Controlling seepage in discrete particle simulations of biological systems

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Abstract

It is now commonplace to represent materials in a simulation using assemblies of discrete particles. Sometimes, one wishes to maintain the integrity of boundaries between particle types, for example, when modelling multiple tissue layers. However, as the particle assembly evolves during a simulation, particles may pass across interfaces. This behaviour is referred to as ‘seepage’. The aims of this paper are: (i) to examine the conditions for seepage through a confining particle membrane; and (ii) to define some simple rules that can be employed to control seepage. Based on the force-deformation response of spheres with various sizes and stiffness, we develop analytic expressions for the force required to move a ‘probe particle’ between confining ‘membrane particles’. We analyse the influence that particle’s size and stiffness have on the maximum force that can act on the probe particle before the onset of seepage. The theoretical results are applied in the simulation of a biological cell under unconfined compression.

Keywords: Discrete element method; Seepage; Particles methods; Cell compression.
1. Introduction

Discrete particle-based methods appear under various names and are commonly used to simulate the behaviour of complex media, such as granular materials [1-3], foams [4-6], and colloids [7]. Discrete particles, often spherical or circular simulation objects, are free to move spatially in response to applied forces. Each simulation particle may represent, for example, a grain, a bubble or a colloidal particle. More recently, these discrete methods have been gaining use to model biological systems, such as cell assemblies like epithelial tissues [8, 9]. These models can be used to investigate micro-deformation mechanisms such as tissue buckling and cell spreading [10-13]. In some approaches a particle may represent a whole cell or a cell component such as a cell nuclei or organelle. In this paper we define a ‘particle’ to be a discrete simulation particle representing a spherical volume of multi-component material such as the membrane and cytoplasm of a cell [14]. Seepage of material through the cell’s membrane affects its structural integrity and may influence normal cell functions. It is therefore important for computational biologists that are interested in using discrete particle methods to model cells to understand this phenomena and the influence of different factors that can be used to control it.

More generally when modelling biological systems, we are often faced with the challenge of defining and then maintaining the integrity of distinct regions within the tissue. Tissues are generally in continuous transformation; an apparently static tissue is actually maintaining itself through continual renewal. Cells maintain themselves, proliferate, grow, differentiate, secrete and migrate to new locations, often undergoing substantial morphological change during these processes. Particle based simulations can easily represent very large deformations and other morphological changes in cells and the extracellular matrix, along with physical interactions between cells and the extracellular matrix [14]. During such simulations, the integrity of cells (and even sub-cellular components, such as the nucleus) must be maintained.

Consider the particle-based simulation of a plate compression test on a single cell shown in Figure 1. In this simulation a single cell is constructed of many particles of a range of types. Specifically particles representing the cytoplasm are shown in yellow and those representing the cell cortex and membrane are shown in green. Under compression in an unconfined ‘plate load test’, the cell undergoes the expected deformation. However as the simulation progresses, and particle loads increase under compression, cytoplasm particles can be forced through the confining cell membrane. We refer to this process as seepage. In some cases this may actually be desirable (e.g. exocytosis, osmotic equilibrium). But in most instances we wish to retain particle type within a region. This observation provides the motivation for this study. Being able to understand and control particle seepage would aid simulation of biological cells using discrete particles.

In this paper we study the factors which determine the retention or loss of simulated particles at an interface. We focus on the characteristic problem of moving a single ‘probe’ particle between two confining ‘membrane’ particles. The effect of particles’ size and mechanical properties are examined analytically to obtain useful rules for controlling seepage in discrete particle simulations. Although the analytical derivation is done, for simplicity, in 2D, the derived rules also apply for 3D simulations.

We begin with an analytical study of the characteristic problem of a probe particle moving between two membrane particles in Section 2. The analytic results are tested by simulating the behaviour of a biological cell under unconfined compression in Section 3. Finally, we discuss the results and present our conclusions in Section 4.
Figure 1. Simulated force plate experiment of a single cell resulting in particle seepage. Discrete particles are used to construct a cell. Yellow particles represent the cell’s cytoplasm, whereas green particles are used to represent the cell cortex and membrane. As the cell is compressed by a plate (shown by blue line) the increase in the cytoplasm particle’s compression (represented by a changing colour towards orange) may result in the seepage of particles out of the cell.

