Reaction-agents : first mathematical validation of a multi-agent system for dynamical biochemical kinetics

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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.

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),

- **Decision** : computation of the amount of consumed reactants (and thus of the amount of formed products),
- **Action** : writing the new concentrations of the reaction components.

Reaction-agents act by the way of chaotic and asynchronous iterations, as described below.

2.2 Chaotic and asynchronous iterations

At each step, the scheduler [HT1] makes one reaction-agent carry out its perception/decision/action cycle. Reaction-agents act one after the other following the scheduler cycle whose length equals the number of agents. The reaction-agents each act once and only once in a sheduler cycle, but the order in which they do so is randomly chosen. Let's precise these notions :

- **Asynchronous iterations** : a fundamental statement is that in the classical approach, time discretisation induces the hypothesis that all reaction occur simultaneously during the same time-step. Indeed, classically used differencial systems numerical resolution algorithms *a priori* do this hypothesis based upon the choice of infinitesimal time-step. *A contrario*, reaction-agent model does the asynchronic hypothesis for chemical reactions. We claim that this hypothesis is not only more realistic, but moreover allows the user to interfere at runtime with the reactions by adding or removing a reaction-agent, at any time of the simulation. Time is then divided into scheduler cycles inside of which each reaction-agent acts once and only once, considering the state of the system at the moment it acts. From a physical point of view, each scheduler cycle corresponds to one time-step of the classical approach.
- **Chaotic iterations** : an unalterable arrangement for reaction-agents operations at each cycle might introduce a bias -we proved some mathematical results that confirm it- in the simulation. In order to avoid this bias the scheduler makes each reaction-agent operate in a random order, which changes for each iteration step. This is what we call chaotic iterations.

Figure 1 illustrates this scheduling strategy.

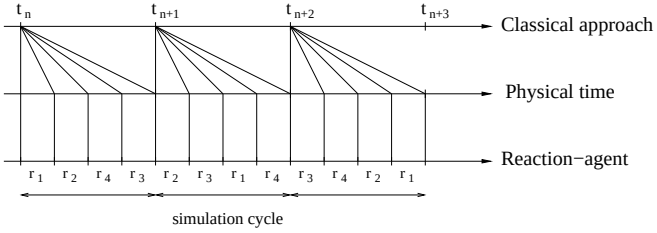

Fig. 1. Classical and reaction-agent points of view for reactions scheduling. Case of 4 reaction-agents r_i, $1 \leq i \leq 4$.

2.3 Illustration

Let's illustrate our views, and consider a medium with no spatial dimension containing several reactants. Let $[C(t)]$ be the concentrations vector at instant t. In this medium m chemical reactions occur. Their respective speeds are given by vectorial functions $f_i,\ 1 \leq i \leq m$, whose arguments are time and concentrations vector. The evolution in time of reactants concentrations are classicaly described by the differential system

$$\frac{d}{dt}[C(t)] = (f_1 + f_2 + \cdots + f_m)(t, C[t]), \tag{1}$$

under conditions $C[t_0]$ for concentrations at initial instant. Such systems are numericaly solved by the mean of very precises algorithms [CL1,HN1], which allows computation of all concentrations at each instant of the discretised time : for one step methods, the concentrations vector C_{n+1} at instant t_{n+1} is computed from the same vector at instant t_n, named C_n. This leads to a computation algorithm such as below :

$$\begin{aligned} C_0 &= C[t_0] \\ C_{n+1} &= C_n + h_n \Phi_{f_1+\cdots+f_m}(t_n, C_n, h_n) \end{aligned} \tag{2}$$

where $h_n = t_{n+1} - t_n$, $\Phi_{f_1+\cdots+f_m}$ is a function dependent on the sum of f_i speeds, and which characterizes the chosen algorithm. As we stated, here reactions are supposed to be simultaneous and the main drawback of this modelisation is its staticness : adding or removing a reaction at runtime implies rewriting the system and reruning the program, which is unsuitable for complex system simulation and runtime modification of these systems. Our method also uses a classical resolution algorithm but applies it for each reaction during the same time-step. Let's consider an elementary example with two reactions, whose speeds are f_1 and f_2. As an alternative to the numerical computation of the system (1) (when $m = 2$) using algorithm (2), that is,

