SIAM J. APPL. MATH.
Vol. 69, No. 2, pp. 375–397

MESENCHYMAL MOTION MODELS IN ONE DIMENSION*

ZHI-AN WANG†, THOMAS HILLEN‡, AND MICHAEL LI‡

Abstract. Mesenchymal motion denotes a form of cell movement through tissue which can be observed for certain cancer metastases. In [T. Hillen, *J. Math. Biol.*, 53 (2006), pp. 585–616], a mathematical model for this form of movement was introduced. In the current paper we present a comprehensive analysis of the one-dimensional mesenchymal motion model. We establish the global existence of classical solutions and rigorously carry out the parabolic limit of the model. We discuss the stationary solutions, prove the existence of traveling wave solutions, and use numerical simulations to illustrate the results. Finally, we discuss the biological implications of the results.

Key words. mesenchymal motion, stationary solutions, global existence, macroscopic limits, traveling waves, hyperbolic systems

AMS subject classifications. 35L45, 35L60, 92B99

DOI. 10.1137/080714178

1. Introduction.

Mesenchymal motion is a form of cellular movement through tissue which is formed from fiber networks. An example is the invasion of tumor metastases through collagen networks [7]. Cells migrate in fiber networks and change their directions according to the orientational distribution of fibers. Moreover, cells actively remodel the matrix by excreting a matrix degrading enzyme (e.g., protease) to generate sufficient space in which to migrate.

The motion of mesenchymal cells in a tissue matrix was reported in a review article by Friedl and Bröcker [7]. Mesoscopic and macroscopic mathematical models for mesenchymal motion were derived by Hillen [12] in a temporally varying network tissue. The mesoscopic models consist of a transport equation for the cell movement and an ordinary differential equation (ODE) for the dynamics of tissue fibers. The macroscopic models have the form of drift-diffusion equations, where the mean drift velocity is given by the mean orientation of the tissue, and the diffusion tensor is given by the variance-covariance matrix of the tissue orientation. The analysis in [12] is divided into the case of undirected and directed tissue according to the distribution of fiber orientation. In undirected tissue, the fibers are symmetrical along their axes and both fiber directions are identical. For example, collagen fibers are undirected and form the basis for many human and animal tissues. For directed tissue, the fibers are unsymmetrical and the two ends can be distinguished (such as microtubules and actin filaments). Branching collagen fiber networks can also be considered directional if the branching points are of significance for the movement of cells [12].

The model from [12] was extended in [3, 4] to include cell-cell interactions and chemotactic forces for the case of undirected fibers. Formal methods were used to derive the corresponding macroscopic models. Painter [21] numerically studied models for cell movement in fiber tissues and showed pattern formation in the form of

*Received by the editors January 24, 2008; accepted for publication (in revised form) June 11, 2008; published electronically November 5, 2008.
http://www.siam.org/journals/siap/69-2/71417.html
†Institute for Mathematics and Its Applications, University of Minnesota, Minneapolis, MN 55455 (zhiwang@ima.umn.edu). This author's work was supported by the IMA postdoctoral fellowship.
‡Department of Mathematical and Statistical Sciences, University of Alberta, Edmonton, AB T6G 2G1, Canada (thillen@math.ualberta.ca, mli@math.ualberta.ca). The work of these authors was supported by the Natural Science and Engineering Council of Canada (NSERC).

macroscopic networks.

In this paper, the one-dimensional mesenchymal motion model is fully analyzed. The global existence of solutions, macroscopic limits, traveling waves, and stationary solutions are investigated. The one-dimensional model is very instructive and we can gain much insight into the mechanisms involved in the model. For example, we find the existence of traveling pulse solutions for the cell population and identify some mechanisms for cell aggregation. We also identify some differences between undirected and directed tissue by analyzing the one-dimensional model. We restrict our attention to the model for directed tissue only and the analysis can be completely adopted to the study for undirected tissue from the mathematical point of view.

The paper is organized as follows. In the rest of this section, we will present the one-dimensional mesenchymal motion model derived in [12] and discuss the stationary solutions based on the telegraph process analysis. In section 2, we classify the one-dimensional model as a degenerated hyperbolic system and conclude that there is no shock solution. In section 3, the global existence of classical solutions is obtained along the characteristics using a fixed point argument and general regularity results for the semilinear hyperbolic system. In section 4, we rigorously carry out the parabolic limit of the one-dimensional mesenchymal transport model, where we show that solutions of the one-dimensional model converge to solutions of the corresponding drift-diffusion limit equation. In section 5, we study the traveling wave solutions and find traveling pulse solutions for the cell population and traveling front waves for fiber orientations. In the final section 6, we summarize and compare our results with the results obtained in [12]. Furthermore, we explain the findings in the context of the biological application of cell movement in tissue.

1.1. Models for mesenchymal motion in one dimension. In this paper, we are primarily interested in the one-dimensional mesenchymal motion model for the case of directed tissue, which reads as follows [12]:

$$
\begin{aligned}
p_t^+ + sp_x^+ &= -\mu p^+ + \mu q^+(p^+ + p^-),\\
p_t^- - sp_x^- &= -\mu p^- + \mu q^-(p^+ + p^-),\\
q_t^+ &= \kappa(p^+ - p^-)(q^- - q^+ + 1)q^+,\\
q_t^- &= \kappa(p^+ - p^-)(q^- - q^+ - 1)q^-.
\end{aligned}
\tag{1.1}
$$

The quantities p^+, p^- denote density of cells moving to the right or left, respectively, with a constant speed s. The functions q^+, q^- are distributions of fibers pointing to the right $(+)$ or left $(-)$. The constant $\mu \geq 0$ denotes the turning rate, and the constant $\kappa \geq 0$ represents the cutting efficiency (rate of fiber degradation). The transport term $sp_x^{\pm}$ in (1.1) accounts for the cell migration in either direction with speed s. The right-hand side of the first two equations describes the change of cell movement in the field of fibers. The third and fourth equations of (1.1) describe the changes of the fibers in either direction due to the interaction with cells. The derivation of the above model is omitted here for brevity and we refer interested readers to [12] for details. It is worthwhile to point out that the model for undirected tissue can be regarded as a special case of (1.1) for $\kappa = 0$ (see also [12]). In this paper, we focus on the model of directed tissue, and most of our results can be applied to the case of undirected tissue. The significant difference, when it appears, will be emphasized.

The system (1.1) is closely related to the Goldstein–Kac system [8, 17] which describes correlated random walk in one space dimension. With $p = p^+ + p^-$,

$j = s(p^+ - p^-)$, $q = q^+ + q^-$, and $\xi = q^+ - q^-$, system (1.1) becomes

$$\begin{aligned} p_t + j_x &= \mu(q-1)p, \\ j_t + s^2 p_x &= -\mu j + \mu s \xi p, \\ q_t &= (\kappa/s) j \xi (1-q), \\ \xi_t &= (\kappa/s) j (q - \xi^2). \end{aligned} \tag{1.2}$$

Since (q^+, q^-) denotes a distribution, $q^+ + q^- = 1$. Hence one is interested in solutions with $q = 1$. The set $q = 1$ is an invariant manifold of the system (1.2) which will be verified later in Lemma 3.1. On this manifold the system (1.2) reduces to

$$\begin{aligned} p_t + j_x &= 0, \\ j_t + s^2 p_x &= -\mu j + \mu s \xi p, \\ \xi_t &= (\kappa/s) j (1 - \xi^2). \end{aligned} \tag{1.3}$$

If q^+ is used instead of ξ, then the system becomes

$$\begin{aligned} p_t + j_x &= 0, \\ j_t + s^2 p_x &= -\mu j + \mu s (2q^+ - 1)p, \\ q_t^+ &= 2(\kappa/s) j q^+ (1 - q^+). \end{aligned} \tag{1.4}$$

Finally, if the Kac's trick is applied to the first two equations of the above equation, then a damped wave equation is obtained:

$$p_{tt} + \mu p_t = s^2 p_{xx} - \mu s((2q^+ - 1)p)_x. \tag{1.5}$$

Any of (1.1)–(1.5) will be used for a particular question as shown later.

Now we investigate the connections between the one-dimensional mesenchymal motion model and the well-known Goldstein–Kac model [8, 17]. We use the normalization condition $q^+ + q^- = 1$ to substitute $q^- = 1 - q^+$ into the first two equations of (1.1) and obtain

$$\begin{aligned} p_t^+ + s p_x^+ &= -\mu(1 - q^+)p^+ + \mu q^+ p^-, \\ p_t^- - s p_x^- &= \mu(1 - q^+)p^+ - \mu q^+ p^-. \end{aligned} \tag{1.6}$$

The model for the case of undirected tissue ($\kappa = 0$) possesses some very interesting properties. Undirected tissue fibers are symmetrical along their axes and both fiber directions are identical, which indicates that $q^+ = q^- = \frac{1}{2}$. Then the model (1.6) becomes the Goldstein–Kac model [8, 17]

$$\begin{aligned} p_t^+ + s p_x^+ &= \frac{\mu}{2}(p^- - p^+), \\ p_t^- - s p_x^- &= -\frac{\mu}{2}(p^- - p^+). \end{aligned} \tag{1.7}$$

The parabolic scaling for the Goldstein–Kac model, which leads to a parabolic equation, has been discussed in [9] and references therein.

For directed tissue, we define $\lambda^+ = \mu(1 - q^+), \lambda^- = \mu q^+$; then (1.6) is converted into

$$\begin{aligned} p_t^+ + s p_x^+ &= -\lambda^+ p^+ + \lambda^- p^-, \\ p_t^- - s p_x^- &= \lambda^+ p^+ - \lambda^- p^-, \end{aligned} \tag{1.8}$$

which is a modification of the Goldstein–Kac model. Extensions of the Goldstein–Kac model and local and global existence of the solution to the extended model have been extensively investigated in the literature [14, 15, 16]. The telegraph process of (1.8) has been briefly discussed recently by Erban and Othmer [5]. The results obtained in [14, 15, 16] can be applied to system (1.8) if the turning rates $\lambda^{\pm}(t,x)$ are given functions. The theory does not, however, apply to (1.1), since the turning rates are coupled with the $q^{\pm}$ equations.

In the next subsection, we will discuss stationary solutions for (1.1) based on the telegraph process examined in [12].

We supply the system (1.1) with the initial condition

$$p^{\pm}(0,x) = p_I^{\pm}(x), \quad q^{\pm}(0,x) = q_I^{\pm}(x), \quad x \in \Omega. \tag{1.9}$$

Due to the biological interest and normalization condition $q^+ + q^- = 1$, we make the following assumptions for the initial data and boundary conditions.

(ic) $p_I^{\pm} \geq 0$, $0 \leq q_I^+, q_I^- \leq 1$, and $q_I^+ + q_I^- = 1$. For undirected tissue, we assume that the initial data is symmetrical, i.e., $q_I^+ = q_I^- = \frac{1}{2}$.

Here we consider two types of boundary conditions.

