TRAVELING WAVE SOLUTIONS FOR A CANCER STEM CELL INVASION MODEL

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(Communicated by Christina Surulescu)

Abstract. In this paper we analyze the dynamics of a cancer invasion model that incorporates the cancer stem cell hypothesis. In particular, we develop a model that includes a cancer stem cell subpopulation of tumor cells. Traveling wave analysis and Geometric Singular Perturbation Theory are used in order to determine existence and persistence of solutions for the model.

1. Introduction. The study of the dynamics of cellular movement throughout the body has been an area at the forefront of mathematical and biological research in recent years: see [3, 16, 19], for example. Many of these papers specifically relate to cancer modeling as well, a topic that has special import due to cancer’s continued role as one of the leading causes of human death. Therefore, understanding the processes inherent to tumor cell movement and migration over time could prove key in better determining effective treatments for cancer.

Many mathematical models have been developed in order to investigate the initial tumor cell movements into the extracellular matrix; see [23, 27] and the references therein. The extracellular matrix, or ECM, is a connective structure and mesh of proteins and carbohydrates formed from materials released by cells into extracellular space. The ECM thus serves to connect the nearby cells and hold tissues together, providing key structural support and integrity for the cells and tissues. The presence of cancer cells, however, can clearly have very negative effects for the extracellular matrix. The invading cancer cells reshape and alter the ECM, thereby allowing themselves to move into the ECM and eventually undergo metastasis and spread to other regions of the body (see [17, 21, 26] for details).

Despite the importance of the movement of cancer cells into the extracellular matrix, few papers have focused on how specific populations of cancer cells (as opposed to simply general tumor cell populations) undertake this invasion. The

2020 Mathematics Subject Classification. Primary: 34C37, 34E17; Secondary: 35C07.

Key words and phrases. Traveling wave solutions, geometric singular perturbation theory, canards, cancer stem cells, extracellular matrix.

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cancer stem cell (CSC) hypothesis says that the majority of tumor growth is caused by a select sub-population of cancer cells, termed cancer stem cells, which are particularly resistant to the usual treatment strategies [10, 20]. This hypothesis implies that to effectively eliminate tumors and tumor cells, treatment needs to be specifically targeted at CSCs. Therefore, understanding how cancer stem cells migrate and invade the surrounding extracellular matrix has the potential to serve as a key area of research.

In this paper, we develop a new model that accounts for the motility of the concentrations of cancer stem cells, differentiated (or non-stem) cancer cells, and extracellular matrix within the body. This paper will extend the work done in [7, 22, 23] by incorporating the CSC hypothesis for a model related to cancer cell invasion (specifically, melanoma cell invasion).

We utilize techniques derived from geometric singular perturbation theory and traveling wave methods in order to analyze this model and understand the analytic behavior of solutions [5]. While traveling waves may be most utilized in mathematical physics, numerous biological phenomena demonstrate wavelike properties. For instance, Wang provides an overview of the different types of traveling waves that can result from chemotaxis, the specific differential movement or motion of cells up or down some chemical gradient (closely related to the concept of haptotaxis that is considered in our model) [35]. Specifically, the traveling wave methods that have been utilized in dealing with the chemotaxis as explored in the Keller-Segel model and other closely related papers provide a nice foundation of related material for our model (see [13] for details). If diffusive terms are dominated by advective terms in the model, though, traveling wave solutions can develop shocks [7]. For instance, this could happen if cells migrate in response to a chemical gradient bound to a surface.

An illustration of the type of non-smooth solution obtained here is given in Figure 1 below. Such solution (called a Type II wave) exhibits shock-like behavior. The graphs in Figure 1 are generated from the numerical solution of (1)-(3) with \( \epsilon_1 = \epsilon_2 = 4 \times 10^{-3} \). A Runge-Kutta solver is used, and the waves evolve from initial conditions such that \( s, w = 0 \) for \( x > x_0 \) and \( u = 1 \) for some \( x_0 \). That is, the initial conditions decayed to the healthy steady state.

\[ \text{Figure 1. Profile of traveling wave solution at } t = 50. \text{ The qualitative behavior is similar to the results presented in [7] and [22] for only one invasive cell population, the latter reference taking } \epsilon = 0 \text{ in their analysis.} \]
Building off of these prior experimental and mathematical papers, we use traveling wave analysis to put our system into a form that allows for the application of geometric singular perturbation theory. We present an existence proof for Type II traveling wave solutions; see Theorem 7.4 for the main result. Uniqueness in this context is a delicate matter, and is related to a transversality condition; this is addressed in Section 8.

2. The model. We develop a coupled system of partial differential equations which models concentrations of cancer stem cells and regular, non-stem cancer cells (termed differentiated cancer cells, or DCCs) and how they invade the extracellular matrix. This model in particular takes into account haptotactic cell movement, and describes the averaged behavior of cells in the direction of invasion.

In [23], the authors developed and discussed a similar model, and worked through the analytic method of traveling waves. Building off of this work, the papers [22] and (in more recent years) [7] expanded upon the results by extending the traveling wave analysis and considering the presence of diffusion. These papers considered a general tumor cell population. On the other hand, the sources [4, 26] both deal directly with CSC populations, albeit in ways that do not lend themselves well to traveling waves and instead primarily rely on numerical methods. In order to reconcile these results, we kept the tumor cell population \( k(x, t) \) in much the same form as in [7, 22, 23], but we split it into two different populations of CSCs \( s(x, t) \) and DCCs \( w(x, t) \). In other words, the relationship
\[
k(x, t) = s(x, t) + w(x, t)
\]
holds. All in all, based off of the models presented in [4, 7, 22, 23, 26], we investigate the following system:

\[
\begin{align*}
\frac{\partial s}{\partial t} &= s(1 - s - w) - \frac{\partial}{\partial x} \left( \frac{\partial u}{\partial x} s \right) + \epsilon_1 \frac{\partial^2 s}{\partial x^2} 
\frac{\partial w}{\partial t} &= w(1 - s - w) - \frac{\partial}{\partial x} \left( \frac{\partial u}{\partial x} w \right) + \epsilon_2 \frac{\partial^2 w}{\partial x^2} 
\frac{\partial u}{\partial t} &= -u^2(s + w) + \epsilon_2 \frac{\partial^2 u}{\partial x^2}.
\end{align*}
\]

In this model, \( s(x, t) \), \( w(x, t) \), and \( u(x, t) \) represent the concentrations of cancer stem cells, regular tumor cells (differentiated cancer cells), and extracellular matrix (ECM), respectively. Also, the \( \epsilon_j \) terms are small diffusion coefficients. These concentrations have all been nondimensionalized and rescaled so that the carrying capacity for the total cell concentration is 1.

2.1. Term-by-term interpretation. For clarity and organizational purposes, the terms appearing in our model are listed and examined below.

First of all, the \( s(1 - s - w) \) and \( w(1 - s - w) \) terms represent logistic growth in the cell populations over time, with the carrying capacity being rescaled to 1. These terms account for the idea that the cancer stem cells (CSCs) and differentiated cancer cells (DCCs) both proliferate at a greater rate than the other normal surrounding cells [23, 33]. These expressions have been adjusted from the typical logistic growth equations in order to account for the total malignant cell population \( k(x, t) = s(x, t) + w(x, t) \), in a similar manner to the equivalent terms presented in [26]. Such logistic type growth has been shown in [33] to be a reasonable model for these cell populations.
Next, the terms \(-\frac{\partial}{\partial x} \left( \frac{\partial u}{\partial x} s \right)\) and \(-\frac{\partial}{\partial x} \left( \frac{\partial u}{\partial x} w \right)\) correspond to haptotactic cell movement for their respective cell populations. Haptotaxis is the movement of given cells up or down the gradient of a certain chemical substance (see [24] for biological details, and [34, 39] for more mathematical aspects of this phenomenon). Here, the cancer cells are moving up an ECM gradient \(\frac{\partial u}{\partial x}\), and the flux for the CSCs and DCCs is proportional to \(\frac{\partial u}{\partial x} s\) and \(\frac{\partial u}{\partial x} w\), respectively. One can think of this haptotaxis as movement of the relevant cells due to chemical properties inherent to the extracellular matrix.

The term \(-u^2(s + w)\) relates to the degradation of the extracellular matrix over time, a development that occurs proportionally to the cell populations that are considered here and the concentration of the ECM itself. Note that the ECM spread is governed by a diffusion process; in [23] diffusion is actually ignored since the ECM is a substrate to which cells bind themselves. Thus we note that previous work such as [23] has focused solely on the role of proteolysis in modeling the dynamics of the ECM.

From a biological perspective, the term \(-u^2(s + w)\) accounts for the effects of proteolysis in this model. Proteolysis is a process by which proteins are broken down further into amino acids and polypeptides, and is catalyzed by the enzyme protease. In [23], the protease concentration was initially included as another differential equation, but was then eliminated due to the assumption that this catalysis process occurs on a much shorter timescale then the general ECM invasion with which the model is primarily concerned. Therefore we make this assumption here as well. Overall, however, this term corresponds to the deterioration of the extracellular matrix (which occurs more quickly when more cancer cells and ECM are both present). In particular, the \(u^2\) term comes from the assumption that upon contact with connective tissue, invasive cells produce a density of protease \(p\) proportional to the product of the ECM population and the invasive cell population \(s + w\), see [22]. However, this is not a crucial assumption, and more general nonlinearities of the form \(ug(u, s + w)\) could also be considered without dramatic change to the qualitative behavior of solutions to the model, see [23] where a few other nonlinearities were considered.

Finally, the terms \(\epsilon_1 \frac{\partial^2 u}{\partial x^2}\), \(\epsilon_2 \frac{\partial^2 w}{\partial x^2}\), and \(\epsilon_2 \frac{\partial^2 u}{\partial x^2}\) are small diffusive perturbations, with diffusion coefficient \(\epsilon_i \ll 1, \ i = 1, 2\). It should be noted that we carry over the assumption from [7] that the diffusion coefficients for the DCCs and the ECM are identical, since even if their ratio is \(O(1)\) the analysis will still remain virtually identical. We also assume that \(\epsilon_1 \leq \epsilon_2\). Since the presence of diffusion does not occur in all the mathematical representations of these biological phenomena, this approach also allows us to take \(\epsilon_i \to 0\) and hence investigate the model without diffusion terms.

