

Competition, feedback and fluctuations in genetic regulatory modules

Ofer Biham

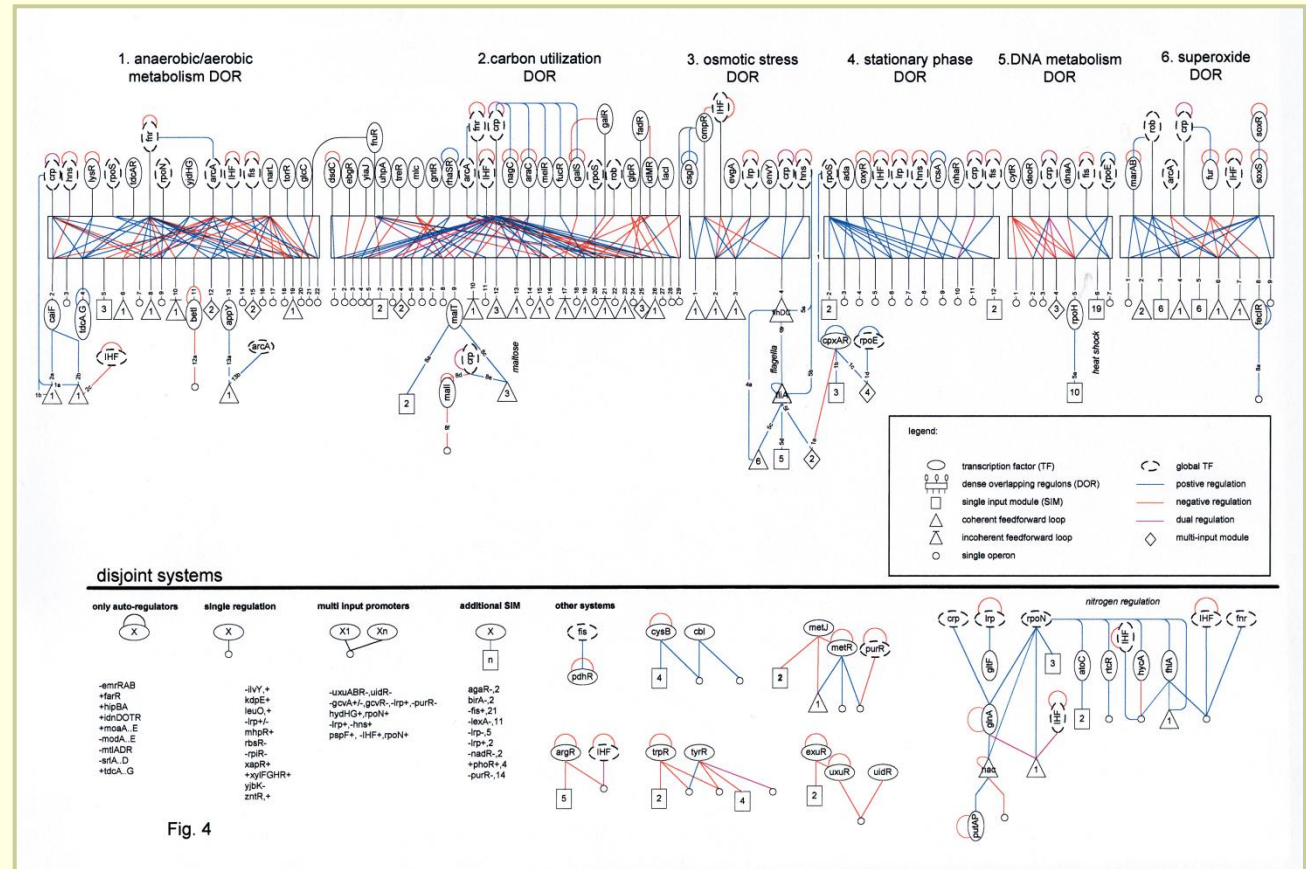
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Hanah Margalit
Shoshy Altuvia

Introduction

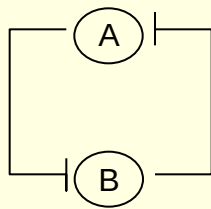
The E. coli transcription network

Taken from: Shen-Orr et al. Nature Genetics 31:64-68(2002)

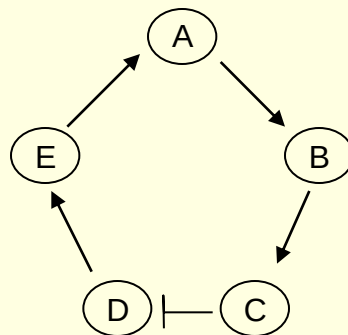


Properties of the Network

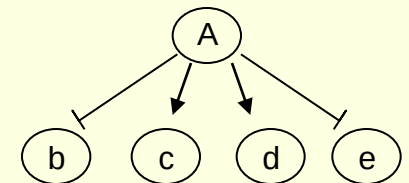
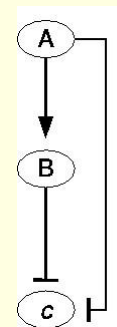
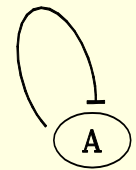
- Approx. Scale-Free Network
- Includes Modular Structures – Motifs
 - Autorepressor
 - Feed-Forward Loop
 - Single-Input Module
- No Feedback Loops



