Dynamical Modeling in Biology: a semiotic perspective

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BIOINFO-USP

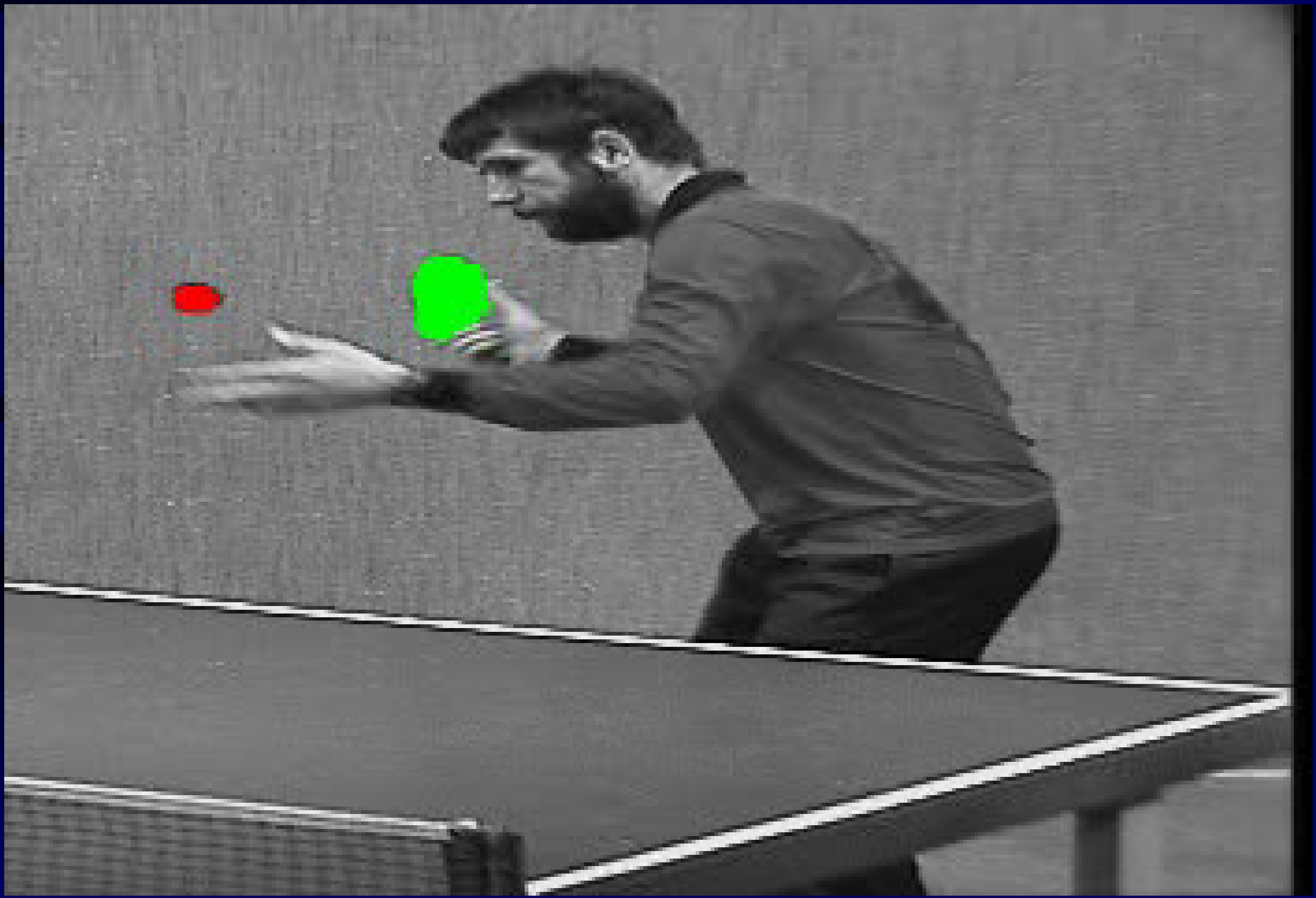
Layout

- Introduction
- Dynamical Systems
- System Families
- System Identification
- Genetic networks design
- Cell Cycle Modeling
- Discussion

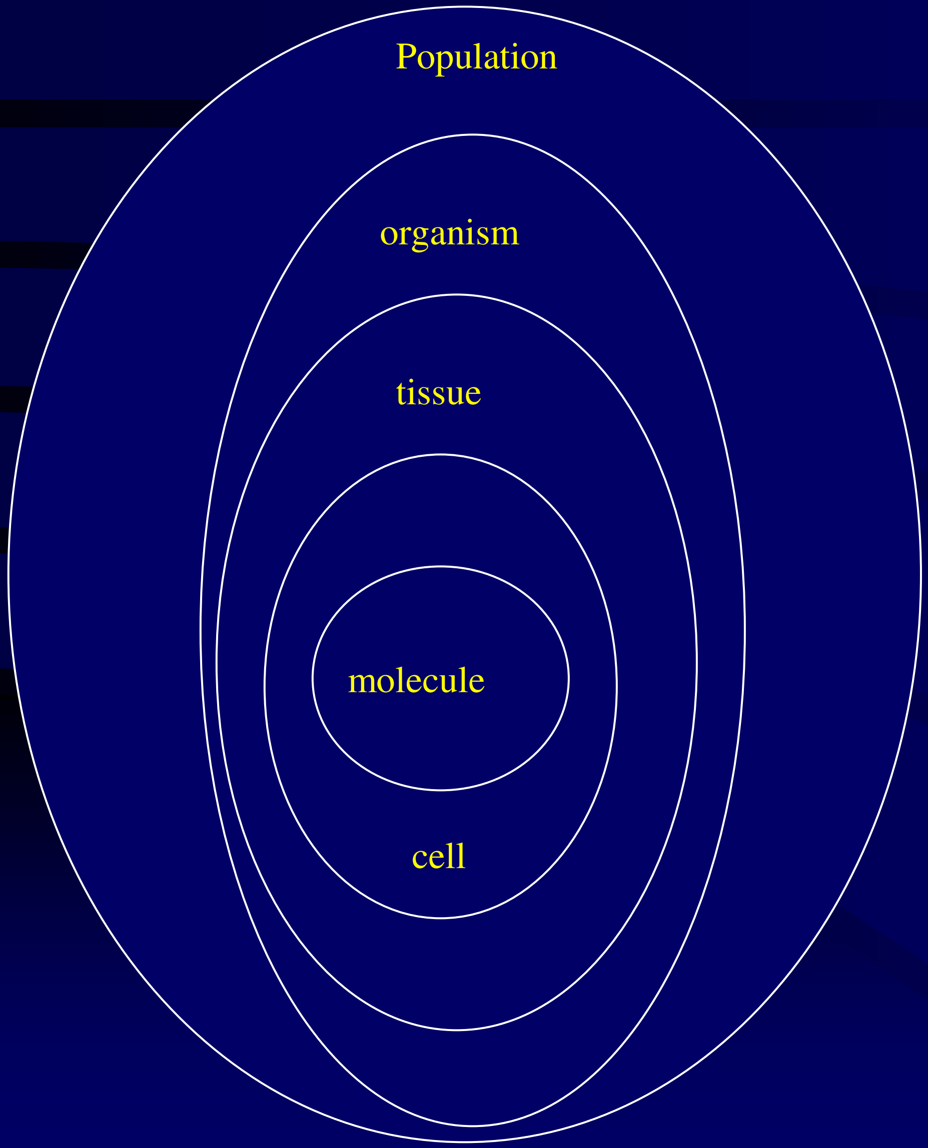
Introduction

- To describe feelings, we have poetry, music, painting, ...
- To describe qualitative concepts, we have natural languages
- To describe quantitative and abstract concepts, we have mathematics
- To study a phenomena requires an adequate language

Dynamical Phenomenon: objects change state in time



- Physics describes natural phenomena by mathematical laws
- The laws of Physics are validated by quantitative measures
- The experimentally validated laws are mathematical models of the phenomena
- The mathematical modeling of phenomena requires quantitative measures

