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INPUT-DEPENDENT WAVE PROPAGATIONS IN ASYMMETRIC CELLULAR AUTOMATA: POSSIBLE BEHAVIORS OF FEED-FORWARD LOOP IN BIOLOGICAL REACTION NETWORK*

Akinori Awazu

Department of Mathematical and Life Sciences, Hiroshima University,
Kagami-yama 1-3-1, Higashi-Hiroshima 739-8526, Japan.

Abstract. Dynamical aspects of the asymmetric cellular automata were investigated to consider the signaling processes in biological systems. As a metamodel of the cascade of feed-forward loop type network motifs in biological reaction networks, we consider the one dimensional asymmetric cellular automata where the state of each cell is controlled by a trio of cells, the cell itself, the nearest upstream cell and the next nearest upstream cell. Through the systematic simulations, some novel input-dependent wave propagations were found in certain asymmetric CA, which may be useful for the signaling processes like the distinction, the filtering and the memory of external stimuli.

1. Introduction.

Signal transduction and gene expression are the most important information processing in several biological systems[1, 2, 3, 4]. In these processes, several functions such as the amplification or distinction of the specific signals, filtering the noises, memory, etc. are realized by several biochemical reactions. The understanding of such non-trivial phenomena are important for not only biology but also non-equilibrium physics and the information engineering.

The biological information pathways often consist of some cascade structures. Then, some types of open flow dynamical systems were studied as models of such reaction systems[4, 5]. Recently, the network motif called 'feed-forward loop (FFL)' has been well known to appear frequently in biological reaction networks[6], where the state of each element is controlled by the states of the nearest upstream elements and those of the next nearest upstream. Such network motif is considered much important for the gene regulations generating the spatial and temporal patterns in morphogenesis[6, 7].

The aim of this paper is to uncover the potential, the possible functional behaviors, of FFL type reaction systems, which should provide important hints to understand several signaling processes. For this aim, we need to prepare simpler dynamical systems that can be treated systematically. Thus, as one of the simplest

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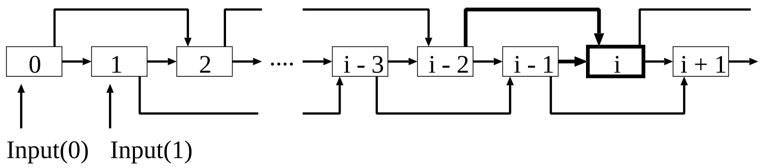

FIGURE 1. (a) Illustration of FFLCA. Numbers indicate the cell indexes.

dynamical systems, the asymmetric cellular automata (CA) inspired by the FFL type network motif are investigated.

In this paper, we mainly focus on the input-dependent phenomena of such asymmetric CA to consider the transduction of the signals in biochemical reaction networks. In the next section, we introduce the model. In section 3, we show some remarkable behaviors of such CA. Here some novel input-dependent wave propagations are found, which can be useful for signaling processes. In the last section, we summarize and show the examples of more complex behaviors in this model.

2. **Model.** Recently, CA has been studied extensively to consider the replications and diversification of lives (or artificial lives)[8, 9], calculation processes of some types of machines[10, 11], pattern formations of reaction diffusion systems[12], flow of various types of particles[13, 14, 15], etc.. To this time, elementary CA are studied systematically by Wolfram, and some variants are proposed[16].

For example, the time evolution of the simplest asymmetric CA are given by,

$$X_{n+1}^i = F(X_n^{i-1}, X_n^i). \tag{1}$$

Hers, X_n^i gives 0 or 1 (i gives the cell number and n gives the time.) and the evolutions of X_n^i are determined by only the states of two cells, itself (X_n^i) and the upstream cell (X_n^{i-1}), through the dynamic rule $F()$. (16 types of $F()$ can be defined.)

On the other hand, the time evolution of the state X of the element i constructing the FFL is roughly described as $X[i]_{t+\delta t} = F(X[i]_t, X[i-1]_t, X[i-2]_t, ...)$. In the living systems, each element has almost two discrete states like "Active - Inactive" or "ON - OFF" in most of the cases[2, 3, 4]. These facts seem the dynamics of such systems can be approximately described by the simple asymmetric CA.

