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PATTERN DYNAMICS OF A MULTI-COMPONENT REACTION–DIFFUSION SYSTEM: DIFFERENTIATION OF REPLICATING SPOTS

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Replication and differentiation of spots in a class of reaction–diffusion equations are studied by extending the Gray–Scott model with self-replicating spots so that it includes many chemical species. By examining many possible reaction networks, the behavior of this model is categorized into three types: replication of homogeneous fixed spots, replication of oscillatory spots, and differentiation from "multipotent spots". These multipotent spots either replicate or differentiate into other types of spots with different fixed-point dynamics, and as a result, an inhomogeneous pattern of spots is formed. This differentiation process of spots is analyzed in terms of the loss of chemical diversity and decrease of the local Kolmogorov–Sinai entropy. Initial condition dependence and robustness of a pattern against macroscopic perturbation are also analyzed. Relevance of the results to developmental cell biology is also discussed.

Keywords: Reaction–diffusion equation; Gray–Scott model; spatiotemporal intermittency; spatiotemporal chaos; cell differentiation; morphogenesis; prebiotic evolution.

1. Introduction

In biological pattern formation, compartment structures for a cell are spontaneously organized, which, not only reproduce themselves stably but also have the potentiality to be differentiated from other types of cells. Furthermore a higher level spatial structure is arranged by these differentiated cells, so that several types of tissues are formed as patterns by differentiated cells.

In physics and chemistry, reaction–diffusion systems are adopted as a basic and standard tool for pattern formation. In spite of the success of this approach, it is not yet sure if such an approach can explain cell differentiation and development, including differentiation from a stem cell. Then it is important to elucidate whether a reaction–diffusion system is enough to discuss a basic level of these biological problems, or some other additional dynamics have to be included. For a first step to answer this question we study here if there exists a reaction–diffusion system that satisfies the following two properties.

- Compartment is formed spontaneously through chemical reactions, and can reproduce itself stably.
- Simultaneously, chemical state of the compartment spontaneously differentiates into a few other types, through interaction among the compartments. These differentiated compartments form a spatial pattern.

As for the first point, spot structure can be regarded as a kind of compartment. For self-replicating spot patterns, there is a prototypical model, that is, the Gray–Scott (GS) model [Gray & Scott, 1984]. It is a simple chemical reaction–diffusion system with two chemical species, which can exhibit self-replicating spots [Pearson, 1993; Petrov *et al.*, 1994; Rasmussen *et al.*, 1996]. Indeed,

such replicating spots have also been found in experiments [Lee *et al.*, 1994; De Kepper *et al.*, 1994]. An analytical solution for such spots and asymptotic analysis for the splitting phenomenon have been developed [Reynolds *et al.*, 1994, 1997; Doelman *et al.*, 1997, 1998], while self-replicating spot dynamics has been mathematically studied by using global bifurcation analysis [Nishiura & Ueyama, 1999, 2001]. In the model systems studied so far, however, only a single type of spot appears, and there is no differentiation to create different types of spots [Wackerbauer *et al.*, 2000].[1]

On the other hand, as for the second requirement, dynamical systems studies for cell differentiation have recently been developed by assuming the existence of cell compartment itself [Kaneko & Yomo, 1994, 1997, 1999; Furusawa & Kaneko, 1998a, 1998b, 2000]. There, each cell has complex internal chemical reaction dynamics, which interacts with each other through diffusion (or transport) of chemicals. These cells are assumed to divide as the total amount of chemicals within is increased. Under these general assumptions, cell differentiation is found to be generally observed with the increase of the number of cells. The differentiated types as well as the number distribution of such cell types are shown to be robust against perturbations. Furthermore, hierarchical differentiation from a stem-type cell is found to occur spontaneously. This stem-type cell has totipotency, i.e. potentiality to produce all other cell types, while the types that appear later maintain ability to produce only a limited type of cells. As the differentiation progresses, this multipotency is lost, and each cell produces its own type, as is called determination in cell biology. This cell differentiation process is consistent with the real biological phenomena.

Then it is natural to ask if these two approaches can be combined to make possible both the spontaneous formation of compartments and differentiation of the compartments. For this purpose, we extend the Gray–Scott model to include many chemical species, that form complex reaction network. Here, in order for spots to continue replication and differentiation, their division process and their internal complex chemical dynamics must somehow organize a proper relationship. By taking a rather complex reaction network, we study how such a relationship is organized.[2]

After introducing our model in the next section, we investigate the model by choosing a variety of random reaction networks in Sec. 3. There the dynamical behaviors of our model are classified into three types, that is the formation of homogeneous fixed point spots, oscillatory dynamics of spots, and differentiation of spot types. Two quantities are introduced to characterize dynamical and statistical aspects of the spot differentiation.

Since we are interested in the differentiation type, we analyze the differentiation process in more detail in Sec. 4, where we examine initial condition dependence and robustness of the differentiation process against macroscopic perturbation. While the classification to the three types is carried out for the one-dimensional case, we also confirm that this classification is valid for the two-dimensional case, by giving some examples of differentiation dynamics. Finally, in Sec. 5, we discuss relevance of our results to the problem mentioned in the beginning.

2. The Model

The Gray–Scott (GS) equation.

$$\begin{aligned}\frac{\partial u(t)}{dt} &= D_u\nabla^2 u(t) - u(t)v(t)^2 + A(1.0 - u(t)) \\ \frac{\partial v(t)}{dt} &= D_v\nabla^2 v(t) + u(t)v(t)^2 - Bv(t)\end{aligned} \tag{1}$$

is thoroughly studied as a reaction–differentiation system that allows for replicating spots. To study a system that both allows for replication and differentiation of spots, we need to extend the GS equation to include more degrees of freedom. Although there can be many possibilities for this extension, we use the following model here [Takagi & Kaneko, 2001];

$$\begin{aligned}\frac{\partial u_i(x,t)}{\partial t} &= D_u\nabla^2 u_i(x,t) + A(1 - u_i(x,t)) \\ &\quad - u_i(x,t)\sum_{j=1}^{Q}\sum_{k=1}^{Q} W_i^{(j,k)} v_j(x,t)v_k(x,t) \\ \frac{\partial v_i(x,t)}{\partial t} &= D_v\nabla^2 v_i(x,t) - Bv_i(x,t) \\ &\quad + v_i(x,t)\sum_{j=1}^{P}\sum_{k=1}^{Q} W_j^{(i,k)} u_j(x,t)v_k(x,t)\end{aligned} \tag{2}$$

[1] They also studied a 3-degrees-of-freedom version of GS model and found phase separation of domains by chaos. Differentiation of spots from a multipotent chaotic spot has not been observed there.

[2] Of course, present organisms adopt more sophisticated mechanisms. Here, we are interested in a minimal condition for differentiation process.

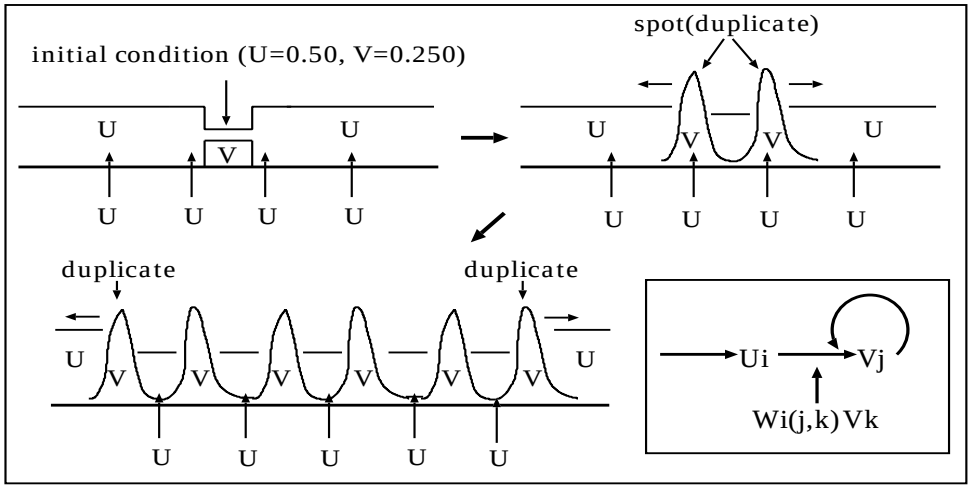


Fig. 1. Schematic representation of our model.

Here P kind of resource chemicals and Q kind of product chemicals exist. $u_i(x,t)$ denotes the concentration of the ith resource chemical and $v_i(x,t)$ that of the ith product chemical, while the term with the connection matrix $W_i^{(j,k)}$ represents complex catalytic reaction network by these chemicals, which takes 1 if there is a reaction path, and 0 otherwise. Each resource chemical $u_i(x,t)$ is produced at a constant rate, A, while both the resource and product chemicals decay at some rates. The diffusion constants of the resource and product chemicals are denoted by D_u and D_v, respectively. We assume that resource chemicals have larger diffusion constant than product ones, which is the necessary condition for spot replication in GS equation. For simplicity, we assume that these constants are independent of chemical species.

This model is a variant of that proposed by Cronhjort and Blomberg [1997], and is reduced to the GS model by setting $P = 1$, $Q = 1$, $W_1^{(1,1)} = 1$. Although we have studied several networks by changing P and Q, we mainly present the case with $P = 3$ and $Q = 20$, here. Schematic representation of our model is shown in Fig. 1.

The reaction matrix W is chosen randomly under the constraint that the reaction for replication of each product is catalyzed by k ($0 \leq k \leq K$) randomly chosen products. If there are catalytic reactions the path number K is chosen to be $K = 4, 5, 6$. Within this choice of K values, however, the qualitative behavior does not depend on specific K values. Hence we show mainly the results from the simulation of the case with $K = 4$.

The behavior of our model depends on the choice of the reaction network W, which represents a prototype of complex intracellular reaction network. We studied a huge number of equations from different reaction matrices. The behavior of these equations will be classified into a few types of dynamics of the system.

Here, specific numbers of chemicals P and Q are not important for the qualitative behavior. It should be noted, however, that the differentiation case we study is hardly observed, when these numbers are small (as long as the reaction network is chosen randomly). As for the spatial dimension, we mostly study the one-dimensional case and briefly discuss the two-dimensional case later.

3. Simulation Results

In this section we classify the behavior of the model (2), by carrying out numerical computations for a variety of randomly chosen reaction networks W. Although we have studied several thousand randomly chosen reaction networks, the observed behaviors can be classified into the following three types that will be shown.

