iNEXT workshop on Integrated methodologies and approaches for structural biology

Name of Speaker: **Gideon Schreiber**
University / Research Institute / Department: **Weizmann Institute of Science Department of biomolecular sciences**

Title of Lecture: **How to proteins function within the crowded cellular milieu**

Abstract:

Most proteins do their work within the living cell. The environment within the cell is very different from the test tube in its composition and crowding. This results in potential hard and soft interactions, which may affect diffusion and binding. In my talk I will go over methods to measure and analyze diffusion and binding in complex environments and provide experimental evidence on how these interactions affect enzyme catalysis and biophysical parameters of protein-protein interactions. For catalytic activity we developed a method to determine enzyme constants using single cell progression curve fitting. Using this method we found that *in vivo* catalytic efficiency, *k*cat/*Km*, is lower than *in vitro*, with significant cell-to- cell variability. To rationalize these findings, we measured enzyme and substrate diffusion rates in the cell and found the latter to be slower than expected. Simulations showed that for attenuated diffusion the substrate flux becomes rate-limiting, explaining why reaction rates *in vivo* can be independent on enzyme concentrations. For protein-protein interactions we followed both structured and natively unfolded proteins in the cell. In addition, we investigated how library methods can be used to evolve promiscuous binding, and suggest that avoiding these is an evolutionary trade.

Research Profile:

For many years, I have been interested in understanding the relationships between the structures of transient protein-protein interactions and their functions. To address this, I adopted a multidisciplinary approach including: wet biophysical bench work, protein-design and engineering, bioinformatics, and algorithm development and applied the gained knowledge and techniques to address biological questions. A system we investigate thoroughly is differential activation of type I interferon signaling where we aim to understand biological function from biophysical and structural characterization of the system. In addition to leading my research group at the Weizmann Institute of Science I am the director of the Israeli Center for Excellence on integrated Structural Cellular Biology and president of the Israel Society for Biochemistry and Molecular Biology.

Selected publications:

1. Schreiber, G. (2017) The molecular basis for differential type I interferon signaling. *J. Biol. Chem.* **292**, 7285-7294
2. Cohen-Khait, R., Dym, O., Hamer-Rogotner, S. and Schreiber, G. (2017) Promiscuous Protein Binding as a Function of Protein Stability. *Structure* **25**, 1867-1874.e3
3. Baeuerle, F., Zotter, A. and Schreiber, G. (2017) Direct determination of enzyme kinetic parameters from single reactions using a new progress curve analysis tool. *Protein Eng. Des. Sel.* **30**, 151-158
4. Cohen-Khait, R. and Schreiber, G. (2016) Low-stringency selection of TEM1 for BLIP shows interface plasticity and selection for faster binders. *Proc. Natl. Acad. Sci. U. S. A.* **113**, 14982-14987

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