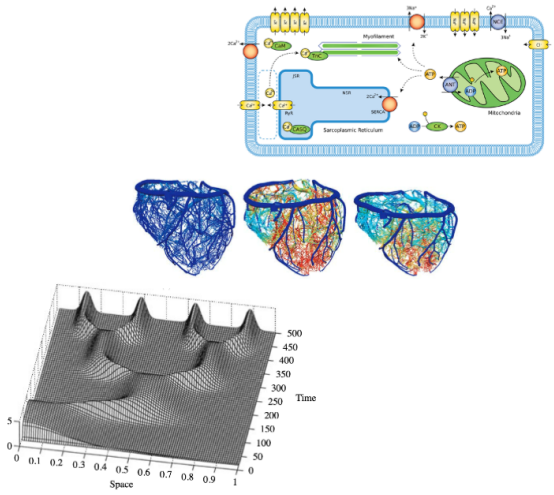
Frontiers of Mathematical Biology:
A workshop honouring Professor Edmund Crampin



Melbourne Mathematical Biology Group
The School of Mathematics and Statistics
The University of Melbourne

14-16 November 2022

Contents

Program information

The Melbourne Mathematical Biology group welcome you to the Frontiers of Mathematical Biology workshop, honouring the late Professor Edmund Crampin.

Keynote addresses will be delivered by:

- Professor Peter Hunter
- Dr Claire Miller
- Dr Hilary Hunt
- Professor Philip Maini

The program will also feature a presentations from invited speakers Dr Walter Muskovic, Dr Stuart Johnston, Niloofar Shahidi, Dr Ivo Siekmann, Dr Robyn Araujo, Dr Adrianne Jenner and Professor Karen Day. A panel discussion on the future of mathematical biology will be hosted by Dr Matt Faria, with panelists Professor James McCaw, Dr Joe Cursons, Dr Claire Miller and Adriana Zanca.

The workshop will be held at the Woodward Conference Centre, Level 10, 185 Pelham Street (the Melbourne Law School). An informal dinner will be held on Monday the 14th of November at the Clyde Hotel. The formal dinner for the program will be held on Tuesday the 15th of November at University House (Professor's Walk). Note that the formal dinner has a strict guest limit, therefore only participants who have registered for the dinner through eventbrite will be able to attend.

The keynote addresses and presentations will be streamed via Zoom for participants who cannot attend in person. The Zoom link will be emailed to registered participants.

The workshop is organised by the Melbourne Mathematical Biology group and is supported by funding from the School of Mathematics and Statistics Special Emphasis Year in Biological Dynamics.

Program schedule

Time	Monday	Tuesday	Wednesday
09:30-10:00		Hilary Hunt	Claire Miller
10:00-10:30			
10:30-11:00		Break	Break
11:00-11:30		Panel discussion:	Niloofar Shahidi
11:30-12:00		the future of	Adrianne Jenner
12:00-12:30		mathematical biology	Closing remarks
12:30-13:00	Lunch	Lunch	Lunch
13:00-13:30			
13:30-14:00	Opening remarks	Peter Hunter	
14:00-14:30	Karen Day		
14:30-15:00	Ivo Siekmann	Break	
15:00-15:30	Break	Stuart Johnston	
15:30-16:00	Walter Muskovic	Robyn Araujo	
16:00-16:30	Philip Maini	Campus walk	
16:30-17:00			
17:00-17:30			
17:30-18:00			
18:00-18:30			
18:30-19:00			
19:00-19:30	Dinner	Program dinner	
19:30-20:00	(The Clyde Hotel)	(University House)	
20:00-20:30			
20:30-21:00			

Table 1: Keynote speakers Invited speakers Panel discussion, opening and closing remarks Lunch, dinner, breaks and activities

Abstracts

Malaria, Mathematics and Computational Biology at The University of Melbourne

14 Nov
14:00

Karen Day

The University of Melbourne

Malaria remains a major public health problem, especially in sub-Saharan Africa. Unlike influenza and HIV, where diversity in immunodominant surface antigens is understood to inform disease surveillance, modelling of transmission dynamics and vaccine design, relatively little is known about the diversity and population structure of the var multigene family encoding the major variant surface antigen of the blood stages of the malaria parasite *Plasmodium falciparum*. Here results of var gene population structure are reported on local and global scales. Deep sequencing of a region of var genes encoding the DBL? domain in local African parasite populations showed extensive diversity of these genes and a non-random population structure of limited overlap of repertoires of the 50-60 var genes per genome revealing an absence of recombinants. Two neutral models that encompass malaria epidemiology but exclude competitive interactions between parasites were developed to test the hypothesis that this structure was a consequence of immune selection. These models, combined with networks of genetic similarity, reveal non-neutral strain structure in both simulated systems and an extensively sampled population in Ghana. The unique population structure we identify underlies the large transmission reservoir characteristic of highly endemic regions in Africa. By also leveraging a bioinformatic approach (jumping hidden Markov model) designed specifically for the analysis of recombination within var genes and applying it to a dataset of DBL? types from 10 countries, population structure of DBL? types was described at the global scale. These analyses show that the evolution of the parasite population emerging "out of Africa" underlies current patterns of DBL? type diversity. Most importantly, we can distinguish geographic population structure within Africa between Gabon and Ghana in West Africa and Uganda in East Africa. These evolutionary findings have translational implications in relation to global malaria surveillance.

