STUDIA UNIV. BABEŞ–BOLYAI, INFORMATICA, Volume **LVI**, Number 4, 2011

PROTEIN CHANNEL FORMATION IN P SYSTEMS

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Abstract. Membrane computing is an area of computer science aiming to abstract computing ideas and models from the structure and the functioning of living cells, as well as from the way the cells are organized in tissues or higher order structures. Membrane systems are usually accompanied by transition rules that represent cellular chemical reactions and transportation rules that represent the movement of cellular molecules through different membranes without changing those molecules. This paper is proposing the addition of channel formation rules to the theory of membrane systems. A simple software simulating the events leading to channel formation within the mitochondrial membrane is used to test the newly suggested rules and the results are satisfactory.

1. Introduction

A P system is one of the natural computing fields that is inspired from the structure and functions of a living cell. In a P system, chemical reactions of a cell are represented by rules. Transition rules and communication rules are the most common types of rules accompanying P systems. Transition rules transform the P system from a status to another by removing and generating objects, i.e., cellular molecules [4]. Communication rules symbolize the movement of objects through membranes [4]. Communication rules assume the preexistence of channels to transport molecules through. Also, some types of rules dealing with the membrane itself were proposed in [4], like membrane division rules and membrane dissolving rules. We are proposing a new type of rules that can accompany a P system. They are the channel formation rules. A channel formation rule allows us to add a new type of data to a P system

Received by the editors: June 12, 2011.

2010 *Mathematics Subject Classification.* 68Q10, 68U20, 92C37.

1998 *CR Categories and Descriptors.* I.1.4 [**Computing Methodologies**]: Symbolic and Algebric Manipulation – *Applications*; I.6.3 [**Computing Methodologies**]: Simulation and Modeling – *Applications*.

Key words and phrases. Channels in P systems, Membrane Computing, P Systems.

and also to use this data as a communication means within the system. This means that a new event in P systems can occur. In addition to membrane division and dissolving, a channel can be created within a membrane and used to transport objects between the two regions sharing this membrane. In this paper, this new type of rules is presented. An application of the channel formation rules is done on the case study of the mitochondrial pathway to cell death. Section 2 gives some of the basic concepts of the P system theory, section 3 explains the biological background needed to understand the case study, section 4 shows a brief history of simulators of cellular activities using P systems, section 5 shows the experiments and results of the proposed case study, and finally section 6 that introduces the results and recommendations of the paper.

2. P Systems

In this section, we are introducing some of the basic definitions and components of the P systems theory.
A P system is a branch of natural computing whose initial goal is to abstract computing models from the structure and the functioning of living cells [3]. It is a computational model that is based on the idea of cellular membrane structure and functions; it was presented by G. Paun [3]. The chemical reactions controlling the change of molecules are represented by evolution rules -also called multiset rewriting rules [3,4]- and the chemical reactions controlling transportation of molecules without changing them are represented by communication rules [3,4]. Communication rules can either be symport/antiport rules or rules with carriers [4]. The above different types of rules are employed and implemented by the P system with the target of transforming from a computational status to another. A simple transition P system is constructed of the form [4]:

$$\Pi = \langle O, C, \mu, w_1, w_2, ..., w_n, R_1, R_2, ..., R_n, i_o \rangle.$$

where:
O: The alphabet of objects, i.e. cellular molecules.
C: The alphabet of catalysts, if any.
μ: The membrane structure. It consists of n membranes labeled with 1,2,3,..,n.
$w_1, w_2, ..., w_n$: The strings over $O \cup C$, representing the multisets of objects initially present in all regions of the system membrane structure [4].

$R_1, R_2, ..., R_n$: The set of evolution rules associated with the regions of the system.
i_o: The output region. It will take one of the labels 1,2, ...,n.

Objects are assigned to rules by choosing rules and objects nondeterministically. Also, the chosen multiset of rules should be applicable to the chosen multiset of objects currently available. When no other rules can be applied on the current multiset of objects, the multiset of rules is said to be maximal. Different rules can be applied on different objects in parallel. We can conclude that P systems run in a maximal parallel nondeterminitic manner [4].

3. The biological background of cell death

This section is concentrating on the biological processes of a living cell that cause channel formation and cell death. Biological concepts, chemical reactions and events leading to channel formation are discussed.