3.1. *Initial conditions and methods*

For each set of simulations, a reaction network was fixed, and also the parameter values were set throughout as $D_u = 2.0$, $D_v = 0.020$, $A = 0.020$ and $B = 0.060$ or 0.070, while later we discuss bifurcation against the change of the parameters A

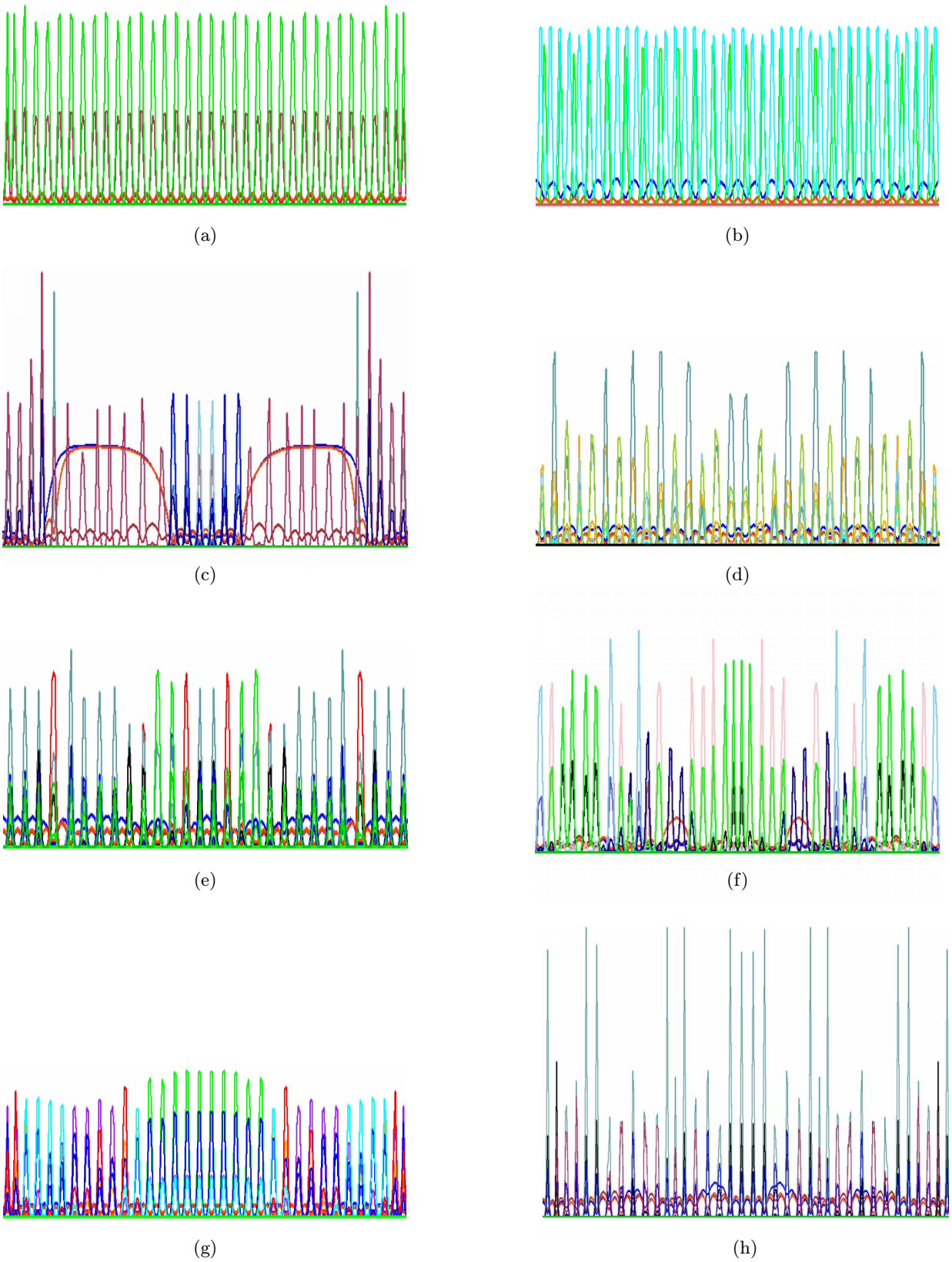


Fig. 2. Examples of snapshot patterns of $u_i(x,t)$ and $v_j(x,t)$ for each case. The states of spots are as follows: (a and b) homogeneous fixed point case, (c and d) nonchaotic oscillation case, (e) spatio-temporal intermittency, (f) spatio-temporal chaos, (g) case I differentiation, (h) case II differentiation. Here we use a different color for each chemical species. Each example uses a different reaction network. The parameter values are $D_u = 2.0$, $D_v = 0.020$, $A = 0.020$, and $B = 0.060$.

and B. These parameters were set at typical values where the spot structure itself is maintained. Indeed, the parameter values are close to those values at which spot structure exists in the original GS model. We used $\Delta t = 0.010$ and $\Delta x = 1.0$ for the numerical integration, while we have confirmed that the numerical results are qualitatively unchanged by using smaller values for Δt.

In general we choose an initial condition, so that $v \neq 0$ only at a localized spatial domain, where two simple spots are formed. These spots then produce additional spots, and the process continues until eventually spots are distributed throughout the entire system. Here, we first classify the (transient) dynamics of our model starting from such initial conditions, while in the next section we study the evolution from random initial conditions also.

Examples of the behavior of dynamics with spot division are given in Fig. 2 as (successive) snapshots. In Fig. 2(a), spots are replicated homogeneously, as in GS equation. In Figs. 2(g) and 2(h), spots differentiate into two types as they replicate. Some other examples of nonchaotic oscillation are also shown in Figs. 2(c) and 2(d), spatio-temporal intermittency is shown in Fig. 2(e), and spatio-temporal chaos is shown in Fig. 2(f).

To characterize these spot dynamics quantitatively, we introduce two quantities measuring the diversity of these dynamics. One is the chemical diversity $S_i(nT)$, which is defined by

$$S_i(nT) = -\sum_{j=1}^{Q} P_i^j(nT) \log(P_i^j(nT)) \,,$$

with

$$P_i^j(nT) = \frac{\overline{v_i^j}(nT)}{\sum_{j=1}^{Q} \overline{v_i^j}(nT)}$$

and

$$\overline{v_i^j}(nT) = \left(\frac{1}{T}\right) \sum_{t=(n-1)T}^{nT} v_i^j(t), \quad (n = 1, 2, \ldots) \,,$$

where v_i^j is the jth product concentration at the center of the ith spot. The interval T used for the average is chosen to be on the order of a time scale for spot division. Here, the interval T was set to 1000, but the results are insensitive to this value as long as it is set at the order mentioned above. This measure shows the effective chemical diversity of spots between successive divisions.

The second quantity is the "local KS-entropy" h_i of the ith spot. This quantity is defined as the sum of positive local Lyapunov exponents [Kaneko, 1989], obtained by using the tangent vectors for chemical dynamics restricted only to the region around a spot. Here it is computed from the product of the Jacobi matrices at each spot over time $T = 1000$, by neglecting the diffusion term to the outside of the spot. The spatial size of pixel is fixed at 7. This measure shows the variety of intra-spot chemical dynamics between successive divisions.

3.2. *Classification of the dynamics*

With these quantities, the spot dynamics are classified into the following three types. Among three thousand reaction networks we have studied, the fraction of each case is as follows: (i) 87.8% (ii) 10% (iii) 2.2% (case I 2%, case II 0.2%).

(i) Fixed-point type

In this type, the set of concentrations within each spot converges either to the same fixed point or to a couple of fixed points. In the former case, each spot has identical fixed chemical concentrations. The spots are separated by equal distance (see Fig. 2(a)). In the latter case, different spots are formed, which use different sets of v for a given resource u^i $(i = 1 \sim P)$, and the interaction between the different spots through chemicals are not important for the dynamics. Here, again, spots are separated by equal distance (see Fig. 2(b)).

(ii) Oscillatory type

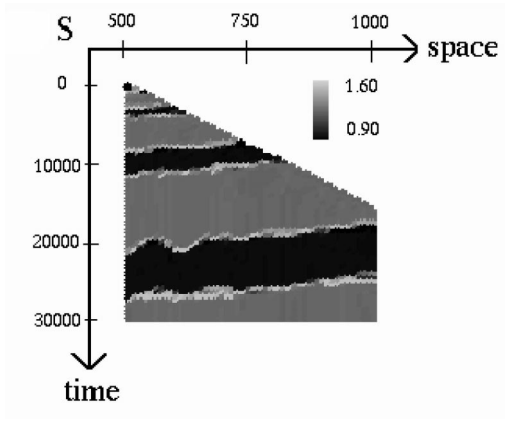
This type is further classified into nonchaotic, intermittent, and highly chaotic cases, depending on the choice of reaction networks and parameter values.

- Non-chaotic oscillation

The spatial pattern of spots is fixed in time, while within each spot, chemical concentrations oscillate periodically or quasiperiodically in time. In some reaction networks, there appears propagating waves, following the difference of the phase of oscillations by spots (see Fig. 3).

