

Constructing solutions for a kinetic model of angiogenesis in annular domains

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Abstract

We present an iterative technique to construct stable solutions for an angiogenesis model set in an annular region. Branching, anastomosis and extension of blood vessel tips is described by an integrodifferential kinetic equation of Fokker-Planck type supplemented with nonlocal boundary conditions and coupled to a diffusion problem with Neumann boundary conditions through the force field created by the tumor induced angiogenic factor and the flux of vessel tips. Convergence proofs exploit balance equations, estimates of velocity decay and compactness results for kinetic operators, combined with gradient estimates of heat kernels for Neumann problems in non convex domains.

Keywords: Angiogenesis, Integrodifferential model, Kinetic-diffusion equations, Fokker-Planck operator, Bounded domains, Nonlocal and Neumann boundary conditions.

1. Introduction

Angiogenesis is a process through which new blood vessels grow from pre-existing ones. Angiogenesis is vital for tissue development and repair. However, angiogenic disorders are often the cause of inflammatory and immune diseases [10]. Moreover, angiogenesis is essential for the transition of benign tumors

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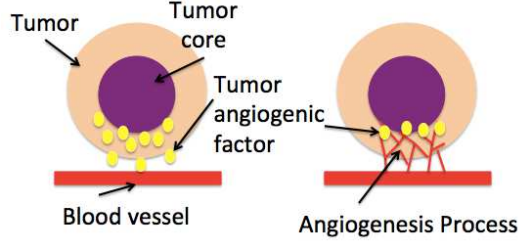


Figure 1: Schematic representation of the formation of a vessel network to increase oxygen supply towards the inner regions of a tumor from a neighboring blood vessel. Drops represent the emitted concentration of tumor angiogenic factor, decreasing from the tumor core in the direction of the closest vessel tips.

into malignant ones, and for subsequent tumor spread [10]. Numerous anti-tumor therapies target blood vessel growth [11, 40] in an attempt to prevent tumor expansion. Mathematical models may help to control the formation and evolution of blood vessel networks for therapeutical purposes. Many models have been proposed to describe different aspects of the process, see references [8, 15, 22, 24, 29, 32, 33, 34, 35, 40] for instance. However, the incessant availability of new experimental observations promotes continued model update and fosters the search for improved descriptions.

In a tumor induced angiogenic process, high cell density in the inner regions of the tumor results in low oxygen and nutrient levels. Cells respond emitting a substance (the tumor angiogenic factor) that eventually reaches neighboring blood vessels, promoting the appearance of new vessel tips that advance in direction to the tumor to supply new resources to the necrotic cells, see Fig. 1. The stochastic evolution of the vessel branching process seems to be a key feature to be taken into account. Recently, a deterministic integrodifferential system has been shown to reproduce some aspects of the development of the stochastic vessel network [1, 2]. This model is derived from a stochastic description of the formation of blood vessel networks using ensemble averages. Comparison of numerical solutions of both descriptions yields good agreement [2]. The evolution of the density of blood vessel tips p in response to the concentration of tumor angiogenic factor released by cells c is described by the following set of equations:

$$\begin{aligned} \frac{\partial}{\partial t} p(\mathbf{x}, \mathbf{v}, t) &= \alpha(c(\mathbf{x}, t)) \delta_{\mathbf{v}_0}(\mathbf{v}) p(\mathbf{x}, \mathbf{v}, t) - \gamma p(\mathbf{x}, \mathbf{v}, t) \int_0^t ds \int d\mathbf{v}' p(\mathbf{x}, \mathbf{v}', s) \\ &\quad - \mathbf{v} \cdot \nabla_{\mathbf{x}} p(\mathbf{x}, \mathbf{v}, t) + \beta \operatorname{div}_{\mathbf{v}}(\mathbf{v} p(\mathbf{x}, \mathbf{v}, t)) + \\ &\quad - \operatorname{div}_{\mathbf{v}} [\mathbf{F}(c(\mathbf{x}, t))] p(\mathbf{x}, \mathbf{v}, t) + \sigma \Delta_{\mathbf{v}} p(\mathbf{x}, \mathbf{v}, t), \end{aligned} \quad (1)$$

$$\frac{\partial}{\partial t} c(\mathbf{x}, t) = d \Delta_{\mathbf{x}} c(\mathbf{x}, t) - \eta c(\mathbf{x}, t) j(\mathbf{x}, t), \quad (2)$$

$$p(\mathbf{x}, \mathbf{v}, 0) = p_0(\mathbf{x}, \mathbf{v}), \quad c(\mathbf{x}, 0) = c_0(\mathbf{x}), \quad (3)$$

where

$$\alpha(c(\mathbf{x}, t)) = \alpha_1 \frac{\frac{c(\mathbf{x}, t)}{c_R}}{1 + \frac{c(\mathbf{x}, t)}{c_R}}, \quad \mathbf{F}(c(\mathbf{x}, t)) = \frac{d_1}{(1 + \gamma_1 c(\mathbf{x}, t))^{q_1}} \nabla_{\mathbf{x}} c(\mathbf{x}, t), \quad (4)$$

$$j(\mathbf{x}, t) = \int_{\mathbb{R}^N} \frac{|\mathbf{v}|}{1 + e^{|\mathbf{v} - \mathbf{v}_0 \chi|^2 / \sigma_v^2}} p(\mathbf{x}, \mathbf{v}, t) d\mathbf{v}, \quad \rho(\mathbf{x}, t) = \int_{\mathbb{R}^N} p(\mathbf{x}, \mathbf{v}, t) d\mathbf{v}, \quad (5)$$

for $\mathbf{x} \in \Omega \subset \mathbb{R}^N$, $\mathbf{v} \in \mathbb{R}^N$, $N = 2, 3$, $t \in [0, \infty)$. The constants β , σ , γ , d , η , α_1 , c_R , d_1 , γ_1 , q_1 are positive. The parameter $\chi \gg 1$ (typically $\chi > 10$) whereas $\sigma_v^2 \ll 1$. $\delta_{\mathbf{v}_0}$ is a Dirac measure supported at a point \mathbf{v}_0 . \mathbf{v}_0 is a typical sprouting velocity for the tips. The source term $\alpha(c)\delta_{\mathbf{v}_0} p$ represents creation of new tips due to vessel tip branching. Tip vessel death when a tip encounters another vessel (anastomosis) is described by the integral sink $-\gamma p \int_0^t \rho(p)$. The Fokker-Planck operator expresses blood vessel extension. The chemotactic force $\mathbf{F}(c)$ is taken to depend on the flux of blood vessel tips through j to represent that consumption of tumor angiogenic factor is mostly due to the additional endothelial cells that produce vessel extensions [8]. The velocity cut-off through the Fermi-Dirac distribution in the definition of j (5) reflects the fact that cell velocities are limited, and small [12]. Similar models may be used to describe retinal angiogenesis [9].

We study the existence of solutions to a regularized version of equations (1)-(5), where $\delta_{\mathbf{v}_0}$ is approximated by a smooth, positive, integrable and bounded function $\nu(\mathbf{v})$,

$$\begin{aligned} \frac{\partial}{\partial t} p(\mathbf{x}, \mathbf{v}, t) &= \alpha(c(\mathbf{x}, t)) \nu(\mathbf{v}) p(\mathbf{x}, \mathbf{v}, t) - \gamma p(\mathbf{x}, \mathbf{v}, t) \int_0^t ds \rho(\mathbf{x}, s) \\ &\quad - \mathbf{v} \cdot \nabla_{\mathbf{x}} p(\mathbf{x}, \mathbf{v}, t) + \beta \operatorname{div}_{\mathbf{v}}(\mathbf{v} p(\mathbf{x}, \mathbf{v}, t)) + \\ &\quad - \operatorname{div}_{\mathbf{v}}[\mathbf{F}(c(\mathbf{x}, t))] p(\mathbf{x}, \mathbf{v}, t) + \sigma \Delta_{\mathbf{v}} p(\mathbf{x}, \mathbf{v}, t), \end{aligned} \quad (6)$$

when Ω is an annular domain $r_0 < r < r_1$. Notice that delta functions can be approximated by sequences of gaussians. The motivation for the annular geometry is simple, in view of Figure 1. Many tumors resemble spheres. An inner necrotic core is surrounded by a corona through which blood vessels spread, driven by the tumor angiogenic factor emitted by core. New vessel tips arise from existing vessels surrounding the outer layers of the tumor. They spread to supply with blood inner tumor regions in need of oxygen and nutrients.

The general form of the boundary conditions in dimension $N = 2, 3$, is as follows. We impose Neumann boundary conditions for c :

$$\frac{\partial c}{\partial r}(\mathbf{x}, t) = c_{r_0}(\mathbf{x}, t) < 0, \quad \mathbf{x} \in S_{r_0}, \quad \frac{\partial c}{\partial r}(\mathbf{x}, t) = 0, \quad \mathbf{x} \in S_{r_1}, \quad t \in [0, T], \quad (7)$$

where c_{r_0} represents the influx of tumor angiogenic factor coming from the inner core of the tumor. S_{r_0} and S_{r_1} are spheres of radius r_0 and r_1 , respectively.

Since diffusion is absent in the \mathbf{x} variable, the transport operator forces boundary conditions of the form:

$$p^-(\mathbf{x}, \mathbf{v}, t) = g(\mathbf{x}, \mathbf{v}, t) \quad \text{on } \Sigma_T^-. \quad (8)$$

The sets $\Sigma_T^\pm = (0, T) \times \Gamma^\pm$, where $\Gamma^\pm = \{(\mathbf{x}, \mathbf{v}) \in \partial\Omega \times \mathbb{R} \mid \pm \mathbf{v} \cdot \mathbf{n}(\mathbf{x}) > 0\}$, $\mathbf{n}(\mathbf{x})$ being the outward unit normal onto the boundary $\partial\Omega$. We denote by p^+ and p^- the traces of p on Σ_T^+ and Σ_T^- , respectively. In our geometry, the boundary conditions for p are defined using the magnitudes that can actually be measured: the marginal tip density $\rho = \int p d\mathbf{v}$ in the inner boundary and the flux of blood vessels $\mathbf{j} = \int \mathbf{v} p d\mathbf{v}$ in the outer boundary. Using coordinates $\mathbf{x} = r\boldsymbol{\theta}$, with $r = |\mathbf{x}|$, $\boldsymbol{\theta} \in S_{N-1}$, and $\mathbf{v} = v_r\boldsymbol{\phi}$, with $v_r = |\mathbf{v}|$, $\boldsymbol{\phi} \in S_{N-1}$, the boundary conditions on Σ_T^- read:

$$p^-(r_0, \boldsymbol{\theta}, v_r, \boldsymbol{\phi}, t) = \frac{e^{-\frac{\beta}{\sigma}|\mathbf{v}-\mathbf{v}_0|^2}}{\mathcal{I}_0} \left[\rho(r_0, \boldsymbol{\theta}, t) - \int_0^\infty d\tilde{v}_r \tilde{v}_r^{N-1} \int_{\{\tilde{\boldsymbol{\phi}} \in S_{N-1} \mid \tilde{\mathbf{v}} \cdot \mathbf{n} > 0\}} d\tilde{\boldsymbol{\phi}} p^+(r_0, \boldsymbol{\theta}, \tilde{v}_r, \tilde{\boldsymbol{\phi}}, t) \right], \quad (9)$$

$$p^-(r_1, \boldsymbol{\theta}, v_r, \boldsymbol{\phi}, t) = \frac{e^{-\frac{\beta}{\sigma}|\mathbf{v}-\mathbf{v}_0|^2}}{\mathcal{I}_1} \left[-j_0 - \int_0^\infty d\tilde{v}_r \tilde{v}_r^{N-1} \int_{\{\tilde{\boldsymbol{\phi}} \in S_{N-1} \mid \tilde{\mathbf{v}} \cdot \mathbf{n} > 0\}} d\tilde{\boldsymbol{\phi}} p^+(r_1, \boldsymbol{\theta}, \tilde{v}_r, \tilde{\boldsymbol{\phi}}, t) f_1(\tilde{\mathbf{v}}) \right], \quad (10)$$

where p^+ and p^- denote the traces of the solution p on Σ_T^+ and Σ_T^- , respectively, and

$$\mathcal{I}_0 = \int_0^\infty d\tilde{v}_r \tilde{v}_r^{N-1} \int_{\{\tilde{\boldsymbol{\phi}} \in S_{N-1} \mid \tilde{\mathbf{v}} \cdot \mathbf{n} < 0\}} d\tilde{\boldsymbol{\phi}} e^{-\frac{\beta}{\sigma}|\tilde{\mathbf{v}}-\mathbf{v}_0|^2}, \quad \mathcal{I}_1 = \int_0^\infty d\tilde{v}_r \tilde{v}_r^{N-1} \int_{\{\tilde{\boldsymbol{\phi}} \in S_{N-1} \mid \tilde{\mathbf{v}} \cdot \mathbf{n} < 0\}} d\tilde{\boldsymbol{\phi}} e^{-\frac{\beta}{\sigma}|\tilde{\mathbf{v}}-\mathbf{v}_0|^2} f_1(\tilde{\mathbf{v}}). \quad (11)$$

The remaining functions are defined as:

$$f_1(\mathbf{v}) = \mathbf{v} \cdot \mathbf{n} \left[1 + e^{|\mathbf{v}-\mathbf{v}_0|^2/\sigma_v^2} \right]^{-1}, \quad (12)$$

$$j_0(\boldsymbol{\theta}, t) = v_0 \alpha(c(r_1, \boldsymbol{\theta}, t)) p(r_1, \boldsymbol{\theta}, v_0, \mathbf{w}_0, t), \quad (13)$$

for the fixed velocity $\mathbf{v}_0 = (v_0, \mathbf{w}_0)$, $v_0 > 0$, $\mathbf{w}_0 \in \mathbb{R}^{N-1}$. Notice that the operators defining these boundary conditions are positive. Thus, these conditions are expected to be absorbing, for positive densities. Boundary conditions with a similar mathematical structure arise in kinetic models of charge transport in semiconductors [3].

Rigorous derivations of these mean field models from the original stochastic systems as well as the development of stable numerical schemes require well posedness results for the integrodifferential set of equations. Equation (1) evokes Vlasov-Poisson-Fokker-Planck (VPFP) systems, with several key differences. First, the force field \mathbf{F} is not related to the marginal tip density $\rho(p)$ through a Poisson equation. It depends on the flux of vessel tips j through the gradient of solutions of heat equations with Neumann boundary conditions. Second, it contains a quadratic anastomosis term involving a nonlocal in time integrodifferential sink. Moreover, the structure of the boundary conditions for the transport operator differs from those usually considered in Boltzmann equations for gas dynamics [14, 21] and studied for VPFP models [13] as well, see also references [16, 23]. Existence results for VPFP systems and related models in the whole space have been formulated under successively milder assumptions, see references [17, 39, 38, 31, 4, 18, 30, 19]. Global solutions for this angiogenesis model in the whole space have been constructed in reference [12]. Spatial

boundaries pose new difficulties, arising from the nonlocal boundary conditions for the transport operator in the equation for the density of blood vessel tips and the presence of Neumann boundary conditions in the diffusion equation for the tumor angiogenic factor. Analyses in unbounded domains rely heavily on the properties of fundamental solutions for linear operators. The unavailability of results on fundamental solutions in bounded domains forces the development of new strategies.

In this paper, we construct stable solutions of regularized versions of system (1)-(5), (7), (9)-(10) where the measure δ_{v_0} is replaced by a smooth positive bounded function. To be more precise, we consider the initial-boundary value problem given by equations (6), (2)-(5), (7), and (9)-(13). Solutions are obtained as limits of solutions of linearized problems where all the nonlocal coefficients, rather than the sink terms, are frozen. This guarantees the nonnegativity of the densities p and concentrations c , but requires L^∞ estimates of velocity integrals. Controlling the velocity decay of the densities provides such estimates. Comparison principles and integral inequalities for both the diffusion and the kinetic equation allow us to control the L^q norms of their solutions. Energy arguments provide basic derivative estimates. To handle the nonlocal coupling of the Neumann problem with the kinetic equation we will have to make use of the theory of heat kernels in bounded domains [27, 36, 37] and sharp gradient estimates for the semigroup of the Neumann problem [41] established by probabilistic methods for non convex regions in order to obtain $L^r - L^q$ estimates of the derivatives of solutions. Compactness results specific of kinetic operators [30, 18, 4] enable the passage to the limit in the linearized problems.

The paper is organized as follows. In Section 2 we adapt existence, uniqueness and stability results for linear boundary value problems involving Fokker-Planck operators, introducing additional lower order terms. Section 3 derives L^∞ estimates for the nonlocal coefficients defined as velocity integrals of the vessel tip densities. Bounds on the velocity decay are essential to pass to the limit in linearized iterative schemes that freeze the nonlocal coefficients. In Section 4 we study the Neumann problem set in the annulus, establishing sharp estimates on the gradient of the solutions. These bounds are fundamental to control the force field created by the tumor angiogenic factor. Section 5 proves the existence and stability result for the nonlinear problem with fixed known boundary condition. Finally, Section 6 addresses the angiogenesis problem with nonlocal boundary conditions and Section 7 states our conclusions.

2. Boundary value problems for linear Fokker-Planck operators

Solutions for the coupled angiogenesis model will be constructed using an iterative scheme that uncouples and freezes each variable to update the other. A good knowledge about the properties of solutions of uncoupled linearized equations is essential. In this section, we collect the needed existence results and estimates for our specific linear problem for the density.

