# Dynamical and mechanical heterogeneities of cancer cells as active deformable particles

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大阪大学
THE UNIVERSITY OF OSAKA

MOONSHOT
RESEARCH & DEVELOPMENT PROGRAM

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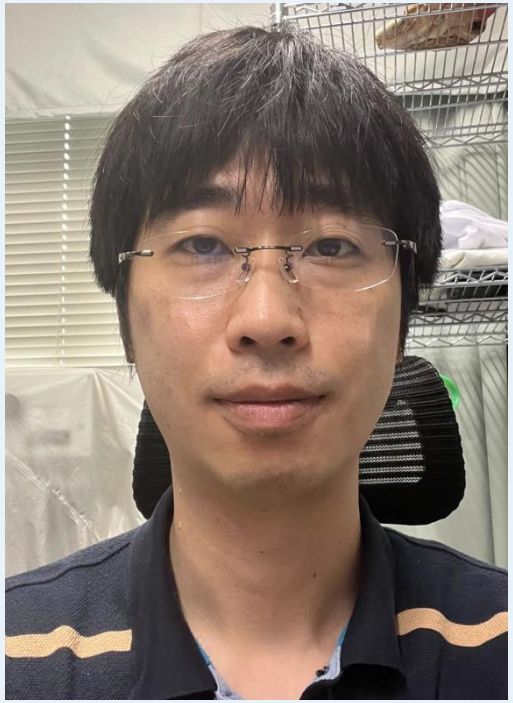

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# Plan of talk

- **Introduction**
  - ❑ Basic feature of deformable cancer cells.
  - ❑ Limitation of previous studies
- **Motivation**
- **Methods and model**
- **Results**
  - ❑ Configuration
  - ❑ Dynamics
- **Future work and perspective**

$y$

$x$

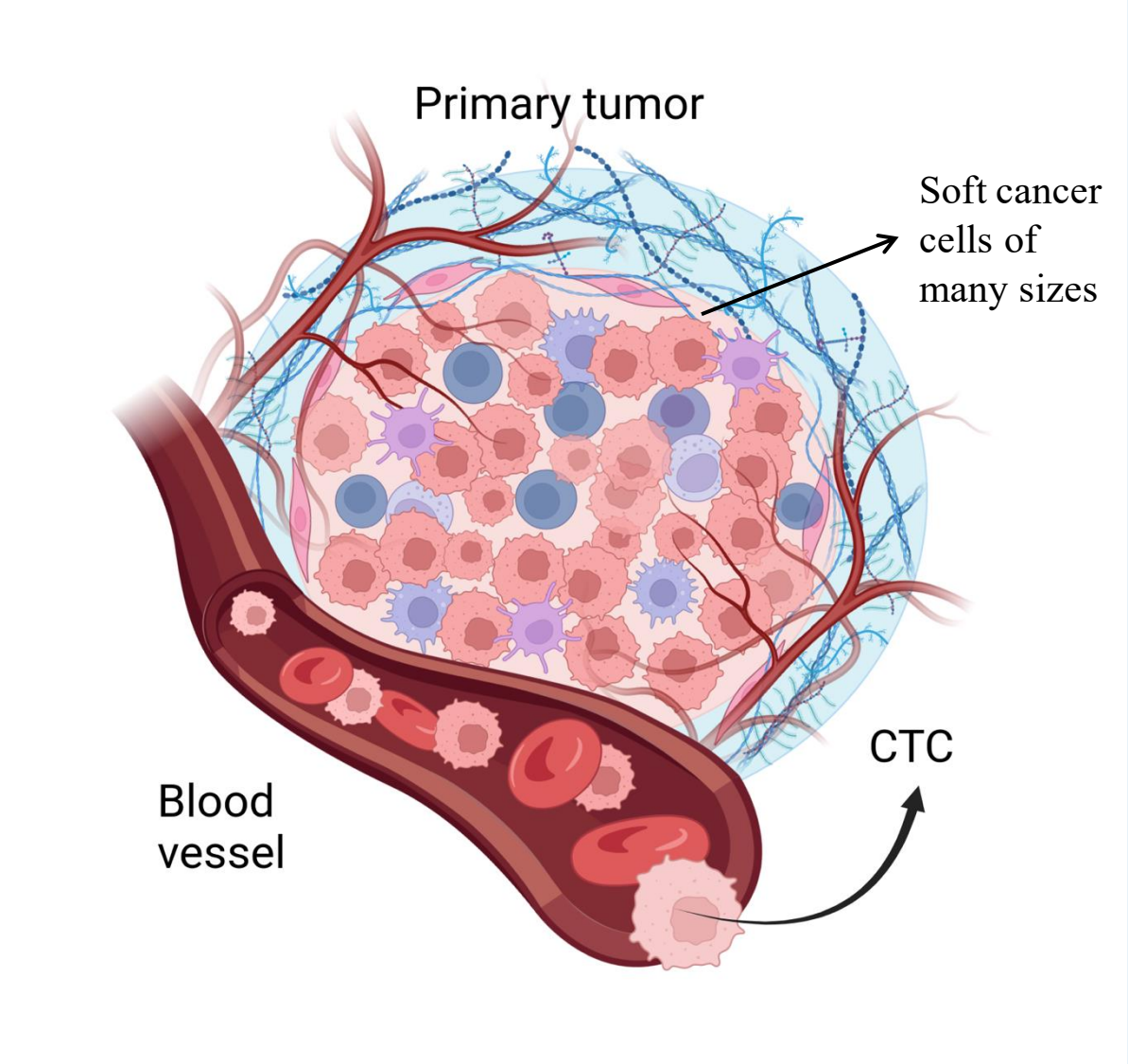
"Cancer is not only a devastating disease. It is also a structural and mechanical problem."

# Deformable Cancer Cells

**Core message**

- Many cancer cells become mechanically softer and more deformable.
- Yet tumour tissue can remain macroscopically stiff.

