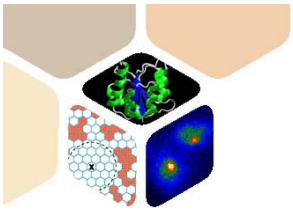

Oxford Centre for Integrative Systems Biology

CABDyN Complexity Centre

Oxford BioNets Day

Friday 3rd October 2008

Martin Wood Lecture Theatre, Department of Physics

Programme

9.30 – 10.30

Opening lecture: Professor Lord Robert M. May, Department of Zoology, Oxford

Title: The nonlinear dynamics of network vulnerability

Abstract: The transmission of infection among humans or other animals, the spread of viruses or worms among computers, transfers of funds within financial markets, and the way ecosystems respond to disturbance are four among many examples of nonlinear dynamical systems whose behaviour depends upon the nature of the network of connections among nodes (that is individuals, computers, banks/traders, species, respectively). Recent and current concern about HIV/AIDS, SARS, and foot and mouth disease among livestock have prompted advances in our understanding of the interplay between network patterns and effective control measures. Separate, but ultimately related, work has recently focussed (often in the context of "homeland security") on protecting IT networks from attack. Perhaps surprisingly, this work has made relatively little contact with older questions about ecosystem resilience, or about the overall stability of financial markets (as distinct from individual funds). My talk aims to be a brief but opinionated overview of all this.

10.30 – 11.00

Context from network theory: Dr Eduardo López, Saïd Business School, Oxford
Tools and ideas from Complex Network Theory

11.00 – Coffee break

11.30 – 1.00

Session 1: Subcellular networks (protein interactions & metabolism)

Chair: Dr Nick Jones, Physics and Systems Biology, Oxford

Speaker 1: Professor Béla Novák, Department of Biochemistry, Oxford

Title: What makes cellular decisions irreversible?

Abstract: Cells are making many decisions during their life, when they select and find nutrients, choose between alternative developmental pathways etc. These decisions are triggered by molecular signals (stimulus) and they are concluded in a change of physiological state. If the decision is irreversible the cellular state reached after the transition is stable even if the initial stimulus is inactivated. Classical examples for irreversible transitions are provided by the eukaryotic cell cycle regulation. In an early stage of the cell cycle, cells can choose between different developmental scenarios: proliferation, quiescence etc. However after passing through a point called 'Start' or 'restriction point', cells become fully committed for cell division. It is common to explain these irreversible transitions by proteolytic degradation of certain regulatory proteins which is a thermodynamically irreversible process. However this simple and appealing view of irreversible cellular transitions is based on ambiguous notion of 'irreversibility'. I will argue that the irreversible nature of cellular transitions is a systems-level property of the underlying molecular control network. Therefore irreversibility transition of a molecular control system cannot be attributed to a single molecule or reaction, but derive rather from systems-level feedback signals. This systems-level view of irreversibility is supported by theoretical considerations and by many experimental observations.

Speaker 2: Dr Charlotte Deane, Department of Statistics, Oxford

Title: Predicting protein characteristics and protein interactions using network information

Abstract: The biological functions of a protein within the cell are governed by its protein interactions. While these interactions have recently become widely available for many organisms, they are not yet fully explored with regards to the insights into protein characteristics they might provide. Here we explore the prediction of protein characteristics, e.g, structure and function, and utilise these characteristics in the prediction of protein interactions.

Our methods consider both pairwise and triple-wise interactions. Prior information from other organisms is also incorporated, and diverse biological characteristics can be integrated simultaneously.

In the task of predicting protein characteristics, for large networks our pair-based score is more accurate than the popular Majority Vote method. Surprisingly, however, our triple-based

score does not outperform the simpler pair-based method. This may be due to poor data quality and/or other unknown biological factors.

In the task of predicting protein interactions, we demonstrate that the inclusion of network structure in the form of triples significantly improves results over three other standard interaction predictors as well as a pair based version of the method. It also achieves a greater coverage. Unsurprising, therefore it appears that different tasks may require different models. A global model for protein interaction networks based on triples is outperformed by a pairwise method when it comes to predicting protein characteristics. Conversely, a triple-base method outperforms a model based on pairwise interactions when it comes to predicting interactions.

The methods offer three main improvements over current approaches. Firstly, they consider network structures of pairs and triples in the prediction. Secondly, multiple protein characteristics can be considered simultaneously, which greatly improves the prediction. Thirdly, data from multiple species can be easily integrated. Interestingly on this last point the result suggests that there may be fundamental differences between the networks of eukaryotes and prokaryotes.

Speaker 3: Dr Mark Poolman, School of Life Sciences, Oxford Brookes

Title: A brief introduction to metabolic modelling

Abstract: Despite investigating a wide range of biochemical systems, the underlying motivation of the Cell Systems Modelling group can be summed up by the question, “Given the (assumed) properties of individual reactions in a network, what is it possible to infer about the properties of the network as a whole?”

