

Interacting Particles and Computational Biology

January 10 - March 10, 2003

The primary aim of this two-months period was to introduce researchers in mathematics, especially Ph.D. and Post Doc students, to a number of modern research topics in mathematical biology, with special emphasis on probabilistic models. The period focused on questions related to the collective behaviour in biological systems, the self-organisation and patterns formation arising from elementary local interactions. Several biological systems have been discussed, ranging from molecular biology to animal societies. Tools from probability, statistical physics and other sciences of complexity have been presented and applied.

The activity consisted mainly in lectures series of about 5-10 lectures, and a number of research talks by invited speakers and young participants. The Scientific Committee was formed by Jean-Louis Deneubourg (University of Brussels), Yuri Manin (Max-Planck Institut), Hans Meinhardt (Max-Planck Institut), Philippe Mathieu (International Solvay Institutes, Brussels), Franco Flandoli (University of Pisa).

The Local Organising Committee was formed by Mariano Giaquinta (Scuola Normale Superiore and De Giorgi Research Centre), Franco Flandoli, Philippe Mathieu, and Giuseppe Tomassini (Scuola Normale Superiore). Moreover, an essential and constant help in the organization was given during the period by Marco Isopi (University of Bari and New York University), who spent the whole period in Pisa.

Brief description of the courses

Thierry Aubin (NAMC- CNRS, Paris Sud), February 3-8
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How to understand the acoustic communication in animals

Acoustic communications, as other communication ways, follow always the same principle: an emitter codes a message which become a signal. This signal, transmitted through a channel of transmission (air, water, solid), is modified because of the limitation of the channel and of the noise generated by the environment. Then, the signal is "decoded" by a receiver and interpreted as a message, message which elicits a behavioural response. Thus, to fully understand an acoustic communication, it is necessary to study each step of the process. This implies:

- to study the coding process, by analysing the structure of the acoustic signal in the time, frequency, intensity domains;
- to evaluate the modifications of the signal during its propagation in the environment;
- to realise experiment with acoustic lures, i.e. to use modified signal broadcast to the animal and to observe the behavioural responses in order to emphasise the key parameters supporting the information.

The lectures have illustrated these ideas and presented two examples: the individual recognition by voice between pups and mothers in fur seals and the individual recognition by voice between mates in penguins.

Vincenzo Capasso (University of Milan)

<http://sauron.mat.unimi.it/~miriam/capasso/Capasso.Vincenzo.html>

Collective behaviour of large populations of interacting active individuals in Biology and Medicine

The course provided an introduction to the mathematical modelling of the collective behaviour of interacting active individuals subject to stochastic fluctuations. Current interest concerns how do properties on the macroscopic level depend on interactions at the microscopic level. Such processes play an important role in biological and social phenomena. The lectures showed how by rather simple models based on stochastic differential equations one may gain remarkable insight in the behaviour of complex systems.

The first part of the course reviewed basic facts, like the source of randomness and other features in interacting individuals, fundamentals on stochastic processes with independent increments, Markov processes and martingales, the Poisson and Wiener processes, and the basic paradigm of the rescaling from the simple random walk to the Brownian motion. Then more advance topics related to diffusion processes, stochastic differential equations and convergence of probability measures have been presented. With these tools, Ito formula was applied to the study of the empirical measure of a system of interacting particles, to understand the rescaling at a mesoscale. Finally, other asymptotic questions have been addressed, about population processes and convergence to ODE's, and similarly for spatially structures populations and convergence to PDE's. Examples in biology have been presented at several instances.

Alessandra Carbone (IHES)

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Cooperativity and Symmetry at Biological Scales

The lecture presented basic ideas behind cooperativity and symmetry in the cell. Biological scales were intended in a broad sense and referred to bio-molecular structures as well as supra-molecular and cellular organizations.

Synonymous codon bias and gene expression

The lecture described an algorithm, based on a measure of codon bias similar to a relative entropy, called Codon Adaptation Index, devised to detect dominating synonymous codon usage bias in genomes. With the set of coding sequences as a sole source of biological information, the algorithm provides a reference set of genes which is highly representative of the bias. An important application concerns the detection of a reference set characterizing translational bias which is known to correlate to expression levels; in this case, the algorithm becomes a key tool to predict gene expression levels, to guide regulatory circuit reconstruction, and to compare species.

