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DIPLOMARBEIT

Numerical Analysis of a Tumor Growth Model using a Travelling Wave Ansatz and Singular Perturbation Theory

Ausgeführt am Institut für Analysis und Scientific Computing der Technischen Universität Wien

unter der Anleitung von

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Unterschrift

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"In the beginning the Universe was created. This has made a lot of people very angry and been widely regarded as a bad move."

Douglas Adams

Abstract

This thesis is concerned with a mechanical tumor growth model used to describe avascular, i.e. early stage, tumor growth. In this phase, increase of tumor mass happens via proliferation which means rapid reproduction of cells. The governing equation is a highly non-linear two dimensional reaction-diffusion-equation with full diffusion matrix which becomes singular at the maximal and minimal values of the two variables. This fact makes mathematical analysis rather challenging.

Global in time existence of bounded weak solutions has been proven under certain parametric restrictions, and numerical solutions persist even beyond these limitations. The shape of resulting curves gives rise to the assumption that some form of travelling wave behaviour is occuring, which is the motivation and main point of interest for this thesis.

Therefore an introduction to travelling wave analysis is given based on a (structurally simpler) example equation, and some notions from dynamical systems theory are introduced, amongst them both *heteroclinic* and *homoclinic orbits*, which are necessary concepts for *Lin's method*. A numerical analysis of the tumor growth model follows where *Lin's method* is applied. Several obstacles arise due to the structure of the diffusion matrix.

An excurse is made into singular perturbation theory. So called *slow-fast-systems* are introduced and an example of how to approach them is given by means of specific types of reaction-diffusion-equations. An attempt is made to extend the presented theory such that it can be applied to the tumor growth model. Furthermore the concepts of wall(s) of singularities and hole(s) in the wall are defined and it is shown how they relate to the model.

Keywords: Tumor growth model, reaction diffusion equation, travelling waves, Lin's method, orbits, singular perturbation theory, slow-fast-systems, canards

Kurzfassung

Diese Arbeit befasst sich mit einem mechanischen Tumorwachstumsmodell, welches verwendet wird um avaskuläres, also im frühen Stadium befindliches, Tumorwachstum zu beschreiben. In dieser Phase expandiert der Tumor durch Proliferation, was rasche Vervielfältigung von Zellen bedeutet. Bei der beschreibenden Gleichung handelt es sich um eine hochgradig nichtlineare, zweidimensionale Reaktions-Diffusions-Gleichung mit vollbesetzter Diffusionsmatrix, die singulär wird bei den Minima bzw. Maxima der beiden Variablen. Diese Tatsache macht eine mathematische Analyse durchaus anspruchsvoll.

Die Existenz einer beschränkten schwachen Lösung für alle Zeiten wurde unter gewissen Paramterbeschränkungen gezeigt, numerische Lösungen existieren sogar jenseits dieser Limitierungen. Die Form der erhaltenen Lösungskurven lässt vermuten, dass ein Wanderndes Wellen Verhalten auftritt, was die Motivation und den zentralen Bezugspunkt dieser Arbeit bildet.

Es wird daher eine Einführung in Wandernde Wellen Analyse anhand einer (strukturell simpleren) Beispielgleichung gegeben, weiters werden einige Begriffe aus der Theorie dynamischer Systeme vorgestellt, unter anderem sogenannte *heterokline* und *homokline Orbits*, welche notwendige Konzepte für *Lin's Methode* sind. Es folgt eine numerische Analyse des Tumorwachstumsmodells, welche *Lin's Methode* benützt. Aufgrund der Struktur der Reaktionsmatrix treten einige Schwierigkeiten auf.

Ein Exkurs wird gemacht in das Thema der Singular Perturbation Theory, wobei sogenannte slow-fast-Systeme vorgestellt werden. Anhand spezifischer Typen von Reaktions-Diffusions-Gleichungen wird ein Beispiel gegeben, wie diese zu behandeln sind. Es wird versucht, die vorgestellte Theorie zu erweitern sodass sie auf das Tumorwachstumsmodell angewendet werden kann. Des weiteren werden die Konzepte der wall(s) of singularites und hole(s) in the wall vorgestellt und gezeigt in welchem Zusammenhang diese zu dem Modell stehen.

Schlagworte: Tumorwachstumsmodell, Reaktions-Diffusions-Gleichung, Wandernde Welle, Lin's Methode, Orbits, Singular Perturbation Theory, slow-fast-Systeme, Canards

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Für Dominik,

der diese Arbeit zur Gänze gelesen hat, obwohl er unter cof etwas grundlegend anderes versteht.

Und weil 42 keine Primzahl ist.

Chapter 1

Introduction

To give an absolute definition of what distinguishes a tumor cell from a "regular cell" is rather impossible, however tumors can in general be recognized by abnormal growth. In particular, standard cellular growth-controlling mechanisms cease to elicit their proper response from the affected tumor cells, see e.g. [FT03, p.4]. There are several ways in which one can classify tumor cells, for instance by their malignancy ([FT03, p.4]):

- Benign tumors that act only locally but do not spread.
- In situ tumors located mainly in epithelium cells (a type of tissue lining cavities and coating blood vessels and inner organs within the human body), which do not invade neighbouring tissue.
- *Malignant*, cancerous tumors that invade and destroy surrounding structures and may develop metastases in distant organs or lymph nodes.

A different, while related, notion is to categorize them by their growth stage ([JS12, p.2]):

- Avascular growth. In this stage, growth occurs due to proliferation, i.e. rapid reproduction of tumor cells. Nutrients reach the center of the tumor through diffusion processes and become more and more sparse as the tumor expands.
- *Vascular growth.* To avoid deficiency of nutrients in its center, the tumor develops its own blood vessels.
- *Metastatic stage.* Via the newly created circulatory system tumor cells are able to reach distant parts of the body and create secondary tumors.

In this thesis only the avascular stage of tumor growth is considered.

There are a number of approaches for modelling avascular tumors which can mostly be described as either discrete cell population models, or continuum models relying on average cell behaviour ([JS12, p.2]). An excellent overview of mathematical tumor modelling for different growth stages is given in [QFV06, Ch.3].

1.1 The model

In this thesis, which is based on the works of Jüngel & Stelzer [JS12] as well as Stelzer [Ste13], we regard a model for avascular tumor growth derived from the mechanical model presented by Jackson and Byrne in [JB02]. In particular we are looking at a continuum model using reaction-diffusion equations, where the tumor-host environment is viewed as a mixture of the three interacting continua *tumor cells* in a cellular phase, *fibrous, collagen rich matrix* in the extra-cellular-matrix (ECM) phase and *water* (a more precise term would be *interstitial fluid*, which has water as its main ingredient) in the aqueous phase, see [JS12, Secs.1-2] or [Ste13, Ch.2]. The model is based on balance laws and conservation principles from continuum mechanics, from which mass and momentum balance equations are derived. It is closed by imposing suitable constitutive relations for mass exchange between different phases, partial stress tensors and momentum transfer equations. For a full derivation of the model we direct the inclined reader towards the original paper [JB02] or a review thereof in e.g. [JS12] or [Ste13].

Following [JS12], let now c denote the volume fraction of tumor cells, m that of the ECM and w that of water. As the mixture is assumed to be saturated, water can be eliminated from the equation by setting w = 1 - c - m. Additionally, due to the fact that we are dealing with volume fractions, the constraints $0 \le c, m, 1 - c - m \le 1$ apply. The PDE that will be the main focus of this thesis, which is a scaled equation-system in one spatial dimension, is given by the following reaction-diffusion equation:

$$\frac{\partial}{\partial t} \begin{pmatrix} c \\ m \end{pmatrix} - \frac{\partial}{\partial x} \left(A(c,m) \cdot \frac{\partial}{\partial x} \begin{pmatrix} c \\ m \end{pmatrix} \right) = R(c,m), \quad \text{in } \Omega, t > 0 \tag{1.1}$$

where $\Omega = (0, 1)$ with Neumann boundary and given initial conditions

$$c_x = m_x = 0 \text{ on } \partial\Omega, t > 0, \quad c(\cdot, 0) = c_0, m(\cdot, 0) = m_0 \text{ in } \Omega.$$
 (1.2)

The production term is given by

$$R(c,m) = \begin{pmatrix} \gamma c(1-c-m) - \delta c \\ \alpha cm(1-c-m) \end{pmatrix}$$
(1.3)

with tumor cell proliferation rate γ , mortality rate δ and ECM production rate α whereas the diffusion matrix reads

$$A(c,m) = \begin{pmatrix} 2c(1-c) - \beta\theta cm^2 & -2\beta cm(1+\theta c) \\ -2cm + \beta\theta(1-m)m^2 & 2\beta m(1-m)(1+\theta c) \end{pmatrix}$$
(1.4)

with pressure coefficients $\beta > 0$ and $\theta \ge 0$.

Remark. Note that methods and results in [JS12] and [Ste13] are mostly identical. We will thus often refer to [JS12] only. Notation in this thesis however more closely follows [Ste13].

System (1.1) poses a few difficulties that make solving this PDE quite challenging, all of which are related to the diffusion matrix A. We can see in (1.4) that A is a full matrix, i.e. the non-diagonal entries do not equal zero, indicating that *cross-diffusion* occurs, see also [Ste13, p.2]. Observe that the determinant of A is given by

$$\det A(c,m) = 4\beta cm(1+\theta c)(1-c-m),$$
(1.5)

which will equal zero if either c, m or w = 1 - c - m equal zero or one, indicating that in these cases A becomes singular. As we are dealing with volume fractions, this may of course happen. Lastly, for general $\beta > 0$ and $\theta \ge 0$, A is neither symmetric nor positive definite, which means that standard PDE theory may not be applied.

1.2 Motivation of this thesis

All is not lost however, as [JS12] and [Ste13] show that under certain parametric restrictions (in particular $\theta < \theta^*$ for some specific value of θ^*) bounded weak solutions exist globally in time, a fact that we will regard more closely in Chapter 4.1. Numerical solutions persist even for $\theta > \theta^*$, however once θ is chosen sufficiently large, peaks begin to form in the ECM spatial position. The production rate R vanishes, and the tumor front as well as ECM peaks begin moving to the right as time increases, see Figure 1.1 and [JS12, p.21] as well as [Ste13, p.44].



FIGURE 1.1: Volume fractions of the tumor cells (left) and the ECM (right) vs. position using $\theta = 1000$ at times t = 0, 1, 2, 3, 4, 5, 6. The production rate vanishes, $R(c, m) = \underline{0}$. The tumor cell front and the ECM peaks are moving from left to the right as time increases. Source: [JS12, Fig.1]

This peak formation and movement suggest a possible travelling wave behaviour of solutions to the tumor model (1.1), which is the main focal point for this thesis. We will thus in the following chapters examine the theory of travelling waves and apply it both analytically as well as numerically to the model, with special attention to the influence of the parameter θ . A short excursus is made into the theory of slow-fast-systems and singular perturbation theory.

1.3 Thesis outline

This thesis is comprised of 5 main chapters, as well as an appendix.

Chapter 1: A general introduction to the medical term *tumor* as well as tumor modelling is given. We introduce a tumor model (1.1) along with its derivation and problems arising in studying it. The structure and goals of this work are defined.

Chapter 2: The theory of travelling waves is presented, starting with the simple example of the Fisher-Kolmogorov-Petrovskii-Piskounov equation (2.3) and continuing with a more general ODE, which is utilized to demonstrate the so-called *Lin's method*. We apply the presented concepts to the tumor model (1.1).

Chapter 3: An introduction to singular perturbation theory is given. We try to extend the notions presented to include the necessary structures of the tumor model (1.1).

Chapter 4: With the concepts presented in Chapter 2 we formulate an algorithm for Lin's method that can be implemented in Matlab. Several key issues that pose a problem during implementation are addressed and resolved. We give an overview over obtained results.

Chapter 5: The work of this thesis is summarized shortly. We draw conclusions regarding the significance of the parameter θ and present some points for future considerations.

Appendix: For the implementation of the travelling wave ansatz, calculating the steady states of (2.28) and a detailed understanding of their stability properties are necessary. While of vital importance, this analysis is somewhat lengthy. In order to not disrupt the flow of the text too much, it was thus placed in the appendix, with key results remarked upon where appropriate in the respective chapters. Furthermore some general mathematical notions are presented that some readers may not be familiar with but which are utilized in this work.

Chapter 2

Theoretical analysis

In this chapter we take a look at the theory of travelling waves and introduce an important analytical tool, the so called *Lin's method*. For this purpose, a detailed analysis of occurring steady states will be necessary.

2.1 About travelling waves

In the theory of partial differential equations we speak of travelling wave solutions, if the solutions of a given problem propagate with a fixed speed without changing their shape. In other words, if a moving frame of reference is applied with correct speed, the solution appears to be stationary. Let u(x,t) be such a solution, that is travelling at constant wave speed σ , then the following holds

$$u(x,t) = u(x - \sigma t) = U(z),$$
 (2.1)

where $z = x - \sigma t$ is called the *travelling wave variable*. Note that for $\sigma > 0$ the wave profile is said to be "right moving", while for $\sigma < 0$ it moves "to the left". The special case of $\sigma = 0$ indicates a so called standing wave, see [Kue15a, p.25]. In particular the given PDE can be reformulated with this ansatz as an ODE with the following coordinate transformation:

$$\frac{\partial u}{\partial t} = -\sigma \frac{dU}{dz}, \quad \frac{\partial u}{\partial x} = \frac{dU}{dz}$$
(2.2)

A classical example whose solutions exhibit travelling wave character is the non-dimensionalized 1D Fisher-Kolmogorov-Petrovskii-Piskounov (FKPP) equation given by

$$u_t = u_{xx} + u(1 - u). (2.3)$$

[Ibe14] provides a good summary on how to proceed, which we will follow here. After application of the travelling wave ansatz, (2.3) reads

$$-\sigma U' = U'' + U(1 - U), \qquad (2.4)$$

with ' = d/dz, which can be transformed into a system of first order ordinary differential equations by setting U' = V:

$$U' = V$$

$$V' = -\sigma V - U(1 - U)$$
(2.5)

or in vectorized form

$$\binom{U}{V}' = \binom{V}{-\sigma V - U(1-U)} =: f(U,V).$$
(2.6)

Now we would like to perform a so called *phase plane analysis*. This technique consists of the following steps:

- Find nullclines,
- as well as steady states of (2.6).
- Investigate stability of these steady states.
- Determine phase plane trajectories.

In order to find the nullclines of (2.6), we have to set both components of f(U, V) equal to zero, and see that the *U*-nullcline is given by V = 0, whereas the *V*-nullcline is given by $V = -U(1 - U)/\sigma$. Steady states of the system are found where the two nullclines intersect, i.e. f(U, V) = 0, at the points $s_1 = (0, 0)$ and $s_2 = (1, 0)$.

