Direct Simulation of the Oregonator Model by Using a Class of P Systems

Mai Umeki and Yasuhiro Suzuki

Department of Complex Systems Science, Graduate School of Information Science, Nagoya University, Furocho Chikusa-ku Nagoya, JAPAN

Summary. We propose a simple method of simulating chemical reactions by using a multiset rewriting systems, the Abstract Rewriting System on Multisets (ARMS). We simulate the Oregonator model, a mathematical model of the Belousov-Zhabotinsky and We obtain the same behavior when the differential equations are used. We also investigate the Oregonator with large stochastic fluctuations and confirm that they may affect its oscillational behaviors.

We simulated the *Oregonator* model [2], which is a mathematical model of the *Belousov-Zhabotinsky reaction* (BZ reaction) [11]. As for the mathematical model of BZ reaction, the *brusselator* [7] and Oregonator are well known. In the brusselator, each reaction rule does not correspond to the actual chemical reactions exhibiting the BZ reaction, while in the Oregonator each reaction rule corresponds to actual chemical reactions exhibiting the BZ reaction. Thus, various parameters of the BZ reaction have been obtained by chemical experiments; these parameters cannot be used for simulation of the burruselator but can be used for the Oregonator. However the Oregonator is not simple and in order to simulate it, usually simplifications of the model by abstracting dimensions of parameters and neglecting variants are required [10]. So, in the simulation of the simplified model, even if we can find interesting behaviors, we cannot feed back to design chemical experiments to confirm them.

Direct methods such as the *Gillespie* method [3] or the *StochSim* [5] allow us to simulate the Oregonator without simplifying and transforming parameters to dimensionless space. the *Abstract Rewriting system on MultiSets* (ARMS) [8], is a direct method and a variant of P Systems, which is closely related to the *Metabolic Algorithm* (MA) (for example [4]) and the Gillespie method.

The main differences between the ARMS and MA are the ARMS is a stochastic model and the rate constants keep the same during computations, while the MA is a deterministic model and the rate constant can change during a computation. And [1] investigated the relationship between P systems and the Gillespie method.

The main differences between the ARMS and Gillespie method is that; the ARMS and Gillespie method based on the rate constants and population size of each chemical species. The probability of one reaction occurring relative to another is obtained by multiplying the rate constant of each reaction with the numbers of its substrate molecules. A random number is then used to choose which reaction will occur, based on relative probabilities. And in the Gillespie method, another random number determines how long the step will last, while in the ARMS such a random number is not used to determine how long the step will last and the steps of intervals between reaction events are given by the rate constants.

1 Abstract Rewriting System on Multisets, ARMS

Formally, in the *ARMS* a chemical solution is a multiset of elements denoted by symbols from a given alphabet, $A = \{a, b, \ldots, \}$; these elements correspond to *chemicals*.Reaction rules that act on the chemicals are specified in the *ARMS* by reaction rules. Let A be an *alphabet* (a finite set of abstract symbols). A *multiset* over a set of objects A is a mapping $M : A \mapsto \mathbf{N}$, where $\mathbf{N}$ is the set of natural numbers, $\mathbf{N}$, 0, 1, 2,....

The number $M(a)$, for $a \in A$, is the *multiplicity* of object a in the multiset M. We denote by $A^{\#}$ the set of all multisets over A, including the B (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 vector $w = (M(a_1)M(a_2)\ldots M(a_n)$.

The union of two multisets $M_1, M_2 : A \mapsto \mathbf{N}$ is addition of vectors w_1 and w_2 that represent the each multisets 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* $u \to v, u, v \in A^{\#}$ is a vector $r, r = -u + v$. Note that u and v can also be zero vector (empty). For example, the reaction a b → c is the vector of (-1 -1 1)=-(1 1 0) + (0 0 1).

