TECHNISCHE UNIVERSITÄT WIEN
Vienna University of Technology

Unterschrift der Begutachter:

.....

.....

DISSERTATION

Existence Analysis of Cross-Diffusion Systems in Biology

Ausgeführt zum Zwecke der Erlangung des
akademischen Grades eines Doktors der technischen Wissenschaften
unter der Leitung von

Univ.Prof. Dr.rer.nat. Ansgar Jüngel
E 101
Institut für Analysis und Scientific Computing

eingereicht an der Technischen Universität Wien
Fakultät für Mathematik und Geoinformation

von

Dipl.-Ing. Ines Stelzer
Matrikelnummer: 0525085
Ehamgasse 43/9/5/10, 1110 Wien

Wien, am 2. Mai 2013 Ines Stelzer

Kurzfassung

In der folgenden Arbeit untersuchen wir zwei spezielle parabolische Kreuzdiffusionsmodelle, mit Bezug zur Biologie, der Form

$$c_t - \operatorname{div}(A(c)\nabla c) = r(c), \quad x \in \Omega, \quad t > 0,$$

wobei $c := (c_1, \ldots, c_N)^\top$ eine vektorwertige Funktion mit Werten in $[0,1]^N$, $N \geq 2$, ist, $\Omega \subseteq \mathbb{R}^d$ ein beschränktes Gebiet für $1 \leq d \leq 3$ bezeichnet und $A(c)$ bzw. $r(c)$ die Diffusionsmatrix bzw. die Produktionsterme des Systems beschreiben. Die Funktionen c_i stellen dabei bestimmte Anteile der i-ten Komponente einer Mischung bestehend aus $(N+1)$ Komponenten (Fluide) dar. Als Besonderheit unserer Systeme sei zu nennen, dass die $(N+1)$-te Komponente in den Gleichungen nie explizit, sondern immer nur implizit, durch die anderen N Anteile ausgedrückt, vorkommt.

Aus biologischer bzw. physikalisch-chemischer Sicht sind Kreuzdiffusionsmodelle von Bedeutung, da sie im Gegensatz zu klassischen Diffusionsmodellen die Interaktionen der Populationen bzw. der chemischen Komponenten in einem Mehrkomponentensystem miteinbeziehen, was bei der Modellierung zu zusätzlichen Einträgen in der Diffusionsmatrix abseits der Hauptdiagonale führt. Wir nennen daher ein System der obigen Gestalt, vereinfacht gesagt, ein Kreuzdiffusionssystem, wenn die Diffusionsmatrix A keine Diagonalmatrix ist. In den von uns betrachteten Modellen besteht A aus nichtlinearen Koeffizienten, die abhängig von c und ungleich 0 sind, sodass eine strenge Kopplung der Systemgleichungen vorliegt.

Die Analyse nichtlinearer Kreuzdiffusionsmodelle ist Gegenstand neuerer Untersuchungen. Oft wird dabei der Spezialfall $N = 2$ oder der Fall, dass die Diffusionsmatrix eine Dreiecksmatrix ist, betrachtet. Die Herausforderung in der Existenzanalyse solcher Systeme besteht darin, dass im Allgemeinen weder Standardresultate noch Maximumprinzipien zur Verfügung stehen, was wünschenswert wäre, um a priori Abschätzungen sowie die Beschränktheit bzw. die Nichtnegativität der Lösungen zu zeigen. Eine weitere Schwierigkeit in den von uns betrachteten Kreuzdiffusionssystemen ist, dass die Diffusionsmatrizen A weder symmetrisch noch positiv semidefinit sind, sodass es uns nicht möglich ist, zumindest die lokale Existenz von Lösungen aus Standardresultaten zu folgern.

Trotz dieser Schwierigkeiten können wir unter geeigneten Anfangsbedingungen und homogenen Neumann-Randbedingungen die globale Existenz beschränkter schwacher Lösungen der entsprechenden Anfangsrandwertprobleme beweisen. Dazu bedienen wir uns der Entropiemethoden. Genauer gesagt führen wir mittels einer geeigneten Variablentransformation sogenannte Entropievariablen ein, die die Beschränktheit und Nichtnegativität unserer Lösungen garantieren, womit wir die Notwendigkeit eines Maximumprinzips umgehen. Ferner beobachten wir, dass unser System ein spezielles Funktional besitzt, das wir Entropie nennen, welches zur Herleitung von a priori Abschätzungen dient.

Wir wenden diese Methoden im ersten Teil der Arbeit auf ein 2×2-Tumorwachstumsmodell in einer Raumdimension an, das in [49] hergeleitet worden ist und welches durch die Volumenanteile von Tumorzellen und extrazellulärer Matrix beschrieben wird. Es stellt sich heraus, dass die Existenz einer Lösung für Werte der Druckkonstante θ kleiner einer explizit berechneten Schranke gezeigt werden kann. Wie numerische Resultate vermuten lassen, können unsere Methoden für allgemeine θ nicht verwendet werden.

Im zweiten Teil der Dissertation widmen wir uns Maxwell-Stefan Systemen, die Kreuzdiffusionssysteme für beliebiges N darstellen und den Diffusionsprozess in Mehrkomponentengasmischungen mittels der Stoffmengenanteile der jeweiligen Komponenten zum Beispiel in der Lunge entsprechend modellieren. Wir erweitern die Beweisidee des Tumorwachstumsmodelles auf das N-Komponentensystem. Eine zusätzliche Schwierigkeit hierbei ist, dass die Diffusionsmatrix nicht explizit gegeben ist und nicht klar ist, ob sie existiert. Durch Kombination unserer Methoden mit den Resultaten aus [15], wo Aussagen über das Spektrum einer mit A in Verbindung stehenden Matrix gemacht werden, unter Verwendung der Perron-Frobenius Theorie für quasipositive, irreduzible Matrizen, können wir die Existenz von schwachen Lösungen dennoch beweisen.

Schließlich zeigen wir, unter Verwendung der relativen Entropie, dass diese Lösungen für den Fall, dass die Produktionsterme gleich 0 sind, exponentiell gegen ihren homogenen Gleichgewichtszustand konvergieren.

Contents

Acknowledgement

First of all, I would like to thank Ansgar Jüngel for granting me the possibility to complete my PhD-thesis, for the mentoring of my thesis and for the exceptional personal and professional support.

I would also like to thank Klemens Fellner, who has willingly accepted to examine my thesis as second examiner. He has always shown great interest in my work and he has supported and encouraged me a lot.

Furthermore, I would like to thank the FWF for financing the project I was working on.

I would like to express the deepest appreciation to my colleagues and friends who have helped with words and deeds and who have contributed to the good working atmosphere that made it possible to complete my PhD-thesis without complications.

Finally, I would like to thank my family, who has always been there for me and who has also supported me throughout the entire process of writing my PhD-thesis.

Chapter 1

Introduction

The following thesis is dedicated to *parabolic cross-diffusion systems* of the form

$$c_t - \operatorname{div}(A(c)\nabla c) = r(c), \tag{1.1}$$

where $c := (c_1, \dots, c_N)^\top$ is a vector-valued function consisting of $N \geq 2$ real functions

$$c_i : Q_T \longrightarrow [0,1], \;\; i = 1, \dots, N,$$

being defined on $Q_T := (0,\infty) \times \Omega$, where $\Omega \subseteq \mathbb{R}^d$, $d \in \{1,2,3\}$, is a bounded domain whose boundary $\partial\Omega$ is (at least) of class $C^{0,1}$, $A(c) := (a_{ij}(c))_{i,j=1,\dots,N}$ denotes an $N \times N$-matrix being called *diffusion matrix* and $r(c) := (r_1(c), \dots, r_N(c))^\top$ is a vector whose entries are—such as those of $A(c)$—real functions depending on c representing *production terms*. For $i = 1, \dots, N$ the function c_i denotes a dimensionless quantity, that is a certain fraction of the i^{th} component in a mixture consisting of $N+1$ components (fluids). Assuming that these fractions describe the mixture completely the fraction of the $(N+1)^{\text{st}}$ component in the mixture can be defined by the other functions as

$$c_{N+1} := 1 - \sum_{k=1}^{N} c_k. \tag{1.2}$$

Furthermore, system (1.1) is equipped with the initial conditions

$$c_i(0,.) = c_i^0 \quad \text{for } x \in \Omega, \quad i = 1, \dots, N, \tag{1.3}$$

where $c_1^0, \dots, c_N^0$ are real measurable functions defined on Ω, satisfying

$$c_i^0 \geq 0, \quad \sum_{i=1}^{N} c_i^0 \leq 1 \quad \lambda_d - a.e.$$

as well as with homogeneous Neumann boundary conditions

$$\nabla c_i \cdot \nu = 0 \quad \text{on} \quad \partial\Omega, t > 0, \quad i = 1, \dots, N, \tag{1.4}$$

where $\nu := (\nu_1, \dots, \nu_d)^\top$ is the exterior unit normal vector on $\partial\Omega$ existing almost everywhere and λ_d denotes the d-dimensional Lebesgue measure. We choose this kind of boundary conditions since we want our systems to be isolated.

In this work we use the following notation. The partial derivative of a vector function with respect to time or space is defined component-by-component. Furthermore, the gradient of a scalar function c_i is regarded as the column vector $\nabla c_i := ((c_i)_{x_1}, \dots, (c_i)_{x_d})^\top$ while the gradient of a vector function $\nabla c := (\frac{\partial c_i}{\partial x_j})_{i=1,\dots,N, j=1,\dots,d}$ is defined as an $N \times d$-matrix. The divergence of an $N \times d$-matrix is considered as vector whose i^{th} component, $i = 1, \dots, N$, is equal to the divergence of the i^{th} row of the matrix.

We call (1.1) a *cross-diffusion system* iff the diffusion matrix A is no diagonal matrix, i.e. there exists at least one $(i, j) \in \{1, \dots, N\}^2$, $i \neq j$, so that $a_{ij} \neq 0$ under the assumption that $a_{ii} \neq 0$. These off-diagonal elements are called *cross-diffusion terms*.

In the problems that we are dealing with A is a full matrix, i.e. $a_{ij}(c) \neq 0$ for all $(i, j) \in \{1, \dots, N\}^2$, being furthermore non-linear coefficients, so that (1.1) represents a quasilinear second-order system in divergence form consisting of N *strongly* or *fully coupled* equations because of the coupling in Δc_i and ∇c_i for $i = 1, \dots, N$.

In order to motivate *cross-diffusion* from the physico-chemical or biological point of view we consider systems of reaction-diffusion equations. Following [74] and [16] *diffusion* is a time-dependent process and can be described as the intermingling of the atoms or molecules of more than one species resulting from the random motions of the individual molecules that spread in space. Here, species refers to the chemical component in a binary or multicomponent mixture. Instead of defining the diffusion process for chemical components we can describe it for more general groups of particles such as cells, chemicals, bacteria or the individuals of a population. In all situations we speak of diffusion if the group of particles distributes as a whole in spite of the irregular movements of the individual particles [60], [64].

Let us consider a system consisting of $N \geq 2$ particle groups and let $u_i(t, x) \in \mathbb{R}$ be the density or concentration of the i^{th} group being a function of time and space, where $t \geq 0$ and x is an element of an adequate domain of $\mathbb{R}^d$, $d \geq 1$. Then, according to [60], the *conservation equation* for the i^{th} component says that the rate of change with respect to time of u_i results from the motion and the production of the i^{th} component, i.e.

$$(u_i)_t + \operatorname{div}(J_i) = R_i(t, x, u), \quad i = 1, \dots, N, \tag{1.5}$$

where $u := (u_1, \dots, u_N)^\top$, the d-dimensional vector $J_i(t, x)$ denotes the flux

and the real function R_i the production term, also called *reaction term*, of the i^{th} component. For u_i describing the molar concentration of the i^{th} species in a binary or multicomponent mixture the production of the i^{th} component is given by chemical reactions, whereas R_i represents the birth-death process if u_i is considered to be a population density. Since the production of a component is influenced by the other components as well in general, the functions R_i depend on u. Assuming that the flux J_i is diffusive only and that it is proportional to the gradient of u_i for $i = 1, \dots, N$ by generalising Fick's first law of diffusion (see chapter 3 for details) we obtain

$$J_i = -D_i \cdot \nabla u_i,\ i = 1, \dots, N, \tag{1.6}$$

where $D_i > 0$ is called the *diffusion coefficient* or the *diffusivity* of the i^{th} component. Usually, the diffusivities are supposed to be constant although it is more realistic to model them as functions depending on u. Thus, we can write (1.5) as

$$(u_i)_t - \operatorname{div}(D_i \cdot \nabla u_i) = R_i,\ \ i = 1, \dots, N,$$

i.e.

$$u_t - \operatorname{div}(D \cdot \nabla u) = R,$$

where $D := \operatorname{diag}(D_1, \dots, D_N)$ denotes the diagonal matrix whose diagonal entries are the diffusivities and $R := (R_1, \dots, R_N)^\top$. A system of this form is called a *reaction-diffusion-system*.

Although modelling the diffusion flux J_i as above is sufficient in many situations, this approach does not include cross-effects, i.e. the influence of the other components on the flux of the i^{th} particle group is ignored. In other words, *cross-diffusion*, described in [79] as the phenomenon, where the flux of a chemical component in a mixture is induced by the concentration gradient of another species, is neglected, while it occurs in fact in reality as experiments show. In chapter 3 we will deal with cross-diffusion effects in multicomponent gas mixtures and refer to [79] for experiments illustrating the importance of cross-diffusion in chemistry. Furthermore, cross-diffusion does also play an important role in biology which seems to be plausible if we think for example of interacting populations and their dynamics. It is clear that the presence or distribution of one population can affect the motion of the individuals of all other groups. A well-known cross-diffusion system in this context is the population model developed by Shigesada, Kawasaki and Teramoto [70]. Let us first consider the Lotka-Volterra competition model with diffusion

$$\begin{pmatrix} u_1 \\ u_2 \end{pmatrix}_t - \operatorname{div}\left(\begin{pmatrix} D_1 & 0 \\ 0 & D_2 \end{pmatrix} \cdot \nabla (u_1, u_2)^\top \right) = \underbrace{\begin{pmatrix} u_1(a_1 - b_1 u_1 - c_1 u_2) \\ u_2(a_2 - b_2 u_1 - c_2 u_2) \end{pmatrix}}_{=:R}$$

described in [57]. It can be regarded as an extension of the classical Lotka-Volterra predator-prey model since two populations of competing animal spe-

cies, instead of a predator and a prey population, described in the equations by the population densities $u_1(t,x)$ and $u_2(t,x)$, are considered not only in time but also in space. Thus, the spatial distribution of the individuals can be taken into account leading to diffusion terms, where the positive constants D_i, $i = 1, 2$, denote diffusion coefficients as before. The coefficients appearing in the production term R are all positive constants, where a_i represents the growth rate of population $i = 1, 2$, b_1, c_2 can be regarded as coefficients of intraspecific competition, leading to the terms $-b_1u_1^2$ as well as $-c_2u_2^2$, appearing in contrast to the classical model on the right hand side of the equations, modelling intraspecific competition and b_2, c_1 denote the coefficients of interspecific competition. Analogously, the interpecific competition is given by the terms $-c_1u_1u_2$ and $-b_2u_1u_2$.

The above system has been generalised by Shigesada, Kawasaki and Teramoto by taking into consideration the interactions of the populations not only in the production term but also in their spatial distribution leading to a spatial segregation of the species [70]. In other words, they assume that the individuals of two competing similar animal species move, amongst others, due to the mutual intraspecific and interspecific interference between the individuals. Let us cite the system

$$(u_1)_t = \operatorname{div}(D_1\nabla u_1 + \alpha_{11}\nabla(u_1)^2 + \alpha_{12}\nabla(u_1u_2)) + u_1(a_1 - b_1u_1 - c_1u_2) \tag{1.7}$$

$$(u_2)_t = \operatorname{div}(D_2\nabla u_2 + \alpha_{21}\nabla(u_1u_2) + \alpha_{22}\nabla(u_2)^2) + u_2(a_2 - b_2u_1 - c_2u_2) \tag{1.8}$$

as a special case of the Shigesada-Kawasaki-Teramoto model extended to higher space dimensions being considered for instance in [23] or [57]. Here we use the same notation as for the Lotka-Volterra competition model. The coefficients α_{ij} for $i, j = 1, 2$ are non-negative constants, where α_{11} as well as α_{22} are called self-diffusion coefficients and α_{21} as well as α_{12} denote cross-diffusion coefficients. Writing these equations in a different form, we obtain the following cross-diffusion system

$$u_t - \operatorname{div}(A(u)\nabla u) = \begin{pmatrix} u_1(a_1 - b_1u_1 - c_1u_2) \\ u_2(a_2 - b_2u_1 - c_2u_2) \end{pmatrix},$$

where $u := (u_1, u_2)^\top$ and

$$A(u) := \begin{pmatrix} D_1 + 2\alpha_{11}u_1 + \alpha_{12}u_2 & \alpha_{12}u_1 \\ \alpha_{21}u_2 & D_2 + \alpha_{21}u_1 + 2\alpha_{22}u_2 \end{pmatrix}$$

is the diffusion matrix, showing that the interaction between the two populations leads to cross-diffusion terms as off-diagonal elements and—compared to the Lotka-Volterra competition model—to more general diagonal elements depending on u_1 and u_2 in the diffusion matrix.

Another phenomenon where cross-diffusion appears in biology is that of chemotaxis describing the situation in which cells move towards or away from chemical species being higher concentrated in a directed way [79]. Therefore, the motion of the cells is influenced by a chemical substance. This behaviour can be described by the Keller-Segel chemotaxis model of the form

$$\begin{pmatrix} u_1 \\ zu_2 \end{pmatrix}_t - \operatorname{div}\left(\begin{pmatrix} D_1(u) & -\chi(u)u_1 \\ 0 & D_2 \end{pmatrix} \cdot \nabla u\right) = \begin{pmatrix} R_1(u) \\ R_2(u) \end{pmatrix}$$

that can be found in [47], where z denotes a non-negative constant, u_1 represents the cell density and the concentration of the chemical species is given by u_2. Again, $u := (u_1, u_2)^\top$, D_i are positive diffusivities and R_i the production terms for $i = 1, 2$. The term $\chi(u)u_1\nabla u_2$, where the non-negative function χ is called chemotactic sensitivity function, measuring the sensitivity of the cells to the chemical species, shows that the cells will move towards higher concentration of the chemical substance and that this effect will be increased by the number of cells being present. Hence, the cells move due to diffusion in the classical sense and due to the flux caused by the chemical species.

Further examples of cross-diffusion systems arising in life science are for example cancer models of certain brain tumours [60] or the tumour growth model developed by Jackson and Byrne [49] that we will deal with in chapter 2 leading in all cases to cross-diffusion terms in the diffusion matrix.

The aim of this work is to analyse particular initial-boundary-value problems of the form (1.1)–(1.4) and to prove the global-in-time existence of bounded weak solutions. The first model of interest is a 2×2-cross-diffusion system for the volume fractions of tumour cells and extracellular matrix in one space dimension representing a special tumour growth model. For details we refer to chapter 2. In chapter 3 we extend our existence analysis to $N \times N$-cross-diffusion systems for $1 \leq d \leq 3$, i.e. we investigate Maxwell-Stefan systems for $N \geq 2$ mole fractions describing the diffusion process in multicomponent gas mixtures such as in the lung.

Generally, non-linear cross-diffusion models have been investigated only in recent years. Most frequently the systems consist of two equations and often the special case of the diffusion matrix being a triangular matrix is considered (see [20] for references). Further references concerning cross-diffusion systems with full diffusion matrix or systems consisting of 3 or more equations can be found in [61] and [20]. The challenge of proving the existence of solutions to such systems is due to the lack of standard tools that can be employed. In fact, there is no general maximum or minimum principle available used in the case of single equations for deriving a priori estimates as well as for proving the non-negativity or boundedness of the solutions, being reasonable from the biological or physical point of view since they usually represent fractions, densities or concentrations. Moreover, in both cross-diffusion systems that we

will deal with in the following chapters the diffusion matrix A is neither symmetric nor positive (semi-)definite such that even the local-in-time existence of solutions does not follow from standard results.

Amann has considered general quasilinear parabolic systems of second order and has proven the local existence of unique classical solutions. In [4] he improves this result and derives sufficient conditions for the solutions to such systems to exist globally in time. The question if a given local solution exists globally is reduced to the problem of finding a priori estimates in suitable Sobolev spaces.

In order to overcome the difficulties mentioned above we will choose an approach that has been developed amongst others in [39], [25], [24] or [47] for 2×2-systems arising in granular material modelling, population dynamics, semiconductor theory or cell biology to treat cross-diffusion systems whose diffusion matrix is full and may be neither symmetric nor positive definite. In [26] and [28] this method has also been applied to thermodynamic models consisting of N equations.

The idea is to exploit the entropy structure of the model. More precisely, so-called *entropy variables* are introduced guaranteeing that the solutions become non-negative respectively bounded so that the maximum principle can be circumvented. Writing the system in terms of these new variables, a new diffusion matrix is obtained possessing properties that are essential for the existence proof. Furthermore, it is observed that the models possess a functional allowing for the derivation of a priori estimates that we will call an *entropy* because of its relation to the physical entropy that can be described, roughly speaking, as a kind of measure of disorder in a thermodynamical system. The entropy functionals that we use in our proofs can be regarded as generalisation of the Boltzmann entropy (see [52] for details) and describe in fact the negative entropy of the system. From the mathematical point of view an entropy, denoted by E, can be regarded as a specific functional defined for appropriate solutions to the corresponding problem for $t > 0$ that describes a Lyapunov-functional. In other words in our case E is defined for appropriate solutions $c := (c_1, \dots, c_N)^\top$ to (1.1)–(1.4) for $t > 0$ and satisfies Boltzmann's H-theorem, i.e.

$$\frac{d}{dt} E(c(t)) \leq 0, \quad t > 0.$$

We remark that the definition of an entropy is not consistent in literature. In [51] or [50] a possible definition can be found. Furthermore, we refer to these two lecture notes for a motivation of entropy-dissipation methods and their historical development. For a given entropy and appropriate solutions we define

$$E_p(c(t)) := -\frac{dE(c(t))}{dt}, \quad t > 0$$

as *entropy dissipation* or *entropy production*. The integrand of the corresponding integral is called *entropy production density* and denoted by p. This density is used for the numerical experiments in section (2.4). The pair (E, E_p) is called an *entropy-entropy dissipation pair*. According to this, a relation between an entropy functional and its entropy dissipation in the form of an inequality is called an *entropy-dissipation inequality*.

In [27] it has been shown that the existence of an entropy functional is equivalent to the existence of a symmetric formulation of the system, that is to a system written in entropy variables whose diffusion matrix is symmetric and positive definite. Indeed, this has also been observed in [25], where the Shigesada-Kawasaki-Teramoto population model (1.7)–(1.8) is considered by assuming that $\alpha_{12} = \alpha_{21} = 1$ and including an additional environmental potential (see [25] and [70]). The entropy considered for this model has the form

$$E(u) := \int_\Omega (u_1(\ln u_1 - 1) + 1) + (u_2(\ln u_2 - 1) + 1) d\lambda_d$$

for $t > 0$, where Ω is a bounded domain of dimension $d \leq 3$. Using the variable transformation

$$u_1 = e^{w_1}, \quad u_2 = e^{w_2},$$

where the functions w_i, $i = 1, 2$, are called entropy variables the positivity of the population densities is obtained due to the exponential function for appropriate functions w_i. It can be shown that the diffusion matrix of the system considered in these new variables is both symmetric and positive definite.

Generally, we cannot expect symmetry or positive definiteness of the new diffusion matrix. In [39], for example, where a cross-diffusion model describing the mixture of two granular materials in a rotating drum is investigated the transformed diffusion matrix is positive semi-definite but not symmetric. In this special model one of the solution functions is assumed to possess values in $[-1, 1]$ influencing the choice of the variable transformation of course. Although the diffusion matrix of the transformed system is at least positive semi-definite in the cited papers [39], [25], [24] and [47] this does not hold true anymore for all parameters in the tumour growth model that we will investigate.

Let us now come to the two cross-diffusion systems that we will deal with in chapter 2 and 3 and that have been investigated in [53] and [54]. In order to prove the existence of solutions we introduce (in both cases) the logarithmic

entropy

$$E(c) := \int_\Omega h(c) d\lambda_d \tag{1.9}$$
$$:= \int_\Omega \left(\sum_{i=1}^N c_i(\ln c_i - 1) + (1 - \sum_{k=1}^N c_k)(\ln(1 - \sum_{k=1}^N c_k) - 1) \right) d\lambda_d,$$

where $h(c)$ denotes the *entropy density*, which is the sum of the logarithmic entropies of all components. It is defined for all $c_i \geq 0$, $i = 1, \ldots, N$, satisfying $\sum_{i=1}^N c_i \leq 1$. Notice that the $(N+1)^{\text{st}}$ component of the mixture does also appear in the functional but only implicitly expressed by the other N functions. As formal calculations in chapter 2 (under the assumption that the production terms vanish) and 3 show (1.9) describes a Lyapunov-functional to the corresponding problems. The choice of a logarithmic entropy turns out to be convenient as it leads to a variable transformation that guarantees the positivity and boundedness of solutions. Let us define the entropy variables

$$w_i := \frac{\partial h}{\partial c_i} = \ln\left(\frac{c_i}{c_{N+1}}\right), \quad i = 1, \ldots, N, \tag{1.10}$$

derived formally as the partial derivatives of h with respect to the functions c_i, $i = 1, \ldots, N$. Inversely, this relation can be written as

$$c_i(w) = \frac{e^{w_i}}{1 + e^{w_1} + \cdots + e^{w_N}}, \quad i = 1, \ldots, N, \tag{1.11}$$

where $w := (w_1, \ldots, w_N)^\top$, leading automatically to positive fractions c_i for $i = 1, \ldots, N$ satisfying $\sum_{i=1}^N c_i < 1$ which implies that $c_{N+1} > 0$ if the functions w_i, $i = 1, \ldots, N$, take finite values or are bounded. Assuming that all second order partial derivatives of h with respect to $c_1, \ldots, c_N$ exist, we can define its Hessian $H(c)$ as

$$H(c) := \begin{cases} H_{ii}(c) := \frac{1}{c_i} + \frac{1}{c_{N+1}}, & i = 1, \ldots, N, \\ H_{ij}(c) := \frac{1}{c_{N+1}}, & i, j = 1, \ldots, N, i \neq j \end{cases}. \tag{1.12}$$

In case that $H(c)$ is invertible its inverse is given by

$$H^{-1}(c) = \begin{cases} H_{ii}^{-1}(c) := c_i(1 - c_i), & i = 1, \ldots, N, \\ H_{ij}^{-1}(c) := -c_i c_j, & i, j = 1, \ldots, N, i \neq j \end{cases}. \tag{1.13}$$

Because of the variable transformation (1.10) and the definition of c_{N+1} (1.2) a formal calculation shows that

$$H^{-1}(c) \cdot \nabla w = \nabla c$$

so that in terms of the variables $w_1, \ldots, w_N$ system (1.1) can be written as

$$(c(w))_t - \operatorname{div}(B(w) \cdot \nabla w) = r(c(w)), \tag{1.14}$$

where

$$w_i : Q_T \longrightarrow \mathbb{R},$$

$c(w) := (c_1(w), \ldots, c_N(w))^\top$, $r(c(w)) := (r_1(c(w)), \ldots, r_N(c(w)))^\top$ and

$$B(w) := A(c(w)) \cdot H^{-1}(c(w))$$

is the diffusion matrix of the transformed system. Thus, (1.14) can be interpreted as a parabolic system in the variables $w_1, \ldots, w_N$, where $c_1, \ldots, c_N$ are functions of $w_1, \ldots, w_N$. Its initial respectively boundary conditions are

$$w_i(0,.) = \ln\left(\frac{c_i^0}{c_{N+1}^0}\right) \quad \text{for } x \in \Omega, \quad i = 1, \ldots, N, \tag{1.15}$$

respectively

$$\nabla w_i \cdot \nu = 0 \quad \text{on} \quad \partial\Omega, t > 0, \quad i = 1, \ldots, N, \tag{1.16}$$

resulting from (1.3) and (1.4), where $c_{N+1}^0 := 1 - \sum_{i=1}^N c_i^0$. The initial conditions only make sense for $c_i^0 > 0$ λ_d-a.e., $i = 1, \ldots, N+1$, of course.

We notice that a related 2×2-cross-diffusion model has been analysed in [20] that describes diffusion of two particles by taking account of size exclusion. It features an entropy functional that is similar to (1.9) and, consequently, the same entropy variables (1.10) for $N = 2$. The diffusion matrix in [20] in the entropy variable formulation is diagonal which simplifies the analysis. However, this is not the case in our systems.

Let us outline the most important steps for proving the existence of bounded weak solutions to the tumour growth model and Maxwell-Stefan systems. The idea of the existence proof is similar for both considered cross-diffusion systems. For details we refer to section 2.3 and section 3.4.

First of all, we assume that there exists $\eta \in (0,1)$ so that

$$c_i^0 \geq \eta \quad \text{a.e.}, \quad i = 1, \ldots, N+1.$$

Thus, for $i = 1, \ldots, N$ $w_i(0,.)$ is well-defined a.e. and an element of $L^\infty(\Omega)$. Next, we consider the initial-boundary cross-diffusion system after the (formal) change of variables (1.14)–(1.16) and discretise it in time by the implicit Euler scheme with time parameter $\tau := T/m$, where $(0,T)$, $T > 0$, denotes a fixed time interval being divided into m subintervals. We want to show the existence of semi-discrete weak solutions to the resulting sequence of non-linear elliptic equations, using the Lax-Milgram lemma as well as the Leray-Schauder fixed point theorem. In chapter 2 we try to solve the time-discrete problems in the space $H^1(\Omega)$. As we consider the tumour growth model in one space dimension only, the embedding $H^1(\Omega) \hookrightarrow L^\infty(\Omega)$ is compact which is needed for the Leray-Schauder theorem. For the Maxwell-Stefan systems we have assumed

that $1 \leq d \leq 3$. Therefore, we consider the space $H^2(\Omega)$ instead in order to guarantee the compact embedding of the Sobolev space into $L^\infty(\Omega)$. Due to this embedding we can further apply the chain rule to the weak derivatives when deriving the discrete entropy inequality. In order to apply the Lax-Milgram lemma we add the elliptic operator $-\epsilon((w_1)_{xx} - w_1, (w_2)_{xx} - w_2)^\top$ to the time-discrete tumour growth model to show the coercivity of the elliptic system in the entropy variables (w_1, w_2). As we require more regularity in the semi-discrete Maxwell-Stefan system (as we consider the space $H^2(\Omega)$ instead of $H^1(\Omega)$) we add the fourth-order operator $\epsilon(\Delta^2 w + w)$ to that model. In both cases ϵ denotes a fixed but arbitrary positive parameter. Furthermore, in chapter 3 we need more regularity on the boundary of Ω in order to show that the corresponding bilinear form is coercive and the discrete entropy variables have to satisfy homogeneous boundary conditions. That is the reason why we introduce the space $\mathcal{V}$. In both models, the coefficients of the matrix B are elements of $L^\infty(\Omega)$ so that the weak formulation of the time-discrete problem is well-defined. We remark that the transformed diffusion matrix $B(w^k)$, where w^k denotes the approximation of w at time step k ($k = 0, \ldots, m$), is symmetric and positive definite a.e. due to the variable transformation in the Maxwell-Stefan system and positive definite a.e. for special parameter values for θ (more precisely for $\theta \leq 4/\sqrt{\beta}$) in the tumour growth model, which is also needed to show coercivity. Thus, we can prove that semi-discrete solutions exist. The next step is the derivation of the discrete entropy inequality. For that purpose, we consider h as a function of the time-discrete solution at time step k, $(c_1^k, \ldots, c_N^k)$, and try to find a relation between its discrete time derivative and the discrete entropy production. Of course, the inequality also contains ϵ-terms. As the production terms can easily be estimated the difficulty of deriving the entropy inequality is the estimation of the term

$$\nabla w^k : B(w^k)\nabla w^k, \tag{1.17}$$

uniformly in w^k, where ":" denotes the Hilbert-Schmidt inner product. Recalling the above variable transformation this expression can be formulated in terms of the diffusion matrix A. For the tumour growth model we obtain

$$\nabla w^k : B(w^k)\nabla w^k \geq K_\theta \int_\Omega (c_1^k)_x^2 + (c_2^k)_x^2 d\lambda_d,$$

where $K_\theta > 0$ depends on the parameters θ and β. The challenge of deriving the discrete entropy inequality in the case of Maxwell-Stefan systems is due to the fact that it is not clear whether the diffusion matrix A exists and that it is not given explicitly. Thanks to the variable transformation we obtain $c_i^k \in (0,1)$ a.e. for $i = 1, \ldots, N+1$. In that case we know that A exists a.e. and information concerning the spectrum of a matrix that is related to A is available using Perron-Frobenius theory. Using this information it can be

shown that (1.17) is greater that or equal to

$$\frac{4}{\Delta}\int_\Omega \sum_{i=1}^{N+1} |\nabla\sqrt{c_i^k}|^2 d\lambda_d,$$

where Δ depends only on the parameters in the diffusion matrix A, yielding H^1-bounds for $\sqrt{c_i^k}$. Solving the discrete entropy inequality recursively and using the fact that the piecewise constant functions in time, denoted as $c_i^{(\tau)}$ for $i = 1, \dots, N$, depending on ϵ, τ and η, are bounded a.e. by 1, we can derive a priori estimates for $c_i^{(\tau)}$. These estimates are independent of τ, η and ϵ which allows us to pass to the limit $\tau \to 0$, $\epsilon \to 0$ using weak compactness methods. Finally, we can pass to the limit $\eta \to 0$ and obtain weak solutions $c_i \in L^2_{\text{loc}}(0, \infty; H^1(\Omega))$ for $i = 1, \dots, N$ that satisfy $0 \le c_i \le 1$ a.e. as we lose the strict inequalities in the limit.

