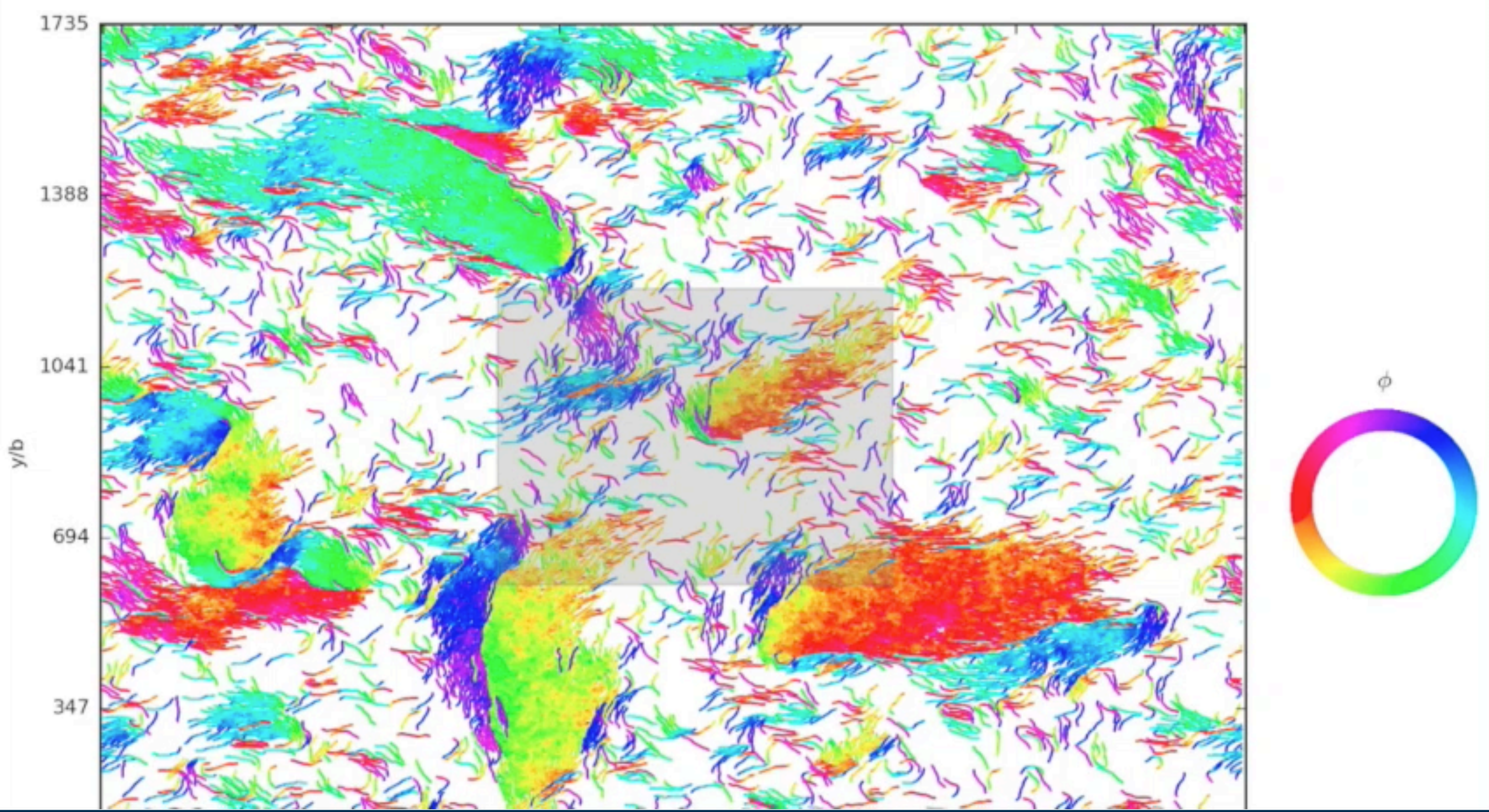


GROWTH MECHANICS - COEXISTENCE AND EVOLUTION

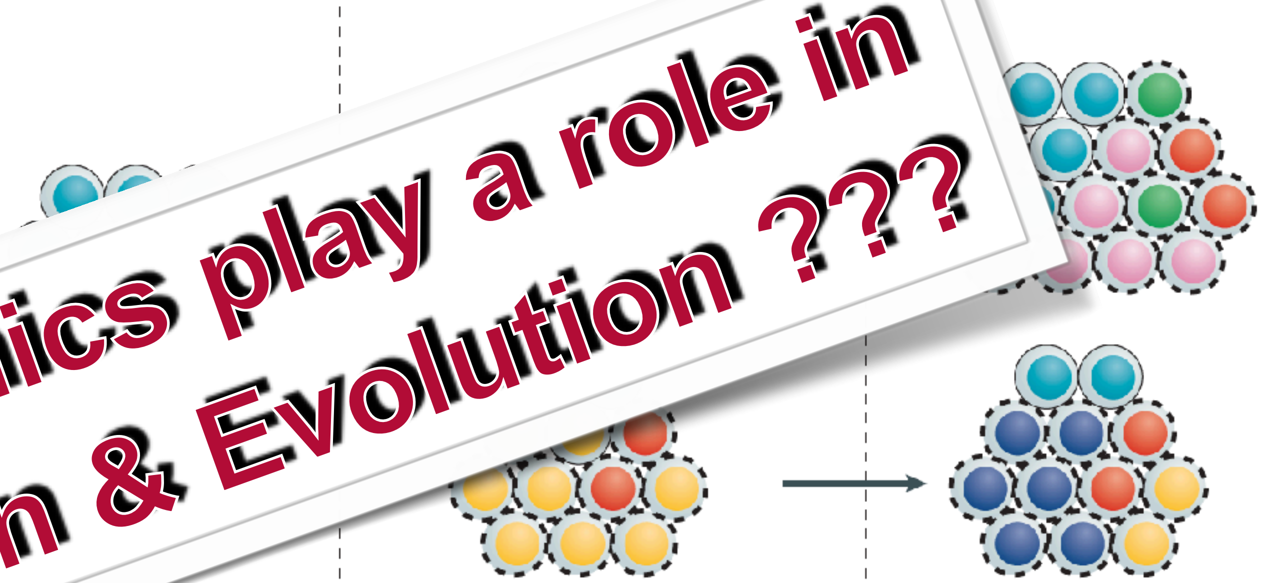
JENS ELGETI

Mitglied der Helmholtz-Gemeinschaft

JÜLICH Forschungszentrum

CANCER IS EVOLUTION WITHIN THE BODY

- Cancer ”evolves” with time
- aquirement of new properties
- typically loss of adhesion and enhanced growth (among others)
- Tumor hetero
- Occult Tu



-Jack and Daw Nature Reviews Clinical Oncology 2018

- Can Mechanics play a role in Competition & Evolution ???

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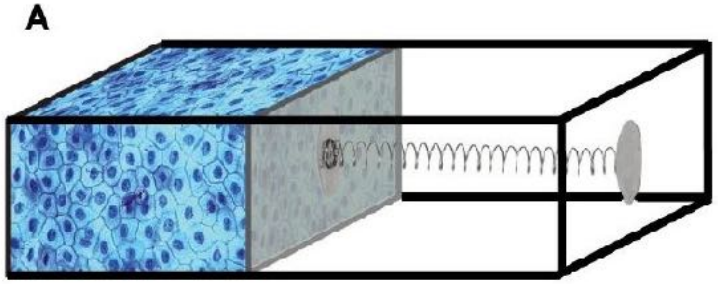
MECHANICS AFFECTING GROWTH

- Growth
- Mecanics

$$k = \kappa(\sigma - \sigma_H)$$

- Affecting (simplest version: Linear expansion)

