NATO ADVANCED STUDY INSTITUTE

Dynamics of Complex Interconnected Systems: Networks and Bioprocesses

Geilo, Norway, 11-21April, 2005

Lecture Abstracts

Physics in the Brain

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ABSTRACT

The fantastic properties of the brain are due to an intricate interplay between billions of neurons connected in a complex network. A central challenge is to understand such network behaviour and establish connections between properties at the microscopic level (single nerve cells) and measurements of brain activity at the macroscopic systems level (using, for example, MEG, EEG, PET, or fMRI).

The primary goal of the lectures is to give the students an introduction to how physics and mathematical modelling can be used to explore this pertinent question.

An outline of the topics of my two 45 minute lectures can be:

- Brief overview of brain structure

- Single nerve cells
  - Biophysical, detailed modelling of nerve cells (one of the biggest success stories of mathematical biology)
  - Illustration of various simplification schemes to obtain more simplified (and thus more tractable) nerve cell models. In particular the so called *integrate-and-fire model* (a workhorse for theoretical exploration of neural network properties) will be described

- Early visual system and examples of network modelling
  - Organization of early visual system (retina $\Rightarrow$ LGN $\Rightarrow$ visual cortex)
  - The concept of *receptive field* of a nerve cell
  - Modelling of LGN responses to various visual stimuli

- Modelling and measuring cortical neural network activity
  - Example of modelling of short-term memory in prefrontal cortex
  - Connection between single-neuron activity and systemic measurements of neural activity (MEG, EEG, PET, or fMRI).
  - Measurement of neural activity in *populations* of cortical neurons using laminar-electrode recordings of extracellular electrical potentials

Clays as Example of Soft and Complex Matter: From Nano to Macro

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ABSTRACT

Clays may be used as experimental model systems for the physics of soft condensed matter, i.e.materials that are easily deformable by externally applied stresses, by electric or magnetic fields, or simply by thermal fluctuations, The level of description for such complex materials typically often starts at the nano scale, i.e. at scales larger than atomic or molecular scales, and the structure and dynamics at the nano scale determine macroscopic physical properties at the human scale. One overall goal of this kind of research is thus to probe and understand the relationship between nano scale and macro scale physics. In general, the materials under study include both natural, synthetic and biological materials, and the broad range of research interests range from fundamental physics to technological applications, from basic materials questions to specific biological problems. Experimental physicists involved in the Complex Systems and Soft Materials (www.phys.ntnu.no/complex) Strategic University Program (SUP) in Norway work together in order to explore this exiting field of physics, and experimental techniques within this SUP range from small table top set ups to advanced international high tech facilities, and include visible light scattering, synchrotron x-ray scattering, neutron scattering, optical microscopy, AFM, ultrafast imaging techniques, rheology and others. In this presentation, we wish to explain how our recent experimental studies of complex physical phenomena in synthetic clays may teach us many general lessons about how the nano world translates into the macro world, and how clays may be made smart. The research is sponsored by the Research Council of Norway through the SUP and NANOMAT Programs.

Main collaborators include: NTNU: Yves Meheust, Ahmed Gmira, Davi de Miranda Fonseca, Kanak Parmar, Kate Washburn, *University of Oslo:* Knut Joergen Maaloey, Grunde Loevoll, Bjoernar Sandnes, *Institute for Energy Technology (IFE), Norway*: Kenneth D. Knudsen, Geir Helgesen, Arne Skjeltorp, *University of Brasilia:* Geraldo Jose da Silva, Jerome Depeyrot, Francisco Augusto Tourinho, Fabio Luis de Oliveira Paula, as well as Fernando Oliveira, *LNLS, Campinas, Brasil:* Roosevelt Droppa.

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Electrical Impedance Analysis of Mammalian Cells.

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ABSTRACT

A unique method and appropriate instrumentation to quantify the behavior of cells in tissue culture has been developed in our laboratory over the last decade. The technique is referred to as Electric Cell-substrate Impedance Sensing (ECIS). (www.biophysics.com) The basic principle of the new method is to culture mammalian cells on small gold electrodes. When cells attach and spread on these electrodes, the measured electrical impedance changes because the cells constrain the current flow. By monitoring the impedance of the cell covered electrodes, the morphology and motion of the cells can be inferred in real time. . The electrical characteristics of the system can be modeled with 3 parameters, the intercellular resistance (R_b), the cell-membrane capacitance (C_m) and the cell-substrate separation (α).

Since these behaviors, such as spreading and locomotion, involve the coordination of many biochemical reactions, they are extremely sensitive to most external parameters including temperature, pH, and a myriad of chemical compounds. This broad response to changes in the environment allows this method to serve as a general biosensor

The Shape of Cracks

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ABSTRACT

Look closely next time at a concrete wall containing fractures. They form a network of seemingly erratic lines but with masks with a well-defined length scale. I will in this talk discuss the various aspects of fracture networks and describe the ongoing research in this field. Starting with the geometry of the network itself, based on geological studies, I will move on to describe the morphology of single fracture surfaces emphasizing their surprising scaling properties.

