I. RESEARCH STATEMENT OF DR. D. BATTOGTOKH

A. Overview

I am interested in pattern formation and self-organization of complex systems where complexities arise not only from nontrivial, individual dynamics of the elementary units but also from strong nonlinear interactions among the modules composed from these units. A population of biological cells is an example of such a complex system where a protein level inside a given cell, which is regulated by a nonlinear biochemical reaction network, can play a role of an elementary unit. Here, another level of complexity arises from cell to cell communications monitoring individual dynamics of the cells. A theoretical study of such complex systems requires exact mathematical models and analyses, efficient computer codes, large scale simulations that include parallel computations, and visualizations of simulation data.

The complex systems can be described by a general mathematical model,

$$\dot{\mathbf{X}}_\mathbf{i} = \mathbf{F}(\mathbf{p}, \mathbf{X}, \nabla, \Delta) + \mathbf{g}(S(\mathbf{r}_i, t)) \tag{1}$$

$$\epsilon \dot{S} = -\gamma S + D\Delta S + \sum_{j=1}^{N} h(\mathbf{X_j})\delta(\mathbf{r} - \mathbf{r_j}). \tag{2}$$

In the above equations, a vector field $\mathbf{X}$ represents a dynamical variable; for example, it may describe concentrations of chemical compounds. $\mathbf{F}$ is a nonlinear function of $\mathbf{X}$, its gradients and diffusion. $\mathbf{p}$, D, γ, and $\epsilon \to 0$ are parameters. S is an inactive, fast, diffusive variable, whose role is coupling different $\mathbf{X}_i$'s through a function $\mathbf{g}$. The production of S depends on $\mathbf{X}$ through a function $h(\mathbf{X})$. In the case of a population of biological cells, $\mathbf{X_i}$ may represent protein levels in the cell with an index i. Then, S can describe a concentration of a signal-agent molecule produced inside the cell, and through which the cells communicate. The right hand side of Eqs.(1-2) may be subject to external forcing and noise.

Synchronization, collective motions, and irregular dynamics in different disciplines, from sociology to biology, can be described by the general mathematical model Eqs. (1-2). I believe that mathematical models based on Eqs. (1-2) will have a great impact in the study of complex systems, including modeling cancer. I studied Eqs. (1-2) for different problems in physics, chemistry, and biology. I have published more than 20 research papers that have been cited more than 170 times.

B. Research on continuous time systems

1. Analysis(via derivation of reduced forms) and simulations of Eqs.(1-2)

As **F** is a nonlinear function, no analytic techniques exist for a mathematical treatment of Eqs.(1-2). However, near the Hopf bifurcation, at the onset of oscillations, Eqs.(1-2) can be reduced to universal equations for amplitude and phase, which can be analytically treated. I derived the universal equations for several biochemical models, e.g. Ref. [4](publication list of D. Battogtokh).

Using different numerical methods, I developed different computer codes for simulations of Eqs.(1-2). I developed parallel codes (spectral and finite difference) for space dimension two and three in the case of local coupling, and 2d codes in the case of nonlocal coupling. I created computer tools for effective visualizations of simulation data. I also developed computer codes for stochastic partial differential equations, i.e., when Eqs. (1-2) include noise terms.

2. Regulation of biochemical reaction networks

In well stirred systems, for example, in a small volume of a cell compartment, diffusion and coupling by S field can be discarded from Eqs.(1-2). In such cases, Eqs. (1-2) can be reduced to kinetic models, nonlinear ordinary differential equations (ODE). Many important problems, such as enzymatic kinetics, gene regulations, and cell cycle, can be studied by systems of ODE's.

Resonance in chains of enzyme-substrate reactions. I and my collaborating authors studied complex enzyme-substrate reactions leading to oscillatory dynamics. We studied robustness of oscillations against periodic perturbations of parameters and variables, and we established resonance conditions in generic models of enzymatic reactions [22].

Gene regulation in QA cluster of Neurospora crassa. I derived a mathematical model for the quinic acid (QA) gene regulation network of *Neurospora crassa*. We developed a new method, a combination of Monte Carlo and kinetic simulations, called the *Ensemble method*, for identification of parameters in large reaction networks [11]. We successfully compared mRNA levels measured in the experiment with our simulation data and made several important predictions [10].

Cell cycle regulation. We conducted detailed bifurcation analysis of the budding yeast cell cycle model [5]. We also studied a generic model for cell cycles in different organisms: fission and budding yeasts, and frog eggs [3].

3. Controlling turbulence using global coupling

When $\sqrt{D} >> (L, l_p)$ (L is a system size and l_p is a wavelength of characteristic patterns in the system), S field in Eqs.(1-2) describes a global coupling. Surface catalytic reactions of CO oxidations are one example of globally coupled systems. In this system, $\mathbf{X}$ represents concentrations at elementary surface areas, while S field represents the pressure in the air phase. We have shown that global coupling can synchronize chemical turbulence in surface catalytic reactions [21]. We predicted dissipative structures in globally coupled systems [20].

