# **The yeast cell-cycle network**: structure vs. function

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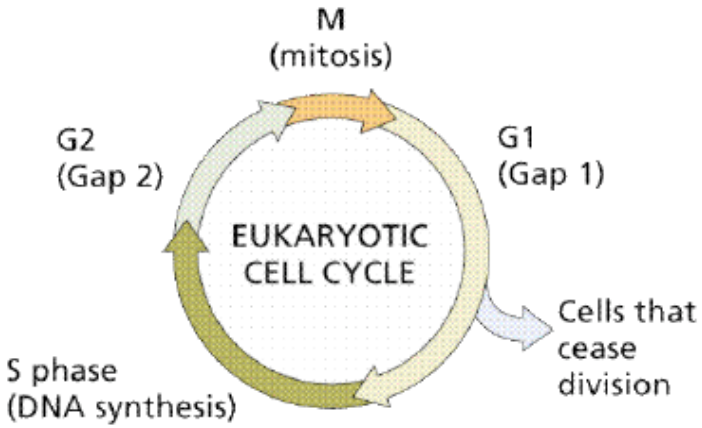
Structure -> function

# The Cell Cycle




The process consists of four phases: G1 (in which the cell grows and, under appropriate conditions, commits to division), S (in which the DNA is synthesized and chromosomes replicated), G2 (a ‘‘gap’’ between S and M), andM(in which chromosomes are separated and the cell is divided into two). After the M phase, the cell enters theG1 phase, hence completing a ‘‘cycle.’’

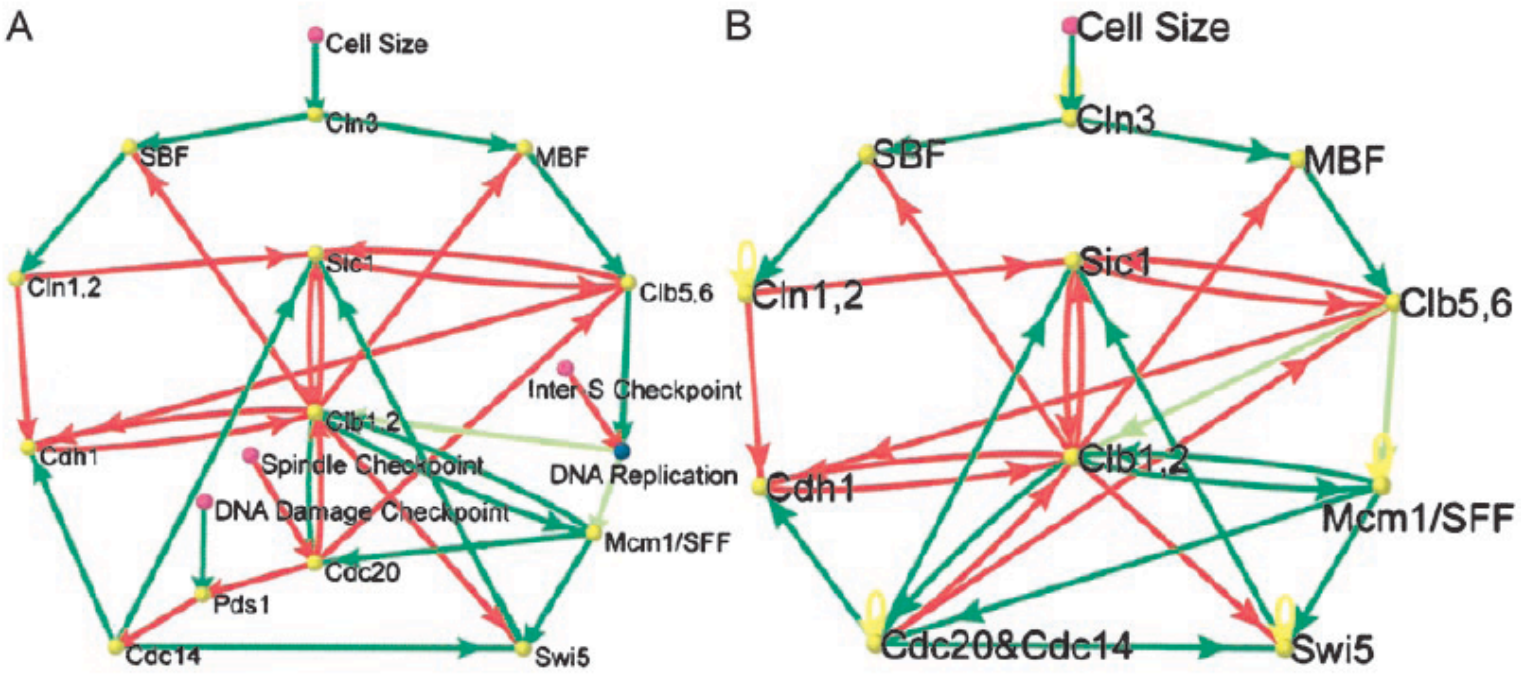



Fig. 1. (*A*) The cell-cycle network of the budding yeast. (*B*) Simplified cell-cycle network with only one checkpoint ''cell size.''