$$k = \kappa(P_H - P)$$

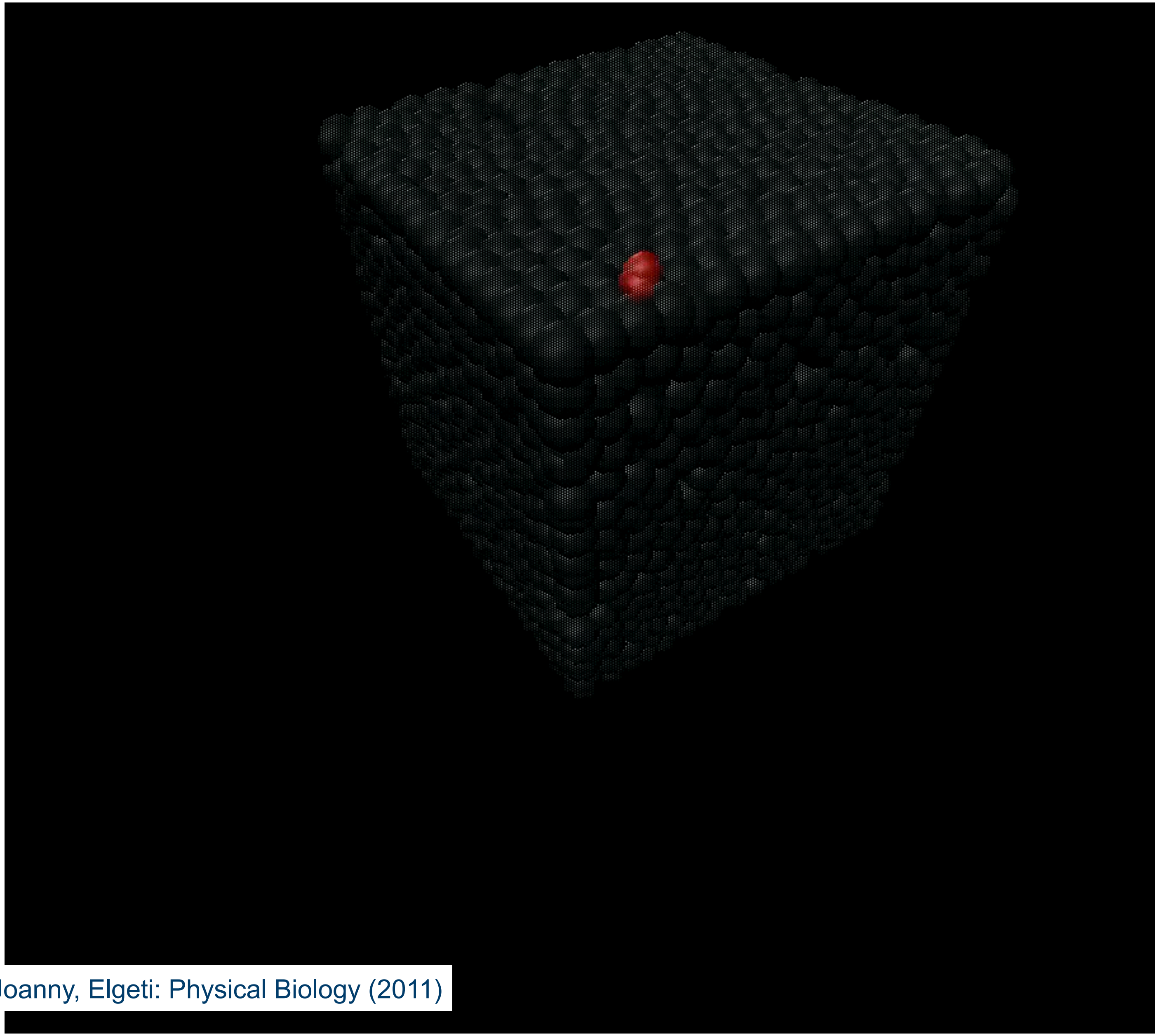


Basan et. al. HFSP 2009

COMPETITION BY PRESSURE

- Two identical tissues besides homeostatic pressure compete in the same box

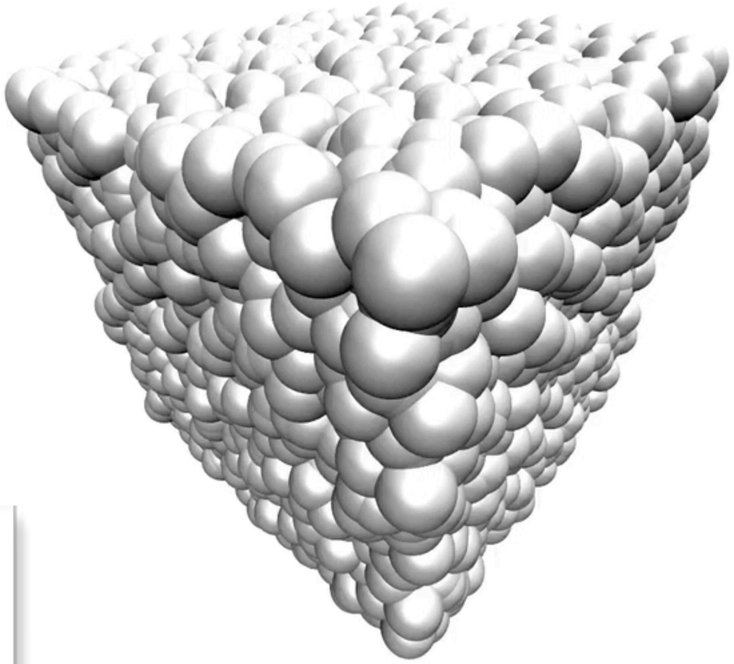
⇒ The stronger wins, even if slower

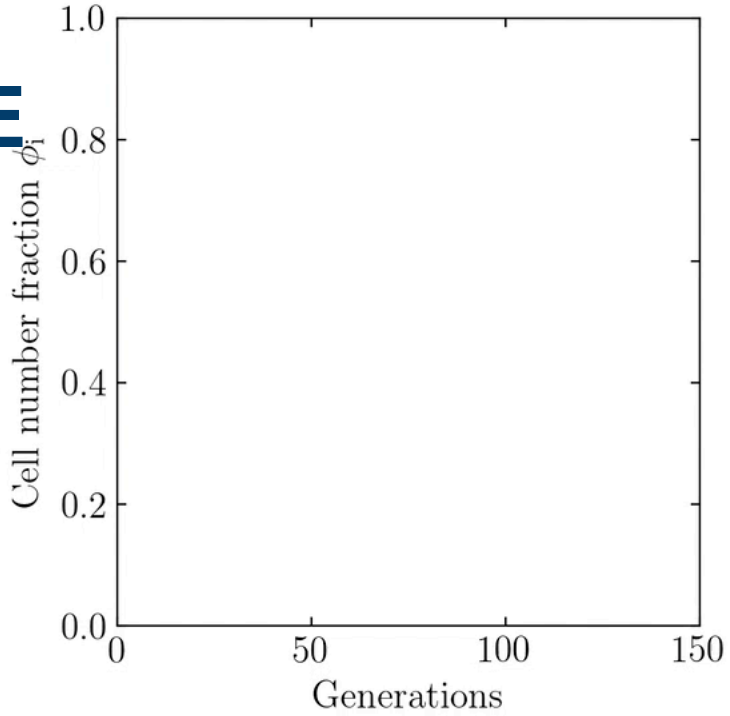


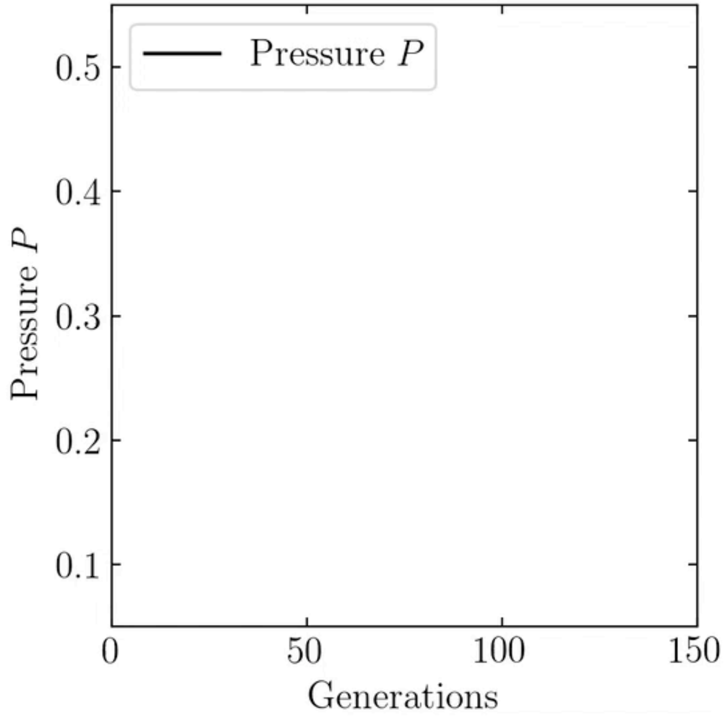
Basan, Prost, Joanny, Elgeti: Physical Biology (2011)

EVOLUTION BY HOMEOSTATIC PRESSURE

- $k = \kappa(P_H - P)$
- subsequent rounds of takeover





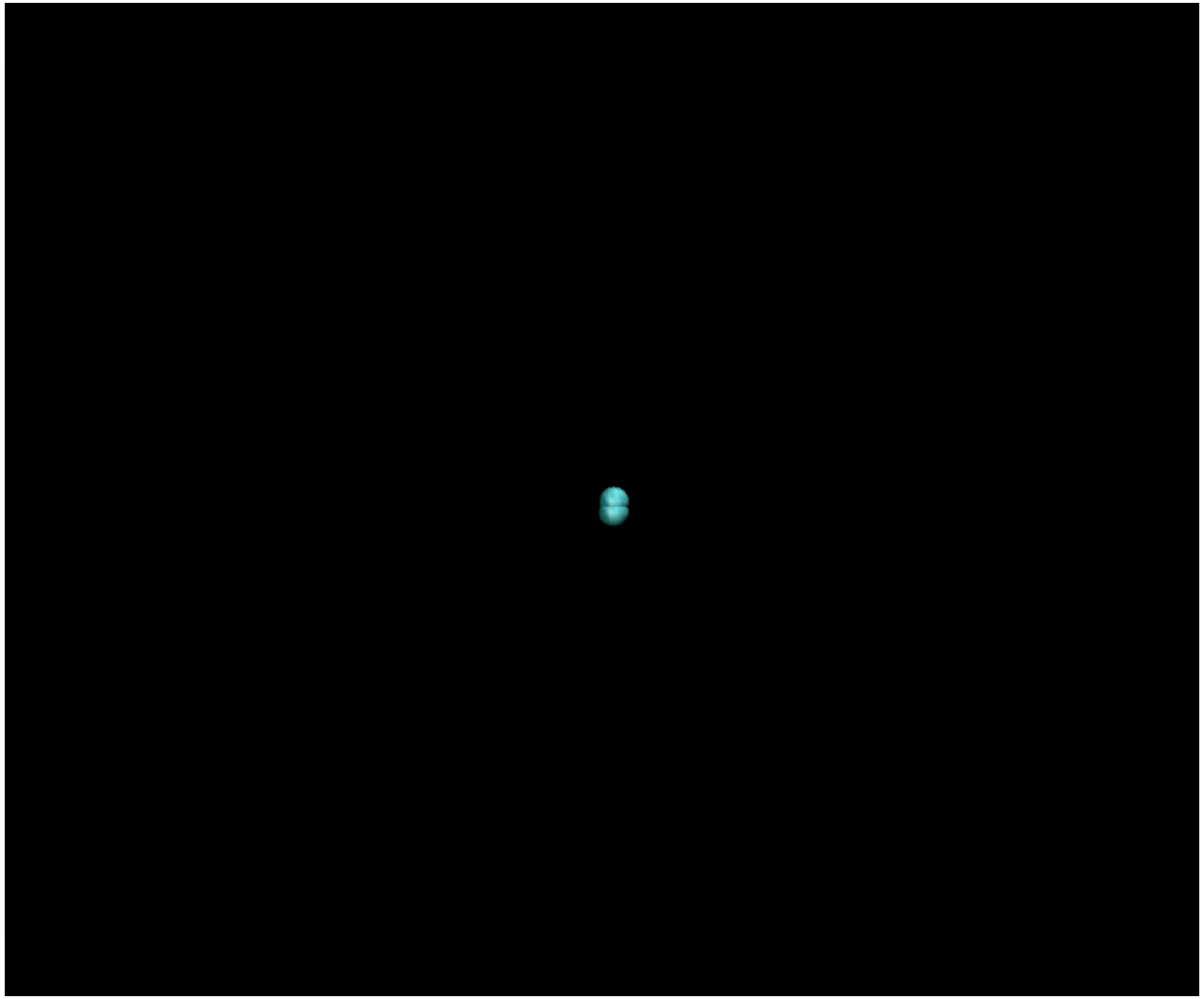


THE PARTICLE-BASED GROWTH MODEL

A minimalistic approach

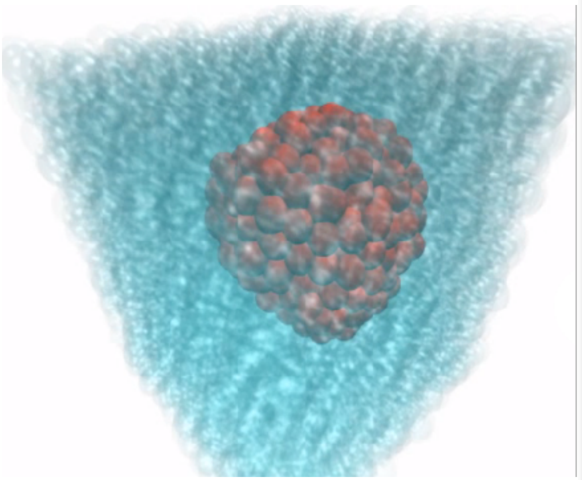
- Cell represented by 2 points
- Active growth force G
- Division at size

  $\Leftrightarrow$ constant apoptotic rate
- Excluded volume interaction
- Constant attractive force f_1
- DPD thermostat

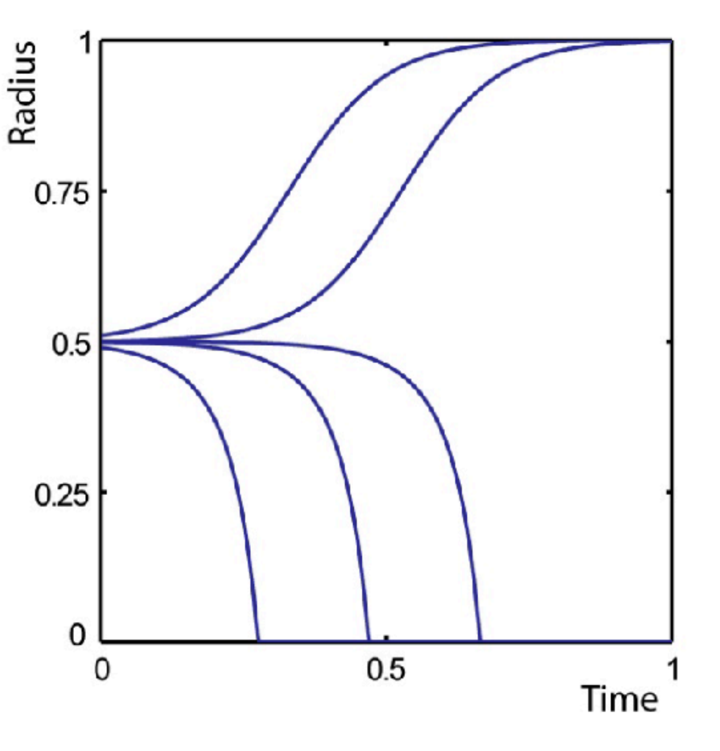


Basan, Prost, Joanny, Elgeti: Physical Biology (2011)

METASTATIC INEFFICIENCY & THE ROLE OF ADHESION



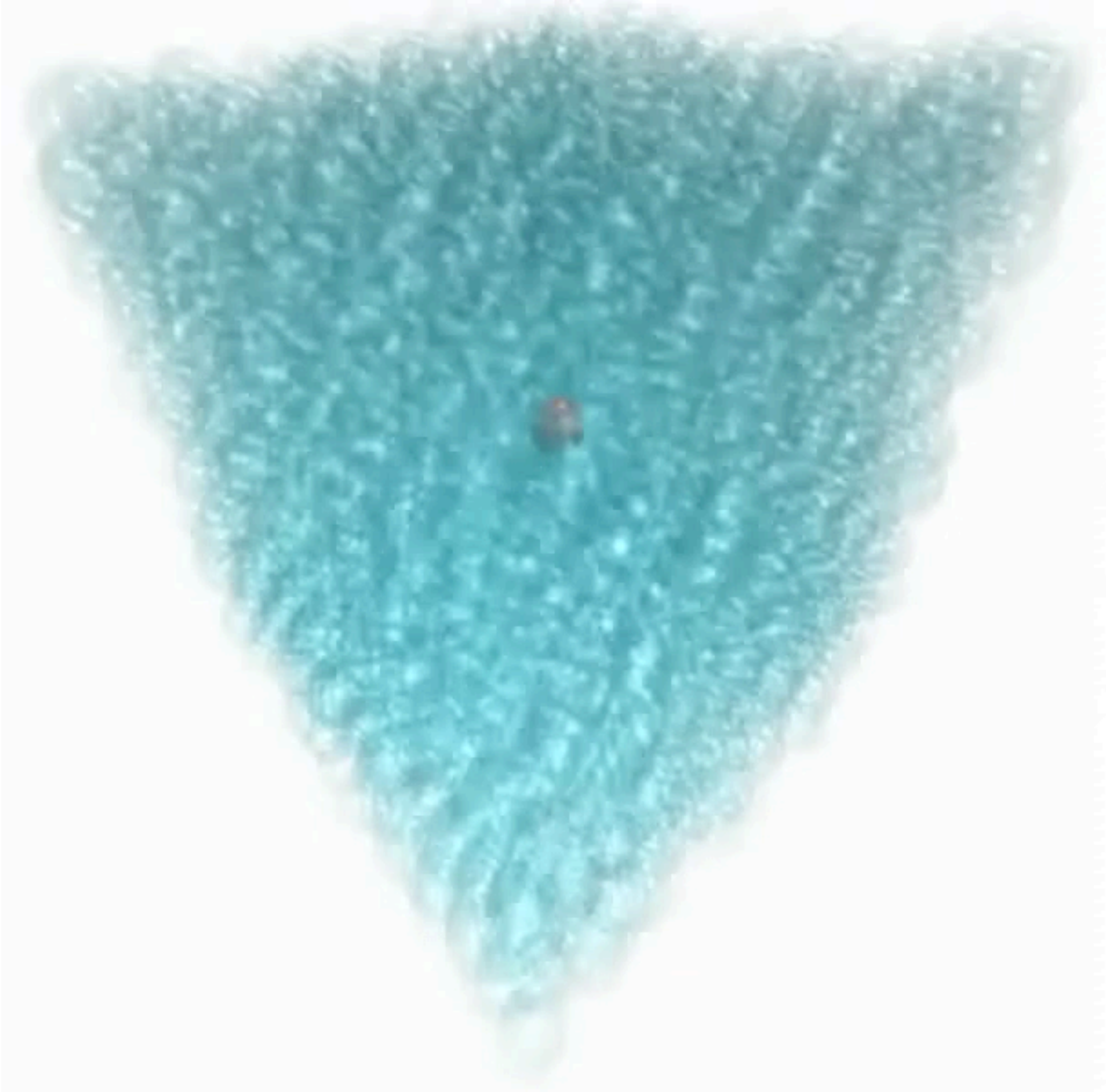
- Surface tension leads to
  Laplace Pressure $P = \frac{2\gamma}{R}$
- => Critical tumor size
  $$R_c = \frac{2\gamma}{\Delta P_H}$$