4. Front propagation and pattern formation in reaction diffusion systems

When $\sqrt{D} << (L, l_p)$, Eqs. (1-2) describe locally coupled systems. I studied front propagations in a reaction diffusion system exhibiting Turing patterns [13]. Also, I studied pattern formation of a front in an externally forced reaction diffusion system [8]. We characterized chemical turbulence near cyclic fold bifurcations in birhythmic media [4].

5. Studies of nonlocally coupled systems

When $l_p << \sqrt{D} << L$, Eqs.(1-2) describe nonlocally coupled systems. Research efforts on nonlocally coupled systems have started only recently. We found that a model for a population of biological cells displays a type of turbulence similar to fluids [15,16]. We derived a new self-consistent equation for a nonlocally coupled phase model and found an analytic solution (chimera oscillators) [7]. I found Turing-Hopf mixed mode solutions in nonlocally coupled systems [14]. I also derived conditions for a weak turbulence in the nonlocally coupled phase equation [9]. My parallel simulations revealed that nonlocally coupled systems display chaotic fronts which, unlike fronts in locally coupled systems, can be stochastically synchronized [2].

C. Research on discrete time dynamics, and stochastic simulations

In some complex systems, individual dynamics displayed by the elementary units can be simplified. For instance, the dynamics can be a switch between the discrete states: active(1) and inactive(0). Coupling between the units in these systems can be also simplified by replacing the Laplacian operator with certain rules. Such a discrete modeling of complex systems is called cellular automata. Using cellular automata models, we studied pattern recognition in the multilayer Hopfield neural networks [27]. We also used cellular automata modeling for interactions between spiral waves and target patterns in excitable media [30].

In other complex systems, internal or external noise can play an important role. For instance, in a small volume with a few interacting chemical species, stochastic effects can rule the dynamics. Using stochastic modeling, I studied CO oxidation [1,6] and gene expressions [10]. I also simulated stochastic differential equations with multiplicative random noise [5,16].

II. RESEARCH PLAN

A. A Short Term Research Plan

In theoretical biology, realistic mathematical models are very important. One of the characteristic features displayed by these models, as a result of enzymatic regulations, is birhythmicity, oscillations with two different frequencies and amplitudes. Simulations of biochemical models indicate that the onset of birhythmicity, the cyclic fold bifurcation, plays a crucial role in cell physiology. For instance, cell cycle progression goes through the cyclic fold bifurcation which can be effectively controlled by perturbations. Despite intensive studies of realistic models, we know only an informal condition for birhythmicity, for two variable systems only: double negative slopes obeyed by one of the nullclines. Therefore, it is highly desirable to formulate physical mechanisms leading to birhythmicity for multi-variable systems. Moreover, a theoretical study is needed to find conditions for controlling oscillations between bistable orbits by external forcing, by diffusion, as well as by fluctuations. These are very actual problems. For instance, recent experiments indicate that the cell cycle oscillator is forced by the circadian rhythm. We have a few published, as well as unpublished results on birhythmicity in glycolytic and cell cycle models, and the amplitude

equation for birhythmic media. If I am selected for a faculty position, I would like to continue research on dynamics near cyclic fold bifurcations and on birythmicity. My research plan on birythmicity will include:

• finding quantitative expressions for the cyclic fold bifurcations

• large scale simulations of spiral waves with different winding numbers in 2d and 3d

• derivation of the complex Ginzburg Landau(CGLE) and the phase equations from the glycolytic(*done*) and cell cycle models

• derivation of the normal forms near cyclic fold bifurcations

• characterization of birhythmic turbulence, computation of Lyaponov exponents, and correlation functions for cell cycle model (*done*) and glycolytic model

• simulation of autonomous target patterns in birhythmic media in 2d and 3d

• external forcing of birhythmic oscillators (*we have some preliminary results*)

• simulation of the effects of stochastic noise on birhythmic oscillators

• visualization of simulation data by computer animations

I will involve undergraduate and graduate students in this research. They will collaborate on analytic techniques, and computer simulations and visualizations. Our research will contribute to a deeper understanding of the nature of birhythmicity. The research results will be reported at scientific meetings and published in the leading international journals.

B. A Long Term Research Goal

Cancer study is one of the challenging areas of theoretical and computational biology. I believe that mammalian cell cycle modeling will provide a crucial contribution to cancer research. Recently, significant progress has been made in modeling cell cycles of yeasts and frog eggs, but to my knowledge a systematic research project on mammalian cell cycle modeling has not yet been started. Obviously, this is a very *serious* problem, and it may take many years of hard work. If I will am selected for a faculty position, I am committed to contributing to mammalian cell cycle modeling. At this stage, the main goals of my research plan are as follows:

• *Mathematical model.* A wiring diagram of the mammalian cell cycle is known, but its current version is already very complex, even though it is updated constantly. I expect that my experience in mathematical modeling of cell cycles in frog eggs and yeasts to be very helpful

in converting the mammalian cell cycle wiring diagram into a set of differential equations. I can effectively use computer tools, such as *Gepasi* and *JigCell*, by making the simulation code modular: differential equations modeling different modules of the wiring diagram will appear in different subroutines. Such a strategy will be helpful in classifications of modules according to their functions and in separation of time scales. It will also save CPU time greatly, as in some mutants, simulations of a whole network is unnecessary, because entire modules can be knocked out.

