Derivation of macroscopic equations for individual cell-based models. A formal approach.

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Abstract — In this paper we review the theory of cells (particles) that evolve according to a dynamics determined by friction and that interact between themselves by means of suitable potentials. We derive by means of elementary arguments several macroscopic equations that describe the evolution of cell density. Some new results are also obtained — a formal derivation of a limit equation in the case of attractive potential as well as in the case of repulsive potential with a hard-core part are presented Finally, we discuss the possible relevance of those results within the framework of individual cell-based models. Several classes of potentials, including hard-core, repulsive and potentials with attractive parts are discussed. The effect of noise terms in the equation is also considered.

1 Introduction

In recent years there has been a large amount of interest in the study of so-called "individual cell-based models" (cf. for instance [11,13,26,41]). In those models, typically, cells interacting by means of some pair potential, are assumed to evolve according to some deterministic or stochastic dynamics.

The purpose of the this paper is to review several results and present a formal derivation for several new ones showing that for a general class of those models the cells dynamics can be described by means of simple macroscopic partial differential equations (PDEs). In such macroscopic equation the key features of the dynamics can be recognized more easily and it is possible to identify how the different ingredients in the microscopic model show up in the macroscopic behaviors of the cells.

Actually, there has been a large amount of work in this direction, largely motivated by similar results in statistical physics. Several approaches can be found in the literature. The main of them are: transport equations (cf. for instance [9, 10, 21–23, 31, 32]), kinetic equation (cf. [8, 44] and references therein) cellular automata (cf. [11, 14, 15, 19, 41, 42]) and stochastic equations (cf. [12,13,26–29,36]). We will focus on a very particular type of

models that are analogous to many of the models studied in the literature. More precisely we will assume that the centers of the cells evolve according to the stochastic differential equation:

$$\frac{d}{dt}X_k(t) = -\sum_{\substack{i=1\\ i\neq k}}^{N} \nabla V(X_k(t) - X_i(t)) + \sigma\xi_k(t)\,, \tag{1.1}$$

where N is a number of cells. In this equation it is assumed that cells interact by means of the potential V. The dominant effect in the dynamics is cell friction and for that reason only one derivative appears on the left-hand side. Finally, the functions $\xi_k(t)$ are uncorrelated "white noises".

These models are basically the type of models considered in the numerical simulations (cf. [12,13]). A detailed mathematical analysis of these or related models has been undertaken in [27–30,36,40]. Several of the results presented in this paper can be found in the mathematical literature [27–30, 36]. The main goal of this paper is to describe how the resulting macroscopic limits might be obtained using elementary arguments that could be followed by a general audience who is not expert in PDEs or stochastic processes. On the other hand, we will also derive, using this kind of heuristic, simple arguments, some new macroscopic models that, to our knowledge, have not been obtained in previous works. In particular the analysis in the papers [27–30, 40] is restricted to the case of repulsive potentials. Nevertheless, in the numerical simulations of individual cell-based models potentials containing an attractive part are used very often (cf. [13, 33, 34]. We will describe the type of difficulties arising in those cases. (Models with potentials with an attractive part might have rather different mathematical properties from those in the repulsive case.)

The paper is organized as follows. In Section 2 we describe the main assumptions of the model considered in the paper and present a summary of the results. In Sections 3 and 4 we present heuristic derivations of the limit equation in the different cases. For repulsive potentials we consider the deterministic case (i.e. $\sigma = 0$ in (1.1) — cf. Subsection 3.1) and the stochastic one (i.e. $\sigma > 0$ in (1.1) — Subsection 3.2). Section 4 is devoted to the study of potentials with attractive parts. Finally, in Section 5 there is some final discussion including the possible ways to introduce mitosis into the presented model.

2 The main results

Assumptions of the model.

(1) Cells motion is dominated by friction and for that reason we assume an evolution equation with the form (1.1) instead of some Newton's like as:

$$m\frac{d^2X_k}{dt^2} + \lambda\frac{dX_k}{dt} = F_k\,, \quad k = 1, 2, ..., N \tag{2.1}$$

where F_k would be the force acting on each cell. In models like (1.1) it is assumed that the first term on the right hand side of (2.1) is negligible.

(2) Related to the previous assumption is the absence of persistence of a cell motion. In another way, cells change instantaneously their velocity of motion as a reaction to external forces. This assumption is probably too restrictive in many cases, since it is known that cells do not change their direction of motion instantaneously in many cases (cf. [37, 43]).

(3) We assume that cell interaction takes place by means of potentials. This would make sense for elastic cell interactions that certainly play a role in cell dynamics. However, it is known that there are also interactions due to the presence of some chemicals on the surface of the cells [25]. The assumption of force induced by a potential is rather restrictive from the mathematical point of view. In particular, notice that (1.1) assumes that force between cells depends only on the distance between them, but is independent on concentrations of chemicals, cell shape or other complicating factors that could play a role in biological settings.

(4) Concerning cell size (1.1) seems to assume that cells are just points. This is not completely true, because in many of the models analyzed in the literature, as well in several of the results described in this paper, the interaction potential will include a "hard-core part" that says that cells cannot become smaller than a sphere with a given radius. Some models have allowed for simple cell deformations (cf. for instance [33], where cells are assumed to be ellipsoids with variable eccentricity). Nevertheless, the possibility of complicated cell deformations like pseudopod formation or similar ones is certainly not taken into account in simple models like (1.1).

(5) Model (1.1) assumes that cell motion contains a "diffusive" or "noisy" component. The mean-rates of cell diffusion have been experimentally measured in [25, 38]. On the other hand, due to the close contact between cells it is not clear if the noise experienced by the cells is uncorrelated, at least for cells that are closely packed. We are not aware of any experimental result concerning noise correlations. Nevertheless, the assumption of uncorrelated noises is commonly used in the study of individual cell-based models and we will use that assumption in the rest of the paper.

(6) The system presented in Eq. (1.1) is a conservation law one, in the sense that the total mass (or the total number of cells) remains constant. This implies, that mitosis is not present the model.

Let us introduce the main length scales in the problem.

- The average distance between cells is denoted as d.
- The range of interactions of the potentials is denoted as $\mathbb{R}$.
- Finally, we will assume that there is a characteristic macroscopic length prescribed by the typical distance for the variation of densities of the initial data. We will normalize the length scales in such a way that such length is of order one.

Our study will be restricted to the 1-dimensional case. We want to measure the macroscopic density of the cells ρ, which can be defined as follows

$$\rho(x,t)\delta x = \frac{\text{the number of cells in } [x, x+\delta x] \text{ at time } t}{N},$$

where δx is a macroscopic differential (containing many cells). We assume that δx is much smaller that the macroscopic length l and much larger that the average distance between cells $d \sim \frac{1}{N}$, i.e.

$$d \ll \delta x \ll l\,.$$

Remark. In precise mathematical terms we define an empirical measure

$$X_N(t) = \frac{1}{N}\sum_{k=1}^{N} \delta_{X_k^N(t)}$$

and consider the weak limit

$$X_N(t) \rightharpoonup \rho(x,t)dx \qquad \text{as} \qquad N \to +\infty$$

The meaning of this mathematical notation is basically that the empirical densities contain, in sets of macroscopic size and the limit $N \to \infty$, the same number of cells that could be computed using the limit densities $\rho\,(x,t)$.

In this paper we investigate the case when the range of the interaction of the potential is of order of the average distance between cells (i.e. $\mathbb{R} \simeq d$) or it is much larger than the average distance between cells (i.e. $\mathbb{R} \gg d$). In the first case each single cell at each given time interacts only with a small number of its neighborhoods. We will refer to this case as the case of "short range" interactions. On the contrary if $\mathbb{R} \gg d$ each cell interacts with a large number of cells surrounding it, and in particular the forces acting over it can be computed by averaging suitable densities. In this case we will say that cell interactions have "long range". Short range interactions are probably more relevant in biological applications. On the other hand the mathematical analysis of this case is also more involved.

