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ON SOME MODELS FOR CANCER CELL MIGRATION THROUGH TISSUE NETWORKS

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Abstract. We propose some models allowing to account for relevant processes at the various scales of cancer cell migration through tissue, ranging from the receptor dynamics on the cell surface over degradation of tissue fibers by protease and soluble ligand production towards the behavior of the entire cell population.

For a genuinely mesoscopic version of these models we also provide a result on the local existence and uniqueness of a solution for all biologically relevant space dimensions.

1. **Introduction.** The migration of tumour cells through the extracellular matrix (ECM) plays an essential role in cancer progression.

The contact with the surrounding tissue enables the cells to move along tissue fibers. However, very tight tissue impedes motion and the cells respond by dissolving fibers of the tissue network. Cell motility is triggered by membrane bound receptors which provide linkages to the tissue fibers and also bind to the ECM fragments resulting by proteolytic degradation. The latter act in turn as a chemotactic signal for the tumor cells.

Existing models for cancer invasion can be divided into three categories:

Microscopic models are concerned with the processes at the intracellular and/or cell surface level which initiate (tumour) cell migration. These processes are usually characterized with the aid of a system of ordinary differential equations for the concentrations of the involved biochemical substances. Examples are [4] with a focus on proteolysis and [20] for lamellipod protrusion, a crucial step in integrin-mediated haptotactic motility.

In the *mesoscopic* framework, cell migration is characterized by way of a transport equation for the cell population density, in which integral operators model changes of the cell velocity. This approach has been introduced by Othmer, Dunbar and Alt [21] in order to describe the dispersal of living organisms whose velocities

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either satisfy some stochastic differential equations or are given by a geometrical description of motion (so-called *velocity jump* models).

The models have been extended by Hillen [14] to characterize the mesenchymal motion of cancer cells and the subsequent tissue modification. The model by Chauviere et al. [7] also accounts for chemotaxis and cell-cell interactions.

Macroscopic descriptions can be derived from the above mesoscopic models by means of averaging processes leading to evolution equations for the moments of the cell distribution function. For the mesoscopic models of the above type this has been done at least formally, e.g., in [10] for hyperbolic models for chemosensitive movement or in [14] in the context of mesenchymal motion of tumor cells. Rigorous results on the hyperbolic, respectively parabolic limit of kinetic equations for chemotaxis have been deduced e.g., in [5] and [22], respectively.

Apart from the kinetic setting, macroscopic models for cell migration have also been derived using mass conservation and/or mechanical force balance or the theory of mixtures. For the latter we refer e.g., to Maini [19] or Barocas and Tranquillo [2]; see also Tosin and Preziosi [24] and the references therein. Models for cell population migration only relying on mass balance equations have been proposed e.g., by Anderson et al. [1] or Chaplain and Lolas [6].

The current aim is to interconnect these three modeling levels in a multiscale setting. Thereby, more or less detailed subcellular information may be integrated in a way which could allow for predictions at the level of a tumor. First attempts toward setting up such multiscale models for E. Coli have been made by Firmani et al. [11], followed among others by Erban and Othmer in [9]. A similar approach to multicellular systems modeling the interaction of tumour cells and the immune system or the growth of biological tissue has been proposed by Bellomo et al., see e.g., [3] and the references therein.

We also refer to [18] for a review on multiscale models along with a careful linking between the modeling levels in a related, but different context.

In this note we set up a multiscale model for cancer cell migration by coupling the dynamics of cell surface receptors with a kinetic equation for the tumor cell population density, thus integrating into a single model the various processes which so far have been treated separately in one of the above three frameworks. For the purely mesoscopic model (i.e. in the absence of cell surface dynamics) we prove the local existence and uniqueness of a solution under some natural assumptions on the data. We refer to [16] for the proof of local existence and uniqueness of the solution to a full multiscale model.

2. Model for mesenchymal and chemosensitive movement.

2.1. Microscopic dynamics of migrating cells.

Let S^{n-1} denote the unit sphere in $\mathbb{R}^n$ and let $\theta \in S^{n-1}$ denote the fibre orientation. Then we denote the density of ECM fibres oriented in the direction θ at time t and at location $\mathbf{x} \in \mathbb{R}^n$ by $Q(t, \mathbf{x}, \theta)$. The total density of ECM fibres is then given by

$$\bar{Q}(\mathbf{x}, t) := \int_{S^{n-1}} Q(t, \mathbf{x}, \theta) d\theta. \tag{1}$$

Let V denote the set of all possible velocities of moving cells. We assume that V is radially symmetric and can be written as

$$V = [s_1, s_2] \times S^{n-1} \ , 0 \leq s_1 \leq s_2 \leq \infty, \tag{2}$$

where $[s_1, s_2]$ is the range of possible speeds. We consider the population of cells as a system of N particles having positions $\mathbf{x}^j \in \mathbb{R}^n$ and velocities $\mathbf{v}^j \in V$ for $j = 1, ..., N$. In the absence of reorientations, the cells move along straight lines obeying Newton's law of motion

$$d_t\mathbf{x}^j = \mathbf{v}^j, \qquad d_t\mathbf{v}^j = 0. \tag{3}$$

For the dynamics on the cell surface, we use a kinetic model for the binding of ECM-proteins $\bar{Q}$ and proteolytic product L (resulting from the cutting of fibres by matrix degrading enzymes) to free integrins denoted by R. The reversible binding of integrins to ECM-proteins leads to a complex RQ, according to the equation

$$\bar{Q} + R \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RQ.$$

The corresponding equation for the formation and dissociation of complexes RL of integrin and proteolytic product writes

$$L + R \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} RL.$$

We denote the concentrations of integrins of cell j bound to ECM-molecules by y_1^j and the concentration of integrins of the same cell bound to the proteolytic product L by y_2^j. As in [4], we assume that the total concentration of integrins (bound or unbound) of each cell is conserved and given by $R_0 \in \mathbb{R}_+$. We then have $R_0 - y_1^j - y_2^j$ for the concentration of unbound integrins of cell j. Clearly, one has $y_1^j, y_2^j \in Y$ with $Y := \{(y_1, y_2) \in (0, R_0)^2 \ : \ y_1 + y_2 < R_0\}$.
The state equations for the cell surface dynamics now read

$$\frac{\partial \mathbf{y}^j}{\partial t} = \mathbf{G}(\mathbf{y}^j, \bar{Q}(t, \mathbf{x}^j), L(t, \mathbf{x}^j)) \tag{4}$$

for $j = 1, ..., N$ and with the mapping $\mathbf{G} : Y \times [0, \infty) \times [0, \infty) \to \mathbb{R}^2$ defined by

$$\mathbf{G}(\mathbf{y}, q, l) := \begin{pmatrix} k_1(R_0 - y_1 - y_2)q - k_{-1}y_1 \\ k_2(R_0 - y_1 - y_2)l - k_{-2}y_2 \end{pmatrix}. \tag{5}$$

3. **Mesoscopic model.** Let $f(t, \mathbf{x}, \mathbf{v}, \mathbf{y})$ be the density function of cells in the $(2n + d)$-dimensional phase space ($n = 1, 2, 3,\ d \geq 1$) with coordinates $(\mathbf{x}, \mathbf{v}, \mathbf{y})$, where $\mathbf{x} \in \mathbb{R}^n$ is the position of a cell, $\mathbf{v} \in V \subset \mathbb{R}^n$ its velocity, and $\mathbf{y} \in Y \subset \mathbb{R}^d_+$ the vector $\mathbf{v}$ characterizing its internal state. The components y_i, $i = 1, \dots, d$ are concentrations of chemical species involved in intracellular signaling pathways controling the motion of the cell or -as in the previous section- in the receptor dynamics on the cell surface. Thus $f(t, \mathbf{x}, \mathbf{v}, \mathbf{y})d\mathbf{x}d\mathbf{v}d\mathbf{y}$ is the number of cells at time t with position between $\mathbf{x}$ and $d\mathbf{x}$, velocity between $\mathbf{v}$ and $d\mathbf{v}$, and internal (respectively receptor binding) state between $\mathbf{y}$ and $d\mathbf{y}$.