(bc1) $\Omega = \mathbb{R}$ and $p_I^{\pm}(x), q_I^{\pm}(x)$ have compact support in Ω.

(bc2) $\Omega = [-l, l]$ and zero flux boundary condition, namely,

$$p^+(t, \pm l) = p^-(t, \pm l).$$

1.2. Stationary solutions. In this section we discuss stationary solutions of the mesenchymal transport model (1.1) using an argument similar to that in [6]. We first present a second-order telegraph equation which is derived from system (1.1). To this end, we add and subtract the first two equations of (1.1) and obtain equations for the total population $p = p^+ + p^-$ and the population flux $j = s(p^+ - p^-)$,

$$\begin{aligned} &p_t + j_x = 0, \\ &j_t + s^2 p_x = -\mu j + \mu(q^+ - q^-) sp, \end{aligned} \tag{1.10}$$

with initial conditions $p(0,x) = p_I(x)$ and $j(0,x) = j_I(x)$, where p_I and j_I are determined from the initial condition (1.9) of p^+ and p^-. We differentiate the first equation of (1.10) with respect to t and the second equation with respect to x. After that, we subtract the resulting equations and end up with a damped wave equation with drift term (see (1.5) or [12])

$$p_{tt} + \mu p_t + \mu(s\xi_q p)_x = s^2 p_{xx}, \tag{1.11}$$

where the drift velocity is given by the expectation of q denoted by $\xi_q = q^+ - q^-$. Equation (1.11) is a form of telegraph equation which describes electrical transmission in a telegraph cable when current leaks to the ground. A drift-diffusion equation can be approximated by taking the limit $\mu \to \infty, s \to \infty$ with diffusivity $D = s^2/\mu < \infty$ and drift velocity $s\xi_q < \infty$. The same drift-diffusion equation also can be obtained by multiscale methods (see [12]).

Suppose that equations (1.10) are defined in the interval $\Omega = [-l, l]$ and satisfy the boundary condition (bc2). In terms of cell population density, the zero flux boundary condition is equivalent to $p^+(\pm l) = p^-(\pm l) = \frac{1}{2}p(\pm l)$. We want to know under what conditions, if any, these equations have time-independent, space-dependent solutions for $p^{\pm}$. The steady state condition $j_x = 0$ of the first equation of (1.10) implies that

j is a constant, and the zero flux boundary condition $j(\pm l) = 0$ furthermore gives that $j = 0$. Consequently the second equation of (1.10) becomes

$$p_x = \frac{\mu}{s}(q^+ - q^-)p.$$

This is a first-order equation for p, whose solution can be easily found:

$$p(x) = p(-l)\exp\left(\frac{\mu}{s}\int_{-l}^{x}(q^+(y) - q^-(y))dy\right). \tag{1.12}$$

The vanishing flux $j = 0$ gives that $p^+ = p^-$, and hence

$$p^{\pm}(x) = \frac{p(-l)}{2}\exp\left(\frac{\mu}{s}\int_{-l}^{x}(q^+(y) - q^-(y))dy\right). \tag{1.13}$$

Note that the above integrals are bounded since q^+ and q^- are bounded by 1, which will be proved in section 3. From the above equations, one can see how the distribution of fiber orientations $q^{\pm}$ affects the distribution of cell populations p and $p^{\pm}$. In particular, if $\mu \neq 0$ and $q^+ \neq q^-$, then p and $p^{\pm}$ are nonconstants which correspond to the stationary solutions of the system (1.10).

Particularly in undirected tissue, $q^+ = q^- = \frac{1}{2}$ due to symmetry; then p and $p^{\pm}$ are constants and $p^+ = p^- = \frac{p(-l)}{2}$, which means that there is no aggregation of cells.

If $q^+ = 1, q^- = 0$, then

$$p^{\pm}(x) = \frac{p(-l)}{2}\exp\left(\frac{\mu}{s}(x + l)\right).$$

The cells accumulate at the end $x = l$. This is not surprising because all cells bias their movement to the right and eventually accumulate at the right end due to the zero flux boundary condition.

Similarly, if $q^+ = 0, q^- = 1$, then

$$p^{\pm}(x) = \frac{p(-l)}{2}\exp\left(-\frac{\mu}{s}(x + l)\right),$$

and $p^{\pm}$ attains the maximum at $x = -l$.

Therefore, here we identify a mechanism which can lead to aggregation, namely, $\mu \neq 0$, and the tissues are directed and cells have a probability 1 moving to the left or right.

2. Classification as hyperbolic system. In this section we show that the system (1.1) is degenerately hyperbolic, and we discuss shock solutions. To this end, we rewrite (1.1) in a matrix form

$$u_t + \Theta u_x = H(u), \tag{2.1}$$

where u, Θ, and $H(u)$ are defined as

$$u = \begin{bmatrix} p^+ \\ p^- \\ q^+ \\ q^- \end{bmatrix},\ \Theta = \begin{bmatrix} s & 0 & 0 & 0 \\ 0 & -s & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix},\ H(u) = \begin{bmatrix} -\mu p^+ + \mu q^+(p^+ + p^-) \\ -\mu p^- + \mu q^-(p^+ + p^-) \\ \kappa(p^+ - p^-)(q^- - q^+ + 1)q^+ \\ \kappa(p^+ - p^-)(q^- - q^+ - 1)q^- \end{bmatrix}.$$

The drift term is linear, and hence the system (2.1) cannot create shock solutions. The 4×4 matrix Θ has eigenvalues $\lambda_1 = -s < 0, \lambda_2 = \lambda_3 = 0, \lambda_4 = s$ satisfying $\lambda_1 < \lambda_2 = \lambda_3 < \lambda_4$ provided that $s > 0$. This implies that the system (2.1) and hence (1.1) are hyperbolic but not strictly hyperbolic since the two eigenvalues λ_2 and λ_3 are identical. The eigenvectors r_i corresponding to eigenvalues λ_i, $i = 1, 2, 3, 4$, are

$$r_1 = \begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}, \; r_2 = \begin{bmatrix} 0 \\ 0 \\ 1 \\ 0 \end{bmatrix}, \; r_3 = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 1 \end{bmatrix}, \; r_4 = \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \end{bmatrix}.$$

It can be verified that $\nabla\lambda_i(u) \cdot r_i(u) = 0$ for $i = 1, 2, 3, 4$, where $\nabla\lambda_i(u) \cdot r_i(u)$ means the directional derivative of the eigenvalues λ_i in the direction of the eigenfunction r_i. Hence all characteristic fields (λ_i, r_i) are linearly degenerate [2, 19]. Thus a shock which separates intersecting characteristics defining a discontinuity does not exist. However, the solution might contain contact discontinuities if data are discontinuous (see [2]).

The characteristic slopes are determined from the eigenvalues of the 4×4 matrix Θ in (2.1) by $\frac{dx}{dt} = \lambda_i$, which is never infinite, so the line $t = 0$ is nowhere tangent to a characteristic. Therefore, if initial data for p^+, p^-, q^+, and q^- are given along the line $t = 0$, the resulting Cauchy problem should be well-posed, as shown in the subsequent section.

3. Global existence. In this section, we will prove the global existence of solutions to the system (1.1) subject to the initial condition (ic) and boundary condition (bc1). For a bounded domain, the analysis for global existence will be a little bit more complicated than for an unbounded domain, due to the boundary conditions, and is left open here.

The system (1.1) is a coupling of two partial differential equations (PDEs) and two ODEs. To prove the global existence of solutions to the system (1.1), we first prove the nonnegativity of solutions.

LEMMA 3.1. *Let $p_I^\pm \geq 0$ and $q_I^\pm \geq 0$ with $q_I^+ + q_I^- = 1$. Assume that $p^\pm, q^\pm \in L^\infty(0, T; L^\infty(\mathbb{R}))$ is a solution to system* (1.1) *for some $T > 0$; then $p^\pm \geq 0$ and $0 \leq q^\pm(t, x) \leq 1$ with $q^+ + q^- = 1$.*

Proof. We first show that $q^+ + q^- = 1$. Toward this end, we consider $q = q^+ + q^-$ and $\xi = q^+ - q^-$. Then we add and subtract the third and fourth equations of (1.1) to obtain equations for q and ξ as follows:

$$\begin{aligned} q_t &= -\kappa(p^+ - p^-)(q - 1)\xi, \\ \xi_t &= \kappa(p^+ - p^-)(q - \xi^2), \end{aligned} \tag{3.1}$$

which can be rewritten in vector form

$$Q_t = -\kappa(p^+ - p^-)F(Q), \tag{3.2}$$

where

$$Q = \begin{pmatrix} q \\ \xi \end{pmatrix}, \qquad F(Q) = \begin{pmatrix} (q-1)\xi \\ \xi^2 - q \end{pmatrix}.$$

The initial data of the system (3.1) is given by

$$q_I = q_I^+ + q_I^- = 1, \qquad \xi_I = q_I^+ - q_I^-. \tag{3.3}$$

It is straightforward to verify that the vector field $F(Q) \in C^1(\mathbb{R}^2)$, and hence it is locally Lipschitz continuous with respect to Q for a given $p^{\pm} \in L^\infty(0,T;L^\infty(\mathbb{R}))$. Then the Cauchy problem (3.1), (3.3) has a unique solution by the fundamental existence-uniqueness theorem. On the other hand, it is trivial to check that $q = 1$ is a solution of the first equation of (3.1) satisfying initial condition (3.3). Hence the system (3.1), (3.3) has a unique solution $(q = 1, \xi)$, where ξ is determined by the equation

$$\xi_t = \kappa(q^+ - q^-)(1 - \xi^2), \qquad \xi_I = q_I^+ - q_I^-.$$

It is worthwhile to point out that we provide an idea here for proving that $q = 1$ and for proving the (local) existence of q and ξ given that $p^{\pm} \in L^\infty(0,T;L^\infty(\mathbb{R}))$. This idea will be used later without repeating this procedure.

We proceed to show that solutions $q^{\pm}$ preserve the positivity. Substituting $q^- = 1 - q^+$ into the third equation of (1.1), we have

$$q_t^+ = 2\kappa(p^+ - p^-)(1 - q^+)q^+. \tag{3.4}$$

There are three cases to consider.

Case 1. $q_I^+ = 1$. Then we conclude that $q^+ = 1$ is a solution to (3.4) with initial condition $q_I^+ = 1$. Since the right-hand side of (3.4) is locally Lipschitz continuous with respect to q^+, the solution of (3.4) is unique. Hence $q^+(t,x) = 1$ for all t, x.

Case 2. $q_I^+ = 0$. Using an argument similar to Case 1 we can show that $q^+(t,x) = 0$ is a unique solution to (3.4).

