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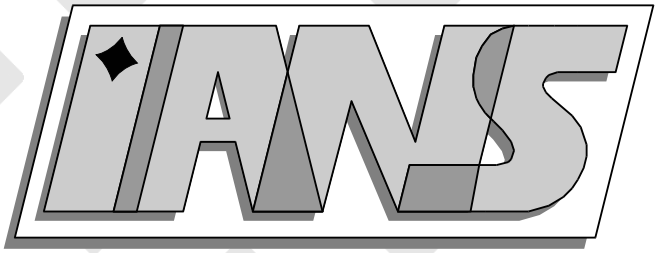

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A MATHEMATICAL MODEL FOR MESENCHYMAL AND CHEMOSENSITIVE CELL DYNAMICS IN TISSUE NETWORKS

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1. Introduction

According to National Cancer Institute SEER data for 1988 – 2001 distant metastasis in breast cancer depreciates the 5-year survival of patients with localised disease from 93% to 18.7% (see [26], Table 13.8). Although less than 0.05% of the circulating tumour cells are able to become stable metastases (see [14]), the by metastasis significantly reduced survival rates of cancer patients demonstrate the necessity of efficient methods of treatment (metastasis occurred in ≈11.1% of total breast cancer cases, in ≈4.2 % even distant metastasis, see [26], Table 13.8). The metastatic cascade comprises cell detachment from the primary tumour, migration through local tissue, intravasation and transit through a blood or lymph vessel. After capillary bed arrest near an organ that supports the cells' survival, extravasation, local crawling and invasion, attachment and further proliferation follow (see [14]). In this paper we focus on the stage of migration through the extracellular matrix (ECM) to a blood or lymph vessel.

The ECM is a dense network of proteins consisting amongst others of collagen, elastin, fibronectin and laminin. Collagen provides structural support whereas elastin gives flexibility to tissues. The principal function of the extracellular matrix protein fibronectin is to connect cells to matrices that contain fibrillar collagen. Laminin provides an adhesive substrate for cells and resists tensile forces in tissues (see [25]).

The locomotion process of cells like fibroblasts, leukocytes and tumour cells is divided into three steps. First, cell protrusions (filopodia) are built at the front and the leading pseudopod adheres to the ECM network. Afterwards, the cell skeleton contracts and detachment at the trailing edge follows (see [13]). This movement can be supported or impeded by the ECM. On the one hand cells can only move along matrix fibres (contact guidance) and on the other hand a very dense network is a hindrance for the cells. There are two different cell migration strategies to overcome these matrix barriers, namely amoeboid and mesenchymal movement. Amoeboid migration results from adaptation and alignment of the spherical cell body along preformed fibre strands. To cross regions of narrow space the cells squeeze through existing matrix gaps. Amoeboid movement has no impact on the network structure. In contrast, mesenchymally moving cells have a less flexible spindle-shaped cell body. They exert traction forces on the fibres and bundle fibre strands towards their leading edge. To enlarge the gaps in the network they produce proteases (protein degrading enzymes like matrix metalloproteases). This happens especially at the leading edge if network fibres lie transverse to the cell orientation between the filopodia. This way cells create a tunnel-like matrix defect at their trailing edge (see [30]). The solute network fragments, produced by protease, act chemotactically on the tumour cells (see [1]). As this concentration gradient is reverse to the migration direction the network fragments might slow down the invasion process (see [24]). In order to reach distant organs, the cells have to find the way to a blood or lymph vessel. In [18] it was shown that macrophages situated near blood vessels produce the epidermal growth factor (EGF), that is a chemoattractant for tumour cells (see also [29] and [9]).

We mention here some of the multiple approaches to model tumour invasion and interactions between cells and the ECM. In [6], Chaplain and Lolas built a macroscopic model to describe cancer invasion and the urokinase Plasminogen Activator (uPA) system, including chemotaxis towards the uPA protease, haptotaxis and proteolysis in an isotropic environment. Perumpanani et al. considered in their isotropic model for tumour invasion that the solubilised fibronectin emerging from proteolysis acts as chemoattractant for the cells and can diminish the invasion velocity (see [24]). A tumour invasion model based on haptotaxis was developed by Marchant et al. in [22]. In this model the invasion speed dependency on the ECM density is treated as biphasic behaviour.

In 1986, Dembo and Harlow used the theory of multicomponent fluids described in [11] to model contractile networks and interpenetrating reactive flow (see [10]). Lubkin and Jackson used this in [20] to model the growth of a tumour and capsule formation. Also based on [10], Barocas and

Tranquillo developed a biphasic theory for cell-fibril mechanical interactions in tissue-equivalent gels (see [4]). In [5], they extended their theory to an anisotropic network, including cell traction forces on the network, fibril alignment subsequent to the macroscopic deformation and cell contact guidance. Shreiber et al. combined this anisotropic biphasic theory (AB-Theory) with a persistent random walk model for single cells (see [27]).

Recently, there have been approaches to model mesenchymal cell dynamics by mesoscopic and thereof derived macroscopic models based on transport equations for correlated random walk. Hillen presented a model comprising contact guidance and proteolysis. The latter depends on the angle between the cell velocity and fibre orientation (see [16]). In [7, 8], Chauviere et al. extended this model by cell-cell interactions and chemotaxis. Painter used models based on [16] to examine amoeboid and mesenchymal movement (see [23]).

The model for mesenchymal and chemotactic movement developed in this paper is based on the anisotropic biphasic theory of Barocas and Tranquillo [5]. We extend the model by chemotaxis and haptotaxis. Additionally we add proteolysis in a way that is motivated by [16]. A beneficial property of the continuum mechanical approach is that the cell traction forces on the network are easily included in the momentum balance equation. The aim of this work is to describe the invasion of tumour cells in metastasis.

The paper is organised as follows. In the next section we derive a continuum mechanical model for mesenchymal motion under chemotactic influences which is summarised in the third section. In the fourth section we nondimensionalise this model and simplify it by assuming that the inertial forces are negligible. A model for amoeboid movement as special case of this model is shown in section five. In the last section, we adapt the model to tumour metastasis by choosing suitable boundary conditions.

2. The mathematical modelling

The model is based on the following assumptions (the first eight are mainly the same as in [5]):

(1) The extracellular matrix consists of two interpenetrating continuous phases, namely the network and the tissue fluid (interstitial solution), and can be modelled as a multicomponent fluid.
(2) The cell density is treated as part of the network phase and the protease and chemoattractant densities are treated as parts of the solution phase.
(3) The intrinsic phase densities of network and solution are constant and nearly equal.
(4) Inertial forces are negligible.
(5) The two phases exhibit interphase frictional drag forces. The network can be modelled as a viscoelastic fluid (Maxwell fluid) and the viscosity of the solution phase can be neglected.
(6) Cells exert traction forces on the network, depending on the cell orientation.
(7) Network fibres are undirected and reorient due to the macroscopic deformation.
(8) Cells reorient and migrate preferentially along network fibres (contact guidance). The orientation is independent of the transport velocity.
(9) Cell dynamics depend on haptotaxis and chemotaxis. The network density gradient is a good approximation for the gradient of adhesion molecules in the matrix.
(10) The cell flux depends on the network density as cells can neither move fast at very low nor at very high densities.
(11) The production of protease depends on the angle between cell orientation and network fibres.

