Modeling and Simulation of Regulatory Networks

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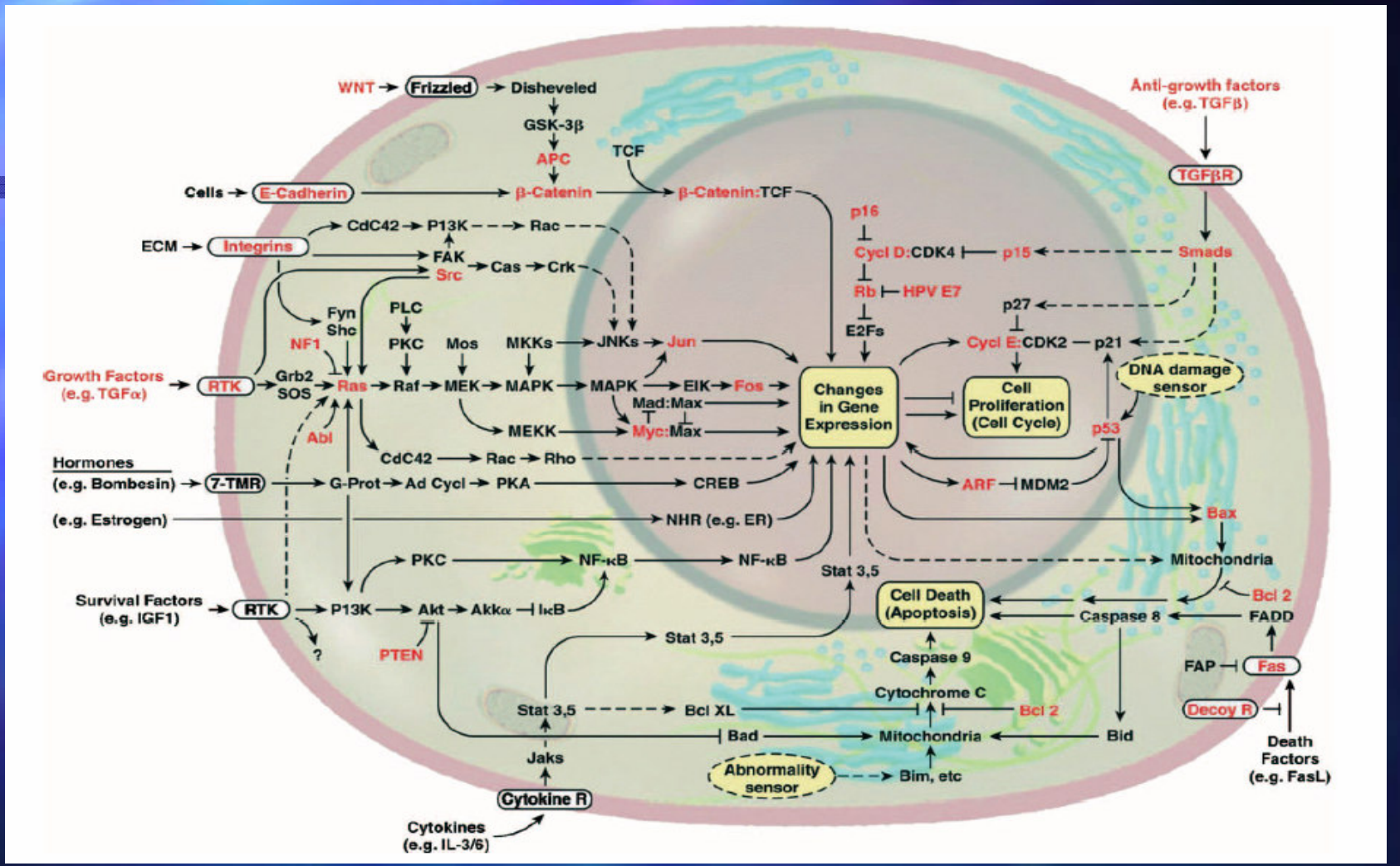
Outline

- Why Modeling and Simulation?
- Discrete Dynamical Systems
- Yeast Cell Cycle Model and Simulations
- The p53 Network
- Combined Application of Experimental and Computational Tools
- Hypothesis-driven Research
- Discussion

Why Modeling and Simulation?

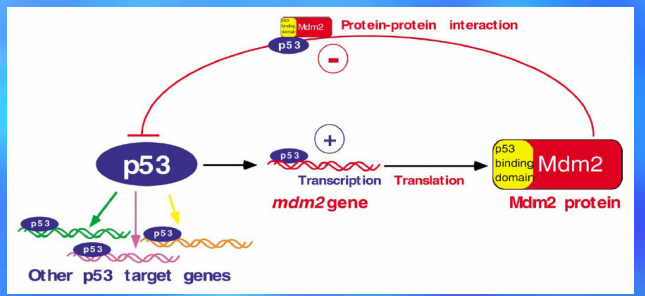


Signaling circuitry of the mammalian cell.

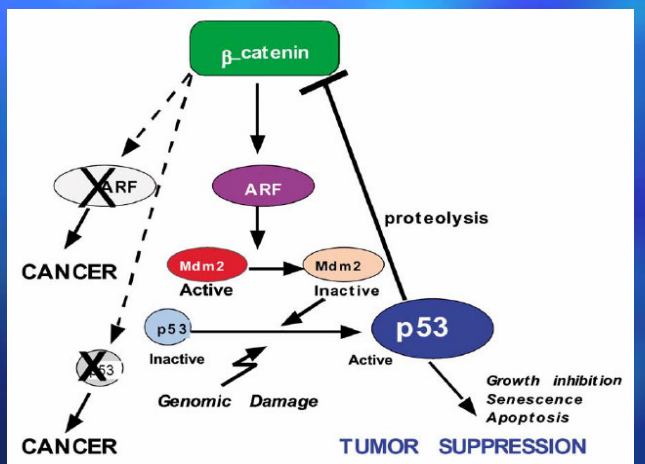
from

THE HALLMARKS OF CANCER - Hanahan, D. and Weinberg, R.A.
CELL 100, 2000 - Pp. 57-70

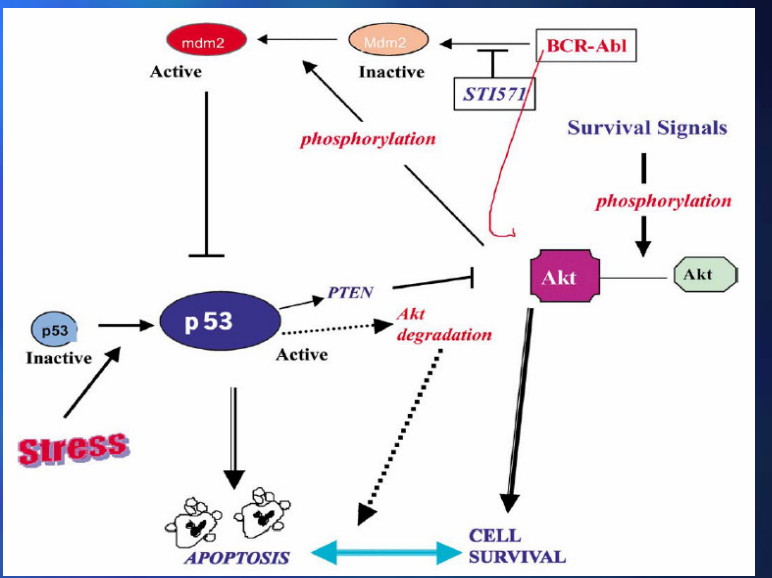
Choose simpler sub-systems:



The p53-Mdm2 loop



The p53-beta catenin loop



The p53-Mdm2-Akt loop

We'll be back to this topic in the last sections...