2. Analysis of the characteristic three-particle seepage event

Consider a collection of three circular particles consisting of two membrane particles of radius $R_m$ and a single probe particle of radius $R_p$ (Figure 2). We can define a $xOy$ coordinate system based on the centre-to-centre orientation of the membrane particles. Specifically let the two membrane particles lay along the $x$-coordinate with centres at $(-R_m, 0)$ and $(R_m, 0)$ and the centre of the probe particle positioned at $(0, Y)$, see Figure 2. The position of the probe particle changes in response to a net force $F_{\text{seep}}$ in the negative $Oy$ direction, due to all other contacts acting on it. As the force acting on the probe particle increases, both the overlap between the probe and membrane particles $\alpha_{\text{mp}}$ and the separation between the centres of the membrane particles $2\alpha_{\text{mm}}$ increase.

![Diagram of a single probe particle of radius $R_p$ moving between two membrane particles of radius $R_m$.](image)

Figure 2. The characteristic seepage event considered here is a single probe particle of radius $R_p$ moving between two membrane particles of radius $R_m$. The initial vertical position at contact $Y_c$ is reduced to an arbitrary $Y$ value, leading to an overlap $\alpha_{\text{mp}}$ between membrane and probe particles. This causes separation of the membrane particles by $2\alpha_{\text{mm}}$. The force acting on the probe particle is $F_{\text{seep}}$, and the horizontal forces preventing the membrane particles’ movement is $F_{\text{resist}}$. 
Based purely on geometry, we obtain
\[
\alpha_{mp} = R_m + R_p - \sqrt{Y^2 + (R_m + \alpha_{mm})^2}
\]
and by assuming \(\alpha_{mp} = \alpha_{mm} = 0\), particles first come into contact at \(Y = Y_c\), where
\[
Y_c = \sqrt{R_p(2R_m + R_p)}
\]
We have used the convention \(\alpha_{mp} > 0\) for a compressive contact between the membrane and probe particles, and \(\alpha_{mm} > 0\) for an increase in the separation between membrane particles from their initial configuration.

From the equilibrium of forces in the x and y directions, we can write
\[
F_{\text{seep}} = 2F_{mp} \frac{\sqrt{Y^2 + (R_m + \alpha_{mm})^2}}{Y}
\]
and
\[
F_{\text{resist}} = F_{mp} \frac{R_m + \alpha_{mm}}{\sqrt{Y^2 + (R_m + \alpha_{mm})^2}}
\]
where \(F_{mp}\) is the normal force at the contact between the probe particle and a single membrane particle. In (4), \(F_{\text{resist}}\) represents the force resisting the separation of the two membrane particles. In a real simulation this force will be influenced by the surrounding particles that interact with the membrane particles and are not explicitly modelled. For the purpose of this study we only consider the attraction between the two membrane particles, modelled as a linear force
\[
F_{\text{resist}} = k_{mn}R_m \alpha_{mm}
\]
The force between the probe particle and the membrane particles can be modelled using different contact laws (linear, Hertzian). In all cases, it will be a function of the penetration:
\[
F_{mp} = F_{mp}(\alpha_{mp})
\]
We can eliminate \(F_{\text{resist}}\) from eqs. (4) and (5), obtaining:
\[
F_{mp} = k_{mn}R_m \alpha_{mm} \frac{\sqrt{Y^2 + (R_m + \alpha_{mm})^2}}{R_m + \alpha_{mm}}
\]
By replacing \(F_{mp}\) from eq. (7) into eq. (3):
\[
F_{\text{seep}} = 2k_{mn}R_m \alpha_{mm} \frac{Y}{R_m + \alpha_{mm}}
\]
In the initial configuration, when cells first touch, we have assumed \(\alpha_{mm} = 0\) and therefore \(F_{\text{seep}} = 0\). From (8) we can see that \(F_{\text{seep}} = 0\) also occurs when \(Y = 0\), that is, when the probe particle centre is in line with the membrane particle centres. This reflects an unstable condition at \(Y=0\), where the probe particle seeps between the membrane particles, without requiring \(F_{\text{seep}} > 0\). The question then arises, where (or at what value of \(Y\)) does the maximum \(F_{\text{seep}}\) occur? We can find the dependency of \(F_{\text{seep}}\) to \(Y\) as follows. The value of \(Y\) can be found from eq. (1) as:
\[
Y = \sqrt{(R_m + R_p - \alpha_{mp})^2 - (R_m + \alpha_{mm})^2}
\]
By replacing this value in eq. (7) we can find the dependency between \(\alpha_{mm}\) and \(\alpha_{mp}\):
\[
\alpha_{mm} = \frac{F_{mp}(\alpha_{mp})R_m}{k_{mn}R_m(R_m + R_p - \alpha_{mp}) - F_{mp}(\alpha_{mp})}
\]
Replacing eq. (10) in eqs. (8) and (9) results in a parametric expression of the dependency between $F_{\text{seep}}$ and $Y$, with $\alpha_{mp}$ as parameter.

