# AGE-STRUCTURED MECHANICAL MODELS FOR TUMOR GROWTH

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Abstract. In this paper, we introduce and analyze a mechanical model for tumor growth that takes into account the life cycle of a tumor cell. The underlying process for tumor growth is the same as in classical mechanical models: The spatial expansion of the tumor is driven by the proliferation of the cells (mitosis) which is only limited by the pressure inside the tissue. The natural incompressibility of the cells, which leads to a movement of the cells away from regions of high pressure, is taken into account via a nonlinear Darcy's law. Compared to similar models studied recently, we include an additional variable, which represents the age of the cells. The various phases of the life of a cell (growth, mitosis and death) are then dependent on this age variable.

We prove the existence of weak solutions and investigate their behavior numerically, focusing on the age distribution of the cells inside the tumor, the convergence to traveling wave solutions and the existence of a threshold for the death rate for expansion/regression of the tumor.

**Keywords:** Tumor growth, Age-structured model, Nonlinear Darcy's law, Cross-diffusion, Existence of solutions

**MSC:** 35Q92, 92-10, 35G61.

## 1. Introduction

1.1. **An age-structured mechanical model.** Numerous mathematical models for tumor growth have been developed and studied. Typically such models take into account several key mechanisms of tumor invasion, such as competition for space (with other cancer cells as well as with healthy cells), the availability of nutrients, phenotypic traits that might affect a cell's behavior, etc. In this paper, we focus on the simplest type of mechanical models in which the growth of the tumor is driven by the proliferation of the cells, which is only limited by the pressure inside the tissue, and by Darcy's law, which describes the movement of the cells away from regions of high pressure [14, 26, 25, 7, 17]. A classical model, introduced in [4] (see also [2, 3, 5]) and studied for example in [21, 19, 10, 6, 20] models the evolution of the cell population distribution function $\rho(x,t)$ by the nonlinear diffusion equation

$$\partial_t \rho - \operatorname{div}(\rho \nabla p) = \rho F(p), \qquad p = \frac{m}{m-1}\left(\frac{\rho}{\rho_M}\right)^{m-1} \tag{1.1}$$

where the growth rate $F(p)$ is a decreasing function of the pressure which vanishes for some $p = p_M$ (this maximal pressure $p_M$ is called the homeostatic pressure). When $m \gg 1$, the pressure is small when $\rho < \rho_M$ and large when $\rho > \rho_M$. If each cells has a fixed finite volume,

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this density $\rho_M$ represents the maximal packing density of cells. In what follows, we take $\rho_M = 1$ (to simplify the notations) and we fix $m > 1$.

The main object of this paper is a mechanical model for tumor growth which is based on the same simple considerations as (1.1), but which takes into account the life cycle of the cancer cells. For our purpose, the cell's life cycle will be assumed to consist of two distinct phases: In the first phase, the so-called *interphase*, the cell grows and copies its genetic material. During the second phase, the *mitotic phase*, it splits into two daughter cells which can then start the cycle from the beginning. We thus associate an age to each individual cell, denoted by $\theta \geq 0$, which we define for now as the time since its last mitosis. We then introduce the cell distribution function $n(x, \theta, t)$ which can be interpreted as the probability of finding a cell of age $\theta \geq 0$ at a position $x \in \mathbb{R}^d$. The evolution of this distribution function under pressure forces and cell duplication is described by the following boundary value problem:

$$
\begin{cases}
\partial_t n + \partial_\theta n - \mathrm{div}_x(n \nabla_x p) = -\nu(\theta, p)\, n - \mu(\theta) n & x \in \mathbb{R}^d,\ \theta > 0,\ t > 0 \\
n(x, 0, t) = 2 \displaystyle\int_0^\infty \nu(\theta, p)\, n(x, \theta, t)\, d\theta & x \in \mathbb{R}^d,\ \ t > 0 \\
n(x, \theta, 0) = n_{in}(x, \theta) & x \in \mathbb{R}^d,\ \theta > 0.
\end{cases}
\tag{1.2}
$$

We note the presence of the term $\partial_\theta n$, which accounts for the aging of a cell, and the coefficient $\nu$, which can be interpreted as the probability that a given cell enters its mitotic phase: That cell is then lost (the term $-\nu n$ in the right hand side of the first equation), but two new cells, of age $\theta = 0$, are created (which gives rise to the boundary condition in (1.2)). In general, $\nu$ depends on both the age of the cell $\theta$ and the local pressure $p = p(x, t)$ (we note that in experiments, there appears to be a lot of variability in the typical time between two mitosis events [13]). Pressure-limited proliferation corresponds to the assumptions

$$
\partial_p \nu(\theta, p) < 0, \qquad \nu(\theta, p_M) = 0.
\tag{1.3}
$$

The coefficient $\mu(\theta)$ denotes the death rate, which can be taken to be constant or more generally a function of the age. A maximum age $\theta_m$ can be imposed by requiring that $\int_0^{\theta_m} \mu(\theta)\, d\theta = +\infty$.

As in (1.1), the redistribution of the cells away from crowed regions is modeled by Darcy's law, but the pressure $p$ now depends not on the local "number" of cells $\int_0^\infty n(x, \theta, t)\, d\theta$ but on the volume occupied by the cells. Indeed, we wish to take into account the first phase of the cells life cycle (growth) by assuming that a cell of age $\theta \geq 0$ occupies a volume $V(\theta)$, where $\theta \mapsto V(\theta)$ is a non-decreasing function. The volume density is then defined as

$$
\rho(x, t) = \int_0^\infty V(\theta) n(x, \theta, t)\, d\theta.
$$

Finally, the pressure is an increasing function of the volume density $\rho$, and as in (1.1) we can take a simple power law:

$$
p(x, t) = \frac{m}{m-1} \rho(x, t)^{m-1}
$$

with parameter $m > 1$ and maximum packing density $\rho_M = 1$.

The purpose of this paper is to prove the existence of weak solutions for (1.2) and to investigate some important properties of the model numerically. We note that the uniqueness for such cross-diffusion model is a challenging and largely open problem and will not be addressed in this paper. Our analysis can be extended to some related models that take into account other phenomena that we have ignored here. We mention some of those below.

**Pressure-limited growth.** In (1.2), we assumed (see (1.3)) that high pressure (or high volume density) prevents the cells from dividing, thus limiting the growth of the tumor. Alternatively, we can assume that high pressure will slow down the whole life cycle of the cell (potentially preventing a newborn cell from growing and reaching its "adult" size). To write such a model, we can change slightly the meaning of the variable $\theta$, to represent a parameter indicating how far along its life cycle a cell has been able to go (i.e. the cell physiological age). In this model, a cell no longer "ages" linearly in time, since its growth is limited by a parameter depending on the pressure $p$, leading to the system:

$$\begin{cases} \partial_t n + r(p)\partial_\theta n - \operatorname{div}_x(n\nabla p) = -r(p)\nu(\theta,p)n - \mu(\theta)n & x\in\mathbb{R}^d,\ \theta>0,\ t>0 \\ n(x,0,t) = 2\displaystyle\int_0^\infty \nu(\theta,p)n(x,\theta,t)\,d\theta & x\in\mathbb{R}^d,\ \ t>0 \\ n(x,\theta,0) = n_{in}(x,\theta) & x\in\mathbb{R}^d,\ \theta>0. \end{cases} \tag{1.4}$$

where $r(p)$ is a decreasing function of $p$ such that $r(0)=1$ and $r(p)=0$ for $p\geq p_M$.

**The role of quiescent cells.** An important feature of many tumor growth models is the fact that not all cells behave similarly and that one should make a distinction between the proliferating cells, with distribution function still denoted by $n(x,\theta,t)$ and the quiescent cells, with distribution function $q(x,\theta,t)$ [15, 11, 16]. After mitosis, a fraction $\lambda$ of the new cells will be quiescent (and the rest proliferating). In addition, cells can switch back and forth from one state to the other with probabilities $\sigma_1$ and $\sigma_2$. This leads to the following system of equations:

$$\begin{cases} \partial_t n + r_1(p)\partial_\theta n - \operatorname{div}_x(n\nabla_x p) = -\mu(\theta)n - r_1(p)\nu(\theta,p)n + \sigma_1 q - \sigma_2 n \\ \partial_t q + r_2(p)\partial_\theta q - \operatorname{div}_x(q\nabla_x p) = -\mu(\theta)q - \sigma_1 q + \sigma_2 n \\ n(x,0,t) = 2(1-\lambda)\displaystyle\int_0^\infty \nu(\theta,p)n(x,\theta,t)\,d\theta \\ q(x,0,t) = 2\lambda\displaystyle\int_0^\infty \nu(\theta,p)n(x,\theta,t)\,d\theta \end{cases} \tag{1.5}$$

with $r_1$ and $r_2$ the different "aging speeds" for the two types of cells and

$$p(x,t) = \frac{m}{m-1}\rho(x,t)^{m-1}, \qquad \rho(x,t) = \int_0^\infty V(\theta)(n(x,\theta,t)+q(x,\theta,t))\,d\theta$$

Note that the quiescent cells do not duplicate and might have a slower evolution if $r_1\neq r_2$. Taking $r_2(p)=0$ amounts to assuming that they have a frozen life cycle: They do not grow or duplicate - unless and until they transition to the proliferating state.

1.2. **Equation for the density.** Equations (1.2) and (1.4) are related to the classical model (1.1) as follows: When $\nu=\nu(p)$, $\mu=\mu_0$ and $V=V_0$ are all independent of the age $\theta$, we can integrate the first equation in (1.4) with respect to $\theta$ to get the following equation for $\rho(x,t) = V_0\int_0^\infty n(x,\theta,t)\,d\theta$:

$$\begin{cases} \partial_t\rho - \operatorname{div}(\rho\nabla p) = \rho\,(\nu(p)r(p)-\mu_0), \qquad p=\frac{m}{m-1}\rho^{m-1} & x\in\mathbb{R}^d,\ t>0 \\ \rho(x,0) = V_0\int_0^\infty n_{in}(x,\theta)\,d\theta & x\in\mathbb{R}^d \end{cases} \tag{1.6}$$

which is (1.1) with growth rate $F(p) = \nu(p)r(p) - \mu_0$.

In this simple case, it is thus possible to solve for $\rho(x,t)$ without determining $n(x,\theta,t)$. In general (when $\nu$, $\mu$ and $V$ do depend on $\theta$), that is not possible: After multiplying the first equation in (1.4) by $V(\theta)$ and integrating with respect to $\theta$ we find the following equation for the volume density $\rho(x,t)$:

(1.7)
$$\partial_t \rho - \operatorname{div}(\rho\nabla p) = r(p)\int_0^\infty V'(\theta)n(x,\theta,t)\,d\theta + r(p)\int_0^\infty \nu(\theta,p)(2V(0)-V(\theta))n(x,\theta,t)\,d\theta - \int_0^\infty \mu(\theta)V(\theta)n(x,\theta,t)\,d\theta.$$

The first term in the right hand side describes the expansion of the tumor due to the volume change of individual cells, while the second term accounts for the change of volume during mitosis. Such events are typically volume preserving (i.e. the total volume of the two daughter cells is equal to the volume of the dividing cell), which can be enforced by assuming that $\nu(\theta,\rho)(2V(0)-V(\theta)) = 0$ for all $\theta > 0$. A simple form for the coefficients $\nu$ and $V$ describing this situation is as follows:

$$V(\theta) = \begin{cases} V_0 + \alpha\theta & \text{if } \theta \in [0, V_0/\alpha] \\ 2V_0 & \text{if } \theta \geq V_0/\alpha \end{cases} \tag{1.8}$$

$$\nu(\theta,p) = 0 \quad \text{for } \theta < V_0/\alpha \tag{1.9}$$

in which case (1.7) reduces to

$$\partial_t \rho - \operatorname{div}(\rho\nabla p) = \alpha r(\rho)\int_0^{V_0/\alpha} n(x,\theta,t)\,d\theta - \int_0^\infty \mu(\theta)V(\theta)n(x,\theta,t)\,d\theta.$$

1.3. **Motivations and related work.** The fact that tumor cells of different ages have different proliferation and mortality rates is well-documented, and age-structured models for tumor cell population without spatial dependence have been investigated by many authors, see [15, 11, 13, 16, 18]. A simple such model is

$$\begin{cases} \partial_t n + \partial_\theta n = -\beta(\theta)\,n - \mu(\theta)n & \theta > 0,\ t > 0 \\ n(0,t) = 2\displaystyle\int_0^\infty \beta(\theta)\,n(\theta,t)\,d\theta & t > 0. \end{cases} \tag{1.10}$$

which corresponds to our model (1.2) in the space homogeneous case. Equation (1.10) has been used to predict the growth of the tumor and the evolution of the distribution of proliferating/quiescent cells in tumors. In [11], for example, Dyson et al. proved that the population eventually follows asynchronous exponential growth and that the final age distribution of the population is independent of the initial age distribution. Age-structure models have also been used to investigate the effects of the immune system, which plays a crucial role in protecting the body against tumor before they are large enough to be detected. The immune system detects and removes cancerous cells via a complex mechanism, but simplified mathematical models have been proposed [18, 24]. In [18], the following simple age-structured tumor immune model is analyzed:

$$\begin{cases} \partial_t n + \partial_\theta n = -\beta(\theta)\, n - \mu(\theta) n - \sigma(\theta) E(t) n & \theta > 0,\ t > 0 \\ n(0,t) = 2\displaystyle\int_0^\infty \beta(\theta)\, n(\theta,t)\, d\theta & t > 0. \end{cases} \tag{1.11}$$

where $E(t)$ denotes the number of effector cells (immune cells responsible for identifying and clearing tumor cells), whose evolution is modeled by

$$\frac{dE(t)}{dt} = s - \mu_E E(t) + \tau N(t) E(t), \qquad N(t) = \int_0^\infty n(\theta,t)\, d\theta$$

The existence and stability of steady states is investigated and the existence of a threshold for the existence of tumor-free steady state is established. We also refer to [1] for a tumor immune model that takes into account the size of tumor cell in the cell division mechanism ($V(\theta)$ in our model).

