THE SCRIPPS RESEARCH INSTITUTE

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

Dear Professor Rob de Ruyter van Steveninck,

This letter is written to provide my strongest support and recommendation for **Dr Florence Tama** for a position as Assistant Professor in the Department of Physics at Indiana University. Florence is an excellent young biophysicist who has already made significant inroads in establishing interactions with biologists across the US and abroad. I believe she is on track to make significant contributions to the area of structure-function relationships in large molecular assemblies by combining her methods and ideas for normal mode analysis using elastic network models with refinement methods and protocols for electron microscopy.

Florence joined my group approximately four years ago after finishing her Ph.D. studies in a joint project between G. Sanejouand (in France) and N. Go (in Japan). She came to the group with strong recommendations from her mentors and has more than met the expectations from these initial comments. Her Ph.D. work involved the implementation and application of the rotation-translation block approach to reducing the size of the matrices that needed to be diagonalized in normal mode analysis. Her doctoral studies were directed toward exploring the relationship between the normal modes of molecular structures and the functionally important motions these systems execute in achieving their biological activity. These studies formed the foundation for the follow-on work that has been ongoing with me over the last several years at Scripps.

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Her tenure at Scripps has been, as is evidenced by her impressive publication record, quite fruitful. The ideas and methods she brought to the group regarding multi-scale representations via elastic networks and the rotation-translation block approach, as well as her interest in moving to larger systems and assemblies, fit well into our ongoing efforts in multi-scale modeling. She rapidly moved in to begin to explore the processes that control pH/salt induced virus particle swelling/shrinking during the process of assembly and maturation in icosahedral RNA viruses. Her work on CCMV provided the jumping-off point for a number of related areas of exploration, including examining the non-linear pathways of maturation of HK97 and NωV, virus structures of specific interest to our colleagues (Jack Johnson, in particular) here at TSRI, and has precipitated collaborative projects with Andy McCammon at UCSD. Additionally, this work suggested that the same approaches and methods could be useful in the refinement of atomic structures into lower-resolution electron density maps from cryo-electron microscopy.

Florence was keen on looking at dynamical movements in large systems using the combined approaches of elastic networks, the rotation-translation block approach and normal mode analysis, and she rose to the challenge of exploring the motions of the full ribosome shortly after the near-atomic resolution structure by Noller et al. became available. Her initial work on this system captured the attention of Joachim Frank, who was very interested in collaborating with us in the interpretation of his cryo-EM maps of different (trapped) functional states of the ribosome during translocation. Florence, working with a postdoc of Joachim's, carried out a nice analysis of the correspondence between the modes observed from the normal mode analysis and the (functional) motions observed in the EM data. This work uncovered a beautiful new principle of design that Nature appears to exploit in "engineering" her molecular machines, that the gross aspects of molecular shape determine the low-energy modes of a molecular assembly and these are exploited to provide robustness to these molecular machines, and is a very important contribution to the field (I believe).

Combining her ideas and approaches for the elucidation of non-linear paths for conformational change in molecular assemblies, Florence and sabbatical visitor, Ken Taylor - an electron microscopist from Florida State University, investigated the functionally important transition between active smooth muscle myosin and its inhibited state using the methods of elastic network normal modes. These studies explained several empirical observations regarding the nature of the linker between the S1 (head) domains and the S2 (coiled-coil tail) domain of myosin, why myosin inhibition is different than what is seen for kinesin and structural observations based on low-resolution electron tomographic experiments. Florence took the lead in these studies as the real leader of the "team".

More recently she has directed her efforts to the development of a method to fit atomic level structures into lower-resolution electron density maps from electron microscopy/tomography. Exploiting the facile ability of elastic network normal mode methods to explore the "natural" distortions of

molecular systems at multiple scales of resolution, she and her coworker, Osamu Miyashita, developed a package to flexibly fit atomic structures into electron density maps. This idea is not completely novel, in that others have used normal modes as the directions for optimization of molecular structures into electron density maps from crystallography; however, the combination of approaches they use is clearly extremely well suited to the problems associated with lower resolution data from cryo-EM, and the approach is quite timely and welcomed by the community of structural biologists working with these methods. I note that Florence presented a brief overview of the methods at a workshop on methods in electron microscopy and was approached by three of the attendees to elicit her assistance in solving problems they were interested in. Florence now has ongoing collaborations on the refinement of the first structural models for substrate-bound GroEL complexes as well as models for anthrax toxin in complex with attendant molecules. I think these interactions point to Florence's ability to pick problems of significance and collaborate and interact with others in a fruitful way.

Overall, Florence is an outstanding young scientist and I recommend her highly. I urge you to consider her seriously for your position. I have considered possibly pursuing a tenure track appointment for her here, but feel that her career will be better served if she goes elsewhere (even though it will be a significant loss to me).

I hope my comments are helpful to your committee. If you have further questions please don't hesitate contacting me.

Sincerely,

Charles L. Brooks III
Professor and Member
TSRI