Modeling Cell Division of *B. subtilis* Using Dynamic Division of Reaction Spaces in a Membrane Artificial Chemistry

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Abstract

Localization of molecules in a natural cell plays important roles in interesting behavior of organisms like cell division and morphogenesis. Such localization is mostly formalized in a continuous space or lattice. This paper takes another approach using an artificial chemistry with membranes; we propose a dynamic division of reaction spaces to deal with molecular localization. As an application of the method, we modeled the cell division of *B. subtilis*. We executed the model on a simulator and observed the intended results.

Introduction

Living organisms show many kinds of interesting behavior whose mechanisms are not easily understood. They include reproduction, morphogenesis, evolution, etc. In some of them, the properties and dynamics of lipid membranes play important roles. As one of the main interests in the field of artificial life is to understand the essence of living system, numerous formalisms have been proposed and used to model the behavior of life in which membranes take their part; artificial chemistries (AChems) are among them (Dittrich et al., 2001). For example, Madina et al. studied the formation of proto-cell structures using their 3D Lattice Artificial Chemistry (Madina et al., 2003). They observed in the model that amphiphilic molecules are organized into membrane-like structures.

Besides the properties of membranes, another factor is also important to understand interesting behavior: localization of molecules. For example, in the early stage of *C. elegans* (a kind of worm) embryogenesis, the point where the sperm enters decides the localization of specific proteins, which induces asymmetric cell division (Kemphues, 2000). It is beneficial for a formalism to be capable of dealing with such localization.

There seem to be two established methods to handle it: one assumes a continuous space and the positions of molecules; the other employs a lattice (1D, 2D or 3D, of squares or other shapes) and places molecules in lattice cells (Arjunan and Tomita, 2010). But both methods would have drawbacks when they are to be applied to modeling and simulating a life-like system with many compartments separated by membranes. The first method may require much computational resource to calculate the behavior of molecules. With the second method, it seems difficult to scale and adapt the lattice size and granularity when, for example, morphogenesis from zygote to adult is to be modeled and simulated.

In this study, we take a different approach. Instead of using the position of molecule in a continuous space or introducing a pre-defined spatial structure, we divide reaction spaces dynamically. To express it, we extend our AChem (Amari and Tominaga, 2009). Then we model the cell division of *B. subtilis* to evaluate the expressiveness of the extended AChem.

The organization of the following sections is as follows. First, we illustrate part of the cell-dividing mechanism of *B. subtilis* which we are going to model. Second we briefly explain the base AChem and its extension. Then we model *B. subtilis* cell division and show the result of its execution. Finally, we discuss the proposed approach.

Mechanism of *B. subtilis* Cell Division

B. subtilis is a gram-negative rod-shaped bacterium (Adams and Errington, 2009). It is a model organism in molecular biology. Its cell division has been studied, by which *B. subtilis* reproduces itself, for it is a single-cell creature. The mechanism of division is not completely understood, yet some details have been elucidated up until today.

This section illustrates part of the mechanism that controls the division of *B. subtilis* cell which we model in our AChem.

Forming of Z-ring and division septum

In the process of division, a *Z-ring* and a *division septum* are formed at the mid-cell of *B. subtilis* (Adams and Errington, 2009; NW and J, 2005) (Fig. 1). A Z-ring is a ring-shaped polymer of cytoplasmic protein named *FtsZ*; it is formed by the polymerization of the protein on the inside surface of cytoplasmic membrane. Then the Z-ring constricts towards the deep-cell, and the septum formation follows it; the septum becomes one pole of each daughter cell when the division is complete.

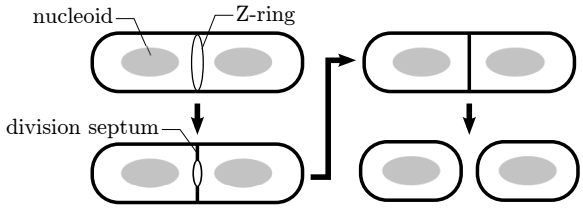

Figure 1: The Z-ring and septum.

In order for a cell to divide evenly, the position of Z-ring (and septum) must be regulated. Two mechanisms are regarded as contributing to the regulation, namely, *nucleoid occlusion* (Adams and Errington, 2009) and the *MinCDJ system* (Adams and Errington, 2009; van Baarle and Bramkamp, 2010; Bramkamp et al., 2008). Nucleoid occlusion prevents the Z-ring from forming near nucleiods (shown as gray ellipses in Fig. 1), while the MinCDJ system prevents one from forming near the cell-poles. In the present study, we model the latter mechanism.

Four kinds of proteins play their roles in the MinCDJ system, namely, *MinC*, *MinD*, *MinJ* and *DivIVA*. DivIVA localizes to the inner surface of cytoplasmic membrane at the cell-poles. It recruits MinJ, and MinJ recruits MinD, and MinD recruits MinC. MinC then prevents the polymerization of FtsZ near the cell-poles. Although the mechanism of the localization of DivIVA to the cell-poles is not yet fully understood, the protein is known to have a characteristic that tends to bind to a concave curve of lipid membrane surface (Ramamurthi and Losick, 2009; Lenarcic et al., 2009).

