

Modeling Cell-Cycle Regulation by Discrete Dynamical Systems

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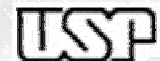
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GENSIPS 2005



Outline

- **Introduction**
- **Genetic Regulatory Networks**
- **Probabilistic Genetic Networks**
- **Cell-Cycle Control System Overview**
- **Yeast Cell-Cycle Model**
- **Our Cell-Cycle Control Model**
- **Discussion**

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MODELING is an important tool for **BIOLOGICAL RESEARCH**

Challenge:

DESIGN A MODEL THAT MIMICS CELL-CYCLE CONTROL

Recently published model of the yeast cell-cycle
(built from documented biological knowledge):

ROBUSTNESS PROBLEMS.

We created a model based on biological hypothesis.

Interactively, it was simulated and modified.

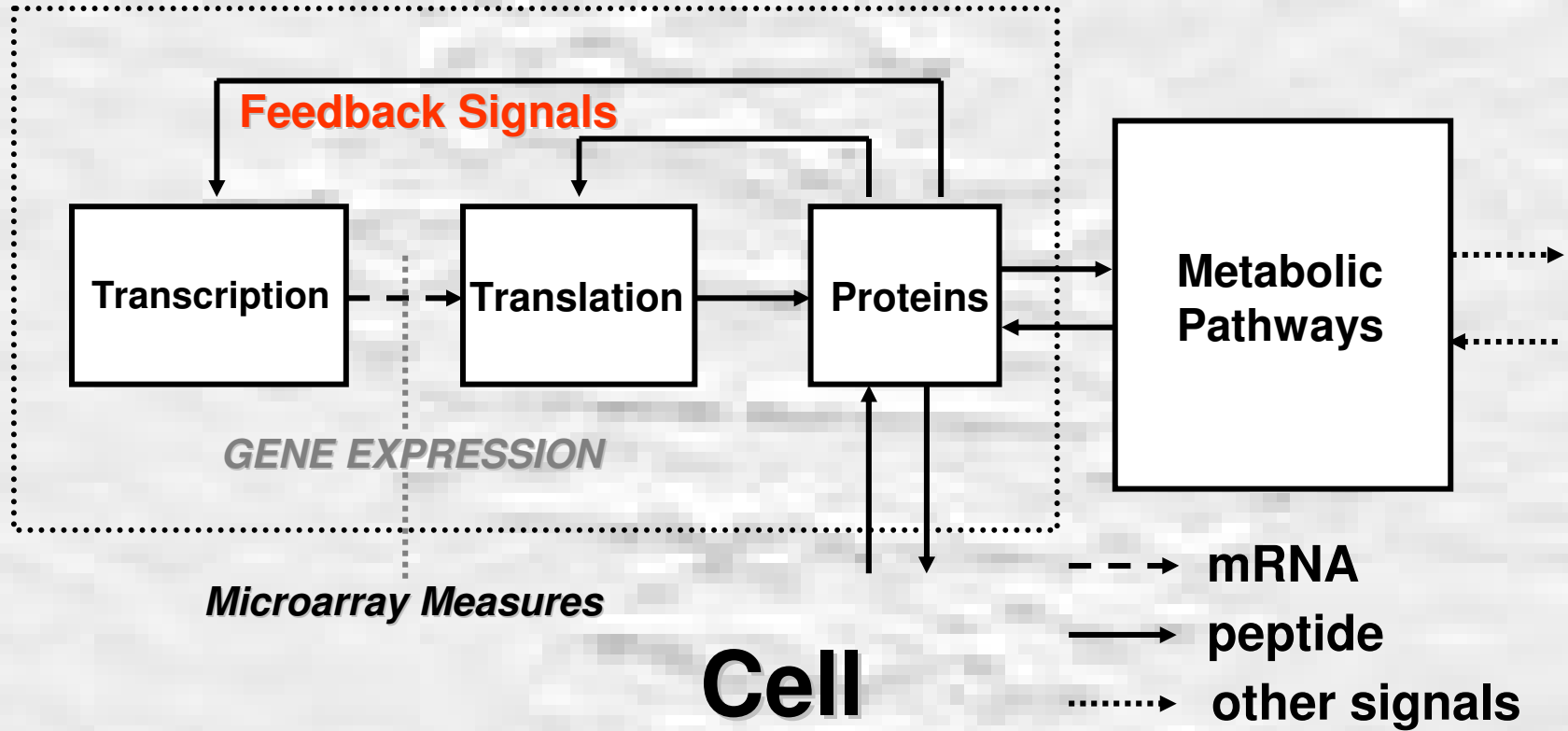
The designed model presents a **Remarkable Robustness**

Our model possesses **MECHANISMS** ensuring **ROBUSTNESS**,
that are not in the previous model and may exist in nature

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GENE REGULATION NETWORK



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GENE is a
NON LINEAR STOCHASTIC GATE

**Expression of a Gene depends on
Activator and Inhibitory Signals**

SYSTEM: built by compiling these gates

Expression of a gene at time t $x_i \in R, R = \{0, 1, 2\}$

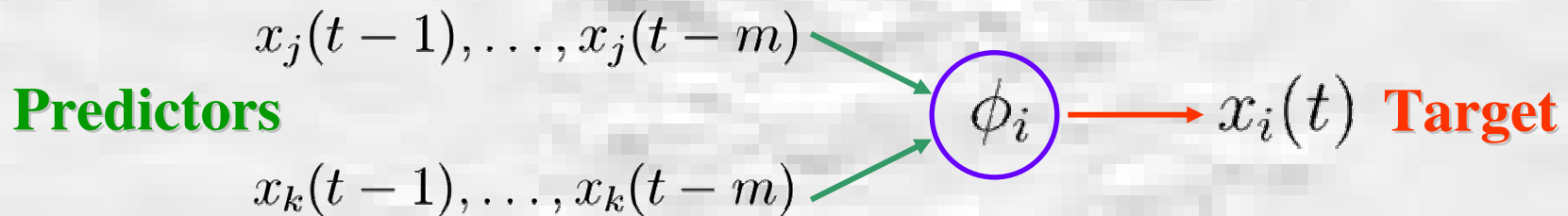
State of the regulatory network at time t $x(t) = \begin{bmatrix} x_1(t) \\ x_2(t) \\ \vdots \\ x_N(t) \end{bmatrix} \in R^N$