Case 3. $0 < q_I^+ < 1$. Then integrating (3.4) with respect to t from 0 to t, one has

$$\frac{q^+}{1-q^+} = \frac{q_I^+}{1-q_I^+} \exp\left(\int_0^t 2\kappa(p^+(\tau,\cdot) - p^-(\tau,\cdot))d\tau \right).$$

Due to $0 < q_I^+ < 1$, we have

$$\frac{q^+}{1-q^+} \geq 0.$$

It follows immediately from the above equality that $0 \leq q^+ \leq 1$. Combining Cases 1, 2, and 3, we get that $0 \leq q^+ \leq 1$ for $0 \leq q_I^+ \leq 1$. Applying $q^+ = 1 - q^-$ in the fourth equation of (1.1) and using the same approach, we can show that $0 \leq q^- \leq 1$.

Finally, we show the positivity of cell density $p^{\pm}(t,x)$. We use the theory of invariant principle from [11] for the hyperbolic random walk system to achieve this goal. To this end, we write the first two equations of the system (1.1) in a matrix form

$$\phi_t = G\phi + B\phi + \mathcal{F}(\phi), \tag{3.5}$$

where

$$\phi = \begin{pmatrix} p^+ \\ p^- \end{pmatrix}, \; G = \begin{pmatrix} -s\dfrac{\partial}{\partial x} & 0 \\ 0 & s\dfrac{\partial}{\partial x} \end{pmatrix}, \; B = \begin{pmatrix} -\mu & \mu \\ \mu & -\mu \end{pmatrix},$$

and

$$\mathcal{F}(\phi) = \begin{pmatrix} \mu q^+(p^+ + p^-) - \mu p^- \\ \mu q^-(p^+ + p^-) - \mu p^+ \end{pmatrix}.$$

Let $\Lambda = [0, \infty) \subset \mathbb{R}$. Then Λ is convex, and for each $z \in \partial\Lambda$, Λ has an outward normal vector. Moreover, define $\Sigma = \Lambda \times \Lambda$. Let $\phi \in \partial\Sigma$, and without loss of generality we assume that $\phi = (\vartheta, 0)$ with $\vartheta \geq 0$. Then for the outward normal vector $\eta(\phi) = (0, -1)$ of ϕ, we have

$$\eta(\phi) \cdot (B\phi + \mathcal{F}(\phi)) = -\mu q^- \vartheta \leq 0,$$

where we have used the positivity of q^-. Then by the theory in [11, Theorem 2], the set Σ is positively invariant for the system (3.5), which shows the positivity of $p^\pm$. The proof is completed. □

By Lemma 3.1, we obtain the following theorem.

THEOREM 3.2. *The set* $\{ (p^+, p^-, q^+, q^-) \mid p^\pm \geq 0, q^\pm \geq 0, q^+ + q^- = 1\}$ *is invariant to the system* (1.1) *provided that* $p^\pm, q^\pm \in L^\infty(0, T; L^\infty(\mathbb{R}))$ *for* $T > 0$.

Remark 1. For $p^+ > p^-$, the term $p^+ - p^- > 0$ and q^+ will increase while q^- decreases. Hence directionality is enhanced by the last two equations of (1.1).

Next, we prove the global existence of solutions to system (1.1) subject to initial condition (ic). Due to Theorem 3.2, we can reformulate the system (1.1) as

$$\begin{aligned} p_t^+ + sp_x^+ &= -\mu p^+ + \mu q^+ (p^+ + p^-), \\ p_t^- - sp_x^- &= -\mu p^- + \mu q^- (p^+ + p^-), \\ \xi_t &= \kappa (p^+ - p^-)(1 - \xi^2), \end{aligned} \tag{3.6}$$

where q^+ and q^- are given by

$$q^+ = \frac{1 + \xi}{2}, \qquad q^- = \frac{1 - \xi}{2}. \tag{3.7}$$

It is worthwhile to note that here ξ represents the expectation of fiber orientation in one dimension subject to the initial condition $\xi_I := \xi(0) = q_I^+ - q_I^-$. Furthermore from initial condition (ic), we have

$$-1 \leq \xi_I \leq 1.$$

We seek the global solutions of the system (3.6) in the following space:

$$\mathbb{X}(0, T) := \{(p^+, p^-, \xi) |\ p^\pm, \xi \in L^\infty(0, T; L^1 \cap L^\infty(\mathbb{R}))\}.$$

We first give the local existence of solutions for the system (3.6).

LEMMA 3.3 (local existence). *Let* $p_I^\pm, q_I^\pm(x) \geq 0$ *and* $q_I^+ + q_I^- = 1$. *Assume* $p_I^\pm \in L^1 \cap L^\infty(\mathbb{R})$ *and* $\xi_I \in L^1(\mathbb{R})$. *Then there exists a time* $T_0 > 0$ *such that the problem* (3.6) *with boundary condition* (bc1) *has a unique solution* $(p^+, p^-, \xi) \in \mathbb{X}(0, T_0)$ *satisfying* $-1 \leq \xi \leq 1$.

Proof. For short we denote $\eta = (p^+, p^-, \xi)^T$. The norm of the vector η is defined as

$$\begin{aligned} \|\eta\|_{L^\infty(\mathbb{R})} &= \max\{\|p^+\|_{L^\infty(\mathbb{R})}, \|p^-\|_{L^\infty(\mathbb{R})}, \|\xi\|_{L^\infty(\mathbb{R})}\}, \\ \|\eta\|_{L^1(\mathbb{R})} &= \max\{\|p^+\|_{L^1(\mathbb{R})}, \|p^-\|_{L^1(\mathbb{R})}, \|\xi\|_{L^1(\mathbb{R})}\}, \end{aligned}$$

Moreover, for the convenience of presentation we denote

$$\begin{aligned} f_1(p^+, p^-, \xi) &= -\mu p^+ + \frac{\mu}{2}(1 + \xi)(p^+ + p^-), \\ f_2(p^+, p^-, \xi) &= -\mu p^- + \frac{\mu}{2}(1 - \xi)(p^+ + p^-), \\ f_3(p^+, p^-, \xi) &= \kappa (p^+ - p^-)(1 - \xi^2). \end{aligned}$$

Clearly the function $f_i (i = 1, 2, 3)$ is differentiable with respect to its arguments and hence is locally Lipschitz continuous in any bounded subset of $L^1 \cap L^\infty(\mathbb{R})$.

It is straightforward to show that system (3.6) is strictly hyperbolic with three distinct uniform bounded eigenvalues λ_1, λ_2 satisfying $-s = \lambda_1 < \lambda_3 = 0 < \lambda_2 = s$. Then for each $i = 1, 2, 3$ and each point (t, x) in the $t - x$ plane, the characteristic equation of (3.6) defined by

$$\frac{d\mathbf{x}_i}{d\tau} = \lambda_i, \qquad \mathbf{x}_i(t) = x,$$

has a unique solution defined for all $t > 0$, describing the ith characteristic through point (t, x). We denote such a solution by $t \mapsto \mathbf{x}_i(\tau; t, x)$, where $\mathbf{x}_i(\tau; t, x) = x + \lambda_i(\tau - t)$ and in particular $\mathbf{x}_3(\tau; t, x) = x$ due to $\lambda_3 = 0$. Following the argument in [2], we define a set

$$\mathcal{D} = \{(t, x) \mid 0 \le t < \ell/s, -\ell + st \le x \le l - st\}.$$

Note that ℓ can be arbitrarily large since the domain is unbounded. Then for every $(t, x) \in \mathcal{D}$ and every $i \in \{1, 2\}$, the characteristic curve $\{(t, x_i(\tau; t, x))| \ 0 \le \tau \le t\}$ is entirely contained inside $\mathcal{D}$ with $\mathbf{x}_i(0; t, x) \in [-\ell, \ell]$. Such a set $\mathcal{D}$ is called a domain of determinacy (see [2]).

The system (3.6) has two independent characteristics. We integrate the first equation of (3.6) along the second characteristic curve $\mathbf{x}_2(\tau; t, x)$, the second equation of (3.6) along the first characteristic $\mathbf{x}_1(\tau; t, x)$, and the third equation along $\mathbf{x}_3(\tau; t, x) = x$. Then (3.6) can be rewritten as an ODE system

$$\begin{aligned} p^+_\tau &= -\mu p^+(\tau, \mathbf{x}_2(\tau)) + \mu q^+(\tau, \mathbf{x}_2(\tau))(p^+(t, \mathbf{x}_2(\tau)) + p^-(\tau, \mathbf{x}_2(\tau))), \\ p^-_\tau &= -\mu p^-(\tau, \mathbf{x}_1(\tau)) + \mu q^-(\tau, \mathbf{x}_1(\tau))(p^+(\tau, \mathbf{x}_1(\tau)) + p^-(\tau, \mathbf{x}_1(\tau))), \\ \xi_\tau &= \kappa(p^+(\tau, x) - p^-(\tau, x))(1 - \xi^2(\tau, x)), \end{aligned} \tag{3.8}$$

where $\mathbf{x}_i(\tau) := \mathbf{x}_i(\tau; t, x)$ for $i = 1, 2$ and $\mathbf{x}_3(\tau) = x$.

In vector form, (3.8) can be reformulated as

$$u_\tau = f(u), \qquad u \in \mathbb{R}^3,$$

where

$$f(u) = \begin{pmatrix} f_1(u(\tau, \mathbf{x}_2(\tau))) \\ f_2(u(\tau, \mathbf{x}_1(\tau))) \\ f_3(u(\tau, x)) \end{pmatrix}.$$

Note that $\mathbf{x}_i(\tau) \in \mathbb{R}$ $(i = 1, 2)$. Then $f(u)$ is locally Lipschitz continuous in any bounded subset of $L^1 \cap L^\infty(\mathbb{R})$, and hence the local existence follows from the fundamental theorem of existence and uniqueness (e.g., see [22]). Due to Theorem 3.2 and the definition of ξ, we have that $-1 \le \xi \le 1$. Then the proof is finished. ∎

We proceed to derive a priori estimates in order to get global existence.

LEMMA 3.4 (a priori estimates). *Let the assumptions in Lemma* 3.3 *hold and let* (p^+, p^-, ξ) *be the solution obtained in Lemma* 3.3. *Then for any* $0 < t \le T_0$, *there exist constants* $C > 0$ *and* $\widetilde{C} > 0$ *such that*

$$\|p^+(t)\|_{L^1 \cap L^\infty(\mathbb{R})} + \|p^-(t)\|_{L^1 \cap L^\infty(\mathbb{R})} + \|\xi(t)\|_{L^1 \cap L^\infty(\mathbb{R})} \le C \exp(\widetilde{C}T),$$

and $-1 \le \xi \le 1$, *where* $\|\cdot\|_{L^1 \cap L^\infty(\mathbb{R})} = \|\cdot\|_{L^1(\mathbb{R})} + \|\cdot\|_{L^\infty(\mathbb{R})}$.

