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Dynamic and collective analysis of membrane protein interaction network based on gene regulatory network model

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ABSTRACT

Membrane protein interactions are vitally important for every process in a living cell. Information about these interactions can improve our understanding of diseases and provide the basis to revolutionize therapeutic treatments. However, current experimental techniques for large-scale detection of protein–protein interactions are biased against membrane proteins, it is necessary to develop novel tools to deal with this kind of bio-network. To realize this, we construct membrane protein interaction network based on gene regulatory network model. Three model forms, basic form, non-dimensionalization form, and more complex form, are proposed to understand the dynamic and collective control of developmental process and the characters of membrane protein interaction network, including small-world network, scale free distributing and robustness, and its significance for biology. Four simulation examples are presented to illustrate the usefulness and flexibility of the GRN model method for the study of membrane protein interaction network. The results show that the proposed approach holds a high potential to become a useful tool in prediction of membrane protein interactions. Moreover, it has biological significance and value for biology and pharmacology.

1. Introduction

The membrane protein, particularly the helical membrane protein interaction network, is an important part of the protein study [1]. Though there exists some experimental techniques that detect interactions between individual transmembrane (TM) [2], mapping the membrane protein is difficult. It has so far been difficult to experimentally construct a genome-wide map of membrane protein interactions and TM interactions in yeast.

Although the basic structure of biological membranes is provided by the lipid bilayer, most of the specific functions are carried out by the membrane proteins. Many fundamental cellular processes involve membrane protein interactions. The identification of the interactome, the set of all interactions among proteins encoded in a genome, is not only an important step towards systematically defining protein function, but also a first step towards understanding the mechanisms of cell behavior [3–8]. The interactions are of interest in biology because they play a significant role in a variety of cellular phenomena, including the transduction of signals across membranes, the transfer of membrane proteins between the plasma membrane and internal organelles, and the assembly of oligomeric protein structures.

It has been summarized that three general factors could lead to a substantial enhancement of the extent of protein association in a membrane relative to that in solution [9]. Firstly, experiments on protein interactions are conventionally carried out in solutions in which volume exclusion is not so obvious. Since membrane protein molecules occupy a substantial fraction of the total volume of biological membranes, as a result, they exclude a significant fraction to each other. Secondly, integral membrane proteins are very different with the proteins in solutions in their orientation. The former has a preferred orientation relative to the plane of the membrane; however proteins in solution are randomly oriented. For example, the overwhelming majority of helical membrane protein interactions are parallel and antiparallel helix-to-helix interactions as shown in Fig. 1 [5]. Lastly, though the local concentrations of these proteins, which determine their thermodynamic activities, are substantially greater, concentrations of membrane proteins are conventionally defined with respect to the entire volume of the membrane or cell suspension. In the past few years, significant progress has been made in genome-wide identification of membrane protein interactions, especially in the budding yeast Saccharomyces cerevisiae [10–12].

There is an increased interest in how lipids interact with membrane proteins and how these interactions lead to various

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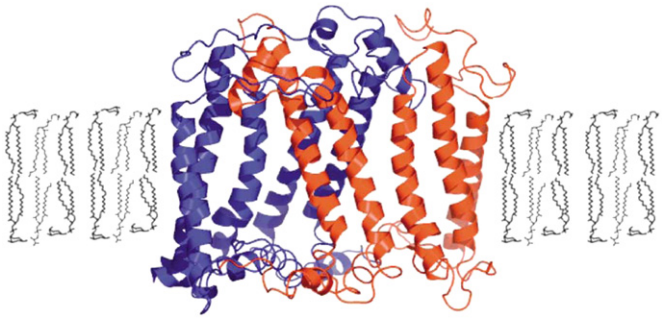

Fig. 1. 3D example of helical membrane protein–protein interaction [5].

cell membrane functions. Therefore, membrane protein interaction models have been studied more and more deeply [13–21]. ToF-SIMS is a unique technique to investigate these interactions by chemically identifying the location of each molecule [13,14]. However, it is extremely difficult to characterize the native structure of cell membranes due to their innate complexity, i.e., the eukaryotic cell membranes consist of up to 500 different lipid species. Models of membrane systems, such as supported lipid bilayers and the Langmuir–Blodgett (LB) monolayers, have been proven to be good mimics of cellular membranes [20,21]. These simplified models can be used with different combinations of lipid and protein molecules to form a membrane, which represents a bottom-up approach to study individual interactions. Nevertheless, the studies above are just restricted in the membrane protein interaction.

