

# Ontological Integration of Data Models for Cell Signaling Pathways by Defining a Factor of Causality Called ‘Signal’

Takako Takai-Igarashi<sup>1</sup>

taka@bi.is.s.u-tokyo.ac.jp

Riichiro Mizoguchi<sup>2</sup>

miz@ei.sanken.osaka-u.ac.jp

<sup>1</sup> Computer Science, Graduate School of Information Science and Technology, University of Tokyo, 7-3-1 Hongou, Bunkyo-ku, Tokyo 113-0033, Japan

<sup>2</sup> The Institute of Scientific and Industrial Research, Osaka University, 8-1 Mihogaoka, Ibaraki, Osaka 567-0047, Japan

## Abstract

Databases have collected masses of information concerning cell signaling pathways that includes information on pathways, molecular interactions as well as molecular complexes. However we have no general data model to represent comprehensive properties of cell signaling pathways, so that this type of information has been represented by two different data models that we call ‘binary relation’ and ‘state transition’. The disagreement between the existing models derives from lack of consensus about a factor of causality in reactions in cell signaling pathways, which is often called ‘signal’. We developed an ontology named CSNO (Cell Signaling Networks Ontology) based on device ontology. As device ontology is a research product of knowledge engineering, CSNO is the first application of it to biological knowledge. CSNO defines the factor of causality called ‘signal’, offers an integrative viewpoint for the two different data models, explicates intrinsic distinctions between signaling and metabolic pathways, and eliminates ambiguity from representation of complex molecules.

**Keywords:** device ontology, cell signaling pathway, database integration, role concept, metabolic pathway

## 1 Introduction

A cell signaling pathway (signaling pathway) represents a series of chemical reactions ending up in achieving cellular functions. Information on signaling pathways is crucial in functional genomics because it gives a clue on how to systematically connect genes or gene products to cellular functions. Databases have accumulated masses of data concerning signaling pathways that include pathways, molecular interactions as well as molecular complexes [1, 2, 7, 9, 11, 13, 15, 16, 20, 22]. The data are collected either from literatures or from large scale high throughput experiments. Speed of data accumulation has been further accelerated because of computerization of the data collecting procedures including information extraction and information retrieval [3, 7, 9, 15].

As all the data collected in databases are descriptions of signaling phenomena at molecular level, we then have to proceed with systematical construction of functional information on the data, so as to reconstruct cellular phenomena in computers. However, the data collected so far have been represented in two different models that we call ‘binary relation’ [1, 11, 13, 16, 20] and ‘state transition’ [2, 5, 22]. Binary relation model regards a signaling pathway as a series of molecular interactions, such as interactions between an enzyme and a substrate, a receptor and a ligand, an ion channel and an ion, and a transcription factor and DNA. The state transition model regards a signaling pathway as a series of state changes of molecules, such as a change of chemical modification states, localization states, and compositions of a molecular complex. Each model represents a different aspect

of signaling pathways. The molecular interaction represents a requirement for starting a reaction. The state transition represents an effect of a reaction on a molecule. However the problem how to integrate them into a general model is yet unsolved. It remains to be elucidated how the two aspects contribute to entire nature of signaling pathways. Such an integrated model will provide us with a unique representation of signaling pathways that enables us to do cross-species comparative analyses of the pathways to find biological essence conserved among species. As represented by [6], precedent comparative analyses of metabolic pathways have already revealed biological features conserved among species, owing to the unique representation of metabolic pathways [23].

The disagreement between the present two data models arises from their simplifying conceptualizations of biochemical phenomena observed in signaling pathways. Both of them lack fundamental concept structures that systematize more abstract characteristics common to the two models. It is a factor of causality in reactions in signaling pathways that we consider such a common abstract characteristic is. The question is what is called ‘signal’. We consider that the existing models fail to define ‘signal’ and in consequence also fail to have a consistent viewpoint for capturing functions that yield a causal sequence of the reactions. Device ontology provides us with a framework to systematize functional concepts at such an abstract level [8]. Device ontology tells us that a function should be defined as an interpretation of ‘B1 behavior’ [8]. B1 behavior is a particular type of behavior that yields outputs from inputs on demand according to a specific context. An output of B1 behavior becomes an input of another B1 behavior in succession. Thus B1 behavior represents an intrinsic property of causality in sequence that finally achieves a purpose at its end. Definition of B1 behavior for signaling pathways will enable us to explicate the causality in signal transduction and to assign an individual molecule a function having a meaning of causing a pathway.

We have developed an ontology for signaling pathways named CSNO (Cell Signaling Networks Ontology) that provides a clear structured framework for systematic, consistent, and shareable description of signaling pathways [19]. CSNO is built on the basis of device ontology and functional concept ontology. Device ontology tells us how to obtain a consistent viewpoint for capturing target functions, while functional concept ontology tells us how to systematically reconstruct the functions based on the viewpoint [8]. This paper reports on accomplished implementation of CSNO based on device ontology, which defines a factor of causality in reactions in signaling pathways, offers a module that integrates two existing different data models, explicates intrinsic distinctions between signaling and metabolic pathways, and eliminates ambiguity from representation of complex molecules. As device ontology is a research product of knowledge engineering, CSNO is the first application of it to biological knowledge.

