Universität Heidelberg
Institut für Informatik
Engineering Mathematics

Bachelor-Thesis

Continuous Modeling of Extracellular Matrix Invasion by Tumor Growth

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Datum der Abgabe: January 23, 2024

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Zusammenfassung

Krebszellen können sich vom Primärtumor lösen und das umgebende Gewebe abbauen. Kontinuierliche mathematische Modelle wurden in der Vergangenheit mehrmals verwendet, um diesen Prozess besser zu verstehen. In diesem Zusammenhang basiert das Modell in der Regel auf mindestens drei Schlüsselkomponenten: den Tumorzellen, dem umgebenden Gewebe oder der extrazellulären Matrix (ECM) und den matrixabbauenden Enzymen (MDE). Frühe Beschreibungen dieses Modelltyps finden sich in den Arbeiten von Anderson et al. [1, 2] und Chaplain et al. [1, 3–5]. Das zugrunde liegende Modell wird wie folgt beschrieben. Seien c, e und m die Dichte der Tumorzellen, die Dichte der extrazellulären Matrix (ECM) und die Konzentration der matrixabbauenden Enzyme (MDE) jeweils. Dann lauten die maßgeblichen Gleichungen:

$$\begin{aligned}
\frac{\partial c}{\partial t} &= D_c \Delta c - \chi \nabla \cdot (c \nabla e) + \mu_1 c \left(1 - \frac{c}{c_0} - \frac{e}{e_0}\right) \\
\frac{\partial e}{\partial t} &= -\delta m e + \mu_2 c \left(1 - \frac{c}{c_0} - \frac{e}{e_0}\right) \\
\frac{\partial m}{\partial t} &= D_{m,} \Delta c + \mu_3 c - \lambda m
\end{aligned}$$

mit zero-flux Randbedingungen.

$$\begin{aligned}
n \cdot (-D_c \nabla c + c \chi \nabla f) &= 0 \\
n \cdot (-D_m \nabla m) &= 0
\end{aligned}$$

Hier sind D_c und D_m die Diffusionskoeffizienten, χ ist der positive haptotaktische Koeffizient, δ ist eine positive Konstante, und μ_1, μ_2, μ_3 sowie λ sind die Produktions- und Zerfallskonstanten.
Die Analyse dieses Modells wird in der Literatur größtenteils in $1D$ durchgeführt, und einzelne Beispiele wurden in $2D$ gemacht. Allerdings zeigen vorläufige Reproduktionen des Modells, dass höhere Dimensionen signifikant unterschiedliche Ergebnisse liefern, wie in Abbildung 1 zu sehen ist.

Daher stellt sich die Frage, ob die Parameter für dieses Modell für Simulationen in $2D$ oder $3D$ unterschiedlich ausgewählt werden müssen oder ob die Ergebnisse und Analysen für den eindimensionalen Fall inkorrekt sind.
Darüber hinaus wurde in der Literatur die heterogene Struktur der extrazellulären Matrix (ECM) bereits behandelt. Die Struktur der epithelialen Schicht und der benachbarten extrazellulären Matrix ist jedoch in biologischem Gewebe organisierter als in den gezeigten Simulationen und anderen Beispielen. Daher könnten einfachere Unterteilungen der Geometrie in ECM-Gewebe aussagekräftigere Ergebnisse liefern.
Das Ziel dieser Arbeit ist es, einerseits die Parameter und das Modell für höhere Dimensionen zu untersuchen und andererseits eine einfache Heterogenität der ECM-Struktur in Betracht zu ziehen.

