Modeling a Cell Motility on the Surface with a Pit

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Abstract: Living cells respond to outside physical environment in many ways including changing their geometry and location. A cell was modeled as a tensegrity structure that consists of the cytoskeleton, the cellular nucleus and lamellipodia. This model was based on the use of isolated elastic components consisting of a set of continuous compression components and a set of continuous tension components. To investigate the influence of surface topography on cellular movement, several representative cases were designed and simulated. By using internal strain energy as a main criterion to estimate the stability of the cell at various locations, we could show that cells have a tendency to move towards and stay on the sidewall of a pit. They also have a tendency to leave the concave corner. The obtained simulation results were in agreement with the available experimental evidence. Thus, the proposed model and approach may be a valuable tool for understanding the mechanics of a cell motion.

Keywords: Cell motion, Strain energy, Tensegrity, Modelling, Surface topology.

1. INTRODUCTION

Living cells are capable to respond to external physical environment by changing their geometry, location [1] and proliferation process [2]. These changes are influenced by the cells' internal balance as they need to maintain structure stability and molecular self-assembly and the interactions that occur between the plasma membrane of cells and the extracellular matrix (ECM). Due to the external mechanical loads or cell-generated forces that appear during the cell's migration, geometry and internal elastic energy changes occur [3]. Mechanical signals that the cell senses are transduced via the cytoskeleton structure. This interconnected structure consisting of microtubules and filaments supports stabilization of the cell's shape and allows the cell to carry out such functions as movement and division.

To investigate the biological signal transduction and the cells' response to different physical environments, number of experimental studies were recently carried out. The cells' response to the stiffness of the surface was investigated by culturing normal rat kidney epithelial and 3T3 fibroblastic cells on a collagen-coated polyacrylamide substrate. The cells' response to the stiffness of the surface was investigated. The result showed that cells on flexible substrates (relatively soft substrates) showed reduced spreading compared with cells on rigid substrates. Focal adhesions on flexible substrates were highly dynamic whereas those on rigid substrates were more stable [4]. This behavior was successfully modeled by using the approach of tensegrity [5].

The research that was focused on eukaryotic cells concluded that the ultimate shape of cells is defined by cycles of mechanosensing, mechanotransduction, and mechanoresponse. Local sensing of the cellular geometry or force is transduced into biochemical signals that result in cell responses to the cell-level formation and cell migration. These responses regulate the cell's growth, differentiation, shape changes and death [6].

The research on cell's signal transduction mechanisms in the guard cells was conducted by Schroeder, Allen in 2011 [7]. Guard cells are the cells that surround each stomata and help to regulate the rate of transpiration. Their signal transduction mechanisms integrate light signals, water status temperature, and other environmental conditions that regulate the plant survival under diverse conditions. This study showed that the manipulation of guard cell signals would not only affect the cell's movements but also control more complex functions of the cell [7].

The focal adhesion is also an important factor that influences cells' migration and signaling, it serves as a force and signal transduction media between the actin cytoskeleton and the extracellular matrix [8, 9].

A human epithelial cell was used to study the influence of surface topography on cells' responses to micropatterned substrates [10]. This experiment indicated that heterogeneity of cells' distribution at different locations was caused by their movement

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behavior at the concave and convex corners of a pit and pillar substrates. It was concluded that the anisotropic topographical features of concave and convex architecture affects cells' spatial growth and distribution.

In the study of cellular behavior on concave and convex microstructures fabricated from elastic PDMS membranes [11], cells' distribution was related to the deformation of the plasma membrane and formation of stress fibers. The experimental results showed that the cells on the micropatterned substrate actively "escaped" from concave patterns, but not from the convex [11].

In addition to the experimental works, a number of computational cell models were developed in recent years in order to provide an explanation of the mechanism of cells' responses to the external environment [12-18].

