Quantitative Systems Biology

King's College London

November 3, 2017

Welcome Address

It is with great pleasure that we welcome you to the Quantitative Systems Biology (QSB) workshop. The aim of this workshop is to bring together experts working at the interface between biology/biomedicine and quantitative sciences, to discuss the latest developments in their research and novel approaches to existing problems.

In recent years there has been a surge in theoretical, computational and data-driven techniques used in the life sciences, due to high throughput experiments, the explosion in big data and an increase in computing performance. Methodologies which have been present in other fields for many years are now crossing the subject border to the benefit of the field. However, things are not as simple as translating the techniques into the language of biology. Living systems are often driven by processes far from equilibrium and require a combination of system-specific knowledge and experimental insights. Thus, researchers on both sides of the interface have valuable skillsets to offer when approaching a problem. It is for this reason that we were motivated to organise this meeting. We hope that the QSB workshop will continue to accelerate the dialogue that is evidently needed in such interdisciplinary work. The workshop will focus on three of the biggest themes in modern biomedicine: regulatory networks; protein folding; and cell fate decisions. Our programme consists of a series of talks from invited speakers and select participants, with two poster sessions providing the opportunity for detailed discussion and networking.

We are fortunate to have the support of the EPSRC through the CANES (Cross-disciplinary Approaches to Non-Equilibrium Systems) Centre for Doctoral Training (CDT), based here at King's College London. Following the Workshop on Localisation in Quantum Systems (WoLQS) back June, this is the second meeting of year facilitated by CANES which showcases both the high quality and diversity of research supported by the CDT. If you enjoy this meeting, we would like to take this opportunity to draw your attention to next June's Conference on Non-Equilibrium Systems - CONES 2018 - of which further details will be made available on the CANES website next year. We also owe many thanks to our sponsor Overleaf for helping to make this event possible. Without their support, QSB would be a much smaller affair.

Finally, we would like to thank all participants, speakers, and the wider scientific community for the fantastic reception we have received whilst organising this workshop. We hope QSB will provide the opportunity for attendees to gain new insights and act as a platform for future collaborations. To this end, we have included a list of all registered participants and their contact details at the end of this booklet, which we hope will act as a catalyst beyond today's event.

We hope you enjoy the exciting scientific programme that we have on offer!

Yours faithfully,

The Organising Committee:
Ryan Hannam
Edgar Herrera Delgado
Kirsten Jenkins
Irene Marzuoli

Contents

Schedule

All talks shall take place in the Nash Lecture theatre, whilst registration, lunch and the poster session will be held in the River room. Both of these rooms are located on the 2^{nd} floor of the King's building.

Time	**Speaker**	**Title**
09:30-09:45		**Introduction & registration**
09:45-10:30	Peter Swain	An intracellular organization of extracellular information
10:30-11:15	Carole Proctor	Using computer simulation models to investigate the molecular mechanisms of ageing
11:15-11:45	Joseph Ng	Functional enrichment of gene expression neighbours reflects diversification of APOBEC3 cytidine deaminases in cancers
11:45-13:15		**Lunch & poster session**
13:15-14:00	Alex Fletcher	Cancer progression and therapeutic response: A role for agent-based and multiscale modelling
14:00-14:45	Charlotte Deane	Improving fragment assembly protein structure prediction
14:45-15:15	Silvia Grigolon	Friction forces position the neural anlage
15:15-16:15		**Poster session**
16:15-17:00	Julian Gough	A computational system for manipulating cell fate control networks (Morgrify)
17:00-17:30	Johannes Pausch	A field-theoretic approach to microtubule growth
17:30-17:45		**Concluding remarks**

Invited Speakers

An intracellular organization of extracellular information

09:30

Peter Swain
Edinburgh University

Using computer simulation models to investigate the molecular mechanisms of ageing

10:30

Carole Proctor
Newcastle University

Cancer progression and therapeutic response: A role for agent-based and multiscale modelling

13:15

Alex Fletcher
University of Sheffield

Improving fragment assembly protein structure prediction

14:00

Charlotte Deane
University of Oxford

A computational system for manipulating cell fate control networks (Morgrify)

16:15

Julian Gough
MRC Laboratory of Molecular Biology

Selected Talks

Functional enrichment of gene expression neighbours reflects diversification of APOBEC3 cytidine deaminases in cancers

11:15

Joseph Ng

King's College London

Apart from their more well-studied function of countering retroviral infection, APOBEC3 enzymes have been associated with a distinct mutational signature in some cancer types. Here we ask if the expression of APOBEC3 genes and their co-expression patterns with other genes entail functional roles they play in cancers. Looking at RNA-seq data from 8,951 tumours covering 25 cancer types, as well as that of cancer cell-lines and normal tissues, we made use of curated and experimentally derived gene sets and functionally annotated networks of co-expression neighbourhoods of the APOBEC3 genes. Expression of APOBEC3B, the primary candidate as a mutagen in cancers, were correlated with cell-cycle and DNA repair genes, while other APOBEC3 members were more related to specific immune cell populations. The analysis highlighted molecular signatures characteristic of tumour types with widespread APOBEC3 mutational patterns, and contrasted the upregulation of different APOBEC3 enzymes in cancers.