## 2 Methods

Device ontology has been developed aiming at systematization of functional knowledge for design of artifacts in engineering [8]. Device ontology provides us with a consistent viewpoint that every constituents of target phenomena founds on, so that we can systematically assign functions to the constituents. Device ontology specifies ‘role concept’ of the individual constituent. Role concept is a concept that is defined only in a certain context of the world. In comparison, ‘basic concept’ is a concept that is defined without premising any contexts. An instance of a basic concept can play a role represented by a role concept. A definition of role concept consists of inherited attributes from a basic concept and intrinsic attributes of the role. We take a role concept ‘teacher role’ as an example [10]. ‘Teacher role’ has ‘name’ attribute inherited from a basic concept ‘human’. An intrinsic attribute of ‘teacher role’ is ‘subjects that the teacher teaches’. Any role can be eliminated from the particular individual without causing any change on its being a basic concept that the role depends on. For example, even when Mr. Smith resigns a ‘teacher role’, he is still a ‘human’. Thus definitions of role concepts can specify intrinsic properties of a certain context.

Device ontology specifies a physical phenomenon caused by device (agent), operand, medium, and B1 behavior and function of the device (Figure 1). It decomposes a target phenomenon into actions of devices. Operand is defined as something that is processed by a

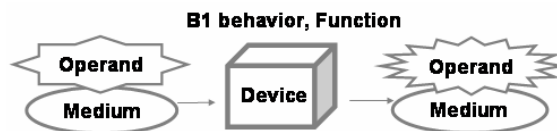


Figure 1: Schematic representation of device ontology.

device. Medium is defined as something that carries an operand. B1 behavior is defined as a change of attribute values of an operand when it is processed by a device. Function of device is defined as teleological interpretation of its B1 behavior. Let us take a heat exchanger as an example [17] whose B1 behavior is ‘to transfer’ heat carried by a warmer stream (medium) to a colder stream (medium). Device ontology specifies the physical phenomenon as ‘to warm’ (function) is an interpretation of B1 behavior of the heat exchanger (device) in a context in which someone focuses on the colder stream and ‘to cool’ in a context in which someone focuses on the warmer stream. Although device ontology has been applied to artifact modeling in engineering, it is powerful enough to provide frameworks for systematization of any physical phenomena in nature. This study shows our successful application of device ontology to knowledge of cellular biology.

Concerning modeling of physical phenomena, there exist two major viewpoints: device-centered and process-centered views [14]. Device ontology specifies the former and process ontology specifies the latter. The major difference between the two is that while device ontology has an agent (device) which plays a main actor role in obtaining an output, process ontology does not have such an agent but has participants which only participate in the phenomena being occurring. It is natural to apply process ontology to model chemical reactions. However we decided to apply device ontology to model the reactions in order to have a viewpoint in which a molecule is not a participant but an agent of a reaction, so that we can specify a function as an interpretation of B1 behavior of a molecule.

We refer to [18] for knowledge of ‘TGF-beta pathway’ and [12] for knowledge of ‘B cell activation pathway’.

## 3 Results

### 3.1 Is-a Hierarchy of CSNO

The skeleton of an ontology is an is-a hierarchy, which consists of is-a relations that represent super-sub (generalized-specialized) relations between concepts. Figure 2 shows is-a hierarchy of CSNO.

### 3.2 Definition of a Factor of Causality in Reactions in Signaling Pathways

#### 3.2.1 Definition of Activity that is Converted by a Molecule

Any biological pathway is a causal sequence of chemical reactions. The causality is an intrinsic property of any pathway either in engineering or in natural science. In signaling pathways biologists assume ‘signal’ to be a factor of the causality. The causality in reactions yields a pathway that ends up in achieving a function. In case of a signaling pathway, a pathway ends up in achieving cellular functions, e.g. cell cycle, gene expression, and cytoskeletal rearrangement.

We firstly investigated a factor of causality in reactions without premising any biological contexts. Physical chemistry tells us of two theories that ‘free energy’ of a reaction determines whether the reaction occurs spontaneously or not and that ‘reaction kinetics’ of reactions determines which reaction is most probable to occur in a certain condition [4]. A pathway in physical chemistry is a sequence of reactions that are most probable to occur in individual conditions changing progressively. Physical chemistry tells that not ‘free energy’ but ‘reaction kinetics’ determines the

Table 1: Definitions of ‘to move’ and ‘to convert’ functions in device ontology.

	Function ‘to move’	Function ‘to convert’
<b>Device</b>	<b>Cellular environment</b>	<b>Reactant</b>
<b>Operand</b>	<b>Cellular-molecule</b>	<b>Activity</b>
<b>Medium</b>	<b>Fluid in cell</b>	<b>Contact Surface</b>