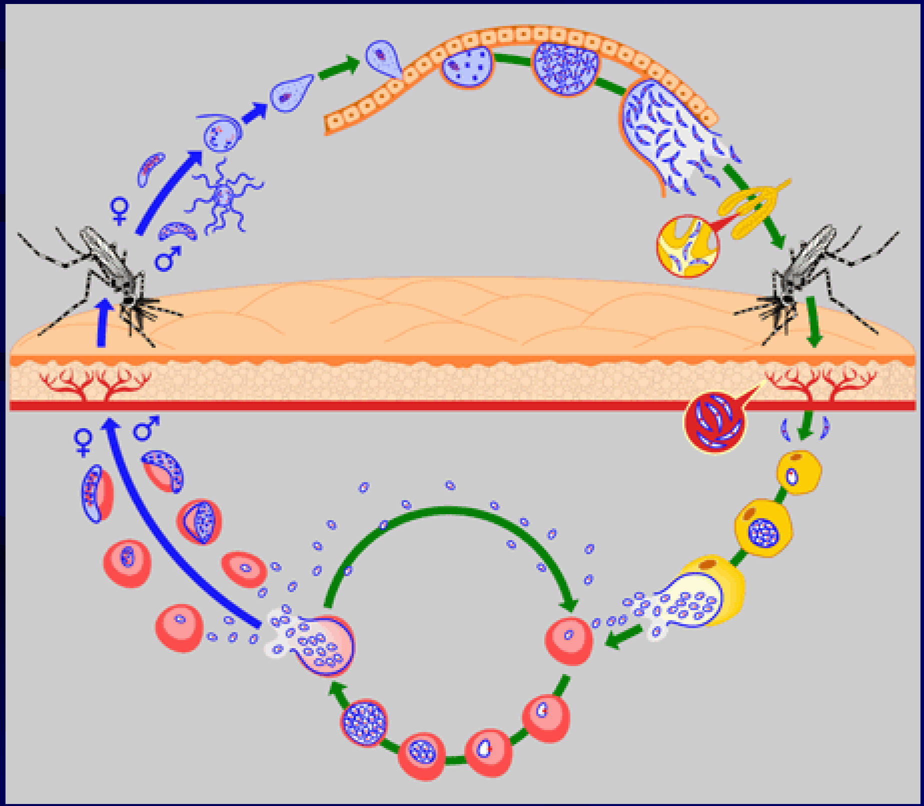


Biological Phenomena are multi-scale, dynamical and, in many cases, measurable

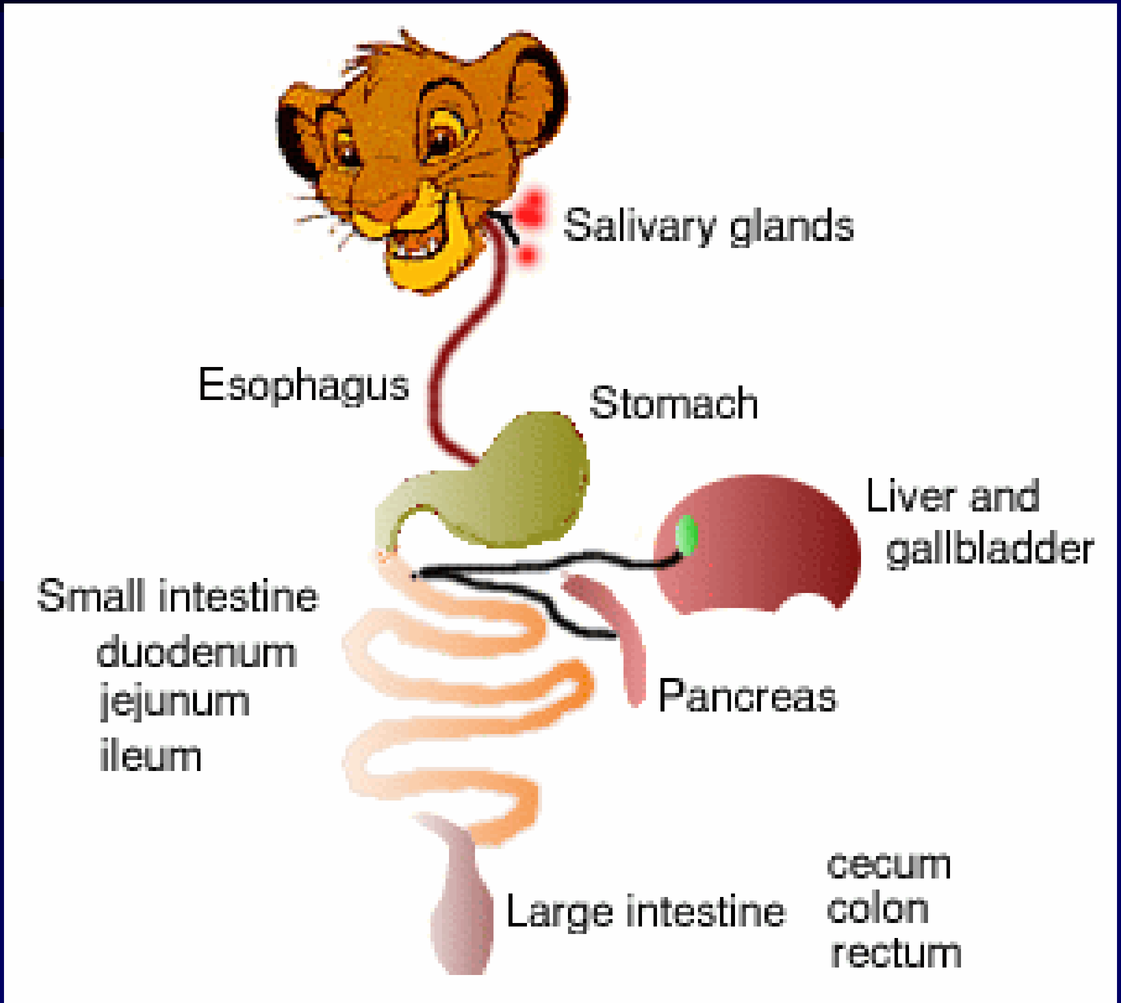
animation

Ecological System

The life cycle of the malaria parasite



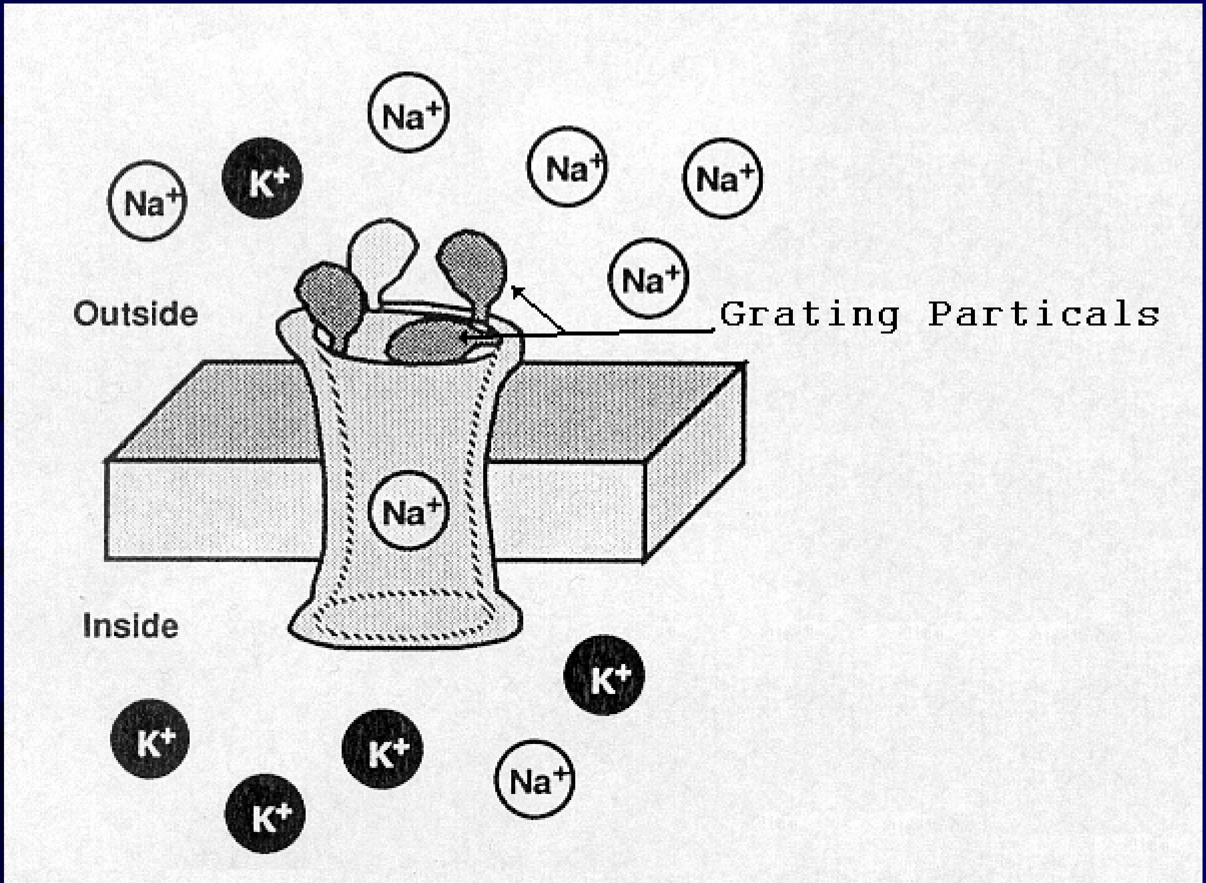
Digestive System



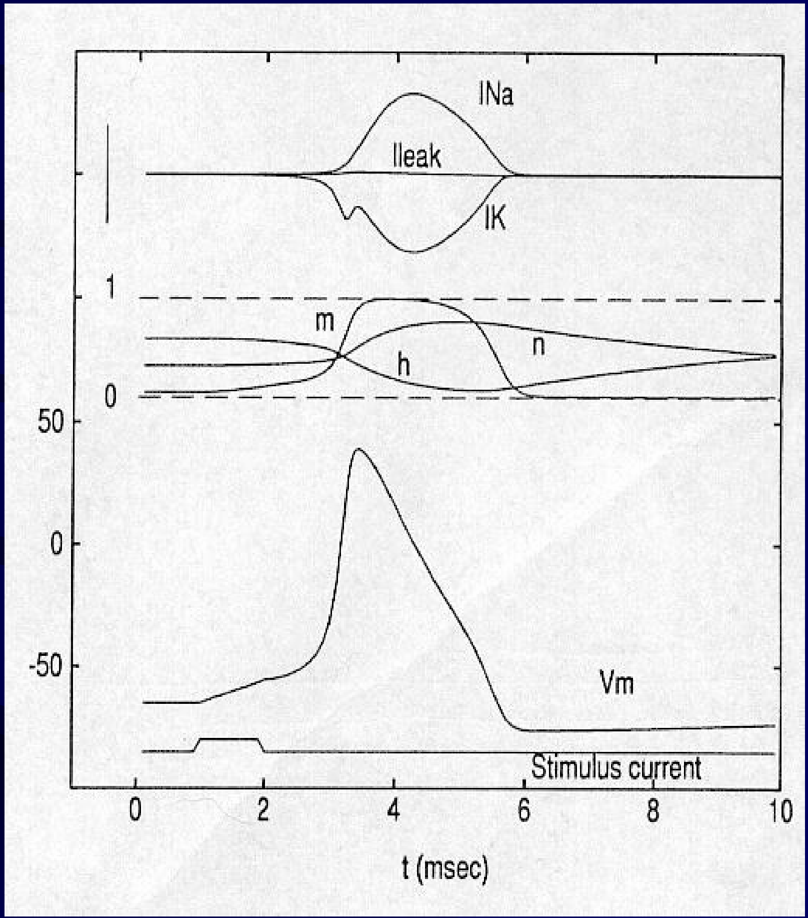
Neuron

The key unit of living beings for electric signal processing

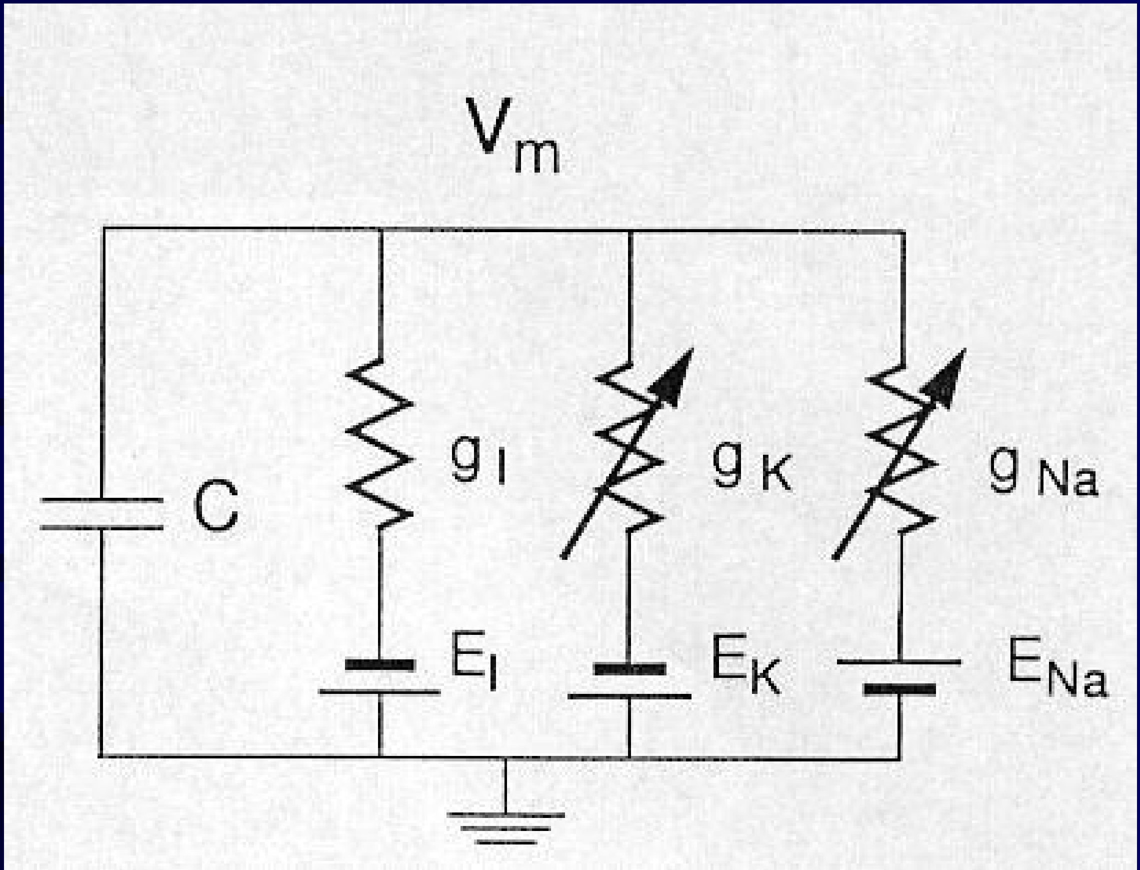
- Nobel Prize in Medicine 1963: Hodgkin - Huxley
- discoveries concerning the ionic mechanisms involved in excitation and inhibition of nerve cell membrane
- presented a mathematical model describing the dynamics of the action potential



Na+
K+
Na+
Na+
Na+
Na+
Outside
Grating Particals
Na+
Inside
K+
K+
K+
Na+
K+



INa
Ileak
IK
1
0
m
h
n
50
0
-50
Vm
Stimulus current
0
2
4
6
8
10
t (msec)



Vm
C
gl
gK
gNa
El
EK
ENa

- The equation derived from the circuit is:

$$C\frac{dVm}{dt} = g_l(E_l - V_m) + g_{Na}(E_{Na} - V_m) + g_K(E_K - V_m)$$

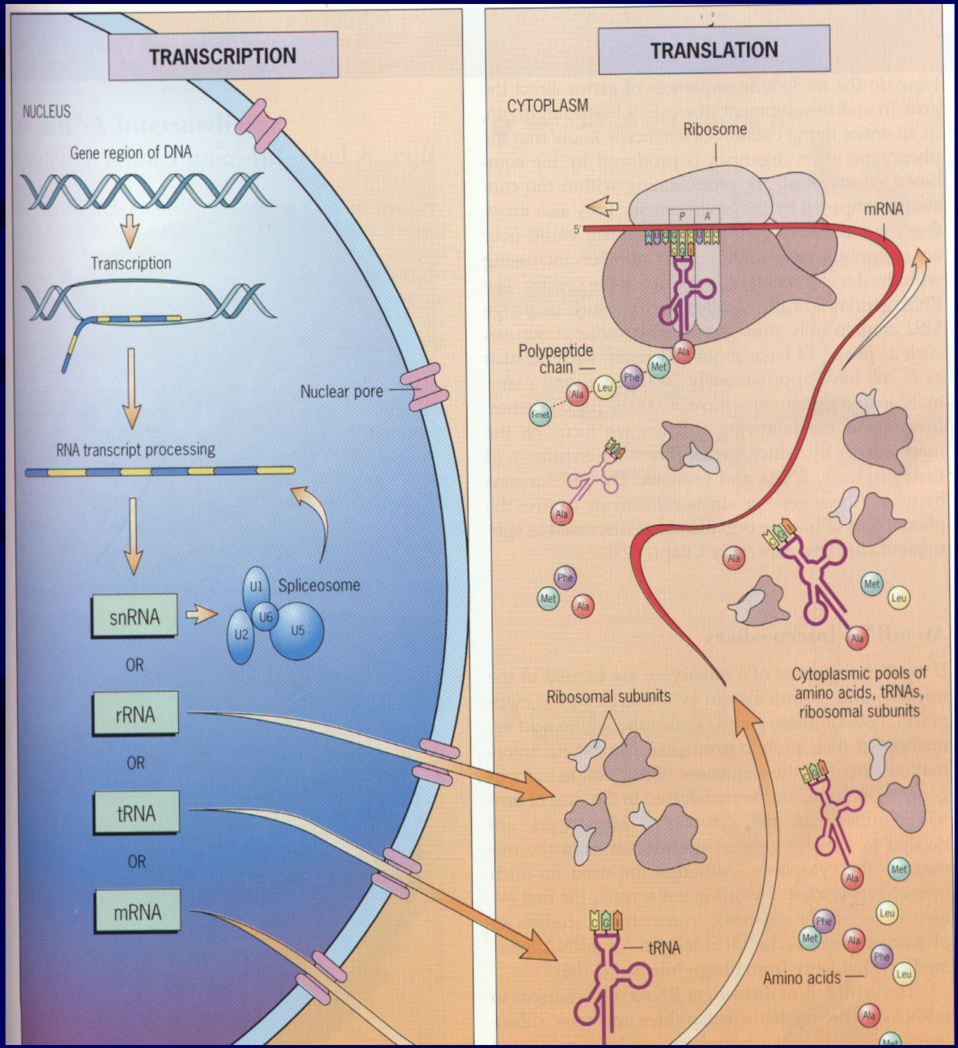
- Where g_l is constant and g_{Na} and g_K are time and voltage dependent, represented by:

$$g_{Na} = \overline{G}_{Na}.m(t)^3.h(t)$$

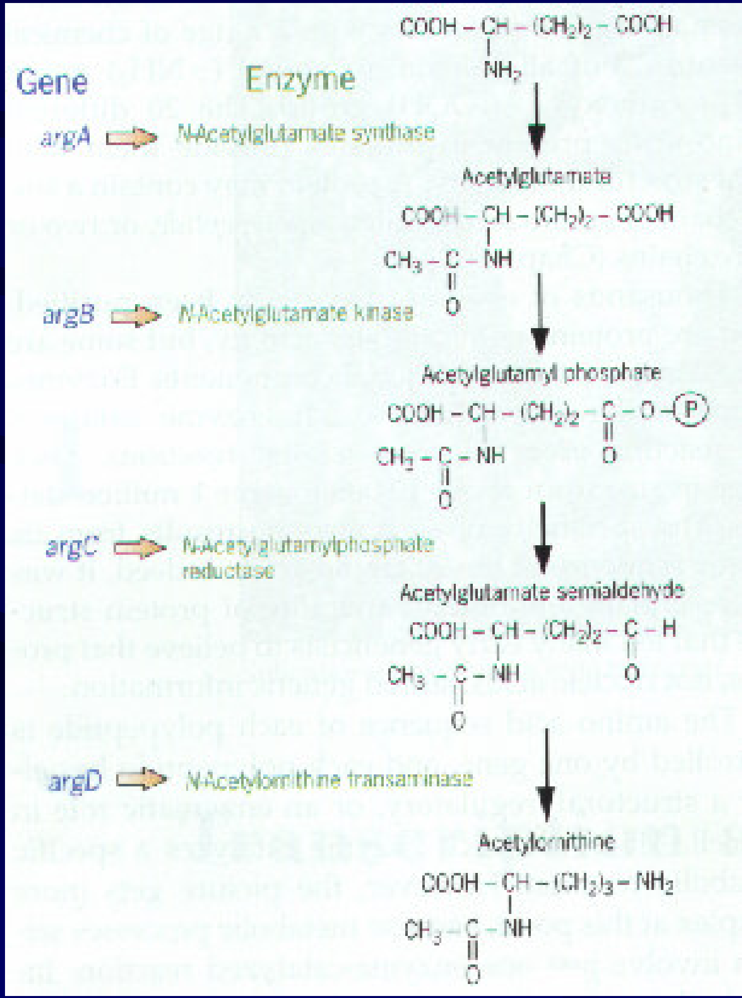
$$g_K = \overline{G}_K.n(t)^4$$

animation

Molecular Biology



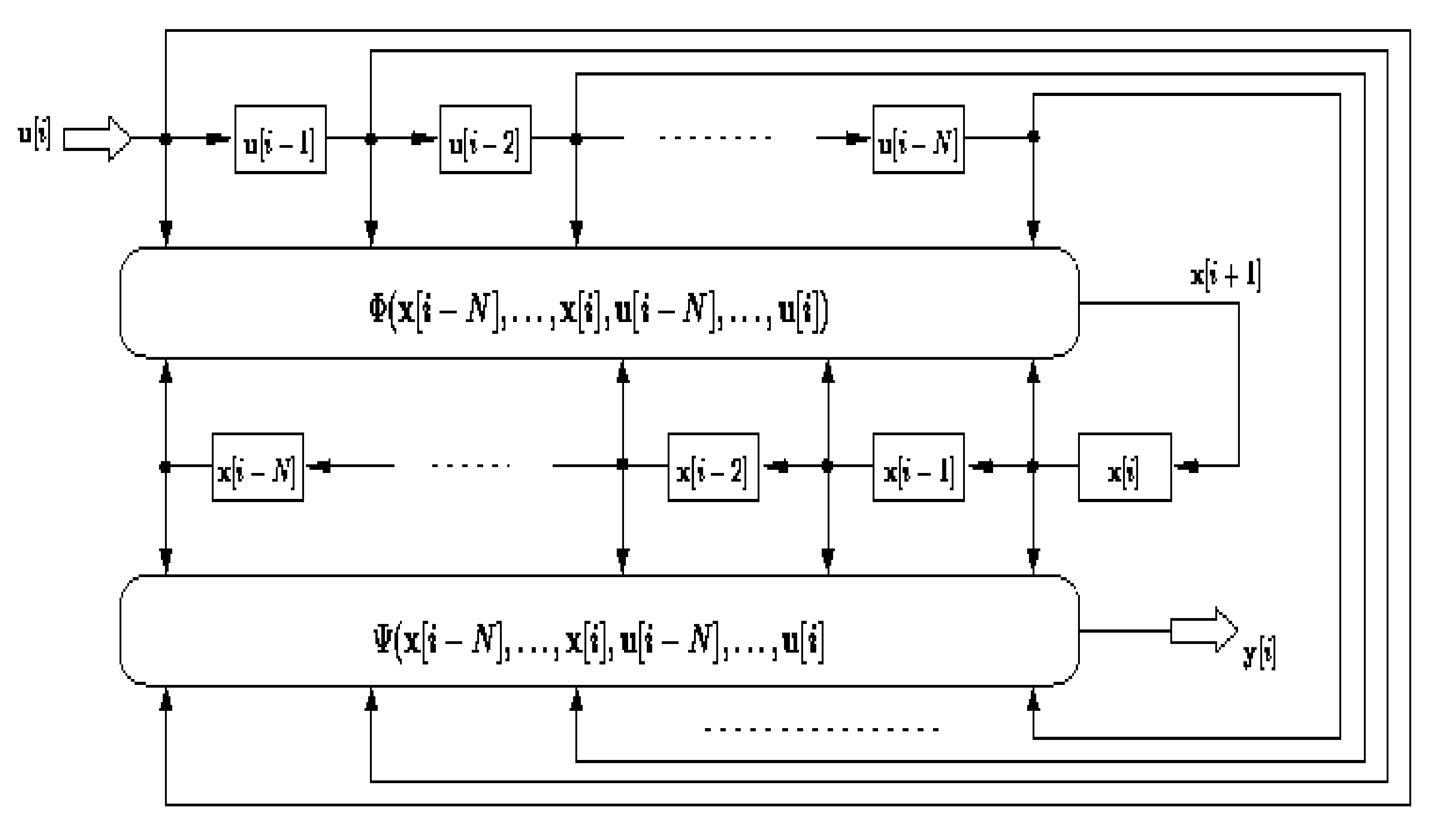
Knowledge evolution in genetics



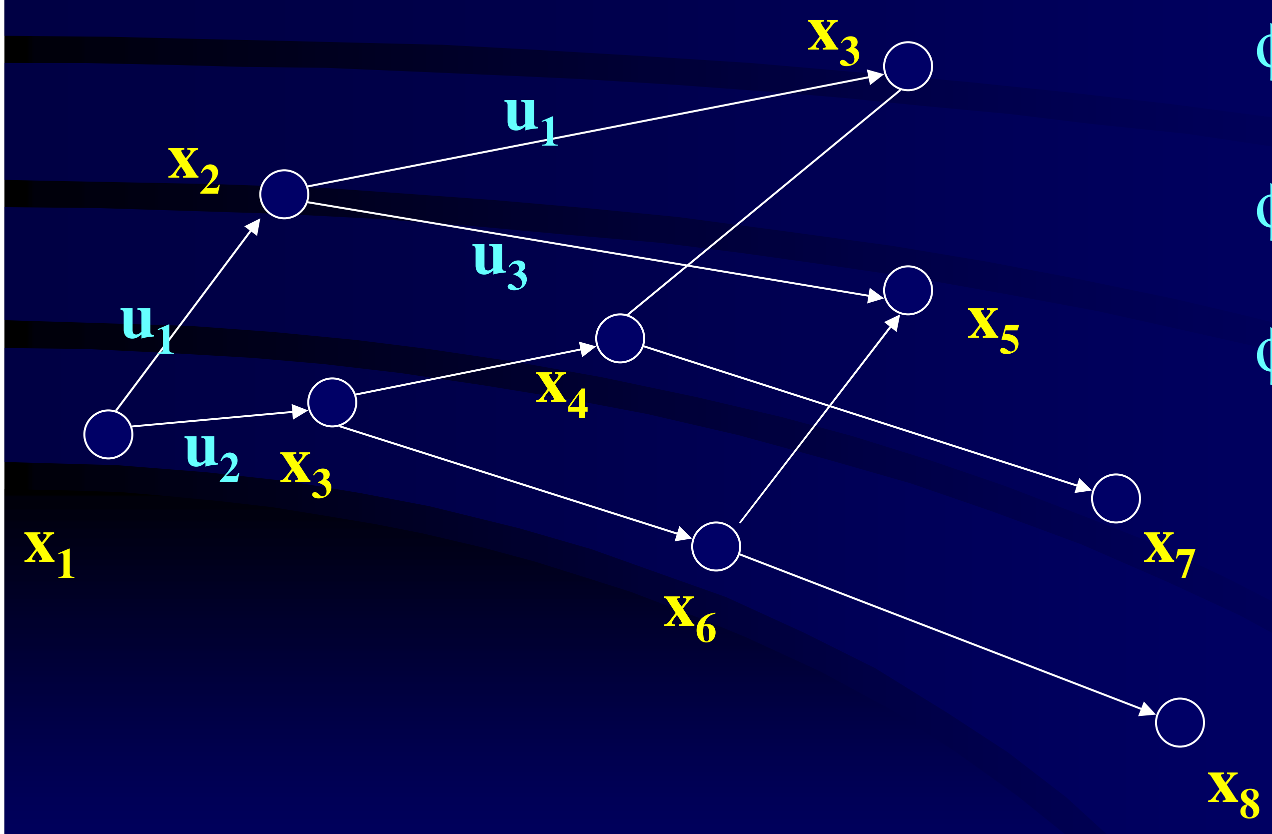
- Fundamental laws apply for all kinds of organisms
- Dynamical phenomena: protein and DNA interaction, gene networks, pathways
- Measurable variables: expression, protein signal, concentrations in biochemical reactions