A hierarchical model of the inositol-trisphosphate receptor (IPR) - Gaining insight into conformational dynamics of ion channels via modal gating analysis

14 Nov
14:30

Ivo Siekmann

Liverpool John Moores University

Ion channels are membrane proteins that regulate the concentrations of ions such as chloride, sodium, potassium or calcium in living cells. They are involved in maintaining the intracellular balance of electrolytes, adjusting the membrane potential and signal transduction. This allows them to play major roles in the physiology of the heart and the brain as well as the perceptive and the digestive system. Remarkably, ion channels carry out all these complex roles by simply adjusting how long they open and close pores that allow ions to travel across the cell membrane.
Transport through ion channels is passive in the sense that it relies on the electrochemical gradient across the cell membrane. But in order to open and close, the channel protein needs to deform its three-dimensional molecular structure. Gaining insight into the dynamics of these conformational changes is challenging. However, in many ion channels, conformational changes have been associated with modal gating dynamics where the channel switches between different levels of open probability. This suggests that investigating modal gating enables us to gain insight into the conformational dynamics of the channel protein. I will present a statistical approach for studying mode changes based on time series data recorded from single ion channels and will show results from a study of the inositol-trisphosphate receptor (IPR). This analysis reveals that ion channel dynamics is a hierarchical process where the stochastic pattern of opening and closing observed at a fast time scale is determined by switching between modes at a slow time scale. Motivated by this observation I will develop the hierarchical Markov model, a model structure which accurately represents modal gating, and use this structure for building a new model of type 1 and type 2 IPRs depending on inositol-trisphosphate (IP3), adenosine triphosphate (ATP) and calcium (Ca).

Using high temporal resolution gene expression data to study lncRNA functional roles

14 Nov
15:30

Walter Muskovic

Garvan Institute

Long non-coding RNAs are an enigmatic class of RNA transcripts that originate outside the boundaries of known protein-coding genes. Despite extensive research, the functional relevance of these transcripts remains undetermined. Intriguingly, lncRNA expression is strongly linked with adjacent protein-coding gene expression, suggesting potential broad-scale cis-regulatory roles. The dynamics of lncRNA expression is an unexplored area that may shed light on these potential regulatory functions. In this study, we carefully examine the precise timing of lncRNA

expression relative to the adjacent protein-coding genes they are speculated to regulate. Despite the diversity of reported lncRNA regulatory mechanisms, where causal cis-regulatory relationships exist, lncRNA transcription is expected to precede changes in target gene expression. Using a high temporal resolution RNA-seq time course, we profiled the expression dynamics of several thousand lncRNAs and protein-coding genes in synchronized, transitioning human cells. We show that differences in gene length and transcript stability have obscured the true dynamics of lncRNA and mRNA expression, and that lncRNAs are in fact expressed synchronously with adjacent protein-coding genes. Analysis of lipopolysaccharide-activated mouse dendritic cells revealed the same temporal relationship observed in transitioning human cells. These findings suggest broad-scale cis-regulatory roles for lncRNAs are not common. Instead, we conclude that the strong association between lncRNAs and adjacent genes may instead indicate an origin as transcriptional by-products from active protein-coding gene promoters and enhancers.

Pattern formation on a growing domain: A tribute to Edmund Crampin

14 Nov
16:00

Philip Maini

University of Oxford

Although growth is a fundamental process in developmental biology, surprisingly, very little work had been done on including growth in models. Edmund was the first person to systematically derive the classical Turing reaction-diffusion model on a growing domain. Two papers resulting from this work [1,2] have gained a combined citation number of over 550. In this talk I will review Edmund's work and findings in the context of pattern formation, then briefly show how his derivation can actually be used for a completely different application in developmental biology.