Most of the papers mentioned above do not, however, take into account the effect of the pressure on the proliferation rate nor the effect of the volume change during the first phase of the cell's life cycle. Pressure plays a determinant role in the long time evolution of the tumor. Because increasing pressure will inhibit the proliferation of cells in the core of the tumor, only cells near the outer rim of the tumor contribute significantly to the growth of the tumor, leading to linear, instead of exponential, growth.

In [16], Liu et al. consider a nonlinear age-structured model in which the proliferation rate is a decreasing function of the number of tumor cells (which is a particular case of our model (1.5)) but still without taking into account the migration of cells toward less crowed regions. As mentioned in the introduction, other studies have focused on this last phenomena and on the role of mechanical stress in the growth of the tumor [4]. The resulting models have been studied by the mathematical community for a decade or so (see for example [21, 19, 10, 8, 6, 20, 9]).

Taking into account the cells' migration in the physical growth of the tumor is crucial, especially in order to account for the interactions with the surrounding tissues (competition for space with other healthy and cancerous cells, availability of nutrients etc.). We point out that when $1 < m < \infty$, migration is modeled in (1.1) by degenerate diffusion (porous media type equation) which leads to finite speed of propagation of the support of $\rho$ (and thus the support of $n$). The limit $m \to \infty$ has been at the topic of numerous papers since the original work of Perthame, Quiros and Vazquez [21] (see for example [19, 9, 23, 20, 8] and references therein). The resulting mathematical model is a Hele-Shaw free boundary problem which describes the motion of the interface (the edge of the tumor). We also refer to [12] for a review of other free boundary problems appearing in the context of tumor growth modeling.

In [4] and [20] both agent-based models and continuum models (similar to (1.1) and its singular limit $m \to \infty$) have been studied numerically. Our model is an intermediate model between these, as it does not track the fate of every individual cell, but nevertheless allows us to take into account the fact that the age distribution in the cell is far from homogeneous. For example, experimental findings have suggested that most mitosis events occur near the edge of the tumor (this is also the case with the individual based models considered in [4]) and point to the development of regions of quiescent cells and of necrosis in the core of the tumor. Finally, we point out that (1.2) also shares some similarities with models with phenotypic heterogeneity studied for instance in [8], but in that case, each cell is associated to a phenotypic variable $y \in [0,1]$ which affects their proliferation rate but does not change with time.

There can thus be significant advantages in keeping track of both the age and the position of the cells. Even in the simple framework where $\nu$ and $V$ are independent of $\theta$, the boundary value problem (1.2) carries more information than (1.1), since the distribution $n$ encodes the age structure of the cell population and can thus give critical insight into the model's prediction. Such a model can then be used to model the effects of various therapies since the response of the cell to the proposed treatment depends on its life cycle (most therapies target cells that are at some specific stage of their life cycle).

As a final remark, we note that the determination of the parameter $\nu$, $\mu$, $V$, $r$ and their dependence on $\theta$ is a delicate issue. We refer for example to [13] for further discussion on this issue.

**Outline of the paper:** The rest of the paper is organized as follows: In Section 2, we state the main result of this paper (the existence of a weak solution for (1.2)). In Section 3, we further discuss the properties of the model and present numerical results to illustrate these. The proof of Theorem 2.1 is developed in Section 4. Additional details about the numerical code are given in Appendix A.

## 2. Main result

In this paper, we prove the existence of a weak solution of the equation (1.2). For simplicity, we take $\mu = 0$ in this section (this term does not add any difficulties), so the system reduces to

$$\begin{cases} \partial_t n + \partial_\theta n - \operatorname{div}_x(n\nabla_x p) = -\nu(\theta,p)\, n & x\in\mathbb{R}^d,\ \theta>0,\ t>0 \\ n(x,0,t) = 2\int_0^\infty \nu(\theta,p)\, n(x,\theta,t)\, d\theta & x\in\mathbb{R}^d,\ \ t>0 \\ n(x,\theta,0) = n_{in}(x,\theta) & x\in\mathbb{R}^d,\ \theta>0. \end{cases} \tag{2.1}$$

and we recall (see (1.7)) that the volume density $\rho(x,t) = \int_0^\infty V(\theta) n(x,\theta,t)\, dx$ solves

$$\partial_t \rho - \operatorname{div}(\rho\nabla p) = \int_0^\infty V'(\theta) n(x,\theta,t)\, d\theta + \int_0^\infty \nu(\theta,p)(2V(0)-V(\theta)) n(x,\theta,t)\, d\theta. \tag{2.2}$$

We assume that the coefficients satisfy the following general assumptions: There exist positive constants $V_0, C$ such that

$$V_0 \le V(\theta) \le C, \quad 0 \le V'(\theta) \le C, \quad \forall\theta\ge 0, \qquad \text{and} \qquad 0 \le \nu(\theta,p) \le C, \quad \forall\theta,\ p\ge 0 \tag{2.3}$$

and

$$|V''(\theta)|, |\partial_\theta \nu(\theta,p)| \le C. \tag{2.4}$$

Assumption (2.3) implies in particular that the volume density $\rho(x,t)$ is bounded above and below by the usual number density $\int_0^\infty n(x,\theta,t)\, d\theta$. Our main result is the following:

**Theorem 2.1.** *For all $m > 2$ and for any initial condition $n_{in}(x,\theta)$ such that*

$$n_{in} \in L^1 \cap L\log L(\mathbb{R}^d\times(0,\infty)), \quad (|x|^2+\theta) n_{in} \in L^1(\mathbb{R}^d\times(0,\infty)), \quad \rho_{in}\in L^\infty(\mathbb{R}^d) \tag{2.5}$$

*there exists a weak solution $n(x,\theta,t)$ of (1.2). The function $n(x,\theta,t)$ is such that*

$$n \in L^\infty(0,T; L^1\cap L\log L(\mathbb{R}^d\times(0,\infty))), \quad (|x|^2+\theta) n \in L^\infty(0,T; L^1(\mathbb{R}^d\times(0,\infty)))$$

*while the density $\rho(x,t)$ and pressure $p(x,t) = \frac{m}{m-1}\rho(x,t)^{m-1}$ are such that*

$$\rho \in L^\infty(0,T;L^1\cap L^\infty(\mathbb{R}^d)), \qquad \nabla p \in L^2(0,T;L^2(\mathbb{R}^d))$$

*and the equation* (1.2) *is satisfied in the following distributional sense:*

(2.6)

$$\int_0^T\!\!\int_{\mathbb{R}^d}\!\int_0^\infty n(x,\theta,t)\big[-\partial_t\psi(x,\theta,t)-\partial_\theta\psi(x,\theta,t)+\nabla_x p(x,t)\cdot\nabla_x\psi(x,\theta,t)+\nu(\theta,p(x,t))\psi(x,\theta,t)\big]\,d\theta\,dx\,dt$$
$$=\int_{\mathbb{R}^d}\!\int_0^\infty n_{in}(x,\theta)\psi(x,\theta,0)\,d\theta\,dx+\int_0^T\!\!\int_{\mathbb{R}^d}\psi(x,0,t)2\int_0^\infty \nu(\theta,p(x,t))n(x,\theta,t)\,d\theta\,dx\,dt$$

*for all $\psi\in\mathcal{D}(\mathbb{R}^d\times[0,\infty)\times[0,T))$. Furthermore, the density $\rho(x,t)$ solves* (2.2).

We point out that the term $\int_0^T\!\int_{\mathbb{R}^d}\!\int_0^\infty n\nabla_x p\cdot\nabla_x\psi\,d\theta\,dx\,dt$ in the weak formulation (2.6) makes sense if we write it as

$$\int_0^T\!\!\int_{\mathbb{R}^d}\left(\int_0^\infty n\nabla_x\psi\,d\theta\right)\cdot\nabla_x p\,dx\,dt$$

since $|\int_0^\infty n\nabla_x\psi\,d\theta|\le C\|\nabla\psi\|_{L^\infty}\rho\in L^2(0,T;L^2(\mathbb{R}^d))$ and $\nabla_x p\in L^2(0,T;L^2(\mathbb{R}^d))$.

Under assumption (2.3), the density equation (2.2) implies in particular

$$\partial_t\rho-\operatorname{div}(\rho\nabla p)\le C\rho, \qquad p=\frac{m}{m-1}\rho^{m-1}.$$

And multiplying this equation by $m\rho^{m-2}$, we deduce the following equation for the pressure $p$:

$$\partial_t p-(m-1)p\Delta p-|\nabla p|^2\le(m-1)Cp. \tag{2.7}$$

This equation will play a role in the proof and it implies the following classical result:

**Proposition 2.2** (Finite speed of propagation of the support)**.** *Under the assumptions of Theorem 2.1, assume further that there exists $R_0$ such that $n_{in}(x,\theta)=0$ for all $|x|\ge R_0$ and $\theta\ge 0$. Then*

$$n(x,\theta,t)=0 \quad \textit{for all } |x|\ge\overline{R}+e^{(m-1)Ct} \textit{ and for all } \theta\ge 0$$

*for some $\overline{R}$ depending on $R_0$ and $\|\rho_{in}\|_{L^\infty}$.*

*Proof.* Setting $A:=(m-1)C$, we note that given a unit vector $e$, the function $\overline{p}(x,t)=e^{At}\left(e^{At}-\sqrt{A}(x\cdot e-\overline{R})\right)_+$ is a super-solution for (2.7) with support in $\{x\cdot e\ge\overline{R}+\frac{1}{\sqrt{A}}e^{At}\}$ and satisfying $\overline{p}(x,0)\ge 1+\sqrt{A}(\overline{R}-R_0)$ on $\operatorname{Supp}p_{in}$. Taking $\overline{R}$ large enough so that $\overline{p}(x,0)\ge p_{in}(x)$, the result follows from the comparison principle applied to (2.7). □

On the other hand, it is not obvious that we can get a bound on $R(t)$ that is uniform with respect to $m$, the main obstacle being the term $\int_0^\infty V'(\theta)n(\theta)\,d\theta$. This term is responsible for another significant difference with (1.1): Even if we assume that $\nu(\theta,p)=0$ for all $p\ge p_M$ and that $p_{in}(x)\le p_M$ it is not true in general that $p(t,x)\le p_M$ for all $t\ge 0$.

Finally, we note that the proof of Theorem 2.1 could easily be adapted to the pressure limited growth model (1.4). In fact, this model has slightly better properties since if we assume that $r(p)=0$ for $p\ge p_M$ (i.e. preventing not only mitosis, but also the growth of cells when $p\ge p_M$), then $p(x,t) \leq p_M$ for all $t \geq 0$ if it is true at $t = 0$. This follows from the fact that the pressure solves

$$\partial_t p - (m-1)p\Delta p - |\nabla p|^2 \leq (m-1)Cr(p)p$$

and the usual maximum principle.

Before we give the proof of Theorem 2.1, we present in the next section some numerical results which illustrate other important properties of our model.

## 3. Properties of the model and numerical results

When the volume $V(\theta)$ and proliferation rate $\beta(\theta)$ are independent of $\theta$, the volume density $\rho(t,x) = V_0 \int_0^\infty n(t,x,\theta)\,d\theta$ solves the classical porous media type equation with growth term (1.6). This classical model has been extensively studied both theoretically and numerically (including the singular limit $m \to \infty$, see [21, 19]). Classical properties include finite speed expansion of the support and the existence of traveling wave solutions which describe the asymptotic spreading speed of any compactly supported initial configuration. Similar properties are expected to hold for general $V(\theta)$ and $\beta(\theta)$ and will be investigated numerically below. But we also note that even in the simplest case mentioned above, our model provides additional information concerning the spreading of tumor under mechanical process described in the introduction. In this section, we further discuss some properties of the model and present numerical results to illustrate them.

### 3.1. **Numerical setting.**

Throughout this section, we fix $m = 4$ (so $p = \frac{4}{3}\rho^3$) and we take

$$\nu(\theta,p) = \beta(\theta)\left(\frac{3}{4} - p\right)$$

where $\beta$ satisfies $\beta(\theta) = 0$ for some small $\theta$. Following [13], we take:

$$\beta(\theta) = \begin{cases} 0 & \text{if } \theta \leq \theta_0 \\ \frac{(\theta-\theta_0)^2}{\sigma(2\sigma^2 + 2\sigma(\theta-\theta_0) + (\theta-\theta_0)^2)} & \text{if } \theta \geq \theta_0 \end{cases} \tag{3.1}$$

where $\theta_0 = 1$ and $\sigma = 20$. We restrict ourselves to the case $V(\theta) \equiv V_0$. Note that for computation purposes, we need to take the age variable $\theta$ in a bounded interval $[0, \theta_{max}]$. When we can take $\theta_{max}$ larger than the maximum computation time, this maximum age does not play a role in determining the solution. But since cells do not live forever, it can be relevant (and numerically less costly) to take $\theta_{max} \leq T$.

In that case, one needs to specify what happens to cells when they reach the age $\theta = \theta_{max}$. In the numerical computations that we present below, we assume that these ”older” cells are still physically present (they contribute to the pressure), but they are no longer proliferating. This amounts to assuming that $\beta(\theta) = 0$ when $\theta > \theta_{max}$.

