Simulator for gene expression networks

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Outline

- Introduction
- Finite Chain Dynamical Systems (FCDS)
- A simulator for FCDS
- Cell cycle control
- Conclusion

Introduction

Gene Expression Network

- A system of genes that control cellular phenomena. For example: cell cycle.

- A gene send messages to other genes

- A set of genes may activate or inactivate other genes.

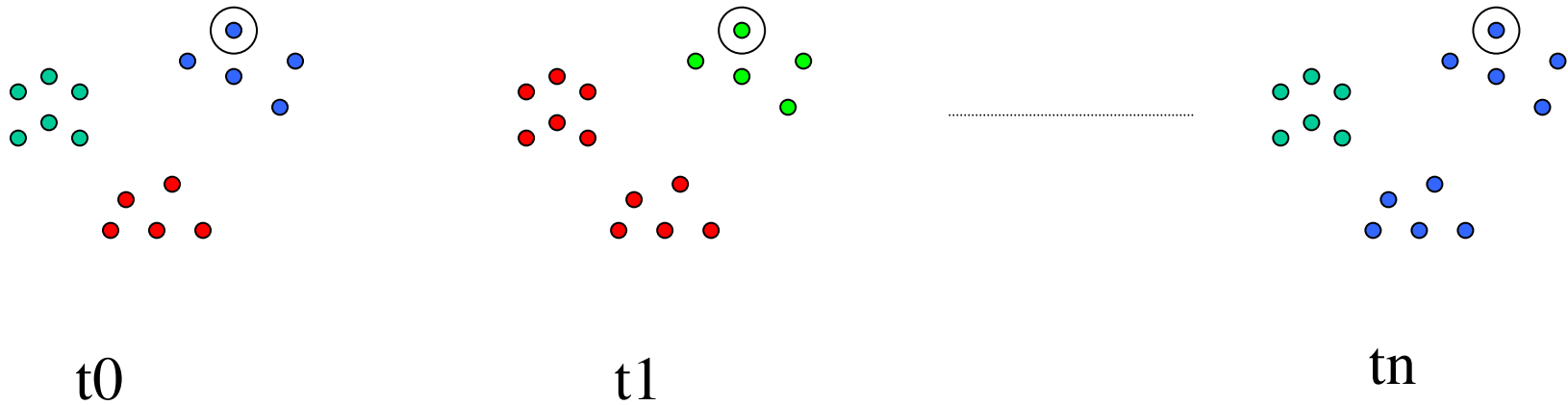- Expression levels change in time

Gene Expression Network
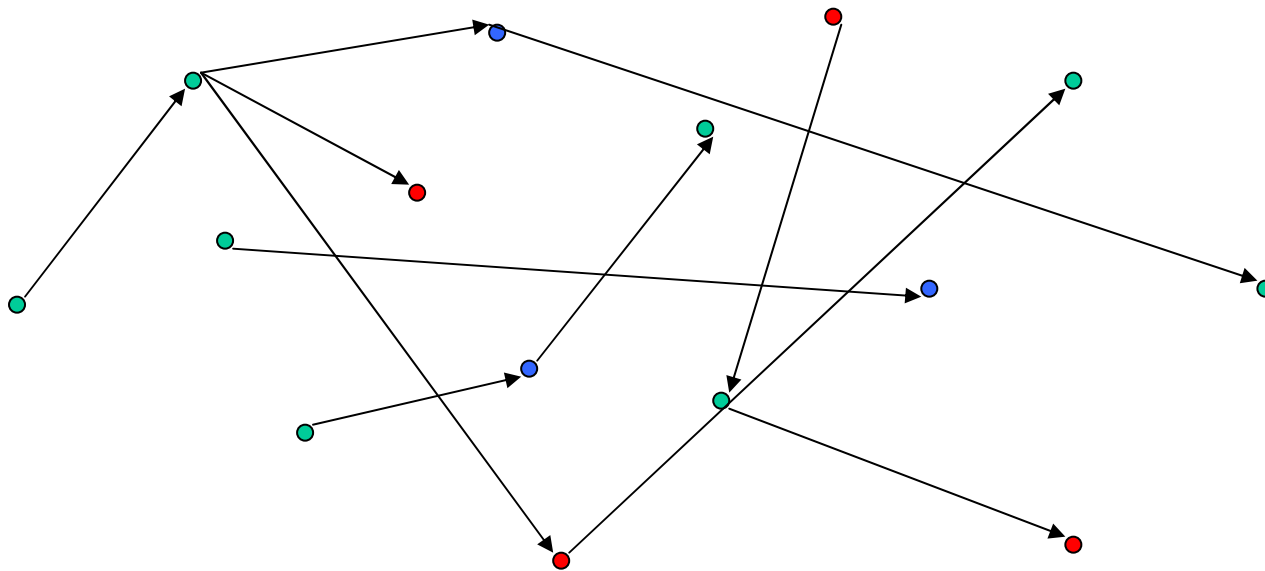
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Genetic Systems

