

Emergence and Self-Organisation in Biological Systems

Erwin Frey

Arnold Sommerfeld Center
for Theoretical Physics

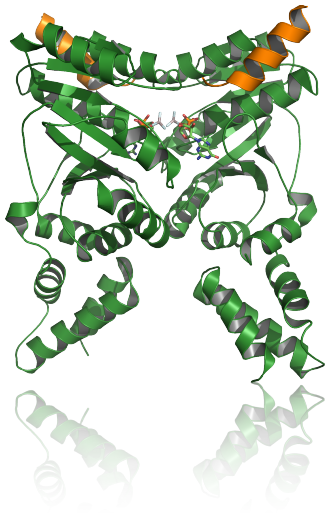


Living matter, while not eluding the 'laws of physics'...is likely to involve 'other laws of physics', hitherto unknown, which, however, once they have been revealed, will form just as integral a part of this science as the former.



Erwin Schrödinger in "What is Life?"

The elementary building blocks of life

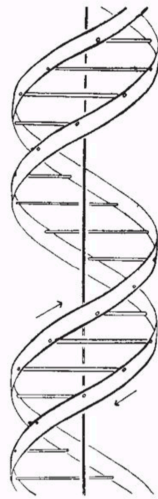


Proteins

Structures

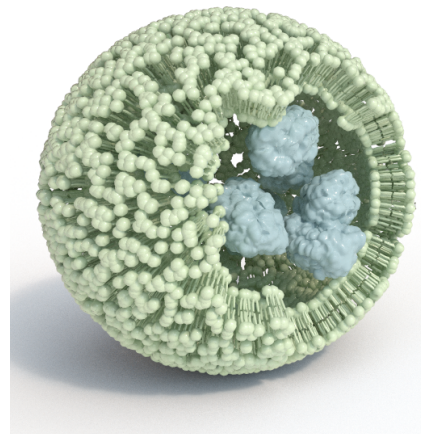
Motors

Chemical
reactions



DNA

Information

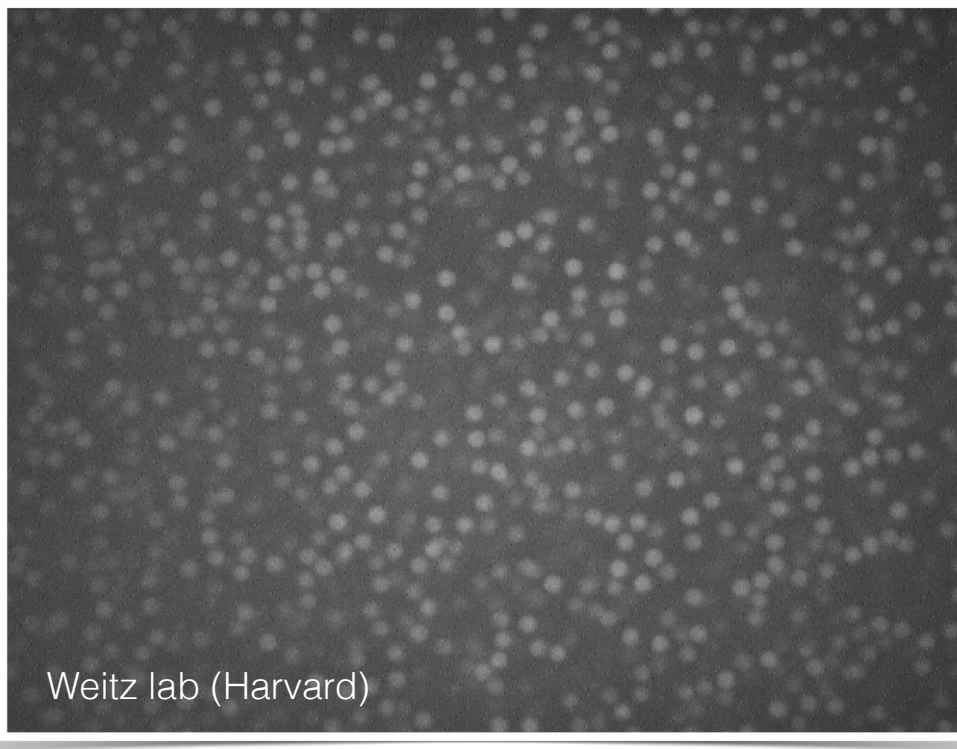


Lipide

Cell membrane

Signal transduction

What is the world like at the scale of a cell?



Brownian Motion



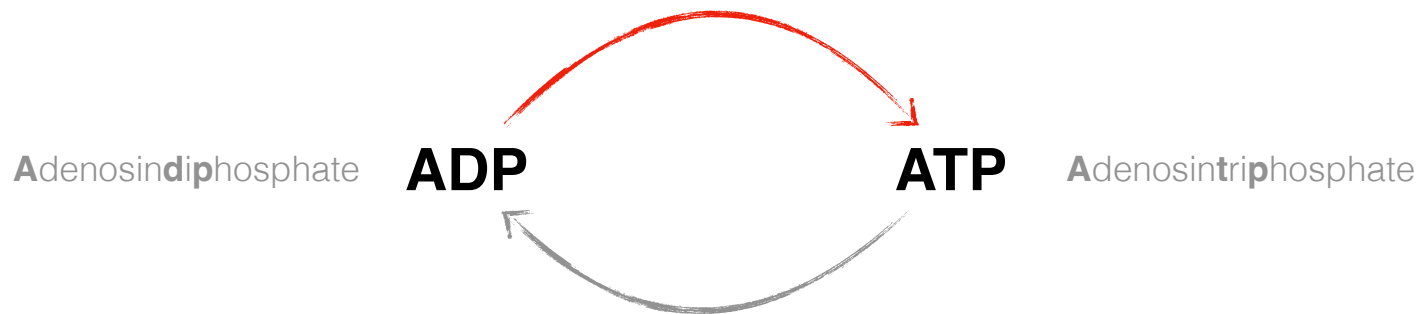
Robert Brown

Before my voyage on the Beagle, Brown asked me to look through a microscope and describe what I saw. [...]

I then asked him what it was that I had seen, but he replied, "That is my little secret."

Charles Darwin

ATP: the energy currency of life



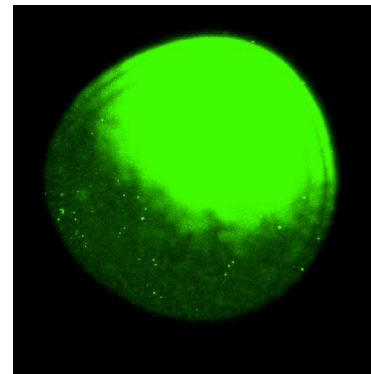
Force generation



Molecular motors

<https://www.youtube.com/watch?v=YAv4g3Pk6k>

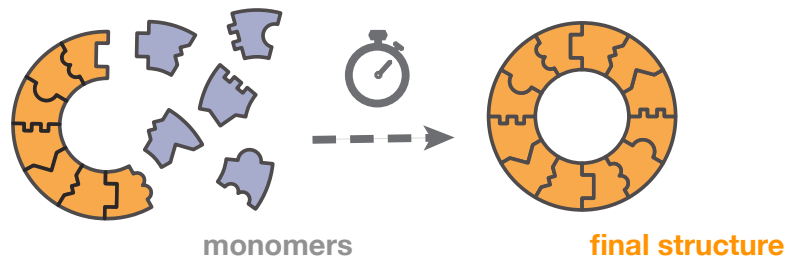
Chemical switch



Chemical reaction networks

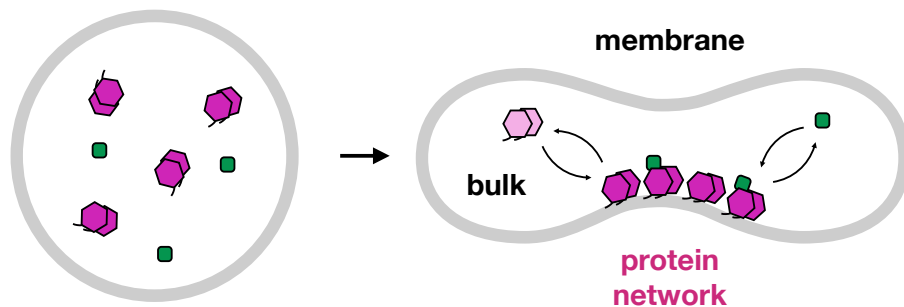
M. C. Wigbers*, T. H. Tan*, ...
E. Frey & N. Fakhri , Nature Physics 2021

