Institution: University of Dundee

Unit of Assessment: 10 Mathematical Sciences

Title of case study: Using Mathematical Modelling to Improve Cancer Treatment

1. Summary of the impact

A dedicated specialist mathematical modelling unit in the H. Lee Moffitt Cancer Center, Tampa, FL, USA, was set up – the Integrated Mathematical Oncology Unit (IMO) – through the movement of three staff with expertise in cancer modelling from the UoA's Mathematical Biology (MB) research group. Clinical practice has been changed and patient treatment improved through the work of IMO.

Modelling by members of the MB research group and the move of a former PDRA led to Cyclacel Ltd. and AstraZeneca obtaining a better understanding of the link between drug-dose and drug-efficacy in a class of cell-cycle-specific anti-tumour drugs called Aurora kinase inhibitors and has led to enhanced business performance.

2. Underpinning research

Led by Professor M. Chaplain, one of the main areas of research of the UoA is the mathematical modelling of all aspects of cancer – growth, spread and treatment. Since the late 1990s, the Mathematical Biology research group has been at the forefront of developing quantitative and predictive mathematical models in this area.

A seminal paper by Anderson and Chaplain in 1998 developed a novel hybrid modelling technique (continuum-discrete, deterministic-stochastic) to study tumour-induced angiogenesis, the process by which a tumour develops its own blood supply [1]. Subsequent refinement of this hybrid technique in collaboration with clinical colleagues at Ninewells Hospital led to a mathematical model of tumour invasion and metastasis [2, 3], the process by which tumour cells break off the main tumour mass and spread throughout the body. The key idea behind the technique involves using a discretized form of a system of nonlinear partial differential equations to develop a biased random-walk model which enables the tracking of individual cells. This naturally introduced stochasticity and a multi-scale aspect to the model. This work led to the award of a London Mathematical Society Whitehead Prize to Chaplain in June 2000:

"*His research establishes a framework in which clinical treatments can be tested and has brought him international recognition amongst the mathematical biology community... He and his group have developed this area of research, are at its forefront, and its results could lead to a massive advance in the treatment and control of malignant cancers.*" [13]

Drawing on the stochastic and multi-scale nature of the modelling approach, this initial research resulted in the subsequent development of models on how best to target tumours via blood-borne drugs [4] leading to new research into anti-cancer drug modelling. EPSRC funding to Chaplain and Davidson through the Mathematics for Business scheme and Mathematics CASE PhD Studentships [10, 11, 12] connected the modelling to the pharmaceutical industry via the biotech companies Cyclacel Ltd. and CXR Biosciences. The modelling undertaken here investigated the role played by Aurora B kinase which is overexpressed in a subset of cancers and is required for mitosis, making it an attractive anti-cancer target. Members of the Mathematical Biology research group, along with colleagues from Cyclacel Ltd., developed a novel stochastic mathematical model of the spindle assembly checkpoint to incorporate **all** signaling kinetochores within a cell rather than just one, and the role of Aurora B within the resulting model [5, 6]. Computational simulation results of the model showed that when Aurora B inhibition is considered, for a certain range of inhibitor concentrations, a prolonged prometaphase/metaphase is observed.

The hybrid modelling of angiogenesis and cancer invasion was carried out by Prof. M. Chaplain (then Chair in Mathematical Biology, now Ivory Chair of Applied Mathematics), Dr. A. Anderson (Senior Lecturer), Dr. K. Rejniak (PDRA), Dr. D. Basanta (PDRA) during the period 1996 – 2008. Drs. Anderson, Rejniak and Basanta left Dundee in August 2008 to set up IMO at Moffitt Cancer Center.

The Aurora B kinase modelling was carried out by Dr. F. Davidson (Reader in Mathematical Biology), Prof. M. Chaplain (as above) and Dr. H. Mistry (PDRA) during the period 2003 – 2009 [11]. Dr. Mistry left Dundee in 2008 to work in AstraZeneca.

