On Representing Biological Systems through Multiset Rewriting

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Abstract. We model qualitative and quantitative aspects of metabolic pathways by using a stochastic version of Multiset Rewriting (SMSR). They offer a natural way of describing both the static and the dynamic aspects of metabolic pathways. We argue that, due to its simple conceptual model, SMSR may be conveniently used as an intermediate language where many higher level specification languages may be compiled (e.g., as in the security protocol example). As a first step, we show also how SMSR may be used to simulate Stochastic Petri Nets for describing metabolic pathways.

Keywords: Metabolic pathways, Bio-molecular Processes, Stochastic processes, Multiset Rewriting.

1 Introduction

In the post-genomic era, the most prominent biological problems are detecting, describing and analyzing the informational flows that make a set of molecules a

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living organism [1]. Genomic and proteomic techniques, in fact, are producing the largest set of biological data available ever, but the problem of detecting and describing how these entities (genes and proteins) interact with each other in the complex molecular machinery of the cell has just begun being addressed. It is necessary to find easy, comprehensive, and biological-friendly *models* to describe molecules and their interactions.

Metabolism can be defined as the sum of all the enzyme-catalyzed reactions occurring in a cell. There are relatively few metabolic pathways, but each of these can be broken down into many individual, enzyme-specific, catalyzed steps. Metabolism is a highly integrated process. Individual metabolic pathways are linked into complex networks through common, shared substrates. A series of nested and cascaded feedback loops are employed to allow flexibility and adaptation to changing environmental conditions and demands. Negative feedback (usually by end-product inhibition) prevents the over-accumulation of intermediate metabolites and it contributes to maintaining homeostasis.

Understanding the mechanisms involved in metabolic regulation has important implications in both biotechnology and in medicine. For example, it is estimated that at least a third of all serious health problems such as coronary heart disease, diabetes and strokes are caused by metabolic disorders. Due to the integrated nature of metabolism, it is often difficult to predict how changing the activity of a single enzyme will affect the entire reaction pathway. Mathematical kinetic models have been applied to help elucidate the behavior of biochemical networks.

It is common opinion [1] that an ideal model for biological enquiring has to satisfy three requirements:

- It must be suitable for describing metabolic networks, in order to create metabolic databases allowing the user to search for and compare biochemical pathways in living organisms (like the genomic and proteomic database are already doing).
- It must be implementable into a simulation machine, in order to realize dynamic models of metabolic pathway that allow studying possible critical situation and steady states, and generally predicting that certain conditions will happen.
- It must be possible to run dynamic simulations in which to evaluate how external agents interfere with molecules and processes, in order to infer the consequences on the metabolic network stability. This kind of applications is a useful in silico test of possible side effects of a drug.

For these reasons, proper theories and instruments of the Formal Methods research community may help in defining formal models and tools (*e.g.*, see [2]), since they have been used so far to represent different kinds of relationships and dynamic interactions among objects and processes in distributed systems. In this paper, we use Multiset Rewriting (MSR) [3, 4], a logic-based formalisms based on rewriting systems. MSR offers both a formal language for a precise description of molecular interaction maps, and an execution model allowing simulation

of the dynamics of molecular networks with the theoretical possibility of predicting optimal values for certain parameters used in the system description. Basic mechanisms in MSR include: (a) a multiset of items, used to describe a system state, which can represent objects or resources or generic entities; (b) a set of rewriting rules which act on a state by consuming and producing items. It is our opinion that those simple and abstract mechanisms are expressive enough in describing a large class interactions happening in molecular systems.

The rest of the paper is organized as follows. Section 2 and 3 recall respectively the multiset rewriting framework and its stochastic extension. The main result of the paper is described in Section 4 where biochemical systems are modeled as multiset rewriting rules. Section 5 gives a complete real example showing the applicability of the framework. Finally, Section 6 show a theoretical results that gives the possibility to transform biological systems represented as petri nets in our MSR model. Section 7 summarize the results and highlight some future related research topics.