- Gene networks are dynamical systems
- The architecture and dynamics of these systems are unknown
- Microarrays permit to observe states of the systems

System Evolution

- Trajectory

t0   t1   tn

Gene Systems identification

- System architecture and dynamics theoretically can be estimated purely from microarray data

- The amount of necessary data is not feasible

- Use of disciplinary (all kinds of information) knowledge together with microarray data is a more realistic approach

Knowledge representation

- Disciplinary knowledge is condensed in models designed heuristically through simulations

- Systems identified from microarrays should have some degree of consistency with the heuristic models.

Chain Dynamical System

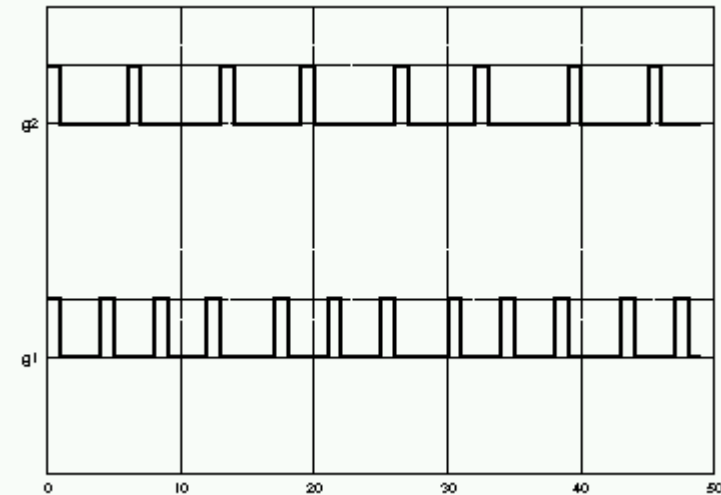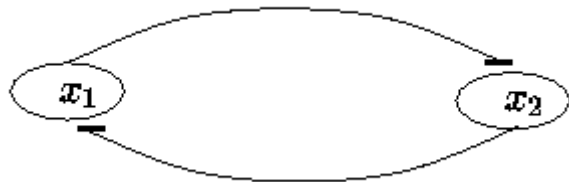# Diagram of a chain dynamical system
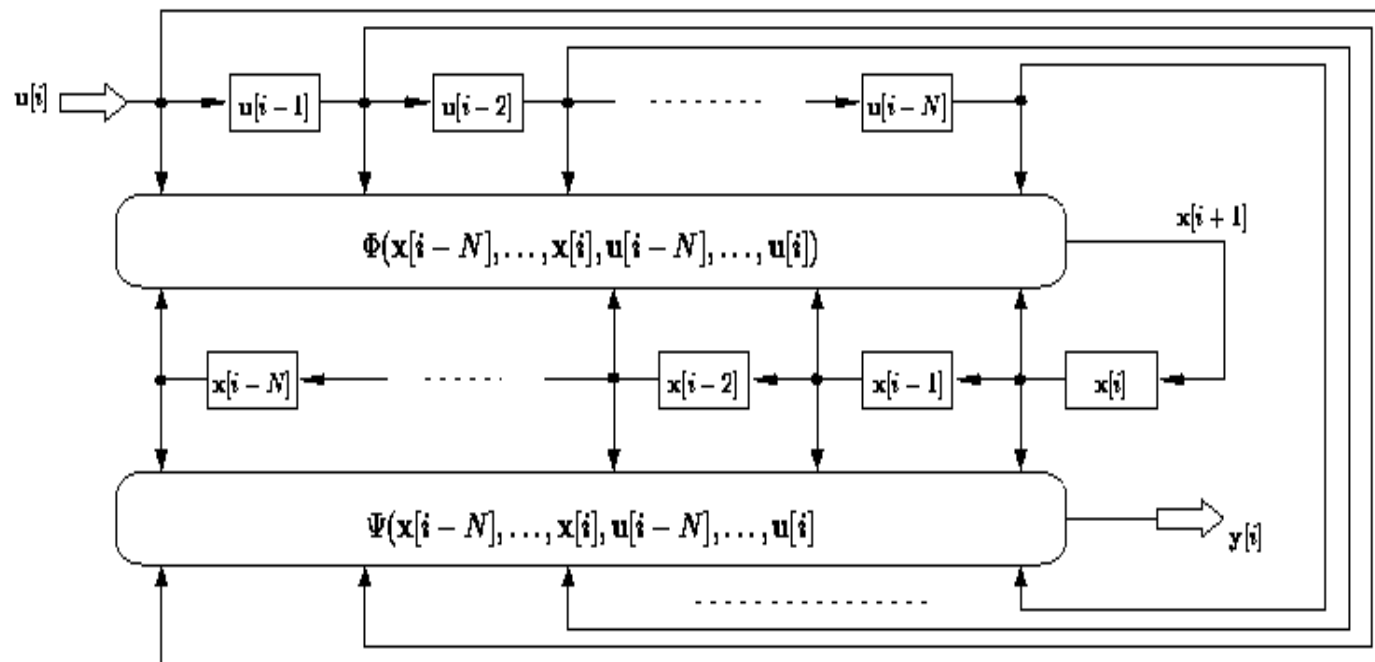
Mathematical Formulation

