Modeling of Cellular Communication by Means of Petri nets

Isaac Barjis[*], Sidi Berri[*;],Joseph Barjis[**]

* Department Biological Sciences and Electrical Engineering, New York City College of Technology,
** Department of Information Technology Georgia Southern University

ABSTRACT

This paper introduces application of Petri nets to cellular biology. In particular, it illustrates how by means of Petri nets the process of cellular communication (cellular signaling) can be modeled, analyzed, and simulated where the model could be used for the research purpose and/ or teaching purposes.

In order to develop a Petri net model for cellular communication, firstly the paper explains cellular and molecular reactions of the processes, because the validity of the developed model depends on how well the real processes are identified and highlighted.

Since the emphasis of this paper is on application of Petri net rather than the underlying molecular aspects, the molecular and biological events and reactions are not covered in depth. Only the most important reactions and processes of the cellular communication, needed as input data for building a Petri net model, are described.

The Petri net model is developed using Colored Petri net tools (CPN), which allows graphical editing, analysis and simulation of Petri net models.

Keywords: Petri net, molecular modeling, cellular signaling

1. INTRODUCTION

Cells face a steady input of signals. In multicellular organisms individual cells need to sense, interpret and respond to multitude of signals they receive from their environment and other cells. For instance during animal development, cells in the embryo exchange signals to determine which specialized role each cell will adopt. All cellular decisions, like survival or apoptosis (cellular suicide), proliferation or secretion of certain compounds are governed by this complex pattern of inputs known as cellular communication. As it is shown in figure 1 information can come in a variety of forms, and communication frequently involves converting molecular signals from one form to another form. Like any other cellular process, the process of cellular communication is a very complex, dynamic and invisible, which makes them difficult to explain, teach, illustrate and understand.

To overcome this problem and represent high-level processes (e.g. cellular communication) in the context of their component functions, this paper introduces modeling and simulation approach and methodologies to illustrate biological processes via graphical notations of Petri net. Graphical notations or representation of the process is the most useful, interesting and important step in developing a model of the process. Based on the graphical notation a process could be simulated and modeled, and its dynamic behavior could be investigated. These graphical notations have to be formulated in such a way that would serve as straightforward step towards code generation or programming.

The use of discrete modeling, in particular Petri nets, is a very interesting and promising research subject. Quite a few papers are published on this issue. It was in 1993 that Reddy et al. introduced Petri nets for the qualitative modeling of biochemical networks. Since then, just a few papers appeared every year with similar approaches in order to model and/or analyze biochemical pathways, dealing with metabolism, gene regulation, or signal transduction respectively. Only recently there seems to be an increasing interest in using Petri nets as a modeling tool for biological processes. Place transition Petri net and stochastic Petri net can be used to model molecular communications within a cell using a linear algebra-based, time-dependent and place-transition Petri net model (Dixon et al 1999).

Modeling the structure of biological molecules and processes is critical for understanding how these structures and processes perform their function. Furthermore, these models can be used for designing compounds to modify or enhance the functions of biological molecules for medical or industrial purpose, or just to interactively animate and simulate biological processes for teaching purposes. Modeling metabolic reactions in a biological process provide insight into responses of the cell to drug treatments (Konig, R. et al 2002). Computer modeling and simulation of biochemical process is a mean to augment the knowledge about the control mechanisms of such processes in particular organism (Genrich et al 2000).

In order to develop a software application for the system under study, one needs to have a proper insight into the essence of action of the system. In a sense, one needs, first, to represent the system in a formalized way (in diagrams) to understand how it operates. There are many modeling methods that can be used for this purpose, but this paper introduces the Petri net methodologies, especially its action diagram as a modeling technique that helps software engineers to understand the system before developing its program.

2. CELLULAR COMMUNICATION

A cell needs to communicate with its environment so that it can make appropriate responses. The external signal may enter a cell by binding to the cell surface receptor. Cell surface receptors fall into three main classes: Ion channels; G-protein-coupled receptors; Enzymes.

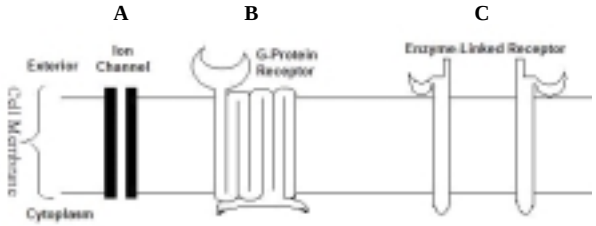


Figure 1: Cell-surface receptors: A) an ion-channel-linked receptor opens and closes in response to extra-cellular signal. B) G-Protein-linked receptor binds to the external signal and activate G-Protein inside the cell (cytoplasm). C) An enzyme-linked receptor.

In many cases, the signal continues to propagate within the cell and often reaches nuclear DNA to express proteins (see figure 2). Binding signal molecule to the surface receptor can alter the cell's shape, movement, metabolism and gene expression. The signal from a cell surface receptor is conveyed into the cell interior (cytoplasm) via set of interacting molecular mediators. Different cells would respond differently to the same molecular signal. For instance *Acetylcholine* would increase the cardiac cell contraction and force when it binds to the cardiac cell receptor; but when salivary gland is exposed to the same molecular signal, it would increase saliva secretion. So in different cell types, different sets of target proteins are available for alteration, or in some instances extra-cellular signal can activate expression of DNA.

