Research Article

Quantitative study on cellular signaling database: management and analysis of signaling network

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ABSTRACT

The amount of information required to determine how cells interact is enormous. Block diagrams are often used to depict the complicated signaling networks that result. This is a critical step in the development of quantitative knowledge of signaling. One of the advantages of studying pathways is that it provides abundant quantitative data. Signal pathways models may be found in the Database for Quantitative Cellular Signaling. As well as serving the expanding area of chemical reaction-level signaling network modeling, it aims to foresee problems with large-scale data management in signal chemistry. The present DOQCS research uses graphical techniques and simulation in a cellular spatial framework to further this convergence. This work links database-specified route models.

Keywords: Cellular signaling, Database, Signaling pathways, Quantitative analysis

INTRODUCTION

Systems of differential equations are used to study the behavior of biological processes in many models (Schoeberl *et al.* 2002; Kholodenko *et al.* 1999). Choosing this option seems logical. Dynamic systems theory provides various mathematical tools for analyzing these networks. A well-understood ontology of behaviors, including steady states, oscillations, and chaos, together with associated linear stability features, is provided at least within the limit of long timeframes (Kholodenko, 2000). Completing a strong workbench that has successfully handled most of the physics and chemical kinetics is the availability of numerical algorithms for solving complex problems. The molecular signaling workbench, however, is exhibiting evident symptoms of breaking under the weighty combinatorial complexity of proteins that interact through various post-translational modifications and physical interactions within a complicated topology of locations (Pawson and Nash, 2003).

Cellular signaling networks are the cell's computational and control systems. Chemical signals are transduced onto cells' surfaces and propagated by a series of biochemical reactions involving proteins and second messengers. This is the classic understanding of signaling (Stryer, 2001). Genes, cytoskeletal structures, and cell trafficking are all part of the cellular signaling network. In-plant signaling, for example, logical representations have been used to conduct qualitative investigations of such networks (Genoud *et al.* 2001). It's a good idea to do this research when it's unclear how something is connected in specific ways. The cellular function may be better understood using mathematical and modeling techniques (Tyson *et al.* 2001)). Analysis of cell signaling at the molecular level has recently been conducted by many researchers, including Bhalla and Iyengar (1999) and Kuroda and colleagues (2001) (Bhalla and Iyengar, 1999; Kuroda, 2001). Three-dimensional, stochastic, and cellular mechanical functions are some of the

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other topics covered in research (Shimizu *et al.* 2000). Test-tube biochemistry is a poor match to biological settings, yet they are now our greatest data sources. Using new experimental approaches, it is expected that more physiologically specific descriptions will become more achievable in the future (Teruel and Meyer, 2001; Voytik-Harbin *et al.* 2001). The unifying denominator in all of these quantitative explanations is mass-action chemistry. Such data necessitates the development of data management and analysis technologies.

This method has resulted in several new projects. Databases, simulators, and model description languages are the three major categories into which they fall. Despite its database structure, the DOQCS research is heavily influenced by simulations of biological signaling (Bhalla and Iyengar, 1999). Many models have been developed due to these investigations, many of which include very specific and precise response schemes and parameters. For example, Models like this may benefit from the quantitative functional analysis of data provided by DOQCS. As the dataset grew and use patterns became evident, another objective of the DOQCS project was to discover and meet specific database needs that differed from those of other databases.

METHOD

Annotations, data sources, and parameter derivations accompany the chemical-reaction level models of signaling pathways in DOQCS. Other than those built for DOQCS, all of these models rely on previously published research. The Kinetikit/GENESIS simulator tests each model before entering it into the database. To guarantee that all models are complete, this first filter verifies that all parameters are specified. An SQL command dump capability is included in Kinetikit, which turns database data into SQL instructions acceptable for uploading to a database.

Design and implementation

Data model

Calculating the temporal evolution of chemical processes may be done by translating chemical equations into the general form and using basic numerical integration techniques (Bhalla, 1998).

$$A + B \underset{k_b}{\overset{k_f}{\longleftrightarrow}} C + D$$

to systems of differential equations of the form;

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

There are several approaches to specify chemical kinetic models. As a result of mass conservation rules, many models are expressed as compact differential equation systems. Equilibrium interactions between molecules are often assumed to eliminate the need to solve numerous differential equations. Certain models have also been described using rate constants derived from concentrations. A more chemically exact technique was used in GENESIS/Kinetikit, which demands that every reaction, enzyme activity, and molecule be detailed. DOQCS made an important design decision to include this chemical-level description. DOQCS was implemented using MySQL rather than an object-oriented database. Because of this, there are different tables for each kind of molecule, process, and enzyme. A DOQCS database item corresponds to a chemical entity in the simulation. There would be a molecular table and a table of enzymes for each enzyme's catalytic reaction with distinct substrates. It is expected that the reaction table would include one item for each of the following: the substrate, the product; the regulatory subunit; the catalytic subunit, and finally, the complex, which would have five entries. The connection between table entries and basic chemistry notions about molecules and processes provides several advantages.

