Modeling of Cellular Communication

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ABSTRACT

The modeling of cellular signaling pathways is an emerging and important field. In this paper we introduce applications of Rule based to biological pathway. In particular, it illustrates how by means of rule based the process of cellular communication can be modeled, and analyzed, where the model could be used for the research purpose and/ or teaching purposes. In order to develop a rule-based model for the process of cellular communication, firstly the paper explains molecular reactions of the processes (G-Protein receptor, G-Proteins and cAMP), 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 rule based modeling rather than the underlying molecular aspects, the molecular and biological events and reactions are not covered in very depth. Only the most important molecular events of the process of cellular communication, needed as an input data for building a rule based model, are described.

INTRODUCTION

Substantial amounts of data on cell signaling, metabolic pathways, gene regulatory and other biological processes have been accumulated in literature and electronic databases. Conventionally, this information is stored in the form of pathway diagrams [4,5]. Current approaches for representing pathways are limited in their capacity to model molecular interactions in their spatial and temporal context. Moreover, the critical knowledge of cause-effect relationships among signaling events is not reflected by most conventional approaches for manipulating pathways.

Because signal flow is tightly regulated with positive and negative feedbacks and is bidirectional with commands traveling both from outside-in and inside-out, dynamic models that couple biophysical and biochemical elements are required to consider information processing both during transient and steady-state conditions. Unique mathematical frameworks will be needed to obtain an integrated perspective on these complex systems, which operate over wide length and time scales. These may involve a two-level hierarchical approach wherein the overall signaling network is modeled in terms of effective "circuit" or "algorithm" modules, and then each module is correspondingly modeled with more detailed incorporation of its actual underlying biochemical/biophysical molecular interactions [2]

An important feature of receptor-mediated cell signaling pathways is the capacity to discriminate between different ligands that bind to the same receptor. McKeithan introduced a kinetic proofreading model to explain such discrimination in T-Cell activation [7]. In the model the bound receptor must complete a series of modification such as phosphorylation, diphosphorylation and association with kinases for a particular cellular response to occur. In rule based modeling phsphorylation and association with kinases can be considered as set of rules and condition for a particular receptor or ligand.

RULE BASED MODELING

A rule-based system consists of set of objects, set of facts on the objects declaring their properties, and set of rules, conditions and actions on them.

IF (AND (condition1) (condition2)) THEN (action1) ELSE (action2)

The advantage of the rule-based model is that it provides a documented, logical structure to the decision-making process that is both intuitive and experiential. Such models can process quantitative data but are most useful when coping with qualitative information to reach decisions. Rule-based models build on what is known using available literature, in-house databases, and the collective knowledge of experts. Examples of rule-based systems are expert systems that have the knowledge of a doctor and can answer complex questions people would normally ask those professionals. These types of models have become known as knowledge-based systems or expert systems.

Using a set of assertions, which collectively form the 'working memory', and a set of rules that specify how to act on the assertion set, a rule-based system can be created. Rule-based systems are fairly simplistic, consisting of little more than a set of if-then statements, but provide the basis for so-called "expert systems" which are widely used in many fields. The biological process of cellular communication is a complex process but it is totally rule-based. For example, binding of signaling messenger to the surface receptor will

either lead to alteration of protein in the cytoplasm or will initiate transcription of RNA (see figure 1 bellow). It allows a user to create a computational model that characterizes the dynamics of a signal transduction system, and that accounts comprehensively and precisely for specified enzymatic activities, potential post-translational modifications and interactions of the domains of signaling molecules. The output defines and parameterizes the network of molecular species that can arise during signaling and provides functions that relate model variables to experimental readouts of interest. Models that can be generated are relevant for rational drug discovery, analysis of proteomic data and mechanistic studies of signal transduction such as cell signaling.

Modeling metabolic reactions in a biological process provide insight into responses of the cell to drug treatments [6]. Computer modeling and simulation of biochemical process is a mean to augment the knowledge about the control mechanisms of such processes in particular organism [3].

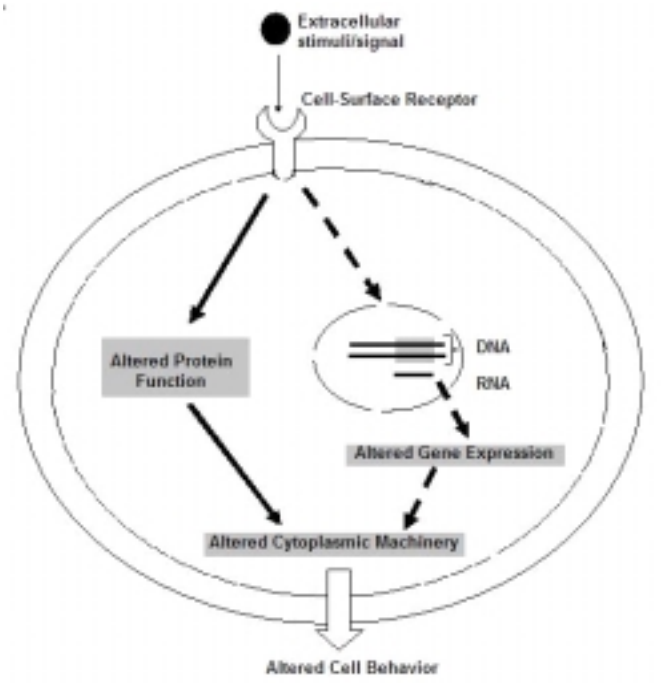

Figure 1*: Extra-cellular signals can either change gene expression (DNA expression and RNA synthesis) or alter cytoplasmic protein (e.g. phosphorylation of target protein).*