Note that it would be easy to assume instead that these cells are proliferating with a constant rate ($\beta(\theta) = \beta(\theta_{max})$ for $\theta > \theta_{max}$). In practice, we actually see very little difference between these two settings in the simulations: Indeed, older cells are primarily found in the center of the tumor, where the proliferation is already negligible because of the high pressure $p \sim 3/4$. This is illustrated in Figure 3 which shows the density of the cells of age $\theta = \theta_{max}$ inside the tumor. We also point to Figure 7, which shows that when the death of cells is taken into account, the

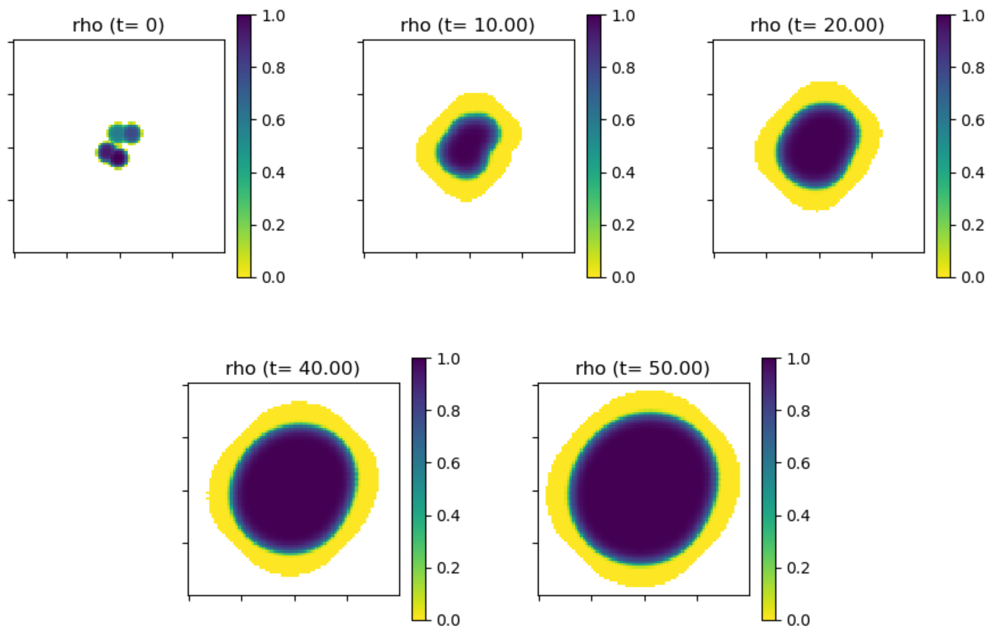


FIGURE 1. The density $x \mapsto \rho(t, x)$ for a 2-dimensional tumor at time $t = 0$, 10, 20, 40 and 50

number of cells of age $\theta$ converges to zero exponentially fast and taking $\theta_{max}$ large enough will again lead qualitatively to the same results as when $\theta_{max} = +\infty$.

Below, we present and discuss 2D simulations where the equation is set in the square $[-10, 10] \times [-10, 10] \subset \mathbb{R}^2$ and the system is supplemented with Neumann boundary conditions. Additional information about the numerical scheme can be found in Appendix A.

3.2. **Growth of the tumor and mitosis events.** Figure 1 shows the evolution of the density $\rho(x, t) = \int_0^\infty n(x, \theta, t)\, d\theta$ with $\theta_{\max} = 20$ for some non-symmetric initial data. One of the most interesting feature of our model, compared with macroscopic models that only describe the evolution of the density $\rho(x, t)$, is that it keeps track of where proliferation is taking place. Indeed, in vitro experiments with cancerous cells suggest that the growth of the tumor is mostly due to the proliferation of cells in a small region near, but not at, the outer edge of the tumor (a similar behavior is observed for the growth of bacteria colonies). Figure 2 shows the distribution of cells that just experienced mitosis $n(x, \theta = 0, t)$ and clearly shows that the model is consistent with this observation: Most mitosis events take place in an annulus close to the edge of the support of $n$.

For comparison, Figure 3 shows the distribution of cells of age $\theta_{max}$ across the tumor. These are the cells have reached their maximal life span and are no longer proliferating (we can also interpret this as a necrotic core).

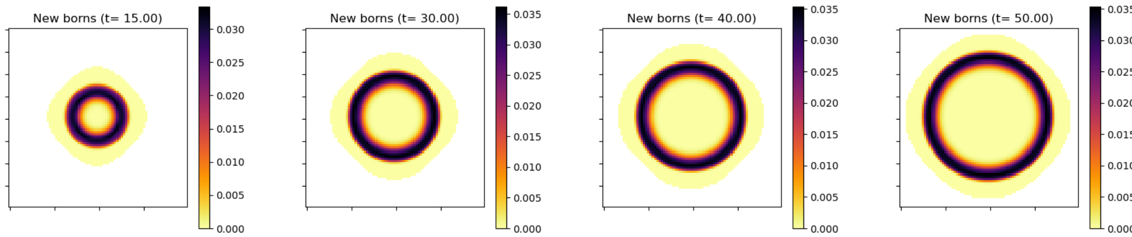


Figure 2. Number of mitosis events inside the tumor

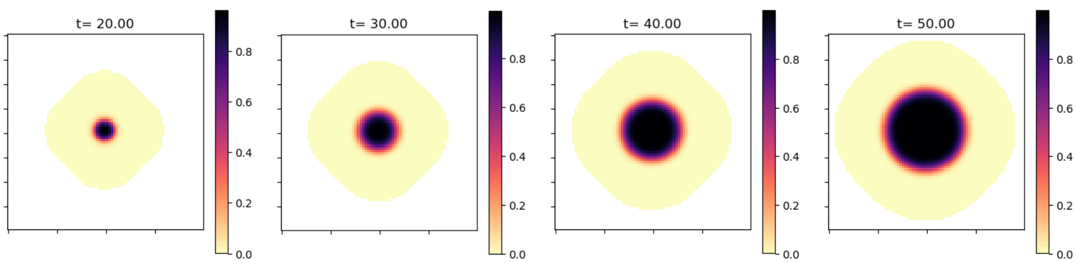


Figure 3. Spatial distribution of the oldest cells

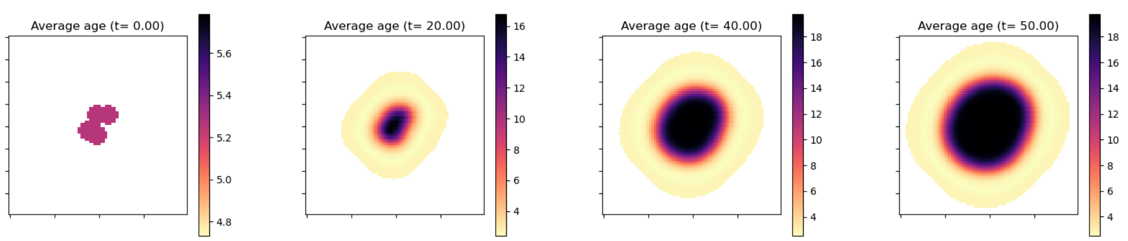


Figure 4. Average age of the cells across the tumor. The lowest average age is found slightly inside the tumor and not at the edge.

This phenomenon is related to another important feature often identified in experiments, the notion of "surfing cells" at the front: The cells at the leading edge of the tumor are being pushed by the growing bulk density so that the minimum average age of the cells is not found at the edge. This is illustrated in Figure 4 which represent the average age

$$\Theta(x,t) := \frac{\int_0^\infty \theta n(x,\theta,t)\, d\theta}{\int_0^\infty n(x,\theta,t)\, d\theta}$$

as a function of $x$ for various time.

3.3. **Long time behavior and traveling wave solutions.** We now turn our attention to the behavior of the solutions for large time. Two important features of tumor growth are the speed of spreading of the tumor and the asymptotic age distribution of the cells across the tumor. Indeed, a motivation for the study of age-structured models is the development (or improvement) of therapies. Since cells in different phases of their life cycle are affected differently by therapies, a precise description of the age distribution of the tumor cells can help develop effective strategies to limit their growth.

**Space homogeneous model.** There is an extensive literature (see for example [11]) devoted to space-homogeneous age-structured models such as (1.10). The long time asymptotic for (1.10) is a classical problem: This system has particular solutions of the form

$$n_\infty(\theta,t) = ce^{\lambda t}\varphi(\theta) \tag{3.2}$$

where $\varphi$ solves

$$\lambda\varphi + \varphi' = -\beta(\theta)\,\varphi - \mu(\theta)\varphi, \qquad \varphi(0) = 1$$

and $\lambda$ is determined by the condition

$$2\int_0^\infty \beta(\theta)\,\varphi(\theta)\,d\theta = 1.$$

The formula (3.2) shows that the parameter $\lambda$ characterizes the *exponential growth* of the tumor, while the function $\varphi$ describes the asymptotic age distribution of the cells. In particular, it can be proved (see [11]) that for any nonzero initial data, the solution of (1.10) satisfies:

$$\frac{n(\theta,t)}{\int_0^\infty n(\theta',t)d\theta'} \to \varphi(\theta) \qquad \text{as } t \to +\infty.$$

**Space-dependent model: Traveling wave solutions.** When pressure and space variable are taken into account, the asymptotic behavior of the solutions is very different. An important property of the reaction-diffusion equation (1.1) is the existence of traveling wave solutions and the finite speed of spreading (see for example [23, 22] and references therein for traveling wave solutions in the context of tumor growth). In particular, we recall that when $F(p) = p_M - p$, (1.1) admits solutions of the form $\bar{p}(x - ct)$ for all $c \geq c^*$ where the smallest speed $c^*$ is also the spreading speed of compactly supported solutions.

The existence of traveling wave solutions for the simple age-structured model

$$\begin{cases} \partial_t n + \partial_\theta n - \operatorname{div}_x(n\nabla_x p) = -\nu(\theta,p)\,n \\ n(x,0,t) = 2\displaystyle\int_0^\infty \nu(\theta,p)\,n(x,\theta,t)\,d\theta \end{cases} \tag{3.3}$$

with $\nu(\theta,p) = \beta(\theta)(p_M - p)$ can be observed numerically in dimension 1 as shown in Figure 5: After some initial transition time, the solution is asymptotically close to a traveling wave, which is a solution of (3.3) of the form $n(x,\theta,t) = \bar{n}(x-ct,\theta)$ where the corresponding pressure variable $\bar{p}(x)$ satisfies the boundary condition

$$\lim_{x\to-\infty} \bar{p}(x) = p_M, \qquad \lim_{x\to+\infty} \bar{p}(x) = 0. \tag{3.4}$$

A rigorous mathematical justification of this fact is the object of a forthcoming work [27]. This implies that the growth of the tumor is no longer exponential: The speed of the traveling wave characterizes the growth of the diameter of the tumor. In dimension 2, for example, this implies that the total mass of the tumor grows quadratically, a phenomenon that can be confirmed numerically (see Figure 6).

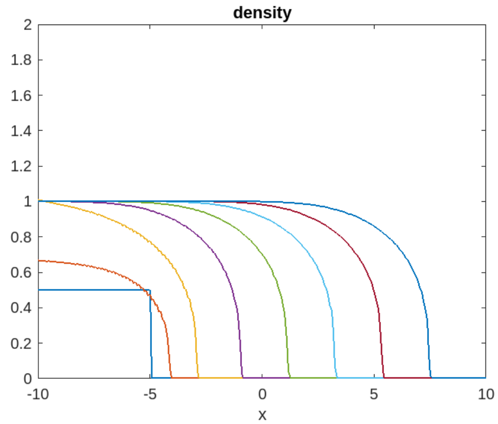


FIGURE 5. Development of a front propagating with constant speed: The figure shows the evolution of the one-dimensional density $\rho(x,t)$ starting from a characteristic function $\frac{1}{2}\chi_{x\leq -5}$ at time $t = 0$, 5, 10, 15, 20, 25, 30 and 35.

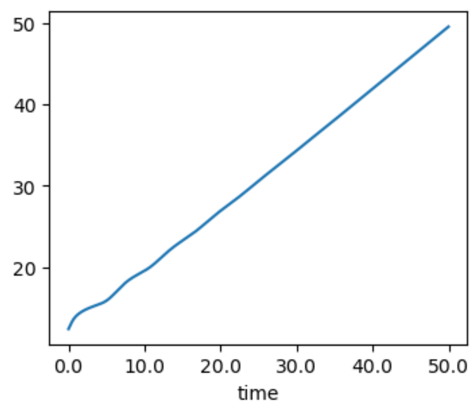


FIGURE 6. Growth of $\left(\int_\Omega \rho(x,t)\, dx\right)^{1/2}$ over time for a two dimensional tumor.

Focusing on the behavior of $n(x,\theta,t)$ for large $t$ we see numerically that the traveling wave solution satisfies

$$n(x,\theta,t) = \bar{n}(x - ct, \theta) \sim \phi(x + c(\theta - t)) \text{ as } t \to \infty \tag{3.5}$$

for fixed $x$ and $\theta$ and for some profile $\phi$. This observation is consistent with the equation since (3.3) implies $\partial_t n + \partial_\theta n = -c\partial_x \bar{n} + \partial_\theta \bar{n} \to 0$ as $x \to -\infty$. This can be explained as follows: As the tumor is spreading, the pressure at a given $x$ converge to $p_M$ when $t \to \infty$ so that both diffusion and proliferation become negligible. The asymptotic behavior (3.5) simply captures the aging of the cells.