Here we consider the gene regulatory network (GRN) model to study membrane protein interaction network [22–27]. In the GRN model, the timing of gene activation is critical to the execution of the regulatory program [28]. The topology of developmental GRNs specifies inputs into the regulatory system of each participating gene, and where this gene encodes a transcription factor, its outputs to target genes in the next tier of the hierarchical network. Thus any given domain of a GRN consists of prior or upstream, responding or downstream, and regulatory gene circuitry. In the operation of the GRN, time flows in the same direction as the causality determined in the GRN topology (except for feedback) [28]. Thus in terms of transcription dynamics, the measurable output of the GRN is a temporal sequence of cohorts of regulatory gene expressions. There is a one way logic relationship between overall GRN architecture and the temporal progression of transcription patterns: GRN topology predicts the kinetics of this progression, barring post-transcriptional modulations; however, it is almost impossible to infer network topology exclusively from dynamic expression data, except for linear cascades of such simplicity as are rarely seen in embryonic development [29].

The main contributions in this paper are as follows. First, we apply three model forms, basic form, non-dimensionalization form, and more complex form, of the GRN model [22,23] into constructing the membrane protein interaction network. According to the membrane protein interaction network constructed, we could study the dynamic and collective control of developmental process and the characters of membrane protein interaction network, including small-world network, scale free distributing and robustness, and its significance for biology. The proposed method is proved to be effective for the study of membrane protein interaction network and holds a high potential to become a useful tool in prediction of membrane protein interactions.

In the following parts, the GRN model for membrane protein interaction network is proposed in Section 2. Next, results and discussion are presented in Section 3. Finally, the concluding remark is given in the last section.

2. Gene regulatory network model for constructing membrane protein interaction network

In the following, we construct membrane protein interaction networks based on the GRN model and study on its dynamic and collective characters. Our more complex form GRN model can well and entirely represent the dynamic and collective mechanism of membrane protein interaction network.

2.1. Basic form

The basic form of the GRN model formulation for membrane protein interaction network is as follows [22,23]:

$$\frac{d[x]_{i,j}}{dt} = A - B \pm C \pm D \tag{1}$$

where A is composing, B is decay, C is transform, D is transfers, i is a membrane protein, and j is membrane protein surface (the interaction of membrane protein). Composing period represents the transfers of membrane proteins. For membrane proteins, there is only one composing period except multi-gene provides quite a few transcriptions. "Disintegration" class represents first order decay process certainly whether the given species disappears, even though it is very slow.

Using the model of differential equation, dynamics interaction is transferred to mathematics formula. These space state equations dominate the dynamics of membrane protein. Some periods like transfers flux are omitted for predigestion [22,23].

The membrane protein dynamics formulation using hedgehog coding masterdom is as follows:

$$\frac{d[hh]_i}{dt} = T_{max}\rho_{hh}\left(\frac{[EN]_i^{v_{ENhh}}}{K_{ENhh}^{v_{ENhh}} + [EN]_i^{v_{ENhh}}}\right) - \frac{[hh]_i}{H_{hh}} \tag{2}$$

$$\frac{d[HH]_{i,j}}{dt} = \frac{P_{max}\sigma_{HH}[hh]_i}{6} - \frac{[HH]_{i,j}}{H_{HH}} - k_{PTCHH}[HH]_{i,j}[PTC]_{n,j+3} \tag{3}$$

$$\frac{d[PH]_{i,j}}{dt} = k_{PTCHH}[HH]_{n,j+3}[PTC]_{i,j} - \frac{[PH]_{i,j}}{H_{PH}} \tag{4}$$

Eq. (2) dominates that hedgehog mRNA focuses on the membrane protein i. Eq. (3) dominates that the hedgehog protein focuses on the surface j of the membrane protein i. Eq. (4) dominates a composition between HH and its receiver for the membrane protein i on the surface j, which is demonstrated by $PH_{i,j}$. In Eq. (2), the whole parameter $T_{\max}$ is most transcription speed decided by RNA polymerases, which can be transferred quickly in DNA and packed in a mRNA unit closely. $P_{\max}$ is the highest translation speed. The non-dimensionalization parameter ρ_{hh} can decide special proteins copied efficiently. The non-dimensionalization equation multiplied by the two parameters represents the hh activation transcribed by EN. K_{ENhh} is the most hh activated place i focused by EN, and v_{ENhh} is a coefficient. For predigestion, the hh regulation is suspended by C_i transcription, which is a character of an integrity model [30].

This conversed stabilization state closed method is the basic in model. No matter how to describe the promoter and enhancer of hedgehog, there is the most speed that can be activated by special conditioner in the *hh* transcription. It obeys the half most speed place, where exits some muster degree (here means membrane proteins). An important parameter is the coefficient v. Much regulation refers to the binding action of ligand dynamics, which seems the cooperation on surface. In this case, v is a hill coefficient.

In Eq. (2), the second period represents the first order decay. Only freedom parameters belong to semi-decay (the inverse decay speed) x. In Eq. (3), the first period is translated to represent