Dynamic Curvotaxis: Can cells surf the waves?

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Abstract

During, development and regeneration cells are subject to dynamic topographic changes as the surrounding tissues shift and grow. Yet, in vitro experiments have shown that cell scale curvatures influence cell migration, whereby, cells tend to avoid convex peaks and are more likely to settle in concave areas. This behavior was demonstrated on static surfaces with a fixed sinusoidal landscape composed of curved hills-and-valleys. Based on these findings, we later proposed a computer model to theoretically explain the underlying physical mechanism. Nonetheless, how dynamic curvature impacts cell motion remains unknown. In this study, we extend our previous model to explore what would happen if substrate curvature were to change over time. Using travelling wave patterns, we simulate a dynamic surface curvature. We investigate the influence of wave height and wave propagation speed and we find that long-distance cell migration can be achieved. Our results open a new area of study to understand cell mobility in dynamic environments, from single cell in vitro experiments to multi cellular in vivo mechanisms involving embryogenesis and regeneration.

Introduction

In embryonic development, various types of processes rely on directed cell migration over long-distances [1–3]. Long-distance directed cell migration is essential for proper organ morphogenesis[3–5] as well as the formation of new blood vessels[6–8]. Moreover, embryonic development involves various events where tissues contract[9,10], bend[11] and shift. Among other things, that means that cells are exposed to dynamic topography, including curvature changes and even curvature inversion as the surrounding tissues grow and develop[11]. This raises the following question: “How are cells influenced by dynamic curvature?”

Mounting experimental evidence based on static substrates indicate that curvature influences single and multi-cellular migration[12–15]. For example, mesenchymal stem cells and fibroblasts cells cultured on a surface landscape defined by rolling hills and valleys were shown to significantly affected by cell-scale curvature[12]. Cells would avoid going over convex peaks and were more likely to go and settle in concave areas (valleys). In other words, cells migration was influenced by substrate curvature, we called this phenomenon curvotaxis[12]. By flipping the substrate over we showed that gravity was not involved[12]. In contrast, nucleus integrity and actomyosin contractility are needed for curvotaxis to occur[12]. Moreover, as cells traversed this curved landscape the nucleus was generally offset closer to concave valleys than the barycenter of the cell. These findings lead us to create a computer model that was able to physically explain the mechanobiological process of curvotaxis based on key known parameters, such as cell contractility and nucleus involvement[13]. On the other hand, on a hill and valley landscape, the observed cell migration was neither guided nor long-distance, instead it resembled a biased free migration.

Another single cell study, on cylinder shaped substrates, showed that stromal cells adjusted their speed and directional persistence to substrate curvature[16]. Cell migration was more isotropic as cells travelled on the inner surface of the cylinder, this implies that cells are not that affected by concavity. On the

contrary, cells cultivated on the convex outer surface of cylinders aligned and migrated primarily parallel to the axis of the cylinder, yet, cells still remained free to move both ways along this axis. The examples above clearly show that curvature influences migration by restricting cell motion but did not show reliable cell guidance in a given direction.

Long distance migration is often observed in vivo during development. In addition, various examples of calcium-mediated contraction waves are known to influence morphogenesis during the early stages of development[17,18]. For instance, in drosophila millihertz contractions were shown to induce ingression[19]. Moreover, the early embryo is composed of several cell layers and during development there are numerous examples of folds, furrows and invaginations that induce dynamic changes in curvature. Many slow calcium waves are seen as indentation waves[20,21]. As one layer transiently contracts due to calcium wave propagation, cells in adjacent layers may perceive these contractions as dynamic topographic variations, akin in many ways to travelling waves moving up and down[20,21]. As we continue to explore the involvement of curvature in single cell migration, the examples above allow us to envision a mechanism of long distance directed migration induced by dynamic curvature. Could dynamic curvature be the missing piece of the puzzle?

Problematic

Here, we therefore aim to understand how dynamic curvature may affect single cell migration. From this knowledge, can we find a way to promote and direct cell migration over long distances? Moreover, can we come up with a simple concept for a substrate that would use dynamic curvature to promote cell migration?

The main idea

In this study, we intend to test how travelling deformation waves of the substrate can be used to promote long distance migration by curving the cell's environment. Let us therefore defined a surface that can change shape dynamically to guide cell migration. In theory, if we can change the shape of the substrate, then it is possible to keep the cell continuously exposed to a curvature gradient. By analogy, we know that on landscapes composed of hills (convex) and valleys (concave), the cell prefers valleys. We can therefore deform the landscape so that the valley is ahead and the hill behind. In the end it is somewhat similar to a surfer riding a wave.