In the presence of external stimuli and accounting for the influence of the internal/surface dynamics, the density f of particles stisfies a Boltzmann like integro-differential PDE:

$$\frac{\partial f}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} f + \nabla_{\mathbf{y}} \cdot (\mathbf{G}(\mathbf{y}, \bar{Q}, L) f) = \mathcal{H}(f, Q) + \mathcal{C}(f, L), \tag{6}$$

where the operator in the right hand side is an integral one and it describes the velocity innovations due to haptotaxis and chemotaxis [14]. For a more detailed formal deduction of this equation we refer to [16].

In order to specify the right hand side in (6) let us observe that changes in the velocity can occur due to one of the following two kinds of events:

- A cell may encounter a collagen fibre and align to the direction of this fibre. We model this with a haptotaxis term $\mathcal{H}(f, Q)$.
- A cell may adjust its orientation to the gradient of the attracting chemical L, leading to a chemotaxis term $\mathcal{C}(f, L)$.

Note that we make a concrete suggestion for the chemoattractant L, assuming that it originates from the degradation of tissue fibers and connecting its evolution to that of cells and tissue via an equation of reaction-diffusion type (equation (17) below), whereas the chemotactic signal in [7] is merely a generic function of space and time.

The biological motivation for the inclusion of L as a chemoattractant is detailed in [23]. There, the authors show that the gradient of proteolytic fragments runs counter to the direction of invasion (given by the direction of fibres), thereby impeding migration. This has important consequences for the use of so called matrix metalloproteinases (MMP) inhibitors as therapeutic agents since by stopping fibre cutting (and thereby the production of proteolytic fragments) they may actually have the effect of enhancing invasion.

Assume the probability of a cell changing its orientation in the time interval under consideration is proportional to dt and denote the corresponding rates by $p_h(t, \mathbf{x}, \mathbf{v}, \mathbf{y})$ and $p_c(t, \mathbf{x}, \mathbf{v}, \mathbf{y})$. The haptotaxis operator $\mathcal{H}$ can be decomposed into a gain term $\mathcal{H}_+$ and a loss term $\mathcal{H}_-$ defined as

$$\mathcal{H}_+(f, Q) = \int_V \int_{S^{n-1}} p_h(t, \mathbf{x}, \mathbf{v}', \mathbf{y}) \psi(\mathbf{v}; \mathbf{v}', \theta') f(\mathbf{v}') Q(\theta') d\mathbf{v}' d\theta' \tag{7}$$

$$\mathcal{H}_-(f, Q) = f(\mathbf{v}) \int_V \int_{S^{n-1}} p_h(t, \mathbf{x}, \mathbf{v}, \mathbf{y}) \psi(\mathbf{v}'; \mathbf{v}, \theta') Q(\theta') d\mathbf{v}' d\theta', \tag{8}$$

where $\psi(\mathbf{v}; \mathbf{v}', \theta')$ denotes the probability of a cell having the velocity $\mathbf{v}'$ before the encounter with a fiber of orientation θ' to continue its motion with the velocity $\mathbf{v}$ after the interaction. Since the cells are conserved during interactions with the fibers, we have the condition

$$\int_V \psi(\mathbf{v}; \mathbf{v}', \theta') d\mathbf{v} = 1. \tag{9}$$

The decomposition of the cheotaxis operator $\mathcal{C}$ into a gain-term and a loss-term writes

$$\mathcal{C}_+(f, L) = \int_V p_c(t, \mathbf{x}, \mathbf{v}', \mathbf{y}) K[L](\mathbf{v}, \mathbf{v}', \mathbf{y}) f(\mathbf{v}') d\mathbf{v}' \tag{10}$$

$$\mathcal{C}_-(f, L) = \int_V p_c(t, \mathbf{x}, \mathbf{v}, \mathbf{y}) K[L](\mathbf{v}', \mathbf{v}, \mathbf{y}) f(\mathbf{v}) d\mathbf{v}'. \tag{11}$$

The turning kernel is given by

$$K[L](\mathbf{v}, \mathbf{v}', \mathbf{y}) = \alpha_1(\mathbf{y}) K(\mathbf{v}, \mathbf{v}') + \alpha_2(\mathbf{y}) K(\mathbf{v}, \nabla L)$$

with $\alpha_1, \alpha_2 : Y \to [0, 1]$ such that $\alpha_1 + \alpha_2 = 1$ on Y and K satisfies the conservation condition

$$\int_V K(\mathbf{v}, \mathbf{v}') d\mathbf{v} = 1. \tag{12}$$

Observe that the turning kernel above does not satisfy the more restrictive supplementary condition

$$\int_V K(\mathbf{v}, \mathbf{v}')d\mathbf{v}' = 1.$$

which was requested in [13], [14], [22].

The macroscopic population density at time t and position $\mathbf{x}$ is obtained by integrating over all possible velocities and internal states

$$\bar{f}(t, \mathbf{x}) := \int_Y \int_V f(t, \mathbf{x}, \mathbf{v}, \mathbf{y}) d\mathbf{v} d\mathbf{y}. \tag{13}$$

The mean projection of movement direction on the fibre orientation has been proposed e.g., in [14]:

$$\Pi[f](t, \mathbf{x}, \theta) = \frac{1}{\bar{f}(t, \mathbf{x})} \int_Y \int_V |\theta \cdot \hat{\mathbf{v}}| f(t, \mathbf{x}, \mathbf{v}, \mathbf{y}) d\mathbf{v} d\mathbf{y}. \tag{14}$$

In order to account for the dependency of proteolytic cutting upon the fibre density in the direction of movement we propose instead of (14)

$$\Pi[f](t, \mathbf{x}, \theta) = \frac{1}{\bar{f}(t, \mathbf{x})} \int_Y \int_V \frac{|\theta \cdot \hat{\mathbf{v}}|}{1 + Q(t, \mathbf{x}, \hat{\mathbf{v}})} f(t, \mathbf{x}, \mathbf{v}, \mathbf{y}) d\mathbf{v} d\mathbf{y}. \tag{15}$$

Our tissue modification model is given by the following evolution equation for the fibre density $Q(t, \mathbf{x}, \theta)$:

$$\frac{\partial Q}{\partial t} = \kappa(\Pi[f](t, \mathbf{x}, \theta) - 1)\bar{f}(t, \mathbf{x})Q(t, \mathbf{x}, \theta). \tag{16}$$

The reaction-diffusion equation for the product L of proteolysis reads

$$\frac{\partial L}{\partial t} = D_L \triangle L + \int_{S^{n-1}} \kappa(1 - \Pi[f](t, \mathbf{x}, \theta))\bar{f}(t, \mathbf{x})Q(t, \mathbf{x}, \theta) d\theta - r_L L \tag{17}$$

where the integral term on the right hand side models the production of L and r_L is the decay rate of L.

