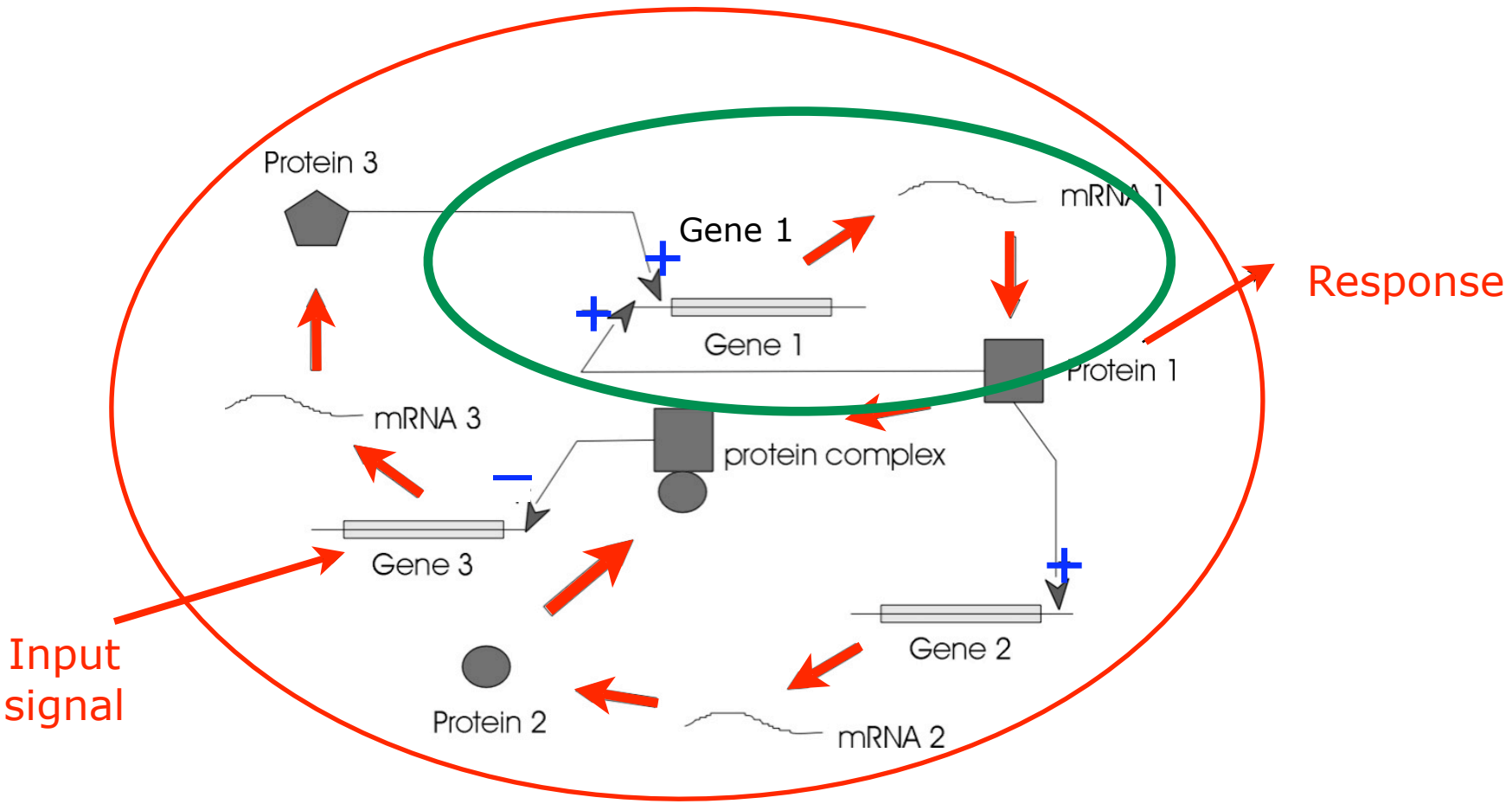

$1 \to 1$: positive loop,
$1 \to 3 \to 1$: negative loop $(-\quad +)$,
$1 \to 2 \to 3 \to 1$: negative loop $(+\quad -\quad +)$

15

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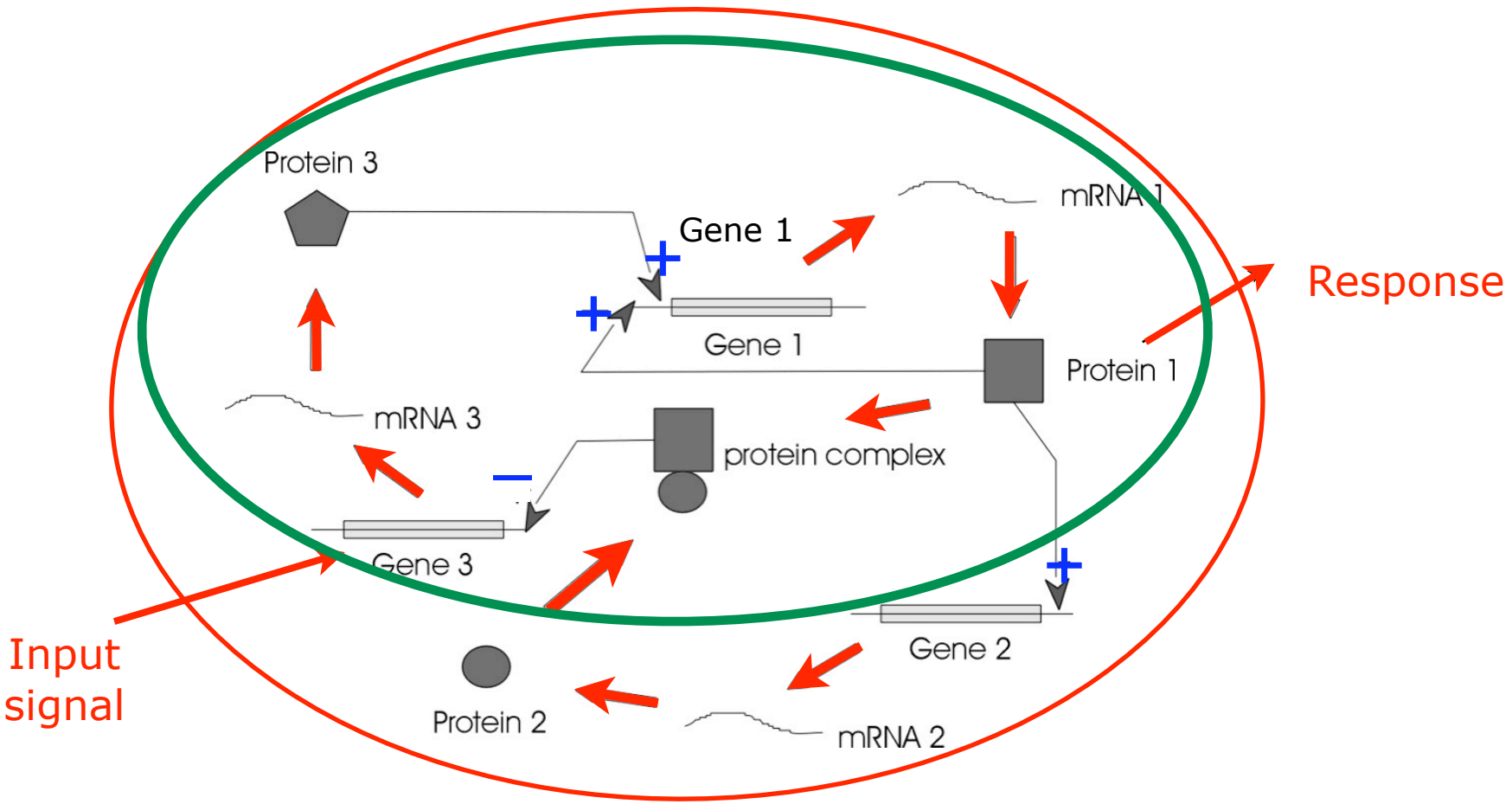

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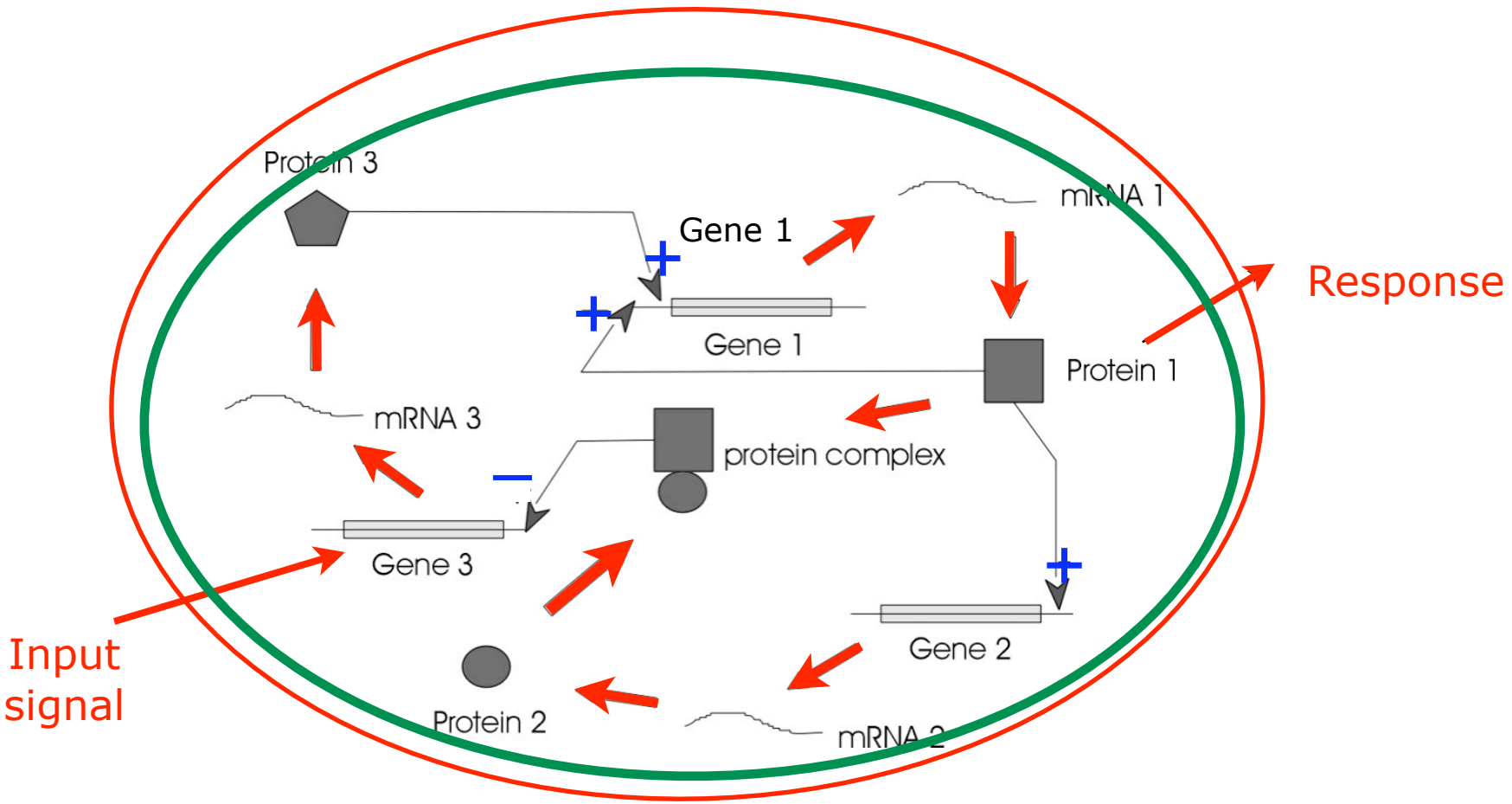

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17

Modelling: are realistic models realistic?

