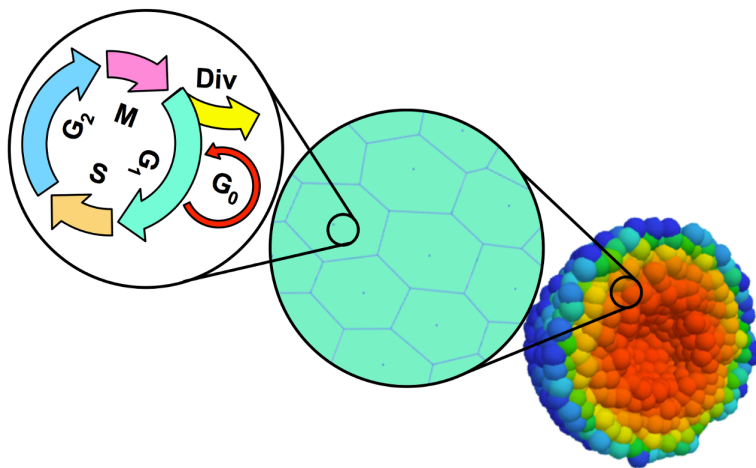# MATRI

Virtual Tissues: Progress and Challenges in Multicellular Systems Biology

July 2nd – 6th 2018

MATRIX Victoria

Workshop Attendees, Abstracts and Themes

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Attendees

- **Axel Almet**, University of Oxford, `Axel.Almet@maths.ox.ac.uk`

- **Sandy Anderson**, Moffit Cancer Centre, `alexander.anderson@moffitt.org`

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- **Michael Watson**, University of Sydney, `michael.watson@sydney.edu.au`

Abstracts

Sandy Anderson, Moffit Cancer Centre

alexander.anderson@moffitt.org, **Talk session: Wednesday 9:00**

The importance of normal tissue homeostasis in cancer initiation, progression and treatment

Abstract

The role of genetic mutations in cancer is indisputable: They are a key source of tumor heterogeneity and drive its evolution to malignancy. But, the success of these new mutant cells relies on their ability to disrupt the homeostasis that characterizes healthy tissues. Mutated clones unable to break free from intrinsic and extrinsic homeostatic controls will fail to establish a tumor. Therefore, an evolutionary view of cancer needs to be complemented by an ecological perspective to understand why cancer cells invade and subsequently transform their environment during progression. Importantly, this ecological perspective needs to account for tissue homeostasis in the organs that tumors invade, because they perturb the normal regulatory dynamics of these tissues, often coopting them for its own gain. Here we will discuss this eco-evolutionary view of cancer through the lens of tumor metabolism.

Metabolism acts as a central integrator to mediate cellular response to the changing microenvironment, linking the effects of hypoxia, acidosis, proliferation and necrosis. Locally-limited selection will drive tumor progression to create a range of phenotypes, which can in turn affect their local environment in different ways. In order to understand the complex interplay between these elements, we have developed a hybrid multi-scale mathematical model of tumor growth in a vascularized tissue. A key component of this model is normal and tumor metabolism and its interaction with microenvironmental factors. The metabolic phenotype of tumor cells is plastic, and microenvironmental selection leads to increased tumor glycolysis and decreased pH. Once this phenotype emerges, the tumor dramatically changes its behavior due to acid-mediated invasion, an effect that depends on the heterogeneity of the tumor cell phenotypes and their spatial distribution within the tumor. The tumors grown within this in silico model display much phenotypic variation, and this heterogeneity depends on the conditions of the microenvironment and the plasticity of the tumor cells.

Using our model, we administer several therapies, including chemotherapy, vascular therapy, pH buffer therapy, and hypoxia-activated drugs. The model predicts that pH buffer therapy will only have a tumor-preventative effect if administered before the tumor acquires the heterogeneous state that leads to acid-mediated invasion. This is in agreement with experimental results from a spontaneous prostate tumor mouse model (TRAMP mouse). In general, the model predicts that the outcomes of each therapy are highly dependent on the initial tumor heterogeneity at the time of commencing treatment. We categorize the ?signatures? of each therapy outcome as a function of the heterogeneity class of the initial tumor. By understanding the signature of each drug in isolation, we implement drug combinations

in a sequence that promotes synergistic response for a given class of tumor heterogeneity. The signature of the first drug in the sequence is used to pick the following complementary drug. This produces a more intelligent treatment regimen that can be designed to harness tumor heterogeneity and modulate its impact on treatment outcomes.

Bartosz Bartmanski, University of Oxford

bartmanski@maths.ox.ac.uk, Talk session: Thursday 14:00

Effects of different discretisations of the Laplacian in stochastic simulations.

Abstract

A deterministic model of biochemical reaction networks is not always appropriate. Gene expression, for example, often involves a small number of molecules which means that noise can significantly influence the dynamics. By discretising space into voxels and letting the molecule dynamics be governed by the reaction-diffusion master equation, it is possible to model the reaction and diffusion of individual molecules on an arbitrary domain. Following on from the work of Meinecke and Ltstedt we apply a variety of numerical methods to the Laplacian operator in order to derive the jump rates that simulate the diffusion of molecules. We discuss how pattern formation within a Turing model might be influenced by the geometry of the spatial discretisation and the numerical method.

