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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 ide Modelle 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 boundry 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. 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.

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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 [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 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 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 blood 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. [3], 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, 4], extended with terms for cell modelling cell proliferation consists of a system of linearly coupled partial differential equations:

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

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

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

with zero-flux boundary conditions,

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

$$n \cdot (-D_m \nabla m) = 0 \tag{5}$$

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, $\{c, e, m\} : \mathbb{R}^3 \times \mathbb{R} \to \mathbb{R}$.
To derive at the expression for the tumor cell concentration c we are going to assume that the tumor cell's moement is subject to two influences, haptotaxis and random movement. Haptotaxis is a directed migratory response of cells to gradients of fixed or bound chemicals [1] 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 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. In general this parameter could also be a function of both extracellular matrix and matrix-degrading enzyme concentration $D_c \to D(e, m)$. 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 logisitic growth model, μ_1 describing the proliferation rate. In the inital model proposed by Anderson et al. [1, 2] and Chaplain et al. [1, 3–5], 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 logisitc growth function for the tumor cells gives us: $\frac{\partial c}{\partial t} + \nabla(J_{hapto} + J_{random}) + \mu_1 c(1 - \frac{c}{c_0} - \frac{e}{e_0}) = \frac{\partial c}{\partial t} + \chi \nabla(c \nabla e) - D_c \Delta c + \mu_1 c(1 - \frac{c}{c_0} - \frac{e}{e_0})$.

Which is equivalent to equation 1.
To model the extracellular-matrix 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 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 haptotatic 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 1 to 5 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:

$$\tilde{c} = \frac{c}{c_0}; \tilde{e} = \frac{e}{e_0}; \tilde{m} = \frac{m}{m_0}$$

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

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

with D being a refrence chemical diffusion coeffizcient.
These modifications make the new system of linearly coupled partial differential equations, where the tildes are dropped for simplicitie's sake:

$$\frac{\partial c}{\partial t} = d_c \Delta c - \gamma \nabla \cdot (c \nabla e) + \mu_1 c \left(1 - \frac{c}{c_0} - \frac{e}{e_0}\right) \tag{6}$$

$$\frac{\partial e}{\partial t} = -\eta m e + \mu_2 c \left(1 - \frac{c}{c_0} - \frac{e}{e_0}\right) \tag{7}$$

$$\frac{\partial m}{\partial t} = d_m \Delta c + \alpha c - \beta m \tag{8}$$

with also updated zero-flux boundary conditions,

$$\zeta \cdot (-d_c \nabla c + c \gamma \nabla e) = 0 \tag{9}$$

$$\zeta \cdot (-d_m \nabla m) = 0 \tag{10}$$

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

$$\left(\frac{\partial c}{\partial t},\varphi_c\right) = -D_c\left(\nabla c,\nabla\varphi_c\right) + \chi\left(c\nabla e,\nabla\varphi_c\right) + \mu_1\left(c\cdot\left(1-\frac{c}{c_0}-\frac{e}{e_0}\right),\varphi_c\right) \tag{11}$$

$$\left(\frac{\partial e}{\partial t},\varphi_e\right) = -\delta\left(me,\varphi_e\right) + \mu_2\left(e\left(1-\frac{c}{c_0}-\frac{e}{e_0}\right),\varphi_e\right) \tag{12}$$

$$\left(\frac{\partial m}{\partial t},\varphi_m\right) = -D_m\left(\nabla m,\nabla\varphi_m\right) + \mu_e\left(c,\varphi_m\right) - \lambda\left(m,\varphi_m\right) \tag{13}$$

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 postive constant. The tumor will have degraded some of its surrounding tissue in every experiment and hence we take the inital 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 inital values are displayed in figure 3.2.