Figures from REGULATION OF P53: INTRINCATE LOOPS AND DELICATE BALANCES
Oren et al - Biochemical Pharmacology 64 (2002) - Pp. 865-871

Discrete Dynamical Systems

Brief Description

A Discrete Dynamical System is given by, for all discrete time $t \geq 0$

$$x(t+1) = \phi[x(t), u(t)]$$

ϕ : Transition Function

$$y(t) = \psi[x(t), u(t)]$$

ψ : Output function

where

$$x(t) = \begin{bmatrix} x_1(t) \\ \vdots \\ x_n(t) \end{bmatrix} \quad u(t) = \begin{bmatrix} u_1(t) \\ \vdots \\ u_m(t) \end{bmatrix} \quad y(t) = \begin{bmatrix} y_1(t) \\ \vdots \\ y_r(t) \end{bmatrix}$$

$x(t)$: State vector, $x_i(t)$: State variables

$u(t)$: Input vector, $u_j(t)$: Input variables

$y(t)$: Output vector, $y_k(t)$: Output variables

Budding Yeast Cell Cycle Model

from

THE YEAST CELL-CYCLE NETWORK IS ROBUSTLY DESIGNED

Li et al

PNAS - Vol. 101 - Number 14, 2004 - Pp. 4781-4786

Model Architecture and Dynamics

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

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

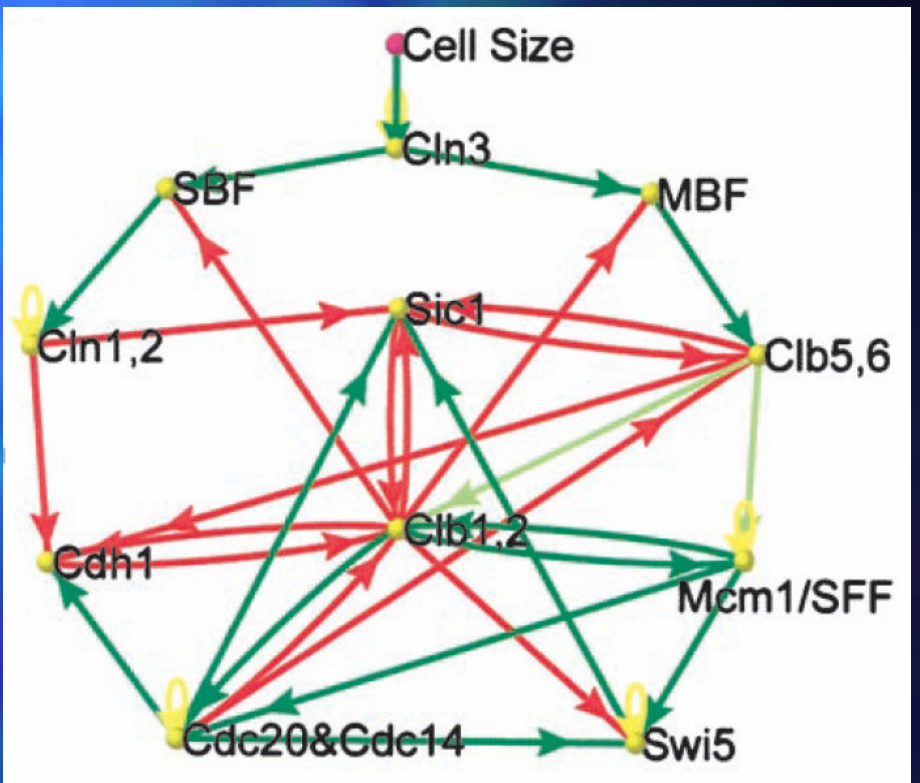
Transition Function

$a_{ij} = a_g$ 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)*

How this Model was Built

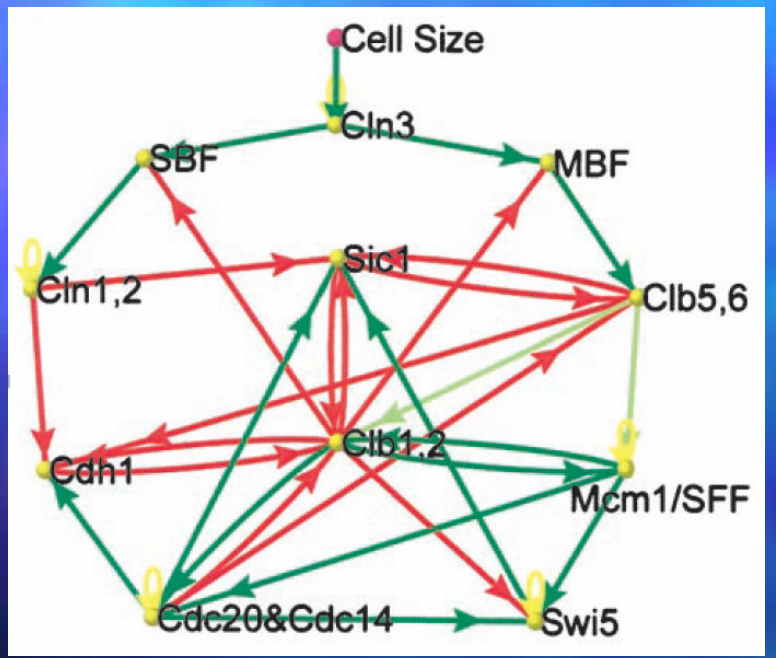


Table 3. References to each interaction

Starting node	Ending node	Description	Reference
Cell size	Cln3	The nuclear concentration of Cln3 is proportional to cell mass. When the cell is large enough, Cln3 is "activated."	1, 2
Cln3	SBF	When the level of Cln3/Cdc28 complex is larger than a certain threshold, it triggers G1/S transcription by activating SBF (Swi4 and Swi6).	1, 3
Cln3	MBF	Cln3/Cdc28 complex activates MBF (Mbp1 and Swi6) by the similar mechanism to SBF.	4
SBF	Cln1,2	SBF is the transcription factor of CLN1,2.	5
MBF	Clb5,6	MBF is the transcription factor of CLB5,6.	4

1. Mendenhall, M. D. & Hodge, A. E. (1998) *Microbiol. Mol. Biol. Rev.* 62, 1191-1243.

2. Cross, F. R., Archambault, V., Miller, M. & Klovstad, M. (2002) *Mol. Biol. Cell* 13, 52-70.

3. Cross, F. R. & Tinkelenberg, A. H. (1991) *Cell* 65, 875-885.

4. Koch, C., Moll, T., Neuberg, M., Ahorn, H. & Nasmyth, K. (1993) *Science* 261, 1551-1557.

5. Nasmyth, K. & Dirick, L. (1991) *Cell* 66, 995-1013.

Temporal Evolution from the Stationary G1 State

Table 2. Temporal evolution of protein states for the simplified cell-cycle network of Fig. 1*B*

Time	Cln3	MBF	SBF	Cln1,2	Cdh1	Swi5	Cdc20 and Cdc14	Clb5,6	Sic1	Clb1,2	Mcm1/SFF	Phase	State of the Biological Pathway
1	1	0	0	0	1	0	0	0	1	0	0	START	S_1
2	0	1	1	0	1	0	0	0	1	0	0	G_1	S_2
3	0	1	1	1	1	0	0	0	1	0	0	G_1	S_3
4	0	1	1	1	0	0	0	0	0	0	0	G_1	S_4
5	0	1	1	1	0	0	0	1	0	0	0	S	S_5
6	0	1	1	1	0	0	0	1	0	1	1	G_2	S_6
7	0	0	0	1	0	0	1	1	0	1	1	M	S_7
8	0	0	0	0	0	1	1	0	0	1	1	M	S_8
9	0	0	0	0	0	1	1	0	1	1	1	M	S_9
10	0	0	0	0	0	1	1	0	1	0	1	M	S_{10}
11	0	0	0	0	1	1	1	0	1	0	0	M	S_{11}
12	0	0	0	0	1	1	0	0	1	0	0	G_1	S_{12}
13	0	0	0	0	1	0	0	0	1	0	0	Stationary G_1	S_{SG1}

The right column indicates the cell-cycle phases. Note that the number of time steps in each phase do not reflect its actual duration.