We begin with deriving the mass and momentum conservation equations for the two phases. For details about the averaging process in modelling multicomponent fluids we refer to [11]. Below all variables with index n or s relate to the fibre network or interstitial solution, respectively. The densities of the network and solution are denoted by $\tilde{\rho}_n = \tilde{\rho}_n(t,x) = \theta_n(t,x)\rho_n \in \mathbb{R}_+$ and $\tilde{\rho}_s = \tilde{\rho}_s(t,x) = \theta_s(t,x)\rho_s \in \mathbb{R}_+$, where t and x represent time and space in the $(d+1)$-dimensional time-space-cylinder $[0,T] \times \overline{\Omega} \subset \mathbb{R}_+ \times \mathbb{R}^d$ for a bounded domain Ω. As the network and tissue fluid fill the whole volume the volume fractions $\theta_n = \theta_n(t,x) \in \mathbb{R}_+$ and $\theta_s = \theta_s(t,x) \in \mathbb{R}_+$ satisfy

Symbol	Description	Approx. size	In equation
G	shear modulus	$11850\,\frac{\text{dyne}}{\text{cm}^2}$	(8)
μ	shear viscosity	$1.24\times10^{8}\,\frac{\text{dyne s}}{\text{cm}^2}$	(8)
ν	Poisson ratio	0.2	(8)
ϕ_{ns}	drag coefficient	$6.4\times10^{6}\,\frac{\text{dyne s}}{\text{cm}^4}$	(6), (20), (21)
τ	cell traction parameter	$0.015\,\frac{\text{dyne cm}}{\text{cell}}$	(20)
D_c	cell diffusion constant	$1.7\times10^{-10}\,\frac{\text{cm}^2}{\text{s}}$	(9), (10)

Table 1: Cell and network parameters extracted from [27].

the equation

$$\theta_n + \theta_s = 1 \quad \text{in } [0,T]\times\overline{\Omega}. \tag{1}$$

We assume that the intrinsic phase densities $\rho_n \in \mathbb{R}_+$ and $\rho_s \in \mathbb{R}_+$ are constant since according to Dembo and Harlow (see [10]) this is a good approximation for protein networks and biological solutions. Following the modelling in [11], the balance of mass equations read

$$\partial_t(\theta_n\rho_n) + \nabla\cdot(\theta_n\rho_n v_n) = R_n \quad \text{in } (0,T)\times\Omega, \tag{2}$$

$$\partial_t(\theta_s\rho_s) + \nabla\cdot(\theta_s\rho_s v_s) = R_s \quad \text{in } (0,T)\times\Omega \tag{3}$$

where ∂_t denotes the partial derivative with respect to time. $v_n = v_n(t,x) \in \mathbb{R}^d$ and $v_s = v_s(t,x) \in \mathbb{R}^d$ are the network and solution velocity, respectively. R_n and R_s represent the rates of reduction and production of mass per unit volume due to the degradation of the network by proteolysis. They are given by

$$R_n = -\delta u\theta_n\rho_n,$$
$$R_s = -R_n = \delta u\theta_n\rho_n$$

where $\delta \geq 0$ is the network degradation constant. The protease concentration $u = u(t,x) \in \mathbb{R}_+$ will be specified later. As balance of momentum equations we have

$$\partial_t(\theta_n\rho_n v_n) + \nabla\cdot(\theta_n\rho_n v_n\otimes v_n) = \nabla\cdot(\theta_n\sigma_n^*) + M + R_n v_n \quad \text{in } (0,T)\times\Omega, \tag{4}$$

$$\partial_t(\theta_s\rho_s v_s) + \nabla\cdot(\theta_s\rho_s v_s\otimes v_s) = \nabla\cdot(\theta_s\sigma_s^*) - M + R_s v_n \quad \text{in } (0,T)\times\Omega. \tag{5}$$

The last term describes the change of momentum as a result of the change of mass. In our case the change of mass is based on proteolysis, thus the degraded fibres have the velocity v_n. The quantity

$$M = P_I\nabla\theta_n + \phi_{ns}\theta_n\theta_s(v_s - v_n) \tag{6}$$

is the force on the network due to interaction with the interstitial solution. $P_I = P_I(t,x) \in \mathbb{R}$ denotes the interface pressure. This term is a result of the averaging theory and describes the static pressure exerted on the network by the solution. The second term of M represents the frictional drag due to the relative motion of the network and solution phases. For the sort of biological networks and solutions considered here the drag coefficient ϕ_{ns} is approximately $6.4\times10^{6}\,\frac{\text{dyne s}}{\text{cm}^4}$ (see [27]). The stress tensor $\sigma_k^* = \sigma_k^*(t,x) \in \mathbb{R}^{d\times d}$ is divided into an isotropic pressure part $-P_k I_d$ and a frictional part $\sigma_k = \sigma_k(t,x) \in \mathbb{R}^{d\times d}$, i.e.

$$\sigma_k^* = -P_k I_d + \sigma_k \tag{7}$$

for $k = n, s$. Here I_d is the identity matrix in $\mathbb{R}^d$ and $P_k = P_k(t,x) \in \mathbb{R}$ is the intraphase pressure. Based on experimental results ([3], [19]) we assume that the fibre network can be modelled as a viscous and elastic fluid like in the anisotropic biphasic theory of Barocas and Tranquillo [5]. More precisely, it behaves like a single-relaxation time compressible upper convected Maxwell fluid (see [21]). According to [4] the single-relaxation time is approximately 13 hours. The upper convected

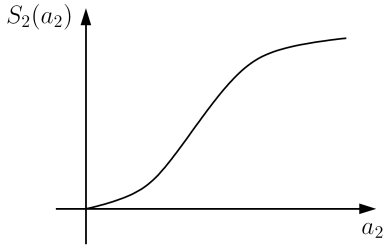

Figure 1: Possible choice for the sensitivity function S_2.

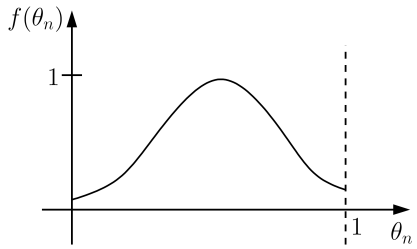

Figure 2: Dependence of f on the network volume fraction θ_n.

time derivative denoted by $\dot{}$ includes rheological nonlinearities in the simple Maxwell model and yields a good approximation for larger strains. Hence, we have the equation

$$\begin{aligned} \frac{1}{2G}\dot{\sigma_n} + \frac{1}{2\mu}\sigma_n &= \frac{1}{2}[\nabla v_n + (\nabla v_n)^T] + \frac{\nu}{1-2\nu}(\nabla \cdot v_n)I_d \qquad \text{in } (0,T)\times\Omega, \\ \dot{\sigma_n} &\equiv \partial_t \sigma_n + (v_n \cdot \nabla)\sigma_n - \nabla v_n \cdot \sigma_n - \sigma_n \cdot (\nabla v_n)^T \end{aligned} \tag{8}$$

for the network stress tensor σ_n where G, μ and ν are the shear modulus, the shear viscosity and the Poisson ratio, respectively. Relevant parameter choices for collagen gel are $G = 11850\frac{\text{dyne}}{\text{cm}^2}$, $\mu = 1.24 \times 10^8 \frac{\text{dyne s}}{\text{cm}^2}$ and $\nu = 0.2$ (see [27]). The parameters for the network and cells are summarised in Table 1. Due to the relatively small viscosity of the solution phase we take $\sigma_s = 0$.

