Combining diverse information and techniques to understand biological function

Mara Prentiss*†[1], Chantal Prevost[2], Claudia Danilowicz[1], and Veronica Godoy[3]

[1]Harvard University – United States
[2]Laboratoire de biochimie théorique [Paris] – Université Paris Diderot - Paris 7, Centre National de la Recherche Scientifique : UPR9080, Centre National de la Recherche Scientifique – France
[3]Northeastern University – United States

Abstract

Biological systems pose many challenges for researchers. The relevant timescales span more than 9 orders of magnitude, and even for bacteria the relevant length scales span 6 orders of magnitude. Many tools offer excellent information within a limited range of time and length. For example, molecular dynamics simulations have provided enormous insight into protein function; however, the time and length scales of the results is limited. Crystallography offers a power tool, but many important functions of proteins are governed by regions that are usually unstructured. Such regions are not readily probed using crystallographic methods. Single molecule measurements have provided many unexpected new results, but great care must be taken in relating those results to in vivo systems.

For more than half a century, physicists have studied general features of biological systems to try to find governing principles that apply to a range of situations. For example, many theorists considered how the search for a particular position in a long linear target. Sequence dependent proteins seeking particular sequences along a bacterial chromosome provide an example of such a search. The physicists showed that optimal searches combine the following: 1. One dimensional "diffusion" long the target 2. Short hops between sites that separated by slightly longer than the typical diffusion length 3. Large jumps between sites that have large separations along the linear target, though they may be physically close if the target is looped. Knowing this general strategy helps people consider how particular proteins behave, but it does not explain how the "diffusion occurs", or when and how the searcher makes the transition between searching modes. Similarly, John Hopfield suggested that biological systems can provide arbitrarily good discrimination between binding sites whose energies are very similar, if the biological system uses kinetic proofreading; however, the time required to establish the correct binding increases as the requirement for discrimination increases. This is a special case of the more general speed/stability paradox, which our group has extended to the speed/stability/stringency paradox.

Our group has combined single molecule experiments, general physics modeling of systems, statistical studies of the sequences of bacterial genomes, and molecular dynamics simulations done in collaboration with the Prévost group to elucidate how double strand break repair in bacteria progresses if it follows the RecBCD pathway. The details of that process will be presented, along with information on general strategies that we learned from studying this system. Interestingly, the overall strategy is similar to that pursued by humans seeking the

*Speaker
†Corresponding author: prentiss@g.harvard.edu

perfect mate. Insights from this system may also help cast light on protein folding and other self-assembly processes in which the correct structure represents a very small minority of all possible structures.