Institution: University of Nottingham

Unit of Assessment: UOA 10 – Mathematical Sciences

Title of case study: Advancing the use of mathematics and statistics to address medical and biological problems

1. Summary of the impact

Research at The University of Nottingham's (UoN) Centre for Mathematical Medicine and Biology (CMMB) has informed a wide array of beneficiaries including public policy-makers, clinicians and industry in biomedical fields such as cancer and hospital infections. Through a wide range of mechanisms such as Study Groups, training, outreach and user-engagement, the CMMB has established an outstanding track record of furthering the use of mathematics and statistics to address medical and biological problems.

2. Underpinning research

The CMMB was formally established in 1998 by Professors John King (UoN 1988 to date) and Helen Byrne (UoN 1998 to 2011). It is currently led by Professor Markus Owen (UoN 2004 to date), and includes 20 academics from the School of Mathematical Sciences, together with over 50 affiliates (from the Science, Engineering and Medical Faculties), PDRAs and PGRs. Its aim is to use mathematical modelling and statistics to understand biological systems and predict their behaviour, thus underpinning systems biology in industrial biological and biomedical research. The CMMB is one of the largest and most successful such groups in the world and has built up a wide network of active links to end users in clinical and industrial settings. Applications such as those below, and numerous other medical and biological areas of research, have served to form a solid foundation for CMMB outreach and advancement activity.

Cancer: Cancer modelling is a key area that contributed to the establishment of the CMMB, members including Byrne, King, Owen, John Ward (PGR and Wellcome Trust Fellow, now at Loughborough) and Steve Webb (PDRA, now at Liverpool) have undertaken seminal work on multi-phase models for tumour spheroids and multi-scale models for avascular tumour growth, e.g. [A1], deepening our understanding of the treatment of cancers including using a patient's own immune cells to deliver drugs deep inside tumours.

Hospital Infections: The CMMB hosts an internationally-recognised team working on stochastic epidemic models, including modelling and data analysis for antibiotic resistant pathogens such as MRSA. Professor Philip O'Neill (UoN 1999 to date) and Dr Theo Kypraios (UoN 2006 to date) have worked with colleagues at the former Health Protection Agency (now Public Health England) and clinical academic colleagues in the USA (e.g. Dr Susan Huang, School of Medicine, University of California, Irvine) [A2] and UK (e.g. Dr Jonathan Edgeworth, Guys' and St Thomas' Hospital Trust, London) [A3] to address questions pertinent to the understanding and control of hospital infections. Recent work by King, Dr Sara Jabbari (PGR, PDRA and MRC Fellow, now at Birmingham) and co-workers pioneered a systems biology approach (combining cutting-edge experimental work and computational modelling and analysis) to accelerate our understanding of e.g. Staphylococcus aureus and Clostridium difficile (see e.g. 2012 Bulletin of Mathematical Biology, 74, 1292-1325).

Neuroscience: Professor Stephen Coombes (UoN 2003 to date) has enabled the CMMB to gain recognition as an internationally leading centre for mathematical and computational neuroscience. Coombes is active in translating ideas toward application, in fostering collaborations with a range of disciplines including Psychology, Engineering and clinical groups e.g. Radiology, and in leading an EC-funded Marie Curie Initial Training Network in Neural Engineering [A8] which is training 20 early career researchers across Europe. Underpinning works include using tools from nonlinear dynamical systems to understand auditory encoding of natural sounds [A4], on the back of which work Jonathan Laudanski (PGR, 2006-2010) gained employment as a research scientist for Neurelec developing cochlear implants.

Plants: CMMB members began collaboration with Professor Malcolm Bennett (Biosciences, UoN 1999 to date) in 2006 on modelling for plant biology (Arabidopsis roots). This led to a grant [A7] to establish the Centre for Plant Integrative Biology (CPIB) in 2007. A combination of multiscale

modelling and statistical inference has proved ideally suited to tackling a wide variety of problems in this field, from how hormone dynamics create root branches through seed germination and plant fertility, to understanding how tomatoes ripen. Underpinning works include [A5].