$$C_{n+1} = C_n + h_n \Phi_{f_1+f_2}(t_n, C_n, h_n), \tag{3}$$

we propose a *reaction-agent version* of this algorithm :

$$\begin{aligned} C_\star &= C_n + h_n \Phi_{f_1}(t_n, C_n, h_n) \\ C_{n+1} &= C_\star + h_n \Phi_{f_2}(t_n, C_\star, h_n) \end{aligned} \tag{4}$$

or, equiprobably,

$$\begin{aligned} C_\star &= C_n + h_n \Phi_{f_2}(t_n, C_n, h_n) \\ C_{n+1} &= C_\star + h_n \Phi_{f_1}(t_n, C_\star, h_n) \end{aligned} \tag{5}$$

Thus, in a single time-step, the algorithm is here applied two times : once for each reaction. Each application takes into account the state of the system at the current time. In order to avoid bias, at each time step a random arrangement of reaction-agents operations is performed.

3 Formalization and principal results

We now give the mathematical formalization of our reaction-agent model, and the validating results we have obtained. The natural integers ring is called $\mathbb{N}$, $\mathbb{R}$ is the reals

field, and S_m the permutations of order m group [Ca1]. For the sake of simplicity we only consider differential systems of a single equation; however definitions and results are easily generalizable. More details about numerical resolution of ordinary differential equations can be found in [HN1].

Remark 1. We have also adapted this autonomous agents point of view for classical multiple steps methods, or for implicits methods [HN2] : we develop this point in section 4. Convergence and stability features are better for these methods than for single step methods. However these methods not only conflict with principles of multi agents systems whose behaviour is markovian; but moreover they rule out the ability to modify the number of agents at runtime.

3.1 General definition

Definition 1. *Let*

$$y_{n+1} = y_n + h_n \Phi_f(t_n, y_n, h_n) \tag{6}$$

be a one step method for Cauchy problem resolution

$$\begin{cases} y(t_0) = y_0 \\ y'(t) = f(t, y(t)). \end{cases} \tag{7}$$

Let $m \in \mathbb{N}^*$. We call reaction-agent version of method (6)*, for resolution of problem*

$$\begin{cases} y'(t) = (f_1 + f_2 + \cdots + f_m)(t, y(t)) \\ y(t_0) = y_0 \end{cases} \tag{8}$$

the method given by

$$y_{n+1} = y_n + h_n \Phi_{\sigma_n}(t_n, y_n, h_n) \tag{9}$$

defined by an equiprobable choice, at each time step $n \to n+1$, of $\sigma_n \in S_m$, and by relations

$$\begin{array}{rl} & y_{\star 1} = y_n + h_n \Phi_{f_{\sigma_n(1)}}(t_n, y_n, h_n) \\ \forall i,\ 1 \leq i \leq m-1, & \\ & y_{\star i+1} = y_{\star i} + h_n \Phi_{f_{\sigma_n(i+1)}}(t_n, y_{\star i}, h_n) \\ & y_{n+1} = y_{\star m} \end{array} \tag{10}$$

Example 1. We remind the reader that for Cauchy problem resolution (7), order 2 Runge-Kutta method is given by

$$y_{n+1} = y_n + h_n \Phi_f(t_n, y_n, h_n)$$

where

$$\Phi_f(t, y, h) = f(t + \frac{h}{2}, y + \frac{h}{2} f(t, y)).$$

The matching reaction-agent version for resolution of problem (8) is given by definition 1, where $\forall i,\ 1 \leq i \leq m$,