CELLULAR COMMUNICATION

Living organisms constantly receive and interpret signals from their environment. Signals can come in the form of light, heat, water, odors, touch, or sound. Cells of multi-cellular organisms also receive signals from other cells, including signals for cell division, secretion and differentiation. The majority of cells in our bodies must constantly receive signals that keep them alive and functioning. All organisms also have signaling systems that warn of the presence of pathogens, leading to a protective response.

The key concept is that the many signaling systems of biology have very similar or related steps. The same signaling system can lead to very different responses in different cells or different organisms. Studies of the mechanisms of cell signaling are leading to new understanding of many diseases, and to new strategies for therapy. In order for the cells to cooperate, cells need to be able to communicate with each other. Many of the genes that cells are capable of synthesizing are thought to be involved in cellular signaling (a.k.a. signal transduction).

CHEMICAL SIGNALING

Chemical signaling can be classified into three categories: local-chemical mediator, hormone, and neurotransmitter Albert). In the local-chemical mediator model, the secreted chemical acts on the cells in the immediate environment. Hormones are used for communication with distant target cells. In this paper we will look at the signaling pathway that leads to activation of G-proteins and production of cAMP. Before we construct our rule-based model lets look at the biological events that occur during the process of G-protein activation and cAMP production [8].

- G-Protein consists of three subunits: α, β, and γ.
- In the inactive state, GDP is bound to the binding site of α subunit.
- When a ligand (e.g. hormone) binds to the G-Protein receptor, an allosteric change takes place in the receptor. This allosteric change in the receptor triggers an allosteric change in G-perotein that causes theα subunit to replace its GDP with GTP.
- Binding of GTP to theα subunit of G-protein activates dissociation of the α subunit from β-γ subunits.
- Activated α subunit in turn activates an effector molecule. In our example the effector is adenylyl cyclase.
- Adenylyl cyclase catalyzes conversion of ATP to cAMP.
- cAMP bind to the regulatory subunits of the cAMP dependant protein kinase (PKA) and leads to dissociation of catalytic subunits from the regulatory subunits.
- Dissociation of catalytical subunits of PKA leads to phosphorylation of CREB that results transcription.

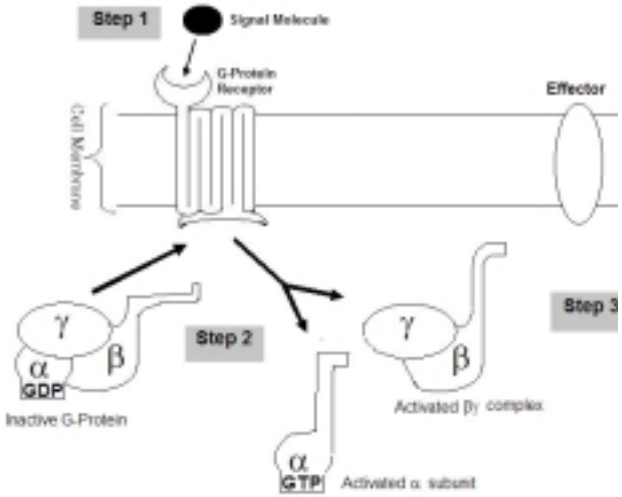

Figure 2: Dissociation of G-protein into two signaling proteins when activated. Stimuli (signal molecule) binding to the G-Protein Receptor causes interaction between the G-protein-coupled receptor and the G protein (inactive G-protein). Their interaction results in the dissociation between α and $\beta\gamma$ subunits of the G protein. The separated α and/or $\beta\gamma$ subunits may then interact with effectors.

Objects: G-Protein receptor, Activated G-Protein Receptor, Activated G-protein, Activated Adenyl Cylase, and AMP
Actions: *Activation of G-Protein Receptor, Dissociation of G-Protein subunits, Activation of Adenyl Cyclase, and conversion of ATP to cAMP*, *transcription*, and *translation*
Rules: rules for G-protein receptor activation, rules for G-protein subunits dissociation, rules for activation of adenyl cyclase, and rule for conversion of ATP to cAMP.
Properties: G-Protein receptor, Activated G-Protein Receptor, Activated G-protein, Activated Adenyl Cylase, and AMP.

