

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

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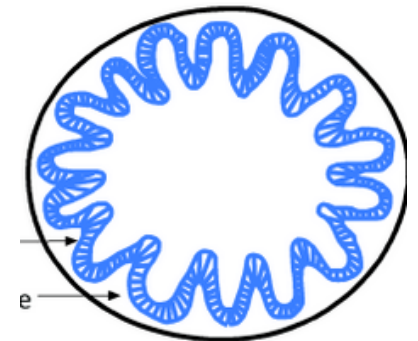
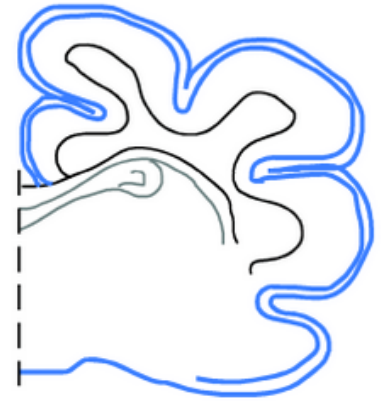
Aix Marseille Université, CNRS, ISM, France

Curvature = topological attribute of the cell's surrounding

Brain, lungs, intestins, ... = wavy structures with lot of folds

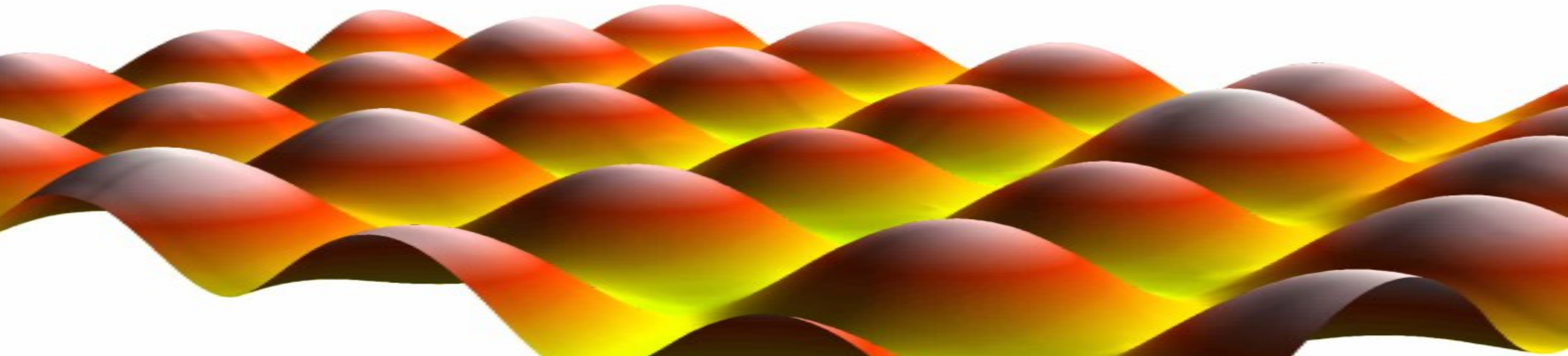
Curvature may impact

- Multi cell organisation [Nelson2016].
- adherent cell morphology [Callens2020]
 - > mechanisms involved ?
 - > mechanical signals ?



How do cells feel curvature ?