2 Multiset Rewriting

The formal language of MultiSet Rewriting, MSR [4, 3], is given by the following grammar, defining multisets, multiset rewriting rules and rule sets:

$$\begin{array}{lrcl} \textit{Multisets} & \tilde{a}, \tilde{b}, \tilde{c}, \tilde{g} & ::= & \cdot \mid a, \tilde{a} \\ \textit{Multiset rewrite rules} & r & ::= & \tilde{a} \to \tilde{b} \\ \textit{Rule sets} & \tilde{r} & ::= & \cdot \mid r, \tilde{r} \end{array}$$

The elements of a multiset, denoted a above, are *facts* $p(\boldsymbol{t})$ where p is a predicate symbol and the terms $\boldsymbol{t} = (t_1, \ldots, t_n)$ are built from a set of symbols Σ and variables $x, y, z, \ldots$. Numerous examples will be given in the sequel. The elements in a multiset $\tilde{a}$ shall be considered unordered, but may contain replicated elements. For convenience, "$\cdot$" will be kept implicit when $\tilde{a}$ has at least one element. Similar conventions apply to rule sets.

In a rule $r = \tilde{a} \to \tilde{b}$, the multisets $\tilde{a}$ and $\tilde{b}$ are called the *antecedent* and the *consequent*, respectively. We will sometimes emphasize that the above rule mentions variables $\boldsymbol{x} = (x_1, \ldots, x_n)$ by writing it $r(\boldsymbol{x}) = \tilde{a}(\boldsymbol{x}) \to \tilde{b}(\boldsymbol{x})$. Then, we denote the rule obtained by substituting the variables $\boldsymbol{x}$ with terms $\boldsymbol{t} = (t_1, \ldots, t_n)$ as $r(\boldsymbol{t}) = \tilde{a}(\boldsymbol{t}) \to \tilde{b}(\boldsymbol{t})$.

An MSR specification describes the situation a system is in at a certain instant as a multiset $\tilde{a}$ without any variable. This is called a *state* and written s possibly subscripted. The transformations that describe the legal evolution of the system are given as a set of rules $\tilde{r}$. We represent the fact that the system evolves from state s to state s' by using one rule r in $\tilde{r}$ as the judgment

$$\textit{Single rule application} \qquad \tilde{r} : s \longrightarrow s'$$

Operationally, this step is described by the following inference rule:

$$\frac{}{(\tilde{r}, \underbrace{\tilde{a}(\boldsymbol{x}) \to \tilde{b}(\boldsymbol{x})}_{r}) : \underbrace{\tilde{c}, \tilde{a}(\boldsymbol{t})}_{s} \longrightarrow \underbrace{\tilde{c}, \tilde{b}(\boldsymbol{t})}_{s'}}$$

In order for r to be *applicable* in s, this state must contain an instance $\tilde{a}(\boldsymbol{t})$ of r's antecedent $\tilde{a}(\boldsymbol{x})$, and possibly some other facts $\tilde{c}$. If r is applicable, s' is obtained from s by removing $\tilde{a}(\boldsymbol{t})$ and replacing it with the corresponding instance of the consequent, $\tilde{b}(\boldsymbol{t})$. Basic execution steps can be chained. The iterated judgment is written $\tilde{r} : s \longrightarrow\!\!\!\!\!\!\ast\ s'$.

3 Stochastic MSR

Stochastic MSR (SMSR) is an extension of MSR aimed at studying reductions quantitatively. The duration of each reduction is exponentially distributed. The rate of that reduction is given as a result of applying a weight function w to the current state s. A stochastic MSR rule with weight w is denoted $\tilde{a}(\boldsymbol{x}) \to_w \tilde{b}(\boldsymbol{x})$. The notion of rule application is modified as follows:

$$\frac{}{(\tilde{r}, \underbrace{\tilde{a}(\boldsymbol{x}) \to_w \tilde{b}(\boldsymbol{x})}_{r}) : \underbrace{\tilde{c}, \tilde{a}(\boldsymbol{t})}_{s} \longrightarrow_{w(s)} \underbrace{\tilde{c}, \tilde{b}(\boldsymbol{t})}_{s'}}$$

Note that the rewriting rule naturally determines a labeled transition systems LTS whose states are the multisets and whose transitions are the reduction rule instances together with their rates. A so-called *race condition* determines the dynamic behavior of the system, i.e. when more of different rules are enabled, only the fastest succeed in being fired. It is worth to note that the continuous character of the exponential distribution assures that the probability of two rules firing at the same time is zero. The race condition has the effect of replacing the *possibilistic* structure of the underlying LTS into a *probabilistic* where the probability of each transition is proportional to its rate. This means that each rule will fire not only when the head of a rule unify with (part of) a the current states, but also depending on other conditions implemented with the function $w(s)$. Specific characteristics of the system can be analyzed instantiating a specific w function (representing the race condition).