Moreover, we have a look at the long-time behaviour of solutions to the Maxwell-Stefan systems for vanishing production rates in section 3.5. Assuming that

$$\min_{i=1,\dots,N+1} \|c_i^0\|_{L^1(\Omega)} > 0$$

the constants $\overline{c}_i^0$ for $i = 1, \dots, N$ defined as

$$\overline{c}_i^0 := \frac{1}{\lambda_d(\Omega)}\int_\Omega c_i^0 d\lambda_d, \quad i = 1, \dots, N+1 \tag{1.18}$$

are steady state solutions of the corresponding cross-diffusion system. We are able to prove that the solutions for the Maxwell-Stefan systems for vanishing right-hand side, whose existence can be shown as we have seen above, converge exponentially fast to this stationary state. For this, we introduce the relative entropy

$$E^*(c) := \sum_{i=1}^{N+1}\int_\Omega c_i \ln\frac{c_i}{\overline{c}_i^0} d\lambda_d \tag{1.19}$$

defined for $c_i \ge 0$, $i = 1, \dots, N+1$. We remark that the choice of the relative entropy functional seems to be plausible as we know that the entropy increases (decreases in our case) with time in a closed thermodynamical system and that its maximum (minimum) is reached for stationary solutions [52]. The relative entropy (1.19) is non-negative and it is minimized by the steady state solutions $(\overline{c}_1^0, \dots, \overline{c}_{N+1}^0)^\top$. The Csiszár-Kullback inequality bounds the L^1-norm of $(c_i(t,.) - \overline{c}_i^0)$, $t > 0$, in terms of the discrete relative entropy. More precisely, again, we assume that the initial data are greater that or equal to $\eta \in (0, 1)$ and consider the time discrete system as in the existence proof. The difficulty of this proof is that the approximate solutions c_i^k do not conserve the L^1-norm because of the presence of the regularising ϵ-terms and we need to derive appropriate bounds leading to additional γ-terms. The proof is based further

on the discrete entropy-dissipation inequality and the logarithmic Sobolev inequality, which links the discrete entropy dissipation to the discrete relative entropy as well as on the Csiszár-Kullback inequality that we use after passing to the limit $\epsilon, \tau, \gamma, \eta \to 0$.

In chapter 2.4 we present some numerical results concerning the tumour growth model. For an introduction and a derivation of this model respectively of the Maxwell-Stefan systems we refer to section 2.1 and 2.2 respectively to section 3.1 and 3.2. In section 3.3 we derive some properties of diffusion matrices being essential for the existence proof of the Maxwell-Stefan systems. General results from matrix analysis that we need in this section are summarised in appendix A. Finally, we outline some open problems in chapter 4 that might be interesting to investigate with regard to future research.

Chapter 2

Entropy Structure of a Cross-Diffusion Tumour Growth Model

2.1 Introduction

In the last years the number of people suffering from cancer, being the most common fatal disease apart from cardiovascular diseases in the industrial nations [12], has been increasing so that today tumour research is of great interest not only in medicine but also in mathematics where tumour models are developed and analysed. Tumours can appear in every part of the body and their behaviour and formation are quite different and not totally clear up to now. The mathematical modelling and simulation of tumour growth may provide biologists with complementary insight into the chemical and biological mechanisms that influence the development of tumours and can therefore help to understand these processes.

A *tumour* or *neoplasm* is by definition an abnormal mass of tissue resulting from the progeny of abnormal cells produced naturally in the body, being called *tumour cells*. For this process regulatory disorders of genes particularly controlling the *proliferation* (growth, progeny), the *apoptosis* (programmed cell death) and the *cell differentiation* (development of various cell types having specialised functions and a special morphology) of cells are responsible [9], [75].

Today we act on the assumption that tumour growth comes from transformed somatic cells that are able to divide. Proliferation of these tumour cells leads to a cluster of cells that becomes heterogeneous as a result of differentiation as well as of mutations. Although these transformed cells are assumed to be not very active regarding cell division they are very important for the survival of the tumour. If the diameter of a tumour exceeds 2 mm the neoplasm cannot

be nurtured by its environment by diffusion anymore but needs its own vascularisation. The proliferation of blood vessels is called *tumour angiogenesis* and it is initiated by the tumour cells themselves so that finally the tumour consists of tumour cells, being called *tumour parenchyma*, and a *tumour stroma* shoring up the tumour and providing its blood supply [9].

Thus, tumour growth can be very roughly classified into three stages. The first stage which is mostly governed by the proliferation of tumour cells is the *avascular growth*. When the tumour starts developing its own blood supply we speak of the *vascular stage*. Later, the tumour cells are able to escape from the tumour via the circulatory system and lead to secondary tumors in the body describing the *metastatic stage* [66].

Generally, tumours are divided in *benign* and *malignant tumours* but there are also *semi-malignant tumours* [9].

Malignant tumours, also called *cancer*, potentially result in death. Usually, they grow very fast, *invasively* and in a destructive way, i.e. they grow into organs and vessels leading to a destruction of the normal tissue. If the primary tumour penetrates lymphatic vessels or blood vessels tumour cells can spread in the body and form *metastases* (daughter or secondary tumours) in other tissues and organs in the course of *metastasis*. Normally, the edges of malignant tumours are not clearly defined, their cells are more or less *dedifferentiated*, i.e. they lose differentiation properties, and show more atypia compared to cells of normal tissues [9], [75].

In contrast, *benign tumours* are usually not perilous. They grow slowly and expansively, i.e. the neighbouring normal tissue is replaced and compressed but not destroyed, their edges are clearly defined, their cells are well-differentiated and homogeneous and they do not form metastases [9].

Semi-malignant tumours can be regarded as a special form of tumours possessing properties of both malignant and benign tumours. They grow invasively and in a destructive way but they do not spread in the body [9].

It has been observed that benign and low grade malignant tumours are often surrounded by a collagen capsule that may prevent the tumour from invasion but up to now the reason for this phenomenon is still unexplained. There are two complementary theories explaining this behaviour and both of them have been supported by experiments. Following the *expansive growth hypothesis* tumour encapsulation is a *passive* reaction of the host. It is assumed that those cells of normal tissue that are adjacent to the tumour die if it grows due to the pressure they experience and that the extracellular matrix that is also compressed forms a capsule then. *Extracellular matrix* (*ECM*) can be described as the constitutive component of tissue apart from cells. Although its

function and its chemical composition depend on the respective tissue it consists basically of matrix and the two structural proteins collagen and elastin. It provides structural support to tissues and affects the motion of their cells [9]. In contrast to that, according to the *foreign body hypothesis* encapsulation is an *active* response of the host to confine the tumour. In this theory it is assumed that normal cells secrete collagen as well as other fibrous components of the extracellular matrix when they are stressed [49].

In order to compare these two theories numerically Jackson and Byrne have developed a mathematical model in [49] describing tumour growth as well as tumour encapsulation of solid tumours in the avascular stage. Following the definition of the National Cancer Institute [81] a *solid tumour* is a tumour that usually does not inclose liquid areas or cysts. According to their simulation results it seems to be more realistic that tumour encapsulation follows from a passive reaction of the host although the capsule becomes denser if both active and passive host response are taken into account. An active response alone does not lead to capsule formation however.

Before explaining their tumour growth model in detail we review briefly the modelling of tumour growth (see also [11] for example).

Most macroscopic models for tumour growth fall into two categories: *discrete cell population models* that track the individual cell behaviour and *continuum models* that formulate the average behaviour of tumour cells and their interactions with the tissue structure leading to a system of partial differential equations for cell populations and chemical substances [12].

In the following, we concentrate on continuum models and in particular only on those which contain cross-diffusion. A possible continuum model ansatz is the use of reaction-diffusion equations for chemicals and mass balance equations for the cellular components. As in [49] the tissue or the tumour is sometimes considered as multiphase material. Using mixture theory mass balances are obtained then for the components that are represented by their volume fractions [12].

These equations need to be closed by defining (or deriving) equations for the corresponding velocities. Thereby, we distinguish between two classes of models: *phenomenological* and *mechanical models* (see section 4 in [12]). In phenomenological models, it is assumed that there are no mechanical effects influencing the motion of the components in the tissue so that the cellular and chemical constituents do not move or that they move due to diffusion, chemotaxis or other mechanisms. Thus, mechanical models differ from phenomenological ones by the fact that the latter ones do not take into account mechanical causes of cell movement due to pressure produced by proliferating tumor cells to the surrounding tissue [12]. An example of such a model is given

by Casciari et al. in [22]. By contrast, the components are supposed to move as a result of physical forces in mechanical models, where force balances and momentum balance equations are used. Examples regarding the modelling of velocities or stresses in mechanical models are given amongst others in [12] or in [18]. More details can be found in the review of Roose et al. [66] giving an overview of tumour growth models of avascular stage.

The cross-diffusion system investigated in [49] represents a mechanical tumour growth model and is of the form (1.1) for $N = 2$. We set

$$c_1 = c, \;\; c_2 = m \;\text{ and }\; c_{N+1} = c_3 = w := (1 - c - m)$$

denoting the volume fraction of tumour cells, extracellular matrix and interstitial fluid respectively composing the control tissue $\Omega := (0, 1)$.

Interstitial fluid denotes the liquid that fills out the spaces between cell membranes in tissue, including lymph, and belongs to the extracellular fluid. It consists mainly of water, nutrients and cellular waste products and is important for the cell communication, the transport of substances to the cells and the removal of their waste [75].

The mass balance equations for the volume fractions of the tumour cells and the ECM are supplemented by equations for the velocities, depending on the gradient of the corresponding pressure. The third component w and its velocity are eliminated from the equations by expressing them in terms of c and m and their velocities.

A particular feature of the model is tumour encapsulation which is triggered by the increase of the pressure of the ECM due to tumour growth. It is assumed in [49] that the pressure of the tumour cells and the ECM increases with the respective volume fraction and that the presence of tumour cells leads to an increase in the ECM pressure, being modelled by the cell-induced pressure coefficient $\theta \geq 0$, which causes a non-linear term in the ECM pressure. When $\theta > 0$, the ECM becomes more compressed as the tumour cell fraction increases. Choosing $\theta = 0$ this effect can be excluded from the model.

The model is given by the following equations

$$\begin{pmatrix} c_t \\ m_t \end{pmatrix} - \left(A(c, m) \begin{pmatrix} c_x \\ m_x \end{pmatrix} \right)_x = r(c, m) \quad \text{in } \Omega, \; t > 0 \tag{2.1}$$

subject to the initial conditions

$$c(0, \cdot) = c_0, \quad m(0, \cdot) = m_0 \;\; \text{in } \Omega \tag{2.2}$$

and the Neumann boundary conditions

$$c_x = m_x = 0 \;\; \text{ on } \;\; \partial\Omega, t > 0. \tag{2.3}$$

The diffusion matrix A is defined as

$$A(c,m) := \begin{pmatrix} 2c(1-c) - \beta\theta cm^2 & -2\beta cm(1+\theta c) \\ -2cm + \beta\theta(1-m)m^2 & 2\beta m(1-m)(1+\theta c) \end{pmatrix} \tag{2.4}$$

with the pressure coefficients $\beta > 0$ and $\theta \geq 0$ and the production terms are given by

$$r(c,m) = \begin{pmatrix} r_c(c,m) \\ r_m(c,m) \end{pmatrix} := \begin{pmatrix} \gamma c(1-c-m) - \delta c \\ \alpha cm(1-c-m) \end{pmatrix}$$

(setting $r_1 = r_c$ and $r_2 = r_m$), where $\gamma \geq 0$ and $\alpha \geq 0$ denote the growth rates of the tumour cells and the ECM respectively and $\delta \geq 0$ is the death rate of the first component. Notice that the scaling we have used in order to obtain (2.1) differs from that proposed in [49] (see section 2.2 for a sketch of the model derivation and the scaling).

This chapter is organised as follows. In section 2.2 we sketch the derivation of the model (2.1). Global-in-time existence of bounded weak solutions to the initial-boundary-value problem (2.1)–(2.3) is proven in section 2.3 using entropy methods for θ being smaller than a certain explicit critical value. Finally, numerical results using a finite-difference discretisation are presented in section 2.4.

2.2 Derivation of the Model and Scaling

For the convenience of the reader and to specify the biological assumptions, we sketch the derivation of the tumour growth model following Jackson and Byrne [49].

They assume that the tumour-host environment, given by a fixed interval $(-\ell, \ell)$ with $\ell > 0$, consists of the tumour cells, the extracellular matrix (ECM) and interstitial fluid (water phase). Notice that normal cells do not appear in their model. Supposing that this mixture is saturated, which means that there are no voids, the volume fractions of the tumour cells c, the ECM m and the water phase w sum up to one so that $c + m + w = 1$. As in [21] it is assumed that cells proliferate by absorbing water and that they release it when they die. Furthermore, the tumour is supposed to be centred at $x = 0$, being free of ECM, and to expand symmetrically around that region in one space direction such that it is sufficient to consider the interval $(0, \ell)$.

Inhibitive factors regarding tumour growth such as nutrient and dioxygen limitation or a response of the host's immune system as well as promotive factors such as *promoters*, i.e. substances that accelerate the proliferation of tumour cells, are not included in the model. In addition, vascularisation of the tumour is also ignored. For tumours being small enough this modelling coincides with

reality (see section 2.1). In [58], where the blood supply of the tumour is also not taken into account in the model, Lubkin and Jackson justify this approach by the fact that they want to consider changes that take place over the time scale of growth instead of the time scale of perfusion. Another reason is to keep the model as simple as possible. The diameter of the tumour is expected to be between 10^{-3} m and 10^{-2} m in [58].

The tumour, the ECM and the water phase are treated as fluids which is a reasonable assumption as water is a main constituent of all three components. Denoting their corresponding mass densities by ρ_c, ρ_m and ρ_w mass balance

$$\frac{\partial \rho_i}{\partial t} + (\rho_i v_i)_x = 0, \quad i = c, m, w, \tag{2.5}$$

stating that the mass of a fluid is constant in time if there is no transfer of mass through its surface and no increase or loss of mass inside the material, such as conservation of momentum

$$\frac{\partial}{\partial t}(\rho_i v_i) + (\rho_i v_i^2)_x = (\sigma_i)_x + \rho_i f_i, \quad i = c, m, w, \tag{2.6}$$

meaning that the rate of change with respect to time of momentum is equal to the sum of the external forces that act on the material, can be formulated for each component, where v_i is the velocity, $\rho_i v_i$ the mass flux, σ_i the stress tensor and f_i the force per unit mass regarding the three fluids, $i = c, m, w$, respectively.

These balance laws, being well-known in continuum mechanics, hold only in the region occupied by the corresponding fluid. In order to obtain mass and momentum balance equations for the tumour cells, the ECM as well as for the interstitial fluid that hold everywhere in the mixture including interactions of the constituents the approach of averaging of Drew can be mentioned, where two materials (phases), that are assumed to be interacting continua, are considered and modelled as a new material being called mixture. For details concerning the averaging technique we refer to [32] or to [33] where it is extended to multiphase material.

Assuming that the three components are interacting continua and incompressible fluids with constant and equal densities, that can w.l.o.g. be supposed to be 1 [21], Drew's method leads to the continuity equations

$$c_t + (cv_c)_x = r_c, \;\; m_t + (mv_m)_x = r_m, \;\; w_t + (wv_w)_x = r_w, \tag{2.7}$$

for $t > 0$, $x \in (0, \ell)$, where $r_c(c, m, w)$, $r_m(c, m, w)$ and $r_w(c, m, w)$ are the corresponding net production rates.

In order to derive momentum balance equations we assume that body forces can be neglected, as in Preziosi's and Vitale's lecture notes ("Mechanical Aspects of Tumour Growth: Multiphase Modelling, Adhesion, and Evolving Natural Configurations") for instance, published in [13], where the authors argue

that it is difficult to imagine relevant body forces acting on the phases except of gravity that is not important for the consideration. Furthermore, as the Reynolds number of each of the three fluids is assumed to be rather small as in [18], where it has been checked to be approximately 10^{-2} in a system consisting of tumour cells and extracellular water, inertial forces can be ignored. Under these assumptions we obtain the force balances

$$\begin{aligned}(\sigma_c c)_x + pc_x + F_c^{\text{int}} &= 0,\\ (\sigma_m m)_x + pm_x + F_m^{\text{int}} &= 0,\\ (\sigma_w w)_x + pw_x + F_w^{\text{int}} &= 0,\end{aligned}$$

where p denotes a common pressure in all three phases. The interfacial force density F_i^{int} for $i = c, m, w$ is supposed to be the force per unit volume acting on phase i by the other two phases, i.e.

$$F_i^{\text{int}} = \sum_{\substack{j=c,m,w\\ j\neq i}} F_{ij},$$

where F_{ij} denotes the force per unit volume that phase j exerts on phase i for $i, j = c, m, w$, $i \neq j$. Due to Newton's third law it is assumed that $F_{ij} = -F_{ji}$ for all $i, j = c, m, w, i \neq j$. Thus, we obtain

$$(c\sigma_c)_x + pc_x + F_{cm} + F_{cw} = 0, \tag{2.8}$$

$$(m\sigma_m)_x + pm_x - F_{cm} + F_{mw} = 0, \tag{2.9}$$

$$(w\sigma_w)_x + pw_x - F_{cw} - F_{mw} = 0. \tag{2.10}$$

Notice that the functions appearing in equation (2.7) and (2.8)–(2.10) have to be understood in an averaged sense due to the averaging process in contrast to the usual non-averaged functions in (2.5) and (2.6). To simplify matters we have used the same notation for the functions and their averaged versions in all balance laws above. A detailed derivation of the equations (2.7)–(2.10) can be found in [32] and [63].

Since the system is supposed to be closed the total net production vanishes,

$$r_c + r_m + r_w = 0. \tag{2.11}$$

Furthermore, with the expression $c + m + w = 1$, the water volume fraction $w = 1 - c - m$ can be expressed in terms of c and m. Using this fact and (2.11) when adding all equations in (2.7) and recalling tumour growth symmetry, which implies that the velocities vanish at $x = 0$, we find that

$$wv_w = -(cv_c + mv_m). \tag{2.12}$$

Next, we have to determine the stresses and forces. Following [32] the force densities F_{ij}, that represent classical drag forces, can be written as

$$F_{cm} = k_1(c, m)(v_m - v_c), \quad F_{cw} = k_2(c, w)(v_w - v_c), \quad F_{mw} = k_3(m, w)(v_w - v_m),$$

where k_1, k_2 and k_3 depend on the corresponding drag coefficient. Although k_1, k_2 and k_3 could be determined empirically the less realistic case is chosen in order to simplify matters assuming them to depend linearly on cm, cw and mw respectively. This approach is common in many tumour growth models (see [18] for example). Thus, we obtain

$$F_{cm} = k_1 cm(v_m - v_c), \quad F_{cw} = k_2 cw(v_w - v_c), \quad F_{mw} = k_3 mw(v_w - v_m), \tag{2.13}$$

where k_1, k_2 and k_3 are positive constants, showing that the force being exerted on the tumour cells by the ECM or the interstitial fluid is equal to 0 in regions without tumour cells.

The stresses are given by

$$\sigma_c = -(p + P_c), \;\; \sigma_m = -(p + P_m), \;\; \sigma_w = -p, \tag{2.14}$$

where the pressures P_c and P_m, respectively, distinguish the cell and the ECM phases from water. We assume that the pressures P_c and P_m are proportional to their respective volume fractions. Moreover, we expect that the tumour cells increase the ECM pressure but not inversely. Therefore, we write

$$P_c = s_c c, \quad P_m = s_m m(1 + \theta c), \tag{2.15}$$

where $s_c \geq 0$, $s_m \geq 0$ are constants, and $\theta \geq 0$ can be regarded as a parameter measuring the strength of the ECM pressure increase due to tumour cells. When $\theta > 0$, the ECM becomes more compressed as the tumour cell fraction increases.

By adding all three force balance equations (2.8)–(2.10), the force terms cancel and inserting (2.14) as well as the above expressions for P_c and P_m (2.15), since $c + m + w = 1$ and $(c + m + w)_x = 0$, we end up with

$$p_x = -(cP_c + mP_m)_x = -\left(s_c c^2 + s_m m^2(1 + \theta c)\right)_x. \tag{2.16}$$

Replacing wv_w by (2.12) and w by $1 - c - m$, (2.8)–(2.9) become, using (2.13) and (2.14),

$$(cP_c)_x + p_x c = F_{cm} + F_{cw} = k\left(-c(m + w)v_c + cmv_m + cwv_w\right) = -kcv_c,$$

$$\begin{aligned}(mP_m)_x + p_x m &= -F_{cm} + F_{mw} = k\left(-cm(v_m - v_c) + mw(v_w - v_m)\right) \\ &= -kmv_m,\end{aligned}$$

where we have set $k_1 = k_2 = k_3 =: k > 0$ which significantly simplifies the equations.

Employing (2.16) to eliminate p_x and (2.15) to eliminate P_c and P_m, it follows that

$$cv_c = -k^{-1}\left((cP_c)_x + p_x c\right) = -k^{-1}\left((1-c)(s_c c^2)_x - c(s_m m^2(1+\theta c))_x\right),$$
$$mv_m = -k^{-1}\left((mP_m)_x + p_x m\right) = -k^{-1}\left((1-m)(s_m m^2(1+\theta c))_x - m(s_c c^2)_x\right).$$

These identities allow us to eliminate the velocities from the mass balance equations (2.7), leading to the system

$$c_t - k^{-1}\left((1-c)(s_c c^2)_x - c(s_m m^2(1+\theta c))_x\right)_x = r_c,$$
$$m_t - k^{-1}\left((1-m)(s_m m^2(1+\theta c))_x - m(s_c c^2)_x\right)_x = r_m,$$

where $x \in (0,\ell)$, $t > 0$.

In order to determine r_c and r_m Jackson and Byrne follow observations but choose the assumptions in such a way that the model becomes as simple as possible. As mentioned before, they assume that tumour cells proliferate by absorbing water at a rate being proportional to the cell and water fractions and that they die at a rate being proportional to c. Furthermore, it is assumed that the presence of tumour cells is the most important factor for the ECM production but that ECM and water are also necessary components for this process. Thus, new ECM is produced only when all three phases are present. The loss of ECM is neglected. Altogether, we obtain

$$r_c(c,m) = \alpha_c c(1-c-m) - \delta_c c, \quad r_m(c,m) = \alpha_m cmw = \alpha_m cm(1-c-m), \tag{2.17}$$

where $\alpha_c, \alpha_m, \delta_c \geq 0$. The water production can be computed from

$$r_w = -(r_c + r_m).$$

Introducing the diffusion matrix

$$\widetilde{A}(c,m) := \frac{1}{k}\begin{pmatrix} 2s_c c(1-c) - s_m\theta c m^2 & -2s_m cm(1+\theta c) \\ -2s_c cm + s_m\theta(1-m)m^2 & 2s_m m(1-m)(1+\theta c)\end{pmatrix}$$

and inserting the production rates (2.17), the above system can be written as

$$\frac{\partial}{\partial t}\begin{pmatrix} c \\ m\end{pmatrix} - \left(\widetilde{A}(c,m)\begin{pmatrix} c_x \\ m_x\end{pmatrix}\right)_x = \begin{pmatrix} \alpha_c c(1-c-m) - \delta_c c \\ \alpha_m cm(1-c-m)\end{pmatrix}.$$

System (2.1) is obtained by assuming that $s_c > 0$ and rescaling time by $t_s := t/\widetilde{\tau}$ and space by $x_s := x/\ell$, where $\widetilde{\tau} := k\ell^2/s_c$. Then

$$\frac{\partial}{\partial t_s}\begin{pmatrix} c \\ m\end{pmatrix} - \left(A(c,m)\begin{pmatrix} c_{x_s} \\ m_{x_s}\end{pmatrix}\right)_{x_s} = \begin{pmatrix} \gamma c(1-c-m) - \delta c \\ \alpha cm(1-c-m)\end{pmatrix},$$

where $x_s \in (0,1)$, $t_s > 0$ are dimensionless variables and $A(c,m)$ is defined in (2.4) depending on

$$\beta := s_m/s_c \geq 0, \qquad \theta \geq 0$$

that are both pressure coefficients. In fact, β denotes the ratio of the pressure coefficients regarding the ECM and the tumour cells. As the case $\beta = 0$ leads to a diffusion matrix that is not full we will assume that $\beta > 0$ which is more interesting from the mathematical point of view. The scaled growth rate and death rate of the tumour cells as well as the growth rate of the ECM are given by the non-negative constants

$$\gamma := \widetilde{\tau}\alpha_c = \alpha_c k l^2/s_c, \quad \delta := \widetilde{\tau}\delta_c = \delta_c k l^2/s_c, \quad \alpha := \widetilde{\tau}\alpha_m = \alpha_m k l^2/s_c.$$

We remark that Jackson and Byrne [49] have employed a different scaling by setting $\widetilde{\tau} := 1/\alpha_c$, where α_c is assumed to be positive. Then the scaled system writes as

$$\frac{\partial}{\partial t_s}\begin{pmatrix} c \\ m \end{pmatrix} - \left(A^{\mathrm{JB}}(c,m)\begin{pmatrix} c_{x_s} \\ m_{x_s} \end{pmatrix}\right)_{x_s} = \begin{pmatrix} c(1-c-m) - \delta c \\ \alpha c m (1-c-m) \end{pmatrix}, \tag{2.18}$$

where

$$A^{\mathrm{JB}}(c,m) := \begin{pmatrix} 2\beta_c c(1-c) - \beta_m \theta c m^2 & -2\beta_m c m(1+\theta c) \\ -2\beta_c c m + \beta_m \theta (1-m) m^2 & 2\beta_m m(1-m)(1+\theta c) \end{pmatrix}$$

for $t_s > 0$, $x_s \in (0,1)$ and

$$\beta_c := s_c/(\alpha_c k \ell^2) \geq 0, \quad \beta_m := s_m/(\alpha_c k \ell^2) \geq 0.$$

The motion of the components is influenced by their mechanical interactions which is emphasised by the coefficients β_c and β_m being dependent on the drag coefficient and the pressure coefficients in the tumour cells and the ECM respectively [49]. The non-negative rates α and δ are defined as above, i.e.

$$\delta = \delta_c/\alpha_c, \quad \alpha = \alpha_m/\alpha_c.$$

Recalling tumour growth symmetry and assuming that the system is isolated at $x = 1$ Jackson and Byrne choose the Neumann boundary conditions

$$c_{x_s} = m_{x_s} = 0 \quad \text{for } x_s \in \{0,1\}, t_s > 0. \tag{2.19}$$

As initial conditions they consider the functions

$$c(0,x_s) := \frac{1}{8}\left(1 + \tanh\left(\frac{0.1 - x_s}{0.05}\right)\right), \quad m(0,x_s) := \frac{1}{8}\left(1 - \tanh\left(\frac{0.1 - x_s}{0.05}\right)\right) \tag{2.20}$$

for $x_s \in (0,1)$ showing that the tumour is localised in a region around $x_s = 0$ and that this region is free of ECM at the beginning (see figure 2.1 plotted with Maple).

In the following we do not differentiate between x and x_s or t and t_s.

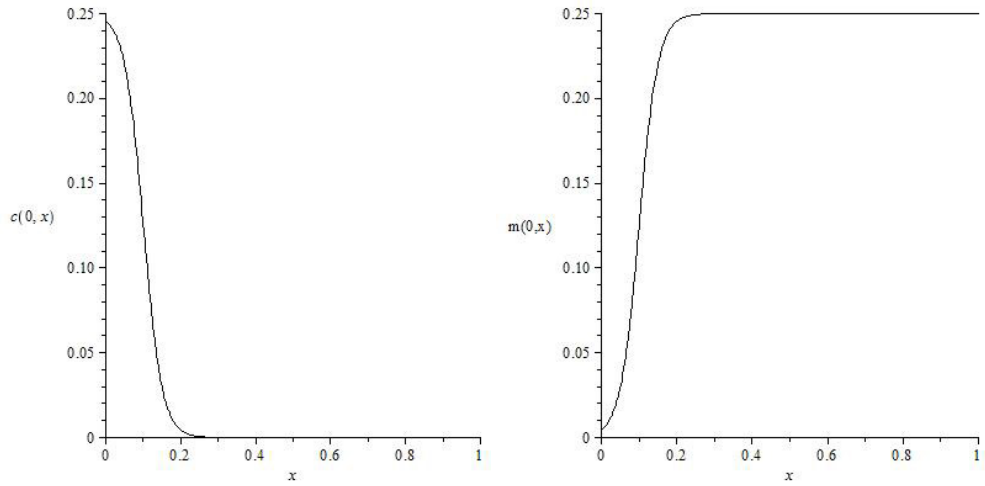

Figure 2.1: Initial conditions for c (left) and m (right) according to [49].

2.3 Existence of Weak Solutions

The aim of this section is to show that there exists a global-in-time solution $(c, m)^\top$ to (2.1)–(2.3) in a weak sense that satisfies $c, m, c + m \in [0, 1]$. For this purpose we observe that the diffusion matrix $A(c, m)$ of the above cross-diffusion system is neither symmetric nor positive semi-definite for general $\beta > 0$ and $\theta \geq 0$ as counterexamples show and apply entropy methods as well as a variable transformation to our system (see chapter 1). The entropy functional used in the following has the form

$$\begin{aligned} E(c,m) &:= \int_\Omega h(c,m)d\lambda \qquad (2.21)\\ &:= \int_\Omega \left(c(\ln c - 1) + m(\ln m - 1) + (1-c-m)(\ln(1-c-m) - 1)\right) d\lambda, \end{aligned}$$

where $\lambda := \lambda_1$ and h denotes the entropy density being defined for $c, m \geq 0$ that satisfy $c + m \leq 1$. Furthermore, we introduce the entropy variables

$$w_1 = u := \frac{\partial h}{\partial c} = \ln\left(\frac{c}{1-c-m}\right), \quad w_2 = v := \frac{\partial h}{\partial m} = \ln\left(\frac{m}{1-c-m}\right), \tag{2.22}$$

leading to positive volume fractions

$$c(u,v) = \frac{e^u}{1+e^u+e^v}, \quad m(u,v) = \frac{e^v}{1+e^u+e^v}$$

that satisfy $c(u, v) + m(u, v) < 1$ if u and v are bounded. In terms of the entropy variables u and v system (2.1) can be written formally as

$$\frac{\partial}{\partial t}\begin{pmatrix} c(u,v) \\ m(u,v) \end{pmatrix} - \left(B(u,v)\begin{pmatrix} u \\ v \end{pmatrix}_x \right)_x = r(c(u,v), m(u,v)), \tag{2.23}$$

for $(t,x) \in Q_T$, where

$$B(u,v) := A(c(u,v), m(u,v)) \cdot H^{-1}(c(u,v), m(u,v))$$

with elements

$$\begin{aligned}
b_{11}(c,m) &:= (2c(1-c) - \beta\theta c m^2)c(1-c) + 2\beta c^2 m^2(1+\theta c)\\
b_{12}(c,m) &:= -(2c(1-c) - \beta\theta c m^2)cm - 2\beta c m^2(1+\theta c)(1-m)\\
b_{21}(c,m) &:= (-2cm + \beta\theta(1-m)m^2)c(1-c) - 2\beta c m^2(1+\theta c)(1-m)\\
b_{22}(c,m) &:= -(-2cm + \beta\theta(1-m)m^2)cm + 2\beta m^2(1-m)^2(1+\theta c)
\end{aligned}$$

and H^{-1} denotes the inverse of the Hessian of h with respect to c and m, i.e.

$$H(c,m) := \begin{pmatrix} (1-m)/c(1-c-m) & 1/(1-c-m) \\ 1/(1-c-m) & (1-c)/m(1-c-m) \end{pmatrix} \tag{2.24}$$

and

$$H^{-1}(c,m) = \begin{pmatrix} c(1-c) & -cm \\ -cm & m(1-m) \end{pmatrix}.$$

In order to derive system (2.23) we have used the fact that

$$H^{-1}(c,m) \begin{pmatrix} u_x \\ v_x \end{pmatrix} = \begin{pmatrix} c_x \\ m_x \end{pmatrix}.$$

For $\theta = 0$ and arbitrary $\beta > 0$ the diffusion matrix B simplifies to

$$B = \begin{pmatrix} 2c^2(1-c)^2 + 2\beta c^2 m^2 & -2c^2(1-c)m - 2\beta c m^2(1-m) \\ -2c^2(1-c)m - 2\beta c m^2(1-m) & 2c^2 m^2 + 2\beta m^2(1-m)^2 \end{pmatrix}.$$

Obviously, it is symmetric and also positive definite if $c, m, c+m \in (0,1)$ which can be seen by using Sylvester's criterion since

$$\det(B) = \det(A)\det(H^{-1}) = (4\beta cm(1-c-m))(cm(1-c-m)) > 0.$$

For general θ and β the matrix B cannot be expected to be symmetric or positive semi-definite. However, assuming that $\theta \le \theta^* := 4/\sqrt{\beta}$ and $0 < c, m, c+m < 1$ it can be proven that B is positive definite. Let us therefore consider $(x,y)^\top \neq (0,0)^\top$, $x, y \in \mathbb{R}$. Then

$$\begin{aligned}
\begin{pmatrix} x \\ y \end{pmatrix}^\top B \begin{pmatrix} x \\ y \end{pmatrix} &= \begin{pmatrix} x \\ y \end{pmatrix}^\top (H^{-1}H)B(HH^{-1}) \begin{pmatrix} x \\ y \end{pmatrix} \\
&= (H^{-1}\begin{pmatrix} x \\ y \end{pmatrix})^\top HA(H^{-1}\begin{pmatrix} x \\ y \end{pmatrix}),
\end{aligned}$$

showing that the definiteness of B is equivalent to that of HA, where

$$H \cdot A = \begin{pmatrix} 2 & 0 \\ \beta\theta m & 2\beta(1+\theta c) \end{pmatrix}. \tag{2.25}$$

From $\theta \in (0, \theta^*]$ it follows that $4\sqrt{\beta(1+\theta c)} > \beta\theta m$ and hence, using Young's inequality,

$$\begin{aligned}\begin{pmatrix} x \\ y \end{pmatrix}^\top (HA) \begin{pmatrix} x \\ y \end{pmatrix} &= 2x^2 + xy\beta\theta m + 2y^2\beta(1+\theta c) \\ &\geq 4|x||y|\sqrt{\beta(1+\theta c)} + xy\beta\theta m > 0\end{aligned} \tag{2.26}$$

if neither x nor y is equal to 0. In that case the positivity of $\begin{pmatrix} x \\ y \end{pmatrix}^\top (HA) \begin{pmatrix} x \\ y \end{pmatrix}$ is also satisfied, of course. We remark that the bound θ^* has no influence on the definiteness of A.