Multistability

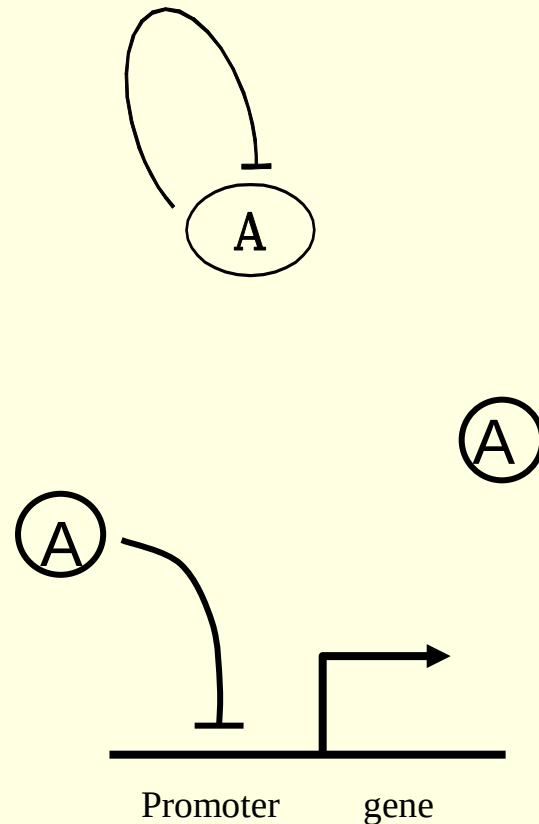


Oscillations



The Auto-repressor

- Protein A acts as a repressor to its own gene
- It can bind to the promoter of its own gene and suppress the transcription



The Auto-repressor

- Rate equations – Michaelis-Menten form

$$\frac{d[A]}{dt} = \frac{g}{1 + k[A]^h} - d[A]$$

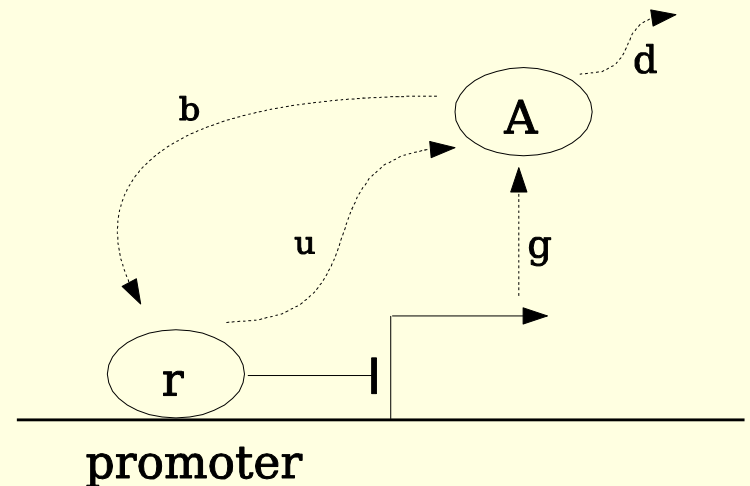
h = Hill coefficient

$k=b/u$ = repression strength

- Rate equations – Extended Set

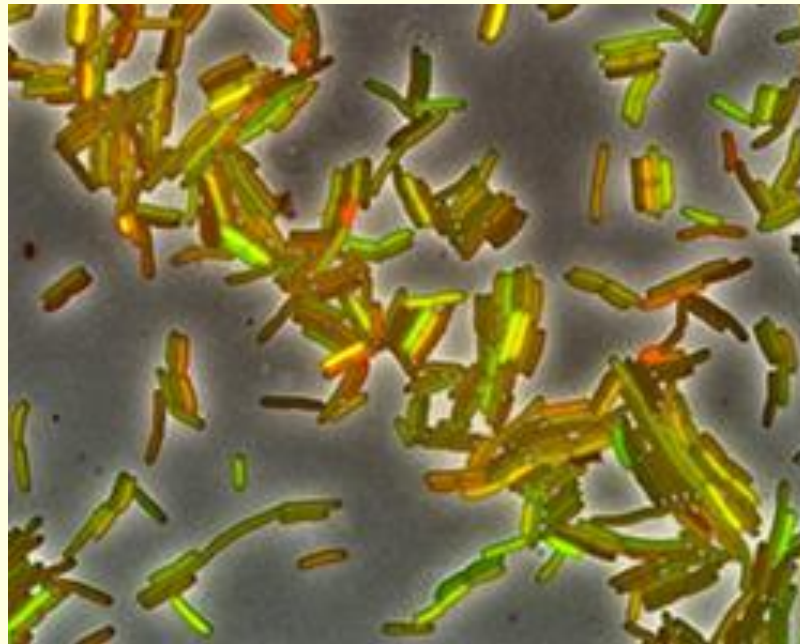
$$\frac{d[A]}{dt} = g(1 - [r]) - d[A] - b[A](1 - [r]) + u[r]$$

$$\frac{d[r]}{dt} = b[A](1 - [r]) - u[r]$$



It's a noisy business!

(McAdams & Arkin, 1999)



From Michael Elowitz, Science (2002)

