# Evolution of Gene Networks

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- Background – Mathematics of gene networks
- Evolution of (model) gene networks

Monod and Jacob (1961)

These examples should suffice to show that, by the use of the principles which they illustrate, any number of systems may be interconnected into regulatory circuits endowed with virtually any desired property. The essential point about the imaginary circuits which we examined, is that their elements are not imaginary. The particular properties of each circuit are obtained only by assuming the proper type of specific interconnection. Such assumptions are freely permitted since, as we have already seen, the specificity of induction-repression and of allosteric inhibition is not re-
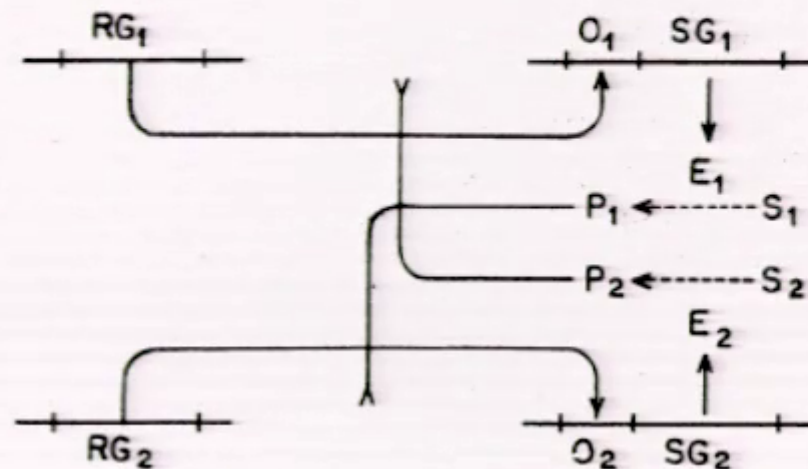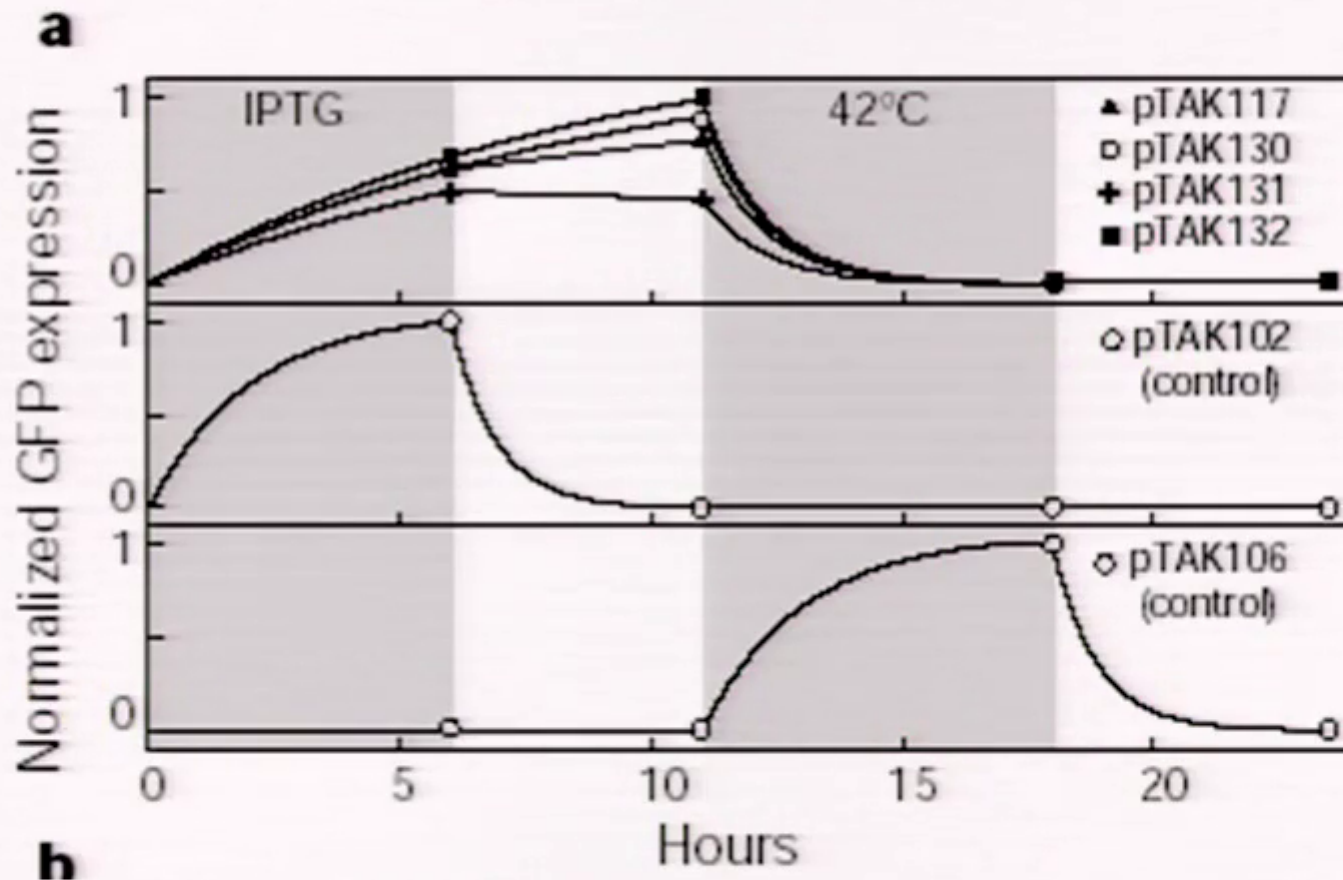
Construction of a genetic toggle switch in *Escherichia coli*
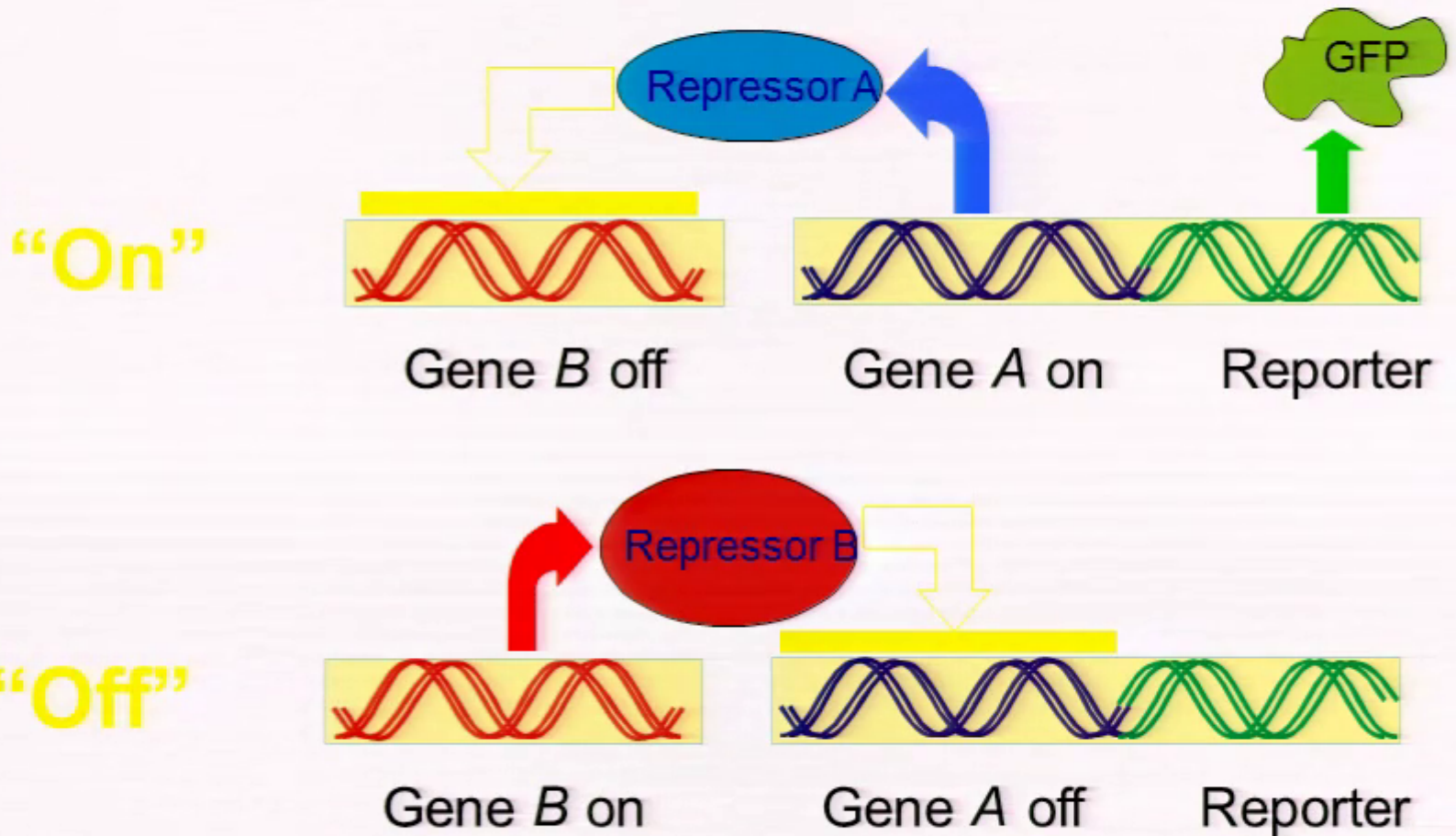
Gardner, Cantor & Collins (2000)