This result can be strengthened: If $0 \leq \theta < 4/\sqrt{\beta}$, i.e. if the strict inequality holds, then there exists a positive constant $K_\theta < \min\{2, 2\beta\}$ depending on θ and β so that

$$(2 - K_\theta)(2\beta - K_\theta) \geq \frac{\theta^2\beta^2}{4}.$$

Applying Young's inequality again and the above relation, it follows that

$$\begin{aligned}(2 - K_\theta)x^2 + xy\beta\theta m + y^2(2\beta(1+\theta c) - K_\theta) \geq \\ 2|x||y|\sqrt{2\beta - K_\theta}\sqrt{2 - K_\theta} + xy\beta\theta m \geq \theta\beta|x||y| + xym\beta\theta \geq 0\end{aligned}$$

which is equivalent to

$$\begin{pmatrix} x \\ y \end{pmatrix}^\top (HA) \begin{pmatrix} x \\ y \end{pmatrix} = 2x^2 + xy\beta\theta m + 2y^2\beta(1+\theta c) \geq K_\theta(x^2 + y^2). \tag{2.27}$$

This property is important for our existence proof. In fact, it provides a priori estimates for the gradients of the variables when we exploit the entropy structure of the cross-diffusion system. More precisely, let $(c, m)^\top$ be an appropriate solution to (2.1)–(2.3). A formal computation, which is made rigorous in the proof of theorem 2.1, shows that for $t > 0$

$$\begin{aligned}\frac{dE(c(t), m(t))}{dt} + \int_\Omega \left(2c_x^2 + \beta\theta m c_x m_x + 2\beta(1+\theta c)m_x^2\right) d\lambda \\ = \int_\Omega \left(r_c(c,m) \ln \frac{c}{1-c-m} + r_m(c,m) \ln \frac{m}{1-c-m}\right) d\lambda.\end{aligned} \tag{2.28}$$

The right-hand side is bounded for all c, $m > 0$ with $c + m < 1$. As the integrand of the second term on the left-hand side is a positive definite quadratic form in c_x and m_x that satisfies inequality (2.27) if $\theta < \theta^*$, we obtain gradient estimates for c and m.

Now, let us formulate the main result of this chapter.

Theorem 2.1. *Let α, γ, $\delta \geq 0$, $\beta > 0$, $0 \leq \theta < 4/\sqrt{\beta}$ and let c_0, m_0 be real measurable functions defined on Ω that satisfy*

$$c_0 \geq 0, \;\; m_0 \geq 0, \quad c_0 + m_0 \leq 1 \;\; \textit{a.e. in } \Omega.$$

Then there exists a weak solution

$$c, m \in H^1_{\mathrm{loc}}(0, \infty; H^1(\Omega))$$

to (2.1)–(2.3) satisfying

$$c, m \geq 0 \;\; \textit{and} \;\; c + m \leq 1 \;\; \textit{a.e. in } \Omega \times (0, \infty).$$

Proof of Theorem 2.1

Step 1: Variable Transformation.

We start by assuming that there exists $\eta \in (0, 1)$ so that the initial data satisfy

$$c_0 \geq \eta, m_0 \geq \eta \;\text{ and }\; c_0 + m_0 \leq 1 - \eta \;\text{ a.e. in } \Omega. \tag{2.29}$$

More precisely, the functions c_0 and m_0 in (2.29) denote a sequence of measurable functions c_0^η respectively m_0^η that converge to the functions c_0 respectively m_0 given in theorem 2.1 for $\eta \to 0$. For the sake of convenience we omit the η in the following.

Next we consider system (2.1) after the change of variables (2.22), i.e. we investigate (2.23) subject to the boundary and initial conditions

$$u_x = v_x = 0 \;\text{ on } \partial\Omega, \;\; t > 0, \;\; u(0, .) = u_0, \quad v(0, .) = v_0 \;\text{ in } \Omega,$$

where

$$u_0 := \ln \frac{c_0}{1 - c_0 - m_0}, \;\; v_0 := \ln \frac{m_0}{1 - c_0 - m_0}.$$

Due to assumption (2.29) function u_0 and v_0 are defined on Ω a.e. and belong to $L^\infty(\Omega)$.

Step 2: Existence of a Time-Discrete Problem.

Let $T > 0$ be arbitrary but fixed and $\tau_m = \tau := T/m$ for $m \in \mathbb{N}$. We define the time steps $t_k := k\tau$ for $k = 0, \ldots, m$ and approximations of u and v at time t_k, i.e.

$$u_k := u(t_k, .), \quad v_k := v(t_k, .)$$

for $k = 0, \ldots, m$. Thus, we obtain the functions

$$c(u_k, v_k) = \frac{e^{u_k}}{1 + e^{u_k} + e^{v_k}}, \quad m(u_k, v_k) = \frac{e^{v_k}}{1 + e^{u_k} + e^{v_k}}.$$

Setting

$$c_{k-1} = c(u_{k-1}, v_{k-1}), \quad m_{k-1} = m(u_{k-1}, v_{k-1}),$$

we wish to solve the sequence of approximate elliptic problems in Ω for given functions u_{k-1}, $v_{k-1} \in L^\infty(\Omega)$, $1 \le k \le m$ and $\tau > 0$

$$\frac{1}{\tau}\begin{pmatrix} c(u_k, v_k) - c_{k-1} \\ m(u_k, v_k) - m_{k-1} \end{pmatrix} - \left(B(u_k, v_k) \begin{pmatrix} (u_k)_x \\ (v_k)_x \end{pmatrix} \right)_x = r(c(u_k, v_k), m(u_k, v_k)), \tag{2.30}$$

subject to the boundary conditions

$$(u_k)_x = (v_k)_x = 0 \text{ on } \partial\Omega. \tag{2.31}$$

Therefore, we consider the weak formulation of (2.30)–(2.31) and add ϵ-terms which ensure the uniform ellipticity of (2.30) with respect to (u_k, v_k), where $\epsilon > 0$ is an arbitrary but fixed regularisation parameter. In other words, we consider

$$\begin{aligned} &\frac{1}{\tau}\int_\Omega \begin{pmatrix} c(u_k, v_k) - c_{k-1} \\ m(u_k, v_k) - m_{k-1} \end{pmatrix} \begin{pmatrix} y \\ z \end{pmatrix} d\lambda + \\ &\int_\Omega \begin{pmatrix} y \\ z \end{pmatrix}_x^\top (B(u_k, v_k) + \epsilon I_2) \begin{pmatrix} u_k \\ v_k \end{pmatrix}_x + \epsilon \begin{pmatrix} u_k \\ v_k \end{pmatrix} \begin{pmatrix} y \\ z \end{pmatrix} d\lambda = \\ &\int_\Omega \begin{pmatrix} r_c(c(u_k, v_k), m(u_k, v_k)) \\ r_m(c(u_k, v_k), m(u_k, v_k)) \end{pmatrix} \begin{pmatrix} y \\ z \end{pmatrix} d\lambda \end{aligned} \tag{2.32}$$

for test functions y and z, where I_2 denotes the identity matrix in $\mathbb{R}^{2\times 2}$. In order to prove the existence of solutions we formulate

Lemma 2.2. *Let $(u_{k-1}, v_{k-1})^\top \in L^\infty(\Omega)^2$ and $0 \le \theta < 4/\sqrt{\beta}$. Then there exists a constant $0 < K_\theta < \min\{2, 2\beta\}$ depending only on β and θ and a solution $(u_k, v_k)^\top \in H^1(\Omega)^2$ to (2.32) satisfying*

$$\begin{aligned} E\left(c(u_k, v_k), m(u_k, v_k)\right) + \tau K_\theta \int_\Omega \left(c(u_k, v_k)_x^2 + m(u_k, v_k)_x^2\right) d\lambda \\ + \tau\epsilon \int_\Omega \left((u_k)_x^2 + (v_k)_x^2 + u_k^2 + v_k^2\right) d\lambda \\ \le E\left(c(u_{k-1}, v_{k-1}), m(u_{k-1}, v_{k-1})\right) + \frac{\tau}{e}(\alpha + \gamma + \delta). \end{aligned} \tag{2.33}$$

Proof. The idea of the proof is to apply the Leray-Schauder fixed-point theorem (see theorem B.5 in [73]). To this end, we linearise our problem first and solve it using the Lax-Milgram lemma. In other words, for $(\overline{u}, \overline{v})^\top \in L^\infty(\Omega)^2$ we show the existence of a unique solution $(u, v)^\top \in H^1(\Omega)^2$ to the linear problem

$$a((u, v), (y, z)) = F(y, z) \quad \text{for all } (y, z)^\top \in H^1(\Omega)^2, \tag{2.34}$$

where

$$a((u,v),(y,z)) := \int_\Omega \begin{pmatrix} y_x \\ z_x \end{pmatrix}^\top B(\overline{u},\overline{v}) \begin{pmatrix} u_x \\ v_x \end{pmatrix} d\lambda + \epsilon \int_\Omega (u_x y_x + v_x z_x + uy + vz)\, d\lambda$$

and

$$F(y,z) := -\frac{1}{\tau} \int_\Omega \begin{pmatrix} c(\overline{u},\overline{v}) - c_{k-1} \\ m(\overline{u},\overline{v}) - m_{k-1} \end{pmatrix} \begin{pmatrix} y \\ z \end{pmatrix} d\lambda + \int_\Omega r(c(\overline{u},\overline{v}), m(\overline{u},\overline{v})) \begin{pmatrix} y \\ z \end{pmatrix} d\lambda.$$

The a.e.-boundedness of $\overline{u}$, $\overline{v}$, u_{k-1} and v_{k-1} and the fact that they are measurable imply that the functions

$$0 < c(\overline{u},\overline{v}),\ \ m(\overline{u},\overline{v}),\ \ c(\overline{u},\overline{v}) + m(\overline{u},\overline{v}),\ \ c_{k-1},\ \ m_{k-1} < 1$$

are bounded a.e. and measurable, i.e. that they are elements of $L^\infty(\Omega)$. Thus, the matrix elements $b_{ij}(\overline{u},\overline{v})$ as well as $r_c(c(\overline{u},\overline{v}), m(\overline{u},\overline{v}))$, $r_m(c(\overline{u},\overline{v}), m(\overline{u},\overline{v}))$ belong to $L^\infty(\Omega)$ so that the bilinear form $a : H^1(\Omega)^2 \times H^1(\Omega)^2 \to \mathbb{R}$ and the linear functional $F : H^1(\Omega)^2 \to \mathbb{R}$ are well-defined due to Hölder's inequality. Obviously, a is a bilinear form and F a linear functional. In order to show that a is continuous let us consider $(u,v)^\top$, $(y,z)^\top \in H^1(\Omega)^2$. Then

$$|a((u,v),(y,z))| \leq$$

$$\|b_{11}(\overline{u},\overline{v}) + \epsilon\|_{L^\infty(\Omega)} \|u_x\|_{L^2(\Omega)} \|y_x\|_{L^2(\Omega)} + \|b_{12}(\overline{u},\overline{v})\|_{L^\infty(\Omega)} \|v_x\|_{L^2(\Omega)} \|y_x\|_{L^2(\Omega)} +$$

$$\|b_{21}(\overline{u},\overline{v})\|_{L^\infty(\Omega)} \|u_x\|_{L^2(\Omega)} \|z_x\|_{L^2(\Omega)} + \|b_{22}(\overline{u},\overline{v}) + \epsilon\|_{L^\infty(\Omega)} \|v_x\|_{L^2(\Omega)} \|z_x\|_{L^2(\Omega)} +$$

$$\epsilon \left(\|u\|_{L^2(\Omega)} \|y\|_{L^2(\Omega)} + \|v\|_{L^2(\Omega)} \|z\|_{L^2(\Omega)} \right) \leq$$

$$C(\beta,\theta,\epsilon) \left(\|u_x\|_{L^2(\Omega)} + \|v_x\|_{L^2(\Omega)} \right) \left(\|y_x\|_{L^2(\Omega)} + \|z_x\|_{L^2(\Omega)} \right) +$$

$$\epsilon \left(\|u\|_{L^2(\Omega)} + \|v\|_{L^2(\Omega)} \right) \left(\|y\|_{L^2(\Omega)} + \|z\|_{L^2(\Omega)} \right) \leq$$

$$(C(\beta,\theta,\epsilon) + \epsilon) \left(\| \begin{pmatrix} u \\ v \end{pmatrix} \|_{H^1(\Omega)^2} + \| \begin{pmatrix} y \\ z \end{pmatrix} \|_{H^1(\Omega)^2} \right),$$

where the positive constant $C(\beta,\theta,\epsilon)$ only depends on β, θ and ϵ. In a similar way we can show that F is continuous. For $(y,z)^\top \in H^1(\Omega)^2$, using the Cauchy-Schwarz inequality

$$|F(y,z)| \leq$$

$$\frac{1}{\tau} \left(\|c(\overline{u},\overline{v}) - c_{k-1}\|_{L^2(\Omega)} \|y\|_{L^2(\Omega)} + \|m(\overline{u},\overline{v}) - m_{k-1}\|_{L^2(\Omega)} \|z\|_{L^2(\Omega)} \right) +$$

$$\|r_c(c(\overline{u},\overline{v}), m(\overline{u},\overline{v}))\|_{L^2(\Omega)} \|y\|_{L^2(\Omega)} + \|r_m(c(\overline{u},\overline{v}), m(\overline{u},\overline{v}))\|_{L^2(\Omega)} \|z\|_{L^2(\Omega)} \leq$$

$$C(\alpha,\gamma,\delta,\tau) \| \begin{pmatrix} y \\ z \end{pmatrix} \|_{H^1(\Omega)^2},$$

where $C(\alpha, \gamma, \delta, \tau)$ is a positive constant depending on α, γ, δ and τ. The last condition that has to be satisfied is the coercivity of a. Therefore, we recall that

$$c(\overline{u}, \overline{v}), \;\; m(\overline{u}, \overline{v}), \;\; c(\overline{u}, \overline{v}) + m(\overline{u}, \overline{v}) \in (0, 1) \;\; \text{a.e.}$$

and that we have assumed $\theta < 4/\sqrt{\beta}$. Thus, it follows that $B(\overline{u}, \overline{v})$ is positive definite a.e. as we have seen above. In other words, using the definition

$$B(\overline{u}, \overline{v}) := A(c(\overline{u}, \overline{v}), m(\overline{u}, \overline{v})) \cdot H^{-1}(c(\overline{u}, \overline{v}), m(\overline{u}, \overline{v}))$$

and (2.26) we compute

$$\begin{aligned}
&\begin{pmatrix} u_x \\ v_x \end{pmatrix}^\top B(\overline{u}, \overline{v}) \begin{pmatrix} u_x \\ v_x \end{pmatrix} = \\
&\left(H(\overline{u}, \overline{v})^{-1} \begin{pmatrix} u_x \\ v_x \end{pmatrix} \right)^\top H(\overline{u}, \overline{v}) B(\overline{u}, \overline{v}) H(\overline{u}, \overline{v}) H(\overline{u}, \overline{v})^{-1} \begin{pmatrix} u_x \\ v_x \end{pmatrix} = \\
&\left(H(\overline{u}, \overline{v})^{-1} \begin{pmatrix} u_x \\ v_x \end{pmatrix} \right)^\top H(\overline{u}, \overline{v}) A(\overline{u}, \overline{v}) \left(H(\overline{u}, \overline{v})^{-1} \begin{pmatrix} u_x \\ v_x \end{pmatrix} \right) \geq 0
\end{aligned}$$

a.e. in Ω. This shows that a is coercive:

$$\begin{aligned}
a((u, v), (u, v)) &= \int_\Omega \begin{pmatrix} u_x \\ v_x \end{pmatrix}^\top B(\overline{u}, \overline{v}) \begin{pmatrix} u_x \\ v_x \end{pmatrix} d\lambda + \epsilon \int_\Omega \left(u_x^2 + v_x^2 + u^2 + v^2 \right) d\lambda \\
&\geq \epsilon \left(\|u\|^2_{H^1(\Omega)} + \|v\|^2_{H^1(\Omega)} \right) = \epsilon \| \begin{pmatrix} u \\ v \end{pmatrix} \|^2_{H^1(\Omega)^2}.
\end{aligned}$$

By the Lax-Milgram lemma, there exists a unique solution $(u, v)^\top \in H^1(\Omega)^2$ to (2.34).

Next, we define the fixed-point operator

$$S : L^\infty(\Omega)^2 \times [0, 1] \to L^\infty(\Omega)^2$$

by setting, for given $(\overline{u}, \overline{v})^\top \in L^\infty(\Omega)^2$ and $\sigma \in [0, 1]$

$$S(\overline{u}, \overline{v}, \sigma) = (u, v)^\top,$$

where $(u, v)^\top \in H^1(\Omega)^2$ is the solution to the linear problem

$$a((u, v), (y, z)) = \sigma F(y, z) \quad \text{for all } (y, z) \in H^1(\Omega)^2. \tag{2.35}$$

We notice that the operator S is well-defined due to the Lax-Milgram lemma respectively due to the uniqueness of the solution $(u, v)^\top \in H^1(\Omega)^2$ and that this solution is also an element of $L^\infty(\Omega)^2$ resulting from the compact embedding $H^1(\Omega) \hookrightarrow L^\infty(\Omega)$ in one space dimension. Because of this embedding S is also compact. Furthermore,

$$S(\overline{u}, \overline{v}, 0) = (0, 0)^\top$$

for all $(\overline{u},\overline{v})^\top \in L^\infty(\Omega)^2$ following from the coercivity of a. In order to show that S is continuous we consider a sequence of functions $(\overline{u_n},\overline{v_n},\sigma_n)^\top$, $n\in\mathbb{N}$, converging to $(\overline{u},\overline{v},\sigma)^\top$ in $(L^\infty(\Omega)^2\times\mathbb{R})$ for $n\to\infty$. We have to show that

$$S(\overline{u_n},\overline{v_n},\sigma_n)=(u_n,v_n)^\top \longrightarrow S(\overline{u},\overline{v},\sigma)=(u,v)^\top$$

in $L^\infty(\Omega)^2$. Therefore, we fix $(\overline{u_n},\overline{v_n},\sigma_n)$ and choose (u_n,v_n) as a test function in (2.35) so that we obtain

$$\int_\Omega \begin{pmatrix}(u_n)_x\\(v_n)_x\end{pmatrix}^\top B(\overline{u_n},\overline{v_n})\begin{pmatrix}(u_n)_x\\(v_n)_x\end{pmatrix} d\lambda +$$

$$\epsilon\int_\Omega ((u_n)_x)^2+((v_n)_x)^2+(u_n)^2+(v_n)^2 d\lambda =$$

$$-\frac{\sigma_n}{\tau}\int_\Omega \begin{pmatrix}c(\overline{u_n},\overline{v_n})-c_{k-1}\\ m(\overline{u_n},\overline{v_n})-m_{k-1}\end{pmatrix}\begin{pmatrix}u_n\\v_n\end{pmatrix} d\lambda+\sigma_n\int_\Omega r(c(\overline{u_n},\overline{v_n}),m(\overline{u_n},\overline{v_n}))\begin{pmatrix}u_n\\u_n\end{pmatrix} d\lambda.$$

From a being coercive it follows

$$\int_\Omega \begin{pmatrix}(u_n)_x\\(v_n)_x\end{pmatrix}^\top B(\overline{u_n},\overline{v_n})\begin{pmatrix}(u_n)_x\\(v_n)_x\end{pmatrix} d\lambda +$$
$$\epsilon\int_\Omega ((u_n)_x)^2+((v_n)_x)^2+(u_n)^2+(v_n)^2 d\lambda \geq \epsilon\| \begin{pmatrix}u_n\\v_n\end{pmatrix}\|^2_{H^1(\Omega)^2}.$$

Using the fact that for $a,b\in\mathbb{R}$ the inequality

$$\frac{a\cdot e^x+b\cdot e^y}{1+e^x+e^y}\geq -(|a|+|b|)$$

holds for all $x,y\in\mathbb{R}$ and that $\sigma_n\leq 1$ we obtain

$$-\frac{\sigma_n}{\tau}\int_\Omega \begin{pmatrix}c(\overline{u_n},\overline{v_n})-c_{k-1}\\ m(\overline{u_n},\overline{v_n})-m_{k-1}\end{pmatrix}\begin{pmatrix}u_n\\v_n\end{pmatrix} d\lambda \leq \frac{2}{\tau}\int_\Omega (|u_n|+|v_n|)\,d\lambda.$$

Estimating

$$\sigma_n\int_\Omega r(c(\overline{u_n},\overline{v_n}),m(\overline{u_n},\overline{v_n}))\begin{pmatrix}u_n\\u_n\end{pmatrix} d\lambda \leq (\alpha+\gamma+\delta)\int_\Omega (|u_n|+|v_n|)\,d\lambda$$

and applying Young's inequality we finally obtain

$$\|\begin{pmatrix}u_n\\v_n\end{pmatrix}\|_{H^1(\Omega)^2}\leq C(\epsilon,\tau,\alpha,\gamma,\delta),$$

where the constant $C(\epsilon, \tau, \alpha, \gamma, \delta) > 0$ depends on $\epsilon, \tau, \alpha, \gamma$ and δ. According to the Eberlein-Šmuljan theorem there exist (not relabeled) subsequences of $(u_n)_{n\in\mathbb{N}}$ and $(v_n)_{n\in\mathbb{N}}$ and $\hat{u}, \hat{v} \in H^1(\Omega)$, so that

$$u_n \rightharpoonup \hat{u}, \;\; v_n \rightharpoonup \hat{v} \tag{2.36}$$

in $H^1(\Omega)$ for $n \to \infty$. Because of the compact embedding $H^1(\Omega) \hookrightarrow L^\infty(\Omega)$ there exist furthermore (not relabeled) subsequences of $(u_n)_{n\in\mathbb{N}}$ and $(v_n)_{n\in\mathbb{N}}$ so that

$$u_n \longrightarrow \hat{u}, \;\; v_n \longrightarrow \hat{v}$$

holds in $L^\infty(\Omega)$. Here and in the following we consider w.l.o.g. the same subsequences. Next, we pass to the limit $n \to \infty$ in

$$\int_\Omega \begin{pmatrix} y_x \\ z_x \end{pmatrix}^\top B(\overline{u_n}, \overline{v_n}) \begin{pmatrix} (u_n)_x \\ (v_n)_x \end{pmatrix} d\lambda +$$

$$\epsilon \int_\Omega (u_n)_x y_x + (v_n)_x z_x + u_n y + v_n z \, d\lambda =$$

$$-\frac{\sigma_n}{\tau} \int_\Omega \begin{pmatrix} c(\overline{u_n}, \overline{v_n}) - c_{k-1} \\ m(\overline{u_n}, \overline{v_n}) - m_{k-1} \end{pmatrix} \begin{pmatrix} y \\ z \end{pmatrix} d\lambda + \int_\Omega r(c(\overline{u_n}, \overline{v_n}), m(\overline{u_n}, \overline{v_n})) \begin{pmatrix} y \\ z \end{pmatrix} d\lambda,$$

where $y, z \in H^1(\Omega)$. From $\overline{u_n} \to \overline{u}$ and $\overline{v_n} \to \overline{v}$ in $L^\infty(\Omega)$ it follows that

$$c(\overline{u_n}, \overline{v_n}) \longrightarrow c(\overline{u}, \overline{v}), \quad m(\overline{u_n}, \overline{v_n}) \longrightarrow m(\overline{u}, \overline{v}), \quad b_{ij}(\overline{u_n}, \overline{v_n}) \longrightarrow b_{ij}(\overline{u}, \overline{v})$$

for $i, j = 1, 2$ in $L^\infty(\Omega)$. The convergence (2.36) leads to

$$u_n \rightharpoonup \hat{u}, \quad v_n \rightharpoonup \hat{v}, \quad (u_n)_x \rightharpoonup \hat{u}_x, \quad (v_n)_x \rightharpoonup \hat{v}_x$$

in $L^2(\Omega)$. Using the fact, that for arbitrary sequences of functions $f_n \in L^\infty(\Omega)$, $g_n \in L^2(\Omega)$ satisfying

$$f_n \longrightarrow f \;\text{ in }\; L^\infty(\Omega) \;\text{ and }\; g_n \rightharpoonup g \;\text{ in }\; L^2(\Omega)$$

we have

$$f_n g_n \rightharpoonup fg \;\text{ in }\; L^2(\Omega)$$

we obtain altogether

$$\int_\Omega \begin{pmatrix} y_x \\ z_x \end{pmatrix}^\top B(\overline{u}, \overline{v}) \begin{pmatrix} \hat{u}_x \\ \hat{v}_x \end{pmatrix} d\lambda + \epsilon \int_\Omega \hat{u}_x y_x + \hat{v}_x z_x + \hat{u} y + \hat{v} z \, d\lambda =$$

$$-\frac{\sigma}{\tau} \int_\Omega \begin{pmatrix} c(\overline{u}, \overline{v}) - c_{k-1} \\ m(\overline{u}, \overline{v}) - m_{k-1} \end{pmatrix} \begin{pmatrix} y \\ z \end{pmatrix} d\lambda + \sigma \int_\Omega r(c(\overline{u}, \overline{v}), m(\overline{u}, \overline{v})) \begin{pmatrix} y \\ z \end{pmatrix} d\lambda,$$

for $y, z \in H^1(\Omega)$. Thus, $S(\overline{u}, \overline{v}, \sigma) = (\hat{u}, \hat{v})^\top$ implying that $\hat{u} = u$ and $\hat{v} = v$. This shows that S is continuous.

It remains to prove that there exists a constant $K > 0$ such that for any $(u, v, \sigma)^\top \in L^\infty(\Omega)^2 \times [0, 1]$ satisfying $S(u, v, \sigma) = (u, v)^\top$, the estimate

$$\| \begin{pmatrix} u \\ v \end{pmatrix} \|_{L^\infty(\Omega)^2} \leq K$$

holds. For $\sigma = 0$ this inequality is clear. In order to prove this bound for $\sigma \neq 0$, we use the test function $(u, v)^\top$ in (2.35), yielding

$$\begin{aligned} &\frac{\sigma}{\tau} \int_\Omega \begin{pmatrix} c(u,v) - c_{k-1} \\ m(u,v) - m_{k-1} \end{pmatrix} \cdot \begin{pmatrix} u \\ v \end{pmatrix} d\lambda + \int_\Omega \begin{pmatrix} u_x \\ v_x \end{pmatrix}^\top B(u,v) \begin{pmatrix} u_x \\ v_x \end{pmatrix} d\lambda \\ &+ \epsilon \int_\Omega (u_x^2 + v_x^2 + u^2 + v^2) d\lambda = \sigma \int_\Omega r(c(u,v), m(u,v)) \cdot \begin{pmatrix} u \\ v \end{pmatrix} d\lambda. \end{aligned} \tag{2.37}$$

Setting $c = c(u, v)$ and $m = m(u, v)$ we consider the discrete entropy density

$$h(c, m) := c(\ln(c) - 1) + m(\ln(m) - 1) + (1 - c - m)(\ln(1 - c - m) - 1)$$

that is defined a.e.. Interpreting h as a real function defined on the open unit triangle $D := \{(x_1, x_2)^\top \in \mathbb{R}^2 : 0 < x_1, x_2, x_1 + x_2 < 1\}$, using Taylor's theorem and exploiting the convexity h with respect to (x_1, x_2), where its Hessian is defined as in (2.24), we obtain

$$h(y) - h(x) \leq \nabla h(y)(y - x) = \begin{pmatrix} \ln\left(\frac{y_1}{1-y_1-y_2}\right) \\ \ln\left(\frac{y_2}{1-y_1-y_2}\right) \end{pmatrix} (y - x)$$

for $x, y \in D$. Thus,

$$h(c, m) - h(c_{k-1}, m_{k-1}) \leq \nabla h(c, m) \cdot \begin{pmatrix} c - c_{k-1} \\ m - m_{k-1} \end{pmatrix}$$

a.e.. By (2.22), $\nabla h(c, m) = (u, v)$ and hence, the first term on the left-hand side of (2.37) can be estimated as

$$\frac{\sigma}{\tau} \int_\Omega \begin{pmatrix} c - c_{k-1} \\ m - m_{k-1} \end{pmatrix} \cdot \begin{pmatrix} u \\ v \end{pmatrix} d\lambda \geq \frac{\sigma}{\tau} \left(E(c, m) - E(c_{k-1}, m_{k-1}) \right).$$

Thus, we obtain

$$-\frac{\sigma}{\tau} \int_\Omega \begin{pmatrix} c - c_{k-1} \\ m - m_{k-1} \end{pmatrix} \cdot \begin{pmatrix} u \\ v \end{pmatrix} d\lambda \leq \frac{3}{\tau}. \tag{2.38}$$

Here, we have used the inequality

$$x \cdot \ln(x) \geq x - 1, \;\; x \geq 0.$$

We turn to the second integral on the left-hand side of (2.37). Therefore, we recall that Ω is a real open interval implying that $H^1(\Omega)$-functions are absolutely continuous, i.e. differentiable a.e.. Thus, we can apply classical derivation rules to the functions a.e., showing that $c(u,v)$ and $m(u,v)$ are elements of $H^1(\Omega)$ and because of (2.22), we have

$$\begin{pmatrix} u_x \\ v_x \end{pmatrix} = H(c,m) \begin{pmatrix} c_x \\ m_x \end{pmatrix}.$$

Therefore, in view of $B(u,v) = A(c,m) \cdot H(c,m)^{-1}$ and (2.25), we find that the second integral on the left-hand side of (2.37) equals

$$\begin{aligned} &\int\limits_\Omega \begin{pmatrix} c_x \\ m_x \end{pmatrix}^\top H(c,m)B(u,v)H(c,m) \begin{pmatrix} c_x \\ m_x \end{pmatrix} d\lambda = \\ &\int\limits_\Omega \begin{pmatrix} c_x \\ m_x \end{pmatrix}^\top H(c,m) \cdot A(c,m) \begin{pmatrix} c_x \\ m_x \end{pmatrix} d\lambda = \\ &\int\limits_\Omega \left(2c_x^2 + \beta\theta m c_x m_x + 2\beta(1+\theta c)m_x^2\right) d\lambda. \end{aligned}$$

By (2.27) there exists a constant $K_\theta > 0$ depending on θ (and β) such that

$$\int\limits_\Omega \left(2c_x^2 + \beta\theta m c_x m_x + 2\beta(1+\theta c)m_x^2\right) d\lambda \geq K_\theta \int\limits_\Omega (c_x^2 + m_x^2) d\lambda.$$

Here, we have used the properties c, $m > 0$ and $c + m < 1$ holding a.e. and the strict inequality $0 \leq \theta < 4/\sqrt{\beta}$.