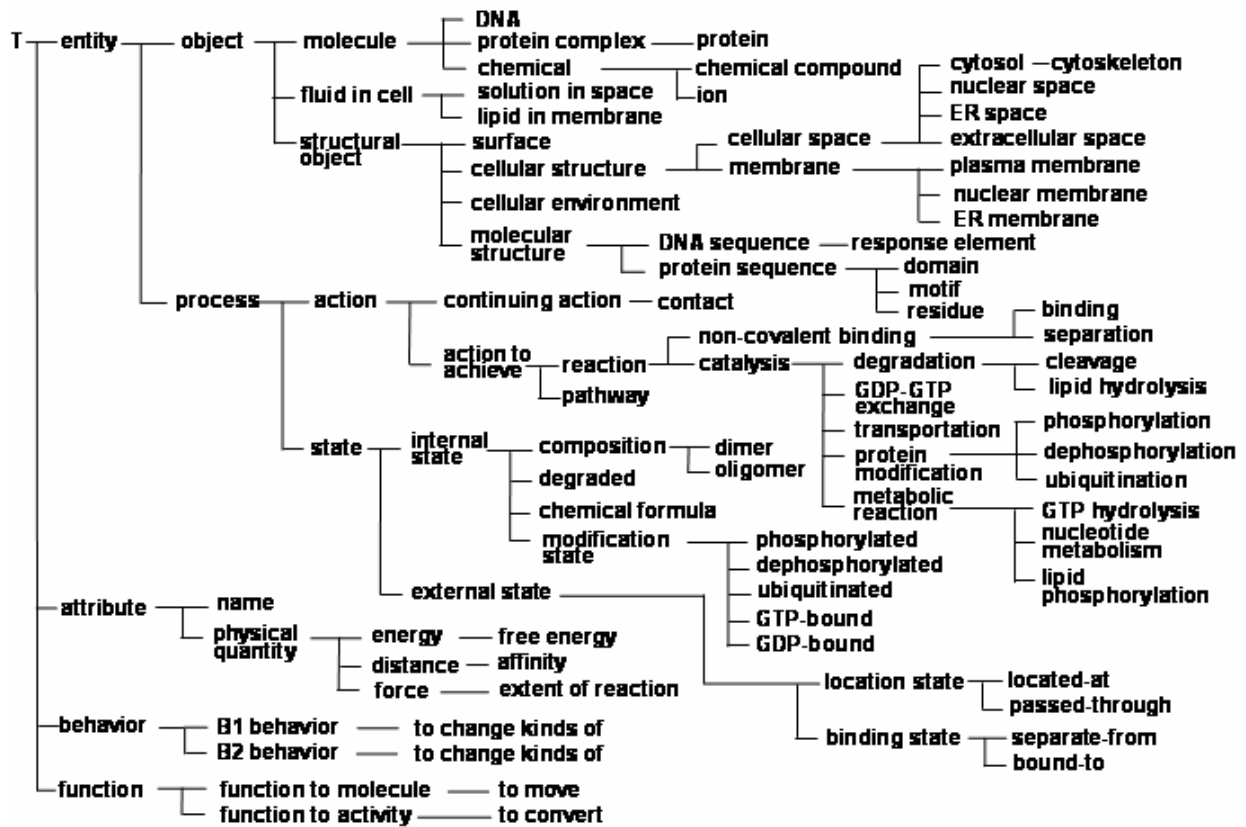


Figure 2: Is-a hierarchy of CSNO.

causal sequence of reactions. ‘Affinity’ is a physical quantity of reaction kinetics that determines the causality attributed to individual molecules when taking a reaction. Thus ‘affinity’ is a concept that represents ‘a factor of causality in reactions in pathways’ in physical chemistry. ‘Affinity’ is obtained by differentiating ‘free energy’ with respect to ‘extent of reaction’ that is a kind of ‘distance’ in physical quantity of reaction kinetics. Because differentiation of ‘energy’ with respect to ‘distance’ yields ‘force’, ‘affinity’ is a kind of ‘force’.

Then we investigated interpretation of ‘affinity’ in a context of signaling pathways. We found ‘activity’ is an interpretation of ‘affinity’ in a context that focuses on inductions of succeeding reactions or cellular functions. Thus ‘activity’ is a ‘force’ not only between molecules but also between a molecule and a reaction or a function, while ‘affinity’ is a ‘force’ only between molecules. Device ontology tells us that ‘activity’ is a role concept whose basic concept is ‘affinity’. Table 1 shows a definition of ‘activity’ based on device ontology. We define ‘reactant’ as device and ‘activity’ as operand of the device. ‘Reactant’ is also a role concept that is an interpretation of basic concept ‘molecule’ in a context of ‘being a participant in a reaction’, which we will give a detailed explanation in section 3.3. We define ‘contact surface’ between reactants as medium, according to a precedent study by Kitamura and Mizoguchi [8]. The study found that contact surface of device can be medium when ‘force’ is operand. Because a ‘force’ is transmitted by no other than a contact surface between devices, the contact surface is regarded as a medium which carries the ‘force’. ‘Activity’ is processed by device so as to be changed like that ‘bind activity is changed into phosphorylate activity’, which is observed in allosteric activation of a phosphorylating enzyme. Such an action ‘to change kinds of activity’ is occurred in every reactant yielding a pathway, so that we define ‘to change kinds of’ as B1 behavior (Figure 2). At last we define ‘to convert’ as function of ‘reactant’ whose behavior is ‘to change kinds of activity’. This is the function to be assigned to individual molecules that cause a sequence ends up in achieving a cellular function.

According to [10], ‘activity’ is a ‘part-role concept’ that is defined dependent on a part-whole relation. ‘Activity’ is defined as a part-role of ‘reactant’ and ‘reactant’ is defined as a part-role of

‘reaction’. Is-a hierarchy of part-role concepts can be defined only in is-a hierarchy of whole concepts that part-role concepts are parts of. In case of definition of ‘activity’, we firstly defined is-a hierarchy of the whole concept of ‘reaction’, secondary defined ‘reactant’ in the definition of ‘reaction’, and lastly defined ‘activity’ in the definition of ‘reactant’ (Figure 3). The conceptual hierarchy in Figure 3 shows that ‘activity’ is specialized into ‘bind activity’, ‘transport activity’, ‘phosphorylate activity’, ‘be-phosphorylated activity’, and so on.