Completion of cell division

These mechanisms restrict the Z-ring and the division septum to be formed at the mid-cell. The constriction of Z-ring makes the septum curve inward, so DivIVA binds to the cytoplasmic membrane near the Z-ring (Ramamurthi and Losick, 2009; Lenarcic et al., 2009). Then DivIVA recruits MinJ, MinD and MinC proteins, which will work again in the next cell division.

Following the completion of Z-ring constriction, the synthesis of division septum is complete, which is the end of cell division. The Z-ring at a new cell-pole is depolymerized by MinC and other proteins (Gregory et al., 2008); the FtsZ monomers will re-polymerize to form the next Z-ring.

The Base Artificial Chemistry

The present study attempts to model the cell division of *B. subtilis* using an extended AChem, which we propose in this paper. Before we describe the extension, we give an outline of the base AChem (Amari and Tominaga, 2009).

A *v-atom* is an atom in this AChem, whose name starts with an upper-case letter followed by lower-case letters and/or digits, such as `Abc` and `D2e`. A *v-molecule* is a stack of one or more lines of v-atoms. Shown in Fig. 2 is an example of v-molecule consisting of two lines, which is denoted by `0#AbCd/1#EfGh/`, where 1 is the displacement of the second line relative to the first.

A *recombination rule* is a chemical equation in this AChem, which is phrased in terms of *patterns*. A pattern matches (or does not match) a v-molecule. A pattern consists of *atomic patterns* and/or *wildcards*.

An atomic pattern is denoted by a name of v-atom, and matches that v-atom; for example, the atomic pattern `Ab` matches a v-atom `Ab`.

There are two kinds of wildcards, namely, *atomic wildcard* and *sequence wildcard*. An atomic wildcard, denoted by a non-negative integer and surrounding angle brackets like `<1>`, matches any v-atom. The integer is the wildcard's ID, which is referred to by recombination. A sequence wildcard, denoted using an asterisk like `<*2>` or `<3*>`, matches any sequence of zero or more v-atoms. The pattern shown in Fig. 3 (left) is denoted by `0#<*0>Ab<1><2*>/0#Cd<3*>/`, and matches all of the three v-molecules shown in the right of the figure.

The left-hand side of recombination rule consists of one or two patterns, and the right-hand side may have any number of patterns. A recombination rule recombines a v-molecule (or v-molecules) matched by its left-hand side to v-molecule(s) represented by the pattern(s) on the right-hand side. Shown below is an example recombination rule.

$$\texttt{0\#<*0>Ab<1><2*>/} + \texttt{0\#Cd<3*>/}$$
$$\rightarrow \texttt{0\#<*0>Ab<1><2*>/0\#Cd<3*>/} \qquad (1)$$

If this rule is applied to the two v-molecules `0#ZyAbEf/` and `0#CdGhIj/`, they are recombined to one v-molecule of the form `0#ZyAbEf/1#CdGhIj/`.

In this AChem, a *membrane* surrounds a *cubicle*. Membranes can be nested to make a *system*. A system can model a natural cell including cell organelles. Each cubicle has a multiset of v-molecules, and so does each membrane; both are called *reaction spaces*. Each reaction space has its own set of recombination rules. Although reaction spaces are assigned to membranes and cubicles, each reaction space has no spatial structure; it is "well-stirred," i.e., any v-molecule can react with any other v-molecule in the space. An example system is shown in Fig. 4(a). A system is represented by a tree structure, where a cubicle corresponds to a node and a membrane to an edge (Fig. 4(b)).

A v-molecule in the reaction space of a membrane (which can model a protein embedded in a lipid bilayer membrane),

Ab	Cd	
	Ef	Gh

Figure 2: An example v-molecule.

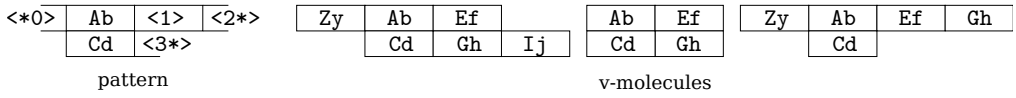

Figure 3: A pattern using sequence wildcards and its matching example v-molecules.

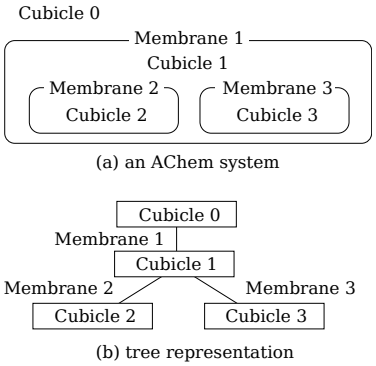

Figure 4: An example system of our AChem.

