A Combined Pathway to Simulate CDK-Dependent Phosphorylation and ARF-Dependent Stabilization for p53 Transcriptional Activity

Atsushi Doi\textsuperscript{1} Masao Nagasaki\textsuperscript{1} Kazuko Ueno\textsuperscript{1}
doi@ims.u-tokyo.ac.jp masao@ims.u-tokyo.ac.jp uepi@ims.u-tokyo.ac.jp

Hiroshi Matsuno\textsuperscript{2} Satoru Miyano\textsuperscript{1}
matsuno@sci.yamaguchi-u.ac.jp miyano@ims.u-tokyo.ac.jp

\textsuperscript{1}Human Genome Center, Institute of Medical Science, University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan
\textsuperscript{2}Graduate School of Science and Engineering, Yamaguchi University, 1677-1 Yoshida, Yamaguchi, 753-8512, Japan

Abstract

The protein p53 is phosphorylated by a member of protein kinases such as CDK7, and stabilized by the protein ARF. The phosphorylation and stabilization of p53 is believed to enhance its transcriptional activity and act simultaneously. Biological pathways composed of experts knowledge obtained from the literature are including these activation mechanisms. However, the map of biological pathways does not reflect the combination effect of phosphorylation and stabilization.

We have conducted some simulations of biological pathways with hybrid functional Petri net (HFPN) after careful reading of papers. In this paper, we constructed the HFPN based biological pathway of CDK-dependent phosphorylation pathway and combine with ARF-dependent pathway described previously, to observe the effect of the phosphorylation on the stabilization with simulation-based validation.

Keywords: biological pathway, Petri net, simulation, p53, transcriptional activity

1 Introduction

Biological processes are usually summarized in a picture composed of figures of various shapes (e.g. circles and rectangles) and several types of arrows. Graphical images in the picture are important since they reflect the knowledge in biology and medicine. The summarized picture makes a network called "Biological Pathway".

Biological pathway databases such as BioCyc [24], KEGG [8, 28], and TRANSPATH [10, 25] have compiled many biological processes between cellular components, providing invaluable information to researchers in the forms of pictures. However, with such databases, it is not easy to grasp the information about quantitative interactions of molecules, since such databases focus on providing qualitative information of biological processes.

We have conducted some simulations of biological pathways with hybrid functional Petri net (HFPN) [4, 6, 15]. HFPN have been introduced by Matsuno et al. [13] and is a representation method for biological pathways.

A gene \textit{p53} is called a tumor suppressor gene since \textit{p53} regulates cell cycle arrest and induces apoptosis. A modification of the protein \textit{p53} complicates the relationship between the concentration of \textit{p53} and its transcriptional activity. The protein \textit{p53} is stabilized by the protein ARF [17] and phosphorylated by kinases [2, 3, 9, 11, 17, 20, 21, 22, 23]. The pathway databases store these information of stabilization and phosphorylation in a map. Although the map describes molecular
interactions between the proteins p53, ARF and kinases, the synegetic effect of the stabilization and the phosphorylation is still unclear.

We have constructed the ARF-dependent stabilization pathway and attempted the simulation-based validation of the p53 transcriptional activity with hybrid functional Petri net [6]. In this paper, we represent the CDK-dependent phosphorylation pathway with HFPN and combine this phosphorylation pathway with ARF-dependent stabilization pathway [6]. We demonstrate the effect which is not observed in the single, combining two pathways by the simulation-based validation.

2 Biological Pathway Representation with Hybrid Functional Petri Net

A Petri net, defined by Carl Adam Petri, is a mathematical method which has visual expression like a pathway and allows us to describe the dynamics of systems [18]. It has been mainly used so far to model artificial systems such as manufacturing systems and communication protocols. A Petri net is a network consisted of “places”, “transitions”, “arcs” and “tokens”. Places are represented by a circle which can hold the tokens. Transitions are represented by a rectangle, having a function of transmitting the tokens from the places. Arcs have a direction and connect a place (transition) and a transition (place).

Biological processes include the information of concentrations of substances such as proteins and mRNAs. Their value is a continuous value. Because of that, to express biological processes, we need the expression which can handle continuous values. However, the information that “a protein is activated or not” is included as the biological processes, which can be expressed by a discrete event. Hence, we need expressions which can handle discrete values. To handle both of the continuous and discrete information, we employed the hybrid Petri net (HPN) [1] for modeling and simulating a biological pathway [14]. Moreover we have defined hybrid functional Petri net (HFPN) [15] as an extension of the HPN and developed a software Cell Illustrator for modeling and simulation of biological pathways [5, 16].

