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

December 10, 2003

Dear Professor Rob de Ruyter van Steveninck:

Please consider my application for a faculty position in the Biocomplexity Institute, at Indiana University, Bloomington. My research in biophysics relies on theory from the physical sciences to study processes important for biological functions. The concepts and approaches involved in this work will form the basis for collaborative programs within your institution.

The objective of my planned research is to identify the physical properties determinant for function in two families of proteins: RNA-binding domains and Ca^{2+}-sensors. These proteins regulate, respectively, gene expression and muscle activity, and act specifically in according to criteria for structure, dynamics, and energetics. Computations will yield measures of such properties, and will also produce descriptors for the molecular mechanisms involved in regulation. My work will be guided by previous findings in which I proposed novel principles of action for these two types of proteins. The ultimate goal will be to design compounds that modulate function and, have therefore, therapeutic implications.

By conducting a rigorous research program I am also committed to become a dynamic and informative educator. It is my aim to attract motivated students to study the biophysics of proteins that are currently of interest in molecular biology and medicinal chemistry. I am qualified to provide specialized training in this discipline, and also to teach introductory and advanced courses in physics, biochemistry, and bioinformatics.

I believe my qualifications make me a good candidate for the tenure-track position in your institution. I would appreciate the opportunity to have a more detailed discussion with you.

Thank you for your time and consideration.

Sincerely,

Felicia Pitici

Felicia Pitici

Enclosed: curriculum vitae, research plans, research funding, teaching interests, references

RESEARCH PLANS – Felicia Pitici

Computational studies of the molecular mechanisms for function in RNA-binding domains and in Ca^{2+}-sensors

To understand the principles for molecular recognition and signal transduction in the function of RNA-binding domains and of Ca^{2+}-sensors, I will study the structural, dynamic, and energetic properties of the systems and of their ensembles with molecular targets. Computations will identify the molecular interactions and mechanisms determinant for biological function in processes as pre-mRNA splicing, telomere maintenance, and regulation of muscle contraction. I will also investigate the implications for molecular design of target systems not yet characterized experimentally, and of therapeutic agents for related metabolic disorders. By developing new directions that I proposed for each of the two classes of proteins, my research will yield information not available from the current models for protein-RNA interaction and for Ca^{2+}-induced signaling.

The objectives of my work will be met using computational techniques derived from physical theories that model the molecular interactions under conditions relevant for biological function. Simulations with Monte Carlo and molecular dynamics protocols, and with algorithms for stochastic path integration of the action will produce ensembles of states favored thermodynamically, and will also describe molecular transitions. The structure and dynamics of the simulated systems will be analyzed in relationship to the energetic contributions to stability, activation, target-binding affinity, solvation, ionic effects, etc. Free energy calculations will be performed using a decomposition scheme for thermocycles, linear response sensitivity analyses, and more costly perturbation techniques. Molecular modeling and computer-aided drug design will be used as explorative tools for identifying new targets and types of interaction, with emphasis on applications in medicinal chemistry. I am well trained to assess the quality of computational software and of the underlying formulations, and I am also committed to test and refine the protocols and methods utilized in my work.

I will study molecular systems that are members of two large families of proteins specialized in binding RNA and Ca^{2+}: RNA-binding domains, and Ca^{2+}-sensors, respectively. The correct assembly of RNA-binding domains to cognate sequences ensures gene regulation by the removal of noncoding intervening regions, and by correct processing of the 3'-end of pre-mRNA. Some proteins in this family play essential roles in cell development, select alternative splicing sites, and might regulate cell senescence by direct action on DNA telomere motifs. Ca^{2+}-sensing proteins act as primary transducers of the cellular Ca^{2+}-signals that modulate enzymatic functions, Ca^{2+} transport, muscle contraction, and also serve for Ca^{2+} storage. The functional diversity of precise operative nature produced by similar structural domains has been the paradigm in molecular biophysics and biology. To understand the principles for function in RNA-binding domains and in Ca^{2+}-sensors, I will study prototype systems that are also suited for experimental determinations, and can, therefore be used to probe the results and predictions from computations.

Despite active research to characterize the function of RNA-binding domains, it is not yet fully understood how the proteins select specific RNA targets. The difficulty originates in the complex interplay of factors that contribute to binding, and include solvation and ionic effects, entropy changes, and intrinsic propensities for structural adaptation. Computations are amenable for the analysis of such factors in relationship to the molecular mechanisms involved in the association process. Reported studies for the prototype U1A protein and RNA targets (Reyes 2000), while important, yield only a partial accord with the experimental data, and do not reproduce the preference for binding. A systematic computational study of the biophysics of protein-RNA systems is, therefore required in order to identify the molecular basis for binding and specificity. My results for the U1A protein produced correct RNA-binding affinities, and also indicated novel principles for recognition in protein-RNA association (Pitici 2002, 2003a). I will investigate the implications of these findings for understanding the specificity of the interaction,

and the preference of RNA-binding domains for other systems, as DNA quadruplexes rich in cytosine. Applications to molecular design will address the current interest in medicinal chemistry for therapeutic agents that modulate the metabolism by direct action on RNA, and on protein-RNA ensembles.