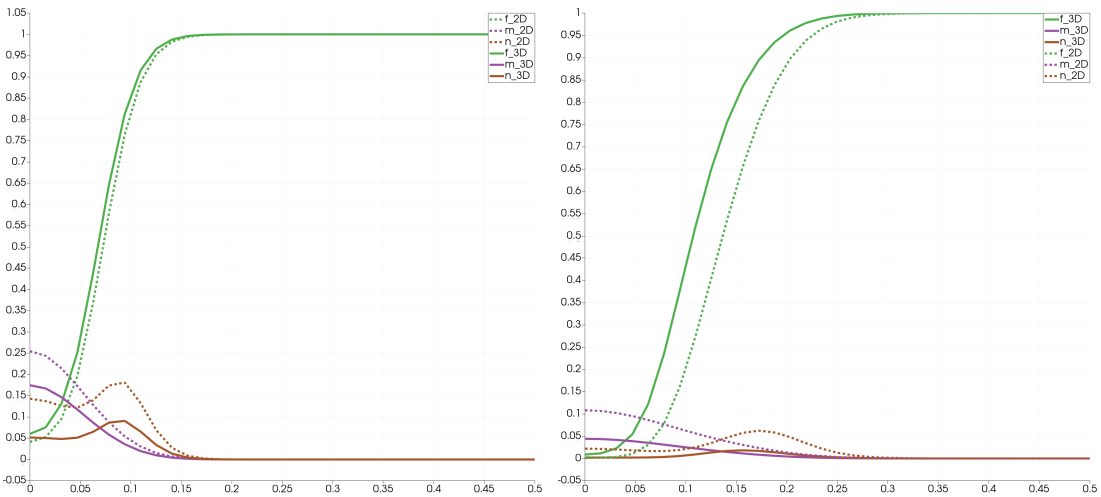

Figure 1: Vorlaeufige Simulationsergebnisse in 2D and 3D des oben beschriebenen Models zur dimensionslosen Zeit $t = 0.7$ und $t = 3$ sowie den Parametern $D_c = D_m = 1e-3$, $\chi = 5e-3$, $\delta = 10$, $\mu_3 = 0.1$ und $\lambda = \mu_1 = \mu_2 = 0$.

Abstract

Cancer cells can migrate from the primary tumor and degrade the surrounding tissue. Continuous mathematical models have been used several times in the past to better understand this process. In this context, the model is usually based on at least three key species, the tumor cells, the surrounding tissue or extracellular matrix (ECM) and the matrix degradative enzymes (MDE). Early descriptions of this model type can be found in the work of Anderson et al. [1, 2] and Chaplain et al. [1, 3–5]. The underlying model is described as follows. Let c, e and m be the tumor cell density, the ECM density and the MDE concentration respectively. Then, the governing equations are given by

$$\begin{aligned}
\frac{\partial c}{\partial t} &= D_c \Delta c - \chi \nabla \cdot (c \nabla e) + \mu_1 c \left(1 - \frac{c}{c_0} - \frac{e}{e_0}\right) \\
\frac{\partial e}{\partial t} &= -\delta m e + \mu_2 c \left(1 - \frac{c}{c_0} - \frac{e}{e_0}\right) \\
\frac{\partial m}{\partial t} &= D_{m_\backsim} \Delta c + \mu_3 c - \lambda m
\end{aligned}$$

with zero-flux boundary conditions

$$\begin{aligned}
n \cdot (-D_c \nabla c + c \chi \nabla f) &= 0 \\
n \cdot (-D_m \nabla m) &= 0
\end{aligned}$$

Here, D_c and D_m are the diffusion coefficients, χ is the positive haptotactic coefficient, δ is a positive constant and μ_1,μ_2,μ_3 and λ are the production and decay constants.
The analysis of this models is mostly done in $1D$ in the literature and individual examples were done in 2D. However, preliminary reproductions of the model show that higher dimensions produce significantly different results, as can be seen in Figure2.

The question therefore arises as to whether the parameters for this model need to be selected differently for simulations in 2D or 3D, or whether the results and analysis for the one dimensional case is incorrect.
Furthermore, the heterogeneous ECM structure has been addressed in the literature. However, the structure of the epithelial layer and the adjacent extracellular matrix is more organized in biological tissue than in the simulations shown in and, for example. Therefore, simpler subdivisions of the geometry into ECM tissue could provide more meaningful results.
The aim of this work is to investigate the parameters and the model for higher dimensions on the one hand, and to consider a simple heterogeneity of the ECM structure on the other hand.

