



Frontiers of Mathematical Biology: A workshop honouring Professor Edmund Crampin

Introduction

From 14–16 November 2022 the University of Melbourne, Australia, hosted the “Frontiers of Mathematical Biology” workshop to honour and celebrate the life of Professor Edmund Crampin (Fig. 1). This essay — co-authored by the organisers of and presenters at the workshop and attended by Edmund’s colleagues, collaborators, friends and family (Appendix Table A.1 and Fig. 2) — serves to document the rich and stimulating discussions that were had on a diverse range of topics in mathematical biology. It also aims to convey the lasting impact that Edmund had on the field, and how not only his academic accomplishments, but his approach to research, to research leadership and to mentoring and career development has shaped the field and the careers of those lucky enough to have worked with him over the decades before his tragic and untimely passing on 15th May 2021 while cycling in Melbourne with his friend and colleague James McCaw.

The essay is organised as follows. First, it provides an overview of Edmund’s academic career from his time as a graduate research student at Oxford University through to his years at the University of Melbourne where he held the position of Rowden White Professor of Systems Biology. Each of the workshop presenters has then provided a personal reflection on their presentation and the role that Edmund played in their research career. This collection of brief essays covers an array of topics in mathematical biology, each one of them connected to or inspired by Edmund’s scholarly contributions and approach to research. Finally, the essay captures some of the key insights from a panel discussion on the future of mathematical biology held during the workshop. It explores both new opportunities and challenges in mathematical biology, as well as reflections on how Edmund helped shape the community itself, and his legacy: a rich, multi-disciplinary and collegial research culture in Melbourne Mathematical Biology at the University of Melbourne. The program booklet — including full scientific abstracts — is provided as Appendix B Supplementary Text S.1.

Professor Edmund Crampin 1973–2021

Professor Edmund Crampin was born in 1973 to Alice and Michael Crampin in Bletchley, Buckinghamshire, United Kingdom. A keen cyclist, hiker (“bush walking” in Australia, “tramping” in New Zealand) and accomplished rower, he lived a full life across three countries: the United Kingdom, New Zealand, and Australia. At the time of his death, 15 May 2021, he had lived in Melbourne, Australia, for some eight years with his partner and two children. He held the position of Rowden White Professor of Systems Biology at the University of Melbourne, where he had quickly become a beloved and respected member of the University community.

Edmund’s educational background was in physics and mathematics, undertaking his DPhil at the University of Oxford. Throughout his distinguished career Edmund applied fundamental mathematical and computational concepts to build models to understand biological processes and human diseases, with a particular interest in heart physiology. He made major contributions to mathematical biology, by establishing new methods, studying complex biological phenomena, and leading diverse teams in the pursuit of scientific knowledge. Just prior to his death, Edmund had been elected as a Fellow of the Royal Society of Biology for his research.

At Melbourne, Edmund has been pivotal in establishing mathematical and systems biology as a research strength and he excelled in the challenging task of bringing the life sciences, biomedicine, mathematics, and engineering disciplines together. Colleagues describe him as a kind and gentle human, with an infectious smile. At the time of his passing, fellow mathematical biologist, Professor James McCaw described him as “my friend, I just happened to be lucky enough to work with him” and his PhD advisor Professor Philip Maini wrote “Edmund was one of the nicest people I have ever met, and also one of the brightest”.

Details of Edmund’s academic career and achievements have been expertly described by Philip, and colleagues Peter Hunter and Peter Gawthrop [1].

Workshop presentations

Over the three-day workshop, presentations were delivered by 11 invited speakers, with extensive opportunities for informal discussions among program participants (Fig. 3). Beyond the scientific content — for which we provide full abstracts (Supplementary Text S1) and extensive references below for those interested — each presentation provided insight into Edmund’s approach to academic scholarship and career development. We emphasise those elements of the presentations here.

The workshop was opened by Professor Michael Stumpf, University of Melbourne, who reflected on Edmund’s career and contributions to mathematical biology. Supported by MACSYS, the recently announced Australian Research Council Centre of Excellence for the Mathematical Analysis of Cellular Systems (www.macsys.org.au), Michael announced the “Professor Edmund Crampin Artist in Residence Fellowship” that will support young and emerging artists. Awardees will use this fellowship to bridge between the arts, the biological and the mathematical sciences. Understanding complex systems requires a multitude of lines

