Assignment 4: Modeling Tumor Cell Invasion into Adipose Tissue

Integrated Workshop

Due 12/01/2022 at 11:59PM EST

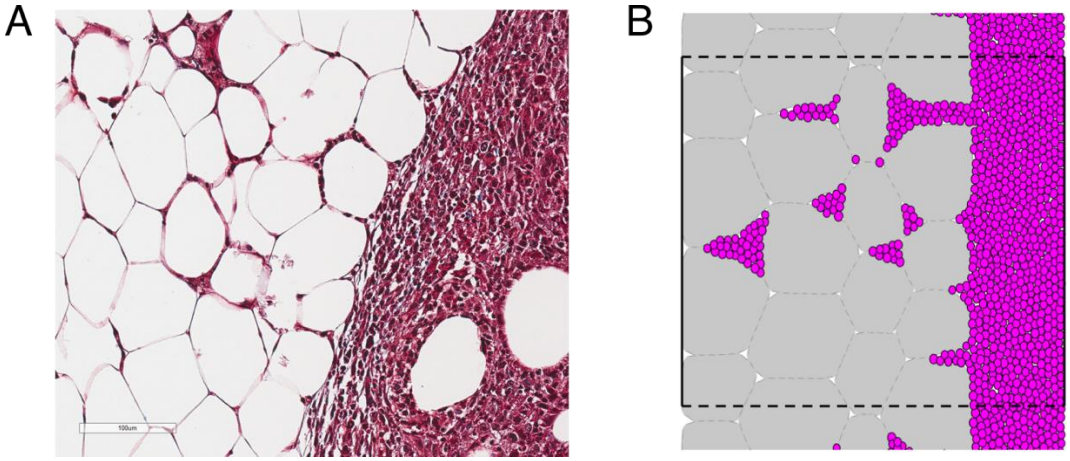

Fig. 1: (A) An image of a histological sample showing the boundary between white adipose tissue (left, white) and invading tumor cells (right, dark red) from a mouse breast tumor. The scale bar in the lower left corner corresponds to 100μm. (B) A snapshot from discrete element method simulations of tumor cells (magenta disks) invading collections of adipocytes (grey deformable polygons). The vertical solid lines indicate planar boundaries and the horizontal dashed lines indicate periodic boundary conditions.

Background: Tumor Cell Invasion into White Adipose Tissue (WAT)

Metastasis is the leading cause of death in patients with advanced breast cancer, during which cancer cells migrate to distant organs through the circulatory system. During this process, breast cancer first spreads from the mammary ducts into adjacent white adipose tissue (WAT), which consists of densely packed adipocytes, or fat cells, embedded in extracellular matrix (ECM). The ability of tumor cells to invade WAT depends on many factors, including the mechanical properties of WAT, motility of the tumor cells, adhesion between tumor cells, and tumor cell proliferation rate. In addition, the adipocytes lose lipid and dedifferentiate in response to chemical factors

released by the tumor cells, which promotes breast cancer invasion. For example, losing lipid decreases the volume of the adipocytes, which exposes more ECM through which tumor cells can migrate. Tumor cells can also increase their metabolism through lipid uptake, which can increase their motility; and dedifferentiation causes adipocytes to become more like myofibroblasts, which allows them to remodel the ECM.

It is important to understand the physical properties that promote or suppress tumor cell invasion, which can provide insight into therapies that would prevent breast cancer metastasis. The specific goal of this module is to learn how to develop a simple, physical model to simulate tumor cell invasion into WAT. We will implement discrete element method (DEM) simulations in two dimensions to model tumor cell invasion into WAT. We will model WAT by generating packings of deformable particles at confluence. We will then shrink the deformable particles and pin them in place. The gaps between adipocytes allow cancer cells to invade and pinning the adipocytes mimics that adipocytes are localized in the ECM. We will then randomly deposit cancer cells, modeled as repulsive disks that are a factor of 5 smaller than the average diameter of the adipocytes, in the void spaces between adipocytes. The velocities of the cancer cells are maintained at temperature T. We will focus on determining how the packing fraction of the adipocytes and temperature of the cancer cells affects invasion into WAT.