Self-assembly of biomolecular structures



What is the time complexity of self-assembly kinetics in forming biomolecular structures?

Protein pattern formation



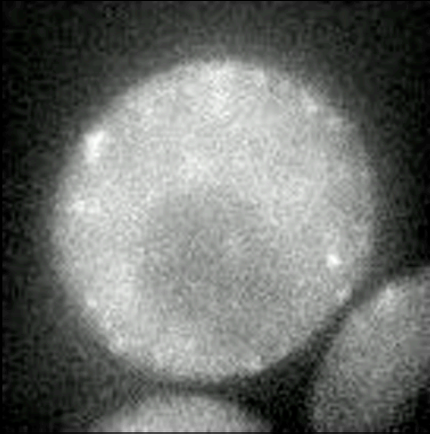
How do protein patterns within a cell self-organize in space and time?

Two things fill the mind with ever new and increasing reverence and awe, the more it reflects upon them:

The starry heavens above me
and the moral law within me.

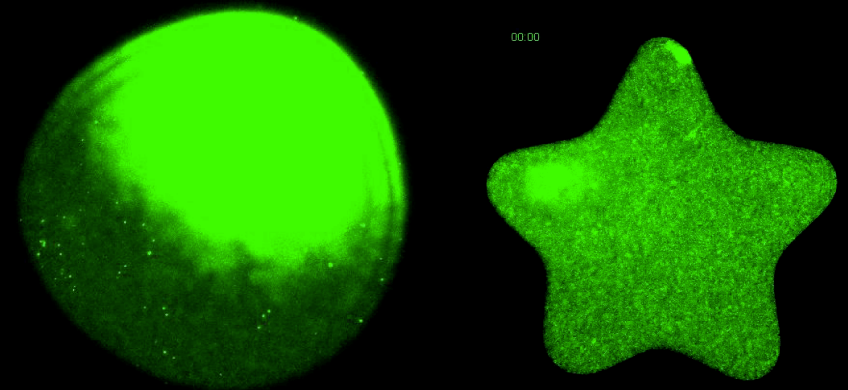
Immanuel Kant (Kritik der praktischen Vernunft)

Cell polarity of yeast



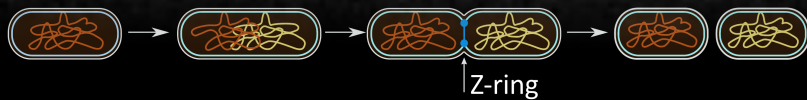
F. Brauns, ... L. Laan & E. Frey, Nature Comm. (2023)

Starfish oocytes



Manon C. Wigbers* Tzer Han Tan*, ...
E. Frey & N. Fakhri, Nature Physics (2021)

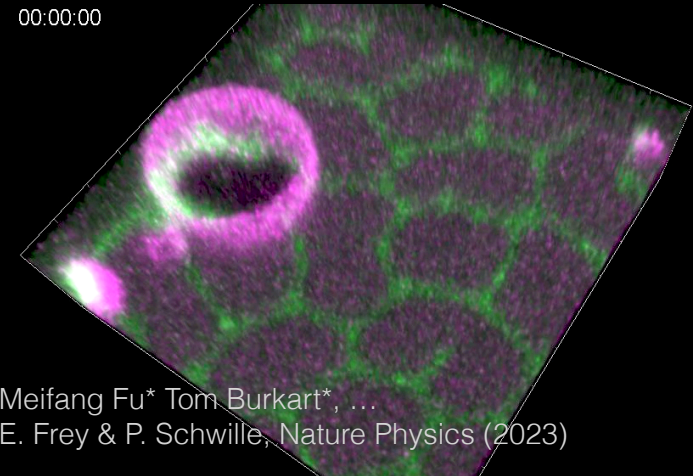
Min oscillations in *E. coli*



Z. Ren*, H. Weyer*, M. Sandler*, L. Würthner* ...,
E. Frey & S. Jun, Nature Physics (2025)

Synthetic cell motility

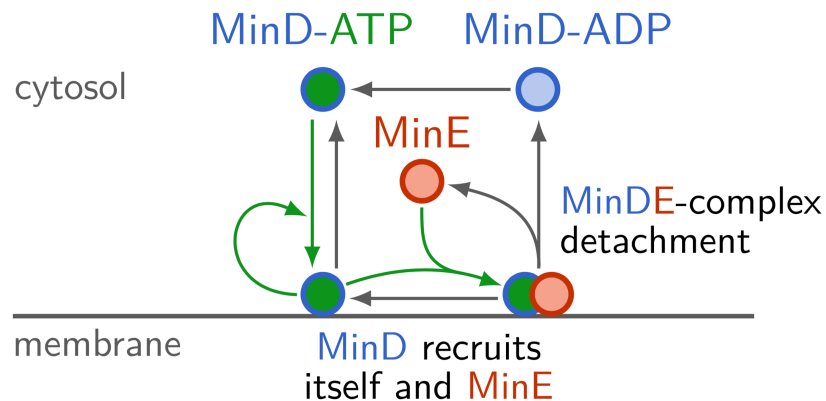
00:00:00



Meifang Fu* Tom Burkart*, ...
E. Frey & P. Schwill, Nature Physics (2023)

Design features of biochemical reaction networks

Two protein species drive the dynamics: **MinD** & **MinE**



Generic 'design' features:

- ▶ driven by NTPase
- ▶ cycling fluxes between states
- ▶ cycling between membrane and cytosol

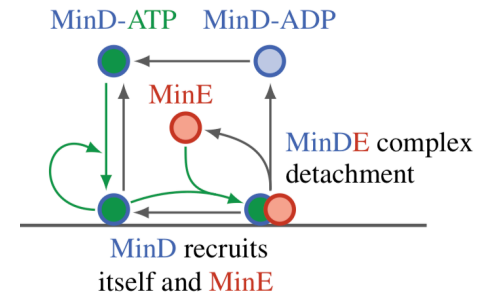
T. Burkart*, M.C. Wigbers*, L. Würthner*, & E. Frey, Nat. Rev. Phys. 4, 511–527 (2022)
J. Halatek, F. Brauns & E. Frey, Phil. Trans. R. Soc. B 373, 20170107 (2018)

What would one like to know?

What is the role of the reaction network?

Denk, Kretschmer, Halatek, Schwille & Frey, PNAS 2018

Ren, Weyer, Sandler, Würthner, ..., Frey & Jun, Nature Physics 2025



Can patterns sense cell geometry?