4. **Existence and uniqueness.**

We assume in the following that the dimension of the physical space is $n = 2$ or $n = 3$. As in the previous chapter we assume that V is radially symmetric and can be written as

$$V = [s_1, s_2] \times S^{n-1} \ , \ 0 \le s_1 \le s_2 \le \infty. \tag{18}$$

The PDE system modeling the dynamics of cell density, fibres and concentration of chemoattractant (proteolytic rests of fibres) etc. writes

$$\frac{\partial f}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} f = \mathcal{H}(f, Q) + \mathcal{C}(f, L). \tag{19}$$

$$\frac{\partial Q}{\partial t} = \kappa(\Pi[f](t, \mathbf{x}, \theta) - 1)\bar{f}(t, \mathbf{x})Q(t, \mathbf{x}, \theta). \tag{20}$$

$$\frac{\partial L}{\partial t} = D_L \triangle L + \int_{S^{n-1}} \kappa(1 - \Pi[f](t, \mathbf{x}, \theta))\bar{f}(t, \mathbf{x})Q(t, \mathbf{x}, \theta) d\theta - r_L L, \tag{21}$$

where Π has been defined in (14). The proof carries over easily to the choice (15) of Π. The system has to be supplemented by initial conditions $f(0, \cdot) = f_0$, $Q(0, \cdot) = Q_0$ and $L(0, \cdot) = L_0$.

4.1. **Properties of the turning operators.**

Lemma 4.1. *Let* $p_h(t) \in L^\infty(\mathbb{R}^n \times V)$ *and* $\psi(\mathbf{v};\mathbf{v}',\theta')$ *be given real nonnegative functions. We assume that* ψ *satisfies condition (9) and that there exists a positive constant* $M_h \geq 1$ *such that*

$$\int_V \psi(\mathbf{v};\mathbf{v}',\theta')d\mathbf{v}' \leq M_h \ , \ \forall(\mathbf{v},\theta') \in \mathbb{R}^n \times S^{n-1}. \tag{22}$$

Then the operator $\mathcal{H} = \mathcal{H}_+ - \mathcal{H}_-$ *defined by (7) and (8) is a bilinear and continuous mapping from* $L^p(\mathbb{R}^n \times V) \times L^\infty(\mathbb{R}^n \times S^{n-1})$ *into* $L^p(\mathbb{R}^n \times V)$ *for* $(p = 1, \infty)$ *and we have for* $t \in (0,T)$

$$||\mathcal{H}(f(t),Q(t))||_{L^p(\mathbb{R}^n\times V)} \leq 2M_h||p_h(t)||_{L^\infty(\mathbb{R}^n\times V)}||\bar{Q}(t)||_{L^\infty(\mathbb{R}^n)}||f(t)||_{L^p(\mathbb{R}^n\times V)}. \tag{23}$$

Moreover with $\widetilde{M_h} := M_h|V|^2$,

$$||\mathcal{H}(f(t),Q(t))||_{L^1(\mathbb{R}^n\times V)} \leq 2\widetilde{M_h}||p_h(t)||_{L^\infty(\mathbb{R}^n\times V)}||\bar{Q}(t)||_{L^1(\mathbb{R}^n)}||f(t)||_{L^\infty(\mathbb{R}^n\times V)}, \tag{24}$$

provided that additionally $Q(t) \in L^1(\mathbb{R}^n \times S^{n-1})$.

Proof. The bilinearity of $\mathcal{H}$ is obvious. From condition (9) follows

$$\begin{aligned}
&||\mathcal{H}_+(f,Q)||_{L^1(\mathbb{R}^n\times V)} \\
= &\int_{\mathbb{R}^n\times V}\left|\int_V\int_{S^{n-1}} p_h(t,\mathbf{x},\mathbf{v}')\psi(\mathbf{v};\mathbf{v}',\theta')f(\mathbf{v}')Q(\theta')d\mathbf{v}'d\theta'\right|d\mathbf{x}d\mathbf{v} \\
\leq &\int_{\mathbb{R}^n}\int_V\int_{S^{n-1}} |p_h(t,\mathbf{x},\mathbf{v}')||f(\mathbf{v}')||Q(\theta')|d\mathbf{v}'d\theta'd\mathbf{x} \\
\leq &||p_h(t)||_{L^\infty(\mathbb{R}^n\times V)}||\bar{Q}(t)||_{L^\infty(\mathbb{R}^n)}||f(t)||_{L^1(\mathbb{R}^n\times V)} \\
\leq &M_h||p_h(t)||_{L^\infty(\mathbb{R}^n\times V)}||\bar{Q}(t)||_{L^\infty(\mathbb{R}^n)}||f(t)||_{L^1(\mathbb{R}^n\times V)}
\end{aligned}$$

and from (22)

$$\begin{aligned}
&||\mathcal{H}_+(f(t),Q(t))||_{L^\infty(\mathbb{R}^n\times V)} \\
= &\sup_{(\mathbf{x},\mathbf{v})\in\mathbb{R}^n\times V}\left|\int_V\int_{S^{n-1}} p_h(t,\mathbf{x},\mathbf{v}')\psi(\mathbf{v};\mathbf{v}',\theta')f(\mathbf{v}')Q(\theta')d\mathbf{v}'d\theta'\right| \\
\leq &M_h||p_h(t)||_{L^\infty(\mathbb{R}^n\times V)}||\bar{Q}(t)||_{L^\infty(\mathbb{R}^n)}||f(t)||_{L^\infty(\mathbb{R}^n\times V)}.
\end{aligned}$$

The estimates for $\mathcal{H}_-$ can be derived along the same lines. The proof of (24) involves only slight modifications. □

Lemma 4.2. *Let* $p_c(t) \in L^\infty(\mathbb{R}^n \times V)$, α_1, α_2 *and* $K(\mathbf{v},\mathbf{v}')$ *(all nonnegative) be given. We assume that* K *satisfies condition (12) and that there exist positive constants* $M_{cl}, M_{cb} > 0$ *such that for all* $\mathbf{v},\mathbf{w} \in \mathbb{R}^n$

$$|K(\cdot,\mathbf{v})| \leq M_{cb}|\chi(\mathbf{v})| \text{ on } V \tag{25}$$

$$|K(\cdot,\mathbf{v}) - K(\cdot,\mathbf{w})| \leq M_{cl}|\chi(\mathbf{v}) - \chi(\mathbf{w})| \text{ on } V \tag{26}$$

with $\chi : \mathbb{R}^n \to V$ *defined by* $\chi(\xi) := \xi$ *for* $||\xi|| \leq s_2$ *and* $\chi(\xi) := s_2\hat{\xi}$ *for* $||\xi|| > s_2$. *Then the operator* $\mathcal{C}$ *defined by (10) and (11) is a linear and continuous mapping from* $L^p(\mathbb{R}^n\times V)$ *into* $L^p(\mathbb{R}^n\times V)$ *for* $(p = 1,\infty)$ *and there exists a constant* $M_C > 0$ *such that for* $t \in (0,T)$

$$||\mathcal{C}(f(t),L(t))||_{L^p(\mathbb{R}^n\times V)} \leq 2M_C||p_c(t)||_{L^\infty(\mathbb{R}^n\times V)}||f(t)||_{L^p(\mathbb{R}^n\times V)}. \tag{27}$$

Proof. Again, the linearity of $\mathcal{C}$ is straightforward. From (25) it follows that

$$\int_V K[L](\mathbf{v},\mathbf{v}')d\mathbf{v}' \leq M_C \ , \forall \mathbf{v} \in V$$

with $M_C := max\{1, M_{cb}s_2|V|\}$. Now the proof of (27) for $p = 1, \infty$ is essentially the same as the one of Lemma 4.1. □

4.2. **Linear theorem.** We linearize the equation for cell movement by decoupling equation (19) from (20) and (21). For given functions $Q_* : [0,T]\times\mathbb{R}^n\times S^{n-1} \to \mathbb{R}_+$ and $L_* : [0,T]\times\mathbb{R}^n \to \mathbb{R}_+$ we consider

$$\frac{\partial f}{\partial t} + \mathbf{v}\cdot\nabla_{\mathbf{x}} f = \mathcal{H}(f,Q_*) + \mathcal{C}(f,L_*) + g(t,\mathbf{x},\mathbf{v}), \tag{28}$$

where we have included an additional source term $g(t,\mathbf{x},\mathbf{v})$ so that the difference of solutions to (28) with $g \neq 0$ resp. with $g \equiv 0$ for different choices of Q_* and L_* still satisfies (28) with g chosen appropriately. This will later (beginning with equation (56) in the next section) allow us to use the estimates obtained in this chapter for the difference of such solutions.

