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# A SIMPLE MEMBRANE COMPUTING METHOD FOR SIMULATING BIO-CHEMICAL REACTIONS

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**Abstract.** There are two formalisms for simulating spatially homogeneous chemical system; the deterministic approach, usually based on differential equations (reaction rate equations) and the stochastic approach which is based on a single differential-difference equation (the master equation). The stochastic approach has a firmer physical basis than the deterministic approach, but the master equation is often mathematically intractable. Thus, a method was proposed to make exact numerical calculations within the framework of the stochastic formulation without having to deal with the master equation directly. However, its drawback remains in great amount of computer time that is often required to simulate a desired amount of system time. A novel method that we propose is Deterministic Abstract Rewriting System on Multisets (DARMS), which is a deterministic approach based on an approximate procedure of an exact stochastic method. DARMS can produce significant gains in simulation speed with acceptable losses in accuracy. DARMS is a class of P Systems in which reaction rules are applied in parallel and deterministically. The feasibility and utility of DARMS are demonstrated by applying it to the Oregonator, which is a well-known model of the Belousov-Zhabotinskii (BZ) reaction. We also consider 1-dimensional and 2-dimensional cellular automata composed of DARMS and confirm that it can exhibit typical pattern formations of the BZ reaction. Since DARMS is a deterministic approach, it ignores the inherent fluctuations and correlations in chemical reactions; they are not so significant in spatially homogeneous chemical reactions but significant in bio-chemical systems. Thus, we also propose a stochastic approach, Stochastic ARMS (SARMS); SARMS is not an exact stochastic approach, but an approximate procedure of the exact stochastic method.

## 1 INTRODUCTION

There are two formalisms for describing the time behavior of spatially homogeneous chemical reactions: the *deterministic approach* regards the time evolution as a wholly predictable process which is governed by a set of coupled reaction rate equations (RRE), while *the stochastic approach* regards the time evolution as a kind of random process which is governed by the *chemical master equation* (CME).

Gillespie [11, 12] proposed a stochastic method of simulating chemical kinetics, which has a firmer physical basis than the deterministic formulation. Since the stochastic master equation is often mathematically intractable, a Monte Carlo procedure is used to simulate the time evolution of the given chemical system. Unlike conventional stochastic methods used for numerically solving the deterministic reaction-rate equation, the Gillespie method never approximates infinitesimal time increments $dt$ by finite time steps. So the Gillespie method is an exact method for simulating chemical reactions, but it requires a great amount of computer time. Therefore, an approximate procedure is needed that in some circumstances can produce significant gains in simulation speed with acceptable losses in accuracy; such a procedure is, for instance, the "$\tau$-leap" method.

In what concerns the relationship between P systems and stochastic methods, the *dynamical probabilistic P systems* [23] have been proposed, where probabilities are associated with the rules and these values vary during the evolution of the system [3], according to the concept of *Mass Action Law*. Also Gillespie's $\tau$-leap method has been introduced in P systems[3].

Manca proposed a biologically inspired procedure, *Metabolic-P Algorithm* (MPA) [17], that can be employed to simulate the dynamics of many biological systems. The MPA can be embedded in the P systems [21] framework in the form of an *MP system* [2].

The first version of the MPA and classical version of the MP systems are inspired by the *Mass Action Law*, where kinetic rates (*rate constants*) are used to partition the mass between the rules of the system. Then the concept of kinetic rate is generalized into the *time-varying reaction maps*, where functions are defined over the state of the system instead of merely using constants [2]. Furthermore, the formalism of the MPA is extended to *MP Graphs*, which allow us to analyze an MP system as a stoichiometric network [18].

## 2 ABSTRACT REWRITING SYSTEM ON MULTISETS, ARMS

ARMS was proposed in [24] as an abstract model of chemical reactions, *Artificial Chemistry* (AC), in the context of the Artificial Life[1]. In this framework, we computationally characterized the *Edge of Chaos* [25] through investigating the relationship between ARMS and Cellular Automata, we showed how (computational) living things emerge from the chemical evolution and how do they evolve by using

[1] [5] is a comprehensive review of the Artificial Chemistry, including ARMS.

an ARMS with membranes; we applied this evolutional system to solve a simple mathematical problem [26]. Furthermore, we proposed a model of evolutional dynamics for the *proto-enzyme* through a evolutional reaction network modeled by an ARMS, where repeated auto-catalytic reaction networks emerged and were catastrophically destroyed [29][2]. Beyond the Artificial Life, ARMS has been used in various fields, such as ecology [28], medical science [31][3], environment engineering [15, 16] and so on.

Apart from AC, ARMS has been considered as an expression of the CME, which is a stochastic expression of the RRE. We rigidly proved that an ARMS can be regarded as a CME, and through continuous approximation, the deterministic RRE, which is denoted by a set of ordinal differential equations, can be obtained from an ARMS [27]. We have used ARMS for modeling bio-chemical systems, we have modeled bio-chemical systems such as the P53 signaling networks [30], and *Belouzov-Zhabotinskii* (BZ) reaction [27, 34, 35, 31]. Since ARMS is based on the RRE, it is related to the probabilistic P systems [21], MA [17] and MP systems [2].

Basically, an ARMS is a construct $\Gamma = (A, w, R)$, where $A$ is an alphabet, $w$ is a multiset present in the initial configuration of the system, and $R$ is the set of multiset rewriting rules.

Let $A$ be an *alphabet* (a finite set of abstract symbols). A *multiset* over $A$ is a mapping $M : A \mapsto \mathbf{N}$, where $\mathbf{N}$ is the set of natural numbers; 0, 1, 2,.... For each $a_i \in A$, $M(a_i)$ is the *multiplicity* of $a_i$ in $M$, we also denote $M(a_i)$ as $[a_i]$.

We denote by $A^{\#}$ the set of all multisets over $A$, with the empty multiset, $\emptyset$, defined by $\emptyset(a) = 0$ for all $a \in A$.

A multiset $M : A \mapsto \mathbf{N}$, for $A = \{a_1, \ldots, a_n\}$ is represented by the state vector $w = (M(a_1), M(a_2), \ldots, M(a_n))$, $w$. The union of two multisets $M_1, M_2 : A \mapsto \mathbf{N}$ is the addition of vectors $w_1$ and $w_2$ that represent the multisets $M_1, M_2$, respectively. If $M_1(a) \leq M_2(a)$ for all $a \in A$, then we say that multiset $M_1$ is included in multiset $M_2$ and we write $M_1 \subseteq M_2$.

