Dynamic simulation of protein interaction networks

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Motivation

Protein interactions support cell organization and mediate its response to any specific stimulus. A realistic simulation of cell physiology would require (at least) genome wide information about protein concentration combined with integration of a quantitative protein interaction network with the metabolic and gene regulatory networks. These data are currently not available. Nevertheless, simple computational models may help to extract general principles from the available noisy and qualitative information. Protein-protein interaction (PPI) networks, like other kinds of complex networks, are not randomly organized. They display properties that are typical of "hierarchical" networks combining modularity and local clustering to scale free topology. From the analysis of the "static" representation of the corresponding graph, it is not clear why biological networks evolve the observed characteristics. In our project we aim at investigating whether the "static" connectivity properties of a PPI network (scale free, modularity and high local clustering), analyzed in a dynamic model, favor the formation of higher order structures and eventually cell organization. To this end, we designed and implemented a computer model to simulate the interaction of a large number of proteins within a naive unstructured cell (devoid of compartments).

Methods

In order to simplify our cell model and render it computationally tractable we made a number of assumptions. The intracellular space is mapped onto either a two-dimensional or a three dimensional lattice. In the lattice, each site represents an average space of 5 nm, which is comparable with the diameter of an average globular protein. The lattice is filled with proteins with a 20% average occupancy that is compatible with the estimated crowding of proteins in the cell cytoplasm. The simulation is carried out in the following steps: diffusion, rotation, association and dissociation. At each time step proteins in neighboring cells may interact and form a complex depending on the interaction rules (i.e., if there is an edge linking the two proteins in the input PPI network) and on the association constants that define the probability for the proteins to bind and to form a complex. Furthermore, any existing complex can break depending on the dissociation constant. This whole procedure can be seen as a sort of "discrete molecular dynamics" applied to protein interactions in the cell.

Results

We performed different simulations using as interaction rules those derived from the experimental interactomes of E. pilori (724 nodes, 1403 edges), E. coli (1289 nodes, 5420 edges) and S. cerevisiae (1378 nodes, 2451 edges) and we compared their dynamic behaviors with that of random networks having an equivalent number of nodes and edges. The simulations have been done both in the three and two dimensional lattice models. We are currently analyzing the dynamic structures that are formed in natural and random networks to identify the characteristics of the natural networks that favor the formation of an organized virtual cell.

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