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Design of smart substrates to control cell migration: an *in silico* approach

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1. Introduction

Cell migration is a key process in the formation and the tissues organization which occurs during the embryo's development and wound healing. Cell motility depends strongly on external stimuli; among them, cells ability to respond to substrate curvature is named curvotaxis. Song et al. (2015) showed that T-cells cultured on wavy substrates migrate mostly in concave grooves. Numerical and in vitro studies suggest that cytoskeleton contractility generates stress on the nucleus which is lower when the cell is in a concave (Pieuchot et al. 2018; Vassaux et al. 2019).

Designing cell-scale curvature substrates is a complex process which requires laser and electrochemical treatments or mechanical stress (Song et al. 2015; Pieuchot et al. 2018; Tomba et al. 2019) and dynamic substrates are even more challenging to develop. By relaxing a tensed irradiated surface, Tomba et al. designed a substrate which transit from flat to wavy. While the rate of change in curvature between the two states is very fast compared to cell motion, this is a promising approach.

Integrating numerical models supports in vitro strategies and refines protocol design. Our study aims to describe a substrate that optimizes cell migration through curvotaxis using modeling techniques. This work supports new ideas for design experiments and tissue engineering technologies.

2. Methods

Single cell motion is represented by its polarity with a persistent random walk (PRW) model involving two parameters for cell persistence and random activity, each defined per spatial dimension due to anisotropy. This results in four parameters; they are fitted to in vitro T-cells trajectories, so each simulated cell is assigned individual parameters values. Two supplementary parameters account for curvature effects on cell polarity with acceleration and reorientation mechanisms inspired from experimental observations (Song et al. 2015; Pieuchot et al. 2018).

We reproduced numerically the experiments of Song et al.: cells migrate over wavy substrate with various wavelengths (Fig. 1.a-b) for 20 minutes. We tested four wavelengths: 20µm (~cell-scale), 40µm, 80µm and 160µm. We also tested a flat homogeneous substrate as control condition.

Then, the substrate is implemented dynamically as a travelling wave with a celerity c. The effect of c on cell motion is tested.

For each trajectory, a directional bias $D_{||}$ is computed as the ratio between the distance traveled along the grooves axis and the total traveled distance. It takes a value of 0.5 when there is no directional bias, approaches 1 when the bias is along the grooves axis, and approaches 0 when there is a bias along the perpendicular axis. $\overline{D_{||}}$ is the mean over the population.

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3. Results and discussion

3.1 Model validation – static substrate

T-cells mean speed is approximately 0.5µm/s,and they can reach speeds of up to 2µm/s; the model reproduces similar speed distributions.

On flat, both in vitro and numerical trajectories do not exhibit any apparent bias, as evidenced by $\overline{D_{||}} = 0.5$, indicating that cells uniformly occupy their surroundings (Fig. 1.c-d.).

With shortest wavelength, the T-cells tendency to migrate along the grooves increases (Fig. 1.e): $\overline{D_{||}}$ takes values from 0.5 (largest wavelength) to 0.8 (shortest wavelength). The modelled population behaves similarly (Fig. 1.f): numerical and in vitro $D_{||}$ distributions present no statistical difference for each wavelength.

3.2 Model prediction – dynamic substrate

The substrate is crossed by a travelling wave with a celerity c and a wavelength fixed at 80µm (Fig.1.g).When c is close to cells velocity (~ 0.5µm/s), $\overline{D_{||}}$ drops below 0.5: cells follow the wave (Fig. 1.h). Cells are even able to follow waves a little bit faster than them.

When the wave is slow compared to cells velocity (~ 0.1 µm/s),cells behave as on static curvature. Finally, when the wave is faster than cells (> 3µm/s), $\overline{D_{||}}$ is close to 0.5 suggesting that cells are unable to sense rapidly changing curvature.

3.3 Discussion

On static, simulated cells favour concave and trajectories are biased, as observed in vitro (Song et al. 2015; Pieuchot et al. 2018).