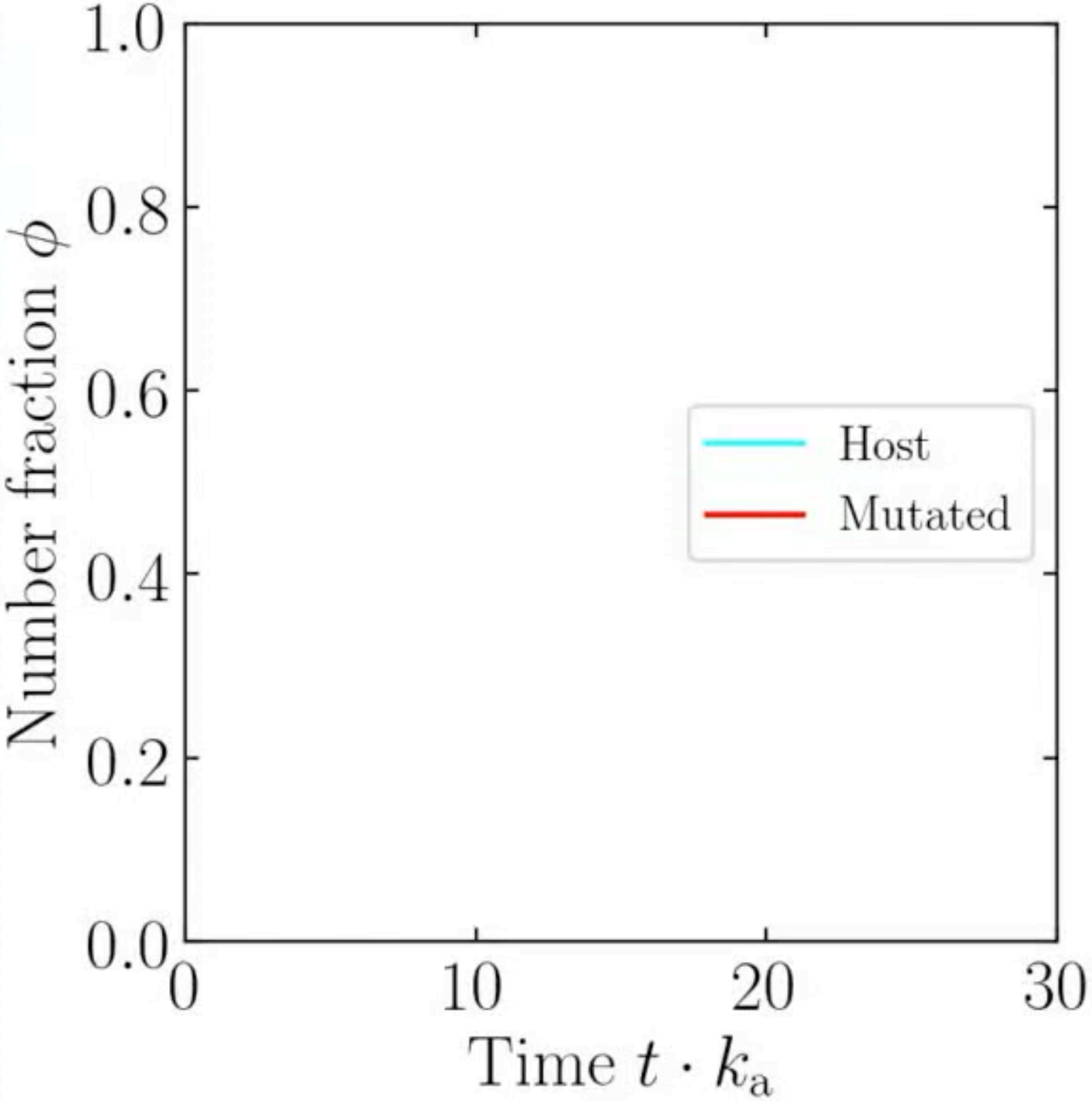


Basan et. al. HFSP 2009

Nirmalendu Ganai, Tobias Büscher, Gerhard Gompper, & **Jens Elgeti**: NJP (2019)

CRITICAL SIZE?!





FLAT INTERFACE

Simplest Case

- Identical Tissues
- Zero Cross adhesion
- Flat Interface

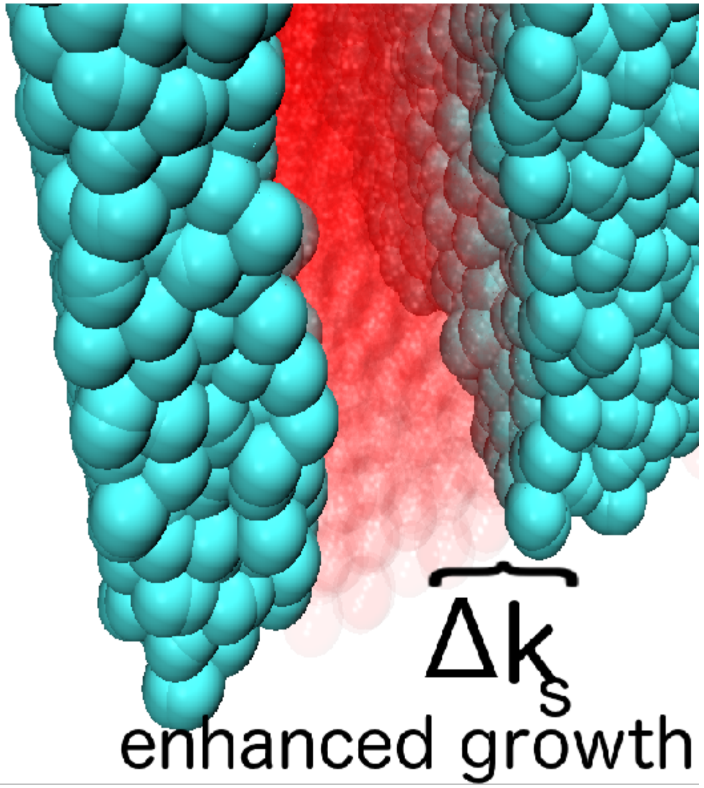
Explanation

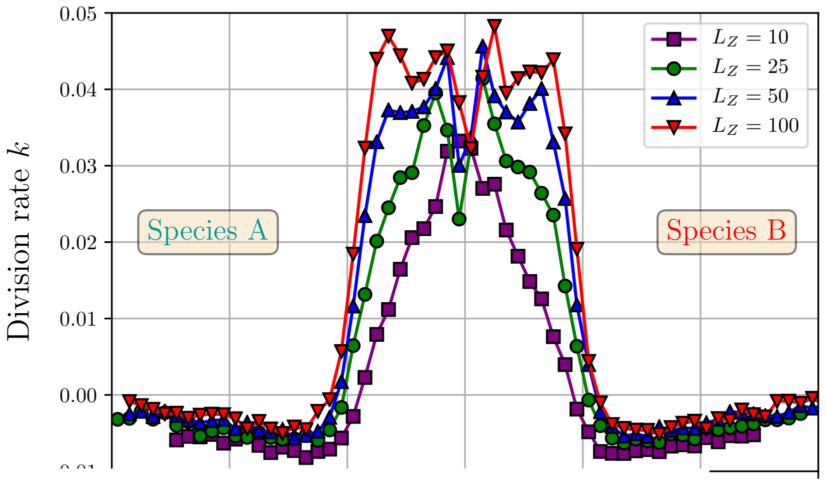
- Zero cross adhesion

⇒ alike to free surface

⇒ interfacial growth

⇒ coexistence





Nirmalendu Ganai, Tobias Büscher, Gerhard Gompper, & **Jens Elgeti**: NJP (2019)

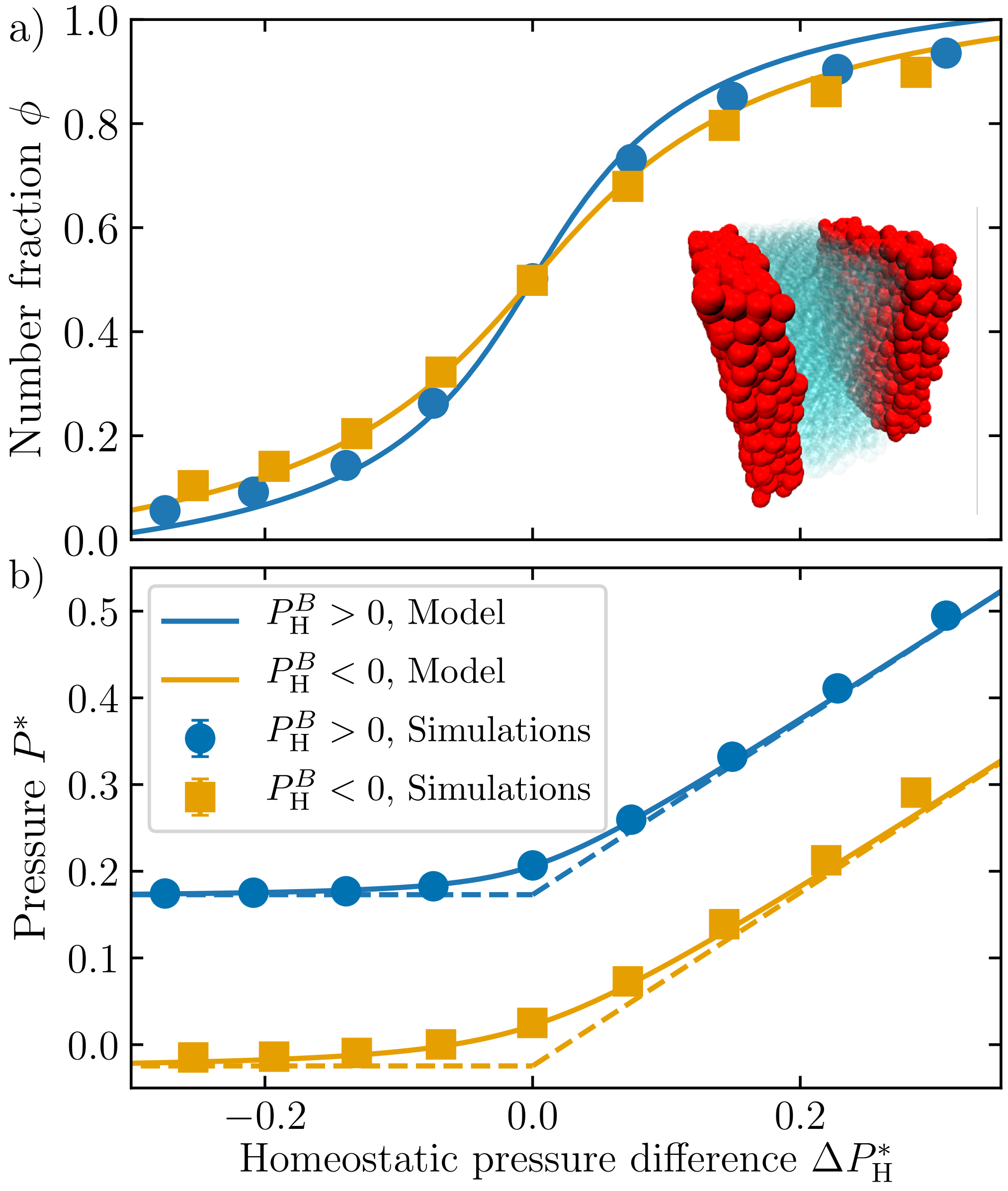
FLAT INTERFACE

Theory

- Homeostatic Pressure: $k = \kappa(P_H - P)$
- Surface Groth $\Delta k_{\mathrm{s}} \simeq \Delta k_{\mathrm{s}}^0 + \Delta k_{\mathrm{s}}^1 (P_{\mathrm{H}} - P)$
- Number Balance =>

$$P = P_{\mathrm{H}} + \frac{4a\Delta k_{\mathrm{s}}^0}{(4a\Delta k_{\mathrm{s}}^1 + \kappa L_z)}$$

- Balance pressures
- Pressure higher than hom. P of stronger tissue!
- Cell death balanced by excess growth at surface.