- The database entries and empirically quantifiable variables like reactant concentrations are inextricably linked.
- Because there are no assumptions about equilibrium conditions, reaction schemes may be used to dynamic chemical circumstances on a timescale shorter than the equilibrium timescale.
- To model stochastic chemical processes, there is no need to alter the database at all. It is possible to get the information you're seeking by reinterpreting the entries for reaction rates as probabilities of response events. It is possible to determine reaction transition probabilities by scaling a rate constant k f in units of M/sec. The database's response schemes and other entries would remain unchanged.
- Incorporating spatial distribution information allows for a logical expansion into 3d reaction-diffusion systems. The chemical structure of the tables does not need to alter.

Database structure

Different table structures in the database represent individual reaction chemistry, route organization, and accession information. As stated before, there were different tables for molecules, processes, and enzymes (Fig. 1). Unique identification for each route and accession is included in each row of these tables. Notes and a user's name were other typical entry points. There have been a few other parameters that depend on the data type. The parent molecule is specified in a separate item in enzymes. A protein may have many enzyme activities, each with a distinct rate of activity and operating on a different substrate.

Because various models' naming conventions for chemicals range so widely, an auxiliary table called 'thesaurus' was included. Using this, you can find the name of every molecule, reaction, and enzyme in one place.

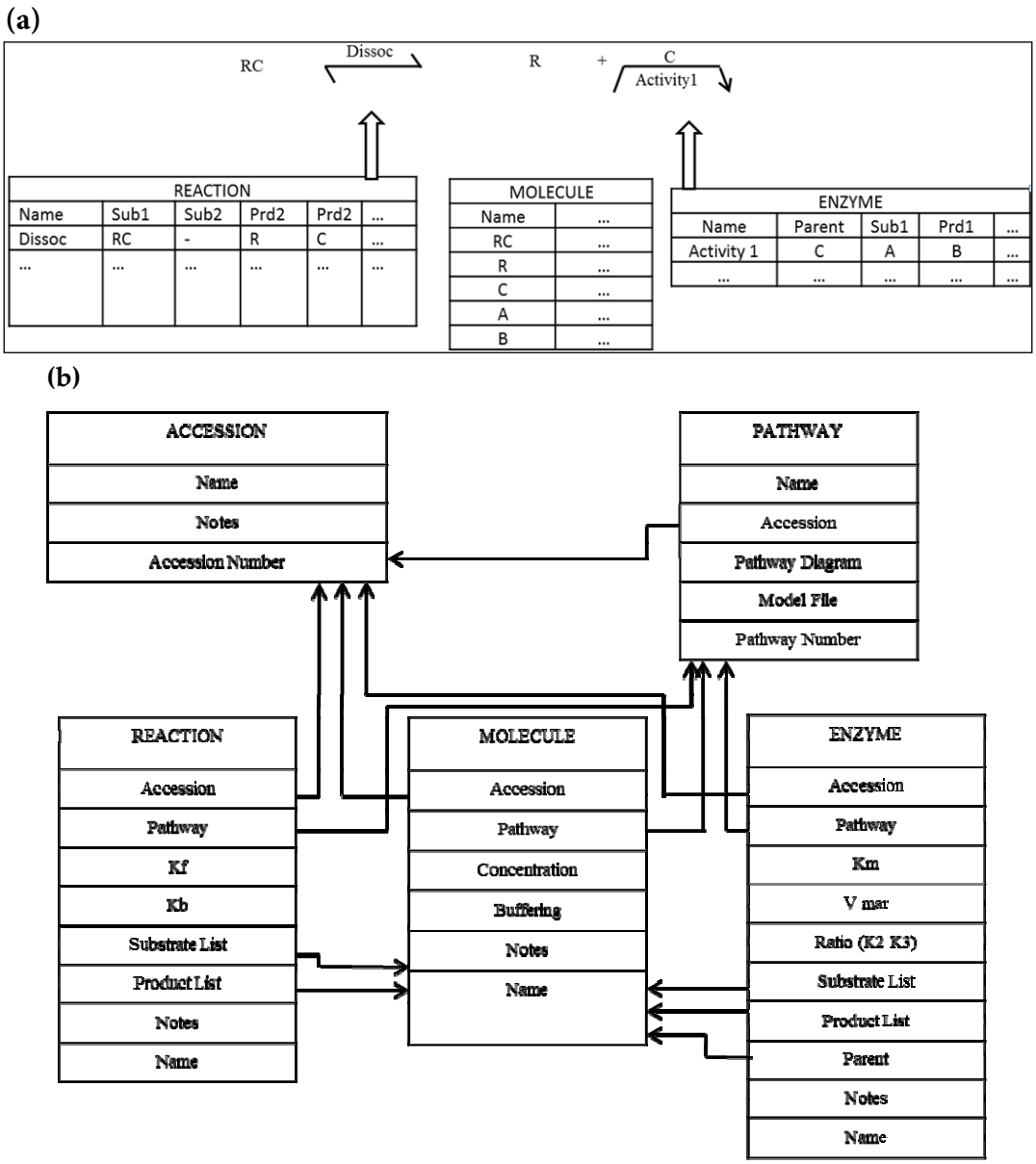

Fig. 1. (a) Reaction data model. Diagram showing enzyme kinetics. This method involves five ingredients, a reaction, and an enzyme. Each process, chemical, and enzymatic activity is a database record. Reactant molecules are included as substrates and products in reaction and enzyme tables. Parent molecule is included in the enzyme table. **(b)** Database structure. Each accession's accession number acts as a unique index in the accession table. The route table comprises a pathway number and structural description. An accession may have several pathways. Each route entry contains an accession ID. Each reaction, molecule, and enzyme entry has a route and accession ID. Reaction substrate and product lists contain molecules. Enzyme tables include the "parent" molecule containing enzyme activity. The thesaurus table (not shown) ties chemicals, processes, and enzymes to canonical forms.

Next in the organizational hierarchy serves as a route. This is quite similar to how signaling pathways were shown in traditional diagrams. An identifier for a particular route organizes chemical entries (reactions, chemicals, and enzymes). Like the chemical tables, the route comprises fields for accession, name, and remarks.