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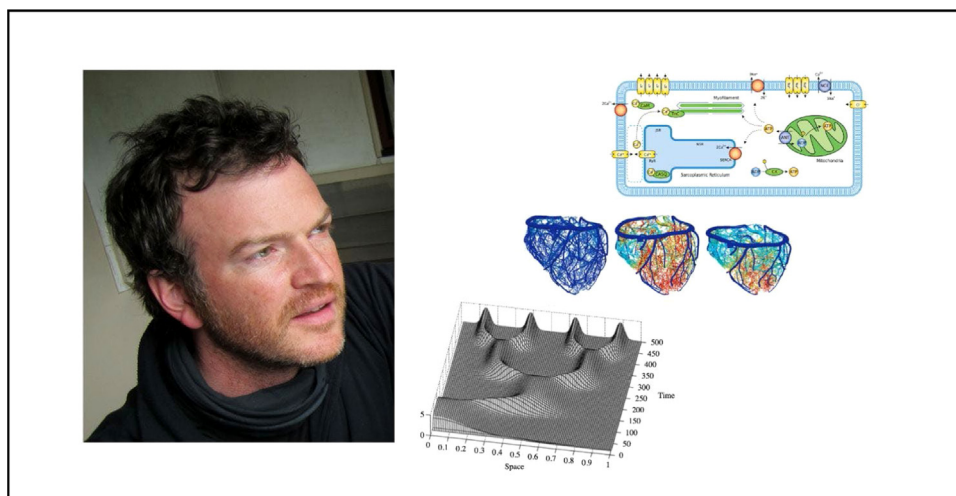


Fig. 1. Workshop announcement flyer for “Frontiers of Mathematical Biology: A workshop honouring Professor Edmund Crampin”, held at the Woodward Centre, University of Melbourne 14–16 November 2022. The workshop was a celebration of Professor Edmund Crampin’s legacy and aimed to be a meeting that he would have liked to attend.



Fig. 2. Attendees at “Frontiers of Mathematical Biology: A workshop honouring Professor Edmund Crampin”, held at the Woodward Centre, University of Melbourne 14–16 November 2022.

of attack, and the lens that art can provide is one that Edmund was very keen on.

Closing remarks for the workshop were provided by Professor James McCaw, University of Melbourne. James first reflected on the breadth of topics — in both mathematics and the life sciences — explored during the workshop (detailed below), before reflecting on the personal friendship he had developed with Edmund and his partner Annalisa Swan, and their two children, since the family had arrived in Melbourne in 2013. Edmund and James, and their close-knit families, shared a love of the outdoors and cycling. Some photos, displayed during the workshop and capturing their friendship and adventures together, are presented at Fig. 4 alongside images from the other presentations.

What follows is a series of accounts, each one written by a speaker at the workshop in their own voice, describing their presentation and relationship with Edmund.

Karen Day: Malaria, Mathematics and Computational Biology and the University of Melbourne

Edmund Crampin and I met after I was appointed to the position of Dean of Science at University of Melbourne (2014–2019). We shared the same vision to build up computational biology at the University of Melbourne, to mirror the diversity and excellence we both had experienced at the University of Oxford. My role as Dean was to find the funding to support this venture, while Edmund provided the scientific leadership, expertise and gravitas to create this interdisciplinary area.

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: the future of mathematical biology	Niloofar Shahidi
11:30-12:00			Adrianne Jenner
12:00-12:30			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			
19:30-20:00	Dinner (The Clyde Hotel)	Program dinner (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

Fig. 3. Workshop program schedule.

The successful enterprise we see today in the School of Mathematics and Statistics reflects his contribution as a fine scholar and a leader of integrity. I am delighted that a number of members of the school, and broader university, share my passion for studying mathematical biology related to malaria.

Unlike other hyper-diverse pathogens such as influenza A and HIV-1,2, relatively little is known about the diversity and population structure of the immunodominant surface antigen of the malaria parasite *Plasmodium falciparum*. The *var* multigene family encodes this variant surface antigen, where *var* genes diversify by recombination. Deep sequencing of a region of *var* genes encoding the DBL α 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 [2]. Two neutral mathematical 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 [3]. The unique population structure we identified proves typical of highly endemic regions in Africa. By also leveraging a bioinformatic approach (using a hidden Markov model [4]) designed specifically for the analysis of recombination within *var* genes and applying it to a dataset of DBL α types from 10 countries, population structure of DBL α 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 α 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.

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

My workshop presentation was about modelling an ion channel. Started in 2009, this project is now (January 2023) very close to completion¹. Here is the *Making of* of this story.

Step 1: A statistical method that ensures a model has just as many parameters as necessary [5,6]. Not more, not less.

When fitting ion channel models to data, the method tells us (kind of [6]) if we have too many parameters. But how many parameters *should* a model have?²

Me: Two, so that the model behaviour can be represented in a two-dimensional map.³

Edmund: Five, so that the elephant can wiggle her/his trunk (https://en.wikipedia.org/wiki/Von_Neumann's_elephant). We both frowned upon “those people who model everything, including the kitchen sink” (Edmund).

Step 2: The ion channel switches between a high and a low level of activity (modal gating). Now, “Everything should be made as simple as possible, but no simpler” (Albert Einstein). So this *had* to be modelled!

¹ Scientist slang for “not quite finished, yet”.

² The discussions that Edmund and I had on this topic were quite passionate!

³ Who really understands more than two dimensions anyway? One anonymous reviewer reminds us that with three or more dimensions you might even get chaos!

