Modelling Cell Motion

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Introduction

- Single cells are the basic unit of life.
- They are subjected to physical processes.
- To understand biological phenomena it is necessary to formulate an abstract model of the too complex elements of cellular life.
- Important examples involving cell motion are patterning phenomena, e.g. embryonal development, wound closure etc.

Langevin Equation 1

The motion of a Brownian particle is described by the Langvin equation

$$m\frac{dv}{dt} + \gamma v = \vec{f}(t) \quad \text{and} \quad v = \frac{d\vec{x}_i}{dt}, \tag{1}$$

where $f(t)$ is a random force, a Gaussian stochastic variable with

$$\langle f(t) \rangle = 0 \quad \text{and} \quad \left\langle f(t) f(t') \right\rangle = g\delta(t - t') \tag{2}$$

$\Rightarrow x(t), v(t)$ are also stochastic, so we consider their expectation values. Integration of 1 and using 2 gives

$$\langle v(t_1) v(t_2) \rangle_\xi = \left(v_0 - \frac{g}{2m\gamma} \right) e^{-(\gamma/m)(t_2+t_1)} + \frac{g}{2m\gamma} e^{-(\gamma/m)(t_2-t_1)},$$

for the velocity v.

Langevin Equation 2

Further integration yields

$$\langle x(t_1)x(t_2)\rangle_\xi = \frac{m^2}{\gamma^2}\left(v_0 - \frac{g}{2m\gamma}\right)\left(1 - e^{-(\gamma/m)t}\right)^2 + \frac{g}{\gamma^2}\left[t - \frac{m}{\gamma}\left(1 - e^{-(\gamma/m)t}\right)\right]$$

Aplication of the equipartition theorem for the kinetic energy $mv_0^2/2 = dkT/2$, consideration of thermal equilibrium (stationary expectation $\Rightarrow v_0 = g/(2m\gamma)$) and the identification $D = kT/\gamma$ gives

$$g = \sigma^2 = 2dD\gamma^2 \quad \text{and} \quad \left\langle (\Delta x)^2(t)\right\rangle = 2dDt.$$

One Cell

Some features of single cells:

- Cells in suspension often adopt a spherical shape.
  $\Rightarrow$ They are modelled as spherical objects.
- In absence of signales they behave like a brownian particle, i.e. the perform a random walk. $\Rightarrow$ Langevin-eqation.
- Due to the cytoskeleton and the surface tension they show an (visco-)elastic behaviour.
- In tissues or colonies the cells adhere to eachother and extracellular matrix. $\Rightarrow$ modified Hertz-Model.
- Cells grow and devide.

  $\Rightarrow$ Division occurs when volume is doubled: 

Overdamped Langevin Equation

$$(\gamma_{st} A^i_{rest} \mathbb{1} + \Gamma_{cs} \frac{A^i_{cs}}{A^i}) \frac{d\vec{x}_i}{dt} + \sum_{<j,i>} \Gamma^{ij}_{cc} A^{ij}_{cc} (\frac{d\vec{x}_j}{dt} - \frac{d\vec{x}_j}{dt}) = \sum_{<i,j>} \vec{F}_{ij} + \vec{f}_i, \quad (3)$$

where $\Gamma = (\gamma_\perp - \gamma_\parallel)(\vec{r} \otimes \vec{r}) + \gamma_\parallel \mathbb{1}$ is the friction matrix.
Overdamped regime = High friction coefficients
$\Rightarrow$ Inertia term can be neglected and a system of linear equations for $d\vec{x}_i$ is obtained For one cell and discrete time, we can do the same as above and get

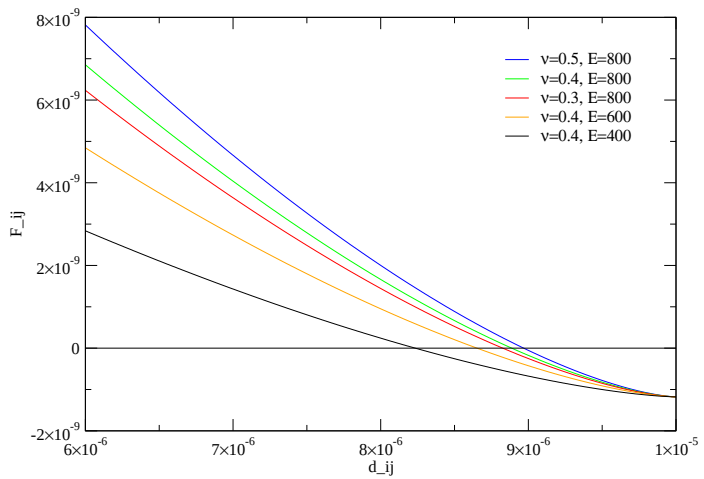
$$\left\langle F(t) F(t') \right\rangle = \frac{2dD\gamma^2}{\Delta t}.$$

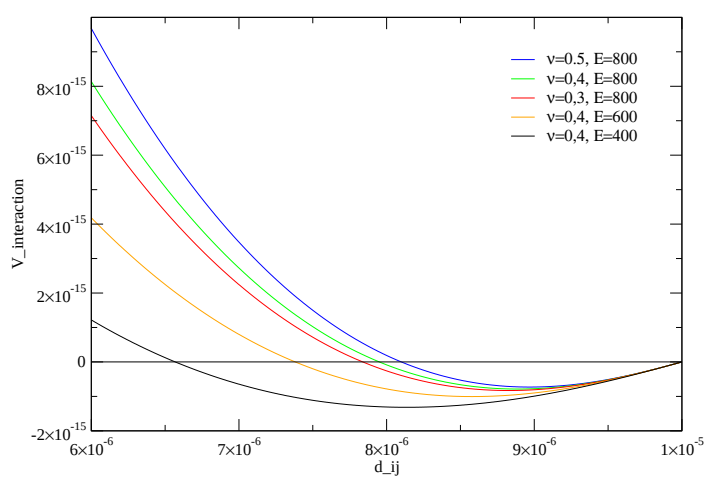
Problem: Coupling terms $-\Gamma^{ij}_{cc} A^{ij}_{cc} \frac{d\vec{x}_j}{dt}$.