Based on the behavior of the micro filamentous structure, the cytoskeletal models were developed. They were based on the tensegrity model, tensed cable network model, and open-cell foam model [19]. The cytoskeleton serves as the main structural component in this approach while the whole pre-stressed cable network is devoted to modeling the deformability of cells [24, 20, 21]. The tensegrity architecture was first described by Buckminster Fuller in 1961 [22]. The discontinuous-compression, continuous-tension structural systems were developed and were named Geodesic Tensegrity [10, 23]. The tensegrity structures are widely used to predict cells' response to mechanical signals transmitted by a cytoskeletal structure [24, 4]. Mechanical signals may transduce into biological or chemical responses by varying the force-dependent scaffold geometry or molecular mechanics [25].

In this study we utilized a tensegrity model representing a cell's cytoskeleton, nucleus and lamellipodia in order to simulate its movement on a micropatterned substrate with concave architecture and use of the total internal elastic strain energy as the main criterion to evaluate the cells' movement tendency at various locations.

2. MATERIALS AND METHODS

2.1. Tensegrity Structure

Tensegrity is a structure consisting of a set of compression members and a set of tensile members connected in such a way that the compressed members do not touch each other and the pre-stressed tensile members delineate the system spatially and make the total structure self-sustainable.

Several research papers used tensegrity structures to model mechanical behavior and deformation of living cells. One specific tensegrity cell model consists of 30 components, including 6 struts representing the microtubules members of the cytoskeleton and 24 cables representing the microfilaments or intermediated filaments in the cytoskeleton (CSK). All struts carry compression loads while all filaments carry tension loads to form a stable 3D structure [26, 27].

Figure 1: Classical cell tensegrity structure.

In this model (Figure **1**) some nodes are attached to the surface. Typically, one node needs to be fixed to a surface to simulate the focal adhesion. The rest of the nodes are free and will exhibit morphing or geometry change when external or internal forces are applied to the cell [28].

A new type of a cell model is introduced here to simulate the cell's movement. The cytoskeleton, the nucleus and the lamellipodium are modelled by using tensegrity approach.

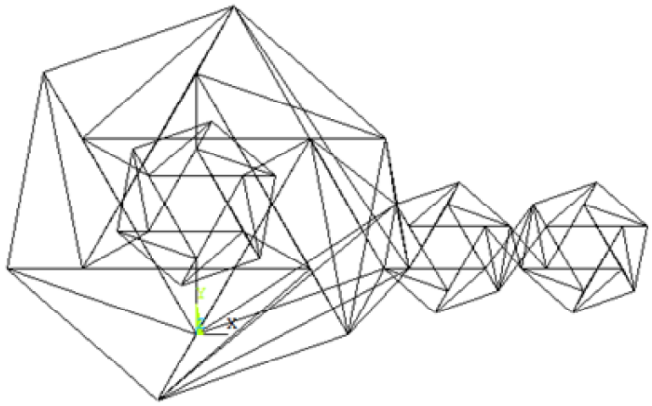

Figure 2: Tensegrity model of a cell model with nucleus and lamellipodium (view in x-y plane).

It is necessary to model the lamellipodium since it has a very important role in the cells' movement. Biologically the lamellipodium is a cytoskeletal protein actin protruding from the leading edge of the cell. When the cell moves, the leading edge of this structure extends first, attaches to the surface and then propels the whole cell forward.

The computational model of this structure was implemented by using ANSYS (Canonsburg, Pennsylvania, US).“Link 180” was selected to model the microfilaments members and “Beam 188” to model the microtubules members. In Figure **2**, the left-hand side refers to the cytoskeleton and nucleus, while on the right-hand side, the long strip structure represents the lamellipodium.

Similar to the classical tensegrity cell structure, the cytoskeletal structure contains 30 members comprising 6 struts and 24 cables. The nucleus is modelled by a similar structure, however the dimensions are smaller than that of the cytoskeleton. The lamellipodium is formed by two classical tensegrity structures of the same size that are oriented in a row.

After defining the geometry of the main structures, connections between each structure were created. To connect the cytoskeleton and nucleus 6 cables were used, 12 cables were used to connect the cytoskeleton and lamellipodium and anothers 6 cables were used to connect both parts of the lamellipodium.

2.2. Mechanical Properties of Cellular Members

The mechanical properties of microtubules and microfilaments were assigned on the basis of the experiment implemented by Mickey *et al*. [29]. Most of the cells properties were extracted from this experiment, but the size of the cross section was enlarged to assure that the whole structure is more stable under the external driving force. The size and mechanical properties of the cellular members are presented in Table **1**.

