Rewriting Logic and Symbolic Systems Biology applied to EGF Signaling Pathway^{*}

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Abstract. The idea of symbolic biological experiments opens up an exciting new world of challenging applications for formal methods. Pathway Logic is a step towards a vision of symbolic systems biology. In this paper we describe the Pathway Logic approach to the modeling and analysis of signal transduction, and the use of the Pathway Logic Assistant (PLA) tool to browse and query these models. The epidermal growth factor (EGF) signaling pathway is used to illustrate the concepts. In particular, formal executable models of processes such as signal transduction, metabolic pathways, and immune system cell-cell signaling are developed using the rewriting logic language Maude and a variety of formal tools are used to query these models.

Keywords: signal transduction, symbolic systems biology, epidermal growth factor signaling, Pathway Logic, rewriting logic, Maude, Petri net, executable model

1 Introduction

Rewriting logic [35, 38] is a logic of concurrent change that can naturally deal with states and with highly nondeterministic concurrent computations. It has good properties as a flexible and general semantic framework for giving semantics to a wide range of languages and models of concurrency. Moreover, it allows userdefinable syntax with complete freedom to choose the operators and structural properties appropriate for each problem.

The naturalness of rewriting logic for modeling and experimenting with mathematical and biological problems has been illustrated in a number of works [9]. The basic idea is that we can model a cell as a concurrent system whose concurrent transitions are precisely its biochemical reactions. In fact, the chemical notation for a reaction like $AB \longrightarrow CD$ is exactly a rewriting notation. In this

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way we can develop symbolic models of biological systems which we can then analyze just as we would analyze any other rewrite theory, for example using search and model checking.

Rewriting logic, through Pathway Logic and Pathway Logic Assistant [57], can: (1) display the network of signaling reactions for a specified model; (2) formulate and submit queries to find pathways, for example activating one protein without activating a second protein, or exhibiting a phenotype signature such as apoptosis; (3) compare two pathways; (4) find single or double knockouts (individual or pairs of proteins whose omission prevents reaching a specified state); (5) compute and display subnets for which given proteins are critical; and (6) map gene expression data onto signaling networks.

The paper is organized as follows. In Section 2 we show the importance of biological pathways and review some approaches, especially symbolic models, which are used at present. Then Section 3 emphasize those aspects of rewriting logic and Maude that will be used in our specifications. Section 4 introduces Pathway Logic. Results of our implementation to the study of the EGFR model are included in Section 5.

2 Biological Signaling Pathways

The growth of genomic sequence information combined with technological advances in the analysis of global gene expression has revolutionized research in biology and biomedicine [5, 59]. However, the vast amounts of experimental data and associated analyses now being produced have created a need for new ways of integrating this information into theoretical models of cellular processes for guiding hypothesis creation and testing. Investigation of mammalian signaling processes, the molecular pathways by which cells detect, convert, and internally transmit information from their environment to intracellular targets such as the genome, would greatly benefit from the availability of such predictive models.

Most signaling pathways involve the hierarchical assembly in space and time of multi-protein complexes or modules that regulate the flow of information according to logical rules [30]. Moreover, these pathways are embedded in networks having stimulatory, inhibitory, cooperative, and other connections to ensure that a signal will be interpreted appropriately in a particular cell or tissue [42].

Computational models of biological processes such as signal transduction fall into two main categories: differential equations to model kinetic aspects; and symbolic/logical formalisms to model structure, information flow, and properties of processes such as what events (interactions/reactions) are checkpoints for or consequences of other events.

Models of system kinetics based on differential equations use experimentally derived or inferred information about concentrations and rates to simulate changes in response to stimuli as a function of time [29, 52, 53, 60]. Such models are crucial for rigorous understanding of, for example, the biochemistry of signal transduction [13, 28]. However, the creation of such models is impeded by the great difficulty of obtaining accurate intra-cellular rate and concentration

3

information, and by the possibly stochastic nature of cellular scale populations of signaling molecules [32, 44]. Analysis of such models by numerical and probabilistic simulation techniques becomes intractable as the number of reactions to be considered grows [17]. Furthermore, for the present purpose the questions we want to ask of a model involve qualitative concepts such as causality and interference rather than detailed quantitative questions [49].