Let $\Omega \subset \mathbb{R}^N$ be a C^∞ bounded domain with boundary $\partial\Omega$. Let us introduce

the set $Q_T = \Omega \times \mathbb{R}^N \times (0, T)$, $T > 0$. We consider the problem:

$$\frac{\partial p}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} p + \operatorname{div}_{\mathbf{v}}((\mathbf{F} - \beta \mathbf{v})p) - \sigma \Delta_{\mathbf{v}} p + ap = h \quad \text{in } Q_T, \quad (14)$$

$$p(\mathbf{x}, \mathbf{v}, 0) = p_0(\mathbf{x}, \mathbf{v}) \quad \text{on } \Omega \times \mathbb{R}^N, \quad (15)$$

with $\beta \geq 0$, $\sigma > 0$, $\mathbf{F}(\mathbf{x}, t) \in L^\infty(\Omega \times (0, T))^N$ and $a \in L^\infty(Q_T)$. We will encounter two typical situations:

- $h \geq 0$, $a \in L^\infty(\Omega \times (0, T))$, $a \geq 0$,
- $h = 0$, $a = a^+ - a^-$, $a^+ \in L^\infty(\Omega \times (0, T))$, $a^- \in L^\infty(Q_T)$.

The initial state p_0 represents a density. Therefore, $p_0 \geq 0$. The transport operator selects absorbing boundary conditions of the form (8) with $g \geq 0$.

We seek weak solutions (in distributional sense) of the problem. For any $T > 0$, a function $f \in L^\infty(0, T; L^1(\Omega \times \mathbb{R}^N))$ is a weak solution of equations (14)-(15) with boundary condition (8) if

$$\begin{aligned} & \int_{Q_T} p \left[\frac{\partial \varphi}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} \varphi - \beta \mathbf{v} \cdot \nabla_{\mathbf{v}} \varphi + \mathbf{F} \cdot \nabla_{\mathbf{v}} \varphi + \sigma \Delta_{\mathbf{v}} \varphi - a \varphi \right] d\mathbf{x} d\mathbf{v} dt \\ & + \int_{\Omega \times \mathbb{R}^N} p_0 \varphi(\mathbf{x}, \mathbf{v}, 0) d\mathbf{x} d\mathbf{v} + \int_{\Sigma_T^-} |\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| g \varphi dS d\mathbf{v} dt = \int_{Q_T} h \varphi d\mathbf{x} d\mathbf{v} dt \end{aligned} \quad (16)$$

for any $\varphi \in C_0^\infty(\bar{\Omega} \times \mathbb{R}^N \times [0, T])$ such that $\varphi = 0$ on Σ_T^+ .

We denote by L^q the standard spaces of functions p for which $|p|^q$ is integrable with respect to the Lebesgue measure in the pertinent domains and by L^∞ the space of bounded functions. We introduce the space $L_k^q(\Sigma_T^\pm)$ of functions g such that $|g|^q$ is integrable in Σ_T^\pm with respect to the kinetic measure $|\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| dS d\mathbf{v} dt$, where dS is the Lebesgue measure on $\partial\Omega$. In an analogous way, we define $L_k^q(\Gamma^\pm)$ with respect to the measure $|\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| dS d\mathbf{v}$.

In absence of the lower order term ap , existence, smoothness, positivity and uniqueness results were established in reference [13]. Theorems 2.1 and 2.2 stated next are straightforward extensions to the case $a \neq 0$ with slight modifications in the proofs to handle the ap term and adequate hypotheses on a .

Theorem 2.1. (Existence, uniqueness, positivity). *Let $\Omega \subset \mathbb{R}^N$ be a bounded domain and set $T > 0$. If*

- i) $\mathbf{F} \in L^\infty(\Omega \times (0, T))$, $a \in L^\infty(Q_T)$,*
- ii) $h \in L^2(Q_T)$, $p_0 \in L^2(\Omega \times \mathbb{R}^N)$ and $g \in L_k^2(\Sigma_T^-)$,*

there exists a unique solution p of equations (14)-(15), (8), satisfying:

- $p \in \{f \in L^2(Q_T) \mid \frac{\partial}{\partial t} f + \mathbf{v} \cdot \nabla_{\mathbf{x}} f - \beta \mathbf{v} \cdot \nabla_{\mathbf{v}} f \in L^2(Q_T)\}$.

- The equations hold in the sense of distributions: for any $\phi \in C_0^\infty(\bar{\Omega} \times \mathbb{R}^N \times [0, T])$ and any $T > 0$

$$\int_{Q_T} p \left(\frac{\partial \phi}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} \phi - \beta \mathbf{v} \cdot \nabla_{\mathbf{v}} \phi + \mathbf{F} \cdot \nabla_{\mathbf{v}} \phi + \sigma \Delta_{\mathbf{v}} \phi - a \phi \right) d\mathbf{x} d\mathbf{v} dt + \int_{\Omega \times \mathbb{R}^N} p_0 \phi(\mathbf{x}, \mathbf{v}, 0) d\mathbf{x} d\mathbf{v} = \int_{\Sigma_T} \mathbf{v} \cdot \mathbf{n}(\mathbf{x}) \text{Tr} p \phi dS d\mathbf{v} dt + \int_{Q_T} h \phi d\mathbf{x} d\mathbf{v} dt. \quad (17)$$

If $\phi = 0$ on Σ_T^+ , the boundary integral becomes

$$- \int_{\Sigma_T^-} (\mathbf{v} \cdot \mathbf{n}(\mathbf{x})) g \phi dt dS d\mathbf{v}.$$

- $\text{Tr} p = g$ on Σ_T^- and $p(\mathbf{x}, \mathbf{v}, 0) = p_0(\mathbf{x}, \mathbf{v})$ in $\Omega \times \mathbb{R}^N$.
- $\|p\|_{L^\infty(0, T; L^2(\Omega \times \mathbb{R}^N))} \leq C_1 \left[\|p_0\|_{L^2(\Omega \times \mathbb{R}^N)} + \|g\|_{L_k^2(\Sigma_T^-)} + \|h\|_{L^2(Q_T)} \right]$, where $C_1 > 0$ depends on T , β and $\|a^-\|_\infty$.
- If $h \geq 0$, $p_0 \geq 0$ and $g \geq 0$, then $p \geq 0$.

Theorem 2.2. (Smoothness, balance laws). Let $\Omega \subset \mathbb{R}^N$ be a bounded domain and set $T > 0$. If

- i) $\mathbf{F} \in L^\infty(\Omega \times (0, T))$, $a \in L^\infty(Q_T)$,
- ii) $h \in L^1 \cap L^\infty(Q_T)$ and $|\mathbf{v}|^2 h \in L^\infty(0, T; L^1(\Omega \times \mathbb{R}^N))$,
- iii) $p_0 \in L^1 \cap L^\infty(\Omega \times \mathbb{R}^N)$ and $|\mathbf{v}|^2 p_0 \in L^1(\Omega \times \mathbb{R}^N)$,
- iv) $g \in L_k^1 \cap L_k^\infty(\Sigma_T^-)$ and $|\mathbf{v}|^2 g \in L_k^1(\Sigma_T^-)$,

the solution p of equations (14)-(15), (8) satisfies

- $p \in L^\infty(0, T; L^1 \cap L^\infty(\Omega \times \mathbb{R}^N))$,
- $|\mathbf{v}|^2 p \in L^\infty(0, T; L^1(\Omega \times \mathbb{R}^N))$,
- $\nabla_{\mathbf{v}} p \in L^2(Q_T)$ and $\text{Tr} p|_{\Sigma_T^+} \in L_k^2(\Sigma_T^+) \cap L^\infty(0, T; L_k^1(\Gamma^+))$,
- $\text{Tr} p^2|_{\Sigma_T^+} \in L^\infty(0, T; L_k^1(\Gamma^+))$,
- Balance of mass: The solution p has trace values in $L^\infty(0, T; L_k^1(\Gamma^+))$ and verifies the continuity equation in integral form

$$\begin{aligned} \frac{d}{dt} \int_{\Omega \times \mathbb{R}^N} p d\mathbf{x} d\mathbf{v} &= \int_{\Gamma^-} |\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| g dS d\mathbf{v} + \int_{\Omega \times \mathbb{R}^N} h d\mathbf{x} d\mathbf{v} \\ &\quad - \int_{\Gamma^+} |\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| \text{Tr} p dS d\mathbf{v} - \int_{\Omega \times \mathbb{R}^N} a p d\mathbf{x} d\mathbf{v}, \end{aligned} \quad (18)$$

- *Balance of momentum:* If $|\mathbf{v}|^\mu h \in L^\infty(0, T; L^1(\Omega \times \mathbb{R}^N))$ and $|\mathbf{v}|^\mu g \in L^\infty(0, T; L^1_k(\Gamma^-))$, then $m_\mu(p) = \int_{\Omega \times \mathbb{R}^N} |\mathbf{v}|^\mu p \, d\mathbf{x} \, d\mathbf{v}$ is absolutely continuous and

$$\begin{aligned} \frac{d}{dt} \int_{\Omega \times \mathbb{R}^N} |\mathbf{v}|^\mu p \, d\mathbf{x} \, d\mathbf{v} &= \int_{\Gamma^-} |\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| |\mathbf{v}|^\mu g \, dS \, d\mathbf{v} + \int_{\Omega \times \mathbb{R}^N} |\mathbf{v}|^\mu h \, d\mathbf{x} \, d\mathbf{v} \quad (19) \\ &- \int_{\Gamma^+} |\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| |\mathbf{v}|^\mu \text{Tr} p \, dS \, d\mathbf{v} - \beta \mu \int_{\Omega \times \mathbb{R}^N} |\mathbf{v}|^\mu p \, d\mathbf{x} \, d\mathbf{v} - \int_{\Omega \times \mathbb{R}^N} a |\mathbf{v}|^\mu p \, d\mathbf{x} \, d\mathbf{v} \\ &+ \mu(\mu - 2 + N) \sigma \int_{\Omega \times \mathbb{R}^N} |\mathbf{v}|^{\mu-2} p \, d\mathbf{x} \, d\mathbf{v} + \mu \int_{\Omega \times \mathbb{R}^N} \mathbf{F} \cdot \mathbf{v} |\mathbf{v}|^{\mu-2} p \, d\mathbf{x} \, d\mathbf{v}, \end{aligned}$$

- *L^q estimates:* If $h \geq 0$, $g \geq 0$ and $p_0 \geq 0$, then $p \geq 0$ and

$$\begin{aligned} \frac{d}{dt} \|p(t)\|_{L^q(\Omega \times \mathbb{R}^N)}^q &= \int_{\Gamma^-} |\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| g^q \, dS \, d\mathbf{v} + q \int_{\Omega \times \mathbb{R}^2} h p^{q-1} \, d\mathbf{x} \, d\mathbf{v} \\ &- \int_{\Gamma^+} |\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| (\text{Tr} p)^q \, dS \, d\mathbf{v} - q \int_{\Omega \times \mathbb{R}^2} a p^q \, d\mathbf{x} \, d\mathbf{v} \\ &+ N\beta(q-1) \|p(t)\|_{L^q}^q \sigma q(q-1) \int_{\Omega \times \mathbb{R}^N} p^{(q-2)} |\nabla_{\mathbf{v}} p|^2 \, d\mathbf{x} \, d\mathbf{v}, \quad (20) \end{aligned}$$

for any $1 \leq q < \infty$. Setting $h = 0$, we find for any $1 \leq q \leq \infty$:

$$\|p\|_{L^\infty(0, T; L^q(\Omega \times \mathbb{R}^N))} \leq e^{[N\beta/q' + \|a^-\|_\infty]T} \left[\|p_0\|_{L^q(\Omega \times \mathbb{R}^N)} + \|g\|_{L^q_k(\Sigma_T^-)} \right], \quad (21)$$

$$\|\text{Tr} p\|_{L^q_k(\Sigma_T^\pm)} \leq e^{[N\beta/q' + \|a^-\|_\infty]T} \left[\|p_0\|_{L^q(\Omega \times \mathbb{R}^N)} + \|g\|_{L^q_k(\Sigma_T^-)} \right]. \quad (22)$$

The positivity result stated in Theorem 2.1 implies a maximum principle for force fields $\mathbf{F}(\mathbf{x}, t)$. A more general maximum principle for bounded fields \mathbf{F} depending on \mathbf{v} such that $\text{div}_{\mathbf{v}} \mathbf{F}$ is bounded will be used later to estimate the velocity decay of solutions p with respect to \mathbf{v} in Proposition 3.7, following reference [17]. In fact, the modified force fields appearing in that proposition arise after a change of variables and consist of the field depending on space and time plus a known term depending on the velocity. The existence of a solution is therefore guaranteed. We state next the key result.

Theorem 2.3. (Maximum principle). *Under the hypotheses of Theorems 2.1 and 2.2, the following two comparison principles hold:*

- (i) *if p_1 and p_2 are two solutions of equations (14)-(15) and (8) with data $h_1 \leq h_2$, $g_1 \leq g_2$, and $p_{1,0} \leq p_{2,0}$, then $p_1 \leq p_2$.*
- (ii) *if p_1 and p_2 are two nonnegative solutions of equations (14)-(15) and (8) with the same data h , g , p_0 , and coefficients $a_1 = a_1^+ - a_1^-$, $a_2 = a_1^+ - \|a_1^-\|_\infty$, so that $a_1^- \leq a_2^-$, then $p_1 \leq p_2$.*

Moreover, if $g \in L^\infty(\Sigma_T^+)$ the solution p satisfies:

$$\|p\|_{L^\infty(Q_T)} \leq e^{[N\beta + \|a^-\|_\infty]T} \left[\|p_0\|_\infty + \|g\|_\infty + \int_0^t \|h(s)\|_\infty \, ds \right]. \quad (23)$$

These estimates still hold true if $\operatorname{div}_{\mathbf{v}}(\mathbf{F}(\mathbf{x}, t)p)$ is replaced by $\mathbf{F} \cdot \nabla_{\mathbf{v}}p$, where \mathbf{F} is a bounded field depending also on \mathbf{v} in such a way that $\operatorname{div}_{\mathbf{v}}\mathbf{F}$ is bounded, and the existence of $p \in C([0, T]; L^2(\Omega \times \mathbb{R}^N))$ such that $\nabla_{\mathbf{v}}p \in L^2(Q_T)$ is assumed.

Proof. Let us first extend the positivity result in Theorem 2.1 to fields \mathbf{F} depending on \mathbf{v} . We set $\bar{p} = e^{-(\lambda+N\beta)t}p(\mathbf{x}, e^{-\beta t}\mathbf{v}, t)$ and $\bar{h} = e^{-(\lambda+N\beta)t}h(\mathbf{x}, e^{-\beta t}\mathbf{v}, t)$. Then, \bar{p} satisfies the equation:

$$\frac{\partial \bar{p}}{\partial t} + e^{-\beta t} \mathbf{v} \cdot \nabla_{\mathbf{x}} \bar{p} + e^{\beta t} \mathbf{F}(\mathbf{x}, e^{-\beta t} \mathbf{v}, t) \cdot \nabla_{\mathbf{v}} \bar{p} - \sigma e^{2\beta t} \Delta_{\mathbf{v}} \bar{p} + (a(\mathbf{x}, e^{-\beta t} \mathbf{v}, t) + \lambda) \bar{p} = \bar{h}.$$

We multiply by \bar{p}^- and integrate to get:

$$\begin{aligned} & - \int_{\Omega \times \mathbb{R}^N} \frac{|\bar{p}^-(T)|^2}{2} d\mathbf{x} d\mathbf{v} - \int_{\partial\Omega \times \mathbb{R}^N \times [0, T]} e^{-\beta t} \mathbf{v} \cdot \mathbf{n} \frac{|\bar{p}^-|^2}{2} dS dv dt + \int_{\Omega \times \mathbb{R}^N \times [0, T]} \operatorname{div}_{\mathbf{v}} \mathbf{F}(\mathbf{x}, e^{-\beta t} \mathbf{v}, t) \frac{|\bar{p}^-|^2}{2} \\ & \quad - \sigma \int_{\Omega \times \mathbb{R}^N \times [0, T]} e^{2\beta t} |\nabla_{\mathbf{v}} \bar{p}^-|^2 - \int_{\Omega \times \mathbb{R}^N \times [0, T]} (a(\mathbf{x}, e^{-\beta t} \mathbf{v}, t) + \lambda) |\bar{p}^-|^2 = \int_{\Omega \times \mathbb{R}^N \times [0, T]} \bar{h} \bar{p}^- \geq 0. \end{aligned}$$

Notice that $\bar{p}^-(0) = 0$ for $p(0) \geq 0$ and $\bar{p}^- = 0$ on Σ_T^- . The only contribution to the integral over $\partial\Omega$ comes from the region where $\mathbf{v} \cdot \mathbf{n} > 0$. Choosing $\lambda \geq \|a^-\|_{\infty} + \|\operatorname{div}_{\mathbf{v}}\mathbf{F}\|_{\infty}$, we conclude that $|\bar{p}^-| = 0$. Therefore, $p \geq 0$ if $p_0 \geq 0$, $h \geq 0$ and $p|_{\Sigma_T^-} \geq 0$.

Assertion (i) is a consequence of the positivity result. Indeed, setting $\bar{p} = p_2 - p_1$, linearity plus the positivity result imply that $p_2 - p_1 \geq 0$.

