Competition, feedback and fluctuations in genetic regulatory modules

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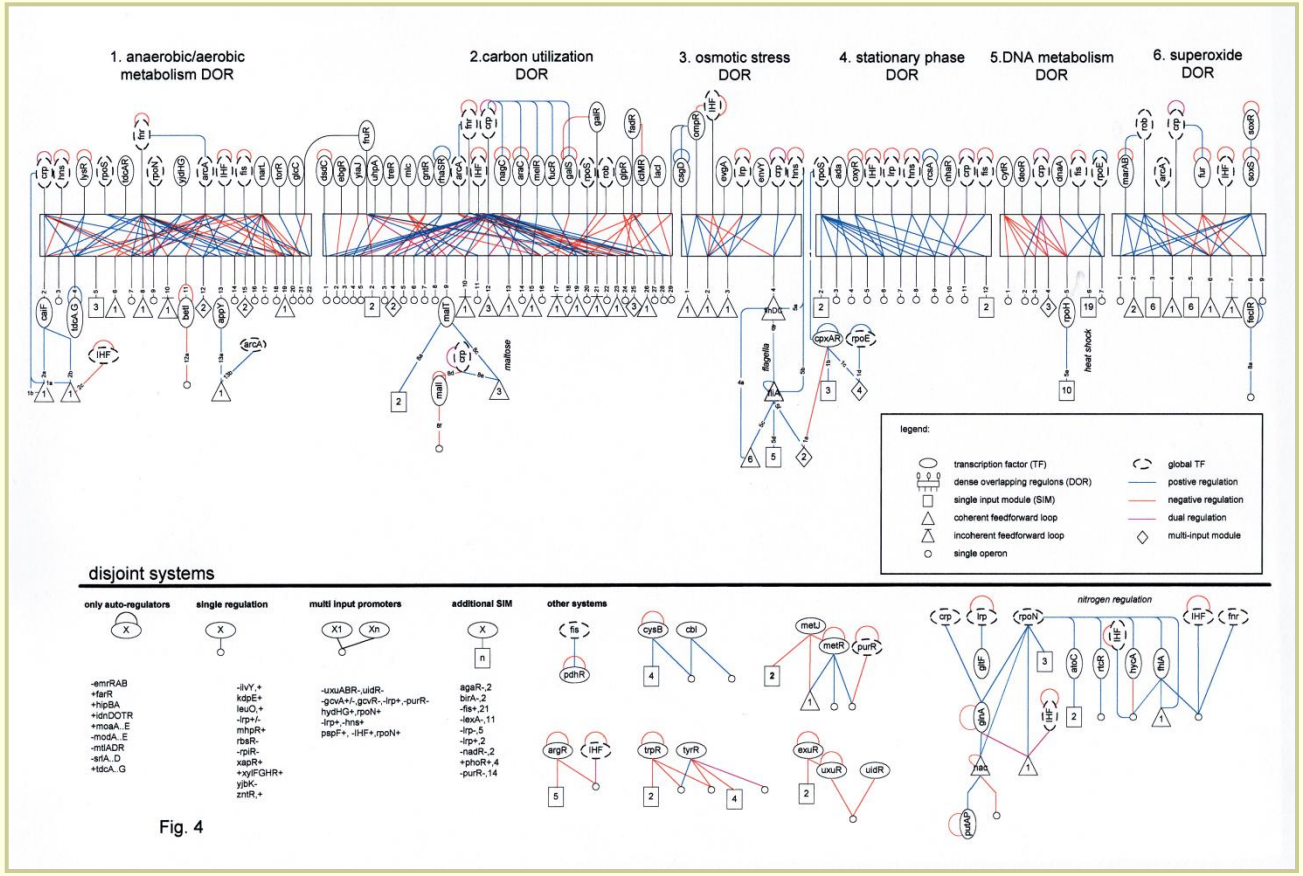
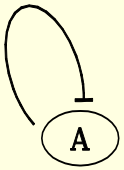
Introduction

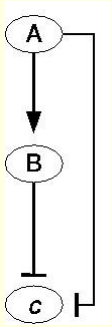
- The E. coli transcription network
- Taken from: Shen-Orr et al. Nature Genetics 31:64-68(2002)