It remains to estimate the right-hand side of (2.37). Using

$$-1/e \leq x \ln x \leq 0$$

for all $0 \leq x \leq 1$ and

$$0 < c, \; m, \; 1 - c - m < 1 \;\text{ a.e.}$$

as well as

$$\ln(c), \;\; \ln(m), \;\; \ln(1-c-m) < 0 \;\text{ a.e.},$$

we find that

$$\begin{aligned} r(c(u,v),m(u,v)) \cdot \begin{pmatrix} u \\ v \end{pmatrix} &= (\gamma c(1-c-m) - \delta c) \ln \frac{c}{1-c-m} \\ &\quad + \alpha cm(1-c-m) \ln \frac{m}{1-c-m} \\ &= \gamma (c \log c)(1-c-m) \\ &\quad - \gamma c(1-c-m) \ln(1-c-m) \\ &\quad - \delta c \ln c + \delta c \ln(1-c-m) \\ &\quad + \alpha (m \ln m) c(1-c-m) \\ &\quad - \alpha cm(1-c-m) \ln(1-c-m) \\ &\leq (\alpha + \gamma + \delta) e^{-1} \end{aligned}$$

a.e.. Altogether, we estimate (2.37) as

$$\begin{aligned} &\sigma E(c,m) + \tau K_\theta \int_\Omega (c_x^2 + m_x^2) d\lambda + \tau \epsilon \int_\Omega (u_x^2 + v_x^2 + u^2 + v^2) d\lambda \\ &\qquad \leq \sigma E(c_{k-1}, m_{k-1}) + \frac{\sigma \tau}{e} (\alpha + \gamma + \delta). \end{aligned}$$

Dividing this inequality by $\sigma \neq 0$ we can deduce

$$\begin{aligned} &E(c,m) + \tau K_\theta \int_\Omega (c_x^2 + m_x^2) d\lambda + \tau \epsilon \int_\Omega (u_x^2 + v_x^2 + u^2 + v^2) d\lambda \\ &\qquad \leq E(c_{k-1}, m_{k-1}) + \frac{\tau}{e} (\alpha + \gamma + \delta). \end{aligned}$$

This shows (2.33). Furthermore, we obtain, using (2.38),

$$\left(\|u\|^2_{H^1(\Omega)} + \|v\|^2_{H^1(\Omega)} \right) \leq C(\alpha, \gamma, \delta, \epsilon, \tau),$$

where $C(\alpha, \gamma, \delta, \epsilon, \tau)$ is a positive constant depending on $\alpha, \gamma, \delta, \epsilon$ and τ. Thus, u and v are bounded in $H^1(\Omega)$, which provides the desired uniform estimate in $L^\infty(\Omega)^2$. We remark that we do not need the estimate of the second integral on the left-hand side of (2.37) here in order to show that $(u,v)^\top$ is bounded as we can use the coercivity of a instead. However, this estimate is needed in the following. The assumptions of the Leray-Schauder fixed-point theorem are verified, proving the existence of a fixed point of $S(\cdot, 1)$, which solves (2.32). ❑

Step 3: Piecewise Constant Functions in Time and Uniform Estimates.

Let $(u_k, v_k)^\top$ be a weak solution to (2.32), $k \in \{1, \ldots, m\}$, whose existence is guaranteed by lemma 2.2. We set $c_k = c(u_k, v_k)$, $m_k = m(u_k, v_k)$ and define the piecewise constant functions in time

$$u^{(\tau)}(t,x) := \begin{cases} u_0(x), & t = 0,\ x \in \Omega \\ u_k(x), & t \in ((k-1)\tau, k\tau],\ k \in \{1, \ldots, m\},\ x \in \Omega \end{cases}$$

and

$$v^{(\tau)}(t,x) := \begin{cases} v_0(x), & t=0,\ x\in\Omega \\ v_k(x), & t\in((k-1)\tau,k\tau],\ k\in\{1,\dots,m\},\ x\in\Omega \end{cases}$$

such as

$$\begin{aligned} c^{(\tau)}(t,x) :&= \left(\frac{e^{u^{(\tau)}}}{1+e^{u^{(\tau)}}+e^{v^{(\tau)}}}\right)(t,x) \\ &= \begin{cases} c_0(x), & t=0,\ x\in\Omega \\ c_k(x), & t\in((k-1)\tau,k\tau],\ k\in\{1,\dots,m\},\ x\in\Omega \end{cases} \end{aligned}$$

and

$$\begin{aligned} m^{(\tau)}(t,x) :&= \left(\frac{e^{v^{(\tau)}}}{1+e^{u^{(\tau)}}+e^{v^{(\tau)}}}\right)(t,x) \\ &= \begin{cases} m_0(x), & t=0,\ x\in\Omega \\ m_k(x), & t\in((k-1)\tau,k\tau],\ k\in\{1,\dots,m\},\ x\in\Omega \end{cases} \end{aligned}$$

for $t\in[0,T]$ and $x\in\Omega$. We notice that the functions $u^{(\tau)}$, $v^{(\tau)}$, $c^{(\tau)}$ and $m^{(\tau)}$ depend not only on τ but also on η and ϵ. Furthermore, we introduce the shift operator

$$s_\tau(f^{(\tau)})(t,x) := \begin{cases} f_0(x), & t\in(0,\tau],\ x\in\Omega \\ f^{(\tau)}(t-\tau,x), & t\in(\tau,T],\ x\in\Omega \end{cases} \tag{2.39}$$

and the discrete time derivative

$$D_\tau(f^{(\tau)})(t,x) := \left(f^{(\tau)}(t,x) - s_\tau(f^{(\tau)})(t,x)\right)/\tau, \tag{2.40}$$

where $f=c,m$ and $t\in(0,T)$, $x\in\Omega$. Then $(c^{(\tau)},m^{(\tau)})^\top$ solves

$$\begin{pmatrix} D_\tau(c^{(\tau)}) \\ D_\tau(m^{(\tau)}) \end{pmatrix} - \left(A(c^{(\tau)},m^{(\tau)})\begin{pmatrix} c_x^{(\tau)} \\ m_x^{(\tau)} \end{pmatrix}\right)_x - \epsilon\begin{pmatrix} u_{xx}^{(\tau)}-u^{(\tau)} \\ v_{xx}^{(\tau)}-v^{(\tau)} \end{pmatrix} = r(c^{(\tau)},m^{(\tau)})$$

in $t\in(0,T)$, $x\in\Omega$ in the sense of distributions. More precisely, we know that

$$\begin{aligned} &-\int_0^T \left\langle \begin{pmatrix} D_\tau(c^{(\tau)}) \\ D_\tau(m^{(\tau)}) \end{pmatrix}(t), \begin{pmatrix} y \\ z \end{pmatrix}(t) \right\rangle_{H^1(\Omega)} d\lambda(t) + \\ &\qquad \int_0^T\int_\Omega \begin{pmatrix} r_c(c^{(\tau)},m^{(\tau)}) \\ r_m(c^{(\tau)},m^{(\tau)}) \end{pmatrix}\begin{pmatrix} y \\ z \end{pmatrix} d\lambda d\lambda(t) = \\ &\int_0^T\int_\Omega \left(A(c^{(\tau)},m^{(\tau)})\begin{pmatrix} c^{(\tau)} \\ m^{(\tau)} \end{pmatrix}_x\right)\begin{pmatrix} y \\ z \end{pmatrix}_x d\lambda d\lambda(t) + \end{aligned} \tag{2.41}$$

$$\epsilon \int_0^T \int_\Omega \begin{pmatrix} u^{(\tau)} \\ v^{(\tau)} \end{pmatrix} \begin{pmatrix} y \\ z \end{pmatrix} + \begin{pmatrix} u^{(\tau)} \\ v^{(\tau)} \end{pmatrix}_x \begin{pmatrix} y \\ z \end{pmatrix}_x d\lambda d\lambda(t)$$

holds for $y, z \in L^2(0,T;H^1(\Omega))$, where the integrand of the first term on the left-hand side has to be interpreted as the sum of the linear functionals. The discrete entropy inequality (2.33) can be solved recursively to yield

$$\begin{aligned} E(c_k, m_k) + \tau K_\theta \sum_{j=1}^k \int_\Omega \left((c_j)_x^2 + (m_j)_x^2\right) d\lambda \\ + \tau\epsilon \sum_{j=1}^k \int_\Omega \left((u_j)_x^2 + (v_j)_x^2 + u_j^2 + v_j^2\right) d\lambda \\ \le E(c_0, m_0) + \frac{T}{e}(\alpha + \gamma + \delta), \quad k = 1, \dots, m, \end{aligned} \tag{2.42}$$

where $T = \tau m$. The definition of $c^{(\tau)}$ and the fact that the functions c_k are bounded a.e. by 1 for $k = 1, \dots, m$ due to the variable transformation lead immediately to the estimate

$$\|c^{(\tau)}\|_{L^\infty(0,T;L^\infty(\Omega))} = \operatorname{ess\,sup}_{t\in(0,T)} \|c^{(\tau)}(t)\|_{L^\infty(\Omega)} < 1.$$

From this and (2.42) it follows that

$$\begin{aligned} \|c^{(\tau)}\|^2_{L^2(0,T;H^1(\Omega))} &= \sum_{j=1}^m \tau \|c_j\|^2_{H^1(\Omega)} \\ &= \sum_{j=1}^m \tau \|c_j\|^2_{L^2(\Omega)} + \sum_{j=1}^m \tau \|(c_j)_x\|^2_{L^2(\Omega)} \\ &\le C(T, \alpha, \gamma, \delta, \beta, \theta). \end{aligned}$$

Furthermore, (2.42) leads to

$$\epsilon \|u^{(\tau)}\|^2_{L^2(0,T;H^1(\Omega))} = \epsilon \sum_{j=1}^m \tau \|u_j\|^2_{H^1(\Omega)} \le C(T, \alpha, \gamma, \delta, \beta, \theta),$$

where $C(T, \alpha, \gamma, \delta, \beta, \theta) > 0$ depends on $T, \alpha, \gamma, \delta, \beta$ and θ. Analogue results can be shown for $m^{(\tau)}$ respectively $v^{(\tau)}$. Thus, we have proven the following

Lemma 2.3. *The following uniform bounds hold:*

$$\begin{aligned} \|c^{(\tau)}\|_{L^2(0,T;H^1(\Omega))} + \|m^{(\tau)}\|_{L^2(0,T;H^1(\Omega))} &\le K, \\ \|c^{(\tau)}\|_{L^\infty(0,T;L^\infty(\Omega))} + \|m^{(\tau)}\|_{L^\infty(0,T;L^\infty(\Omega))} &\le K, \\ \sqrt{\epsilon}\|u^{(\tau)}\|_{L^2(0,T;H^1(\Omega))} + \sqrt{\epsilon}\|v^{(\tau)}\|_{L^2(0,T;H^1(\Omega))} &\le K, \end{aligned}$$

where $K > 0$ is here and in the following a generic constant independent of τ, ϵ and η.

We also need uniform estimates for the discrete time derivatives of $c^{(\tau)}$ and $m^{(\tau)}$.

Lemma 2.4. *The following uniform bounds hold:*

$$\|D_\tau(c^{(\tau)})\|_{L^2(0,T;(H^1(\Omega))')} + \|D_\tau(m^{(\tau)})\|_{L^2(0,T;(H^1(\Omega))')} \leq K.$$

Proof. Let $\phi \in L^2(0,T;H^1(\Omega))$. Then, by (2.41), the Hölder's inequality and the bounds on $c^{(\tau)}$, $m^{(\tau)}$ as well as on $\sqrt{\epsilon}u^{(\tau)}$

$$\left| \int_0^T \left\langle D_\tau(c^{(\tau)})(t), \phi(t) \right\rangle_{H^1(\Omega)} d\lambda(t) \right| \leq$$

$$\left| -\int_0^T \int_\Omega \left(2c^{(\tau)}(1-c^{(\tau)})c_x^{(\tau)} - \beta\theta c^{(\tau)}(m^{(\tau)})^2 c_x^{(\tau)} \right) \phi_x d\lambda d\lambda(t) \right| +$$

$$\left| \int_0^T \int_\Omega \left(2\beta c^{(\tau)} m^{(\tau)}(1+\theta c^{(\tau)}) m_x^{(\tau)} \right) \phi_x d\lambda d\lambda(t) \right| +$$

$$\left| -\epsilon \int_0^T \int_\Omega \left(u_x^{(\tau)}\phi_x + u^{(\tau)}\phi \right) d\lambda d\lambda(t) \right| +$$

$$\left| \int_0^T \int_\Omega \left(\gamma c^{(\tau)}(1-c^{(\tau)}-m^{(\tau)}) - \delta c^{(\tau)} \right) \phi d\lambda d\lambda(t) \right| \leq$$

$$\epsilon \|u^{(\tau)}\|_{L^2(0,T;L^2(\Omega))} \|\phi\|_{L^2(0,T;L^2(\Omega))} + \epsilon \|u_x^{(\tau)}\|_{L^2(0,T;L^2(\Omega))} \|\phi_x\|_{L^2(0,T;L^2(\Omega))} +$$

$$C(\beta,\theta) \|c_x^{(\tau)}\|_{L^2(0,T;L^2(\Omega))} \|\phi_x\|_{L^2(0,T;L^2(\Omega))} +$$

$$C(\beta,\theta) \|m_x^{(\tau)}\|_{L^2(0,T;L^2(\Omega))} \|\phi_x\|_{L^2(0,T;L^2(\Omega))} + C(\gamma,\delta) \|\phi\|_{L^2(0,T;L^2(\Omega))} \leq$$

$$C(T,\alpha,\gamma,\delta,\beta,\theta) \|\phi\|_{L^2(0,T;H^1(\Omega))} + 2\epsilon \|u^{(\tau)}\|_{L^2(0,T;H^1(\Omega))} \|\phi\|_{L^2(0,T;H^1(\Omega))} =$$

$$C(T,\alpha,\gamma,\delta,\beta,\theta) \|\phi\|_{L^2(0,T;H^1(\Omega))} + 2\sqrt{\epsilon}\sqrt{\epsilon} \|u^{(\tau)}\|_{L^2(0,T;H^1(\Omega))} \|\phi\|_{L^2(0,T;H^1(\Omega))} \leq$$

$$C(T,\alpha,\gamma,\delta,\beta,\theta) \|\phi\|_{L^2(0,T;H^1(\Omega))},$$

where we have assumed that $\epsilon < 1$. Analogously,

$$\left| \int_0^T \left\langle D_\tau(m^{(\tau)})(t), \phi(t) \right\rangle_{H^1(\Omega)} d\lambda(t) \right| \leq$$

$$\left| -\int_0^T \int_\Omega \left(-2c^{(\tau)} m^{(\tau)} c_x^{(\tau)} + \beta\theta(1-m^{(\tau)})(m^{(\tau)})^2 c_x^{(\tau)} \right) \phi_x d\lambda d\lambda(t) \right| +$$

$$\left| \int_0^T \int_\Omega \left(2\beta m^{(\tau)}(1-m^{(\tau)})(1+\theta c^{(\tau)}) m_x^{(\tau)} \right) \phi_x d\lambda d\lambda(t) \right| +$$

$$\left| -\epsilon \int_0^T \int_\Omega \left(v_x^{(\tau)} \phi_x + v^{(\tau)} \phi \right) d\lambda d\lambda(t) \right| +$$

$$\left| \int_0^T \int_\Omega \alpha c^{(\tau)} m^{(\tau)} (1 - c^{(\tau)} - m^{(\tau)}) \phi d\lambda d\lambda(t) \right| \leq$$

$$\epsilon \|v^{(\tau)}\|_{L^2(0,T;L^2(\Omega))} \|\phi\|_{L^2(0,T;L^2(\Omega))} + \epsilon \|v_x^{(\tau)}\|_{L^2(0,T;L^2(\Omega))} \|\phi_x\|_{L^2(0,T;L^2(\Omega))} +$$

$$C(\beta,\theta) \|c_x^{(\tau)}\|_{L^2(0,T;L^2(\Omega))} \|\phi_x\|_{L^2(0,T;L^2(\Omega))} +$$

$$C(\beta,\theta) \|m_x^{(\tau)}\|_{L^2(0,T;L^2(\Omega))} \|\phi_x\|_{L^2(0,T;L^2(\Omega))} + C(\alpha) \|\phi\|_{L^2(0,T;L^2(\Omega))} \leq$$

$$C(T,\alpha,\gamma,\delta,\beta,\theta) \|\phi\|_{L^2(0,T;H^1(\Omega))} + 2\epsilon \|v^{(\tau)}\|_{L^2(0,T;H^1(\Omega))} \|\phi\|_{L^2(0,T;H^1(\Omega))} =$$

$$C(T,\alpha,\gamma,\delta,\beta,\theta) \|\phi\|_{L^2(0,T;H^1(\Omega))} + 2\sqrt{\epsilon}\sqrt{\epsilon} \|v^{(\tau)}\|_{L^2(0,T;H^1(\Omega))} \|\phi\|_{L^2(0,T;H^1(\Omega))} \leq$$

$$C(T,\alpha,\gamma,\delta,\beta,\theta) \|\phi\|_{L^2(0,T;H^1(\Omega))},$$

where C denotes a generic constant being dependent on the respective constants. ❑

Step 4: The Limit $(\epsilon,\tau,\eta) \to 0$.

Before passing to the limit of $\epsilon \to 0$ and $\tau \to 0$ we set $\epsilon = \tau < 1$ and remark that the convergence $\tau \to 0$ is equivalent to $m \to \infty$. Thus, $c^{(\tau)}$ and $m^{(\tau)}$ denote sequences (and not nets) of functions. In the following we will choose w.l.o.g. same subsequences and we will not relabel them.

Lemma 2.3 and lemma 2.4 allow us to apply the Aubin lemma in the version that can be found in [31] as the embedding

$$H^1(\Omega) \hookrightarrow L^2(\Omega)$$

is continuous and the embedding

$$L^2(\Omega) \hookrightarrow (H^1(\Omega))'$$

is compact. Thus, we can conclude that $c^{(\tau)}$ and $m^{(\tau)}$ are relatively compact in $L^2(0,T;L^2(\Omega))$, i.e. there exist subsequences of $c^{(\tau)}$ respectively $m^{(\tau)}$ and functions c respectively m that are elements of $L^2(0,T;L^2(\Omega))$ such that, as $\tau \to 0$,

$$c^{(\tau)} \to c, \quad m^{(\tau)} \to m \quad \text{strongly in } L^2(0,T;L^2(\Omega)).$$

As $L^p(0,T;L^p(\Omega))$ can be identified by $L^p(Q_T)$ for $p \in [1,\infty)$ (see [67]) there exist subsequences so that

$$c^{(\tau)} \longrightarrow c, \quad m^{(\tau)} \longrightarrow m$$

a.e. in Q_T implying that

$$0 \leq c, \;\; m, \;\; c+m \leq 1$$

a.e. in $Q_T := (0,T) \times \Omega$. We remark that we lose the strict inequalities for c and m here.

As $c^{(\tau)}$ and $m^{(\tau)}$ are uniformly bounded in $L^\infty(0,T;L^\infty(\Omega)) \subseteq L^p(0,T;L^p(\Omega))$ for $p = [1,\infty)$ and because of the a.e.-convergence of the sequences in Q_T we can deduce that

$$c^{(\tau)} \to c, \;\; m^{(\tau)} \to m \;\; \text{ strongly in } L^p(0,T;L^p(\Omega)) \;\; \text{ for all } 1 \leq p < \infty.$$

See [23] for a general formulation of this result and a reference of its proof. Arguing in a similar way, it can be shown that

$$\begin{aligned} a_{ij}(c^{(\tau)}, m^{(\tau)}) &\longrightarrow a_{ij}(c,m), \\ r_c(c^{(\tau)}, m^{(\tau)}) &\longrightarrow r_c(c,m), \\ r_m(c^{(\tau)}, m^{(\tau)}) &\longrightarrow r_m(c,m) \end{aligned}$$

strongly in $L^p(0,T;L^p(\Omega))$ for $i,j = 1,2$ and $p \in [1,\infty)$.

Moreover, because of lemma 2.3 and the Eberlein-Šmuljan theorem, up to subsequences,

$$c^{(\tau)} \rightharpoonup c, \quad m^{(\tau)} \rightharpoonup m \quad \text{ weakly in } L^2(0,T;H^1(\Omega)).$$

Thus,

$$c_x^{(\tau)} \rightharpoonup c_x, \quad m_x^{(\tau)} \rightharpoonup m_x \quad \text{ weakly in } L^2(0,T;L^2(\Omega))$$

and

$$\begin{aligned} a_{11}(c^{(\tau)}, m^{(\tau)}) c_x^{(\tau)} &\rightharpoonup a_{11}(c,m) c_x, \\ a_{12}(c^{(\tau)}, m^{(\tau)}) m_x^{(\tau)} &\rightharpoonup a_{12}(c,m) m_x, \\ a_{21}(c^{(\tau)}, m^{(\tau)}) c_x^{(\tau)} &\rightharpoonup a_{21}(c,m) c_x, \\ a_{22}(c^{(\tau)}, m^{(\tau)}) m_x^{(\tau)} &\rightharpoonup a_{22}(c,m) m_x, \end{aligned}$$

weakly in $L^1(0,T;L^1(\Omega))$. As these sequences are uniformly bounded in $L^2(0,T;L^2(\Omega))$ the above convergences also hold in $L^2(0,T;L^2(\Omega))$.

Furthermore, due to lemma 2.3, for $\epsilon \to 0$

$$\epsilon u^{(\tau)} = \sqrt{\epsilon}\sqrt{\epsilon} u^{(\tau)} \to 0, \;\; \epsilon v^{(\tau)} = \sqrt{\epsilon}\sqrt{\epsilon} v^{(\tau)} \to 0 \quad \text{ strongly in } L^2(0,T;H^1(\Omega)).$$

From lemma 2.4 it follows

$$D_\tau(c^{(\tau)}) \rightharpoonup c_t, \quad D_\tau(m^{(\tau)}) \rightharpoonup m_t \quad \text{weakly in } L^2(0,T;(H^1(\Omega))').$$

Altogether, these convergence results are sufficient to pass to the limit $\tau = \epsilon \to 0$ in (2.41), so that we obtain

$$\int_0^T \left\langle \begin{pmatrix} c_t \\ m_t \end{pmatrix}(t), \begin{pmatrix} y \\ z \end{pmatrix}(t) \right\rangle_{H^1(\Omega)} d\lambda(t) +$$

$$\int_0^T \int_\Omega \left(A(c,m) \begin{pmatrix} c \\ m \end{pmatrix}_x \right) \begin{pmatrix} y \\ z \end{pmatrix}_x d\lambda d\lambda(t) =$$

$$\int_0^T \int_\Omega \begin{pmatrix} r_c(c,m) \\ r_m(c,m) \end{pmatrix} \begin{pmatrix} y \\ z \end{pmatrix} d\lambda d\lambda(t),$$

where $y, z \in L^2(0,T;H^1(\Omega))$. This shows that $(c,m)^\top$ is a weak solution to (2.1)–(2.3). The initial conditions are satisfied as

$$c^{(\tau)} \to c, \quad m^{(\tau)} \to m$$

in $C^0([0,1];(H^1(\Omega))')$. However, the initial data such as the solution function $(c,m)^\top$ still depend on η. In view of the uniform bounds above we can perform the limit $\eta \to 0$ in the initial data. This concludes the proof since T has been chosen arbitrarily.

Remark.

1. The method of our proof can be extended in principle to several space dimensions as shown for example in [25], where the dimension of the considered domain is less than or equal to 3, or in [24], where arbitrary space dimensions are allowed. In this paper the method of Galerkin approximation is used. We consider the case of one space dimension only, since this is the situation of the original model in [49].

2. The functional $E\left(c(u_k,v_k), m(u_k,v_k)\right)$ used in lemma 2.2 for $k = 0,\dots,m$ is called the *discrete entropy* and inequality (2.33) is called the *discrete entropy inequality.*

3. In order to prove the discrete entropy inequality we have assumed that $\theta \in [0,\theta^*)$ so that the matrix B becomes positive definite. For general $\theta > \theta^*$ and $\beta > 0$ counterexamples can be constructed showing that B is not even positive semi-definite anymore. Thus, we need this bound in order to apply our method. Of course, the question whether this bound is optimal or not remains open.

2.4 Numerical Results

In this section we investigate the tumour growth model numerically using the scaling of Jackson and Byrne, i.e. we investigate (2.18)–(2.20), where we set

$$\begin{pmatrix} r_c^{\mathrm{JB}}(c,m) \\ r_m^{\mathrm{JB}}(c,m) \end{pmatrix} := \begin{pmatrix} c(1-c-m)-\delta c \\ \alpha c m(1-c-m) \end{pmatrix}. \tag{2.43}$$

In the experiments we concentrate on the behaviour of the entropy production density since the dependence of the system on the model parameters has been extensively studied by Jackson and Byrne in [49]. Nevertheless, we want to summarise their results briefly.

In order to test the expansive growth hypothesis and the foreign body hypothesis by means of their model Jackson and Byrne choose the parameters α and θ appropriately. More precisely, assuming that capsule formation is a passive reaction of the host, they choose

$$\alpha = 0, \;\; \beta_m, \theta > 0,$$

where they suppose

$$\alpha > 0, \;\; \theta = 0$$

to obtain a model supporting the foreign body hypothesis. Generally, they choose all five parameter values in such a way that the resulting simulations coincide with experimentally observed behaviour finding out that $\alpha < 1$ and $\theta >> 1$ are realistic parameter values. Furthermore, they set

$$\delta = 0.35, \;\; \beta_m = 0.0015$$

in most of their simulations. Their numerical results, regarding the expansive growth hypothesis, show that the tumour grows into the surrounding tissue with constant speed and a sharp leading edge. The ECM forms a capsule at the migrating tumour front leading to a peak in the ECM volume fraction in the simulations whose height and width are rather constant in time. The peak values can be influenced by the choice of θ. We observe that the height of the capsule such as the height of the peak becomes smaller for smaller θ but that the speed of tumour growth increases. Varying the parameter β_c shows that the leading edge of the tumour and the ECM capsule respectively the peak become smoother for smaller values. Setting $\alpha \neq 0$ in these experiments, i.e. assuming that both theories describe the capsule formation phenomenon leads to an additional increase of ECM within the tumour constraining its growth. Assuming that capsule formation is caused by an active response of the body no peaks can be observed in the plots and there is no capsule formation. Moreover, in contrast to the expansive growth hypothesis, the numerical results show accumulation of ECM within the tumour, suppressing tumour growth, which increases for greater values of α.

We discretise system (2.18) using finite differences in space and the implicit or explicit Euler method in time.

The Neumann boundary conditions are discretised in such a way that, in the absence of production rates, the approximated total volume fractions $\int_\Omega c dx$ and $\int_\Omega m dx$ are exactly constant in time.

It turns out that the discretisation of the formulation (2.18) has stability problems due to the restrictions $0 \leq c,\, m \leq 1$ which may be violated numerically during the iteration procedure. The entropy variable formulation does not require any restriction on the variables and behaves numerically more stably than the direct formulation (2.18).

We have compared our results from the explicit Euler discretisation and from the implicit discretisation (solved by Newton's method) with the output of the software Multiphysics from COMSOL and all three algorithms lead to the same results.

Denoting by c_i^k and m_i^k the approximations of $c(x_i, t_k)$ and $m(x_i, t_k)$ respectively, where

$$x_i = ih, \;\; i = 0, \ldots, M, \;\; hM = \ell$$

and

$$t_k = k\tau, \;\; k \in \mathbb{N}, k \geq 0, \;\; \tau > 0$$

the discretisation (using an implicit time discretisation) reads as follows:

$$\begin{aligned} \frac{1}{\tau}(c_i^k - c_i^{k-1}) =& \frac{1}{h^2}(B^{\mathrm{JB,k}}_{11,i+1/2}(u_{i+1}^k - u_i^k) + B^{\mathrm{JB,k}}_{12,i+1/2}(v_{i+1}^k - v_i^k) \\ & - B^{\mathrm{JB,k}}_{11,i-1/2}(u_i^k - u_{i-1}^k) - B^{\mathrm{JB,k}}_{12,i-1/2}(v_i^k - v_{i-1}^k)) + r_c^{\mathrm{JB}}(c_i^k, m_i^k), \end{aligned} \tag{2.44}$$

where $i = 1, \ldots, M-1$, $k \geq 1$,

$$\begin{aligned} B^{\mathrm{JB,k}}_{jl,i\pm1/2} &:= \frac{1}{2}\left(B^{\mathrm{JB}}_{jl}(c^k_{i\pm1}, m^k_{i\pm1}) + B^{\mathrm{JB}}_{jl}(c_i^k, m_i^k)\right), \\ u_i^k &:= \ln\frac{c_i^k}{1 - c_i^k - m_i^k}, \quad v_i^k := \ln\frac{m_i^k}{1 - c_i^k - m_i^k} \end{aligned}$$

and $B^{\mathrm{JB}}_{ij}(c, m)$, $i, j = 1, 2$, are the coefficients of the matrix

$$B^{\mathrm{JB}} := A^{\mathrm{JB}}(c, m) H^{-1}(c, m).$$

The equation for m is discretised in a similar way. When an explicit time discretisation is used, the index k on the right-hand side of (2.44) has to be replaced by $k - 1$.

The numerical parameters are chosen, if not stated otherwise, as follows. We take the interval length $\ell = 1$, $M = 200$ grid points and the discretisation parameters $h = 1/M$ and $\tau = 5 \cdot 10^{-5}$. The initial data are defined as in [49], i.e. they are given by (2.20). In order to avoid stability problems, we add the factor $2 \cdot 10^{-4}$ to the initial cell volume fraction. The pressure coefficients are taken as in most experiments in [49]:

$$\beta_c = 0.2, \quad \beta_m = 0.0015.$$

First, we consider the case of vanishing production rates, i.e. we set

$$r_c^{\mathrm{JB}} = r_m^{\mathrm{JB}} = 0.$$

Figure 2.2 shows the volume fractions of the tumour cells and the ECM at various times, where we have used the cell-induced pressure coefficient $\theta = 1000$. The cross-diffusion term $A_{21}^{\mathrm{JB}} c_x$ causes a drift of the ECM to the right boundary, induced by variations of the tumour volume. The diffusion A_{22}^{JB} of the ECM outside of the tumour is very small, $A_{22}^{\mathrm{JB}} \approx 0.001$, such that the ECM cannot diffuse and forms a peak. The peak is not too singular since the discrete H^1-seminorm of m, $\|m_x\|_{1,h}$ and its maximal value, $\max_{x\in\Omega} m(x)$, stay bounded when $h \to 0$ numerically (see table 2.1). However, the peak indicates a loss of regularity of m, and we conjecture that global *classical* solutions to the tumour growth model do not exist. With increasing times, the tumour cell front moves to the right boundary, i.e. the tumor penetrates the surrounding ECM. The tumour cell fraction at the left boundary $x = 0$ is decreasing in time since the total volume fraction $\int_0^1 c dx$ is constant in time.

M	400	600	800	1000	1200
$\|m_x\|_{1,h}$	4.070	4.465	4.484	4.526	4.567
$\max_{x\in\Omega} m(x)$	0.630	0.646	0.637	0.645	0.649

Table 2.1: Discrete H^1-seminorm and maximum of m as a function of the number of grid points. Computed by using the explicit Euler scheme.

Using the scaling of Jackson and Byrne and assuming that the production rates vanish, (2.28) becomes

$$-\frac{dE(c(t),m(t))}{dt} = \int_\Omega p dx = \int_\Omega \left(2\beta_c c_x^2 + \beta_m \theta m c_x m_x + 2\beta_m(1+\theta c) m_x^2\right) dx,$$

i.e. the entropy production density is equal to

$$p(t,x) := 2\beta_c c_x^2 + \beta_m \theta m c_x m_x + 2\beta_m(1+\theta c) m_x^2. \tag{2.45}$$

In section 2.3 we have seen that the positivity of (2.45) is important for the existence proof and that this property can be achieved for θ being smaller than a special value θ^*. In the scaling used in [49] this critical value becomes

$$\theta^* = 4\sqrt{\beta_c/\beta_m}.$$

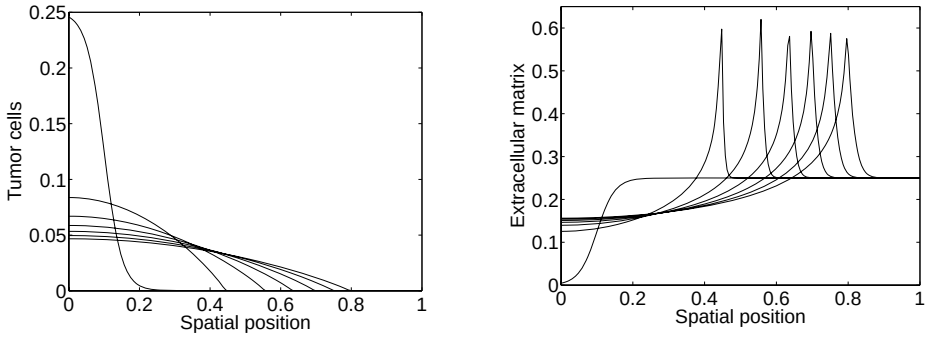

Figure 2.2: Volume fractions of the tumour cells (left) and the ECM (right) versus position using $\theta = 1000$ at times $t = 0, 1, 2, 3, 4, 5, 6$. The production rates vanish, $r_c^{\mathrm{JB}} = r_m^{\mathrm{JB}} = 0$. The tumour cell front and the ECM peaks are moving from left to right as time increases.

In figure 2.3 we have plotted p at time $t = 1$. It turns out that $p(1, x)$ is non-negative for all $x \in [0, 1]$ if θ is sufficiently small but it may become negative at some points if θ is large enough. As a consequence, the entropy production density does *not* lead to pointwise gradient estimates if θ is sufficiently large. This means that the existence analysis presented in section 2.3 using entropy estimates does *not* work for arbitrary θ. Clearly, the question remains if the existence of global solutions can be proven by another method.

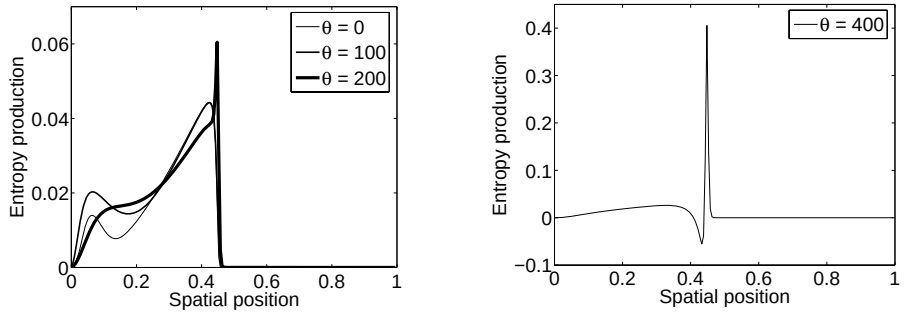

Figure 2.3: Entropy production density p at time $t = 1$ versus position. The production rates vanish, $r_c^{\mathrm{JB}} = r_m^{\mathrm{JB}} = 0$.