Two stable steady states

Gardner, Cantor & Collins (2000)
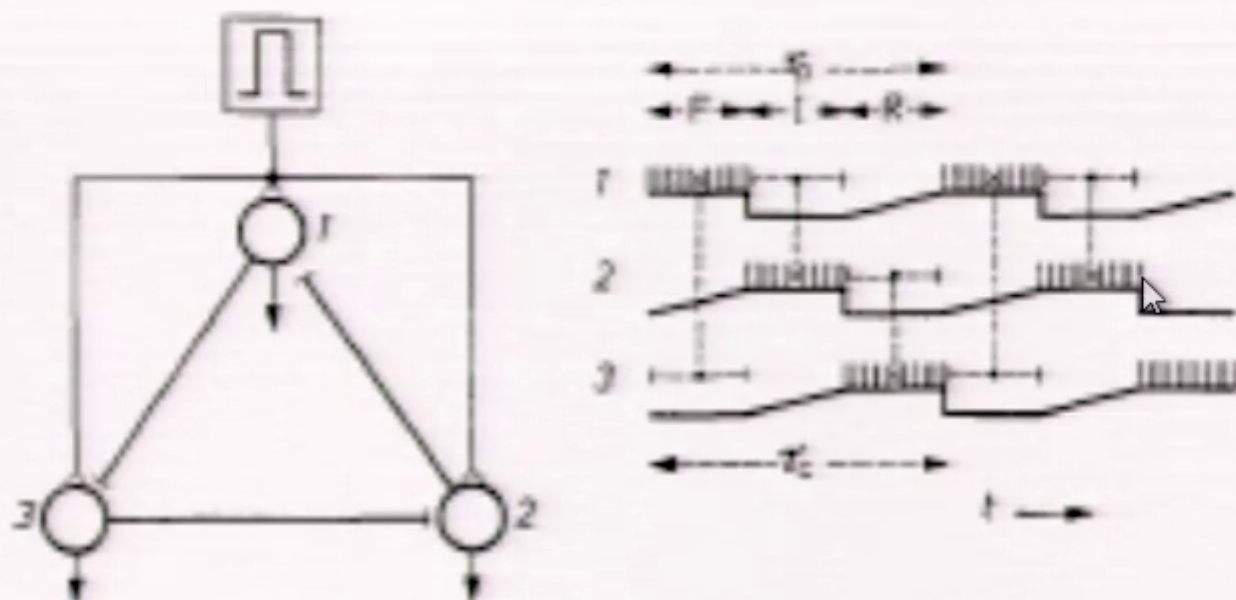
Kling and Szekely, Kybernetik, 1968

Fig. 2. Network with three neuron models. The neurons receive excitatory stimuli (fork-shaped endings) from a common source. The interconnections (terminating in bars) deliver inhibitory impulses. Arrows indicate the output to the recording device. On the output diagram (right) the membran potential changes are recorded. τ_a activity period of a neuron model, τ_c activity cycle of the network (see in text). Broken lines indicate the inhibitory action of a neuron on the other to which it is connected. (Note that in the output diagram here and in Fig. 10, R is twice as long as in the rest of Figs.)

A synthetic oscillatory network of transcriptional regulators
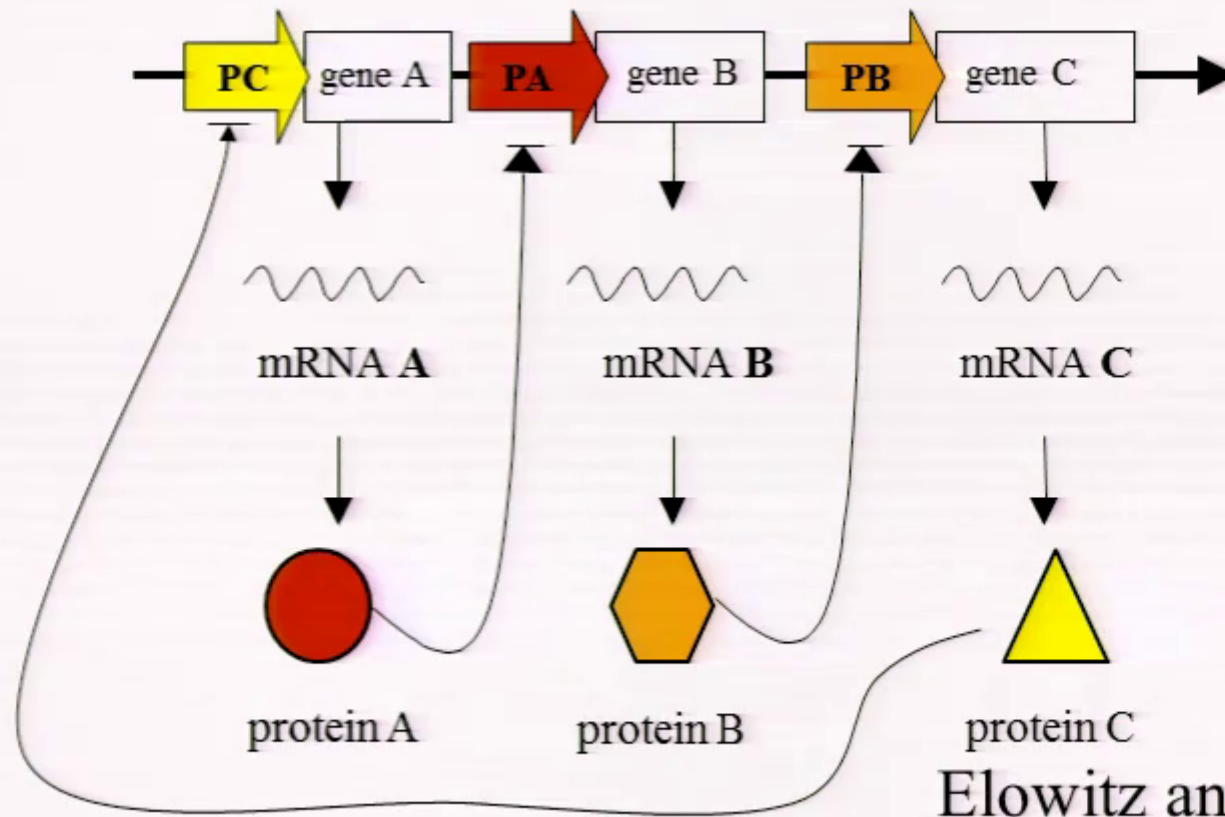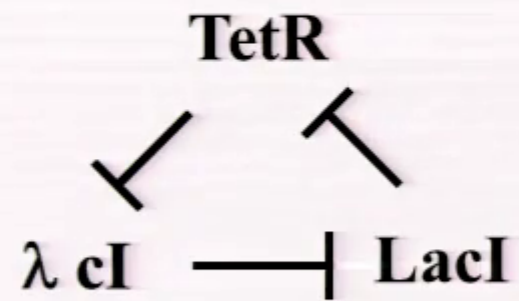