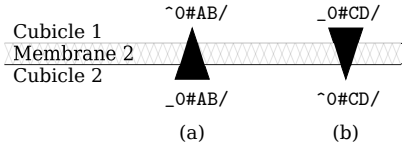

Figure 5: Directions of membrane v-molecules.

called *membrane v-molecule*, has its direction, as the membrane protein does. The direction of membrane v-molecule is *top* (represented by a preceding hat sign (^)) or *bottom* (by an underscore (_)), and is relative to an adjacent cubicle from which the v-molecule is viewed. If a membrane v-molecule is top when it is viewed from a cubicle (as ^0#AB/ viewed from Cubicle 1 in Fig. 5(a) for example), it is bottom when viewed from the opposite cubicle (_0#AB/ from Cubicle 2).

A recombination rule specifies the types of v-molecules using directions. In a recombination rule of cubicle, if a pattern has no direction such as those in Rule (1), it represents a v-molecule in the reaction space of the cubicle. If a pattern has a preceding direction, as in the following examples, it represents a v-molecule having that direction in the reaction space of an adjacent membrane.

$$\texttt{\_0\#AB/} + \texttt{0\#Z/} \rightarrow \texttt{\_0\#ABZ/} \quad (2)$$

$$\texttt{\^{}0\#CD/} + \texttt{0\#Z/} \rightarrow \texttt{\^{}0\#CDZ/} \quad (3)$$

For example, if Rule (2) is applied to a bottom v-molecule _0#AB/ of a membrane (suppose the rule is defined in Cubicle 2 of Fig. 5 and we are viewing the v-molecule (a) from Cubicle 2) and a cubicle v-molecule 0#Z/ (in Cubicle 2, not shown in the figure), they are recombined to a bottom membrane v-molecule (of Membrane 2) of the form 0#ABZ/, i.e., _0#ABZ/.

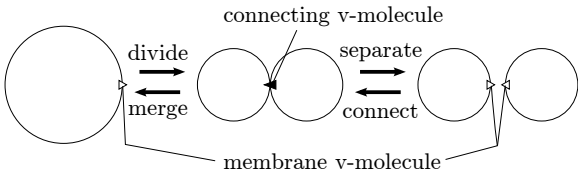

Figure 6: Membrane dynamics in this AChem.

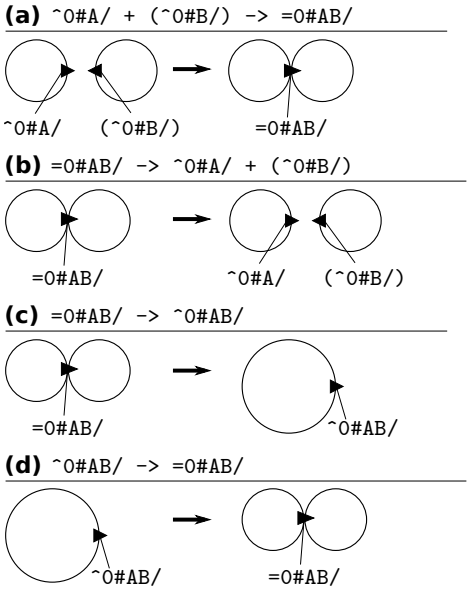

Figure 7: Recombination rules change membrane structure.

The AChem can express the division and merger of membranes (Fig. 6). The processes go through an intermediate state where two membranes are connected by a v-molecule. This v-molecule is called *connecting v-molecule*; it is represented by equal sign (=) in a pattern. The division and merger of membranes are not described by specifying membranes explicitly; instead, they are defined in terms of recombinations of v-molecules. Four kinds of recombination rules that change membrane structures are shown in Fig. 7 (the rules are supposed to be given to the parent cubicle of the membranes in this case). A pattern surrounded by parentheses like the second term of "^0#A/ + (^0#B/)" expresses that the two patterns represent v-molecules of different membranes.

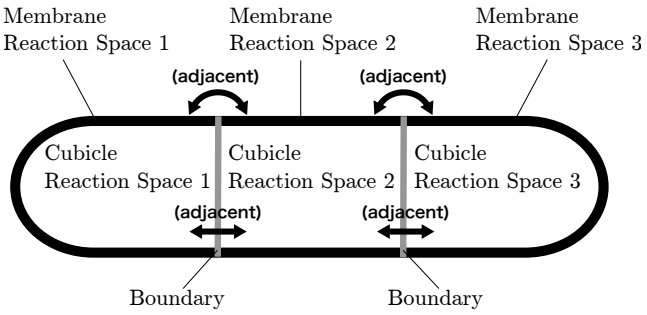

Figure 8: Membrane, cubicle and reaction spaces.

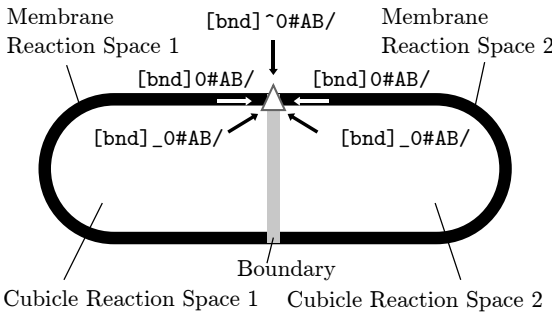

Figure 9: Reference to a boundary v-molecule.

A system is interpreted nondeterministically as follows.

