数理解析研究所講究録
第 353 巻 1979 年 152-164

MATHEMATICAL CONSIDERATIONS ON MULTI-CELLULAR DEVELOPMENTAL SYSTEMS

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1 Introduction

Multi-cellular organisms like filamentous plants, early embryos, nervous systems, neuro-muscular systems, retino-tectal systems and other systems of various complexity levels, are considered to emerge from origin cells through successive unequal cell divisions. Upon the philosophy that the processes of cell proliferation and interconnection are deterministically controlled by division history of each component cell, we proposed a mathematical theory of developmental processes [1], [2]. We did not consider cell migration and growth explicitly. These papers contain biological foundation and discussion as well as theoretical results.

In this paper, let us develop further mathematical analysis of our cell lineage and connection relation system (CLR system) in the framework of automata theory.

2 Preliminary Explanations

For the sake of simplicity, let us assume throughout in this paper that the alphabet used for identifying each cell is binary, i.e. $\underline{B=\{a,b\}}$. This constraint brings into no loss of mathematical generality.

2.1 CL System

A cell lineage system (CL system) is a pair $(B,\mathcal{D})$, where $\mathcal{D}$ is the division time spectrum satisfying the following conditions:

(1) $\mathcal{D}$ is a family of mutually disjoint subsets of B^*. That is,

$$\mathcal{D} = \{D_0, D_1, D_2, \ldots, D_i, \ldots\},$$

where D_i's are called components of $\mathcal{D}$ and especially D_0 the terminal component.

(2) For every i, if $w=uv \in D_i$, then there is a non-terminal component D_j (depending on u) such that $u \in D_j$.

Meaning of CL system: If $w \in D_i$ with $i \neq 0$, then the cell having the division history w bifurcates in i units of time and its daughters obtain those of wa and wb. If $w \in D_0$, then the cell w never divides. λ is the origin cell (a spore or a fertilized egg). A CL system is often identified with its division time spectrum $\mathcal{D}$.

Finite Regular CL Systems: When the number of components of $\mathcal{D}$ is finite and every component is a possibly empty regular set on B, then the system is called a finite regular CL system. In the following we treat this kind of CL systems mainly.

2.2 Rational Relations

$(B^*, \cdot)$ and $(N, +)$ are monoids, whose unit elements are λ and 0 respectively, where N is the set of nonnegetive integers.

A subset R of $B^* \times \mathbf{N}$ is called a rational relation in $B^* \times N$, if R is defined by means of a rational machine M as follows:

$$M=(Q, f, q_0, F)$$

where Q is the finite set of states,

f is the set of nondeterministic transitions defined by arcs $q \xrightarrow[(x,n)]{} q'$, where $x \in B_\lambda = B \cup \{\lambda\}$ and $n \in N$, and $(x,n) \neq (\lambda, 0)$,

q_0 is the initial state and

F is the set of accepting states.

$w \in B^* \times N$ is called to be accepted by M, if $q_0 w \cap F \neq \emptyset$, where $q_0 w$ means the set of states which are reached through a path from q_0. Paths are defined as usual by means of the jaxtaposition of operations in the product monoid $B^* \times N$. The relation defined by a rational machine M is denoted by R(M) and defined by

$$R(M)=\{ w \in B^* \times N \mid q_0 w \cap F \neq \emptyset \}.$$

R is called a rational relation if there is a rational machine M such that R=R(M).

In the similar way, rational relations in $B^* \times B^* \times N$ are defined by means of rational machines.

Note that the above defined notion of rational relation is essentially the same as the "transduction" defined by Elgot and Mezei [3] and the "rational relation" by Eilenberg [4].

2.3 Semi-direct Product

Let R and S be relations in $B^* \times N$. Then the relation in $B^* \times B^* \times N$ $T = \{(w,v,n) \mid n \in N, (w,n) \in R$ and $(v,n) \in S\}$ is called the semi-direct product of R and S and denotedby $R \odot S$.

Proposition 1

If R and S are rational relations in $B^* \times N$, then their semi-direct product T is also rational.

Proof

Let M_R and M_S be rational machines defining R and S, respectively. From M_R, for example, by adding new states, construct a "canonical" rational machine

M_R' such that $R(M_R')=R$ and every transition arc is labeled with $(x,1)$ where $x \in B_\lambda$. That is, if $q \xrightarrow[(x,n)]{} q'$ is an arc of M_R, then it is replaced by a chain of arcs $q \xrightarrow[(x,1)]{} q_1 \xrightarrow[(\lambda,1)]{} q_2 \rightarrow \cdots \rightarrow q_{n-1} \xrightarrow[(\lambda,1)]{} q'$. Every augmented state is a non-accepting state.