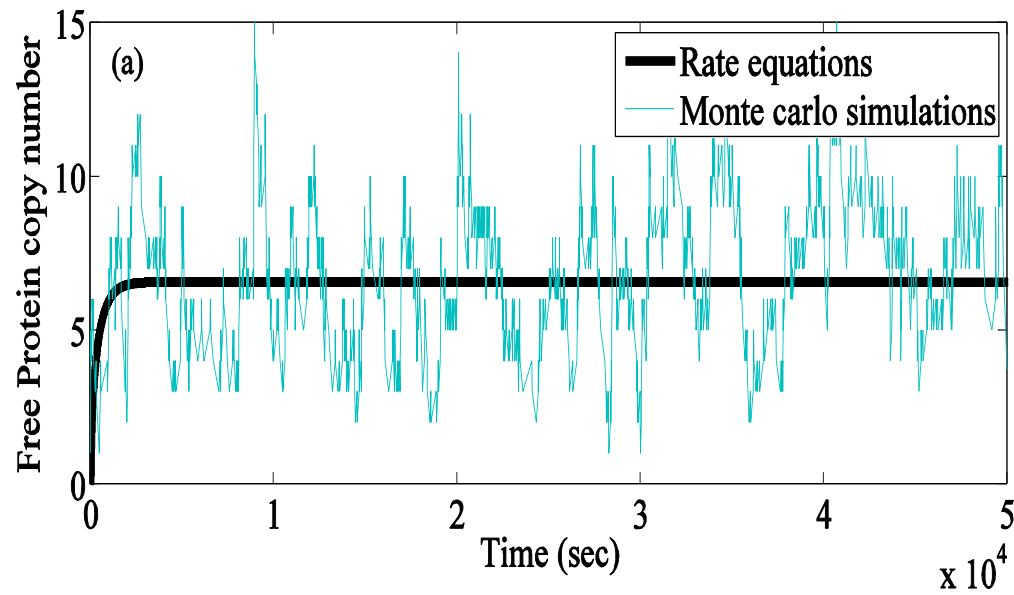
The Auto-repressor

$P(N_A, N_r)$: Probability for the cell to contain N_A free proteins and N_r bound proteins

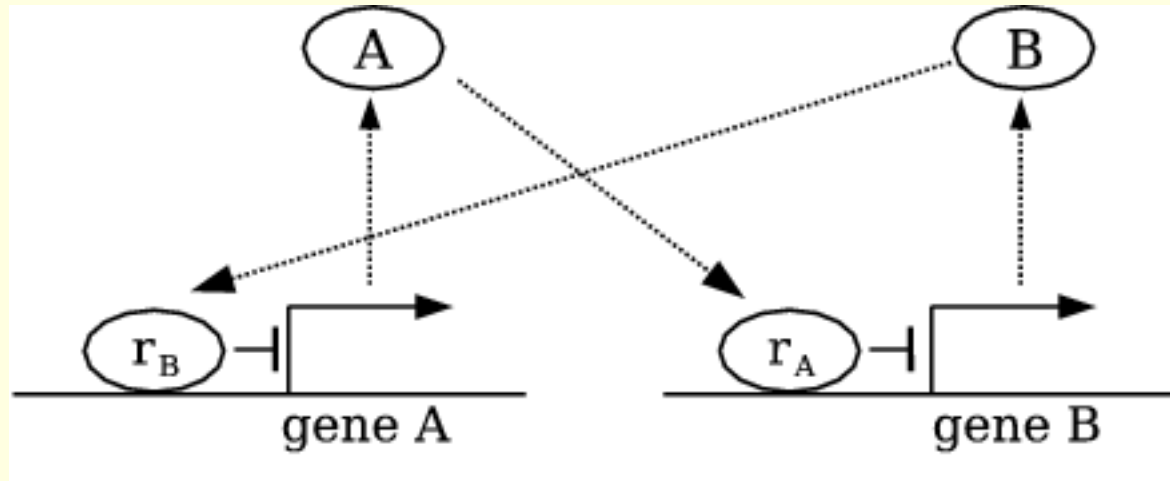
The Master Equation

$$\begin{aligned} \frac{d}{dt} P(N_A, N_r) = & g(1 - N_r)[P(N_A - 1, N_r) - P(N_A, N_r)] \\ & + d[(N_A + 1)P(N_A + 1, N_r) - N_A P(N_A, N_r)] \\ & + b[N_r(N_A + 1)P(N_A + 1, N_r - 1) - (1 - N_r)N_A P(N_A, N_r)] \\ & + u[(N_r + 1)P(N_A - 1, N_r + 1) - N_r P(N_A, N_r)] \end{aligned}$$

The Auto-repressor



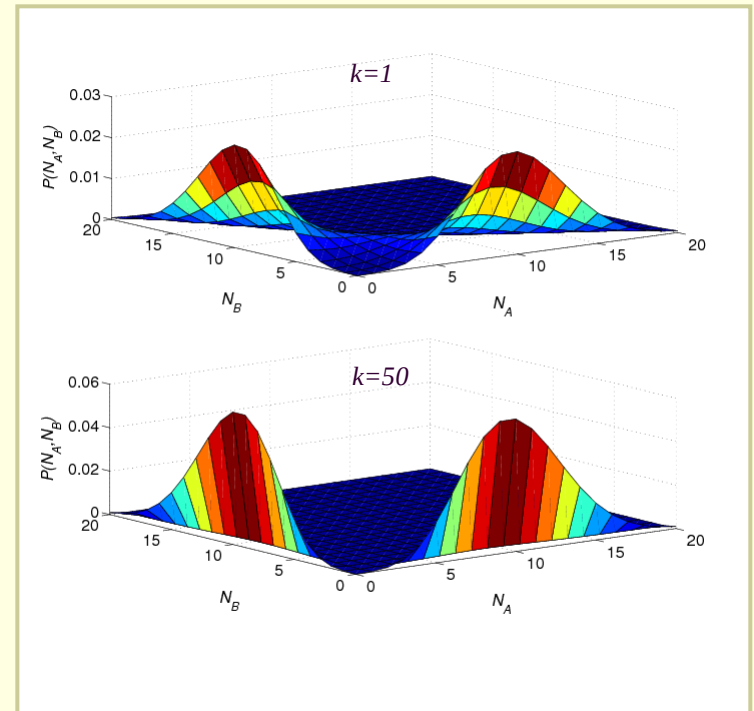
The Genetic Switch



- A mutual repression circuit.
- Two proteins A and B negatively regulate each other's synthesis