A *reaction* is the addition of vectors $M \in A^{\#}$ and $r \in R$,and it can be defined only when r ⊆ M.We can define over $A^{\#}$ a relation: (→): for $M, M' \in A^{\#}, r \in R$ we write $M \to M'$ iff $M' = (M + r)$. As for *strategy of rule application*, one rule will be applied in each step, conventionally. But we can easily realize maximal parallel rule application.

Application of rules in the ARMS

Kinetics of bio-chemical reactions have traditionally been described by the reaction-diffusion (RD) equations based on the mass-action law (MAL). The chemical equation of

$$A + B \to C + D \tag{1}$$

indicates that molecules A and B react together to form molecules C and D. From this chemical equation we can obtain the rate equation. It is important to note that most chemical reactions are assumed to follow the mass action law (MAL)

kinetics, meaning that the reaction rate is proportional to the concentration of the molecules. Thus the rate equation of the equation (1) is $-[\dot{A}] = r_a = k[A][B]$, where $[A]$ represents the concentration of molecules A, r_a is the reaction rate and k is the rate constant of the reaction.

The reactions in the ARMS obey the Mass Action Law (MAL), where the frequency of a reaction follows the concentration of chemicals and a rate constant. In the ARMS, reaction rules are selected probabilistically, where each probability of selecting a rule is in proportion to the total number of collisions of chemicals. Concretely, the probability is given by the ratio of the total number of colliding chemicals of a reaction to the sum of the total number of colliding chemicals of every reactions in the rule; for example, there are only two reaction rules $a, b \stackrel{k_1}{\rightarrow} c : (r_1)$ and $c, d \stackrel{k_2}{\rightarrow} a : (r_2)$, the probabilities of selecting r_1 and r_2 are respectively given by,

$$P_{r_1} \equiv \frac{k_1[a][b]}{k_1[a][b] + k_2[c][d]}, \tag{2}$$

$$P_{r_2} \equiv \frac{k_2[c][d]}{k_1[a][b] + k_2[c][d]}. \tag{3}$$

In this contribution, the change of concentration of chemicals are given by the expectation value of selected a rule and its stoichiometric constants, for example, the case when r_1 is selected, the change of concentration a is given as $P_{r_1} \times -1$, b, $P_{r_1} \times -1$, c, $P_{r_1} \times 1$ and d, $P_{r_1} \times 1$, respectively. In this contribution, the changes of concentrations obey those of expectation values.

Oregonator

The Oregonator is proposed by [2] as follows;

$$X, Y, H \stackrel{k_1}{\rightarrow} 2W : (r_1), \tag{4}$$

$$A, Y, 2H \stackrel{k_2}{\rightarrow} X, W : (r_2), \tag{5}$$

$$2X \stackrel{k_3}{\rightarrow} A, W, H : (r_3), \tag{6}$$

$$A, X, H \stackrel{k_4}{\rightarrow} 2X, 2Z : (r_4), \tag{7}$$

$$B, Z \stackrel{k_5}{\rightarrow} 0.5Y : (r_5), \tag{8}$$

where k_1 ... k_5 are obtained through chemical experiments and proposed [2]; $k_1 = 10^6 M^{-2} S^{-1}$, $k_2 = 2M^{-3}S^{-1}$, $k_3 = 2 \times 10^3 M^{-1} S^{-1}$, $k_4 = 10M^{-2}S^{-1}$, $k_5 = B \times 2 \times 10^{-2} S^{-1}$, where M stands for one molar, S stands for a second. And A corresponds to the concentration of B_rO_3, B, $CH(COOH)_2$, X, HB_rO_2, Y, B_r, Z, C_e^{4+}, W,HOB_r and H, H^+, respectively.