Straightforward continuous mass-action and Michaelis-Menten dynamics

18

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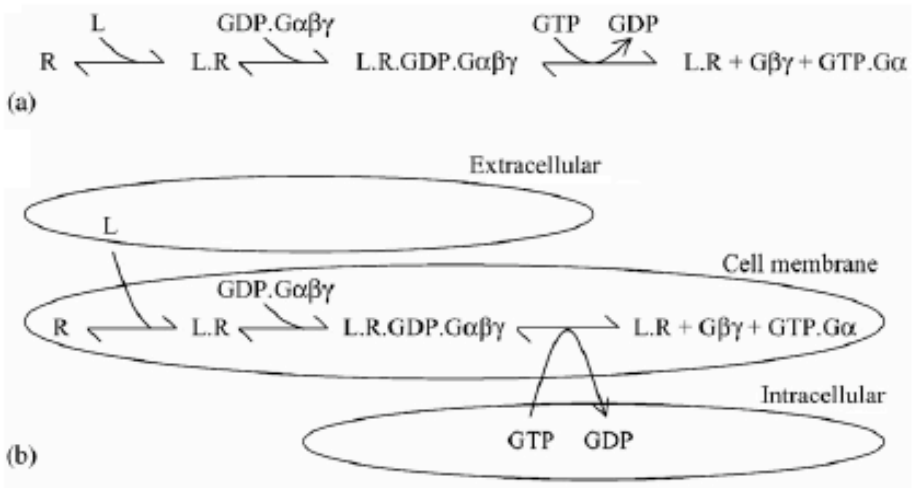

Straightforward continuous mass-action and Michaelis-Menten dynamics

Continuous reaction dynamics with compartments

18

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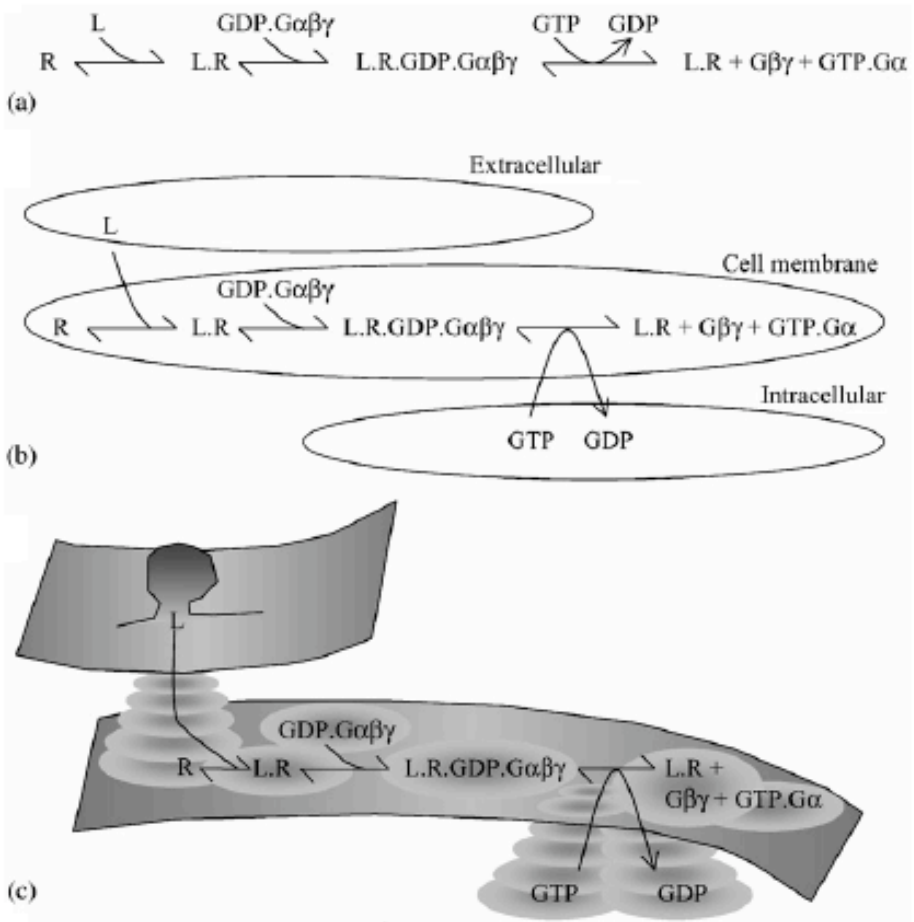

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Continuous reaction dynamics with compartments

Continuous reaction-diffusion 3D model

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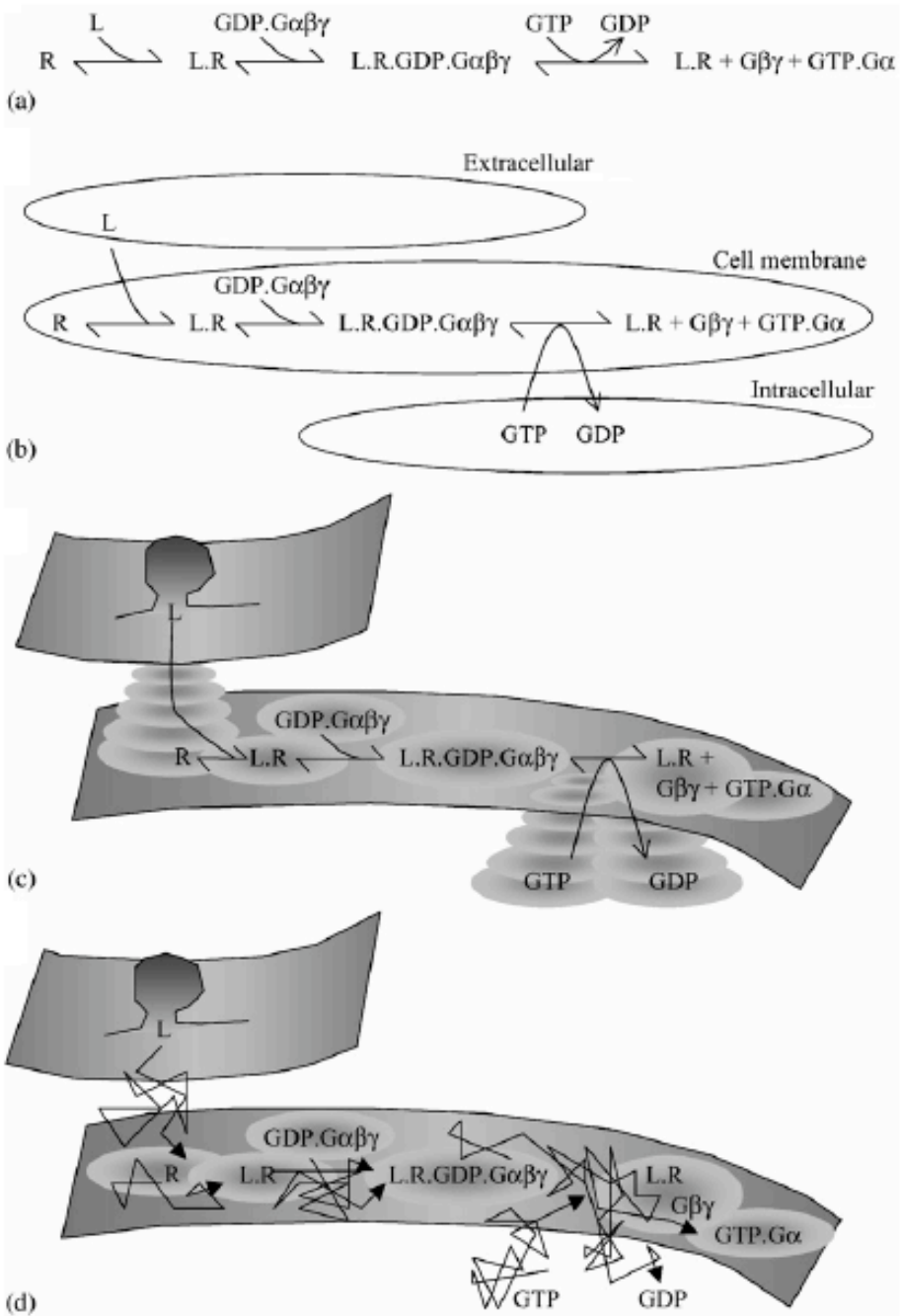


Straightforward continuous mass-action and Michaelis-Menten dynamics

Continuous reaction dynamics with compartments

Continuous reaction-diffusion 3D model

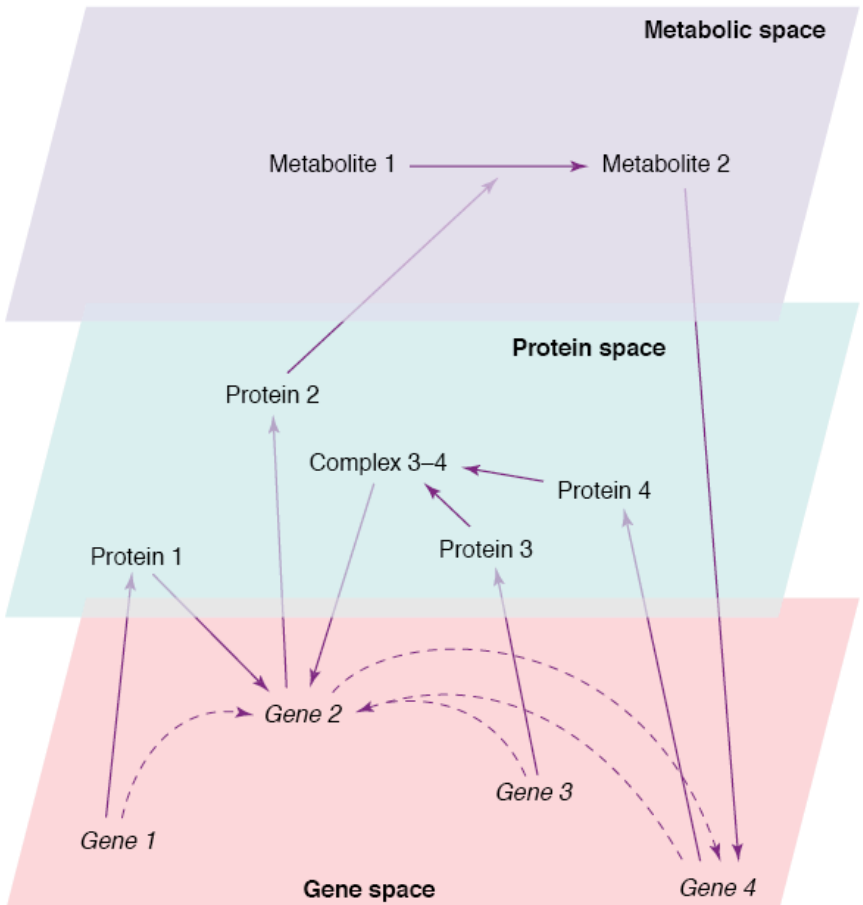
Stochastic 3D model of discrete molecules with Brownian motion in space.

Is this model more correct? More useful? If this is the answer, what is the question?

(From U.S. Bhalla, Progr. Biophys. & Mol. Biol. (2003))

18

Collapsing the real network to a gene regulatory network model



"An increasingly popular model of regulation is to represent networks of genes *as if they directly affect each other*. Although such gene networks are phenomenological because they do not explicitly represent the proteins and metabolites that mediate cell interactions, they are a logical way of describing phenomena observed with transcription profiling..."

From Brazhnik, de la Fuente and Mendes, Trends in Biotechnology (2002)

Real actions

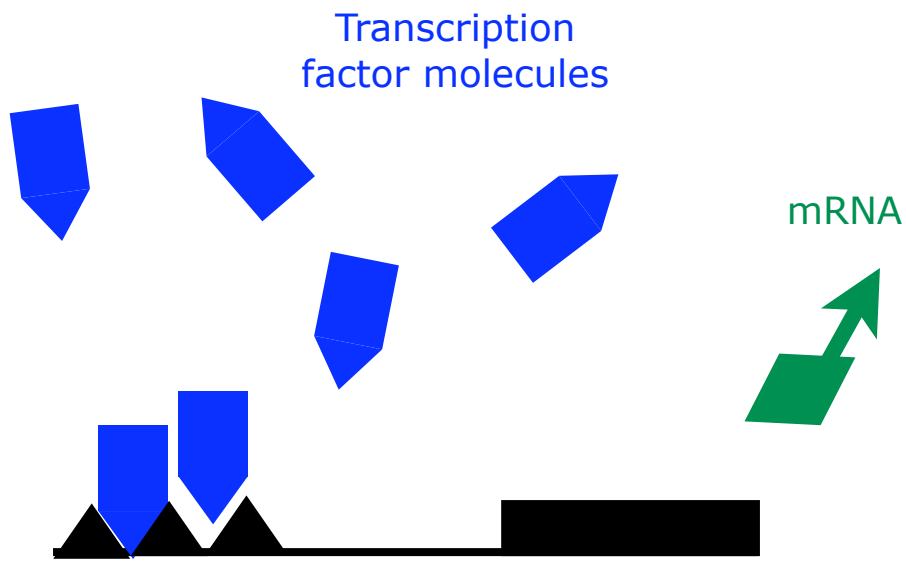
The actions in the corresponding gene regulatory network

19

Simple-minded transcription regulation

Few transcription factor (TF) molecules:
Very low transcription rate

Many TF molecules:
Full transcription rate



20

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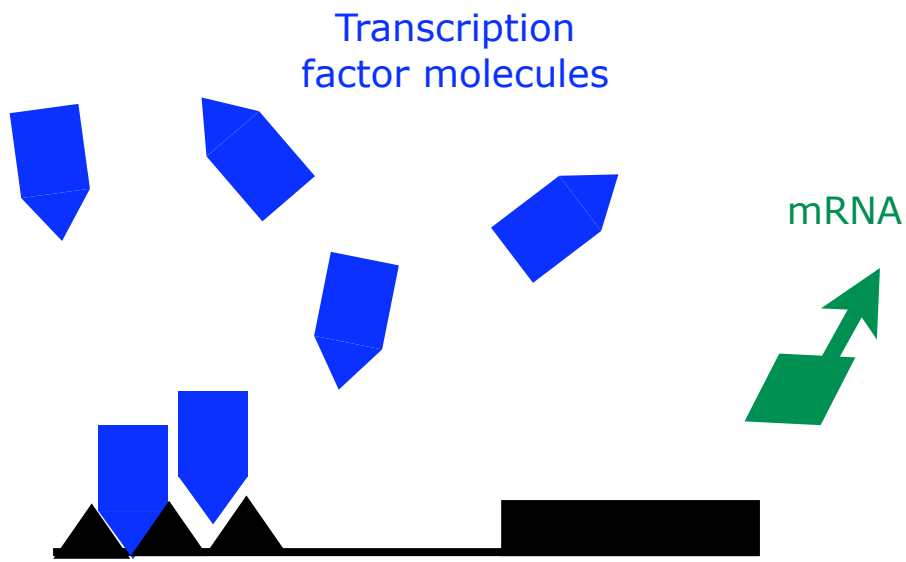


How is the transition between the two extreme cases:

Gradual?
Gradual, but threshold dependent?
Binary (switch-like)?