Hypothesis

We hypothesize that dynamically changing the curvature of the substrate should stimulate and drive cell migration over large distances.

What is needed

To use dynamic curvature to stimulate and drive cell migration we need a substrate that can dynamically change shape in order to continuously expose cells to a curvature gradient. Over the past 20 years,

significant developments have been made in cellular substrate engineering to study and control cell migration[12,22–25]. Although there is a plethora of substrates that were engineered to influence cell migration[26–28], some are dynamic[25,29], but only a few change shape dynamically[25,30]. Some can change their topology on the submicrometric scale[30], but none actually fit the requirements to test our hypothesis[15]. Consequently, building an experiment to test this idea requires new technologies that have not been invented yet. This also includes testing different hypotheses, trying various dynamic substrate designs, parameters sets… In other words, starting out with an experimental approach would cost a lot of time and money to iterate towards a viable design. Instead, we asked ourselves whether if it would be possible to test this idea on a computer? Doing so would allow us to test the concept and formulate a dynamic substrate design that is more likely to work in the future. In addition, we could try to test relevant substrate design parameters ahead of production, saving unnecessary iterative design steps and countless prototypes. And, since we already had a validated computer model of curvotaxis, this is exactly what we did:

What we did

We used our previously developed cell model to predict single cell migration on travelling waves to offer an initial proof-of-concept. The model predicts that, with appropriate wave height and wave propagation speed, cells are able to undergo curvotaxis over long distances. Moreover, simulation results show that wave height promotes the speed at which cells can keep up with travelling waves and consequently undergo sustained curvotaxis. In addition in the discussion we analyses how curvotaxis, which is non deterministic[12], can be exploited to generate reliable and sustained cell migration. Finally, we defined substrate specifications to achieve reliable sustained migration.

Method

The 3D cell model used in this study was previously developed and validated to provide an explanation for curvotaxis. The inner working of the model has been extensively described in Vassaux et al[13]. Here, the model has been adapted to inquire whether traveling waves could, in conjunction with curvotaxis, lead to sustained long-distance cell migration. Since the technical details of the model have already been explained in our previous papers, here, we will only provide context and focus on what is new.

Mechanical modeling paradigms

The model is composed of a substrate (the surface) and a cell avatar, both are modeled using divided medium mechanics (LMGC90 software). This method allows us to subdivide the substrate and the cell avatar into rigid spheres. These spheres can mechanically interact with one another through predefined contact and cohesive forces and are ultimately subject to a numerical adaptation of Newton's laws of motion. The model is in open access[31] via https://github.com/mvassaux/adhSC/tree/v1.0.0 and in Vassaux et al. 2019 we further explained and tested the model[13].

The dynamic substrate

The topology of the substrate (surface) is controlled by imposing its local vertical positions z(x,t), without changing its local horizontal position. We consequently create a dynamic substrate topology by moving different areas of the substrate up and down between each time step. These vertical movements form travelling waves which propagate across the substrate plane.

$$z(x,n) = \frac{h}{2}\sin\left(\frac{2\pi}{\lambda}x + vn\right) \quad \text{(eq.1)}$$

In equation 1, we locally calculate the vertical position of the substrate at the x coordinate along the x axis and time step n. The sinusoidal waves are defined by the height h, wave length , and travel velocity v expressed in micrometer per iteration (see figure 1.c). Consequently, the topological deformation of the substrate forces the cell avatar to adapt its shape and react accordingly.

Implementation of curvotaxis in the cell model

Here, we use the same physical mechanisms to model curvotaxis than in our previous studies[13,31], all other phenomena that would either promote or guide cell migration were not considered.

Supported by previously published results[12,13], we hypothesize that the topography-induced a force imbalance on the nucleus between the side that is oriented toward the concavity versus the one aimed at the convex side. It consequently becomes harder for the cell to drag its nucleus toward convexities than concavities. As a result, a bias arises which favors movements toward concave areas. In this study, we considered waves with curvature parameters known to induce a migration bias[12] that were observed to dominate cell steering during migration. The cell avatar is able to reproduce this bias by predicting the mean displacement of the cells lead by the drifting motion of the nucleus. Using the cell avatar, we predicted how cells would migrate due to the dynamic curvatures defined by the travelling waves.