- Spatio-temporal intermittency (STI)

The spatial pattern of spots is clearly separated into laminar and burst regions to form some characteristic patterns (see Fig. 4). Each spot continues



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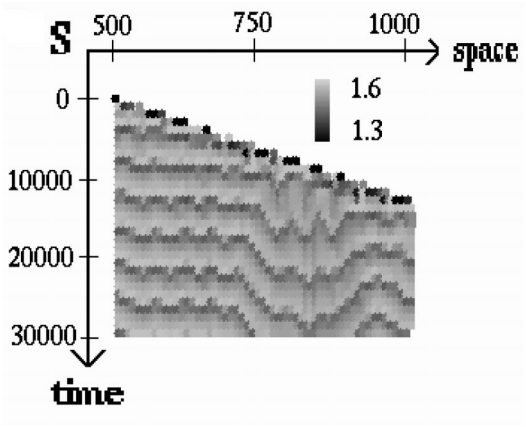

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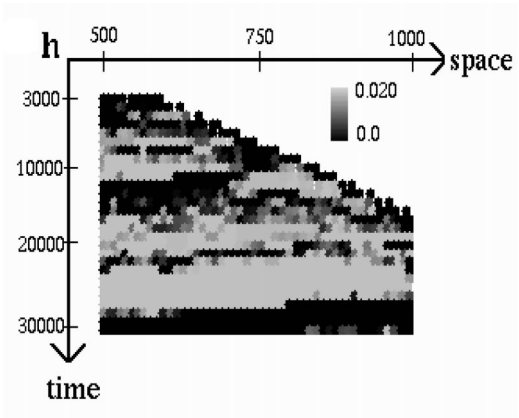

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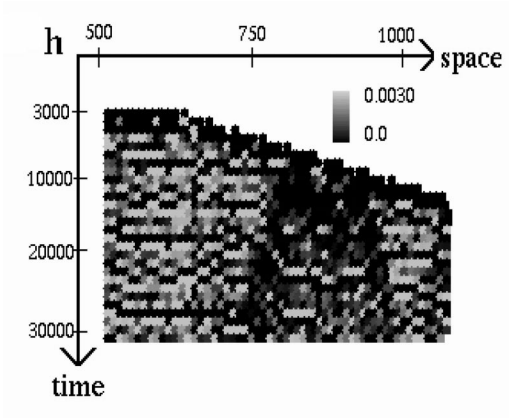
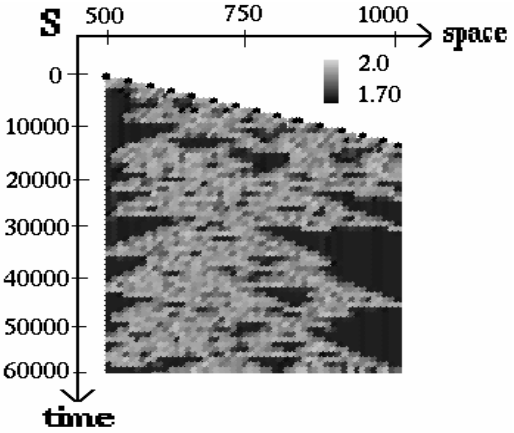


(d)

Fig. 3. Examples of spatio-temporal pattern of chemical diversity $S_i(nT)$ and local KS entropy h_i for propagating wave pattern cases ((a) and (c); (b) and (d)). Two examples from different reaction networks are plotted. (Since the average of local KS entropy requires some time steps, h is plotted only for time > 3000). These quantities of the half-space (from the center to the right edge) pattern are plotted using a gray scale. All the examples here and Figs. 4, 6 and 7 adopt the same initial conditions, i.e. at $t = 0$ only a single spot is put with $u_i = 0.50$ and $v_j = 0.250$ for all i and j. The system size is $N = 1000$. Spot structures are preserved through the simulations. Throughout the paper, the diversity S and local KS entropy h are computed by taking a spacetime pixel with space $= 7$ and time $= 1000$.



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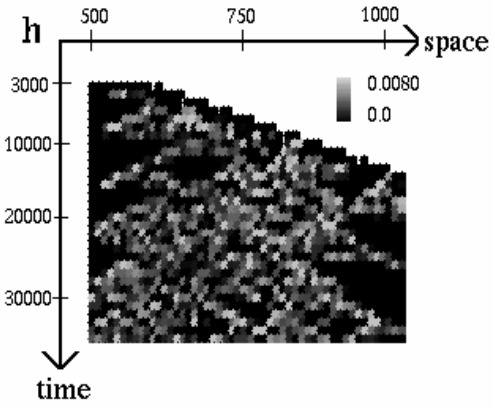


(b)

Fig. 4. An example of the spatio-temporal pattern of chemical diversity $S_i(nT)$ and local KS entropy h_i for STI case. Only half of the pattern from the center to the right edge is also plotted using a gray scale as in Fig. 3.

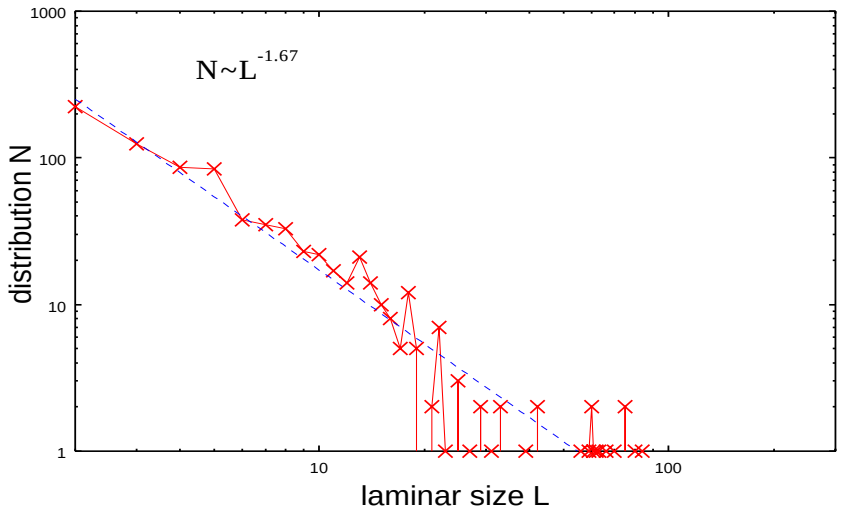


Fig. 5. The distribution of the size of spatial laminar region for STI case, shown in Fig. 4. The size is computed as that of spatial domain that is laminar, at every $T = 1000$ step, while the region with smaller chemical diversity $S_i(nT) < 1.75$ is regarded as laminar. It obeys the power law form.

to exhibit regular dynamics over some time, and then switch to chaotic dynamics, and this alternation is repeated. During this switching dynamics, the spot structure itself is maintained. The intermittent alternation between regular dynamics and chaotic bursts is known as spatio-temporal intermittency (STI), which has been studied extensively in coupled map lattices (CML) [Kaneko, 1985, 1989; Chaté & Manneville, 1988]. In STI, the distribution of the size of laminar region obeys the power law form, with power around 1.67 (see Fig. 5). We have also computed the laminar size distribution in our case, and the power law behavior is again observed with the exponent around the above value, although we have not determined its precise value yet. The pattern here will be regarded to belong to the same universality class as STI in CML.

For a given reaction network, by changing the parameter values A or B, we have observed the phase transition from fixed point pattern of spots to spatio-temporal intermittency, and then to spatio-temporal chaos (see Fig. 6).

- Spatio-temporal chaos (STC)

The chemical concentrations in each spot change chaotically in time, around a heteroclinic orbit (see Fig. 7), but the spot structure itself is not damaged for most of the time. At any instance, the chemical concentrations vary from spot to spot, but their long-term average is almost identical for all spots. In this case, spots not only replicate themselves but also annihilate sometimes [Nishiura & Ueyama, 2001].

(iii) Differentiation type

Spots differentiate into a few types. This case is further classified into case I and case II differentiations, depending on the choice of reaction networks.

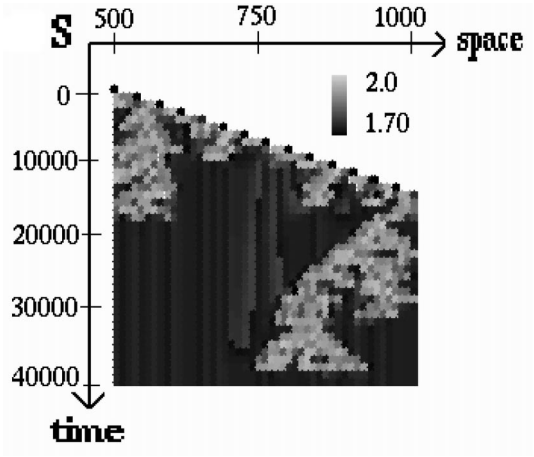
- Case I differentiation

In this case, with time, spots differentiate into different types, namely, inner and outer types (see Figs. 8(a) and 8(c)). For the inner type, the set of chemical concentrations converges to a fixed point, which contains less resource chemicals. Outer type spots exhibit either fixed-point, periodic, or chaotic oscillations, depending on the reaction matrix and the parameter values.

Here, the diversity of chemicals is larger for the outer type. The inner type has a smaller chemical diversity, and the local KS entropy is zero, as the dynamics fall onto fixed points. For the parameter values we used, the local KS entropy of the outer part can be either positive or zero, depending on the network. (The sign also changes depending on the parameter values.)

- Case II differentiation

Here, spots differentiate into two types, as in case I. Spots of the initial type exhibit chaotic oscillations. After a split of a spot, it produces either the same type of spot (with chaotic oscillations) or a different



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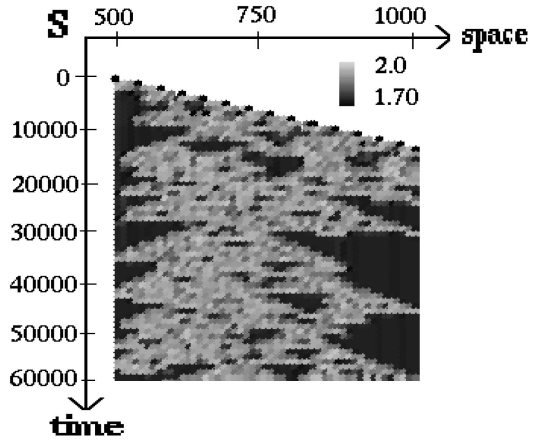

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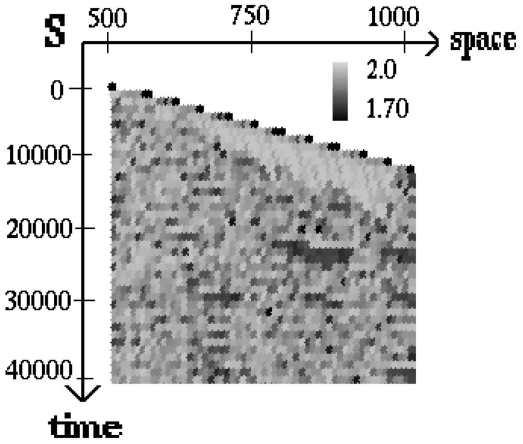
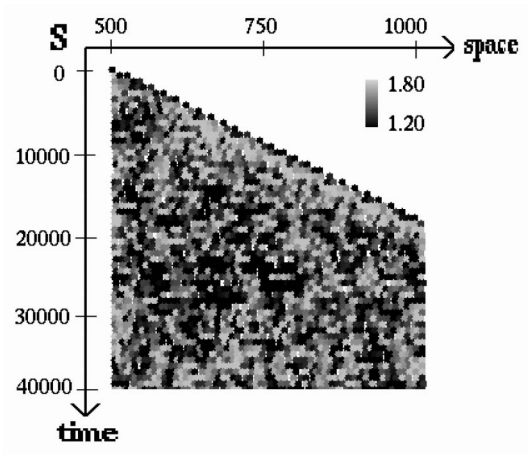


(c)

Fig. 6. Examples of the spatio-temporal pattern of chemical diversity $S_i(nT)$ for (a) stationary fixed point pattern, (b) spatio-temporal intermittency and (c) spatio-temporal chaos. Here the reaction network is fixed, and the parameter value B is changed as (a) 0.06, (b) 0.057 and (c) 0.045, while the parameter A is fixed at 0.02.