Figure 2.3 shows that the entropy production density p is non-negative in $[0, 1]$ even for $\theta = 200$. However, the existence analysis works for much smaller

values of θ only, namely, using the above parameters,

$$\theta < \theta^* \approx 46.$$

In the following, we explore this gap. We claim that there exist initial data such that $p(t,x) < 0$ at some (t,x) for θ close to the critical value θ^*.

Indeed, let us modify the initial data by replacing $1/8$ with 0.01 in the initial tumour cell fraction and by replacing $1/8$ with 0.475 in the initial ECM fraction (the other parameters are unchanged). Figure 2.4 (left) illustrates the volume fraction of the ECM at times $t = 0, 0.3, 0.6$ for $\theta = 70$. We see that no peaks appear in the plot. This behaviour has also been observed by Jackson and Byrne in [49] for small θ. The right figure shows that the corresponding entropy production density p becomes negative in some region:

$$p_{\min} \approx -0.0051 \ \text{ at } \ t = 0.6.$$

This holds true even for smaller values of θ: for $\theta = 55$, we have

$$p_{\min} \approx -0.0005 \ \text{ at } \ t = 0.6$$

and for $\theta = 50$ (replacing the factor 0.01 in the initial tumour cell fraction with 0.015)

$$p_{\min} \approx -1.6 \cdot 10^{-6} \ \text{ at } \ t = 0.4.$$

In the last two experiments, we have taken $M = 500$ grid points to improve the accuracy. However, in spite of these results it is not clear whether the bound θ^* is optimal and it might happen that solutions exist globally in time also for cell-induced pressure coefficients larger than the critical value.

Next, we include the production terms (2.43) in the equations. In figure 2.5, we see the time evolution of the volume fractions with $\theta = 1000$. In this experiment, we have added the factor $5 \cdot 10^{-4}$ to the initial cell volume fraction. Compared to figure 2.2, the cell front and the ECM peaks are moving much faster. Furthermore, because of the production rates, the tumour cell volume is increasing. The height of the peak becomes smaller for smaller values of θ, see figure 2.6. This phenomenon has been also observed by Jackson and Byrne [49]. We remark that their scaling seems to be different such that we obtain different numerical results than those presented in [49].

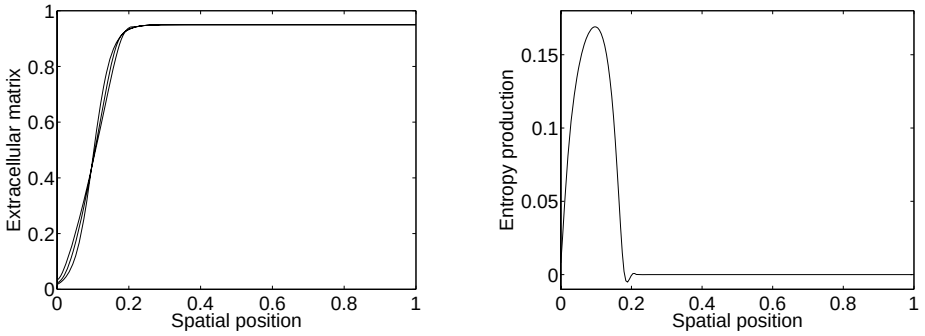

Figure 2.4: Volume fraction of the ECM versus position at times $t = 0, 0.3, 0.6$ (left) and entropy production density p versus position at time $t = 0.6$ (right) using $\theta = 70$. The production rates vanish, $r_c^{\mathrm{JB}} = r_m^{\mathrm{JB}} = 0$. The minimal value of p is -0.0051.

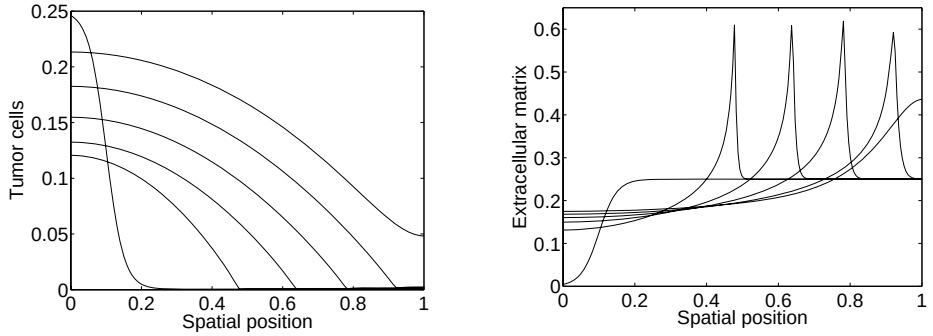

Figure 2.5: Volume fractions of the tumour cells (left) and the ECM (right) versus position using $\theta = 1000$ at times $t = 0, 1, 2, 3, 4, 5$. The production rates are $\alpha = 0.1$ and $\delta = 0.35$.

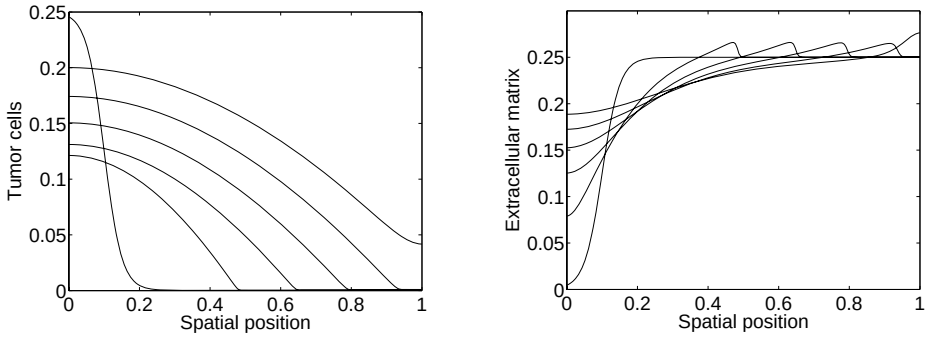

Figure 2.6: Volume fractions of the tumor cells (left) and the ECM (right) versus position using $\theta = 100$ at times $t = 0, 1, 2, 3, 4, 5$. The production rates are $\alpha = 0.1$ and $\delta = 0.35$.

Chapter 3

Existence Analysis of Maxwell-Stefan Systems for Multicomponent Mixtures

3.1 Introduction

Maxwell-Stefan diffusion equations or Maxwell-Stefan relations are systems of equations that have been developed by the Austrian scientist Josef Stefan and the Scottish physicist James Maxwell independently from each other in order to describe the diffusion phenomenon accurately in gaseous multicomponent mixtures (see [74], [72] and [59]).

In order to understand the importance of these equations let us consider a gas mixture consisting of $N+1$, $N \geq 2$, chemical components. According to chapter 1, where the diffusion process has been considered not only in the chemical but in a more general sense, the change in the molar concentration u_i of the i^{th} component with respect to time considered at a fixed point in space results from the motion of the i^{th} component and chemical reactions producing this component, i.e.

$$(u_i)_t + \operatorname{div}(J_i) = R_i(t,x,u) \quad \text{in } \Omega,\ t>0,\ \ i=1,\dots,N+1, \tag{3.1}$$

where $\Omega \subseteq \mathbb{R}^d$ $(1 \leq d \leq 3)$ is a bounded domain,

$$J_i := u_i \cdot v_i \tag{3.2}$$

is called the molar flux of component i and $v_i(t,x)$ denotes its velocity. This continuity equation, holding for binary or multicomponent mixtures, can be found in [74] or [14] for example. If J_i is a pure diffusive flux, then it is described by Fick's first law of diffusion most frequently, especially in the case of binary mixtures, i.e. it is assumed that the flux of a chemical component is proportional to the gradient of the concentration of this component—see equation (1.6)—where the minus sign in the formula indicates that the flux

goes from regions of higher concentration to regions of lower concentration. However, as experiments show it may happen that the diffusive flux of a chemical component in a mixture is not totally proportional to its concentration gradient, that the flux goes from lower to higher concentration regions which is called *uphill-diffusion* or *reverse diffusion* or that diffusion of a chemical component takes place although its concentration gradient is equal to 0, being called *osmotic diffusion* [15], [16], [17].

These diffusion phenomena have been observed in the well-known experiments by Duncan and Toor. They consider a ternary gaseous mixture consisting of hydrogen (H_2), nitrogen (N_2) and carbon dioxide (CO_2) being contained in two bulbs that are connected with a capillary tube. At the beginning of the experiment the first bulb contains carbon dioxide and no hydrogen whereas the other bulb contains hydrogen and no carbon dioxide. In both containers nitrogen can be found and its mole fraction is equal almost everywhere in the device and coincides approximately with the mole fraction of carbon dioxide in the first and the mole fraction of hydrogen in the second bulb. Opening the stopcock that separates the two bulbs carbon dioxide diffuses from the first bulb to the second one and hydrogen diffuses from the second to the first bulb according to the usual Fickian diffusion model. Although nitrogen is almost in equilibrium at the beginning its flux goes from the first to the second bulb and increases the concentration of N_2 in the second bulb leading to uphill-diffusion. This behaviour can be explained by the fact that carbon dioxide drags nitrogen from the first into the second bulb due to the higher friction forces between CO_2 and N_2 compared to those between H_2 and N_2. When the so-called *diffusion barrier* is reached the diffusive flux of nitrogen becomes equal to 0. The influence of the concentration gradient on the diffusive flux becomes more important than the friction forces and nitrogen diffuses classically so that finally the mole fractions of all three components are in equilibrium. For details regarding this experiment we refer to [17] and [55].

In situations as described above Fick's first law of diffusion fails at modelling the diffusion phenomenon accurately as it neglects the influence that the various chemical components may have on each other even if the diffusion coefficients D_i, $i = 1, \dots, N+1$, are assumed to be functions of the concentrations of all mixture components.

In the theory of non-equilibrium thermodynamics cross-effects in multicomponent mixtures are taken into account by assuming that the diffusive fluxes are linear combinations of the components' concentration gradients, i.e. for $i = 1, \dots, N+1$

$$J_i = -\sum_{j=1}^{N+1} D_{ij}^{\mathrm{b}} \nabla u_j,$$

where in general the binary diffusivities D_{ij}^{b}, $i, j = 1, \dots, N+1$, depend on

$u := (u_1, \dots, u_{N+1})^\top$. Thus, (3.1) becomes

$$u_t + \operatorname{div}(-D_{\mathrm{b}}(u)\nabla u) = R(u),$$

where $R := (R_1, \dots, R_{N+1})^\top$ and D_{b} denotes the matrix of the binary diffusivities. This model requires the knowledge of all binary diffusion coefficients and the positive semi-definiteness of the diffusivity matrix D_{b} which follows from thermodynamical principles [15].

The approach of Maxwell and Stefan describes the diffusive transport in multicomponent systems by assuming interspecies force balances, relating the velocities of the species in the mixture.

In [17] this model is compared to Fick's first law of diffusion numerically with regard to the description of diffusion in the human lung. At first, the authors consider usual air breathing of healthy patients. It turns out that both diffusion models lead to almost the same results for the mole fractions of the mixture components and that these results coincide with experimentally determined data. Next, they investigate diffusion in the lung of patients suffering from chronic obstructive pulmonary diseases (COPD) inhaling heliox. COPD denotes a group of chronic diseases of the lung, such as asthma, leading to airway obstruction. Hence, ventilation has to happen faster, which is achieved by administering heliox, being a mixture of helium and oxygen, speeding up the transport of oxygen as the density of heliox is lower than that of air so that the gas exchange can take place faster. The simulations for the mole fraction of oxygen and carbon dioxide show that the Fickian and the Maxwell-Stefan models lead to different results due to helium being present in the gas mixture. The latter model seems to be closer to reality as experiments indicate as it takes into account the effect that helium has on the other components. Details can be found in [17].

We will consider the Maxwell-Stefan relations for ideal gaseous mixtures only consisting of $N + 1$ components. Since we concentrate our study on cross-diffusion effects, we suppose isothermal and isobaric conditions. More general situations are investigated in [42] for example. Then the total molar concentration

$$u_{\mathrm{tot}} := \sum_{i=1}^{N+1} u_i$$

is constant and we set this constant equal to one (see section 3.2 for details). Thus, we do not have to differentiate between the molar concentration u_i of a component and its mole fraction c_i in the following as

$$c_i = \frac{u_i}{u_{\mathrm{tot}}} = u_i \tag{3.3}$$

for $i = 1, \dots, N + 1$. Of course, the physical dimension of these two functions is not equal. In the following we will concentrate on the components' mole

fractions in our formulations. Using equation (3.1) we obtain

$$(c')_t + \operatorname{div}(J') = r'(c'), \tag{3.4}$$

where $c' := (c_1, \dots, c_{N+1})^\top$,

$$r' := (r_1, \dots, r_{N+1})^\top := (R_1/u_{\text{tot}}, \dots, R_{N+1}/u_{\text{tot}})^\top$$

and J' denotes a real $(N+1) \times d$-matrix whose i^{th} row is given by $J_i^\top$ for $i = 1, \dots, N+1$. The Maxwell-Stefan relations yield equations for the fluxes J_i under the assumptions that they are diffusion fluxes. For that purpose we assume that the molar average velocity

$$v := \sum_{i=1}^{N+1} c_i v_i \tag{3.5}$$

vanishes (see section 3.2). Thus, we obtain using (3.3)

$$\sum_{i=1}^{N+1} J_i = \sum_{i=1}^{N+1} u_i v_i = u_{\text{tot}} \sum_{i=1}^{N+1} c_i v_i = 0$$

which is equivalent to

$$J_{N+1} = -\sum_{i=1}^{N} J_i. \tag{3.6}$$

The Maxwell-Stefan diffusion equations can be written in matrix form (as in [15]) as

$$\nabla c' = A_0^{-1}(c') \cdot J', \tag{3.7}$$

where

$$A_0^{-1}(c') := \begin{pmatrix} -\sum\limits_{j=1, j\neq 1}^{N+1} d_{1j}c_j & c_1 d_{12} & \cdots & c_1 d_{1(N+1)} \\ c_2 d_{21} & -\sum\limits_{j=1, j\neq 2}^{N+1} d_{2j}c_j & \cdots & c_2 d_{2(N+1)} \\ \vdots & \vdots & \ddots & \vdots \\ c_{N+1} d_{(N+1)1} & c_{N+1} d_{(N+1)2} & \cdots & -\sum\limits_{j=1, j\neq N+1}^{N+1} d_{(N+1)j}c_j \end{pmatrix} \tag{3.8}$$

and the coefficients $d_{ij} = d_{ji}$, $i, j = 1, \dots, N+1$, $i \neq j$, are assumed to be positive. The derivation of these relations is sketched in section 3.2. Thus, we have to invert the flux-gradient relations (3.7) before inserting them into (3.4). From

$$c_{N+1} = 1 - \sum_{i=1}^{N} c_i, \tag{3.9}$$

the definition of A_0^{-1} and the symmetry of the diffusivities d_{ij} it follows that the Maxwell-Stefan equations are linearly dependent showing that A_0^{-1} is not invertible. This can also be seen immediately as the rows of A_0^{-1} are linearly dependent. Moreover, (3.6) and (3.9) imply that the total production rate vanishes

$$\sum_{i=1}^{N+1} r_i(c') = 0.$$

Using the Perron-Frobenius theory for quasi-positive and irreducible matrices, Bothe [15] characterised the spectrum of $A_0^{-1}(c')$ in case that $c_i > 0$ for $i = 1, \ldots, N$ and $\sum_{i=1}^{N} c_i < 1$. Under these conditions, $A_0^{-1}(c')$ can be inverted on its image (see section 3.3 for details). In the engineering literature, the inversion of Maxwell-Stefan relations is often done in an approximate way. For instance, a numerical solution procedure for $N = 2, 3$ in the one-dimensional space has been developed in [6] and the special case $D_{ij} = \overline{D}/(F_i F_j)$ can be found in [7], where $\overline{D}$ denotes a reference diffusion coefficient and F_i a diffusion factor of species $i = 1, \ldots, N + 1$. Giovangigli suggested in [40] an iterative procedure, using the Perron-Frobenius theory as well.

Another approach, when dealing with Maxwell-Stefan relations, frequently used in engineering literature, is the reduction of (3.7) to a system consisting of N equations (rows) by removing one equation (row). Eliminating (w.l.o.g) the $(N+1)^{\text{st}}$ equation from (3.4) and (3.7) by using (3.6) and (3.9) we obtain

$$(c)_t + \operatorname{div}(J) = r(c) \quad \text{in } \Omega,\ t > 0, \tag{3.10}$$

where $c := (c_1, \ldots, c_N)^\top$, $r := (r_1, \ldots, r_N)^\top$, $J := (J_1, \ldots, J_N)^\top$ and

$$\nabla c = -A^{-1}(c) \cdot J, \tag{3.11}$$

where

$$A^{-1}(c) := \begin{cases} a_{ii}^{-1}(c) & := \sum\limits_{j=1, j\neq i}^{N} (d_{ij} - d_{i(N+1)})c_j + d_{i(N+1)}, \quad i = 1, \ldots, N, \\ a_{ij}^{-1}(c) & := c_i(d_{i(N+1)} - d_{ij}), \quad i, j = 1, \ldots, N, i \neq j \end{cases}. \tag{3.12}$$

Considering the case of $N = 2$ this matrix becomes

$$A^{-1}(c_1, c_2) = \begin{pmatrix} c_2(d_{12} - d_{13}) + d_{13} & c_1(d_{13} - d_{12}) \\ c_2(d_{23} - d_{12}) & c_1(d_{12} - d_{23}) + d_{23} \end{pmatrix}$$

and its determinant

$$\det(A^{-1}(c_1, c_2)) = c_1 d_{12} d_{13} + c_2 d_{12} d_{23} + (1 - c_1 - c_2) d_{13} d_{23}$$

is positive for all $c_1, c_2 \geq 0$ that satisfy $c_1 + c_2 \leq 1$. Hence, the flux-gradient relations (3.11) can be inverted and the inverse of A^{-1}, denoted by A, can be

given explicitly:

$$A(c_1,c_2)=\frac{1}{\det(A^{-1}(c_1,c_2))}\begin{pmatrix} c_1(d_{12}-d_{23})+d_{23} & c_1(d_{12}-d_{13}) \\ c_2(d_{12}-d_{23}) & c_2(d_{12}-d_{13})+d_{13}\end{pmatrix}. \tag{3.13}$$

Assuming that all diffusion coefficients $d_{ij}>0$ are equal in (3.12) the matrix A^{-1} becomes a diagonal matrix that is invertible of course and (3.10) reduces to a reaction-diffusion system as considered in chapter 1. However, for general N and general d_{ij} the invertibility of the matrix A^{-1} is *not* clear.

The aim of this chapter is to prove the global-in-time existence of solutions to system (3.10)–(3.11) supplemented with the initial conditions

$$c_i(0,\cdot)=c_i^0 \quad \text{in } \Omega, \tag{3.14}$$

and the boundary conditions

$$\nabla c_i\cdot\nu=0 \quad \text{on } \partial\Omega,\ t>0 \tag{3.15}$$

for $i=1,\ldots,N$.

It has to be mentioned that there are only very few analytical results in the mathematical literature for Maxwell-Stefan systems. Under some general assumptions on the non-linearities, Giovangigli could prove that there exists a unique global solution to the whole-space Maxwell-Stefan system if the initial datum is sufficiently close to the equilibrium state (see theorem 9.4.1 in [42]). Bothe [15] has shown the existence of a unique classical local-in-time solution for general initial data. A local existence theorem in full vibrational non-equilibrium was obtained by Giovangigli and Massot [43]. In [16] Boudin et al. consider a ternary system ($N=2$) and assume that two diffusivities are equal. In this situation, the Maxwell-Stefan system reduces to a heat equation for the first component and a drift-diffusion-type equation for the second species. Under these assumptions they prove the existence of a unique global solution and investigate its long-time decay to the stationary state. Up to now, there does not exist a global existence theory for the Maxwell-Stefan systems (3.10)–(3.11) for general positive symmetric d_{ij} and general initial data.

This chapter is organised as follows. In section 3.2 we sketch the derivation of the Maxwell-Stefan relations and in section 3.3 we prove some properties of the diffusion matrices $A_0^{-1}(c')$ and $A^{-1}(c)$. Some definitions and results from matrix theory needed in section 3.3 are summarised in the appendix. Based on these properties, the global-in-time existence of bounded weak solutions to (3.10)–(3.11) satisfying (3.14)–(3.15) is proven in section 3.4. In section 3.5 we deal with the long-time behaviour of the solutions converging exponentially fast to the homogeneous steady state when the production rates vanish.

3.2 Derivation of the Maxwell-Stefan Relations

In this section we derive the Maxwell-Stefan equations (3.7) following [16], [74] and [15].

We consider an ideal gaseous mixture consisting of $N+1$ chemical species, where $N \geq 1$, in a suitable subset of $\mathbb{R}^d$, $1 \leq d \leq 3$, for $t > 0$. Then the ideal gas law

$$p_i = u_i \cdot R \cdot T \tag{3.16}$$

holds for each component $i = 1, \ldots, N+1$ of the mixture, where p_i denotes the partial pressure of the i^{th} component, u_i its molar concentration, R is the ideal gas constant and T the absolute temperature. Assuming that the total pressure of the mixture

$$p_{\text{tot}} := \sum_{i=1}^{N+1} p_i$$

and the temperature are constant

$$p_{\text{tot}} = RT \sum_{i=1}^{N+1} u_i = RT u_{\text{tot}} \tag{3.17}$$

shows that the total concentration u_{tot} is constant. We set this constant equal to 1. Furthermore, we assume that p_{tot} is positive. The molar flux J_i defined in (3.2) can be split into diffusive and convective fluxes for $i = 1, \ldots, N+1$:

$$J_i = J_i^{\text{d}} + u_i v,$$

where the molar average velocity v is defined as in (3.5) and the molar diffusion flux is given by

$$J_i^{\text{d}} := u_i(v_i - v).$$

We neglect convection by assuming that $v = 0$ so that J_i becomes a pure diffusive flux that has to be modelled appropriately. For that purpose we consider $-\nabla p_i$, representing the net force acting on species i per unit volume for $i = 1, \ldots, N+1$ [74], and assume that this force is balanced by the drag forces between species i and j, where $j = 1, \ldots, N+1$, $j \neq i$ [16]. Similarly as in section 2.2 the drag forces between two species are assumed to be proportional to the difference of their velocities and their mole fractions. Thus, we obtain the force balances

$$-\nabla p_i = \sum_{j=1, j\neq i}^{N+1} f_{ij}(v_i - v_j)c_i c_j, \quad i = 1, \ldots, N+1,$$

where the proportionality constants $f_{ij} = f_{ji} > 0$ can be regarded as drag coefficients, which is equivalent to

$$\frac{\nabla p_i}{p_{\text{tot}}} = -\sum_{j=1, j\neq i}^{N+1} \frac{1}{D_{ij}}(v_i - v_j)c_i c_j. \tag{3.18}$$

Here we have used

$$D_{ij} := \frac{p_{\text{tot}}}{f_{ij}}, \quad i,j = 1,\dots N+1, i \neq j.$$

Using (3.3), (3.16)–(3.17) and the fact that T and u_{tot} are constant the left-hand side of equation (3.18) becomes

$$\frac{\nabla p_i}{p_{\text{tot}}} = \frac{RT\nabla u_i}{RTu_{\text{tot}}} = \frac{u_{\text{tot}}\nabla c_i}{u_{\text{tot}}}.$$

The relation between the molar concentrations and the mole fractions (3.3) as well as the definition of the molar fluxes (3.2) lead to

$$\nabla c_i = -\sum_{j=1, j\neq i}^{N+1} d_{ij}\frac{1}{u_{\text{tot}}}(c_j J_i - c_i J_j) = -\sum_{j=1, j\neq i}^{N+1} d_{ij}(c_j J_i - c_i J_j) \tag{3.19}$$

for $i = 1,\dots,N+1$ being called the *Maxwell-Stefan relations* or *Maxwell-Stefan diffusion equations* in ideal gaseous mixtures under isobaric and isothermal conditions with $u_{\text{tot}} = 1$, where $d_{ij} := 1/D_{ij}$ for $i,j = 1,\dots,N+1$, $i \neq j$. The coefficients D_{ij} are called *Maxwell-Stefan diffusivities* or *Maxwell-Stefan diffusion coefficients* between i and j. According to the assumptions made above these $((N+1)^2-(N+1))/2$ coefficients appearing in (3.19) are positive and symmetric. In general they depend on the components of the system. Writing these equations in matrix form we obtain (3.7).

3.3 Properties of the Diffusion Matrices

Let us consider matrix $A_0^{-1}(c')$ defined in (3.8) whose elements are given by

$$(a_0^{-1})_{ij} := d_{ij}c_i \quad \text{for } i,j = 1,\dots,N+1,\ i \neq j,$$

$$(a_0^{-1})_{ii} := -\sum_{j=1,\, j\neq i}^{N+1} d_{ij}c_j \quad \text{for } i = 1,\dots,N+1,$$

where the coefficients $d_{ij} = d_{ji}$, $i,j = 1,\dots,N+1$, $i \neq j$ are assumed to be positive and $N \geq 2$. In the following we assume that $c' := (c_1,\dots,c_{N+1}) \in \mathbb{R}^{N+1}$ is a strictly positive vector satisfying $\sum_{i=1}^{N+1} c_i = 1$. We refer to appendix A for the definitions and results from matrix analysis used in this section.

In [42] (section 7.7.1), the matrix with elements $(-a_0^{-1})_{ij}c_j$ is analysed and it is shown that it is symmetric, positive semi-definite, irreducible and a singular M-matrix as well as that a generalised inverse can be defined. Our approach is to apply the Perron-Frobenius theory to A_0^{-1}, following [15].

Lemma 3.1 (*Properties of* A_0^{-1})**.** *Let*

$$\delta := \min_{i,j=1,\dots,N+1,\, i\neq j} d_{ij} > 0$$

and

$$\Delta := 2 \sum_{i,j=1,\, i\neq j}^{N+1} d_{ij}.$$

Then the spectrum $\sigma(-A_0^{-1})$ *of* $-A_0^{-1}$ *satisfies*

$$\sigma(-A_0^{-1}) \subseteq \{0\} \cup [\delta, \Delta).$$

The inclusion $\sigma(-A_0^{-1}) \subseteq \{0\} \cup [\delta, \infty)$ is shown in [15]. For the convenience of the reader and since some less known results from matrix analysis are needed, we present a full proof.

Proof. The matrix A_0^{-1} is quasi-positive since all off-diagonal elements are non-negative and A_0^{-1} cannot be equal to the zero matrix due to the fact that $c_{N+1} = 1 - \sum_{i=1}^{N} c_i$. Furthermore, it is irreducible. Therefore, by theorem A.2 of Perron-Frobenius for quasi-positive irreducible matrices (see appendix A), the spectral bound of A_0^{-1},

$$s(A_0^{-1}) := \max\{\Re(\lambda) : \lambda \in \sigma(A_0^{-1})\},$$

is a simple eigenvalue of A_0^{-1} associated with a strictly positive eigenvector and

$$s(A_0^{-1}) > \Re(\lambda) \text{ for all } \lambda \in \sigma(A_0^{-1}),\ \ \lambda \neq s(A_0^{-1}).$$

Thus,

$$\sigma(A_0^{-1}) \subseteq \{s(A_0^{-1})\} \cup \{z \in \mathbb{C} : \Re(z) < s(A_0^{-1})\}.$$

An elementary computation shows that c' is a (strictly) positive eigenvector to the eigenvalue $\lambda = 0$ of A_0^{-1}, i.e.

$$A_0^{-1} \cdot \begin{pmatrix} c_1 \\ \vdots \\ c_{N+1} \end{pmatrix} = \begin{pmatrix} 0 \\ \vdots \\ 0 \end{pmatrix} = 0 \cdot \begin{pmatrix} c_1 \\ \vdots \\ c_{N+1} \end{pmatrix}.$$

According to the Perron-Frobenius theory, only the eigenvector to $s(A_0^{-1})$ is positive. This implies that $s(A_0^{-1}) = 0$ and

$$\sigma(A_0^{-1}) \subseteq \{0\} \cup \{z \in \mathbb{C} : \Re(z) < 0\}.$$

We can describe the spectrum $\sigma(A_0^{-1})$ in more detail. Let

$$C^{1/2} := \operatorname{diag}(\sqrt{c_1}, \ldots, \sqrt{c_{N+1}})$$

be a diagonal matrix in $\mathbb{R}^{(N+1)\times(N+1)}$ with inverse $C^{-1/2}$ that exists due to the fact that c' is a strictly positive vector. Then we can introduce the symmetric matrix

$$A_S := C^{-1/2} \cdot A_0^{-1} \cdot C^{1/2}$$

whose elements are given by

$$A_S := \begin{cases} a_{ii}^S := (a_0^{-1})_{ii} & \text{for } i = 1, ..., N+1, \\ a_{ij}^S := \sqrt{c_i c_j} d_{ij} & \text{for } i, j = 1, ..., N+1, i \neq j. \end{cases}$$

The matrix A_S is real and symmetric since $d_{ij} = d_{ji}$ and therefore, it has only real eigenvalues. Since A_0^{-1} and A_S are similar matrices, their spectra coincide:

$$\sigma(A_S) = \sigma(A_0^{-1}) \subseteq \{0\} \cup \{z \in \mathbb{R} : z < 0\} = (-\infty, 0].$$

Now, consider the matrix

$$A_S(\alpha) := A_S - \alpha \sqrt{c'} \sqrt{c'}^\top,$$

whose elements are given by

$$\begin{aligned} (a_S^\alpha)_{ii} &:= (a_0^{-1})_{ii} - \alpha c_i \quad \text{for } i = 1, ..., N+1, \\ (a_S^\alpha)_{ij} &:= \sqrt{c_i c_j}(d_{ij} - \alpha) \quad \text{for } i, j = 1, ..., N+1, i \neq j, \end{aligned}$$

where $\alpha > 0$ and

$$\sqrt{c'} := (\sqrt{c_1}, \ldots, \sqrt{c_{N+1}})^\top.$$

Then $A_S(\alpha)$ is quasi-positive for $\alpha \leq \delta$ and irreducible for $\alpha < \delta \leq d_{ij}$. Using $\sum_{i=1}^{N+1} c_i = 1$, a computation shows that $-\alpha$ is an eigenvalue of $A_S(\alpha)$ associated to the strictly positive eigenvector $\sqrt{c'}$. By theorem A.2 of Perron-Frobenius, the spectral bound of $A_S(\alpha)$ equals $-\alpha$ and

$$\sigma(A_S(\alpha)) \subseteq (-\infty, -\alpha].$$

Since $A_S(\alpha)$ and $\alpha \sqrt{c'} \sqrt{c'}^\top$ are symmetric matrices, we can apply theorem A.4 of Weyl:

$$\lambda_i(A_S) = \lambda_i\big(\alpha \sqrt{c'} \sqrt{c'}^\top + A_S(\alpha)\big) \leq \lambda_i\big(\alpha \sqrt{c'} \sqrt{c'}^\top\big) + \lambda_{N+1}(A_S(\alpha)),$$

where $i = 1, \ldots, N+1$ and the eigenvalues $\lambda_i(\cdot)$ are arranged in increasing order. Because of

$$\lambda_{N+1}(A_S(\alpha)) = -\alpha$$

and

$$\lambda_i(\alpha \sqrt{c'} \sqrt{c'}^\top) = 0 \text{ for } i = 1, \ldots, N, \;\; \lambda_{N+1}(\alpha \sqrt{c'} \sqrt{c'}^\top) = \alpha$$

due to the fact that

$$\sigma\Big(\begin{pmatrix} \sqrt{c_1} \\ \vdots \\ \sqrt{c_{N+1}} \end{pmatrix} \cdot \begin{pmatrix} \sqrt{c_1} \\ \vdots \\ \sqrt{c_{N+1}} \end{pmatrix}^T\Big) = \{0, ..., 0, 1\}$$

(see proposition A.1), we find that

$$\lambda_i(A_S) \leq -\alpha \text{ for } i = 1, \ldots, N \text{ and } \lambda_{N+1}(A_S) \leq 0.$$

Thus, for all $\alpha < \delta$,

$$\sigma(A_0^{-1}) = \sigma(A_S) \subseteq \{0\} \cup (-\infty, -\alpha],$$

implying that $\sigma(-A_0^{-1}) \subseteq \{0\} \cup [\delta, \infty)$.