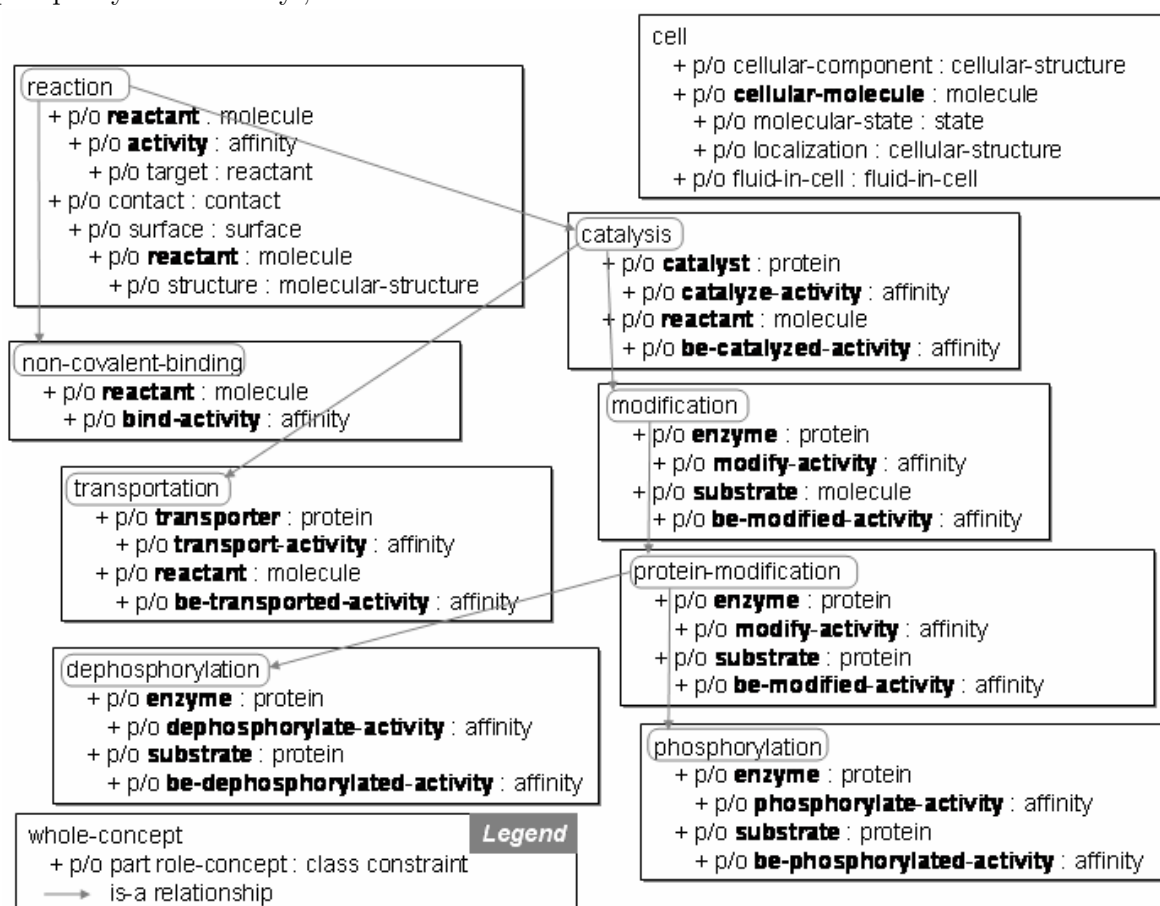


Figure 3: Is-a hierarchy of ‘activity’ (portion) defined in is-a hierarchy of the whole concept of ‘reaction’ that ‘activity’ is a part-role of. This figure also shows a part-whole relation between ‘cellular-molecule’ (part-role concept) and ‘cell’ (whole concept). Role concepts of interest are in bold.

### 3.2.2 Definition of Movement of a Molecule Carrying Activity

Although ‘activity’ is a factor of causality in reactions, it fails to explain localization changes of the reactions in a cell. Localizations of reactions are progressively changed from plasma membrane to mostly nucleus or to other organelles. A signaling pathway is then considered as an orthogonal combination of a sequence of ‘to convert’ functions to ‘activity’ and a sequence of localization changes. Purpose of the former sequence is to finally achieve a certain cellular function. Purpose of the latter sequence is to bring the final reaction to a certain place in a cell where the target cellular function should occur. While the former sequence is considered as a main stream that is essential in finally achieving the target function, the latter sequence is considered as an auxiliary stream that assists the main stream to be in succession. The assistance of the auxiliary stream is indispensable because cells are compartmentalized into functional areas by organelles where only certain reactions can occur.

Based on device ontology we define the localization change as B1 behavior and ‘cellular-molecule’ as operand of the behavior (Table 1). ‘Cellular-molecule’ is a role concept that is an interpretation of a basic concept ‘molecule’ in a context of ‘being a constituent of a cell’, which we will give a detailed explanation in section 3.3. ‘Cellular environment’ and ‘fluid in cell’ are defined as device and medium,

respectively. Then we define ‘to move’ as function whose behavior is ‘to change (kinds of) localization of cellular-molecule’.

The two functions ‘to convert’ and ‘to move’ are orthogonal because each function has distinct agent (device) and operand. Thus we finally define that ‘a factor of causality in reactions in signaling pathways’ is **activity and cellular-molecule carrying the activity**.

