1 Simulation of interacting particles

We simulate the system of interacting particles under the interaction kernel

\[ K_{\alpha,R}(x) = g_{\alpha,R}(|x|) \frac{x}{|x|} \]

where \( R > 0 \) is a cut-off parameter which allows us to appreciate the difference between long or short range interaction and \( \alpha \) is a (possibly multidimensional) intensity parameter which again helps to see different cases.

The function \( g_{\alpha,R} \) will be chosen with some criterion. The kernel \( K_{\alpha,R} \), applied to the difference between particle positions

\[ K_{\alpha,R}(X_{i,N}^t - X_{j,N}^t) = g_{\alpha,R}\left( |X_{i,N}^t - X_{j,N}^t| \right) \frac{X_{i,N}^t - X_{j,N}^t}{|X_{i,N}^t - X_{j,N}^t|} \]

has the direction of the line between the particles, hence produces a displacement of \( X_{i,N}^t \) in this direction; and it has intensity \( g_{\alpha,R}\left( |X_{i,N}^t - X_{j,N}^t| \right) \). We may distinguish between repulsive and attracting kernel: if

\[ g_{\alpha,R}(|x|) > 0 \]

it is repulsive, because the vector \( X_{i,N}^t - X_{j,N}^t \) moves \( X_{i,N}^t \) away from \( X_{j,N}^t \). If

\[ g_{\alpha,R}(|x|) < 0 \]

on the contrary it is attracting.

Usually, if we think to a repulsive mechanism, we want that it is stronger when the particles are closer. Hence we take \( g_{\alpha,R} \) positive and decreasing. A simple example, which takes into account the range-parameter \( R \), is

\[ g_{\alpha,R}(|x|) = \alpha \cdot \left( 1 - \frac{|x|}{R} \right) 1_{|x| \leq R} \]

with \( \alpha > 0 \).

To simulate such system we may introduce a few functions

```r
norma=function(x,y) sqrt(x^2+y^2)
H=function(r) (sign(r)+1)/2
g=function(r,R,alp) alp*H(1-r/R)*(1-r/R)
```

and run the code, for different values of \( \alpha \) and \( R \):

```r
N=100; n=5000; dt=0.001; sig=1; h=sqrt(dt); T=20; L=15; L0 = 2
```
Here for instance are two samples for \( \alpha=10; \ R=100 \), at short distance of time:

It is interesting also to run the code for negative values of \( \alpha \).

1.1 Dependence of \( g_{\alpha,R} \) on \( R \)

In the example above, there is a function \( g_{\alpha}(r) \) such that

\[
 g_{\alpha,R}(r) = g_{\alpha}(r/R).
\]

In the example it is

\[
 g_{\alpha}(r) = \alpha \cdot (1 - r) 1_{r \leq 1}.
\]

We shall always assume such kind of dependence below, also in the theoretical arguments.
2 Local interaction

Assume now we want to simulate a family of cancer cells which are subject only to the following mechanisms: a random motion and the volume constraint. By the latter we mean that two cells cannot overlap (they have to occupy different portions of space). In reality, cells have a very high degree of deformation, hence if we idealize them as balls we have to accept some degree of overlapping of the balls, but not too much.

A simple way to include in our dynamics the volume constraint is to introduce a repulsive kernel $K_{\alpha,R}$ which has a very short range $R$, of the order of cell size. In the simulation above, since we have taken cells of radius 0.5 (recall $\text{cir}=(1:N)*0+0.5$), and $K_{\alpha,R}$ acts on the centers $X_i^j,N$, $X_i^j,N$ of the cells, it must act only when the centers have a distance between 0 and 1 (when the distance between the centers is larger than 1, the cells do not touch and thus no volume constraint applies). Thus we have to take $R = 1$. Moreover, since the volume constraint is really mandatory, we choose $\alpha$ very large. Here are two pictures of the simulation when $\alpha p=1000$; $R=1$:

![Simulation Pictures]

3 The macroscopic limit of particles with a size

3.1 Rescaling the radius of cells

Let us now examine the macroscopic limit. If we idealize particles as points, the concept of macroscopic limit is the one discussed until now in the lectures. However, when we assume that particles have a size, some additional arguments apply.