Dynamical trajectories of the 1764 states flowing to stationary G_1

(Total number of states: $2^{11} = 2048$)

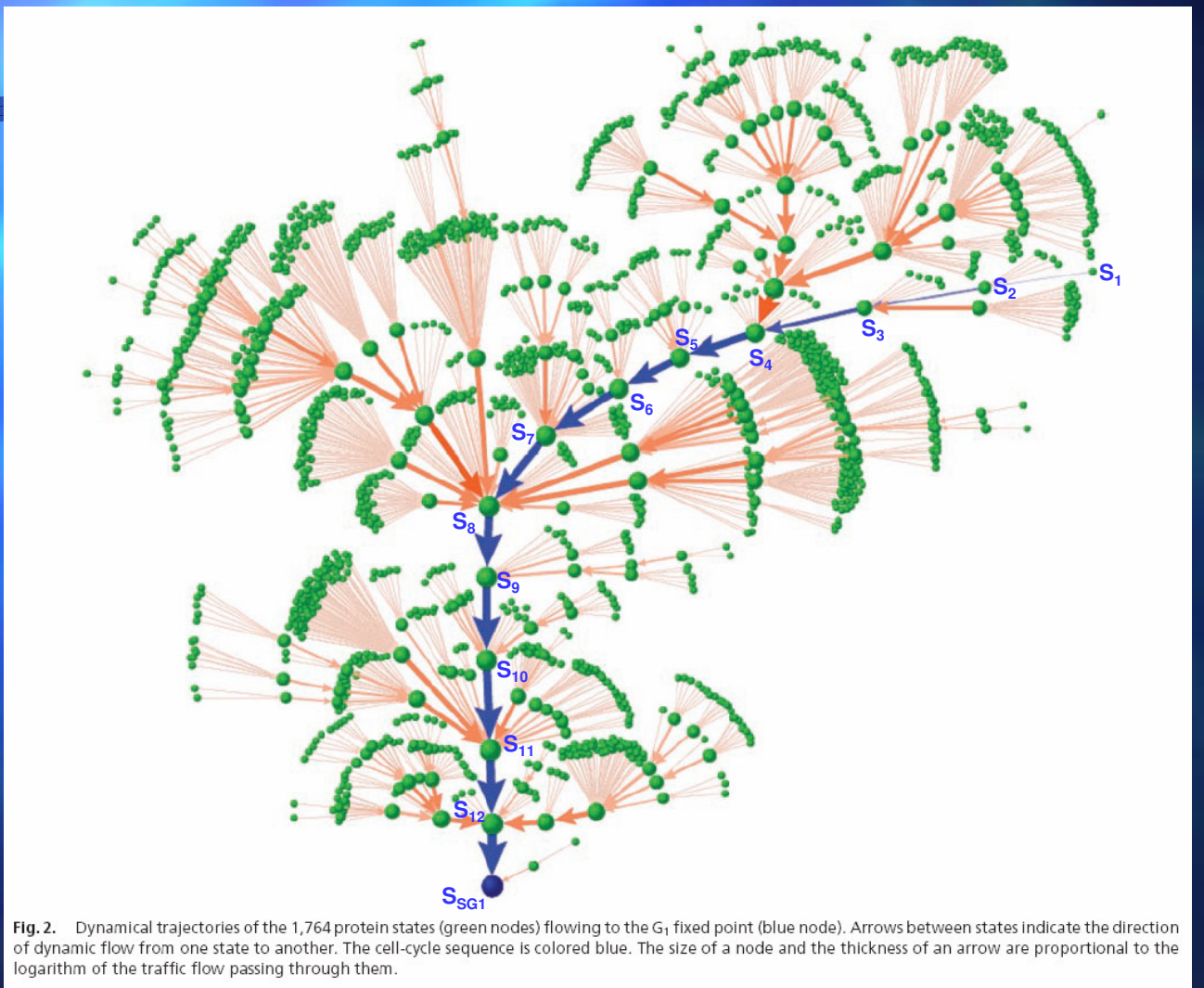
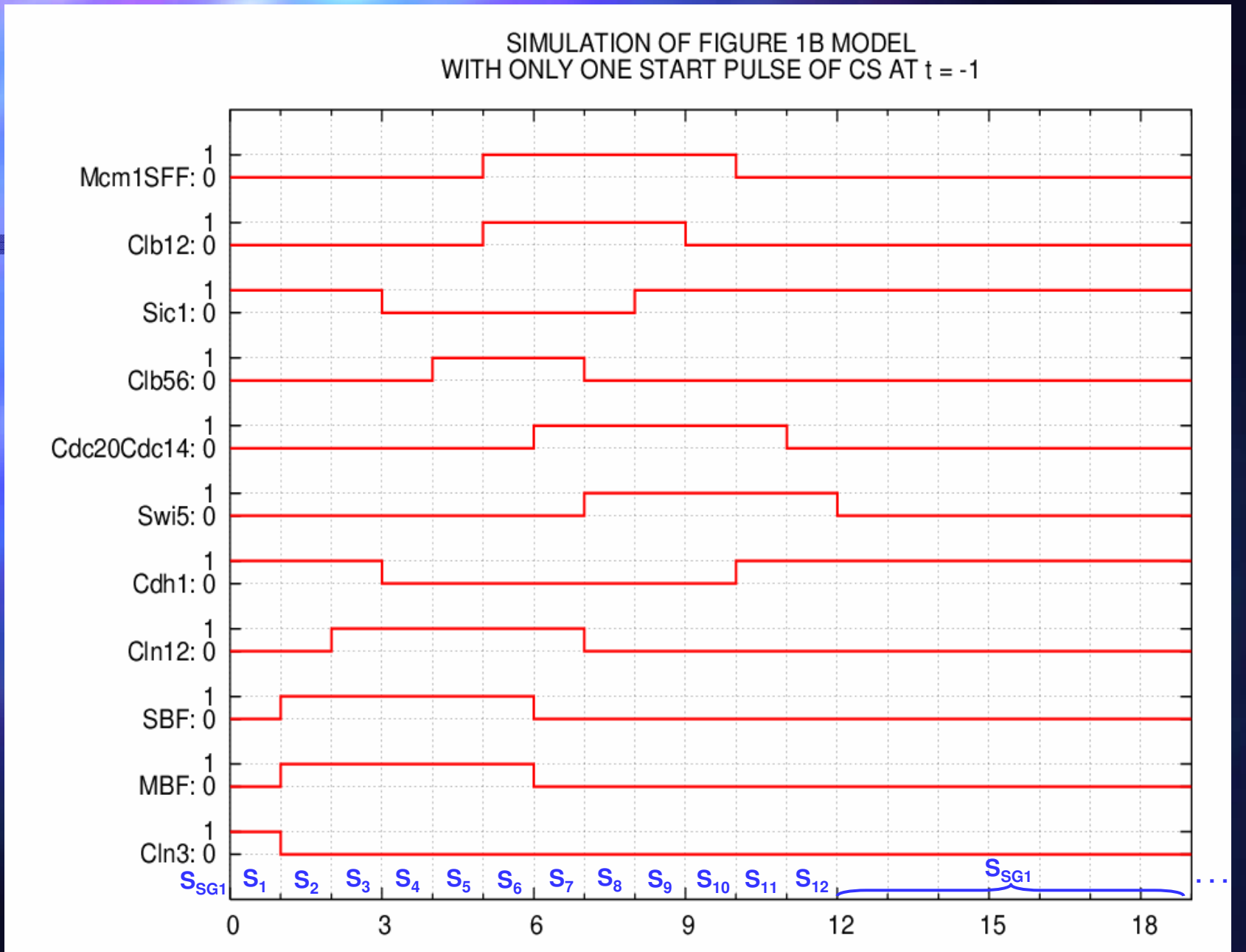


Fig. 2. Dynamical trajectories of the 1,764 protein states (green nodes) flowing to the G_1 fixed point (blue node). Arrows between states indicate the direction of dynamic flow from one state to another. The cell-cycle sequence is colored blue. The size of a node and the thickness of an arrow are proportional to the logarithm of the traffic flow passing through them.