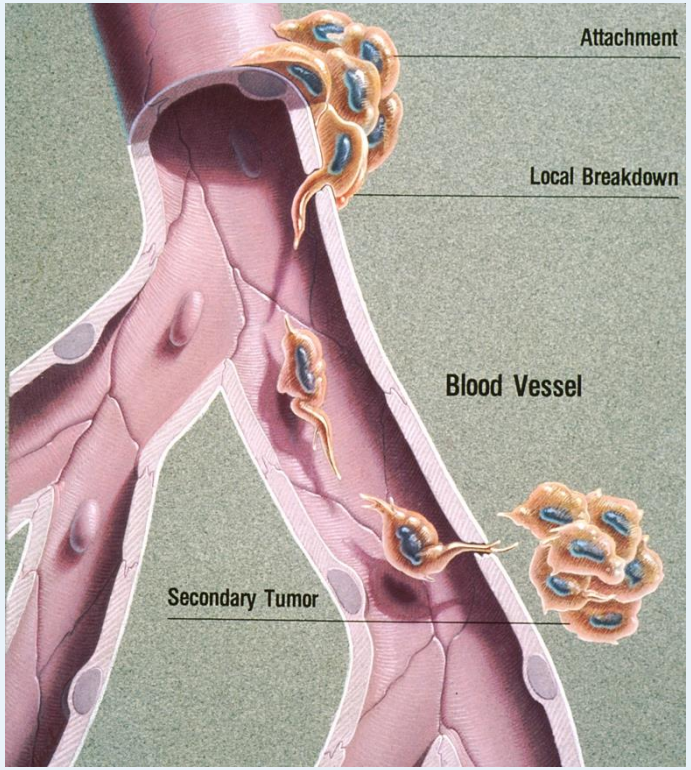
**A deformable cell is not simply "soft"; it is structurally and mechanically adaptable.**




*Ref: Classic public-domain NCI illustration of circulating tumor cells leaving a primary tumor*

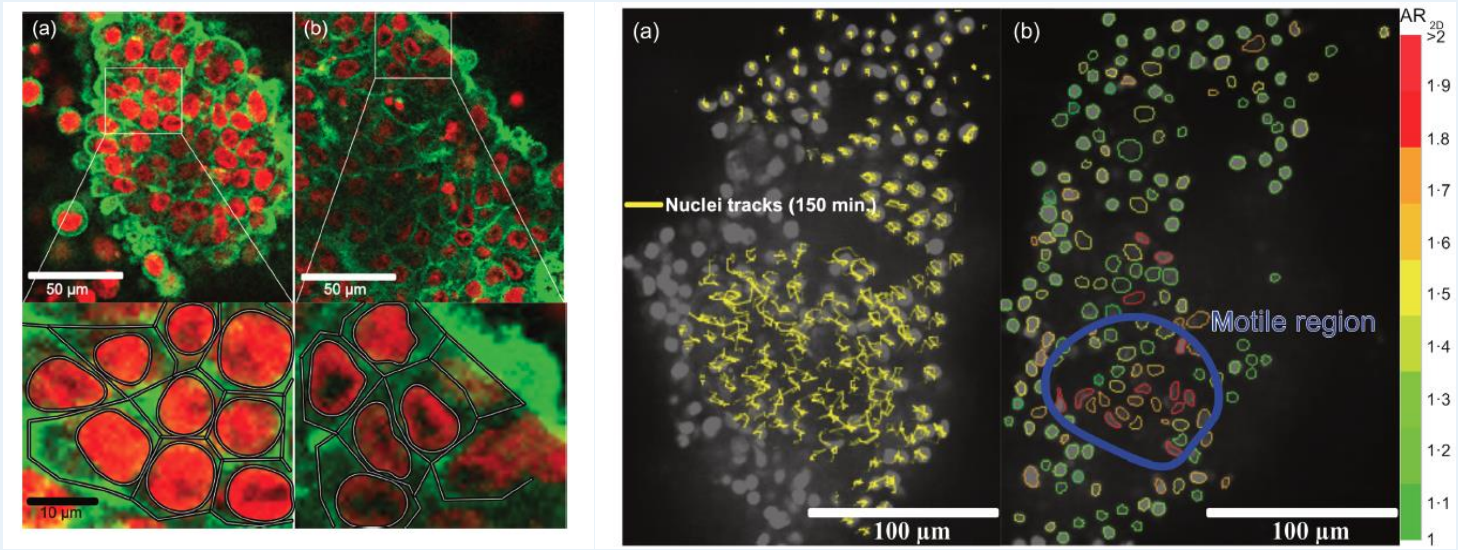
# The metastatic dynamical journey is also a mechanical journey

*A cancer cell must deform at several stages, not just once.*




*Ref: Classic public-domain NCI illustration of cancer spreading through blood vessels*