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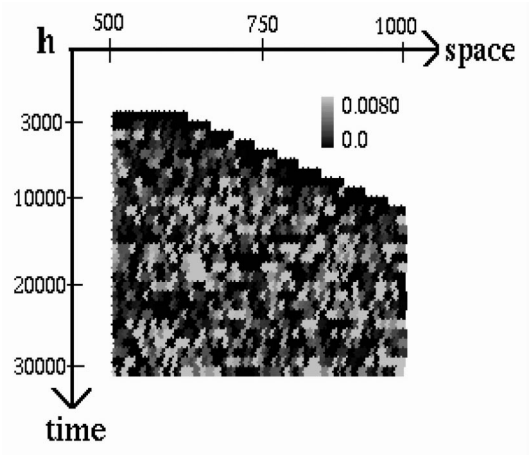


(b)

Fig. 7. An example of the spatio-temporal pattern of chemical diversity $S_i(nT)$ and local KS entropy h_i for STC case. Only half of the pattern from the center to the right edge is also plotted using a gray scale as in Fig. 3.

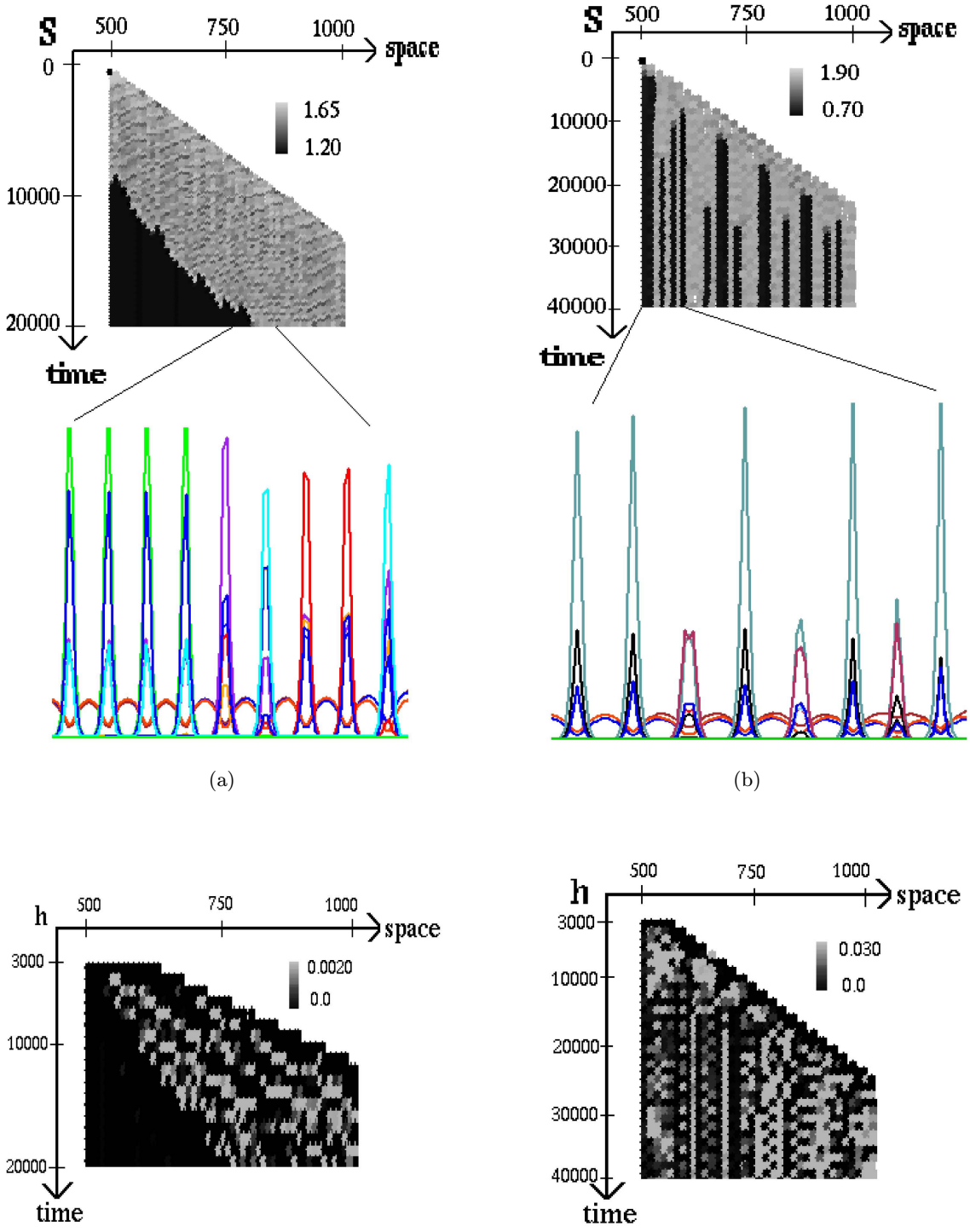
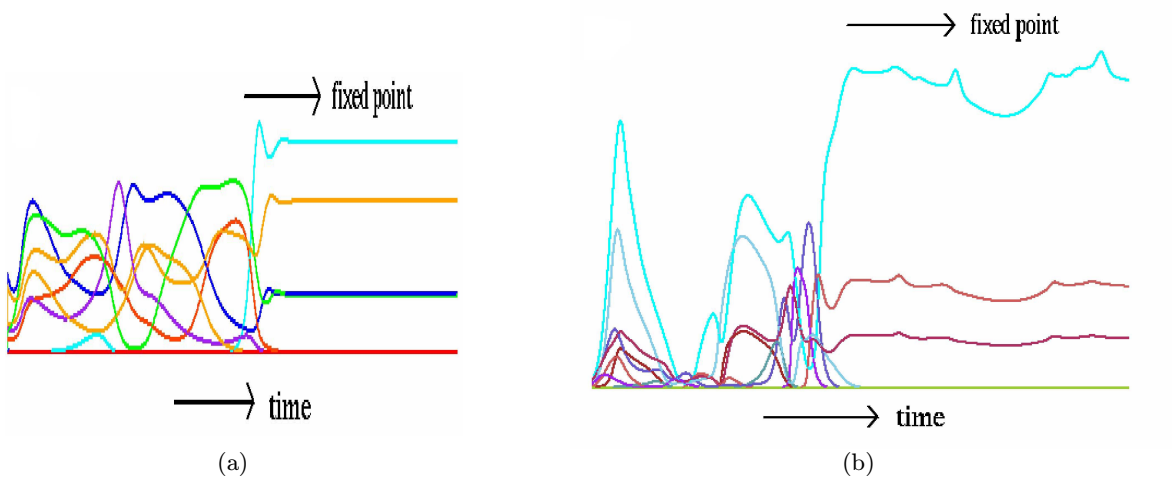


Fig. 8. Chemical diversity $S_i(nT)$ and local KS entropy h_i for case I and case II differentiation, where each figure adopts different reaction networks. (a) and (c) are examples of case I differentiation while (b) and (d) are examples of case II differentiation. A part of snapshot patterns of $u_i(x,t)$ and $v_j(x,t)$ is also plotted for each case of (a) and (b). Here we use a different color for each chemical species. Only half of the pattern from the center to the right edge is also plotted as in Fig. 3.



(a) (b)

Fig. 9. An example of the temporal course of differentiation, where change from weakly chaotic dynamics state to a fixed point progresses. (a) Gives an example for the case I differentiation while (b) gives that for the case II differentiation. Time series of all v at a given spatial position (around the peak position of a spot) are overlaid. Here we use a different color for each chemical species.

type with fixed-point dynamics. Here, differentiation is not governed by its inner/outer location, but, rather, spots with chaotic oscillations appear periodically in space with some interval (see Figs. 8(b) and 8(d)). Thus in this case there is pattern formation on two distinct spatial scales, that of the spot size and that of the average distance between two chaotic spots. In this case, the chaotic spots have a larger chemical diversity, while the other type has much smaller chemical diversity. In the first type, chaotic dynamics are maintained, as is confirmed by positive local KS entropy, while for the other types, the local KS entropy vanishes.

Both for cases I and II differentiations, dynamics of chemical concentration in a spot exhibit a change from weakly chaotic oscillation to fixed point. This differentiation process occurs within a short time span. Hence, each spot type is clearly classified into two types, except for a very short transient process for the differentiation (see Fig. 9).

3.3. *Classification by statistical measures*

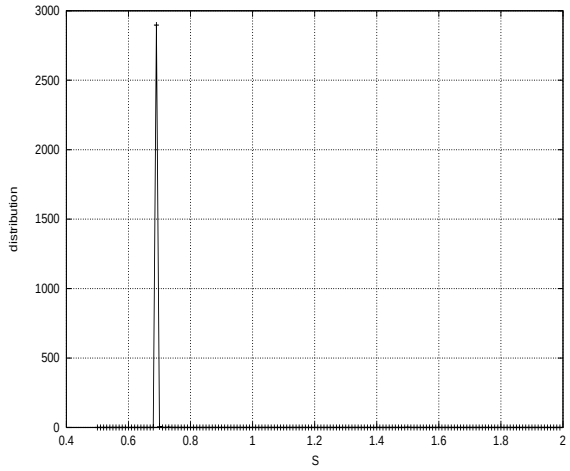
Distributions of the two quantities introduced in Sec. 3.1 provide a useful measure on statistical property of spot pattern dynamics for each case. The distribution of the chemical diversity S has a single peak in the fixed point type, while it has two peaks in the oscillatory case with propagating wave, STI, case I and case II differentiations. In the latter three cases, the sharper peak at a lower S value corresponds to the spot dynamics with fixed point. The broader peak at a higher S value corresponds to the chaotic spot dynamics. For the STI case, the tails of two peaks merge. In STC, the distribution is broad to form a continuous spectrum, without any sharp peaks (see Fig. 10).