The biological pathway (cell-cycle sequence) is colored blue

Our Simulations of this Model



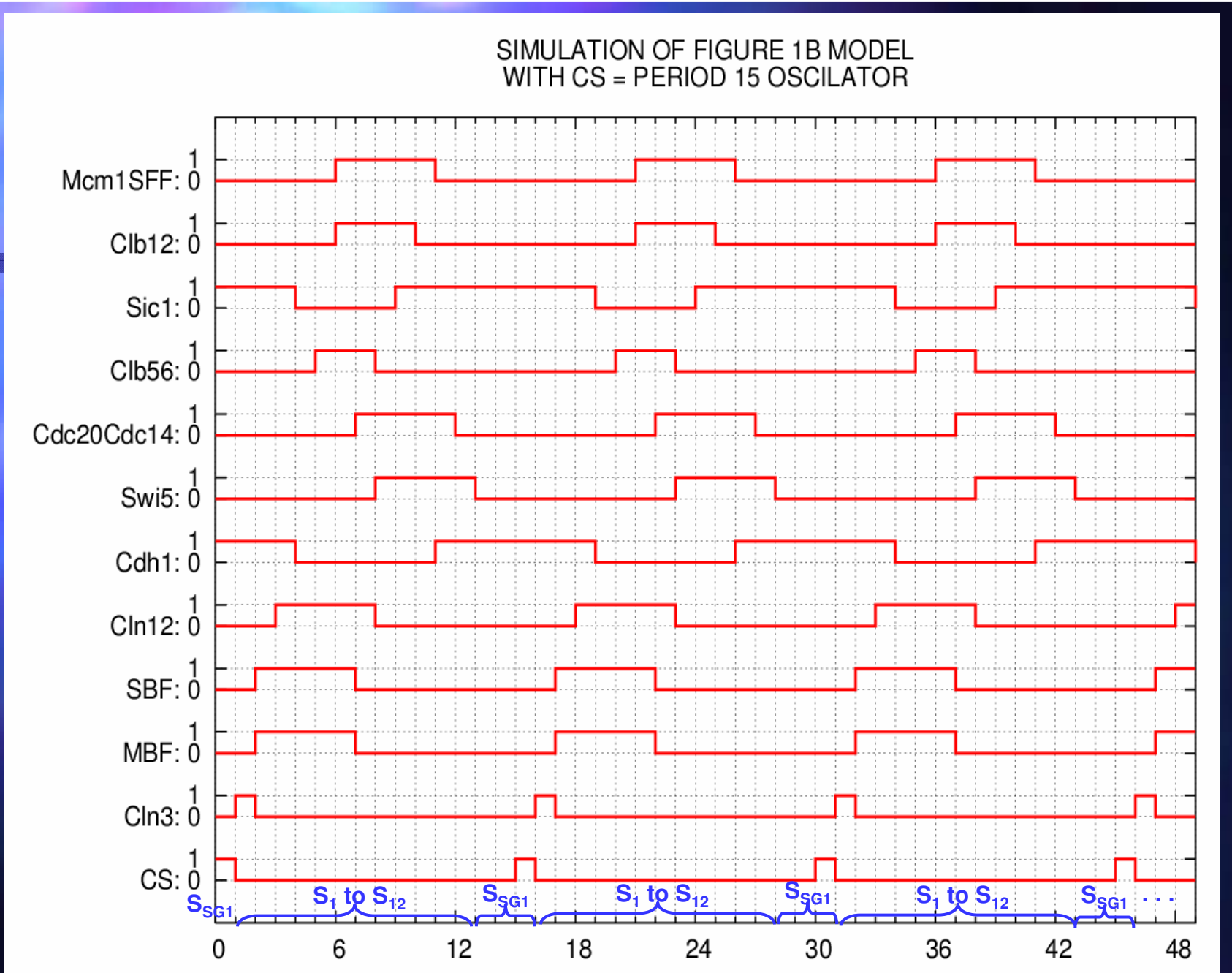
CS = Cell Size checkpoint

Simulation steps

Simplified List of the State Values

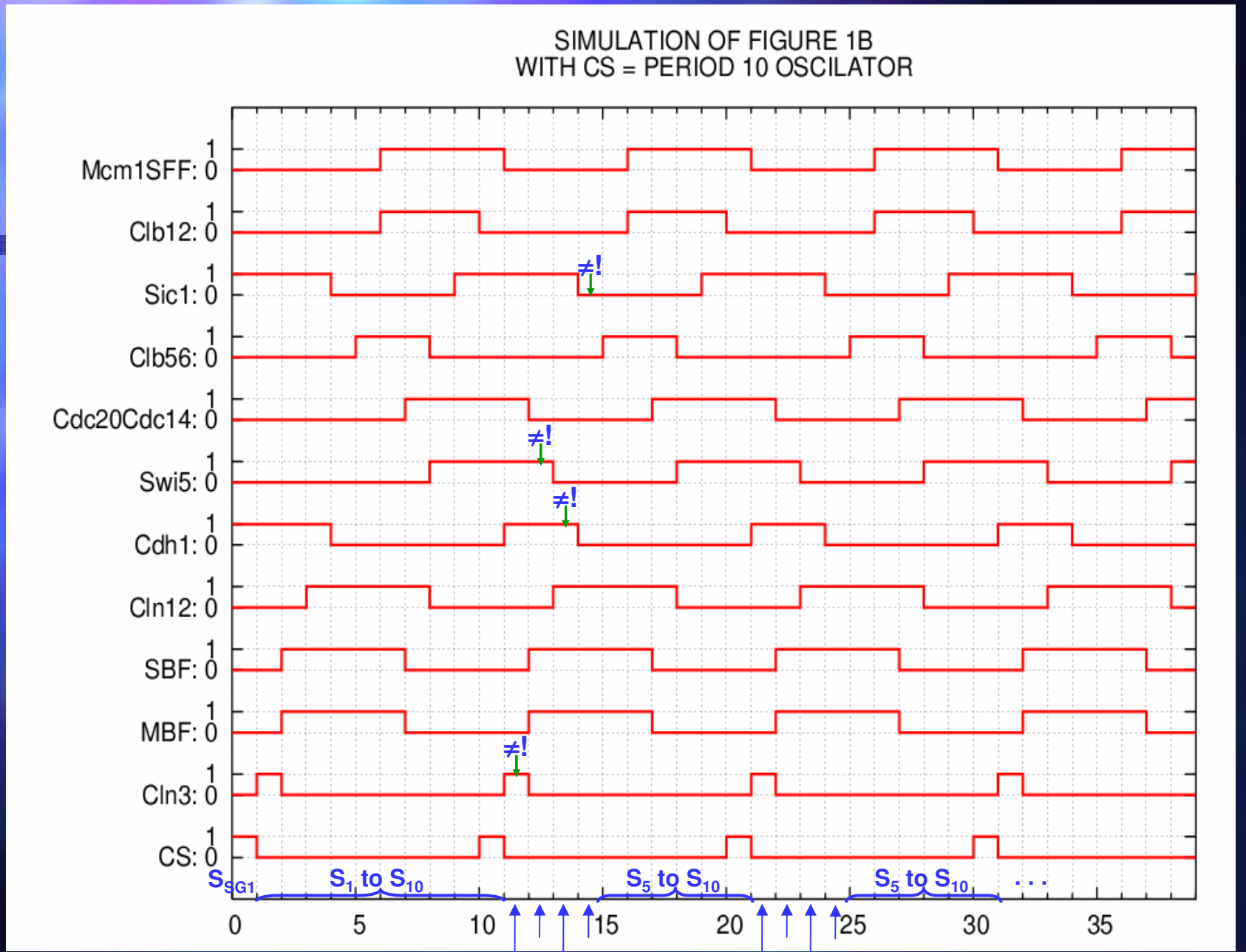
of the Biological Pathway (Cell-Cycle Sequence)

