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Mathematical Analysis of Multiple Molecular Switches of Phosphorylation/dephosphorylation with Feedback

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フィードバック付き複数リン酸化と脱リン酸化分子スイッチの数学的な分析

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Abstract Based on a binary tree structure, multiple molecular switches of phosphorylation/dephosphorylation in which feedback is embedded are formalized by logical operators. The complexity of corresponding pathway reconstruction process is discussed as well.

概要 二値化ツリーの構造に基づく複数リン酸化と脱リン酸化分子スイッチの中にフィードバックを導入し、論理操作によるこのプロセス公式化の方法を提案する、これに対する信号パスウェイの再構造プロセスの複雑性を議論する。

1. Introduction

The goal of our research is to study the signal transduction network of the fission yeast *S. pombe*, which is commonly used in the research on cell cycle [1,2], in terms of systems biology [3,4] and computer science. The network of signal transduction pathways in cells [5] is one of the most important networks for computational signal transduction, which refers to the studies on computational biology of signal transduction [6]. In spite of rapid progress that has been made in bioinformatics research on the budding yeast *S. cerevisiae* [7~9], the available empirical data for modeling the signal transduction network of the fission yeast *S. pombe* is not still sufficient for induction reasoning of the pathway structure. In addition, the deduction reasoning can not be efficiently applied here because the entire rules of pathway

reconstruction are unknown. The abduction reasoning, using part of rules and part of data where estimation or inference are necessary to achieve complete knowledge of global structure of pathway networks, will be helpful for the reconstruction of the pathway structure. We will build the partially interacted pathway structure in a bottom-up way and then infer global interactions of the signal transduction networks. The Bayesian network method [10], which is with logical links with abduction logic [11], is beneficial to the non-monotonic reasoning where probabilistic models are involved [12]. The integration of identification of the pathway network structure and probabilistic reasoning for discovering global rules on interactions of pathways are crucial tasks for us. The first step to reconstruct the pathway network by the above-mentioned methodology is to formalize the basic patterns from the building blocks of known pathways. In this summary, we extend our previous work on binary phosphorylation/dephosphorylation trees [6, 13] to their derived graph representation based on binary phosphorylation/dephosphorylation trees with feedback.

2. Phosphorylation/dephosphorylation Tree and Derived Graph Representation

The data structure we adopted for description of the pathways is a binary tree. The binary structure of the tree is consistent with the mechanism of signaling route of reversible phosphorylation/dephosphorylation processes, which is also called molecular switch in biochemistry. As shown in Figure 1, a binary phosphorylation/dephosphorylation tree is given. In the tree, x refers to the protein in the state of non-phosphorylation, x' refers to the protein in the state of phosphorylation. From the viewpoint of cellular signaling, the input to the pathway is y or y' and the output is x or x', where y refers to phosphatase and y' refers to kinase. The rule for the construction of the binary phosphorylation/dephosphorylation tree is made as follows:

$y \rightarrow x$ the dephosphorylation process for generating dephosphorylated protein

$y' \rightarrow x'$ the phosphorylation process for generating phosphorylated protein

under the condition of the reversible molecular switch of phosphorylation/dephosphorylation.

Atomic pathway is the basic building blocks of the combinatorial form of the interacted pathways. The term "atomic" pathway means the indivisible pathway, that is, the pathway that can not be divided into any sub-pathways any more. For example, the phosphorylation pathway for one protein, which is not involved in any cross-talks with other signal molecules except the corresponding kinase.