Symbolic/logical models allow one to represent partial information and to model and analyze systems at multiple levels of detail, depending on information available and questions to be studied. Such models are based on formalisms that provide language for representing system states and mechanisms of change such as reactions, and tools for analysis based on computational or logical inference. Symbolic models can be used for simulation of system behavior. In addition properties of processes can be stated in associated logical languages and checked using tools for formal analysis. A variety of formalisms have been used to develop symbolic models of biological systems, including Petri nets [24, 31, 40]; ambient/membrane calculi [39, 43, 47]; statecharts [14]; live sequence charts; and rule-based systems [12, 15, 18, 26]. Each of these formalisms was initially developed to model and analyze computer systems with multiple processes executing concurrently. Several tools for finding pathways in reaction and interaction network graphs have been developed. However as pointed out in [11], paths found in these graphs do have not much to do with biochemical pathways.

Models that rely on quantitative information (BioSPI [46, 48], PRISM [6], Psystems [43]) are limited by the difficulty in obtaining the necessary rate data. Missing or inconsistent data (from experiments carried out under different conditions, and on different cell types) are likely to yield less reliable predictions. Models that abstract from quantitative details avoid this problem, but the abstractions may lead to prediction of unlikely behavior, or miss subtle interactions.

The Pathway Logic Assistant extends the basic representation and execution capability with the ability to support multiple representations, to use different formal tools to simplify and analyze the models, and to visualize models and query results. Other efforts to integrate tools for manipulating models include the Systems Biology Workbench [25], the Biospice Dashboard [21], and IBM Discoverylink [23].

Our approach focuses on developing abstract qualitative models of metabolic and signaling processes that can be used as the basis for analysis by powerful tools, such as those developed in the formal methods community, to study a wide range of questions.

Currently there are several implementations of Pathway Logic models [9, 38, 41, 56]. Some of these models are: *STM6* (a model of cellular response to external stimuli), *Protease* (a network model of gram+ bacterial proteases), *Mycolate* (a model of the Mycobacterial Mycolic Acid Biosynthesis Pathway), *GlycoSTM* (a model of glycosylation extending the KEGG pathways).

3 Rewriting Logic Computation: Maude

Rewriting logic was first proposed by Meseguer in 1990 as a unifying framework for concurrency [35]. Since then a large body of work by researchers has contributed to the development of several aspects of the logic and its applications in different areas of computer science [34, 36–38]. Rewriting logic has been applied to bioinformatics [1, 3, 41], to modeling the dynamics of chemical systems [2], and to chemically and biologically inspired membrane systems [33].

Rewriting logic is a logic of change in which the distributed states of a system are understood as algebraically axiomatized data structures, and the basic local changes that can concurrently occur in a system are axiomatized as rewrite rules that correspond to local patterns that, when present in the state of a system, can change into other patterns.

A rewrite theory consists of a signature (which is taken to be an equational theory) and a set of labelled (conditional) rewrite rules. The signature of a rewrite theory describes a particular structure for the states of a system (e.g., multiset, binary tree, etc.) so that its states can be distributed according to the laws of such a structure. The rewrite rules in the theory describe which elementary local transitions are possible in the distributed state by concurrent local transformations. The deduction rules of rewriting logic allow us to reason formally about which general concurrent transitions are possible in a system satisfying such a description. Thus, computationally, each rewriting step is a parallel local transition in a concurrent system. Alternatively, however, we can adopt a logical viewpoint instead, and regard each rewriting step as a logical entailment in a formal system.

Maude [8–10] is a high performance language and system supporting both equational and rewriting logic computation. A key novelty of Maude is the efficient support for rewriting, narrowing, and unification modulo equational theories such as those used to model lists or multisets. Maude modules are theories in rewriting logic. The most general Maude modules are called system modules and are written as mod T endm, with T the rewrite theory in question expressed with a syntax quite close to the corresponding mathematical notation.

Maude provides a high-performance rewriting engine featuring matching modulo associativity, commutativity, and identity axioms. Matching is used to determine if a rule applies to a system state and the result of application. The associativity, commutativity, and identity axioms are used to describe states that are mixtures. In this case, the order in which the elements are presented does not matter. This allows rules for reactions in such mixtures to be described very compactly and naturally. Maude also provides search and model-checking capabilities. Thus, given a specification S of a system, one can execute S by rewriting to find one possible behavior, use search to see if a state meeting a given condition can be reached; or model-check S to see if a temporal property is satisfied, and if not to see a computation that is a counter example.