$$\Phi_{f_i}(t, y, h) = f_i(t + \frac{h}{2}, y + \frac{h}{2} f(t, y)).$$

For instance, two reaction-agents case leads to

$$y_{n+1} = y_n + h_n \Phi_{\sigma_n}(t_n, y_n, h_n)$$

with, equiprobably,

$$\begin{array}{l}\Phi_{\sigma_n}(t,y,h)\\ = f_1(t+\frac{h}{2}, y+\frac{h}{2}f_1(t,y))\\ + f_2\Big(t+\frac{h}{2}, y+h f_1(t+\frac{h}{2}, y+\frac{h}{2}f_1(t,y))\\ \qquad\qquad + \frac{h}{2}f_2(t, y+h f_1(t+\frac{h}{2}, y+\frac{h}{2}f_1(t,y)))\Big)\\ \text{if } \sigma_n = \mathrm{Id}\end{array}$$

or

$$\begin{array}{l}\Phi_{\sigma_n}(t,y,h)\\ = f_2(t+\frac{h}{2}, y+\frac{h}{2}f_2(t,y))\\ + f_1\Big(t+\frac{h}{2}, y+h f_2(t+\frac{h}{2}, y+\frac{h}{2}f_2(t,y))\\ \qquad\qquad + \frac{h}{2}f_1(t, y+h f_2(t+\frac{h}{2}, y+\frac{h}{2}f_2(t,y)))\Big)\\ \text{if } \sigma_n(1) = 2.\end{array}$$

3.2 Average order of a reaction-agent method

Acoording to definition 1, the computation of y_{n+1} in function of y_n depends upon the choice of the permutation σ_n. Thus we have to keep this in mind to characterize the convergence. With the same notations as above, the average evolution on one step is given by

$$\begin{array}{c} y_{n+1} = y_n + \bar{\Phi}(t_n, y_n, h_n),\\ \bar{\Phi} = \dfrac{1}{m!}\displaystyle\sum_{\sigma_n \in S_m} \Phi_{\sigma_n}\end{array} \tag{11}$$

Definition 2. *The order (in the usual sense) of the method given by (11) is called the* average order *of the method given by definition 1.*

Remark 2. This definition is consistent, for during the execution of reaction-agent algorithm, all elements of S_m intervene with the same probability, even though only one of these elements is chosen at each time step. As we consider the average of $m!$ algorithms, each one bound to one permutation, a reaction-agent method of average order p will in fact be less efficient than a method of order p in the classical sense. Actually, we prove that its efficiency is intermediate between two methods of order $p-1$ and p, respectively. Example in section 5 illustrates this fact.

3.3 Main results

We enounciate here our main results about convergence of reaction-agent methods. We just provide the main ideas of the proofs, detailed ones can be asked to first author.

Theorem 1. *1. Reaction-agent version of Euler's method is convergent of average order* 1.

2. *Reaction-agent version of order* 2 *Runge-Kutta method is convergent of average order* 2.
3. *Consider a one step method, convergent of order* $p \geq 3$. *Thus its reaction-agent version is convergent of average order* 2.

Theorem 1 claims in substance that there is no point in using reaction-agent's version of a Runge-Kutta method of order ≥ 3.

One can regret that the efficiency of our reaction-agent model is not better. However, we stress again the point that it is the only model -to our knowledge- that enables *in virtuo* experimentation.

Proof. We now give a few elements about the proof of theorem 1, which comprises two parts : we first prove the stability of a given reaction-agent method, then we evaluate the consistency error. We keep the same notations as in definitions 1 and 2.

1. Stability.
   We suppose that functions Φ_{f_i} are lipschitzian in y. Thus there are $(\lambda_1, \lambda_2, \ldots, \lambda_m) \in \mathbb{R}^m$ such that :
   $$|\Phi_{f_i}(t, y_2, h) - \Phi_{f_i}(t, y_1, h)| \leq \lambda_i |y_2 - y_1| \tag{12}$$
   This implies the following lemma, proved by induction :
   $$\begin{array}{l} |\Phi_{\sigma_n}(t, y_2, h) - \Phi_{\sigma_n}(t, y_1, h)| \\ \quad \leq \sum_{i=1}^{m} \lambda_i |y_2 - y_1| \\ \qquad + h \sum_{i<j}^{m} \lambda_i \lambda_j |y_2 - y_1| \\ \qquad + \cdots \\ \qquad + h^{m-1} \lambda_1 \lambda_2 \cdots \lambda_m |y_2 - y_1|. \end{array} \tag{13}$$
   As Φ_{σ_n} is lipschitzian, the stability is proved for reaction-agent version of any classical method.
2. Consistency.
   According to the following lemma :