Next we perform a Taylor series expansion on (2.6) at the steady states, which we truncate at second order. Let $J(U^*, V^*)$ be the Jacobian of of this Taylor sum evaluated



FIGURE 2.1: Phase plane (a) and solution (b) of the FKPP equation in the case of $\sigma \geq 2$. Source: [Ibe14]

at the steady state (U^*, V^*) , then we regard the linearised problem

$$\binom{U}{V}' = J(U^*, V^*) \cdot \binom{U}{V} = \binom{0 \quad 1}{-(1 - 2U^*) \quad -\sigma} \cdot \binom{U}{V}.$$
(2.7)

From this notation we can already see that the eigenvalues of $J(U^*, V^*)$ play a crucial role in the stability of solutions. At $(U^*, V^*) = (1, 0)$, one eigenvalue will always be positive, while the other will always be negative, making s_2 a so called saddle node. At $(U^*, V^*) = (0, 0)$ we have to regard 2 different cases dependent on σ : if $\sigma \ge 2$, both eigenvalues are real and negative, making s_1 a stable node, whereas $\sigma < 2$ means that the eigenvalues are complex conjugated with negative real part, and thus s_1 is a stable spiral. A full classification of all types of equilibria for 2×2 matrices can be found in Chapter A.3.

We now look at the phase plane, which is determined by (2.5), see Figure 2.1 (a). Note that for $\sigma < 2$, solutions may become negative. Dependent on the setting for which the equation is regarded, this may not be a desirable outcome. For all $\sigma \ge 2$ however, travelling wave solutions U exist that fulfil $0 \le U(z) \le 1$, $\lim_{z\to-\infty} U(z) = 1$ and $\lim_{z\to+\infty} U(z) = 0$ for the travelling wave variable $z = x - \sigma t$, see Figure 2.1 (b).

2.2 Lin's method

Let us now consider a more general case, as discussed in [Eva10, Ch.4.2.1.c], of a scalar reaction-diffusion equation given in the form

$$u_t = u_{xx} + f(u) \text{ in } \mathbb{R} \times (0, \infty)$$
(2.8)

where $f : \mathbb{R} \to \mathbb{R}$ is smooth and satisfies

$$\begin{cases}
(a) f(0) = f(a) = f(1) = 0 \\
(b) f < 0 \text{ on } (0, a), f > 0 \text{ on } (a, 1) \\
(c) f'(0) < 0, f'(1) < 0 \\
(d) \int_0^1 f(z) dz > 0
\end{cases}$$
(2.9)

for some 0 < a < 1. In particular, f is "cubic-like" shaped, or bistable (due to condition (c)), as can be seen in Figure 2.2. This time we are interested in a wave front originating at value 0 and with terminal value 1, i.e. $\lim_{z\to-\infty} U(z) = 0$ and $\lim_{z\to+\infty} U(z) = 1$.



FIGURE 2.2: Schematic graph of the function f. Source: [Eva10, p.180]

To clarify notation, we now introduce the following definition from [Kue15a, Def. 5.3] (see also e.g. [Kue15b, Ch.6]):

Definition 1. Consider the ODE $\frac{du}{dt} = f(u), u \in \mathbb{R}^d$, with steady states u^* and \tilde{u}^* .

- A solution $u(\xi)$ is called a **periodic orbit** (or periodic trajectory) of minimal **period** $\xi_T > 0$ if $u(\xi) = u(\xi + \xi_T)$, and there exists no smaller ξ_T such that [this] holds.
- A solution $u(\xi)$ is called a **heteroclinic orbit** (or heteroclinic trajectory, or just heteroclinic) between u^* and \tilde{u}^* if $\lim_{\xi \to -\infty} u(\xi) = u^*$ and $\lim_{\xi \to +\infty} u(\xi) = \tilde{u}^*$.
- A solution u(ξ) is called a homoclinic orbit (or homoclinic trajectory, or just homoclinic) to u^{*} if lim_{ξ→-∞} u(ξ) = u^{*} = lim_{ξ→+∞} u(ξ).

There is in fact an accordance between orbits occuring for travelling wave ODEs, and the behaviour of solutions of the PDE from which said ODE was derived, see e.g. [Kue15b, p.114]. Figure 2.3 illustrates the different cases.

- 1. A periodic orbit of the travelling wave ODEs corresponds to a **travelling wave train** solution of the associated PDE.
- 2. A homoclinic orbit of the travelling wave ODEs corresponds to a **travelling pulse** solution of the associated PDE.
- 3. A heteroclinic orbit of the travelling wave ODEs corresponds to a **travelling front** solution of the associated PDE.

In this context, the "associated PDE" refers to the original equation, from which the ODE was derived by application of the travelling wave ansatz (2.2). Note that after doing so, (2.8) can again be systemized and thus brought to the form of the ODE in Definition 1 with d = 2:

$$-\sigma U' = U'' + f(U), \qquad (2.10)$$

or in other terms with U' = V, $\underline{u} = (U, V)^{\top}$,

$$\underline{u}' = \begin{pmatrix} U \\ V \end{pmatrix}' = \begin{pmatrix} V \\ -\sigma V - f(U) \end{pmatrix} =: \tilde{f}(\underline{u})$$
(2.11)

Remark. Observe that for any PDE of the form $u_t + u_{xx} = f(u)$, the travelling wave analysis will lead to a formulation as in (2.11).

In particular we are now looking for a heteroclinic orbit connecting the steady states $\underline{u}^* = (0,0)$ and $\underline{\tilde{u}}^* = (1,0)$, i.e. a wave front travelling from 0 to 1. Note now as in [Eva10] that for the corresponding linearisations the eigenvalues are given by

$$\lambda_0^{\pm} = \frac{-\sigma \pm \sqrt{\sigma^2 - 4f'(0)}}{2}, \quad \lambda_1^{\pm} = \frac{-\sigma \pm \sqrt{\sigma^2 - 4f'(1)}}{2}, \quad (2.12)$$



FIGURE 2.3: Correspondences between ODE orbits and PDE solutions. Panel a1: Homoclinic orbit depicted in the (u, v)-phase plane. Panel a2: The associated PDE solutions form travelling pulses. Panel b1: Heteroclinic orbit depicted in the (u, v)phase plane. Note that both steady states are on the same v-level. Panel b2: The PDE solution has a travelling front in the u component (darker curve), but a pulse in the v component (lighter curve). Panel c1: Periodic orbit in the (u, w)-phase plane. Solutions travel faster in de- or increasing u-direction than in w-direction as indicated by the arrow. Panel c2: The corresponding PDE solutions show steeper gradients in theu-component (darker curve) than in the w-component (lighter curve). Source: Provided by C. Kühn. Figure used with permission of the author.

which due to the restrictions posed on f in (2.9) are real and have alternating signs, making both (0,0) and (1,0) saddle points. [Eva10, p.181f.] now introduces two curves W^u and W^s . The former leaves (0,0) along the unstable eigendirection and is thus called unstable, while the latter approaches (1,0) along the stable eigendirection and is called stable, compare with Figure 2.4. Let in particular $\lambda_{0/1}^{\pm}$ be the eigenvectors given by (2.12), then

$$\begin{cases} W^{u} \text{ is tangent to the line } V = \lambda_{0}^{+}U \text{ at } (0,0) \\ W^{s} \text{ is tangent to the line } V = \lambda_{1}^{-}(U-1) \text{ at } (1,0). \end{cases}$$

$$(2.13)$$

It is furthermore pointed out that $\lambda_0^{\pm}, \lambda_1^{\pm}, W^u$ and W^s are all dependent upon the parameter σ .

Remark. $W^{u}(u^{*})$ and $W^{s}(u^{*})$ are called unstable and stable manifolds of the steady state u^{*} , see e.g. [Kue15a, p.8].

Remember that we were looking for a heteroclinic orbit leaving $\underline{u}^* = (0,0)$ and travelling into $\underline{\tilde{u}}^* = (1,0)$. This is equivalent to finding a wave speed $\sigma < 0$ such that

$$W^{u} = W^{s}$$
 in $\{U > 0, V > 0\}.$ (2.14)



FIGURE 2.4: Stable and unstable curves. Note that v corresponds to U and w to V. Source: [Eva10, p.182]

In order to achieve this, we apply the following procedure as e.g. presented in [Eva10, Ch.4.2], which is is known as *Lin's method* in the literature.

Let $\varepsilon > 0$ be fixed, and select a 1 dimensional submanifold L of the phase space given by a vertical line through $(a + \varepsilon, 0)$. [Eva10, p.182f.] claims that

$$W^u \cap L \neq \emptyset, \quad W^s \cap L \neq \emptyset$$
 (2.15)

as long as $\sigma < 0$, which can be shown with the aid of the following function

$$E(u,v) := \frac{v^2}{2} + \int_0^u f(z)dz \quad (u,v \in \mathbb{R}).$$
(2.16)

With (2.11) it follows that

$$\frac{d}{dt}E(U(t), V(t)) = V(t)V'(t) + f(U(t))U'(t) = -\sigma V^2(t), \qquad (2.17)$$

which means E is non-decreasing along the trajectories of (2.11) due to $\sigma < 0$. The level sets of E are depicted in Figure 2.5.

Let now R denote the region in the phase plane that is bounded by L on the right side, U = 0 on the left side by some (suitable) level curve of E from below as illustrated in Figure 2.6, such that the unstable curve W^u enters R from (0,0). As W^u is a level curve itself, we reason that it cannot exit through the bottom, top or left-hand side of R. We



FIGURE 2.5: Level curves of E. Note that v corresponds to U and w to V. Source: [Eva10, p.183]

can thus conclude that W^u must exit R through the line L, at a point $(a + \varepsilon, V_0(\sigma))$. Analogously, W^s intersects L at a point $(a + \varepsilon, V_1(\sigma))$, which verifies (2.15).



FIGURE 2.6: The region R. Note that v corresponds to U and w to V. Source: [Eva10, p.183]

Definition 2. The distance between $V_0(\sigma)$ and $V_1(\sigma)$ is called the Lin gap.

The next step is now to observe that trajectories of (2.11) are contained in level sets of E for $\sigma = 0$, which implies

$$V_0(0) < V_1(0). (2.18)$$

Our goal is now to show that for $\sigma < 0$ sufficiently small,

$$V_0(\sigma) > V_1(\sigma), \tag{2.19}$$

indicating that since both V_0 and V_1 depend smoothly on σ there must exist at least one σ^* such that $V_0(\sigma^*) = V_1(\sigma^*)$. (It can in fact be shown that σ^* is unique!)



FIGURE 2.7: The region S. Note that v corresponds to U and w to V. Source: [Eva10, p.184]

To achieve this let $\beta > 0$ be fixed, and define the region S to be bounded by U = 0 on the left, L on the right, and $T := \{0 \le U \le a + \varepsilon, V = \beta U\}$ from below as shown in Figure 2.7. Along T, it holds that

$$\frac{V'}{U'} = \frac{-\sigma V - f(U)}{V} = -\sigma - \frac{f(U)}{\beta U} \ge -\sigma - \frac{C}{\beta} > \beta$$
(2.20)

for $\sigma < 0$ and $|\sigma|$ sufficiently large since |f(U)/U| is bounded on $0 \le U \le a + \varepsilon$. In particular, $V' > \beta U'$ and we see immediately that W^u cannot exit S through T where $V = \beta U$. Therefore we conclude that

$$V_0(\sigma) \ge \beta(a+\varepsilon) \quad \text{for } \sigma = \sigma(\beta).$$
 (2.21)

Note however also that

$$V_1(\sigma) \le V_1(0) \quad \forall \sigma \le 0, \tag{2.22}$$

implying that since V_0 and V_1 depend smoothly on σ , (2.19) will follow for β sufficiently large and then σ sufficiently negative. [Eva10] concludes this section with a short remark, that proof of uniqueness of σ^* is possible with a more refined analysis, which in turn concludes our summary.

2.2.1 The dimension of steady and unsteady manifolds

In the previous section we introduced the concept of the stable and unstable manifolds W^s and W^u associated with the steady states \underline{u}^* and $\underline{\tilde{u}}^*$ of a given ODE problem (2.11). Recall that the eigenvalues of the linearisations of these steady states were given by (2.12), which due to restrictions posed onto the function f in (2.9) were real and, more importantly, non-zero. If no eigenvalues equal zero, a steady state is called hyperbolic, see e.g. [Eva10, p.421], as was the case in Chapter 2.2.

In the case of non-hyperbolic steady states, the nomenclature has to be refined. Consider for example the linear ODE x' = Ax with $x \in \mathbb{R}^3$ and A given by

$$A = \begin{pmatrix} 2 & -3 & 1 \\ 3 & 1 & 3 \\ -5 & 2 & -4 \end{pmatrix}.$$
 (2.23)

This ODE has a trivial steady state at x = 0, with eigenvalues given by $\lambda_1 = 1$, $\lambda_2 = -2$ and $\lambda_3 = 0$ and associated eigenvectors v_{1-3} . From the signs of λ_1 and λ_2 we can immidiately determine that this system has an unstable eigendirection along v_1 , and a stable one along v_2 , refer to Chapter A.3 for a more detailed explanation. In case of a zero eigenvalue however, stability is a priorily unclear (especially if we are dealing with the linearization of an ODE instead of a linear ODE to begin with). Consider the following definition for stable and unstable manifolds given by [Kue15a, p.8], which is equivalent to (2.13):

Definition 3. Let $\phi(u_0, t)$ be the flow associated to an ODE $u' = f(u), u(0) = u_0 \in \mathbb{R}^d$ with a steady state u^* . Define the stable and unstable manifolds by

$$W^{s}(u^{*}) := \{ v \in \mathbb{R}^{d} : \phi(v, t) \to u^{*}, \text{ as } t \to +\infty \},$$

$$W^{u}(u^{*}) := \{ v \in \mathbb{R}^{d} : \phi(v, t) \to u^{*}, \text{ as } t \to -\infty \}.$$
(2.24)

From Definition 3 is it apparent, that $v_1 \in W^u(0)$ and $v_2 \in W^s(0)$, in particular both $W^u(0)$ and $W^s(0)$ are of at least dimension 1. But there might be further trajectories leading towards $u^* = 0$ in either forward or backward time along the eigenvector v_3 (or linear combinations thereof), the manifolds may therefore be of at most dimension 2.

We thus define the strongly stable manifold $W^{ss}(u^*)$ that is spanned only by the eigenvectors of negative eigenvalues at u^* , and the center stable manifold $W^{cs}(u^*)$ which is spanned by eigenvectors of negative and zero eigenvalues, as well as their unstable

counterparts respectively. In case of the ODE given by (2.23) this amounts to

$$1 = \dim(W^{ss}(0)) \le \dim(W^{s}(0)) \le \dim(W^{cs}(0)) = 2,$$

as well as

$$1 = \dim(W^{su}(0)) \le \dim(W^{u}(0)) \le \dim(W^{cu}(0)) = 2.$$

Observe that for hyperbolic steady states the three types of stable/unstable manifolds coincide.

2.3 Phase plane analysis and steady states of the tumor model

As we have seen in the previous sections, in order for heteroclinic orbits to exist, we require one steady state with an unstable eigendirection and one with a stable eigendirection. This suggests that a stability analysis for any possible steady states of our tumor model (1.1) is necessary.

We recall that (1.1) is given by

$$\frac{\partial}{\partial t} \begin{pmatrix} c \\ m \end{pmatrix} - \frac{\partial}{\partial x} \left(A(c,m) \cdot \frac{\partial}{\partial x} \begin{pmatrix} c \\ m \end{pmatrix} \right) = R(c,m)$$

which we transform with travelling wave ansatz $z = x - \sigma t$, ' = d/dz to

$$-\sigma \begin{pmatrix} c \\ m \end{pmatrix}' - \left(A(c,m) \cdot \begin{pmatrix} c \\ m \end{pmatrix}'\right)' = R(c,m).$$
(2.25)

Let $U = (c, m)^{\top}$ and subsequently V = U' then we can rewrite (2.25) to

$$\begin{cases} U' = V \\ A(U) \cdot V' = (-\sigma \cdot I_d - (A(U))') \cdot V - R(U) \end{cases}$$
(2.26)

where I_d denotes the identity matrix. (2.26) is problematic because of the term A(U) multiplied to V' in the second line. As we have seen in Chapter 1.2, A(U) = A(c,m) becomes singular whenever c, m or 1 - c - m equal 0 or 1. In particular, we know that it is not invertible.