Different test conditions

We ran simulations with the following substrate conditions:

Testing the influence of wave propagation speed with constant wave height (10 µm), (figure 1.d & Supplementary Movie 1):

1- “Static” substrate deformation: static reference

2- “Very slow” travelling waves: 1µm/it

3- “Slow” travelling waves: 2µm/it

4- “Medium speed” travelling waves: 4µm/it

5- “Fast” travelling waves: 8µm/it

6- “Very fat” travelling waves: 16µm/it

Testing the influence of wave amplitude with a constant speed, figure 1.e (8 µm/it):

7- “Low” traveling waves: 10 µm high

8- “High” traveling waves: 40 µm high

Sustained curvotaxis in function of the height and the propagation speed of the waves (figure 1.f & results with unstained migration were not published) (Supplementary Movie 4):

9- “Low & slow” traveling waves: 10 µm high, with a propagation speed of 2 µm/it

10- “Medium height & medium speed” traveling waves: 40 µm high, with a propagation speed of 4 µm/it

11- “Fast & high” traveling waves: 40 µm high, with a propagation speed of 8 µm/it

Steering cell migration (Supplementary Movie 1)

12- Dynamically changing cell direction

Results

We used our previously developed cell model to study the effect of dynamic substrate topology on cell migration. More precisely we wanted to know if traveling wave deformations could be used to promote sustained cell locomotion, for this reason all other source of cell migration were ignored.

Static substrate (reference test)

As a reference, we first ran a simulation with a “static” substrate deformation in the shape of a sinus wave (wave propagation speed of 0 µm/it). The cell is initially located in a concave region, the ensuing travel is negligible (see figure 1.d)

Influence of traveling wave speed

When traveling waves are involved, the deformation travels across the substrate plane, in other words, the substrate does not translate, instead it locally moves up and down to recreate the motion of the waves. In many ways, this is similar to the surface of the ocean swelling up and down as waves pass by. We generated a first testing set with wave heights of 10 µm to study how the wave propagation speed may affect the overall distance travelled by cells (figure 1.d), which under sustained migration is directly proportional to migration speed. We found that the best overall travel speed and distance is achieved when the waves propagate at 2 µm/it. Bellow this optimal propagation speed, we see that cells achieve sustained migration by “riding” the wave, this indicates that wave speed is the limiting factor. On the

other hand, when the propagation speed of the wave is above the optimal value of 2 μm/it, we observe that the waves overtake the cell avatars, thus indicating that the cell's speed is now the limiting factor. Interestingly, when waves go faster than the cell, the model predicts that overall cell speed decreases the faster the waves go. Surprisingly, it would seem that when waves propagate "very fast", the model predicts that the cell may even travel in the opposite direction.

Influence of traveling amplitude

With 10 μm wave heights the cell avatar is not able to keep up with waves propagating at 8 μm/it. However, when wave heights are increased to 40 μm the cell can sustain curvotaxis without being overtaken by the waves (figure 1.e), in addition, we observe that the cell avatar is better able to center itself in the valley. In the results from figure 1.f, we see that the cell avatars can undergo sustained and reliable curvotaxis at higher speeds when wave heights are increased. Comparative cases where migration was unstained due to lower wave heights are not shown in this figure.

Steering cell migration dynamically by changing the direction of propagating waves

We started the simulation by generating unidirectional traveling waves at the surface of the substrate. Then during the simulation, we changed the direction the waves traveled to by 90°, which prompted the cell avatar to adapt its direction of travel, we than again changed the direction waves propagated and observed the cell avatar adapting its course once again (Supplementary Movie 1). We conclude that the cell avatar can dynamically adapts its trajectory.

Discussion

The results of the model suggest that dynamic substrate curvature can be used to guide cell migration over long distances. This finding may have a profound impact on the way we apprehend single and multi-cell migration. In the end, these findings may trigger new ways to tackle and explain a plethora of phenomena in developmental biology and tissue engineering.

However, by themselves the results of the model are not sufficient to fully describe the essential characteristics of a future dynamic substrate. Firstly, in the model, the speed of the traveling waves was not described in physical units, therefore quantitative estimates will require additional analysis. Secondly, although curvotaxis is known to impact cell migration, in some cases its influence is non-deterministic. In other words, cell migration remains partially random which was not considered by the model. We will address both of these dilemmas below.

Estimating the speed of the traveling waves

To calculate the maximum speed of the traveling wave, we observe that cells must be able to keep up. When the waves were traveling at a slow and medium speed the cell avatar was able to keep up and migrate over large distances. However, if the waves traveled too fast, the cell was not able to keep up and

migrated poorly. Based on previous studies[12], for a wave height of 10 µm, we observe that mesenchymal stem cells can generally migrate at about 20 µm/h and up to 40 µm/h. We therefore conclude that traveling waves should propagate slower than 20 µm/h to allow cells to keep up.

