From individual to collective behaviour in biological systems

September to December, 2001

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Scientific Background

In the last thirty years there has been an enormous increase in our knowledge of biological pro-cesses, especially at the molecular and cellular level, but understanding the behaviour of individual enzymes, cells or organisms in isolation is only a first step in understanding the collective behaviour of a population of such individuals. Incorporating individual aspects of behaviour into macroscopic descriptions of population behaviour is a challenging problem, even if only deterministic aspects are considered. The four-month program 'From individual to collective behaviour in biological systems' was devoted to the question of how microscopic information can be incorporated into macroscopic or population-level descriptions in developmental biology, physiology, ecology, immunology and epidemiology.

Program for part I: Developmental biology and physiology

The first half of the programme focussed on developmental biology and physiology. The former concentrated on pattern formation, gene networks, and developmental mechanics, while the latter was devoted to various aspects related to cardiac physiology, including calcium dynamics, analysis of ion channels in excitable systems, muscle mechanics and integrated models of the heart. A notable aspect of this component of the program was the strong and deep interaction between theoreticians and experimentalists on the fundamental questions from both perspectives. For instance, the detailed presentations by experimentalists such as Paul Kulesa, Kees Weijer and Ray Keller stimulated numerous discussions and several new collaborations between experimentalists and the-oreticians.

The work here has also highlighted many questions relating to stromal cell development and organisation and the aggregation and pattern formation behaviour of Dictyostelium. An important feature of the programme was that in-depth tutorials on both experimental and theoretical aspects were given prior to the workshop and continued throughout the program. For instance, programme participants benefited greatly from the tutorials on modelling of the heart given by Peter Hunter and his associates, since it pointed to the possible use of mathematical techniques developed there in tissue modelling in other areas.

Part I Tutorials and Workshops

Date	Topic	Presenter
12/9	Dictyostelium discoideum development	Hans Othmer
13/9	Molecular motors/cell motility	Alex Mogilner
14/9	Developmental/evolutionary dynamics	Johannes Jaeger
17/9	Stochastic analysis of channel dynamics	Hans Othmer/Jianfeng Feng
18/9	Developmental Biology	Nick Monk/Kevin Painter
19/9	Cardiology I	Nic Smith/Rob Hinch
20/9	Cardiology II	Peter Hunter/Alexander Panfilov
21/9	Group Reports	Edmund Crampin/Eric Cytrnbaum
1/10	Developmental mechanics	Paul Kulesa
2/10	Fundamentals of solid mechanics	J. Willis
3/10	Gastrulation	Ray Keller
4 & 15/10	Homogenization	Pedro Ponte-Castenada

First workshop:

Vertical integration in biology: from molecules to organisms

24 September - 28 September 2001

Major themes:
The principal theme of this workshop was vertical integration, focusing on specific examples from developmental biology and physiology, viz., gene networks, cell signalling, morphogenesis, neural networks, neurophysiology and cardiology. Three criteria were used to select these particular areas:

(1) there exist extensive studies of behaviour at both the individual and collective levels;

(2) well-founded mathematical modelling frameworks are in place for each of these levels;

(3) there is a pressing need for a directed attempt to combine modelling and experimental investigations to elucidate the mechanisms of vertical integration, bridging the gap between the two levels of understanding.

To foster efforts aimed at providing insight into vertical integration, it is important to (a) bring together researchers from different backgrounds who would not normally find the opportunity to meet to discuss this general issue, (b) to train truly interdisciplinary researchers. The workshop has succeeded in this by (i) bringing together experimentalists and theoreticians, as well as those who have successfully combined the two approaches; (ii) inviting researchers whose focus is primarily on either the individual or collective levels, which proved productive because the modelling techniques applicable to the two levels are often quite distinct, and (iii) inviting a significant number of young researchers to expose them to a wide range of presentations in the interactive environment fostered by the Newton Institute, thereby giving them access to some of the most active researchers in these different fields.

Programme of the first workshop:

Monday 24 September

- D Bray (Cambridge) Modelling molecular events in a small volume of living cytoplasm
- G Forgacs (Missouri) The role of the cytoskeleton in intracellular signalling
- T Hoefer (Humboldt Berlin) GATA-3 transcriptional memory in T helper lymphocytes a mathematical model of steady-state and temporal behaviour