But how? Edmund (and James Sneyd) convinced me of going through with my first idea — that I very soon disliked — the “Park/Drive” model⁴ [7]. Instead, I really wanted to create the most beautiful of all ion channel models

Step 3: The “most beautiful of all ion channel models”

True, there were some difficulties getting the statistical analysis of modal gating to work [8] (Edmund: “Maybe something that you could look at on Fridays, 3–4 pm?”). Then, we had to combine switching *between* modes with the dynamics *within* mode. [9] Finally, the resulting hierarchical Markov model had to be fitted to the data. But... this model now describes how an ion channel switches between high and low activity and how the channel protein has to transition between different three-dimensional arrangements to do so [10].

The most important message of my talk? Edmund was involved in every single step towards this model of ion channels. Unfortunately, he did not see the end result. I worked as Edmund’s postdoc for seven years (2009–2015). Over time, the better I got to know Edmund, the more I realised how much I owe him. Thanks a lot, Edmund!

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

My collaboration with Edmund arose during my PhD studies at the Children’s Cancer Institute, through the Centre of Excellence in Convergent Bio-Nano Science and Technology (CBNS), of which Edmund was a chief investigator and I was a member. Through a CBNS conference I was introduced to Edmund, as well as Joseph Cursons, and the three of us had an interesting conversation about the dearth of genomics studies that captured dynamic information. Most experiments capture cells at a single point in time, providing only a static snapshot of the transcriptome.

I had a strong interest in non-coding RNAs and we were interested in developing a novel approach evaluating the potential functional roles of non-coding transcripts. We realised that genome-wide gene expression measurements of sufficiently high resolution would be an excellent way to investigate causal regulatory relationships that were proposed to exist between long non-coding RNAs (lncRNAs) and adjacent protein-coding target genes.

Running with this idea, we designed an experiment to sample synchronised transitioning human cells at high temporal resolution. As is usually the case, generating the data was the quick part. The analysis of this unique dataset took several years to complete. Unfortunately, Edmund was not here to see the work published, however in 2022 the work appeared in *Genome Research* [11]. In the study, we demonstrated that the majority of lncRNAs are unlikely to maintain broad-scale cis-regulatory roles, as they are transcribed synchronously with their proposed target genes. We concluded that the majority of lncRNAs likely represent transcriptional by-products associated with active protein-coding gene promoters and enhancers.

While working with Edmund, I found him to be a kind and patient collaborator with an infectious enthusiasm. During the project I travelled to Melbourne to meet with Edmund and Joseph to discuss the modelling of the time series data. I was new to computational work and found the analysis intimidating. Edmund was very encouraging and generous with his time, inspiring me to pursue a transition from lab experiments towards computational biology.

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

John von Neumann famously said, “With four parameters I can fit an elephant, and with five I can make him wiggle his trunk”. This is a statement used very often by mathematical biologists and it captures the idea that by making a mathematical model increasingly complicated (and introducing new parameters) it is possible to make the model do whatever you want. Edmund’s work on pattern formation

provided a counter-example to this. He showed that introducing domain growth (hence more parameters) actually restricted the patterning behaviour of the classical Turing model for pattern formation [12]. It also provides an hypothesis for why many patterns (for example, limb development, feather germs etc.) do not form all at once but, instead, form behind a propagating front. Controlling the patterning domain in this way selects certain patterns, allowing for more robust pattern generation. For example, the hexagonal pattern of feathers on the back of a chick first forms as a row of spots along the head to tail axis and then propagates outwards in a sequential fashion to form hexagons. Were the pattern to form on the full domain, such a hexagonal structure would not be stable. Remarkably, even though Edmund moved on to work in completely different areas in mathematical biology after his doctorate, the legacy of his highly cited work in growing domains lives on.

Hilary Hunt: Getting to the heart of hypertrophic signalling

Edmund had been researching the signalling mechanisms that cause a healthy heart to undergo pathological hypertrophy — a condition in which heart cells undergo growth and structural remodelling in response to stress that often leads to even greater strain on the heart [13,14] — for some time before I joined his lab at the University of Melbourne. At the time, Greg Bass had recently returned from a research visit with Llew Roderick to measure calcium in heart cells under normal and hypertrophy-like signals and an experimental paper detailing molecular calcium sensing based on precisely controlled calcium signals had just been released [15] so working out the details of calcium’s role in the hypertrophic pathway was within reach. It was an exciting time to join the lab, although I would later come to learn that it was always an exciting time to join Edmund’s lab. He was full of ideas of what we could accomplish through research and the kind of enthusiasm that drew people to join him.

At the memorial workshop, I described our work connecting the aspects of the cardiac calcium signal that might induce cardiac hypertrophy with the calcium signals cardiac myocytes might be capable of producing given our knowledge of their calcium channels and pumps [16], as well as our modelling of the concurrent downstream calcium signals in the nucleus that are also necessary for hypertrophic remodelling to occur, and briefly touched on more recent work that has since been carried out in the Rajagopal lab [17].