To prove statement (ii), we set $\hat{p}_1 = e^{-\|a_1^-\|_{\infty} t} p_1$ and $\hat{p}_2 = e^{-\|a_1^-\|_{\infty} t} p_2$. These functions are solutions of similar problems, with source $\hat{h} = e^{-\|a_1^-\|_{\infty} t} h$, boundary datum $\hat{g} = e^{-\|a_1^-\|_{\infty} t} g$ and initial datum p_0 :

$$\begin{aligned} \frac{\partial \hat{p}_1}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} \hat{p}_1 + \mathbf{F} \cdot \nabla_{\mathbf{v}} \hat{p}_1 - \beta \operatorname{div}_{\mathbf{v}}(\mathbf{v} \hat{p}_1) - \sigma \Delta_{\mathbf{v}} \hat{p}_1 + a_1^+ \hat{p}_1 &= (a_1^- - \|a_1^-\|_{\infty}) \hat{p}_1 + \hat{h} \\ \frac{\partial \hat{p}_2}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} \hat{p}_2 + \mathbf{F} \cdot \nabla_{\mathbf{v}} \hat{p}_2 - \beta \operatorname{div}_{\mathbf{v}}(\mathbf{v} \hat{p}_2) - \sigma \Delta_{\mathbf{v}} \hat{p}_2 + a_1^+ \hat{p}_2 &= \hat{h}. \end{aligned}$$

Since $(a_1^- - \|a_1^-\|_{\infty}) \hat{p}_1 \leq 0$, assertion (i) implies that $p_1 \leq p_2$.

For the L^{∞} estimate, let us first notice that if p is a solution with data $h, g, p_0 \leq 0$ then $-p$ is a solution with data $-h, -g, -p_0 \geq 0$ by linearity. Therefore, $-p \geq 0$ and $p \leq 0$. The reverse inequality holds too. Now, let us set $p = e^{\lambda t} \hat{p}$ with $\lambda = N\beta + \|a^-\|_{\infty}$. The function \hat{p} is a solution of equations (14)-(15), (8) with an additional source term $-\lambda e^{-\lambda t} p = -\lambda \hat{p}$. Set $M(t) = \int_0^t e^{-\lambda s} \|h(s)\|_{\infty} ds + \|g\|_{\infty} + \|p_0\|_{\infty}$ and $\bar{p} = \hat{p} - M$. Then, \bar{p} satisfies:

$$\begin{aligned} \frac{\partial \bar{p}}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} \bar{p} + \mathbf{F} \cdot \nabla_{\mathbf{v}} \bar{p} - \beta \operatorname{div}_{\mathbf{v}}(\mathbf{v} \bar{p}) - \sigma \Delta_{\mathbf{v}} \bar{p} + (a + \lambda) \bar{p} \\ = -a^+ M - (\|a^-\|_{\infty} - a^-) M \leq 0 \end{aligned}$$

with initial and boundary conditions $p_0 - M \leq 0$ and $e^{-\lambda t} g - M \leq 0$. Notice that $e^{-\lambda t} < 1$ because $-\lambda < 0$. Therefore, $\bar{p} \leq 0$, $\hat{p} \leq M$ and $p \leq e^{\lambda t} M$. The reverse inequality follows in a similar way by linearity.

3. Estimates on velocity integrals

The nonlinear problem includes the velocity integrals $\rho(p)$ and $j(p)$ of the density p as coefficients. In this section we discuss strategies to estimate velocity integrals in terms of density norms. Let us start with the variable j .

Lemma 3.1. *For any $p \geq 0$, the norms $\|j\|_{L_{\mathbf{x}}^q}$, $1 \leq q \leq \infty$, of the flux j defined in equation (5) can be bounded in terms of $\|p\|_{L_{\mathbf{x}\mathbf{v}}^\infty}$.*

Proof. Let us set $|\mathbf{v}|w(\mathbf{v}) = |\mathbf{v}|[1 + e^{|\mathbf{v}-\mathbf{v}_0\mathbf{x}|^2/\sigma_v^2}]^{-1}$. This function is bounded and integrable. Then,

$$\|j\|_{L_{\mathbf{x}}^\infty} \leq \| |\mathbf{v}|w \|_{L_{\mathbf{v}}^1} \|p\|_{L_{\mathbf{x}\mathbf{v}}^\infty}, \quad (24)$$

$$\|j\|_{L_{\mathbf{x}}^q} \leq \text{meas}(\Omega)^{1/q} \|j\|_{L_{\mathbf{x}\mathbf{v}}^\infty}, \quad 1 \leq q < \infty. \quad (25)$$

$$(26)$$

The anastomosis term may be controlled using the kinetic equation, as we show below.

Lemma 3.2. *Under the hypotheses of Theorems 2.1 and 2.2, let p be a nonnegative solution of problem (6),(3),(4) with boundary condition (8) and nonnegative data. Assume that $c \geq 0$. Then, $\|\int_0^T \int p d\mathbf{v} ds\|_{L_{\mathbf{x}}^2}$ is bounded by the parameters of the problem and $\|p\|_{L_{\mathbf{t}}^\infty L_{\mathbf{x}\mathbf{v}}^\infty}$.*

Proof. Let us recall the equation of mass conservation from Theorem 2.1:

$$\begin{aligned} \frac{\partial}{\partial t} \int \int p d\mathbf{v} d\mathbf{x} + \gamma \int \left[\int_0^t \int p d\mathbf{v}' dt' \right] \left[\int p d\mathbf{v} \right] d\mathbf{x} &= \int \int \alpha(c) \nu p d\mathbf{v} d\mathbf{x} \\ &+ \int_{\Gamma^-} |\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| g dS d\mathbf{v} - \int_{\Gamma^+} |\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| \text{Tr } p dS d\mathbf{v}. \end{aligned}$$

Setting $a(\mathbf{x}, t) = \int_0^t \int p(\mathbf{x}, \mathbf{v}', t',) d\mathbf{v}' dt'$, we notice that $\frac{da}{dt}(\mathbf{x}, t) = \int p(\mathbf{x}, \mathbf{v}', t) d\mathbf{v}'$. Therefore:

$$\left[\int_0^t \int p d\mathbf{v}' dt' \right] \int p(\mathbf{x}, \mathbf{v}, t) d\mathbf{v} = a(\mathbf{x}, t) \frac{da}{dt}(\mathbf{x}, t) = \frac{1}{2} \frac{da^2}{dt}(\mathbf{x}, t).$$

Integrating (27) in time and inserting (27), we find:

$$\begin{aligned} \int \int p(t) d\mathbf{v} d\mathbf{x} - \int \int p(0) d\mathbf{v} d\mathbf{x} + \frac{\gamma}{2} \int a(\mathbf{x}, t)^2 d\mathbf{x} - \frac{\gamma}{2} \int a(\mathbf{x}, 0)^2 d\mathbf{x} &= \\ \int_0^t \int \int \alpha(c) \nu p ds d\mathbf{v} d\mathbf{x} + \int_{\Sigma^-} |\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| g dS d\mathbf{v} - \int_{\Sigma^+} |\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| \text{Tr } p dS d\mathbf{v}. \end{aligned}$$

Notice that $a(0, \mathbf{x})^2 = 0$. Therefore:

$$\int d\mathbf{x} \left[\int_0^t \int p d\mathbf{v} ds \right]^2 \leq C(\gamma, \alpha_1, \text{meas}(\Omega), \|p\|_\infty, \|\nu\|_{L^\infty(0, T, L_{\mathbf{x}\mathbf{v}}^1)}, \|g\|_{L^1(\Sigma_T^-)}).$$

To ensure the positivity of the solutions of linearized versions of equation (6), $b(p) = \int_0^t \rho(p) ds$ is taken to be a known coefficient. To apply Theorem 2.1, it should be a bounded function. L_x^q estimates of $\rho(p)$ are obtained controlling the moments.

Lemma 3.3. *Under the hypotheses of Theorems 2.1 and 2.2, let p a nonnegative solution of the linear equations (14)-(15) with boundary condition (8) and nonnegative data. If $(1 + |\mathbf{v}|^2)^{\mu/2} p_0 \in L^1(\Omega \times \mathbb{R}^N)$, $(1 + |\mathbf{v}|^2)^{\mu/2} h \in L^\infty(0, T; L^1(\Omega \times \mathbb{R}^N))$ and $(1 + |\mathbf{v}|^2)^{\mu/2} g \in L_k^1(\Sigma_T^-)$ for a positive integer μ , then, for $\ell = 0, 1, \dots, \mu$ and $t \in [0, T]$, all the moments*

$$m^\ell(p(t)) = \int_{\Omega \times \mathbb{R}^N} |\mathbf{v}|^\ell p \, d\mathbf{x} \, d\mathbf{v}, \quad m_k^\ell(\text{Tr } p^+) = \int_{\Sigma_T^+} |\mathbf{v} \cdot \mathbf{n}| |\mathbf{v}|^\ell \text{Tr } p^+ \, dS \, d\mathbf{v} \, dt,$$

are bounded in terms of the parameters β, σ, N, T, μ , the norms of the data $\|(1 + |\mathbf{v}|^2)^{\mu/2} p_0\|_{L_{\mathbf{xv}}^1}$, $\|(1 + |\mathbf{v}|^2)^{\mu/2} h\|_{L^\infty(0, T; L_{\mathbf{xv}}^1)}$, $\|(1 + |\mathbf{v}|^2)^{\mu/2} g\|_{L_k^1(\Sigma_T^-)}$, $\|a^-\|_\infty$, $\|\mathbf{F}\|_\infty$, and $\|p\|_{L^\infty(0, T; L_{\mathbf{xv}}^\infty)}$, $\|p\|_{L^\infty(0, T; L_{\mathbf{xv}}^1)}$.

Proof. Notice that the integral

$$\int_{\mathbb{R}^N} \frac{p}{|\mathbf{v}|} \, d\mathbf{v} \leq \|p\|_{L_{\mathbf{xv}}^\infty} \int_{|\mathbf{v}| < R} \frac{d\mathbf{v}}{|\mathbf{v}|} + \frac{1}{R} \int_{\mathbb{R}^N} p \, d\mathbf{v} \leq \|p\|_{L_{\mathbf{xv}}^\infty} \frac{R^{N-1}}{N-1} + \frac{1}{R} \int_{\mathbb{R}^N} p \, d\mathbf{v}.$$

Since Ω is a bounded set, $\int_{\Omega \times \mathbb{R}^N} \frac{p}{|\mathbf{v}|} \, d\mathbf{x} \, d\mathbf{v}$ is bounded in terms of $\|p\|_{L_{\mathbf{xv}}^\infty}$ and $\|p\|_{L_{\mathbf{xv}}^1}$. We first apply identity (19) with $\mu = 1$ to find:

$$\begin{aligned} \frac{d}{dt} \int_{\Omega \times \mathbb{R}^N} |\mathbf{v}| p \, d\mathbf{x} \, d\mathbf{v} &= \int_{\Gamma^-} |\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| |\mathbf{v}| g \, dS \, d\mathbf{v} + \int_{\Omega \times \mathbb{R}^N} |\mathbf{v}| h \, d\mathbf{x} \, d\mathbf{v} \\ &- \int_{\Gamma^+} |\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| |\mathbf{v}| \text{Tr } p \, dS \, d\mathbf{v} - \beta \int_{\Omega \times \mathbb{R}^N} |\mathbf{v}| p \, d\mathbf{x} \, d\mathbf{v} - \int_{\Omega \times \mathbb{R}^N} a |\mathbf{v}| p \, d\mathbf{x} \, d\mathbf{v} \\ &+ (N-1)\sigma \int_{\Omega \times \mathbb{R}^N} |\mathbf{v}|^{-1} p \, d\mathbf{x} \, d\mathbf{v} + \int_{\Omega \times \mathbb{R}^N} \mathbf{F} \cdot \mathbf{v} |\mathbf{v}|^{-1} p \, d\mathbf{x} \, d\mathbf{v}. \end{aligned}$$

Integrating in time, we find:

$$\int_{\Omega \times \mathbb{R}^N} |\mathbf{v}| p \, d\mathbf{x} \, d\mathbf{v} \, ds \leq C(p_0, g, h, \mathbf{F}, p) + \|a^-\| \int_0^t \int_{\Omega \times \mathbb{R}^N} |\mathbf{v}| p \, d\mathbf{x} \, d\mathbf{v} \, ds,$$

where $C(p_0, g, h, \mathbf{F}, p)$ depends on the norms and parameters mentioned in the statement. Gronwall's Lemma provides the required bound on $\int_{\Omega \times \mathbb{R}^N} |\mathbf{v}| p \, d\mathbf{x} \, d\mathbf{v} \, ds$. Once the moment of p is bounded, the estimate on the moment of its trace follows inserting this information in the differential equation.

We reason by induction. Assuming that the moments $m_\ell(p)$ are bounded in terms of the required norms for $\ell \leq M-1$, let us see that the same holds true of $m_M(p)$. Integrating in time (19), using the bounds on $m_{M-1}(p)$ and $m_{M-2}(p)$, together with Gronwall's lemma, we find the desired estimate. By induction, it holds up to $M = \mu$. Once the moments of p are bounded, the estimate on the

moment of its trace follows inserting this information in the differential equations.

The relation between velocity moments and norms of the marginal density $\rho(p) = \int_{\mathbb{R}^N} p d\mathbf{v}$ is established in the following lemma, proven in [12] when $\Omega = \mathbb{R}^N$. $L^q_{\mathbf{x}}$ estimates follow reference [5]. $L^\infty_{\mathbf{x}}$ estimates of the marginal density $\rho(p)$ rely on a strategy involving velocity weights introduced in reference [17]. The bounded or unbounded nature of Ω plays no role in the proofs, and \mathbb{R}^N can be replaced by bounded subsets as we state next.

Lemma 3.4. *Let $\Omega \subset \mathbb{R}^N$ be bounded. For any nonnegative p the following inequalities hold:*

$$\| |\mathbf{v}|^\ell p \|_{L^1(\Omega \times \mathbb{R}^N)} \leq \| p \|_{L^1(\Omega \times \mathbb{R}^N)}^{1-\frac{\ell}{\mu}} \| |\mathbf{v}|^\mu p \|_{L^1(\Omega \times \mathbb{R}^N)}^{\frac{\ell}{\mu}}, \quad \mu > \ell > 0, \quad (27)$$

$$\| \int_{\mathbb{R}^N} |\mathbf{v}|^\ell p d\mathbf{v} \|_{L^{\frac{N+\mu}{N+\ell}}(\Omega)} \leq C_{N,\mu,\ell} \| p \|_{L^\infty(\Omega \times \mathbb{R}^N)}^{\frac{\mu-\ell}{N+\mu}} \| |\mathbf{v}|^\mu p \|_{L^1(\Omega \times \mathbb{R}^N)}^{\frac{N+\ell}{N+\mu}}, \quad \mu > \ell > 0, \quad (28)$$

$$\| \int_{\mathbb{R}^N} |\mathbf{v}| p d\mathbf{v} \|_{L^\infty(\Omega)} \leq C_\mu \| p \|_{L^\infty(\Omega \times \mathbb{R}^N)}^{1-(N+1)/\mu} \| (1+|\mathbf{v}|^2)^{\frac{\mu}{2}} p \|_{L^\infty(\Omega \times \mathbb{R}^N)}^{(N+1)/\mu}, \quad \mu > N+1, \quad (29)$$

$$\| \int_{\mathbb{R}^N} p d\mathbf{v} \|_{L^\infty(\Omega)} \leq C_\mu \| p \|_{L^\infty(\Omega \times \mathbb{R}^N)}^{1-N/\mu} \| (1+|\mathbf{v}|^2)^{\frac{\mu}{2}} p \|_{L^\infty(\Omega \times \mathbb{R}^N)}^{N/\mu}, \quad \mu > N, \quad (30)$$

$$\| (1+|\mathbf{v}|^2)^{\frac{\mu-1}{2}} p \|_{L^\infty(\Omega \times \mathbb{R}^N)} \leq C_\mu \| p \|_{L^\infty(\Omega \times \mathbb{R}^N)}^{1/\mu} \| (1+|\mathbf{v}|^2)^{\frac{\mu}{2}} p \|_{L^\infty(\Omega \times \mathbb{R}^N)}^{1-1/\mu}, \quad \mu > 1, \quad (31)$$

provided the involved integrals and norms are finite.

Revising the proofs of these inequalities in references [5, 12, 17], we see that they extend to the traces on the boundary, with respect to either the Lebesgue or the kinetic measure. This fact is stated in the next two corollaries.

Corollary 3.5. *The inequalities in Lemma 3.4 hold for $\text{Tr } p^+$ replacing the spaces $L^q_{\mathbf{x}} L^1_{\mathbf{v}}(\Omega \times \mathbb{R}^N)$ by $L^q_{\mathbf{x}} L^1_{\mathbf{v}}(\Gamma^+)$ and $L^q(\Omega \times \mathbb{R}^N)$ by $L^q(\Gamma^+)$ provided the involved integrals and norms are finite.*

Corollary 3.6. *The inequalities in Lemma 3.4 hold for $|\mathbf{v} \cdot \mathbf{n}| \text{Tr } p^+$ replacing the spaces $L^q_{\mathbf{x}} L^1_{\mathbf{v}}(\Omega \times \mathbb{R}^N)$ by $L^q_{\mathbf{x}} L^1_{\mathbf{v}}(\Gamma^+)$ and $L^q(\Omega \times \mathbb{R}^N)$ by $L^q(\Gamma^+)$ provided the involved integrals and norms are finite.*

Let us now estimate the velocity decay of p , and the $L^\infty_{\mathbf{x}}$ norms of velocity integrals, which extend to traces on the boundary.

