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Prof. Rob de Ruyter van Steveninck
Biocomplexity Faculty Search Committee
Biocomplexity Institute
Indiana University

Dear Professor Steveninck,

I am a researcher at Boston University's Center for Polymer Studies working in the field of analysis and modeling of biological and physiological systems, applying concepts and methods originating in statistical physics, and nonlinear dynamics.

I am writing in response to the advertisement of a faculty position in the Biocomplexity Institute at Indiana University. I believe that my background, area of research and interests are suited to the nature of the position as I am a biophysicist devoted to research in interdisciplinary fields of application.

My original training is in condensed matter and solid state physics where I have worked on quantum antiferromagnetic and strongly correlated spin systems. In the past nine years my research activities have focused on understanding integrated biological and physiological systems. Using mainly computational approaches I have been investigating multiple-component nonlinear mechanisms such as neuroautonomic controll of cardiac dynamics, neural regulation of human motor activity, vasoconstriction and cerebral blood flow dynamics, as well as neural clusters and networks of functional synchronization between cortical centers. In addition to examining complex dynamics at the system level, I have studied biological mechanisms at cellular and molecular length scales. In particular I study (i) excitation, wave propagation and mechanical contraction in myocardial cells using nonlinear cellular automata models, and also (ii) electronic transport in low-dimensional disordered systems with the goal of understanding the conducting properties of biological macromolecules such as DNA, and how these properties affect genomic function. In addition I pursue research focused on understanding level statistics in disordered systems with spatial correlations in relation to DNA and proteins. This work is described in more than sixty publications, including the journals *Nature*, *PNAS*, *Circulation* and *Physical Review Letters*. It was also featured in media and press reviews including *New Scientist*, *Science News*, *Physical Review Focus* and *The American Mathematical Society*. Applying concepts from physics where simple interactions between many units can lead to complex phenomenological behavior, the central goal of my research is to understand the principal components contributing to the underlying mechanisms controlling the behavior of different biological and physiological systems, and to develop an "integrative" picture where these systems are seen in their dynamic interaction.

My investigations have the potential to lead to methods of medical diagnosis and development of technology. My finding of multifractality in heart rate dynamics and the loss of this feature with congestive heart failure is currently the subject of a provisional patent application filed with the Community and Technology Fund of Boston University, and my approach to modeling heart rate variability based on a stochastic feedback mechanism has the potential to improve pacemaker devices by introducing "healthy" variability.

In the process of pursuing my research goals I realized that beyond the scope of my own research investigations there is a need for extended collaboration to diversify ideas, methods and approaches and areas of application. Since 1994, while still a graduate student in biophysics at Boston University, I have initiated and developed collaborations with scientists and research groups in the U.S., Europe and Japan. These include (1) Nonlinear Dynamics Group, Institute of Physics, University of Potsdam, Germany; (2) Department of Applied Physics, University of Malaga, Spain; (3) Center for Complex Biophysical and Biomedical Systems, University of Bari, Italy; (4) Department of Engineering, Cambridge University, England; (5) Divisions of Cardiology and Gerontology, Beth Israel Deaconess Medical Center, Boston; (6) Circadian, Neuroendocrine and Sleep Disorders Section, Brigham and Women's Hospital, Boston; (7) MEG Division, Institute of Medicine, Research Center Juelich, Germany; (8) Sleep Laboratory, Clinic for Internal Medicine, Philipps University, Marburg, Germany; (9) Educational Physiology Laboratory, University of Tokyo, Japan. I have worked to formalize these collaborations by preparing grant proposals and obtaining financial support from the National Institute of Health and European agencies.

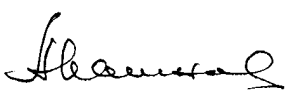
Realizing the responsibility of a researcher, not only to produce high quality work, but to facilitate the exchange of ideas across disciplines I worked on the development and was a founding member of the Research Resource for Complex Physiologic Signals (Physionet;—www.physionet.org) which is a National Resource funded by the National Institute of Health/ Center for Research Resources. Based on a collaboration between HST at MIT, the Center for Polymer Studies at Boston University and the Institute for Nonlinear Dynamics and Medicine at Harvard Medical School, Physionet provides a forum whereby diverse and unique physiological data meet concepts and methods derived from statistical physics, biomedical engineering and nonlinear mathematics to facilitate interdisciplinary research.