We define that an active transportation across a membrane is not ‘to move’ but ‘to convert’ function, although the transportation contributes to a localization change. As device of ‘to move’ function is ‘cellular environment’, the function allows only processes of diffusion within a certain organelle. However the active transportation is a process that a device called ‘channel’ or ‘transporter’ lets a ‘cellular-molecule’ traverse between organelles. ‘Transport activity’ is a subsumption of ‘catalyze activity’ in CSNO (Figure 3).

### 3.3 A Consistent Viewpoint for Capturing a Complex Molecule

In contrast to metabolic pathways composed of only catalytic reactions, signaling pathways include non-covalent bindings as well as catalytic reactions. Because of that, complex molecules often participate in signaling pathways. It has been controversial among biologists whether a whole complex molecule or a component of the complex should be regarded as an agent. Either binary relation or state transition model has not answered this question.

CSNO answers the question as follows. CSNO explains that a molecule has two roles: operand of ‘to move’ function and device of ‘to convert’ function. In case that operand of ‘to move’ function is a complex molecule, the complex molecule as a whole is regarded as the operand, since all the components of the complex molecule actually move at a time (Figure 4). This view focuses on existence of a molecule as a constituent of a cell. We then define a complex molecule in this context as a ‘cellular-molecule’ that is a role concept whose basic concept is ‘molecule’. ‘Cellular-molecule’ has the attribute of ‘localization’ intrinsic to the role and the attribute of ‘molecular state’ inherited from the basic concept (Figure 3).

On the other hand, in case that device of ‘to convert’ function is a complex molecule, a component of the complex is regarded as the device, since the component actually makes a ‘contact surface’ and converts an ‘activity’ (Figure 4). This view focuses on participation of a molecule in a reaction. We then define a component of a complex in this context as a ‘reactant’ that is another role concept whose basic concept is ‘molecule’. ‘Reactant’ has the attribute of ‘activity’ intrinsic to the role and the attribute of ‘structure’, such as domain and motif structures, inherited from the basic concept (Figure 3).

In contrast to a complex molecule, a single molecule plays both roles of ‘cellular-molecule’ and ‘reactant’ as intact (Figure 4). Thus CSNO provides us with a consistent representation of roles in signaling pathways played by both complex molecules and single molecules so as to eliminate ambiguity from representation of them. CSNO also explains us that a complex molecule can include several reactants in it. Such a complex can accumulate several reactions in it so as to diverge or integrate signaling effects at a certain point in a pathway.

### 3.4 Definition of a Module that Integrates Existing Data Models

Since ‘to move’ and ‘to convert’ are intrinsic functions common to all the reactions of signaling pathways, an orthogonal combination of the functions can determine a module common to all the reactions.

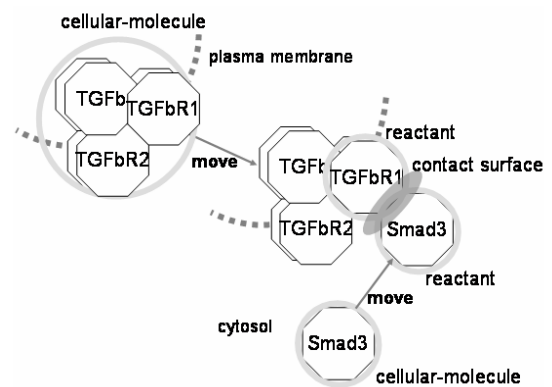


Figure 4: Schematic representation of ‘cellular molecule’ and ‘reactant’ roles played by a complex molecule (TGFb dimer, TGFbR1 dimer, and TGFbR2 dimer) and a single molecule (Smad3). This figure represents the same reaction described in Figure 6. Please refer to Figure 6 for abbreviations.

We name the module ‘CSNO-module’, which is a standardized and independent unit used in construction of pathways. Schematically CSNO-module represents a process in which two cellular-molecules move and meet at a certain place in a cell, a contact surface is made, and an ‘activity’ is converted by an individual reactant (Figure 5A). CSNO-module is defined as a simple combination of definitions of ‘to move’ and ‘to convert’ functions in device ontology (Figure 5B).

