Parallel Session

Cell and Intra-Cell Dynamics III

CELLULAR DECISION MAKING MODELS IN MICROORGANISMS

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Joint work with James Marshall (The University of Sheffield), Andreagiovanni Reina (The University of Sheffield) and Thomas Bose (The University of Sheffield).

Keywords: Cellular decision making, Dynamical systems analysis.

Decision making is ubiquitous throughout all levels of biological complexity, from social insect colonies to multicellular organisms to individual cells. Here we present a theoretical study of cellular decision making mechanisms that describe the choice between different extracellular carbon sources. Such decision making mechanisms give rise to different consumption strategies the cell can adopt in response to the specific growth rate supported by each nutrient, as well as their environmental abundance; cells thus often show contrasting expression levels between their cognate metabolic pathways. In the present work, the system of coupled differential equations that represent the decision making processes are studied by means of bifurcation analysis and stochastic time-dependent simulations. We show that by assigning values to the sugar alternatives in correspondence with the growth rate each of them support, the transition between a deadlock state and decision deadlock breaking is enabled by the strength and nature of the inhibition signal. By comparing the dynamic behaviour of two different inhibitory signalling strategies, we find that the consumption regimes available to the cell are dependent on the structure of the inhibition signalling motif. Our results accentuate the importance of the inhibition signalling motif in cellular decision making and motivate a functional and integrated study of decision making of cells and microorganisms.

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TEMPORAL AND SPATIAL INFORMATION PROCESSING IN CELL SIGNALLING NETWORKS

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Keywords: Cell signalling, Multisite phosphorylation, Compartmentalization, Spatial organization.

Cell signalling networks underlie basic aspects of cellular function and their response to the environment. There are multiple factors which make the dissection and elucidation of signalling networks challenging. In this talk, we focus on two topics associated with the complexity of cell signalling networks at different levels, chemical mechanism and spatial organization. In the first part of the talk, we focus on multisite phosphorylation. Multisite phosphorylation is a basic way of encoding substrate function and a basic constituent of cell signalling networks. Multiple studies have focussed on both distributive and processive mechanisms of multisite phosphorylation and shown how these mechanisms are associated with distinct patterns of information processing. We discuss mixed mechanisms of multisite phosphorylation which combine processive and distributive mechanisms. We focus on how the interplay of processive and distributive mechanisms in phosphorylation/dephosphoprylation can allow for or prevent behaviour such as biphasic dose response curves, multistability and oscillations. We then build on this to discuss multiple aspects of multisite phosphorylation as part of cell signalling networks. In the second part of the talk we focus on the effect of spatial organization in cell signalling. Cell signalling is typically studied in kinetic terms, and yet it is very clear that multiple forms of spatial organization exist, in eukaryotes, and in bacteria as well. We systematically examine the effect of spatial organization and compartmentalization in multiple classes of cascades (enzymatic modification cascades, substrate modification cascades, phosphorelays). This reveals when and how the spatially organization may contribute significantly in cell signalling pathways. We then discuss how this can be used as a bridge towards the dissection of concrete signalling pathways.

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MODELLING OF THE ERK PATHWAY IN HEPATOCELLULAR CARCINOMA CELLS EXPOSED TO SORAFENIB

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Keywords: Extracellular signal-Regulated Kinase pathway, Mitogen-Activated Protein Kinase pathway, Cell signaling, Mathematical modelling.

The RAS-RAF-MEK-ERK pathway is an important signal transduction cascade that is found activated in many types of human tumours. Its activation results in a coordinated regulation of effectors controlling cell survival and mitogene. The hepatocellular carcinoma (HCC), the most frequent form of primary liver tumour, is a cancer with one of the worst prognoses, partially due to the small number of efficient therapeutic strategies. Complex and indirect mechanisms lead to the activation of the RAS-RAF-MEK-ERK cascade in HCC. Multiple internal feed-back regulations and cross-regulations among signal transduction pathways determine whether the cancer cells resist to the medical treatment or undergo cell death by apoptosis. The only current treatment is sorafenib which has been initially developed for its ability to inhibit the RAF kinases. This targeted therapy has proven efficiency on the patients survival with advanced HCC. Nevertheless, this survival remains low in the HCC context.