J.P. Crutchfield (Santa Fe)

<http://www.santafe.edu/~chaos/>

Patterns and Pattern Discovery

The lectures started from the problem of quantifying structures with respect to randomness. Measures of randomness are quite classical, but the world is often highly structured and the description of them is less understood. The questions are: what is a structure? How do we detect and then describe and quantify natural patterns? The lectures developed an answer

to these questions, providing both mathematical foundations and concrete analysis of familiar complex systems. Patterns originated in cellular automata have been investigated in great detail.

Felipe Cucker (University of Hong Kong) <http://www.cityu.edu.hk/ma/staff/cucker.html>

Learning theory

The lectures presented the mathematical theory of learning developed by Cucker and Smale. Application to evolutionary linguistics and other problems have been discussed throughout the whole lecture course.

At the beginning, the fundamental concepts of learning theory have been given, starting from examples like curve fitting, recognition of hand-written characters, Monte Carlo integration, PAC learning. In general terms, the goal of learning theory is to find an approximation of a function known only through a set of data drawn from an unknown probability measure.

The formal setting was developed, based on concepts of statistics (like sampling and hypothesis space) and of functional analysis (like Sobolev and reproducing kernel Hilbert spaces). A number of rigorous results have been given, usually expressed as probabilistic bounds on various errors arising in the estimation procedures.

A second approach based on the concept of regularisation was then presented, a modern and adapted version of the theory of Ivanov and Tikhonov on inverse problems. Other confidence estimates have been derived by this approach. Relevance for applications and problems arose by them have been discussed.

Patrick de Kepper (CNRS Bordeaux)

http://www.crpp.u-bordeaux.fr/index.php?rubrique=2&page=activite_scientifique.php&activite=253&sujet=455

Turing structures and other reaction-diffusions in open chemical reactors

In 1952, the British mathematician Alan Turing suggested that reaction and diffusion processes could combine to produce stable chemical patterns and that such a mechanism was adequate to account for some fundamental aspects of pattern and shape development in biological systems. Turing's counterintuitive idea that diffusion, a process that usually wipes out any concentration heterogeneity in a solution, can participate in the spontaneous formation of well organised stationary concentration patterns when associated with appropriate chemical reactions became an object of theoretical speculations and of pursuit for experimental chemists and biologists.

The lectures described the basic ideas of the theory and showed several recent experimental studies of chemical Turing patterns and other reaction-diffusion structures in open chemical reactors.

J.-D. Deuschel (TU Berlin)

<http://www.math.tu-berlin.de/stoch/HOMEPAGES/deuschel.html>

Random effective interface models

The lectures focused on the understanding of the ergodic properties of some large interacting stochastic system: the Ginzburg-Landau model. This is an effective model describing the dynamic of a random interface. The lectures were mainly concerned with convergence rates to equilibrium and with the entropic repulsion. These phenomena take place when the interface is delocalized under the effect of a reflective wall. The

mathematical tools are provided by the random walk representation that expresses the covariance of the interface in terms of the Green function of a symmetric random walk in random environment. Aging phenomena, taking place when the process starting far away from equilibrium exhibits a long time memory, have been also discussed.

One of the objective of these lectures was to present some techniques which could be applicable in various other situations, like models in population genetic such as the stepping stone model.

Mauro Giacca (Scuola Normale Superiore)

<http://www.icgeb.trieste.it/RESEARCH/TS/Giacca.htm>

Introduction to Molecular Biology:

Mammalian stem cells: from cell fate determination to therapeutic applications

Complex organisms all develop from undifferentiated, pluripotent cells that, along the course of differentiation, progressively acquire specialized functions. Stem cells and specialized cells share the same content in terms of genetic information, but express different sets of genes. The understanding of the molecular events underlying stem cells proliferation and differentiation, and the possibility of obtaining stem cells by cloning, will open the way to a number of clinical applications for the treatment of human degenerative disorders.

Combinatorial protein complexes governing DNA transactions (replication, gene expression, recombination and repair)

Most molecular events in eukaryotic cells are carried out by large protein complexes. The specific participation of individual proteins to the formation of these complexes often dictates complex specificity and permits the achievement of sophisticated levels of regulation. In the post-genomic era, the study of protein complex formation can be now tackled by the use of microchip hybridization, to visualize gene expression levels, and by proteomics, to analyze protein content and post-translational modification.