Then, in this paper, we consider a following CA with stochastic inputs, as a meta-model of FFL cascade;

$$S_n^0 = \text{Input}(0), \tag{2}$$

$$S_n^1 = \text{Input}(1), \tag{3}$$

$$S_{n+1}^i = F_R(S_n^{i-2}, S_n^{i-1}, S_n^i). \tag{4}$$

Here, i gives the cell index ($2 \leq i < N$ in (4)), n is the discrete time and S_n^i is the state of ith cell at time n. S_n^i can have two values, 0 or 1, where $S_n^i = 1$ and $S_n^i = 0$ states correspond to the active and inactive states of each element in signaling pathways respectively. Input(0) and Input(1) are the external stimuli to the system which are given 1 with probability P or 0 with probability $1 - P$ independently in each n.

$F_R()$ gives reaction rules. Here, the index R is the rule number as mentioned in the below. Note that $(S_n^{i-2}, S_n^{i-1}, S_n^i)$ has 8 patterns from $(0,0,0)$ to $(1,1,1)$, and S_{n+1}^i is given 0 or 1 for each case obeying the dynamic rules $F_R()$. Then, 256 types of $F_R()$ are allowed from

$F_R(0,0,0) = 0$, $F_R(0,0,1) = 0$, $F_R(0,1,0) = 0$, $F_R(0,1,1) = 0$,
$F_R(1,0,0) = 0$, $F_R(1,0,1) = 0$, $F_R(1,1,0) = 0$, $F_R(1,1,1) = 0$
to
$F_R(0,0,0) = 1$, $F_R(0,0,1) = 1$, $F_R(0,1,0) = 1$, $F_R(0,1,1) = 1$,
$F_R(1,0,0) = 1$, $F_R(1,0,1) = 1$, $F_R(1,1,0) = 1$, $F_R(1,1,1) = 1$.

In other word, we can model 256 types of reaction pathways by $F_R()$. Referring to the Wolfram's way, we name all types of rules by the rule number R which is defined as, $R = 2^0 F_R(0,0,0)$ $+2^1 F_R(0,0,1)$ $+2^2 F_R(0,1,0)$ $+2^3 F_R(0,1,1)$ $+2^4 F_R(1,0,0)$ $+2^5 F_R(1,0,1)$ $+2^6 F_R(1,1,0)$ $+2^7 F_R(1,1,1)$. In convenience, we call such CA as FFLCA (feed-forward loop CA). The illustration of FFLCA is given in Fig. 1.

Note, FFLCA with $R = 0$, 17, 34, 51, 68, 85, 102, 119, 136, 153, 170, 187, 204, 221, 238 or 255, are completely equivalent to one of the asymmetric CA described by Eq. (1). It is known that such type of CA cannot realize any remarkable complex dynamics as obtained in FFLCA or those like type IV dynamics named by Wolfram[16] because such CA are too simple. However, some of the other FFLCA exhibit several non-trivial dynamics, several types of input-dependent wave propagations, as shown in the following sections.

3. **Typical input-dependent wave propagations in FFLCA.** In this section, the dynamical aspects of FFLCA are considered. Depending on the rule number R, FFLCA show a variety of patterns in $i - n$ space: uniform states, stripe or checker flag patterns, chaotic pattern, etc.. It is noted that at least the system needs to exhibit the input-dependent dynamics in order to realize the behaviors like signaling processes. Then, we only focus on a part of FFLCA which can show the input-dependent phenomena.

In this section, we consider FFLCA showing two types of wave dynamics against the change in the input properties.

I) FFLCA showing two distinct pulses.

As the first example, we consider the behaviors of the FFLCA with $R = 120$ obeying the following reaction rule:

0) $F_{120}(0,0,0) = 0$, 1) $F_{120}(0,0,1) = 0$, 2) $F_{120}(0,1,0) = 0$, 3) $F_{120}(0,1,1) = 1$,
4) $F_{120}(1,0,0) = 1$, 5) $F_{120}(1,0,1) = 1$, 6) $F_{120}(1,1,0) = 1$, 7) $F_{120}(1,1,1) = 0$.

This FFLCA show the following input-dependent behaviors; i) No waves of $S_n^i = 1$ are created when both Input(0) and Input(1) are 0. ii) When only one of the inputs, Input(0) or Input(1), are given 1, the particle like traveling waves of $S_n^i = 1$ appear as shown in Fig. 2(a). iii) When both Input(0) and Input(1) are given 1, the traveling structure in which $S_n^i = 1$ and $S_n^i = 0$ are mixed in i - n space appear as shown in Fig. 2(b) (we call it mixed wave.). Thus, two types of traveling waves are observed depending on the inputs.