3.1. **Protein Channels.** A protein channel is a watery pathway through the interstices of a protein molecule by which ions and small molecules can cross a membrane into or out of a cell. Protein channels play a vital role in depolarization and repolarization of nerve and muscle fibers, and may have physical characteristics such as shape or diameter that particularly attract certain ions [15]. Various cellular conditions and chemical reactions lead to the formation of a protein channel. Also, most of the protein channels obey certain rules to open and close in order to organize the concentration of different ions and molecules inside the cell.

3.2. **Apoptosis.** Apoptosis which is also known as Programmed Cell Death (PCD) is a conserved cell death mechanism essential for normal development and tissue homeostasis in multi-cellular organisms [11]. These cells are either superfluous or potentially harmful, for instance, apoptosis can serve a protective function by killing off virus-contaminated cells before they spill over with virus particles. This type of cell death is a natural, carefully planned part of the cell life cycle. During apoptosis, the cell shrinks and pulls away from its neighbors [6]. Then, the surface of the cell appears to boil, with fragments breaking away and escaping like bubbles from a pot of boiling water [6]. The DNA in the nucleus condenses and breaks into regular-sized fragments, and

soon the nucleus itself, followed by the entire cell, disintegrates [6]. A cellular cleanup crew rapidly mops up the remains [6]. Apoptosis is led to by a great deal of cellular signals, proteins and pathways. One of the most famous organelles that play an important role of regulation of apoptosis is the mitochondrion. We will focus on the mitochondrial pathway of apoptosis which is also known as the intrinsic pathway.

3.3. **The Mitochondrial Regulation.** There are various proteins that promote apoptosis such as bax protein and others that inhibit apoptosis like bcl-2 and bcl-X_L proteins. The bax protein exists in the cytosol of the cell and bcl-2 and bcl-X_L exist in the space between the outer and inner mitochondrial membranes. Bax has the tendency to form a channel through the outer mitochondrial membrane, and bcl-2 and bcl-X_L tend to prevent it. A trophic factor or a growth factor is a cellular signal that helps the cell to stay alive, figure 1-a [10]. It provides a signal blocking the path to apoptosis. The binding of the trophic factor to a specific trophic factor receptor on the cell surface triggers the signaling cascade resulting in the phosphorylation of the Bcl-2-associated death promoter, the Bad protein, see figure 1-b [10]. Bad is one of the apoptosis initiators. This phorphorylated Bad protein is unable to bind and inhibit the bcl-2-bcl-X_L complex at the outer mitochondrial membrane. That is, the anti-apoptotic activity of this complex is unhindered and the cell survives figure 1-c [10]. The chemical equations 1, 2 represent the reactions the cell takes to survive. In the absence of the trophic factor, most cells undergo apoptosis.

$$\text{Trophic\_factor} + Bad \rightarrow \text{Phosphorylated\_Bad}. \quad (1)$$
$$\text{Phosphorylated\_Bad} + bcl\_2\_bcl\_X_L \rightarrow \text{Inactive\_Bad}. \quad (2)$$

Without a trophic factor signal, the Bad protein is un-phosphorylated and associates with the bcl-2-bcl-X_L complex inhibiting anti-apoptotic activity [10], see figure 2-a [10] and figure 2-b [10]. When the bcl-2-bcl-X_L complex is inhibited, the pro-apoptotic regulator Bax is free to permit the influx of ions through the mitochondrial membrane by creating a channel [10]. This channel is called the Mitochondrial Apoptosis-Induced Channel or MAC [8], see figure 2-c [10]. Once the ions go through the channel into the mitochondrion, the release of cytochrome c -which is a protein found loosely associated with

