

Universität Heidelberg
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Bachelor-Thesis

Continuous Modeling of Extracellular
Matrix Invasion by Tumor Growth

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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). Das hier verwendete Modell beschreibt die obigen drei genannten Parameter, wobei Nullstrom Randbedingungen verwendet werden.

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. 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.

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). The investigated model in this work describes the above mentioned 3 parameters, with zero-flux boundary conditions.

The analysis of this models is mostly done in $1D$ in the literature and individual examples were done in $2D$. However, reproductions of the model show that higher dimensions produce significantly different results. 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.

Ergebnis einfuegen

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. herefore, 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.

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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 [**anderson_continuous_1998**, **anderson_mathematical_2000**] model for tumor modelling.

The dynamics of tumor growth are an intricate system, which is influenced by numerous biological and chemical factors, as well as genetic pre-dispositions, the surrounding tissue of cancer cells, angiogenic processes and 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 surround 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 discrete case, a entity based model is used, pursued with the goal to better understand the phenomena 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. [**anderson_continuous_1998**, **anderson_mathematical_2000**] to analyse tumor 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 initiation, 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 focus 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 of 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 Basics

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 surrounding 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 angiogenesis 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 surrounding tissuse. The tumor cells break through the normal tissue barrier and infiltrate neighboring 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 resistant 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 macromolecules 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 adhesion properties which healthy cells have, to allow migrating into surrounding tissue.

2.2 Mathematical Methods in Oncology

Mathematical Methods and Models in Oncology play a crucial role in analysing, understanding and predicting cancer development. Since the objective of this research underlies complex and intricate biological systems and mechanisms, there exist many models, which find their respective 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 logistic 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 accelerating factors. These models in general 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.

Hybrid models combine both aforementioned methods, of using continuous and discrete models. Like in the model proposed by Franssen et al. [franssen_mathematical_2019], these approaches allow to incorporate the exactness of continuous models with the wide range of biological effects of discrete models.

But not all models try to model tumor growth, there are others concerning for example optimality regarding drug dosages or radiation exposition, offering personalized treatment, or Machine Learning and Data Mining methods analysing large datasets, to identify patterns 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 a 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 proposed by Anderson et al. [anderson_continuous_1998, anderson_mathematical_2000] and Chaplain et al. [anderson_continuous_1998, chaplain_mathematical_2006, chaplain_mathematical_2006-1, franssen_mathematical_2019], extended with terms for cell modelling cell proliferation consists of a system of linearly coupled partial differential equations:

$$\frac{\partial c}{\partial t} = D_c \Delta c - \chi \nabla \cdot (c \nabla e) + \mu_1 c \left(1 - \frac{c}{c_0} - \frac{e}{e_0} \right) \quad (1)$$

$$\frac{\partial e}{\partial t} = -\delta m e + \mu_2 c \left(1 - \frac{c}{c_0} - \frac{e}{e_0} \right) \quad (2)$$

$$\frac{\partial m}{\partial t} = D_m \Delta c + \mu_3 c - \lambda m \quad (3)$$

with zero-flux boundary conditions,

$$n \cdot (-D_c \nabla c + c \chi \nabla e) = 0 \quad (4)$$

$$n \cdot (-D_m \nabla m) = 0 \quad (5)$$

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 density, e the density 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 and a point in time to a scalar value describing the concentration at a specific point in space and time, $\{c, e, m\} : \mathbb{R}^3 \times \mathbb{R} \rightarrow \mathbb{R}$.

To derive at the expression for the tumor cell concentration c we are going to assume that the tumor cell's movement is subject to two influences, haptotaxis and random movement. Haptotaxis is a directed migratory response of cells to gradients of fixed or bound chemicals [anderson_continuous_1998] and random movement is influenced by for example mechanical stress, electric voltage or other such physical effects. To get an expression for how much or how fast the tumor cells move, we need to define what flux is, flux is defined to be the amount of a substance which crosses a unit area in unit time. Incorporating the two assumed influencing factors into our mathematical model we define the haptotactic flux $J_{haptot} = \chi c \nabla e$, where χ is the haptotactic flux coefficient, and the random flux $J_{random} = -D_c \nabla c$, where D_c is random mobility constant. In general this parameter could also be a function of both extracellular matrix and matrix-degrading enzyme concentration $D_c \rightarrow D(e, m)$. As we know cells proliferate and grow over time, so we want to respect this in our model with a term for tumor cell proliferation: $\mu_1 c (1 - \frac{c}{c_0} - \frac{e}{e_0})$. The idea is that this term describes the cell proliferation with a logistic growth model, μ_1 describing the proliferation rate. In the initial model proposed by Anderson et al. [anderson_continuous_1998, anderson_mathematical_2000] and Chaplain et al. [anderson_continuous_1998, chaplain_mathematical_2006,