Elowitz and Leibler, 2000

Observation in Individual Cells
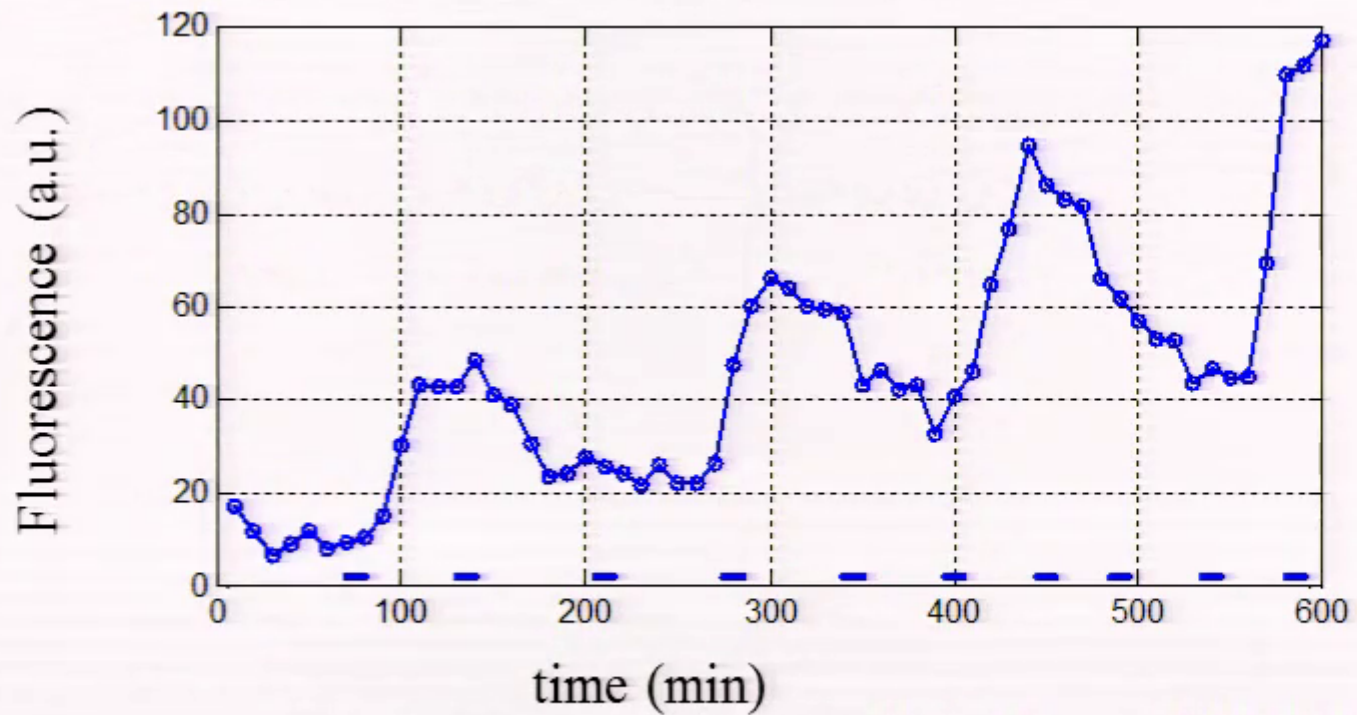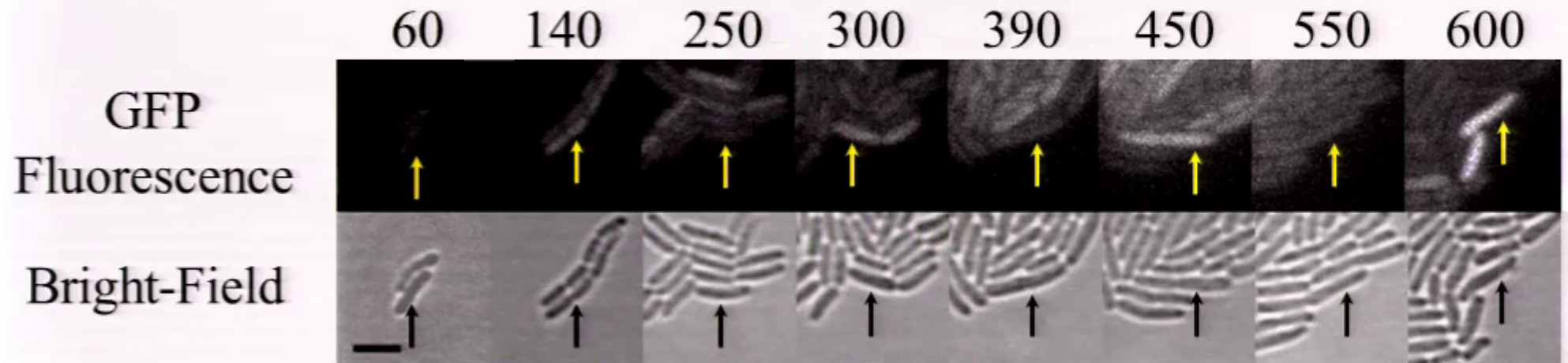
Elowitz and Leibler, 2000

The logical analysis of continuous, non-linear biochemical control networks
(Glass and Kauffman, JTB 1973)

We propose a mapping to study the qualitative properties of continuous biochemical control networks which are invariant to the parameters used to describe the networks but depend only on the logical structure of the networks. For the networks, we are able to place a lower limit on the number of steady states and strong restrictions on the phase relations between components on cycles and transients. The logical structure and the dynamical behavior for a number of simple systems of biological interest, the feedback (predator-prey) oscillator, the bistable switch, the phase dependent switch, are discussed. We discuss the possibility that these techniques may be extended to study the dynamics of large many component systems
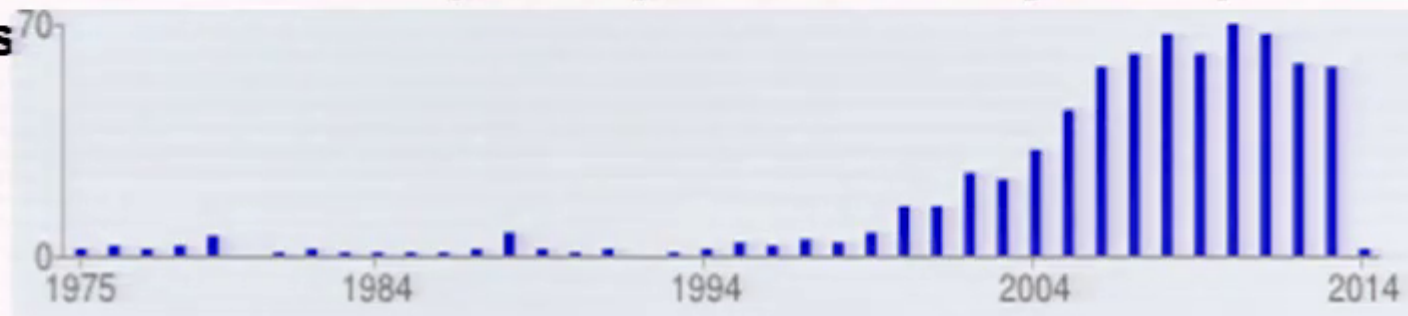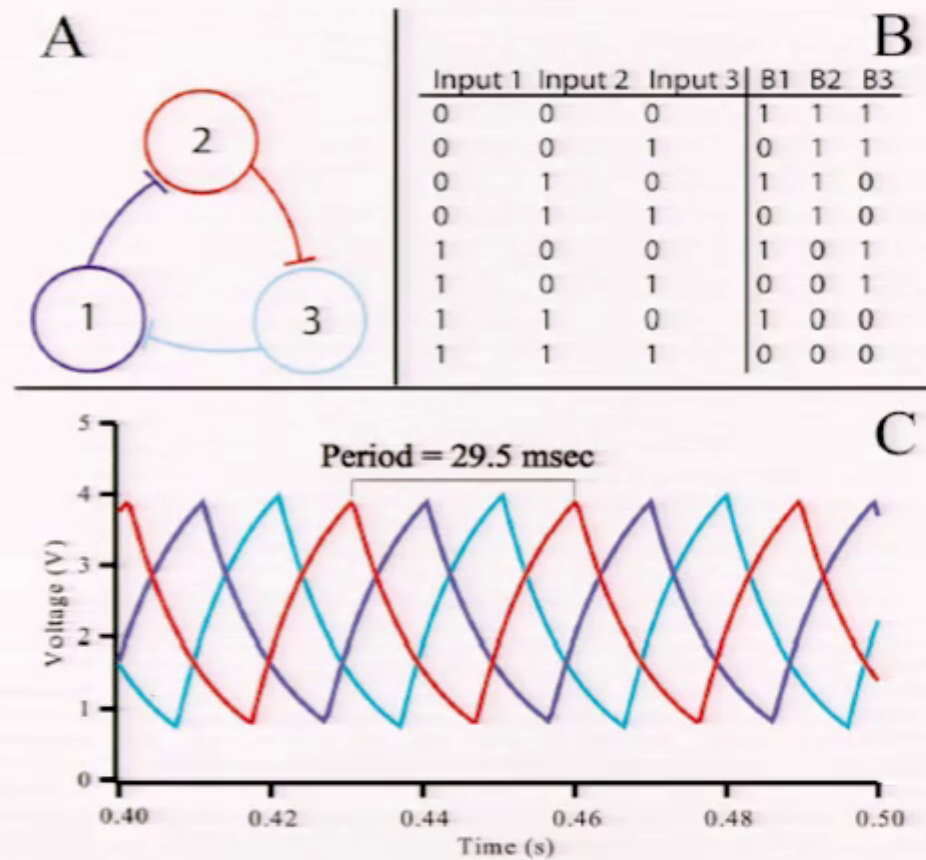
Architecture of the human regulatory network derived from ENCODE data

Transcription factors bind in a combinatorial fashion to specify the on-and-off states of genes; the ensemble of these binding events forms a regulatory network, constituting the wiring diagram for a cell. To examine the principles of the human transcriptional regulatory network, we determined the genomic binding information of 119 transcription-related factors in over 450 distinct experiments. We found the combinatorial, co-association of

a Proximal regulatory edges

Distal regulatory edges

b

TFs

miRNAs

Decreasing out-degree for transcription factors and miRNAs

Gerstein et al. Nature, Sept 6 2012

The Repressilator

A

B

Input 1	Input 2	Input 3	B1	B2	B3
0	0	0	1	1	1
0	0	1	0	1	1
0	1	0	1	1	0
0	1	1	0	1	0
1	0	0	1	0	1
1	0	1	0	0	1
1	1	0	1	0	0
1	1	1	0	0	0