Diffusion, Fragmentation and Merging Processes: Ice Crystals, alpha Helices and Scale Free Networks

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ABSTRACT

We investigate systems of nature where the common physical processes diffusion, fragmentation and merging compete. Initially, without merging we derive a rate equation for the size distribution of fragments. The equation leads to a third order differential equation which we solve exactly in terms of Bessel functions. The stationary state is a universal Bessel distribution described by one parameter, which fits perfectly experimental data from two very different system of nature, namely the distribution of ice crystal sizes from the Greenland ice sheet and the length distribution of alpha-helices in proteins [1]. Adding a merging term, the distribution generally changes its tail from the Bessel-like behaviour to a pure exponential [2]. Without diffusion, we find a specific critical point, with a balance between the fragmentation and merging events, where the distribution becomes scale free with scaling exponent of -3/2 [3]. This is supported by a numerical model in which the total mass is conserved leading to a scale free distribution over five decades. This model is easily generalized to a dynamical network where the number of links and notes are conserved [3].

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Principle of in-vitro gene expression; application to a vesicle bioreactor and to self-reproducing systems

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ABSTRACT

We show first how a temperature gradient can lead to giant DNA accumulation by thermophoresis and to DNA sequence amplification in a convection set-up. Non-equilibrium thermodynamics can thus help to solve some nagging problems of critical concentration and sequence selection in a prebiotic soup.

We show that a vesicle bioreactor can function for many days in a homeostatic state producing proteins. This is a first necessary step to artificial cells. The next step will be vesicle replication.

Detecting topological patterns in complex networks

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ABSTRACT

My lectures are currently scheduled to be given on two consecutive days. On the first day I will be talking mostly about the topological properties of bio-molecular (protein) networks while on the second day I will concentrate on networks behind Internet which operate on two very different levels:
1) that of interconnected Autonomous Systems (AS) corresponding to all servers and routers of big companies, universities, etc.
2) that of WWW webpages connected by hyperlinks.

Day 1: Bio-molecular networks lack the top-down design.
Instead, selective forces of biological evolution shape them from raw material provided by random events such as gene duplications and single gene mutations. As a result individual connections in these networks are characterized by a large degree of randomness. One may wonder which connectivity patterns are indeed random, while which arose due to networks's growth, evolution, and/or its fundamental design principles and limitations?

Here I will introduce a general method [1,2] allowing one to construct a random version of a given network while preserving the desired set of its low-level topological features, such as, e.g., the number of neighbors of individual nodes, the average level of modularity, numbers of small network motifs, etc. Such a null-model network can then be used to detect and quantify non-random topological patterns. In particular, we measure correlations between numbers of neighbors of interacting nodes in protein binding and regulatory networks in yeast [1]. It was found that in both these networks, links between highly connected proteins are systematically suppressed.

I proceed by presenting a set of empirical findings about how gene duplications shape protein interaction and genetic regulatory networks in several organisms [3]. I will also describe how the ability of a protein to self-interact (form a homodimer) is affected by topological properties of protein interaction network around it [4].

Day 2. On this day I will describe how a virtual diffusion process on a given network allows one to detect its highly interconnected modules and its "extreme edges". For the Internet on the level of Autonomous Systems the modules defined by this method correspond to individual countries [5]. A very similar diffusion-like algorithm is behind a popular web-search engine Google. I will proceed by describing how a modular (community) structure of the World Wide Web affects the ranking of webpages within individual communities [6].

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Organisation of living matter, from the single molecule to whole cell level - an optical study

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As optical tweezers and image based analyses are nearly non-invasive we use these nano-techniques to investigate physical properties of living organisms from the single molecule to the whole cell level. The first part of the talk will introduce optical tweezers and related techniques, in particular pointing at the principles behind and the calibration nescessary for a thorough understanding of the results obtained.

The main part of the talk will focus on applying the optical techniques to study biological systems which are involved in the central dogma of molecular biology, namely DNA, RNA and proteins at the single molecule level:

The TATA-binding protein is a promoter for the polymerase, and as it specifically binds to a TATA-box sequence in DNA it bends the DNA by ~80 deg. By observing the Brownian motion of a bead tethered by a DNA string containing a TATA-box individual on and off events has been observed, the binding kinetics deducted, and the study has even revealed the presense of intermediate states in the binding pathway.

When the ribosome during translation of RNA encounters a pseudoknot it often performs a frameshift. This frameshift might be related to the mechanical strength of the pseudoknot. To probe this hypothesis we have genetically engineered different pseudoknots giving rise to different degrees of frameshifting and are presently unripping the pseudoknots to get a measure of its mechanical strength.