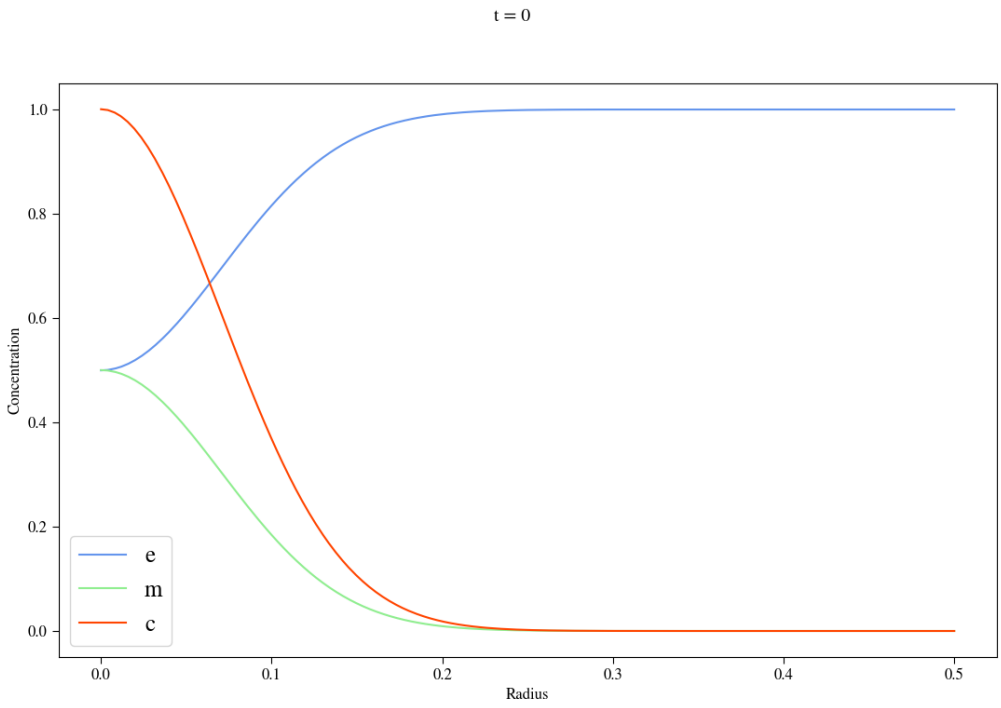

Figure 1: Visualization of the initial value distribution for an experiment in two space dimensions, radially symmetrical

4 Method

This work will investigate how the free parameters of the model given by the equations 6 - 10 will affect the spatial temporal progress of the numerical simulation. For the numerical simulation we will use the weak form given with equations 11 - 13 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 in time. For this we rely on the tool Plot Over Line to give radially symmetrical reulsts of the three variables of tumour and extracellular matrix density and matrix-degrading enzymes, an example for this can be seen in figure 3.2 showing the initial conditions. In figure 2 you can see the configuraion for the Plot Over Line tool, since we are consider the experiments on the unit squre in 2D dimensional case, the line starts at $x = 0.5, y = 0.5$ and ends at $x = 0.5, y = 1$.
For the three dimensional experiments a different tool was used *explain3Dexperientsmethodology*

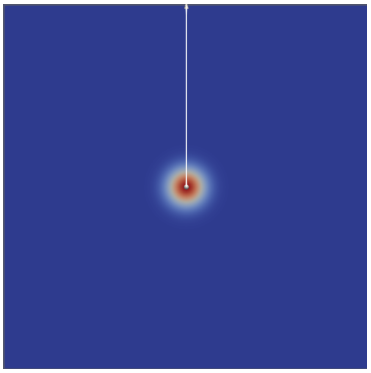

Figure 2: Plot Over Line Tool Configuration

All experiments that consider the ECM to be homogenous start with the same initial values as seen in figure 3.2. Experiments observing the effects of a heterogenous ECM use different initial values, like seen in *initialvaluesheterogenousECM*
This work starts with trying to replicate/replicating numerical simulations done by other papers. Since there were only 1D simulations done previously, the model will be adjusted in such a way, that the Plot Over Line graphs mimick the plots given by the previous experiments. This will serve two purposes, first and minor it will verify a correct implemntation of the model and second this will give us a starting point by which we can vary the parameters, investigating the phenomena this model exhibits.
We will start with exmaining 2D experiments with homogenous ECMs, using our model with the parameters mu_1 and mu_2 both set to zero, considering a case with no proliferation, after this we will introduce proliferation, varying also mu_1 and mu_2. The same will be done for the 3D cases, also at first neglecting proliferation to apply it in a later stage. Our focus here lies on investigating the effects of the parameters, but also on how the dimension changes results, with fixed free parameters. At last we will have a brief outlook on how a heterogenous ECM influences our results
The results of the above experiments will be summarized and discussed in the Conclusion and Discussion part, pointing out the important characteristics of the simulations and disucssing the sensitivity of each of the parameters and the influence of the dimension.

At this point we will have an outlook on how to extend the model with more continuous and or discrete adaptations.

Looking at the parameter estimates from [2] to non-dimensionalise the time, we see that with $L \in [0.1cm, 1cm]$ and $D \approx 10^{-6} \frac{cm^2}{s}$, $\tau = \frac{L^2}{D}$ gives a relative big temporal range, $\tau_{min} = 1000s = 16.66min$ and $\tau_{max} = 1000000s = 16666.66min$, which makes it hard, to find the correct time step value to compare our simulation results with the one from [2] and [6]. Another challenge are the diffusion coefficients, since they are dependent on the dimension we are in, we have to find our own estimate as a baseline value.
For our experiments we will use a set of baseline parameters, which will be evaluated experimentally, and from there vary one parameter at a time to get a overview of their effects and later we will incorporate variation of multiple paramters in accordance with the numerical model.