• *Parameter identification.* Because a mathematical model for mammalian cell cycle will have hundreds of parameters, it is expected that most of their actual values will be unknown. Therefore, the central problem is identification of these parameters. I expect the ensemble method we developed for study of large reaction networks will be very helpful. However, the parameter ensemble obtained with the method will go through several filtering steps before being used for actual simulations of the model. First, the parameter ensemble will be sorted into sub-groups according to what bifurcations they generate. Then, the sub-groups that lead to qualitative dynamics in agreement with the cell cycle physiology will be selected. These selections will go through a next level of filtering by comparing simulations with kinetics of real experiments. Next, local optimization methods will be used for further refining the parameter sets.

• *Cancer as a network instability.* Some types of cancer can be associated with reaction network instabilities. Some of these instabilities can be due to coupling between different reaction modules. By considering a reaction module as an active element, a statistical mechanical theory of coupled active units, based on Eqs. (1-2), can be developed to identify network instabilities. Indeed, many interesting ideas based on statistical mechanical approach have been proposed recently for modeling complex reaction networks. Other types of instabilities can be due to coupling between cells and cell populations. I believe that the theory of collective dynamics and synchronization of populations of coupled active units, where my expertise is, will be very useful in the integration of different levels of cancer modeling.

III. TEACHING STATEMENT OF DR. D. BATTOGTOKH

My teaching experience includes three courses, Mathematical Biology, Theory of Solid State Physics and Nonlinear Dynamics. The two semester course, Mathematical Biology, I taught at Mongolian State University, was mainly based on L. Edelstein-Keshet's book *Mathematical Models in Biology.* I also used J. Murray's book *Mathematical biology.* The main topics of this course were basic models in ecology and population biology, phase plane and bifurcation analysis, epidemiology and infectious diseases, and diffusion and advection. The two semester graduate course, Theory of Solid State Physics that I taught at Mongolian State University, was based on the classic books: by J. Ziman *Principles of the Theory of Solids* and by A. Abrikosov et. al. *Methods of Quantum Field Theory in Statistical Physics.* The main topics of this graduate course were electrons in crystals, Hartree-Fock approach, quasi-particles, electron phonon interactions, superconductivity. Finally, the two semester graduate course on Nonlinear Dynamics that I taught at Mongolian Pedagogical University, was based on two books, by E. Ott *Chaos in Dynamical Systems* and Y. Kuramoto *Chemical Oscillations, Waves and Turbulence.* The first part of this course focused on chaos in autonomous systems, and the second part discussed spatio-temporal chaos.

During my eight years of postdoc at different Labs, I shared office space with many students. I think that I helped many of them in making quick progress in their research. As a theoretical physicist, I always try to give to students clear and simple explanations of a problem. And as a interdisciplinary scientist, I try to look into the problems from unifying elements of science. It is essential to tell students how problems arise from real world applications.

If I am selected for a faculty position, I would like to develop an interdisciplinary course on scientific computation. I think that teaching analytic skills is very important even for a course on computation. I will pay special attention to derivation and analysis of mathematical models from basic principles, as the correct mathematical formulation of a problem is the starting point of any computation. Today many students can use softwares like *Mathematica*, *Matlab*, *Maple* etc., but learning numerical methods and algorithmic programming languages is also important, because students who can write computer codes design a better problem-solving strategy.

The interdisciplinary course on scientific computation will focus on four main topics:

• mathematical formulation of problems and rendering a mathematical model in a suitable form for computation

• elementary(e.g. Runge-Kutta method) and high level simulation algorithms(e.g., Monte Carlo method, spectral methods)

• data mining and analysis (e.g., Salford)

• visualization of simulation data(IDL, PW-WAVE)

In this course, students will learn by studying broad scientific problems, such as estimations of fish biomass in water resources, gene regulation, modeling gene expression data, fluid dynamics, spin waves, propagation of reaction fronts, pattern formation and chemical turbulence. One of the main goals of this course will be to make students comfortable and familiar with computation so that they will be able to learn new methods and algorithms on their own.

My long term educational goal is to convert the course on scientific computation into Virtual labs, Web-based software applications designed to provide a flexible user-friendly environment for simulating complex systems. They will be written in the Java object-oriented programming language and are run on a "virtual machine" that can be implemented on any platform. As a result, virtual labs can be accessed not only in the classroom or campus computer labs, but from any machine connected to the Internet. This feature allows students greater freedom in working with virtual labs and makes these tools ideal for distance learning, education for the severely disabled, and other non-traditional modes of instruction.