Peter Hunter: Whole-cell modelling with bond graphs and CellML

In my presentation at the commemorative workshop, I talked about Edmund’s time in Auckland and the impact he had had on our work on computational physiology, particularly his work on the biological application of bond graphs.

Edmund came to Auckland in 2003 to do a postdoc in the Auckland Bioengineering Institute (ABI) and shortly afterwards also took up a lectureship in the Engineering Science Dept, within the Faculty of Engineering at the University of Auckland. Before this he had been a Wellcome Trust Research Fellow at Oxford University, having completed a physics degree at Imperial College and then a DPhil (PhD) with Professor Philip Maini in Oxford. He led our systems biology work at the ABI and was promoted to Associate Professor in 2010. From 2006 to 2012 he was Associate Director Postgrad at ABI. He moved to the University of Melbourne in 2013 to take up a chair in Systems Biology and Computational Biology. Edmund’s wife Annalisa was also an ABI alumni, having undertaken her PhD with Professor Merryn Tawhai as primary supervisor.

In recent years Edmund, together with Peter Gawthrop and (more recently) with Michael Pan in Melbourne, pioneered the application of bond graph approaches to systems biology. Using the bond graph approach to modelling biological processes ensures that they satisfy mass conservation, charge conservation and energy conservation [18, 19]. These papers with Peter Gawthrop are in my view some of the most important papers to have appeared in the systems biology literature in the last 10 years. Professor Denis Noble at Oxford University, widely

⁴ Edmund and James disliked this name, though.

regarded as the father of systems biology, has commented that Edmund was a leading light on what systems biology *should* be doing.

At the ABI we are now building comprehensive generic cell models that put all sub-cellular processes into a single bond graph framework linked with a library of protein reaction models in the Physiome Model Repository (PMR). This work, which is coupled into our multiscale physiome models, owes a great deal to the extraordinary vision that Edmund had, working with Peter Gawthrop, 10 years ago.

As well as being a much-valued academic colleague, for many of us in the ABI Edmund was also a close personal friend. With the permission of his family we have created a new competitive ‘Edmund Crampin’ scholarship at the ABI to support students pursuing research projects related to systems biology, cellular systems modelling, and multi-scale modelling of cell-to-organ scale function.

Stuart Johnston: Mathematical models of nanoparticle–cell interactions

Edmund was a Chief Investigator (CI) in the Australian Research Council Centre of Excellence in Convergent Bio-Nano Science and Technology (CBNS). The CBNS focused on understanding the interactions between nanotechnological and biological entities. Edmund was a rarity in the CBNS: he focused on modelling, while the other CIs’ expertise were primarily in materials chemistry, cell biology and pharmacology.

One of Edmund’s research interests was standardisation and reproducibility; having been involved in creating the reporting standards for biochemical modelling, he saw the value in creating similar standards for bio-nano experimentation. An international group of bio-nano researchers, led by group member Matt Faria, published the MIRIBEL reporting standard [20]. Prior to this, it was rare for sufficient information to be published alongside experimental data so that the results could be meaningfully compared against the existing experimental literature.

I joined Edmund’s group in 2017 after a conversation where he pointed out that there was very little mathematical modelling work conducted in bio-nano science. He believed there was an opportunity to make a sizable difference, and that modelling could help push the field toward the rational design of nanoparticles for specific applications [21,22]. It was not always straightforward to convince more experimentally-focused researchers of the value of modelling. However, work done by the group has demonstrated that modelling allows us to reliably quantify nano-bio interactions by explicitly modelling and accounting for the relevant physical transport processes. This has revealed how experimental results can be confounded by nanoparticle sedimentation [23], polydispersity [24], cell heterogeneity [25] and organoid structure [26].

Robyn Araujo: ‘Unpicking’ integrals in cellular signalling networks

What always impressed me deeply about Edmund’s research was both the extraordinary breadth of his interests in mathematical biology, as well as his enthusiasm for pursuing big scientific questions. My talk in Edmund’s honour briefly summarised some of the recent contributions within my own research group to a big scientific question that I hope Edmund would have enjoyed: how is biological complexity organised, and how is this organisation maintained across evolutionary time or perturbed due to experimental or clinical interventions? I focused particularly on the keystone biological function known as Robust Perfect Adaptation (RPA), since we now understand the network structures that support this functionality in complete generality — for both the network macroscale in terms of overarching network topology [27], as well as the network microscale, at the level of individual intermolecular interactions [28].

RPA refers to a system response whereby the concentration of a particular molecule or activation state returns exactly to a prescribed baseline (the “setpoint”) after some disturbance or stimulus to the system, independently of the values of the system parameters (e.g. total expression levels for the interacting molecules) [27–29]. RPA is

fundamental to life itself, and is observed at all scales of biological organisation, and across all domains of life [28,30–32]. What is particularly interesting about this type of robust response from a mathematical standpoint is that it imposes tremendous structure on the organisation of biological networks [27,28]. In particular, these special network structures must endow collections of biochemical reactions with the ability to construct and compute robustness-conferring integrals. Now that these integral-constructing network structures are fully understood [28], we can exploit this understanding to propose and solve entirely new classes of biological problems.