20

The Biochemical Basis of an All-or-None Cell Fate Switch in *Xenopus* Oocytes

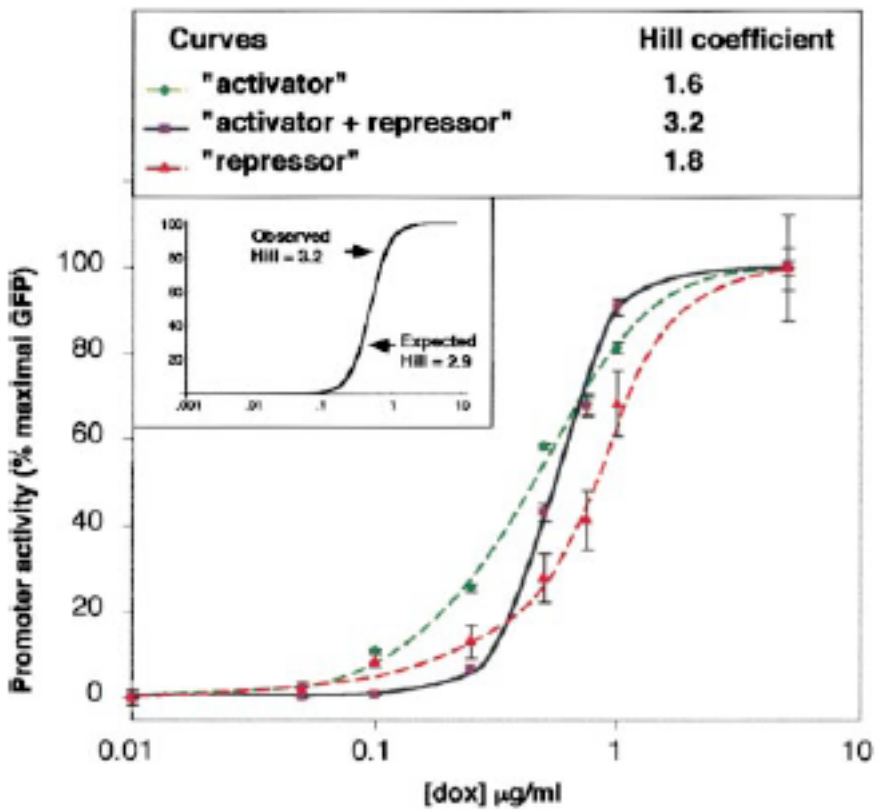
James E. Ferrell Jr.* and Eric M. Machleder

www.sciencemag.org • SCIENCE • VOL. 280 • 8 MAY 1998

Molecular Cell, Vol. 6, 723–728, September, 2000, Copyright ©2000 by Cell Press

Transcriptional Control: Rheostat Converted to On/Off Switch

Fabio M. V. Rossi,* Andrew M. Kringstein,* Albert Spicher,* Oivin M. Guicherit,† and Helen M. Blau*‡



21

Proc. Natl. Acad. Sci. USA
Vol. 95, pp. 13670–13675, November 1998
Cell Biology

Graded transcriptional response to different concentrations of a single transactivator

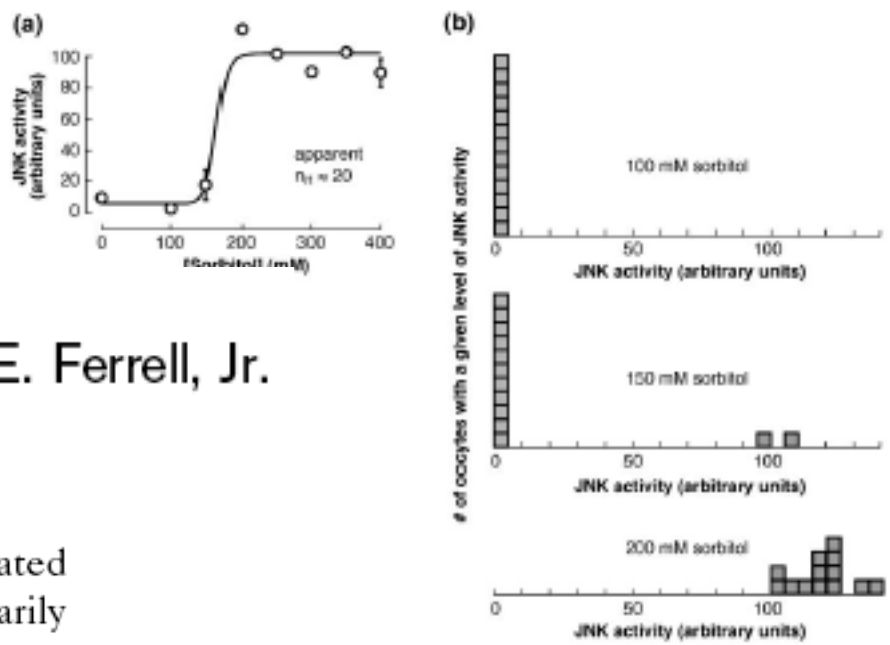
ANDREW M. KRINGSTEIN*, FABIO M. V. ROSSI*, ANDREAS HOFMANN†, AND HELEN M. BLAU‡

Department of Molecular Pharmacology, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94305-5332

The EMBO Journal Vol. 20 No. 12 pp. 3167–3176, 2001

Cell signaling can direct either binary or graded transcriptional responses

Stephen R.Biggar and Gerald R.Crabtree[1]



Bistability in the JNK cascade

Christoph P. Bagowski and James E. Ferrell, Jr.

Current Biology 2001, 11:1176–1182

The Jun N-terminal kinases (JNKs) or stress-activated protein kinases (SAPKs) are a family of evolutionarily conserved protein kinases implicated in stress responses and apoptosis [1–4]. Fibroblasts from mouse embryos with

22

The EMBO Journal Vol. 20 No. 12 pp. 3167–3176, 2001

Cell signaling can direct either binary or graded transcriptional responses

Stephen R.Biggar and Gerald R.Crabtree[1]

The majority of existing evidence suggests that, within individual cells, a gene is either maximally expressed or is not expressed at all (Moreau *et al.*, 1981; Weintraub, 1988; Fiering *et al.*, 1990; Moon and Ley, 1990; Walters *et al.*, 1995, 1996; Magis *et al.*, 1996; Hollander *et al.*, 1998).

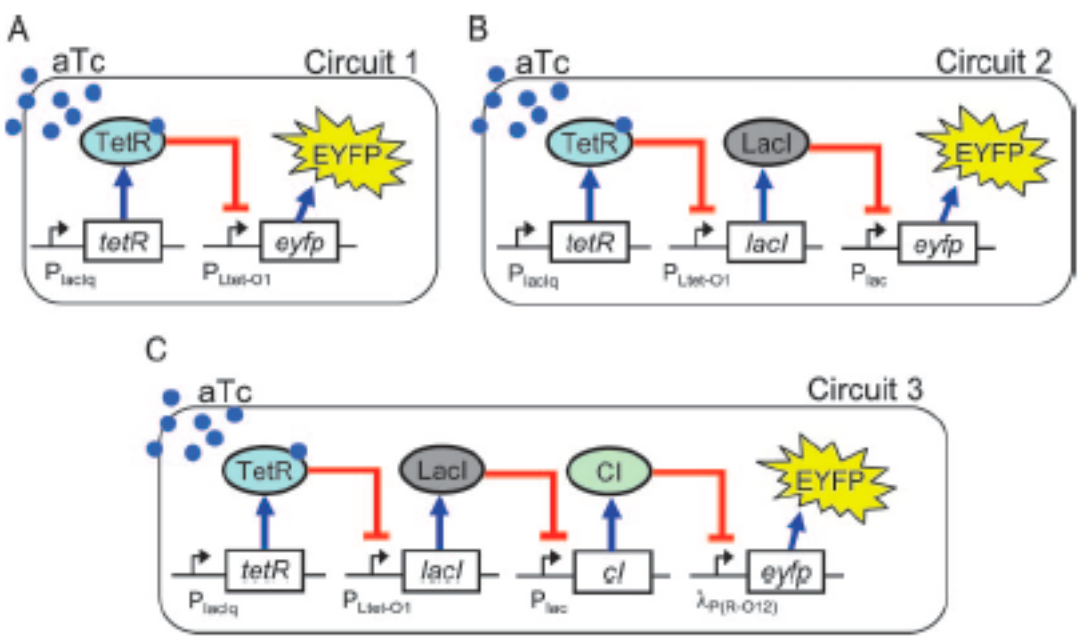
23

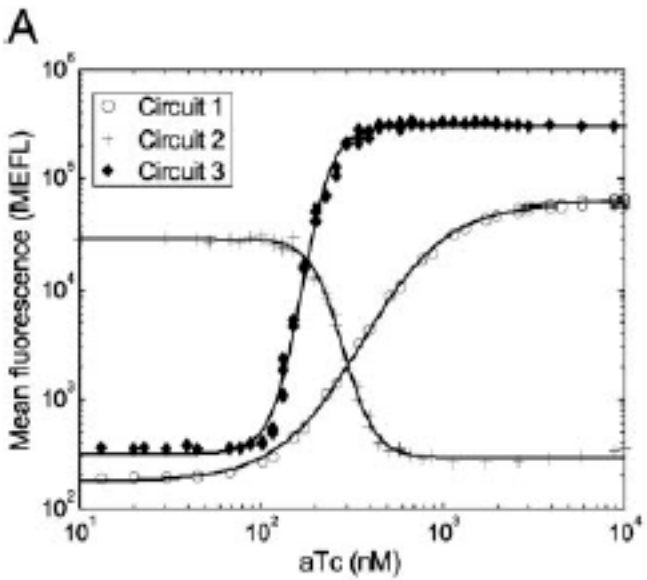
Can sigmoidal response functions describe the whole gene regulation process?

Ultrasensitivity and noise propagation in a synthetic transcriptional cascade

Sara Hooshangi*, Stephan Thiberge*, and Ron Weiss*†‡

PNAS | March 8, 2005 | vol. 102 | no. 10 | 3581–3586



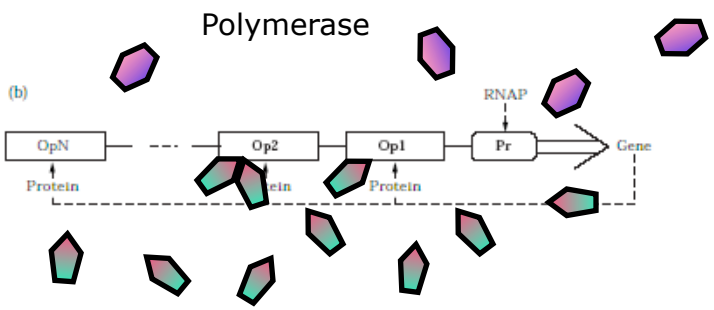


Synthetic transcriptional cascades in *E. coli* behaving like a single transcription response function.

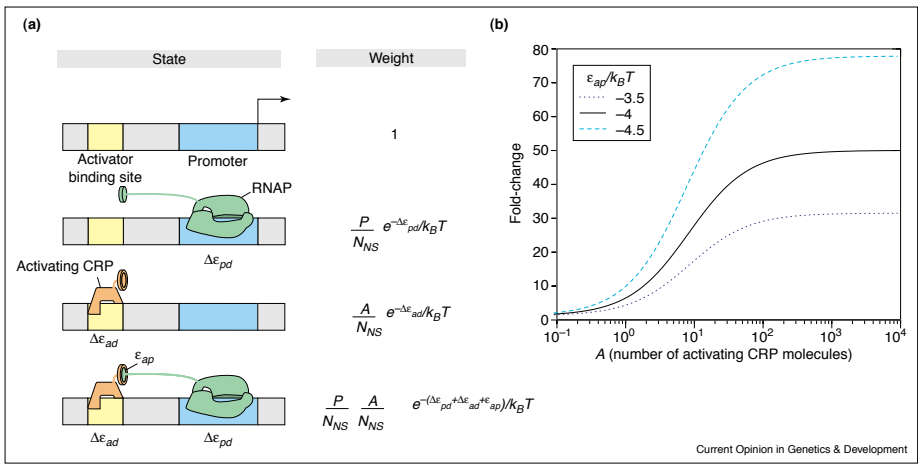
24

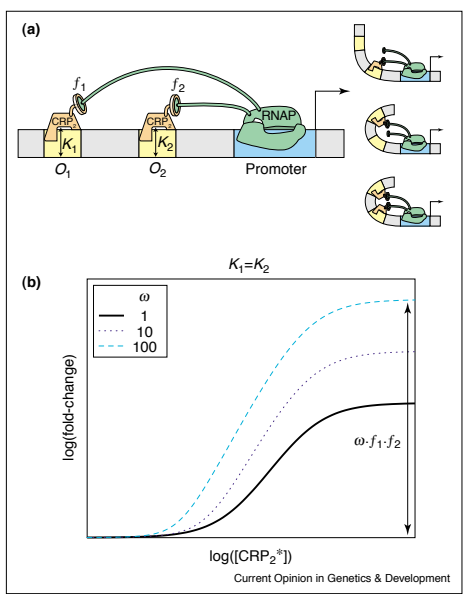
Transcription modelled by statistical thermodynamics

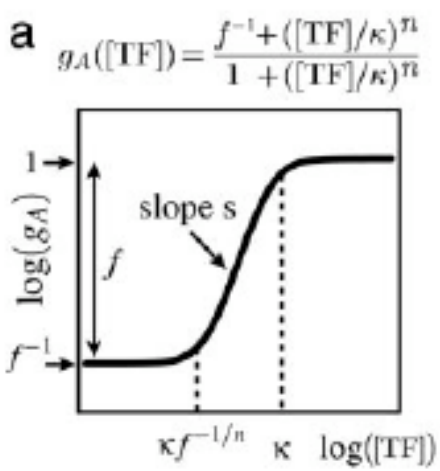
- What is the probability that the protein molecules necessary to initiate transcription (transcription factors and polymerase) bind to the DNA?
- Assumption: Transcription rate ~ binding probability.
- Depends on:
  - number of active molecules,
  - number of alternative binding sites,
  - the binding energies for the different sites,
  - the geometric configuration of the DNA.
- Can be solved by classical methods (Boltzmann).