Phillip Brown, University of Adelaide

phillip.j.brown@adelaide.edu.au, **Talk session: Thursday 9:00**

Modelling Colon Cancer: Serrated Sessile Polyps

Abstract

Serrated sessile polyps (SSPs) are a type of lesion found in the colon that are known to lead to colorectal cancer. They develop when there are disruptions in the processes controlling the function of colonic crypts - the test-tube shaped structures that make up the lining of colon. They are currently much harder to detect than conventional polyps, owing to their flat (sessile) appearance, and hence are less likely to be identified early, increasing the likelihood that they progress to cancer.

The term "serrated" comes from the saw-tooth appearance of the crypt walls seen in histology images. It is currently not clear what will cause a healthy crypt to become serrated, but it has been shown that SSPs are associated with mutations to the BRAF or KRAS genes which may cause resistance to apoptosis and an increase in proliferation rates.

This project hopes to shed light on the physical and mechanical processes that lead to serrations by using agent-based modelling techniques to recreate the serrated morphology. In particular, it will use the package CHASTE to achieve this.

In this talk I will give an overview of the biology of SSPs and describe the preliminary modelling work done to recreate the aspects of a healthy colonic crypt that may be important to SSP formation.

Josh Bull, University of Oxford

bull@maths.ox.ac.uk, **Talk session: Wednesday 9:00**

Agent-based modelling demonstrates the impact of localised tumour cell proliferation and death on macrophage infiltration

Abstract

Joshua A. Bull, Prof. Sarah Waters, Prof. Vicente Grau, Dr. Tom Quaiser, Dr. Franziska Mech, and Prof. Helen Byrne.

Growing tumours are infiltrated by a variety of immune cells, including macrophages, a type of immune cell which can adopt a range of pro- or anti-tumour phenotypes depending on microenvironmental cues. The spatial distribution of macrophages within a tumour varies from patient to patient and between different tumour types, and is related to patient outcome. There is considerable interest in understanding the mechanisms regulating the spatial localisation of macrophages within solid tumours and in exploiting tumour associated macrophages to deliver treatment to cancer cells [1, 4]. As a first step to understanding patterns of macrophage localisation within solid tumours, we consider the roles played by tumour cell proliferation and death in driving cell movement from proliferative tumour regions to hypoxic regions. This movement, induced by oxygen gradients within a tumour, must be taken into consideration when characterising patterns of macrophage infiltration. To understand the impact that this background movement has on macrophage infiltration, we first consider the infiltration of inert polystyrene microbeads into a tumour spheroid using data from [2]. We use the CHASTE modelling framework [3] to develop an agent-based model of microbead infiltration into a spheroid, and show how varying the rates of tumour cell proliferation and death influences the patterns of bead infiltration into the tumours. We then extend our model to include macrophages and CSF-1, a macrophage chemoattractant produced by hypoxic tumour cells. By comparing the infiltration patterns of the macrophages in this model with those of the microbeads, we identify components of macrophage infiltration due to active (chemotactic) movement and passive components associated with tumour cell proliferation and death. Identifying which variations in macrophage distribution are due to active or passive processes may help determine which patients are most likely to respond to treatment with CSF-1 inhibitors [4].

[1] Bronte, V., & Murray, P. J. (2015). Understanding Local Macrophage Phenotypes In Disease: Modulating macrophage function to treat cancer. Nature Medicine, 21(2), 117–119. http://doi.org/10.1038/nm.3794

[2] Dorie, M. J., Kallman, R. F., Rapacchietta, D. F., Van Antwerp, D., & Huang, Y. R. (1982). Migration and internalization of cells and polystyrene microspheres in tumor cell spheroids. Experimental Cell Research, 141(1), 201–209. http://doi.org/10.1016/0014-4827(82)90082-9

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Gavaghan, D. J. (2013). Chaste: An Open Source C++ Library for Computational Physiology and Biology. PLoS Computational Biology, 9(3). http://doi.org/10.1371/journal.pcbi.1002970

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Jess Crawshaw, University of Melbourne

`jessica.crawshaw@student.unimelb.edu.au`, **Talk session: Tuesday 9:00**

A computational model of vascular deformation

Abstract

Blood pulsating through our vessels places an unyielding mechanical load on the vessel walls. Recent years have seen a substantial increase in the understanding of the interplay between the dynamics of blood flow (haemodynamics) and vascular morphology. Disturbances to the homeostatic distribution of forces on the vessel wall is correlated with various cardiovascular diseases, including atherosclerosis and aneurysm development and rupture. Furthermore, changes in the local haemodynamics has a notable effect on vascular development and remodeling. Experimental analysis of this relationship is invasive and extremely difficult to measure in real time. As such, the development of computational models to analyse the relationship between the local haemodynamics and the surrounding vasculature is invaluable.