chaplain_mathematical_2006-1, franssen_mathematical_2019], they did not respect proliferation of tumor cells and extracellular matrix and therefore applied a conservation equation for the tumor cells $\frac{\partial c}{\partial t} + \nabla \cdot (J_{hapto} + J_{random}) = 0$, in our model we extend this conservation formula with a proliferation rate. Explicitly inserting the flux formulas and logisitic growth function for the tumor cells gives us: $\frac{\partial c}{\partial t} + \nabla \cdot (J_{hapto} + J_{random}) + \mu_1 c (1 - \frac{c}{c_0} - \frac{e}{e_0}) = \frac{\partial c}{\partial t} + \chi \nabla \cdot (c \nabla e) - D_c \Delta c + \mu_1 c (1 - \frac{c}{c_0} - \frac{e}{e_0})$. Which is equivalent to equation ??eq1.

To model the extracellular-matrix concentration e , we assume 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 annihilation process. To this we also add a term describing the proliferation process: $\frac{\partial e}{\partial t} = -\delta m e + \mu_2 c (1 - \frac{c}{c_0} - \frac{e}{e_0})$.

Modelling the matrix-degrading enzyme concentration m , we combine a diffusion term with production and decay terms. The diffusion term is described like in tumor cell concentration, with the addition that haptotactic fluxes are neglected and only random mobility is assumed, $J_{random} = -D_m \nabla m$. The production term depends on the tumor cell concentration and the decay term on the extracellular matrix concentration. This results in the term: $\frac{\partial m}{\partial t} = \nabla J_{random} + \mu c - \lambda e = D_m \Delta m + \mu_3 c - \lambda m$, μ and δ describing production and decay rates.

3.2 Numerical Model and Parameters

To make solving the model easier we are first going to non-dimensionalise all the equations ??eq1 - ??eq5 in a standard way, with the goal to rescale the space domain onto unit size. For one space dimension this results in the unit interval $[0, 1]$, for two dimensions the unit square $[0, 1] \times [0, 1]$ and for three dimensions the unit cube $[0, 1] \times [0, 1] \times [0, 1]$. We start with rescaling the distance with an appropriate length scale L and the time with $\tau = \frac{L^2}{D}$ (D being a chemical diffusion coefficient). The three variables are being rescaled with their initial values respectively c_0, e_0, m_0 , which gives us this:

$$\tilde{c} = \frac{c}{c_0}; \tilde{e} = \frac{e}{e_0}; \tilde{m} = \frac{m}{m_0} \quad (6)$$

Next we modify the system's free parameters $D_c, \chi, \delta, D_m, \mu_3, \lambda$:

$$d_c = \frac{D_c}{D}, \quad \gamma = \chi \frac{e_0}{D}, \quad \eta = \tau m_0 \delta, \quad d_m = \frac{D_m}{D}, \quad \alpha = \tau \mu_3 \frac{c_0}{m_0}, \quad \beta = \tau \lambda.$$

with D being a reference chemical diffusion coefficient.

These modifications make the new system of linearly coupled partial differential equations, where the tildes are dropped for simplicity's sake:

$$\frac{\partial c}{\partial t} = d_c \Delta c - \gamma \nabla \cdot (c \nabla e) + \mu_1 c \left(1 - \frac{c}{c_0} - \frac{e}{e_0}\right) \quad (7)$$

$$\frac{\partial e}{\partial t} = -\eta m e + \mu_2 c \left(1 - \frac{c}{c_0} - \frac{e}{e_0}\right) \quad (8)$$

$$\frac{\partial m}{\partial t} = d_m \Delta m + \alpha c - \beta m \quad (9)$$

with also updated zero-flux boundary conditions,

$$\zeta \cdot (-d_c \nabla c + c \gamma \nabla e) = 0 \quad (10)$$

$$\zeta \cdot (-d_m \nabla m) = 0 \quad (11)$$

where ζ is an appropriate outward unit normal vector.