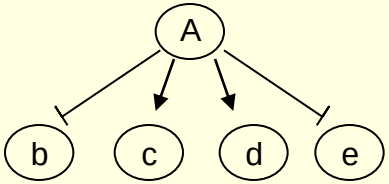


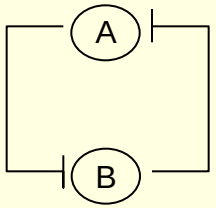
Properties of the Network

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

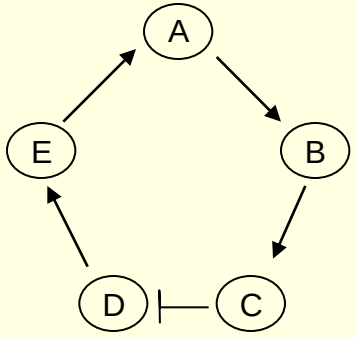








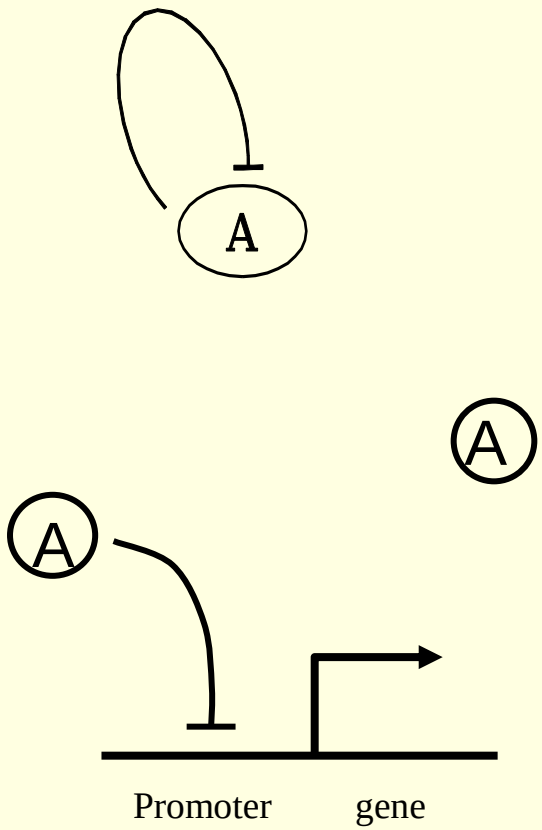
Multistability



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



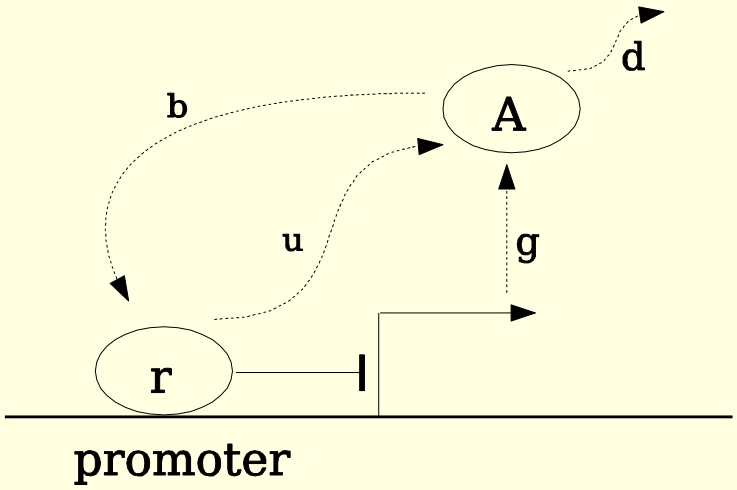
The Auto-repressor

- 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



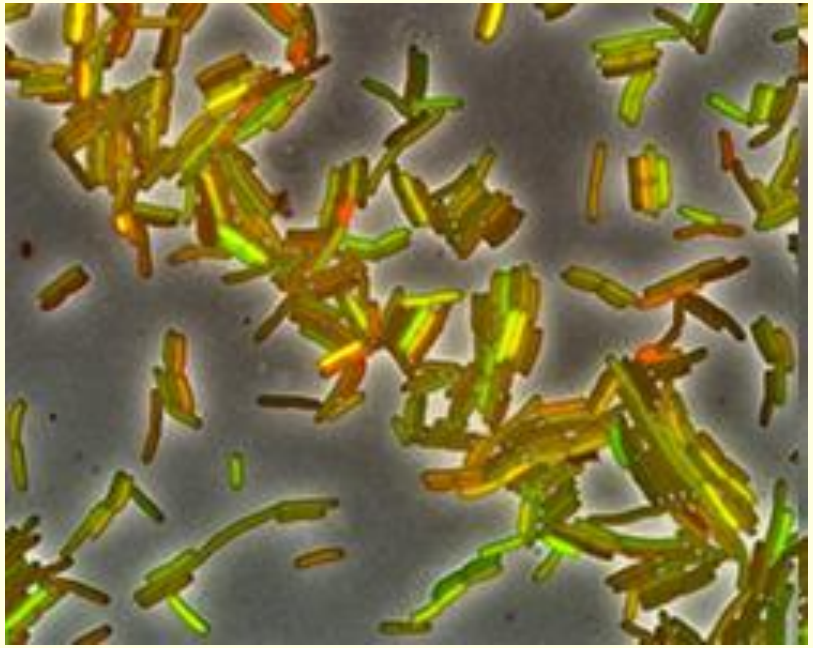
- Rate equations – Extended Set

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

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

It's a noisy business!

(McAdams & Arkin, 1999)



From Michael Elowitz, Science (2002)