Bistability

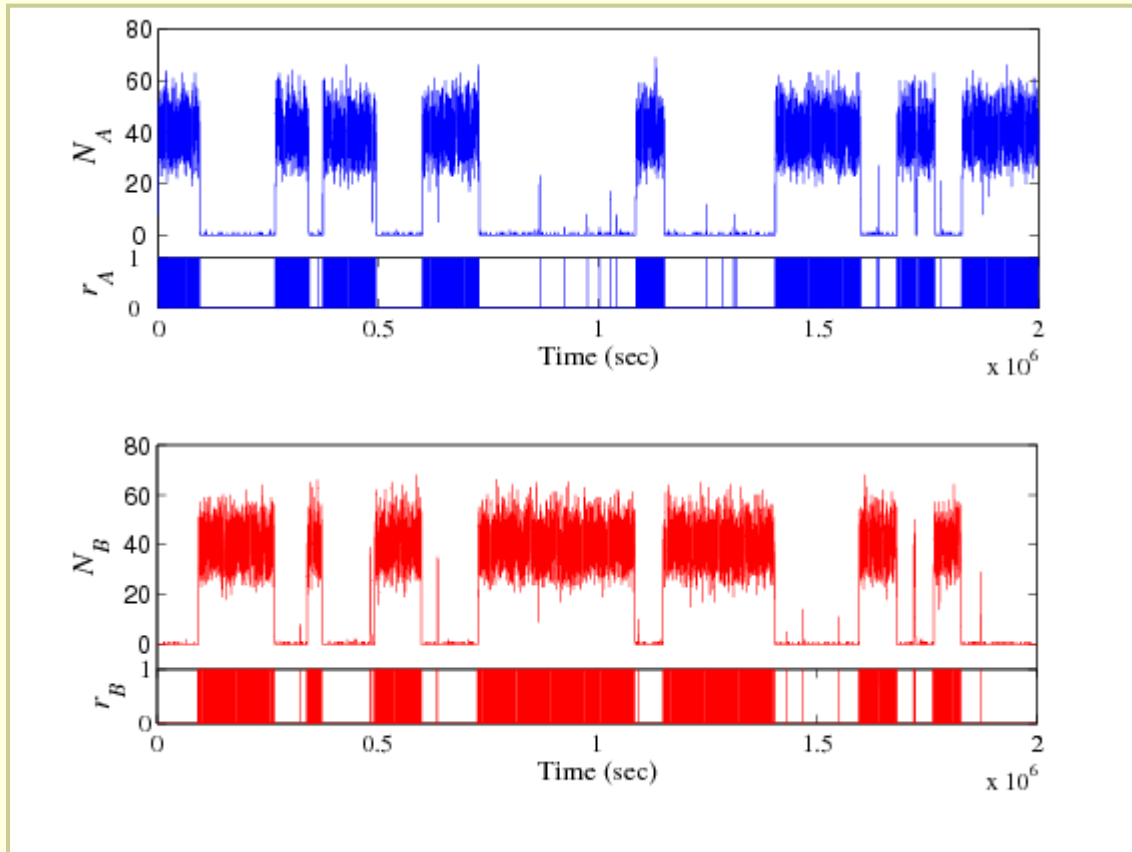
- The probability distribution is composed of two peaks
- The separation between these peaks determines the quality of the switch



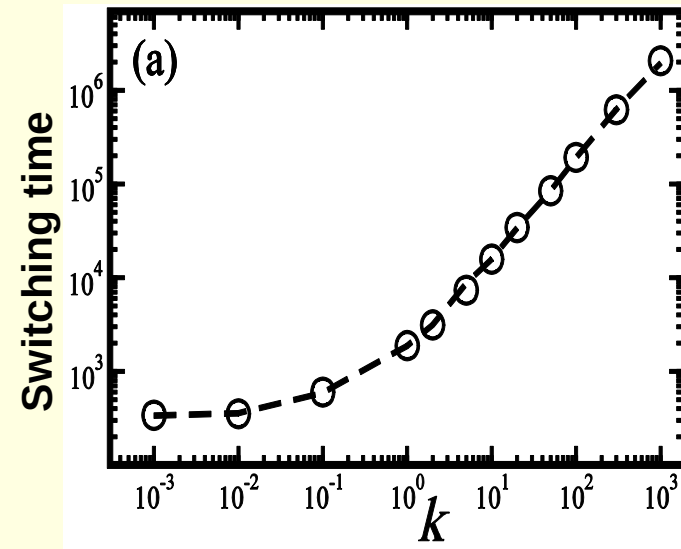
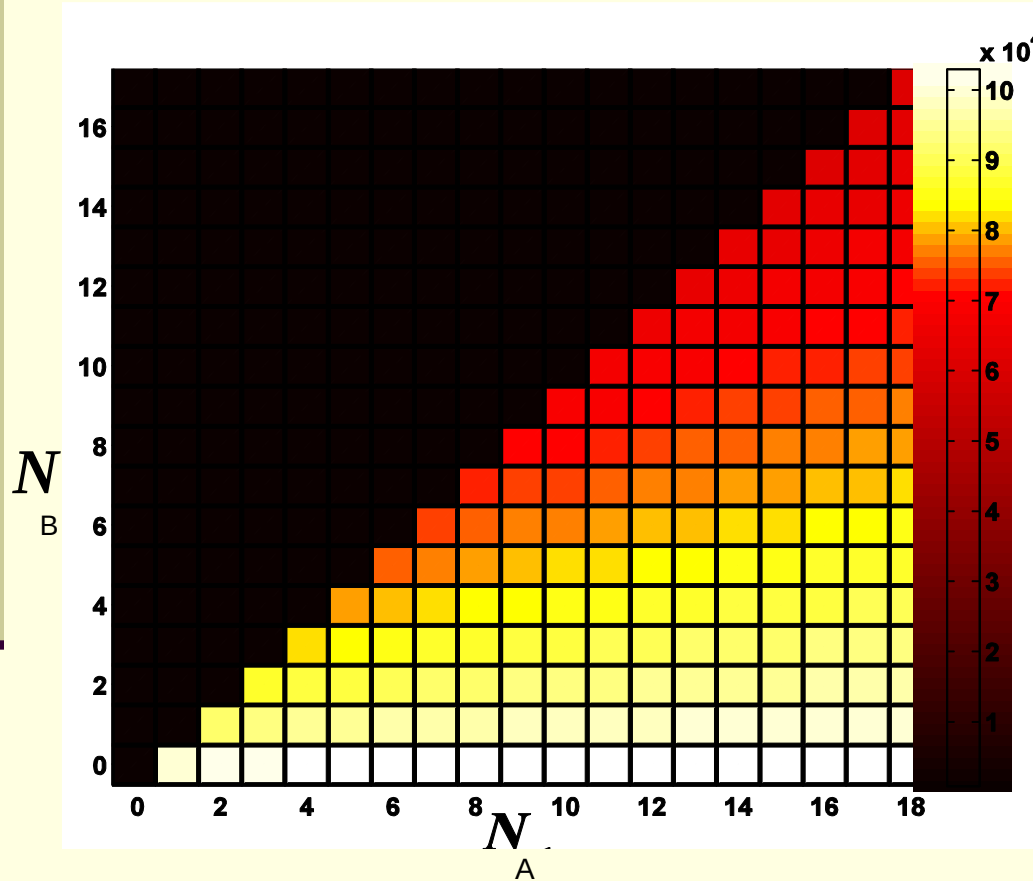
Lipshtat, Loinger, Balaban and Biham, Phys. Rev. Lett. 96, 188101 (2006)