Assume the particles are cells. Idealize them as balls of radius $R_{cell}$. In doing the macroscopic limit we increase the number of cells. Compare then the case of 100 and 10000 cells. Do we take the same radius or do we rescale the radius? This dilemma corresponds precisely to two different viewpoints, that we now explain.

We may decide that we do not rescale the radius: the radius is always $R_{cell}$, say 1/2, independently of the increasing number of cells. This vision corresponds to an observer
than lives at the level of cells, that see the cells as "large" individuals. A small tumor (say 100 cells) occupies then a small portion of space, a larger tumor (say 10000 cells) occupies a portion of cells which is much larger (say 100 times the previous one). This is the *microscopic vision*. To make a comparison with different kind of mathematical models (the so called cellular automata), this vision is captured very well by considering the lattice \( \mathbb{Z}^d \) and assume that each node of the lattice can be either empty or occupied by a cell.

The *macroscopic vision*, on the contrary, corresponds to our vision of a tissue, where the presence of 100, 10000 or \( 10^9 \) cells just corresponds to a different degree of smoothness, granularity of the object we observe. The cells occupy a portion \( D \) of the macroscopic space (independent of the number of cells); we see them more or less as a continuum, with a different degree of smoothness depending on their number. If we adopt this vision, the radius \( R_{\text{cell}} \) must be rescaled depending on the number of cells, otherwise cells should necessarily overlap. The correct rule comes from the limit case of cells of maximal density and uniformly distributed: a cube \([0,1]^d\) is completely filled by cubic cells occupying the space \( \prod_{i=1}^{d} [a_i, a_i + \frac{1}{n}] \). The cube \([0,1]^d\) is covered by \( n^d \) of such small cubes. So, if the number of cells is \( N \), their diameter must be a number \( \frac{1}{n} \) such that \( n^d = N \). We deduce \( n = N^{1/d}, \frac{1}{n} = N^{-1/d} \). Summarizing, the radius of a cell must be of the order

\[
R_{\text{cell}}^N \sim \frac{1}{2} N^{-1/d}.
\]

This rule implies that, at the macroscopic level, we should expect a density function \( \rho(t, x) \) which does not exceed the threshold 1, up to exceptional events which should rapidly relax to 1.

### 3.2 Contact interactions when the radius is rescaled

Assume now we consider interacting cells in the case when the interaction is of contact type, like the volume constraint (or others which occur at the membranes of the cells, like adhesion, that we shall discuss later on). The radius of interaction is therefore of the order of the radius (or diameter) of the cells. Thus we take

\[
R_N = N^{-1/d}
\]

in the definition of the function \( g_{\alpha,R}(r) \). Moreover, assuming the form \( g_{\alpha,R}(r) = g_\alpha(r/R) \), we reach the following fact: the interaction kernel, for contact interactions and for the purpose of a macroscopic description, should be of the form

\[
K^N_\alpha(x) \sim g_\alpha \left( N^{1/d} |x| \right) \frac{x}{|x|}
\]

This prescription however is not completely correct or, more precisely, in the symbol \( \sim \) we could still have a factor depending on \( N \). Let us see why. When we have written above
that the interaction kernel is $K_{\alpha,R} (x)$, we had in mind the mean field model

$$dX_{t}^{i,N} = \frac{1}{N} \sum_{j=1}^{N} K_{\alpha,R} \left( X_{t}^{i,N} - X_{t}^{j,N} \right) dt + \sigma dB_{t}^{i}. \quad (\text{1})$$

Namely, we had in mind to average the contributions of all particles $X_{t}^{j,N}$. Such vision is natural when $X_{t}^{i,N}$ interacts with all particles, or at least with a non-negligible proportion. On the contrary, in the case of contact interaction, the cell $X_{t}^{i,N}$ interacts only with a very small and finite number of cells, those in contact with itself. If we average their contribution by means of the factor $\frac{1}{N}$, in the limit as $N \to \infty$ the interaction becomes evanescent and only the noise remains. Therefore we have to impose a different scaling:

$$dX_{t}^{i,N} = \alpha_{N} \sum_{j=1}^{N} g \left( N^{1/d} |X_{t}^{i,N} - X_{t}^{j,N}| \right) \frac{X_{t}^{i,N} - X_{t}^{j,N}}{X_{t}^{i,N} - X_{t}^{j,N}} dt + \sigma dB_{t}^{i}. \quad (\text{1})$$