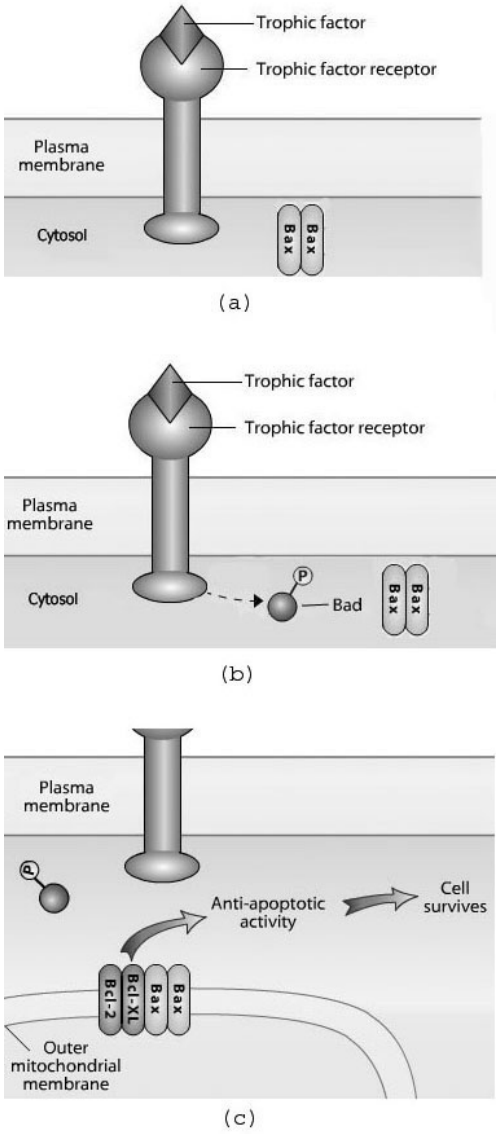

FIGURE 1. Signals of cell survival

the inner membrane of the mitochondrion- to the cytosol through the channel is triggered as in figure 2-d [10]. In cytosol, cytochrome-c binds to the Apoptotic Protease Activating Factor-1 (Apaf-1) which activates the caspase cascade, see figure 2-e [10]. Caspases are a family of special enzymes called

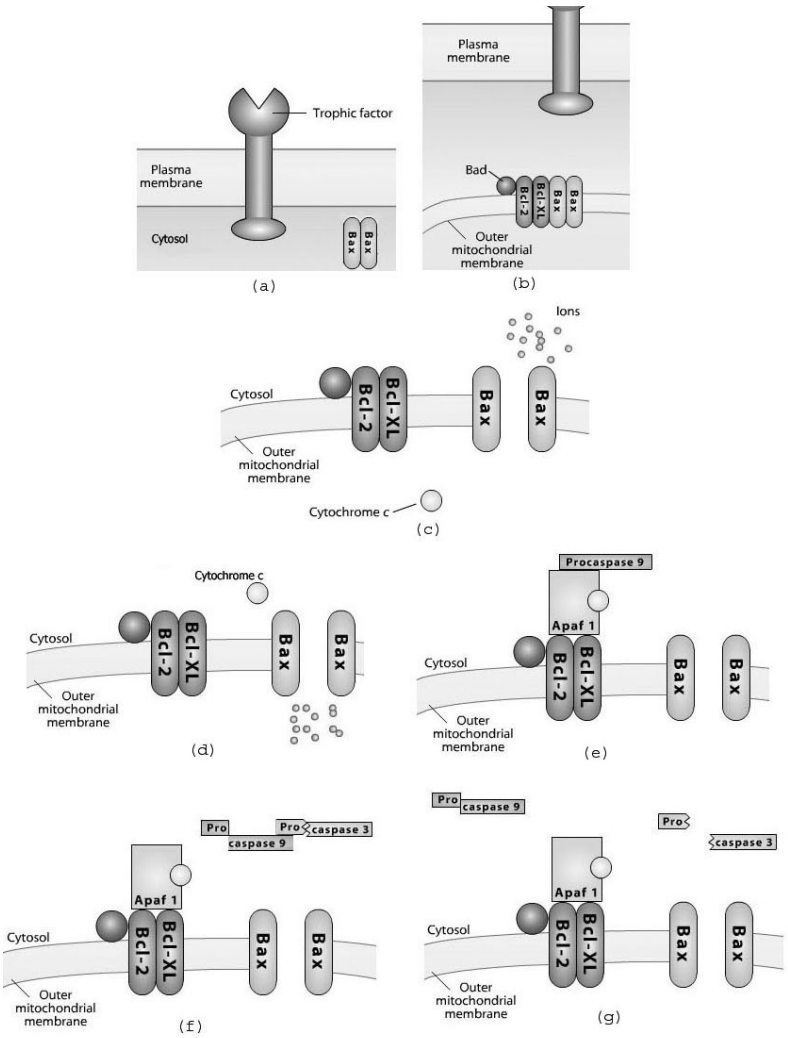

FIGURE 2. Signals of cell death

cysteine proteases that are targeting the proteins of the nuclear lamina and cytoskeleton in order to fragment them as a step of cell death. The complex Apaf-1-cytochrome-c binds to procaspase-9 to create a protein complex known as an apoptosome [2,8]. The apoptosome cleaves the procaspase to its active form of caspase-9, which in turn activates the effector caspase-3, see figure 2-f [10] and figure 2-g [10]. The chemical reactions 3, 4 and 5 represent the events

that lead to cell death:

