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A MULTISCALE APPROACH TO CELL MIGRATION IN TISSUE NETWORKS

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ABSTRACT. We derive a model allowing to account for the receptor-mediated movement of cancer cells, the degradation of tissue fibers and the subsequent production of a soluble ligand whose concentration gradient then acts together with the distribution of tissue fibers as a directional cue for the cells. We then present a result on the local existence and uniqueness of a solution to our model for all biologically relevant space dimensions.

1. INTRODUCTION

The migration of tumour cells through the extracellular matrix is a crucial step in the so called metastatic cascade since it allows the cells to reach a blood or lymph vessel and invade other parts of the body after extravasation [14].

The contact with the surrounding tissue both enables the cells to move along tissue fibers and stimulates the production of proteolytic enzymes that dissolve fibers of the tissue network, thus enhancing cell migration. The product of the tissue degradation is seen as a chemotactic signal influencing the movement direction of the cells. Receptors on the cell surface not only provide linkages to the tissue fibers (thus allowing the cell to move), but they may also bind to the ECM fragments resulting by proteolytic degradation. The dynamics of cell surface receptors and the cytoskeleton structure are decisive in determining the speed of the cell, as well as the secretion of proteolytic enzymes.

A large number of models for cancer invasion accounting for the interactions of the cells with their environment have been set up; they can be divided into three categories:

Microscopic models are concerned with the processes at the intracellular and/or cell surface level which trigger (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. To give only a few examples, the interactions between extracellular matrix (ECM) proteins, proteinases (enzymes that degrade the ECM), proteolytic fragments and integrins have been studied by Berry [5]. A simple mathematical model directed toward elucidating the dependence of cell speed on receptor and ligand densities and receptor-ligand binding constants has been presented by Lauffenburger [21]. Mallet and Pettet [24] proposed a model for the space-time dynamics describing the onset of lamellipod protrusion, a crucial step in integrin-mediated haptotactic cell migration.

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In the *mesoscopic* framework, cell migration is characterized by way of a transport equation for the cell population density, in which changes of the cell velocity are modelled with the aid of an operator of the type used in the Boltzmann equation from physical kinetic theory. This approach has been introduced by Othmer, Dunbar and Alt [25] in order to describe the dispersal of living organisms by way of some classes of stochastic processes. Thereby, either the particle velocities satisfy some stochastic differential equations, or the so-called *velocity jump* models are used, which rely on a geometrical description of motion. The latter have been extensively used in the context of bacterial dispersal: the cell experiences discontinuous changes in its motion, which consists of a sequence of runs interrupted by reorientations allowing to choose a new velocity dictated by a turning kernel. Stimulation with a chemoattractant leads to prolongation of the runs in the direction of its gradient; the outcome is a random walk biased towards the chemoattractant.

Hillen [17] proposed to extend this approach towards modeling the mesenchymal motion of cancer cells and the subsequent tissue modification. His setting was further widened in [8] to include chemotaxis and cell-cell interactions. In a recent contribution [18] Hilllen et al. proved a.o. the global existence of measure-valued solutions for such a kinetic model.

Macroscopic descriptions can be derived from the above mesoscopic models by means of averaging processes. This corresponds to the derivation of 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 [13] for hyperbolic models for chemosensitive movement or in [17] in the context of mesenchymal motion of tumor cells. Rigorous results on the hyperbolic limit of kinetic equations for chemotaxis have been deduced e.g., in [6] and a rigorous convergence result (under some additional assumptions) for the parabolic limit of the model in [17] can be found in [18].

There are also several types of macroscopic models for cell migration which have not been derived from kinetic settings, but directly rely on mass conservation and/or mechanical force balance, respectively on the theory of mixtures. For the latter we refer e.g., to Maini [23], Traqui [32], Barocas and Tranquillo [3], Kettemann [19], see also Tosin and Preziosi [31] and the references therein. Models for cell population migration only relying on mass balance equations have been proposed e.g., by Anderson et al. [2] or Chaplain and Lolas [7].

In order to increase the realism and thus to enhance the performance of the models, the current aim is to interconnect these three modeling levels, which would lead to a large multiscale setting. The latter seems particularly suitable to integrate more or less detailed subcellular information in a way which could allow for predictions at the level of a tumor. First attempts toward setting up such multiscale models have been made by Erban and Othmer in [11], where intracellular signal transduction was introduced in the form of a simple excitation-adaptation dynamics into a kinetic model for chemotaxis of E. Coli. A global existence result in 1D for such a model can be found in [12]. 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., [4] and the references therein.

In this paper we start from the mesoscopic framework to deduce a multiscale model describing the evolution of tumor cell population density, whereby at the microscopic scale we do not account for intracellular pathways, but rather for the receptor dynamics on the cell surface. Our model is thus able to accommodate the various processes which so far have been treated separately in one of the above three frameworks. Besides including more elaborate effects on the micro scale, we also make a concrete suggestion for the inclusion of a chemoattractant originating from the degradation of tissue fibers whose evolution is connected to that of cells and tissue via an equation of reaction-diffusion type, while the chemotactic signal in [8] is merely a given function of space and time. Moreover, the probability kernel we introduce to describe the velocity change is more general than those used for previous kinetic settings, see e.g., [16], [26], [12], [17]. For our new model we prove the local existence and uniqueness of a solution under some natural assumptions on the data.

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 $\mathbf{x} \in \Omega \subset \mathbb{R}^n$ by $Q(t, \mathbf{x}, \theta)$. The total concentration of ECM molecules 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

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

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

$$\begin{aligned} \frac{d\mathbf{x}^j}{dt} &= \mathbf{v}^j \\ \frac{d\mathbf{v}^j}{dt} &= 0. \end{aligned} \tag{3}$$

For the dynamics on the cell surface, we use a kinetic model for the binding of ECM-proteins $\bar{Q}$ and proteolytic product L 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 reads

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

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. 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

We now derive a transport equation for the population density $f(t, \mathbf{x}, \mathbf{v}, \mathbf{y})$ of cells that have velocity vector $\mathbf{v}$ and internal state $\mathbf{y}$ at time t at location $\mathbf{x}$. Consider first the measure-valued function

$$\mu^N(t, d\mathbf{x}, d\mathbf{v}, d\mathbf{y}) = \frac{1}{N} \sum_{j=1}^{N} \delta(\mathbf{x} - \mathbf{x}^j(t)) \otimes \delta(\mathbf{v} - \mathbf{v}^j(t)) \otimes \delta(\mathbf{y} - \mathbf{y}^j(t)) \tag{6}$$

where $(\mathbf{x}^j(t), \mathbf{v}^j(t), \mathbf{y}^j(t))$, $j = 1, ..., N$ ist the trajectory of cell j in $\mathbb{R}^n \times V \times Y$ and δ denotes the Dirac measure. Let

$$I(t, \phi) := \frac{1}{N} \sum_{j=1}^{N} \phi(\mathbf{x}^j(t), \mathbf{v}^j(t), \mathbf{y}^j(t)) = \int_{\mathbb{R}^n \times V \times Y} \mu^N(t, d\mathbf{x}, d\mathbf{v}, d\mathbf{y}) \phi(\mathbf{x}, \mathbf{v}, \mathbf{y}) \tag{7}$$

for every function $\phi \in C_0^\infty(\mathbb{R}^n \times Y \times V)$. Take $|\Delta t| << 1$. The change $\Delta I(t, \phi) = I(t + \Delta t, \phi) - I(t, \phi)$ of $I(t)$ during the time interval $[t, t + \Delta t]$ can be written as a sum

$$\Delta I(t, \phi) = \Delta I_1(t, \phi) + \Delta I_2(t, \phi), \tag{8}$$

where $\Delta I_1(t,\phi)$ is the change due to the evolution of the system according to (3), (4) and $\Delta I_2(t,\phi)$ is the change resulting from reorientations. We then have

$$\begin{aligned}\Delta I_1(t,\phi) &\approx \frac{1}{N}\sum_{j=1}^{N}[\phi(\mathbf{x}^j(t+\Delta t),\mathbf{v}^j(t+\Delta t),\mathbf{y}^j(t+\Delta t)) - \phi(\mathbf{x}^j(t),\mathbf{v}^j(t),\mathbf{y}^j(t))] \\ &= \frac{1}{N}\sum_{j=1}^{N}\Big[\frac{d\mathbf{x}^j}{dt}\nabla_{\mathbf{x}}\phi(\mathbf{x}^j(t),\mathbf{v}^j(t),\mathbf{y}^j(t)) + \frac{d\mathbf{v}^j}{dt}\nabla_{\mathbf{v}}\phi(\mathbf{x}^j(t),\mathbf{v}^j(t),\mathbf{y}^j(t)) \\ &\quad + \frac{d\mathbf{y}^j}{dt}\nabla_{\mathbf{y}}\phi(\mathbf{x}^j(t),\mathbf{v}^j(t),\mathbf{y}^j(t))\Big]\Delta t + o(\Delta t) \\ &= \frac{1}{N}\sum_{j=1}^{N}[\mathbf{v}^j\nabla_{\mathbf{x}}\phi(\mathbf{x}^j(t),\mathbf{v}^j(t),\mathbf{y}^j(t)) \\ &\quad + \mathbf{G}(\mathbf{y}^j,\bar{Q}(t,\mathbf{x}^j),L(t,\mathbf{x}^j))\nabla_{\mathbf{y}}\phi(\mathbf{x}^j(t),\mathbf{v}^j(t),\mathbf{y}^j(t))]\Delta t + o(\Delta t).\end{aligned}$$

Note that this is only an approximation since due to reorientations not all of the N particles will move according to (3), (4) during the whole time interval $[t, t+\Delta t]$. This approximation is justified as long as Δt is small enough. Contributions to $\Delta I_2(t,\phi)$ are the increase of I as a result of cells undergoing a change in orientation from $\widehat{\mathbf{v}'} \neq \hat{\mathbf{v}}$ to $\hat{\mathbf{v}}$ and the decrease of I due to cells changing their orientation from $\hat{\mathbf{v}}$ to $\widehat{\mathbf{v}'} \neq \hat{\mathbf{v}}$. Here $\hat{\mathbf{v}}$ denotes the unit vector in direction of $\mathbf{v}$. Such 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 term $\mathcal{H}(f,Q)$.
- A cell may adjust its orientation to the gradient of the attracting chemical L, leading to a term $\mathcal{C}(f,L)$.