Interaction 1: Short range

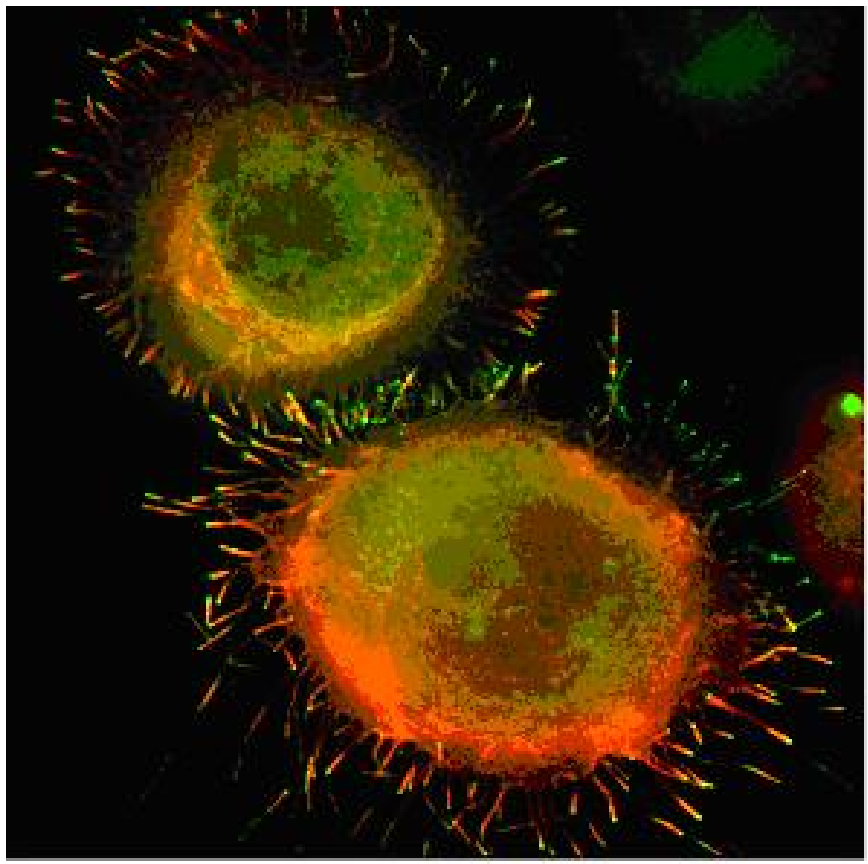
The cell-cell interaction is modelled by a slightly modified Hertz model, which includes an adhesion term:

$$
\begin{aligned}
V_{interaction} &= V_{Hertz} + V_{adhesion} \\
&= \frac{8}{15} \frac{1}{\frac{1-\nu_1^2}{E_1} + \frac{1-\nu_2^2}{E_2}} \sqrt{\frac{R_1 R_2}{R_1 + R_2}} (R_1 + R_2 - d_{ij})^{5/2} \\
&\quad - \pi \varrho V_{sb} \frac{R_1 R_2}{R_1 + R_2} (R_1 + R_2 - d_{ij}).
\end{aligned}
$$





The only really nice picture



Filopodia of Macrophages(Wikipedia, English, Filopodia).

Interaction 2: Long range

As cells use pseudopodia to move, they cover a range bigger than their spherical volume. This can be modelled as a long range interaction:

$$F_{interaction} = \begin{cases} \frac{4}{3} \frac{1}{\frac{1-\nu_1^2}{E_1} + \frac{1-\nu_2^2}{E_2}} \sqrt{\frac{R_1 R_2}{R_1+R_2}} (R_1 + R_2 - d_{ij})^{3/2} & \\ -\pi \varrho V_{sb} \frac{R_1 R_2}{R_1+R_2} & : \quad d_{ij} \leq R_1 + R_2 \\ -\pi \varrho V_{sb} \frac{R_1 R_2}{R_1+R_2} \exp\left(\frac{-(R_1+R_2-d_{ij})^2}{2\sigma^2}\right) & : \quad d_{ij} > R_1 + R_2 \end{cases}$$

Interaction 3: Filopodia

Simple recipe:

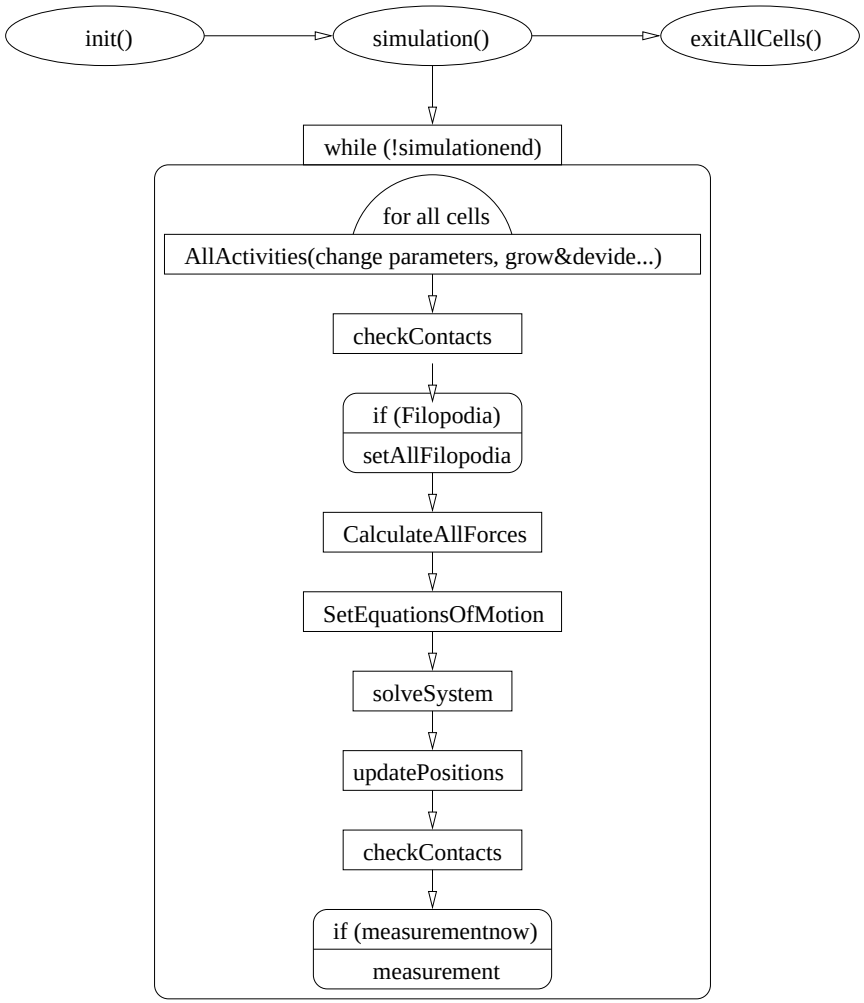
- Draw random vectors as filopodia.
- Cut down at the intersecetion with neighboring cells and store the information.
- Associate a force with the 'filopodium' and it into the equation of motion.

