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

Re.: **Application for Faculty Position**

Dear Prof. Steveninck,

Herewith please find my application for the faculty position. Besides this letter, the package contains my curriculum vitae and a research outline. The names and contact details of personal references can be found in the CV.

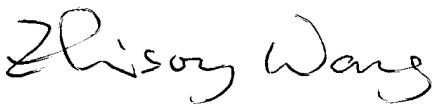
My research interest lies in the field of nanoscale mechanics and machinery (nano2M), which is largely a biological physics and bio-mimetic engineering. Inspired by Feynman's famous claim of "plenty of room at the bottom", the nano2M is emerging out of the daring scientific endeavors of last two decades that have been touching the very bottom for real. In particular, single-molecule studies of biological systems have discovered a surprising level of mechanical flexibility, motional controllability and machining possibilities down to molecular scale. Being essentially a physics, the nano2M field, as I understand, should seek answers to such fundamental questions as mechanical capacity and controllability of individual molecules, fundamental limits due to intrinsic molecular dynamics as well as quantum/thermal fluctuations, and basic mechanisms for work cycles at molecular scale. However, molecular biology has been an indispensable component of the nano2M field from very beginning, since complex biological phenomena, *e.g.* protein folding and track-walking of biomotors in cell, are characterized of robust and regulated molecular motion, providing the largest source of model systems for the nano2M field.

My latest research focuses on (A) photonic nano-devices for protein folding measurement at single-molecule level, and (B) conceptual development of bio-mimicking, track-walking synthetic molecular motors. These projects, being pursued in collaboration with Dr. M.O. Scully's quantum optics group at Texas A&M University, have been developed from my earlier work on single-molecule mechanical/spectroscopic study of proteins and on intramolecular energy flow between different motional modes. Computer simulation has been heavily used in most of my research. In fact, I often took pleasure in developing computational methods by myself.

Committed to quality teaching and research, I am seeking a career in higher education. Fully aware of the academic prestige of your Department, which I am now applying to join, I hope I may have the opportunity to benefit from the strength of the Department as well as contribute my part to it.

Thank you and other members of the Search Committee for consideration.

With best regards,
Yours sincerely



Nanoscale mechanics and machinery: from biocomplexity to new physics and new engineering

Nano2M – What is it? And why is it fascinating?

In sharp contrast to traditional methods dealing with a big number of molecules (typically > 10^{13}), technological advancement over last two decades has made it possible to directly measure mechanical force down to nano-/picoNewton relevant to mechanical unfolding of an individual protein molecule[1], to monitor single folding events of proteins and working of a biomotor[2], and even to make and run artificial molecular motors[3]. Inspired by Richard Feynman's declaration of **"plenty of room at the bottom"**, these daring thrusts start to touch the very bottom for real, revealing an astounding level of mechanical flexibility, motional controllability and machine-making possibility down to molecular scale. In making his famous statement, Feynman admitted, **"I am, as I said, inspired by biological phenomena"**. Indeed, robust and regulated molecular motion is ubiquitous in living organisms. For example, after synthesis in cell a protein molecule folds into a unique, three-dimensional structure largely predetermined by the amino acid sequence; and in cytoplasma a biomotor such as kinesin or dynein processively walks a molecular track by a periodic cycle of energy supply via ATP hydrolysis and rectification of uni-directional move[4]. Biological motors, being tiny molecular compounds though, are not anonymous, random particles. Instead they function as genuine machines with unique "blueprints" (*i.e.* genetic code carried by DNA) and specific work cycles, holding the secrets of what is possible down to molecular world and how it is done.