Now the rational machine M_T is constructed from M_R' by making the "product" machine as follows: The state set is $Q_R \times Q_S$, where Q_R and Q_S are those of M_R and M_S, respectively. An arc $(p,q) \xrightarrow[(x,1)]{} (p',q')$ is drawn in M_T, whenever arcs $p \xrightarrow[(x,1)]{} p'$ and $q \xrightarrow[(x,1)]{} q'$ are in M_R and M_S, respectively. $F_T = F_R \times F_S$ and $q_{0T} = (q_{0R}, q_{0S})$. From this construction of M_T, it will be clear that $R(M_T) = T = R \odot S$. Q.E.D.

<u>Proposition 2</u> [3]

If $R \subset B^* \times B^* \times N$ is rational, its projections to the components $R_1 = \{ w \mid (w,v,n) \in R \}$ and so on are regular sets on B.

<u>Proof</u>

Clear from the definition of rational machines.

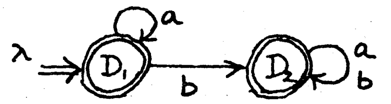
3 Cell Proliferation Process

Suppose that a finite regular CL system $(B, \mathcal{D})$ is given with $\mathcal{D} = \{D_0, D_1, \ldots, D_k\}$. Then construct a finite automaton $A_{\mathcal{D}}$ as described in Nishio [1], which defines the family of regular sets D_i's. Note that no arc emerges from the states defining D_0.

Example 1 (defining automaton of CL system)

$\mathcal{D} = \{D_1, D_2\}$, where $D_1=a^*$ and $D_2=B^*-a^*$

$A_{\mathcal{D}}$:



⇛ initial state

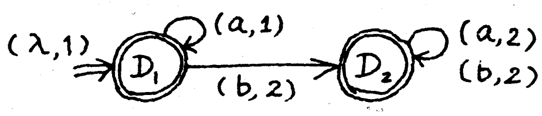
◎ accepting state

Next, from $A_{\mathcal{D}}$, we construct a corresponding rational machine $M_{\mathcal{D}}'$ by taking into account the division time. Indeed, attach the division time i to an arc of $A_{\mathcal{D}}$, if it enters a state accepting D_i. Then it is clear that $M_{\mathcal{D}}'$ defines a (rational) relation $R_{\mathcal{D}}'$ in $B^* \times N$ such that if $(w,n) \in R_{\mathcal{D}}'$, the cell w is produced by the CL system $\mathcal{D}$ at time n.

Example 2 (rational machine)

CL system is the same as in Example 1.

$M_{\mathcal{D}}'$

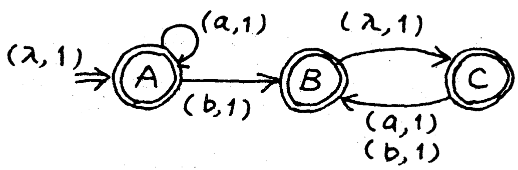


Finally, as is described in the proof of Proposition 1, canonical machine is constructed from $M_{\mathcal{D}}'$ and every state is defined to be an accepting state. Furthermore, from a state defining D_0, if any, an arc with label $(\lambda,1)$ is drawn to itself. Denote this machine by $M_{\mathcal{D}}$. Then,

$$R(M_{\mathcal{D}}) = R(M_{\mathcal{D}}') \cup \{(w,n+j) \mid (w,n) \in R_{\mathcal{D}}' \text{ and } \\ j=1,\ldots,i-1 \text{ if } w \in D_i \text{ and } \\ j=1,2,\ldots \text{ if } w \in D_0$$

Example 3 (modified canonical machine)

$M_{\mathcal{D}}$ corresponding to $M_{\mathcal{D}}'$ in Example 2.



Meaning of $R(M_{\mathcal{D}})$: If $(w,n) \in R(M_{\mathcal{D}})$, then the cell w exists at time n. Let us call $R(M_{\mathcal{D}})$ or simply $R_{\mathcal{D}}$ the proliferation relation of CL system $\mathcal{D}$.

Next the cell population at time t is given by

$$W_t = \{ w \mid (w,t) \in R \} .$$

$$W = W_0, W_1, W_2, \dots, W_t, \dots .$$

is called the proliferation process of $\mathcal{D}$, Nishio [2].