We assume that the probability that a cell changes its orientation in the time interval under consideration is proportional to Δt 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 operator for haptotaxis $\mathcal{H}$ can be decomposed into a gain term $\mathcal{H}_+$ and a loss term $\mathcal{H}_-$ defined as

$$\mathcal{H}_+(f,Q) = \int_V\int_{S^{n-1}} p_h(t,\mathbf{x},\mathbf{v}',\mathbf{y})\psi(\mathbf{v};\mathbf{v}',\theta')f(\mathbf{v}')Q(\theta')d\mathbf{v}'d\theta' \tag{9}$$

$$\mathcal{H}_-(f,Q) = f(\mathbf{v})\int_V\int_{S^{n-1}} p_h(t,\mathbf{x},\mathbf{v},\mathbf{y})\psi(\mathbf{v}';\mathbf{v},\theta')Q(\theta')d\mathbf{v}'d\theta'. \tag{10}$$

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

$$\int_V \psi(\mathbf{v};\mathbf{v}',\theta')d\mathbf{v} = 1. \tag{11}$$

The decomposition for the operator related to chemotaxis $\mathcal{C}$ into a gain-term and a loss-term reads

$$\mathcal{C}_+(f,L) = \int_V p_c(t,\mathbf{x},\mathbf{v}',\mathbf{y})K[L](\mathbf{v},\mathbf{v}',\mathbf{y})f(\mathbf{v}')d\mathbf{v}' \tag{12}$$

$$\mathcal{C}_-(f,L) = \int_V p_c(t,\mathbf{x},\mathbf{v},\mathbf{y})K[L](\mathbf{v}',\mathbf{v},\mathbf{y})f(\mathbf{v})d\mathbf{v}'. \tag{13}$$

The turning kernel is given by

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

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

$$\int_V K(\mathbf{v},\mathbf{v}')d\mathbf{v} = 1. \tag{14}$$

We then have

$$\Delta I_2(t,\phi) = [I(t,\mathcal{H}(\phi,Q)) + I(t,\mathcal{C}(\phi,L))]\Delta t + o(\Delta t).$$

Combining the expressions for ΔI_1 and ΔI_2 after taking the limit $\Delta t \to 0$, we get

$$\frac{d}{dt}I(t,\phi) = I(t,\mathbf{v}\cdot\nabla_{\mathbf{x}}\phi) + I(t,\mathbf{G}\cdot\nabla_{\mathbf{y}}\phi) + I(t,\mathcal{H}(\phi,Q)) + I(t,\mathcal{C}(\phi,L)).$$

In other words $\mu^N(t,\cdot)$ is a weak solution of the transport equation

$$\frac{\partial f}{\partial t} + \mathbf{v}\cdot\nabla_{\mathbf{x}} f + \nabla_{\mathbf{y}}\cdot(\mathbf{G}(\mathbf{y},\bar{Q},L)f) = \mathcal{H}(f,Q) + \mathcal{C}(f,L). \tag{15}$$

We can thus think of the density $f(t,\mathbf{x},\mathbf{v},\mathbf{y})$ as the limit

$$I(t,\phi) \overset{N\to\infty}{\longrightarrow} \int_{\mathbb{R}^n\times V\times Y} f(t,\mathbf{x},\mathbf{v},\mathbf{y})\phi(\mathbf{x},\mathbf{v},\mathbf{y})d\mathbf{x}d\mathbf{v}d\mathbf{y}. \tag{16}$$

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

$$\bar{f}(\mathbf{x},t) := \int_Y\int_V f(t,\mathbf{x},\mathbf{v},\mathbf{y})d\mathbf{v}d\mathbf{y}. \tag{17}$$

We define the mean projection of movement direction on the fibre orientation:

$$\Pi[f](t,\mathbf{x},\theta) = \frac{1}{\bar{f}(t,\mathbf{x})}\int_Y\int_V |\theta\cdot\hat{\mathbf{v}}| f(t,\mathbf{x},\mathbf{v},\mathbf{y})d\mathbf{v}d\mathbf{y}. \tag{18}$$

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

$$\frac{\partial Q}{\partial t} = \kappa(\Pi[f](t,\mathbf{x},\theta) - 1)\bar{f}(t,\mathbf{x})Q(t,\mathbf{x},\theta). \tag{19}$$

Note that we assume here and in the following that the encounter rate η is independent of both the incoming velocity of the cell and the fibre orientation. The reaction-diffusion equation for the product L of proteolysis reads

$$\frac{\partial L}{\partial t} = D_L \triangle L + \int_{S^{n-1}} \kappa(1 - \Pi[f](t,\mathbf{x},\theta))\bar{f}(t,\mathbf{x})Q(t,\mathbf{x},\theta)d\theta - r_L L \tag{20}$$

where r_L is the decay rate of L.

4. Existence and Uniqueness

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

$$V = [s_1, s_2] \times S^{n-1} \text{ , } 0 \le s_1 \le s_2 \le \infty. \tag{21}$$

Let Y be a bounded, open, nonempty and connected subset of $\mathbb{R}^\nu$ ($\nu \in \mathbb{N}$) such that there exist linear forms $\mu_1, ..., \mu_r$ on $\mathbb{R}^\nu$ with

$$Y = \{\mathbf{x} \in \mathbb{R}^\nu \mid \mu_1(\mathbf{x}) > 0, ..., \mu_r(\mathbf{x}) > 0\}.$$

Remark. *The space* $Y := \{(y_1, y_2) \in (0, R_0)^2 \mid y_1 + y_2 < R_0\}$ *from the last chapter can be written in this form with* $\nu = 2$*,* $r = 3$ *and*

$$\mu_1 = R_0 - y_1 - y_2 \text{ , } \mu_2 = y_1 \text{ , } \mu_3 = y_2.$$

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

$$\frac{\partial f}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} f + \nabla_{\mathbf{y}} \cdot (\mathbf{G}(\mathbf{y}, \bar{Q}, L) f) = \mathcal{H}(f, Q) + \mathcal{C}(f, L). \tag{22}$$

$$\frac{\partial Q}{\partial t} = \kappa(\Pi[f](t,\mathbf{x},\theta) - 1)\bar{f}(t,\mathbf{x})Q(t,\mathbf{x},\theta). \tag{23}$$

$$\frac{\partial L}{\partial t} = D_L \triangle L + \int_{S^{n-1}} \kappa(1 - \Pi[f](t,\mathbf{x},\theta))\bar{f}(t,\mathbf{x})Q(t,\mathbf{x},\theta)d\theta - r_L L \tag{24}$$

where Π has been defined in (18). The system has to be supplemented by initial conditions $f(0,\cdot) = f_0$, $Q(0,\cdot) = Q_0$ and $L(0,\cdot) = L_0$. Here $\mathbf{G}$ may be any function $\mathbf{G} : Y \times [0,\infty) \times [0,\infty) \to \mathbb{R}^\nu$ satisfying the following assumptions:

- **G1)** $Tr\,(\nabla_{\mathbf{y}} \mathbf{G}) \le 0$ on $Y \times [0,\infty) \times [0,\infty)$.
- **G2)** For all $\mathbf{y}^* \in Y$, and all $j = 1, ..., r$ such that $\mu_j(\mathbf{y}^*) = 0$, the inequality $\mu_j(\mathbf{G}(\mathbf{y}^*, \cdot)) \ge 0$ is satisfied on $[0,\infty) \times [0,\infty)$.
- **G3)** There are constants $C_{G1}, C_{G2} > 0$ such that

$$\begin{aligned} ||\nabla_{\mathbf{y}} \mathbf{G}(\mathbf{y}, q, l)||^2_{\mathbb{R}^\nu} &\le C_{G1}(1 + |q| + |l|) \\ \sum_{i,j=1}^{\nu} |\frac{\partial^2}{\partial y_i \partial y_j} \mathbf{G}_i(\mathbf{y}, q, l)| &\le C_{G2}(1 + |q| + |l|) \end{aligned}$$

for all $\mathbf{y} \in Y$ and $q, l \in [0, \infty)$.

G4) There is a constant $C_{GL} > 0$ such that

$$||\mathbf{G}(\mathbf{y}, q, l) - \mathbf{G}(\mathbf{y}, \hat{q}, \hat{l})||_{\mathbb{R}^\nu} + |\nabla_{\mathbf{y}} \cdot [\mathbf{G}(\mathbf{y}, q, l) - \mathbf{G}(\mathbf{y}, \hat{q}, \hat{l})]| \leq C_{GL}(|q - \hat{q}| + |l - \hat{l}|)$$

for all $\mathbf{y} \in Y$, $l, \hat{l} \in [0, \infty)$ and $q, \hat{q} \in [0, \infty)$.

