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Professor Yves Brun
Systems Biology/Microbiology Faculty Search
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Dear Professor Brun,

I learned from a letter by Professor Glazier that you are looking for candidates for a faculty position in systems biology/microbiology. I believe that my enclosed cv demonstrates that I have the characteristics and experience that you seek. I would like to mention that my work experience includes lecturing equivalent to the graduate level in the US and research on biophysical problems such as Turing patterns, Hydra regeneration and calcium dynamics.

As a research assistant at institutes in Germany, Spain and the USA I gained experience on diverse fields of complex systems analysis such as pattern formation, hybrid numerical simulations and cell signalling. I describe prospective topics in the enclosed research statement.

I would be glad to discuss these and other qualifications with you. If you are interested, please contact me at sten.ruediger@hmi.de. I thank you for the consideration of my application and look forward to hearing from you.

Sincerely yours,

S. Rüdiger

Sten Rüdiger

Summary of research – Sten Rüdiger

My work focuses on the development of analytical and numerical methods to study pattern-formation in systems driven out of thermodynamic equilibrium. Projects include examples from nano-materials, biochemical reactions, and morphogenesis. I have written numerical software to analyze these systems from the point of view of phase transitions and nonlinear dynamics. The general aim of this approach is to analyze the transitions from an equilibrium state of a physical or biochemical system to a complex non-equilibrium behavior.

A first project that I want to mention is the **pattern formation in melts of diblock copolymers.** Block copolymers are unique materials with very unusual mechanical and structural properties. The connectivity of the copolymers prevents the macroscopic phase separation observed in homopolymer blends. The chemically distinct blocks can establish a variety of microphases such as lamellar structures and hexagonal arrays of cylinders. Mathematically, model equations similar to classical examples of pattern formation describe the formation and evolution of the blocks. To answer the important question of creation of long-range orientational order under external shear flows I considered a novel approach by coupling the equations for a non-Newtonian fluid to the order parameter equation. I have studied the flow generated by ordered solutions under the conditions of visco-elastic contrast between the two blocks (Rüdiger, 2005). It turned out that for certain orientations, the effective shear flow is either amplified or reduced, which changes the stability of these orientations. The most important feature of this model is that it captures two experimentally observed flips of the preferred stripe orientation.

In collaboration with an experimental biophysics group, I studied a wave-forming mechanism in a biological system. Since a long time it is believed, that the Turing instability underlies many biological growth processes. We study an activator-inhibitor system that is assumed an essential part of the **regeneration process in Hydra**. Hydra is a multicellular organism capable of building up a complete new animal starting from a small group of cells from the body column. In the process of recovery, the cell cluster constitutes a head-specific region, which acts as the organizer for the further development and maintenance of the body structures of the animal. In the past, a reaction-diffusion system, where high levels of an activator morphogen correspond to the head organizer, modelled this process successfully. A recent study found that the expression of a head-specific gene, which signals the establishment of the organizer, coincides with a change in mechanical oscillations of the cell cluster (Soriano, Rüdiger, and Ott, 2005). This suggests that mechanical oscillations of the cluster trigger the formation of a morphogenetic pattern in the system. We showed that an appropriate reaction-diffusion system coupled to periodic variations in its parameters leads to the formation of the head organizer.

In the following, I want to describe two research projects that can be central to my future work. One relates to an experiment in reaction diffusion models, but here most of the theoretical results apply to different systems that exhibit a similar phase transition. I started this work four years ago, but I believe that there are still many open questions and possibilities for further work. The second topic concerns a novel modelling and computational approach on cytosolic calcium oscillations.

1. Spatial and spatio-temporal forcing of pattern forming systems

Reaction-diffusion equations describe many non-equilibrium processes in chemistry and biophysics. To treat the complex nonlinearities of such models, one frequently simplifies the analysis of pattern formation by assuming a homogeneous medium. However, in biological self-organization, perturbations breaking the homogeneity are ubiquitous, since many time-dependent processes and spatial structures such as periodic rhythms and concentration gradients influence these systems. Moreover, perturbations are often externally applied to probe a chemical system experimentally. Often, the applied perturbations imprints unstable modes into the system and one can then observe different mechanisms of relaxation to stable configurations.