1. Initialize the system: each reaction space is given initial v-molecules.
2. Choose a reaction space S.
3. Choose a recombination rule R from S.
4. Choose one or two v-molecules, if any, that R can apply to.
5. Recombine the v-molecule(s); change the membrane structure if specified.
6. Go to Step 2.

When a system is run on a simulator software, choices are made by a specific algorithm of the simulator (called its *reactor algorithm*). Some of our simulators make choices randomly; others employ physicochemical methods.

Extensions to the Base Artificial Chemistry

This study extends the base AChem described in the previous section, and models the cell division of *B. subtilis* with the extended AChem. This section illustrates the extension.

In the process of the cell division, there occur the recruitment of division proteins (DivIVA, MinC, etc.) to the cell-poles and the localization of FtsZ at the mid-cell. Since the base AChem gives one reaction space to a cubicle and employs the well-stirred reactor algorithm, it cannot express such localization of proteins in a straightforward manner.

The present study extends the AChem so that a cubicle can have multiple reaction spaces, and so can a membrane, to express such localization. Reaction spaces of a cubicle (or a membrane) have adjacency relationships among them. Figure 8 depicts a cubicle that have three reaction spaces (Cubicle Reaction Spaces 1, 2 and 3), and its surrounding membrane that also have three reaction spaces (Membrane Reaction Spaces 1, 2 and 3); the arrows indicate their adjacency relationships.

Boundary between reaction spaces

Two adjacent reaction spaces of a cubicle/membrane have a *boundary* between them. Unlike a membrane, a boundary has no reaction space. A boundary can be specified by a membrane v-molecule. This special kind of v-molecule is called *boundary v-molecule*. A boundary v-molecule has a direction. It can be viewed from the outside and the inside of the membrane (same as a normal membrane v-molecule), and also can be viewed from the reaction spaces it specifies. Figure 9 illustrates how a boundary v-molecule can be viewed from reaction spaces around it. The boundary separates the membrane into two reaction spaces (Membrane Reaction Spaces 1 and 2) and the cubicle into two (Cubicle Reaction Spaces 1 and 2). Each reaction space can refer to the boundary v-molecule in its recombination rules using the pattern shown near the arrow from the space; a boundary v-molecule is expressed by a tag "`[bnd]`" in a pattern.

Migration of v-molecules between reaction spaces

In a natural cell, most of materials in cytoplasm can freely diffuse in the cytoplasm. To express such behavior, a recombination rule that makes v-molecules migrate between adjacent reaction spaces can be defined. This type of rule is called *migration rule*. An example rule is shown below:

$$\texttt{0\#AB/} \rightarrow \texttt{[as]0\#AB/} \tag{4}$$

The tag "`[as]`" means "another space." When a rule of this type is applied to a v-molecule, the v-molecule migrates to any of the reaction spaces adjacent to the current space.

Membrane division on a boundary

In the base AChem, a membrane is divided into two when a dividing rule is applied to a membrane v-molecule in the membrane. The division also divides the cubicle surrounded by the membrane; the contents of the cubicle (i.e., v-molecules and child membranes) are distributed to the new cubicles nondeterministically. This property, however, is not desirable when the AChem is to model cell division, because the contents of the cell should be divided evenly.

(a) `[bnd]^0#AB/ -> =0#AB/`

(b) `[bnd]_0#AB/ -> =_0#AB/`

(c) `[bnd]_0#AB/ -> =^0#AB/`

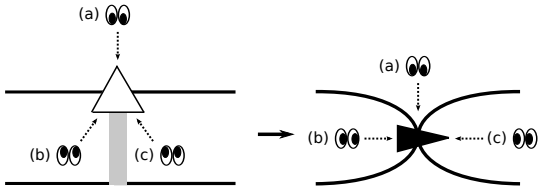

Figure 10: Membrane division on a boundary.

Dividing membrane and its inside cubicle on a specified boundary enables the system to distribute the contents of membrane/cubicle as intended. One can distribute the contents of a membrane/cubicle to its reaction spaces (by recombination rules) before division, then can divide the membrane/cubicle to make two membranes/cubicles.

Such division is performed when a specific type of recombination rule is applied to a boundary v-molecule. Three types of rules and their effects are depicted in Fig. 10. Each pair of eyeballs indicates the reaction space where the recombination rule is defined. An application of any of the rules (a), (b) or (c) divides the membrane/cubicle on the left to the two distinct membranes/cubicles on the right; the black triangle represents a connecting v-molecule. At the same time, the boundary disappears.

Dividing a reaction space

A reaction space is divided dynamically by the application of recombination rule to a membrane v-molecule. There are two types of rules. One is a rule that creates a boundary molecule (Fig. 11(a)). An application of such a rule makes the membrane v-molecule a boundary v-molecule, divides the membrane reaction space where the membrane v-molecule has been residing, and also divides the inside cubicle reaction space from which the v-molecule can be viewed. The contents of each of the original reaction spaces are distributed nondeterministically to its daughter spaces.