We change the symbols of ”place” and ”transition” to biological images on Cell Illustrator. Although these changes have no effect on mathematical meaning, it is helpful for biologists to understand the pathway. Each substance such as proteins or mRNAs corresponds to an HFPN element “place” (originally a double circle, but it is changed to a picture reflecting the biological meaning of the place: see Fig. 1), which holds the concentration of the substance.

3 CDK-Dependent Phosphorylation Pathway with Hybrid Functional Petri Net

The protein p53 is a tumor suppressor and has a transcriptional activity. The transcriptional activity of the protein p53 depends on the concentration of the protein p53 or the phosphorylation at the N-terminal and C-terminal regions of p53. If the protein p53 is stabilized by the protein p19ARF, the concentration of p53 increases [7]. If p53 is phosphorylated by kinases, its sequence-specific DNA binding activity is enhanced [12].

Proteins p53, MDM2, and p19ARF are closely related to cancer. The protein p53 suppresses the formation of tumors, and the protein MDM2 is a negative regulator of p53. MDM2 ubiquitinates p53 and decreases the activity and stability of the protein p53. In contrast, the protein p19ARF is an inhibitor of the protein MDM2. p19ARF interacts with MDM2 and p53, and inhibits ubiquitin-mediated degradation. Thus, the ARF-dependent stabilization pathway is consisted of proteins p53, MDM2, and p19ARF. The stabilization of p53 is a quantitative alteration for transcriptional activity of p53. We have constructed the ARF-dependent stabilization pathway and attempted the simulation-based validation of the p53 transcriptional activity with hybrid functional Petri net [6]. The simulation
results suggested that p53 should have the transcriptional activity in the trimeric complex of p53, MDM2, and p19ARF.

On the other hand, the phosphorylation of p53 is a qualitative alteration. The protein CDK7 is a kinase and interacts with proteins cycH and p36 [12].

### 3.1 CDK-Dependent Phosphorylation Pathway

Fig. 2 shows an HFPN model of CDK-dependent phosphorylation pathway which has been constructed by compiling and interpreting the information of complex CDK7-cycH-p36 and the protein p53 interactions in the literature [12]. In Fig. 2, we assign the symbols of biological images to places and transitions on Cell Illustrator instead of circles and rectangles (Fig. 1). Each place is labeled with the name of the substance (e.g. p53, CDK7 mRNA). In this paper, the name of complex of two proteins A and B is represented as A_B, where places for proteins A and B are labeled with A and B. An additional name (C) or (N) is attached at the tail of a substance name, when we need to distinguish locations of substances in the cytoplasm or in the nucleus. Moreover, an additional name \( p \) attached at the p53 means the phosphorylated p53.

In HFPN model of this paper and [6], all places are continuous and hold a real number as its content (Table 1). Table 1 summarizes name and variable of places in Fig. 2. Note that Initial Values which are initial contents of places are zero in this pathway. The transitions are related to p53-CDK7 interactions summarized in the second column of Table 2. Ten events (transitions \( T_{13}, \ldots, T_{22} \)) have been extracted from the literature [12]. All transitions are continuous and fire at the speed of the assigned parameters in the fourth column of Table 2. The transitions \( d_j (j = 1, \ldots, 19) \) represent natural degradation of the corresponding substances. We define the speed of natural degradation as \( nX \times 0.01 \) (\( nX \) indicates the concentration of a corresponding substances (Table 1)).

By means of these transitions and notations for molecules, the CDK-dependent phosphorylation pathway can be described as follows: The mRNAs of the genes p53, CDK7, cycH, and p36 are synthesized by the transcriptions \( (T_1, T_4, T_7, \text{and } T_{10}) \), and translated \( (T_2, T_5, T_8, \text{and } T_{11}) \) to the proteins (p53(C), CDK7(C), cycH(C), and p36(C)) in a cytoplasm. Then the proteins are transported \( (T_3, T_6, T_9, \text{and } T_{12}) \) into a nucleus as transcription factors (p53(N), CDK7(N), cycH(N), and p36(N)). CDK7(N) forms the complex CDK7-cycH with cycH(N) (\( T_{13} \)). After forming the CDK7-cycH dimeric complex, CDK7-cycH forms the CDK7-cycH-p36 trimeric complex with p36 (\( T_{15} \)). p36(N) forms the complex p36-p53 with p53(N) (\( T_{16} \)). Hence, CDK7-cycH-p36 binds to p53(N) (\( T_{14} \). More-
over, the complex CDK7,cycH binds to the complex p36,p53 ($T_{17}$). After forming the complex CDK7,cycH,p36,p53, the protein p53 is phosphorylated by the complex CDK7,cycH,p36 ($T_{18}$).

