Partial Differential Equations in Cancer Modelling

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1 Overview of the Field

Cancer is not just one disease, but rather a complicated interaction of many abnormal features and many different cell types, which are situated in a heterogeneous habitat of normal tissue. The mathematical modelling of cancer growth and treatment is at full swing, and a significant challenge arises due to the interactions of cancer with a complicated and structured microenvironment of healthy tissue. Many of the spatial models in cancer modelling are based on partial differential equations (PDEs) that include spatial heterogeneity, orientational tissue structure, tissue stiffness and deformability. The analysis of these coupled non-linear PDEs is challenging. Specific problems relate to reaction-diffusion equations, transport equations, continuum equations, and to their local and global existence and uniqueness, pattern formation, invasion, free boundary problems, anisotropic diffusion, and control.

In this workshop we gathered leading experts and young researchers from PDE modelling in mathematics, medicine and biology to discuss the analysis and application of PDE models for cancer and cancer treatment.

2 Recent Developments and Open Problems

The traditional understanding of cancer is the view that through mutations a very aggressive cell type is created, which grows unlimited, is able to evade treatment and, at later stages, invades into other parts of the body (metastasis). All cells of the tumor were considered as basically identical clones. In recent years, however, the picture has changed drastically. It is now well accepted that cancer does not describe one disease, or one type of aggressive cells, but rather a complicated interaction of many abnormal features (Merlo et al. 2006, Hanahan, Weinberg 2011, Gatenby 2009). Hanahan and Weinberg state in their 2011 hallmark paper on page 646:

> *... tumors are more than insular masses of proliferating cancer cells. Instead they are complex tissues composed of multiple distinct cell types that participate in heterotypic interactions with one another. ... tumors can no longer be understood simply by enumerating the traits of the cancer cells but instead must encompass the contributions of the "tumor microenvironment" to tumorigenesis.*

The interaction of different species in heterogeneous environments is the object of mathematical ecology. Over the past decades, the mathematical modelling of ecosystems has produced some sophisticated theories. For example, there is a vast literature on invasion of foreign species (Murray, Lewis, Cosner), on persistence

or permanence of species under stress (Cosner, Cantrell), on bio-control (Lewis), on genetics, mutations and selection (U Diekmann, Doebeli), on competition and predator-prey interactions (Thieme, Zhao) and many forms of structured population models (Thieme, O Diekmann).

Some of these methods have been adapted to the situation of cancer modelling, and we believe that the research on cancer modelling can even further benefit from these methods. Specifically, PDE models have been used for solid tumors and tumor cords (see Preziosi' book, 2003), for a-vascular tumors (Byrne), for angiogenesis (Chaplain, Anderson), for vascular tumors, and tumor invasions (Chaplain), and for many specific tumor types such as brain, prostate, colon, breast cancers and leukemia. We see close resemblances in the mathematical treatment of models in ecology and cancer modelling. In particular questions related to invasions, mutation and selection, competition, predator-prey interactions, extinctions, periodic forcing, spatial pattern formation, harvesting and treatment. This list, however, is too wide to be covered in a single meeting. Hence we focused on selected aspects of the above: *(i) PDE models for tumor growth in healthy tissue, (ii) tumor invasions in non-homogeneous environments, (iii) PDE models for evolution and selection*, and *(iv) the use of these models for control and optimization.*

(i) PDE models for tumor growth in healthy tissue. As a tumor grows in healthy tissue it is producing a cell mass that pushes healthy cells aside. The mechanical interactions of tumor cells with healthy tissue have been modelled in several ways, including continuum equations (Preziosi, Byrne, Loewengrub, Macklin, Chauviere), multi-phase flow models (Byrne, Owen), transport equations (Hillen, Painter), and individual based models (Anderson, Deutsch, Drasdo). For example tumors in brain tissue are exposed to white matter tracks and grey matter regions as well as macroscopic barriers such as the falx celebri. The models become complicated very quickly and sophisticated methods are needed for analysis and simulations. One powerful tool are scaling limits, homogenization and moment closure methods which enable us to reduce the full (physical) PDE to macroscopic models that can be analysed. Another tool relates to free boundary problems as studied by Friedman.

(ii) Models for Invasions. After the tumor has grown to a certain size, it starts to actively invade into healthy tissue. This can have two forms; active movement to nearby sites (invasion) or passive transport by the blood system or the lymphatic system (metastasis). Metastasis is often the last step of a malignant tumor and leads to eventual death of the patient. Recent mathematical modelling has focused on various aspects of tumor invasion. Most models are of the form of advection-reaction-diffusion equations or transport equations (Preziosi). In recent studies (Swanson, Konukoglu, Clatz, Mosayabi, Hillen, Painter), it has been shown that reaction-diffusion models can be used to describe glioma growth in the heterogeneous environment of the brain. The brain is made out of white and grey matter. While the grey matter is mostly homogeneous, the white matter is a fibrous structure. Tumor cells are known to use these fibrous structures to invade new areas. In this context we encounter anisotropic diffusion equations describing different mobility in different directions of the tissue. These models have not been analysed in depth and first results show the ability to create unexpected spatial patterns (see e.g. Hillen et al 2011). Some of these patterns include blow-up solutions that have not been studied before. The analysis requires the introduction of *very weak solutions*, and the uniqueness of these solutions is still an open problem.