Dynamical System

Graphical Interpretation



State Transition Graph

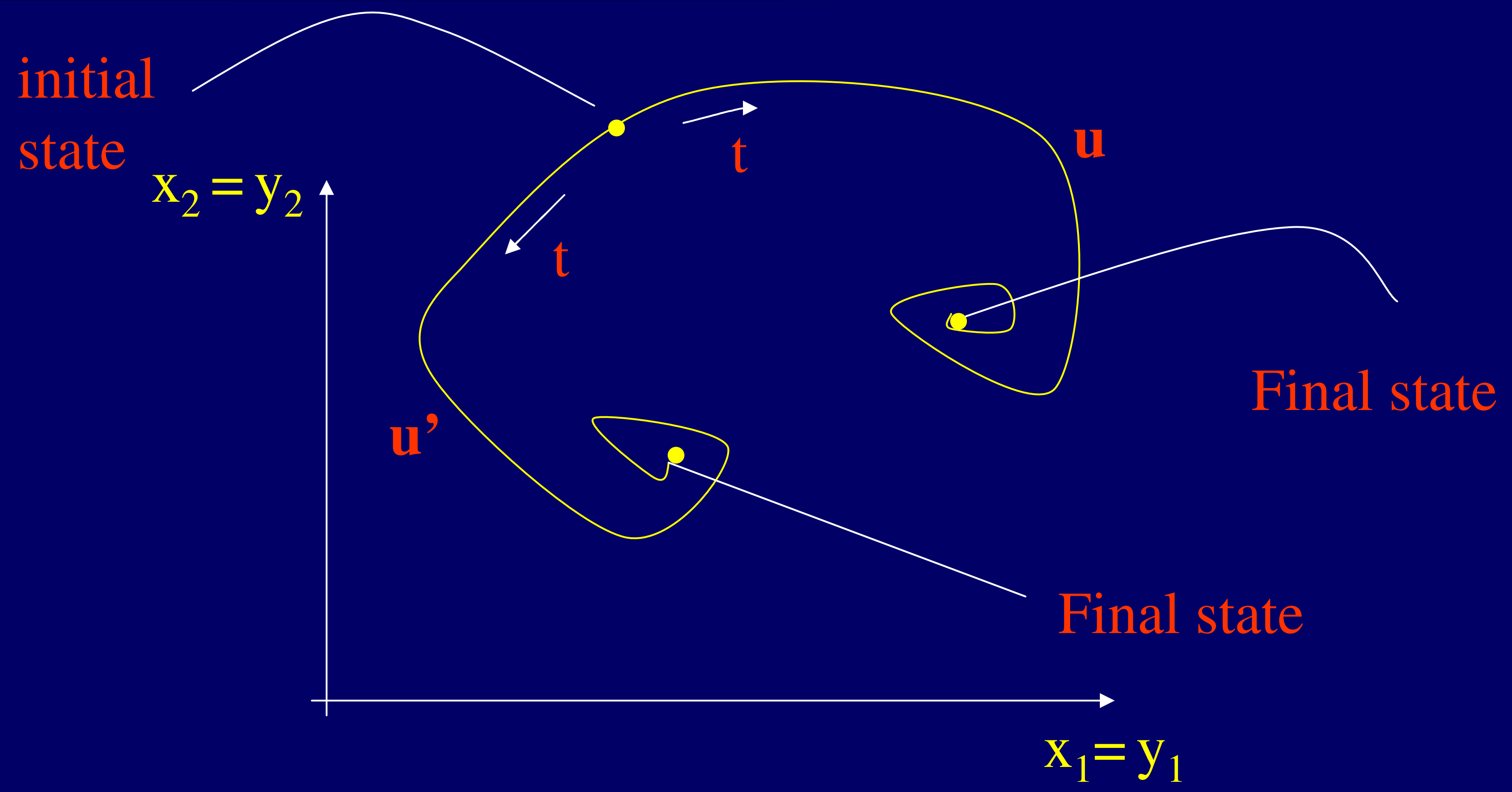


$$\phi_t \Leftrightarrow \{\phi_{xi} : L^{mN} \rightarrow L^{nN}\}$$

$$\phi_{x1}(\mathbf{u}_1) = \mathbf{x}_2$$

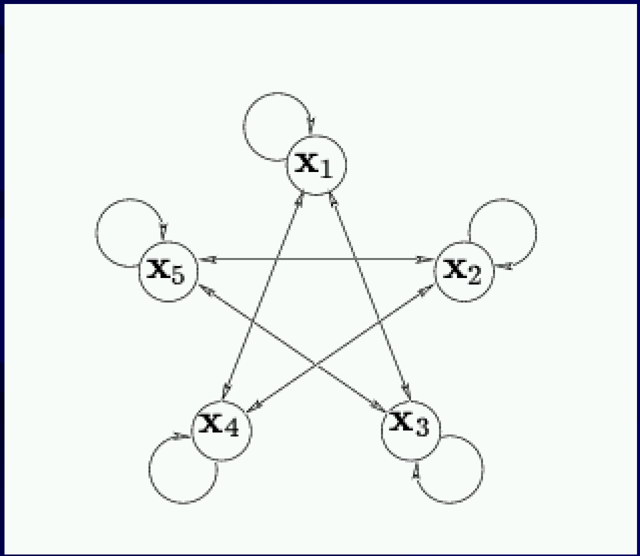
$$\phi_{t,j} \Leftrightarrow \{\phi_{xi,j} : L^{mN} \rightarrow L\}$$

Simulation



Example - architecture

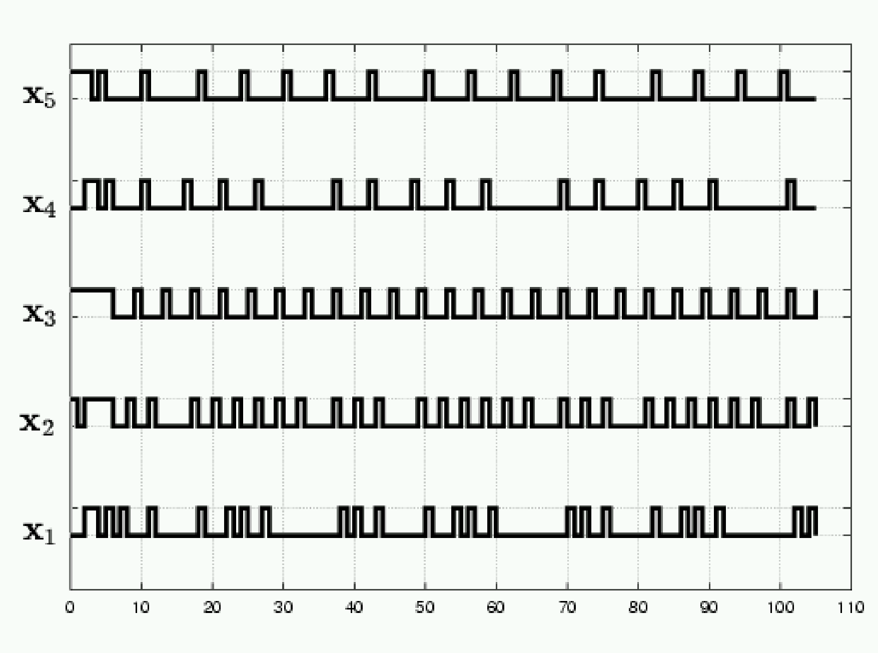
Graph representing the transition function components ($\phi_{t,j}$) states association

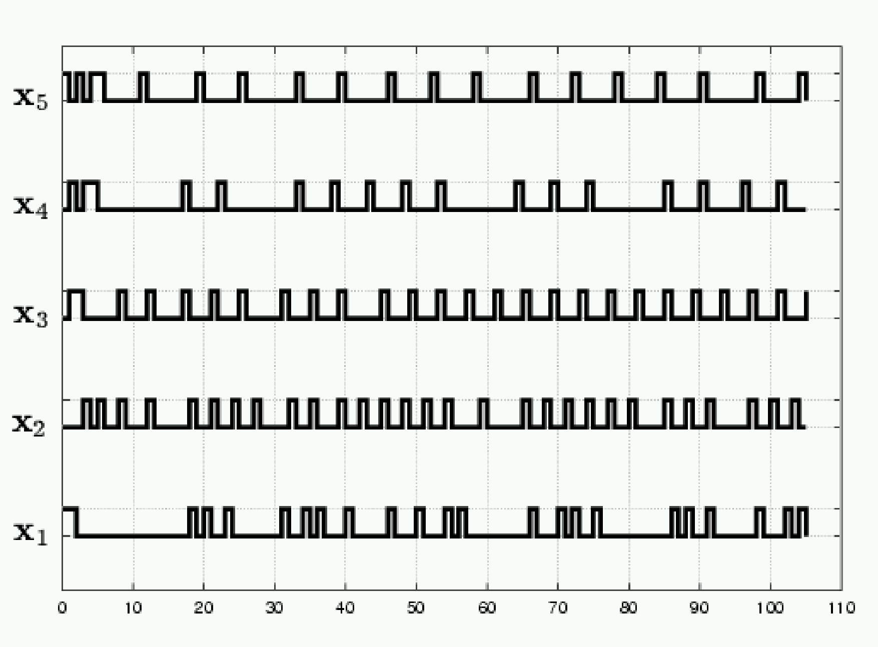


Example - dynamics

$$\mathbf{x}_1[t+1] = 1 \iff \begin{cases} \mathbf{x}_1[t] = 0 \\ \text{and} \\ \Big[\Big((\mathbf{x}_3[t] = 1 \text{ or } \mathbf{x}_3[t-1] = 1 \text{ or } \mathbf{x}_3[t-2] = 1) \text{ and} \\ \quad (\mathbf{x}_4[t] = 1 \text{ or } \mathbf{x}_4[t-1] = 1 \text{ or } \mathbf{x}_4[t-2] = 1) \Big) \\ \quad \text{or} \\ \quad \Big(\mathbf{x}_3[t] = \mathbf{x}_3[t-1] = \mathbf{x}_3[t-2] = \mathbf{x}_3[t-3] = \mathbf{x}_3[t-4] = 0 \text{ and} \\ \quad \mathbf{x}_4[t] = \mathbf{x}_4[t-1] = \mathbf{x}_4[t-2] = \mathbf{x}_4[t-3] = \mathbf{x}_4[t-4] = 0 \Big) \Big] \end{cases}$$

Example - simulation

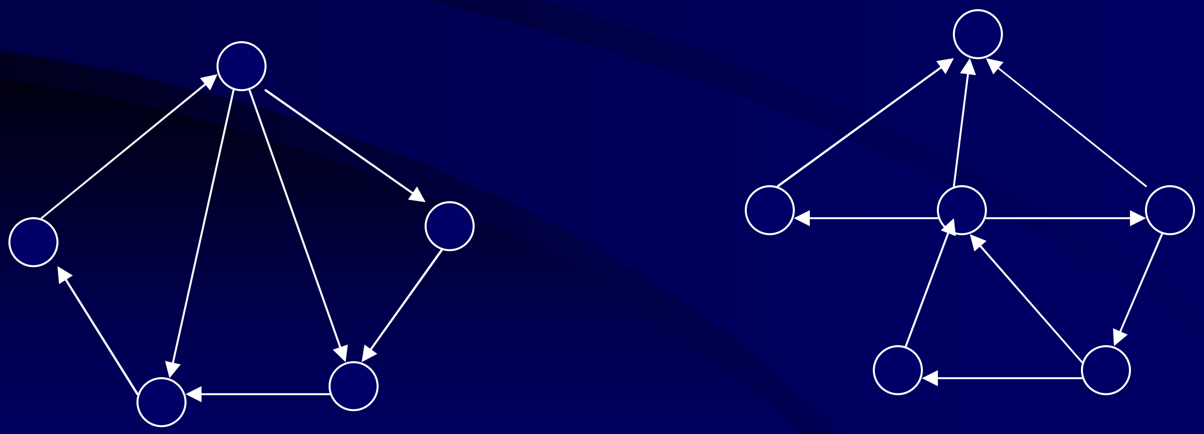




System Families

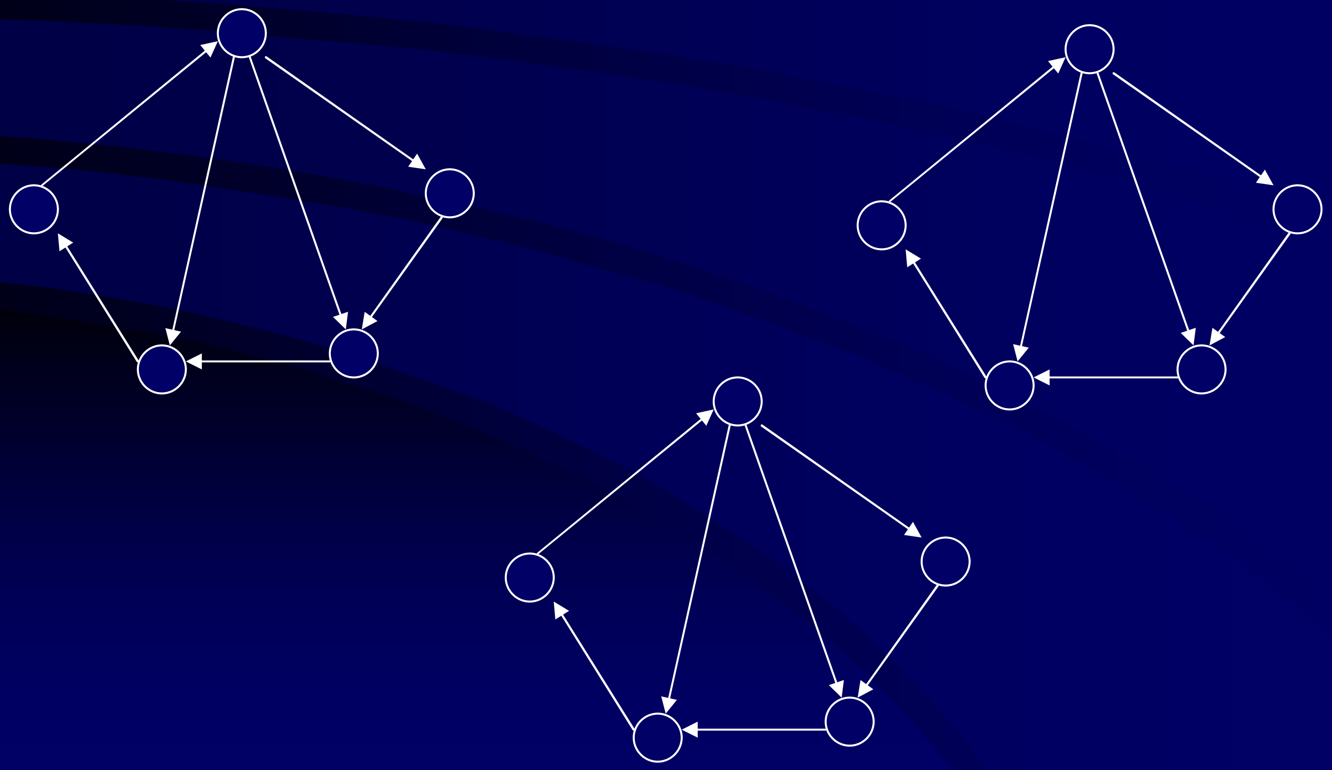
Independent Subsystems

- If the system architecture has more than one connected component, it is composed of independent subsystems



