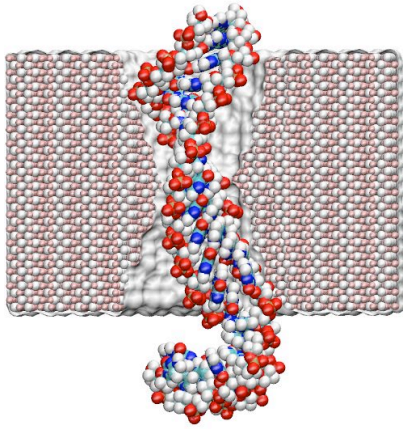
Research Plans and Accomplishments

A ribosome recognizes the sequence of three consecutive nucleotides to produce one of the twenty amino acid side chains. Truly remarkable is the fact that the difference between sets of recognized nucleotides as well as the difference between possible products is only a few atoms. Such extreme selectivity of function to atomic detail pervades cell biology. Understanding any structure-function relation requires looking at the system with atomic precision. Currently, no instrument exists that can visualize microscopic processes taking place in bio-molecular systems at atomic detail. Advances in computational technology permit one today to use microscopic simulations as a kind of a computational microscope to obtain dynamic images of bio-molecular systems. My research methodology combines microscopic simulations with analytical modeling, providing complementary descriptions of bio-molecular machinery on several time scales.

The research projects I would like to focus on in the future are introduced below. As my research methodology requires substantial computations resources I plan to receive an allocation of the computer time at national supercomputer centers. At the same time, I will need to have access to local computational facilities or acquire several computer clusters for exclusive use.

Electronic recognition of DNA with nanopore sensors

Silicon nanotechnology makes it possible to manufacture electronic circuits with features comparable in size to the building blocks of life, i.e., proteins and DNA. A device for ultra-fast DNA sequencing can be built around a 2-nm-diameter pore in a thin (2-5nm) synthetic membrane. The chemical sequence of a DNA molecule can be discerned by such a device in principle through semiconductor detectors, integrated with the pore, that record electric signals induced by the DNA molecule passing through the pore. Several groups have received funding from government agencies in the USA for building a prototype of such a device. In order to achieve the goal of sequencing, the measured electric signals need to be related to the microscopic conformation and the sequence of DNA strands. This task can be accomplished through large-scale microscopic simulations.



Accomplishments. In collaboration with the experimental group developing such pores and measuring signals in response to the presence of DNA (Gregory Timp, UIUC), I have carried out the first-ever atomistic simulations of DNA translocation through synthetic nanopores. Measuring duration of DNA translocation at experimental fields brought about estimates of the resolution that the bio-electrical sensor should have in order to detect DNA sequences. Visualizing interaction of DNA with the surface of the pore revealed hydrophobic adhesion of DNA bases to the pore walls. Varying the pore geometry in MD simulations permitted us to predict which pore size would select single stranded and double stranded DNA and produce the strongest sequence-specific electric signals. Results of this study are reported in two papers [17,18][*]; four more are expected to appear in print within the next six months.

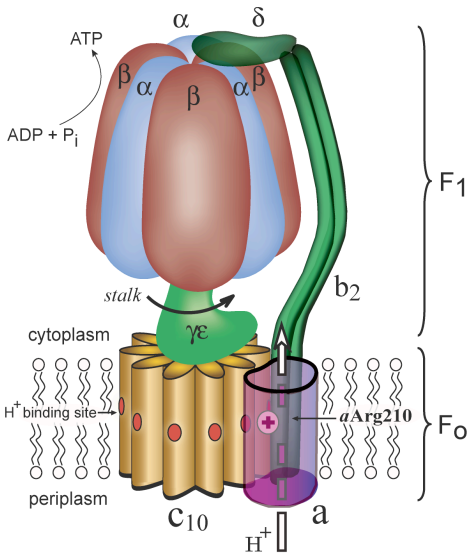
Plans. My goal is to build a DNA sequence device *in silico* to test the designs and detections methods of the nanopore sensor. I plan to investigate ideal nanopore shapes, coatings of nanopore walls, aid forces stabilizing DNA conformation, and the application of various types of electrical field, e.g., alternating fields. The future studies will also address assemblies of proteins, lipids, and silicon electrical circuits. To carry out these studies, molecular dynamics simulations will be performed in parallel with a self-consistent Poisson-Boltzmann solver accounting for electronic structure of semiconductor. This

[*] References are given to the papers from my list of publications

computational methodology is being developed in collaboration with J.P. Leburton (UIUC).

Although this research area might appear to belong to the realm of technology, there are several fundamental questions that are going to be addressed. What is the nature of interaction between materials used for building electronic circuits and DNA, protein, lipid and water? What mechanical stresses can DNA and protein withstand without breaking and if they break then how? How are electronic fingerprints on DNA strands recognized in nature?