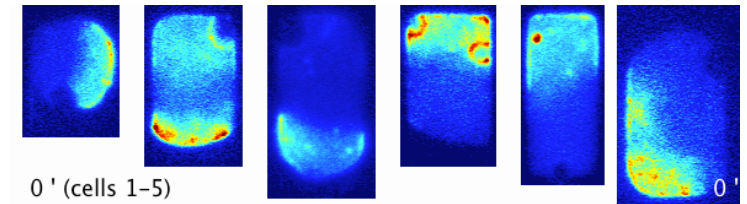
Thalmeier, Halatek, & Frey, PNAS 2016

Wu, Halatek, ..., Frey & Dekker, Mol. Sys. Biol. 2016

Geßele, ..., Frey, Nature Comm. 2020

Brauns, Pawlik, ..., Frey & Dekker, Nature Comm. 2021

Würthner, Brauns, ..., Dekker & Frey, PNAS 2022



Are there some general principles and new laws?

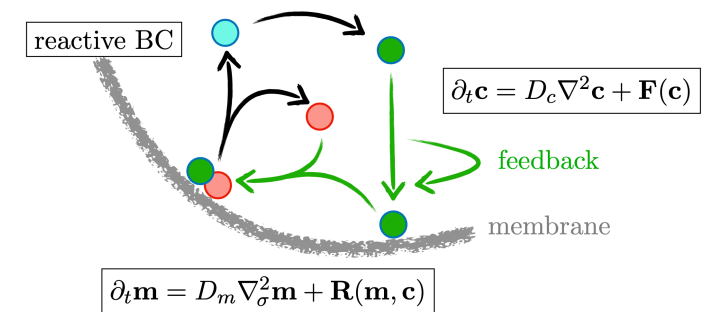
Halatek & Frey, Nature Physics 2018

Brauns, Halatek & Frey, Phys. Rev. X 2020

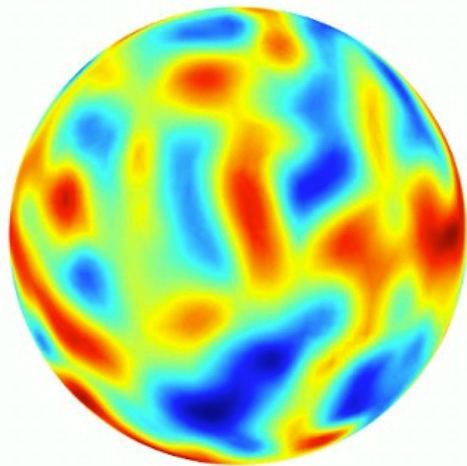
Halatek, Brauns & Frey, Phil. Trans. R. Soc. B 2018

Brauns, Weyer et al., Phys. Rev. Lett. 2021

Weyer, Roth & Frey, Nature Physics 2025



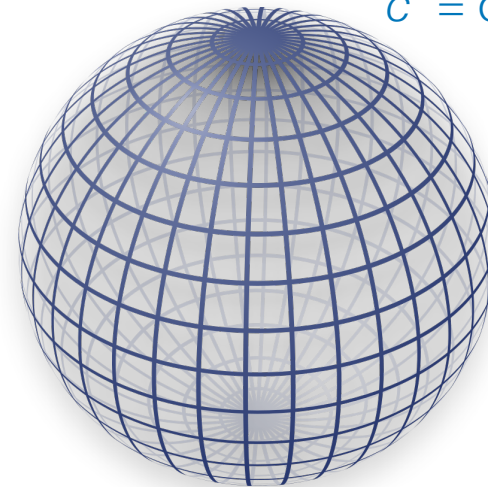
Molecular model



Finite Element Simulations

Freisinger et al., Nature Comm. (2013)
Klunder et al. PLoS Comp. Biol. (2013)

Conceptual model



m = membrane density
 c = cytosolic density

one protein species

Brauns, Halatek & Frey, Phys. Rev. X (2020)
Brauns, Weyer et al., Phys. Rev. Lett. (2021)

Conceptual two-component model

Conceptual two-component model for protein pattern formation

protein mass: $n = m + c$

m = membrane density

c = cytosolic density

$$\partial_t m = f(m, c) + D_m \nabla^2 m$$

$$\partial_t c = g(m, c) + D_c \nabla^2 c$$

A.M. Turing, *The chemical basis of morphogenesis*,
Phil. Trans. Roy. Soc. London 237, 37-72 (1952)

Conceptual two-component model

Conceptual two-component model for protein pattern formation

protein mass: $n = m + c$

m = membrane density

c = cytosolic density

$$\partial_t m = +f(m, c) + D_m \nabla^2 m$$

$$\partial_t c = -f(m, c) + D_c \nabla^2 c$$

mass-conserving diffusion-reaction equations

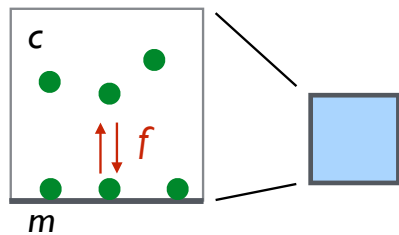
$$\partial_t n(x, t) = D_c \partial_x^2 c(x, t) + D_m \partial_x^2 m(x, t) \equiv D_c \nabla^2 \eta$$

$$\partial_t \eta = (D_m + D_c) \nabla^2 \eta - D_m \nabla^2 n - \tilde{f}$$

J. Halatek & E. Frey, Nature Physics 2018;
F. Brauns, J. Halatek & E. Frey, Phys. Rev. X 2020

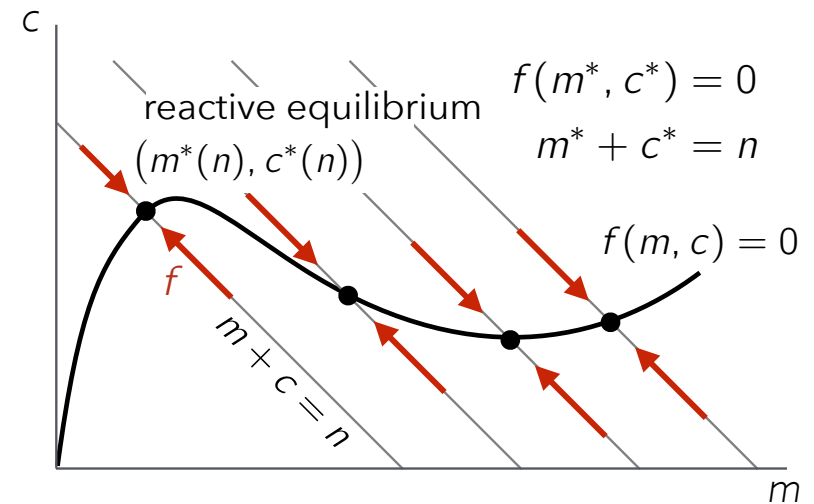
Phase space analysis

Well-mixed compartment



$$f(m, c) = a(m)c - d(m)m$$

membrane $\partial_t m = +f(m, c)$
 cytosol $\partial_t c = -f(m, c)$
 $m + c = n = \text{const.}$