Proposition 3.7. *Let $p \geq 0$ be a solution of the initial value problem (14)-(15) with boundary conditions given by (8). Under the hypotheses:*

- (i) $a \in L^\infty(\Omega \times \mathbb{R}^N \times (0, T))$,
- (ii) $(1+|\mathbf{v}|^2)^{\mu/2} p_0(\mathbf{x}, \mathbf{v}) \in L^1 \cap L^\infty(\Omega \times \mathbb{R}^N)$, $\mu > N$, $p_0 \geq 0$,
- (iii) $(1+|\mathbf{v}|^2)^{\mu/2} g(\mathbf{x}, \mathbf{v}, t) \in L^1 \cap L^\infty(\Sigma_T^-)$,

(iv) $\mathbf{F} \in L^\infty(\Omega \times (0, T))$,

the norms $\|(1 + |\mathbf{v}|^2)^{\mu/2} p\|_{L^\infty(0, T; L^\infty_{\mathbf{xv}})}$, and $\|p\|_{L^\infty(0, T; L^\infty_{\mathbf{x}} L^1_{\mathbf{v}})}$ are bounded by constants depending on T , σ , β , μ , as well as $\|(1 + |\mathbf{v}|^2)^{\mu/2} p_0\|_{L^\infty_{\mathbf{xv}}}$, $\|(1 + |\mathbf{v}|^2)^{\mu/2} g\|_{L^\infty(\Sigma_T^-)}$, $\|a^-\|_{L^\infty(Q_T)}$, $\|\mathbf{F}\|_{L^\infty(\Omega \times (0, T))}$ and $\|p\|_{L^\infty(0, T; L^\infty_{\mathbf{xv}})}$. Moreover, if

(v) $(1 + |\mathbf{v}|^2)^{\mu/2} g(\mathbf{x}, \mathbf{v}, t) \in L^1_k \cap L^\infty_k(\Sigma_T^-)$,

then, for any $1 \leq q \leq \infty$:

$$\|(1 + |\mathbf{v}|^2)^{\frac{\mu}{2}} p\|_{L^\infty(0, T; L^q_{\mathbf{xv}})} \leq e^{\|D\|_\infty T} \left[\|p_0\|_{L^q_{\mathbf{xv}}} + \|(1 + |\mathbf{v}|^2)^{\frac{\mu}{2}} g\|_{L^q_k(\Sigma_T^-)} \right], \quad (32)$$

$$\|(1 + |\mathbf{v}|^2)^{\frac{\mu}{2}} \text{Tr } p\|_{L^q_k(\Sigma_T^\pm)} \leq e^{\|D\|_\infty T} \left[\|p_0\|_{L^q(\Omega \times \mathbb{R}^N)} + \|(1 + |\mathbf{v}|^2)^{\frac{\mu}{2}} g\|_{L^q_k(\Sigma_T^-)} \right], \quad (33)$$

where $\|D\|_\infty$ depends on σ , β , μ , N , $\|a^-\|_{L^\infty(Q_T)}$ and $\|\mathbf{F}\|_{L^\infty(\Omega \times (0, T))}$.

Proof. We follow reference [17] and set $Y(\mathbf{x}, \mathbf{v}, t) = (1 + |\mathbf{v}|^2)^{\mu/2} p(\mathbf{x}, \mathbf{v}, t)$. Multiplying equation (14) by $(1 + |\mathbf{v}|^2)^{\mu/2}$, $\mu > 0$, we get:

$$\frac{\partial}{\partial t} Y + \mathbf{v} \nabla_{\mathbf{x}} Y + \left(\mathbf{F} + 2\sigma\mu \frac{\mathbf{v}}{1 + |\mathbf{v}|^2} - \beta\mathbf{v} \right) \nabla_{\mathbf{v}} Y - \Delta_{\mathbf{v}} Y = (N\beta - a)Y + R \quad (34)$$

where $R = R_1 + R_2 + R_3$, with

$$\begin{aligned} R_1 &= \mu(1 + |\mathbf{v}|^2)^{\mu/2-1} \mathbf{F} \cdot \mathbf{v} p, & R_2 &= -\beta\mu \frac{|\mathbf{v}|^2}{(1 + |\mathbf{v}|^2)} Y, \\ R_3 &= \sigma\mu(\mu + 2) \frac{|\mathbf{v}|^2}{(1 + |\mathbf{v}|^2)^2} Y - N\sigma\mu \frac{1}{1 + |\mathbf{v}|^2} Y. \end{aligned}$$

Thanks to Theorem 2.3:

$$\|Y(t)\|_{L^\infty_{\mathbf{xv}}} \leq C(p_0, g) + \int_0^t \left[N\beta + \|a^-\|_\infty \right] \|Y\|_{L^\infty_{\mathbf{xv}}} + \|R_1\|_{L^\infty_{\mathbf{xv}}} + \|R_2\|_{L^\infty_{\mathbf{xv}}} + \|R_3\|_{L^\infty_{\mathbf{xv}}} ds,$$

where $C(p_0, g)$ is a constant depending on $\|(1 + |\mathbf{v}|^2)^{\mu/2} p_0\|_\infty$ and $\|(1 + |\mathbf{v}|^2)^{\mu/2} g\|_\infty$. The factors $\frac{|\mathbf{v}|^\varepsilon}{1 + |\mathbf{v}|^2} \leq 1$, for $0 \leq \varepsilon \leq 2$. Therefore,

$$\begin{aligned} \|R_1\|_{L^\infty_{\mathbf{xv}}} &\leq \mu \|(1 + |\mathbf{v}|^2)^{\mu/2-1} \mathbf{F} \cdot \mathbf{v} p\|_{L^\infty_{\mathbf{xv}}}, \\ \|R_2\|_{L^\infty_{\mathbf{xv}}} &\leq \beta\mu \|Y\|_{L^\infty_{\mathbf{xv}}}, & \|R_3\|_{L^\infty_{\mathbf{xv}}} &\leq \sigma\mu(\mu + 2 + N) \|Y\|_{L^\infty_{\mathbf{xv}}}. \end{aligned}$$

To bound $\|(1 + |\mathbf{v}|^2)^{\mu/2-1} \mathbf{F} \cdot \mathbf{v} p\|_{L^\infty_{\mathbf{xv}}}$, we set:

$$\|(1 + |\mathbf{v}|^2)^{\mu/2-1} \mathbf{F} \cdot \mathbf{v} p\|_{L^\infty_{\mathbf{xv}}} \leq \frac{N|\mathbf{v}|}{1 + |\mathbf{v}|^2} \|\mathbf{F}\|_\infty \|Y\|_{L^\infty_{\mathbf{xv}}} \leq N\|\mathbf{F}\|_\infty \|Y\|_{L^\infty_{\mathbf{xv}}}.$$

Taking $A = (N\|\mathbf{F}\|_\infty + \beta)\mu + \sigma\mu(\mu + 2 + N) + N\beta + \|a^-\|_\infty$ and $B = C(p_0, g)$, Gronwall's inequality implies

$$\|Y(t)\|_{L^\infty_{\mathbf{xv}}} \leq B e^{At}, \quad t \in [0, T].$$

Once the velocity decay has been established, the L^∞ bounds on $\int_{\mathbb{R}^N} p d\mathbf{v}$ follow from inequality (30) in Lemma 3.4.

Writing down the analogous of equation (20) for equation (34) we find:

$$\begin{aligned} \frac{d}{dt} \|Y(t)\|_{L^q(\Omega \times \mathbb{R}^N)}^q &= \int_{\Gamma_-} |\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| (1 + |\mathbf{v}|^2)^{\mu/2} g^q dS d\mathbf{v} \\ &\quad - \int_{\Gamma_+} |\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| (1 + |\mathbf{v}|^2)^{\mu/2} (\text{Tr } p)^q dS d\mathbf{v} \\ &\quad - \sigma q(q-1) \int_{\Omega \times \mathbb{R}^N} Y^{(q-2)} |\nabla_{\mathbf{v}} Y|^2 d\mathbf{x} d\mathbf{v} - q \int_{\Omega \times \mathbb{R}^N} D Y^q d\mathbf{x} d\mathbf{v}, \end{aligned}$$

where D is a bounded coefficient. Integrating in time, we recover estimates (21) and (22) for Y updating the data, and replacing the exponent of the exponential by $\|D\|_\infty$.

4. Coupling to the diffusion equation with Neumann boundary condition

In this section, we consider diffusion problems of the form:

$$\frac{\partial}{\partial t} c(\mathbf{x}, t) = d \Delta_{\mathbf{x}} c(\mathbf{x}, t) - \eta c(\mathbf{x}, t) j(\mathbf{x}, t) + h(\mathbf{x}, t), \quad \mathbf{x} \in \Omega, t > 0, \quad (35)$$

$$\begin{aligned} \frac{\partial c}{\partial r}(\mathbf{x}, t) &= c_{r_0}(\mathbf{x}, t), \quad \mathbf{x} \in S_{r_0}, \quad \frac{\partial c}{\partial r}(\mathbf{x}, t) = 0, \quad \mathbf{x} \in S_{r_1}, \quad t > 0, \quad (36) \\ c(\mathbf{x}, 0) &= c_0(\mathbf{x}), \quad \mathbf{x} \in \Omega, \quad (37) \end{aligned}$$

where $d, \eta > 0$, $c_{r_0} < 0$ and $j(\mathbf{x}, t) = j(p) = \int_{\mathbb{R}^2} \frac{|\mathbf{v}|}{1 + e^{|\mathbf{v} - \mathbf{v}_0 \mathbf{x}|^2 / \sigma_0^2}} p(\mathbf{x}, \mathbf{v}, t) d\mathbf{v}$. The domain $\Omega = \{\mathbf{x} \in \mathbb{R}^N \mid r_0 < r = |\mathbf{x}| < r_1\}$, with boundaries $S_{r_0} = \{\mathbf{x} \in \mathbb{R}^N \mid |\mathbf{x}| = r_0\}$ and $S_{r_1} = \{\mathbf{x} \in \mathbb{R}^N \mid |\mathbf{x}| = r_1\}$.

When $j(\mathbf{x}, t)$ is a bounded function, existence of a unique global solution for equations (35)-(37) can be proved by classical galerkin or spectral methods [25]. Coercitivity of the associated bilinear form is not necessary. However, it holds whenever $j(t)$ is continuous and does not vanish identically for any $t \in [0, T]$.

Let us now establish comparison and maximum principles that will be essential in the sequel.

Proposition 4.1. (Comparison principle). *Let $c \in C([0, T]; L^2(\Omega))$ be a solution of problem (35)-(37) with initial datum $c_0 \in L^2(\Omega)$, boundary condition $c_{r_0} \in C([0, T]; L^2(\partial\Omega))$ and nonnegative coefficient $j \in L^\infty(\Omega \times (0, T))$. If $c_0 \geq 0$, $h \geq 0$ and $c_{r_0} \leq 0$, then $c \geq 0$. Moreover, the following comparison principle holds. Given two solutions c_1 and c_2 with sources h_1, h_2 , initial data $c_{1,0}, c_{2,0}$ and normal derivatives at the boundary g_1, g_2 , if $g_1 \leq g_2$, $c_{1,0} \leq c_{2,0}$, $h_1 \leq h_2$, then $c_1 \leq c_2$.*

Proof.

Multiplying the equation

$$\frac{\partial}{\partial t}c(\mathbf{x}, t) = d\Delta_{\mathbf{x}}c(\mathbf{x}, t) - \eta c(\mathbf{x}, t)j(\mathbf{x}, t) + h,$$

by $c^- = \text{Max}(-c, 0)$ and integrating, we get

$$\begin{aligned} \frac{1}{2}\|c^-(t)\|_2^2 + \int_0^t \int_{\Omega} [|\nabla c^-|^2 + \eta j|c^-|^2] = \\ \frac{1}{2}\|c^-(0)\|_2^2 - \int_0^t \int_{\partial\Omega} \frac{\partial c}{\partial \mathbf{n}} c^- - \int_0^t \int_{\Omega} h c^- \leq 0, \end{aligned} \quad (38)$$

since, in our case,

$$- \int_{\partial\Omega} \frac{\partial c}{\partial \mathbf{n}} c^- = - \int_{r=r_1} \frac{\partial c}{\partial r}(r_1) c^- + \int_{r=r_0} \frac{\partial c}{\partial r}(r_0) c^- = \int_{r=r_0} \frac{\partial c}{\partial r}(r_0) c^- \leq 0.$$

This implies that $c^- = 0$ and $c \geq 0$.

If $h \geq 0$, $\frac{\partial c}{\partial \mathbf{n}} \geq 0$ and $c(0) \geq 0$, inequality (38) implies immediately $c \geq 0$. Reproducing the computations for $\bar{c} = c_2 - c_1$, inequality (38) implies $c_2 \geq c_1$ by linearity.

Corollary 4.2. *If c is a solution of equations (2)-(3),(7) with nonnegative data c_0 and coefficient j , then $c \geq 0$ and $c \leq u$, u being the solution of the heat equation with the same initial and boundary data, but zero source.*

Proof. Positivity is a straightforward consequence of the previous maximum principle. Similarly, the comparison principle applied with $h_1 = -cj$ and $h_2 = 0$ implies $c \leq u$.

To control the tumor angiogenic factor (TAF) induced force field $\|\mathbf{F}(c)\|_{L_{xt}^\infty}$, we will need $L^r - L^q$ estimates of c analogous to the known estimates for solutions of heat equations in the whole space. Let us first consider the pure initial value problem:

$$u_t(\mathbf{x}, t) = d\Delta_{\mathbf{x}}u(\mathbf{x}, t), \quad \mathbf{x} \in \Omega, t > 0, \quad (39)$$

$$\frac{\partial u}{\partial \mathbf{n}}(\mathbf{x}, t) = 0, \quad \mathbf{x} \in S_{r_0} \cup S_{r_1}, t > 0, \quad (40)$$

$$u(\mathbf{x}, 0) = u_0(\mathbf{x}), \quad \mathbf{x} \in \Omega. \quad (41)$$

For any $u_0 \in L^2(\Omega)$, there is a unique global solution $u \in C([0, T], L^2(\Omega)) \cap L^2(0, T; H^1(\Omega))$, see reference [25]. Ω being bounded, this remains true when $u_0 \in L^\infty(\Omega)$. We can construct the solution using eigenfunction expansions. Let ϕ_n , $n = 1, 2, \dots$, be the orthonormalized eigenfunctions for the homogeneous Neumann problem:

$$-d\Delta\phi_n = \lambda_n\phi_n \quad \text{on } \Omega, \quad \frac{\partial}{\partial \mathbf{n}}\phi_n = 0 \quad \text{on } \partial\Omega. \quad (42)$$

The smallest eigenvalue is $\lambda_1 = 0$ with constant eigenfunction. Using separation of variables, u takes the form:

$$u(\mathbf{x}, t) = \sum_{n \geq 1} u_{0,n} \phi_n(\mathbf{x}) e^{-\lambda_n t}, \quad u_{0,n} = \int_{\Omega} u_0(\mathbf{y}) \phi_n(\mathbf{y}) d\mathbf{y}. \quad (43)$$

The series expansion allows us to prove the ‘smoothing effect’ for $t > 0$: $u(t) \in H^2(\Omega)$. In fact, $u(t) \in H^k(\Omega)$, for all k .

Since Ω is a bounded domain, a $L_{\mathbf{x}}^2$ estimate implies a $L_{\mathbf{x}}^q$ estimate for $q \in [1, 2]$. In the same way, a $L_{\mathbf{x}}^{\infty}$ estimate implies a $L_{\mathbf{x}}^q$ estimate for $1 \leq q \leq \infty$. The decay of the norms of the solutions of the pure initial value problem is summarized in the following result.

Theorem 4.3. (Decay for the initial value Neumann problem). *If $u_0 \in L^{\infty}(\Omega)$, the solution u of equations (39)-(41) satisfies:*

$$\|u(t)\|_{L_{\mathbf{x}}^{\infty}} \leq \|u_0\|_{L_{\mathbf{x}}^{\infty}}, \quad (44)$$

$$\|u(t)\|_{L_{\mathbf{x}}^2} \leq \|u_0\|_{L_{\mathbf{x}}^2}, \quad (45)$$

$$\|\nabla_{\mathbf{x}} u(t)\|_{L_{\mathbf{x}}^2} \leq \frac{1}{t^{1/2}} \|u_0\|_{L_{\mathbf{x}}^2}, \quad (46)$$

$$\|\nabla_{\mathbf{x}} u(t)\|_{L_{\mathbf{x}}^q} \leq \frac{C_{rq}}{t^{1/2+N/2(1/q-1/r)}} \|u_0\|_{L_{\mathbf{x}}^q}, \quad 1 \leq q \leq r \leq \infty, C_{rq} > 0, \quad (47)$$

for $t \in (0, T]$, $T > 0$. Moreover, if $\nabla_{\mathbf{x}} u_0 \in L_{\mathbf{x}}^2$ and $\Delta_{\mathbf{x}} u_0 \in L_{\mathbf{x}}^{\infty}$, then

$$\|\nabla_{\mathbf{x}} u(t)\|_{L_{\mathbf{x}}^2} \leq \|\nabla_{\mathbf{x}} u_0\|_{L_{\mathbf{x}}^2}, \quad (48)$$

$$\|\nabla_{\mathbf{x}} u(t)\|_{L_{\mathbf{x}}^{\infty}} \leq C(\|u_0\|_{L_{\mathbf{x}}^{\infty}}, \|\Delta_{\mathbf{x}} u_0\|_{L_{\mathbf{x}}^{\infty}}). \quad (49)$$

Proof.

By Proposition 4.1, u is bounded from above and below by the solutions of equations (39)-(41) with initial data $\|u_0\|_{\infty}$ and $-\|u_0\|_{\infty}$, respectively. This proves (44).

Multiplying equation (39) by u and integrating, we find the energy identity:

$$\frac{1}{2} \|u(t)\|_2^2 + d \int_0^t \int_{\Omega} |\nabla_{\mathbf{x}} u|^2 = \frac{1}{2} \|u_0\|_2^2, \quad (50)$$

which implies estimate (45).

