Mathematical Ecology of Cancer

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"The idea of viewing cancer from an ecological perspective has many implications, but fundamentally it means that we cannot just consider cancer as a collection of mutated cells but as part of a complex balance of many interacting cellular and microenvironmental elements". (quoted from the website of the Anderson Lab, Moffit Cancer Centre, Tampa Bay, USA.)

Abstract It is an emerging understanding that cancer does not describe one disease, or one type of aggressive cell, but, rather, a complicated interaction of many abnormal features and many different cell types, which is situated in a heterogeneous habitat of normal tissue. Hence, as proposed by Gatenby, and Merlo et al., cancer should be seen as an ecosystem; issues such as invasion, competition, predator-prey interaction, mutation, selection, evolution and extinction play an important role in determining outcomes. It is not surprising that many methods from *mathematical ecology* can be adapted to the modeling of cancer. This paper is a statement about the important connections between ecology and cancer modelling. We present a brief overview about relevant similarities and then focus on three aspects; treatment and control, mutations and evolution, and invasion and metastasis. The goal is to spark curiosity and to bring together mathematical oncology and mathematical ecology to initiate cross fertilization between these fields. We believe that, in the long run, ecological methods and models will enable us to move ahead in the design of treatment to fight this devastating disease.

Keywords Cancer modelling · Cancer ecology · Microenvironment · Cancer treatment · Mutation and selection · Competition · Immune response

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1 Introduction

The traditional understanding of cancer is based on the view that, through mutations, a very aggressive cell type is created, which grows unlimitedly, is able to evade treatment and, at later stages, invades into other parts of the body (metastasis). All cells of the tumor are considered as basically identical clones. In recent years, however, the picture has changed greatly. It is now well accepted that cancer does not describe one type of aggressive cells, or even one disease, but rather a complicated interaction of many abnormal features (Merlo et al. [46], Hanahan and Weinberg [23, 24] and Gatenby et al. [18, 19]).

A tumor is a result of accumulation of mutations (sometimes 600–1000 mutations), and the tumor mass consists of a heterogeneous mix of cells of different phenotypes. It is these accumulation of mutations which make cancer so dangerous. One mutation might only change a metabolic pathway, but this alone will not suffice for a malignant tumor. As outlined in [24], a full grown invasive tumor can express *cancer stem cells*, which have infinite replicative potential, *progenitor cells* of different abilities, *mesenchymal cells* which result from an endothelial-mesenchymal transition (EMT) and are able to aggressively invade new tissue, *recruited endothelial cells*, which begin to form a vascular network to supply nutrients, *recruited fibroblasts*, which support the physical integrity of the tumor, and *immune cells*, which can be both, tumor-antagonizing and tumor-promoting. All of this resides in a heterogeneous environment of healthy tissue. If such a cancer is challenged by a specific treatment, then only a specific strain of tumor cells will respond to it, and the treatment will select for those cell types that are more resistant to treatment. Hence an immediate consequence of this new understanding is that a single specific treatment is likely to lead to resistance, since only a sub-population is targeted by the treatment. To have any hope of treatment success, a combination therapy should be applied, as is done nowadays in most clinical applications.

Hanahan and Weinberg published a list of six *hallmarks of cancer* in 2000 [23], which has been very highly cited. Just recently [24], in March 2011, they revised their *hallmarks* and adding two *enabling characteristics* and two *emerging hallmarks*. The ten hallmarks, including those of the "next generation" are:

1. sustained proliferative signalling;
2. avoidance of growth suppressors;
3. resistance of cell death;
4. replicative immortality;
5. induction of angiogenesis;
6. invasion and metastasis;
7. genome instability and mutation;
8. deregulation of cellular energetics;
9. tumor promoting inflammation;
10. avoidance of immune destruction.

Hanahan and Weinberg suggest that, to understand tumors, we must look deeper into the microscale processes governing these traits:

> *…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.* (page 646 of [24])

This is where dynamical mathematical models play a key role. If hypotheses about the processes at the microscale can be formulated quantitatively, then the dynamics of these processes can form the inputs to a mathematical model, whose analysis then makes predictions about emergent outcomes. The mathematical model thus builds a bridge connecting microscale process dynamics to predicted traits or hallmarks of cancer tumours. A test of the model, and its underlying hypotheses, comes from comparing model predictions for the emerging traits or hallmarks for cancer tumors to actual observations.