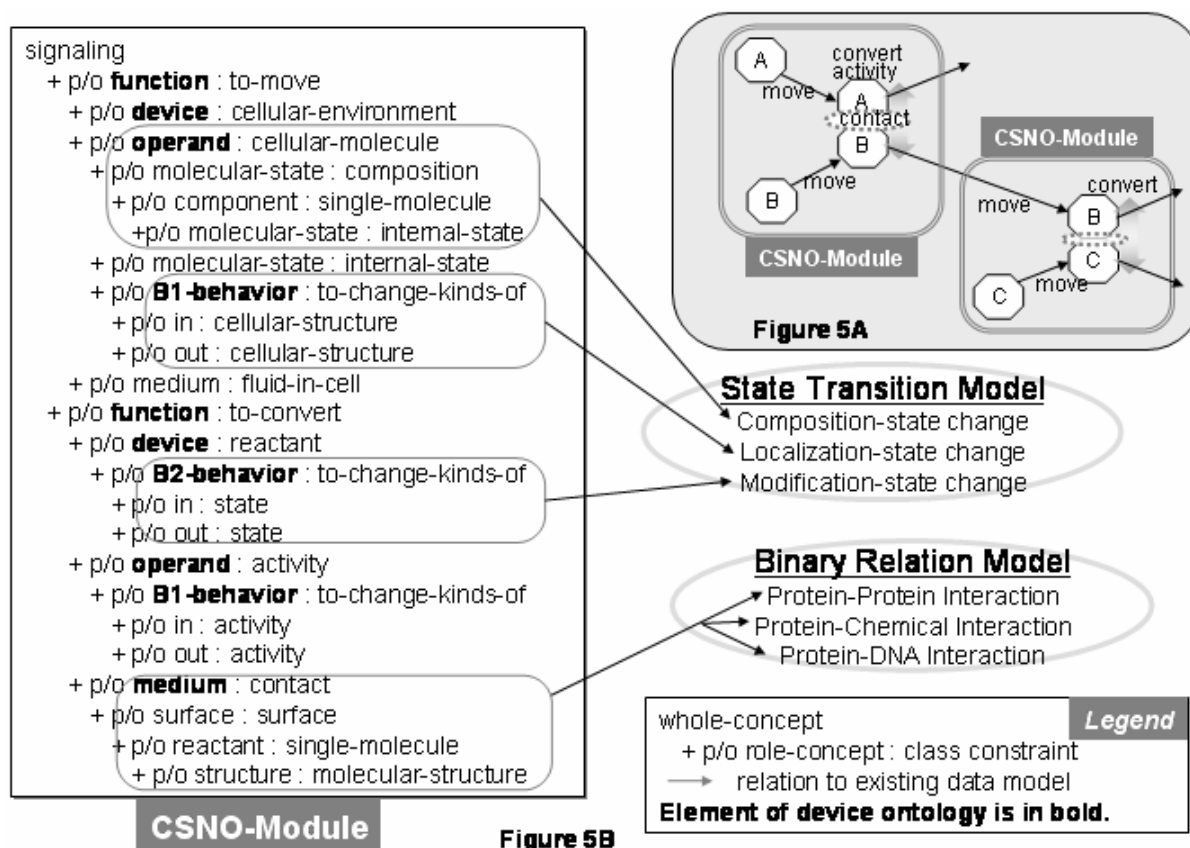


Figure 5: CSNO-module. Schematic explanation of CSNO-module (Figure 5A). Definition of CSNO-module and relations between its constituents and exiting data models (Figure 5B).

CSNO-module integrates two existing data models; binary relation and state transition, and provides a unique representation of signaling pathways (Figure 5B). Operand of ‘to move’ function represents information equivalent to what state transition model represents as ‘composition-state change’. B1 behavior of ‘to move’ function represents information equivalent to what state transition model represents as ‘localization-state change’. Medium of ‘to convert’ function represents information equivalent to what binary relation model represents as ‘molecular interaction’ that contains protein-protein, protein-chemical, and protein-DNA interactions. B2 behavior (explanation is given in the next paragraph) of ‘to convert’ function represents information equivalent to what state transition model represents as ‘modification-state change’. Thus CSNO-module represents comprehensive aspects of signaling pathways including not only aspects that have been modeled so far but also a new aspect introduced in this study which is an intrinsic factor of causality yielding a pathway to achieve a function.

CSNO-module includes B2 behavior which is usually disregarded in definitions of device ontology. B2 behavior represents an internal change of device, but it is not a factor related to causality because it does not yield any output [8]. In a context of signaling pathways, B2 behavior of reactant (device) is defined as ‘state’ including ‘modification state’ and ‘binding state’ (Figure 2). In signaling pathways instances of B2 behavior is frequently observed and described in biological literatures.

### 3.5 Instances of CSNO-Module

We take ‘TGF-beta pathway’ and ‘B cell activation’ as examples to show instances of CSNO-module. Figure 6 shows an instance that represents complex formation between TGF-beta receptor 1 (TGFbR1) and Smad3 occurred in ‘TGF-beta pathway’. Operand of ‘to move’ function indicates that TGFbR1 constitutes a complex with TGF-beta (TGFb) and TGF-beta receptor 2 (TGFbR2). B1 behavior of ‘to move’ function indicates that the complex is located at plasma membrane. B1 behavior of ‘to convert’ function indicates that Smad3 causes a new ‘activity’ to ‘be-phosphorylated’ against TGFbR1. Medium of ‘to convert’ function indicates domain and motif structures at a contact surface between TGFbR1 and Smad3. B2 behavior of ‘to convert’ function indicates that state of TGFbR1 changes into ‘bound-to state’ targeting Smad3 as well as that state of Smad3 changes into ‘bound-to state’ targeting TGFbR1, which represents construction of a complex at the contact surface between TGFbR1 and Smad3.