Here, the particle like wave is realized by the rule 4) which give the temporal evolution as $S_m^{j-2} = 1$, $S_m^j = 0 \to S_{m+1}^{j-2} = 0$, $S_{m+1}^j = 1$ when $S_m^{j-1} = 0$. Then, $S_{m'}^{j'} = 1$ state can propagate to downstream.

On the other hand, the rule 3), 5), 6) and 7) construct the mixed wave. These rules indicate that S_{m+1}^j becomes 1 if two of three cells' states, S_m^{j-2}, S_m^{j-1} and S_m^j are 1 but S_{m+1}^j becomes 0 if all of them are 1. The former effect increases the area

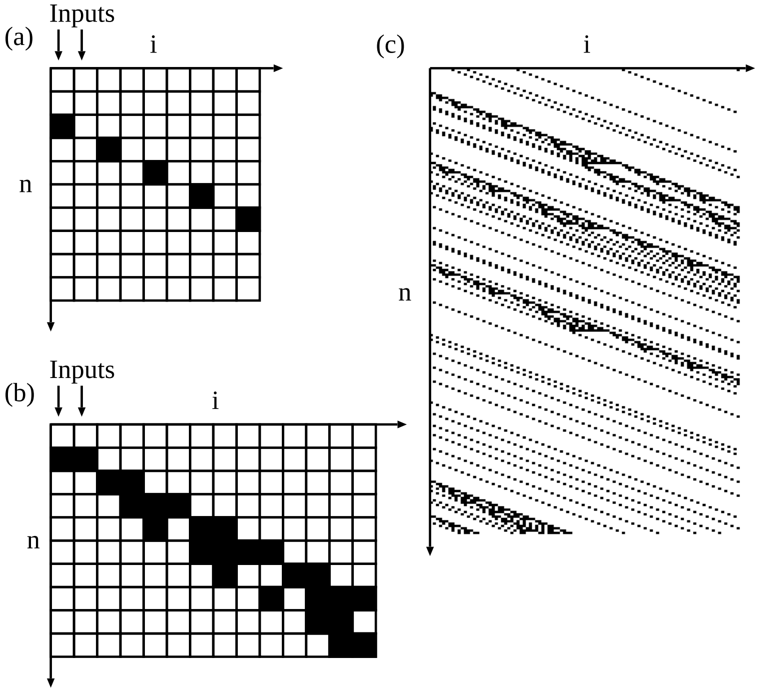

FIGURE 2. Typical temporal evolution of the FFLCA with R=120. (a) Particle like wave. (b) Mixed wave. (c) Typical temporal evolution with $P = 0.2$ ($N = 100$). White cells indicate $S_n^i = 0$ and blacks indicate $S_n^i = 1$.

$S_{m'}^{j'} = 1$ as well as the latter effect creates the voids of $S_{m'}^{j'} = 0$. Thus, the mixed wave propagate with the gradual expansion in $i - n$ space.

Figure 2(c) show the typical temporal evolution of this FFLCA with $N = 100$ and $P = 0.2$ where two types of pulse like traveling waves coexist. It is noted that the rule 1) and 2) are not important to realize the present behavior. The similar behaviors are found in some other FFLCA for example $R = 88$, 108, 113, 133, 180, 225 and 229.

II) FFLCA showing the wave filtering.

As the second example, we consider the behaviors of the FFLCA with $R = 248$ obeying the following reaction rule:

0) $F_{248}(0,0,0) = 0$, 1) $F_{248}(0,0,1) = 0$, 2) $F_{248}(0,1,0) = 0$, 3) $F_{248}(0,1,1) = 1$,
4) $F_{248}(1,0,0) = 1$, 5) $F_{248}(1,0,1) = 1$, 6) $F_{248}(1,1,0) = 1$, 7) $F_{248}(1,1,1) = 1$.

This FFLCA show the following input-dependent behaviors; i) No waves of $S_n^i = 1$ are created when both Input(0) and Input(1) are 0. ii) When only one of the inputs, Input(0) or Input(1), are given 1, the particle like traveling waves of $S_n^i = 1$ appear as shown in Fig. 3(a). iii) When both Input(0) and Input(1) are given 1, the traveling wave of $S_n^i = 1$ where the front of this propagates fast but the rear of this moves slowly as shown in Fig. 3(b). Then, such waves expand rapidly in i - n space (we call it expanding wave.).