Table 1: Physical and Mechanical Properties of the Cellular Members Used the Cell Model

Properties	Micro-Tubules	Micro-Filaments
Element type (ANSYS APDL)	Beam 188	Link 180
Radius (nm)	36.0	15.00
Cross section area (nm^2)	4070	707
E (GPa) (Elastic modulus)	1.200	2.60
Poison's ratio	0.30	0.30

2.3. Boundary Conditions

After defining the geometry and mechanical properties of the cellular members, appropriate boundary conditions have to be set. The important factor that allows a tensegrity structure to maintain its shape is pre-stress. Pre-stress is generated by the tensile forces in microfilaments. These tensile forces will keep each microfilament under tension and exert a compression force on the microtubules elements via each node. The current model consists of 48 nodes distributed in three-dimensional space.

Boundary conditions are defined to simulate the cells' focal adhesion. Focal adhesions are large macromolecular assemblies through which a mechanical force is transmitted between an extracellular matrix (ECM) and an interacting cell. In this study (Figure **3**), node 3 is constrained in all translational and rotational degrees of freedom. Node 1 and node 2 are constrained in z-direction and all rotational degrees of freedom, which allow them to move in x-y plane. For the rest of the bottom nodes, nodes 25, 26, 27 and nodes 46, 47, 48, the type of constraint set is the same as node 1 and node 2, which means these nodes can slide on x-y plane but cannot leave the surface plane.

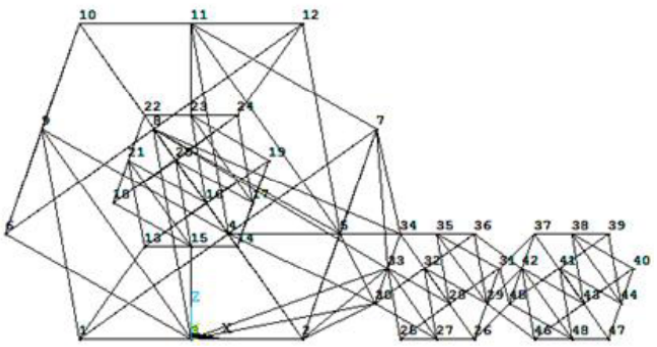

Figure 3: Cell structure in x-z plane showing boundary conditions.

2.4. Energy Calculation

To assess a single cell's stability when it is moving across the substrate, the total internal elastic energy of the cell is evaluated. A higher internal elastic energy means the cell is not likely to stay in this location and it will try to move to another location that will result in a lower energy. When the cell is at the lowest energy level, it means the stable or preferable state for the cell. After applying pre-stress or an external force, displacement of nodes will occur.

To calculate the total elastic energy of the cell modeled by the tensegrity structure, the elastic energy of each element (*i.e*. the strain energy of microtubules and microfilaments) has to be added up. The governing equations to calculate the total energy are

$$E = E_s + E_c \tag{1}$$

$$E_s = \frac{1}{2}\int_V \{\sigma\}_s \{\varepsilon\}_s dV \tag{2}$$

$$E_c = \frac{1}{2}\int_V \{\sigma\}_c \{\varepsilon\}_c dV \tag{3}$$

where E denotes the total energy of the cell, E_s denotes the total energy in all tensile elements and E_c denotes the total energy stored in all compression elements; $\{\sigma\}_s$ refers to the components of the stress in each tensile filament, $\{\varepsilon\}_s$ refers to the components of strain of each tensile filament, $\{\sigma\}_c$ and $\{\varepsilon\}_c$ refer to the components of stress and strain in each microtubules, respectively.

2.5. Simulation of the Cell Movement

To investigate the tendency of a cell movement on the surface, especially for the surface with concave architecture, a tensegrity cell model with a nucleus and a lamellipodium structure (Figure **2**) was used. The pre-stress within the model was set by imposing the corresponding tension and compression forces to the nodes [26]. The goal of this study was to find the relationship between the cell's location and the total energy change during its movement along the substrate.