Deformable Particle Model for the Adipocytes

To model the adipocytes, we will use the deformable particle (DP) model developed in the O'Hern research group (Boromand *et al*., Phys. Rev. Lett **121**, 248003 (2018); Treado *et al*., Phys. Rev. Materials **5**, 055605 (2021); Wang *et al*., Soft Matter **17**, 9901 (2021); Cheng *et al*., Soft Matter **17**, 8071 (2022)). Deformable particles can change their shape in response to applied forces. In two dimensions, each particle is modeled by a deformable polygon with N_v vertices with a shape-energy function U that includes three terms:

$$U = U_a + U_l + U_{int},$$

where

$$U_a = \frac{\varepsilon_a}{2}\left(\frac{a}{a_0} - 1\right)^2,$$

$$U_l = \frac{\varepsilon_l}{2}\sum_{i=1}^{N_v}\left(\frac{l_i}{l_0} - 1\right)^2, \text{ and}$$

$$U_{int} = \frac{\varepsilon_c}{2}\sum_{i=1}^{N_v}\sum_{j}\left(\frac{r_{ij}}{\sigma_{ij}} - 1\right)^2 \Theta\left(1 - \frac{r_{ij}}{\sigma_{ij}}\right).$$

U_{int}, with energy scale ε_c, gives the purely repulsive linear spring interaction energy between circular vertices i and j with average diameter σ_{ij} and separations r_{ij} on different deformable particles. $\Theta(.)$ is the Heaviside step function, ensuring that the vertices do not interact when they do not overlap. U_a and U_l (with energy scales ε_a and ε_l) penalize deviations of the polygon shape from its preferred area a_0 and side length l_0. We can tune the shape of the particle by varying the preferred shape parameter $A_0 = (N_v l_0)^2/(4\pi a_0)$.

We first compress a collection of deformable particles to confluence and then shrink the particles to half of their area at confluence. Shrinking the adipocytes creates gaps between the cells, which provides pathways for the tumor cells to invade. In addition, we will fix the locations of all vertices of the deformable particles, which models strong tethering of the adipocytes to the ECM.

Numerical Models for Breast Cancer Cells: Thermalized Soft Disks

To model the tumor cells, we will consider thermalized, bidisperse disks (half large disks and half small disks with diameter ratio σ_l/σ_s =1.4) using a Langevin thermostat. The equations of motion for the center of mass $\vec{r}_i$ of each tumor cell *i* is given by

$$\frac{d\vec{r}_i}{dt} = \vec{v}_i, \qquad \text{and}$$

$$m\frac{d\vec{v}_i}{dt} = \vec{F}_i - \beta\vec{v}_i + \sqrt{2\beta k_B T}\dot{W},$$

where m is the mass of the tumor cell, $\vec{v}_i$ is the velocity of the *i*-th tumor cell, $\vec{F}_i$ is the force on the *i*-th tumor cell, β is the drag coefficient, k_B is the Boltzmann constant, T is the temperature, and $\dot{W}$ is the time derivative of a Wiener process. We assume that the force on tumor cell *i* from other tumor cells or adipocytes is obtained by taking the negative gradient of the purely repulsive linear spring potential:

$$U = \frac{\varepsilon}{2}\sum_j \left(\frac{r_{ij}}{\sigma_{ij}} - 1\right)^2 \Theta\left(1 - \frac{r_{ij}}{\sigma_{ij}}\right),$$

where the index j corresponds to another tumor cell or vertex of a fixed adipocyte. In the overdamped regime ($\beta \gg 2\sqrt{m\varepsilon/\sigma^2}$, where σ is the average particle diameter), the diffusion coefficient D is given by the fluctuation-dissipation theorem, $D = k_B T/\beta$.

The tumor cells are initialized with velocities selected randomly from a Gaussian distribution at temperature T, with total kinetic energy K = $\frac{m}{2}\sum_{i=1}^{N} v_i^2 = Nk_BT$. To numerically solve the Langevin equations of motion, we implement the "BAOAB" method from Leimkuhler and Matthews, Appl. Math. Res. Express **1**, 34-56 (2013):

$$\vec{v}_i\left(t + \frac{\delta t}{2}\right) = \vec{v}_i(t) + \frac{\delta t}{2}\vec{F}_i(t)/m,$$

$$\vec{r}_i\left(t + \frac{\delta t}{2}\right) = \vec{r}_i(t) + \frac{\delta t}{2}\vec{v}_i(t),$$

$$\vec{v}_i'\left(t + \frac{\delta t}{2}\right) = e^{-\beta\delta t/m}\vec{v}_i\left(t + \frac{\delta t}{2}\right) + \sqrt{1 - e^{-2\beta\delta t/m}}\sqrt{k_BT/m}G,$$

$$\vec{r}_i(t + \delta t) = \vec{r}_i\left(t + \frac{\delta t}{2}\right) + \frac{\delta t}{2}\vec{v}_i'\left(t + \frac{\delta t}{2}\right), \text{and}$$

$$\vec{v}_i(t + \delta t) = \vec{v}_i'\left(t + \frac{\delta t}{2}\right) + \frac{\frac{\delta t}{2}\vec{F}_i(t + \delta t)}{m},$$

where δt is the time step and G is a Gaussian random number drawn (for each component of the velocity) from a normal distribution with mean 0 and standard deviation 1.