C

Period = 29.5 msec

Voltage (V)

Time (s)

The Hypercube Representation

Input 1	Input 2	Input 3	B1	B2	B3
0	0	0	1	1	1
0	0	1	0	1	1
0	1	0	1	1	0
0	1	1	0	1	0
1	0	0	1	0	1
1	0	1	0	0	1
1	1	0	1	0	0
1	1	1	0	0	0
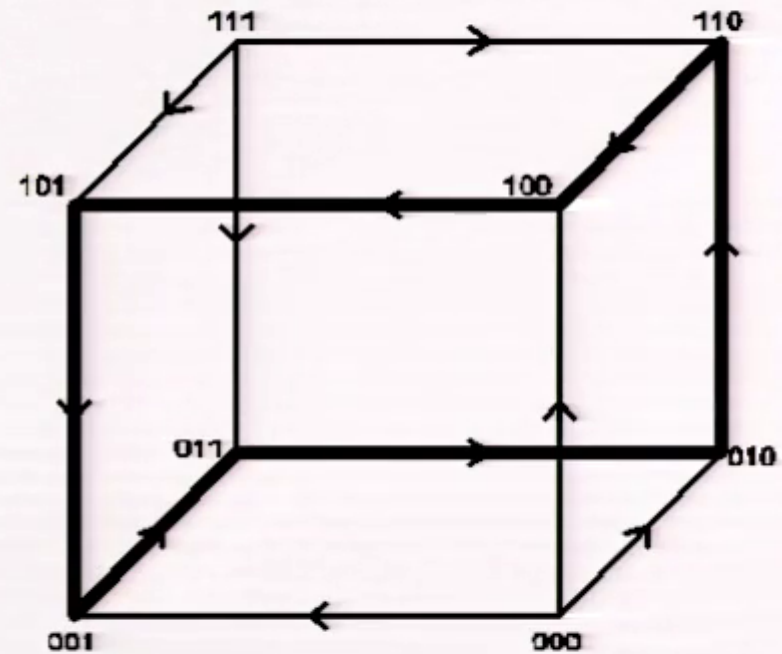
A differential equation

$$\frac{dx_i}{dt} = B_i(\mathbf{X}) - x_i, \quad i = 1, N,$$

where $X_i = 0$, if $x_i < \theta_i$ and $X_i = 1$ if $x_i \geq \theta_i$.
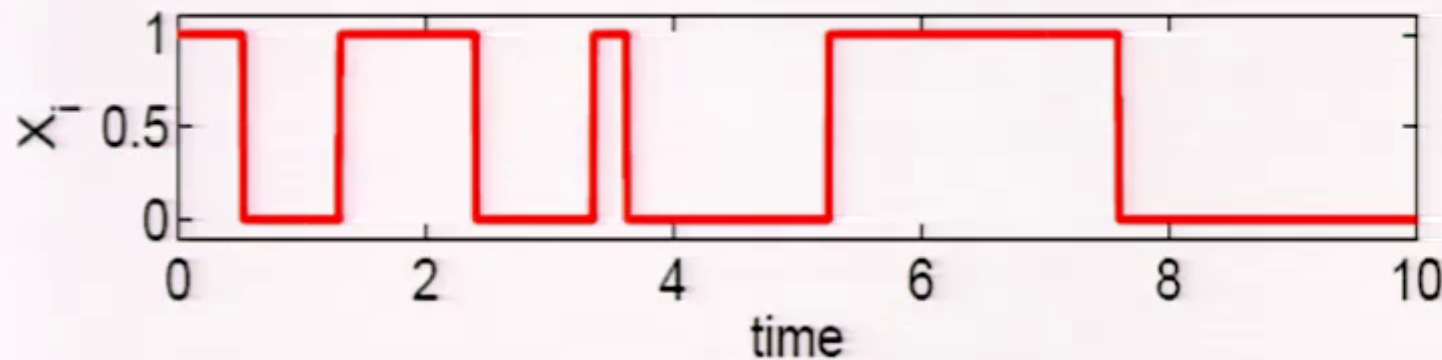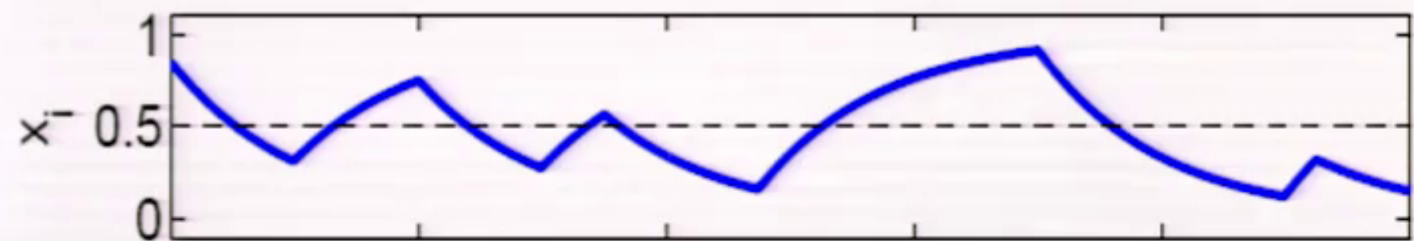
"on and off states of the genes"

Glass, Kauffman, Pasternack, 1970s

Rationale for the equation

- A method was needed to relate the qualitative properties of networks (connectivity, interactions) to the qualitative properties of the dynamics

- The equations allow detailed mathematical analysis. Discrete math problems (classification), nonlinear dynamics (proof of limit cycles and chaos in high dimensions)

The Hypercube Representation for Dynamics (N genes)

- 2^N vertices – each vertex represents an orthant of phase space

- $N \times 2^{N-1}$ edges – each edge represents a transition between neighboring orthants

- For networks with no self-input, there is a corresponding directed N-cube in which each edge is oriented in a unique orientation

- The representation is also valid for networks with asynchronous/stochastic updating

Main Problems

- Given a directed graph on a hypercube, what are the restrictions on dynamics in the associated differential equations?

- Given observed dynamics what are the equations?

- Can we evolve equations with specific dynamics?

Properties of Networks Based on Logical Structure

- "Extremal" stable fixed points
- Robust trajectories and limit cycles
- Necessary conditions for limit cycles and chaos
- Analysis of chaos in some networks
- Upper limit on topological entropy

Evolution of gene networks

The number of different networks in N dimensions

N	number	lower bound
2	4	2.0
3	112	85.333
4	11,223,994	11,184,810.666
5	$3.14824455\ldots \times 10^{20}$	$3.14824432\ldots \times 10^{20}$

$$number > \frac{2^N \times 2^{N-1}}{N!2^N}$$

Glass, 1975; Edwards and Glass, 2000

Evolving Rare Dynamics

- Long cycle

- Chaotic dynamics - increased complexity using topological entropy as a measure of complexity