- The cell-cycle sequence starts when the cell commits to division by activating Cln3 (the START). The subsequent activity of Clb5 drives the cell into the S phase. The entry into and exit from the M phase is controlled by the activation and degradation of Clb2. After the M phase, the cell comes back to the stationary G1 phase, waiting for the signal for another round of division. Thus the cell-cycle process starts with the ''excitation'' from the stationary G1 state by the ''cell-size'' signal and evolves back to the stationary G1 state through a well defined sequence of states.

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

In the cell-cycle network much of the biology seems to be reflected in the on–off characteristics of the network components and we are mainly concerned herewith the overall dynamic properties and the stability of the network, we use a simplified dynamics on the network, which treats the nodes and arrows as logic-like operations.

**Table 1. The fixed points of the cell-cycle network**

| Basin size | Cln3 | MBF | SBF | Cln1,2 | Cdh1 | Swi5 | Cdc20 | Clb5,6 | Sic1 | Clb1,2 | Mcm1 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1,764 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| 151 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 109 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| 9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| 7 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| 7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |

Each fixed point is represented in a row. The first column is the size of the basin of attraction for the fixed point; the other 11 columns show the protein states of the fixed point. The protein states of the biggest fixed point correspond to that of the $G_1$ stationary state.

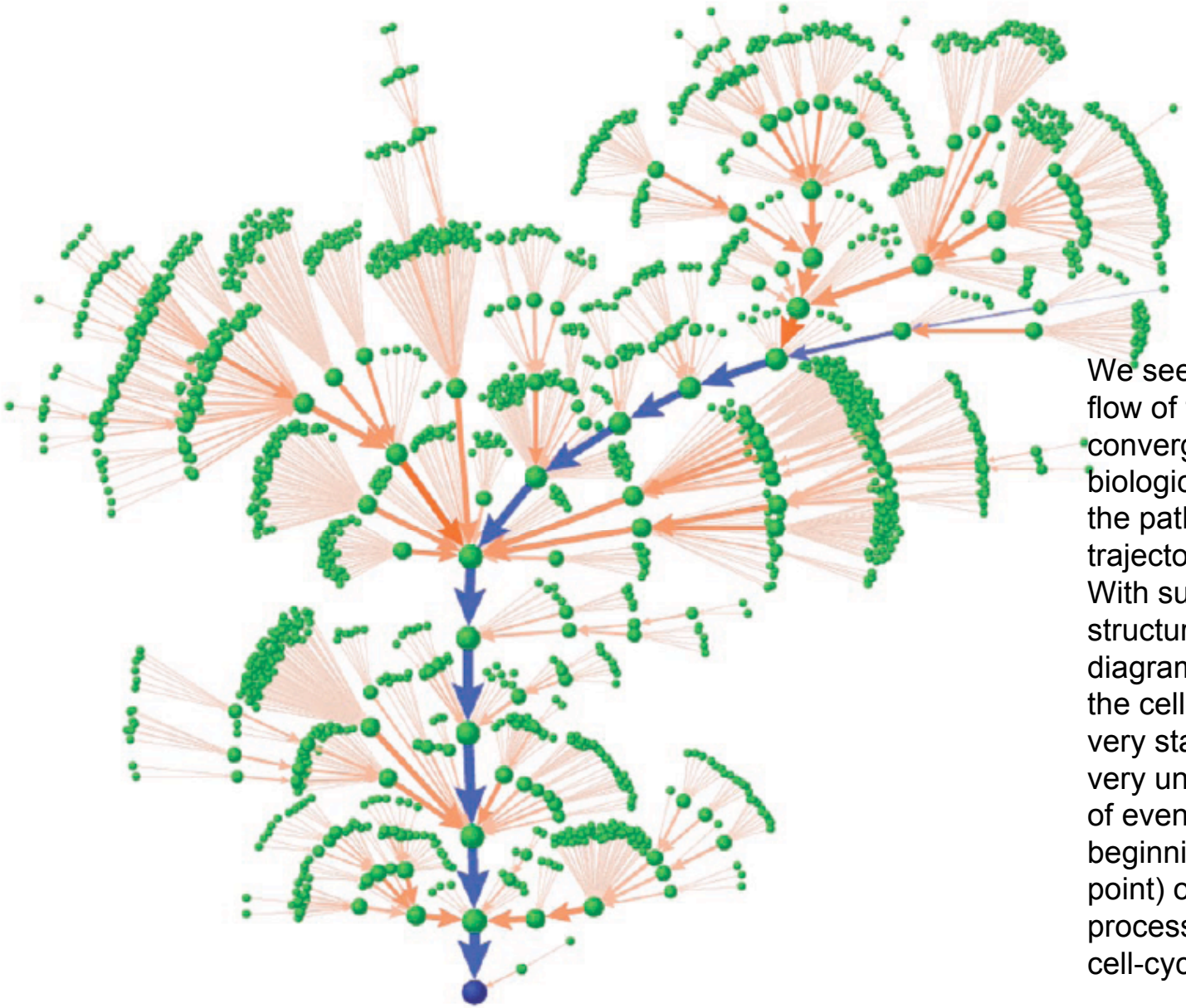
We use the dynamic model described above to study the time evolution of the protein states. we study the attractors of the network dynamics by starting from each of the 2^11= 2,048 initial states in the 11-node network. We find that all of the initial states eventually flow into one of the seven stationary states (fixed points). Among the seven fixed points, there is one big fixed point attracting 1,764 or 86% protein states. Remarkably, this super stable state is the biological G1 stationary state.