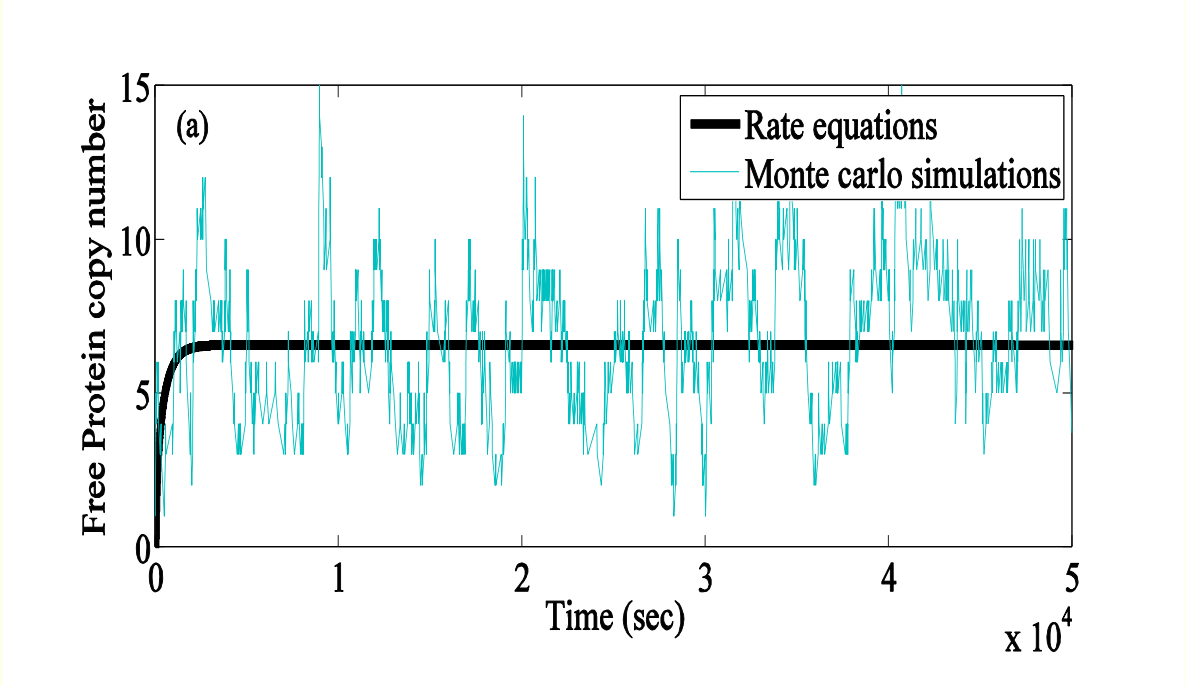
The Auto-repressor

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

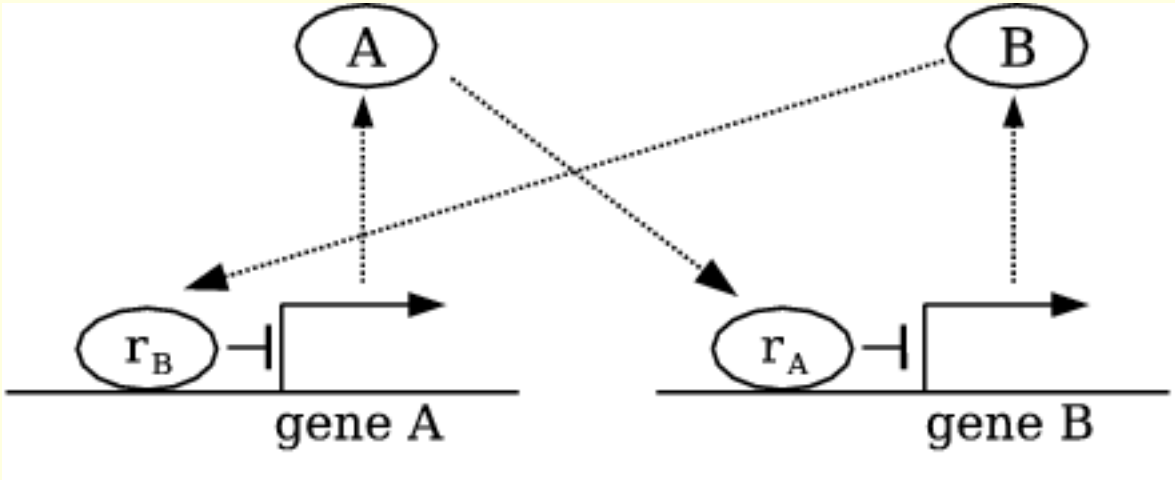
The Master Equation

$$\frac{d}{dt}P(N_A,N_r) = g(1-N_r)[P(N_A-1,N_r)-P(N_A,N_r)]$$
$$+d[(N_A+1)P(N_A+1,N_r)-N_AP(N_A,N_r)]$$
$$+b[N_r(N_A+1)P(N_A+1,N_r-1)-(1-N_r)N_AP(N_A,N_r)]$$
$$+u[(N_r+1)P(N_A-1,N_r+1)-N_rP(N_A,N_r)]$$

