Ontology Based Petri Net Modeling of Signaling Networks

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1 Introduction

Petri nets become popular for modeling of biological networks, owing to the intuitive and concise graphical representation of biological concepts as well as the quantitatively analytical notation of dynamical behaviors of biological entities. Petri nets are of great advantage to applying the conceptual representation in the nets to simulation studies, so that it is promising to integrate simulation analysis with knowledge representation on the basis Petri net modeling. Our final goal is about modeling of the entire cellular networks, which requires the Petri net models to be reused, shared, and scaled up. However some inconsistency appears in existing Petri net models of catalytic reactions in molecular complexes. Therefore the Petri net models should be standardized, which makes us free of ambiguity in constructing the models.

While metabolic pathways consist of catalytic reactions uniformly, signaling pathways consist of combinations of catalytic reactions, complex formations, and transportations. The chemical view draws a distinction between the three types of reactions. However, in the context of signaling pathways, every kind of reactions ought to play a common role of the process of signaling. While an entire Petri net is obviously modeled with the intention of representing a certain signaling process, individual reactions are modeled with the intention of the process of chemical reactions. One sees semantic discrepancy between the entire net and the individual reactants. If both these semantics become consistent, then the representation will be uniformed. The individual reactions should be represented on the basis of not only chemical reactions but also the common essence unique to the process of signaling. The essence is in need of ontological explication.

2 Results

We have developed an ontology for signaling pathway, Cell Signaling Networks Ontology (CSNO), which gives an intrinsic definition to the process of signaling. CSNO defines the process of signaling as 'the transmission of *activity* through *molecular recognition*'. The definition enables us to specify Petri net units (Tab. 1), which standardize Petri net representation. Each unit coincides with a unit of the process of signaling. Places are associated with reactants holding *activity* and *molecular recognition*. Transitions are associated with reactions transmitting *activity*. Tokens are associated with the concentration of reactants holding *activity* and *molecular recognition*. The four units in Tab. 1 are disjoint and cover all the reactions in signaling pathways, as is indicated in is-a conceptual hierarchy for signaling reactions in Fig. 1A.

For the purpose of consistent representation of signaling pathways in Petri nets, a new way of denotation of molecules is introduced, which is included in labels attached to places. A label consists of a name of the focused reactant holding *activity* and *molecular recognition*, external states of the reactant, and components of a complex if the reactant belongs to the complex. External states are listed in Fig. 1B. For instance, 'TGFbR1(BP)*[TGFb:TGFbR1:TGFbR2]*' indicates that 'bound and phosphorylated TGFbR1 in a complex composed of TGFb, TGFbR1, and TGFbR2'.

Based on the Petri net units, one does not need to describe all the states of all the components in a Petri net model. A state of a component can be omitted when it is regarded as not to hold *activity* and *molecular recognition* but to serve for keeping the structure and location of the other focused components. Such simplification is upheld by the ontological explication that *activity* and *molecular recognition* accounts for the common essence of the process of signaling. Thus the ontological explication prevents Petri net graphs

Table 1: Petri net units for signaling pathways.

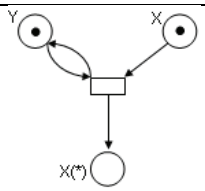
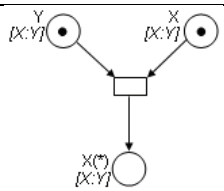
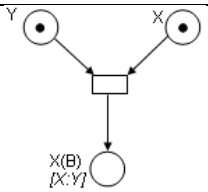
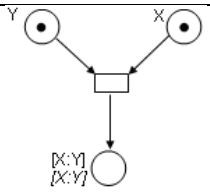
Type of signaling reaction	**Productive reaction**	**Regulatory reaction**
Subtype of signaling reaction	(Any)	Catalytic reaction in complex
Petri net unit		
Type of signaling reaction	**Regulatory reaction**	**Regulatory reaction**
Subtype of signaling reaction	Complex formation for allosteric effect	Complex formation for transportation
Petri net unit		

Figure 1A

external state	symbol
bound	B
separated	S
phosphorylated	P
dephosphorylated	D
ubiquitinated	U
cleaved	C
GTP-bound	Gt
GDP-bound	Gd

Figure 1B

from being too complicated and unmanageable as well as from being inconsistent.

In the Petri net representations of biological pathways, *tokens* at a *place* account for the concentration of molecules in a certain state that the *place* indicates. Because the Petri net units coincide with units of transmitting *activity*, the tokens account for the concentration of molecules carrying *activity*. It is the remarkable advantage of Petri nets that the progression of activated states is concisely visualized by execution of a token game in the nets.

3 Conclusion and Discussion

Ontology based Petri net units represent a signaling network without ambiguity on the basis of 'transmission of *activity*', whose essential properties have been implicit in existing knowledge representation.

A database integrating simulation analysis with knowledge representation is under construction on the basis of the standardization of Petri net modeling. The database will enable us to retrieve pathways including a target molecule in Petri net models, to simulate the pathways about their dynamical behaviors caused by deterioration of the target molecule in abnormal cells or under pharmaceutical treatments, and to interpret the simulation results with existing biological knowledge contained in the database.

Legends

Table 1: **Productive reaction**: Reactant Y changes a state of reactant X to a certain state X(*) reiteratively, inducing activation or inactivation of the reactant X (*: one of the external states indicated in Fig. 1B). **Complex formation for allosteric effect**: Complex formation between X and Y changes a state of a focused component X to a bound state X(B), inducing activation or inactivation of the component X, with the consequence that a complex *[X:Y]* is formed. **Complex formation of transportation**: Complex formation between X and Y produces a complex [X:Y], which is recognized as a whole in a succeeding transportation reaction. **Catalytic reaction in complex**: Reactant X and reactant Y forms a complex in advance (X*[X:Y]*, Y*[X,Y]*) and reactant Y changes a state of reactant X to a certain state X(*) only once, inducing activation or inactivation of the reactant X (*: one of the external states indicated in Fig. 1B).

Figure 1: **A**, Is-a conceptual hierarchy of signaling reactions. A symbol '+' indicates an is-a relation between an upper concept and a lower concept; **B**, A list of external states of reactants and symbols standing for the external states.

References

[1] Takai-Igarashi, T., Ontology based standardization of Petri net modeling for signaling pathways, *In Silico Biol.*, 5:0047, 2005.

[2] Takai-Igarashi, T. and Mizoguchi, R., Development of an ontology for systems functions of signal transduction. *VIIIth European Conference on Artificial Life*, UK, 2005.

[3] Takai-Igarashi, T. and Mizoguchi, R., An integrative model for representation of signaling pathways on the basis of device ontology. *Transaction of the Japanese Society for Artificial Intelligence*, 20:406-416 (in Japanese), 2005.

[4] Takai-Igarashi, T. and Mizoguchi, R., Ontological integration of data models for cell signaling pathways by defining a factor of causality called 'signal', *Genome Inform.*, 15:255-265, 2004.

[5] Takai-Igarashi, T. and Mizoguchi, R., Cell signaling networks ontology, *In Silico Biol.*, 4:81-87, 2004.