In order to use the finite element method we will change to the variational formulation. If we assume each species to be in the Hilbert space $H^1(\Omega)$, the variational formulation can be derived by multiplying with a test function, integrating over the domain Ω and use integration by parts and the Gauss theorem. This will give us a broader solution space and reduces the requirements of the solution regarding differentiability. With (\cdot, \cdot) denoting the L^2 -scalar product on Ω the following equation system results

$$\left(\frac{\partial c}{\partial t}, \varphi_c \right) = -D_c (\nabla c, \nabla \varphi_c) + \chi (c \nabla e, \nabla \varphi_c) + \mu_1 \left(c \cdot \left(1 - \frac{c}{c_0} - \frac{e}{e_0} \right), \varphi_c \right) \quad (12)$$

$$\left(\frac{\partial e}{\partial t}, \varphi_e \right) = -\delta (m e, \varphi_e) + \mu_2 \left(e \left(1 - \frac{c}{c_0} - \frac{e}{e_0} \right), \varphi_e \right) \quad (13)$$

$$\left(\frac{\partial m}{\partial t}, \varphi_m \right) = -D_m (\nabla m, \nabla \varphi_m) + \mu_e (c, \varphi_m) - \lambda (m, \varphi_m) \quad (14)$$

For the initial conditions we will assume that at dimensionless time $\tau = 0$, there is already a nodule of cells present centered around the origin in every dimension. For example

in one dimension c is having the initial density distribution, $c(x, 0) = \begin{cases} \exp(\frac{-x^2}{\epsilon}), & x \in [-0.25, 0.25] \\ 0, & x \notin [-0.25, 0.25] \end{cases}$,

with ϵ being a positive constant. The tumor will have degraded some of its surrounding tissue in every experiment and hence we take the initial profile of the extracellular matrix to be $e(x, 0) = 1 - 0.5c(x, 0)$. At last we assume the initial matrix-degrading enzyme concentration to be proportional to the initial tumor cell density and therefore take $m(x, 0) = 0.5c(x, 0)$. These initial values are displayed in figure 1.

For each of the modified free parameters $d_c, \gamma, \eta, d_m, \alpha, \beta, \mu_1, \mu_2$ we are going to take look at values or ranges which were used in previous experiments:

- $d_c = 0.001$
- $\gamma \in \{0.001, 0.002, 0.005\}$
- $\mu_1 \in \{0.1, 0.5\}$
- $\eta \in \{10, 20\}$
- $\mu_2 \in \{0.1, 0.5\}$
- $d_m \in \{0.001, 0.01\}$
- $\alpha \in \{0.1, 10\}$
- $\beta \in \{0, 0.07, 0.5\}$