A *reaction rule* $r$ over $A$ can be defined as a couple of multisets, $(s, u)$, with $s, u \in A^{\#}$. A set of reaction rules is expressed as $R$. A rule $r = (s, u)$ is also represented as $r = s \rightarrow u$. Given a multiset $w \subseteq s$, the application of a rule $r = s \rightarrow u$ to the multiset $w$ produces a multiset $w'$ such that $w' = w - s + u$. Note that $s$ and $u$ can also be zero vector (empty).

The *reaction vector*, $\nu_{ji}$ denotes the change of the number of $a_i$ molecules produced by one reaction of rule $r_j$.

**Chemical Kinetics.** A living system is a huge bio-chemical system and it is not easy to understand the whole reaction mechanism, but a plenty of bio-chemical experimental data, such as reaction rates, will give us hints to expose the mechanism.

[2] [6] also reported this type of behavior by using a replicator system.

[3] In this paper, we address the modeling of *inflammatory response* caused by external injury.

Chemical kinetics is the study of reaction rates in chemical reactions and has been described by the reaction rate equation (RRE), which is a set of coupled ordinary differential equations. RRE links the reaction rate to the concentration of each reactant and describes the time evolution as a *continuous deterministic* process.

For a generic chemical reaction $A + B \to C$, the RRE is expressed as

$$\frac{d[c]}{dt} = v = k[A][B],$$

where $[X]$ ($X$ is $A$ or $B$) denotes the concentration of $X$ (usually in mol/litre), and $k$ is a *rate constant*. A rate constant is not really a constant but includes everything that affects the reaction rate besides concentration, such as temperature, ionic strength or surface area of the absorbent, etc. Usually (and in this paper), the reaction rate $v$ is expressed in mol/sec.

### 2.1 ARMS with Chemical Kinetics

We modify the ARMS for modeling chemical kinetics and this enables us to use experimentally obtained reaction rates directly, similarly to the derivation of the Gillespie's "$\tau$-leap method" [13].

In order to handle experimental data, we employ multisets with real multiplicities; such a multiset $X : A \mapsto \mathbf{R}$ for $A = \{a_1, \ldots, a_n\}$ is represented by the state vector $\mathbf{x} = (X(a_1), X(a_2), \ldots, X(a_n))$. $X(a_i)$ denotes the molar concentration of specie $a_i$.

Let us assume that there are $N \geq 1$ molecular species $\{a_1, \ldots, a_n\}, a_i \in A$ that interact through reaction rules $R = \{r_1, \ldots, r_m\}$. As the time evolution of $\mathbf{x}$ unfolds from a certain initial state, let us suppose the state transition of the system to be recorded by marking on a time axis the successive instants $t_1, t_2, \ldots$ as $X(t_j)$ $(j = 1, 2, \ldots)$. We specify the dynamical state of $\mathbf{x}(t) \equiv (X(a_1(t), X(a_2(t)), \ldots, X(a_N(t)))$, where $X(a_i(t))$ is the molar concentration of $a_i$ specie at time $t$, $t \in \mathbf{R}$.

**Chemical Kinetics.** We assume that all chemical reactions take place in a well-stirred reactor; this assumption is required due to the strong dependence of the reaction rate on the concentration of the reagent species.

We define the function $f_j$, called the *propensity function* for $r_j \in R$ by

$$f_j(x) = c_j h_j, \tag{1}$$

where $c_j$ denotes the average probability that a particular combination of $r_j$ reactant molecules will react in the next infinitesimal time interval $dt$ and $h_j$ is the number of possible combinations of the species of $r_j$ in $dt$.

$f_j\mathbf{x}(t)dt$ means that the probability that reaction $r_j$ will occur in the next infinitesimal time interval $[t, t + dt)$, $(j = 1, \ldots, m)$.

The time evolution of $\mathbf{x}(t)$ is a jump Markov process on the $N$-dimensional non-negative lattice. In this case, an ARMS has a *macroscopically infinitesimal*

*time scale*, $\Delta$, where reaction rules can be applied several times simultaneously, yet since the stoichiometrical change of the state during $\Delta$ is small enough, none of the propensity functions changes appreciably.

The parameter $\Delta$ corresponds to $\tau$ (small time interval) in the Gillespie's method [13] and it satisfies the *Leap Condition* given below; an amount $\Delta$ that spans a *very large* number of applying every reaction rules *still* satisfies the Leap Condition.

**Leap Condition:** We require $\Delta$ to be small enough that the change in the state during $[t, t+\Delta]$ will be so small that no propensity function will suffer an appreciable (i.e., macroscopically noninfinitesimal) change in its value.

We also assume that the number of applications of each reaction rule in $\Delta$ obeys

$$\langle P(f_j(\mathbf{x}), \Delta\rangle = f_j(\mathbf{x})\Delta \gg 1 (\forall j = 1, \ldots, m), \tag{2}$$

where $P(f_j(\mathbf{x}), \Delta)$ is the *Poisson* random variable, which indicates the number of reactions that occur in $\Delta$.

Here, let us consider the probability function $Q$, defined by $Q(z_1, \ldots, z_k|\Delta, \mathbf{x}, t)$, which means the probability, given $\mathbf{X}(\mathrm{t}) = \mathbf{x}$, that in the time interval $[t, t+\delta)$ exactly $z_j$ times of rule applications or $r_j$ will occur, for each $j = 1, \ldots, m$. $Q$ is evidently the joint probability density function of the $M$ integer random variables, $Z_j(\Delta, \mathbf{x}, t)$ means the number of times, given $\mathbf{X(t)}$=$\mathbf{x}$, that reaction rule $r_j$ will apply in the time interval $[t, t+\Delta)$ $(j = 1, \ldots, m)$.

If the equation (2) is satisfied, the *Poisson* random numbers will be practically indistinguishable from *normal* random numbers, which are uncorrelated statistically independent normal random variables with mean 0 and variance 1.

Then the jump Markov process can be approximated by the *continuous* Markov process defined by the standard form of *chemical Langevin equation* (CLE).

$$\begin{aligned}\lambda_i = \sum_{j=1}^{m} z_j \nu_{ij} \quad &= \quad \sum_{j=1}^{m} f_j \nu_{ji} = \sum_{j=1}^{m} [f_j(\mathbf{x})\Delta + (f_j(\mathbf{x})\Delta)^{\frac{1}{2}} n_j]\nu_{ji} = \\ &\sum_{j=1}^{m} \nu_{ji} f_j(\mathbf{x})\Delta + \sum_{j=1}^{m} \nu_{ji} f_j^{\frac{1}{2}}(\mathbf{x}) n_j \Delta^{\frac{1}{2}},\end{aligned} \tag{3}$$

where $n_j$ is temporally uncorrelated statistically independent normal random variable. Since $Z_j(\Delta, \mathbf{x}, t) = P(f_j(\mathbf{x}, \Delta))$, it is equal to $f_j(\mathbf{x})\Delta$, by the equation (2).