Definition 4.3. A weak solution of equation (28) is a function f satisfying

$$\begin{aligned} &- \int_0^T\int_{\mathbb{R}^n\times V} f\frac{\partial\phi}{\partial t}d\mathbf{x}d\mathbf{v}dt - \int_{\mathbb{R}^n\times V} f_0\phi(0,\cdot)d\mathbf{x}d\mathbf{v} - \int_0^T\int_{\mathbb{R}^n\times V} f\mathbf{v}\cdot\nabla_{\mathbf{x}}\phi d\mathbf{x}d\mathbf{v}dt \\ &- \int_0^T\int_{\mathbb{R}^n\times V}[\mathcal{H}(f,Q_*) + \mathcal{C}(f,L_*) + g(t,\mathbf{x},\mathbf{v})]\phi d\mathbf{x}d\mathbf{v}dt = 0\end{aligned}$$

for all test functions $\phi \in C_0^\infty([0,T]\times\mathbb{R}^n\times V)$.

Concerning the existence and uniqueness of a solution to (28) we have the following

Theorem 4.4. *Let $f_0 \in L^\infty(\mathbb{R}^n\times V)\cap L^1(\mathbb{R}^n\times V)$ and $g \in L^1(0,T;L^\infty(\mathbb{R}^n\times V)\cap L^1(\mathbb{R}^n\times V))$. Suppose further that:*

- *Q_* and L_* satisfy*

$$||\bar{Q}_*||_{L^\infty(0,T;L^\infty(\mathbb{R}^n))} \leq K_Q \ , \qquad ||L_*||_{L^\infty(0,T;L^\infty(\mathbb{R}^n))} \leq K_L$$

and

$$Q_*(t,\mathbf{x},\theta) \geq 0 \text{ a.e. on } (0,T)\times\mathbb{R}^n\times S^{n-1} \tag{29}$$
$$L_*(t,\mathbf{x}) \geq 0 \text{ a.e. on } (0,T)\times\mathbb{R}^n; \tag{30}$$

- *f_0 satisfies*

$$f_0 \geq 0 \text{ a.e. on } \mathbb{R}^n\times V; \tag{31}$$

- *p_c and p_h satisfy*

$$||p_h||_{L^\infty(0,T;L^\infty(\mathbb{R}^n\times V))} \leq K_h, \qquad ||p_c||_{L^\infty(0,T;L^\infty(\mathbb{R}^n\times V))} \leq K_c.$$

Then there exists a unique weak solution f of (28) in $L^1(\mathbb{R}^n\times V)\cap L^\infty(\mathbb{R}^n\times V)$ corresponding to the initial condition f_0. Additionally, we have the estimates

$$||f(t)||_{L^1(\mathbb{R}^n\times V)} \leq \left(||f_0||_{L^1(\mathbb{R}^n\times V)} + \int_0^T ||g(\tau)||_{L^1(\mathbb{R}^n\times V)}d\tau\right)(1+Cte^{Ct}) \tag{32}$$

$$||f(t)||_{L^\infty(\mathbb{R}^n\times V)} \leq \left(||f_0||_{L^\infty(\mathbb{R}^n\times V)} + \int_0^T ||g||_{L^\infty(\mathbb{R}^n\times V))}dt\right)(1+Cte^{Ct}), \tag{33}$$

where $C = C(K_Q, K_L)$ denotes generical constants depending on K_Q, K_L and the parameters of the problem.

Proof. We are now going to show that there exists a unique solution $f \in C(0,T;C^1(\mathbb{R}^n \times V))$ of

$$\frac{\partial f}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} f = \mathcal{H}(f, Q_*) + \mathcal{C}(f, L_*) + g(t, \mathbf{x}, \mathbf{v}) \tag{34}$$

in $(0,T) \times \mathbb{R}^n \times V$ satisfying $f|_{t=0} = f_0$ in $\mathbb{R}^n \times V$. Our approach is similar to the one employed in Chapter XI of [12].

The characteristics of equation (34) are given as

$$\frac{d\mathbf{X}}{ds} = \mathbf{V}, \qquad \frac{d\mathbf{V}}{ds} = 0 \tag{35}$$

Along backward characteristics starting at $(\mathbf{x}, \mathbf{v}, t)$, we have for $0 \le s \le t$,

$$\mathbf{X}(s; \mathbf{x}, \mathbf{v}, t) = \mathbf{x} - \mathbf{v}(t - s). \tag{36}$$

Integrating the second equation of (35) for initial points in the support of the initial data f_0 we have that $|\mathbf{V}(s)| = |\mathbf{V}(0)| \le s_2$ for all $s \in [0,T]$. We transform equation (34) by multiplication with $e^{-\lambda t}$ $(\lambda > 0)$ into the equivalent problem

$$\frac{\partial f_\lambda}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} f_\lambda + \lambda f_\lambda - \mathcal{H}(f_\lambda, Q_*) - \mathcal{C}(f_\lambda, L_*) = g_\lambda(t, \mathbf{x}, \mathbf{v}) \tag{37}$$

with $f_\lambda = e^{-\lambda t} f$ and $g_\lambda = e^{-\lambda t} g$.

The unique solution to equation (37) with $\mathcal{H}, \mathcal{C} \equiv 0$ is given by

$$f_\lambda(t, \mathbf{x}, \mathbf{v}) = e^{-\lambda t} f_0(\mathbf{X}(0), \mathbf{v}) + \int_0^t e^{-\lambda(t-\tau)} g_\lambda(\tau, \mathbf{X}(\tau), \mathbf{v}) d\tau. \tag{38}$$

We denote by $S_\lambda(g_\lambda, f_0)$ the solution of (37) with $\mathcal{H}, \mathcal{C} \equiv 0$, right hand side g_λ and initial condition f_0.