The simulations were performed on a flat surface with a concave corner (a pit on the surface). Several cases were simulated:

- a cell moves along a flat surface,
- a cell encounters a wall when it reaches the concave corner,
- a cell moves up when it approaches a wall,
- a cell moves sideways when it approaches a wall.

In all the cases, the effect of gravity was neglected. Node 3 was always anchored to simulate focal adhesion. The strain energy of the cell changed when the lamellipodium extended and the cell's body moved. Based on the minimum energy criterion, the tendency of the cell's movement was identified.

2.5.1. Cell Moves Along a Flat Surface

The first step is to impose the boundary constraints then a pre-stress is applied. It will result in a slight change of the cell's shape and in the length of each strut and filament. The lamellipodium always extends first and then it pulls the main cell's body forward. So in this study, after applying the pre-stress, two nodes (node 40 and node 44, Figure **4**) on the forward edge of the lamellipodia were selected. We applied one and two micron displacements along x-direction to these nodes; the displacements were parallel to the flat

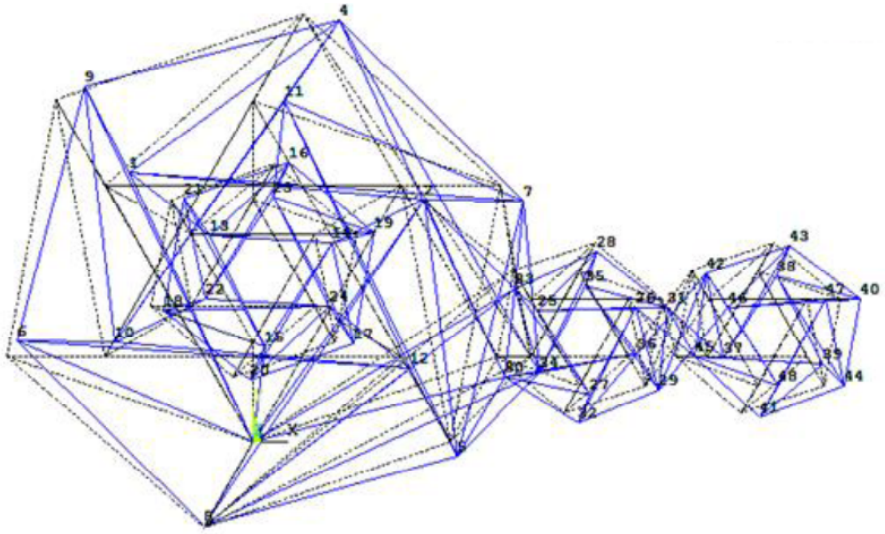

Figure 4: Cell model moves forward one micron (view in x-z plane).

surface. Figure **4** (front view) shows the cell's geometry after it moved forward one micron. The solid blue line is the cell's deformed shape after the one micron movement and the solid black line is the original shape.

2.5.2. Cell Encounters a Wall

Let us assume that the cell is currently on the bottom of a flat pit (Figure **5**) and while moving it encounters a vertical wall.

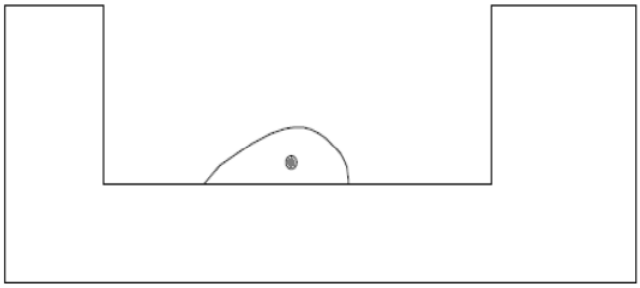

Figure 5: Cell in a pit.

The following procedure was developed to simulate an encountering process. It is assumed that originally the cell is at the surface on the bottom of the pit and the side wall is at the distance of one micron from the cell's front edge. Since the cell does not "know" there is a wall on its path, what will happen if it initially "wants" to move forward two microns? In order to move, it needs to generate the inside forces that will drive the front of lamellipodium two microns. Thus, if the cell "plans" to move forward two microns, but encounters a wall after one micron movement, the remaining force will push it against the wall.