Toward the same goal I have served on the editorial board of a newly founded journal, Fluctuations and Noise Letters published by World Scientific Inc. which focuses on natural stochastic processes in physical, biological, physiological and technological systems. I am also organizing a symposium on Interdisciplinary Approaches to Physiology at the American Physical Society March meeting in Montreal 2004, and I have served on the scientific organizing committee of the conference "Fluctuations and Noise in Biological, Biophysical, and Biomedical Systems" within SPIE's FaN'2003 symposium in Santa Fe.

Having been invited to give many talks and lectures at conferences and universities in the U.S. and abroad, I am confident that I have demonstrated my ability to lecture. I have also guided the research work and proposed scientific problems to five physics PhD students at Boston University, a physics PhD student at UNED Madrid, an engineering PhD student at Cambridge University, UK, and three post-doctoral researchers at Boston University and Harvard Medical School. Projects I have initiated with these students resulted in twelve articles and manuscripts currently under review. I enjoy drawing the best out of my students, watching them develop into colleagues with whom I can work side by side. I enjoy the challenge of working out the optimal way to engage students in ideas. It is also a rewarding experience to share knowledge with undergraduate students, as they gain confidence in their ability to understand difficult concepts.

The Biocomplexity Institute in interaction with other departments at Indiana University offers an unique environment and opportunities to accomplish significant scientific research, and to interact with talented students and researchers with diverse backgrounds. It would be a privilege to join such a distinguished institution.

Yours Sincerely,



Plamen Ch. Ivanov.

Enclosed please find my CV, research statement, and list of publications.

STATEMENT OF RESEARCH INTERESTS

My research interests focus on the application of concepts and methods originating in nonlinear dynamics, chaos, fractal theory, cellular automata, stochastic and random walk approaches, wavelets and signal processing methods, and statistical physics to complex biological and physiological systems. These systems appear to be good candidates for such an approach since they are often controlled by multiple-component hierarchical feedback mechanisms operating on a range of time and space scales, leading to very large numbers of degrees of freedom. In my work I investigate how the integrated "macroscopic" outputs of such complex systems depend on the intrinsic "microscopic" interactions among the components.

The outputs of biological and physiological systems often display nonstationary behavior with noisy and erratic fluctuations resembling those found in dynamical systems driven away from a single equilibrium state. The quantitative analysis of such systems raises serious challenges to current methods and approaches. My interests are both in developing novel techniques and approaches of analysis suitable for nonstationary data , and in investigating whether such noisy fluctuating signals contain dynamical patterns essential for understanding the underlying structure and mechanisms of physiologic control.

Based on the experience I have accumulated over the last nine years I have the vision to develop a particular research program focused on the emergence of dynamical and mechanistic properties from cellular level information about protein and genomic structure and function, and information about the mechanisms of regulation of physiological systems. Ideally, this research can enhance current diagnostic methods.

In addition to following the reductionist approach of research — i.e. studying complex systems by disassembling them to their individual components — I believe that there is a need to develop new integrative approaches, where different systems are studied from the point of view of their dynamical interaction. In particular I envision a long-term research program which would address questions related to:

1. The networks of interactions and synchronization between cellular functional responses, as well as interactions between different neural groups and cortical centers under external stimuli, locomotion and coordination, and under medications. Understanding the complex topology and structure of biological and physiological networks has relevance to the mechanisms of how information is transferred within and between cells and between cortical centers, as well as to the regulatory mechanisms of blood flow and pressure in the brain. Adapting concepts from random networks and graph theory to develop a "map" of these inter- and intra-cellular interactions.

2. The nature of cardiac neuroautonomic regulation and interactions with the neuronal regulation of respiration and locomotion. Developing methods to quantify synchronization between these systems. Investigating effects of medications blocking specific pathways (sympathetic or parasympathetic) to model nonlinear feedback neuronal interactions. Developing methods and algorithms which are robust for analysis of nonstationary signals with application for computer-based medical diagnosis.

3. The mechanistic basis of sleep stage transitions. How do cerebral networks of sleep-promoting and wake-promoting neural cells interact in order to "switch" on and off rhythmically to account for specific sleep or wake stages. Modeling the dynamics of these cellular interactions on a biochemical level.

4. Understanding the behavior of excitable media (e.g. the myocardium) at the cellular and ionic levels. Investigating the mechanisms of interaction between periodic fronts and nonlinear spiral waves leading to irregular mechanical contractions of the myocardium (cardiac fibrillation). Formulation of differential equations and discrete cellular-automata methods which appropriately describe the dynamics on a cellular level beyond the current standard FitzHugh-Nagumo model. Developing improved pacemaker devices based on novel stochastic feedback modeling approaches which more adequately reflect dynamical features in heart rate variability.