The two major approaches to answer this question are kinetic modeling which assumes knowledge of the rate equations of all reactions in the system, and structural modelling, which depends only upon knowledge of reaction stoichiometry (and possibly reversibility). Kinetic modelling allows the prediction of individual reaction rates and metabolite concentrations and, perhaps more usefully, the response of these to environmental perturbations. Such responses may be usefully analysed within the context of Metabolic Control Analysis. Structural modelling is used to identify absolute constraints on system behaviour, and other invariant properties that are independent of reaction kinetics. Although it is feasible to construct such models on a “genome scale” using publically available databases, a number of practical and theoretical issues remain to be resolved before the full potential of such models can be realised.

1.00 – Lunch for registered attendees

2.00 – 3.30

Session 2: Networked Cells (neurons and fungal mycelia)
Chair: Dr David Smith, Mathematical Biology, Oxford

Speaker 1: Dr Wyeth Bair, Department of Physiology, Anatomy and Genetics, Oxford

Title: Inter-neuronal correlation in feedforward and feedback cortical networks?

Abstract: Inter-neuronal correlation is an important feature of cortical activity because it impacts the ability of populations of cells to encode information and it provides a set of constraints for unraveling the functional connectivity of the cortical network. Using computer simulations, we studied the correlation between responses of nearby and directly connected neurons in two distinct network architectures, one feedforward and one feedback, that have been proposed to account for the orientation selectivity of neurons in the primary visual cortex (V1). I will demonstrate how our results place constraints on the networks in terms of the correlation within the thalamic inputs, between the inputs and the outputs of V1 neurons, and between similarly-tuned V1 neurons. I will also show how the correlation in the two networks reacts differently to changes in the pattern and strength of the visual stimulus that is used to drive the inputs.

Speaker 2: Dr Ole Paulsen, Department of Physiology, Anatomy and Genetics, Oxford

Title: Neuronal networks in learning and memory

Abstract: A fundamental scientific mystery that confronts us in the 21^st century is how activity of neurons in the brain gives rise to the lasting traces of experience that underlies memory. How is it that an experience can be captured by neuronal circuits of the brain and be vividly recollected years later? It is generally assumed that memory is stored as changes in the connections between neurons, but these synaptic changes are distributed within and across networks, and understanding the code for how information is stored as such distributed changes in synaptic weights remains a major challenge.

To understand such a code, we will need to understand not only the mechanisms that operate at individual synaptic connections, but also the network architecture and the dynamics of the circuits in which the neurons are embedded. These properties are quite different from most artificial neural networks. In my presentation, I will highlight some salient features of cortical network architecture, and explain how they determine the dynamic properties of the network. I will argue that the rhythmic nature of these dynamics enables a temporal code for representing information, and that established rules of synaptic modifiability supports the storage of such temporally-encoded information.

Speaker 3: Dr Mark Fricker, Department of Plant Sciences, Oxford

Title: Transport efficiency and resilience in mycelial networks

Abstract: Transport networks are vital components of multicellular organisms, distributing nutrients and removing waste products. Animal cardiovascular and respiratory systems, and plant vasculature, are fractal-like branching trees whose architecture determines universal scaling laws in these organisms. In contrast, transport systems in multicellular fungi are not expected to fit into this conceptual framework, as they have evolved to explore the environment rather than ramify as a three-dimensional organism. Many fungi grow as a foraging mycelium, formed by the branching and fusion of threadlike hyphae. This process gives rise to a complex network that continuously adapts to its environment. However, the properties of the network and its dynamic behaviour have not yet been characterised. Using a range of woodland saprotrophic basidiomycetes, we have examined network development and its nutrient transport characteristics over a range of scales, using a combination of imaging, modelling, gene expression profiling and metabolomics.

We have found that fungal networks can display both a high transport capacity and high resilience to damage. These properties are enhanced as the network grows, while the relative amount of material used to build the network decreases. Thus, mycelia achieve the seemingly competing goals of efficient transport and resilience, with decreasing relative investment, by selective reinforcement and recycling of transport pathways. The fungal network demonstrates that indeterminate, decentralised systems can yield highly adaptive networks.

To test the predictions from the theoretical analysis of transport, we have mapped the distribution of non-metabolised, radiolabelled amino-acid and sugar analogues during mycelial development in spatially heterogenous resource environments using photon-counting scintillation imaging. These studies have revealed a number of novel phenomena, including a marked pulsatile transport component superimposed on a rapid underlying flux, preferential resource allocation to C-rich sinks, abrupt switching between different pre-existing transport routes and organization of the network into well demarcated domains differing in phase or frequency of oscillations. Furthermore, fusion between compatible individuals leads to rapid nutrient re-distribution and formation of a fully synchronised super-colony.