The analogy between biochemical reactions and SMSR is given in Table 1.

4 Modeling Biochemical Systems with SMSR

Biochemical Reactions. Biochemical reactions are usually represented by the following notation:

$$aA + bB \rightleftharpoons^{k}_{k_{-1}} cC + dD \tag{1}$$

where A, B, C and D are molecules, $a, b, c, d, \ldots$ are their stoichiometric coefficients (which are constants), and k, k_{-1} are the kinetic constants. The previous

Predicate name	molecular species
Predicate	molecule
Rewriting	reaction
To be enabled	for a reaction to be possible
To fire	for a reaction to occur
Weight	reaction rate

Table 1. Analogy between Biochemical Notions and SMSR.

formula may be considered as a declaration of the different proportions of *reactants* and *products*, namely the objects at the left, and respectively at the right of a rule $\rightharpoonup^k$. This proportion is given by the following formula:

$$K = \frac{k}{k_{-1}} = \frac{[C]^c[D]^d}{[A]^a[B]^b}$$

which expresses the equilibrium constant, and $[A], [B], \ldots$ are the *concentrations* (*i.e.*, , moli over volume unit) of the respective molecules. The reaction rate (*i.e.*, the number of moli produces per time unit) depends usually on the kinetic constant and on the concentration of the reactants. In some situations the reaction rate may be influenced by other entities that slow its rate.

We can note that aA may be simply considered as:

$$\overbrace{A + \ldots + A}^{a}$$

and so the whole equation 1 may be considered a shortcut of for

$$\overbrace{A + \ldots + A}^{a} + \overbrace{B + \ldots + B}^{b} \rightleftharpoons^{k}_{k_{-1}} \overbrace{C + \ldots + C}^{c} + \overbrace{D + \ldots + D}^{d}$$

This intuition give a first idea about how a reaction can be modeled in SMSR. We encode each reactions in the two directions as two separate SMSR rules. For example equation 1 may be encoded in the two following SMSR rules:

$$\overbrace{A, \ldots, A}^{a}, \overbrace{B, \ldots, B}^{b} \rightarrow_{w_k} \overbrace{C, \ldots, C}^{c}, \overbrace{D, \ldots, D}^{d}$$

and

$$\overbrace{C, \ldots, C}^{c}, \overbrace{D, \ldots, D}^{d} \rightarrow_{w_{k_{-1}}} \overbrace{A, \ldots, A}^{a}, \overbrace{B, \ldots, B}^{b}$$

where w_k and $w_{k_{-1}}$ are the functions (which here depend on the kinetic values k and k_{-1}, on the stoichiometric coefficients a, b, c and d, and on the overall number of predicates A, B, C and D currently in the state defining the application rate of the rule. With abuse of notation, if we consider that

$$aA \equiv \overbrace{A, \ldots, A}^{a}$$

then the equation (1) may be very naturally expressed by the following two rewriting rules:

$$aA, bB \rightarrow_{w_k} cC, dD$$

and

$$cC, dD \rightarrow_{w_{k_{-1}}} aA, bB$$

where $w_k, w_{k_{-1}}$ are the functions that will define the actual reaction rate of the reduction depending on several factors, as the kinetic constants, and the concentrations/quantities of reactants. (Indeed, as stated in [5, 2], under certain assumptions concentration and quantities may be exchanged.) If we use the notation

$$\tilde{a} \rightleftarrows_{w_{k_{-1}}}^{w_k} \tilde{b}$$

to abridge

$$\tilde{a} \rightarrow_{w_k} \tilde{b}$$

and

$$\tilde{b} \rightarrow_{w_{k_{-1}}} \tilde{a}$$

then the equation 1 may be represented in the SMSR framework as:

$$aA, bB \rightleftarrows_{w_{k_{-1}}}^{w_k} cC, dD \tag{2}$$

that nicely resembles the traditional notation.