(iii) Evolution. The important role of mutations and genetic information in carcinogenesis and tumor development is well established. Hanahan and Weinberg 2011 include genetic instability as one of the enabling hallmarks, and much of modern cancer research is focussed on gene expressions. However, knowing the genes will not suffice to understand and control cancer. As Gatenby wrote in Nature Reviews 2011 on p. 237:

> *A full understanding of cancer biology and therapy through a cataloguing of the cancer genome is unlikely unless it is integrated into an evolutionary and ecological context.*

The mathematical modelling of evolution in cancer is in full swing and many methods from ecological modelling are already implemented into cancer modelling. Nagy 2005 wrote a review highlighting recent success in the modelling of cancer evolution; Merlo et al 2006 explain cancer as an evolutionary process, and Gatenby 2009, 2011 highlight the interaction between evolution, selection and the tumor microenvironment. Anderson et al 2001 used the genetic makeup of tumor cells to successfully model reoccurrence of breast tumors. An

emerging focus of interest is the role played by *Cancer Stem Cells* (Enderling, Hahnfeldt, Hillen, Loewengrub) which was an important issue in our workshop.

The evolutionary theories are strongly connected with the other focus points of this workshop. Spatial structure leads to selection pressures on the tumor; spatial niches might arise, where metastasis can form. Related to treatment, each treatment agent forms a selection pressure on the tumor and often resistant tumors arise as a result of treatment.

(iv) Tumor Control and Treatment A specific challenge of cancer treatment is the way how a cytotoxic agent (or radiation) gets delivered to the tumor cells. The complicated spatial extend of a tumor must be understood, as well as the connection to the vascular system. These aspects can be informed from the above PDE models which are then combined with treatment strategies. Unfortunately, treatments have side effects on the healthy tissue and they impose selection pressures on the tumor. Certain agents can only be used up to a certain limit. Hence we are faced with non-linear optimization problems for PDEs and for ODEs. Over the last 10 years much progress has been made on the optimization of chemotherapies, and combination therapies (Swierniak, Agur, Ledzewicz, Schaettler, d'Onofrio). They identified optimal treatment strategies that are different from bang-bang strategies as they involve *singular controls*.

Another example of recent research involves the *tumor control probability* (TCP). The TCP (mostly used in radiation treatment) describes the probability that a tumor is eradicated by a given treatment. Mathematically, it is the same object as the *extinction probability*, which describes the probability that a certain species goes extinct. Kendall 1998 developed a birth-death framework for the extinction probability, which since has been developed as TCP. There are various mathematical models for the TCP, which are based on stochastic processes and their corresponding PDE descriptions, such as the Poisson process, birth-death processes (Zaider, Minerbo, Stavrev, Hillen), and branching processes (Hanin, Lutscher). First studies have shown that these TCP models are powerful tools in the prediction of treatment success (Gong, Stavrev), however, further studies of their qualitative properties and further data analysis is needed.

3 Presentation Highlights

(i) PDE models for tumor growth in healthy tissue

- Adrian Lam (Ohio) and Tracey Stepien (Arizona) introduced mathematical models for tumor spread in form of free boundary value problems. A fundamental question is the relation of cell-cell adhesion to the surface tension term in the equations. This was, in fact, later been posted as one of the open problems for the workshop (see Section 4).

- Rebecca Everett (Arizona) presented a system of ordinary differential equations (ODEs) for the growth of ovarian cancer. She found that a high ratio of phosphorus to carbon was symptomatic for a large tumor growth rate.

- Victor Oluwole (U Alberta) presented a partial differential equation model for the bystander effect. The bystander effect denotes the effect that through radiation some healthy cells are damaged although they have not received direct radiation. Oluwole could use his model to explain a curious "hypersensitivity" in experimental dose-response curves for low radiation doses.

- Amanda Swan and Thomas Hillen (both U Alberta) presented mathematical models for anisotropic diffusion of glioma. The models are motivated from detailed modelling of cell guidance along white matter fibre tracks and they use data from diffusion tensor imaging (DTI). DTI allows to measure dominant direction in the brain tissue which can then be used to parametrize a fully anisotropic diffusion model.