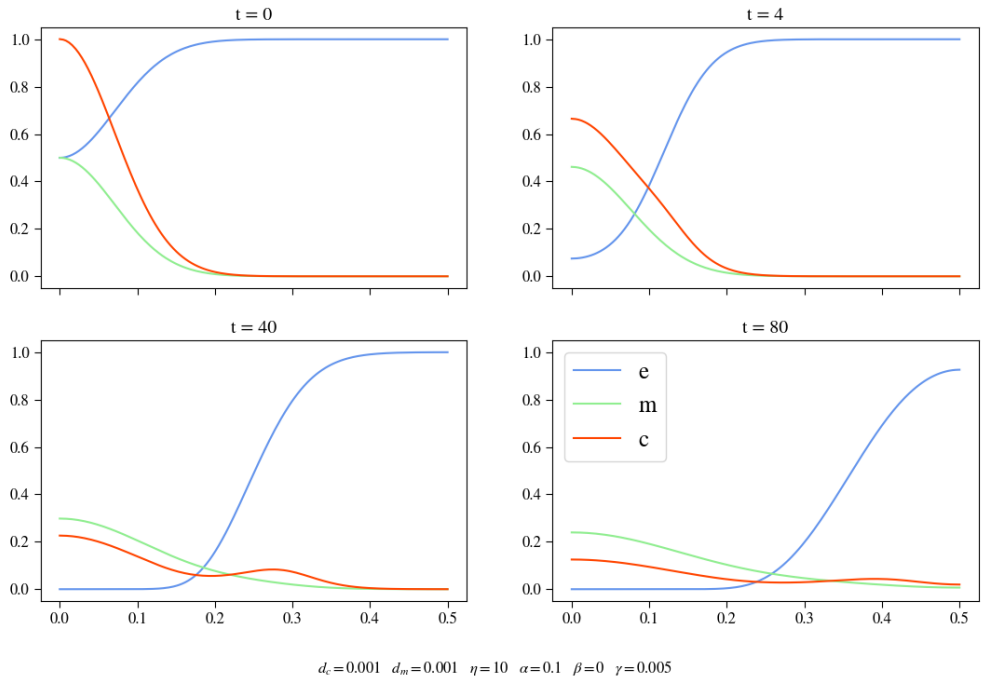

Figure 3: Caption

5 Experiments and Results

For all the plots of the experiments the red curve indicates the tumour cell density, the blue curve the ECM density and the green curve the MDE concentration. In all of the experiments we used the value of $\epsilon = 0.01$ to match the inital conditions from [2] and [6]. Mathematical Intuition of the three curves and how the parameters interact.

5.1 Two dimensional Results without Proliferation

5.1.1 Replicating results

We will start with replicating previous results from Anderson et al.[2], Figure 1, making our curves fit the findings in their diagramms.

In the first simulation the same parameter were used as in Anderson et al. first one dimensional experiment; $d_c = 0.001, d_m = 0.001, \gamma = 0.005, \eta = 10, \alpha = 0.1, \beta = 0, \mu_1 = 0, \mu_2 = 0$. Figure 3 shows 4 snapshots of different points in time of tumour cell density, extracellular matrix density and matrix degrading enzymes concentration. In the conducted experiments it was shown that for every step in time done in the original paper we have done 4 steps, this is the reason for our time scale. Starting from the inital values seen at $t = 0$ we see that after four time steps a very small unevenness has formed for the tumour cell density at $x \approx 0.1$. Both concentrations of MDEs and ECM have decreased as expected, looking at the model, MDEs have also invaded into the surrouding

tissue, stretching the initial concentration around the origin. In the next image showing the simulation after 40 timesteps we see that this unevenness has been propagated to form a hill at the leading edge of the tumour cells invading the surrounding tissue, at $x \approx 0.28$. MDEs also continued their diffusion into the area, decaying the ECM in their wake, decreasing them further. The last image, after 80 simulation time steps, we see that as well the hill that has formed at the leading edge of the tumour cells as well as the concentration of tumour cells at the origin, has decreased, due to the diffusion factor and the haptotactic flux. If we were to look at the simulation at later points in time, this curve will flatten even more, since with more time the ECM will be decayed and therefore the haptotactic flux coefficient γ will lose its influence, leaving the movement of the cells to diffusion only. The curve for the MDEs has also flattened, yet not as strongly as the tumour cells concentration and as the observed before the ECM decayed where the MDEs were previously.
Comparing 3 to figure 1 in [2], we can see major differences. The first image showing $t = 0$ looks the same, which confirms that both experiments start with the same initial values. In the images showing the simulation at the second time checkpoint we see that though the tumour concentration and ECM density values are approximately the same, the MDE concentration is slightly lower in our experiment, which will get more pregnant in the later images. The unevenness having formed at the leading edge of the tumour cell concentration also looks to be slightly smaller. The differences in the third image are more strikingly, both c and m have considerably lower concentrations, yet the ECM value looks to in line. In our case the diffusion of the tumour cells into the tissue also seems to happen a littel bit too fast. The last time checkpoints manifest our findings, showing the same behaviour with ECM being approximately the same, tumour cell density and MDE concentration being clearly lower in our experiment and invasion of tissue happening too fast, leaving the lump at the origin $x = 0$ too small.
This first of all confirms the initial supposition that with changing the dimension for the simulations the results also vary. We will now adjust the parameters iteratively to align our results with above compared experiment. For this we will now start with varying the MDE production coefficient α, to get higher concentration values, and also change the diffusion terms d_c and d_m, to adjust the pace of the invasion of tumour cells and MDEs into the area.