- **Invade local tissue**
- **Survive circulation**
- **Exit and colonize**

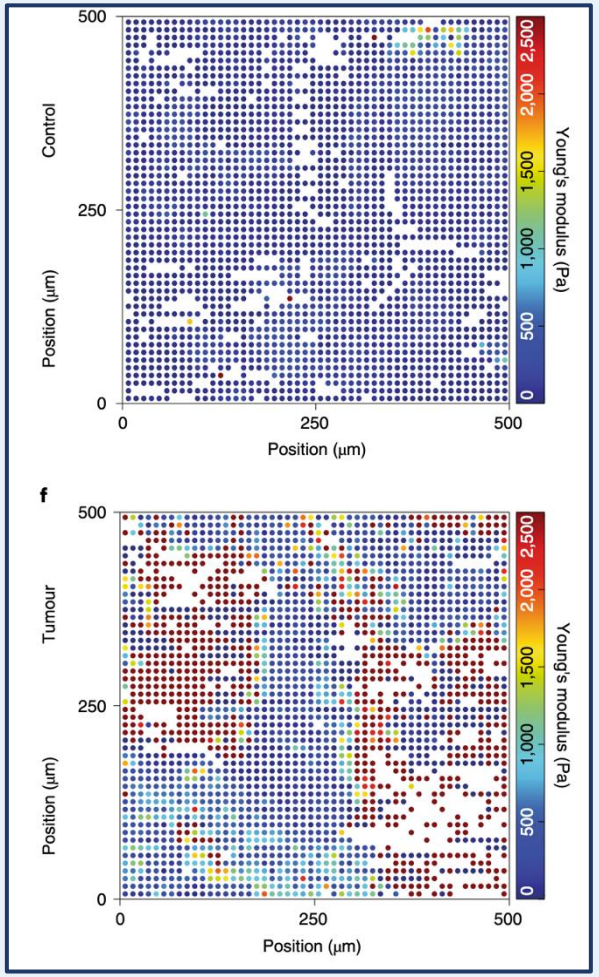



P. Gottheil et al., Phys. Rev. X **13**, 031003 (2023).

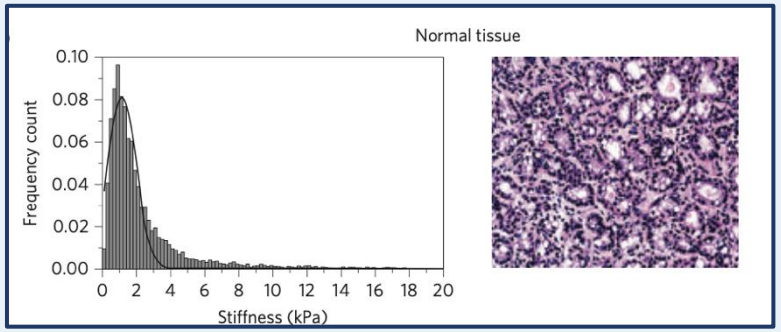
- The more the metastasis, the greater is the “dynamical heterogeneity”.
- Understanding the origin of this heterogeneity is critical for metastasis and potential biomarkers.

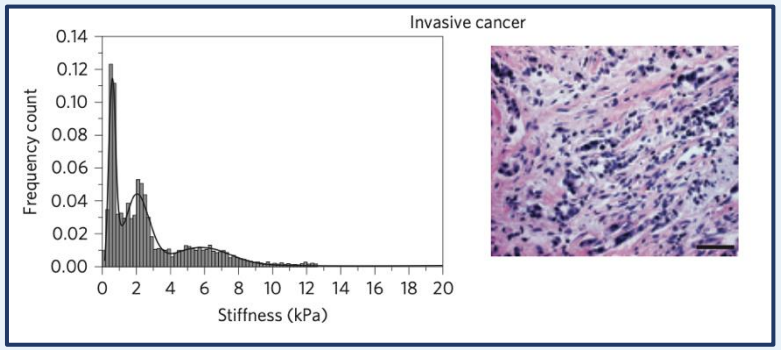
# Experimental evidence

## Various AFM experiments




T. Fuhs. et al. Nat. Phys. 18, 1510 (2022)




M. Plodinec, et al. Nat. Nanotechnol. 7, 757 (2012)

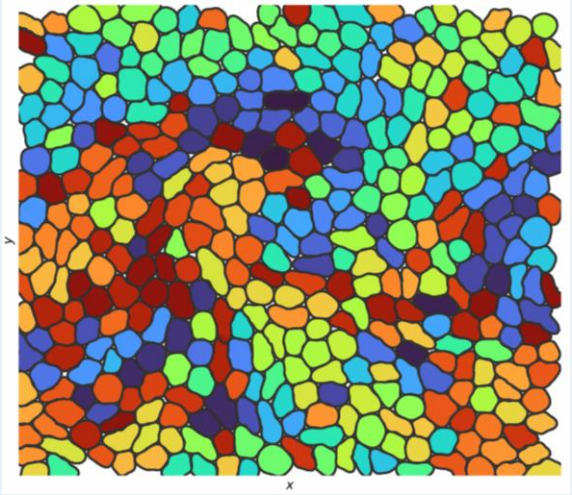
**Physical paradox: Tumours contain mixture of soft and hard cancer cells.**

# Motivation

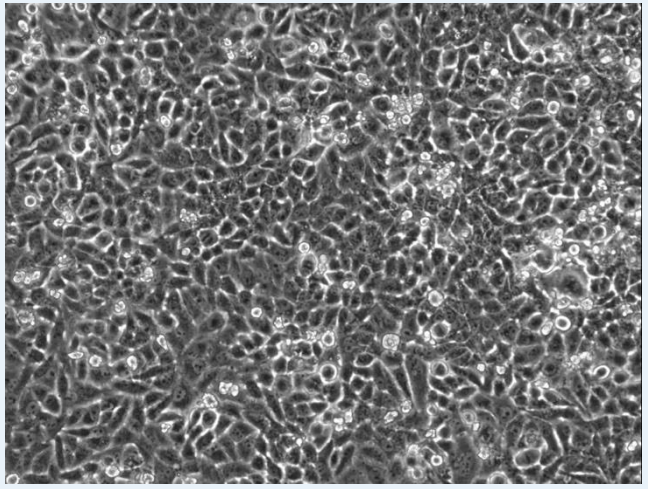
- What makes the tumour hard?
- What makes them migrate despite being hard?

**Scheme of work :**

- **Phase field Fourier node simulation of deformable cells.**
- **Light microscopy experiment of HeLa P{i} cancer cells.**