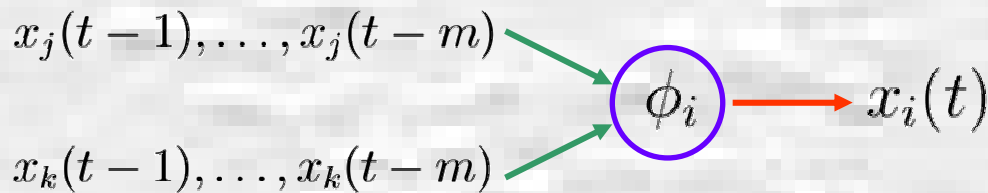
Network Dynamics $x(t) = \phi [x(t-1), x(t-2), \dots, x(t-m)]$

Transition Function

$$\phi \in \mathbb{R}^{N \times m} \rightarrow \mathbb{R}$$

$$\phi = \begin{bmatrix} \phi_1 \\ \phi_2 \\ \vdots \\ \phi_N \end{bmatrix}, \quad x_i(t) = \phi_i [x(t-1), x(t-2), \dots, x(t-m)]$$





**Stochastic
Transition
Function:**

$$x_i(t) = \begin{cases} 0 & p(0|x_j(t-1), \dots, x_j(t-m), x_k(t-1), \dots, x_k(t-m)) \\ 1 & p(1|x_j(t-1), \dots, x_j(t-m), x_k(t-1), \dots, x_k(t-m)) \\ 2 & p(2|x_j(t-1), \dots, x_j(t-m), x_k(t-1), \dots, x_k(t-m)) \end{cases}$$

$\exists y, w, z \in \{0, 1, 2\}, \quad y \neq w \neq z :$

$$\begin{aligned} & p(y|x_j(t-1), \dots, x_j(t-m), x_k(t-1), \dots, x_k(t-m)) \gg \\ & p(w|x_j(t-1), \dots, x_j(t-m), x_k(t-1), \dots, x_k(t-m)) + \\ & p(z|x_j(t-1), \dots, x_j(t-m), x_k(t-1), \dots, x_k(t-m)) \end{aligned}$$

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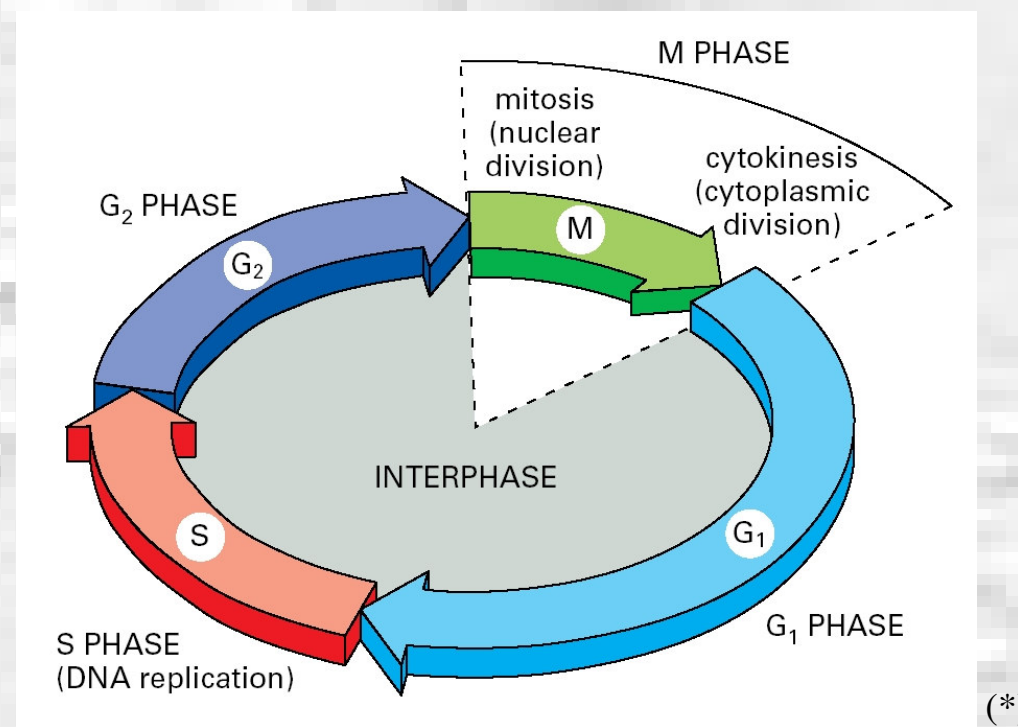
CELL CYCLE:

Orderly sequence of events for the
the **duplication** and **division** of the cell in two daughter cells

(mechanism by which all living things reproduce)

The **basic organization** of the cycle and its **control system**
are essentially **the same in all eucaryotic cells**

Phases of the Cell Cycle



Interphase: (the cell continuously grows)

- **G₁ phase:** gap between M and S phases
- **S phase:** DNA replication
- **G₂ phase:** gap between S and M phases

M phase:

- **Mitosis:** nuclear division
- **Cytokinesis:** cytoplasmic division

* from: Molecular Biology of the Cell - Alberts et al - Garland Science

The control system can **arrest** de cell-cycle
at specific **CHECKPOINTS**,
if some events have not been completed.

Checkpoints generally operate
through
NEGATIVE INTRACELLULAR SIGNALS.

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Model Architecture and Dynamics

Each node i has a binary value $S_i = 1$ or $S_i = 0$

$$S_i(t + 1) = \begin{cases} 1, & \sum_j a_{ij} S_j(t) > 0 \\ 0, & \sum_j a_{ij} S_j(t) < 0 \\ S_i(t), & \sum_j a_{ij} S_j(t) = 0 \end{cases}$$