The emerging field of nanoscale mechanics and machinery (nano2M) addresses individual nano-systems, biological or not, and study their force, motion, energy, intrinsic dynamics, and active control for desired purpose. Thus the nano2M is primarily a nanoscale physics, which but deeply roots in a multi-disciplinary ground. First of all, molecular biology provides the largest source of model systems and inspiration for the nano2M field. For example, at the heart of protein folding problem is a typical physics problem – negotiation of a potential energy surface of vast dimensions and extreme complexity for the most stable state, often without formation of new chemical species through the folding process. Chemo-mechanical mechanisms of biomotors have their most intriguing part not in ATP consumption, rather in mechanical conversion and motional regulation in a molecular world otherwise dominated by thermal and quantum fluctuations. Synthetic molecular machines or fabricated nano-devices[3], far less abundant than their biological counterparts though, provide an alternative, interdisciplinary avenue for advancing the nano2M field. In parallel to Newtonian mechanics and thermodynamics forming basis for traditional machine-making at macroscopic scale, and quantum mechanics for electronic engineering and quantum engineering in a broader definition, accumulated knowledge on nanoscale mechanics will inevitably lead to a new class of engineering, of which nano-machine-making is the highest level.

The nano2M field faces new and unique challenges of its own. There exist some fundamental limits to mechanical and machining capacity of a nano-system, in particular a macromolecule, due to its intrinsic motional modes and energy-flow channels, which are largely determined by sophisticated interplay between quantum-mechanical motion of the bonding electrons and the atomic motion to which classical trajectories are often a good approximation. A control action from outside either cooperates with the intrinsic dynamics towards the desired target or twists or even breaks the molecule unexpectedly. Therefore, nanoscale control is better done in a learning and adaptive fashion[5]. Extra complexity arises from thermal fluctuations of the environment, which may couple to internal motion of the macromolecule to defy control. These limits pose a fundamental question that the nano2M field must seek answer for, *i.e.* **how "plenty" is actually the room at the very bottom** for active control and machine-making? Another principal responsibility of the nano2M field is, how to 'convert' elusive microscopic particles into a robust union of unique mission, which can be controlled with sufficient certainty so that energy is repeatedly pumped in and desired work rectified out. A prominent example of established mechanisms for nano-machinery is Brownian motor [6]. Fair enough to say, **the**

nano2M promises a new physics and a new engineering, which remain largely an unexplored territory for experiment as well as for theory.

Compared to mechanical tools such as atomic force microscope (AFM) and electrical tools such as scanning tunneling microscope (STM), laser-based optical methods are particularly powerful for the nano2M purpose. Using ultrashort laser pulses and confocal optical microscopy setup, radiation field can be projected to a single molecule with great energy density in spatial as well as temporal dimension, guaranteeing excitation of selected states. For a light-responding molecular machine laser can be used as energy source as well as operational tool. Laser operation can be carried out a distance from the machine and its microenvironment, free of diffusive supply of chemical fuel or regulating chemical agents. Since absorption or emission of a single photon is able to drastically change structure, motion, energy, even physical and chemical stability of an individual molecule, this is essentially single-photon regime of radiation-matter interaction. Single-photon devices may be developed from or to serve nano2M research. Therefore, nanoscale photonic devices are an indispensable component of the nano2M field.

What am I doing and going to do about the nano2M?

While constantly collaborating with experimenters, my interest and expertise are primarily on theory part of the nano2M. My latest research focuses on (A) bio-inspired, track-walking molecular machines based on optomechanical effects and, (B) photonic nano-devices for protein folding measurement at single-molecule level.