We are now beginning to identify the types of interventions — whether spontaneous and naturally occurring, or engineered in either a synthetic biology setting or a pharmacological setting — that can subvert the network’s capacity for RPA, or introduce approximate adaptation to pre-existing non-robust networks. In my talk, I described our recent mathematical proof that if RPA already exists in a network, then no competitive inhibition strategy can ever remove it, no matter which, or how many, molecules are targeted by the drug(s). On the other hand, we have been able to show that certain RPA-capable networks might be sensitive to some classes of non-competitive or allosteric agents, albeit only for certain molecular targets that possess a specific relationship to the overarching RPA-conferring chemical reaction structures. These intriguing results have tremendous implications for the design of molecular-targeted therapies, and for understanding permissible alterations to complex signalling networks in an evolutionary context.

Claire Miller: Multiscale agent-based modelling of the epidermis

My presentation for this workshop reflected on the work I did with Edmund during my time as his Ph.D. student at the University of Melbourne. We were interested in connecting subcellular and cellular scale dynamics, on which Edmund was an expert, with resulting dynamics at a multicellular scale, using agent-based modelling approach, using the expertise of my other supervisor, Dr James Osborne. The application we settled on for studying this dynamic regulation process was the thickness of the epidermis, the outermost layer of the skin. The epidermis is a tissue which undergoes a constant turnover of cells, and so it is necessary for the system to maintain a tight balance between cell proliferation and desquamation (cell loss). During my PhD we proposed that regulation of division direction may be critical for the maintenance of proliferative cell populations [33]. We developed a subcellular dynamics model for the reduction in adhesion, based on a reaction hypothesised in the literature, and shows that this mechanism enabled a steady state tissue thickness to be maintained when incorporated into the multicellular model as a regulator of desquamation [34].

I also used my presentation as an opportunity for reflection on how Edmund’s research ethos, as I experienced it, influenced my career. I believe that Edmund had a remarkable ability to both “think big” on potential exciting opportunities for mathematical modelling, but also maintain a focus on the small things, such as what do our models really mean and are our assumptions about our models correct? His excitement about all aspects of the science we do was infectious.

Niloofer Shahidi: Towards automation in model composition for systems biology

In my presentation I introduced a framework to automatically compose biological models in a modular manner. Using this framework, modellers can spend more time understanding the behaviour of complex systems and less time dealing with model composition. This automated composition is made possible by using bond graphs and semantic annotations.

Many existing computational models in biology are not developed in a way that supports assembly into larger models. In cases where the assembly is possible, the resulting model may be inconsistent with physiological phenomena. To generate a realistic model, different physical domains must be considered. The bond graph approach is an