In this project we will develop a computational model to study how vessels deform when subject to internally and externally applied forces. Using the open source multicellular modeling software package, Chaste, we will employ a discretised approach to simulate long time scale vascular wall deformation. A voronoi tessellation-based model will be used to model vessel walls. This discretised model will enable us to examine how blood vessels deform when subject to internal and external forces, thus laying the foundations for future research examining vascular deformation due to haemodynamic pressure.

Bruce Gardiner, Murdoch University

b.gardiner@murdoch.edu.au, Talk session: Thursday 9:00

Computational modelling of articular cartilage: from continuum to discrete approaches

Abstract

Articular cartilage sits at the end of the long bones in a hostile mechanical environment. It is often considered a relatively inert and simple tissue, as it contains one cell type, no blood vessels, no lymphatics or nerves and is slow to repair following injury. For some time now we have been developing computational models to systematically integrate the various chemical and mechanical processes that determine how the tissue develops and maintains its functional mechanical properties. These models include biomechanical continuum models of poro-elasticity, reaction-advection-diffusion models for transport of various growth factors, cytokines and ECM components, discrete models of cell migration and shape changes and statistical models of osteoarthritis risk analysis. These various approaches will be described in the context of a dynamic understanding of how cartilage "works" as a tissue.

James Glazier, Indiana University

glazier@indiana.edu, Talk session: Tuesday 9:00

Multiscale Multicell Virtual Tissue Modeling Using CompuCell3D

Abstract

The difficulty of predicting the emergent development, homeostasis and disfunction of tissues from cells? molecular signatures limits our ability to integrate molecular and genetic information to make meaningful mechanistic predictions of the effects of molecular perturbations at the organ or organism level. Virtual Tissues are an approach to constructing quantitative, predictive mechanistic models starting from cell behaviors and combining subcellular molecular kinetics models, the physical and mechanical behaviors of cells and the longer range effects of the extracellular environment. Because construction of Virtual Tissue models from scratch is extremely time consuming and limits the number of researchers who can apply these methods, we developed an open-source Virtual-Tissue model-building environment (CompuCell3D) to simplify the construction of sophisticated Virtual-Tissue models. Because CompuCell3D models are written in modular and compact Python scripts and a simple XML (CC3DML), they facilitate initial model development and submodel reuse and extension, even by non-specialists

As an example of such a model, I will discuss autosomal dominant polycystic kidney disease (ADPKD). Extensive research has uncovered genetic changes associated with ADPKD and their effects on signaling pathways. However, we still do not know the precise sequence of events that lead to cyst initiation. One of the key changes during the initiation of cysts is abnormal expression of the juvenile cell adhesion molecule cadherin-8. We examined hypothetical cell-level mechanisms by which abnormal expression of cadherin-8 could initiate cyst formation to show that reduced cell adhesion appeared to be the dominant mechanism leading to cystogenesis. Gene expression analysis based on the connection between adhesion defects and regulation of cell cycle identified increased expression of cGMP phosphodiesterases as likely pathways connecting cell adhesion to cystogenesis. We then applied cGMP phosphodiesterase inhibitors already FDA approved for other uses to both in vitro human cystic kidney lines and mouse strains which spontaneously developed ADPKD-like cysts. In both cases, the cGMP phosphodiesterase greatly reduced or eliminated cystogenesis.

Guillermo Gomez, University of South Australia

Guillermo.Gomez@unisa.edu.au, Talk session: Tuesday 11:00

Active mechanical relaxation at adherens junctions mediates topological transitions for cell extrusion.

Abstract

Cell extrusion allows the elimination of minorities of cells from the epithelium. Although this process entails active events that occur within the extruding cell, much less is known on the role of its neighbouring cells. Using apoptotic cell extrusion as a model, we found that as cell extrusion completes, the junctions on neighbouring cells, elongate and form multicellular junctions or 'rosettes'. Computational modelling and experimentation show that active mechanical softening of junctions plays a key role during these junctional rearrangements that have all the characteristic of a topological transition. Junctional mechanotransduction is essential for epithelial topological transitions during extrusion as tension-sensitive junctional accumulation of cofilin-1 activates SFKs that are required for active junctional softening. We therefore propose that softening of the tissue plays a key role facilitating the topological that favours extrusion.

Edward Green, University of Adelaide

edward.green@adelaide.edu.au, **Talk session: Monday 11:00**

More than meets the eye: quantifying spatial patterns in model simulations and experimental results

Abstract

Spatial patterns arise in a wide variety of biological systems, important examples being the arrangements of individual animals within a swarm, or of cells of different types in a tissue. These patterns occur as a result of self-organisation, i.e. they emerge naturally from the interactions between individual animals or cells. Understanding what types of interactions lead to different types of pattern is therefore a fundamental problem in areas such as tissue growth and development,regenerative medicine and cancer research.

In this talk, I will discuss some recent work where we have used pair-correlation functions to quantify spatial patterns, and how this can facilitate comparison between simulations and experimental results, and potentially give insights into the underlying pattern-forming mechanisms.

Daniel Hahne, Leipzig University

hahne@bioinf.uni-leipzig.de, Session: Friday 9:00

Multiscale modeling of liver regeneration in 3D

Abstract

Hoehme S., D'Alessandro L.A., Hengstler J., Klingmueller U., and Drasdo D.