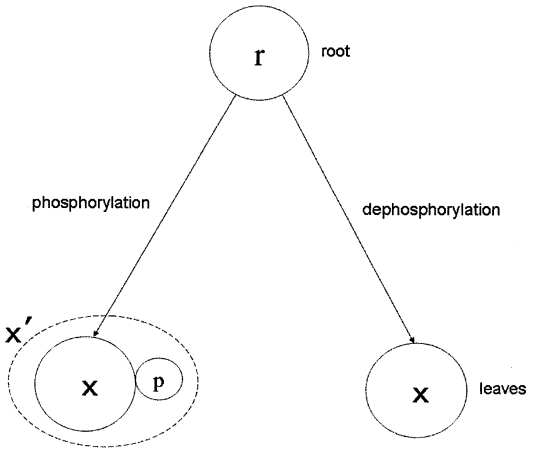

Figure 1 Binary phosphorylation/dephosphorylation tree

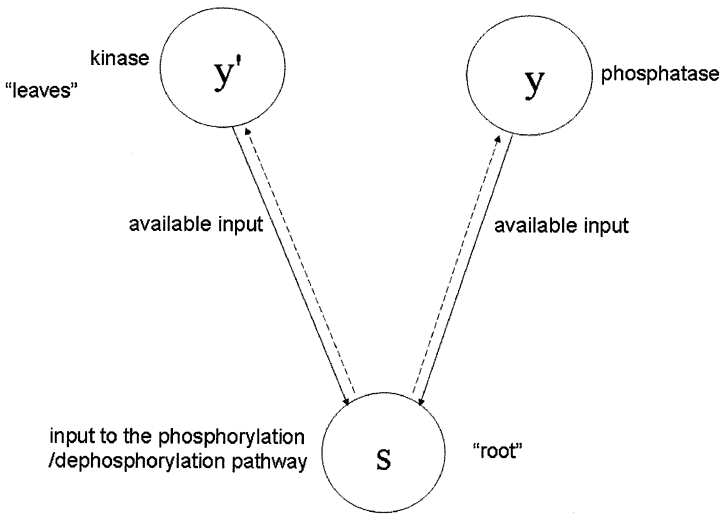

Figure 2 Graph in an inverse tree for kinase/phosphatase

3. Interactions of Phosphorylation/dephosphorylation with Feedback

In order to reconstruct pathway structure, the logical representation is used for the description of reconstruction operators and programming of pathway simulation. The predicate form in logic is denoted as the primitive

bpd-tree (r, x, x')

for the data structure shown in Figure 1.
The primitive

kp-graph (y, y', s)

is used for the data structure shown in Figure 2.

Considering the signal molecules outside the phosphorylation and dephosphorylation processes, we need the structure shown in Figure 3 and denoted it as the primitive

sm-tree (w, u, v)

In the graphs (trees), the labels of the edges refer to the relation among the nodes.

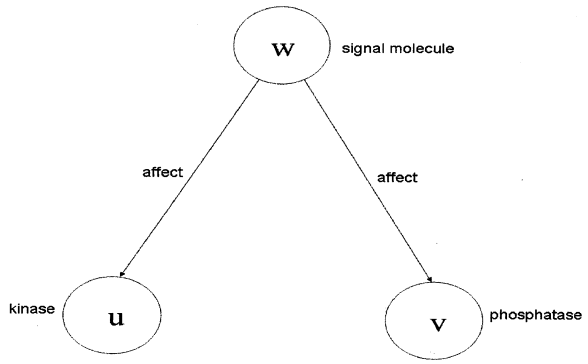

Figure 3 Influence of signal molecule on kinase/phosphatase

The patterns of the pathway structure can be described by grammar. The pattern of the pathway structure, shown in Figure 1, Figure 2 and Figure 3, is described by items: "*p/dp*", "*k/ph*" and "*sm*", respectively. The pattern for the interaction of two items can be "*sm&k/ph*" or "*k/ph&p/dp*", and the pattern for the interaction of three items can be "*sm&k/ph&p/dp*".

Let i = 0, 1, …, n-1. Multiple variables can be introduced into the mathematics models of pathway structure (Cf. Figure 4). Based on the graphs derived by a binary phosphorylation/dephosphorylation tree, the building blocks of pathways are classified into
Set A: n graphs in parallel,
and
Set B: k graphs, each graph is a m-layer network.
The graph for set A and set B is described in Figure 5.

The constraints for interactions based on the building blocks are listed as follows:

(a) The proteins in a pathway activate the kinases/phosphatases in other pathways [6,13];

(b) The kinases in a pathway or a network of signaling cascade activate or inactivate the kinases/phosphatases in other pathways;

(c) There exist cross-talks among different networks of signaling cascades.