From the distribution of h, two peaks in the negative range are observed for the fixed point type, some peaks in the negative range for the oscillation type. The distribution is broad, ranging from negative to positive values, for the oscillatory motion with propagating wave. Two distinct peaks are observed in STI and case I differentiation. For STI, there is a sharp peak around $h = 0$, and the two peaks partially merge. In the case II differentiation, the distribution is broader than that for the case I differentiation. In STC case, the distribution has a larger portion at positive values, and has a smooth one-humped shape (see Fig. 11).

To sum up, each case of spot dynamics can be classified by statistical distributions of the two quantities.

4. Further Analysis of the Differentiation Case

The difference between the two cases I and II lies in the ability for spontaneous differentiation. In case I, spots located in the outer region are maintained only through the flow of chemicals from the outside of the region where spots exist. The differ-



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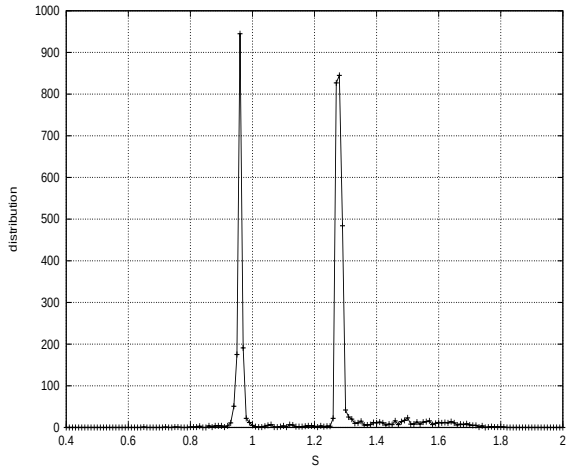

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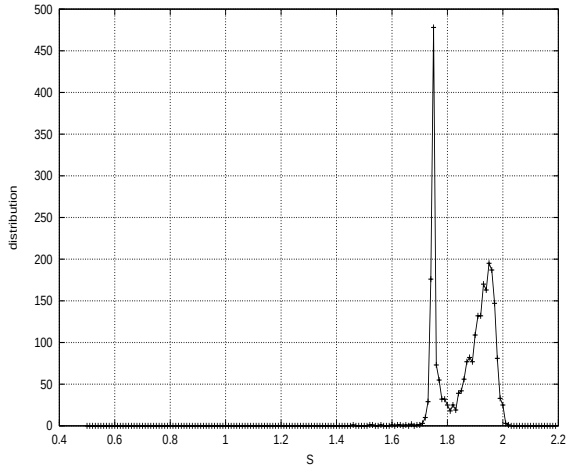
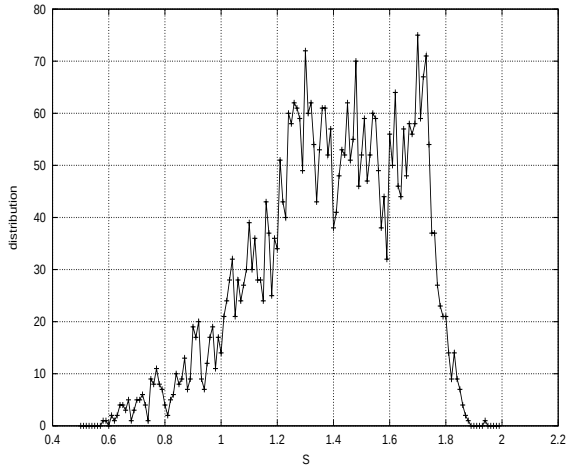
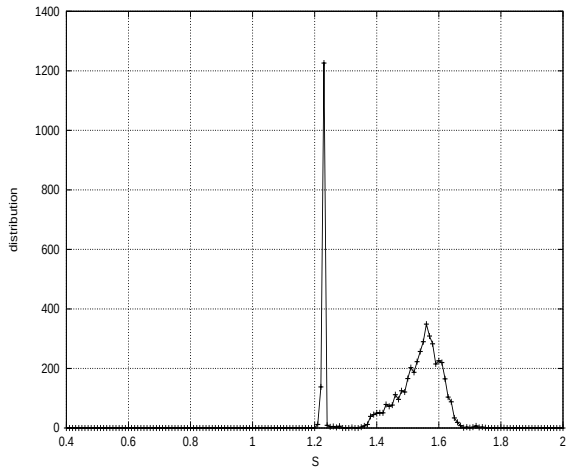


(c)



(d)



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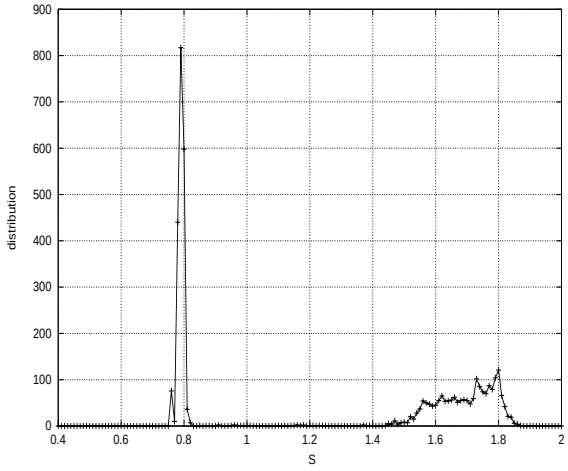
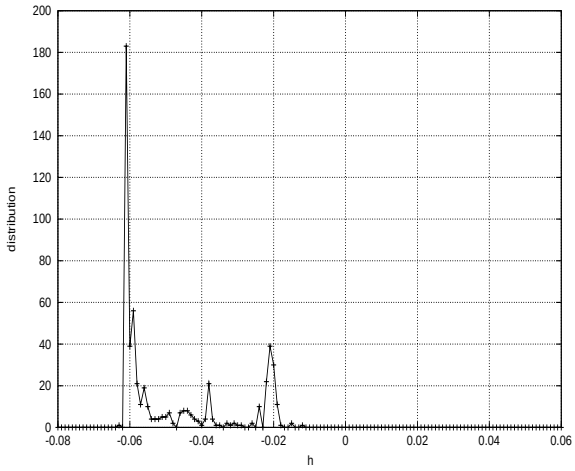
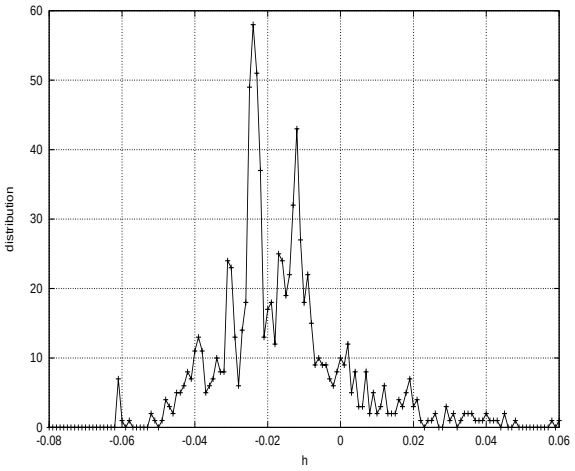


(f)

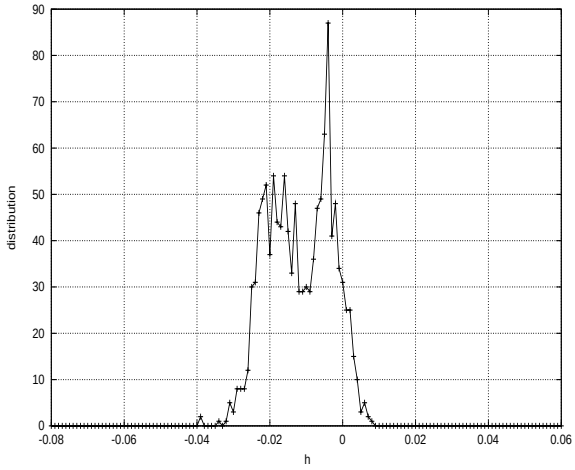
Fig. 10. The distribution of chemical diversity $S_i(nT)$ for each case. (a) Homogeneous fixed point, (b) nonchaotic oscillation, (c) spatio-temporal intermittency, (d) spatio-temporal chaos, (e) case I differentiation and (f) case II differentiation. The distribution is obtained by sampling $S_i(nT)$ for each example over all simulation time (from $t = 0$ to $t = 30000$ or $t = 40000$), where each S_i is computed using a spacetime pixel with space = 7 and time = 1000.



(a)



(b)



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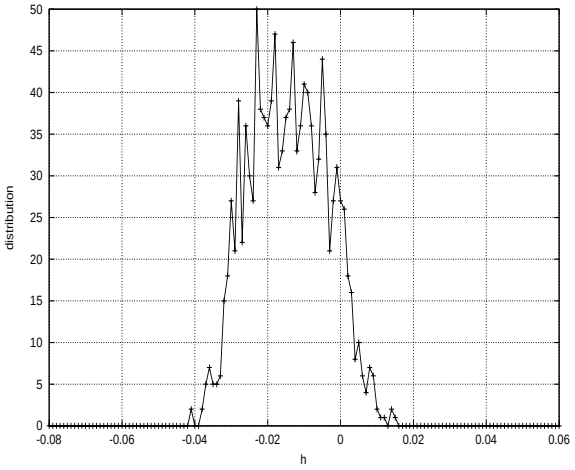
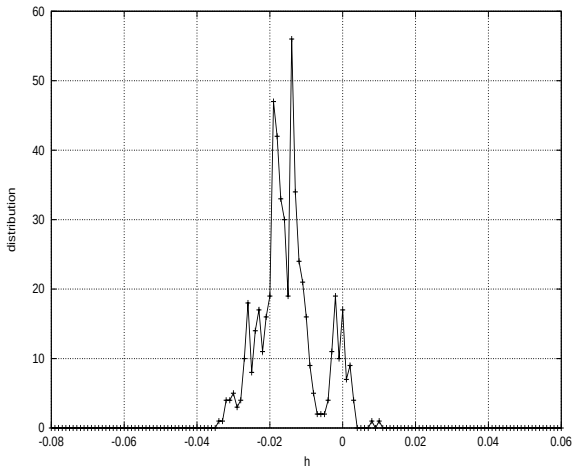
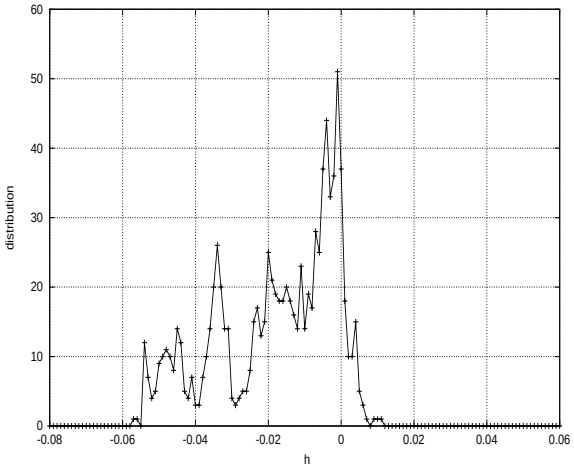


(d)



(e)



(f)

Fig. 11. The distribution of local KS entropy h_i for each case. (a) Homogeneous fixed point, (b) nonchaotic oscillation, (c) spatio-temporal intermittency, (d) spatio-temporal chaos, (e) case I differentiation and (f) case II differentiation. The distribution is obtained by sampling h_i for each example over all simulation time (from $t = 0$ to $t = 30000$ or $t = 40000$), where each h_i is computed using a spacetime pixel with space = 7 and time = 1000.

entiation from the outer region into the inner region continues if the dynamics in the outer region remain to be chaotic. However, if the dynamics of the outer spots converge to a fixed point, the differentiation is terminated, and as a result, growth of the inner part ceases.