5. Level statistics, electron transport and conductivity in low-dimensional disordered systems with long-range spatial correlations. This problem is pertinent to the mechanical and conduction properties of biological macromolecules such as DNA, where differences in the properties of coding and non-coding segments may have importance in the processes of transcription and

mutation repair. This work has also implication for drug design and for engineering of nanotubes and biological nanodevices.

In a current study I investigate the synchronization patterns between local current signals obtained by magnetic field tomography for a spatially distributed set of two thousand source points in the human brain using concepts from graph theory and the theory of random networks. Based on estimates of entropy and cross-synchronization measures I define a metric between each pair of source points to determine the degree of synchronization in their functional response to extrinsic and intrinsic stimuli, and I develop a spanning tree optimization algorithm to investigate the relation between the functional and anatomical structure of the network of interactions. The goal is to identify hierarchies of functional patterns in the cerebral network through clusters of source points with different levels of synchronization, to appropriately quantify this network, and to map it to the anatomical structure of the brain. My results surprisingly show that geometrically distant source points from different anatomic areas of the brain can often be stronger synchronized in their functional response to a given stimulus compared to geometrically close source points from identical anatomic areas. Moreover, some source points exhibit much higher connectivity (i.e. a larger number of synchronized links) compared with others. The structure of the network also provides unique information about the locales through which different cortical areas communicate. Further, I find that the structure of these networks changes when I analyze cross-synchronization in different frequency bands, suggesting that different cortical areas can communicate simultaneously through multiple networks which may or may not have common nodes.

I have been invited to present results of this work at the WE-Heraeus-Seminar on Synchronization in Physics and Neurosciences, Physikzentrum Bad Honnef, Germany, 10-12 Dec. 2001 and at the International Workshop on Randomness and Complexity, Eilat, Israel, 5-9 Jan. 2003. Of particular interest is to extend these studies to cerebral functional response under different physical and cognitive tests, and to investigate interactions of brain control with other mechanisms of physiologic regulation such as cardiac, respiratory, blood flow and blood pressure regulation, and peripheral motor coordination.

Utilizing transfer matrix methods my present work has focused on the effects of strong electronic delocalization when long-range power-law correlations are introduced in 1-D disordered solids [Nature, vol.418, 955 (2002)]. For large but finite systems the long-range correlations lead to a considerable extension of the localization length for a large fraction of the electrons and within a broad energy band. This finding has implications for developing highly conducting biological materials. Further, since the DNA chain can be considered a disordered binary solid with different types of correlations for the coding and non-coding regions, mapping the areas of enhanced vibrational modes and electronic transport in DNA may help to understand the biological function of different DNA segments, as well as the mechanisms of mutation repair.

In the past nine years in the field of physiology I have studied the statistical properties and the mechanisms of control of human cardiac dynamics, respiration, sleep and gait dynamics, as well as the effects of endogenous circadian rhythms on physiologic function. The broad objective is to gain insight into the basic principles and mechanisms governing individual physiologic systems as well as the dynamic interaction between different physiological systems, and to develop an integrative picture of human physiology, under healthy and pathologic conditions.

My work on cardiac dynamics has concentrated primarily on fluctuations in the time intervals between consecutive heartbeats. My studies indicate that when appropriately analyzed at different time scales by means of wavelet and Hilbert transforms, heartbeat fluctuations exhibit remarkable hierarchical cascades characterized by branching patterns with self-similar fractal properties [Physica A, vol.249, 587 (1998); Chaos, vol.11, 641 (2001)]. Such fractal behavior indicates a structure in the heartbeat fluctuations which is common for healthy subjects, and can be consistently described by a single mathematical formula. It also reflects important new aspects of the mechanisms of *cardiac regulation*, since these patterns are lost under pathological conditions related to cardio-pulmonary disorders [Nature, vol.383, 323 (1996)].

Further, my studies show that the healthy heartbeat is even more complex than previously suspected, since its fluctuations exhibit not only fractal, but *multifractal* behavior — a complex mixture of fractals within fractals [Nature, vol.399, 461 (1999)]. Based on estimates of the local singular behavior of the heart rate signal this finding demonstrates that the cardiac system is

characterized by a high degree of complexity similar only to that observed in physical systems in the state of turbulence. This multifractal ("turbulence"-like) complexity is lost with disease, and is altered under the influence of medications which block the sympathetic or parasympathetic branches of the neuroautonomic system. This may have significance for clinical applications [Physical Review Letters, vol.81, 2388 (1998); Physical Review Letters, vol.86, 1900 (2001)].