The phosphorylated p53 enhances its sequence-specific DNA binding activity [12], therefore p53 has a higher transcriptional activity than unphosphorylated p53 (p53(N)). The transcriptional activity of the protein p53 is represented by test arcs from the places p53(N), p53, and p36.p53 to the transitions $T_{19}$, $T_{20}$, and $T_{21}$, respectively. Furthermore, the difference of the transcriptional activity between phosphorylated protein p53 and unphosphorylated protein p53 is represented by the speeds of each transition (Table 2).

Our HFPN pathway model, we manually tuned the parameters for the speeds of transitions and initial contents of places so that the model is consistent with the biological experiments in [12]. Thus we defined the speed of transition $T_{19}$ is two times faster than the speed of transition $T_{20}$ ($T_{21}$). The HFPN model in Fig. 2 is available from http://www.csml.org including all parameters in the model and can be simulated on Cell Illustrator 2.0 [27]

### Table 1: Places in the HFPN model of Fig. 2. Initial Values of all places are 0.

<table>
<thead>
<tr>
<th>Places Name</th>
<th>Variable (nX)</th>
<th>Places Name</th>
<th>Variable (nX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53(N)</td>
<td>n1</td>
<td>p21</td>
<td>n11</td>
</tr>
<tr>
<td>p53{p}</td>
<td>n2</td>
<td>CDK7 mRNA</td>
<td>n12</td>
</tr>
<tr>
<td>CDK7,cycH.p36</td>
<td>n3</td>
<td>CDK7(C)</td>
<td>n13</td>
</tr>
<tr>
<td>CDK7(N)</td>
<td>n4</td>
<td>cycH mRNA</td>
<td>n14</td>
</tr>
<tr>
<td>cycH(N)</td>
<td>n5</td>
<td>cycH(C)</td>
<td>n15</td>
</tr>
<tr>
<td>p36(N)</td>
<td>n6</td>
<td>p36 mRNA</td>
<td>n16</td>
</tr>
<tr>
<td>CDK7,cycH</td>
<td>n7</td>
<td>p36(C)</td>
<td>n17</td>
</tr>
<tr>
<td>CDK7,cycH.p36.p53</td>
<td>n8</td>
<td>p53 mRNA</td>
<td>n18</td>
</tr>
<tr>
<td>p36.p53</td>
<td>n9</td>
<td>p53(C)</td>
<td>n19</td>
</tr>
<tr>
<td>p21 mRNA</td>
<td>n10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 3.2 The Simulation Results of CDK-Dependent Phosphorylation Pathway

Fig. 3 shows the results of simulation of the CDK-dependent phosphorylation pathway (Fig. 2). Concentration behaviors of p53(N), p36.p53, p53{p}, CDK7(N), p36(N), CDK7,cycH.p36, and p21 mRNA are observed in the following combinations of two genes: CDK7 and p36. We suppose that genes p53, CDK7, cycH, and p36 are found in the wild type cells. We considered the following cases:

1. All genes p53, CDK7, cycH, and p36 are expressed (wild type).

2. Only the transcription of the gene CDK7 is prohibited (CDK7− single mutant; remove the transition $T_7$).

3. The transcriptions of genes CDK7 and p36 are prohibited (CDK7−p36− double mutant; remove the transitions $T_7$ and $T_{10}$).