2 Connecting Ecology to Cancer Modelling

As described above, the process of connecting microscale dynamics to emergent traits is a central endeavour of field of mathematical oncology (see, for example, [1, 30]). However, a similar rubric has also been developed in another subfield of mathematical biology, namely mathematical ecology. Here ecological processes on a small scale are connected to emergent ecosystem properties [42]. The structure of modelling dynamics shares many similarities with the complex interactions between cell types and the environment found in mathematical oncology, although the processes act on organismal rather than cellular scales. However, the area of mathematical ecology was developed earlier than mathematical oncology and so, in some respects, has matured further as a field. The goal of this paper is to draw the connections between mathematical oncology and ecology at the process level, with a view to inspire curiosity and identify areas where *technology transfer* is possible, from one subfield to the other.

The ultimate goal of cancer research is to understand and control cancer growth and to heal the patient. As seen in Hanahan and Weinberg's classification scheme, the process of tumor development, growth and spread is very complex. In addition, inclusion of different treatment modalities, such as surgery, radiation or chemotherapy, makes the whole issue even more complex. Mathematical modelling has helped scientists to navigate through the complicated interactions and to identify basic mechanisms of tumor growth and control. Specifically, models for angiogenesis, for anti-angiogenesis, for non-vascular tumor growth and for optimization of chemotherapy or radiation therapy have been used to improve treatment outcomes. Furthermore, mathematical models link the genetic make-up of a cancer to the dynamics of cancer in tissue. It is, however, a long way from a mathematical result to a clinical contribution, and we, as modellers, need to work very hard to convince the medical sciences about the usefullness of mathematical modelling. The ecological community has understood the relevance of modelling already.

Understanding the distribution and abundance of organisms over space and time is the goal of ecology. Mathematical ecology uses quantitative methods to connect the distribution and abundance of organisms to processes such as behavior, competition, food webs, predation, evolution, genetics and environmental fluctuations. 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 [28], on persistence or permanence of species under stress [3], on bio-control [13] and optimal control [41], on genetics, mutations and selection [34], on competition [60] and predator-prey interactions [27] and many forms of structured population models [7]. 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, we see close resemblances between ecology and cancer biology in relation to

(a) **Mutations and Selection**: Genetic instability allows a tumor to adapt to a changing environment, to avoid destruction from the immune system and to evade treatments. In ecology, mutation and selection are the driving principles behind evolution of ecosystems and species.
(b) **Competition**: Cancer cells compete with healthy cells for nutrients. In ecology, many species compete for resources.
(c) **Predator-Prey dynamics**: The immune system can be seen as a predator on the cancer cells. However, the "predator" is not only killing the cancer cells, but might as well promote tumor growth (see [24]).
(d) **Food Chains**: Food chains in ecosystems resemble biochemical pathways and cell metabolism.
(e) **Extinction**: While species extinction is to be avoided in many ecological species, cancer extinction is desired for cancer treatment.
(f) **Age Structure**: Species proliferation naturally depends on the age of the individuals. Similarly, cells are constrained by a cell cycle and they need to transfer through the cell cycle phases (G_0, G_1, S, G_2, M) before mitosis.
(g) **Periodic Forcing**: Ecosystems underlay day-to-day cycles and seasonal cycles. An important cycle in humans is the circadian rhythm, which has an influence on all cells of the body.
(h) **Cell Movement**: Cancer cells move through a complex heterogeneous tissue network. Similarly animals move through heterogeneous environments. Much work has been done on both, tracking cells (via tagging and microscopy) and tracking animals (via radiocollars and measurement through global positions systems (GPS)).
(i) **Invasions**: Invasions of metastasis is the last step of tumor progression. It is usually responsible for the death of the patient. Invasions of foreign species into native ecosystems is one of the major challenges of modern ecology.
(j) **Fragmentation and patchy spread**: Cancer tumours often appear to be fragmented or patchy. Similarly, population densities are notoriously patchy. Reasons for such patchy distributions, ranging from nonlinear pattern formation to stochastic effects, to environmental heterogeneity, can equally well be applied to

cancer tissues or ecological populations. Furthermore, in ecosystems, the spatial organization of species is an important feature, which enables coexistence of otherwise exclusive species.

(k) **Path generation**: many animal species lay down a network of paths to popular foraging locations. Here we see an analogy to vasculature formation during angiogenesis.

(l) **Control**: Cancer control through treatment resembles ecological control mechanisms such as hunting and harvesting. Also biological control, through parasites, is a possible strategy, which is currently discussed in the context of cancer (e.g. bacterial cancer therapies [15]).