Simulation: colours indicate particle indexes



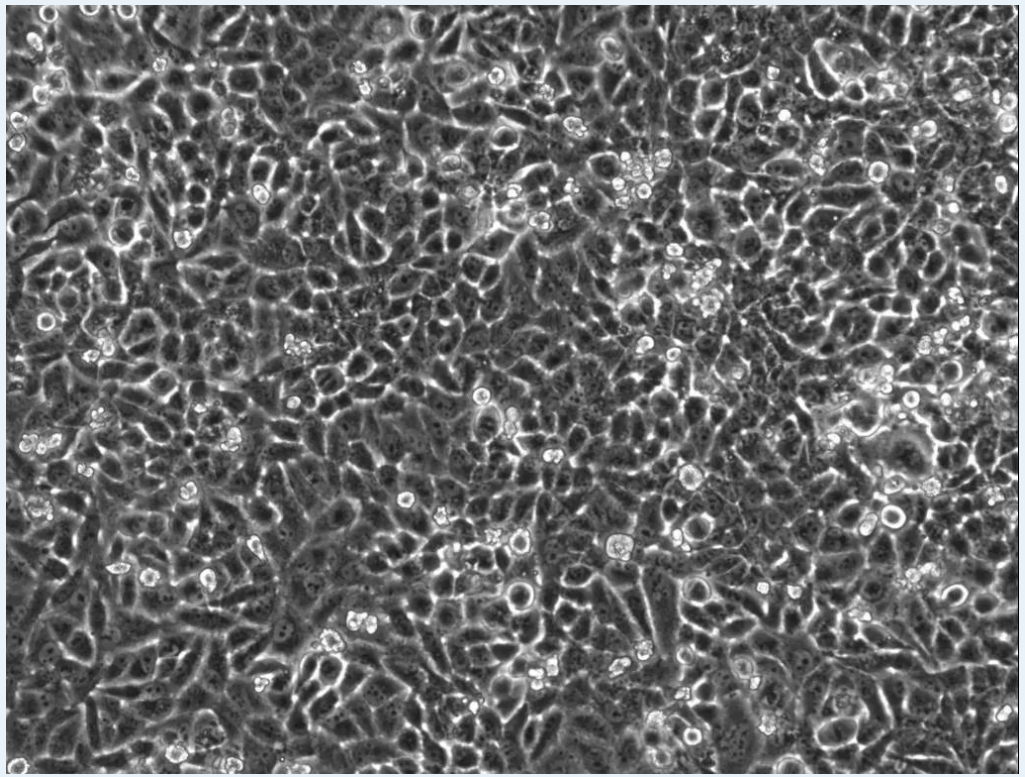
Experiment

# **Results:** Experiments of HeLa P4 cells

## ■ HeLa P10 cells experiment

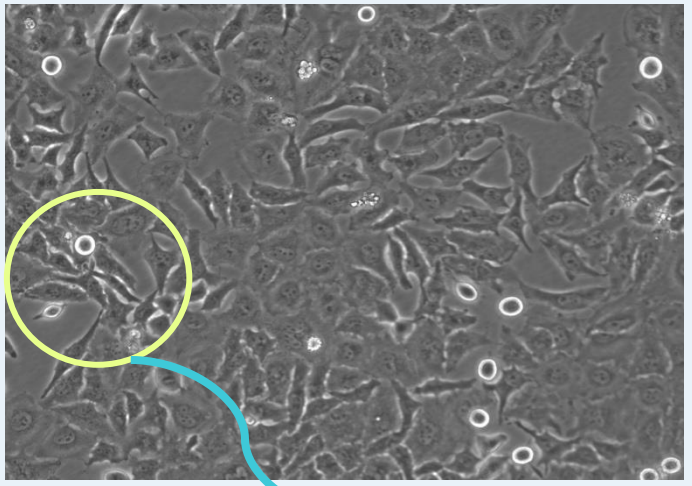
➢ Movie captured in one day.

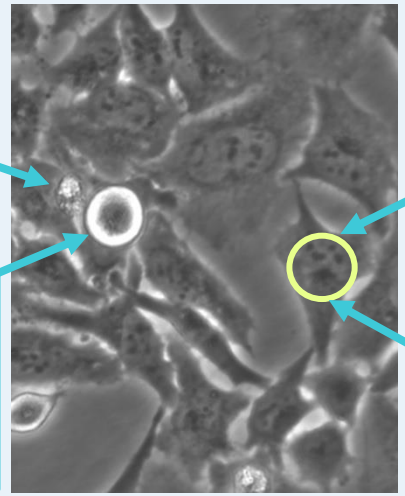
Frame rate 1/f =1/7200 1/s



100 $\mu m$

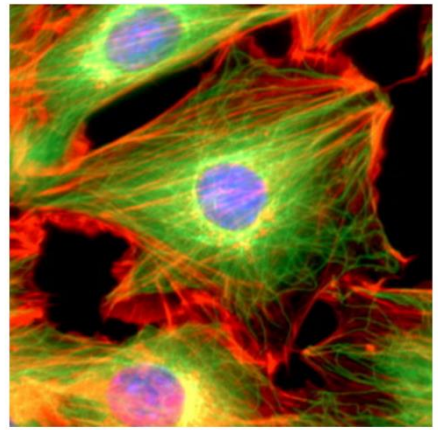
- Glass like movement as a glance






Similar cell under fluorescent microscopy

(Image courtesy of and with permission from Andrew E. Pelling (London Centre for Nanotechnology and Department of Medicine, University College London).)