In fact, we can show the above inclusion more directly circumventing Weyl's theorem. We claim that

$$\sigma(A_S)\backslash\{0\} = \sigma(A_S(\alpha))\backslash\{-\alpha\}$$

for $\alpha < \delta$. Let

$$A_S(\alpha)v_i = \lambda_i v_i \text{ for } i = 1, \ldots, N+1$$

with $v_{N+1} = \sqrt{c'}$ and $\lambda_{N+1} = -\alpha$. Let $V := \text{span}\{v_1, \ldots, v_N\}$. Then

$$\mathbb{R}^{N+1} = V \oplus \text{span}\sqrt{c'}.$$

By proposition A.1 in appendix A, the eigenvalues of $\alpha\sqrt{c'}\sqrt{c'}^\top$ are α with eigenspace span$\sqrt{c'}$ and 0 with eigenspace V. Then

$$A_S v_i = A_S(\alpha)v_i + \alpha(\sqrt{c'}\sqrt{c'}^\top)v_i = \lambda_i v_i \text{ for } i = 1, \ldots, N,$$

since $v_i \in V$ and

$$A_S v_{N+1} = A_S(\alpha)v_{N+1} + \alpha(\sqrt{c'}\sqrt{c'}^\top)v_{N+1} = 0.$$

This shows that

$$\sigma(A_0^{-1})\backslash\{0\} = \sigma(A_S)\backslash\{0\} = \sigma(A_S(\alpha))\backslash\{-\alpha\} \subseteq (-\infty, -\alpha),$$

implying that

$$\sigma(-A_0^{-1}) \subseteq \{0\} \cup [\delta, \infty).$$

It remains to prove the upper bound of the spectrum. Denoting by $\|.\|_F$ the Frobenius norm, we find for the spectral radius of $-A_0^{-1}$ that

$$\begin{aligned} r(-A_0^{-1}) \leq \| - A_0^{-1}\|_F &= \left(\sum_{i,j=1}^{N+1} (a_0^{-1})_{ij}^2 \right)^{1/2} \\ &= \left(\sum_{i=1}^{N+1} \left(\sum_{j=1,\, j\neq i}^{N+1} d_{ij}c_j \right)^2 + \sum_{i,j=1,\, j\neq i}^{N+1} (d_{ij}c_i)^2 \right)^{1/2} \\ &< 2 \sum_{i,j=1,\, j\neq i}^{N+1} d_{ij} =: \Delta, \end{aligned}$$

since $0 < c_i < 1$, finishing the proof. ❑

Remark. Notice that the quasi-positivity of A_0^{-1} does also hold if $c_i \in [0,1]$ for $i = 1, \dots, N+1$ but that A_0^{-1} is not irreducible anymore. Choose for example $M = \{2, \dots, N+1\}$ and assume that $c_1 = 0$. Then $(a_0^{-1})_{1j} = 0$ for all $j \in M$.

Lemma 3.2 (*Properties of restrictions of* A_0^{-1} *and* A_S)**.** *Let*

$$\tilde{A}_0^{-1} := A_0^{-1}|_{\mathrm{im}(A_0^{-1})}$$

and

$$\tilde{A}_S := A_S|_{\mathrm{im}(A_S)}.$$

Then $\tilde{A}_0^{-1}$ *and* $\tilde{A}_S$ *are invertible on the images* $\mathrm{im}(A_0^{-1})$ *and* $\mathrm{im}(A_S)$*, respectively and*

$$\sigma(-\tilde{A}_0^{-1}),\, \sigma(-\tilde{A}_S) \subseteq [\delta, \Delta), \quad \sigma((-\tilde{A}_S)^{-1}) \subseteq (1/\Delta, 1/\delta]. \tag{3.20}$$

Proof. Direct inspection shows that

$$\ker(A_0^{-1}) = \mathrm{span}\{c'\}, \;\; \mathrm{im}(A_0^{-1}) = \{\begin{pmatrix} 1 \\ \vdots \\ 1 \end{pmatrix}\}^{\perp}$$

and

$$\ker(A_S) = \mathrm{span}\{\sqrt{c'}\}.$$

By the symmetry of A_S, it follows that

$$\mathbb{R}^{N+1} = \ker(A_S)^{\perp} \oplus \ker(A_S) = \mathrm{im}(A_S^{\top}) \oplus \ker(A_S) = \mathrm{im}(A_S) \oplus \ker(A_S). \tag{3.21}$$

Furthermore, using theorem A.1, since $\lambda = 0$ is a semi-simple eigenvalue of A_0^{-1},

$$\mathbb{R}^{N+1} = \mathrm{im}(A_0^{-1}) \oplus \ker(A_0^{-1}). \tag{3.22}$$

We observe that both

$$\tilde{A}_0^{-1} : \mathrm{im}(A_0^{-1}) \to \mathrm{im}(A_0^{-1}) \quad \text{and } \tilde{A}_S : \ker(A_S)^{\perp} \to \ker(A_S)^{\perp}$$

are endomorphisms. Clearly,

$$\sigma(\tilde{A}_0^{-1}) \subseteq \sigma(A_0^{-1}) \quad \text{and } \sigma(\tilde{A}_S) \subseteq \sigma(A_S).$$

We claim that 0 is not contained in $\sigma(\tilde{A}_0^{-1})$ or $\sigma(\tilde{A}_S)$. Indeed, otherwise there exists $x \in \mathrm{im}(A_0^{-1})$ (or $x \in \mathrm{im}(A_S)$), $x \neq 0$, such that $\tilde{A}_0^{-1} x = 0$ (or $\tilde{A}_S x = 0$). This implies that $x \in \ker(A_0^{-1})$ (or $x \in \ker(A_S)$) and because of (3.22) (or (3.21)), it follows that $x = 0$, which is a contradiction. Hence, $\tilde{A}_0^{-1}$ and $\tilde{A}_S$ are invertible on their respective domain and (3.20) follows. ❑

The above lemma shows that under the assumption that $c_i > 0$ for $i = 1, \dots, N+1$ the flux-gradient relation (3.7) can be inverted since

$$\sum_{i=1}^{N+1} J_i = 0$$

implies that each column of J is an element of

$$\mathrm{im}(A_0^{-1}) = \{x \in \mathbb{R}^{N+1} : \sum_{i=1}^{N+1} x_i = 0\}.$$

In fact, we can write (3.7) as

$$\nabla c' = \tilde{A}_0^{-1} J'$$

and hence,

$$J' = \tilde{A}_0 \nabla c'.$$

The next step is to reduce the Maxwell-Stefan relations of $N+1$ components to a system of N components only and to use the above results for A_0^{-1} in order to obtain properties for the spectrum of A^{-1}defined as (3.12). Still, we assume that

$$c_i > 0 \quad \text{for all } i = 1, \dots, N+1 \quad \text{and} \quad \sum_{i=1}^{N+1} c_i = 1.$$

We define the matrix

$$X := I_{N+1} - \begin{pmatrix} 0 \\ \vdots \\ 0 \\ 1 \end{pmatrix} \begin{pmatrix} 1 \\ \vdots \\ 1 \\ 0 \end{pmatrix}^\top = \begin{pmatrix} 1 & 0 & \cdots & 0 \\ 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ -1 & -1 & \cdots & 1 \end{pmatrix}$$

and its inverse

$$X^{-1} = I_{N+1} + \begin{pmatrix} 0 \\ \vdots \\ 0 \\ 1 \end{pmatrix} \begin{pmatrix} 1 \\ \vdots \\ 1 \\ 0 \end{pmatrix}^\top = \begin{pmatrix} 1 & 0 & \cdots & 0 \\ 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 1 & 1 & \cdots & 1 \end{pmatrix}$$

in $\mathbb{R}^{(N+1)\times(N+1)}$, where I_{N+1} is the unit matrix of $\mathbb{R}^{(N+1)\times(N+1)}$. A computation shows that

$$X^{-1} \cdot A_0^{-1} \cdot X = \begin{pmatrix} -A^{-1} & b \\ 0 \dots 0 & 0 \end{pmatrix},$$

where A^{-1} is an $N \times N$-matrix and the vector $b \in \mathbb{R}^N$ is given by

$$b_i := d_{i(N+1)} c_i, \quad i = 1, \dots, N.$$

Lemma 3.3 (*Properties of* A^{-1})**.** *The matrix* $A^{-1} \in \mathbb{R}^{N\times N}$*, defined in* (3.12)*, is invertible with spectrum*

$$\sigma(A^{-1}) \subseteq [\delta, \Delta).$$

Furthermore, the elements of its inverse A *are uniformly bounded in* $c_1, \dots, c_N \in [0, 1]$*.*

Proof. Since the blockwise upper triangular matrix $-X^{-1}A_0^{-1}X$ is similar to $-A_0^{-1}$, their spectra coincide and

$$\sigma(A^{-1}) \cup \{0\} = \sigma(-X^{-1}A_0^{-1}X) = \sigma(-A_0^{-1}) \subseteq \{0\} \cup [\delta, \Delta). \tag{3.23}$$

Observing that 0 is a simple eigenvalue of $-A_0^{-1}$, it follows that

$$\sigma(A^{-1}) \subseteq [\delta, \Delta)$$

and hence, A^{-1} is invertible.

It remains to show the uniform bound for the elements a_{ij} of A. By Cramer's rule,

$$A = \operatorname{adj}(A^{-1})/\det A^{-1},$$

where $\operatorname{adj}(A^{-1})$ is the adjugate of A^{-1}. The definition of A^{-1} implies that

$$|a_{ij}^{-1}| \le \sum_{k=1,\, k\neq i}^{N} |d_{ik} - d_{i(N+1)}| + |d_{i(N+1)}| =: K_i \le K, \quad i, j = 1, \dots, N,$$

where $K := \max_{i=1,\dots,N} K_i$. Therefore, for the elements of $\operatorname{adj}(A^{-1})$ we have

$$(\operatorname{adj}(A^{-1}))_{ij} \le (N-1)!K^{N-1}$$

for $i, j = 1, \dots, N$. By (3.23), the eigenvalues of A^{-1} are bounded from below by δ. Consequently, since the determinant of a matrix equals the product of its eigenvalues,

$$\det(A^{-1}) \ge \delta^N.$$

This shows that

$$|a_{ij}| \le (N-1)!K^{N-1}\delta^{-N} \quad \text{for all } i, j = 1, \dots, N.$$

❑

Consider the matrix $H(c)$ defined as (1.12) in the variables $c_1, \dots, c_N$ whose elements are given by

$$H_{ij}(c) = \frac{1}{c_{N+1}} + \frac{\delta_{ij}}{c_i}, \quad i, j = 1, \dots, N,$$

where δ_{ij} denotes the Kronecker delta and c is defined as in section 3.1. Obviously, matrix H is symmetric and positive definite by Sylvester's criterion, since all principle minors $\det H_k$, $k = 1, \ldots, N$, of H are positive:

$$\det H_k = (c_1 \cdots c_k c_{N+1})^{-1} \left(\sum_{i=1}^{k} c_i + c_{N+1} \right) > 0, \quad k = 1, \ldots, N \tag{3.24}$$

as $c_i > 0$ for $i = 1, \ldots, N$ and $\sum_{i=1}^{N} c_i < 1$. That the above equality holds can be seen by induction. The case $k = 1$ is clear. Let us assume that (3.24) holds for $k-1$, where $k \in \{2, .., N\}$. Then, applying Laplace's formula

$$\det(H_k) = \sum_{j=1}^{k-1} (-1)^{k+j} \frac{1}{c_{N+1}} \det(H_k^{kj}) + (-1)^{2k} (\frac{1}{c_k} + \frac{1}{c_{N+1}}) \det(H_{k-1}),$$

where H_k^{kj} results from H_k by removing the k^{th} row and the j^{th} column. Applying elementary row operations the determinant of H_k^{kj} can be shown to be equal to

$$\det H_k^{kj} = \prod_{l=1, l \neq j}^{k-1} \frac{1}{c_l} \frac{1}{c_{N+1}} (-1)^{k-(j+1)}$$

showing that (3.24) holds. Thus, the eigenvalues of H are positive implying that it is invertible.

Lemma 3.4 (*Properties of* B)**.** *The matrix* $B(c) := A(c) \cdot H^{-1}(c)$ *is symmetric and positive definite. Furthermore, the elements of* B *are bounded uniformly in* $c_1, \ldots, c_{N+1} \in [0, 1]$.

Proof. Let us consider the inverse of B, that exists since A and H^{-1} are invertible, in order to prove its properties. Using

$$d_{ij} = d_{ji} \quad \text{and} \quad \sum_{i=1}^{N+1} c_i = 1,$$

for $i, j = 1, \ldots, N$, $i \neq j$, a calculation shows that the elements B_{ij}^{-1} of $B^{-1} = HA^{-1}$ equal

$$B_{ii}^{-1}(c) := d_{i(N+1)} \left(1 - \sum_{k=1,\, k \neq i}^{N} c_k \right) \left(\frac{1}{c_i} + \frac{1}{c_{N+1}} \right) + \sum_{k=1,\, k \neq i}^{N} \left(\frac{d_{k(N+1)}}{c_{N+1}} + \frac{d_{ik}}{c_i} \right) c_k$$

for $i = 1, \ldots, N$ and

$$B_{ij}^{-1}(c) := \frac{d_{i(N+1)}}{c_{N+1}}\left(1 - \sum_{k=1,\,k\neq i}^{N} c_k\right) + \frac{d_{j(N+1)}}{c_{N+1}}\left(1 - \sum_{k=1,\,k\neq j}^{N} c_k\right) + \sum_{k=1,\,k\neq i,j}^{N} d_{k(N+1)}\frac{c_k}{c_{N+1}} - d_{ij},$$

for $i, j = 1, \ldots, N$ and $i \neq j$. Hence, B^{-1} is symmetric. We have proven above that H^{-1} is symmetric and positive definite. According to theorem A.3, the number of positive eigenvalues of $A^{-1} = H^{-1}B^{-1}$ equals that for B^{-1}. However, by (3.23), A^{-1} has only positive eigenvalues. Therefore, also B^{-1} has only positive eigenvalues. This shows that B^{-1} and consequently B are symmetric and positive definite.

It remains to show the uniform boundedness of B. The inverse H^{-1} can be computed explicitly (see (1.13) in chapter 1):

$$H_{ij}^{-1} := \begin{cases} (1-c_i)c_i & \text{if } i = j = 1, \ldots, N, \\ -c_i c_j & \text{if } i \neq j,\ i, j = 1, \ldots, N. \end{cases}$$

The elements b_{ij} of B equal

$$b_{ii} = a_{ii}(1-c_i)c_i - \sum_{k=1,\,k\neq i}^{N} a_{ik}c_i c_k, \quad i = 1, \ldots, N,$$
$$b_{ij} = -a_{ii}c_i c_j + a_{ij}(1-c_j)c_j - \sum_{k=1,\,k\neq i,j}^{N} a_{ik}c_j c_k, \quad i \neq j,\ i, j = 1, \ldots, N.$$

By lemma 3.3, the elements a_{ij} are uniformly bounded. Thus, since $c_i \in [0, 1]$ for $i = 1, \ldots, N$,

$$|b_{ij}| \leq N! K^{N-1} \delta^{-N}$$

for all $i, j = 1, \ldots, N$ and the uniform bound for b_{ij} follows. ❑

3.4 Existence of Weak Solutions

In this section we want to prove the existence of a weak and global-in-time solution $(c_1, \ldots, c_N)^\top$ to the Maxwell-Stefan system (3.10)–(3.11) with initial and boundary conditions (3.14)–(3.15) that satisfies

$$c_1, \ldots, c_N, \sum_{i=1}^{N} c_i \in [0, 1].$$

Let us summarise the difficulties that arise in the analysis of the Maxwell-Stefan system.

First, the molar fluxes J_i for $i = 1, \dots, N$ are not defined *a priori* as a linear combination of the mole fraction gradients, which makes it necessary to invert the flux-gradient relations (3.11). However, as mentioned in section 3.1, the invertibility of A^{-1} is not clear for $0 \le c_1, \dots, c_N, \sum_{i=1}^N c_i \le 1$.

Second, equations (3.10)–(3.11) are coupled. Assuming that A^{-1} is invertible this translates into the fact that its inverse A is generally a full matrix with non-linear coefficients depending on the mole fractions. Thus, standard tools like the maximum principle or regularity theory are not available. In particular, it is not clear how to prove non-negative lower and upper bounds for the mole fractions c_i. Moreover, A^{-1} and hence A is not symmetric and in general A cannot be assumed to be positive semi-definite if it exists. Indeed, for $N = 2$, where A is given explicitly by (3.13) counterexamples can be constructed showing that this is not the case. Therefore, even the proof of local-in-time existence of solutions is non-trivial.

Third, it is not standard to find suitable a priori estimates which allow us to conclude the global-in-time existence of solutions.

In order to overcome these difficulties we combine and extend the results presented by Bothe in [15] with the entropy-dissipation technique used in chapter 2. Let us mention, that we work only with the Maxwell-Stefan systems consisting of N equations respectively components—in contrast to Bothe, whose existence result is proven for systems as (3.4) and (3.7)—as it turns out to be more convenient to use our methods. Thus, we lose the "nice" structure of the diffusion matrix A_0^{-1} of the cross-diffusion system (3.4) consisting of $N+1$ components and consider the matrix A^{-1} instead. However, the entropy variable formulation of (3.10)–(3.11) restores the "nice" structure of the system leading to a symmetric and positive definite transformed diffusion matrix.

We assume that the flux-gradient relations (3.11) can be inverted, i.e. we invert A^{-1} formally so that (3.10)–(3.11) lead to the cross-diffusion system

$$(c)_t - \operatorname{div}(A(c) \cdot \nabla c) = r(c) \quad \text{in } \Omega,\ t > 0. \tag{3.25}$$

Our main idea to handle (3.25) is to exploit its entropy structure. We associate to this system the entropy density

$$h(c) := \sum_{i=1}^N c_i(\ln c_i - 1) + c_{N+1}(\ln c_{N+1} - 1), \quad c_1, \dots, c_N \ge 0,\ \sum_{i=1}^N c_i \le 1, \tag{3.26}$$

where

$$c_{N+1} := 1 - \sum_{i=1}^N c_i$$

is interpreted as a function of the other mole fractions. The corresponding entropy functional is defined in (1.9). Notice that this entropy is a natural

extension of the entropy (2.21) used in chapter 2. Furthermore, we define the entropy variables w_i as in (1.10) so that c_i can be written as (1.11) for $i = 1, \dots, N$ and (3.25) becomes (1.14), where

$$B(w) := A(c(w)) \cdot H^{-1}(c(w)), \tag{3.27}$$

$w := (w_1, \dots, w_N)^\top$, $c(w) := (c_1(w), \dots, c_N(w))^\top$ and H^{-1} is defined as in (1.13). Let us recall that the mole fractions satisfy

$$0 < c_1(w), \dots, c_N(w), \sum_{i=1}^{N} c_i(w) < 1 \tag{3.28}$$

for bounded functions w_i, $i = 1, \dots, N$. Under these conditions Bothe [15] has analysed the spectrum of matrix A_0^{-1}defined in (3.8). In section 3.3 we have extended these results in order to show that $A^{-1}(c(w))$ is invertible and $A(c(w))$ exists (see lemma 3.3). Moreover, the matrix $B(w)$ is symmetric and positive definite for $c(w)$ satisfying (3.28) (see lemma 3.4). The positive definiteness of B allows us to apply the Lax-Milgram lemma to a linearised version of (1.14).

An important ingredient for the global existence proof is the derivation of a priori estimates. Therefore, we assume that $(c_1, \dots, c_N)^\top$ is a sufficient solution to (3.10)–(3.11) and (3.14)–(3.15). Differentiating the entropy

$$E(c) := \int_\Omega h(c) d\lambda_d$$

(now $h(c)$ is interpreted as a function of $c_1, \dots, c_{N+1}$) with respect to time, a formal computation (made rigorous in lemma 3.8) shows the entropy-dissipation inequality for $t > 0$

$$\begin{aligned} \frac{dE(c_1(t), \dots, c_{N+1}(t))}{dt} + K \int_\Omega \sum_{i=1}^{N+1} |\nabla \sqrt{c_i}|^2 d\lambda_d &\le \int_\Omega r'(c') \cdot \begin{pmatrix} \ln(c_1) \\ \vdots \\ \ln(c_{N+1}) \end{pmatrix} d\lambda_d \\ &\le 0, \end{aligned} \tag{3.29}$$

where $K > 0$ is a constant which depends only on the coefficients d_{ij}, $i, j = 1, \dots, N+1$, $i \neq j$ and $|.|$ denotes the Euclidean norm in $\mathbb{R}^d$. In order to prove this inequality we need the formulation of the Maxwell-Stefan system (3.4) and (3.7), i.e. of the system consisting of $N+1$ equations as well as the properties of the diffusion matrices shown in section 3.3. The inequality

$$\int_\Omega r'(c') \cdot \begin{pmatrix} \ln(c_1) \\ \vdots \\ \ln(c_{N+1}) \end{pmatrix} d\lambda_d \le 0$$

is obtained under the assumptions made on $r'(c')$ for $0 < c_1, \dots, c_{N+1} \le 1$ (see below). Estimate (3.29) yields H^1-bounds for $\sqrt{c_i}$, $i = 1, \dots, N+1$. A diffusion inequality that directly implies (3.29) was first established in [41] (also see theorem 7.6.1 in [42]).

Under the following assumptions we are able to prove the global-in-time existence of weak solutions $(c_1, \dots, c_N)^\top$, where $N \ge 2$, to (3.10)–(3.11) and (3.14)–(3.15) for arbitrary diffusion coefficients d_{ij} and general initial data:

- *Domain*: $\Omega \subseteq \mathbb{R}^d$, $1 \le d \le 3$, is a bounded domain with $\partial\Omega \in C^{1,1}$.
- *Initial data*: The real functions

  $$c_1^0, \dots, c_N^0$$

  are assumed to be non-negative a.e. in Ω and measurable, defining

  $$c_{N+1}^0 := 1 - \sum_{i=1}^N c_i^0,$$

  and satisfy

  $$\sum_{i=1}^N c_i^0 \le 1 \quad \text{a.e. in } \Omega.$$

- *Diffusion coefficients*: The coefficients d_{ij} are symmetric and positive for $i, j = 1, \dots N+1$, $i \ne j$.
- *Production rates*: The functions $r_i \in C^0([0,1]^{N+1}; \mathbb{R})$, $i = 1, \dots, N+1$, satisfy

  $$\sum_{i=1}^{N+1} r_i(c') = 0, \quad \sum_{i=1}^{N+1} r_i(c') \ln c_i \le 0 \quad \text{for all } 0 < c_1, \dots, c_{N+1} \le 1.$$

Theorem 3.5. *Let the above assumptions hold. Then there exists a weak solution* $(c_1, \dots, c_N)^\top$ *to* (3.10)–(3.11) *and* (3.14)–(3.15) *satisfying*

$$c_i \in L^2_{\mathrm{loc}}(0, \infty; H^1(\Omega)), \quad \partial_t c_i \in L^2_{\mathrm{loc}}(0, \infty; \mathcal{V}')$$

for $i = 1, \dots, N$ *and*

$$0 \le c_1, \dots, c_N, \sum_{i=1}^N c_i \le 1 \quad \text{a.e. in } \Omega \times (0, \infty),$$

where $\mathcal{V}'$ *is the dual space of*

$$\mathcal{V} := \{f \in H^2(\Omega) : \nabla f \cdot \nu = 0 \quad \text{a.e.} \quad \text{on} \quad \partial\Omega\}.$$

The proof of this theorem is similar to that of theorem 2.1 in section 2.3.

Proof of Theorem 3.5

Step 1: Variable Transformation.

As in the proof of theorem 2.1 we assume that there exists $\eta \in (0,1)$ so that the initial data satisfy

$$c_i^0 \geq \eta \quad \text{for } i = 1, \dots, N \quad \text{and} \quad \sum_{i=1}^{N} c_i^0 \leq 1 - \eta \quad \text{a.e. in } \Omega. \tag{3.30}$$

Using the variable transformation (1.10) we consider the problem

$$\partial_t c(w) - \operatorname{div}(B(w)\nabla w) = r(c(w)) \quad \text{in } \Omega,\ t > 0,$$

where $B(w)$ is defined as in (3.27), with the boundary and initial conditions

$$\nabla w_i \cdot \nu = 0 \quad \text{on } \partial\Omega, t > 0, \quad w_i(0,.) = w_i^0 \quad \text{in } \Omega, \quad i = 1, \dots, N,$$

where

$$w_i^0 := \ln\left(\frac{c_i^0}{c_{N+1}^0}\right),$$

satisfying $w_i^0 \in L^\infty(\Omega)$ due to (3.30).

Step 2: Existence of an Approximate System.

Let $T > 0$, $m \in \mathbb{N}$ and set $\tau_m = \tau := T/m$ so that the time steps $t_k := k\tau$ can be defined for $k = 0, \dots, m$. We consider the approximate system

$$\frac{1}{\tau}(c(w^k) - c(w^{k-1})) - \operatorname{div}(B(w^k)\nabla w^k) = r(c(w^k)) \quad \text{in } \Omega,$$

$$\nabla w_i^k \cdot \nu = 0 \quad \text{on } \partial\Omega, \quad i = 1, \dots, N,$$

for $k = 1, \dots, m$, where $w^k := (w_1^k, \dots, w_N^k)^\top$, $c(w^k) = (c_1(w^k), \dots, c_N(w^k))^\top$ and

$$w_i^k := w_i(t_k, .), \quad c_i(w^k) = e^{w_i^k} \Big/ \left(1 + \sum_{j=1}^{N} e^{w_j^k}\right) \tag{3.31}$$

for $i = 1, \dots, N$ and $k = 0, \dots, m$. In order to find a weak solution to the above problem we formulate its weak formulation and add additional ϵ-terms, i.e. we consider

$$\begin{aligned} &\frac{1}{\tau}\int_\Omega \left(c(w^k) - c(w^{k-1})\right) \cdot v d\lambda_d + \int_\Omega \nabla v : \left(B(w^k)\nabla w^k\right) d\lambda_d \\ &\quad + \epsilon \int_\Omega (\Delta w^k \cdot \Delta v + w^k \cdot v) d\lambda_d = \int_\Omega r(c(w^k)) \cdot v d\lambda_d, \quad v \in \mathcal{V}^N, \end{aligned} \tag{3.32}$$

where $\epsilon > 0$ is an arbitrary but fixed parameter, the Laplace operator of a vector is defined component-by-component and ":" denotes the Hilbert-Schmidt inner product for real $N \times d$-matrices; in particular,

$$\nabla v : \Big(B(w^k)\nabla w^k\Big) = \sum_{i=1}^{N}\sum_{j=1}^{d}(v_i)_{x_j}(b_{i1}(w^k)\cdot(w_1^k)_{x_j} + \ldots + b_{iN}(w^k)\cdot(w_N^k)_{x_j}).$$

We remark that $(\mathcal{V}, \|.\|_{H^2(\Omega)})$ is a Banach space. The implicit Euler discretisation of the time derivative makes the system elliptic which avoids problems related to the regularity in time. The additional ϵ-term guarantees the coercivity of the elliptic system.

Lemma 3.6. *Let the assumptions of theorem 3.5 hold and let $w^{k-1} \in L^\infty(\Omega)^N$. Then there exists a solution $w^k \in \mathcal{V}^N$ to* (3.32).

Proof. Again, we apply the Leray-Schauder fixed-point theorem (see the proof of theorem 2.1 in section 2.3). Let $\overline{w} \in L^\infty(\Omega)^N$ and $\sigma \in [0,1]$. We wish to find a unique solution $w \in \mathcal{V}^N$ to

$$a(w,v) = F(v) \quad \text{for all } v \in \mathcal{V}^N, \tag{3.33}$$

where

$$a(w,v) := \int_\Omega \nabla v : B(\overline{w})\nabla w d\lambda_d + \epsilon\int_\Omega(\Delta w\cdot\Delta v + w\cdot v)d\lambda_d,$$
$$F(v) := -\frac{\sigma}{\tau}\int_\Omega\Big(c(\overline{w}) - c(w^{k-1})\Big)\cdot v d\lambda_d + \sigma\int_\Omega r(c(\overline{w}))\cdot v d\lambda_d.$$

For $v, w \in \mathcal{V}^N$ and $\overline{w}, w^{k-1} \in L^\infty(\Omega)^N$ the bilinear form $a : \mathcal{V}^N \times \mathcal{V}^N \to \mathbb{R}$ and the linear functional $F : \mathcal{V}^N \to \mathbb{R}$ are well-defined since

$$0 < c_i(\overline{w}), \quad \sum_{j=1}^{N} c_j(\overline{w}), \quad c_i(w^{k-1}) < 1$$

a.e. for $i = 1, \ldots, N$ so that $A(c(\overline{w}))$ exists a.e. (see lemma 3.3) and

$$b_{ij}(\overline{w}), \quad c_i(\overline{w}), \quad c_i(w^{k-1}) \in L^\infty(\Omega)$$

(see lemma 3.4) for $i, j = 1, \ldots, N$. From the assumptions made on the production terms it follows that $r_i(c(\overline{w})) \in L^\infty(\Omega)$ for $i = 1, \ldots, N$.

From the triangle inequality, the a.e.-boundedness of the elements of $B(\overline{w})$ and Hölder's inequality it follows that a is continuous in $\mathcal{V}^N \times \mathcal{V}^N$. Indeed, for $w, v \in \mathcal{V}^N$

$$|a(w,v)| \le C(\epsilon, d, N, d_{ij})\|w\|_{H^2(\Omega)^N}\cdot\|v\|_{H^2(\Omega)^N},$$

where $C(\epsilon, d, N, d_{ij}) > 0$. Moreover, due to the fact that $c_i(\overline{w}), c_i(w^{k-1})$ and $r_i(c(\overline{w}))$ are bounded a.e. for $i = 1, \ldots, N$, it can be shown, that F is a continuous map, being bounded by a positive constant that depends on the bound of the production terms r_i, τ and $\lambda_d(\Omega)$.

Since $B(\overline{w})$ is positive definite a.e., by lemma 3.4, a is furthermore coercive,

$$a(w,w) = \int_\Omega \sum_{i=1}^{N}\sum_{j=1}^{d}(w_i)_{x_j}(b_{i1}(\overline{w})(w_1)_{x_j} + \ldots + b_{iN}(\overline{w})(w_N)_{x_j})d\lambda_d +$$

$$+\epsilon\int_\Omega \left(|\Delta w|^2 + |w|^2\right) d\lambda_d =$$

$$\int_\Omega \begin{pmatrix}(w_1)_{x_1}\\ \vdots \\ (w_N)_{x_1}\end{pmatrix}^\top B(\overline{w}) \begin{pmatrix}(w_1)_{x_1}\\ \vdots \\ (w_N)_{x_1}\end{pmatrix} + \ldots + \begin{pmatrix}(w_1)_{x_d}\\ \vdots \\ (w_N)_{x_d}\end{pmatrix}^\top B(\overline{w}) \begin{pmatrix}(w_1)_{x_d}\\ \vdots \\ (w_N)_{x_d}\end{pmatrix} d\lambda_d +$$

$$\epsilon\int_\Omega \left(|\Delta w|^2 + |w|^2\right) d\lambda_d \geq \epsilon\int_\Omega \left(|\Delta w|^2 + |w|^2\right) d\lambda_d \geq \frac{\epsilon}{3C^2}\|w\|^2_{H^2(\Omega)^N},$$

where $C > 0$ is a constant. The last inequality follows from elliptic regularity, using the assumption $\partial\Omega \in C^{1,1}$ and the fact that $w_i \in \mathcal{V}$ satisfies homogeneous Neumann boundary conditions for $i = 1, \ldots, N$ [77].

Then the Lax-Milgram lemma provides the existence of a unique solution $w \in \mathcal{V}^N$ to (3.33). Since the space dimension is assumed to be at most three, the embedding

$$H^2(\Omega) \hookrightarrow L^\infty(\Omega)$$

is continuous (and compact) such that $w \in L^\infty(\Omega)^N$. This shows that the fixed-point operator

$$S : L^\infty(\Omega)^N \times [0,1] \to L^\infty(\Omega)^N,$$

defined by

$$S(\overline{w}, \sigma) = w,$$

where w is the solution to (3.33), is well-defined. By construction,

$$S(\overline{w}, 0) = 0 \quad \text{for all } \overline{w} \in L^\infty(\Omega)^N.$$

Standard arguments show that S is continuous and compact.

It remains to prove a uniform bound for all fixed points of $S(\cdot, \sigma)$ in $L^\infty(\Omega)^N$.

Let $w \in L^\infty(\Omega)^N$ be such a fixed point and assume $\sigma \neq 0$ (for $\sigma = 0$ the case is clear). Then w solves (3.33) with $\overline{w}$ replaced by w. Taking the test function $v = w \in \mathcal{V}^N$, it follows that

$$\frac{\sigma}{\tau} \int_\Omega \Big(c(w) - c(w^{k-1}) \Big) \cdot w d\lambda_d + \int_\Omega \left(\nabla w : B(w) \nabla w + \epsilon(|\Delta w|^2 + |w|^2) \right) d\lambda_d$$
$$= \sigma \int_\Omega r(c(w)) \cdot w d\lambda_d. \tag{3.34}$$

In order to estimate the first term on the left-hand side, we consider the discrete entropy density h, defined as in (3.26), on the open unit simplex $D := \{(x_1, \dots, x_N)^\top \in \mathbb{R}^N : 0 < x_1, \dots, x_N, \sum_{i=1}^N x_i < 1\}$. Then its Hessian is positive definite (see the proof of lemma 3.4) and hence, h is convex, i.e. we obtain, using Taylor's theorem,

$$h(y) - h(x) \le \nabla h(y) \cdot (y - x) = \begin{pmatrix} \ln\left(\frac{y_1}{(1 - \sum_{i=1}^N y_i)} \right) \\ \vdots \\ \ln\left(\frac{y_N}{(1 - \sum_{i=1}^N y_i)} \right) \end{pmatrix} (y - x) \quad \text{for all } x, y \in D.$$

Using $w = \nabla h(c(w))$ and arguing similar as in the proof of theorem 2.1, we find that

$$\frac{\sigma}{\tau} \int_\Omega \Big(c(w) - c(w^{k-1}) \Big) \cdot w d\lambda_d \ge \frac{\sigma}{\tau} \int_\Omega \Big(h(c(w)) - h(c(w^{k-1})) \Big) d\lambda_d$$
$$\ge -\frac{1}{\tau} \lambda_d(\Omega)(N+1).$$

By lemma 3.4, $B(w)$ is positive definite a.e.:

$$\int_\Omega \nabla w : B(w) \nabla w d\lambda_d \ge 0.$$

Finally, using the assumptions $\sum_{i=1}^N r_i(c) = -r_{N+1}(c)$ and $\sum_{i=1}^{N+1} r_i(c) \ln c_i \le 0$ for $0 < c_1, \dots, c_N, \sum_{i=1}^N c_i < 1$,

$$\int_\Omega r(c(w)) \cdot w d\lambda_d = \int_\Omega \left(\sum_{i=1}^N r_i(c(w)) (\ln c_i(w) - \ln c_{N+1}(w)) \right) d\lambda_d$$
$$= \int_\Omega \sum_{i=1}^{N+1} r_i(c(w)) \ln c_i(w) d\lambda_d \le 0.$$

Therefore, (3.34) becomes

$$\sigma \int_\Omega h(c(w))d\lambda_d + \epsilon\tau \int_\Omega \left(|\Delta w|^2 + |w|^2\right) d\lambda_d \le \sigma \int_\Omega h(c(w^{k-1}))d\lambda_d.$$

This yields an $H^2(\Omega)^N$-bound uniform in w and σ but depending on ϵ and τ (and d, N, Ω). The embedding $H^2(\Omega) \hookrightarrow L^\infty(\Omega)$ implies the desired uniform bound in $L^\infty(\Omega)^N$ and the Leray-Schauder fixed point theorem gives a solution to (3.32). ❑

Step 3: Entropy Dissipation.