Transcription factors (proteins)







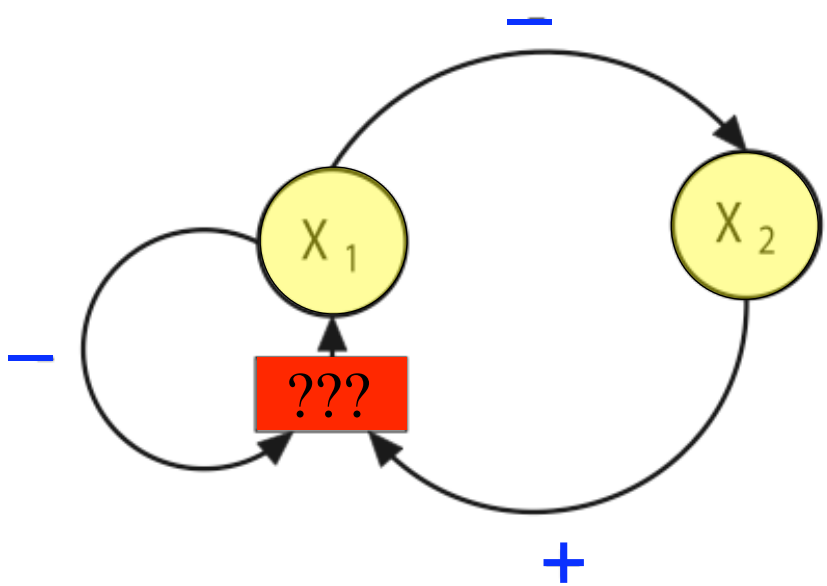
activator

n = # binding sites

25

Multiple input gates – how do several transcription factors interact?

A gene may be regulated by several transcription factors.



What kind of function coordinates the two inputs?

- Are both inputs necessary, or is one sufficient?
- Saturation?
- Thresholds?
- Is the effect of one of them dependent on the other?

26

Multiple input gates – how do several transcription factors interact?

Detailed map of a cis-regulatory input function

Y. Setty*†, A. E. Mayo*†, M. G. Surette‡, and U. Alon*†§

7702–7707 | PNAS | June 24, 2003 | vol. 100 | no. 13

OPEN ACCESS Freely available online PLoS BIOLOGY

Plasticity of the *cis*-Regulatory Input Function of a Gene

Avraham E. Mayo¤, Yaakov Setty, Seagull Shavit, Alon Zaslaver, Uri Alon*

Combinatorial Synthesis of Genetic Networks

Călin C. Guet,[1,3] Michael B. Elowitz,[3] Weihong Hsing,[1] Stanislas Leibler[1,2,3]*

24 MAY 2002 VOL 296 SCIENCE www.sciencemag.org

27

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Genomic Cis-Regulatory Logic: Experimental and Computational Analysis of a Sea Urchin Gene

Chiou-Hwa Yuh, Hamid Bolouri, Eric H. Davidson*

SCIENCE • VOL. 279 • 20 MARCH 1998 • www.sciencemag.org

BioLogic Gates Enable Logical Transcription Control in Mammalian Cells

Beat P. Kramer, Cornelius Fischer, Martin Fussenegger

BIOTECHNOLOGY AND BIOENGINEERING, VOL. 87, NO. 4, AUGUST 20, 2004

Logic functions of the genomic cis-regulatory code

Sorin Istrail†‡ and Eric H. Davidson§¶

4954–4959 | PNAS | April 5, 2005 | vol. 102 | no. 14

Development 128, 617-629 (2001)
Printed in Great Britain © The Company of Biologists Limited 2001
DEV5441

617

Cis-regulatory logic in the *endo16* gene: switching from a specification to a differentiation mode of control

Chiou-Hwa Yuh[1,2], Hamid Bolouri[3] and Eric H. Davidson[2,*]

27

Logical functions (Boolean functions)

- Logical (Boolean) variable: $X \in \{0, 1\}$

  $0 + 0 = 0, \quad 0 + 1 = 1, \quad 1 + 1 = 1,$

  $0 \cdot 0 = 0, \quad 0 \cdot 1 = 0, \quad 1 \cdot 1 = 1.$

- Boolean function: a function of Boolean variables that only gets Boolean values.

- One variable: $Y = f(X)$.
  Just four different functions:

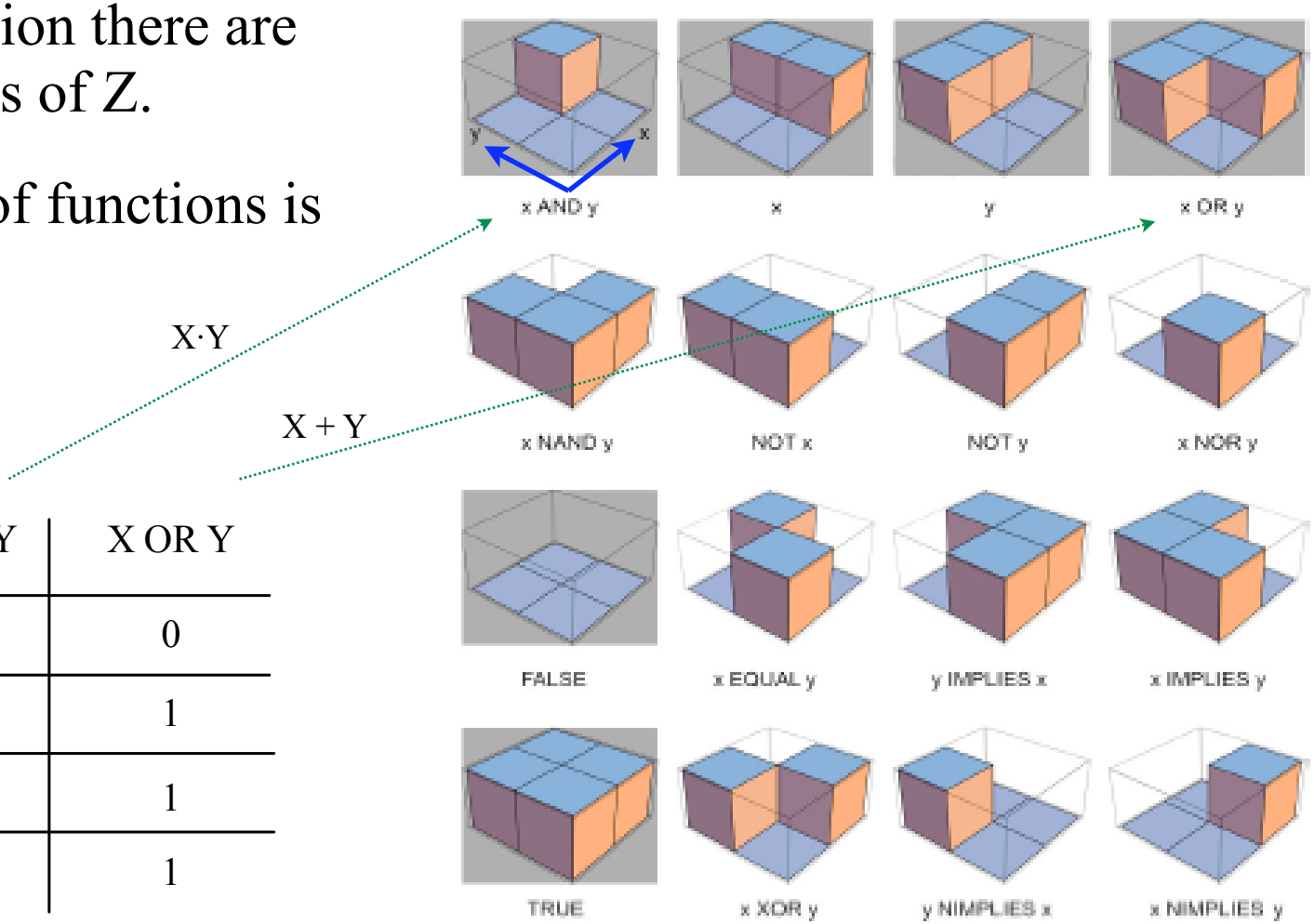
X	FALSE	TRUE	ID	NOT
0	0	1	0	1
1	0	1	1	0

28

Logical functions (Boolean functions)

- Two variables: $Z = f(X,Y)$:
  Four combinations of X and Y.
  For each combination there are two possible values of Z.
- The total number of functions is $2^4 = 16$.
- Examples:

X	Y	X AND Y	X OR Y
0	0	0	0
0	1	0	1
1	0	0	1
1	1	1	1



29

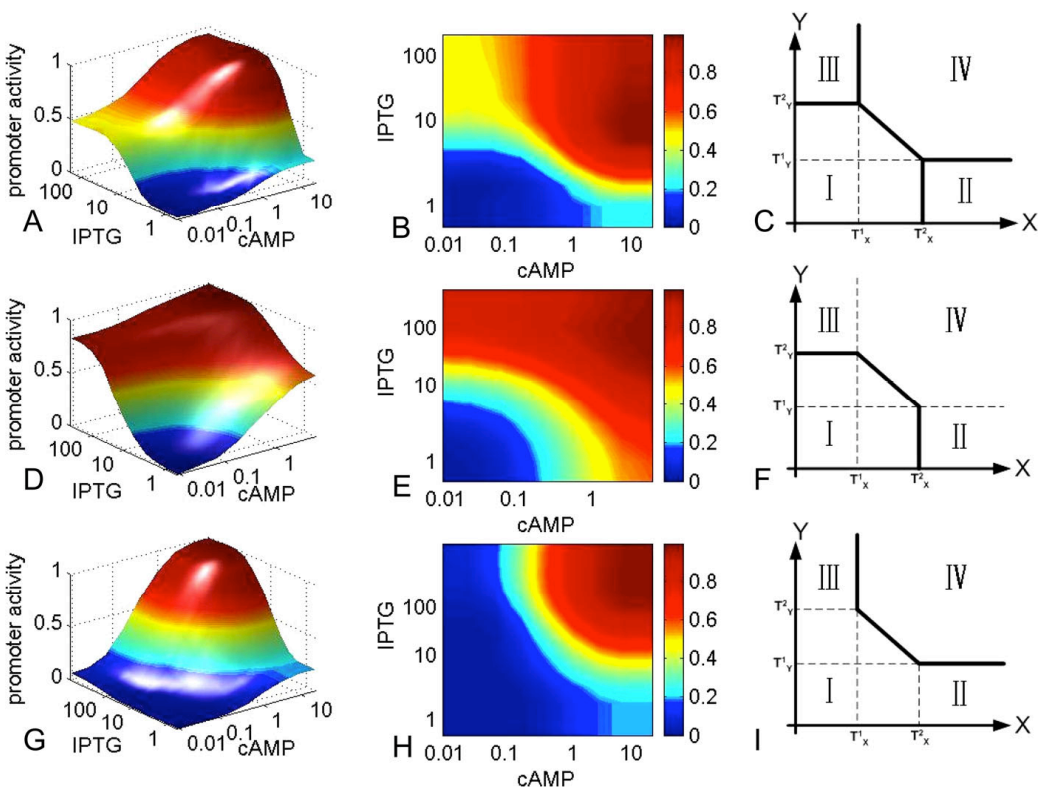
Boolean regulatory functions in the *E. coli lac* operon

