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Protein-Protein Interactions: From Mechanism to Protein Design

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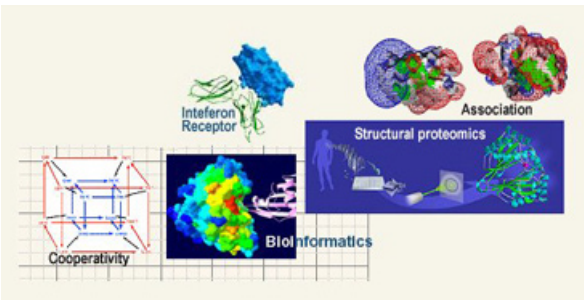
Proteins are amazing macromolecules with many faces. One of their most intriguing functions relate to their ability to communicate fast and specific with other macromolecules, including other proteins. The degree of complexity of inter-protein communication is related to the complexity of the organism in study. The information flow of the protein network is dictated by biophysical parameters, which include local concentrations, specificity of binding, and the kinetics and affinities of binding. These can be approximated experimentally for each case individually, or calculated using physico-chemical principles. The experimental approach is very time consuming and not feasible for a complex organism. Therefore, the prediction of protein-protein interactions and protein interaction networks by bioinformatic means is a desirable goal. However, these calculations are not yet mature, and therefore have to be combined with the experimental study of well-defined systems to improve the basic understanding of protein-protein interactions.

We study the basic physico-chemical principles governing protein-protein interactions, how these relate to complex biological processes and how they can be generalized using computational tools.

In particular, our research focuses on the following:

- Investigating the biophysical nature of protein-protein interactions
- Design of proteins with altered activities
- Bioinformatics of protein-interactions:
- Studying the differential response to Type I interferons using biophysical tool, as an exemple of a defined signal trunduction network.
- Structural proteomics

Detailed description of the work:
Investigating the biophysical nature of protein-protein binding sites:



Protein complexes are stabilized by non-covalent interactions similar to those, which stabilize the folded conformation of a protein. Simple mutagenesis studies have failed to reveal the nature of the complex interactions in the interface. Our current view, steaming from experimental evidence, and bioinformatics work has led us to the hypothesis that a binding site is composed of a number of patches composed of residues bonded by a continues inter-protein interaction network. Preliminary data have shown a strong cooperativity between residues located in the same patch, and additivity between residues located on different patches. The result seems to hold both energetically and structurally. This research direction is currently extended.

Design of proteins with altered activities:

The process of protein-protein interactions can be divided into two kinetic, physically different processes. The first is the association process, where two proteins located far away have to find each other in a short time and form a complex. The second process is of the dissociation of the two proteins, to form monomers. For the association process we introduced a thermodynamic framework for the association reaction, which enabled us to present a general formulation for the calculation of rates of association for mutant protein

complexes using the computer program PARE **(www.weizmann.ac.il/home/bcges/PARE.html).** Moreover, we established a design protocol, which enables us to specifically alter rates of association, without affecting the rates of dissociation of a protein complex. This formulation was used for the successful design of a number of protein complex including TEM-BLIP and Ras-effector. Currently, we are investigating the relevance of faster association in the biological environment both by mimicking the crowded environment and by relating faster binding with enhanced biological activity.

Bioinformatics of protein-interactions:

In the last couple of years we have started to explore the huge wells of structure and sequence information available in the database to obtain a better understanding of protein-protein interactions in general. Our main goals include: the development of an algorithm which will be able to identify protein binding sites on the surface of unbound proteins (see http://bioportal.weizmann.ac.il/promate/); improving on existing docking algorithms and using bioinformatics to analyze the structure of protein binding sites. In addition we perform Molecular Dynamic simulations on a number of systems to complement experimental results.

Studying the differential response to Type I interferons using biophysical tools:

Here, we aim to decipher the relation between biophysical parameters of protein-protein interactions and biological activity. We were intrigued by the complex network of a large number of interferon subtypes binding the same two cell surface receptors, but seemingly causing differential activation. We assume that this differential activation is related to distinct modes of receptor binding, which can be investigated using purified proteins in vitro. Therefore, we developed methods to express, purify, mutate and measure the interaction between the different pieces of the puzzle in vitro. This work resulted both in a structural and functional model of the system. Yet, the interferon system is complex and still far from being understood, which is part of our plan for the future.

Structural proteomics:

Structure does not replace biochemical and biophysical work, but it can guide it. Therefore, the PI, together with Joel Sussman and Yigal Burstein have established the Israel Structural Proteomics Center (ISPC - **www.weizmann.ac.il/ISPC),** which goal it is to support Israeli academia and industry in all stages of protein structure determination. The structural work done in our lab is done in collaboration with the ISPC.

Selected Publications

Selzer, T., Albeck, S. and Schreiber, G. (2000) Rational design of faster associating and tighter binding protein complexes. Nature Struct. Biol., 7, 537-541.

Roisman, L.C., Piehler, J., Trosset, J.Y., Scheraga, H.A. and Schreiber, G. (2001) Structure of the interferon-receptor complex determined by distance constraints from double-mutant cycles and flexible docking. Proc. Natl. Acad. Sci. U S A, 98, 13231-13236.

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Neuvirth, H., Raz, R. and Schreiber, G. (2004) ProMate: A Structure Based Prediction Program to identify the location of Protein-Protein Binding Sites. J. Mol. Biol, 338, 181-99.

Peleg-Shulman, T., Roisman, L.C., Zupkovitz, G. and Schreiber, G. (2004) Optimizing the binding affinity of a carrier protein: a case study on the interaction between soluble ifnar2 and IFN beta. J Biol Chem, 279, 18046-53.

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