Lipshtat, Loinger, Balaban and Biham, Phys. Rev. E 75, 021904 (2007)

The Exclusive Switch

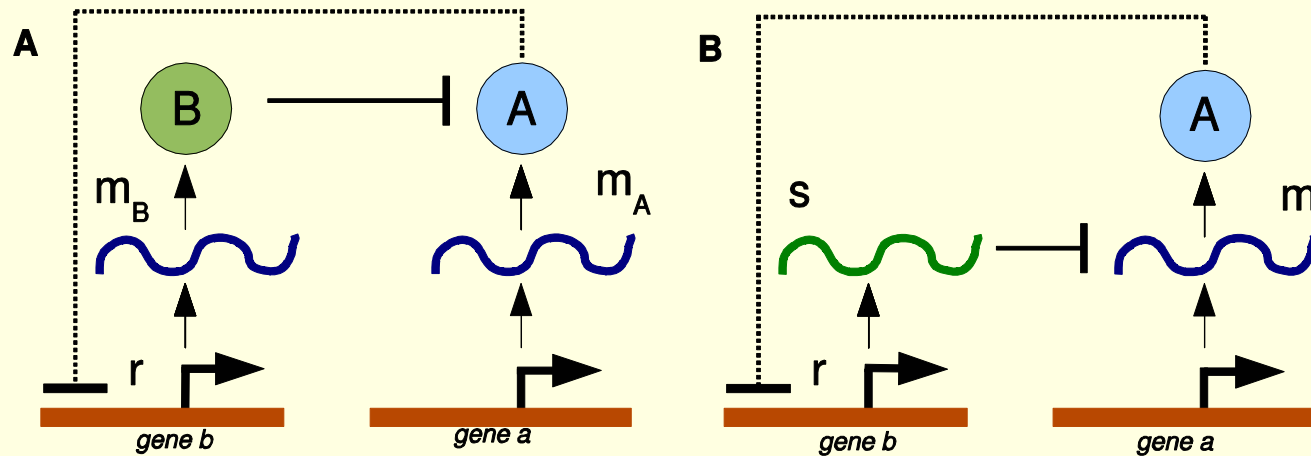


Switching Time as a first passage problem



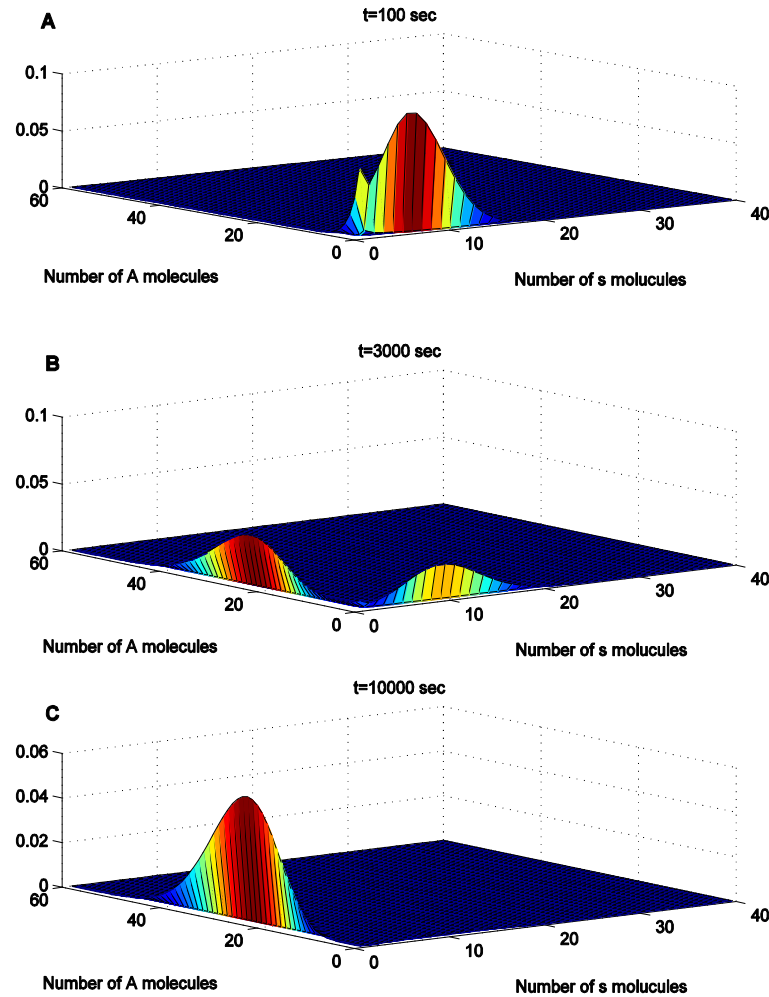
B. Barzel and O. Biham, Phys. Rev. E 78, 041919 (2008)