2.1. Limit case – infinite membrane tensile stiffness

When the membrane tensile stiffness is very large compared to the contact stiffness, the membrane particles do not separate during seepage. At the limit the membrane tensile stiffness is infinite resulting in immobile membrane particles, $\alpha_{mm} = 0$.

For such a case, the penetration between the probe and membrane particles can be obtained as a function of $Y$ from eq. (1):

$$\alpha_{mp} = R_m + R_p - \sqrt{Y^2 + R_m^2}$$

and $F_{\text{seep}}$ can be derived as a function of $Y$ from eq. (3), considering that the contact force $F_{mp}$ is a function of $\alpha_{mp}$ (as stated in eq. (6)):

$$F_{\text{seep}} = 2F_{mp} \frac{Y}{\sqrt{Y^2 + R_m^2}}$$

The maximum value of $F_{\text{seep}}$ for this limit case can be obtained from eq. (12) using numerical methods.

2.2. Limit case – infinite contact stiffness

When the contact stiffness is much larger than the membrane tensile stiffness the probe particle will move in between the membrane particles with very little penetration between them. At the limit the contact stiffness is infinite, resulting in zero penetration, $\alpha_{mp} = 0$. For this case we can compute $\alpha_{mm}$ from eq. (1):

$$\alpha_{mm} = \sqrt{(R_m + R_p)^2 - Y^2 - R_m}$$

The computed $\alpha_{mm}$ can be replaced in eq. (8) to obtain the relation between $F_{\text{seep}}$ and $Y$:

$$F_{\text{seep}} = 2k_{mm}R_m \left( \frac{(R_m + R_p)^2 - Y^2 - R_m}{\sqrt{(R_m + R_p)^2 - Y^2}} \right) \frac{Y}{\sqrt{(R_m + R_p)^2 - Y^2}}$$

The maximum value of $F_{\text{seep}}$ for this limit case can be obtained from eq. (14) using numerical methods.

2.3. Analysis with linear contact law between particles

We will first analyse the behaviour of the three particle system in the simple case of a linear contact force:

$$F_{mp} = k_{mp} \frac{R_m R_p}{R_m + R_p} \alpha_{mp}$$

The results, presented in Figures 3 and 4, offer some interesting insights into how seepage develops and possible ways of preventing it.
Figure 3. The dependency between different analysis parameters in case of a linear contact law. a) $\alpha_{mm}$ versus $\alpha_{mp}$ for equally sized particles. b) $Y$ versus $\alpha_{mm}$ for equally sized particles. c) $F_{seep}$ versus $Y$ for equally sized particles. d) $F_{seep}$ versus $Y$ for particles of different size, $k_{mm} = k_{mp}$. e) Influence of particle sizes on the maximum $F_{seep}$. f) Influence of particle contact stiffness on the maximum $F_{seep}$. The horizontal lines represent the maximum value of $F_{seep}$ corresponding to infinite contact stiffness derived from eq. (14). All variables have been normalized with regard to $R_m$ and $k_{mm}$. 
Figure 4. The influence of different parameters on $F_{seep}$ in case of a linear contact law. 