The other is a rule that creates "neighboring space" (Fig. 11(b)), which is indicated by the tag "`[nsp]`". When this type of rule is applied to a membrane v-molecule, a new cubicle reaction space that is adjacent only to the current (i.e., one having the rule) cubicle reaction space is created, and also a new membrane reaction space adjacent only to the current membrane reaction space (where the membrane v-molecule belongs to) is created. The contents of the original reaction spaces are distributed nondeterministically to the daughter spaces in the same manner as that for the previous case. In this type of division, the created boundary has no boundary v-molecule.

Modeling the Cell Division of *B. subtilis*

Using the extended AChem, we constructed a model for the cell division of *B. subtilis*.

Overview of the model

The conceptual diagram of the model is shown in Fig. 12. A small triangle represents a complex of MinC, MinD and MinJ, a small square represents DivIVA, and a small circle represents FtsZ. The process of division progresses as follows. (The numbers correspond to those in the figure.)

1. DivIVA-MinCDJ complex localizes to the inner surface of the both ends of the rod-shaped cell. FtsZ molecules are scattered over the whole cytoplasm.
2. FtsZ binds to any part of the inner surface of cytoplasmic membrane and starts to polymerize.
3. DivIVA-MinCDJ complex at the rod ends depolymerizes FtsZ polymers around it.
4. Since DivIVA-MinCDJ does not exist at the mid-cell, FtsZ polymerizes there.
5. The polymer of FtsZ becomes a Z-ring.
6. A septum starts to be synthesized as the Z-ring constricts. As the septum grows, DivIVA in the cytoplasm binds near the Z-ring.
7. The cell divides into two when the Z-ring constricts completely and the septum is fully synthesized.
8. MinC, MinD and MinJ binds to DivIVA that is recruited by the Z-ring, to make DivIVA-MinCDJ complex.
9. MinC in the complex depolymerizes the remaining FtsZ polymer. Go to Step 1.

Definition of the model

The model is defined by the following specifications: the structure of the AChem system (membranes, cubicles and reaction spaces), the initial multiset of v-molecules for each reaction space, and the set of recombination rules for each reaction space.

The structure of the system is shown in Fig. 13. It consists of a membrane and a cubicle surrounded by the membrane. The membrane has three reaction spaces, namely, m-left-pole, m-mid-cell and m-right-pole; the cubicle also has three reaction spaces, left-pole, mid-cell and right-pole. All the membrane reaction spaces share the same set of four recombination rules; the cubicle reaction spaces also share the same set with each other, which comprises 13 rules.

Initial v-molecules are given as follows. The membrane reaction spaces at both ends of the cell, m-left-pole and m-right-pole, are given v-molecules representing DivIVA (`_0#Div4a/`). The space m-mid-cell is given no v-molecule. All the cubicle reaction spaces, left-pole, mid-cell

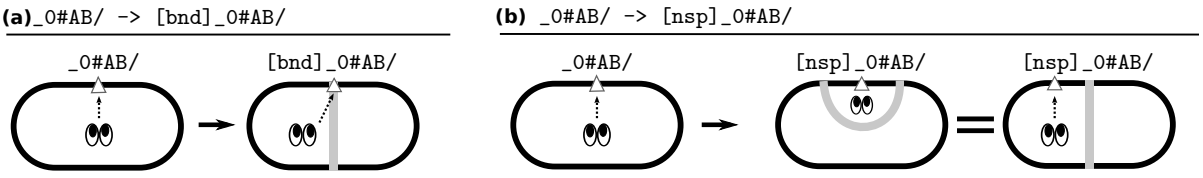

Figure 11: Examples of boundary creation.

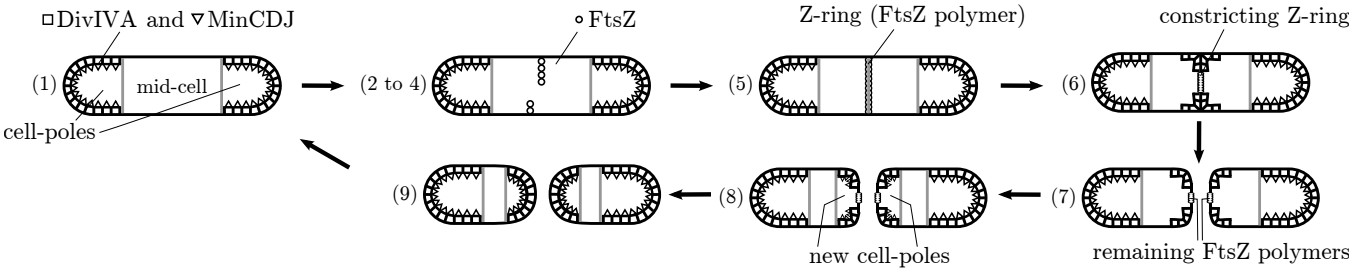

Figure 12: A conceptual diagram of the model.

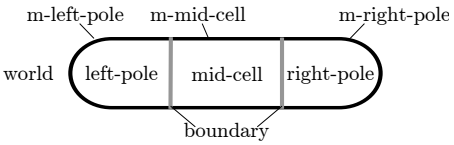

Figure 13: Initial structure of the system.

and right-pole, are given v-molecules for FtsZ, `0#Ftsz/`, and v-molecules `_0#Mincdj/`, which represent MinC, MinD and MinJ at once. We deal with the three proteins as an abstract molecule to make the description short.

