teach these laboratory classes a classroom equipped with personal computers and a license for the software (for example, “Mathematica 4.1 for students”, $85 per PC) installed on them are necessary.

In addition such an interactive course can be placed on the web and utilized for distance education. This will require a so-called “webMathematica” package (webMathematica 2 Pro, $ 9500).

Teaching Experience

1. Courses

1998-2003 I taught four 1-semester courses for **graduates** at the Technical University Munich entitled

1. Micromechanics of Biomembrane
2. Gels and biogels
3. Mathematical description of biochemical reactions
4. Basics of Bioadhesion

The characteristic common to these courses is that they are all related to scientific problems on which the Department is focusing. I gave a basic knowledge of the subjects and discussed the most recent results so as to enable the students to appreciate the challenges and the excitement of research at the cutting edge.

1995/1996 I gave a 2-semester course in **Biophysics** accompanied by **Computer classes** for undergraduates at the Department of Physics of Rostov University, Russia. The Computer classes taught the students to perform computer analyses of problems concerned with the course.

1991/1992 I gave a 2-semester course (192 hours) in **Mathematical Analysis and Calculus** for 2nd year undergraduates at the University of Picardie (Amiens, France) during my work there.

1990 I gave a 1-semester course in “Bifurcations of Nonlinear Equations for Physicists**” at the Department of Physics, Rostov University (Russia) for undergraduates. The aim was to teach students to apply simple methods of analysis of bifurcations of nonlinear equations.**

2. Supervision of students

1996-2004 I was a co-adviser (together with Prof. E. Sackmann) of 4 PhD students-experimentalists (the theses are defended) and the adviser of one PhD student-theorist (the thesis is in preparation)

1988-1991 I was as adviser of the PhD Thesis (defended in 1991, Rostov, Russia)

1986-1990 I supervised the research of 4 diploma students and 3 postgrads.

A. Boulbitch

STATEMENT OF TEACHING INTERESTS

I consider teaching and research as complementary aspects of scientific life. My students like my lectures. In the course of my lectures at the Technical University Munich I was evaluated by graduate students. Such evaluations in Germany are graded between 1.0 and 6.0, where the best note is 1.0. I received the grade 1.6 with the remark "Taught in this way, theory is a real pleasure". My high standard of teaching has been recognized by the Department of Physics of the Technical University Munich by awarding me the Habilitation degree in Theoretical Biophysics in 2001.

I am ready to teach any course for both undergraduates and graduates in offered by Department of Physics. However, I would be especially effective in teaching the courses on Mechanics of Solids with the focus on mechanisms, Thermodynamics as well as on Biological Micromechanics which are most close to my experience (see the chapter Teaching Experience below).

Courses I could offer:

I could propose to introduce two **courses for graduates.** These courses are closely related to different aspects of my research interests. The first of them entitled 'Modern Biological Micromechanics" will contain an introduction to cutting edge results concerning micromechanical properties of biological objects ranging from the level of a single macromolecule up to the cellular scale. Experiments and the experiment-oriented theory will be dealt with.

The second course entitled "Introduction to Soft Matter: Liquid Crystals, Polymers, Membranes" will summarize basic facts and provide a simple theoretical discussion of this rapidly developing area.

Both courses would also be appropriate for engineers or for students with the specialization in Materials Science.

Modern biological micromechanics

?? Theoretical background of modern methods used in micromechanics: AFM, optical and magnetic tweezers, micropipettes, passive and active microrheology.
?? Manipulations with single molecules. Mechanical properties of a single DNA molecule, enforced unfolding of a protein, enforced unbinding of a ligand receptor bond, manipulations with motor proteins, manipulations with a single semiflexible polymer: filamentous actin molecules and microtubules.
?? Multiple molecular bonds. Specific adhesion of biomembranes. Enforced unbinding of multiple bonds.
?? Introduction in mechanical properties of vesicles and cells: vesicles and red blood cells, fibroblasts and endothelial cells, bacteria.