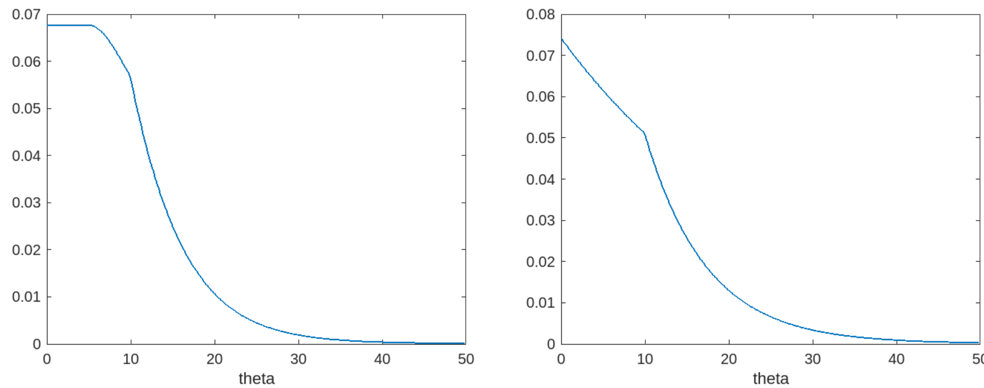


FIGURE 7. The function $\phi_\infty(\theta)$ when $\mu(\theta)$ is given by (3.7) and $\beta(\theta)$ is given by (3.1) (left) or $\beta(\theta) \equiv 1$ (right)

**Death rate: Expansion vs. Regression of the tumor.** The long time behavior of the solutions is quite different when we include the death rate $\mu(\theta)$ in the model:

$$\begin{cases} \partial_t n + \partial_\theta n - \operatorname{div}_x(n\nabla_x p) = -\nu(\theta,p)\, n - \mu(\theta) n \\ n(x,0,t) = 2\displaystyle\int_0^\infty \nu(\theta,p)\, n(x,\theta,t)\, d\theta. \end{cases} \tag{3.6}$$

First, we observe numerically that for large enough $\mu$, the tumor might shrink and eventually disappear ($\lim_{t\to\infty} n(t) = 0$), while for small $\mu$, a moving front with positive speed develops as in the case $\mu = 0$. We also note that traveling wave solutions cannot satisfy (3.4) when $\mu > 0$ since the right-hand side of (3.6) no longer vanishes for $p = p_M$. Finally, when the tumor spreads, numerical simulations show that there exists a unique profile $\phi_\infty(\theta)$ such that

$$n(x,\theta,t) \to \phi_\infty(\theta) \qquad \text{as } t \to \infty$$

for all $x \in \mathbb{R}^d$ (which is very different from the asymptotic behavior (3.5)). Examples of this profile $\phi_\infty(\theta)$ are shown in Figure 7 when $\mu$ is given by

$$\mu(\theta) = \begin{cases} 0 & \text{if } \theta < 10 \\ 0.1 & \text{if } \theta \geq 10 \end{cases} \tag{3.7}$$

and for two different choices of $\beta(\theta)$.

This behavior can be investigated analytically: Going back to (3.3) we see that the asymptotic profile $\phi_\infty(\theta)$ (if it exists) must solve

$$\begin{cases} \phi'(\theta) = -\nu(\theta,p_0)\phi(\theta) - \mu(\theta)\phi(\theta), & \theta > 0 \\ \phi(0) = 2\displaystyle\int_0^\infty \nu(\theta,p_0)\phi(\theta)\, d\theta \\ p_0 = \dfrac{m}{m-1}\left(\displaystyle\int_0^\infty V(\theta)\phi(\theta)\, d\theta\right)^{m-1} \end{cases} \tag{3.8}$$

and we can show the following result:

**Proposition 3.1.** *Assume that $m > 1$, that $\mu(\theta)$ satisfies $\int_0^\infty \mu(\theta)\,d\theta = \infty$ (every cell dies eventually) and that $\nu(\theta, p)$ satisfies (1.3). Then (3.8) has a unique positive solution $\phi_\infty(\theta)$ if and only if*

$$\int_0^\infty \mu(\theta) e^{-\int_0^\theta \nu(s,0)+\mu(s)\,ds}\,d\theta < \frac{1}{2}. \tag{3.9}$$

*Proof.* For a given $p_0$ the solutions of the first equation in (3.8) are given by

$$\phi(\theta) = \alpha e^{-\int_0^\theta \nu(s,p_0)+\mu(s)\,ds}$$

with $\alpha \in \mathbb{R}$. The second equation in (3.8) is then equivalent to

$$1 = 2\int_0^\infty \nu(\theta, p_0) e^{-\int_0^\theta \nu(s,p_0)+\mu(s)\,ds}\,d\theta \tag{3.10}$$

which is a condition on $p_0$. The non-degeneracy condition $\int_0^\infty \mu(\theta)\,d\theta = \infty$ implies

$$\int_0^\infty \nu(\theta, p_0) e^{-\int_0^\theta \nu(s,p_0)+\mu(s)\,ds}\,d\theta = 1 - \int_0^\infty \mu(\theta) e^{-\int_0^\theta \nu(s,p_0)+\mu(s)\,ds}\,d\theta$$

and so (3.10) is equivalent to

$$\int_0^\infty \mu(\theta) e^{-\int_0^\theta \nu(s,p_0)+\mu(s)\,ds}\,d\theta = \frac{1}{2}.$$

Under assumptions (1.3), the left-hand side is monotone increasing with respect to $p_0$ and equal to 1 when $p_0 = p_M$. The existence of a unique $p_0 \in (0, p_M)$ satisfying (3.10) is thus equivalent to the condition (3.9).

Under condition (3.9), the discussion above shows that there is a unique $p_0 \in (0, p_M)$ such that (3.10) holds. We deduce the existence of $\phi_\infty$ solution of (3.8) given by

$$\phi_\infty(\theta) = \alpha e^{-\int_0^\theta \nu(s,p_0)+\mu(s)\,ds}$$

where the constant $\alpha$ is determined by the last equation in (3.8). □

In view of this proposition, we conjecture that (3.9) identifies the threshold that characterizes the long time behavior (expansion vs. regression) of the tumor mass and that when (3.9) holds, the long time dynamic of the tumor will be described by traveling wave solutions of (3.3) which satisfy the boundary conditions

$$\lim_{x\to-\infty} \bar{p}(x) = p_0, \quad \lim_{x\to-\infty} \bar{n}(x,\theta) = \phi_\infty(\theta), \qquad \lim_{x\to+\infty} \bar{p}(x) = \lim_{x\to+\infty} \bar{n}(x,\theta) = 0.$$

When $\mu$ and $\nu(p) = \beta(p_M - p)$ are independent of $\theta$, condition (3.9) is equivalent to $\mu < \beta\, p_M$ which is indeed a necessary and sufficient condition for the growth of the tumor. This is easy to show since in that case the equation for the density reduces to

$$\partial_t \rho - \Delta \rho^m = \rho(\beta p_M - \mu - p).$$

When $\nu(p,\theta) = \beta(\theta)(p_M - p)$ with $\beta(\theta)$ given by (3.1), Figure (8) shows the evolution of the mass of the tumor for different values of $\mu$ (independent of $\theta$). The behavior is consistent with condition (3.9) which identifies $\mu = 0.1076$ as the threshold value when the death rate is constant.

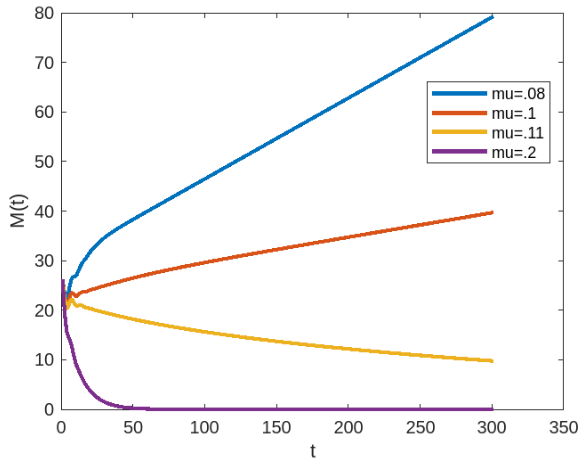


FIGURE 8. Evolution of the mass of the tumor when $\beta(\theta)$ is given by (3.1) and for different values of the death rate $\mu$. The first two values of $\mu$ are below the threshold $\mu = 0.1076$ determined by condition (3.9), while the last two values are above.

## 4. PROOF OF THEOREM 2.1

We now turn to the proof of Theorem 2.1. We will prove the existence of a solution for (1.2) in two steps: First we will show that the following regularized system

$$\begin{cases} \partial_t n + \partial_\theta n - \operatorname{div}_x(n\nabla_x p(\rho)) - \varepsilon\Delta_x n = -\nu(\theta,p)\, n & x\in\mathbb{R}^d,\ \theta>0,\ t>0 \\ n(x,0,t) = 2\displaystyle\int_0^\infty \nu(\theta,p)\, n(x,\theta,t)\, d\theta & x\in\mathbb{R}^d,\ \ t>0 \\ n(x,\theta,0) = n_{in}(x,\theta) & x\in\mathbb{R}^d,\ \theta>0. \end{cases} \tag{4.1}$$

has a solution for all $\varepsilon > 0$ where we recall that

$$p(\rho) = \frac{m}{m-1}\rho^{m-1}, \qquad \rho(x,t) = \int_0^\infty V(\theta) n(x,\theta,t)\, d\theta.$$

Then we will pass to the limit $\varepsilon \to 0$ to construct a solution of (1.2) and prove our main result.

4.1. **Existence of a solution for the regularized system** (4.1)**.** The existence of a solution for (4.1) will be proved by using a discrete time scheme which splits the transport in $\theta$ and the diffusion in $x$: We initialize the scheme by setting $n_0(x,\theta) = n_{in}(x,\theta)$ and for all $k \geq 0$, we proceed as follows:

**Step 1:** Given $n_k(x,\theta)$, define $n_{k+\frac12}(x,\theta)$ solution of

$$\begin{cases} n_{k+\frac12} - n_k + \tau\partial_\theta n_{k+\frac12} = -\tau\nu(\theta,p_k)\, n_{k+\frac12} & x\in\mathbb{R}^d,\ \theta>0 \\ n_{k+\frac12}(x,0) = 2\displaystyle\int_0^\infty \nu(\theta,p_k)\, n_k(x,\theta)\, d\theta & x\in\mathbb{R}^d. \end{cases} \tag{4.2}$$

where $p_k = p(\rho_k) = \frac{m}{m-1}\rho_k^{m-1}$ and $\rho_k(x) = \int_0^\infty V(\theta) n_k(x,\theta)\, d\theta$. Note that the space variable $x$ is a parameter in this equation.

**Step 2:** Then define $n_{k+1}(x,\theta,t)$ solution of

$$n_{k+1} - n_{k+\frac{1}{2}} - \tau \mathrm{div}_x(n_{k+1}\nabla_x p(\rho_{k+1})) - \varepsilon\tau\Delta n_{k+1} = 0 \qquad x\in\mathbb{R}^d,\ \theta>0. \tag{4.3}$$

Note that the age variable $\theta$ is a parameter in this equation.

This iterative scheme defines $n_k(x,\theta)$ for all $k\in\mathbb{N}$. We then define $n_\tau(x,\theta,t)$ piecewise constant function in $t$ by

$$n_\tau(x,\theta,t) = n_k(x,\theta), \qquad t\in[k\tau,(k+1)\tau) \tag{4.4}$$

and

$$\rho_\tau(x,t) = \int_0^\infty V(\theta) n_\tau(x,\theta,t)\,d\theta.$$

We also define the piecewise linear function $\widetilde{n}_\tau(x,\theta,t)$ which satisfies $\widetilde{n}_\tau(x,\theta,k\tau) = n_k(x,\theta)$:

$$\widetilde{n}_\tau(x,\theta,t) = \left(\frac{(k+1)\tau - t}{\tau}\right) n_k(x,\theta) + \left(\frac{t-k\tau}{\tau}\right) n_{k+1}(x,\theta), \qquad t\in[k\tau,(k+1)\tau) \tag{4.5}$$

and the corresponding volume density

$$\widetilde{\rho}_\tau(x,t) = \int_0^\infty \widetilde{n}_\tau(x,\theta,t)\,d\theta.$$

The well-posedness of the scheme (i.e. the existence and uniqueness of a solution to (4.2) and (4.3)) will be proved below. We then note that by combining (4.2) and (4.3), we find

$$\begin{cases} \frac{n_{k+1}-n_k}{\tau} + \partial_\theta n_{k+\frac{1}{2}} - \mathrm{div}_x(n_{k+1}\nabla_x p(\rho_{k+1})) - \varepsilon\Delta n_{k+1} = -\nu(\theta,p(\rho_k))\,n_{k+\frac{1}{2}} & x\in\mathbb{R}^d\ \theta>0\\ n_{k+\frac{1}{2}}(x,0) = 2\int_0^\infty \nu(\theta,p(\rho_k))\,n_k(x,\theta)\,d\theta & x\in\mathbb{R}^d. \end{cases} \tag{4.6}$$

Our goal is then to derive appropriate bounds on $n_k,\rho_k$ and on the interpolations $n_\tau$, $\rho_\tau$ and $\tilde{\rho}_\tau$ in order to pass to the limit $\tau\to 0$ in (4.6)

### 4.2. Iterative scheme: Existence and estimates from $n_k$, $\rho_k$.

**Proposition 4.1** (Well-posedness of Step 1). *Given $n_k(x,\theta)$ non-negative function in $L^1(\mathbb{R}^d\times(0,\infty))$, there exists $n_{k+\frac{1}{2}}(x,\theta)$ solution of* (4.2)*. Furthermore, the volume density satisfies*

$$\rho_{k+\frac{1}{2}}(x) \le \frac{1+C\tau}{1-C\tau}\rho_k(x) \qquad \forall x\in\mathbb{R}^d \tag{4.7}$$

$$|\rho_{k+\frac{1}{2}}(x) - \rho_k(x)| \le C\tau\rho_k(x) \qquad \forall x\in\mathbb{R}^d \tag{4.8}$$

*for some constant $C$ independent of $k$ and $\tau$ and for all $\tau>0$ small enough. Finally, we also have*

$$\int \varphi(\theta)[n_{k+\frac{1}{2}}(x,\theta) - n_k(x,\theta)\,d\theta| \le C\|\varphi'(\theta)\|\rho_k(x)\tau \qquad \forall x\in\mathbb{R}^d. \tag{4.9}$$

*Proof.* We rewrite (4.2) as

$$\begin{cases} (1+\tau\nu(\theta,p_k))n_{k+\frac12} + \tau\partial_\theta n_{k+\frac12} = n_k & \theta>0 \\ n_{k+\frac12}(x,0) = 2\displaystyle\int_0^\infty \nu(\theta,p_k)\, n_k(x,\theta)\, d\theta. \end{cases}$$