3. References to the research

The three publications that best indicate the quality of the research are indicated *

Cancer:

[A1]* Ward, J.P. and King, J.R., 1997. Mathematical modelling of avascular-tumour growth, IMA Journal of Mathematics Applied in Medicine and Biology [now Mathematical Medicine and Biology: A Journal of the IMA]. 14(1), 39-69. DOI: 10.1093/imammb/14.1.39

Its impact includes via inclusion amongst the '100 seminal papers' as part of the centenary of Oxford University Press in 2006. http://www.oxfordjournals.org/news/centenary.html

Hospital Infections:

[A2]* Kypraios, T., O'Neill, P.D., Huang, S.S., Rifas-Shiman, S.L. and Cooper, B.S., 2010. Assessing the role of undetected colonization and isolation precautions in reducing Methicillin-Resistant Staphylococcus aureus transmission in intensive care units, BMC Infectious Diseases. 10, 29. DOI: 10.1186/1471-2334-10-29

[A3] Kypraios, T., O'Neill, P.D., Jones, D.E., Ware, J., Batra, R., Edgeworth, J.D. and Cooper, B.S., 2011. Effect of systemic antibiotics and topical chlorhexidine on methicillin-resistant Staphylococcus aureus (MRSA) carriage in intensive care unit patients. Journal of Hospital Infection 7, 222-226. DOI: 10.1016/j.jhin.2011.05.008

Neuroscience:

[A4] Laudanski, J., Coombes, S., Palmer, A. R. and Sumner, C. J., 2010. Mode-locked spike trains in responses of ventral cochlear nucleus chopper and onset neurons to periodic stimuli. Journal of Neurophysiology. 103, 1226-1237. DOI: 10.1152/jn.00070.2009.

Plants:

[A5]* Middleton, A.M., King, J.R., Bennett, M.J. and Owen, M.R., 2010. Mathematical modelling of the Aux/IAA negative feedback loop. Bulletin of Mathematical Biology. 72(6), 1383-1407. DOI: 10.1007/s11538-009-9497-4.

Grants:

[A6] (2006-2010) EC FP6 project 20723, Marie Curie Training Programme: MMBNOTT – Mathematical Medicine and Biology at Nottingham, PI Jensen, €1.7m.

[A7] (2007-2012) BBSRC project BB/D019613/1, Centre for Plant Integrative Biology, PI Hodgman, Biosciences, Nottingham; 20 Co-Is including Byrne, Dryden, Jensen, King, Owen, Wood from Mathematical Sciences, £9.2m.

[A8] (2012-2016) EC FP7 project 289146, Marie Curie Initial Training Network: NETT – Neural Engineering Transformative Technologies, PI Coombes, €5.3m.

4. Details of the impact

CMMB established and has utilised a number of distinct mechanisms to increase the visibility and uptake of mathematical and statistical methods in medical and biological problems. These include:

Industrial skills development through training courses and Study Groups: The BBSRC Modular Training for Industry course 'Introduction to Mathematical Modelling for Life Scientists' from 2008, the 'Noise in Life' conference in 2009 and the 'Introduction to Biological Modelling' summer schools led by Owen have all been well received by industry. Ian Barrett (Astra Zeneca): *"…I am actually currently leading a project using modelling to support one of our drug projects… and also line manage a mathematical modeller. I would say your course was an important factor in enabling that progression, and I came away from it feeling inspired to learn more."* [B1]. Owen was further consulted by Roche regarding the implementation of multiscale modelling for oncology (from molecular targets right up to patient health and survival).

CMMB members established Study Groups for Mathematics in Medicine (MMSG) in 2000, for Plant Sciences in 2007 and for the Virtual Physiological Human in 2009. These engendered new industrial collaborations (e.g. AstraZeneca, Health and Safety Laboratory, Pfizer, Syngenta, Unilever) and changed company procedures. Unilever ran an internal Study Group (Facilitator: King), with Brendan O'Malley (ex-Systems Biology Project Leader, Unilever) stating: *"Critically the*

Study Group also offered an opportunity to familiarise both mathematicians and biologists with the different approaches and ways of working of their respective disciplines". [B2]

This and other activity (CASE, MSc project, consulting) contributed to Unilever's Framework Partnership with the University (tinyurl.com/d8dypj8), one of only three in the UK, to carry out research in certain strategic areas exclusively at UoN.