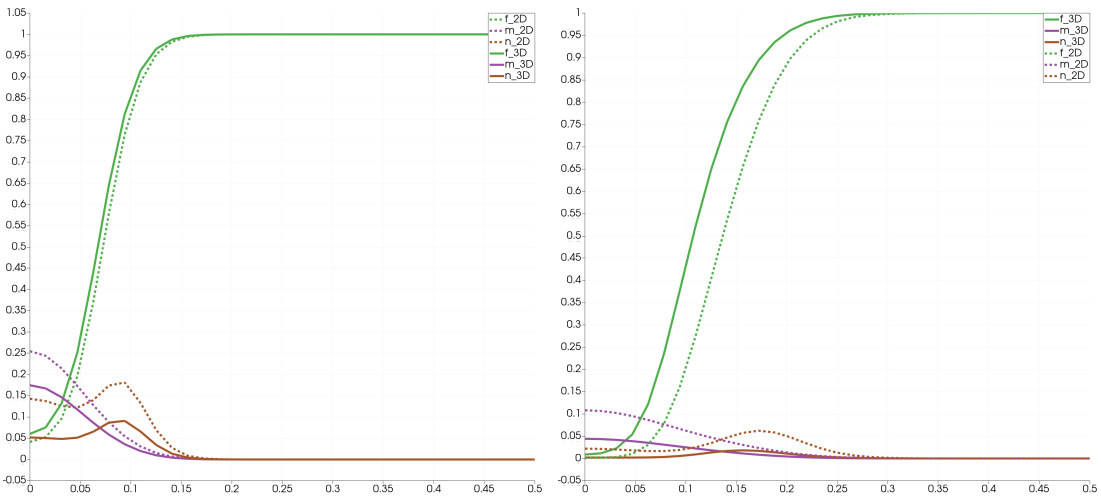

Figure 2: Preliminary simulation results in 2D and 3D of the above described model at dimensionless time $t = 0.7$ and $t = 3$ and parameters $D_c = D_m = 1e-3$, $\chi = 5e-3$, $\delta = 10$, $\mu_3 = 0.1$ and $\lambda = \mu_1 = \mu_2 = 0$.

Contents

1 Introduction

Modelling tumor growth plays a key role in understanding the complex mechanisms, governing development and progression of cancer diseases. Since cancer is one of the leading death causes worldwide and many of its forms are incurable, challenges in the area of Oncology require researchers to have a deep understanding in as well the biological foundation, which lead to malignant cell mutation and factors for tumor growing and spreading, as well as the mathematical models used for simulating these events. This Bachelorthesis is dedicated to analyse Anderson et al.'s [1, 2] model for tumor modelling. The dynamics of tumerous growth are an intricate system, which is influenced by numerous biological and chemical factors, as well as genetic pre-dispostitions, the surrouding tissue of cancer cells, angiogene processes an interactions with the immune system. The integration of these factors in mathematical models allow us to decode these complex interactions with quantification and help us understand the fundamental mechanisms, which surroud cancerous diseases, as the last year's experience has shown.
Mathematical models are a very important part in Oncology. They are used to quantify biological phenomena and therefore help to predict and understand tumor development and treatment response. In Mathematical Oncology we differentiate between continuous, discrete and hybrid models. For the continuous type, cells and tissue are described over time with differential equations modelling continuous quantities like in our case the cell or extracellular matrix density. In the discreate case, a entity based model is used, pursued with the goal to better understand the phenoma on cell level. This approach allows the researcher to better implement biological effects a cell has with its outer circumstances, like interaction with other cells, nutrients or other microorganisms. As the name implies do these models use discrete values to describe the temporal course of events. Hybrid models try to combine both approaches, to offer efficient systems capturing cell level events as well as continuous changes in outer circumstances.
In this work we are investigating how a continuous model proposed by Anderson et al. [1, 2] to analyse tumur development in the early stages performs in the case of different dimensions and free parameter values. The model examines the first two stages of a cancer disease; tumor initiaition, where the tumor cells are localized to a small area and have not yet spread throughout the body; and tumor promotion, with the tumor cells growing and proliferating, invading the surrounding tissue. From examples of the original paper we can already see that the model's results vary with the dimensionality of the space we are modelling the partial differential equations in. Our main focuse lies on comparing simulations of two dimensions with those of three dimensions of extracellular matrix invasion by the tumor growth. Additionally to the variation of dimensions we will have a closer look on how the geometry of the extracellular matrix will influence the tumor development.
Another point fo interest is the investigation of how the model's free parameters influence the tumor dynamics growth. An important task is to give those parameters a biological meaning and to eventually gain insight to how to adjust them to make the simulation more realistic.