Tuesday 25 September

- H Bolouri (Hertfordshire) Reverse engineering of a developmental genetic regulatory network
- J J¨ager (SUNY) Looking at the future of functional genomics from inside the Drosophila blastoderm
- G Von Dassow (Washington) Models of modules: putting the molecular parts together into genetic devices
- H Causton (Imperial) Microarrays and yeast: insights into gene regulation
- K Vass (Glasgow) Normalisation and local variation in microarray
- A Brazma (Euro Bioinformatics Institute) Reconstructing elements of gene networks from genome scale microarray data
- D Pe’er (Hebrew University Jerusalem) From gene expression to gene interaction
- O Wolkenhauer (UMIST) System theoretic models of gene expression and gene interactions
- C Thompson, B Parsons, P Durham (Daresbury Laboratory) Funding opportunities in bioin-formatics and theoretical biology

Wednesday 26 September

- J Lewis (ICRF) Notch signalling in spatial and temporal patterning
- J Sherratt (Heriot-Watt University) Extracellular matrix alignment by cells: discrete and continuous models compared
- P Kulesa (California Int of Tech) In vivo imaging as a bridge between molecular, cellular and tissue level data in embryonic vertebrate development
- R Winslow (John Hopkins School of Med) Intracellular calicum cycling and control of action potential duration

Thursday 27 September

- R Keller (Virginia) Mechanisms, variation, conservation, and integration of early morphogenic machanies in vertebrates
- R Adams (Bath) Cell movements during early zebrafish morphogenesis

- K Weijer (Dundee) The control of cell movement during Dictyostelium morphogenesis
- P Hunter (Auckland) Physiome Projects: The heart, lungs and musculo-skeletal system

Friday 28 September

- F Ashcroft (Oxford) ATP-sensitive K-channels and insulin secretion in health and disease
- D Noble (Oxford) From genes to whole organs: vertical integration using mathematical simulation of the heart

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Program for Part II: Ecology, immunology and epidemiology

The second half of the programme was devoted to spatial ecology, immunology and epidemiology. One significant outcome of discussions in these areas was the realisation that the mathematical models developed in one area are often similar to those in another area (e.g. compare immunology and epidemiology). This cross fertilisation of ideas may well have important implications for future research. On the more mathematical front the complementary ideas on stochastic modelling and reinforced random walks discussed by Dirk Drasdo, Andreas Deutch, Angela Stevens and Hans Othmer has opened up a number of novel ways in which phenomena at the cell level may be scaled up to the population level. Open problems include how the limiting processes involved should be interpreted and validated. There is also the excluded volume problem relating to taking account of cell size.

Part II Tutorials and Workshops

Date	Topic	Presenter
5/11	General introduction on Immunology	Robin Callard
6/11	General Tutorial on Epidemiology	Pejman Rohani
9/11	Pair approximations	Minus van Baalen
12/11	General discussion on epidemiology	
14/11	Moment closure methods	Ben Bolker
16/11	Cell-Cell interactions and signalling in immunology	Nigel Burroughs
20/11	Tutorial on Stochastic Modelling	Vincenzo Capasso
21/11	Metapopulations	Otso Ovaskainen
27/11	Introduction to Adaptive Dynamics	Vincent Jansen
27/11	Discussion day on Immunology	
28/11	The Organisation of insect societies	David Sumpter

5/12	Mathematica for moment equations	Ben Bolker

Second workshop:

Euromech satellite meeting (Leeds)

3 December - 5 December 2001

The workshop on ‘Pattern Formation by Swimming Micro-Organisms and Cells’ was hosted by the Department of Applied Mathematics at the University of Leeds on 3th to 5th December. Professor Nick Hill (Glasgow) chaired the meeting with Dr Martin Bees (Surrey) as the co-chairman. It was organised as an international meeting (Euromech Colloquium 422) under the auspices of the European Mechanics Society, and was funded jointly by the Isaac Newton Institute and the London Mathematical Society. The sixty participants contributed a total of 45 presentations including a lively poster session. Prizes for the best student posters were awarded to Rachel Bearon (University of Cambridge) and Richard Hillary (University of Surrey).

A notable feature of the workshop was bringing together of mathematical modellers in plankton population dynamics, where dispersion is mainly caused by oceanic currents, and those in biocon-vection with theorists in the growth of bacterial colonies and the behaviour of slime moulds. The standard of the talks was excellent, and there was much energetic discussion enhanced by keynote experimental and biological presentations. The vigorous state of mathematical biology in the UK and worldwide was demonstrated by the wide range of new mathematical models and mathematical results which were presented, e.g. on travelling waves, Taylor dispersion in suspensions of swimming micro-organisms, angiogenesis, and the uid mechanics of swarming bacterial colonies.

The very successful theme of a workshop devoted to mechanics applied to biology was a timely new venture for Euromech, and points the way forward for future developments of the Society’s interests.