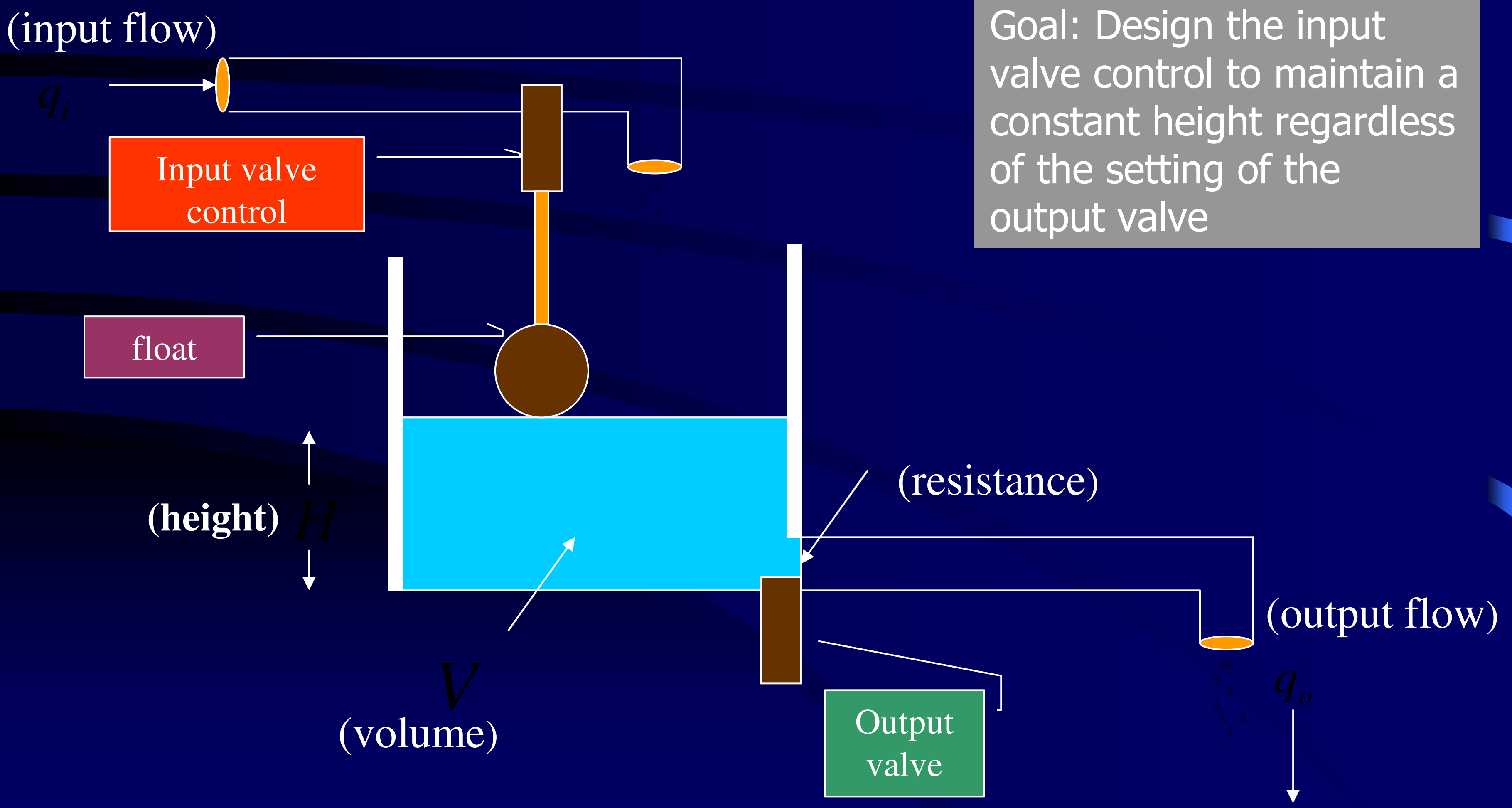
Replication

- Crucial systems may be replicated for safety

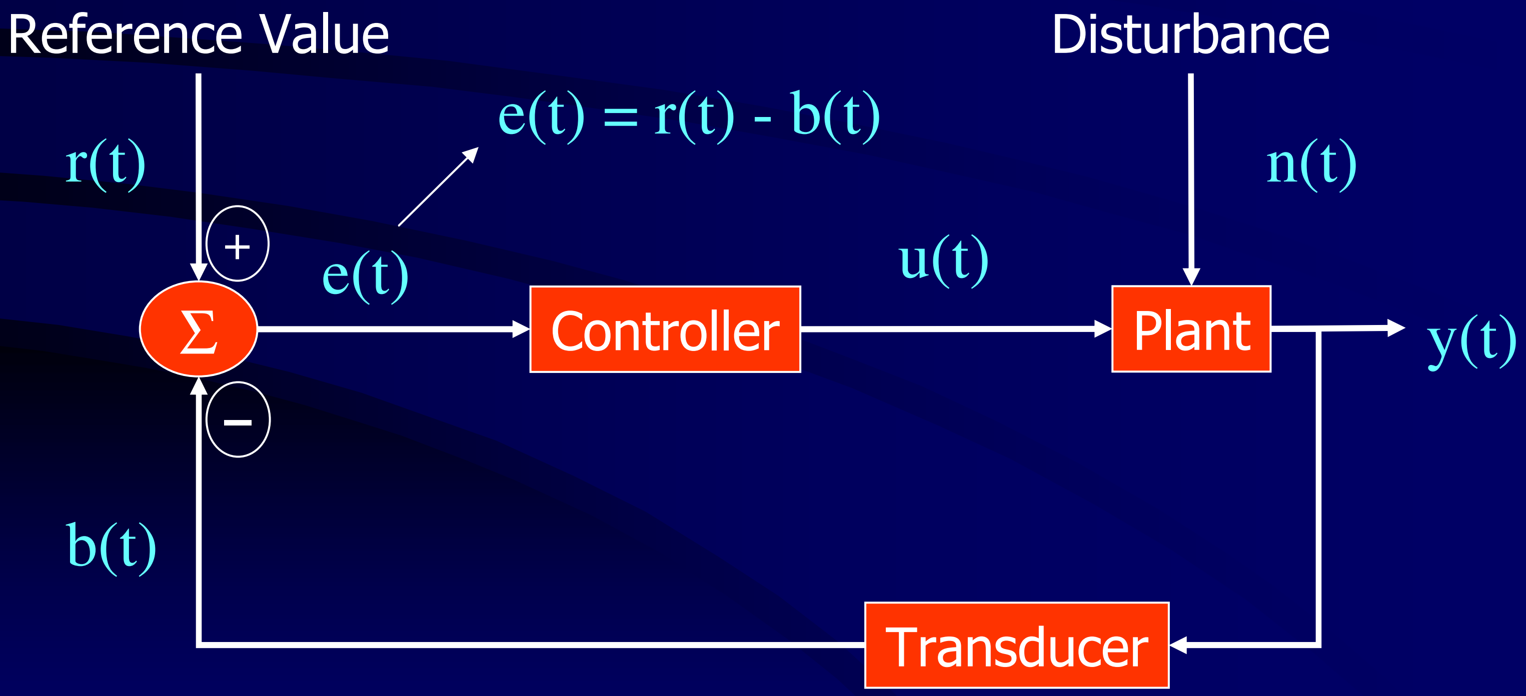


Example 1: Liquid Level System

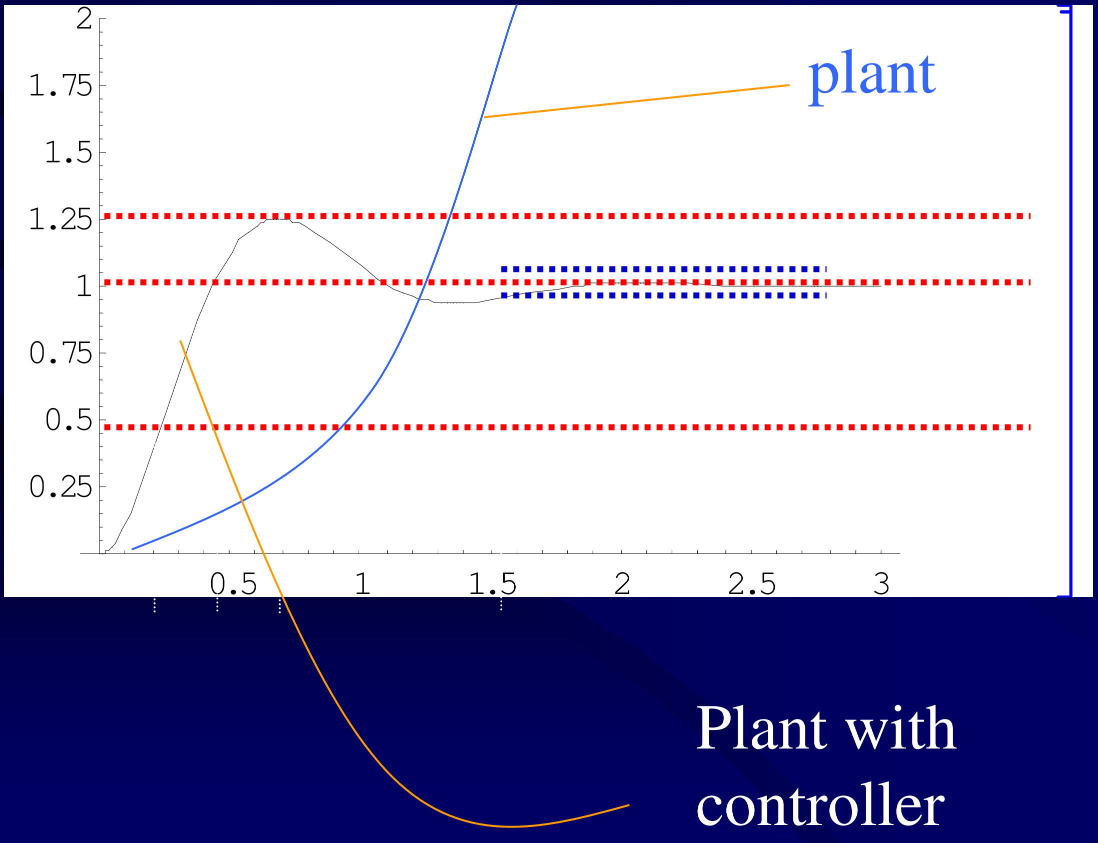
Goal: Design the input valve control to maintain a constant height regardless of the setting of the output valve



Feedback Control System



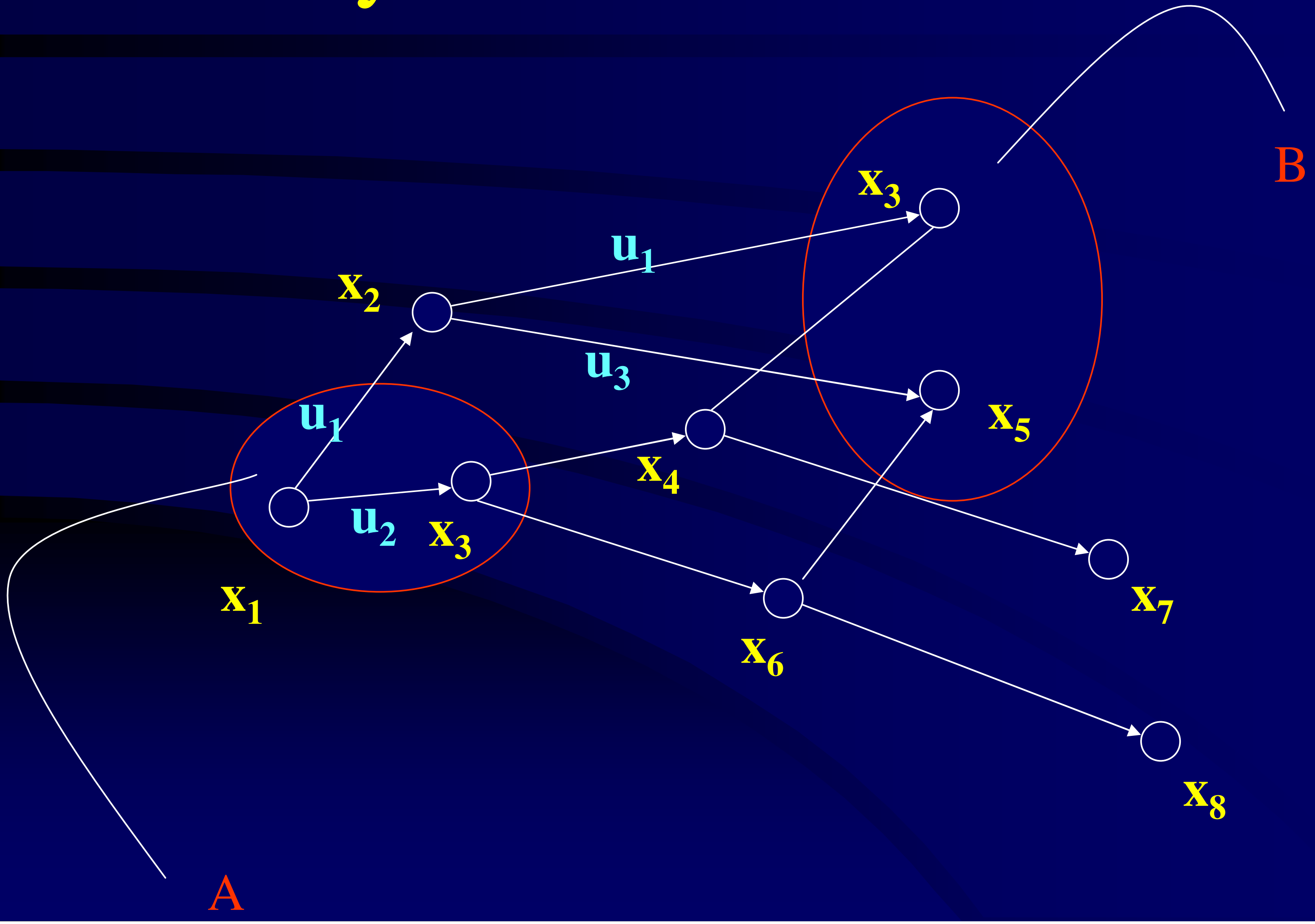
Transient Response Characteristics



AB-Controlability

- Let A and B be subsets of possible states
- A LDS is AB-controlable if, for every $a \in A$ and $b \in B$, there is a path in the transition graph from a to b.

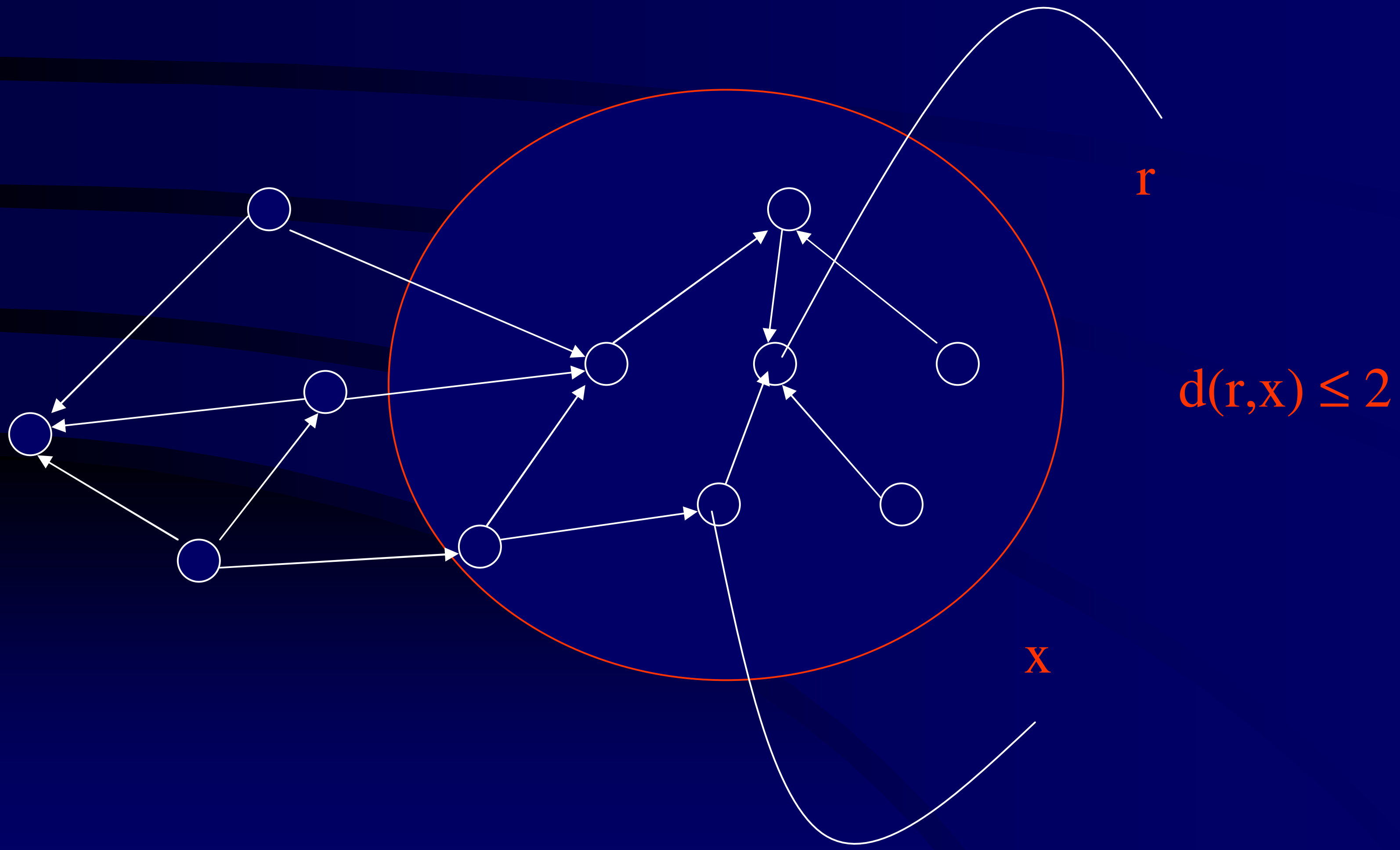
System AB-Controlable



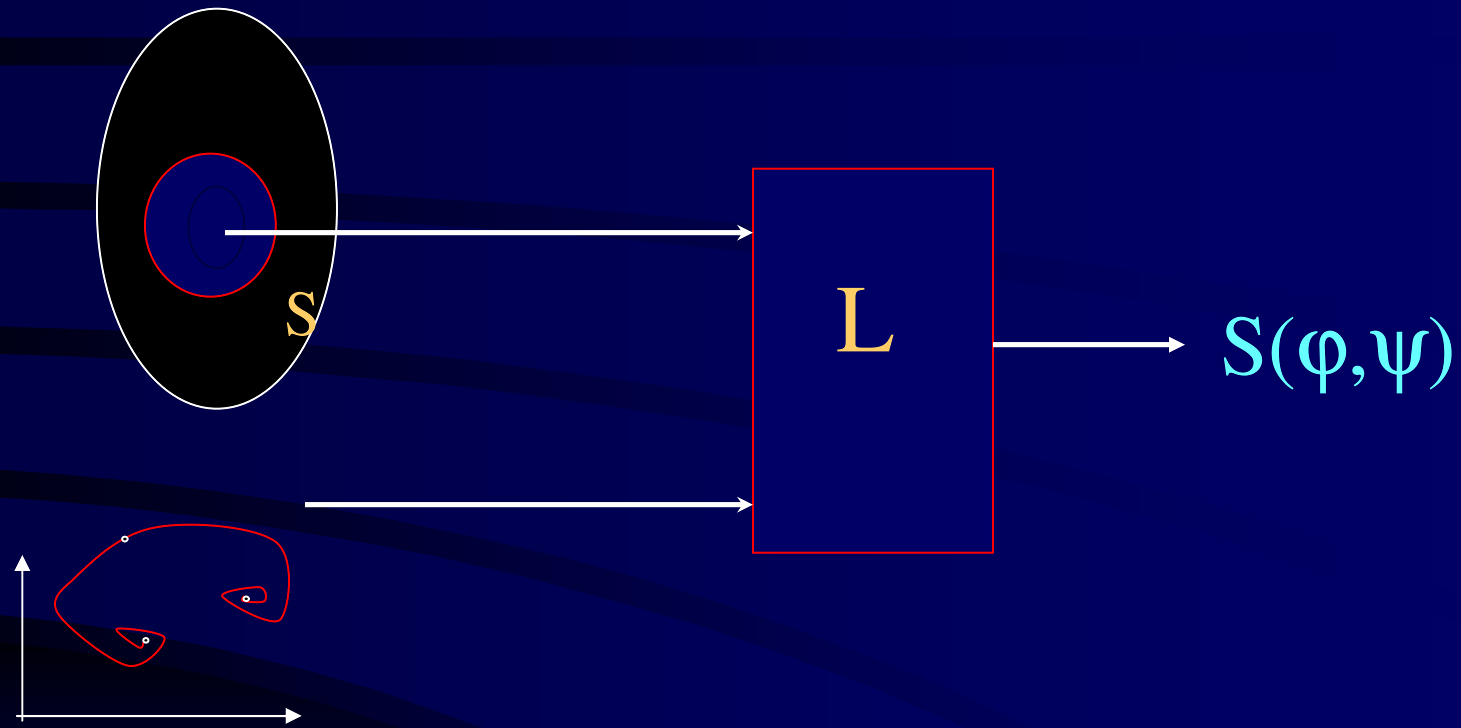
N-Robustness

- A state r is N-robust if there is an unconditional path in the transition graph from every x such that $d(r,x) \le N$.

Robust and no Robust States



System identification

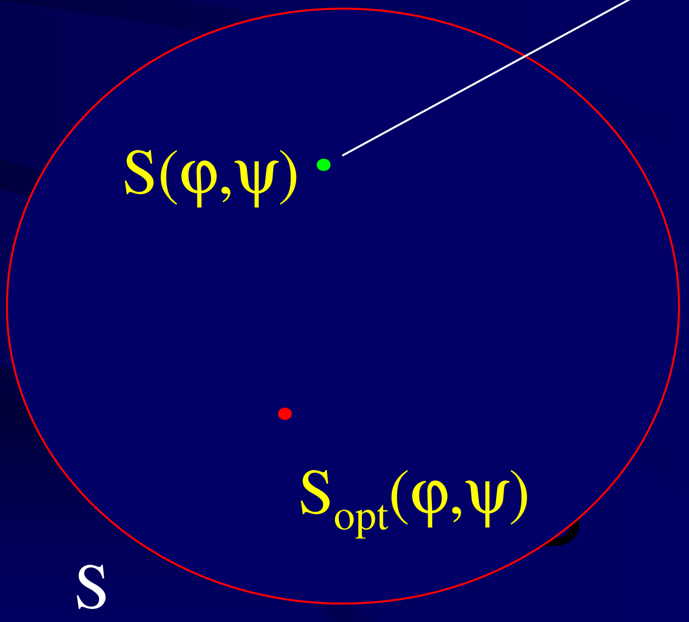

S
L
S(φ,ψ)

Stochastic Non Linear problem

u and **y** **are random processes**

$S_{xo}(\varphi, \psi)(\mathbf{u})$ is an estimator of **y**

$Er[S(\varphi,\psi)(\mathbf{u}), \mathbf{y}]$



vector of functions

each component function has a basis

Stochastic Linear Problem

- Model Structure

$$y(t) = ay(t-1) + bu(t-1) + e(t)$$

- Given:

$$\{u(1), y(1)\}, \{u(2), y(2)\}, \ldots, \{u(N), y(N)\}$$

- To determine:

a and b

- Prediction

$$\hat{y}(t) = ay(t-1) + bu(t-1)$$

- Prediction Error

$$y(t)-\hat{y}(t)=y(t)-ay(t-1)-bu(t-1)$$

- Cost Function

$$J(a,b)=\sum_{t=2}^{N}\{y(t)-ay(t-1)-bu(t-1)\}^2$$

- Results

$$\begin{pmatrix}\hat{a}\\ \hat{b}\end{pmatrix}=\left(\Phi^T\Phi\right)^{-1}\Phi^T\begin{pmatrix}y(2)\\ y(3)\\ \cdots\\ y(N)\end{pmatrix}$$

$$\Phi=\begin{pmatrix}y(1) & u(1)\\ y(2) & u(2)\\ \ldots\ldots & \\ y(N-1) & u(N-1)\end{pmatrix}$$