(a) The influence of membrane particle size on the maximum $F_{seep}$. All variables have been normalized with regard to $R_p$ and $k_{mm}$. 

(b) Influence of membrane tensile stiffness on the maximum $F_{seep}$. The horizontal lines represent the maximum value of $F_{seep}$ corresponding to infinite membrane tensile stiffness derived from eq. (12). All variables have been normalized with regard to $R_m$ and $k_{mp}$.

As seen in Fig. 3a, when the contact stiffness between the probe and membrane particles is much higher than the membrane’s tensile stiffness, the membrane particles separate ($\alpha_{mm}$ increases) at a very fast rate as compared to the particle penetration $\alpha_{mp}$. On the other hand, when the contact stiffness between the probe and membrane particles is much lower than the membrane’s tensile stiffness, the seepage occurs ($Y = 0$) with very little separation between the membrane particles (small $\alpha_{mm}$), as seen in Fig. 3b. Fig. 3c shows the relation between $F_{seep}$ and $Y$ for different stiffness ratios of equally sized probe and membrane particles and Fig. 3d shows the same relation for different size probe and membrane particles for equal contact and membrane stiffness. In all cases, a maximum value of $F_{seep}$ can be determined; if a constant force acting on the probe particle is larger than this maximum value, then seepage will occur. The variation of the maximum $F_{seep}$ with particle size ratios and stiffness ratios is presented in Fig. 3e, Fig. 4a and Fig 3f, Fig. 4b respectively. Based on these results we conclude that:

- The maximum $F_{seep}$ increases with the probe particle size for constant membrane particle size (Fig. 3e).
- The maximum $F_{seep}$ increases with the membrane particle size for constant probe particle size. The increase is significant only at large ratios $k_{mp}/k_{mm}$ (Fig. 4a).
- The maximum $F_{seep}$ increases with the contact stiffness $k_{mp}$ for constant membrane tensile stiffness $k_{mm}$. The limit on the maximum $F_{seep}$ that can be achieved is obtained considering infinite contact stiffness. Controlling maximum $F_{seep}$ by increasing contact stiffness is only effective for $k_{mp} < k_{mm}$ (Fig 3f).
- The maximum $F_{seep}$ increases with the membrane tensile stiffness $k_{mm}$ for constant contact stiffness. The limit on the maximum $F_{seep}$ that can be achieved is obtained considering infinite tensile membrane stiffness. Controlling maximum $F_{seep}$ by increasing membrane tensile stiffness is only effective for $k_{mm} < k_{mp}$ (Fig 4b).
Because the forces and displacements are normalized, the graphs in Fig. 3 and 4 can be easily interpreted only for constant values of the stiffness and radius used for normalisation. In order to do a comparative assessment of the effect of the change in stiffness on $F_{seep}$ we present the variation of $F_{seep}$ and $F_{resist}$ for different combinations of $k_{mm}$ and $k_{mp}$ in Fig. 5, for equally sized particles having a radius of 1 μm. The effect of changes in the radius of the membrane particles is presented in Fig. 6.

Figure 5. Influence of stiffness variation on forces for equally sized particles having a radius of 1 μm. a) $F_{seep}$ variation. b) $F_{resist}$ variation.

Figure 6. Influence of membrane particle radius on forces for $k_{mm} = k_{mp} = 1 \times 10^5 N/m^2$ a) $F_{seep}$ variation. b) $F_{resist}$ variation.