This equation can be solved explicitly: With $A(\theta) = \int_0^\theta 1+\tau\nu(\theta',p_k)\,d\theta' \geq \theta$, the unique solution of (4.2) is given by:

$$n_{k+\frac12}(x,\theta) = 2e^{-\frac{1}{\tau}A(\theta)}\int_0^\infty \nu(\theta',p_k)\, n_k(x,\theta')\,d\theta' + \frac{1}{\tau}\int_0^\theta e^{-\frac{1}{\tau}[A(\theta)-A(\theta')]} n_k(x,\theta')\,d\theta'.$$

Multiplying the equation (4.2) by $V(\theta)$ and integrating with respect to $\theta$, we get the following relation (using (2.3)):

$$\begin{aligned} \rho_{k+\frac12}(x)-\rho_k(x) &= \tau\left[\int_0^\infty \nu(\theta,p_k)2V(0)n_k(x,\theta)\,d\theta - \int_0^\infty \nu(\theta,p_k)V(\theta)n_{k+\frac12}(x,\theta)\,d\theta \right. \\ &\quad \left. + \int_0^\infty V'(\theta)n_{k+\frac12}(x,\theta)\,d\theta\right] \qquad (4.10) \\ &\leq C\tau[\rho_k+\rho_{k+\frac12}] \qquad (4.11) \end{aligned}$$

which yields first (4.7) and then (4.8). Multiplying the equation (4.2) by $\varphi(\theta)$ and integrating with respect to $\theta$ also gives (4.9). □

**Proposition 4.2** (Well posedness of Step 2)**.** *Given $n_{k+\frac12}$ non-negative function in $L^1(\mathbb{R}^d\times(0,\infty))\cap L^\infty(\mathbb{R}^d;L^1((0,\infty))$, there exists a non-negative function $n_{k+1}\in L^1(\mathbb{R}^d\times(0,\infty))\cap L^\infty(\mathbb{R}^d;L^1((0,\infty))$ solution of (4.3). Furthermore the density satisfies:*

(4.12)
$$\int_{\mathbb{R}^d}\rho_{k+1}^q\,dx + \frac{4q(q-1)}{(m+q-1)^2}\tau\int_{\mathbb{R}^d}\left|\nabla(\rho_{k+1}^{\frac{m+q-1}{2}})\right|^2 dx + \varepsilon\tau\frac{4(q-1)}{q^2}\int_{\mathbb{R}^d}\left|\nabla\rho_{k+1}^{\frac{q}{2}}\right|^2 dx \leq \int_{\mathbb{R}^d}\rho_{k+\frac12}^q\,dx$$

*for all $q\in[1,\infty)$ and*

$$\|\rho_{k+1}\|_{L^\infty(\mathbb{R}^d)} \leq \|\rho_k\|_{L^\infty(\mathbb{R}^d)}. \qquad (4.13)$$

*Proof.* In order to prove that a solution exists, we first notice that by multiplying (4.3) by $V(\theta)$ and integrating with respect to $\theta$, we get

$$\rho_{k+1} - \tau\mathrm{div}_x(\rho_{k+1}\nabla_x p(\rho_{k+1})) - \tau\varepsilon\Delta\rho_{k+1} = \rho_{k+\frac12} \qquad x\in\mathbb{R}^d, \qquad (4.14)$$

which is a classical nonlinear elliptic equation (recall that $p(\rho)=\frac{m}{m-1}\rho^{m-1}$). Given $\rho_{k+\frac12}\in L^1\cap L^\infty(\mathbb{R}^d)$, this equation has a unique solution with $\rho_{k+1}\in L^1\cap L^\infty(\mathbb{R}^d)$. We then define $n_{k+1}(x,\theta)$ the solution of (4.3) with $p(\rho_{k+1}(x))$ given by the solution of (4.14). This solution exists: indeed, $\theta$ is a parameter in this equation, so we only need to solve this equation for a fixed $\theta\geq 0$, and when $\varepsilon>0$, the solution $\rho_{k+1}$ of (4.14) is smooth, so the advection term $\nabla_x p(\rho_\varepsilon)$ is smooth and the existence of a solution is straightforward.

Since we first found $\rho_{k+1}(x)$ and then $n_{k+1}(x,\theta)$, we need to make sure that $\int_0^\infty V(\theta)n_{k+1}(\cdot,\theta)\,d\theta = \rho_{k+1}$ in order to show that $n_k(x)$ solves (4.3). For that we note that the function $u(x) = \rho_{k+1}(x) - \int_0^\infty V(\theta)n_{k+1}(x,\theta)\,d\theta$ solves

$$u - \mathrm{div}\,(u\nabla p(\rho_{k+1})) - \varepsilon\Delta u = 0.$$

In order to prove that $u=0$, we take $\beta_\delta(s) = \sqrt{s^2+\delta^2} - \delta$ and multiply this equation by $\beta_\delta'(u)$ to find:

$$\begin{aligned}\int u\beta_\delta'(u)\,dx &= -\varepsilon\int \beta_\delta''|\nabla u|^2\,dx - \int u\beta_\delta'(u)\nabla p(\rho_{k+1})\cdot\nabla u\,dx\\ &\le -\int \nabla p(\rho_{k+1})\cdot\nabla(u\beta_\delta'(u)-\beta_\delta(u))\,dx\\ &\le \int \Delta p(\rho_{k+1})(u\beta_\delta'(u)-\beta_\delta(u))\,dx\end{aligned}$$

Since $|s\beta_\delta'(s)-\beta_\delta(s)|\le\delta$ and $s\beta_\delta'(s)\to|s|$ with $s\beta_\delta'(s)\le|s|$, we deduce $\int|u|\,dx\le 0$, that is, $u=0$ and so

$$\int_0^\infty V(\theta)n_{k+1}(x,\theta)\,d\theta = \rho_{k+1}(x), \qquad \text{a.e. } x\in\mathbb{R}^d$$

thus proving that $n_k(x)$ is the solution of (4.3).

Next we derive (4.12): we multiply (4.14) by $\rho_{k+1}^{q-1}$ (for $q>1$) and integrate in $x$ to get:

$$\int_{\mathbb{R}^d}\rho_{k+1}^q\,dx - \tau\rho_{k+1}^{q-1}\mathrm{div}\,(\rho_{k+1}\nabla p_{k+1})\,dx - \tau\varepsilon\int_{\mathbb{R}^d}\rho_{k+1}^{q-1}\Delta\rho_{k+1}\,dx = \int_{\mathbb{R}^d}\rho_{k+\frac12}\rho_{k+1}^{q-1}\,dx.$$

Rearranging, and using the convexity of the function $s\mapsto s^q$ for any $q>1$ and $s\ge 0$, we deduce:

$$\begin{aligned}\tau q(q-1)\int_{\mathbb{R}^d}\rho_{k+1}^{m+q-3}|\nabla\rho_{k+1}|^2\,dx + \tau\varepsilon(q-1)\int_{\mathbb{R}^d}\rho_{k+1}^{q-2}|\nabla\rho_{k+1}|^2\,dx &= \int_{\mathbb{R}^d}\rho_{k+1}^{q-1}(\rho_{k+\frac12}-\rho_{k+1})\,dx\\ &\le \int_{\mathbb{R}^d}\frac1q\rho_{k+\frac12}^q - \frac1q\rho_{k+1}^q\,dx.\end{aligned}$$

which implies (4.12). To get (4.13), we can apply the maximum principle to (4.14) or pass to the limit $q\to\infty$ in the inequality $\|\rho_{k+1}\|_{L^q(\mathbb{R}^d)}\le\|\rho_k\|_{L^q(\mathbb{R}^d)}$. □

4.3. **Estimates for $n_\tau$ and $\rho_\tau$.** We recall that once the $n_k$ and $\rho_k$ have been iteratively constructed, we can define the piecewise constant functions $n_\tau(x,\theta,t)$ and $\rho_\tau(x,t)$ and the piecewise linear interpolations $\widetilde{n}_\tau(x,\theta,t)$, $\widetilde{\rho}_\tau(x,t)$ (see (4.4) and (4.5)). In what follows, we fix $T=K\tau>0$. We start with the following straightforward consequence of Propositions 4.1 and 4.2:

**Proposition 4.3.** *There exists $C$ such that if $\tau\le\frac1C$, then $\rho_\tau\ge0$ is bounded in $L^\infty(0,T;L^q(\mathbb{R}^d))$ for all $q\in[1,\infty]$ uniformly with respect to $\tau$.*

*Furthermore, for all $q\in(1,\infty)$, there exists $C_q$ such that if $\tau\le\frac{1}{C_q}$, then*

$$\|\nabla\rho_\tau^{\frac{m+q-1}{2}}\|^2_{L^2(0,T;L^2(\mathbb{R}^d))} + \varepsilon\|\nabla\rho_\tau^{\frac q2}\|^2_{L^2(0,T;L^2(\mathbb{R}^d))}\le C_q \tag{4.15}$$

*Proof.* Combining (4.12) with (4.7) yields

$$\begin{aligned}\int_{\mathbb{R}^d} \rho_{k+1}^q \, dx + \frac{4q(q-1)}{(m+q-1)^2}\tau \int_{\mathbb{R}^d} |\nabla(\rho_{k+1}^{\frac{m+q-1}{2}})|^2 \, dx \\ + \varepsilon\tau \frac{4(q-1)}{q^2}\int_{\mathbb{R}^d} |\nabla \rho_{k+1}^{\frac{q}{2}}|^2 \, dx \le \left(\frac{1+C\tau}{1-C\tau}\right)^q \int_{\mathbb{R}^d} \rho_k^q \, dx.\end{aligned} \tag{4.16}$$

Similarly, combining (4.13) with (4.7) yields:

$$\|\rho_{k+1}\|_{L^\infty(\mathbb{R}^d)} \le \frac{1+C\tau}{1-C\tau}\|\rho_k\|_{L^\infty(\mathbb{R}^d)}. \tag{4.17}$$

Using the fact that $\frac{1+x}{1-x} \le 1+4x$ when $x \in [0,1/2]$, and iterating (4.17), we get

$$\|\rho_K\|_{L^\infty(\mathbb{R}^d)} \le (1+4C\tau)^K \|\rho_0\|_{L^\infty(\mathbb{R}^d)} \le e^{4CK\tau}\|\rho_0\|_{L^\infty(\mathbb{R}^d)}$$

as long as $\tau < \frac{1}{2C}$. Similarly, (4.16) gives

$$\|\rho_K\|_{L^q(\mathbb{R}^d)} \le (1+4C\tau)^K \|\rho_0\|_{L^q(\mathbb{R}^d)} \le e^{4CK\tau}\|\rho_0\|_{L^q(\mathbb{R}^d)}.$$

These inequalities imply the first statement.

Next, we can rewrite (4.16) as

$$\begin{aligned}\int_{\mathbb{R}^d} \rho_{k+1}^q \, dx + \frac{4q(q-1)}{(m+q-1)^2}\tau \int_{\mathbb{R}^d} |\nabla(\rho_{k+1}^{\frac{m+q-1}{2}})|^2 \, dx + \varepsilon\tau\frac{4(q-1)}{q^2}\int_{\mathbb{R}^d} |\nabla \rho_{k+1}^{\frac{q}{2}}|^2 \, dx \\ \le \int_{\mathbb{R}^d} \rho_k^q \, dx + \left[\left(\frac{1+C\tau}{1-C\tau}\right)^q - 1\right]\int_{\mathbb{R}^d} \rho_k^q \, dx \\ \le \int_{\mathbb{R}^d} \rho_k^q \, dx + C_q\tau\int_{\mathbb{R}^d} \rho_k^q \, dx\end{aligned}$$

as long as $C_q\tau \le 1$ for some constant $C_q$ depending on $q$. Summing up for $k = 0, \dots K$, we deduce:

$$\begin{aligned}\frac{4q(q-1)}{(m+q-1)^2}\sum_{k=0}^K \tau \int_{\mathbb{R}^d} |\nabla(\rho_{k+1}^{\frac{m+q-1}{2}})|^2 \, dx \\ + \varepsilon\frac{4(q-1)}{q^2}\sum_{k=0}^K \tau\int_{\mathbb{R}^d} |\nabla\rho_{k+1}^{\frac{q}{2}}|^2 \, dx \le \left(1 + C_qK\tau e^{4qCK\tau}\right)\|\rho_0\|_{L^q(\mathbb{R}^d)}^q\end{aligned}$$

which implies (4.15). □

Next, we prove the following result, which will be used to control the values of $n_\tau$ at infinity (in $x$ and $\theta$):

**Proposition 4.4.** *There exists a constant $C$ such that if $\tau \le \frac{1}{C}$, then*

$$\sup_{t\in[0,T]} \int_{\mathbb{R}^d}\int_0^\infty (|x|^2+\theta) n_\tau(x,\theta,t) \, d\theta \, dx \le C \tag{4.18}$$

*with $C$ dependent on $T$ by not on $\tau$.*

*Proof.* Multiplying (4.2) by $(|x|^2+\theta)\geq 0$ and integrating in $x$ and $\theta$ gives

$$
\begin{aligned}
\int_0^\infty \int_{\mathbb{R}^d} (|x|^2+\theta) n_{k+\frac12}\,dx\,d\theta
&\leq -\tau \int_0^\infty \int_{\mathbb{R}^d} \partial_\theta n_{k+\frac12}(|x|^2+\theta)\,dx\,d\theta + \int_0^\infty \int_{\mathbb{R}^d} (|x|^2+\theta) n_k\,dx\,d\theta \\
&\leq \tau \int_0^\infty \int_{\mathbb{R}^d} n_{k+\frac12}\,dx\,d\theta + \tau \int_{\mathbb{R}^d} n_{k+\frac12}(x,0)|x|^2\,dx + \int_0^\infty \int_{\mathbb{R}^d} (|x|^2+\theta) n_k\,dx\,d\theta \\
&\leq \tau \int_{\mathbb{R}^d} \rho_{k+\frac12}\,dx + \tau \int_{\mathbb{R}^d} 2\int_0^\infty \nu(\theta,p_k) n_k(x,\theta)|x|^2\,d\theta\,dx + \int_0^\infty \int_{\mathbb{R}^d} (|x|^2+\theta) n_k\,dx\,d\theta \\
&\leq \tau \int_{\mathbb{R}^d} \rho_{k+\frac12}\,dx + (1+C\tau)\int_0^\infty \int_{\mathbb{R}^d} (|x|^2+\theta) n_k\,dx\,d\theta.
\end{aligned}
\tag{4.19}
$$