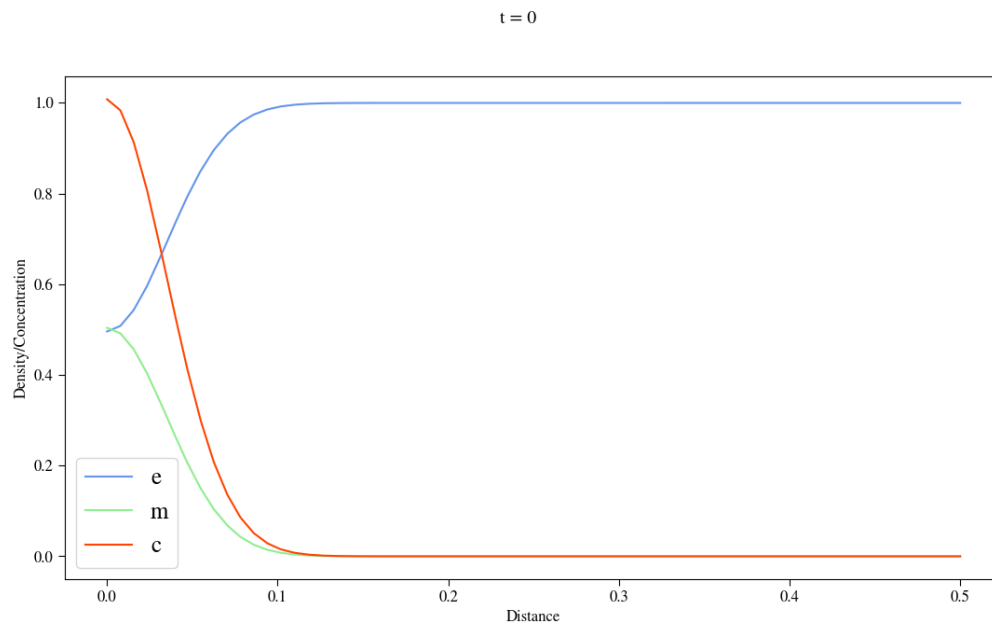


Figure 1: Visualization of the initial value distribution for an experiment in two space dimensions, radially symmetrical

4 Method

This work will investigate how the free parameters of the model given by the equations 7-11 will affect the spatial temporal progress of the numerical simulation. For the numerical simulation we will use the weak form given with equations 12-14 and solve it using HiFlow. To study the results of the numerical simulation ParaView is used, producing informative plots to compare the evolution of the simulation. For this we rely on the tool Plot Over Line to give radially symmetrical results of the three variables of tumour and extracellular matrix density and matrix-degrading enzymes, like seen in the initial distribution in figure , in figure you can see the configuration for the Plot Over Line tool used, the grey line in the middle of the simulation to the middle of the top of the square.

First replications of simulations of previous works will be discussed which serves the purpose to first verify the correctness of our result, as well as to give a starting point describing the phenomena this model exhibits. We start with the 2D case, since for this there are many examples already given and then move on to 3D simulation where the examples are fewer.

After having taken a look at the preexisting experiments the main part of this work will begin with a systematic parameter analysis. Like before it will start investigating 2D simulation and will then move on to 3D simulation. Here we will compare what effect the dimensionality has on the simulation and try replicating the behaviour of the 2D cases in the 3D variant.

At last we will have a prospect on how an heterogeneous extracellular matrix influences the results, which is the more realistic case, since tumourous cells tend to appear at border regions of tissue where we do not have a homogenous ECM.

The results of the above experiments will be summarized and discussed in the Conclusion and Discussion part, pointing out the important characteristics of the simulation and discussing the sensitivity of each of the parameters. At this point we will have an outlook on how to extend the model in more continuous and or discrete adaptations.

Looking at these estimates of section 3 we are left with plenty of room to investigate the effects of every single non-fixed parameter. According to previous experiments cite anderson and chaplain, numerical simulation and stuff.... this work will use the baseline set of parameters with $(d_c, \gamma, \mu_1, \eta, \mu_2, d_m, \alpha, \beta) = (0.001, 0.005, 0, 10, 0, 0.001, 0.1, 0)$ for experiments without proliferation and $(d_c, \gamma, \mu_1, \eta, \mu_2, d_m, \alpha, \beta) = (0.001, 0.005, 0.3, 10, 0.3, 0.001, 0.1, 0.1)$ for experiments with proliferation. The systematic variation will be same for 2D as well as 3D experiments and will then look like follows:

1D					2D					3D				
λ	δ	μ_1	μ_2	μ_3	λ	δ	μ_1	μ_2	μ_3	λ	δ	μ_1	μ_2	μ_3
a	b	c	d	e	a	b	c	d	e	a	b	c	d	e
a	b	c	d	e	a	b	c	d	e	a	b	c	d	e
a	b	c	d	e	a	b	c	d	e	a	b	c	d	e
a	b	c	d	e	a	b	c	d	e	a	b	c	d	e