A first example is the **spatiotemporal forcing of Turing patterns**. The Turing mechanism is of great importance in biological self-organization. It was predicted 1952 by A. Turing, who showed that the competition between autocatalytic reaction steps and the large contrast in diffusivity of two reactants leads to a stripe forming instability. I studied the effect of traveling-wave forcing to the Turing instability in collaboration with an experimental group. The experiments were performed on a photosensitive CDIMA reaction. We considered the effect of forcing that is spatially of the same scale as the inherent Turing wavelength. Interesting phenomena such as localized structures appear close to spatial resonance. I have examined corresponding model and amplitude equations and found transitions from homogeneous states to modulated waves and moving kinks (Rüdiger et al., 2003). Under certain conditions, a phase diffusion equation that assumes the form of a pendulum equation sufficiently describes the system. For the case of a purely spatial resonance, the localized states in the experiments relate to soliton solutions of the pendulum equation (Rüdiger et al., 2005). Furthermore, I analyzed the interaction of kinks and the stability properties of periodic and non-periodic arrays of kinks.

A natural extension of this work is the effect of spatial and spatio-temporal forcing on **bistable, oscillatory and excitable systems**. Reaction-diffusion systems with bistable, oscillatory, or excitable local dynamics support uniformly translating wave solutions. The spatial wave number and the propagation speed characterize these waves. Further perturbations of the system may occur in form of a standing wave pattern. If the wavelength of the chemical waves and of the external perturbation is similar, then the interaction of the two waves may result in effects similar to those considered above. To my knowledge, this problem was not studied experimentally or theoretically.

There is a second spatial resonance for the case, in which the length scale of the perturbation is of the order of the width of a single front. This problem relates to the problem of localized calcium release caused by the clustering of ion channels (see below). Earlier work by Keener, 2000 and others considered the effect of such localization or **discreteness on the propagation of waves**. If some of the chemical reactions occur at localized spots, their reaction terms must be space-dependent. In contrast to the spatial or spatio-temporal forcing considered above, this perturbation is multiplicative, i.e., a space-dependent factor multiplies the reaction term. Motivated by the clustering of calcium release channels in the endoplasmic reticulum, Keener considered a simple model equation, where the local dynamics is bistable if the system is unperturbed. The distance of the reaction spots is similar to the width of a single front. The localization leads to a disruption of the communication between adjacent reaction sites. For small localization the propagation speed of fronts decreases, for large localization the fronts stop moving (propagation failure). I suggest reconsidering this problem for oscillatory and excitable local dynamics. Furthermore, it is conceivable that the addition of

noise generates very interesting dynamics in the case of interaction with localization. This is in particular interesting as a model for the processes during the generation and motion of waves by stochastic effects and may serve as a model to understand the complex behavior found in realistic models for calcium dynamics considered below.

2. Noise and oscillations in discrete membrane bound reactions

Recently a trend to consider the spatial evolution in biochemical processes at the cellular level has emerged. Traditional approaches such as the study of metabolic or gene-regulatory networks rely on the averaging of protein concentrations over a cell or cell organelle. As it becomes clear that for many cellular processes the spatial distribution is important, there exists a need to import concepts from the well-established theory of pattern formation. Furthermore, the characteristic number of molecules that perform a localized regulatory function such as a membrane bound reaction may be small. Therefore, intrinsic, molecular noise becomes important. There is now more and more evidence that one cannot neglect the associated fluctuations in concentrations.

As an important example of spatial and fluctuation effects, I study the **nucleation and propagation of waves of cytosolic calcium**. I want to clarify to what extent models for the calcium signalling network yield new stable states if one takes into account the combined effects of spatial heterogeneity and noise. Recently Thul and Falcke (2003) showed that the small spatial extent of ion channels destroys the possibility of limit cycle oscillations that are basic to traditional (spatially averaging) models of calcium signals.

Briefly, calcium is an important second messenger in cellular communications. The liberation and uptake by cellular stores and reactions with buffer proteins determine its intracellular dynamics. One such store is the endoplasmic reticulum (ER). Its membrane contains inositol-1,4,5 trisphosphate (IP3) receptor channels, which transiently release calcium from the ER into the cytosol and pumps, which use ATP to pump calcium back against the gradient of calcium. There is a hierarchy of length scales and dynamical processes of calcium release through the ER membrane. Single events are openings and closings of IP3 receptors and result in calcium elevations in nanometer-domains. At the next step, so-called Ca^{2+} puffs comprise the concerted opening of channels in clusters of receptors. An obvious cause for this synchronization is diffusion of calcium to neighboring channels. Finally, the interaction of these local events, again mediated by diffusion, leads to global Ca^{2+} waves, typically of micrometer size, which travel through the whole cell.