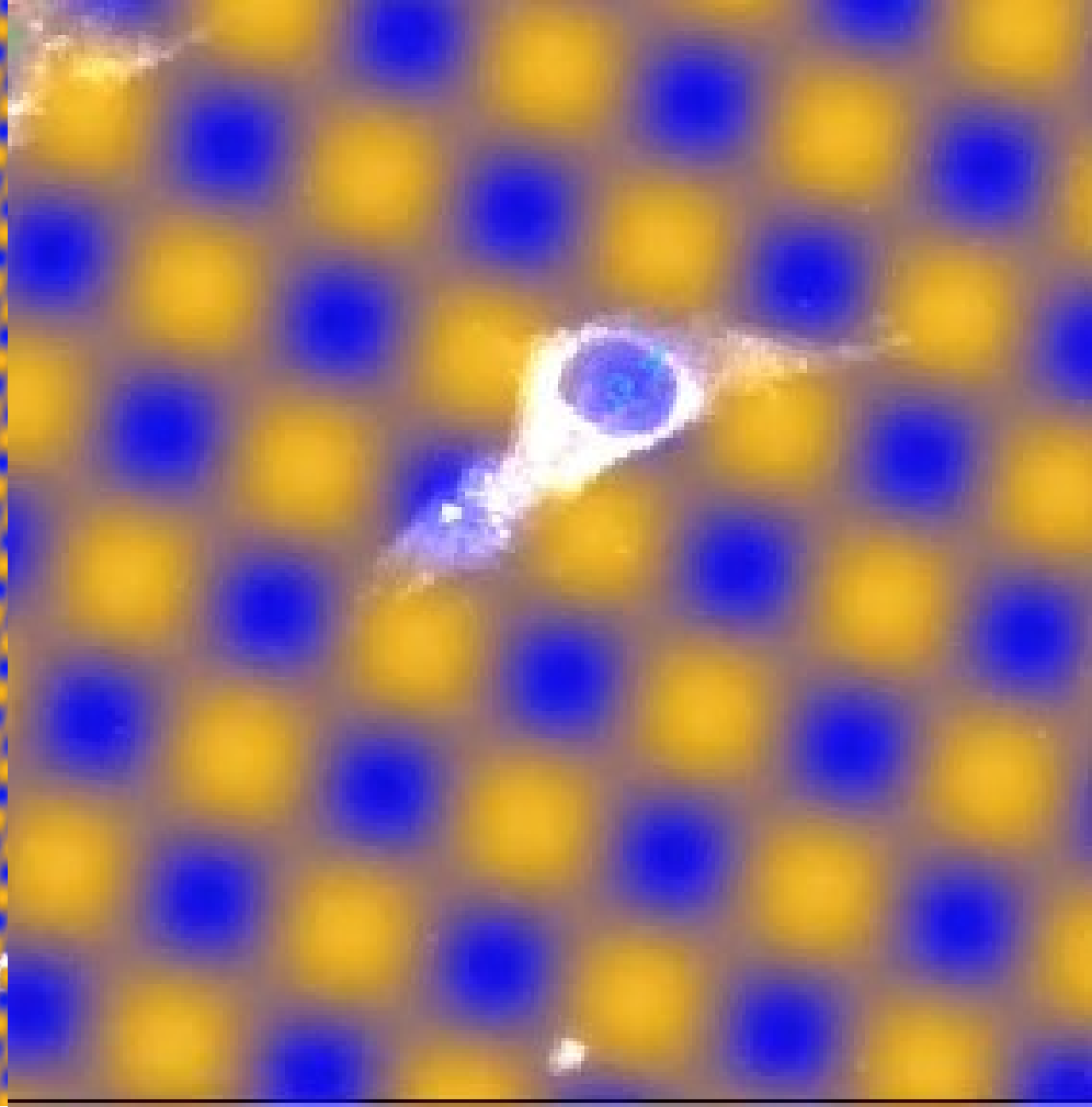
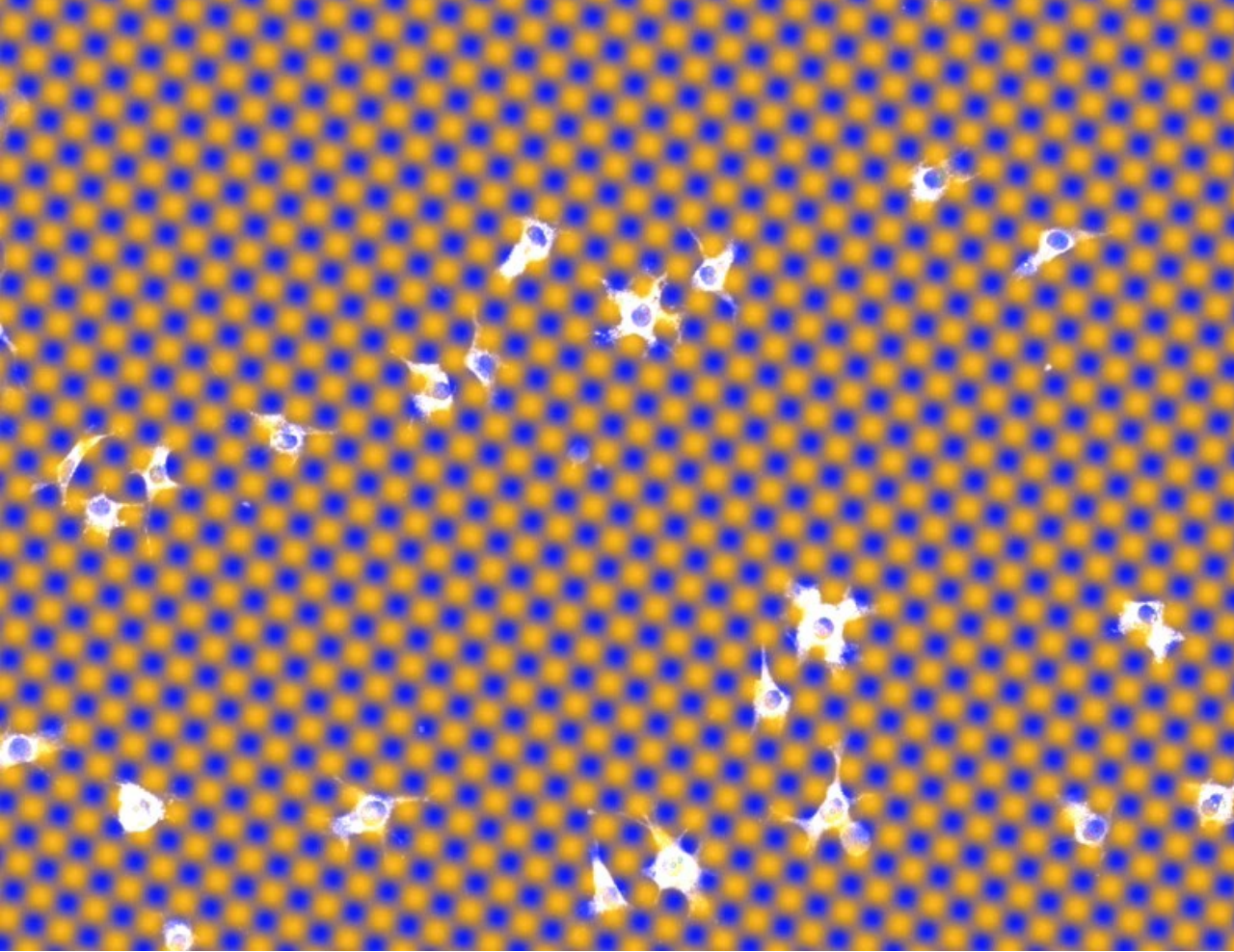
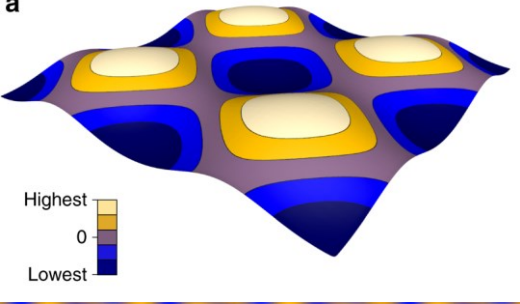
-> Development of idealized **sinusoidal surfaces**