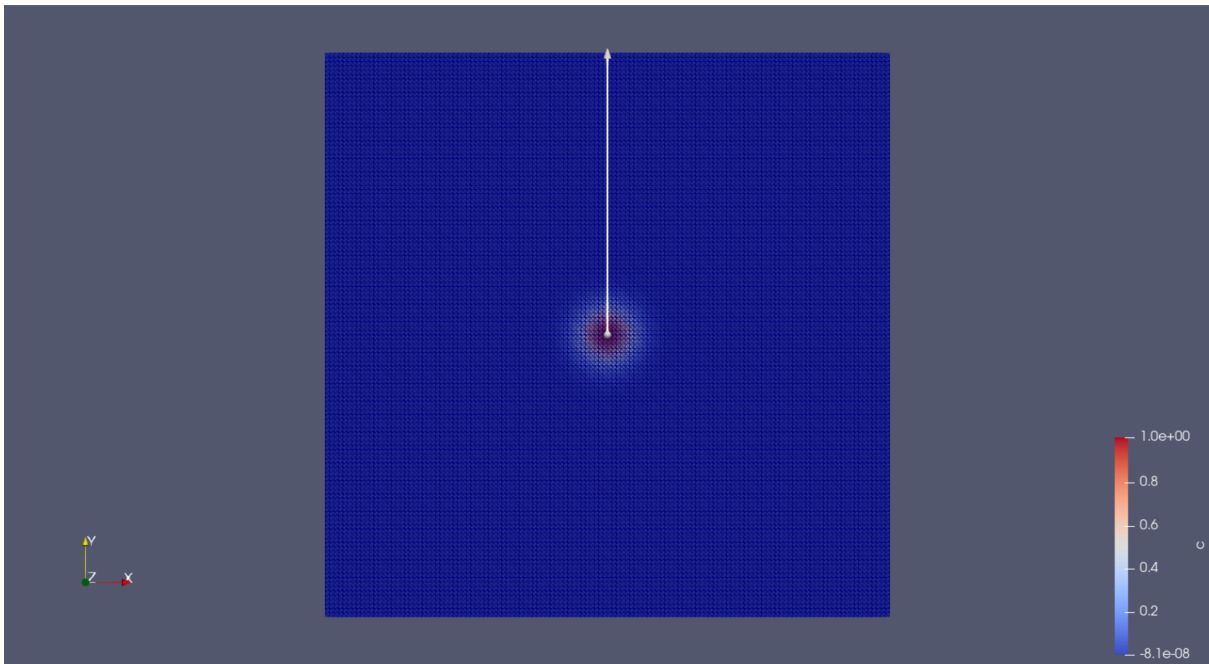


Figure 2: Write here

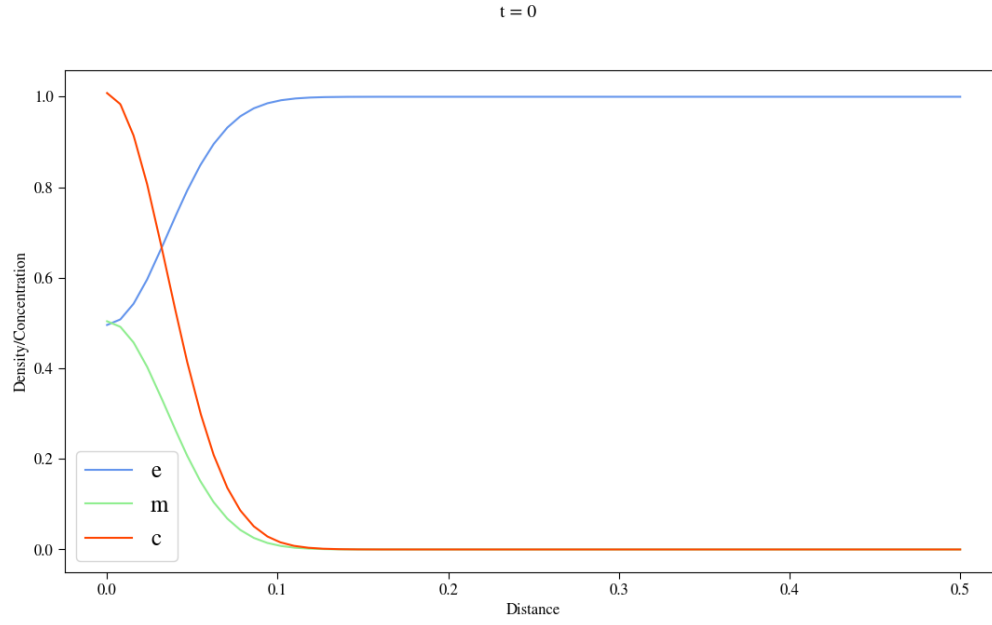


Figure 3: Caption

5 Experiments and Results

5.1 Reproducing Results

5.2 2D Parameter Analysis

5.3 3D Parameter Analysis