Overall, we present a self-contained investigation of this novel model by seeking type II traveling wave solutions (see [7] and Definition 7.1). We begin by looking into the boundary conditions.

2.2. Boundary conditions. In order to determine the boundary conditions, the steady state solutions of the spatially homogeneous system must first be analyzed. This is done by assuming that all of the concentrations do not change as a function of time or position, and hence this section proceeds by setting \(\frac{\partial}{\partial t} = 0\) and \(\frac{\partial}{\partial x} = 0\).
We are left with the following system:

\[
\begin{align*}
0 &= s(1 - s - w) \\
0 &= w(1 - s - w) \\
0 &= -u^2(s + w).
\end{align*}
\]

We solve this to arrive at the two solutions \((s, w, u) = (0, 0, u_0)\) and \((s, w, u) = (1 - w_0, w_0, 0)\), for any fixed constants \(u_0, w_0 \in [0, 1]\). From a biological perspective, the first of these solutions, \((0, 0, u_0)\), corresponds to a sort of healthy state (since both populations of the tumor cells are zero). On the other hand, the second of these solutions, \((1 - w_0, w_0, 0)\), relates to a cancer persistence state (since the cancer has completely degraded the ECM). And from a more mathematical perspective, these correspond to two non-intersecting line segments of steady states in \(s - w - u\) space.

Before determining the explicit boundary conditions for our system, we can get a sense for analytic solutions by neglecting the effects of cellular movement (i.e. assuming no haptotaxis and diffusion occur, so taking \(\frac{\partial}{\partial x} = 0\)) in order to consider the system

\[
\begin{align*}
\frac{\partial s}{\partial t} &= s(1 - s - w) \\
\frac{\partial w}{\partial t} &= w(1 - s - w) \\
\frac{\partial u}{\partial t} &= -u^2(s + w).
\end{align*}
\]

Solving this, we find the explicit solutions

\[
\begin{align*}
s(t) &= \frac{e^t}{e^t + e^{c_2} + c_1 e^t} \\
w(t) &= \frac{c_1 e^t}{e^t + e^{c_2} + c_1 e^t} \\
u(t) &= \frac{1}{-c_3 + \ln(e^{c_2} + e^t(1 + c_1))}.
\end{align*}
\]

where \(c_1, c_2,\) and \(c_3\) are arbitrary constants in \(\mathbb{R}\). We can then examine the behavior of these solutions to our simplified system as \(t \to \infty\). As we take this limit, we see that \(s(t) \to \frac{1}{1+c_1}\), \(w(t) \to \frac{c_1}{1+c_1}\), and \(u(t) \to 0\). Since \(c_1\) is simply an arbitrary constant, this behavior implies that as \(t \to \infty\), the cell populations approach the cancer persistence state \((1 - w_0, w_0, 0)\).

Moving back to boundary conditions, we want to look at solutions that lie between our steady states. To do this, we can consider solutions between the healthy state \((0, 0, u_0)\) and the cancer persistence state \((1 - w_0, w_0, 0)\). Therefore we take
the boundary conditions:
\[
\lim_{x \to -\infty} u(x, t) = 0 \\
\lim_{x \to \infty} u(x, t) = u_0 \\
\lim_{x \to -\infty} w(x, t) = w_0 \\
\lim_{x \to \infty} w(x, t) = 0 \\
\lim_{x \to -\infty} s(x, t) = 1 - w_0 \\
\lim_{x \to \infty} s(x, t) = 0.
\]

3. Preliminary traveling wave analysis. Through traveling wave methods, namely the substitution \( z = x - ct \), we transform the system of partial differential equations into a system of ordinary differential equations. The constant \( c \in \mathbb{R} \setminus \{0\} \) corresponds to the speed of the traveling wave.

We see that the system (1)-(3) is transformed into the new ODE system below:

\[
\begin{align*}
\frac{ds}{dz} & = \frac{-s}{c}(1 - s - w) + \frac{1}{c} \frac{d}{dz} \left( \frac{du}{dz}s \right) - \epsilon_1 \frac{d^2 s}{dz^2} \\
\frac{dw}{dz} & = \frac{-w}{c}(1 - s - w) + \frac{1}{c} \frac{d}{dz} \left( \frac{du}{dz}w \right) - \epsilon_2 \frac{d^2 w}{dz^2} \\
\frac{du}{dz} & = \frac{u^2}{c}(s + w) - \epsilon_2 \frac{d^2 u}{dz^2}.
\end{align*}
\]

This system will be analyzed using geometric singular perturbation theory methods. To accomplish this, we start by looking at the hole in the wall of singularities.

3.1. Constructing a hole in the wall of singularities. Clearly, a system of ordinary differential equations of the form
\[
\frac{dy}{dz} = \hat{a}(x, y) \\
d(x, y) \frac{dx}{dz} = \rho(x, y)
\]
cannot have a valid and well-defined solution at points \((x_0, y_0)\) where \(d(x_0, y_0) = 0\) and \(\rho(x_0, y_0) \neq 0\). Therefore, a system of ODEs of this form has singularities at these points in the \(xy\) phase plane. We will use this idea to define the following:

**Definition 3.1.** For a system of the form of (7)-(8), the set of points in the positive quadrant of the \(xy\) phase plane for which \(d(x, y) = 0\) is called the **wall of singularities**, \(W\). In other words,
\[
W = \{(x, y) \in (\mathbb{R}_{\geq 0})^2 : d(x, y) = 0\}.
\]

A point \((x, y) \in W\) where \(d(x, y) = \rho(x, y) = 0\) is called a **hole in the wall**, \(H\).

We note that such a point need not exist in general. However, we can still attempt to find such a point for our system. If we look specifically at the form of the model generated from traveling wave solutions, we first neglect the diffusion terms by taking \(\epsilon_1 \to 0\) and \(\epsilon_2 \to 0\) at the same rate in order to consider a system based solely on haptotaxis. Namely, we expand the expressions \(\frac{1}{c} \frac{d}{dz} (\frac{du}{dz}s)\) and \(\frac{1}{c} \frac{d}{dz} (\frac{du}{dz}w)\) with (6) after taking the \(\epsilon_i\)'s to zero in order to change (4) and (5) into
\[
\begin{align*}
\left(\frac{2u^2s}{c} + \frac{2u^2w}{c} - c\right) \frac{ds}{dz} &= s(1 - s - w) - \frac{2u^3s^2(s + w)}{c^2} - \frac{2u^3sw(s + w)}{c^2} \quad (9) \\
\left(\frac{2u^2w}{c} + \frac{2u^2s}{c} - c\right) \frac{dw}{dz} &= w(1 - s - w) - \frac{2u^3w^2(s + w)}{c^2} - \frac{2u^3sw(s + w)}{c^2}. \quad (10)
\end{align*}
\]

We still have the third equation \( \frac{du}{dz} = \frac{u^2}{c}(s + w) \), so this can be viewed as an extension of the wall of singularities and the hole in the wall method to three dimensions. Again, the solution to the ODE system will clearly not be well-defined when the term premultiplying \( s' \) and \( w' \) (where \( ' = \frac{d}{dz} \)) is zero but the right hand side of the respective differential equations are nonzero. That is to say, the system will exhibit singularities when \( d(s, w, u) := \left( \frac{2u^2s}{c} + \frac{2u^2w}{c} - c \right) = 0 \) but

\[
\rho(s, w, u) := \begin{bmatrix} \rho_1(s, w, u) \\ \rho_2(s, w, u) \end{bmatrix} = \begin{bmatrix} s(1 - s - w) - \frac{2u^3s^2(s + w)}{c^2} - \frac{2u^3sw(s + w)}{c^2} \\ w(1 - s - w) - \frac{2u^3w^2(s + w)}{c^2} - \frac{2u^3sw(s + w)}{c^2} \end{bmatrix} \neq \begin{bmatrix} 0 \\ 0 \end{bmatrix}.
\]

To determine the defining features of the wall of singularities \( W \), we consider the equation

\[
d(s, w, u) = \left( \frac{2u^2s}{c} + \frac{2u^2w}{c} - c \right) = 0.
\]

Hence we have \( W = \{(s, w, u) \in (\mathbb{R}^+)^3 : 2u^2(s + w) = c^2\} \). Next, we find the point in \( W \) at which the hole in the wall \( H \) occurs. We do this by solving the system

\[
\begin{align*}
2u^2(s + w) &= c^2 \\
s(1 - s - w) &= \frac{2u^3s^2(s + w)}{c^2} + \frac{2u^3sw(s + w)}{c^2} \\
w(1 - s - w) &= \frac{2u^3w^2(s + w)}{c^2} + \frac{2u^3sw(s + w)}{c^2}.
\end{align*}
\]

The last two of these equations are identical, so we reduce our system. After simple algebraic manipulations, we arrive at the hole in the wall

\[
H = (s_H, w_H, u_H) = \left( \frac{1}{1 + u_H} - w_H, w_H, \frac{c}{4}(c + \sqrt{c^2 + 8}) \right) \quad (11)
\]

Next, we explain the basic ideas of geometric singular perturbation theory for a general system and work towards adjusting our model to represent it in a form that allows for the application of this theory.

4. Geometric singular perturbation theory.

4.1. Basic ideas. Now we provide some background material on the basics of geometric singular perturbation theory. The material in this section is largely based off of [5, 9, 12]. For ease of analysis and representation, we will introduce the two new variables \( b \) and \( a \). Specifically we take \( b \in \mathbb{R}^k \) and \( a \in \mathbb{R}^m \) for \( k, m \in \mathbb{N} \). We will also consider \( \epsilon \in \mathbb{R} \). We can think of the vector \( b \) as corresponding to a vector \( (s, w, u) \) in \( \mathbb{R}^3 \), for \( s, w, u \) to be defined later; similarly, \( a \) relates to a vector \( (s, w, u, v) \) in \( \mathbb{R}^4 \), for \( v \) to be defined in the next section. We will also consider
functions \( g : \mathbb{R}^k \times \mathbb{R}^m \times \mathbb{R} \to \mathbb{R}^k \) and \( f : \mathbb{R}^k \times \mathbb{R}^m \times \mathbb{R} \to \mathbb{R}^m \) both \( C^\infty \) on an open subset of their domains. Again, we recall that \( \epsilon' = \frac{d}{d\tau} \).