Next we want to introduce the evolution equations for the cell concentration $c = c(t,x) \in \mathbb{R}_+$, the protease concentration $u = u(t,x) \in \mathbb{R}_+$ and for the chemoattractant concentrations of the solubilised fibronectin $a_1 = a_1(t,x) \in \mathbb{R}_+$ and of the epidermal growth factor $a_2 = a_2(t,x) \in \mathbb{R}_+$. The latter is only important in a metastasis framework. Since we have a two-phase fluid model these concentrations are part of one of the phases. The cells adhere to the fibrillar network in order to move. Thus we assume that the cells are part of the network phase. In contrast, the concentrations of the protease, solubilised fibronectin and EGF are solute and therefore part of the solution phase.

The active cell flux

$$J_c = -D_c f(\theta_n) dF \nabla c + c f(\theta_n) dF \left[\nabla S_H(\theta_n \rho_n) + \nabla S_1(a_1) + \nabla S_2(a_2)\right] \tag{9}$$

contains four different terms. The first term models diffusion with diffusion coefficient $D_c \approx 1.7 \times 10^{-10} \frac{\text{cm}^2}{s}$ (see [27]) and the second term represents the haptotactic movement. Haptotaxis denotes the movement in the direction of undissolved adhesion sites. We associate here the concentration of adhesion molecules with the network density. The haptotactic sensitivity function S_H describes the ability of the cells to sense concentration differences (in the adhesion molecules) of the network. The third and forth term stand for the chemotactic movement in response to the concentration differences of the solubilised fibronectin and EGF with the chemotactic sensitivity functions S_1 and S_2, respectively. The simplest choice are linear sensitivity functions. A more realistic choice for S_2 is shown in Fig. 1 considering the saturation of the cell receptors at high attractant concentrations. As the cells can only move along network fibres all terms contain the factor dF where $F = F(t,x)$ is the fibre orientation tensor which will be specified later. The dimension d is a scaling factor, necessary here in order to have $dF = I_d$ if the fibre orientation is isotropic. The function f reproduces the dependency of the cell speed on the density of the network. At low network densities the cells have only few possibilities to adhere to the network. If the density is high the cells have to squeeze through the gaps or use proteolysis to degrade the network. In both cases the movement speed is reduced. So the maximum of f should be somewhere in-between, depending for example on the size of the cells (see Fig. 2 for a possible choice of f). Additionally, as part of the network phase the cells are transported with the network velocity v_n. Consequently, we get the equation

$$\partial_t c = \nabla \cdot \{D_c f(\theta_n) dF \nabla c - c v_n - c f(\theta_n) dF \nabla [S_H(\theta_n \rho_n) + S_1(a_1) + S_2(a_2)]\} \quad \text{in } (0,T)\times\Omega \tag{10}$$

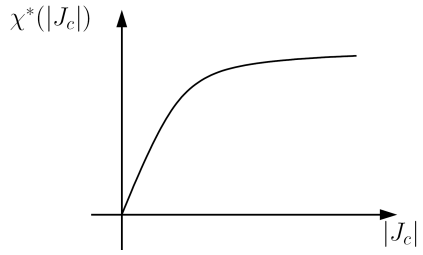

Figure 3: Dependence of the protease production on the norm of the cell flux.

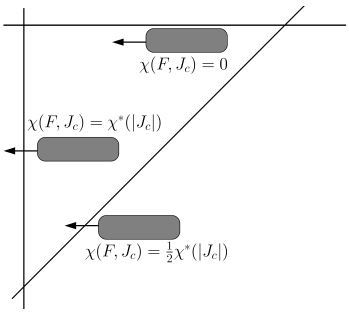

Figure 4: Dependence of the protease production on the angle between the fibres and the cell flux.

for the cell concentration c. We do not include a term for cell proliferation or cell death as there is experimental evidence that invasiveness is elevated in metastasis but cells are neither proliferating nor apoptotic (see [15], [28]).

In a dense network mesenchymal cells produce protease in order to degrade the network and consequently remove matrix barriers. We assume that the production not only depends on the concentration of the network and the cells but additionally on the angle between the cell velocity and the fibre orientation. In [16], Hillen modelled orientation dependent proteolysis in his mesoscopic model by including the scalar product of the normalised cell velocity with the fibre orientation in the matrix degradation term. We convey this idea to our model by defining the protease production function

$$\chi(F, J_c) = \chi^*(|J_c|)(1 - \hat{J}_c^T F \hat{J}_c) \tag{11}$$

where

$$\hat{J}_c = \begin{cases} \frac{J_c}{|J_c|}, & J_c \neq 0, \\ 0, & J_c = 0 \end{cases} \tag{12}$$

and $\chi^* : \mathbb{R}_+ \to \mathbb{R}_+$ is a monotonic function that is zero if the cell flux J_c is zero since we assume that motionless cells do not produce protease and that is bounded as cells cannot produce protease arbitrary fast (see Fig. 3). Due to the second factor in (11) there is no production of protease if the cells move parallel to the fibres while the production reaches its maximum if they move orthogonal to the fibres (see Fig. 4). Moreover, the production is proportional to the cell concentration c and to the network density $\tilde{\rho}_n = \theta_n \rho_n$. The protease is transported by the interstitial solution with velocity v_s. We assume that it diffuses with diffusion constant $D_u > 0$ although orientation dependency in proteolysis is rather the case in contact dependent proteolysis in which the protease does not diffuse. Adding the self degradation of protease, the equation has the form

$$\partial_t u = \nabla \cdot [D_u \nabla u - u v_s] - \beta u + \chi(F, J_c)\theta_n \rho_n c \quad \text{in } (0, T) \times \Omega \tag{13}$$

where $\beta > 0$ is the protease degradation constant.

Next, we give the equations for the two chemoattractants, namely the solubilised fibronectin a_1 and the epidermal growth factor a_2. They diffuse with diffusion constants $D_1 > 0$ and $D_2 > 0$, respectively, and are transported with the solution velocity v_s. We assume that a_2 binds to cell receptors and hence is reduced proportionally to the concentration of a_2 and the concentration of cells c. The proportionality constant is denoted by $\gamma \in \mathbb{R}_+$. When we define the boundary conditions for a metastasis framework later on, we will let this chemoattractant flow in the domain through the boundary. On the contrary the solubilised fibronectin arises from the degradation of the network proportional to the protease concentration u and the network density $\theta_n \rho_n$ with a fibronectin solubilising constant $h_2 \geq 0$. Its concentration is further increased by the solute proteases in the tissue fluid. Larger parts of network fragments can be further broken down in smaller fragments. Thus new adhesion sites are uncovered. Perumpanani et al. showed that

Symbol	Description	In equation
δ	network degradation constant	(2), (3), (4), (5), (20), (21)
β	protease degradation constant	(13)
h_2	fibronectin solubilising constant	(14)
γ	EGF degradation constant	(15)
D_u	protease diffusion constant	(13)
D_1	solubilised fibronectin diffusion constant	(14)
D_2	EGF diffusion constant	(15)

Table 2: Parameters with respect to protease and chemoattractants. All parameters are nonnegative.

therefore invasiveness can be diminished by high protease concentrations (see [24]). Hence, we get the equations

$$\partial_t a_1 = \nabla \cdot [D_1 \nabla a_1 - a_1 v_s] + h(u, a_1) + h_2 u \theta_n \rho_n \quad \text{in } (0,T) \times \Omega, \tag{14}$$

$$\partial_t a_2 = \nabla \cdot [D_2 \nabla a_2 - a_2 v_s] - \gamma a_2 c \quad \text{in } (0,T) \times \Omega \tag{15}$$

where $h(u, a_1)$ is the production function, representing further decomposition of solute network fragments. An overview over the parameters relevant for proteolysis and chemotaxis is given in Table 2.