The results derived later in this paper are collected Table 1 of Section 5 on the page 22.

The precise model. Let us precise in more mathematical terms the type of models to be considered. We will study the evolution of the system:

$$\frac{dX_k^N(t)}{dt} = -\frac{1}{N}\sum_{\substack{i=1\\ i\neq k}}^{N} \nabla V_N(X_k^N(t) - X_i^N(t)) + \sigma\xi_k(t)\,, \quad k = 1,\dots,N\,, \tag{2.2}$$

where $X_k(t)$ denotes the position of the center of the call at the time t, N is the number of cells, V_N is some interaction potential between the cells and the functions ξ_k are uncorrelated "white noises" terms, i.e. they are statistical objects satisfying

$$\begin{aligned}\langle \xi_k(t)\rangle &= 0\\ \langle \xi_k(t)\xi_l(t')\rangle &= \delta_{k,l}\delta(t-t')\,,\end{aligned}$$

where $\langle\cdot\rangle$ denote averaging with respect to all possible realization of the white noise process. All coefficients of the model (2.2) are assumed to be dimensionless. Finally we will assume that the potential V_N rescales in the following manner with N

$$V_N(x) = N^\beta V_1(N^\beta x)\,, \quad 0 < \beta \leq 1\,. \tag{2.3}$$

Notice that this choice of rescalings corresponds to taking $R = \frac{1}{N^\beta}$, $d = \frac{1}{N}$. This choice of length scales is not the most general one, but it gives a large class of interesting dynamics. If $\beta = 1$ we have that $R \simeq d$ and the interactions have short range. If on the contrary $0 \leq \beta < 1$ there holds $R \gg d$ and we have long range interactions. Notice that in the particular case $\beta = 0$ the macroscopic length and the interaction length are the same.

The key idea used repeatedly in the whole paper is the assumption of a local equilibrium analogous to the one used in the study of gas-dynamics (cf. [24]). It will be assumed that in some suitable regions that are very small compared with the macroscopic length of the system, but large enough to contain many cells the statistical distribution of cells can be considered to be near equilibrium for some suitable variables of the cell density. However, these values of the density can be assumed to vary in a slow manner over distances of the order of the macroscopic length. This kind of assumption is the usual one in statistical physics (cf. [24]). The key problem reduces just to computing the fluxes of cells between the different regions that are assumed to be at equilibrium due to the changes on the macroscopic quantities. We are not showing in a rigorous manner that cells are locally at equilibrium. Nevertheless this assumption is a natural one because the problem (2.2) is a gradient flow that is naturally driven to the equilibrium. On the other hand approach to equilibrium is faster in smaller regions and for that reason is reasonable to make the local equilibrium assumption.

3 Derivation of the limit equations: repulsive potentials

In this Section we will deal with the cases when the potential V_N is a repulsive one or, more precisely, we will assume that V_N is a decreasing function on $[0, +\infty)$ and vanishing at $+\infty$ sufficiently fast. We do not assume V_N to be necessarily smooth at 0. More precisely we will allow a discontinuity in the derivative of V at the origin. We will present an elementary formal derivation of the results rigorously obtained by Oelschläger in the deterministic case (see [27]), for both short and long range interactions. For the stochastic case the derivation is valid only for the case of long range interactions. Actually the proof in [28] requires an additional assumption, namely, that the range of interactions is long enough compared with the distance between cells. The formal arguments below seem to indicate that this restriction is just a technical one, but that however, the same limit equation can be obtained also in that case.

3.1 Deterministic case

In the case of deterministic motion (i.e. $\sigma = 0$ in (2.2)) the changes on cell density are just due to the following. If cells placed in one side of a given point, say to the right, are more closely packed than those placed to the left, the cells in region that is more closely packed produces an stronger repulsive force than the ones having smaller density. This generates a tendency of cells to move from regions having a larger cell density to regions with smaller one. In this Section we give a precise statement of this argument. The rigorous proof of the results derived in this Section can be found in [27].

As stated before, our main assumption is that cells are locally near equilibrium. In the deterministic case, this means that cells are approximately at the same distance (at least for repulsive potentials). Nevertheless, cell density can change over distances much larger than the average distance between cells. Let assume that at time t cells are located at points x_i, where $i = -\left[\frac{N}{2}\right], \ldots, \left[\frac{N}{2}\right]$. Let us denote as $d(x_i)$ the distance between the cell i-th and cell $i+1$-th. Then

$$x_i = x_{i-1} + d\,(x_{i-1})\ . \tag{3.1}$$

Since we are assuming that cell density changes in a length scale larger than the average distance between cells, with convenient assumptions on the smoothness of the macroscopic cell density we can write

$$d(x_i) \approx d(x_{i-1}) + \alpha\ (x_i - x_{i-1}) = d(x_{i-1}) + \alpha\, d\,(x_{i-1})\ , \tag{3.2}$$

where $\alpha \equiv \partial_x d(x_{i-1})$ can be supposed to be approximately constant over regions that are small compared with the macroscopic length. Iterating (3.2) we obtain

$$d(x_i) = (1+\alpha) d(x_{i-1}) = (1+\alpha)^i d_0\,. \tag{3.3}$$

Let the function ρ be a cell's density and N be the number of cells for unit of length. By assumption, density variations take place in macroscopic scales. Then $\alpha \sim \frac{1}{N}$. If we want to compute a cell velocity at a given point, we need to add the contributions to the force of cells placed at a distance of the order of the range of interactions. Since cell's density is of order N and the range of interactions is of order $\frac{1}{N^\beta}$ (cf. (2.3)), we need to add the contributions of $N^{1-\beta}$ interactions. In particular, notice that in (3.3) $|\alpha \cdot i| \leq \frac{C}{N} N^{1-\beta} = \frac{C}{N^\beta} \ll 1$ for large N. Therefore, we can replace (3.3) by

$$d(x_i) = (1 + i\alpha) d_0\,.$$

Plugging this formula into (3.1) and iterating we obtain

$$x_i = x_0 + i d_0 + d_0 \frac{i(i-1)}{2} \alpha\,. \tag{3.4}$$

Using (3.4) we can compute the potential at each point x_0

$$g_N(x_0, t) \stackrel{\text{def}}{=} \frac{1}{N} \sum_{i=-\frac{N}{2}}^{+\frac{N}{2}} V_N(x_0 - x_i) \approx \frac{1}{N} \sum_{i=-\infty}^{+\infty} V_N\left(-i d_0 - d_0 \frac{i(i-1)}{\alpha}\right)\ . \tag{3.5}$$

We do not want to assume necessarily that the potential V_N is symmetric. Non symmetric potentials would provide some directional bias for cell motion. Suppose that the potential V_N can be decomposed on the symmetric part and the rest in the following form

$$V_N = V_{N,\text{symm}} + V_{N,\text{drift}}\,.$$

The function $V_{N,\text{symm}}$ is a symmetric around zero (i.e. $V_{N,\text{symm}}(x) = V_{N,\text{symm}}(-x)$) and $V_{N,\text{drift}}$ is the rest. Cell velocity is given by $\partial_x g_N(x,t)$. Differentiating (3.5), and using Taylor's expansion we obtain

$$\begin{aligned}\partial_x g_N(x,t) &\approx \frac{1}{N}\sum_{i=-\infty}^{+\infty} V_N'(-id_0) - \frac{1}{N}\sum_{i=-\infty}^{+\infty} V_N''(-id_0)\cdot\frac{d_0 i^2}{2}\alpha \\ &= \frac{1}{Nd_0}\sum_{i=-\infty}^{+\infty} V_{N,\text{drift}}'(-id_0)\cdot d_0 - \frac{\alpha}{2Nd_0^2}\sum_{i=-\infty}^{+\infty} V_N''(-id_0)(id_0)^2\cdot d_0\,,\end{aligned}$$

due to symmetry of $V_{N,\text{symm}}$. Consequently,

$$\begin{aligned}\partial_x g_N(x,t) =& \frac{N^\beta}{Nd_0}\sum_{i=-\infty}^{+\infty} V_{1,\text{drift}}(-iN^\beta d_0)\cdot N^\beta d_0 \\ &- \frac{\alpha}{2Nd_0^2} V_1''\left(-iN^\beta d_0\right)(iN^\beta d_0)^2\cdot N^\beta d_0\,.\end{aligned} \tag{3.6}$$