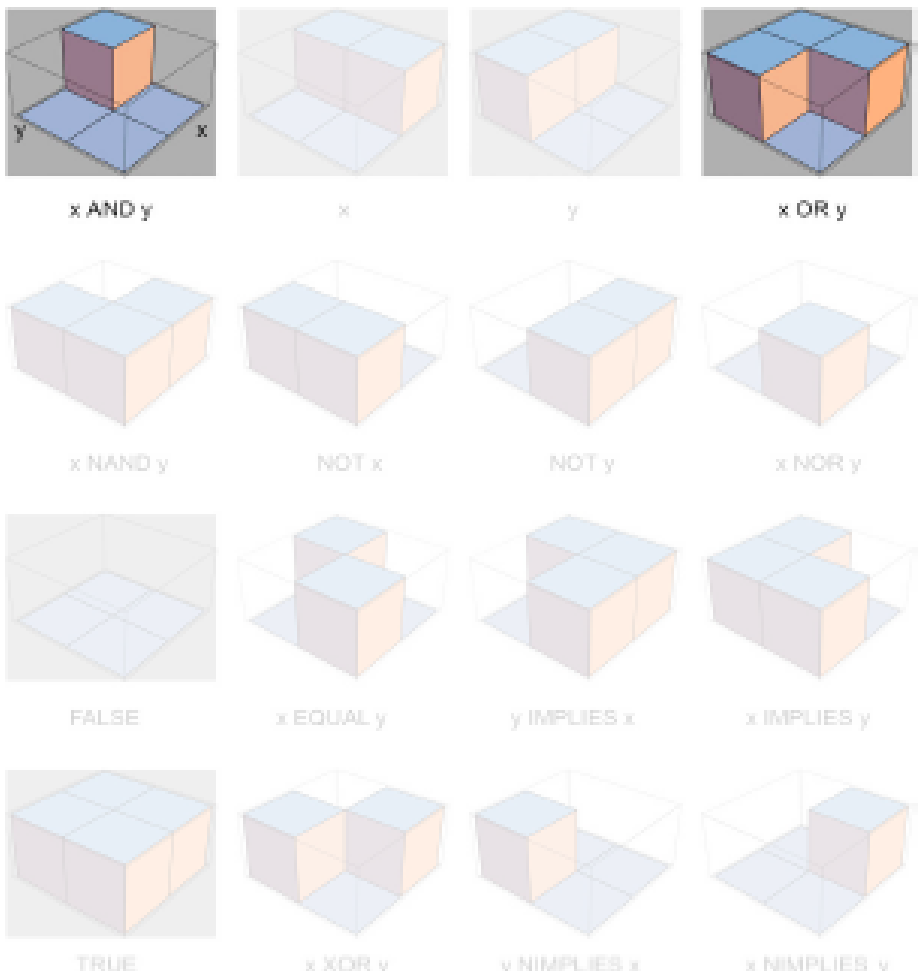
OPEN ACCESS Freely available online PLOS BIOLOGY

Plasticity of the *cis*-Regulatory Input Function of a Gene

2006

Avraham E. Mayo, Yaakov Setty, Seagull Shavit, Alon Zaslaver, Uri Alon*

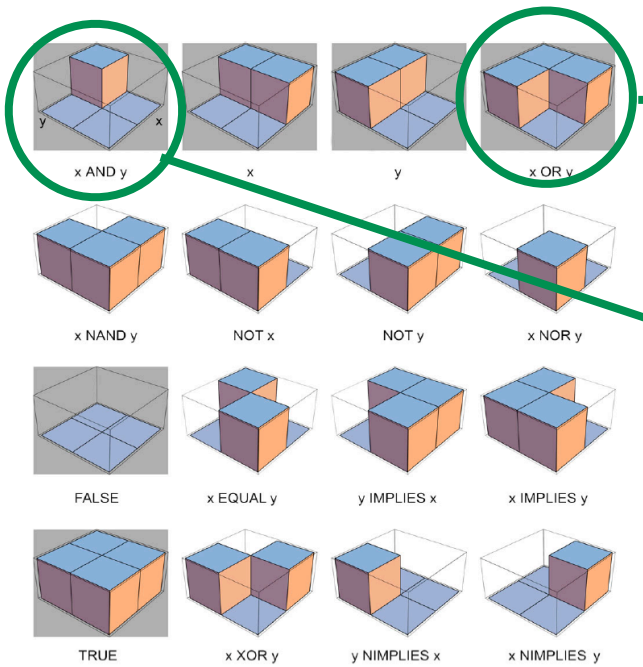




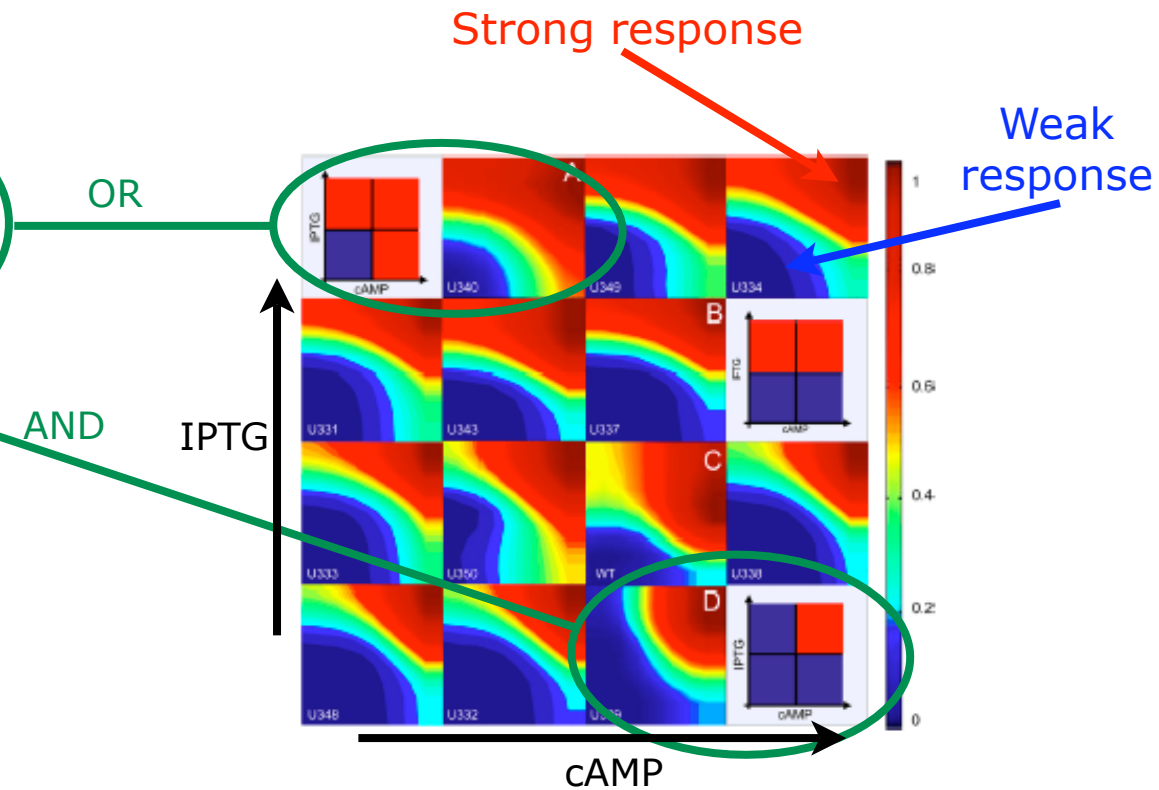
Response function of the wild-type *lac* promoter region and two variant *cis*-regulatory regions.

30

Boolean regulatory functions in the *E. coli lac* operon



The 16 Boolean logical gates for two inputs



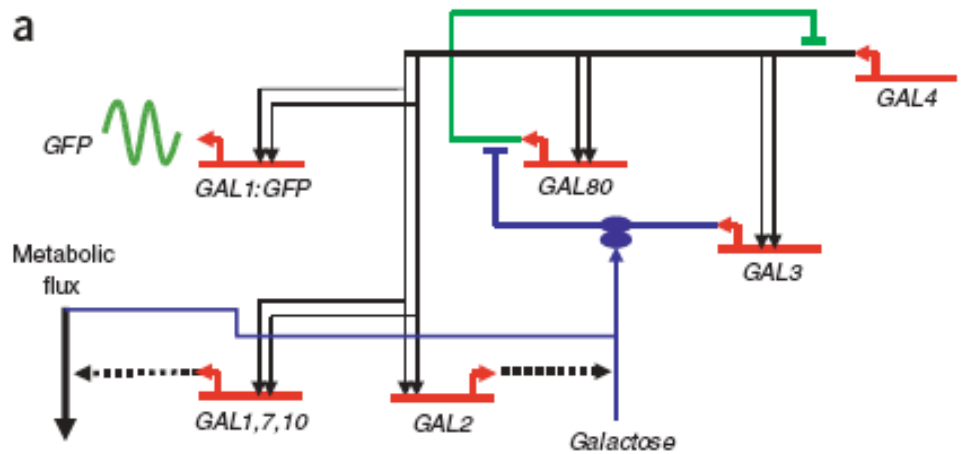
Mutant promoter response functions resembling AND and OR gates

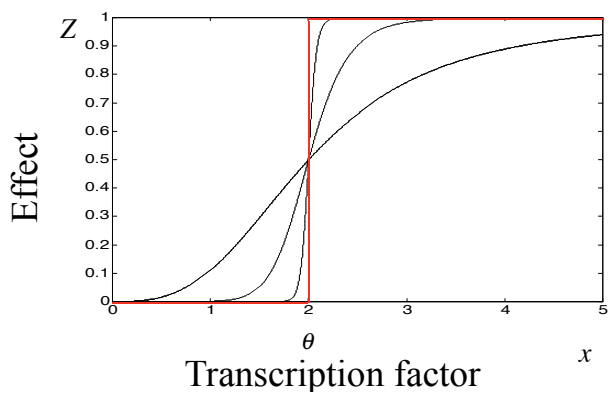
(from Mayo et al. PLoS Biology, 2006)

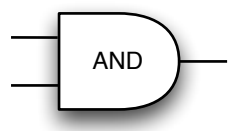
31

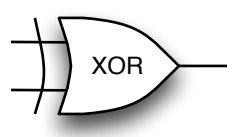
Key ingredients in gene regulation – network models

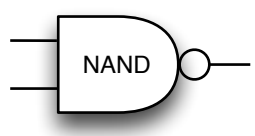
- Genes are represented by the nodes in the network (graph).
- Arrows show which genes act on which.
- Actions are either positive or negative.
- Positive action $G_1 \rightarrow G_2$: The gene product of G_1 enhances the activity of G_2.
- Negative action $G_1 \rightarrow G_2$: The gene product of G_1 inhibits the activity of G_2.
- The action of a gene is modelled by a Boolean function, a step function or a sigmoidal function.
- The effects of several genes are combined by logical functions.





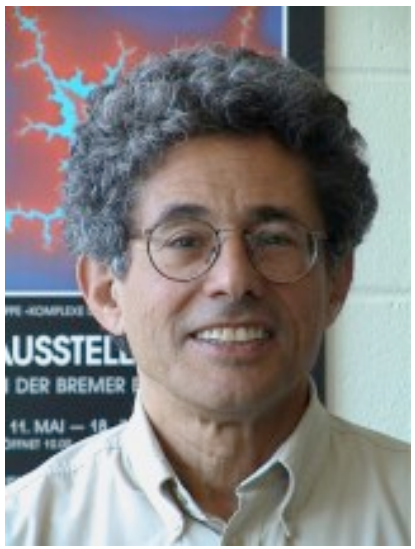






32

Three pioneers in gene regulation modelling from the early 1970s



Leon Glass

Stuart Kauffman

René Thomas

Key concepts:
Feedback, threshold dominated response, rate limitation, Boolean logic.

How can these be integrated into a mathematical modelling framework?

33

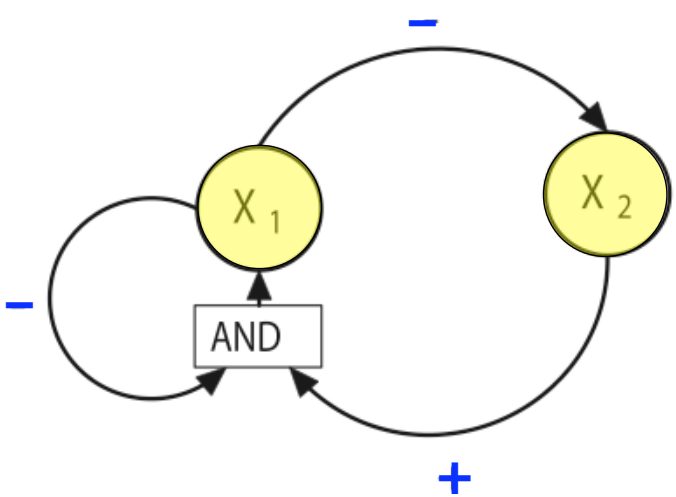
Logical functions (Boolean functions)

- Logical (Boolean) variable: X {0, 1}
  $0 + 0 = 0$, $0 + 1 = 1$, $1 + 1 = 1$,
  $0 \cdot 0 = 0$, $0 \cdot 1 = 0$, $1 \cdot 1 = 1$.
- Boolean function: a function of Boolean variables that only gets Boolean values.
- One variable: $Y = f(X)$.
  Just four different functions:

X	FALSE	TRUE	ID	NOT
0	0	1	0	1
1	0	1	1	0

34

Boolean modelling framework



X_i = state of gene *i*
X_i = 0: the gene is "off"
X_i = 1: the gene is "on"

State 01 = gene 1 is "off", gene 2 is "on"
etc.

