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Managing models of signaling networks

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Abstract

Signaling pathways participate in complex information processing networks. These networks handle housekeeping functions of the cell as well as specialized functions such as synaptic plasticity. I report two developments in managing such networks: a compilation of mass-action kinetic models of signaling pathways, and shared motifs in the chemistry of interactions between signaling pathways. These motifs may prove useful in abstracting signaling networks, without compromising chemical reaction details. The combination of a library of signaling pathway models, and high-level rules to connect these pathways, may simplify development of complex signaling network models.

Keywords: Mass-action chemistry; Signaling pathways; Simulation; Database

1. Introduction

Cellular signaling chemistry involves a set of networks that rival neuronal networks in complexity. These networks participate in nearly all cellular functions, from metabolism to structure to development and differentiation, but information handling is clearly one of their key attributes [5]. Some of the best studied signaling networks are those involved in synaptic plasticity [4]. Model construction is a valuable way of understanding the functioning and emergent properties of signaling networks [3]. Data management issues become severe in large networks of this kind, which can involve hundreds of molecular species and reactions. I address two related aspects of data management: a library of models, and an abstraction of connectivity between signaling pathways that facilitates modularity.

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A first-order description of such networks using mass-action chemical kinetics is mathematically simple. Most such models are based on simple chemical rate equations such as

$$A + B \underset{k_b}{\overset{k_f}{\rightleftharpoons}} C.$$

This can be described using stereotyped systems of first-order differential equations of the form

$$d[A]/dt = k_b[C] - k_f[A][B].$$

This uniformity of representation makes it easier to devise a repository of biochemical signaling models than, for example, neuronal models. Only a limited number of parameter types need to be stored. Typical models are completely specified by a reaction scheme, the initial concentrations of molecules, rate constants, and Michaelis–Menten parameters for enzymes in the model. Although the numerical methods are very different, the same representation is also applicable to point stochastic models, where the rate constants are interpreted as reaction probabilities. Spatial and cytoskeletal factors in signaling are increasingly recognized [1,7], but even these much more complex models require the basic reaction definitions as a common denominator.

In contrast to this mathematical simplicity, signaling networks are very complex in the number of components [8]. This makes it essential to use abstracted representations of signaling pathways for humans to be able to manage models and understand their function. Block diagrams are a common form of abstraction, where signaling pathways are represented as blocks connected by arrows to form a network. Although individual signaling pathways appear to be natural candidates for encapsulating into modules consisting of sets of reactions, the interactions between pathways still require specification at the level of individual reactions. A formulation of signaling pathways and the chemistry of their interactions in an object-oriented manner would be a valuable step towards handling complex chemical circuits at the block-diagram level.

This paper discusses management of complex signaling networks such as those found at the synapse. First, a library of signaling models has been compiled into a database to provide a ready source for building blocks for such networks. Second, I describe a shared motif in the chemistry of signaling interactions that emerges from an analysis of many examples in this library [2]. Together these developments may facilitate modeling of signaling phenomena using the library of pathway modules, and interconnecting these at a block-diagram level using rules about the chemical motifs to fill in the chemical details.

2. Results

2.1. Library and database of models

A library of models of signaling pathways was developed as part of a network model of synaptic signaling pathways [3]. This library has since been extended and is now