Proof. For each $(t,x) \in \mathcal{D}$ and $\mathbf{x}_i(0;t,x) \in [-\ell,\ell]$, we integrate the first two equations of (3.8) with respect to τ over $[0,t]$ and obtain that

$$
\begin{aligned}
p^+(t,x) &= p^+(\mathbf{x}_2(0)) + \int_0^t f_1\big(p^+(\tau,\mathbf{x}_2(\tau)), p^-(\tau,\mathbf{x}_2(\tau)), \xi(\tau,\mathbf{x}_2(\tau))\big)d\tau,\\
p^-(t,x) &= p^-(\mathbf{x}_1(0)) + \int_0^t f_2\big(p^+(\tau,\mathbf{x}_1(\tau)), p^-(\tau,\mathbf{x}_1(\tau)), \xi(\tau,\mathbf{x}_1(\tau))\big)d\tau,\\
\xi(t,\xi) &= \xi_I + \int_0^t (p^+(\tau,x) - p^-(\tau,x))(1-\xi^2(\tau,x))d\tau.
\end{aligned} \tag{3.9}
$$

Using the terminology from [2], we call (p^+,p^-,ξ) a *broad* solution for the Cauchy problem of (3.8) if (p^+,p^-,ξ) satisfies (3.9), at almost every point $(t,x) \in \mathcal{D}$. In the circumstance of semigroup theory, the broad solution defined above is called a mild solution if the transport operator in (3.6) generates a continuous semigroup (see [13] for details).

Taking the L^∞-norm on both sides of (3.9), using the fact that f_i is Lipschitz continuous, and taking into account $f_i(0,0,\xi) = 0$ for $i = 1,2$, we infer that

$$
\begin{aligned}
&\|p^+(t)\|_{L^\infty(\mathbb{R})} + \|p^-(t)\|_{L^\infty(\mathbb{R})} + \|\xi(t)\|_{L^\infty(\mathbb{R})}\\
&\quad \le C_1 + C_2 \int_0^t (\|p^+(\tau)\|_{L^\infty(\mathbb{R})} + \|p^-(\tau)\|_{L^\infty(\mathbb{R})} + \|\xi(\tau)\|_{L^\infty(\mathbb{R})})d\tau,
\end{aligned}
$$

where C_1 is a constant such that $\|p_I^+\|_{L^\infty(\mathbb{R})} + \|p_I^-\|_{L^\infty(\mathbb{R})} + \|\xi_I\|_{L^\infty(\mathbb{R})} \le C_1$ and C_2 depends on the Lipschitz constants of the functions $f_i (i = 1,2,3)$ and the turning rate μ.

The application of Gronwall's inequality to the above inequality gives

$$
\|p^+(t)\|_{L^\infty(\mathbb{R})} + \|p^-(t)\|_{L^\infty(\mathbb{R})} + \|\xi(t)\|_{L^\infty(\mathbb{R})} \le C_1 \exp(C_2 t).
$$

Similarly, one can deduce that there exist constants $C_3, C_4 > 0$ such that

$$
\|p^+(t)\|_{L^1(\mathbb{R})} + \|p^-(t)\|_{L^1(\mathbb{R})} + \|\xi(t)\|_{L^1(\mathbb{R})} \le C_3 \exp(C_4 t).
$$

The last two inequalities imply the first conclusion of the lemma. The second conclusion $-1 \le \xi \le 1$ follows directly from Theorem 3.2 and the definition of ξ. ∎

By Lemmas 3.3 and 3.4, the existence theorem of global solutions is obtained.

THEOREM 3.5 (global existence). *Let initial condition* (ic) *hold. Assume* $p_I^\pm, \xi_I \in L^1 \cap L^\infty(\mathbb{R})$. *Then the problem* (3.6) *with boundary condition* (bc1) *has a unique global solution* $(p^+,p^-,\xi) \in \mathbb{X}(0,\infty)$ *satisfying* $-1 \le \xi \le 1$ *and* $p^\pm \ge 0$. *Consequently, the problem* (1.1) *with initial condition* (ic) *and boundary condition* (bc1) *has a unique global solution* (p^+,p^-,q^+,q^-) *such that* $p^\pm, q^\pm \in L^\infty(0,\infty; L^1 \cap L^\infty(\mathbb{R}))$ *with* $p^\pm \ge 0$ *and* $0 \le q^\pm \le 1$ *with* $q^+ + q^- = 1$.

Proof. We suppose that the maximal time $T_{\max}$ of existence for the solution of (3.6) is finite, namely, $T_{\max} < \infty$. From Lemma 3.4, we know that $-1 \le \xi \le 1$ for any $0 \le t \le T_{\max}$. Hence according to the well-known alternative results (e.g., see [20, 22]), one has that

$$
\lim_{t \to T_{\max}} \|p^+(t)\|_{L^1 \cap L^\infty(\mathbb{R})} = \infty \quad \text{or} \quad \lim_{t \to T_{\max}} \|p^-(t)\|_{L^1 \cap L^\infty(\mathbb{R})} = \infty. \tag{3.10}
$$

On the other hand, when $-1 \le \xi \le 1$, we have proven in Lemma 3.4 that for any $t \le T_{\max}$, it holds that

$$\|p^+(t)\|_{L^1\cap L^\infty(\mathbb{R})} + \|p^-(t)\|_{L^1\cap L^\infty(\mathbb{R})} \le C\exp(\widetilde{C}T_{\max}),$$

which contradicts (3.10) for $0 < T_{\max} < \infty$. This contradiction in turn shows that $T_{\max} = \infty$, and hence the global solution of (3.6) follows. Due to Theorem 3.1, the second conclusion is an immediate consequence. ∎

Remark 2. Mathematically, when cutting efficiency $\kappa = 0$, the system (1.1) becomes the one-dimensional mesenchymal motion model for undirected tissue (see [12]). Due to the assumption $q^+(t,x) = q^-(t,x)$ for undirected tissue, we obtain the following global existence theorem for the model associated with undirected tissue.

THEOREM 3.6. *Suppose* $\kappa = 0$. *Let initial condition* (ic) *hold and let* $q_I^+ = q_I^- = 1/2$. *Assume* $p_I^\pm \in L^1 \cap L^\infty(\mathbb{R})$. *Then there exists a unique global solution to system* (3.6) *such that* $(p^+, p^-, \xi) \in \mathbb{X}(0,\infty)$ *with* $\xi = 0$ *and* $p^\pm \ge 0$. *Hence there is a unique global solution* $(p^+, p^-, 1/2, 1/2)$ *to* (1.1) *with initial condition* (ic) *and boundary condition* (bc1) *such that* $p^\pm \in L^\infty(0,\infty; L^1 \cap L^\infty(\mathbb{R}))$ *satisfying* $p^\pm \ge 0$.

Since the functions on the right-hand side of (1.1) are continuously differentiable with respect to p^+, p^-, q^+, and q^-, by a theory for semilinear hyperbolic systems in [2] (see Theorem 3.6 in [2]), the broad solution of Cauchy problem (1.1) obtained in Theorem 3.5 is indeed a classical solution provided that the initial data (1.9) are continuously differentiable, namely, we have the following results.

THEOREM 3.7. *Let the assumptions in Theorem* 3.5 *hold. In addition, we assume that the initial data in* (1.9) *are continuously differentiable. Then the broad solution* $u : \mathcal{D} \to \mathbb{R}^2$ *obtained in Theorem* 3.5 *provides a classical solution. Moreover, if initial data in* (1.9) *are nonnegative, the solution is nonnegative. Its partial derivatives* u_t *and* u_x, *respectively, are broad solutions of the following semilinear system:*

$$\begin{aligned}(u_t)_t &= H_u u_t - \Theta\cdot(u_t)_x,\\ (u_x)_t &= H_u u_x - \Theta\cdot(u_x)_x,\end{aligned}$$

where u, H, *and* Θ *are defined as in section* 2 *and* H_u *denotes the derivative of* H *with respect to* u.

Proof. The proof is similar to the argument in [2]. We omit the details. ∎

4. Macroscopic limits. For the given fiber distribution $q^\pm(t,x)$, formal parabolic and hydrodynamic limits were derived in [12] for the mesenchymal motion models (1.1) in $n (n \ge 1)$ dimensions. In this section we rigorously carry out the parabolic limits for system (1.1) under some suitable assumptions.

To derive a limiting diffusion model for (1.1), we use the parabolic scaling of space and time, with $\bar{x} = \varepsilon x$ denoting a macroscopic space scale and $\bar{t} = \varepsilon^2 t$ a long time scale. Now we use the equivalent system (1.3) in a slightly different form using the flux $J = p^+ - p^-$. Upon substituting the above scaling variable into (1.3), and dropping the bar for convenience, we end up with the following equations:

$$\begin{aligned}\varepsilon^2\partial_t p_\varepsilon + \varepsilon s\partial_x J_\varepsilon &= 0,\\ \varepsilon^2\partial_t J_\varepsilon + \varepsilon s\partial_x p_\varepsilon &= \mu\xi_\varepsilon p_\varepsilon - \mu J_\varepsilon,\\ \varepsilon^2\partial_t\xi_\varepsilon &= \kappa(p_\varepsilon^+ - p_\varepsilon^-)(1-\xi_\varepsilon^2),\end{aligned} \tag{4.1}$$

with initial data $p_\varepsilon(0) = p_I = p_I^+ + p_I^-$, $J_\varepsilon(0) = J_I = p_I^+ - p_I^-$, $\xi_\varepsilon(0,\cdot) = q_I^+ - q_I^-$. The system (4.1) is equivalent to the following second-order damped hyperbolic equation (see (1.5) or [12]):

$$\frac{\varepsilon^4}{\mu}\partial_t^2 p_\varepsilon + \varepsilon^2 \partial_t p_\varepsilon + \varepsilon \partial_x(s\xi_\varepsilon p_\varepsilon) = \varepsilon^2 \frac{s^2}{\mu}\partial_x^2 p_\varepsilon, \tag{4.2}$$

which indicates that the drift term is a dominating term for ε small. As in [12], we assume that the expectation of fiber directions is small as to the order of ε:

$$\xi_q(t,x) = \lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\xi_\varepsilon\left(\frac{t}{\varepsilon^2},\frac{x}{\varepsilon}\right) = \lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\left[q^+\left(\frac{t}{\varepsilon^2},\frac{x}{\varepsilon}\right) - q^-\left(\frac{t}{\varepsilon^2},\frac{x}{\varepsilon}\right)\right] < \infty. \tag{4.3}$$

Under the above assumption, we formally obtain a drift-diffusion model with diffusion coefficient $\frac{s^2}{\mu}$ and drift velocity $s\xi_q$ from (4.2) by sending $\varepsilon \to 0$ (see [12]),

$$\partial_t p + \partial_x(s\xi_q p) = \frac{s^2}{\mu}\partial_x^2 p, \tag{4.4}$$

where p is the limit of p_ε as $\varepsilon \to 0$. The goal of this section is to show that the solution of (4.2) is convergent to the solution of (4.4) in the weak sense as $\varepsilon \to 0$. To proceed we give the definition of weak solutions that we address here.