The Auto-repressor



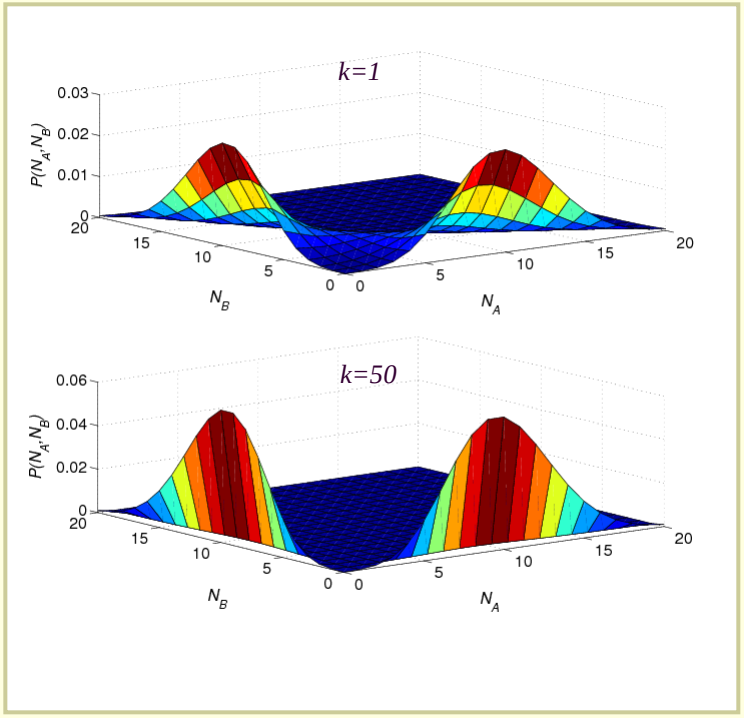
The Genetic Switch



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

Bistability

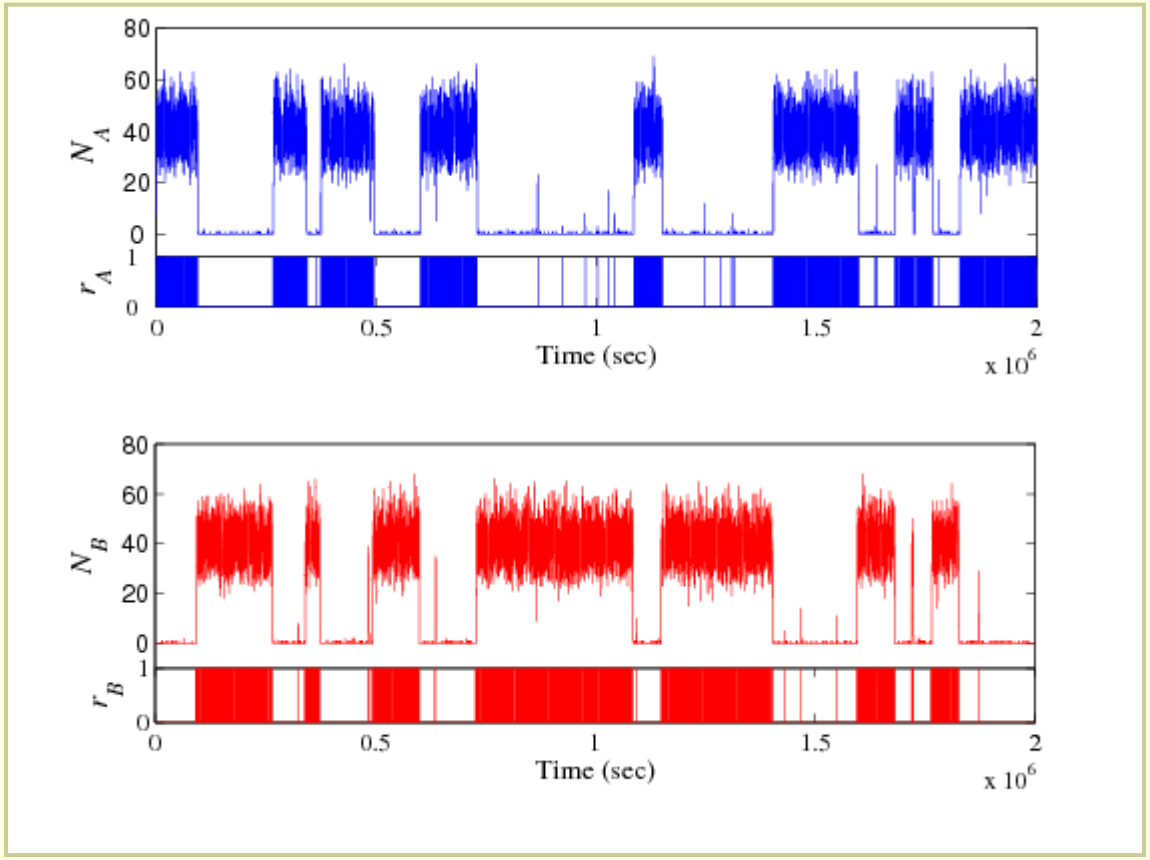
- The probability distribution is composed of two peaks
- The separation between these peaks determines the quality of the switch



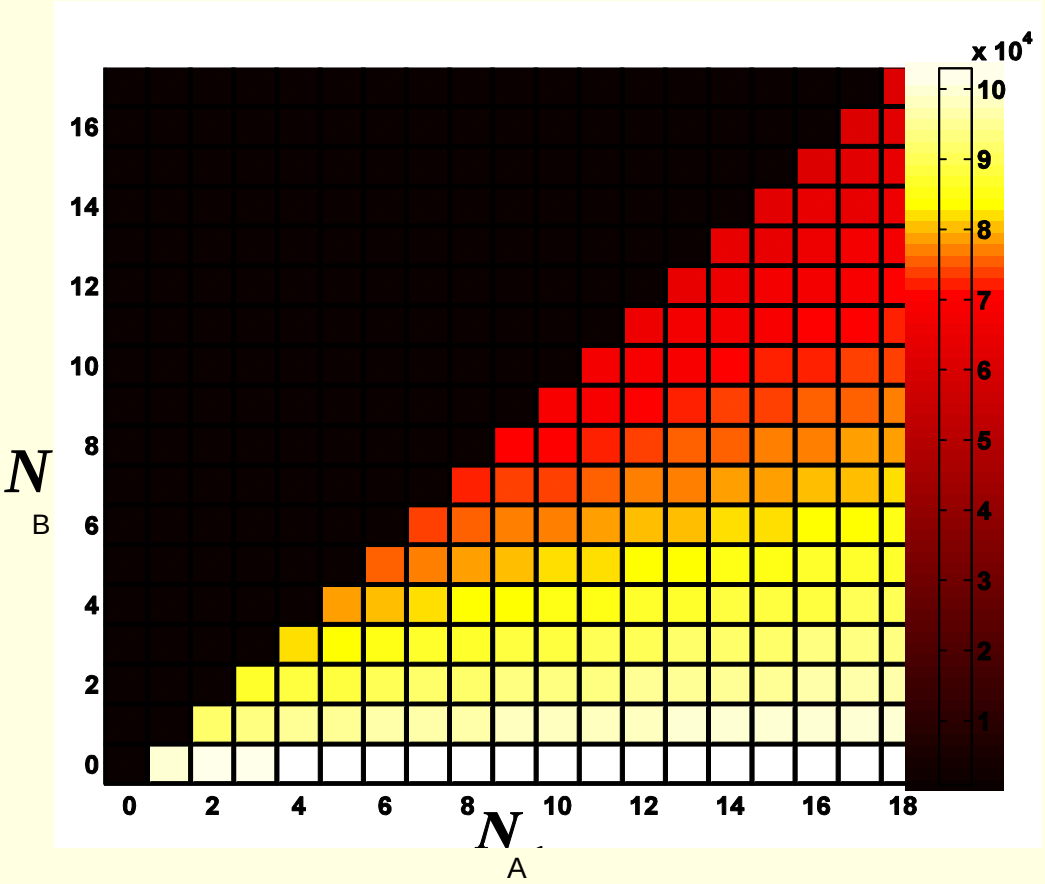
Lipshtat, Loinger, Balaban and Biham, Phys. Rev. Lett. 96, 188101 (2006)