We start the cell-cycle process by ‘‘exciting’’ the G1 stationary state with the cell size signal, and observe that the system goes back to the G1 stationary state. The temporal evolution of the protein states, presented in Table 2, indeed follows the cell-cycle sequence, going from the excited G1 state (the START) to the S phase, the G2 phase, the M phase, and finally to the stationary G1 state. This is the biological trajectory or pathway of the cell-cycle network.

**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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | START |
| 2 | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | $G_1$ |
| 3 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | $G_1$ |
| 4 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | $G_1$ |
| 5 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | S |
| 6 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 1 | $G_2$ |
| 7 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | M |
| 8 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | M |
| 9 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | M |
| 10 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 1 | M |
| 11 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | M |
| 12 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | $G_1$ |
| 13 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | Stationary $G_1$ |

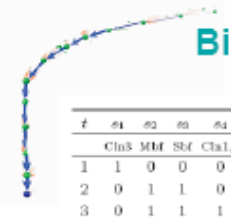
The right column indicates the cell-cycle phases. Note that the number of time steps in each phase do not reflect its actual duration.



We see that the dynamic flow of the protein states is convergent onto the biological pathway, making the pathway an attracting trajectory of the dynamics. With such a topological structure of the phase diagram of protein states, the cell-cycle pathway is a very stable trajectory; it is very unlikely for a sequence of events, starting at the beginning (or at any other point) of the cell-cycle process, to deviate from the cell-cycle pathway.

**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.

Function -> structure



## Biological Function

| $t$ | $s_1$ | $s_2$ | $s_3$ | $s_4$ | $s_5$ | $s_6$ | $s_7$ | $s_8$ | $s_9$ | $s_{10}$ | $s_{11}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cln3 | MBF | SBF | Cln1,2 | Cdh | Swi | Cdc | Clb5,6 | Sic | Clb1,2 | Mem |
| 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| 2 | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| 3 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| 4 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| 6 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 1 |
| 7 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 |
| 8 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| 9 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 0 |
| 10 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 11 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| 12 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |

TABLE I: The biological pathway $S^*(t)$ of the cell cycle process. The names of the biomolecules are listed in the second row.

$$s_i(t+1) = \begin{cases} 1 & \sum_j a_{ji} s_j > 0 \\ 0 & \sum_j a_{ji} s_j < 0 \\ 0 & \sum_j a_{ji} s_j = 0 \ \& \ a_{ii} = -1 \\ s_i(t) & \sum_j a_{ji} s_j = 0 \ \& \ a_{ii} = 0 \ , \end{cases}$$

where $s_i(t) \in \{0,1\}$ denotes the state of node $i$.

