Reaction-Agents: First Mathematical Validation of a Multi-agent System for Dynamical Biochemical Kinetics

Pascal Redou[1], Sébastien Kerdelo[1], Christophe Le Gal[1], Gabriel Querrec[1], Vincent Rodin[1], Jean-François Abgrall[2], and Jacques Tisseau[1]

[1] CERV, European Center for Virtual Reality, BP 38, F-29280 Brest, France
Pascal.Redou@enib.fr
[2] Hematology Laboratory, CHU Brest, Bd Tanguy Prigent, 29609, Brest, France

Abstract. In the context of multi-agent simulation of biological complex systems, we present a reaction-agent model for biological chemical kinetics that enables interaction with the simulation during the execution. In a chemical reactor with no spatial dimension -e.g. a cell-, a reaction-agent represents an autonomous chemical reaction between several reactants : it reads the concentration of reactants, adapts its reaction speed, and modifies consequently the concentration of reaction products. This approach, where the simulation engine makes agents intervene in a chaotic and asynchronous way, is an alternative to the classical model -which is not relevant when the limits conditions change- based on differential systems. We establish formal proofs of convergence for our reaction-agent methods, generally quadratic. We illustrate our model with an example about the extrinsic pathway of blood coagulation.

1 Introduction

Simulation in biology makes use of algorithms for the numerical resolution of differential systems. These algorithms, though they give precise results, do not fit well with the study of complex systems [At1]. Indeed, complex systems are *a priori* open (dynamical appearance/disappearance of components), heterogenous (various morphology and behaviours) and made of entities that are composite, mobile and distributed in space ; their number changes during time, and they interact with each other. Describing the evolution of such systems by means of deterministic methods like differential systems is uneasy, for limits conditions and number of processus fluctuate. As an alternative, the multi–agent approach [Fe1, WC1], already used in several biochemical models [HX1, JS1, WW1], provides a conceptual, methodological and experimental framework well-fitted for imagination, modelisation and experimentation of complexity. In this context, our work applies to the simulation of biological chemical kinetics phenomenons taking into account the variability of the number of implied reactants.

In a dimensionless chemical reactor -e.g. a cell-, a reaction-agent represents a chemical reaction which loops into a perception/decision/action cycle : it reads the concentration of reactants, adapts its reaction speed, and modifies consequently the concentration of reaction products. Each agent independently executes a classical ordinary differential system algorithm [CL1]. For each of these classical methods, we build the matching reaction-agent method.

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The simulation engine evolves reaction-agents asynchronously and chaotically (see section 2), in order to avoid the typical inflexibility of synchronous systems, as well as bias in numerical results.

From a more general point of view, we set up agents autonomy as a basic principle [TH1] : firstly autonomy is characteristic of living organisms, from the cell to the man (they are *essentially autonomous*); secondly the model should be able, at runtime, to sense changes in environment and thus the limits conditions, especially if the man is part of the system (*necessarily autonomous*); lastly, they are *autonomous by ignorance* since we are for now unable to report the behaviour of complex systems by the way of analysis reductionist method.

Therefore we gain the ability to interact with a running simulation, opening the path to a new way of experimenting : the *in virtuo* experimentation [Ti1]. *In virtuo* experimentation makes it possible to interfere with a chemical kinetics model by adding or removing reactions. The main interest of such an experimentation is that these alterations are possible without having to stop the progress of the simulation : experimental conditions of the *in virtuo* way are therefore very close to the *in vivo* and *in vitro* (with "man in the loop") ones, and fundamentally different from the *in silico* one (without "man in the loop").

In section 2 of this paper, we present the reaction-agent model for numerical computation of differential systems for chemical kinetics. In section 3 we formalize our model and state the main results about convergence of one step reaction-agent methods. In section 4 we describe how we adapt reaction-agent point of view for multistep methods, in the special case where the number of reactions is constant. Section 5 shows an illustrating example of our approach for a blood coagulation simulation. For the sake of concision, we will not expose the detailed demonstrations of mathematical results. Please contact first author to obtain proofs.

2 Reaction-Agent Model

2.1 Principle

The reaction-agents based methods are numerical methods for computation of differential systems which permit to take into account, at runtime, the evolvingness of these systems. Chemical kinetics is a natural application context for these methods : a classical example is given by cancer, since chromosomic instability [HW1] implies on a regular basis modifications or creations of new reactions [Bo1]. We have also used our reaction agent model for simulation of MAPK pathway [QR1]. We propose here (see section 5) an example about the extrinsic pathway of blood coagulation [LB1].

To achieve modelisation of such a processus we propose to reify chemical reactions. These reified reactions should be able, independently of each other, to carry out or not. Since it's the reactions that are reified in our model, we called it *reaction-agent*. Each reaction-agent matches a reaction of the system we want to modelize. Each agent behaviour loops in the following cycle :

- **Perception:** sensing of concentration of all reactions components (*i.e.* reactants and products),