Moreover, the particle like wave disappears when it collides to the expanding waves (Fig. 3(b)). Thus, the waves created by the input "Input(0) or Input(1) are

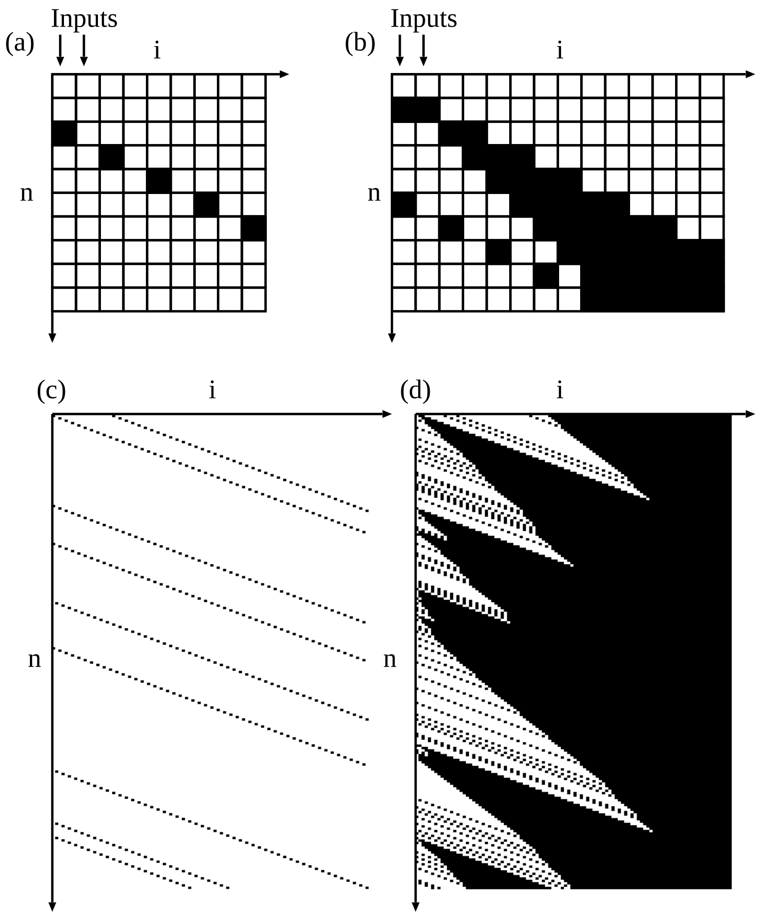

FIGURE 3. Typical temporal evolution of the FFLCA with R=248. (a) Particle like wave. (b) Expanding wave. Typical temporal evolution with (c) $P = 0.01$ and (d) $P = 0.15$ ($N = 100$). Colors of each cell are the same meaning as the previous figure.

1", tend to be blocked with the increase in the frequency of the input "Input(0) and Input(1) are 1".

Here, the particle like wave is realized by the rule 4) with the same manner as the previous. On the other hand, the rule 3), 5), 6) and 7) construct the expanding wave. These rules indicate that S^j_{m+1} becomes 1 if more than one cells' states of three, S^{j-2}_m, S^{j-1}_m and S^j_m are 1. Thus, the area of $S^{j'}_{m'} = 1$ expands rapidly in $i - n$ space.

Figure 3(c) and 3(d) show the typical temporal evolution of this FFLCA with (c) $P = 0.01$ and (d) $P = 0.15$ ($N = 100$). As shown in these figures, the propagations of the particle like waves are blocked by the expanding waves when P is large while only the particle like wave propagates when P is smaller. Here, it is noted that the rule 1) and 2) are not important to realize such behavior. Similar behaviors with the wave blocking are found in some other FFLCA for example $R = 37$, 49, 67, 111, 115, 131 and 216.