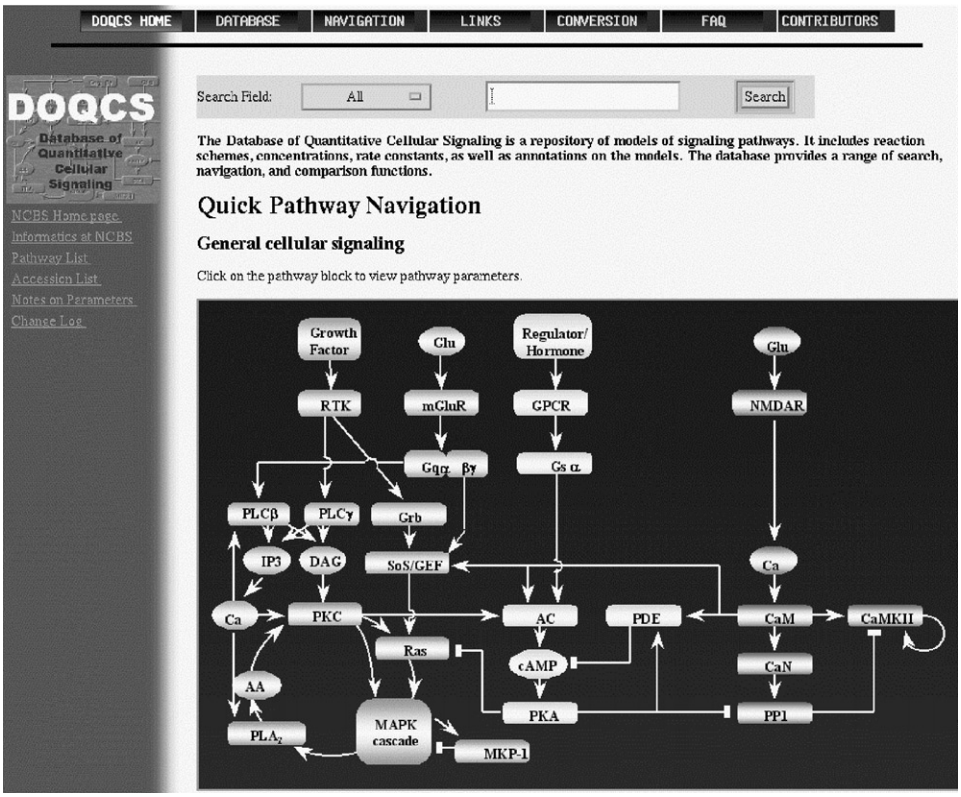

Fig. 1. Home page of DOQCS database.

on-line as the Database of Quantitative Cellular Signaling [6] (DOQCS, http://doqcs.ncbs.res.in; Fig. 1). A major goal of the database is to act as a repository of signaling models. The models in the database are heavily annotated, with the objective of encouraging reuse of models and their evolution towards greater biological accuracy and tissue specificity. All models in the database have been implemented using the simulator Kinetikit/GENESIS. Models in Kinetikit and the library consist of three chemical entities: molecules, reactions and enzymes. Molecules are characterized by an initial concentration and a flag to indicate whether they are buffered, that is, held fixed during the simulation. Reactions are characterized by a list of substrates and products, and forward and backward rate constants. Enzymes are characterized in terms of the protein molecule that exhibits the enzyme activity, a list of substrates and products, and the Michaelis–Menten constants. These chemical entities are grouped into pathways. Based on a literature search, the database now contains a significant fraction (approximately 25%) of the published models of signaling pathways.

2.2. The chemical architecture of signaling interactions

A recurring theme in developing network models of multiple signaling pathways is the difficulty in setting up interactions between signaling pathways. Examples of such interactions include the binding of an activated G-protein alpha subunit to an effector such as adenylyl cyclase, or the phosphorylation of a downstream substrate by a kinase. One the one hand, it is desirable to encapsulate all reactions in a given pathway. On the other, these chemical interactions by definition involve reactions from two or more pathways. The traditional way of setting up interactions between upstream and downstream signaling pathways is to explicitly define the reactions between constituents of the interacting pathways. The availability of complex signaling network models in the dataset has made it possible to analyze a large number of such interactions between signaling pathways [2]. This analysis suggested the following chemical motif common to all interactions analyzed: All signaling interactions consist of one or more communicating molecules from one pathway, and a replicating set of reactions and molecules from another pathway. Replicating reactions are a set of reactions at the intersection of the two pathways, which have to be repeated for every unique combination of interacting pathways. This principle is illustrated in Fig. 2.

