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LEARNING THE MODELING OF ENDOCYTIC PATHWAY OF TRANSFERRIN-BOUND IRON TO CELLS USING P SYSTEMS

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Abstract- Membrane systems were introduced in 1998 as distributed, parallel and nondeterministic computing models, inspired by the compartmentalized structure of eukaryotic cells. In recent years, modeling and analysis of living cells are developed in the area of formal languages. In this paper we show how to model and analyze the Transferrin-Bound iron uptake in living cells and illustrated the receptor-mediated Endocytosis and exocytosis operations.
Key words- P Systems, Membrane Rules, Receptor-mediated Endocytosis, Biologically motivated models.

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Introduction

One of the directions of research of Computer Science in the last years saw the creation of new computability models directly inspired by cell biology. The initial goal was to learn from cell biology something possible useful to computer science. When a P system is considered as a computing device, it is investigated in terms of theoretical computer science and the main issues are related to the computing power and computing efficiency. It combines the power of distributed parallel rewriting systems with the power and context evolution to achieve computational universality. The aim of this paper is to show how to model and analyze the transferrin-Bound iron uptake in living cells.

The structure of this paper is organized as follows: in section 2, we recall the introductory part of Membrane Computing [1,2] along with its definition. We define two membrane rules for endocytosis and exocytosis in section 2. The Biology example model is given in section 4. Analysis and modeling of the Endocytic pathway of Transferrin-Bound Iron to cells is found in section 5. The last part is the conclusions and future work.

Membrane Computing

Membrane computing (or P Systems) is a part of natural computing, just an attempt to formulate a model of computation of a living cell. It is introduced by Gh. Paun as a class of distributed parallel computing devices. Graphically, a Membrane structure is represented by a Venn diagram (Fig. 1) in which two sets can be either disjointed, or one a subset of the other.

The membranes are labeled in a one-to-one manner as they are nested within other membranes. A membrane without any other membrane inside is said to be elementary. Outside the skin membrane is called the environment. The space inside the membranes is called region (or compartment). For this membrane structure, we can write parenthesis expressions as follows

$[\,[\,]_2\,[\,]_3\,[\,[\,]_7\,[\,]_5\,[\,[\,]_8\,[\,]_9\,]_6\,]_4\,]_1$

We recall the basic model of membrane computing which is usually called transition membrane systems.

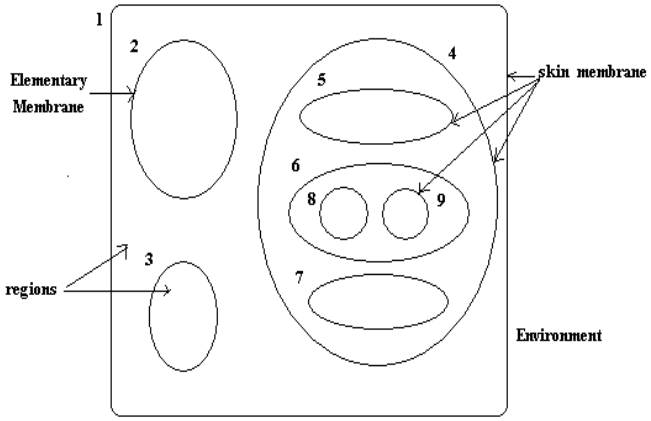


Fig. 1- General Structure of Membrane

Definition

A *transitive membrane computing* of degree n ≥ 1 is a construct Π = (V, H, T, C, μ ,w_1,... w_n, (R_1, ρ 1), … (R_n, ρ n), i_0) where V denotes variables or Non-terminals; H denotes the membrane labels; T Î V is the terminal symbols; $\mu \subset$ H x H describes the membrane structure, such that (i, j) Î μ denotes that the membrane labeled by j is contained within the membrane labeled by i; w_i Î V^* represents objects, for each 1 ≤ i ≤ n; R_i, for all 1 ≤ i ≤ n is the set of multiset rewriting rules which is associated with membrane i; ρ_i, for all 1 ≤ i ≤ n, is a partial order relationship defined over the rules in R_i, specifying a priority relation between these rules; i_0 is the label of an elementary membrane of μ which identifies the output region.