5.4 3D Simulations with heterogenous ECM structure

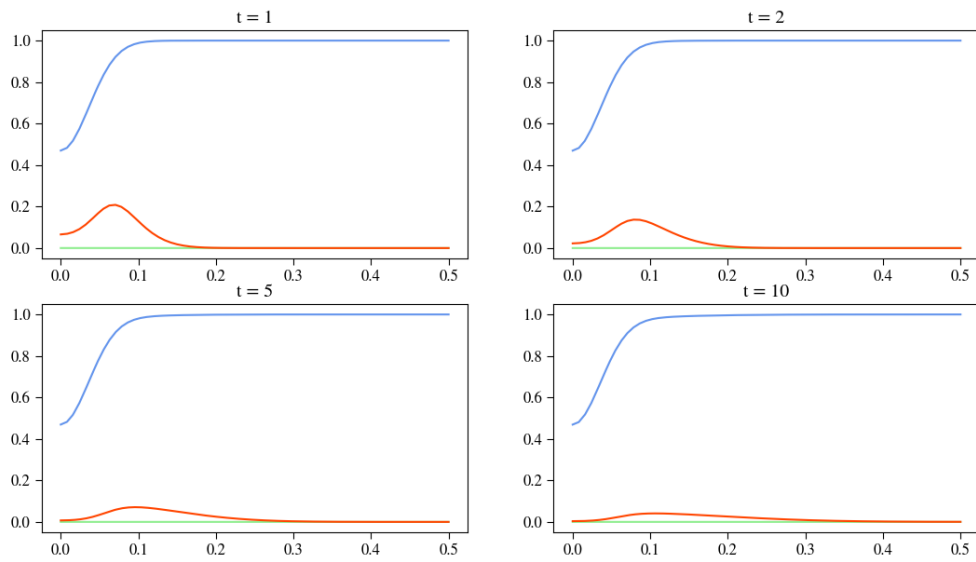


Figure 4: Caption

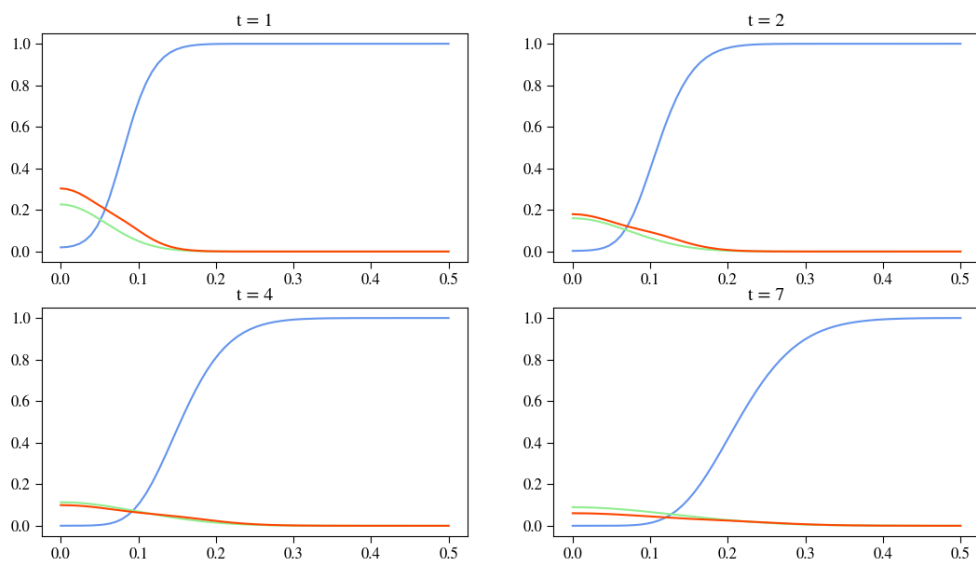


Figure 5: Caption

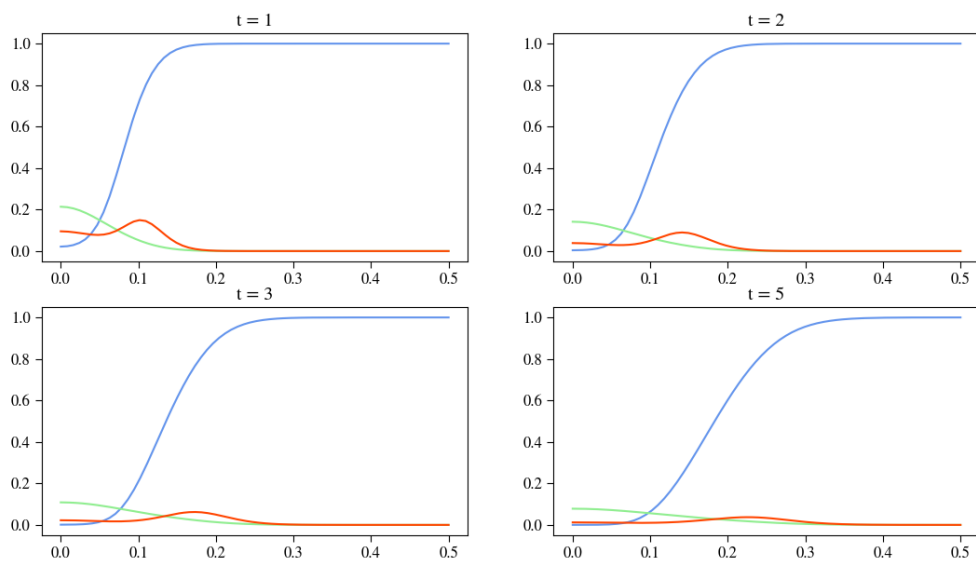