To avoid this we revert to the (c, m) notation instead of U and V and define

$$\begin{pmatrix} p \\ q \end{pmatrix} := A(c,m) \cdot \begin{pmatrix} c \\ m \end{pmatrix}'.$$

Invertibility of A(c, m) is still not given, however we now apply a formal coordinate transformation:

$$z = \det A(c,m) \cdot \eta, \qquad (2.27)$$

and note that $A^{-1} = (\det A)^{-1} \cdot \operatorname{cof}(A)^{\top}$, see Chapter A.4 for further details. Let $\dot{=} d/d\eta$, then (2.25) becomes

$$\begin{cases} \begin{pmatrix} \dot{c} \\ \dot{m} \end{pmatrix} = \operatorname{cof}(A)^{\top} \cdot \begin{pmatrix} p \\ q \end{pmatrix} \\ \begin{pmatrix} \dot{p} \\ \dot{q} \end{pmatrix} = -\sigma \cdot \operatorname{cof}(A)^{\top} \cdot \begin{pmatrix} p \\ q \end{pmatrix} - \det A \cdot R. \end{cases}$$
(2.28)

Recall that σ was wave speed. The cofactor matrix $\operatorname{cof}(A)^{\top} = \operatorname{cof}(A(c,m))^{\top}$ is given by

$$\operatorname{cof}(A)^{\top} = \begin{pmatrix} 2\beta m(1-m)(1+\theta c) & 2\beta cm(1+\theta c) \\ 2cm - \beta\theta m^2(1-m) & 2c(1-c) - \beta\theta cm^2 \end{pmatrix}.$$

Consider (2.28) to be abstractly of the form $\dot{y} = F(y)$, then we are now looking for steady states given by F(y) = 0. The calculation steps for this are listed in Chapter A.1. It turns out that we can in fact not identify isolated points as steady states for this systems, but rather whole families, i.e. manifolds of steady states:

$$F(y) = 0 \Leftrightarrow$$

$$y \in \left\{ \begin{pmatrix} 0\\1\\p\\q \end{pmatrix}, \begin{pmatrix} 1\\0\\p\\q \end{pmatrix}, \begin{pmatrix} 0\\0\\p\\q \end{pmatrix}, \begin{pmatrix} 0\\m\\0\\q \end{pmatrix}, \begin{pmatrix} c\\0\\p\\0 \end{pmatrix}, \begin{pmatrix} c\\1-c\\p\\-p \end{pmatrix} \right\}$$
(2.29)

Let the six families in (2.29) be denoted y_1 to y_6 from left to right, then $y_1 = (0, 1, p, q)^{\top}$ indicates that $F(y_1) = 0$ for any value of p and q. Since we have found whole families of steady states instead of single points, a closer look at their properties is necessary. The following are some key features:

- y_{1-3} appear to be the most "natural" families of steady states as they are the only ones independent of p and q in the sense that these values may be chosen arbitrarily. They would still be steady states for the un-transformed system (2.26).
- y_6 occurs artificially due to the variable transformation (2.27), while y_4 and y_5 are both rather degenerate (they each have a zero, i.e. generalized, eigenvector).
- We have therefore decided to restrict ourselves to searching for heteroclinics (or homoclinics) between y_{1-3} .
- y_{1-3} each have two zero and two general eigenvalues (in the sense that they are given by as yet unspecified functions, not to be confused with generalized eigenvalues). None of these depend on σ , and θ influences the stability properties only for y_1 .

A detailed analysis of the properties and behaviours of the families of steady states y_{1-6} can be found in Chapter A.2.

The methods presented in Chapters 2.1-2.2 were both based on two dimensional systems of first order ODEs, where varying one parameter, i.e. the wave speed σ , was sufficient to find intersections between steady/unsteady trajectories and a codimension one submanifold of the phase space. In our case, the system of first order ODEs (2.28) is of dimension four, the codimension one submanifold subsequently of dimension three. We will vary σ as well as θ which was shown to be a critical parameter in [JS12] and [Ste13]. The other parameters should be kept fixed, as we wish to stay as closely as possible to the example shown in Figure 1.1, which served as the cause for this thesis.

A variant of Lin's method for higher dimensional problems has been discussed in [KR08], which we will not use as it would go beyond the scope of this thesis. We will argue in Chapter 4 that heteroclinics likely exist between the two steady states $y_1 = (0, 1, p, q)^{\top}$ and $y_2 = (0, 1, p, q)^{\top}$.

Chapter 3

A geometric approach

As an alternative way of analysing the existence and behaviour of possible travelling waves, several researchers chose more geometric approaches to the problem, amongst them G. Pettet and M. Wechselberger in their individual PhD theses, [Wec98] and [Pet96] respectively. While both works originated independently at approximately the same time, the authors in 2010 published a paper together, [WP10], showing how the ideas and techniques applied coincide, and linking both methods. [WP10] uses geometric singular perturbation techniques to study the existence of travelling waves in coupled advection-reaction-diffusion (ARD) models, where both smooth and sharp interfaces might occur. A perk of this method is that it includes and explains jump and entropy conditions known to apply for shocks in PDE-theory (namely the *Rankine-Hugoniot* and *Lax* entropy conditions). A special focus is given to a particular type of solutions called *canards*.

Harley *et al* (amongst them both Pettet and Wechselberger) in 2014 revisited this technique and further expanded on how it is linked to the theory of *walls of singularities*, singularities in a given problem that may occur after a transformation from PDE to ODE by travelling wave ansatz, passable only by solutions going through the *hole in the wall*, [HVHM⁺14].

We will discuss both approaches in this chapter and subsequently see how they may be applied to the tumor model (1.1).

3.1 On "Folds, canards and shocks in advection-reactiondiffusion models"

In [WP10], Wechselberger and Pettet consider a class of nonlinear ARD models of the the form

$$W_t + \{G(W)\}_x = F(W) + \varepsilon W_{xx}, \qquad (3.1)$$

where $W \in \mathbb{R}^k$, F(W), $G(W) \in \mathbb{R}^k$ sufficiently smooth with k = 3 and $0 < \varepsilon \ll 1$, implying that the diffusion is considered "small"¹. As the authors remark, systems like (3.1) represent coupled balance laws with small viscous perturbations when regarded in the classical PDE setting. The limit $\varepsilon \to 0$ may cause physical shocks due to dissipative mechanisms, see [WP10, p.1950]. Their ansatz combines solutions obtained from singular limit subsystems to a solution of the full system, which persist under small perturbations. Both the Rankine-Hugoniot and Lax entropy conditions are fulfilled. Furthermore it is commented upon how this theory fits in with the concepts of walls of singularities and holes in the walls, two highly linked notions that we will explain and regard more thoroughly in Chapter 3.3. Additionally the role of *canards*, which are a special type of solutions that may occur when regarding singular perturbations problems, is studied. We shall now review and summarize some parts of [WP10, Sec. 2], and then reproduce the calculation steps from [WP10, Sec. 3] in a slightly alternate version such that they may be applied to the tumor model (1.1). In particular, any ideas, calculation steps or results presented in Chapters 3.1.1-3.1.2 are taken or immediately follow from [WP10], if not explicitly stated otherwise.

3.1.1 ARD models motivated by haptotactic cell migration

The basic form of the analysed model is given by

$$\begin{pmatrix} u \\ w \end{pmatrix}_{t} + \begin{pmatrix} 0 \\ g(u, w)u_{x} \end{pmatrix}_{x} = \begin{pmatrix} h(u, w) \\ f(u, w) \end{pmatrix} + \varepsilon \begin{pmatrix} u \\ w \end{pmatrix}_{xx}$$
(3.2)

with $(x,t) \in \mathbb{R} \times \mathbb{R}$ representing spatial domain and time, and $W = (u,w)^{\top} \in \mathbb{R}^2$ denoting a feedback and a density variable. The term $J = (0, g(u, w)u_x)^{\top}$, called the advective flux term, indicates that the so-called feedback variable u has no advective component, but its gradient works as a driving factor for the density variable w. In particular this means that u functions as a chemoattractant in this case. The source

¹Note that W in this chapter corresponds to U in the previous chapter. This is due to a difference in notation in the cited sources.
term (also known as production/degradation or birth/death rate in biological models) is given by $F = (h(u, w), f(u, w))^{\top}$, where we consider nonlinear functions h and f. Since $\varepsilon \ll 1$, diffusion is small, meaning that the flux term is dominant for w. In the absence of any advection-reaction terms, diffusion however small is still dominant for u.

Now a new variable $v = u_x$ is inserted, which enables us to write the flux term J without second order derivations.

$$\begin{pmatrix} u \\ v \\ w \end{pmatrix}_{t} + \begin{pmatrix} 0 \\ -h(u,w) \\ g(u,w)v \end{pmatrix}_{x} = \begin{pmatrix} h(u,w) \\ 0 \\ f(u,w) \end{pmatrix} + \varepsilon \begin{pmatrix} u \\ v \\ w \end{pmatrix}_{xx}$$
(3.3)

Observe that (3.3) exactly fulfils the form of (3.1) with $W = (u, v, w)^{\top}$.

As the main interest lies in travelling wave solutions, we now introduce a travelling wave coordinate $z = x - \sigma t$ with wave speed σ . Recall that for the case of $\sigma > 0$, the wave is considered to be right moving. In this new coordinate system, (3.3) becomes stationary (i.e. an ODE, as the spatial domain was considered one dimensional only), and can thus be rewritten as

$$\{\varepsilon u_z + \sigma u\}_z = -h(u, w)$$

$$\{\varepsilon v_z + \sigma v + h(u, w)\}_z = 0$$

$$\{\varepsilon w_z + \sigma w - g(u, w)v\}_z = -f(u, w),$$

(3.4)

which allows us to perform a *Liénard transformation* (see e.g. [Kue15b, p.9]) where we define

$$\hat{u} := \varepsilon u_z + \sigma u$$
$$\hat{v} := \varepsilon v_z + \sigma v + h(u, w)$$
$$\hat{w} := \varepsilon w_z + \sigma w - g(u, w)v.$$
(3.5)

With this notation we finally obtain a singularly perturbed system in Liénard form

$$\hat{u}_{z} = -h(u, w)$$

$$\hat{w}_{z} = -f(u, w)$$

$$\varepsilon u_{z} = \hat{u} - \sigma u$$

$$\varepsilon v_{z} = \hat{v} - \sigma v - h(u, w)$$

$$\varepsilon w_{z} = \hat{w} - \sigma w + g(u, w)v$$
(3.6)

with $(u, v, w) \in \mathbb{R}^3$ denoting so-called fast variables, $(\hat{u}, \hat{w}) \in \mathbb{R}^2$ slow variables and \hat{v} a fixed parameter. In fact, $\hat{v} = 0$, which can be seen when setting $v = u_z$ in the second line of (3.4) and plugging this into the definition of \hat{v} in (3.5). The independent variable z is considered to be a "slow" travelling wave coordinate. Thus a rescaling of $z = \varepsilon y$ in (3.6) gives the equivalent *fast system*

$$\hat{u}_{y} = -\varepsilon h(u, w)$$

$$\hat{w}_{y} = -\varepsilon f(u, w)$$

$$u_{y} = \hat{u} - \sigma u$$

$$v_{y} = -\sigma v - h(u, w)$$

$$w_{y} = \hat{w} - \sigma w + g(u, w)v.$$
(3.7)

3.1.2 The viscous limit $\varepsilon \to 0$ - reduced and layer problem

"The basic idea of geometric singular perturbation theory is to study the singular limit $\varepsilon \to 0$ of the slow system (3.6) and the fast system (3.7) which are distinct lower dimensional subsystems [...]. We then concatenate solutions of these two distinct lower dimensional subsystems and show that these solutions persist as (sufficiently) smooth solutions of the full (five-dimensional) system for sufficiently small perturbations $\varepsilon \ll 1$." ([WP10, p.1953])

Beginning with the fast system (3.7), the limit $\varepsilon \to 0$ leads to the so-called layer problem

$$\hat{u}_{y} = 0$$

$$\hat{w}_{y} = 0$$

$$u_{y} = \hat{u} - \sigma u$$

$$v_{y} = -\sigma v - h(u, w)$$

$$w_{y} = \hat{w} - \sigma w + g(u, w)v$$
(3.8)

where the slow variables (\hat{u}, \hat{w}) are invariant under y and are thus considered parameters. It follows that the layer flow occurs along three-dimensional fast fibres $\{(\hat{u}, \hat{w}, u, v, w) \in \mathbb{R}^5 : \hat{u} = k_1, \hat{w} = k_2\}$, and that the set of equilibria of the layer problem takes the form of a two-dimensional *critical manifold*

$$S := \{ (\hat{u}, \hat{w}, u, v, w) \in \mathbb{R}^5 : \hat{u} = \sigma u, v = -h(u, w) / \sigma, \hat{w} = \sigma w - g(u, w) / \sigma \}.$$
(3.9)

To ascertain the stability of the set of equilibria we now have to compute the eigenvalues of the Jacobian of the layer problem, and evaluate them along the critical manifold S. The Jacobian matrix of (3.8) is given by

$$\begin{pmatrix} -\sigma & 0 & 0\\ -h_u & -\sigma & -h_w\\ g_u v & g & -\sigma + g_w v \end{pmatrix}$$
(3.10)

with eigenvalues $\lambda_1 = -\sigma < 0$ and $\lambda_{2/3} = -\sigma + (g_w v \pm \sqrt{(g_w v)^2 - 4h_w g})/2$ where $\lambda_2 < \lambda_3$. Here Wechselberger and Pettet impose a set of assumptions² ([WP10, p.1954]) on the functions g(u, w) and h(u, w) as well as the wave speed σ .

Assumption 1. The functions g(u, w) and h(u, w) of system (3.3) together with the wave speed $\sigma > 0$ have the following properties:

- (i) The inequality $(g_w(-h/\sigma))^2 > 4h_w g$ holds in the domain of interest $U \subseteq \{(u, w) \in \mathbb{R}^2\}$, i.e. all eigenvalues of the layer problem (3.8) are real.
- (ii) The three real eigenvalues of the layer problem (3.8) are distinct in U.

In particular, Assumption 1 implies that the corresponding conservation law of (3.1) is a strictly hyperbolic PDE problem, in the sense of being diagonisable, compare to e.g. [Eva10, p.421]. In order to determine stability properties of the critical manifold S, we have to look at several cases:

- If $h_w g > 0$ and $g_w h > 0$ in U, then $\lambda_2 < \lambda_3 < \lambda_1 = -\sigma$. In this case, S is called an attracting critical manifold.
- If $h_w g > 0$ but $-2\sigma^2 < g_w h < 0$ in U, then $\lambda_1 < \lambda_2 < \lambda_3$, where $\lambda_{1/2} < 0$ but λ_3 may change sign.
- If $h_w g < 0$ in U, then $\lambda_2 < \lambda_1 < \lambda_3$, where again $\lambda_{1/2} < 0$ and λ_3 may change sign.