Third workshop:

From Worker to Colony: Understanding the Organisation of Insect Societies

7 December - 8 December 2001

Preliminaries to the workshop

For the two weeks running up to the ’worker to colony’ meeting, we hosted informal discussions outlining the important research questions in social insects. Over these two weeks the institute had short-term visits from nine experimental biologists, two researchers involved in computer tracking and automatic analysis of insect behaviour and two computer scientists involved in ant algorithms (novel methods of solution, inspired by ants, for solving computationally complex problems). These visitors interacted with the mathematicians already resident at the institute and others who also visited for a short time. For example, van Baalen and Beekman worked on a paper on the benefits of genetic diversity for disease resistance, Couzin and Despland worked on automated tracking of locusts, and Martin and Sumpter began modelling bee colony virus dynamics.

As well as having seminars and informal problem presentations by the visitors, we organised a discussion group on ’robustness in insect societies’, taking as inspiration some of the talks earlier in the programme on robustness in other biological systems. Reuter, Sumpter, Beekman, Middendorf and Merkel all gave presentations on this theme, resulting in a great deal of lively discussion. Such discussions also set the scene for the workshop itself.

The workshop

The ’worker to colony’ workshop was the largest meeting dedicated to the study of insect societies in the UK for at least five years. There were 90 attendees (70 of whom were short term or ’on the day’ participants), who heard both extended one hour research talks by leading international researchers and shorter presentations of particular projects. One main theme was construction and digging by ants: in one talk Theraulaz presented, to the great interest of attendant mathematical biologists, convincing evidence for Turing mechanisms underlying ant cemeteries and other constructions. Another theme was nest choice by ants and bees, with excellent and detailed talks by Seeley, Franks and Pratt. During the breaks between talks there were poster presentations, where younger members got an opportunity to present their work and get some input on possible mathematical modelling. Many new collaborations were formed as biologists found out what mathematics could contribute to the study of insect societies and mathematicians discovered that these societies are a perfect example of individual to collective behaviour in biology.

Fourth workshop

Macroscopic organisation from microscopic behaviour in immunology, ecology and epidemiology

10 December - 14 December

Major themes

The purpose of the workshop was to bring together experimentalists and theoreticians working in immunology, ecology and epidemiology with the aim of fostering interaction and research. Approaches using classical deterministic mathematical models have had some limited success in describing these spatial ecological processes. However, there is a growing realization, amongst ecologists and theoreticians alike, that stochastic factors, both demographic and environmental, play a fundamental role in determining ecological outcomes.

Because of new technology the quantification of cellular populations is now routine in immunology laboratories. This has led to a steadily increasing stream of kinetic data on the population dynamics of various types of immune cells. With this accumulation of data comes a realization that a proper understanding of the underlying dynamical systems will only be achieved when the data are considered within the organising framework of a formal theoretical model. Mathematical immunologists have energetically responded to this newly felt need, forming a growing number of close collaborations between theoretical and laboratory immunologists. Some of these collaborations have been rich sources of new insights; not only into biological processes, but also in showing the usefulness of mathematical modelling to large branches of a biological community. Fundamental to such interactions is the question of how one manages the wealth of molecular detail, and where appropriate, how this detail might be incorporated into a macroscopic or population level description. In seeking answers to these questions a major objective was to attempt to identify mathematical and computational methods common to these areas, whether the individuals are molecules, cells or organisms.

Programme of the fourth workshop

Monday 10 December

- L Segel (Weizmann Institute) Appropriate macroscopic behaviour of the immune system, from distributed microscopic feedback
- D Wodarz (IAS) Treatment strategies against immuno-suppressive diseases
- S Bonhoeffer (Zurich) The times' tables of viral resistance
- RN Antia (Emory) Modeling CD8 Memory

Tuesday 11 December

- A Hastings (UC Davis) The dependence of the design of marine reserve networks on dispersal behaviour
- HCJ Godfray (Imperial) Age-structured models of insect natural-enemy interactions
- MA Lewis (Utah) Territorial pattern formation through scent marking
- Y Iwasa (Kyushu) Masting of forest trees - intermittent and synchronised

Wednesday 12 December

- RJ De Boer (Utrecht) Extensive MHC polymorphism requires frequency-dependent selection by coevolving pathogens
- C Bangham (Imperial) Genetic, dynamic and functional definition of the efficency of the anti-viral T cell response
- A Sasaki (Kyushu) Word frequency distribution under the restriction avoidance
- N Burroughs (Warwick) Inequalitites during life and death of T cells

Thursday 13 December

- AP Dobson (Princeton) Epidemics at different spatial scales, from social behaviour to community dynamics
- SDW Frost (UC San Diego) The roles of chance and spatial structure within host evolution of HIV
- B Grenfell (Cambridge) Waves and sparks in the spatio-temporal dynamics of microparasitic infections
- H Fisher, G Brown (Wellcome Trust) Presentation on funding opportunities
- DA Rand (Warwick) Optimising the effectiveness of T cell activation