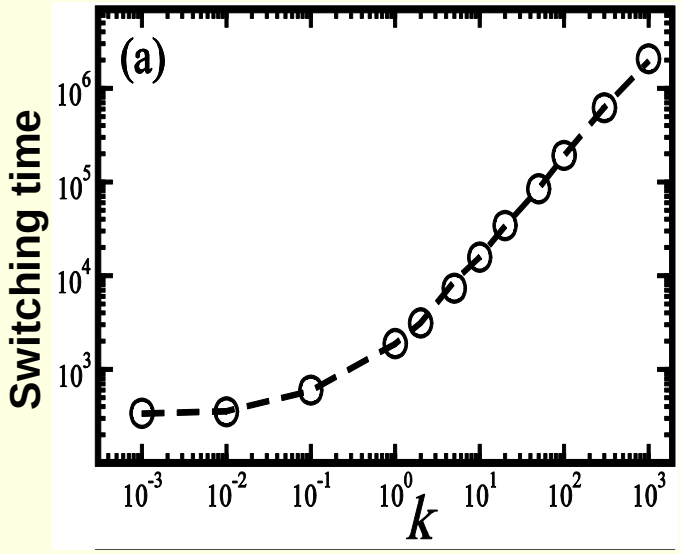
Lipshtat, Loinger, Balaban and Biham, Phys. Rev. E 75, 021904 (2007)

The Exclusive Switch



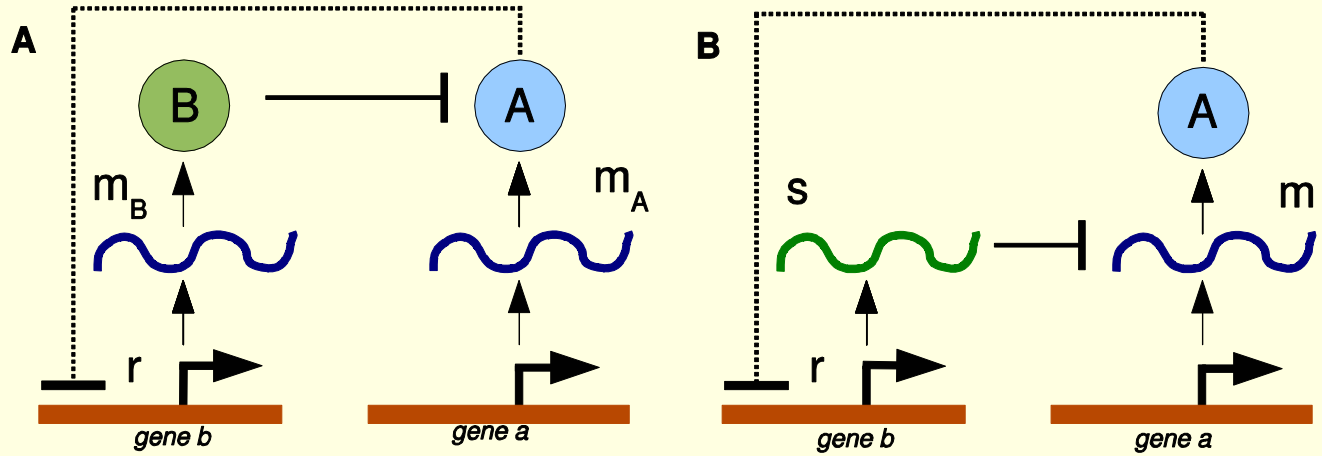
Switching Time as a first passage problem





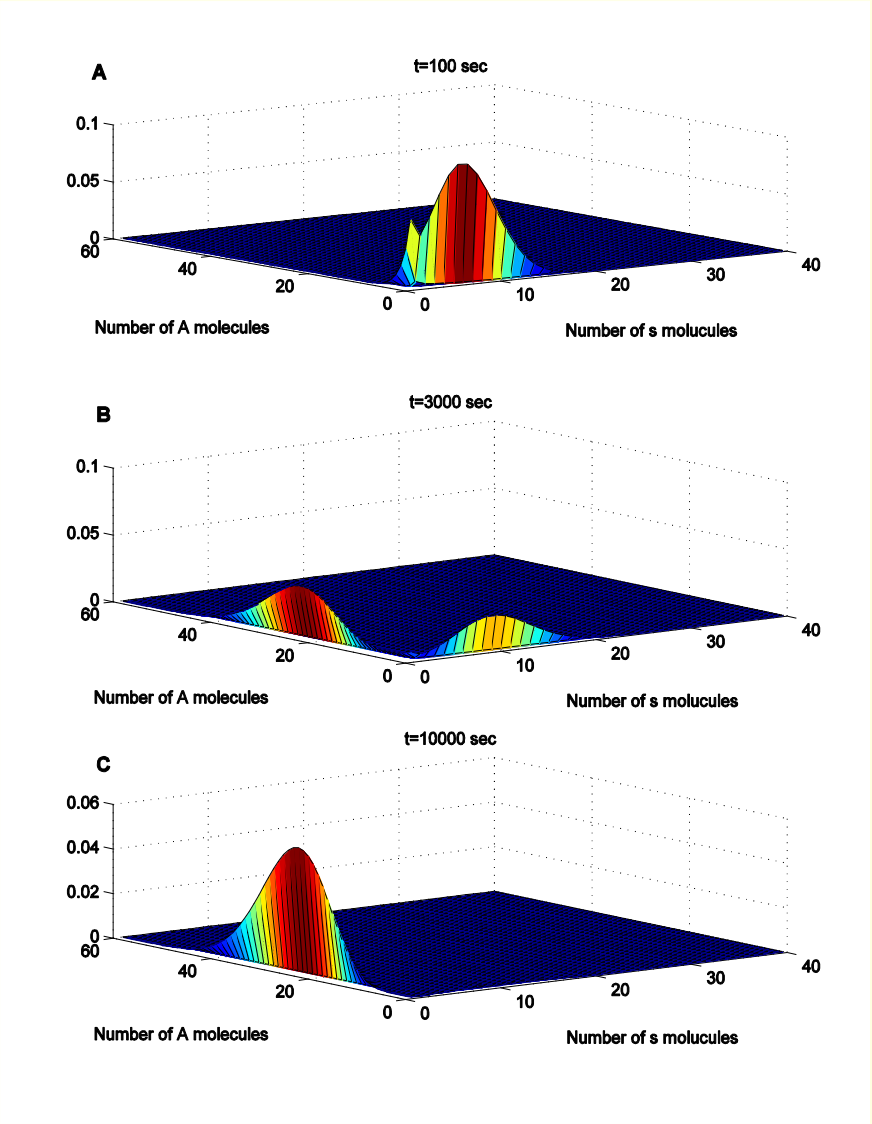
B. Barzel and O. Biham, Phys. Rev. E 78, 041919 (2008)

