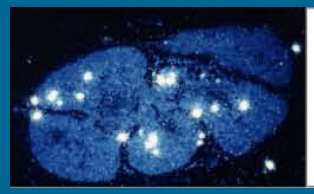

Interdisciplinary Research Institute
from interacting molecules to cellular regulatory networks

CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE

A compositional approach to the stochastic dynamics of gene networks

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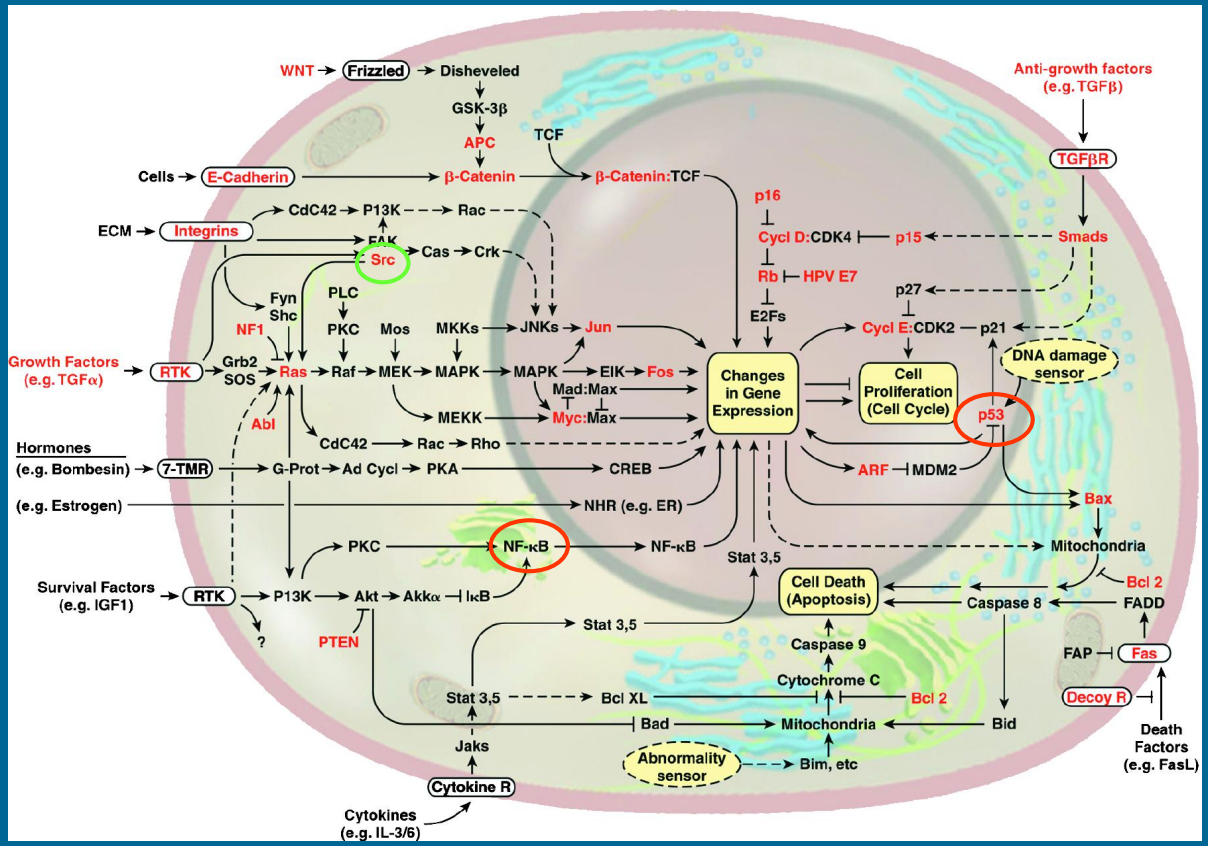
(Microsoft Research, Cambridge UK)

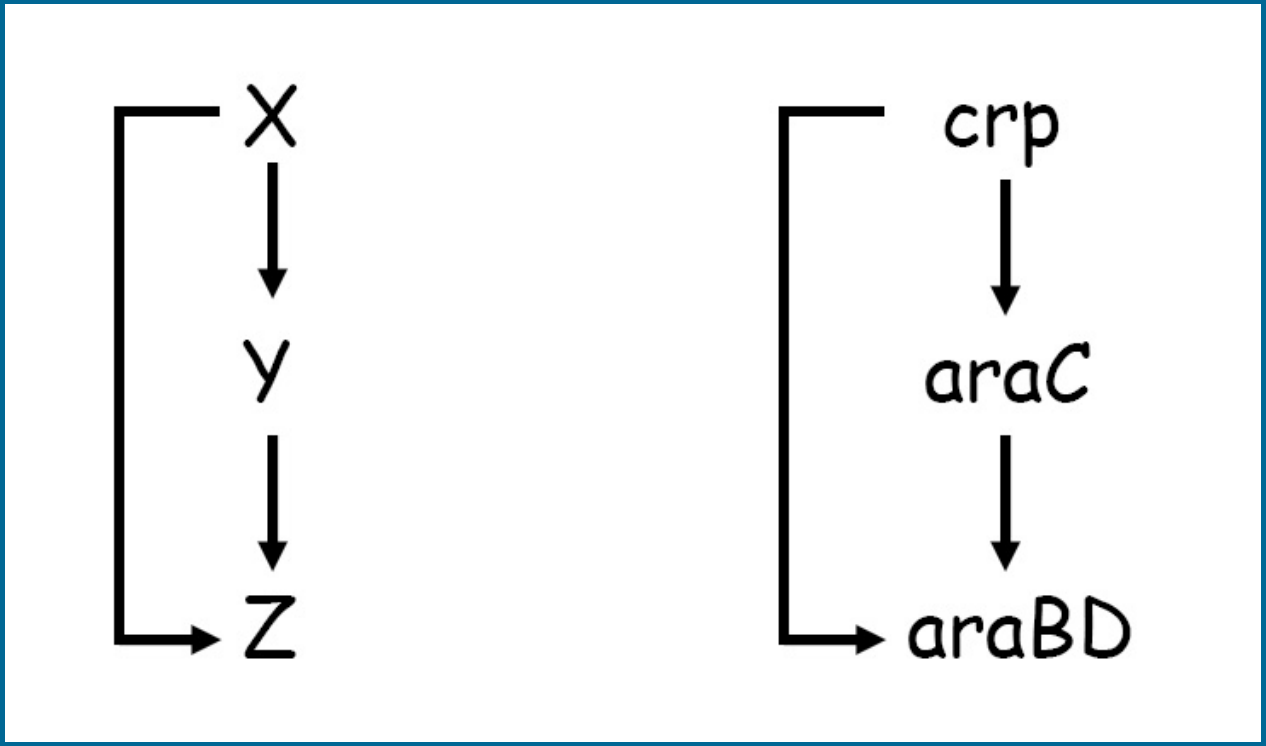
The menu:

- Motivation
- Gene networks as gene circuits in stochastic π-calculus
- Examples, from simple to less simple
- Outlook

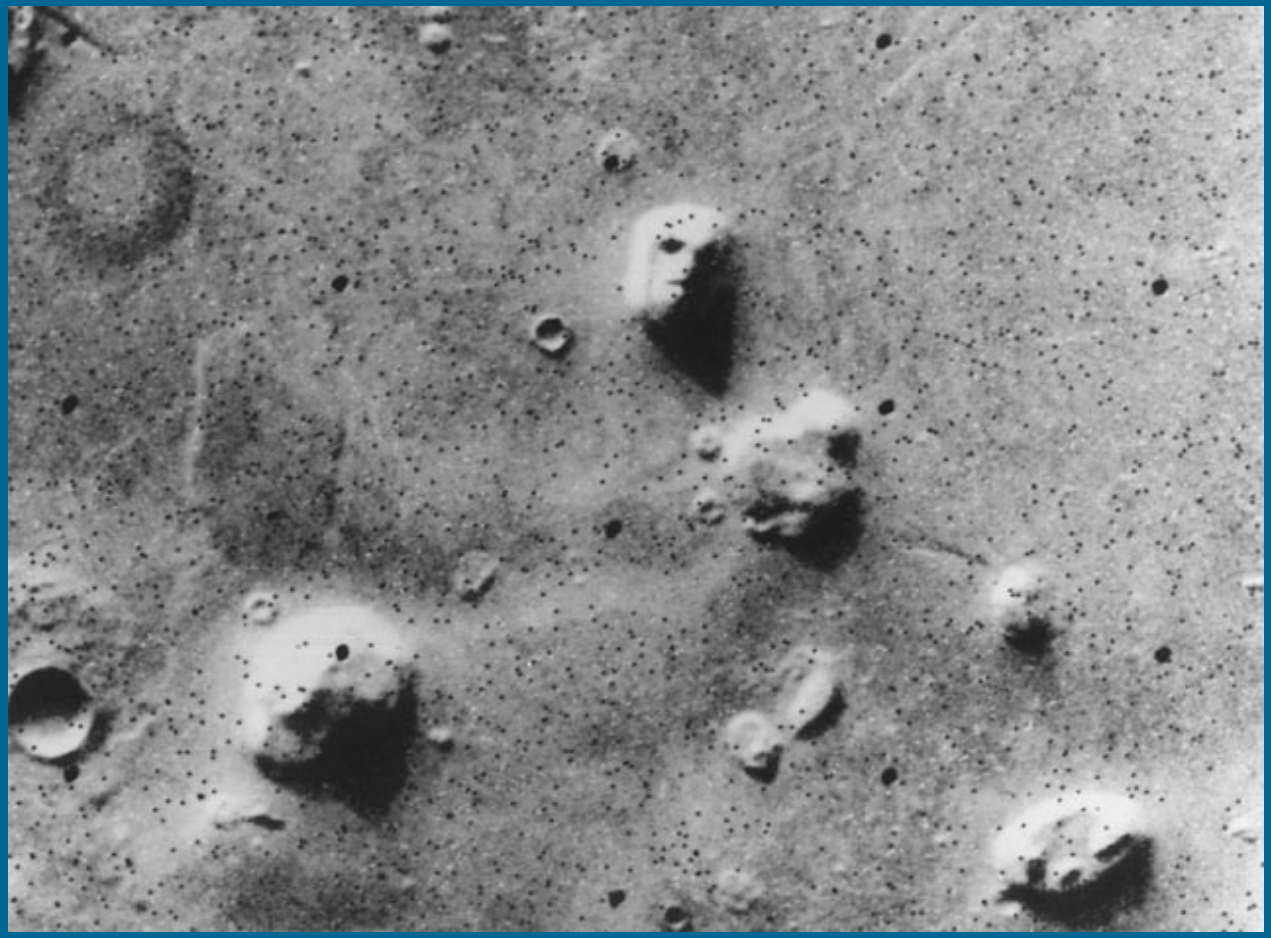
...finding structures in complexity...