DEFINITION 4.1. *We say that a function $P \in L^\infty([0,T];H^1(\mathbb{R}))$ is a weak solution of* (4.4) *if $P(t,x)$ satisfies the following:*

(a) *For any test function $\phi \in C_0^\infty([0,T)\times\mathbb{R})$, it holds that*

$$-\int_0^T\int_{\mathbb{R}} P\partial_t\phi dxdt - \int_0^T\int_{\mathbb{R}}(s\xi_q P)\partial_x\phi dxdt = \frac{s^2}{\mu}\int_0^T\int_{\mathbb{R}} P\partial_x^2\phi dxdt + \int_{\mathbb{R}} P(0)\phi(0)dx.$$

(b) $P(0) = p_I = p_I^+ + p_I^-$.

Next we establish the convergence properties of the solution $(p_\varepsilon, J_\varepsilon)$ as $\varepsilon \to 0$. It suffices to derive a uniform estimate for the solutions of system (4.1), which is given in the following lemma.

LEMMA 4.2. *Let $p_I^\pm \in H^1(\mathbb{R})$ and let the assumption* (4.3) *hold. Assume further that there exists a constant $C_1 > 0$, independent of ε, such that*

$$|\xi_\varepsilon|, |\partial_x\xi_\varepsilon| \le C_1\varepsilon. \tag{4.5}$$

Then there is a constant C_2, independent of ε, such that the solution $(p_\varepsilon, J_\varepsilon)$ of system (4.1) *satisfies, for any $0 \le t \le T$,*

$$\begin{aligned}&\|p_\varepsilon(t)\|_{H^1(\mathbb{R})} + \|J_\varepsilon(t)\|_{H^1(\mathbb{R})} + \|\varepsilon\partial_t p_\varepsilon\|_{L^2(\mathbb{R})}\\ &\quad\le C_2(C_1,\mu,T)(\|p_I\|_{H^1(\mathbb{R})} + \|J_I\|_{H^1(\mathbb{R})}),\end{aligned} \tag{4.6}$$

where the constant C_2 depends on C_1, μ, and T.

Proof. We use the energy method to prove the lemma. First, note that $p_\varepsilon(0) = p_I = p_I^+ + p_I^- \in H^1(\mathbb{R})$ and $J_\varepsilon(0) = J_I = p_I^+ - p_I^- \in H^1(\mathbb{R})$. Multiplying the first equation of (4.1) by p_ε and the second by J_ε, adding the resultant equations, and

integrating over $[0,t)\times\mathbb{R}$, we end up with the following inequality:

$$\begin{aligned}
&\frac{1}{2}\int_{\mathbb{R}}(|p_\varepsilon|^2+|J_\varepsilon|^2)dx+\int_0^t\int_{\mathbb{R}}\mu\varepsilon^{-2}|J_\varepsilon|^2dxd\tau\\
&\quad=\frac{1}{2}\int_{\mathbb{R}}(|p_I|^2+|J_I|^2)dx+\int_0^t\int_{\mathbb{R}}\mu\varepsilon^{-2}\xi_\varepsilon p_\varepsilon J_\varepsilon dxd\tau\\
&\quad\le\frac{1}{2}\int_{\mathbb{R}}(|p_I|^2+|J_I|^2)dx+\int_0^t\int_{\mathbb{R}}\mu C_1|\varepsilon^{-1}p_\varepsilon J_\varepsilon|dxd\tau,
\end{aligned}\tag{4.7}$$

where we have used the assumption (4.5). Applying Young's inequality $|C_1\varepsilon^{-1}p_\varepsilon J_\varepsilon|\le\frac{1}{2}(\varepsilon^{-2}|J_\varepsilon|^2+C_1^2|p_\varepsilon|^2)$ in (4.7), we have

$$\begin{aligned}
&\int_{\mathbb{R}}(|p_\varepsilon|^2+|J_\varepsilon|^2)dx+\int_0^t\int_{\mathbb{R}}\mu\varepsilon^{-2}|J_\varepsilon|^2dxd\tau\\
&\qquad\le\int_{\mathbb{R}}(|p_I|^2+|J_I|^2)dx+\mu C_1^2\int_0^t\int_{\mathbb{R}}|p_\varepsilon|^2dxd\tau.
\end{aligned}$$

By Gronwall's inequality, we immediately get an L^2-estimate of p_ε and J_ε independent of ε such that for $0\le t<T$,

$$\|p_\varepsilon\|^2_{L^2(\mathbb{R})}+\|J_\varepsilon\|^2_{L^2(\mathbb{R})}\le(\|p_I\|^2_{L^2(\mathbb{R})}+\|J_I\|^2_{L^2(\mathbb{R})})\exp(\mu C_1^2T).\tag{4.8}$$

Next we go to the higher order estimates. To this end, we multiply the first equation of (4.1) by $-\partial_x^2p_\varepsilon$ and the second by $-\partial_x^2J_\varepsilon$. Then we end up with the following estimates using the same procedure as that deriving (4.7):

$$\begin{aligned}
&\frac{1}{2}\int_{\mathbb{R}}(|\partial_xp_\varepsilon|^2+|\partial_xJ_\varepsilon|^2)dx+\int_0^t\int_{\mathbb{R}}\mu\varepsilon^{-2}|\partial_xJ_\varepsilon|^2dxd\tau\\
&=\frac{1}{2}\int_{\mathbb{R}}(|\partial_xp_I|^2+|\partial_xJ_I|^2)dx+\int_0^t\int_{\mathbb{R}}\mu\varepsilon^{-2}\partial_x(\xi_\varepsilon p_\varepsilon)\partial_xJ_\varepsilon dxd\tau\\
&\le\frac{1}{2}\int_{\mathbb{R}}(|\partial_xp_I|^2+|\partial_xJ_I|^2)dx+\int_0^t\int_{\mathbb{R}}\mu C_1\varepsilon^{-1}(|p_\varepsilon|+|\partial_xp_\varepsilon|)|\partial_xJ_\varepsilon|dxd\tau.
\end{aligned}$$

Using Young's inequality and the fact that $(a+b)^2\le2(a^2+b^2)$ for $a,b\in\mathbb{R}$, we deduce that

$$\begin{aligned}
&\int_0^t\int_{\mathbb{R}}\mu C_1\varepsilon^{-1}(|p_\varepsilon|+\partial_xp_\varepsilon|)|\partial_xJ_\varepsilon|dxd\tau\\
&\le\frac{1}{2}\int_0^t\int_{\mathbb{R}}\mu\varepsilon^{-2}|\partial_xJ_\varepsilon|^2dxd\tau+\frac{C_1^2}{2}\int_0^t\int_{\mathbb{R}}\mu(|p_\varepsilon|+|\partial_xp_\varepsilon|)^2dxd\tau\\
&\le\frac{1}{2}\int_0^t\int_{\mathbb{R}}\mu\varepsilon^{-2}|\partial_xJ_\varepsilon|^2dxd\tau+C_1^2\int_0^t\int_{\mathbb{R}}\mu|\partial_xp_\varepsilon|^2dxd\tau+C(T,p_I,J_I),
\end{aligned}\tag{4.9}$$

where (4.8) has been used and

$$C(T,p_I,J_I)=\mu C_1^2T(\|p_I\|^2_{L^2(\mathbb{R})}+\|J_I\|^2_{L^2(\mathbb{R})})\exp(\mu C_1^2T).$$

Now substituting (4.9) into (4.7) and applying Gronwall's inequality to the resulting inequality, we infer that

$$\begin{aligned}
&\|\partial_xp_\varepsilon\|^2_{L^2(\mathbb{R})}+\|\partial_xJ_\varepsilon\|^2_{L^2(\mathbb{R})}\\
&\quad\le C(T,p_I,J_I)(\|\partial_xp_I\|^2_{L^2(\mathbb{R})}+\|\partial_xJ_I\|^2_{L^2(\mathbb{R})})\exp(\mu C_1^2T)\\
&\quad\le\mu C_1^2T(\|p_I\|_{H^1(\mathbb{R})}+\|J_I\|_{H^1(\mathbb{R})})^2\exp(2\mu C_1^2T).
\end{aligned}\tag{4.10}$$

Furthermore, by (4.1) we have

$$\|\varepsilon\partial_t p_\varepsilon\|_{L^2(\mathbb{R})} = \|\partial_x J_\varepsilon\|_{L^2(\mathbb{R})}. \tag{4.11}$$

Then the combination of (4.8), (4.10), and (4.11) gives (4.6) and completes the proof. ∎

THEOREM 4.3. *Let the assumptions in Lemma* 4.2 *hold and let* $p_\varepsilon(0) = p_I = p_I^+ + p_I^-$. *Then as* $\varepsilon \to 0$, *the solutions* p_ε *of* (4.2) *converge to a limit function* p_0, *which is a weak solution of* (4.4) *such that* $p_0(t=0) = p_I$.

Proof. According to the energy estimates (4.6), we see that the solution sequence p_ε is uniformly bounded in $L^\infty_{\rm loc}([0,\infty); H^1(\mathbb{R}))$ and $\varepsilon\partial_t p_\varepsilon$ is uniformly bounded in $L^\infty_{\rm loc}([0,\infty); L^2(\mathbb{R}))$ for every $\varepsilon > 0$.

As a consequence of the Rellich–Kondrachov compactness theorem, there exist a subsequence of p_ε and $\varepsilon\partial_t p_\varepsilon$, still denoted by p_ε and $\varepsilon\partial_t p_\varepsilon$, and functions $p_0 \in L^\infty_{\rm loc}([0,\infty); H^2(\mathbb{R}))$ and $p_1 \in L^\infty_{\rm loc}([0,\infty); L^2(\mathbb{R}))$ such that

$$\begin{cases} p_\varepsilon \rightharpoonup p_0 \quad \text{weakly}^* \text{ in } \ L^\infty_{\rm loc}([0,\infty); H^1(\mathbb{R})), \\ \varepsilon\partial_t p_\varepsilon \rightharpoonup p_1 \quad \text{weakly}^* \text{ in } \ L^\infty_{\rm loc}([0,\infty); L^2(\mathbb{R})). \end{cases} \tag{4.12}$$

Next we show that p_0 is a weak solution of (4.4) subject to the given initial data. To this end we multiply (4.2) by a test function $\phi \in C_0^\infty([0,T)\times\mathbb{R})$ with $\phi(T) = 0$ and integrate the resultant equation to get

(4.13)

$$\begin{aligned} &\frac{\varepsilon^2}{\mu}\int_0^T\int_{\mathbb{R}} p_\varepsilon\partial_t^2\phi dxdt + \frac{\varepsilon^2}{\mu}\int_{\mathbb{R}}[p_\varepsilon(T)\partial_t\phi(T) - \partial_t p_\varepsilon(0)\phi(0)]dx \\ &\quad - \frac{\varepsilon^2}{\mu}\int_{\mathbb{R}}[\partial_t p_\varepsilon(T)\phi(T) - p_\varepsilon(0)\partial_t\phi(0)]dx - \int_0^T\int_{\mathbb{R}} p_\varepsilon\partial_t\phi dxdt + \int_{\mathbb{R}} p_\varepsilon(T)\phi(T)dx \\ &\quad - \frac{1}{\varepsilon}\int_0^T\int_{\mathbb{R}}(s\xi_\varepsilon p_\varepsilon)\partial_x\phi dxdt = \int_{\mathbb{R}} p_\varepsilon(0)\phi(0)dx + \frac{s^2}{\mu}\int_0^T\int_{\mathbb{R}} p_\varepsilon\partial_x^2\phi dxdt. \end{aligned}$$