Using $\nabla_{\mathbf{x}} \mathbf{X} = \mathbb{I}_n$, we have

$$\begin{aligned}
||S_\lambda(g_\lambda, 0)||_{L^1(0,T;L^1(\mathbb{R}^n \times V))} &= \int_0^T \int_0^t \int_{\mathbb{R}^n \times V} |e^{-\lambda(t-\tau)} g_\lambda(\tau, \mathbf{X}(\tau), \mathbf{v})| d\mathbf{x} d\mathbf{v} d\tau dt \\
&= \int_0^T \int_0^t \int_{\mathbb{R}^n \times V} |e^{-\lambda(t-\tau)} g_\lambda(\tau, \mathbf{X}(\tau), \mathbf{v})| (\det \nabla_{\mathbf{x}} \mathbf{X})^{-1} d\mathbf{X} d\mathbf{v} d\tau dt \\
&= \int_0^T e^{-\lambda t} \int_0^t \int_{\mathbb{R}^n \times V} |e^{\lambda \tau} g_\lambda(\tau, \mathbf{X}(\tau), \mathbf{v})| d\mathbf{X} d\mathbf{v} d\tau dt \\
&\le \frac{1}{\lambda} \int_0^T \int_{\mathbb{R}^n \times V} |g_\lambda(t, \mathbf{X}(t), \mathbf{v},)| d\mathbf{X} d\mathbf{v} dt = \frac{1}{\lambda} ||g_\lambda||_{L^1(0,T;L^1(\mathbb{R}^n \times V))},
\end{aligned}$$

where in the last step we used integration by parts w.r.t. t.

We move on to the case with general $\mathcal{H}$ and $\mathcal{C}$. We choose $\lambda > ||\mathcal{H}(\cdot, \bar{Q}_*) + \mathcal{C}(\cdot, L_*)||$ (the operator norm from $L^1(\mathbb{R}^n \times V)$ into itself). We look for a solution to (37) having the form $f_\lambda = S_\lambda(\widetilde{g_\lambda}, f_0)$ with $\widetilde{g_\lambda} \in L^1(0,T;L^1(R^n \times V))$ to be determined. Then f_λ solves (37) if and only if

$$\widetilde{g_\lambda} - \mathcal{H}(S_\lambda(\widetilde{g_\lambda}, f_0), \bar{Q}_*) - \mathcal{C}(S_\lambda(\widetilde{g_\lambda}, f_0), L_*) = g_\lambda. \tag{39}$$

Since we can write f_λ as the sum of the solution to (37) with zero initial data and right hand side $\widetilde{g_\lambda}$ and the solution to (37) with initial data f_0 and zero right hand side, (39) becomes

$$(\mathcal{I} + Z_\lambda)\widetilde{g_\lambda} = g_\lambda + \mathcal{H}(S_\lambda(0, f_0), \bar{Q}_*) + \mathcal{C}(S_\lambda(0, f_0), L_*) \tag{40}$$

with

$$Z_\lambda \widetilde{g_\lambda} = -\mathcal{H}(S_\lambda(\widetilde{g_\lambda}, 0), \bar{Q}_*) - \mathcal{C}(S_\lambda(\widetilde{g_\lambda}, 0), L_*). \tag{41}$$

From the estimate on the norm of the solution operator S_λ, we have that $||Z_\lambda|| \leq \lambda^{-1}||\mathcal{H}(\cdot, \bar{Q}_*) + \mathcal{C}(\cdot, L_*)|| < 1$ (the operator norms are again from $L^1(\mathbb{R}^n \times V)$ into itself). Thus (39) has the unique solution

$$\widetilde{g_\lambda} = \sum_{m=0}^{\infty} (-Z_\lambda)^m [g_\lambda + \mathcal{H}(S_\lambda(0, f_0), \bar{Q}_*) + \mathcal{C}(S_\lambda(0, f_0), L_*)].$$

From f_λ we get the unique solution f to (34) by multiplication with $e^{\lambda t}$. That f has the stated regularity follows from the explicit construction of the solution and the regularity of the data.

Integrating (34) along the backward characteristic (36) from 0 to t, we get

$$\begin{aligned} f(\mathbf{x}, \mathbf{v}, t) &= f_0(\mathbf{X}(0), \mathbf{v}) + \int_0^t \mathcal{H}(\mathbf{X}(\tau), f(\mathbf{X}(\tau), \mathbf{v}, \tau), Q_*(\mathbf{X}(\tau), \theta, \tau)) d\tau \quad (42) \\ &+ \int_0^t \mathcal{C}(\mathbf{X}(\tau), f(\mathbf{X}(\tau), \mathbf{v}, \tau), L_*(\mathbf{X}(\tau), \tau)) + g(\tau, \mathbf{X}(\tau), \mathbf{v}) d\tau. \end{aligned}$$

With the estimates for $\mathcal{H}$ (Lemma 4.1) and $\mathcal{C}$ (Lemma 4.2), we arrive at

$$\begin{aligned} &||f(t)||_{L^\infty(R^n \times V)} \leq ||f_0||_{L^\infty(\mathbb{R}^n \times V)} \\ &+ \quad 2M_h ||p_h||_{L^\infty(0,T;L^\infty(\mathbb{R}^n \times V))} ||\bar{Q}_*(t)||_{L^\infty(\mathbb{R}^n)} \int_0^t ||f(\tau)||_{L^\infty(\mathbb{R}^n \times V)} d\tau \\ &+ \quad 2M_c ||p_c||_{L^\infty(0,T;L^\infty(\mathbb{R}^n \times V))} \int_0^t ||f(\tau)||_{L^\infty(\mathbb{R}^n \times V)} d\tau + \int_0^t ||g(\tau)||_{L^\infty(\mathbb{R}^n \times V)} d\tau \end{aligned}$$

a.e. on $(0, T)$. Application of Gronwall's inequality yields

$$||f(t)||_{L^\infty(\mathbb{R}^n \times V)} \leq \left(||f_0||_{L^\infty(\mathbb{R}^n \times V)} + \int_0^T ||g(t)||_{L^\infty(\mathbb{R}^n \times V))} dt \right) (1 + Cte^{Ct}) \tag{43}$$

with

$$C = 2M_h K_h K_Q + 2M_c K_c.$$

Using $\nabla_{\mathbf{x}} \mathbf{X} = \mathbb{I}_n$, we have

$$\int_{\mathbb{R}^n \times V} |f(\mathbf{X}(\tau), \mathbf{v}, \tau)| d\mathbf{x} d\mathbf{v} \leq \int_{\mathbb{R}^n \times V} |f(\mathbf{X}(\tau), \mathbf{v}, \tau)| d\mathbf{X} d\mathbf{v}.$$

Obviously, the same result also holds for g. Integrating (42) w.r.t. $\mathbf{x}, \mathbf{v}$ yields

$$\begin{aligned} & ||f(t)||_{L^1(\mathbb{R}^n\times V)} \leq ||f_0||_{L^1(\mathbb{R}^n\times V)} \\ + \quad & 2M_h||p_h||_{L^\infty(0,T;L^\infty(\mathbb{R}^n\times V))}||\bar{Q}_*||_{L^\infty(0,T;L^\infty(\mathbb{R}^n))}\int_0^t ||f(\tau)||_{L^1(\mathbb{R}^n\times V)}d\tau \\ + \quad & 2M_c||p_c||_{L^\infty(0,T;L^\infty(\mathbb{R}^n\times V))}\int_0^t ||f(\tau)||_{L^1(\mathbb{R}^n\times V)}d\tau \\ + \quad & \int_0^t ||g(\tau)||_{L^1(\mathbb{R}^n\times V)}d\tau. \end{aligned}$$

Applying the Gronwall inequality, we obtain

$$||f(t)||_{L^1(\mathbb{R}^n\times V)} \leq \left(||f_0||_{L^1(\mathbb{R}^n\times V)} + \int_0^T ||g(\tau)||_{L^1(\mathbb{R}^n\times V)}d\tau\right)(1+Cte^{Ct}), \tag{44}$$

with

$$C = 2M_hK_hK_Q + 2M_cK_c. \tag{45}$$

It is easy to see that f is a weak solution of (28). □

We next turn our attention to the equation for tissue modification and linearize it by decoupling equation (20) from the rest of the system (19)-(21). For a given function $f_* : [0,T]\times\mathbb{R}^n\times V \to \mathbb{R}$ we consider

$$\frac{\partial Q}{\partial t} = \kappa(\Pi[f_*](t,\mathbf{x},\theta)-1)\bar{f}_*(t,\mathbf{x})Q(t,\mathbf{x},\theta) + h(t,\mathbf{x},\theta). \tag{46}$$

The additional source term h in (46) has been included for the same reason as g in equation (28) above.