Friction forces position the neural anlage

14:45

Silvia Grigolon

The Francis Crick Institute

During embryonic development, mechanical forces are essential for cellular rearrangements driving tissue morphogenesis. In this talk, we show that in the early zebrafish embryo, friction forces are generated at the interface between two tissues moving in opposite directions, anterior axial mesoderm (prechordal plate, ppl) progenitors and neurectoderm progenitors. By a combination of experiments and modelling, we show that this process depends on hydrodynamic coupling between neurectoderm and ppl as a result of E-cadherin-mediated adhesion between those tissues. These friction forces lead to global rearrangement of cells within the neurectoderm and determine the position of the neural anlage. Our results thus establish the emergence of friction forces at the interface between moving tissues as a critical force-generating process shaping the embryo.

A field-theoretic approach to microtubule growth

17:00

Johannes Pausch

Imperial College

Microtubule filaments are a major part of the cytoskeleton. They influence the shape and movement of the cell and are used for transport processes inside the cell. Microtubules grow and shrink by polymerising and depolymerising, that is by absorbing and emitting tubulin which diffusively spread in the cytoplasm. Here, we model the stochastic process of microtubule growth as a field theory.

In our model, we recover the classic diffusion and diffusion-convection results. Furthermore, we are able to model the tubulin-absorption-induced spatially discrete growth of the microtubule filament and find analytic real space results. Our approach produces analytic expressions in Fourier space that require a short-length scale cutoff in two dimensions and above. It is particularly flexible to incorporate more complex interactions between microtubules and tubulin. In one dimension, our results are easily compared to corresponding results using probabilistic techniques.

Poster Presentations

Mathematical modelling of cancer immunology: Receptor-ligand interactions and T cell signaling

Joseph R. Egan, Ben D. MacArthur and Tim J. Elliott
University of Southampton

T cell receptors can bind with antigens presented on the surface of tumour cells allowing an activating signal to be sent to the T cell. However, a tumour cell can avoid such an immune response by sending an inhibitory signal to the T cell via a second binding event. Let R represent a receptor, L represent its associated ligand, and B represent the complex that is formed when the ligand and receptor bind together. This interaction can be described as a reversible hetero-dimerization reaction where the ratio of the unbinding and binding rates is known as the dissociation constant, K_d. In a stochastic framework we have showed that if K_d is approximately equal to the larger of the total number of receptors, R_T, or the total number of ligands, L_T, then the number of bound complexes, B, is in a regime of high variability. We speculate that these high fluctuations in the number of bound complexes may have an impact on the immune response of T cells against tumour cells.

Correlations and hyperuniformity in the avalanche size of the Oslo Model

Rosalba García Millán
Imperial College London

Hyperuniformity is a property of some point patterns and time series where there is an anomalous suppression of fluctuations. It has been shown that certain patterns in living tissues display a hyperuniform behaviour (Jiao et al., PRE 89 022721, 2014). We are interested in avalanche models, which have applications on avalanches in networks of cortical neurons (Lombardi et al., PRL 108 228703, 2012). We study the fluctuations of the avalanche size of the Oslo rice pile Model and prove that this model displays hyperuniformity in the long timescales (preprint arXiv:1710.00179, 2017).

Cell reprogramming modeled as transitions in a hierarchy of cell cycles

Ryan Hannam

King's College London

We construct a minimal model for cell reprogramming which builds on key elements of cell biology viz. cell cycles and cell lineages. Although reprogramming has been demonstrated experimentally, much of the underlying processes governing cell fate decisions remain unknown. This work aims to bridge this gap, using a complex systems approach to model cell types as a set of hierarchically related dynamical attractors that represent cell cycles. Stages of each cell cycle are characterised by the configuration of gene expression levels, and reprogramming corresponds to triggering transitions between such configurations. Two mechanisms were found for reprogramming in a two level hierarchy: cycle specific perturbations and a noise-induced switching. These reprogramming protocols were found to be effective in large regimes of the parameter space and make specific predictions concerning reprogramming dynamics which are broadly in line with experimental findings.

[1] RH, A Annibale, R Kuhn J. Phys. A: Math. Theor. 50 (2017) 425601

Investigating spatial regulation through synthetic physical interactions with the yeast centrosome

Rowan Howell

King's College London, The Francis Crick Institute

Background: The Mitotic Exit Network (MEN) is a group of proteins which coordinate late mitotic events to ensure timely mitotic exit and faithful chromosome segregation. The Spindle Pole Body (SPB), or yeast centrosome, plays a key role as a scaffold for MEN proteins. However, a systems level view of how spatial factors influence the regulation of the MEN is still lacking.