Figure 4 shows a comparison of the parameters α, d_c and γ have on a specific curve. Comparing different values for α and their effect on the curve of the MDE concentration, shows that, especially looking at the later points in time $t = 4$ and $t = 8$, with values for α between 0.3 and 0.4 we will get a good approximation. The values of the original paper for the MDEs are for $t = 4$ $m(0) = 0.6$ and at $t = 8$ $m(0) = 0.7$. Fine tuning this parameter led us to $\alpha = 0.35645$.
Looking at d_c we chose a value of $d_c = 5e - 4$. Using higher values for this parameter will result in numerical instability and results that are not useable. For γ we made a slight adjustment upwards to $\gamma = 0.0055$ to have a little bit more pull on the tumour cells outward, to match the invasion speed observed in the original paper. This yields results where the small hill at the leading edge of the tumour cell concentration in the latter two points in time is a higher values for x, yet not as steep as for example $\gamma = 0.007$.

These adjustments leave with the final configuration for replicating the system with the curves in figure 5 and the parameter settings also seen in the same figure. Slightly adjusting the haptotatic flux to $\gamma = 0.0055$ yields the following results, seen in figure 5. comparing our final version with the original one we can see that in the second point in time, at $t = 4$ in our case, the values of the three curves at the $x = 0$ are nearly the same. In the original experiment the bump in the curve for the tumour concentration looks more pregnant, but this is only due to the fact, that this experiment was most likely done on the unit line, not the unit cube, and therefore the x-scale has been streched to $y_{max} = 1$ where in our case it is $x_{max} = 0.5$. The two later points in time confirm the similarity with having also nealy the same values for the three curves at $x = 0$ but also their respective propagations in time look to be in line with the original experiment.

5.1.2 Parameter Analysis

From the replicated results shown in figures 5, we saw that if we variate certain parameters the results also vary strongly. Therefore we are now going to have a look at how changing one parameter affects the output of the whole system. For this we assume the parameter values of the replicated results to be our set of baseline parameters, from there in each experiment only one parameter is changed.

d_c Variation

ersetzen The parameter analysed in this section describes the diffusion of the tumour cells and is integrated into the equations as being dependent on the laplacian of the tumour cells $\Delta c = (\frac{\partial c}{\partial x} + \frac{\partial c}{\partial y} + \frac{\partial c}{\partial z})$. Leaving out the proliferation term our equation for $\frac{\partial c}{\partial t}$ also depends on γ a coefficient for the haptotatic flux. The mathematical intuition is that if we will decrease d_c we will see the effects of γ taking over the simulation results for the c curve, meaning that the tumour cells are more likely to drift outward and let themselves be pulled by the ECM concentration e, leaving ony a little concentration at the origin, creating a bigger hill on the leading edge of the tumour concentration, below where $c\nabla e$ will be highest. On the other hand if we increase d_c the effects of haptotaxis will diminish, the tumour cells will be subject to bigger diffusion pulling them more evenly into the tissue, there will be no leading hill being pulled outwards, since the diffusion will happen too fast, making this effect irrelevant.

Looking at both experiments in figure 6, we can see these assumptions confirmed. The smaller d_c gets the higher the influence of γ will be and vice versa. In the first four images we can see the results for $d_c = 1e-5 = 0.00005$, while in the it looks mostly normal with little of the secession building at the leading edge, we can see that in the third image, this secession has not only seperated itself from the main lump of cells, but has also developed a sharp peak, which would have negative consequence regarding the differentiability of the c curve. In the fourth image this behaviour is even more extreme and looking closely at this simulation in ParaView, the values for c take on a negative sign, which from a biological perspective does not make any sense since there can't be less than zero cells at a position in space. This indicates a numerical instability, which decreasing d_c even furhter also resulted in oscilations in the c curve and even more negative values for the

tumour cells. This instability is due to numercial model used, which only yields useful results if γ and d_c are in a certain range. This could be a point for further investigation, inspecting how the results change if γ and d_c are both varied at the same time and finding this range γ and d_c need to be in to make sense. However looking at the other two curves e and m we can see that they still make sense, especially also in the first experiment with $d_c = 1e-5$, m at the start following where c was high, exceeding c at some point due to the production factor α and e decaying where the MDEs have higher values. Interesting is that having high values for the diffusion coefficient the concentration is faster evenly distributed in space, which indicates a higher invasion pace, which in turn makes the degradation of e happen a lot faster, though the MDEs have taken on a near constant niveau throughout space. This also indicates, that we don't need to have a visibly higher concentration of m to degrade the ECM.

γ Variation

Inspecting the effects of γ we can assume the same as for d_c if we select higher values for γ the effects of haptotaxis, pulling the tumour cells into the tissue faster, leaving no cells at the origin, taking lower values for γ, the diffusion will be superior factor for the tumour cell motility, which will result in no secession at the leading edge of the tumour cells.