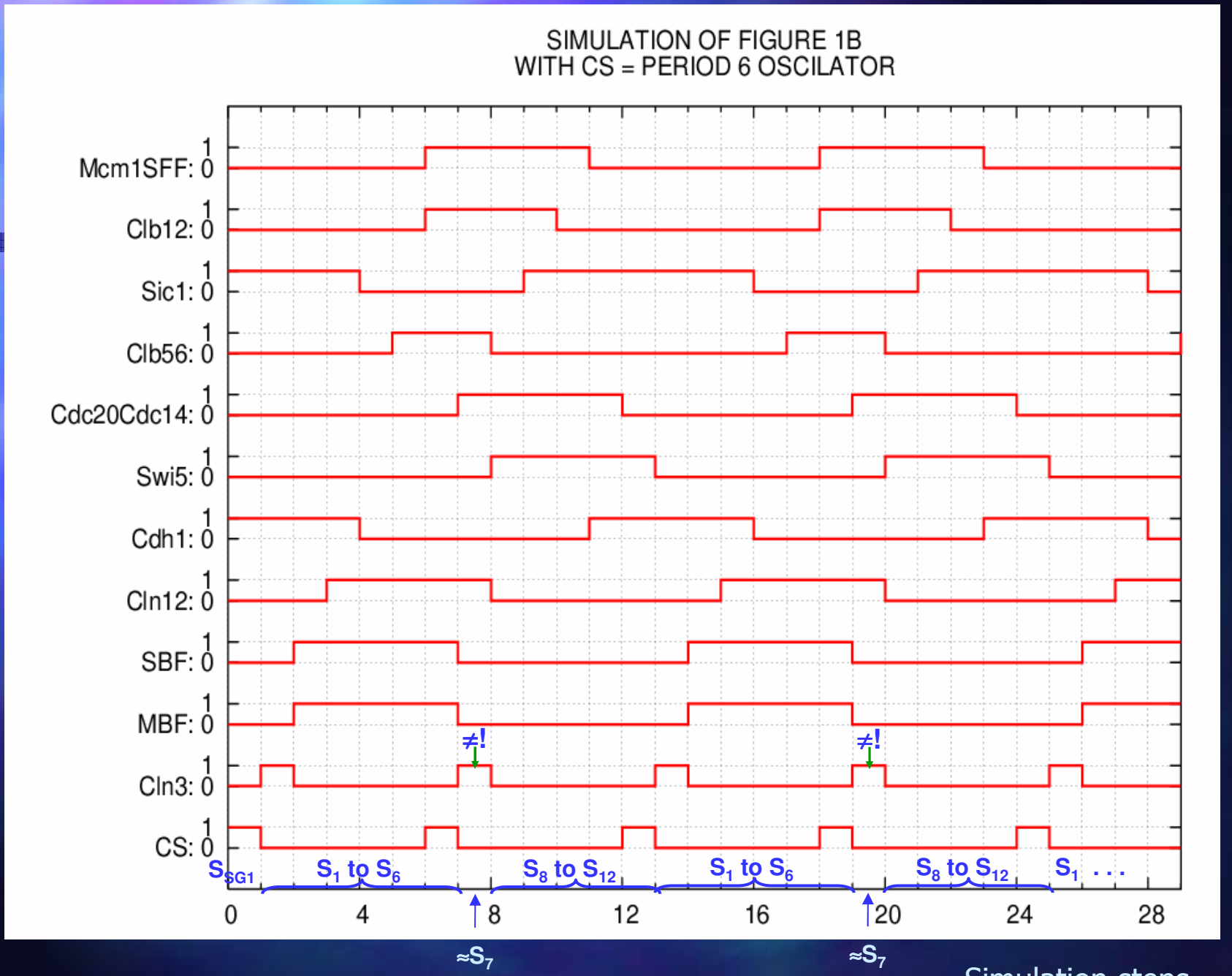
State	Cln3 … Mcm1	Phase
S_1	1000 1000 100	START
S_2	0110 1000 100	G_1
S_3	0111 1000 100	G_1
S_4	0111 0000 000	G_1
S_5	0111 0001 000	S
S_6	0111 0001 011	M
S_7	0001 0011 011	M
S_8	0000 0110 011	M
S_9	0000 0110 111	M
S_{10}	0000 0110 101	M
S_{11}	0000 1110 100	M
S_{12}	0000 1100 100	G_1
S_{SG1}	0000 1000 100	Stationary G_1



CS = Cell Size checkpoint

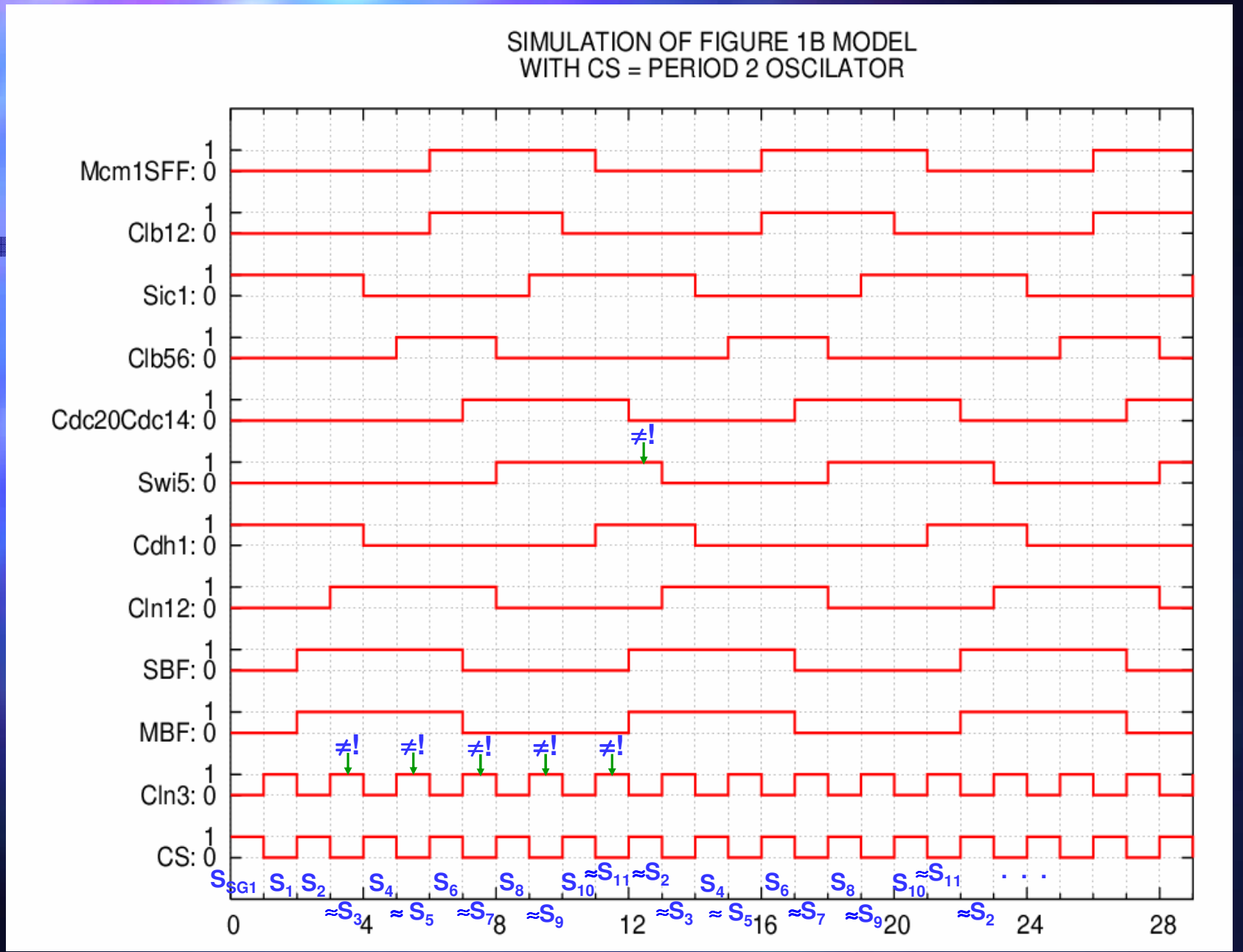
Simulation steps


SIMULATION OF FIGURE 1B
WITH CS = PERIOD 10 OSCILATOR
Mcm1SFF: 1 0
Clb12: 1 0
Sic1: 1 0
Clb56: 1 0
Cdc20Cdc14: 1 0
Swi5: 1 0
Cdh1: 1 0
Cln12: 1 0
SBF: 1 0
MBF: 1 0
Cln3: 1 0
CS: 1 0
≠!
S_SG1
S1 to S10
S5 to S10
S5 to S10
. . .
0
5
10
15
20
25
30
35
≈S2 ≈S4
≈ S11 ≈S3
≈S2 ≈S4
≈S11 ≈S3
CS = Cell Size checkpoint
Simulation steps