Results: A high-throughput method was used to force over 4000 different proteins to localize to the SPB and screen for a slow growth phenotype. Synthetic physical interactions were detected between the proposed MEN scaffold protein Nud1 and several MEN proteins as well as kinases and phosphatases involved in MEN regulation.

Conclusion: A synthetic physical interaction screen has provided evidence that misregulating the localisation of MEN components can result in slow growth phenotypes. A pipeline for integrating these phenotypes with literature data to build a Boolean model of mitotic exit is suggested.

ZoomVar: automated annotation of NGS data onto 3D protein interactions

Anna Laddach

King's College London

A plethora of methods have been developed for the mapping of nsSNVs to protein interactions and structures. Unfortunately, to the best of our knowledge, no tools currently exist for the large scale automated mapping of variants from NGS data to experimentally resolved binary complexes. To fill this niche we present a tool, ZoomVar, which consists of a database and query script. The tool enables users to annotate NGS data in several formats (e.g. ANNOVAR, VEP output) and retrieve residue level information from a 3D integrated protein-protein interaction (PPI) network. Users are also able to calculate the statistical enrichment of submitted variants in the core, surface and interface regions of a protein.

We believe that the interrogation of ZoomVar's 3D integrated protein-protein interaction network may offer new insights into the molecular mechanisms of genetic variants.

De Novo Peptide Self-Assembly for Antimicrobial and Gene Delivery Strategies

Irene Marzuoli

King's College London

Antimicrobial resistance has massively increased in the last decades qualifying itself as a threat to human health. In the last decade, the lack of newly discovered antibiotics have pointed out the emerging potential of antimicrobial peptides (AMP): short fragments of larger proteins naturally occurring in the mammal organisms and exerting a broad spectrum of weak antibiotic actions. AMPs attack selectively the bacterial membrane and not the mammalian one due to the different charge and structure between them, and have a low potential for resistance development as any mutation reducing the binding affinity of AMPs is likely to impact negatively on the life related functions of the membrane. AMPs potential can be enhanced when many copies are collected together: recently engineered units at the Biophysics section of the National Physical Laboratory includes a short antimicrobial sequence derived from the bovine lactoferricin (1LFC) and have been shown to self-assemble into hollow spherical capsules viable for gene delivery [1]. The atomistic structure of such self system though is not entirely accessible to current experiments, as well as the precise antimicrobial mechanism of these artificial units. Molecular dynamics (MD) simulations can uncover the structure and processes at the atomistic scale describing the dynamics of the system studied in [1]. We use a hierarchical approach to test small crucial entities involved in the recognition mechanism between units and in shaping their geometry, identifying the role of hydrogen bonds and of hydrophobic segregation in the stability of the structure. In parallel, simulations on model membranes mixtures resembling the ones used in experimental conditions highlight the relation of such structure with the antimicrobial activity observed. The atomistic simulations of larger assemblies are possible including stronger hypotheses in building its putative geometry, thus many of these are being tested to identify the features which lead to a stable system. Once characterised the structures, a Coarse Grain approach will be followed to monitor the self-assembly itself.

[1] Castelletto V. et al., Chem. Sci., 7(3):1707?1711, 2016

Medical imaging based computational modelling of Cardiac arrhythmias

Aditi Roy

King's College London

Catheter ablation is a well-established therapy for atrial fibrillation (AF), but clinical outcomes remain suboptimal due to a lack of knowledge of patient-specific ablation sites. Increasing evidence suggest both fibrosis distributions and atrial wall thickness (AWT) can influence the dynamics of re-entrant drivers (RDs) sustaining AF. This study aims to analyse the role of fibrosis and AWT in determining RD sites in realistic human atrial models. 4 Right (RA) and 4 left (LA) atrial geometries were obtained with a novel black-blood PSIR MRI protocol. In the LA, fibrosis distributions were obtained from LGE MRI, and in the RA synthetic fibrotic patches were added. These subject-specific geometries were integrated into 3D atrial models with the Fenton-Karma model adopted to reproduce atrial electrophysiology. In the RA without fibrosis, RDs anchored only to crista terminalis (CT). In the LA, RDs either anchored to or broke into multiple wavelets around fibrotic tissue.

The observer effect in cell biology: A tale of two alleles

Rosana Smith

University of Southampton

Fluorescence reporters allow investigation of temporal changes in protein expression in live cells and are consequently an essential measurement tool in modern molecular biology. However, their utility is dependent on their accuracy, and the effects of reporter constructs on endogenous gene expression kinetics are not well understood. Here, using a combination of mathematical modelling and experiment, we show that widely used reporter strategies can systematically disturb the dynamics they are designed to monitor, sometimes giving profoundly misleading results. We illustrate these results by considering the dynamics of the pluripotency regulator Nanog in embryonic stem cells, and show how reporters can induce heterogeneous Nanog expression patterns in reporter cell lines that are not representative of the wild-type. These findings help explain the range of published observations of Nanog variability and highlight the problem of measurement in cell biology in relation to genetic reporters.

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