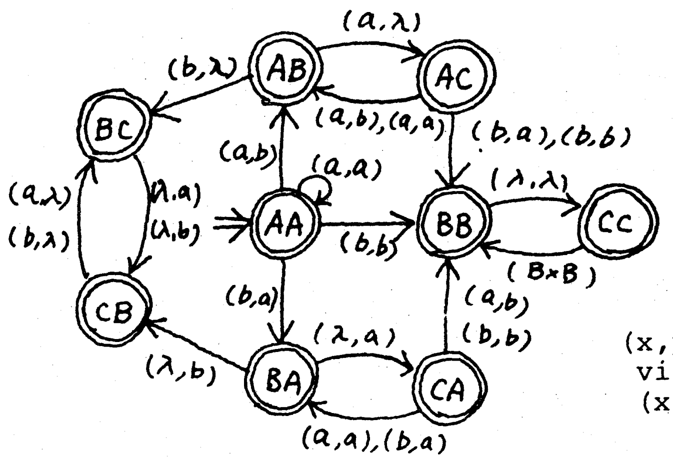
4 Connectability Relation and Developmental Process

A connectability relation is a rational relation $S \subset B^* \times B^* \times N$. It is considered to be given a priori from some biological ground and is interpreted as follows: If a pair of cells w and v exist at time t and $(w,v,t) \in S$, then w is connected to v at time t. Contrarily, even when (w,v,t) is in S, a connection from w to v is not established if w or v is not in W_t. Note that this interpretation of instant emergence of a connection is biologically questionable in cases where spacially separated cells are to be connected after migration and growth. But, for the sake of simplicity, we dare adopt it in this analysis.

Now let $R_{\mathcal{D}}$ be the proliferation relation derived from a CL system $\mathcal{D}$ as in Section 3. Then the semi-direct product $R_{\mathcal{D}} \odot R_{\mathcal{D}}$ is a connection relation among cell population produced by $\mathcal{D}$, such that there exists a connection between every pair of cells. So, the relation $R_{\mathcal{D}} \odot R_{\mathcal{D}}$ will be called the perfect connection relation.

Example 4 (perfect connection relation)

$M_{R_{\mathcal{D}} \odot R_{\mathcal{D}}}$, where M_R is given in Example 3.



(x,y) is abbreviation of (x,y,1).

Relation describing developmental processes:

Now we define our final relation r in $B^* \times B^* \times N$.

$$r = S \cap R_{\mathcal{D}} \odot R_{\mathcal{D}} \quad ,$$

where S is a rational connectability relation. Obviously r is a relation describing a process of cell proliferation and connection in the following sense. If $(w,v,t) \in r$, then the cell w is connected in reality to v at time t. Thus, r represents the developmental process generated by a developmental system $G=(B, \mathcal{D}, S)$, where $(B, \mathcal{D})$ is its CL system and S is a connectability relation. G is called a CLR system too.

5 Some Results on Properties of r

In general the set of rational relations is not closed under intersection [3]. But there had remained the problem to determine, whether r is always rational or not, since $R_{\mathcal{D}} \odot R_{\mathcal{D}}$'s constitute a special class of rational relations in $B^* \times B^* \times N$. Indeed we obtained

Theorem 1

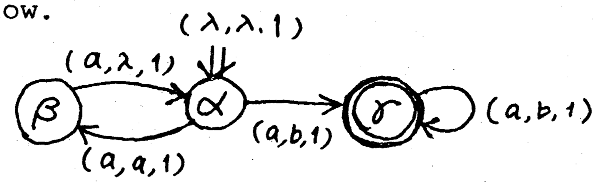
There is a developmental system $G=(B,\mathcal{D}, S)$ with $\mathcal{D}$ finite regular and S rational, such that

$$r_G = S \cap R_{\mathcal{D}} \odot R_{\mathcal{D}}$$

is not a rational relation.

Proof

We show an example of G which satisfies the theorem. Let $\mathcal{D}$ be as given in Example 1 and S be defined by M_S below.



Clearly, $S= \{(a^{2i+j}, a^i b^j, 2i+j) \mid i \geq 0 \text{ and } j \geq 1\}$. Note that $R_{\mathcal{D}} \odot R_{\mathcal{D}}$ is defined by the machine illustrated in Example 4. Then,

$$r_G = \{(a^{3i}, a^i b^i , 3i) \mid i \geq 1\} .$$

Since $\{a^i b^i \mid i \geq 1\}$ is not a regular set, r_G is not a rational relation from Proposition 2. Q.E.D.