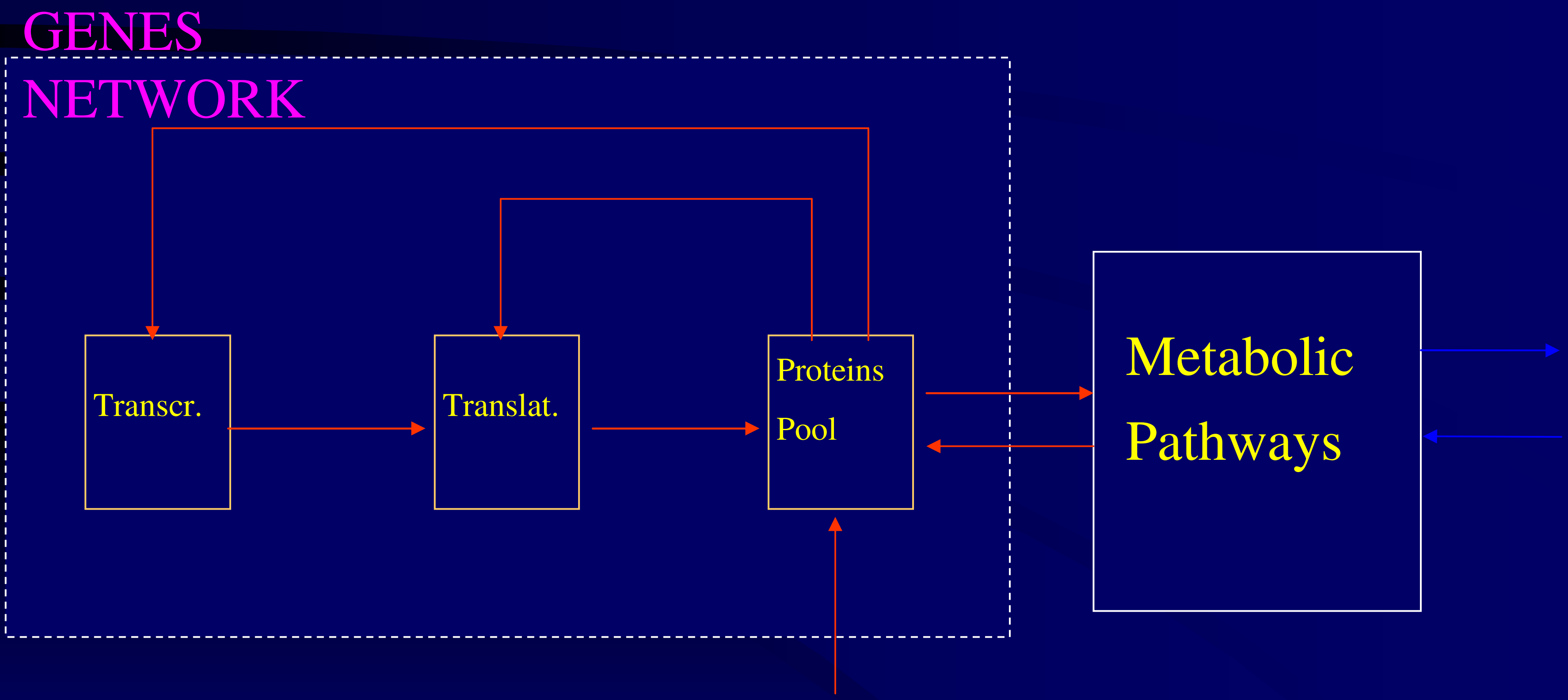
$$for \quad y(t)=ay(t-1)+bu(t-1)+e(t)$$

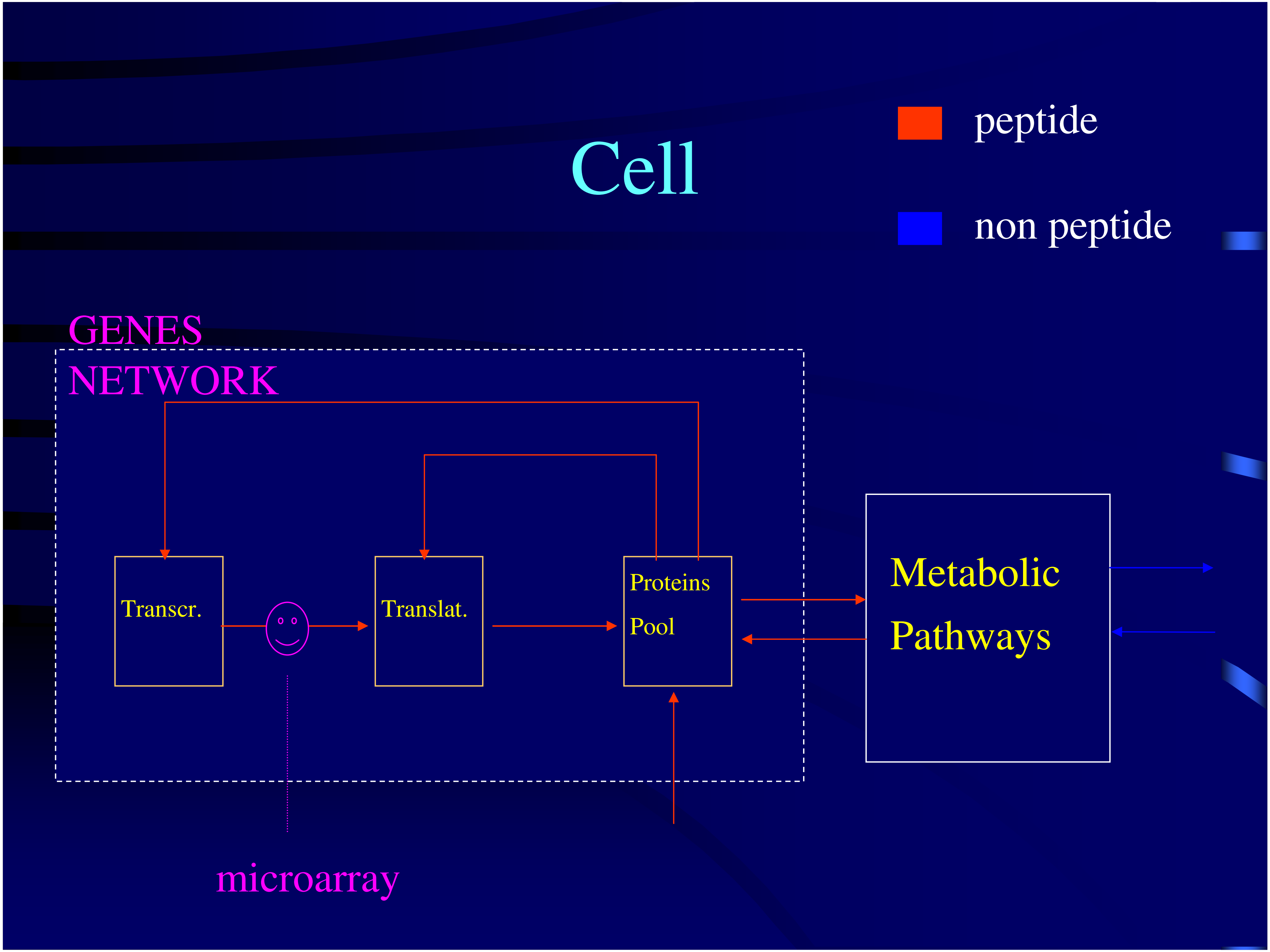
Genetic Network Design

Cell

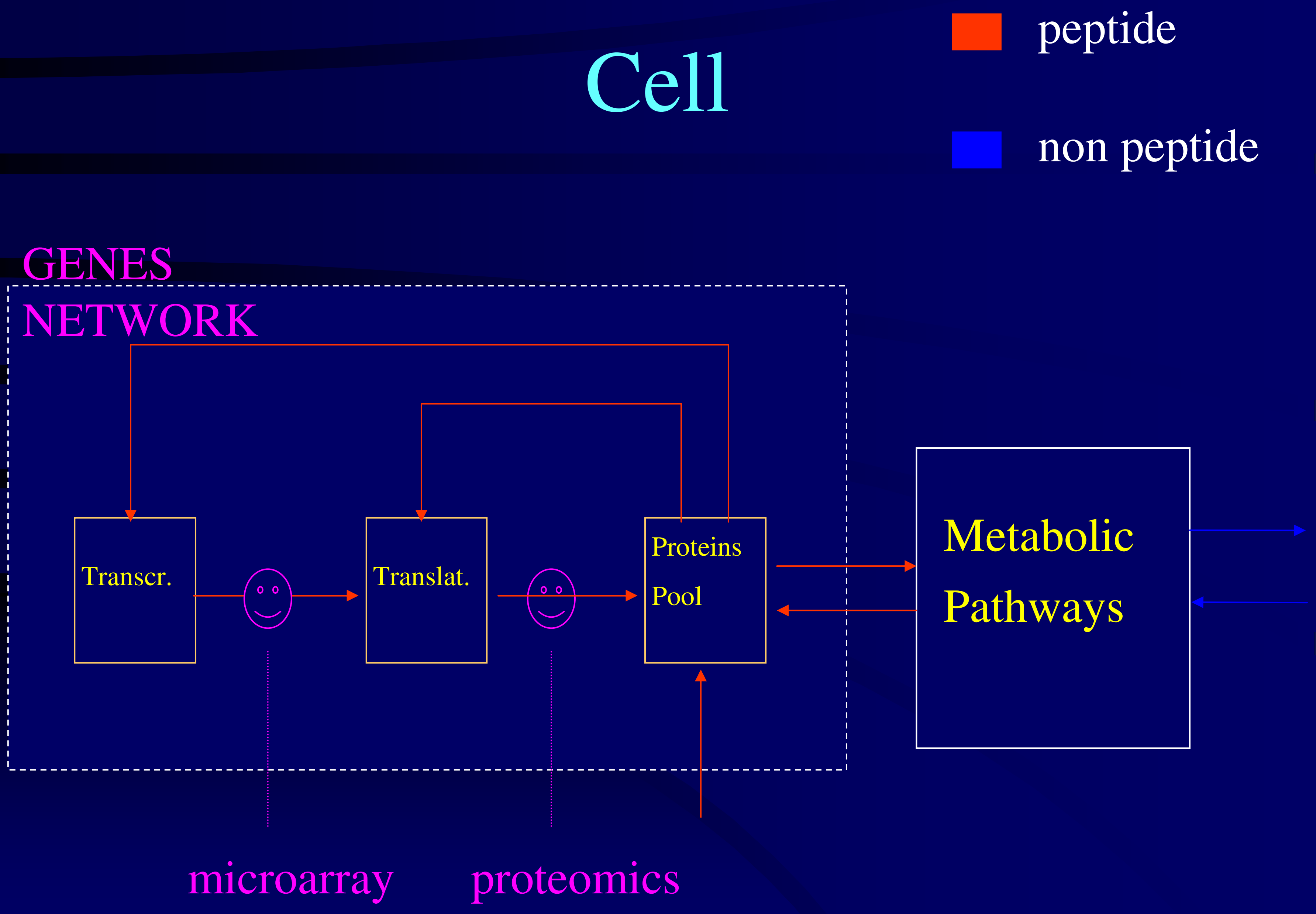
peptide

non peptide

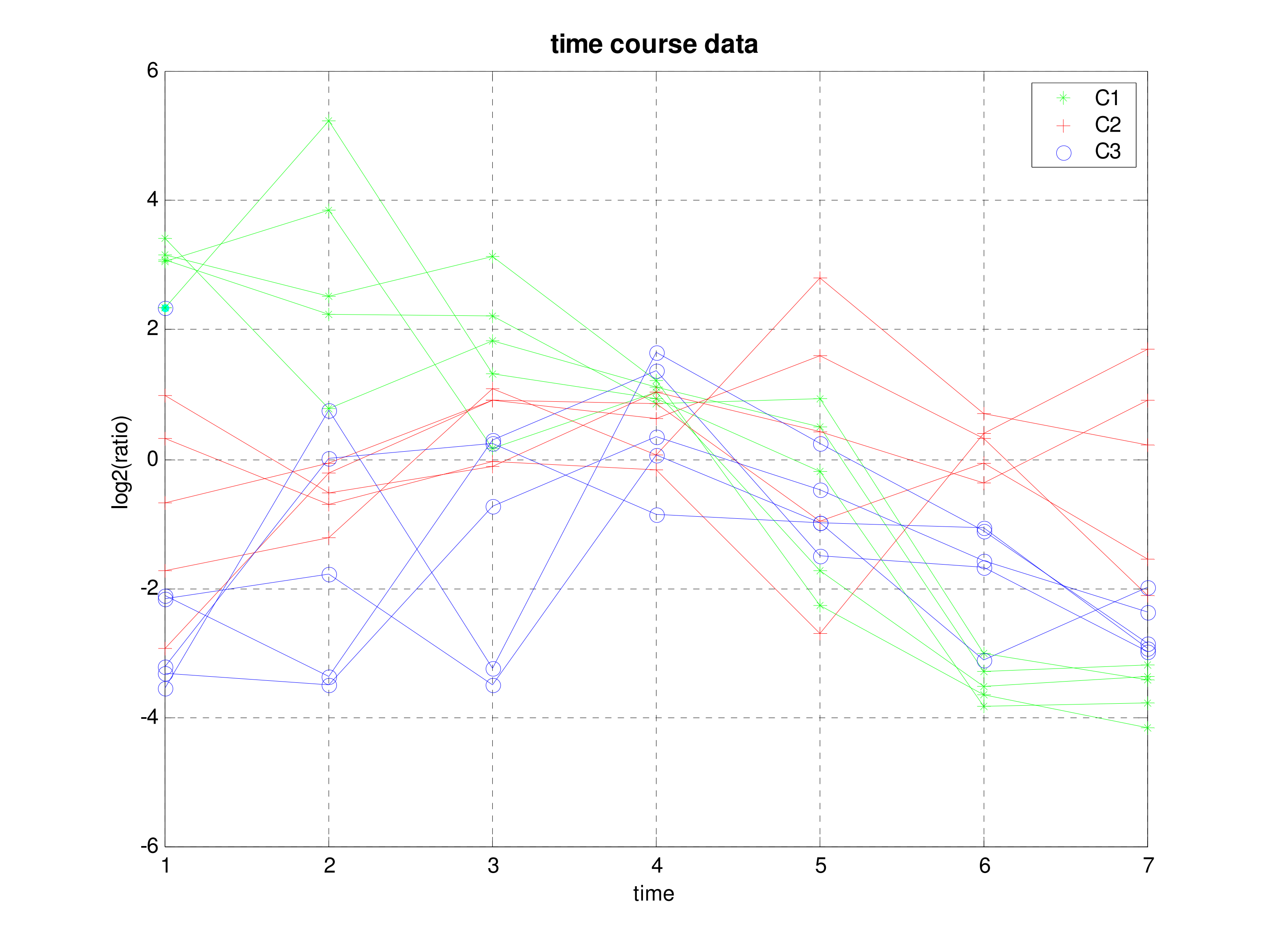


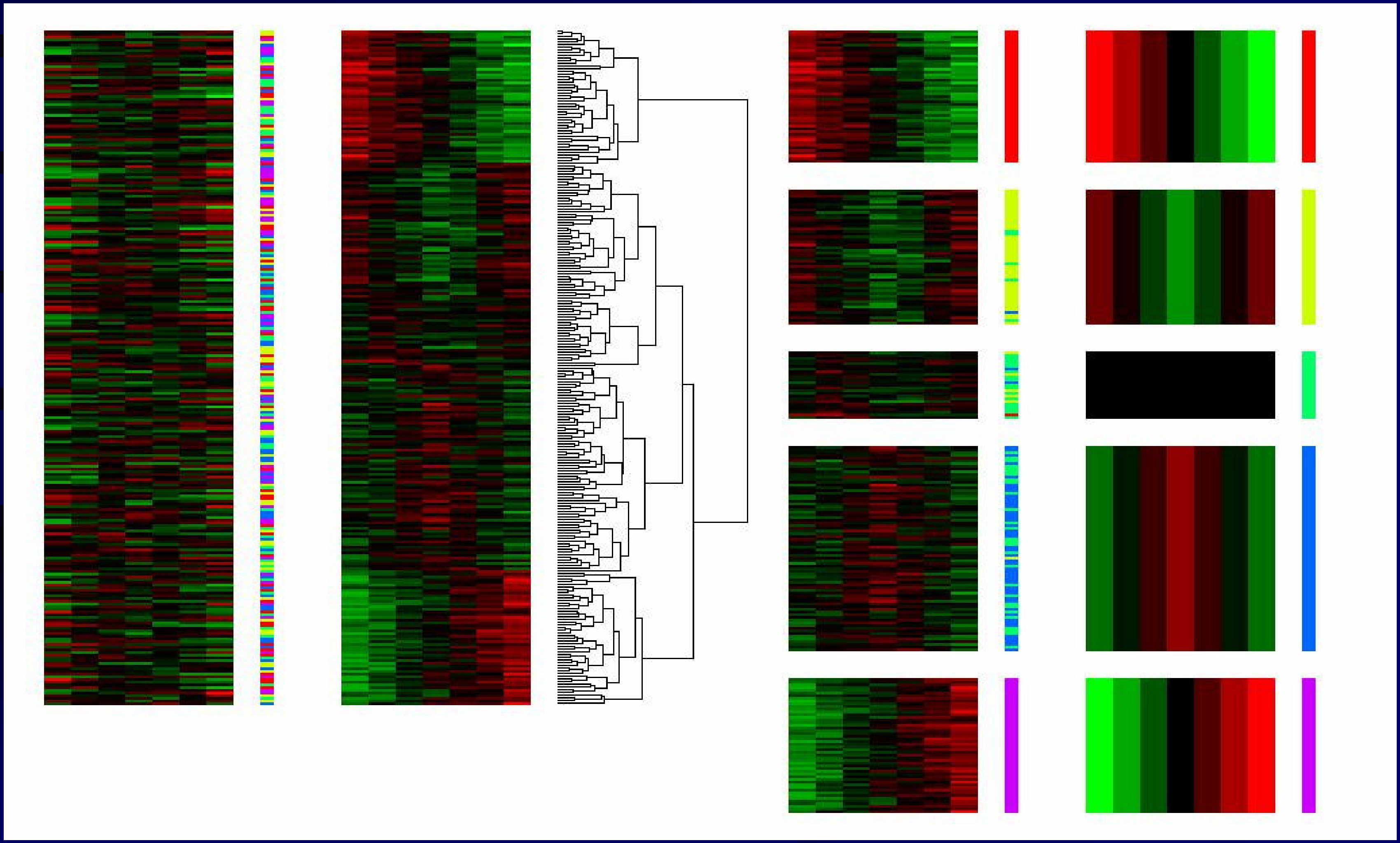

Cell
peptide
non peptide
GENES
NETWORK
Transcr.
Translat.
Proteins
Pool
Metabolic
Pathways
microarray

Cell


peptide
non peptide
GENES
NETWORK
Transcr.
Translat.
Proteins
Pool
Metabolic
Pathways
microarray
proteomics

Hypothesis: the system is fault tolerant, that is, there is more than one system doing the same task.