On dynamic, the mechanical model of Manifacier et al. (2023) arrived at similar results. Interestingly, in our model, cells are able to accelerate for long time range to follow waves a little bit faster than them.

Our model predicts that cells cannot respond to fast waves suggesting that there is a delay between the signal of curvature and the cell response to it. Similarly, Tomba et al. cultured HeLa cells on substrate transiting from flat to wavy; these cells respond to the appearing curvature, suggesting that cells are able to sense dynamic change of curvature within a certain delay. The model also suggests that the wave celerity must be calibrated in a certain range close to cells mean velocity to impose a direction of migration.

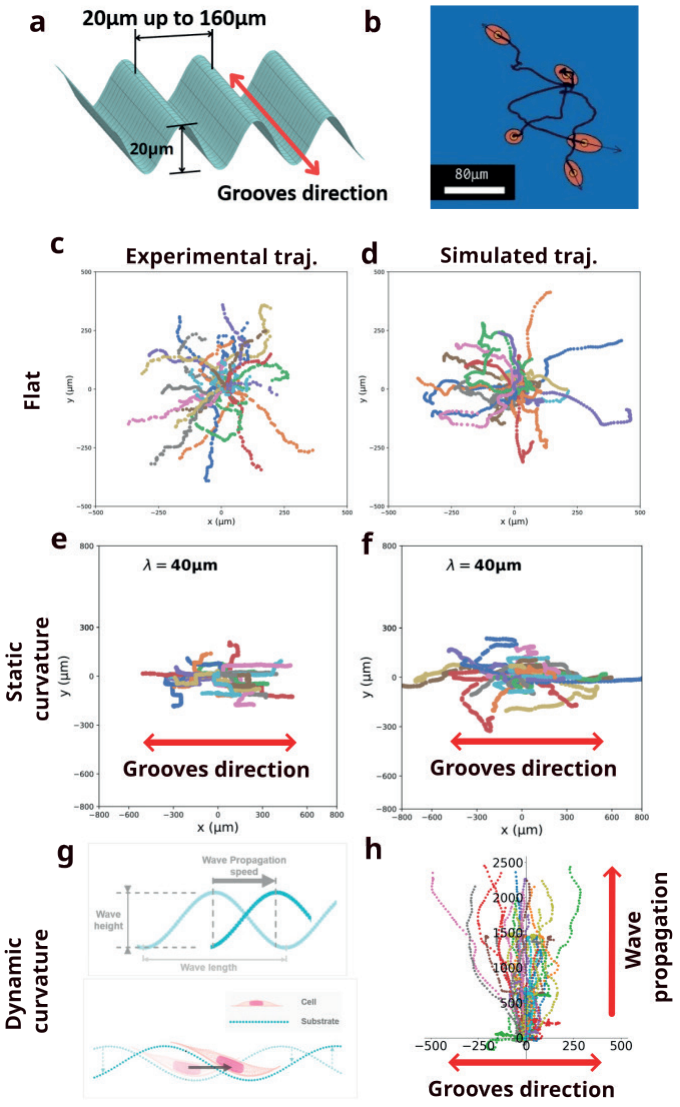

Figure 1. (a) Curved substrate scheme. In vitro and simulated trajectories over flat surface (c-d) or over curved static substrate (e-f). (g) Travelling wave scheme (credit: Manifacier et al. 2023). (h) Simulation over dynamic curved substrate.

4. Conclusion

Simulations on dynamic substrate are at the moment not confronted to in vitro data. However, the model deserves some credit as it has been validated in similar situations where in vitro data are available. In the meantime, it provides experimentalists with guidance on what to develop, paving the way for new substrates and tissue engineering technologies.

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Contributor Roles

G.C.: Conceptualization, Formal analysis, Funding acquisition, Investigation Methodology, Writing original draft; I.M.: Conceptualization, Formal analysis, Funding acquisition, Supervision, Writing-review & editing; V.M., M.B. and E.D.: Formal analysis, Methodology, Visualization; J.-L.M.: Conceptualization, Funding acquisition, Supervision, Writing- review & editing.

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