On the other hand, for the case II, the number ratio of the two types of spots remains almost constant (with small fluctuations). In this case, differentiation from chaotic spots continues with some rate, and the spot is distributed in space at some rate. The pattern formed by the different types of spots is also independent of the boundary conditions.

Since we are interested in this differentiation process, we study this type in more detail, with regards to the phase diagram, initial condition dependence, and robustness of pattern against macroscopic perturbation. Although we use a few specific reaction networks showing spot differentiation, the qualitatively same results are obtained for a variety of reaction networks.

4.1. *Phase diagram*

Now we study the parameter dependence of each type of dynamics, in particular, the bifurcation diagram against the change of the parameters A and B, while keeping the other parameter values and initial conditions fixed.

First, for the homogeneous type, the bifurcation diagram is qualitatively same with that for the original GS equation. Typical phase diagrams for differentiation type are shown in Fig. 12. Note that for the case II differentiation, there appears a transition to case I, as the parameters are changed, while there are some cases in which only case I differentiation exists in the phase diagram. Generally, as the decay rate for v^i is decreased, there are bifurcations from a uniform system to a system with a single type of spots and then finally to turbulent spatial structure without any clear spots. This sequence of bifurcations is observed generally for a variety of reaction networks W.

Now, we investigate the transition from the case II differentiation to case I in more detail. In the example of Fig. 12(b), as the parameter A is changed from 0.026 to 0.028 with fixing the parameter $B = 0.06$, there appears a transition from case II to case I differentiation. This transition process is represented by the increase of the distance of the neighboring chaotic spots as A is varied. At

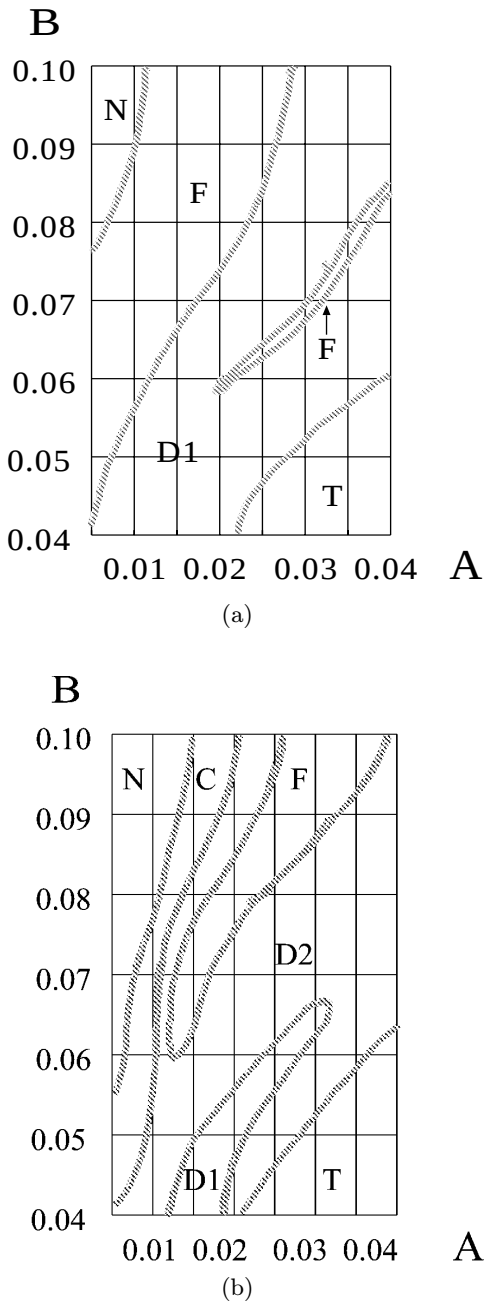
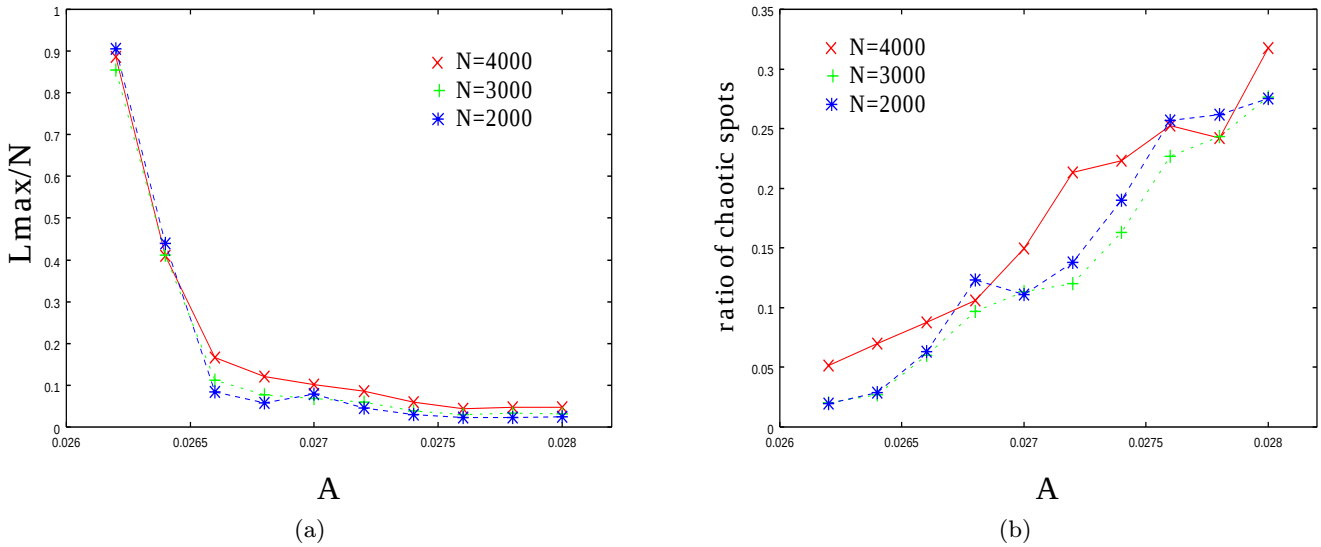


Fig. 12. Rough phase diagrams for the network adopted in Fig. 8(a) (case I, (a)), and Fig. 8(b) (case II, (b)). For a given network, the temporal evolution is computed for a fixed initial condition with two spots with $u^i = 0.50$ and $v^i = 0.250$ for all i. The diagram is obtained by changing A and B by 0.0025. The phases are denoted as follows: N: spatially uniform state with $u^i = 1$ and $v^j = 0$ (without any spots). F: fixed point spots. C: chaotic spots. $D1$: case I differentiation. $D2$: case II differentiation. T: chemical turbulence, without clear spots.

$A = 0.026$, the maximal distance between neighboring chaotic spots ($L_{\max}$) is almost equal to the total system size and all the spots except for those at the two edges are fixed point type. Hence the



(a) (b)

Fig. 13. (a) The ratio of the maximal distance of the neighboring chaotic spots ($L_{\max}$) to the system size (N), plotted as a function of the parameter A for case II differentiation (by fixing the parameter at $B = 0.06$). The transition from the case II differentiation to case I is seen as the increase $L_{\max}$ to N. Results from the system size $N = 2000$, 3000 and 4000 are overlaid, which suggests that the transition is independent of the system size. (b) The number ratio of chaotic spots to the total number of spots, plotted as a function of the parameter A for the case II differentiation (by fixing the parameter $B = 0.06$). Again the results from the system size $N = 2000$, 3000 and 4000 are overlaid.

separation from outer to inner type is resulted, which means the case I differentiation. At $A = 0.028$, $L_{\max}$ is small and there are many chaotic spots within the domain where spots exist.

The decrease of $L_{\max}$ with the increase of A is shown in Fig. 13(a), and this form is independent of the total size of the system. The transition from case II to I differentiations is now represented as the increase of $L_{\max}$ up to the system size. In the case II differentiation, the number ratio of the two types of spots remains nearly fixed, and is independent of the system size, although there remain some small fluctuations [See Fig. 13(b)]. In this case, differentiation from chaotic spots continues with some rate, and the spot is distributed in space at some rate. The pattern thus formed by these two types of spots is independent of the boundary conditions.

4.2. *Initial condition dependence*

In the differentiation type, spots with fixed point dynamics no longer differentiate to the other type with chaotic dynamics, but only replicate. The differentiation from the chaotic type is irreversible. Hence, if there are only spots with fixed point dynamics in the beginning, no differentiation occurs and the pattern with homogeneous spots is obtained. On the other hand, the pattern with chaotic spots is recovered from a single chaotic spot. For example, when a single chaotic spot is selected from a final pattern, and is used as an initial condition, then almost the same differentiation pattern is recovered from this single chaotic spot (see Fig. 14).

Accordingly, the differentiation of spots depends on the choice of initial conditions. We now study this initial condition dependence of patterns in more detail, for the case II differentiation.

First we adopt initial conditions with $v^i \neq 0$ only within a restricted interval so that two spots are formed. Chemical concentrations of v^i are set to be at random, from which the initial chemical diversity S is computed. For initial conditions with sufficiently large chemical diversity, a chaotic spot will appear, while the ratio to have such chaotic spots decreases as the initial chemical diversity is decreased (see Fig. 15). Once a chaotic spot does appear, the differentiation process we have discussed always follows in the parameter regime for the case II differentiation. The resulting pattern has almost the same fraction of chaotic spots.