Let $\rho(x)$ be the macroscopic density at the point x. Therefore,

$$d(x) = \frac{1}{N\rho(x)} \qquad \text{and} \qquad \alpha = \partial_x d(x) = -\frac{\rho'(x)}{N\rho^2(x)}\,. \tag{3.7}$$

Let us denote $h = N^\beta d_0 = \frac{1}{\rho N^{1-\beta}}$. Therefore, due to (3.7), the formula (3.6) becomes

$$\partial_x g_N(x,t) = \frac{N^\beta}{\rho}\sum_{i=-\infty}^{+\infty} V_{1,\text{drift}}(-ih)\cdot h - \frac{\rho'}{2}\sum_{i=-\infty}^{+\infty} V_1''\left(-ih\right)(ih)^2 h\,. \tag{3.8}$$

Notice, that if we assume that $V_{1,\text{drift}}$ does not depend on N, than the drift term is a dominating one. In this case we get an equation dominated by a convection. We restrict our analysis to the case in which both the effect of the symmetric part of the potential and drifting are of the same order of magnitude, but the equations could be easily modified otherwise. Therefore, we will assume that $V_{1,\text{drift}}'(x) = \frac{1}{N^\beta} V_{\text{drift}}'(x)$. Now we can state the result. Consider first the case of long range interactions (i.e. $\beta < 1$). We might then approximate the sum in the formula (3.8) by the integral

$$\partial_x g(x,t) = \frac{1}{\rho(x)}\int\limits_{\mathbb{R}} V_{\text{drift}}'(x)dx + \frac{\rho'(x)}{2}\int\limits_{\mathbb{R}} V_1''\left(x\right)x^2 dx\,.$$

Integration by parts yields

$$\partial_x g(x,t) = \frac{N^\beta}{\rho(x)} \int\limits_{\mathbb{R}} V'_{1,\text{drift}}(x)dx + \frac{\rho'(x)}{2} \int\limits_{\mathbb{R}} V_1(x)dx \tag{3.9}$$

as in [27]. In the case of short range interactions (i.e. $\beta = 1$) the approximation of the sum by an integral is not valid any more. Therefore, we get

$$\partial_x g_N(x,t) = \frac{1}{\rho} \sum_{i=-\infty}^{+\infty} V'_{\text{drift}}\left(\frac{i}{\rho}\right) + \frac{\rho'(x)}{2} \sum_{i=-\infty}^{+\infty} V_1''\left(\frac{i}{\rho(x)}\right)\left(\frac{i}{\rho(x)}\right)^2 . \tag{3.10}$$

Notice, that formulas (3.9) and (3.10) describes the speed of the cells at the time t and at the point x. Therefore, the final equations are

$$\frac{\partial}{\partial t}\rho(t,x) = \frac{\partial}{\partial x}\left(\rho(x,t) \int\limits_{\mathbb{R}} V_1(x)dx \frac{\partial}{\partial x}\rho(t,x)\right) + N^\beta \int\limits_{\mathbb{R}} V'_{1,\text{drift}}(x)dx \tag{3.11}$$

$$\begin{aligned}\frac{\partial}{\partial t}\rho(t,x) =& \frac{\partial}{\partial x}\left(\frac{1}{2}\frac{\partial}{\partial x}\rho(t,x) \sum_{i=-\infty}^{+\infty} V_1''\left(\frac{i}{\rho(t,x)}\right)\left(\frac{i}{\rho(t,x)}\right)^2\right) \\ &+ \sum_{i=-\infty}^{+\infty} V'_{\text{drift}}\left(\frac{i}{\rho(t,x)}\right) ,\end{aligned} \tag{3.12}$$

for the case $\beta < 1$ and $\beta = 1$, respectively. Equations (3.11) and (3.12), without the drifting part, are exactly the same and equivalent, respectively, as those obtained by Oelschläger in [27]. We emphasize again the fact that the the cause of the diffusive effect is the difference between the forces induced by the cells on the right and on the left of a given cell.

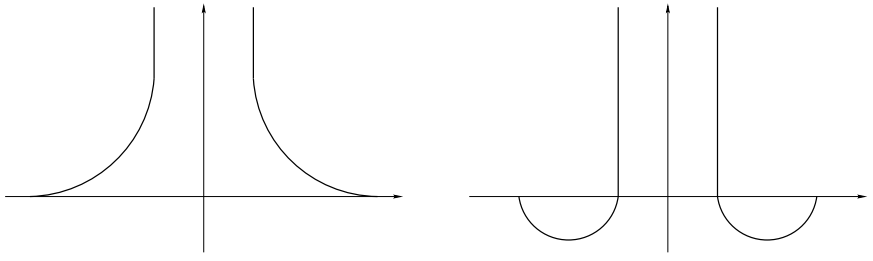


Figure 1: Examples of potentials with a hard-core.

Remark. Notice that result (i.e. Eqs. (3.11) and (3.12)) remains unchanged if we assume that the potential V_1 contains a hard-core part like in Fig. 1. Of course in that case one has to assume that distances between cells (their centers), initially, are larger than the radius of the hard-core. The limit equation keeps this property due to the classical maximum principle for parabolic equations (cf. [17]).

3.2 Stochastic case

3.2.1 Smooth potentials

In order to illustrate the main ideas used later we will derive the diffusion equation from the stochastic equation (2.2) in the case $V_N \equiv 0$ and $\sigma = 1$.

Derivation of the diffusion equation in the absence of interaction potentials. The key point is to calculate the flux of the cells between different neighboring regions of mesoscopic size. We understand by this regions which are small compared with the characteristic distance where density changes but large enough to contain many cells. Let divide the original system into set of such mesoscopic regions. Let the length of each such interval be l_N. The above assumptions implies that $l_N \ll 1$ (the interval is much smaller than the macroscopic length) and $l_N \gg \frac{1}{N}$ (the interval contains a large number of cells).

We choose two neighboring regions and then calculate the number of cells which, being at one interval at time 0, are at a contiguous one at some time t. Our goal is to compute the flux of the cells between these contiguous intervals. Without lost of the generality we choose intervals $I_L = [-l_N, 0]$ and $I_R = [0, l_N]$.