Fig. 5 gives us a clearer understanding of the influence of the stiffness parameters on the force $F_{seep}$. We notice that we can increase $F_{seep}$ by either increasing $k_{mm}$ or $k_{mp}$, but there is a limit in the maximum force increase achievable – even if one of the stiffness parameters is increased 100
times, the force increase is only limited. An increase of \( k_{mp} \) is effective at very low ratios for \( k_{mp}/k_{mm} \). At ratios \( k_{mp}/k_{mm} \) close to 1 and higher the most effective way of increasing \( F_{seep} \) is to increase both \( k_{mm} \) and \( k_{mp} \) – the force \( F_{seep} \) will increase proportionally with the stiffness. Fig. 6 shows that the maximum \( F_{seep} \) decreases as the radius of the membrane particles gets smaller, for a constant probe particle size.

A graphical representation of the seepage phenomena including the force variation analysed above is presented in Fig. 7.

![Figure 7. A graphical representation of seepage, including variation of forces. a) Infinite particle contact stiffness and finite inter-membrane particle tensile stiffness. b) Finite particle contact stiffness and infinite inter-membrane particle tensile stiffness. c) Equal particle contact stiffness and inter-membrane particle tensile stiffness.](image)

One interesting observation is that, in the case of a linear contact law, the angle \( \beta \) between \( F_{resist} \) and \( F_{mp} \) for the position of the particle system corresponding to maximum \( F_{seep} \) can be obtained from

\[
\cos(\beta) = \left( \frac{R_m}{R_m + R_p} \right)^{1/3}
\]

and is independent of the particles’ contact stiffness and membrane tensile stiffness.

The obtained results indicate two effective ways of controlling seepage. A first possibility is to increase the size of the membrane particle (the size of the probe particles should not be altered in order to maintain the density of particles in a cell). This method is only effective at large ratios \( k_{mp}/k_{mm} \), which may not be the case in practice. The second method is to increase \( k_{mp} \) (at very low ratios \( k_{mp}/k_{mm} \)), or both \( k_{mm} \) and \( k_{mp} \) (at ratios \( k_{mp}/k_{mm} \) close to one or higher). The disadvantage of this method is that it may alter the mechanical response of the cell and it would decrease the stable time step when using explicit time integration of the equation of motions (although this can be counteracted by using mass scaling, especially for quasi-static simulations where inertial effects are not important [15]).
In practice we expect that the contact stiffness is much lower than the membrane tensile stiffness (very low ratio $k_{mp}/k_{mm}$), therefore the easiest and most practical method of controlling seepage would be to increase the contact stiffness $k_{mp}$.

2.4. Analysis with Hertzian contact law between particles

A Hertzian contact force between two particles is defined as [16]:

$$ F_{mp} = k_{mp} \frac{R_m R_p}{R_m + R_p} \alpha_{mp}^{3/2} \quad (17) $$

By replacing this expression of the contact force in eqs. (8), (9) and (10) we obtain the results presented in Fig. 8. By qualitatively comparing these results with the ones obtained for a linear contact law between particles (Fig. 3) we notice that the use of a Hertzian contact law has no significant influence on the seepage behaviour, and all the conclusions drawn in the previous section hold.

The contact law used will influence the maximum value of $F_{seep}$. To better compare the forces obtained using the linear contact law with those obtained using the Hertzian contact law between particles, for the same value of the contact stiffness $k_{mp}$, we define the relative difference between the maximum values of $F_{seep}$ as

$$ dF_{rel} = \frac{\max(F_{seep}^H) - \max(F_{seep}^L)}{\max(F_{seep}^L)} \quad (18) $$

The superscripts $H$ and $L$ identify the forces corresponding to the Hertzian and linear contact laws, respectively.

In systems where the potential elastic energy is much larger compared to the kinetic energy of the particles (slow moving particles), the maximum $F_{seep}$ offers a good indication of the point when seepage is expected to occur. In case of fast moving particles, the kinetic energy of the particle may be the one that leads to seepage. In such a case the area under $F_{seep}$ as a function of $Y$ is more important, as it represents the energy required to push a probe particle through the membrane. Any measure taken to increase $F_{seep}$ will also increase this energy. The influence of the contact law used is more difficult to assess without making a direct comparison. Therefore we define the relative energy difference as

$$ dE_{rel} = \frac{\int_{0}^{Y_c} F_{seep}^H \, dy - \int_{0}^{Y_c} F_{seep}^L \, dy}{\int_{0}^{Y_c} F_{seep}^L \, dy} \quad (19) $$