In case $f_j(\mathbf{x})\Delta \to \infty$, (2) implies that in the part $f_j(\mathbf{x})\Delta + (f_j(\mathbf{x}\Delta)^{\frac{1}{2}} n_j$ of the equation (3) the second term becomes negligibly small compared to the first term and $\lambda_i$ in the limit $(f_j(\mathbf{x})\Delta \to \infty)$, because

$$\begin{aligned}\lambda_i = \sum_{j=1}^{m} z_j \nu_{ji} \quad &= \quad \sum_{j=1}^{m} [f_j(\mathbf{x})\Delta]\nu_{ji} = \\ &\sum_{j=1}^{m} \nu_{ji} f_j(\mathbf{x})\Delta.\end{aligned} \tag{4}$$

This is the Euler formula (piecewise linear approximation) for numerically solving the RRE. It shows how to derive the continuous and deterministic RRE of traditional chemical kinetics from the stochastic method. Since $\nu_{ji} f_j(\mathbf{x})$ represents the stoichiometric change in the next infinitesimal time, it can be regarded as the reaction rate of $r_j$, $v_j$, and we obtain:

$$\lambda_i = \sum_{j=1}^{m} \nu_{ji} f_j(\mathbf{x})\Delta \equiv \sum_{j=1}^{m} v_j(\mathbf{x})\Delta. \tag{5}$$

In the Gillespie $\tau$ leap method, the number of applications of each rule within $\tau$ is randomly generated according to the *Poisson* or *Normal* distribution and $\lambda_i$ is calculated.

In the ARMS, $\lambda_i$ is calculated by using the reaction rate given by the equation (5). As in the numerically solving an ordinary differential equation of the form $dX/dt = f(X)$ by the Euler method, a leap down the stepwise time axis by $\Delta$ according to $X(t+\Delta) = X(t) + f(X(t))\Delta$ will produce errors whenever the function $f$ changes during that $\Delta$ increment.

It is well-known that the second-order Runge-Kutta procedure can reduce these errors; use the simple Euler method to estimate the "midpoint" value of $X$ during $\Delta$, and then calculate the actual increment in $X$ by evaluating the slope function $f$ at that estimated midpoint. The midpoint value can be obtained from the expected state change $\lambda$ as $\mathbf{x} + \frac{\lambda}{2}$. In the Gillespie's $\tau$ leap method, this procedure is used and it shows that this procedure can reduce numerical errors [13].

### 2.2 Algorithm of DARMS

In Deterministic Abstract Rewriting System on multisets (DARMS) [34], reaction rules are applied in maximally parallel and deterministic way. Hence, the DARMS accommodates P Systems, while it has background in theoretical chemistry.

**Step 0 (Initialization).** The time $t$ is set to 0 and the set of vectors $V = (\delta_1, \delta_2, \ldots, \delta_N)$ $(j = 1, 2, \ldots, m)$, expressing the stoichiometric change of each species, are initialized. Then all inputs of the system are assigned to their respective variables,

- $X(a_1), X(a_2), \ldots, X(a_N)$ are set to the initial quantities of species;
- $k_1, \ldots, k_m$ to set $m$ rate constants corresponding to the $m$ reactions;
- $t_{stop}$ to the ending instant of simulation;
- set the value of $\Delta$.

**Step 1 (Calculation of state change vector $\Lambda_t$).** According to reaction rules, stoichiometric change of each specie $\lambda_i$ is calculated as well as the state change vector; $\Lambda_t = (\lambda_1, \lambda_2, \ldots, \lambda_N)$ is calculated, where $\lambda_i = \sum_{j=1}^{m} \nu_{ji} v_j \mathbf{x}(t)\Delta$.

**Step 2 (System update and branching).** The quantity of each species and $t$ is updated, by using $\Lambda_t$ and $\Delta$:

$$\begin{aligned} \mathbf{x}(t) &= \mathbf{x}(t-\Delta) + \Lambda_{t-\Delta}, \\ t &:= t + \Delta. \end{aligned}$$

If $t \geq t_{stop}$ or if there are no reactions left in the reactor, the simulation is stopped and the results are sent to the output stream. Otherwise, the simulation returns to *Step 1*.

## 3 THE OREGONATOR

The Belouzov-Zhabotinskii (BZ) reaction displays a remarkable repertoire of exotic behavior, including periodic and chaotic temporal oscillations, multiple stable stationary states, temporally and spatially periodic expanding target patterns, rotating multi-armed spiral waves [9].

A simple abstract chemical scheme of BZ reaction has been proposed by Prigogine and co-workers [20] (in Brussels that is why J.J. Tyson named it "Brusselator") in the form of the following rules

$$\begin{aligned} A &\xrightarrow{k_1} X : (b_1), \\ B, X &\xrightarrow{k_2} Y : (b_2), \\ 2X, Y &\xrightarrow{k_3} 3X : (b_3), \\ X &\xrightarrow{k_4} E : (b_4), \end{aligned}$$

because in $(b_3)$ is third order in the concentrations of transient intermediates.

(Process A)
$$\begin{aligned} B_r^- + HOB_r + H^+ &\rightarrow B_{r2} + H_2O \quad (R1), \\ HB_rO_2 + B_r^- + H^+ &\rightarrow 2HOB_r \quad (R2), \\ B_rO_3^- + B_r^- + 2H^+ &\rightarrow HB_rO_2 + HOB_r \quad (R3) \end{aligned}$$

(Process B)
$$\begin{aligned} 2HB_rO_2 &\rightarrow B_rO_3^- \quad (R4), \\ B_rO_3^- + HB_rO_2 + H^+ &\rightarrow 2B_rO_2 + H_2O \quad (R5), \\ B_rO_2 + C_e(III) + H^+ &\rightarrow HB_rO_2 + C_e(IV) \quad (R6) \end{aligned}$$

(Process C)
$$\begin{aligned} CH_2(COOH)_2 &\rightleftharpoons (HO)_2C = CHCOOH \quad (C1), \\ (HO)_2C = CHCOOH + Br_2 &\rightarrow BrCH(COOH)2 + H^+ + B_r^- \quad (C2), \end{aligned}$$

Table 1. FKN mechanism

The chemical kinetic description of BZ reaction was put forward by Field, Kőrős (FKN) [7]. FKN (Table 1) can be considered as the best understanding of the process

by recognizing that there are two different overall processes that can occur in the system.