As it was described in Section 2 we assume that cells are locally in equilibrium. This assumption is justified because in small regions cells distribution should go to equilibrium faster then the whole macroscopic system. In the case with $V_N \equiv 0$ this means that the cells are randomly distributed in each mesoscopic region. The number of cells placed in each region depends on the density. We assume also that the density ρ changes slowly at the mesoscopic scale. Then, we may approximate it as a linear function, i.e.

$$\rho(x) = \rho_0 + \alpha x \qquad \text{for} \qquad x \in [-l_N, l_N]\,, \tag{3.13}$$

where $\rho_0 = \rho(0)$ and $\alpha = \rho'(0)$. The characteristic length for diffusion in times Δt is $\sqrt{\Delta t}$. If we assume $\frac{1}{N} \ll \sqrt{\Delta t}$ then many cells would diffuse from I_R to I_L and inversely. On the other hand we want the intervals I_L and I_R to be large enough to be able to neglect the influence of all the others intervals. We then need to assume that $\sqrt{\Delta t} \ll l_N$. Summarizing, we choose the time scale Δt satisfying:

$$\frac{1}{N} \ll \sqrt{\Delta t} \ll l_N\,. \tag{3.14}$$

Suppose that in the interval I_L at time 0 we have M cells located at the points a_i, $(i = 1, \ldots, M)$. The cells are moving independently, each due to the Brownian motion. Therefore, the probability that the i-th cell, initially placed at $x = a_i$ is in the interval I_R is the following

$$p_i = p(a_i) = \frac{1}{\sqrt{4\pi\Delta t}} \int\limits_{I_R} e^{-\frac{(x-a_i)^2}{4\Delta t}}\, dx\,. \tag{3.15}$$

Let N_{lr} be a random variable which counts how many cells at time $t + \Delta t$ are in the interval I_R assuming that they were in I_L at time t and N_{rl} be a random variable which counts how many cells at time $t + \Delta t$ are in the interval I_L assuming that they were in I_R

at time t. Since the cells move independently this variable has a multinomial distribution. The mean value and the standard deviation of N_{lr} is given by (cf. [16])

$$\begin{aligned} \langle N_{lr}|a_1,\ldots,a_M\rangle &= \sum_{i=1}^{M} p(a_i)\,, \\ \mathrm{var}(N_{lr}|a_1,\ldots,a_M) &= \sqrt{\sum_{i=1}^{M} p(a_i)(1-p(a_i))}\,, \end{aligned}$$

where $\langle N_{lr}|a_1,\ldots,a_M\rangle$ denotes a mean value assuming the initial positions a_i. We want to determine under which conditions we can approximate cell velocities using deterministic quantities. The classical law of large numbers (cf. [16]) ensures that this is possible if $\mathrm{var}(N_{lr}-N_{rl}) \ll |\langle N_{lr}-N_{rl}\rangle|$.

Since the cells are distributed independently (with a probability proportional to cells density given in (3.13)), we obtain

$$< N_{lr} >= \frac{\int\limits_{(I_L)^M} < N_{lr}|a_1,\ldots,a_M > \prod\limits_{i=1}^{M}\rho(a_i)d^M a}{\left(\int\limits_{I_L}\rho(a)da\right)^M} = \frac{\sum\limits_{i=1}^{M}\int\limits_{I_L} p(a)\rho(a)da}{\int\limits_{I_L}\rho(a)da}\,. \tag{3.16}$$

Using (3.15), the assumption (3.14) and integrating by parts obtain

$$\int\limits_{-l_N}^{0} p(x)\rho(x)dx = \frac{\rho_0\sqrt{\Delta t}}{\sqrt{\pi}} - \frac{\alpha\Delta t}{2}\,. \tag{3.17}$$

Hence, applying (3.15) and (3.17) to (3.16) and assuming that $M=\rho_0 l_N$, we obtain

$$\langle N_{lr}\rangle = \frac{\frac{\rho_0\sqrt{\Delta t}}{\sqrt{\pi}} - \alpha\Delta t}{1+\frac{l_N\alpha}{2\rho_0}} \approx \frac{\sqrt{\Delta t}\rho_0}{\sqrt{\pi}} - \frac{\alpha\Delta t}{2} \tag{3.18}$$

due to the assumption $l_N \ll 1$. In the same way we obtain

$$\langle N_{rl}\rangle = \frac{\sqrt{\Delta t}\rho_0}{\sqrt{\pi}} + \frac{\alpha\Delta t}{2}\,. \tag{3.19}$$

Therefore, combining (3.18) and (3.19) the total flux of the cell during the time Δt

$$\langle N_{lr}\rangle - \langle N_{rl}\rangle = \alpha\Delta t\,. \tag{3.20}$$

In the similar way we can obtain that for Δt small enough

$$\mathrm{var}N_{lr} \approx \rho_0\sqrt{(\Delta t)} \ll \alpha\Delta t\,.$$

Since $\rho_0 \sim N$ it follows that under additional condition

$$\Delta t \gg \frac{1}{N^{2/3}} \tag{3.21}$$

that is compatible with (3.14), we can use the law of large numbers in order to derive that the flux obtained in (3.20) is a deterministic quantity.

Let us emphasize the fact that diffusion is a collective effect. The number of cells crossing in each direction is much larger then total flux of the cells. (see equations (3.18) and (3.19), respectively).

Letting $\Delta t \to 0$ in (3.20) we obtain $(\alpha = \rho'(x))\ \vec{j}(x) = \rho'(x)$ and therefore,

$$\frac{\partial \rho(x)}{\partial t} = \frac{\partial^2 \rho(x)}{\partial x^2}\,.$$

This well known derivation of the heat equation was presented because it contains the main ideas that are used later in more complicated cases.

The case of a repulsive potential. As in the previous paragraph we want to calculate the flux of the cells between the neighboring intervals of the length l_N. We assume (3.14) to hold. As a first step we want to show, that for the scales that we have introduced the speed of each cell is approximately constant and equal to some constant v. Let define

$$g_N(x) = -\frac{1}{N}\sum_{i=0}^{N} \nabla V_N(x - x_i)\,. \tag{3.22}$$

To simplify the notation we will write $g(x)$ instead of $g_N(x)$ in this paragraph.

The key point is to show that standard deviation of $g(x)$ is small, i.e. approaches zero if the number of cells goes to infinity. This would allow to assume that $g\,(x)$ is a deterministic (as opposite to stochastic) variable.

$$\mathrm{corr}(g(x), g(y)) = \langle g(x), g(y)\rangle - \langle g(x)\rangle\langle g(y)\rangle$$

and

$$\langle g(x), g(y)\rangle = \frac{1}{N^2}\sum_{i,j}\int_{\Omega^N} \nabla V_N(x - x_i)\nabla V_N(y - x_j) d\mu(x_1, \ldots, x_N)\,,$$

where Ω is the region containing the cells. For simplicity, and without much lost of generality, we will assume that Ω is a circle of the length 1 and $d^N\mu$ is a probability

measure in Ω^N. Symmetry of V_N implies

$$\begin{aligned}\langle g(x), g(y)\rangle &= \frac{1}{N^2}\sum_{i=j}\int\limits_{\Omega^N} \nabla V_N(x-x_i)\nabla V_N(y-x_i)d\mu(x_1,\dots,x_N)\\ &\quad+\frac{1}{N^2}\sum_{i\neq j}\int\limits_{\Omega^N} \nabla V_N(x-x_i)\nabla V_N(y-x_i)d\mu(x_1,\dots,x_N)\\ &= N^{4\beta-1}\int\limits_{\Omega^N} \nabla V_1(N^\beta(x-x_1))\nabla V_1(N^\beta(y-x_1))d\mu(x_1,\dots,x_N)\\ &\quad+N^{4\beta-1}(N-1)\int\limits_{\Omega^N} \nabla V_1(N^\beta(x-x_1))\nabla V_1(N^\beta(y-x_2))d\mu(x_1,\dots,x_N)\\ &= N^{4\beta-1}I_1+N^{4\beta-1}(N-1)I_2\,.\end{aligned}$$

We assume as it is common in statistical physics (see [24]) that, locally, cells are near the equilibrium state, i.e. the distribution of the cell is close to the Gibbs distribution (cf. [39]).