Distribution of Cycle Lengths in Electronic Circuit (300 random circuits with stable oscillations)
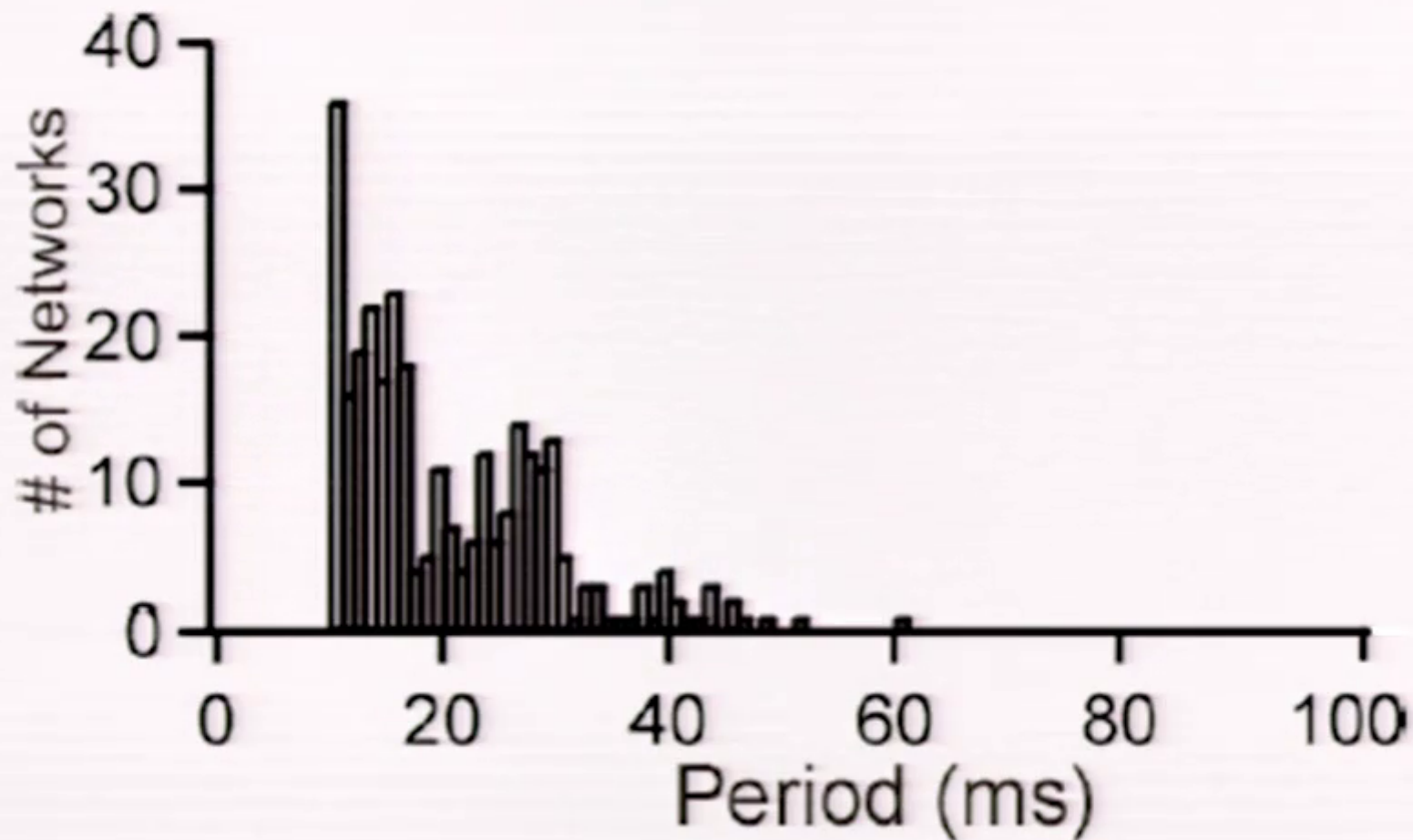
Choose a target period of 80 ms
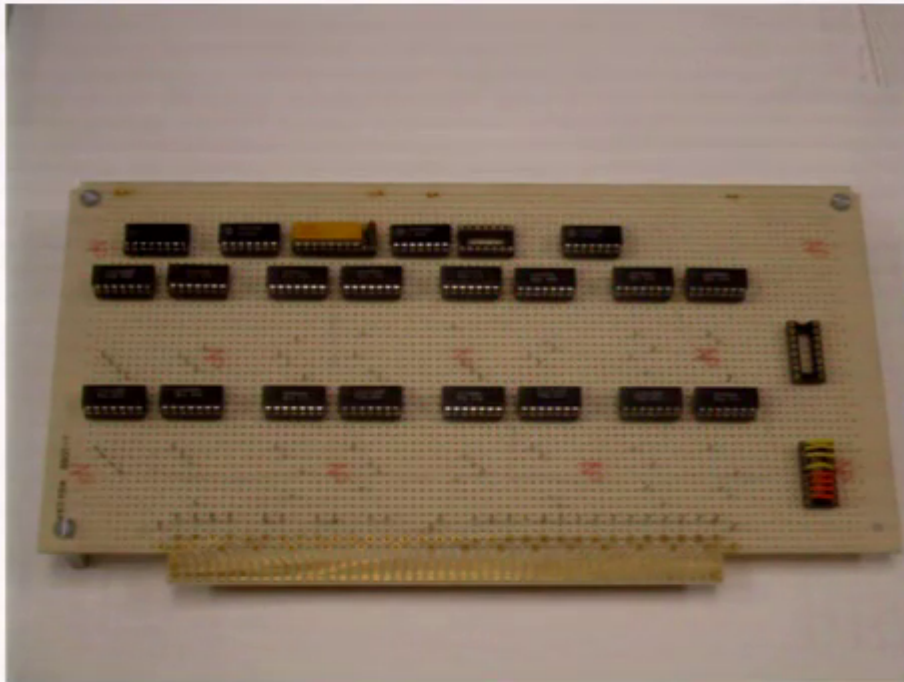
An Evolvable Circuit
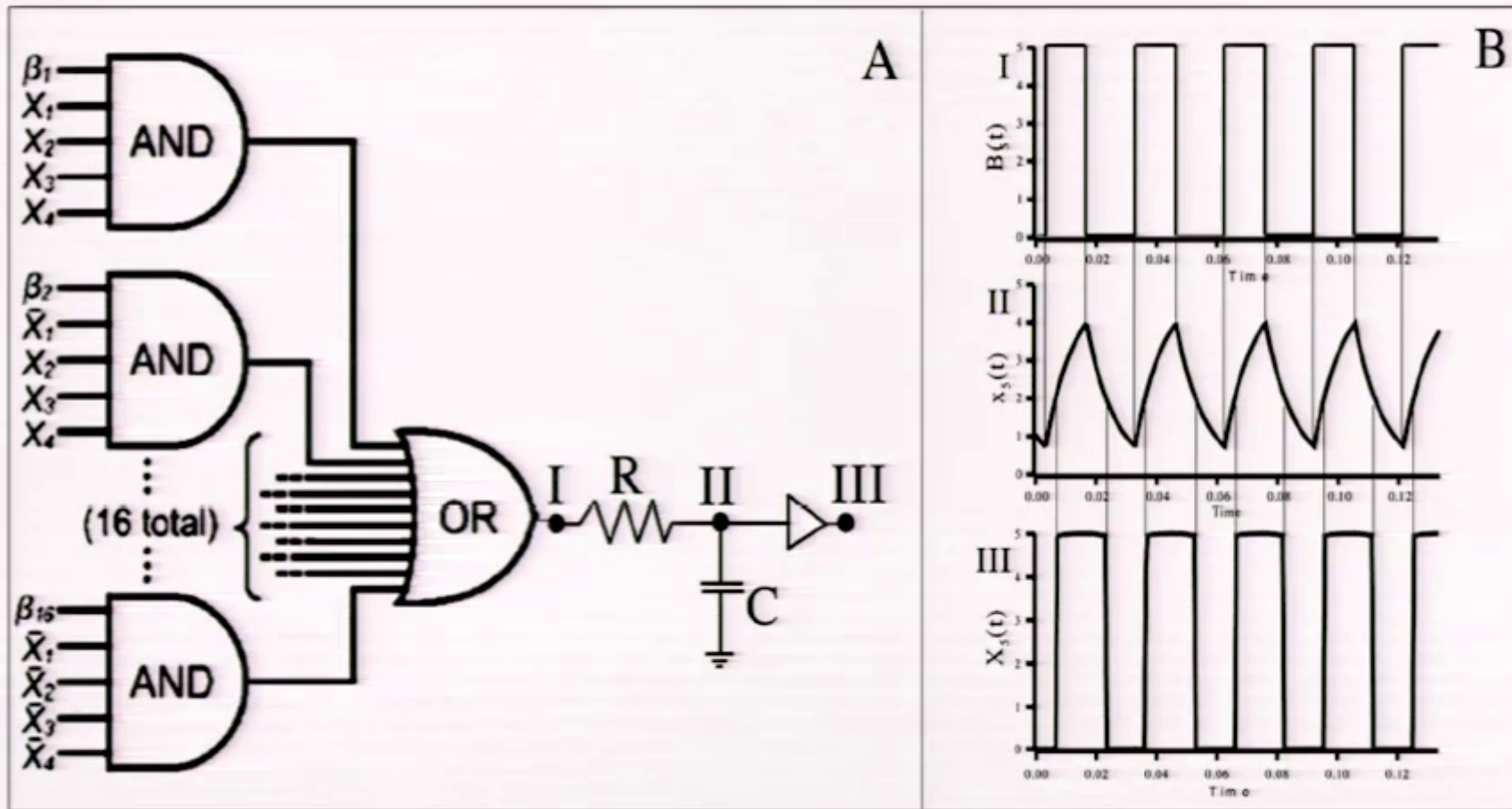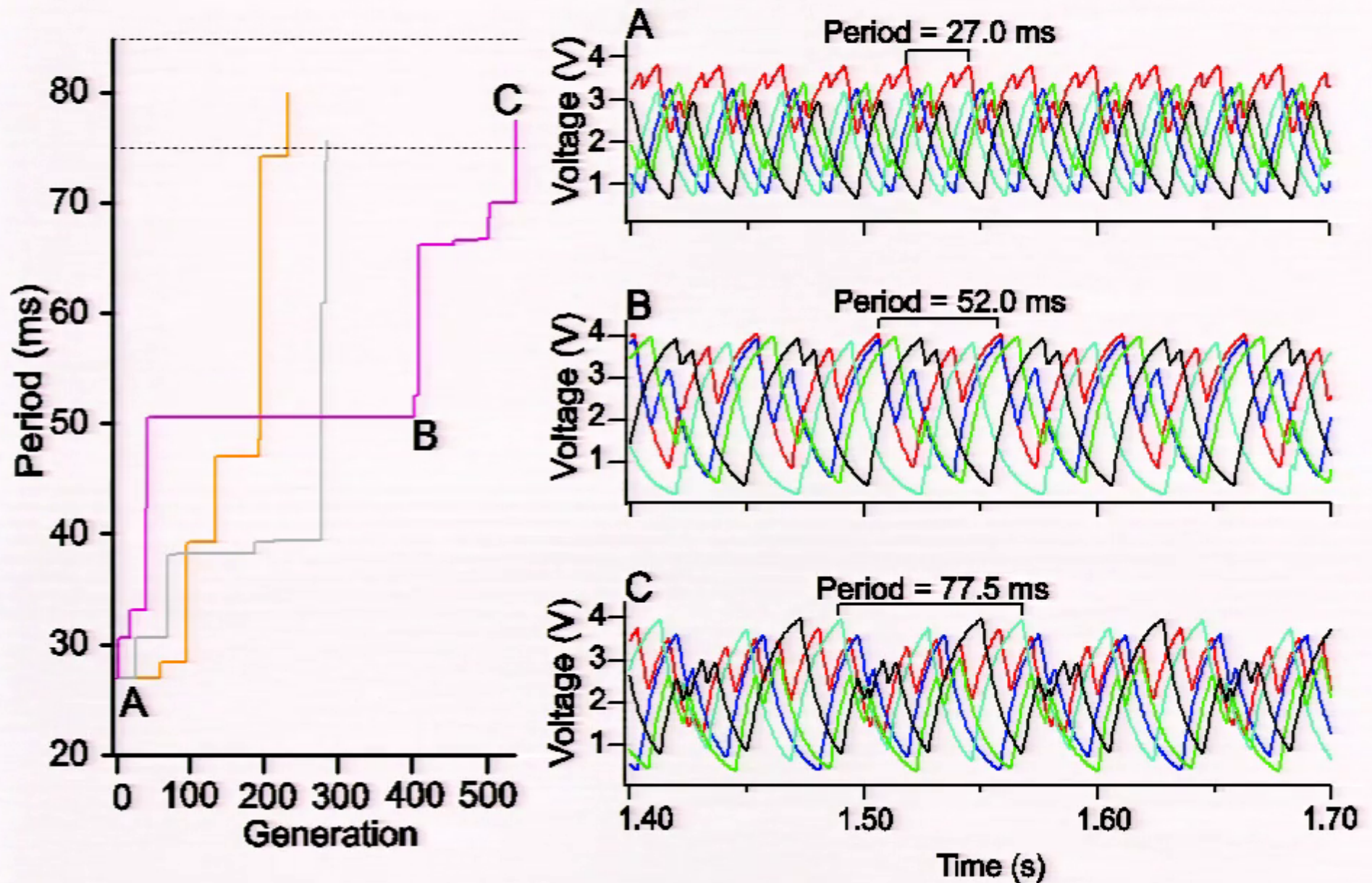