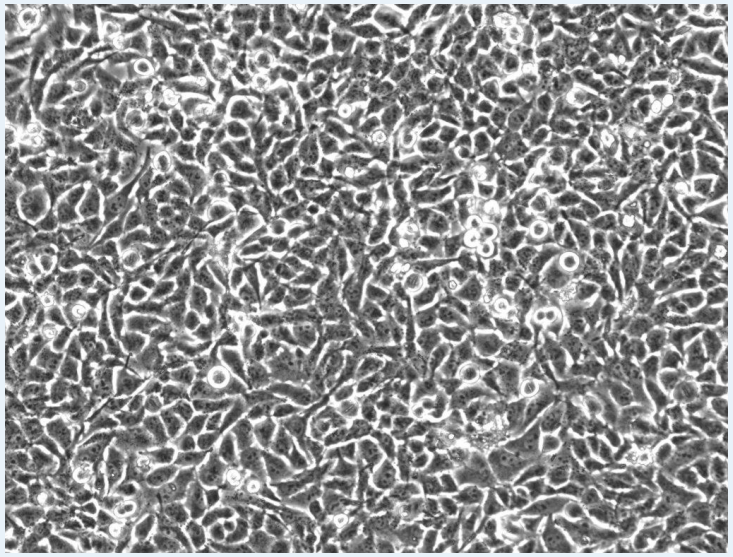
# **Results:** Segmentation analysis

## Segmentation analysis using machine learning

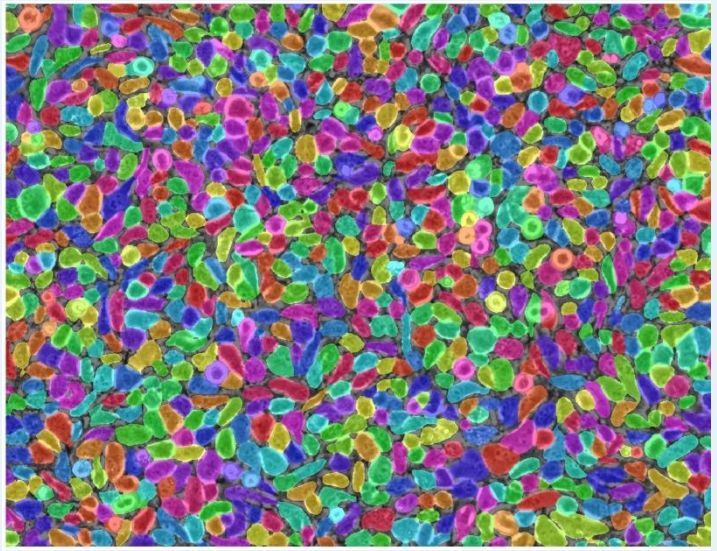
*Segment Anything Model for Microscopy*: μSAM A. Archit, *Nature Methods*, **22**, 579–591 (2025)

- Training the deep neural network with hand-segmented annotations: Whole system is segmented and cells are labeled with different colours

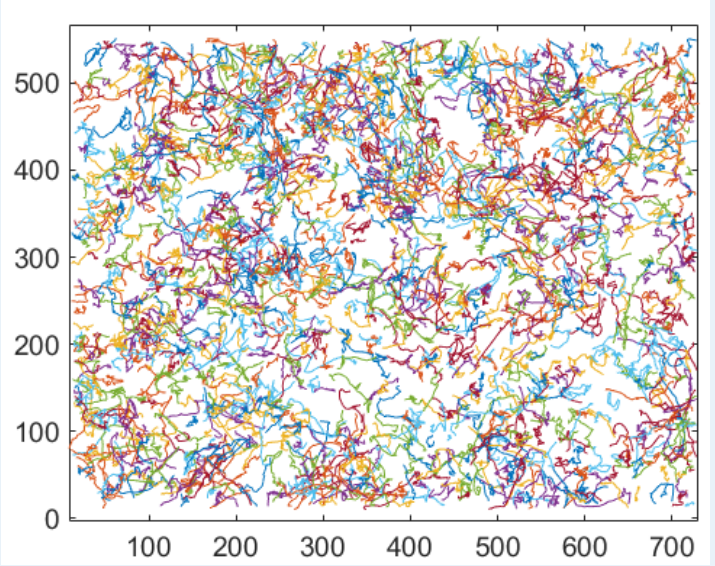
100 $\mu m$



Time lapse image from light microscopy



Labeled image after segmentation



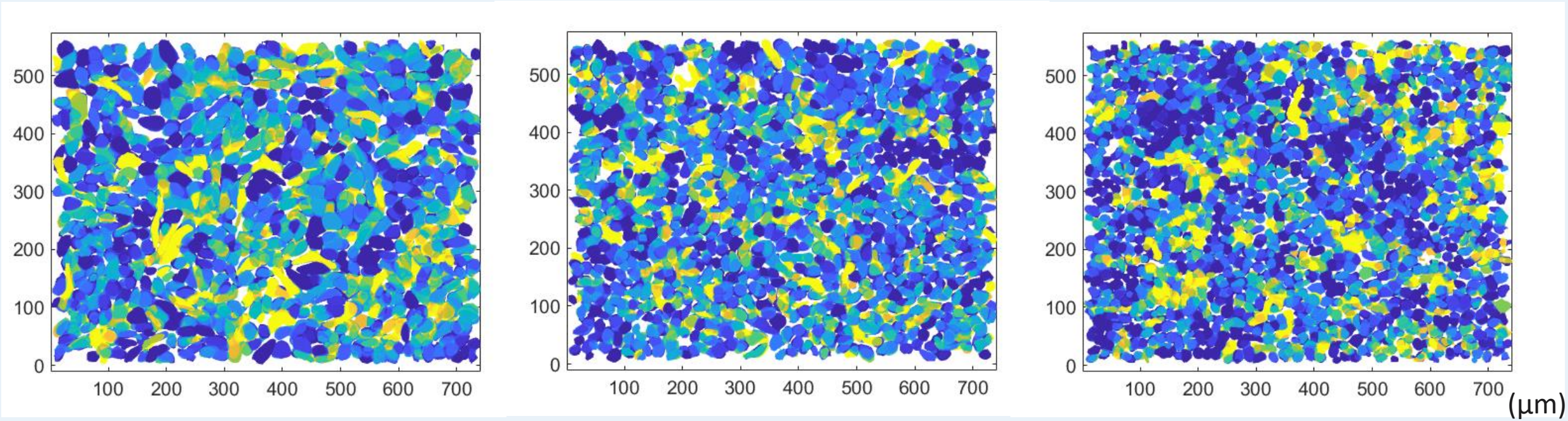

Tracked trajectory of cells 4 hours

Cancer tissues exhibit dynamical heterogeneity.

# **Results:** Segmentation analysis

## Growth of heterogeneity with density: Segmentations labeled on displacements.

- Observe an increase in heterogeneity as the density increases.