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?

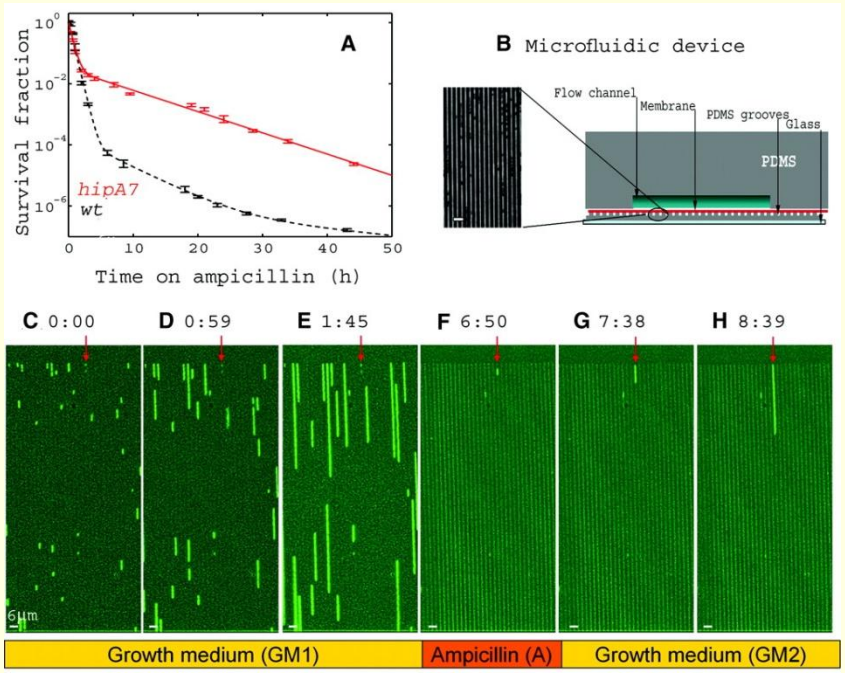
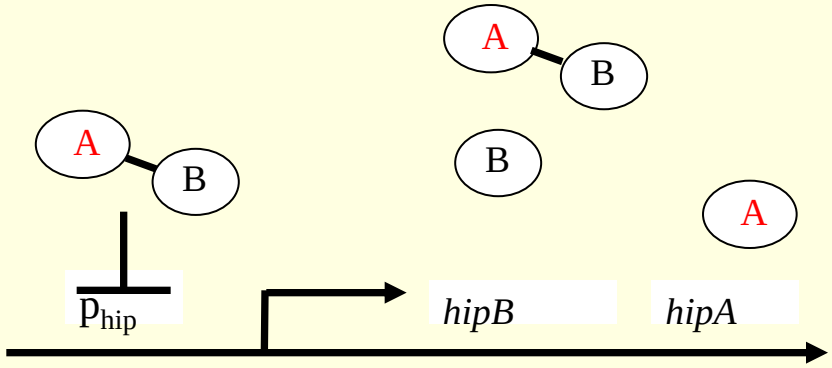


Figure taken from: N.Q Balaban et al., Science **305**, 1951 (2004)