During the last years, modeling of different physiological and pathological aspects of the liver advanced significantly with the development of increasingly realistic models on molecular, cellular, tissue and whole organ scale. Nevertheless, model driven liver research is still hampered by a lack of techniques that allow robust integration of these different scales into unifying frameworks. We here present a novel multiscale spatio-temporal 3D model of liver tissue (Fig.1) that is based on in-vivo 3D imaging and that may serve as such unifying framework. We use this model to study liver regeneration upon damage or tissue loss which depends on intracellular and tissue scale processes, which interplay with tissue mechanics. In order to capture all these processes at their respective scales, the presented multiscale modelling framework integrates sub-models at all relevant scales from intracellular signalling to body level. It thereby allows predictions on a wide range of possible regeneration scenarios and helps to identify on one hand particularly informative experiments permitting to distinguish between alternative mechanisms, on the other hand impossible scenarios that should not be pursued experimentally. In this way, the model predictions can guide the experimental strategy. The multiscale tissue model is able to simultaneously reproduce all experimental observations including the regeneration process kinetics on the tissue scale. The presented study is an example for how the tight systems-biological integration of experimentation and modelling, both covering multiple scales, can facilitate understanding of complex multi-scale processes as liver regeneration.
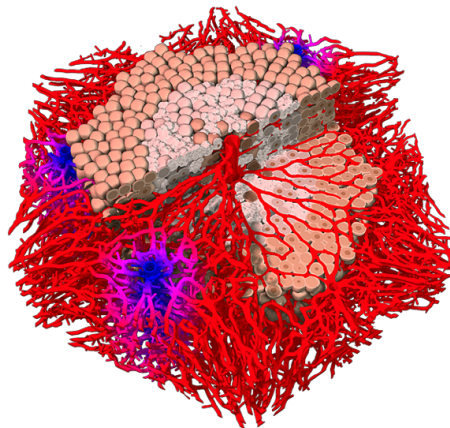
Figure 1: Visualisation of spatio-temporal model of a liver lobule

Yangjin Kim, Konkuk University

ahyouhappy@konkuk.ac.kr, Talk session: Wednesday 9:00

Role of extracellular matrix and microenvironment in regulation of tumor growth and LAR-mediated invasion in glioblastoma: A multi-scale mathematical model

Abstract

Yangjin Kim, Hyunji Kang, Gibin Powathil, Hyeongi Kim, Dumitru Trucu, Wanho Lee, Sean Lawler, and Mark Chaplain.

The cellular dispersion and therapeutic control of glioblastoma, the most aggressive type of primary brain cancer, depends critically on the migration patterns after surgery and intracellular responses of the individual cancer cells in response to external biochemical cues in the microenvironment. Recent studies have shown that miR-451 regulates downstream molecules including AMPK/CAB39/MARK and mTOR to determine the balance between rapid proliferation and invasion in response to metabolic stress in the harsh tumor microenvironment. Surgical removal of main tumor is inevitably followed by recurrence of the tumor due to inaccessibility of dispersed tumor cells in normal brain tissue. In order to address this complex process of cell proliferation and invasion and its response to conventional treatment, we propose a mathematical model that analyses the intracellular dynamics of the miR-451-AMPKmTOR-cell cycle signaling pathway within a cell. The model identifies a key mechanism underlying the molecular switches between proliferative phase and migratory phase in response to metabolic stress in response to fluctuating glucose levels. We show how up- or down-regulation of components in these pathways affects the key cellular decision to inltrate or proliferate in a complex microenvironment in the absence and presence of time delays and stochastic noise. Glycosylated chondroitin sulfate proteoglycans (CSPGs), a major component of the extracellular matrix (ECM) in the brain, contribute to the physical structure of the local brain microenvironment but also induce or inhibit glioma invasion by regulating the dynamics of the CSPG receptor LAR as well as the spatiotemporal activation status of resident astrocytes and tumor associated microglia. Using a multiscale mathematical model, we investigate a CSPG-induced switch between invasive and non-invasive tumors through the coordination of ECM-cell adhesion and dynamic changes in stromal cells. We show that the CSPG-rich microenvironment is associated with non-invasive tumor lesions through LAR-CSGAG binding while the absence of glycosylated CSPGs induce the critical glioma invasion. We illustrate how high molecular weight CSPGs can regulate the exodus of local reactive astrocytes from the main tumor lesion, leading to encapsulation of non-invasive tumor and inhibition of tumor invasion. These different CSPG conditions also change the spatial proles of ramied and activated microglia. The complex distribution of CSPGs in the tumor microenvironment can determine the nonlinear invasion behaviors of glioma cells, which suggests the need for careful therapeutic strategies.

Melissa Knothe-Tate, University of New South Wales

m.knothetate@unsw.edu.au, **Talk session: Monday 11:00**

nverse and Recursive Approaches to Understand and Emulate Tissue Design

Abstract

Computational Modeling provides a robust platform which, when paired with novel experimental methods and technological platforms, enables unprecedented understanding of mechanisms underpinning tissues' smart (stimuli responsive) properties as well as the application of this understanding to engineer and manufacture materials that emulate nature's designs. This talk will discuss how my MechBio Team uses this approach across length and time scales, in collaboration with mathematicians, computational modelers, cell biologists, physiologists, physicists and physicians.