Ensuring reliable migration

Experimentally, curvotaxis is one of many phenomena that influence cell migration, yet the model did not consider these other phenomena. With the limited curvature generated by low waves, curvotaxis contributes to cell migration, but it is not dominant. As a result, curvotaxis has a probabilistic effect on cell migration. However, the pronounced curvature of high waves significantly increases the guiding effect of curvotaxis[12,13], to the point that it can become dominant. At which stage, cells seldom go over convex summits[12] when wave heights are 10 µm or higher. In other words, being able to generate wave that are at least 10 µm high should reliably promote and guide cell migration.

Are our results quantitatively consistent with existing in vivo observations?

During development, various ultraslow calcium waves travel at 3 to 60 µm/h, making such waves plausible inducers of dynamic curvotaxis [20,21]. Our simulation results show that effective migration can be induced by waves travelling at optimum speeds of 20 µm/h when wave heights are low. With a wavelength of 100 µm, this speed corresponds to a wave frequency of 0.06mHz. Sokolow et al. 2012 found the contraction waves responsible for cell ingression belonged to the frequency band ranging from 0.01 to 0.1mHz, this suggest a possible adequation[19].

Substrate specifications defined by the model

We have estimated an appropriate wave speed of 20 µm/h and wave heights of 10 µm/h to induce reliable cell migration over long distances and showed promising biological examples[19–21]. We can now define have been addressed and simulation results shown to be compatible with in vivo. We can define the specifications of a functional substrate. Based on our results, we predict that reliable and sustained migration can be achieved by generating traveling waves with:

- wavelengths of 100 µm
- heights between 10 and 40 µm
- travel speeds ranging from 10 to 20 µm/h.

This low wave height substrate would consequently generate waves with frequencies ranging from 0.06mHz to 0.12mHz. On the other hand, on strongly curved substrates[12], speeds up to 40 µm/h may temporarily be achieved at the detriment of reliability.

Perspectives and applications

Once confirmed experimentally, we believe that dynamic curvotaxis may significantly impact our understanding of cell mobility. Not only will it become an additional phenomenon to consider when trying to explain single cell motility, such as ingression, but we expect that dynamic curvotaxis may also have a profound impact on our understanding of collective cell migration and the behavior of cell groups. Several examples have demonstrated that for collective cell migration to emerge, various phenomena have to work in synergy, otherwise the collective behavior becomes undefined[32–34]. Therefore, it is reasonable to assume that dynamic curvotaxis may be one of the key phenomena required to explain several processes involving collective cell migration and control tissue growth[35]. As a result, in addition to dynamic curvotaxis, dynamic curvature may have a significant impact on embryogenesis, regeneration and cancer metastasis.

Interestingly, up to now most models of cell migration with a strong emphasis on cell mechanics have only been used to explain known experimental results. At this time, in our field, it is still rare to use a model as a predictive tool to both engineer experiments and estimate their outcome. Although only experiment will tell whether if our forecast is valid; we nonetheless believe that predictive cell modeling is the future.

Conclusion

The results of the model suggest that dynamic substrate curvature can be used to guide cell migration over long distances and that traveling waves is a way to do it. In addition, we propose specifications for an innovative design of a dynamic substrate to promote cell locomotion.