The membrane computing has some basic operations like dissolution, creation, division, merging, endocytosys, exocytosis, gemmination and so on. It is pictorially described in (Fig. 2). Each operation can be written in its respective rule form.

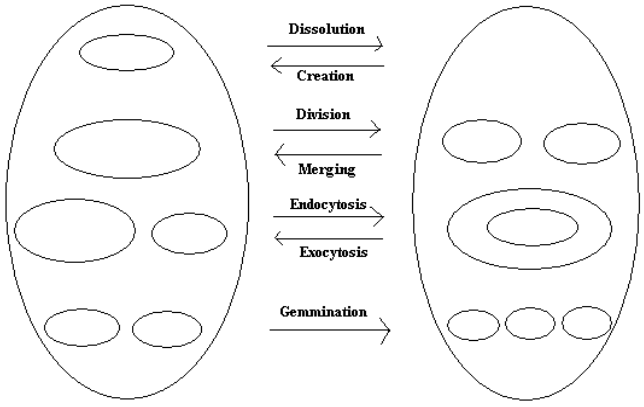


Fig. 2- Basic Membrane Handling Operations

Membrane Rules for Endocytosis and Exocytosis

These rules are applied in parallel, non-deterministic way. Moreover only active membrane can involve in rule formation. Here membrane h is active and m is passive. Whenever a membrane is moved across another membrane, its full contents get moved.

Endocytosis

An elementary membrane labeled h enters the neighboring membrane labeled m, under the control of object p. The labels of the membranes remain unchanged till the end of the process. Only object p changes to q. M_1, M_2 denotes the multiset of objects (can be empty) and M_3 denotes the elementary and other membranes. This is pictorially represented as follows

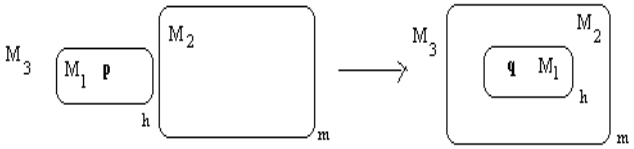


Fig. 3- Endocytosis

The final constructed rule for endocytosis is
[p]$_h$ [ ]$_m$ ⟶ [[q]$_h$]$_m$, for h, m Î H and p, q Î V.

3.2 Exocytosis

Here, an elementary membrane labeled h is sent out of its neighboring membrane m, under the control of object p. The labels of the membranes remain unchanged till the end of the process. Only object p gets modified to q. M_1, M_2 denotes the multiset of objects (can be empty) and M_3 denotes the elementary and other membranes. This is pictorially represented as follows

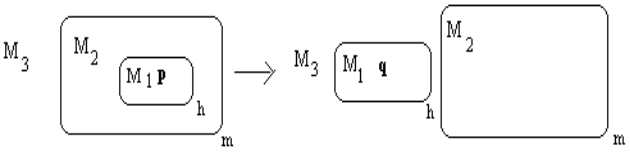


Fig. 4- Exocytosis

The final constructed rule for exocytosis is
[[p]$_h$]$_m$ ⟶ [q]$_h$ [ ]$_m$, for h, m Î H and p, q Î V.
Hence, the above computation is structured as follows: it starts with the initial configuration, then computation proceeds and stops after the required result is obtained.

Mobility in Cell Biology

In this paper, the mobility of membranes is expressed using the biological operations of endocytosis and exocytosis only [6].

Endocytosis

Cell transport certain macromolecules (large sized particles) across the plasma membrane. It is nothing but the engulfing of food or foreign particles through the plasma membrane. The Endocytosis can be differentiated into phagocytosis and pinocytosis. Phagocytosis (or cell eating) is the engulfing of solid particles and pinocytosis (or cell drinking) is the engulfing of fluid particles through the plasma membranes. The cells exhibiting phagocytosis are called phagocytes. During this process, the food particles are adsorbed at the surface of the membrane. Later, they are taken into the cytophasm by the infolding of the plasma membrane. The plasma membrane near the infoldings gets pinched off in the form of a small vesicle called phagosomes. Then, the phagosomes fuse with lysosomes to form the digestive vacuoles. The food is digested inside the vacuole and the digested food diffuses into the