5. Properties of the turning operators

Lemma 5.1. *Let $p_h(t) \in L^\infty(\mathbb{R}^n \times V \times Y)$ and $\psi(\mathbf{v}; \mathbf{v}', \theta')$ be given real nonnegative functions. We assume that ψ satisfies condition (11) and that there exists a positive constant $M_h \geq 1$ such that*

$$\int_V \psi(\mathbf{v}; \mathbf{v}', \theta') d\mathbf{v}' \leq M_h \text{ , } \forall (\mathbf{v}, \theta') \in \mathbb{R}^n \times S^{n-1}. \tag{25}$$

Then the operator $\mathcal{H} = \mathcal{H}_+ - \mathcal{H}_-$ defined by (9) and (10) is a bilinear and continuous mapping from $L^p(\mathbb{R}^n \times V \times Y) \times L^\infty(\mathbb{R}^n \times S^{n-1})$ into $L^p(\mathbb{R}^n \times V \times Y)$ for $(p = 1, \infty)$ and we have for $t \in (0, T)$

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

(26)

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

Moreover,

(27)

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

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

Proof. We have from condition (11)

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

and from (25)

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

The estimates for $\mathcal{H}_-$ can be derived along the same lines. For (27), only slight modfications are necessary. □

Lemma 5.2. *Let $p_c(t) \in L^\infty(R^n \times V \times Y)$, $\alpha_1(\mathbf{y}), \alpha_2(\mathbf{y}) \in L^\infty(Y)$ and $K(\mathbf{v}, \mathbf{v}')$ (all nonnegative) be given. We assume that K satisfies condition (14) and that there exist positive constants $M_{cl}, M_{cb} > 0$ such that for all $\mathbf{v}, \mathbf{w} \in \mathbb{R}^n$*

$$|K(\cdot, \mathbf{v})| \leq M_{cb}|\chi(\mathbf{v})| \text{ on } V \tag{28}$$

$$|K(\cdot, \mathbf{v}) - K(\cdot, \mathbf{w})| \leq M_{cl}|\chi(\mathbf{v}) - \chi(\mathbf{w})| \text{ on } V \tag{29}$$

with $\chi : \mathbb{R}^n \to V$ defined by $\chi(\xi) := \xi$ for $||\xi|| \leq s_2$ and $\chi(\xi) := s_2\hat{\mathbf{xi}}$ for $|\xi| > s_2$. Then the operator $\mathcal{C}$ defined by (12) and (13) is a linear and continuous mapping from $L^p(\mathbb{R}^n \times V \times Y)$ into $L^p(\mathbb{R}^n \times V \times Y)$ for $(p = 1, \infty)$ and there exists a constant $M_C > 0$ such that for $t \in (0, T)$

$$||\mathcal{C}(f(t), L(t))||_{L^1(\mathbb{R}^n \times V \times Y)} \leq 2M_C||p_c(t)||_{L^\infty(\mathbb{R}^n \times V \times Y)}||f(t)||_{L^1(\mathbb{R}^n \times V \times Y)}. \tag{30}$$

$$||\mathcal{C}(f(t), L(t))||_{L^\infty(\mathbb{R}^n \times V \times Y)} \leq 2M_C||p_c(t)||_{L^\infty(\mathbb{R}^n \times V \times Y)}||f(t)||_{L^\infty(\mathbb{R}^n \times V \times Y)}. \tag{31}$$

Proof. From (28) it follows

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

with $M_C := max\{1, M_{cb}s_2|V|\}$. Now the proof of (30) and (31) is essentially the same as the one of Lemma 5.1. □

Remark. *The Operator $\mathcal{C}$ with $\alpha_1(y)$, $\alpha_2(y)$ replaced by their derivative w.r.t. y_j ($j = 1, ..., \nu$) vanishes. This can be easily seen with a reasoning as above since*

$$\frac{\partial}{\partial y_j}(\alpha_1(y) + \alpha_2(y)) = 0.$$

6. Linear theorem

We linearize the equation for cell movement by decoupling equation (22) from (23) and (24). 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

$$\frac{\partial f}{\partial t} + \mathbf{v} \cdot \nabla_\mathbf{x} f + \nabla_\mathbf{y} \cdot [\mathbf{G}(\mathbf{y}, \bar{Q}_*, L_*)f] = \mathcal{H}(f, Q_*) + \mathcal{C}(f, L_*) + g(t, \mathbf{x}, \mathbf{v}, \mathbf{y}), \tag{32}$$

where we have included an additional source term $g(t, \mathbf{x}, \mathbf{v}, \mathbf{y})$ so that the difference of solutions to (32) with $g \equiv 0$ for different choices of Q_* and L_* still satisfies (32) with g chosen appropriately. This will later (beginning with equation (74) in the next section) allow us to use the estimates obtained in this chapter for the difference of such solutions.

Definition 6.1. *A weak solution of equation (32) is a function f satisfying*

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

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

Concerning the existence of a solution to (32) we have the following theorem

Theorem 6.1. *Let $f_0 \in L^\infty(\mathbb{R}^n \times V \times Y) \cap L^1(\mathbb{R}^n \times V \times Y)$ and $g \in L^1(0,T; L^\infty(\mathbb{R}^n \times V \times Y) \cap L^1(\mathbb{R}^n \times V \times Y))$. Suppose further that*

- *Q_* and L_* satisfy*

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

  and

$$
\begin{aligned}
Q_*(t, \mathbf{x}, \theta) &\geq 0 \text{ a.e. on } (0,T) \times \mathbb{R}^n \times S^{n-1} && (33) \\
L_*(t, \mathbf{x}) &\geq 0 \text{ a.e. on } (0,T) \times \mathbb{R}^n. && (34)
\end{aligned}
$$

- *f_0 is also in $L^\infty(\mathbb{R}^n \times V; L^1(Y))$ and satisfies*

$$
\begin{aligned}
f_0 &\in L^\infty(\mathbb{R}^n \times V; W^{1,\infty}(Y)) \cap L^1(\mathbb{R}^n \times V; W^{1,1}(Y)) && (35) \\
f_0 &\geq 0 \text{ a.e. on } \mathbb{R}^n \times V \times Y. && (36)
\end{aligned}
$$

- *p_c and p_h satisfy*

$$
\begin{aligned}
||p_h||_{L^\infty(0,T;L^\infty(\mathbb{R}^n \times V \times Y))} &\leq K_h \\
||\nabla_{\mathbf{y}} p_h||_{L^\infty(0,T;L^\infty(\mathbb{R}^n \times V \times Y))} &\leq \tilde{K}_h \\
||p_c||_{L^\infty(0,T;L^\infty(\mathbb{R}^n \times V \times Y))} &\leq K_c \\
||\nabla_{\mathbf{y}} p_c||_{L^\infty(0,T;L^\infty(\mathbb{R}^n \times V \times Y))} &\leq \tilde{K}_c
\end{aligned}
$$

Then, there exists a weak solution f of (32) in $L^1(\mathbb{R}^n \times V \times Y) \cap L^\infty(\mathbb{R}^n \times V \times Y)$ corresponding to the initial condition f_0. Additionally, we have the estimates

$$
||f(t)||_{L^1(\mathbb{R}^n \times V \times Y)} \leq (||f_0||_{L^1(\mathbb{R}^n \times V \times Y)} + \int_0^T ||g(\tau)||_{L^1(\mathbb{R}^n \times V \times Y)} d\tau)(1 + Cte^{Ct}) \tag{37}
$$

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

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

If $g \equiv 0$, we also have the estimate

(39)
$$||\nabla_{\mathbf{y}} f(t)||_{L^\infty(\mathbb{R}^n\times V\times Y)} \le (||\nabla_{\mathbf{y}} f(0)||_{L^\infty(\mathbb{R}^n\times V\times Y)} + C_2||f_0||_{L^\infty(\mathbb{R}^n\times V\times Y)}(T+CT^2e^{CT}))e^{C_3 t}.$$

Proof. We regularize $\bar{Q}_*, L_*$ and f_0 by convolution with respect to $\mathbf{x}$ using

$$\rho_\epsilon(\mathbf{x}) = \frac{1}{\epsilon^n}\rho\left(\frac{\mathbf{x}}{\epsilon}\right),\ \int_{R^n}\rho d\mathbf{x} = 1.$$

We set $\bar{Q}^\epsilon_* = \bar{Q}_* \star \rho_\epsilon$, $L^\epsilon_* = L_* \star \rho_\epsilon$ and $f^\epsilon_0 = f_0 \star \rho_\epsilon$. We are now going to show that there exists a unique solution $f^\epsilon \in C(0,T;C^1(\mathbb{R}^n \times V \times Y))$ of

(40) $$\frac{\partial f^\epsilon}{\partial t} + \mathbf{v}\cdot\nabla_{\mathbf{x}} f^\epsilon + div_{\mathbf{y}}[\mathbf{G}(\mathbf{y}, \bar{Q}^\epsilon_*, L^\epsilon_*)f^\epsilon] = \mathcal{H}(f^\epsilon, Q^\epsilon_*) + \mathcal{C}(f^\epsilon, L^\epsilon_*) + g(t,\mathbf{x},\mathbf{v},\mathbf{y})$$

in $(0,T)\times\mathbb{R}^n\times V\times Y$ satisfying $f^\epsilon|_{t=0} = f^\epsilon_0$ in $\mathbb{R}^n\times V\times Y$. Our approach is similar to the one employed in Chapter XI of [15].

The characteristics of equation (40) are given as

(41) $$\frac{d\mathbf{X}}{ds} = \mathbf{V}$$

(42) $$\frac{d\mathbf{V}}{ds} = 0$$

(43) $$\frac{d\mathbf{Y}}{ds} = \mathbf{G}(\mathbf{Y}(s), \bar{Q}^\epsilon_*(\mathbf{X}(s),s), L^\epsilon_*(\mathbf{X}(s),s)).$$

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

(44) $$\mathbf{X}(s;\mathbf{x},\mathbf{v},\mathbf{y},t) = \mathbf{x} - \mathbf{v}(t-s),$$

(45) $$\mathbf{Y}(s;\mathbf{x},\mathbf{v},\mathbf{y},t) = \mathbf{y} - \int_s^t \mathbf{G}(\mathbf{Y}(\tau), \bar{Q}^\epsilon_*(\mathbf{X}(\tau),\tau), L^\epsilon_*(\mathbf{X}(\tau),\tau))d\tau.$$

Integrating (42) for initial points in the support of the initial data f^ϵ_0 we have that $|\mathbf{V}(s)| = |\mathbf{V}(0)| \le s_2$ for all $s\in[0,T]$. Using Lemma A.1, we have from G2) and $\bar{Q}^\epsilon_* \ge 0$, $L^\epsilon_* \ge 0$ that Y is an invariant set for (43) i.e. $\mathbf{Y}(s)\in Y$ for $s\in[0,T]$.