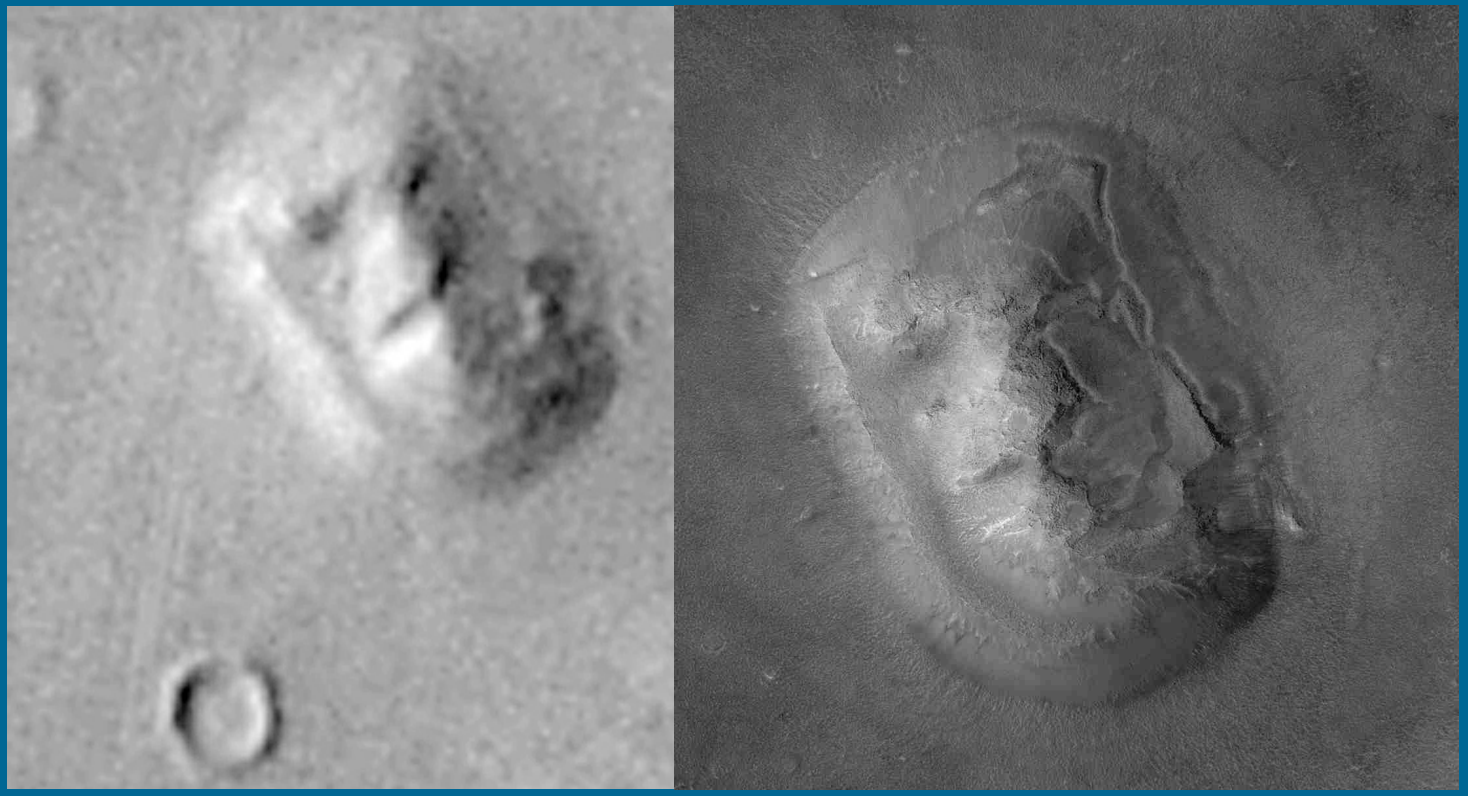
...modules and motifs...



...but watch out for anthropomorphisms...

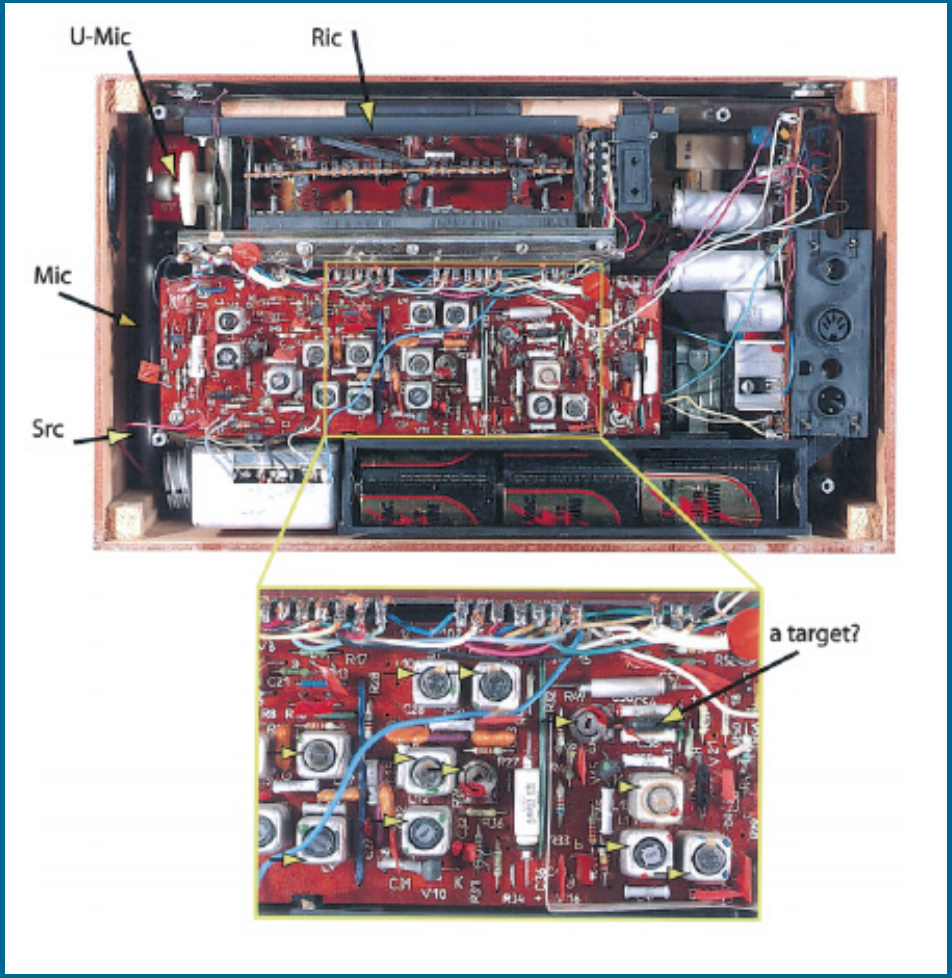


...with better resolution...



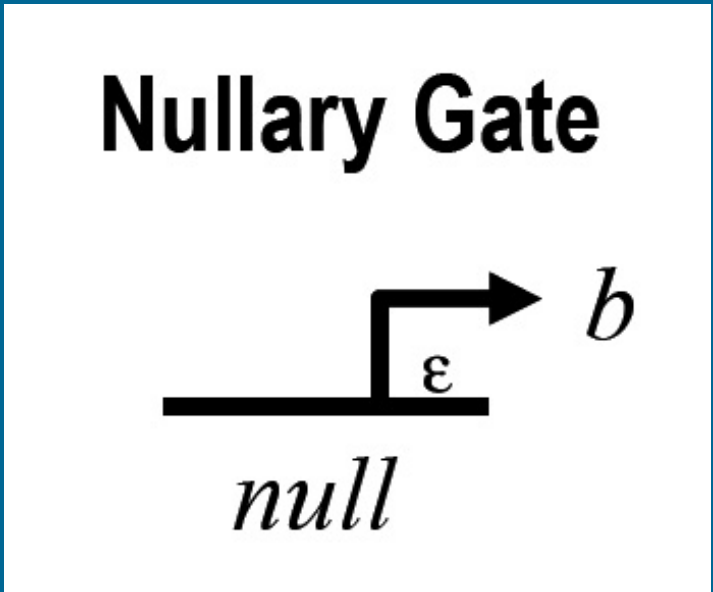
...what you see might not be there!

... engineered modules: a useful paradigm?



...let’s try to build gene networks as gene circuits...

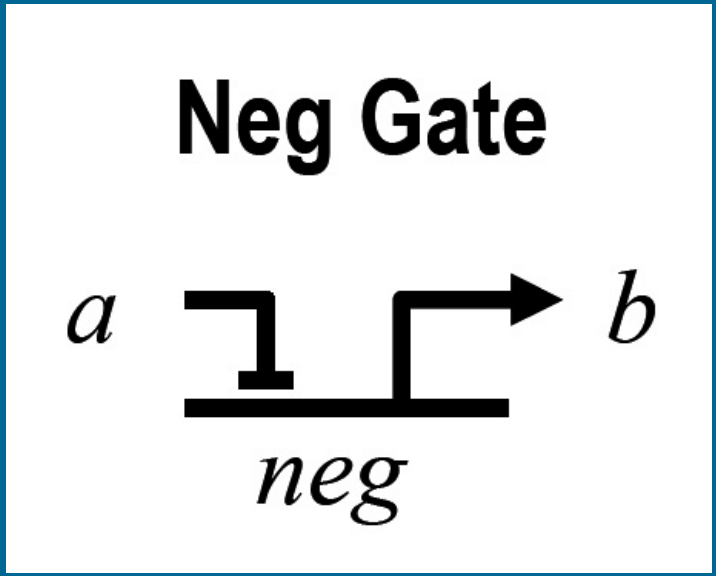
a) A gene gate which transcribes constitutively:



$$null(b) = \tau_{\varepsilon}.(tr(b)|null(b))$$

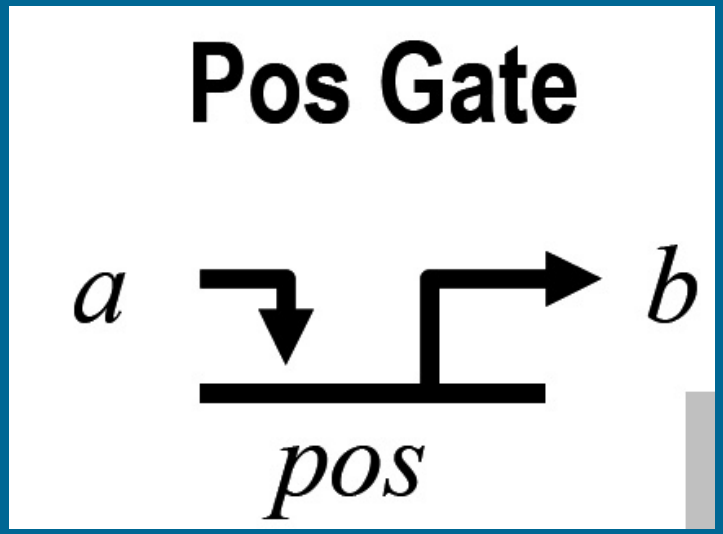
$$tr(b) = !b.tr(b) + \tau_{\delta}.0$$

b) an inhibitory gate:



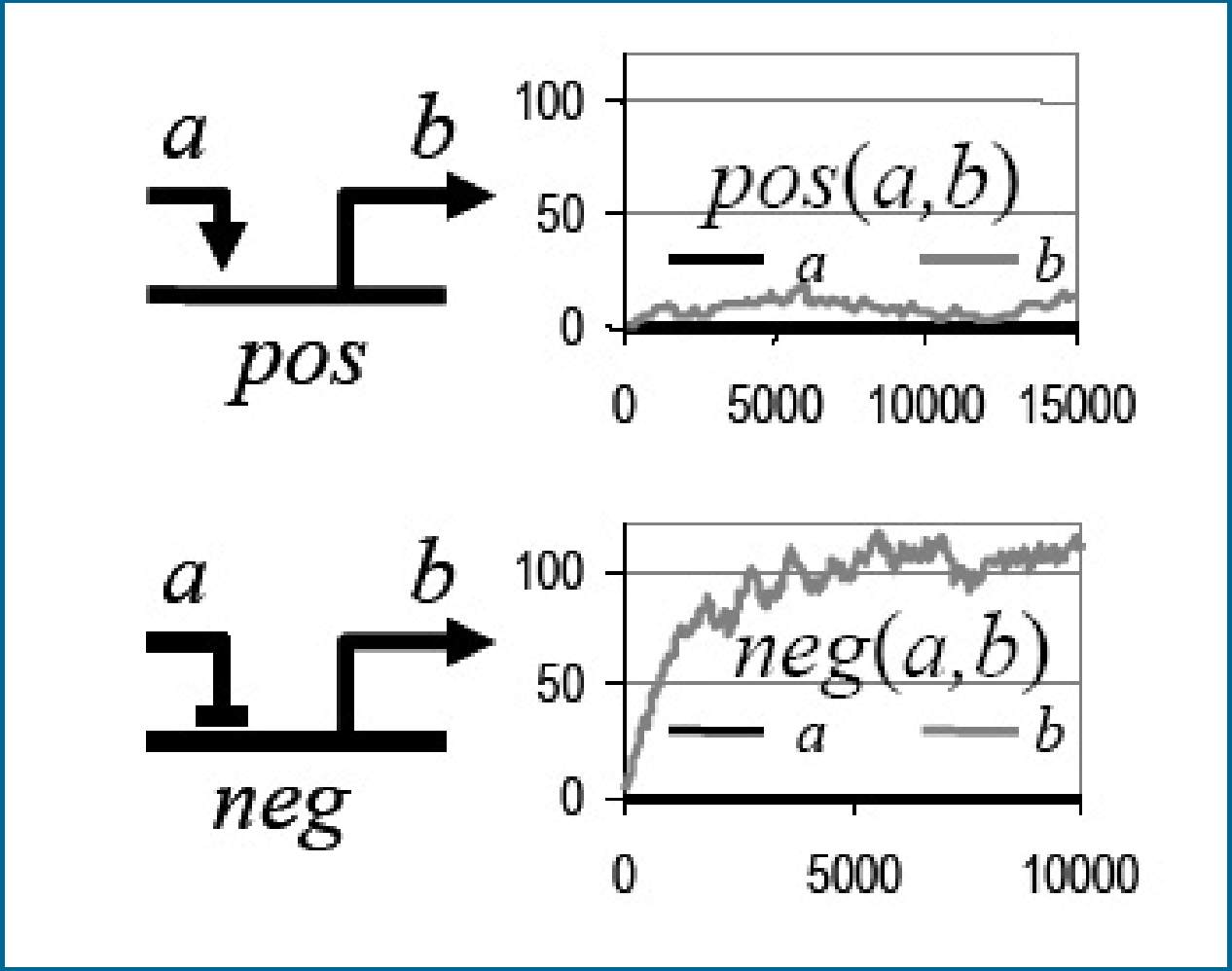
$$neg(a,b) = ?a.\tau_{\eta}.neg(a,b) + \tau_{\varepsilon}.(tr(b)|neg(a,b))$$

c) an excitatory gate:

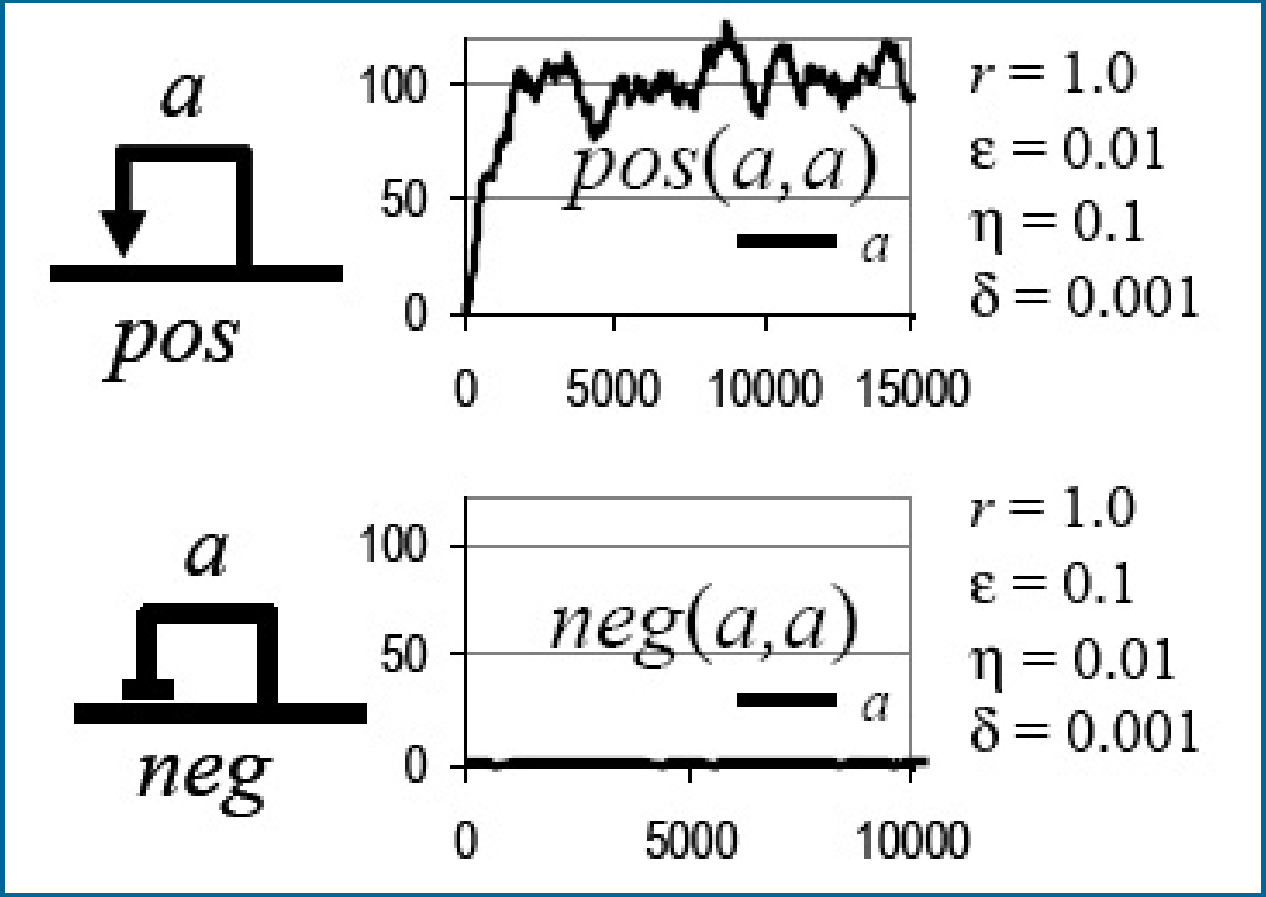


$$pos(a,b) = ?a.\tau_{\eta}.(tr(b)|pos(a,b)) + \tau_{\varepsilon}.(tr(b)|pos(a,b))$$