When all genes p53, CDK7, cycH, and p36 are expressed, p21 mRNA is activated by phosphorylated p53 (p53{p}) (Fig. 3 (1)). When the transcription of the gene CDK7 is prohibited, p21 mRNA is activated by complex p36.p53 (Fig. 3 (2)). When the transcriptions of the genes CDK7 and p36 are prohibited, p21 mRNA is activated by p53 itself (p53(N)) (Fig. 3 (3)). Fig. 3 (1) shows that the concentration of p21 mRNA becomes higher compared to its concentration in Fig. 3 (2) and 3 (3). Because we assign the faster speed for transition $T_{19}$ than transitions $T_{20}$ and $T_{21}$. Although the simulation results of CDK-dependent phosphorylation pathway are consistent with the literature [12], we could not obtain other suggestions.
Table 2: Biological facts extracted from the literature and assignments to transitions in the HFPN model of Fig. 2

<table>
<thead>
<tr>
<th>Transition</th>
<th>Biological phenomena on the literature</th>
<th>Type of biological processes</th>
<th>Speeds of transitions in the HFPN model (Fig. 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_1$</td>
<td>Transcription of the gene p53.</td>
<td>transcription</td>
<td>$n18 * 0.1$</td>
</tr>
<tr>
<td>$T_2$</td>
<td>Translation of p53 mRNA.</td>
<td>translation</td>
<td>$n18 * 0.1$</td>
</tr>
<tr>
<td>$T_3$</td>
<td>Nuclear import of the protein p53.</td>
<td>nuclear import</td>
<td>$n19 * 0.1$</td>
</tr>
<tr>
<td>$T_4$</td>
<td>Transcription of the gene CDK7.</td>
<td>transcription</td>
<td>$n19 * 0.1$</td>
</tr>
<tr>
<td>$T_5$</td>
<td>Translation of CDK7 mRNA.</td>
<td>translation</td>
<td>$n12 * 0.1$</td>
</tr>
<tr>
<td>$T_6$</td>
<td>Nuclear import of the protein CDK7.</td>
<td>nuclear import</td>
<td>$n12 * 0.1$</td>
</tr>
<tr>
<td>$T_7$</td>
<td>Transcription of the gene cycH.</td>
<td>transcription</td>
<td>$n13 * 0.1$</td>
</tr>
<tr>
<td>$T_8$</td>
<td>Translation of cycH mRNA.</td>
<td>translation</td>
<td>$n13 * 0.1$</td>
</tr>
<tr>
<td>$T_9$</td>
<td>Nuclear import of the protein cycH.</td>
<td>nuclear import</td>
<td>$n15 * 0.1$</td>
</tr>
<tr>
<td>$T_{10}$</td>
<td>Transcription of the gene p36.</td>
<td>transcription</td>
<td>$n15 * 0.1$</td>
</tr>
<tr>
<td>$T_{11}$</td>
<td>Translation of p36 mRNA.</td>
<td>translation</td>
<td>$n16 * 0.1$</td>
</tr>
<tr>
<td>$T_{12}$</td>
<td>Nuclear import of the protein p36.</td>
<td>nuclear import</td>
<td>$n17 * 0.1$</td>
</tr>
<tr>
<td>$T_{13}$</td>
<td>The protein CDK7 binds to cycH.</td>
<td>binding</td>
<td>$n4 * n5 * 0.01$</td>
</tr>
<tr>
<td>$T_{14}$</td>
<td>The protein p53 binds to complex CDK7(<em>{cycH</em>{p36}}).</td>
<td>binding</td>
<td>$n1 * n3 * 0.01$</td>
</tr>
<tr>
<td>$T_{15}$</td>
<td>The protein p36 binds to complex CDK7(_{p36}).</td>
<td>binding</td>
<td>$n6 * n7 * 0.01$</td>
</tr>
<tr>
<td>$T_{16}$</td>
<td>The protein p53 binds to p36.</td>
<td>binding</td>
<td>$n1 * n6 * 0.01$</td>
</tr>
<tr>
<td>$T_{17}$</td>
<td>Complex CDK7(<em>{cycH</em>{p36}}) binds to complex p36(_{p53}).</td>
<td>binding</td>
<td>$n7 * n9 * 0.01$</td>
</tr>
<tr>
<td>$T_{18}$</td>
<td>Complex CDK7(<em>{cycH</em>{p36}}) phosphorylates the protein p53.</td>
<td>phosphorylation</td>
<td>$n8 * 0.1$</td>
</tr>
<tr>
<td>$T_{19}$</td>
<td>The phosphorylated p53 efficiently activates the transcription of the gene p21.</td>
<td>transcription</td>
<td>$n2 * 0.2$</td>
</tr>
<tr>
<td>$T_{20}$</td>
<td>Complex p36(_{p53}) activates the transcription of the gene p21.</td>
<td>transcription</td>
<td>$n9 * 0.1$</td>
</tr>
<tr>
<td>$T_{21}$</td>
<td>The protein p53 activates the transcription of the gene p21.</td>
<td>transcription</td>
<td>$n1 * 0.1$</td>
</tr>
<tr>
<td>$T_{22}$</td>
<td>Translation of p21 mRNA.</td>
<td>translation</td>
<td>$n10 * 0.1$</td>
</tr>
</tbody>
</table>