- Jack Tuszynski (U Alberta) discussed altered energy metabolism as major characteristic of cancer. This view has many interesting and also provocative implications. It highlights the role of energy metabolism, which is indeed altered in cancer cells. One consequence is the increase of lactic acid in a tumor region (also described in Dr. Maini's talk). Another consequence is the hypothesis that the genetic makeup is less important and might be overshadowed by the microenvironment and energy

metabolism. While this approach leads to interesting challenges, the mathematical modelling of energy metabolism in cancer is in its infancy. Dr. Tuszynski invited the audience to become active in this developing field.

(ii) Models for invasions

- Jake Taylor-King (Oxford) presented generalized velocity jump processes as models for tumor spread. Velocity jump processes are currently used in the modelling of glioma spread for example (see Swan and Hillen), and the generalized models of Taylor-King allow us to include non-Poissonian events of cell reorientation. These new models motivate very interesting and challenging open questions about existence, uniqueness, qualitative behavior and parabolic scaling limits. Some of these problems were proposed for the working groups of this workshop (see Section 4).

- Robert Strehl (Ryerson) focused on numerical methods to solve invasion PDE. His examples included chemotaxis, but his methods are applicable to a wide variety of cancer invasion models.

- Hildur Knutsdottir (UBC) presented a individual model for tumor cell invasion and metastasis, where leader cells develop. Leader cells are highliy invasive cancer cells which can actively destroy the extracellular matrix and lead an invasion, followed by less mobile cells.

- Philip Maini (Oxford) followed an idea of Gatenby and Glawinski, that a tumor is often surrounded by high lactic acid concentrations. This high acid concentration damages healthy tissue and allows tumor cells to invade further. Maini presented PDE models that can explain the invasion advantage that tumor cells gain through the production of lactic acid.

- Andreas Buttenschoen used an individual based model to investigate cancer invasion types that were classified by P. Friedl. Friedl identified different invasion mechanisms that range from individual to small groups to population invasions. Buttenschoen could show that the type of invasion depends on cell adhesion strength as well as the tumor growth rates.

(iii) Evolution

- Jean Clairambault (Paris) and Tommaso Lorenzi (Paris) discussed drug resistance in cancer as an evolutionary process. Integro-partial differential equations can be used to describe mutation and selection of resistant streams. Drs. Clairambault and Lorenzi explained how these models can be used to device treatment strategies that reduce resistance. One such idea is based on Gatenby's proposed approach that a tumor does not necessarily be eradicated, but rather kept at a low, but manageable size.

- Peter Kim (Sydney) presented two types of models for the evoluation of leukemia. He started with a cellular automata simulation and he then passed to a formal continuum limit to obtain a PDE. This continuum limit is usually difficult to obtain and Peters results form a mathemaical highlight of the meeting.

(iv) Treatments

- Siv Sivaloganathan (Waterloo) discussed the mathematical modelling of focussed ultrasound therapy. Focussed ultrasound therapy is a new treatment modality where high frequency sound waves are used to heat a certain area of tissue to remove tumor cells. This ultrasound therapy creates wounds in the tissue and it is a question of open research to understand the role of these wounds on possible tumor relapse. Further mathematical challenges arise throng the heterogeneity of the tissue and the diffusivity of the sound signal.

- Yangjin Kim (Konkuk, South Korea) discussed a mathematical model for a new treatment idea, virus thearpies. In those therapies viruses are loaded with an anti-cancer antibody and then the tumor is infected by this virus. First results are very promising.

- Lisette de Pillis (Harvey-Mudd) discussed the role of the immune system with respect to chemotherapy and development of resistance. Her use of ODEs allowed her and coworkers to find optimal dosage protocols to minimize resistance.

- Jose Hector Morales (UA Mexico) presented models for liposome therapy. In that therapy liposomes are loaded with an anti-cancer drug and then injected into the tumor region. A Fokker-Planck advection-diffusion approach is able to quantify the time scale of drug release as compared to the time scale of diffusion and transport. Extensions of the model to virus-therapies are currently discussed.
- Dominik Wodarz (UC Irvine) focussed his studies on the modelling of treatment of leukemia. Again, an important question is the occurrence of resistance and possible strategies to delay resistance for as long as possible.