For filamentous organisms (see [1]), we have the following theorem.

Theorem 2

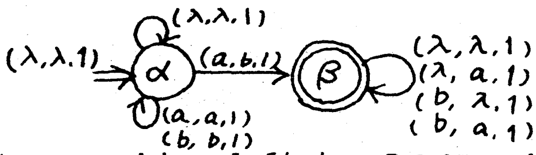
Let R_f be the filamentous connectivity relation, i.e. $R_f = \{wab^* \times wba^* \times t \mid w \in B^* \text{ and } t \in N\}$. (see [2]).

Then, for an arbitrary finite regular CL system $\mathcal{D}$,

$$r_f = R_f \cap R_{\mathcal{D}} \odot R_{\mathcal{D}} \quad \text{is a rational relation.}$$

Proof

R_f can be represented by the following machine M_f.



We denote a machine defining $R_{\mathcal{D}} \odot R_{\mathcal{D}}$ by M_D. Now we construct a rational machine M_r which represents r_f.

First of all, the state set of M_r is defined to be the direct product of those of M_D and M_f. Of M_D, suppose there is an arc going from the state q to q' and having the label (x,x,1) where $x \in B_\lambda$. Then in M_r an arc is drwan from state (q,α) to state (q',α) with label (x,x,1). If in M_D there is an arc going from q to q' with label (a,b,1), then M_r has an arc from (q,α) to(q',β) with the same label. Finally, if in M_D arcs from q to q' with labels (λ,λ,1), (λ,a,1), (b,λ, 1) or (b,a,1) exist, then in M_r an arc from (q,β) to (q',β) with the respective label is defined.

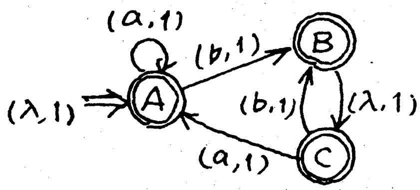
The initial state of M_r is (q_0,α) where q_0 is that of M_D and the accepting states are those which are of the form (q,β).

Since in this construction of M_r, no pathological phnomenon, which might arise from the non-freeness of B*×B*×N, does not occur, M_r defines r_f in reality.

Q.E.D.

Example 5

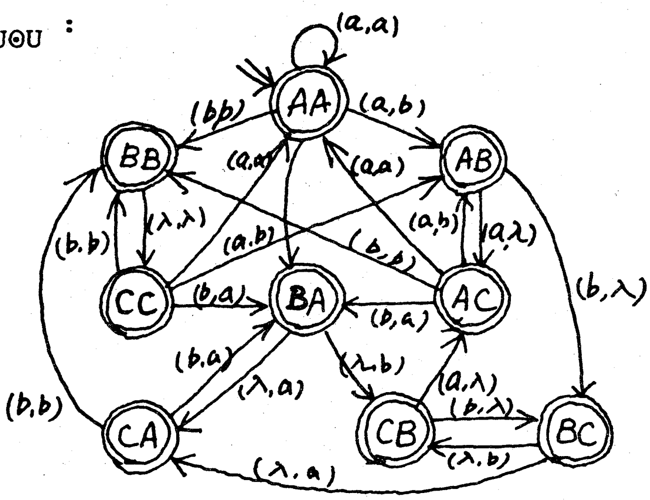
$M_{\mathcal{D}}$:



Example 5 continued.

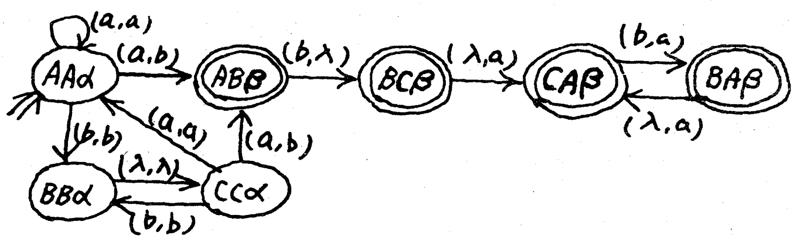
$R(M_{\mathcal{D}})$ is denoted by U.

$M_{U \odot U}$:



$r_U = R_f \cap U \odot U$ is defined by the following M_U.

M_U



Significance of Theorem 1: In general a developmental process can not be represented by a finite state machine, while its generating system G is defined by rational machines. This is an example which would support the belief that to describe directly a mature organism is more complicated than to do its generating rule.

The following problems remain unsolved.