Postgraduate and postdoctoral training: Through extensive mathematical biology MSc and PhD programmes (the latter with support from European funding [A6, A8]), internships of students with industry (via e.g. CASE or [A8]) and tailored training in both scientific and professional development skills, individuals trained within CMMB have made significant contributions to the adoption of UoN's mathematical and statistical methods by industry and other end users:

Robert Jenkins (CRUK), the first theoretician recruited by CRUK with a background purely in mathematics, stated that: *"…the expertise I developed there [CMMB] was crucial to my being awarded a permanent contract as a Senior Scientific Officer at the London Research Institute, which reflects the growing profile and impact of mechanistic modelling approaches within CRUK's research and the increasing confidence in their value for improving our understanding of a wide range of cancers."* [B3];

Greg Lemon (Fellow at Harvard Bioscience, PDRA in CMMB until 2011 and recent collaborator) applies mathematical modelling frameworks and skills he developed while in CMMB in work with Harvard Apparatus (USA), Novalung (Germany) and others to (for example) optimise performance of a membrane oxygenator for paracorporeal lung support, and to quantify cell coverage of tissue engineering scaffolds in a patent for a novel colorimetric assay;

Susan Franks (Health and Safety Laboratory) also benefitted: *"My own training as a PhD student and postdoctoral student within CMMB (1997-2004) was instrumental in the formulation, and in establishing the direction, of a significant (c. £900K) programme of work (of which I was lead Investigator) funded by HSL to enhance their capabilities in using mathematical modelling…"* [B4].

Public engagement and widening dissemination: CMMB engages extensively with a wider public audience, including through: YouTube 2009 'Meet the Mathematicians' (tinyurl.com/db2q72), 77k visitors with 97% positive feedback, 'Biology Meets Mathematics' (tinyurl.com/ox28q26), 31k visitors with 95% positive feedback; outreach activities with CPIB in local primary schools to stimulate interest from an early age; and the annual UoN 'MayFest' community open day where CMMB and CPIB ran a multicellular image competition judged by the public.

A drive by CMMB and the School more broadly to publish in prestigious and highly visible outlets, such as Nature and PNAS, has raised the profile and coverage of our research. CMMB papers have been cited by numerous clinical groups, such as Bart's in London, Mt. Sinai Hospital in Toronto and Shanghai Peoples Hospital in areas such as allergy, cardiology, gene therapy, microbiology, oncology and wound repair, as well as industry, e.g. AstraZeneca, GSK, Pfizer, Roche and Unilever. In particular, [A2] has been cited by cardiac surgeons, epidemiologists and infectious disease units in hospitals, microbiologists, the Health Protection Agency (now Public Health England) and the Health Policy Research Institute in California: this publication in a BMC journal read by clinicians and policy-makers has led to impact on public health policy (see below).

Two specific examples detailed below further illustrate the scope of the impact of CMMB's work:

Software development for clinical and industrial use: UoN work in the late 1990s on tumour growth (e.g. [A1]) inspired a topic at the first MMSG in 2000, on the effects of a new anti-tumour drug. This was taken further with Sheffield Medical School and led to a patent filed in 2007 and published in 2009 (tinyurl.com/kdnhb3d). Following this and similar successes, CMMB members made founding contributions to the open source C++ library for computational biology 'Chaste' (Cancer Heart and Soft Tissue Environment), UoN leading the cancer strand on the EPSRC grant *eScience Pilot Project in Integrative Biology*, GR/S72023/01, 2004-2008 that funded UoN

researchers Inge van Leeuwen, Gary Mirams and Alex Walter. Mirams, now at Oxford, continued to work on Chaste with academic and industrial partners, participating in producing the first public release in 2009.