My more recent work on human gait dynamics and forearm motion suggests that not all physiological processes regulated by the central nervous system have these multifractal properties. Although gait exhibits some fractal features which are similar to those of the heartbeat, it does not exhibit multifractal complexity. Thus the methods I focus on can be used to discern between different levels of complexity in various physiologic processes. Further, in collaboration with others I have studied the process of gait maturation with age, and I modeled gait dynamics considering stochastic interactions between "neural centers" within the cortex and the spinal cord.

The experimental findings of new features in the dynamics of physiological systems support new modeling approaches; e.g., my analysis shows that nonlinear stochastic feedback mechanisms may have relevance to the neuroautonomic regulation of the heart and can account for key characteristics of healthy cardiac variability [Europhysics Letters, vol.43, 363 (1998)]. In a more recent study of 12-hour long records from patients with heart failure and frequent abnormal ventricular beats, we show that the complex and transient patterns of abnormal ventricular heartbeats in the normal heart rhythm can be described by a model of two weakly coupled oscillators with stochastic elements. Our model indicates that in addition to the total number of abnormal beats a key risk factor may be the patterns that they form [Physical Review Letters, vol.87, 068104(4) (2001).].

Such modeling efforts may also have applications in improving the design of microelectronic implantable pacemakers, capable of preventing heart fibrillation by releasing weak correlated impulses which do not scar the myocardium. Controlling the behavior of excitable media (e.g. the myocardium) at the cellular and ionic levels is currently one of the challenges of nonlinear dynamics and nanoscience. My current work in this direction focuses on the interaction between periodic fronts and nonlinear spiral waves in the myocardium cell tissue which can be a source of cardiac fibrillation — dynamics which require formulation of a new set of differential equations beyond the standard FitzHugh-Nagumo model.

In a different line of research related to human sleep dynamics I hypothesized that, in addition to the generally slower heart rate during sleep, there might be more fundamental dynamical differences in cardiac regulation that occur during wake and sleep. In particular, I found that the dynamical patterns in heartbeat fluctuations (at scales from one minute to many hours) are very different during sleep and wake states — with stronger anti-correlations during sleep, suggesting stronger neuroautonomic control. In fact, my studies show that this difference is as significant as the difference between healthy subjects and subjects with congestive heart failure. This may have important implications for diagnosis. Such marked change in the heart rate dynamics during sleep and wake states leads to reassessment of the sleep phase as a surprisingly active dynamical state [Europhysics Letters, vol.48, 594 (1999)]. My more recent work in this direction indicates that different sleep stages (i.e., light, deep, rapid-eye-movement sleep) are associated with different linear or nonlinear features in heartbeat dynamics [Physical Review E, vol.65, 051908(6) (2002)]. These findings may have important implications for quantifying, assessing, and treating sleep disorders, and may lead to a better understanding of the mechanisms of sleep regulation.

My interests in exploring the interface between physics, biomedical engineering and physiology/biology are stimulated by the academic challenge which biological and physiological problems pose to us, as well as by my vision that work in this interdisciplinary area can lead to dramatic improvements in preventive medicine. Recent technological advances such as (i) the discovery of how to extract diagnosis and prognosis information from the analysis of physiologic rhythms, (ii) improvements in information technology and (iii) the miniaturization of monitoring equipment will make it possible in the immediate future to offer a broad range of health-monitoring services. Such new technologies will be used as pre-screening methods which can enhance current medical diagnostics and monitor effects of medications using changes in

individual rhythms.

COLLABORATIONS AND CURRENT PROJECTS:

In the past seven years I have initiated several collaborations, and I am currently working on the following projects:

1. Prof. S. Shea and Dr. M. Hilton, *Harvard University, Medical School, Brigham and Women's Hospital, Circadian, Neuroendocrine and Sleep Disorders Section, Boston.* Since 2000 — investigating the effects of circadian rhythms and time shifts on physiological function and regulation. Current project — a multiparameter study of the effects of forced desynchrony (wake at night and sleep during day) on muscular activity, temperature fluctuations, cardiac and respiratory dynamics; search for cardiac risk factors related to the "circadian clock" and to the level of human motor activity as measured by forearm motion.