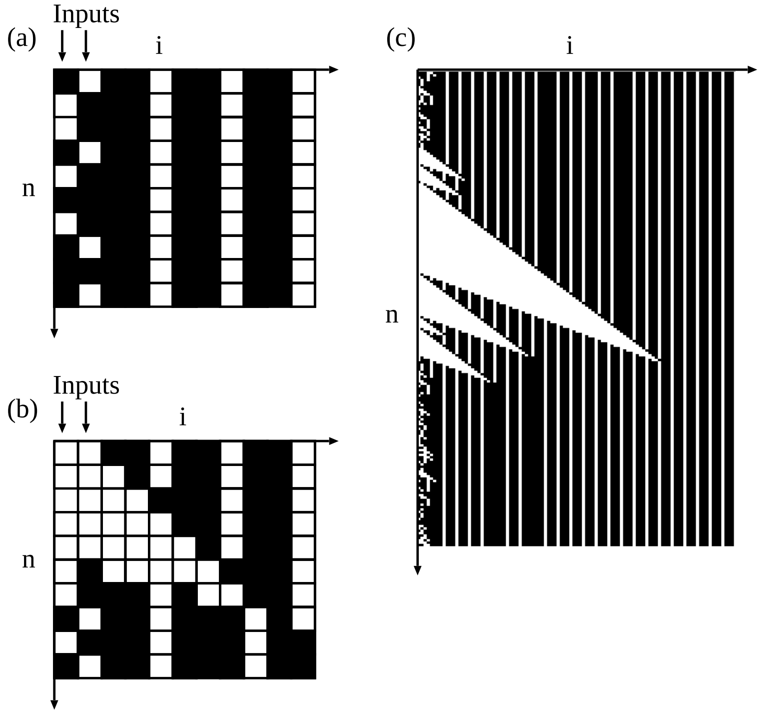

FIGURE 4. Typical temporal evolution of the FFLCA with R=188. (a)Pattern is sustained. (b) Pattern is re-created by $S_n^i = 0$ waves. (c) Typical temporal evolution with $P = 0.5 \to 0.01 \to 0.5$ ($N = 100$).

III) FFLCA behaves like memory.

As the third example, we consider the behaviors of the FFLCA with $R = 188$ obeying the following reaction rule:

0) $F_{188}(0,0,0) = 0$, 1) $F_{188}(0,0,1) = 0$, 2) $F_{188}(0,1,0) = 1$, 3) $F_{188}(0,1,1) = 1$, 4) $F_{188}(1,0,0) = 1$, 5) $F_{188}(1,0,1) = 1$, 6) $F_{188}(1,1,0) = 0$ 7) $F_{188}(1,1,1) = 1$.

This FFLCA realizes the sustainment and the re-creation of the pattern of S_n^i as shown in Fig. 4. i) When Input(0) or/and Input(1) are 1, the pattern of S_n^i is sustained temporally as shown in Fig. 4(a). Here, several patterns can be constructed by the area of $S_n^i = 1$ with several length and the area of $S_n^i = 0$ with the unit length. ii) When Input(0) and Input(1) are kept 0 for a enough time span, the traveling cluster of $S_n^i = 0$ appears and re-creates the patterns of S_n^i as shown in Fig. 4(b).

Figure 4(c) shows the typical temporal evolution of this FFLCA with $N = 100$. Here, we change P as $P = 0.5 \to 0.01 \to 0.5$. When $P = 0.01$, the pattern of S_n^i is re-created where several patterns can be formed depending on the sequence of Input(0) and Input(1), and such formed patterns are sustained when P is large. Thus, this FFLCA can behaves like the memory.

The sustainment of the formed patterns is realized by the rule 2) $\sim$ 7) as follows. The rule 2) $\sim$ 5) indicates that S_n^2 becomes 1 if one of the inputs, Input(0) or Input(1), are 1. Moreover, by the rule 7) and 8), S_n^2 does not change if Input(0) and Input(1) are 1. Thus, $S_n^2 = 1$ is sustained unless Input(0) and Input(1) are 0. In such a case, S_n^3 is also 1 and this state is sustained because S_n^2 is given 1. Then, S_n^4 (= 0 or 1) is fixed temporally because $S_n^2 = S_n^3 = 1$. By the similar way, the sequences of S_n^j for $j > 5$ are also fixed; $S_n^j = 1$ is fixed if S_n^{j-1} or S_n^{j-2} are 1 while $S_n^j = 0$ or 1 is fixed if S_n^{j-1} and S_n^{j-2} are 1.

The rule 0) and 1) indicates that if $S_m^{j-2} = 0$, $S_m^{j-1} = 0$ appear, S_{m+1}^j become 0. Then, the area $S_n^i = 0$ can expand to downstream cells if Input(0) and Input(1) continues to be 0 for a long time span. The profiles of the re-created pattern depends on the number and the propagating distance of $S_n^i = 0$ clusters.

The similar behaviors are found in some other FFLCA for example $R = 158$, 159, and 194.

4. **Summary and discussions.** In this paper, feed-forward loop cellular automata (FFLCA) is introduced to study the possible dynamical behaviors of FFL type network motif in biochemical reaction systems. Against the inputs to upper cells, several types of input-dependent wave propagations are observed in FFLCA with certain rules.