Theorem 4.5. *Let $Q_0 \in L^1(\mathbb{R}^n\times S^{n-1})\cap L^\infty(\mathbb{R}^n\times S^{n-1})$ be a positive function and $h \in L^1(\mathbb{R}^n\times S^{n-1})\cap L^\infty(\mathbb{R}^n\times S^{n-1})$. Then there exists a unique solution $Q(t) \in L^1(\mathbb{R}^n\times S^{n-1})\cap L^\infty(\mathbb{R}^n\times S^{n-1})$ to equation (46) with initial condition $Q(0) = Q_0$ and we have the estimates $(p = 1,\infty)$*

$$||Q(t)||_{L^p(\mathbb{R}^n\times S^{n-1})} \leq ||Q_0||_{L^1(\mathbb{R}^n\times S^{n-1})} + \int_0^T ||h(\tau)||_{L^p(\mathbb{R}^n\times S^{n-1})}d\tau \tag{47}$$

Moreover, if $h\equiv 0$, then $Q(t)\geq 0$ a.e.

Proof. The estimate (47) can be obtained for $p=1$ by integrating (46) w.r.t. time and then w.r.t. $\mathbf{x}$, θ, respectively for $p=\infty$ upon taking the supremum w.r.t. $\mathbf{x}$ and θ. □

We finally linearize the equation for the soluble ligand by decoupling equation (21) from the rest of the system (19)-(21). For given functions
$f_* : [0,T]\times\mathbb{R}^n\times V\to\mathbb{R}$ and $Q_* : [0,T]\times\mathbb{R}^n\times S^{n-1}\to\mathbb{R}$ we consider

$$\frac{\partial L}{\partial t} = D_L\triangle L + \int_{S^{n-1}} \kappa(1-\Pi[f_*](t,\mathbf{x},\theta))\bar{f}_*(t,\mathbf{x})Q_*(t,\mathbf{x},\theta)d\theta - r_LL. \tag{48}$$

For simplicity, we only consider the case $L(0,\cdot) = L_0 = 0$. The generalization to the case $L_0 \neq 0$ is straightforward. A direct application of a standard result for the heat equation proves the following

Theorem 4.6. *Let $f_* \in L^\infty(0,T;L^\infty(\mathbb{R}^n\times V))$ and $Q_* \in L^\infty(0,T;L^\infty(\mathbb{R}^n\times S^{n-1}))$ be nonnegative functions. Then there is a unique nonnegative solution L to equation (48) with initial condition $L(0,\cdot)=0$. Moreover, we have the estimate*

$$||L(t)||_{L^\infty(\mathbb{R}^n\times S^{n-1})} \leq \frac{\kappa}{D_L r_L}|V||S^{n-1}|||f_*(t)||_{L^\infty(\mathbb{R}^n\times V)}||Q_*(t)||_{L^\infty(\mathbb{R}^n\times S^{n-1})}. \quad (49)$$

4.3. **The non-linear problem.** We are now going to show the existence-uniqueness result for our primal (nonlinear) system (19)-(21).

Theorem 4.7. *Suppose that f_0 and Q_0 satisfy the conditions in Theorems 4.4 and 4.5. Then the system of partial differential equations (19)-(21) with initial conditions $f(0,\cdot)=f_0$, $Q(0,\cdot)=Q_0$ and $L(0,\cdot)=L_0\equiv 0$ has locally in time a unique solution (f,Q,L) with*

$$\begin{aligned} f &\in L^\infty(0,T;L^1(\mathbb{R}^n\times V)\cap L^\infty(\mathbb{R}^n\times V)) \\ Q &\in L^\infty(0,T;L^\infty(\mathbb{R}^n\times S^{n-1})\cap L^1(\mathbb{R}^n\times S^{n-1})) \\ L &\in L^\infty(0,T;W^{1,1}(\mathbb{R}^n)). \end{aligned}$$

Here the solution f to (19) is to be understood in the weak sense (see Definition 4.3).

Proof. We construct a sequence of functions $(f_m,Q_m,L_m)_{m\in\mathbb{N}}$ and show that it converges to the solution of the nonlinear system (19)-(21).

Let (f_1,Q_1,L_1) be the solution of

$$\frac{\partial f_1}{\partial t} + \mathbf{v}\cdot\nabla_{\mathbf{x}} f_1 = \mathcal{H}(f_1,Q_0) + \mathcal{C}(f_1,L_0) \quad (50)$$

$$\frac{\partial Q_1}{\partial t} = \kappa(\Pi[f_0](t,\mathbf{x},\theta)-1)\bar{f}_0(\mathbf{x})Q_1(t,\mathbf{x},\theta) \quad (51)$$

$$\frac{\partial L_1}{\partial t} = D_L\triangle L_1 + \int_{S^{n-1}}\kappa(1-\Pi[f_0](t,\mathbf{x},\theta))\bar{f}_0(\mathbf{x})Q_0(\mathbf{x},\theta)d\theta - r_L L_1 \quad (52)$$

with initial conditions $f_1(0,\cdot)=f_0(\cdot)$, $Q_1(0,\cdot)=Q_0(\cdot)$ and $L_1(0,\cdot)=L_0(\cdot)=0$. The existence and uniqueness of f_1 follows from Theorem 4.4. The existence and uniqueness of Q_1 and L_1 is a consequence of Theorems 4.5 and 4.6.
Moreover, we have that $f_1(t)\in L^\infty(\mathbb{R}^n\times V)$, $Q_1(t)\in L^\infty(\mathbb{R}^n\times S^{n-1})$ and $L_1(t)\in L^\infty(\mathbb{R}^n)$ are a.e. nonnegative functions with

$$\begin{aligned} ||Q_1(t)||_{L^\infty(\mathbb{R}^n\times S^{n-1})} &\leq ||Q_0||_{L^\infty(\mathbb{R}^n\times S^{n-1})} \\ ||L_1(t)||_{L^\infty(\mathbb{R}^n\times S^{n-1})} &\leq \frac{\kappa}{D_L r_L}|V|\cdot|S^{n-1}|||f_0||_{L^\infty(\mathbb{R}^n\times V)}\cdot||Q_0||_{L^\infty(\mathbb{R}^n\times S^{n-1})} \\ ||f_1(t)||_{L^\infty(\mathbb{R}^n\times V)} &\leq (1+e)||f_0||_{L^\infty(\mathbb{R}^n\times V)}, \end{aligned}$$

provided that (WLOG assume $||Q_0||_{L^\infty(\mathbb{R}^n\times S^{n-1})}>0$.)

$$T \leq \frac{1}{C(||Q_0||_{L^\infty(\mathbb{R}^n\times S^{n-1})},0)},$$

where C is the constant from estimate (33). In fact, to get uniform bounds on the iterates, we will assume in the following that

$$T \leq \frac{1}{C(2||Q_0||_{L^\infty(\mathbb{R}^n\times S^{n-1})}, 2(1+e)|V||S^{n-1}|||Q_0||_{L^\infty(\mathbb{R}^n\times S^{n-1})}||f_0||_{L^\infty(\mathbb{R}^n\times V)})}.$$