cytoplasm. Examples: Capturing and ingestion of diatoms by Amoeba, Devouring of disease causing germs by WBC, Macrophages, etc. Pinocytosis is the property of all cells and leads to the cellular uptake of fluid and fluid contents. Two main types are fluid-phase pinocytosis and absorptive pinocytosis. Fluid-phase pinocytosis is a non selective process, in which the uptake of the solute by formation of small vesicles is simply proportional to its concentration in the surrounding extracellular fluid. The formation of these vesicles is an extremely active process. The other type of pinocytosis is called absorptive pinocytosis. It is a receptor-mediated selective process, primarily responsible for the uptake of macromolecules for which there are a finite number of binding sites on the plasma membrane. These high affinity receptors permit the selective concentration of ligands from the medium. They minimize the update of fluid and markedly increase the rate at which specific molecules enter the cell. These vesicles formed during the absorptive pinocytosis are derived from invaginations (pits) that are coated on the cytophasmic side with a filamentous material called Clathrin.

Receptor-Mediated Endocytosis

In this, a specific receptor on the surface of the membrane binds tightly to the extracellular macromolecules that are recognized, called the ligand. But the rate of ligand is limited by the amount of its corresponding cell surface receptor. Vertebrate cells bear many types of receptors on the surface that bind specific ligands tightly and with the high degree of specificity. Receptor-mediated Endocytosis occurs via Clathrin coated pits and vesicles.

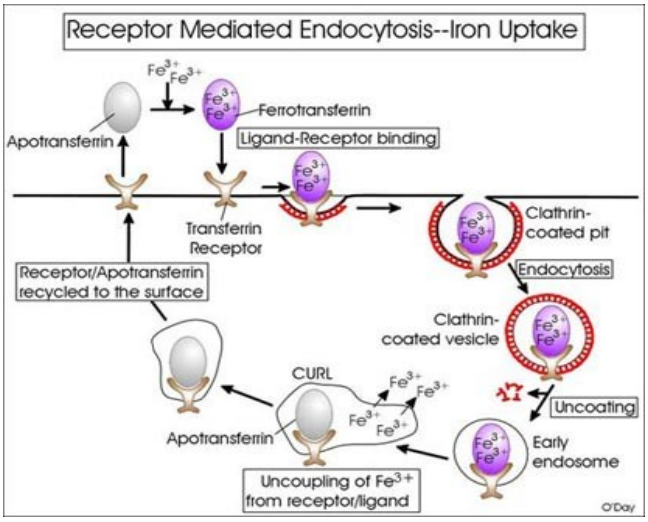
Exocytosis

The process of exudating the secretory products from the secretory cells to the outside of the cell cytoplasm are known as exocytosis or cell vomiting. For example, in pancreatic cells, the enzymatic secretions are passed out with the help of the plasma membrane.

An Example – Iron Uptake in Cells

Iron is the cofactor for various metabolic processes. Cells take up iron from the extracellular environment via receptor-mediated endocytosis. Since iron cannot interact with the receptor directly, it associates itself with the protein transferrin, and the complex together undergoes endocytosis. In the environment, apo transferrin protein has extreme high affinity to tightly bind ferric iron and later forms ferrotransferrin. All growing cells contain surface receptors that bind ferrotransferrin at natural pH [7].

Then this receptor bound ferrotransferrin is subjected to endocytosis. Ferrotransferrin-receptor complex is internalized in a Clathrin coated pit. This pit pinches off to become a coated vesicle. Then the coated vesicle is removed, resulting in early endosomes and it fuses with a sorting vesicle known as curl or late endosomes. The pH of late endosomes is less and so it affinity of transferrin proteins for iron weakens, resulting in iron disassociation. Ferrotransferrin becomes apo transferrin and the other iron atoms are transferred from late endosomes vesicle into the cytosol. Apo transferrin remains bound to the receptor in the endosomes. The apo transferrin receptor complex recycles to the cell surface by exocytosis and the process gets continued. The diagram of transferrin receptor-mediated endocytosis is as follows.