2. Prof. J. Kurths and Dr. M.G. Rosenblum, *Nonlinear Dynamics Group at the Institute of Physics, University of Potsdam, Germany.* Since 1995 work on developing time series analysis methods, nonlinear dynamics methods and synchronization approaches to bivariate data and multivariate data. Current project — synchronization of physiological signals.

3. Prof. S. Havlin, *Department of Physics and Gonda-Goldschmied-Center for Medical Diagnosis, Bar-Ilan University, Ramat-Gan, Israel.* Since 2000 — studying the mechanisms of neuroautonomic regulation of cardiac activity during intense exercise and rest.

4. Prof. P. Bernaola and Prof. P. Carpena, *Department of Applied Physics, University of Malaga, Malaga, Spain.* Since 1998 — developing algorithms to quantify and model nonstationarities in signals; in particular, algorithms to segment signals based on transient changes in local properties with applications to DNA and physiology. Current project — investigating propagation of mechanical waves and conductivity in disordered atomic chains and biological macromolecules with long-range spatial correlations. Such correlations change the physical properties of the electron wave functions and may lead to a correlation-induced transition from insulating to conducting state; implications may be important for designing chains of biomolecules with desired electrical properties, which is currently a challenge for the newly emerging field of bio-nanotechnology. Another objective of the study is to understand the role of conductivity for the transcription and mutation repair functions of the coding and non-coding regions of DNA.

5. Prof. F. Moss and Dr. A. Neiman, *Center for Neurodynamics, University of Missouri at St. Louis, St. Louis.* Since 2001 — studying the role of random processes and noise in neural detection, transmission, and processing of sensory information; detection and statistical characterization of low-dimensional dynamics and chaos in neural systems.

6. Prof. Y. Yamamoto, *Educational Physiology Laboratory, Graduate School of Education, University of Tokyo, Tokyo, Japan.* Since 1999 — testing the effects of drugs which block the sympathetic or parasympathetic system and how this affects the mechanisms of cardiac regulation; in particular, we tested that the multifractal complexity observed in heart rate data is not a consequence of the response of neuroautonomic control mechanisms to activity-related stimuli; instead the neuroautonomic control mechanisms endogenously generate multifractal dynamics [Physical Review Letters, vol.86, 6026 (2001)]. Since 2002 — investigating the process of maturation of the regulation of cardiac dynamics in babies.

7. Prof. T. Penzel, *Sleep Laboratory, Clinic for Internal Medicine, Philipps University, Marburg, Germany.* Since 1998 — characterizing dynamical features in the human heart rate during sleep and wake activity, and how these features change with pathological conditions (e.g. heart failure) and in space under conditions of microgravity. Current project — developing a "sleep finder" algorithm to determine sleep stages and quantify quality of sleep from heart rate. Since 1999 — analysis and modeling of the dynamics of sleep

stage transitions and the corresponding mechanisms of brain regulation. We have investigated the statistics of the intermittent periods of brief waking that occur during nocturnal sleep and found that the duration of the waking periods follows a power-law distribution, which indicates the absence of a typical, characteristic time scale — while the sleep stages are associated with a typical time scale. This discovery [Europhysics Letters, vol.57, 625 (2002); New Scientist, vol.173, 38 (2002)] raises important questions about the nature of sleep regulation, and whether a single or two different mechanisms are responsible for regulating sleep dynamics.

8. Prof. P. Tass, *Institute of Medicine (MEG), Research Centre Juelich, Germany.* Since 2001 — detection of hierarchies in cerebral synchronization patterns; synchronization between muscular activity (e.g. finger tapping) and cortical centers, as well as between specific cortical centers; developing a synchronization map of the brain based on information derived from the local current density measured in a 3-D grid of several thousand source points with the aim to elucidate physiological function and interaction between brain areas.

9. Dr. K. Arai and Dr. M. Yoneyama, *Mitsubishi Chemical Corporation, Yokohama, Japan.* Since 1998 — developing portable devices to measure and analyze human gait. We test the hypothesis that human gait dynamics belongs to the same higher "complexity class" of multifractal processes as cardiac dynamics, since gait (as well as heartbeat) are physiological processes under integrated higher-supraspinal neural regulation and both exhibit fractal $1/f - like$ power spactra. Surprisingly, we find that gait and heartbeat dynamics belong to different classes of complexity — human gait fluctuations exhibit linear monofractal properties, while heartbeat fluctuations exhibit nonlinear multifractal properties.