The Maude system, its documentation, a collection of examples, some case studies, and related papers are available on the Maude web page at http://maude.csl.sri.com.

4 Pathway Logic

Pathway Logic [15, 58, 56] is an approach to the modeling and analysis of molecular and cellular processes based on rewriting logic. Pathway Logic models of biological processes are developed using the Maude system. A Pathway Logic knowledge base includes data types representing cellular components such as proteins, small molecules, or complexes; compartments/locations; and post-translational modifications. Rewrite rules describe the behavior of proteins and other components depending on modification state and biological context. Each rule represents a step in a biological process such as metabolism or intra/inter-cellular signaling. A collection of such facts forms a formal knowledge base. A model is then a specification of an initial state (cell components and locations) interpreted in the context of a knowledge base. Such models are executable and can be understood as specifying possibly ways a system can evolve. Logical inference and analysis techniques are used for simulation to study possible ways a system could evolve, to assemble pathways as answers to queries, and to reason about dynamic assembly of complexes, cascading transmission of signals, feedback-loops, cross talk between subsystems, and larger pathways. Logical and computational reflection can be used to transform and further analyze models.

Given an executable model such as that described above, there are many kinds of computation that can be carried out, including: static analysis, forward simulation, forward search, backward search, explicit state model checking, and meta analysis. All types of search are extremely fast, thanks to the natural definition of biological processes in the form of rewriting rules. Despite the initial NP-complete complexity [20] with a large number of rules, the Maude language (underlying Pathway Logic) efficiently handles this situation.

Pathway Logic models are structured in four layers: sorts and operations, components, rules, and queries. The *sorts* and *operations* layer declares the main sorts and subsort relations, the logical analog to ontology. The sorts of entities include Chemical, Protein, Complex, and Location (cellular compartments), and Cell. These are all subsorts of the Soup sort that represents unordered multisets of entities. The sort Modification is used to represent post-translational protein modifications. They can be abstract, just specifying being activated, bound, or phosphorylated. Modifications are applied using the operator [-]. For example the term [EgfR - act] represents the activation of the epidermal growth factor receptor EgfR.

A cell state is represented by a term of the form [cellType | locs] where cellType specifies the type of cell, for example Fibroblast, and locs represents the contents of a cell organized by cellular location. Each location is represented by a term of the form {locName | components} where locName identifies the location (for example CLm for cell membrane, CLc for cell cytoplasm, CLo for the outside of the cell membrane, CLi for the inside of the cell membrane) and components stands for the mixture of proteins and other compounds in that location.

The *components* layer specifies particular entities (proteins, chemicals) and introduces additional sorts for grouping proteins in families. The *rules* layer



Fig. 1. Pathway Logic Assistant: Rac1 activation model as a Petri net. Ovals are occurrences, with initial occurrences darker. Rectangles are transitions. Two way dashed arrows indicate an occurrence that is both input and output. The full net is shown in the upper right thumbnail. A magnified view of the portion in the red rectangle is shown in the main view.

contains rewrite rules specifying individual steps of a process. These correspond to reactions in traditional metabolic and interaction databases. The *queries* layer specifies initial states and properties of interest.

The Pathway Logic Assistant (PLA) provides an interactive visual representation of Pathway Logic models and facilitates the following tasks: display the network of signaling reactions for a given dish; formulate and submit queries to find pathways; visualize gene expression data in the context of a network; or compute and display the downstream subnet of one or more proteins. Given an initial dish, the PLA selects the relevant rules from the rule set and represents the resulting reaction network as a Petri net. This provides a natural graphical representation that is similar to the hand drawn pictures used by biologists, as well as very efficient algorithms for answering queries.

PLA manages the different model and computation representations and provides functions for moving from one representation to another, for answering user queries, displaying and browsing the results. The principle data structures are: PLMaude models, Petri net models, Petri subnets, PNMaude modules, computations (paths), and Petri graphs [57]. Figure 1 gives an overview of the PLA interface.

Model checking expands the collection of properties that can be investigated. Model-checking tools are based on algorithms to determine if all computations of a system satisfy a given property. PLA can acquire new knowledge, it allows to infer results for specific input states which are not known a priori.