Currently, it is not possible to relate specific physical properties to the observed modulatory action of Ca^{2+}-sensors in biological processes. The available structural and biochemical data are important, but do not indicate the molecular basis for the intrinsic and induced sensitivity of the systems to Ca^{2+}-signals. Computations can address such issues and identify the interactions and mechanisms determinant for Ca^{2+}-dependent function in specialized sensors. My work on skeletal troponin-C showed that the protein has an intrinsic propensity for adaptation to the functionally active form, which interacts with molecular targets and transduces the Ca^{2+}-signal (Pitici 2003b). I will conduct a similar study for the cardiac isoform of troponin-C, and I will complement the structural and dynamic characterization with an analysis of the energetics for the Ca^{2+}-induced response. My research will identify principles for tuning the Ca^{2+}-binding affinity in skeletal and cardiac troponin-C, and will extend the approach to related Ca^{2+}-sensing proteins, e.g. oncomodulin, S100 proteins, and calbindin. The results will be used to design sensitizers for Ca^{2+}-dependent functions, and nano Ca^{2+}-sensors with potential applications in medicine and technology.

The projects described here center on important issues in molecular biophysics and biology that have direct impact on drug design for disorders involving erroneous pre-mRNA processing, or impaired Ca^{2+}-dependent response. The proposed computations are also an interesting investigation in the biophysics of protein-RNA association, and of Ca^{2+}-sensing processes, and may as well have implications for the development of new methods and protocols. My research will foster collaborations with faculty members in the department, and with colleagues in medicine and molecular biology. In addition, these projects will create many opportunities for students to conduct valuable research in computational biophysics.

References

Reyes C.M., and Kollman P.A. (2000). Structure and thermodynamics of RNA-protein binding: using molecular dynamics and free energy analyses to calculate the free energies of binding and conformational change, *J. Mol. Biol.* 295:1145-1158

Pitici F., Baranger A., and Beveridge D.L. (2002). Computational studies of induced fit in U1A-RNA binding: do molecular substates code for specificity?, *Biopolymers* 65:424-435

Pitici F., and Beveridge D.L. (to be submitted, 2003a). Energetics of binding the spliceosomal U1A protein to hairpin RNA: a free energy decomposition analysis, *Biophys. J.*

Pitici F. (2003b). Structural preference for changes in the direction of the Ca^{2+}-induced transition: a study of the regulatory domain of skeletal troponin-C, *Biophys. J.* 84:82-101 (Journal Cover Illustration)

RESEARCH FUNDING – Felicia Pitici

To support my research and to supplement start-up funds, I will submit grant applications to several agencies. The investigations I plan to pursue in the biophysics of molecular systems are funded by such agencies as the National Institutes of Health, and the American Cancer Society.

I plan to submit a first proposal to the division of Biophysics at the National Institute of General Medical Sciences. The foundation has a targeted area of support for computational research on biomolecular structure and dynamics in relationship to the biological functions. In addition, I will pursue grants for young faculty from the Alfred P. Sloan Foundation and the American Chemical Society. Also, I hope that the department will nominate me for an award from the Camille and Henry Dreyfus Foundation.

My main expense will be the acquisition of performant personal computers ad of a UNIX workstation for graphics applications. Additional funds will be applied toward student support, travel to scientific conferences, and publication of research articles.

TEACHING INTERESTS – Felicia Pitici

Teaching is an important part of a professor's responsibilities. My goal is to become a dynamic and informative educator while simultaneously establishing and maintaining a rigorous research program. I am qualified to teach a range of introductory and upper-level undergraduate courses, such as general physics, atomic and molecular physics, physical chemistry, biochemistry, and science for non-science majors. I am also interested in teaching advanced graduate courses in biophysics, with emphasis on biomolecular modeling, computational biophysics, and biomolecular structure and dynamics. Laboratory classes are also a vital part of undergraduate and graduate education, as they expand upon and illustrate concepts learned in lectures. As a visiting professor in physics, I enjoyed instructing and supervising students in laboratory classes, and I would welcome the opportunity to do so again as a professor.

I also aim to attract intelligent and motivated students to my research group. Working in my group will expose the students to international, peer-reviewed science in a way not otherwise possible at such early point in their careers. From personal experience, I have found that mentoring undergraduate and graduate students is occasionally challenging, but very rewarding overall. Consequently, I look forward to leading my own research group. In addition to working with my students and monitoring their academic progress, I will encourage them to give presentations at scholarly meetings. I found that such interactions are instructive as a great deal of learning occurs when a student must clearly and concisely explain his or her work to strangers. Attending conferences will help prepare my students for future careers as scientists.

My specific **teaching interests in physics** include:
Atomic and molecular physics
Condensed matter
Quantum mechanics
Computational methods in physics

My specific **teaching interests in chemistry** include:
Physical chemistry
Statistical thermodynamics
Biochemistry
Computational methods in chemistry

My specific **teaching interests in biophysics** include:
Biomolecular modeling
Computational biophysics
Biomolecular structure and dynamics
Signal transduction mechanisms
Biophysical methods

My specific **teaching interests in bioinformatics** include:
Sequence and genome analysis
Protein structure prediction