Interaction 3: Filopodia

Here two ways of calculating the force is implemented.

- $F_{\mathrm{filo}} = \alpha l_{\mathrm{filo}} w_{\mathrm{filo}} \varrho E_{\mathrm{sb}}$. This resembles the stochastic force of the Langevin approach.
- The force associated with a filopodium depends on the type of cell it encounters. A force ($\propto \varrho$)is only assigned to filopodia according the following priorities:
  1. Some filopodium is in contact to the same celltype.
  2. If no contact to a cell of the same type exists, all other contacts.
  3. If 1 and 2 is not the case, the proportionality to filopodium length applies.

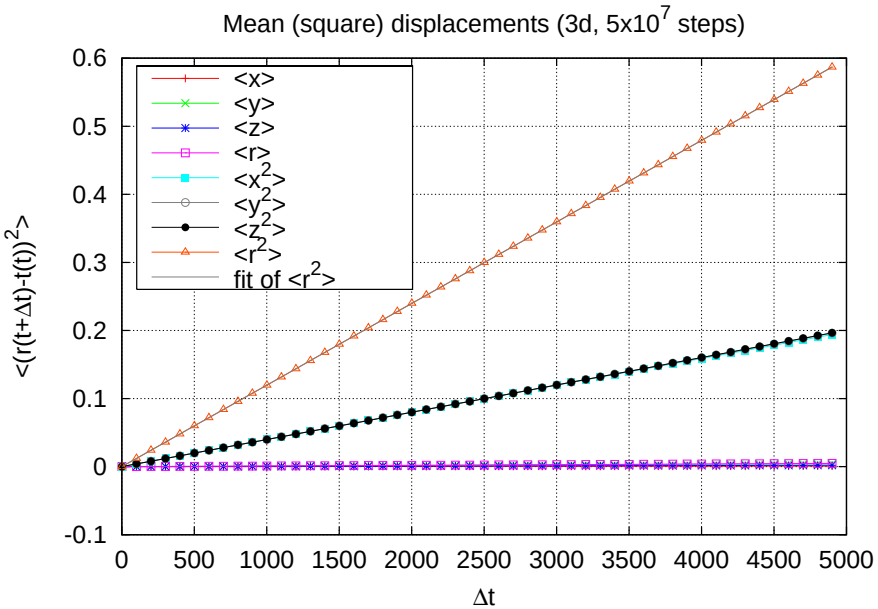
One Simulationstep

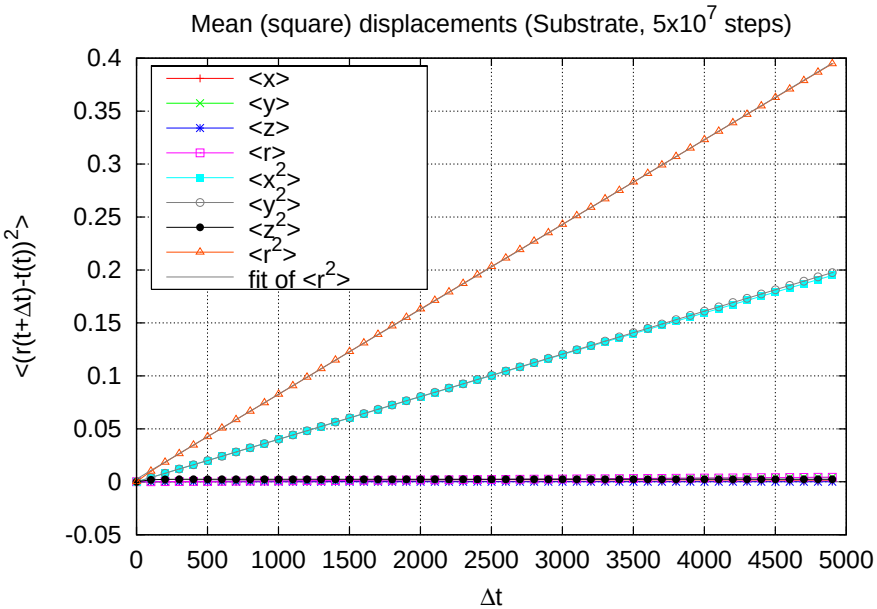


Schematic diagram of Simulation.