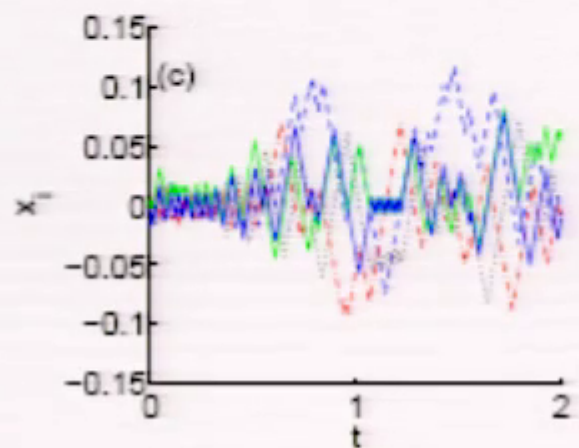(J. Mason, J. Collins, P. Linsay, LG, Chaos, 2004)
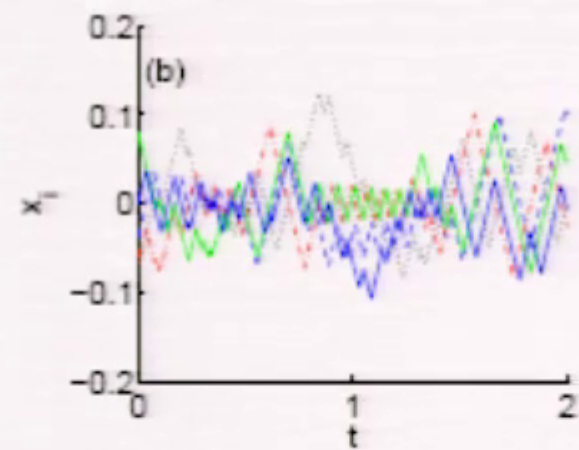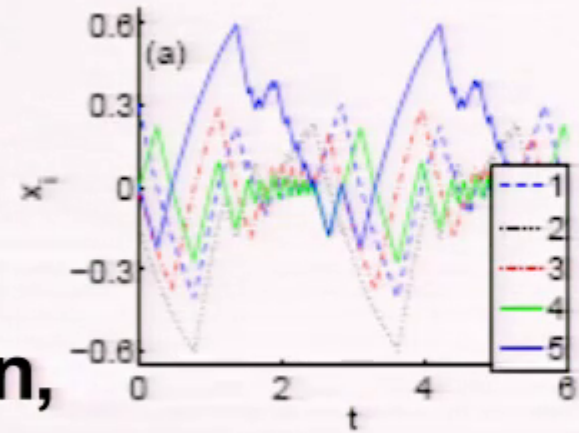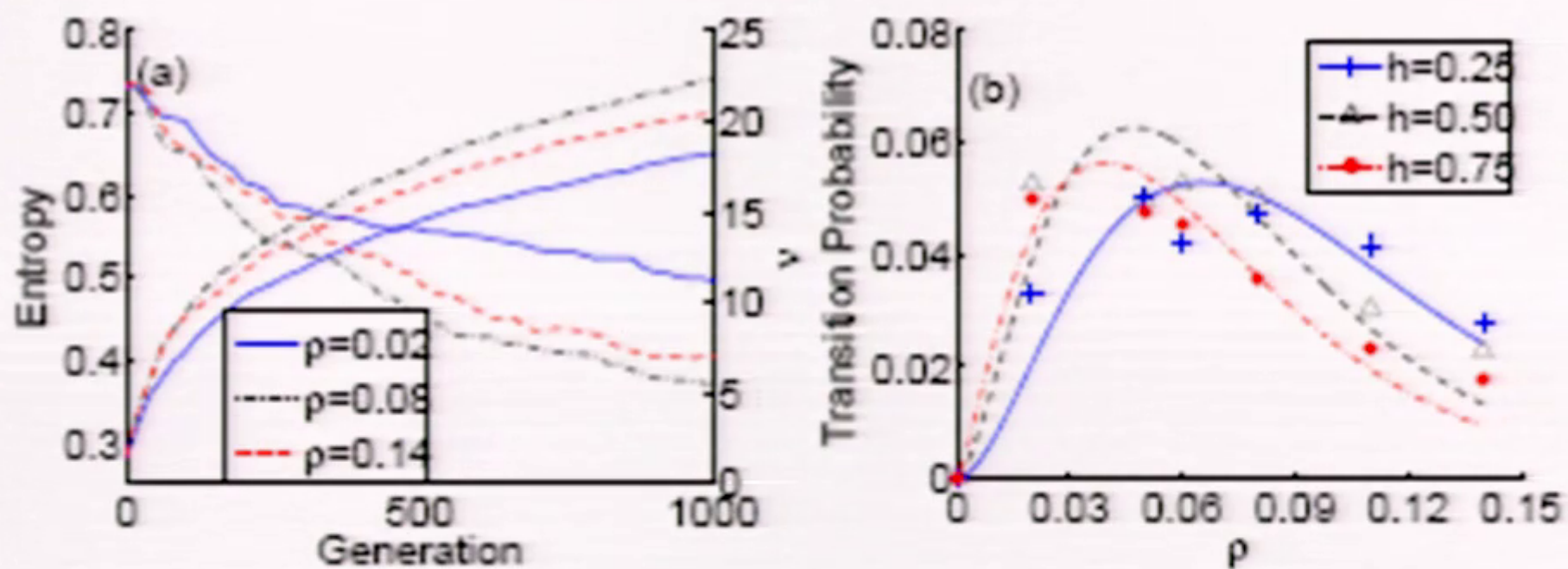
The Hybrid Analog-Digital Circuit
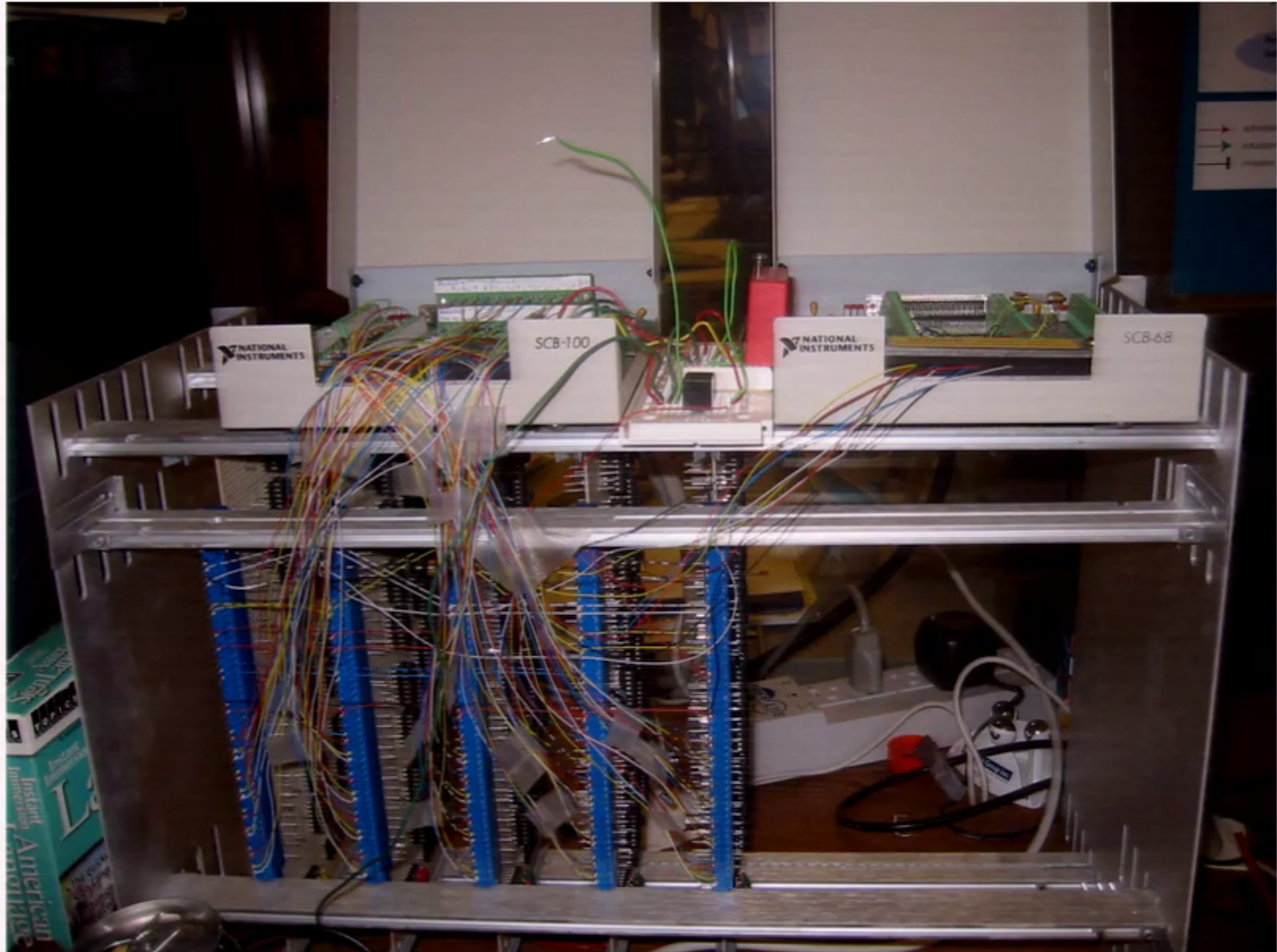
Circuit Elements
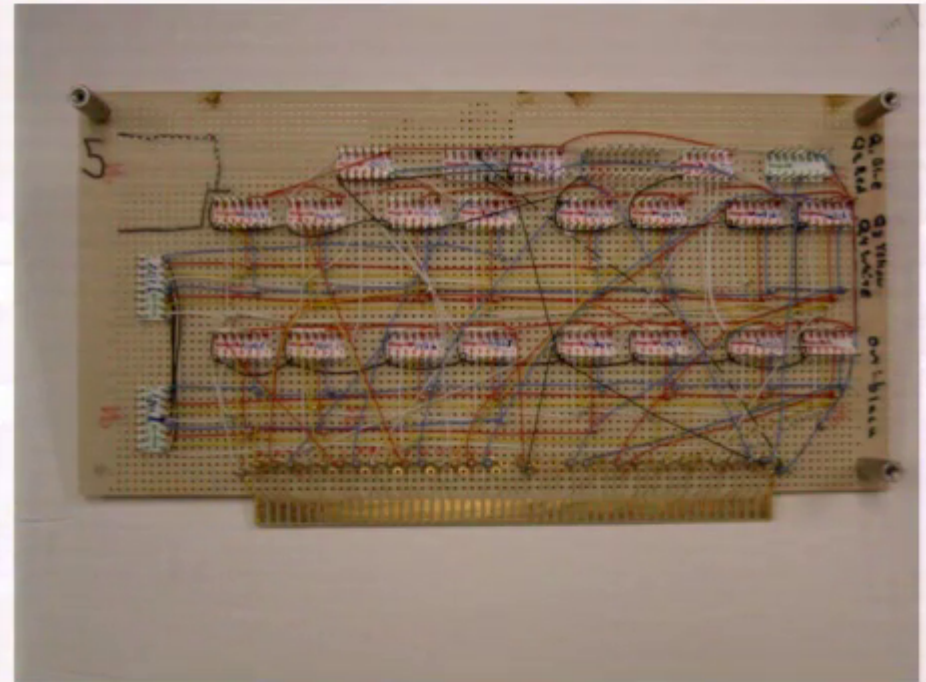
Sample Evolutionary Run