Giambattista Giacomini (University of Paris VII)

<http://www.proba.jussieu.fr/pageperso/giacomini/GBpage.html>

Localisation phenomena in polymer models

The lectures focused on basic models of directed polymers interacting with an environment, like either the case of a polymer composed by monomers that are attracted to certain spatial regions or heterogeneous polymers whose monomers present competing tendencies. Particular stress was put on some aspects of statistical mechanics modelling of DNA/RNA chains, on localization of polymers on fixed structures, wetting phenomena and delocalization transition induced by pulling and DNA unzipping. The key issues was the understanding of the underlying entropy-energy competition.

Attention was restricted to simple models on which one can obtain rigorous results, and presented in detail mathematical techniques as well as the field of applicability beyond the specific model. The central mathematical tools were the ones of Large Deviations.

Marco Isopi (University of Bari & Courant Institute New York)
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Modelling stem cells: from ODE's to particles systems

The aim of this series of 15 lectures, divided into three parts, was to give an overview of mathematical modelling of stem cell dynamics with emphasis on stochastic models and discrete models with a spatial structure. Relevant mathematical notions were introduced when not familiar to the audience. The use of computer simulations was discussed with the help of a tool available to the students to experiment with. The first part of the course presented a description of stem cell dynamics: why we need to model it and what are the difficulties involved; the concepts of homeostasis and hematopoiesis of the stem cell system; extrinsic vs. intrinsic control; strong stability w.r.t. perturbations, recovery after exposure to radiations.

First mean field models have been presented, deterministic, based on ordinary differential equations as well as a dynamical systems approach, the so called "chaos hypothesis" of Furosawa-Kaneko.

In the second part, a second class of mean field models, of stochastic nature, have been presented. The subject were an introduction to the arguments for the stochastic nature of stem cell dynamics, birth and death processes, stochastic stem cell models for cancirogenesis. The third part was devoted to discrete models with spatial structure: deterministic models based on cellular automata, stochastic models based on particle systems, accompanied by simulation of particle systems with an interactive software.

Paul Malliavin (University of Paris)
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Reduction of dimensionality of dynamical phase space for large biological Systems

The lectures have been addressed to structural biology in the sense of the determination of three dimensional crystallised structures of proteins and the understanding of protein dynamics in water solution (in particular protein folding). The chemical formula of a protein could answer in principle all these questions, but effective realisation of automatic routines going from chemical formula to structure determination is presently more a dream than a fact. The purpose of the lectures was then to show a number of ideas, coming from Hamiltonian dynamics and stochastic analysis, to reduce the dimensionality of the problem still preserving basic features.

The first approach to dimensionality reduction is based on a splitting into fast and slow motions. This is obtained by a spectral-probabilistic method, similar to principal component analysis. The reduced dynamics obtained in this way incorporates the missing information as a random driving force. Computer simulations have been provided and compared with experimental results.

The second approach works nearby an equilibrium, a minimum of the energy, and it is based on the normal modes approximation. The energy is replaced by its Hessian computed at equilibrium. One obtains Langevin stochastic differential equations. Again numerical simulation have been shown and discussed.

Alcherio Martinoli (Caltech)

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Biologically Inspired Collective Robotics

The symposium on Interacting Particle and Computational Biology aimed to understand collective behaviours in particle and biological systems. The seminar on Biologically Inspired Collective Robotics extended the study of collective behaviours to artificial systems consisting of autonomous robots endowed with biologically inspired controllers. While the aim of physicists and biologists is mainly understanding Nature, that of engineers involves also a synthesis part. Robots, conversely to simulated agents, operate in the real world and share therefore similar properties with physical and biological systems (time continuity, noise, small heterogeneities, and so on). This seminar covered an introduction to bio-inspired autonomous robotics (behaviour-based and neural based controllers), gave an overview of the collective robotics field with particular emphasis on swarm robotics, and illustrated analysis and synthesis methodologies currently used at Caltech to design, optimise, and model collective robotic systems. The discussion was supported with concrete case studies.

Hans Meinhardt (Max-Planck-Institut)

<http://www.eb.tuebingen.mpg.de/dept4/meinhardt/theory.html>

Models of biological pattern formation

The development of higher organisms is controlled by a complex network of biochemical reactions that are under genetic control. The aim of the seminar was to demonstrate that it is possible to formulate models in a mathematical precise way that describe essential steps, in spite of the appearing complexity of the process. Many of these models have found direct support by molecular-genetic experiments. By computer simulations it was shown that the models describe precisely the regulatory phenomena as they have been experimentally observed.

The first lecture described the basic mechanisms in biological pattern formation: local self-enhancement and long range inhibition. Organised regions, gradients, stripes arise in this way.