$$C\cdot e^{-\sum_{i,j}V_N(x_i-x_j)}dx_1\dots dx_N\,,$$

where C is a normalization constant that is chosen to have a probability measure. Therefore, we assume that

$$d\mu(x_1,\dots,x_N)=\bar{C}\rho_N(x_1,\dots,x_N)\cdot e^{-\sum_{i,j}V_N(x_i-x_j)}dx_1\dots dx_N\,, \tag{3.23}$$

where ρ_N is close to a function $\rho(x_1)\dots\rho(x_N)$, ρ is a cell density and $\bar{C}$ is a normalization constant. In order to calculate the resulting integrals we introduce new variables $\xi_1 = N^\beta x_1,\dots\xi_N = N^\beta x_N$. In the case $x=y$ we get

$$I_1=\frac{1}{N^\beta}\int\limits_{(N^\beta\Omega)^N}\nabla\left(V_1(N^\beta x-\xi_1)\right)\Big)^2\tilde{\rho}(\xi_1,\dots,\xi_N)e^{-N^\beta\sum_{i,j}V_1(\xi_i-\xi_j)}d\xi_1\dots d\xi_N\,.$$

We want to have $N^{4\beta-1}I_1\to 0$ as $N\to+\infty$. Let us suppose that V_1 has a compact support of a radius a (a fast enough decay would work similarly with minor changes). We can divide $(N^\beta\Omega)^N$ into two sets: Ω_0 and Ω_1 defined as follows

$$\begin{aligned}\Omega_0&=\{y\in(N^\beta\Omega)^N\ :\ \exists i,j\,,\quad V_1(y_i-y_j)\neq 0\}\\ \Omega_1&=\{y\in(N^\beta\Omega)^N\ :\ V_1(y_i-y_j)=0\}\,.\end{aligned}$$

It is easy to see, that

$$I_1=\frac{1}{N^\beta}\int\limits_{\Omega_0}+\int\limits_{\Omega_1}\nabla\left(V_1(N^\beta x-\xi_1)\right)\Big)^2\tilde{\rho}(\xi_1,\dots,\xi_N)e^{-N^\beta\sum_{i,j}V_1(\xi_i-\xi_j)}d\xi_1\dots d\xi_N=I_{10}+I_{11}$$

and that $N^{4\beta-1}I_{10}\to 0$ as $N\to+\infty$. On the other hand

$$N^{4\beta-1}I_{11}=N^{4\beta-1}C\cdot\left(\frac{N^\beta-a}{N^\beta}\right)^N\,,$$

where C is a constant, which does not depend on N. This expression tends to zero if $\beta < 1$. The same arguments allow us to get $I_2 \to 0$ for $N \to +\infty$. Therefore, $\mathrm{var}(g(x)) \to 0$. Hence, for $\beta < 1$ we can assume (using the law of large numbers), that the speed is locally constant for short time intervals.

Notice that we have obtained that the velocities given in (3.22) are a deterministic quantity assuming only that $\beta < 1$ if the cells are distributed according to the Gibbs measure (3.23). If it had been assumed that cells were distributed uniformly, we would obtain that the velocities would be deterministic if $\beta < \frac{1}{3}$, that is exactly the restriction in the exponents obtained by Oeshläger in [28]. Therefore this restrictions seems to be just technical and due to the method of proof used in [28] but it does not seem to be essential in order to derive the limit model (3.24).

The case $\beta = 1$ is usually called hydrodynamic limit. In that case the variance of the cells speed does not tend to 0 as $N \to +\infty$. Therefore, cell's velocity cannot be assumed to be a deterministic quantity as for $\beta < 1$ but on the contrary is a stochastic variable. To our knowledge, this interesting mathematical limit has not been analyzed rigorously yet.

In order to derive the evolution equations we can argue as in previous paragraph of this Subsection. Under the assumption (3.21) we can assume that each cell is moving independently as a Brownian cell but with some external speed v. Therefore, the probability that cell located at a_i will be in the interval $[0, l_N]$ at time $t + \Delta t$ is:

$$p_i = p(a_i) = \frac{1}{\sqrt{4\pi\Delta t}} \int_{I_R} e^{-\frac{(x-a_i-v\Delta t)^2}{4\Delta t}} dx\,.$$

Now, taking into account the definition of cell density as well as the fact that l_N is chosen in the mesoscopic scale (i.e. $d_N \ll l_N \ll 1$) we obtain

$$< N_{lr} >= \frac{M \int\limits_{I_L} p(x)\rho(x)dx}{\int\limits_{I_L} \rho(x)dx} = \frac{\rho_0 \int\limits_{I_L} p(x)\rho(x)dx}{1 + \frac{l_N \alpha}{2\rho_0}} \approx \int\limits_{I_L} p(x)\rho(x)dx\,,$$

where M denotes the number of the cells in the interval I_L. Using the method presented for the derivation of the heat equation we obtain $\langle N_{lr}\rangle$ and $\langle N_{rl}\rangle$. We define

$$\varphi(x) = \int\limits_{\frac{x}{\sqrt{4t}}}^{+\infty} e^{-x^2} dx \qquad \phi(x) = \int\limits_{0}^{\frac{x}{\sqrt{4t}}} x e^{-x^2} dx \qquad \eta(x) = \int\limits_{0}^{\frac{x}{\sqrt{4t}}} x^2 e^{-x^2} dx\,.$$

Henceforth, elementary computations yield

$$\begin{aligned} < N_{lr} > = {} & \frac{\rho_0 - \alpha v \Delta t}{2\sqrt{\pi}} \left(\sqrt{4\Delta t} + 2v\Delta t \varphi(-v\Delta t) - 2v\Delta t \phi(v\Delta t) \right) \\ & + \frac{\alpha}{2\sqrt{pi}} \left(-\Delta t \sqrt{\pi} + (v\Delta t)^2 \varphi(-v\Delta t) 4\Delta t \eta(v\Delta t) \right) \end{aligned}$$

and also

$$< N_{rl} > = \frac{(\rho_0 - \alpha v\Delta t)}{2\sqrt{\pi}} \left(\sqrt{4\Delta t} - 2v\Delta t\varphi(v\Delta t) - 2v\Delta t\sqrt{4\Delta t}\phi(v\Delta t) \right) + \frac{\alpha}{2\sqrt{\pi}} \left(\Delta t\sqrt{\pi} - (v\Delta t)^2\varphi(v\Delta t) - 4\Delta t\eta(v\Delta t) \right) .$$

Therefore,

$$< N_c >=< N_{rl} > - < N_{lr} >= -\rho_0 v \cdot \Delta t + \alpha \cdot \Delta t + O(\Delta t^2)$$

Letting $\Delta t \to 0$ we finally obtain

$$\frac{\partial \rho(x,t)}{\partial t} = G(V_1)\frac{\partial}{\partial x}\left(\rho(x,t)\frac{\partial}{\partial x}\rho(x,t) \right) + \frac{\partial^2 \rho(x,t)}{\partial x^2} , \tag{3.24}$$

where $G(V_1) = \int_{\mathbb{R}} V_1(x)dx$.

3.2.2 The case of pure hard-core potential

This problem was solved by Rost in [36]. We intend to present here the main idea of Rost method. We will combine Rost method with the ideas of Section 3.2.1 in order to derive results for potentials containing hard core and repulsive part.

The validity of the method is restricted only to the one-dimensional case. The main idea of the method proposed by Rost in [36] is the following. Due to the presence of hard core potentials the cells remain ordered in the same manner as for the initial time. Each cell evolves in Brownian manner until their collision with another cell. In order to estimate the effect of the collision between cells Rost uses the following trick.

We define a new cell system approaching the centers of the cells by elimination of the hard core part of them. It turns out that the resulting system of cells evolves basically as a set of independent Brownian cells described at the beginning or Subsection 3.2.1. At a first glance it could seen that the evolution of the obtained "compressed" system is different from a set of independent Brownian cells because the last ones cross each other when they collide, and cells obtained from the hard core cells "rebound" in collisions. However, since all the evolving cells are identical the evolution of the cells is identical if we just relabel the indexes of the cells in collisions. We can then compute the fluxes of hard core cells computing the fluxes of cells in the compressed system as will be indicated below. This implies that at every time we may compute how many cells are between two certain points.