Cytochrome_c + Apaf_1+ procaspase_9 → apoptosome. (3)
Apoptosome + procaspase_3→caspase_3. (4)
Caspase_3 → Apoptosis. (5)

4. Literature Survey

This section is about previous researches done in P system with channels as well as some of the P simulators of cellular activities.
Communication within a P system through channels was achieved by symport/antiport rules in [1]. Means of channel controllers were added to formulate channels that can be activated or prohibited in [13]. In [9] a variant of P Systems is defined in which transport of objects across the regions of the system is possible by means of rules associated with membranes and involving proteins attached to them. Such proteins can be attached/deattached to/from membranes by means of rules.
A biological model of Mechanosensitive Channels and their conformations (closed, extended closed, subconducting open and open) was represented in the framework of P systems in [14]. A P-simulator of the mitochondrial functions and chemical reactions to produce energy was published in [7]. The cellular respiratory system of the bacterium Escherichia Coli was presented using logic gates in [5]. There were other published metabolic simulators like MetaPlab which was produced by the Italian university Verdona [16]. It was a deterministic P system developed to model dynamics of biological phenomena related to metabolism. It added a new plugin based framework for processing metabolic P systems. Also, there was a simulator for Biological Processes produced by University of Sheffield, UK in 2006[18]. It simulated the evolution of Multi-compartmental Gillespie algorithm over a hierarchy of compartment structures. Another simulator, CytoSim simulator which was produced by the Microsoft Research - University of Trento Centre for Computational and Systems Biology, Trento, Italy. This simulator was a stochastic simulator of biochemical processes in hierarchical compartments. The compartments might be isolated or may communicate via peripheral and integral membrane proteins [19]. There are many other simulators that are concerned with the implementation of P systems on other research fields like neural networks, dynamical probabilistic P systems and membrane approximation algorithms [17].

5. The Problem and an Application

This section is defining the problem, a method to solve it and some experiments on this method. The experiments are employing the case of the mitochondrial activities that cause one protein channel or more to be formed within the mitochondrial membrane.

5.1. **The problem.** In a living cell, some chemical reactions may lead to form a channel within a given membrane. On the other hand, channels are assumed to be preexisting in P systems. Therefore, a new type of rules that can create a channel within a given membrane is to be introduced. Also, the type of objects passing through the formed channel is to be controlled by traditional evolution rules.

5.2. **The Construct of the P System.** We are proposing the following P system construct that models the channel formation within the mitochondrial membrane. This construct includes evolution rules in addition to the proposed channel formation rules. The following P system construct is illustrated in figure 3.

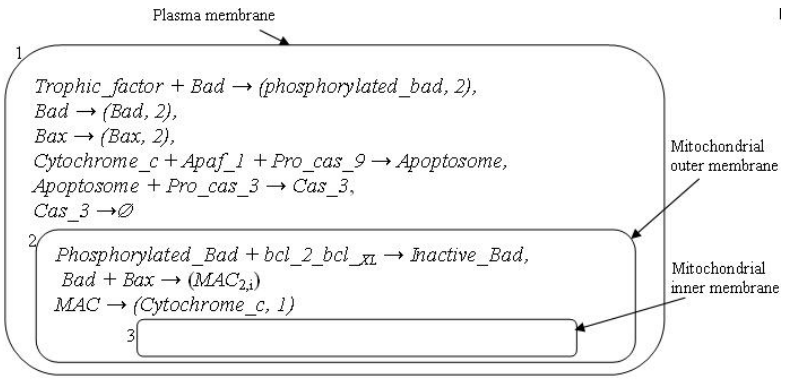

Figure 3. The mitochondrial pathway to apoptosis

The P system will be in the form:

$$\Pi_{sim} = \langle O, \mu, Ch_{2,n}, w_1, w_2, R_{e1}, R_{e2}, R_{c2} \rangle.$$

where:
- O: The alphabet of objects.
O= $\{Trophic\_factor, Bad, phorphorylated\_Bad, bcl\_2\_bcl\_XL, Bax, Apaf\_1,$ $procaspase\_9, procaspase\_3, MAC, Cytochrome\_c, apoptosome, caspase\_3,$ $Inactive\_Bad\}$.

-μ: The membrane structure [4]. The plasma membrane will take label 1, the outer mitochonrdial membrane will take label 2 and the inner mitochondrial membrane will take label 3. The structure is $\mu = [_1[_2[_3]_3]_2]_1$.