We summarize the relations between cancer and ecology and the type of modelling in the following Table 1. In Fig. 1 we attempt a visual representation of the similarities between these areas.

The resemblance is indeed more than striking, and we can use these relations to our advantage. We should not be shy, but cross borders to benefit from the insights of mathematical ecology. In fact, Merlo et al. [46] write in their abstract on page 924:

> *The tools of evolutionary biology and ecology are providing new insights into neoplastic progression and the clinical control of cancer*

The above list, however, is too wide to be covered in a single short paper. Hence here we will focus on areas that we believe the connections stand out most clearly: *control*, *evolutionary theories* and *cell movement and invasion models*.

3 Investigating the Connections

3.1 Tumor Control and Treatment

The common therapies against cancer include surgical removal of cancerous tissue, radiation treatment, chemotherapy and hormone therapy. Quite often a combination of these modalities is used (see e.g. [2]). The modelling of the expected treatment success by radiation treatment is an excemplary showcase of cross fertilization between ecology and cancer modelling. The quantity of interest is the *tumor control probability* (TCP). In its simplest form it is given by the *linear quadratic model* [63]

$$TCP = e^{-S(D)}, \qquad S(D) = N_0 e^{-\alpha D - \beta D^2},$$

where N_0 denotes the initial number of tumor cells, $S(D)$ denotes the surviving cell number of a treatment with dose D, and α and β are the radiosensitivity parameters, which depend on the type of tissue and the type of cancer. The TCP describes the probability that a tumor is eradicated by a given treatment. Mathematically, the TCP is the same object as the *extinction probability*, which describes the probability that a certain species of interest (for example an endangered species [48]) goes extinct. Kendal

Table 1 Similarities between the hallmarks in oncology to ecological mechanisms and typical mathematical models. ODE refers to ordinary differential equations and PDE to partial differential equations. The numbers 1.–10. relate to the hallmarks of Hanahan and Weinberg and the letters (a)–(l) relate to the ecological process as listed above

Hallmark	Cancer process	Ecological process	Typical model
1. Sustained prolif. signalling	Tumor growth	Population growth (d) Food chains	ODE
2. Avoidance of growth suppressors	Tumor growth	Population growth (d) Food chains	ODE
3. Resistance to death	Tumor growth	Population growth (e) Extinctions	ODE stochastic processes
4. Immortality	Tumor growth	Population growth (e) Extinctions	ODE
5. Angiogenesis	Tumor vascularization	(j), (k) Spatial heterogeneity	PDEs stochastic processes
6. Invasion metastasis	Tumor spread	(i), (h) Population spread	PDEs stochastic process
7. Genome instability	Carcinogenesis	(a) Evolution	Integral equations adaptive dynamics
8. Cellular energetics	Competition with healthy tissue	(b) Competition	Dynamical systems
9. Inflammation	Immune response	(c) Predator prey and biological control	Dynamical systems
10. Avoidance of immune destruction	Immune response	(c) Predator prey and biological control	Dynamical systems
Additional feature			
Cell cycle	Cell cycle specific sensitivities	(f) Structured populations	PDEs
Treatment	Tumor control	(l) Control of biological species and harvesting	Optimal control problems
Periodic forcing	Circardian rythms	(g) Seasonality	Nonautonomous ODEs