The accession is at the very top of the tabular hierarchy. In this section, you'll find information on how to manage the database's access permissions. Individual paths and networks are the two forms of accession currently in use. In the case of the former, there is just one model for accessing the data. As a starting point for more complex signaling models, these entries are designed to be used. The term "network accessions" refers to a set of signaling pathways that all lead to a single accession. An important organizational question is raised by these entries: how to show the interplay between paths. Interactions inside particular routes would be confusing since it would indicate that one pathway includes reactions and chemicals from another. Paths that rely on the contents of other pathways are no longer considered neatly wrapped in object-oriented concepts. For now, Kinetikit's answer is to establish a "basic route," which includes chemicals and processes that interact with many pathways.

Database interface and utilities

Searches

As a result of DOQCS's multi-level data arrangement, it also calls for a multi-level search strategy. The database's five primary tables, Enzyme, Molecule Reaction, Accession, and Pathway, may be searched using the internet interface. Links to accession numbers and pathways may be found in search results for chemicals and processes. Enzymes, on the other hand, may be recognized by both their activity and their molecular name. For enzyme search results, this extra information must be provided. For decoding search results, the search results provide useful annotations for the specific component that is being looked for, one of the most crucial entries.

The ability to respond and navigate a route

DOQCS displays a map of the connection of molecules and signaling pathways to offer a graphical, qualitative picture of pathway interactions. Graphic representations of all interactions between the database and a selected molecule or route are depicted using arrows in this tool. Three degrees of detail are available for the presentation. Molecule-to-molecule connection data is retrieved from the database at the most granular level. A molecule's whole set of molecular inputs and outputs may be seen. This map depicts the relationship between molecules and pathways at a lower level. Changing the display's focal point by clicking on one of the pathway's essential molecules changes the pathway's input or output pathway focus. A mouse click is all that is required to reach the database's greatest degree of pathway-to-pathway connection.

Comparisons

It turns out that a lot of pathways have a lot in common. This requires the creation of several different methodologies for evaluating potential routes. Component, parameter, and note comparisons are the three types of comparisons now being used. An average of all the similarity indices will be computed for each entry. Then, we'll hunt for pathways that incorporate related substances, processes, or enzymes as a general rule." Models of a specific route are compared using a comparison tree to show how similar they are. There are many different route models represented in this tree, some of which are connected and others that are unrelated.

