

ICMS Workshop Report:

Mathematical Modelling and Analysis of Cancer Invasion of Tissues
March 26, 2007 - March 30, 2007
West Park Conference Centre, Dundee

Organizer: Prof. Mark Chaplain, Division of Mathematics, University of Dundee

1. Overall Summary:

The Workshop went ahead as planned and did not deviate significantly from the original proposal.

2. Short Description of the Meeting

Elucidating the complex interplay of factors regulating tissue level phenomena via lower level cell-cell and cell-matrix interactions has emerged as a major scientific challenge in the post-genomic era, generating a great deal of interest in what is now called “Systems Biology”. In this general area of research, mathematical modelling of cancer growth is now a well-established field in its own right. Predicting how cancers develop, grow and spread and how they are best treated is providing many challenging and novel problems for applied mathematicians. The principal objective of this workshop, with its scientific and mathematical focus on the modelling and analysis of cancer invasion and metastasis, was to provide a deeper understanding of the links between intracellular processes and cancer cell population dynamics through the use of multiscale analysis, mathematical modelling and numerical/computational techniques. With recent advances in analytical and computational tools and techniques, mathematical models of cancer growth are becoming ever more sophisticated, accurate, quantitative and predictive. The plenary talks at the Workshop demonstrated the “state-of-the-art” in this field and generated much fruitful discussion amongst the participants. Modelling in this area has evolved to a point where many of the mathematical models are capable of generating predictions which can be tested experimentally. The Workshop was highly stimulating for all participants and proved to be a success, both scientifically and “socially”.

3. Comprehensive Report

3.1 Workshop Structure

The Workshop took place in the Balbeggie Room of The Westpark Conference Centre, Dundee. The room was well-equipped and provided a relaxed atmosphere for the talks to take place in. Coffee/tea was served from an adjoining room. The Workshop took place over five days, Monday-Friday 26-30 March. There were fifteen plenary speakers in total. Each morning had three, one-hour plenary talks with a half-hour coffee break. Lunch each day took place in the Westpark Centre dining room, 12:30-14:00. Each afternoon had between three and five contributed talks, each of half-hour duration. Wednesday afternoon was a “free-afternoon” and on the Thursday evening the Workshop dinner took place. The Workshop was attended by forty-nine participants.

3.2 Workshop Highlights

The overall highlight of the Workshop was the plenary talks, which were all excellent in content and presentation. Each morning's plenary talks had a general theme.

Monday 26th March:

The general theme in this session was analytical and computational tools. Professor Nicola Bellomo (Politecnico di Torino) and Professor Mirosław Lachowicz (Warsaw University) gave presentations on theoretical approaches to multi-scale modelling using ideas and techniques from statistical mechanics and Boltzmann-type equations. Professor Yannis Kevrekidis (University of Princeton) gave a presentation on a very interesting numerical/computational technique known as “equation free modelling”. So far this technique has been used to model other multiscale systems (e.g. material science) but not yet for cancer growth modelling. The talk by Professor Kevrekidis gave much food for thought to the participants as to how this technique may be modified and developed and applied to cancer modelling problems.

Tuesday 27th March:

The general theme of this session was modelling cell migration. Professor Angela Stevens (University of Heidelberg) presented a new model of cell migration dependent upon the underlying fibre orientation in the extracellular matrix. The model consisted of coupled integro-differential partial differential equations. Professor Thomas Hillen (University of Alberta) presented a multiscale approach to cell migration. Initially transport equations were formulated at a mesoscopic level and then using hyperbolic and parabolic scaling techniques, corresponding macroscopic advection-diffusion equations were derived. Computational simulations revealed interesting migration patterns. The final plenary talk by Professor Hans Othmer (University of Minnesota) presented a novel hybrid discrete-continuum model for the growth of an avascular spheroid. The approach presented challenging computational problems in 2- and 3-dimensions, but the model represented a big step-forward over existing models.

Wednesday 28th March:

The general theme of this session was modelling cancer invasion of tissue, with the first two talks linked through theory and experiment. Dr. Alexander Anderson (University of Dundee) presented a hybrid discrete-continuum model of cancer cell invasion of tissue. One major strength of the model was its ability to allow for the modelling of genetic mutations in cancer cells and to study the evolutionary dynamics of the cancer cells as they became progressively more aggressive and cancerous. The second talk by Professor Vito Quaranta (Vanderbilt University) described a range of experiments currently being undertaken in Vanderbilt University to verify certain predictions made by the model of A. Anderson concerning cancer cell invasion. The experiments had been suggested solely on the basis of the theoretical and computational results of the mathematical model. The talk of Professor Avner Friedman (Ohio State University) focussed on free- and moving-boundary models of cancer invasion. Analytical techniques from the theory of partial differential equations were used to analyse the properties of solutions of the equations, including existence and uniqueness results. Subsequent bifurcation analysis showed exactly how the growth of an initially radially-symmetric solid tumour could break down and become asymmetric.