Lemma 6.1. *Derivation of the backward characteristics given by (44) and (45) with respect to the initial conditions gives, for $0\le s\le t$,*

(46) $$\nabla_{\mathbf{x}}\mathbf{X} = \mathbb{I}_n,\ \nabla_{\mathbf{y}}\mathbf{Y}(s) = exp\left(-\int_s^t \nabla_{\mathbf{y}}\mathbf{G}(\tau)d\tau\right)$$

where $\nabla_{\mathbf{y}}\mathbf{G}$ *denotes the Jacobian of* $\mathbf{G}$ *with respect to* $\mathbf{y}$. *Moreover,*

$$\det \nabla_{\mathbf{y}}\mathbf{Y}(s) = J(t,s) \geq 1 \tag{47}$$

with $J(t,s)$ *given by*

$$J(t,s) = \exp\left(-\int_s^t div_y \mathbf{G}(\mathbf{Y}(\sigma), \bar{Q}_*^\epsilon(\mathbf{X}(\sigma),\sigma), L_*^\epsilon(\mathbf{X}(\sigma),\sigma))d\sigma\right). \tag{48}$$

Proof. We have that $\nabla_{\mathbf{y}}\mathbf{Y}$ satisfies the differential equation

$$\frac{d}{ds}\nabla_{\mathbf{y}}\mathbf{Y} = \nabla_{\mathbf{y}}\mathbf{G}\nabla_{\mathbf{y}}\mathbf{Y}$$

with the condition $\nabla_{\mathbf{y}}\mathbf{Y}(t) = \mathbb{I}_n$, leading to the solution

$$\nabla_{\mathbf{y}}\mathbf{Y}(s) = exp\left(-\int_s^t \nabla_{\mathbf{y}}\mathbf{G}(\sigma)d\sigma\right).$$

Using the Liouville Formula (Lemma A.2), we get (due to the fact that $\det \nabla_{\mathbf{y}}\mathbf{Y}(t) = \det \mathbb{I} = 1$)

$$\det \nabla_{\mathbf{y}}\mathbf{Y}(s) = J(t,s) \geq 1$$

where the inequality follows from Assumption G1) and $\bar{Q}_*^\epsilon \geq 0$ and $L_*^\epsilon \geq 0$ a.e. $\square$

We transform equation (40) by multiplication with $e^{-\lambda t}$ $(\lambda > 0)$ into the equivalent problem

$$\frac{\partial f_\lambda^\epsilon}{\partial t} + \mathbf{v}\cdot\nabla_{\mathbf{x}} f_\lambda^\epsilon + div_{\mathbf{y}}[\mathbf{G}(\mathbf{y}, \bar{Q}_*^\epsilon, L_*^\epsilon) f_\lambda^\epsilon] + \lambda f_\lambda^\epsilon - \mathcal{H}(f_\lambda^\epsilon, Q_*^\epsilon) - \mathcal{C}(f_\lambda^\epsilon, L_*^\epsilon) = g_\lambda(t,\mathbf{x},\mathbf{v},\mathbf{y}) \tag{49}$$

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

The unique solution to equation (49) with $\mathcal{H}, \mathcal{C} \equiv 0$ is given by

$$f_\lambda^\epsilon(t,\mathbf{x},\mathbf{v},\mathbf{y}) = e^{-\lambda t} J^{-1}(0,t) f_0^\epsilon(\mathbf{X}(0),\mathbf{v},\mathbf{Y}(0)) + \int_0^t e^{-\lambda(t-\tau)} J^{-1}(\tau,t) g_\lambda(\tau,\mathbf{X}(\tau),\mathbf{v},\mathbf{Y}(\tau))d\tau. \tag{50}$$

We denote by $S_\lambda(g_\lambda, f_0^\epsilon)$ the solution of (49) with $\mathcal{H}, \mathcal{C} \equiv 0$, right hand side g_λ and initial condition f_0^ϵ.

Using Lemma 6.1, we have (since $J^{-1}(\tau,t) = J(t,\tau) > 0$)

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

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 $\lambda > ||\mathcal{H}(\cdot, \bar{Q}^\epsilon_*) + \mathcal{C}(\cdot, L^\epsilon_*)||$ (the operator norm from $L^1(\mathbb{R}^n \times V \times Y)$ into itself). We look for a solution to (49) having the form $f^\epsilon_\lambda = S_\lambda(\widetilde{g_\lambda}, f^\epsilon_0)$ with $\widetilde{g_\lambda} \in L^1(0,T; L^1(R^n \times V \times Y))$ to be determined. Then f^ϵ_λ solves (49) if and only if

(51) $$\widetilde{g_\lambda} - \mathcal{H}(S_\lambda(\widetilde{g_\lambda}, f^\epsilon_0), \bar{Q}^\epsilon_*) - \mathcal{C}(S_\lambda(\widetilde{g_\lambda}, f^\epsilon_0), L^\epsilon_*) = g_\lambda.$$

Since we can write f^ϵ_λ as the sum of the solution to (49) with zero initial data and right hand side $\widetilde{g_\lambda}$ and the solution to (49) with initial data f^ϵ_0 and zero right hand side, (51) becomes

(52) $$(\mathcal{I} + Z_\lambda)\widetilde{g_\lambda} = g_\lambda + \mathcal{H}(S_\lambda(0, f^\epsilon_0), \bar{Q}^\epsilon_*) + \mathcal{C}(S_\lambda(0, f^\epsilon_0), L^\epsilon_*)$$

with

(53) $$Z_\lambda \widetilde{g_\lambda} = -\mathcal{H}(S_\lambda(\widetilde{g_\lambda}, 0), \bar{Q}^\epsilon_*) - \mathcal{C}(S_\lambda(\widetilde{g_\lambda}, 0), L^\epsilon_*).$$

From the estimate on the norm of the solution operator S_λ, we have that $||Z_\lambda|| \leq \lambda^{-1}||\mathcal{H}(\cdot, \bar{Q}^\epsilon_*) + \mathcal{C}(\cdot, L^\epsilon_*)|| < 1$ (the operator norms are again from $L^1(\mathbb{R}^n \times V \times Y)$ into itself). Thus (51) has the unique solution

$$\widetilde{g_\lambda} = \sum_{m=0}^{\infty} (-Z_\lambda)^m [g_\lambda + \mathcal{H}(S_\lambda(0, f^\epsilon_0), \bar{Q}^\epsilon_*) + \mathcal{C}(S_\lambda(0, f^\epsilon_0), L^\epsilon_*)].$$

From f^ϵ_λ we get the unique solution f^ϵ to (40) by multiplication with $e^{\lambda t}$. That f^ϵ has the stated regularity follows from the explicit construction of the solution and the regularity

of the data.
Integrating (40) along backward characteristics (44)-(45) from 0 to t, we get

$$
\begin{aligned}
f^\epsilon(\mathbf{x},\mathbf{v},\mathbf{y},t) &= f_0^\epsilon(\mathbf{X}(0),\mathbf{v},\mathbf{Y}(0)) \\
&+ \int_0^t \mathcal{H}(\mathbf{X}(\tau),\mathbf{Y}(\tau),f^\epsilon(\mathbf{X}(\tau),\mathbf{v},\mathbf{Y}(\tau),\tau),Q_*^\epsilon(\mathbf{X}(\tau),\theta,\tau))d\tau \\
&+ \int_0^t \mathcal{C}(\mathbf{X}(\tau),\mathbf{Y}(\tau),f^\epsilon(\mathbf{X}(\tau),\mathbf{v},\mathbf{Y}(\tau),\tau),L_*^\epsilon(\mathbf{X}(\tau),\tau))d\tau \\
&+ \int_0^t g(\tau,\mathbf{X}(\tau),\mathbf{v},\mathbf{Y}(\tau))d\tau \\
&+ \int_0^t div_{\mathbf{y}}\mathbf{G}(\mathbf{Y}(\tau),\bar{Q}_*^\epsilon(\mathbf{X}(\tau),\tau),L_*^\epsilon(\mathbf{X}(\tau),\tau))f^\epsilon(\mathbf{X}(\tau),\mathbf{v},\mathbf{Y}(\tau),\tau)d\tau.
\end{aligned} \tag{54}
$$

With the estimates for $\mathcal{H}^\epsilon$ (Lemma 5.1), $\mathcal{C}^\epsilon$ (Lemma 5.2) and Assumption G3 on $div_y\mathbf{G}$ and by using the fact that the norms under consideration do not increase upon mollification, we arrive at

$$
\begin{aligned}
& ||f^\epsilon(t)||_{L^\infty(R^n\times V\times Y)} \\
\leq\ & ||f_0||_{L^\infty(\mathbb{R}^n\times V\times Y)} \\
+\ & 2M_h||p_h||_{L^\infty(0,T;L^\infty(\mathbb{R}^n\times V\times Y))}||\bar{Q}_*(t)||_{L^\infty(\mathbb{R}^n)}\int_0^t ||f^\epsilon(\tau)||_{L^\infty(\mathbb{R}^n\times V\times Y)}d\tau \\
+\ & 2M_c||p_c||_{L^\infty(0,T;L^\infty(\mathbb{R}^n\times V\times Y))}\int_0^t ||f^\epsilon(\tau)||_{L^\infty(\mathbb{R}^n\times V\times Y)}d\tau \\
+\ & C_{G1}(1+||\bar{Q}_*||_{L^\infty(0,T;L^\infty(\mathbb{R}^n))}+||L_*||_{L^\infty(0,T;L^\infty(\mathbb{R}^n))})\int_0^t ||f^\epsilon(\tau)||_{L^\infty(\mathbb{R}^n\times V\times Y)}d\tau \\
+\ & \int_0^t ||g(\tau)||_{L^\infty(\mathbb{R}^n\times V\times Y)}d\tau
\end{aligned}
$$

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

$$
||f^\epsilon(t)||_{L^\infty(\mathbb{R}^n\times V\times Y)} \leq \left(||f_0||_{L^\infty(\mathbb{R}^n\times V\times Y)} + \int_0^T ||g(t)||_{L^\infty(\mathbb{R}^n\times V\times Y))}dt\right)(1+Cte^{Ct}) \tag{55}
$$

with

$$
C = 2M_hK_hK_Q + 2M_cK_c + C_{G1}(1+K_Q+K_L).
$$

Using Lemma (6.1), we have

$$
\left(det\frac{\partial\mathbf{Y}}{\partial\mathbf{y}}\right)^{-1} \leq 1,\ \left(det\frac{\partial\mathbf{X}}{\partial\mathbf{x}}\right)^{-1} = 1 \tag{56}
$$

and so

$$
\begin{aligned}
& \int_{\mathbb{R}^n\times V\times Y} |f^\epsilon(\mathbf{X}(\tau),\mathbf{v},\mathbf{Y}(\tau),\tau)| d\mathbf{x}d\mathbf{v}d\mathbf{y} \\
= & \int_{\mathbb{R}^n\times V\times Y} |f^\epsilon(\mathbf{X}(\tau),\mathbf{v},\mathbf{Y}(\tau),\tau)| \left(det\frac{\partial \mathbf{Y}}{\partial \mathbf{y}}\right)^{-1}\left(det\frac{\partial \mathbf{X}}{\partial \mathbf{x}}\right)^{-1} d\mathbf{X}d\mathbf{v}d\mathbf{Y} \\
\leq & \int_{\mathbb{R}^n\times V\times Y} |f^\epsilon(\mathbf{X}(\tau),\mathbf{v},\mathbf{Y}(\tau),\tau)| d\mathbf{X}d\mathbf{v}d\mathbf{Y}
\end{aligned}
$$