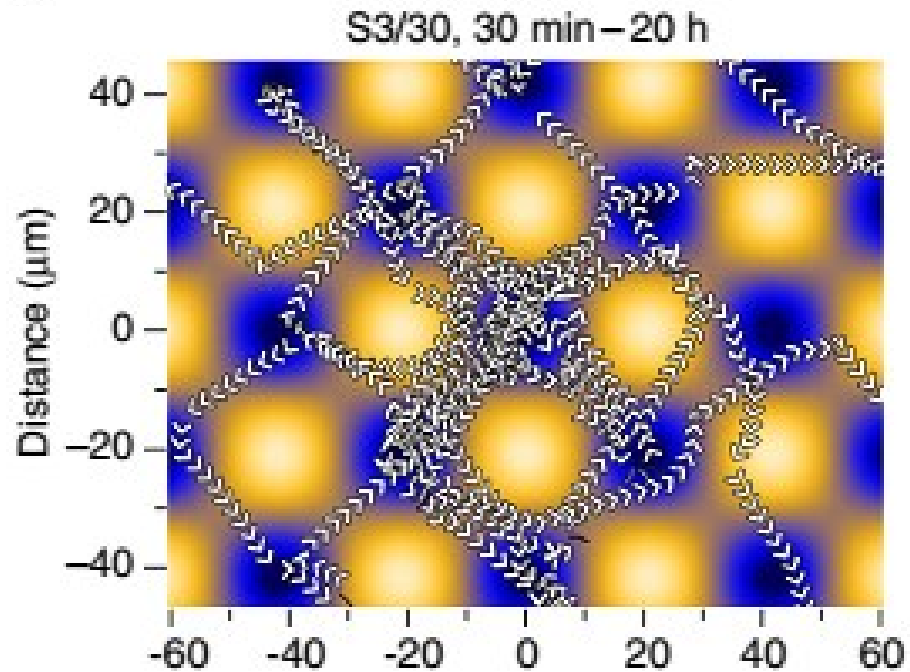
In vitro observations

Karine Anselme & Laurent Pieuchot Mulhouse IS2M

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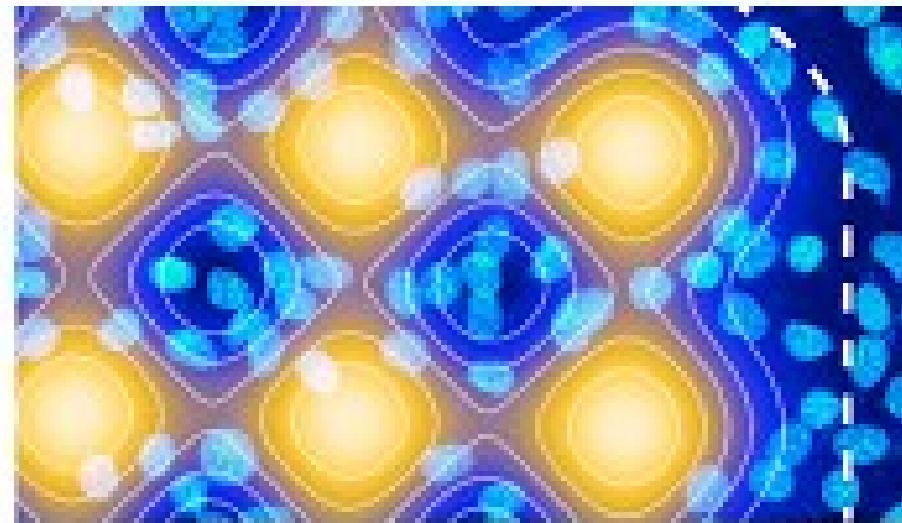


Cell trajectories



Cell proliferation

120 h, S10/100, 90% confluency



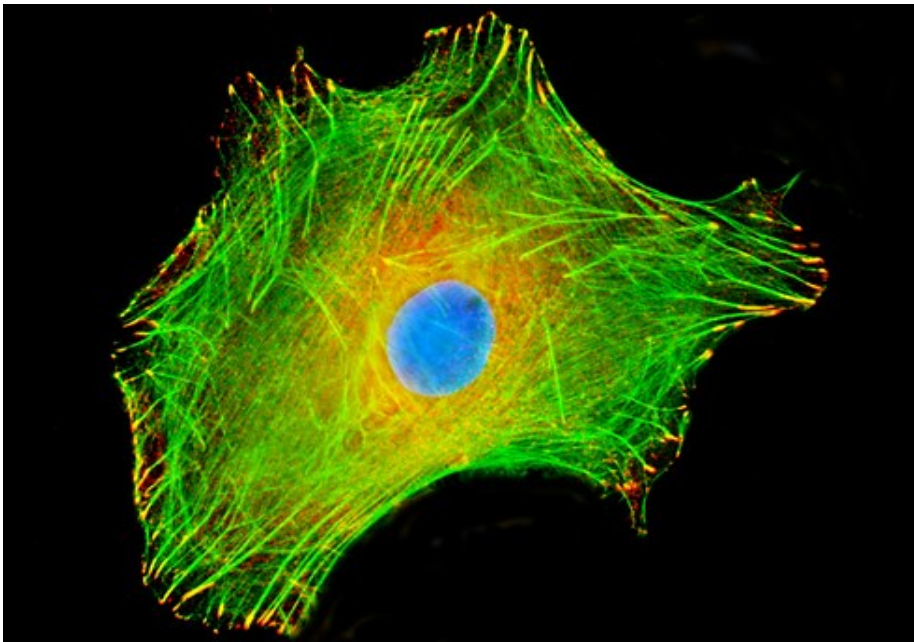
*Pieuchot et al. Nature Comm.
2018 Groupe de Karine Anselme
IS2M Mulhouse*

-> called « Curvotaxis »

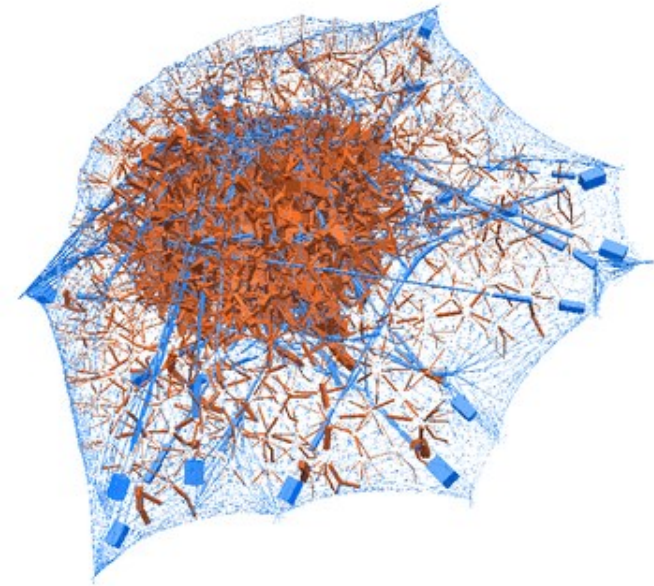
(gravity is not involved !)