 $^{^{2}}$ Note that these assumptions ascertain the existence of *canard* solutions and may not be strictly necessary for other types of travelling wave solutions.

In the instances where λ_3 changes sign in U, S can no longer be called attracting. Instead we find that along the 2D critical manifold, one or several codimension one bifurcationcurve(s) occur. In general, S is locally folded, with fold curve(s) L_j corresponding to saddle-node bifurcations of the layer problem. These are defined by the condition

$$\sigma^{2} + \{g(u, w)h(u, w)\}_{w} = 0, \qquad (3.11)$$

which we obtain by setting $\lambda_3 = 0$, keeping in mind that $v = -h(u, w)/\sigma$. These fold curves separate attracting from repelling parts of the critical manifold, the former ones characterized by the condition $\lambda_{1/2/3} < 0$, the latter ones by $\lambda_{1/2} < 0$ but $\lambda_3 > 0$.

Let us now look at the slow system (3.6). By letting $\varepsilon \to 0$ we obtain the *reduced* problem

$$\hat{u}_{z} = -h(u, w)$$

$$\hat{w}_{z} = -f(u, w)$$

$$0 = \hat{u} - \sigma u$$

$$0 = -\sigma v - h(u, w)$$

$$0 = \hat{w} - \sigma w + g(u, w)v$$
(3.12)

where again $\hat{v} = 0$. Through (3.12) we can describe the behaviour of the slow variables (\hat{u}, \hat{w}) along S. In this sense the critical manifold works as an interface between the reduced and layer problem. Note that S is defined over $U \subseteq \{(u, w) \in \mathbb{R}^2\}$ which is independent of g(u, w) and h(u, w), thus we need to examine the reduced flow on S over U. The reduced vector field has to be tangent to S by definition, which is accomplished by differentiating line 3 and 5 of (3.6) and inserting the results into lines 1 and 2 respectively. Under the condition $v = -h(u, w)/\sigma$, this yields the projection of the reduced vector field onto U

$$\begin{pmatrix} \sigma & 0\\ \frac{1}{\sigma} \{g(u,w)h(u,w)\}_u & \sigma + \frac{1}{\sigma} \{g(u,w)h(u,w)\}_w \end{pmatrix} \begin{pmatrix} u_z\\ w_z \end{pmatrix} = \begin{pmatrix} -h(u,w)\\ -f(u,w) \end{pmatrix}, \quad (3.13)$$

which we observe is equivalent to the non-diffusive limit $\varepsilon \to 0$ of (3.4) in travelling wave coordinates. (3.13) is singular where $\sigma + \frac{1}{\sigma} \{g(u, w)h(u, w)\}_w = 0$, or in other terms where $\lambda_3 = 0$, i.e. along the fold curve(s) L_j . We would now like to learn more about the behaviour of the reduced flow, in particular $(u_z, w_z)^{\top}$, in the phase plane (u, w). As was the case earlier, we cannot get rid of the matrix term on the lhs entirely, for invertibility can not be assumed in general, so again we multiply system (3.13) from the left side with the transpose of the co-factor matrix,

$$\begin{pmatrix} \sigma + \frac{1}{\sigma} \{g(u, w)h(u, w)\}_w & 0 \\ -\frac{1}{\sigma} \{g(u, w)h(u, w)\}_u & \sigma \end{pmatrix}$$

giving

$$(\sigma^{2} + \{g(u,w)h(u,w)\}_{w}) \begin{pmatrix} u_{z} \\ w_{z} \end{pmatrix} = \begin{pmatrix} -\sigma h(u,w) - \frac{1}{\sigma}h(u,w)\{g(u,w)h(u,w)\}_{w} \\ -\sigma f(u,w) + \frac{1}{\sigma}h(u,w)\{g(u,w)h(u,w)\}_{u} \end{pmatrix}.$$
 (3.14)

System (3.14) becomes singular when $(\sigma^2 + \{g(u, w)h(u, w)\}_w) = 0$, which as in Chapter 2.3 is the determinant of the matrix on the lhs in (3.13). In order to *desingularize*, we rescale and define $z = (\sigma^2 + \{g(u, w)h(u, w)\}_w)\overline{z}$ to finally obtain

$$\begin{pmatrix} u_{\overline{z}} \\ w_{\overline{z}} \end{pmatrix} = \begin{pmatrix} -\sigma h(u,w) - \frac{1}{\sigma} h(u,w) \{g(u,w)h(u,w)\}_w \\ -\sigma f(u,w) + \frac{1}{\sigma} h(u,w) \{g(u,w)h(u,w)\}_u \end{pmatrix}.$$
 (3.15)

[WP10] explain now how (and why) the phase portraits of the reduced problem (3.13)and the desingularized problem (3.15) are equivalent up to parametrization change of the independent variable z in domains where the determinant of the lhs matrix in (3.13)is negative. In particular, singularities of (3.15) correspond to singularities of (3.13) and fall in two different categories:

- Equilibria of the desingularized problem (3.15) occuring where f(u, w) = h(u, w) =
 0. These correspond directly to equilibria of the reduced problem (3.13) and include the asymptotic states (u[±], w[±]) of travelling waves.
- Equilibria of (3.15) defined by

$$\{g(u,w)h(u,w)\}_w f(u,w) + \{g(u,w)h(u,w)\}_u h(u,w) = 0$$

These are in general not equilibria of the reduced problem (3.13) but correspond to so-called *folded singularities* which can be found on fold-curves L_j . Depending on their behaviour as singularities of the desingularized problem (3.15), they are classified as folded saddles, folded nodes and folded foci.

Any of these cases may provide for 'interesting' behaviour, for the folded foci in particular generic solutions will always terminate at a fold curve, as a blow-up occurs in



FIGURE 3.1: Example of reduced flow on the critical manifold S near a folded saddle singularity: (a) '5D' view, (b) projection of the reduced flow onto (u, w) space. There exist two canard solutions; one crosses from S_a to S_r through the folded singularity while the other crosses in the opposite direction. Source: [WP10, Fig.1]

finite time (either forward or backward time). In the case of folded saddles or nodes on the other hand, a so called *singular canard* may occur, where certain trajectories of the reduced flow cross from one branch of the critical manifold to the other branch in finite time, an example of which can be seen in Figure 3.1. [SW01, p.421] describes the phenomenon of *canards* as follows: "A canard solution is a solution of a singularly perturbed system which follows an attracting slow manifold, passes close to a bifurcation point of the critical manifold and then follows, rather surprisingly, a repelling slow manifold for a considerable amount of time. In geometric terms a canard solution corresponds to the intersection of an attracting and a repelling slow manifold near a non-hyperbolic point of [the critical manifold] S." Note that folded foci do not provide this opportunity.

At this point the authors impose another set of assumptions defining minimum requirements on system (3.3) such that *canard* type travelling waves with smooth and sharp interfaces will occur, which gives a good overview over minimal requirements for *canard* solutions ([WP10, p.1956f.]):

Assumption 2. "Given system (3.3). The (sufficiently smooth) functions f(u, w), g(u, w) and h(u, w) along with wave speeds $\sigma > 0$ lead to the following properties:

- (i) In the domain of interest U, there are two negative eigenvalues $\lambda_{1/2} < 0$ along the critical manifold S of the layer problem (3.8). The third eigenvalue λ_3 changes sign.
- (ii) The 2D critical manifold $S = S_a \cup L \cup S_r$ (3.9) is a folded surface, i.e. there exists a fold-curve $L = \{(\hat{u}, \hat{w}, u, v, w) \in S : \lambda_3 = 0\}$, hence the layer problem has a saddle-node bifurcation along L. S_a denotes the attracting branch of S where $\lambda_3 < 0$, while S_r denotes the repelling branch of S where $\lambda_3 > 0$.

- (iii) The reduced problem (3.12) possesses two ordinary singularities (u[±], w[±]) which are equilibrium states of the reaction terms, i.e. f(u[±], w[±]) = h(u[±], w[±]) = 0, away from the fold-curve L. One equilibrium, (u⁻, w⁻), has at least a one-dimensional unstable eigendirection (saddle, unstable node/focus) and the other equilibrium, (u⁺, w⁺), has at least a one-dimensional stable eigendirection (saddle, stable node/focus). These equilibria (u[±], w[±]) are the asymptotic states of travelling waves under study.
- (iv) The reduced problem also possesses a folded singularity (u_f, w_f) which is either a folded saddle or a folded node."

Throughout [WP10, Sec. 2.3] several examples are presented that exhibit travelling waves with smooth and sharp interfaces, while [WP10, Sec. 2.4] is concerned with showing how the *Lax* and *RH entropy conditions* hold for canard solutions. We refer the interested reader directly to the original paper for these considerations.

Lastly, in [WP10, Sec. 2.5] it is shown how travelling waves with smooth and sharp interfaces persist under sufficiently small perturbations with $0 < \varepsilon \ll 1$. This property is critical in making singular perturbation theory a powerful analytical tool, and is shown using Fenichel theory (see e.g. [Fen79]), which states that for the full systems in Liénard-form (3.6) and fast form (3.7) the respective attracting and repelling branches $S_{a,\varepsilon}$ and $S_{r,\varepsilon}$ away from L are within $O(\varepsilon)$ to the unperturbed S_a and S_r . The flow on the perturbed branches is a smooth perturbation of $O(\varepsilon)$ of the reduced flow, and hyperbolic equilibria away from L are persistent under sufficiently small $0 < \varepsilon \ll 1$ as well.

3.1.3 Coupled ARD models

Of particular interest for us is [WP10, Sec. 3], where Wechselberger and Pettet look at a (dimensionless) system of two coupled ARD equations,

$$\begin{pmatrix} u \\ w \end{pmatrix}_{t} + \begin{pmatrix} g_{1}(u,w) \\ g_{2}(u,w) \end{pmatrix}_{x} = \begin{pmatrix} f_{1}(u,w) \\ f_{2}(u,w) \end{pmatrix} + \varepsilon \begin{pmatrix} u \\ w \end{pmatrix}_{xx}.$$
(3.16)

Put into vector form this is equivalent to

$$W_t + \{G(W)\}_x = F(W) + \varepsilon W_{xx}, \qquad (3.17)$$

where $x \in \mathbb{R}$ represents the spatial domain, $t \in \mathbb{R}$ time and $\varepsilon \ll 1$ indicates that diffusion is "small". Note that (3.17) is identical to (3.1). $W = (u, w)^{\top} \in \mathbb{R}^2$ is a densitive

function, $G = (g_1(u, w), g_2(u, w))^{\top}$ denotes the flux. $F = (f_1(u, w), f_2(u, w))^{\top}$, which is nonlinear, models the kinetic (reaction) term. Note that setting $g_1(u, w) \equiv 0$ does not give us the form of system (3.2), as the second part of the flux term would have to read $g_2(u, w)u_x$ instead of $g_2(u, w)$.

Let us recall the basic form of our tumor model, (1.1):

$$\frac{\partial}{\partial t} \begin{pmatrix} c \\ m \end{pmatrix} - \frac{\partial}{\partial x} \left(A(c,m) \cdot \frac{\partial}{\partial x} \begin{pmatrix} c \\ m \end{pmatrix} \right) = R(c,m)$$

or in other terms by setting $W = (c, m)^{\top}$,

$$W_t = R(W) + \{A(W)W_x\}_x$$
(3.18)

It is clear that there are parallels between (3.17) and (3.18), and indeed the authors remark that their arguments carry through when assuming a diffusion term of the form εBW_{xx} with diffusion constant $B = (B_1, B_2)^{\top} \in \mathbb{R}^2_+$ or even $\varepsilon(B(W)W_x)_x$ with appropriate viscosity matrix $B(W) = (B_1(W), B_2(W))^{\top}$, but concede that this was omitted as calculations would become tedious (see [WP10, p.1963]). We will at this point depart from our previous approach of mainly reviewing [WP10] and instead try to extend the calculations from [WP10, Sec. 3] to include the mentioned viscosity matrix, keeping in mind that $G \equiv 0$ and $\varepsilon \equiv 1$ in our model. Let us now consider the following system,

$$W_t + \{G(W)\}_x = F(W) + \varepsilon \{B(W)W_x\}_x, \tag{3.19}$$

or after introducing the travelling wave coordinate $z = x - \sigma t$ and a re-arrangement of terms

$$\{\sigma W + \varepsilon B(W)W_z - G(W)\}_z = -F(W). \tag{3.20}$$

By setting $\hat{W} := \sigma W + \varepsilon B(W) W_z - G(W)$ we obtain:

$$\begin{cases} \hat{W}_z = -F(W) \\ \varepsilon B(W)W_z = \hat{W} - \sigma W + G(W) \end{cases}$$
(3.21)

Even though they look quite similar in structure, we remember that the *Liénard form* defined in (3.6) is different from (3.21) in not containing the factor B(W) on the right-hand-side of line 2. As it was the case in Chapter 2.3, invertibility of the viscosity matrix is one of the major problems we encounter, as it can not a priorily be guaranteed. Two

approaches appear plausible: we can either keep the viscosity term on the left-handside and see whether (or rather, where) this gives rise to further problems; or we may follow our approach from Chapter 2.3 and eliminate B(W) from the left-hand-side by multiplying the first line of (3.21) with det(B(W)) and the second line with cof $(B(W))^{\top}$, giving

$$\begin{cases} \det(B(W))\hat{W}_z = -\det(B(W))F(W) \\ \varepsilon \det(B(W))W_z = \operatorname{cof}(B(W))^\top (\hat{W} - \sigma W + G(W)). \end{cases}$$

Now by substituting $z = \det(B(W))\tilde{z}$ we finally obtain

$$\begin{cases} \hat{W}_{\tilde{z}} = -\det(B(W))F(W) \\ \varepsilon W_{\tilde{z}} = \operatorname{cof}(B(W))^{\top}(\hat{W} - \sigma W + G(W)). \end{cases}$$
(3.22)

In order to best see where problems or advantages arise from either approach, we elect to apply both variants, which is feasible as several subsequent calculation steps can be performed on either variant simultaneously. To provide for easier reading, we will try to align both versions directly above each other wherever possible, separated by a horizontal line, starting with the systems derived from (3.21). This makes the output appear as follows:

$$\begin{cases} \hat{W}_z = -F(W) \\ \varepsilon B(W)W_z = \hat{W} - \sigma W + G(W) \end{cases}$$
(3.21)

$$\begin{cases} \hat{W}_{\tilde{z}} = -\det(B(W))F(W)\\ \varepsilon W_{\tilde{z}} = \operatorname{cof}(B(W))^{\top}(\hat{W} - \sigma W + G(W)). \end{cases}$$
(3.22)

3.1.4 Reduced and layer problems for coupled ARD models

As before, $W = (u, w) \in \mathbb{R}^2$ represents fast variables and $\hat{W} = (\hat{u}, \hat{w}) \in \mathbb{R}^2$ slow ones. Rescaling the (slow) independent variable $z = \varepsilon y$ in (3.21), $\tilde{z} = \varepsilon \tilde{y}$ in (3.22) resp., leads us to the equivalent *fast systems*:

$$\begin{cases}
\hat{W}_{y} = -\varepsilon F(W) \\
B(W)W_{y} = \hat{W} - \sigma W + G(W)
\end{cases}$$

$$\begin{cases}
\hat{W}_{\tilde{y}} = -\varepsilon \det(B(W))F(W) \\
W_{\tilde{y}} = \operatorname{cof}(B(W))^{\top}(\hat{W} - \sigma W + G(W)).
\end{cases}$$
(3.24)