Here we have dropped the dependence of $g$ from an intensity parameter and collect the intensity with its dependence on the rescaling in the prefactor $\alpha_{N}$. Which $\alpha_{N}$? Just to confirm the feeling, in the previous model particle $X_{t}^{i,N}$ interacts only with very few particles $X_{t}^{j,N}$, those at distance of the order $N^{-1/d}$ from $X_{t}^{i,N}$; the huge sum $\sum_{j=1}^{N}$ reduces to the sum of very few terms. The intensity of each single term is however $\alpha_{N}$ (not $\frac{1}{N}$).

3.3 The intensity factor $\alpha_{N}$: time rescaling

The choice of $\alpha_{N}$ can be made in two different ways. One, not "honest", is to conjecture the limit, macroscopic, PDE and see which $\alpha_{N}$ intuitively is required to converge. The other is to investigate more closely the microscopic picture.

The factor $\alpha_{N}$ is a sort of artefact due to the desire of a macroscopic description. If we go back to the microscopic vision, the one where the particles have a fixed radius, the interaction kernel should not depend on the number of particles. In that vision particles are described by their positions $Y_{t}^{i,N}$ subject to the dynamics

$$dY_{t}^{i,N} = \sum_{j=1}^{N} b \left( Y_{t}^{i,N} - Y_{t}^{j,N} \right) dt + \sigma dW_{t}^{i}. \quad (\text{1})$$

Here, for shortness of notation, we have set

$$b(y) = \sum_{j=1}^{N} g \left( |y| \right) \frac{y}{|y|}$$

with $g$ having a relatively small support, if we have in mind contact interactions; say support of diameter 1, and particles have also diameter 1. The initial conditions $Y_{t}^{i,N}$
cannot be independent of \( N \), otherwise we start with a huge number of particles one over the other. To have some spreadness of particles also at time \( t = 0 \) we take, for instance, \( Y_t^{i,N} \) with Gaussian law of standard deviation (which is proportional to the radius of the occupied space) equal to \( N^{1/d} \) (so the occupied volume is of the order \( N \)). We expect that, during the dynamics, the particles remain at a distance of that order from the origin.

Now let us rescale the positions \( Y_t^{i,N} \) in such a way that we see all cells in a region of diameter of order 1. Thus we introduce

\[
N^{-1/d} Y_t^{i,N}.
\]

However, if we do so, the equation satisfied by the new positions \( N^{-1/d} Y_t^{i,N} \) contains the rescaled Brownian motions

\[
N^{-1/d} W_t^i.
\]

Such random motion is too small. To understand this, assume we have no interaction (the theory should cover this particular case). If we take the empirical measure associated to \( N^{-1/d} W_t^i \), then the macroscopic PDE does not contain the Laplacian (recall that \( \sigma W_t^i \) produced \( \frac{\sigma^2}{2} \Delta u \); repeating that proof one can see that an infinitesimal diffusion coefficient leads to \( 0 \cdot \Delta u \)). So, there is something wrong in the simple idea that the rescaling is \( N^{-1/d} Y_t^{i,N} \).

What is wrong is that also time has to be rescaled. Intuitively, think to the case without interaction and with a discretized form of the Brownian displacements. At the microscopic level, each time unit every particle has a displacement of order 1. If we just rescale \( N^{-1/d} W_t^i \), each time unit the particles have displacements of order \( N^{-1/d} \). Essentially they do not move, for very large \( N \). The dynamics is too slow to be visible. There is a dynamics, but the rescaling \( N^{-1/d} W_t^i \) has frozen it. If we want to continue to see it, we need to accelerate, to rescale also time.

Recall that \( N^{-1/d} W_t^i \) has the law of a Brownian motion. Hence the time rescaling must be \( t \mapsto t \cdot N^{2/d} \). Therefore we consider the new positions

\[
X_t^{i,N} := N^{-1/d} Y_t^{i,N}.
\]

The particle \( X \) at time \( t = 1 \) is the same as the particle \( Y \) at time \( N^{2/d} \); we accelerate the movie of particles \( Y \)’s.