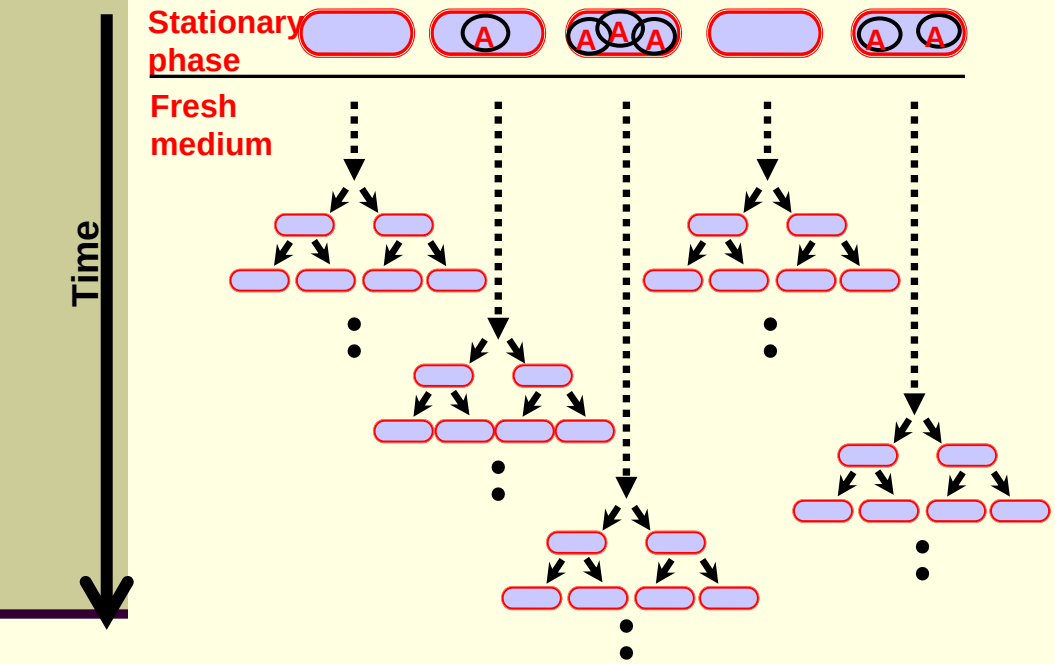
Toxin-Antitoxin Module



HipA – Stable toxin

HipB – Unstable Antitoxin, Neutralizes HipA

Toxin-Antitoxin Module

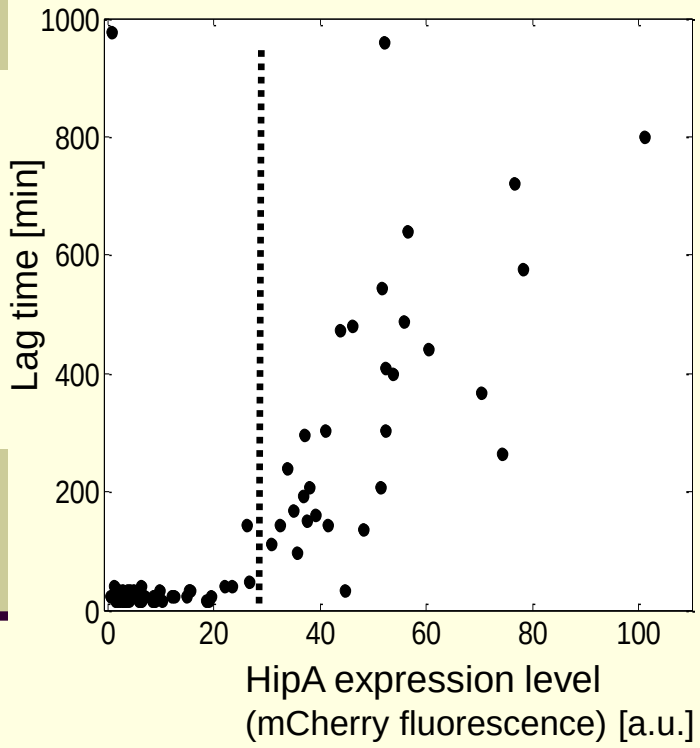


Cells that contain a large number of A proteins divide slowly and are not affected by antibiotics.

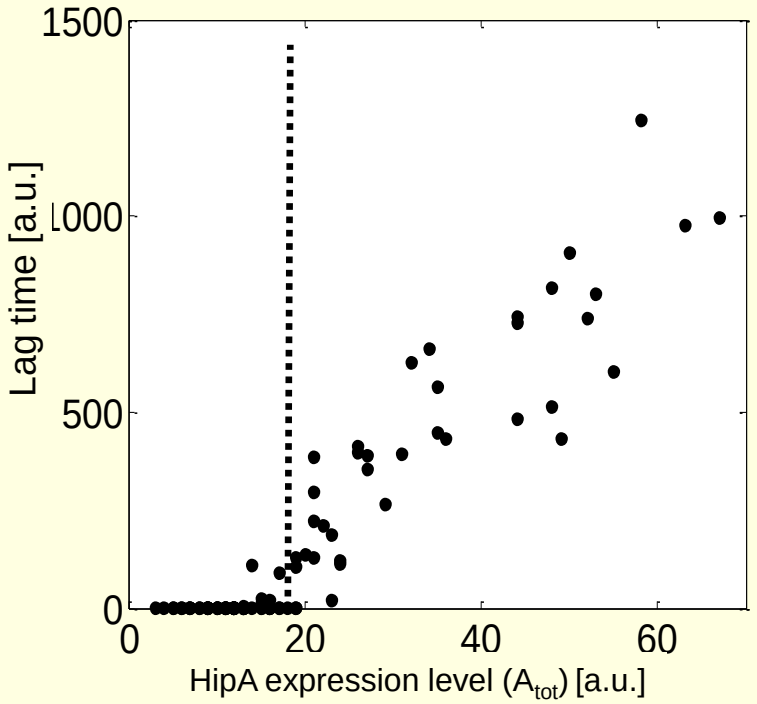
This state is characterized by a long **lag time**.