Beginning with the fast subsystems (3.23-3.24), we obtain the layer problems by applying the limit $\varepsilon \to 0$

$$\begin{cases} \hat{W}_y = 0\\ B(W)W_y = \hat{W} - \sigma W + G(W) \end{cases}$$
(3.25)

$$\begin{cases} \hat{W}_{\tilde{y}} = 0\\ W_{\tilde{y}} = \operatorname{cof}(B(W))^{\top} (\hat{W} - \sigma W + G(W)), \end{cases}$$
(3.26)

making \hat{W} a parameter. In particular, the flow occurs along two-dimensional fast fibres $\{(\hat{W}, W) \in \mathbb{R}^4, \hat{W} = const\}$. The critical manifolds S_1 and S_2 resp. that define the set of equilibria are given by

$$S_1 := \{ (\hat{W}, W) \in \mathbb{R}^4, \hat{W} = \sigma W - G(W) \}$$
(3.27)

$$S_2 := \{ (\hat{W}, W) \in \mathbb{R}^4, \operatorname{cof}(B(W))^\top \hat{W} = \operatorname{cof}(B(W))^\top (\sigma W - G(W)) \}$$
(3.28)

As before, we now need to consider the stability of the critical manifolds S_i , which is dependent on the eigenvalues of their respective Jacobians

$$JS_1 := (D_W G - \sigma I)$$

$$JS_2 := \{D_W \operatorname{cof}(B(W))^\top (\hat{W} - \sigma W + G(W)) + \operatorname{cof}(B(W))^\top (D_W G - \sigma I)\}$$

$$= \operatorname{cof}(B(W))^\top (D_W G - \sigma I),$$

by definition of \hat{W} . $D_W G$ denotes the component wise derivative of the function $G = (g_1(u, w), g_2(u, w))^\top$ wrt. W = (u, w), i.e.

$$D_W G = \begin{pmatrix} g_{1,u} & g_{1,w} \\ g_{2,u} & g_{2,w} \end{pmatrix}.$$
 (3.29)

Once again, in order to ascertain hyperbolicity of the problem, we require that the eigenvalues $\lambda_{1/2}^i$, i = 1, 2, of the layer problems (3.25-3.26) are real and distinct in the domain of interest U. Similar to the results from Chapter 3.1.2, an eigenvalue crosses zero where det $JS_i = 0$. If we assume that λ_2^i changes sign in U, then as before a codimension one bifurcation curve L has to exist, along which $\lambda_2^i = 0$ holds. The authors further remark that the generic case are saddle-node bifurcations, see [WP10, p.1963].

Returning to the systems (3.21-3.22) given in Liénard-form, we obtain the reduced problems by letting $\varepsilon \to 0$:

$$\begin{cases} \hat{W}_z = -F(W) \\ 0 = \hat{W} - \sigma W + G(W) \end{cases}$$
(3.30)

$$\begin{cases} \hat{W}_{\tilde{z}} = -\det(B(W))F(W)\\ 0 = \operatorname{cof}(B(W))^{\top}(\hat{W} - \sigma W + G(W)) \end{cases}$$
(3.31)

Again this system describes the evolution of a slow variable \hat{W} along a 2D critical manifold S_i and is given as a graph over U which is structurally independent of G(W). In order to understand the projection of the reduced vector fields onto U, we need to differentiate S_i with respect to z or \tilde{z} and plug the resulting equation into the first line of system (3.30) or (3.31) respectively. In particular, this yields

$$JS_1W_z = F(W) \tag{3.32}$$

$$JS_2W_{\tilde{z}} = \det(B(W))F(W), \qquad (3.33)$$

with the JS_i defined as above. These systems are singular along the fold-curves L_j^i , which were defined by $\lambda_2^i = 0$, meaning that we cannot simply eliminate the matrices JS_i on the lhs. As seen before, we can however multiply these systems from the left with the appropriate transposed co-factor matrices $cof(JS_i)^{\top}$, resulting in

$$\det JS_1 W_z = \operatorname{cof}(JS_1)^\top F(W) \tag{3.34}$$

$$\det JS_2 W_{\tilde{z}} = \operatorname{cof}(JS_2)^\top \det(B(W))F(W).$$
(3.35)

Now we finally rescale once more by setting $z = \det JS_1\overline{z}$ or $\tilde{z} = \det JS_2\overline{\tilde{z}}$ respectively to obtain the desingularized flows:

$$W_{\overline{z}} = \operatorname{cof}(JS_1)^\top F(W) \tag{3.36}$$

$$W_{\overline{z}} = \operatorname{cof}(JS_2)^{\top} \det(B(W))F(W).$$
(3.37)

Here we observe that indeed all calculations and considerations we presented in this chapter mostly correspond to what was done in [WP10, Sec. 3]. In fact, the resulting equation (3.36) exactly corresponds to (36) in [WP10]. This suggests that the second approach, leading to (3.37), might have been the more sensible one as there the presence of a diffusion matrix B(W) actually plays a role for our outcome. We will regard this issue further when we apply the results from this chapter to our tumor model in Chapter

3.2. However, note that all further conclusions concerning phase portraits and equilibria of reduced and desingularized problems do not differ from what is presented by Wechselberger and Pettet. Hence at this point we return to reviewing and summarizing the remainder of [WP10, Sec. 3-4].

As before in the case of haptotactically driven ARD models, the phase portraits of the reduced (3.32-3.33) and desingularized problems (3.36-3.37) are equivalent up to a change of parametrization where det $JS_i < 0$. Singularities of (3.36-3.37) correspond to those of (3.32-3.33) in two ways:

- Equilibria W_e^i of the desingularized problems that fulfil $F(W_e^i) = 0$ and for which JS_i evaluated at W_e^i has no zero eigenvalue. Asymptotic states $W_e^{\pm,i}$ of travelling waves fall in this category.
- Equilibria W_f^i of the desingularized problems where JS_i evaluated at W_f^i has a zero eigenvalue $\lambda_2^i = 0$. These are in general not eigenvalues of the reduced problems but correspond to folded singularities, on fold-curves L_{j_i} , $j_i = 1, ..., j_{i\max}$. Depending on the singularities of the desingularized problems, these are considered folded saddles, folded nodes or folded foci.

The following assumption from [WP10, p.1965] defines minimum requirements on system (3.16) such that *canard* type travelling waves as defined by [SW01] with smooth and sharp interfaces (shocks) may be observed.

Assumption 3. Given system (3.16). The (sufficiently smooth) functions F and G together with wave speeds $\sigma > 0$ lead to the following properties:

- (A1) In the domain of interest U, there is one negative eigenvalue $\lambda_1 < 0$ of the layer problem. The second eigenvalue λ_2 changes sign.
- (A2) The 2D critical manifold $S = S_a \cup L \cup S_r$ is a folded surface, i.e. there exists a fold-curve $L = \{(\hat{W}, W) \in S : \lambda_2 = 0\}$, i.e. the layer problem has a saddle-node bifurcation along L. S_a denotes the attracting branch of S where $\lambda_2 < 0$, while S_r denotes the repelling branch of S where $\lambda_2 > 0$.
- (A3) The reduced problem possesses two ordinary singularities W_e^{\pm} which are equilibrium states of the reaction term, i.e. $F(W_e^{\pm}) = 0$, away from the fold-curve L. The equilibrium W_e^- has at least a one-dimensional unstable eigendirection (saddle, unstable node/focus) while W_e^+ has at least a one-dimensional stable eigendirection (saddle, stable node/focus).

(A4) The reduced problem also possesses a folded singularity W_f which is either a folded saddle or a folded node.

Once again the geometric results are compared to shock conditions from classical PDE theory in [WP10, Sec. 3.4], followed by a brief remark about how small viscious perturbations with $\varepsilon \neq 0$ persist, see [WP10, Sec. 3.5]. This concludes our summary.

3.2 Application of the Geometric Perturbation Method

We now want to apply the results from the previous section to the tumor model (1.1),

$$\frac{\partial}{\partial t} \begin{pmatrix} c \\ m \end{pmatrix} - \frac{\partial}{\partial x} \left(A(c,m) \cdot \frac{\partial}{\partial x} \begin{pmatrix} c \\ m \end{pmatrix} \right) = R(c,m)$$

or in equivalent form, by setting $W = (c, m)^{\top}$, (3.18),

$$W_t = R(W) + \{A(W)W_x\}_x.$$

As shown in [WP10], Assumption 3 defines minimum requirements on a given ARDsystem such that canard type travelling waves may occur, hence we want to analyse (3.18) accordingly. We see immediately that with the notation from [WP10], we get $F(W) = R(W), G(W) \equiv 0, B(W) = A(W)$. On the first glance it appears that in our case $\varepsilon \equiv 1$, which may definitely not be considered 'small'. Note however that we have not specified any boundaries for x. We can therefore always scale x by setting $x = \tilde{x} \cdot \sqrt{\varepsilon}$. Let us thus regard the adjusted version where have we scaled x and B(W) accordingly, and immidiately dropped the tilde again for conveniency:

$$W_t = F(W) + \varepsilon \{B(W)W_x\}_x,\tag{3.38}$$

We remember that our analysis required the eigenvalues of the layer problems (3.25-3.26) to be real and distinct in the domain of interest $U = (0, 1)^2 \subset \mathbb{R}^2$. These eigenvalues are the ones of $JS_1 = (D_W G - \sigma I)$ and $JS_2 = \operatorname{cof}(B(W))^\top (D_W G - \sigma I)$ respectively. At this point we see already that our first approach, which was 'keeping' the diffusion term on the lhs in the Liénard-form (3.21), is not applicable here as the eigenvalues of $JS_1 = (D_W G - \sigma I) = -\sigma I$ (since $G \equiv 0$) are given by $\lambda_1 = \lambda_2 = -\sigma$ and are thus not distinct, nor will either of them ever change sign. The second variant however yields eigenvalues $\lambda_{1/2}$ dependent on $JS_2 = -\sigma \operatorname{cof}(B(W))^\top$. One can show that they are in fact real and distinct in U for a reasonable range of parameters σ and θ . It also follows that the smaller eigenvalue, which we denote by λ_1 , fulfils $\lambda_1 < 0$ in U, while λ_2 changes sign where det $\operatorname{cof}(B(W))^{\top} = 0$, thus sufficing (Ass.3.A1).

The next requirement, (Ass.3.A2) is immediately satisfied as well, as the fold curve $L = \{(\hat{W}, W) \in S : \lambda_2 = 0\}$ is given by $\det(\operatorname{cof}(B(W))^{\top}) = 0$ which indeed is a subset of $S_2 = \{(\hat{W}, W) \in \mathbb{R}^4 : \operatorname{cof}(B(W))^{\top} \hat{W} = \sigma \operatorname{cof}(B(W))^{\top} W\}$. Problems arise however when we have to identify equilibrium states W_e^{\pm} of the reaction term F(W) = R(W), as all of them are found along L, which is a violation of (Ass.3.A3).

In particular, the tumor model given by (1.1) does not exhibit travelling wave behaviour of the *canard* type that [WP10] were investigating, since all equilibrium points are to be found along the fold curve of the critical manifold. Systems of this type are not easily investigable, which is consistent to the results found in Chapter 2 where we only managed to determine families of steady states instead of discret equilibrium points. Note that other, more complicated *canard* solutions may still exist.

3.3 On "Existence of travelling wave solutions for a model of tumor invasion"

In [HVHM⁺14], K. Harley et al. (including both G. Pettet and M. Wechselberger) revisit the techniques presented above for a concrete example, and link it to the concept of *walls* of singularities and hole(s) in the wall. The following is a (very brief) overview of their results. In general they regard PDE problems that can by travelling wave ansatz be brought to the form

$$\frac{\partial u}{\partial z} = R(u, w)$$

$$P(u, w) \frac{\partial w}{\partial z} = Q(u, w).$$
(3.39)

It is possible to study equations of this type using dynamical systems theory, analysing solutions in the (u, w) phase plane. Note however that problems arise where P(u, w) = 0while $Q(u, w) \neq 0$. (Compare this to the formulation in (3.21)) For sufficiently smooth P and Q, this occurs along a curve in the phase plane that we denote by the wall of singularities. Solution trajectories can only cross it at the hole in the wall, the point where P(u, w) = Q(u, w) = 0 and thus (3.39) is no longer singular. Systems that exhibit several walls of singularities or multiple holes in the wall are not regarded in [HVHM⁺14]. The model considered in [HVHM⁺14] is a tumor growth model given by

$$\frac{\partial u}{\partial t} = -u^2 w$$

$$\frac{\partial w}{\partial t} = w(1-w) - \frac{\partial}{\partial x} \left(\frac{\partial u}{\partial x}w\right),$$
(3.40)

with boundary conditions

$$\lim_{x \to -\infty} u(x,t) = 0, \qquad \lim_{x \to \infty} u(x,t) = \hat{u}, \qquad \lim_{x \to -\infty} w(x,t) = 1, \qquad \lim_{x \to \infty} w(x,t) = 0,$$

where $(x,t) \in \mathbb{R} \times \mathbb{R}^+$. u(x,t) denotes the extracellular matrix (ECM) concentration and w(x,t) the invasive tumor cell population. After application of the travelling wave ansatz with $z = x - \sigma t$, (3.40) can be rearranged to

$$\frac{\partial u}{\partial z} = \frac{u^2 w}{\sigma}$$

$$\left(\frac{2u^2 w}{\sigma} - \sigma\right) \frac{\partial w}{\partial z} = w(1 - w) - \frac{2u^3 w^3}{\sigma^2}.$$
(3.41)

The *wall of singularities* is defined by the zeros of the term next to the w derivative, or alternatively

$$w = \frac{\sigma^2}{2u^2} =: F(u). \tag{3.42}$$

The hole in the wall is defined by the intersection of F(u) with the nontrivial w-nullcline, and is given by

$$(u_H, w_H) = \left(\frac{\sigma}{4}(\sigma + \sqrt{\sigma^2 + 8}), \frac{1}{1 + u_H}\right).$$
 (3.43)

The authors now perturb the system (3.40) with a small diffusive term and follow the calculations from [WP10, Sec. 2], obtaining analogous general and problem-specific results. A nondegeneracy and a transversality condition are formulated that ensure the foldedness of the critical manifold S ([HVHM⁺14, p.376]):

- $p \cdot (D^2_{UU}G)(U, \hat{U})(q, q) \neq 0$
- $p \cdot (D_{\hat{U}}G)(U,\hat{U}) \neq 0$

Keeping the notation from Chapter 3.1, U = (u, v, w), $\hat{U} = (\hat{u}, \hat{w})$ and $G = (u_y, v_y, w_y)$, while the vectors p and q are the respective left and right null vectors of J satisfying $q \cdot q = p \cdot q = 1$. It is further remarked that the fold curve of the critical manifold Swhere $\lambda_2 = 0$ exactly corresponds to the *wall of singularities* (3.42). Harley et al. identify four different types of travelling wave solutions for their model, represented by singular heteroclinic orbits. Those are characterized in the following way ([HVHM⁺14, p.372]):

- Type I: any smooth travelling waves
- Type II: waves that exhibit a shock in w and have infinite support
- Type III: waves that exhibit a shock in w with semicompact support in w
- $\bullet\,$ Type IV: waves that exhibit a shock and have a negative component in w

Type IV waves are nonphysical and were not observed numerically in [HVHM⁺14]. Figure 3.2 provides an illustration of the four different types of waves. Lastly, [HVHM⁺14, Sec. 4] is concerned with numerical estimations of the wave speed required such that travelling wave solutions may occur in the PDE setting.