We define the slow system as a system of ordinary differential equations of the form

\[
\begin{align*}
  b' &= g(b, a, \epsilon) \\
  \epsilon a' &= f(b, a, \epsilon).
\end{align*}
\]

By rescaling, specifically taking \( z = \epsilon \tau \) and \( \dot{} = \frac{d}{d\tau} \), we also define the fast system as the related system of ordinary differential equations

\[
\begin{align*}
  \dot{b} &= \epsilon g(b, a, \epsilon) \quad (12) \\
  \dot{a} &= f(b, a, \epsilon). \quad (13)
\end{align*}
\]

Again, a substitution allows us to move back and forth between these systems of ODEs. Thus they will lead to the same general solution behavior for \( \epsilon \neq 0 \). These systems can be reduced by taking the limit \( \epsilon \to 0 \). This, fittingly, leads to the reduced problem

\[
\begin{align*}
  b' &= g(b, a, 0) \quad (14) \\
  0 &= f(b, a, 0) \quad (15)
\end{align*}
\]

and the layer problem

\[
\begin{align*}
  \dot{b} &= 0 \quad (16) \\
  \dot{a} &= f(b, a, 0). \quad (17)
\end{align*}
\]

**Definition 4.1.** Given the systems (14)-(15) and (16)-(17) above, the critical manifold of these systems is the set \( S_c \) defined by

\[
S_c = \{(b, a) \in \mathbb{R}^k \times \mathbb{R}^m : f(b, a, 0) = 0 \}.
\]

We can see that the critical manifold \( S_c \) is simply the set of equilibrium points of the layer problem (16)-(17). Equivalently, since the function \( g(b, a, 0) \) is given, \( S_c \) can also be realized as the phase space of the reduced problem (14)-(15).

**Definition 4.2.** A subset of the critical manifold \( S_h \subseteq S_c \) is normally hyperbolic if for all \( (b, a) \in S_h \), the Jacobian of \( f \) evaluated at that \((b, a)\) has no eigenvalues \( \lambda \) with \( \text{Re}(\lambda) = 0 \).

**Definition 4.3.** A subset of the critical manifold \( S_- \subseteq S_c \) is attracting if for all \((b, a) \in S_-\), all of the eigenvalues \( \lambda \) of the Jacobian of \( f \) evaluated at that \((b, a)\) satisfy \( \text{Re}(\lambda) < 0 \). A subset of the critical manifold \( S_+ \) is repelling if for all \((b, a) \in S_+\), at least one of the eigenvalues \( \lambda \) of the Jacobian evaluated at that \((b, a)\) satisfy \( \text{Re}(\lambda) > 0 \).
4.2. Introducing new variables. To start, we define a new variable \( v \) by
\[
v = \frac{\partial u}{\partial x}.
\]
Then we have the system of equations:
\[
\begin{align*}
\frac{\partial s}{\partial t} &= s(1 - s - w) - \frac{\partial}{\partial x} (vs) + \epsilon_1 \frac{\partial^2 s}{\partial x^2} \\
\frac{\partial w}{\partial t} &= w(1 - s - w) - \frac{\partial}{\partial x} (vw) + \epsilon_2 \frac{\partial^2 w}{\partial x^2} \\
\frac{\partial u}{\partial t} &= -u^2 (s + w) + \epsilon_2 \frac{\partial^2 u}{\partial x^2} \\
\frac{\partial v}{\partial t} &= -\frac{\partial}{\partial x} (u^2 (s + w)) + \epsilon_2 \frac{\partial^2 v}{\partial x^2}.
\end{align*}
\]
Letting \( \epsilon_1 = \epsilon_2 = \epsilon \), we can write the previous system as
\[
\begin{bmatrix} s \\ w \\ u \\ v \end{bmatrix}_t + \begin{bmatrix} g_1(s, w, u)v \\ g_2(s, w, u)v \\ 0 \\ -h(s, w, u) \end{bmatrix}_x = \begin{bmatrix} f_1(s, w, u) \\ f_2(s, w, u) \\ h(s, w, u) \\ 0 \end{bmatrix} + \epsilon \begin{bmatrix} s \\ w \\ u \\ v \end{bmatrix}_{xx},
\]
for \( g_1(s, w, u) = s, \ g_2(s, w, u) = w, \ h(s, w, u) = -u^2(s + w), \ f_1(s, w, u) = s(1 - s - w), \) and \( f_2(s, w, u) = w(1 - s - w) \). As mentioned previously, we could perform a similar analysis if \( \epsilon_1/\epsilon_2 \) was \( O(1) \) and not equal to 1 (see e.g. [37]), so we do not strictly require that both CSCs and DCCs diffuse at the same rate. In fact, this was shown explicitly in [8] for the Keller-Segel model, and that argument can easily be extended to this case.

4.3. Altering the form of the system. Given the system in the previous section
\((18)-(21)\), we seek traveling waves once again (substituting \( z = x - ct, \) \( ' = \frac{\partial}{\partial z} \)). By performing this change of variables and collecting terms, we obtain the system
\[
\begin{align*}
(\epsilon s' - vs + cs)' &= -s(1 - s - w) \\
(\epsilon w' - vw + cw)' &= -w(1 - s - w) \\
(\epsilon u' + cu)' &= u^2(s + w) \\
(\epsilon v' - u^2(s + w) + cv)' &= 0.
\end{align*}
\]
In order to simplify this, we expand our system by introducing the new variables
\[
\begin{align*}
s' &= \epsilon s' - vs + cs \\
w' &= \epsilon w' - vw + cw \\
u' &= \epsilon u' + cu \\
v' &= \epsilon v' - u^2(s + w) + cv.
\end{align*}
\]
First of all, we note that these new variables change and evolve on a slower scale than the original variables (\( z \) is called the slow traveling wave coordinate)\(^1\). Once

\(^1\)The slow-fast terminology is standard in GSPT, and we have adopted it here as well.
these new variables are thus defined, we rewrite the system (23)-(26) as
\[
\begin{align*}
\dot{s}' &= -s(1 - s - w) \\
\dot{w}' &= -w(1 - s - w) \\
\dot{u}' &= u^2(s + w) \\
\dot{v}' &= 0 \\
\epsilon s' &= \dot{s} + vs - cs \\
\epsilon w' &= \dot{w} + vw - cw \\
\epsilon u' &= \dot{u} - cu \\
\epsilon v' &= \dot{v} + u^2(s + w) - cv.
\end{align*}
\]
From the fourth equation above, we know that \(\dot{v} = d\) for some constant \(d \in \mathbb{R}\). We can further see that, from (25) and the fact that \(v = u'\),
\[
\epsilon v' + cv - u^2(s + w) = 0,
\]
and hence by definition \(\dot{v} = 0\). We simplify the above system to a seven-dimensional slow system given by
\[
\begin{align*}
\dot{s}' &= -s(1 - s - w) \\
\dot{w}' &= -w(1 - s - w) \\
\dot{u}' &= u^2(s + w) \\
\epsilon s' &= \dot{s} + vs - cs \\
\epsilon w' &= \dot{w} + vw - cw \\
\epsilon u' &= \dot{u} - cu \\
\epsilon v' &= u^2(s + w) - cv.
\end{align*}
\]
We can also make the alternate traveling wave substitution to the fast traveling wave coordinate \(y = \frac{1}{c}(x - ct)\) so that we can examine the fast system in seven-dimensions given by (with \(\dot{\cdot} = \frac{d}{dy}\))
\[
\begin{align*}
\dot{\hat{s}} &= -\epsilon s(1 - s - w) \\
\dot{\hat{w}} &= -\epsilon w(1 - s - w) \\
\dot{\hat{u}} &= \epsilon u^2(s + w) \\
\dot{\hat{s}} &= \dot{\hat{s}} + vs - cs \\
\dot{\hat{w}} &= \dot{\hat{w}} + vw - cw \\
\dot{\hat{u}} &= \dot{\hat{u}} - cu \\
\dot{\hat{v}} &= \dot{\hat{v}} + u^2(s + w) - cv.
\end{align*}
\]
Through simple algebra, we determine the steady states of these systems (the steady states are clearly identical for the fast and slow systems, since they are identical up to multiplication by a constant). Therefore, we have the fixed points
\[
(s, \hat{w}, \hat{u}, s, w, u, v) = (cs_0, c(1 - s_0), 0, s_0, 1 - s_0, 0, 0),
\]
\[
(0, 0, c u_0, 0, 0, u_0, 0), \quad \text{and}
\]
\[
(0, 0, 0, 1, 0, 0).
\]
Naturally, we continue our adoption of geometric singular perturbation theory by taking $\epsilon \to 0$ in order to simplify our problem to a reduced problem and a layer problem with constraints. Taking this limit leaves us with the simplified slow system

\begin{align*}
\hat{s}' &= -s(1 - s - w) \quad (27) \\
\hat{w}' &= -w(1 - s - w) \quad (28) \\
\hat{u}' &= u^2(s + w) \quad (29) \\
0 &= \hat{s} + vs - cs \quad (30) \\
0 &= \hat{w} + vw - cw \quad (31) \\
0 &= \hat{u} - cu \quad (32) \\
0 &= u^2(s + w) - cv, \quad (33)
\end{align*}

which can be conceptualized as a system in three dimensions corresponding to the variables $\hat{s}, \hat{w}, \hat{u}$ with four constraints. This is called the reduced problem. In a similar fashion, the fast system is reduced to

\begin{align*}
\dot{s} &= 0 \quad (34) \\
\dot{w} &= 0 \quad (35) \\
\dot{u} &= 0 \quad (36) \\
\dot{s} &= \hat{s} + vs - cs \quad (37) \\
\dot{w} &= \hat{w} + vw - cw \quad (38) \\
\dot{u} &= \hat{u} - cu \quad (39) \\
\dot{v} &= u^2(s + w) - cv. \quad (40)
\end{align*}

which can be thought of as a four-dimensional system with three parameters. This is called the layer problem. Hence we use the theoretical approach of GSPT in order to analyze each of these systems individually and then reconcile the behavior into an overall coherent picture of the system dynamics.

