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 experimental studies 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 thermodynamics and kinetics of protein-protein interactions
- Design of proteins with new or altered binding characteristics
- Bioinformatics of protein-interactions
- Studying the differential response to Type I interferons using biophysical tools.
- Structural proteomics

Our research is conducted on a number of systems, depending on the question we want to address. Basic research into the mechanism of complex formation and stability is mostly carried out on the interaction between TEM1-β-lactamase with its protein inhibitor BLIP. Structure-function studies are conducted on the interaction between type I interferons and their receptors, using either the soluble extracellular domains of the receptors (for in vitro studies) or cell cultures for functional studies. Protein-design is carried out on the interactions between TEM1-BLIP (basic principles) and interferon-receptors to engineer improved interferons with medical potential. In addition we carry out bioinformatic work, which currently is focused on developing new methods and
force-fields for protein-design. Structural work is carried out at the Israel Structural Proteomics Center (http://www.weizmann.ac.il/ISPC), which is located at the department of structural biology, and of which the PI is co-director.

**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 the interface between proteins is built in a modular fashion; each module is comprised of a number of closely interacting residues, with few interactions between the modules. The boundaries between modules are defined by clustering contact maps of the interface. We show that mutations in one module do not affect residues located in a neighboring module. As a result, the structural and energetic consequences of the deletion of entire modules are surprisingly small. Contrary, mutations cause complex energetic and structural consequences within their module. The modular architecture of binding-sites, which resembles human engineering design, greatly simplifies the design of new protein interactions, and provides a feasible view of how these interactions evolved.

**Design of proteins with new or altered binding 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. 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 the association reaction, which enabled us to present a feasible view of how these interactions evolved.

**Bioinformatics of protein-interactions**

In recent 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. Particularly we are interested in the structure of water at the vicinity of protein binding sites.

**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 found that the differential activation can be related to binding affinity of interferon to the IFNAR1, but not the IFNAR2 receptor. Engineering new interferons with enhanced binding activities towards IFNAR1 resulted in significantly more potent proteins, with up to 100-fold higher antiproliferative activity relative to wt. In parallel we work on establishing a structural and functional model of the interferon-receptor interaction, and how this relates to activity.

**Structural proteomics**

Structure does not replace biochemical and biophysical work, but it can guide it. Therefore, the PI, together with Joel Sussman, Israel Silman and Yigal Burstein have established the Israel Structural Proteomics Center (ISPC - http://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 in my group is done in collaboration with the ISPC.

**Selected publications**


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