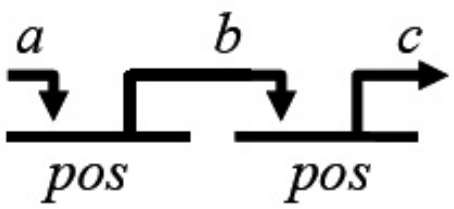
Examples: very simple 1



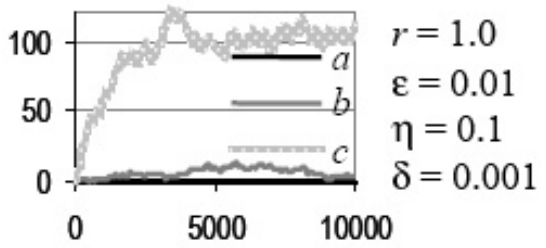
Examples: very simple 2

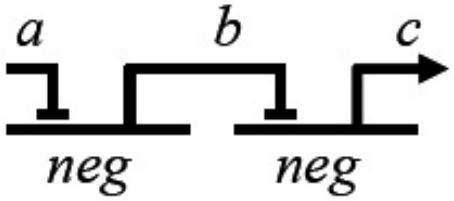


Examples: very simple 3

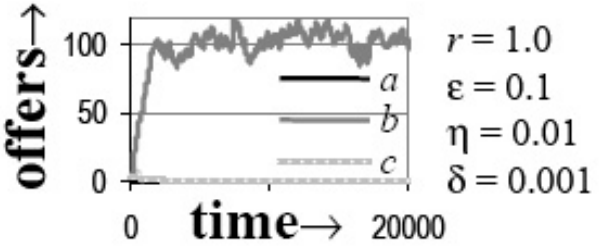


$pos(a,b) \mid pos(b,c)$

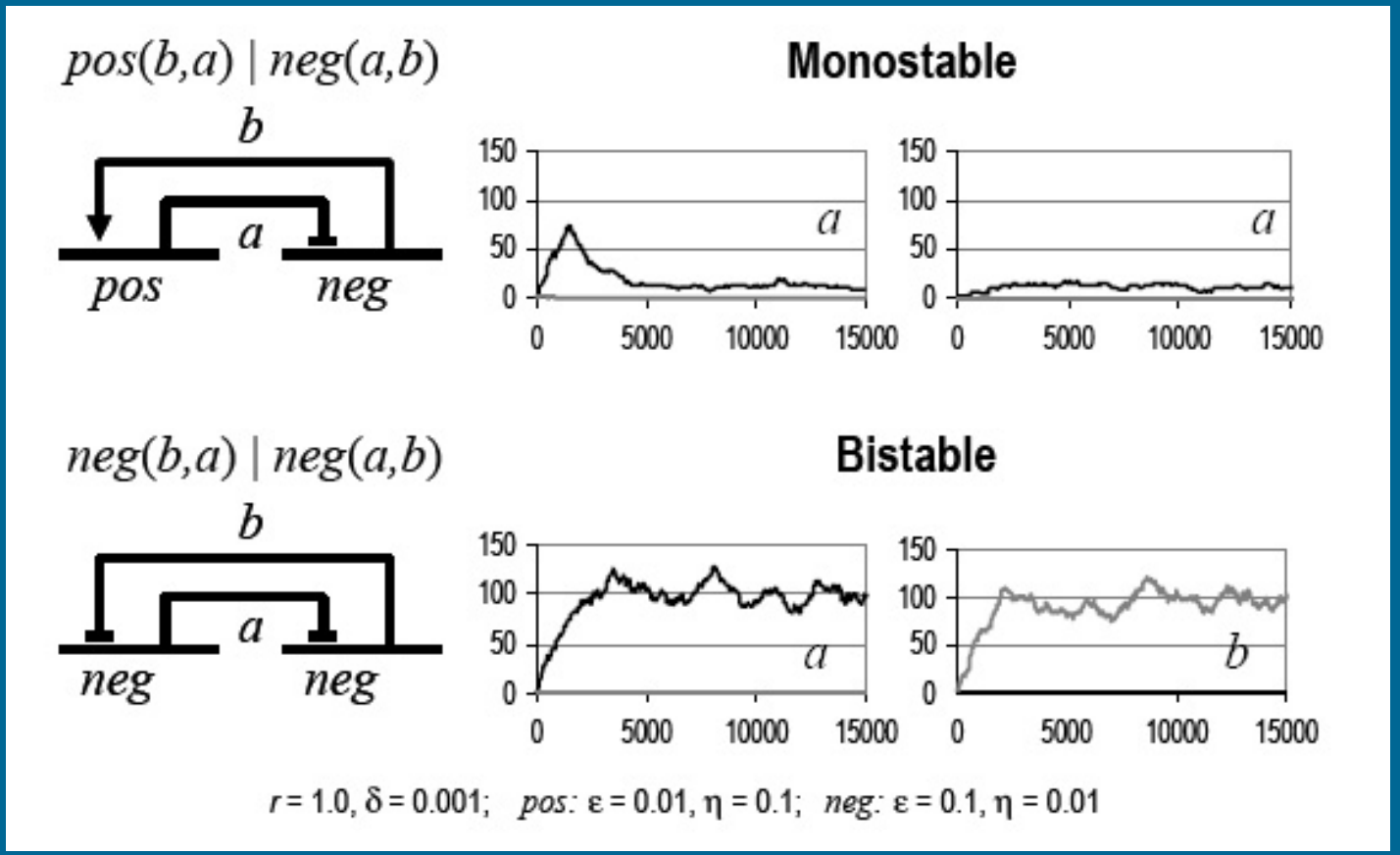




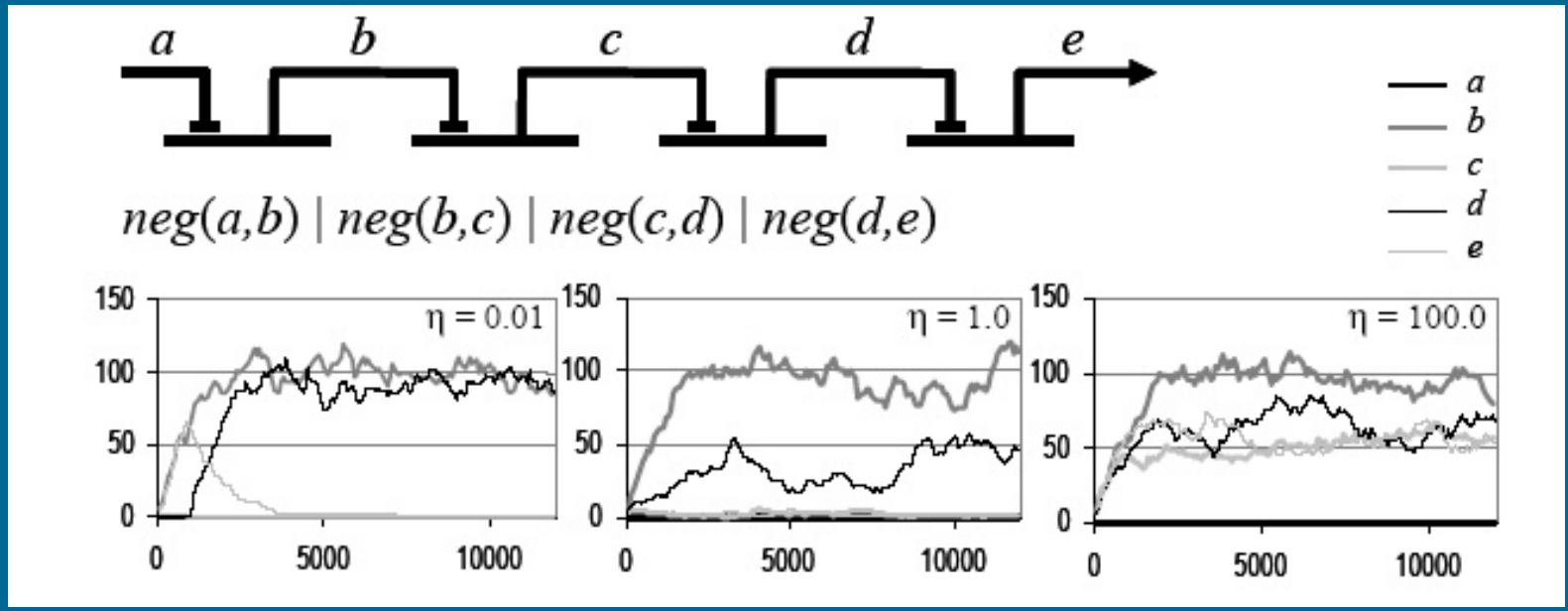
$neg(a,b) \mid neg(b,c)$



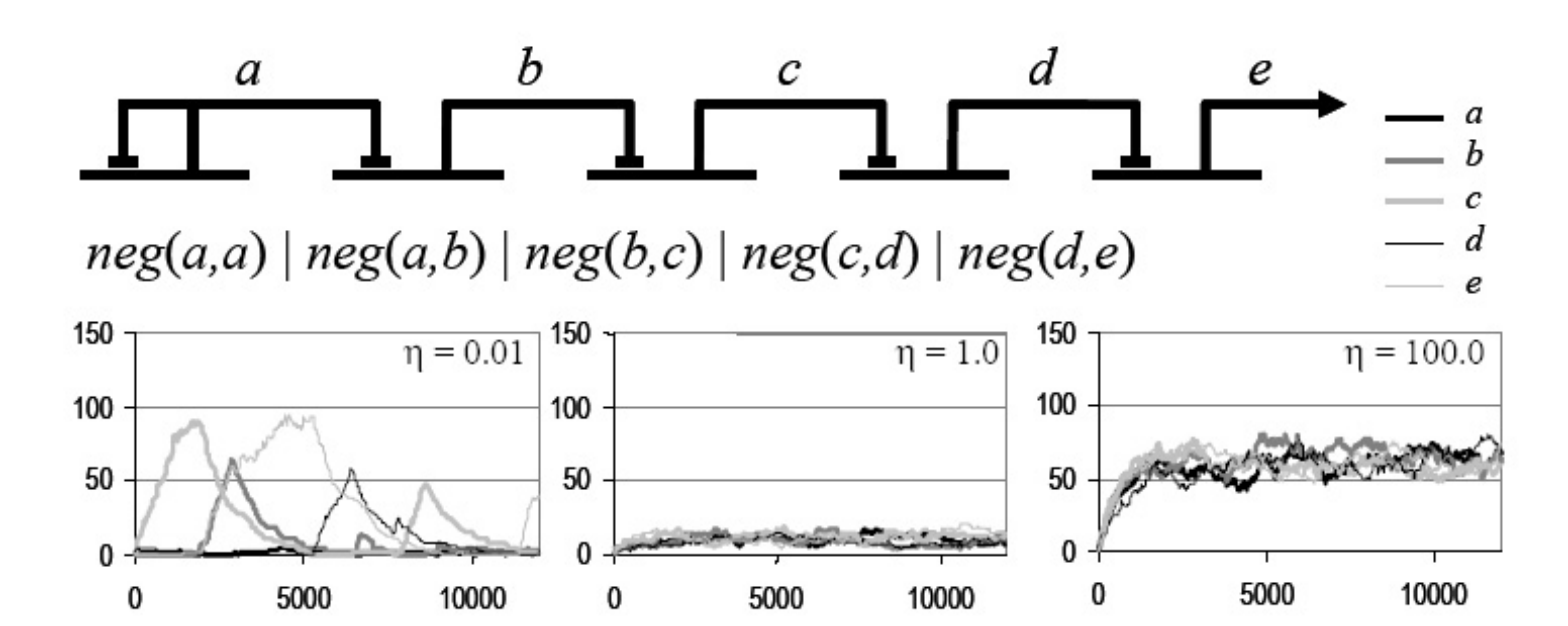
Examples: simple



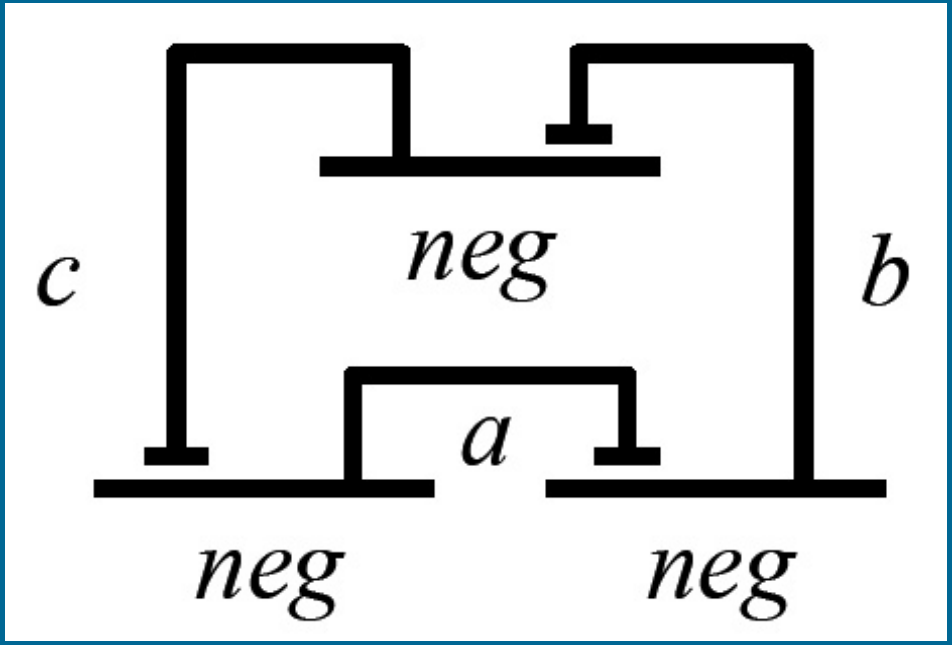
Examples: less simple 1



Examples: less simple 2

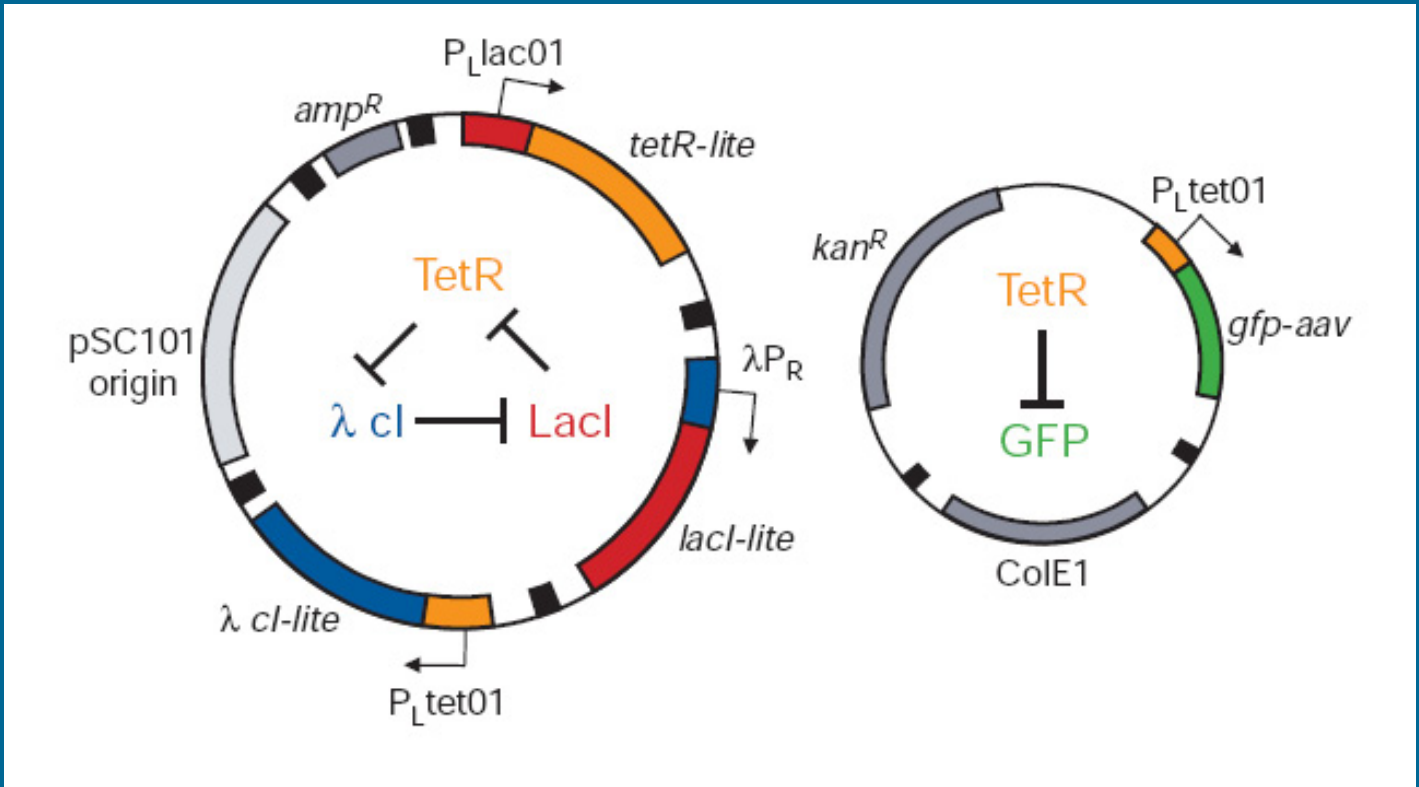


Example: The Repressilator



$$neg(c,a)|neg(a,b)|neg(b,c)$$

...the real system: three bacterial genes (+ GFP)



M. B. Elowitz, S. Leibler, Nature (2000)

...ODE modeling...