Langevin: One Cell

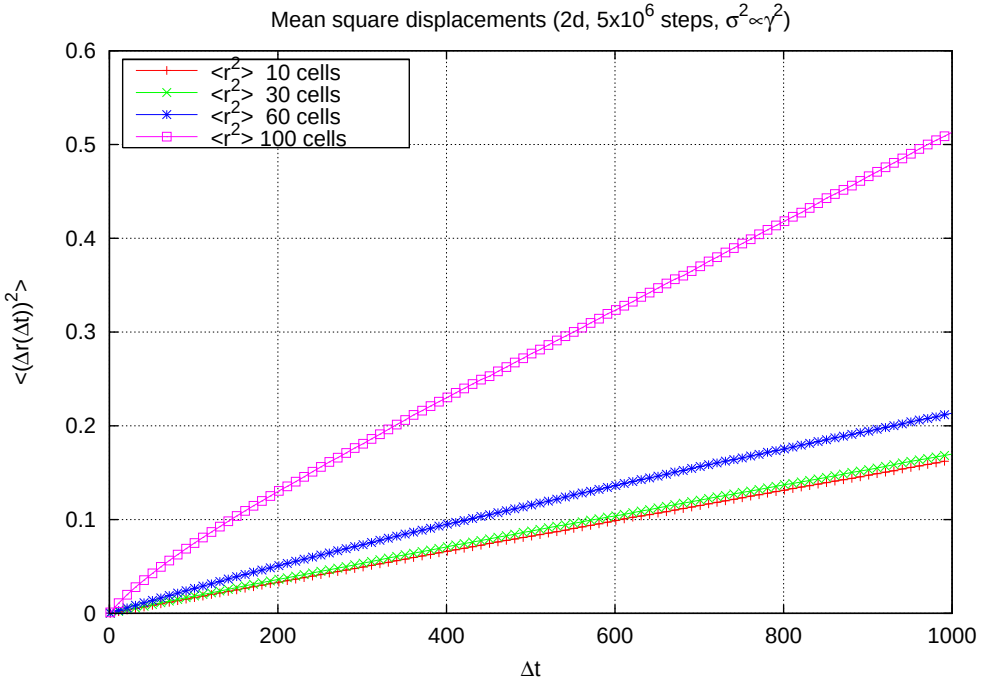
According to the diffusion coefficient of the cell is calculated and gives the input parameter $D = 1 \times 10^{-16} \mathrm{m/s^2}$.





Langevin: More Cells

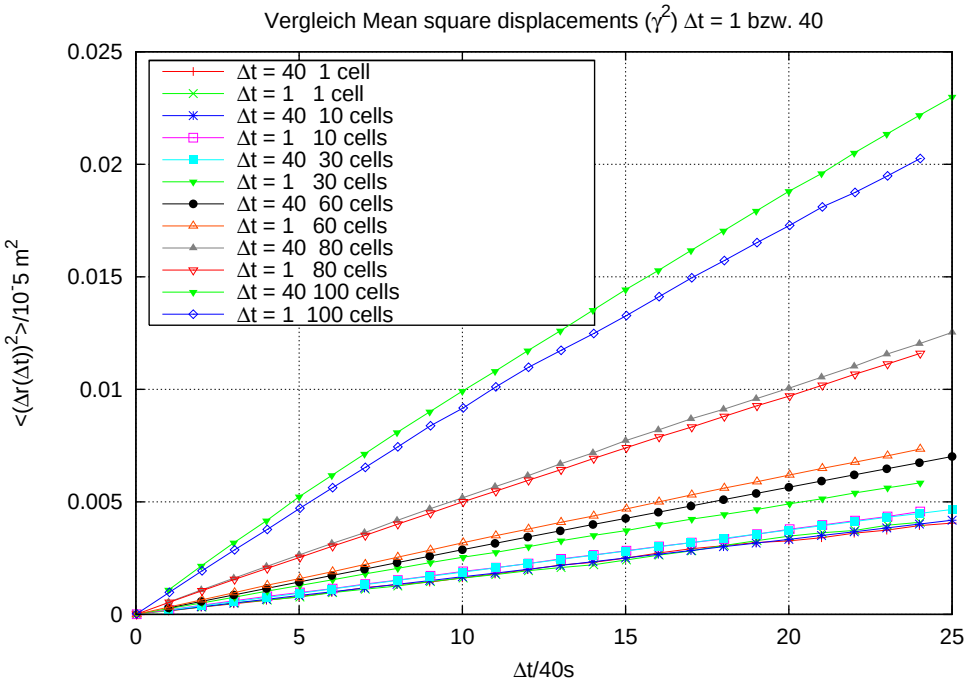
But what happens if the number of cells is increased?



An increasing motility within the aggregate is not the expected result, one would assume that the cells rather move more slowly.

Langevin: More Cells

Incrasing motility: Why does this happen? Is the finite simulation time step because of wrong averaging of the interaction forces, the reason?