As a next choice of initial conditions, we put many spots all of which have the same initial condition so that there exists high chemical diversity enough to produce chaotic spots. In this case, all the spot dynamics switch to the type of fixed point dynamics. In other words, the state with all chaotic

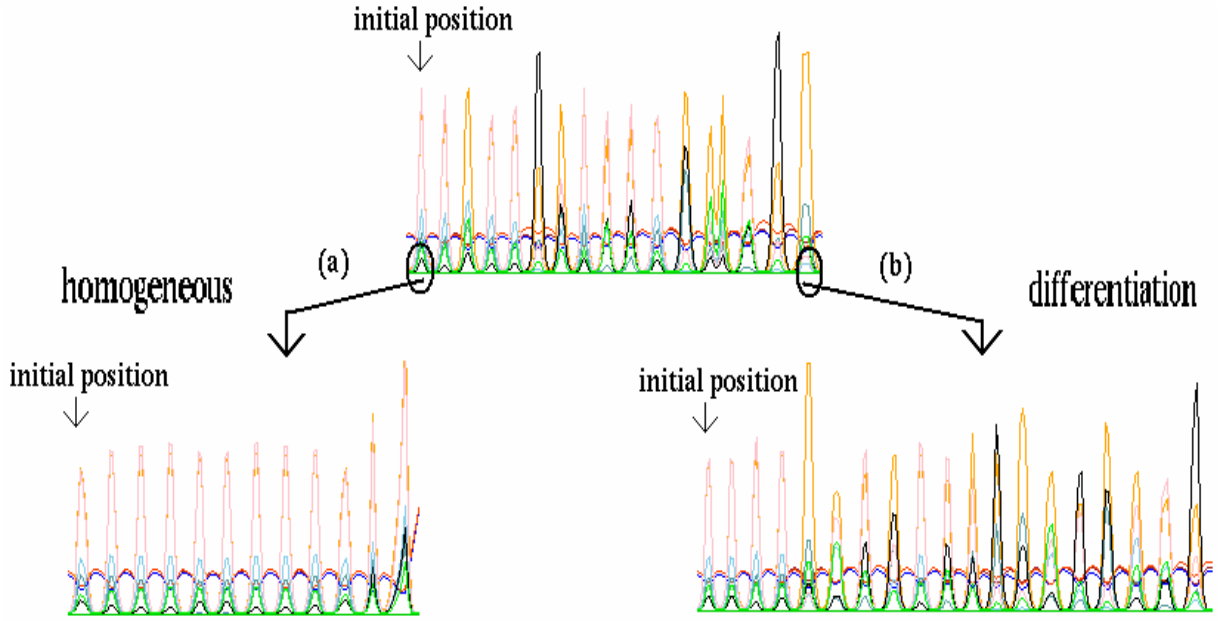


Fig. 14. An example of snapshot pattern of $u_i(x,t)$ and $v_j(x,t)$ after "transplant experiment" of (a) single fixed point spot or (b) chaotic spot of the top figure to the new medium. The top pattern is obtained after the evolution from a single spot, for the case II differentiation. For each of the lower figures, a spot from the top figure is used as an initial condition. If there is only a spot with fixed point dynamics in the beginning, no differentiation progresses (a). On the other hand, the pattern with differentiation is recovered from single chaotic spot (b).

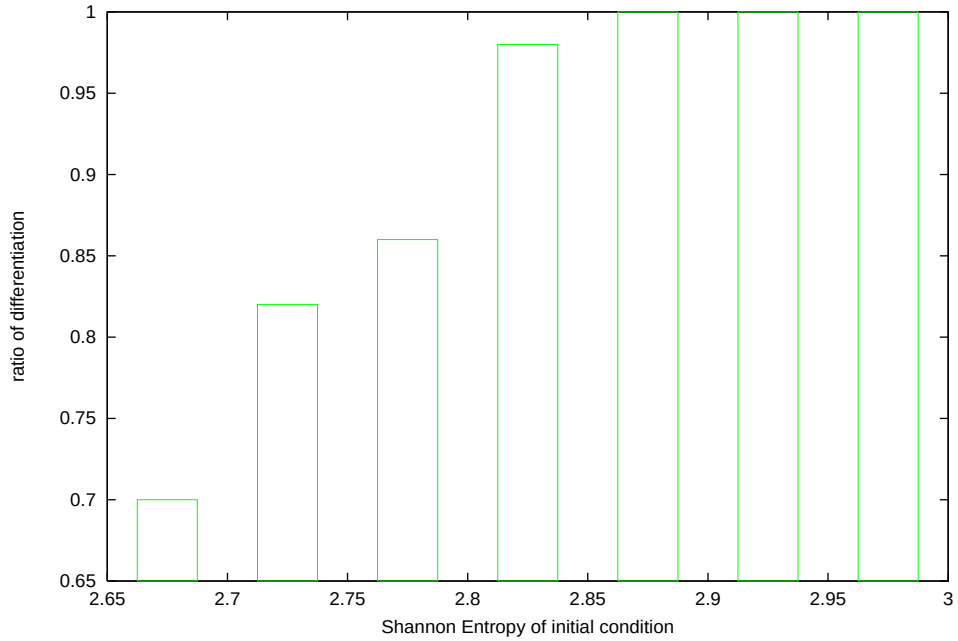


Fig. 15. The relation between initial chemical diversity and the frequency of occurrence of differentiation events for the case II differentiation. As initial conditions, chemical concentrations of v are chosen randomly only in a small interval supporting two spots (in the other region they are set at 0). Then chemical diversity $S(0)$ at the center of space is computed by this initial condition. Each histogram is constructed from 50 samples whose initial conditions fall in each bin of the chemical diversity.

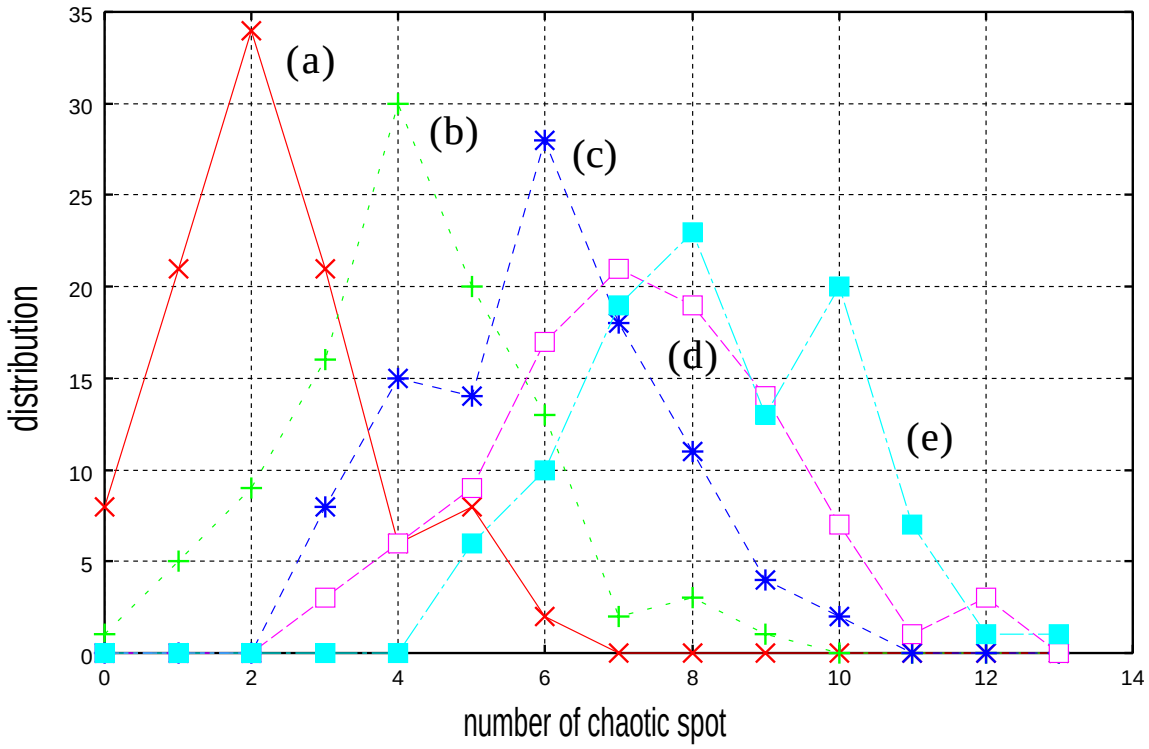


Fig. 16. Initial condition dependence of the case II differentiation. Starting from initial conditions with random distribution throughout the whole system, the temporal evolution is computed, to compute the final fraction of chaotic spots. In each sample, the initial variance of v is varied by setting the initial concentration as $v_i(x,0) = 0.25 + 0.05 \times \mathrm{rand}_h(x)$ where $\mathrm{rand}_h(x)$ is a uniform random variable over $[-h, h]$. By changing the integer value h, the initial variance of v is changed. For each value of h, 50 samples of initial conditions are chosen to get the histogram of the final number of chaotic spots. The distributions for (a) $h = 1$, (b) $h = 2$, (c) $h = 3$, (d) $h = 4$ and (e) $h = 5$ are plotted.

spots is unstable, and due to the symmetry of initial condition, all the spots fall into a fixed point through the interaction of spots.

Note that the fraction of chaotic spots is not identical, if we do not start from a few chaotic spot initial conditions. For example, we study the case that product chemicals v are randomly distributed throughout the whole system initially. When the variance of the initial concentrations of v is large, the fraction of chaotic spots changes by initial conditions. Thus, the final pattern (i.e. the fraction of chaotic spots) has strong initial condition dependence. On the other hand, if we start from initial conditions with just two chaotic spots, the final fraction of chaotic spots is almost the same (see Fig. 16).

4.3. *Spot differentiation in two-dimensional case*

So far, we studied the reaction–diffusion Eq. (2) in one-dimensional space. It is interesting to check if the spot differentiation also occurs in a higher dimensional case. Here we take the same reaction network for the previous example, and compute the partial differential equation (2) for a two-dimensional case. Again we find both case I and II differentiations by changing the parameters A and B (see Figs. 17 and 18). In the case II, the location of chaotic spots form a complex pattern as in Fig. 2(h).