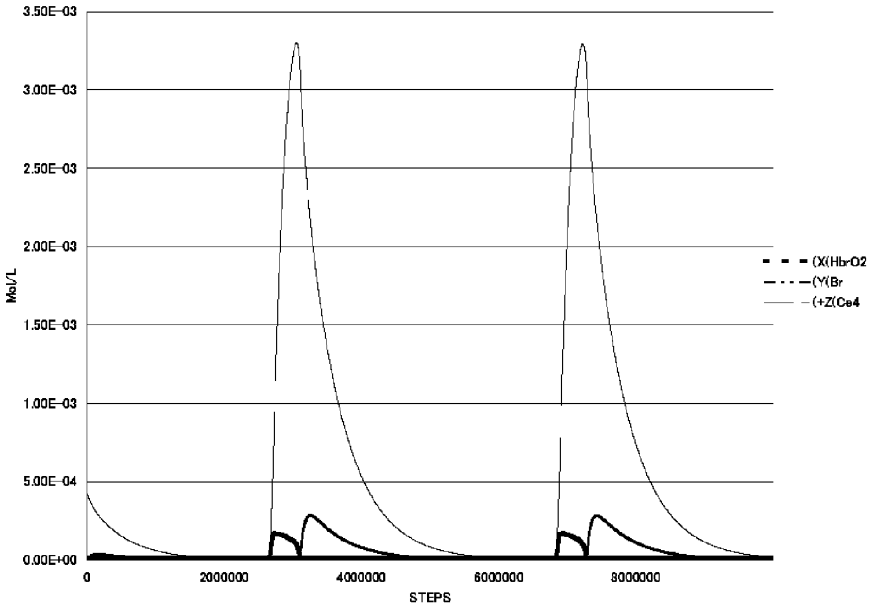

Fig. 1. Population dynamics of X,Y,Z in the Oregonator, where the vertical axis illustrates the number of chemicals and the horizontal axis illustrates the step

In the Oregonator, chemicals A and B are resources and assumed that they are continuously supplied or largely existed than other chemicals. W is the final product through these reactions and oscillations among X, Y and Z emerge.

2 Results

We confirmed that the ARMS can simulate conventional behavior of the Oregonator by using the differential equations (figure 1), where reactions of generating X (Hb_rO_2) are trigger of oscillations and these reactions increase the concentration of Z (C_e^{4+}) then high concentration of Z leads reactions of generating Y (B_r), since this reaction required Z, the concentration of Z is decreased.

The reaction mechanism of the Oregonator is illustrated by the usage of reaction rules (figure 2). Basically, the r_1 $(X, Y, H \rightarrow 2W)$ and $r_5(B, Z \rightarrow 0.5Y)$ are used continuously. And r_2 $(A, Y, 2H \rightarrow X, W)$ is also mainly used, however by the increase of X with r_4 $(A, X, H \rightarrow 2X, 2Z)$, occasionally applications of r_2 is switched by r_3 $(2X \rightarrow A, W, H)$. These usages of rules fit to actual chemical mechanism of the BZ reactions. Therefore, this result indicates not only the ARMS exhibits the same behavior that of modeled by the differential equations but also shows the correctness of chemical mechanism of the Oregonator.