Recombination rules define how the system works as follows. First, MinCDJ binds to DivIVA (5).

$$\text{\^{}0\#Div4a/} + \text{0\#Mincdj/} \rightarrow \text{\^{}0\#Div4aMincdj/} \quad (5)$$

And FtsZ binds to the plasmic membrane (6). To the protein, an FtsZ monomer binds to polymerize (7); FtsZ polymers in the membrane also join (8).

$$\text{0\#Ftsz<0*>/} \rightarrow \text{\^{}0\#Ftsz<0*>/} \quad (6)$$

$$\text{0\#<*0>Ftsz/} + \text{\^{}0\#Ftsz<1*>/} \rightarrow \text{\^{}0\#<*0>FtszFtsz<1*>/} \quad (7)$$

$$\text{0\#<*0>Ftsz/} + \text{0\#Ftsz<1*>/} \rightarrow \text{0\#<*0>FtszFtsz<1*>/} \quad (8)$$

MinC in DivIVA-MinCDJ complex binds to FtsZ polymer (9) and depolymerizes it (10).

$$\text{\^{}0\#Div4aMincdj/} + \text{0\#<*1>Ftsz<2*>/} \rightarrow \text{0\#Div4aMincdjFtsz<2*>/} + \text{0\#<*1>/} \quad (9)$$

$$\text{\^{}0\#Div4aMincdjFtsz<1*>/} \rightarrow \text{\^{}0\#Div4aMincdj/} + \text{0\#Ftsz<1*>/} \quad (10)$$

Because FtsZ polymerization is prevented at the ends of cell by DivIVA-MinCDJ complex, FtsZ polymerizes at the mid-cell. Eventually a Z-ring is formed (11) (we regard a polymer of twenty FtsZ as a Z-ring; the number is arbitrary). The Z-ring is represented by a boundary v-molecule. The rule divides each of m-mid-cell and mid-cell into two reaction spaces.

$$\text{\^{}0\#Ftsz<0..18><19*>/} \rightarrow \text{[bnd]\^{}0\#Ftsz<0..18><19*>/} \quad (11)$$

The Z-ring constricts to the deep-cell and divides the membrane (12); the constricted Z-ring becomes a connecting v-molecule.

$$\text{[bnd]\_0\#Ftsz<0*>/} \rightarrow \text{=\_0\#/0\#Ftsz<0*>/0\#/} \quad (12)$$

DivIVA in cytoplasm binds to the plasmic membrane near the constricted Z-ring (13, 14). Note that the viewpoints of the two rules are in the opposite cubicle to each other. DivIVA near the Z-ring is expressed by a v-molecule with multiple lines.

$$\text{=\^{}0\#<0*>/0\#Ftsz<1*>/0\#<2*>/} + \text{0\#Div4a/} \rightarrow \text{=\^{}0\#Div4a<0*>/0\#Ftsz<1*>/0\#<2*>/} \quad (13)$$

$$\text{=\_0\#<0*>/0\#Ftsz<1*>/0\#<2*>/} + \text{0\#Div4a/} \rightarrow \text{=\_0\#<0*>/0\#Ftsz<1*>/0\#Div4a<2*>/} \quad (14)$$

The divided membranes separate when a particular number (ten) of DivIVA have bound to the both sides of Z-ring (15), meaning sufficient time has elapsed for the complete constriction of Z-ring. (The first term is folded to fit in the

column.)

$$
\begin{aligned}
&\texttt{=0\#<0..9><10*>/0\#<*11><12..31><32*>/}\\
&\qquad\qquad\qquad\qquad\texttt{0\#<33..42><43*>/}\\
&\quad\rightarrow \texttt{\_0\#<0..9><10*>/0\#<*11><12..21>/}\\
&+\texttt{(\_0\#<33..42><43*>/0\#<22..31><32*>/)}
\end{aligned}
\tag{15}
$$

After the division, there are remaining FtsZ and DivIVA binding nearby at the new cell-pole. In other words, they indicate the new cell-pole. The following rule creates a new reaction space that represents the new cell-pole (16).

$$
\begin{aligned}
&\texttt{\^{}0\#<0..9><10*>/0\#Ftsz<11*>/}\\
&\rightarrow \texttt{[nsp]\^{}0\#<0>/} + \texttt{[nsp]\^{}0\#<1>/} + \texttt{[nsp]\^{}0\#<2>/}\\
&+\texttt{[nsp]\^{}0\#<3>/} + \texttt{[nsp]\^{}0\#<4>/} + \texttt{[nsp]\^{}0\#<5>/}\\
&+\texttt{[nsp]\^{}0\#<6>/} + \texttt{[nsp]\^{}0\#<7>/} + \texttt{[nsp]\^{}0\#<8>/}\\
&\qquad +\texttt{[nsp]\^{}0\#<9>/} + \texttt{[nsp]\^{}0\#<10*>/}\\
&\qquad\qquad +\texttt{[nsp]\^{}0\#Ftsz<11*>/}
\end{aligned}
\tag{16}
$$

Then MinCDJ binds to DivIVA at the new cell-pole to make DivIVA-MinCDJ complex (5), and MinC there depolymerizes the FtsZ polymer remaining at the pole (6).

