Molecular simulation

Using 400,000 personal computers donated from around the world

PROTEIN FOLDING & MISFOLDING

Proteins serve a seemingly infinite number of physiological functions, and they do so by taking on specific three dimensional shapes, or “folds.”

- How is this folding achieved?
- What are the rules that govern these events?
- Is there a general mechanism for folding that can be applied universally?

These are the primary questions that the folding community is addressing by experimental, theoretical, and computational means. However, many related questions remain unanswered, and our research group probes these questions using massive computer simulations and a variety of sampling algorithms.

The misfolding of proteins has been linked to neurological diseases involving plaque formation on the brain due to protein aggregation. What are the mechanisms and causes of protein misfolding?

RNA FOLDING & CONFORMATIONAL DYNAMICS

Like proteins, some ribonucleic acids (RNAs) also fold into specific 3D shapes in order to function. Unlike proteins, RNA molecules are highly charged and have a chemistry that is dramatically different from that of proteins. RNA folding thus provides a vastly different set of challenges and concerns to address in computational studies.

Our research has pioneered modern computational studies of nucleic acids, beginning with the most fundamental units of RNA structure, the GMP tetraloop hairpin motif, which was the target of our 2010 cover article in Nucleic Acids Research. We also are interested in the folding and function of larger RNA systems, including

- Riboswitches: RNAs that moderate gene activity
- Transfer RNA: delivers amino acids for protein synthesis
- Ribozymes: biocatalysts (enzymes) composed of RNA

MOLECULAR MODELS OF BIOMOLECULES

Creating and maintaining the fAMBER molecular potential port for the GROMACS simulation suite, our research group actively contributes to and participates in the bio-simulation community. Our previous work includes assessing the accuracy and physical relevance of molecular dynamics and developing the state-of-the-art all-atom models to describe the helix-coil transition in proteins.

Current and future efforts in this area will focus on further analyzing and improving upon molecular models of proteins, lipids, nucleic acids, and ions.

Biomembranes: Although biological membranes play fundamental roles in a vast array of physiological processes, we know very little about the molecular basis of the physical behavior of biological membranes. The accurate modeling of membranes is vital to future computational studies in many biological areas, such as drug delivery, transport channel structure and function, and molecular virology.

SOLVATION & CONFINEMENT EFFECTS

- The role of water: Water not only serves as an ideal buffering solvent for biochemical processes, but also participates in many molecular events. Our lab studies the interactions of water with biomolecules during events of interest, such as protein/RNA folding and molecular docking.

- Confinement: The behavior of biomolecules in confined spaces is important in several contexts including protein folding in chaperones and pores, and both vehicle- and nanotube-based drug delivery. We seek to better understand the role of confinement on biopolymer structure & dynamics.

- Conflined water: Our previous work has demonstrated that the confinement of water changes the properties of the solvent, and that the molecular nature of water is an important factor in molecular biology. We are currently seeking to gain insight into the role of water in molecular recognition and drug binding.

MOLECULAR SIMULATION

Computational Chemistry, Biochemistry, & Biophysics

Real world applications in biochemical & biomedical science

Drug Design & Molecular Recognition

- Non-covalent interactions between biomolecules, such as proteins or RNAs, and other chemical systems form the basis by which a myriad of biochemical phenomena are achieved. There is an endless number of examples such as protein-receptor-ligand interactions, including
- protein-peptide and protein-protein interactions
- antigen-antibody and enzyme-substrate docking

How do these molecules recognize each other?

While the general physics behind these interactions is well understood, there are a number of models that seek to describe the basic mechanism of such interactions:

- Lock & Key: a rigid geometric fit between receptor and ligand
- Induced Fit: one body causes a change in shape of the other
- Conformational Selection: the ligand selects the best-fitting "shape" of the other, even if that structure occurs rarely

Collagen Mutations & Disease

Making up ~25% of the protein content in the human body, collagen is the most abundant type of protein in all mammals and a main component of flesh, bones, cartilage, and the reticular fiber of which most soft tissue and organs are composed. Stiff, collagen often overlooked in modern computational science, which is stricking given their redundant sequence patterns, unique triple-helical structural motif, and obvious physiological importance. Collagen related diseases include, among others:

- Rheumatoid arthritis: inflamed collagen causes erosion of the bones and cartilage
- Osteogenesis imperfecta: "brittle bone disease" (right) results from deficiencies in collagen quantity or quality

Using massively parallel simulations of model [PPO1]3_ and [PPO2]3_ collagen systems, as well as both human wild type and mutated sequences, our collagen modeling project seeks to elucidate relationships between disease-causing single point mutations and deviations in the structure and energetics of collagen. Our ultimate goal is to observe the structural biology of these and other collagen-related diseases using solid-state molecular simulations.

CHEMICAL BIOLOGY

Real world applications in biochemical & biomedical science

WANTED: Motivated research students from all scientific disciplines!

About Prof. Eric J. Sorin

Before entering college, Dr. Sorin worked as an ornamental glass blower for several years, married, and had three beautiful children. He earned an A.A. in Liberal Arts and an A.S. in Mathematics & Science at Victor Valley College before earning a B.S. in Chemistry/Chemical Physics at U.C. Riverside, where he pursued research in FTIR and Raman spectroscopy and microscopy. He completed his Ph.D. in Chemistry/Chemical Physics at Stanford University, where he was first introduced to computational chemistry and biophysics, and became one of the founding members of the Folding@Home Distributed Computing Project, authoring and co-authoring 12 research articles and 2 review articles in the areas of protein folding and RNA folding. After completing his graduate work, Dr. Sorin accepted a faculty position at CSULB, where he enjoys teaching physical chemistry for the biosciences and engaging students in a broad array of research activities including project design, data analysis, and scientific writing.

Biomolecular Physics

Studying questions in molecular biology using modeling & simulation

Chemical Biology

Real world applications in biochemical & biomedical science

Drug Design & Molecular Recognition

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