Then the talk will concern the organization and motility of a single protein, a lambda-receptor, in the outer membrane of living E. coli bacteria; the protein is found to exhibit tethered diffusion within an area of linear dimension around 50 nm. Also, this motion is found to be not only a thermal motion but to have an active component too.

The final part of the talk takes one step up in complexity and focuses on the organization and functioning of a whole living cell. By optically tracking the motion of lipid granules naturally occuring inside living S. Pombe yeast cells we monitor the viscoelastic properties of the cell cytoplasm, where different types of diffusional motion are observed. Also, the topological changes of the cell envelope during the division cycle are investigated.

Molecular mechanisms in biosignalling: visual reception

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ABSTRACT

There are three physiological phenomena of visual reception: phototransduction, light and dark adaptation, and colour discrimination (colour vision). Molecular mechanisms all of these phenomena, first of all phototransduction, will be considered.

Visual phototransduction, the conversion of incoming light to an electrical signal, takes place in the outer segments of the rod and cone photoreceptor cells.

Light reduces the concentration of cGMP, which, in darkness, keeps open cationic channels present in the plasma membrane of the outer segment. $Ca2+$ plays an important role in phototransduction by modulating the cGMP-gated channels as well as cGMP synthesis and breakdown. $Ca2+$ is involved in a negative feedback that is essential for photoreceptor adaptation to background illumination.

Visual phototransduction represents one of the best-characterized G-protein-coupled receptor-mediated signaling pathways. Structural analyses of visual pigment rhodopsin, G protein, and several other phototransduction components have revealed common folds and motifs that are important for function.

Given the accelerated pace of structure and functional determination, it is anticipated that visual phototransduction will be the first G-protein-coupled pathway for which a complete molecular description is ultimately available.

Because light in vision is not only a carrier of information, but also a risk factor of damage to the eye structures, the complex photoprotective system, along with physiological system of visual reception, has been developed in the course of evolution. The sophisticated photoprotective system is able to solve the photobiological paradox of vision. The impairment of the system can lead to human retina diseases or play role in progression of eye diseases like age-related macula degeneration.

Molecular mechanisms of potential light hazard to the eye structures, first of all to the retina, and main components of natural photoprotective system (permanent renewal of rod and cone outer segment, antioxidants and optical media of the eye) will be considered.

The Minority Game: statistical physics of adaptive cooperatioon of speculative agents in a market

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ABSTRACT

The minority game is a simple model emulating aspects of the a system of speculative agents in a stockmarket. It poses several interesting issues as a frustrated disordered many body system, complementary to those in normal condensed matter physics but of possiblerelevance to other situations requiring prediction on the basis of incomplete information and learning from experience, and exhibits interesting cooperation, phase transition and non-ergodic, as well as ergodic, behaviour.

Both simulations and analytic techniques developed for spin glasses, both thermodynamic and dynamic, can be employed to study, expose and understand these systems and open the door for extensions.

I shall provide an overview of interesting aspects of the problem from the perspective of statistical physics and then report some recent studies of the effect of strategy correlations and timing of adaptation in minority games, which turn out to be relevant and instructive. This will involve a combination of simulations and analytic studies, especially the use of an exact generating functional approach complementing replica studies of statics.

Braided Space-Time Particle Networks

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ABSTRACT

The lecture will address the following problems:

- Complex dynamics of magnetic particles dispersed in fluids (ferrofluids)
- Particle response to ac magnetic fields

We approach these problems by:

- Introducing "world lines" – in space-time description of the particle trajectories.
- Using braid theory and rank-ordering statistics to describe the networks of " frozen dynamics" of the particles.

Our findings:

- Braids are useful for compact description of space-time particle network trajectories
- First experimental verification of the Zipf-mAndelbrot relation
- Good agreement between numerical simulations and observations

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The SOS response of bacteria to DNA damage at the single cell level

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ABSTRACT

Upon encountering damage to their genomes, bacteria such as E. coli respond by activating a set of about forty genes whose task is to repair/bypass the DNA damage, in order to enable DNA replication and thus cell division. The SOS genetic network deploys a variety of specific functions such as detecting damage, repairing it correctly by nucleotide excision (the NER mechanism) or by recombination, and if these functions do not succeed, bypassing damage by mutagenesis. The activation of all these functions requires a high degree of coordination and regulation, whose understanding is poor in spite of decades of study. I will survey recent findings in which the execution of the response was followed at the level of single cells. These findings illuminate certain aspects of the concerted response, which are inaccessible to techniques in which large cell ensembles are interrogated. In particular, the findings show that the response exhibits highly precise modulations in the activation of a number of gene promoters, modulations which possess a digital character. Importantly, the precise timing mechanism responsible for the modulations is independent of the cell cycle, the main built-in clock of the cell. Genes responsible for the precision are identified. I will highlight the importance of this network as one of the main forces driving the evolution of bacterial genomes, and skim over the behaviour of the wonderful molecular machines driving the SOS network.