Overall the spatial organisation of these mycelial systems provide an almost unique opportunity for any eukaryotic system to directly correlate metabolite levels, nutrient fluxes, gene expression patterns and morphological development.

3.30 – 4.00 Coffee break

4.00 – 5.30

Session 3: Networked Organisms (food webs and epidemiology)
Chair: Dr Felix Reed-Tsochas, James Martin Institute, Oxford

Speaker 1: Dr Owen Lewis, Department of Zoology, Oxford

Title: Quantitative food webs: patterns, processes and applications

Abstract: Food webs describe networks of feeding interactions among species within ecological communities. I will describe empirical studies of food webs that are fully quantified in terms of the abundance of interacting species and the frequency of each pair-wise interaction. Evidence is accumulating that these 'quantitative food webs' can inform us about (1) the dynamic processes structuring and organising biological diversity; (2) the consequences of extinction or invasion of individual species; and (3) the effects of human disturbance on the organisation, integrity and functioning of ecosystems.

Speaker 2: Professor Angela McLean, Department of Zoology, Oxford

Title: Within-host evolution and between-host transmission of HIV

Abstract: During the course of a single infection HIV evolves to escape from the selective pressures imposed by its host's immune response. Such changes have been recorded under selection from all three arms of the specific immune response, but escape from CD8+ cytotoxic T lymphocytes (CTLs) is particularly well documented. HIV variants that cannot be recognised by current host CTLs are termed "CTL escape mutants". Such mutants have been shown to transmit from one host to another raising their status from potential causes of pathogenesis within individuals to potential drivers of evolutionary change across the global HIV pandemic.

Different hosts make immune responses to different parts of HIV (known as epitopes) and for CTL responses the epitopes that can be recognised are determined by the host's class 1 human leucocyte antigen (HLA) type. CTL escape mutants can revert to the wild type when they are no longer under selection pressure from host immune responses. Global change in HIV's antigens is therefore driven by three parallel processes: the selection of escape mutants in hosts whose immune response can recognise a given epitope (i.e. HLA matched hosts), transmission to new hosts, and reversion of escape mutants in hosts unable to recognise the epitope in question (i.e. HLA mismatched hosts).

It would be useful to understand the global tempo of antigenic change in HIV for a number of reasons. HIV is a relatively recently emerged infection of humans, is it still adapting to its new hosts , and if so, how fast? What is the relationship between the tempo of adaptation within individuals and the rate of genetic change across the entire pandemic? If HIV is still adapting,

what patterns can we expect to unfold across the population of infected people and how will those patterns be different in people of different HLA types? Finally, what are the practical implications of viral adaptation in CTL epitopes? Is it really the case that HIV evolves so quickly that any CTL based vaccine would rapidly become obsolete through vaccine escape, or is the global rate of change much more sedate?

In order to explore these questions we have developed a mathematical model of the within-host evolution and between-host transmission of HIV. The model allows host heterogeneity with respect to HLA type, and viral heterogeneity with respect to escape mutations in a given epitope. HLA matched hosts drive the evolution of CTL escape mutations whilst HLA mis-matched hosts allow their reversion to wild-type. Both viral types are transmitted within the population of hosts at rates driven by the proportion of hosts infected with each type of virus. This talk will present this mathematical model and use it to analyse and compare diverse sources of data on the evolution of CTL escape mutants in humans.

Speaker 3: Professor Michael Goldacre, Department of Public Health, Oxford

Title: Epidemiology: what, why and how

Abstract: Epidemiology is the study of the distribution of disease in populations. Its uses include public-health surveillance; aetiological studies of disease using population-based methodologies; 'completing the clinical picture' (eg the study of pre-clinical and asymptomatic disease); and investigating needs for, uses of, and outcomes of health services.

In aetiological studies of disease, first clues about the possible relationship between an 'exposure', and a disease that it might cause, often come from clinical or laboratory observations. A common next step is to test predictions about the epidemiological profile of a disease that might be expected, if the fledgling hypothesis is correct (eg if an industrial exposure is hypothesised to cause a disease, the disease should be more common in workers in, or residents near, the relevant industry). Data resources for studying the epidemiological profile of disease include such record-based public-health surveillance systems as mortality statistics, hospital admission statistics, and cancer registries.

Then, the further refinement of epidemiological hypothesis-testing generally involves case-control and/or cohort and/or intervention studies (the latter include randomised controlled trials of the exposure (or of avoiding it)).

Brief examples will be given of studies that have drawn on information from some of the large public-health surveillance systems. The aim is to interest the attendees in these epidemiological "data laboratories", in the hope that the "laboratories" may sometimes be of use to them in their own work.

Thank you for attending the Oxford BioNets Day. If you would like to be added to the mailing list for either the **Oxford Centre for Integrative Systems Biology** or the **CABDyN Complexity Centre** or if you would like to give feedback about this event, please email bionets@sbs.ox.ac.uk.