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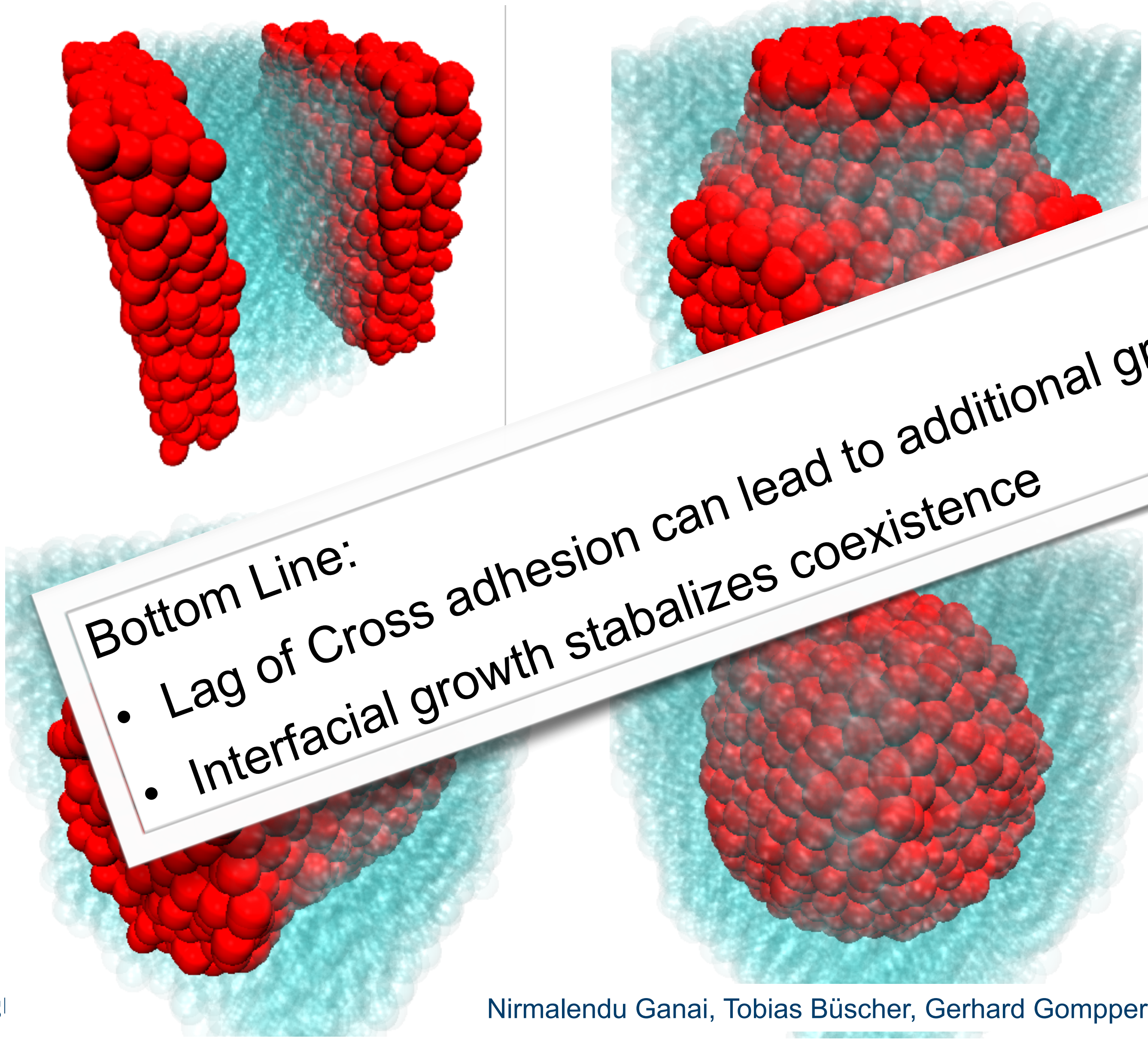
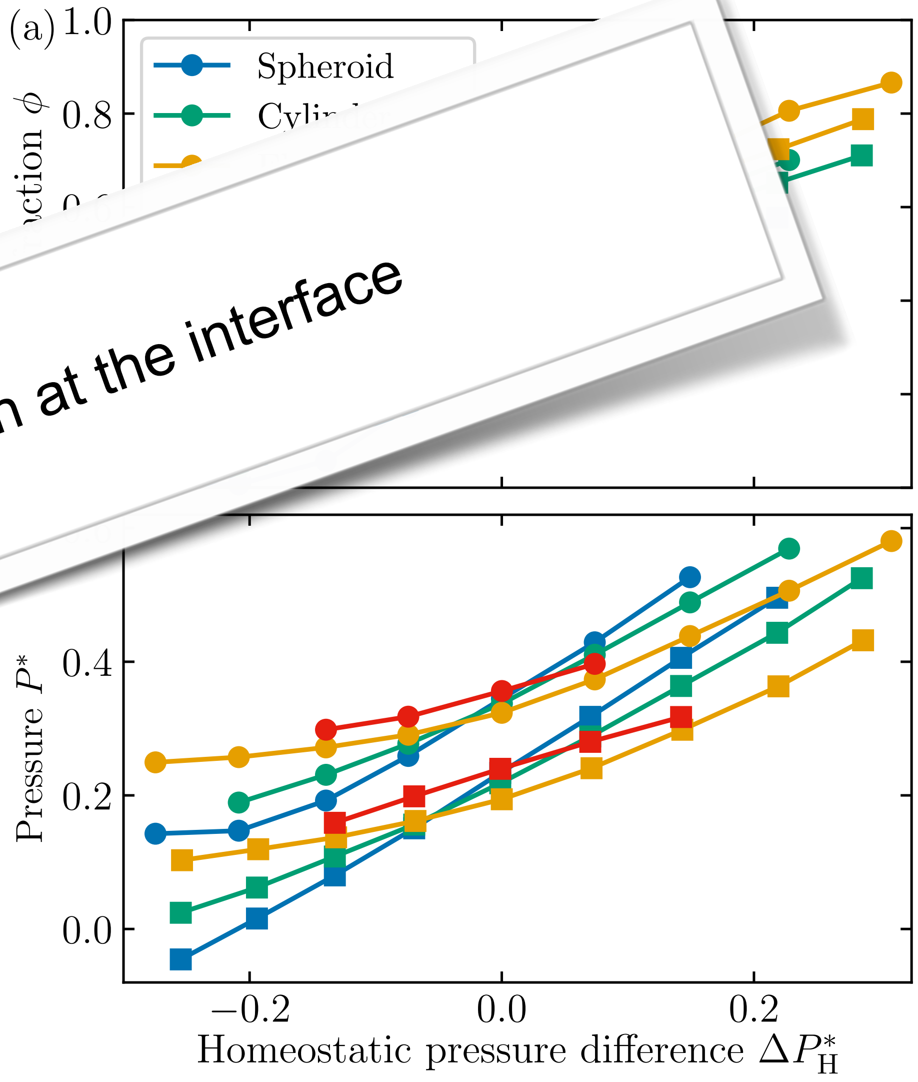
COMPLEX STRUCTURES



Bottom Line:

- Lag of Cross adhesion can lead to additional growth at the interface
- Interfacial growth stabalizes coexistence



Nirmalendu Ganai, Tobias Büscher, Gerhard Gompper, & **Jens Elgeti**: NJP (2019)

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EVOLUTION

Evolution of parameters

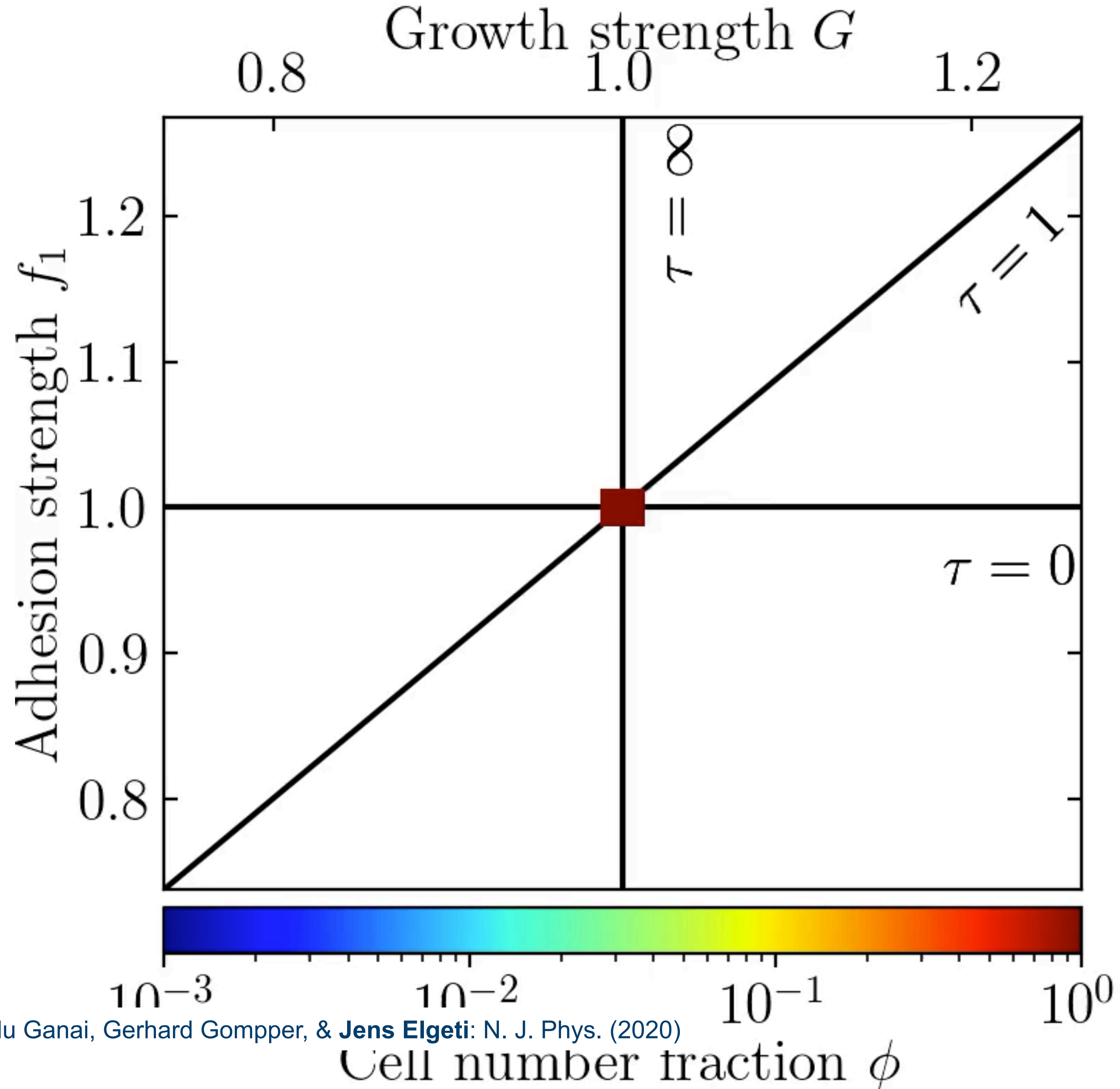
- Mutation possibility after each division
- Evolves to low adhering, strong growing tissue.

Coupling of parameters

- Tradeoff τ between growth strength and adhesion:

$$f_1 = \tau G$$

- Motivated by cadherine biology



Tobias Büscher, Nirmalendu Ganai, Gerhard Gompper, & **Jens Elgeti**: N. J. Phys. (2020)

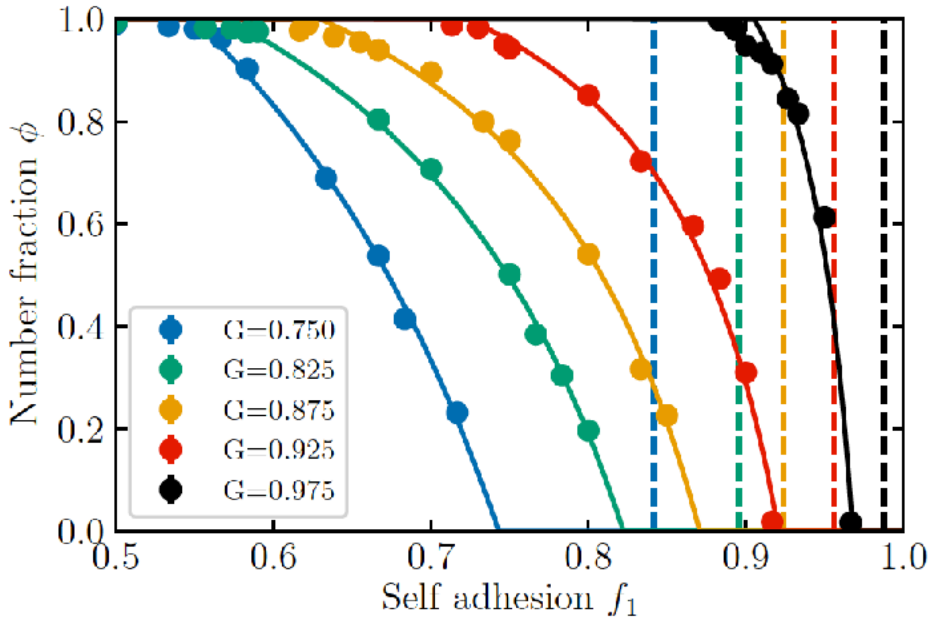
SMALL DIFFERENCES IN CROSS ADHESION & GENETIC DRIFT

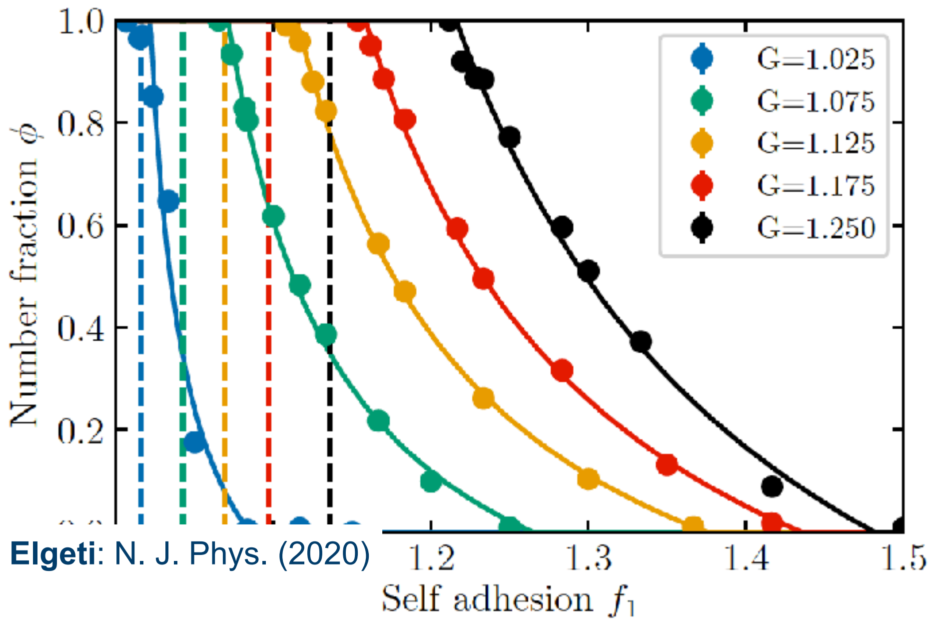
- Assume that cells can mutate, changing cross adhesion and growth strength
- (Imagine mutating Catherines: Adhesion and growth signalling)
- Assume well mixed state, surface growth proportional to $\phi(1-\phi)$
- Number balance:

$$\partial_t \phi = \kappa(P_\mathrm{H}^\mathrm{A} - P)\phi + \Delta k_\mathrm{s}^\mathrm{A} \phi(1-\phi) \qquad (2)$$

$$\partial_t (1-\phi) = \kappa(P_\mathrm{H}^\mathrm{A} + \Delta P_\mathrm{H} - P)(1-\phi) + \Delta k_\mathrm{s}^\mathrm{B} \phi(1-\phi),$$

$$\phi_3 = \frac{\kappa \Delta P_H + \Delta k_S^A}{\Delta k_s^A + \Delta k_s^B}$$