The FKN mechanism can be described as three concurrent (and at times competing) processes:

**Process A:** The three steps reduction of bromate to bromine.

**Process B:** The introduction of hypobromous acid to compete as a reducing agent for bromate.

**Process C:** The reduction of the catalyst formed from Processes A and B.

In Process A, we have the reduction of bromate ($B_rO_3^-$) to bromine ($Br$) by the reducing agent bromide ($Br^-$). This three-step process makes up $(R1) - (R3)$. As a result, the bromate is reduced, bromomalonic acid ($B_rMA$) is produced, and the concentration of bromide eventually falls below some critical level. It is at this point that Process B begins to dominate Process A: the hypobromous acid ($HB_rO_2$) begins to compete with the bromide to reduce the bromate. Reactions $(R5)$ and $(R6)$ constitute a two-step autocatalytic sequence. As a result, the amount of hypobromous acid increases at an accelerating rate and $C_e(IV)$ is produced. This causes the solution to change suddenly from red to blue (in the presence of a ferroin indicator). Then the $B_rMA$ and $C_e(IV)$ react causing the concurrent oxidation of the organic species and then it causes the solution change from blue to red (Process C).

Following the conventional notation used in this area, let

$$\begin{aligned} X &\equiv HB_rO_2 \text{ (hypobromous acid)}, \\ Y &\equiv B_r^- \text{ (bromide)}, \\ Z &\equiv C_e(IV) \text{ (cerium-4)}, \\ A &\equiv B_rO_3^- \text{ (bromate)}, \\ B &\equiv CH(COOH)_2 \text{ (organic species)}, \\ W &\equiv HOB_r, \\ H &\equiv H^+. \end{aligned}$$

The Oregonator scheme is outlined in Table 2.

Note the correspondence between the Oregonator scheme and the FKN mechanism: $(r_1)$ is equivalent to reaction (R2), $(r_2)$ is equivalent to reaction (R3), $(r_3)$ is equivalent to reaction (R4), $(r_4)$ is equivalent to the autocatalytic sequence given by $(R5) + 2(R6)$ and can be consolidated into the single reaction, and $(r_5)$ represents the organic species in Process C.

Field, Kőrős (FKN)[7] did not only propose the FKN chemical scheme but they also incorporated all kinetic data known at that time. These are called the FKN values[4]. The FKN rate constants have been successful at reproducing in computer

[4] It was later redefined and extended by Barkin et al. [1]

| | | |
|---|---|---|
| (Process A) | | |
| $X, Y, H$ | $\stackrel{k_1}{\rightarrow}$ | $2W : (r_1)$, |
| $A, Y, 2H$ | $\stackrel{k_2}{\rightarrow}$ | $X, W : (r_2)$, |
| (Process B) | | |
| $2X$ | $\stackrel{k_3}{\rightarrow}$ | $A, W, H : (r_3)$, |
| $A, X, H$ | $\stackrel{k_4}{\rightarrow}$ | $2X, 2Z : (r_4)$, |
| (Process C) | | |
| $B, Z$ | $\stackrel{k_5}{\rightarrow}$ | $0.5Y : (r_5)$. |

Table 2. Oregonator

simulations. However, Tyson pointed out that when the FKN values are propagated into the Oregonator model [8], FKN rate constants seem much too large and proposed "Lo" and "Hi" values [33]. Since then, several contributions were dedicated to examine its accuracy and confirmed that the "Lo" value is in accordance with experimental data. Field and Fősterling further refined to the "Lo" value [10]. In this paper, a combination of Tyson's "Lo" [33] and Field-Fősterling values [10] (TFF parameter) are used [19]: $k_1 : 10^6 M^{-2} S^{-1}, k_2 : 2M^{-3} S^{-1}, k_3 : 2 \times 10^3 M^{-1} S^{-1}, k_4 : 10M^{-2} S^{-1}, k_5 : B \times 2 \times 10^{-2} S^{-1}$, where $M$ stands for one molar, and $S$ stands for a second.

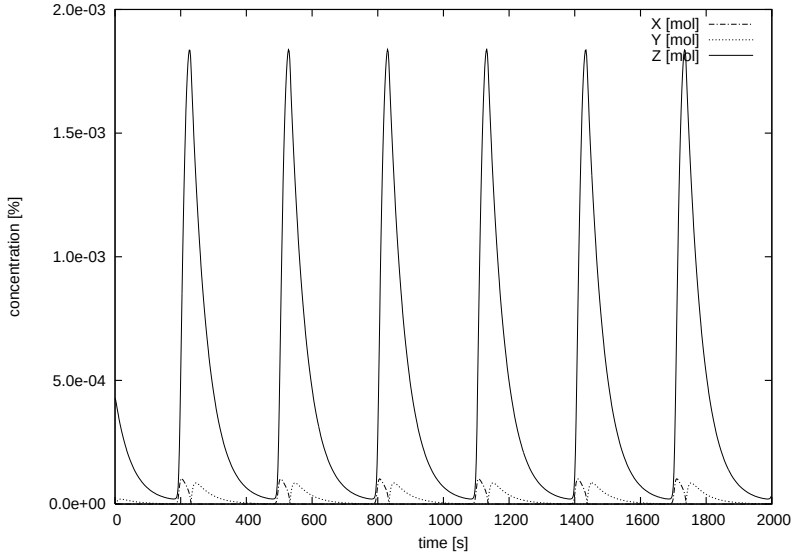


Fig. 1. DARMS, $\Delta = 0.0001$: Population dynamics of $X$, $Y$, $Z$, where the vertical axis illustrates the molar concentration of chemicals (mole) and the horizontal axis illustrates the time, where each step is $\Delta$. It shows a typical pattern of oscillations.