2.3. Modularity of signaling pathways

Given the above result for signaling interactions, it becomes possible to encapsulate all signaling pathways in an object-oriented manner. The chemistry for each signaling pathway is completely internal to the pathway object. Interactions between pathways can now be set up using a well-defined interface based on the above chemical motif for interactions. One side of the interaction consists of one or more communicating molecules, and the other side consists of a reaction scheme designed to be replicated for each combination of pathways. The only additional data needed to set up any specific interaction are the parameters for the replicated reaction scheme. It is no longer necessary for one pathway to know about the internal design of any other in order to communicate. For example, it is possible for the reaction scheme of one of the pathways to be completely redesigned. Provided the interaction interface remains consistent, the second pathway can be connected to the redesigned pathway in the same manner as it was to the original.

3. Conclusion

This paper discusses two aspects of data management for complex signaling network models: the compilation of a database of such models, and an abstraction of the chemical architecture of signaling that facilitates modularity in signaling pathways and their interactions. The first aspect provides a library of models, and the second a way of easily connecting them. Together these are intended to make it possible to build network models of signaling pathways at the level of pathway modules rather than individual reactions. This may be valuable for sharing and reusing models, and

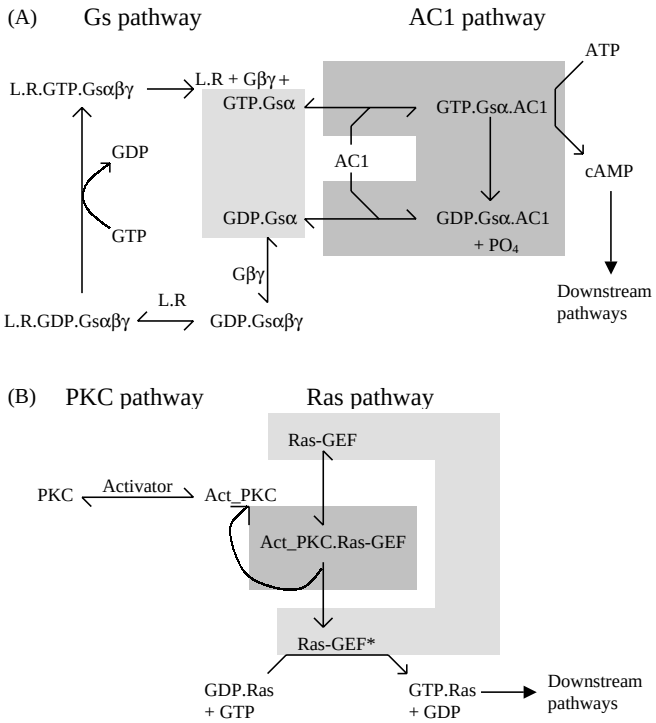

Fig. 2. Interactions between pathways expressed in terms of replicating reactions. In both examples the communicating molecules are shaded in light gray, and the replicating reactions are shaded in dark gray. (A) The molecules GTP.Gsα and GDP.Gsα (shaded in light gray) are communicating molecules from the Gs pathway. The reactions shaded in dark gray are the replicating reactions involving molecules from both the Gs and AC1 pathways. If Gs were to interact with AC2, then the same two molecules from the Gs pathway would be involved. If AC1 were to interact with a different G protein, the replicating reaction scheme would be duplicated but with different rate constants. (B) Activated PKC catalyzes the phosphorylation of Ras-GEF. The kinase catalytic reaction steps in dark gray are replicating reactions because the equivalent set of reactions would be involved for another substrate. The communicating molecules in this case are Ras-GEF and its phosphorylated state. Abbreviations: L—ligand, R—receptor, Gs—G-protein type s, GTP—guanosine triphosphate, GDP—guanosine diphosphate, ATP—adenosine triphosphate, AC—adenylyl cyclase, cAMP—cyclic adenosine monophosphate, GEF—guanine exchange factor, Act_PKC–activated protein kinase C.

focusing on the emergent computational properties of signaling networks rather than on the chemical details.

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