Similarly, (4.3) yields:

$$\int_0^\infty \int_{\mathbb{R}^d} (|x|^2+\theta) n_{k+1}\,dx\,d\theta = \int_0^\infty \int_{\mathbb{R}^d} (|x|^2+\theta) n_{k+\frac12}\,dx\,d\theta + 2d\tau \int_{\mathbb{R}^d} \rho_{k+1}^m + \varepsilon \rho_{k+1}\,dx.$$

Combining these inequalities give:

$$\int_0^\infty \int_{\mathbb{R}^d} (|x|^2+\theta) n_{k+1}\,dx\,d\theta \leq (1+C\tau)\int_0^\infty \int_{\mathbb{R}^d} (|x|^2+\theta) n_k\,dx\,d\theta + C\tau \int_{\mathbb{R}^d} \rho_{k+\frac12} + \rho_{k+1}^m + \varepsilon\rho_{k+1}\,dx$$

and the bounds from Proposition 4.3 (together with (4.7) to control $\rho_{k+\frac12}$) implies

$$\int_0^\infty \int_{\mathbb{R}^d} (|x|^2+\theta) n_{k+1}\,dx\,d\theta \leq (1+C\tau)\int_0^\infty \int_{\mathbb{R}^d} (|x|^2+\theta) n_k\,dx\,d\theta + C(T)\tau$$

for all $k\leq K$ (with $K\tau = T$). which implies

$$\int_0^\infty \int_{\mathbb{R}^d} (|x|^2+\theta) n_k\,dx\,d\theta \leq (1+C\tau)^k \int_0^\infty \int_{\mathbb{R}^d} (|x|^2+\theta) n_{in}\,dx + C(T)(1+C\tau)^{k+1} \leq C(1+C\tau)^k \tag{4.20}$$

and the result follows.

□

Finally, we note that while $\rho_\tau$ is bounded in $L^\infty(0,T;L^p(\mathbb{R}^d))$ for $p\in[1,\infty]$, we only have $n_\tau$ bounded in $L^\infty(0,T;L^1(\mathbb{R}^d\times(0,\infty)))$. In order to show that we do not get a measure (in $\theta$) in the limit $\tau\to 0$, we will make use of the following result:

**Proposition 4.5.** *The piecewise constant function $n_\tau\geq 0$ is bounded in $L^\infty(0,T;L^1(\mathbb{R}^d\times(0,\infty)))$ and satisfies:*

$$\sup_{t\in(0,T)} \int_{\mathbb{R}^d}\int_0^\infty n_\tau(x,\theta,t)\log_+ n_\tau(x,\theta,t)\,d\theta\,dx \leq C \tag{4.21}$$

*for some constant depending only on $T$ and the initial condition.*

This proposition follows from the following Lemma which we prove below:

**Lemma 4.6.** *There exists a constant $C$ such that*

(4.22)
$$\int_{\mathbb{R}^d}\int_0^\infty n_{k+1}(x,\theta)\log(n_{k+1}(x,\theta))V(\theta)\,d\theta\,dx + \frac{4\tau}{m}\int_{\mathbb{R}^d}|\nabla(\rho_{k+1})^{m/2}(x)|^2\,dx \leq (1+C\tau)\int_{\mathbb{R}^d}\int_0^\infty n_k(x,\theta)\log(n_k(x,\theta))V(\theta)\,d\theta\,dx + C\tau(1+C\tau)^k.$$

Note that inequality (4.22) also yields a bound on $\nabla\rho_\tau^{m/2}$. We did not include this estimate in Proposition 4.5 since we will not be using it.

*Proof of Proposition 4.5.* Iterating (4.22), we get:
$$\int_{\mathbb{R}^d}\int_0^\infty n_k(x,\theta)\log(n_k(x,\theta))V(\theta)\,d\theta\,dx \leq (1+C\tau)^k\int_{\mathbb{R}^d}\int_0^\infty n_{in}(x,\theta)\log(n_{in}(x,\theta))V(\theta)\,d\theta\,dx + Ck\tau(1+C\tau)^k.$$

Recalling that $k\tau = T$, we deduce
$$\sup_{k=1,\dots,K}\int_{\mathbb{R}^d}\int_0^\infty n_k(x,\theta)\log(n_k(x,\theta))V(\theta)\,d\theta\,dx \leq e^{CT}\int_{\mathbb{R}^d}\int_0^\infty n_{in}(x,\theta)\log(n_{in}(x,\theta))V(\theta)\,d\theta\,dx + CTe^{CT}.$$

Next, we recall the classical inequality $|s\log s|\chi_{0\leq s\leq 1} \leq s\omega + Ce^{-\omega/2}$ (for all $\omega$) with $\omega = \theta + |x|^2$. We deduce:
$$\int_{\mathbb{R}^d}\int_0^\infty n_\tau \log_+(n_\tau)V(\theta)\,d\theta\,dx \leq \int_{\mathbb{R}^d}\int_0^\infty n_\tau\log(n_\tau)V(\theta)\,d\theta\,dx + \int_{\mathbb{R}^d}\int_0^\infty \left((\theta+|x|^2)n_\tau + Ce^{-(\theta+|x|^2)/2}\right)V(\theta)\,d\theta\,dx$$
and so (4.18) implies
$$\int_{\mathbb{R}^d}\int_0^\infty n_\tau\log_+(n_\tau)V(\theta)\,d\theta\,dx \leq \int_{\mathbb{R}^d}\int_0^\infty n_\tau\log(n_\tau)V(\theta)\,d\theta\,dx + C(T) \tag{4.23}$$
for all $t\in[0,T]$ and the result follows.

□

*Proof of Lemma 4.6.* Multiplying (4.3) by $V(\theta)(\log(n_{k+1})+1)$ and integrating with respect to $\theta$ and $x$ yields:
$$\int_{\mathbb{R}^d}\int_0^\infty (n_{k+1}-n_{k+\frac{1}{2}})(\log(n_{k+1})+1)V(\theta)\,d\theta\,dx + \tau\int_{\mathbb{R}^d}\nabla p(\rho_{k+1})\cdot\nabla\rho_{k+1}\,dx = 0$$
and so the convexity of $s\mapsto s\log s$ and the definition of $p(\rho)$ gives

(4.24)
$$\int_{\mathbb{R}^d}\int_0^\infty n_{k+1}\log(n_{k+1})V(\theta)\,d\theta\,dx + \frac{4\tau}{m}\int_{\mathbb{R}^d}|\nabla(\rho_{k+1})^{m/2}|^2\,dx \leq \int_{\mathbb{R}^d}\int_0^\infty n_{k+\frac{1}{2}}\log(n_{k+\frac{1}{2}})\,V(\theta)d\theta\,dx$$

Similarly, multiplying (4.2) by $V(\theta)(\log(n_{k+\frac{1}{2}})+1)$, we get

$$\begin{aligned}
&\int_{\mathbb{R}^d}\int_0^\infty (n_{k+\frac{1}{2}}-n_k)(\log(n_{k+\frac{1}{2}})+1)V(\theta)\,d\theta\,dx\\
&\quad= -\tau\int_{\mathbb{R}^d}\int_0^\infty \partial_\theta(n_{k+\frac{1}{2}}\log(n_{k+\frac{1}{2}}))V(\theta)\,d\theta\,dx-\tau\int_{\mathbb{R}^d}\int_0^\infty \nu(\theta,p_k)\,n_{k+\frac{1}{2}}(\log(n_{k+\frac{1}{2}})+1)V(\theta)\,d\theta\,dx\\
&\quad\le \tau\int_{\mathbb{R}^d} n_{k+\frac{1}{2}}(x,0)\log(n_{k+\frac{1}{2}}(x,0))V(0)\,dx+\tau\int_{\mathbb{R}^d}\int_0^\infty (n_{k+\frac{1}{2}}\log(n_{k+\frac{1}{2}}))V'(\theta)\,d\theta\,dx\\
&\qquad -\tau\int_{\mathbb{R}^d}\int_0^\infty \nu(\theta,p_k)\,n_{k+\frac{1}{2}}\log(n_{k+\frac{1}{2}})V(\theta)\,d\theta\,dx.
\end{aligned}$$

Using the convexity of $s\mapsto s\log s$ again, we deduce

$$\begin{aligned}
\int_{\mathbb{R}^d}\int_0^\infty n_{k+\frac{1}{2}}\log(n_{k+\frac{1}{2}})V(\theta)\,d\theta\,dx&-\int_{\mathbb{R}^d}\int_0^\infty n_k\log(n_k)V(\theta)\,d\theta\,dx\\
&\le \tau\int_{\mathbb{R}^d} n_{k+\frac{1}{2}}(x,0)\log_+(n_{k+\frac{1}{2}}(x,0))V(0)\,dx\\
&\quad+\tau\int_{\mathbb{R}^d}\int_0^\infty (n_{k+\frac{1}{2}}\log(n_{k+\frac{1}{2}}))[V'(\theta)-\nu(\theta,p_k)V(\theta)]\,d\theta\,dx.
\end{aligned}$$

The first term can be bounded using the monotonicity of $s\mapsto s\log_+ s$ and the fact that $n_{k+\frac{1}{2}}(x,0)\le C\rho_k(x)$ which is bounded in $L^1\cap L^\infty(\mathbb{R}^d)$ (by a constant depending only on $T$). For the second term, we use the fact that $|V'(\theta)-\nu(\theta,p_k)V(\theta)|\le CV(\theta)$ and get:

$$\begin{aligned}
\int_{\mathbb{R}^d}\int_0^\infty n_{k+\frac{1}{2}}\log(n_{k+\frac{1}{2}})V(\theta)\,d\theta\,dx&-\int_{\mathbb{R}^d}\int_0^\infty n_k\log(n_k)V(\theta)\,d\theta\,dx\\
&\le C\tau+C\tau\int_{\mathbb{R}^d}\int_0^\infty \left|n_{k+\frac{1}{2}}\log(n_{k+\frac{1}{2}}))\right|V(\theta)\,d\theta\,dx
\end{aligned}$$

and we can proceed as in (4.23) (we combine (4.19) and (4.20) to get the required bound on the moments of $n_{k+\frac{1}{2}}$) to get:

$$\begin{aligned}
\int_{\mathbb{R}^d}\int_0^\infty n_{k+\frac{1}{2}}\log(n_{k+\frac{1}{2}})V(\theta)\,d\theta\,dx&-\int_{\mathbb{R}^d}\int_0^\infty n_k\log(n_k)V(\theta)\,d\theta\,dx\\
&\le C\tau+C\tau\int_{\mathbb{R}^d}\int_0^\infty (n_{k+\frac{1}{2}}\log(n_{k+\frac{1}{2}}))V(\theta)\,d\theta\,dx+C\tau(1+C\tau)^k.
\end{aligned}\tag{4.25}$$

which implies (assuming $\tau$ is small enough so that $C\tau<1/2$ and $\frac{1}{1-C\tau}\le(1+C\tau)$):

$$\int_{\mathbb{R}^d}\int_0^\infty n_{k+\frac{1}{2}}\log(n_{k+\frac{1}{2}})V(\theta)\,d\theta\,dx\le(1+C\tau)\int_{\mathbb{R}^d}\int_0^\infty n_k\log(n_k)V(\theta)\,d\theta\,dx+C\tau(1+C\tau)^k.\tag{4.26}$$

We combine this inequality with (4.24) to get (4.22). □

4.4. **Weak convergence of $n_\tau$ and strong convergence of $\rho_\tau$ as $\tau \to 0$.** Since $n_\tau$ is bounded in $L^\infty(0,T;L^1(\mathbb{R}^d \times (0,\infty))$, Propositions 4.4 implies that it converges up to a subsequence for the narrow topology to $n \in L^\infty(0,T;\mathcal{M}(\mathbb{R}^d \times (0,\infty))$. From now on, we thus fix a subsequence (still denoted $n_\tau$ for simplicity) such that

$$\int_0^T \int_{\mathbb{R}^d} \int_0^\infty n_\tau(x,\theta,t)\psi(x,\theta,t)\,d\theta\,dx\,dt \to \int_0^T \int_{\mathbb{R}^d} \int_0^\infty n(x,\theta,t)\psi(t,x,\theta)\,d\theta\,dx\,dt \tag{4.27}$$

for all $\psi \in C_b^0([0,T]\times\mathbb{R}^d\times(0,\infty))$. Furthermore 4.5 and Dunford Pettis theorem imply that $n \in L^\infty(0,T;L^1(\mathbb{R}^d\times(0,\infty))$ and that the limit (4.27) holds for function $\psi \in L^\infty([0,T]\times\mathbb{R}^d\times(0,\infty))$. If we take $\psi(x,\theta,t) = V(\theta)\phi(x,t)$ in (4.27), we deduce (along the same subsequence)

$$\rho_\tau(x,t) \rightharpoonup \rho(x,t) = \int_0^\infty n(x,\theta,t)V(\theta)\,d\theta.$$