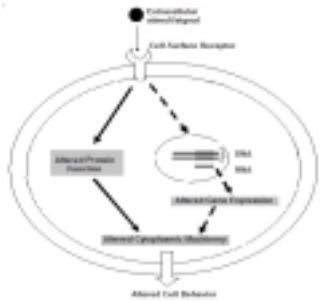


Figure 2: Extra-cellular signals can either change gene expression (DNA expression and RNA synthesis) or alter cytoplasmic protein (e.g. phosphorylation of target protein).

As it is shown in figure 2 above an extra-cellular signal can activate expression of DNA in the cell nucleus, thus leading to transcription of RNA and than translation of RNA into a protein. The synthesis of new protein inside the cell will lead to the changes in the cellular behavior.
In this paper we will concentrate on the activation of G-protein-linked receptors that lead to activation of G-proteins subunits (see figure 3).

When an extra-cellular signal molecule binds to the G-protein-linked receptors on the membrane, the protein receptor undergoes conformational changes that enable it to activate a G protein located in the cytoplasm (see figure 3).

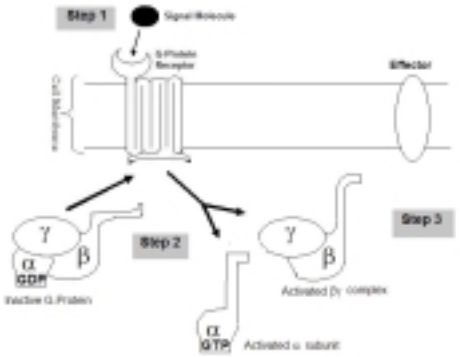


Figure 3: Dissociation of G-protein into two signaling proteins when activated. Stimuli (signal molecule) binding to the G-Protein Receptor causes interaction between the G-protein-coupled receptor and the G protein (inactive G-protein). Their interaction results in the dissociation between α and $\beta\gamma$ subunits of the G protein. The separated α and/or $\beta\gamma$ subunits may then interact with effectors.

In un-stimulated state the α- subunit is bound to GDP, but when an extra-cellular ligant binds to its receptor, it leads to activation of G-protein by causing the α-subunit of the G-protein to lose its affinity for GDP, and exchange the GDP with GTP. This activation makes the α-subunit to detach from the $\beta\gamma$-complex thus give rise to two separate activated molecules (see figure 3). Both active molecules can interact directly with target proteins and transport the signals to yet other destination.

3. PETRI NET METHODOLOGY

The Petri nets are formalism and a graphical language for the design, specification, simulation and verification of systems (1). The Petri net structure consists of places and transitions. Corresponding to these, a Petri net graph has two types of nodes - place and transition (see figure 3). A circle represents a place (state); a rectangle represents a transition (events, activities, actions, operations).
Tokens are data objects (class instances). An action associated to each transition, when the transition is fired, its action is performed in order to compute the output token(s) and perform external actions (e.g., tool invocations).
Arcs connect input places to transitions and transitions to output places. Arcs can have an associated integer weight as well. A transition is enabled only if all its input places

contain at least as many tokens as the arc weight. An enabled transition may eventually fire (non-determinism).
A transition firing atomically removes as many tokens from all the transition input places as the weight of the connecting arcs; inserts as many tokens in all the transition output places as the weight of the connecting arcs.

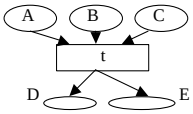
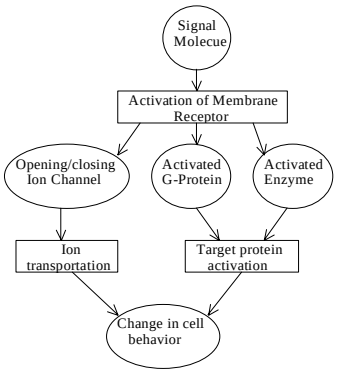


Figure 4:Petrinet Place and Transaction diagram

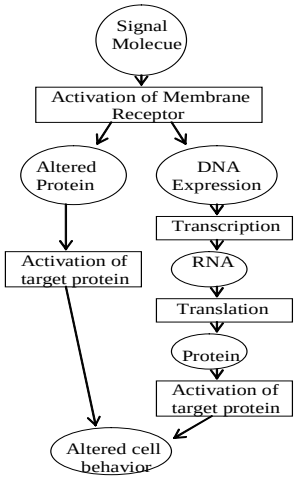
For instance, let's assume that in the diagram, A, B, and C are the input places (e.g. extra-cellular signal molecules) for transition t (e.g. Transduction or cell surface protein receptor activation). Output places are D and E (e.g. G-protein activation).

