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► **To cite this version:**

Jean-Louis Milan, Maxime Vassaux, Laurent Pieuchot, Karine Anselme, Ian Manifacier. IN SILICO AVATARS OF CELLS TO PREDICT CELL MIGRATION ON TRAVELLING WAVES. 18th International Symposium on Computer Methods in Biomechanics and Biomedical Engineering, CMBBE, Jun 2023, Paris, France. hal-04463371

**HAL Id: hal-04463371**

**<https://hal.science/hal-04463371>**

Submitted on 16 Feb 2024

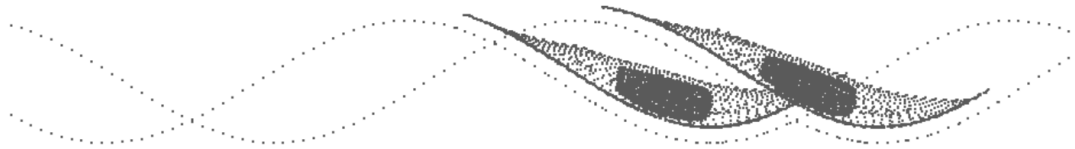
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## ***In silico* avatars of cells to predict cell migration on travelling waves**

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### **Introduction**

We showed previously that cell migration is guided towards concave areas by a curvature gradient [1]. We called this phenomenon *curvotaxis* that is not induced by gravity. We showed that curvotaxis is a mechanobiological process involving the cytoskeleton and nucleus. The nucleus, is pushed by apical cortex pressure and is consequently displaced toward concave areas where the stress is lower [2, 3]. Influenced by the repositioning of the nucleus, the cell migrates to concave areas until a more relaxed mechanical state is reached. Nonetheless static curved surfaces guide cell migration only locally. We hypothesize that changing curvature dynamically by generating travelling waves at the surface of the substrate should stimulate and drive cell migration over large distances. Verifying our hypothesis directly by *in vitro* methods would require a long-time to develop the working prototype of a dynamic wavy substrate able to stimulate and drive cell migration. We proposed to verify it first using *in silico* with cell avatars.

### **Methods**

We have developed *in silico* cell avatars that reproduce the mechanisms by which the cells sense the curvature of the substrate dynamically during cell migration [2, 3]. Cell model is a network of mechanical interactions that reproduce the contractile and dynamic structure of the cytoskeleton bound to the extracellular environment via focal adhesions. The cell model, in open access [4] is developed using LMGC90, a computational framework dedicated to non-smooth contact dynamics and multi interaction systems. Waves of 10 $\mu\text{m}$  of amplitude and 160 $\mu\text{m}$  of wave-length were simulated at the surface of a virtual substrate at a speed of 4 $\mu\text{m}$ /iteration. Migration of the cellular model was then initiated and driven by curvotaxis.

### **Results**

The cell model follows the progression of the wave and migrates indefinitely as long as the wave exists. Influenced by the travelling wave, the nucleus moves towards the concavity and the cell migrates in that direction. When retaining the same wavelength and velocity parameters, the speed of the cellular avatar decreased by a third when we lowered the amplitude of the wave 5  $\mu\text{m}$ . But, with a wave amplitude of 20 $\mu\text{m}$ , cell model migrated 1.5 times faster.

### **Discussion & Conclusion**

Using the model, concerning the impact of travelling waves on cell migration, we answer a question that would otherwise be hard to directly address by experimental means. We propose the first *in-silico* proof-of-concept to guide cell migration by generating travelling waves. This will help in the designing of dynamic substrates to stimulate cell migration *in vitro*. Our *in-silico* avatar of migrating cells can later be implemented for cell engineering and lab-on-chip technology, as a live augmented reality tool to drive smart substrate actuation and control cells *in vitro*.

- [1] Pieuchot *et al.*, *Nature Commun.*, 2018, <https://doi.org/10.1038/s41467-018-06494-6>.
- [2] Vassaux *et al.*, *Biophys. J.*, 2019, <https://doi.org/10.1016/j.bpj.2019.07.022>.
- [3] Vassaux *et al.*, *Adv. Struct. Materials*, 2020, [https://doi.org/10.1007/978-3-030-50464-9\\_12](https://doi.org/10.1007/978-3-030-50464-9_12)
- [4] Vassaux *et al.*, *Zenodo available in Github* <https://doi.org/10.5281/zenodo.1187087>