To prove inequality (46) we argue by density, assuming first that $u_0 \in H^1(\Omega)$. We multiply equation (39) by u_t and integrate over Ω to get

$$\|u_t(t)\|_2^2 + \frac{d}{2} \frac{d}{dt} \int_{\Omega} |\nabla_{\mathbf{x}} u(t)|^2 = 0.$$

We conclude that $\int_{\Omega} |\nabla u(t)|^2$ decreases with time. Inserting this information in identity (50), we find:

$$\frac{1}{2} \|u(t)\|_2^2 + t \int_{\Omega} |\nabla_{\mathbf{x}} u(t)|^2 \leq \frac{1}{2} \|u_0\|_2^2 \Rightarrow \|\nabla_{\mathbf{x}} u(t)\|_{L_{\mathbf{x}}^2} \leq \frac{1}{t^{1/2}} \|u_0\|_{L_{\mathbf{x}}^2}.$$

The inequality extends to $u_0 \in L^2_{\mathbf{x}}$ by density.

To prove the $L^r - L^q$ estimate on the gradients, we resort to expressions of the solutions in terms of heat kernels [27] and pointwise estimates of the kernels [41]. Our annular domain Ω is not convex, therefore we can only apply results valid for C^2 compact manifolds. In terms of the heat kernel for the Neumann problem, the solution of equations (39)-(41) reads:

$$u(\mathbf{x}, t) = \int_{\Omega} K(\mathbf{x}, \mathbf{y}, t) u_0(\mathbf{y}) d\mathbf{y}, \quad K(\mathbf{x}, \mathbf{y}, t) = \sum_{n \geq 1} e^{-\lambda_n t} \phi_n(\mathbf{x}) \phi_n(\mathbf{y}),$$

where ϕ_n and λ_n are the eigenvalues and eigenfunctions of the homogeneous Neumann problem, see reference [27], pp. 104-106. The kernel function K is positive, symmetric in the \mathbf{x} and \mathbf{y} variables, and satisfies $\int_{\Omega} K(\mathbf{x}, \mathbf{y}, t) d\mathbf{y} = 1$. It is the solution of a Neumann problem with measure valued initial data $\delta_{\mathbf{x}}(\mathbf{y})$. For compact Riemannian manifolds with C^2 smooth boundary, the gradient of the heat kernel satisfies:

$$|\nabla K(\mathbf{x}, \mathbf{y}, t)| \leq \frac{C}{t^{\frac{(N+1)}{2}}} e^{-\frac{\rho(\mathbf{x}, \mathbf{y})^2}{ct}}, \quad t > 0, \mathbf{x}, \mathbf{y} \in \Omega,$$

for some positive constants C, c , where N is the dimension, and ρ the Riemannian distance. Our domain Ω is a ring in \mathbb{R}^N . We may find a constant d' such that $\rho(\mathbf{x}, \mathbf{y}) \geq d'|\mathbf{x} - \mathbf{y}|$. Extending the upper bound to an integral over the whole space:

$$|\nabla u(\mathbf{x}, t)| = \left| \int_{\Omega} \nabla K(\mathbf{x}, \mathbf{y}, t) u_0(\mathbf{y}) d\mathbf{y} \right| \leq \frac{C}{t^{\frac{(N+1)}{2}}} \int_{\mathbb{R}^N} e^{-\frac{d'|\mathbf{x}_i - \mathbf{y}|^2}{ct}} |u_0(\mathbf{y})| d\mathbf{y},$$

the $L^r - L^q$ estimates (47) follow from standard $L^r - L^q$ estimates for solutions of the heat equation in the whole space [20].

Expressing the solution in terms of eigenfunctions (43), the $L^2_{\mathbf{x}}$ norm of the gradient becomes:

$$\begin{aligned} \int_{\Omega} |\nabla u(\mathbf{x}, t)|^2 d\mathbf{x} &= \sum_{n, m \geq 1} u_{0,n} u_{0,m} e^{-\lambda_n t} e^{-\lambda_m t} \left[\int_{\Omega} \nabla \phi_n(\mathbf{x}) \nabla \phi_m(\mathbf{x}) d\mathbf{x} \right] \\ &= \sum_{n, m \geq 1} u_{0,n} u_{0,m} e^{-\lambda_n t} e^{-\lambda_m t} \frac{\lambda_m}{d} \left[\int_{\Omega} \phi_n(\mathbf{x}) \phi_m(\mathbf{x}) d\mathbf{x} \right] \\ &= \sum_{n \geq 1} u_{0,n}^2 e^{-2\lambda_n t} \lambda_m \leq \sum_{n \geq 1} u_{0,n}^2 \frac{\lambda_m}{d} = \int_{\Omega} |\nabla u_0(\mathbf{x})|^2 d\mathbf{x}, \quad (51) \end{aligned}$$

after integrating by parts, using definition (42) and the orthogonality of the eigenfunctions. This proves estimate (48).

To estimate the $L^{\infty}_{\mathbf{x}}$ norm of the gradient, we notice that differentiating

formula (43) and assuming $\frac{\partial u_0}{\partial \mathbf{n}}$ we find:

$$\begin{aligned} \Delta u(\mathbf{x}, t) &= \sum_{n \geq 1} u_{0,n} \Delta \phi_n(\mathbf{x}) e^{-\lambda_n t} = - \sum_{n \geq 1} u_{0,n} \frac{\lambda_n}{d} \phi_n(\mathbf{x}) e^{-\lambda_n t} = \\ &= \sum_{n \geq 1} \left[\int_{\Omega} u_0(\mathbf{y}) \Delta \phi_n(\mathbf{y}) d\mathbf{y} \right] \phi_n(\mathbf{x}) e^{-\lambda_n t} = \sum_{n \geq 1} \left[\int_{\Omega} \Delta u_0(\mathbf{y}) \phi_n(\mathbf{y}) d\mathbf{y} \right] \phi_n(\mathbf{x}) e^{-\lambda_n t}. \end{aligned}$$

This expression defines a solution of

$$\begin{aligned} \tilde{u}_t(\mathbf{x}, t) &= d \Delta_{\mathbf{x}} \tilde{u}(\mathbf{x}, t), & \mathbf{x} \in \Omega, t > 0, \\ \frac{\partial \tilde{u}}{\partial \mathbf{n}}(\mathbf{x}, t) &= 0, & \mathbf{x} \in S_{r_0} \cup S_{r_1}, t > 0, \\ \tilde{u}(\mathbf{x}, 0) &= \Delta u_0(\mathbf{x}), & \mathbf{x} \in \Omega. \end{aligned}$$

The comparison principle in Proposition 4.1 yields $\|\Delta_{\mathbf{x}} u\|_{L_{\infty}^{\infty}} \leq \|\Delta u_0\|_{L_{\infty}^{\infty}}$. This inequality extends to $u_0 \in W^{2,\infty}(\Omega)$ by density. Finally, Gagliardo-Nirenberg's inequalities [6] provide an estimate on the gradients: $\|\nabla_{\mathbf{x}} u\|_{L_{\infty}^{\infty}} \leq C(\|\Delta_{\mathbf{x}} u\|_{L_{\infty}^{\infty}}, \|u\|_{L_{\infty}^{\infty}}) \leq C(\|\Delta_{\mathbf{x}} u_0\|_{L_{\infty}^{\infty}}, \|u_0\|_{L_{\infty}^{\infty}})$. This proves inequality (49) and concludes the proof.

Let us now consider the diffusion problem with a source but zero initial and boundary values:

$$u_t(\mathbf{x}, t) = d \Delta_{\mathbf{x}} u(\mathbf{x}, t) + h(\mathbf{x}, t), \quad \mathbf{x} \in \Omega, t > 0, \quad (52)$$

$$\frac{\partial u}{\partial \mathbf{n}}(\mathbf{x}, t) = 0, \quad \mathbf{x} \in S_{r_0} \cup S_{r_1}, t > 0, \quad (53)$$

$$u(\mathbf{x}, 0) = 0, \quad \mathbf{x} \in \Omega. \quad (54)$$

For any $h \in L^{\infty}(0, T; L^2(\Omega))$, there is a unique global solution $u \in C([0, T], L^2(\Omega))$, see reference [25]. It is given by the series expansion:

$$u(\mathbf{x}, t) = \sum_{n \geq 1} \phi_n(\mathbf{x}) \int_0^t h_n(s) e^{-\lambda_n(t-s)} ds, \quad h_n(s) = \int_{\Omega} h(\mathbf{y}, s) \phi_n(\mathbf{y}) d\mathbf{y}.$$

The series expansion implies again the 'smoothing effect': $u(t) \in H^2(\Omega)$ for $t > 0$. In fact, $u(t) \in H^k(\Omega)$, for all k and $t > 0$. This solution can be rewritten using the semigroup formalism [28]. The initial value problem (39)-(41) defines a semigroup $S(t)u_0 = u(t)$, u being the solution of equations (39)-(41). The solution of an inhomogeneous initial value problem with initial datum u_0 and source h can be expressed as:

$$u(t) = S(t)u_0 + \int_0^t S(t-s)h(s)ds. \quad (55)$$

Theorem 4.3 establishes decay estimates for the semigroup $S(t)$ and its derivatives, applied to different types of initial data. We can exploit those estimates to infer the decay of the integral term representing solutions with a source. The following estimates hold:

Proposition 4.4. (Decay for the inhomogeneous problem). *For sources $h \in L^\infty([0, T] \times \Omega)$, the solution u of equations (52)-(54) satisfies:*

$$\|u(t)\|_{L^\infty} \leq t \|h\|_{L_t^\infty L_x^\infty}, \quad \|\nabla_{\mathbf{x}} u(t)\|_{L^\infty} \leq 2t^{1/2} \|h\|_{L_t^\infty L_x^\infty}, \quad (56)$$

$$\|u(t)\|_{L_x^2} \leq t \|h\|_{L_t^\infty L_x^2}, \quad \|\nabla_{\mathbf{x}} u(t)\|_{L_x^2} \leq 2t^{1/2} \|h\|_{L_t^\infty L_x^2}, \quad (57)$$

$$\|\nabla_{\mathbf{x}} u(t)\|_{L_x^q} \leq C_{rq} t^{1/2 - N/2(1/q - 1/r)} \|h\|_{L_t^\infty L_x^q}, \quad C_{rq} > 0, \quad \frac{1}{N} > \frac{1}{q} - \frac{1}{r} > 0, \quad (58)$$

for $t \in [0, T]$.

Proof. Consequence of the semigroup expression (55) for the solutions and Proposition 4.3.

Let us now apply the previous decay estimates to solutions c of equations (2)-(3),(7). Let c_b be a function such that $c_b = c_{r_0}$ on $r = r_0$ and $c_b = 0$ on $r = r_1$. For simple choices of c_{r_0} this can be done explicitly. Otherwise, we may resort to solutions c_b of the boundary value problem for the heat equation, with zero initial data, zero source term, and non homogeneous boundary conditions $c_b = c_{r_0}$ on $r = r_0$ and $c_b = 0$ on $r = r_1$. Existence of such solutions has been established in reference [7] by the method of layer potentials for boundary data satisfying integrability conditions that always hold for bounded data. We set $c = \tilde{c} + c_b$. Then,

$$\tilde{c}_t - d\Delta_{\mathbf{x}} \tilde{c} = -\eta c_j - c_{b,t} + d\Delta_{\mathbf{x}} c_b, \quad \mathbf{x} \in \Omega, t > 0, \quad (59)$$

$$\frac{\partial \tilde{c}}{\partial \mathbf{n}}(\mathbf{x}, t) = 0, \quad \mathbf{x} \in S_{r_0} \cup S_{r_1}, t > 0, \quad (60)$$

$$\tilde{c}(\mathbf{x}, 0) = c_0(\mathbf{x}) - c_b(\mathbf{x}, 0), \quad \mathbf{x} \in \Omega. \quad (61)$$

The term $z = -c_{b,t} + d\Delta_{\mathbf{x}} c_b$ appearing in the right hand side may vanish when c_b is chosen to be a solution of the heat equation. We have the following estimates.

Theorem 4.5. *Let c be a solution of equations (2)-(3),(7) with initial and boundary data verifying $c_0 \in W^{2,\infty}(\Omega)$, $c_0 \geq 0$ and $c_{r_0} \in L^\infty(0, T; L^\infty(\partial\Omega))$, $T > 0$. Let $c_b \in W^{1,\infty}(0, T; W^{2,\infty}(\Omega))$ be a function satisfying $c_b = c_{r_0}$ on $r = r_0$ and $c_b = 0$ on $r = r_1$. Set $K = \max(\|c_0 - c_b\|_\infty, \|c_{b,t} - d\Delta c_b\|_\infty)$. Then, $c \geq 0$ and*

$$\|c(t)\|_q \leq [\|c_b\|_\infty + K(1 + T)] \text{meas}(\Omega)^{1/q}, \quad t \in [0, T], 1 \leq q \leq \infty. \quad (62)$$

Moreover,

$$\begin{aligned} \|\nabla c(t)\|_\infty &\leq \|\nabla c_b(t)\|_\infty + C(\|c_0 - c_b(0)\|_\infty, \|\Delta c_0 - \Delta c_b(0)\|_\infty) \\ &\quad + 2t^{1/2} \|c_{b,t} - d\Delta c_b\|_\infty + \eta C_q t^{\frac{1}{2} - \frac{N}{2q}} \|c_j\|_{L_t^\infty L_x^q}, \quad q > N, \end{aligned} \quad (63)$$

$$\begin{aligned} \|\nabla c(t)\|_2 &\leq \|\nabla c_b(t)\|_2 + \|\nabla c_0 - \nabla c_b(0)\|_2 \\ &\quad + 2t^{1/2} \|c_{b,t} - d\Delta c_b\|_{L_t^\infty L_x^2} + 2t^{1/2} \eta \|c_j\|_{L_t^\infty L_x^2}, \end{aligned} \quad (64)$$

$$d \int_0^t \int_{\Omega} |\nabla c(s)|^2 ds d\mathbf{x} \leq d \int_0^t \int_{\Omega} |\nabla c_b(s)|^2 ds d\mathbf{x} + \frac{1}{2} \|c_0 - c_b(0)\|_2^2 \quad (65)$$

$$+ \|c_{b,t} - d\Delta c_b\|_{L^2(0,t;L_x^2)} \|c\|_{L^2(0,t;L_x^2)}.$$

Proof. By the comparison principle 4.1, we know that $c \geq 0$ and that \tilde{c} is bounded from above by the solution \tilde{C} of system (59)-(61) with right hand side $z = -c_{b,t} + d\Delta c_b$. By Proposition 4.1, $|\tilde{C}| \leq K(1+t)$. Since Ω is a bounded domain, estimate (62) follows.

Let us now study the derivatives of \tilde{c} . The energy inequality provides a uniform $L_{\mathbf{x}t}^2$ estimate that implies inequality (65):

$$\frac{1}{2} \|\tilde{c}(t)\|_{L_x^2}^2 + d \int_0^t \int_{\Omega} |\nabla \tilde{c}(s)|^2 ds d\mathbf{x} \leq \frac{1}{2} \|\tilde{c}(0)\|_{L_x^2}^2$$

$$+ \|d\Delta c_b - c_{b,t}\|_{L^2(0,T;L_x^2)} \|c\|_{L^2(0,T;L_x^2)}.$$

To prove inequalities (64) and (63), we split $\tilde{c} = \tilde{c}_1 + \tilde{c}_2$. By linearity, we take \tilde{c}_1 to be a solution of a heat equation with initial datum \tilde{c}_0 , zero source and zero boundary condition. We choose \tilde{c}_2 to be the solution of another heat problem, with source $-\eta c_j + z$, plus zero initial and boundary conditions. The estimates stated in Theorem 4.3 hold for \tilde{c}_1 and those in Proposition 4.4 to \tilde{c}_2 . Differentiating $-\eta c_j$ must be avoided, not to introduce the spatial derivatives of c we intend to control. In this way, we obtain inequalities (64) and (63).