In addition, the system has migration rules (like (17)) that let v-molecules migrate to adjacent cubicle reaction spaces, and a rule that expresses the decomposition of DivIVA (18).

$$
\texttt{0\#Div4a/} \rightarrow \texttt{[as]0\#Div4a/} \tag{17}
$$

$$
\texttt{0\#Div4aDiv4a<0*>/} \rightarrow \texttt{0\#Div4a/} + \texttt{0\#Div4a<0*>/} \tag{18}
$$

Execution of the model

We built a prototype simulator for the extended AChem by modifying a simulator for the base AChem; the both simulators are written in Ruby. When we ran the description for the cell division illustrated in the previous section, the model worked as intended.

A snapshot taken from the execution is shown in Figure 14. The text above is the output of simulator, and it is depicted in the illustration below. In this state, the first cell division is complete, and each daughter cell has started the next cycle of cell division. In Membrane 11 and Membrane 13, remaining FtsZ polymers (`_0#FtszFtsz`$\cdots$`/`) are observed.

Discussion

In the extended AChem, while each reaction space is well-stirred, a cubicle/membrane can consist of multiple reaction spaces, so localization of molecules within the cubicle/membrane can be expressed.

The division of reaction spaces is performed by the application of recombination rule to a molecule. This is in the same framework we used to formalize membrane division and merger (Tominaga et al., 2007). The main advantage of this approach is that the same set of rules can be applied after the structure of system has changed because rules do not refer to membranes, cubicles or reaction spaces by their IDs, positions, coordinates or addresses; the behavior is determined only by v-molecules they have. Though we did not model nucleoid occlusion, we think it can also be modeled using the division of reaction spaces.

Possible topologies of reaction spaces are limited. For example, a membrane reaction space and the cubicle reaction space inside (and adjacent to) it always correspond in a one-to-one manner.

In the illustrated application, the execution of the system is somewhat like a reaction-diffusion system; the number of FtsZ in the mid-cell space (or "concentration") seems to contribute to the formation of the Z-ring. This is because the implementation of the simulator uses random numbers to decide which reaction to occur. The current implementation does not take physicochemical dynamics of molecules into account. Doing it will be our future work.

In (Madina et al., 2003), the formation of membrane-like structures is studied. They define the lattice and interaction among particles in the space. A membrane-like structure is observed as a collection of particles in lattice cells that enclose an area. So the lattice should be suitable for the study. In our AChem, a membrane is a primary entity and cannot be decomposed into parts; this property will be beneficial in modeling the behavior of membrane at a high level of abstraction.

A work using E-Cell to simulate the E-ring formation of *E. coli* (Arjunan and Tomita, 2010) predefines a hexagonal lattice with voxels having 12 neighbors in order to simulate the behavior of proteins in cytoplasm. In contrast, our study first only gives three reaction spaces to express the areas of cytoplasm and they divide dynamically as the execution progresses. This flexibility will contribute to the scalability of model, especially the membrane structure of which changes considerably, like the process of complete ontogenesis.

In this aspect, our approach has similarities with L-systems (Lindenmayer, 1968): symbols in an L-system can increase as rules are applied, and rules specify no position or ID of each symbol occurrence. Since ours is an artificial chemistry, membranes and cubicles can have (v-)molecules, and reactions among them can be described as recombination rules. We think this is advantageous in modeling a system based on known biochemical reactions.

Concluding Remarks

In this paper, we presented a membrane artificial chemistry that can dynamically divide reaction spaces, as an extension to our previous artificial chemistry. The extension is introduced to express the localization of molecules.