Thursday 29th March:

The general theme of this session was multiscale modelling of cancer. Professor Robert Gatenby (University of Arizona) examined the growth of a cancer from an evolutionary perspective and showed that certain features the “cancer phenotype” must emerge through adaptation to a generally “harsh microenvironment” of low oxygen levels and high acid levels. Predictions from the mathematical model were consistent with experimental observations from multicellular spheroids and clinical specimens. Professor Philip Maini (Oxford University) presented a multiscale mathematical model of vascular tumour growth. This model linked intracellular signalling pathways (oxygen production and the HIF pathway), with blood vessel growth and cancer cell growth in a solid tumour. In vascular tumours, nutrient is supplied by blood vessels whose growth and structure are affected by the blood flow in them. Pressure/stress within the solid tumour compress the vessels, thus shutting down nutrient supply. However, starved of oxygen, the cancer cells respond by secreting more growth factors to stimulate new blood vessels, thus “completing the loop” between blood vessels, cancer cells and intracellular pathways. The model consisted of systems coupled partial and ordinary differential equations and a cellular automaton. The results of the computational simulations had implications for treatment of cancers using chemotherapy. The final talk of the session was given by Professor Helen Byrne (Nottingham University) who presented a multiscale mathematical model for colorectal cancer (CRC) which is one of the best characterised cancers, with extensive data documenting the sequential gene mutations that underlie its development. Complementary datasets have also been generated describing changes in protein and RNA expression, tumour biology and clinical outcome. This increase in the quantity and variety of information that can be collected has stimulated the development of multiscale mathematical models that can integrate these highly disparate datasets. The talk showed that the new multiscale model provided insight into CRC growth by its ability to describe phenomena occurring at different spatial scales.

Friday 30th March:

The general theme of this final plenary session focussed on mechanical approaches to modelling solid tumour growth. The first talk by Professor John Lowengrub (University of California, Irvine) focussed on a moving-boundary model of avascular tumour growth where the internal pressure field of the solid tumour drove the initially radially symmetric growth. Under certain parameter regimes, cell-cell adhesion forces at the tumour surface were sufficient to maintain this initial growth. Using a combination of analysis and computational techniques, Professor Lowengrub elegantly demonstrated how a solid tumour may subsequently change its morphology in response to cues from the microenvironment. A wide range of growth behaviour (resulting in different “patterns” of growth) was predicted for different ranges of key parameters (cell adhesion and cell proliferation being two). These predictions from the computational simulations of the model were consistent with a range of recently performed in vitro experiments. Implications for cancer treatment protocols were also discussed in light of the model predictions. The talk of Professor Luigi Preziosi (Politecnico di Torino) focussed on key mechanical aspects of solid tumour growth. After describing some of the main features of tumour growth and in particular the phenomena involving stress and deformation, Professor Preziosi described the use of “multiphase models” and of the concept of evolving natural configurations to describe solid tumour growth. Some specific examples were then given according to the type of constitutive equation used, specifically focusing on contact inhibition of growth,

nutrient limited avascular growth and interaction with the environment. The final plenary talk of the workshop was given by Professor Jonathan Sherratt (Heriot-Watt University) and concerned modelling the role of cell-cell and cell-matrix adhesion in cancer growth. Changes in cell-cell and cell-matrix adhesion play key roles in the development of many solid tumours. However, they are difficult to incorporate into mathematical models and are often neglected. Professor Sherratt presented an elegant new continuum modelling approach for cellular adhesion, using integro-differential equations. The model was able to reproduce a range of standard in vitro experiments on cell aggregation. Professor Sherratt then discussed the implications of developing the model for solid tumour growth.

3.3 Participant Involvement:

As described in Section 3.1, the afternoon sessions were devoted to contributed talks by the other participants. A total of twelve, 30-minute contributed were presented. In addition to the general discussion session after each plenary talk and each contributed talk, there was ample time for discussion amongst participants during the morning and afternoon coffee breaks, during the lunches and during each evening. Many of the participants have commented on the many opportunities for fruitful discussion in the questionnaire.

3.4 New Collaborations:

There are several new collaborations which have already arisen from the Workshop:

(i) Hillen (Alberta), Painter (Heriot-Watt), Chaplain (Dundee) – modelling cell migration via taxis-diffusion-reaction equations. A proposal to EPSRC is being written and will be submitted later this summer.

(ii) Lowengrub (UCI), McDougall (Heriot-Watt), Chaplain, Anderson (Dundee) – multiscale modelling of vascular tumour growth. A paper is currently being written on this subject and a Visiting Fellowship Grant will be submitted to EPSRC later this summer for Prof. Lowengrub to visit Dundee/Heriot-Watt in 2008.

(iii) Gerisch (Halle), Chaplain (Dundee), Szymańska (Warsaw), Lolas (Athens) – development of a new model of cancer growth incorporating cell-adhesion. A paper is currently being prepared for submission.

3.5 General Summary

Overall, the workshop ran smoothly, achieved its aims and objectives and was a success, as can be seen from the questionnaires submitted by the participants.