5. Nonlinear problem with known boundary condition

Solutions for the the nonlinear angiogenesis model may be constructed employing an iterative scheme. For $m \geq 2$, we consider the linearized system of equations

$$\frac{\partial}{\partial t} p_m(\mathbf{x}, \mathbf{v}, t) + \mathbf{v} \cdot \nabla_{\mathbf{x}} p_m(\mathbf{x}, \mathbf{v}, t) + \nabla_{\mathbf{v}} \cdot [(\mathbf{F}(c_{m-1}(\mathbf{x}, t)) - \beta \mathbf{v}) p_m(\mathbf{x}, \mathbf{v}, t)] \quad (66)$$

$$- \sigma \Delta_{\mathbf{v}} p_m(\mathbf{x}, \mathbf{v}, t) + \gamma b_{m-1}(\mathbf{x}, t) p_m(\mathbf{x}, \mathbf{v}, t) = \alpha (c_{m-1}(\mathbf{x}, t)) \nu(\mathbf{v}) p_m(\mathbf{x}, \mathbf{v}, t),$$

$$b_{m-1}(\mathbf{x}, t) = \int_0^t ds \int_{\mathbb{R}^N} d\mathbf{v}' p_{m-1}(\mathbf{x}, \mathbf{v}', s), \quad (67)$$

$$\alpha(c_{m-1}) = \alpha_1 \frac{c_{m-1}}{c_R + c_{m-1}}, \quad \mathbf{F}(c_{m-1}) = \frac{d_1}{(1 + \gamma_1 c_{m-1})^{q_1}} \nabla_{\mathbf{x}} c_{m-1}, \quad (68)$$

$$p_m(\mathbf{x}, \mathbf{v}, 0) = p_0(\mathbf{x}, \mathbf{v}), \quad (69)$$

$$\frac{\partial}{\partial t} c_{m-1}(\mathbf{x}, t) = d \Delta_{\mathbf{x}} c_{m-1}(\mathbf{x}, t) - \eta c_{m-1}(\mathbf{x}, t) j_{m-1}(\mathbf{x}, t), \quad (70)$$

$$j_{m-1}(\mathbf{x}, t) = \int_{\mathbb{R}^N} \frac{|\mathbf{v}|}{1 + e^{|\mathbf{v} - \mathbf{v}_0 \mathbf{x}|^2 / \sigma_v^2}} p_{m-1}(\mathbf{x}, \mathbf{v}, t) d\mathbf{v}, \quad (71)$$

$$c_{m-1}(\mathbf{x}) = c_0(\mathbf{x}, 0), \quad (72)$$

supplemented with the boundary conditions:

$$\frac{\partial c_{m-1}}{\partial \mathbf{n}}(\mathbf{x}, t) = c_{r_0}(\mathbf{x}, t) < 0, \quad \mathbf{x} \in S_{r_0}, \quad \frac{\partial c_{m-1}}{\partial \mathbf{n}}(\mathbf{x}, t) = 0, \quad \mathbf{x} \in S_{r_1}, \quad (73)$$

$$p_m(\mathbf{x}, \mathbf{v}, t) = g(\mathbf{x}, \mathbf{v}, t) \geq 0, \quad \text{for } \mathbf{v} \cdot \hat{\mathbf{n}} < 0, \quad \mathbf{v} \in \mathbb{R}^N, \quad \mathbf{x} \in S_{r_0} \cup S_{r_1}. \quad (74)$$

We initialize the scheme setting $p_1 = 0$ and $j_1 = 0$. c_1 is the solution of the associated heat equation. The function p_2 is a nonnegative solution of the Fokker-Planck problem with smooth and bounded coefficient fields $\mathbf{F}(c_1)$ and $\alpha(c_1)$ in a bounded domain. Let us see that the resulting sequence is well defined under our hypotheses on the data and we may extract a subsequence converging to a solution of the original problem.

Theorem 5.1. *Let us assume that*

$$p_0 \geq 0, c_0 \geq 0, g \geq 0, \quad (75)$$

$$c_0 \in W^{2,\infty}(\Omega), \quad (76)$$

$$(1 + |\mathbf{v}|^2)^{\mu/2} p_0 \in L^\infty \cap L^1(\Omega \times \mathbb{R}^N), \quad \mu > N, \quad (77)$$

$$c_{r_0} \in L^\infty(0, T; L^\infty(S_{r_0})), \quad (78)$$

$$(1 + |\mathbf{v} \cdot \mathbf{n}|)(1 + |\mathbf{v}|^2)^{\mu/2} g \in L^\infty(0, T; L^\infty \cap L^1(\Gamma^-)), \quad (79)$$

and that a function c_b is found verifying the hypotheses of Theorem 4.5. Then, there exists a nonnegative solution (p, c) of equations (2)-(8) satisfying:

$$c \in L^\infty(0, T; W^{1,\infty}(\Omega)), \quad (80)$$

$$p \in L^\infty(0, T; L^\infty \cap L^1(\Omega \times \mathbb{R}^N)), \nabla_{\mathbf{v}} p \in L^2(0, T; L^2(\Omega \times \mathbb{R}^N)), \quad (81)$$

$$(1 + |\mathbf{v}|^2)^{\mu/2} p \in L^\infty(0, T; L^\infty \cap L^1(\Omega \times \mathbb{R}^N)), \quad (82)$$

$$p \in L^\infty(0, T; L_{\mathbf{x}}^\infty(\Omega, L_{\mathbf{v}}^1(\mathbb{R}^N))), \quad (83)$$

for any $T > 0$.

The proof is organized in several steps. First, we argue that the scheme is well defined. Then, we obtain uniform estimates on the L^q norms of the solutions of the iterative scheme. Next, we derive L^∞ estimates on the coefficients \mathbf{F}_{m-1} , j_{m-1} and b_{m-1} using the velocity decay. Estimates on the derivatives of the densities with respect to \mathbf{v} allow us to pass to the limit in the equations using compactness results for the specific of FP operator, obtaining a nonnegative solution of the nonlinear problem with the stated regularity.

Proof.

Step 1: Existence of nonnegative solutions for the scheme.

First, let us argue that the scheme (66)–(74) is well defined. Setting $p_1 = 0$, we have $j_1 = 0$ and due to (70), $c_1(\mathbf{x}, t)$ is the solution of the associated heat equation

$$\frac{\partial}{\partial t} c_1(\mathbf{x}, t) = d \Delta_{\mathbf{x}} c_1(\mathbf{x}, t) \quad \mathbf{x} \in \Omega, t > 0,$$

$$c_1(\mathbf{x}, 0) = c_0(\mathbf{x}), \quad \mathbf{x} \in \Omega,$$

$$\frac{\partial c_1}{\partial \mathbf{n}}(\mathbf{x}, t) = c_{r_0}(\mathbf{x}, t) < 0, \quad \mathbf{x} \in S_{r_0}, \quad \frac{\partial c_1}{\partial \mathbf{n}}(\mathbf{x}, t) = 0, \quad \mathbf{x} \in S_{r_1}, \quad t > 0,$$

satisfying the properties of Theorem 4.5. The function p_2 is the nonnegative solution of the Fokker-Planck problem with smooth and bounded coefficient

fields $\mathbf{F}(c_1)$ and $\alpha(c_1)$ in a bounded domain, i.e.,

$$\alpha(c_1) = \alpha_1 \frac{c_1}{c_R + c_1}, \quad \mathbf{F}(c_1) = \frac{d_1}{(1 + \gamma_1 c_1)^{q_1}} \nabla_{\mathbf{x}} c_1.$$

Let us proceed by induction. We assume that $j(p_{m-1})$ and $b(p_{m-1})$ are nonnegative bounded functions. Then, c_{m-1} is the unique solution of equations (70)-(72) with boundary conditions (73), whose existence can be proven by Galerkin or spectral methods [25]. By Proposition 4.1 we know that $c_{m-1} \geq 0$ if $c_0 \geq 0$. This implies that $0 \leq \alpha(c_{m-1}) \leq \alpha_1$ and $0 \leq \frac{d_1}{(1 + \gamma_1 c_{m-1})^{q_1}} \leq d_1$. Moreover, Theorem 4.5 provides L^∞ and L^q bounds for c_{m-1} . Then, Theorem 4.5 implies that $\nabla_{\mathbf{x}} c_{m-1}$ is a bounded function and also $\mathbf{F}(c_{m-1})$. Since $\alpha(c_{m-1})$ and $\mathbf{F}(c_{m-1})$ are bounded, and $b(p_{m-1})$ is assumed to be bounded, p_m is the unique nonnegative solution of equations (66),(69) with boundary conditions (74) that satisfies the estimates collected in Theorems 2.1, 2.2 and 2.3. This implies that $\gamma b(p_{m-1}) p_m \geq 0$ and $\alpha(c_{m-1}) \nu \leq \alpha_1 \|\nu\|_\infty$. By Lemma 3.1, $\|j(p_m)\|_{L^\infty_{\mathbf{x}}}$ is bounded in terms of $\|p_m\|_{L^\infty_t L^\infty_{\mathbf{xv}}}$. Proposition 3.7 implies that $b(p_m) \in L^\infty(\Omega \times (0, T))$. This allows us to construct c_m and p_{m+1} , and so on.

Step 2: A priori estimates on the tumor angiogenic factor c_m .

By Theorem 4.5, setting $K = \max(\|c_0 - c_b\|_{L^\infty_{\mathbf{x}}}, \|c_{b,t} - d\Delta c_b\|_{L^\infty_{\mathbf{x}t}})$, we get

$$\|c_m(t)\|_{L^q_{\mathbf{x}}} \leq (\|c_b\|_\infty + KT) \text{meas}(\Omega)^{1/q}, \quad t \in [0, T], 1 \leq q \leq \infty. \quad (84)$$

The energy inequality yields a bound on the gradient independent of $j(p_{m-1})$:

$$\frac{d}{dt} \int_{\Omega} c_m^2 d\mathbf{x} + d \int_{\Omega} |\nabla_{\mathbf{x}} c_m|^2 d\mathbf{x} \leq d \int_{\partial\Omega} c_{r_0} c_m.$$

Integrating in time we find

$$d \int_0^T \int_{\Omega} |\nabla_{\mathbf{x}} c_m|^2 d\mathbf{x} \leq \|c_0\|_{L^2_{\mathbf{x}}}^2 + d \|c_{r_0}\|_{L^1(\partial\Omega \times (0, T))} \|c_m\|_\infty. \quad (85)$$

Theorem 4.5 provides alternative energy estimates (65) on the $L_t^2 L_{\mathbf{x}}^2$ norm of $\nabla_{\mathbf{x}} c_{m-1}$ and the $L_{\mathbf{x}t}^\infty$ norm of $\nabla_{\mathbf{x}} c_{m-1}$:

$$\begin{aligned} \|\nabla c_{m-1}(t)\|_\infty &\leq \|\nabla_{\mathbf{x}} c_b(t)\|_\infty + C(\|c_0 - c_b(0)\|_\infty, \|\Delta_{\mathbf{x}} c_0 - \Delta_{\mathbf{x}} c_b(0)\|_\infty) \\ &\quad + t^{1/2} \|c_{b,t} - d\Delta_{\mathbf{x}} c_b\|_\infty + \eta C_q t^{\frac{1}{2} - \frac{N}{2q}} \|c_{m-1} j(p_{m-1})\|_{L_t^\infty L_{\mathbf{x}}^q}, \quad q > N, \end{aligned} \quad (86)$$

for $t \in [0, T]$.

Step 3: A priori estimates on the tip vessel density p_m .

Let us revisit the L^q estimates in Theorem 2.2. The conservation of mass implies inequality (21) with $q = 1$:

$$\|p_m(t)\|_{L^1_{\mathbf{xv}}} \leq \left(\|p_0\|_{L^1_{\mathbf{xv}}} + \int_{\Sigma_T^-} |\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| g \right) e^{\alpha_1 \|\nu\|_\infty t}, \quad t \in [0, T]. \quad (87)$$

Applying inequality (21) with $1 < q < \infty$, we find:

$$\|p_m(t)\|_{L^q_{\mathbf{xv}}}^q \leq \left(\|p_0\|_{L^q_{\mathbf{xv}}}^q + \int_{\Sigma_T^-} |\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| g^q \right) e^{(N\beta(q-1) + \alpha_1 \|\nu\|_\infty)t}, \quad t \in [0, T]. \quad (88)$$

Uniform L^∞ estimates follow either inequality (21) with $q = \infty$:

$$\|p_m\|_{L^\infty(Q_T)} \leq \left(\|p_0\|_{L^\infty(\Omega \times \mathbb{R}^N)} + \|g\|_{L^\infty_k(\Sigma_T^-)} \right) e^{(N\beta + \alpha_1 \|\nu\|_\infty)t}, \quad (89)$$

or Theorem 2.3 with $\|g\|_{L^\infty_k(\Sigma_T^-)}$ replaced by $\|g\|_{L^\infty(\Sigma_T^-)}$.

To be able to extract a converging subsequence from the sequence p_m , we need estimates on its derivatives. Let us revisit the L^2 estimate (20) provided by Theorem 2.2 for p_m :

$$\begin{aligned} \frac{d}{dt} \|p_m(t)\|_{L^2_{\mathbf{xv}}}^2 &= \int_{\Gamma_-} |\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| g^2 dS d\mathbf{v} + \int_{\Omega \times \mathbb{R}^N} \alpha(c_{m-1}) \nu p_m^2 d\mathbf{x} d\mathbf{v} \\ &\quad - \int_{\Gamma_+} |\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| (\text{Tr} p_m)^2 dS d\mathbf{v} - \int_{\Omega \times \mathbb{R}^N} \gamma b(p_{m-1}) p_m^2 d\mathbf{x} d\mathbf{v} \\ &\quad + N\beta \|p_m(t)\|_{L^2_{\mathbf{xv}}}^2 - 2\sigma \int_{\Omega \times \mathbb{R}^N} |\nabla_{\mathbf{v}} p_m|^2 d\mathbf{x} d\mathbf{v}. \end{aligned}$$

Integrating in time and neglecting negative terms, we find

$$\begin{aligned} 2\sigma \int_{Q_T} |\nabla_{\mathbf{v}} p_m|^2 d\mathbf{x} d\mathbf{v} ds &\leq \|p_0\|_{L^2_{\mathbf{xv}}}^2 + \int_{\Sigma_T^-} |\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| g^2 dS d\mathbf{v} ds \\ &\quad + (\alpha_1 \|\nu\|_\infty + N\beta) \int_{Q_T} p_m^2 d\mathbf{x} d\mathbf{v} ds. \end{aligned}$$

The uniform estimates on $\|p_m\|_{L^2(Q_T)}$ yield a uniform estimate on $\|\nabla_{\mathbf{v}} p_m\|_{L^2(Q_T)}$.

Step 4: Uniform bounds on velocity integrals and velocity decay of p_m .

In Steps 2 and 3 we have obtained uniform estimates on the blood vessel density norms $\|p_m\|_{L^\infty(0, T; L^q_{\mathbf{xv}})}$ and the tumor angiogenic factor norms $\|c_m\|_{L^\infty(0, T; L^q_{\mathbf{x}})}$ for $1 \leq q \leq \infty$.

Lemma 3.1 provides a uniform bound of the $L^q_{\mathbf{x}}$ norms of the fluxes j_{m-1} , $1 \leq q \leq \infty$ in terms of the bounds (89) on $\|p_m\|_{L^\infty(0, T; L^q_{\mathbf{xv}})}$ established in Step 3. Thanks to inequality (86) in Step 2, we obtain a uniform estimate on $\|\nabla_{\mathbf{x}} c_{m-1}\|_{L^\infty(0, T; L^\infty(\Omega))}$. A uniform estimate on $\|\mathbf{F}(c_{m-1})\|_{L^\infty(0, T; L^\infty(\Omega))}$ follows.

Next, we apply Proposition 3.7 to equation (66), setting $a = \gamma b(p_{m-1}) - \alpha(c_{m-1})\nu$ and $\mathbf{F} = \mathbf{F}(c_{m-1})$, with $j = j_{m-1}$ depending on p_{m-1} . Step 1 guarantees that $a \in L^\infty$. Its negative part $a^-(c_{m-1}) = \alpha(c_{m-1})\nu$ satisfies $\|a^-\|_\infty \leq \alpha_1 \|\nu\|_{L^\infty}$. Thanks to the uniform estimate on $\|\mathbf{F}(c_{m-1})\|_\infty$ and $\|p_m\|_\infty$, Proposition 3.7 provides a uniform estimate on $\|(1 + |\mathbf{v}|^2)^{\mu/2} p_{m-1}\|_{L^\infty_{\mathbf{xv}}}$. Then, inequality (30) in Lemma 3.4 yields a uniform estimate on $\|p_m\|_{L^\infty(0, T; L^\infty_{\mathbf{x}} L^1_{\mathbf{v}})}$. We also

obtain as a consequence an upper bound of the form

$$|p_m| \leq \frac{C}{(1 + |\mathbf{v}|^2)^{\mu/2}} = \mathcal{P}, \quad \mu > N, C > 0. \quad (90)$$

This upper bound \mathcal{P} is integrable, and belongs to $L^q(\Omega \times \mathbb{R}^N)$ for any $q \in [1, \infty]$ since $\mu > N$ and Ω is bounded.

In conclusion, the coefficients b_{m-1} , $\alpha(c_{m-1})$, j_{m-1} and $F(c_{m-1})$ appearing in the equations are uniformly bounded in $L^\infty(0, T; L^\infty)$.

Step 5: Compactness of the iterates.

Once we have obtained uniform estimates on p_m and their velocity derivatives, we resort to the compactness results in reference [4] to extract converging subsequences.

Lemma 5.2. [4] *Let $\sigma > 0$, $\beta \geq 0$, $T > 0$, $1 \leq q < \infty$, $p_0 \in L^q(\mathbb{R}^N)$, $h \in L^1(0, T; L^q(\mathbb{R}^N \times \mathbb{R}^N))$ and consider the solution $p \in C([0, T], L^q(\mathbb{R}^N \times \mathbb{R}^N))$ of:*

$$\begin{aligned} \frac{\partial p}{\partial t} + \mathbf{v} \nabla_{\mathbf{x}} p - \beta \operatorname{div}_{\mathbf{v}}(\mathbf{v} p) - \sigma \Delta_{\mathbf{v}} p &= h \quad \text{in } \mathbb{R}^N \times \mathbb{R}^N \times (0, T), \\ p(0) &= p_0 \quad \text{in } \mathbb{R}^N \times \mathbb{R}^N. \end{aligned} \quad (91)$$

Assume that p_0 belongs to a bounded subset of $L^q(\mathbb{R}^N \times \mathbb{R}^N)$ and h belongs to a bounded subset of $L^1(0, T; L^q(\mathbb{R}^N \times \mathbb{R}^N))$ with $1 < r \leq \infty$. Then, for any $\eta > 0$ and any bounded open subset ω of $\mathbb{R}^N \times \mathbb{R}^N$, p is compact in $C([\eta, T], L^q(\omega))$.