Figure 6: Caption

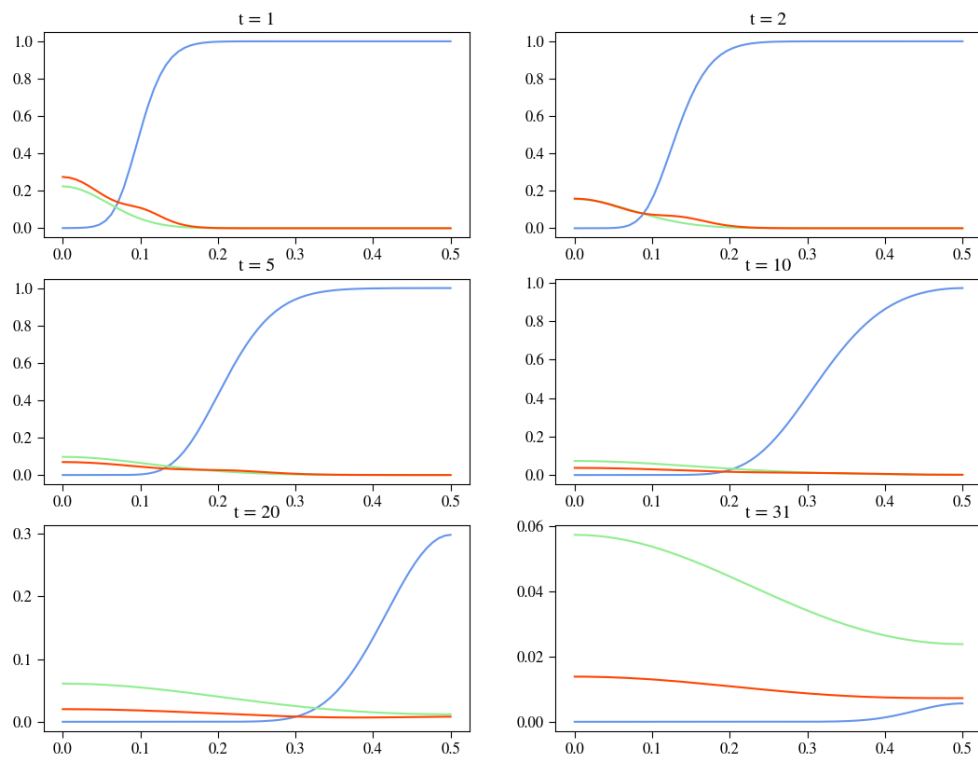


Figure 7: Caption

6 Conclusion and Discussion

6.1 Extra-Dimension Evaluation

Ergebnisse reporuzieren und vergleichen.

6.2 Inter-Dimension Evaluation