Transition Function

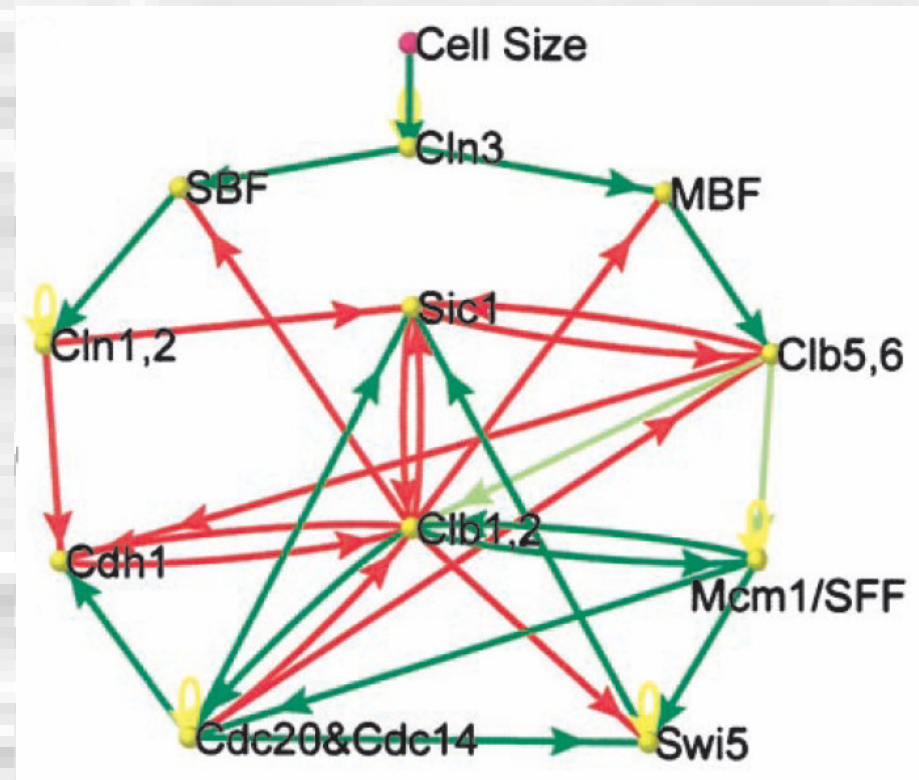
$a_{ij} = a_g$ **green arrow** from i to j

$a_{ij} = a_r$ **red arrow** from i to j

Self Degradation: (yellow loops)

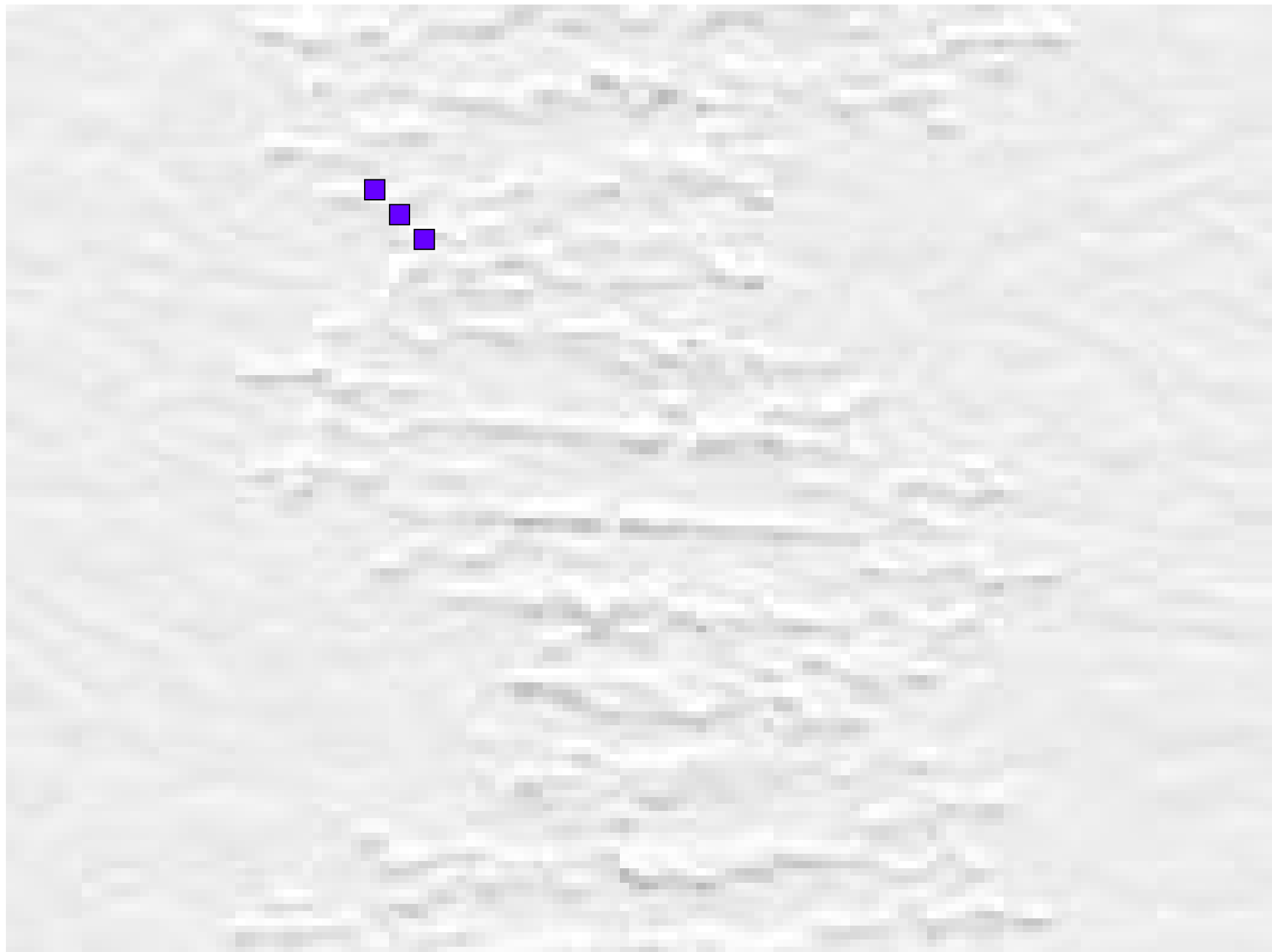
If a node i with a self yellow arrow has value $S_i(t) = 1$ and its total input from $t + 1$ to $t = t + t_d$ is zero then $S_i(t + t_d) = 0$