Understanding curvatoxis by modeling cell mechanics

Cytoskeleton represented as **contractile network**
attached to substrate
connected to the nucleus



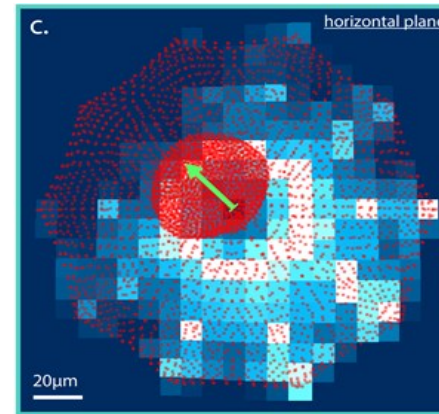
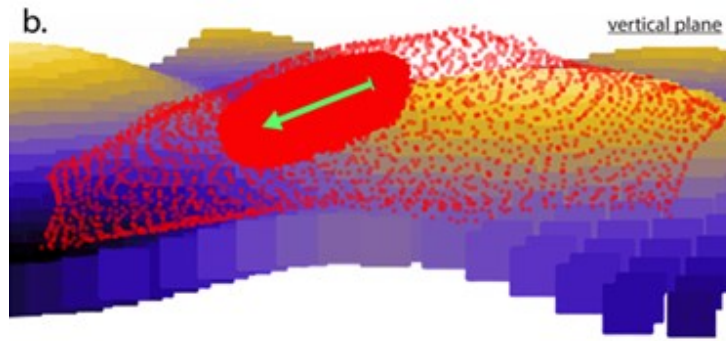
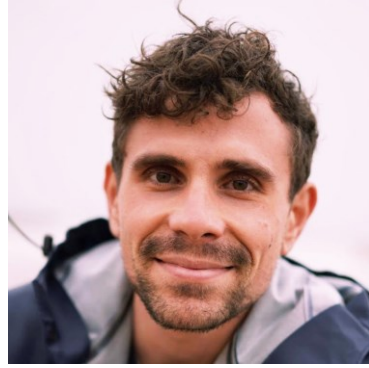
≈



Divided Medium Mechanics using LMG90
(Fred Dubois, LMGC, Montpellier)

Simulation of adhesion on Sinus Surfaces

Post-Doc
Maxime Vassaux
CR CNRS 2022



Results -> **Decentering of the nucleus toward concave area**

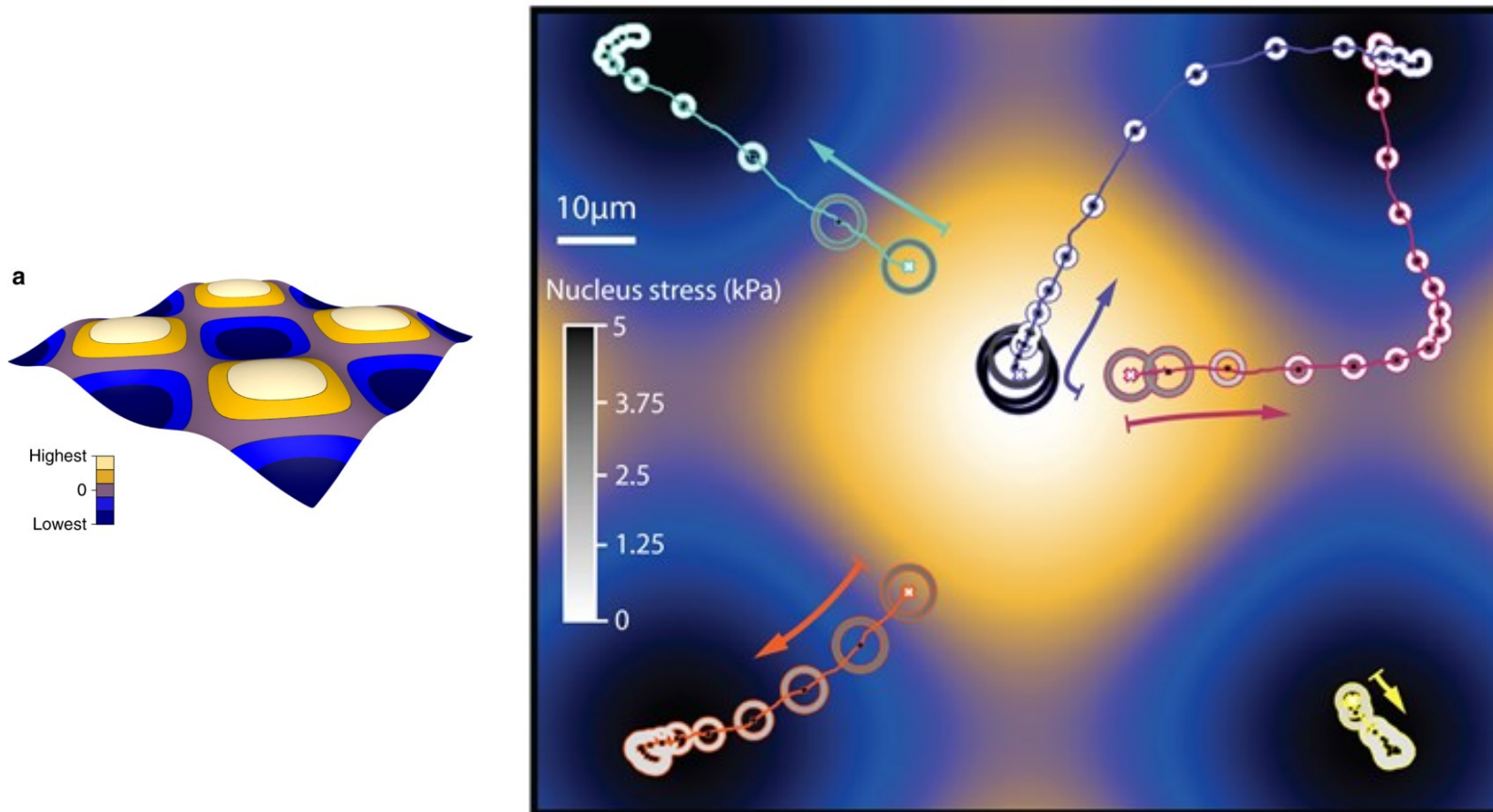
Explanation Cytoskeleton (Cortex) squeezes nucleus and pushes it toward concave regions