Suppose we constructed the sequence (f_m, Q_m, L_m) up to a certain $m \in \mathbb{N}$ with $f_m(t) \in L^\infty(\mathbb{R}^n \times V)$, $Q_m \in L^\infty(\mathbb{R}^n \times S^{n-1})$ and $L_m(t) \in L^\infty(\mathbb{R}^n)$ a.e. nonnegative functions satisfying

$$\begin{aligned} & \|f_m(t)\|_{L^\infty(\mathbb{R}^n\times V\times Y)} \le (1+e)\|f_0\|_{L^\infty(\mathbb{R}^n\times V)}, \\ & \|Q_m(t)\|_{L^\infty(\mathbb{R}^n\times S^{n-1})} \le \|Q_0\|_{L^\infty(\mathbb{R}^n\times S^{n-1})}, \\ & \|L_m(t)\|_{L^\infty(\mathbb{R}^n\times S^{n-1})} \\ \le\ & \frac{\kappa}{D_L r_L}(1+e)|V||S^{n-1}|\|f_0\|_{L^\infty(\mathbb{R}^n\times V)}\|Q_0\|_{L^\infty(\mathbb{R}^n\times S^{n-1})}. \end{aligned}$$

Then, for this $m \in \mathbb{N}$, there is a solution $(f_{m+1}, Q_{m+1}, L_{m+1})$ to

$$\frac{\partial f_{m+1}}{\partial t} + \mathbf{v}\cdot\nabla_{\mathbf{x}} f_{m+1} = \mathcal{H}(f_{m+1}, Q_m) + \mathcal{C}(f_{m+1}, L_m),$$

$$\frac{\partial Q_{m+1}}{\partial t} = \kappa(\Pi[f_m](t,\mathbf{x},\theta) - 1)\bar{f}_m(t,\mathbf{x})Q_{m+1}(t,\mathbf{x},\theta),$$

$$\frac{\partial L_{m+1}}{\partial t} = D_L\triangle L_{m+1} + \int_{S^{n-1}} \kappa(1-\Pi[f_m](t,\mathbf{x},\theta))\bar{f}_m(t,\mathbf{x})Q_m(t,\mathbf{x},\theta)d\theta - r_L L_{m+1},$$

with initial conditions $f_{m+1}(0,\cdot) = f_0(\cdot)$, $Q_{m+1}(0,\cdot) = Q_0(\cdot)$ and $L_{m+1}(0,\cdot) = L_0(\cdot) = 0$. The existence and uniqueness of f_{m+1} follows from Theorem 4.4. The existence and uniqueness of Q_{m+1} and L_{m+1} is a result of Theorems 4.5, 4.6. Moreover, the functions $f_{m+1}(t) \in L^\infty(\mathbb{R}^n \times V)$, $Q_{m+1}(t) \in L^\infty(\mathbb{R}^n \times S^{n-1})$ and $L_{m+1}(t) \in L^\infty(\mathbb{R}^n)$ are nonnegative a.e. and satisfy

$$\begin{aligned} & \|f_{m+1}(t)\|_{L^\infty(\mathbb{R}^n\times V\times Y)} \le (1+e)\|f_0\|_{L^\infty(\mathbb{R}^n\times V)}, \\ & \|Q_{m+1}(t)\|_{L^\infty(\mathbb{R}^n\times S^{n-1})} \le \|Q_0\|_{L^\infty(\mathbb{R}^n\times S^{n-1})}, \\ & \|L_{m+1}(t)\|_{L^\infty(\mathbb{R}^n\times S^{n-1})} \\ \le\ & \frac{\kappa}{D_L r_L}(1+e)|V||S^{n-1}|\|f_0\|_{L^\infty(\mathbb{R}^n\times V)}\|Q_0\|_{L^\infty(\mathbb{R}^n\times S^{n-1})} \end{aligned}$$

which yields the existence of the next iterates $(f_{m+2}, Q_{m+2}, L_{m+2})$ and so on.

Now $Q_{m+1} - Q_m$ satisfies the equation

$$\frac{\partial}{\partial t}(Q_{m+1} - Q_m) = \kappa(\Pi[f_m](t,\mathbf{x},\theta) - 1)\bar{f}_m(t,\mathbf{x})(Q_{m+1} - Q_m)(t,\mathbf{x},\theta) + h(t,\mathbf{x},\theta)$$

with h defined by

$$h := \kappa\left[\int_V |\theta\cdot\hat{\mathbf{v}}|(f_m - f_{m-1})d\mathbf{v} + \bar{f}_{m-1} - \bar{f}_m\right]Q_m.$$

Then from (47) we have the estimate

$$\begin{aligned} & \|Q_{m+1} - Q_m\|_{L^\infty(0,T;L^1(\mathbb{R}^n\times S^{n-1}))} \\ & \le 2T\kappa|S^{n-1}|\|Q_0\|_{L^\infty(\mathbb{R}^n\times S^{n-1})}\|(f_m - f_{m-1})\|_{L^\infty(0,T;L^1(\mathbb{R}^n\times V))}. \end{aligned} \tag{53}$$

Similarly, $L_{m+1} - L_m$ satisfies

$$\frac{\partial}{\partial t}(L_{m+1} - L_m) - D_L\triangle(L_{m+1} - L_m) = \rho - r_L(L_{m+1} - L_m)$$

with ρ defined by

$$\rho := \int_{S^{n-1}} \kappa(1-\Pi[f_m])\bar{f}_m Q_m d\theta - \int_{S^{n-1}} \kappa(1-\Pi[f_{m-1}])\bar{f}_{m-1}Q_{m-1}d\theta.$$

For ρ we then have the estimate

$$\begin{aligned}&||\rho||_{L^\infty(0,T;L^1(\mathbb{R}^n))}\\&\leq 2\kappa|S^{n-1}|^2||(f_m-f_{m-1})||_{L^\infty(0,T;L^1(\mathbb{R}^n\times V))}||Q_0||_{L^\infty(\mathbb{R}^n\times S^{n-1})}\\&+2\kappa|V|||f_{m-1}||_{L^\infty(0,T;L^\infty(\mathbb{R}^n\times V))}||Q_m-Q_{m-1}||_{L^\infty(0,T;L^1(\mathbb{R}^n\times S^{n-1}))},\end{aligned}$$

so that we can deduce using a standard result for the heat equation

$$\begin{aligned}&||L_{m+1}-L_m||_{L^\infty(0,T;L^1(\mathbb{R}^n))}\\&\leq 2C(r_L,D_L)\kappa|S^{n-1}|^2||(f_m-f_{m-1})||_{L^\infty(0,T;L^1(\mathbb{R}^n\times V))}||Q_0||_{L^\infty(\mathbb{R}^n\times S^{n-1})}\\&+2\kappa C(r_L,D_L)|V|||f_{m-1}||_{L^\infty(0,T;L^\infty(\mathbb{R}^n\times V))}||Q_m-Q_{m-1}||_{L^\infty(0,T;L^1(\mathbb{R}^n\times S^{n-1}))}\end{aligned}\tag{54}$$

and

$$\begin{aligned}&||\nabla L_{m+1}-\nabla L_m||_{L^\infty(0,T;L^1(\mathbb{R}^n))}\\&\leq 4C(r_L,D_L)\kappa|S^{n-1}|^2||(f_m-f_{m-1})||_{L^\infty(0,T;L^1(\mathbb{R}^n\times V))}||Q_0||_{L^\infty(\mathbb{R}^n\times S^{n-1})}\\&+4\kappa C(r_L,D_L)|V|||f_{m-1}||_{L^\infty(0,T;L^\infty(\mathbb{R}^n\times V))}||Q_m-Q_{m-1}||_{L^\infty(0,T;L^1(\mathbb{R}^n\times S^{n-1}))}.\end{aligned}\tag{55}$$

