



Michael Levitt

Robert W. and Vivian K. Cahill Professor in Cancer Research in the School of Medicine and Professor, by courtesy, of Computer Science

Structural Biology

 NIH Biosketch available Online

 Curriculum Vitae available Online

Bio

BIO

Is it possible to understand the molecular structure and function of proteins and nucleic acids in enough detail to make accurate predictions about structure and function? We are mounting a two-pronged attack on this problem using both molecular dynamics simulation and molecular modeling. (i) Simulation attempts to reproduce the structural, thermodynamic and dynamic properties of a macromolecule in as accurate a way as possible. Starting with simple but realistic expressions for the interactions between atoms and classical laws of motion, we calculate a trajectory that specifies the position and velocity of every atom as a function of time. The time-step between calculated structures is small at 10-15 seconds, and we need to reduce hundreds of thousands of sets of atomic coordinates into a simple coherent description. We have simulated with reasonable fidelity the measurable static and dynamic properties of the several different proteins surrounded by thousands of water molecules. Simulation at different temperatures has allowed exploration of the pathways of protein denaturation of entire proteins and small fragments of protein secondary structure (a-helices and β -hairpins). Companion studies of DNA double-helix segments in solution preserve the classical double helix while still showing a wide repertoire of interesting motions. (ii) Molecular modeling attempts to build a model of a macromolecule using known three-dimensional structures and energy minimization as complementary guidelines. Specific examples of this work include the automatic modeling of antibody variable domains, the general modeling of homologous proteins and studies of DNA base-pair mismatches. Questions we are trying to answer include: How can a protein be stabilized by a single amino acid change? How does the sequence of DNA cause local variations of double-helix conformation and stability? Extensive use is made of sophisticated programming, sequence and structural data bases, and computer graphics.

ACADEMIC APPOINTMENTS

- Professor, Structural Biology
- Professor (By courtesy), Computer Science
- Member, Bio-X
- Member, Wu Tsai Neurosciences Institute

ADMINISTRATIVE APPOINTMENTS

- Chair, Department of Structural Biology, (1993-2004)

1 OF 2

HONORS AND AWARDS

- Member, European Molecular Biology Organization. (1981)

1 OF 10

BOARDS, ADVISORY COMMITTEES, PROFESSIONAL ORGANIZATIONS

- Member, National Academy of Sciences (2013 - present)

PROFESSIONAL EDUCATION

- PhD, Gonville and Caius College, Cambridge , Structural Biology (1971)

LINKS

- Levitt Site: <http://csb.stanford.edu/levitt/>

Research & Scholarship

CURRENT RESEARCH AND SCHOLARLY INTERESTS

I pioneered of computational biology setting up the conceptual and theoretical framework for a field that I am still actively involved in at all levels. More specifically, I still write and maintain computer programs of all types including large simulation packages and molecular graphics interfaces. I have also developed a high-level of expertise in Perl scripting, as well as in the advanced use of the Office Suite of programs (Word, Excel and PowerPoint), which is more important and rare than it may seem. My research focuses on three different but inter-related areas of research. First, we are interested in predicting the folding of a polypeptide chain into a protein with a unique native-structure with particular emphasis on how the hydrophobic forces affect the pathway. We expect hydrophobic interactions to energetically favor structure that are more native-like. In this way, the same stabilizing interactions that exist in the final folded state the search tractable. Second we are interested in predicting protein structure from sequence without regard for the process of folding. Such prediction relies on the well-established paradigms that similar protein sequences imply similar three-dimensional structures. We have focused on the hardest problem in homology modeling: the refinement of a near-native structure to make it more precisely like the actual native structure of protein. We have also focused on how the general similarity of all protein sequences resulting from their evolution from common ancestor sequence affects the nature of the protein universe. Third, we are focusing on mesoscale modeling of large macromolecular complexes such as RNA polymerase and the mammalian chaperonin. In this work, done in close collaboration with experimentalists, we use new morphing strategies combined with normal mode analysis in torsion angle space to overcome problems caused by the size and complexity of these critical, biomedically important systems. All this work depends on the way a molecular structure is represented in terms of the force-field that allows calculation of the potential energy of the system. We employ a very wide variety of such energy functions that extend from knowledge-based statistical potentials for a single interaction center per residue to quantum-mechanical force-fields that include inductive effects as well as polarization.

Teaching

STANFORD ADVISEES

Postdoctoral Faculty Sponsor

Nicholas Corsepius, Joao Pedro Garcia Lopes Maia Rodrigues, Fatima Pardo Avila, Frédéric Poitevin

GRADUATE AND FELLOWSHIP PROGRAM AFFILIATIONS

- Biomedical Informatics (Phd Program)

1 OF 3

Publications

PUBLICATIONS

- **Automatic Inference of Sequence from Low-Resolution Crystallographic Data.** *Structure (London, England : 1993)*
Ben-Aharon, Z., Levitt, M., Kalisman, N.
2018

1 OF 175