Obviously, the same result also holds for g. Integrating (54) w.r.t. $\mathbf{x}$, $\mathbf{v}$ and $\mathbf{y}$ yields

$$
\begin{aligned}
& ||f^\epsilon(t)||_{L^1(\mathbb{R}^n\times V\times Y)} \\
\leq\ & ||f_0||_{L^1(\mathbb{R}^n\times V\times Y)} \\
+\ & 2M_h||p_h||_{L^\infty(0,T;L^\infty(\mathbb{R}^n\times V\times Y))}||\bar{Q}_*||_{L^\infty(0,T;L^\infty(\mathbb{R}^n))}\int_0^t ||f^\epsilon(\tau)||_{L^1(\mathbb{R}^n\times V\times Y)}d\tau \\
+\ & 2M_c||p_c||_{L^\infty(0,T;L^\infty(\mathbb{R}^n\times V\times Y))}\int_0^t ||f^\epsilon(\tau)||_{L^1(\mathbb{R}^n\times V\times Y)}d\tau \\
+\ & C_{G1}(1+||\bar{Q}_*||_{L^\infty(0,T;L^\infty(\mathbb{R}^n))}+||L_*||_{L^\infty(0,T;L^\infty(\mathbb{R}^n))})\int_0^t ||f^\epsilon(\tau)||_{L^1(\mathbb{R}^n\times V\times Y)}d\tau \\
+\ & \int_0^t ||g(\tau)||_{L^1(\mathbb{R}^n\times V\times Y)}d\tau.
\end{aligned}
$$

where we have used

$$||f_0^\epsilon||_{L^1(R^n\times V\times Y)} \leq ||f_0||_{L^1(R^n\times V\times Y)}$$

which can be easily obtained with the help of Young's inequality for convolutions since $\int_{\mathbb{R}^n}\rho_\epsilon d\mathbf{x}=1$. Applying the Gronwall inequality, we obtain

(57)

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

with

(58) $$C=(2M_hK_h+C_{G1})K_Q+2M_cK_c+C_{G1}K_L+C_{G1}.$$

Now, in view of (55) and (57), f_ϵ is bounded in $L^\infty(0,T;L^\infty(\mathbb{R}^n\times V\times Y))$ and $L^\infty(0,T;L^1(\mathbb{R}^n\times V\times Y))$ uniformly in ϵ. Extracting subsequences if necessary, we may assume that

$$f_\epsilon \overset{*}{\rightharpoonup} f \text{ in } L^\infty(0,T;L^\infty(\mathbb{R}^n\times V\times Y))$$

for some f. The interpolation inequality for L^p-norms gives us $f_\epsilon\in L^\infty(0,T;L^2(\mathbb{R}^n\times V\times Y))$ and

$$||f_\epsilon||_{L^\infty(0,T;L^2(\mathbb{R}^n\times V\times Y))} \leq ||f_\epsilon||^{1/2}_{L^\infty(0,T;L^1(\mathbb{R}^n\times V\times Y))}||f_\epsilon||^{1/2}_{L^\infty(0,T;L^\infty(\mathbb{R}^n\times V\times Y)}$$

so that $\{f_\epsilon\}$ is also uniformly bounded in $L^\infty(0,T;L^2(\mathbb{R}^n \times V \times Y))$. Therefore $\{f_\epsilon\}$ is (locally) equiintegrable (lemma B.3), and by the Dunford-Pettis theorem B.1 (and extracting subsequences if necessary)

$$f_\epsilon \rightharpoonup f \text{ in } L^\infty(0,T;L^1_{loc}(\mathbb{R}^n \times V \times Y)).$$

It is easy to see that f is a weak solution of (32). Moreover, it follows from Lemma B.2 that both estimates (55) and (57) also hold for the corresponding norms of the limit function f.
We now compute estimates on the derivatives of f with respect to y_i $(i = 1, ..., \nu)$ in the case $g \equiv 0$. Differentiating (40) with respect to y_i $(i = 1, ..., \nu)$ gives

$$\begin{aligned}
&\frac{\partial}{\partial t}\left[\frac{\partial}{\partial y_i} f^\epsilon\right] + \mathbf{v}\cdot\nabla_{\mathbf{x}}\left[\frac{\partial}{\partial y_i} f^\epsilon\right] + div_{\mathbf{y}}\left[\mathbf{G}(\mathbf{y},\bar{Q}^\epsilon_*,L^\epsilon_*)\left[\frac{\partial}{\partial y_i} f^\epsilon\right]\right]\\
=\;& \mathcal{H}\left(\left[\frac{\partial}{\partial y_i} f^\epsilon\right], Q^\epsilon_*\right) + \mathcal{C}\left(\left[\frac{\partial}{\partial y_i} f^\epsilon\right], L^\epsilon_*\right) + \mathcal{H}_{y_i}(f^\epsilon, Q^\epsilon_*) + \mathcal{C}_{y_i}(f^\epsilon, L^\epsilon_*)\\
-\;& \partial_{y_i}\mathbf{G}(\mathbf{y},\bar{Q}^\epsilon_*,L^\epsilon_*)\cdot\nabla_{\mathbf{y}} f^\epsilon - div_{\mathbf{y}}[\partial_{y_i}\mathbf{G}(\mathbf{y},\bar{Q}^\epsilon_*,L^\epsilon_*]f^\epsilon
\end{aligned}$$

where $\mathcal{H}_{y_i}$ denotes the operator $\mathcal{H}$ with the turning rate p_h replaced by $\partial_{y_i} p_h$ and $\mathcal{C}_{y_i}$ is the operator $\mathcal{C}$ with the turning rate p_c replaced by $\partial_{y_i} p_c$. There are no terms containing derivatives of α_1 or α_2 (see the remark after lemma 5.2). Integrating along the backward characteristics (44),(45), taking the absolute value and summing up from 1 to ν yields

$$\begin{aligned}
||\nabla_{\mathbf{y}} f^\epsilon(t)||_{\mathbb{R}^\nu} \;\leq\;& ||\nabla_{\mathbf{y}} f^\epsilon(0)||_{\mathbb{R}^\nu}\\
+\;& \sum_{i=1}^{\nu}\int_0^t |\mathcal{H}\left(\left[\frac{\partial}{\partial y_i} f^\epsilon(\tau,\mathbf{X}(\tau),\mathbf{v},\mathbf{Y}(\tau))\right], Q^\epsilon_*(\tau,\mathbf{X}(\tau))\right)|d\tau\\
+\;& \sum_{i=1}^{\nu}\int_0^t |\mathcal{C}\left(\left[\frac{\partial}{\partial y_i} f^\epsilon(\tau,\mathbf{X}(\tau),\mathbf{v},\mathbf{Y}(\tau))\right], L^\epsilon_*(\tau,\mathbf{X}(\tau))\right)|d\tau\\
+\;& \int_0^t \left|\left|\nabla_y \mathbf{G}(\mathbf{Y}(\tau),\bar{Q}^\epsilon_*(\tau,\mathbf{X}(\tau)),L^\epsilon_*(\tau,\mathbf{X}(\tau)))\right|\right|^2 ||\nabla_{\mathbf{y}} f^\epsilon(\tau,\mathbf{X}(\tau),\mathbf{v},\mathbf{Y}(\tau)||\,d\tau\\
+\;& \int_0^t |div_{\mathbf{y}}\left[\mathbf{G}(\mathbf{Y}(\tau),\bar{Q}^\epsilon_*(\tau,\mathbf{X}(\tau)),L^\epsilon_*(\tau,\mathbf{X}(\tau)))\right]|\;||\nabla_y f^\epsilon(\tau,\mathbf{X}(\tau),\mathbf{v},\mathbf{Y}(\tau)||\,d\tau\\
+\;& \int_0^t \sum_{i=1}^{\nu} |\mathcal{H}_{y_i}(f^\epsilon(\tau,\mathbf{X}(\tau),\mathbf{v},\mathbf{Y}(\tau),Q^\epsilon_*(\tau,\mathbf{X}(\tau)))|d\tau\\
+\;& \int_0^t \sum_{i=1}^{\nu} |\mathcal{C}_{y_i}(f^\epsilon(\tau,\mathbf{X}(\tau),\mathbf{v},\mathbf{Y}(\tau),L^\epsilon_*(\tau,\mathbf{X}(\tau)))|d\tau\\
+\;& \int_0^t |f^\epsilon(\tau,\mathbf{X}(\tau),\mathbf{v},\mathbf{Y}(\tau)|\sum_{i=1}^{\nu}|div_{\mathbf{y}}[\partial_{y_i}\mathbf{G}(\mathbf{Y}(\tau),\bar{Q}^\epsilon_*(\tau,\mathbf{X}(\tau)),L^\epsilon_*(\tau,\mathbf{X}(\tau))]|d\tau.
\end{aligned}$$

And further

$$\begin{aligned} ||\nabla_{\mathbf{y}} f^{\epsilon}(t)||_{L^\infty(\mathbb{R}^n\times V\times Y)} &\leq ||\nabla_{\mathbf{y}} f^{\epsilon}(0)||_{L^\infty(\mathbb{R}^n\times V\times Y)} \\ &+ C_2||f_0||_{L^\infty(\mathbb{R}^n\times V\times Y)}(T+CT^2e^{CT}) \\ &+ C_3\int_0^t ||\nabla_y f^{\epsilon}(\tau)||_{L^\infty(\mathbb{R}^n\times V\times Y)}\,d\tau \end{aligned}$$

with

$$\begin{aligned} C_2 &:= (2M_h\tilde{K}_h||\bar{Q}_*||_{L^\infty(\mathbb{R}^n)} + 2M_c\tilde{K}_c + C_{G2}(1+K_Q+K_L)) \\ C_3 &:= (2M_hK_h||\bar{Q}_*||_{L^\infty(\mathbb{R}^n)} + 2M_cK_c + 2C_{G1}(1+K_Q+K_L)). \end{aligned}$$