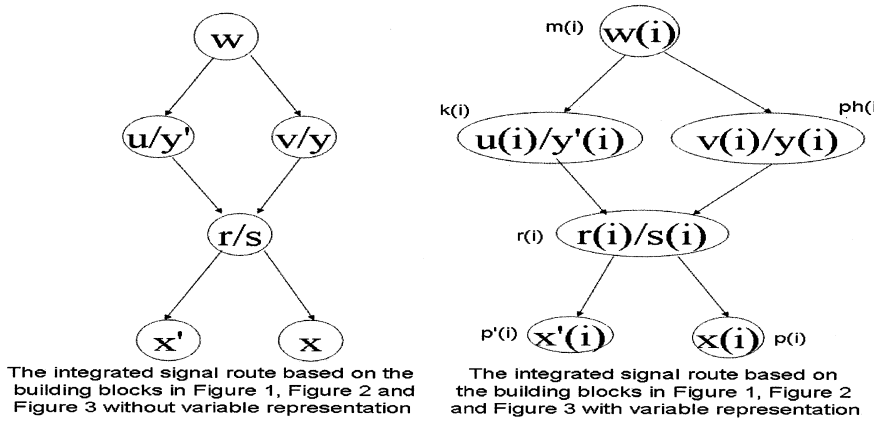

Figure 4 Graph derived from a binary tree as a building block

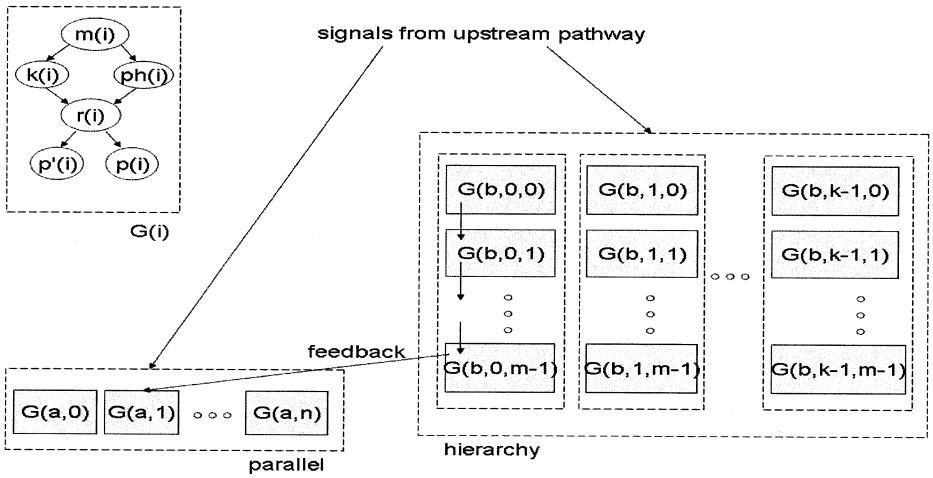

Figure 5 Pathway structure with interactions

4. Complexity of the Partial-Interaction Processes

From the basic graph shown in Figure 4, we can see that the number of node is 6 and the number of links is 6. The space complexity of this graph is *O(1)*. For set *A*, the space complexity is *O(n)*. For set *B*, the space complexity is *O(km)*. The space complexity for the

entire pathway structure is $O(n+km)$.

The time complexity of interaction process is the number of steps needed for reconstruction of the partially interacted pathway network. In [13], the time complexity for interaction process under the constraint (a) has been discussed under certain condition. In order to describe the pathway network where a kinase in a pathway of kinase-cascade activates another kinase in another pathway, we need the operations under the constraints of (b) and (c). In the case of signal cascade of kinases, the kinase in the upstream pathway activates the kinase in the downstream pathway, e.g., the signal transduction of MAPK-MAPKK-MAPKKK. We only consider this kind of waterfall-like signaling process within the set B. For the general structure of the kinase-cascade, the operation that connects different kinases in the same hierarchy of pathways in set B needs m steps. For k graphs, the step number of the interaction process realized by the operation under the constraint (c) becomes km. Assuming that the connection between set A and set B by the operation under the constraint (b) is one directional (e.g., the output of the pathway in set B activate or inactivate a kinase in set A), the step number of the corresponding interaction process exerted on the set A and set B will becomes $nkm(n-1)(n-2)/2$. Thus, the time complexity of the interaction process for above-mentioned partially interacted pathways is $O(km(0.5n^3-1.5n^2+n))$.

