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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 Prof. Prof. Rob de Ruyter van Steveninck:

I am writing to apply for the position of Assistant Professor at the Physics Department of the Indiana University.

Currently, I am working as Research Associate at the Physics Department of the Duke University with an interdisciplinary team of researchers in the general area of biophysics. Our collaboration includes: Prof. D.J. Gauthier (Physics Department), Prof. D.G. Schaeffer (Department of Mathematics) and Prof. W. Krassowska (Biomedical-Engineering Department). We are conducting theoretical and experimental investigations of cardiac dynamics, where the goal of the research is to understand the mechanisms leading to abnormal cardiac behavior and developing appropriate methods to control such behavior. My responsibilities include the theoretical investigation of the cardiac tissue as a nonlinear excitable system using different techniques developed by the physics and mathematics communities. The primary result of my work is the development a completely new technique for investigating multiple aspects of the dynamics of nonlinear excitable media. This method contrasts with current techniques that can measure only single characteristics.

For my future academic career, I will develop an interdisciplinary experimental and theoretical biophysics research program, which will build my strong physical and mathematical background along with my comprehensive knowledge of electrophysiology. A brief research statement is enclosed that outlines my long-term goals as well as my short-term plan.

In addition to developing a vigorous research program, I am committed to becoming a first-class teacher. My broad physics background allows me to be relatively open for the various courses I could teach. The main idea of my teaching philosophy is to teach students the fundamental content of the courses as well as fostering critical thinking, thereby preparing the students to function effectively in the field they choose and to develop problem-solving strategies. I have enclosed a brief statement of my teaching philosophy I am hoping to implement at the University.

To give you a better sense of my qualifications and research/teaching interests I have attached my resume, research and teaching statements and selected copies of recent publications.

Sincerely Yours

Dr. Alena Talkachova

Research statement

1. Statement of the main goal

My **general goal** is to investigate experimentally and theoretically the dynamics of complex nonlinear excitable media using different techniques developed by the physics and mathematics communities. One example of an examples media that I will investigate is a heart -- a very complicated biological system that involves multiple levels of interacting between electro-chemical processes in the cardiac muscle, resulting in various dynamical behaviors of the entire system. Some aspects of cardiac dynamics describe normal heart operation while others characterize abnormal heart behavior, often leading to sudden cardiac death. The mechanisms preceding abnormal cardiac rhythms (such as ventricular arrhythmias) are not very well understood, leading to big open question in cardiac dynamics.

Recently, I developed a new technique for investigating multiple aspects of the dynamics of nonlinear excitable media. This new method contrasts with current techniques that can measure only single aspects of the dynamics. My **major goal** is to use this technique to characterize more accurately the dynamical behavior of cardiac systems, especially mechanisms leading to ventricular arrhythmias.

2. Introduction

My research is in general field of biophysics where I am currently investigating cardiac dynamics that considers the *heart as a complex nonlinear system* designed to pump blood effectively. In this nonlinear system, waves of electro-chemical excitation that sweep through specialized conduction systems and the muscle of the heart mediate its mechanical contractions. These waves are followed by a refractory period when the tissue cannot respond to further stimulation, implying that cardiac cells behave as an *excitable media*. Under normal and healthy conditions, the contraction of the muscle is coordinated. In some situations, this orderly procession of waves can evolve into a spatially complex dynamical state known as fibrillation, in which the waves of excitations and consequent contractions of the heart are not coordinated, causing a ventricular arrhythmias and, as a result, sudden cardiac death. Thus, one of the *major problems* in the study of *cardiac dynamics* is to understand the dynamical behavior of the heart, in particular, the mechanisms causing cardiac electrical instability for a more rational assessment of vulnerability to severe ventricular arrhythmias.

One of the main techniques for investigating dynamics of the complex excitable media such as heart is to perturb its behavior using well-defined sequence of external stimuli. The response of the nonlinear excitable system to such perturbation is measured and analyzed to find nonlinear functional relations between important parameters of the system. It is believed that the dynamical behavior of the nonlinear excitable medium can be understood and characterized by analyzing such nonlinear functional relations.

For instance, the dynamics of cardiac tissue is usually characterized using nonlinear functional relation between the duration of the waves of excitations and the preceding refractory period, known as the *restitution curve*. It is believed that the slope of this curve determines whether the normal cardiac rhythm is stable, where instability usually leads to abnormal cardiac behavior. In particular, it was proposed that normal cardiac rhythm becomes unstable when the magnitude of the slope of the restitution curve exceeds one (known as the *restitution relation)*. This restitution relation has been confirmed in some experiments and has led to the *restitution hypothesis*, which states that flattening the restitution curve will help prevent fibrillation. This restitution hypothesis is firmly engrained in the minds of most researchers and clinicians leading to classical description of the cardiac dynamics through the restitution curve.

However, this general technique for investigating dynamics of complex excitable media is insufficient to completely characterize the system's behavior: the response of the nonlinear system depends on the manner in which perturbations are applied. Thus, different nonlinear functional relations can be observed between parameters of the complex excitable medium, indicating that the dynamics of the system is much more complicated than it was assumed initially. In this case, the great challenge is to combine all nonlinear functional relations together to obtain multiple representation of the dynamical behavior of the nonlinear system.