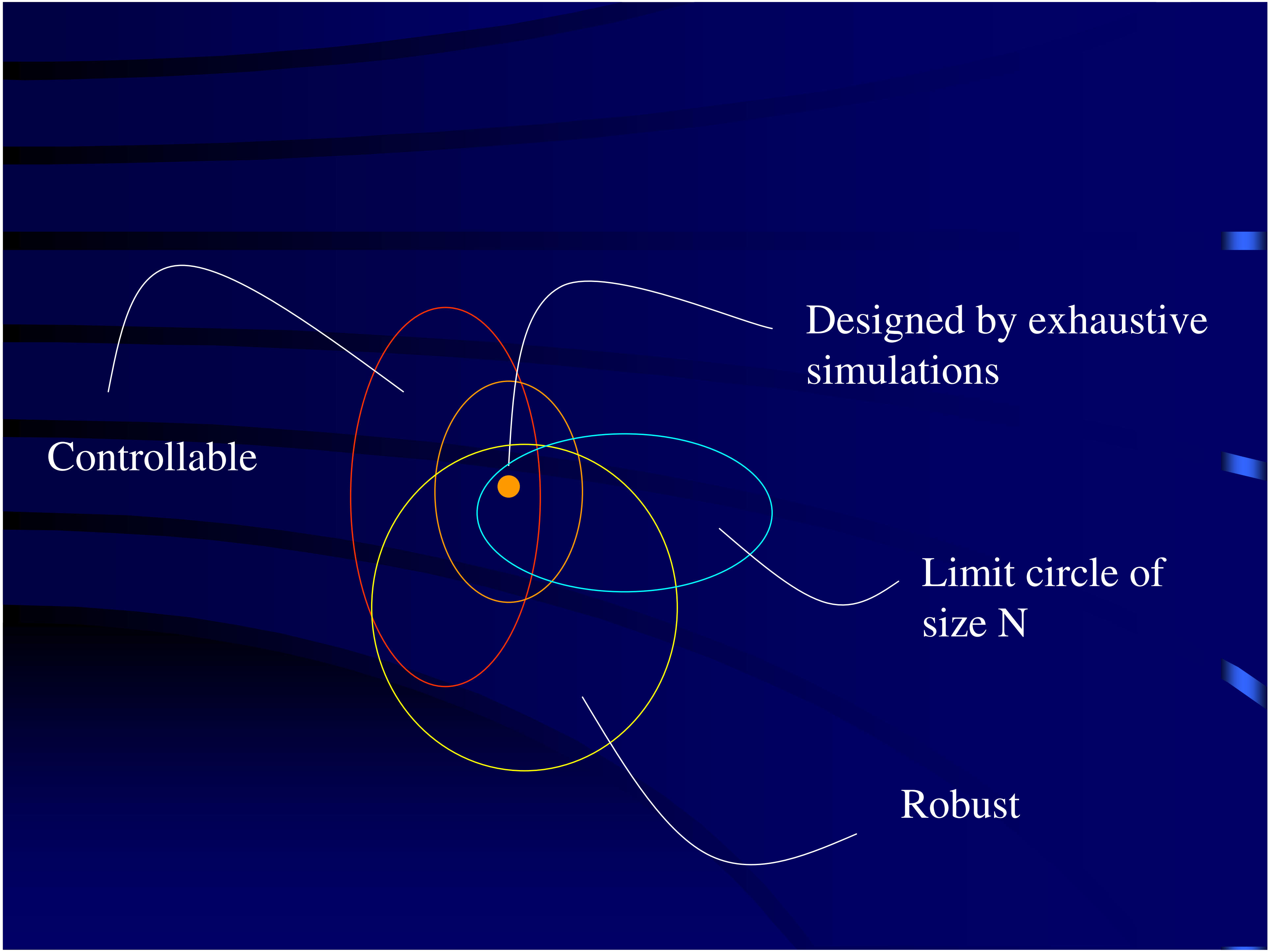

time course data
C1
C2
C3
log2(ratio)
6
4
2
0
-2
-4
-6
1
2
3
4
5
6
7
time

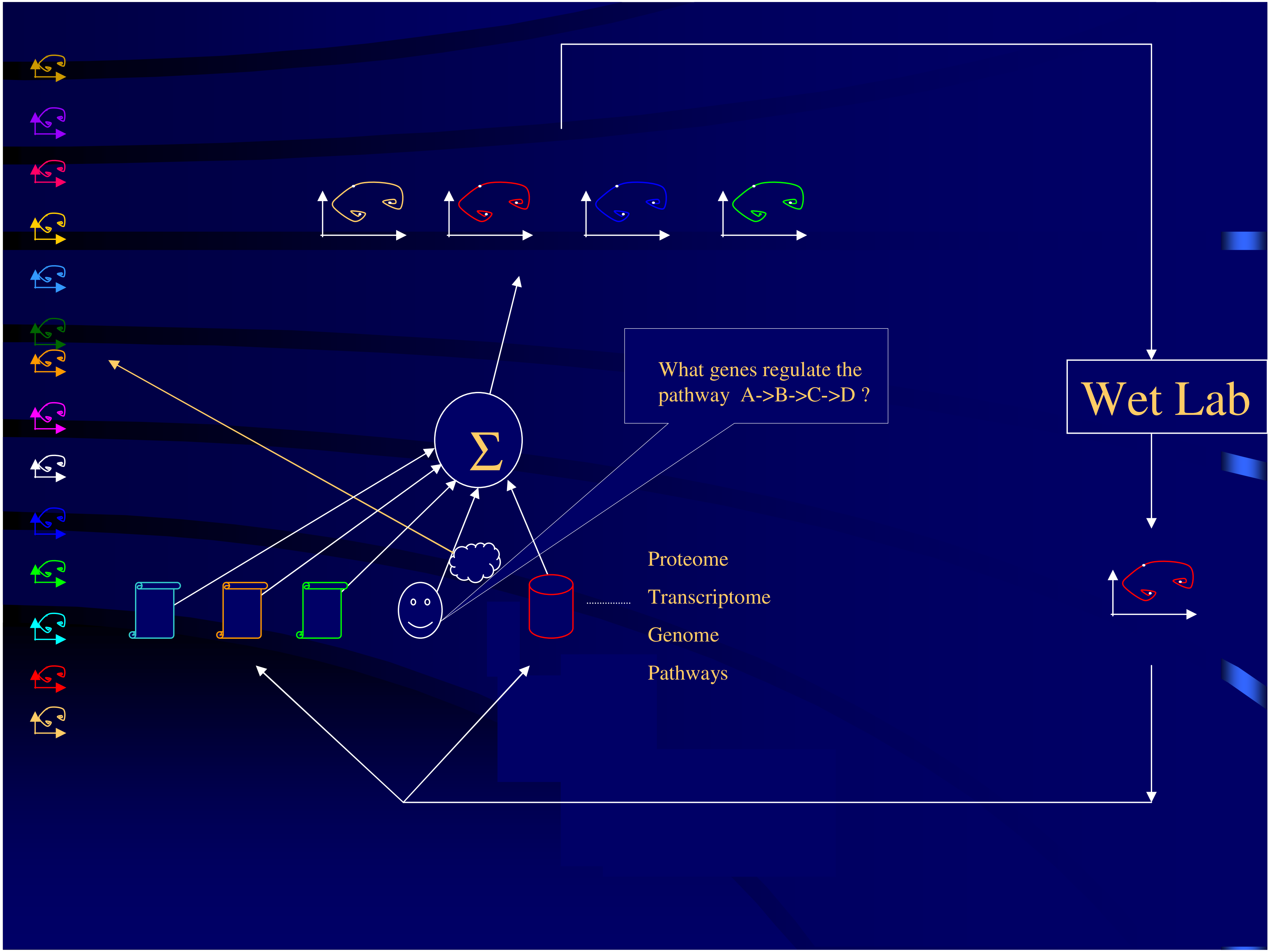


System Sampling

$$\begin{bmatrix} 0 & 1 & 0 & 0 & 1 & 0 & -1 & 1 \\ 1 & 1 & -1 & 0 & 1 & 0 & 1 & 1 \\ 0 & 1 & 0 & 1 & 1 & 0 & 1 & 1 \\ 0 & 1 & 1 & 1 & 1 & 0 & -1 & 1 \\ 0 & 1 & 0 & 0 & 0 & 0 & -1 & 1 \end{bmatrix}$$

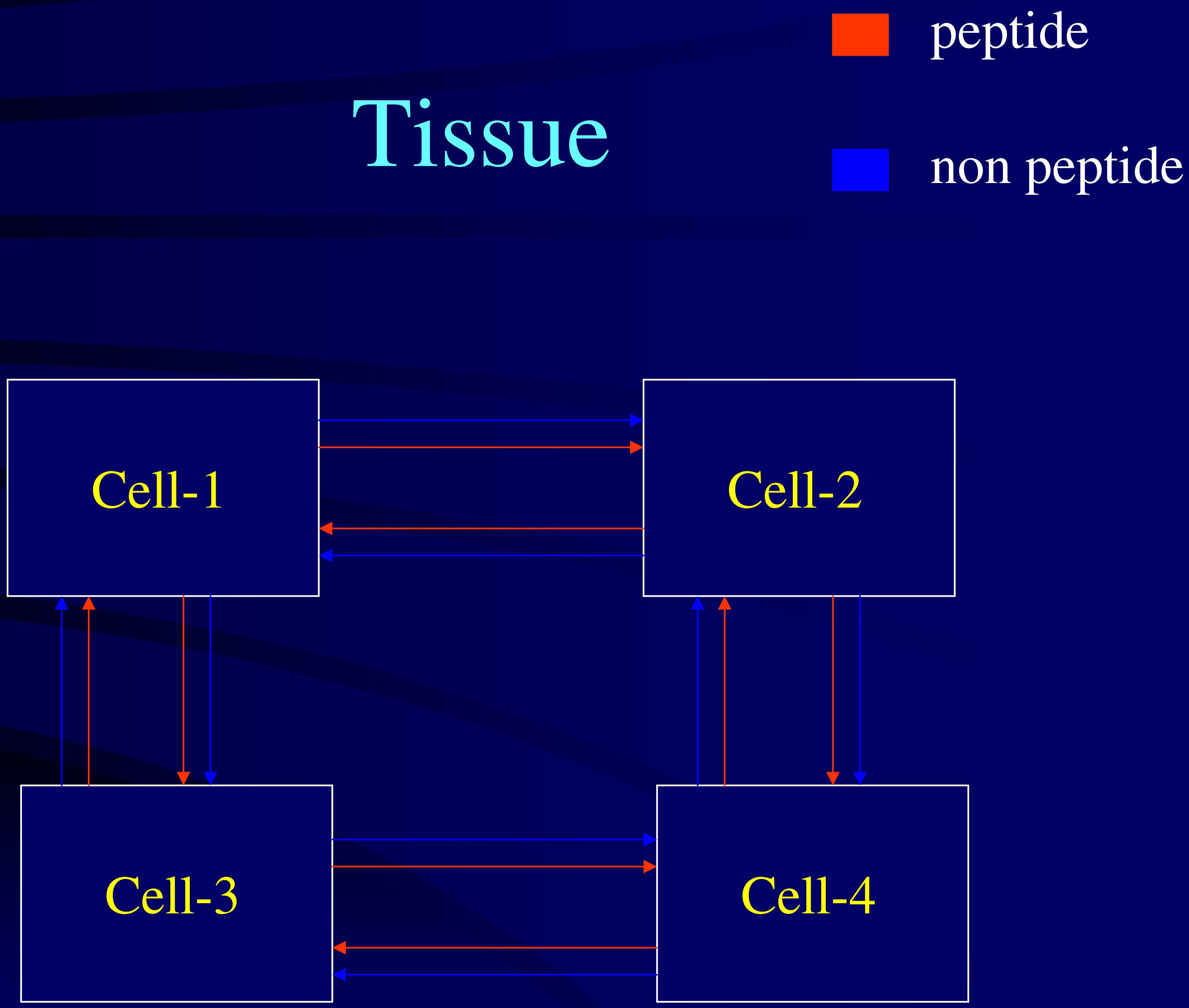
each line comes from one gene clustering

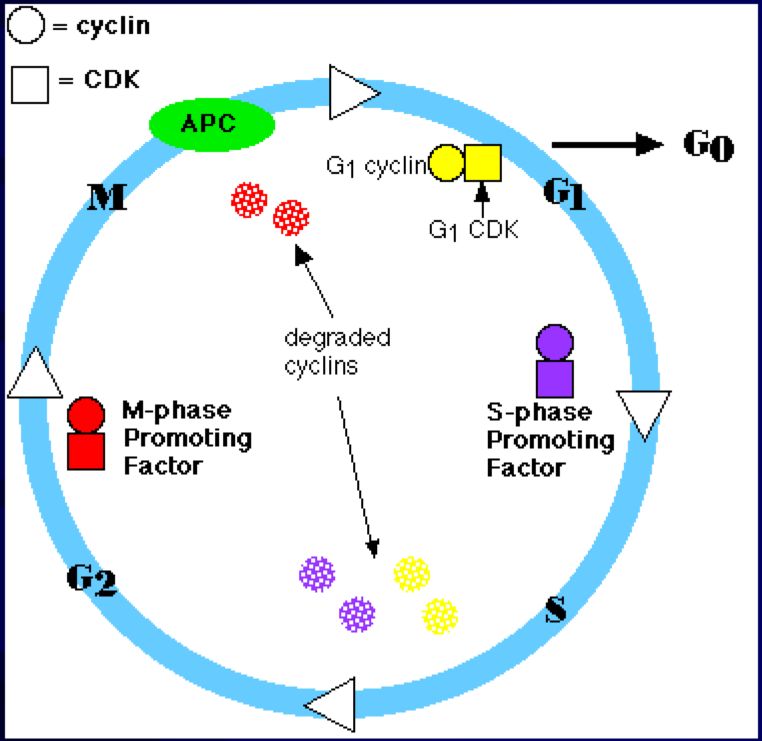

Designed by exhaustive simulations
Controllable
Limit circle of size N
Robust


What genes regulate the
pathway A->B->C->D ?
Wet Lab
Σ
Proteome
Transcriptome
Genome
Pathways

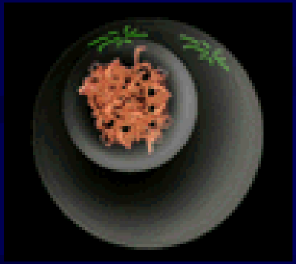
Cell Cycle Modeling

Tissue

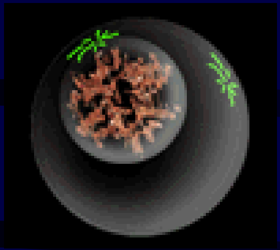


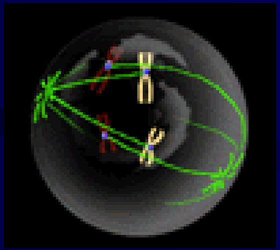

= cyclin
= CDK
APC
G1 cyclin
G1 CDK
G0
M
G1
degraded
cyclins
M-phase
Promoting
Factor
S-phase
Promoting
Factor
G2
S