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

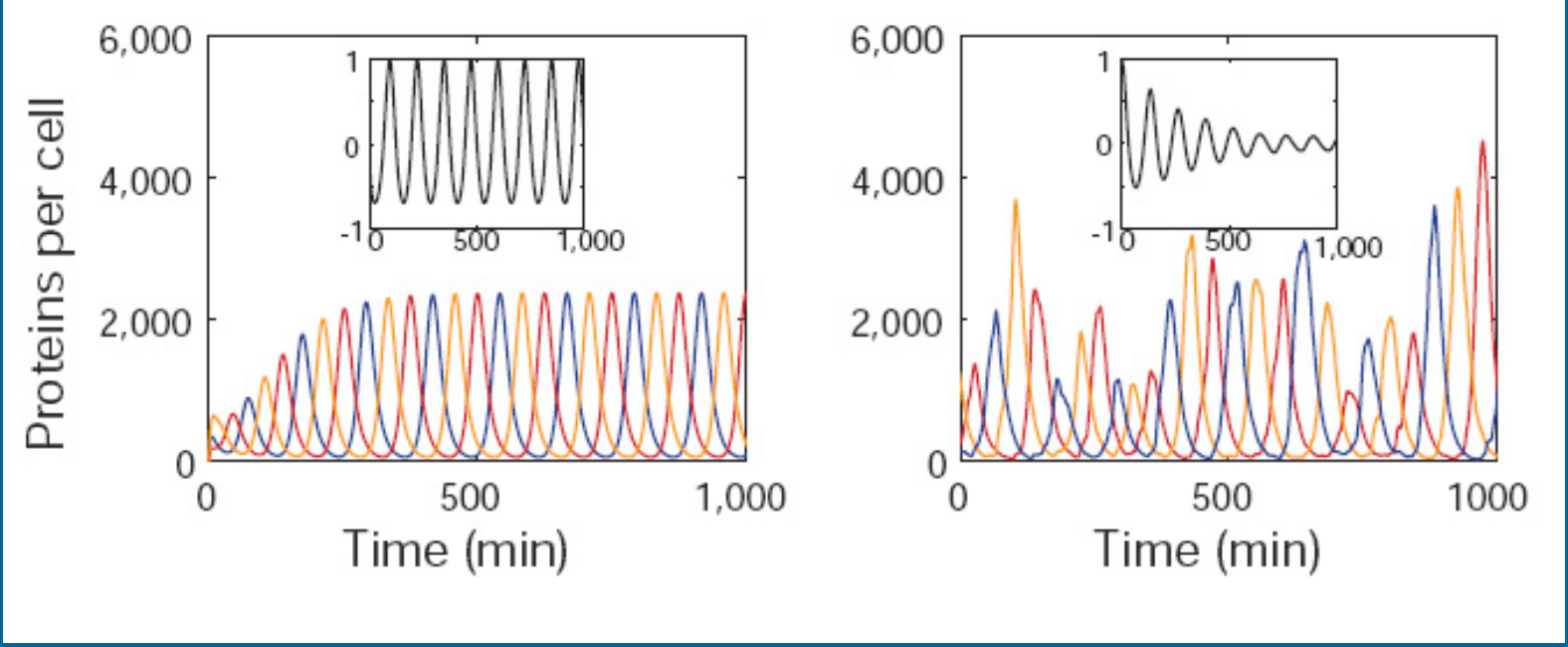
$$\frac{dp_i}{dt} = -\beta(p_i - m_i)$$

$$i = (lacI, tetR, cI)\,, \quad j = (cI, lacI, tetR)$$

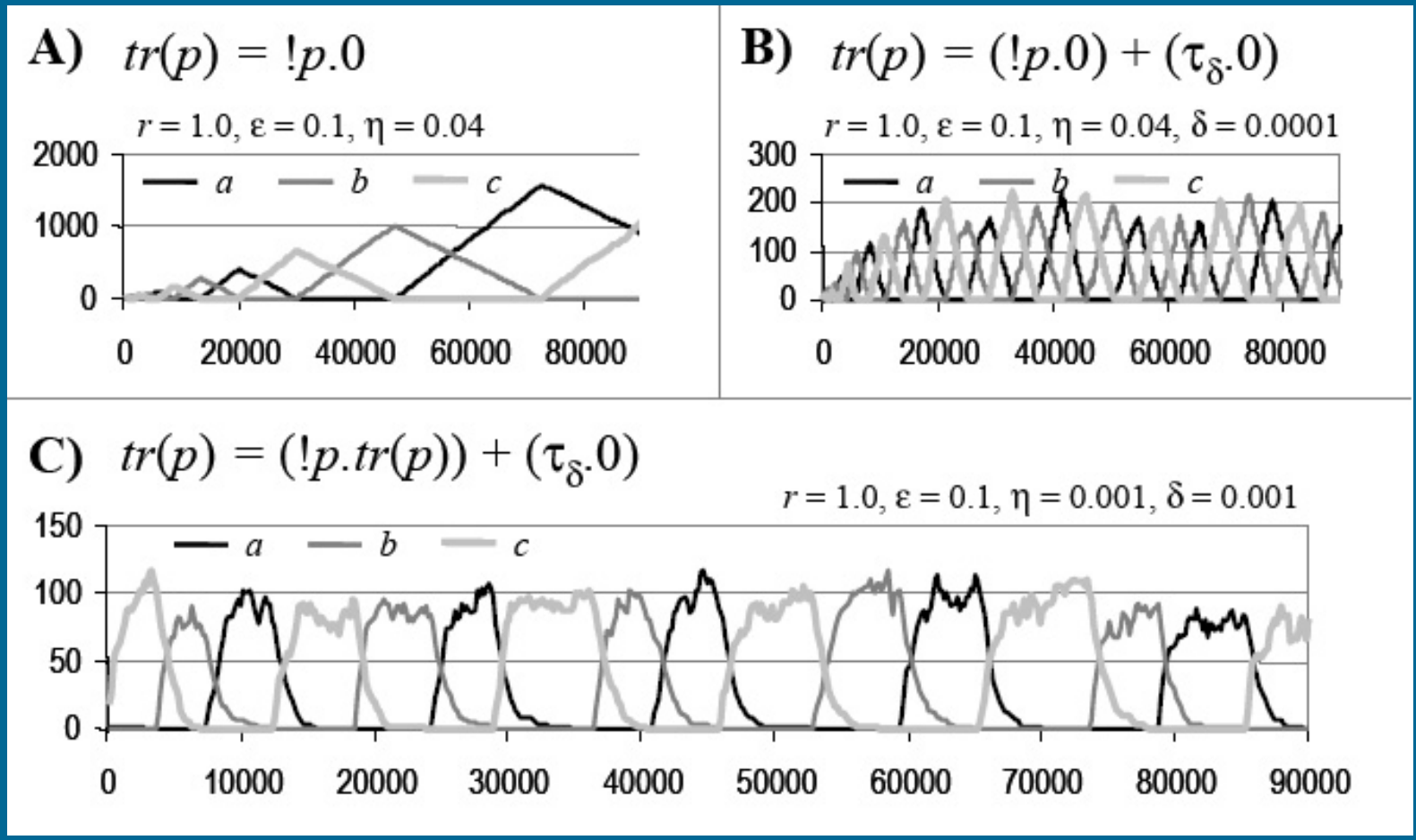
... compare with

$$neg(c, a)|neg(a, b)|neg(b, c)$$

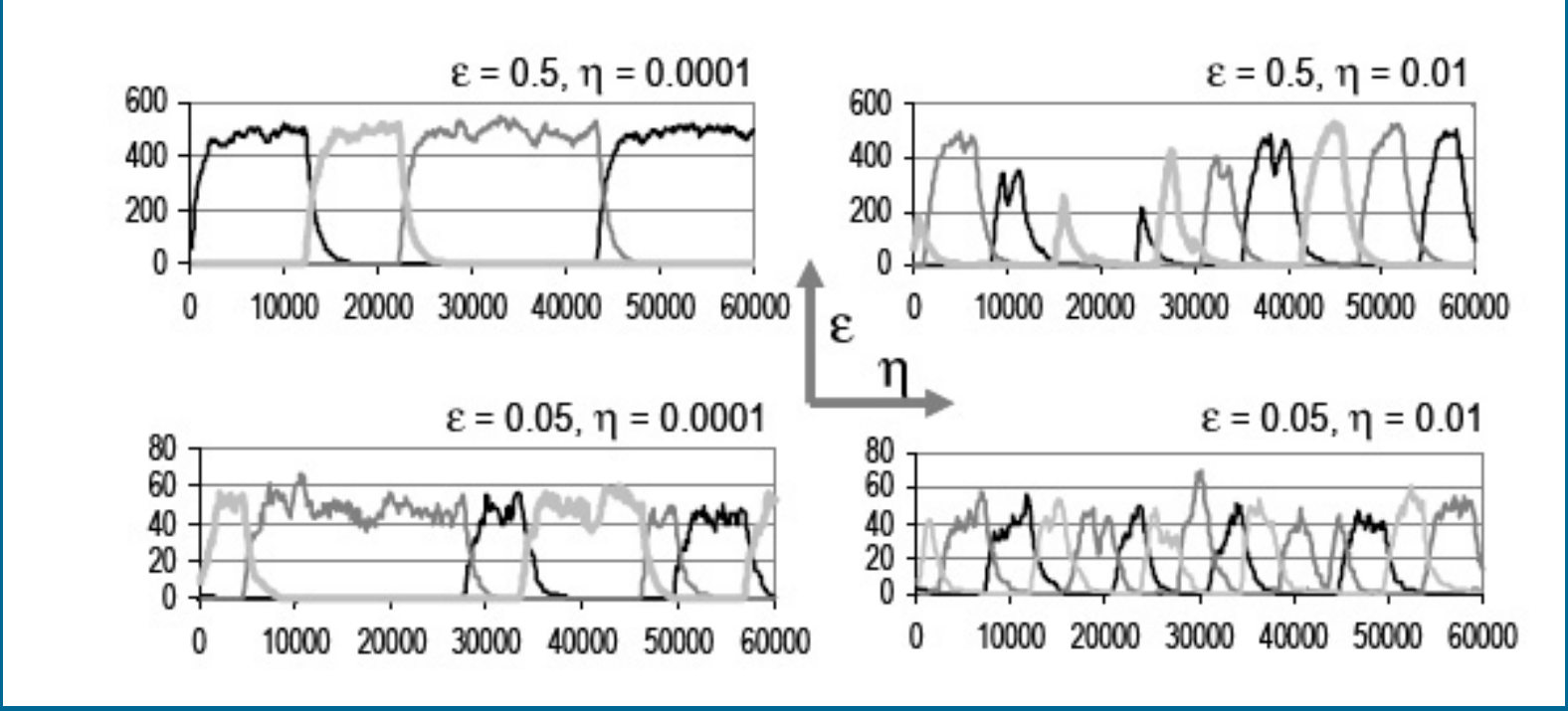
...the ODE results...and Gillespie...



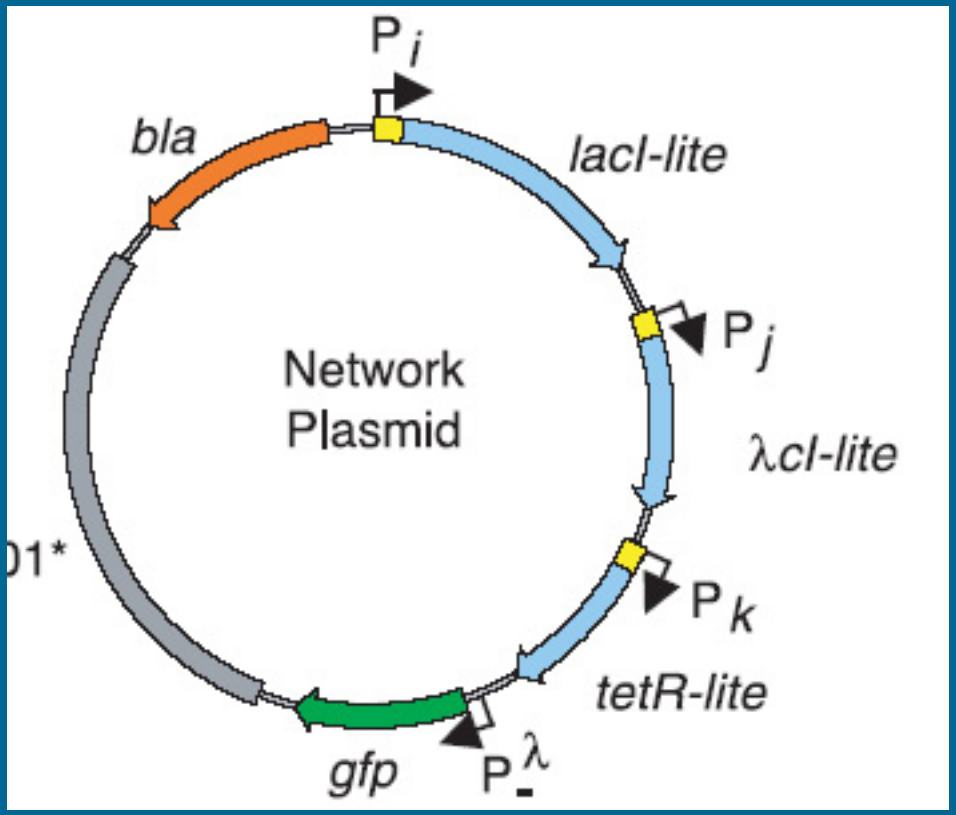
...to be compared with...



... and more parameter play...