   Lemma 1. *The algorithm*
   $$y(t_0) = y_0, \quad y_{n+1} = y_n + h_n \Phi_f(t_n, y_n, h_n) \tag{14}$$
   is consistent of order p *if and only if*
   $$\begin{array}{l} \Phi_f(t, y, h) = \displaystyle\sum_{k=1}^{p} \frac{h^{k-1}}{k!} f^{[k-1]}(t, y) + O(h^p), \\ \text{where } f^{[n]}(t, z(t)) = \dfrac{d^n}{dt^n}\Big(f(t, z(t))\Big). \end{array} \tag{15}$$
   Thus, we end by establishing the following equality :
   $$\begin{array}{l} \dfrac{1}{m!} \displaystyle\sum_{\sigma_n \in S_m} \Phi_{\sigma_n}(t, y, h) \\ \qquad = \displaystyle\sum_{k=1}^{p} \frac{h^{k-1}}{k!} \Big(\sum_{i=1}^{m} f_i\Big)^{[k-1]}(t, y) + O(h^p), \end{array} \tag{16}$$
   which is true if and only if $p \leq 2$.

□

4 Multistep and implicit methods

Simulation of systems submitted to constant perturbations *a priori* empeaches the use of implicit or multistep methods [HN1,HN2], since the number of constituants of the system can change from one time step to the other. However, in the case where, during the simulation, the system is stable, involving for instance a constant number of chemical reactions, we wish to keep the efficiency of such methods. We can keep the point of view of autonomous agents and use implicit and multisteps methods in this case, where reaction-agent model is unprofitable.

4.1 Description

Recall that if we want to solve the Cauchy problem (1), Adams $k+1$-step classical methods [HN1] are based on algorithms like :

$$C_{n+1} = C_n + h_n \sum_{i=-1}^{k-1} \beta_i (f_1 + \cdots + f_m)(t_{n-i}, C_{n-i}), \tag{17}$$

where the sum $\beta_i(f_1+\cdots+f_m)(t_{n-i},C_{n-i})$ is the interpolation polynomial of function $f_1+\cdots+f_m$ at points (t_l,C_l), $n-k+1 \leq l \leq n+1$. Or, this can also be written, for any permutation σ_n in S_m,

$$\begin{aligned} C_{\star 1} &= C_n + h_n \textstyle\sum_{i=-1}^{k-1} \beta_i f_{\sigma_n(1)}(t_{n-i}, C_{n-i}) \\ C_{\star 2} &= C_{\star 1} + h_n \textstyle\sum_{i=-1}^{k-1} \beta_i f_{\sigma_n(2)}(t_{n-i}, C_{n-i}) \\ &\vdots \\ C_{\star m} &= C_{\star(m-1)} + h_n \textstyle\sum_{i=-1}^{k-1} \beta_i f_{\sigma_n(m)}(t_{n-i}, C_{n-i}) \\ C_{n+1} &= C_{\star m}. \end{aligned} \tag{18}$$

The algorithm described above enables one to keep the point of view of autonomous agents carrying their own execution of implicit and multistep algorithm.

4.2 Simulation strategy

Hence, simulation of chemical kinetics phenomenons using reaction-agents can be summarized the following way :

- If, during the simulation, the system is perturbed by a new phenomenon (e.g. a new chemical reaction), a one step reaction-agent method is embraced, to take this perturbation into account.
- During a long non-perturbation period, we embrace a multistep Adams method, however keeping the autonomy principiæ for our multi-agent system.