Two diffusively coupled compartments



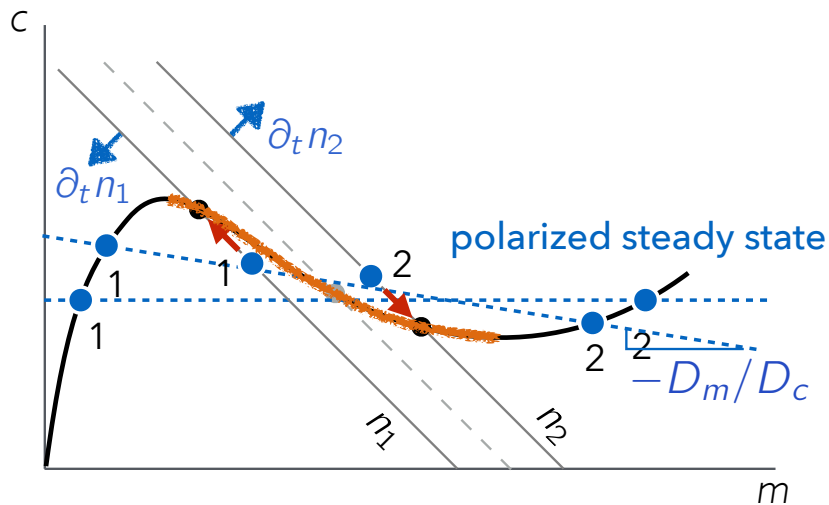
diffusive mass exchange

$$D_c \gg D_m$$

$$\partial_t n_1 = \mathcal{D}_c(c_2 - c_1) + D_m(m_2 - m_1)$$

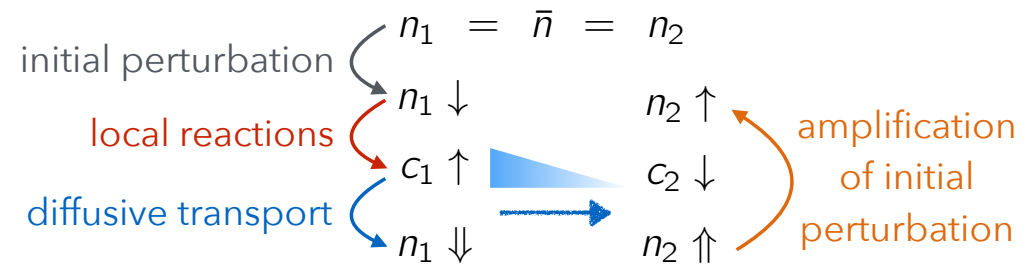
$$\partial_t n_2 = -\partial_t n_1$$

$$n_1 + n_2 = 2\bar{n} = \text{const.}$$



- Local masses are parameters for the local reactive dynamics (**local equilibria**)
- Local masses are variables, governed by **diffusive mass exchange**

How do patterns emerge?

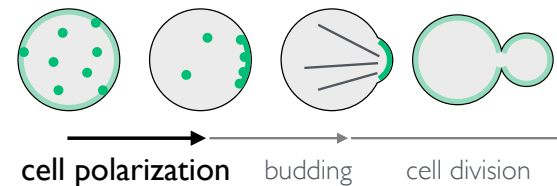


$$\partial_m c^*(m) < 0$$

$\Rightarrow$

mass-redistribution instability
symmetry breaking / cell polarization

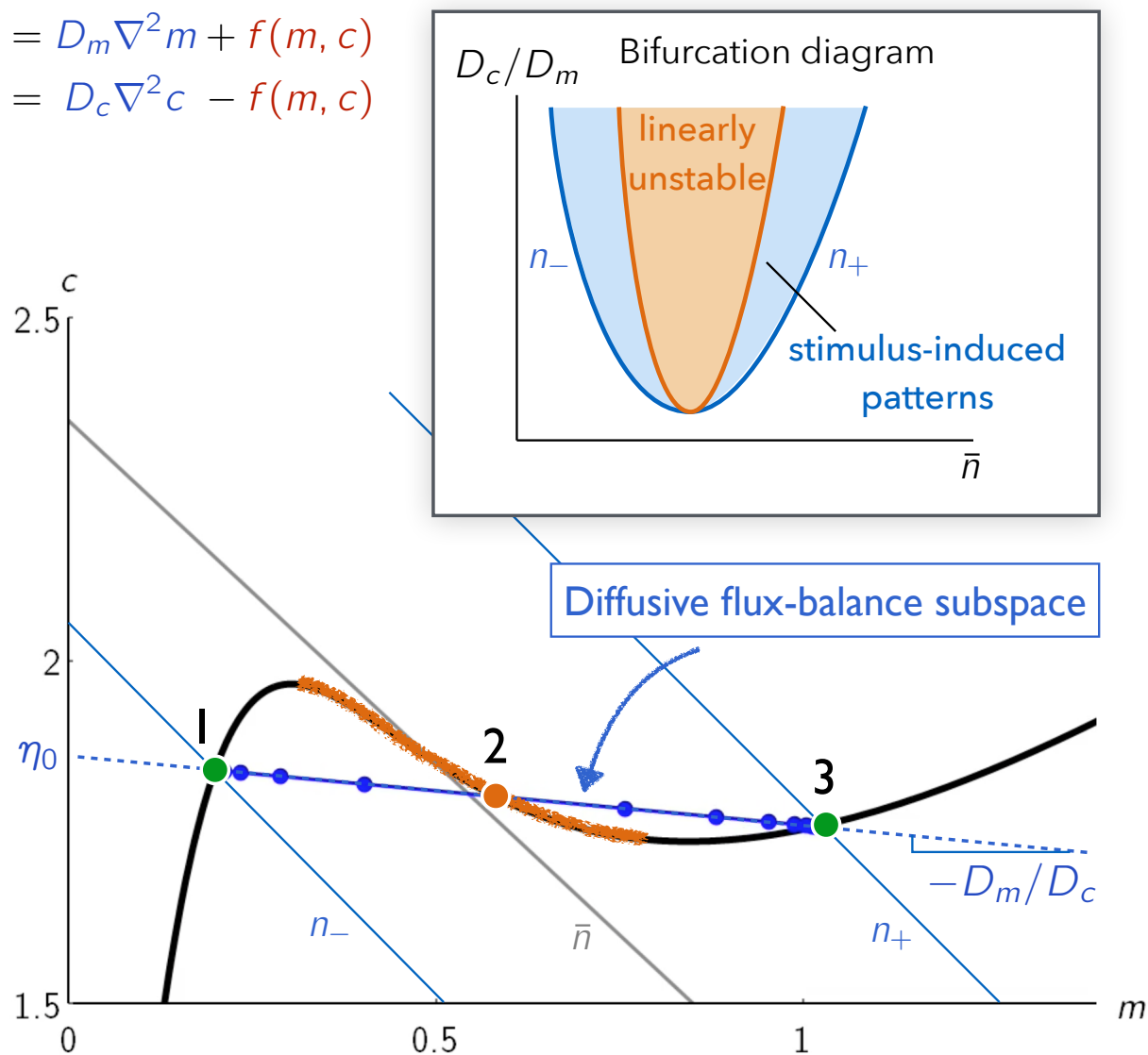
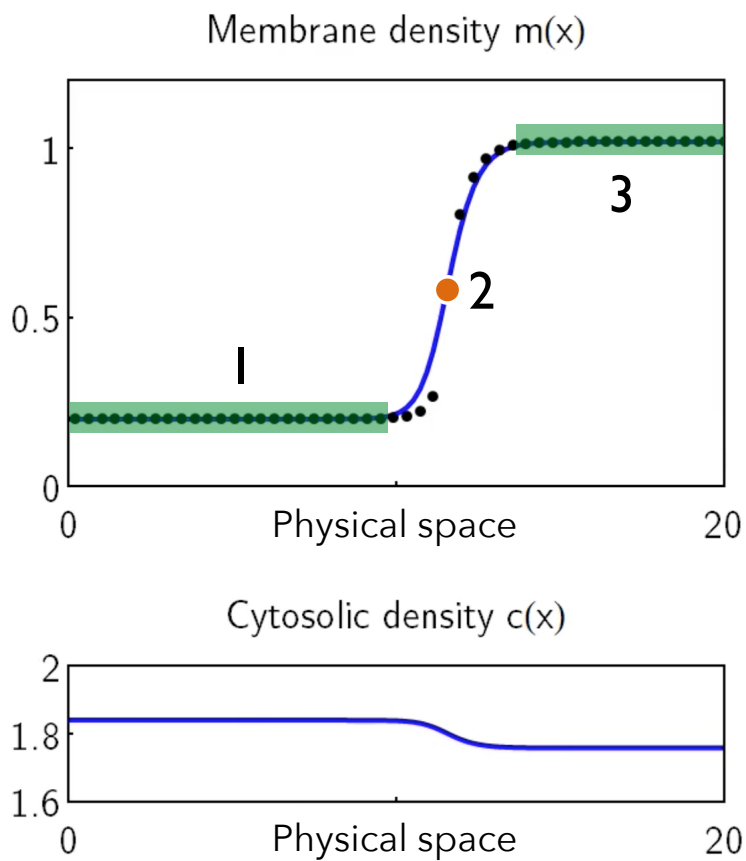
General mechanism giving rise to protein-based patterns.