Now we want to define the fibre orientation tensor $F = F(t,x) \in \mathbb{R}^{d \times d}$. We do not aim to model the highly entangled fibril network and the detailed network microstructure. Instead we use the ansatz of Barocas and Tranquillo (see [5]) by assuming that all fibres have the unit length 1 and do not occupy any volume. The fibre directions define the fibre orientation tensor as described below. This way we can treat the change of fibre orientations but disregard any stretching processes. The fibre orientation at time t is the result of the macroscopic deformation φ exerted on fibres with initial orientation F_0. This tensor is defined as

$$F_0(x) = \int_{S^{d-1}, r_d \geq 0} (r \otimes r) W_0(r,x) ds_r \tag{16}$$

for $x \in \overline{\Omega}$, where S^{d-1} is the sphere in $\mathbb{R}^d$ and $W_0(r,x)$ is the probability density for finding a fibre with orientation r at location x. That means we do not necessarily have only one fibre direction at a location x. As we assume that there is no difference between a fibre in direction r and $-r$ it is sufficient to integrate over the positive half sphere. For an isotropic orientation we choose $W_0(r,x) = \frac{2}{|S_{d-1}|}$ and thus get $F_0 = \frac{1}{d} I_d$.

The deformation $\varphi = \varphi(t; x_0) \in \mathbb{R}^d$ tells us where a point of the network which was located at $x_0 \in \overline{\Omega}$ in the beginning is located at time t, that means $x = \varphi(t; x_0)$. As the time derivative of the deformation is the velocity of the network we get the deformation from the equation

$$\partial_t \varphi(t; x_0) = v_n(t, \varphi(t; x_0)) \quad \text{for } (t, x_0) \in (0,T) \times \overline{\Omega} \tag{17}$$

with $\varphi(0; x_0) = x_0$. We now need a relation between the deformation and the initial fibre orientations. The orientation $\tilde{r}$ of a fibre at location $x = \varphi(t; x_0)$ and time t is given by

$$\tilde{r} = \varphi(t; x_0 + r) - \varphi(t; x_0) \approx \nabla \varphi(t; x_0) r \qquad \text{for small } |r|$$

where r is the initial fibre orientation (see Fig. 5). We can use this to define the fibre orientation tensor by

$$F(t,x) = \frac{\nabla \varphi(t; x_0) F_0(x_0) \nabla \varphi(t; x_0)^T}{\operatorname{tr}(\nabla \varphi(t; x_0) F_0(x_0) \nabla \varphi(t; x_0)^T)} \tag{18}$$

for $(t,x) \in [0,T] \times \overline{\Omega}$ (see [2] for treatment of magnetic prealignment in media equivalents). The standardisation with the trace secures that the length of the fibres remains 1 if there is only one fibre direction.

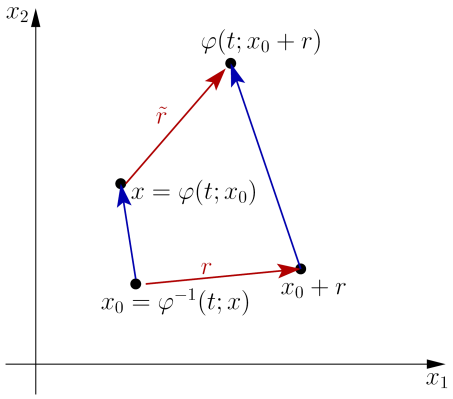

Figure 5: Deformation of a network fibre with direction r in the (x_1, x_2)-plane.

Now we have introduced all underlying variables but we still need some constitutive relations for the pressures P_n, P_s and P_I. Dembo and Harlow (see [10]) therefore introduced two new stresses, namely the solvation stress $\Gamma := P_s - P_I$ and the contractile stress $\Psi = P_s - P_n$. According to [10] $\Gamma = 0$ is a good approximation for the biological tissues we consider here. For the contractile stress we refer to [4] and assume that $\Psi = \tau c F_c$, where $\tau \geq 0$ is the cell traction parameter and $F_c = F_c(t, x) \in \mathbb{R}^{d \times d}$ represents the cell orientations. This term describes the stress that is exerted by the cells on the network during the contraction of the cytoskeleton. We assume here that the contractile stress is anisotropic although it is derived from the isotropic pressure difference $P_s - P_n$. The cell orientation tensor F_c is defined similar to the initial fibre orientation tensor by

$$F_c(t, x) = \int_{S^{d-1}, w_d \geq 0} (w \otimes w) W_c(w, t, x) \, ds_w \tag{19}$$

in $[0, T] \times \overline{\Omega}$, where $W_c(w, t, x)$ is the probability density of finding a cell orientated in direction w at time t and location x. We present here two possible choices for W_c:

- $\mathbf{F_c \equiv dF}$: Parameterising the surface integral

  $$\int_{S^{d-1}, r_d \geq 0} ((\nabla \varphi(t; x_0)\ r) \otimes (\nabla \varphi(t; x_0)\ r)) W_0(r, x_0) ds_r$$

  in (18) by

  $$r(z) = \frac{(\nabla \varphi)(t; x_0)^{-1} y(z)}{|(\nabla \varphi)(t; x_0)^{-1} y(z)|} \quad \text{with } y(z) = \begin{pmatrix} z \\ \sqrt{1 - z^2} \end{pmatrix} \text{ and } x = \varphi(t; x_0)$$

  yields

  $$F = \frac{1}{\operatorname{tr}(\nabla \varphi(t; x_0) F_0(x_0) \nabla \varphi(t; x_0)^T)} \int_{-1}^{1} y(z) \otimes y(z) \frac{W_0\left(r(z), x\right) |r'(z)|}{|(\nabla \varphi)(t; x_0)^{-1} y(z)|^2} dz.$$

  If we now parameterise F_c by $w(z) = y(z)$ and choose

  $$W_c(y(z), t, x) = \frac{d}{\operatorname{tr}(\nabla \varphi(t; x_0) F_0(x_0) \nabla \varphi(t; x_0)^T)} \sqrt{1 - z^2} \frac{W_0\left(r(z), x\right) |r'(z)|}{|(\nabla \varphi)(t; x_0)^{-1} y(z)|^2}$$

  we get $F_c \equiv dF$. These calculations are done in 2D for simplicity only. The choice of W_c corresponds to the cell orientation tensor in the AB-model in [5] for the case $\kappa = 1$.
- $\mathbf{F_c \equiv \hat{J}_c \hat{J}_c^T}$: We choose $W_c(w, t, x) = \delta_{\hat{J}_c(t,x)}(w)$. In this case we heuristically expect a regularity problem. On the one hand, an explicit solution of (2) can be found by the method of characteristics depending on u, v_n and φ. We expect from this equation that θ_n has one spatial differentiation order less then v_n. On the other hand, for this choice of F_c there are second order derivatives of θ_n in the second order parabolic equation (4) for v_n. So it is reasonable to expect the same differentiation order with respect to x for v_n

and θ_n resulting in a regularity problem. This could be avoided by either simply choosing for a fixed small $\varepsilon > 0$

$$W_c(w,t,x) = \eta\left(\frac{w - \hat{J}_c(t,x)}{\varepsilon}\right)$$

where η is the standard mollifier (see e.g. [12], p. 629), or by regularising the contractile stress Ψ such that

$$\Psi(t,x) = \frac{\tau}{\varepsilon^d}\int_\Omega \eta\left(\frac{x-y}{\varepsilon}\right) c(t,y)\hat{J}_c(t,y)\hat{J}_c^T(t,y)dy.$$

We suppose that the second possibility for regularising is more realistic as the fibres in a network are connected and the forces of the cells in the vicinity could also affect the dynamics at location x.