The influence of contact law on the seepage behaviour is presented in Fig. 9. As shown by the comparison results, the variation in behaviour due to the contact law is limited. Therefore, the contact law should not be used as a control parameter for seepage.
Figure 8. The dependency between different analysis parameters in case of a Hertzian contact law. a) $\alpha_{mm}$ versus $\alpha_{mp}$ for equally sized particles. b) $Y$ versus $\alpha_{mm}$ for equally sized particles. c) $F_{seep}$ versus $Y$ for equally sized particles. d) $F_{seep}$ versus $Y$ for particles of different size, $k_{mm} = k_{mp}$. e) Influence of particle sizes on the maximum $F_{seep}$. f) Influence of particle contact stiffness on the maximum $F_{seep}$. The horizontal lines represent the maximum value of $F_{seep}$ corresponding to infinite contact stiffness. All variables have been normalized with regard to $R_m$ and $k_{mm}$. 
3. Cell compression

Given the results of Section 2, based on a characteristic three-particle system, the question then arises as to how this translates into a simulation based on multiple particles. When a multiple particle system is simulated it is difficult to predict the actual value of $F_{\text{seep}}$ as particle rearrangements distant from the three–particle pairing at the membrane can lead to local changes of the net force acting on the probe and membrane particles. We are going to test whether the proposed seepage control strategy can be applied in cases of more realistic simulation examples.

We consider a cell undergoing unconfined compression. The cell is modelled using two particle types: one set of particles represents the cell’s membrane, whereas the other represents the cell’s cytoplasm and nucleus (although we refer to them here as just cytoplasm particles). A
A detailed presentation of the forces involved in the cell compression simulation is presented in [14]. This cell model uses only two particle types, to illustrate the seepage behaviour. More complex cell models, including the procedure for initializing the cell, fitting the model parameters to experimental data, and validation results are included in [14].

Different algorithms can be used to create an initial particle assembly [16]. The initial configuration used in our experiment, shown in Figure 10, has been obtained as follows: 155 membrane particles (radius of $R_m=0.15\,\mu m$) are placed in a circular configuration, with the circle having a radius of 15 μm. Then, 450 cytoplasm particles are randomly placed within the ring of membrane particles. The size of the cytoplasm particles is initialized at $R_p=0.2\,\mu m$. The cytoplasm particles are then allowed to grow in size and split into two when they reached twice their initial area, resulting in 900 cytoplasm particles. The cytoplasm particles are then allowed to grow until each of them reaches a threshold radius of $R_p=0.35\,\mu m$. At this point the cell membrane is under tension while the cytoplasm particles are under compression; this leads to the round shape of the cell. The final diameter of the cell is approximately $D=16.3\pm0.5\,\mu m$. During this initialization process we also introduce adhesive interaction between the membrane particles and the bottom horizontal surface. This attraction force is linear with a proportionality constant of $10^{11}\,N\,\mu m^{-1}$ and a cut-off distance of 0.3 μm. This attraction results in the observed flat cell basement.

![Figure 10: Cell compression experiment for studying seepage.](image)
(a) Cell initialization starts with a circular line of membrane particles in which cytoplasm particles fill the interior of this circle. Then the cytoplasm particles are allowed to grow, divide into two and then continue growing until the membrane stress reaches a set threshold. (b) Compression experiment; the compression ratio is defined as the ratio between the compression distance and the cell diameter, $\varepsilon = l/D$. 

![Diagram: Cell initialization and initialized cell]
- Random placement of cytoplasm particles
- Fully grown cytoplasm particles
- Adhesion to basement by membrane particles
- Start of compression
- Compression by $l$ distance
- Initial diameter of cell $D$
Compression is applied to the cell via top plate vertically descending at a speed of 0.025 µms$^{-1}$. The solution is obtained using the discrete element method. The time step used in simulation is $10^{-7}$ s. In the figures the colour of cytoplasm particles is used to indicate the net contact force on each particle (darker colour represents higher forces).