The following are the steps for calculating similarity. The 'thesaurus' table transforms the molecule names from each route to their canonical form. Names of reactions and enzymes are also searched for in the same way. Consequently, the several comparisons grow, and the reliability of the findings improves as more chemically equivalent but differently named entries are included. The percentage of canonical names that match each other is then determined:

$$Match\ \% = 200 * M / (nA + nB)$$

Pathways A and B each have nA and nB components, and the number of names matches between them is M. A set of components with canonical names matching each other is then compared for their parameters. The smaller parameter is divided by, the larger one to get the similarity index.

$$\begin{aligned} Match\ \% &= 100 \quad if\ pA = pB \\ &= pA / pB \quad if\ pA < pB \\ &= pB / pA \quad if\ pB < pA \end{aligned}$$

This is followed by a comparison of each pathway's annotated string lengths. In the same way as before, the lengths of these strings are utilized as arguments. Compared to the other two, a tenth of the weight is given to this comparison.

Reports

For the construction of signaling models, the database report formats provide parameter lists that humans and machines can read. Currently, four different types of this file format are in use:

- A basic table of parameters in tabular form.
- An annotated collection of parameters for use as additional material in publications.
- Using the specification file format of Kinetikit model.
- The differential equations. Other simulators and the CellML file format (http://www.cellml.org/) and SBML (ERATO/SBML-Systems Biology Workbench) (http://www.cds.caltech.edu/erato/) (Hucka *et al.* 2001; Hucka, 2001) formats are planned.

RESULTS AND DISCUSSION

More than 2800 chemicals, processes, and enzymes are currently included in the database, which contains 26 additions and 146 pathways. There are about one-third of published chemical kinetics models of signaling pathways in the database, based on a literature review.

Currently, the database does not offer a much bigger variety of metabolic and neural biophysical models. While a mechanism for online submissions and their curation is being built, all accessions are being handled internally for the time being. When the online system is put into place, it is predicted that the pace of data input would rise. In addition, we anticipate that as technology advances in parameter determination, the number of models that are now accessible from the literature will rise quickly.

The names of chemicals, processes, and enzymes vary widely between models, as shown by our database and earlier studies (Juty *et al.* 2001). One advantage of employing acronyms in models is that formal names for molecules and enzymes are time-consuming for modelers. On the other side, name variations make comparisons more difficult and could cause uncertainty. These ambiguities are often intentional; for example, the generic Protein Kinase C (Bhalla and Iyengar, 1999) and Adenylyl Cyclase (Bhalla *et al.* 2002) models in the database reflect several isoforms using a single, averaged model. There are many potential remedies for inconsistent naming. For instance, creating a matrix to find comparable compounds in various pathway models might be a step in the annotation process. As previously described by Juty *et al.* (2001), we have achieved this by building a thesaurus of canonical names, although this requires extra curation work. Additionally, there are heuristic methods for matching compounds, reactions, and enzymes based on the locations of those entities in reaction graphs (Bagnall *et al.* 2018; Legewie *et al.* 2008). There are disadvantages to each of these strategies. For instance, certain important phosphatases in the MAPK pathway operate on various molecules at various places. When should these responses be compared as a group and when should they be handled differently? The original nomenclature is always kept since DOQCS emphasizes supplying original models. The next section discusses a few model comparison strategies.

According to the available data, signaling pathway models have a definite propensity to be implemented in a variety of forms, sharing the majority of routes but having different iterations of others. It should come as no surprise that there is a propensity for an evolutionary link between models that have been built through time. For instance, the MAPK pathway has eight different iterations in DOQCS right now. The only difference between four of them is the annotations. Two of them are updated versions of older models. The last two models are based on first-person writing, and they are both distinctive. It's unclear how similar these models are. One approach of similarity calculation has been put into practice based on parameter comparisons between equivalent molecules and processes. As was previously said, this works well when a thesaurus (Juty *et al.* 2001) is used to create correlation between model elements. When models represent response schemes that are fundamentally distinct from one another, the similarity calculation method fails.

Detailed point-by-point comparisons across models indicate to a potential superior, longer-term strategy (Schacherer *et al.* 2001). The comparison of the models' functional behavior rather than their internal features is the tactic used in this approach. This could be a better method of comparing models if functional analysis and prediction are the main objectives of model construction.

Additionally, it would avoid many of the previously mentioned name and model structure problems. In terms of database comparisons, this would call for the database to compare the outcomes of model simulations by either storing them or producing them online. As far as we are aware, no database presently uses such comparisons.