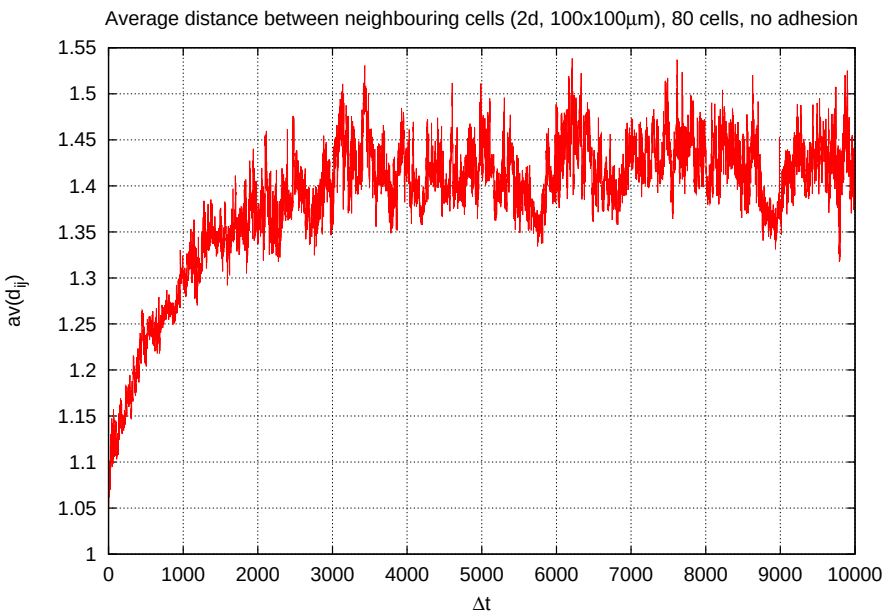


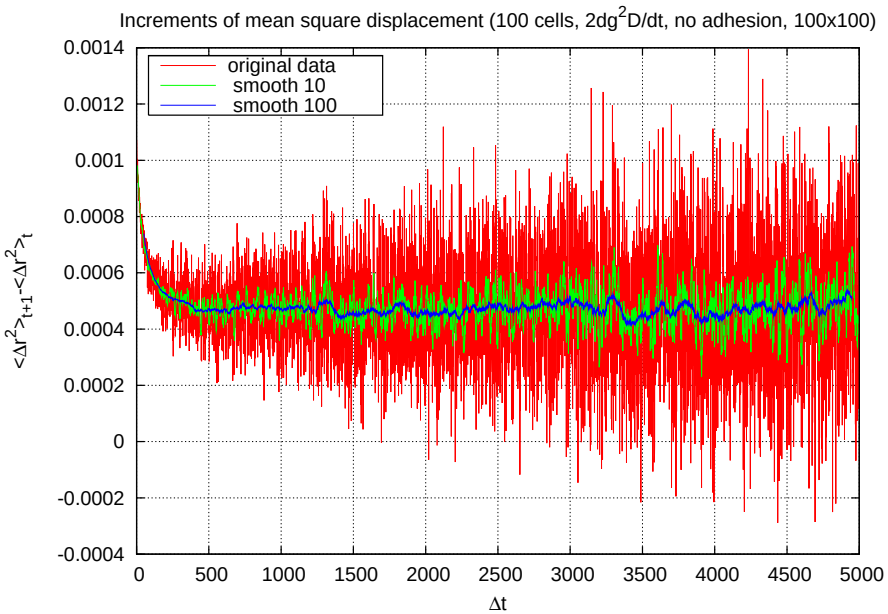
$\Rightarrow$ NO!!!

Langevin: More Cells

Variation of the slope:

- Which is the average distance between two cells?
- Where starts the linear behaviour?



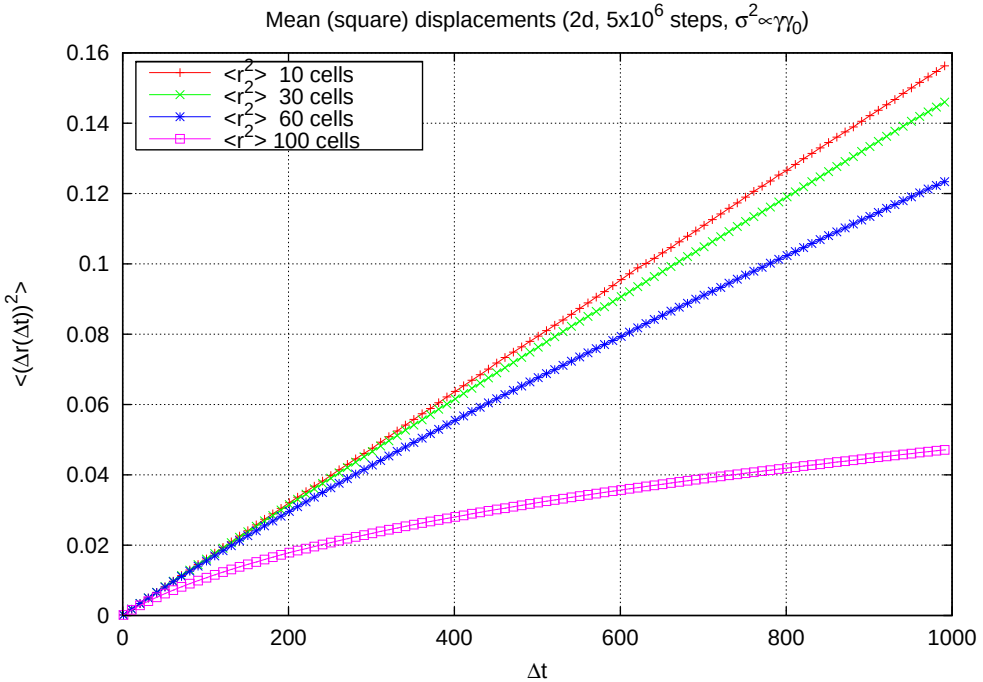


Langevin: More Cells

Nr. of cells	1	10	30	60	80	100
$\overline{d_{ij}}/10^{-5}$m	–	3.25	2.29	1.47	1.38	1.25
$D_{\text{fit},1}/10^{-16}\text{m}^2/\text{s}$	1.08	0.98	1.06	1.08	1.95	2.94
$D_{\text{fit},2}/10^{-16}\text{m}^2/\text{s}$	–	0.98	0.91	0.76	—	0.26
onset of linear	–	–	–	2500	800	400
$\sqrt{\langle \Delta r^2 \rangle}$	–	–	–	0.69	0.5	0.47