2 Theoretical Background

2.1 Basics of Tumor Biology

The body of a living creature is made up of more than 200 different types of cells, the coordination between the cells and their surroundings keep the body running. Each of these cells is built from the genetic information encoded in the DNA, located in the cells' nuclei. Though the nucleotide sequence of DNA is well checked and maintained throughout the cell's life, mutations still occur that cause the changes in the DNA of a cell. These mutations may be of a positive, negative or neutral nature. In the case of a negative mutation this alternation of the DNA may cause diseases, with cancer being one of them. The failure of the complex system managing cell birth, proliferation, and cell death (apoptosis) causes cancer, resulting in an uncontrolled cell proliferation in a at first local area. An conglomeration of cancer cells is called a tumor.
A cancer disease typically follows five stages. First the tumor initiation phase where it comes to the above explained genetic mutations of normal cells. The next stage is the tumor promotion stage, in which the mutated cells of phase one may experience further genetic alterations, with the result of uncontrolled growth and proliferation of the cancerous cells. The third stage is the tumor progression stage, where the cancerous cells progress in growing and proliferating, reaching a critical mass, they form a tumor at a local site of the body. Fourth comes the invasion stage, here the tumor is able to invade surrouding tissue and enter the blood circulation system or the lymphatic system. Next the tumor cells which have invaded the blood circulation of lymphatic system spread throughout the body and form new tumors. This stage is called Metastization. To further grow the tumors need to have access to nutrient and oxygen supply. During angiogensis a tumor develops blod vessels of its own securing its nutritional provision. At this stage first symptoms of host may appear, enabling medical treatment.
In our model the focus lies on the first two stages; tumor invasion and tumor progression, so we are going to have a deeper look at those two phases. The tumor invasion stage is characterized by the malignant cells gaining the ability to penetrate and invade the surrouding tissuse. The tumor cells break through the normal tissue barrier and infiltrate neigbhoring structures. In order to do so the cancer cells produce so called matrix-degrading enzymes which break down the extracellular-matrix. This not only helps local spreading but also destroys otherwise healthy tissue and cells in the affected area. In the next phase the tumor progresssion stage, the tumor has grown larger and the cancerous cells take on more aggressive behaviour, by invading the surrounding area further. Whilst they keep growing uncontrolled they are also affected by further genetic instabilities, which lead to more mutations among the tumor cells, resulting possibly in the development of resistent cancer cells. Already in this stage the affected area is exposed to heavy tissue damage and functional disabilities.
The most important factors influencing those two phases are the genetic dispoistions of the tumor cells towards proliferation and the evasion of apoptosis, which increase the invasive potential. Another important factor is geometry of the extracellular matrix, as well as the exact macromolcules which make it up. A strong immune biological defense reaction also helps the body defend against the spreading of the cancer cells, so evasion

of detection and destruction of the tumor cells plays a key role for the first stages. To invade the affected area the malignant cells need to be able to move freely and fastly. In order to do so cancer cells can gain the ability to lose adhestion properties which healthy cells have, to allow migrating into surrouding tissue.

2.2 Mathematical Methods in Oncology

Mathematical Methods and Models in Oncology play a cruical role in analysing, understanding and predicting cancer development. Since the obejctive of this research underlies complex and intricate biological systems and mechanisms, there exist many models, which find their repsective application in many distinct areas of this research field. These methods can be coarsely divided into three sections; continuous, discrete and hybrid models. For describing tumor growth, exponential and logisitc growth models are often used, the later allowing limiting factors to play a role during modelling. These methods are a subclass of the differential equations approach which base their functionality on a ordinary or partial differential equation, studying the continuous approach. Like in our model they are not limited to consist of one equation but can of many, therefore also incorporating limiting or accellerating factors. These models in generals deal with continuous parameters like densities, or fluid concentrations, for example spacial and temporal nutritional supply or drug concentration, as well as their effects on the affected area over time. Discrete models use a agent-based approach, where the participating individual entities are modeled as objects which can interact on their environment, this means for example cell-cell interaction or cell-tissue interaction. This enables researchers to focus on biological effects during modelling. With these approaches we can also simulate genetic and evolutionary events. For example studying the genetic alternations of tumor cells.
Hybid models combine both aforementioned methods, of using continuous and discrete models. Like in the model proposed by Franssen et al. [5], these apporoaches allow to incorporate the exactness of continuous models with the wide range of biological effects of discrete models.
But no all models try to model tumor growth, there others concerning for example optimality regarding drug dossages or radition exposition, offering personalized treatment, or Machine Learining and Data Mining methods analysing large datasets, to identify patters and predict outcomes. The later method may be used in all kinds of applications, for example spacial or temporal cancer development but also for drug dosage optimization for individual patients. Putting all these methods together gives us an powerful toolbox to simulate and understand cancer biology. Like the last years have shown they are applied in a wide range, offering insight for all areas of cancer research. Therefore it is important not only to come up with methods but to also evaluate their usefulness and meaningfulness regarding different areas of research.