Applying the Gronwall inequality, we arrive at

$$||\nabla_{\mathbf{y}} f^{\epsilon}(t)||_{L^\infty(\mathbb{R}^n\times V\times Y)} \leq (||\nabla_{\mathbf{y}} f(0)||_{L^\infty(\mathbb{R}^n\times V\times Y)} + C_2||f_0||_{L^\infty(\mathbb{R}^n\times V\times Y)}(T+CT^2e^{CT}))e^{C_3t}.$$

A very similar computation shows that $\nabla_{\mathbf{y}} f_\epsilon(t)$ is bounded in $L^1(R^n\times V\times Y)$ uniformly in ϵ. Extracting subsequences if necessary, we may assume that (as with f_ϵ above)

$$\begin{aligned} \nabla_{\mathbf{y}} f_\epsilon(t) &\overset{*}{\rightharpoonup} \nabla_{\mathbf{y}} f(t) \text{ in } L^\infty(0,T;L^\infty(\mathbb{R}^n\times V\times Y)) \\ \nabla_{\mathbf{y}} f_\epsilon(t) &\rightharpoonup \nabla_{\mathbf{y}} f(t) \text{ in } L^\infty(0,T;L^1_{loc}(\mathbb{R}^n\times V\times Y)) \end{aligned}$$

for some $\nabla_{\mathbf{y}} f(t)$. It is easy to see that this is in fact the gradient of f. Finally Lemma B.2 yields the estimate (39) for the limit function $\nabla_{\mathbf{y}} f(t)$. □

Concerning the uniqueness of a solution to (32) we have the following

Theorem 6.2. *Under the assumptions of Theorem 6.1, the weak solution of (32) is unique.*

The proof of Theorem 6.2 is based on a lemma which we state and prove first.

Lemma 6.2. *Let $f\in L^\infty(0,T;L^1\cap L^\infty(\mathbb{R}^n\times V\times Y))$ be a solution of (32) with $g\equiv 0$. Let ρ_{γ_1} and ρ_{γ_2} be two regularization kernels in the variables $\mathbf{x}$, $\mathbf{v}$ and $\mathbf{y}$ respectively. Then $f_\alpha = (f\star\rho_{\gamma_1})\star\rho_{\gamma_2}$ is a smooth solution of*

(59)

$$\frac{\partial f_{\gamma_1,\gamma_2}}{\partial t} + \mathbf{v}\cdot\nabla_{\mathbf{x}} f_{\gamma_1,\gamma_2} + div_{\mathbf{y}}[\mathbf{G}(\mathbf{y},\bar{Q}_*,L_*)f_{\gamma_1,\gamma_2}] = \mathcal{H}(f_{\gamma_1,\gamma_2},Q_*) + \mathcal{C}(f_{\gamma_1,\gamma_2},L_*) + \epsilon_{\gamma_1,\gamma_2}$$

with

(60) $$\lim_{\gamma_2\to 0}\lim_{\gamma_1\to 0}\epsilon_{\gamma_1,\gamma_2} = 0 \text{ in } L^\infty(0,T;L^1\cap L^\infty(R^n\times V\times Y)).$$

Proof. The proof is almost the same as the one of Lemma 2.1 in [22]. The idea ist to first regularize (32) in the $\mathbf{x}$ and $\mathbf{v}$ variable by convoluting with ρ_{γ_1} and then in the $\mathbf{y}$ variable by convoluting with ρ_{γ_2}. Finally, one lets first γ_1 and then γ_2 go to zero. One only has to take care of the additional error terms for $\mathcal{C}$ and $\mathcal{H}$. These are (for $\mathcal{H}$)

$$\rho_{\gamma_2}\star\mathcal{H}(f,Q_*) - \mathcal{H}((f\star\rho_{\gamma_2}),Q_*) \overset{\gamma_2\to 0}{\to} 0 \text{ in } L^1(R^n\times V\times Y)$$

for the convolution with ρ_{γ_2}, and

$$\rho_{\gamma_1} \star \mathcal{H}(f_{\gamma_2}, Q_*) - \mathcal{H}((f_{\gamma_2} \star \rho_{\gamma_1}), Q_*) \overset{\gamma_1 \to 0}{\to} 0 \text{ in } L^1(R^n \times V \times Y).$$

for the convolution with ρ_{γ_1}. For $\mathcal{C}$, the same results hold. □

Proof of Theorem 6.2. Suppose we had two solutions f_1 and f_2 to (32) with the same initial value in $L^\infty(0,T; L^1 \cap L^\infty(R^n \times V \times Y))$. Due to Lemma 6.2, $w = f_1 - f_2$ satisfies

$$\frac{\partial w_\alpha}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} w_\alpha + div_{\mathbf{y}}[\mathbf{G}(\mathbf{y}, \bar{Q}_*, L_*) w_\alpha] = \mathcal{H}(w_\alpha, Q_*) + \mathcal{C}(w_\alpha, L_*) + \epsilon_{\gamma_1,\gamma_2}. \tag{61}$$

Since we now have sufficient regularity to apply the chain rule, we may multiply the last equation by $\beta'(w_\alpha)$ for some function $\beta \in C^1(\mathbb{R})$ with β' bounded, and obtain

$$\begin{aligned} &\frac{\partial \beta(w_\alpha)}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} \beta(w_\alpha) + \mathbf{G}(\mathbf{y}, \bar{Q}_*, L_*) \cdot (\nabla_{\mathbf{y}} \beta(w_\alpha)) + (\nabla_{\mathbf{y}} \cdot \mathbf{G}(\mathbf{y}, \bar{Q}_*, L_*)) w_\alpha \beta'(w_\alpha) \\ = \;& \mathcal{H}(w_\alpha, Q_*)\beta'(w_\alpha) + \mathcal{C}(w_\alpha, L_*)\beta'(w_\alpha) + \epsilon_{\gamma_1,\gamma_2}\beta'(w_\alpha) \end{aligned}$$

By letting γ_1 and γ_2 go to zero, we obtain the equation

$$\begin{aligned} &\frac{\partial \beta(w)}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} \beta(w) + \mathbf{G}(\mathbf{y}, \bar{Q}_*, L_*) \cdot (\nabla_{\mathbf{y}} \beta(w)) + (\nabla_{\mathbf{y}} \cdot \mathbf{G}(\mathbf{y}, \bar{Q}_*, L_*)) w \beta'(w) \\ = \;& \mathcal{H}(w, Q_*)\beta'(w) + \mathcal{C}(w, L_*)\beta'(w). \end{aligned}$$

Letting β approximate the absolute value, it is possible to deduce in the limit

$$\frac{d}{dt} \int_{\mathbb{R}^n \times V \times Y} |w| d\mathbf{x} d\mathbf{v} d\mathbf{y} \leq C \int_{\mathbb{R}^n \times V \times Y} |w| d\mathbf{x} d\mathbf{v} d\mathbf{y} \tag{62}$$

as in Lemma 2.2 of [22] or Theorem II.2 of [10]. The only difference is that we have to estimate in $L^1(\mathbb{R}^n \times V \times Y)$ the terms $\mathcal{H}(w, Q_*)\beta'(w)$ and $\mathcal{C}(w, L_*)\beta'(w)$ which is possible with the help of (27) and (30). Applying the Gronwall inequality to (62) finally yields $w = 0$ for all times and thus $f_1 = f_2$. □

We next turn our attention to the equation for tissue modification and linearize it by decoupling equation (23) from the rest of the system (22)-(24). For a given function $f_* : [0,T] \times \mathbb{R}^n \times V \times Y \to \mathbb{R}$ we consider

$$\frac{\partial Q}{\partial t} = \kappa(\Pi[f_*](t, \mathbf{x}, \theta) - 1)\bar{f}_*(t, \mathbf{x}) Q(t, \mathbf{x}, \theta) + h(t, \mathbf{x}, \theta). \tag{63}$$

The additional source term h in (63) has been included for the same reason as g in equation (32) above.

Theorem 6.3. *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 (63) with initial condition $Q(0) = Q_0$ and we have the estimates

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

(65) $$||Q(t)||_{L^\infty(\mathbb{R}^n\times S^{n-1})} \le ||Q_0||_{L^\infty(\mathbb{R}^n\times S^{n-1})} + \int_0^T ||h(\tau)||_{L^\infty(\mathbb{R}^n\times S^{n-1})} d\tau.$$

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

Proof. The estimates (64) and (65) can be obtained by integrating (63) w.r.t. time and then w.r.t. $\mathbf{x}$, θ, respectively taking the supremum w.r.t. $\mathbf{x}$ and θ. □

We finally linearize the equation for the soluble ligand by decoupling equation (24) from the rest of the system (22)-(24). For given functions $f_* : [0,T] \times \mathbb{R}^n \times V \times Y \to \mathbb{R}$ and $Q_* : [0,T] \times \mathbb{R}^n \times S^{n-1} \to \mathbb{R}$ we consider

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

For simplicity, we only consider the case $L(0,\cdot) = L_0 = 0$. The generalization to the case $L_0 \ne 0$ is straightforward. A direct application of Theorem C.1 proves the following

Theorem 6.4. *Let $f_* \in L^\infty(0,T; L^\infty(\mathbb{R}^n \times V \times Y))$ 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 $L \in \mathcal{S}'(\mathbb{R}^n)$ to equation (66) with initial condition $L(0,\cdot) = 0$. Moreover, we have the estimate*

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

7. The non-linear problem

We are now going to show the existence-uniqueness result for our primal (nonlinear) system (22)-(24).