Introduction to Soft Matter: Liquid Crystals, Polymers, Membranes

I. Liquid Crystals.
?? Introduction. Molecules-mesogens. Types of liquid crystalline order in thermotropic liquid crystals: Nematics, Cholesterics, Smectics A, B, C, C*, hexatics and Discotics. Order in liotropic liquid crystals: hydrophilic and hydrophobic interactions, micelles.
?? Transitions in liquid crystals. The transition from the Isotropic to the Nematic phase. The transition from the Nematic to the Smectic A phase.
?? Elasticity of nematics. Elastic constants. Anisotropy of a dielectric and magnetic susceptibility. Effect of magnetic field in nematics. Frederick's transition.
?? Optical properties of cholesterics. Elastic properties of smectics. Motion of smectics. Acoustics in smectics.
II. Polymers
?? A freely joint polymer chain. Flexibility. Size. Persistent length.
?? Gaussian coil. A Gaussian chain in an external field. Adsorption of a chain.
?? Polymer chain with volume interactions. Coil-globule transition.
?? Dynamics of a polymer. The Rause and Zimm models of the coil motion. Dynamic properties of real coils. Reptation model.
?? Semiflexible polymers. DNA and actin as semiflexible biopolymers. Persistent length of a semiflexible polymers. End-to-end distance in semiflexible polymers. Liquid-crystalline order in polymers.
III.Membranes
?? Lipid molecules. Formation of membranes. Energy of a curved membrane (Helfrich energy). Vesicles.
?? Shape transformations in lipid vesicles.
?? Adhesion of vesicles.

Special Teaching Technology

In my work I use a lot a software for making analytical calculations (such as Mathematica). I would be interested in developing a course with Mathematica-based classes aiming to teach students to solve problems analytically and numerically using such software. The most efficient method would be in combining lectures with the "laboratory" Mathematica-based classes. Each session can be started with a short discussion of available approaches, and continued by each student working at his/her terminal with files prepared for this purpose. In order to

Project 3.
Dynamics of enforced unbinding of the membrane

Membrane unbinding. Based on the equation of adhesion dynamics recently established by the applicant[38]. I will study enforced unbinding of the membrane in relevant geometries. To understand typical features of the unbinding dynamics I will first analyze unbinding of the membrane in simple configurations such as

?? enforced unbinding of an adhered stripe pulled by one of its ends

?? enforced unbinding of a cylindrically-symmetric membrane pulled in its center.

I will then study

?? the unbinding of the adhered a vesicle sucked into a micropipette (as used in the measurements[36]).

Control of the adhesion dynamics by the amount of repeller molecules. I will study a system consisting of mobile ligands and repellers reconstituted into a biomembrane adhered on a substrate covered with receptors. I will deduce the kinetic equation which takes into account the effect of repeller molecules and the adhesion dynamics depending on the relative amounts of ligands, receptors and repellers.

Effect of pinning center on resistance to unbinding. Formation of clusters consisting of a group of receptors is usually followed by local membrane pinning. I intend to describe kinetics of unbinding of a single pinning center and of a pinned membrane and its control by a configuration of pinning centers and by the number of ligand-receptor pairs constituting the pinning center.

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The analytical approach. Simulations will enable me to describe the motion network in front of the moving bead. My aim is to obtain the force acting on the bead from the network and resisting the bead motion, and to deduce equation of motion of the bead.

Project 3
Simulation of Micro- and Macrorheology of the Networks with Nematic Ordering and/or Cross-linking

Simulation of macrorheometry. The microrheometry simulation will be done as described in the Project 2. To simulate the macrorheometry within the Dissipative Particle Dynamics approach I will model the entangled network in a box as described above. One of the walls of the box will be kept oscillating along its own plane. The non-slip boundary conditions will transmit the oscillations to the network. With these systems I will model the reological measurements in

?? networks with the weak and/or specific cross-linkers

?? networks whose concentration is close to that of a nematic ordering.