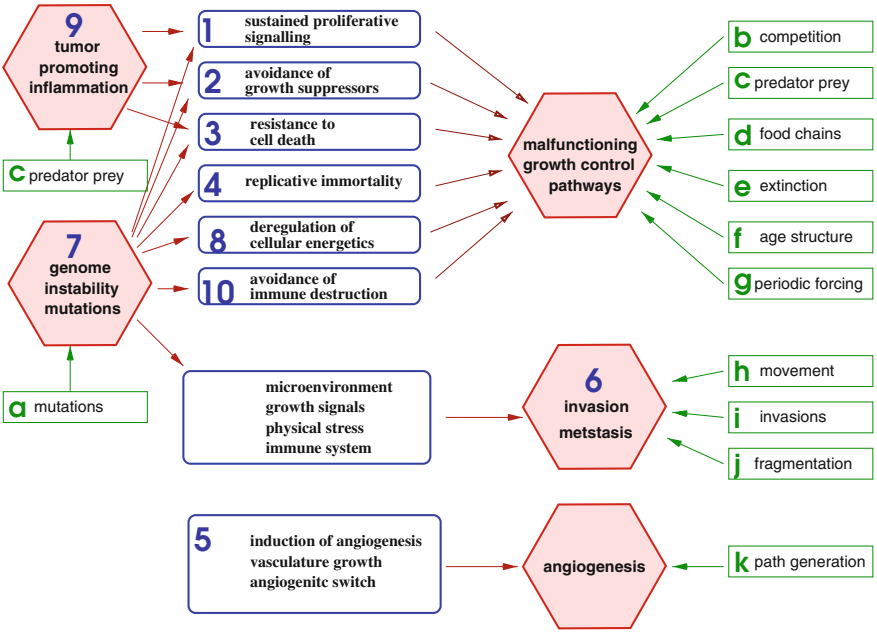

Fig. 1 Schematic representation of the relations between the cancer hallmarks, ecological processes, and mathematical modelling. The *blue numbers* 1–10 refer to the hallmarks as described by Hanahan and Weinberg [24] and the *green letters* a–k refer to the ecological processes as listed above. The *red hexagons* relate to biological or ecological processes that have been analyzed through mathematical modelling. The *arrows* indicate what kind of information from experiments or observation is used to inform the corresponding models. There are many more feedback loops, from modelling to biology, which we needed to omit due to readability

[37] developed a birth-death framework for the extinction probability, which since has been developed as a more accurate TCP model than the above linear quadratic model. The mathematical framework comes directly from ecological applications, but the interpretations, and some of the details are specific to cancer modelling. This direction of research has blossomed in beautiful theories on brith-death processes and branching processes, which are able to include cell cycle dynamics and differential radiosensitivities depending on the cell cycle state (see [22, 25, 26, 31, 43, 61, 66]). In a recent PhD thesis, Gong [21] included cancer stem cells into the TCP models and she confirmed that it is critical to control the stem cells for treatment to be successful. First studies have shown that the above TCP models are powerful tools in the prediction and planning of radiation treatments ([22, 61]), however, further studies of their qualitative properties and further data analysis is needed.

Ecologists have long assessed the probability of local extirpation of a species of interest using the method of population viability analysis (PVA). This mathematically depicts the birth and death process via a stochastic process with drift, as described by a partial differential equation. Here hitting probabilities and times to extinction can

be calculated based on classical diffusion theory [57]. More recently this approach has been modified to address the problem of preventing establishment of a species, rather than preventing extinction of a species. Here the goal is to determining how to prevent introduced exotic species establishing as an invader, with the goal of making them go extinct [9]. This approach shares much with that of controlling cancer.

In a spatial context, ecological modellers have investigated the problem of optimal spatial control of an invader, determining the size and duration of treatment needed to spatially control the spread of an invader as it moves across a landscape [12, 54]. This approach has parallels with the issue of optimal radiation treatment for controlling the spread of a cancer tumour. The optimization of chemotherapy has been the focus of many research groups around the world, for example: Swierniak (Poland); Agur (Israel); Ledzewicz, Schaettler (USA); d'Onofrio, (Italy). A common theme is the occurrence of resistance. We expect that the above mentioned evolutionary theories, can help to better understand the process of tumor resistance.

As outlined above, the understanding of cancer as an ecological system immediately suggests the application of combination therapies including chemotherapy, hormone therapy and radiation. Mathematical optimization of combination therapies has not been carried out in detail but it will be a focus for future studies [2].

3.2 Evolution

The important role of mutations and genetic information in carcinogenesis and tumor development is well established. Hanahan and Weinberg [24] 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 [20] 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 [49] wrote a review highlighting recent success in the modelling of cancer evolution; Merlo et al. [46] explain cancer as an evolutionary process, and Gatenby [18–20] highlight the interaction between evolution, selection and the tumor microenvironment. Enderling et al. [10] used the genetic makeup of tumor cells to successfully model re-occurence of breast tumors. An emerging focus of interest is the role played by *cancer stem cells* [8, 11, 32].

The mathematical modelling of evolution, selection, mutation, and gene expressions has a long history in ecology [34]. Sophisticated theories include models for adaptive dynamics [6], concepts of evolutionary stable strategies [44], game theoretic approaches [5], and analysis of phylogenetic trees and speciations. Many of these are currently discussed in the context of cancer, in particular to understand development of drug resistance during treatment [35, 38].

The evolutionary theories are strongly connected with all of the other cancer hallmarks. 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 develop as a result of treatment.