$$\mathbf{x}[i], \mathbf{u}[i] \in \mathcal{L}^n \qquad\qquad \mathbf{y}[i] \in \mathcal{L}^m$$

$$\Phi_i : \mathcal{L}^{2(N+1)n} \to \mathcal{L}^n \qquad\qquad \Psi_i : \mathcal{L}^{2(N+1)n} \to \mathcal{L}^m$$

$$\mathbf{x}[i+1] = \Phi_i(\mathbf{x}[i-N], \ldots, \mathbf{x}[i], \mathbf{u}[i-N], \ldots, \mathbf{u}[i])$$

$$\mathbf{y}[i] = \Psi_i(\mathbf{x}[i-N], \ldots, \mathbf{x}[i], \mathbf{u}[i-N], \ldots, \mathbf{u}[i]),$$

Example

$$\phi_1(\mathbf{x}[i-5],\mathbf{x}[i-4],\mathbf{x}[i-3],\mathbf{x}[i-2],\mathbf{x}[i-1],\mathbf{x}[i]) = \overline{x}_1[i-3] \cdot \overline{x}_1[i-2] \cdot \overline{x}_1[i-1] \cdot \overline{x}_2[i-5] \cdot \overline{x}_2[i-3] \cdot \overline{x}_2[i-1]$$
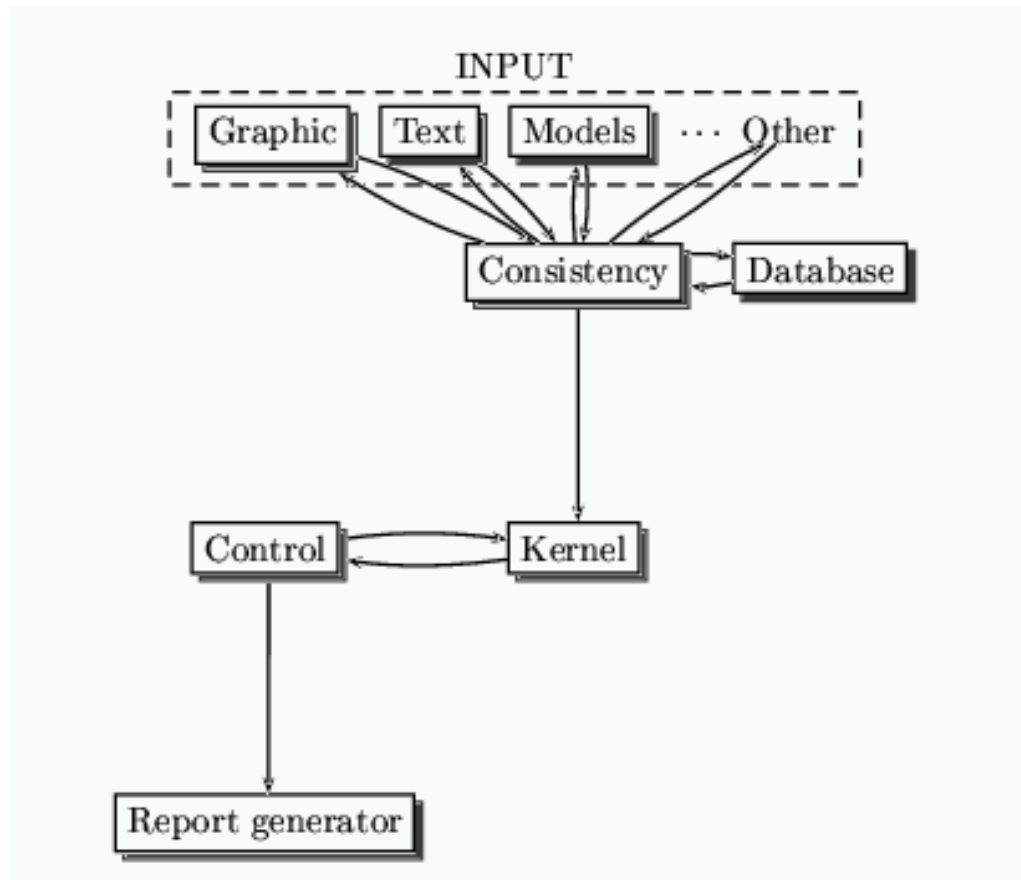
$$\phi_2(\mathbf{x}[i-5],\mathbf{x}[i-4],\mathbf{x}[i-3],\mathbf{x}[i-2],\mathbf{x}[i-1],\mathbf{x}[i]) = \overline{x}_1[i-4] \cdot \overline{x}_2[i-5] \cdot \overline{x}_2[i-4] \cdot \overline{x}_2[i-3] \cdot \overline{x}_2[i-2] \cdot \overline{x}_2[i-1]$$
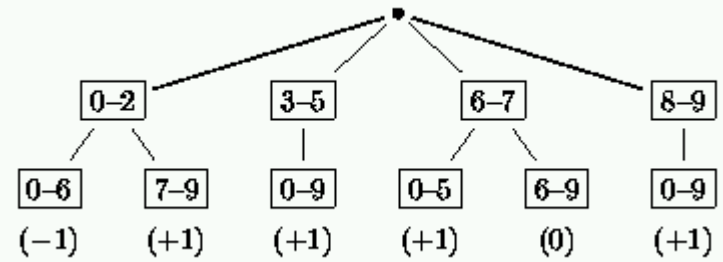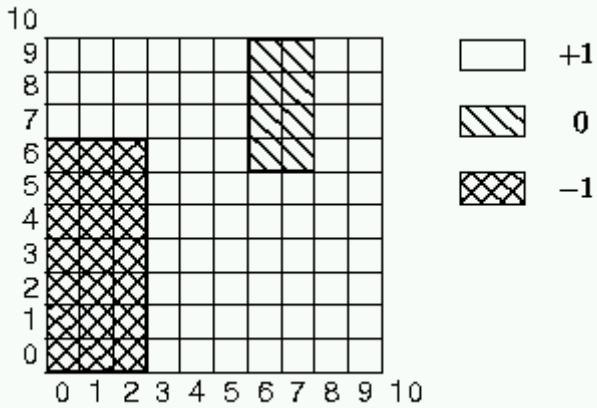