4 Scientific Progress Made

On the first day of the workshop we gathered interesting open problems to be studied in working groups during the workshop. The proposed problems were:

1. **Steady states for the adhesion model of Armstrong et al.** In 2006 Armstrong, Painter and Sherratt introduced a non-local partial differential equation as model for cell-cell adhesions. The basic model has the form
$$u_t = D\Delta u - \nabla(u(I(u)) + f(u)$$
where the adhesion term is an integral
$$I(u) = \int_{B_R(0)} h(u(x+\xi,t))\frac{\xi}{|\xi|}\Omega(\xi)d\xi$$
with adhesion strength function h and weight function Ω. This model has been used to describe cell aggregation and cell sorting dynamics. However, the steady states have never been analysed. Hence Dr. Hillen proposed the following questions:
   (a) Consider steady states for $f = 0$ and for $D + 0$, $D \approx 0$ and $D > 0$.
   (b) In 1-D: When do non-trivial steady states exist?
   (c) What is a typical profile of a steady state?
   (d) In 2-D: Do steady states form circular swarms with 90 degree angle at domain boundaries?
2. **Derivation of a curvature term on the swarm boundary by adhesion.** The free boundary problems of Friedman et al. often use a curvature term for the pressure p on the domain boundary $p = \gamma\kappa$, where κ denotes the curvature and γ is the surface tension. It is an open problem to relate the curvature and surface tension to the cell-cell adhesion forces that are active between cells. The question at hand is:
   (a) Can the adhesion model of Armstrong et al. be used to mathematically derive a curvature term for the boundary pressure?
   (b) Can discrete or individual based adhesion models be used to derive such a pressure term?

   Any answer to these question would be a big step forward in the motivation of free boundary problems in cancer modelling.
3. **Generalized velocity jump processes.** The generalized velocity jump processes were introduced by Jake Taylor-King in his talk. These models allow the inclusion of more general turning rate distributions. In the Poissonian case, a large theory for velocity jump processes had been developed over the years including modelling (Othmer, Dunbar, Alt), applications (Othmer, Hillen) and theory (Hillen et al.). It is interesting to see if these results can be carried over to the general velocity jump processes. In particular Dr. Taylor-King proposed to ask
   (a) Can certain jump distributions lead to anomalous diffusion in a parabolic limit scaling?
   (b) Can these models be applied to movement of E. coli or the sea gull L. Fuscus?
   (c) How do these models relate to the modelling of brain tumor invasion as done by Swanson et al, and Hillen et al?

4. **Formulation of an IBVP for a concentric porous cylinder for bones.** Siv Sivaloganathan introduced the modelling problem to understand the distribution of heat in the bone, if exposed to high frequency ultrasound therapy. The formulation of an appropriate initial boundary value problem (IBVP) is not straight forward since bone is a heterogeneous and porous medium which is embedded in healthy tissue. The main question is

   - How to formulate one, or a hirachy of, IBVP for the temperature distribution in the bone tissue due to high frequency ultrasound therapy?

   To estimate the maximum time of exposure to ultrasound therapy before thermal necrosis arises, scientists use an expression for the "thermal dose" as

   $$TD(t) = \int_0^t r^{43-T(t)} dt, \text{ with } r = \begin{cases} 0.25 & \text{if } T \leq 43°C \\ 0.5 & \text{if } T > 43°C. \end{cases}$$

   This formula is rather ad hoc and we were interested to see if

   - Is there a mechanistic model that can explain the above formula for the thermal dose, based on the interaction of tissue with an ultrasound heat source?

5. **A comprehensive model for breast cancer and chemotherapy.** Several talks during the meeting focussed on chemotherapy and also the modelling of breast cancer. The idea arose to combine expertise in those two areas to come up with a comprehensive mathematical model for drug resistance in chemotherapy.

5 Outcome of the Meeting

The meeting was very successful. The scientific presentations as outlined above were of high scientific level and many lead to lively discussions that were continued over lunch, dinner and free time. The variety in different but related topics allowed participants to branch out and to connect their own work to a broader context.

The work on open problems as mentioned above was a great success. The working groups formed quickly and several good ideas were generated:

Problem 1. For problem 1 we found an article by T. Xiang on steady states for the non-local chemotaxis model. The methods of this paper seem to be applicable to compute the steady states for the adhesion model. A. Buttenschoen and T. Hillen decided to continue this line of investigation in a joint project.

Project 3. The generalized velocity jump processes were discussed in a small group and a collaboration ensued, involving Taylor-King, Oluwole, Maini and Hillen. After the meeting we involved two more colleagues, A. Marinelli (Italy) and S. Fedotov (UK) forming a multinational research group on generalized velocity jump processes. Several ideas that were generated at BIRS are currently developed further.

Project 4. The formulation of an IBVP for ultrasound heating of bone tissue was completely solved in the working groups at BIRS and the result will find its way into a new publication.

Project 5. The group working on a breast cancer chemotherapy model made a huge step forward and a continuing collaboration ensued between Clairambault, Lorenzi, Kim and others. We are convinced that new insight will arise from this new model.

Finally, there were many more interactions, exchanges and common interests and many more good results are expected as outcome of this meeting. Several researchers who attended the BIRS meeting will soon meet again at the Mathematical Biosciences Institute in Ohio and the collaborations will continue.

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