Friday 14 December

- S Ruan (Dalhousie) Multiple parameter bifurcations in ecological and epidemiological models
- M Pascual (Michigan) Modified mean-field models and self-organisation in spatial systems for antagonistic interactions

Outcome and Achievements

The consensus of those who attended the programme, either as a short-term visitor or a long-term participant, is that the programme was very successful in achieving the stated objective of bringing together leading theoreticians and experimentalists to discuss major biological problems that may benefit from mathematical modelling and analysis. In addition the programme successfully attracted a very young group of researchers (of 238 participants, 55 were in the 22-30 age group, 99 in the 31-40 range, 52 in the 41-50 range, 26 in the 51-60 range, and 6 in the 61-70 range), of which 52 were female.

Future directions

The programme has highlighted a number of important issues and directions for the future development of research at the interface between biology and mathematics. Some of these are as follows.

- Biological organization at every level, from molecular to population, is based on complex networks for signal detection, transduction, processing and response, and at present there are few suitable mathematical techniques for analyzing and understanding these systems. One conclusion from numerous talks and discussions is that the level of complexity observed may reflect the need for robust performance in the face of fluctuating inputs. Heretofore the mathematical focus has been on how complex the dynamical behavior of a network can be, but from a biological standpoint a better question is how complex must the network be to function robustly in a given environment. A major objective should be to identify canonical structures in networks that produce stereotypical outputs, i.e. to identify the resistors and transistors of biological networks. This requires detailed modeling of well-characterized systems to provide the basis for the development of new mathematical techniques.
- Training issues: Future success in interdisciplinary research can only be realized by increasing the pool of suitably trained young scientists. This will require cross-disciplinary training of students at a much earlier age than is currently done, and retraining of faculty for this purpose. In addition, sustained support at later stages, including postgraduate training and research is needed.

Insights and collaborations

This program was unusual in that a major objective was to foster constructive engagement between biologists and mathematicians in order to identify some major biological problems amenable to theoretical approaches. This aspect of the program was a resounding success, as judged by the response of the participants. Several examples of new insights and collaborations are as follows.

(1) A minisymposium on developmental mechanics following the first workshop led to extended discussions between Professor Ray Keller and Hans Othmer, amongst others, concerning the feasibility of mathematical modeling and simulation of the process of convergent extension in early embryonic development. This is a major process in early development, and the ability to simulate this process would lead to many new insights into the interplay between mechanics and gene expression. The end result of these discussions is a new collaboration between Keller, Othmer, and John Dallon, a short-term participant in the program.

(2) One of the major themes of the second half wasimmunology, and we were fortunate to have the immunologists Robin Callard and Andrew Yates in residence for much of the time. Their presence stimulated wide-ranging discussions involving the mathematicians Nigel Burroughs, Jaroslav Stark and David Rand, and resulted in a one-day focus meeting on current theories of T-cell selection. Stimulated by these discussions, Callard, Stark and Yates have developed a PDE model of the gene networks that control differentiation of Th1 and Th2 cells.

Many other new collaborations resulted from this meeting. Angiogenesis, which is the growth and migration toward a tumor of new vessels from a pre-existing vasculature, and currently being extensively studied both experimentally and theoretically. Sleeman, in collaboration with Levine, and stimulated by discussions with A.Stevens, H.Othmer, D.Horstman., P.Kulesa, Robin Callard, and Dirk Drasdo, has developed a new PDE model of this process. The new model predicts, not only the initiation of new capillary growth but also the formation of "empty" capillaries recently found experimentally and referred to as "vasculogenic mimicry". Work has also progressed on the fundamental p53 gene; a key player in understanding avascular tumour growth. In a different vein, Othmer and Kevin

Painter (mathematicians) and Paul Kulesa (developmental biologist) have begun development of a mathematical model for stripe formation in zebrafish. This is a new approach in that the theoretical work will make predictions that will be tested directly in the laboratory. Professor Maini, in collaboration with Sanchez-Garduno, Sleeman, and Crampin, made significant progress on modelling and analysing growing domains with possible application to pattern formation during early development.

Another goal of the program was to expose workers in one area to mathematical techniques used in other areas. A number of participants mentioned this as an unexpected benefit of their stay at the Newton. For instance, techniques used in continuum modelling of chemotaxis may prove useful for those studying trail-following behavior in insects, and similarly, widely-used methods in population dynamics may find application in the analysis of models for cell behavior in the immune system.

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