$$s_i(t+1) = \left( \sum_{j \neq i} \left( s_j(t) g_{ji} \right) + s_i(t) \bar{r}_{ii} \right) \prod_{j \neq i} \left( \overline{s_j(t) r_{ji}} \right)$$

| | |
|---|---|
| + | OR |
| x | AND |
| bar | NOT |

George Boole

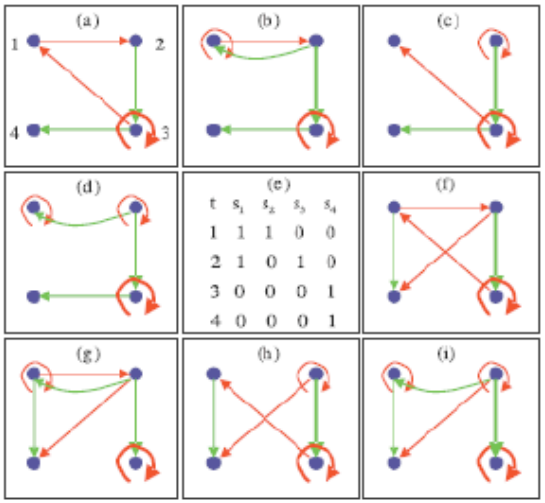
## Biological Networks

$$\prod_{i=1}^{L-1} R_{S_j(i) \to S_j(i+1)} \left( g_{1j}, \overline{g}_{1j}, r_{1j}, \overline{r}_{1j}, \cdots, g_{kj}, \overline{g}_{kj}, r_{kj}, \overline{r}_{kj}, \cdots, g_{Nj}, \overline{g}_{Nj}, r_{Nj}, \overline{r}_{Nj} \right) = 1.$$

## A simple example

$N = 4$ and $T = 4$

| t | $s_1$ | $s_2$ | $s_3$ | $s_4$ |
|---|---|---|---|---|
| 1 | 1 | 1 | 0 | 0 |
| 2 | 1 | 0 | 1 | 0 |
| 3 | 0 | 0 | 0 | 1 |
| 4 | 0 | 0 | 0 | 1 |




$$\bar{r}_{21}\bar{g}_{41}\left(n_{11}r_{31} + g_{21}r_{31} + r_{11}g_{21}n_{31}\right) = 1$$

$$\bar{g}_{42}\left(r_{12} + n_{12}r_{22}r_{32} + n_{12}r_{22}n_{32}\right) = 1$$

$$n_{13}g_{23}r_{33}\bar{g}_{43} = 1$$

$$\bar{r}_{14}\bar{r}_{34}n_{44}\left(g_{14}r_{24} + r_{24}g_{34} + n_{14}n_{24}g_{34}\right) = 1$$

| | |
|---|---|
| + | OR |
| x | AND |
| bar | NOT |

$$n_{ji} = \overline{r_{ji} + g_{ji}} = \overline{r_{ji}}\,\overline{g_{ji}}$$

$$
\begin{aligned}
\bar{r}_{21}\bar{g}_{41}\left(n_{11}r_{31}+g_{21}r_{31}+r_{11}g_{21}n_{31}\right) &= 1\\
\bar{g}_{42}\left(r_{12}+n_{12}r_{22}r_{32}+n_{12}r_{22}n_{32}\right) &= 1\\
n_{13}g_{23}r_{33}\bar{g}_{43} &= 1\\
\bar{r}_{14}\bar{r}_{34}n_{44}\left(g_{14}r_{24}+r_{24}g_{34}+n_{14}n_{24}g_{34}\right) &= 1
\end{aligned}
$$

## Conserved Edges: $g_{23}$ and $r_{33}$

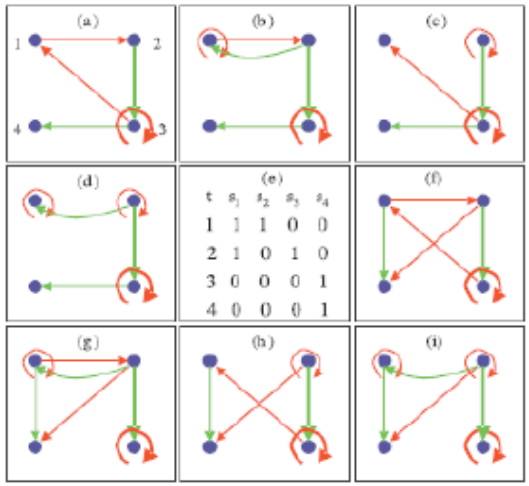
**Node 1:** $\bar{r}_{21}\bar{g}_{41}\left(n_{11}r_{31} + g_{21}r_{31} + r_{11}g_{21}n_{31}\right) = 1$