These results are stated for problems set in the whole space. Here, we deal with a problem set in $\Omega \subset \mathbb{R}^N$. We may extend them to the whole space multiplying by functions $\phi \in C_c^\infty(\Omega)$. The truncated sequences $q_m = \phi p_m$ satisfy

$$\frac{\partial q_m}{\partial t} + \mathbf{v} \nabla_{\mathbf{x}} q_m - \beta \operatorname{div}_{\mathbf{v}}(\mathbf{v} q_m) - \sigma \Delta_{\mathbf{v}} q_m = h_m \quad \text{in } \mathbb{R}^N \times \mathbb{R}^N \times (0, T),$$

where the sources

$$h_m = -\mathbf{v} \cdot \nabla_{\mathbf{x}} \phi p_m - \phi \mathbf{F}(c_{m-1}) \cdot \nabla_{\mathbf{v}} p_m - \gamma b(p_{m-1}) p_m \phi + \alpha(c_{m-1}) \nu p_m \phi$$

are bounded in $L^2(Q_T)$ and the initial state $\phi p_0 \in L^1_{\mathbf{x}\mathbf{v}} \cap L^\infty_{\mathbf{x}\mathbf{v}}$ is fixed. The sequence p_m is therefore locally compact and by a diagonal extraction procedure we may extract a subsequence $p_{m'}$ converging to a limit p pointwise, and strongly in $C([\eta, T], L^2(\omega))$ for any $\omega \subset \Omega \times \mathbb{R}^N$. Uniform bounds together with uniform control of the velocity decay allow us to extend compactness up to the borders [6, 12]. Weak convergences of p_m and $\nabla_{\mathbf{v}} p_m$ hold in all the spaces in which we have uniform estimates.

In Step 2, we have obtained a uniform bound on c_m in $L^2(0, T; H^1(\Omega))$. Step 4 provides a uniform estimate on $j(p_m)$ in $L^\infty(0, T; L^\infty(\Omega))$. Using equation (70), we conclude that $\frac{\partial c_m}{\partial t}$ is bounded in $L^2(0, T; H^{-1}(\Omega))$. Standard

compactness results in reference [26] yield compactness for the sequence c_m in $L^2(0, T; L^2(\Omega))$. A subsequence $c_{m'}$, converges pointwise and strongly in L^2 to a function c . Weak convergences hold in all the spaces for which uniform bounds have been established.

Step 6: Convergence to a solution.

Let us first pass to the limit in the nonlocal terms using the integrable upper bound \mathcal{P} defined in (90). We know that $p_{m'}$ and $\mathbf{v}w(\mathbf{v})p_{m'}$ converge pointwise to p and $w(\mathbf{v})p$. The bounds $0 \leq p_{m'} \leq \mathcal{P} \in L^\infty(0, T; L^1(\Omega \times \mathbb{R}^N))$ and $|\mathbf{v}|w(\mathbf{v})p_{m'} \leq |\mathbf{v}|w(\mathbf{v})\mathcal{P} \in L^\infty(0, T; L^1(\Omega \times \mathbb{R}^N))$ imply pointwise convergence for the nonlocal coefficients:

$$b(p_{m'}) \rightarrow b(p) \geq 0, \quad j(p_{m'}) \rightarrow j(p), \quad a.e. \mathbf{x} \in \Omega, t \in [0, T].$$

Let us now consider the nonlinear products. Pointwise convergence of $b(p_{m'-1})p_{m'}$ to $b(p)p$, together with the bound $0 \leq b(p_{m'-1})p_{m'} \leq b(\mathcal{P})\mathcal{P} \in L^1(0, T; L^1(\Omega \times \mathbb{R}^N))$, imply strong convergence in $L^1(0, T; L^1(\Omega \times \mathbb{R}^N))$. Similarly, pointwise convergence of $\alpha(c_{m'-1})\nu p_{m'}$ to $\alpha(c)\nu p$, together with the bound $|\alpha(c_{m'-1})\nu p_{m'}| \leq \alpha_1 \|\nu\|_\infty \mathcal{P} \in L^1(0, T; L^1(\Omega \times \mathbb{R}^N))$, ensure strong convergence in $L^1(0, T; L^1(\Omega \times \mathbb{R}^N))$. Finally, pointwise convergence of $j(p_{m'-1})c_{m'-1}$ to $j(p)c$, together with the bound $j(p_{m'-1})c_{m'-1} \leq \max_{m'} \|j(p_{m'-1})\|_{L^\infty(\Omega \times (0, T))} (\|c_b\|_{L^\infty(\Omega \times (0, T))} + KT) \in L^1(0, T; L^1(\Omega))$, yield strong convergence in $L^1(0, T; L^1(\Omega))$. Strong convergences extend to any L^q with q finite.

The term involving the force field is more complex. Notice that the sequence $p_{m'} \frac{d_1}{(1+\gamma_1 c_{m'-1})^{q_1}}$ tends pointwise to $p \frac{d_1}{(1+\gamma_1 c)^{q_1}}$ and is bounded by $\mathcal{P} d_1 \in L^q(0, T; L^q(\Omega \times \mathbb{R}^N))$ for any $q \in [1, \infty]$. Thus, we have strong convergence in $L^q_{\mathbf{x}\mathbf{v}t}$ for all finite q . The sequence $\nabla_{\mathbf{x}} c_{m'-1}$ is bounded in $L^2(0, T; L^2(\Omega \times \mathbb{R}^N))$. Therefore, it tends weakly to $\nabla_{\mathbf{x}} c$ in $L^2_{\mathbf{x}\mathbf{v}t}$.

Using these convergences we pass to the limit in the weak formulation of the equations for $p_{m'}$:

$$\begin{aligned} & \int_{Q_T} p_{m'} \left[\frac{\partial \varphi}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} \varphi - \beta \mathbf{v} \cdot \nabla_{\mathbf{v}} \varphi + \mathbf{F}(c_{m'-1}) \cdot \nabla_{\mathbf{v}} \varphi + \sigma \Delta_{\mathbf{v}} \varphi - b(p_{m'-1}) \varphi \right] d\mathbf{x} d\mathbf{v} dt \\ & + \int_{\Omega \times \mathbb{R}^N} p_0 \varphi(\mathbf{x}, \mathbf{v}, 0) d\mathbf{x} d\mathbf{v} + \int_{\Sigma_T^-} |\mathbf{v} \cdot \mathbf{n}(\mathbf{x})| g \varphi dS d\mathbf{v} dt = \int_{Q_T} \alpha \nu p_{m'} \varphi d\mathbf{x} d\mathbf{v} dt, \end{aligned}$$

for any $\varphi \in C^\infty(\overline{\Omega} \times \mathbb{R}^N \times [0, T])$ with compact support in \mathbf{v} such that $\varphi = 0$ on Σ_T^+ . Weak convergence of $p_{m'}$ is enough to pass to the limit in the linear terms. For the rest, we use the strong convergences established above and the weak convergence of $\nabla_{\mathbf{x}} c_{m'-1}$. A similar argument can be applied in the weak formulation of equation (70). Therefore, p and c solve the original angiogenesis problem (2)-(8).

6. Nonlocal boundary conditions

In the previous section we constructed solutions for the angiogenesis model assuming the boundary values for the density known. The general problem

with nonlocal boundary condition (9)-(10) becomes more complex. Let us address first the linear problem with nonlocal boundary conditions. We define the functions:

$$K_1(\beta, \sigma, \chi, \sigma_v) = \text{Max}_{\{\mathbf{v} \cdot \mathbf{n} > 0\}} |\mathbf{v} \cdot \mathbf{n}| e^{-\frac{\beta}{\sigma} |\mathbf{v} - \mathbf{v}_0|^2} \left[\int_{\{\mathbf{v} \cdot \mathbf{n} < 0\}} \frac{|\tilde{\mathbf{v}} \cdot \mathbf{n}| e^{-\frac{\beta}{\sigma} |\tilde{\mathbf{v}} - \mathbf{v}_0|^2} d\tilde{\mathbf{v}}}{1 + e^{|\tilde{\mathbf{v}} - \chi \mathbf{v}_0|^2 / \sigma_v^2}} \right]^{-1},$$

$$K_2(\chi, \sigma_v) = \int_{\{\mathbf{v} \cdot \mathbf{n} > 0\}} \frac{d\mathbf{v}}{1 + e^{|\mathbf{v} - \chi \mathbf{v}_0|^2 / \sigma_v^2}}. \quad (92)$$

For $\chi |\mathbf{v}_0| \gg 1$ fixed, $K_2 < 1$ choosing σ_v small enough. Then, $K_1 < 1$, $K_1 K_2 < 1$ choosing $\frac{\beta}{\alpha}$ small.

Theorem 6.1. *Let us assume that*

$$p_0 \geq 0, \quad (1 + |\mathbf{v}|^2)^{\mu/2} p_0 \in L^\infty \cap L^1(\Omega \times \mathbb{R}^N), \quad \mu > N, \quad (93)$$

$$a \in L^\infty(Q_T), \quad \mathbf{F} \in L^\infty(\Omega \times (0, T)), \quad (94)$$

$$j_0 \geq 0, \quad j_0 \in L^\infty(\Sigma_T^-). \quad (95)$$

Then, there exists a nonnegative solution p of the linear equations (14)-(15) with boundary conditions (9)-(10) satisfying:

$$p \in L^\infty(0, T; L^\infty \cap L^1(\Omega \times \mathbb{R}^N)), \quad \nabla_{\mathbf{v}} p \in L^2(0, T; L^2(\Omega \times \mathbb{R}^N)), \quad (96)$$

$$(1 + |\mathbf{v}|^2)^{\mu/2} p \in L^\infty(0, T; L^\infty \cap L^1(\Omega \times \mathbb{R}^N)), \quad (97)$$

$$(1 + |\mathbf{v} \cdot \mathbf{n}|)(1 + |\mathbf{v}|^2)^{\mu/2} \text{Tr } p^\pm \in L^\infty(0, T; L^\infty \cap L^1(\Sigma_T^\pm)), \quad (98)$$

$$p \in L^\infty(0, T; L_x^\infty(\Omega, L_v^1(\mathbb{R}^N))), \quad (99)$$

for any $T > 0$, provided the parameters $\beta, \sigma, \sigma_v, \chi$ satisfy $K_1(\beta, \sigma, \chi, \sigma_v) K_2(\chi, \sigma_v) < 1$.

Proof. The solution is constructed as the limit of solutions p_m of approximating problems defined by equations (14)-(15) with boundary condition of the form:

$$p_m^-(\mathbf{x}, \mathbf{v}, t) = g(p_{m-1}^+(\mathbf{x}, \mathbf{v}, t)) \quad \text{on } \Sigma_T^-, \quad (100)$$

The operators g defining these boundary conditions in formulas (9)-(10) are positive. The proof follows the same lines as the proof of Theorem 5.1, with changes to handle the boundary conditions, that we summarize.

The scheme is well defined thanks to Theorems 2.1 and 2.2, starting from $p_1 = 0$ and choosing boundary values p_2^- for p_2 on Σ_T^- with the regularity (79). All the estimates established in Step 3 of the proof of Theorem 5.1 hold. However, now $g = g(p_{m-1}^+(\mathbf{x}, \mathbf{v}, t))$ and we need to obtain uniform bounds of the traces at the boundaries. Let us analyze the explicit expressions given by (9)-(10).

We analyze first the bounds associated to the boundary condition at S_{r_0} . From identity (9), we deduce:

$$p_m^-(r_0, \boldsymbol{\theta}, v_r, \boldsymbol{\phi}, t) = \frac{e^{-\frac{\beta}{\sigma}|\mathbf{v}-\mathbf{v}_0|^2}}{\mathcal{I}_0} \left[\int_0^\infty d\tilde{v}_r \tilde{v}_r^{N-1} \int_{\{\tilde{\boldsymbol{\phi}} \in S_{N-1} | \tilde{\mathbf{v}} \cdot \mathbf{n} < 0\}} d\tilde{\boldsymbol{\phi}} p_{m-1}^-(r_0, \boldsymbol{\theta}, \tilde{v}_r, \tilde{\boldsymbol{\phi}}, t) \right]. \quad (101)$$

Multiplying (101) by v_r^{N-1} and integrating over Σ_T^- , we find:

$$\|p_m^-\|_{L^1(\Sigma_T^-)} = \|p_{m-1}^-\|_{L^1(\Sigma_T^-)} = \dots = \|p_2^-\|_{L^1(\Sigma_T^-)}. \quad (102)$$

Multiplying (101) by $v_r^{N-1} v_r^\ell$, $\ell > 0$, integrating, and inserting (102) we obtain:

$$\|\|\mathbf{v}\|^\ell p_m^-\|_{L^1(\Sigma_T^-)} \leq \int_0^\infty dv_r v_r^{N-1+\ell} \int_{\{\tilde{\boldsymbol{\phi}} \in S_{N-1} | \tilde{\mathbf{v}} \cdot \mathbf{n} < 0\}} d\tilde{\boldsymbol{\phi}} \frac{e^{-\frac{\beta}{\sigma}|\mathbf{v}-\mathbf{v}_0|^2}}{\mathcal{I}_0} \|p_2^-\|_{L^1(\Sigma_T^-)}. \quad (103)$$

Multiplying (101) by v_r^{N-1} and integrating over $(0, \infty) \times \{\tilde{\boldsymbol{\phi}} \in S_{N-1} | \tilde{\mathbf{v}} \cdot \mathbf{n} < 0\}$, we find:

$$\begin{aligned} \int_0^\infty dv_r v_r^{N-1} \int_{\{\tilde{\boldsymbol{\phi}} \in S_{N-1} | \tilde{\mathbf{v}} \cdot \mathbf{n} < 0\}} d\boldsymbol{\phi} p_m^-(r_0, \boldsymbol{\theta}, v_r, \boldsymbol{\phi}, t) &= \int_0^\infty d\tilde{v}_r \tilde{v}_r^{N-1} \int_{\{\tilde{\boldsymbol{\phi}} \in S_{N-1} | \tilde{\mathbf{v}} \cdot \mathbf{n} < 0\}} d\tilde{\boldsymbol{\phi}} p_{m-1}^-(r_0, \boldsymbol{\theta}, \tilde{v}_r, \tilde{\boldsymbol{\phi}}, t) \\ &= \dots = \int_0^\infty d\tilde{v}_r \tilde{v}_r^{N-1} \int_{\{\tilde{\boldsymbol{\phi}} \in S_{N-1} | \tilde{\mathbf{v}} \cdot \mathbf{n} < 0\}} d\tilde{\boldsymbol{\phi}} p_2^-(r_0, \boldsymbol{\theta}, \tilde{v}_r, \tilde{\boldsymbol{\phi}}, t). \end{aligned} \quad (104)$$

Therefore, for any $q \in (1, \infty)$:

$$\|p_m^-\|_{L^q(\Sigma_T^-)}^q \leq \int_0^\infty dv_r \int_{\{\tilde{\boldsymbol{\phi}} \in S_{N-1} | \tilde{\mathbf{v}} \cdot \mathbf{n} < 0\}} d\boldsymbol{\phi} v_r^{N-1} \frac{e^{-\frac{q\beta}{\sigma}|\mathbf{v}-\mathbf{v}_0|^2}}{\mathcal{I}_0^q} \left\| \int_0^\infty d\tilde{v}_r \tilde{v}_r^{N-1} \int_{\{\tilde{\boldsymbol{\phi}} \in S_{N-1} | \tilde{\mathbf{v}} \cdot \mathbf{n} < 0\}} d\tilde{\boldsymbol{\phi}} p_2^-(r_0, \boldsymbol{\theta}, \tilde{v}_r, \tilde{\boldsymbol{\phi}}, t) \right\|_{L_{\boldsymbol{\theta}, t}^\infty}^q.$$

We may estimate uniformly the norms $\|p_m^-\|_{L^\infty(\Sigma_T^-)}$, $\|(1+|\mathbf{v}|^2)^{\frac{\beta}{\sigma}} p_m^-\|_{L^\infty(\Sigma_T^-)}$ and $\|p_m^-\|_{L_k^q(\Sigma_T^-)}$, for $1 \leq q \leq \infty$, in a similar way.

Let us recall the boundary condition at $r = r_1$:

$$p_m^-(r_1, \boldsymbol{\theta}, v_r, \boldsymbol{\phi}, t) = \frac{e^{-\frac{\beta}{\sigma}|\mathbf{v}-\mathbf{v}_0|^2}}{|\mathcal{I}_1|} \left[j_0 - \int_0^\infty d\tilde{v}_r \tilde{v}_r^{N-1} \int_{\{\tilde{\boldsymbol{\phi}} \in S_{N-1} | \tilde{\mathbf{v}} \cdot \mathbf{n} > 0\}} d\tilde{\boldsymbol{\phi}} p_{m-1}^+(r_1, \boldsymbol{\theta}, \tilde{v}_r, \tilde{\boldsymbol{\phi}}, t) f_1(\tilde{\mathbf{v}}) \right]. \quad (105)$$

Multiplying by $\mathbf{v} \cdot \mathbf{n}$ we get:

$$\|p_m^-\|_{L_k^\infty(\Sigma_T^-)} \leq K_1(\beta, \sigma, \chi, \sigma_v) \left[\|j_0\|_\infty + K_2(\chi, \sigma_v) \|p_{m-1}^+\|_{L_k^\infty(\Sigma_T^+)} \right]. \quad (106)$$

Set $\omega_q = \frac{N\beta}{q} + \|a^-\|_\infty$. From identity (20) in Theorem 2.2, we deduce:

$$\|e^{-\omega_q t} p_{m-1}^+\|_{L_k^q(\Sigma_T^+)} \leq \left[\|p_0\|_{L^q(\Omega \times \mathbb{R}^N)} + \|e^{-\omega_q t} p_{m-1}^-\|_{L_k^q(\Sigma_T^-)} \right], \quad (107)$$

for any $q \in [1, \infty]$. Set $\omega = N\beta + \|a^-\|_\infty$. Multiplying equation (105) by $e^{-\omega t} \mathbf{v} \cdot \mathbf{n}$ and integrating over Σ_T^- , we find that

$$\|e^{-\omega t} p_m^-\|_{L_k^\infty(\Sigma_T^-)} \leq K_1 \|e^{-\omega t} j_0\|_\infty + K_1 K_2 \|e^{-\omega t} p_{m-1}^+\|_{L_k^\infty(\Sigma_T^+)}. \quad (108)$$

Inserting (107) in (108) and iterating we obtain:

$$\|e^{-\omega t} p_m^-\|_{L_k^\infty(\Sigma_T^-)} \leq \frac{1}{1-K_1 K_2} [C(j_0, \omega, T, K_1) + \|p_0\|_{L_{\infty}^{\infty}}] + (K_1 K_2)^{m-2} \|e^{-\omega t} p_2^-\|_{L_k^\infty(\Sigma_T^-)}. \quad (109)$$

Using (107), we extend this uniform estimate to $\|p_m^+\|_{L_k^\infty(\Sigma_T^+)}$.