3 Modelling

3.1 Mathematical Formulation

The model propsed by Anderson et al. [1, 2] and Chaplain et al. [1, 3–5] consists of a system of linearly coupled partial differential equations;

$$\begin{aligned}
\frac{\partial c}{\partial t} &= D_c \Delta c - \chi \nabla \cdot (c \nabla e) + \mu_1 c \left(1 - \frac{c}{c_0} - \frac{e}{e_0}\right) \\
\frac{\partial e}{\partial t} &= -\delta m e + \mu_2 c \left(1 - \frac{c}{c_0} - \frac{e}{e_0}\right) \\
\frac{\partial m}{\partial t} &= D_{m_\text{s}} \Delta c + \mu_3 c - \lambda m
\end{aligned}$$

with zero-flux boundary conditions,

$$\begin{aligned}
n \cdot (-D_c \nabla c + c \chi \nabla f) &= 0 \\
n \cdot (-D_m \nabla m) &= 0
\end{aligned}$$

where the free parameters are D_c, D_m, χ, δ, μ_1, μ_2, μ_3 and λ.
The variable c describes the tumor cell concentration, e the concentration of the extracellular matrix and m the matrix-degrading enzyme concentration. All of those functions are mathematically defined to be mapping a 1,2 or 3 dimensional spacial value to a scalar value describing the concentration at this point in space at a point in time, $\{c, e, m\} : \mathbb{R}^3 \times \mathbb{R} \to \mathbb{R}$.
To derive at the expression for the tumor cell concentration c we are going to assume that the tumor cell's moement is only subject to two effects, first haptotaxis and second random movement. Haptotaxis is a directed migratory response of cells to gradients of fixed or bound chemicals [1] and random movement is influenced by mechanical stress, electric voltage or other such physical effects. A flux is defined as the amount of substance which crosses a unit area in unit time. Incorporating these two factors into our mathematical model we define the haptotatic flux $J_{hapto} = \chi c \nabla e$, where χ is the haptotactic flux coefficient, and the random flux $J_{random} = -D_c \nabla c$, where D_c is random mobility constant, but in general this parameter could also be a function of both extracellular matrix concentration and matrix-degrading enzyme concentration $D_c \to D(e, m)$. Combining both formulas for flux, our model for the tumor cell concentration looks like follows: $\frac{\partial c}{\partial t} + \nabla(J_{hapto} + J_{random}) = \frac{\partial c}{\partial t} + \chi \nabla(c \nabla e) - D_c \Delta c)$.
To model the matrix-degrading enzyme concentration e, we asssume that the enzymes degrade the extracellular matrix upon contact. This assumption is simply modeled by the equation $\frac{\partial e}{\partial t} = -\delta m e$, δ is a positive constant describing this mutual dissolution(Aufloesung/Ausloeschung) process.
Modelling the extracellular-matrix concentration m, we need to incorporate a diffusion term, as well as production and decay terms. The diffusion term is described like in tumor cell concentration, with the addition that haptotatic fluxes are neglected and only random mobility is observed, $J_{random} = -D_m \nabla m$ (?????). The production terms depends on the momentarily tumor cell concentration and the decay term on the momentarily

extracellular matrix concentration. This results in the term: $\frac{\partial m}{\partial t} = \nabla J_{random} + \mu c - \lambda e = D_m \Delta c + \mu c - \lambda m$, μ and δ describing production and decay rates.

Check variables, parameters

3.2 Modelparameters and Assumptions

For each of the above parameters we are going to look reasonable ranges in which they are definded:

- D_c:
- D_m:
- χ:
- δ:
- μ_1:
- μ_2:
- μ_3:
- λ:

These ranges will later govern the parameter analysis in the Experiment section.

4 Methods

4.1 Data

4.2 Numerical Model

5 Simulation

5.1 1D Simulations

5.2 2D Simulations

6 Evaluation

7 Conclusion

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