5. The layer problem. We first analyze the layer problem, before looking at the reduced problem and then the overall traveling wave solution behavior. Again setting $b = (\hat{s}, \hat{w}, \hat{u}) \in \mathbb{R}^3$ and $a = (s, w, u, v) \in \mathbb{R}^4$, we can represent the equilibria of the layer problem as defining the critical manifold

\[ S_c = \{ (\hat{s}, \hat{w}, \hat{u}, s, w, u, v) \in \mathbb{R}^7 : \hat{s} = cs - vs, \hat{w} = cw - vw, \hat{u} = cu, v = \frac{u^2(s + w)}{c} \}. \]

We view the critical manifold as three dimensional, being a graph over the variables $(s, w, u)$. The Jacobian $J$ of the layer problem is similarly easy to compute:

\[ J = \begin{bmatrix}
v - c & 0 & 0 & s \\
0 & v - c & 0 & w \\
0 & 0 & -c & 0 \\
u^2 & u^2 & 2u(s + w) & -c
\end{bmatrix}.\]
We find that the eigenvalues are given by
\[ \lambda_1 = -c \]
\[ \lambda_2 = -c + v \]
\[ \lambda_{3,4} = -c + \frac{v}{2} \pm \sqrt{u^2(s + w) + \frac{v^2}{4}} \]
(for \( \lambda_3 \) corresponding to the positive square root and \( \lambda_4 \) the negative). Since we see that
\[ \sqrt{u^2(s + w) + \frac{v^2}{4}} \geq \frac{v}{2} \]
and all our variables and parameters are positive, we know that \( \lambda_1 < 0 \) and \( \lambda_4 < 0 \). The other two have the ability to change signs as the wave-speed value \( c \) and the variables alter in value, however. We must therefore perform a bifurcation analysis in order to understand the stability of our critical manifold for the layer problem.

First of all, we notice that \( v \leq \frac{v}{2} + \sqrt{u^2(s + w) + \frac{v^2}{4}} \). Using this, it is trivial to note that \( \lambda_3 < 0 \) implies that \( \lambda_2 < 0 \) and that \( \lambda_2 > 0 \) implies that \( \lambda_3 > 0 \). Further, \( \lambda_3 < 0 \) when
\[ c > \frac{v}{2} + \sqrt{u^2(s + w) + \frac{v^2}{4}}, \] (41)
so this is a sufficient condition to establish the existence of an attracting manifold. Observe that
\[ v > c \] (42)
is sufficient to imply that \( \lambda_2 > 0 \), and hence means that our critical manifold is repelling. We also note that, since we are operating on the critical manifold \( S_c \), we also have the equation
\[ v = \frac{u^2(s + w)}{c}. \]
This allows us to eliminate \( v \) from the expressions given for the eigenvalues if we wish. We will not complete this procedure here for ease of representation, but when investigating the assumptions for a folded critical manifold later in the paper this fact will be important.

Next, we consider the points at which \( S_c \) loses normal hyperbolicity, by having one or more eigenvalue with a zero real part. First of all, this clearly occurs when \( c = v \), since \( \lambda_2 = 0 \). This same phenomenon occurs when \( c = \frac{v}{2} + \sqrt{u^2(s + w) + \frac{v^2}{4}} \), as in this case \( \lambda_3 = 0 \). We note that we have a bifurcation of the fold or saddle-node variety for our system in the cases listed above, due to the fact that all of our eigenvalues are real and we will have one zero eigenvalue and the others nonzero. We see that this is in fact the case by noting again that (with the assumption that the wavespeed \( c \) and all concentrations are positive) \( v < \frac{v}{2} + \sqrt{u^2(s + w) + \frac{v^2}{4}} \), and hence \( \lambda_2 = 0 \) implies \( \lambda_3 > 0 \) and \( \lambda_3 = 0 \) implies \( \lambda_2 < 0 \). In the case that the concentration term \( u^2(s + w) = 0 \), however, we cannot rely upon these results and must thus consider this case separately. Specifically, we can understand that \( \lambda_2 = \lambda_3 \) in this case, and hence when \( c = v \) we will have \( \lambda_2 = \lambda_3 = 0 \) and the fold bifurcation behavior will not persist. This assumption is only relevant in the biologically insignificant cases that the extracellular matrix concentration \( u \) is zero or the total cancer cell concentration \( s + w \) is zero, however. Additionally, \( \lambda_3 = 0 \)
(together with the assumption that \( v = \frac{u^2(s+w)}{e} \)) implies that \( c^2 = 2u^2(s+w) \). We are taking wavespeed \( c \neq 0 \), so we will assume that \( u > 0 \) and \( (s+w) > 0 \) when considering the fold in the next subsection.

In sum, we have found that (41) implies that the critical manifold is attracting. Similarly, (42) implies that the critical manifold is repelling. Again, either of these conditions clearly imply that the critical manifold is normally hyperbolic.

5.1. Folds. We now examine the concept of a folded critical manifold, determine the conditions needed to prove its existence, and then apply these ideas to our specific critical manifold \( S_c \). The discussion of geometric singular perturbation theory presented in [36, 11] covers fold points of critical manifolds in some detail.

**Definition 5.1.** A point \((b_0, a_0) \in S_c\) is called a **fold point** if \( f(b_0, a_0, 0) = 0 \), \( \frac{\partial f}{\partial a}(b_0, a_0, 0) = 0 \), but \( \frac{\partial^2 f}{\partial a^2}(b_0, a_0, 0) \neq 0 \) (for \( f \) given in the system (12) and (13)).

With this definition in mind, we progress to proving that the critical manifold of our system is folded.

**Lemma 5.2.** The critical manifold \( S_c \) is folded when \( \lambda_2 < 0 \) and \( \lambda_3 = 0 \).

**Proof.** From [36, pgs. 3292-3296], we can see that the simultaneous conditions needed for the critical manifold to be folded are given by

\[
\begin{align*}
p \cdot (D^2_{aa} G(b, a)(q, q)) &\neq 0 \text{ and } (43) \\
p \cdot (D_q G(b, a)) &\neq 0, \quad (44)
\end{align*}
\]

where \( b \) and \( a \) are defined as above, \( G = (s, \dot{w}, \dot{u}, \dot{v}) \) and \( p \) and \( q \) are the left and right unit null vectors of the jacobian \( J \) of the layer problem (given above), respectively. These conditions can be derived as consequences of applying the implicit function theorem, and thereby expressing \( S_c \) as the graph representation of a function \( h : \mathbb{R}^3 \rightarrow \mathbb{R}^4 \).

The conditions given in (43) and (44) can be explicitly computed in the distinct cases that \( \lambda_2 = 0 \) and \( \lambda_3 = 0 \). For completeness, we will consider each of these cases in turn. Indeed, we use the key assumptions that \( v = \frac{u^2(s+w)}{e} \) (since we’re considering \( S_c \)) and \( c = v \) (if we’re assuming that \( \lambda_2 = 0 \)) or \( c^2 = 2u^2(s+w) \) (if we’re assuming \( \lambda_3 = 0 \)) to see that

\[
p = \begin{cases} 
\frac{1}{P_1} (w, -s, 0, 0) & \text{if } \lambda_2 = 0 \\
\frac{1}{P_2} (2u^3, 2u^3, c^2, uc) & \text{if } \lambda_3 = 0
\end{cases}
\]

for \( P_1 = \frac{\sqrt{2}}{(s+w)} \) and \( P_2 = \frac{1}{Q_2} \left( \frac{4u^3s+4u^3w+uc^2}{2uw} \right) \). In a similar fashion, we determine that the right null vector \( q \) is represented by

\[
q = \begin{cases} 
\frac{1}{Q_1} (1, -1, 0, 0) & \text{if } \lambda_2 = 0 \\
\frac{1}{Q_2} (\frac{1}{w}, \frac{1}{s}, 0, \frac{c}{2w}) & \text{if } \lambda_3 = 0
\end{cases}
\]

for \( Q_1 = \frac{\sqrt{2}}{2} \) and \( Q_2 = \sqrt{\frac{4u^2+4u^2+c^2}{4u^2w^2}} \). Next, we use a simple calculation approach in order to verify that the conditions provided in the previous definition apply to our critical manifold. We provide the highlights of these calculations here. Specifically, we need to show that the critical manifold is folded, which is equivalent to showing
that the conditions (43) and (44) hold for points at which either \( \lambda_2 = 0 \) or \( \lambda_3 = 0 \). Condition (43) is in turn equivalent to showing that

\[
p \cdot \sum_{j,k \in \{1,2,3,4\}} \left( \frac{\partial^2 G}{\partial U_k \partial U_j} q_j q_k \right) \neq 0
\]

for \( U = (s, w, u, v) \) and \( G = (\dot{s}, \dot{w}, \dot{u}, \dot{v}) \). We compute this expression for the case \( \lambda_2 = 0 \), and find that in fact

\[
\sum_{j,k \in \{1,2,3,4\}} \left( \frac{\partial^2 G}{\partial U_k \partial U_j} q_j q_k \right) = 0
\]

in this case. Recall that, since we’re still dealing with the layer problem here, \( G \) can also be represented as

\[
G = (\hat{s} + vs - cs, \hat{w} + vw - cw, \hat{u} - cu, u^2(s + w) - cv).
\]

Hence we do not have a folded critical manifold when \( \lambda_2 = 0 \) (although we may have a higher degeneracy when this occurs), and we move on to solely consider the \( \lambda_3 = 0 \) and \( \lambda_2 \neq 0 \) case. From our previous analysis, we note that \( \lambda_3 = 0 \) implies \( \lambda_2 = v - c < 0 \), so this case is consistent with our previous work. Introducing the assumptions inherent to this case allows us to calculate that

\[
\sum_{j,k \in \{1,2,3,4\}} \left( \frac{\partial^2 G}{\partial U_k \partial U_j} q_j q_k \right) = \left( 2 \frac{\partial^2 G}{\partial s \partial v}(q_1 q_4) + 2 \frac{\partial^2 G}{\partial w \partial v}(q_2 q_4) \right)
\]

\[
= (2, 0, 0, 0) \left( \frac{c}{Q^2(2sw^2)} \right) + (0, 2, 0, 0) \left( \frac{c}{Q^2(2s^2w)} \right)
\]

\[
= \left( \frac{2c}{2Q^2sw^2}, \frac{2c}{2Q^2s^2w}, 0, 0 \right).
\]