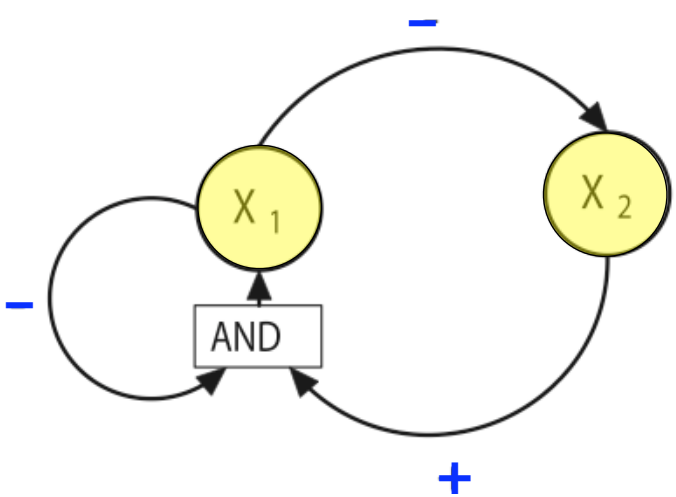
X_1^{next} = (NOT X_1^{now}) AND X_2^{now},
X_2^{next} = NOT X_1^{now}.

X_1^{next} = $(1 - X_1^{now})X_2^{now}$,
X_2^{next} = $1 - X_1^{now}$.

X_1 now	X_2 now	X_1 next	X_2 next
0	0	0	1
0	1	1	1
1	0	0	0
1	1	0	0

35

Boolean modelling framework



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35

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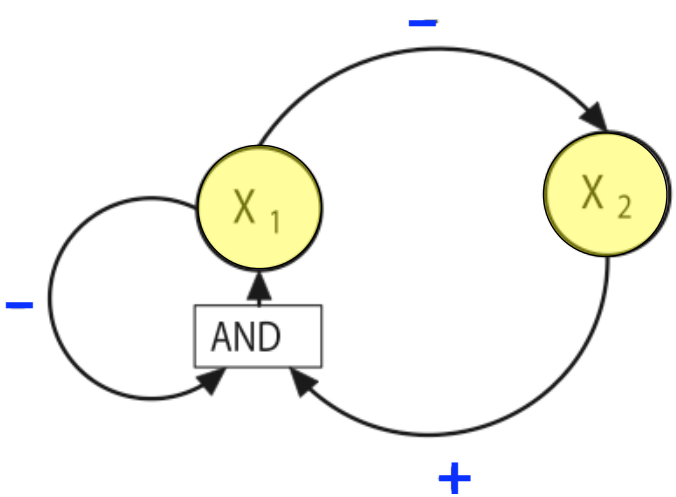

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35

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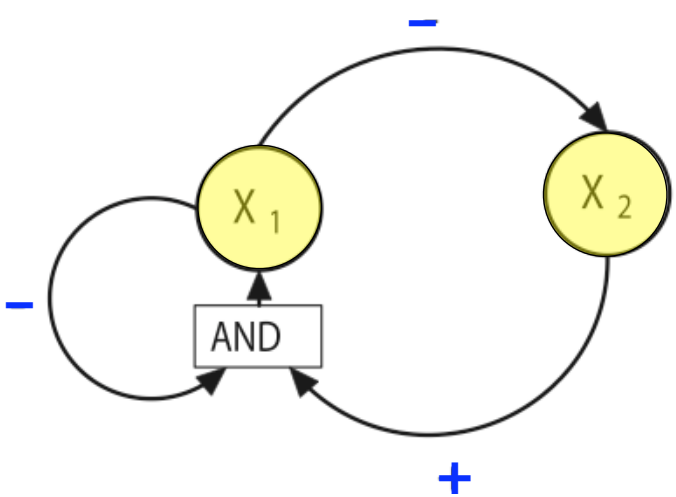

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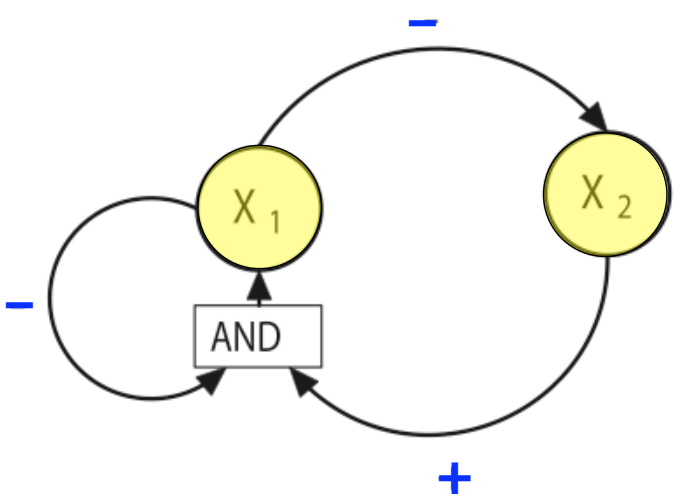
35

Boolean modelling framework



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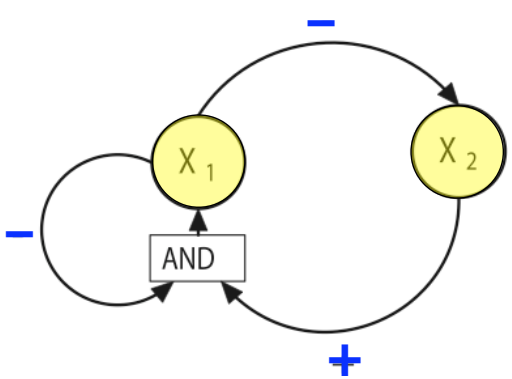
35

Boolean modelling frameworks



X_1 now	X_2 now	X_1 next	X_2 next
0	0	0	1
0	1	1	1
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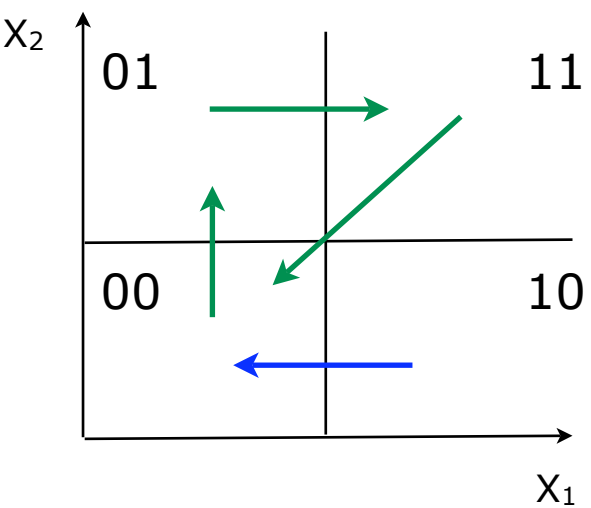
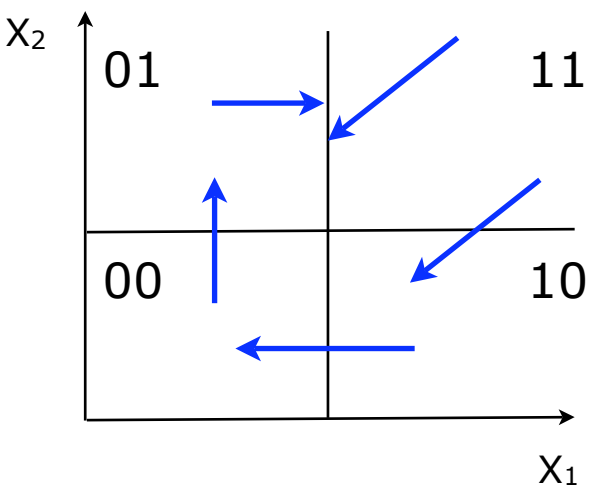
1	1	0	0

X_i = state of gene i (0 = off, 1 = on)



Synchronous



Asynchronous

Interpretation of asynchronous networks

Only one variable changes: OK

Two variables change simultaneously. Unrealistic! It means:

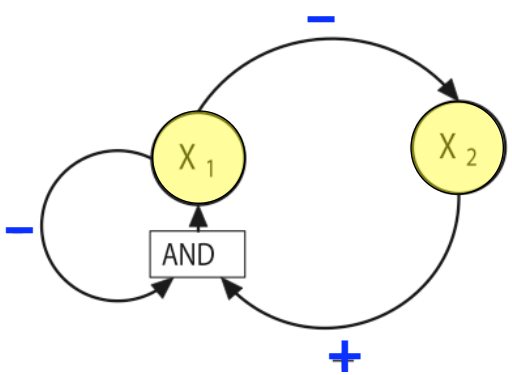
either

or

X1 now	X2 now	X1 next	X2 next
1	1	0	1
1	1	1	0

36

Transition to ordinary differential equation (ODE) models



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x_i = concentration of gene product # i

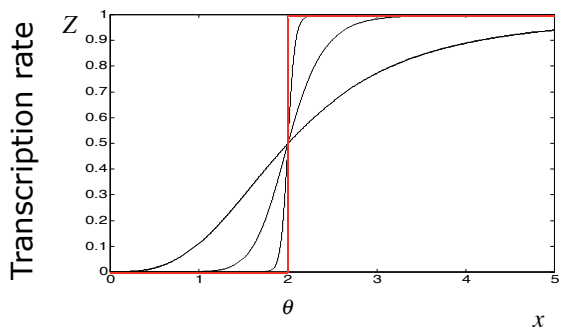
x_i-rate = production rate – decay rate

$X_i^{now} \rightarrow Z_i$

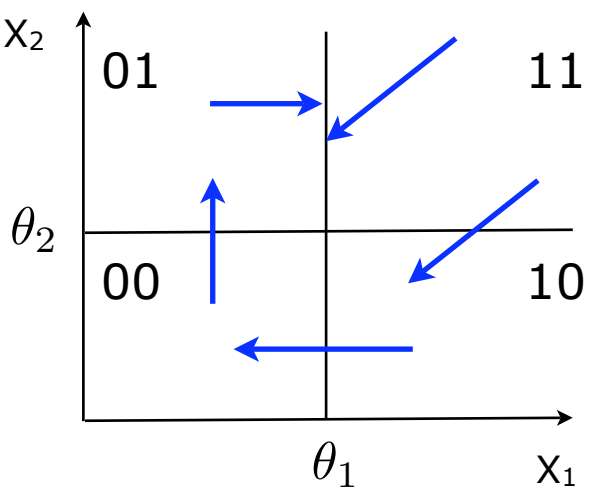
$$Z_i = \frac{x_i^p}{x_i^p + \theta_i^p}$$

or

$$Z_i = \text{step}(x_i, \theta_i)$$



Transcription factor concentration



Asynchronous

Continuous Boolean model

$$\dot{x}_1 = \alpha_1(1 - Z_1)Z_2 - \gamma_1 x_1,$$
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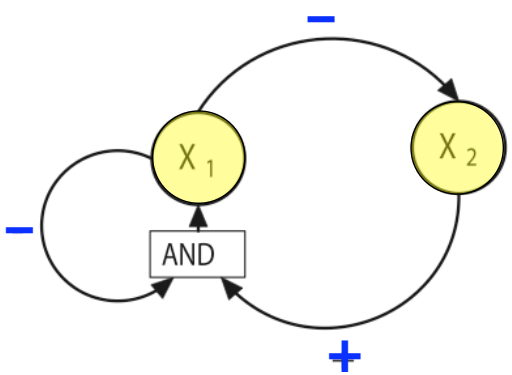
37

Transition to ordinary differential equation (ODE) models



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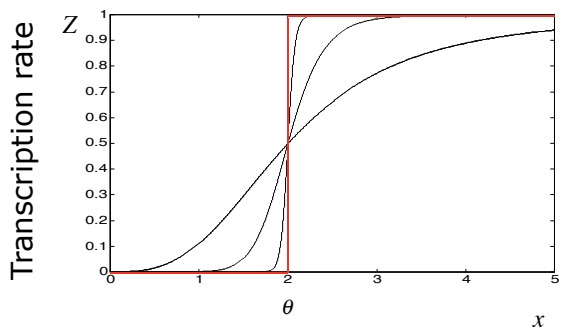

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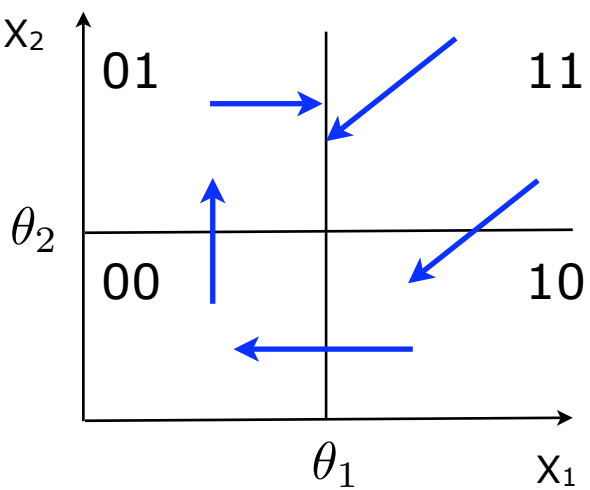