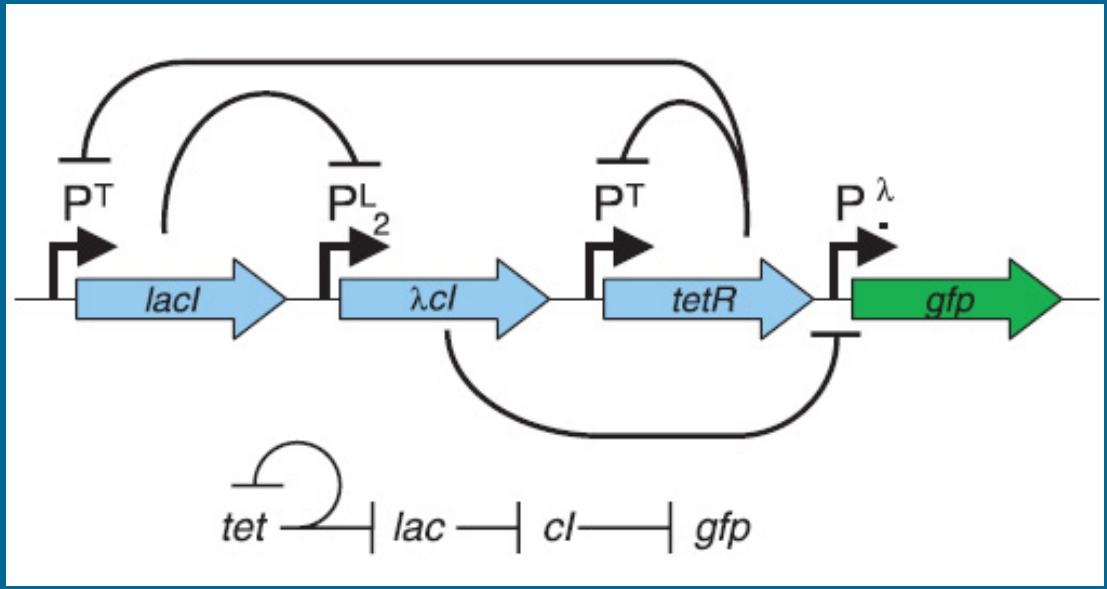


More complex example: combinatorial gene circuits

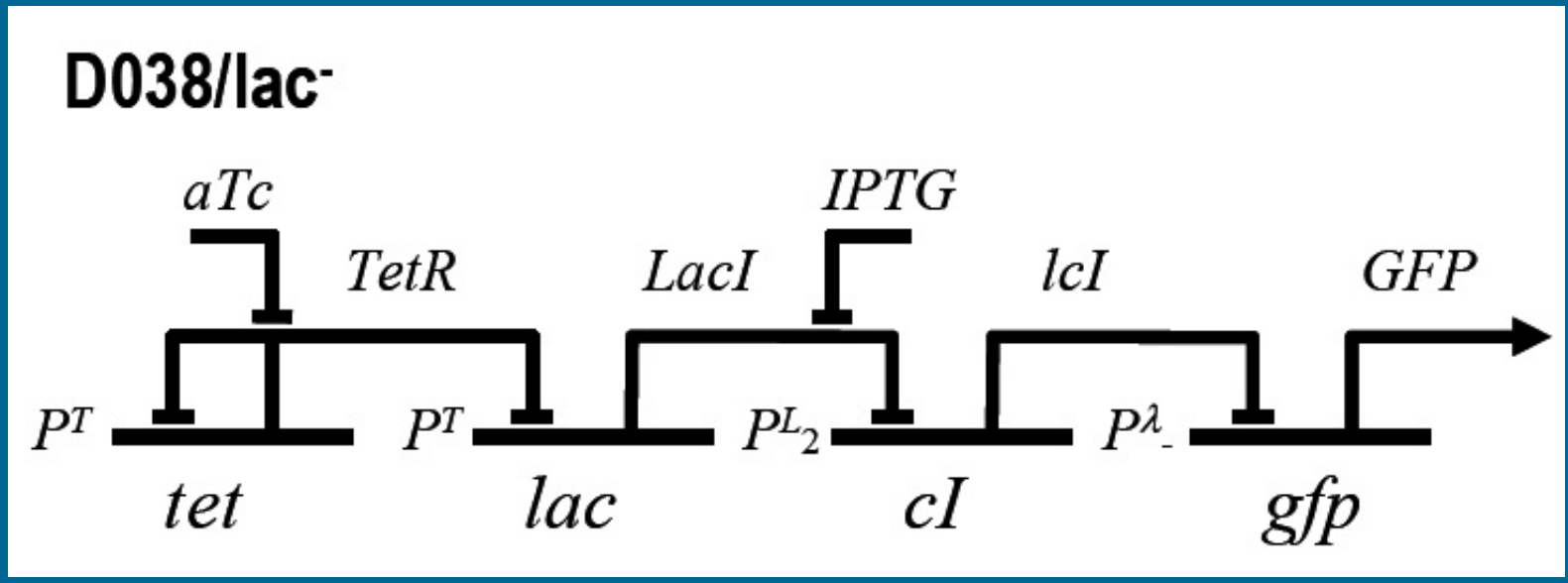


C. C. Guet, M. B. Elowitz, W. Hsing, S. Leibler, Science (2002)

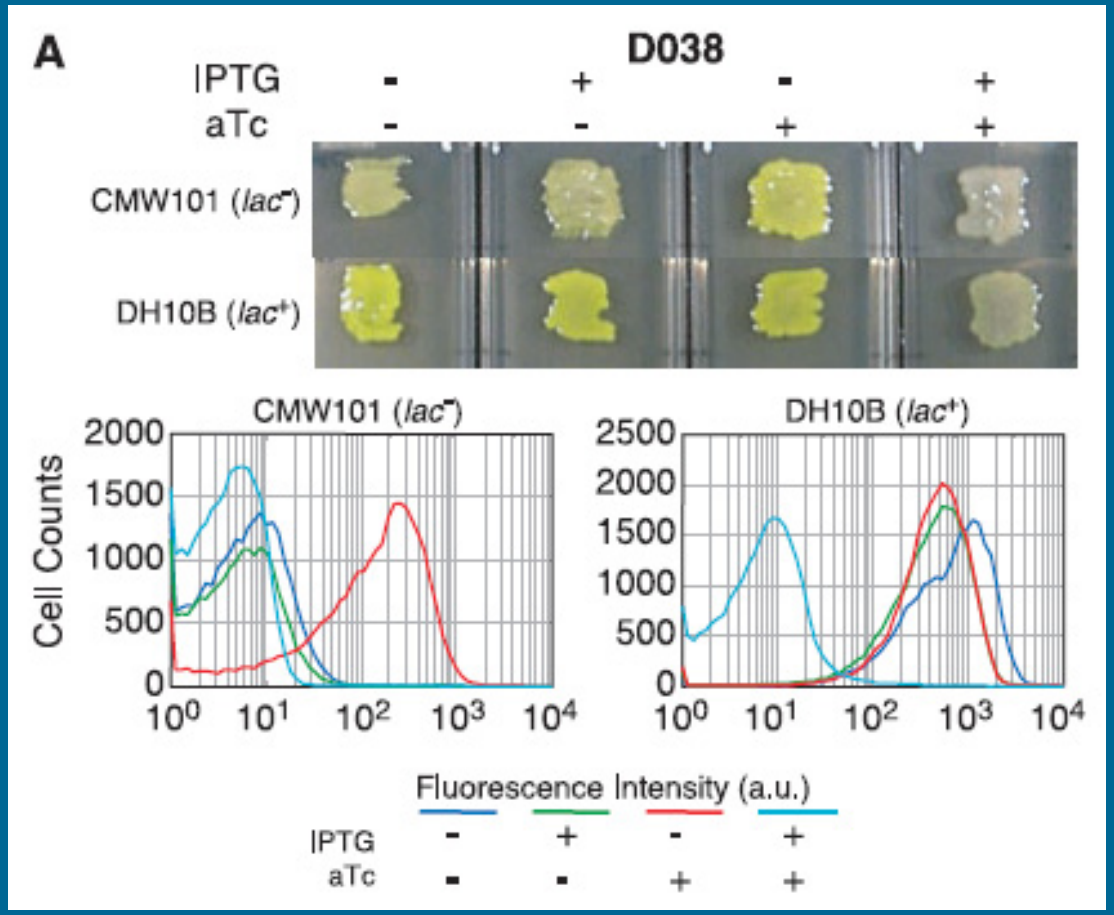
A specific case study: D038



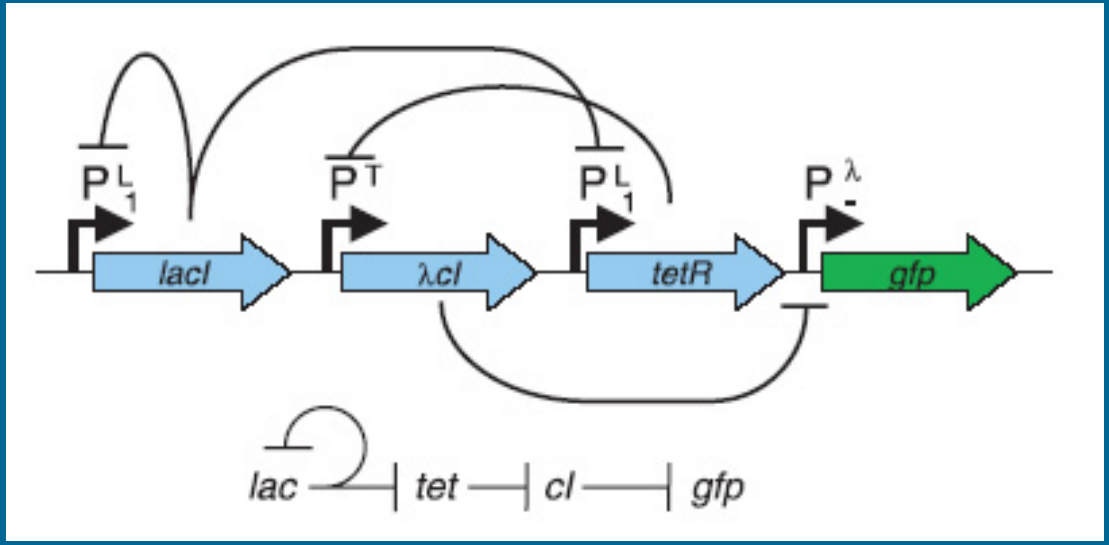
D038 in π-gate modelling



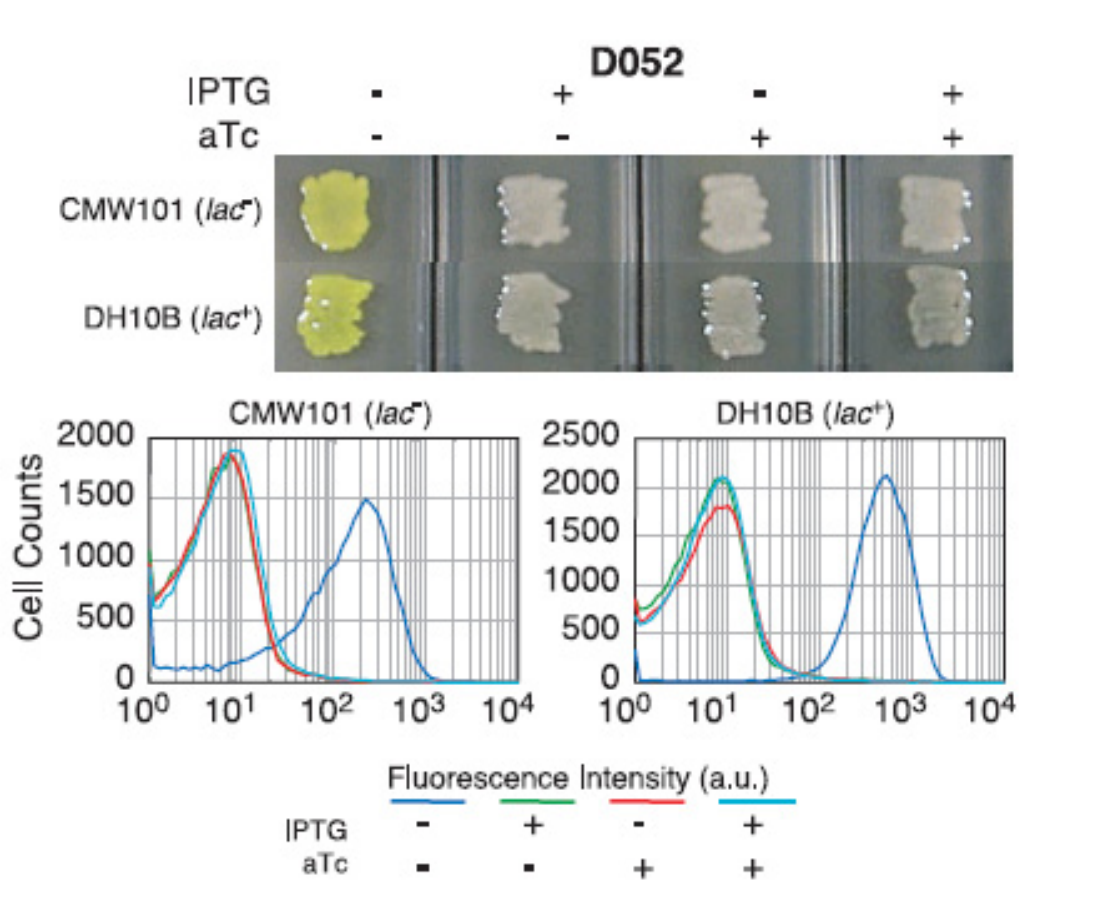
D038: Experimental results



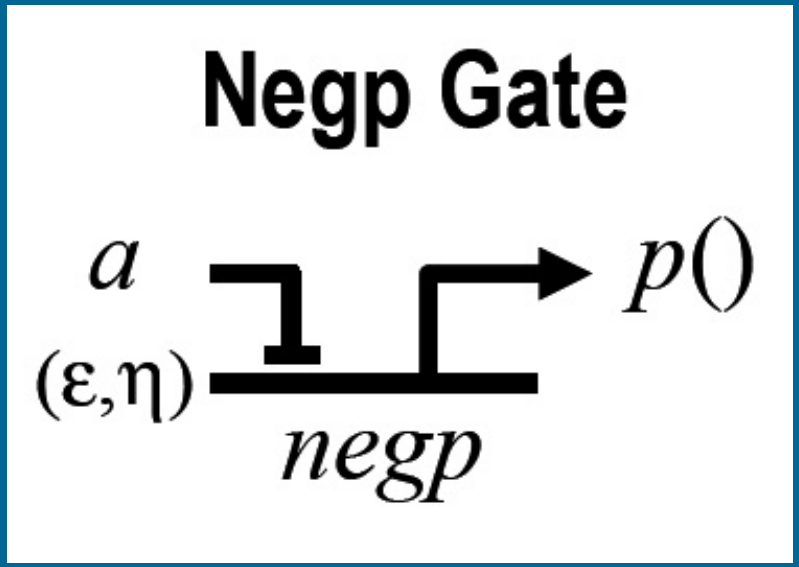
A second example: D052



A second example

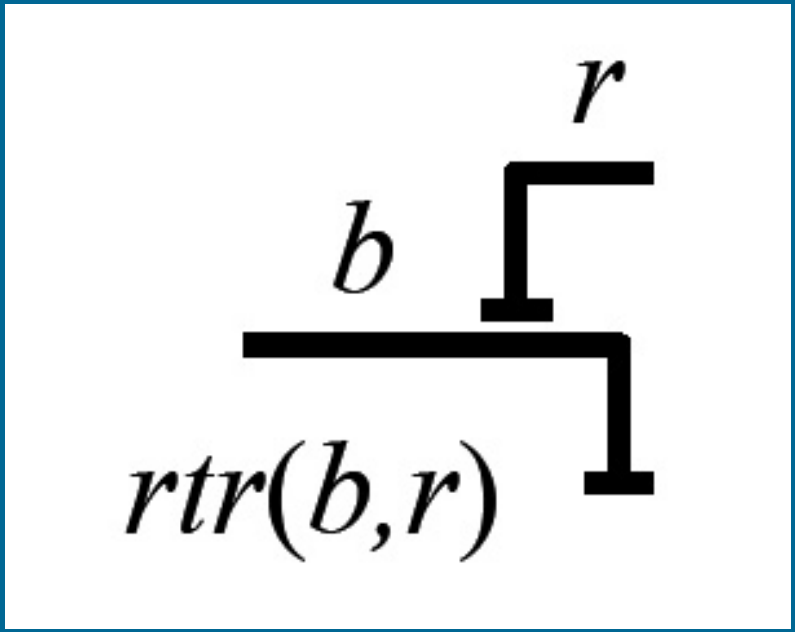


D038 in π-gate modelling: ...more complex gates needed...