Note that $p_\varepsilon(0) = p_I = p_I^+ + p_I^- \in H^1(\mathbb{R})$. Hence $J_\varepsilon(0) = J_I = p_I^+ - p_I^- \in H^1(\mathbb{R})$ and $\varepsilon\partial_t p_\varepsilon(0) = \partial_x J_\varepsilon(0) \in L^2(\mathbb{R})$ from (4.1). Thus the second, third, and fourth terms in (4.13) vanish as $\varepsilon \to 0$ by (4.12). Using assumption (4.3) and sending $\varepsilon \to 0$ in (4.13), we obtain from (4.12) that

$$\begin{aligned} &-\int_0^T\int_{\mathbb{R}} p_0\partial_t\phi dxdt - \int_0^T\int_{\mathbb{R}}(s\xi_q p_0)\partial_x\phi dxdt \\ &\quad = \int_{\mathbb{R}} p_I\phi(0)dx + \frac{s^2}{\mu}\int_0^T\int_{\mathbb{R}} p_0\partial_x^2\phi dxdt, \end{aligned} \tag{4.14}$$

which shows that p_0 is a weak solution of (4.4) satisfying the initial condition. ∎

Remark 3. It is worthwhile to note that assumptions (4.5) and (4.3) are automatically satisfied for the case of undirected tissue where $\xi_\varepsilon = 0$ (see also Remark 2). Then the limit equation for the case of undirected tissue is a pure diffusion equation without a drift term.

5. Traveling waves. Since the system (1.1) models the invasion of cells through tissue, it is of interest to look for traveling wave solutions for (1.1) and see what kinds

of movement patterns are used by cells for invasion. To this end, we first use the invariant of motion $q^+ + q^- = 1$ and consider the equivalent system (1.4).

We introduce the wave variable

$$z = x - ct,$$

where $c \geq 0$ denotes the wave speed. Then we can define the wave profile by

$$\begin{aligned} p(z) &= p(t,x) = p(x-ct), \\ j(z) &= j(t,x) = j(x-ct), \\ q^+(z) &= q^+(t,x) = q^+(x-ct). \end{aligned} \tag{5.1}$$

Substituting (5.1) into (1.4), we convert (1.4) into an ODE system as follows:

$$\begin{aligned} -cp_z + j_z &= 0, \\ -cj_z + s^2 p_z &= -\mu j + \mu s(2q^+ - 1)p, \\ -cq_z^+ &= \frac{2\kappa}{s} j(1-q^+)q^+. \end{aligned} \tag{5.2}$$

We prescribe the boundary conditions by

$$\begin{aligned} p(-\infty) &= p(+\infty) = 0, \\ j(-\infty) &= j(+\infty) = 0, \\ q^+(-\infty) &= q_l^+,\ q^+(+\infty) = q_r^+, \end{aligned} \tag{5.3}$$

where q_l^- and q_r^+ are constants and satisfy $0 \leq q_l^-, q_r^+ \leq 1$, and $q_l^- > q_r^+$. That is, we look for the traveling pulse wave for p and decreasing traveling front wave for q^+.

From (5.2) and the boundary conditions (5.3), we obtain an invariant of motion for j and p such that

$$j = cp. \tag{5.4}$$

Then the system (5.2) is reduced to a two-dimensional system by the substitution of (5.4) into (5.2):

$$\begin{aligned} (c^2 - s^2)p_z &= \mu p[c - s(2q^+ - 1)], \\ q_z^+ &= -\frac{2\kappa}{s} p(1-q^+)q^+. \end{aligned} \tag{5.5}$$

It is clear that (5.5) becomes a singular problem when $c = s$ and that this singular problem has no solution satisfying the boundary conditions (5.3). Indeed if $c = s$, then $q^+ = 1$ due to $\mu \neq 0$, which biologically means cells continuously move to the right without changing movement direction. Also, $q^+ = 1$ does not agree with the boundary conditions (5.3). Thus we assume $c \neq s$ hereafter. We will see later that biologically meaningful waves exist only for $c < s$. However, for now, we just assume $c \neq s$, and system (5.5) can be rewritten as

$$\begin{aligned} p_z &= -\alpha p[c - s(2q^+ - 1)], \\ q_z^+ &= -\beta p(1-q^+)q^+, \end{aligned} \tag{5.6}$$

where $\alpha = -\frac{\mu}{c^2 - s^2}$, $\beta = \frac{2\kappa}{s} > 0$. Due to the biological interest, we consider only nonnegative solutions where $p \geq 0$ and $0 \leq q^\pm \leq 1$. In fact, the nonnegativity of solutions to the system (5.6) with boundary conditions (5.3) can be analogously obtained by following the argument used in section 3. Therefore we are interested only in those heteroclinic orbits that remain nonnegative.

5.1. Phase plane analysis. System (5.6) has a continuum of steady states $(0,\theta)$ with $0 \le \theta \le 1$. The Jacobian matrix linearized about the steady state $(0,\theta)$ is

$$J_s = \begin{bmatrix} -\alpha\big(c - s(2\theta-1)\big) & 0 \\ -\beta(1-\theta)\theta & 0 \end{bmatrix}.$$

The eigenvalues of J_s are

$$\lambda_1 = -\alpha\big(c - s(2\theta-1)\big), \qquad \lambda_2 = 0. \tag{5.7}$$

The corresponding eigenvectors are

$$r_1 = \begin{bmatrix} \lambda_1 \\ -\beta(1-\theta)\theta \end{bmatrix}, \qquad r_2 = \begin{bmatrix} 0 \\ 1 \end{bmatrix}. \tag{5.8}$$

When $c \neq s$, we have two cases to consider corresponding to the sign of eigenvalue λ_1.

Case 1. If $c > s > 0$, then $\alpha < 0$. It is straightforward to check that $\lambda_1 > 0$, which indicates every steady state $(0,\theta)$ with $0 \le \theta \le 1$ is unstable, and consequently there is no nonnegative heteroclinic connection due to the lack of the stable manifold. We thus claim that $0 \le c < s$ is a necessary condition for the existence of a traveling wave and s is then a critical traveling speed. Thus we assume that $c < s$ hereafter.

Case 2. If $0 \le c < s$, then $\alpha > 0$. We first fix the traveling speed c and solve $c - s(2\theta^* - 1) = 0$ to get $\theta^* = \frac{c+s}{2s}$. Clearly we have that $0 < \theta^* < 1$. Furthermore the following properties hold:

$$\begin{aligned} &\theta < \theta^* \Rightarrow \lambda_1 < 0, \\ &\theta = \theta^* \Rightarrow \lambda_1 = 0, \\ &\theta > \theta^* \Rightarrow \lambda_1 > 0. \end{aligned} \tag{5.9}$$

Next, we show that there exists a pair of equilibria which generates a heteroclinic connection for each fixed c satisfying $0 \le c < s$. From (5.7), we see that every steady state $(0,\theta)$ of the system (5.6) with $0 \le \theta \le 1$ has two manifolds, one of which is a one-dimensional center manifold corresponding to zero eigenvalue λ_2. Since each center manifold is invariant under the flow of the system (5.6), and the set $\{(p,q^+) : p = 0, 0 \le q^+ \le 1\}$ consists of steady states only and hence is invariant, the center manifold is the q^+ axis where $0 \le q^+ \le 1$. So the heteroclinic connection is determined only by the stable and unstable manifolds corresponding to positive and negative eigenvalues given by λ_1, respectively. The existence of a heteroclinic orbit connecting the unstable manifold of one fixed point with the stable manifold of another fixed point corresponds to the existence of a traveling wave (heteroclinic orbit). Below we rigorously prove the existence of such a heteroclinic connection. Beyond this, we also shall prove the existence of a family of traveling waves since a continuum of steady state exists for the system (5.6). Before proceeding, we give a remark as follows.

Remark 4. The constants $q^+ = 0$ and $q^+ = 1$ are solutions of the second equation of (5.6), and furthermore it holds that

(a) if $q^+ = 0$, then $p \to +\infty$ as $z \to -\infty$;

(b) if $q^+ = 1$, then $p \to +\infty$ as $z \to +\infty$.

Therefore, neither the orbit $q^+ = 0$ nor $q^+ = 1$ can form a heteroclinic connection, although $\{q^+ = 1\}$ is the unstable manifold of the equilibrium $(0,1)$ and $\{q^+ = 0\}$ is the stable manifold of the equilibrium $(0,0)$. So hereafter we assume that $0 < q^+ < 1$ in order to obtain the existence of traveling waves.

5.2. Existence of traveling waves. To show that an unstable manifold can be connected by a stable manifold, we need to investigate the global structure of the original nonlinear system. Below we shall apply LaSalle's invariant principle (see [10, 18]) to study the asymptotic behavior of solutions of the system (5.6), which is described in the following lemma.

LEMMA 5.1. *Assume* $0 \le c < s$. *Let* (p, q^+) *be a solution of* (5.6) *subject to initial conditions* $p_I > 0$ *and* $0 < q_I^+ < 1$. *Then the* ω*-limit set of solutions to system* (5.6) *is contained in the following set:*

$$\mathbb{N} = \{(p, q^+)|\ p = 0,\ 0 < q^+ < \theta^*\}, \tag{5.10}$$

and the α*-limit set is contained in the set*

$$\mathbb{G} = \{(p, q^+)|\ p = 0,\ \theta^* < q^+ < 1\}, \tag{5.11}$$

where θ^* *is a constant between* 0 *and* 1 *determined by* $\theta^* = \frac{c+s}{2s}$.

Proof. Define a function $V(p, q^+)$ by $V(p, q^+) = q^+$. Then in the set $\{(p, q^+)|\ p \ge 0, 0 < q^+ < 1\}$, $V(p(z), q^+(z)) > 0$ and $\frac{dV}{dz} \le 0$ thanks to the second equation of (5.6). Given a number $L > 0$, we now define a set

$$\Omega_L = \{(p, q^+)|\ V(p, q^+) \le L, p > 0, 0 < q^+ < 1\}.$$

Since we restrict our attention to the case of $0 < q^+ < 1$, we let $0 < L < 1$. Hence it holds that

$$\Omega_L = \{(p, q^+)|\ p > 0, 0 < q^+ < L\}.$$

We now proceed to justify that the set Ω_L is bounded for given $0 < L < 1$. Toward this end, we divide the first equation of (5.6) by the second equation to obtain that

$$\frac{dp}{dq^+} = -\frac{\alpha(c+s)}{\beta}\frac{1}{(1-q^+)q^+} + \frac{2\alpha s}{\beta}\frac{1}{1-q^+}. \tag{5.12}$$

Integrating this equation and recovering α and β yield a first integral

$$p(q^+) = \frac{\mu s}{2\kappa}\left[\frac{\ln(1-q^+)}{c+s} - \frac{\ln q^+}{c-s}\right] + C, \tag{5.13}$$

where C is a constant of integration determined by the boundary condition of q^+ given in (5.3).