First, we applied a two micron displacement to nodes 40 and 44. This deformation generated the nodal forces at all nodes that correspond to the inside forces of the deformed cell, let's call them F_2. At the next step, we applied a one micron displacement to the same two nodes and calculated the corresponding nodal forces, let's call them F_1. The remaining part of the "planned" forces were calculated by,

$$\{F_3\} = \{F_2\} - \{F_1\} \quad (1)$$

where $\{F_3\}$ is a 48 by 1 vector that denotes the "planned" force.

To simulate the situation when the cell moves forward but encounters a wall in its path, we applied the remaining forces $\{F_3\}$ to each node to simulate the effect of encountering the wall. The total strain energy of the cell when it encounters the wall was calculated.

2.5.4. Cell Moves Up or Sideways

After the cell encounters a wall, the next possible movement could be up the wall or sideways. In the case of upward movement, one micron displacement was given to the forward nodes (Figure **4**, nodes 40 and 44). The constraints in y direction were also applied in order to keep the forward nodes moving in x direction. After the front side of the lamellipodium contacted the wall, one micron movement in a positive y direction (up the wall) or positive z direction (sidewise motion) was applied to the front two nodes respectively. To simulate the case of the cell's upward movement, the constraints of three bottom nodes in z direction were released to ensure that the lamellipodium can move off the surface. As a result, Figure **6** (front view) shows the cell's upward movement and Figure **7** (top view) shows the cell's sideways movement.

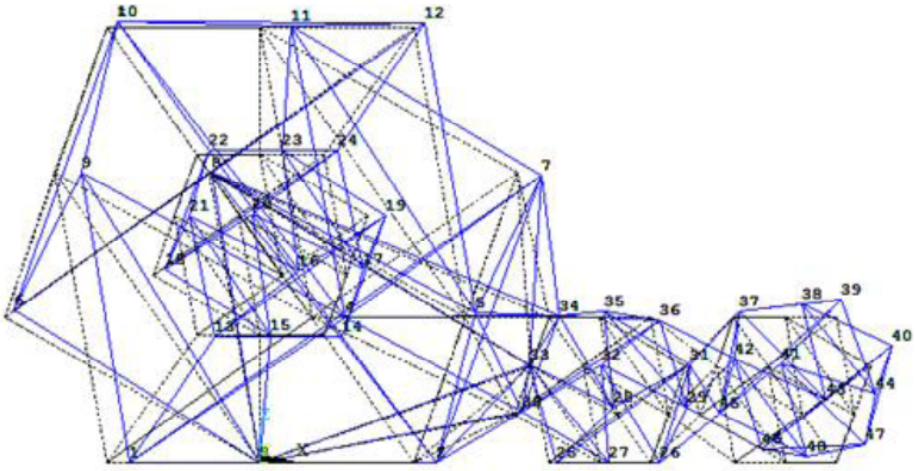

Figure 6: Cell moves up (view in the x-z plane).

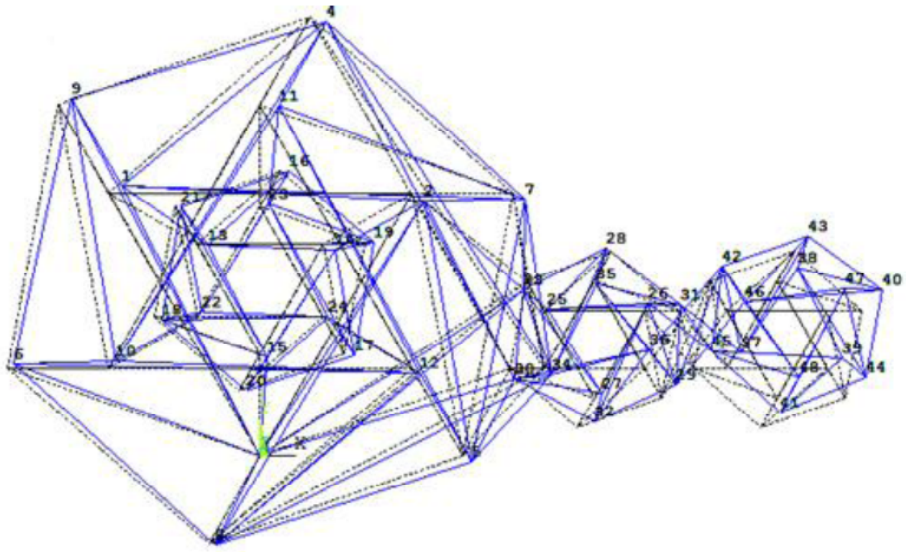

Figure 7: Cell moves sideways (view in the x-y plane).