Under these assumption on the pressures and using (6), (7) the momentum balance equations (4)–(5) read

$$\partial_t(\theta_n\rho_n v_n) + \nabla\cdot(\theta_n\rho_n v_n\otimes v_n) = \nabla\cdot[\theta_n(\sigma_n + \tau c F_c)] - \theta_n\nabla P_s + \phi_{ns}\theta_n\theta_s(v_s - v_n) + R_n v_n, \tag{20}$$

$$\partial_t(\theta_s\rho_s v_s) + \nabla\cdot(\theta_s\rho_s v_s\otimes v_s) = -\theta_s\nabla P_s - \phi_{ns}\theta_n\theta_s(v_s - v_n) - R_n v_n \tag{21}$$

in $(0,T)\times\Omega$. We will now recapitulate all model equations.

3. The full mathematical model

The complete model consists of $(7+3d+d^2)$ equations for the $(7+3d+d^2)$ unknowns θ_n, θ_s, v_n, v_s, σ_n, P_s, φ, c, u, a_1 and a_2. Due to its complexity we summarise all model equations for clarity, beginning with the equation for the volume fractions

$$\theta_n + \theta_s = 1, \tag{1}$$

the mass balance equations

$$\partial_t(\theta_n\rho_n) + \nabla\cdot(\theta_n\rho_n v_n) = -\delta u\theta_n\rho_n \quad \text{in } (0,T)\times\Omega, \tag{2}$$

$$\partial_t(\theta_s\rho_s) + \nabla\cdot(\theta_s\rho_s v_s) = \delta u\theta_n\rho_n \quad \text{in } (0,T)\times\Omega, \tag{3}$$

the momentum balance equations

$$\begin{aligned}\partial_t(\theta_n\rho_n v_n) + \nabla\cdot(\theta_n\rho_n v_n\otimes v_n) &= \nabla\cdot[\theta_n(\sigma_n + \tau c F_c)]\\ &\quad - \theta_n\nabla P_s + \phi_{ns}\theta_n\theta_s(v_s - v_n) - \delta u\theta_n\rho_n v_n,\end{aligned} \tag{20}$$

$$\partial_t(\theta_s\rho_s v_s) + \nabla\cdot(\theta_s\rho_s v_s\otimes v_s) = -\theta_s\nabla P_s - \phi_{ns}\theta_n\theta_s(v_s - v_n) + \delta u\theta_n\rho_n v_n \tag{21}$$

in $(0,T)\times\Omega$ and the Maxwell model for the network stress tensor

$$\begin{aligned}\frac{1}{2G}\dot{\sigma_n} + \frac{1}{2\mu}\sigma_n &= \frac{1}{2}[\nabla v_n + (\nabla v_n)^T] + \frac{\nu}{1-2\nu}(\nabla\cdot v_n)I_d,\\ \dot{\sigma_n} &\equiv \partial_t\sigma_n + (v_n\cdot\nabla)\sigma_n - \nabla v_n\cdot\sigma_n - \sigma_n\cdot(\nabla v_n)^T\end{aligned} \tag{8}$$

in $(0,T)\times\Omega$. Furthermore, we have the evolution equations for the cells, protease, solubilised fibronectin and EGF

$$\partial_t c = \nabla\cdot\{D_c f(\theta_n)dF\nabla c - c v_n - c f(\theta_n)dF\nabla[S_H(\theta_n\rho_n) + S_1(a_1) + S_2(a_2)]\}, \tag{10}$$

$$\partial_t u = \nabla\cdot[D_u\nabla u - u v_s] - \beta u + \chi^*(|J_c|)(1 - \hat{J}_c^T F\hat{J}_c)\theta_n\rho_n c, \tag{13}$$

$$\partial_t a_1 = \nabla\cdot[D_1\nabla a_1 - a_1 v_s] + h(u,a_1) + h_2 u\theta_n\rho_n, \tag{14}$$

$$\partial_t a_2 = \nabla\cdot[D_2\nabla a_2 - a_2 v_s] - \gamma a_2 c \tag{15}$$

in $(0,T)\times\Omega$, and the ordinary differential equation

$$\partial_t\varphi(t;x_0) = v_n(t,\varphi(t;x_0)) \quad \text{for } (t,x_0)\in(0,T)\times\overline{\Omega} \tag{17}$$

with $\varphi(0;x_0)=x_0$ for the deformation. Additionally, there are the constitutive relations for the fibre, the initial fibre and the cell orientation tensors

$$F(t,x)=\frac{\nabla\varphi(t;x_0)F_0(x_0)\nabla\varphi(t;x_0)^T}{\mathrm{tr}(\nabla\varphi(t;x_0)F_0(x_0)\nabla\varphi(t;x_0)^T)} \quad \text{for } (t,x)\in[0,T]\times\overline{\Omega},\ x=\varphi(t;x_0), \tag{18}$$

$$F_0(x_0)=\int_{S^{d-1},r_d\geq 0}(r\otimes r)W_0(r,x_0)ds_r \qquad \text{for } x_0\in\overline{\Omega}, \tag{16}$$

$$F_c(t,x)=\int_{S^{d-1},w_d\geq 0}(w\otimes w)W_c(w,t,x)ds_w \qquad \text{for } (t,x)\in[0,T]\times\overline{\Omega} \tag{19}$$

as well as for the active cell flux J_c

$$J_c=-D_cf(\theta_n)dF\nabla c+cf(\theta_n)dF\nabla[S_H(\theta_n\rho_n)+S_1(a_1)+S_2(a_2)], \tag{9}$$

$$\hat{J}_c=\begin{cases}\frac{J_c}{|J_c|}, & \text{for } J_c\neq 0,\\ 0, & \text{else.}\end{cases} \tag{12}$$

As our full equation system is very complex we will simplify it in the next section. The model extensions and changes we made with respect to the AB-model will become clear at its end.