The experiments verify this behaviour, in the first one where $\gamma = 0.002$ we can see the effects of haptotaxis only slightly in the third image, with a small bump for the tumour cells the farthest out. Increasing $\gamma = 0.008$ we see the haptotatic effects stronger now than in the base case, the secession that gets pulled into the tissue is getting bigger and also the invasion pace at which tumour cells reach the outer regions is faster. Selecting even higher values as $\gamma = 0.01$ we see this behaviour increasing the secession at the leading edge of the tumour cells is now almost as big as the remaining part at the origin, the invasion pace and therefore also the degradation of the ECM is accellerated. When we now take a step further and increase γ by one potence, we can observe that the invasion pace, has gotten so high, that before finishing the simulation at $t = 8$ the tumour cells have not only invaded completely up to the border but have also been pulled back towards the origin upon getting reflected at the border of the unit square and also since degradation of the ECM has not kept up with the tumour cells, leaving a situation where the tumour cells have spread further than the ECM and are now being pulled backwards again. This is therefore the first experiment which has in eight times produced results that are not longer resemble radial symmetry as seen in image ..., where we can see that the diffusion and haptotaxis properties of the tumour cells push them into the corners of the unit square, where there is still the highest concentration of ECM and afterwards back in from corners again due to haptotaxis. Taking a look at the other curves we also get interesting results, as expected when we decrease γ and let d_c stay constant the invasion pace will decrease, having also degraded the ECM in the outer regions than the base case and also having higher MDE concentrations towards the origin since it stayed longer in these regions during the experiment. Increasing γ over the value of the base case resulted also in hihger invasion pace, ECM degradation and lower MDE values at the origin, but this behaviour does not increase linearly. Looking at the experiment with $\gamma = 0.1$ we see that

though the tumour cells have reached the border regions faster, the ECM degradation could not keep up with the pace, resulting in areas where the ECM is still high, the tumour cells have already surpassed, but have not produced enough MDEs to degrade it. Where in all of the other experiments the tumour cells invaded at such a pace, that the produced MDEs in their wake were sufficient to degrade the ECMs to not pull the tumour cells back to the remaining ECMs later. This is also only experiment where the MDe curve m is not monotone decreasing, with higher values at the origin and bordering regions, but lower one in between. If we were to increase γ further we would see this behaviour mirrored, with the tumour cells spreading so fast throughout the space that we would get oscilations.

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η Variation

The parameter η only directly influences the degrading of the ECM, which happens faster for higher η coefficients in regions where both MDE and ECM concentration are high. Varying this parameter yet may have a high impact of the solution because, the gradient of the ECM is a deciding factor for the effects of haptotaxis on the tumour cells.
The first experiment in figure .. shows that if $\eta = 0$, which means that the ECM is not degraded by the MDEs, we get completely differnt results comparing it to the base case. Not only does η influcence the curve for the ECM e but has also a high impact on both tumour cell density and MDE concentration. Due that no degrading happens e stays constant all the time, with $\frac{\partial e}{\partial t} = 0$, this also means that ∇e stays also constant, we see this effect in the images, showing that c does not invade further than the point where ∇e is highest, this implies that if c converges towards this point it will also have its maximum at this point, which also fixes the point $c\nabla e$, what does this mean for the MDEs? After initially increasing slightly around the point $x = 0$ and increasing where c was high previously, it also converges with its highest concentration at $c\nabla e$. Since the motility of c is highly restricted due to no degradation of the ECM, the MDEs will progress to increase c takes on values higher than 0. If this simulation for $\eta = 0$ will be continued we will see that the MDEs m will also a curve that is not monotone decreasing. Increasing η to $\eta = 20$ the behaviour change is not so drastically comparing it to the base case. The degradation of the ECM happens twice as fast, which results in a faster invasion pace of the tumour cells, though with decreased influcence of haptotaxis, making the hill at the leading edge smaller. After dimensionless time $t = 8$ the ECMs have degrading has visibly increased, but the MDE concentration is still higher. This only makes sense since, needing a lower concentration to degrade the ECM, this process happens faster, and also since haptotactic influences are lower the concentration of tumour cells at the origin is higher, which will also produce more MDEs at the origin. η has a strong influcene on all curves, if its value is lower the degradation of e happens slower, slowing also c and m's invasion pace down.

d_m Variation

d_m is the parameter describing the diffusion of the matrix degrading enzymes MDEs, it is influcenced by the second derivative of c. Looking at the equations we can expect with higher values for d_m a faster degradation of e, since the MDEs can invade faster into the space and there are not too much MDEs needed to degrade e. This will then cause a faster invasion pace of c, because the haptotatic flux pulls heavier outward. Setting d_m to zero, so no movement of the MDEs, we see that the curve still changes, which is due to the tumour cells producing them where they are. We see that the value for m around the origin is higher than 1 which is possible since their concentration could be soo high that there are more than one MDE per mesh point, although this would requiring to make the mesh finer I think. If we look in the other direction, setting d_m to $1e-1 = 0.1$ we see that after already $t = 0.4$ the MDEs have spread completely throughout space, from this point on, they are mostly subject to the production term yielded by the tumour cells, but as fast as they are produced, so fast they are also distributed in space, causing a semmingly equillibrium throughout space for the MDE concentration regardless of the local tumour cell density. As we saw earlier a low concentration for MDEs is needed to efficiently degrade the ECM, therefore degradation happens a lot faster here, even so fast, that the gradient of e diminishes as fast that the haptotatic influcences of the tumour cells are reduced, causing tumour spread to slow down. This is contrary to our initial assumption that with higher values for d_m the tumour invasion pace will also increase. This parameter therefore seems to have influence on the haptotatic effects and the overall extra cellular matrix degradation.