Evolution of complex dynamics. Wilds, Kauffman, Glass Chaos (2008)

Evolution and mutation rate

Robustness and evolution in the natural systems – insect development

- **The segment polarity network is a robust developmental module.** von Dassow, Meir, Munro, Odell (Nature 2000)

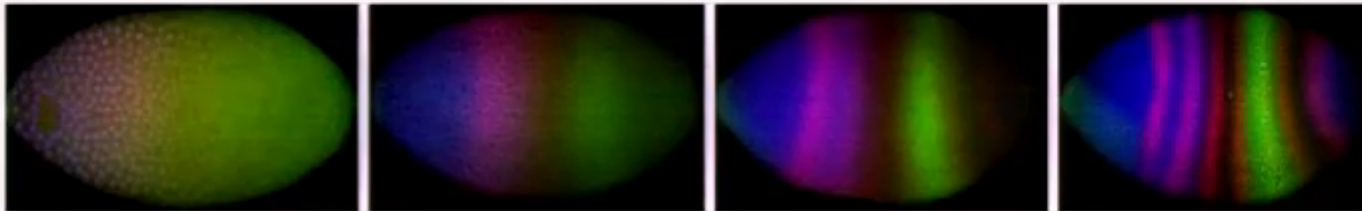   Mathematical models are insensitive to changes in parameters.

Gene expression in Drosophila

Perkins, Jaeger, Reinitz, Glass

PLOS Computational Biology 2006

Dynamics of gene expression

- Gene expression changes over time

- **Problem:** Given time-series expression data, learn a dynamical model of gene expression, explaining expression in terms of regulatory relationships between genes.

  - Which genes regulate which?

  - How do regulatory influences combine to determine gene activity?

Idea: combine supervised learning with "simulate & optimize"