$$negp(a,(\varepsilon,\eta),p) = ?a.\tau_{\eta}.negp(a,(\varepsilon,\eta),p) + \tau_{\varepsilon}.(p()|negp(a,(\varepsilon,\eta),p))$$

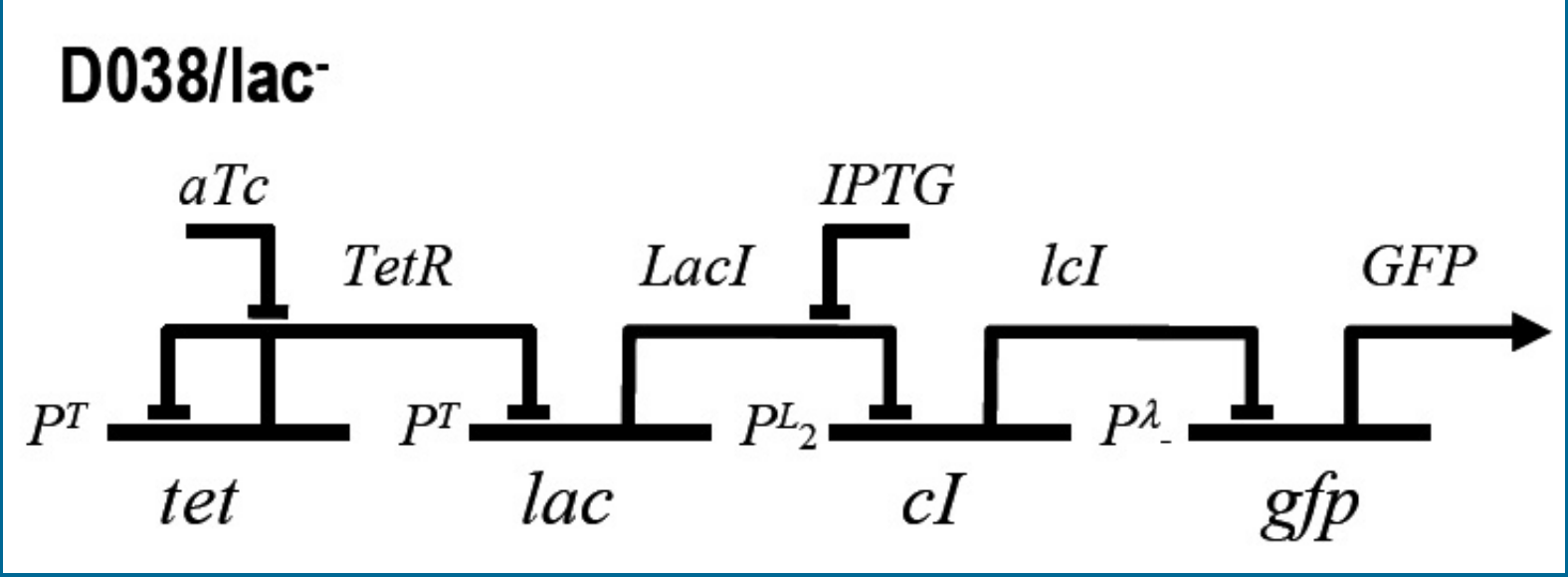
...repressible transcription factors...



$$rtr(b,r) = !b.rtr(b,r) + !r.0 + \tau_\delta.0$$

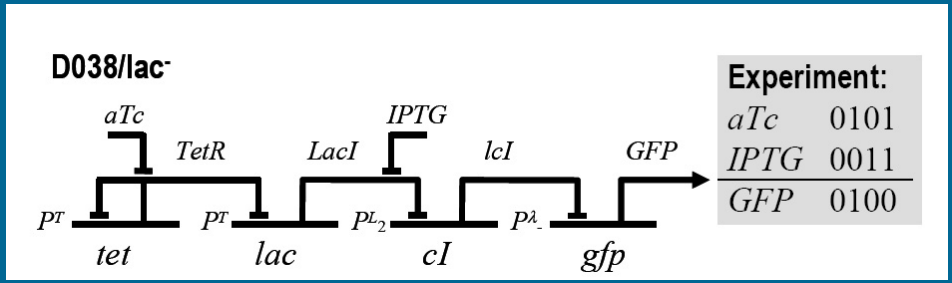
$$rep(r) = ?r.rep(r)$$

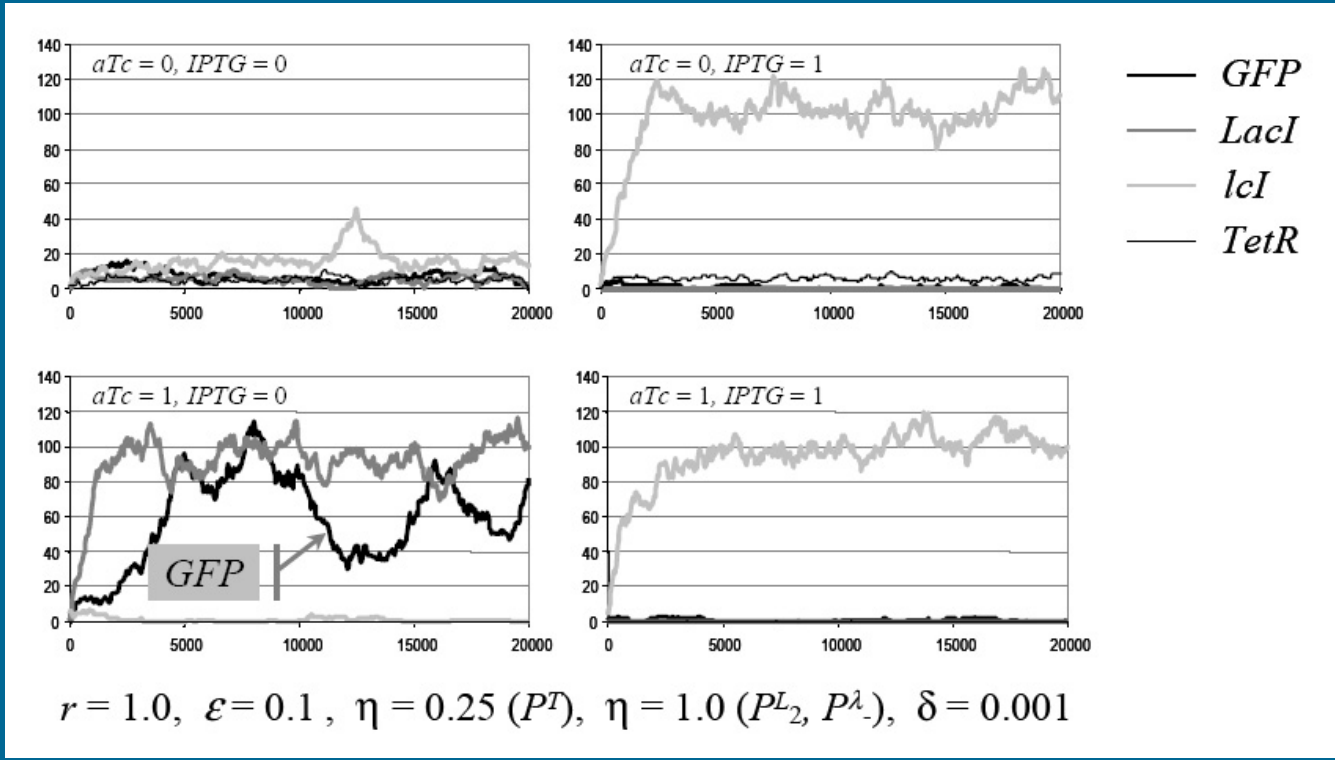
D038: Boolean analysis



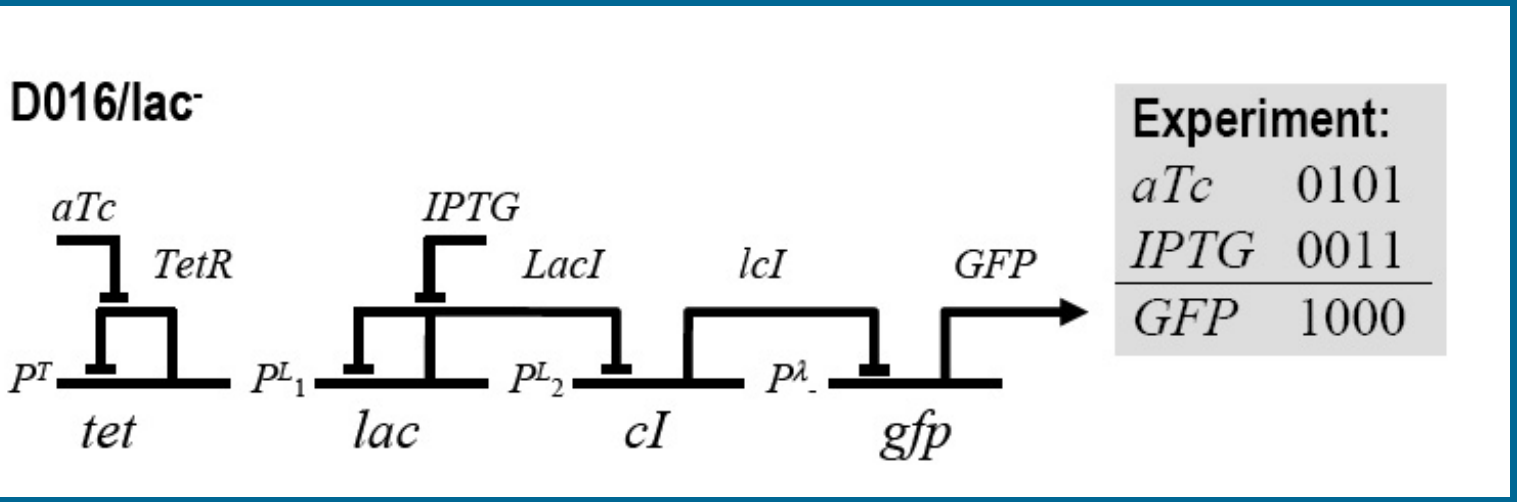
no repressors: GFP $= 0 \rightarrow$ lcI $= 1 \rightarrow$ LacI $= 0 \rightarrow$ TetR $= 1$;
self-loop: TetR $= 1 \rightarrow$ TetR $= 0 \rightarrow$ GFP $= 0.5$.