Figure **8** shows the flow chart that summarizes the simulation process for different cases.

Case 1: Cell Moves Forward for 1 Micron	
1.	Apply pre-stress.
2.	Apply to nodes 40 and 44 a one micron displacement in the positive x direction, while constraining nodes 40 and 44 in the y direction.
Case 2: Cell Moves Forward for 2 Micron	
1.	Apply pre-stress.
2.	2. Apply to nodes 40 and 44 a two micron displacement in the positive x direction, while constraining nodes 40 and 44 in the y direction.
Case 3: Cell Encounters the Wall	
1.	Apply pre-stress.
2.	Apply to nodes 40 and 44 a one micron displacement in the positive x direction and constrain nodes 40 and 44 in the y direction.
3.	Calculate force $F_3 = F_2 – F_1$.
4.	4. Apply F_3 to each node and release constraints for nodes 40 and 44 in the y direction.
Case 4: Cell Moves Up	
1.	Apply pre-stress.
2.	Apply to nodes 40 and 44 a one micron displacement in the positive x direction, while constraining nodes 40 and 44 in the y direction.
3.	3. Apply to nodes 40 and 44 a one micron displacement in the positive z direction and release nodes 46, 47 and 48 in the z direction (they were constrained).
Case 5: Cell Moves Sideways	
1.	Apply pre-stress.
2.	Apply to nodes 40 and 44 a one micron displacement in the positive x direction while constrain nodes 40 and 44 in the y direction.
3.	3. Release constraints of nodes 40 and 44 in the y direction and then apply to nodes 40 and 44 a one micron displacement in the positive y direction.

Figure 8: Flow charts of the simulation processes.

RESULTS

In order to investigate the relationship between cell's movements and total internal elastic energy, the elastic energy of each element of the model was calculated and they were added up for each case described above. The total resultant energy for the deformed shape after cell's movements is summarized in Table **2**.

Table 2: Resultant Energy Values for the Final Configurations in Different Cases

Case	Resultant Energy (J/m^2)
Cell model with pre-stress only	$0.133*10^{-13}$
Cell moves forward for one micron	$0.212*10^{-12}$
Cell moves forward for two micron	$0.855*10^{-12}$
Cell encounters the wall	$0.382*10^{-12}$
Cell moves up	$0.230*10^{-12}$
Cell moves sideways	$0.291*10^{-12}$

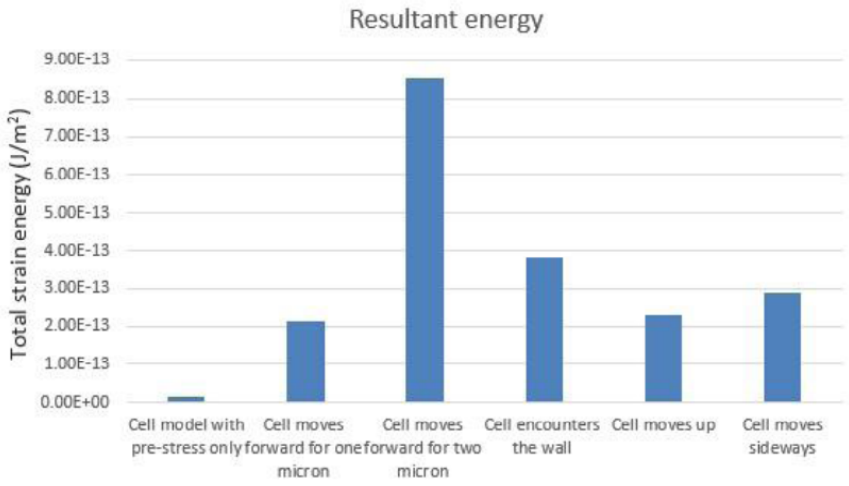

Figure 9: Resultant strain energy for the various configurations.