Weakly cross-linked network. We will study weakly cross-linked network (with the binding energy of few kT) which is typically mediated by divalent ions or salt bridges. First by simulations and then analytically we will analyze the effect of the weak cross-linking on the self-diffusion of the polymers and on the enforced bead motion.

Specifically cross-linked networks. Different type of molecules provide various types of specific cross-linking of actin networks *in vivo*. On this stage our aim is to develop a simple model of the specifically cross-linked network with the stress-dependent affinity of the cross-linkers and to test its viscoelastic properties.

Measurement-induced nematic ordering of the network. Nematic ordering of the network of semiflexible polymers can be induced by steric interactions (as soon as its concentration exceeds a certain value) and is assisted by the cross-linkers. Conditions which cause the nematic ordering of the network may be achieved locally in front of the moving bead giving rise to a non-linear microrheological response. I will simulate such a system search for the local ordering and characterize the resulting non-linearity.

II. Theory of dynamics of adhesion of biomembranes and its control by mobility, affinity and clusterization of ligand-receptor pairs, and by mechanical stress

Introduction. Though adhesion of cells represents an essential stage in various biological processes [21] its physical basis is still poorly understood. The importance of this area is demonstrated by the fact that nearly 21000 publications on adhesion appeared during last few years [22]. Despite of the biological relevance few theoretical models have been proposed recently to describe specific interactions between biomembranes[22-31]. To study basic physical properties of specific adhesion one needs a simplified model experimental system. Recently such a model system has been developed. It revealed new properties of the adhesion[32-36]. Theoretical description of these new features is addressed in the present proposal based on the recent results of the applicant[37, 38].

Project 1
Adhesion and unbinding of a membrane due to the competition of chemical reactions

Unbinding by a competitive inhibition. A very important biological situation is the impeding of adhesion by antibodies to receptors. Experiments show that the adhesion process is very sensitively affected by antibodies in the bulk phase. This yields a tool to control the adhesion process. A mathematical model will be developed to describe the observed weakening of adhesion depending on the concentration of antibodies in the bulk.

Adhesion in the presence of two competing ligand-receptor pairs. A usual situation in bioadhesion is that two types of ligand-receptor pairs compete. I will study a membrane-substrate system carrying two types of ligand-receptor pairs possessing different values (i) of the lateral diffusion coefficient, (ii) of the dissociation constants, (iii) of the reaction rates and (iv) of the ligand-receptor distances. I expect that such a system will exhibit different regimes of the adhesion kinetics.

Project 2
Adhesion triggered by the aggregation or the lateral phase separation of receptors

Dissociation constant of ligands and receptors during phase separation. I will study the interplay of the phase separation and chemical equilibrium in the ligand-receptor system. The aim is to establish a phase diagram in coordinates temperature-concentration and its relation with the weak and strong binding of the ligand-receptor pair.

The lateral phase separation of receptors during adhesion. Two particularly interesting situations to be studied are the following.

?? If adhesion occurs only in the high-concentration phase, one can expect that the process will be dominated by the phase separation. I will study the effect of the kinetics of the phase separation on the kinetics of adhesion.

?? The lateral attraction between the receptors may arise due to their binding to ligands. I will study how in this case adhesion triggers either the phase separation process of receptors or their aggregation in clusters.

Lateral phase separation of receptors induced by mechanical loading of the membrane. The mechanical loading of the membrane shifts the chemical equilibrium of the ligands and receptors. In the system in which the phase separation is coupled to the ligand-receptor binding this should induce the phase transition. Various scenarios of such a transition under the mechanical load will be studied within this project.

A. Boulbitch

RESEARCH PLANS

In my research I will focus on new aspects of mechanical behavior of biological objects (such as biomembranes, biogels, single biomolecules, etc.) following from (i) their **meso- or nanoscales** and (ii) from the **interplay between their mechanics and biochemistry**. My **research proposals** (see below) are divided into 2 groups.