Then for any $q^+ = V(p, q^+) < L$, it is clear from (5.13) that p is bounded as a function of q^+. As a result, the set Ω_L defined above is bounded.

We now define another set

$$\mathbb{N}_1 = \left\{(p, q^+)\middle|\frac{dV}{dz} = 0, 0 < q^+ < 1\right\}.$$

From the second equation of (5.6), we know that

$$\frac{dV}{dz} = 0 \Longleftrightarrow p = 0 \ \text{ or } \ q^+ = 0 \ \text{ or } \ q^+ = 1.$$

Therefore, $\mathbb{N}_1 = \{(p, q^+)|\ p = 0, 0 < q^+ < 1\}$ and is invariant since it is composed of only steady states. With the help of LaSalle's invariant principle, the ω-limits set of

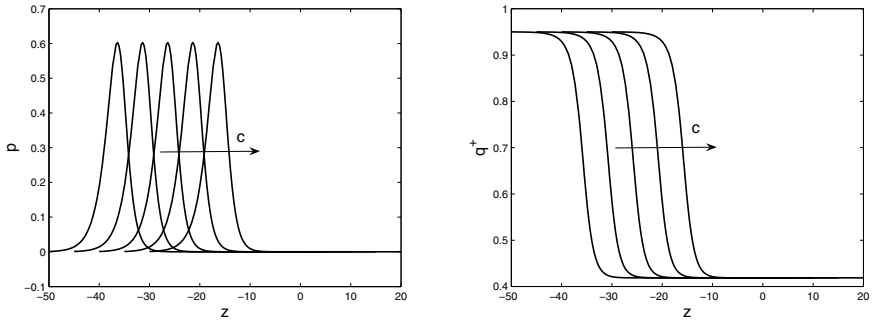

FIG. 1. *The traveling wave for the system* (5.6)*, where* $c = 1, s = 2, \mu = 2, \kappa = 1$*. The waves travel from the left to the right and* c *denotes the traveling speed and* $z = 0, 5, 10, 15, 20$*.*

any trajectories of the system starting in the set Ω_L for $0 < L < 1$ is contained in the set $\mathbb{N}_1$. Indeed, we can characterize the asymptotic behavior of the solution more precisely. From (5.9), we know that $\lambda_1 > 0$ for all $\theta^* < \theta < 1$. Then the equilibrium $(0, \theta)$ with $\theta^* < \theta < 1$ is unstable. If we define $\mathbb{N}_2 = \{(p, q^+)|\ p = 0, \theta^* < q^+ < 1\}$, then all solutions of the system (5.6) converge to the set as $z \to +\infty$:

$$\mathbb{N} = \mathbb{N}_1 \setminus \mathbb{N}_2 = \{(p, q^+)|\ p = 0,\ 0 < q^+ < \theta^*\}.$$

In a similar fashion, if we study the problem (5.6) backward on variable z, we can prove that all solutions of (5.6) converge to the set $\mathbb{G}$ when $z \to -\infty$, which completes the proof. □

Lemma 5.1 shows that any trajectory of the system (5.6) starting in a neighborhood of an equilibrium $(0, \theta)$ with $\theta^* < \theta < 1$ converges, as $z \to +\infty$, to another equilibrium $(0, \theta)$ with $0 < \theta < \theta^*$, which gives a nonnegative heteroclinic orbit (traveling wave) connecting these two equilibria. This heteroclinic orbit can be explicitly given by a level curve equation in the form of (5.13). It is worthwhile to point out that the traveling speed c can be 0 from our analysis, which corresponds to a standing wave. Hence we obtain the following existence theorem of traveling waves.

THEOREM 5.2. *Let us consider the system* (5.6) *given traveling speed* c *with* $0 \le c < s$ *and* $\theta^* = \frac{c+s}{2s}$*. Then for any equilibrium* $(0, c_1)$ *with* $\theta^* < c_1 < 1$ *there exists another equilibrium* $(0, c_2)$ *with* $0 < c_2 < \theta^*$ *such that there is a bounded, nonnegative, heteroclinic orbit connecting* $(0, c_1)$ *to* $(0, c_2)$*. That is, there exists a traveling solution* (p, q^+) *of the system* (5.6) *connecting two equilibria. Particularly, the system* (5.6) *admits a standing wave for* $c = 0$*.*

Notice that in Lemma 5.3 we will give an explicit relation between c_1 and c_2.

An example of traveling solution (p, q^+) for system (5.6) is numerically plotted in Figure 1. From the definition of p and the relation (5.4), we can derive that

$$p^+ = \frac{s + c}{2s} p, \qquad p^- = \frac{s - c}{2s} p. \tag{5.14}$$

In addition to the relation

$$q^- = 1 - q^+, \qquad j = cp, \tag{5.15}$$

we find the traveling waves for p^+, p^-, q^-, and j in terms of p and q^+, as given above. The plots of the traveling structures of these quantities are given in Figure 2.

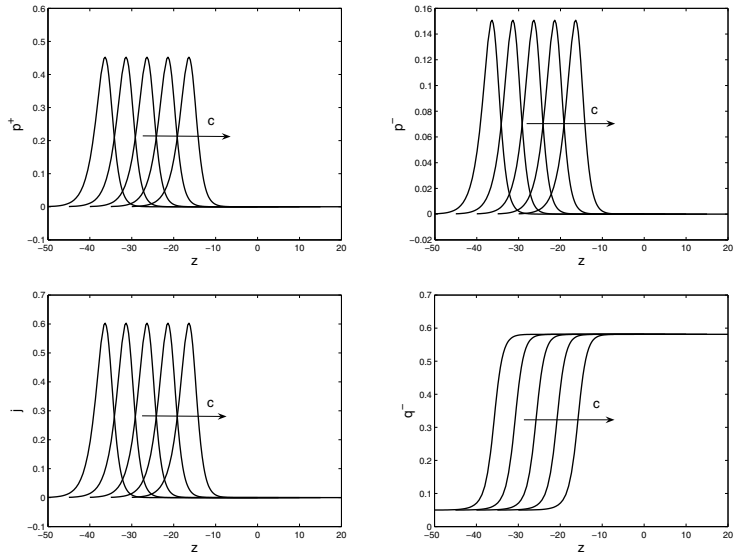

FIG. 2. *Numerical illustration of traveling waves for p^+, p^-, j, and q^-, where $c = 1, s = 2, \mu = 2, \kappa = 1$. The waves shift from the left to the right and c denotes the traveling speed and $z = 0, 5, 10, 15, 20$.*

A plot of all these quantities in a coordinate system is given in Figure 3 from which the transition properties between cell movement direction and fiber orientation are clearly indicated.

From the first equation of (1.4), we know that the total mass of cells is conserved and so traveling pulse waves are expected, as we found analytically and numerically above. The numerical simulation for p in Figure 1 indicates that individual cells can move to the left or the right, but the whole cell group will move to the right continuously. However, when the waves travel through, the fiber orientations are modified by cells, and alignment to cell movement direction is enhanced, which is indicated by the numerical simulation for q^+ in Figure 3.

5.3. Family of traveling waves. Note that for each left state q_l^+ with $\theta^* < q_l^+ < 1$ we find a corresponding right state $(0, q_r^+)$ connecting to $(0, q_l^+)$ which gives a traveling wave. Here we give an explicit formula which relates q_l^+ and q_r^+.

LEMMA 5.3. *Given a speed c satisfying $0 \le c < s$, the left and right equilibria $(0, q_l^+)$ and $(0, q_r^+)$ are related as*

$$\left(\frac{1-q_r^+}{1-q_l^+}\right)^{s-c} = \left(\frac{q_l^+}{q_r^+}\right)^{s+c}, \qquad 0 \le c < s. \tag{5.16}$$

Proof. An explicit heteroclinic connection has been given by (5.13). By Lemma 5.1, we infer that $p(q_l^+) = p(q_r^+) = 0$. Applying this condition to (5.13), one has that

$$\frac{\ln(1-q_l^+)}{c+s} - \frac{\ln q_l^+}{c-s} = \frac{\ln(1-q_r^+)}{c+s} - \frac{\ln q_r^+}{c-s}.$$

Rearranging the above identity yields (5.16). ∎

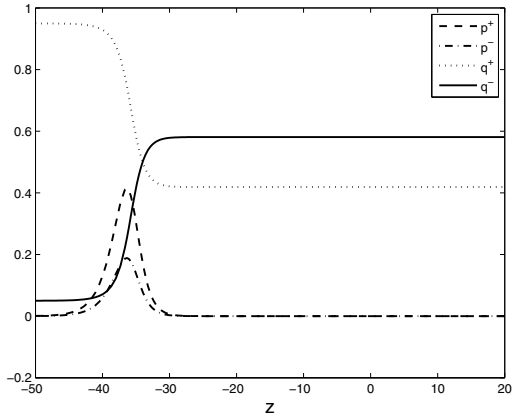

FIG. 3. *A plot of traveling solutions of system* (1.1) *in a coordinate system, where* $c = 1, s = 2, \mu = 2, \kappa = 1$, *and* $z = 0, 5, 10, 15, 20$.

By Lemma 5.3 we identify a family of heteroclinic orbits as shown in Figure 4.

From (5.13) we see that p is bounded as a function of q^+ if $0 < q^+ < 1$. It would be of interest also to find the upper bound for each orbit and to see how the upper bound varies with respect to the right/left states of q^+. Indeed, by (5.12), we get a unique critical point $q^+ = \theta^*$ such that $\frac{dp}{dq^+}|_{q^+=\theta^*} = 0$. The second derivative of p with respect to q^+ is

$$\frac{d^2p}{dq^{+2}} = -\frac{\mu s}{2\kappa}\left[\frac{1}{(c+s)(1-q^+)^2} + \frac{1}{(s-c)q^{+2}}\right], \tag{5.17}$$

Noting that $0 \le c < s$, it is easy to verify that $\frac{d^2p}{dq^{+2}} < 0$ at $q^+ = \theta^*$. Moreover, we know that $p(q_l^+) = p(q_r^+) = 0$. Hence p attains the maximal value at $q^+ = \theta^*$ given by

$$p_{\max} = \frac{\mu s}{2\kappa}\left[\frac{\ln(1-\theta^*)}{c+s} - \frac{\ln\theta^*}{c-s}\right] + \sigma, \tag{5.18}$$

where

$$\sigma = -\frac{\mu s}{2\kappa}\left[\frac{\ln(1-q_l^+)}{c+s} - \frac{\ln q_l^+}{c-s}\right], \qquad \theta^* = \frac{c+s}{2s}. \tag{5.19}$$

Remark 5. From the above equation, we know that the upper bound $p_{\max}$ of p depends on the left states q_l^+ of q. Also, we can easily verify that upper bound $p_{\max}$ increases with respect to $q_l^+ > \theta^*$ (see Figure 4).