Why chain dynamical systems?

- Discrete systems are enough to represent phenomena of interest

- Quite general non linear systems can be represented

- Learning techniques available are appropriate to include prior knowledge

A simulator for chain dynamical systems

Simulator Architecture

Functions Representation

System Description

```
Gene g1:{1.00 f1 g1[4] g1[3] g1[2] g1[1] g2[6] g2[5] g2[4] g2[3] g2[2] g2[1];};
Gene g2:{1.00 f2 g1[4] g1[3] g1[2] g1[1] g2[6] g2[5] g2[4] g2[3] g2[2] g2[1];};

# Function definitions
# ----------------------

def f1: [0000000000..1000101010]: 1;
def f2: [0000000000..0111100000]: 1;

# History
# ------------------------
hist g1: [0 0 0 0 0 0 0 0 0 0 0 0 0];
hist g2: [0 0 0 0 0 0 0 0 0 0 0 0 0];

end
```

Cell Cycle Control

Biological Model

- Cell cycle control by Fibroblast Growth Factor 2 (FGF2) and Adrenocorticotropic Hormone (ACTH) in the Y1 adrenocortical cell line

- FGF2 has long been considered a candidate for participating in cell cycle control, but its molecular mechanisms remain obscure

Mitogenic response in G0/G1 cell cycle to FGF2:

- Rapid and transient activation of extra cellular signal-regulated kinases
- Transcription activation of c-fos, c-jun and c-myc genes
- Induction of c-Fos and c-Myc proteins and cyclin D1 protein
- DNA synthesis stimulation

Anti-mitogenic response in G0/G1 cell cycle to ACTH:

- Blocks FGF2 mitogenic response
- Keeps ERK activation and c-Fos and cyclin D1 induction on
- Down regulates the levels of the c-Myc protein
- Down regulates the active form of Akt/PKB enzyme

A model for the FGF2/ACTH influence on cell cycle
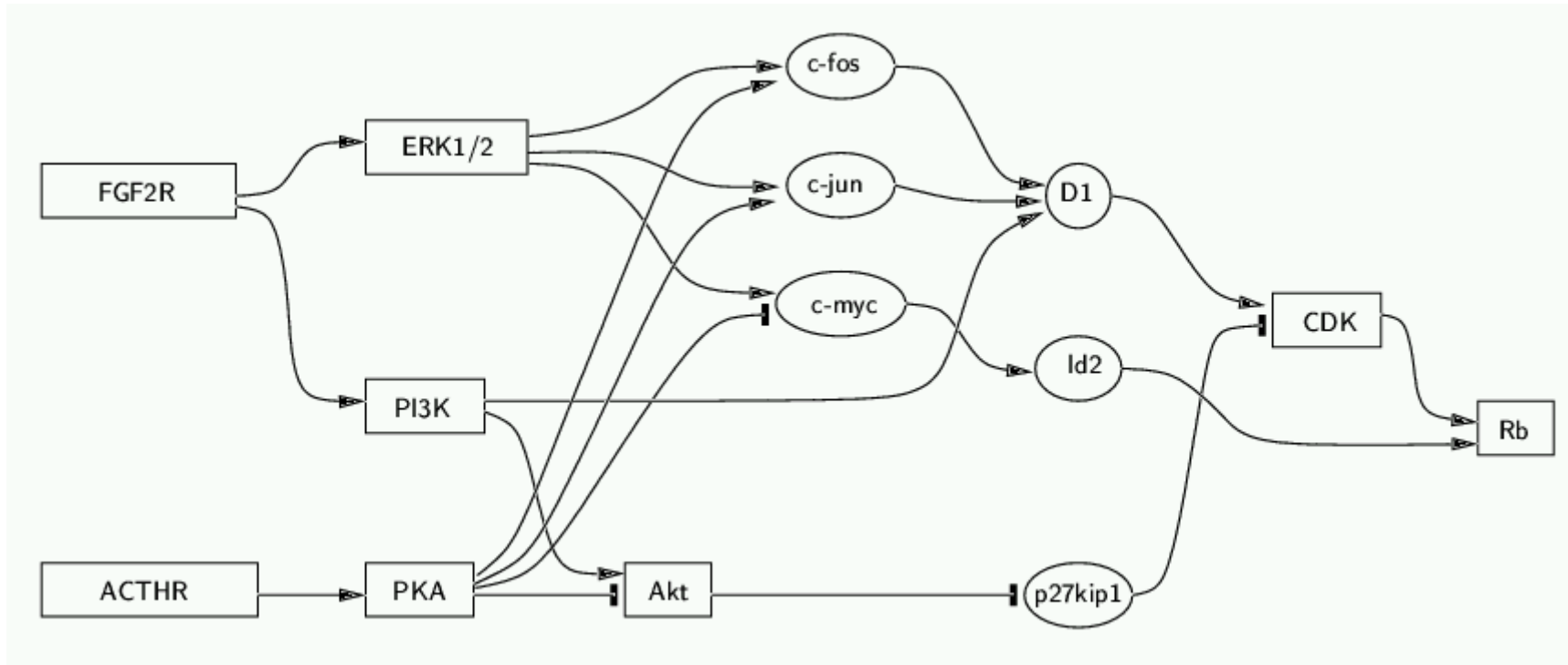
Model Formalization