Kynan Lawlor, Murdoch Children's Research Institute

kynan.lawlor@mcri.edu.au, **Talk session: Tuesday 14:00**

Nephron progenitor cell migration and stochastic commitment during mouse kidney development

Abstract

The kidney contains a tightly packed array of nephrons that filter blood and output waste. Renal organogenesis is driven by interactions between epithelial cells that form the branched urine collecting system, and the surrounding mesenchyme that gives rise to the nephrons. A niche composed of mesenchymal nephron progenitors and the tips of branching epithelia provide signals that maintain the nephron progenitor pool during development, while distinct inductive signals trigger cells to differentiate and form nephrons. New nephrons form continually through an iterative process where branching events initiate nephrogenesis at sites adjacent to the ureteric epithelial tips. We have been studying kidney development in mouse and organoid models with a focus on live quantitative imaging and high resolution phenotyping using imaging and single cell RNA-seq. We have used multiscale imaging and mathematical modelling to quantify mouse kidney development at the niche and organ scale. Using live imaging we established that the mesenchymal nephron progenitor population behaves like a motile swarm rather than a static domain, with cells frequently moving within and between domains in response to signals from the niche. The mechanism by which this population exits in a dynamic state, but continually gives rise to nephrons at defined locations has been one focus of our recent work. Using an inducible marker of committing cells we find that stochastic migration events enable a proportion of committing cells to escape commitment and accumulate within the progenitor pool. Single cell RNA-seq reveals that these 'escapers' exist in the same range of transcriptional states as uninduced progenitors, suggesting that cells may bi-directionally traverse the transcriptional hierarchy between self-renewal and commitment. Our observations are consistent with a computational model of positionally-triggered stochastic commitment. We propose that nephron progenitor commitment is a stochastic process where the duration of exposure to spatially defined inductive cues is dependent on migration events. Progenitor plasticity may enable robust regulation of nephrogenesis as niches grow and are remodelled during organogenesis.

Sharon Lubkin, North Carolina State University

`lubkin@ncsu.edu`, Talk session: Monday 14:00

Assessing physical control mechanisms in early morphogenesis of the lung

Abstract

We have developed several models of the physical control of branching morphogenesis in the lung, considering a variety of factors, including transport, static lumen pressure, and dynamic pressure waves (peristalsis). How reasonable a model initially seems is not necessarily correlated with its explanatory power. In this talk, we will present a variety of continuous deterministic models of the early lung and its morphogenesis, and compare their implications.

Paul Macklin, Indiana University

macklinp@iu.edu, Talk session: Thursday 9:00

Open source software for 3-D multicellular cancer systems biology

Abstract

Cancer involves complex, spatial dynamical interactions between processes at the molecular and multicellular scales. Cancer cells deplete growth substrates while releasing metabolic products, contributing to phenotypic adaptations in cancer and non-cancer cells. Cancer and stromal cells communicate, compete, and sometimes coordinate their behaviors through biochemical and biomechanical signals. Multiscale computational models can serve as ?virtual laboratories? to help detangle, understand, and control these complex systems. Ideally, a virtual tissue lab should simulate secretion, uptake, and diffusion of tens or hundreds of chemical signals, while many virtual cells adapt their phenotypes to local information and remodel the tissue microenvironment. Building such systems is difficult, particularly while maintaining cross-platform compatibility on Linux, OSX, Windows, and other architectures.

In this talk, we present our work to create open source tools for 3-D multicellular cancer systems biology. BioFVM [1] can simulate diffusion of tens or hundreds of secreted factors in 3-D tissues; PhysiCell [2] is an off-lattice agent-based model that includes cell cycling, multiple death models, chemical communication, and volume changes, with cell motion driven by the balance of mechanical forces. PhysiCell was written to be extensible, and third-party groups have already contributed new functionality such as Boolean signaling networks via MaBoSS [3]. Both codes are written in fully cross-platform C++ with OpenMP parallelization, and have been tested on platforms ranging from the Raspberry PI to Cray supercomputers. Simulations of 10 signaling factors on 1 million computational voxels with 10^6 off-lattice cells are feasible on desktop workstations and single HPC compute nodes. We will present joint work with Argonne National Lab to run a 3-D model of tumor immunosurveillance in high throughput, performing a large-scale (1.5 years of computing) investigation on the role of stochasticity and heterogeneity in a couple of days [4]. We will show early results to build cloud-hosted simulations with graphical interfaces via Jupyter notebooks, with a focus on cancer nanotherapy. We will also touch on work to standardize simulation and experimental data (MultiCellDS [5]), and discuss opportunities for the community to build and publish ecosystems of compatible tools and data [6].