Such input-dependent behaviors are realized by the interactions among two or more types of propagating structures with different velocities. It is noted that we can observe similar structures also in simpler asymmetric CAs as described by Eq. (1) with certain dynamic rules. However, their velocities are given unique for each dynamic rule. Then, such simpler CAs cannot realize the input-dependent phenomena as shown in FFLCA.

We expect our results may provide some insight to biological phenomena. Of course the presented CA is too simple to give a good approximation of the real biological network. However, the results obtained in such simple dynamical systems should give a base to characterize the behaviors in several signaling processes.

The living cells can sense and respond to environmental signals. For example, Eukaryotic cells can sense the chemical gradient and move with directional preference toward or away from the source of the chemical cues[17, 18, 19], many species of bacteria regulate gene expression in response to changes in cell population density (Quorum sensing)[20, 21, 22], etc..

We expect some of the signaling pathways in these organisms exhibit similar properties to FFLCA because such properties seem useful to sense environmental changes. For example, it is expected that these organisms may easily sense the change in the concentrations of chemicals in the environment if their signaling pathways can form two or more different patterns depending on the frequency of the receipt of chemicals. Such "amplification" can be realized by FFLCA as shown in Fig. 2 and 3; where P is assumed as the frequency of the receipt of chemicals like cAMP, autoinducer released by quorum sensing bacteria, etc..

Moreover, large phenotype fluctuations in isogenetic cells have been reported in several organisms recently[23, 24, 25]. We also expect the formation of several quasi-stable patterns in FFLCA that behaves like memory may provide some hints to such large fluctuations.

In the presented study, we mainly focus on the example FFLCA showing two types of pattern dynamics depending on the input sequence. Of course, more complex input-dependent behaviors were also observed in FFLCA with certain dynamic rules.

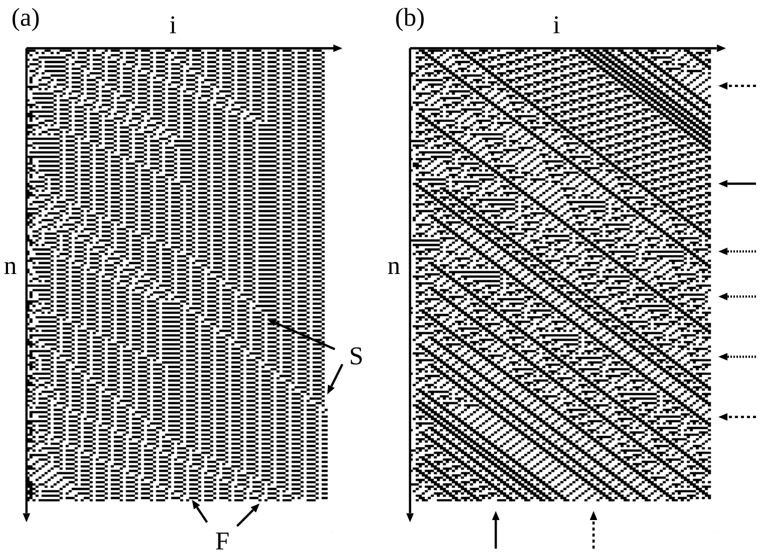

FIGURE 5. Typical temporal evolution of FFLCA with (a) $R = 65$ ($P = 0.5$) and (b) $R = 73$ ($P = 0.5$).(a) F indicates the fast wave and S indicates the slow waves. (b) Types of arrows indicates the types of patterns.

For example, in the FFLCA with $R = 65$, three types of defect waves, the standing wave, the slow wave and the fast wave, appear and show the annihilation or the change to the other wave types by the collision with each other (Fig. 5(a). Similar behaviors are found also in the FFLCA with $R = 54$, 61, 125 and 147.). In the FFLCA with $R = 73$, moreover, three types of traveling patterns appear depending on the input sequences and coexist with each other (Fig. 5(b). Similar behaviors are found also in the FFLCA with $R = 109$). We need to clear the relation between the dynamics and the rules for such complex cases.

Thus, as given in our results, FFL type network motif involves a rich potential to realize a variety of signaling processes. In addition, we should consider the characteristics of the other types of network motifs like the single-input modules (SIM) and the dense overlapping regulons (DOR), and the cross-talk among them[1, 2, 3, 4, 6]. The relation between each FFLCA rules showing some functional behaviors and the dynamical aspects of the chemical reactions, the mechanical properties of biological molecule, etc. should also be uncovered in the future.

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E-mail address: awa@hiroshima-u.ac.jp