4. Model simplifications

First, we are going to nondimensionalise the equation system. This way, it will be easier to judge which terms in the equations are important and which are not. We therefore introduce new constants, namely the characteristic length L, the characteristic velocity V and the characteristic concentrations of cells C, of protease U, of solubilised fibronectin A_1 and of EGF A_2. Using these and assuming, that functions with a ˜ are functions of $(\tilde{x},\tilde{t})$, we define the dimensionless variables

$$\begin{array}{llll}\tilde{x}:=\frac{x}{L}, & \tilde{v}_n:=\frac{v_n}{V}, & \tilde{u}:=\frac{u}{U}, & \tilde{\varphi}:=\frac{1}{L}\varphi,\\ \tilde{t}:=\frac{V}{L}t, & \tilde{v}_s:=\frac{v_s}{V}, & \tilde{a}_1:=\frac{a_1}{A_1}, & \tilde{F}=F,\\ \tilde{\theta}_{n/s}:=\theta_{n/s} & \tilde{J}_c:=\frac{1}{CV}J_c, & \tilde{a}_2:=\frac{a_2}{A_2}, & \tilde{F}_c=F_c,\\ \tilde{P}:=\frac{L}{\mu V}P_s, & \tilde{\sigma}_n:=\frac{L}{\mu V}\sigma_n, & \tilde{c}:=\frac{c}{C}, & \end{array}$$

and the dimensionless parameters and functions

$$\begin{array}{llll}\tilde{D}_c:=\frac{D_c}{LV}, & \tilde{\delta}:=\frac{\delta UL}{V}, & \tilde{\tau}:=\frac{LC\tau}{\mu V}, & \tilde{\chi}^*(|\tilde{J}_c|):=\frac{LC\rho_n}{UV}\chi^*(|J_c|),\\ \tilde{D}_u:=\frac{D_u}{LV}, & \tilde{\beta}:=\frac{\beta L}{V}, & \tilde{h}_2:=\frac{UL\rho_n}{VA_1}h_2, & \tilde{S}_H(\tilde{\theta}_n):=\frac{1}{LV}S_H(\theta_n\rho_n),\\ \tilde{D}_1:=\frac{D_1}{LV}, & \tilde{\gamma}:=\frac{\gamma LC}{V}, & \tilde{h}(\tilde{a}_1,\tilde{u}):=\frac{L}{VA_1}h(a_1,u), & \tilde{S}_1(\tilde{a}_1):=\frac{1}{LV}S_1(a_1),\\ \tilde{D}_2:=\frac{D_2}{LV}, & \tilde{G}:=\frac{GL}{\mu V}, & \tilde{f}(\tilde{\theta}_n)=df(\theta_n), & \tilde{S}_2(\tilde{a}_2):=\frac{1}{LV}S_2(a_2),\\ \mathrm{Re_n}:=\frac{\rho_nVL}{\mu}, & \tilde{\phi}_{ns}:=\frac{L^2\phi_{ns}}{\mu}, & & \end{array}$$

where $\mathrm{Re_n}$ is the Reynolds number of the network. Thus, we also get the transformed domain $\widetilde{\Omega}$ and the transformed time period $\tilde{T}:=\frac{V}{L}T$. With these definitions we can rewrite our equation system. Apart from the mass and momentum balance equations the system hardly changes. Dembo and Harlow note in [10] that the intrinsic phase densities of protein networks and biological solutions are nearly equal. Thus, we use $\rho_n=\rho_s$ to transform the mass balance equations. Dividing (2) and (3) by ρ_n and substituting (3) by the sum of these equations gives the overall incompressibility relation. The new mass and momentum balance equations read

$$\partial_{\tilde{t}}\tilde{\theta}_n+\nabla_{\tilde{x}}\cdot\left(\tilde{\theta}_n\tilde{v}_n\right)=-\tilde{\delta}\tilde{u}\tilde{\theta}_n \quad \text{in } (0,\tilde{T})\times\widetilde{\Omega}, \tag{22}$$

$$\nabla_{\tilde{x}}\cdot\left(\tilde{\theta}_n\tilde{v}_n+\tilde{\theta}_s\tilde{v}_s\right)=0 \qquad \text{in } (0,\tilde{T})\times\widetilde{\Omega}, \tag{23}$$

and

$$\begin{aligned}\mathrm{Re_n}\left[\partial_{\tilde{t}}\left(\tilde{\theta}_n\tilde{v}_n\right)+\nabla_{\tilde{x}}\cdot\left(\tilde{\theta}_n\tilde{v}_n\otimes\tilde{v}_n\right)\right]=&\nabla_{\tilde{x}}\cdot\left[\tilde{\theta}_n\left(\tilde{\sigma}_n+\tilde{\tau}\tilde{c}\tilde{F}_c\right)\right]\\ &-\tilde{\theta}_n\nabla_{\tilde{x}}\tilde{P}+\tilde{\phi}_{ns}\tilde{\theta}_n\tilde{\theta}_s\left(\tilde{v}_s-\tilde{v}_n\right)-\mathrm{Re_n}\,\tilde{\delta}\tilde{u}\tilde{\theta}_n\tilde{v}_n \text{ in } (0,\tilde{T})\times\widetilde{\Omega},\\ \mathrm{Re_n}\left[\partial_{\tilde{t}}\left(\tilde{\theta}_s\tilde{v}_s\right)+\nabla_{\tilde{x}}\cdot\left(\tilde{\theta}_s\tilde{v}_s\otimes\tilde{v}_s\right)\right]=&-\tilde{\theta}_s\nabla_{\tilde{x}}\tilde{P}+\tilde{\phi}_{ns}\tilde{\theta}_n\tilde{\theta}_s\left(\tilde{v}_n-\tilde{v}_s\right)+\mathrm{Re_n}\,\tilde{\delta}\tilde{u}\tilde{\theta}_n\tilde{v}_n \text{ in } (0,\tilde{T})\times\widetilde{\Omega},\end{aligned}$$

respectively. The equations (8) for the stress tensor change into

$$\frac{1}{2\widetilde{G}}\dot{\tilde{\sigma}}_n + \frac{1}{2}\tilde{\sigma}_n = \frac{1}{2}\left[\nabla_{\tilde{x}}\tilde{v}_n + (\nabla_{\tilde{x}}\tilde{v}_n)^T\right] + \frac{\nu}{1-2\nu}\left(\nabla_{\tilde{x}}\cdot\tilde{v}_n\right) I_d, \tag{24}$$
$$\dot{\tilde{\sigma}}_n \equiv \partial_{\tilde{t}}\tilde{\sigma}_n + (\tilde{v}_n\cdot\nabla_{\tilde{x}})\,\tilde{\sigma}_n - \nabla_{\tilde{x}}\tilde{v}_n\cdot\tilde{\sigma}_n - \tilde{\sigma}_n\cdot(\nabla_{\tilde{x}}\tilde{v}_n)^T$$

in $(0,\tilde{T})\times\widetilde{\Omega}$ and the equations (10), (13)–(15) for the cells, the protease and the chemoattractants become

$$\partial_{\tilde{t}}\tilde{c} = \nabla_{\tilde{x}}\cdot\left[\tilde{D}_c\tilde{f}(\tilde{\theta}_n)\tilde{F}\nabla_{\tilde{x}}\tilde{c} - \tilde{c}\tilde{v}_n - \tilde{c}\tilde{f}(\tilde{\theta}_n)\tilde{F}\nabla_{\tilde{x}}\left(\tilde{S}_H(\tilde{\theta}_n) + \tilde{S}_1(\tilde{a}_1) + \tilde{S}_2(\tilde{a}_2)\right)\right], \tag{25}$$