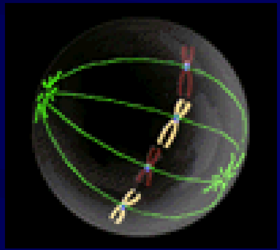
animation



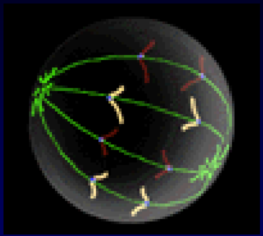
Interphase

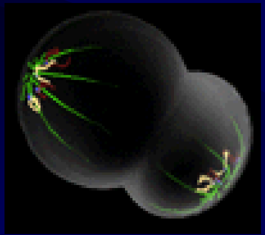


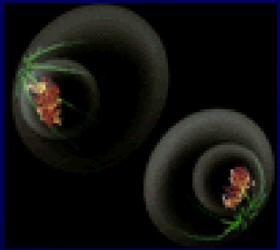




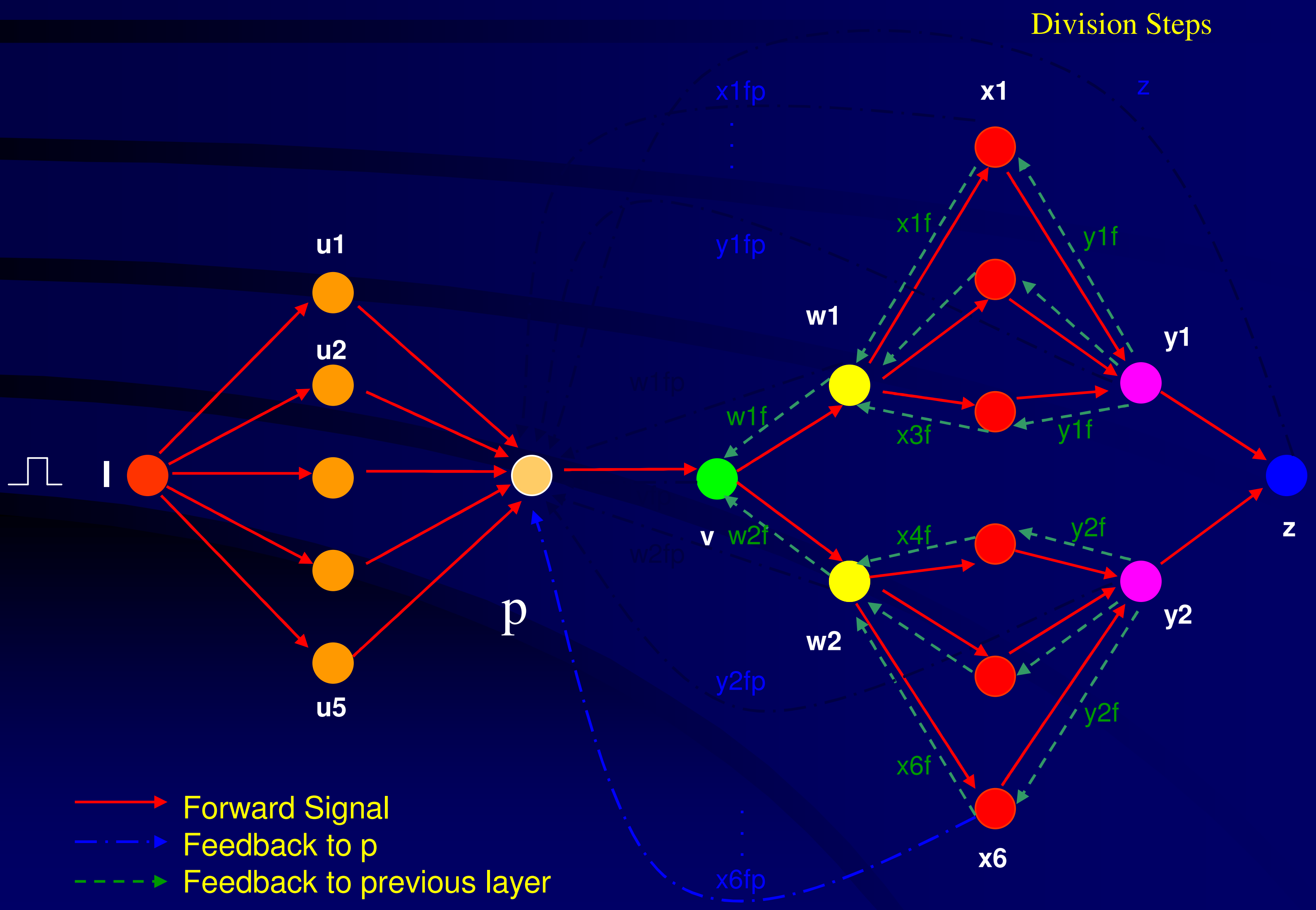
Mitosis

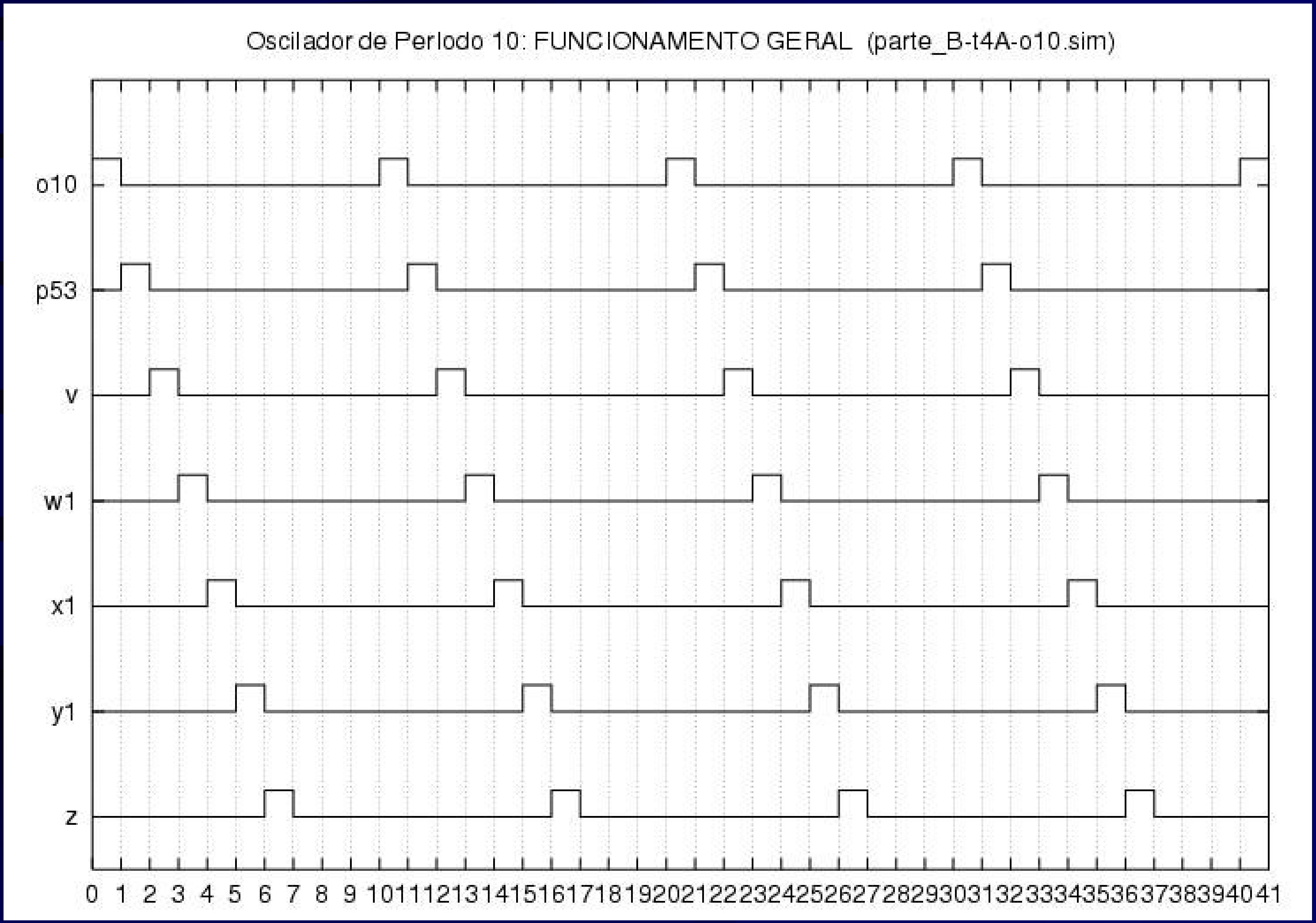


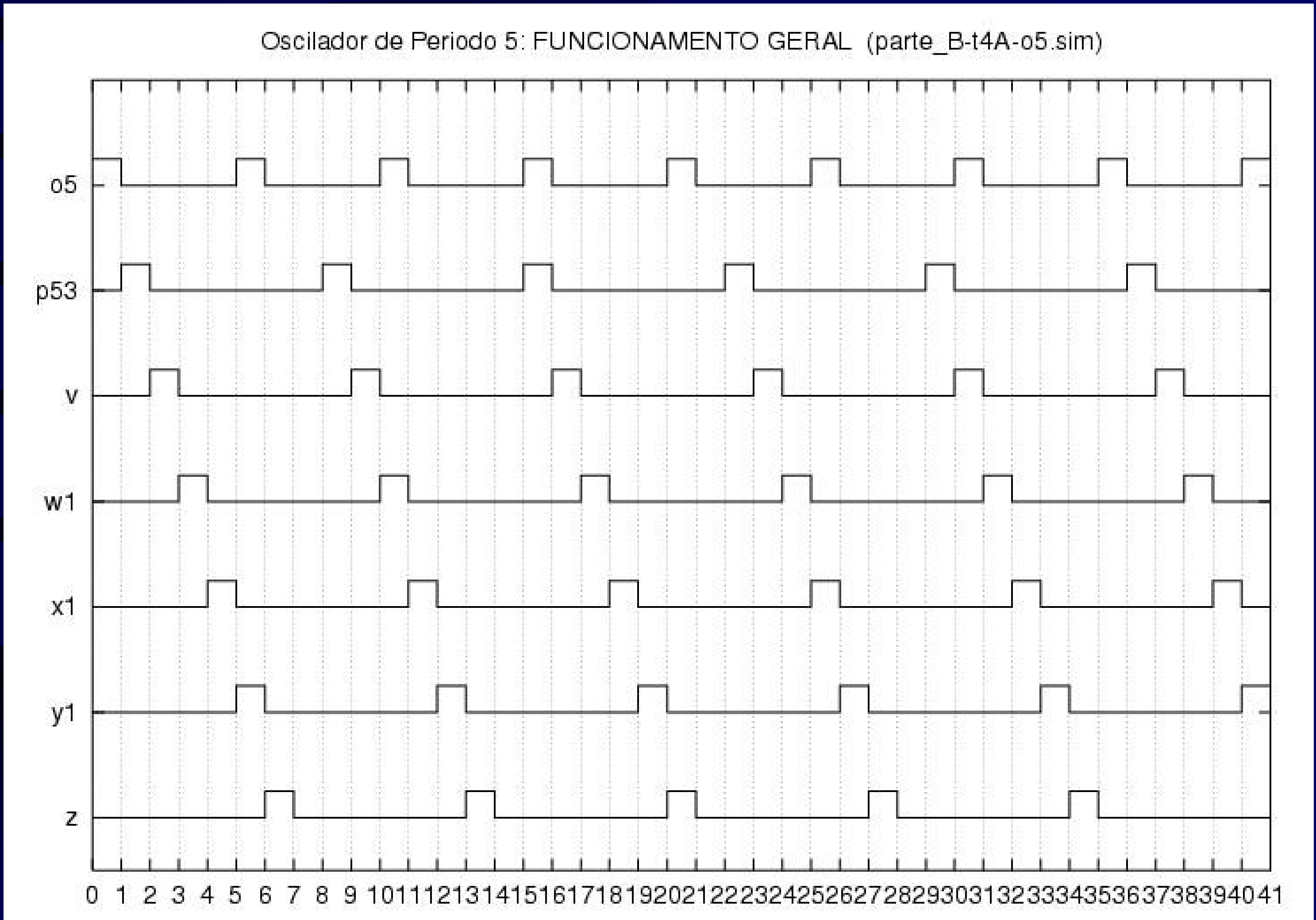




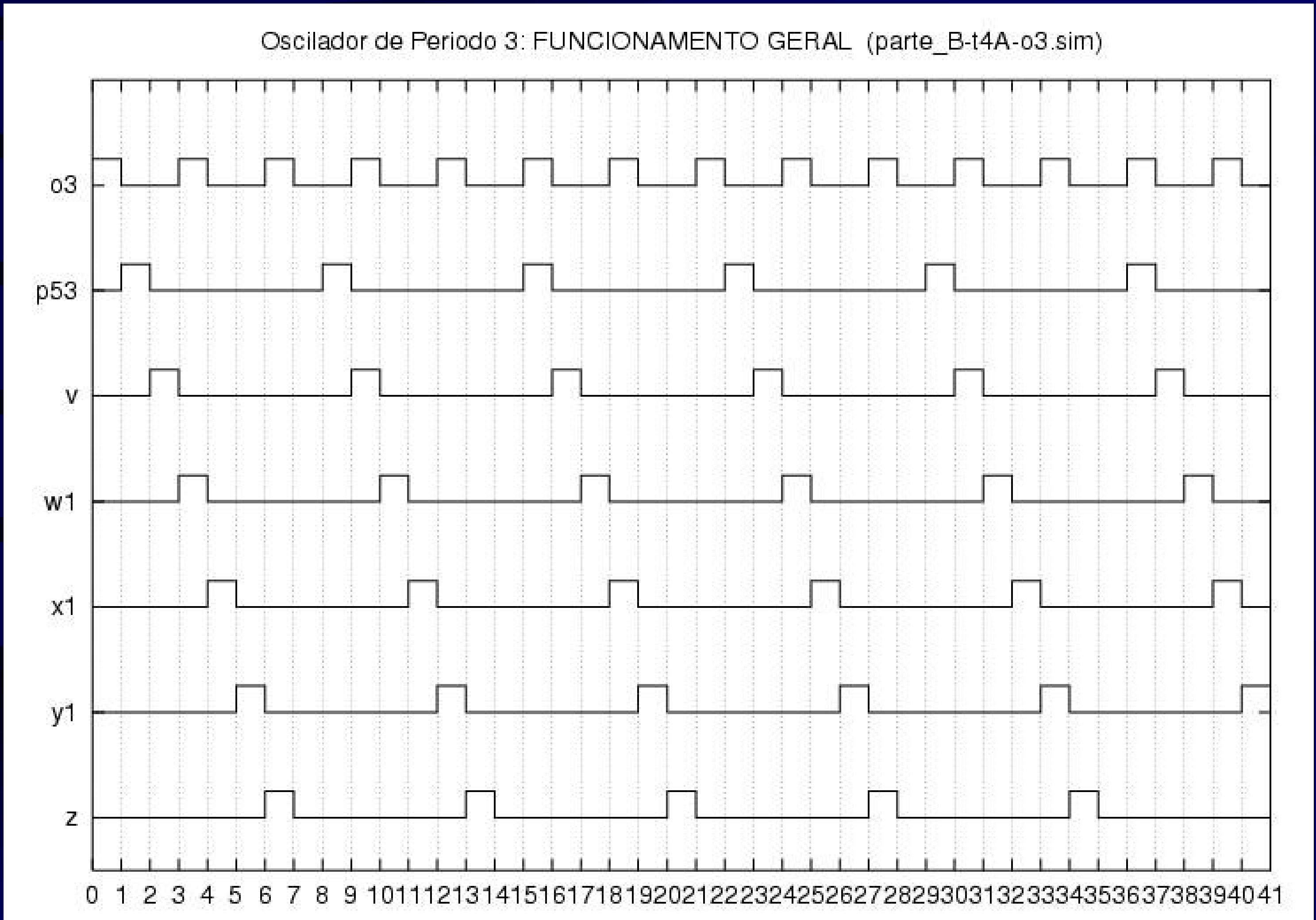
Cell Cycle Modeling

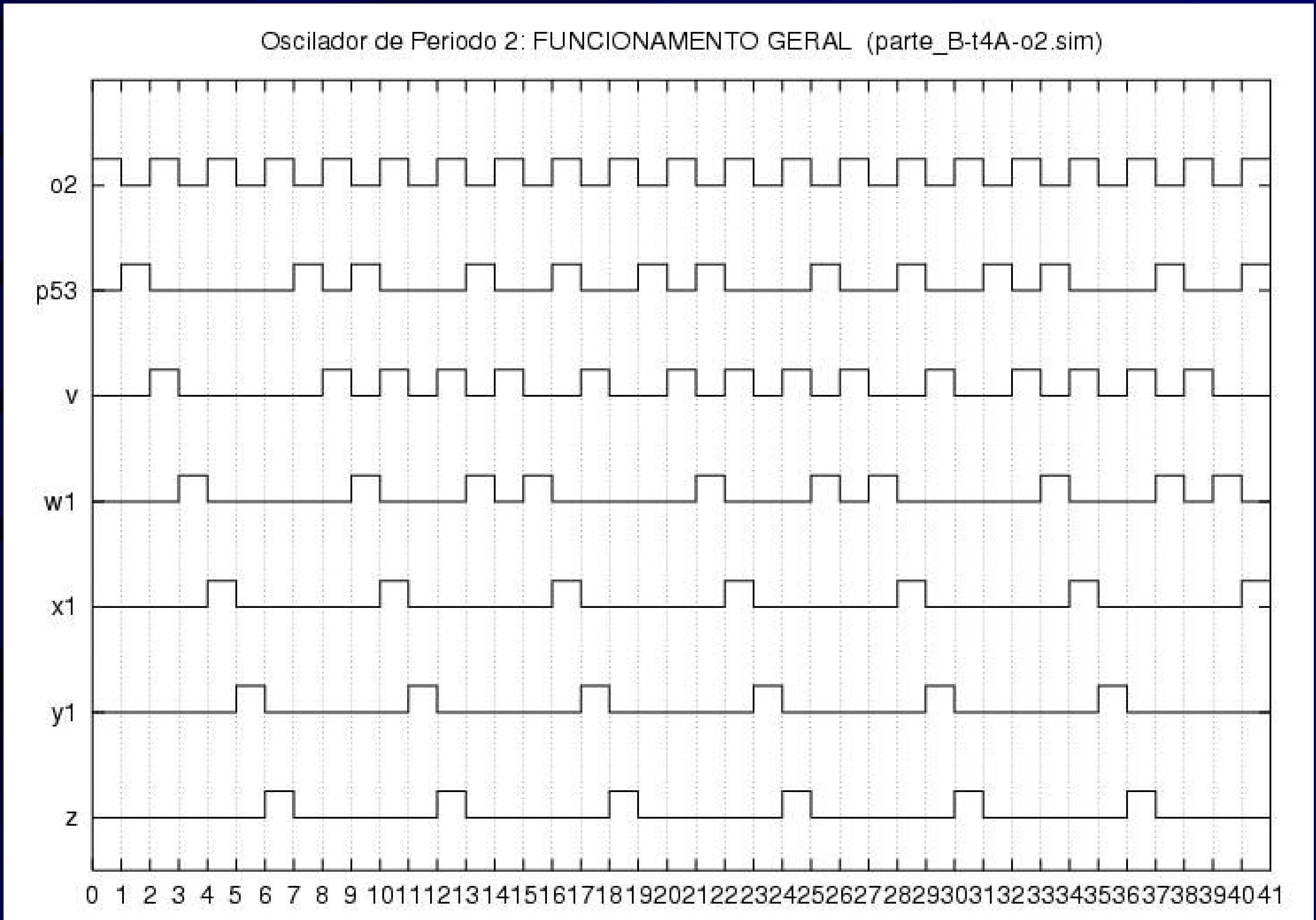



Oscilador de Perlodo 10: FUNCIONAMENTO GERAL (parte_B-t4A-o10.sim)
o10
p53
v
w1
x1
y1
z
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41

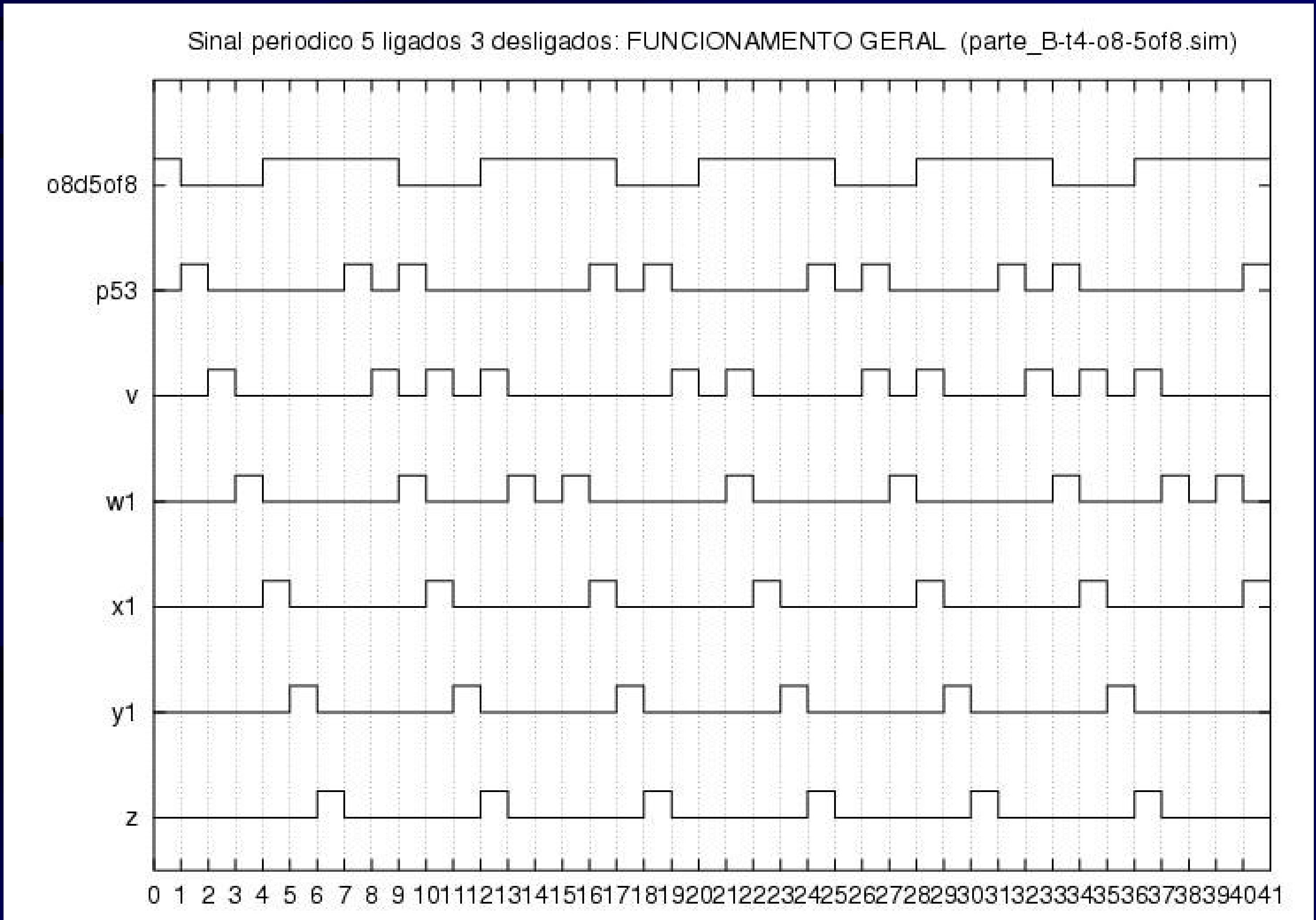


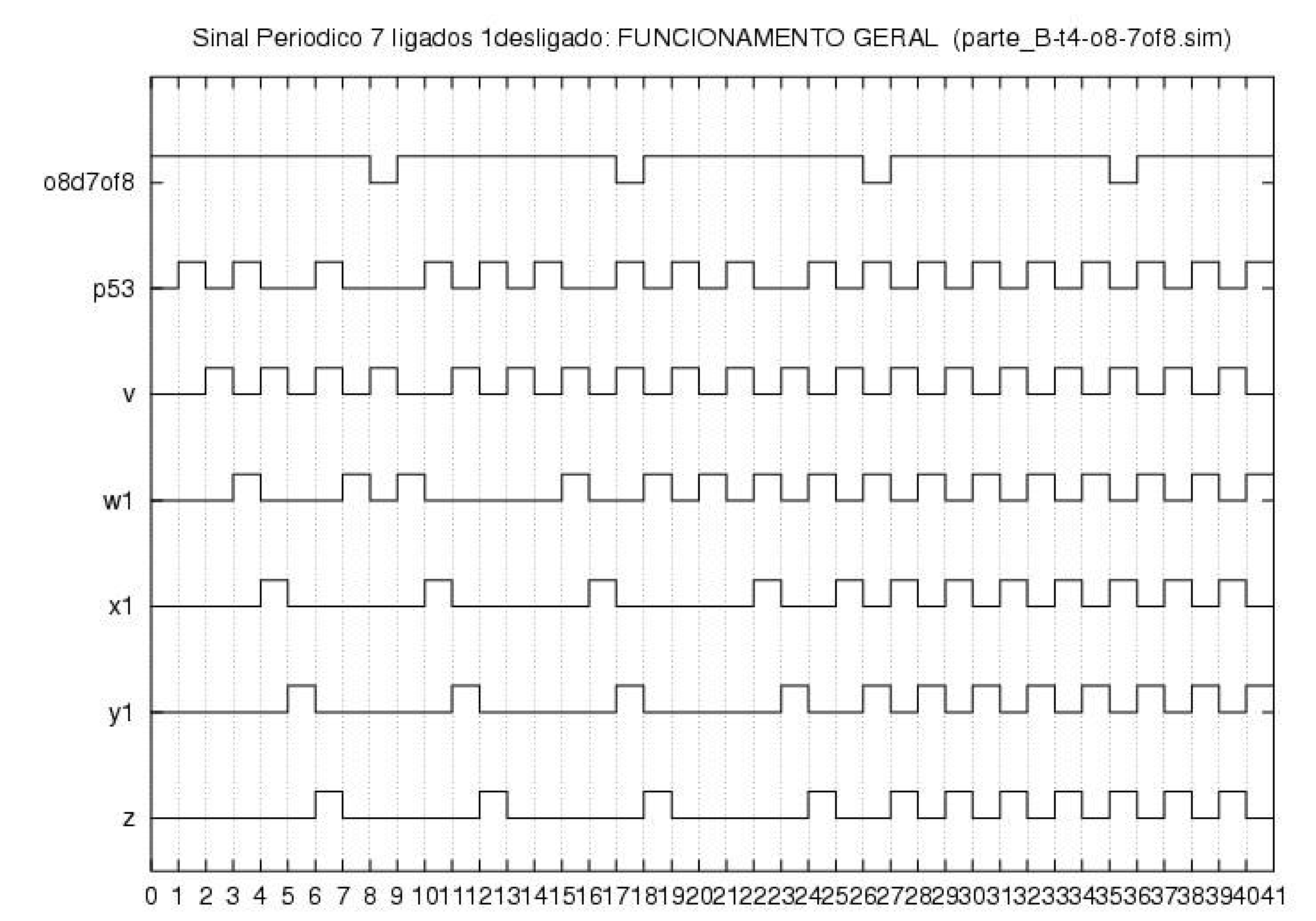
Oscilador de Periodo 5: FUNCIONAMENTO GERAL (parte_B-t4A-o5.sim)
o5
p53
v
w1
x1
y1
z
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41