We then dot this expression with the vector \( p \) (for \( \lambda_3 = 0 \)) in order to determine whether our critical manifold is folded in this case. We see that

\[
p \cdot \sum_{j,k \in \{1,2,3,4\}} \left( \frac{\partial^2 G}{\partial U_k \partial U_j} q_j q_k \right) = \frac{2u^3c(s + w)}{P_2Q^2s^2w^2} \neq 0
\]

for \( (s + w) > 0 \) and \( u > 0 \). Hence we have satisfied the first condition for a folded critical manifold in this case. We proceed, noting that for \( \hat{U}_k = (\dot{s}, \dot{w}, \dot{u}, \dot{v}) \) the second condition (44) is equivalent [7] to

\[
p \cdot \sum_{k \in \{1,2,3,4\}} \frac{\partial G}{\partial \hat{U}_k} \neq 0.
\]
Hence we are able to easily compute that

\[
p \cdot \sum_{k \in \{1, 2, 3, 4\}} \frac{\partial G}{\partial \hat{U}_k} = p \cdot \left( \frac{\partial G}{\partial \hat{s}} + \frac{\partial G}{\partial \hat{w}} + \frac{\partial G}{\partial \hat{u}} + \frac{\partial G}{\partial \hat{v}} \right) = 4u^3 + c^2\frac{P_2}{P_2}.
\]

We observe that this expression is clearly not equal to zero. Hence we have verified that the critical manifold \( S_c \) is folded here, with the fold curve given by the points where \( \lambda_3 = 0 \). Specifically, this corresponds to the points where \( c = \frac{v}{2} + \sqrt{u^2(s + w)} + \frac{u^2}{2} \). With the definition of the critical manifold, specifically, the fact that \( v = \frac{u^2(s + w)}{c} \), we simplify this to the condition \( c^2 = 2u^2(s + w) \).

Notice that this fold curve corresponds to the definition of the wall of singularities \( W \) given previously.

Additionally, we now have the ability to consider the portions of phase space within which the critical manifold \( S_c \) is attracting and repelling. In combination with our previous analysis, we now are able to more clearly determine that the attracting and repelling subsets of \( S_c \) are divided along the fold curve; that is, the fold curve is the boundary between these two regions. We summarize some of our main findings from the previous sections in the following.

If \( c^2 > 2u^2(s + w) \) \( \implies \lambda_3 < 0 \) and hence \( S_c \) is attracting in this region. We’ll call this portion of the critical manifold \( S_- \).

If \( c^2 < 2u^2(s + w) \) \( \implies \lambda_3 > 0 \) and hence \( S_c \) is repelling in this region. We’ll call this portion of the critical manifold \( S_+ \).

We’d like to expand our knowledge of the properties of this fold curve and our critical manifold now, so we step back and examine the conditions that define \( S_c \) and the layer problem. Using these, we notice that our critical manifold has a symmetric structure around the fold curve.

**Lemma 5.3.** The folded critical manifold \( S_c \) is symmetric in the total cancer cell population \( s + w \) about the fold curve.

**Proof.** We note again that the fold curve is given by the condition \( c^2 = 2u^2(s + w) \), or alternately \((s + w) = \frac{c^2}{2u^2} := F(u) \) (equivalent to the wall of singularities presented previously). We will demonstrate that

\[
\hat{s} + \hat{w}|_{s+w=F(u)+C_1} = \hat{s} + \hat{w}|_{s+w=F(u)-C_1}
\]
for constant $C_1 \in \mathbb{R}$. To verify this equality, we compute

$$
\begin{align*}
\hat{s} + \hat{w}|_{s+w=F(u)+C_1} &= (cs - vs + cw - vw)|_{s+w=F(u)+C_1} \\
&= \left( c(s + w) - \left( \frac{u^2(s + w)}{c} \right) (s + w) \right)|_{s+w=F(u)+C_1} \\
&= \frac{c^3}{2u^2} + cC_1 - \left( \frac{u^2}{c} \left( \frac{c^2}{2u^2} + C_1 \right) \right) \left( \frac{c^2}{2u^2} + C_1 \right) \\
&= \frac{c^3}{2u^2} + cC_1 - \left( \frac{c}{2} + \frac{u^2C_1}{c} \right) \left( \frac{c^2}{2u^2} + C_1 \right) \\
&= \frac{c^3}{4u^2} - \frac{u^2C_1}{c} \\
&= \frac{c^3}{2u^2} - cC_1 - \left( \frac{c}{2} - \frac{u^2C_1}{c} \right) \left( \frac{c^2}{2u^2} - C_1 \right) \\
&= \left( c(s + w) - \left( \frac{u^2(s + w)}{c} \right) (s + w) \right)|_{s+w=F(u)-C_1} \\
&= \hat{s} + \hat{w}|_{s+w=F(u)-C_1},
\end{align*}
$$

as desired. Therefore the critical manifold is symmetric about the fold curve in $s + w$. 

**Remark 1.** Note that when $\epsilon = 0$ solutions can exhibit shocks, which must obey the Rankine-Hugoniot conditions [22], which in this setting are given by

$$
\begin{align*}
\begin{align*}
\frac{\partial u}{\partial t} + A_x u &= C, \\
A &= A(U, x, t), \\
C &= C(U, x, t)
\end{align*}
\end{align*}
$$

Comparing the conditions (45) with the previous definition of $S_c$ shows that these conditions are indeed satisfied since $\hat{s}, \hat{w}, \hat{u}$ are constant along any shocks.

We have now finished our detailed examination of the layer problem in particular, and therefore we move on to consider the reduced problem.

6. **The reduced problem.** We next examine the slow system in the limit $\epsilon \to 0$, also known as the reduced system. The equations that comprise this system are given in (27)-(33). One of our goals in this section will be to demonstrate that the reduced problem has a folded saddle canard point. Generally, canard solutions are solutions of a singularly perturbed system which follow an attracting manifold, pass close to a bifurcation of the critical manifold, and then follow a repelling manifold [31].
We recall:

**Definition 6.1.** A singular canard is a trajectory of the reduced problem that crosses in finite time from one part of the critical manifold to the other (i.e. from \( S_- \) to \( S_+ \) or vice versa). This crossing occurs at a folded singularity (see [36] for more details).

**Definition 6.2.** A folded saddle canard is a point at which the canard solution crosses from one part of the critical manifold to the other, and furthermore \( \omega_1 \cdot \omega_2 < 0 \) for \( \omega_1, \omega_2 \) the nonzero eigenvalues corresponding to this fixed point of the desingularized system (which we create in (49)-(51)).

Using these definitions, we can then verify the existence of such a singular canard. From the definition, we can see that this is equivalent to checking that a folded singularity point (specifically one that behaves like a saddle) exists. We show:

**Theorem 6.3.** A folded saddle canard point exists in the reduced problem (27)-(33).

**Proof.** We first put our reduced system into vector form:

\[
\begin{bmatrix}
\dot{s} \\
\dot{w} \\
\dot{u}
\end{bmatrix} = \begin{bmatrix}
-s(1 - s - w) \\
-w(1 - s - w) \\
u^2(s + w)
\end{bmatrix}.
\]

We then use the conditions given in the definition of \( S_c \) (namely \( \dot{s} = cs - vs, \dot{w} = cw - vw, \dot{u} = cu, \) and \( v = \frac{u^2(s+w)}{c} \)) in order to see that

\[
\begin{bmatrix}
\dot{s} \\
\dot{w} \\
\dot{u}
\end{bmatrix} = \begin{bmatrix}
cs - (v's + vs') \\
cw' - (v'w + vw') \\
cu'
\end{bmatrix}
\]

\[
= \begin{bmatrix}
c - \frac{u^2s}{c} - \frac{w^2(s+w)}{c} \\
-\frac{w^2w}{c} \\
0
\end{bmatrix} \begin{bmatrix}
s \\
w \\
u
\end{bmatrix}
\]

\[
\begin{bmatrix}
\dot{s} \\
\dot{w} \\
\dot{u}
\end{bmatrix} = \begin{bmatrix}
c - \frac{u^2s}{c} - \frac{w^2(s+w)}{c} \\
-\frac{w^2w}{c} \\
0
\end{bmatrix} \begin{bmatrix}
s \\
w \\
u
\end{bmatrix}
\]

This allows us to analyze our system in a cleaner way. We define the \( 3 \times 3 \) matrix in (47) to be \( M \), and then we compute the cofactor matrix of \( M \) (call it \( C \)):

\[
C = \begin{bmatrix}
c^2 - u^2w - u^2(s+w) & u^2w & 0 \\
u^2s & c^2 - u^2s - u^2(s+w) & 0 \\
M_1 & M_2 & M_3
\end{bmatrix}
\]

for \( M_1 = 2u(s+w)s - \frac{2u^3(s+w)^2}{c^2}, M_2 = 2u(s+w)w - \frac{2u^3(s+w)^2w}{c^2}, \) and \( M_3 = c^2 - 3u^2(s+w) + \frac{2u^2(s+w)^2}{c^2}. \)

We then compute the transpose of this cofactor matrix and multiply through, thus obtaining an equation of the form

\[
C^T M \begin{bmatrix}
s \\
w \\
u
\end{bmatrix} = C^T \begin{bmatrix}
-s(1 - s - w) \\
-w(1 - s - w) \\
u^2(s + w)
\end{bmatrix}.
\]
After performing this simple matrix multiplication, we obtain

$$C^T M = \det(M) I = \left( c^3 - 3cu^2(s + w) + \frac{2u^4(s + w)^2}{c} \right) I =: K(s, w, u) I,$$

for $I$ denoting the $3 \times 3$ identity matrix. We now have the system

$$K(s, w, u) \frac{ds}{dz} = -c^2 s(1 - s - w) + M_1 u^2(s + w) + u^2 s(1 - s - w)(s + w)$$

$$K(s, w, u) \frac{dw}{dz} = -c^2 w(1 - s - w) + M_2 u^2(s + w) + u^2 w(1 - s - w)(s + w)$$

$$K(s, w, u) \frac{du}{dz} = M_3 u^2(s + w).$$

which is still singular when $K(s, w, u) = 0$.