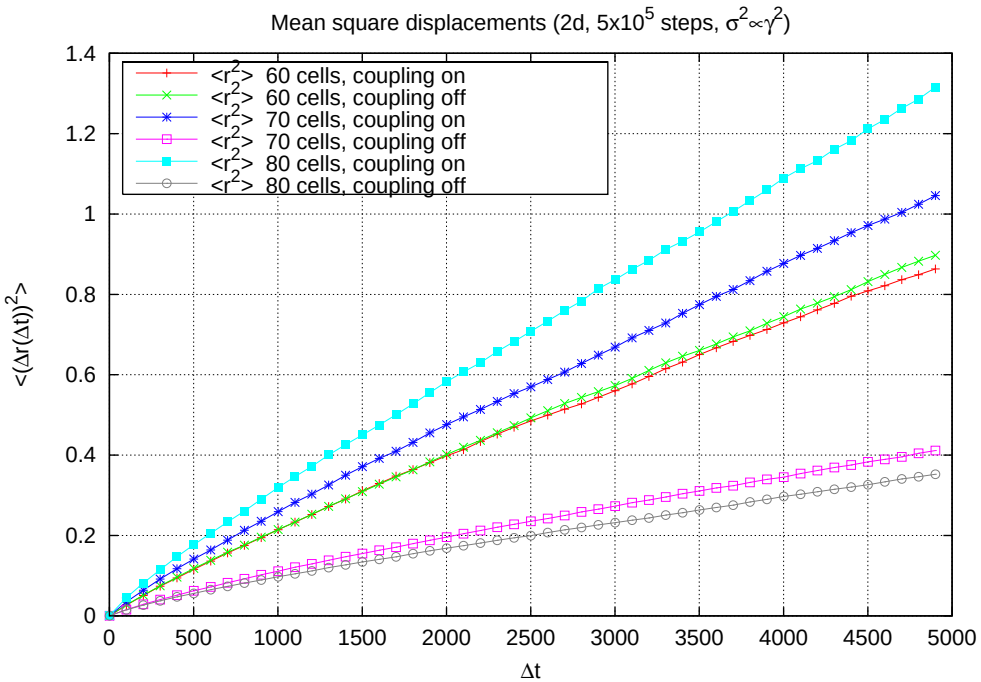
Langevin: More Cells

Another way of calculating the correlation of the force is using an energy equivalent to parametrize the cell's motility. $\sigma^2 = 2dF_T\gamma$, where $F_T = D\gamma_0$ for consistency.



Langevin: More Cells - Coupling

So lets have a look at the Diffusioncoefficient of a varying number of cells with and without the coupling of (3).

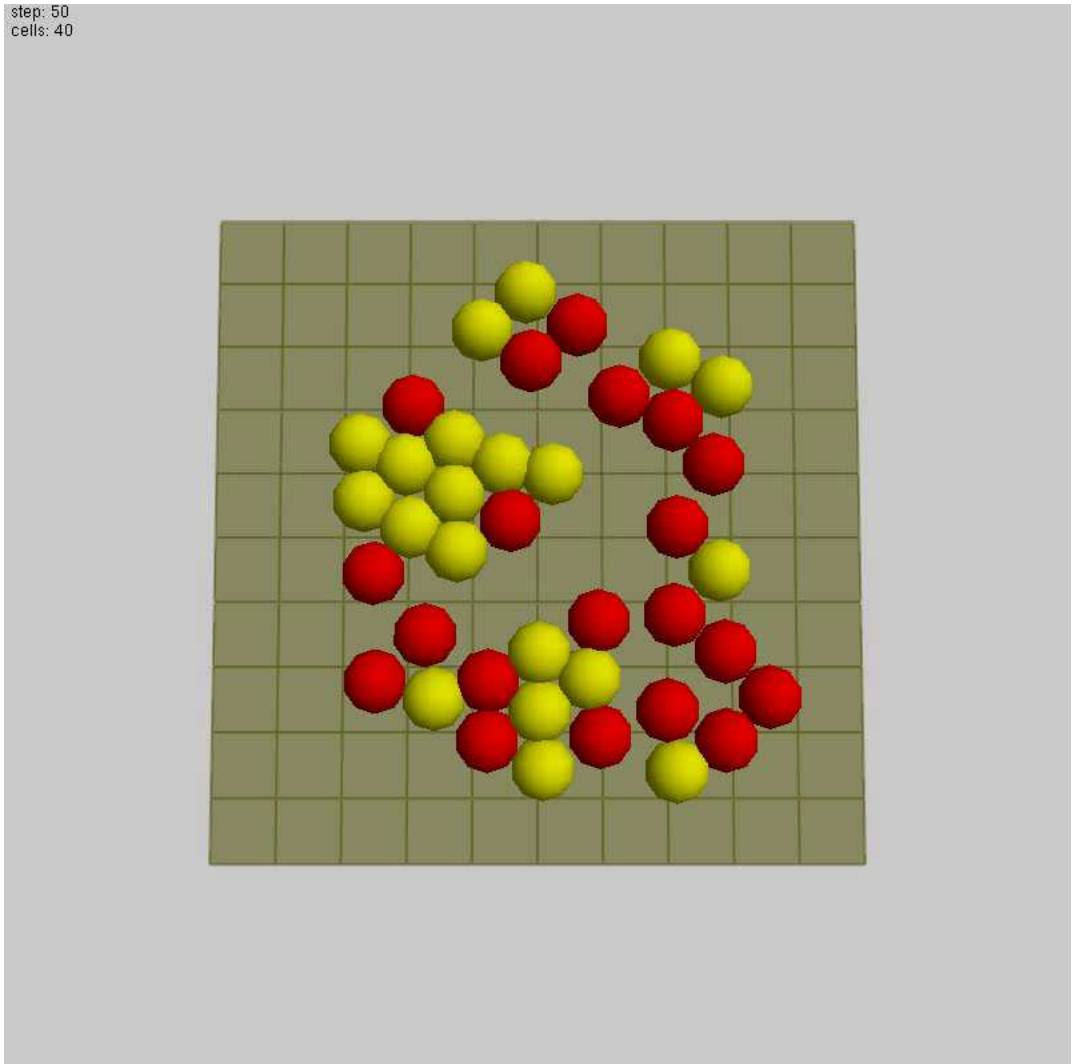


One sees a significant difference, which aparently arises from the motion of the center of mass.