Remark 6. The results obtained above for traveling waves are valid only for the case of directed tissue. For undirected tissue, traveling waves with $c < s$ do not exist. Indeed, in the undirected case, we know that $q^+ = q^- = \frac{1}{2}$, and the system (5.6) is reduced to a scalar equation

$$p_z = \frac{\mu^2}{c^2 - s^2} cp. \tag{5.20}$$

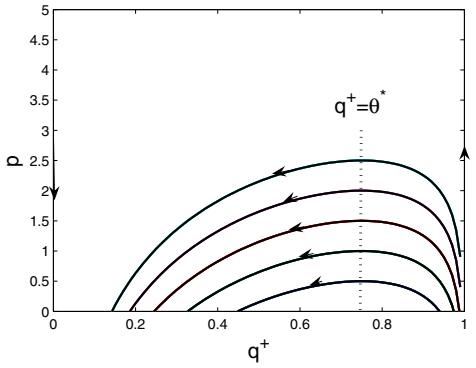

FIG. 4. *The illustration of a family of heteroclinic orbits for the system* (5.6)*, where* $c = 1, s = 2, \mu = 2, \kappa = 1$*, and* $\theta^* = 0.75$*. The arrow denotes the orientation of trajectories to the system* (5.6)*.*

Clearly, equation (5.20) has no solution satisfying boundary conditions (5.3).

Remark 7. The situation of nested heteroclinic orbits which correspond to traveling waves is also known from other biological applications, for example, for an epidemic with moving infectives (see [24]).

6. Conclusions. In this study, we analyze the one-dimensional mesenchymal motion model proposed by Hillen [12]. We establish the global existence of classical solutions for both cases of directed and undirected tissue. Particularly, we show that the model of undirected tissue ($\kappa = 0$) has a constant solution for fiber orientation distribution such that $q(t, x, +s) = q(t, x, -s) = \frac{1}{2}$, which means cells have no preference in choosing a particular movement direction and they have equal probability of moving to the right or left. We discuss the existence of inhomogeneous steady states for the case of directed tissue and identify a mechanism of cell aggregation. We rigorously show the convergence of macroscopic limits of the model; i.e., the solution of the mesoscopic model converges to that of the corresponding macroscopic continuum model. Moreover, we study the traveling wave solutions and establish the existence of a traveling pulse in total cell population $p(t, x)$ and traveling front waves in fiber orientation distribution $q^{\pm}(t, x)$. The standing wave ($c = 0$) is admitted in our analysis. This is not surprising considering the fact that cells can move in two directions (left and right) and two traveling waves with opposite direction can eliminate each other to result in a standing wave. All our results are fairly consistent with the biological relevance discussed in paper [12].

The one-dimensional model appears artificial when compared to the real three-dimensional process of cell movement in fiber tissue. The benefit of studying the one-dimensional model in detail is twofold. First of all, this model and its properties give good intuition into mechanisms that might be important in the higher dimensional case. For example, the existence of nonhomogeneous steady states will also be expected for higher dimensional models. Also, the model with directed fibers seems to have a richer behavior. Essentially we identify three distinctions between directed and undirected tissue which are hard to see from the three-dimensional model. We show that for the one-dimensional model, there is no aggregation for undirected tissue, whereas aggregation is possible for directed tissue. In addition, for the macroscopic limit, there are no constraints of convergence for the model of undirected tissue. However, some suitable restriction is needed for directed tissue. Moreover, the model of

undirected tissue does not admit traveling waves and the model of directed tissue does. All these distinctions might be true for higher dimensional models.

Second, the model considered here can be used to describe cell movement in highly aligned tissue. In fact, many tissues show a predominant orientation; for example, the rapid spread of glioma cells across the *corpus callosum* results from the migration of individual glioma cells along the highly aligned white matter tracks inside brain tissue [1]. F-actin filaments in vascular smooth muscle cells (VSMCs) are highly aligned on textured polydimethylsiloxane (PDMS) scaffolds [23], and skeletal muscles have a highly organized structure which consists of parallel bundles of multinucleated myotubes that are formed by the fusion of myoblast satellite cells [25]. The model studied here can be used to describe spread and propagation of cells along those aligned tissues. In that case, the traveling pulse waves shown in section 5 correspond to an application of a "comb" to the tissue which is aligned positively or negatively in a common direction. If a brush is applied upstream, say, the fibers will be flipped and higher alignment to the right results, we call these waves *alignment waves*; see also our simulations in Figures 1–3.

For the application of these models to cancer invasion through collagen tissue, the undirected formalism is important. The result of no traveling pulses for that case does not preclude invasions. It precludes only invasion in a self-similar fashion. It is still possible that cells invade new areas, in particular if nonlinear proliferation terms are added. The existence of traveling waves under incorporation of cell proliferation is an interesting open question that comes out of the research done here.

Mathematically, the higher dimensional mesenchymal motion models show significant differences when compared to the one-dimensional case. In one dimension, fiber orientation $q(t, x, \theta)$ has only two directions and hence is bounded due to the normalization condition $q^+ + q^- = 1$. However, in higher dimensions, fibers have infinitely many directions, and highly aligned tissue corresponds to $q(t, x, \theta)$ being a Dirac delta function along that direction. Hence the function spaces have to be chosen to include nonintegrable distributions, and standard L^2 or L^∞ methods do not apply. In a forthcoming paper [13], we will study the existence of solutions for the high dimensional mesenchymal motion models in a Banach space of measurable functions using semigroup theory. If the existence theory stands, we can look into the interesting network formation dynamics, which were found numerically in Painter [21].

Acknowledgments. We thank Dr. D. Wrzosek and Dr. K. P. Hadeler for stimulating discussions and suggestions. We also thank an anonymous referee for remarks that helped to improve the manuscript.

REFERENCES

[1] A. C. Bellail, S. B. Hunter, D. J. Brat, C. Tan, and E. G. Van Meir, *Microregional extracellular matrix heterogeneity in brain modulates glioma cell invasion*, Int. J. Biochem. Cell Biol., 36 (2004), pp. 1046–1069.

[2] A. Bressan, *Hyperbolic System of Conservation Laws: The One-Dimensional Cauchy Problem*, Oxford University Press, New York, 2001.

[3] A. Chauviere, T. Hillen, and L. Preziosi, *Modeling cell movement in anisotropic and heterogeneous network tissues*, Networks and Heterogeneous Media, 2 (2007), pp. 333–357.

[4] A. Chauviere, T. Hillen, and L. Preziosi, *Modeling the motion of a cell population in the extracellular matrix*, Discrete Contin. Dyn. Syst., Dynamical Systems and Differential Equations. Proceedings of the 6th AIMS International Conference, Suppl., (2007), pp. 250–259.

[5] R. Erban and H. Othmer, *From signal transduction to spatial pattern formation in E. coli: A paradigm for multiscale modeling in biology*, Multiscale Model. Simul., 3 (2005), pp. 362–394.

[6] R. Erban and H. Othmer, *Taxis equations for amoeboid cells*, J. Math. Biol., 54 (2007), pp. 847–885.

[7] P. Friedl and E. B. Bröcker, *The biology of cell locomotion within three dimensional extracellular matrix*, Cell. Mol. Life Sci., 57 (2000), pp. 41–64.

[8] S. Goldstein, *On diffusion by discontinuous movements and the telegraph equation*, Quart. J. Mech. Appl. Math., 4 (1951), pp. 129–156.

[9] K. P. Hadeler, *Reaction transport systems in biological modelling*, in Mathematics Inspired by Biology, Lecture Notes in Math. 1714, V. Capasso and O. Diekmann, eds., Springer-Verlag, Heidelberg, 1999, pp. 95–150.

[10] J. P. Hespanha, *Uniform stability of switched linear systems: Extensions of LaSalle's invariant principle*, IEEE Trans. Automat. Control, 49 (2004), pp. 470–482.

[11] T. Hillen, *Invariant principle for hyperbolic random walk systems*, J. Math. Anal. Appl., 210 (1997), pp. 360–374.

[12] T. Hillen, *M^5 mesoscopic and macroscopic models for mesenchymal motion*, J. Math. Biol., 53 (2006), pp. 585–616.

[13] T. Hillen, P. Hinow, and Z. A. Wang, *Measure-valued solutions for a kinetic model of cell movement in network tissues,* submitted.

[14] T. Hillen, C. Rohde, and F. Lutscher, *Existence of weak solutions for a hyperbolic model for chemosensitive movement*, J. Math. Anal. Appl., 260 (2001), pp. 173–199.

[15] T. Hillen and A. Stevens, *Hyperbolic models for chemotaxis in 1-D*, Nonlinear Anal. Real World Appl., 1 (2000), pp. 409–433.

[16] H. J. Hwang, K. Kang, and A. Stevens, *Global existence of classical solutions for a hyperbolic chemotaxis model and its parabolic limit*, Indiana Univ. Math. J., 55 (2006), pp. 289–316.

[17] M. Kac, *A stochastic model related to the telegrapher's equation*, Rocky Mountain J. Math., 4 (1956), pp. 497–509.

[18] J. P. LaSalle, *The Stability of Dynamical Systems*, CBMS-NSF Reg. Conf. Ser. Appl. Math. 25, SIAM, Philadelphia, 1976.

[19] P. G. LeFloch, *Hyperbolic Systems of Conservation Laws: The Theory of Classical and Nonclassical Shock Waves*, Lectures in Math., ETH Zürich, Birkhäuser Verlag, Basel, 2002.

[20] H. Matano, *Convergence of solutions of one-dimensional semilinear parabolic equations*, J. Math. Kyoto Univ., 18 (1978), pp. 221–227.

[21] K. Painter, *Modelling cell migration strategies in the extracellular matrix*, J. Math. Biol., 2008 (electronic).

[22] J. C. Robinson, *Infinite-Dimensional Dynamical Systems: An Introduction to Dissipative Parabolic PDEs and the Theory of Global Attractors*, Cambridge University Press, Cambridge, UK, 2001.

[23] S. Sarkar, D. Manisha, P. Rourke, T. A. Desai, and J. Y. Wong, *Vascular tissue engineering: Microtextured scaffold templates to control organization of vascular smooth muscle cells and extracellular matrix*, Acta Biomater., 2005, pp. 93–100.

[24] N. Shigesada and K. Kawasaki, *Biological Invasions: Theory and Practice*, Oxford University Press, Oxford, UK, 1997.

[25] P. M. Wigmore and G. F. Dunglison, *The generation of fiber diversity during myogenesis*, J. Dev. Biol., 42 (1998), pp. 117–25.