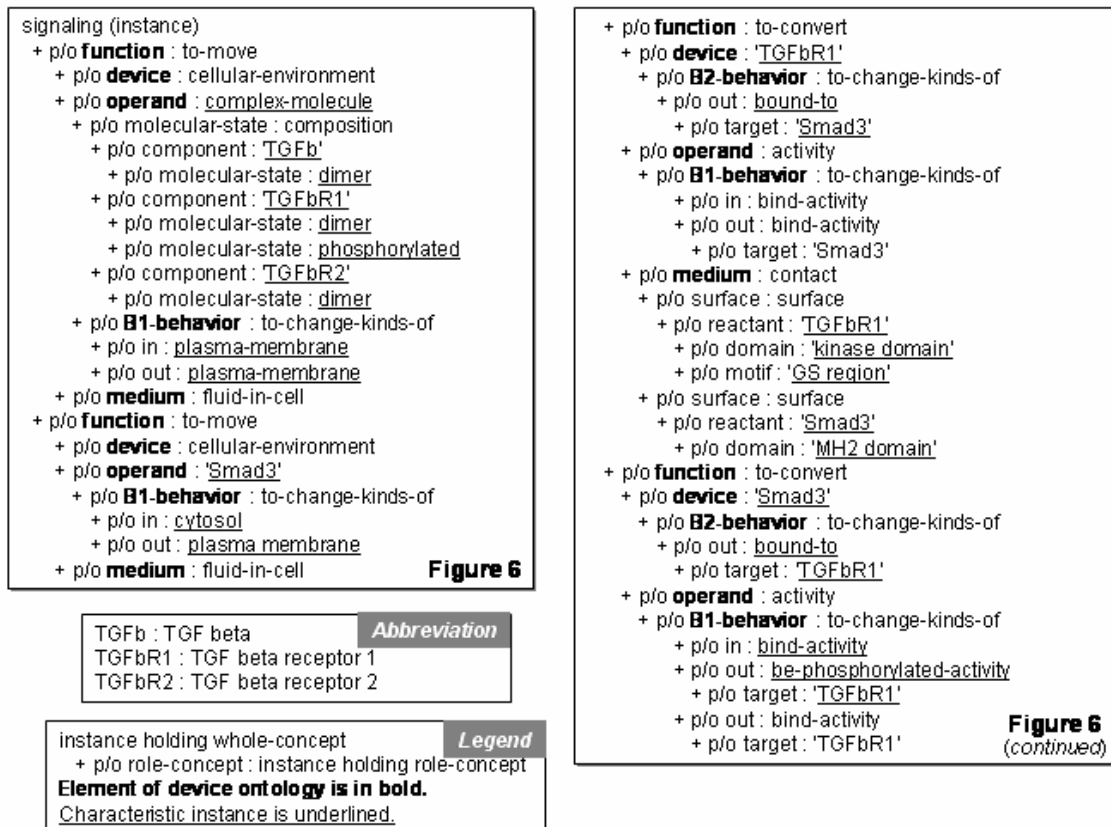


Figure 6: An instance of CSNO-module that represents a complex formation between TGF-beta receptor 1 and Smad3.

Figure 7A shows an instance that represents a metabolic reaction in the signaling pathway of ‘B cell activation’. Even if it is a metabolic reaction, it is regarded as having ‘to convert’ function when it occurs in signaling pathways. As figure 7A shows, the reaction not only produces IP3 but also causes ‘activity’ to bind to a protein having ‘IP3 binding’ motif. Change of chemical formula from PIP(4,5)P2 to IP3 is indicated as B2 behavior of the device of ‘phospholipid’.

A complete set of instances for ‘TGF-beta pathway’ and ‘B cell activation’ is not shown in this article but available from <http://athos.is.s.u-tokyo.ac.jp/CSNO/>.

### 3.6 Intrinsic Distinctions between Signaling and Metabolic Pathways

When we represent metabolic pathways in device ontology, we find that metabolic pathways consist of sequences of ‘to convert’ functions without any interventions of ‘to move’ functions. Table 2 shows a definition of ‘to convert’ function in metabolic pathways based on device ontology. We define ‘enzyme’