Therefore, we’d like to rescale the variable $z$ in order to eliminate these singularities. Specifically, our goal is to define $\bar{z}$ such that

$$\frac{dz}{d\bar{z}} = \left( c^3 - 3cu^2(s + w) + \frac{2u^4(s + w)^2}{c} \right).$$

In pursuit of this, we take $z = c^3 \bar{z} - 3c \int (u^2(s + w)) d\bar{z} + \frac{2}{c} \int u^4(s + w)^2 d\bar{z}$. We notice that this definition makes sense, in that the cell concentrations $s$, $w$ and $u$ are obviously continuous and hence integrable. We then arrive at the adjusted system

$$\frac{ds}{d\bar{z}} = -c^2 s(1 - s - w) + M_1 u^2(s + w) + u^2 s(1 - s - w)(s + w) \quad (49)$$

$$\frac{dw}{d\bar{z}} = -c^2 w(1 - s - w) + M_2 u^2(s + w) + u^2 w(1 - s - w)(s + w) \quad (50)$$

$$\frac{du}{d\bar{z}} = M_3 u^2(s + w). \quad (51)$$

In Figure 2, a sample traveling wave profile (in terms of $\bar{z}$) for the system (49)-(51) can be seen. This profile is obtained by directly simulating (49)-(51) and manually inserting the jump; compare with [7], Figure 7.
Next, we analyze the phase space behavior of the solutions to this system. The equilibrium points are given by the following:

\((s_1, w_1, u_1) = (1 - w^*, w^*, 0)\)

\((s_2, w_2, u_2) = (0, 0, u^*)\)

\((s_3, w_3, u_3)_\pm = \left(1 - w^{**} + \frac{c^2}{4} \pm \frac{c\sqrt{8 + c^2}}{4}, w^{**}, \frac{c^2}{4} \mp \frac{c\sqrt{8 + c^2}}{4}\right),\)

for \(w^*, u^*\) and \(w^{**}\) values in \([0, 1]\). First of all, we note that \(\frac{c^2}{4} - \frac{c\sqrt{8 + c^2}}{4} < 0\), and hence the point \((s_3, w_3, u_3)_+\) is biologically unrealistic for the model. On the other hand, \((s_3, w_3, u_3)_-\) will be biologically relevant under the assumptions that \(0 < c\) and \(w^{**} < 1 + \frac{c^2}{4} - \frac{c\sqrt{8 + c^2}}{4}\).

Therefore we will define \((s_3, w_3, u_3) := (s_3, w_3, u_3)_-\), and we will not consider \((s_3, w_3, u_3)_+\) for the remainder of the paper.

We can utilize the Jacobian of our new desingularized system (49)-(51) in order to compute the eigenvalues and eigenvectors of our three different equilibria points. We call the system (49)-(51) desingularized as the singularities have been removed by rescaling via the variable \(\bar{z}\). We compute the relevant matrix and evaluate it at each of the equilibrium points, in turn. First, we consider the equilibrium point \((s_1, w_1, u_1)\) and determine its stability. We see that

\[
J^*_{|(s_1, w_1, u_1)} = \begin{bmatrix}
c^2(1 - w) & c^2(1 - w) & 0 \\
c^2 w & c^2 w & 0 \\
0 & 0 & 0
\end{bmatrix},
\]

and hence we find the eigenvalues \(\lambda_1^* = 0\) (with multiplicity 2) and \(\lambda_2^* = c^2\). The corresponding eigenvectors are given by \(v_0 = (0, 0, 1), v_{0*} = (-1, 1, 0),\) and \(v_{c^2} = \left(\frac{1-w^*}{w^*}, 1, 0\right)\) (corresponding to the 0, 0, and \(c^2\) eigenvalues, respectively). We then perform similar calculations for the next equilibrium point, \((s_2, w_2, u_2)\). In this case, we determine that

\[
J^*_{|(s_2, w_2, u_2)} = \begin{bmatrix}
-c^2 & 0 & 0 \\
0 & -c^2 & 0 \\
c^2 u^2 & c^2 u^2 & 0
\end{bmatrix},
\]

and thus we are able to determine the eigenvalues and eigenvectors for this equilibrium point as well. Specifically, the eigenvalues are given by \(\lambda_1^* = -c^2\) (with multiplicity 2) and \(\lambda_2^* = 0\) with corresponding eigenvectors \(v_{-c^2} = (-\frac{1}{w^*}, 0, 1), v_{-c^2*} = (-1, 1, 0)\) and \(v_0 = (0, 0, 1)\), respectively.

Analysis of the third equilibrium point \((s_3, w_3, u_3)\) is more complicated due to the formulation for the equilibrium point itself. Nevertheless, we compute the Jacobian matrix of our system evaluated at this third equilibrium. Since the matrix form of this expression does not simplify very cleanly, we simply pass over the matrix itself and provide the eigenvalue and eigenvector pairs for \(J^*_{|(s_3, w_3, u_3)}\). These are given
We see that of our critical manifold, we see that similarly recalling the conditions needed for the attracting and repelling portions (can classify this point as center-stable. S by being on the critical manifold and similarly classify this point as center-unstable. That earlier is sufficient to guarantee that \( f \) has roots at \( c > 0 \) and \( c < 0 \). And furthermore \( f^- = 0 \) only has roots at \( c = 0 \) and \( c = \pm 2i\sqrt{2} \). From this we can see that the condition \( c > 0 \) that we imposed earlier is sufficient to guarantee that \( f^- < 0 \) and \( f^+ > 0 \). More rigorously we note that \( (f^+)'(c) > 0 \) for \( c > 0 \), which guarantees that \( f^+ > 0 \) under this condition.

Now that we have calculated these eigensystems for the various equilibria, we naturally move to the stability analysis of these points.

\((s_1, w_1, u_1)\): We see that \( \lambda_1^1 = 0 \) (with multiplicity 2) and \( \lambda_2^1 > 0 \). Hence we can classify this point as center-unstable.

\((s_2, w_2, u_2)\): We see that \( \lambda_1^2 < 0 \) (with multiplicity 2) and \( \lambda_2^2 = 0 \). Hence we can classify this point as center-stable.

\((s_3, w_3, u_3)\): We see that \( \lambda_1 = 0 \) and \( f^+(c) > 0 \) and \( f^-(c) < 0 \) under our \( c > 0 \) assumption. Hence we can classify this point as a saddle-type.

Thinking back to the definition of a singular canard, we recall that we must demonstrate the existence of a folded saddle equilibrium in order to be able to verify the existence of a folded saddle canard point. Hence the nature of \((s_3, w_3, u_3)\) as this saddle-type steady state is a key to furthering our analysis of this model.

We then proceed by remembering that \( \frac{dz}{dt} = (c^3 - 3cu^2(s + w)) + 2u^4(s + w)^2 \). Similarly recalling the conditions needed for the attracting and repelling portions of our critical manifold, we see that

\[
\frac{dz}{dt} > 0 \text{ on } S_+ \cap A_1
\]

and similarly

\[
\frac{dz}{dt} < 0 \text{ on } S_+ \cap A_2,
\]

for \( A_1 = \{(s, w, u) : c^2 > 3u^2(s + w)\} \) and \( A_2 = \{(s, w, u) : c^4 + 2u^4(s + w)^2 < 3c^2u^2(s + w)\} \).

These results stem from analysis of the sign of \( \frac{dz}{dt} \) under the constraints imposed by being on the critical manifold \( S_c \). Using this information, we observe that the
direction of the trajectories in our new set \( S_- \cap A_1 \) will be preserved when transitioning between the phase space with respect to \( z \) and the phase space with respect to \( \tilde{z} \). On the other hand, when in \( S_+ \cap A_2 \) the trajectories under the original \( z \) parametrization will move in the opposite direction than they do in our new \( \tilde{z} \) phase space. Furthermore, we note that while the other equilibrium points \((s_1, w_1, u_1)\) and \((s_2, w_2, u_2)\) are preserved under the rescaling, \((s_3, w_3, u_3)\) is no longer an equilibrium point of the system when parametrized by \( z \) (see [37]). This is due to the fact that \( K(s, w, u)\) is zero, and so the relevant derivatives \( \frac{ds}{dz}, \frac{dw}{dz}, \) and \( \frac{du}{dz} \) will be nonzero at this point. Thus, this point changes from a steady state (when considered with respect to \( \tilde{z} \)) to a point at which trajectories cross the fold curve in the original system (when considered with respect to \( z \)). Therefore, if we have a saddle equilibrium point at \((s_3, w_3, u_3)\), then the trajectories will still cross from \( S_- \) to \( S_+ \) (and vice versa) in finite time, and hence we will have a canard solution. Moreover, the folded saddle canard point will correspond to the point at which this solution crosses over the fold curve.

7. Traveling waves. Now that the layer problem and the reduced problem have both been analyzed in depth, we transition to an in-depth discussion of the behavior of traveling wave solutions. While we will focus on Type II traveling waves for our analysis here, we recall the characteristics and classifications of the other types for completeness.

**Definition 7.1.** A **Type I** traveling wave is a smooth traveling wave. A **Type II** traveling wave is a traveling wave that has a shock and infinite support. A **Type III** traveling wave is a traveling wave that has a shock and semicompact support.

We wish to examine and prove the existence of Type II traveling waves for our model. In preparation for this, we first state the following definitions of relevant terms.

**Definition 7.2.** A **singular orbit** is a heteroclinic orbit that is composed of orbits in the layer problem and orbits in the reduced problem and serves to connect invariant manifolds of the reduced problem.