Let us precise the argument. We denote as $\rho(x)$ the cell density in the original system in which the cells interact by means of hard-core potentials. As in Subsection 3.2.1, we denote by l_N a characteristic mesoscopic length satisfying (3.14). We define a new compressed system as follows. Let us pick up a cell at the point x_0 that without lost of generality we will assume to be the origin. Our main goal is to compute the flux of cells crossing through $x_0 = 0$ during a time Δt satisfying (3.14) and (3.21).

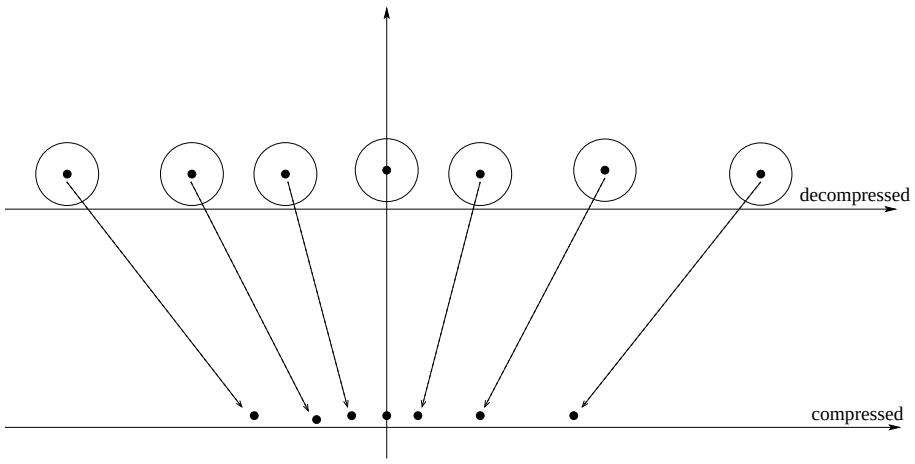


Figure 2: A process of compression

To this end, arguing as in [36] we define a new compressed system of points just eliminating the cores of the cells having diameter c. We do this in a non ambiguous manner keeping fixed the position of the cell at $x_0 = 0$ (see Fig. 2).

By assumption, the original cells move in a Brownian manner with the only constraint that their cores cannot traverse each other. This means that the cells in the compressed system move in a similar Brownian manner, but with the constraint that their trajectories cannot cross. However, if we are not concerned with keeping a fixed ordering for the cells, we can assume that the cells of the compressed system move in an unconstrained and independent Brownian manner, because the Brownian paths are independent on their previous history and are invariant under reflections with respect to a given point. In other words, they move exactly as the cells studied in Subsection 3.2.1

Arguing as in Subsection 3.2.1 we then obtain that the number of cells crossing the origin during the time Δt is $\alpha \Delta t$ where $\alpha = \tilde{\rho}'(0)$, and where $\tilde{\rho}'$ is the cell density for the compressed system. Notice that this density is larger than the one in the original uncompressed system because the same number of cells is packed in a smaller region. It only makes sense to compute the densities $\rho, \tilde{\rho}$ in mesoscopic regions larger than the average distance between cells $\frac{1}{N}$. Suppose that $dx \gg \frac{1}{N}$. The number of cells in the original system in a region that size is ρdx. The length of the interval were these cells are placed after compressing the system is

$$dy = (1 - c\rho)dx$$

Therefore, the cell density in the compressed system would be

$$\tilde{\rho} = \frac{\rho dx}{dx - c\rho dx} = \frac{\rho}{1 - c\rho}\,.$$

Then

$$\alpha = \frac{d}{dy}\tilde{\rho}(y) = \frac{d}{dx}\frac{\rho(x)}{1 - c\rho(x)} \cdot \frac{dx}{dy} = \frac{\rho'(x)}{(1 - c\rho(x))^3}\,.$$

Notice, however, that $\alpha\Delta t$ is not the number of cells crossing the origin in the initial decompressed system. The reason is that the original cell that has been used as a center for the compression process has moved. Since the paths followed by the cells must be continuous, in order to obtain the position of the cells for the original decompressed system we must take as center for the decompression procedure the same cell that was initially used for the compression in its new position.

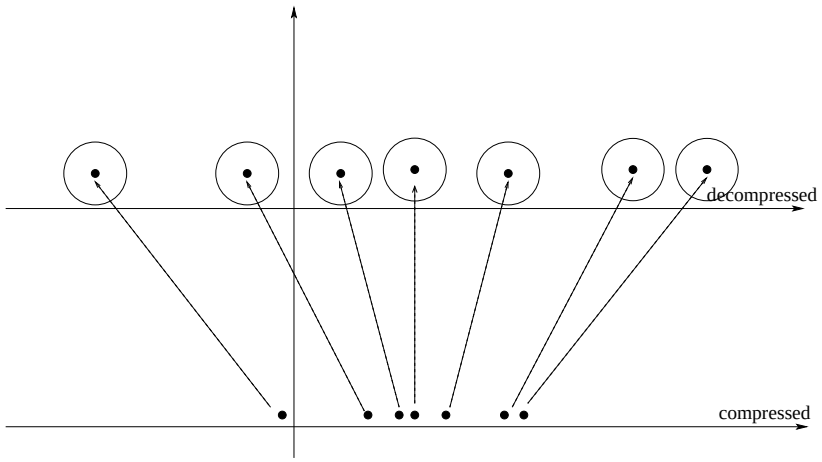


Figure 3: A process of decompression

Since in the compressed system the average distance between cells is $\frac{1}{\tilde{\rho}}$, it follows that the center of the original cell has shifted to a distance $\frac{\alpha\Delta t}{\tilde{\rho}}$ from the origin. We then decompress taking this point as a center (see Fig. 3. In this decompression process the length of the interval $[0, \frac{\alpha\Delta t}{\tilde{\rho}}]$ expands to $\frac{\alpha\Delta t}{\tilde{\rho}} + \alpha\Delta tc$. Assuming that the cells in this interval are approximately homogeneously distributed we then obtain that the total number of cells that in the decompressed system would had cross to the right of the point $x_0 = 0$ is

$$\frac{\frac{\alpha\Delta t}{\tilde{\rho}}}{\frac{\alpha\Delta t}{\tilde{\rho}} + \alpha\Delta tc} \cdot \alpha\Delta t = \frac{\alpha\Delta t}{1 + \tilde{\rho}c} = \alpha(1 - c\rho)\Delta t\,. \tag{3.25}$$

This is that the number of cells crossing the line $x_0 = 0$ during the time Δt, i.e. the desired cell flux

$$\Delta t \cdot \frac{\rho'(x)}{(1 - c\rho(x))^2}\,.$$

Letting $\Delta t \to 0$ we obtain the final equation (as in [36])

$$\frac{\partial\rho(x,t)}{\partial t} = \frac{\partial}{\partial x}\left(\frac{1}{(1 - c\rho(x,t))^2}\frac{\partial\rho(x,t)}{\partial x}\right)\,. \tag{3.26}$$

Equation (3.26) is the well known "fast diffusion" equation that has been throughly studied (cf. [6, 18, 35]). It can be written in a more familiar form using the variable $u = 1 - c\rho(x,t)$ that transforms (3.26) into

$$u_t = \left(u^{-2}u_x\right)_x\,. \tag{3.27}$$

It is well known that (3.27) can be explicitly solved by means of a Bäcklund transformation that brings the fast diffusion equation to the classical heat equation (cf. [6,18,35]). This Bäcklund transformation is just the change of coordinates that would be made during the previously described compression-decompression procedure.

3.2.3 Repulsive potentials with hard-core part

We now use Rost method described in previous Subsection to derive suitable macroscopic limits for cells interacting by means of repulsive potentials containing hard core potentials parts.