Element	Rule
FGF2R$[i]$	receives external signal
ACTHR$[i]$	receives external signal
ERK1/2$[i]$	FGF2R$[i-1] \cdot \overline{\text{anti-ERK}[i-1]}$
PI3K$[i]$	FGF2R$[i-1] \cdot \overline{\text{anti-PI3K}[i-1]}$
PKA$[i]$	ACTHR$[i-1] \cdot \overline{\text{anti-PKA}[i-1]}$
Akt$[i]$	$(\text{PI3K}[i-2] + \text{PI3K}[i-1]) \cdot \overline{\text{PKA}[i-2]} \cdot \overline{\text{PKA}[i-1]}$
c-fos$[i]$	ERK1/2$[i-3]$ + ERK1/2$[i-2]$ + PKA$[i-3]$ + PKA$[i-2]$
c-jun$[i]$	ERK1/2$[i-3]$ + ERK1/2$[i-2]$ + PKA$[i-3]$ + PKA$[i-2]$
c-myc$[i]$	$\overline{\text{PKA}[i-2]} \cdot \overline{\text{PKA}[i-1]} \cdot (\text{ERK1/2}[i-3] + \text{ERK1/2}[i-2])$
D1$[i]$	c-fos$[i-1] \cdot$ c-jun$[i-1] \cdot (\text{PI3K}[i-4] - \text{PI3K}[i-3])$
Id2$[i]$	c-myc$[i-1]$
p27kip1$[i]$	$\overline{\text{Akt}[i-2]}$
CDK$[i]$	D1$[i-1] \cdot \overline{\text{p27kip1}[i-1]}$
Rb$[i]$	CDK$[i-1] \cdot$ Id2$[i-2]$

Effect of one pulse of FGF2

Effect of one pulse of ACTH
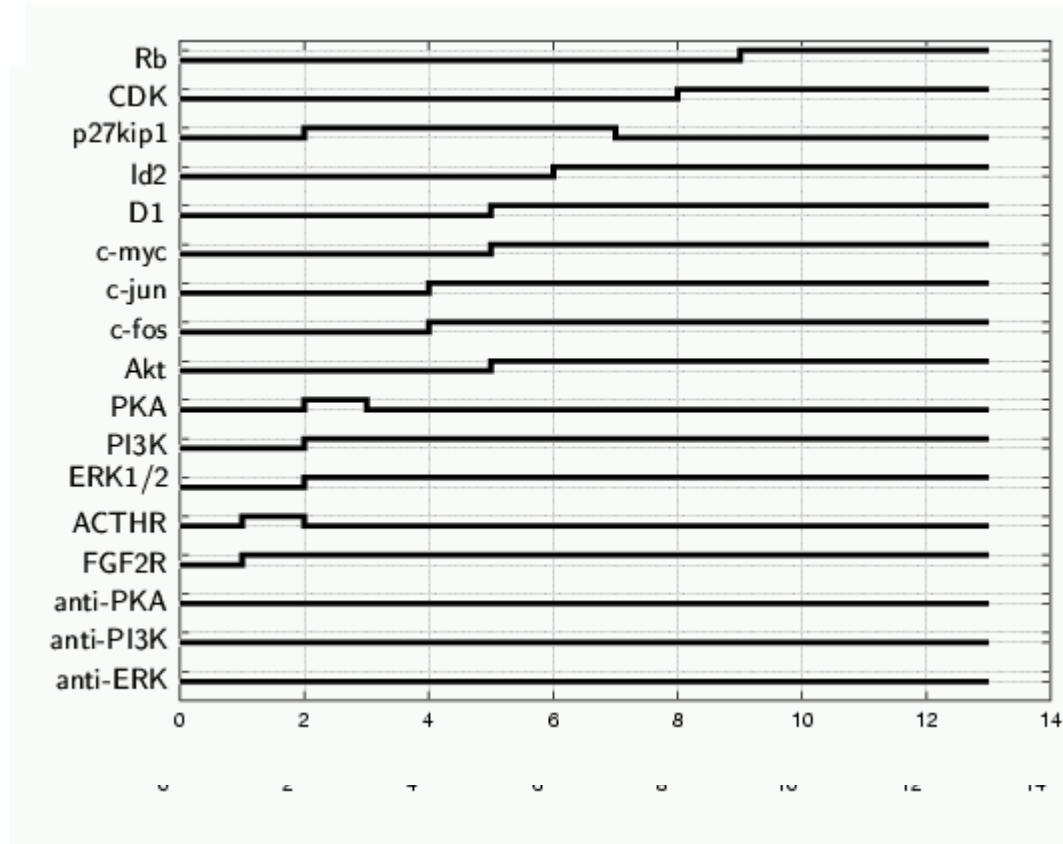
Conclusion

- We proposed chain dynamical systems as a model for studying genetic networks,

- presented the architecture of a chain dynamical system simulator,

- proposed a model for a subsystem of genes and proteins that control a cell cycle,

- simulated the proposed model

- The next step of this research is to incorporate microarray information.