A 2013 review prepared in collaboration with partners such as Microsoft Research UK and Fujitsu Laboratories of Europe Ltd stated: *"A number of other groups are using Chaste for a large variety of simulations… the effects of radiation on tissue (Shaowen Hu, NASA); …cardiac electrophysiological modelling (US Food and Drug Administration); drug-induced changes to cardiac rhythm (Safety Pharmacology, GlaxoSmithKline)…"* [B5]. Mirams adds that: *"A Chaste simulation tool is now in use by GlaxoSmithKline Safety Pharmacology teams in the UK and USA. … A recent paper [B7] evaluates how well this tool predicts the results of later animal-based safety tests that are performed at GlaxoSmithKline with a view to 3Rs benefits."* and further that: *"This work has led directly to the US drug regulators (Food & Drug Administration, FDA) including a simulation aspect in their proposed replacement for an expensive … human trial for pro-arrhythmic side effects …"* [B6]

Influence on public health policy: Work undertaken by O'Neill and Kypraios on MRSA stimulated UK Government policy debate and led to a review of the current screening policy. Dr Julie Robotham (Public Health England) stated: *"…your [Kypraios'] work directly informed the model-based evaluation of MRSA control policies, undertaken for the Department of Health (DoH), England" and "… [A2] was critical in that it represented the only study able to provide direct estimates of the effectiveness of contact precautions in reducing MRSA transmission…it enables the national policy of MRSA screening to be evaluated with more realistic estimates of how much benefit MRSA screening can actually provide."* [B8].

The research suggested that the current national MRSA screening policy in England was unlikely to be cost-effective [B9]. Whilst a change in policy itself is still under discussion with the DoH, Robotham stated that this finding: *"generated discussions both nationally … and internationally …"* and moreover caused the DoH to commission *"… a direct follow on to this work such that a cost-effectiveness evaluation at a national level, including a national MRSA audit, could be conducted. This follow on project, whilst using previous estimates, also used more up-to-date estimates, including estimates taken directly from your study Estimating the effectiveness of isolation and decolonization measures in reducing transmission of methicillin-resistant Staphylococcus aureus in hospital general wards. Worby CJ,[et al.] Am J Epidemiol. 2013 Jun 1;177(11):1306-13. doi: 10.1093/aje/kws380. Again, these estimates represented the best available evidence, and directly informed the cost-effectiveness model."*

In addition, Kypraios presented his work on avian influenza (to model and predict in real-time spread of a potential epidemic in the UK poultry industry) to Professor Sir John Beddington as UK Government Chief Scientific Adviser 2008-2013.

5. Sources to corroborate the impact

[B1] Associate Principal Scientist, Astra Zeneca, UK. (email on file)
[B2] European Study Group with Industry 59 Case Study with Unilever – webpage www.smithinst.ac.uk/Events/ESGI59/CaseStudy (copy also on file)
[B3] Senior Scientific Officer, Cancer Research UK London Research Institute, UK. (email on file)
[B4] Group Leader in Biomathematical Modelling, Health and Safety Laboratory, UK. (email on file)
[B5] Mirams, G.R. et al., 2013, Chaste: an open source C++ library for computational physiology and biology, PLoS Computational Biology, 9(3), e1002970. DOI:10.1371/journal.pcbi.1002970
[B6] Senior Research Fellow, Dept. of Computer Science, University of Oxford, UK. (email on file)
[B7] Beattie, K.A. et al., Evaluation of an In Silico Cardiac Safety Assay: Using Ion Channel Screening Data to Predict QT Interval Changes in the Rabbit Ventricular Wedge, Journal of Pharmacological and Toxicological Methods, 68(1), 88-96. DOI:10.1016/j.vascn.2013.04.004
[B8] Modelling and Economics Unit, Public Health England, UK. (email on file)
[B9] The Department of Health-commissioned report 'National One Week Prevalence Audit of MRSA Screening' (copy on file)