Enzymatic reactions are described similarly. The enzyme is considered as a persistent predicate that is not consumed by the reaction:

For example in the urea cycle (see Figure 5), the stoichiometric reaction (3)

$$E_{a2} + S \rightharpoonup_k E_{a2} + A + F \tag{3}$$

where the production of a certain amount of *Arginine* A and *Fumarate* F, from *Arginsuccinate* S and catalyzed by the enzyme *Arginosuccinase* E_{a2}, is controlled by the concentration of the *Arginine* in the environment. Precisely if the *Arginine* concentration strongly increases the probability of this reaction decreases.

Reaction 3 may be expressed in SMSR with the following rule:

$$r_4 : E_{a2}, S \rightarrow_{w_k} E_{a2}, A, F$$

where the reaction rate $w_k = f(k, [A])$ is an inverse function depending on the kinetic constant k and on the number of predicates A (thus the quantity of arginine) in the actual state.

4.1 A Small Example

Consider the example in [6] about the dimerization reaction of a molecule R. Assume that the biochemical rule is:

$$2R \rightleftarrows_{k_{-1}}^{k} R_2$$

also written as

$$R + R \rightleftharpoons^{k}_{k_{-1}} R_2$$

With our formalism, it has been split in the two rules:

$$R, R \rightarrow^{w_k} R_2$$

and

$$R_2 \rightarrow^{w_{k_{-1}}} R, R$$

or equivalently

$$R, R \rightleftarrows^{w_k}_{w_{k_{-1}}} R_2$$

During the construction of the rule we need to build the rate function of the reduction. This rate is usually function of concentrations or quantities. In a monomolecular reaction, the weight function is given $w_{k-1} = c_{k_{-1}} \cdot |R_2|$, i.e. the product among the quantity of molecules and a constant depending on the kinetic one k. In higher order molecular reaction, the weight function is $w_k = c_k \cdot |R| \cdot (|R| - 1)$, where c_k depends on the kinetic constant k.

5 The Urea Cycle: A Complete Modeling Example

This section shows how to express in SMSR the reactions in the urea cycle. In particular we refer to the pathway in Figure 5, representing the main interaction occurring the human urea cycle.

In the urea cycle a sequence of chemical reactions, occurring primarily in the liver, the ammonia is converted to urea in mammalian tissue. The urea, far less toxic than ammonia, is subsequently excreted in the urine of most mammals. Also known as the ornithine-citrulline-arginine-urea cycle, this cycle also serves as a major source of the amino-acid arginine.

Assume the following abbreviations:

Enzymes	
Arginase	E_{a1}
Arginosuccinase	E_{a2}
Arginosuccinase Synthase	E_{a3}
Ornitine Transcarbamoylase	E_o

Molecules			
Arginine	A	*Arginosuccinate*	S
Aspartate	P	*Carbamoylphosaphate*	C_p
Citrulline	C_t	*Fumarate*	F
Ornithine	O	*Urea*	U
Water	H_2O		

Table 2. Abbreviations

the reactions in the urea cycle are described by the stoichiometric equations in Table 3, where both a continuous production of H_2O and C_p, and a destruction of U are assumed in the environment. Here we assume these environmental condition to be guaranteed by external reaction (that we express as [5-7] in Table 4). The kinetic constants k_i (here left unspecified) define the rate of the relative reactions. Usually these rates are calculated experimentally by biologist

$$
\begin{array}{ll}
[\mathbf{1}] & E_o + O + C_p \rightleftharpoons_{k_{-1}}^{k_1} C_t + E_o \\
[\mathbf{2}] & E_{a3} + C_t + P + ATP+ \rightleftharpoons_{k_{-2}}^{k_2} S + AMP + E_{a3} \\
[\mathbf{3}] & E_{a2} + S+ \rightleftharpoons_{k_{-3}}^{k_3} A + F + E_{a2} \\
[\mathbf{4}] & E_{a1} + A + H_2O+ \rightharpoonup_{k_4} U + O + E_{a1}
\end{array}
$$

Table 3. Stoichiometric equations for the urea cycle.

and their exact values are available in the literature or retrieved from one of the public database on the web (*e.g.*, from KEGG pathways database).

In the urea cycle two fundamentals feed-back regulations contribute to the right production of *Arginine* and *Ornithine*. Informally they can be described as in the following:

1. if *Arginine* concentration strongly increases, the probability of reaction [**3**] decreases;
2. if *Ornithine* concentration strongly increases, the probability of reaction [**4**] decreases;

These mean that the *Arginine* and *Ornithine* production directly controls their own rate of production. For example an excessive production of *Arginine* causes negative feedback on the reaction producing the *Arginine* itself, decreasing the probability of that reaction to happen.

