Constraint Based Languages for Biological Reactions

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Abstract. In this paper, we study the modelization of biochemical reaction by using concurrent constraint programming idioms. In particular we will consider the stochastic concurrent constraint programming(sCCP), the Hybrid concurrent constraint programming languages (Hcc) and the Biochemical Abstract Machines (BIOCHAM).
Keywords: Biochemical Reactions, Blood coagulation, Concurrent Constraint Programming(CCP), stochastic Concurrent Constraint Programming (sCCP), Hybrid concurrent constraint programming languages (Hcc), Biochemical Abstract machines (BIOCHAM).

1 Introduction

Systems biology is a science integrating experimental activity and mathematical modeling. They study the dynamical behaviors of biological systems. While current genome project provide a huge amount of data on genes or proteins, lots of research is still necessary to understand how the different parts of a biological system interact in order to perform complex biological functions. Mathematical and computational techniques are central in this approach to biology, as they provide the capability of formally describing living systems and studying their proprieties.

A variety of formalisms for modeling biological systems has been proposed in the literature. In [13], the author distinguishes three basic approaches: discrete, stochastic, continuous, additionally we have various combinations between them. Discrete models are based on discrete variables and discrete state changes; continuous models are based on differential equations that typically model biochemical reactions; finally in the stochastic the probabilities may appear explicitly in random variables and random numbers, or implicitly like in kinetics laws. In the latest approach we have a simplified representation of processes, an integration of stochastic noise in order to get more realistic models. The need to capture both discrete and continuous phenomena, motivates the study of dynamical systems [6].

The goal of this paper is to show different kinds of languages to model biochemical reactions in order to compare and to use their appropriate features in different ways.

2 Background on Biochemical reactions and Blood Coagulation

In this paper, we want to examine the Biochemical Reactions; they are chemical reactions involving mainly proteins. In a cell, there are many different proteins, hence, the number of reactions that can take place, can be very high. All the interactions that take place in a cell, can be used to create a diagram, obtaining a biochemical reaction network.

We will examine in the following, one of the thirteen enzymatic reaction of the blood coagulation [14], in the generic form, through the Michaelis-Menten kinetics:

$$XI + XIIa \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} XI : XIIa \overset{k_2}{\rightharpoonup} XI + XIa$$
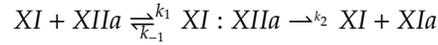
where XI is the enzyme (E) that binds substrate (S) = $XIIa$, to form an enzyme-substrate complex (ES) = $XI : XIIa$. After we have the formation of product (P) = XIa and the release of the unchanged enzyme (E) = XI, ready for a new reaction (see Appendix A for further details).

We are interesting at the Blood Coagulation [14]. It is part of an important host defense mechanism termed hemostasis (the cessation of blood loss from a damaged vessel). Blood clotting is a very delicately balanced system; when hemostatic functions fail, hemorrhage or thromboembolic phenomena results. The chemical reactions that constitute all the process, can be see as a decomposition of many kinds of enzymatic reactions, involved reactants, products, enzymes, substrates, stoichiometric coefficients, proteins, inhibitors and chemical accelerators.

3 Concurrent Constraint Programming

The Concurrent Constraint (cc) programming paradigm [10] concerns the behaviour of a set of concurrent agents with a shared store, which is a conjunction of constraints. Each computation step possibly adds new constraints to the store. Thus information is monotonically added to the store until all agents have evolved. The final store is a refinement of the initial one and it is the result of the computation. The concurrent agents do not communicate directly with each other, but only through the shared store, by either checking if it entails a given constraint (*ask* operation) or adding a new constraint to it (*tell* operation).

For the CCP's syntax, we have that P is the class of programs, F is the class of sequences of procedure declarations (or clauses), A is the class of agents, c ranges over constraints, and x is a tuple of variables. Each procedure is defined (at most) once, thus nondeterminism is expressed via the + combinator only. We also assume that, in $p(x) :: A$, we have $vars(A) \subseteq x$, where $vars(A)$ is the set of all variables occurring free in agent A. In a program $P = F.A$, A is the initial agent, to be executed in the context of the set of declarations F. This corresponds to the language considered in [10] which allows only guarded nondeterminism.