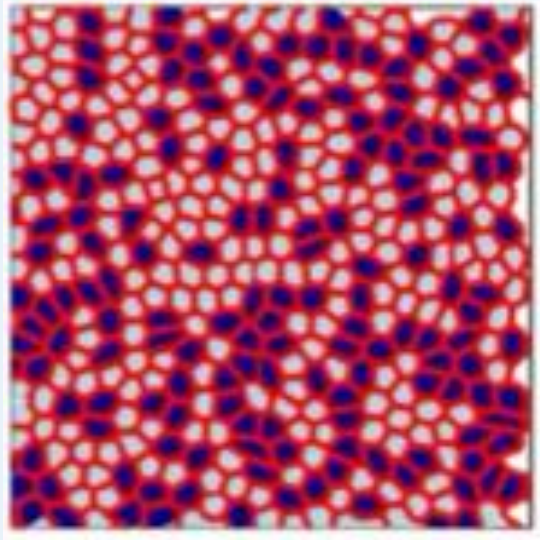
# Motivation for simulation

**Message from experiment: This motivates a simulation model of mixed population of deformable cells with tunable density and void space.**

- Construct **a precise theoretical model** to match with experimental analysis.
- Do further advancement on **macroscopic hardness** of tumours.

## Limitation of previous studies: Cell vertex model

- Density is effectively fixed near confluence ~ unity.
- Cellular gaps and weak adhesion are hard to represent explicitly.
- Softness and deformability are not controlled in a direct, particle-like way.



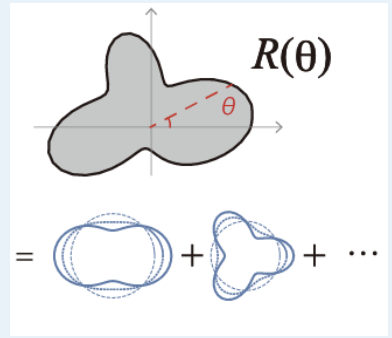
T. Fuhs. et al. Nat. Phys. 18, 1510 (2022)

# System and model

- Phase field model of deformable cells as proposed earlier by Saito and Ishihara, *Sci. Adv.* **10**, eadi8433 (2024).

**Branch radius of each cell**

$$R^i(\theta) = R_0 \sum_{n=0}^{M} \left[ a_n^i \cos n\left(\theta - \theta^i\right) + b_n^i \sin n\left(\theta - \theta^i\right) \right]$$




**Interaction Hamiltonian**

$$H = \sum_i H_{\mathrm{l}}^i + \sum_{i<j} H_{\mathrm{int}}^{ij}$$
$$= \eta^i l^i + \textstyle\sum_{i>j} \int \mathrm{d}\boldsymbol{r} \phi^i \phi^j$$

Where,

$$l^i = \int_{-\pi}^{\pi} \sqrt{(R^i)^2 + \left(\frac{\mathrm{d}R^i}{\mathrm{d}\theta}\right)^2}\, \mathrm{d}\theta$$

**Equations of motions : ABP model**

**Translation** : $\dot{\boldsymbol{r}}^i = \boldsymbol{v}^i + \boldsymbol{F}_{\mathrm{int},\boldsymbol{r}}^i = \boldsymbol{v}^i - \mu_r \frac{\mathrm{d}H_{\mathrm{int}}}{\mathrm{d}\boldsymbol{r}^i}$

**Rotation** : $\dot{\theta}^i = F_{\mathrm{int},\theta}^i + \sqrt{2D_r}\xi^i$
$$= -\mu_\theta \frac{\mathrm{d}H_{\mathrm{int}}}{\mathrm{d}\theta^i} + \sqrt{2D_r}\xi^i$$

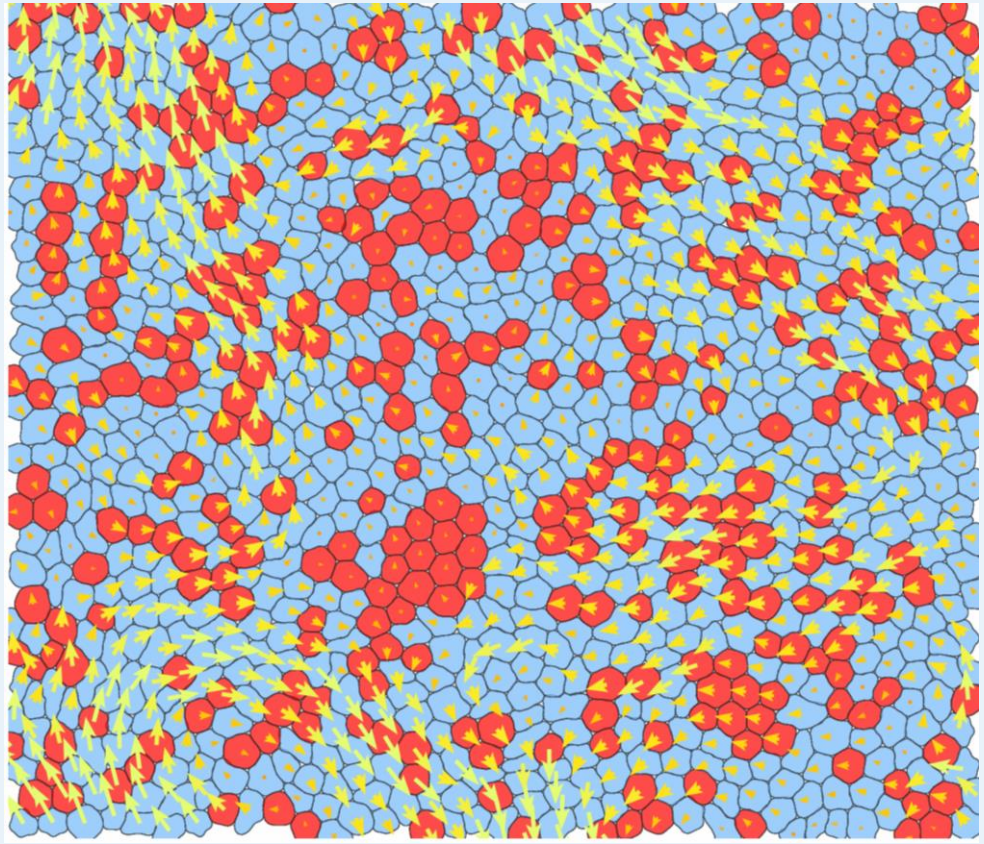
**Shape** :

$$\dot{a}_n^i = F_{l,a_n}^i + F_{\mathrm{int},a_n}^i = -\mu_{ab}\eta^i \frac{\mathrm{d}l^i}{\mathrm{d}a_n^i} - -\mu_{ab} \frac{\mathrm{d}H_{\mathrm{int}}^i}{\mathrm{d}a_n^i}$$

$$\dot{b}_n^i = F_{l,b_n}^i + F_{\mathrm{int},b}^i = -\mu_{ab}\eta^i \frac{\mathrm{d}l^i}{\mathrm{d}b_n^i} - \mu_{ab} \frac{\mathrm{d}H_{\mathrm{int}}^i}{\mathrm{d}b_n^i}$$