3. References to the research

[1] Anderson ARA, Chaplain MAJ (1998)
Continuous and discrete mathematical models of tumour-induced angiogenesis.
Bull. Math. Biol. **60**, 857-899. http://link.springer.com/article/10.1006/bulm.1998.0042
[2] Anderson ARA, Chaplain MAJ, Newman EL, Steele RJC, Thompson AM (2000)
Mathematical modelling of tumour invasion and metastasis. *J. Theor. Med.* **2**, 129-154. http://dx.doi.org/10.1080/10273660008833042
[3] Anderson AR, Weaver AM, Cummings PT, Quaranta V (2006)
Tumor morphology and phenotypic evolution driven by selective pressure from the microenvironment. *Cell* **127**, 905-15. doi:10.1016/j.cell.2006.09.042
[4] McDougall S, Anderson ARA, Chaplain MAJ (2006)
Mathematical Modelling of Dynamic Adaptive Tumour-Induced Angiogenesis: Clinical Implications and Therapeutic Targeting Strategies.
J. Theor. Biol. **241**, 564-589. http://dx.doi.org/10.1016/j.jtbi.2005.12.022
[5] Mistry HB, MacCallum DE, Jackson RC, Chaplain MAJ, Davidson FA (2008)
Modelling the Role of Aurora Kinases in Centrosome Separation and the Spindle Assembly Checkpoint, *PNAS* **105 (51)**, 20215-20220. doi:10.1073/pnas.0810706106
[6] Kamei H, Jackson RC, Zheleva D, Davidson FA (2010)
An integrated pharmacokinetic-pharmacodynamic model for an Aurora kinase inhibitor. *J. Pharmacokinetics and Pharmacodynamics* **37**, 404-434. doi:10.1007/s10928-010-9166-0

Evidence of Research Quality:
(i) Grants:
[7] PI – Prof. M.A.J. Chaplain (co-I – Prof. S.L. Schor, Dr. A.M. Schor): "The mathematical modelling, simulation and prediction of matrix modulation of angiogenesis". BBSRC/EPSRC Mathematical Biology Initiative (grant 94/MMI09008). 36 months, October 1997 – September 2000; £223,876.
[8] PI – Dr. A.R.A. Anderson: "Multi-scale mathematical modelling of cancer invasion". National Institutes of Health (NIH, USA). 60 months, January 2003 – December 2007; $500,000
(c. £330,461).
[9] PI – Prof. M.A.J. Chaplain: "From mutations to metastases: Multiscale mathematical modelling of cancer growth and spread." European Research Council Advanced Investigator Grant (ERC AdG). 60 months, September 2009 – August 2014; €1.68Million.
[10] PI – Prof. M.A.J. Chaplain: "Mathematical modelling of cell-cycle dependent anti-cancer drugs." EPSRC CASE PhD Studentship with Cyclacel Ltd. 36 months, October 2003 – October 2006; c.£40,000.
[11] PI - Dr. F. Davidson; co-I – Prof. M.A.J. Chaplain: "The modelling and analysis of the pharmacodynamics of anti-cancer drugs." EPSRC "Mathematics for Business" initiative (grant EP/D043859/1). 36 Months, October 2006 – September 2009; £152,908.
[12] PI – Prof. M.A.J. Chaplain: "Mathematical modelling of Drug Metabolism: Using in silico Techniques to Investigate the Cytochrome P450 Enzyme System in Hepatic Reductase Null Mice." EPSRC CASE PhD Studentship with CXR Biosciences. 36 months, October 2006 – October 2009; c.£50,000.

(ii) Prizes and Awards:
[13] Award of London Mathematical Society Whitehead Prize to Professor M. Chaplain for research work on the mathematical modelling of cancer growth, July 2000.
[14] Professor M. Chaplain elected Fellow of the Royal Society of Edinburgh, March 2003
[15] Professor M. Chaplain awarded a Leverhulme Personal Research Fellowship, April 2007

4. Details of the impact

Improved clinical practice and patient health outcomes at H. Lee Moffitt Cancer Center
[Dates Impact Occurred: September 2008 – present]

The Moffitt Cancer Center (MCC) is a not-for-profit health institute in Tampa, FL, USA. It opened in 1986 with a mission to "*contribute to the prevention and cure of cancer*". Today it has over 4200 staff, treats over 8900 patients per year, with over 4600 inpatient surgeries being carried out. It is a nationally ranked hospital in the USA for cancer treatment.

In 2008 the MCC set up the Institute for Mathematical Oncology (IMO), with three researchers from the Mathematical Biology research group (Dr. Alexander Anderson, 1996-2008; Dr. Kasia Rejniak, 2003-2008; Dr. David Basanta, 2006-2008) recruited specifically for their specialist expertise in cancer modelling. The success of the initial recruitment has subsequently resulted in the further investment of $3Million by the MCC in the IMO which has grown to five staff.