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Figures

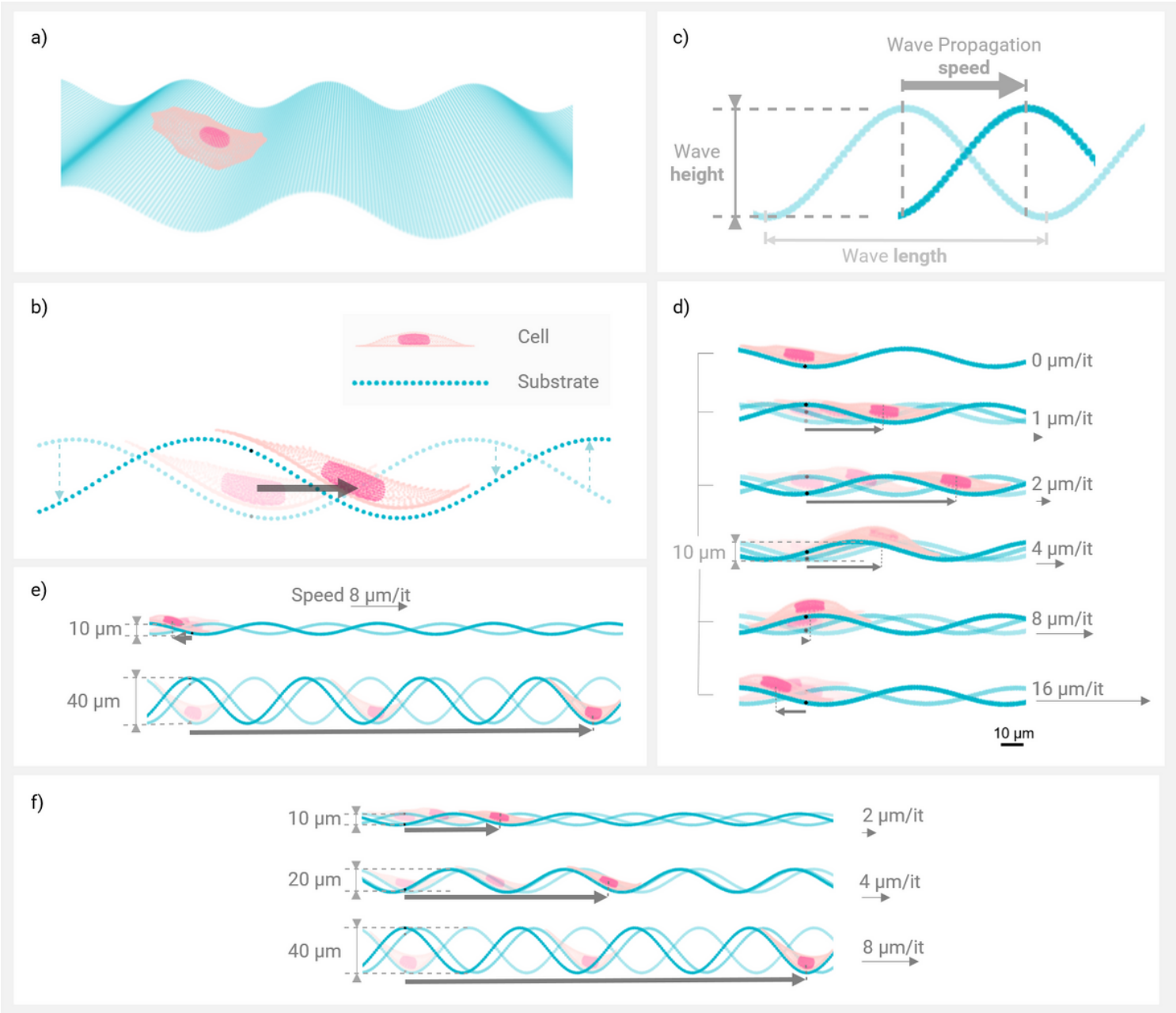

Figure 1

(a-f) Cell avatars (salmon) and their nucleus (pink) on dynamically undulated substrates (turquoise). The undulation is defined by propagating sinusoidal waves. The waves propagate horizontally along a single axis by making the local surface move up and down. As the wave moves, so does the concavity (valley). Subject to curvotaxis, the movement of the cell avatar is prone to move toward concavities. As a result, the cell avatar moves over the surface of the substrate as it continuously seeks the closest valley. (b-f) are side views.

a) Sky view of a cell avatar on the undulated substrate (Supplementary Movie 1).

b) The surface of the substrate is defined by a set off individual contact spheres (drawn smaller to identify them individually). These substrate spheres are fixed horizontally, in contrast, their vertical movement generate the travelling wave pattern. As the wave travels, so does the concavity (valley), which in turn attracts the cell avatar (Supplementary Movie 2).

c) The propagating waves are parametrically defined by their wave length (100 µm), their height varies between conditions (10 µm, 20 µm, 40 µm) and their horizontally uniaxial propagation defined in µm/it (arbitrary simulation speed unit).

d) The total distance travelled by the cell avatar is compared based on different wave propagation speeds for identical wave heights of 10 µm (Supplementary Movie 3).

e) Cell avatars were placed on substrates with identical wave propagation speeds, however, the difference in wave height leads to different outcomes.

f) Sustained curvotaxis achieved at different speeds, based on different wave heights (Supplementary Movie 4).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymovie1.avi
- Supplementarymovie2.avi
- supplementarymovie3wavespeed.mp4
- Supplementarymovie4.mp4