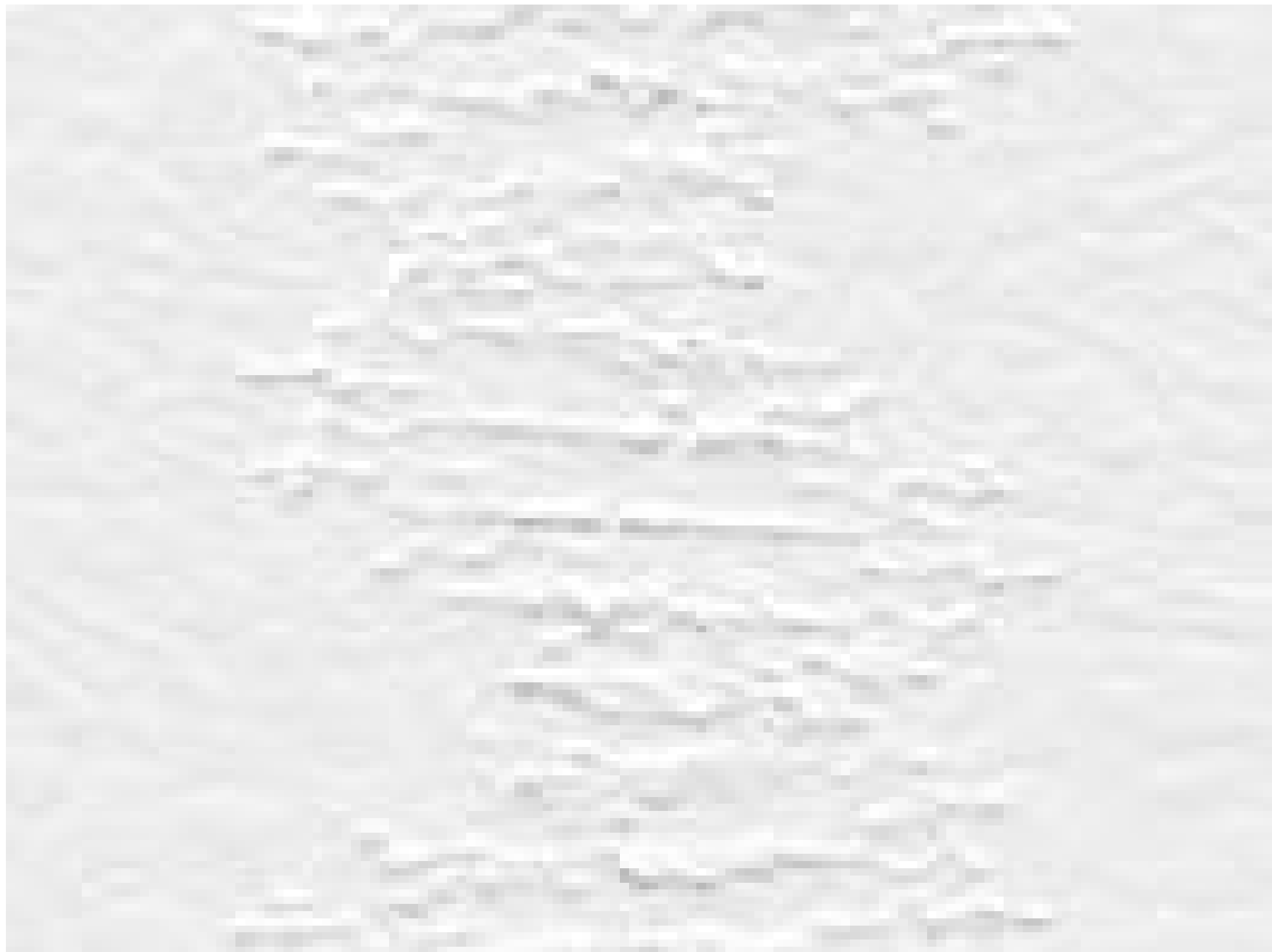
Simulation parameters: $a_g = -a_r = 1$, $t_d = 1$



Simplified Cell-Cycle Network

Fig. 1 (B)



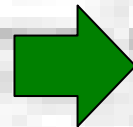


Binary

1 → **2**
0 → **0**

3 Levels (0, 1, 2)

$\sum_j a_{ij} S_j(0)$	$S_j(t+1)$	
	$S_j(t)=0$	$S_j(t)=1$
⋮	⋮	⋮
3	1	1
2	1	1
1	1	1
0	0	1
-1	0	0
-2	0	0
-3	0	0
⋮	⋮	⋮



$\sum_j a_{ij} S_j(0)$	$y_j(t+1)$		
	$S_j(t)=0$	$S_j(t)=1$	$S_j(t)=2$
⋮	⋮	⋮	⋮
3	2	2	2
2	2	2	2
1	1	2	2
0	0	1	2
-1	0	0	1
-2	0	0	0
-3	0	0	0
⋮	⋮	⋮	⋮

Self Degradation

Stochastic Transition Function

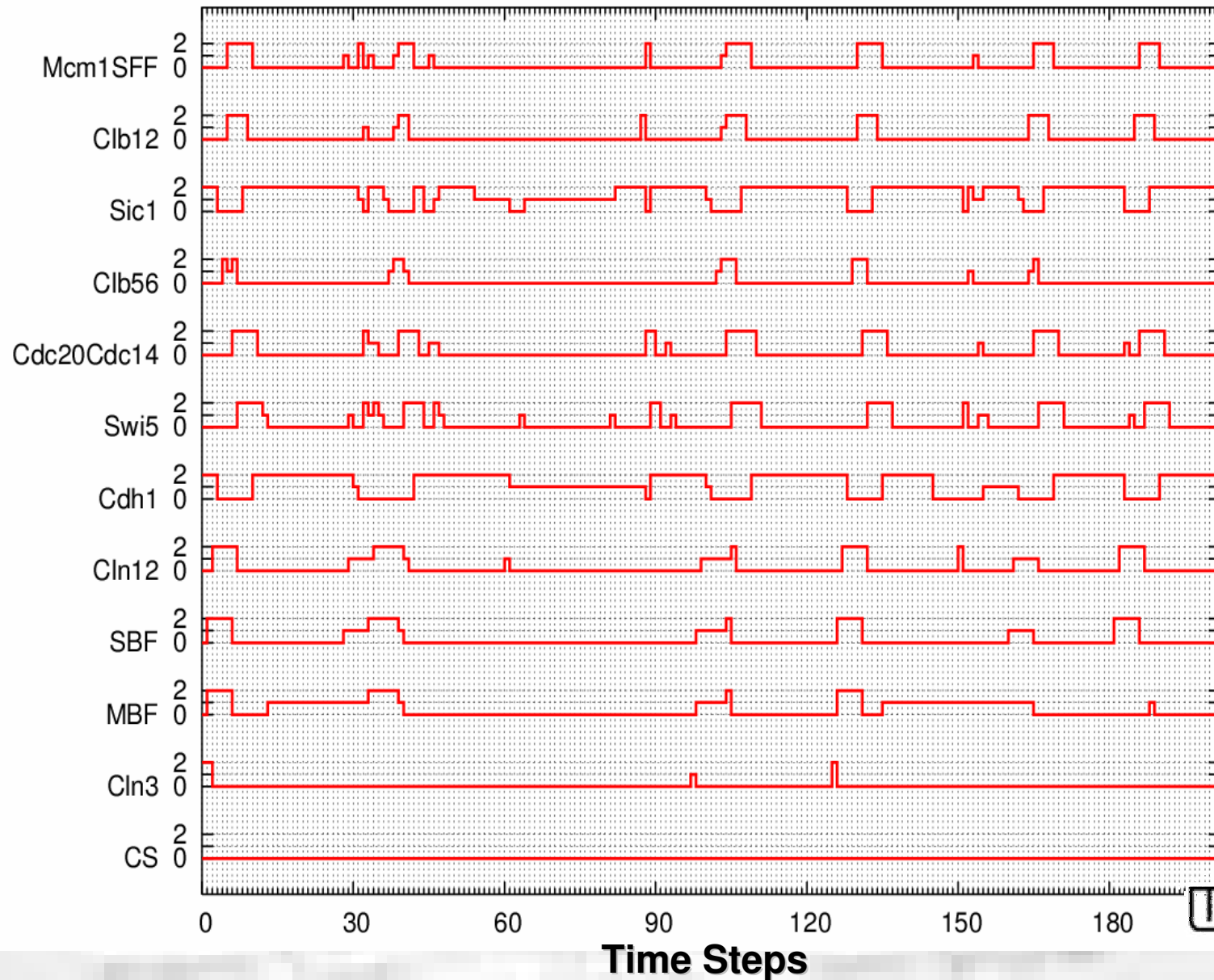
$\sum_j a_{ij} S_j(0)$	$y_j(t+1)$		
	$S_j(t) = 0$	$S_j(t) = 1$	$S_j(t) = 2$
\vdots	\vdots	\vdots	\vdots
3	2	2	2
2	2	2	2
1	1	2	2
0	0	1	2
-1	0	0	1
-2	0	0	0
-3	0	0	0
\vdots	\vdots	\vdots	\vdots