Similar situation occurs when characterizing cardiac dynamics, where it is found experimentally that the nonlinear functional relation – the restitution curve -- depends on the manner in which it is measured. The experimental observation is not consistent with some of the existing theories of cardiac dynamics, where it is assumed that there is only a single restitution curve. As a result, the large area of biophysics that characterizes dynamics of cardiac muscle based on the slope of restitution curve is inappropriate because it is unclear which restitution curve has to be measured.

In *my theoretical studies* I derived a *new perturbation technique* for measuring simultaneously a multiple aspects of the dynamics of complex nonlinear excitable media. Applying this technique to cardiac tissue, it is possible to measure simultaneously a *combination of different restitution curves* (so-called *restitution portrait*) in contrast to the present-day technique that can measure only single restitution curve. My investigation proves that different restitution curves describe different aspects of cardiac dynamics and thus all of them have to be taken into account in order to fully characterize the dynamical behavior of cardiac tissue.

3. Research plan

In my **5-year research**, I plan to apply a *modern perturbation technique* to describe more accurately the dynamical behavior of the excitable media in general and cardiac tissue specifically. The advantage of the new technique I have developed is that multiple aspects of cardiac dynamics can be visualized simultaneously, in contrast to present-day techniques that investigate only single aspects of the dynamics. My **primary goal** is to develop an experimental biophysics laboratory to measure the restitution properties of *in vitro* cardiac tissue and compare the observations to mathematical models. Understanding the dynamics of cardiac tissue is crucial for determining the mechanisms giving rise to abnormal cardiac rhythms, such as ventricular arrhythmias that potentially lead sudden cardiac death.

My **first long-term goal** is to use a new technique to obtain restitution portraits (combination of different restitution curves measured simultaneously) for different animals and for different parts of the heart. These restitution portraits will then be compared to the restitution portraits obtained for the human hearts (and its different parts) to determine the most full correspondence between its dynamical behaviors. In my research I will concentrate on analyzing multiple aspects of cardiac dynamics both during the normal cardiac rhythms as well as just before the abnormal cardiac rhythms. This investigation will allow me to identify the possible mechanisms causing ventricular arrhythmias. This part of the research project may lead to new methods for preventing abnormal cardiac rhythms using different pharmacological agents.

My **second long-term goal** is to develop a general *tissue-independent* mathematical model that will take into account multiple aspects of cardiac dynamics and which will base on real experimental data. This model has to be complex enough in order to describe various aspects cardiac tissue dynamics and simple enough to be basis for renewal restitution hypothesis. The parameters of the model could be adjusted for each pieces of tissue accordingly to fit with experimental results. This is in contrast to current physiological models that describe the dynamical behavior of the specific cardiac tissue and that are highly complicated for analysis.

The **short-term goal** of the proposed research includes setting up the experimental laboratory for *in vitro* studies of cardiac tissue. The specific goals for the first *2 years* are the following:

Goal 1: To implement experimentally a new perturbation technique for visualizing multiple aspects of cardiac dynamics. Using the new technique, I will measure slopes of different types of restitution curves both far away and close to the region of abnormal cardiac behavior for the different species.

Goal 2: To test the hypothesis that the restitution relation depends on a combination of the slopes of different types of restitution curves simultaneously at the onset of abnormal cardiac rhythm.

Statements of Teaching Philosophy

The main idea of my teaching philosophy is to teach students the fundamental content of the courses as well as fostering critical thinking, thereby preparing the students to function effectively in the field they choose and to develop problem-solving strategies.

My teaching philosophy is firmly based on several principles that I consider important for the successful teaching process.

- I think that the most important element in learning is active participation by the learner – egocentric involvement in the process. A person will learn more if they feel they are important and active part of the process.
- For undergraduate student, the type of learning and the amount of learning are strongly influenced by the type of assessment and the amount of student participation. I believe that the objective tests should encourage short-term memorization and motivate students to participate up to their capacity.
- For graduate students, I believe that the deep understanding of the presented material is crucial for formation of critical physical thinking that is absolutely necessary in developing a good scientist.

Below, I present some statements of my teaching philosophy:

- *My responsibility:*
  - ✓ I, as Instructor, should have a mastery of the subject matter I am teaching;
  - ✓ Careful preparation for each lecture, including an introduction, motivation and a conclusion.
  - ✓ Point out and emphasize transitions between concepts;
  - ✓ Always be punctual for all classes;
  - ✓ Be available by appointment to those students who can't attend my regular office hours;
- *Active teaching process:*
  - ✓ Realize the goals that my students are trying to achieve in the course, and being certain to relate to that in a very meaningful manner;
  - ✓ Make my students active participants during the lecturing/learning process;
  - ✓ Encourage my students to ask questions;
  - ✓ Inviting my students to discuss difficulties with me;
  - ✓ Be supportive to students who give incorrect answers;
  - ✓ Ask my student periodically to give me a comprehensive list of questions they had difficulties with in order for me to identify which concepts needs to be re-emphasized;
- *General methodology:*
  - ✓ simple demonstration of different concepts using all possible analogues;
  - ✓ wide using of the literature;
  - ✓ encourage students to think independently;
- *Preparation for the tests:*
  - ✓ Maintain high standards, but always be fair in asking questions on examinations, based on what was covered and learnt in class, that students can answer within an allotted time frame;
  - ✓ Test my students' comprehension during lectures by regularly asking questions and allowing them sufficient time to respond;
  - ✓ Hand out study guides/materials and sample test questions with corresponding solutions;
  - ✓ Tell my students how to study for the kind of tests I give;