It is obvious that the least resultant energy is when only pre-stress is introduced. In order to migrate a cell needs to generate internal forces and this process will lead to an energy increase.

Figure **9** illustrates the comparison of the resultant energy value for cells in several cases. The energy needed for the two micron forward movement is much larger than in all other cases. By comparing the internal elastic energy of a cell moving forward for one micron with two micron, we could see that the two micron movement needs a significantly larger amount of energy than the one micron movement.

In the case where the cell encounters the wall the resultant energy is between the energy needed for one micron and two micron. Therefore it must be an energy consuming process when the cell encounters the wall. Some energy is released by this process and it may also lead to a change in shape of the cell. Thus, it is clear that the resultant energy after encountering the wall is smaller than the resultant energy for two micron free-of-wall forward movement.

Since the internal elastic energy of a cell encountering the wall is higher than the energy of a cell moving up the wall, the cell will not stay at the concave corner after encountering the wall but it will have a tendency to leave the concave corner and move up to stay on the sidewall. An experiment was conducted by Park, *et al.* where the L929 mouse fibroblast cells were cultured on a surface with a concave microstructure. The experimental results showed that the cells sensed the three-dimensional microscale curvature and actively escaped from the concave corner.

For the cases of upward and sideways movements, the resultant energies of both are more than the energy for one micron movement but less than the energy for two micron movements. Compared to the energy of one micron movement, the energy increments of these two cases are much smaller than the increment of two micron movements. This means that the configuration of the cell's movement up or sideways is more stable than the cell's movement of two microns on a flat surface. Thus, the cell has a tendency to move up or sideways. If a large number of cells are observed in the pit substrate, they are expected to move towards the side walls. If a time-lapsed observation is carried out, the cell's density on the sidewalls might be higher than on the other locations in this pit substrate. A corresponding experiment was conducted by Kim *et. al.* [30]. Cells were cultured on micropatterned substrates with pits. After a period of time, the density of the cells was measured and the result showed that at the side walls it was higher than on the bottom surface. Thus, we can conclude that the results produced by the introduced model match the results generated by experiments.

To evaluate the effect of the movement in y direction and verify the correctness of this model furthermore, we released the constraints for nodes 40 and 44 in y direction in each step. The resultant energies for this situation are summarized in the Table **3**.

After allowing for the edge of the lamellipodium to move in y direction, the resultant energy in each case will change, except in the first and the last cases. The reason is that there is no movement in y direction in the first case. In the last case, the value of the movement

Table 3: Resultant Energy Values for the Final Configuration in Different Cases after Releasing the y-Direction Constrain

Case	Resultant Energy (J/m^2)
Cell with pre-stress only	$0.133*10^{-13}$
Cell moves forward for one micron	$0.895*10^{-13}$
Cell moves forward for two micron	$0.325*10^{-12}$
Cell encounters the wall	$0.225*10^{-12}$
Cell moves up	$0.197*10^{-12}$
Cell moves sideways	$0.291*10^{-12}$

in y direction is one micron that results in the same value of resultant energy.

Although the specific values of the resultant energies change, in comparison with the results generated by the cases where y-direction movement is constrained, the qualitative energy relationships do not change. The resultant energy of two micron movement still shows the highest value. The resultant energies of the later three situations are still between one and two micron forward movements. Furthermore, by comparing the energy of the cells encountering the wall with the energy of the cells moving upwards, we can conclude that they have the tendency to leave the concave corner after encountering a wall.

DISCUSSION

To predict a cell's movement on the flat substrate and on the substrate with a pit, a new type of tensegrity model was developed. This model contains the cell's cytoskeleton, the nucleus and the lamellipodium. The cell's movement is initiated by the lamellipodium protrusions in the direction of migration. They are usually driven by actin polymerization and are stabilized by adhering to the extracellular matrix (ECM) or adjacent cells via transmembrane receptors linked to the actin cytoskeleton. These adhesions serve as traction sites for migration.