The cancer modelling techniques developed in Dundee have already impacted on the clinical culture at MCC by changing clinical practice. Modelling work in collaboration with Drs. Susan Minton (Clinical Director of Breast Medical Oncology), Julio Pow-Sang (Chair of Genitourinary Oncology) and Damon Reed (Medical Director of the Sarcoma Department) has had an impact on their clinical practice and consequently on patient health. Specifically, the mathematical modelling developed in Dundee and carried out by the IMO personnel has led to an improved ability to sub-classify patients into potential responders or non-responders for a given therapy as well as aid in the early identification of aggressive cancers that need to be treated immediately as opposed to non-aggressive cancers that can be monitored. Mathematical modelling has also helped to optimise treatment scheduling in a patient-specific manner by tailoring scheduling, dosing and drug combinations for individual patients [FS1]. In this way, patient health outcomes have been improved through the mathematical and computational modelling work of the IMO department.

"…via the initiation of extraordinarily productive collaborations with clinicians, researchers (who originated at the UoA) have successfully integrated mathematics into a wide range of subjects in tumour biology and oncology. Via the routine integration of mathematics and empirical work, their work is having world-wide impact." [FS2]

Development of a new anti-cancer drug at Cyclacel
[Dates Impact Occurred: September 2008 – December 2010]

Founded in 1996, Cyclacel Pharmaceuticals Inc. is a biopharmaceutical company that develops cell-cycle specific oral therapies for the treatment of cancer and other serious diseases. As a consequence of the fundamentally nonlinear nature of the cell cycle, the efficacy of cell-cycle-specific drugs cannot (typically) be well-understood using verbal (linear) reasoning. Hence Cyclacel, in collaboration with the UoA, have developed mathematical models of key aspects of the cell-cycle pertinent to the drug pathways they wish to target with pharmaceutical compounds.
The mathematical models have been used to predict the behavior of potential anti-cancer drugs that are now undergoing Phase 1 trials [FS3]. Specifically, the models were used directly in the selection of drug doses for trials, the prediction of toxicity effects and the analysis of biomarkers.

"The research (at the UoA) developed novel mathematical models of Aurora kinase inhibitors (potential anticancer drugs) .. that were of direct relevance to the development of Cyclacel's early-stage drugs. Specifically, the drug CYC116 (an Aurora Kinase inhibitor) is in a Phase 1 trial in patients with solid tumors. The pharmacokinetic/ pharmacodynamic (PK/PD) model of CYC116 drug action was a useful tool in selecting starting doses for clinical trials, in predicting possible toxicity, and in selecting sampling times for biomarkers. … the PK/PD model may assist in design of later-stage trials, in design of combination protocols, and in individualising treatment protocols to optimise response against tumours with defined gene expression patterns." [FS4]

Performance improvement at AstraZeneca
[Dates Impact Occurred: December 2008 – November 2012]

AstraZeneca is a multinational biopharmaceutical company that specialises in the discovery, development and manufacture of prescription medicines. Their largest research and development site is at Alderley Park, UK, and employs 2,900 people and hosts their global lead centre for cancer research.

Working in their Systems Biology group in Alderley Park, Dr. Hitesh Mistry brought mathematical modelling and simulation skills developed at the UoA to processes involved in the industrial design of pharmaceuticals. Dr. Mistry's research had an impact in a number of anti-cancer drug projects and he was awarded a prestigious AstraZeneca Oncology Award in recognition of his unique and highly valued role.

"Whilst here at AstraZeneca Dr. Mistry's work was seen as so valuable to the organisation that he was awarded a prestigious 'Oncology Award' in recognition of his unique and highly valued role. Such is the recognition of the work that this area will be expanded and will be used for focus for financial development. The hypothesis that was generated undoubtedly saved months of development time and indirectly affected patients lives." [FS5]

5. Sources to corroborate the impact (indicative maximum of 10 references)

Factual Statements have been obtained from:

[FS1] Chair, Department of Integrated Mathematical Oncology, H. Lee Moffitt Cancer Center, Tampa, FL, USA..
[FS2] Chair, Radiology, H. Lee Moffitt Cancer Center, Tampa, FL, USA.
[FS3] Programme Manager, Research and Development, Cyclacel Ltd.
[FS4] Director, Pharmacometrics Ltd.
[FS5] Therapeutic Area Pharmacometrics Expert, Clinical Oncology and Infection, Clinical Pharmacology and Pharmacometrics, AstraZeneca UK Ltd.