Many database initiatives with a variety of objectives now center on signaling networks. To track signaling interactions, the TRANSPATH database (Takai-Igarashi *et al.* 1998) provides comprehensive, searchable maps of signaling pathways. The database's data architecture can handle information on chemical reactions, which is one of its goals. Currently, blockdiagram data rather than chemical-reaction level data makes up the majority of the data in TRANSPATH. Although not explicitly characterized in terms of reaction kinetics, the related database CSNDB (Xenarios *et al*. 2002) contains molecular information as well. The databases DIP (Heinemeyer *et al.* 1998), GeneNet (Bader and Hogue, 2000), and BIND (Gilman, 2000) give reaction maps and descriptions of chemicals participating in pathways, however most do not provide information on reaction kinetics. Biocarta's block-diagram representations of numerous signaling pathways are visually appealing and annotated. Although GeneNet presently lacks a repository for signaling models, it does include two genetic models that can be accessed over the web and a kinetic model implementation schema. The Alliance for Cellular Signaling (AFCS) database, which can be viewed at http://www.cellularsignaling.org, offers quantitative information on signaling as well as well-annotated protein lists and a range of signaling maps (Burgard and Maranas, 2001). However, although BRENDA (Schomburg *et al.* 2004) and EMP (Loew and Schaff, 2001) are excellent resources for enzyme kinetics, they do not offer complete pathway models that incorporate upstream and downstream interactions, as well as regulatory information.

The Virtual Cell project provides online access to a variety of signaling models (Kubo *et al.* 2002). It is possible to express numerical model descriptions in a "Mathematical Model" via the use of the Virtual Cell Model Description Language (VCMDL). It is no longer the primary goal of Virtual Cell to maintain a library of signaling model data, but rather to conduct simulations. Numerous databases include information on protein-protein interactions, such as KEGG, ASPD, and SPiD (Astier *et al.* 2002; Goddard *et al.* 2001). No matter how much data we collect, we'll never have enough to design response plans or fully complete the kinetics of signaling networks. Chemical kinetics-based DOQCS is a unique set of models for functional simulations. To distinguish themselves from competing databases, they have developed search and comparison capabilities that are unique.

It is impossible to compare DOQCS to other simulator software packages like V-Cell, DBsolve, E-Cell, MCell and Kinetikit since DOQCS lacks simulator features. In the future, when conversion tools are developed, the models in DOQCS may be useful for these simulators.. CellML (http://www.cellml.org/) and SBML (http://www.cds.caltech.edu/erato/) are two XML-based model description languages that may be used to facilitate this interconversion (Juty *et al.* 2001).

Biological models are moving away from the "word model" phase into more accurate, predictive and practical simulations. There is still a problem with data. As a result, modeling methods specifically tailored to today's high-quality data have emerged (McDonald *et al.* 2012). There is currently a very small market for signaling pathway modeling in biology, but multiple factors are working together to accelerate up cell biology quantification and considerably expand the usage of signaling models. The bulk of existing chemical kinetic models of signaling interactions incorporate a little level of compartmentalization, but spatial detail is not included. The DOQCS schema has now been completed. The trend in computer simulations and signaling models is certainly toward greater cellular realism. Some examples of these characteristics include spatial information, stochasticity in single-molecule interactions, cytoskeletal effects, cellular mechanics, and the integration of all of these with genetic linkages (Williams *et al.* 2002). In addition to these model features, the DOQCS schema should include response modifiers, wider rate laws, and stimulus descriptions designed to replicate specific research.

Integration of database, simulator, and model description formats is becoming more commonplace, as is the incorporation of a greater biological realism to models. XML-based languages seem to be one way to make this integration easier, although there are currently just a few simulators that can read these model description languages (Juty *et al.* 2001). Additionally, integrating many route models into a signaling network model is difficult at the moment. New signaling network

simulators and object-oriented descriptions are starting to solve these challenges (Bhalla, 2003).

CONCLUSION

For this constantly expanding body of knowledge, we created a data and knowledge platform for quantitative study on cellular signal transduction in human cells. All of the biological aspects of cellular signal transduction were included in the database, including the biological processes that convey cellular signals and the molecular characteristics represented by sequences, structures, and functions. To manage this varied and complicated biological information, the database's object-oriented foundation necessitates extremely flexible ways of data construction and updating. The present DOQCS research is seen as one stage towards this very desired convergence of technologies, where established individual route models may be brought together using graphical techniques and simulated in an appropriate cellular spatial context.

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