Multiplying equation (105) by $|\mathbf{v}|^\ell$, $\ell = 0, \dots, \mu$, we find:

$$\| |\mathbf{v}|^\ell p_m^- \|_{L^\infty(\Sigma_T^-)} \leq \frac{\| |\mathbf{v}|^\ell e^{-\frac{\beta}{\sigma} |\mathbf{v}-\mathbf{v}_0|^2} \|_\infty}{|\mathcal{I}_1|} \left[\|j_0\|_\infty + K_2 \|p_{m-1}^+\|_{L_k^\infty(\Sigma_T^+)} \right]. \quad (110)$$

$$\| |\mathbf{v}|^\ell p_m^- \|_{L^1(\Sigma_T^-)} \leq \frac{\| |\mathbf{v}|^\ell e^{-\frac{\beta}{\sigma} |\mathbf{v}-\mathbf{v}_0|^2} \|_1}{|\mathcal{I}_1|} \text{meas}(\Omega) \left[\|j_0\|_\infty + K_2 \|p_{m-1}^+\|_{L_k^\infty(\Sigma_T^+)} \right]. \quad (111)$$

In a similar way, we bound uniformly $\| |\mathbf{v}|^\ell p_m^- \|_{L_k^\infty(\Sigma_T^-)}$ and $\| |\mathbf{v}|^\ell p_m^- \|_{L_k^1(\Sigma_T^-)}$ for $\ell = 0, \dots, \mu$.

The above uniform estimates on the boundary values yield the uniform estimates on p_m in Steps 3 and 4 of Theorem 5.1. We can extract converging subsequences as in Step 5, with $\mathbf{F}(c_m)$ and $a = b(p_m) + \alpha\nu$ fixed, and pass to the limit in the weak formulation as in Step 6, with obvious simplifications. For the boundary term, an extracted subsequence $\text{Tr } p_{m'}^\pm = p_{m'}^\pm \rightharpoonup \pm$ in $L^q(\Sigma_T^\pm)$ and $L_k^q(\Sigma_T^\pm)$ weak for $1 \leq q < \infty$ and weak* for $q = \infty$. This allows to pass to the limit in the boundary term but we must justify that g^- and g^+ satisfy the equations defining the boundary conditions. Multiplying (9)-(10) by a test function $\psi \in C_c(\Sigma_T)$ and integrating, we find

$$\begin{aligned} \int_{\Sigma_T^- \cap \{|\mathbf{x}|=r_0\}} p_{m'}^- \psi dS d\mathbf{v} dt &= \int_{\Sigma_T^- \cap \{|\mathbf{x}|=r_0\}} e^{-\frac{\beta}{\sigma} |\mathbf{v}-\mathbf{v}_0|^2} \mathcal{I}_0^{-1} \left[\int_0^\infty d\tilde{v}_r \tilde{v}_r^{N-1} \int_{\{\tilde{\phi} \in S_{N-1} | \tilde{\mathbf{v}} \cdot \mathbf{n} < 0\}} d\tilde{\phi} p_{m'-1}^- \right] \psi dS d\mathbf{v} dt, \\ \int_{\Sigma_T^- \cap \{|\mathbf{x}|=r_1\}} p_{m'}^- \psi dS d\mathbf{v} dt &= \int_{\Sigma_T^- \cap \{|\mathbf{x}|=r_1\}} e^{-\frac{\beta}{\sigma} |\mathbf{v}-\mathbf{v}_0|^2} j_0 \psi dS d\mathbf{v} dt \\ &+ \int_{\Sigma_T^- \cap \{|\mathbf{x}|=r_1\}} e^{-\frac{\beta}{\sigma} |\mathbf{v}-\mathbf{v}_0|^2} |\mathcal{I}_1|^{-1} \left[\int_0^\infty d\tilde{v}_r \tilde{v}_r^{N-1} \int_{\{\tilde{\phi} \in S_{N-1} | \tilde{\mathbf{v}} \cdot \mathbf{n} > 0\}} d\tilde{\phi} p_{m'-1}^+ f_1(\tilde{\mathbf{v}}) \right] \psi dS d\mathbf{v} dt. \end{aligned}$$

Taking limits, the same identities hold for g^+ and g^- .

Once we have understood the difficulties introduced by the nonlocal boundary conditions, we can combine the strategies developed in the proofs of Theorems 5.1 and 6.1 to obtain an existence result for the original angiogenesis problem.

Theorem 6.2. *Let us assume that*

$$p_0 \geq 0, c_0 \geq 0, \quad (112)$$

$$c_0 \in W^{2,\infty}(\Omega), \quad (113)$$

$$(1 + |\mathbf{v}|^2)^{\mu/2} p_0 \in L^\infty \cap L^1(\Omega \times \mathbb{R}^N), \quad \mu > N, \quad (114)$$

$$c_{r_0} \in L^\infty(0, T; L^\infty(S_{r_0})), \quad (115)$$

and that a function c_b is found verifying the hypotheses of Theorem 4.5. Then, there exists a positive solution (p, c) of the initial value problem (2)-(7) with boundary conditions given by (9)-(10) satisfying:

$$c \in L^\infty(0, T; W^{1,\infty}(\Omega)), \quad (116)$$

$$p \in L^\infty(0, T; L^\infty \cap L^1(\Omega \times \mathbb{R}^N)), \nabla_{\mathbf{v}} p \in L^2(0, T; L^2(\Omega \times \mathbb{R}^N)), \quad (117)$$

$$(1 + |\mathbf{v}|^2)^{\mu/2} p \in L^\infty(0, T; L^\infty \cap L^1(\Omega \times \mathbb{R}^N)), \quad (118)$$

$$(1 + |\mathbf{v} \cdot \mathbf{n}|)(1 + |\mathbf{v}|^2)^{\mu/2} \text{Tr } p^\pm \in L^\infty(0, T; L^\infty \cap L^1(\Sigma_T^\pm)), \quad (119)$$

$$p \in L^\infty(0, T; L_x^\infty(\Omega, L_v^1(\mathbb{R}^N))), \quad (120)$$

provided the functions K_1, K_2 defined in (92) satisfy $K_1 K_2 < 1$. The norms of the solution are bounded in terms of the norms of the data and the parameters.

Proof.

We consider the scheme (66)-(73) with boundary conditions (100), where g is given by (9)-(10). We set $p_1 = 0$, so that c_1 is the solution of a heat equation. Then, p_2 is the solution of the problem with bounded coefficients $\mathbf{F}(c_1)$ and $\alpha(c_1)$ and fixed boundary condition p_2^- with the regularity (79). As in step 1 of the Proof of Theorem 5.1, the sequence of iterates (c_{m-1}, p_m) is well defined thanks to Proposition 4.1, Theorem 4.5, Theorems 2.1, 2.2 and 2.3, Lemma 3.1 and Proposition 3.7. The iterates are nonnegative, and the coefficients $j(p_{m-1})$, $b(p_{m-1})$, $\alpha(c_{m-1})$ and $\mathbf{F}(c_{m-1})$ are bounded functions. As we have seen in the proof of Theorem 6.1, the boundary conditions for p_m^- satisfy the regularity (79).

The estimates for c_m and p_m in Steps 2 and 3 of the Proof of Theorem 5.1 hold. However, we do not obtain immediate uniform estimates on the L^q norms of p_m unless we estimate first the boundary conditions. Setting $a = b(p_{m-1}) - \alpha(c_{m-1})\nu$, we have $\|a^-\|_\infty \leq \alpha_1 \|\nu\|_\infty$. Then, we may reproduce the computations in the Proof of Theorem 6.1 to get uniform bounds of $(1 + |\mathbf{v} \cdot \mathbf{n}|)(1 + |\mathbf{v}|^2)^{\mu/2} p_m^-$ in $L^1 \cap L^\infty(\Sigma_T^+)$. This provides uniform estimates on the L^q norms of p_m thanks to Theorem 2.2. Steps 4, 5 and 6 proceed as in the proof of Theorem 5.1. The passage to the limit in the boundary conditions is analogous to that in the proof of Theorem 6.1. The final solution inherits all the bounds established for the iterates, as a result of weak convergences.

7. Conclusions

The increasing availability of experimental observations forces the appearance of updated angiogenesis models, taking into account new features. The enhanced complexity displayed by such models fosters the development of new mathematical strategies for their numerical simulation and analysis. We consider here a model that is able to describe the effect of blood vessel branching and anastomosis, as well as blood vessel spread due to diffusion of the concentration of tumor angiogenic factor. A kinetic equation for the density of blood vessel tips involving a Fokker-Planck operator as well as nonlocal terms and boundary conditions, is coupled to a diffusion equation for the tumor angiogenic factor with Neumann boundary conditions. These models entail measure

valued coefficients. Replacing Dirac measures by gaussians, a regularization frequent in numerical approximations, we are able to construct solutions as limits of solutions of iterative schemes. Stability bounds in terms of the norms of the data follow. Whether the solutions of families of regularized problems approximating Dirac measures with gaussians effectively converge to the original measure valued problem is an open problem.

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References

- [1] L.L. Bonilla, V. Capasso, M. Alvaro, M. Carretero, Hybrid modeling of tumor induced angiogenesis, *Phys. Rev. E* 90, 062716, 2014.
- [2] F. Terragni, M. Carretero, V. Capasso, L. L. Bonilla, Stochastic model of tumor-induced angiogenesis: Ensemble averages and deterministic equations, *Phys. Rev. E* 93, 022413, 2016.
- [3] L.L. Bonilla, H.T. Grahn, Non-linear dynamics of semiconductor superlattices, *Rep. Prog. Phys.* 68, 577-683, 2005
- [4] F. Bouchut, J. Dolbeault, On long time asymptotics of the Vlasov-Fokker-Planck equation and of the Vlasov-Poisson-Fokker-Planck system with coulombic and newtonian potentials, *Diff. Int. Eqs.* 8, 487-514, 1995.
- [5] F. Bouchut, Existence and uniqueness of a global smooth solution for the Vlasov-Poisson-Fokker-Planck system in three dimensions, *J. Funct. Anal.* 111, 239-258, 1993.
- [6] H. Brézis, *Functional analysis, Sobolev spaces and partial differential equations*, Springer, 2011.
- [7] R.M. Brown, The initial Neumann problem for the heat equation in Lipschitz cylinders, *Trans. Amer. Math. Soc.* 320, 1-52, 1990.
- [8] V. Capasso and D. Morale, Stochastic modelling of tumour-induced angiogenesis, *J. Math. Biol.* 58, 219-233, 2009.
- [9] V. Capasso, D. Morale, G. Facchetti, Randomness in self-organized phenomena. A case study: Retinal angiogenesis, *BioSystems* 112, 292-297, 2013.
- [10] P. F. Carmeliet, Angiogenesis in life, disease and medicine, *Nature* 438, 932-936, 2005.
- [11] P. Carmeliet and R. K. Jain, Molecular mechanisms and clinical applications of angiogenesis, *Nature* 473, 298-307, 2011.

- [12] A. Carpio, G. Duro, Well posedness of an integrodifferential kinetic model of Fokker-Planck type for angiogenesis, *Nonlinear Analysis: Real World Applications* 30, 184-212, 2016.
- [13] J.A. Carrillo, Global weak solutions for the initial-boundary-value problems to the Vlasov-Poisson-Fokker-Planck system, *Math. Meth. Appl. Sc.* 21, 907-938, 1998.
- [14] C. Cercignani, On the initial-boundary value problem for the Boltzmann equation, *Arch. Rat. Mech. Anal.* 116, 307-315, 1992.
- [15] S. L. Cotter, V. Klika, L. Kimpton, S. Collins, and A. E. P. Heazell, A stochastic model for early placental development, *J. R. Soc. Interface* 11, 20140149, 2014.
- [16] J.C. Chen, C. He, On local existence of the Vlasov-Fokker-Planck equations in a 2D anisotropic space, *Boundary value problems*, 2013:233, 2013.
- [17] P. Degond, Global existence of smooth solutions for the Vlasov-Fokker-Planck equation in 1 and 2 space dimensions, *Ann. Sci. Ec. Norm. Super.*, 19(4), 519-542, 1986.
- [18] R.J. DiPerna, P.L. Lions, On the Fokker-Planck-Boltzmann equation, *Comm. Math. Phys.* 120, 1-23, 1988.
- [19] R. Duan, S. Liu, Cauchy problem on the Vlasov-Fokker-Planck equation coupled with the compressible Euler equations through the friction force, *Kinetic and Related Models* 4(4), 687-700, 2013.
- [20] M.H. Giga, Y. Giga, J. Saal, *Nonlinear partial differential equations*, Birkhauser, 2010.
- [21] K. Hamdache, Initial-boundary value problems for the Boltzmann equation: global existence of weak solutions, *Arch. Rat. Mech. Anal.* 119, 309-353, 1992.
- [22] T.A.M. Heck, M.M. Vaeyens, H. Van Oosterwyck, Computational models of sprouting angiogenesis and cell migration: towards multiscale mechanochemical models of angiogenesis, *Math Model Nat Phenom* 10, 09735348, 2015
- [23] H.J. Hwang, J. Jung, J.L.L Velazquez, On global existence of classical solutions for the Vlasov-Poisson system in convex bounded domains, *Discrete Cont Dyn S* 33 (2), 723-737, 2012.
- [24] F. Milde, M. Bergdorf, P. Koumoutsakos, A hybrid model for three-dimensional simulations of sprouting angiogenesis, *Biophys J.* 95, 3146-3160, 2008.
- [25] P.A. Raviart, J.M. Thomas, *Introduction a l'Analyse numérique des équations aux dérivées partielles*, 1998

- [26] J.L. Lions, *Quelques méthodes pour les problèmes aux limites nonlinéaires*, Gauthier-Villards, 1969.
- [27] P. Li, *Geometric analysis*, Cambridge Studies in Advanced Mathematics 134, Cambridge University Press, 2012.
- [28] A. Pazy, *Semigroups of linear operators and applications to partial differential equations*, Applied Mathematical Sciences 44, Springer-Verlag 1983.
- [29] S.M. Peirce, *Computational and mathematical modeling of angiogenesis*, *Microcirculation* 15(8), 739-751, 2008.
- [30] P.L. Lions, B. Perthame, *Propagation of moments and regularity for the three dimensional Vlasov-Poisson system*, *Invent. Math.* 105, 415-430, 1991.
- [31] G. Rein, J. Weckler, *Generic global classical solutions of the Vlasov-Fokker-Planck-Poisson system in three dimensions*, *J. Diff. Eq.* 99, 59-77, 1992.
- [32] M. Scianna, L. Munaron, and L. Preziosi, *A multiscale hybrid approach for vasculogenesis and related potential blocking therapies*, *Prog. Biophys. Mol. Biol.* 106, 450-462, 2011.
- [33] M. Scianna, C.G. Bell, L. Preziosi, *A review of mathematical models for the formation of vascular networks*, *J. Theor. Biol.* 333, 174-209, 2013.
- [34] S. Sun, M.F. Wheeler, M. Obeyesekere, Ch. Patrick Jr., *Multiscale angiogenesis modeling using mixed finite element methods*, *Multiscale Model. Simul.* 4(4), 1137-1167, 2005.
- [35] K. R. Swanson, R. C. Rockne, J. Claridge, M. A. Chaplain, E. C. Alvord Jr., and A. R. A. Anderson, *Quantifying the role of angiogenesis in malignant progression of gliomas: in silico modeling integrates imaging and histology*, *Cancer Res* 71, 7366-7375, 2011.
- [36] S. R. S. Varadhan, *On the behavior of the fundamental solution of the heat equation with variable coefficients*. *Comm. Pure Appl. Math.* 20 (2), 431-455, 1967.
- [37] S. R. S. Varadhan, *Diffusion processes in a small time interval*, *Comm. Pure Appl. Math.* 20, 659-685, 1967.
- [38] H.D. Victory, *On the existence of global weak solutions for Vlasov-Poisson-Fokker-Planck systems*, *J. Math. Anal. Appl.*, 160, 525-555, 1991.
- [39] H.D. Victory, B.P. O'Dwyer, *On classical solutions of Vlasov-Poisson-Fokker-Planck systems*, *Ind. Univ. Math. Math. J.*, 3 (1), 105-155, 1990.
- [40] L. Yadav, N. Puri, V. Rastogi, P. Satpute, V. Sharma, *Tumour angiogenesis and angiogenic inhibitors: a review*, *J. Clin. Diagn. Res.* 9, XE01-XE05, 2015.
- [41] F.Y. Wang, L. Yang, *Gradient estimate on the Neumann semigroup and applications*, arXiv:1009.1965