The first group deals with a simulation of micromechanical behavior of **semiflexible polymers and their networks during micromanipulations.** As a model semiflexible polymer the filamentous protein actin will be studied. The simulation will be followed by analytical estimates.

The second part groups projects involving development of a theory of **dynamics of spontaneous adhesion and enforced unbinding of biomembranes**.

Below these projects are briefly outlined.

I. Modeling of actin filaments and actin networks: manipulation with single filaments and microrheology

Introduction. The filamentous protein, F-actin, is a major component of the cytoskeleton which makes it possible for cells to bear and respond mechanical loads. Its *in-vivo* coontour length ranges from few to few tens micrometers, diameter is 9nm and the persistent length is 17?m.

A single actin filaments can be manipulated by optical tweezers[1, 2], by the use of magnetic tweezers[3], or by the functionalizing of a surface[4, 5].

Semi-dilute solutions of F-actin exhibit viscoelasticity even without cross-linking[6]. Mechanical behavior of actin filaments in solution was studied experimentally by several techniques, such as dynamic light scattering[7], enforced oscillations[8], macrorheology[9] and magnetic tweezers[3, 10-14]. The main challenge is to understand the viscoelastic properties of actin networks.

Theoretical models have been proposed to describe the high-frequency viscoelastic behavior of the semi-dilute actin solutions (see recent reviews[15, 16]. However, the most biologically interesting low-frequency properties of actin networks are still not understood.

Prerequisites: computer simulation code. The project requires computer simulations. In collaboration with Prof. D. Pink (St. Xavier University, Antigonish, Canada) we developed a program exploiting the so-called Dissipative Particle Dynamics method enabling one to simulate such a multi-scale system as actin network in water. The program successfully works[17].

Project 1
Simulation of the Molecular Weaving Loom

This proposal is motivated on the one hand by a four-head, 10nm-step micromanipulator mounted on the inverted microscope which is under the development by Prof. Dr. L. Pagel (Institut für Gerätesysteme und Schaltungstechnik, University Rostock, Germany) and on the other hand by the experimental manipulation with actin filaments[1, 2]. Such a set up enables one to manipulate simultaneously with several micro-objects, such as actin filaments. In this project I address the possibility of spinning the actin bundle out of single molecules or a network (**molecular spinning**), and formation of ordered structures out of such filaments and bundles (**molecular weaving**).

Molecular spinning. The process of formation by a micromanipulator of a braid out of single biochemically stabilized actin molecules as well as of bundles previously formed from such molecules will be studied. The electrostatic interaction and divalent ions will be accounted for to understand

?? possible algorithms of the manipulation
?? the character of motion of the filaments during the manipulations depending on the pH and the salt concentration
?? forces and torques required.

Molecular weaving. We will develop and simulate simple algorithms of formation of a sheet of textile out of several filaments (bundles of filaments).

Stabilization of the thread and tissue. In this part of the project various scenarios of using specific cross-linkers will be simulated.

Project 2
Microrheology of actin networks: simulation and analytic theory

This proposal is motivated by recent experiments[18] revealing a new regime of the behavior of the actin network.

Simulation of the enforced motion of the bead through the entangled network. A simulations of the enforced motion of the bead through the actin network will be performed using the Dissipative Particle Dynamics approach. The latter is known to account correctly for the hydrodynamics. The entangled network consisting of polymers in water will be simulated in a box whose size exceeds the polymer length. The bead will be embedded into the network and subjected to a constant force. This is expected to establish relations between the system parameters and to study the character of motion of polymers in the vicinity of the bead.

Simulation of a two-bead microrheometry. The two-bead microrheometry has been used to characterize the network[19, 20]. We will simulate the network containing several beads and extract the autocorrelation functions of fluctuations of the beads. This will enable us to establish how the binary and many-body correlation functions depend on the parameters of the system such as the concentration of the polymers, their contour and persistent length, the vis cosity and the temperature of the solvent.