5 Epidermal Growth Factor Signaling in Pathway Logic

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In this section we explain some of the ways an experimental biologist might use the Pathway Logic knowledge bases and PLA in their research. We will focus on the Pathway Logic model of response to Epidermal growth factor (Egf) stimulation. This is an important model for the study of cancer and many other phenomena as Epidermal growth factor receptor (EgfR) signaling regulates growth, survival, proliferation, and differentiation in mammalian cells.

We use rewrite rules to express biochemical processes or reactions involving single or multiple subcellular compartments. For example, consider a rule (Rule 757) that establishes: In the presence of PIP3, activated Pdk1 recruits PKCe from the cytoplasm to the cell membrane and activates it. In Maude syntax, this signaling process is described by the following rewrite rule:

```
rl[757.PIP3.Pdk1.act.PKCe]:
  {CM | cm:Soup PIP3 [Pdk1 - act] {cyto:Soup PKCe}}
  =>
  {CM | cm:Soup PIP3 [Pdk1 - act] [PKCe-act] {cyto:Soup}}
  [metadata "cite = 11964154"] .
```

A rule declaration may also contain additional information. The metadata attribute allows rules to be annotated with arbitrary information that is ignored by the core rewriting engine, but available for use by metalevel operations. In the above rule, the metadata cite = "11964154" gives the unique identifier for the MedLine database citation as justification for the rule [7].

To support reliable manual curation of the experimental literature, we are developing a system [41], called *datums*, to collect, store, and retrieve curated information so that it can be understood and shared by a community of experimental biologists, and used to is developing models of cellular processes.

The queries layer specifies initial states (called dishes) to be studied. Initial states are in silico Petri dishes containing a cell and ligands of interest. An initial state is represented by a term of the form PD(out cell), where cell represents a cell state and out represents a soup of ligands and other molecular components in the cells surroundings. Our analysis begins with the initial dish state rasDish defined by

```
eq rasDish = PD(Egf [HMEC | {CLo | empty }
   {CLm | EgfR PIP2 } {CLi | [Hras - GDP] Src }
   {CLc | Gab1 Grb2 Pi3k Plcg Sos1 }]).
```

Figure 2 shows the Petri net representation of rasDish. Ovals are occurrences, with initial occurrences darker. Rectangles are transitions. Two way dashed arrows indicate an occurrence that is both input and output.

8 Santos-García, De Las Rivas, and Talcott



Fig. 2. RasDish as a Petri net using Pathway Logic.

Suppose we want to find out if a pathway (computation) leading to activation of Hras (loaded with GTP) one can use the search command with a suitable search pattern and parameters ([1] -- the first solution, =>+ at least one step).

Maude> search [1] rasDish =>+
PD(out:Soup [HMEC | cyto:Soup {CLi | cli:Soup [Hras - GTP]}]) .

The solution to this query given by Maude is:

Then we can ask Maude for the rule labels:

Maude> show path labels 15 .
1.EgfR.act
5.Grb2.reloc

g

4.Gab1.Yphosed
8.Pi3k.act
9.PIP3.from.PIP2.by.Pi3k
13.Sos1.reloc
6.Hras.act.1

Models of cellular response to many different stimuli, including a much more complete model of Egf signaling, as well as a tutorial guide for using PLA to query the models can be found at http://pl.csl.sri.com using the PLA On-line menu.

6 Conclusions

Pathway Logic is a symbolic systems biology approach to modeling biological processes based on rewriting logic. It provides many benefits, including the ability to build and analyze models with multiple levels of detail, represent general rules, define new kinds of data and properties, and execute queries using logical inference. We are interested in formalizing models that biologists can use to think about signaling pathways and other processes in familiar terms while allowing them to computationally ask questions about possible outcomes. We have described the use of Pathway Logic to model signal transduction processes, and the use of the Pathway Logic Assistant to browse and analyse these models.

Model validation is done both by experimental testing of predictions and by using the analysis tools to check consistency with known results. Already the Pathway Logic models are useful for clarifying and organizing experimental data from the literature. The eventual goal is to reach a level of maturity that supports prediction of new and possibly unexpected results.

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¹⁰ Santos-García, De Las Rivas, and Talcott

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