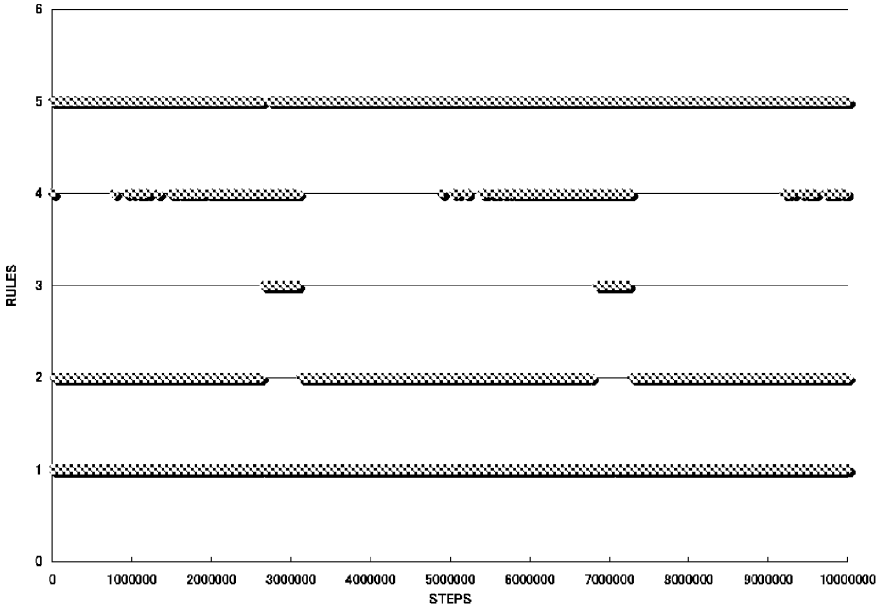

Fig. 2. The usage of reaction rules, the When the vertical axis illustrates r_1, r_2 ... r_5 from the top to bottom. The horizontal axis illustrates the steps. Each dot illustrates the usage of a rule

3 Discussion

Next, we consider the case when the system with large stochastic fluctuations. The change of concentration by a reaction is small and it can be approximated as continuous; however, most of the chemical reactions in a living system are performed with few molecules. In the reactions with few molecules, its developments are not approximated as continuous but discrete, where stochastic fluctuations can not be ignore.

In order to introduce discreteness in the developments, we define an exernal parameter $\rho(0.0 < \rho)$, it is multiplied by the denominator of the probability of selecting a rule. Under the same extent of concentration change by a reaction when the value of ρ is small, the probability of selecting a rule will be changed easier compared to the case when ρ is large.

For example, probabilities of selecting $a, b \stackrel{k_1}{\rightarrow} c : (r_1)$ and $c, d \stackrel{k_2}{\rightarrow} a : (r_2)$ are given by

$$P_{r_1} \equiv \frac{k_1[a][b]}{(k_1[a][b] + k_2[c][d])\rho}, \tag{9}$$

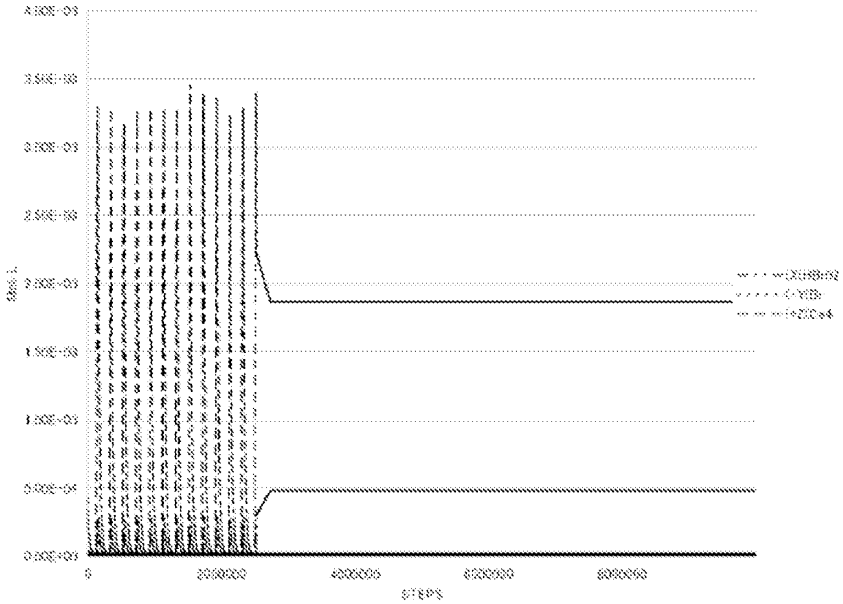

Fig. 3. un-stable oscillations: population dynamics of X,Y,Z in the Oregonator when ρ is small (ρ is an external parameter), where the vertical axis illustrates the number of chemicals and the horizontal axis illustrates the step

$$P_{r_2} \equiv \frac{k_2[c][d]}{(k_1[a][b] + k_2[c][d])\rho}, \tag{10}$$

where when $\rho = 1.0$ the probabilities are the same as the conventional definition, while $\rho < 1.0$, as the denominator is getting small, the probability becomes sensitive to the slight change of the value of the numerator. So, the value of ρ is getting smaller, probabilities are getting easier to suffer from the fluctuations, it corresponds to the case when the system with few molecules. And also, as the value of ρ is getting smaller, the change of concentration by a reaction becomes large and discretely.