[1] E.J. Crampin et al, Reaction and diffusion on growing domains: Scenarios for robust pattern formation, Bull. Math. Biol., 61, 1093-1120 (1999)
[2] E.J. Crampin et al, Pattern formation in reaction-diffusion models with non-uniform growth, Bull. Math. Biol. 64, 747-769 (2002)

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15 Nov
09:30

Getting to the heart of hypertrophic signalling

Hilary Hunt
University of Oxford

Cardiovascular disease is the leading cause of death in Australia; responsible for 30% of deaths. Heart problems are commonly foreshadowed or accompanied by a condition known as pathological hypertrophy – heart enlargement through cell growth. While hypertrophy develops as a response to other conditions such as atherosclerosis or diabetes, without being able to affect the underlying problem, it only leads to further problems. As pathological heart growth worsens, it leads to uneven heart beats and, eventually, heart failure. If we understood the signalling pathway that leads to hypertrophic growth, we could control the progression of hypertrophy and avoid the additional complications and reduce the lethality of the conditions it accompanies.
Both calcium ions and IP3 are known to be part of the cardiac hypertrophic signalling pathway, with IP3 believed to trigger the calcium signal. Calcium then recruits gene regulatory factors from within both the cytosol and the nucleus to stimulate hypertrophic growth. However, regular release of calcium within the cytosol of each cell also causes the heart to beat. How intracellular calcium can encode these two, specific signals at once is not well understood.
Several hypotheses as to how the modified signal transmits the hypertrophic signal to downstream signalling proteins have been proposed, including changes to amplitude, duration, duty cycle, and signal localisation. Modelling of calcium release and signal interaction in heart cells, we categorise the nature of the signals responsible for altering the structure of the cell.

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15 Nov
13:30

Whole-cell modelling with bond graphs and CellML

Peter Hunter, Weiwei Ai, Alan Garny, Jagir Hussan, David Nickerson, Soroush Safaei, Niloofar Shahidi, Hugh Sorby, Alan Wu, Tommy Yu
Auckland Bioengineering Institute

Together with Peter Gawthrop, Edmund showed us why the bond graph (BG) approach is so powerful for ensuring mass, charge, and energy conservation in biophysical systems. Many researchers in the Auckland Bioengineering Institute (ABI) have now adopted this approach and coupled it with CellML concepts. This talk will advocate that we should now be building generic whole-cell models based on bond graphs, in which all reactions (enzymes, ion channels, exchangers, etc.) are defined by BG 1-nodes with corresponding constitutive models encoded in CellML and available in the Physiome Model Repository (PMR). The generic whole cell model contains all 0-nodes (chemical potentials associated with energy storage for each species) and all the BG connectivity including appropriate compartmentalisation. The 1-nodes are the ?constitutive laws? that hide the detailed physics of each reaction inside a black box, ensuring the ability to independently provide the parameterization for different cell types. The talk will

also discuss the graphical, semantic, and computational tools needed to implement BG/CellML models within the OpenCOR modelling software using a library of CellML components from PMR.

Mathematical models of nanoparticle-cell interactions

15 Nov
15:00

Stuart Johnston

The University of Melbourne

Nanoparticles have the potential to revolutionise medicine via the targeted delivery of therapeutic, diagnostic and imaging agents. The delivery of nanoparticles to cells is a complex tapestry of interwoven biological, chemical and physical processes. As such, it is not yet fully understood how nanoparticle design choices influence the uptake of nanoparticles by cells. I will discuss the development of mathematical models that allow us to isolate the processes of nanoparticle-cell interactions from the physical transport processes of nanoparticle delivery. These models provide a method for robust comparison of experiments, independent of experimental conditions. This work was conducted alongside Edmund as part of the ARC Centre of Excellence in Convergent Bio-Nano Science and Technology.

'Unpicking' integrals in cellular signalling networks

15 Nov
15:30

Robyn Araujo

Queensland University of Technology

In this talk I will give a brief overview of the internal model principle of control theory, and how this principle applies to biological robustness in complex cellular networks. In fact, for the persistent network disturbances that are common in biology – for instance, via a mutation, or an altered extracellular milieu – the internal model principle is equivalent to the requirement for integral control. I will briefly discuss the severe structural constraints on chemical reaction networks that arise from the necessity to construct these robustness-conferring integrals, and will demonstrate how difficult these integrals can be to 'unpick' pharmacologically, via the addition of competitive or non-competitive enzyme inhibitors.

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16 Nov
09:30

Multiscale agent-based modelling of the epidermis

Claire Miller

Auckland Bioengineering Institute

In this talk I will mainly discuss the work I did with Edmund during my PhD. The topic of my PhD was multiscale modelling of the epidermis, with the goal to improve understanding of how the tissue regulates its thickness. The epidermis tightly balances proliferation, at the base of the tissue, and cell loss, at the top. This constant cell turnover helps prevent the ingress of toxins into the tissue. We investigated this cell balance using an agent-based modelling approach. Firstly, we investigated cellular mechanisms for maintenance of a proliferative layer. Secondly, we developed a subcellular model for the molecular processes hypothesised to regulate cell loss in the epidermis, which we then incorporated into a multicellular agent-based model to investigate its role in tissue homeostasis.
I will also talk briefly about the work I have done since completion of my PhD. This includes, firstly, research done during my first postdoc on in silico clinical trials for acute ischemic stroke and, secondly, my recent fellowship which will focus on developing spatiotemporal models of endometriosis onset. The latter project will build strongly on the work I did during my PhD. Through this, I hope to touch on how I believe the time I spent working with Edmund influenced how I approach both my research and my career.