Toxin-Antitoxin Module

Experiment



Model



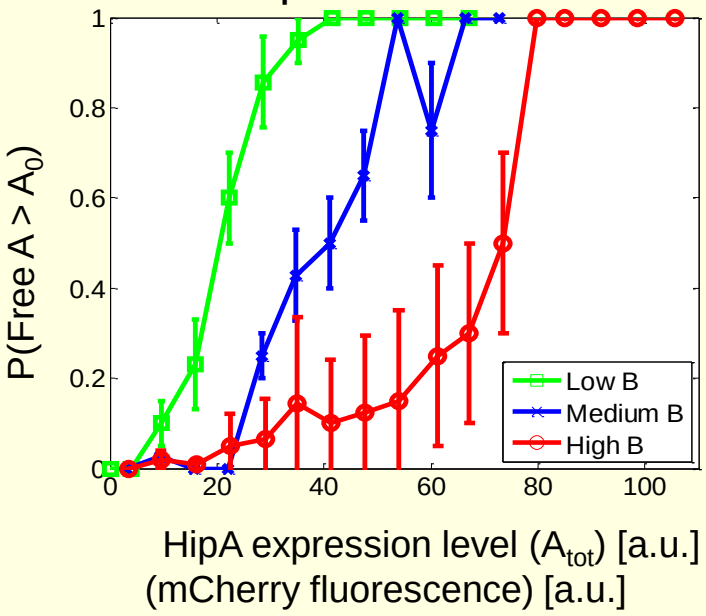
Threshold behavior

Toxin-Antitoxin Module

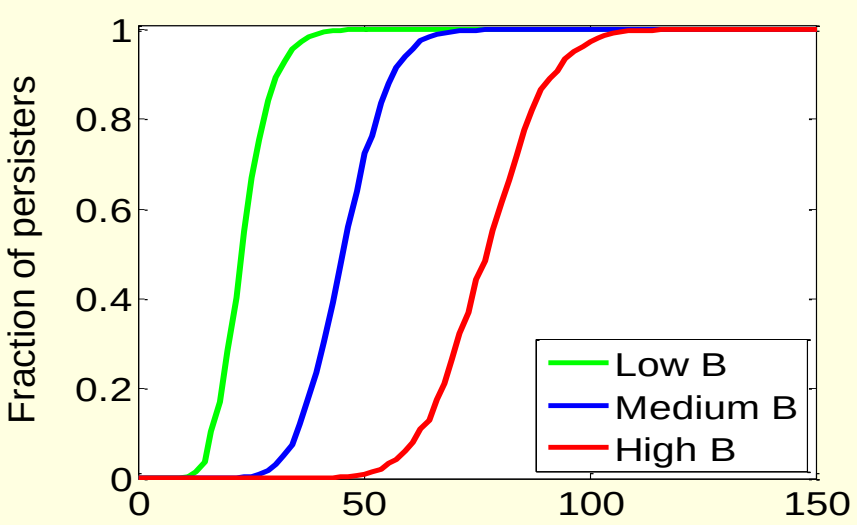
Fraction of persisters = Prob($A>A_0$) [Threshold]

Dependence on A and B production

Experiment

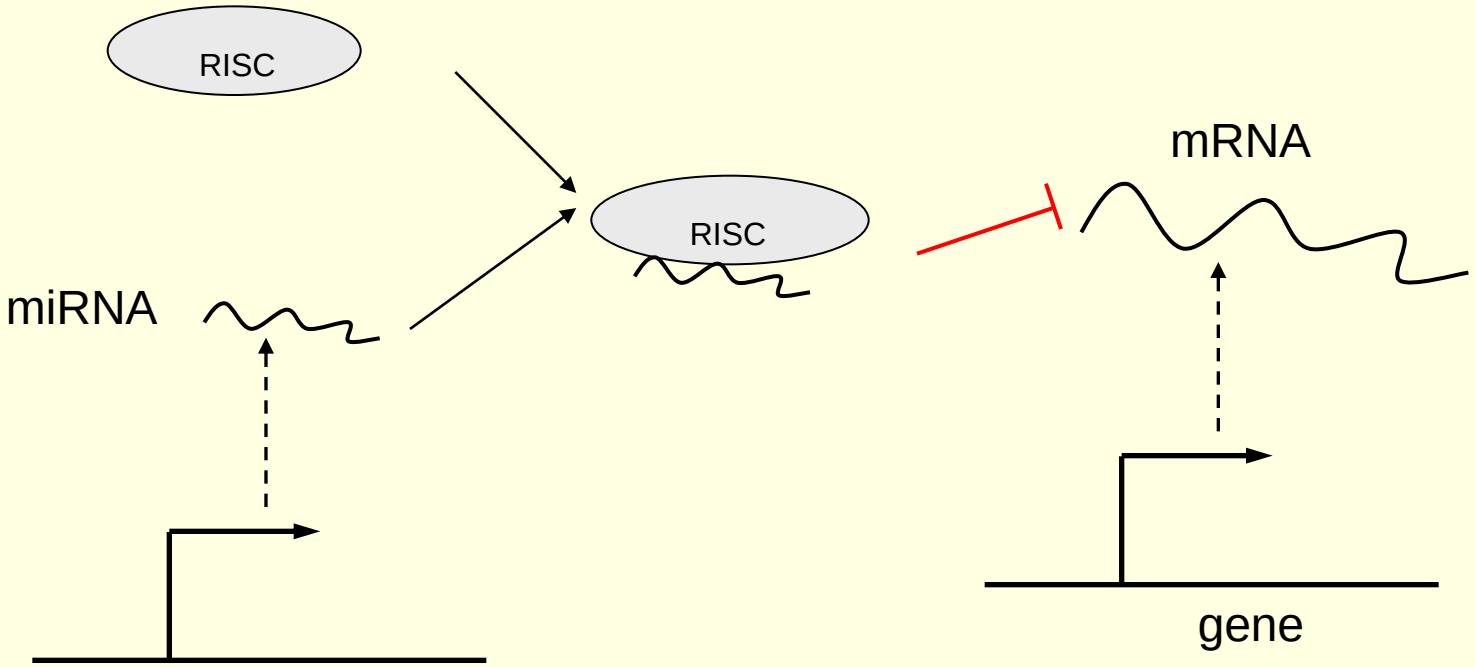


Model



E. Roten, A. Loinger, I. Ronin, I. Levin-Reizman, H. Gabay, N. Shoresh, O. Biham and N.Q. Balaban, PNAS **107**, 12541 (2010)

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