System with large fluctuations

We found that there exists three cases of behaviors according to the value of ρ. As decreasing the value of ρ to 0.0, it shows stable oscillations, quasi-stable oscillations and un-stable oscillations, where stable oscillations means that conventional oscillations, quasi-stable oscillations, in some trials oscillations disappear in a lapse of steps while others show conventional oscillations, un-stable oscillations(figure 3 and 4), in every trials oscillations disappear in a lapse of steps. The usage of rules

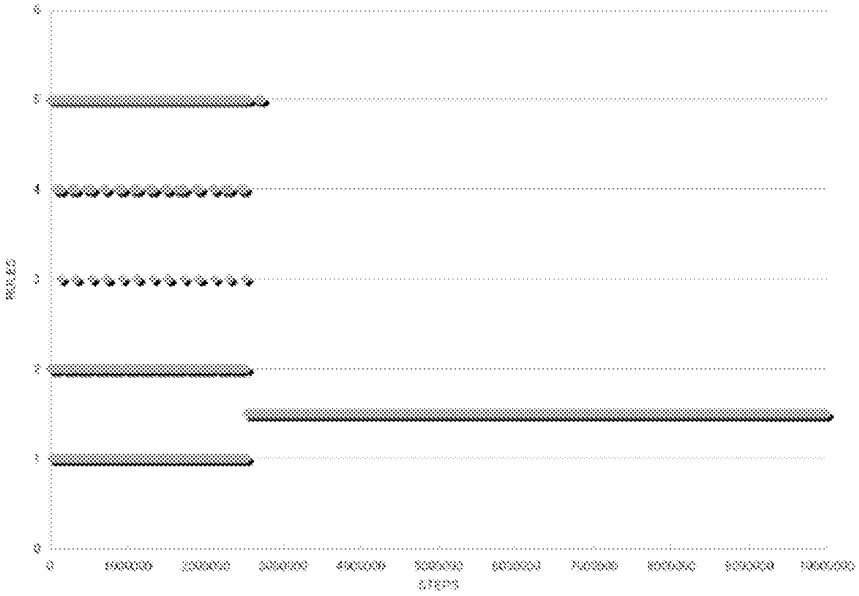

Fig. 4. The usage of reaction rules the case when un-stable oscillations occur (ρ is an external parameter and this graph indicates when it is small), the vertical axis illustrates r_1, r_2 ... r_5 from the top to bottom. The horizontal axis illustrates the steps. Each dot illustrates usage of a rule. From around 250,000 steps, the usage of reactions indicates a rule between 1 and 2 are used, it means that rule 1 and 2 selected but cannot be applied, because of the concentration of X, Y and Z become under 1.0

(figure 4) indicates that, since the concentration of X, Y and Z become under 1.0, no rule can be applied. This result illustrates that discreteness can be induced by low concentration of chemicals, as for this phenomena, the same mechanism has been reported in another abstract chemical system [9].

4 Final remarks

In this contribution, we report our preliminary results on direct simulation of the Oregonator. We confirm that when the Oregonator is affected by large stochastic fluctuations, the oscillatory behaviors may change. More detailed investigation on it is our future work, where in order to confirm the correctness of the investigation, chemical experiment might be required, it is also our future work.

And also, chemical systems could give a good analogy when we consider the complex interaction systems such as protein-protein interactions etc. We will try to apply this method to investigate such a biological netwrok.

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