Hypothesis on curvotaxis : **Nucleus decentering = Migration bias**

≈ « **ball and chain** » which limits cell migration in other directions

Simulation of cell migration following nucleus motion

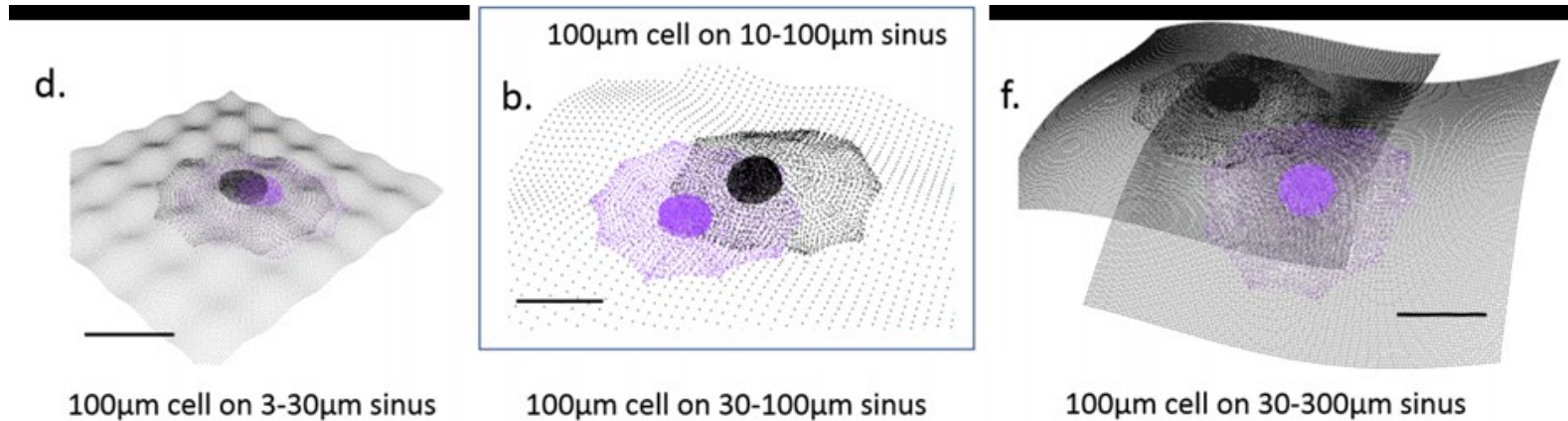
Trajectories of the cell model for different initial locations



Curvotaxis

allows cells to reach a relaxed mechanical state

Key parameters of curvotaxis identified in silico



- 1) Curvotaxis possible for waves lengths ranging between $10\mu\text{m}$ to $200\mu\text{m}$
larger than nucleus size & **smaller** than cell size
-> verified in vitro
- 2) Curvotaxis needs a contractile cytoskeleton and rigid nucleus
-> verified in vitro (inhibitors)

New Problematic

Up to now,

- static curvature -> only limits migration in concave areas
- How to guide migration in a given direction & over long distances ?