$$\partial_{\tilde{t}}\tilde{u} = \nabla_{\tilde{x}}\cdot\left[\tilde{D}_u\nabla_{\tilde{x}}\tilde{u} - \tilde{u}\tilde{v}_s\right] - \tilde{\beta}\tilde{u} + \tilde{\chi}^*(|\tilde{J}_c|)\left(1 - \hat{\tilde{J}}_c^T\tilde{F}\hat{\tilde{J}}_c\right)\tilde{\theta}_n\tilde{c}, \tag{26}$$

$$\partial_{\tilde{t}}\tilde{a}_1 = \nabla_{\tilde{x}}\cdot\left[\tilde{D}_1\nabla_{\tilde{x}}\tilde{a}_1 - \tilde{a}_1\tilde{v}_s\right] + \tilde{h}(\tilde{a}_1,\tilde{u}) + \tilde{h}_2\tilde{u}\tilde{\theta}_n, \tag{27}$$

$$\partial_{\tilde{t}}\tilde{a}_2 = \nabla_{\tilde{x}}\cdot\left[\tilde{D}_2\nabla_{\tilde{x}}\tilde{a}_2 - \tilde{a}_2\tilde{v}_s\right] - \tilde{\gamma}\tilde{a}_2\tilde{c} \tag{28}$$

in $(0,\tilde{T})\times\widetilde{\Omega}$. Neither the form of the deformation equation, nor the equations for the fibre, initial fibre and cell orientation tensor change. The system is now written in dimensionless variables, so we have a look what is known about the dimensionless parameters. In the following we will omit the $\tilde{}$ for simplicity. For biological tissues like the fibre network the Reynolds number is very low, so we formally set $\mathrm{Re_n} = 0$. Thus, we get momentum equations that do no longer include inertial effects, i.e.

$$\nabla\cdot[\theta_n(\sigma_n + \tau c F_c)] - \theta_n\nabla P + \phi_{ns}\theta_n\theta_s(v_s - v_n) = 0 \quad \text{in } [0,T]\times\Omega, \tag{29}$$

$$-\theta_s\nabla P + \phi_{ns}\theta_n\theta_s(v_n - v_s) = 0 \quad \text{in } [0,T]\times\Omega. \tag{30}$$

We will now bring equations (1), (22)–(23), (29) and (30) in a form that is easier to handle. Therefor we substitute $\theta_s = 1-\theta_n$ in all equations. From (30) we calculate

$$v_s = v_n - \frac{1}{\phi_{ns}\theta_n}\nabla P. \tag{31}$$

Adding (30) to (29) simplifies the latter equation. Dividing (30) by θ_n, taking the divergence of the resulting equation and using (23) reduces equations (1), (22)–(23), (29) and (30) to the three equations

$$\partial_t\theta_n + \nabla\cdot(\theta_n v_n) = -\delta u\theta_n \quad \text{in } (0,T)\times\Omega, \tag{32}$$

$$\nabla\cdot[\theta_n(\sigma_n + \tau c F_c)] - \nabla P = 0 \quad \text{in } [0,T]\times\Omega, \tag{33}$$

$$-\nabla\cdot\left[\frac{1-\theta_n}{\theta_n}\nabla P\right] + \phi_{ns}\nabla\cdot v_n = 0 \quad \text{in } [0,T]\times\Omega. \tag{34}$$

Equations (32)–(34) and (24) are almost identical with the AB-model of Barocas and Tranquillo (see [5]). In (32) we additionally have the nontrivial degradation term $R_n = -\delta u\theta_n$ describing proteolysis, which is an important effect in mesenchymal cell dynamics. Moreover, we extended the evolution equation (25) for the cells by haptotaxis and chemotaxis with respect to the two chemoattractants solubilised fibronectin and epidermal growth factor. Thus, our model contains the additional equations (27) and (28) for the chemoattractants and equation (26) for the protease u which is needed for the degradation term R_n in (32). Due to the tactic movement we suggest different choices for the probability W_c in equation (19). With these we allow cell orientations that are not necessarily the main fibre directions like in the case of very strong contact guidance (see [5]), but which are geared by the cell flux. Furthermore, our model incorporates initial fibre orientations. The structure of the initial fibre orientation tensor F_0 is the same as for the fibre orientation tensor in the AB-model, but the evolution equation for F is different in our model as we believe that this choice is rather suggesting and even easier to handle. Thus, we have adjusted the AB-model to a situation of mesenchymal and chemosensitive cell dynamics.

Summarising, equations (24)–(28) and (32)–(34) with (9), (16)–(19) and (31) represent a system of partial differential equations for the volume fraction, the velocity and the stress tensor of the network, the pressure of the interstitial solution and the concentrations of cells, protease and

chemoattractants. As far as we know it is the first model (MC-model) describing the **m**esenchymal and **c**hemosensitive dynamics of cells in a tissue network where the combination of fibre orientation dependence, cell traction forces on the fibres and chemosensitivity is included.

5. A special case: amoeboid movement

In the case of amoeboid movement there is much less interaction between the fibre network and the cells. The most obvious difference is that cells do not produce proteases, so we remove the u-equation (26) from our system, set $u = 0$ in (32) and get

$$\partial_t \theta_n + \nabla \cdot (\theta_n v_n) = 0 \quad \text{in } (0,T) \times \Omega. \tag{35}$$

Furthermore, the adhesion of amoeboid cells to the network fibres is weakened and consequently the cells do not exert traction forces on the network ($\tau = 0$ in (33)). Thus, for the pressure, network velocity and stress tensor we get the equations

$$\nabla \cdot (\theta_n \sigma_n) - \nabla P = 0 \quad \text{in } [0,T] \times \Omega, \tag{36}$$

$$-\nabla \cdot \left[\frac{1-\theta_n}{\theta_n} \nabla P \right] + \phi_{ns} \nabla \cdot v_n = 0 \quad \text{in } [0,T] \times \Omega, \tag{37}$$

$$\begin{aligned} \frac{1}{2G} \dot{\sigma}_n + \frac{1}{2} \sigma_n = \frac{1}{2} [\nabla v_n + (\nabla v_n)^T] + \frac{\nu}{1-2\nu} (\nabla \cdot v_n) I_d \quad \text{in } (0,T) \times \Omega, \\ \dot{\sigma}_n \equiv \partial_t \sigma_n + (v_n \cdot \nabla) \sigma_n - \nabla v_n \cdot \sigma_n - \sigma_n \cdot (\nabla v_n)^T. \end{aligned} \tag{38}$$

(35)–(38) form a closed system and can be treated separately. Hence, the deformation φ, the fibre orientation tensor F and the solution velocity v_s can be calculated by (17), (18) and (31), respectively. As tumour cells normally move mesenchymally we do not assume here that we have the two chemoattractants solubilised fibronectin and EGF but give an equation for an unspecified chemoattractant a. Moreover, amoeboid cells do not move haptotactically ($S_H = 0$ in (25)) as adhesion is lessened. Thus, the equations for the cell and chemoattractant concentrations are

$$\partial_t c = \nabla \cdot [D_c f(\theta_n) F \nabla c - c v_n - c f(\theta_n) F \nabla S(a)] \quad \text{in } (0,T) \times \Omega, \tag{39}$$

$$\partial_t a = \nabla \cdot [D_a \nabla a - a v_s] - g_1(a,c) + g_2(c,a,\theta_n) \quad \text{in } (0,T) \times \Omega \tag{40}$$

where g_1 is a degradation and g_2 a production term. Equations (39) and (40) are similar to the standard Keller-Segel model (see [17]), but apart from the convection terms they differ in the inclusion of fibre orientation and network density influences. In order to model an *in vitro situation* the velocity and hence equations (35)–(38) can be neglected and the system reduces to the rather simple system (39)–(40) with $v_n = v_s = 0$, given network density θ_n and given fibre orientation tensor F_0.