Continuous system

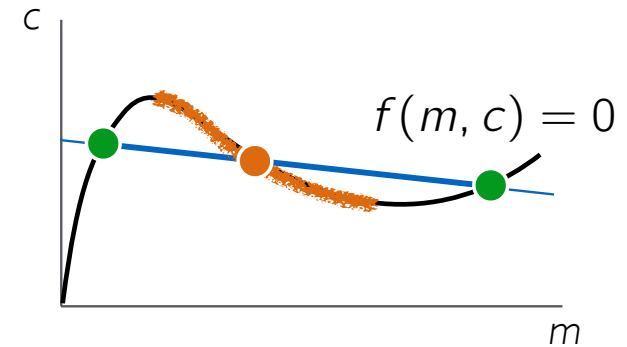
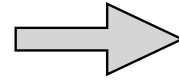
$$\begin{aligned}\partial_t m(x, t) &= D_m \nabla^2 m + f(m, c) \\ \partial_t c(x, t) &= D_c \nabla^2 c - f(m, c)\end{aligned}$$

$$\partial_t c(x, t) = D_c \nabla^2 c - f(m, c)$$



Conceptual Insights

$$\begin{aligned}\partial_t m(x, t) &= D_m \nabla^2 m + f(m, c) \\ \partial_t c(x, t) &= D_c \nabla^2 c - f(m, c)\end{aligned}$$



Why do proteins self-organize into concentration patterns?

Mass-redistribution instability $\partial_m c^*(m) < 0$

Geometric classification of instabilities

What determines the patterns' properties?

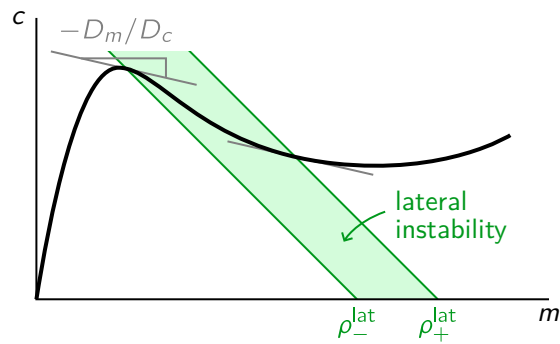
Local reactive equilibria & diffusive mass transport

Local equilibria theory: conserved protein masses drive dynamics

Geometric Constructions

$$\partial_t m_\alpha(\mathbf{x}, t) = D_m^\alpha \nabla^2 m_\alpha + f_\alpha(\mathbf{m}, \mathbf{c})$$

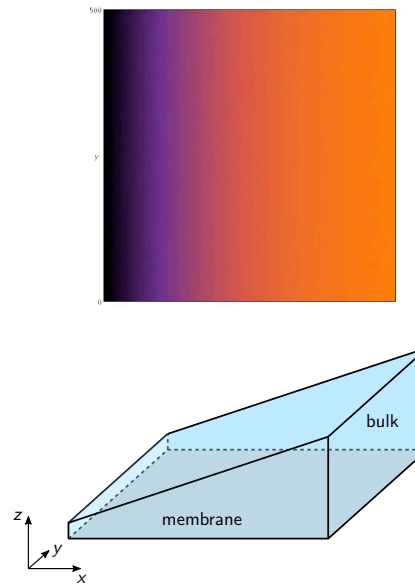
$$\partial_t c_\alpha(\mathbf{x}, t) = D_c^\alpha \nabla^2 c_\alpha - f_\alpha(\mathbf{m}, \mathbf{c})$$



F. Brauns, J. Halatek & E. Frey, Phys. Rev. X 2020

Poster by **Ching Yee Leung**: *Generic Criteria for Pattern Formation in Multi-Component Protein Systems*

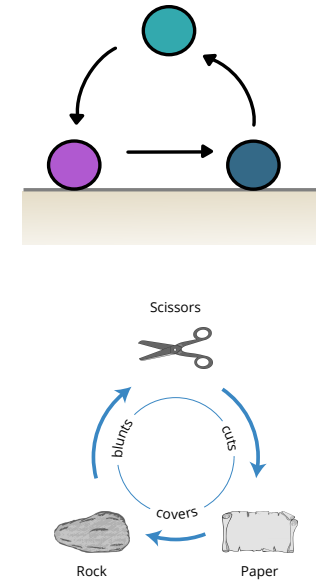
Geometry Sensing



L. Würthner, F. Brauns, ..., C. Dekker & E. Frey, PNAS (2022)

Poster by **Antonia Winter**: *Phase Separation on Deformable Membranes*

Make is as simples as ...

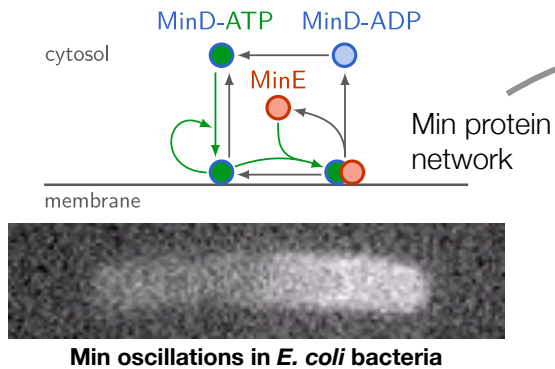


T. Reichenbach, M. Mobilia & E. Frey, Nature (2007)

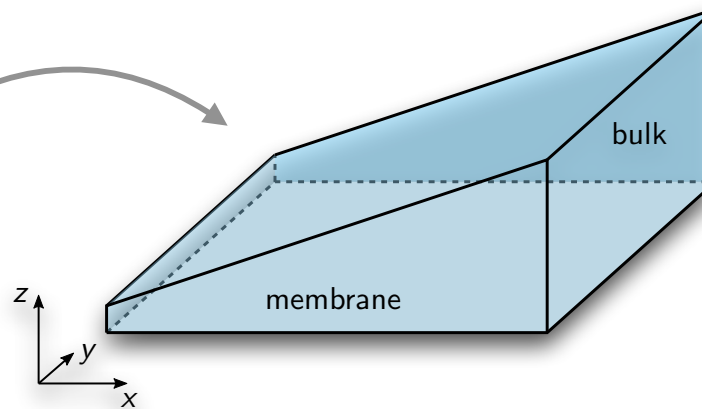
Poster by **Davide Toffenetti** and **Beatrice Nettuno** on *Theory of Pattern Formation in Multi Components Mass-Conserving Reaction-Diffusion System*