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16 Nov
11:00

Towards automation in model composition for systems biology

Niloofar Shahidi

Auckland Bioengineering Institute

Simulating complex biological and physiological systems and predicting their behaviour under different conditions is currently challenging. Decomposing systems into smaller and more manageable modules (hierarchical modelling) can address this challenge, assisting both model development and simulation. However, it is challenging to automatically compose models such that the resulting model is physically plausible (i.e. satisfies conservation of mass, charge, energy, etc.). The Bond Graph (BG) is a powerful framework for constructing physically plausible models of biology. Here, we consider the use of semantic annotations to automate the composition of BG models. We have developed a framework that converts SBML (from BioModels) and CellML (from PMR) models into BG models. For SBML models, the reaction network was sufficient to construct a BG model whereas, for CellML models, existing templates were used to construct BG models. In both cases, simulation data were used to parameterise the BG models. When composable BG modules are created, they can be automatically merged. The automated model composition was performed by identifying and linking the similarly annotated components of the annotated BG modules. We have tested our framework on multiple SBML and CellML models (such as the EGFR pathway,

the MAPK cascade, and the TCA cycle) and we observed similar behaviours to the original models. Physically plausible behaviours of the composed models (for example energy consumption) were also verified. Our BG conversion and semantic model composition framework provide a physically plausible environment in which we can automatically convert and compose a considerable number of existing SBML and CellML models.

Using mathematics to add insight into Multiple Sclerosis

16 Nov
11:30

Adrianne Jenner

Queensland University of Technology

Multiple sclerosis (MS) is a life-long disease arising from the immune system mistakenly attacking the protective insulation of nerve cells causing irreversible damage in the brain and impairment in physical and mental activity. This damage results in lesions (scarring) in the brain which are visible on MRIs. Currently, these MRIs are only used for diagnosis and little-to-no information about patient disease prognosis can be extracted from an MRI. In addition, there is a lack of mathematical modelling of this disease. This year, our group has been working on laying a foundation for mathematical models of MS and trying to develop ways to predict the expansion of lesions and the local immune kinetics using deterministic and stochastic modelling. In this talk, I'll provide an overview of the challenges and successes we have had with modelling this disease and the future impact mathematics could have on this disease prognosis for patients.

Participants

Abell, Isobel
Adams, Matthew
Ai, Weiwei
Alahakoon, Punya
Alipour, Hossein
Ammentorp, Bronte
Anwar, Md Nurul
Arachchi, Sudaraka Mallawa
Araujo, Robyn
Bondell, Howard
Brumley, Douglas
Cao, Pengxing
Chung, Joshua
Coomer, Megan
Cursons, Joe
Day, Karen
Dharma, Rodney
Diao, Jiahao
Dowling, Celia
Faria, Matt
Flegg, Jennifer
Forrest, Joshua
Frascoli, Federico
Germano, Domenic
Ghosh, Shouryadipta
Harrison, Lucinda
Hassen, Nadhir
Hsiao, Yi-Wen
Hunt, Hilary
Hunter, Peter
I, Elizabeth
Jayathilaka, Chathranee
Jenner, Adrianne
Johnston, Stuart
Kearney, Taylor
Kogios, Anton
Korsah, Maame
Kumar, Sandeep
Ladd, David
Landman, Kerry
Li, Ke
Li, Peijing
Lu, Yiwen
Lyu, Ruqian
Maini, Philip
Maclaren, Oliver
Mao, Jiadong
Maqbool, Ahsan
McCaw, James
Miller, Claire
Morselli, David
Moss, Robert
Muskovic, Walter
Neufeld, Zoltan
Nguyen, Steven
Noroozbabaee, Leyla
Osborne, James
Pan, Michael
Perera, Prabhavi
Rajagopal, Vijay
Rasmussen, Rebecca
Seghouane, Karim
Shahidi, Niloofar
Shee, Jack
Shen, Ke
Shim, Heejung
Siekmann, Ivo
Simonds, Tamas
Simpson, Matthew
Stumpf, Michael
Swan, Annalisa
Taylor, Peter
Tran, Kenneth
Turoczy, Alex
Vollert, Sarah
Walker, Camelia
Williams, Thomas
Wong, Spencer
Yang, Xinyi
Yin, Alan
Zanca, Adriana