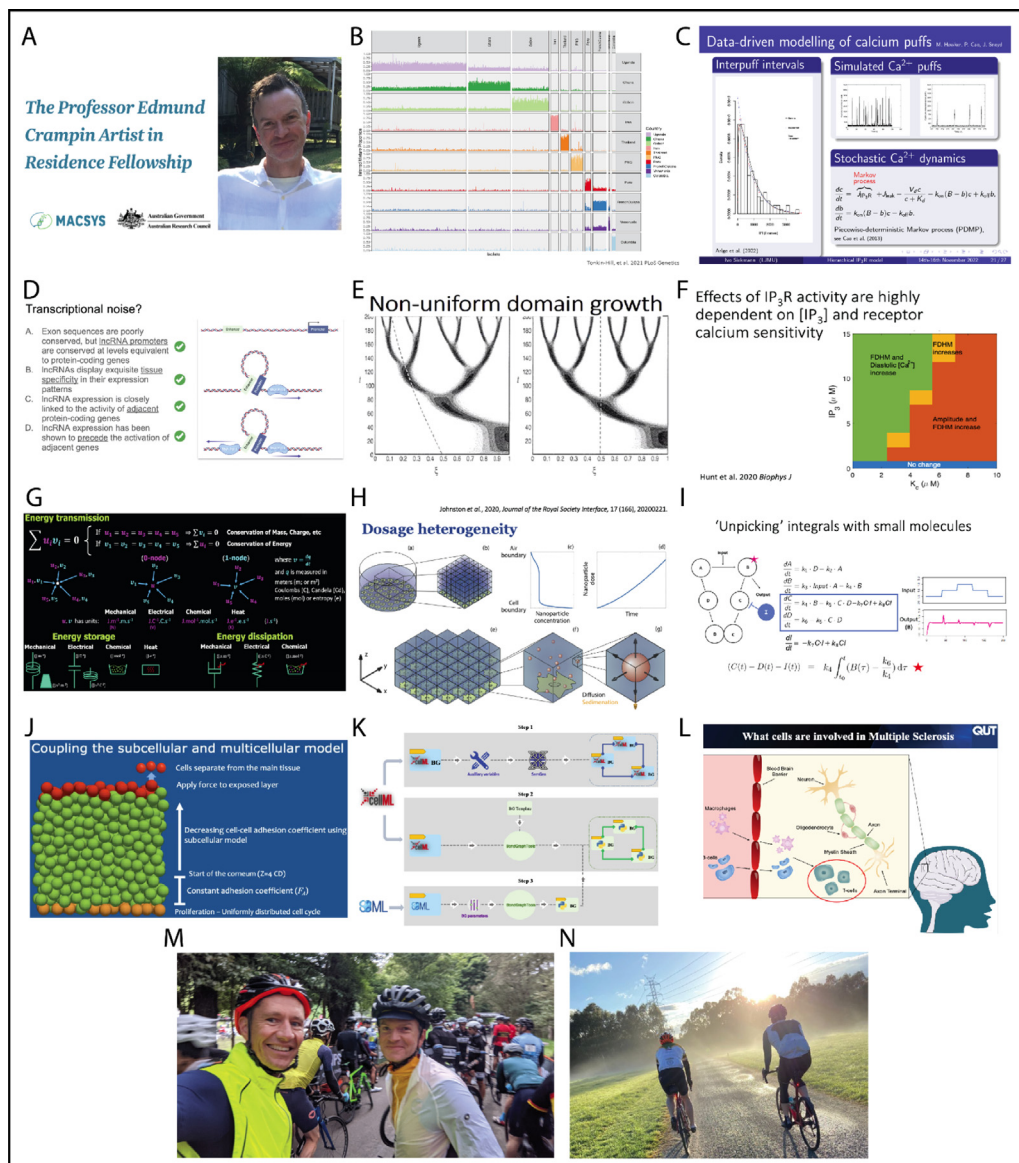


Fig. 4. (A)–(L) Slides presented from the workshop. (A) Michael Stumpf, (B) Karen Day, (C) Ivo Siekmann, (D) Walter Muskovic, (E) Philip Maini, (F) Hilary Hunt, (G) Peter Hunter, (H) Stuart Johnston, (I) Robyn Araujo, (J) Claire Miller, (K) Niloofar Shahidi and (L) Adrienne Jenner, (M) James McCaw (left) and Edmund Crampin (right) at the Giro Della Donna start line, Warbuton, Victoria, 28 March 2021 and (N) riding the Mullum Mullum trail, Melbourne, Victoria, 20 June 2020.

energy-conserving, domain-independent scheme that supports hierarchical modelling. This makes bond graphs a powerful tool to utilise in model composition.

Moreover, labelling the contents of physiological models with standard vocabularies (annotations) remarkably enhances the reusability of models as well as adding a layer of automation to model composition.

Adrienne Jenner: Using mathematics to add insight into Multiple Sclerosis

At the panel discussion on Wednesday, the panel members spoke about the depth and breadth of academic research and how doing academic research can be a lot like digging. A researcher may spend a large majority of their time digging a single hole as deep as possible to get to the gold or they may dig lots of small surface level holes looking for possible interesting areas of investigation. As the workshop centred on the frontiers in mathematical biology, my presentation looked at a new patch of ground ripe for digging: modelling of Multiple Sclerosis (MS). Multiple Sclerosis is a neuroinflammatory disease where the body's immune system attacks the protective coating around neurons in the central nervous system. To date, mathematical investigations

in this area have been significantly lacking, with only a handful of investigatory works. In our research, we have been developing deterministic mathematical models to capture the inflammation of this disease. Current progress has seen us start by developing a two-ODE system capturing the cyclic nature of T cell regulation in MS patients, characterised by a non-linear centre. We further extended this research to a 6-PDE model of myelin degeneration which has been initialised with real patient MRI measurement. Our hope for 2023 and beyond is to further validate this model and calibrate it with patient data so that it could be used as a diagnostic tool for MS patients.

The future of mathematical biology: a panel discussion

One of the things many of us cherished about our time with Edmund were the deep and meandering intellectual conversations, which could range from mathematics to politics. On day two of the workshop, Matt Faria hosted a discussion on the future of mathematical biology with panelists James McCaw, Joe Cursons, Claire Miller and Adriana Zanca. This panel intended to capture the spirit of so many cherished conversations with Edmund. The panel discussed topics such as the pursuit of mathematical beauty, the different approaches to mathematical

Table A.1

Program attendees.

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

modelling, the differences between mathematical modelling in different domains and the techniques of the future in mathematical biology.

The panel discussed the balance between biological and mathematical relevance of a mathematical model. The panel members agreed that simple models can often provide answers to important questions and developing new approaches to model simplification while ensuring that models retain their biological interpretation stands as a major opportunity in mathematical biology. They also raised that while statistical models and machine learning are useful early in the modelling process, mechanistic models are still required to capture core processes driving the biological process; a balanced approach is required that draws upon both mechanistic and statistical models to gain the most comprehensive insight into biological systems.