# System and model

## Configuration movie



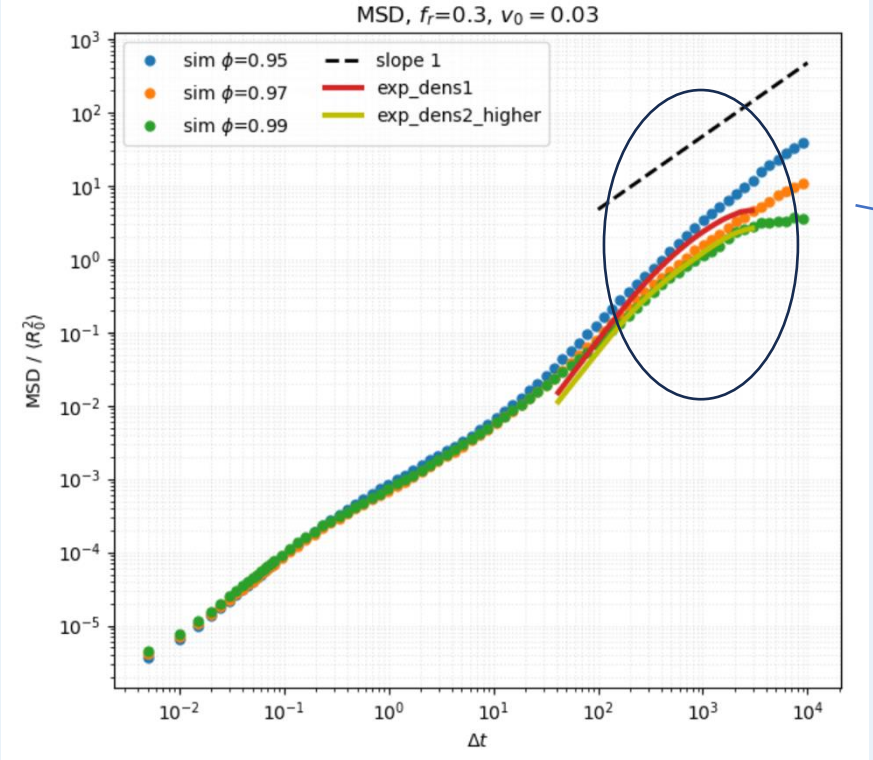
Soft particles
Hard particles
Arrows represent displacement

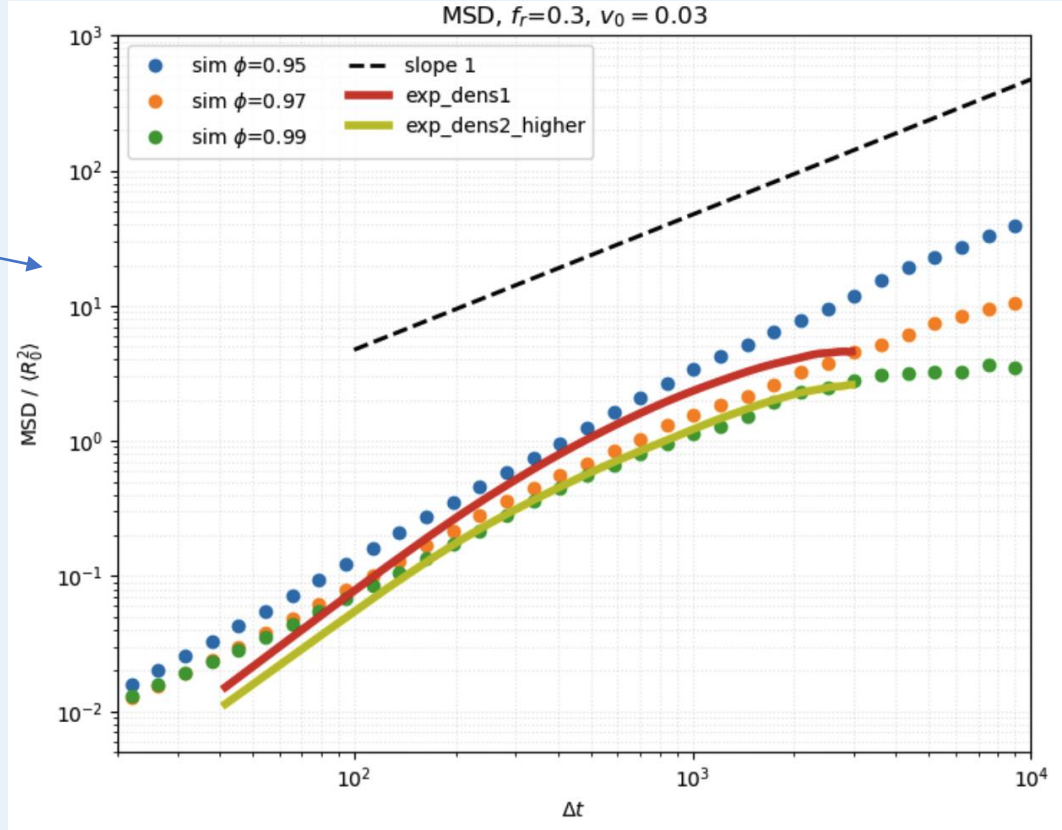
- **System size**: $N_p = 1024$
- **Mixture** → hard particles($\eta_{hard}$)+ soft particles($\eta_{soft}$)
- **Rigidity fraction** : $f_r = \frac{N_{hard}}{N_p}$
- **Varying area fraction**: $\Phi = 0.99, 0.95, 0.90$ etc.