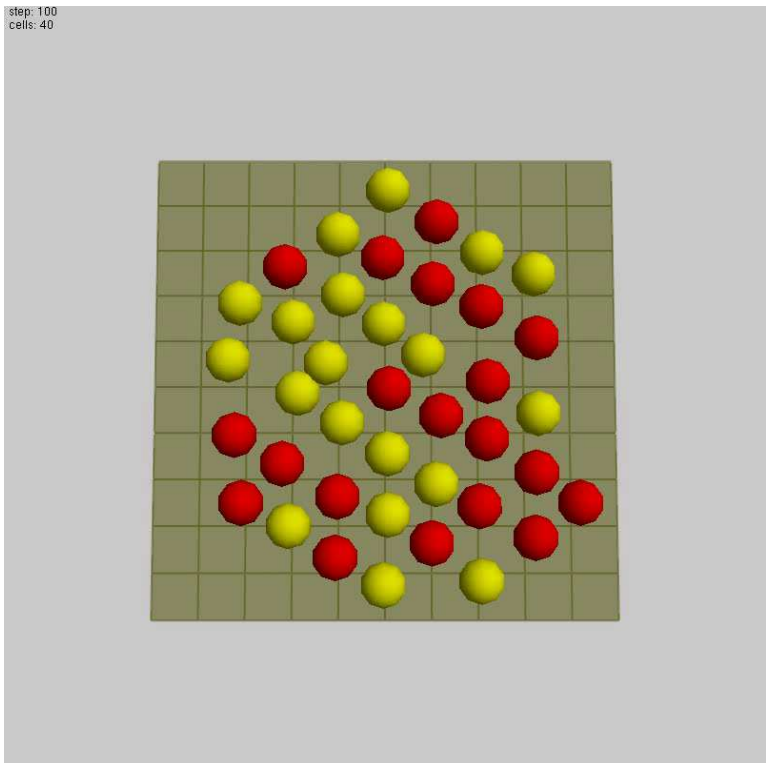
Lessons from the Langevin approach

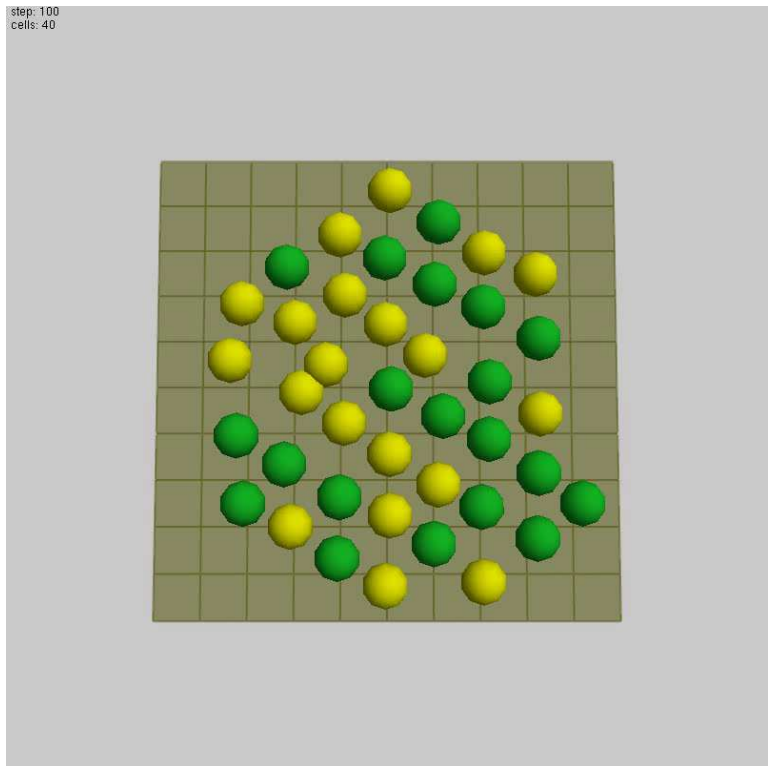
- Physical concepts can be used for modelling purposes and yield reasonable results.
- One should not expect to solve the biological aplications analytically.
- Therefore modelling is should be treated as a “serious scientific playground” and construction site.
- The final tuning strongly depends on the system to model.