Micro-mechanics of molecular motors



Molecular motors are miniature devices created by nature to perform various functions in living cells. They carry out cell division, produce contractions of our muscles, transport nutrients between cell's compartments, move cells in space, and do much more. A common function of these diverse enzymes is the transformation of chemical energy into mechanical motion and vice versa, often performed at nearly 100% efficiency. The ubiquitous enzyme that uses the transmembrane electrochemical potential to synthesize ATP is F_1F_O-ATP synthase, a complex of two molecular motors, F_O and F_1, mechanically coupled by a common central stalk (see figure). The membrane embedded F_O unit efficiently converts the proton-motive force into mechanical rotation of the central stalk inside the solvent-exposed F_1 unit. The rotation causes cyclic conformational changes in F_1, thereby driving ATP synthesis. The enzyme can also function in the reverse direction, hydrolyzing ATP and utilizing the released energy to pump protons across the membrane. The enzyme is central for cellular function, as the ATP it produces is used to fuel other cellular processes.

Accomplishments. In collaboration with the experimental group of R. Fillingame (U of Wisconsin), I investigated molecular mechanism of energy conversion in the membrane unit of F_1F_O -ATP synthase. A microscopic model of the membrane unit was constructed from available structural data. The gap between the time scales of processes driving energy conversion in this enzyme mandates a multi-scale approach: an elementary proton transfer event occurs on the picosecond time scale, whereas internal rotation that drives synthesis of ATP requires milliseconds. By combining large-scale molecular dynamics with a mathematical model built on stochastic equations of motion we simulated physiological function of the enzyme. We found that concerted rotation of internal subunits is required for coupling trans-membrane proton flux to ATP production. The details of this study can be found in [15].

Plans. While several groups around the world compete to solve the complete crystallographic structure of F_1F_O-ATP synthase, many relevant questions can be addressed already today. The molecular mechanism of F_1F_O-ATP remains an enigma after 30 years of extensive studies. The wealth of information about the factors that inhibit or distort function of this enzyme, along with the bioinformatics data, identified the key regions in the enzyme structure. However, many, if not all, experimental observations are not understood at the molecular level. I would like to model a set of most well documented experiments on the available structure to find out what effect this or that harmful mutation, or the introduction of an inhibitor, has on functionally relevant inter-domain motions. By identifying the molecular origin of these observations, I hope to get insights into the mechanism underlying the enzyme function. Results of these molecular dynamics simulations will be incorporated into a mathematical model, linking the atomic scale events to the physiologically relevant time scale.

Propagation of mechanical stresses in motor proteins is another direction that I would like explore. In F_1F_O-ATP synthase, mechanical stresses are believed to coordinate cooperative catalysis of ATP and simultaneously be the source of energy driving the catalysis. I would like to investigate through a combination of microscopic simulations and analytical theory the stress lines arising in the protein upon twisting the torque-transmitting subunit. Analytical part of the study will be carried out within the framework of molecular rheology developed to describe stresses in dense polymer systems.

Computational methodology for multi-subunit proteins

The time scale of microscopic simulations is often much shorter than the time scale of physiologically relevant inter-domain motions in a protein assembly. To investigate such motions without loosing atomic resolution I would like to combine methodologies of mesoscopic and atomistic simulations, producing a coherent computational scheme for studying multi-subunit bio-molecular assemblies.

I had my postdoctoral training in both atomistic and mesoscopic simulations. My experience in the area of atomistic as well as multi-scale simulations is summarized above. Below I describe my accomplishments in the area of mesoscopic simulations.

Accomplishments. With a background in elementary particle physics, I applied methods of field theory to predict phase diagrams of polymer mixtures [4], focusing on the conformational properties of single macromolecules [1,2]. I worked on developing an efficient method for analyzing NMR spectroscopy data [4], targeted to determine the structure of complex liquids such as surfactant solutions and block copolymer melts. I continued to investigate polymer mixtures by quantitatively characterizing the topology of the three-dimensional patterns that emerge during phase transitions [6-12]. It was a surprising finding that the connectivity of such patterns developing in time obeys a simple scaling law [6], independent of the nature of the interactions underlying kinetics of the phase transition [11]. Jointly with the experimental group at Mitsui Chemicals Inc, I investigated reactive processing of polymer blends and developed a code for predicting rheological properties of multiphase fluids and dense suspensions of rubber-like particles.

Plans. The starting point for developing this hybrid computational scheme will be the method I have developed to describe a flow of dense rubber-like particles (unpublished). Starting from a microscopic structure, each protein subunit is represented by a visco-elastic particle having shape, charge and visco-elastic properties of the original protein. The interactions between these particles are described within the framework of visco-elastic fluid mechanics. To propagate conformational changes on the atomic scale, the stress pattern developing within each particle is imposed on the microscopic model of the corresponding subunit through molecular dynamics.

Teaching interests

I consider teaching to be an indispensable part of the research process. More, I share the belief that teaching is the opportunity for us, researchers, to give back to society. I think that in order to be efficient, learning should also be exciting. Every subject that is taught, even those in the most basic course, was once an exciting research project and a topic of inspiration for many people. By reconstructing the logic that stands behind someone's discovery and by bringing back that spirit into the classroom, I want to make students feel connected with the material. From my personal experience I know that new information without an immediate use is easily forgotten. Therefore I will dedicate a lot of time for designing practical exercises that are easy to follow but also include elements that stimulate creating thinking.

With my background, I could teach all basic courses of theoretical physics. The list of the special topics includes: polymer physics, non-equilibrium statistical mechanics, mesoscopic physics, computational physics and chemistry, and bio-molecular modeling.