In order to pass to the limit $\tau \to 0$ and derive (4.1), we need to establish the strong convergence of $\rho_\tau$ and $\nabla\rho_\tau^{m-1}$. A key ingredient for that is the following equation for $\rho_k$, which we obtain by combining (4.10) and (4.14):

$$\rho_{k+1} - \rho_k - \tau \mathrm{div}_x(\rho_{k+1}\nabla_x p(\rho_{k+1})) - \tau\varepsilon\Delta\rho_{k+1} = \tau F_k \tag{4.28}$$

where

$$F_k(x) = \int_0^\infty \nu(\theta,p_k)2V(0)n_k(x,\theta)\,d\theta - \int_0^\infty \nu(\theta,p_k)V(\theta)n_{k+\frac12}(x,\theta)\,d\theta + \int_0^\infty V'(\theta)n_{k+\frac12}(x,\theta)\,d\theta.$$

We have

$$|F_k(x)| \le C\rho_k(x) + C\rho_{k+\frac12}(x)$$

and so $F_\tau$ is bounded in $L^\infty(0,T;L^1\cap L^\infty(\mathbb{R}^d))$. We will deduce the following proposition:

**Proposition 4.7.** *Up to another subsequence $\rho_\tau(x,t)$ converges strongly to $\rho(x,t)$ in $L^2(0,T;L^2(\mathbb{R}^d))$ and almost everywhere in $[0,T]\times\mathbb{R}^d$.*

*Proof.* First, we will prove the convergence of the piecewise linear function $\tilde\rho_\tau(t)$: The bound (4.15) with $q=2$ gives

$$\varepsilon\|\nabla\rho_\tau\|_{L^2(0,T;L^2(\mathbb{R}^d))} \le C$$

(this bound is the main reason we added the regularization $\varepsilon\Delta n$). Since $\tilde\rho_\tau$ is the linear interpolation with the same value as $\rho_\tau$, it is easy to check that we also have

$$\varepsilon\|\nabla\tilde\rho_\tau\|_{L^2(0,T;L^2(\mathbb{R}^d)} \le C.$$

Furthermore, we have

$$\partial_t\tilde\rho_\tau = \frac{\rho_{k+1}-\rho_k}{\tau} = \mathrm{div}_x(\rho_{k+1}\nabla_x p(\rho_{k+1})) + \varepsilon\Delta\rho_{k+1} + \tau F_k \qquad \text{for } t \in (k\tau,(k+1)\tau)$$

and so

$$\|\partial_t\tilde\rho_\tau\|_{L^2(0,T;H^{-1}(\Omega))} \le C.$$

Together with the bound on $\int_{\mathbb{R}}^d |x|^2\tilde\rho_\tau\,dx$ (see Proposition 4.4), we have all we need to apply Aubin-Lions and show that $\{\tilde\rho_\tau\}_{\tau>0}$ is pre-compact in $L^2(0,T;L^2(\mathbb{R}^d))$: There exists $\rho \in L^2(0,T;H^1(\mathbb{R}^d))$ such that $\tilde\rho_\tau$ converges (up to a subsequence) to $\rho$ strongly in $L^2(0,T;L^2(\mathbb{R}^d))$.

Finally, note that for $t \in [k\tau, (k+1)\tau)$, we have

$$\begin{aligned}\rho_\tau(x,t) - \tilde\rho_\tau(x,t) &= \frac{t-k\tau}{\tau}(\rho_{k+1}-\rho_k) \\ &= (t-k\tau)[\operatorname{div}_x(\rho_{k+1}\nabla_x p(\rho_{k+1})) + \varepsilon\Delta\rho_{k+1} + F_k\end{aligned}$$

and so

$$\|\rho_\tau - \tilde\rho_\tau\|_{L^2(0,T;H^{-1}(\mathbb{R}^d))} \le C\tau$$

It follows that $\rho_\tau$ converges to $\rho$ in $L^2(0,T;H^{-1}(\mathbb{R}^d))$ and since $\rho_\tau$ is bounded in $L^2(0,T;H^1(\mathbb{R}^d))$, it also converges strongly in $L^2(0,T;L^2(\mathbb{R}^d))$.

□

Finally, since $\rho_\tau$ is bounded in $L^\infty(0,T,L^\infty(\mathbb{R}^d))$, we deduce the convergence of the pressure $p_\tau = \frac{m}{m-1}\rho_\tau^{m-1}$:

**Corollary 4.8.** *Along the same subsequence as above, $\rho_\tau$ converges to $\rho$ strongly in $L^p((0,T)\times\mathbb{R}^d)$ and so $p_\tau(x,t) = \frac{m}{m-1}\rho_\tau(x,t)^{m-1}$ converges to $p(x,t) = \frac{m}{m-1}\rho(x,t)^{m-1}$ strongly in $L^p$ and almost everywhere in $(0,T)\times\mathbb{R}^d$.*

4.5. **Strong convergence of $\nabla p_\tau$ as $\tau \to 0$.** The strong convergence of $p_\tau$ allows us to pass to the limit in most terms in the weak formulation of (4.1) except for the term $n_\tau\nabla p_\tau$. Since $n_\tau$ only converges weakly, we have to show that $\nabla p_\tau$ converges strongly. This is proved by using the $\rho_\tau$ equation (4.28) and its limit:

First we define the piecewise constant function

$$F_\tau(x,t) = F_k(x) \qquad t \in [k\tau,(k+1)\tau).$$

We note that (4.9) implies

$$F_k(x) = \int_0^\infty \nu(\theta,p_k)2V(0)n_k(x,\theta)\,d\theta - \int_0^\infty \nu(\theta,p_k)V(\theta)n_k(x,\theta)\,d\theta + \int_0^\infty V'(\theta)n_k(x,\theta)\,d\theta + \mathcal{O}(C\rho_k(x)\tau)$$

with $C$ depending on $\|V\|_\infty$, $\|V'\|_\infty$, $\|\partial_\theta\nu\|_\infty$ and $\|V''\|_\infty$. We can thus write:

$$F_\tau(x,t) = \int_0^\infty \nu(\theta,p_\tau)2V(0)n_\tau(x,\theta,t)\,d\theta - \int_0^\infty \nu(\theta,p_\tau)V(\theta)n_\tau(x,\theta,t)\,d\theta + \int_0^\infty V'(\theta)n_\tau(x,\theta,t)\,d\theta + \mathcal{O}(\tau)$$

The weak convergence of $n_\tau$ and the strong convergence of $p_\tau$ imply that $F_\tau$ converges weakly in $L^2(0,T;L^2(\mathbb{R}^d))$ to

$$F(x) = \int_0^\infty \nu(\theta,p)2V(0)n(x,\theta)\,d\theta - \int_0^\infty \nu(\theta,p)V(\theta)n(x,\theta)\,d\theta + \int_0^\infty V'(\theta)n(x,\theta)\,d\theta.$$

Furthermore, we can rewrite equation (4.28) as

$$\partial_t\tilde\rho_\tau - \Delta\rho_\tau^m - \varepsilon\Delta\rho_\tau = F_\tau$$

and passing to the limit $\tau \to 0$ (since $\rho_\tau^m \to \rho^m$) in the sense of distribution, we see that the limit $\rho(x,t)$ solves

$$\partial_t\rho - \Delta\rho^m - \varepsilon\Delta\rho = F \tag{4.29}$$

in $\mathcal{D}'((0,T)\times\mathbb{R}^d)$. This will be the key to proving the following proposition:

**Proposition 4.9.** *Up to another subsequence, $\nabla\rho_\tau^{m-1}$ converges strongly to $\nabla\rho^{m-1}$.*

*Proof.* Multiplying (4.28) by $\rho_k^{m-2}$, and using the convexity of $s \mapsto s^m - 1$, we get

$$\begin{aligned}\int \frac{\rho_{k+1}^{m-1}}{m-1} - \frac{\rho_k^{m-1}}{m-1}\,dx + \tau \int \rho_{k+1}\nabla_x p(\rho_{k+1})\nabla\rho_{k+1}^{m-2}\,dx \\ \leq \int (\rho_{k+1}-\rho_k)\,\rho_{k+1}^{m-2}\,dx + \tau \int \rho_{k+1}\nabla_x p(\rho_{k+1})\nabla\rho_{k+1}^{m-2}\,dx \\ \leq \tau \int F_k \rho_{k+1}^{m-2}\,dx\end{aligned}$$

which yields

$$\int \frac{\rho_{K+1}^{m-1}}{m-1} - \frac{\rho_0^{m-1}}{m-1}\,dx + \frac{m-2}{m}\sum_{k=0}^{K}\tau \int |\nabla_x p(\rho_{k+1})|^2\,dx \leq \sum_{k=0}^{K}\tau\int F_k\rho_{k+1}^{m-2}\,dx$$

that is

$$\int \frac{\rho_\tau(T)^{m-1}}{m-1} - \frac{\rho_0^{m-1}}{m-1}\,dx + \frac{m-2}{m}\int_0^T\int |\nabla_x p(\rho_\tau)|^2\,dx \leq \int_0^T\int F_\tau\rho_\tau^{m-2}\,dx + \mathcal{O}(\tau)$$

so that

$$\liminf_{\tau\to 0}\frac{m-2}{m}\int_0^T\int |\nabla_x p(\rho_\tau)|^2\,dx \leq -\int \frac{\rho(T)^{m-1}}{m-1}\,dx + \int\frac{\rho_0^{m-1}}{m-1}\,dx + \int_0^T\int F\rho^{m-2}\,dx.$$

We now use the limiting equation for $\rho$, (4.29): Multiplying that equation by $\rho^{m-2}$ and integrating in $x$ and $t$ gives

$$\int \frac{\rho(T)^{m-1}}{m-1} - \frac{\rho_0^{m-1}}{m-1}\,dx + \frac{m-2}{m}\int_0^T\int |\nabla_x p(\rho)|^2\,dx = \int_0^T\int F\rho^{m-2}\,dx$$

Together, these two relations imply

$$\liminf_{\tau\to 0}\frac{m-2}{m}\int_0^T\int |\nabla_x p(\rho_\tau)|^2\,dx \leq \frac{m-2}{m}\int_0^T\int|\nabla_x p(\rho)|^2\,dx$$

which in turn means that $\nabla_x p(\rho_\tau)$ converges strongly to $\nabla_x p(\rho)$ in $L^2(0,T;L^2(\mathbb{R}^d))$. □

4.6. **The limit $\tau \to 0$: Solutions of** (4.1)**.** Given a smooth test function $\varphi(x,\theta,t)$, compactly supported in $\mathbb{R}^d \times [0,\infty) \times [0,\infty)$, we multiply (4.6) by $\varphi_k = \varphi(x,\theta,k\tau)$, integrate with respect to $x$ and $\theta$ and sum over $k$:

$$\begin{aligned}&\sum_{k=0}^{\infty}\tau\int_{\mathbb{R}^d}\int_0^\infty \frac{1}{\tau}(n_{k+1}\varphi_k - n_k\varphi_k) - n_{k+\frac12}\partial_\theta\varphi_k + n_{k+1}\nabla_x p(\rho_{k+1})\cdot\nabla_x\varphi_k - \varepsilon n_{k+1}\Delta_x\varphi_k\,d\theta\,dx\\ &= -\sum_{k=0}^{\infty}\tau\int_{\mathbb{R}^d} 2\int_0^\infty \nu(\theta,p_k)\,n_k(x,\theta)\,d\theta\varphi_k(0)\,dx - \sum_{k=0}^{\infty}\tau\int_{\mathbb{R}^d}\int_0^\infty \nu(\theta,p_k)\,n_{k+\frac12}\varphi_k\,d\theta\,dx\end{aligned}$$

and writing $\sum_{k=0}^{\infty} n_{k+1}\varphi_k - n_k\varphi_k = \sum_{k=1}^{\infty} n_k(\varphi_{k-1}-\varphi_k) - n_0\varphi_0$, we deduce:

$$\begin{aligned}&\int_0^\infty\int_{\mathbb{R}^d}\int_0^\infty -n_\tau\partial_t\varphi - \bar n_\tau\partial_\theta\varphi + n_\tau\nabla_x p(\rho_\tau)\cdot\nabla_x\varphi\,d\theta - \varepsilon n_\tau\Delta_x\varphi\,dx\,dt\\ &= -\int_0^\infty\int_{\mathbb{R}^d} 2\int_0^\infty \nu(\theta,p_\tau)\,n_\tau(x,\theta,t)\,d\theta\varphi(x,0,t)\,dx\,dt - \int_0^\infty\int_{\mathbb{R}^d}\int_0^\infty \nu(\theta,p_\tau)\,\bar n_\tau\varphi\,d\theta\,dx\,dt + \mathcal{O}(\tau)\end{aligned}$$

where $\bar{n}_\tau$ is the piecewise constant function equal to $n_{k+\frac{1}{2}}$ on the interval $[k\tau,(k+1)\tau)$.

We note (see (4.19) and (4.26)) that $n_{k+\frac{1}{2}}$ satisfies the same bounds on $n_k$ so that $\bar{n}_\tau(x,\theta,t)$ converges weakly in $L^1(0,T;L^1(\mathbb{R}^d\times(0,\infty))$ as well (up to another subsequence) and (4.9) implies that this limit must be $n(x,\theta,t)$ (and therefore that the original subsequence converges).

We can thus pass to the limit in all the terms. For the diffusion term, we have to write

$$\int_0^\infty\int_{\mathbb{R}^d}\int_0^\infty n_\tau\nabla_x p(\rho_\tau)\cdot\nabla_x\varphi\,d\theta\,dx\,dt=\int_0^\infty\int_{\mathbb{R}^d}\int_0^\infty n_\tau\nabla_x\varphi\,d\theta\cdot\nabla_x p(\rho_\tau)\,dx\,dt$$

and note that $\int_0^\infty n_\tau\nabla_x\varphi\,d\theta$ converges weakly in $L^2(0,T;L^2(\mathbb{R}^d))$ to $\int_0^\infty n\nabla_x\varphi\,d\theta$ in order to pass to the limit in that term (using the fact that $\nabla_x p(\rho_\tau)$ converges strongly).