-$Ch_{2,n}$: The newly formed n channels over membrane two. Notice that for any given membrane m, the following equality shows the n number of channels belonging to m:

$Ch_{m,n} = \{MAC_{m,1}, MAC_{m,2}, ..., MAC_{m,n}\}$.

This means that the channels formed over membrane two are:

$Ch_{2,n} = \{MAC_{2,1}, MAC_{2,2}, ..., MAC_{2,n}\}$.

- w_1, w_2: The strings over O $\cup$ C [4], representing the multisets of cellular molecules and channels present in region 1 and 2 respectively.

-$w_1 = \{Bad, Bax, Trophic\_factor, phosphorylated\_Bad, Apaf\_1, procaspase\_9,$ $procaspase\_3, apoptosome, Cytochrome\_c, caspase\_3\}$,

-$w_2 = \{Bad, Bax, bcl\_2\_bcl\_XL, MAC, Cytochrome\_c, Phosphorylated\_Bad,$ $Inactive\_Bad\}$.

-R_{e1}, R_{e2}: The set of evolution rules associated with the three regions of the system. They are in the form u$\rightarrow$ v where u is a string over O and v is a string over O_{tar}, where $O_{tar} = O\times$ TAR [4] for TAR= 1,2. This means that every reaction indicates the output objects and the region to which the output objects will be moved. When there is no target indicator i.e. 1 or 2, this means that the outcome of the applied reaction will remain in the current region.

$-R_{e1} =$
$\{$
$r_1 = Trophic\_factor + Bad \rightarrow \langle Phosphorylated\_Bad, 2\rangle,$
$r_2 = Bad \rightarrow \langle Bad, 2\rangle,$
$r_3 = Bax \rightarrow \langle Bax, 2\rangle,$
$r_4 = Cytochrome\_c + Apaf\_1 + procaspase\_9 \rightarrow Apoptosome,$
$r_5 = Apoptosome + procaspase\_3 \rightarrow caspase\_3,$
$r_6 = caspase\_3 \rightarrow \oslash$
$\},$
$-R_{e2} =$
$\{$
$r_7 = Phosphorylated\_Bad + bcl\_2\_bcl\_XL \rightarrow Inactive\_Bad,$
$r_8 = MAC \rightarrow \langle Cytochrome\_c, 1\rangle$
$\}.$
-R_{c2}: The set of channel creation rules associated with membrane two, i.e., the outer mitochondrial membrane.

$-R_{c2} =$
$\{$
$r_9 = Bad + Bax \rightarrow \langle MAC_{2,i}\rangle$
$\}.$
where i is the number of the last formed channel.

5.3. **Experimental results.** Any experiment in the framework of P systems initially requires the predefined membrane structure, the set of rules that describe the functions of the proposed system and the multisets of data within each region of the P system. This application has the first and the second initial inputs, the membrane structure defined in figure 3 and the set of rules explained in section 5.2. We will assume some initial multisets in order to get to our aim which is observing the behavior of the channel formation rules and the results of using them. Figure 4 shows a simple diagram of the main processes of the proposed software. Notice that the right hand side of rule r_6 is $\oslash$. We used this symbol to indicate that the P system would halt because the cells died.

Table 1 shows the possible inputs to the proposed system. We focused on the $bcl\_2\_bcl\_XL$ and Bax molecules because they are the inhibitor and promoter