(1) Decision problem: for arbitrarily given finite regular CL system $\mathcal{D}$ and rational connectability relation S,

decide whether the developmental process r is rational or not. We conjecture that it is unsolvable.

(2) Characterization problem: Investigate conditions for $\mathcal{D}$ and s such that r is rational.

6 Positional Information in Filamentous Organisms

As described in [1], a filamentous organism without branches like a blue green alga *anabaena* consists of a string of linearly connected cells. If we consider wa as the apical and wb the basal daughter produced by division of a cell w, a CLR system $G_f=(B,\mathcal{D}, R_f)$ with the filamentous connectability relation R_f generates a time series of filamentous organisms. (In this section, we do not assume the regularity of $\mathcal{D}$).

As the simplest case of positional information, let us consider the cells located at the center of an organism during the time course of development. So, we define and investigate the relation of central cells $P_{1/2} \subset B^* \times N$:

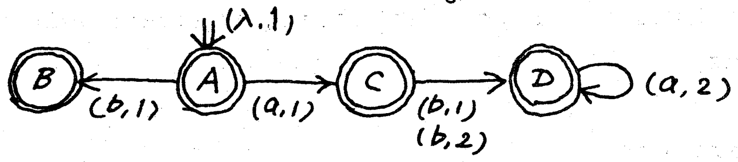
$$P_{1/2} = \{(w,t) \mid w \in B^*,\ t \in N \text{ and } w \text{ is located at the center at time } t\} .$$

When an organism contains even number of cells at a time, $P_{1/2}$ has two elements corresponding to this time.

We show some examples which might be useful for understanding properties of $P_{1/2}$. Proofs will be omitted.

<u>Example 6</u>

The CL system is the same as in Example 1, i.e. $D_1=a^*$ and $D_2=B^*-a^*$. Then, $P_{1/2}$ is rational and defined by the following machine M_6.



Example 7

$D_1=aB^* \cup \{\lambda\}$ and $D_2=bB^*$

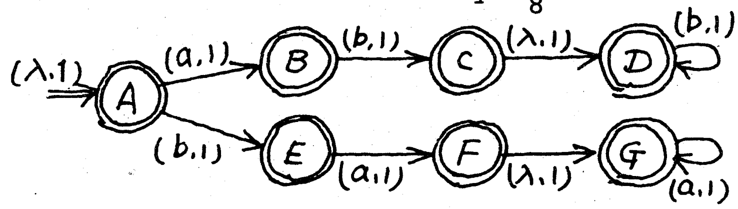
$$P_{1/2}= \{(\lambda,0),(a,1),(b,1),(ab,2),(aba,3),(abb,3)\}$$
$$\cup\{(\{aba^{t/2-1}ba^{t/2-2},\ aba^{t/2}b^{t/2-2}\},t)\ |\ t=2n,\ n\geq 1\}$$
$$\cup\{(\{aba^{(t-1)/2-1}ba^{(t-1)/2-1},\ aba^{(t-1)/2}b^{(t-1)/2-1}\},t)\ |\ t=2n+1,\ n\geq 1\}$$

From Proposition 2, this $P_{1/2}$ is not a rational relation.

Example 8

$D_1=B^*-D_2$ and $D_2= \{a^ib^i,\ b^ia^i\ |\ i\geq 1\}$.
This CL system is obviously finite nonregular. But, $P_{1/2}$ is rational and indeed defined by M_8.

M_8:



The decision problem that given an arbitrary finite regular CL system, decide if $P_{1/2}$ is rational or not has not been solved.

As is $P_{1/2}$, for example, the "one third position" $P_{1/3}$ from the apical end can be defined. As to rationality, $P_{1/2}$ and $P_{1/3}$ seem to have similar character, but this problem has not been studied.

The author thanks Y.Kobuchi, H.Okabe, S.Seki, T.Nishida and H.Doi for their interests and discussions.

References

[1] H.Nishio (1978), Cell Lineage System for Describing Growths of Filamentous Organisms, Information and Control, 37, 280-301.

[2] H.Nishio (1978), A Mathematical Theory of Developmental Processes Bases upon the Cell Lineage, Proc. International Symposium on Mathematical Topics in Biology, Sept. 11-12, 1978, Kyoto, 164-173

[3] C.C.Elgot and J.E.Mezei (1965), On Relations Defined by Generalized Finite Automata, IBM Journal, Jan. 47-68.

[4] S.Eilenberg (1974), 'Automata, Languages, and Machines, Vol.A', (Chapter IX), Academic Press.