Mixed feedback loops



Shimoni, G. Friedlander, S. Altuvia, H. Margalit and O. Biham, Preprint (2011)

Stochastic Timer



Persistence

Bacterial persistence is a phenomenon in which a small fraction of genetically identical bacteria cells survives after an exposure to antibiotics

What is the mechanism?

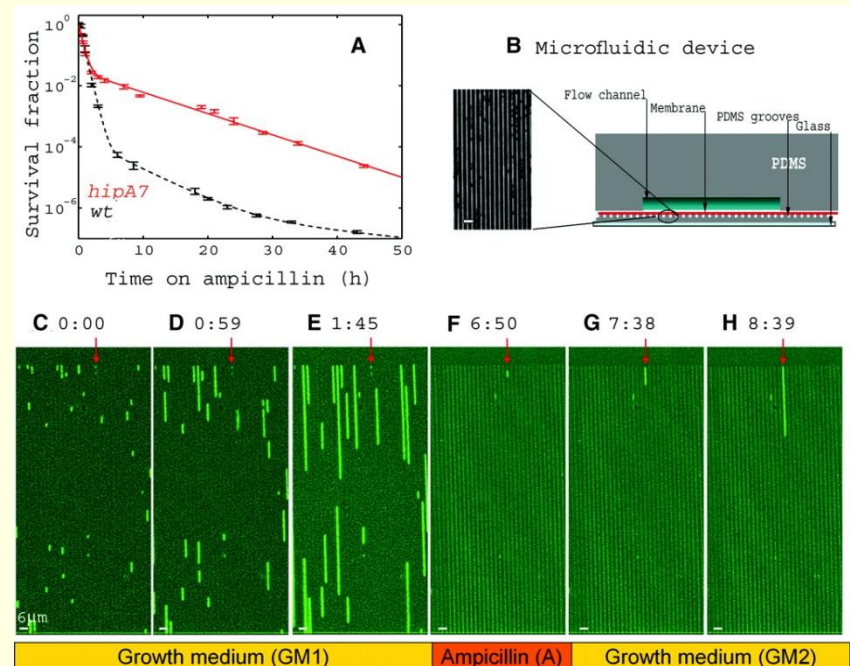
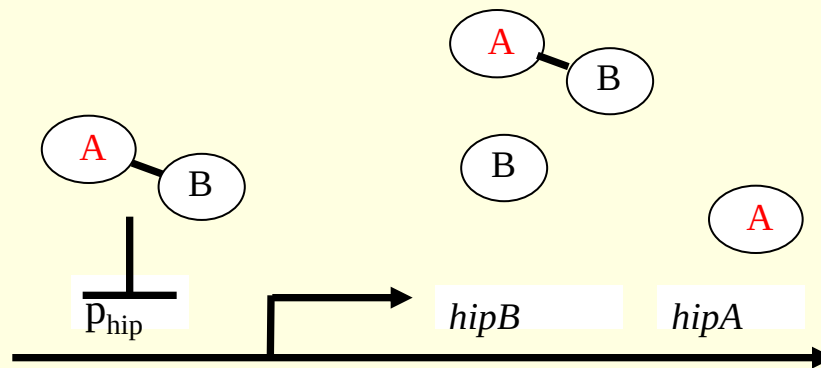


Figure taken from: N.Q Balaban et al., Science **305**, 1951 (2004)