α Variation

When we look at α in a range from 0.0 to 1.0 we can expect with growing α a faster degrading of the ECM and higher values form the MDEs themselves. Faster ECM degrading could mean fast invasion of the tissue of the tumour cells. As we saw in the previous comparison, the MDEs can take on values higher than one, we can also expect this here when α is sufficiently high. Looking at the experiment with $\alpha = 0.0$ we can see that at the end the ECM has still much higher values than compared with the baseline experiment at dimensionless time $t = 8$ and as expected the invasion pace of the tumour cells is considerably slower. Comparing this to the plots for $\alpha = 1.0$ we can see that after already $t = 4$ the MDEs have taken on a contration of greater than one at $x = 0$. Overall is the degradation happening faster and therefore also the tumour invasion happens faster. In the end we are left with a clearly lower ECM concentration than for example the baseline experiment.

β Variation

Looking at β which is the parameter describing decay of the MDEs, we can assume that with varying β the MDE curve will be lower, influcencing the ECM degrading process and therefore also the invasion pace. Since all previous experiments assumed a value of $\beta = 0$ we can expect that with growing β these effects will increase contininuously. We first of

all needed to determine a range in which to experiment. Starting with a range of values between 0.1 and 1.0, since this is the range α yields reasonable results we saw that those values were much too high. Even for $\beta = 0.1$ the MDEs are almost completely decayed after only $t = 0.4$, looking closer at ParaView this happened after already $t = 0.1$. This also affects the haptotatic effects of the tumour cell invasion, having no secession formed at the leading edge of the tumour cells. Reducing the range for β one potence we can see the same behaviour, with a fast dacay of the MDEs therefore lower ECM degrading and slower invasion pace. Yet looking at $\beta = 0.01$ we see the effects of haptotaxis now again and the ECM degrading happens here visibly faster, though the MDE concentration is generally lower. This lead us to decrease β even further. Though if we look at $\beta = 0.001$ we see that the effects of β are barely recognizable anymore. Taking the middle of those and setting β to 0.005, we see all the presumed effects of slowed degradation of the ECM therefore also slowed invasion pace, yet still having the effects of haptotaxis also clearly visible.

Cross Variation

Having done all those experiments it will be interesting to compare countering effects and supporting effects two at a time

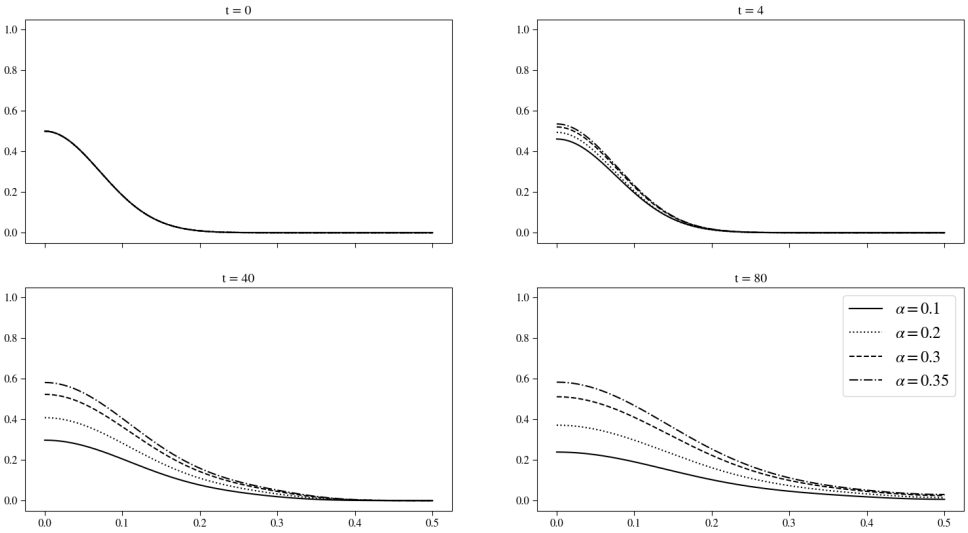
5.2 Two dimensional Results with Proliferation