Local Equilibria Theory can forecast Complex Patterns

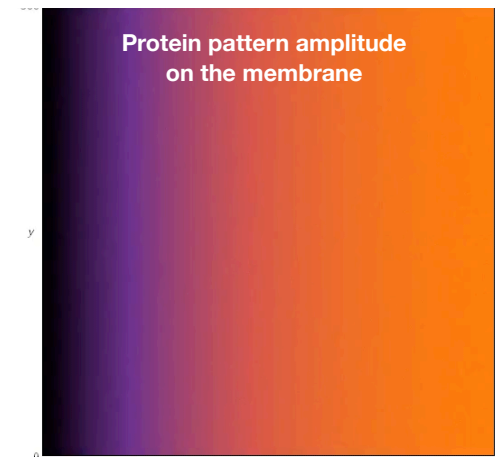
Bacterial cells



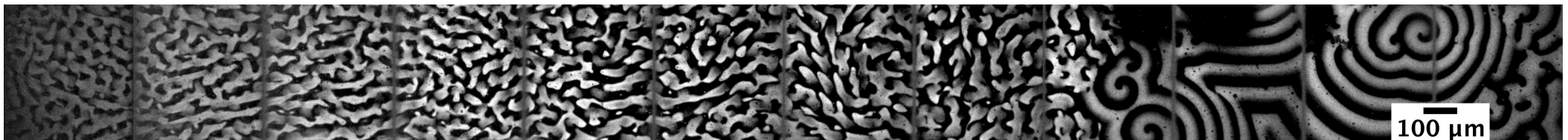
Reconstituted system



Numerical simulations



Experimental data



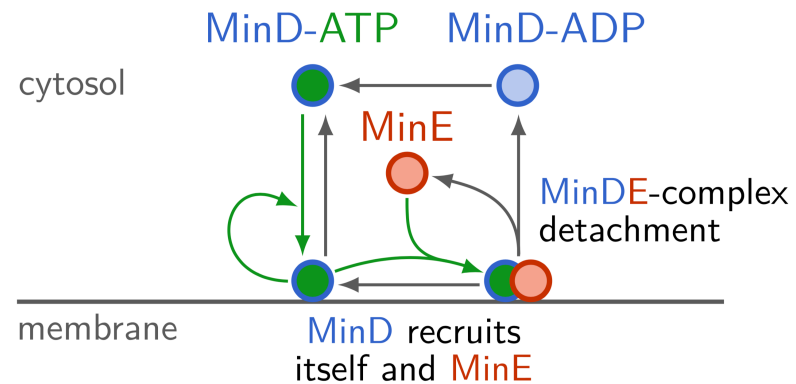
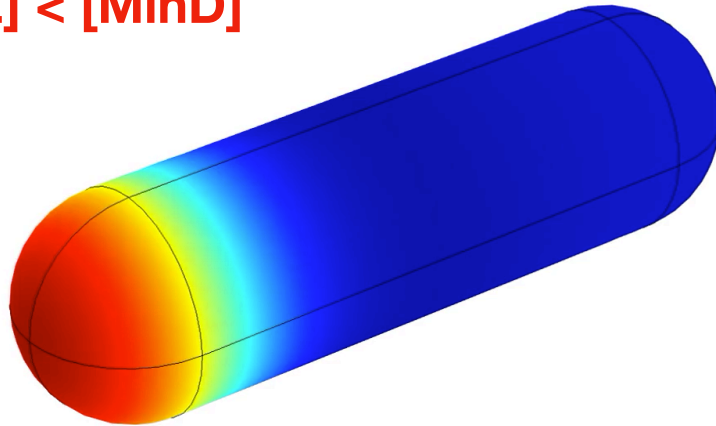
Bridging scales in a multiscale pattern-forming system, L. Würthner*, F. Brauns*, ..., C. Dekker & E. Frey, PNAS (2022)

F. Brauns*, J. Halatek*, and E. Frey, Phys. Rev. X 2020

How molecular is molecular?

Self-organised formation of attachment and detachment zones, that alternate due to the combined effect of 'recruitment' and an 'activation-deactivation' cycle.

[MinE] < [MinD]

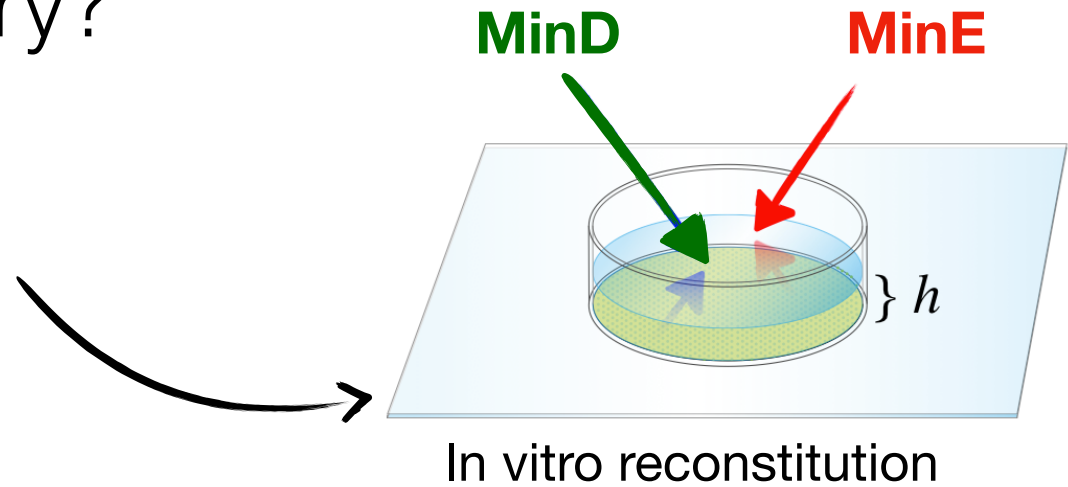


MinD dominance <-> MinE dominance

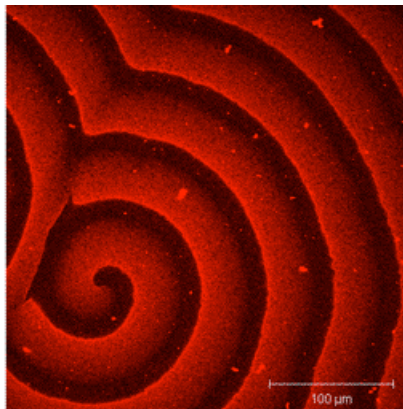
How to test the theory?