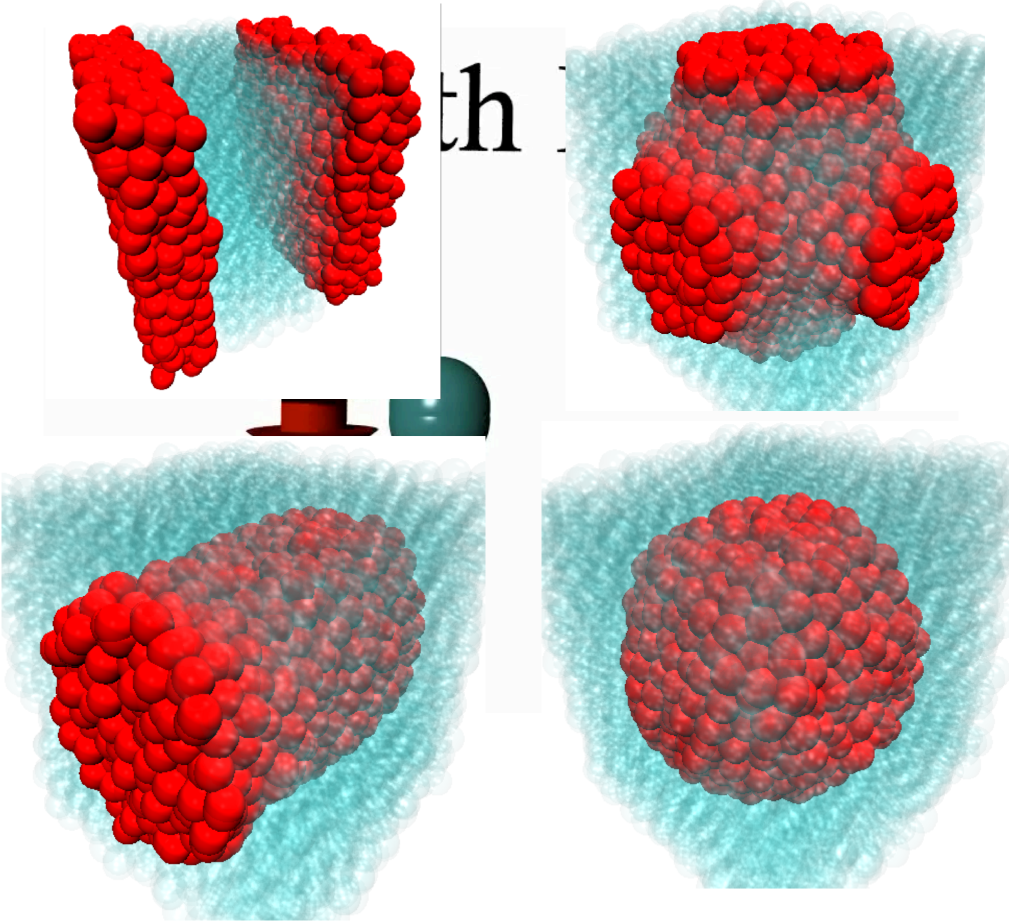




Tobias Büscher, Nirmalendu Ganai, Gerhard Gompper, & **Jens Elgeti**: N. J. Phys. (2020)

INTERMEDIATE SUMMARY

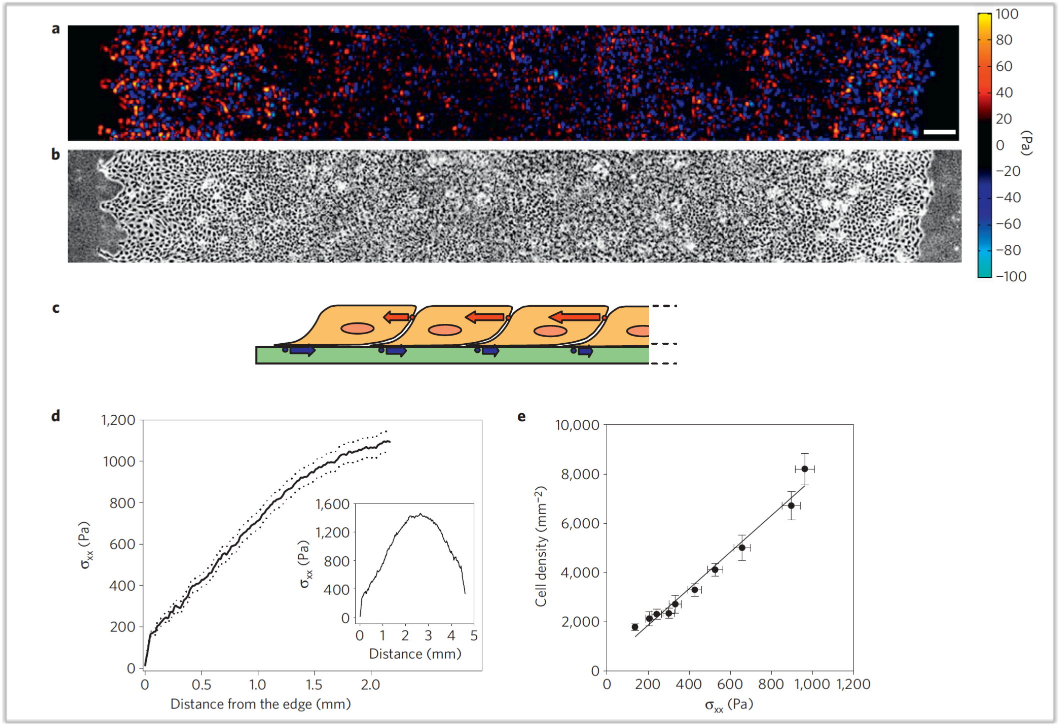
- Mechanics can controle tissue growth and competition
- Homeostatic Pressure Key controle parameter
- Surface and Interface Effects lead to additional complexity
- Coexistence and divergent evolution possible



MOTILE (GROWING) TISSUES

- Many motile cells move ”fluid like”, but remain cohesively in a colony.
- corresponds to ”Fluid-vacuum” coexsistence

- Furthermore the Colony is under ***tension***



Trepat et al. (2009). Nat. Phys. 5, 426

Puliafito et al. (2012). Proc. Natl. Acad. Sci. USA 109, 739

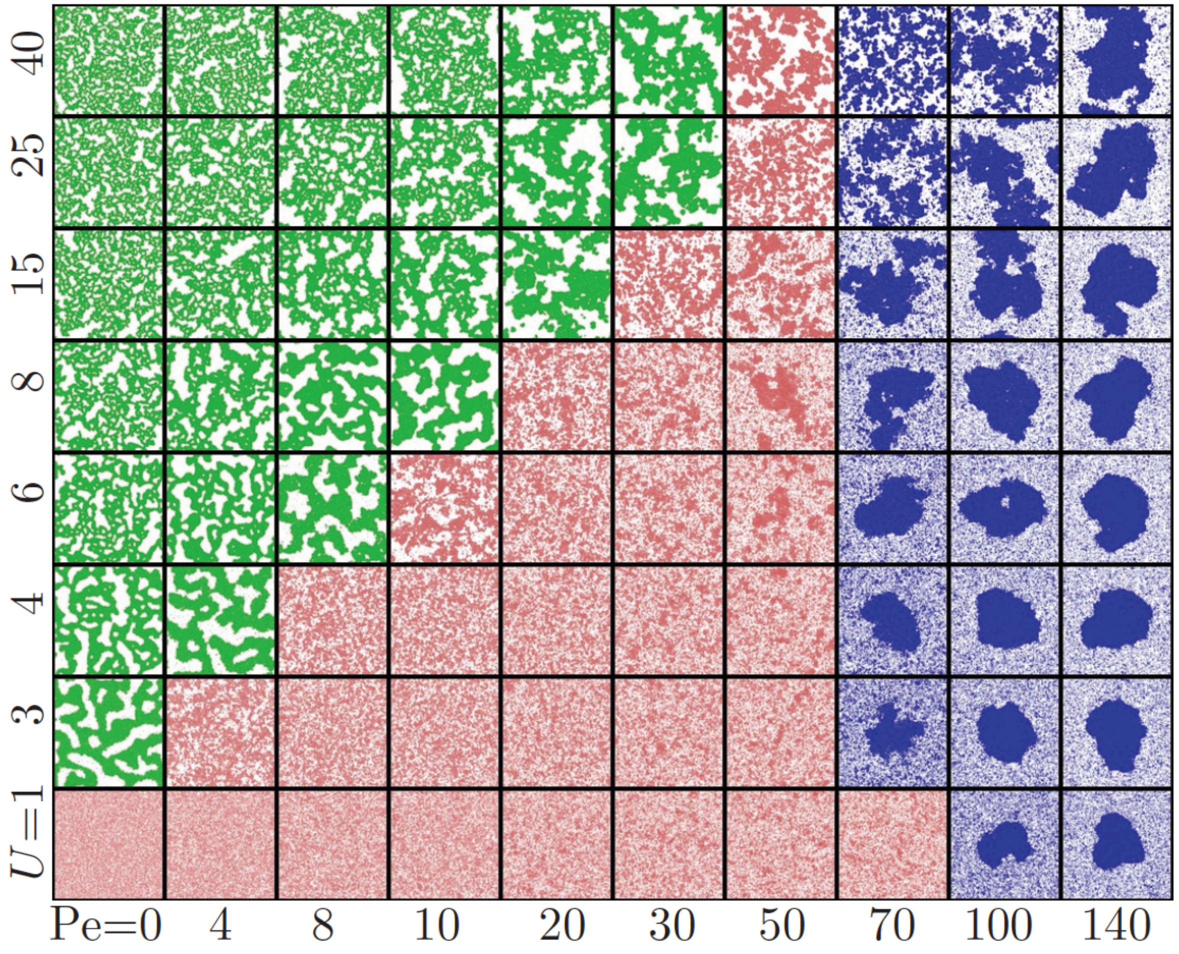
ACTIVE BRONIAN PARTICLE

ABP Model

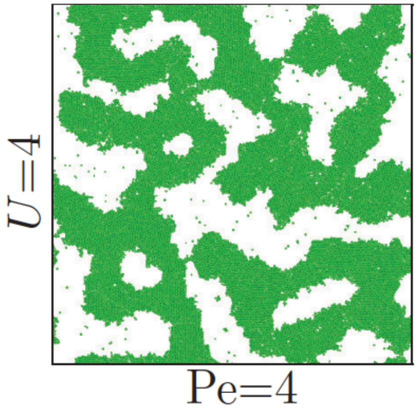
- Brownian Diffusion (incl. rotation)
- Active Propulsion
- LJ Interaction

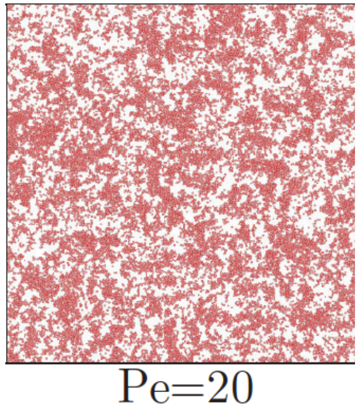
Three Situations

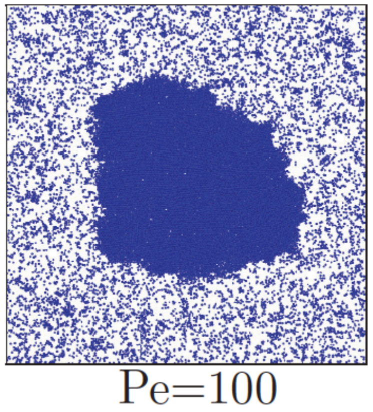
- Solid+Vacuum
- Fluid+Gas
- Gas+MIPS



Redner et al. PRE & PRL 2013

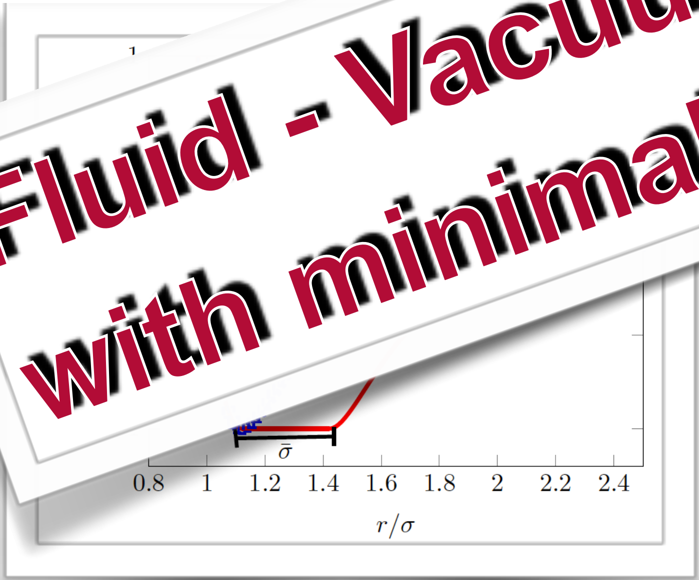




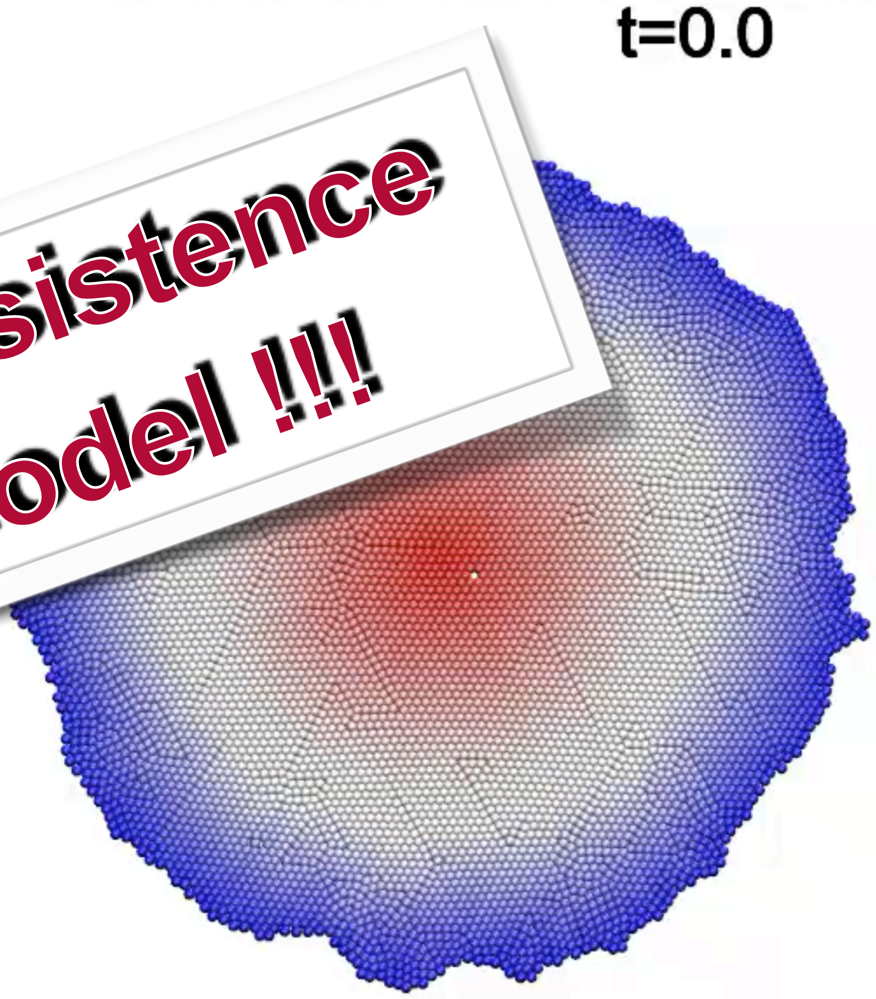


WIGGLE ROOM

- ”Ususual” ABP Model
  - Brownian colloid with orientational and translational diffusion
  - Propulsion along orientation
- Plus **extended** LJ Potential pot-width $\bar{\sigma}$



Fluid - Vacuum Coexsistence with minimal ABP Model !!!