In order to design a more efficient strategy against cancer cells, we decided to investigate the dynamic regulation of the RAS-RAF-MEK-ERK cascade in HCC cells exposed to sorafenib by using a systems biology approach. We introduced a mathematical modelling based on the mass action and on the Michaelis-Menten equation to analyse the dynamic regulation of the ERK pathway in the cell lines Hep3b, PLC/PRF5 and Huh7, which constitute different models in terms of sentivity to sorafenib. A first model was built on the CRAF, BRAF, MEK and ERK components in order to improve our understanding on the sorafenib action in the pathway regulation. Then, this model was extended to all of the pathway components to find out the possible mechanims underlying the sorafenib resistance. Some highlights of our results will be presented.

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COOPERATIVITY ACROSS DIMERS AND THE EFFECT ON LIGAND BINDING: LINEAR AND NONLINEAR MODELS

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Keywords: Receptors, Dimers, Cooperativity, G protein-coupled receptors.

Evidence suggests that many G protein-coupled receptors (GPCRs) are bound together forming dimers. The implications of dimerisation for cellular signalling outcomes, and ultimately drug discovery and therapeutics, remain unclear. Consideration of ligand binding and signalling via receptor dimers is therefore required as an addition to classical receptor theory, which is largely built on assumptions of monomeric receptors. A key factor in developing theoretical models of dimer signalling is cooperativity across the dimer, whereby binding of a ligand to one protomer affects the binding of a ligand to the other protomer. We present and analyse linear models for ligand binding dynamics at homodimerised receptors, as an essential building block in the development of dimerised receptor theory. In particular, we derive new conditions on cooperativity factors for which multi-phasic log dose response curves are seen [1]. This could help explain data extracted from pharmacological experiments that does not fit to the standard Hill curves that are often used in this type of analysis. Furthermore, different receptor types may dimerise in response to ligand binding which leads to a related but nonlinear model. Vascular endothelial growth factor (VEGF) is a signalling protein that is produced by endothelial cells and promotes the growth of new blood vessels, and as such cells that can express VEGF are able to deliver the required blood supply to allow tumors to grow; a process that is known as angiogenesis. This process of angiogenesis is initiated when VEGF binds to a VEGF receptor and the receptor becomes activated. It is widely accepted that in order to become activated, VEGF receptors must be dimerised. The first step in exploring the implications for drug discovery and therapeutics is studying the process of binding and dimerisation. We assume all receptors initially exist as monomers and dimerise in response to ligand binding one of these monomers. As affinity for a ligand binding a second monomer, and initiation of dimerisation, is affected by the first ligand pole being bound, we describe this as cooperativity in this model. Along with analysing the effects of cooperativity we use parameter estimation to fit our model to observed experimental data both with and without the drug Cediranib; a drug that is an inhibitor of VEGF tyrosine kinases.

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MULTISCALE MODELLING AND ANALYSIS OF INTERCELLULAR SIGNALLING PROCESSES IN BIOLOGICAL TISSUES

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Keywords: Cellular signalling processes, Homogenization, Coupled bulk-surface PDEs, Two-scale numerical simulations, Nonlinear PDEs.

In order to better understand development, growth and remodelling of biological tissues and organs a better understanding of interactions between cells in a tissue is required. Essential parts of communications between cells, as well as cell responses to external and internal stimuli, are governed by intercellular signalling processes. In this talk we consider derivation and analysis of mathematical models for cellular signalling processes on the level of a single cell. A coupled system of nonlinear bulk-surface partial differential equations is used to model the dynamics of signalling molecules in the inter- and intra-cellular spaces and of cell membrane receptors. Using multiscale analysis techniques we derive macroscopic two-scale model for signalling processes defined on the tissue level. Two-scale numerical method is developed and implemented for simulations of the macroscopic bulk-surface problem. The nonlinear coupling between microscopic and macroscopic scales induces formation of patterns in the dynamics of solutions of the macroscopic model for cellular signalling processes, which may correspond to heterogeneity in cellular response mechanisms.