**Proposition 1** If \( Y_t^{i,N} \) satisfy (1), then \( X_t^{i,N} \) satisfy

\[
dx_t^{i,N} = N^{1/d} \sum_{j=1}^{N} b \left( N^{1/d} \left( X_t^{i,N} - X_t^{j,N} \right) \right) dt + \sigma dB_t^{i,N}
\]

with the initial conditions \( X_0^{i,N} := N^{-1/d} Y_0^{i,N} \), where the independent Brownian motions \( B_t^{i,N} \) are given by

\[
B_t^{i,N} := N^{-1/d} W_{tN^{2/d}}^i.
\]
Proof.

\[ Y_{t}^{i,N} = Y_{0}^{i,N} + \sum_{j=1}^{N} \int_{0}^{t} b(Y_{s}^{i,N} - Y_{s}^{j,N}) \, ds + \sigma W_{t}^{i} \]

\[ Y_{t}^{i,N} = Y_{0}^{i,N} + \sum_{j=1}^{N} \int_{0}^{t} b(Y_{s}^{i,N} - Y_{s}^{j,N}) \, ds + \sigma W_{t}^{i} \]

\[ r = s^{-2/d} \]

\[ Y_{0}^{i,N} + \sum_{j=1}^{N} \int_{0}^{t} b \left( Y_{s}^{i,N} - Y_{s}^{j,N} \right) N^{2/d} \, dr + \sigma W_{t}^{i} \]

\[ X_{t}^{i,N} = N^{-1/d} Y_{0}^{i,N} + N^{-1/d} \sum_{j=1}^{N} \int_{0}^{t} b \left( X_{s}^{i,N} - X_{s}^{j,N} \right) N^{2/d} \, dr + \sigma N^{-1/d} W_{t}^{i} \]

\[ X_{0}^{i,N} + \sum_{j=1}^{N} \int_{0}^{t} N^{1/d} b \left( N^{1/d} (X_{s}^{i,N} - X_{s}^{j,N}) \right) \, dr + \sigma B_{t}^{i,N} \]

**Corollary 2** The correct rescaled dynamics to investigate the macroscopic limit has the form

\[ dX_{t}^{i,N} = N^{1/d} \sum_{j=1}^{N} g \left( N^{1/d} \left| X_{t}^{i,N} - X_{t}^{j,N} \right| \right) \frac{X_{t}^{i,N} - X_{t}^{j,N}}{\left| X_{t}^{i,N} - X_{t}^{j,N} \right|} \, dt + \sigma dB_{t}^{i} \]

### 3.4 Simulations

The correct code for a contact interaction of repulsive form is therefore:

```plaintext
N=300; n=5000; dt=0.000001; sig=1; h=sqrt(dt); T=20; L=2; L0 = 1; d=2
alp=1000*N^(1/d); R=N^(-1/d)
X=matrix(0,N,n); Y=X; X[,1]=runif(N,-L0/2,L0/2); Y[,1]=runif(N,-L0/2,L0/2)
plot(c(-L,L), c(-L,L), type="n")
for(t in 1:(n-1)){
  for (i in 1:N){
    DX= X[i,t]-X[,t]; DY= Y[i,t]-Y[,t]
    Kx=g(norma(DX,DY),R,alp)*DX/(norma(DX,DY)+ 0.000001)
    Ky=g(norma(DX,DY),R,alp)*DY/(norma(DX,DY)+ 0.000001)
    X[i,t+1]=X[i,t] + dt*mean(Kx) + h*sig*rnorm(1)
  }
}
```
Here we have rescaled $\alpha, R$ and the size of the circles according to the theory. Moreover, we have taken a much better time step to avoid that overlap between particles could cause too high artificial displacements. Finally, we have replaced the Gaussian initial condition with a uniform one in order to impose, at time zero, an initial condition very close to density 1.

We suggest to run the code for $N = 100, 200, 300$ and see that the image is very similar, just less and less granular.