5.3 Three Dimensional Results

5.3.1 Replicating Results

5.3.2 Parameter Analysis

5.4 Three Dimensional Simulations with Heterogenous ECM Structure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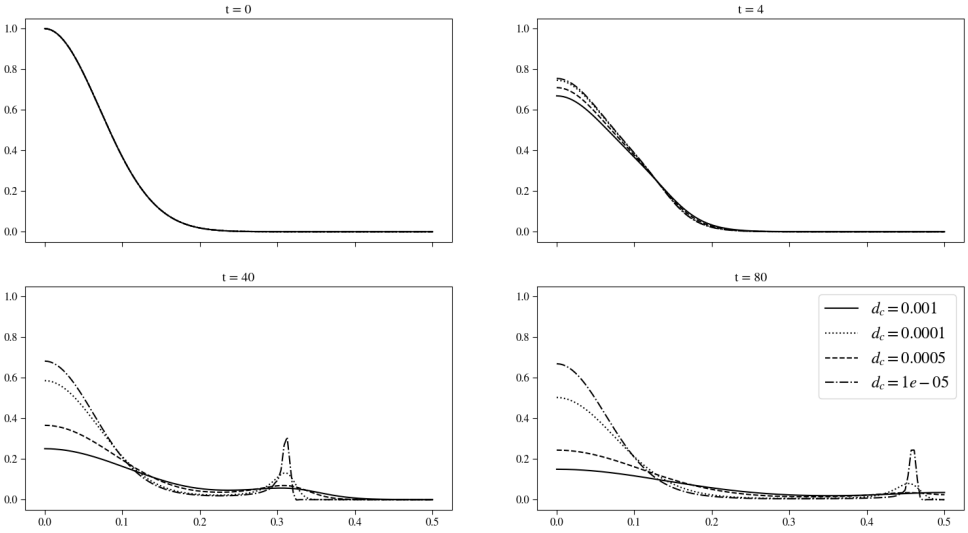
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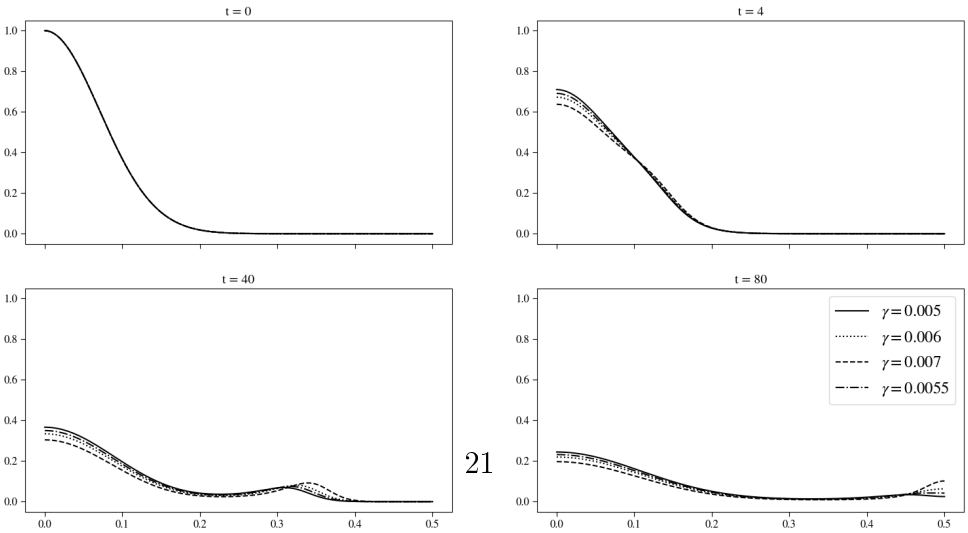
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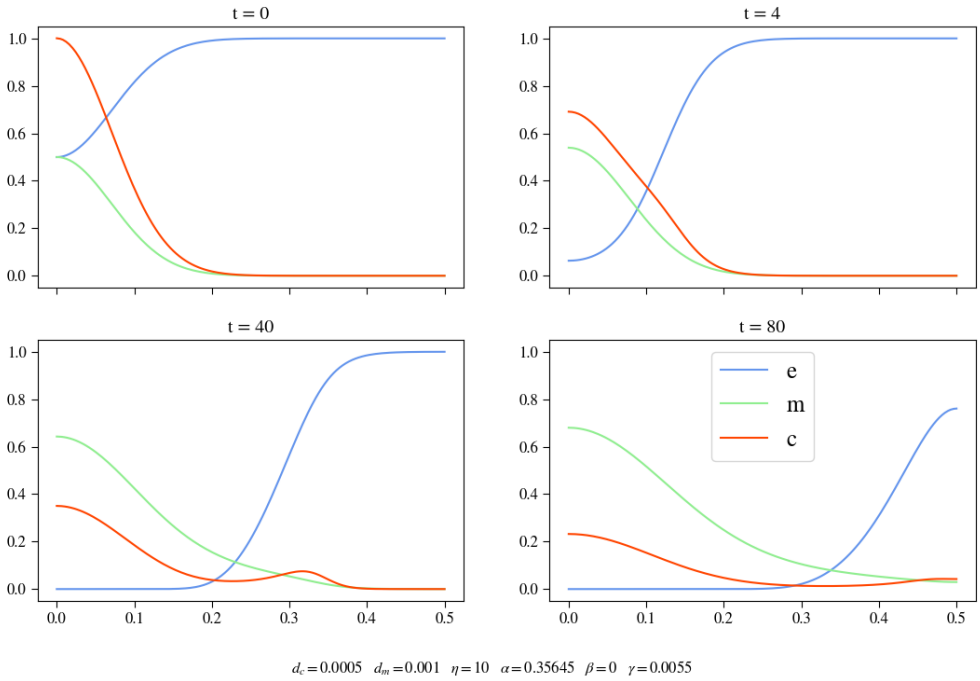
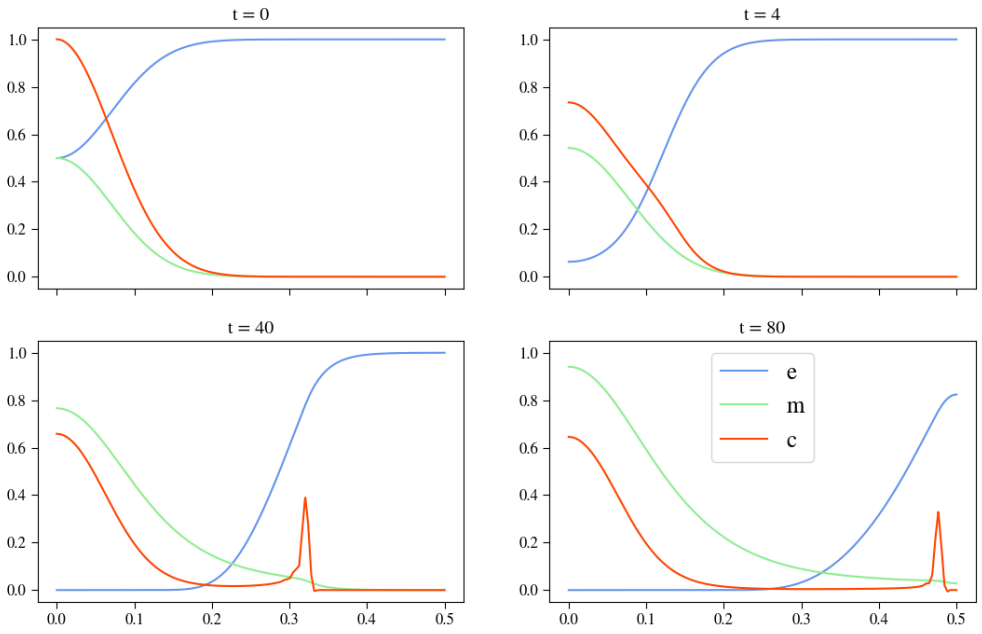