$$x_i(t+1) = \begin{cases} y_i(t+1) & \text{with } P = 0.99 \\ a & \text{with } P = 0.005 \\ b & \text{with } P = 0.005 \end{cases}$$

where $a, b \in \{0, 1, 2\} - \{y_i(t+1)\}$

PGN with $P = 0.99$

One single pulse of $CS = 2$ at $t = -1$



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Gene Model

Driving Function

Total input signal driving a generic variable

$$x_i(t) \in \{0, 1, 2\} \quad (1 \leq i \leq N)$$

is

$$d_i(t - 1) = \sum_{j=1}^N \sum_{k=1}^m a_{ji}^k x_j(t - k)$$

Driving function for x_i

m : memory of the system

a_{ji}^k : weight for variable x_j at time $t - k$

Gene Model

Transition Function

$$\text{Let } y_i(t) = \begin{cases} 2 & \text{if } d_i(t-1) \geq th2_{x_i} \\ 1 & \text{if } th1_{x_i} \leq d_i(t-1) < th2_{x_i} \\ 0 & \text{if } d_i(t-1) < th1_{x_i}. \end{cases}$$

$th1_{x_i}, th2_{x_i}$: threshold values for one and two.

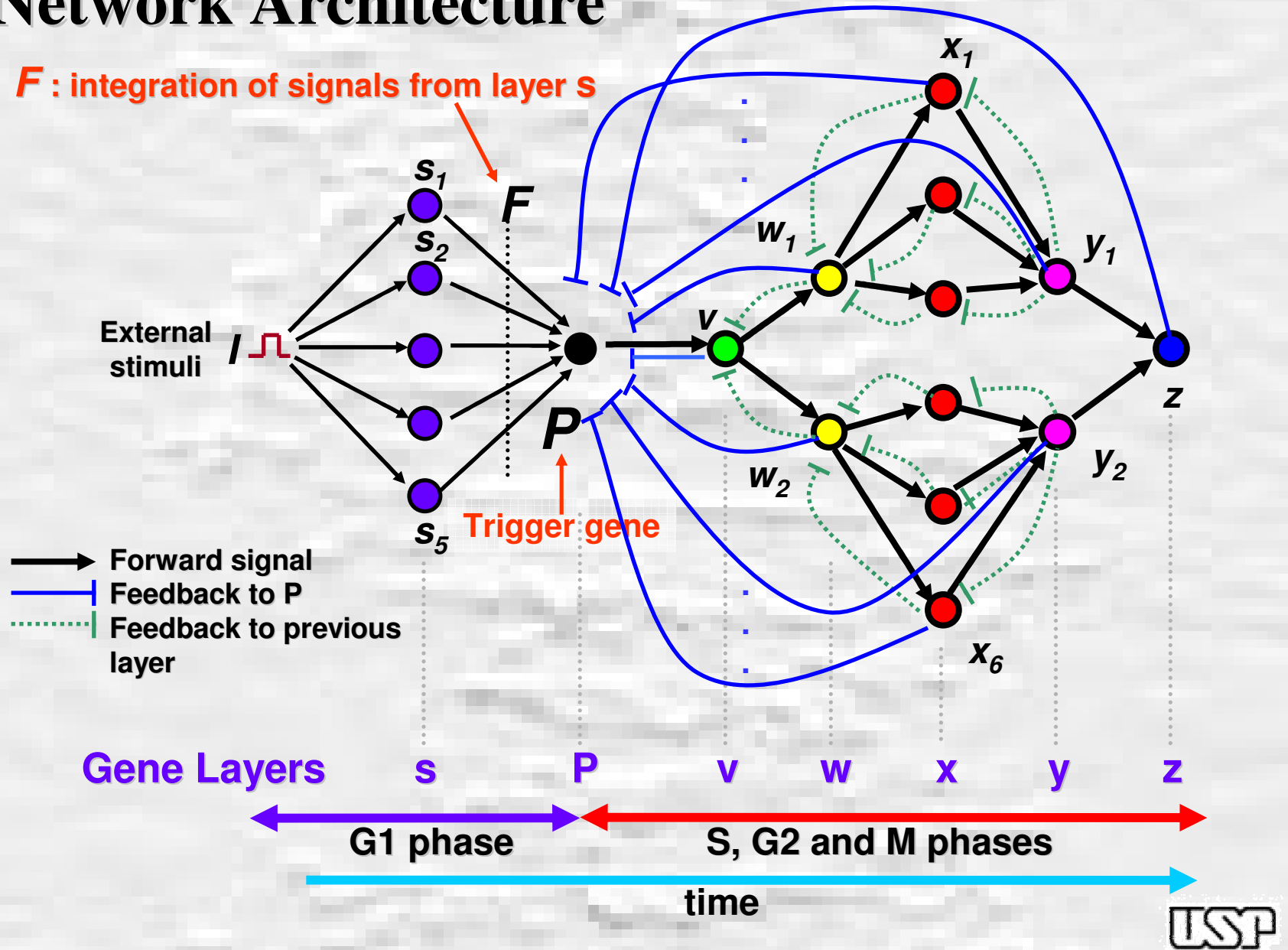
Stochastic Transition Function

$$x_i(t) = \begin{cases} y_i(t) & \text{with } P \approx 1 \\ a & \text{with } (1-P)/2 \\ b & \text{with } (1-P)/2. \end{cases}$$