Since the diffusion matrix $B(w^k)$ defines a self-adjoint endomorphism a.e., the entropy-dissipation estimate

$$\int_\Omega \nabla w^k : B(w^k)\nabla w^k d\lambda_d \ge \sum_{i=1}^N \int_\Omega \lambda_{\min} |\nabla w_i^k|^2 d\lambda_d$$

holds, where $\lambda_{\min}$ is the smallest eigenvalue of $B(w^k)$. Unfortunately, we have no information about the spectrum of the matrix B and we do not know whether there is a positive lower bound of $\lambda_{\min}$ independent of $c(w^k)$.

However, we are able to prove an entropy-dissipation inequality in the variables $\sqrt{c_i(w^k)}$ for $i = 1, \dots, N+1$ with a uniform positive lower bound. Let us recall that $c_i(w^k)$ is defined as in (3.31) for $i = 1, \dots, N$ and

$$c_{N+1}(w^k) = 1 - \sum_{i=1}^N c_i(w^k).$$

Lemma 3.7. *Let $w^k \in \mathcal{V}^N$ be a weak solution to* (3.32)*. Then*

$$\int_\Omega \nabla w^k : B(w^k)\nabla w^k d\lambda_d \ge \frac{4}{\Delta} \int_\Omega \sum_{i=1}^{N+1} |\nabla \sqrt{(c')_i^k}|^2 d\lambda_d,$$

where $(c')^k := (c_1(w^k), \dots, c_{N+1}(w^k))^\top$.

Proof. First, we claim that

$$\int_\Omega \nabla w^k : B(w^k)\nabla w^k d\lambda_d = \int_\Omega \nabla \ln(c')^k : (-\tilde{A}_0)\nabla (c')^k d\lambda_d,$$

where the endomorphism $\tilde{A}_0$, given in lemma 3.2, applied to a matrix is defined column by column and the logarithm of a vector is defined component-by-component. To prove this identity we remark that because of $w_1^k, \dots, w_N^k \in H^1(\Omega)$

$$c_i(w^k) \in H^1(\Omega) \quad \text{for } i = 1, \dots, N$$

and that these functions can be differentiated a.e. according to the classical chain rule (see [56]). We set

$$z := (z_1, \dots, z_N)^\top := B(w^k)\nabla w^k \in \mathbb{R}^{N\times d},$$

where $z_i \in \mathbb{R}^d$ for $i = 1, \dots, N$ and

$$z_{N+1} := -\sum_{i=1}^{N} z_i \in \mathbb{R}^d.$$

Then the definitions of w^k and z_{N+1} yield

$$\nabla w^k : B(w^k)\nabla w^k = \nabla w^k : z = \sum_{i=1}^{N} (\nabla w_i^k \cdot z_i) =$$

$$\sum_{i=1}^{N} \left(\nabla(\ln(c')_i^k - \ln(c')_{N+1}^k)\right) \cdot z_i = \sum_{i=1}^{N} \left(\nabla \ln(c')_i^k - \nabla \ln(c')_{N+1}^k\right) \cdot z_i =$$

$$\sum_{i=1}^{N+1} \nabla \ln(c')_i^k \cdot z_i = \nabla \ln(c')^k : z', \tag{3.35}$$

where we have used $\ln(c_i(w^k)) \in H^1(\Omega)$ for $i = 1, \dots, N+1$, that can be differentiated a.e. according to the classical chain rule, due to the fact that $w_i^k \in L^\infty(\Omega)$ for $i = 1, \dots, N$ and $(c')_i^k \in H^1(\Omega)$ for $i = 1, \dots, N+1$ (see [85]), as well as the definition $z' := (z_1, \dots, z_N, z_{N+1})^\top$. Using

$$\nabla w^k = H(c(w^k))\nabla c(w^k)$$

and

$$B(w^k) = A(c(w^k))H^{-1}(c(w^k)),$$

where $H(c(w^k))$ is the Hessian of h and B is defined as in lemma 3.4, it follows that

$$z = A(c(w^k))\nabla c(w^k)$$

or, equivalently,

$$\nabla c(w^k) = A(c(w^k))^{-1} z.$$

A computation shows

$$-\tilde{A}_0^{-1} z' = \nabla (c')^k$$

using the definition of $c_{N+1}(w^k)$ and the fact that each column of z' is an element of $\mathrm{im}(A_0^{-1})$ being mapped to an element of $\mathrm{im}(A_0^{-1})$ and consequently,

$$z' = -\tilde{A}_0 \nabla (c')^k.$$

Inserting this into (3.35) proves the claim. We recall from the proof of lemma 3.2 that the images of

$$\tilde{A}_0^{-1} := A_0^{-1}|_{\mathrm{im}(A_0^{-1})} \quad \text{and } \tilde{A}_S := A_S|_{\mathrm{im}(A_S)}$$

are given by

$$\mathrm{im}(A_0^{-1}) = \{(1,\dots,1)^\top\}^\perp$$

and

$$\mathrm{im}(A_S((c')^k)) = \mathrm{span}\{\sqrt{(c')^k}\}^\perp = \{C^{-1/2}((c')^k)x : x \in \mathrm{im}(A_0^{-1})\},$$

where

$$C^{\pm 1/2}((c')^k) := \mathrm{diag}(((c')_1^k)^{\pm 1/2},\dots,((c')_{N+1}^k)^{\pm 1/2}) \in \mathbb{R}^{(N+1)\times(N+1)}$$

and the square root of a vector is defined component-by-component here and in the following. Then the definition

$$-A_0^{-1} = C^{1/2}(-A_S)C^{-1/2}$$

implies that

$$-\tilde{A}_0^{-1} = C^{1/2}(-\tilde{A}_S)C^{-1/2}$$

and hence,

$$(-\tilde{A}_S)^{-1} = C^{-1/2}(-\tilde{A}_0)C^{1/2}.$$

We infer that

$$\begin{aligned}\nabla \ln(c')^k : (-\tilde{A}_0)\nabla(c')^k &= 4\nabla\sqrt{(c')^k} : C^{-1/2}((c')^k)(-\tilde{A}_0)C^{1/2}((c')^k)\nabla\sqrt{(c')^k} \\ &= 4\nabla\sqrt{(c')^k} : (-\tilde{A}_S)^{-1}\nabla\sqrt{(c')^k} \ge \frac{4}{\Delta}\sum_{i=1}^{N+1}|\nabla\sqrt{(c')_i^k}|^2.\end{aligned}$$

The inequality follows from lemma 3.2 since $(-\tilde{A}_S)^{-1}$ is a self-adjoint endomorphism whose smallest eigenvalue is larger than $1/\Delta$ and the fact that $\sqrt{(c')_i^k} \in H^1(\Omega)$ can be differentiated a.e. according to the classical chain rule for $i = 1,\dots,N+1$. ❑

Step 4: A Priori Estimates.

Next, we derive some estimates uniform in τ, ϵ and η by means of the entropy-dissipation inequality. The following lemma is a consequence of (3.34) (with w replaced by w^k and $\sigma = 1$), the proof of lemma 3.6 and lemma 3.7.

Lemma 3.8 (*Discrete Entropy Inequality*)**.** *Let $w^k \in \mathcal{V}^N$ be a weak solution to* (3.32)*. Then for $1 \le k \le m$,*

$$\begin{aligned}E(c(w^k)) + \frac{4\tau}{\Delta}\int_\Omega \sum_{i=1}^N |\nabla\sqrt{c_i(w^k)}|^2 d\lambda_d + \epsilon\tau\int_\Omega \left(|\Delta w^k|^2 + |w^k|^2\right) d\lambda_d \\ \le E(c(w^{k-1})),\end{aligned}$$

where $E(c(w^k)) := \int_\Omega h(c(w^k))d\lambda_d$ *for* $k = 0, \dots, m$. *Solving this estimate recursively, it follows that*

$$E(c(w^k)) + \frac{4\tau}{\Delta}\sum_{j=1}^{k}\int_\Omega \sum_{i=1}^{N} |\nabla\sqrt{c_i(w^j)}|^2 d\lambda_d + \epsilon\tau\sum_{j=1}^{k}\int_\Omega \left(|\Delta w^j|^2 + |w^j|^2\right) d\lambda_d \leq E(c(w^0)).$$

Let $w^k \in \mathcal{V}^N$ be a weak solution to (3.32) for $k \in \{1, \dots, m\}$ and set $c^k := c(w^k)$. We define the piecewise-constant-in-time functions

$$w^{(\tau)}(t,x) := \begin{cases} w^0(x), & t = 0,\ x \in \Omega \\ w^k(x), & t \in ((k-1)\tau, k\tau],\ k \in \{1,\dots,m\},\ x \in \Omega \end{cases}$$

such as

$$c^{(\tau)}(t,x) := \begin{cases} (c_1^0(x), \dots, c_N^0(x))^\top, t = 0,\ x \in \Omega \\ c^k(x), t \in ((k-1)\tau, k\tau],\ k \in \{1,\dots,m\},\ x \in \Omega \end{cases}$$

for $t \in [0,T]$ and $x \in \Omega$. The functions $w^{(\tau)}$ and $c^{(\tau)}$ depend on τ, η and ϵ. Recalling the definition of the shift operator (2.39) and the discrete time derivative (2.40) where $f = c$ and $c_0 = (c_1^0, \dots, c_N^0)^\top$ the functions $(c^{(\tau)}, w^{(\tau)})$ solve the following equation in the distributional sense (assuming sufficient boundary conditions):

$$D_\tau c^{(\tau)} - \operatorname{div}(A(c^{(\tau)})\nabla c^{(\tau)}) + \epsilon(\Delta^2 w^{(\tau)} + w^{(\tau)}) = r(c^{(\tau)}), \quad t \in (0,T), x \in \Omega. \tag{3.36}$$

Lemma 3.8 implies the following a priori estimates.

Lemma 3.9. *There exists a constant* $K > 0$ *independent of* ϵ, τ *and* η *such that*

$$\|\sqrt{c_i^{(\tau)}}\|_{L^2(0,T;H^1(\Omega))} + \sqrt{\epsilon}\|w_i^{(\tau)}\|_{L^2(0,T;H^2(\Omega))} \leq K, \tag{3.37}$$

$$\|c_i^{(\tau)}\|_{L^2(0,T;H^1(\Omega))} + \|D_\tau c_i^{(\tau)}\|_{L^2(0,T;\mathcal{V}')} \leq K. \tag{3.38}$$

for $i = 1, \dots, N$.

In the following, $K > 0$ denotes a generic constant independent of ϵ, τ and η.

Proof. From the a.e.-boundedness of $c_i(w^k)$ for $i = 1, \dots, N$ and $k = 1, \dots, m$ it follows

$$\|c_i^{(\tau)}\|_{L^\infty(0,T;L^\infty(\Omega))}, \quad \|\sqrt{c_i^{(\tau)}}\|_{L^\infty(0,T;L^\infty(\Omega))} \leq 1 \tag{3.39}$$

for $i = 1, \dots, N$. This and the entropy inequality of lemma 3.8 yield

$$\|\sqrt{c_i^{(\tau)}}\|^2_{L^2(0,T;H^1(\Omega))} =$$

$$\|\sqrt{c_i^{(\tau)}}\|^2_{L^2(0,T;L^2(\Omega))} + \tau \sum_{k=1}^{m} \left\| \left(\sqrt{c_i^k}\right)_{x_1} \right\|^2_{L^2(\Omega)} + \ldots + \tau \sum_{k=1}^{m} \left\| \left(\sqrt{c_i^k}\right)_{x_d} \right\|^2_{L^2(\Omega)} \leq$$

$$C(N, d, \Omega, \Delta, d_{ij})$$

as well as

$$\sqrt{\epsilon}\|w_i^{(\tau)}\|_{L^2(0,T;H^2(\Omega))} \leq C(N, d, \Omega),$$

where $C(N, d, \Omega, \Delta, d_{ij})$ respectively $C(N, d, \Omega)$ are positive constants that depend on $N, d, \Omega, \Delta, d_{ij}$ respectively N, d, Ω only.

To prove (3.38), we employ the generalised Hölder inequality and obtain for $i = 1, \ldots, N$ and $l = 1, \ldots, d$:

$$\begin{aligned}
\|(c_i^k)_{x_l}\|^2_{L^2(\Omega)} &= 4 \left\| \sqrt{c_i^k} \left(\sqrt{c_i^k}\right)_{x_l} \right\|^2_{L^2(\Omega)} \\
&\leq 4 \left\| \left(\sqrt{c_i^k}\right)_{x_l} \right\|^2_{L^2(\Omega)} \cdot \left\| \sqrt{c_i^k} \right\|^2_{L^\infty(\Omega)} \\
&\leq 4 \left\| \left(\sqrt{c_i^k}\right)_{x_l} \right\|^2_{L^2(\Omega)}
\end{aligned}$$

and thus

$$\|c_i^{(\tau)}\|^2_{L^2(0,T;H^1(\Omega))} = \|c_i^{(\tau)}\|^2_{L^2(0,T;L^2(\Omega))} + \tau \sum_{l=1}^{d} \sum_{k=1}^{m} \|(c_i^k)_{x_l}\|^2_{L^2(\Omega)} \leq$$

$$\|c_i^{(\tau)}\|^2_{L^2(0,T;L^2(\Omega))} + 4\tau \sum_{l=1}^{d} \sum_{k=1}^{m} \left\| \left(\sqrt{c_i^k}\right)_{x_l} \right\|^2_{L^2(\Omega)} \leq C(N, d, \Omega, \Delta, d_{ij})$$

using (3.37) and (3.39).

Let $i = 1, \ldots, N$ and $\phi \in L^2(0, T; \mathcal{V})$. By (3.36) and Hölder's inequality,

$$\left| \int_0^T \left\langle D_\tau c_i^{(\tau)}(t), \phi(t) \right\rangle_{\mathcal{V}} d\lambda(t) \right| \leq$$

$$\sum_{j=1}^{N} \sum_{k=1}^{d} \|a_{ij}(c^{(\tau)})\|_{L^\infty(0,T;L^\infty(\Omega))} \|\phi_{x_k}\|_{L^2(0,T;L^2(\Omega))} \|(c_j^{(\tau)})_{x_k}\|_{L^2(0,T;L^2(\Omega))} +$$

$$\epsilon\|w_i^{(\tau)}\|_{L^2(0,T;L^2(\Omega))}\|\phi\|_{L^2(0,T;L^2(\Omega))} + \epsilon\|\Delta w_i^{(\tau)}\|_{L^2(0,T;L^2(\Omega))}\|\Delta\phi\|_{L^2(0,T;L^2(\Omega))} +$$

$$\|r_i(c^{(\tau)})\|_{L^2(0,T;L^2(\Omega))}\|\phi\|_{L^2(0,T;L^2(\Omega))}.$$

Using estimate (3.38) and the fact that $r_i(c^{(\tau)})$ and $a_{ij}(c^{(\tau)})$ are bounded uniformly in $c^{(\tau)}$ for $i,j=1,\dots,N$ (see lemma 3.3) the above term is smaller that or equal to

$$(1+d)\sqrt{\epsilon}\sqrt{\epsilon}\|w_i^{(\tau)}\|_{L^2(0,T;\mathcal{V})}\|\phi\|_{L^2(0,T;\mathcal{V})}+$$

$$C_{r_i}\|\phi\|_{L^2(0,T;\mathcal{V})}+K^{N-1}(N-1)!(1/\delta^N)C(N,d,\Omega,\Delta,d_{ij})\|\phi\|_{L^2(0,T;\mathcal{V})}\leq$$

$$C(N,d,\Omega,\Delta,d_{ij},C_{r_i})\|\phi\|_{L^2(0,T;\mathcal{V})}.$$

In order to obtain the last inequality we have assumed $\epsilon<1$ and we have used (3.37). Thus,

$$\|D_\tau c_i^{(\tau)}\|_{L^2(0,T;\mathcal{V}')}\leq C(N,d,\Omega,\Delta,d_{ij},C_{r_i}),$$

where $C(N,d,\Omega,\Delta,d_{ij},C_{r_i})>0$, finishing the proof. ❑

Step 5: Limits $\epsilon\to 0$, $\tau\to 0$ and $\eta\to 0$.

As in the proof of theorem 2.1 we assume that $\epsilon<1$ and we will choose w.l.o.g. same subsequences that are not relabeled.

We apply the compactness result of [31] (theorem 1) to the family $(c_i^{(\tau_m)})_{m\in\mathbb{N}}$ for $i=1,\dots,N$. Since the embedding $H^1(\Omega)\hookrightarrow L^p(\Omega)$ is compact and the embedding $L^p(\Omega)\hookrightarrow\mathcal{V}'$ is continuous for $1<p<6$, (3.38) implies the existence of a subsequence, which is not relabeled, such that, as $(\epsilon,\tau)\to 0$,

$$c_i^{(\tau)}\to c_i\quad\text{strongly in } L^2(0,T;L^p(\Omega)),\quad 1<p<6,\quad i=1,\dots,N.$$

We set $c:=(c_1,\dots,c_N)^\top$. As a consequence,

$$0\leq c_i,\quad \sum_{i=1}^N c_i\leq 1\quad\text{and}\quad c_{N+1}:=1-\sum_{i=1}^N c_i\geq 0.$$

a.e. in $Q_T:=(0,T)\times\Omega$ for $i=1,\dots,N$. Because of the uniform L^∞-bounds for $c_i^{(\tau)}$ and the a.e.-convergence of the sequences in Q_T, the above convergence holds even in the space $L^p(Q_T)$ for all $1\leq p<\infty$.

Furthermore, by (3.37)–(3.38) and the Eberlein-Šmuljan theorem, up to subsequences,

$$\begin{aligned}(c_i^{(\tau)})_{x_l}&\rightharpoonup (c_i)_{x_l}\quad\text{weakly in } L^2(0,T;L^2(\Omega)),\\ D_\tau c_i^{(\tau)}&\rightharpoonup \partial_t c_i\quad\text{weakly in } L^2(0,T;\mathcal{V}'),\\ \epsilon w_i^{(\tau)}&\to 0\quad\text{strongly in } L^2(0,T;H^2(\Omega)).\end{aligned}$$

for $i = 1, \dots, N$ and $l = 1, \dots, d$. Since $c_i^{(\tau)}$ converges strongly to c_i in $L^p(Q_T)$ for all $1 \le p < \infty$ and since $c_i^{(\tau)}$ and c_i are uniformly bounded in $L^\infty(Q_T)$ by 1, we obtain

$$\det(A^{-1}(c^{(\tau)})) \longrightarrow \det(A^{-1}(c))$$
$$a_{ij}(c^{(\tau)}) \longrightarrow a_{ij}(c)$$

strongly in $L^p(0,T;L^p(\Omega))$ for $1 \le p < \infty$ and $i,j = 1, \dots, N$, as well as

$$\det(A^{-1}(c)) \ge \delta^N > 0 \quad \text{a.e.},$$

showing that

$$a_{ij}(c^{(\tau)})(c_j^{(\tau)})_{x_l} \rightharpoonup a_{ij}(c)(c_j)_{x_l}$$

weakly in $L^2(0,T;L^2(\Omega))$ for $i,j = 1, \dots, N$, $l = 1, \dots, d$. Furthermore,

$$r_i(c^{(\tau)}) \to r_i(c) \quad \text{strongly in } L^2(0,T;L^2(\Omega)),$$

for $i = 1, \dots, N$.

The above convergence results are sufficient to pass to the limit $(\epsilon, \tau) \to 0$ in the weak formulation of (3.36), showing that c satisfies

$$\partial_t c - \operatorname{div}(A(c)\nabla c) = r(c) \quad \text{in } L^2(0,T;\mathcal{V}').$$

This proves the existence of a weak solution to (3.10)–(3.11) and (3.14)–(3.15) with initial data satisfying $c_i^0 \ge \eta > 0$ a.e. for $i = 1, \dots, N$ and $\sum_{i=1}^N c_i^0 \le 1 - \eta$ a.e.. In order to perform the limit $\eta \to 0$, we observe that the initial entropy is finite and that the estimates in lemma 3.9 are independent of η such that the above compactness arguments can be applied. Furthermore, the coefficients of $A(c)$ are well-defined if $c_i = 0$ or $c_i = 1$ for any $i = 1, \dots, N$ (see lemma 3.3), which allows us to perform the limit also in the diffusion matrix. In this way, we obtain the existence result for general initial data with $c_i^0 \ge 0$ a.e. and $\sum_{i=1}^N c_i^0 \le 1$ a.e.. This proves theorem 3.5 as T has been chosen arbitrarily.

Remark. 1. The regularity on the boundary $\partial\Omega \in C^{1,1}$ is needed for the a priori estimate

$$\|f\|_{H^2(\Omega)} \le C\|g\|_{L^2(\Omega)}$$

of the elliptic problem

$$-\Delta f + f = g \quad \text{in } \Omega, \quad \nabla f \cdot \nu = 0 \quad \text{on } \partial\Omega$$

that is used to prove the existence of solutions to the time-discrete problem in step 2 of the proof. As the inequality does only holds for functions that satisfy homogeneous Neumann boundary conditions we have chosen the space $\mathcal{V}$ instead of $H^2(\Omega)$ in our existence proof.

2. Notice that our proof also works for diffusion coefficients depending on the mole fractions $c_1, \ldots, c_N$ if the coefficients d_{ij}, $i, j = 1, \ldots, N+1$, $i \neq j$, are continuous functions of c that are uniformly bounded from above and below.

3. The inequality imposed on the production rates is needed to prove that the entropy is non-increasing in time. It is satisfied if, for instance, $N = 4$ and

$$r_1 = r_3 = c_2 c_4 - c_1 c_3, \quad r_2 = r_4 = c_1 c_3 - c_2 c_4$$

[30]. For the existence result, the inequality can be weakened by

$$\sum_{i=1}^{N+1} r_i(c') \ln c_i \leq C_r \quad \text{for all } 0 < c_1, \ldots, c_{N+1} \leq 1,$$

where $C_r > 0$ is some constant independent of c_i, $i = 1, \ldots, N+1$. This condition is satisfied, for instance, in the tumour growth model in [53].

4. Our existence result is valid for at most three space dimensions. This restriction comes from the compact embedding

$$H^2(\Omega) \hookrightarrow L^\infty(\Omega)$$

holding for $1 \leq d \leq 3$ only and the fact that this case is natural in view of the application. The boundedness property allows us to apply the chain rule needed for the derivation of the entropy inequality. However, the restriction to three space dimensions can be overcome by employing the regularisation Δ^{2k} in (3.32) instead of Δ^2 with $k > d/4$, $k \in \mathbb{N}$. Indeed, in this situation, the solutions of the time-discrete problem are considered in the space $H^{2k}(\Omega)$ and the embedding

$$H^{2k}(\Omega) \hookrightarrow L^\infty(\Omega)$$

is compact.

3.5 Long-Time Behaviour of Solutions

We consider (3.10)–(3.11) and (3.14)–(3.15) under the assumptions of theorem 3.5 for vanishing production rates, i.e. we assume

$$r_1 = 0, \ldots, r_N = 0,$$

as well as its homogeneous steady state

$$\overline{c}_1^0, \ldots, \overline{c}_{N+1}^0 := 1 - \sum_{i=1}^{N} \overline{c}_i^0$$

defined in (1.18). We remark that $\overline{c}_i^0$ exists due to the assumptions made on the initial data and that it is an element of $[0,1]$ for $i = 1, \ldots, N+1$. Under the assumption that $\overline{c}_i^0$ is positive for $i = 1, \ldots, N+1$ we are able to prove that the solution $(c_1, \ldots, c_{N+1})^\top$, where

$$c_{N+1} := 1 - \sum_{i=1}^{N} c_i,$$

constructed in theorem 3.5, converges exponentially fast to this stationary state. Recalling the definition of the relative entropy $E^*(c)$ for c given in (1.19) we can formulate

Theorem 3.10. *Let the assumptions of theorem 3.5 hold. We suppose that $r_i = 0$ for $i = 1, \ldots, N$ and*

$$\min_{i=1,\ldots,N+1} \|c_i^0\|_{L^1(\Omega)} > 0.$$

Let $(c_1, \ldots, c_{N+1})^\top$ be the weak solution constructed in theorem 3.5 and define

$$c^0 := (c_1^0, \ldots, c_N^0)^\top.$$

Then there exist constants $C > 0$, depending only on Ω and $\lambda > 0$, depending only on Ω and d_{ij}, $i, j = 1, \ldots, N$, $i \neq j$ such that

$$\|c_i(t,.) - \overline{c}_i^0\|_{L^1(\Omega)} \leq Ce^{-\lambda t}\sqrt{E^*(c^0)}, \quad t > 0, \quad i = 1, \ldots, N+1,$$

where $\overline{c}_i^0$ is defined in (1.18) for $i = 1, \ldots, N+1$.

Let us remark that $E^*(c^0)$ is non-negative which follows from

$$E^*(c^0) = \sum_{i=1}^{N+1} \int_\Omega c_i^0 \ln \frac{c_i^0}{\overline{c}_i^0} d\lambda_d = \sum_{i=1}^{N+1} \int_\Omega c_i^0 \ln \frac{c_i^0}{\overline{c}_i^0} - c_i^0 + \overline{c}_i^0 d\lambda_d$$

and the inequality

$$x \cdot \ln\left(\frac{x}{y}\right) - x + y \geq 0$$

holding for $x \geq 0$ and $y > 0$.

Proof of Theorem 3.10

First, we prove that, if the production rates vanish, the L^1-norms of the semi-discrete mole fractions are bounded. We assume that there exists $0 < \eta < 1$ such that $c_i^0 \geq \eta$ a.e. for $i = 1, \ldots, N+1$.

Lemma 3.11 (*Bounded L^1-Norms*)**.** *Let $r = 0$. Then there exists a constant $\gamma_0 > 0$, only depending on c^0, such that for all $0 < \gamma \leq \min\{1, \gamma_0\}$ and*

sufficiently small $\epsilon > 0$, depending on γ, the semi-discrete mole fractions $c^k := c(w^k)$, where $w^k \in \mathcal{V}^N$ solves (3.32), satisfy

$$(1-\gamma)\|c_i^0\|_{L^1(\Omega)} \le \|c_i^k\|_{L^1(\Omega)} \le (1+\gamma)\|c_i^0\|_{L^1(\Omega)}, \quad i=1,\ldots,N, \tag{3.40}$$

$$\|c_{N+1}^0\|_{L^1(\Omega)} - \gamma\sum_{i=1}^N \|c_i^0\|_{L^1(\Omega)} \le \|c_{N+1}^k\|_{L^1(\Omega)} \le \|c_{N+1}^0\|_{L^1(\Omega)} + \gamma\sum_{i=1}^N \|c_i^0\|_{L^1(\Omega)} \tag{3.41}$$

for $k \in \{1,\ldots,m\}$, where $c_{N+1}^k := c_{N+1}(w^k)$. Furthermore,

$$\|c_{N+1}^k\|_{L^1(\Omega)} \ge \frac{1}{2}\|c_{N+1}^0\|_{L^1(\Omega)} > 0$$

for $1 \le k \le m$.

Proof. We recall that $\tau := T/m$ for $T > 0$ and $m \in \mathbb{N}$. Let $k \in \{1,\ldots,m\}$. Using the test function $v = e_i$ in (3.32), where e_i is the i^{th} unit vector of $\mathbb{R}^N$, we find that

$$\int_\Omega c_i^k d\lambda_d = \int_\Omega c_i^{k-1} d\lambda_d - \epsilon\tau\int_\Omega w_i^k d\lambda_d, \quad i=1,\ldots,N,$$

where we abbreviated $c_i^k = c_i(w^k)$. Solving these recursive equations, we obtain

$$\int_\Omega c_i^k d\lambda_d = \int_\Omega c_i^0 d\lambda_d - \epsilon\tau\sum_{j=1}^k\int_\Omega w_i^j d\lambda_d, \quad 1 \le k \le m. \tag{3.42}$$

Because of the ϵ-terms, we do not have discrete "mass conservation" but we will derive uniform L^1-bounds.

The entropy inequality in lemma 3.8 shows that

$$\begin{aligned} E(c^k) + \epsilon\tau\int_\Omega \left((\Delta w_i^k)^2 + (w_i^k)^2\right) d\lambda_d &\le E(c^k) + \epsilon\tau\int_\Omega \left(|\Delta w^k|^2 + |w^k|^2\right) d\lambda_d \\ &\le E(c^{k-1}), \quad 1 \le k \le m, \quad i=1,\ldots,N. \end{aligned}$$

Solving this inequality recursively, we infer from $E(c^k) \ge -\lambda_d(\Omega)(N+1)$ that

$$\epsilon\tau\sum_{j=1}^k \|w_i^j\|_{L^2(\Omega)}^2 \le E(c^0) - E(c^k) \le E(c^0) + \lambda_d(\Omega)(N+1).$$

Consequently, using the continuous embedding $L^2(\Omega) \hookrightarrow L^1(\Omega)$, the inequality

$$\sum_{j=1}^k x_j \le \sqrt{k}\left(\sum_{j=1}^k x_j^2\right)^{1/2} \qquad \text{for } x_j \ge 0, \;\; j=1,\ldots,k, \quad k \in \mathbb{N}$$

(see [69]) as well as $k\tau \le T$,

$$\begin{aligned}\epsilon\tau\sum_{j=1}^{k}\int_\Omega |w_i^j|d\lambda_d &\le \epsilon\tau\lambda_d(\Omega)^{1/2}\sum_{j=1}^{k}\|w_i^j\|_{L^2(\Omega)}\\ &\le \epsilon\tau\lambda_d(\Omega)^{\frac12}\sqrt{k}\left(\sum_{j=1}^{k}\|w_i^j\|_{L^2(\Omega)}^2\right)^{1/2}\\ &\le \lambda_d(\Omega)^{1/2}\sqrt{\epsilon\tau k(E(c^0)+\lambda_d(\Omega)(N+1))}\\ &\le \lambda_d(\Omega)^{1/2}\sqrt{\epsilon T(E(c^0)+\lambda_d(\Omega)(N+1))}.\end{aligned}$$

Let $\gamma > 0$ and $0 < \epsilon < 1$ satisfy

$$0 < \gamma \le \min\left\{1, \gamma_0 := \left(2\sum_{i=1}^{N}\|c_i^0\|_{L^1(\Omega)}\right)^{-1}\|c_{N+1}^0\|_{L^1(\Omega)}\right\}, \tag{3.43}$$

$$0 < \sqrt{\epsilon} \le \frac{\gamma\min_{l=1,\dots,N}\|c_l^0\|_{L^1(\Omega)}}{\lambda_d(\Omega)^{1/2}\sqrt{T(E(c^0)+\lambda_d(\Omega)(N+1))}}. \tag{3.44}$$

Then, in view of (3.42),

$$(1-\gamma)\|c_i^0\|_{L^1(\Omega)} \le \|c_i^k\|_{L^1(\Omega)} = \|c_i^0\|_{L^1(\Omega)} - \epsilon\tau\sum_{j=1}^{k}\int_\Omega w_i^j d\lambda_d \le (1+\gamma)\|c_i^0\|_{L^1(\Omega)}.$$

These relations hold for all $i = 1,\dots,N$ and $k = 1,\dots,m$. In the case of $E(c^0)+\lambda_d(\Omega)(N+1) = 0$ (3.40) is trivial. For $i = N+1$, we estimate (using (3.40))

$$\begin{aligned}\int_\Omega c_{N+1}^k d\lambda_d &= \int_\Omega\left(1-\sum_{i=1}^{N}c_i^k\right)d\lambda_d \ge \int_\Omega\left(1-(1+\gamma)\sum_{i=1}^{N}c_i^0\right)d\lambda_d\\ &= \int_\Omega c_{N+1}^0 d\lambda_d - \gamma\sum_{i=1}^{N}\int_\Omega c_i^0 d\lambda_d \ge \frac12\|c_{N+1}^0\|_{L^1(\Omega)} > 0,\end{aligned}$$

by definition of γ_0 for $k = 1,\dots,m$. A similar computation yields

$$\int_\Omega c_{N+1}^k d\lambda_d \le \int_\Omega\left(1-(1-\gamma)\sum_{i=1}^{N}c_i^0\right)d\lambda_d = \|c_{N+1}^0\|_{L^1(\Omega)} + \gamma\sum_{i=1}^{N}\|c_i^0\|_{L^1(\Omega)}.$$

This proves the lemma. ❑

For the proof of theorem 3.10, we use the notation introduced in section 3.4 and define further:

$$c^k = (c_1^k,\dots,c_N^k)^\top := c(w^k), \quad (c')^k := (c_1^k,\dots,c_{N+1}^k)^\top, \quad 0 \le k \le m,$$

where $w^k \in \mathcal{V}^N$ solves (3.32) for $k = 1, \dots, m$ and $c_{N+1}^k := 1 - \sum_{i=1}^N c_i^k$,

$$\overline{c}^k = (\overline{c}_1^k, \dots, \overline{c}_N^k)^\top, \quad \overline{c'}^k := (\overline{c}_1^k, \dots, \overline{c}_{N+1}^k)^\top, \quad 0 \le k \le m,$$

where

$$\overline{c}_i^k := \lambda_d(\Omega)^{-1} \int_\Omega c_i^k d\lambda_d \quad \text{for } i = 1, \dots, N+1.$$

Furthermore, we set

$$w^k = (w_1^k, \dots, w_N^k)^\top \quad \text{and} \quad \overline{w}^k = (\overline{w}_1^k, \dots, \overline{w}_N^k)^\top,$$

where

$$\overline{w}_i^k := \ln(\overline{c}_i^k / \overline{c}_{N+1}^k) \quad \text{for } i = 1, \dots, N, \quad 1 \le k \le m.$$

We recall the definition of the discrete relative entropy for $0 \le k \le m$

$$E^*(c^k) := \sum_{i=1}^{N+1} \int_\Omega c_i^k \ln \frac{c_i^k}{\overline{c}_i^0} d\lambda_d.$$

Employing the test function $w^k - \overline{w}^k$ in (3.32), we obtain for $k \in \{1, \dots, m\}$

$$\frac{1}{\tau} \int_\Omega (c(w^k) - c(w^{k-1})) \cdot (w^k - \overline{w}^k) d\lambda_d + \int_\Omega \nabla w^k : B(w^k) \nabla w^k d\lambda_d$$

$$+\epsilon \int_\Omega (|\Delta w^k|^2 + w^k \cdot (w^k - \overline{w}^k)) d\lambda_d = 0.$$

We estimate the integrals term by term.