### 3.1 Simulation of the Oregonator

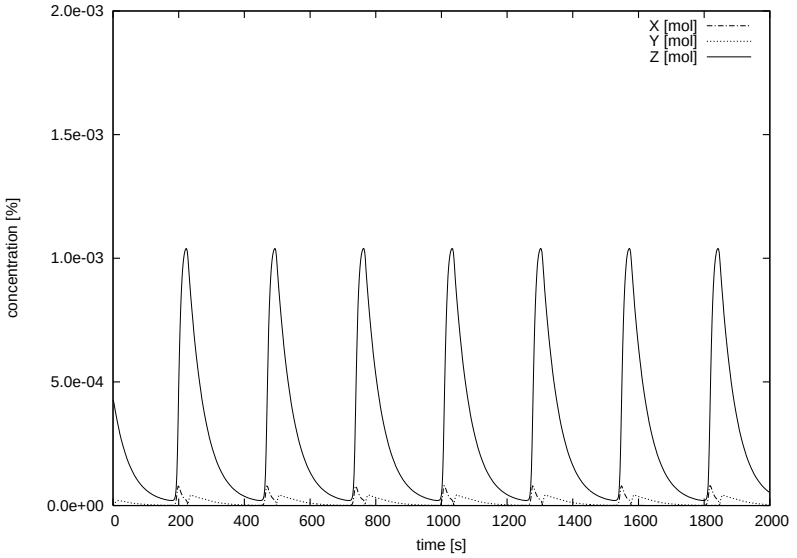


Fig. 2. DARMS, $\Delta = 0.1$: Population dynamics of $X$, $Y$, $Z$, where the vertical axis illustrates the molar concentration of chemicals (mole) and the horizontal axis illustrates the time, where each step is $\Delta$. The amplitudes of oscillations are smaller than the case when $\Delta$ is smaller than 0.1.

In the Oregonator [8], chemicals $A$ and $B$ are resources and it is assumed that they are continuously supplied or largely existing in comparison with other chemicals. $W$ is the final product of these reactions and typical oscillations among $X$, $Y$ and $Z$ emerge. Reactions of generating $X$ ($Hb_rO_2$) are triggers of oscillations and these reactions increase the concentration of $Z$ ($C_e^{4+}$) and then high concentration of $Z$ leads to reactions generating $Y$ ($B_r$); since this reaction required $Z$, the concentration of $Z$ is decreased.

We simulate the Oregonator by using the DARMS with the TFF parameter. We examine each case when $\Delta = 0.0001, 0.001, 0.01, 0.1, 1.0$. When the values of $\Delta$ are between 0.0001 and 0.01, the stoichiometric change of species show typical oscillations (Figure 1); these typical oscillations can also be seen through numerical simulation of the reaction rate equation that are expressed by a set of differential equations. At $\Delta = 0.1$, the amplitude of oscillation becomes small, while the patterns of oscillations were kept the same (Figure 2).

At $\Delta = 1.0$, the pattern of oscillations becomes different from the typical one, where the amplitude of oscillation of $X$ and $Z$ becomes small, and the amplitude of $Y$ declines to nearly zero (Figure 3). The reason is that the value of $\Delta$ becomes large: since the calculation of the DARMS requires piecewise linear approximation,

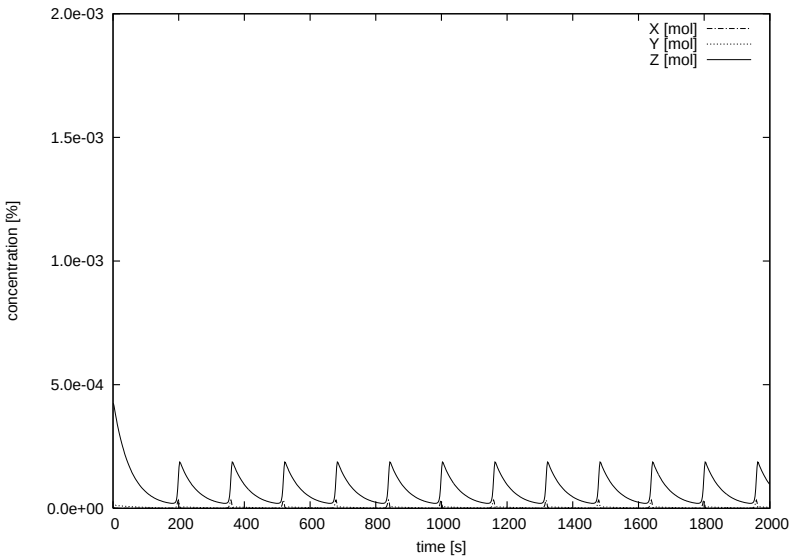


Fig. 3. DARMS, $\Delta = 1.0$: Population dynamics of $X$, $Y$, $Z$, where the vertical axis illustrates the molar concentration of chemicals (mole) and the horizontal axis illustrates the time, where each step is $\Delta$. The pattern of oscillation is different from the typical one.

as the $\Delta$ becomes larger, the quality of approximation decreases.

### 3.2 Simulation of Pattern Formation

In order to simulate pattern formation, we compose cellular automata by using the DARMS and call it Cellular Automata of Abstract Rewriting System on Multisets (CARMS) [35]. Let us assume that $n$ DARMSes are placed in a grid space. An $n$ dimensional CARMS is called $n$D-CARMS. A periodic boundary condition is assumed. Each of the DARMS in a CARMS is distinguished by lower and upper suffix; the lower suffix denotes the position of a DARMS in the grid space and the upper suffix denotes the evolution time. The multiset $M$ of a DARMS is denoted by the same suffixes of the DARMS. As for the calculation of diffusion, we use conventional explicit scheme of difference method [5] to solve partial differential equation of diffusion.

We use diffusion constants $D$ obtained by chemical experiments [19]; the diffusion constant ($\mathrm{cm}^2$/sec.) of $X, D_X$ and $Z, D_Z$ are $1.5 \times 10^{-5}$ and $D_X = 0.9 \times 10^{-5}$. The size of reactor of the 1D-CARMS is 6 cm, where 50 DARMSes are placed, while

[5] In order to improve the quality of the method, we should employ the Crank and Nicolson method [4]

in the 2D-CARMS the reactor is a 6 cm × 6cm square, where $50 \times 50$ DARMSes are placed. So, the distance between DARMSes is $\Delta x = \frac{6}{50}$ cm.

**Algorithm of CARMS.**

**Step 0 (Initialization).** The time $t$ is set to 0 and we initialize all DARMSes referred in *Step 0* of the Algorithm of the DARMS.

**Step 1 (Calculation of state change).**
- According to *Step 1* and *2* in the algorithm of the DARMS reactions of all DARMSes are calculated and each state is updated.
- $t := t + \Delta$.

**Step 2 (Calculation of diffusion).** Diffusions are calculated by the following method and each state is updated.

- – (1D-CARMS)

$$M_j^{t+1} = D_s \Delta \frac{(M_{j+1}^t - 2M_j^t + M_{j-1}^t)}{(\Delta x)^2},$$

  where $D_s$ denotes the diffusion constant of species $s$, and $\Delta x$ is the distance to the neighboring DARMS.
  - $t := t + t_{diff}$
- – (2D-CARMS)

$$M_{j,i}^{t+1} = D_s \Delta \frac{(M_{j+1,i}^t - 2M_{j,i}^t + M_{j-1,i}^t)}{(\Delta x)^2} + D_s \Delta \frac{(M_{j,i+1}^t - 2M_{j,i}^t + M_{j,i-1}^t)}{(\Delta x)^2},$$

  where $D_s$ denotes the diffusion constant of species $s$, and $\Delta x$ is the distance to the neighboring DARMS.
  - $t := t + t_{diff}$
- If $t \geq t_{stop}$ or if there are no reactions left in the reactor, the simulation is stopped and the results are sent to the output stream. Otherwise, the simulation returns to *Step 1*.