† Corresponding transitions in the HFPN model (Fig. 2). ‡ Speeds of transitions in the HFPN model (Fig. 2). $nX(X = 1, \ldots, 19)$ is the concentration of the corresponding substances in Table 1.
A Combined Pathway of p53 Transcriptional Activity

4 Combined Pathway Model and Simulation

We have conducted the protein interactions of p53, MDM2, and p19ARF as the ARF-dependent stabilization pathway for the validation of p53 transcriptional activity with hybrid functional Petri net [6]. For the incorporation of quantitative and qualitative alteration of the protein p53, we combine the ARF-dependent stabilization pathway and CDK-dependent phosphorylation pathway.

Fig. 4 shows the combined pathway model which includes whole ARF-dependent stabilization pathway (surrounded with a line) and CDK-dependent phosphorylation pathway (Fig. 2). We add three transitions for the transcriptional activity of phosphorylated p53 and complex p53

\[ \text{MDM2} \times \text{p19ARF} \]

The transitions \( T_{23} \) and \( T_{24} \) mean the transcriptional activity of phosphorylated p53 \( (p53_p) \) for genes \( \text{MDM2} \) and \( \text{Bax} \), respectively. The transition \( T_{25} \) represents the transcriptional activity of complex p53\_MDM2\_p19ARF that was suggested by our simulation-based validation [6]. The speeds of transitions \( T_{23} \) and \( T_{24} \) are the same speed of the transition \( T_{19} \), as well as the speed of \( T_{25} \) is equal to \( T_{19} \) \( (T_{20}) \) in the model of [6] (Table 3).

Fig. 5 is the simulation results of concentration behaviors of p53(N), p36, p53, p36\{p\}, CDK7(N), p36(N), CDK7\_cyclH\_p36, and p21 mRNA on combinations of p19ARF, CDK7, and p36 expressions. We considered the following cases:

1. All genes including genes \( p19ARF \), CDK7, and p36 are expressed.

2. Only the transcription of the gene \( p19ARF \) is prohibited (remove the transition for the transcription of \( p19ARF \)).

3. The transcriptions of genes \( p19ARF \) and CDK7 are prohibited (remove the transition for the transcription of \( p19ARF \) and the transition \( T_3 \)).

4. The transcriptions of three genes ARF, CDK7, and p36 are prohibited (remove the transition for the transcription of \( p19ARF \), the transition \( T_4 \), and \( T_{10} \)).
Figure 3: The simulation results of concentration behaviors of p53(N), p36_p53, p53{p}, CDK7(N), p36(N), CDK7_cycH_p36 and p21 mRNA in Fig. 2. +; transactivate the expression of the corresponding genes, -; prohibit the expression of the corresponding genes.
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When all genes are expressed, the concentration of p21 mRNA is increased by phosphorylated p53 (p53\(\text{p}\)) and complex p53,MDM2,p19ARF. After reaching the peak, it slightly decreases. Because the ubiquitination of p53 by MDM2 decreases the amount of p53. When the transcription of the gene p19ARF is prohibited, the concentration of p21 mRNA is increased by phosphorylated p53 (p53\(\text{p}\)). As well as the case 1, the concentration of p21 mRNA is slightly decreased by the effect of MDM2. When the transcriptions of genes p19ARF and CDK7 are prohibited, the concentration of p21 mRNA is increased by complex p36,p53, and is slightly decreased by the effect of MDM2. When the transcriptions of three genes p19ARF, CDK7, and p36 are prohibited, the concentration of p21 mRNA do not increase. From Fig. 5 (1) and 5 (2), we observed the effect of ARF-dependent stabilization pathway. In spite of the destabilization of p53(N), phosphorylated p53 still have a efficient transcriptional activity (Fig. 5 (2)). Comparing Fig. 5 (2) and 5(3), we could not observed the obvious difference in the amount of p21 mRNA.

Table 3: The transitions \(T_{23}, T_{24}, \) and \(T_{25}\) are for the combined pathway (Fig. 4).