We deduce that $n(x,\theta,t)$ is a weak solution of (4.1) in the sense that

$$\begin{aligned}&\int_0^\infty\int_{\mathbb{R}^d}\int_0^\infty -n\partial_t\varphi-n\partial_\theta\varphi+n\nabla_x p(\rho)\cdot\nabla_x\varphi\,d\theta-\varepsilon n\Delta_x\varphi\,dx\,dt\\&=-\int_0^\infty\int_{\mathbb{R}^d}2\int_0^\infty\nu(\theta,p)\,n(x,\theta,t)\,d\theta\varphi(x,0,t)\,dx\,dt-\int_0^\infty\int_{\mathbb{R}^d}\int_0^\infty\nu(\theta,p)\,\bar{n}\varphi\,d\theta\,dx\,dt.\end{aligned}\tag{4.30}$$

4.7. **The limit $\varepsilon\to 0$: Proof of Theorem 2.1.** From now on, we denote by $n_\varepsilon(x,\theta,t)$ the solution of (4.1) constructed in the previous section and by $\rho_\varepsilon(x,t)$ the corresponding volume density. We saw that $n_\varepsilon$, $\rho_\varepsilon$ satisfies (4.30) and we now need to pass to the limit $\varepsilon\to 0$.

Much of the arguments are similar to the limit $\tau\to 0$: Indeed, Proposition 4.3 implies that $\rho_\varepsilon$ is bounded in $L^\infty(0,T;L^q(\mathbb{R}^d))$ for all $q\in[1,\infty]$ and by passing to the limit $\tau\to 0$ in (4.15), (4.18) and (4.21), we easily get the following bounds (uniform in $\varepsilon$):

$$\|\nabla\rho_\varepsilon^{\frac{m+q-1}{2}}\|^2_{L^2(0,T;L^2(\mathbb{R}^d))}\le C_q\qquad\forall q>1\tag{4.31}$$

$$\sup_{t\in[0,T]}\int_{\mathbb{R}^d}\int_0^\infty(|x|^2+\theta)n_\varepsilon(x,\theta,t)\,d\theta\,dx\le C\tag{4.32}$$

$$\int_{\mathbb{R}^d}\int_0^\infty|n_\varepsilon\log n_\varepsilon|\,dx\,d\theta\le C\tag{4.33}$$

In particular, we can proceed as Section 4.4 to prove the existence of a subsequence $\varepsilon\to 0$ along which

$$\int_0^T\int_{\mathbb{R}^d}\int_0^\infty n_\varepsilon(x,\theta,t)\psi(x,\theta,t)\,d\theta\,dx\,dt\to\int_0^T\int_{\mathbb{R}^d}\int_0^\infty n(x,\theta,t)\psi(t,x,\theta)\,d\theta\,dx\,dt$$

for all $\psi\in L^\infty([0,T]\times\mathbb{R}^d\times(0,\infty))$ and

$$\rho_\varepsilon(x,t)\rightharpoonup\rho(x,t)=\int_0^\infty n(x,\theta,t)V(\theta)\,d\theta.$$

The main difference is in the way we prove the strong convergence of $\rho_\varepsilon$, since in the proof of Proposition 4.7, we used the bound on $\nabla\rho_\tau$ which was not uniform in $\varepsilon$. Instead, we will use (4.31) to prove the strong convergence of $\rho_\varepsilon^s$ for $s$ large enough (the argument below does not appear to work with the time approximation, which is the reason we had to introduce the regularization $\varepsilon>0$ in the system):

**Proposition 4.10.** *The sequence* $\rho_\varepsilon^{m+2}$ *is precompact in* $L^2(0,T;L^2(\mathbb{R}^d))$.

We immediately note that this implies the existence of a subsequence along which $\rho_\varepsilon^{m+2}$ converges strongly in $L^2$ and almost everywhere. This implies the convergence almost everywhere of $\rho_\varepsilon$ and the uniform bounds in $L^\infty(0,T;L^q(\mathbb{R}^d))$ implies that $\rho_\varepsilon$ converges strongly in $L^q(0,T;L^q(\mathbb{R}^d))$ for all $q\in[1,\infty)$.

We can then prove the strong convergence of $\nabla p_\varepsilon = \frac{m}{m-1}\nabla\rho_\varepsilon^{m-1}$ as in Proposition 4.9 and pass to the limit in (4.30) to get (2.6) and complete the proof of Theorem 2.1.

*Proof of Proposition 4.10.* Taking $q=m+5$ in (4.31) implies that $\rho_\varepsilon^{m+2}$ is bounded in $L^2(0,T;H^1(\mathbb{R}^d))$. Furthermore, we recall that $\rho_\varepsilon$ solves (see (4.29))

$$\partial_t\rho_\varepsilon - \Delta\rho_\varepsilon^m - \varepsilon\Delta\rho_\varepsilon = F_\varepsilon$$

with $F_\varepsilon$ bounded in $L^2(0,T;L^2(\mathbb{R}^d))$ and so

$$\frac{1}{m+2}\partial_t\rho_\varepsilon^{m+2} = \rho_\varepsilon^{m+1}\Delta\rho_\varepsilon^m + \varepsilon\rho_\varepsilon^{m+1}\Delta\rho_\varepsilon + F_\varepsilon\rho_\varepsilon^{m-1}$$

To show that the right-hand-side is bounded, we rewrite

$$\rho_\varepsilon^{m+1}\Delta\rho_\varepsilon^m = \operatorname{div}(\rho_\varepsilon^{m+1}\nabla\rho_\varepsilon^m) - \nabla\rho_\varepsilon^{m+1}\cdot\nabla\rho_\varepsilon^m$$

and

$$\rho_\varepsilon^{m+1}\Delta\rho_\varepsilon = \operatorname{div}(\rho_\varepsilon^{m+1}\nabla\rho_\varepsilon) - \nabla\rho_\varepsilon^{m+1}\cdot\nabla\rho_\varepsilon = \frac{1}{m+2}\Delta\rho_\varepsilon^{m+2} - \frac{2(m+1)}{(m+2)^2}\left|\nabla\rho_\varepsilon^{\frac{m+2}{2}}\right|^2$$

Since (4.31) implies that $\nabla\rho_\varepsilon^s$ is bounded in $L^2(0,T;L^2(\mathbb{R}^d))$ for all $s>\frac{m}{2}$, we see that these two terms are bounded in $L^2(0,T;H^{-1}(\mathbb{R}^d)) + L^1(0,T;L^1(\mathbb{R}^d))$.

We have thus shown that $\rho_\varepsilon^{m+2}$ is bounded in $L^2(0,T;H^1(\mathbb{R}^d))$ and that $\partial_t\rho_\varepsilon^{m+2}$ is bounded in $L^2(0,T;H^{-1}(\mathbb{R}^d))+L^1(0,T;L^1(\mathbb{R}^d))$. Together with (4.32), this is enough to apply Aubin-Lions lemma to prove that $\rho_\varepsilon^{m+2}$ is precompact in $L^2(0,T;L^2(\mathbb{R}^d))$. □

## Appendix A. Numerical scheme and algorithm

Focusing on the discretization of the variables $\theta$ and $t$, we write $n_{k,i}(x) = n(x,k\Delta t, i\Delta\theta)$. Using first-order approximations, Equation (1.2) leads to

$$\frac{n_{k+1,i}-n_{k,i}}{\Delta t} + \frac{n_{k,i}-n_{k,i-1}}{\Delta\theta} - \operatorname{div}_x(n_{k,i}\nabla_x p_k) = -\nu_{k,i}n_{k,i} - \mu_i n_{k,i}, \tag{A.1}$$

for $i=1,\dots,i_M-1$. Setting $\lambda \coloneqq \Delta t/\Delta\theta$, and rearranging (A.1), we obtain

$$n_{k+1,i} = n_{k,i} + \lambda(n_{k,i-1}-n_{k,i}) + \operatorname{div}_x(n_{k,i}\nabla_x p_k)\Delta t - \nu_{k,i}n_{k,i}\Delta t - \mu_i n_{k,i}\Delta t. \tag{A.2}$$

Since cells that reach the age $\theta_{max} = i_M\Delta\theta$ do not age or duplicate, the equation for $n_{k+1,i_M}$ is:

$$n_{k+1,i_M} = n_{k,i_M} + \lambda n_{k,i_M-1} + (\Delta t)[\operatorname{div}_x(n_{k,i_M}\nabla_x p_k) - \nu_{k,i_M}n_{k,i_M} - \mu_{i_M}n_{k,i_M}] \tag{A.3}$$

The density at time $k\Delta t$ is then given by

$$\rho_k = \sum_{i=0}^{i_M} n_{k,i}\Delta\theta$$

and using (A.1)-(A.2), we get

(A.4)

$$\rho_{k+1} - n_{k+1,0}\Delta\theta = \rho_k - n_{k,0}\Delta\theta + n_{k,0}\Delta t + (\Delta t\Delta\theta)\sum_{i=1}^{i_M}[\operatorname{div}_x(n_{k,i}\nabla_x p_k) - \nu_{k,i}n_{k,i} - \mu_i n_{k,i}].$$

With a slight abuse of notation, we write $\nu_k\rho_k = \sum_{i=0}^{i_M}\nu_{k,i}n_{k,i}\Delta\theta$ and $\mu\rho_k = \sum_{i=0}^{i_M}\mu_i n_{k,i}\Delta\theta$, so that equation (A.4) can be rewritten as

$$\begin{aligned}\rho_{k+1} =&\rho_k + (n_{k+1,0} - n_{k,0})\Delta\theta + n_{k,0}\Delta t + \operatorname{div}_x(\rho_k\nabla_x p_k)\Delta t - \operatorname{div}_x(n_{k,0}\nabla_x p_k)\Delta t\Delta\theta \\ &- \nu_k\rho_k\Delta t + \nu_{k,0}n_{k,0}\Delta t\Delta\theta - \mu\rho_k\Delta t + \mu_0 n_{k,0}\Delta t\Delta\theta.\end{aligned} \tag{A.5}$$

With the same notation, the equation for the density (1.7) can be discretized as $\rho_{k+1} = \rho_k + \operatorname{div}_x(\rho_k\nabla_x p_k)\Delta t + \nu_k\rho_k\Delta t - \mu\rho_k\Delta t$. Combining these two equations leads to

$$2\nu_k\rho_k\Delta t = (n_{k+1,0} - n_{k,0})\Delta\theta + n_{k,0}\Delta t - \operatorname{div}_x(n_{k,0}\nabla_x p_k)\Delta t\Delta\theta + \nu_{k,0}n_{k,0}\Delta t\Delta\theta + \mu_0 n_{k,0}\Delta t\Delta\theta,$$

which gives the appropriate discretization of the condition at $\theta = 0$ ($i = 0$):

$$\begin{aligned}n_{k+1,0} &= 2\sum_{i=0}^{i_M}\nu_{k,i}n_{k,i}\Delta t + n_{k,0}\,(1-\lambda) + \operatorname{div}_x(n_{k,0}\nabla_x p_k)\Delta t - \nu_{k,0}n_{k,0}\Delta t - \mu_0 n_{k,0}\Delta t \\ &= 2\sum_{i=1}^{i_M}\nu_{k,i}n_{k,i}\Delta t + n_{k,0}\,(1-\lambda+\nu_{k,0}\Delta t - \mu_0\Delta t) + \operatorname{div}_x(n_{k,0}\nabla_x p_k)\Delta t.\end{aligned} \tag{A.6}$$

Equations (A.2)-(A.3)-(A.6) provide the numerical scheme for the aging/duplication/death of the cells. Importantly, we note that in order to reduce the computational cost, it might be necessary to take $\Delta\theta$ to be much larger than $\Delta t$ ($\lambda \ll 1$). The discretization with respect to the spatial variable $x$ is done with a uniform grid $\Delta x_1 = \Delta x_2 = \Delta x$ and the gradients are calculated by the centered difference

$$(\nabla_{x_i}p)_{l,m} = \frac{p_{l+1,m} - p_{l-1,m}}{2\Delta x}, \qquad i = 1, 2.$$

Algorithm 1 provides the pseudocode for the algorithm used for the simulation.

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**Algorithm 1** Pseudocode for the simulation

$T \leftarrow$ total time
$i_M \leftarrow$ (Final age)$/\Delta\theta$
Calculate the gradient operators for $x_1$ and $x_2$ each.

**for** $k = 1$ **to** $T/\Delta t$ **do**
  Calculate $\nabla_{x_1} p$ and $\nabla_{x_2} p$.

  $D_{i_M} \leftarrow \nabla_{x_1}(n_{k,i_M}\nabla_{x_1} p) + \nabla_{x_2}(n_{k,i_M}\nabla_{x_2} p)$ ▷ Diffusion term for the oldest
  $n_{k+1,i_M} \leftarrow n_{k,i_M}[1 - (\Delta t)\mu(i_M)] + \lambda n_{k,i_M-1} + (\Delta t)D_{i_M}$

  **for** $i = i_M - 1$ **to** $1$ **do**
    $D_i \leftarrow \nabla_{x_1}(n_{k,i}\nabla_{x_1} p) + \nabla_{x_2}(n_{k,i}\nabla_{x_2} p)$
    $\mathrm{Pro}_i \leftarrow \nu_{k,i} n_{k,i}$ ▷ Proliferation at each age
    $n_{k+1,i} \leftarrow n_{k,i}[1 - (\Delta t)\mu(i)] + \lambda(n_{k,i-1} - n_{k,i}) + (\Delta t)(\mathrm{Pro}_i + D_i)$
  **end for**

  $\mathrm{Newborn}_k \leftarrow 2\sum_{i=1}^{i_M} \mathrm{Pro}_i(\Delta t)$ ▷ Newborn cells
  $n_{k+1,0} \leftarrow \mathrm{Newborn}_k + n_{k,0}[1 - \lambda - (\Delta t)\mu(0)]$

  $\rho_k \leftarrow \sum_{i=0}^{i_M} n_{k,i}(\Delta\theta)$
  $p_k \leftarrow \frac{m}{m-1}\rho_k^{m-1}$
**end for**


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