**1D-CARMS.** We assume that a reactor is homogeneous (well-stirred). However, if there is a focal excitation point, a traveling chemical wave pattern will appear from the point. In the chemical experiment of BZ reaction, usually an excitation point is generated by stinging a sliver stick, which evokes oxidation reaction[6].

In order to express the generation of the excitation point the CARMS, we change the state of the multiset of $D_{25}^{t_0}$, where the concentration of $X$ and $Y$ are smaller,

[6] Since fine refuses or defects in a reactor also evoke excitation points, well cleansed new vessel and super-pure water must be used.

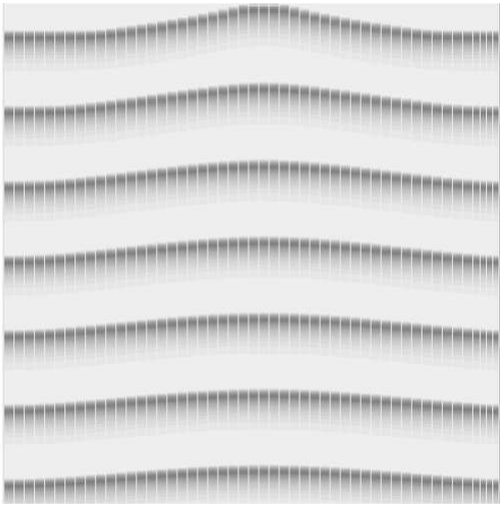

Fig. 4. Traveling wave from the focal excitation point in a 1D-CARMS with $\Delta = 0.01$, where thickness of color expresses the molar concentration of $Z$. In this figure, each of DARMS is placed horizontally and their time evolution is expressed vertically.

while that of $Z$ is larger. We confirm that a traveling wave emerges from $D_{25}^{t_0}$ (Figure 4).

**2D-CARMS.** A typical type of chemical waves in BZ reaction is a circle wave, where the chemical wave is evoked from an excitation point. We express the excitation point by changing the state of $D_{25,25}$ as in the 1D-CARMS (concentration of $X$ and $Y$ are small, while that of $X$ is large).

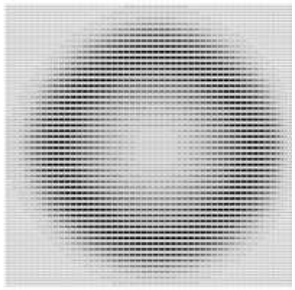

Fig. 5. A Cycle wave in 2D CARMS, where thickness of color expresses the molar concentration of $Z$. There are $50 \times 50$ DARMSes.

We confirm that a single wave emerges from the excitation point, as we can see in a chemical experiment (Figure 5).

Chemical waves in BZ reaction are non-linear waves. Where more than two waves collide, they will disappear and when more than two linear waves collide, they are linearly lapped.

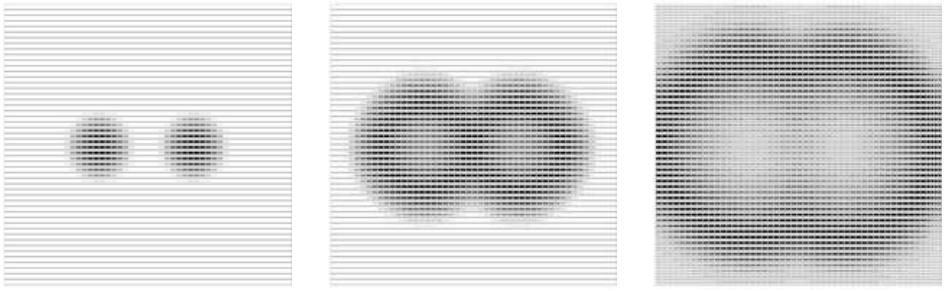

Fig. 6. When two waves collide, they disappear and merge into a single wave; the thickness of color expresses the molar concentration of $Z$

We set two excitation points in a 2D-CARMS and generate two cycle waves (left part of Figure 6); when two waves collide (middle part of Figure 6), their wave fronts disappear and they are merged into a single wave (right part of Figure 6).

## 4 DISCUSSION

In the case when $\Delta$ is small enough, the system becomes stochastic. A Stochastic Abstract Rewriting System on multisets (SARMS) is based on the assumption that $\Delta$ is small enough to apply only one rule between $t$ and $t+\Delta$, hence in the case when $\Delta$ is small enough, the SARMS is close to the Gillespie method without $\tau$-leap.

### 4.1 The Algorithm of SARMS

**Step 0 (Initialization).** Set the time variable $t$ to zero. Initialize the pseudo-random sequence generator. Then all inputs of the system are assigned to their respective variables:

- $X(a_1), X(a_2), \ldots, X(a_N)$ are set to the initial quantities of species;
- $k_1, \ldots, k_m$ to set $m$ rate constants corresponding to the $m$ reactions;
- $t_{stop}$ to the ending instant of simulation;
- set the value of $\Delta$;

**Step 1 (Reaction rate computation).** For each reaction $r_j$ $(j = 1, \ldots, m)$, the corresponding reaction rate $v_j$ is calculated as

$$v_j = k_i h_j$$

and

$$v_{all} = \sum_{j=1}^{m} v_j$$

is calculated.

**Step 2 (Monte Carlo step).** A random number $\gamma$ having a uniform distribution in the unit interval $[0, v_{all}]$ is generated. Then a rule to be applied is selected according to the appropriate probability distribution, by choosing that $j$ such that;

$$\sum_{v=1}^{j-1} v_v < \gamma < \sum_{v=1}^{j} v_v;$$

**Step 3 (System update and branching).** The rule $r_j$ selected at the previous step applied and the system is updated accordingly:

- $t := t + \Delta$;
- the population of $a_i$ involved in the reaction $r_j$ (either as reactants or as products) is updated according to the stoichiometry of the rule, reaction rate of $r_j$ and $\Delta$.

$$\delta_{a_i} = \nu_{ij} v_j \mathbf{x}(t)\Delta,$$

and $\mathbf{x}(t) = \mathbf{x}(t - \Delta) + \delta_{a_i}$.