FIGURE 3.2: Illustration of the four types of travelling wave solutions identified. The lighter curves represent the ECM concentration u, the darker ones the tumor cells w. Source: [HVHM⁺14, Fig.2]

Remark. For the tumor model given in (1.1), an analysis in terms of the wall of singularities and hole in the wall is not possible in a straightforward manner.

Recall that the vectorized form of (1.1) is given by (3.18)

$$W_t - \{A(W)W_x\}_x = R(W),$$

or after application of the travelling wave ansatz $z = x - \sigma t$ by

$$-\sigma W_z - \{A(W)W_z\}_z = R(W).$$
(3.44)

Set $V = W_z$ then we can systemize this to read

$$\begin{cases} W_z = V\\ A(W)V_z = -\sigma V - \left(\frac{\partial}{\partial z}A(W)\right)V - R(W). \end{cases}$$
(3.45)

Observe that the wall of singularities for system (3.45) is given by the three points $(c,m) \in \{(0,1), (1,0), (0,0)\}$ only instead of by a curve, which is conceptionally very different from what Harley et al. presented in [HVHM⁺14]. The approach that we used in Chapter 2 is not helpful either, since we have to substitute $A(c,m) \cdot (c_z,m_z)^{\top} = (p,q)^{\top}$ as before to avoid division by zero where det A(c,m) = 0. Recall that this yields

$$\begin{cases} \begin{pmatrix} p \\ q \end{pmatrix}' = -\sigma \begin{pmatrix} c \\ m \end{pmatrix}' - R(c,m) \\ A(c,m) \begin{pmatrix} c \\ m \end{pmatrix}' = \begin{pmatrix} p \\ q \end{pmatrix} \end{cases}$$

where we have yet to express $(c', m')^{\top}$ in the first line by means of $(p, q)^{\top}$. The alleged *wall of singularities* in this form is in fact a definition that by construction holds true for all (c, m).

As we have seen, the notions of *wall of singularities* and *hole in the wall* are quite closely linked to the concepts of singular perturbation theory, a fact that is remarked upon both in [WP10] and [HVHM⁺14]. In both cases we were not able to apply the methods presented to the tumor model (1.1) owing to structural discrepancies.

Chapter 4

Numerical approach

In this chapter we leave singular perturbation theory behind and return to the more straight forward methods presented in Chapter 2. First we take a closer look at the entropy method employed in [JS12] and [Ste13], and illustrate why it was rejected for the travelling wave analysis. Since methods and results are equivalent in both sources, we will refer only to [JS12]. Observe however that notation may differ slightly. A motivation and description of the final algorithm as well as the obtained results follow.

All calculations were done on a personal computer (Intel Core i5, 3.4-GHz CPU with 8-GB RAM), the model was implemented in Matlab[®] version 8.0.0.783 (R2012b). Additional computations utilized MapleTM 18.01.

4.1 The entropy method

As we have already remarked, [JS12] have shown that under certain parameter restrictions and initial conditions, a bounded weak solution to (1.1) exists globally in forward time, which is stated as

Theorem 1 ([JS12]). Let $\alpha, \gamma, \delta \geq 0, \beta > 0, 0 \leq \theta \leq 4/\sqrt{\beta}$ [=: θ^*], and let $c_0, m_0 \in L^1(\Omega)$ satisfy $c_0 \geq 0, m_0 \geq 0, c_0 + m_0 \leq 1$ in Ω , and $H(c_0, m_0) < \infty$. Then there exists a weak solution $c, m \in L^2_{loc}(0, \infty; H^1(\Omega)) \cap H^1_{loc}(0, \infty; (H^1(\Omega))')$ to (1.1)-(1.2) satisfying $c, m \geq 0$ and $c + m \leq 1$ in $\Omega \times (0, \infty)$.

Here, the function H(c,m) is a logarithmic entropy defined as follows (with entropy density h(c,m)):

$$H(c,m) = \int_{\Omega} h(c,m)dx$$

= $\int_{\Omega} c(\log c - 1) + m(\log m - 1) + (1 - c - m)(\log(1 - c - m) - 1)dx.$

As [JS12, p.4] points out, system (1.1)-(1.2) possesses an entropy functional as long as $\theta < \theta^* := 4/\sqrt{\beta}$, which is essential for the proof.

With this notation, it is possible to introduce entropy variables

$$u = \frac{\partial h}{\partial c} = \log \frac{c}{1 - c - m}, \quad v = \frac{\partial h}{\partial m} = \log \frac{m}{1 - c - m},$$
 (4.1)

with inverse formulation

$$c = \frac{e^u}{1 + e^u + e^v}, \quad m = \frac{e^v}{1 + e^u + e^v},$$
 (4.2)

and thus rewrite (1.1) to

$$\frac{\partial}{\partial t} \begin{pmatrix} c(u,v) \\ m(u,v) \end{pmatrix} - \frac{\partial}{\partial x} \left(L(u,v) \cdot \frac{\partial}{\partial x} \begin{pmatrix} u \\ v \end{pmatrix} \right) = R(c(u,v),m(u,v)).$$
(4.3)

Note that $(u, v)^{\top} = \nabla h(c, m)$ where the gradient is taken wrt. (c, m). L is defined as $L(c,m) := A(c,m) \cdot (\nabla^2 h(c,m))^{-1}$ (with Hessian matrix $\nabla^2 h$ of h). The entropy formulation is beneficial in several aspects, namely that for $\theta = 0$ and c > 0 and m > 0 such that c+m < 1, L becomes symmetric and positive definite, as well as that due to the inverse transformation (4.2), the maximum principle (which is not available) is no longer necessary since we automatically get positive volume fractions satisfying c + m < 1. ([JS12, p.4f.])

In particular, we do not have to concern ourselves with boundedness of c, m and 1-c-min this formulation. However it has become apparent that for numerical travelling wave analysis this method is not favourable. To understand this, recall that the steps for a travelling wave analysis will transform PDEs of the form $u_t + (A(u) \cdot u_x)_x = f(u)$ into first order systems

$$\begin{cases} U' = V\\ A(U) \cdot V' = -\sigma V - f(U). \end{cases}$$
(4.4)

Should A be invertible, which is the case for A(U) = L(u, v) with $u, v \neq \pm \infty$ in (4.3) then we now have to identify steady states of

$$\begin{cases} U' = V \\ V' = -\sigma A(U)^{-1} \cdot V - A(U)^{-1} \cdot f(U). \end{cases}$$
(4.5)

Naturally, for any steady state we require V = 0 and subsequently f(U) = 0 since we noted already that A should be a regular matrix. In (4.3), f(U) = R(c(u, v), m(u, v))can be expressed in terms of (u, v) as

$$R(u,v) = \frac{1}{(1 + e^u + e^v)^3} \begin{pmatrix} (1 + e^u + e^v)e^u(\gamma - \delta - \delta e^u - \delta e^v) \\ \alpha e^u e^v \end{pmatrix}.$$
 (4.6)

We can now immediately see that the second line of R(u, v) will become zero if and only if either u or v equal $-\infty$, which is a case we initially excluded, since L would no longer be invertible. The necessity that for possible steady states of (4.3) either u and/or vhave to tend to $-\infty$ in fact corresponds to c or m becoming 0. While we have shown this to be true (except for y_6 , which occurred due to transformation with the determinant of A), it is problematic in a numerical simulation, as "convergence to $-\infty$ " is not well defined and can not be distinguished from numerical error or non-convergence with a specific sign.

4.2 Implementation in Matlab

As we have seen in the previous chapter, the entropy formulation (4.3) of the tumor model has its advantages for the theoretical analysis performed in [JS12] and [Ste13], but is unfortunately not applicable in numerical travelling wave analysis. Regardless of notation, we wish to apply Lin's method to find possible orbits between steady states. The final algorithm should thus include the following steps:

- 1. Out of the families of steady states select one and fix initial values of (c, m, p, q)where necessary such that the steady state has an unstable eigendirection.
- 2. Perturb the steady state a little bit along the unstable eigenvector.
- 3. Repeat with a stable steady state.
- 4. Compute the strongly unstable and stable trajectories W^{su} and W^{ss} .
- 5. Chose a submanifold L of the phase space, vary σ and θ to minimize the Lin Gap on L.

During implementation key issues arose for every step, which we will shortly address in the following sections.

4.2.1 Choice of steady states and initial points

As we have discussed in Chapter 2.3, the tumor model in it's $\dot{y} = F(y)$ -formulation (2.28) does not have isolated steady states, but rather six families y_{1-6} of them, with stability properties varying in $y = (c, m, p, q) \in (0, 1) \times (0, 1) \times \mathbb{R} \times \mathbb{R}$. Even discounting the changing stabilities aspect, this allows for 15 possible pairs in searching for heteroclinic orbits, or 21 if we include homoclinics, which is quite a large number, and most likely not all possible combinations will exhibit travelling wave behaviour in any case. We therefore need to make an educated choice as to which steady states we want to select, and in which range of starting values.

Based on the results presented in Chapter A.2 we shall restrict ourselves to searching orbits between y_{1-3} . This still leaves the question of starting points which, as can be seen in Figure A.1 and Figure A.2 have critical impact on the stability of the eigenvalues λ^{1-3} . Here a "trial and error" approach was chosen. The best results were achieved when starting from y_1 and y_2 in regions where they both act as saddle nodes.

4.2.2 Calculation of eigenvalues and eigenvectors

Next we need to consider how we wish to calculate eigenvalues and eigenvectors. As we are working in Matlab, a natural idea is to implement the Jacobian dF(y), evaluate it at y_{1-6} and then use the inbuilt **eigs**-function to calculate eigenvalues and eigenvectors at the respective starting points. A downside of this method is that we can not directly control "which eigenvalue is which": The Matlab-documentation states that "D=eigs(A) returns a vector of A's 6 largest magnitude eigenvalues" where it is implied that they are sorted by magnitude of absolute value. In particular, the order in which the eigenvalues are returned may change in z = (c, m, p, q), which is not necessarily a problem but we have to keep this in mind nontheless. Note that [V,D]=eigs(A) returns eigenvectors as well as eigenvalues of a given matrix A.

Another issue arising with using the inbuilt **eigs**-function is that in order to better understand the behaviour of the families of steady states we do not want to evaluate dF(y)at one specific value of y but rather over a whole range. This can of course be realised in matlab but requires a large number of function calls which may be quite costly in terms of computation time. The second issue with **eigs** is that it requires the Jacobian dF(y) entered by hand, which is prone to error. Making use of Matlab's Symbolic Math toolbox to avoid this was briefly considered, but rejected due to problems with reconversion of the obtained symbolic functions.

Alternatively, since for some of the families of steady states the eigenvalues are relatively "nice" functions (see Table A.2), one could argue that a sensible approach is to have them calculated symbolically by appropriate programmes such as Maple or Mathematica and then import these functions into Matlab. This guarantees control over the order of eigenvalues, must however be handled with suitable care. Another downside of this ansatz is that we need eigenvectors as well as eigenvalues, which in general are no longer "nice" functions but can get rather complicated. Importing these from an external programme seemed not advisable at this point.

In the end we decided to use both methods. Importing the eigenvalues as functions from Maple seemed to be the appropriate choice for the stability analysis which is presented in Chapter A.2, while when needing information on eigenvalues and eigenvectors at specific points (see next section), **eigs** was applied.

4.2.3 Perturbation of the initial points along their eigenvectors

When provided with appropriate starting values, our algorithm should permute the given starting points "a little bit" along the desired eigenvector, such that the ODE-solver starts "near" an equilibrium point. As discussed above, we need access to the Jacobian $dF(y_0)$ evaluated at the given starting value y_0 for this, and then use **eigs** to calculate its eigenvalues and eigenvectors. Since we have already decided to allow only the first three families of steady states y_{1-3} as possible starting points, we know that **eigs** will always return 2 general¹ and 2 zero eigenvalues. Depending on the choice of y_0 we can thus exactly predict what sign the 2 general eigenvalues will have and decide accordingly along which eigenvector we want to perturb.

Consider for example the case of starting at $y_1 = (0, 1, p, q)$, for some fixed value of θ . As we can see in Figure A.1, the signs of the 2 eigenvalues (and thus the stability of y_1) critically depend on the choice of p_0 and q_0 . Say we would like this point to act as a saddle and perturb along the unstable eigenvector, then we may choose $p_0 > 0$ such that

¹A general eigenvalue denotes an eigenvalue that is given by some function, but $\neq 0$. This is not to be confused with a generalized eigenvalue!

 $p_0 + q_0 < 0$. It is now easy to find the positive eigenvalue λ and select the corresponding eigenvector v, which is provided in a normalized form. Multiplying v with a given $\varepsilon \leq 1$ of our choice and adding it to y_0 will provide us with the proper starting value for the ODE-routine.

To specify sign conventions consider the following example (case Ia from Table 4.1): Let $y_1 = (0, 1, 6, -7)$ and choose $\theta = 0.2$ and $\sigma = 8.08$. eigs in this case returns the eigenvalues $\{-1281.9, 1.9, 0, 0\}$ along with eigenvectors

$$\begin{pmatrix} -0.1222 & 0.0799 & 0 & 0 \\ 0.0120 & -0.0933 & 0 & 0 \\ 0.9877 & -0.6454 & 0 & 1 \\ -0.0972 & 0.7539 & 1 & 0 \end{pmatrix}$$

The case we are interested in is therefore $\lambda = 1.9$ with $v = (0.08, -0.09, -0.64, 0.75)^{+}$. Multiplying v with $0 < \varepsilon \ll 1$ thus provides the appropriate perturbation without resulting in the c or m component leaving the interval [0, 1].

4.2.4 Stable and unstable trajectories

The next step is to calculate the trajectories originating from the two modified starting values. Since we perturbed the modified starting points along their respective eigenvalues, in case of the unstable steady state the solution thus obtained coincides with the strongly unstable manifold W^{su} , a fact that holds true for any given ODE system. However perturbation along a stable eigendirection yields solutions tending back towards the original point, which is no surprise as we specifically chose a (partially) stable equilibrium as starting point.

A reasonable approach to this problem seems to be backwards integration, which is easily done for ODEs in Matlab by simply calling the solver with a negative time interval. Observe however that integrating backwards in time reverts stability and may cause problems by numerical error. This can be circumvented if we choose a grid of starting points close to the initial one, and calculate a trajectory from each grid point. By interpolation between these solutions we can thus find the desired stable trajectory, i.e. W^{ss} . It turns out however that this method is not necessary. The reason for this is linked to the applied variable transformation (2.27), where we multiplied with the determinant of the diffusion matrix:

$$z = \det A(c,m) \cdot \eta.$$

As we have seen in Chapter 3.1 this transformation has to be considered when comparing phase portraits of the original, untransformed ODE with the transformed one. In areas where det A(c, m) is negative, trajectories of the original version change direction which implies a change of stability properties as well. Hence it is feasible to select two unstable starting points and compute unstable trajectories - corresponding to their strongly unstable manifolds W^{su} - for both, as long as det A(c, m) will be negative along the one and positive along the other. Fortunately for us, y_1 and y_2 exhibit exactly such behaviour when parameters σ and θ as well as the initial p_0 's and q_0 's are chosen correctly, see Chapter A.2. We shall in the following refer to the computed W^{su} with negative determinant as W^{ss} , since it serves as the strongly stable manifold for all intents and purposes. Likewise, the associated starting point will be called the stable steady state.