5 Example

Recall that our reaction-agent model is not intented to simulate chemical kinetics phenomenons when the number of reactions is constant. However, in order to illustrate results of section 3, we consider such a case.

We take, as an example of application of our method, the mathematical model of the extrinsic pathway of blood coagulation published by [LB1], see figure 2. In their study, they used a kinetic model based on ordinary differential equations in order to show that factor IXa could be a major product of the extrinsic pathway. We have implemented this model and solved it using either our reaction-agent (here denoted RA) methods, either classical methods. When the system is solved using our reaction-agent methods, a Euler or an order 2 Runge-Kutta or an order 4 Runge-Kutta method is embedded in each reaction-agent. When the system is solved using classical methods, a euler or an order 2 Runge-Kutta or an order 4 Runge-Kutta is used. We focus solely on factor Xa generation (*i.e.* only on the solution of one equation). We have compared the local error obtained on 6 points with each method (RA euler, RA rk2, RA rk4, ODE euler, ODE rk2, ODE rk4) to the solution given when the system is solved using an adaptative step size Runge-Kutta-Fehlberg method (here denoted ODE rk4 and supposed to be the exact solution). Results are shown in table 1.

Table 1. Results. The set of ODE of the kinetic model is solved using either our reaction agent (RA) method, either classical methods. Local errors (obtained with a constant step size of 1.0 s) on 6 points are reported. We intentionally use a huge step size, in order to get a significant error.

time (s)	RA euler	RA rk2	RA rk4
50	2.77 %	0.30 %	0.54 %
100	3.26 %	0.33 %	0.62 %
150	3.67 %	0.41 %	0.68 %
200	4.10 %	0.50 %	0.58 %
250	4.75 %	0.55 %	0.47 %
300	5.65 %	0.86 %	0.48 %
time (s)	**ODE euler**	**ODE rk2**	**ODE rk4**
50	2.93 %	0.05 %	0.00 %
100	2.59 %	0.04 %	0.00 %
150	2.39 %	0.04 %	0.00 %
200	2.16 %	0.04 %	0.00 %
250	1.90 %	0.04 %	0.00 %
300	1.61 %	0.04 %	0.00 %

As expected, when classical methods are used, the higher the order of the method, the smaller the local error. This table confirms that the local error obtained using the RA Euler method is approximatively of the same order than the classical one. The RA order 2 Runge-Kutta method gives a smaller error than the Euler one but the classical order 2 Runge-Kutta is a bit more precise. The RA order 4 Runge-Kutta method shows a local

error similar to the RA order 2 Runge-Kutta one, which confirms that the precision of the reaction-agent method could not exceed order 2.

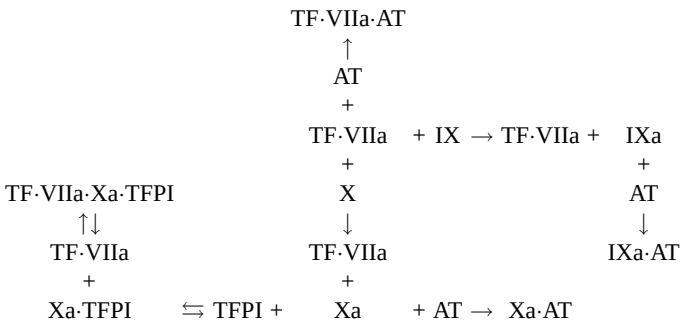

Fig. 2. Kinetic model of blood coagulation extrinsic pathway proposed by [LB1].

6 Conclusion

We have exposed the proof of efficiency of reaction-agent based methods for the *in virtuo* simulation of biological chemical kinetics phenomenons. We have chosen to autonomize reactions. This leads to a lesser convergence than the one obtained by one step classical methods, since this order is at best quadratic, even if superior order classical method is chosen. Nevertheless, as far as we know, reaction-agent model is the only one which allows *in virtuo* simulation of a true dynamic chemical kinetics, as can be found only in life.

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