Using SMSR, the stoichiometric reactions in Table 3 may be quite literally expressed as rewriting rules and the predicate symbols used to represent molecular entities are exactly the one used in the stoichiometric equations. In Table 4 we report the SMSR rewriting rules which model the urea cycle.

In the rewriting rules in Table 4 it worth stressing that the catalyzing enzymes are expressed as persistent predicates, i.e. they are not consumed in practice (clearly we can model also other situations). The stochastic parameters w_{k_i} are indeed function of the kinetic constant k_i, or the stoichiometric coefficients c (here all equal to 1), of the relative stoichiometric equation.

Generally speaking we can assume that, for a stoichiometric equation $[i]$, $w_{k_i} = f_i(k_i, c_i, s)$, where f_i is a monotonic increasing function coming from biological enquiring. For example the regulation feedback of the urea cycle forces the following definitions:

$$
\begin{aligned}
w_{k_3} &= f_3(k_3, |A|^{-1}) \\
w_{k_{-3}} &= f_{-3}(k_{-3}, |A|) \\
w_{k_4} &= f_4(k_4, |O|^{-1}) \\
w_{k_{-4}} &= f_{-4}(k_{-4}, |O|)
\end{aligned}
$$

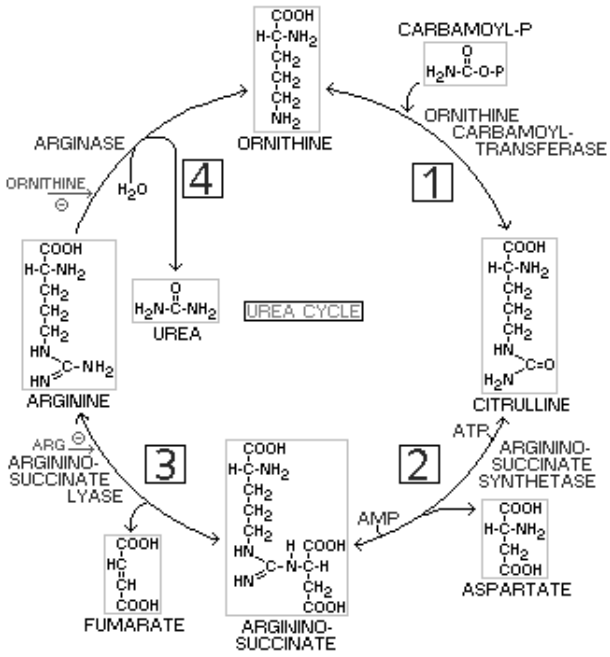

Fig. 1. The Urea Cycle

where we want to express that the value of w_{k_3} (resp. w_{k_4}) inversely depend on the number of predicates A (resp. O) in the global state[7]. Similarly $w_{k_{-3}}$ (resp. $w_{k_{-4}}$) directly depends on the number of predicate A (resp. O) in the global state.

6 Simulating Stochastic Petri Nets for Metabolic Pathways Modeling with SMSR

In this section we show how SMSR can simulate the analysis performed on metabolic pathways done using Stochastic Petri Nets (SPN's) [6]. We argue that this is not an isolate case and many other modeling approaches based on formalisms for distributed and concurrent systems may be encoded in our framework.

Petri Nets (PNs) are a family of distributed calculi, based on the notions of *places*, *tokens*, *markings* and *transitions*. The idea is that places stores resources, i.e. tokens. A marking is an instantaneous picture of the tokens present in the places. A transition is a relation among set of places to set of places and describes how markings change during the computation. A link from a place to a transition

[7] Here $|A|$ returns the number of occurrences of the predicates A in s

$[\mathbf{1}]$ $E_o, O, C_p \rightleftarrows^{w_{k_1}}_{w_{k_{-1}}} C_t, E_o$

$[\mathbf{2}]$ $E_{a3}, C_t, P, ATP, \rightleftarrows^{w_{k_2}}_{w_{k_{-1}}} S, E_{a3}$

$[\mathbf{3}]$ $E_{a2}, S \rightleftarrows^{w_{k_3}}_{w_{k_{-3}}} A, F, E_{a2}$

$[\mathbf{4}]$ $E_{a1}A, H_2O \rightarrow^{w_{k_4}} U, O, E_{a1}$

$[\mathbf{5}]$ $. \rightarrow C_p$

$[\mathbf{6}]$ $. \rightarrow H_2O$

$[\mathbf{7}]$ $U \rightarrow .$

Table 4. SMSR rules for the urea cycle.

is equipped with a number which expresses how many token are necessary from that place to enable the transition. A link from a transition to a place is equipped with a number that expresses how many token are produced when the transition is fired. Transitions in stochastic Petri Nets are not instantaneous (as in many other PNs), have a duration determined by a given probability distribution, usually exponential. This duration is inserted in the transition.

