Toward an in silico Cell

Organizers: Tom S. Leyh (Albert Einstein College of Medicine) and Jennifer Henry (The New York Academy of Sciences)
Speakers: Adrian H. Elcock (University of Iowa), Ruben L. Gonzalez, Jr. (Columbia University), Zaida Luthey-Schulten (University of Illinois at Urbana–Champaign), Julio Ortiz (Max Planck Institute of Biochemistry, Germany), and Klaus Schulten (University of Illinois at Urbana–Champaign)Presented by the Chemical Biology Discussion Group and the New York Chapter of the American Chemical Society

Reported by Stephanie B. H. Kelly | Posted May 31, 2011

Overview

Accurately modeling the spatial arrangement and activity of all the components within a cell over the time frame of a cell cycle (or longer) requires the integration of vast amounts of data from many different types of investigations. A successful model, however, promises to provide unprecedented insight into the interaction between the thousands of processes ongoing in each cell. Molecular simulations allow for direct "observation" of such processes, without the need for fluorescent tagging and other complicated visualization tools. But such models also tend toward oversimplification, in part because researchers need to select simulation projects that will be possible within current computational limits. With these limits and assets of simulations in mind, researchers convened at the New York Academy of Sciences' Toward an *in silico* Cell on March 18, 2011, to discuss recent advances on the path to computational modeling of an entire cell, its components, and its biochemistry.

Ultimately, **Adrian Elcock** from the University of Iowa wants to "move beyond static images of cellular components" to see proteins and RNA molecules being synthesized, folded, degraded, and so forth. To get there, Elcock and his group began by using 3D reconstruction of a polyribosome as a starting point for thinking about how amino acid chains are synthesized. To investigate the crowding pressures on protein synthesis, his group modeled the cytoplasm of *E. coli* bacteria. By detailing all the necessary components of a successful model of the cytoplasm—knowledge of protein abundances and structures, an understanding of the intermolecular forces at play, a simulation algorithm, and the computer code to implement it all—Elcock explained the assets of his model as well as the directions for its improvement. The group has already been able to use their understanding of cytoplasm crowding, electrostatic and hydrophobic interactions, and non-specific interactions to investigate the thermodynamics of protein folding *in vivo*. Such an understanding will undoubtedly shape future studies of protein synthesis, especially as the group begins to project these data over longer time scales.

As some of the largest molecules (occupying 6%–15% of cellular volume) in bacterial cells, ribosomes are an important piece of the cellular modeling puzzle. As such, they have been the focus of a good deal of research, some of which was featured at the symposium. **Julio Ortiz** from the Max Planck Institute of Biochemistry showed how experiments in the lab can be combined with computational analysis to get a better understanding ribosomes and their functioning. In particular he used cryoelectron microscopy to assess the structure of ribosomes *in vitro* and *in situ*. After imaging and mapping the ribosomes using a process called "template matching," Ortiz and colleagues were able to employ multivariate statistical analysis to identify and classify subpopulations of ribosomes with different conformational states, for example. They could then relate these subpopulations to cellular microenvironments such as the proximity to the cell membrane or to other ribosomes. This combination of experimental work in imaging the ribosomes and computational work to parse the images and relate the structures to other features of the *E. coli* cells grounded Ortiz's further investigation of the detailed structure and orientation of polyribosomes.

Zaida Luthey-Schulten, a professor at the University of Illinois, uses similar information about the location of

ribosomes in a cell, but she is interested in the areas devoid of ribosomes. In her group's attempts to simulate transcription for the duration of an entire cell cycle, they were able to assume that the DNA could be packed anywhere ribosomes were absent. The group used this assumption to investigate how the rebinding kinetics of the *lacY* gene's repressor were affected by crowding in the DNA environment. They concluded that changing the cellular packing had a noticeable effect on repressor rebinding kinetics, and that, in fact, the repressor would diffuse away from the DNA 60%–70% of the time. These results can help Luthey-Schulten and others see the implications of fundamental questions such as whether an mRNA that encodes a membrane protein diffuses to the membrane before translation or whether the ribosome carrying the nascent protein must diffuse to the membrane after translation.

Delving into the mechanics of translation from a physical chemistry perspective, **Ruben L. Gonzalez**, a professor at Columbia University, presented his group's work on single molecule studies of ribosomes. His group focuses on the conformation changes underpinning the elongation cycle in translation and specifically on the formation of the "hybrid conformation" in which the tRNA acts as a supplemental intersubunit bridge connecting the small and large ribosome subunits and stabilizing a rotation of the subunits with respect to one another. The scheme involved fluorescence resonance energy transfer between donor and acceptor fluorophore pairs strategically located on the ribosome. These single molecule studies gave the group access to conformational states, the thermodynamics of these states, and ultimately the diverse mechanisms of control exerted on polypeptide elongation. These features are unavailable to whole-cell studies because individual ribosomes' features are averaged out in those studies. One of the important results of their studies was their evaluation of how the translocation factor deals with the energetic barrier to translocation in order to control the directionality of the tRNA's movement through the ribosomes.

Building on the benefits of computational methods demonstrated by his colleagues, **Klaus Schulten** from the University of Illinois closed the symposium with an optimistic view of the power of modern computing. Considering the modern computer by analogy to a microscope, Schulten reviewed the components of the physics, chemistry, mathematics, and computer science tools that helped him uncover the H1N1 virus's mechanism for developing resistance to the Tamiflu anti-viral. As Schulten explained it, when H1N1 was spreading rapidly, researchers needed answers more quickly than biochemical experiments would have produced them, but GPUs (graphics processing units) allowed fast processing of molecular simulation algorithms to visualize the protein changes accompanying resistance. GPUs, by contrast to CPUs (central processing units), run many processes in parallel and have important functions hardwired into the chips, which speeds up processing time considerably. Schulten reviewed some experiments his group has performed to combine results from cryo-electron microscopy and crytallography in detailed, accurate simulations, and he concluded his talk by urging his colleagues to take advantage of the computing power that is available for single-molecule or whole-cell studies.