$$a, b \in \{0, 1, 2\} - \{y_i(t)\}$$

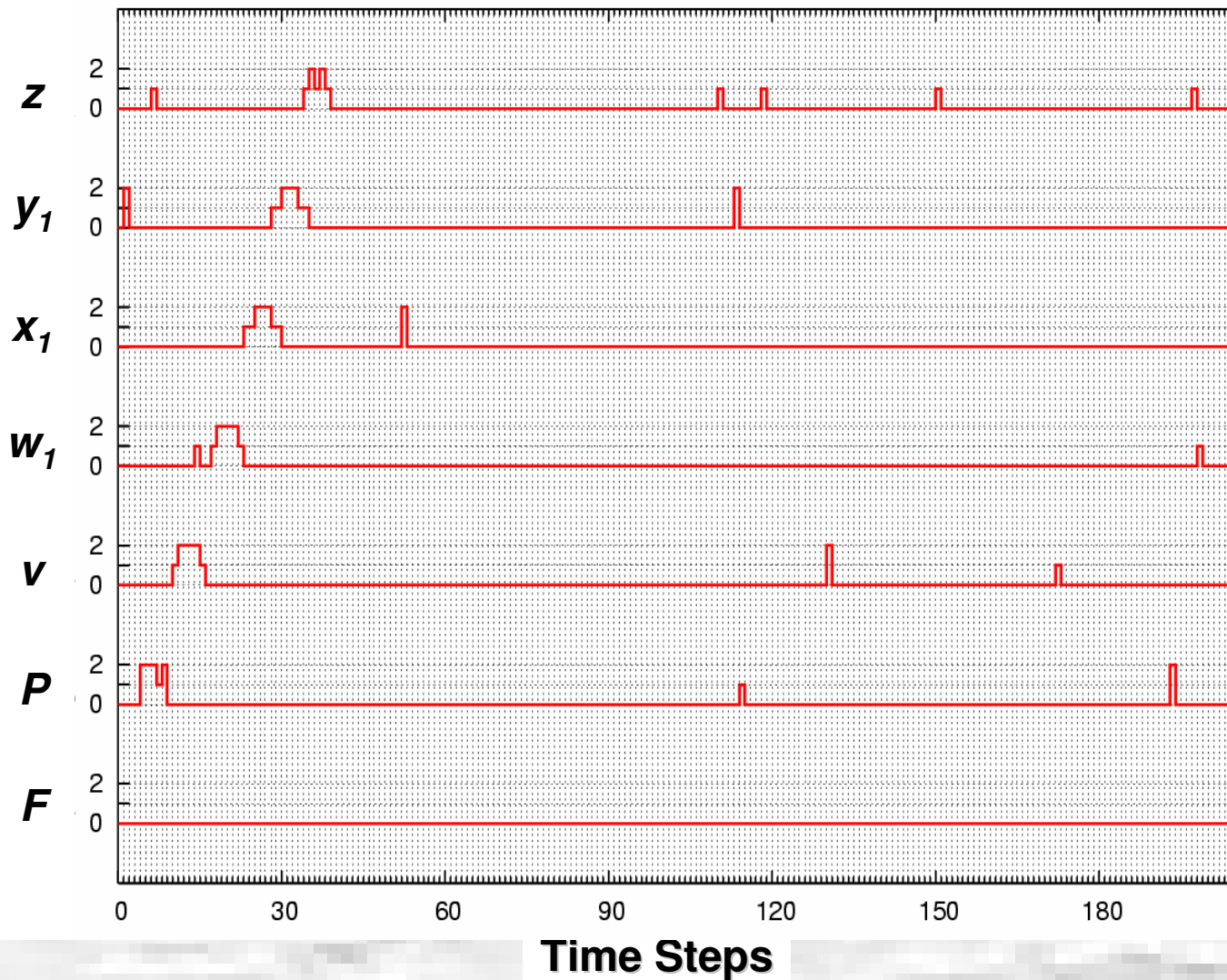
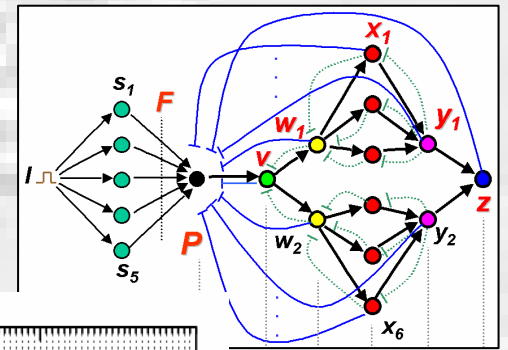
Network Architecture