**Definition 7.3.** A **fast fiber** of the layer problem corresponds to a trajectory in phase space that connects a point on \( S_- \) to another point on \( S_+ \), independently of the slow variables \( \hat{s}, \hat{w}, \) and \( \hat{u} \).

In different language, [38] conceptualizes the fast fiber of an arbitrary point \( p = (s_p, w_p, u_p, \hat{s}_p, \hat{w}_p, \hat{u}_p) \) on the critical manifold \( S_c \) as the set \( \mathcal{F}_f(p) = \{(s_p, w_p, u_p, s, w, u, v) \in \mathbb{R}^7 : (s, w, u, v) \in \mathbb{R}^4 \} \). So this is the set of points that are fixed points of the layer problem. Since \( \hat{s}_p, \hat{w}_p, \) and \( \hat{u}_p \) are fixed, the set will correspond to a trajectory independent of the slow variables. With this in hand, we will prove the following theorem.

**Theorem 7.4.** Given that \( \frac{2u^2(s+w)^2}{1-s-w} < c^2 \), there exist singular heteroclinic orbits that correspond to Type II traveling waves.

**Proof.** Type II traveling waves correspond to solutions which follow the trajectory passing through the folded saddle canard point onto \( S_- \), see [7], Lemma 2.6. So we consider the canard solution, a trajectory that passes through the folded saddle canard point \((s_3, w_3, u_3)\) (when we rescale our system back into \((s, w, u)\) coordinates).
First of all, we verify that this point corresponds to the hole in the wall of singularities. We recall that

\[(s_3, w_3, u_3) = \left(1 - w^{**} + \frac{c^2}{4} - \frac{c\sqrt{8 + c^2}}{4}, \frac{c^2}{4} + \frac{c\sqrt{8 + c^2}}{4}\right),\]

\[(s_H, w_H, u_H) = \left(\frac{1}{1 + u_H} - w_H, w_H, \frac{c}{4}(c + \sqrt{c^2 + 8})\right).\]

After performing the necessary calculations, we see that if we take \(w^{**} = w_H\), then \((s_3, w_3, u_3) = (s_H, w_H, u_H)\) as desired. Therefore, we move on to consider the behavior of the canard solution, \(C_s\), that passes through the hole in the wall. If we consider a solution that starts at the unstable equilibrium point \((s_1, w_1, u_1)\), then we want to show that the trajectory will end up at the stable equilibrium point \((s_2, w_2, u_2)\). We thus consider the location of these equilibria: clearly \((s_1, w_1, u_1) = (1 - w^*, w^*, 0)\), and hence \(2u^2(s + w)|_{(s_1, w_1, u_1)} < c^2\), so by definition \((s_1, w_1, u_1) \in S_+\).

Furthermore, \((s_2, w_2, u_2) = (0, 0, u^*)\) means that \(2u^2(s + w)|_{(s_2, w_2, u_2)} < c^2\), so similarly \((s_2, w_2, u_2) \in S_-\). We know that a Type II traveling wave solution will correspond to a trajectory that follows \(C_s\) in \(S_-\) until the folded saddle canard point, and then crosses over into \(S_+\). Once this happens, the trajectory will cross back into \(S_-\) via a fast fiber of the layer problem, as we detail below.

We can proceed to note that the solution will then tend back into \(S_-\) via one of these fast fibers, an action that corresponds to a shock (or a jump, as in [7]). This will return the solution from \(S_+\) to \(S_-\) on a trajectory with constant \(\hat{s}, \hat{w}, \text{and} \hat{u}\), by definition, via a discontinuity that satisfies the Rankine-Hugoniot conditions: see [37] for more details. Once the trajectory has returned to \(S_-\), we wish to show that the trajectory tends to the stable equilibrium \((s_2, w_2, u_2)\). To complete this task, we must consider the signs of the derivatives

\[
\frac{ds}{du} = -c^2s(1 - s - w) + M_1u^2(s + w) + u^2s(1 - s - w)(s + w)
\]

\[
\frac{dw}{du} = -c^2w(1 - s - w) + M_2u^2(s + w) + u^2w(1 - s - w)(s + w)
\]

(52)

(53)

We wish to demonstrate that on the portion of \(S_-\) that is connected to a point in \(S_+\) via a fast fiber, these derivatives are negative. On \(S_-\), we know that \(c^2 > 2u^2(s + w)\) by definition of this attracting portion of the critical manifold. Hence, after recalling that \(M_1 = 2u(s + w)s - \frac{2u^4(s+w)^2}{c^2}, M_2 = 2u(s + w)w - \frac{2u^4(s+w)^2}{c^2}, \text{and} M_3 = c^2 - 3u^2(s + w) + \frac{2u^4(s+w)^2}{c^2}\), we can see that

\[
\frac{ds}{du} = \frac{-c^2s(1 - s - w) + M_1u^2(s + w) + u^2s(1 - s - w)(s + w)}{M_3u^2(s + w)}
\]

\[
= s \left(\frac{-c^2(1 - s - w) + 2u^2(c^2(s + w))^2 - 2u^5(s + w)^3 + c^2u^2(s + w)(1 - s - w)}{c^2u^2(s + w) - 3c^2u^4(s + w)^2 + 2u^6(s + w)^3}\right)
\]

\[
= \frac{s}{u^2(s + w)(c^2 - u^2(s + w)(2c^2 + c^2 - 2u^2(s + w)))}
\]

We note that on \(S_-\) we’ll have \(c^2 > 2u^2(s + w) > 0\), and hence

\[c^4 - u^2(s + w)(2c^2 + c^2 - 2u^2(s + w)) > c^4 - 2c^2u^2(s + w) > 0,\]
so the denominator of the fractional expression for $\frac{ds}{du}$ is positive. Additionally, we can see that under the additional assumption that $\frac{2u^2(s+w)^2}{1-s-w} < c^2$, then the numerator of the fraction is negative. In this case the derivative itself is negative. In a similar fashion, the other derivative $\frac{dw}{du}$ can also be shown to be negative under the above assumption. Hence we know that once the trajectory reaches $S_\infty$ via the fast fiber, it will tend towards the stable equilibrium point $(s_2, w_2, u_2) = (0, 0, u^*)$. Thus singular heteroclinic orbits exist by definition, and we can see from our construction that they correspond to Type II traveling waves.

8. **Transversality and uniqueness.** Next we wish to address uniqueness of the singular heteroclinic orbits constructed in the previous section. The first step towards this goal is showing that the intersection of certain singular unstable and stable manifolds is transversal.

Our starting points are the adjusted form of the reduced problem (27)-(33) and the layer problem (34)-(40) with an appended equation $\dot{c} = 0$. Relating this to the general form of the systems studied in [30]; namely, their system (1.2) - (1.4), we have $x = (\hat{s}, \hat{w}, \hat{u}, c)$, $y = (s, w, u, v)$, $f = (-s(1-s-w), -w(1-s-w), u^2(s+w), 0)$, and $g = (\hat{s} + vs - cs, \hat{w} + vw - cw, \hat{u} - cu, u^2(s + w) - cv)$. From this, we can use the relationships $A = D_y(g)$ and $B = D_x(g)$ in order to compute $A$ and $B$:

$$A = \begin{bmatrix} v - c & 0 & 0 & s \\ 0 & v - c & 0 & w \\ 0 & 0 & -c & 0 \\ u^2 & u^2 & 2u(s + w) & -c \end{bmatrix} \quad \text{and} \quad B = \begin{bmatrix} 1 & 0 & 0 & -s \\ 0 & 1 & 0 & -w \\ 0 & 0 & 1 & -u \\ 0 & 0 & 0 & -v \end{bmatrix}.$$ 

Define

$$M := \int_{-\infty}^{\infty} (\psi(z) \cdot B(z))dz$$

where the function $\psi$ is the unique (up to a scalar multiple) bounded solution of the adjoint equation

$$\psi' = -A^T \psi.$$ 

We assume:

$$M \neq 0 \quad (54)$$

If $v > c$ then we form the stable manifold $W^{s,c}_1$ and unstable manifold $W^{u,c}_1$ of the extended system (34)-(40) with appended equation $\dot{c} = 0$, and if $c > \frac{v^2 + \sqrt{u^2(s + w) + \frac{v^2}{4}}}{2}$ then we form the analogous manifolds.

Assuming (54), we have $W^{s,c}_j$ intersects $W^{u,c}_j$ transversally for $j = 1, 2$ from the following result:

**Theorem 8.1** ([30], Theorem 4.1). Suppose $N_1$ and $N_2$ are $j_1$ and $j_2$ dimensional invariant manifolds of a dynamical system with a $j_1 + j_2^*$ dimensional stable manifold $W^s_1$ and $j_1 + j_2^*$ dimensional unstable manifold $W^u_1$, for $i = 1, 2$. Let $N_1^{s*}$ and $N_2^{s*}$ denote the singularly unstable manifold of $N_1$ and singularly stable manifold of $N_2$. The manifolds $N_1^{s*}$ and $N_2^{s*}$ intersect transversally if and only if there exist exactly $d - 1$ linearly independent solutions $\xi$ of the equation

$$(M, \xi) = 0$$
where $(\cdot, \cdot)$ denotes the scalar product. Above, the dimension $d$ is given by

$$d = j_1 + j_2 + k_1^u + j_2^u + k_1^s + k_2^s - n - k$$

where $k_1^u, k_1^s$ denote the number of eigenvalues in the left half plane and right half plane, respectively, $n$ is the dimension of the reduced problem, and $k$ is the dimension of the layer problem (corresponding to the dynamical system).

Note that we compute explicitly that $d = 1$ for our system using the eigenvalues given in Section 6: we have $n + k = 8$, $k_1^u + k_2^s = 4$, $j_1 + j_1^u = 2$, and $j_2 + j_2^u = 3$. Additionally, for the system considered here, i.e. (34)-(40) and $\dot{c} = 0$, we have $W_1^{u,c} = \mathcal{N}_1$ and $W_2^{s,c} = \mathcal{N}_2$. Then, since $d = 1$ here, we have that $W_1^{u,c}$ intersects $W_2^{s,c}$ transversally provided $M \neq 0$, i.e. under assumption (54).