4.2.5 Selecting a suitable L

In the examples presented in Chapters 2.1 - 2.2 it was comparatively easy to identify a convenient codimension one submanifold L of the phase space and then vary the wave speed σ such that the distance between the intersection points of the stable and unstable manifolds W^s and W^u with L tends to zero. However, there the ODE system was hyperbolic and only two-dimensional, and L thus one-dimensional. In our case the model (2.28) has four independent variables and the steady states are not hyperbolic either. The necessary dimension for L is calculated in the following way:

$$\dim(W^{cu}) + \dim(W^{cs}) - \text{dimension of the ODE} = \dim(L)$$

$$3 + 3 - 4 = 2$$
(4.7)

Somewhat unexpectedly the variable transformation (2.27) is supplying a convienient candidate for L. The choices of starting values and parameters leading to solutions with alternating sign of the determinant, which we exploited in the previous section 4.2.4, provide us with trajectories that eventually converge to the family y_6 of steady states where m = 1 - c, q = -p and det A(c, m) = 0, which is in fact a two-dimensional submanifold of the phase space. In theory variation of σ and θ will lead (very closely) to a concurrence of the intersections of W^{cu} and W^{cs} with L, i.e. a closure of the Lin gap. Note however that we previously elected to perturb only along W^{su} and W^{ss} , and might therefore not exactly achieve said concurrence. In practice we may fail also if solutions cease to exist for certain values of σ and/or θ , or if the minimal distance occurs e.g. for some $\theta < 0$.

4.2.6 The variation of θ and σ

As discussed, once suitable starting values have been selected and perturbed along their eigenvectors, and we have determined L, the variation of θ and σ will hopefully give us heteroclinic orbits or at least solutions that come close to this notion. Since θ is a parameter that occurs with several fixed values in [JS12] it seems feasible to fix a few values and vary σ for each one. We do this by letting the algorithm run several times, each with a slightly increased value of σ , and noting the solution where the Lin gap becomes smallest. Should this return either end of the predefined interval as an optimum, the interval has to be adjusted accordingly and the simulation restarted. In this manner, we can find a local minimum for the Lin gap.

4.3 Results

As we have already mentioned, the best results in terms of minimizing the Lin gap were obtained when choosing $y_1 = (0, 1, p, q)$ and $y_2 = (1, 0, p, q)$ as starting points. For $0 < p_0 < -q_0$, y_1 has an unstable eigendirection with positive sign of det A, while y_2 has an unstable eigendirection with negative det A for $0 < -q_0 < p_0$, making it a substitute for a starting point with stable eigendirection. Both y_1 and y_2 act as saddle points here, with trajectories from either starting point terminating in the submanifold L of the phase space defined by $y_6 = (c, 1 - c, p, -p)$, which can be realised in Matlab by terminating the ODE routine with an appropriate Events argument. Table 4.1 as well as Figures 4.1-4.2 show examples of solutions obtained with different choices of starting values for p_0 and q_0 as well as parameters σ and θ .

From Table 4.1 it seems that simulation IIa) at $\theta = 0.2$ is the best option in the sense that at L, the Lin gap is smallest. Hoewever from the associated plot (Figure 4.1) we can see that the trajectory leaving $y_1(1,0,6,-7)$ in the beginning overshoots, i.e. c > 1. Such 'solutions' are non-physical, and would not appear in the original PDE setting (1.1). Their occurence in the travelling wave setting is presumably an artifact resulting from the variable transformation (2.27). The overshoot can not be avoided, however it can be significantly reduced by choosing different p_0 and q_0 , e.g. as is done in simulation Ia). Unfortunately, that specific set of starting values results in a quite large gap in L in the *c*-component, see Figure 4.2. An optimization which minimizes Lin gap and overshoot simultaniously may probably be found if one perturbs along further directions in W^{cs} and W^{cu} , which we however omitted. During the numerical simulation runs it became apparent that the algorithm is not very stable regarding parameter and starting value variations, in the sense that solutions often yielded severe numerical errors, oscillating trajectories or no convergence of the ODE routines at all when even one value was adjusted a little bit too much. The best outcomes where attained with p_0 and $-q_0$ approximately within distance 2 or less, as well as low values of θ . Choosing σ too large or small also caused troubles, but here trial and error was the only way to determine 'good' ranges.

Since selecting an appropriate L is rather difficult, no heteroclinics or homoclinics were obtained with different sets of starting conditions.

Simul. no.	y_1	y_2	θ	optimal σ	$\begin{array}{c c} \text{Lin gap a} \\ c_1 - c_2 \end{array}$	t $L = (c, 1 + p_1 - p_2)$	-c, p, -p) sum
Ι	(0,1,6,-7)	(1,0,1.2, -1)	$ \begin{array}{c} 0.2 \\ 0.4 \\ 1.0 \end{array} $	$8.08 \\ 10.84 \\ 13.56$	$\begin{array}{c} 0.2577 \\ 0.3545 \\ 0.4421 \end{array}$	$0.0082 \\ 0.9930 \\ 1.5620$	$\begin{array}{c} 0.2659 \\ 1.3476 \\ 2.0041 \end{array}$
II	(0,1,6, -7)	(1,0,3,-0.5)	$ \begin{array}{c} 0.2 \\ 0.4 \\ 1.0 \\ 1.5 \end{array} $	6.40 6.72 7.48 7.96	0.0173 0.0309 0.1297 0.1827	$\begin{array}{c} 0.0128 \\ 0.0143 \\ 0.0105 \\ 0.0055 \end{array}$	0.0301 0.0451 0.1402 0.1882
III	(0,1,6.5, -7)	(1,0,0.65, -0.5)	$ \begin{array}{c c} 0.2 \\ 0.4 \\ 1.0 \\ 1.5 \end{array} $	$13.08 \\ 13.32 \\ 13.76 \\ 14$	$\begin{array}{c} 0.5030 \\ 0.5118 \\ 0.5280 \\ 0.5358 \end{array}$	0.0020 0.0035 0.0041 0.0002	$\begin{array}{c} 0.5050 \\ 0.5153 \\ 0.5321 \\ 0.5360 \end{array}$

TABLE 4.1: Results for various starting and parameter values. The optimal σ is decided by the algorithm in order to minimize distance between the respective trajectories in L (with an error margin of $\varepsilon = 10^{-4}$).



FIGURE 4.1: Trajectories starting from $y_1(0, 1, 6, -7)$ (solid line) and $y_2(1, 0, 3, -0.5)$ (dashed line) with $\theta = 0.2$ and $\sigma = 6.4$ (IIa). (a) shows components c and m, (b) p and q. A small jump (=Lin gap) is visible in L, i.e. where the dashed and solid lines meet, making this solution a heteroclinic only up to some error. Note the overshoot in c.



FIGURE 4.2: Trajectories starting from $y_1(0, 1, 6, -7)$ (solid line) and $y_2(1, 0, 1.2, -1)$ (dashed line) with $\theta = 0.2$ and $\sigma = 8.08$ (Ia). (a) shows components c and m, (b) p and q. Compared to Figure 4.1 the overshoot in c is drastically reduced, but the Lin gap (i.e. the distance at transition from solid to dashed lines) is considerably higher.

Chapter 5

Conclusion

In this thesis we took a look at a tumor growth model (1.1) in the form of a reactiondiffusion equation as presented in [JS12] and [Ste13]. They could prove the existence of global in time bounded weak solutions as long as a certain parameter, θ , did not exceed a specific value. We applied a travelling wave analysis and Lin's method, which were introduced in Chapters 2.1 and 2.2 respectively, and numerically searched for so called heteroclinic orbits (see Def. 1) in Chapter 4. This search was complicated by the fact that at all equilibrium points of (1.1), its diffusion matrix becomes singular. A variable transformation was thus necessary, however this had the effect that the transformed system (2.28) now possessed six whole families of steady states instead of a number of distinguished equilibrium points.

Nevertheless, we saw in Table 4.1 and Figures 4.2-4.1 that heteroclinic orbits exist in some sense between the families of steady states y_1 and y_2 . However these solutions were far from optimal in terms of either the jump in L between the trajectories being considerably large, or in there being a notable overshoot in the *c*-variable. Ideally, we do not want any overshoot at all, as such a solution has to be regarded as non-physical. With a different set of starting conditions, this might still hold.

A short excurse was made into singular perturbation theory and so called slow-fast systems in Chapter 3. We presented [WP10], who worked with a reaction-diffusion-equation that was structurally related to (1.1), and extended their theories to include our case, as well as [HVHM⁺14], who defined the notions of *wall of singularities* and *hole in the wall*. These concepts are closely related to our model as well, however their methods were not directly applicable due to structural discrepancies.

5.1 θ as a critical parameter

In Chapter 4.3 we saw that the optimal choice of σ and θ in order to minimize the Lin gap, i.e. the distances between both trajectories in L, strongly depends on the initial values p_0 and q_0 , as well as on each other. For fixed starting values, increasing θ means that most certainly the optimal value for σ will increase as well. From Table 4.1 we can see that in general, lower values of θ seem to be preferable. Still, contrary to [JS12] and [Ste13] we could not affirm greater significance to the case where θ reaches/crosses $\theta^* := 0.4$.

5.2 Outlook

Points that are yet left open for future analysis therefore first and foremost include the continued search for better starting conditions. Maybe there exist solutions for large values of θ (say around 1000), if p_0 and q_0 are chosen accordingly. We have restricted ourselves to perturbations along eigenvectors from W^{ss} and W^{su} , which is not necessary. Further variation here may provide better, physiological results.

What would also be of interest is to analyse what happens in the regions around the solutions we found. They all had in common that they would break down when tweaking any of p_0 , q_0 , θ or σ just a little bit too much. Is there an "area of stability" around the selected starting conditions? If so, how does this relate to stability of the (families of) steady states, if at all?

A different issue would be finding the optimal value of σ . The algorithm we utilized selects an optimal value of σ from a given, pre-defined range, which we altered should either of the extrema be the result. This method may have only provided us with localized minima, with little to no chance to determine whether there could be a different, maybe even global, minimum elsewhere.

Lastly, there may of course exist heteroclinics or even homoclinics between other sets of steady states. With a reasonable idea what to use as L, one could search for those solutions.

Appendix

In this chapter we present calculations that are necessary for this thesis but of no greater interest in themselves, and which were taken out of the main text due to being rather lengthy. Some general mathematical notions follow that are utilized in this work, but which may not be familiar to all readers.

A.1 Identifying the families of steady states

We wish to calculate the steady states of (2.28) which we recall was given by

$$\begin{cases} \begin{pmatrix} \dot{c} \\ \dot{m} \end{pmatrix} = \operatorname{cof}(A)^{\top} \cdot \begin{pmatrix} p \\ q \end{pmatrix} \\ \begin{pmatrix} \dot{p} \\ \dot{q} \end{pmatrix} = -\sigma \cdot \operatorname{cof}(A)^{\top} \cdot \begin{pmatrix} p \\ q \end{pmatrix} - \det A \cdot R,$$

or abstractly $\dot{y} = F(y)$, with wave speed σ ,

$$\operatorname{cof}(A)^{\top} \cdot \begin{pmatrix} p \\ q \end{pmatrix} = \begin{pmatrix} 2\beta m(1-m)(1+\theta c)p + 2\beta cm(1+\theta c)q \\ 2cmp - \beta\theta m^2(1-m)p + 2c(1-c)q - \beta\theta cm^2q \end{pmatrix},$$
(A.1)

and

$$\det A \cdot R = 4\beta cm(1+\theta c)(1-c-m) \cdot \begin{pmatrix} \gamma c(1-c-m) - \delta c \\ \alpha cm(1-c-m) \end{pmatrix}.$$
 (A.2)

Since det $A = \det \operatorname{cof}(A) = \det \operatorname{cof}(A)^{\top}$ (see Chapter A.4), it is feasible to first look for equilibria where det A = 0, i.e. either c, m or 1 - c - m = 0. The following cases arise:

- 1) c = 0: (A.1) requires m = 0, m = 1 or p = 0
- 2) c = 1: (A.2) requires m = 0
- 3) m = 0: (A.1) requires c = 0, c = 1 or q = 0

4) m = 1: (A.2) requires c = 0

From these considerations we can already see that $y_1 = (0, 1, p, q)^{\top}$, $y_2 = (1, 0, p, q)^{\top}$ and $y_3 = (0, 0, p, q)^{\top}$ are steady states, where p and q may be chosen arbitrarily in \mathbb{R} . In fact, as p and q are not fixed values, we have found whole families of steady states instead of single equilibrium points. Analogously we see that we can define $y_4 = (0, m, 0, q)^{\top}$ and $y_5 = (c, 0, p, 0)^{\top}$.

The case where 1 - c - m = 0 is a bit of a speciality. Obviously here (A.2) immidiately becomes zero, however (A.1) now reads

$$\begin{pmatrix} 2\beta(1-c)c(1+\theta c) & 2\beta c(1-c)(1+\theta c) \\ 2c(1-c) - \beta\theta(1-c)^2 c & 2c(1-c) - \beta\theta c(1-c)^2 \end{pmatrix} \cdot \begin{pmatrix} p \\ q \end{pmatrix},$$

where we have set m = 1 - c. This becomes zero when choosing q = -p. We can thus identify $y_6 = (c, 1 - c, p, -p)$. To summarize, we get

$$F(y) = 0 \Leftrightarrow$$

$$y \in \left\{ \begin{pmatrix} 0\\1\\p\\q \end{pmatrix}, \begin{pmatrix} 1\\0\\p\\q \end{pmatrix}, \begin{pmatrix} 0\\0\\p\\q \end{pmatrix}, \begin{pmatrix} 0\\0\\p\\q \end{pmatrix}, \begin{pmatrix} 0\\m\\0\\q \end{pmatrix}, \begin{pmatrix} c\\0\\p\\0 \end{pmatrix}, \begin{pmatrix} c\\1-c\\p\\-p \end{pmatrix} \right\}$$

A.2 A detailed study of the eigenvalues and eigenvectors

In order to better understand and maybe to some point predict the behaviour of system (2.28) in simulations, we want to analyse the eigenvalues generated by plugging the six families of equilibrium points y_{1-6} calculated in Chapter A.1 into the Jacobian dF of the rhs F = F(c, m, p, q) of (2.28). To avoid calculation errors, this was done using a symbolic math program. For this analysis as well as further numerical simulations, the parameter set listed in Table A.1, used also in [JS12, p.23] was applied.