6. Adjusting the MC-model to metastasis

To adjust the MC-model to metastasis we have to add adequate boundary conditions. However, we want to summarise the equations of the MC-model first: it consists of partial differential equations for the volume fraction of the network θ_n,

$$\partial_t \theta_n + \nabla \cdot (\theta_n v_n) = -\delta u \theta_n \quad \text{in } (0,T) \times \Omega \tag{41}$$

for the concentrations of cells c, protease u and the chemoattractants a_1 and a_2,

$$\partial_t c = \nabla \cdot [D_c f(\theta_n) F \nabla c - c v_n - c f(\theta_n) F \nabla (S_H(\theta_n) + S_1(a_1) + S_2(a_2))], \tag{42}$$

$$\partial_t u = \nabla \cdot [D_u \nabla u - u v_s] - \beta u + \chi^*(|J_c|)(1 - \hat{J}_c^T F \hat{J}_c) \theta_n c, \tag{43}$$

$$\partial_t a_1 = \nabla \cdot [D_1 \nabla a_1 - a_1 v_s] + h(a_1, u) + h_2 u \theta_n, \tag{44}$$

$$\partial_t a_2 = \nabla \cdot [D_2 \nabla a_2 - a_2 v_s] - \gamma a_2 c, \tag{45}$$

in $(0,T)\times\Omega$ and for the network velocity v_n, the fibre stress tensor σ_n and the fluid pressure P

$$\nabla\cdot[\theta_n(\sigma_n+\tau cF_c)]-\nabla P=0 \quad \text{in } [0,T]\times\Omega, \tag{46}$$

$$-\nabla\cdot\left[\frac{1-\theta_n}{\theta_n}\nabla P\right]+\phi_{ns}\nabla\cdot v_n=0 \quad \text{in } [0,T]\times\Omega, \tag{47}$$

$$\begin{aligned}\frac{1}{2G}\dot\sigma_n+\frac{1}{2}\sigma_n&=\frac{1}{2}[\nabla v_n+(\nabla v_n)^T]+\frac{\nu}{1-2\nu}(\nabla\cdot v_n)I_d \quad \text{in } (0,T)\times\Omega,\\ \dot\sigma_n&\equiv\partial_t\sigma_n+(v_n\cdot\nabla)\sigma_n-\nabla v_n\cdot\sigma_n-\sigma_n\cdot(\nabla v_n)^T.\end{aligned} \tag{48}$$

Additionally, there are an ordinary differential equation for the deformation φ of the network

$$\partial_t\varphi(t;x_0)=v_n(t,\varphi(t;x_0)) \quad \text{for } (t,x_0)\in(0,T)\times\overline{\Omega} \tag{49}$$

with $x_0=\varphi(0;x_0)$ and algebraic equations for the fibre orientation tensor F, the initial fibre orientation tensor F_0 and the cell orientation tensor F_c,

$$F(t,x)=\frac{\nabla\varphi(t;x_0)F_0(x_0)\nabla\varphi(t;x_0)^T}{\mathrm{tr}(\nabla\varphi(t;x_0)F_0(x_0)\nabla\varphi(t;x_0)^T)} \quad \text{for } (t,x)\in[0,T]\times\overline{\Omega},\ x=\varphi(t;x_0), \tag{50}$$

$$F_0(x_0)=\int_{S^{d-1},r_d\geq 0}(r\otimes r)W_0(r,x_0)ds_r \qquad \text{for } x_0\in\overline{\Omega}, \tag{51}$$

$$F_c(t,x)=\int_{S^{d-1},w_d\geq 0}(w\otimes w)W_c(w,t,x)ds_w \qquad \text{for } (t,x)\in[0,T]\times\overline{\Omega} \tag{52}$$

as well as for the solution velocity v_s and the active cell flux J_c

$$v_s=v_n-\frac{1}{\phi_{ns}\theta_n}\nabla P, \tag{53}$$

$$J_c=-D_cf(\theta_n)F\nabla c+cf(\theta_n)F\nabla[S_H(\theta_n)+S_1(a_1)+S_2(a_2)]. \tag{54}$$

We now include boundary conditions which reproduce a part of the metastatic process, precisely, the migration to a blood vessel after detaching from the tumour. Therefor we consider a domain Ω where the boundary Γ_T represents the tumour and the opposite boundary Γ_V represents a blood vessel. Inbetween, there are boundaries Γ_N through which non of our variables may leave the domain (see Fig. 6). The fibre network is fixed on the whole boundary, i.e.

$$v_n=0 \quad \text{on } \partial\Omega. \tag{55}$$

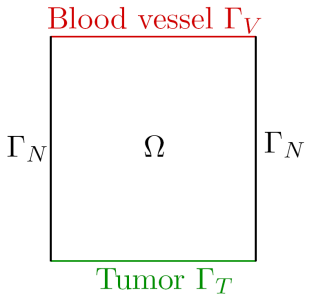

Figure 6: The domain Ω with boundaries Γ_T, Γ_V and Γ_N.

For this reason, boundary conditions for θ_n and σ_n are not required. For the pressure we take Dirichlet boundary conditions, that means

$$P(t,x)\big|_{\partial\Omega}=P_\Gamma(x) \tag{56}$$

with a given function $P_\Gamma:\partial\Omega\to\mathbb{R}$. On Γ_V this will be the blood pressure. The tumour cells that detach from the tumour are represented by the production function $k_1(t,x)\geq 0$ on Γ_T and can leave the domain by entering the blood vessel. Thus, we have

$$J_c\cdot n=\begin{cases}k_1(x,t) & \text{for } x\in\Gamma_T,\\ -k_2(x)c & \text{for } x\in\Gamma_V,\\ 0 & \text{for } x\in\Gamma_N\end{cases} \tag{57}$$

where n is the outer normal vector and $k_2(x)\geq 0$. Since protease and solubilised fibronectin are produced by cell activity in the domain we impose zero boundary conditions, i.e.

$$D_u\partial_n u-uv_s\cdot n=0 \qquad \text{for } x\in\partial\Omega, \tag{58}$$

$$D_1\partial_n a_1-a_1v_s\cdot n=0 \qquad \text{for } x\in\partial\Omega. \tag{59}$$

We model the production of EGF by macrophages near a blood vessel by assuming that a_2 flows into the domain through the blood vessel boundary Γ_V with an amount $k_3(t,x) \geq 0$. Moreover, a_2 can leave the domain through the tumour boundary Γ_T. Hence,

$$D_2 \partial_n a_2 - a_2 v_s \cdot n = \begin{cases} k_3(x,t) & \text{for } x \in \Gamma_V, \\ -k_4(x) a_2 & \text{for } x \in \Gamma_T, \\ 0 & \text{for } x \in \Gamma_N \end{cases} \tag{60}$$

with $k_4(x) \geq 0$. By equations (41)–(54) and boundary conditions (55)–(60) we have introduced a mathematical model that describes the chemosensitive and mesenchymal dynamics of metastatic tumour cells. In order to validate this model, it will be investigated analytically and numerically in future publications.

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