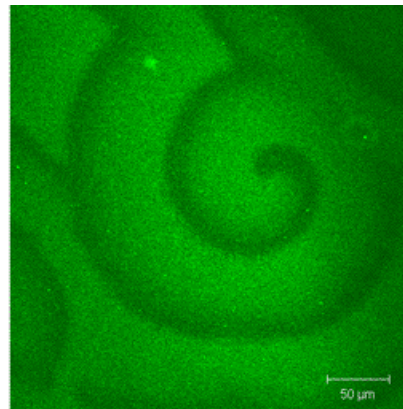
MinD & MinE



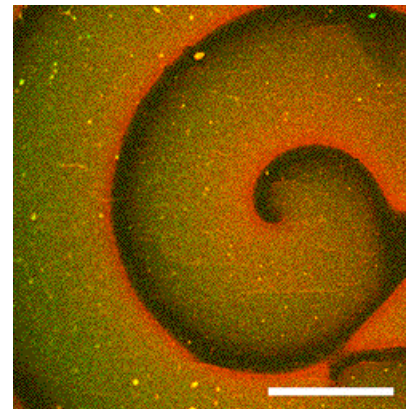
MinE



MinD



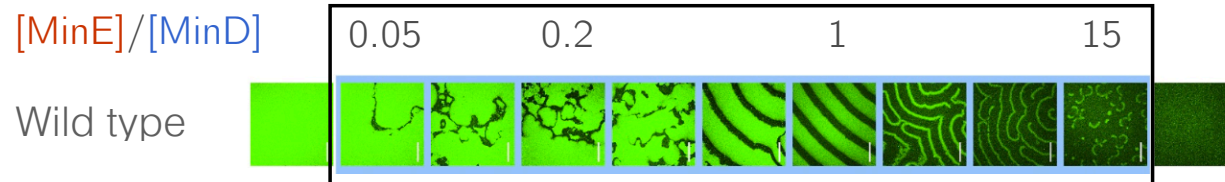
MinD & MinE



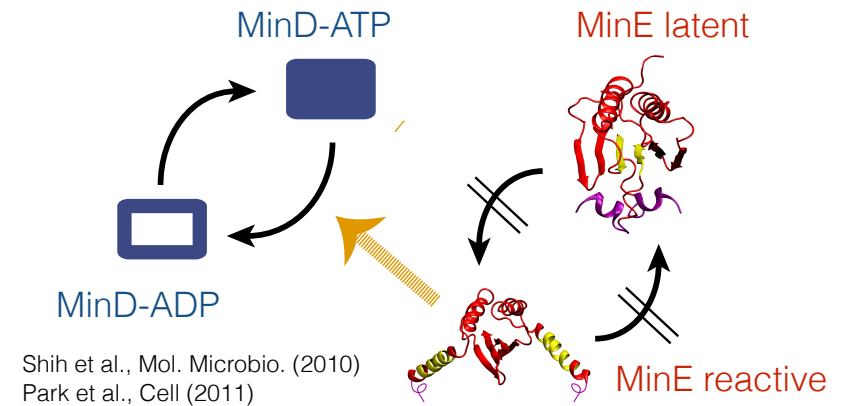
M. Loose, E. Fischer-Friedrich, J. Ries, K. Kruse & P. Schwille, Science 320, 789 (2008)

Pattern formation is robust!

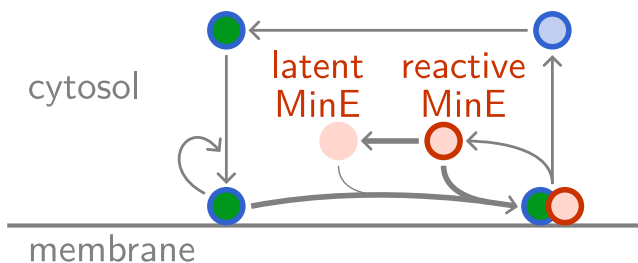
In vitro experiment



Structural biology



MinE-switch Model

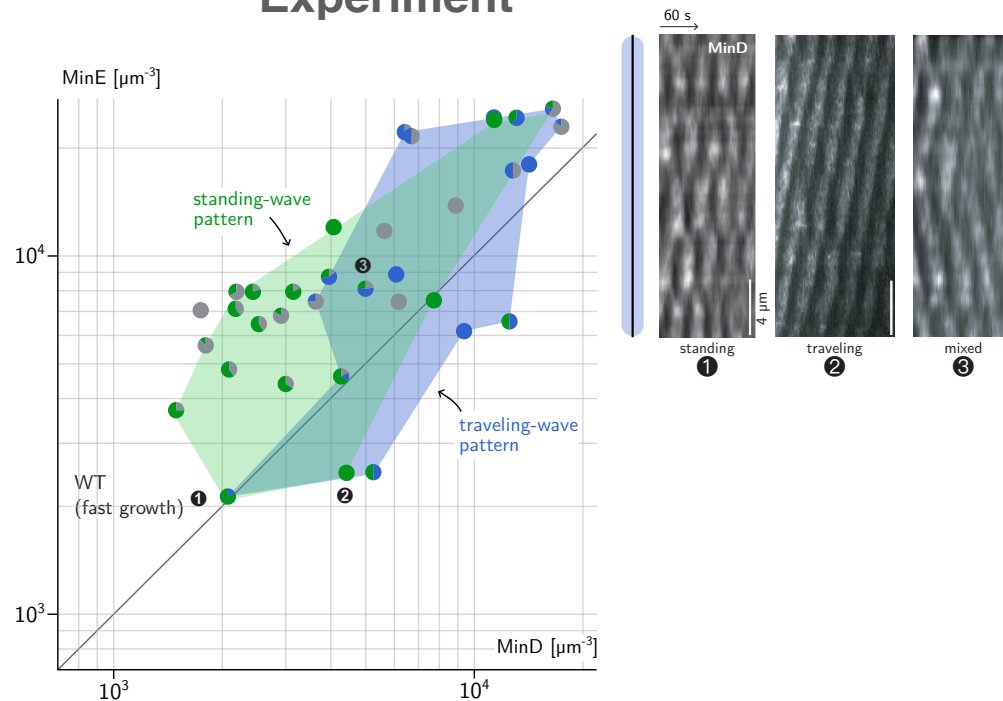


The latent MinE state serves as a buffer for high MinE concentrations.

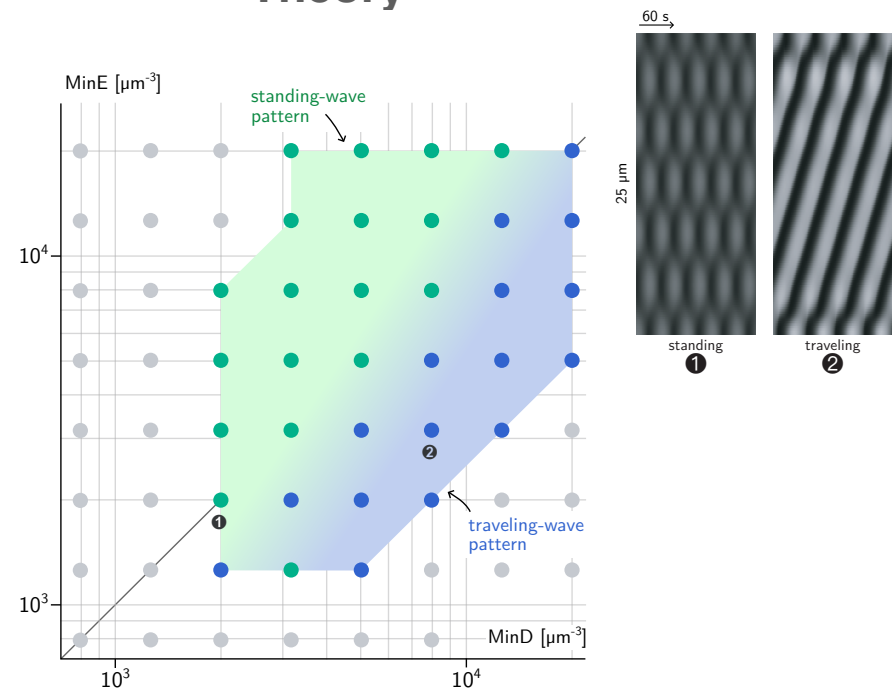
J. Denk*, S. Kretschmer*, J. Halatek*, ..., P. Schwille & E. Frey, PNAS 115, 4553 (2018)

