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Biocomplexity Faculty Search Committee
c/o Prof. Rob de Ruyter van Steveninck
Biocomplexity Institute
Indiana University
Swain Hall West 117
Bloomington IN, 47405-7105

Dear Biocomplexity Faculty Search Committee,

I would like to apply for the Assistant Professorship position in the Biocomplexity Institute (affiliation: Department of Chemistry) at Indiana University, Bloomington. I am enclosing my curriculum vitae, list of publications, scientific accomplishments and research proposal. I asked 3 referees to send directly letter of recommendation.

Sincerely,



Ronen Zangi

The proposed research is aimed at understanding fundamental physical phenomena in structural biology and soft condensed matter physics. It utilizes classical Molecular Dynamics (MD) simulation techniques. However, in cases where Newtonian dynamics is insufficient for describing the system or for addressing particular aspects that are needed for the modeling (e.g. some molecular force-field parameters), results from quantum mechanical calculations will be used as an input for the classical simulations.

Dynamic and Thermodynamic Behavior of Peptides

The research in this project is directed toward understanding the driving forces that lead to the stability of secondary structure motifs found in proteins, namely, α -helix and β -sheet. The thermodynamic stability of these repetitive units is a result of a delicate balance between many factors. It is tempting, however, to characterize the transition to such defined structures in terms of one or more global parameters. Currently, it is unknown which of the many degrees of freedom, if any, can be collectively represented and in what way. Therefore, atomistic Molecular Dynamics simulations with explicit solvent are used to identify and isolate relevant parameters responsible for the transitions. Treating these systems at this level of description is computationally very demanding, thus, the initial stage of the investigation will employ small peptides where reversible spontaneous folding from extended conformations can be observed. Preliminary results that describe the helix-coil transition induced by varying the side-chain interactions are obtained for 9–6 residue model peptides, from which a relation between the free energy of the folded state as a function of the potential energy (determined by the side-chain interactions) is obtained.

Unlike first order phase transitions, where the density of states of the system is sharply peaked around the most probable state, the magnitude of thermal fluctuations in systems where the number of degrees of freedom is small enable the system to sample conformations, in the field of equilibrium states, that do not correspond to the global minimum. This is revealed by the observation that small peptides exhibit an ensemble of distinguishable states (corresponding to local minima) while proteins exhibit a single thermodynamic stable (native) state. Nevertheless, even for the smallest peptides there are only few local minima. A question to address is whether it is possible to characterize these states of the peptide. What is the dependency of the number of such states on the length of the peptide?

In related studies, the kinetic behavior of the peptides will be investigated as well. The transition rate from one state into another is determined by the frequencies of dihedral angle transitions. Therefore, knowledge of the factors that determine these frequencies is essential. In addition, it is required to know the degree of cooperativity. To what extent does the transition of one dihedral angle influence the transition of another angle that participate in the same secondary structure motif? The two limiting cases of complete dependency (two-state model) and complete independency (random polymer) are obviously not appropriate. There seems to be a complex dependency that not only determines the identity of the partially folded (unfolded) states but also governs the kinetics between all states of the system. Cooperativity in the dynamics is a result of concerted motion of group of atoms. It can be described by low frequency normal modes that allow simultaneous transitions of the associated dihedral angles. The activation energy of such concerted transition is likely to be lower than the sum of the activation energies of the individual dihedral angle transitions. However, the later is associated with a larger pre-exponential factor due to a higher probability of finding the participating atoms in high frequency modes. Results from normal modes analysis of the backbone atoms correlated with the information regarding the transitions of the dihedral angles will provide information needed for answering these issues.

In addition to cooperativity, the relationship between the kinetics and thermodynamics stability will be examined. A widely accepted concept for resolving the paradox of the fast folding kinetics of a protein given its astronomical number of degrees of freedom (Levinthal's Paradox) is the 'Energy Landscape approach'. The main assumption of this approach is that the energy landscape of a protein has a funnel shape. Although it is riddled with traps in which the protein can transiently reside, it has an overall slope toward the native structure. The steepness of the energy gradient is expected to be correlated with the energy of the native state relative to the average energy of the random coil conformations. In light of this picture, it is important to know whether the thermodynamic stability of the secondary state influences the time it takes the peptide (or the protein) to reach that state? For example, do helices that are more stable form faster?

The crossing rate over a free energy barrier is determined by the amplitude of the fluctuations in the system relative to the height of the barrier. Any mechanism that changes the degree of the fluctuations will influence the crossing rate. If the overall folding rate can be approximated by a single exponential and the pre-exponential factor has a weak temperature dependence than the free energy barrier for the folding (unfolding) process can be estimated

from the dependence of the folding (unfolding) rate on the temperature. Simulations at different temperatures will be performed to construct Arrhenius plots from which the validity of these assumptions can be tested and estimation of the effective activation free energy can be obtained. Apart from the change of the overall folding rate with the temperature, the individual dihedral angle transition rates will also be affected. A question arises whether the temperature dependence of these two transition rates are the same or different? As mentioned before, as the number of degrees of freedom of the system decreases the magnitude of the thermal fluctuations increases. Accordingly, it is natural to ask what is the dependency of the the transition rates of dihedral angles or of the overall folding rate of the peptide on the peptide length?