If $t \geq t_{stop}$ or if there are no reactions left in the reactor, the simulation is stopped and the results are sent to the output stream. Otherwise, the simulation returns to *Step 1*.

When simulating the Oregonator, the DARMS and SARMS exhibit almost the same behavior (Figure 7). In the DARMS, since reaction rules are applied in parallel, the time evolution of the system is faster than the SARMS (Figure 7) and the frequency of oscillations of DARMS is higher, while the amplitudes are smaller than that of the SARMS.

Until the $\Delta$ is equal to or smaller than 0.04, SARMS exhibits almost the same oscillating patterns, however when $\Delta$ is equal to or larger than 0.05, the oscillating pattern is changed (Figure 8).

### 4.2 $\Delta$ and Rule Dynamics

We examine now how the value of $\Delta$ affects the time evolution of the system.

**DARMS.** We examine the derivation of $r_i$ for $\mathbf{x}(t)$, which is given by $D_{r_1}\mathbf{x}(t) = v_i\mathbf{x}(t)\Delta$. In order to investigate the contribution ratio (CR) of $r_i$, we calculate

$$C_{r_i} = \frac{D_{r_i}}{\sum_{j=1}^{m} D_{r_j}}.$$

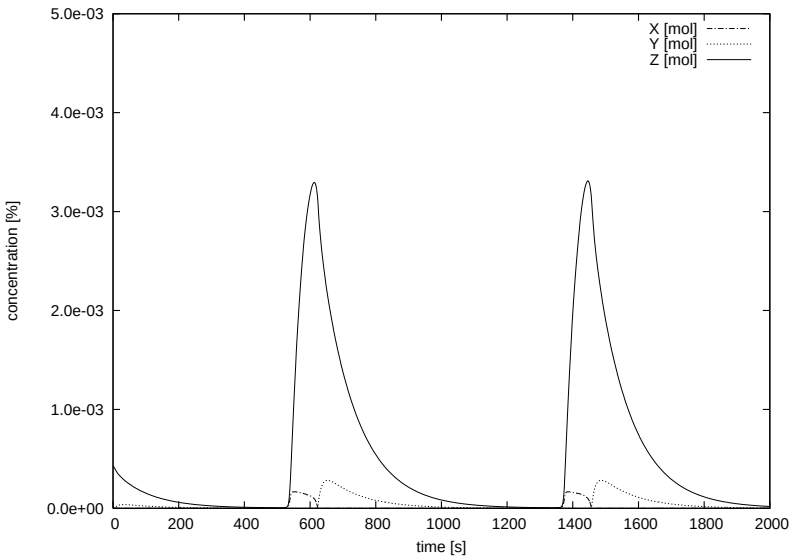


Fig. 7. SARMS, $\Delta = 0.0001$, population changes of $X$, $Y$ and $Z$

The schematic pattern of CR shows that the reaction mechanism of the Oregonator reflects the FKN mechanism. In the Oregonator, processes A, B and C are not triggered alternately, where process $C(r_5)$ is always triggered and $r_1$ (part of process A) is also always triggered. Switching from process A to B is not abrupt; when process A is dominant, the derivation of $r_4$ gradually becomes larger and it leads the switching between process A and B. On the other hand, switching from process B to A is abrupt. Even if $\Delta$ is changed, the schematic pattern of CR is almost the same: however, when $\Delta$ becomes large, $C_{r_3}$ becomes small. Since the schematic pattern of CR of $\Delta = 0.01$ and 0.001 are the same, $\Delta = 0.01$ can be considered as the appropriate value for simulating the Oregonator (Figure 9).

**SARMS.** In order to compare the deterministic modeling (DARMS) and the stochastic modeling (SARMS), we examine the schematic pattern of probability of rule selecting (SPP). It should be noted that this schematic pattern does not indicate derivations but probabilities.

When $\Delta$ is small, the SPP is almost the same as the CR of DARMS. It indicates that, in simulating the Oregonator, when $\Delta$ is small DARMS and SARMS will show the same results (Figure 10).

However, when $\Delta$ is large, they show different results (Figure 11). In SARMS, since the rate constant of $r_1$ ($10^6 M^{-2} S^{-1}$) is extremely larger than others, the probability of selecting $r_1$ is very large. Thus, if $\Delta$ becomes large, $\nu_{X1} v_{r_1} \Delta$ or $\nu_{Y1} v_{r_1} \Delta$ surpasses $[X]$ or $[Y]$ and $r_1$ cannot be applied. So, almost always $r_1$ is selected, but it cannot be applied, therefore the mechanism of the Oregonator loses its functionality.