Modeling the Endocytic Pathway of Transferrin-Bound Iron to cells.

We show how the iron uptake process in section 4.4 can be modeled using P systems as follows. Consider a system Π = (V, H, μ, w_0,… w_n, R_0,…R_3, i_0) where

V = {S, fero_trans, fero_rcpt, clath, late_endo, iron}, μ = [[[[ ]$_3$]$_2$]$_1$]$_0$, i_0 = 3, w_0 = {fero_trans}, w_1 = {fero_rcpt}, w_2 = { Clath, late_endo }, w_3 = $\emptyset$,

R_0 = { fero_trans + fero_rcpt → fero_trans & fero_rcpt }, R_1 = { [fero_rcpt]$_1$ → fero_rcpt [ ]$_1$ } $\cup$ {fero_trans & fero_rcpt [ ]$_1$ → [fero_trans & fero_rcpt]$_1$} $\cup$ { fero_rcpt [ ]$_1$ → [fero_rcpt]$_1$} R_2 = {clath, fero_trans & fero_rcpt [ ]$_2$ → [clath, fero_trans & fero_rcpt]$_2$ } $\cup$ { clath, fero_rcpt [ ]$_2$ → [clath, fero_rcpt]$_2$} $\cup$ { late_endo + fero_trans → late_endo & fero_trans } $\cup$ {fero_trans & fero_rcpt → fero_trans + fero_rcpt} $\cup$ { [fero_rcpt]$_2$ → fero_rcpt [ ]$_2$} R_3 = { late_endo & fero_trans [ ]$_3$ → [late_endo & fero_trans]$_3$} $\cup$ { late_endo & fero_trans → late_endo + fero_trans} $\cup$ { [late_endo]$_3$ → late_endo [ ]$_3$}

Analysis Part

The system works in the following way. Initially, FerroTransferin particle (fero_trans) is present in region 0 (environment). As soon as a molecule of this type enters from outside the skin membrane, the process gets started.

The rule *[fero_rcpt]$_1$ → fero_rcpt [ ]$_1$* moves FerroTransferin receptors (fero_rcpt) from region1 to region 0. Hence, the receptors is eventually bound to FerroTransferin particle by the rule, *fero_trans + fero_rcpt → fero_trans & fero_rcpt* and then this FerroTransferin complex is moved back again in region 1, by the rule *fero_trans & fero_rcpt [ ]$_1$ → [fero_trans & fero_rcpt]$_1$*.

After FerroTransferin receptor is bound to FerroTransferin particle,

the rule *clath, fero_trans & fero_rcpt [ ]$_2$ → [clath, fero_trans & fero_rcpt]$_2$* is applied, and the two molecules are brought to region 2.

Here the Clathrin molecules start immediately another process of rewriting and then will move again to region 1 to import another molecule of FerroTransferin. The complex FerroTransferin receptor and FerroTransferin particle enter the process to release iron. In two steps, by the rules *late_endo + fero_trans → late_endo & fero_trans* and *fero_trans & fero_rcpt → fero_trans + fero_rcpt* , the complex *late endo & fero_trans* is created and the FerroTransferin receptors are left free.

Apo Transferin receptor complex are sent back to region 1 using the rule *[fero_rcpt]$_2$ → fero_rcpt [ ]$_2$* and finally to region 0, while the remaining iron particles moves to cytosol. Here, the complex is separated by the rule *late_endo & fero_trans → late_endo + fero_trans*. FerroTransferin is then transformed to iron and apo transferrin, while *late_ endo* is sent back to region 2.

The system is ready again to start to import a new FerroTransferin particle molecule, as soon as such a molecule will be present in region 0, so that the evolution of the system can continue for ever.

Conclusion and Future Research

In this paper we show how to model and analyze the iron uptake in cells and the operations of endocytosis and exocytosis using membrane systems, the emergent research front in computer science. Due to the non halting sequence of transitions, membrane systems are applied to the study of biological processes. We can extend this paper to find the computational complexity and efficiency of mobile membranes.

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