[1] Ghaffarizadeh et al., Bioinformatics (2016). BioFVM: an efficient, parallelized diffusive transport solver for 3-D biological simulations. DOI: `10.1093/bioinformatics/btv730`

[2] Ghaffarizadeh et al., PLoS Comput. Biol. (2018). PhysiCell: an open source physics-based cell simulator for 3-D multicellular systems. DOI: `10.1371/journal.pcbi.1005991`

[3] Letort et al., Bioinformatics (in review). PhysiBoSS: a multi-scale agent based modelling framework integrating physical dimension and cell signalling. Preprint link: `http://dx.doi.org/10.1101/267070`

[4] Ozik et al., BMC Bioinformatics (2018, in press). High-throughput cancer hypothesis testing with an integrated PhysiCell-EMEWS workflow. Preprint link: `http://dx.doi.org/10.1101/196709`

[5] Friedman et al., bioRxiv (2016, in revision). MultiCellDS: a community-developed standard for curating microenvironment-dependent multicellular data. Preprint link: `10.1101/090456`

[6] Macklin. GigaScience (2018, invited paper, in review). Key challenges facing data-driven multicellular systems biology. Preprint link: `https://arxiv.org/abs/1806.04736`

Claire Miller, University of Melbourne

millerc2@student.unimelb.edu.au, **Talk session: Tuesday 14:00**

Maintaining the stem cell niche in cell-based models of epithelia

Abstract

Epithelial tissue homeostasis requires continual renewal of cells in the basal layer of the tissue. This occurs via stem cell differentiation into epithelial cells, which takes place in the stem cell niche.

Maintaining the stem cell niche is therefore crucial to producing a physically-realistic multicellular model of epithelial tissue homeostasis. We have found that current multi-cellular modelling methods can cause loss of stem cells from the niche in epithelia if no additional maintenance mechanisms are specified. We suggest a new methodology to maintain the niche; a rotational force applied to the two daughter cells during the mitotic phase of division.This methodology enforces a particular division direction, reflecting the regulation of orientation of the mitotic spindle during the final phase of the cell cycle.

We use an overlapping spheres model to demonstrate the loss of the niche in the interfollicular epidermis. We will discuss how this loss occurs, and how we implement the new force to counteract it. Finally, we will discuss the limitations of the model, and how we intend to improve on the methodology in future work.

Zoltan Neufeld, University of Queensland

`z.neufeld@uq.edu.au`, **Talk session: Tuesday 11:00**

Models of collective migration of mesenchymal and epithelial cells

Abstract

The collective migration of cells plays essential role during embryogenesis, wound healing and the spreading of cancer cells. First we consider a simple model for migration of mesenchymal cells in a channel, where the cells move independently and interact only transiently during cell-cell collisions. The model produces two distinct types of motion corresponding to well-ordered collective migration, and inefficient disordered migration. We characterise the different types of collective behaviour and propose a theoretical description to determine the conditions for coherent collective cell movement. We also consider the collective cell migration in an epithelial monolayer with a free edge, where the cells are tightly coupled at cell junctions, and they regulate their motility according to mechanical signals from neighbouring cells. We show that the mechanical interactions result in a backward propagating travelling wave which initiates and coordinates the motile behaviour of the cells.

Don Newgreen, Murdoch Children's Research Institute

don.newgreen@mcri.edu.au, Talk session: Monday 11:00

Agent-based models give novel explanations for puzzling differences in 'penetrance' of birth defects affecting the gut nervous system.

Abstract

The nervous system in the gut (enteric nervous system: ENS) is huge in cell numbers but is derived from a small number of progenitor cells termed enteric neural crest cells (ENCCs). In embryos these cells initially occur at the oral end of the gut but colonise the entire gut by cell movement in a narrow layer in the wall of the gut while simultaneously proliferating. These cells then differentiate into many neuron and glial cell types of which collectively control gut function.

We constructed cellular automata models of early ENS development, encoding rules in which individual ENCCs (agents) move on a 2D domain representing the gut. Movement is directionally stochastic (random walk) and proliferation is under logistical control with stochastic placement of daughters. The ENC agents operate under exclusion constraints. The domain could be growing, representing the normal gut, or static, representing gut in organ culture. There are many pathologies of ENS development including a failure to complete colonisation (Hirschsprung disease) and distal functional insufficiency (slow transit constipation). Notable for these neuropathies is their unpredictable 'incomplete penetrance' and 'variable expressivity', which occurs even in identical (MZ) twins and inbred mice. Two scenarios are presented where stochastic events at individual agent level do not 'even out' at the agent population level but lead to unpredictably variable results.

Firstly we used summed agent based models to plot the position of the distal ENC agent while imposing different proliferation rates. At high proliferation the distal ENC agent always attained the end of the growing domain; at low proliferation the distal agent never reached the end of the domain (Hirschsprung outcome). At intermediate rates, a Hirschsprung outcome occurred probabilistically, and the failure distance varied. This resembles the puzzlingly incomplete penetrance and variable extent of non-colonisation observed even in Hirschsprung MZ twins and in inbred Hirschsprung mice.