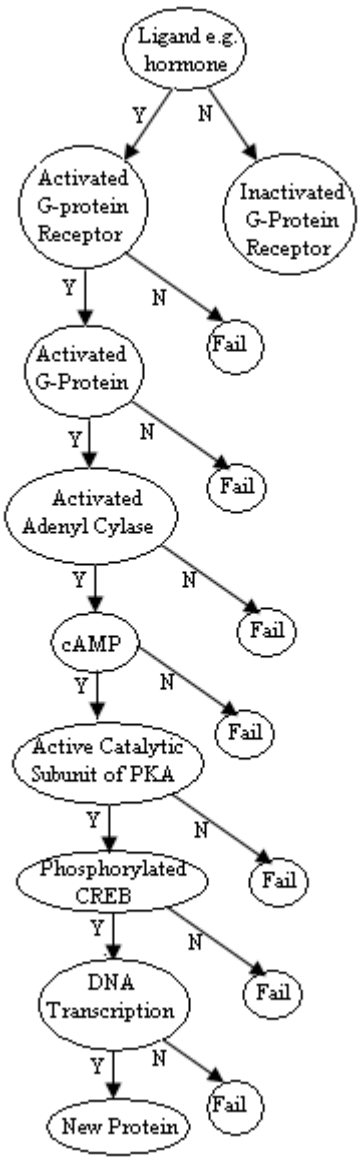

Figure 3: Rule-based network of G-protein, cAMP pathways

In *object* LIGAND,
IF (LIGAND BOUND TO THE G-PROTEIN RECEPTOR), THEN (ALLOSTERIC CHANGE IN THE G-PROTEIN RECEPTOR), ELSE (FAIL)
In *object* ACTIVATED G-PROTEIN RECEPTOR,
IF (GTP BINDS TO THE ALFA SUBUNIT OF G-PROTEIN), THEN (DISSOCIATE THE G-PROTEIN INTO ALFA SUBUINT AND BETA –GAMA COMPLEX SUBUINIT), ELSE (FAIL)
In *object* ACTIVATED G-PROTEIN,
IF (ALFA SUBUINT OF G-PROTEIN BOUND TO ADENYL CYCLASE), THEN (ADENYLYL CYCLASE ACTIVATION), ELSE (FAIL)
In *object* ACTIVATED ADENYLYL CYCLASE
IF (ATP), THEN (cAMP), ELSE (FAIL)
In object cAMP

IF (cAMP IS BOUND TO THE REGULATORY SUBUNITS OF PKA), THEN (DISSOCIATE THE CATALYTIC SUBUINTS OF PKA), ELSE (FAIL).
In object ACTIVE CATALYTIC SUBUNITS
IF (BOUND TO CREB PROTEIN), THEN (PHOSPHORYLATE THE CREB PROTEIN), ELSE (FAIL)
In object PHOSPHORYLATED CREB
IF (PHSPHORYLATED CREB IS BOUND TO THE TRANSCRIPTION FACTORS), THEN (INITIATE TRANSCRIPTION), ELSE (FAIL).

In the rule based modeling if the rule for a particular object is true than an action could take place. For instance in the case of G-protein, if the G-protein receptor is activated and the α-subunit of the G-protein is bound to GTP than an action. In this case the action would be dissociation of the G-protein into α-subunit and βγ-complex. In our example we include neither all the molecular and biochemical reaction, nor the precursors, enzymes, and molecules that are needed for each reaction. However in this research paper we illustrated how one could use Rule Based modeling to model a complex biological process.

CONCLUSION

The main purpose of this paper was to develop a modeling methodology for the cellular signaling using rule based modeling methodologies. Modeling methodologies help the visualization, formalization, and simulation of complex molecular and biochemical processes such as cellular communication pathway (G-Protein cascade and cAMP cascade). It allows the researchers to develop an abstract description of biological processes; 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 help to reduce costs of the experiment by using the computer model instead of wet lab. A detailed Virtual lab would create more realistic simulated experiences for users.

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 cellular signaling. Computer simulation offers tremendous potential for the enhancement of the teaching and learning science concept. It would help students to see this process visually, and understand it better. 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.

REFERENCE

1. Alberts,B., Bray,D., Lewis,J., Raff,M., Roberts,K., and Watson,J.D., (1994). Molecular Biology of the Cell, (3rd edition). New York: Garland Sciences.
2. Anand R., & Lauffenburger D. (2000). Bioengineering models of cell signaling. Annual Review of Biomedical Engineering, 2:31-53
3. Genrich, H.; Kuffner, R.; & Voss,K. (2001). Executable Petri net Models for the Analyzes of Metabolic Pathways. International Journal on Software Tools for Technology Transfer 3 (4) 394-404
4. Huing M., Bellenson J., Shankey C., &Cherkasov A., (2004). Modeling of cell signaling pathways in macrophages by semantic network. Journal of Bioinformatics, 5:156
5. Ideker T., & Lauffenburger D., (2003). Building with a scaffold: emerging strategies for high-to-low-level cellular modeling. Trends Biotechnology, 21, 255-262.
6. Konig, R.; Weismuller,M; Elis,R.: Generating Petri Nets for Metabolic Network Modelling. 10th International Conference on Inteligent System for Molecular Biology (ISMB), Edmonton, Canada, August 2002.
7. McKeithan T. W., (1995). Kenetic Proofreading Model. Nal. Acad. Sci. 92, 5042-5046
8. Stryer,L., 1995. Biochemistry, (4th edition). Freeman, USA.