Theorem 7.1. *Let the assumptions (G1)-(G4) be satisfied and suppose that f_0 and Q_0 satisfy the conditions in Theorems 6.1 and 6.3. Then the system of partial differential equations (22)-(24) 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*

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

Hereby the solution f to (22) is to be understood in the weak sense (see Definition 6.1).

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 (22)-(24).
Let (f_1, Q_1, L_1) be the solution of

$$\frac{\partial f_1}{\partial t} + \mathbf{v}\cdot\nabla_{\mathbf{x}} f_1 + div_{\mathbf{y}}[\mathbf{G}(\mathbf{y}, \bar{Q}_0, L_0) f_1] = \mathcal{H}(f_1, Q_0) + \mathcal{C}(f_1, L_0) \tag{68}$$

$$\frac{\partial Q_1}{\partial t} = \kappa(\Pi[f_0](t,\mathbf{x},\theta) - 1)\bar{f}_0(\mathbf{x}) Q_1(t,\mathbf{x},\theta) \tag{69}$$

$$\frac{\partial L_1}{\partial t} = D_L \triangle L_1 + \int_{S^{n-1}} \kappa(1 - \Pi[f_0](t,\mathbf{x},\theta))\bar{f}_0(\mathbf{x}) Q_0(\mathbf{x},\theta) d\theta - r_L L_1 \tag{70}$$

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 Theorems 6.1 and 6.2. The existence and uniqueness of Q_1 and L_1 is a consequence of Theorems 6.3 and 6.4.
Moreover, we have that $f_1(t) \in L^\infty(\mathbb{R}^n \times V \times Y)$, $Q_1(t) \in L^\infty(\mathbb{R}^n \times S^{n-1})$ and $L_1(t) \in L^\infty(\mathbb{R}^n)$ are a.e. nonnegative functions with

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

provided that

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

where C is the constant from estimate (38). In fact, to get uniform bounds on the iterates, we will assume in the following that

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

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

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

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

$$\frac{\partial f_{m+1}}{\partial t} + \mathbf{v}\cdot\nabla_{\mathbf{x}} f_{m+1} + div_{\mathbf{y}}[\mathbf{G}(\mathbf{y}, \bar{Q}_m, L_m) f_{m+1}] = \mathcal{H}(f_{m+1}, Q_m) + \mathcal{C}(f_{m+1}, L_m),$$

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

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

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 Theorems 6.1 and 6.2. The existence and uniqueness of Q_{m+1} and L_{m+1} is a result of Theorems 6.3, 6.4.
Moreover, the functions $f_{m+1}(t) \in L^\infty(\mathbb{R}^n \times V \times Y)$, $Q_{m+1}(t) \in L^\infty(\mathbb{R}^n \times S^{n-1})$ and $L_{m+1}(t) \in L^\infty(\mathbb{R}^n)$ are nonnegative a.e. and satisfy

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

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

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

Then from (64) we have the estimate

$$\begin{aligned}
&||Q_{m+1}-Q_m||_{L^\infty(0,T;L^1(\mathbb{R}^n\times S^{n-1}))}\\
&\leq 2T\kappa|S^{n-1}|||Q_0||_{L^\infty(\mathbb{R}^n\times S^{n-1})}||(f_m - f_{m-1})||_{L^\infty(0,T;L^1(\mathbb{R}^n\times V\times Y))}.
\end{aligned} \tag{71}$$

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

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

so that we can deduce from Lemma C.1

(72)
$$\begin{aligned}
&||L_{m+1}-L_m||_{L^\infty(0,T;L^1(\mathbb{R}^n))}\\
&\le 2C(r_L,D_L)\kappa|S^{n-1}|^2||(f_m-f_{m-1})||_{L^\infty(0,T;L^1(\mathbb{R}^n\times V\times Y))}||Q_0||_{L^\infty(\mathbb{R}^n\times S^{n-1})}\\
&+2\kappa C(r_L,D_L)|Y||V|||f_{m-1}||_{L^\infty(0,T;L^\infty(\mathbb{R}^n\times V\times Y))}||Q_m-Q_{m-1}||_{L^\infty(0,T;L^1(\mathbb{R}^n\times S^{n-1}))}
\end{aligned}$$

and

(73)
$$\begin{aligned}
&||\nabla L_{m+1}-\nabla L_m||_{L^\infty(0,T;L^1(\mathbb{R}^n))}\\
&\le 4C(r_L,D_L)\kappa|S^{n-1}|^2||(f_m-f_{m-1})||_{L^\infty(0,T;L^1(\mathbb{R}^n\times V\times Y))}||Q_0||_{L^\infty(\mathbb{R}^n\times S^{n-1})}\\
&+4\kappa C(r_L,D_L)|Y||V|||f_{m-1}||_{L^\infty(0,T;L^\infty(\mathbb{R}^n\times V\times Y))}||Q_m-Q_{m-1}||_{L^\infty(0,T;L^1(\mathbb{R}^n\times S^{n-1}))}.
\end{aligned}$$

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

$$\begin{aligned}
&\frac{\partial}{\partial t}(f_{m+1}-f_m)+\mathbf{v}\cdot\nabla_{\mathbf{x}}(f_{m+1}-f_m)+\nabla_{\mathbf{y}}\cdot[\mathbf{G}(\mathbf{y},\bar{Q_m},L_m)(f_{m+1}-f_m)]\\
&=\mathcal{H}(f_{m+1}-f_m,Q_m)+\mathcal{C}(f_{m+1}-f_m,L_m)+g
\end{aligned}\tag{74}$$

with g defined by

$$\begin{aligned}
&g(\mathbf{x},\mathbf{v},\mathbf{y},t):=\mathcal{H}(f_m,Q_m-Q_{m-1})+\mathcal{C}(f_m,L_m)-\mathcal{C}(f_m,L_{m-1})\\
+\ \ &\nabla_{\mathbf{y}}\cdot\left[(\mathbf{G}(\mathbf{y},\bar{Q}_{m-1},L_{m-1})-\mathbf{G}(\mathbf{y},\bar{Q}_m,L_m))f_m\right].
\end{aligned}$$

Since g satisfies (due to (38) and (27))

$$\begin{aligned}
&\int_0^T||g(\tau)||_{L^1(\mathbb{R}^n\times V\times Y)}\\
\le\ &\int_0^T||\mathcal{H}(f_m,Q_m-Q_{m-1})(\tau)||_{L^1(\mathbb{R}^n\times V\times Y)}d\tau\\
+\ &\int_0^T||\mathcal{C}(f_m,L_m)-\mathcal{C}(f_m,L_{m-1})||_{L^1(\mathbb{R}^n\times V\times Y)}\\
+\ &\int_0^T||\nabla_{\mathbf{y}}\cdot\left[(\mathbf{G}(\mathbf{y},\bar{Q}_{m-1}(\tau),L_{m-1}(\tau))-\mathbf{G}(\mathbf{y},\bar{Q}_m(\tau),L_m(\tau))f_m(\tau)\right]||_{L^1(\mathbb{R}^n\times V\times Y)}d\tau\\
\le\ &\int_0^T 2M_h||p_h(\tau)||_{L^\infty(\mathbb{R}^n\times V\times Y)}|V|^2|Y|||(Q_m-Q_{m-1})(\tau)||_{L^1(\mathbb{R}^n\times S^{n-1})}||f_m(\tau)||_{L^\infty(\mathbb{R}^n\times V\times Y)}d\tau\\
+\ &\int_0^T 2M_{cl}||p_c(\tau)||_{L^\infty(\mathbb{R}^n\times V\times Y)}|V|^2|Y|||\nabla L_m-\nabla L_{m-1}||_{L^1(\mathbb{R}^n)}||f_m(\tau)||_{L^\infty(\mathbb{R}^n\times V\times Y)}d\tau\\
+\ &\int_0^T C_{GL}(||(Q_m-Q_{m-1})(\tau)||_{L^1(\mathbb{R}^n\times S^{n-1})}+||(L_m-L_{m-1})(\tau)||_{L^1(\mathbb{R}^n)})\cdot\\
\cdot\ \ &(||f_m(\tau)||_{L^\infty(\mathbb{R}^n\times V\times Y)}+||\nabla_{\mathbf{y}}f_m(\tau)||_{L^\infty(\mathbb{R}^n\times V\times Y)})d\tau
\end{aligned}$$

and further

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

From the estimate on g, using (37), we can derive the following estimate for $f_{m+1} - f_m$

(75)

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

Combining (71), (72), (73) and (75) we have the following estimate (for T sufficiently small)

(76)

$$\begin{aligned} & ||f_{m+1} - f_m||_{L^\infty(0,T;L^1(\mathbb{R}^n\times V\times Y))} + ||Q_{m+1} - Q_m||_{L^\infty(0,T;L^1(\mathbb{R}^n\times S^{n-1}))} + ||L_{m+1} - L_m||_{L^\infty(0,T;W^{1,1}(\mathbb{R}^n))} \\ & \leq \lambda(||f_m - f_{m-1}||_{L^\infty(0,T;L^1(\mathbb{R}^n\times V\times Y))} + ||Q_m - Q_{m-1}||_{L^\infty(0,T;L^1(\mathbb{R}^n\times S^{n-1}))} + ||L_m - L_{m-1}||_{L^\infty(0,T;W^{1,1}(\mathbb{R}^n))}) \end{aligned}$$

with a $\lambda < 1$, i.e. (f_m, Q_m, L_m) is a Cauchy sequence in

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

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

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

Using (65), we have

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

and taking the supremum

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

Since $f_m \to f$ in $L^\infty(0,T;L^1(\mathbb{R}^n \times V \times Y))$, there exists a subsequence (which we again denote by (f_m)) that converges to f in $L^\infty(0,T;L^\infty(\mathbb{R}^n \times V \times Y))$. 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 (22)-(24). The uniqueness follows from the fact that any solution to (22)-(24) is a fixed point of the mapping $(f_*,Q_*,L_*) \mapsto (f,Q,L)$. □

8. CONCLUSIONS

In this paper we proposed a multiscale modeling framework for cancer cell dispersal through a tissue. We mathematically deduced our model from basic principles; it allows to explicitly include more realistic features like the influence of a chemoattractant and of the cell surface dynamics on cell motility, along with 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 [16], [26], in a slightly different context. For our mesoscopic model we relied on an iterative method to prove the local existence of a unique solution.