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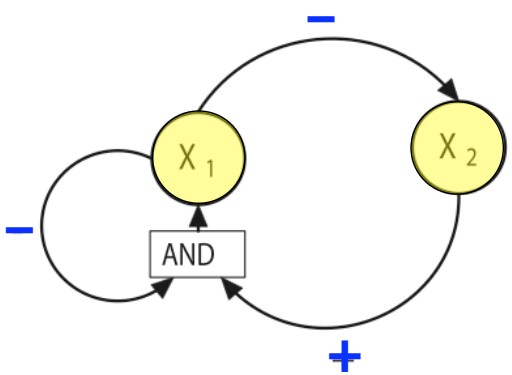
Transition to ordinary differential equation (ODE) models



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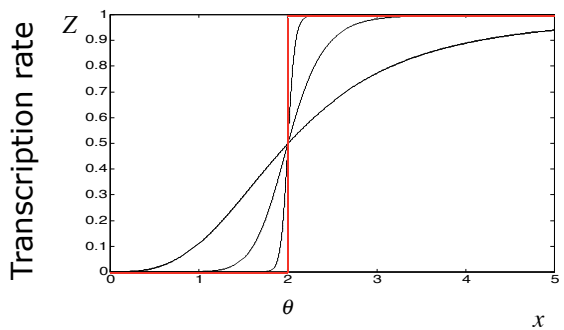

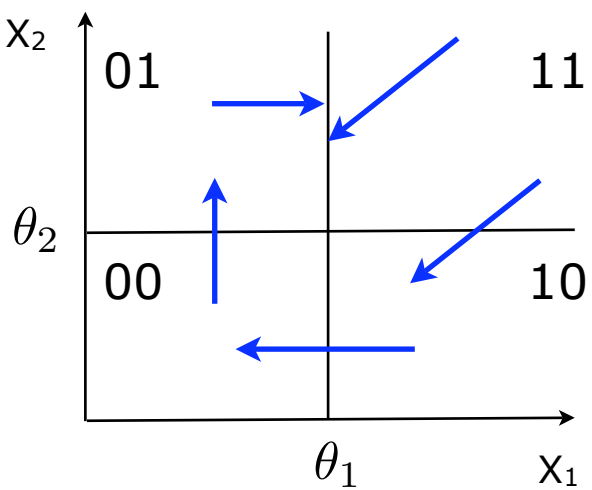

Phase space

Continuous Boolean model

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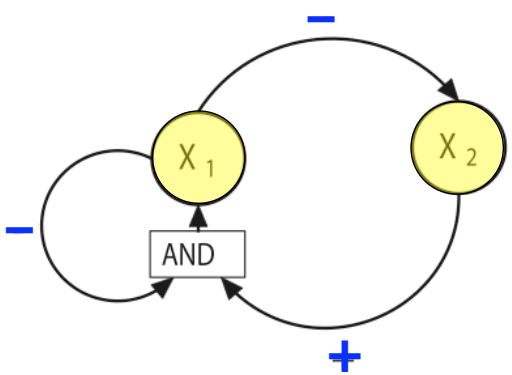
Transition to ordinary differential equation (ODE) models



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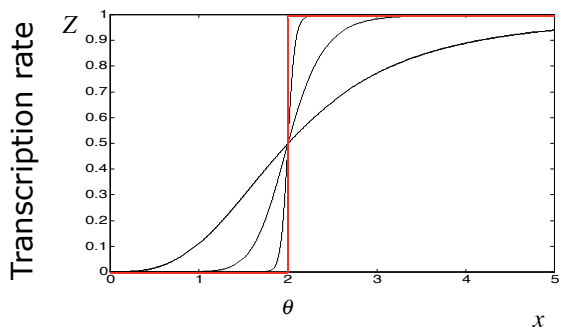
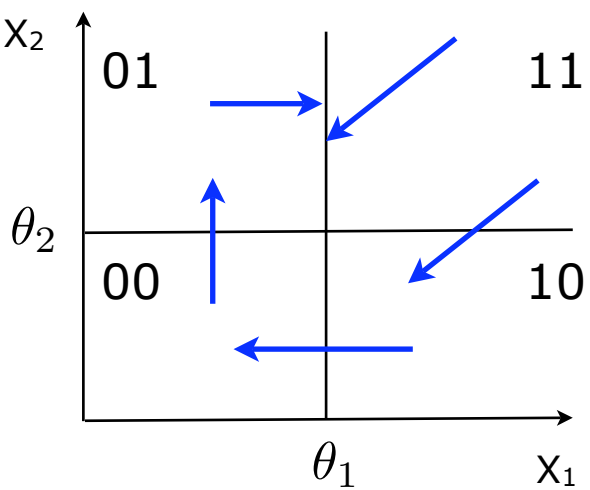


Transcription factor concentration



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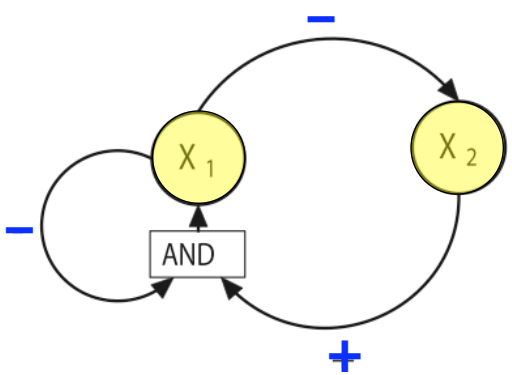
37

Ordinary differential equation model with step functions



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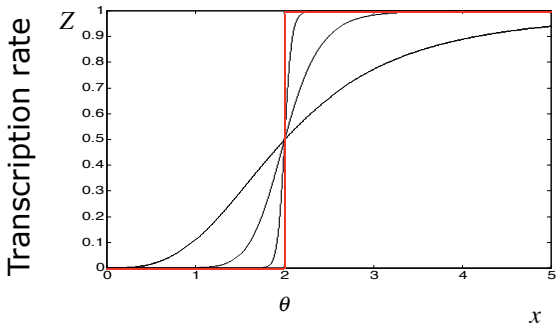
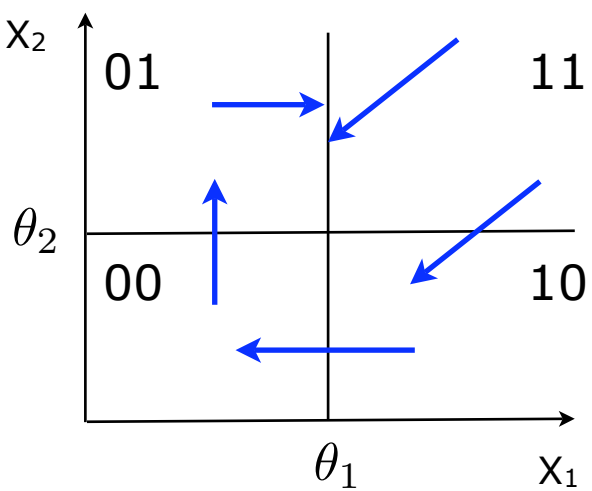
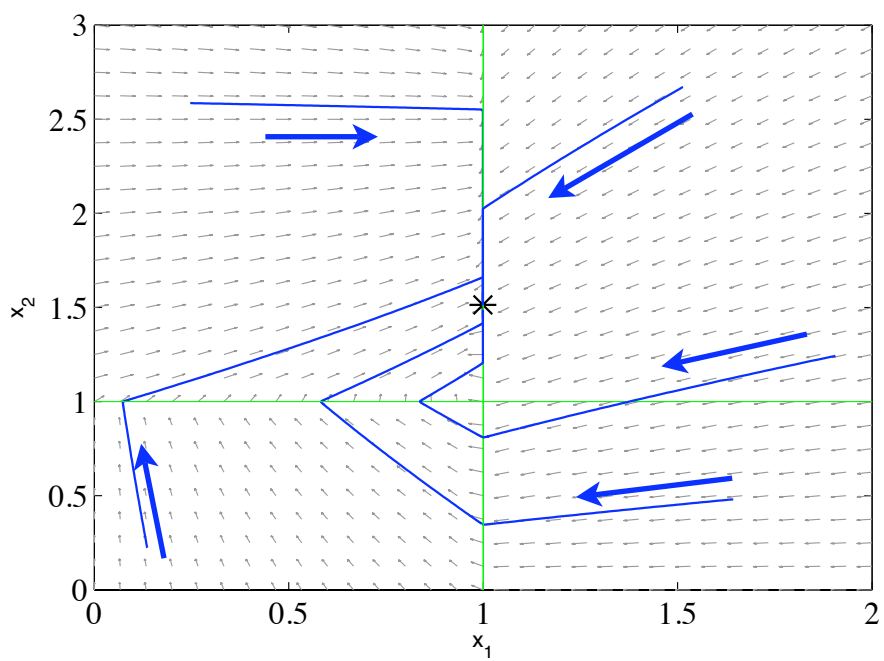


Transcription factor concentration

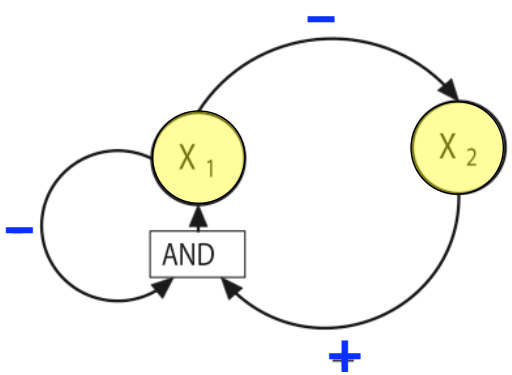
$$Z_i = \mathrm{step}(x_i, \theta_i)$$





38

Ordinary differential equation model with step functions



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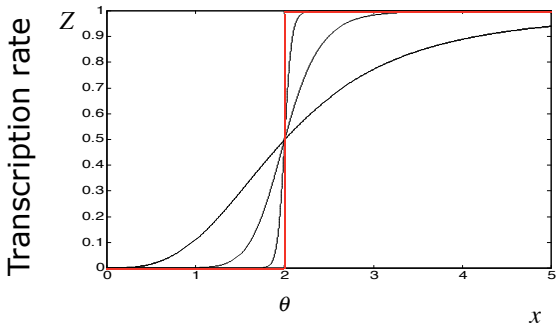
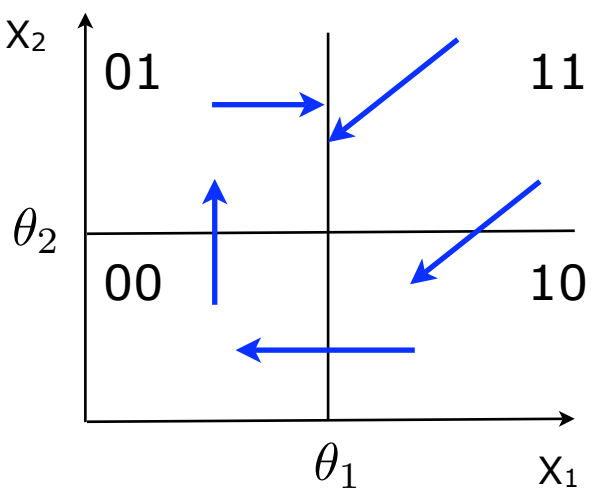
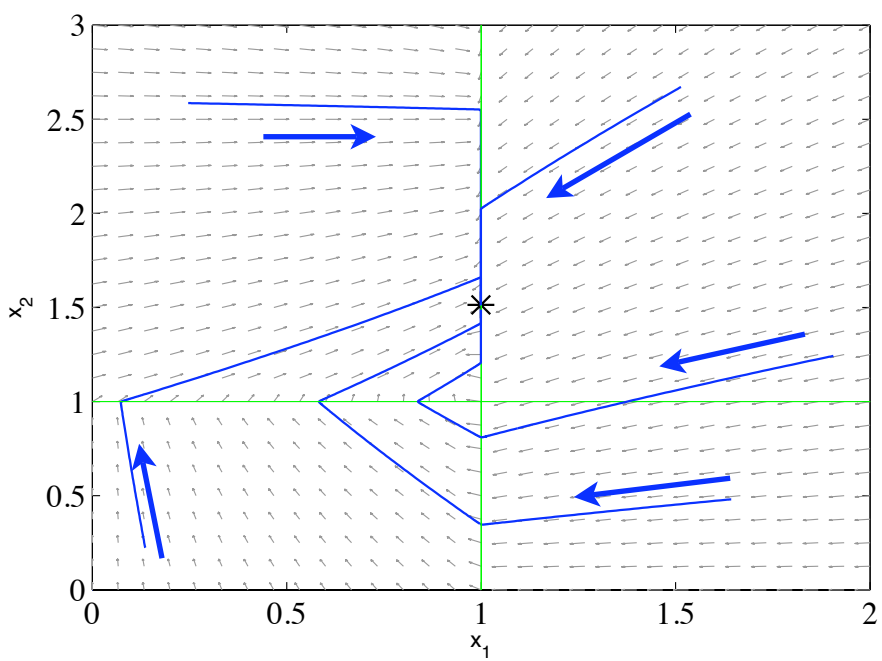