4 Stochastic Concurrent Constraint Programming

sCCP [2] is obtained by adding a stochastic duration to the instruction interacting with the constraint store *C*, i.e. *ask* and *tell*. The most important feature added in the sCCP is the continuous random variable *T*, associated with each instruction. It represents the time needed to perform the corresponding operations in the store. *T* is exponentially distributed, and its probability density function is $f(\tau) = \lambda e^{-\lambda\tau}$ where λ is a positive real number (rate of the exponential random variable) representing the expected frequency per unit of time. The duration of an ask or a tell can depend on the state of the store at the moment of the execution.

The main difference of sCCP with classical cc, is the presence of two different actions with temporal duration, *ask* and *tell*, identified by a rate function λ: $tell_\lambda(c)$ and $ask_\lambda(c)$, following the probability law. It means that the reaction occurs in a stochastic time T, $f(\tau) = \lambda e^{-\lambda\tau}$ whose mean is $1/\lambda$; i.e. $tell_\infty$ is an instantaneous execution while $tell_0$ never occurs.
Other functions are the same that in CCP, except for the variables, that in CCP are rigid, in the sense that, whenever they are instantiated, they keep that value forever. Time-varying variables (called stream variables) can be easily modeled in sCCP as growing lists with a unbounded tail: $X = [a_1, ..., a_n | T]$. When the quantity changes, we simply need to add the new value, say *b*, at the end of the list by replacing the old tail variable with a list containing *b* and a new tail variable: $T = [b | T']$. When we need to know the current value of the variable *X*, we need to extract from the list, the value immediately preceding the unbounded tail. The stream variables are denoted with assignment \$=.

We model model the biochemical equation [5], in sCCP, with the following recursively defined method:

$$react(XIIa, XIa, K_M, V_0) : -$$
$$ask_{r_{MM}(K_M, V_0, XIIa)}(XIIa > 0).$$
$$(tell_\infty(XIIa \;\$=\; XIIa - 1) \| tell_\infty(XIa \;\$=\; XIa + 1)).$$
$$react(XIIa, XIa, K_M, V_0)$$

Where the rate λ of the *ask*, is computed by the Michaelis-Menten kinetics: $r_{MM(K_M, V_0, XIIa)} = \frac{V_0 \times XIIa}{XIIa + K_M}$. Roughly the program inserts in the store the current value for the variables $K_M, V_0, XIIa$; it checks the value of the factor *XIIa*, then, with an immediate effect, it updates the values for the factors *XIIa* (reagent) and *XIa* (product) with the new values. Subsequently it executes a new instance of the program.

5 Hybrid cc

Hybrid concurrent constraint programming languages (Hybrid cc [8, 1]) is a powerful framework for modeling, analyzing and simulating hybrid systems, i.e., systems that exhibit both discrete and continuous change. It is an extension

of Timed Default cc [12] over continuous time. One the major difficulty in the original cc framework is that cc programs can detect only the presence of information, not the absence [13]. Default cc extends cc by a negative *ask* combinator (*if a else A*) which imposes the constraint *a* at the program *A*.

```
e = 100, s = 10, es = 0, p = 0, k1 = 1, km1 = 0.1, k2 = 00.1,
{ hence cont(e), cont(s), cont(es), cont(p),
if (e > 0 && s > 0.1) then
{ e = (((km1+k2) * prev(es)) - (k1 * (prev(e) * prev(s)))),
s = ((km1 * prev(es)) - (k1 * (prev(e) * prev(s)))) ,
es= ((k1 * (prev(e) * prev(s))) - ((km1+k2) * prev(es))),
p = (k2 * prev(es))
} else e' = 0, s' = 0, es' = 0, p' = 0 },
sample(e, s, es, p)
```

We can observe that in the first row, we have the initial conditions with the quantity of Enzyme (100), Substrate (10), Enzyme-Substrate (0), Product (0), and the rate of the three reactions: $k_1 = 1$ for the first one, $k_{-1} = 0.1$ for the second one and $k_2 = 0.01$ for the third reaction. With the syntax $cont(e, s, es, p)$ we assert that the rates of e, s, es, p are continuous. Subsequently we control the current values of e and s then we can start the reaction; the && and = operators, has the usual meaning of "and" and "equal". With the derivation rules in the Appendix A (Par.9), we can easily obtain the quantity of e, s, es, p in the next time instant. If the "if condition" doesn't hold, we obtain the previous amount of factors.