3.1. A Petri Net Model of Cellular Communication

In developing a Petri net model of the cellular communication, we find operations (in terms of Petri net referred to as events or activities), which take place in the process of cellular communication, and states, which are reached after each of these operations. In other words we trace the sequence of operations from molecular signal (stimuli) to the change in the behavior of the cell.
A Petri net model of the cellular communication is shown in figure 4. Information in this model is based on figures 1&2 and description of the cellular communication in previous section. In this diagram we observe five states, namely Signal molecule ligant, Activated G-protein, Activated enzyme, opening or closing of ion channels. All these states, in the Petri net model of figure 5, are represented by places (graphically represented by circles/ ellipses). The operations, which take place in this process, are Membrane receptor activation, Ion transportation, and Target protein activation. All these operations are represented by transitions in the figure 5 (graphically represented by rectangles)



A



B

Figure 5A and B shows a compact Petrinet model of Cellular communication

With reference to the Petri net model of the cellular communication it is easy to analyze and simulate it with the common techniques. However the results of such models will not be adequate enough and correct, as this model is at a very high level and contains insufficient information of other molecular/biochemical events and operation, which take place in each steps of this model. For instance just the transcription step requires more than 20 molecular precursors (states) and 5 reaction processes (transitions) (Barjis et. all, 1999)
In order to develop a detailed and accurate model of cellular communication, it is necessary to look at molecular events and reactions that occur in each step (i.e. process) in same details.

3.2. A Detailed Petri Net Model of Cellular Communication

The major role of G-protein-coupled receptors is to transmit signals into the cell. They are characterized by seven transmembrane segments. This class of membrane proteins can respond to a wide range of agonists, including photon, amines, hormones, neurotransmitters and proteins. Some agonists bind to the extra-cellular loops of the receptor, others may penetrate into the transmembrane region.

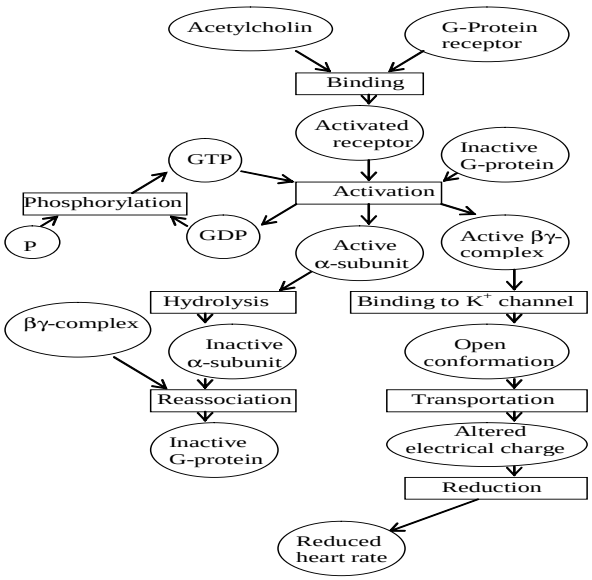


Figure 6:Detailed model of cellular communication

The heartbeat in animals is controlled by two sets of nerve fibers: one speeds up the the heart, the other slows it down. The heart rate decreases when acetylcholine is released by the nerve fiber and binds to the G-proteins receptor on the surface of cardiac muscle cells. As we can see from the diagram 6 above, the binding of acetylcholine to the G-protein receptor leads to the activation of the protein receptor, and subsequently activation of the receptor leads to dissociation G protein into two active subunits. In this particular model the βγ-complex is the signaling component that eventually leads to reduced heart rate.

4. CONCLUSION

The main purpose of this paper was to develop a modeling methodology for the lipid metabolism using Petri nets. Modeling methodologies help visualization, formalization, and simulation of molecular processes (like the lipid metabolism example in this paper). It allows the researchers to develop an abstract description of biological processes (in this case the process of lipid metabolism); furthermore simulation and modeling allows decisions to be pre-tested before implementation; and finally, as real-life laboratory experimentation or standard analysis of a process is often too complex or/and expensive, this methodology will reduce costs of the experiment by using the computer model instead of material in the laboratory.

Two areas can benefit from such a methodology that has been presented in this paper: to stimulate research and to assist teaching. For the teaching purposes, this model would help educational institutions in teaching the process of lipid metabolism in particular and any other biological process in general. It would help students to see this process visually, and understand it better. It would help to follow the molecular events and reactions that occur through out the process of lipid metabolism. The model will help to visualize the processes by the movement of tokens of the Petri nets from state to state, and explain how molecular events, reactions and operations together provide these processes to occur. It would help to visualize the actual biological process and see how the substrates and precursors bind or disassociate in order to complete the process of lipid metabolism. This paper can also be useful for the training programs offering molecular biology with modeling and information sciences integrated into the individual courses, to train students in the use of computational techniques in the study of molecular and biological processes (systems).

For the research purposes, one can use this methodology to understand the potential advances in biological process based on recent developments such as improved understanding of the biochemical metabolisms, the use of metabolic modeling of individual microorganisms, and new biochemical probing tools for modeling and simulation. So it would allow researchers to be in control of the experiment because they would be able to pre-test their laboratory experiment by touch of few buttons, without spending time and material in laboratory.

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