We assume, that for the time scale we have introduced (see (3.14) and (3.21)) we may approximate the behavior of our system by the system of the independent Brownian cells, which in addition, are moving with some constant speed v. We use the technique of the compressed system, presented in the subsection 3.2.2 combined with the method presented in subsection 3.2.1 for smooth potentials. From the previous section we know that the flux for the compressed system is

$$j_c \stackrel{\text{def}}{=} -\tilde{\rho}_0 \cdot v\Delta t + \tilde{\rho}' \cdot \Delta t$$

Following the calculation from the subsection 3.2.2 we obtain that the flux

$$j_c = -\left(\frac{\rho(x)}{1-c\rho(x)} \cdot v\Delta t + \frac{\rho'(x)}{(1-c\rho(x))^3} \cdot \Delta t\right)(1-c\rho)$$

and finally, letting $\Delta t \to 0$ we obtain the following limit equation

$$\frac{\partial \rho(x,t)}{\partial t} = G(V_1)\frac{\partial}{\partial x}\left(\rho(x,t)\frac{\partial}{\partial x}\rho(x,t)\right) + \frac{\partial}{\partial x}\left(\frac{1}{(1-c\rho(x,t))^2}\frac{\partial \rho(x,t)}{\partial x}\right). \tag{3.28}$$

This equation is a combination of the well known porous medium equation with the fast diffusion equation mentioned before. Both equations have been much studied in the literature and their properties are well known. (cf. [1–3, 18]). Notice that the density $\rho(x,t)$ has a maximal value $1/c$. In the next paragraph we describe some simple solutions of (3.28) yielding front propagation.

Traveling waves. In this paragraph we study the existence of traveling wave for Eq. (3.28). The motivation for calculating traveling waves is to determine which effect is a dominant one for Eq. (3.28): repulsion or aggregation.

For simplicity we rewrite Eq. (3.28) rescaling space in order to absorb constant $G(V_1)$. Hence, Eq. (3.28) takes the form

$$\frac{\partial}{\partial t}\rho(x,t) = \frac{1}{2}\frac{\partial^2}{\partial x^2}\rho^2(x) + \frac{\partial}{\partial x}\left(\frac{1}{(1-c\rho(x,t))^2}\frac{\partial}{\partial x}\rho(x,t)\right). \tag{3.29}$$

We are looking for traveling wave in the form $\rho(x,t) = \varphi(x-vt)$. Substituting this to Eq. (3.29) we get the ODE

$$-v\frac{d}{dy}\varphi(y) = \frac{1}{2}\frac{d^2}{dy^2}\varphi^2(y) + \frac{d}{dy}\left(\frac{1}{(1-c\varphi(y))^2}\frac{d}{dy}\varphi(y)\right).$$

After integration of both sides and some algebraical calculations we obtain

$$\varphi' = -\frac{(v\varphi+\beta)(1-c\varphi)^2}{1+\varphi(1-c\varphi)^2}\,, \tag{3.30}$$

where β is an integration constant. We are interested in finding solutions of Eq (3.30) such that $\varphi \le \frac{1}{c}$, since this a maximal density allowed for cells having a hard core of diameter c. We can try to constructs orbits of Eq. (3.30) connecting the steady states $\varphi = \frac{1}{c}$ and $\varphi = -\frac{\beta}{v} = L$ are of (3.30). Since in our context ρ is a positive density, we should assume $L \ge 0$. Due to the symmetry under reflections of the equations we can assume that $\varphi(-\infty) = \frac{1}{c}$ and $\varphi(+\infty) = -\frac{\beta}{v}$

A classical ODE linearization of (3.30) around the steady state $\varphi = \frac{1}{c}$ yield the asymptotics

$$\varphi(y) \sim \frac{1}{c} + \frac{1}{vc\,(1-cL)}\frac{1}{y} \qquad \text{as } \; y \to -\infty \tag{3.31}$$

Then it follows that for $v < 0$ there are not traveling waves of the Eq. (3.30) satisfying $0 \le \varphi \le \frac{1}{c}$ except the trivial one $\varphi \equiv \frac{1}{c}$. In the case $v = 0$ a similar result can be obtained using the fact that in that case the only steady state of Eq. (3.30) is $\varphi = \frac{1}{c}$.

Classical ODE theory shows that for each $v > 0$ and $K > 0$ there exists a unique solution of Eq. (3.30) satisfying (3.31) and

$$\varphi(y) \sim L + K\exp\left(-\frac{v\,(1-cL)^2}{1+L\,(1-cL)^2}y\right) \qquad \text{as } \; y \to \infty\,.$$

Summarizing, equation (3.29) has solutions having the form of translating fronts for which cell density jumps from the value $\rho = L \in \left[0, \frac{1}{c}\right]$ to the value $\rho = \frac{1}{c}$, i.e. the density can jump from any value below the maximal density to the maximal density where cells are as closely packed as possible. The admissible fronts are always compressing fronts. Fronts for which cell density is reduced do not exist for (3.29). Moreover, the final value of cell density for this equation after the pass of the front is always the maximal one.

4 Derivation of the equations: potentials with an attractive part

In this section we want to give some explanation what happens if the interaction potential have an attractive part. More precisely we are interested in potential which are attracting enough. By this we mean $\int_{\mathbb{R}} V(x)dx < 0$.

We begin studying the case of deterministic evolution of the cells. Arguing formally as in Subsection 3.1 we would derive, in the case of long range potentials the ill posed parabolic equation:

$$\rho_t = -\left(\rho\rho_x\right)_x\,. \tag{4.1}$$

The onset of the ill-posed problem (4.1) as a macroscopic limit strongly indicates that the arguments in Subsection 3.1 cannot be applied in this case. Roughly speaking, since

we obtained an ill-posed problem, the macroscopic equation may not have any solution while the original system certainly have. Therefore, the derivation cannot be considered true in this case. Nevertheless the limit equation (4.1) contains to some extent a "portion of truth". Indeed, the reason for the onset of an ill posed problem as a macroscopic limit is that for attractive potentials cells might aggregate in clusters. Ill posed equations like (4.1) with suitable regularizations can yield easily clustering phenomena (cf. for instance the numerical simulations in [20]). Roughly speaking, cell aggregation could be stopped, at least in principle for cell densities having important variations in length scales of the order of the length of interaction for the potentials. This length scale would be zero at the macroscopic limit and for that reason the corresponding equation for the density becomes the ill-posed problem (4.1) in such a limit. One can think that equations like (4.1) in some sense try to create fine variations for the density in length scales of order zero. In order to obtain a more reasonable equation it is then natural to use as length scale the mesoscopic length scale that for the potential (2.3) is just $\frac{1}{N^\beta}$. We then rescale a space variable in such a way that the range of the potential is of order 1.

We may assume that cells are located at points x_i, $i = -\frac{N}{2}, \ldots, \frac{N}{2}$. If the potential V decreases fast enough (say, exponentially) we may assume, without lost of generality, that $i = \mathbb{Z}$. Then, the speed of each cell is the following

$$v_i = -\frac{1}{N}\left(\sum_{j=-\infty}^{i-1} V'(x_i - x_j) + \sum_{j=i+1}^{+\infty} V'(x_i - x_j)\right). \tag{4.2}$$

In the case of long rang interactions the sum in the formula (4.2) might be approximated by an integral and thus, we obtain

$$v(x) = -\int_{\mathbb{R}} V'(x-y)\rho(y)dy\,, \tag{4.3}$$

where ρ is the macroscopic density. It is known, that a macroscopic density fulfills the equation

$$\frac{\partial \rho}{\partial t} + \frac{\partial j}{\partial x} = 0\,, \tag{4.4}$$

where $j = \rho \cdot v$ is a flux of cells (see [24]). Combining formulas (4.3) and (4.4) we obtain the following integro-differential equation

$$\frac{\partial \rho(x,t)}{\partial t} = \frac{\partial}{\partial x}\left(\rho(x,t)\int_{\mathbb{R}} V'(x-y)\rho(y,t)dy\right) \tag{4.5}$$

that in the case of $\int_{\mathbb{R}} V(x)dx > 0$ might be considered as generalization of the classical porous medium equation. Indeed if the characteristic length scale for the variation of $\rho(x,t)$ is much larger then the range of interaction of V it would be natural to use the approximation

$$\int_{\mathbb{R}} V'(x-y)\rho(y,t)dy = \int_{\mathbb{R}} V(x-y)\rho_x(y,t)dy \approx \left(\int_{\mathbb{R}} V(y)dy\right)\rho_x(x,t)$$

Therefore Eq. (4.5) (without the drifting part) becomes Eq. (3.11) If on the contrary $\int_{\mathbb{R}} V(x)dx < 0$ a similar argument leads to Eq. (4.1) and the approximation cannot be expected to be true.