Cell compression ratio is defined as the change in the position of the top plate relative to its initial position divided by the diameter of the cell. We examined the compression ratio of the cell at which seepage of cytoplasm particles through its confining membrane particle chain first occurs, denoted by $\varepsilon^*$. We observed if this compression ratio can be adjusted, as expected from the theoretical results presented in Section 2, by varying the contact stiffness between membrane and cytoplasm particles. The results are presented in Figure 11. As expected, seepage is delayed for larger values of the contact stiffness.

![Figure 11: Influence of contact stiffness on seepage. As the contact stiffness increases, the compression ratio at which seepage occurs also increases. Seepage is visible in the upper left side of the cell in all simulations.](image)

4. Conclusions

This paper presents a theoretical analysis of the seepage phenomena in the context of simulating cell behaviour using the discrete particle methods. Seepage occurs when an internal cell particle (modelling cytoplasm) crosses the layer of particles representing the membrane.

The theoretical study uncovered the influence that different simulation parameters have on the seepage behaviour. The parameters we included in the analysis are the membrane tensile stiffness $k_{mm}$, the contact stiffness between membrane and cytoplasm particles $k_{mp}$, and the radius of the membrane particles $R_m$. By studying the variation of the maximum $F_{seep}$ (the force required to push a cytoplasm particle between two membrane particles) with respect to these parameters, we reached the following conclusions:

$$
\frac{k_{mp}}{k_{mm}} = 0.0445, \varepsilon = 0.22
$$

$$
\frac{k_{mp}}{k_{mm}} = 0.0593, \varepsilon = 0.46
$$

$$
\frac{k_{mp}}{k_{mm}} = 0.0667, \varepsilon = 0.49
$$

$$
\frac{k_{mp}}{k_{mm}} = 0.0711, \varepsilon = 0.54
$$

$$
\frac{k_{mp}}{k_{mm}} = 0.0741, \varepsilon = 0.57
$$

$$
\frac{k_{mp}}{k_{mm}} = 0.0762, \varepsilon = 0.63
$$
• We can increase $F_{\text{seep}}$ by increasing the size of the membrane particle. This method is only effective at large stiffness ratios ($k_{mp}/k_{mn} > 1$).
• We can increase $F_{\text{seep}}$ by increasing the contact stiffness $k_{mp}$. This method is effective at low stiffness ratios ($k_{mp}/k_{mn} < 1$).
• We can always increase $F_{\text{seep}}$ by increasing both $k_{mp}$ and $k_{mn}$.

Our results show that the use of Hertzian contact law instead of linear contact law does not have a large influence on the seepage behaviour.

The parameters investigated in this paper have a large influence on cell integrity (seepage prevention) while having little influence on the mechanical behaviour of the cell. This allows the treatment of seepage to be loosely coupled to the modelling of mechanical properties of the cell (which are mainly influenced by the stiffness of the cytoplasm and nucleus particles). The membrane tensile stiffness affects, together with membrane adhesion, the shape of the cell; therefore, changes to this parameter must be done carefully [14].

The theoretical results have been verified using a cell compression simulation. Given the low stiffness ratio, we have chosen to control seepage by increasing the contact stiffness. As expected, the compression of the cell at which seepage occurs is increased.

Given the speed of biological changes, in most simulations of biological systems we are looking for a quasi-static solution. Damping forces are introduced in the simulation [14] to eliminate the transients in order to obtain an quasi-static response. Because damping forces are proportional to velocity, they do not influence the particle positions at equilibrium. Nevertheless, excessive damping can prevent the propagation of motion through the particle system and increase the possibility of seepage during the transient phase.

The presented results lay the theoretical foundation for seepage control in biological systems simulations using discrete particle methods. While it is not possible to have complete control over seepage in a complex particle system, these results show which and how parameters should be changed in order to improve seepage behaviour in such simulations. The results can be used in other particle based simulations, for example for simulating membrane behaviour in mechanical systems.

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