Oscilador de Periodo 3: FUNCIONAMENTO GERAL (parte_B-t4A-o3.sim)
o3
p53
v
w1
x1
y1
z
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41

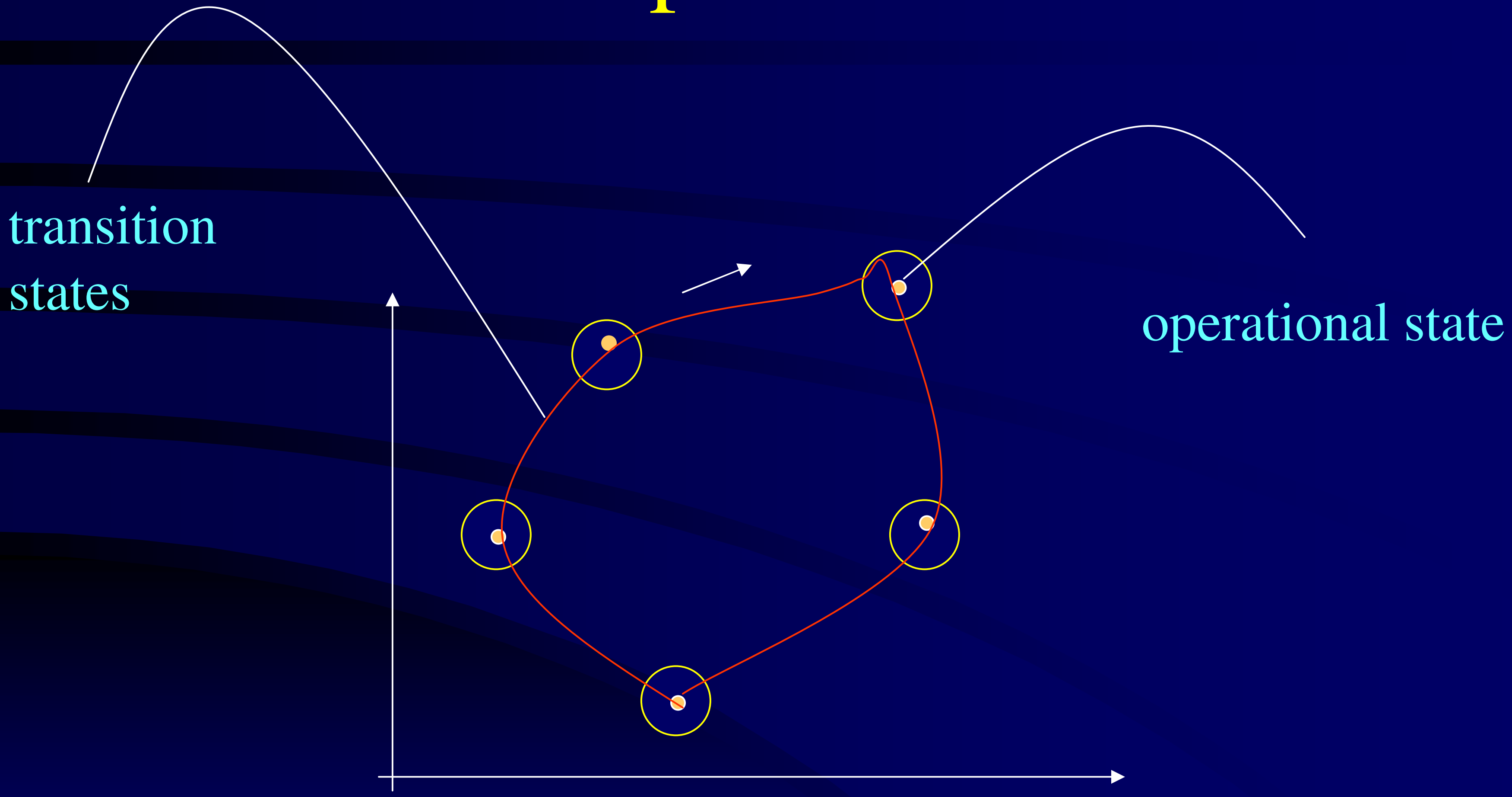


Oscilador de Periodo 2: FUNCIONAMENTO GERAL (parte_B-t4A-o2.sim)
o2
p53
v
w1
x1
y1
z
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41

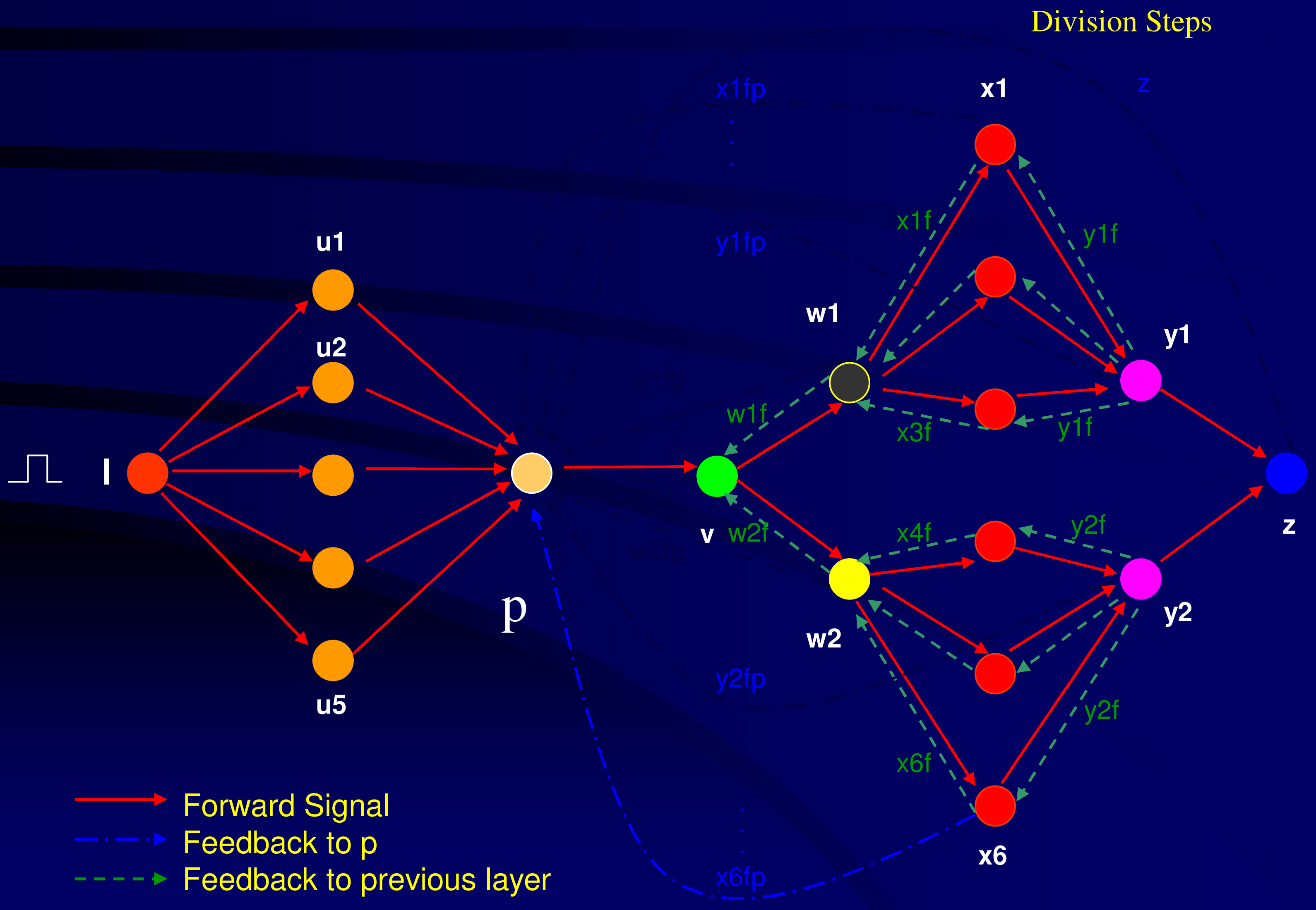

Sinal periodico 5 ligados 3 desligados: FUNCIONAMENTO GERAL (parte_B-t4-o8-5of8.sim)
o8d5of8
p53
v
w1
x1
y1
z
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41

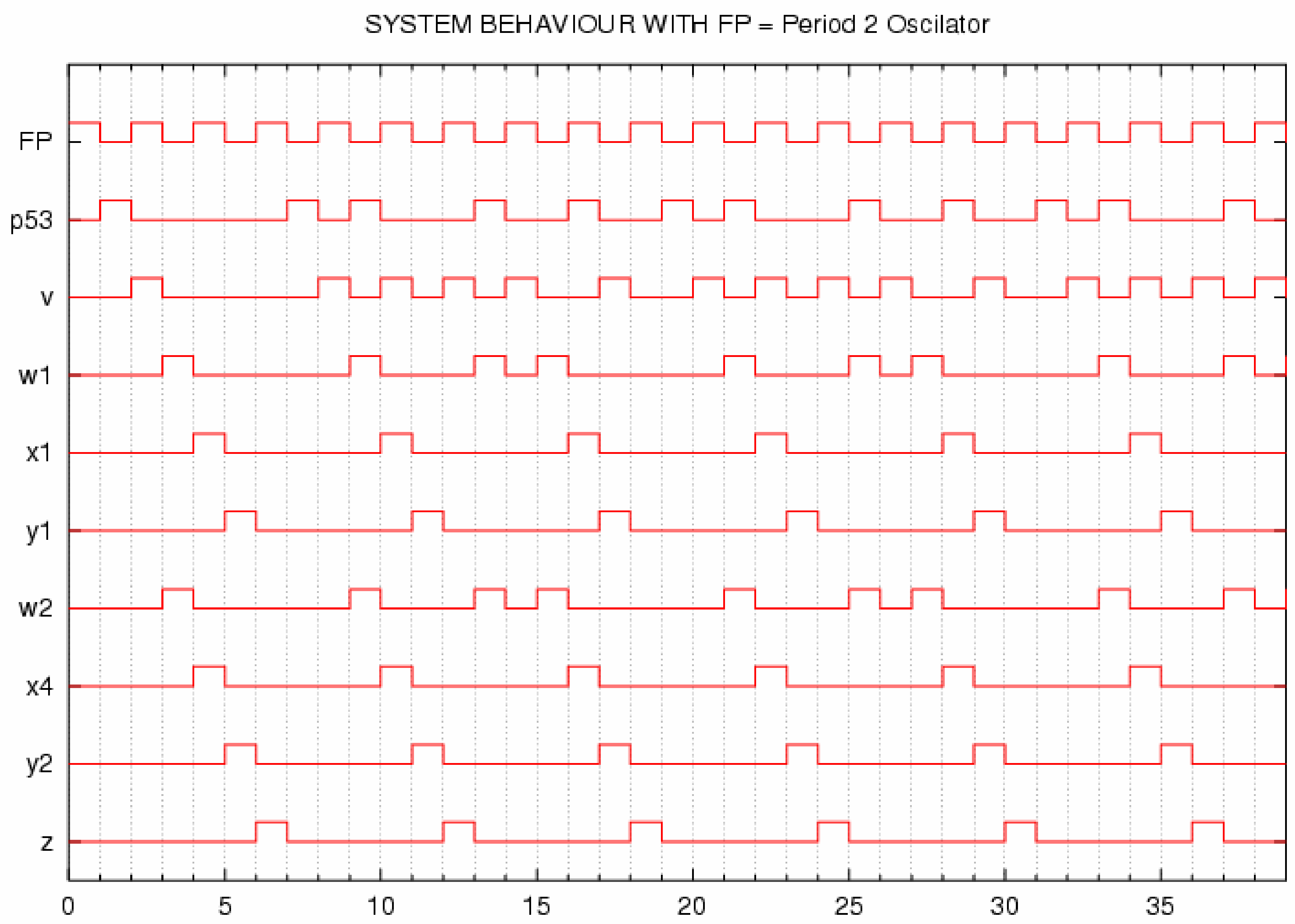

Sinal Periodico 7 ligados 1desligado: FUNCIONAMENTO GERAL (parte_B-t4-o8-7of8.sim)
o8d7of8
p53
v
w1
x1
y1
z
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41

Robust Operational States

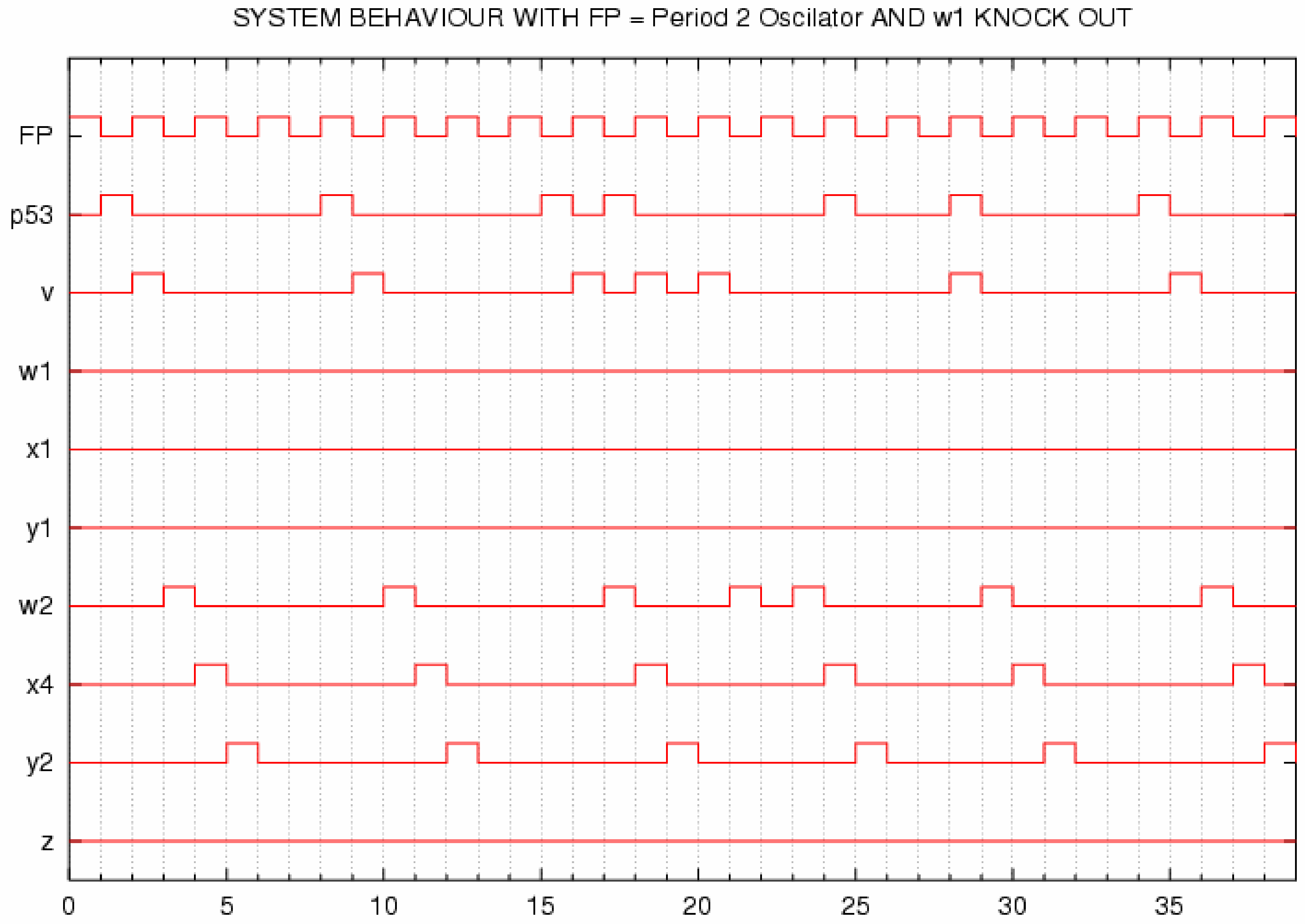


Knock out


Division Steps
x1fp
z
x1
u1
x1f
y1f
y1fp
w1
y1
u2
w1f
x3f
y1f
I
v
w2f
x4f
y2f
z
p
w2
y2
y2fp
u5
y2f
x6f
x6
x6fp
Forward Signal
Feedback to p
Feedback to previous layer



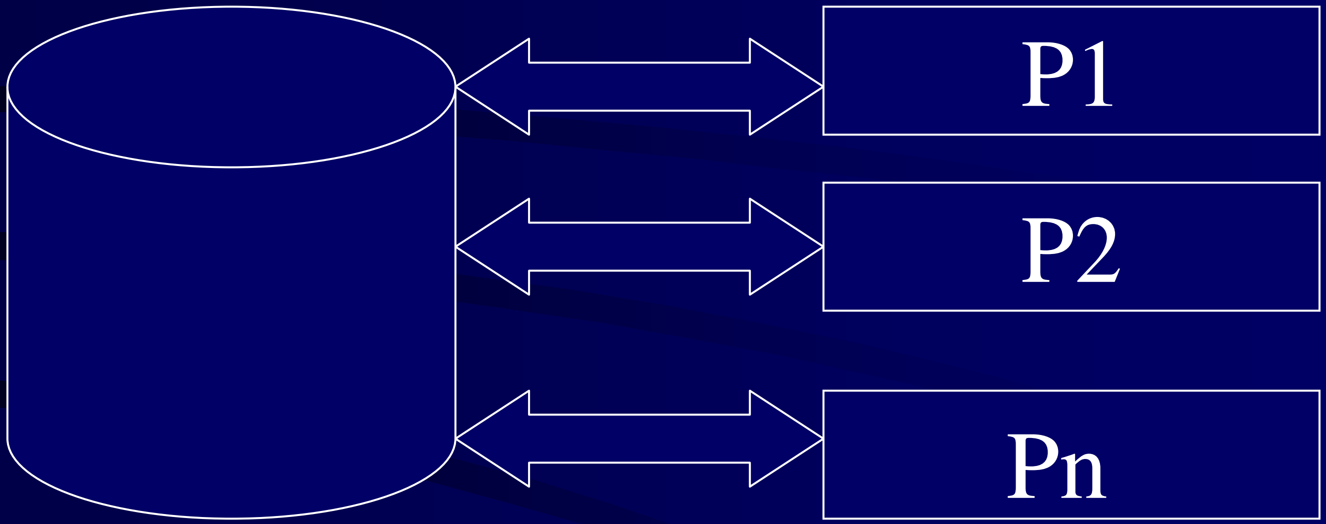
SYSTEM BEHAVIOUR WITH FP = Period 2 Oscilator
FP
p53
v
w1
x1
y1
w2
x4
y2
z
0
5
10
15
20
25
30
35


SYSTEM BEHAVIOUR WITH FP = Period 2 Oscilator AND w1 KNOCK OUT
FP
p53
v
w1
x1
y1
w2
x4
y2
z
0
5
10
15
20
25
30
35

Discussion

- Dynamical systems is an adequate language to express biological phenomena
- To discuss individual gene functionality does not make sense
- Gene functionality is the action of a set of genes working in concert, the genetic networks
- Challenge: design dynamical systems that mimic genetic networks
- In the future, functional data basis will store dynamical models. The research challenge will be to improve and integrate them.

Objected oriented database



Pi : analytical and mining procedures (kernel parallel)

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