Figure 5: Caption



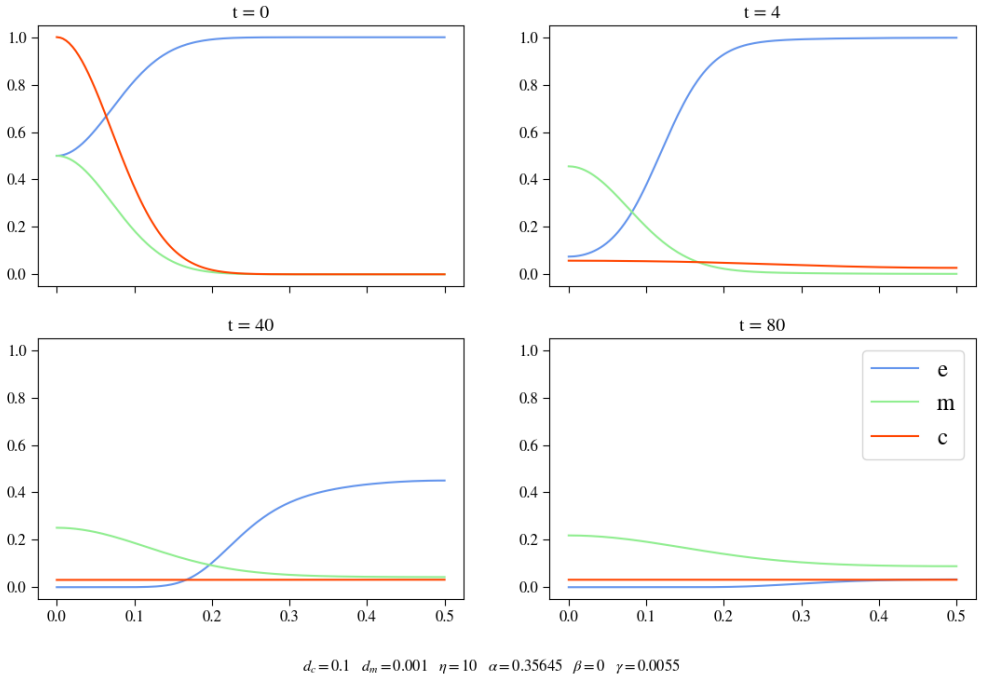


Figure 6: Caption

6 Conclusion and Discussion

6.1 Extra-Dimension Evaluation

Ergebnisse reporuzieren und vergleichen.

6.2 Inter-Dimension Evaluation

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