5. An Example of Mathematics Description for Signal Transduction in the Fission Yeast *S. pombe*

As shown in Figure 6, part of Ste11-MAP-kinase-cascade-Pat1-Mei2 pathway [14] can be logically inferred. Let $m(1) = m(2)$ = Ste11, $k(2)$ = Byr2, $k(3)$ = Byr1, $k(4)$=Spk1, $k(1)$=Pat1, $p(1)$ = Mei2, the graph structure for description of the feedback from Byr2-Byr1-Spk1 cascade on Pat1 marked in Figure 7 can be extracted from Figure 6. In the coarse-grained representation for cellular pathways in Figure 6, the feedback is introduced into the graph structure derived from phosphorylation/dephosphorylation trees. This is the prerequisite for modeling the pathway network of the fission yeast *S. pombe*.

6. Conclusion

We have designed a graph structure derived from phosphorylation/dephosphorylation trees and discussed the time complexity and space complexity of the corresponding interaction operators on the partially interacted pathways. This theoretical result shows that the graph extended from binary phosphorylation/dephosphorylation trees can describe the interaction of signal cascade of kinases and Pat1-Mei2 pathway, which are the basic pathways for reconstruction of network of signal transduction pathways of the fission yeast *S. pombe*, through low cost of simulation.

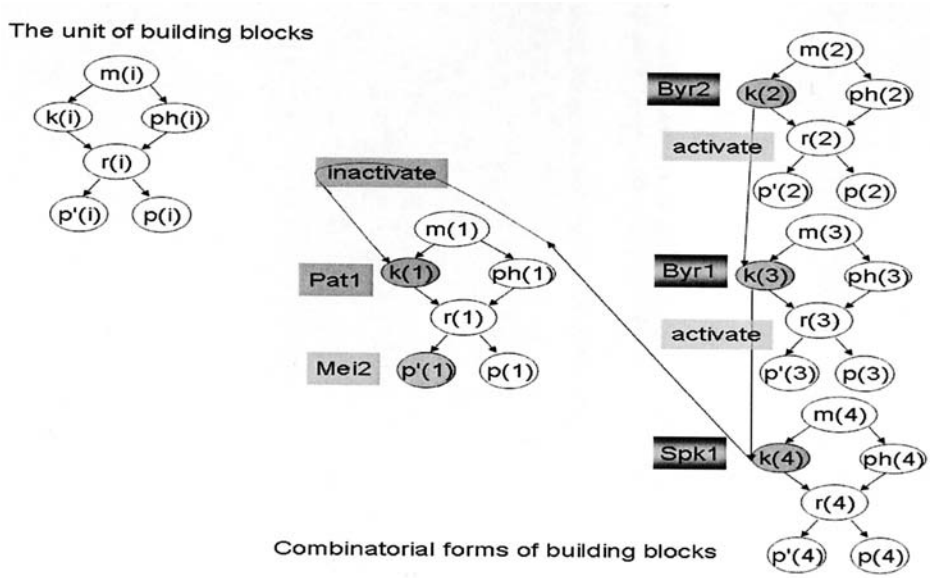

Figure 6 Interaction between the signaling cascade of MAP kinases and the Pat1-Mei2 pathway

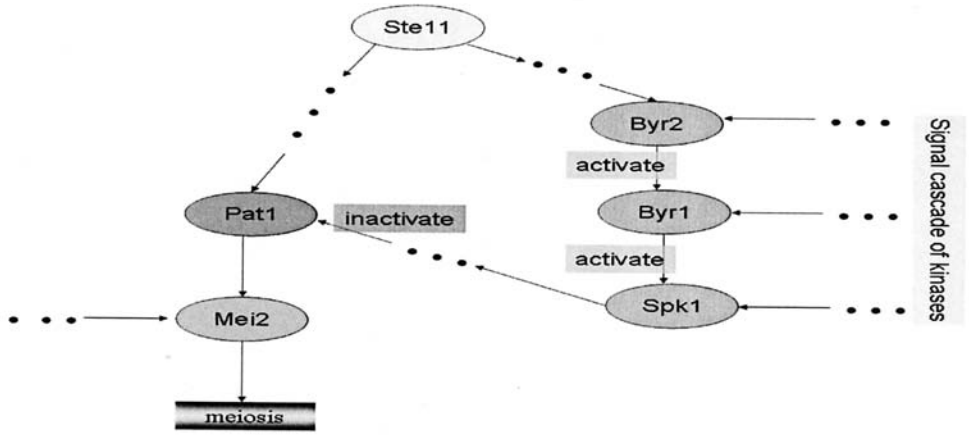

Figure 7 Part of nodes in the pathway network of the fission yeast S. Pombe

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