As an example [6], consider the dimerization reaction of the molecule R as represented in Section 4.1, and whose corresponding SPN is represented in figure 2.

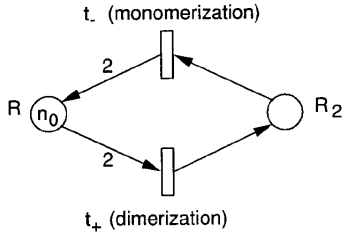

Fig. 2. SPN representation of the dimerization of molecule R

In [6], it has been advocated that Stochastic Petri Nets may be very useful when considering dozen (hundreds) of different species but a small absolute number of molecule. The analogy among metabolic pathways used in [6] is given in Table 5.

The computation of an SPN's is a graph that shows how markings evolve in time. There is a weighted link from a marking to another whenever there is a transition enabled in the previous marking that, due to its. Note that, as usual, two transitions are not assumed to fire at the same time. The weight of the transition, which clearly, denotes the rate of a reaction may depend on the global marking.

Place	molecular species
Token	molecule
Marking	quantities for each molecular species
Transition	reaction
Transition enabled	for a reaction to be possible
Transition fired	for a reaction to occur

Table 5. Analogy between biochemical notions and SPN's.

We can propose an analogy among SPN's and SMSR as follows: Places correspond to Predicate names; a token in a place is a predicate of a certain kind in the multiset and thus a marking is essentially a multiset of atomic predicates. Transitions are encoded as rewriting rules: A transition that consumes n token from a certain place is is encoded through a rule which requires n instances of the predicate corresponding to the place in the left hand side; a transition that produces m token in a place corresponds to a rule which requires m predicates on the right end side. The weight function of the rewriting rule is the same of the transition, provided the analogy among the marking and the multiset.

Thus, the LTS produced by the SMSR from an initial multiset precisely corresponds to the computation graph of the initial marking.

7 Conclusions, Future and Related Work

The MSR formalism has been used to study several forms of concurrent distributed computation [4, 7]. We advocate a simple stochastic variant of MSR, named SMSR, as a natural framework to model biochemical reactions. It has a clear and rigorous formal semantics. Moreover, its rules are readily understandable and seem quite close to textual descriptions of chemical reactions, at a functional level. From the specification and analysis point of view, we started to explore a line of research already successfully followed for security protocols analysis. Indeed, many analysis tools compile high level specifications into simpler MSR specifications [8]. Due to the simplicity and uniformity of the MSR rewrite mechanism, many researchers feel it is easier to develop analysis algorithms for MSR. In this paper, we show that a well known model of analysis may be encoded into the SMSR, i.e. SPN's. We argue that it will be possible to faithfully encode also other specification languages as the stochastic process algebra [2] into stochastic MSR (similarly to the encoding we proposed in [7] for security analysis). An advantage is that the intermediate language is itself a significant one for biologists.

Future work. We have two main goals:

- We plan to produce an optimized simulation environment based on the input syntax of $SMSR$ (possibly refined with built-in predicates or constraints) and map into other specification formalisms;

– We plan also to adapt the rich theory already developed for MSR for a suitable definition within biological systems of very useful formal notions like composition, abstraction, equivalence, congruences and so on.

Related work. Other notable approaches using forms of (multiset)-rewriting are presented in [9, 10]. The first approach exploits the modeling system Maude based on algebraic notions and rewrite theory. The structure and hierarchy of biological elements are represented through terms from a rich algebra. The emphasis is more on the qualitative aspects of the interactions. The latter is closer to ours since it is mainly based on simulation of biochemical reactions. The language, however, does not allow generic terms as ours. Moreover, our work instead is more focused on showing the ability of SMSR of acting as natural low level language for more complex description languages.

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