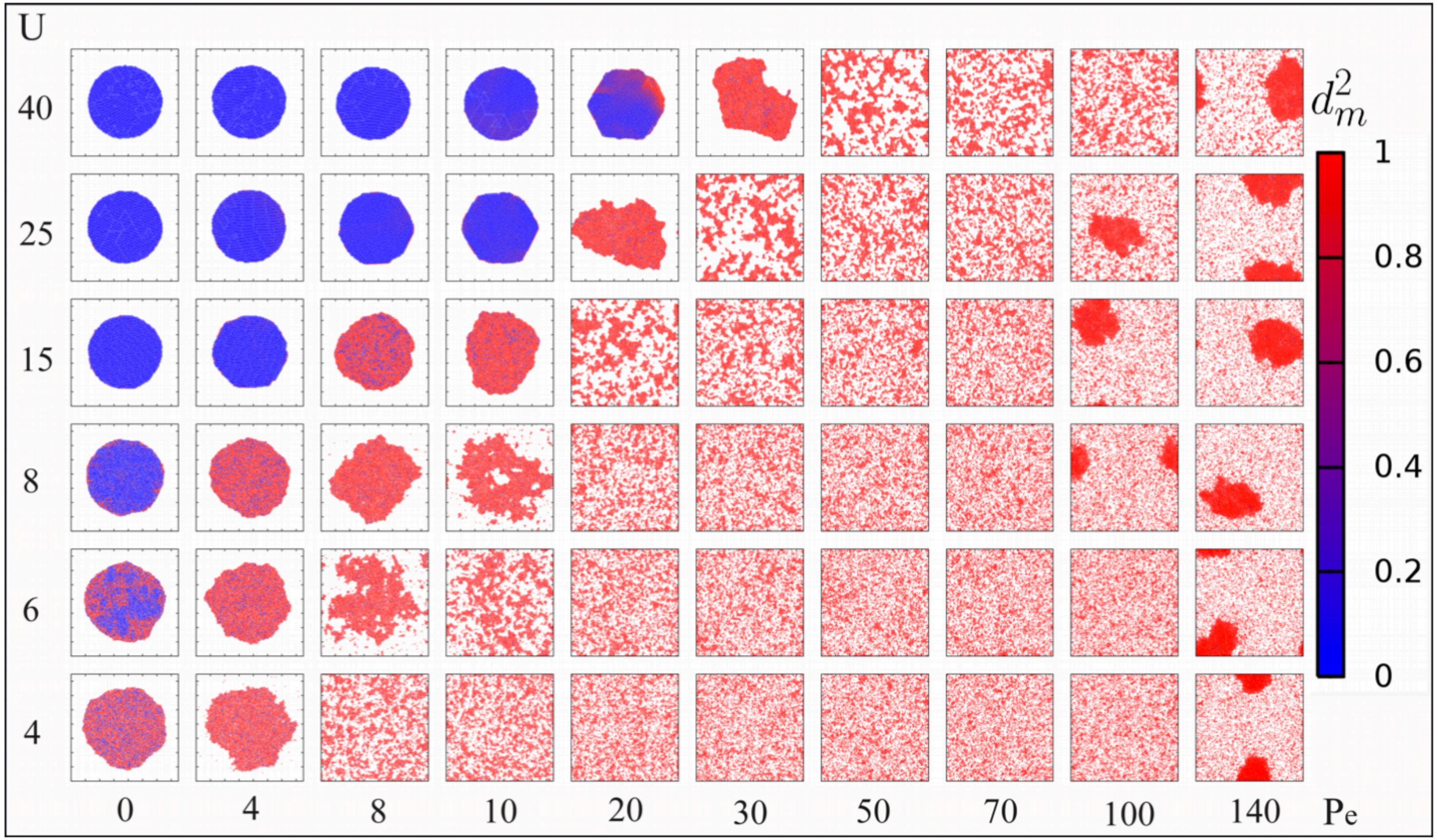


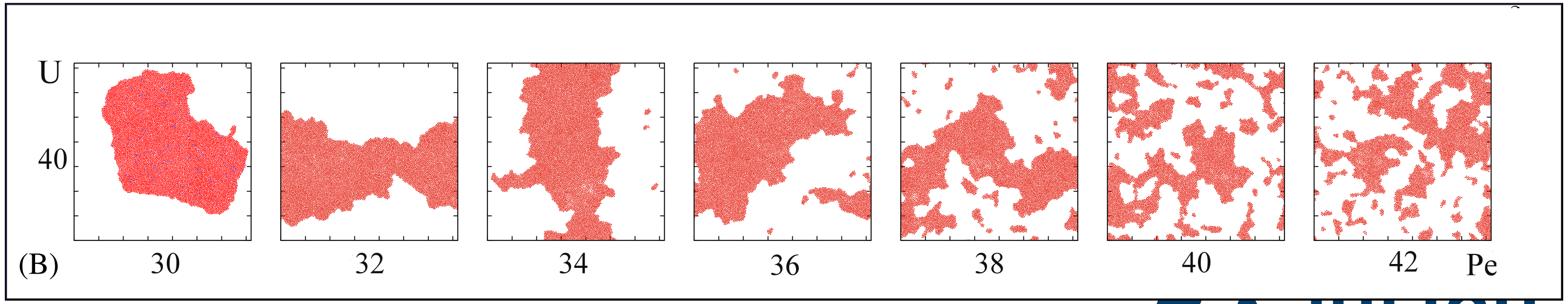
Sarkar, Gompper, **Elgeti**: Com. Phys. (2021)

PHASE BEHAVIOR

Observed "Phases"

- Solid + Vaccuum
- Liquid + Vaccum
- rarly small Clusters detach
- many clusters detach
- Many Clusters
- MIPS (compare e.g. Talk of Thomas Speck or Roland Winkler)





Sarkar, Gompper, **Elgeti**: Com. Phys. (2021)

”QUANTIFYING” THE PHASES

Liquidity:

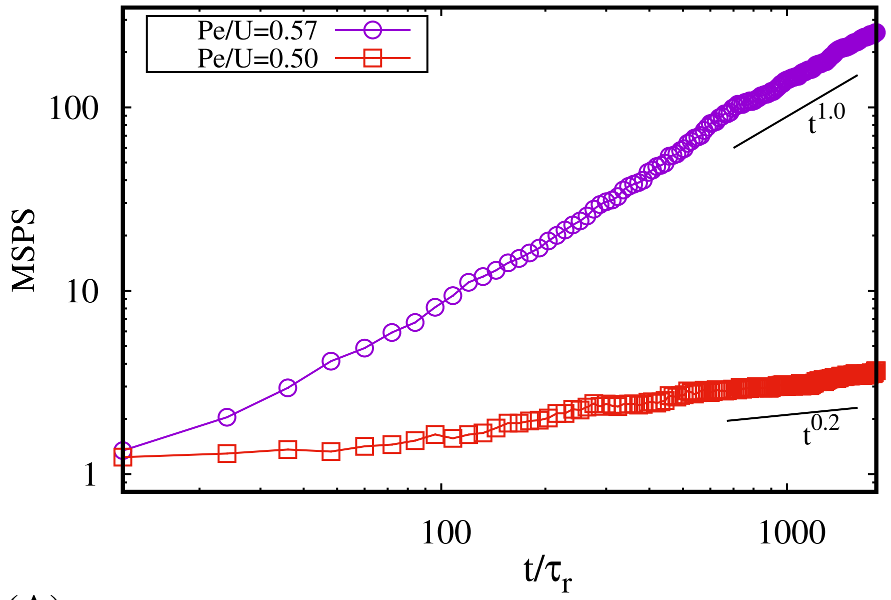
- Liquidity defined by neighbour exchange
- Define Mean squared separation of particle-pairs touching at t=0:

$$MSPS(t) = \frac{1}{N_p} \sum_{N_p} (\mathbf{r}_m(t_p + t) - \mathbf{r}_n(t_p + t))^2$$

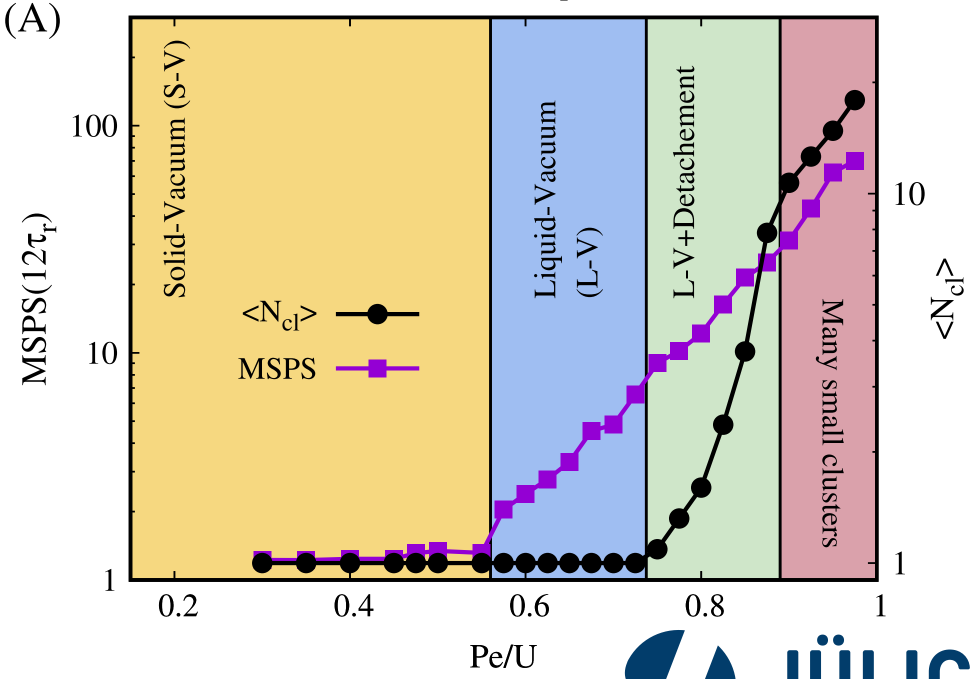
- $MSPS(12\tau_r) > 1.2\sigma^2$ indicates liquidity

”Vacuum”:

- Number of Clusters =1
  indicates ”**vacuum**” coexistence



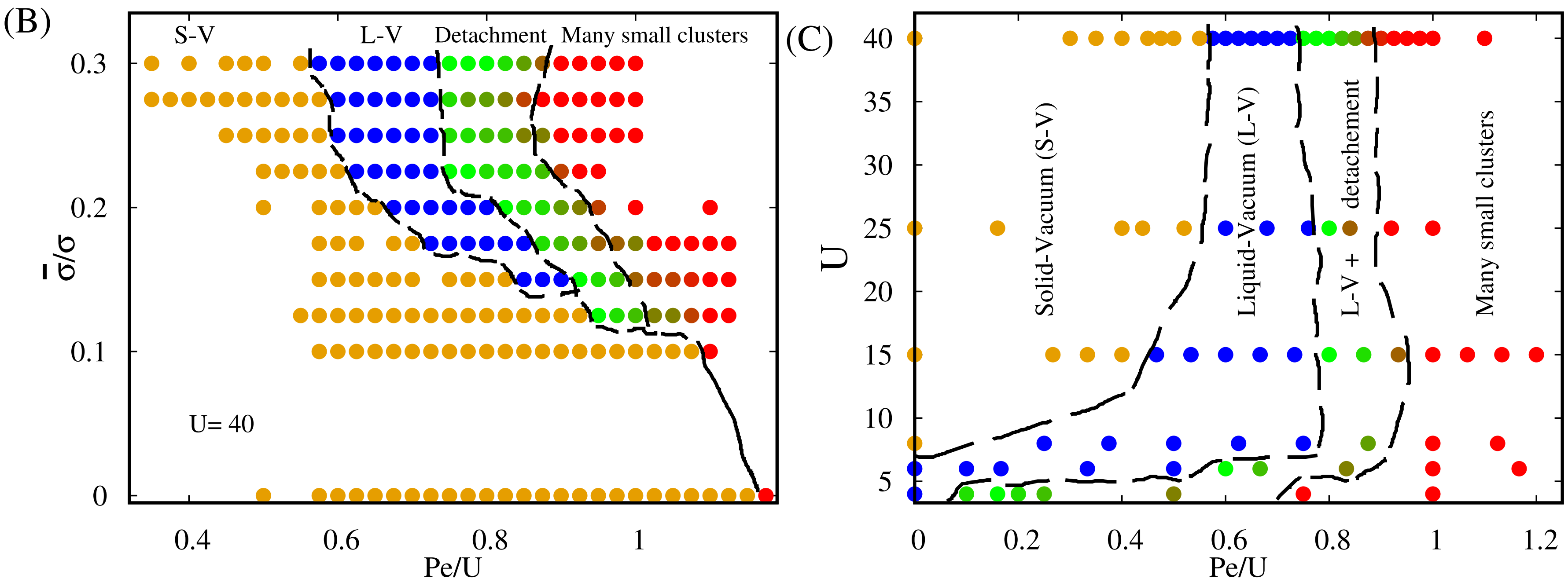
(A)



Sarkar, Gompper, **Elgeti**: Com. Phys. (2021)