To model migration of the cell located in the center of a pit several cases were investigated:

- cell movement along the flat surface for one micron and two microns,
- cell movement up when encountering a wall,
- cell movement sideways when encountering a wall,
- cell movement upward when encountering a wall.

Based on the principle of the minimum elastic internal energy, the cell has a higher probability of moving to and staying in a location that results in lower energetic state. The elastic internal energy was calculated for each one of the above mentioned situations. The one micron movement led to minimum energy while two micron forward movement led to maximum energy compared to all other simulated here cases. The resultant internal cell energy of the upward and sideways movement was less than the energy of two micron movement. Since both the upward and the sideways movements resulted in the situation that cells are located on the sidewalls, it could be concluded that cells have a tendency to move to and locate on sidewalls when they are in a pit.

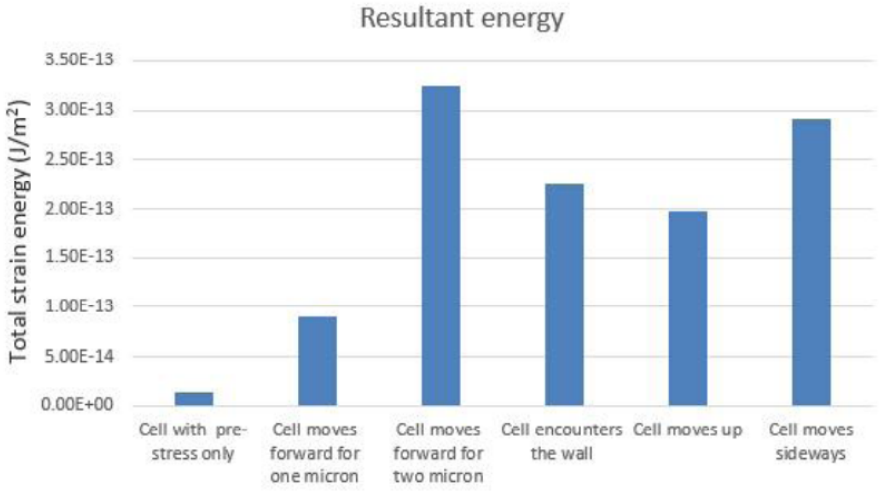

Figure 10: Resultant energy values for various cases after releasing the y-direction constrains.

The situation when cells encounter a wall was also observed. If cells encountered a wall along their path they had a potential of the remaining forces that were not utilized during the "planned" motion. To simulate the wall encountering, the remaining forces were calculated and applied when cells encountered the wall after a certain distance movement. By comparing the resultant energy of the cell encountering the wall with all other cases, the case for the cell's upward movement led to a lower energy than when encountering the wall. This indicates that the cells may ultimately leave the concave corner, move up and stay on the side wall.

The related experimental results were presented by Kim *et al.* in the study of the influence of surface topography on the human epithelial cell response to micropatterned substrates with convex and concave architectures. In this study, a micropatterned substrate with pit architecture was established to assess the responses of human epithelial cells and investigate the cells' distribution. A number of cells were cultured on micropatterned substrates with a pit. After a period of time, the density of the cells was measured and the result showed that the density of the cells on the side walls was higher than at the bottom. In addition, it was observed that the formation of the stress fiber with the lamellipodium and filopodium were seldom seen at the concave corner of the pit substrate, which indicated the cells hardly stayed in the corner and had a tendency to leave the concave corner. The experimental observation clearly indicates that our model is capable to predict the preferable migration pattern of a cell as a function of the surface topology. It may be used to predict the topology of the artificial scaffolds that will enhance the cell migration in desired direction or to the desires location.

CONCLUSION

A cell model including a nucleus and a lamellipodium based on the tensegrity structure was developed. The cell was initially placed on a flat surface and then we simulated its movement within the pit in the substrate. The proposed model predicted that the cell's upward and sideways movements would lead to a lower internal elastic strain energy than if a cell would move along a flat substrate. Thus, one may conclude that the cell has a tendency to move up the side walls in a pit in order to leave the concave corner and settle on the side. The model predictions correspond to the experimental observations. Therefore, this newly created cell model may become a valuable tool for investigating cells' responses to the surface topography.

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