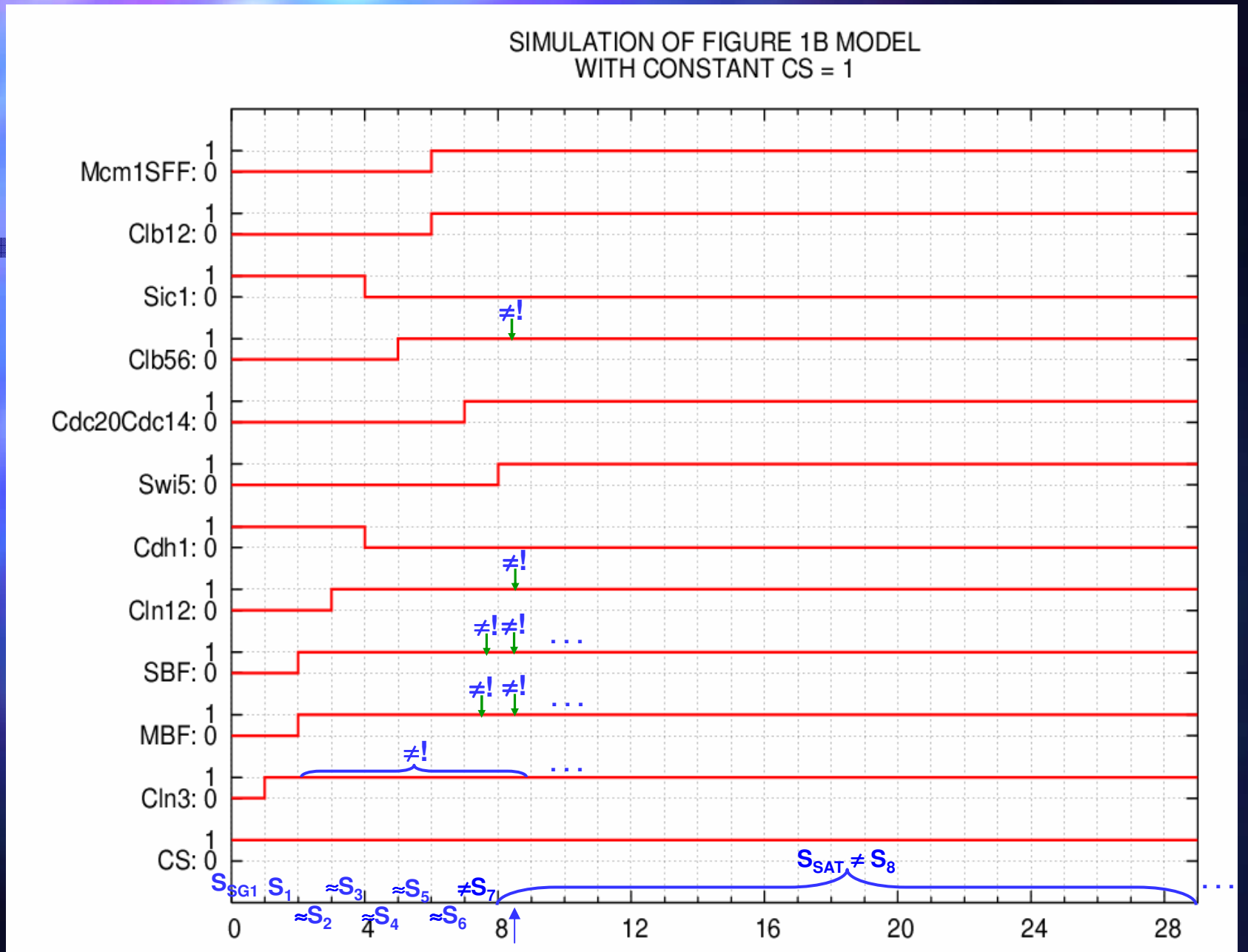
CS = Cell Size checkpoint

Simulation steps



CS = Cell Size checkpoint

Simulation steps

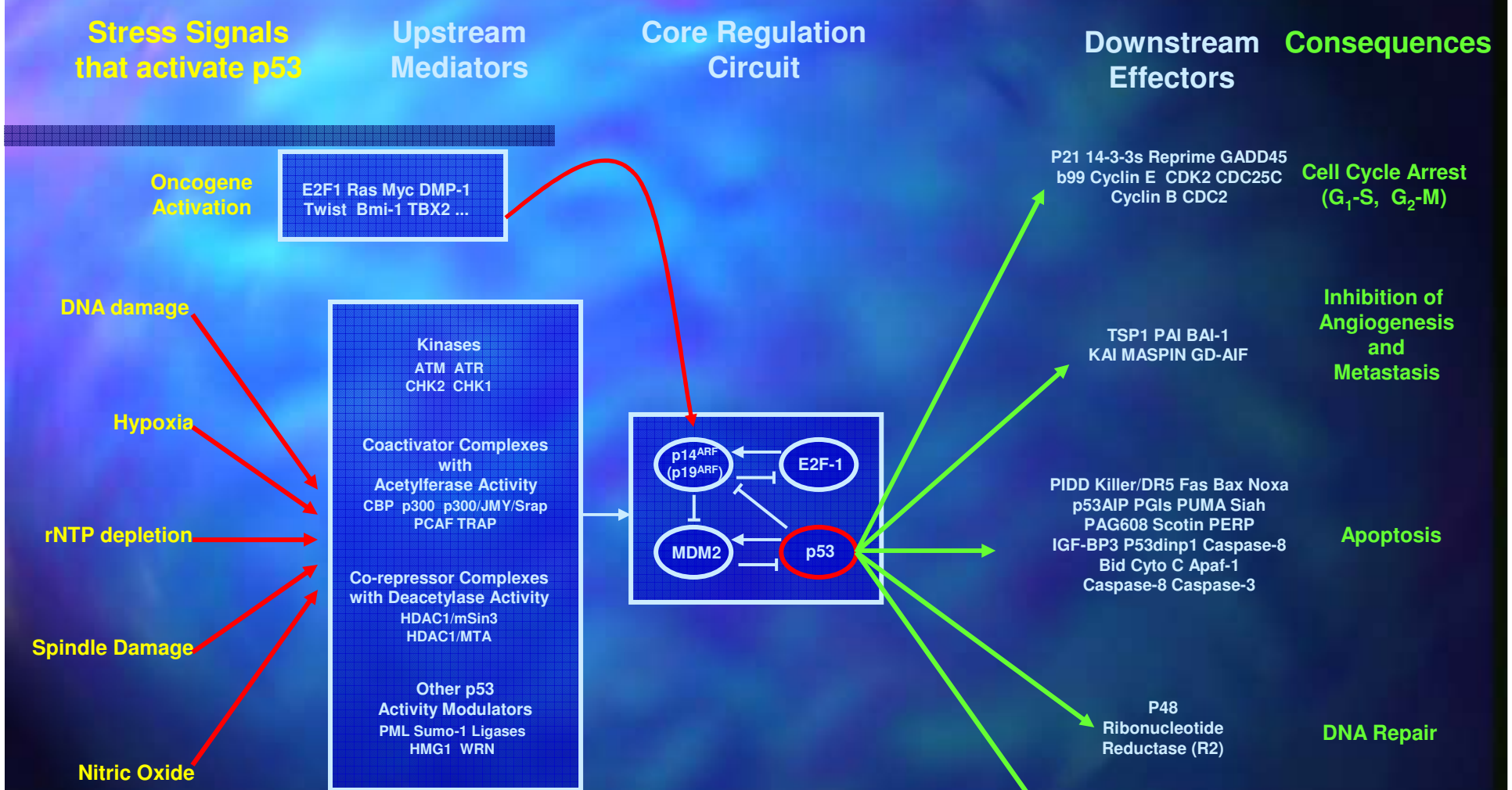

SIMULATION OF FIGURE 1B MODEL
WITH CONSTANT CS = 1
Mcm1SFF: 1 0
Clb12: 1 0
Sic1: 1 0
Clb56: 1 0
Cdc20Cdc14: 1 0
Swi5: 1 0
Cdh1: 1 0
Cln12: 1 0
SBF: 1 0
MBF: 1 0
Cln3: 1 0
CS: 1 0
≠!
. . .
S_{SG1} S_1 ≈S_2 ≈S_3 ≈S_4 ≈S_5 ≈S_6 ≠S_7
$S_{SAT} \neq S_8$
0 4 8 12 16 20 24 28
$S_{SAT} \neq S_8$
CS = Cell Size checkpoint
Simulation steps

Future Work on this Model:

- Extend the budding yeast cell-cycle model from binary to multilevel.
- Relax the model by introducing stochacity in the state transitions.
- Reformulate the model in terms of a Probabilistic Genetic Networks (PGN).
- Simulate and iteratively make corrections of the model.
- Simulate the Fig. 1 *(A)* cell-cycle network (with four checkpoints).