$(r_{31} = 1)$ or $(r_{31})$ $(g_{21}\ r_{31})$, and $(r_{11}\ g_{21})$

**Node 2:**
$(r_{12})$ and $(r_{22})$

**Node 3:**
$(g_{23}\ r_{33})$

**Node 4:**
$(g_{34})$ and $(g_{14}\ r_{24})$




$$\mathcal{M} \subseteq \mathcal{I} \subseteq \mathcal{P} \subseteq \mathcal{W}$$

$$|\mathcal{W}| = 8.5 \times 10^6$$

$$|\mathcal{P}| = 1024$$

$$|\mathcal{I}| = 8$$

$$|\mathcal{M}| = 2$$

| $t$ | $s_1$ | $s_2$ | $s_3$ | $s_4$ | $s_5$ | $s_6$ | $s_7$ | $s_8$ | $s_9$ | $s_{10}$ | $s_{11}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cln3 | Mbf | Sbf | Cln1,2 | Cdh | Swi | Cdc | Clb5,6 | Sic | Clb1,2 | Mcm |
| 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| 2 | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| 3 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| 4 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| 6 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 1 |
| 7 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 |
| 8 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| 9 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 0 |
| 10 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 11 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| 12 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |

TABLE I: The biological pathway $\mathrm{S}^*(t)$ of the cell cycle process. The names of the biomolecules are listed in the second row.

$$\frac{n_{2,10}n_{3,10}n_{4,10}r_{7,10}g_{8,10}\bar{r}_{11,10}}{\left(r_{5,10}+r_{9,10}+\bar{g}_{1,10}\bar{g}_{5,10}\bar{g}_{6,10}\bar{g}_{9,10}\right)} = 1 \qquad \frac{n_{54}n_{94}\bar{g}_{14}\bar{r}_{24}\bar{r}_{34}\bar{g}_{64}\left(g_{24}+g_{34}\right)}{\left(r_{74}\bar{r}_{84}\bar{r}_{10,4}\bar{r}_{11,4}+r_{44}\bar{g}_{74}n_{84}n_{10,4}n_{11,4}\right)} = 1$$

| Node | Conserved | Non-conserved |
|---|---|---|
| 1 | - | $(r_{11})^*$, $(r_{51})$, $(r_{91})$ |
| 2 | $(g_{12})^*$ | $(r_{10,2})^*$, $(r_{11,2})$ |
| 3 | $(g_{13})^*$ | $(r_{10,3})^*$, $(r_{11,3})$ |
| 4 | - | $(g_{24}\ r_{44})$,$(g_{34}\ r_{44})^*$,$(g_{24}\ r_{74})$,$(g_{34}\ r_{74})$ |
| 5 | $(r_{45})^*$ | $(g_{75})^*$, $(g_{11,5})$ |
| 6 | $(r_{66}\ g_{76})^*$ | $(r_{46})$, $(r_{86})$, $(r_{10,6})^*$ |
| 7 | - | $(r_{57}\ g_{10,7})$, $(r_{57}\ g_{11,7})$, $(r_{77}\ g_{11,7})^*$, $(r_{67}\ g_{11,7})$, $(r_{67}\ g_{10,7})$, $(r_{97}\ g_{10,7})$, $(r_{97}\ g_{11,7})$ |
| 8 | - | $(g_{28}\ r_{58}\ r_{78})$, $(g_{28}\ r_{58}\ r_{88})$, $(g_{28}\ r_{78}\ r_{98})^*$, $(g_{28}\ r_{88}\ r_{98})$, $(g_{38}\ r_{58}\ r_{78})$, $(g_{38}\ r_{58}\ r_{88})$, $(g_{38}\ r_{78}\ r_{98})$, $(g_{38}\ r_{88}\ r_{98})$, $(g_{48}\ r_{58}\ r_{78})$, $(g_{48}\ r_{78}\ r_{98})$ |
| 9 | $(r_{49})^*$ | $(g_{79})^*$, $(g_{11,9})$ |
| 10 | $(r_{7,10}\ g_{8,10})^*$ | - |
| 11 | $(g_{8,11}\ r_{11,11})^*$ | - |

TABLE II: The irreducible edges (conserved and non-conserved). The starred edges are known to have naturally occurred in the cell cycle of budding yeast [4].

# Reference


- **F. Li, T. Long, Y. Lu, Q. Ouyang, and C. Tang,** *The yeast cell-cycle network is robustly designed*, **PNAS (2004).**
- **G. Wang, R. Simha, and C. Zeng,** *A Logic-Based Technique that Characterizes the Class of Boolean Networks Producing a Given Biological Pathway*, **(2008)**