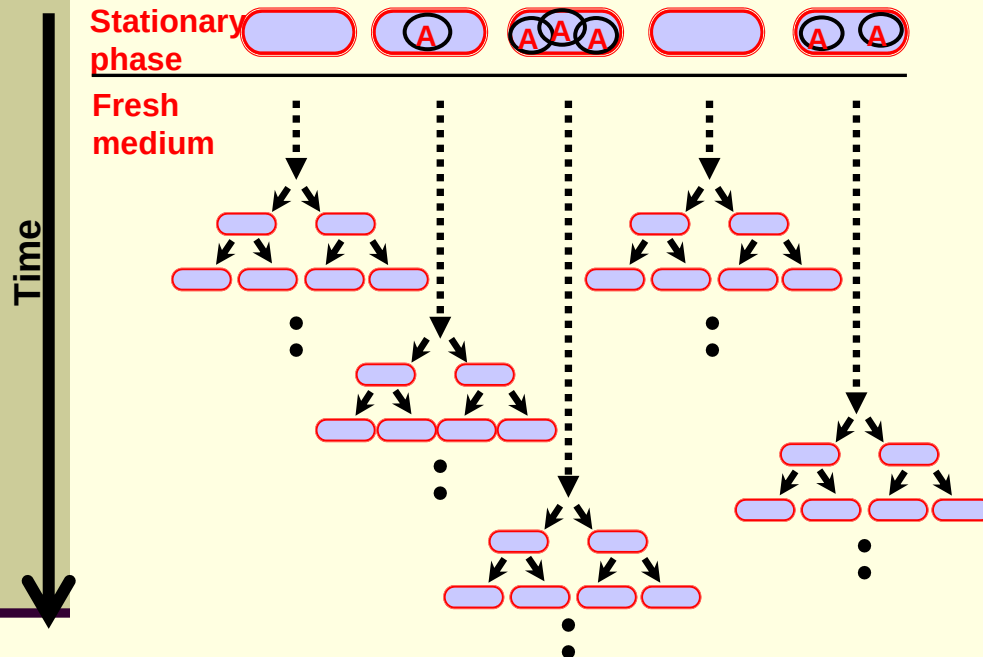
Toxin-Antitoxin Module



HipA – Stable toxin

HipB – Unstable Antitoxin, Neutralizes HipA

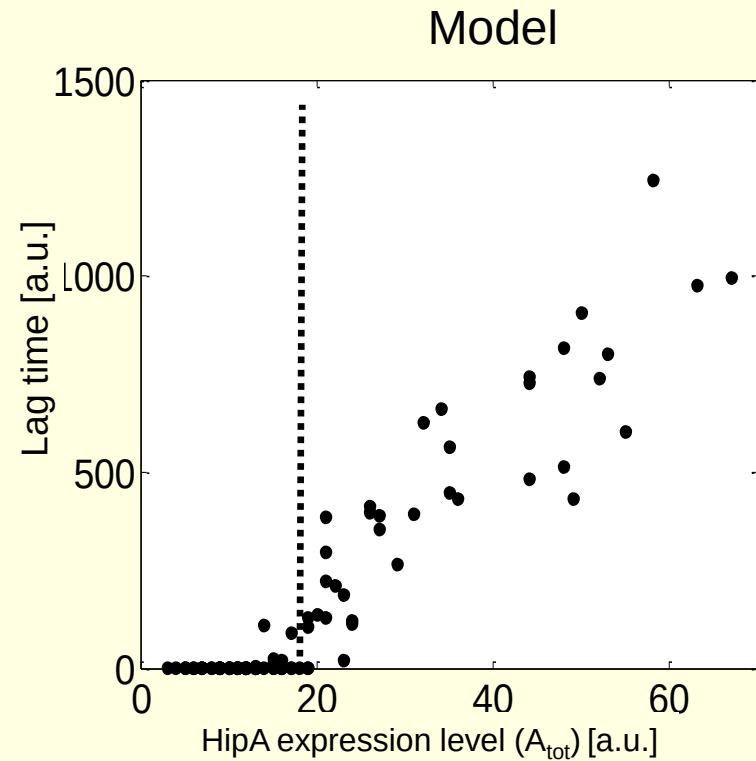
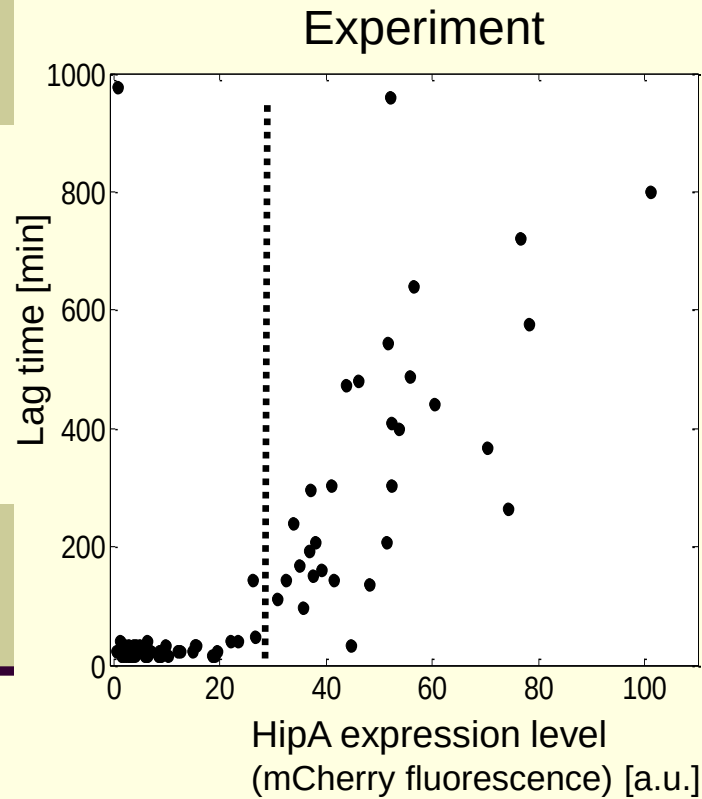
Toxin-Antitoxin Module



Cells that contain a large number of A proteins divide slowly and are not affected by antibiotics.

This state is characterized by a long **lag time**.