# Dynamical comparison

## ■ Dynamics over time

➢ Showing MSD with changing the parameters → comparison with experiment.



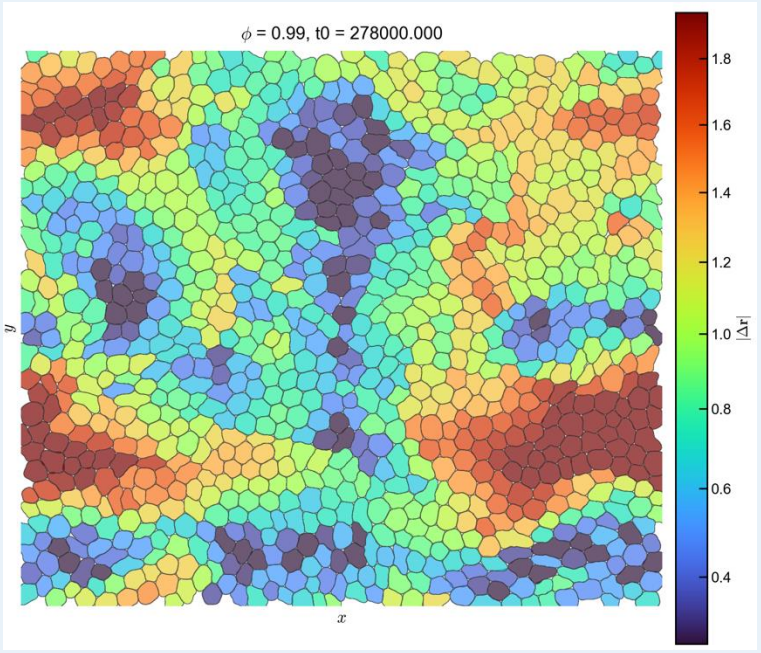




➢ Simulation model makes good agreement with experimental result.

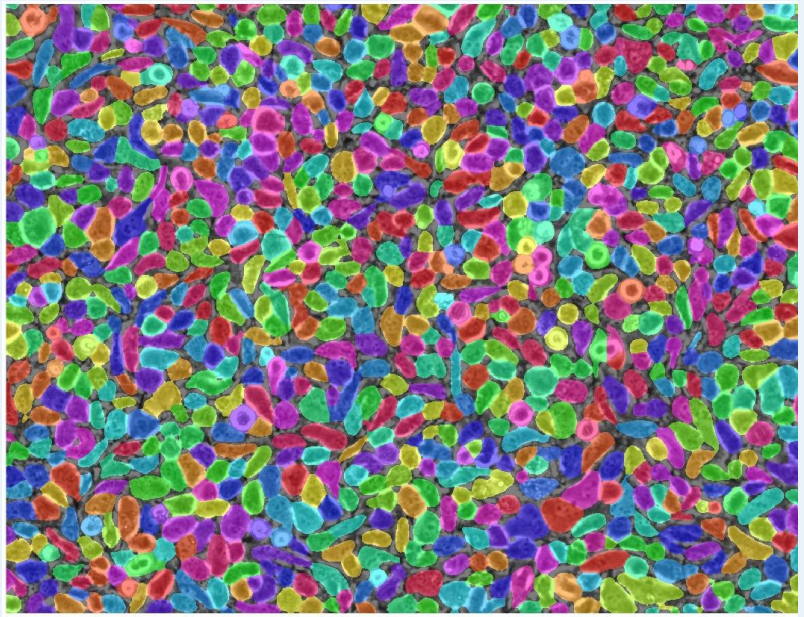
➢ However, parameter set is vast, hence, need deeper understanding of the model.

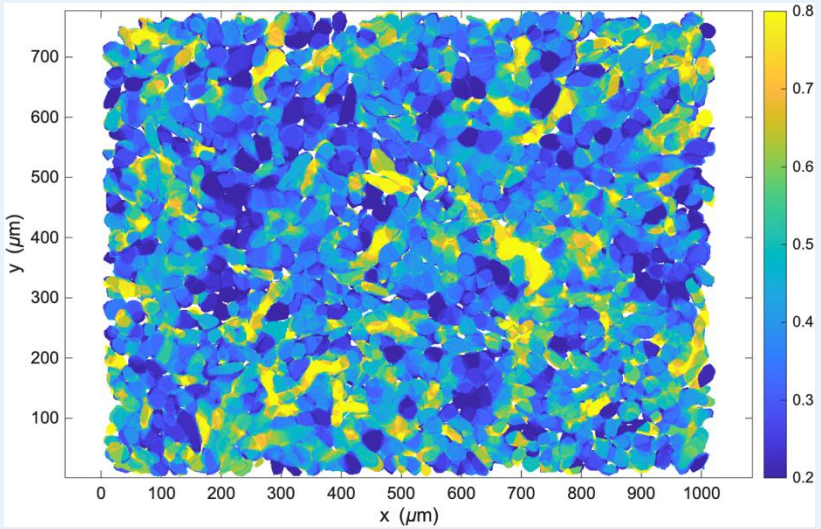
# Summary and Perspective

- Density and softness tune how cells pack, leave voids, and rearrange.
- MSD and displacement distributions reveal crossover from fluid-like to glassy motion.
- Segmentation technique in experiments to make better theoretical modeling.




simulation






experiment

**Perspective**

- Macroscopic viscoelasticity, hardening of tumour and stronger experiment–theory matching are natural next steps.
- Co-culture experiments for understanding the mechanisms of cancer metastasis.

> It's a devilish thing. As a materials scientist, it's exciting to find this new weird state of matter. As a human, it scares you.
>
> —JOSEF KÄS, UNIVERSITY OF LEIPZIG

# Thank you