The panel also explored the importance and value in having academic mentors, like Edmund, who bring a deeply principled and considered approach to all aspects of their work: from careful consideration of the biological or mathematical problem being studied, to support and encouragement for students and staff to develop their own independent research careers. Those qualities, which Edmund exemplified, were identified as a major draw card into the field of mathematical biology itself. The mathematical biology community, and its culture, reflects Edmund's values, one of his (many) lasting legacies.

Acknowledgements

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*Doug Brumley, Domenic Germano, Matt Faria, Jennifer Flegg, Stuart Johnston, James McCaw, James Osborne, Michael Pan, Vijay Rajagopal, Michael Stumpf, Adriana Zanca

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A

See Table A.1.

Appendix B. Supplementary text

Supplementary material related to this article can be found online at <https://doi.org/10.1016/j.mbs.2023.109007>.

References

- [1] P.K. Maini, P.J. Hunter, P.J. Gawthrop, N.P. Smith, Edmund John Crampin 1973–2021, *Bull. Math. Biol.* 84 (3) (2022) 35, <http://dx.doi.org/10.1007/s11538-021-00987-0>.
- [2] K.P. Day, et al., Evidence of strain structure in *Plasmodium falciparum* var gene repertoires in children from Gabon, West Africa, *Proc. Natl. Acad. Sci. USA* 114 (20) (2017) <http://dx.doi.org/10.1073/pnas.1613018114>.
- [3] Q. He, et al., Networks of genetic similarity reveal non-neutral processes shape strain structure in *Plasmodium falciparum*, *Nature Commun.* 9 (1) (2018) 1817, <http://dx.doi.org/10.1038/s41467-018-04219-3>.
- [4] G. Tonkin-Hill, et al., Evolutionary analyses of the major variant surface antigen-encoding genes reveal population structure of *Plasmodium falciparum* within and between continents, *PLoS Genet.* 17 (2) (2021) e1009269, <http://dx.doi.org/10.1371/journal.pgen.1009269>.
- [5] I. Siekmann, et al., MCMC estimation of Markov models for ion channels, *Biophys. J.* 100 (8) (2011) 1919–1929, <http://dx.doi.org/10.1016/j.bpj.2011.02.059>.
- [6] I. Siekmann, J. Sneyd, E.J. Crampin, MCMC can detect nonidentifiable models, *Biophys. J.* 103 (11) (2012) 2275–2286, <http://dx.doi.org/10.1016/j.bpj.2012.10.024>.
- [7] I. Siekmann, L.E. Wagner, D. Yule, E.J. Crampin, J. Sneyd, A kinetic model for type I and II IP3R accounting for mode changes, *Biophys. J.* 103 (4) (2012) 658–668, <http://dx.doi.org/10.1016/j.bpj.2012.07.016>.
- [8] I. Siekmann, J. Sneyd, E.J. Crampin, Statistical analysis of modal gating in ion channels, *Proc. R. Soc. A* 470 (2166) (2014) 20140030, <http://dx.doi.org/10.1098/rspa.2014.0030>.
- [9] I. Siekmann, M. Fackrell, E.J. Crampin, P. Taylor, Modelling modal gating of ion channels with hierarchical Markov models, *Proc. R. Soc. A* 472 (2192) (2016) 20160122, <http://dx.doi.org/10.1098/rspa.2016.0122>.
- [10] I. Siekmann, A hierarchical Markov model of the IP3 receptor, Dedicated to Edmund Crampin (in preparation).
- [11] W. Muskovic, et al., High temporal resolution RNA-seq time course data reveals widespread synchronous activation between mammalian lncRNAs and neighboring protein-coding genes, *Genome Res.* 32 (8) (2022) 1463–1473, <http://dx.doi.org/10.1101/gr.276818.122>.
- [12] A.M. Turing, The chemical basis of morphogenesis, *Phil. Trans. R. Soc. B* 237 (641) (1952) 37–72.
- [13] M. Cooling, P. Hunter, E.J. Crampin, Modeling hypertrophic IP3 transients in the cardiac myocyte, *Biophys. J.* 93 (10) (2007) 3421–3433, <http://dx.doi.org/10.1529/biophysj.107.110031>.
- [14] M.T. Cooling, P. Hunter, E.J. Crampin, Sensitivity of NFAT cycling to cytosolic calcium concentration: Implications for hypertrophic signals in cardiac myocytes, *Biophys. J.* 96 (6) (2009) 2095–2104, <http://dx.doi.org/10.1016/j.bpj.2008.11.064>.
- [15] P. Hannanta-anan, B.Y. Chow, Optogenetic control of calcium oscillation waveform defines NFAT as an integrator of calcium load, *Cels* 2 (4) (2016) 283–288, <http://dx.doi.org/10.1016/j.cels.2016.03.010>.
- [16] H. Hunt, Mathematical models of calcium signalling in the context of cardiac hypertrophy, 2020, [Online]. Available: <http://minerva-access.unimelb.edu.au/handle/11343/241392>. (Accessed 15 January 2021).
- [17] J. Chung, et al., IP3R activity increases propensity of RyR-mediated sparks by elevating dyadic [Ca²⁺], *Math. Biosci.* 355 (2023) 108923, <http://dx.doi.org/10.1016/j.mbs.2022.108923>.
- [18] P.J. Gawthrop, E.J. Crampin, Energy-based analysis of biochemical cycles using bond graphs, *Proc. R. Soc. A* 470 (2171) (2014) 20140459, <http://dx.doi.org/10.1098/rspa.2014.0459>.
- [19] P.J. Gawthrop, E.J. Crampin, J. Cursons, Hierarchical bond graph modelling of biochemical networks, *Proc. R. Soc. A* 471 (2184) (2015) 20150642, <http://dx.doi.org/10.1098/rspa.2015.0642>.