2D Sorting - 40 Cells - 2 Types - Longrange

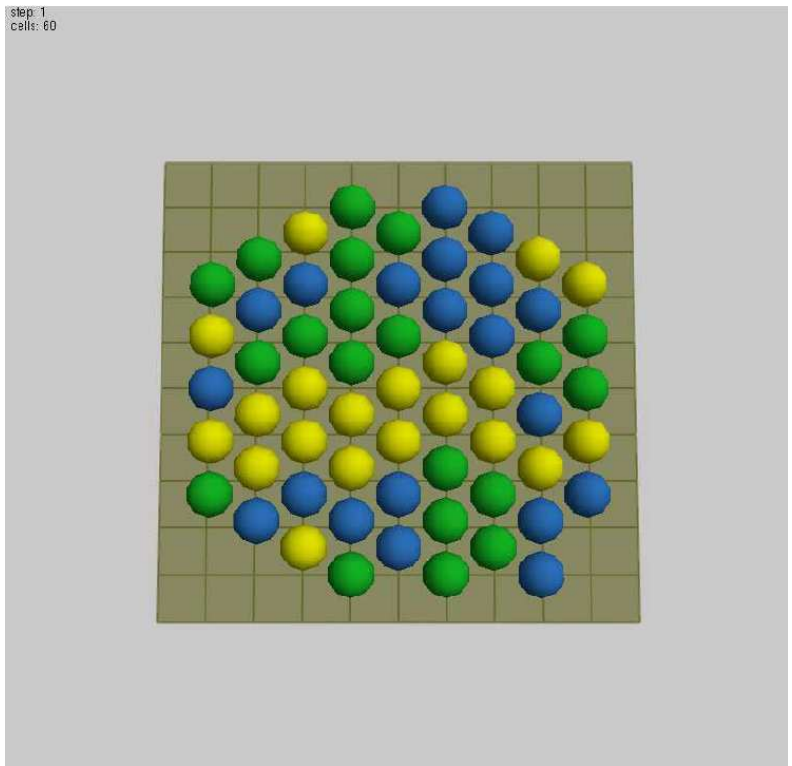


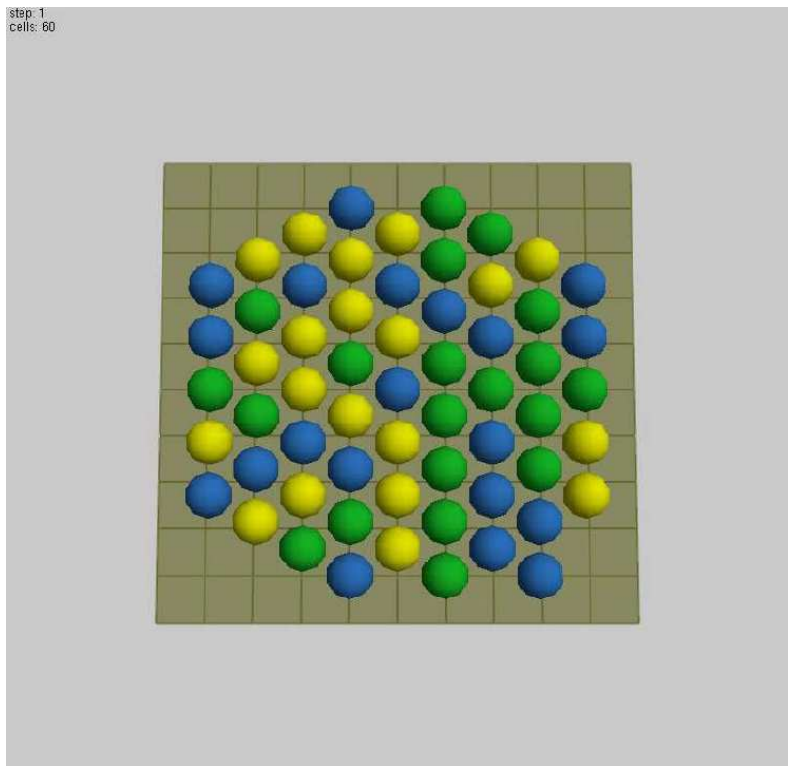
2D Sorting(?) - 40 Cells - 2 Types - Filopodia



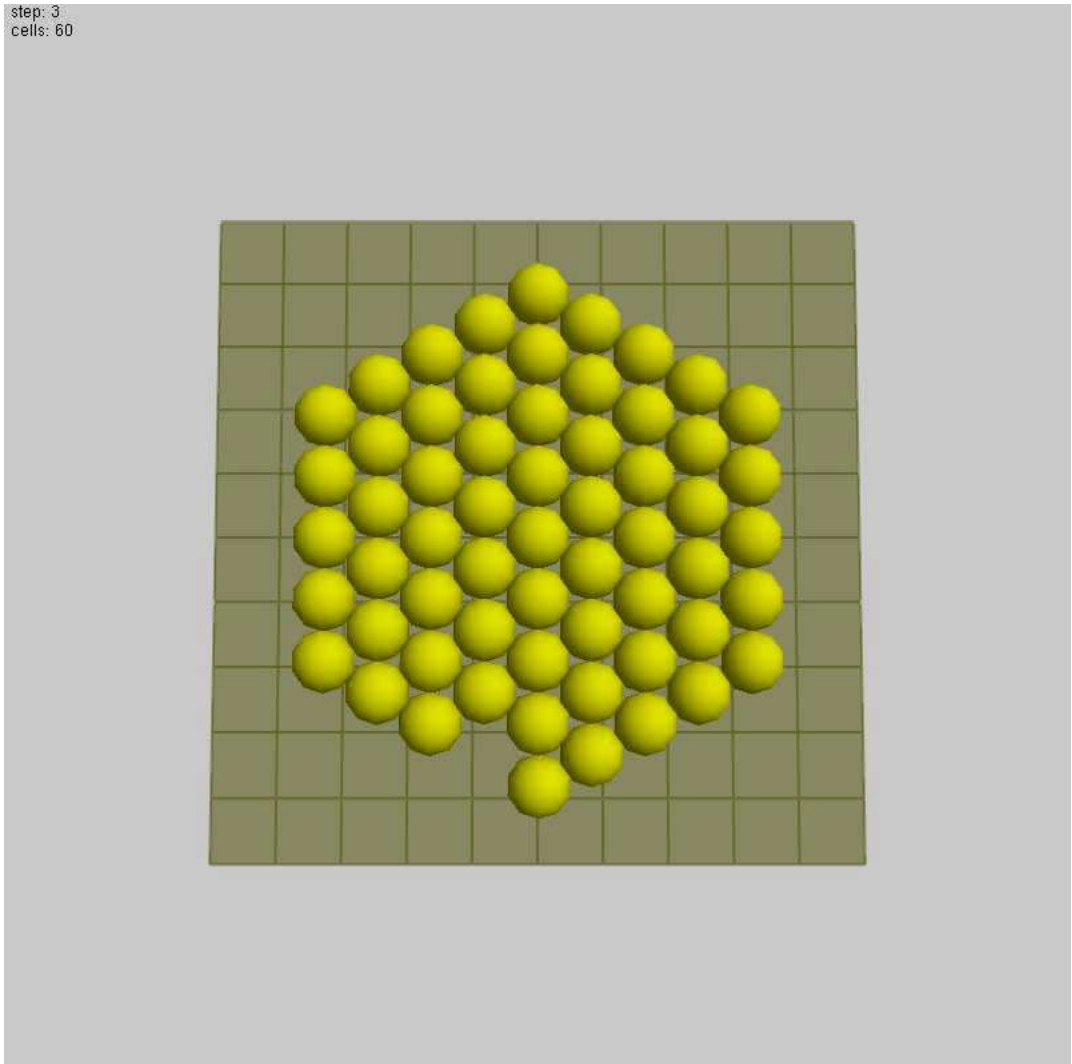


2D Sorting - 60 Cells - 3 Types - Longrange





2D Equidistant Patterning - 60 Cells - Filopodia



2D Growth & Division