Since ion channel molecules are relatively large compared to typical length scales of single release events and puffs, the usual continuum assumption does not apply. Consequently, the release of calcium cannot be spatially averaged. I will incorporate the localization of calcium channels and the ensuing randomness in molecular processes by simulating a set of reaction-diffusion equations with localized source terms and a coupling to Markovian transitions of membrane molecules. Currently I am setting up a simulation package for such hybrid deterministic and stochastic models. The deterministic part of the program utilizes finite elements. The stochastic part is based on the Gillespie algorithm. The following projects will use this computer program.

A first question concerns the **effects of buffers on calcium signalling**. Buffers are calcium-binding proteins that exist in the cytosol and ER, but are also frequently added artificially to the cell to perform experiments. An obvious consequence of the different molecular dimensions of various buffers is their different mobility and thus the different effect on calcium diffusion between clusters. Hybrid computations will identify the various responses by different cells (local and global release events; different forms of temporal modulation of global release activity in a cell upon stimulation with hormones).

Furthermore, recent experiments suggest that buffers not only control the diffusion of calcium between clusters but also the cooperation of the channels inside a cluster and thus presumably its noise level. A precise **resolution of the "fine structure" of a cluster** is therefore useful. A central question of these studies is to relate qualitatively and quantitatively regimes of different calcium signalling with internal parameters. This is specifically important for many neuronal functions, which rely on accurately organized calcium signals. For example, there is evidence that the calcium dysregulation accompanying Alzheimer's disease is related to physiological parameters of the ER membrane such as the activity of pumps (Stutzmann, 2005).

A further very interesting application of the software consists in the study of **effects of external inhomogeneities on calcium waves** in neutrophils. I want to analyze the influence of external perturbations to cellular calcium signaling. Calcium waves are important in the dynamics of collective cellular phenomena such as migration or phagocytosis. For example, during phagocytosis, where a neutrophil cell internalizes a target cell, a calcium wave travels from the membrane to the engulfed target (Kindzelskii and Petty, 2003). This wave promotes the fusion of the target with internal organelles for digestion. I plan to incorporate external perturbations by introducing geometrical and chemical constraints in the computer model and numerically study the response of calcium waves.

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Teaching interests

From the time when I was a graduate student, I have enjoyed working with younger students. This includes advising student projects, teaching problem courses, organizing seminars and giving advanced lectures. During all of these occasions, my aim is to inspire the interest of students and to stimulate if possible their own research work.

I have made first experiences in teaching in the physics departments of the University of Potsdam, Germany, where I held a problem course in nonlinear dynamics. In this course, I gave the undergraduate students their own projects and I supervised the progress of these projects. I also enjoyed the international atmosphere during a summer school on pattern formation in Potsdam. There I was teaching on instabilities of hydrodynamical systems. Later, at the University of Bayreuth, Germany, I taught a problem course to students in the third to fifth year (equivalent to master degree courses). This course was on hydrodynamics. I enjoyed very much the activity of the students that included working on minor research problems with my supervision.

In Bayreuth, I have also taught an advanced lecture on non-equilibrium physics in biology. This course was directed at students of a biophysics program. Because of the international attendants in this program, I held this course in English.

Currently, I am organising the seminar of our theoretical biophysics group at Hahn-Meitner Institute. Talks in this seminar include introductory and advanced topics in cell physiology, numerical analysis and pattern formation. Furthermore, I am advising a diploma and a Ph.D. student who work on numerical simulations of cellular calcium buffers.

I am prepared to teach all undergraduate courses in mathematics and theoretical physics. I would also like to teach advanced courses on nonlinear dynamics, partial and ordinary differential equations. In physics, I am interested in courses on pattern formation, statistical physics and non-equilibrium thermodynamics. Furthermore, I have much experience in computational methods and I would thus like to participate in appropriate computer science courses. As I am becoming more familiar with mathematical physiology, I would like to organize seminars on this topic.