EXPLORING PHASE SPACE

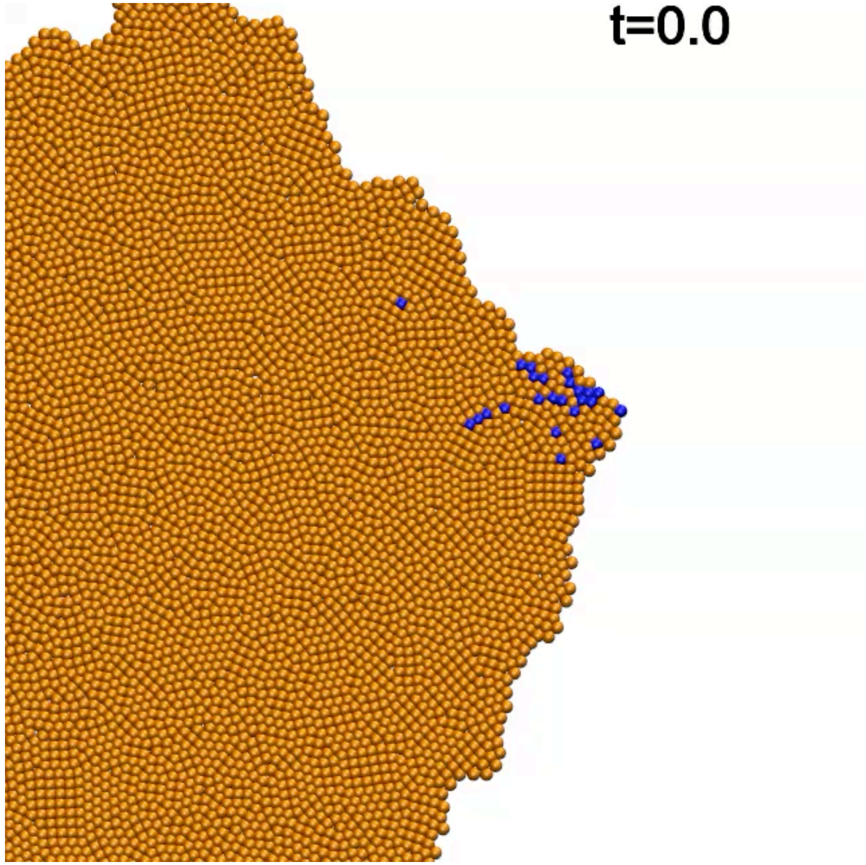
- Extend of the Liquid-Vaccuum phase, close to Activity ~ Attraction
- Strong adhesion compared to noise requiered
- Minimal potential width $\bar{\sigma}$ necessary

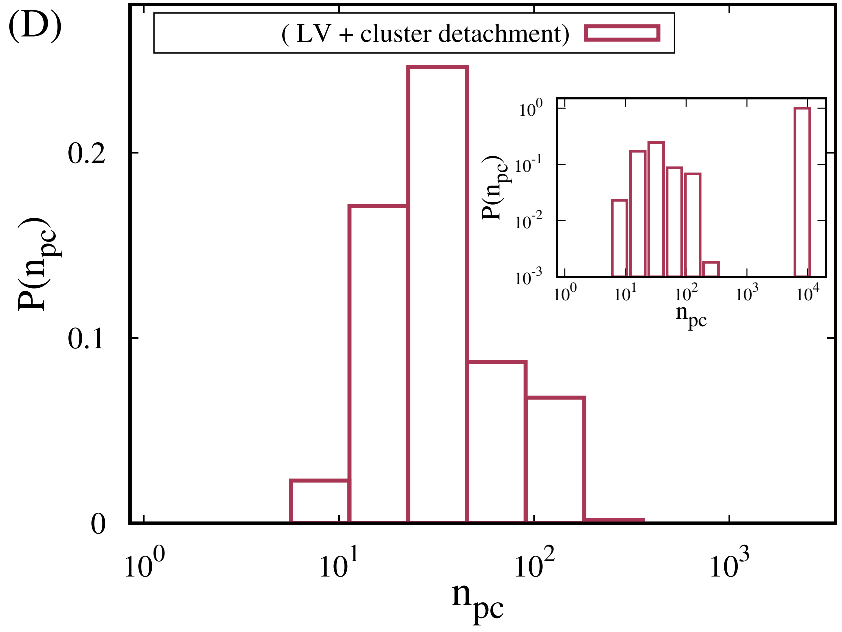


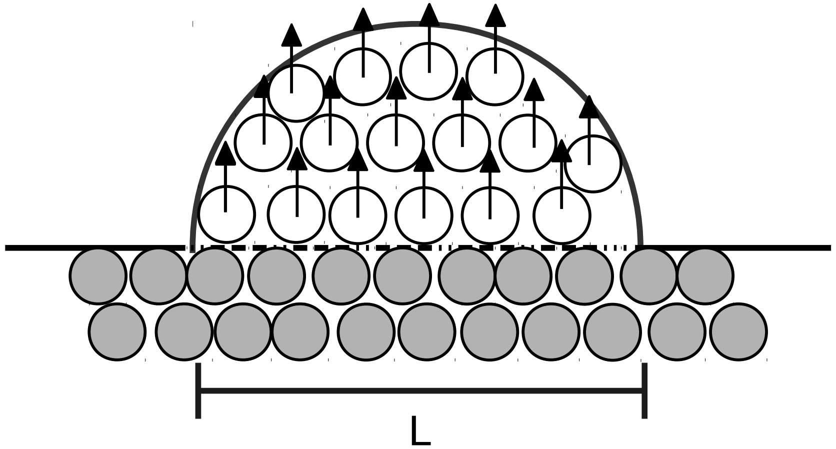
Sarkar, Gompper, **Elgeti**: Com. Phys. (2021)

A NOTE ON CLUSTERS

- Cells detach in **clusters**
- No single Cell detaches
- Simple explanation: Single cells to ”weak” to detach - aligned can.
- Note that cancer cells also often detach from the tumor in clusters!







Sarkar, Gompper, **Elgeti**: Com. Phys. (2021)

MOTILE TISSUES

- Many motile cells move ”fluid like”, but remain cohesively in a colony.
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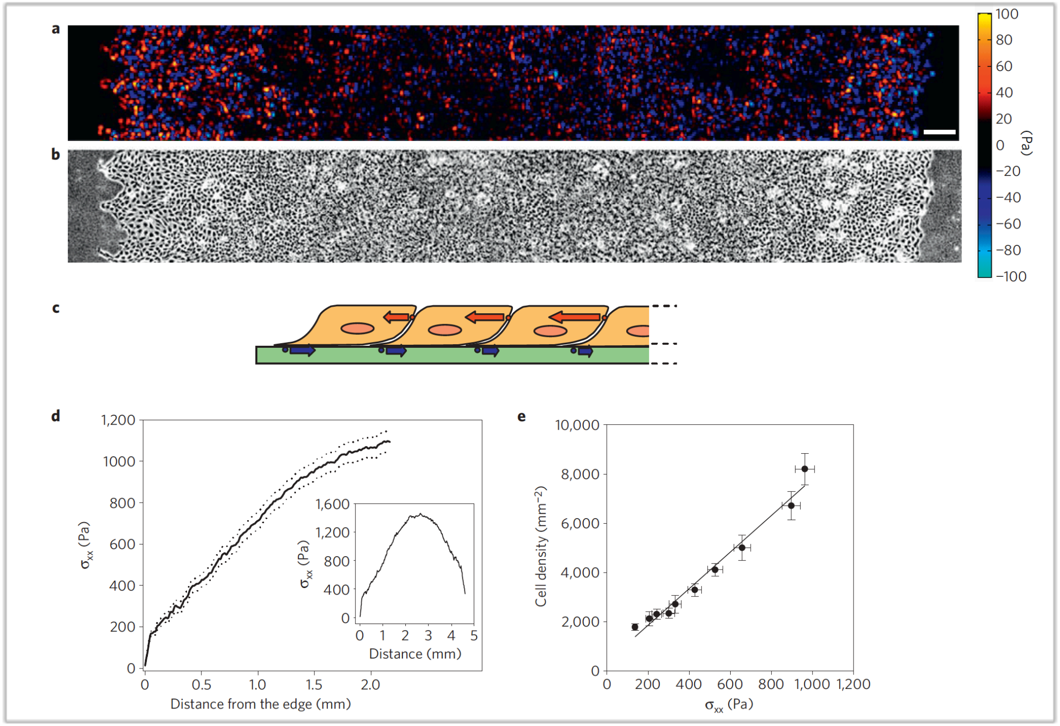
- Furthermore the Colony is under ***tension***



Trepat et al. (2009). Nat. Phys. 5, 426

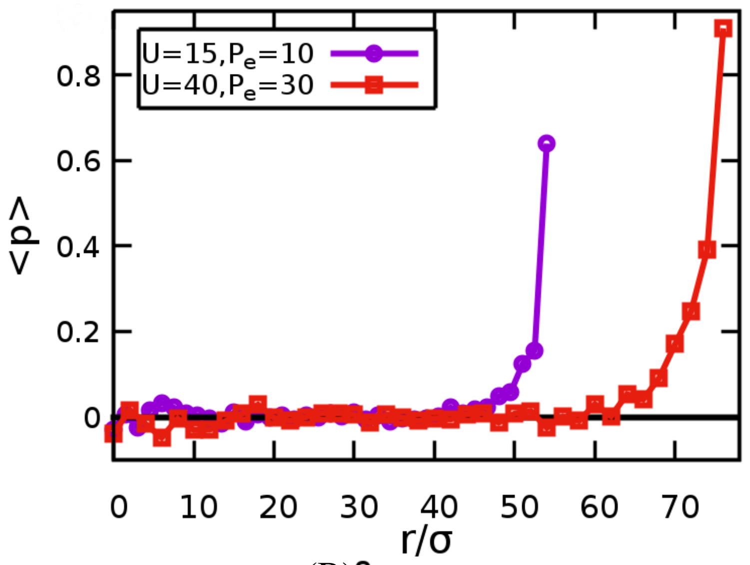
STRESS PROFILE

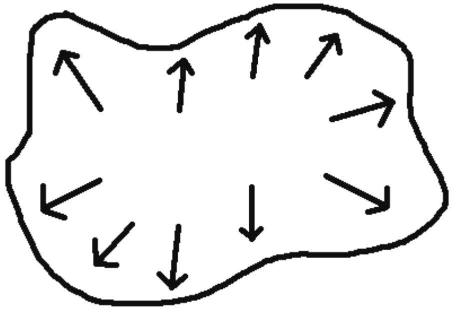
Polarity

Polarisation is defined as,

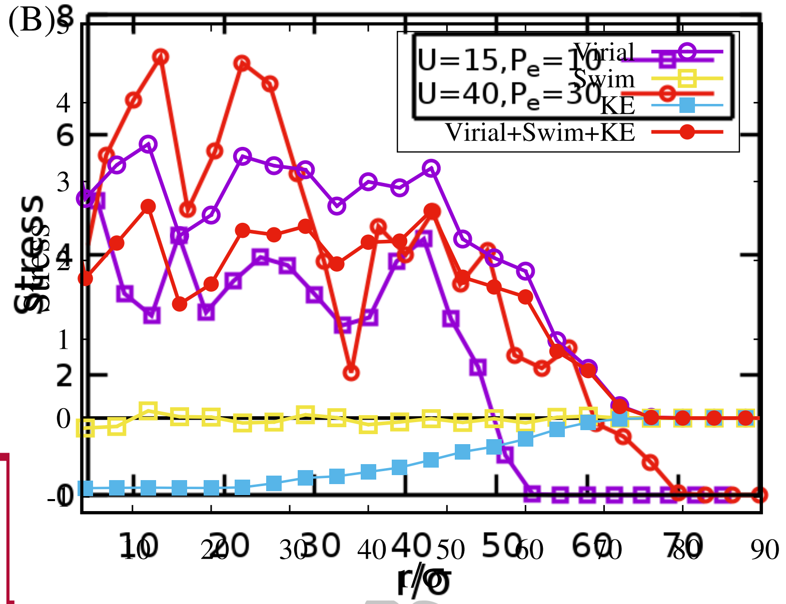
$$\langle p \rangle = \frac{1}{N} \sum_{i=1}^{N} (\hat{\mathbf{n}}_i \, . \, \hat{\mathbf{r}}'_i) \quad \text{here,} \quad \mathbf{r}'_i = \mathbf{r}_i - \mathbf{r}_{cm}$$

- Due to fluidity, **outward** alignment of mobility forces at the boundary of cell colony





Stress profile



Stress Ω

- Stress is **positive**, hence **tensile** in nature.

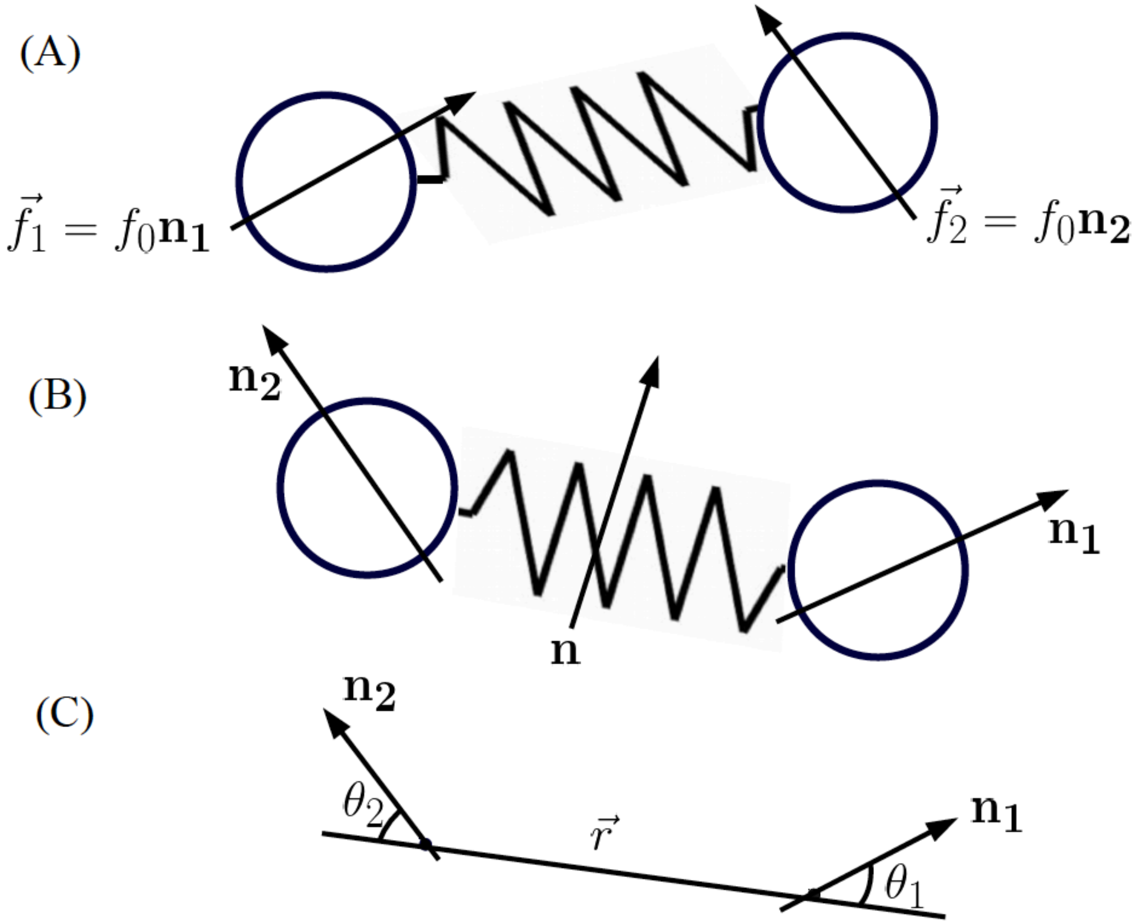
Fluidity ➜ Outward alignment of active force ➜ Tensile stress