5. Discussion

In the present paper, we have shown differentiation of spots in a class of reaction–diffusion equations. Here one type of spots replicates or differentiates into another type of spot that has fixed point dynamics. Since the first type can have multipotency, i.e. the ability to produce the other type of spots, it can be regarded as a "stem-cell-type" spot. This differentiation from a stem-cell-type to fixed point spots is generally observed for a class of

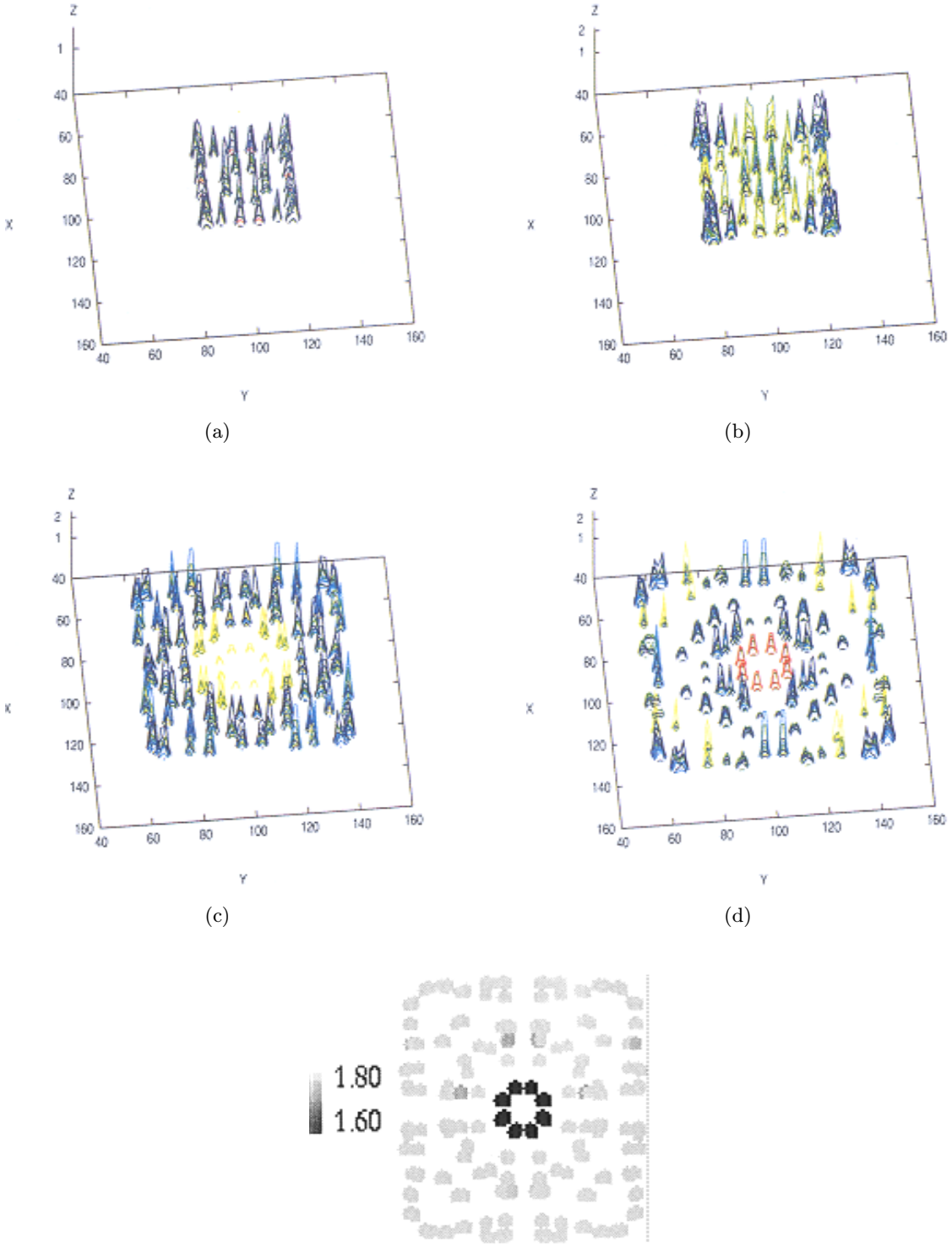
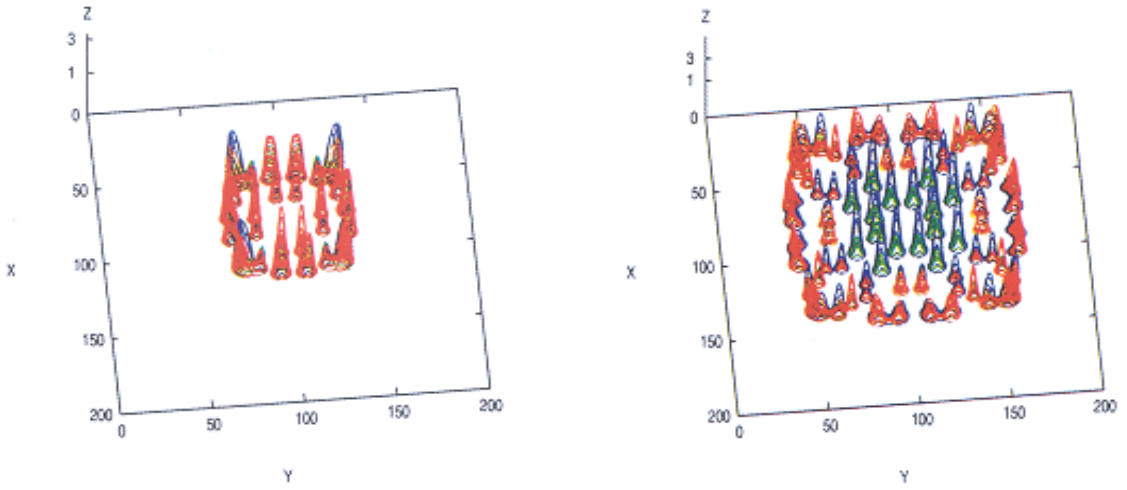
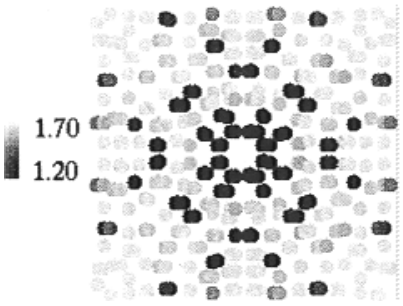


Fig. 17. An example of case I differentiation in a two-dimensional space. A series of snapshot patterns is plotted ((a) $t = 600$, (b) $t = 900$, (c) $t = 1500$ and (d) $t = 1800$). Chemical diversity $S_i(nT)$ at the time for the snapshot pattern (d) is represented in (e). The parameter values are $A = 0.02$, $B = 0.15$, $D_u = 3.0$ and $D_v = 0.03$.



(a) (b)

(c) (d)



(e)

Fig. 18. An example of case II differentiation in a two-dimensional case. A series of snapshot patterns is plotted ((a) $t = 600$, (b) $t = 1200$, (c) $t = 1800$ and (d) $t = 3600$). Chemical diversity $S_i(nT)$ at the time for the snapshot pattern (d) is represented in (e). The parameter values are $A = 0.02$, $B = 0.08$, $D_u = 5.0$ and $D_v = 0.05$.

reaction–diffusion equations. Since the pioneering study of Turing [1952], there has been a great deal of efforts dedicated to relating reaction–diffusion systems to morphogenesis in biological systems. However, the systems studied so far are not enough to describe the complexity observed in biological pattern formation, which includes cell differentiation from stem cells, determination of fixed types, irreversibility and robustness in development. Our reaction–diffusion equations studied here give a first example towards this direction.

In both cases of differentiation, spot types with smaller diversity and fixed-point dynamics are differentiated from the initial type with high chemical diversity and chaotic dynamics. The differentiation process here reminds us of that from stem cells to determine differentiated cells in biological development. In a biological stem cell system, initial cell types can either replicate or differentiate into different types. Through the differentiation, multipotency comes to be lost, and eventually cell types that can only replicate are produced. In [Furusawa & Kaneko, 2000], appearance of stem cell is discussed as a natural consequence of dynamical systems with intracellular biochemical reactions and cell-to-cell interaction, by assuming a cellular structure itself. In the present paper, it is shown that such "stem cell" systems naturally appear in a reaction–diffusion system, without assuming the cellular structure in advance. When differentiation is observed in our model, the diversity and local KS entropy always decrease as the differentiation progresses [Furusawa & Kaneko, 2000]. Differentiation into a spot with fixed-point type dynamics is irreversible. This is consistent with the loss of multipotency observed in real cellular systems.

With regard to a broader context of the study of reaction–diffusion equations, it is interesting to note that a pattern with two distinct spatial scales is formed in case II differentiation, i.e. the size of spot and the mean distance between two chaotic spots. In a variety of pattern formation in nature and society, hierarchical structure with several spatial scales is observed. Our example gives a demonstration that such structure is formed from a reaction–diffusion equation.

Also it is interesting to note that the behaviors from a variety of reaction networks are classified just into the three types, although we have studied more than a thousand reaction networks. It will be important to classify possible types of spatio-temporal patterns that appear when the complexity of the internal reaction dynamics is increased. On the other hand, to find the minimal number of chemicals for differentiation process in this model, and to elucidate the mechanism of the differentiation remain to be a future problem.

Since our model includes only reaction and diffusion, without any other type of mechanism, the present study is also relevant to the study of prebiotic evolution leading to proliferation and diversification of cells. Indeed, the importance of autocatalytic nature of the reaction networks studied here is already stressed in the hypercycle proposed by Eigen and Shuster [1979]. On the other hand, possible relevance of the spatial structure in hypercycles to resist parasites [Bresch *et al.*, 1980] or short cuts of network structure [Niesert *et al.*, 1980] has been discussed from various contexts [Cronhjort & Blomberg, 1997; Boerljist & Hogeweg, 1991; McCaskill, 1997; Chaòon & Nuño, 1995]. In contrast to the previous studies, the present study explains not only the robust replication process but also the diversification to different cell types.

Since Turing's pioneering study, the reaction–diffusion system has been studied in depth and the analytic tools have already been developed for those with few degrees of chemical species. Reaction–diffusion equations with many degrees of freedom can produce a variety of novel spatio-temporal patterns. In the present paper, we have shown reproduction and differentiation of spots, irreversible differentiation process with the loss of diversity of dynamics, initial condition dependence of pattern formation, and robust pattern formation against macroscopic perturbation. In future, it will be important to explore further possibility in reaction–diffusion equations, in connection with development of biological organisms.

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