D038

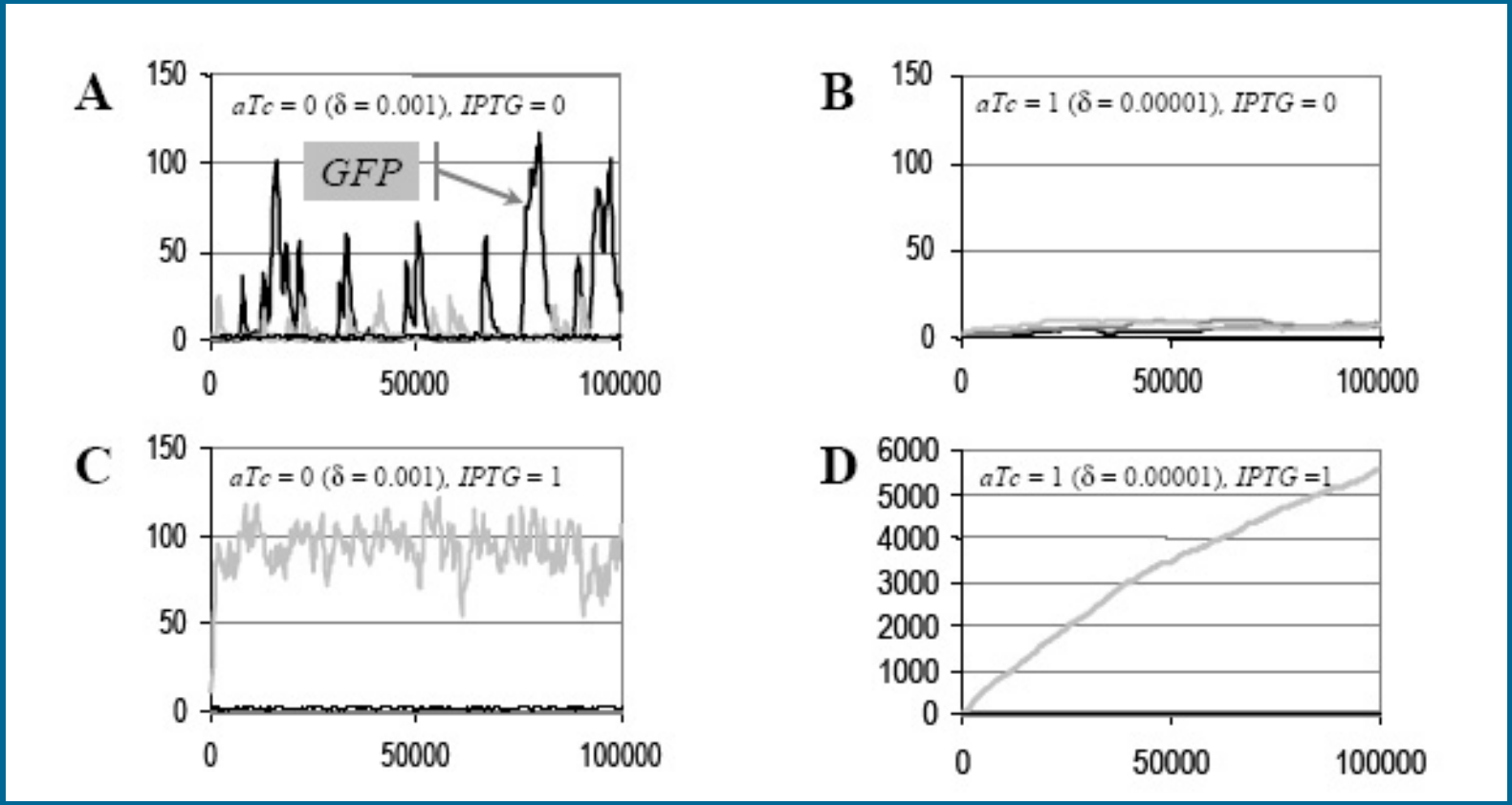

D038/lac-
aTc
TetR
LacI
IPTG
lcI
GFP
tet
lac
cI
gfp
Experiment:
aTc 0101
IPTG 0011
GFP 0100


aTc = 0, IPTG = 0
aTc = 0, IPTG = 1
aTc = 1, IPTG = 0
aTc = 1, IPTG = 1
GFP
GFP
LacI
lcI
TetR
r = 1.0, ε = 0.1 , η = 0.25 (P^T), η = 1.0 (P^L2, P^λ-), δ = 0.001

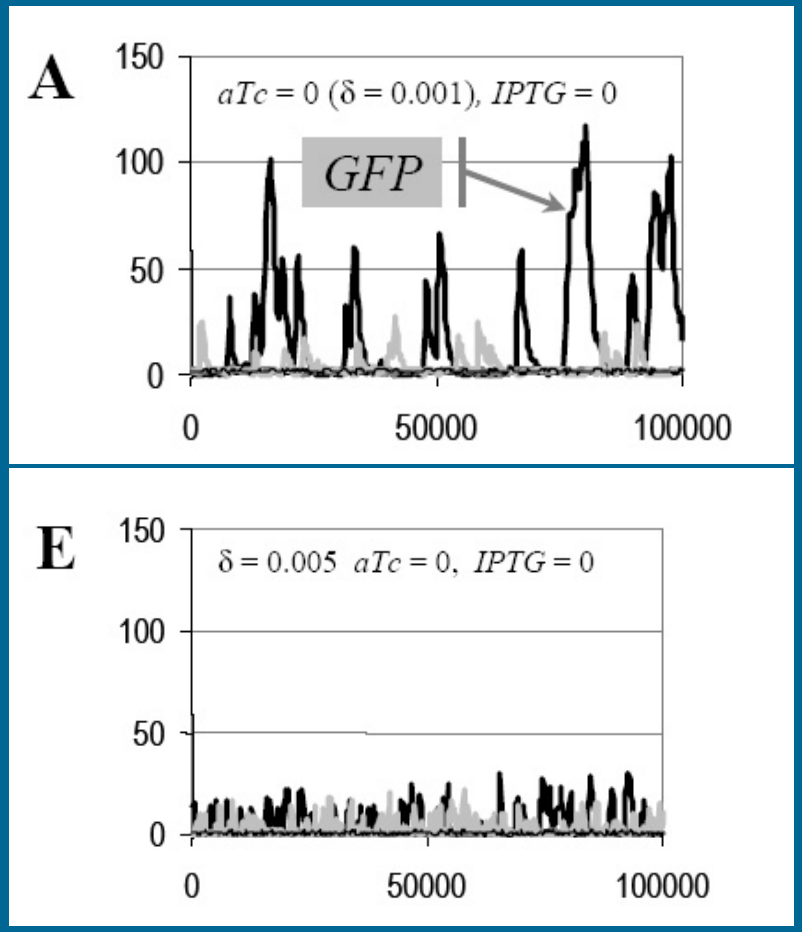
A final example: D016



A final example: D016

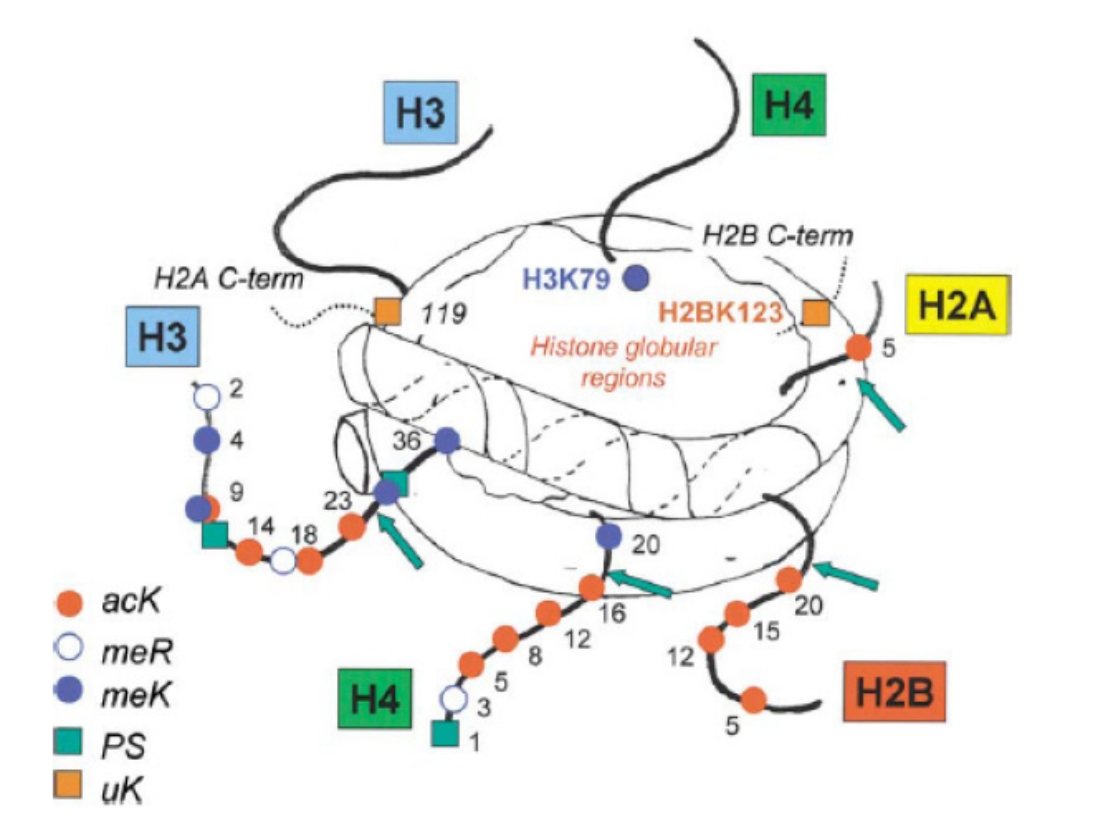


A final example: D016

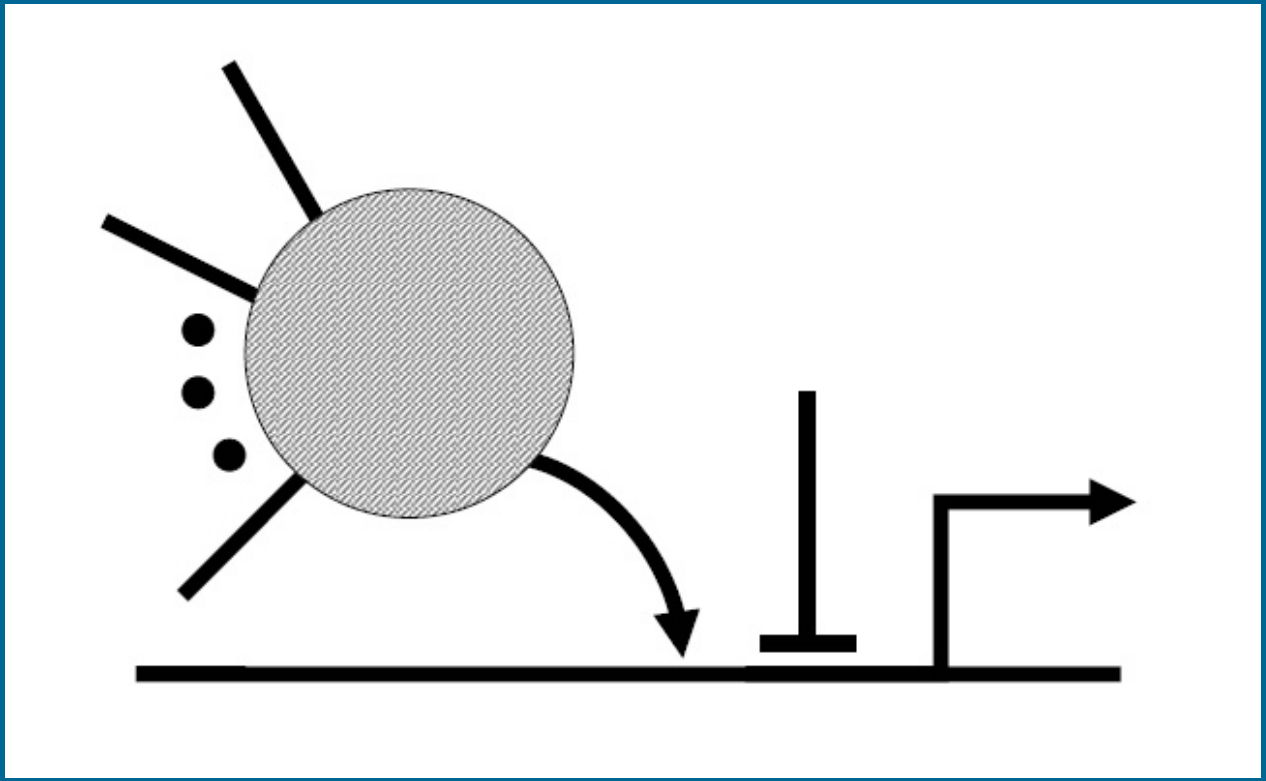


Outlook: chromatin, the nucleosome

Outlook: chromatin, histone tail modifications



Outlook: chromatin, stochastic π-network



Organisational outlook: next meeting Aci VicAnne

Modélisation et Cancer

Institut de Biologie de Lille

17/18 mai 2006