Now $f_{m+1}-f_m$ satisfies the equation

$$\frac{\partial}{\partial t}(f_{m+1}-f_m)+\mathbf{v}\cdot\nabla_{\mathbf{x}}(f_{m+1}-f_m)=\mathcal{H}(f_{m+1}-f_m,Q_m)+\mathcal{C}(f_{m+1}-f_m,L_m)+g \tag{56}$$

with g defined by

$$g(\mathbf{x},\mathbf{v},t):=\mathcal{H}(f_m,Q_m-Q_{m-1})+\mathcal{C}(f_m,L_m)-\mathcal{C}(f_m,L_{m-1}).$$

Since g satisfies (due to (33) and (24))

$$\begin{aligned}&\int_0^T||g(\tau)||_{L^1(\mathbb{R}^n\times V)}\\\leq\;&\int_0^T||\mathcal{H}(f_m,\delta Q_m)(\tau)||_{L^1(\mathbb{R}^n\times V)}+||\mathcal{C}(f_m,L_m)-\mathcal{C}(f_m,L_{m-1})||_{L^1(\mathbb{R}^n\times V)}d\tau\\\leq\;&\int_0^T 2M_h||p_h(\tau)||_{L^\infty(\mathbb{R}^n\times V)}|V|^2||\delta Q_m(\tau)||_{L^1(\mathbb{R}^n\times S^{n-1})}||f_m(\tau)||_{L^\infty(\mathbb{R}^n\times V)}d\tau\\+\;&\int_0^T 2M_{cl}||p_c(\tau)||_{L^\infty(\mathbb{R}^n\times V)}|V|^2||\nabla L_m-\nabla L_{m-1}||_{L^1(\mathbb{R}^n)}||f_m(\tau)||_{L^\infty(\mathbb{R}^n\times V)}d\tau\end{aligned}$$

(where $\delta Q_m := Q_m-Q_{m-1}$) and further

$$\begin{aligned}&\int_0^T||g||_{L^1(\mathbb{R}^n\times V)}d\tau\\\leq\;&T(2M_hK_h|V|^2||f_m||)||\delta Q_m||_{L^\infty(0,T;L^1(\mathbb{R}^n\times S^{n-1}))}\\+\;&T(2M_{cl}K_c|V|^2||f_m||)||\nabla L_m-\nabla L_{m-1}||_{L^\infty(0,T;L^1(\mathbb{R}^n))}.\end{aligned}$$

From the estimate on g, using (32), we can derive the following estimate:

$$\begin{aligned}&||f_{m+1}-f_m||_{L^\infty(0,T;L^1(\mathbb{R}^n\times V))}\\&\leq T(1+e)(2M_hK_h|V|^2||f_m||_{L^\infty(0,T;L^\infty(\mathbb{R}^n\times V))})||Q_m-Q_{m-1}||_{L^\infty(0,T;L^1(\mathbb{R}^n\times S^{n-1}))}\\&+T(1+e)(2M_{cl}K_c|V|^2||f_m||)_{L^\infty(0,T;L^\infty(\mathbb{R}^n\times V))}||\nabla L_m-\nabla L_{m-1}||_{L^\infty(0,T;L^1(\mathbb{R}^n))}\end{aligned}\tag{57}$$

Let $\mathcal{X}$ denote the space

$$L^\infty(0,T;L^1(\mathbb{R}^n\times V))\times L^\infty(0,T;L^1(\mathbb{R}^n\times S^{n-1}))\times L^\infty(0,T;W^{1,1}(\mathbb{R}^n))$$

equipped with the norm given by the sum of the norms of the components. With the abbreviations $\delta f_m := f_m - f_{m-1}$, $\delta L_m := L_m - L_{m-1}$ and $\delta Q_m := Q_m - Q_{m-1}$, combining (53), (54), (55) and (57) we have the following estimate (for T sufficiently small) in $\mathcal{X}$:

$$||(\delta f_{m+1},\delta Q_{m+1},\delta L_{m+1})||_{\mathcal{X}} \le \lambda(||(\delta f_m,\delta Q_m,\delta L_m)||_{\mathcal{X}} \tag{58}$$

with a $\lambda<1$, i.e. (f_m,Q_m,L_m) is a Cauchy sequence in $\mathcal{X}$ and therefore converges to a limit (f,Q,L) in this space. Next, $Q-Q_m$ satisfies the equation

$$\frac{\partial}{\partial t}(Q-Q_m)=\kappa(\Pi[f](t,\mathbf{x},\theta)-1)\bar{f}(t,\mathbf{x})(Q-Q_m)(t,\mathbf{x},\theta)+h(t,\mathbf{x},\theta)$$

with h defined by

$$h:=\kappa\left[\int_V|\theta\cdot\hat{\mathbf{v}}|(f-f_{m-1})d\mathbf{v}+\bar{f}_{m-1}-\bar{f}\right]Q_m.$$

Using (47), we have

$$\begin{aligned}&||(Q-Q_m)(t)||_{L^\infty(\mathbb{R}^n\times S^{n-1})}\\&\le 2\kappa|V|\int_0^T||(f_{m-1}-f)(\tau)||_{L^\infty(\mathbb{R}^n\times V)}||Q_m(\tau)||_{L^\infty(\mathbb{R}^n\times S^{n-1})}d\tau\end{aligned}$$

and taking the supremum

$$\begin{aligned}&||Q-Q_m||_{L^\infty(0,T;L^\infty(\mathbb{R}^n\times S^{n-1}))}\\\le\ &2\kappa|V|T||f_{m-1}-f||_{L^\infty(0,T;L^\infty(\mathbb{R}^n\times V))}||Q_0||_{L^\infty(\mathbb{R}^n\times S^{n-1})}.\end{aligned}$$

Since $f_m\to f$ in $L^\infty(0,T;L^1(\mathbb{R}^n\times V))$, there exists a subsequence (which we again denote by (f_m)) that converges to f in $L^\infty(0,T;L^\infty(\mathbb{R}^n\times V))$. Therefore we have that a subsequence of (Q_m) converges to a limit function Q in $L^\infty(0,T;L^\infty(\mathbb{R}^n\times S^{n-1}))$. It is easy to see that (f,Q,L) is a solution to (19)-(21). The uniqueness follows from the fact that any solution to (19)-(21) is a fixed point of the mapping $(f_*,Q_*,L_*)\mapsto(f,Q,L)$. □

5. **Conclusions.** In this paper we proposed a multiscale modeling framework for cancer cell dispersal through a tissue network. Our models allow to explicitly include more realistic features like the influence of a chemoattractant and of the cell surface dynamics on cell motility, along with new features for the interaction between cells and tissue fibres. Thereby, we used quite general probability kernels for describing the velocity change. In particular, they do not satisfy an essential assumption allowing to apply the usual techniques of passing to macroscopic limits, as it was required e.g., in [13], [22], in a slightly different context. For the genuinely mesoscopic model (in the absence of surface dynamics) we relied on an iterative method to prove the local existence of a unique solution. A similar technique has been employed in [17] to prove existence and uniqueness of a solution to a stochastic PDE system modeling pattern formation.

We refer to [16] for the proof of local existence and uniqueness of the solution to a full multiscale model of the type presented in Section 2.

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