The p53 Network

The p53 Functional Circuit

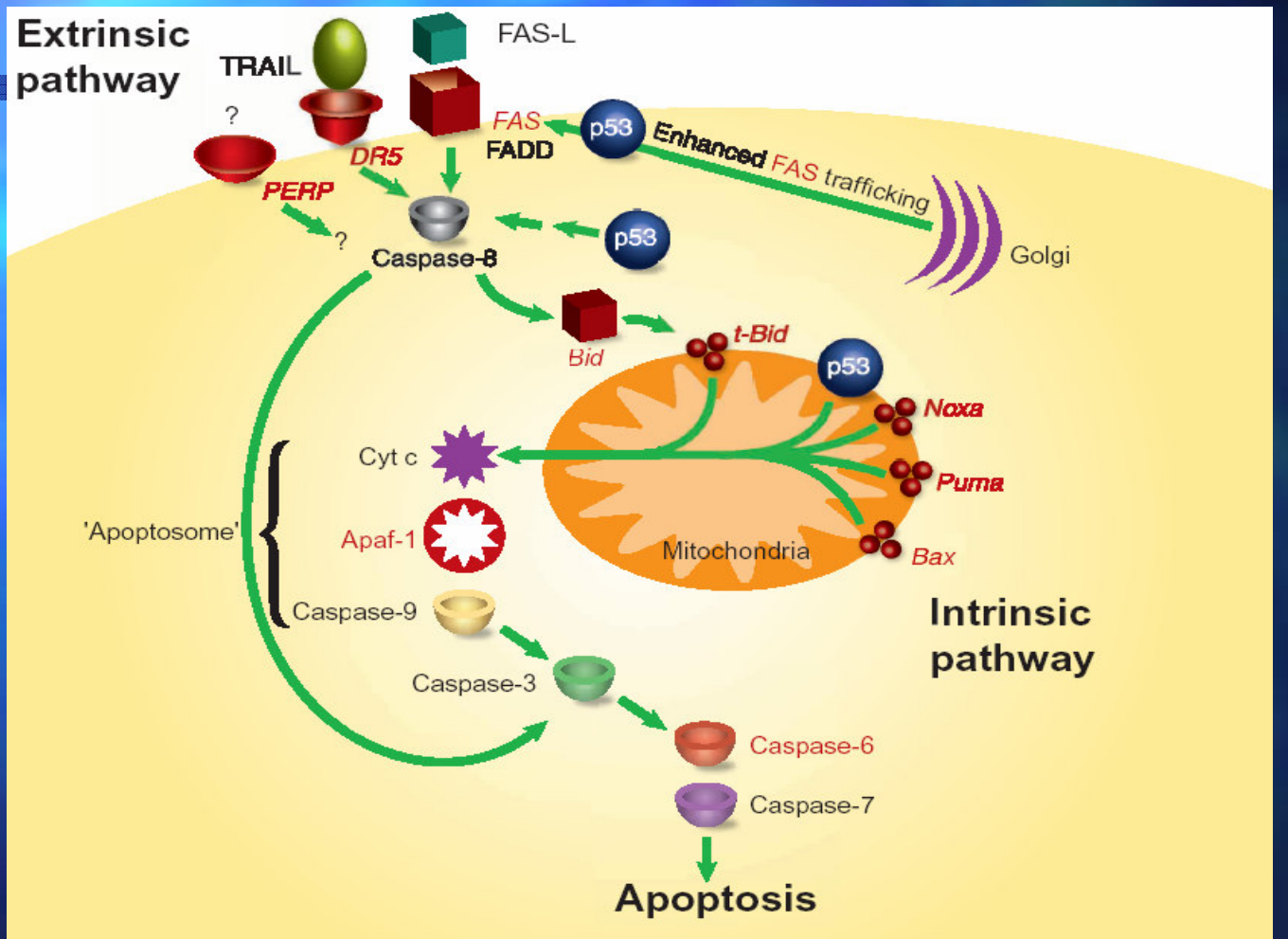


Adapted from

THE P53 FUNCTIONAL CIRCUIT - Shengkan Jin and Arnold J. Levine

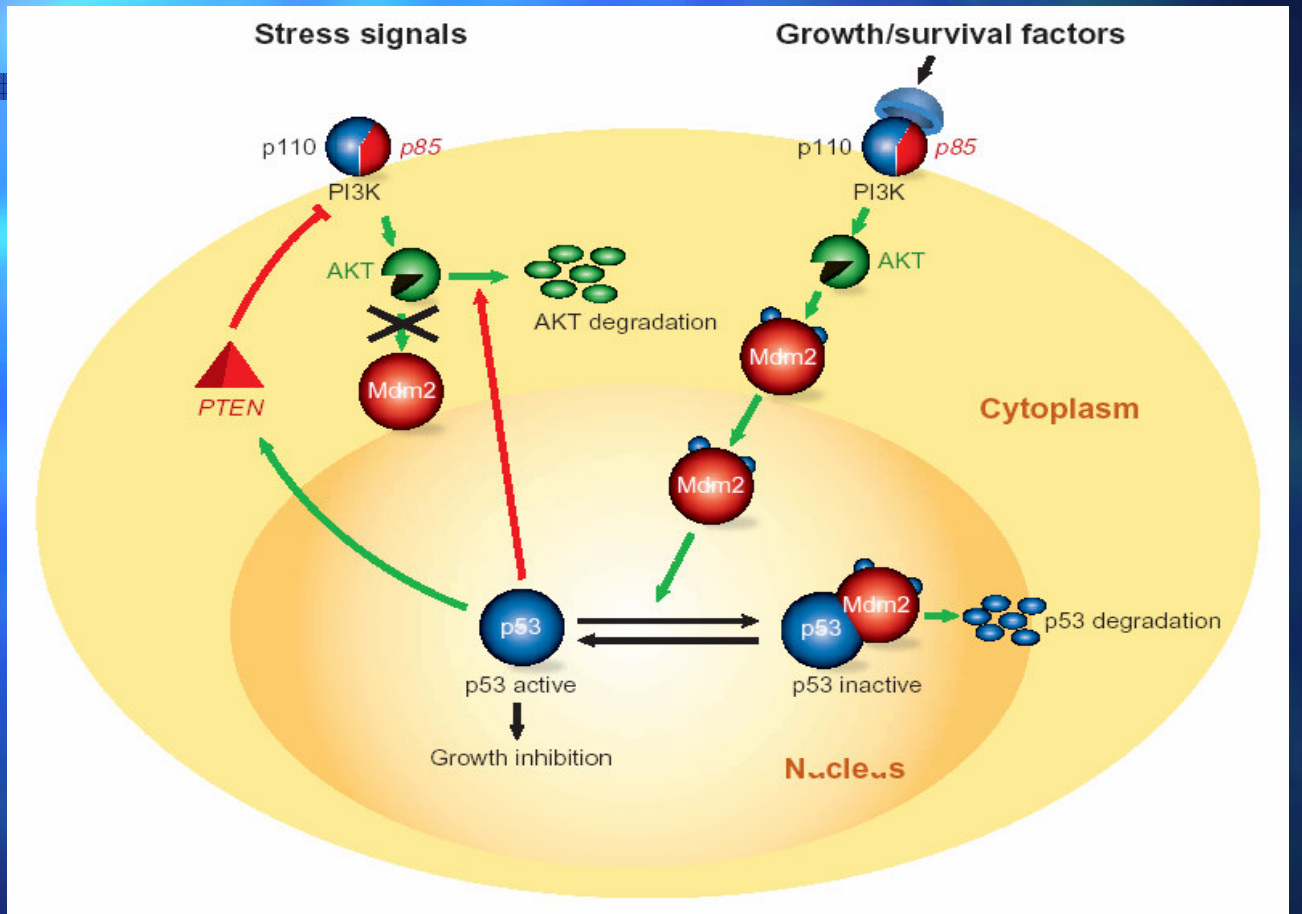
Journal of Cell Science 114, 4139-4140 (2001)