We showed an application of it: a model for the cell division of *B. subtilis*. The model is defined by the initial structure, the initial v-molecules and 17 recombination rules. We executed the model on our simulator, and observed that a

```
xxxdcl> ao ←user input to show the current contents of pools
Cubicle 0 [ object: NumObjects: 0 ]
Membrane 1 == m-world ( object: NumObjects: 0)
Cubicle 2 == world [ object: <0#Dummy/: 1> NumObjects: 1 ]
Membrane 3 == m-left-pole ( object: <_0#Div4aMincdj/: 12> NumObjects: 12)
Cubicle 4 == left-pole [ object: <0#Div4a/: 3> <0#Mincdj/: 3> NumObjects: 6 ]
Membrane 5 == m-mid-cell ( object: <_0#FtszFtszFtszFtszFtszFtszFtszFtszFtszFtszFtszFtsz/: 1>
<_0#FtszFtszFtszFtszFtszFtszFtszFtsz/: 1> NumObjects: 2)
Cubicle 6 == mid-cell [ object: <0#Div4a/: 8> <0#Mincdj/: 4> NumObjects: 12 ]
Membrane 7 == m-right-pole ( object: <_0#Div4aMincdj/: 11> NumObjects: 11)
Cubicle 8 == right-pole [ object: <0#Div4a/: 6> <0#Mincdj/: 2> NumObjects: 8 ]
Membrane 9 == m-mid-cell_0 ( object: <_0#FtszFtsz/: 1> NumObjects: 1)
Cubicle 10 == mid-cell_0 [ object: <0#Div4a/: 11> <0#Mincdj/: 5> NumObjects: 16 ]
Membrane 11 == m-mid-cell_1 ( object: <_0#FtszFtszFtszFtszFtsz/: 1> <_0#Div4a/: 1>
<_0#Div4aMincdj/: 10> <_0#FtszFtsz/: 1> NumObjects: 13)
Cubicle 12 == mid-cell_1 [ object: <0#Div4a/: 4> <0#Mincdj/: 3> NumObjects: 7 ]
Membrane 13 == m-mid-cell_2 ( object: <_0#Div4a/: 4> <_0#Div4aMincdj/: 6>
<_0#FtszFtszFtszFtszFtszFtszFtszFtszFtszFtszFtsz/: 1> NumObjects: 11)
Cubicle 14 == mid-cell_2 [ object: <0#Div4a/: 4> <0#Mincdj/: 4> NumObjects: 8 ]
```

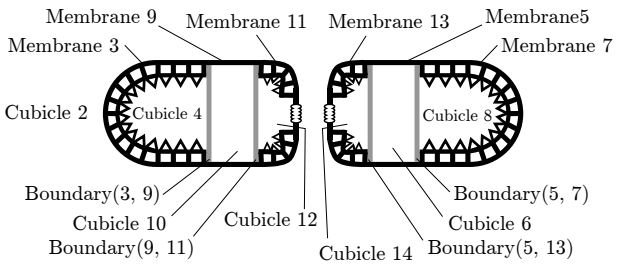

Figure 14: A snapshot from the execution of the model.

cell divides as intended. The small set of description was able to simulate the cell division on the generic simulator; this we think demonstrated the effectiveness of the present approach.

We speculate this approach is useful in other applications; we are currently modeling the division of *E. coli* and the embryogenesis of *C. elegans*. The AChem may be further extended to be able to express more complex phenomena and structures such as forming cytoskeleton.

References

Adams, D. W. and Errington, J. (2009). Bacterial cell division: assembly, maintenance and disassembly of the Z ring. *Nat Rev Micro*, 7:642–653.

Amari, N. and Tominaga, K. (2009). Simulation minus one makes a game. In *EvoWorkshops'09*, pages 273–282, Berlin, Heidelberg. Springer-Verlag.

Arjunan, S. N. V. and Tomita, M. (2010). A new multicompartmental reaction-diffusion modeling method links transient membrane attachment of E. coli MinE to E-ring formation. *Systems and synthetic biology*, 4(1):35–53.

Bramkamp, M., Emmins, R., Weston, L., Donovan, C., Daniel, R. A., and Errington, J. (2008). A novel component of the division-site selection system of Bacillus subtilis and a new mode of action for the division inhibitor MinCD. *Molecular Microbiology*, 70(6):1556–1569.

Dittrich, P., Ziegler, J., and Banzhaf, W. (2001). Artificial chemistries-a review. *Artif. Life*, 7:225–275.

Gregory, J. A., Becker, E. C., and Pogliano, K. (2008). Bacillus subtilis MinC destabilizes FtsZ-rings at new cell poles and contributes to the timing of cell division. *Genes & Development*, 22(24):3475–3488.

Kemphues, K. (2000). Parsing embryonic polarity. *Cell*, 101(4):345 – 348.

Lenarcic, R., Halbedel, S., Visser, L., Shaw, M., Wu, L. J., Errington, J., Marenduzzo, D., and Hamoen, L. W. (2009). Localisation of DivIVA by targeting to negatively curved membranes. *EMBO J*, 28:2272–2282.

Lindenmayer, A. (1968). Mathematical models for cellular interactions in development. *Journal of Theoretical Biology*, 18:280–315.

Madina, D., Ono, N., and Ikegami, T. (2003). Cellular evolution in a 3d lattice artificial chemistry. In *in: Proceedings of ECAL 03 W.Banzhaf*, pages 59–68. Dortmund, Springer.

NW, G. and J, B. (2005). Diverse paths to midcell: assembly of the bacterial cell division machinery. *Current Biology,*, 15:514–526.

Ramamurthi, K. S. and Losick, R. (2009). Negative membrane curvature as a cue for subcellular localization of a bacterial protein. *Proceedings of the National Academy of Sciences*, 106(32):13541–13545.

Tominaga, K., Watanabe, T., and Suzuki, M. (2007). Formulating membrane dynamics with the reaction of surface objects. In *Proceedings of the 9th European conference on Advances in artificial life*, ECAL'07, pages 12–21, Berlin, Heidelberg. Springer-Verlag.

van Baarle, S. and Bramkamp, M. (2010). The MinCDJ System in *Bacillus subtilis* Prevents Minicell Formation by Promoting Divisome Disassembly. *PLoS ONE*, 5(3):e9850.