6 Biochemical Abstract Machine

Biochemical Abstract Machines (BIOCHAM [9]) is a software environment for modeling complex cell processes, making simulations (i.e. in silico experiments), formalizing the biological properties of the system know from real experiments, checking them and using them as specification when refining a model. BIOCHAM [3] is based on two aspects: the analysis and simulation of boolean, kinetic and stochastic model and the simulation of biological proprieties in temporal logic. For kinetics model, BIOCHAM can search for appropriate parameter values in order to reproduce a specific behavior observed in experiments and formalized in temporal logic.

We can use the Michaelis-Menten kinetics to represent the first enzymatic reaction of blood coagulation. To explain the language used to model the reaction in the BIOCHAM [4] language, we can translate the syntax in the following way:

```
(k1*[E]*[S],km1*[ES]) for E + S <=> ES.
k2*[ES] for ES => E + P.
parameter(k1,1).
parameter(km1,0.1).
parameter(k2,0.01).
present(E,100).
```

```
present(S,10).
absent(ES).
absent(P).
```
There are two different syntax operator, used to model the different kinds of reaction: <=> and =>. The first one model the reversible reaction, involved in the ES formation, this reaction can be reversible. The second one model the irreversible reaction which produce the P factor. The *for* operator show us for which substances, the reaction is performed: the first *for* is for the $E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E : S$ reaction, the second one for the $E : S \overset{k_2}{\rightharpoonup} E + P$ reaction.

7 Difference and similarity among four languages

In the following table, we encode the main differences and the similarities of the previous three languages to describe biological reactions and their simulation methods.

Language name	Time intervals	Use ODE's	Simulation program plotting	Formal specification
sCCP	continuous	no	no	constraints
Hcc	both	yes	no	constraints
BIOCHAM	continuous	yes	yes, GNU Plot	logic programming

8 Related and future works

Most important features are represented in [11, 7]. In [11] the authors suggests to model biomolecular process i.e. protein networks, by using the pi-Calculus, while in [7] is shown that there are two formalisms for mathematically describing the time behavior of a spatially homogeneous chemical systems: the deterministic approach and the stochastic one. The first regards the time evolution as a continuous and predictable process which is governed by a set of ordinary differential equations (the "reaction-rate equations"), while the seconds regards the time evolution as a kind of random-walk process which is governed by a single differential-difference equation (the "master equation").

From the application point of view, the examined languages allows the biologist to model biological systems in a high-level and declarative way, using different kinds of applications and languages construct that capture directly a variety of biological phenomena.

The aim of many researches in the bioinformatics field is to improve the modeling features of data in order to describe biological behaviors in a more accurate way, such that they can be used in in silico modeling in the drug sperimentations (preclinic) area; we aim to save time and money in the last sperimental phase on humans. Biological reactions are the first step towards a description of cycles cellular-based mechanisms.

9   Appendix A

Under the **Michaelis-Menten** hypotheses [5], the most important equations are:
$K_M = \frac{k_{-1}+k_2}{k_1}$ Michaelis constant. It measures the affinity of the enzyme for the substrate: if K_M is small there is a high affinity, and viceversa.

$V_{MAX} = V_0 = k_2[E_0]$. This is the maximum rate, would be achieved when all of the enzyme molecules have substrate bound (Hp1). $[E_0]$ is the starting quantity of enzyme E. k_2 is also called k_{cat}.

$\frac{d[P]}{dt} = \frac{V_{MAX}[S]}{K_M + [S]}$. This final equation, is usually called the "Michaelis-Menten equation". It shows the speed of the formation of the product.

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