In the case of attractive potential cells can aggregate and create cluster structures. This clusters corresponds to the steady states of Eq. (4.5). We are not going to analyze Eq. (4.5) in details in the present paper. For detailed analysis of the Eq. (4.5) and rigorous proofs we refer to [7].

First, notice that System (4.5) is a gradient flow. In particular, the following energy function

$$E(t) = \int\limits_{\mathbb{R}} \int\limits_{\mathbb{R}} V(x-y)f(x,t)f(y,t)dxdy \tag{4.6}$$

decreases along trajectories. Elementary computations yield

$$\frac{d}{dt}E(t) = -2\int\limits_{\mathbb{R}} f(x,t)\left(\int\limits_{\mathbb{R}} V'(x-y)f(y,t)\right)^2 dxdy \leq 0\,.$$

Then, the solutions of the system (4.5) approach to stationary states.In general, in the deterministic case, these steady states are not global minima.

However, in the stochastic case, solutions should approach to global minima with probability close to one, although perhaps such approximation could take place in very long times for some initial data. Nevertheless, a key problem in order to describe the long time asymptotics of (4.5) is to study the steady states of System (4.5) and to determine which ones have minimum energy.

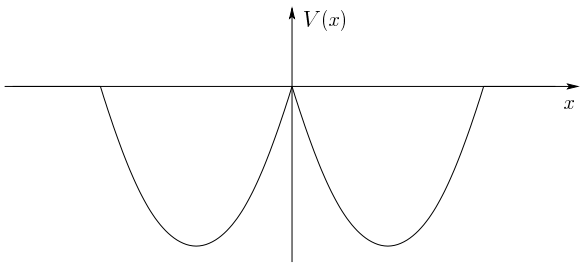


Figure 4: An example of a potential given by (4.7)

It can be shown that, for suitable choices of $V(x)$, there are many non homogeneous steady states of the Eq. (4.5) for potentials containing an attractive and a repulsive part (see [7]). In some special cases we can give a detailed description of some steady states. If the potential V has the form (see Fig. 4)

$$V(x) = \begin{cases} 0 & \text{for } |x| > r \\ V_-(x) = \alpha(x+r) & \text{for } -2r < x < 0 \\ V_+(x) = \alpha(x-r) & \text{for } 0 < x < 2r\,, \end{cases} \tag{4.7}$$

where

$$\alpha(x) = \alpha(-x)\,, \qquad\qquad \alpha(-r) = \alpha(r) = 0\,. \tag{4.8}$$

the following lemma is true

Lemma 4.1 (cf. [7]). *If V is defined by* (4.7) *and the condition* (4.8) *is fulfilled then for any $c > 0$ a function $\rho(x) = c\mathbb{I}_{[0,2r]}$ (where $\mathbb{I}_A$ is a characteristic function of a set A) is a steady state of Eq.* (4.5).

A general study of the main mathematical properties of Eq. (4.5) as for instance classes of functions where the problem is well posed, steady states, blow-up phenomena and others can be found in [7].

In the case of the potential including also a hard-core part combining the arguments used in Subsections 3.2.1 and 3.2.2 with those in this section it is possible to obtain an evolution equation with the form

$$\rho_t = \left(\frac{\rho_x}{(1-c\rho)^2}\right)_x + \left(\rho \int V'(x-y)\rho(y)dy\right)_x .$$

5 Conclusions

Let us present a summary of the results derived in the paper. We define

$$D_1 = \frac{\left(\int_{\mathbb{R}} V(y)\,dy\right)}{2} \qquad \text{and} \qquad D(\rho) = \sum_{\substack{i=-\infty \\ i\neq 0}}^{+\infty} \left(-\frac{i}{\rho}\right) V'\left(\frac{i}{\rho}\right) ,$$

We remark that in particular these coefficients determine the characteristic time scale in which relevant variations of densities take place.

The results derived in this paper are collected in Table 1.

In this paper we have reviewed many results concerning the macroscopic limits of cell equations of the form (1.1). We have seen some of the limit results available in the literature as well as other cases might be explained using elementary arguments.

As a general conclusion we can say that in the case of repulsive potentials the interactions between cells yield nonlinear diffusive equations. On the other, the noise term yields classical linear fickian diffusive terms as could be expected.

On the contrary in the case of attractive potentials the limit equations are kinetic equations like for instance (4.5). In that case, the densities could exhibit clustering phenomena that do not appear in the case of repulsive potentials where the dynamics is just a diffusive one.

There are several interesting mathematical problems that has not been analyzed in detail in the literature. Perhaps the most relevant one is the so-called hydrodynamic limit, in which the cell velocity cannot be assumed to be a deterministic quantity. On the

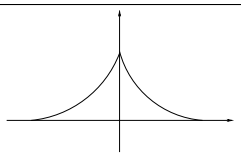
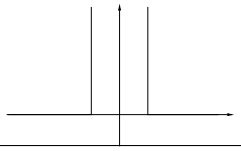
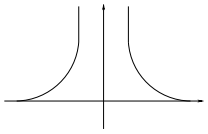
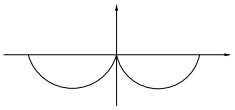
$V(x)$	σ	range	limit equation	derivation — in Section
	0	$d \ll R$	$\rho_t = D_1(\rho^2)_{xx}$	3.1
	0	$d \simeq R$	$\rho_t = \frac{1}{2}(\rho D(\rho))_{xx}$	3.1
	$\neq 0$	$s \gg R$	$\rho_t = D_1(\rho^2)_{xx} + \sigma^2 \rho_{xx}$	3.2
	0	$d \simeq R$	$\rho_t = 0$	3.2.2
	$\neq 0$	$d \simeq R$	$\rho_t = (\sigma^2 \frac{\rho_x}{(1-c\rho)^2})_x$	3.2.2
	$\neq 0$	$d \gg R$	$\rho_t = D_1(\rho^2)_{xx} + \sigma^2(\frac{\rho_x}{(1-c\rho)^2})_x$	3.2.3
	0	$d \gg R$	$\rho_t = (\rho \int V(x-y)\rho(y)dy)_x$	4

Table 1: Summary of the macroscopic limits

contrary, in this case, cell velocity is a stochastic variable. On the other hand, given the short range of some of the cell interactions this case is perhaps the most interesting one from the point of view of biological applications.

Finally, we discuss briefly the possible effect of mitosis in the limit equations. Probably the most interesting approach would be to introduce mitosis at the microscopic level by means of some branching process, and to compute the effect of this process in the resulting equations. A simpler, more phenomenological approach would be to add a typical logistic growth law in the equation with the form $\alpha\rho\,(\beta - \rho)$. Notice that particular choice of the mitosis term a typical model with cells containing hard cores (cf. Eq. (3.24)), would contain two characteristic "maximal densities", namely the one associated to the maximum cell packing, $1/c$ and the one associated to the maximum biological capacity of the system β. Depending on the relative size between these two parameters one could expect different behaviors for the resulting model.

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