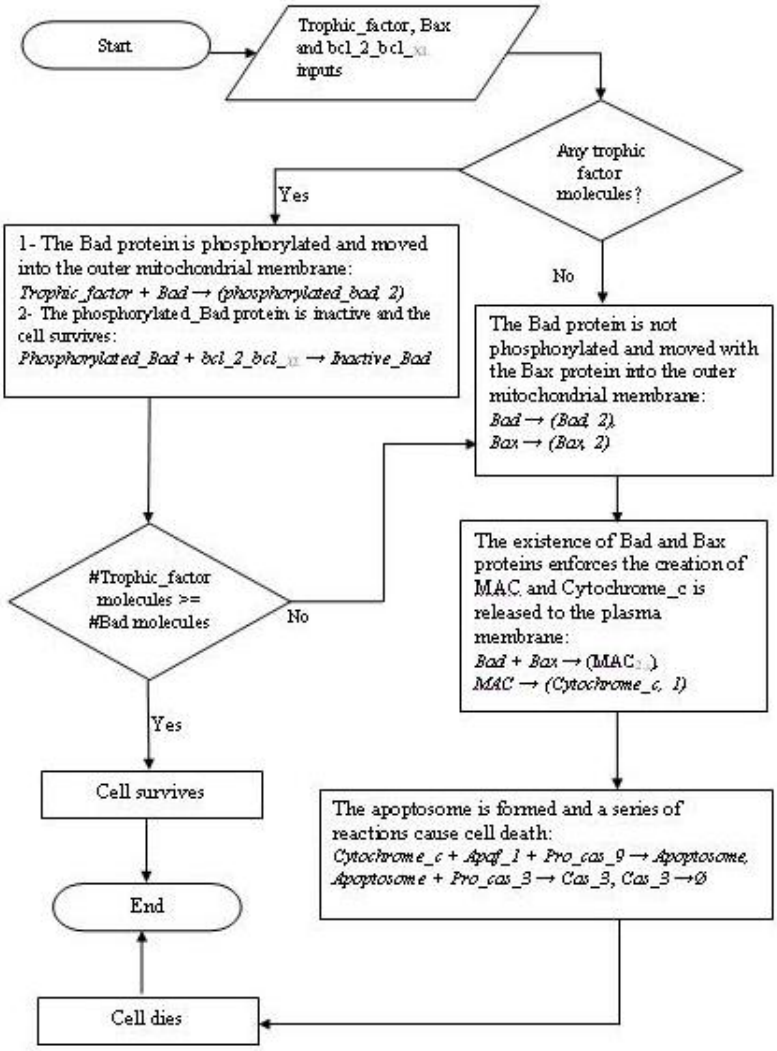

FIGURE 4. A flowdiagram of the proposed software

of apoptosis respectively. Combinations 1 and 3 in table 1 were experimented 4 times. For combination 1, experiments showed that a channel may be formed only if there is a molecule of Bad protein that can be moved from membrane one into membrane two or there are not enough $bcl\_2\_bcl\_XL$ molecules to inhibit the channel formation, otherwise the channel formation rule will not

TABLE 1. Possible inputs to the proposed P system and their outputs

Combination #	bcl_2_bcl_XL	Bax	Channel formation
1	Yes	Yes	Yes or No
2	Yes	No	No
3	No	Yes	Yes or No
4	No	No	No

be fired. For combination 2, it is impossible to create a channel in the absence of Bax protein. In combination 3, the experiments showed that it is possible to create a channel only if there are enough molecules of Bad, Apaf_1, Procaspase-9 and Procaspase-3 proteins. Finally, in combination 4 it is impossible to create a channel because of the absence of the Bad promoting protein. The following three points were observed:

1- Multiple channels can be formed within a single membrane. That is because of the condition of the maximal parallel non deterministic manner in which rules are executed.

2- A channel may be created within a membrane, but the cell still might not go through apoptosis. This means that a living cell does its best to stay alive. This feature can be applied to maintain the durability of a P system and it is already achieved in the current situation. A P system can not halt until it consumes the last chance to function.

3- In addition to membrane division and dissolving rules, channel formation rules became one type of rules that can affect the membrane itself.

In [12], two different types of channels were proposed, transport channels and diffusion channels. A diffusion channel definition is the most relevant definition to the channel formation rule. In diffusion channels, some proteins create a small hole through which molecules can freely pass [12]. The main purpose in [12] was to differentiate between the rules controlling diffusion channels and transport channels, not the process of channel creation itself. Although diffusion channels enable the passing through the membrane of an arbitrary number of objects [12], diffusion channels cannot appear more than

once [12]. On the other hand, we showed that a channel or more could be created within a membrane which is more close to biological systems, preserving the condition of the maximal parallelism of rule application. Also, in [12], a diffusion channel had to be opened and closed every time it was used, while we can create a channel once and control it by rules to constraint the passage to specific objects.

6. Conclusion and Future Work

Biological activities can be computerized using P systems. The structure and functions of a cell can be well used in different fields of computer applications. This paper is intended as a representation of a P system with channel formation rules that used the case study of the mitochondrial pathway to cell death. Results showed that one channel or more were created simultaneously in the same membrane according the current number of cellular molecules. Results also showed that a P system was able maintain its durability the same way a living cell did. The channel formation rules could result in causing the modification of the membrane structure. Instead of attempting to control the preexisting channels, promoters and inhibitors can be combined with the channel formation rules to formulate a new type of rules that creates and controls channels. Fuzzification of the rules controlling channel formation can be an extension of this paper too. The proposed software has successfully achieved the expected results and P systems proved its power. We think our work above contributes and adds to the field of membrane systems.

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