Secondly, we used the same model to follow ENC agent clones. This revealed that the final clones varied: most were very small but a few were huge. These 'superstar' clones were generated stochastically in the model. We created biological clonal labelling experiments using avian ENC cells and gut: these confirmed the 'superstar' phenomenon. However, real 'superstars' could be predetermined rather than stochastic. Reducing the size of the starting ENC population would be predicted increase the proportion of 'superstars' if they were generated stochastically but not if they were predetermined. We performed biological assays (600 vs 40 ENC cells) and confirmed the stochastic model's prediction. The 'superstar' impact implies that clonal diversity is diminished in the ENS. Since each cell is likely to have 1-2 thousand stochastic somatic mutations, this in turn means that somatic mutations may

affect ENS function in an unpredictable manner.

The phenomena of 'incomplete penetrance' and 'variable expressivity' have been a clinical puzzle in developmental disease. Explanations have been proposed at all levels but all have been at some level deterministic; these models presented here suggest another entirely different contribution based on stochasticity of individual cell behaviour.

James Osborne, University of Melbourne

jmosborne@unimelb.edu.au, Talk session: Monday 9:30

Comparing individual-based approaches to modelling the self-organization of multicellular tissues

Abstract

The coordinated behaviour of populations of cells plays a central role in tissue growth and renewal. Cells react to their microenvironment by modulating processes such as movement, growth and proliferation, and signalling. Alongside experimental studies, computational models offer a useful means by which to investigate these processes. To this end a variety of cell-based modelling approaches have been developed, ranging from lattice-based cellular automata to lattice-free models that treat cells as point-like particles or extended shapes. However, it remains unclear how these approaches compare when applied to the same biological problem, and what differences in behaviour are due to different model assumptions and abstractions. Here, we exploit the availability of an implementation of five popular cell-based modelling approaches within a consistent computational framework, Chaste (http://www.cs.ox.ac.uk/chaste). This framework allows one to easily change constitutive assumptions within these models. We compare model implementations using four case studies, chosen to reflect the key cellular processes of proliferation, adhesion, and short- and long-range signalling. These case studies demonstrate the applicability of each model and show how the model compare.

(a)   (b)   (c)   (d)   (e)
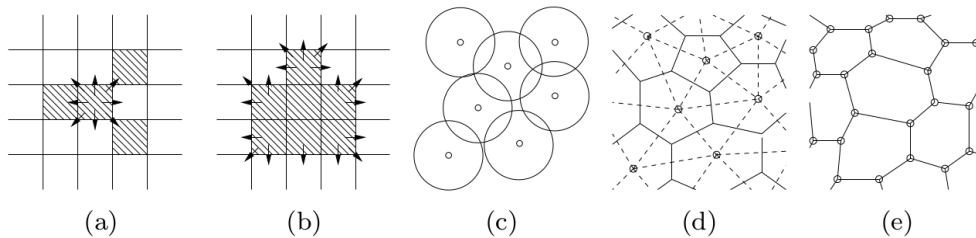
Margriet Palm, Leiden University

`m.m.palm@lacdr.leidenuniv.nl`, Talk session: Monday 14:00

A 3D cell-based model of ECM invasion facilitated by filopodia, ECM degradation, and cell deformation

Abstract

Margriet M. Palm, Andreas Buttenschn, Paul Van Liedekerke, Dirk Drasdo

Cell migration in Extracellular matrix (ECM) or ECM-like environments is driven by the pulling of cells at ECM fibers. However, this same ECM also acts as a physical barrier for cell migration if cells experience the ECM as mechanical obstacles at too high densities. To migrate, cells need to maneuver through the ECM network to find holes they can squeeze through their body. Alternatively, cells can mechanically adapt the elastic ECM and/or break down the ECM using matrix metalloproteinases (MMPs). The combination of these space negotiation mechanisms results in cells that move optimally in an ECM of intermediate density where the cells have a substrate for force transmission while the cells can still squeeze through the ECM gaps. Here we ask if these aforementioned space negotiation mechanisms in combination with migration via pulling are sufficient to explain cell migration pattern such as directed migration in microtrack assays and single cell ECM invasion. Furthermore, we ask if these three mechanisms do also determine multicellular coordinated migration.

We built a computational, cell-based model of cell migration using cells that can adapt their shape, mechanically interact with an elastic ECM, and break down this ECM. Cells are modelled as elastic, adhesive objects that can adapt their shape to the environment by changing from spheres to rods or vice versa. The ECM is represented by a nodal network of springs that mimics the collagen scaffolding structure. Active motion is included in the model by extension of filopodia that attach to ECM nodes and generate transient pulling forces. ECM nodes that are in direct contact with cells may also be degraded, thereby reducing the mechanical resistance of the nodes and the connected springs. This model is then used to study single cell migration of cells in a microtrack or cells embedded in ECM, as well as the collective behavior of cells inside a small spheroid that is embedded in the ECM. This model will eventually be used to predict the invasive capacity of cells in ECM as a function of the mechanical and conformation properties of the ECM and the ability of cells to modify themselves and the ECM.

Chin Wee Tan, Walter and Eliza Hall Institute of Medical Research

cwtan@wehi.edu.au, Talk session: Thursday 14:00

Systems Biology of Colon Crypt Cells, Disease and Development

Abstract

Chin Wee Tan, Ruiyan Zhu, James Osborne, and Antony W. Burgess.