$$\frac{\partial x_i(s,t)}{\partial t} = P_i(x(s,t)) - \gamma_i x_i(s,t) + D_i \frac{\partial^2 x_i(s,t)}{\partial s^2}$$
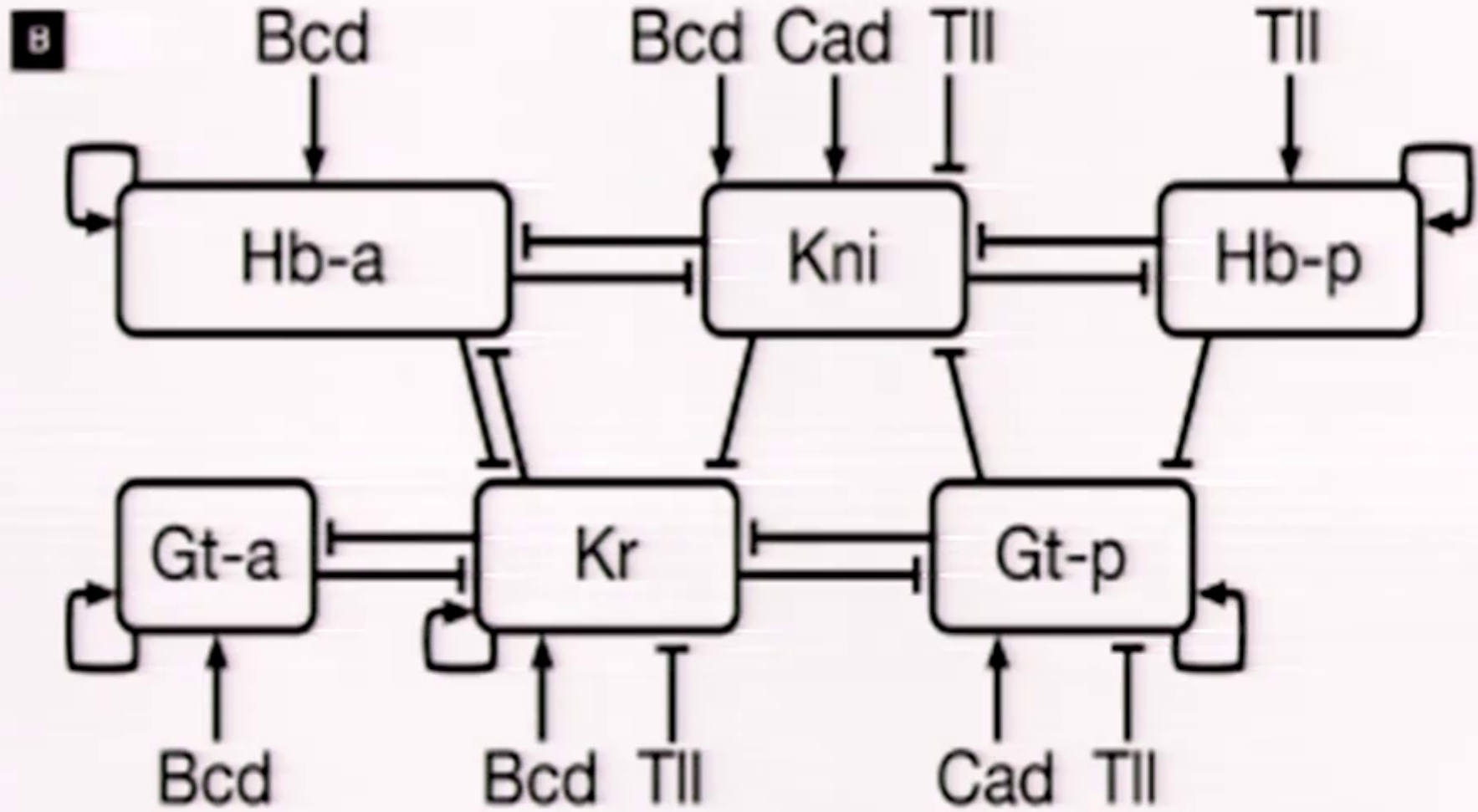
1. Estimate l.h.s. values for each i, s, t

2. Supervised learning—optimize r.h.s. parameters to fit l.h.s. values

3. Take results of step 2 as starting point for a simulate & optimize approach

(Perkins, Jaeger, Reinitz, Glass, PLOS Computational Biology 2006)
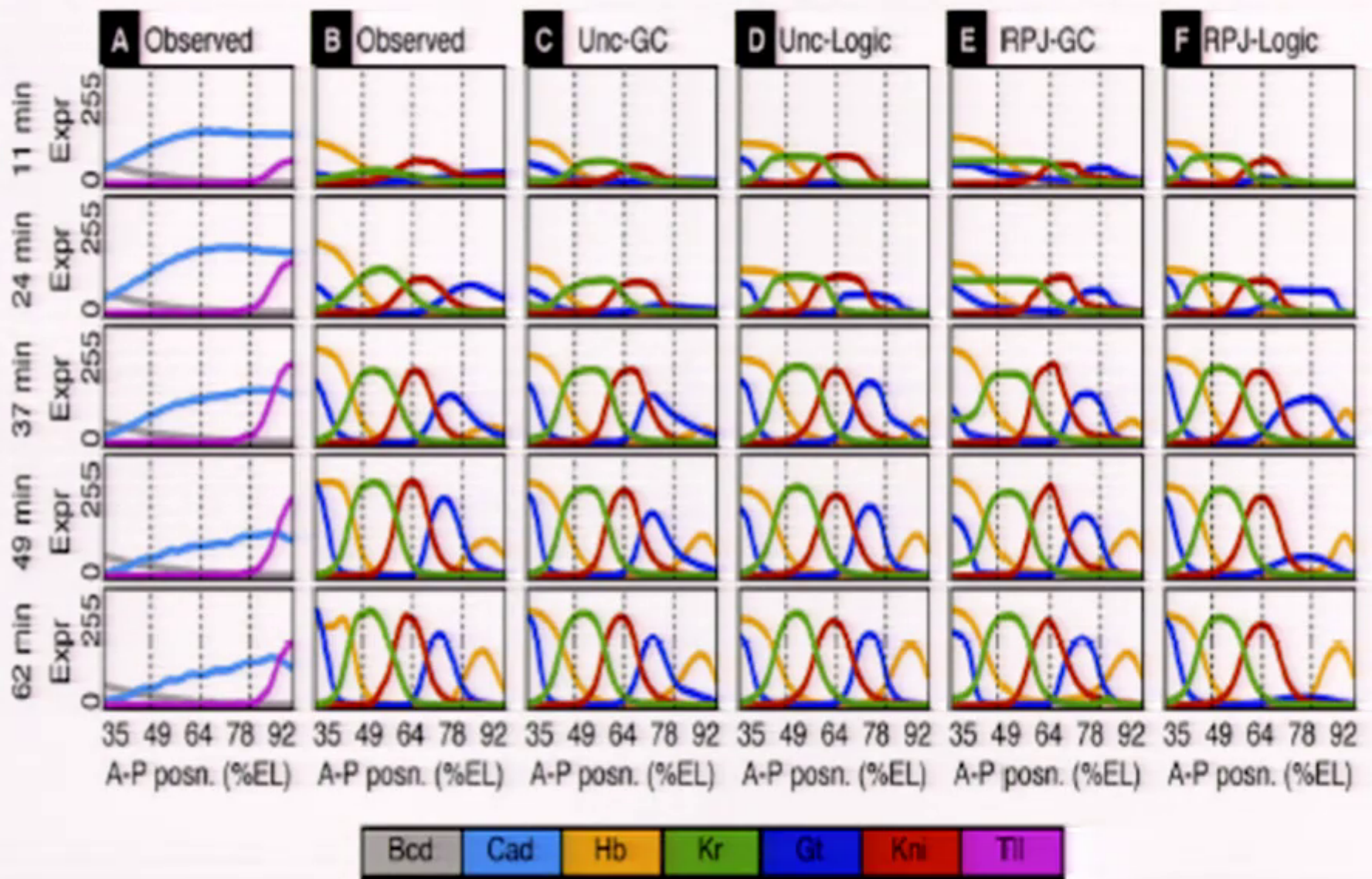
(Perkins, Jaeger, Reinitz, Glass, PLOS Computational Biology 2006)

Proposed network for gene control

Do species with similar phenotype have similar gene expression patterns?

- NOT always. Similar phenotypes in related species can be associated with different patterns of gene expression – "developmental system drift"
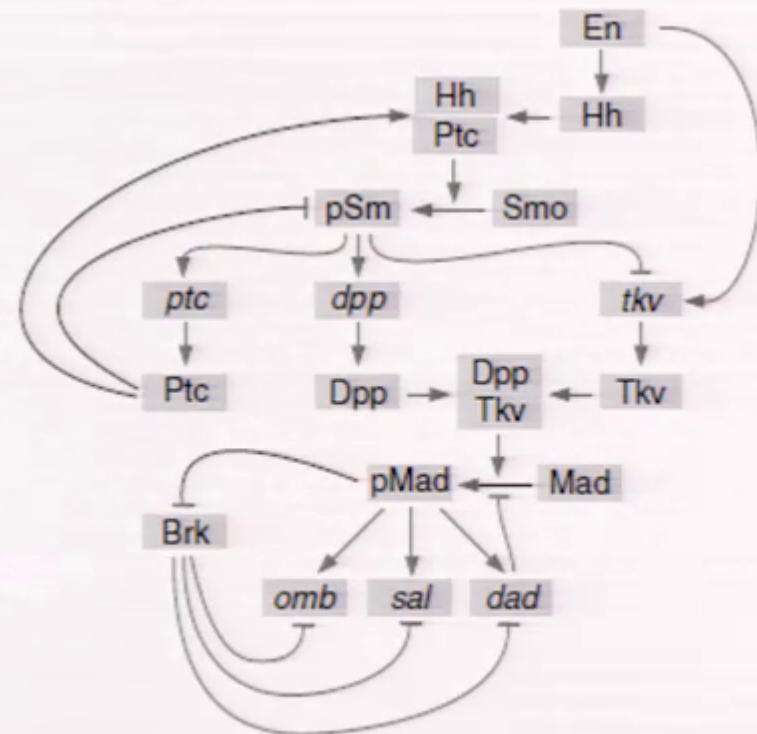
(Nahmad, Glass Abouheif, 2008)

- Problems of huge networks, huge sets of parameters, huge phase spaces can be addressed using methods that relate the underlying logical structure and dynamics of complex networks.