The second lecture proceeded to discuss the generation of complex structures, with coupled reactions. The polyp HYDRA was considered as an example of how to achieve the organisation of head and foot.

The third lecture discussed gene activation as a pattern formation in the gene space, and the coupling of positional information and gene activation. The other lectures presented theories for the initiation of substructures such as legs and wings, always formed at particular positions, for the formation of pigment patterns on shells (travelling waves and solitons are relevant concepts), and for the generation of highly dynamic patterns.

Robert Turner (Mathematics Department , Wisconsin-Madison)

<http://www.math.wisc.edu/~turner/>

An introduction to Neural Dynamics

The aim of the lectures was to acquaint the listener with the ionic basis for voltage variations in single neurons and to discuss models of small numbers of interconnected neurons. The program was:

Neural anatomy, some electrophysiology, and stochastic models for ion channels.

The Hodgkin-Huxley cell model, action potentials, and propagation. Analysis of reduced models. Bursting cells.

Simple circuits, synchrony, and antiphase oscillations.

Analysis of direct versus delayed inhibition of linked neurons via singular perturbation.

Computer simulations were also available to demonstrate the properties of the models.

Tamàs Vicsek (Budapest)

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Fractal growth phenomena

Biological growth frequently leads to objects with fractal geometry. Most of the models describing such growth phenomena involve aggregating particles in presence of fluctuations. The course gave a wide overview of different models and their results. One theme was the study of group motion ("flocking"), related to a great variety of everyday phenomena, including group motion of humans (i.e. rhythmic applause, escape panic); it was shown that there is a special type of ordering and synchronization in systems consisting of a large number of moving and interacting organisms (such as schools of fish, flocks, human crowds).

Research Seminars

Paolo Dai Pra' (Padova)

<http://www.math.unipd.it/~daipra/>

Hitting time estimates for exclusion processes

Michael Lässig (Köln)

<http://www.thp.uni-koeln.de/~lassig/index.html>

1. Chance and Rule in Molecular Networks
2. Evolution of Gene Regulation

Andrea Montanari (Paris)

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Pulling RNA and single-stranded DNA

Luca Peliti (Napoli)

<http://people.na.infn.it/~peliti/>

Why is the DNA denaturation transition first order?

Andrea Pugliese (Trento)

<http://www-math.science.unitn.it/~pugliese/>

Persistence and extinction in models for fragmented populations, Part I, Part II

Tutorials

Massimiliano Gubinelli (Pisa)

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Introduction to large deviations and applications in statistical mechanics; the phase transition in the spherical model

Marco Isopi (Bari and New York)

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A short introduction to particle systems

Roberto Marangoni (Pisa)

www.ib.pi.cnr.it/staff/roberto.marangoni.html

Information, Evolution and Complexity: some studies on genes families

Francesco Morandin (Parma)

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Some elementary facts about branching and birth-death processes

Participants' Seminars

Johannes Berg (Köln)

<http://www.thp.uni-koeln.de/~berg/>

Random networks and statistical modelling of protein interaction networks

Andreas Degenhard (Bielefeld)

<http://www.icr.ac.uk/cmagres/staff/andreas.html>

Artificial neural network approach to tumor classification

Martin Grothaus (Bonn)

<http://wiener.iam.uni-bonn.de/~grothaus/>

Scaling limit of stochastic dynamics in classical continuous systems

Deborah Lacitignola (Lecce)

deborah.lacitignola@unile.it Lotka-Volterra systems as models of competing species with adaptation

Giulia Menconi (Pisa)

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Computable Information Content: the Kolmogorov-Sinai entropy down to earth

Daniela Morale (Milano)

<http://www.mat.unimi.it/users/miriam/morale/Daniela.Morale.html>

Particles models for vasculogenesis

Cristina Zucca (Torino)

<http://www2.dm.unito.it/paginepersonali/zucca/index.htm>

On the relationship between interspikes distribution and boundary shape in the Ornstein-Uhlenbeck neuronal model

Participants supported by the Center:

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Daniela Morale, Milano

Francesco Morandin, Parma

Nicolas Petrelis, Paris VII

Alexey Polotsky, Bielefeld

Cristina Zucca, Torino

Other participants

David Barbato, Scuola Normale Superiore

Michele Barsanti, Dipartimento di Matematica Applicata, Pisa

Hakima Bessaih, Dipartimento Matematica Applicata, Pisa

Sandra Cerrai, Università di Firenze

Irene Crimaldi, Scuola Normale Superiore

Giuseppe Da Prato, Scuola Normale Superiore

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