The regulation of cellular homeostasis in the intestine is highly complex with numerous signaling pathways (e.g. Wnt, Notch, EGF, BMP, TGF?) shown to play various roles in the growth of the colon epithelium (Crosnier et al, Nat. Rev. Genet. 2006). In particular, Wnt signaling has been implicated in animal studies (Hirata et al. 2013 Development, Ootani et al. 2009 Nat Med) in colon crypt production and cell production, differentiation, movement and location. And all these processes play critical roles in the growth of and structure of human colorectal adenomas and hyperplastic polyps (Wong et al. 2002 Gut). Using an integrated colon culture 3D imaging system (Tan et al, Sci. Rep. 2015), colon crypt cells can now be grown in vitro as organoids to recapitulate their development and growth in vivo.

We are now able to systematically interrogate the morphological and biochemical development of colon crypt cells in vitro. We are now able to follow and record the morphological development using time-lapsed 3D bright-field imaging as well as quantify the spatial and temporal changes of key developmental proteins (e.g. β-catenin, E-cadherin) under specific cytokines (e.g. EGF) stimulation using 3D confocal microscopy. Subcellular protein dynamics and morphological data will be used to develop computational mathematical models of an in silico colon crypt.

Morphological development of colon mouse adenoma organoids has been followed, providing critical time-line of the crucial developmental stages (e.g. growth rate, developmental phases, timing of crypt formation etc). We have since quantify the Wnt pathway output protein β-catenin subcellular levels and dynamics in normal colon crypt cultures (Tan et al, Sci. Rep. 2015). Quantifying of the corresponding levels and subcellular dynamics of these proteins in mouse colon adenoma are underway, results of which will provide critical data for modelling these pathways in colon crypts cells.

This integrated technique provides a quantitative 3D colon crypt cells assay where perturbation can be conducted in both normal colon and adenoma cultures. Growth morphology and spatial dynamic data of proteins in these colon cells can then be obtained, an invaluable resource for computational modelling to simulate the properties of colon crypt cells in silico. A quantitative understanding of the signaling events during normal and disease colon crypt development will provide critical information for developing both in silico models and therapeutics targeting colon cancer.

Erika Tsingos, Heidelberg University

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Homeostatic growth of multiple tissues in a complex organ: Insights from modeling clonal lineages in the eye of fish

Abstract

How do anatomically and functionally distinct tissues coordinate to direct growth and shape in complex organs?

We address this question using in vivo and in silico clonal lineage tracing in the neural retina and retinal pigmented epithelium of the eye of medaka fish (Oryzias latipes). These tissues lack cell death or rearrangement, such that the shape of labelled clones represents a footprint of the stem cells? previous behavior during the animal's several month-long lifespan.

Using a 3D cell-centre agent-based paradigm, we distil the system to its minimal components. Our model serves as a virtual playground to explore hypotheses about fundamental growth modes and the impact of stochastic cell behaviour on the growth of retinal tissues. Quantitative comparisons of in vivo and in silico experiments revealed that stem cells in the neural retina behave less stochastically and control their division axis to direct growth and shape the organ, whereas stem cells for the retinal pigmented epithelium display greater stochasticity and follow external instructive signals.

Our work highlights how a minimal target node for evolution – the proliferation of neuroretinal stem cells – can be exploited to adapt whole-organ morphogenesis in a complex vertebrate organ.

Michael Watson, University of Sydney

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Investigating in vitro Fibroblast Behaviour with a Generalised Model of Cell Migration

Abstract

Over a series of papers in the late 1990s and early 2000s, Dallon and colleagues developed a novel, off-lattice model of fibroblast migration to investigate extracellular matrix remodelling during dermal wound healing. The model attracted significant interest from the modelling community, but wider applications of the approach are hampered by the assumptions made in the cell migration methodology. In this talk, I will discuss the development of a generalised model formulation that not only maintains the original modelling philosophy, but also broadens the future utility of the approach. Amongst other new features, the generalised model includes a stochastic migratory cue, biophysical cell-cell interactions and dynamically adapting cell morphologies. I will demonstrate the value of the updated model by benchmarking individual and collective movement of in silico cells against experimental data from in vitro fibroblasts. Subsequent simulations of an in vitro scrape wound healing assay reveal an unexplained discrepancy that provides an interesting challenge for future modelling studies.

Discussion topics/ Workshop Themes

Fitting models to data

Types of data available? What is best? Single cell vs tissue level.

How to fit multicellular models? Accuracy and computational considerations.

Multicellular software

Software vs own code? Developing your own code vs using established software: advantages and disadvantages.

Convergence or comparison of software? Should we have one tool to do everything? How should you compare software? Could we compare to data?

Comparing models

Standards for multicellular models and software? SMBL, MultiCellML, Ontologies and mark up languages.

Comparison of models? Which models work best when, how to show a model is "best".

Future of multicellular modelling

Multicellular modelling in drug discovery. As part of the drug discovery pipeline, bridging single cell experiments and tissue/animal experiments.

Multicellular modelling for predictive medicine. Can we do this? Auditability of models and simulations.

Adaptive multicellular models. Combining discrete and continuum models. Coupling multicellular models.