F : integration of signals from layer s



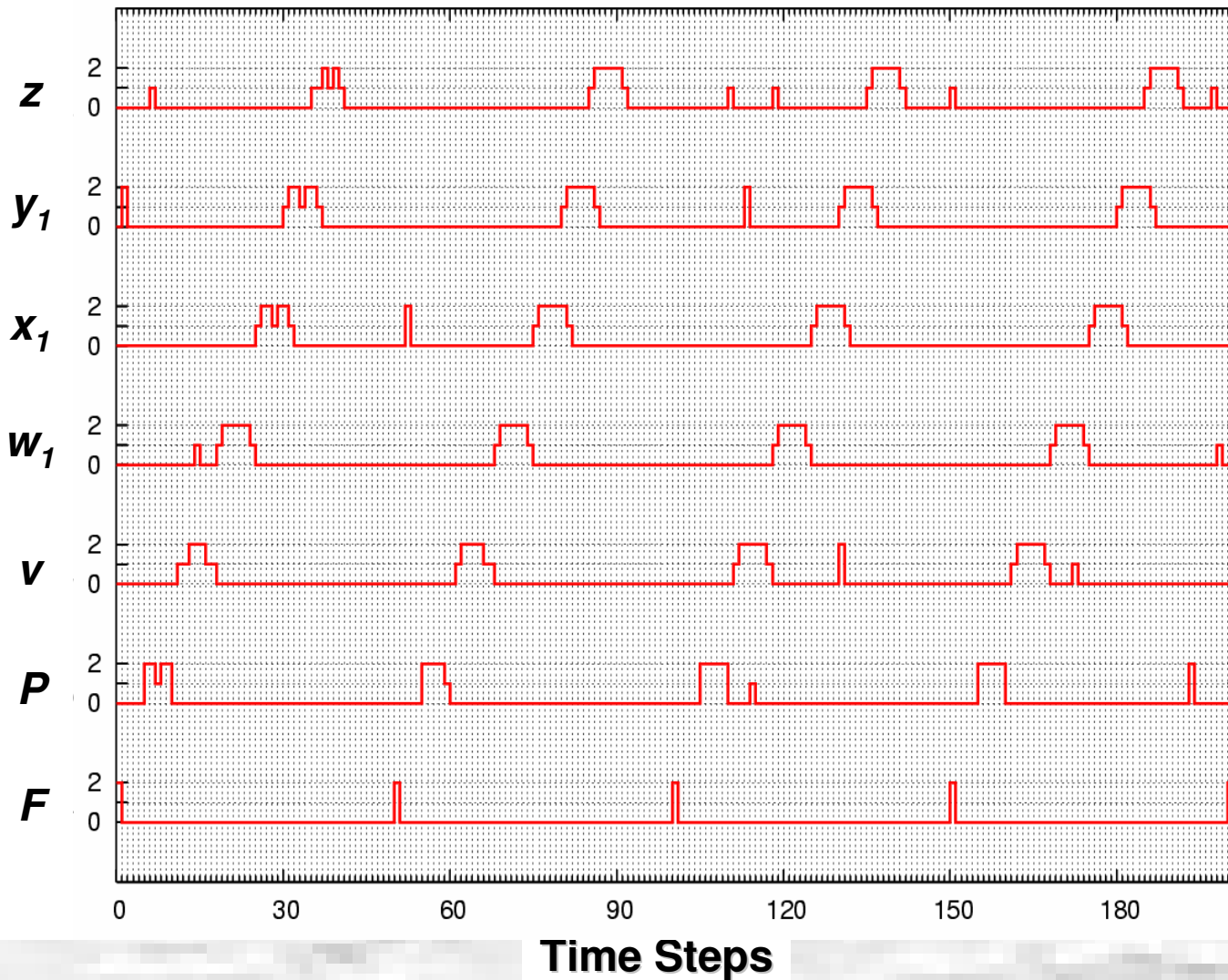
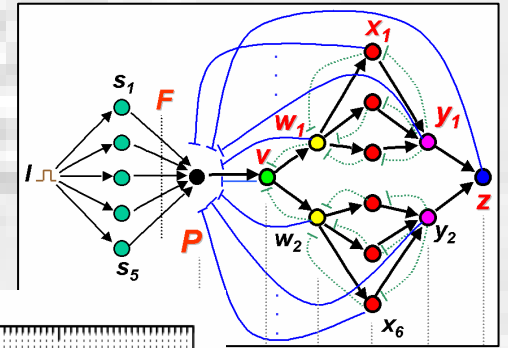
PGN with $P = 0.99$

One single pulse of $F = 2$ at $t = -1$



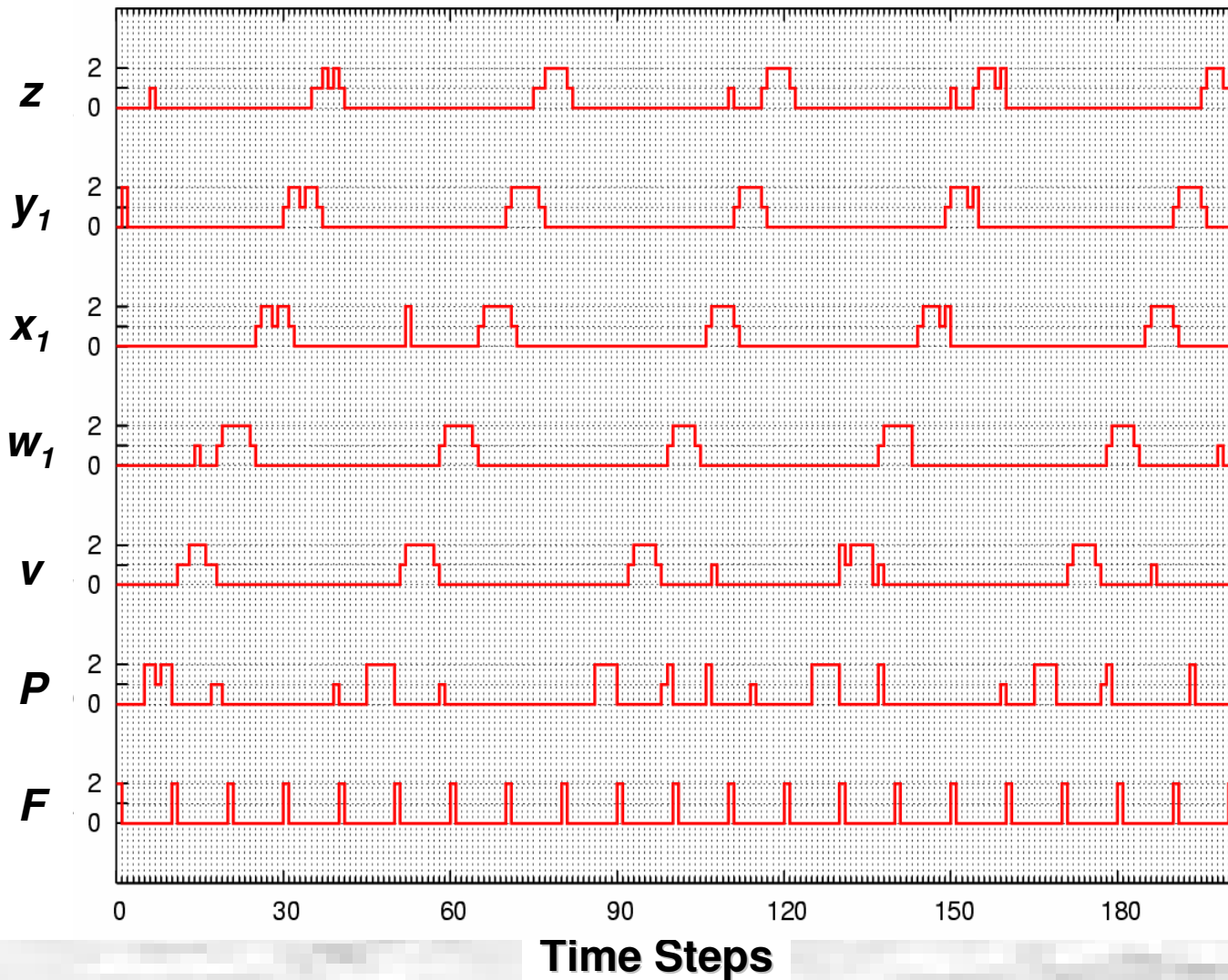
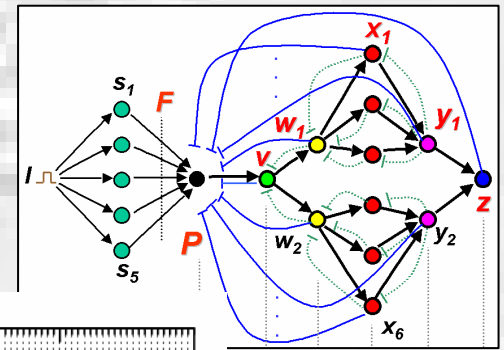
PGN with $P = 0.99$