(A) Bio-mimicking, laser-operated molecular locomotive

Interaction between a running motor and its ground should be strong enough to hold them together, yet not too strong to hinder lateral mobility. Bio-motors prove that fluctuating forces of molecular world can do the job if they are properly regulated. I have designed a laser-powered molecular locomotive that is able to do climb an easily constructed track in inchworm fashion. The locomotive is made of a single linear polymer molecule, which is conveniently available from the vast pool of synthetic optomechanical polymers. The core of the machine is its work cycle that periodically converts optical energy into mechanical work, which is further rectified into processive, directional motion. Beyond a molecular shuttle, which is confined between a couple of stations, the locomotive can move a few μm per second under optimal, automated laser operation, comparable to its biological counterparts. However, this artificial motor is capable of conveniently switchable, dual directional motion in contrast to common uni-directionality of biomotors. The locomotive is also different from the big category of Brownian motors in the sense that move of the locomotive is not a result of biasing pre-existing thermal fluctuations, rather it is directly and decisively driven by optomechanical strokes of the work cycle, generating a pulling force ten times greater than those of biomotors. Being a novel type of molecular motor as well as a powerful molecular engine, this machine will potentially enable automatic, forceful delivery of molecular building blocks with nanometer accuracy. Well within reach of established techniques, its implementation will be a significant step towards Feynman's vision of "a physical way to synthesize" "absolutely anything".

Two projects are going on. One is to continue to improve the machine design for its molecular modules as well as on system level. The proposed motor mechanism is being quantitatively modeled, and also examined from machine design perspective. The other research project is development of optimal laser operation for the molecular locomotive specifically and for light-responsive artificial nano-machines/devices in general. Molecular machine operation by laser is a new frontier of single-molecule optics. To run a work cycle laser switching must be decisive for minimum miss-steps, yet the laser intensity should be low to minimize photodamage of the machine. In addition, system-level requirements such as heat generation and thermodynamic stability, speed and work output must also be considered in optimization of the laser scheme. Significantly, an infrared (IR) laser operation scheme - closed-loop learning control of vibrational ladder climbing (VLC) might enable the locomotive to deliver drugs precisely to tumor sites *in vivo* under skin that is IR-transparent. Major methods being used for both projects include established

tools such as single-molecule quantum optics, laser optimal control and non-adiabatic molecular dynamics simulation, as well as means still being vigorously sought for such as model-building for molecular machines and system-level design strategy.

(B) Photonic nano-devices for protein folding measurement at single-molecule level

The nano2M field can contribute its unique concepts and tools to the ultimate solution of the protein folding problem. Literally proteins operate all of life – all living organisms indeed. Yet there are only 20 amino acids! The great secret of how 20 amino acids manage all is largely buried in the folding problem. There lies also the core lesson of the nano2M field, i.e. programmed formation of desired structural patterns and motional modes. For decades a theory/computational route for solving the folding problem has been pursued with little success. In addition to computer simulation efforts, I also follow a technological route towards the folding problem. Specifically, one technique of hope is single-molecule spectroscopy (SMS) based on fluorescence resonance energy transfer (FRET)[2]. A pair of organic dye molecules is tethered at a couple of complementary sites of the backbone of a protein molecule. While the protein molecule folds, FRET occurs between the dye pair dependent sharply on the changing inter-dye distance, and resulting fluorescence is collected in a time-resolved manner. When the measurement is performed one molecule at a time, ensemble-average is avoided, and the so-called single-pair FRET (sp-FRET) yields unprecedented details of the folding dynamics.

Two bottlenecks are there for sp-FRET (actually for SMS in general): the first is natural lifetime of an emitter – emission cannot be faster than spontaneous decay; the second is photophysical/-chemical vulnerability of the emitter such as photobleaching that prevents fast driving and long irradiation by intense laser beam. Consequently, photon number out of a single emitter is low, limiting time resolution to milliseconds, which is three orders of magnitude larger than typical protein reconfiguration time (μs). In collaboration with Dr. M.O. Scully of Texas A&M University, I have proposed a group of nanoscale photonic devices that are able to substantially overcome these limits. Further integration with current nanofabrication capability and sp-FRET technique is leading to the possibility of a bio-photonic micro-lab on chip that is specifically designed and optimized for protein folding measurement promising drastically improved photon statistics and time resolution. Quantitative testing of different designs is under way by means of quantum optics modeling and realistic protein simulation. Such a single-molecule dynamic spectroscopy, task-oriented and nano-machinery-enhanced, exemplifies a promising strategy for a technological solution of the folding problem.

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