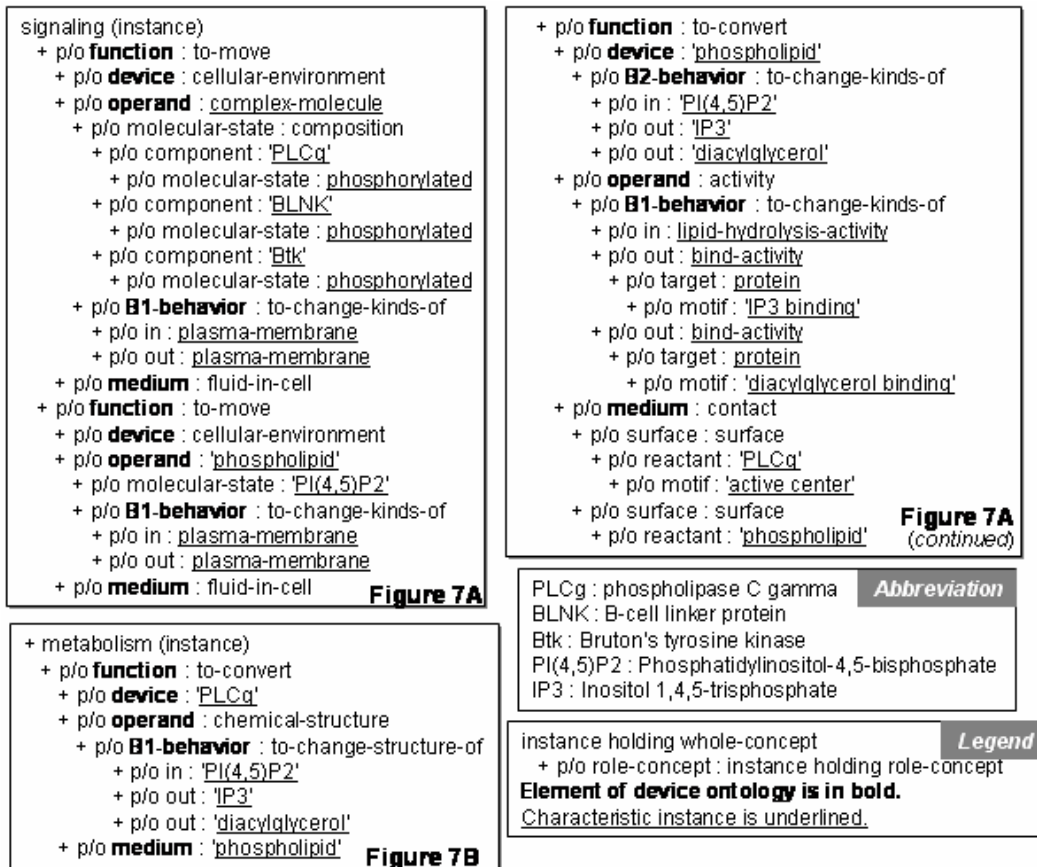


Figure 7: Instances of CSNO-module that represent production of IP3 from PI(4,5)P2 occurred in a signaling pathway (Figure 7A) as well as occurred in a metabolic pathway (Figure 7B).

as device. ‘Enzyme’ is a role concept that is an interpretation of a basic concept ‘molecule’ in a context of ‘metabolism’. ‘Chemical structure’ and ‘chemical compound’ are defined as operand and medium, respectively.

An intrinsic distinction between signaling and metabolic pathways is in their definitions of operand. In a signaling pathway, ‘activity’ and ‘cellular-molecule’ carrying the ‘activity’ are operands, which enable both progressive activations of reactions and progressive localization changes of the reactions. In a metabolic pathway, in contrast, chemical structure is operand, which enables progressive changes of chemical structures of chemical compounds. The difference depends on biological functions that the individual pathways finally achieve. A signaling pathway ends up in achieving a cellular function required in a cell. A metabolic pathway ends up in producing a chemical compound required in a cell. We also point out that a signaling pathway may also control a metabolic pathway as another end point.

The same metabolic reactions producing IP3 from PIP(4,5)P2 occur both in signaling and metabolic pathways. When it occurs in a metabolic pathway, e.g. a pathway for production of IP6P [23], a change of chemical structure from PIP(4,5)P2 to IP3 is an intrinsic property (B1 behavior) of the reaction (Figure 7B). When it occurs in a signaling pathway, obtaining ‘bind activity’ by phospholipid is an intrinsic property (B1 behavior) of the reaction (Figure 7A).

Table 2: Definitions of ‘to convert’ functions in cell signaling and metabolic pathways in device ontology.

	Cell signaling pathway	Metabolic pathway
<b>Device</b>	Reactant	Enzyme
<b>Operand</b>	Activity	Chemical Structure
<b>Medium</b>	Contact Surface	Chemical Compound

## 4 Conclusions and Discussion

Device ontology provides us with a viewpoint that a physical process is an action of an agent (device). Based on device ontology we define a signaling pathway as an orthogonal combination of a sequence

of ‘to move’ functions and a sequence of ‘to convert’ functions. ‘To move’ function is an action of ‘cellular environment’ that moves a molecule playing the role of ‘cellular-molecule’ in a cell. ‘To convert’ function is an action of a molecule playing the role of ‘reactant’ that converts ‘activity’ that is a factor of causality in reactions. In comparison, we define a metabolic pathway as a sequence which consists of only ‘to convert’ functions that convert chemical structures. The intrinsic difference between the two pathways depends on biological functions that the individual pathways finally achieve. A signaling pathway ends up in achieving cellular functions required in a cell. A metabolic pathway ends up in producing chemical compounds required in a cell. All the definitions described in this article comprise CSNO. CSNO also provides us with a consistent viewpoint for capturing complex molecules so as to eliminate ambiguity from representation of them.

Gene Ontology (GO) is an ontology to provide a controlled and structured vocabulary to describe functions associated with gene products [21]. GO is now indispensable for functional analyses of OMICS data. GO actually contains many concepts concerning signaling phenomena, e.g. ‘protein amino acid phosphorylation’ (GO:0006468) and ‘protein binding’ (GO:0005515). Although both of the concepts play main roles in signaling pathways, GO defines each of them in a different ontology with neither relations between them nor explications of their individual roles in signaling pathways. ‘Protein amino acid phosphorylation’ is defined in *Biological Process Ontology* under ‘metabolism’. ‘Protein binding’ is defined in *Molecular Function Ontology* under ‘binding’. Basically GO consists of certain relations that represent only certain aspects of biological phenomena, thus other ontologies are needed to supply missing relations between concepts in GO on the basis of missing viewpoints. CSNO can supply one kind of such missing relations on the basis of a viewpoint of signaling phenomena. CSNO and GO are different in computational semantics. CSNO is built explicitly based on a consistent model that is device ontology, while models GO is based on are implicit.

We define a module for signaling pathways based on CSNO. CSNO-module indicates how to integrate two existing data models; binary relation and state transition, and provides a unique representation of signaling pathways. We offer CSNO-module to biological community as a general model to describe signaling pathways. To facilitate that, we started to open an extensive collection of representative instances of CSNO-module to the public (<http://athos.is.s.u-tokyo.ac.jp/CSNO/module/>).

This study offers a comprehensive model to describe functions in signaling pathways at basal level. Next we have to proceed with systematization of other functional information based on CSNO, so that we can finally reconstruct cellular phenomena in computers. Functional decomposition based on device ontology sheds light on such a systematization of functions, as our previous study has shown [19].

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