-> Dynamic curvature ?

during embryogenesis :

Cells migrate on adjacent cell layers that undulate dynamically

[Harmand 2021]

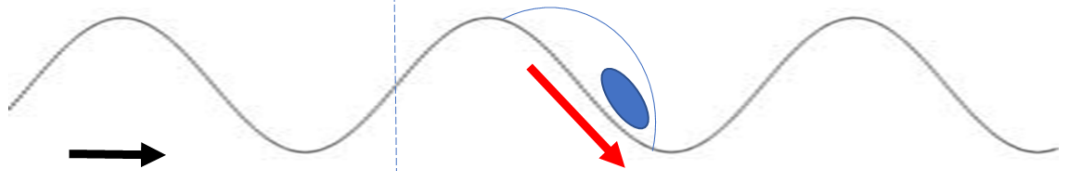
Guide cell migration via Dynamic Curvotaxis

-> generate travelling waves

Vitesse des
ondulations



Migration vers concave



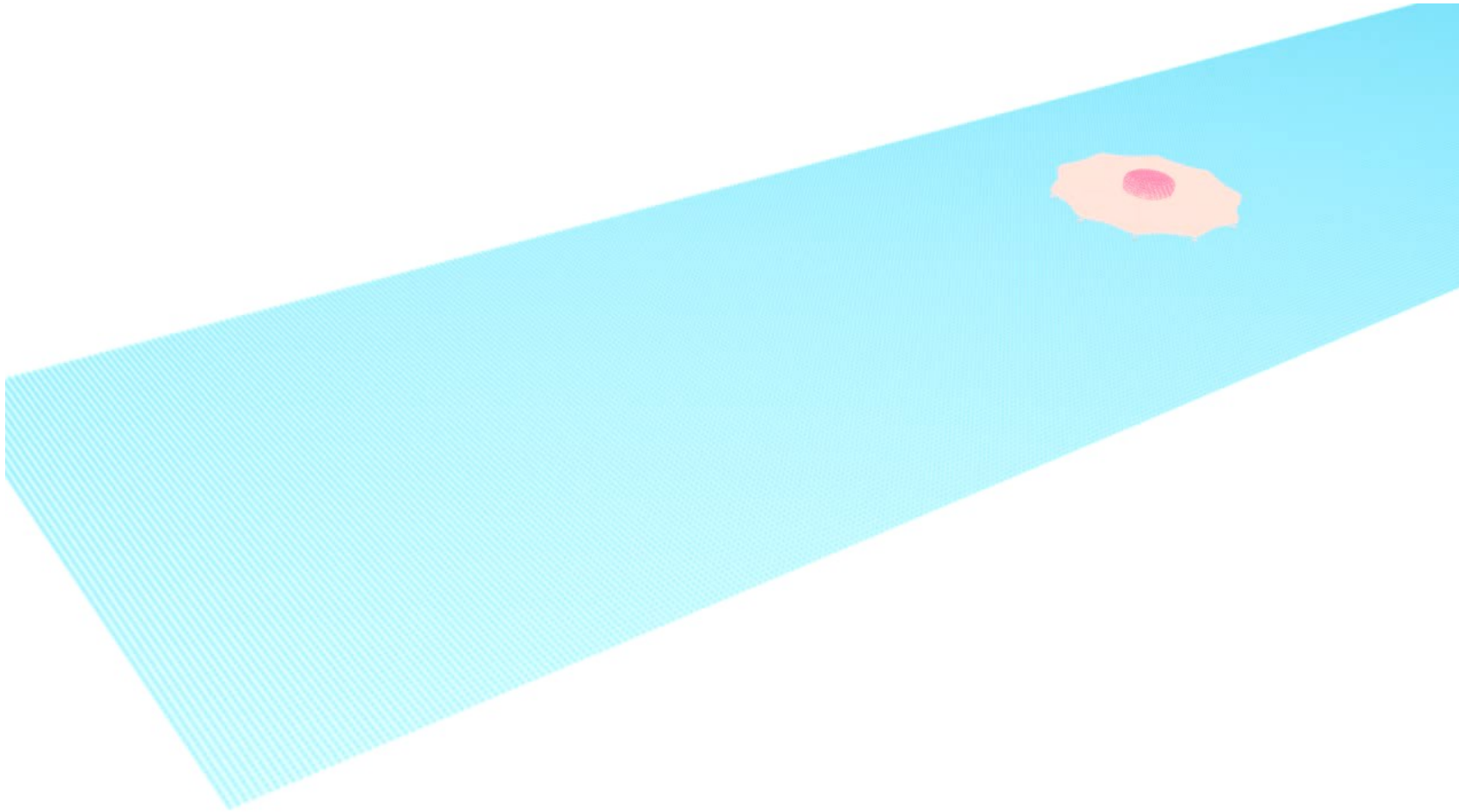
Migration et déplacement nets

Advantage of the model

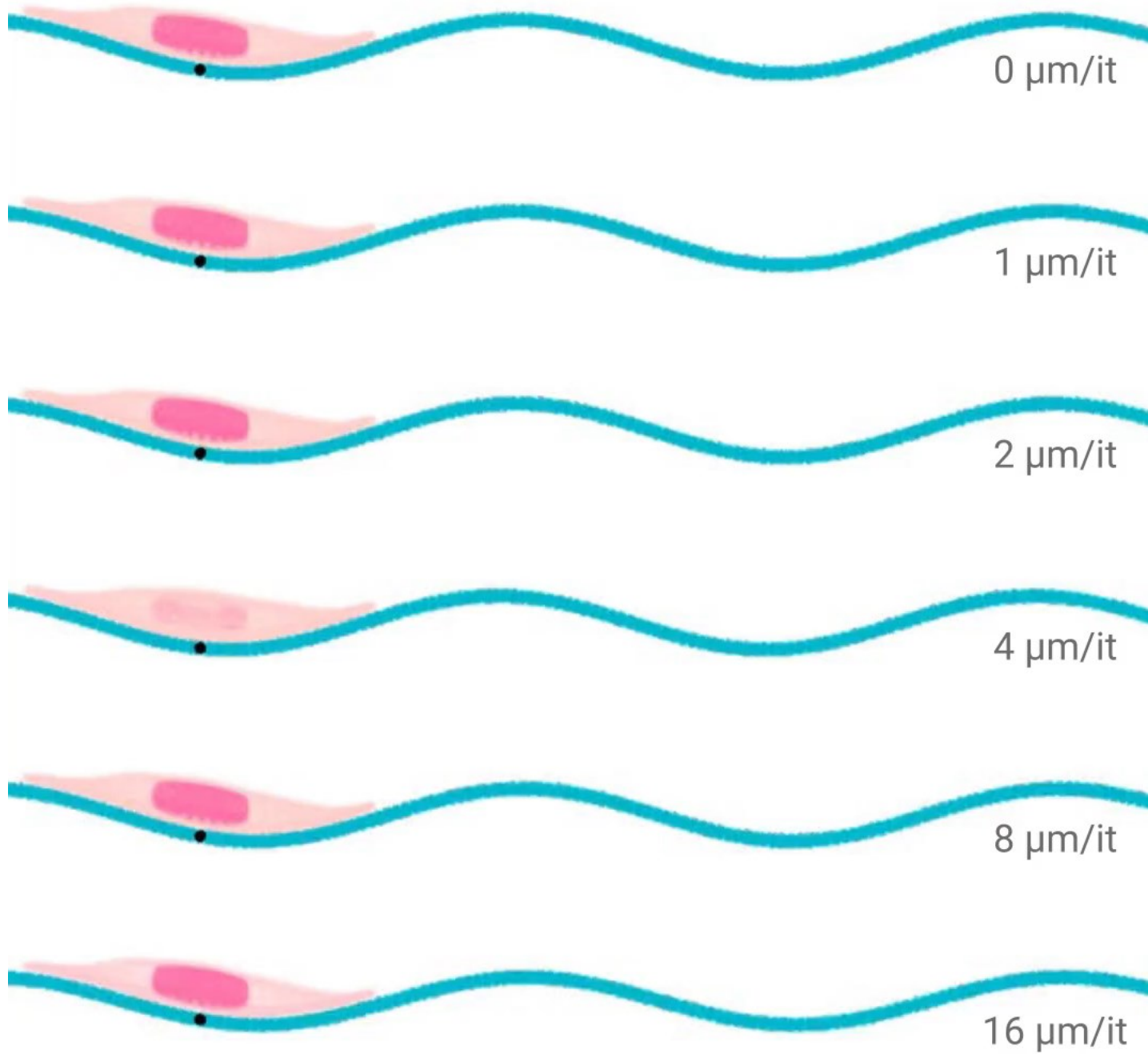
Simulate what we can't do
experimentally

Guide cell migration via Dynamic Curvotaxis

-> generate travelling waves



Ian Manificier
(Post- Doc)



Ian Manificier
(Post- Doc)



speed $2 \mu\text{m}/\text{it}$ & height $10 \mu\text{m}$



speed $4 \mu\text{m}/\text{it}$ & height $10 \mu\text{m}$



speed $8 \mu\text{m}/\text{it}$ & height $40 \mu\text{m}$



Ian Manificier
(Post- Doc)

Conclusions

With our **cell model** we propose:

- 1st « proof of concept » of **dynamic cuvotaxis**
- Design for **future dynamic substrates**
that generate waves for long distance & directed cell migration