Recently, an equation free nonparametric approach has been proposed [27], which allows to handle cell dispersal in realistic, highly complex settings and offers an alternative to the usual PDE approach along with their numerical treatment via passage to macroscopic limits. Moreover, when a PDE can be written for the cell density in the context of those models, then the nonparametric technique can be seen as a reliable numerical method for solving that PDE, an issue which was already addressed in [27] and is currently further investigated in [28]. This seems to be a promising approach for modeling more complex situations, like bacteria movement in a porous medium [28] or even a multiscale model for cancer invasion in a detailed description.

Following the approach in [11] to include intracellular dynamics a multiscale model for bacterial chemotaxis is currently studied in [29], where we also provide an in-depth modeling of the turning kernel involving the intracellular dynamics and the concentration of chemoattractant. The global existence of a mild solution has been shown in any relevant space dimension and the use of the nonparametric technique proposed in [27] is expected to allow assessing the behavior of the cell population under the influence of the intracellular dynamics and of a chemotactic signal.

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Appendix A. Ordinary Differential Equations

Let $I \subseteq \mathbb{R}$ be an open interval and $V \subseteq \mathbb{R}^n$ an open, nonempty and connected set.

Definition A.1. *Let $q : I \times V \to \mathbb{R}^n$ be a continuous map that is locally Lipschitz in $\mathbf{x}$. We call a subset Y of V positively invariant for the differential equation $\dot{\mathbf{x}} = q(t, \mathbf{x})$ if for every point $y \in Y$ and every $t_0 \in I$ the solution $\mathbf{x}(t)$ of the initial value problem $\dot{\mathbf{x}} = q(t, \mathbf{x})$, $\mathbf{x}(t_0) = \mathbf{y}$, satisfies $\mathbf{x}(t) \in Y$ for all $t \geq t_0$ in the maximal existence interval.*

We have the following criterion for positive invariant sets (this is Lemma 1.1 in [20]):

Lemma A.1. *Let $\mathbf{x} = q(t, \mathbf{x})$ be given, and let μ_1,...,μ_r be linear forms on $\mathbb{R}^n$ such that*

$$W := \{x \in \mathbb{R}^n : \mu_1(\mathbf{x}) > 0, ..., \mu_r(\mathbf{x}) > 0\} \cap V$$

is nonempty. Then W (as well as its closure $\bar{W}$) is positively invariant for $\mathbf{x} = q(t, \mathbf{x})$ if and only if the following holds: for all $(t^*, \mathbf{x}^*) \in I \times V$ such that $\mathbf{x}^* \in \bar{W}$, and all $j \in 1, ..., r$ such that $\mu_j(\mathbf{x}^*) = 0$, the inequality $\mu_j(q(t^*, \mathbf{x}^*)) \geq 0$ is satisfied.

Liouville's formula expresses the determinant of a square-matrix solution of a first-order system of homogeneous linear differential equations in terms of the sum of the diagonal coefficients of the system:

Lemma A.2. *Consider the linear differential equation $\dot{\mathbf{x}} = A(t)x$. Let Φ denote a matrix-valued solution on I. If the trace of A is a continuous function, then the determinant of Φ satisfies*

$$\det \Phi(t) = \det \Phi(t_0)\, \exp\left(\int_{t_0}^{x} \operatorname{tr} A(\tau)\, d\tau\right)$$

for all t and t_0 in I.

Appendix B. Functional Analysis and Function Spaces

Lemma 2.42 in [1]:

Lemma B.1. *Let $f : X \to [-\infty, \infty]$ be a function on a topological space. Then f is lower semicontinuous if and only if*

$$x_\alpha \to x \Rightarrow \liminf_{\alpha} f(x_\alpha) \geq f(x).$$

Lemma 6.22 in [1]:

Lemma B.2. *If X is a normed space, then the norm function $x \mapsto ||x||$ is weakly lower semicontinuous on X, and the dual norm function $x' \mapsto ||x'||$ is weak* lower semicontinuous on X'.*

The concept of equiintegrability is crucial for weak compactness in L^1:

Definition B.1. *Let $\Omega \subset \mathbb{R}^n$ and $\mathcal{U} \subset L^1(\Omega)$ be a family of integrable functions. We say that $\mathcal{U}$ is an equiintegrable family if the following two conditions hold:*

(1) *For any* $\epsilon > 0$ *there exists a measurable set* A *with* $|A| < \infty$ *such that*

$$\int_{\Omega \backslash A} |u| < \epsilon,$$

for all $u \in \mathcal{U}$.

(2) *For any* $\epsilon > 0$ *there exists* $\delta > 0$ *such that for every measurable set* E *with* $|E| < \delta$ *there holds*

$$\int_E |u| < \epsilon$$

for all $u \in \mathcal{U}$.

A sufficient condition for equiintegrability is the following

Lemma B.3. *Let* $|\Omega| < \infty$ *and* $u_n : \Omega \to \mathbb{R}$ *be a sequence of functions that are uniformly bounded in* $L^1(\Omega)$. *Then a sufficient condition for the sequence* u_n *to be equiintegrable is that* u_n *is uniformly bounded in* $L^2(\Omega)$.

The Dunford-Pettis theorem gives a necessary and sufficient condition for compactness with respect to the weak convergence in L^1:

Theorem B.1. *Let* $u_n : \Omega \to \mathbb{R}$ *be a sequence in* $L^1(\Omega)$. *Suppose that* u_n *is uniformly bounded in* $L^1(\Omega)$ *and equiintegrable. Then there exists a subsequence of* u_n *that converges weakly in* $L^1(\Omega)$. *Conversely, if* u_n *converges weakly in* $L^1(\Omega)$, *then* u_n *is uniformly bounded and equiintegrable.*

In the context of partial differential equations, we need the Schwartz space $\mathcal{S}$ (or rather its dual space $\mathcal{S}'$):

Definition B.2. *The Schwartz space or space of rapidly decreasing functions* $\mathcal{S}$ *on* $\mathbb{R}^n$ *is the function space*

$$\mathcal{S}\left(\mathbb{R}^n\right) = \{f \in C^\infty(\mathbb{R}^n) \mid \|f\|_{\alpha,\beta} < \infty \, \forall \, \alpha, \beta\},$$

where α, β *are multi-indices,* $C^\infty(\mathbb{R}^n)$ *is the set of smooth functions from* $\mathbb{R}^n$ *to* C, *and*

$$\|f\|_{\alpha,\beta} = \sup_{x \in \mathbf{R}^n} |x^\alpha D^\beta f(x)|.$$

Appendix C. Partial Differential Equations

By Γ we denote the fundamental solution of the differential operator $\partial_t - \triangle_x + \beta$ in $\mathbb{R}_+ \times \mathbb{R}^2$,

$$\Gamma(t,x) = \frac{1}{4\pi t} exp\left(-\frac{|x|^2}{4t} - \beta t\right). \tag{77}$$

For each time $t > 0$,

$$\int_{\mathbb{R}^2} \Gamma(t,x)dx = e^{-\beta t}. \tag{78}$$

According to Lemma 2.12 in [30], $\Gamma(s,\cdot)$ and $\nabla\Gamma(s,\cdot)$ are in $L^1(\mathbb{R}^2)$ for every $s \in \mathbb{R}_+$ and satisfy

$$\int_0^t ||\nabla\Gamma(s,\cdot)||_{L^1(\mathbb{R}^2)} ds \leq C(\beta) \tag{79}$$

$$\int_0^t ||\nabla\Gamma(s,\cdot)||_{L^1(\mathbb{R}^2)} ds \leq 2C(\beta). \tag{80}$$

The existence and uniqueness of a solution to the Cauchy Problem

$$\partial_t S - \kappa \triangle S = \rho - \beta S \text{ in } \mathbb{R}_+ \times \mathbb{R}^2 \tag{81}$$

$$S = 0 \text{ on } \{t = 0\} \times \mathbb{R}^2 \tag{82}$$

with $\beta \geq 0$ is ensured by the following

Theorem C.1. *Let ρ be a locally integrable function that is bounded in every strip $0 \leq t \leq T$. Then there is a unique solution $S \in \mathcal{S}'(\mathbb{R}^2)$ to the Cauchy Problem (81)-(82) given by*

$$S(t,x) = \int_0^t \int_{\mathbb{R}^2} \Gamma(\kappa(t-s), x-y)\rho(s,y)dyds. \tag{83}$$

Clearly, S is non-negative for non-negative ρ.

Lemma C.1. *Let S be the solution of (81) with initial condition (82). Then $S(t) \in L^\infty(\mathbb{R}^2)$ for every $t \in \mathbb{R}_+$ and*

$$||S(t)||_{L^\infty(\mathbb{R}^2)} \leq \frac{1}{\beta\kappa}||\rho||_{L^\infty(0,T;L^\infty(\mathbb{R}^2))} \tag{84}$$

$$||S(t)||_{L^1(\mathbb{R}^2)} \leq C(\beta,\kappa)||\rho||_{L^\infty(0,T;L^1(\mathbb{R}^2))}. \tag{85}$$

The gradient ∇S of S satisfies the estimate

$$||\nabla S(t)||_{L^1(\mathbb{R}^2)} \leq 2C(\beta,\kappa)||\rho||_{L^\infty(0,T;L^1(\mathbb{R}^2))}. \tag{86}$$

Proof. Starting from the representation formula (83), the estimate (84) is a direct consequence of (78) and (85), (86) are readily obtained with Young's inequality and (79), (80):

$$\begin{aligned}
||\nabla S(t)||_{L^1(\mathbb{R}^2)} &\leq \int_0^t \int_{\mathbb{R}^2} |\int_{\mathbb{R}^2} \nabla\Gamma(\kappa t - \kappa s, x-y)\rho(s,y)dy| dxds \\
&\leq \int_0^t ||\nabla\Gamma(\kappa t - \kappa s, \cdot)||_{L^1(\mathbb{R}^2)} ||\rho(s,\cdot)||_{L^1(\mathbb{R}^2)} ds \\
&\leq 2C(\beta,\kappa)||\rho||_{L^\infty(0,T;L^1(\mathbb{R}^2))}.
\end{aligned}$$

□

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