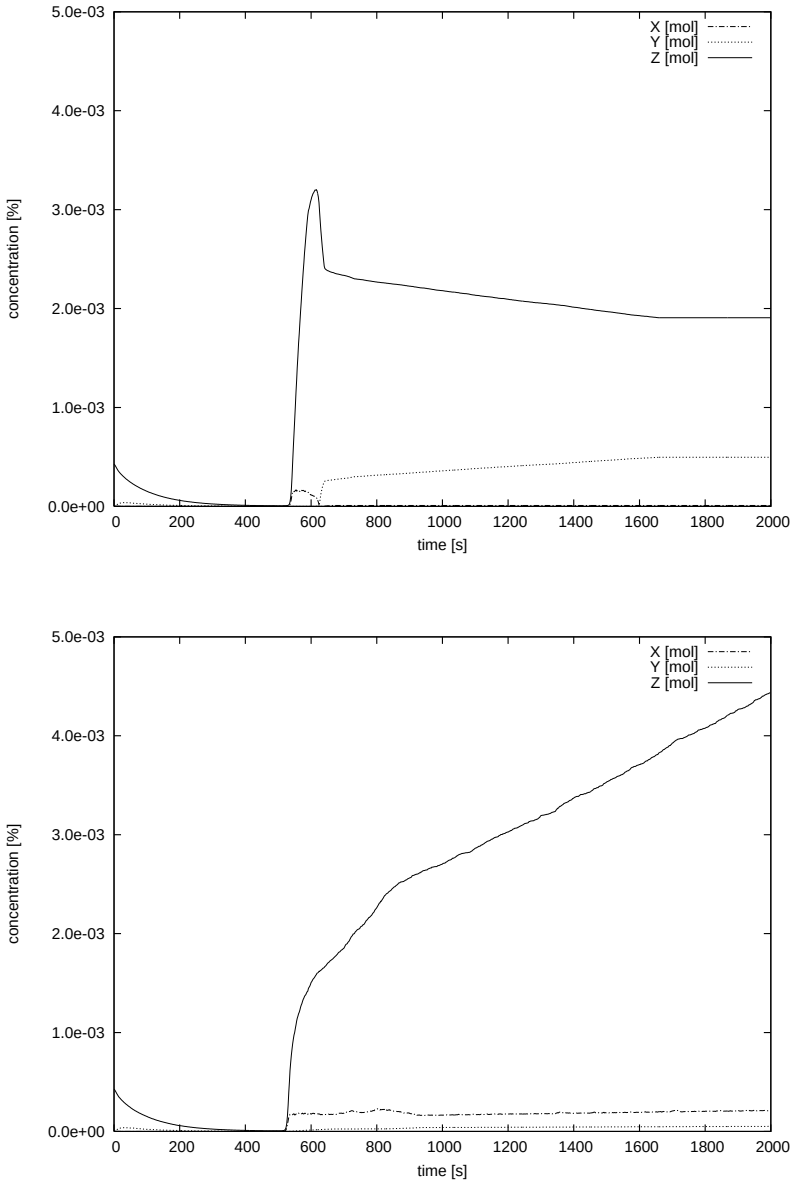


Fig. 8. SARMS $\Delta$=0.05, population changes of $X$, $Y$ and $Z$

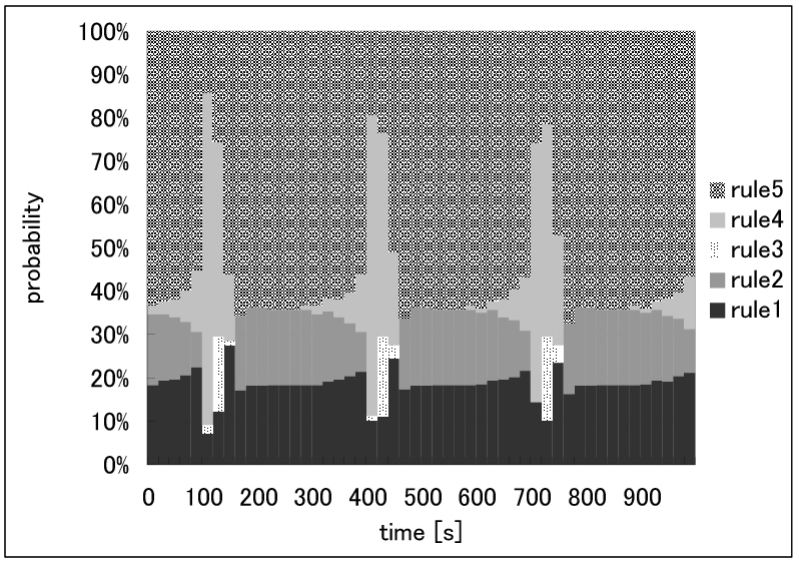


Fig. 9. Schematic plot of CR of DARMS, when $\Delta = 0.001$

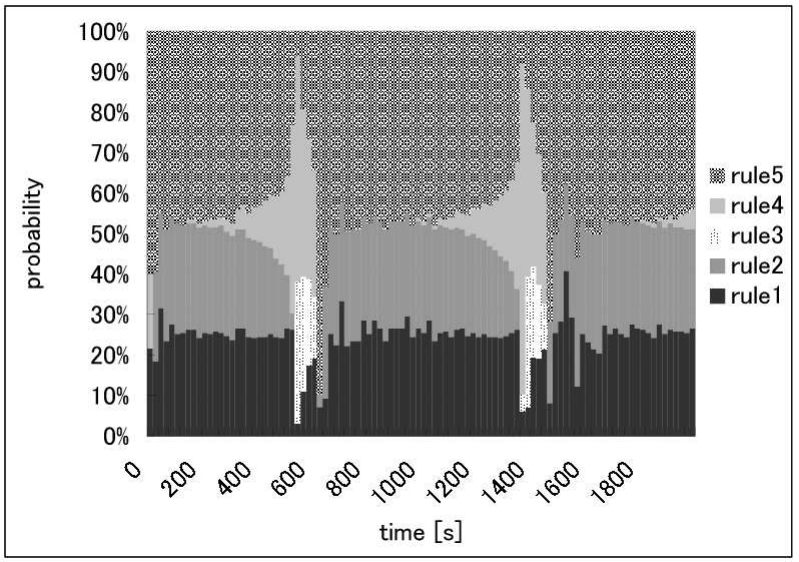


Fig. 10. Schematic plot of SPP of SARMS, when $\Delta = 0.001$

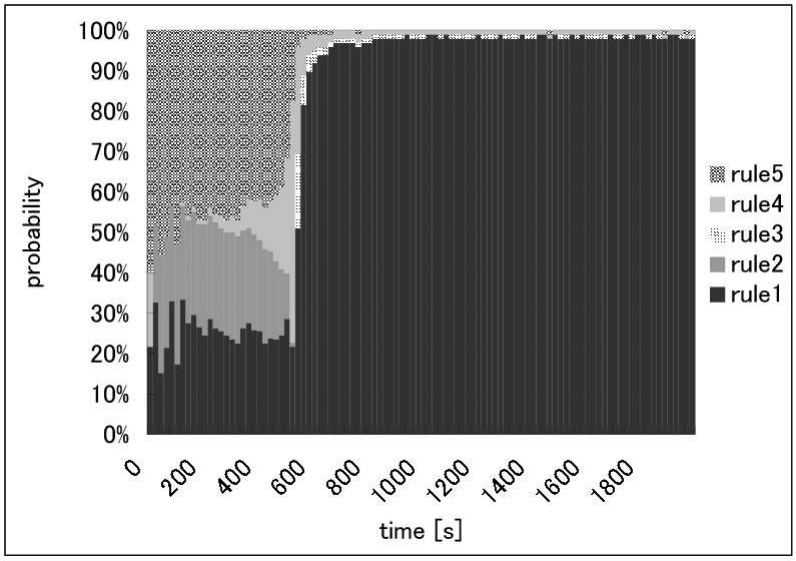


Fig. 11. Schematic plot of SPP of SARMS, when $\Delta = 0.1$

### 4.3 Final Remarks

If *Leap Condition* is satisfied ($\Delta$ is small enough and stoichiometric change is macroscopically noninfinitesimal), we can approximate the stoichiometric change deterministically. Thus we do not have to employ a stochastic approach but we can employ a deterministic approach such as DARMS. DARMS can produce significant gains in simulation speed with acceptable losses in accuracy.

SARMS combines the stochastic and deterministic approach, hence it will be suitable for modeling a chemical system with few molecules, such as biochemical processes in a cell.

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