Example: A Model for p53-mediated Apoptosis



from
APOPTOSIS - THE P53 NETWORK - Haupt et al.
Journal of Cell Science 116, 4077-4085, 2003

Example: A Model for the Regulation of p53 (by de AKT Pathway) under Growth/Survival Conditions or Stress Signals



from
APOPTOSIS - THE P53 NETWORK - Haupt et al.
Journal of Cell Science 116, 4077-4085, 2003

Combined Application of Experimental and Computational Tools

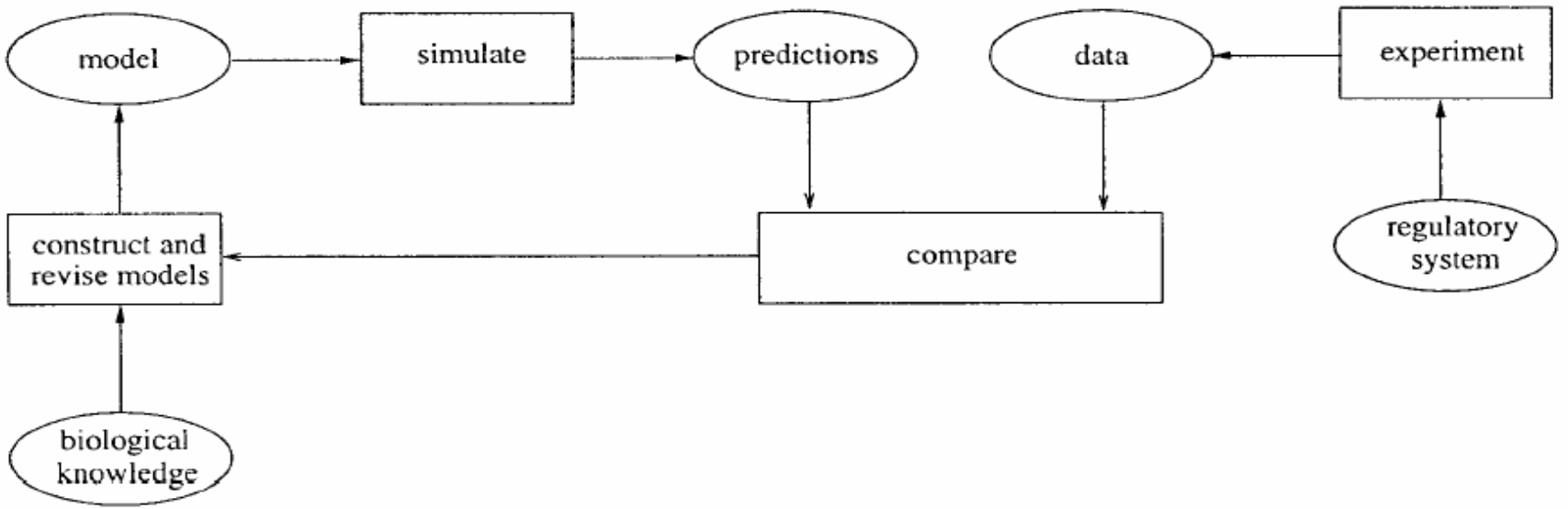


FIG. 2. Analysis of genetic regulatory systems. The boxes represent activities, the ovals information sources, and the arrows information flows.

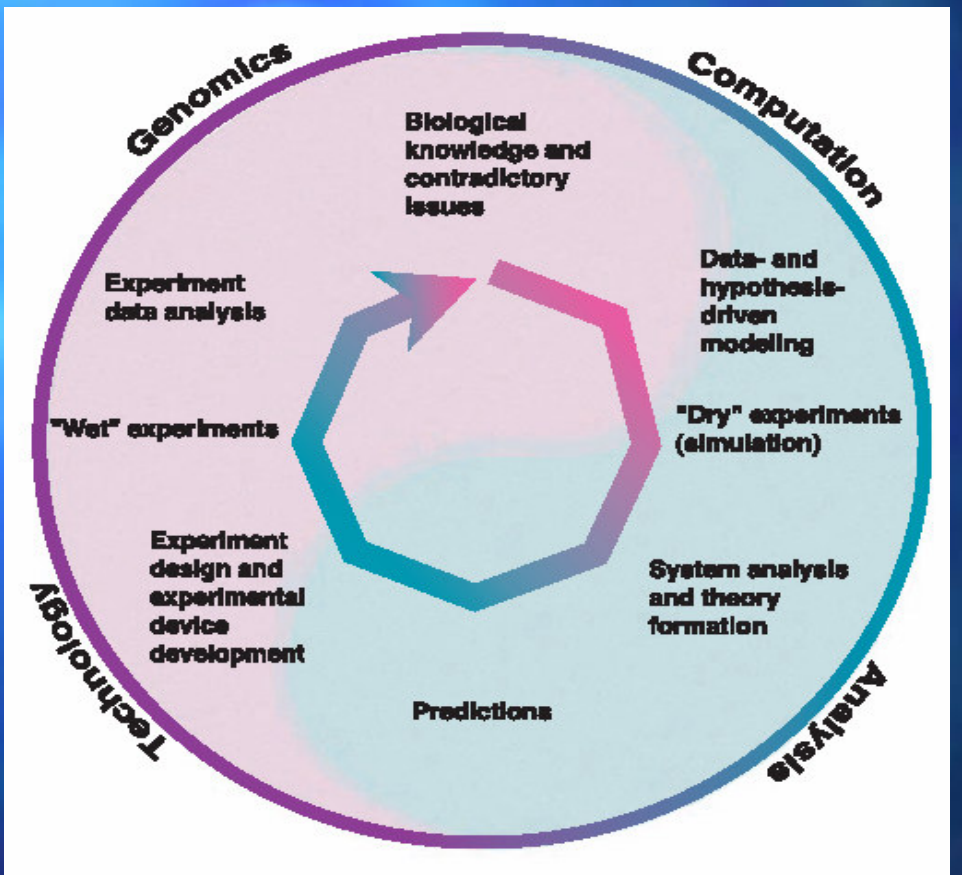
from

MODELING AND SIMULATION OF GENETIC REGULATORY SYSTEMS: A LITERATURE REVIEW

Hidde de Jong

Journal of Computational Biology - Vol. 9 - Number 1, 2002 - Pp. 67-103

Hypothesis-driven Research



from
SYSTEMS BIOLOGY: A BRIEF OVERVIEW - Hiroaki Kitano
SCIENCE - Vol. 295, 2002 - Pp. 1662-1664

Discussion

- Current experimental molecular biology is producing increasing amounts of quantitative data needed to support SIMULATION-BASED RESEARCH.
- Importance of a SYSTEM-LEVEL APPROACH (identification of their STRUCTURES and DYNAMICS)
- Advances in software and computational power enable the creation and analysis of REASONABLY REALISTIC yet intricate biological models to study the STRUCTURE and FUNCTION of biological circuits.
- Computational modelling and analysis are now able to provide useful BIOLOGICAL INSIGHTS and PREDICTIONS (analysis of the cell cycle, metabolic analysis, studies of robustness, etc.)