Toxin-Antitoxin Module

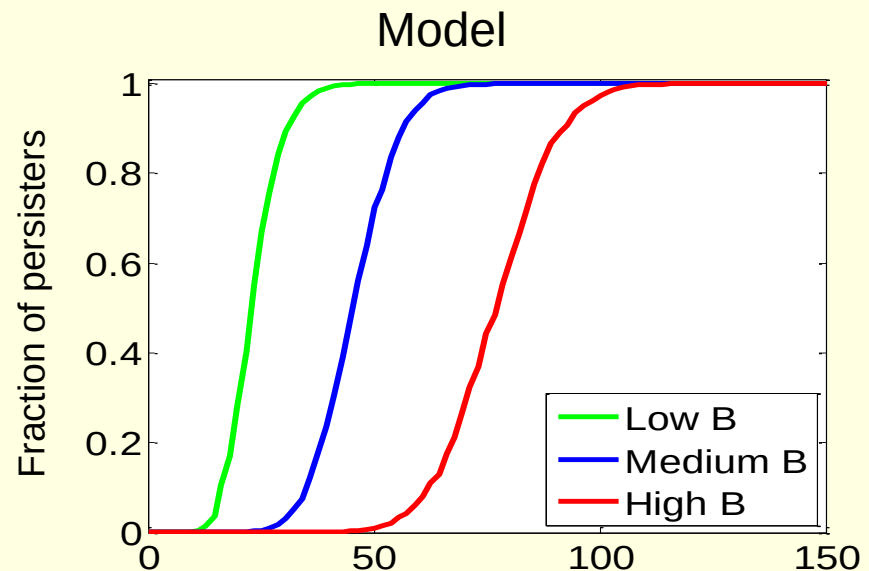
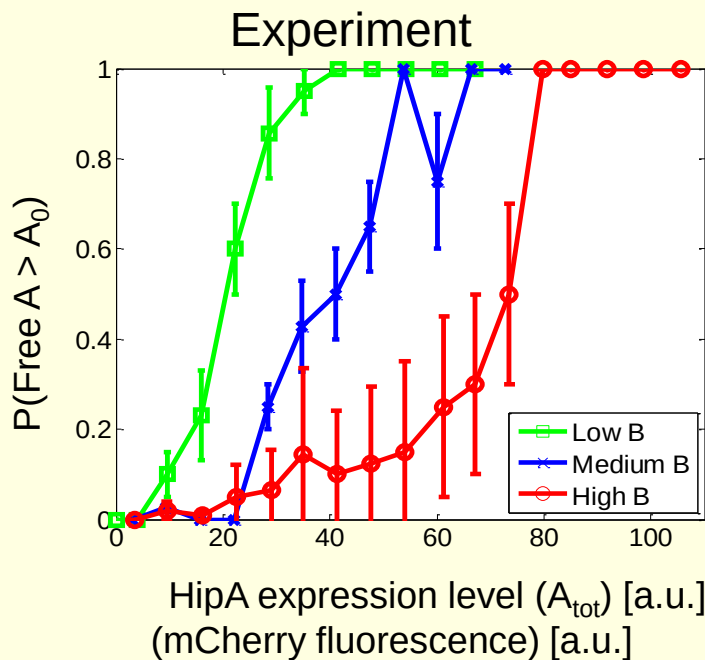


Threshold behavior

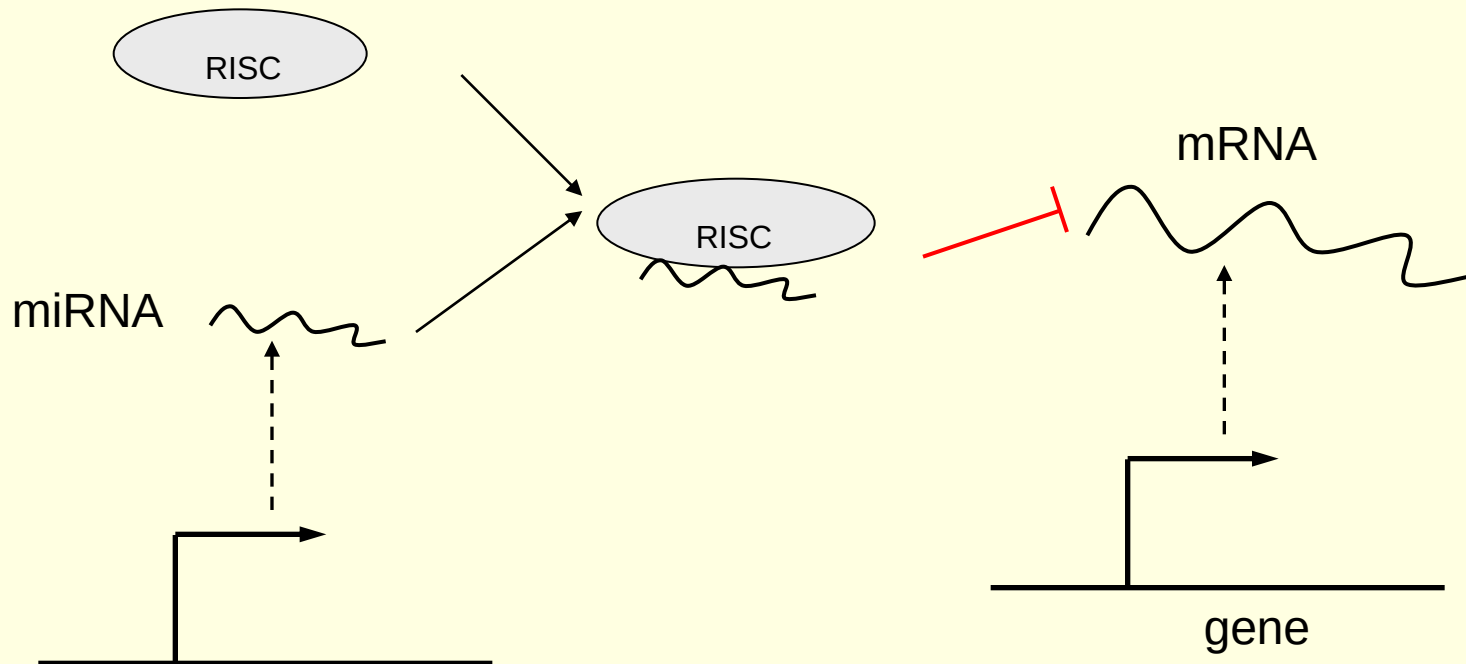
Toxin-Antitoxin Module

Fraction of persisters = $\text{Prob}(A > A_0)$ [Threshold]

Dependence on A and B production



miRNA Regulation



Summary

- We have studied several modules of genetic networks using deterministic and stochastic methods
- The combination of competition, feedback and fluctuations has an important effect on the function of these modules. In particular, it gives rise to phenotypic diversity in populations of identical cells.
- Current work is aimed at extending the results to more complex networks