Signal F = period 50 oscillator



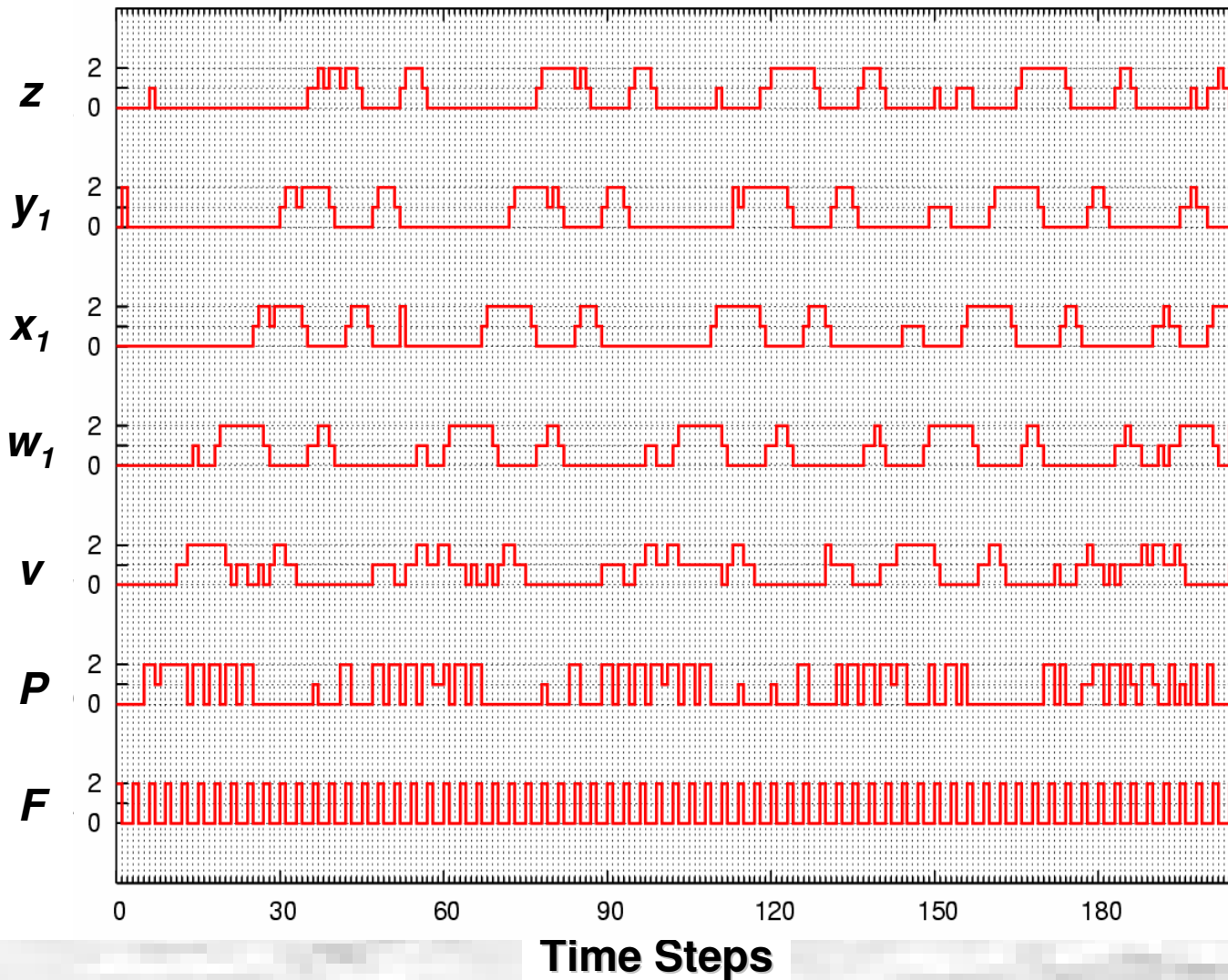
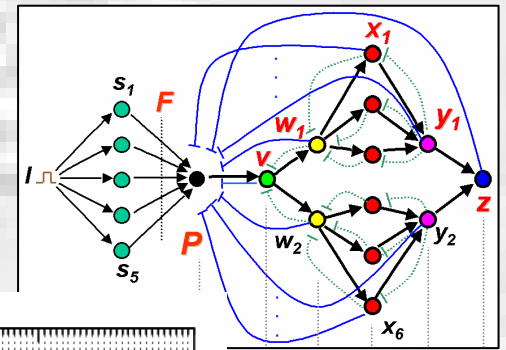
PGN with $P = 0.99$

Signal $F =$ period 10 oscillator



PGN with $P = 0.99$

Signal $F =$ period 3 oscillator



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Model Design

**Hypothetical,
based on observed
behavior**

X

**Based on
documented
biological interactions**

Similarities:

Checkpoint triggers cycle progression

Signal wave propagation

Stability in the presence of variable excitation (without noise)

New Characteristics

- Hierarchical **negative feed back** structure
- **Robustness** in the presence of **noise** and **variable excitation**

Hierarchical **NEGATIVE FEEDBACK LOOPS** provide
STABILITY and **ROBUSTNESS**

Thanks!

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