<table>
<thead>
<tr>
<th>(T_i)</th>
<th>biological phenomena on the literature</th>
<th>type of biological processes</th>
<th>(\hat{\mathcal{f}})</th>
<th>literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>(T_{23})</td>
<td>The phosphorylated p53 activates the transcription of the gene MDM2.</td>
<td>transcription</td>
<td>(n_2) * 0.2</td>
<td>–</td>
</tr>
<tr>
<td>(T_{24})</td>
<td>The phosphorylated p53 activates the transcription of the gene Bax.</td>
<td>transcription</td>
<td>(n_2) * 0.2</td>
<td>–</td>
</tr>
<tr>
<td>(T_{25})</td>
<td>The complex p53,MDM2,p19ARF activates the transcription of the gene p21.</td>
<td>transcription</td>
<td>(m_3) * 0.1</td>
<td>–</td>
</tr>
</tbody>
</table>

Corresponding transitions in the HFPN model (Fig. 4). Speeds of transitions in the HFPN model (Fig. 4). \(n_2\) is the concentration of phosphorylated p53 (p53\(\text{p}\)). \(m_3\) is the concentration of complex p53,MDM2,p19ARF [6].

5 Discussion and Conclusion

Through the simulations (Fig. 3 and Fig. 5), we observed the effects of CDK-dependent phosphorylation and ARF-dependent stabilization. Since phosphorylated protein p53 has a enhanced transcriptional activity for p21 mRNA, CDK-dependent phosphorylation pathway provides the results that the lack of CDK decreases the concentration of p21 mRNA, comparing Fig. 3 (1) and Fig. 3 (2). As shown in Fig. 5 (2) and Fig. 5(3), contrary to expectation, the lack of CDK7 seemed to have no effect to the concentration of p21 mRNA. In addition to the concentration of p21 mRNA, the phosphorylated protein p53 (p53\(\text{p}\)) increases the concentration of MDM2 mRNA (Fig. 4). While the protein p53 is phosphorylated, the protein MDM2 decreases the concentration of the protein p53 more effectively. Although the complex p36,p53 has a lessor transcriptional activity than that of p53\(\text{p}\), the concentration of p36,p53 is higher than that of p53\(\text{p}\). From these fact, the concentration of p21 mRNA was not changed whether or not the transcription of CDK7 was prohibited.

On the assumption that the protein MDM2 could not phosphorylate the complex p36,p53, we combined CDK-dependent phosphorylation pathway and ARF-dependent stabilization pathway. Thereby, the protein p36 performed like the protein p19ARF and stabilized the concentration of the protein p53 (Fig. 5(3) and (4)). Actually, biologists suggested that the protein MDM2 has a low binding affinity with the phosphorylated protein p53 [19].

We demonstrated the effect which was not observed in the single pathway, combining two pathways. Therefore we have to consider both phosphorylation and stabilization pathway when we investigate the transcription activity of the protein p53. Modeling and simulation of biological pathways saves the costs of biological experiments from both sides of expance and time. In fact, we could not estimate the
Figure 4: A merged pathway that includes the ARF-dependent stabilization pathway (surrounded with a line) and CDK-dependent phosphorylation pathway (Fig. 2). The transitions $T_{23}$ and $T_{24}$ mean the transcriptional activity of phosphorylated p53 ($p53^p$) for genes $MDM2$ and $Bax$, respectively. The transition $T_{25}$ represents the transcriptional activity of complex $p53_{MDM2}, p19ARF$ that was suggested by our simulation-based validation [6].
A Combined Pathway of p53 Transcriptional Activity

Figure 5: The simulation results of concentration behaviors of p53(N), p36, p53[p], CDK7(N), p36(N), CDK7_cycH_p36, MDM2 mRNA and p21 mRNA in Fig. 4. +; transactivate the expression of the corresponding genes, -; prohibit the expression of the corresponding genes.
accuracy of the simulation result, since there are considerable differences in the biological experiments such as cell types, tissue types, and experimental protocols. Furthermore, the protein p53 has several phosphorylation sites at the N-terminal and C-terminal regions. A kinase specifically phosphorylates p53 at different positions. Recently, we have developed a new biological pathway description format in XML called Cell System Markup Language (CSML) [26]. By using the CSML, we intend to store the information of phosphorylation sites with pathway models and apply the positional information to the simulation.

References