THE ORIGIN OF TENSION

- Two ABPs + Spring
- Simple all-state average yields Average Tension:

$$< f_{ext} > = \frac{2f_0}{\pi}$$

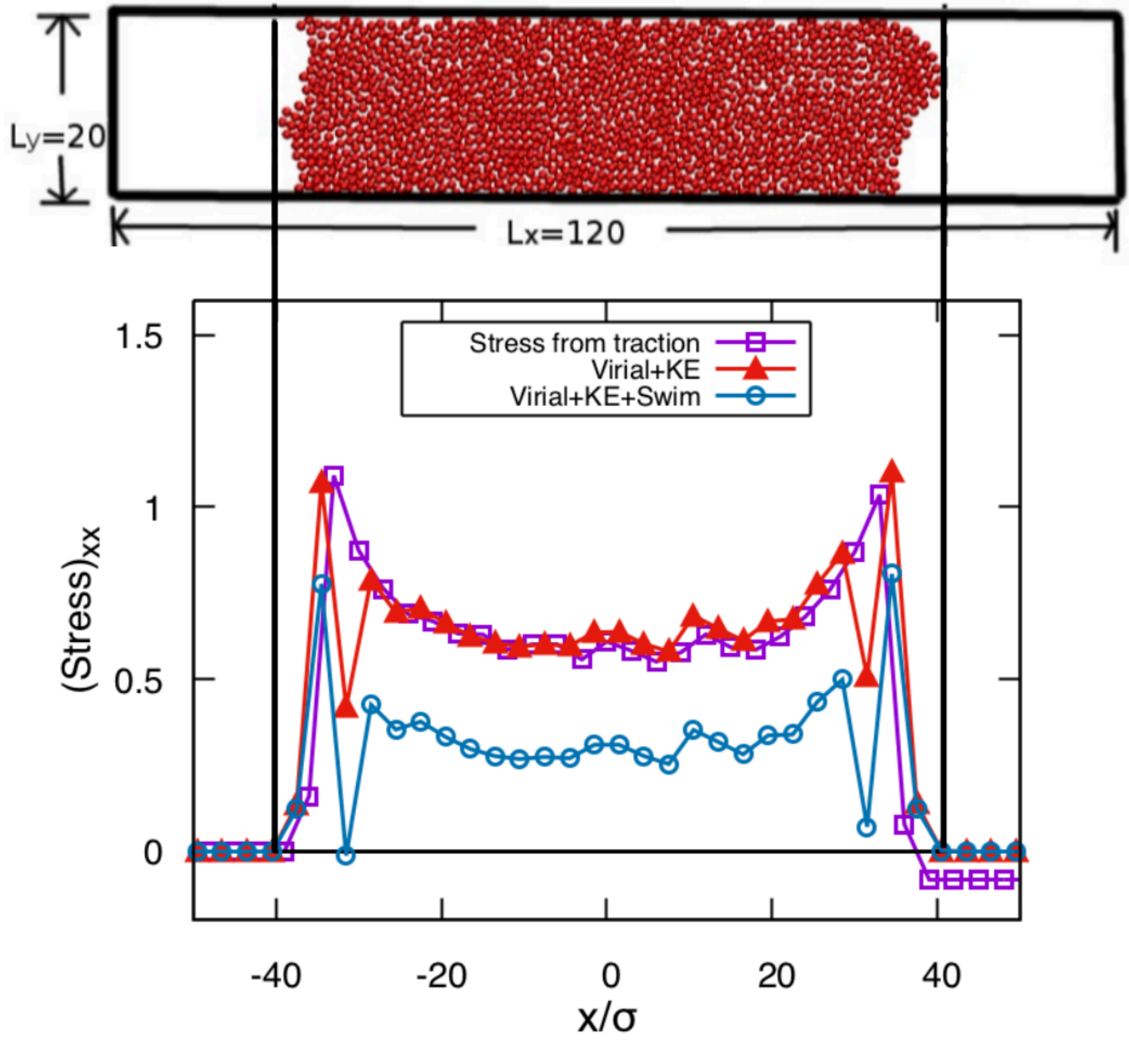
- Origin: Dumbells aligne such that the radial force component points outward



Sarkar, Gompper, **Elgeti**: Com. Phys. (2021)

A NOTE ON STRESS:

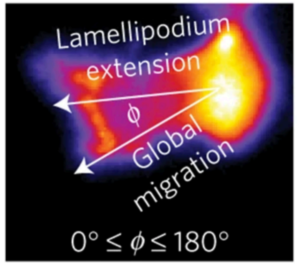
- Definition of Stress in ABP-Systems is non-unique in the literature
- Disagreement on role of active contributions
- Passive contributions (KE + Virial) clear
- The underlying physical system is important:
  Here a ***cell crawling on a substrate!***
- We discuss the stress in the cell layer
  => Force balance can define the stress



Sarkar, Gompper, **Elgeti**: Com. Phys. (2021)

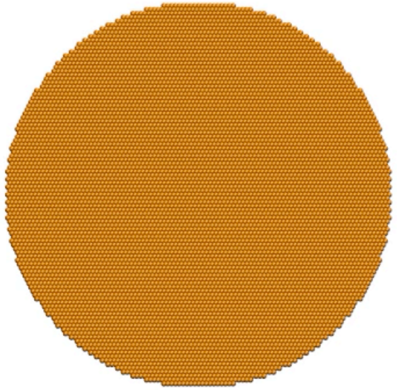
VELOCITY ALIGNEMENT INTERACTIONS

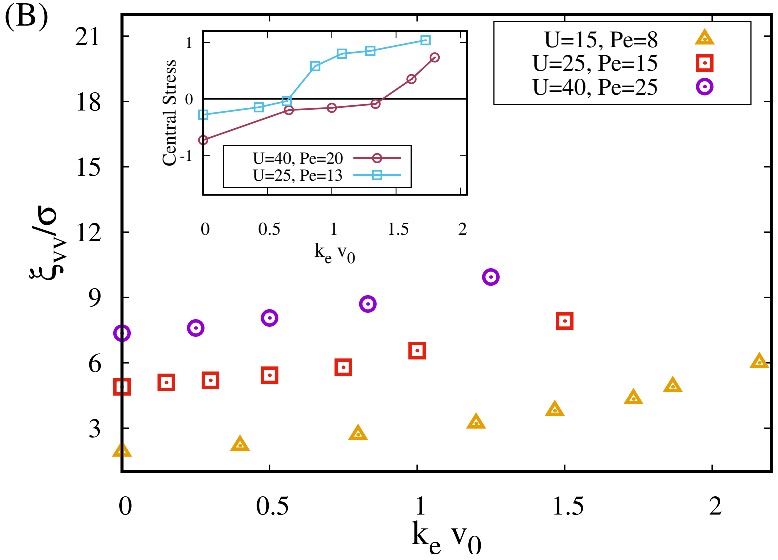
- Alignement of direction with velocity
  $$\dot{\theta}_i = \sqrt{2D_r}\eta_i^R - k_e D_r \frac{\partial}{\partial\theta}(\mathbf{n}_i \, . \, \mathbf{v}_i)$$
- Enhances effects, and leads to more "cell like" behavior
- Longer correlation lengths
- Larger clusters detaching
- More tension

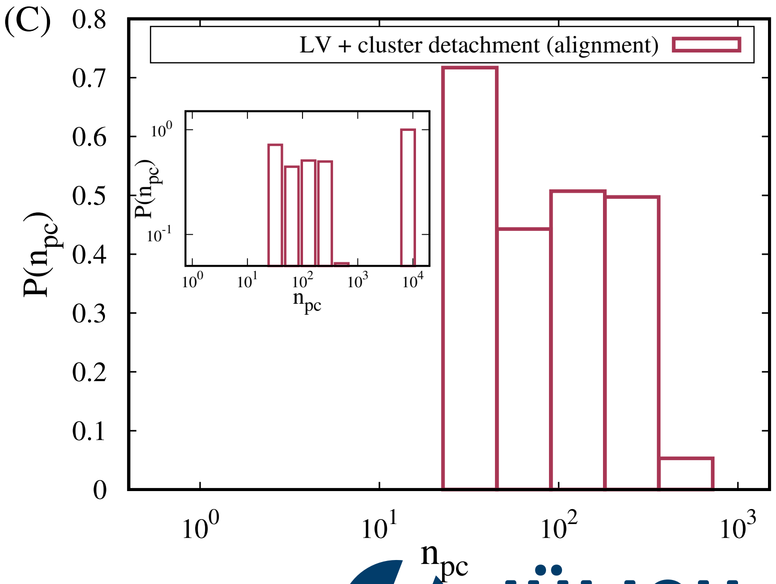


compare talk from Roberto Cerbino yesterday

Malinverno et al. Nat. Mat. (2017)



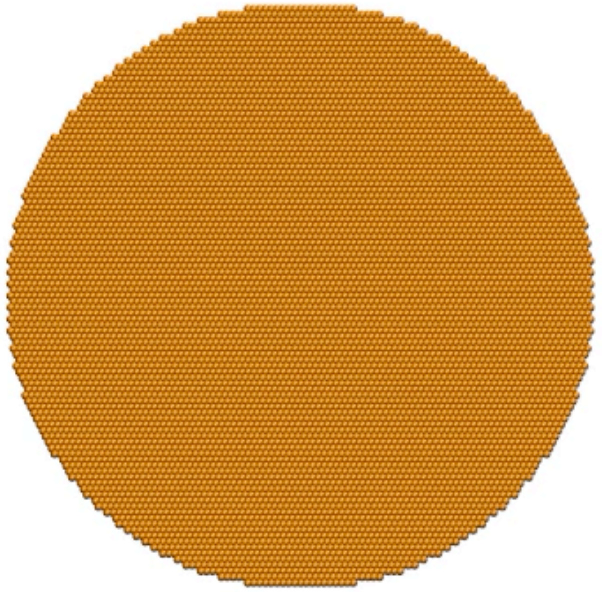




Sarkar, Gompper, **Elgeti**: Com. Phys. (2021)

SECOND CONCLUSIONS

- Liquid-"Vacuum" coexistence in a simple ABP Model
- Tension arises naturally
- "Cells" detach in clusters
- Velocity alignement enhances these effects



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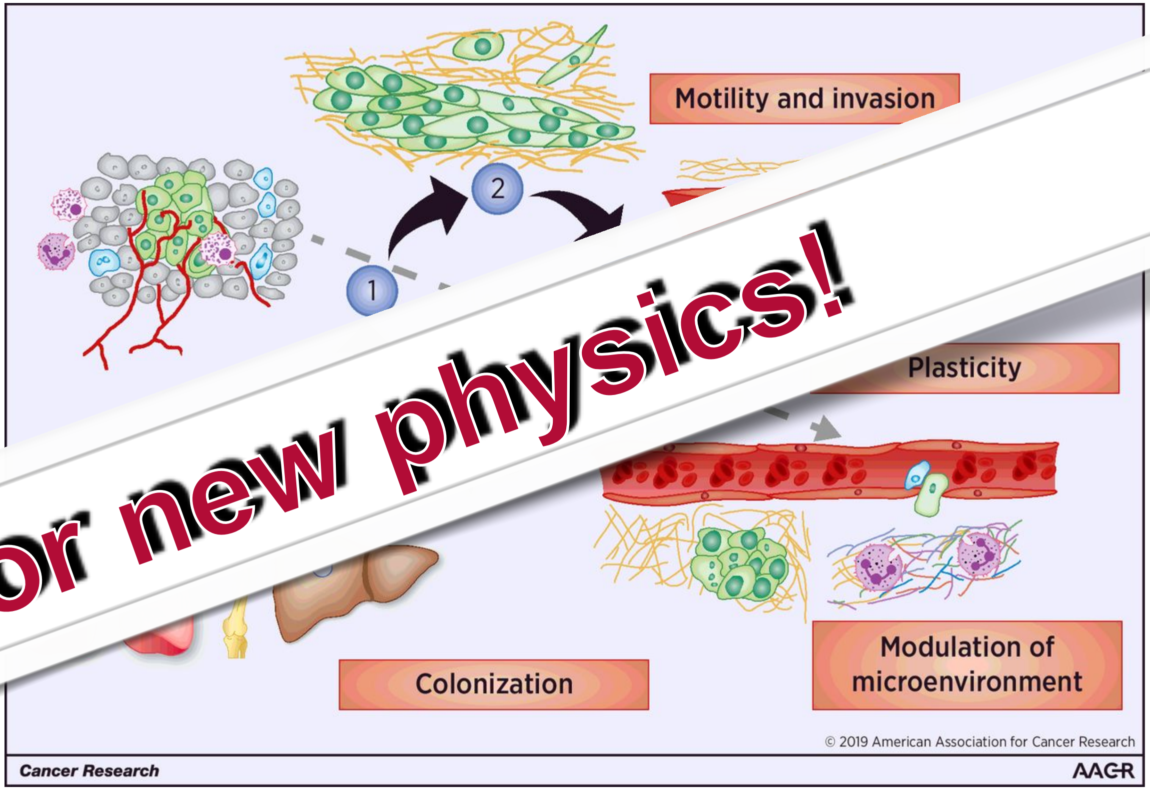
THE BIG QUESTION

- What happens if we combine growth and motility?
- Does motility induced tension help growth?
- Can a ”cost” of motility be over-compensated due to mechanical advantages?
- How does the met… evolve?



Welch and Hurst (2019). Cancer Research 79, 12

- **Lots of room for new physics!**

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THANKS

Support

- IBI-5: Theoretical Physics of Living Matter
- Computing Time: JARA-HPC VSR-Grant jics23 & jiff26
- Priority Programme SPP 1726
- Helmholtz-Society/FZJ

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- Sebastian Rode
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- Lucas Campos
- Özer Duman
- Tobias Büscher
- Nils Podewitz
- Guglielmo Saggiorato
- Nirmalendu Ganai
- Rolf Isele-Holder
- Debarati Sarkar

Let’s talk!!!

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