- [20] M. Faria, et al., Minimum information reporting in bio-nano experimental literature, *Nature Nanotechnology* 13 (9) (2018) 777–785, <http://dx.doi.org/10.1038/s41565-018-0246-4>.
- [21] S.T. Johnston, M. Faria, E.J. Crampin, Understanding nano-engineered particle-cell interactions: biological insights from mathematical models, *Nanoscale Adv.* 3 (8) (2021) 2139–2156, <http://dx.doi.org/10.1039/D0NA00774A>.
- [22] M. Faria, S.T. Johnston, A.J. Mitchell, E. Crampin, F. Caruso, Bio-nano science: Better metrics would accelerate progress, *Chem. Mater.* 33 (19) (2021) 7613–7619, <http://dx.doi.org/10.1021/acs.chemmater.1c02369>.
- [23] M. Faria, et al., Revisiting cell-particle association in vitro: A quantitative method to compare particle performance, *J. Control. Release* 307 (2019) 355–367, <http://dx.doi.org/10.1016/j.jconrel.2019.06.027>.
- [24] S.T. Johnston, M. Faria, E.J. Crampin, An analytical approach for quantifying the influence of nanoparticle polydispersity on cellular delivered dose, *J. R. Soc. Interface* 15 (144) (2018) 20180364, <http://dx.doi.org/10.1098/rsif.2018.0364>.
- [25] S.T. Johnston, M. Faria, E.J. Crampin, Isolating the sources of heterogeneity in nano-engineered particle-cell interactions, *J. R. Soc. Interface* 17 (166) (2020) 20200221, <http://dx.doi.org/10.1098/rsif.2020.0221>.
- [26] A. Ahmed-Cox, et al., Spatio-temporal analysis of nanoparticles in live tumor spheroids impacted by cell origin and density, *J. Control. Release* 341 (2022) 661–675, <http://dx.doi.org/10.1016/j.jconrel.2021.12.014>.
- [27] R.P. Araujo, L.A. Liotta, The topological requirements for robust perfect adaptation in networks of any size, *Nature Commun.* 9 (1) (2018) 1757, <http://dx.doi.org/10.1038/s41467-018-04151-6>.
- [28] R. Araujo, L. Liotta, Universal structures for embedded integral control in biological adaptation, 2022, <http://dx.doi.org/10.21203/rs.3.rs-1571178/v1>, in Review, preprint.
- [29] R.P. Araujo, S.T. Vittadello, M.P.H. Stumpf, Bayesian and algebraic strategies to design in synthetic biology, *Proc. IEEE* 110 (5) (2022) 675–687, <http://dx.doi.org/10.1109/JPROC.2021.3129527>.
- [30] R.P. Araujo, L.A. Liotta, E.F. Petricoin, Proteins, drug targets and the mechanisms they control: the simple truth about complex networks, *Nat. Rev. Drug Discov.* 6 (11) (2007) 11, <http://dx.doi.org/10.1038/nrd2381>.
- [31] C. Jeynes-Smith, R.P. Araujo, Ultrasensitivity and bistability in covalent-modification cycles with positive autoregulation, *Proc. R. Soc. A* 477 (2252) (2021) 20210069, <http://dx.doi.org/10.1098/rspa.2021.0069>.
- [32] C. Jeynes-Smith, R.P. Araujo, Protein-protein complexes can undermine ultrasensitivity-dependent biological adaptation, *J. R. Soc. Interface* 20 (198) (2023) 20220553, <http://dx.doi.org/10.1098/rsif.2022.0553>.
- [33] C. Miller, E. Crampin, J.M. Osborne, Maintaining the proliferative cell niche in multicellular models of epithelia, *J. Theoret. Biol.* 527 (2021) 110807, <http://dx.doi.org/10.1016/j.jtbi.2021.110807>.
- [34] C. Miller, E. Crampin, J.M. Osborne, Multiscale modelling of desquamation in the interfollicular epidermis, *PLoS Comput. Biol.* 18 (8) (2022) e1010368, <http://dx.doi.org/10.1371/journal.pcbi.1010368>.

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