Parameter	value
α	0.1
β	100
γ	1
δ	0.35

TABLE A.1: Parameter values used for numerical simulation as stated in [JS12]

The wave speed σ as well as θ , which appears to be a critical parameter in relation to β in [JS12] and [Ste13] were varied. Let further e_i denote the i^{th} euclidian vector that is equal to 1 in the i^{th} component and zero elsewhere, and v_i^j be a general non-zero eigenvector associated with the j^{th} eigenvector of y_i , λ_i^j . We first take a look at the Jacobians $dF(y_i)$.

$$dF(y_1) = \begin{pmatrix} 2\beta q & -2\beta p & 0 & 0\\ 2(p+q) - \beta\theta q & \beta\theta p & 0 & 0\\ -2\sigma\beta q & 2\sigma\beta p & 0 & 0\\ -\sigma(2p+2q-\beta\theta q & -\sigma\beta\theta p & 0 & 0) \end{pmatrix}$$
$$dF(y_2) = \begin{pmatrix} 0 & 2\beta(1+\theta)(p+q) & 0 & 0\\ -2q & 2p & 0 & 0\\ 0 & -2\sigma\beta(1+\theta)(p+q) & 0 & 0\\ 2\sigma q & -2\sigma p & 0 & 0 \end{pmatrix}$$
$$dF(y_3) = \begin{pmatrix} 0 & 2\beta p & 0 & 0\\ 2q & 0 & 0 & 0\\ 0 & -2\sigma\beta p & 0 & 0\\ -2\sigma q & 0 & 0 & 0 \end{pmatrix}$$
$$dF(y_4) = \begin{pmatrix} 2\beta mq & 0 & 2\beta m(1-m) & 0\\ 2q - \beta\theta m^2 q & 0 & -\beta\theta(1-m)m^2 & 0\\ -2\sigma\beta mq & 0 & -2\sigma\beta m(1-m) & 0\\ -\sigma(2q - \beta\theta m^2 q) & 0 & \sigma\beta\theta(1-m)m^2 & 0 \end{pmatrix}$$

 $dF(y_5) = \begin{pmatrix} 0 & 2\beta(1+\theta c)p & 0 & 0\\ 0 & 2cp & 0 & 2c(1-c)\\ 0 & -2\sigma\beta(1+\theta c)p - 4\beta c(1-c)(1+\theta c)(\gamma c(1-c) - \delta c) & 0 & 0\\ 0 & -2\sigma cp & 0 & -2\sigma c(1-c) \end{pmatrix}$

$$dF(y_{6}) = \begin{pmatrix} -2\beta(1-c)(1+\theta c)p & -''- & 2\beta c(1-c)(1+\theta c) & -''- \\ 2cp + \beta\theta(1-c)^{2}p & -''- & 2c(1-c) - \beta\theta c(1-c)^{2} & -''- \\ 2\sigma\beta(1-c)(1+\theta c)p - 4\beta c^{2}(1-c)(1+\theta c)\delta & -''- & -2\sigma\beta c(1-c)(1+\theta c) & -''- \\ -2\sigma cp - \sigma\beta\theta(1-c)^{2}p & -''- & -2\sigma c(1-c) + \sigma\beta\theta c(1-c)^{2} & -''- \end{pmatrix}$$

Note that the second and fourth columns of $dF(y_6)$ are exactly the same as the first and third ones, which for brevity's sake is indicated by ditto signs (-''-). As we can see, dF is singular in all six cases. $dF(y_5)$ and $dF(y_6)$ are however the only instances, where the third and fourth line are not simply obtained by multiplying the first and second line respectively by $-\sigma$. In the case of y_6 this slight structural difference occurs due to transformation of the travelling wave variable with det A which we know to become singular whenever c, m or 1 - c - m equal 0 or 1.

When looking at eigenvalues and eigenvectors of $dF(y_{1-6})$ as listed in Table A.2, we see that the families of steady states indeed structurally fall into three different groups:

- 1. $y_1 y_3$. These three represent the "most natural" families of steady states, as without reverting to (c, m, p, q) notation they would be actual points rather than families of points. This is reflected in them having 2 zero and 2 nonzero eigenvalues each, and their eigenvectors 3 and 4 being given by the standard euclidian unit vectors e_3 and e_4 .
- 2. $y_4 \& y_5$. These two are rather degenerate, as they both have 3 zero eigenvalues and even a zero eigenvector. The nonzero eigenvalues are dependent on σ .
- 3. y_6 . A special case resulting, as mentioned, from a variable transformation. y_6 is the only family that has 4 eigenvectors that are different from standard euclidian unit vectors. (Note hoewever that the eigenvectors corresponding to zero eigenvalues are given by $v_3^6 = (-1, 1, 0, 0)^{\top}$ and $v_4^6 = (0, 0, -1, 1)^{\top}$.) The nonzero eigenvalues are dependent on σ .

Since we are interested in the stability of the respective steady states, we have to examine where, if at all, the general non-zero eigenvalues change sign. The corresponding conditions are listed in Table A.3. Note hoewever that a change of sign may also occur adjacent to an area with complex values. For y_1 - y_3 , a change of sign is dependent only on p and q (assuming at this point that θ is a fixed parameter). For y_4 and y_5 zero-crossing is dependent on σ , but as we have seen these two families and their eigenvalues appear to be rather degenerate, see also Figures A.1-A.3.

Of further interest for us may be the various variable ranges such that the families of eigenvalues have complex parts. These areas are shaded light green in Figures A.1-A.3. Observe that the location of areas with complex parts depends on θ only for y_1 .

Dependencies	$p,q;eta, heta,\sigma$	$p,q;eta, heta,\sigma$	$p,q;eta, heta,\sigma$	$m,q;eta, heta,\sigma$	$c,p;eta,\gamma,\delta, heta,\sigma$	$c,p;eta, heta, \sigma$
Eigenvectors	(v_1^1,v_2^1,e_3,e_4)	(v_1^2,v_2^2,e_3,e_4)	(v_1^3,v_2^3,e_3,e_4)	$(v_1^4, e_2, e_4, \underline{0})$	$(v_1^5, e_1, e_3, \underline{0})$	$(v_1^6,v_2^6,v_3^6,v_4^6)$
Eigenvalues	$\lambda_{1/2}^{1} = \frac{1}{2}\beta\theta p + \beta q \pm \frac{1}{2}\sqrt{(\beta\theta p)^{2} + 4\beta^{2}\theta pq + 4\beta^{2}q^{2} - 16\beta p^{2} - 16\beta pq} \\ \lambda_{3/4}^{1} = 0$	$\lambda_{1/2}^2 = p \pm \sqrt{p^2 - 4\beta q (1+ heta)(p+q)} \ \lambda_{3/4}^2 = 0$	$\lambda_{1/2}^3=\pm 2\sqrt{\beta pq}\\\lambda_{3/4}^3=0$	$\lambda_1^4=2eta m(-\sigma+\sigma m+q) \ \lambda_{2/3/4}^4=0$	$\lambda_1^5=2c(-\sigma+\sigma c+p)\ \lambda_{2/3/4}^5=0$	$\lambda_{1/2}^6 = $ function of $(c, p; \beta, \delta, \sigma, \theta)$ $\lambda_{3/4}^6 = 0$
Eq. point	(0,1,p,q)	(1,0,p,q)	(0,0,p,q)	(0,m,0,q)	(c,0,p,0)	(c, 1-c, p, -p)
	y_1	y_2	y_3	y_4	y_5	y_6

TABLE A.2: Eigenvalues and eigenvectors of y_{1-6} of (2.28)



FIGURE A.1: Zero-crossings and complex areas of λ_1^1 (red) and λ_2^1 (blue) for different values of θ . Shaded areas represent the presence of complex parts, these vanish for $\theta > 2$. Observe that zero-crossing conditions also change for $\theta > 2$.



FIGURE A.2: Zero-crossings and complex areas of $\lambda_1^{2/3}$ (red) and $\lambda_2^{2/3}$ (blue). Shaded areas represent presence of complex parts. The +, - and 0 symbols indicate signs of $\operatorname{Re}(\lambda)$ in the given area.
Eigenvalue	zero-crossing conditions		
λ_1^1	$\{p=0,q\leq 0\}$	$\{p\leq 0,q=0\}$	$\{p = -q, q(1 - \theta/2) \le 0\}$
$\lambda_2^{\scriptscriptstyle 1}$	$\{p=0, q \ge 0\}$	$\{p \le 0, q = 0\}$	$\{p = -q, q(1 - \theta/2) \ge 0\}$
λ_1^2	$\{p\leq 0,q=0\}$	$\{p \le 0, q = -p\}$	$\{p=0,q\}$
λ_2^2	$\{p\geq 0,q=0\}$	$\{p \ge 0, q = -p\}$	$\{p=0,q\}$
$\lambda_{1,2}^3$	$\{p=0,q\}$	$\{p, q = 0\}$	-
λ_1^4	$\{m=0,q\}$	$\{m, q = \sigma(1-m)\}$	-
λ_1^5	$\{c=0,p\}$	$\{c, p = \sigma(1 - c)\}$	-
λ_1^6	$\{c=0,p\}$	$\{c=1,p\}$	-

TABLE A.3: Variable ranges such that the real part of an in general nonzero eigenvalue of the steady states y_{1-6} equals zero. Note that zero crossing may also occur adjacent to complex areas



FIGURE A.3: Zero-crossings of λ_1^4 occur at m = 0 or $q = \sigma(1 - m)$, those of λ_1^5 at c = 0 or $p = \sigma(1 - c)$ (note the axis label change). The eigenvalues have no complex parts, and take positive values above, and negative values below the respective lines as indicated by the + and - symbols.

A.3 Stability of eigenvalues - a classification

Sources: [Szm13, Ch. 5.2], [Kuz04, Ch. 2.2], [Tse08].

In general, a full classification of all cases of stability of eigenvalues is not possible, especially for nonlinear systems. We will take a look at the case of autonomous linear systems in 2 variables, which can be fully classified in the trace - determinant plane of the describing matrix. Let therefore A be a real 2×2 matrix, then the system

$$x' = Ax$$

has the trivial equilibrium point at x = 0. The eigenvalues $\lambda_{1,2}$ of A are given by

$$\lambda_{1,2} = \frac{t}{2} \pm \sqrt{\frac{t^2}{4} - d},$$

where t := trace A and $d := \det A$. We can distinguish between three cases depending on the sign of the discriminant:

1. $\lambda_{1,2} \in \mathbb{R}$, $\lambda_1 \neq \lambda_2$ where $\frac{t^2}{4} - d > 0$, wlog. $\lambda_1 < \lambda_2$, 2. $\lambda_{1,2} \in \mathbb{R}$, $\lambda_1 = \lambda_2$ where $\frac{t^2}{4} - d = 0$, 3. $\lambda_{1,2} \in \mathbb{C}$, $\lambda_1 = \overline{\lambda_2}$ where $\frac{t^2}{4} - d < 0$,

If two eigenvectors v_1, v_2 exist, the general solution will be given by

$$x(t) = c_1 \mathrm{e}^{\lambda_1 t} v_1 + c_2 \mathrm{e}^{\lambda_2 t} v_2, \quad c_1, c_2 \in \mathbb{R}$$

Contingent upon the sign of $\operatorname{Re}(\lambda_i)$, several subcases arise, which are listed in Table A.4. Schematics of the respective phase portraits can be seen in Figure A.4, cases where one or both eigenvalues equal zero are however omitted there. Note that there is a difference between *stable* and *assymptotically stable* points x. For the first case, all trajectories stay within finite distance of the critical point for all times (positive and negative). They never converge to the critical point. This is only the case for purely imaginary eigenvectors. In the assymptotically stable cases however, the trajectories converge to the critical point as $t \to \infty$.

For inhomogenious linear systems and nonlinear systems see e.g. [Tse08].

	(n_{+}, n_{-})	Eigenvalues	Phase portrait	Stability
	(0, 2)	•	node	stable
	(-) _)		G focus	
	(1, 1)	•	saddle	unstable
	(2, 0)		node	unstable
	(_, ;)		focus	

FIGURE A.4: Topological classification of hyperbolic equilibria on the plane. (n_+, n_-) indicate the number of eigenvalues with positive or negative real part respectively. The position of the eigenvalues in the plane is indicated schematically in the 2^{nd} column. Note that cases with one or two eigenvalues equalling zero are omitted. Source: [Kuz04, Fig. 2.5]

Eigenvalues	t	d	stability properties		
$\lambda_1 \neq \lambda_2, \ \lambda_{1,2} \in \mathbb{R}$:					
$\lambda_1 < \lambda_2 < 0$	t < 0	d > 0	stable node, $x = 0$ is asymptotically stable		
$\lambda_1 < \lambda_2 = 0$	t < 0	d = 0	$x = 0$ stable, attractant along v_1		
$\lambda_1 < 0 < \lambda_2$	-	d > 0	saddle node, $x = 0$ unstable		
$0 = \lambda_1 < \lambda_2$	t > 0	d = 0	$x = 0$ unstable, repellant along v_2		
$0 < \lambda_1 < \lambda_2$	t > 0	d > 0	unstable node, x = 0 unstable		
$\lambda_1 = \lambda_2 = \lambda \in \mathbb{R}$ - distinguish between A diagonizable (i)/not diag. (ii):					
$\lambda < 0$	t < 0	-	(i) stable star, (ii) stable improper node		
$\lambda = 0$	t = 0	d = 0	(i) stable, (ii) unstable, very degenerate		
$\lambda > 0$	t > 0	-	(i) unstable star, (ii) unstable improper node		
$\lambda_{1/2} = \alpha \pm i\beta \in \mathbb{C}, \alpha = t/2, \beta \neq 0:$					
$\alpha < 0$	t < 0	-	stable spiral, $x = 0$ asymptotically stable		
$\alpha = 0$	t = 0	-	center, $x = 0$ stable		
$\alpha > 0$	t > 0	-	unstable spiral, $x = 0$ unstable		

TABLE A.4: Full classification of stability for 2×2 -matrices (Source: [Szm13])

A.4 Concerning cofactor-matrices and matrix inversion

Sources: Any standard volume on linear algebra, e.g. [Hav08] or [Hog07].

Definition 4. Let $A = (a_{i,j})_{i,j=1}^n \in \mathbb{R}^{n \times n}$, $n \in \mathbb{N}$ be an $n \times n$ matrix. Define for $i, j \in \{1, ..., n\}$ the number $m_{i,j}$, called the (i, j)-minor, by $m_{i,j} := \det A(\{i\}, \{j\})$, where $A(\{i\}, \{j\})$ is the sub-matrix of A obtained by deleting the *i*th row and the *j*th column. Equivalently, $m_{i,j} = \det \tilde{A}$ where

$$\tilde{A}_{k,l} := \begin{cases} 1 & \text{ if } (k,l) = (i,j) \\ 0 & \text{ if } k = i \text{ or } l = j \\ a_{k,l} & \text{ else} \end{cases}$$

Define further the (i, j)-cofactor of A by $c_{i,j} := (-1)^{i+j} m_{i,j}$. Then the cofactor-matrix is given by $cof(A) := (c_{i,j})_{i,j=1}^n$.

For 2×2 matrices this means

$$A = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix} \Leftrightarrow \operatorname{cof}(A) = \begin{pmatrix} a_{22} & -a_{21} \\ -a_{12} & a_{11} \end{pmatrix},$$

and in particular, $\det A = \det(\operatorname{cof}(A))$.

Observe that the transpose of the cofactor-matrix is sometimes called the adjugate matrix, adj(A). Laplace's formula states that for any $i \in \{1, ..., n\}$,

$$\det A = \sum_{j=1}^{n} (-1)^{i+j} a_{i,j} m_{i,j} = \sum_{j=1}^{n} a_{i,j} c_{i,j}.$$

From this it also follows, that

$$A \cdot \operatorname{cof}(A)^{\top} = \operatorname{cof}(A)^{\top} \cdot A = \det A \cdot I_n,$$

with $(n \times n)$ -identity matrix I_n or equivalently, if A is a regular matrix i.e. invertible, that

$$\frac{1}{\det A} \cdot \operatorname{cof}(A)^{\top} = A^{-1}.$$

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