Transcription factor concentration

$$Z_i = \mathrm{step}(x_i, \theta_i)$$

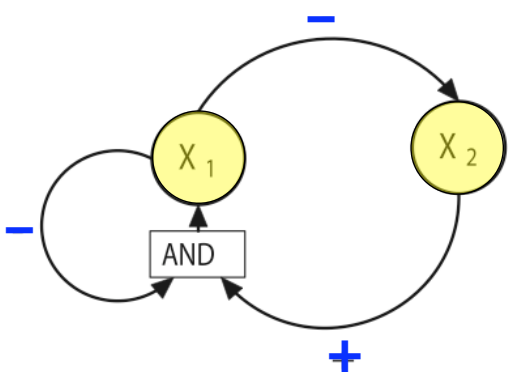


Phase space



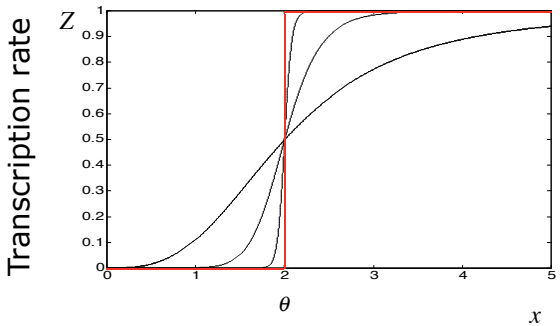
38

Ordinary differential equation model with step functions



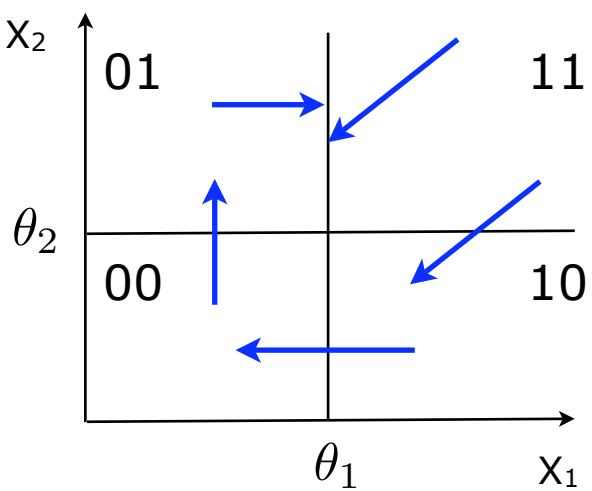
Continuous Boolean model

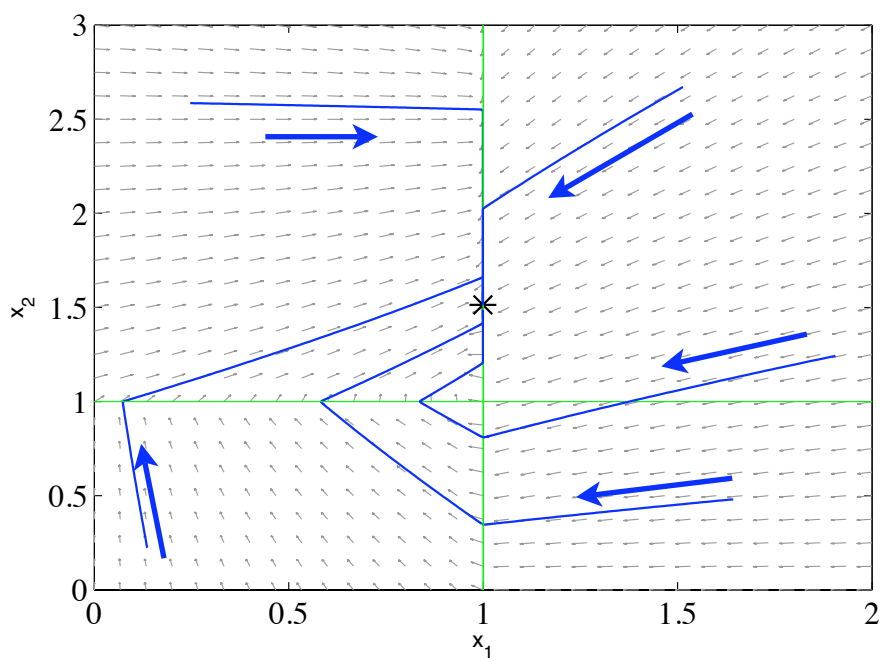
$$\dot{x}_1 = \alpha_1(1 - Z_1)Z_2 - \gamma_1 x_1,$$
$$\dot{x}_2 = \alpha_2(1 - Z_1) - \gamma_2 x_2.$$



Transcription factor concentration

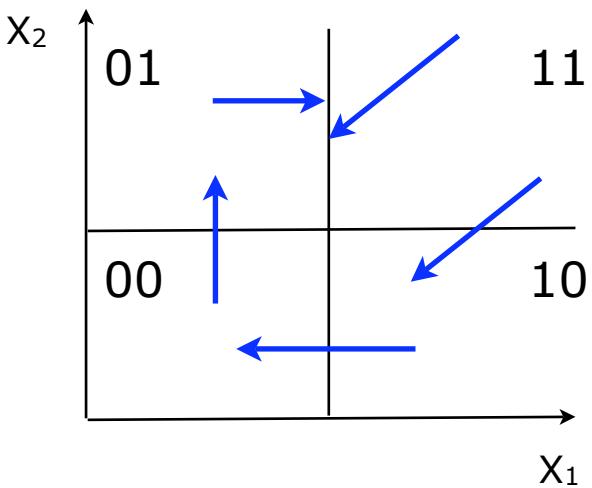
$$Z_i = \mathrm{step}(x_i, \theta_i)$$



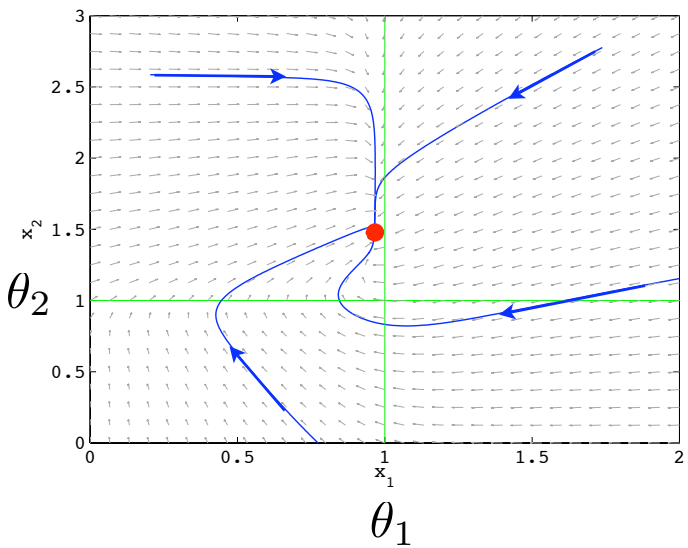


38

Ordinary differential equation model with sigmoidal functions



Asynchronous



Corresponding ODE model,
Hill exponent = 10

$$X_1^{next} = (1 - X_1^{now})X_2^{now},$$
$$X_2^{next} = 1 - X_1^{now}.$$

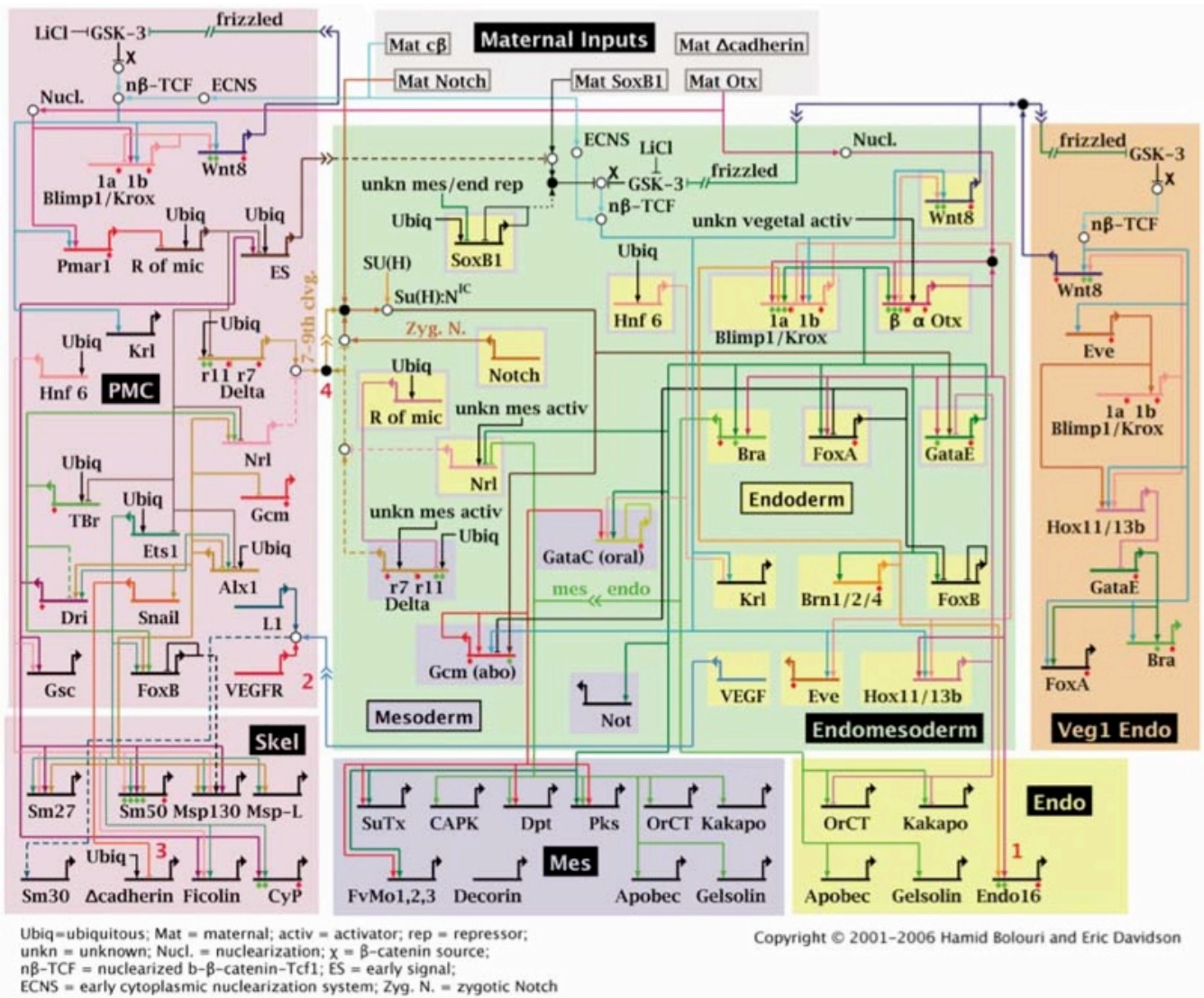
$$\dot{x}_1 = \alpha_1(1 - Z_1)Z_2 - \gamma_1 x_1,$$
$$\dot{x}_2 = \alpha_2(1 - Z_1) - \gamma_2 x_2.$$

Modelling frameworks:

- Discrete Boolean models.
- Continuous ODE models with on/off response functions.
- Continuous ODE models with graded (sigmoidal) response functions.

39

Modelling of more complex models: endo-mesoderm specification in sea urchin



Hard to predict the behaviour of this network without a mathematical model...

40

Some conclusions

- Recent experimental evidence support the basic assumptions for GRNs from the 1970s, but...
- also shows that gene regulation is much more complex.
- The “classical” GRN frameworks are definitely too simple-minded, but...
- can be considered as phenomenological approximations to the real networks, and...
- nevertheless, at least they work in simple cases.
- Dedicated mathematical methods to analyse GRN framework models have been developed, which...
  - can deal with both binary and sigmoidal responses,
  - have been generalised to models with other, additional non-linearities,
  - and reveal a number of generic properties which could be tested experimentally.
- Recently discovered regulatory mechanisms need to be expressed mathematically and incorporated into more realistic model frameworks.

Central references

- Historical
  - L. Glass, S.A. Kauffman. The logical analysis of continuous, non-linear biochemical control networks. Journal of Theoretical Biology 39 (1973) 103-129.
  - R. Thomas. Boolean Formalization of Genetic-Control Circuits. *Journal of Theoretical Biology* **42** (1973) 563-585.
- Reviews of gene regulatory models and modelling approaches
  - H. de Jong. Modeling and simulation of genetic regulatory systems: A literature review. *Journal of Computational Biology* **9** (2002) 67-103.
  - G. Karlebach, R. Shamir. Modelling and analysis of gene regulatory networks. Nat Rev Mol Cell Biol 9 (2008) 770-780.
- Boolean logic models
  - R. Thomas, D. Thieffry, and M. Kaufman. Dynamical Behavior of Biological Regulatory Networks. 1. Biological Role of Feedback Loops and Practical Use of the Concept of the Loop-Characteristic State. *Bulletin of Mathematical Biology* **57** (1995) 247-276.
  - Cavenaugh, James S: Kinetic Logic: What it is, why it's useful. www.urmc.rochester.edu/smd/biostat/events/sysbiofiles/KineticLogic.ppt
- Piece-wise linear models
  - H. de Jong et al. Qualitative simulation of genetic regulatory networks using piecewise-linear models. *Bulletin of Mathematical Biology* **66** (2004) 301-340.
  - H. de Jong et al. Qualitative simulation of the initiation of sporulation in *Bacillus subtilis*. *Bulletin of Mathematical Biology* **66** (2004) 261-299.
- Steep sigmoid models
  - S.R. Veflingstad, E. Plahte. Analysis of gene regulatory network models with graded and binary transcriptional responses. *Biosystems* **90** (2007) 323-339.

42