**Remark 2.** Uniqueness of heteroclinic orbits in both cases is expected to follow under the assumption (54) coupled with the fold condition from Lemma 5.2; see e.g. [37, Corollary 2.1] for a lower-dimensional case. Specifically we note that this corresponds to the case presented in [37, Figure 5], since we are considering a traveling wave with a shock and a canard. However, this requires that the projection along the fast fiber of the unstable manifold of the hole in the wall onto the attracting sheet be transverse to the stable subspace of the endpoint, and this is unclear for the higher dimensional system considered in this work.

### 9. Persistence of solutions for $0 < \epsilon \ll 1$

The traveling wave solution constructed in the previous sections can be shown to persist for $0 < \epsilon \ll 1$. Indeed, this follows directly from the assumption (54) which implies transversal intersections of the corresponding stable and unstable manifolds. The following analysis is inspired by [6].

First we suppose that $v > c$ so $S_c$ is repelling (i.e. we are on the repelling sheet of the critical manifold). Then by Fenichel Theory [5], $S_c$ perturbs to an invariant manifold for the fast system with $\epsilon > 0$. Call this manifold $S^\epsilon_c$: the distance between $S_c$ and $S^\epsilon_c$ is order $\epsilon$, and for $\epsilon$ sufficiently small, there holds that $S^\epsilon_c$ is normally hyperbolic and repelling (attracting in the other case).

Additionally, Fenichel’s Theorem [5] implies that any invariant set for the fast system that’s close enough to $S_c$ is located on $S^\epsilon_c$. As equilibrium points are an invariant set, we conclude that the equilibria $E_1, E_2, E_3$ belong to $S^\epsilon_c$.

The next idea is to show that the heteroclinic orbit is constructed where the unstable manifold $W^u_v$ for $(s_1, w_1, u_1)$ intersects transversally the stable manifold $W^s$ for $(s_2, w_2, u_2)$. This will be done on $S^\epsilon_c$ as a perturbation of the same construction on $S_c$. The following is easy to see, and guarantees the validity of the reduction of the problem to $S^\epsilon_c$:

**Lemma 9.1.** For $\epsilon > 0$ small enough, any heteroclinic orbit connecting the cancer persistence state to the healthy state must lie in $S^\epsilon_c$.

If we again allow $c$ to vary, we may consider the analogous invariant manifolds $W^{u,c}_\epsilon = W^{u,c}_\epsilon(s_1, w_1, u_1, c, \epsilon)$ and similarly we consider $W^{s,c}_\epsilon$. We need to show that

$$W^{u,c}_\epsilon \cap W^{s,c}_\epsilon \neq \emptyset$$

(55)

Assumption (54) shows this holds for $\epsilon = 0$; a corresponding transversality assumption for $0 < \epsilon \ll 1$ will show that the intersection remains non-empty for $\epsilon \neq 0$. Canard theory [31] guarantees the existence of a maximal folded saddle canard in our full system for $\epsilon \neq 0$. Notice that the transverse intersection, again under assumption (54), defines what is known as the maximal canard; see [7].
10. **Estimation of wavespeed.** Consider the Jacobian near the equilibrium point \((s_2, w_2, u_2)\) as discussed previously:

\[
J^*|_{(s_2, w_2, u_2)} = \begin{bmatrix}
-c^2 & 0 & 0 \\
0 & -c^2 & 0 \\
c^2w^2 & c^2w^2 & 0
\end{bmatrix},
\]

Linearizing the desingularized system \((49)-(51)\) around this equilibrium point gives

\[
\frac{ds}{d\tilde{z}} = -c^2 s, \quad \frac{dw}{d\tilde{z}} = -c^2 w, \quad \frac{du}{d\tilde{z}} = c^2 u_0^2 s + c^2 u_0^2 w
\]

whose solution takes the form

\[
\begin{pmatrix}
s \\
w \\
u
\end{pmatrix} = \begin{pmatrix}
0 \\
0 \\
u_0^2(c_1 + c_3) + c_2
\end{pmatrix} + e^{-c^2 \tilde{z}} \begin{pmatrix}
c_1 \\
c_3 \\
-u_0^2(c_1 + c_3)
\end{pmatrix}
\]

for integration constants \(c_1, c_2, c_3\).

Now, near \((0, 0, u_0)\), we have that \(dz/d\tilde{z} \approx c^3\) so that \(\tilde{z} \approx z/c^3\). Thus near this point,

\[
\begin{pmatrix}
s \\
w \\
u
\end{pmatrix} = \begin{pmatrix}
0 \\
0 \\
u_0^2(c_1 + c_3) + c_2
\end{pmatrix} + e^{-z/c} \begin{pmatrix}
c_1 \\
c_3 \\
-u_0^2(c_1 + c_3)
\end{pmatrix}
\]

We hence make an ansatz that the leading edges of the solutions behave in the following way for asymptotically large \(x\), with \(\xi, c_1, c_2, c_3 > 0\):

\[
\begin{align*}
s(x, t) &= c_1 e^{-\xi(x-ct)} \\
w(x, t) &= c_3 e^{-\xi(x-ct)} \\
u(x, t) &= u_0^2(c_1 + c_3) + c_2 - u_0^2(c_1 + c_3)e^{-\xi(x-ct)} \\
&= u_0^2(c_1 + c_3) + c_2 - u_0^2(s(x, t) + w(x, t))
\end{align*}
\]

Next we plug this ansatz into \((1)-(3)\); for \((1)\) we obtain

\[
\xi c s(x, t) = s(x, t) - s(x, t)^2 - s(x, t)w(x, t) + u_0^2 \xi^2 (2s(x, t)^2 + 2w(x, t)s(x, t)) + \xi^2 s(x, t)
\]

after taking \(\epsilon_1 = \epsilon_2 = \epsilon\). Neglecting the order second order terms (since \(s, w \to 0\) as \(x \to \infty\)) we obtain the same dispersion relation:

\[
\xi c = 1 + \epsilon \xi^2, \quad \text{or} \quad c = \xi \epsilon + \frac{1}{\xi}
\]

For equation \((2)\), the same dispersion relation is obtained. Finally, for \((3)\), we obtain

\[
c_\xi = u_0^2(c_1 + c_3)^4 + 2c_2(c_1 + c_3)^2 + c_2^2 u_0^2 + c_\xi^2
\]

But, since \(u \to u_0\) as \(x \to \infty\), we may infer that \(c_2 = u_0 - u_0^2(c_1 + c_3)\), so in fact the ansatz for \(u(x, t)\) takes the form

\[
u(x, t) = u_0 - u_0^2(s(x, t) + w(x, t))
\]

Again plugging this ansatz into \((3)\) and neglecting second order terms in \(s\) and \(w\), we obtain the same dispersion relation as above. Notice this dispersion relation is
the same as for the Fisher KPP equation $v_t = dv_{xx} - bv(1 - v)$ for certain parameters $b, d$. Thus, for $\xi < \frac{1}{\sqrt{\epsilon}}$, we conclude by [18] that in this range $c = \frac{1}{\xi} + \epsilon \xi$. The case $\xi \geq \frac{1}{\sqrt{\epsilon}}$ is not treated in that article, however. But, by Theorem 5 in [14], since the dispersion relations above are all the same, we conclude that for (1)-(3) we have

$$c = \begin{cases} \frac{1}{\xi} + \epsilon \xi & \text{if } \xi < \epsilon^{-1/2} \\ 2\sqrt{\epsilon} & \text{if } \xi \geq \epsilon^{-1/2} \end{cases} \quad (62)$$

for solutions that evolve from initial conditions that behave as in (61).

**Remark 3.** These wavespeeds are consistent with the results of [7]. From (62), it would appear that a wavespeed of $c = 1/\xi$ for all $\xi$ should hold; this has been verified numerically for these types of waves (that is to say, Type II traveling waves) in [22].

11. **Conclusion.** In this paper, we have developed a new model of cancer cell motility. This model is novel in that it accounts for the cancer stem cell hypothesis by adding a third partial differential equation that corresponds to the concentration of cancer stem cells. After developing this model, we have utilized traveling wave methods in combination with geometric singular perturbation theory in order to uncover some results about the solution behavior for this new model. We then made use of GSPT on an altered system in order to perform a phase space analysis of both the reduced problem and the layer problem. Eventually, we were able to investigate questions about the existence of Type II traveling waves for our model. We also demonstrated the persistence of solutions for $0 < \epsilon \ll 1$.

Future research entails refining the cancer stem cell equation in order to better model the dynamics of cancer stem cells. In this paper we assumed that the cancer stem cells behaved very similarly to the differentiated cancer cells, with the exception of their rate of diffusion (as modeled by differences in the diffusion coefficient $\epsilon_1$ and $\epsilon_2$) and differences in the boundary conditions. Given more relevant empirical data, this equation could be further refined in order to reflect the inherent differences in motility between differentiated cancer cells and cancer stem cells. In particular, our current model does not take into account that cancer stem cells can differentiate into non-stem cancer cells [25, 29]. Nor does it take into account the fact that non-stem cancer cells can perform only a limited number of divisions [15]. A significant extension of our model would be to include these two phenomena. In particular, this would yield key insights into the emergence of resistance in cancer cell populations [28]. One way to include the fact that cancer stem cells can differentiate into non-stem cancer cells would be to introduce a flux from $s(x, t)$ to $u(x, t)$. In this case, further restrictions are expected in order to obtain existence of Type II traveling waves; see e.g. [1] where restrictions involving the Fourier transform of a certain interaction kernel are required in order to obtain traveling wave solutions.

Additionally, we have neglected production of the ECM in our model, but this can also be taken into account; see e.g. [32] where this was done in a glioma model.

On another note, future research can expand upon this work by analyzing different types of traveling waves that arise in this system (as was done in [7], for their model). Further work also involves obtaining uniqueness from the assumption
\(M \neq 0\), as well as proving that \(M \neq 0\). This is expected to hold due to the uniqueness result from Lemma 2.8 in [7] as well as the classical Melnikov calculation for a similar problem in [6].

**Acknowledgments.** The authors are very grateful to the anonymous referees for a careful reading of the manuscript and for several constructive suggestions.

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Received December 2019; revised September 2020.

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