Symposium 4: Systems Biology

72-Symp
Designing Biological Systems
Pamela Silver.
Harvard Medical School, Boston, MA, USA.
Biology presents us with an array of design principles. From studies of both simple and more complex systems, we understand at least some of the fundamentals of how Nature works. We are interested in using the foundations of biology gleaned from Systems Biology to engineer cells in a logical way to perform certain functions. In doing so, we learn more about the fundamentals of biological design as well as engineer useful devices with a myriad of applications. For example, we are interested in building cells that can perform specific tasks, such as counting mitotic divisions, measuring life span and remembering past events. Moreover, we design and construct proteins and cells with predictable biological properties that not only teach us about biology but also serve as potential therapeutics, cell-based sensors and factories for generating bioenergy.

73-Symp
Design principles of biological circuits
Uri Alon.
Weizmann Institute of Science, Rehovot, Israel.

74-Symp
Nature, nurture, or just blind chance: Stochastic gene expression and its consequences
Alexander van Oudenaarden.
Massachusetts Institute of Technology, Cambridge, MA, USA.

75-Symp
Information is critical for cellular life
Ravi Iyengar.
Mount Sinai School of Medicine, New York, NY, USA.
Functional Organization of Cells
The ability to receive, process and respond to information is critical for cellular life. This ability arises from the cell signaling network that processes information from external and internal sources. There are at least three sources of information: chemical signals, cell shape and mechanical forces. Integrating and processing information from all of these sources to coordinately control multiple cellular machines is essential for both homeostasis and regulated change in cell state. A key feature of signaling networks is the topology of regulatory motifs. Determining regulatory motif topology and the resultant information processing capability requires an integrated computational approach that blends graph theory-based analyses to identify and characterize regulatory motifs with differential equation-based models to determine functional capabilities of these motifs and how information processing changes with time and specific locations within the cell. Graph theory analyses indicate that large networks have a head-to-head topology that results in a depletion of long loops and such systems appear to be more dynamically stable. Interactions between motifs such as feedfoward loops and bifans indicate that multi-motif organization may be critical for biological processes. Differential equation models show that a set of three stacked and nested feedforward loops that is spatially specified is required for the β-adrenergic receptor triggering of the differentiated state in podocytes. These predictions have been experimentally verified. Thus the size of regulatory motifs and how the motifs are juxtaposed with respect to each other give rise to functional organization. There is partial overlap between the structural organization that arises from the presence and location of intracellular organelles and functional organization. Together the functional and structural organization of the cell determines how information is integrated, and how this integrated information is used to co-ordinate and regulate biological processes.

Minisymposium 1: Virus Mechanics: Material Properties and Assembly

76-MiniSymp
Biophysical Studies of Virus Particles and their Maturation: Insights into Elegantly Programmed Nano-machines
Jack Johnson.
Scripps Research Inst, La Jolla, CA, USA.
Complex virus particles such as HIV, Herpes Viruses and dsDNA bacteriophages are programmed nano machines that assemble in a fragile shell that matures through a series of intermediates to form an infectious, robust particle. We have analyzed mature bacteriophage and intermediates in maturation with X-ray crystallography and a variety of biophysical methods, defining the biochemical nature of the transitions and their driving forces. Through experimentally defined chemistry and physics, these particles shape an energy landscape resulting in an exothermic transition and continued maturation that relies on a Brownian ratchet. The presentation will describe the synthesis of structural and biophysical data that lead to an understanding of emergent biological behavior.

77-MiniSymp
Modeling the Size and Structure of RNA: Viral vs. Non-viral Sequences
Avinoam Ben-Shaul[1], Aron M. Yoffe[2], Peter Prinsen[2], William M. Gelbart[2].
[1]Hebrew University Jerusalem, Jerusalem, Israel, [2]Department of Chemistry and Biochemistry, University of California, Los Angeles, CA, USA.
Based on a simple linear polymer model we derive a scaling relationship between the ''maximum-ladder-distance'' characterizing the secondary structure of folded, single stranded, RNA and the radius of gyration characterizing its spatial dimensions. Secondary structures are calculated for a large number of viral RNA sequences as well as non-viral sequences of comparable length and nucleotide composition. The results show that viral RNAs fold into significantly smaller 3D structures than non-viral sequences, consistent with an evolutionary pressure to package the viral sequences inside small rigid protein capsids. We also present a theory explaining why the two ends of a folded RNA are generally found close to each other, independent of nucleotide sequence and length.

78-MiniSymp
Structural Mechanics of Viral Shells: Stretching the Limits of Continuum Models
William S. Klug.
UCLA, Los Angeles, CA, USA.
The last several years have seen a number of successful applications of continuum elasticity theory to the study of virus mechanics. Continuum modeling has been particularly effective in connection with atomic force microscopy nanoindentation experiment for understanding and predicting capsid material properties, and may hold promise for illuminating the physics of capsid assembly as well. I will consider the question of the limitations of continuum modeling of capsids, and discuss some examples of how conventional continuum theory is being extended or "stretched" to study features linked to the inherently discrete character of these molecular assemblies.

79-MiniSymp
The Influenza Virus Mechanical Properties Are Dominated By Its Lipid Envelope
Frederic Eghiaian[1], Iwan Alexander Schaap[2], Amédéé Des Georges[3], John James Skehel[1], Claudia Veigel[1].
[1]Medical Research Council, Mill Hill, United Kingdom, [2]University of Gottingen, Gottingen, Germany, [3]Medical Research Council, Cambridge, United Kingdom.
The influenza (flu) virus causes yearly epidemics, and has claimed the life of tens of millions of people in the last century. Flu viruses need to travel from one host to a new one, where they inject their RNA genome by a membrane fusion mechanism. Before fusion the flu virus RNA genome protected by an envelope made of a matrix protein (M1) layer surrounded by a lipid membrane. The exact role of M1 protein and its mode of interaction with the viral membrane are unknown.
We have set out to investigate the mechanical design of influenza virus: we imaged and characterized mechanical properties of influenza virions by atomic force microscopy (AFM). We compared the response of the viral particle with the behavior of simplified model systems to understand the role of the various parts of the viral structure in its mechanical properties.
Influenza virions proved to be very soft compared to the other ''protein-enveloped'' viruses that have been characterized by AFM so far. The stiffness of viral particles was comparable to that of similar-sized small unilamellar lipid vesicles and virosomes. Our results suggest that the M1 protein does not mechanically reinforce the flu virus envelope and that M1 may not directly interact with the inner side of the viral membrane. Hypothesis on the conditions under which influenza virus will persist during transmission will be discussed.

80-MiniSymp
Single-Molecule Studies of Viral DNA Packaging with Optical Tweezers: Molecular Motor Function and DNA Confinement
Douglas E. Smith, James M. Tsay.
University of California, San Diego, La Jolla, CA, USA.
A key step in the assembly of many viruses is the packaging of double-stranded DNA into a procapsid shell by the action of an ATP-powered molecular motor. We use optical tweezers to measure the packaging of single DNA