Using the definition of c_{N+1}^k for $k = 0, \dots, m$, recalling the variable transformation and the definition of $\overline{w}^k$, a computation shows that

$$(c(w^k) - c(w^{k-1})) \cdot w^k = ((c')^k - (c')^{k-1}) \cdot \ln(c')^k$$

and

$$(c(w^k) - c(w^{k-1})) \cdot \overline{w}^k = ((c')^k - (c')^{k-1}) \cdot \ln(\overline{c'})^k,$$

where the logarithm of a vector is defined component-by-component as usual. Therefore, by the definition of $\overline{w}^k$ we find that

$$\begin{aligned}
&\int_\Omega (c(w^k) - c(w^{k-1})) \cdot (w^k - \overline{w}^k) d\lambda_d \\
&\quad = \int_\Omega ((c')^k - (c')^{k-1}) \cdot \ln(c')^k - ((c')^k - (c')^{k-1}) \cdot \ln(\overline{c'}^k) d\lambda_d \\
&\quad = \int_\Omega ((c')^k - (c')^{k-1}) \cdot \ln \frac{(c')^k}{\overline{c'}^0} d\lambda_d + \int_\Omega ((c')^k - (c')^{k-1}) \cdot \ln \frac{\overline{c'}^0}{\overline{c'}^k} d\lambda_d,
\end{aligned}$$

where the logarithm of the quotient of two vectors is defined as the difference of the logarithms of the vectors. The first integral on the right-hand side can be estimated by employing the convexity of the entropy density h as a function of $c_1, \dots, c_{N+1}$, which implies that

$$\begin{aligned} h((c')^k) - h((c')^{k-1}) &\le \nabla h((c')^k) \cdot ((c')^k) - (c')^{k-1}) \\ &= \ln((c')^k) \cdot ((c')^k - (c')^{k-1}). \end{aligned}$$

Thus, because of $\sum_{i=1}^{N+1} c_i^k = 1$ and the definition of $E^*(c^k)$ for $k = 0, \dots, m$,

$$\int_\Omega ((c')^k - (c')^{k-1}) \cdot \ln \frac{(c')^k}{\overline{c'}^0} d\lambda_d \ge E^*(c^k) - E^*(c^{k-1}).$$

For the second integral, we employ the bounds (3.40)–(3.41) as well as $\gamma < 1$ and $\epsilon > 0$ sufficiently small, which yields

$$\frac{1}{1+\gamma} \le \frac{\overline{c}_i^0}{\overline{c}_i^k} \le \frac{1}{1-\gamma}, \quad i = 1, \dots, N, \quad \frac{1}{1+\overline{\gamma}} \le \frac{\overline{c}_{N+1}^0}{\overline{c}_{N+1}^k} \le \frac{1}{1-\overline{\gamma}}$$

for $k \in \{1, \dots, m\}$, where $\overline{\gamma} := \gamma(1/\overline{c}_{N+1}^0 - 1) \in (0,1)$. Here, we have used again that $\sum_{i=1}^{N+1} \overline{c}_i^0 = 1$. Then, with $C_1 := \lambda_d(\Omega)$,

$$\begin{aligned} &\int_\Omega ((c')^k - (c')^{k-1}) \cdot \ln \frac{\overline{c'}^0}{\overline{c'}^k} d\lambda_d \ge \\ &- \int_\Omega \sum_{i=1}^N c_i^k \ln(1+\gamma) d\lambda_d - \int_\Omega c_{N+1}^k \ln(1+\overline{\gamma}) d\lambda_d \\ &+ \int_\Omega \sum_{i=1}^N c_i^{k-1} \ln(1-\gamma) d\lambda_d + \int_\Omega c_{N+1}^{k-1} \ln(1-\overline{\gamma}) d\lambda_d \ge \\ &- C_1 \ln \frac{(1+\gamma)(1+\overline{\gamma})}{(1-\gamma)(1-\overline{\gamma})}. \end{aligned}$$

We have already proven in section 3.4 that

$$\int_\Omega \nabla w^k : B(w^k) \nabla w^k d\lambda_d \ge \frac{4}{\Delta} \int_\Omega \sum_{i=1}^{N+1} |\nabla \sqrt{(c')_i^k}|^2 d\lambda_d.$$

Applying Young's inequality to the ϵ-term, it follows for $k = 1, \dots, m$ that

$$E^*(c^k) - E^*(c^{k-1}) + \frac{4\tau}{\Delta} \int_\Omega \sum_{i=1}^{N+1} |\nabla \sqrt{(c')_i^k}|^2 d\lambda_d \le$$

$$\frac{\epsilon\tau}{2}\int_\Omega |\overline{w}^k|^2 d\lambda_d + C_1 \ln\frac{(1+\gamma)(1+\overline{\gamma})}{(1-\gamma)(1-\overline{\gamma})}.$$

The logarithmic Sobolev inequality (see [44] or [29] for instance) as well as the bounds (3.40)–(3.41) show that

$$\begin{aligned}
E^*(c^k) &= \sum_{i=1}^{N+1}\int_\Omega c_i^k \ln\frac{c_i^k}{\overline{c}_i^k} d\lambda_d + \sum_{i=1}^{N+1}\int_\Omega c_i^k \ln\frac{\overline{c}_i^k}{\overline{c}_i^0} d\lambda_d \le C(\Omega)\sum_{i=1}^{N+1}\int_\Omega |\nabla\sqrt{c_i^k}|^2 d\lambda_d \\
&\quad + \sum_{i=1}^{N}\int_\Omega c_i^k \ln(1+\gamma) d\lambda_d + \int_\Omega c_{N+1}^k \ln(1+\overline{\gamma}) d\lambda_d \\
&\le C(\Omega)\int_\Omega \sum_{i=1}^{N+1} |\nabla\sqrt{(c')_i^k}|^2 d\lambda_d + C_1\ln((1+\gamma)(1+\overline{\gamma})),
\end{aligned}$$

where $C(\Omega)$ denotes a positive constant depending on Ω and d only and $C_1 > 0$ depends on N and $\lambda_d(\Omega)$, from which we infer that

$$(1+C_2\tau)E^*(c^k) \le E^*(c^{k-1}) + \frac{\epsilon\tau}{2}\int_\Omega |\overline{w}^k|^2 d\lambda_d + C_\gamma$$

for $k = \{1,\dots,m\}$, where $C_2 := 4/(C(\Omega)\Delta)$ and

$$C_\gamma := C_1 \ln\frac{(1+\gamma)(1+\overline{\gamma})}{(1-\gamma)(1-\overline{\gamma})} + \frac{4C_1}{C(\Omega)\Delta}\ln((1+\gamma)(1+\overline{\gamma})).$$

In the above inequality, we have assumed that $\tau \le 1$. We can estimate $\overline{w}^k$ by using the bounds for $\overline{c}^k$ of lemma 3.11:

$$\int_\Omega |\overline{w}^k|^2 d\lambda_d \le \sum_{i=1}^N \int_\Omega \left(|\ln\overline{c}_i^k| + |\ln\overline{c}_{N+1}^k|\right)^2 d\lambda_d \le C_3,$$

where $C_3 > 0$ depends on the L^1-norm of c_i^0 for $i = 1,\dots,N+1$, γ, $\lambda_d(\Omega)$ and N. Hence

$$E^*(c^k) \le (1+C_2\tau)^{-1}E^*(c^{k-1}) + \frac{\epsilon\tau}{2}C_3(1+C_2\tau)^{-1} + C_\gamma(1+C_2\tau)^{-1}.$$

Solving these recursive inequalities, we conclude that for $k = 1,\dots,m$

$$E^*(c^k) \le (1+C_2\tau)^{-k}E^*(c^0) + \frac{\epsilon\tau}{2}C_3\sum_{j=1}^k (1+C_2\tau)^{-j} + C_\gamma\sum_{j=1}^k (1+C_2\tau)^{-j}.$$

The sum contains the first terms of the geometric series:

$$\sum_{j=1}^k (1+C_2\tau)^{-j} \le \frac{1}{1-(1+C_2\tau)^{-1}} - 1 = \frac{1}{C_2\tau},$$

yielding

$$E^*(c^{(\tau)}(t,\cdot)) \leq (1+C_2\tau)^{-t/\tau}E^*(c^0) + \frac{\epsilon C_3}{2C_2} + \frac{C_\gamma}{C_2\tau}, \quad 0 < t \leq T.$$

Now, we choose sequences for ϵ, τ and γ such that $\gamma \to 0$, $C_\gamma/\tau \to 0$ and (3.44) is satisfied (then also $\epsilon \to 0$). This is possible since $C_\gamma \to 0$ as $\gamma \to 0$. Then, because of $c_i^{(\tau)} \to c_i$ in $L^2(0,T;L^2(\Omega))$ for $i = 1,\ldots,N$, the limit $(\epsilon,\tau,\gamma) \to 0$ leads to

$$E^*(c(t,\cdot)) \leq e^{-C_2 t}E^*(c^0), \quad 0 < t \leq T.$$

Moreover, we can pass to the limit $\eta \to 0$. Finally, since $\int\limits_\Omega c_i(t,\cdot)d\lambda_d = \int\limits_\Omega c_i^0 d\lambda_d$ for $i = 1,\ldots,N+1$, $t > 0$ (see lemma 3.11), we can apply a Csiszár-Kullback type inequality (see for instance [78]) to finish the proof as T has been chosen arbitrary.

Chapter 4

Outlook

Let us mention some open problems in this chapter that could be the subject of future research.

In chapter 2 and 3 we have considered two particular cross-diffusion systems and could prove the existence of bounded weak solutions to the corresponding initial-boundary-value problems. A question that remains open is whether these solutions are unique or not.

Furthermore, in section 2.3 we have shown that a solution of the tumour growth model exists if the pressure coefficient θ is smaller than $4/\sqrt{\beta}$. Although our methods do not work for general θ it would be interesting to analyse whether this bound can be improved. Another important aspect would be the investigation of other methods leading to an existence result for the tumour growth model for arbitrary θ. When we recall the numerical results presented in section 2.4 we notice that the peak in the volume fraction of the extracellular matrix indicates a travelling wave structure of our system so that we could use travelling wave solutions as a possible approach to the problem. For an application of travelling wave solutions to a model arising from biology we refer to [45], where the FitzHugh-Nagumo nerve model is considered. The idea of analysing cross-diffusion systems with travelling wave solutions has been used in [80] for example, where their existence is proven for the Shigesada-Kawasaki-Teramoto model (1.7)–(1.8).

Under isobaric and isothermal conditions we have proven the existence of solutions to Maxwell-Stefan systems for ideal gaseous mixtures in section 3.4. The question whether there exist solutions in the non-isobaric, non-isothermal case or for non-ideal gaseous mixtures is still open however.

It would certainly be rewarding to have a look at more general cross-diffusion systems. In [65] a general 2×2-cross-diffusion system is derived for two spa-

tially interacting populations

$$\begin{pmatrix} u_1 \\ u_2 \end{pmatrix}_t - \operatorname{div}\left(A(u_1, u_2) \nabla \begin{pmatrix} u_1 \\ u_2 \end{pmatrix} \right) = 0, \tag{4.1}$$

where u_i denotes the density of the i^{th} population for $i = 1, 2$. This system is obtained by starting from a model in one space dimension that is continuous in time but discrete in space and passing to a model that is also continuous in space. The coefficients in the diffusion matrix A are of general form. Neglecting the external potentials respectively the right-hand side in the model considered in [20] respectively in the Shigesada-Kawasaki-Teramoto population model (1.7)–(1.8) we notice that these cross-diffusion systems are special cases of the model analysed in [65]. It would be interesting to investigate under which assumptions made on the coefficients of A we can prove an existence result to (4.1) equipped with initial and homogeneous Neumann boundary conditions using similar methods as in chapter 2 and 3.

Appendix A

Matrix Analysis

We recall some definitions and results from matrix analysis regarding the eigenvalues of special matrices such as symmetric, quasi-positive and irreducible or rank-one matrices. Although most of the results in this appendix are valid for matrices with complex elements, we consider the real case only and refer to the literature for the general situation [48], [68], [76]. In the following the unit matrix in $\mathbb{R}^{n\times n}$ is denoted by I_n and $n \in \mathbb{N}$.

Definition A.1. A vector $x \in \mathbb{R}^n$ is called *positive* if all components are non-negative and at least one component is positive. It is called *strictly positive* if all components are positive [76].

Definition A.2. Let $A \in \mathbb{C}^{n\times n}$ be a square matrix and let $\sigma(A)$ denote its spectrum. Then the *spectral radius* of A is given by

$$r(A) := \max\{|\lambda| : \lambda \in \sigma(A)\}$$

and the *spectral bound* of A is defined as

$$s(A) := \max\{\Re(\lambda) : \lambda \in \sigma(A)\}.$$

Definition A.3. An eigenvalue of $A \in \mathbb{C}^{n\times n}$ is called *semi-simple* if its algebraic and geometric multiplicities coincide and *simple* if its algebraic multiplicity (and hence also its geometric multiplicity) equals one.

The following theorem is proven in [68] (see theorem 3.4).

Theorem A.1. *Let $A \in \mathbb{R}^{n\times n}$ and let $\lambda \in \sigma(A)$ be a real eigenvalue. Then λ is semi-simple if and only if*

$$\mathbb{R}^n = \operatorname{im}(A - \lambda I_n) \oplus \ker(A - \lambda I_n).$$

Definition A.4. A matrix $A \in \mathbb{R}^{n\times n}$ is called *quasi-positive* if $A \neq 0$, i.e. A is not equal to the zero matrix and $a_{ij} \geq 0$ for all $i, j = 1, \ldots, n$, $i \neq j$. For $n \geq 2$ a matrix A is called *irreducible* if for any proper non-empty subset $M \subseteq \{1, \ldots, n\}$ there exist $i \in M$ and $j \notin M$ such that $a_{ji} \neq 0$ and for $n = 1$ A is said to be irreducible if $A \neq 0$.

For quasi-positive and irreducible matrices, the following result holds (see theorem A.45 and remark A.46 in [76]).

Theorem A.2 (*Perron-Frobenius*)**.** *Let $A \in \mathbb{R}^{n\times n}$ be a quasi-positive and irreducible matrix. Then its spectral bound $s(A)$ is a simple eigenvalue of A associated with a strictly positive eigenvector and $s(A) > \Re(\lambda)$ for all $\lambda \in \sigma(A)$, $\lambda \neq s(A)$. All eigenvalues of A different from $s(A)$ have no positive eigenvector.*

The spectrum of rank-one matrices can be determined explicitly (see lemma 2 in section 3.8 in [68]). Notice that any rank-one matrix $A \in \mathbb{R}^{n\times m}$, $m, n \in \mathbb{N}$, can be written in the form $A = x \cdot y^\top$, where $x \in \mathbb{R}^n$, $y \in \mathbb{R}^m$.

Proposition A.1 (*Spectrum of Rank-One Matrices*)**.** *Let x, $y \in \mathbb{R}^n$. Then*

$$\sigma(x \cdot y^\top) = \{0, \ldots, 0, x \cdot y\},$$

i.e. $x \cdot y$ is a simple eigenvalue.

We recall two results on eigenvalues of products and sums of symmetric matrices.

Theorem A.3. *Let $A \in \mathbb{R}^{n\times n}$ be symmetric and positive definite and let $B \in \mathbb{R}^{n\times n}$ be symmetric. Then the number of positive (respectively negative) eigenvalues of AB equals that for B.*

For a proof, we refer to proposition 6.1 in [68].

Theorem A.4 (*Weyl*)**.** *Let A, $B \in \mathbb{R}^{n\times n}$ be symmetric and let the eigenvalues $\lambda_i(A)$ of A and $\lambda_i(B)$ of B, $i = 1, \ldots, n$, be arranged in increasing order. Then, for $i = 1, \ldots, n$,*

$$\lambda_i(A) + \lambda_1(B) \leq \lambda_i(A + B) \leq \lambda_i(A) + \lambda_n(B).$$

A proof is given in [48] (see theorem 4.3.1).

Bibliography

[1] Adams R.: *Sobolev Spaces*. Academic Press, New York (et al.) 1975.

[2] Alt H.: *Lineare Funktionalanalysis. Eine anwendungsorientierte Einführung*. Springer, Berlin (et al.) 2006, 5th edition.

[3] Altenbach J., Altenbach H.: *Einführung in die Kontinuumsmechanik*. Teubner, Stuttgart 1994.

[4] Amann H.: *Dynamic Theory of Quasilinear Parabolic Systems. III. Global Existence*. Mathematische Zeitschrift, 202 (1989), 219–250.

[5] Amann H., Escher J.: *Analysis III*. Birkhäuser, Basel (et al.) 2008, 2nd edition.

[6] Amundson N., Pan T.-W., Paulsen V.: *Diffusing with Stefan and Maxwell*. American Institute of Chemical Engineers Journal, 49 (2003), 813–830.

[7] Bartlett E., Kendall R., Rindal R.: *An Analysis of the Coupled Chemically Reacting Boundary Layer and Charring Ablator. Part IV. A Unified Approximation for Mixture Transport Properties for Multicomponent Boundary-Layer Applications*. Report NASA, CR-1063 (1968).

[8] Batchelor G.: *An Introduction to Fluid Dynamics*. Cambridge University Press, Cambridge (et al.) 1981, 8th edition.

[9] Böcker W., Denk H., Heitz P., Moch H.: *Pathologie*. Urban und Fischer, München 2008, 4th edition.

[10] Becker E., Bürger W.: *Kontinuumsmechanik. Eine Einführung in die Grundlagen und einfache Anwendungen*. Teubner, Stuttgart 1975.

[11] Bellomo N., Chaplain M., De Angelis E.: *Selected Topics in Cancer Modeling. Genesis, Evolution, Immune Competition, and Therapy*. Birkhäuser, Boston (et al.) 2008.

[12] Bellomo N., Li N., Maini P.: *On the Foundations of Cancer Modelling: Selected Topics, Speculations, and Perspectives*. Mathematical Models and Methods in Applied Sciences, 18 (2008), 593–646.

[13] Ben Amar M., Goriely A., Müller M., Cugliandolo L.: *New Trends in the Physics and Mechanics of Biological Systems*. Oxford University Press, Oxford (et al.) 2011.

[14] Bird R., Stewart W., Lightfoot E.: *Transport Phenomena*. John Wiley and Sons, New York (et al.) 2007, 2nd edition.

[15] Bothe D.: *On the Maxwell-Stefan Approach to Multicomponent Diffusion*. Progress in Nonlinear Differential Equations and their Applications, 80 (2011), 81–93.

[16] Boudin L., Grec B., Salvarani F.: *A Mathematical and Numerical Analysis of the Maxwell-Stefan Diffusion Equations*. Discrete and Continuous Dynamical Systems, Series B 17, 5 (2012), 1427–1440.

[17] Boudin L., Götz D., Grec B.: *Diffusion Models of Multicomponent Mixtures in the Lung*. ESAIM Proceedings, 30 (2010), 90–103.

[18] Breward C., Byrne H., Lewis C.: *The Role of Cell-Cell Interactions in a Two-Phase Model for Avascular Tumour Growth*. Journal of Mathematical Biology, 45 (2002), 125–152.

[19] Breward C., Byrne H., Lewis C.: *A Multiphase Model describing Vascular Tumour Growth*. Bulletin of Mathematical Biology, 65 (2003), 609–640.

[20] Burger M., Di Francesco M., Pietschmann J.-F., Schlake B.: *Nonlinear Cross-Diffusion with Size Exclusion*. SIAM Journal on Mathematical Analysis, 42 (2010), 2842–2871.

[21] Byrne H., Owen M.: *A New Interpretation of the Keller-Segel Model based on Multiphase Modelling*. Journal of Mathematical Biology, 49 (2004), 604–626.

[22] Casciari J., Sotirchos S., Sutherland R.: *Mathematical Modelling of Microenvironment and Growth in EMT6/Ro Multicellular Tumour Spheroids*. Cell Proliferation, 25 (1992), 1–22.

[23] Chen L., Jüngel A.: *Analysis of a Parabolic Cross-Diffusion Population Model without Self-Diffusion*. Journal of Differential Equations, 224 (2006), 39–59.

[24] Chen L., Jüngel A.: *Analysis of a Parabolic Cross-Diffusion Semiconductor Model with Electron-Hole Scattering*. Communications in Partial Differential Equations, 32 (2007), 127–148.

[25] Chen L., Jüngel A.: *Analysis of a Multidimensional Parabolic Population Model with Strong Cross-Diffusion*. SIAM Journal on Mathematical Analysis, 36 (2004), 301–322.

[26] Degond P., Génieys S., Jüngel A.: *An Existence Result for a Strongly Coupled Parabolic System arising in Nonequilibrium Thermodynamics*. Comptes Rendus de l'Académie des Sciences Paris, 325 (1997), 227–232.

[27] Degond P., Génieys S., Jüngel A.: *Symmetrization and Entropy Inequality for General Diffusion Equations*. Comptes Rendus de l'Académie des Sciences Paris, 325 (1997), 963–968.

[28] Degond P., Génieys S., Jüngel A.: *A System of Parabolic Equations in Nonequilibrium Thermodynamics including Thermal and Electrical Effects*. Journal de Mathématiques Pures et Appliquées, 76 (1997), 991–1015.

[29] Desvillettes L., Fellner K.: *Entropy Methods for Reaction-Diffusion Equations with Degenerate Diffusion Arising in Reversible Chemistry*. Preprint, 2007.

[30] Desvillettes L., Fellner K., Pierre M., Vovelle J.: *About Global Existence for Quadratic Systems of Reaction-Diffusion*. Advanced Nonlinear Studies, 7 (2007), 491–511.

[31] Dreher M., Jüngel A.: *Compact Families of Piecewise Constant Functions in $L^p(0,T;B)$*. Nonlinear Analysis, 75 (2012), 3072–3077.

[32] Drew D.: *Mathematical Modelling of Two-Phase Flow*. Annual Review of Fluid Mechanics, 15 (1983), 261–291.

[33] Drew D., Segel L.: *Averaged Equations for Two-Phase Flows*. Studies in Applied Mathematics, 50 (1971), 205–231.

[34] Dunford N., Schwartz J.: *Linear Operators. Part I. General Theory*. Interscience Publishers, New York (et al.) 1958.

[35] Elstrodt J.: *Maß- und Integrationstheorie*. Springer, Berlin (et al.) 1996.

[36] Evans L.: *Partial Differential Equations*. American Mathematical Society, Providence, Rhode Island 2008.

[37] Fischer G.: *Lineare Algebra. Eine Einführung für Studienanfänger*. Vieweg, Wiesbaden 2005, 15$^{\text{th}}$ edition.

[38] Gajewski H., Gröger K., Zacharias K.: *Nichtlineare Operatorgleichungen und Operatordifferentialgleichungen*. Akademie-Verlag, Berlin 1974.

[39] Galiano G., Jüngel A., Velasco J.: *A Parabolic Cross-Diffusion System for Granular Materials*. SIAM Journal on Mathematical Analysis, 35 (2003), 561–578.

[40] Giovangigli V.: *Convergent Iterative Methods for Multicomponent Diffusion*. IMPACT of Computing in Science and Engineering, 3 (1991), 244–276.

[41] Giovangigli V.: *Plane Laminar Flames with Multicomponent Transport and Complex Chemistry*. Mathematical Models and Methods in Applied Sciences, 9 (1999), 337–378.

[42] Giovangigli V.: *Multicomponent Flow Modeling*. Birkhäuser, Boston (et al.) 1999.

[43] Giovangigli V., Massot M.: *The Local Cauchy Problem for Multicomponent Reactive Flows in Full Vibrational Non-equilibrium*. Mathematical Methods in the Applied Sciences, 21 (1998), 1415–1439.

[44] Gross L.: *Logarithmic Sobolev Inequalities*. American Journal of Mathematics, 97 (1975), 1061–1083.

[45] Guckenheimer J., Kühn C.: *Homoclinic Orbits of the FitzHugh-Nagumo Equation: Bifurcations in the Full System*. SIAM Journal on Applied Dynamical Systems, 9 (2010), 138–153.

[46] Hadjadj L., Hamdache K., Hamroun D.: *An Existence Result to a Strongly Coupled Degenerated System arising in Tumor Modeling*. Abstract and Applied Analysis, 2008 (2008).

[47] Hittmeir S., Jüngel A.: *Cross Diffusion preventing Blow Up in the Two-Dimensional Keller-Segel Model*. SIAM Journal on Mathematical Analysis, 43 (2011), 997–1022.

[48] Horn R., Johnson C.: *Matrix Analysis*. Cambridge University Press, Cambridge (et al.) 1999.

[49] Jackson T., Byrne H.: *A Mechanical Model of Tumor Encapsulation and Transcapsular Spread*. Mathematical Biosciences, 180 (2002), 307–328.

[50] Jüngel A.: *Entropy-Entropy Dissipation Methods for Nonlinear PDEs*. Lecture notes, 2008.

[51] Jüngel A.: *Entropy Dissipation Methods for Nonlinear Partial Differential Equations*. Lecture notes, 2012.

[52] Jüngel A., Matthes D.: *Entropiemethoden für nichtlineare partielle Differentialgleichungen*. Internationale Mathematische Nachrichten, 209 (2008), 1–14.

[53] Jüngel A., Stelzer I.: *Entropy Structure of a Cross-Diffusion Tumor-Growth Model*. Mathematical Models and Methods in Applied Sciences, 22 (2012).

[54] Jüngel A., Stelzer I.: *Existence Analysis of Maxwell-Stefan Systems for Multicomponent Mixtures*. Submitted for publication (2012).

[55] Krishna R., Wesselingh J.: *The Maxwell-Stefan Approach to Mass Transfer*. Chemical Engineering Science, 52 (1997), 861–911.

[56] Lieb E., Loss M.: *Analysis*. American Mathematical Society, Providence, Rhode Island 2001, 2nd edition.

[57] Lou Y., Ni W.-M.: *Diffusion, Self-Diffusion and Cross-Diffusion*. Journal of Differential Equations, 131 (1996), 79–131.

[58] Lubkin S., Jackson T.: *Multiphase Mechanics of Capsule Formation in Tumors*. Journal of Biomechanical Engineering, 124 (2002), 237–243.

[59] Maxwell J.: *On the Dynamical Theory of Gases*. Philosophical Transactions of the Royal Society of London, 157 (1867), 49–88.

[60] Murray J.: *Mathematical Biology. I. An Introduction*. Springer, New York (et al.) 2002, 3rd edition.

[61] Naldi G., Pareschi L., Toscani G.: *Mathematical Modeling of Collective Behavior in Socio-Economic and Life Sciences*. Birkhäuser, Basel (et al.) 2010.

[62] Ni W.-M.: *Diffusion, Cross-Diffusion, and their Spike-Layer Steady States*. Notices of the American Mathematical Society, 45 (1998), 9–18.

[63] O'Dea R.: *Multiphase Modelling of Tissue Growth in Dynamic Culture Conditions*. PhD thesis, University of Nottingham (2008).

[64] Okubo A., Levin S.: *Diffusion and Ecological Problems. Modern Perspectives*. Springer, New York (et al.) 2001, 2nd edition.

[65] Ostrander S.: *Macroscopic Cross-Diffusion Models derived from Spatially Discrete Continuous Time Microscopic Models*. SIAM Undergraduate Research Online, 4 (2011).

[66] Roose T., Chapman S., Maini P.: *Mathematical Models of Avascular Tumor Growth*. SIAM Review, 49 (2007), 179–208.

[67] Roubíček T.: *Nonlinear Partial Differential Equations with Applications*. Birkhäuser, Basel (et al.) 2005.

[68] Serre D.: *Matrices. Theory and Applications*. Springer, New York (et al.) 2002.

[69] Serrin J.: *Local Behavior of Solutions of Quasi-Linear Equations*. Acta Mathematica, 111 (1964), 247–302.

[70] Shigesada N., Kawasaki K., Teramoto E.: *Spatial Segregation of Interacting Species*. Journal of Theoretical Biology, 79 (1979), 83–99.

[71] Simon J.: *Compact Sets in the Space $L^p(0,T;B)$*. Annali di Matematica Pura ed Applicata, 146 (1987), 65–96.

[72] Stefan J.: *Über das Gleichgewicht und die Bewegung, insbesondere die Diffusion von Gasgemengen*. Sitzungsberichte der mathematisch-naturwissenschaftlichen Classe der kaiserlichen Akademie der Wissenschaften, 63 (1871), 63–124.

[73] Taylor M.: *Partial Differential Equations III. Nonlinear Equations*. Springer, New York (et al.) 2011, 2nd edition.

[74] Taylor R., Krishna R.: *Multicomponent Mass Transfer*. John Wiley and Sons, New York (et al.) 1993.

[75] Thews G., Mutschler E., Schaible H.: *Anatomie, Physiologie, Pathophysiologie des Menschen*. Wissenschaftliche Verlagsgesellschaft, Stuttgart 2007, 6th edition.

[76] Thieme H.: *Mathematics in Population Biology*. Princeton University Press, Princeton (et al.) 2003.

[77] Troianiello G.: *Elliptic Differential Equations and Obstacle Problems*. Plenum Press, New York (et al.) 1987.

[78] Unterreiter A., Arnold A., Markowich P., Toscani G.: *On Generalized Csiszár-Kullback Inequalities*. Monatshefte für Mathematik, 131 (2000), 235–253.

[79] Vanag V., Epstein I.: *Cross-Diffusion and Pattern Formation in Reaction-Diffusion Systems*. Physical Chemistry Chemical Physics, 11 (2009), 897–912.

[80] Wu Y., Zhao X.: *The Existence and Stability of Travelling Waves with Transition Layers for some Singular Cross-Diffusion Systems*. Physica D, 200 (2005), 325–358.

[81] www.cancer.gov/dictionary/?CdrID=45301 (October 25, 2010).

[82] Zeidler E.: *Nonlinear Functional Analysis and its Applications. I: Fixed-Point Theorems*. Springer, New York (et al.) 1986.

[83] Zeidler E.: *Nonlinear Functional Analysis and its Applications. II/A: Linear Monotone Operators*. Springer, New York (et al.) 1990.

[84] Zeidler E.: *Nonlinear Functional Analysis and its Applications. II/B: Nonlinear Monotone Operators*. Springer, New York (et al.) 1990.

[85] Ziemer W.: *Weakly Differentiable Functions. Sobolev Spaces and Functions of Bounded Variation*. Springer, New York (et al.) 1989.

Curriculum Vitae

Personal Data

Name:	Ines Viktoria Stelzer
Date of birth:	December 30, 1986
Place of birth:	Vienna, Austria
Citizenship:	Austria

Education

1993–1997:	Primary school Braunhubergasse, Vienna
1997–2005:	Grammar school Bundesrealgymnasium Geringergasse, Vienna
2005:	School leaving examination (Matura) with distinction Begin of studies of technical mathematics at the Technical University of Vienna and of Scandinavian studies at the University of Vienna
2005–2010:	Studies of technical mathematics specialising in the natural scientific branch at the Technical University of Vienna
2010:	Master's degree in technical mathematics with distinction Master thesis: "Fraktale Dimensionen mit Anwendung auf Tumorzellen"
Since February, 2010:	Project assistant (PhD-student) at the Institute of Analysis and Scientific Computing at the Vienna University of Technology in the FWF-project "Cross-Diffusion in Chemotaxis and Tumor Growth Models"