An important difference between ecology and cancer arises related to the relevant time scales. A generation in a developing tumor can be as short as one cell division cycle. i.e. 1/2 day. Hence selection, adaptation and genetic drifts will show up very quickly. Also, a tumor does not have a long ancestry, which goes back for thousands of generations. Finally, the outcome of a tumor in general, is death and destruction. Hence concepts of survival and fitness need to be understood in the correct context.

3.3 Models for Cell Movement and Invasions

The invasion of cancer into healthy tissue is one of the hallmarks of cancer, as described by Hanahan and Weinberg [24]. It is often the last step of a malignant tumor and leads to metastasis and to eventual death of the patient. Recent mathematical modelling has focused on various aspects of tumor invasion. Models are of the form of advection-reaction-diffusion equations and transport equations [55] on the one hand and individual based models (cellular automata [29], Potts model etc., [56]) on the other. The choice of model is largely guided by the available data.

For example, in the lab of Friedl and Wolf [16, 17] in Nijmegen in The Netherlands, individual moving cancer metastasis are visualized by confocal microscopy. Parameters such as mean velocities, mean turning rates and turning angle distributions can be measured. Suitable models on this microscopic scale are individual based models [56], transport equations [30], or stochastic processes [51]. The situation is similar in ecology, where individual movement can be measured through GPS tracking, for example, and also entire populations are observed (e.g. via remote sensing). In ecology a whole range of models is used, from individual based models to population models employing the Fokker Plank equations. Here the challenge arises to combine these approaches and to carefully investigate the transition between scales.

On the other hand, macroscopic data are available that measure the extent of a tumor as a whole. For example MRI imaging of glioma, which show tumor regions and the corresponding edema. For these types of data, we use macroscopic models such as advection-reaction-diffusion models [53]. This process is similar to the biological invasion of an introduced pest species. Here ecologists have a history of characterizing the invasion process by a spreading speed that summarizes the rate at which the population spatially colonizes into the new environment. The approach of using a spreading speed was first pioneered by R. A. Fisher [14] for the spread of an advantageous gene into a new environment, and was later applied in an ecological context by Skellam [59] and many others. It has been modified to include the effects of ecological interactions, such as competition, predator-prey and parasite [58]. More

recently authors have shown how long-distance dispersal can dramatically increase spreading speeds [40] and have also assessed the sensitivity of the spreading speed to life history and dispersal parameters [50]. We believe that the metastasis stage in cancer is very similar to the biological invader population with long-distance dispersal, and that the assessment of sensitivity of spreading speeds to local physiological conditions may give new insights into the control of cancer spread.

Related to glioma growth, in recent studies [36, 39, 53, 62], 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 yet been analysed in depth and first results show the ability to create unexpected spatial patterns (see e.g. [33, 52]). Interestingly, non-isotropic diffusion models are used to model wolf movement in habitats with seismic lines [33, 45], and again, cross fertilization is imminent.

An important difference between tumors and species arises in relation to the surrounding tissue. A tumor lives in a tissue that consists of healthy cells, blood vessels and structural components of the extracellular matrix (ECM). Hence a growing tumor will exert stress onto the tissue and be exposed to stress from the tissue. The inclusion of these physical properties is challenging and first attempts have been made by Loewengrub et al. [64, 65], Preziosi et al. [47] for tumor growth and by Chaplain and Anderson et al. for angiogenesis [4]. These models take the form of continuum mechanics equations and a whole new skill set is needed to study these models. A careful physics based modelling of tumors in tissue, including the appropriate mechanics, is a necessity and a challenge for modern cancer research.

4 Conclusion

Understanding the dynamics of cancer is a major challenge for clinicians. The move towards process-oriented cancer models raises many mathematical and modelling challenges. Indeed, it is often the case that even small changes in model formulation can render a model difficult if not impossible to analyse. Under these circumstances it is natural to draw broadly on the collective knowledge of the research community, embracing results from research problems on similar processes that have arisen in different contexts. Here mathematical ecology has a lot to offer, and the potential impact of moving in this direction of research is imminent.

The goal of this paper is to promote the cross disciplinary exchange of ideas and encourage the reader to assess how methods from one area can be made available to another area. We have made a first step in identifying common mathematical theories and problems and also to identify important differences between ecology and cancer. However, there are many more connections that can be made. Most importantly, we

hope that this work will provide a new approach to harness the powerful mathematical tools used in ecology to further advance the treatment planning of cancer.

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