The difficulties in addressing these questions arise from time scales that are too fast to be accessible by experiments and that are too long to be accessible by simulations. However, recent advancement in computer technology have increased dramatically the possibility of gaining valuable knowledge by performing MD simulations. Specifically, the ability to observe multiple events of transitions between different states in the course of a complete sampling of the modeled system is the data required to elucidate such information. These computational studies, although very intensive, are now becoming feasible for short peptides.

Answers to these questions will help to construct theories of peptide dynamics and thermodynamics to rationalize the findings obtained from the simulations. It is desired to use analytical tools, borrowed from polymer physics and from phase transitions in finite systems to achieve this goal.

Properties of condensed phase systems in confined geometries and at interfaces

The research is directed toward understanding the properties of systems confined to length scales comparable to that of the particles diameter. There are many geometries of confinement, however, the slab (quasi-two-dimensional) and the cylindrical (quasi-one-dimensional) are the most general.

Already more than 30 years ago it was realized that broken continuous symmetries are impossible if the dimension of the system is smaller than three. At any finite temperature, long wavelength phonon excitations destroy long range periodicity. As a consequence, the character and degree of ordering of a confined substance can be qualitatively different than

that of the bulk. The simulations will be designed to investigate the influence of these thermal fluctuations on the phase diagram and the dynamics of simple systems (such as hard spheres, Lennard Jones particles and dipolar soft rods) in the confined geometries mentioned above. Confined systems in nature are necessarily characterized by some degree of freedom along the constraint direction(s). Therefore, the goal is also to elucidate the effect of this spatial anisotropy on the possible structural ordering (emergence of unique phases) of the system.

As a consequence of the lack of a long range translational order in two-dimensions it is predicted that a truly two-dimensional solid does not exist. However, confinement of many liquids to thickness smaller than 8–6 molecular diameters promote solidification. A question arises, how do these two concepts are bridged together? In order to address this question, studies on the freezing transition of the system as a function of the distance between the two confining walls will be performed.

The single particle dynamics in a condensed phase is a result of many-body forces. However, at short and long times the many-body problem can be described as a result of one-body dynamics with deterministic and stochastic nature, respectively. As a consequence, the distribution of the single particle displacement in these two limiting time regimes has a Gaussian form. Deviations from the Gaussian distribution, that occur at intermediate times, are very small in three-dimensional systems. However, this is not the case if the dimensionality of the system is reduced below three. Large deviations of the single particle displacement from a Gaussian form is observed at intermediate times. These deviations are signature of extensive correlated motion in the system. The aim is to understand the behavior and the origin of the dynamical heterogeneities and cooperative motions found in lower dimensions and to compare them to those found in the bulk in the vicinity of the glass transition.

Obtaining understanding of the behavior under confinement of systems with relatively simple interparticle interactions is necessary for understanding the behavior of more realistic systems with much more complex interparticle interactions. Characterizing the behavior of water, the most important solvent in nature, is of great interest to many fields in science. In addition, other solvents that are of interest to technological developments (e.g. surfactants, alcohols and oils) will be modeled. Due to the restricted phase space sampling and the enhanced nucleation rate that is observed under confinement such molecular systems can be readily investigated by computer simulations where, for example, spontaneous crystallization from the liquid phase can be observed.

The properties of the interface between water and another medium is central for understanding many processes. An interesting situation occur at the interface between water and a medium with low dielectric constant such as hard hydrophobic wall. As is the case with any liquid next to a hard wall, the transverse density profile of water exhibits stratification that extends over 2–3 particle diameters. However, for hydrophobic walls, these stratified layers are oriented in such a way that there is a net polarization that generate an electric potential. In general, it is believed that the close approach of an ion from aqueous solution to the interface with a low dielectric constant is an energetically unfavorable process. However, experimental studies, mainly measurements of electrophoretic mobility of oil droplets immersed in water, indicate accumulation of substantial negative charge at the interface with hydrophobic medium. Many explanations regarding the origin of the high concentration of negative charge at the interface were proposed. They ranged from contamination of the sample with amphiphilic molecules that contain ionic heads to long range orientation of the water dipoles. The preliminary results obtained indicate that the attraction of certain types of ions to the hard hydrophobic surface is caused by preferential orientation of the water molecules in the first two layers from the surface. The research here will be directed to provide explanation for the driving force that lead to the preferential orientation of the water molecules at the interface. In related studies, systematic investigations on the behavior of many ions next to a surface that represents the interfacial environment between water and protein will be carried out. Information obtained from these studies can be used to explain the striking systematic effects of different salts on the solubility of proteins, a phenomenon that is know as the Hofmeister effect.

Both research categories demand a dedicated computational facility. A convenient solution is to build a PC Linux cluster of approximately 40 dual processor nodes. Such computer facility requires a relatively low-budget for construction and maintenance.