For bulk systems of thermalized disks, the mean-square displacement (MSD) increases with time more slowly as the packing fraction φ increases. At low packing fractions, the MSD transitions from ballistic $\langle(\Delta r)^2\rangle \sim t^2$ to diffusive behavior $\langle(\Delta r)^2\rangle \sim t$ at a relatively short time t*. As the packing fraction increases, a plateau forms in the MSD causing t* to increase dramatically. The relaxation time t* appears to diverge at a characteristic packing fraction ϕ_g that increases with the temperature T of the system. We find that $\phi_g - \phi_c \sim T^2$, where $\phi_c \sim 0.84$ is random close packing of disks in two dimensions in the large system limit.

In the present studies, we will fix the size of the tumor cells and increase the packing fraction in the void regions between adipocytes by increasing the number of tumor cells. To give you an idea of the simulated systems, run the following Matlab command to deposit different numbers of tumor cells in the void regions:

```
% N is the number of tumor cells, choose numbers between 0 and 50
PlotInitialConfig(N);
```

Assignment: Tumor Cell Diffusion within Adipose Tissue

In this assignment, you will study how the packing fraction of tumor cells affects their ability to move through the adipose tissue using the DEM simulations described above. First, you will develop your own code to simulate the motion of a single particle (in a heat bath) at constant temperature. Then, you will complete the velocity and position updates for constant temperature (T) simulations on collections of N cancer cells. In all of the simulations, you can set the mass to be 1.

Prepare your answers to the following questions in a document entitled: Assignment4-write-up-LASTNAME-FIRSTNAME.txt

1. Write your own Matlab code to simulate the motion of a single particle in a heat bath at a constant temperature using the "BAOAB" method. In this case, the total force on the particle only consists of the drag force and random forces from thermal noise. In the simulation, set the time step $\delta t = 10^{-4}$, number of time steps $N_t = 10^5$, and temperature $T = 10^{-4}$. Initialize the particle velocity based on T. Select several values of the drag coefficient $\beta = 2, 10, 50, \text{and } 100$. For each β, calculate the velocity autocorrelation $C_{vv}(t) = \langle \vec{v}(t_0 + t) \cdot \vec{v}(t_0) \rangle / \langle \vec{v}(t_0)^2 \rangle$, where $\langle . \rangle$ indicates an average over starting times t_0. Plot $C_{vv}(t)$ as a function of t. You should see that $C_{vv}(t) = e^{-\beta t/m}$ decays exponentially with t. Plot the expected result on top of the data you measured for $C_{vv}(t)$. (Use a logarithmic scale for $C_{vv}(t)$ and a linear scale for t when making this plot.) To speed up the calculations for $C_{vv}(t)$, select evenly spaced time steps on a logarithmic scale.
2. In this question, you will study how cancer cells diffuse in a matrix of adipocytes using NVT simulations. You need to implement the NVT algorithm in the Matlab function LorentzCancer.m. In this function, the drag coefficient $\beta = 5$, time step dt = 0.01, and total number of steps $N_t = 1 \times 10^6$ have been set. You will again implement the "BAOAB" method, where the functions to calculate cancer-cancer and cancer-adipocyte forces have been provided. Initialize the cancer cell velocities by selecting the components from a Gaussian

distribution with variance T. Store the x- and y-positions of cancer cells every 10 steps in variables named `x_t` and `y_t`. Also store the x- and y-velocities of cancer cells every 10 steps in variables named `vx_t` and `vy_t`. These steps are marked as "TO DO" on lines 102, 109, and 128 in LorentzCancer.m. After you complete the required steps in this function, you can now call the function LorentzCancer(N, T):

```
[phi, x_t, y_t, vx_t, vy_t, xa, ya, AC_para] = LorentzCancer(N, T);
```

The output variable `phi` gives the packing fraction φ for the cancer cell packing at the given N. Select several values N = 20, 42, 43, and 44 at T = 10^{-12}. For N = 44, calculate the instantaneous temperature for all time steps you've recorded. Plot the instantaneous temperature as a function of time. What is the mean value for the instantaneous temperature? Is it close to T? What are the fluctuations of the instantaneous temperature compared to the mean value? For each N, calculate the mean-squared displacement (MSD): $\langle \Delta r(t)^2 \rangle = \langle \vec{r}(t_0 + t) \cdot \vec{r}(t_0) \rangle$. You can use the same trick used for calculating $C_{vv}(t)$ to speed up the computation of the MSD. Plot the MSD versus time for each packing fraction (or N value) on a log-log scale. Generate plots of the MSD versus time for each value of N. What are the general features of the MSD? Do you observe slowing down of the dynamics as N increases? At what φ_g does the timescale t* that signals the crossover between diffusive dynamics and caging appear to diverge?