Bonds and Breakups, a stressful model

Modeling Cell Adhesion to Extra-cellular Matrix with Focal Adhesion Complexes

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How do cells move or remain in place?

Cells are supported by a network of collagen and fibrin bundles known as the extracellular matrix (ECM). In the case of mammals, these two independent networks are coupling due to the presence of focal adhesion complexes (FA), linkage points in the cell surface through which physical forces and regulatory signals are transmitted between the cell and the ECM, generating thus a mechanism of adhesion (See Figure 1A). So far in literature, modeling of FA behavior assumes that the Cell Membrane and ECM are rigid solids, completely neglecting surface fluctuations![2] Our model (See Figure 1B) does incorporate these fluctuations, allowing insight into how bond breakage propagates.

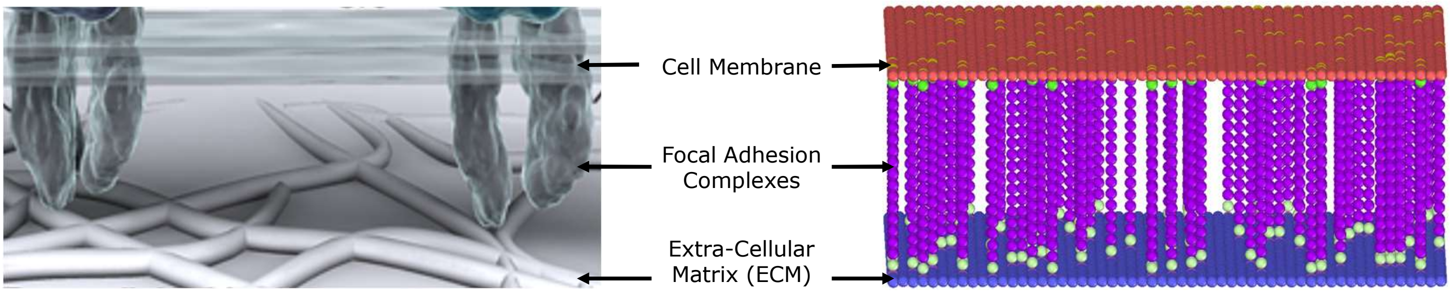

Figure 1. a) A molecular model of the Focal Adhesion Complexes mediating Cell adhesion to the Extra Cellular Matrix.[1] b) The initial configuration of the molecular dynamics model for the FA's

What influences Cell-ECM adhesion strength?

The aim of building this model was to visualize and measure the effect of various influences (FA-ECM attraction, force pulling on surfaces, number of chains) on polymer chain bonds between surfaces. This will help us determine the response of cells to orthogonal.

How and when do FA bonds break?

Fraction bond breakage over time

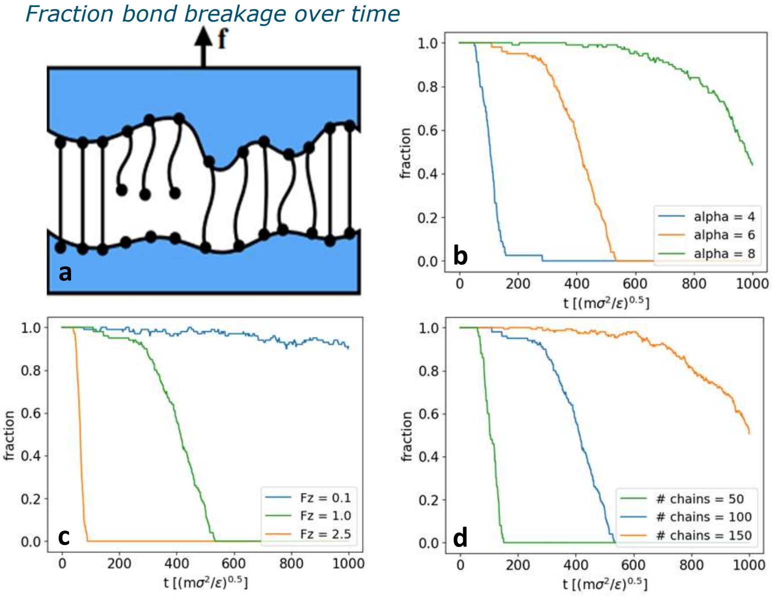

Figure 2. a) Illustration of bonds breaking between surfaces. b),c),d) Graphs displaying the fraction of bound bonds vs total bonds over time. Parameters change for different graphs with a different α attraction force in the top right, different force Fz in the bottom left and a different number of chains in the bottom right.

Figure 2 shows all parameters affect the rate of bond breakage.

- A greater FA-ECM attraction force α results in a more stable system which requires much greater stress to fail (figure 2b).
- The opposite is true for the force Fz with which the two surfaces are pulled apart (figure 2c).
- The number of connecting chains also affects stability, as a high number of chains stabilizes the system significantly (figure 2d).

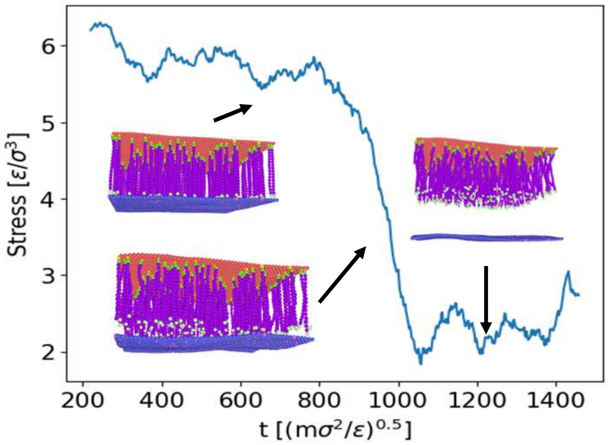

Figure 3. The stress in the z-axis of the whole system over time. A sharp decrease in stress can be seen at the timepoint at which the bonds break and the system falls apart.

The sharp decrease in stress seen in figure 3 shows a similar pattern as the number of bonds, how this stress is propagated over the surface is investigated in the following graph.

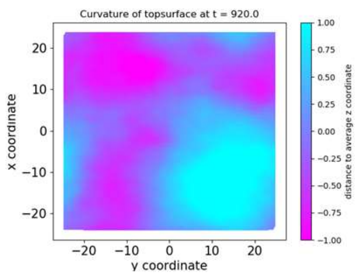

Figure 4. The curvature of the ECM from a top view at the breaking point of the system. The purple regions are still bound to the polymer while the light-blue is already broken loose.

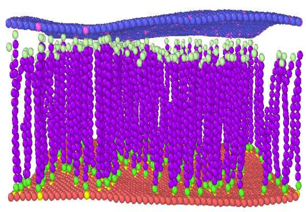

Figure 5. The model at timepoint 920 at which the system is breaking. Polymers in the front left part are already breaking while polymers in the middle left are still bound to the top surface.

The breaking of the polymers is clearly non-random as we can conclude from figure 4. After a break in an initial nucleation point, the breaking of the polymer propagates over the surface.

Conclusions

- The bonds between the cell and the ECM can resist some force before failure. However, when this failure happens, a domino effect occurs and many other bonds connecting the ECM and cell will break shortly after. The first to break are the bonds closest to the initial failing bond.
- Factors with a very high impact on the amount of force which can be resisted are the FA-ECM attraction force α and the number of FA-ECM bonds.

Sources

1. https://www.reading.ac.uk/nitricoxide/intro/migration/adhesion.htm
2. https://doi.org/10.1063/1.1805496

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