In vivo phase diagram

Experiment



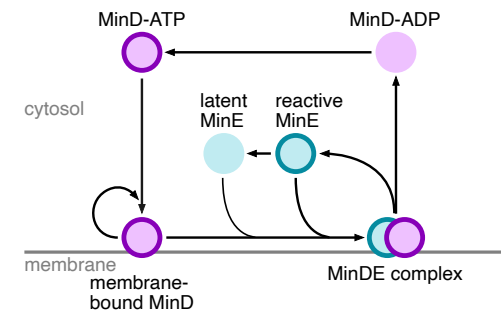
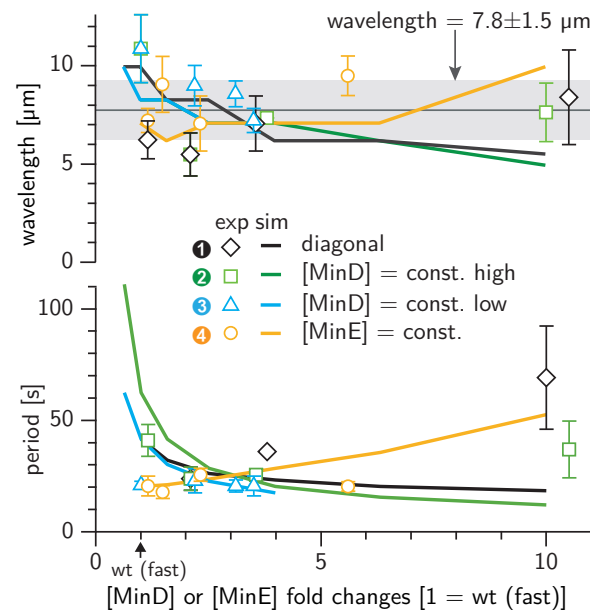
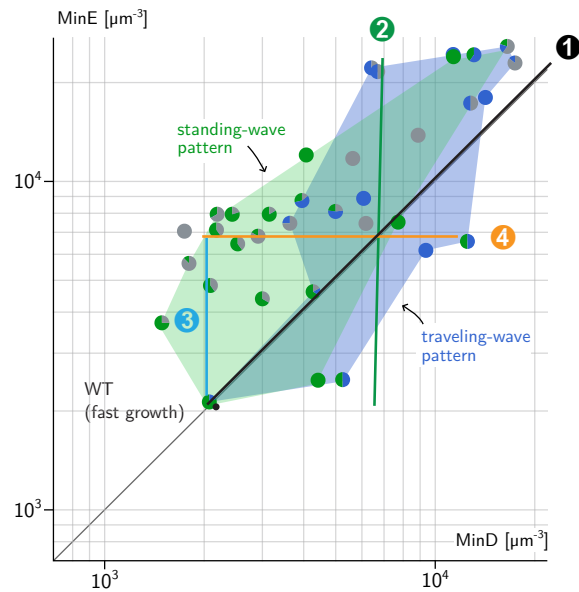
Theory



- ▶ Robust pattern formation
- ▶ Wild-type is resource-efficient
- ▶ MinE-switch model captures robustness and pattern types quantitatively

Z. Ren*, H. Weyer*, M. Sandler*, L. Würthner*, ..., E. Frey & S. Jun, Nature Physics (2025)

Oscillation period and wavelength of Min patterns



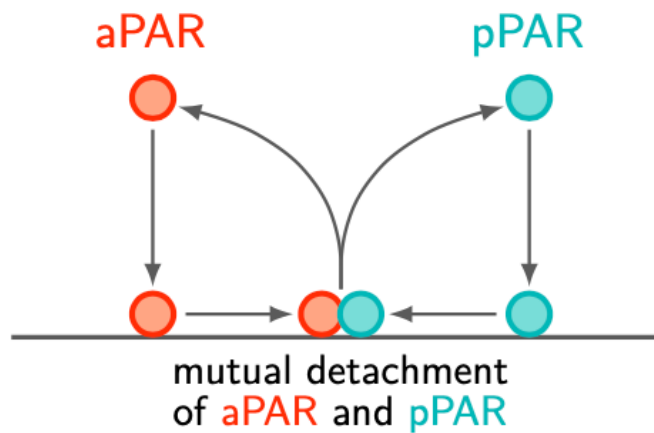
Constant wavelength throughout phase diagram: $\sim 8 \mu\text{m}$
Oscillation period decreases at larger MinE densities

MinE-switch model describes the key molecular interactions

Fully quantitative model explaining the biological process and its biological relevance.

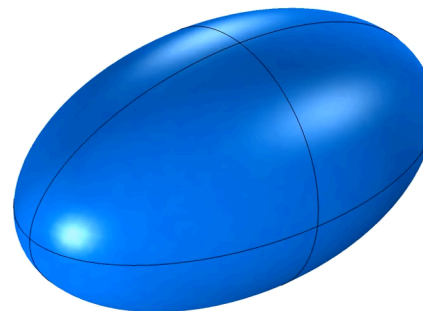
Is there novel non-equilibrium physics?

Interface dynamics in cells



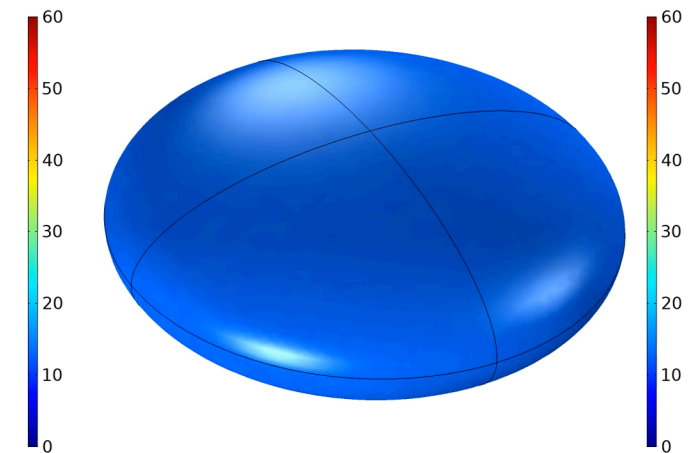
Time=0 s

Surface: ma1+ma12



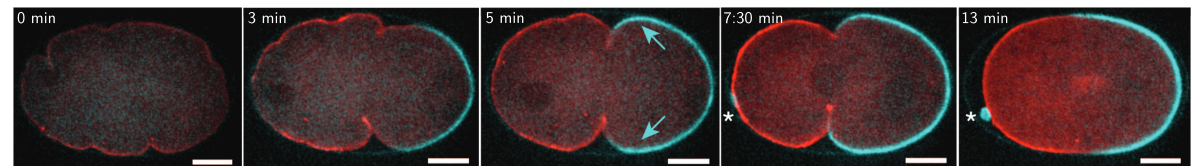
=0 s

Surface: ma1+ma12



PAR reaction–diffusion model

Goehring et al., Science 334, 1137 (2011)



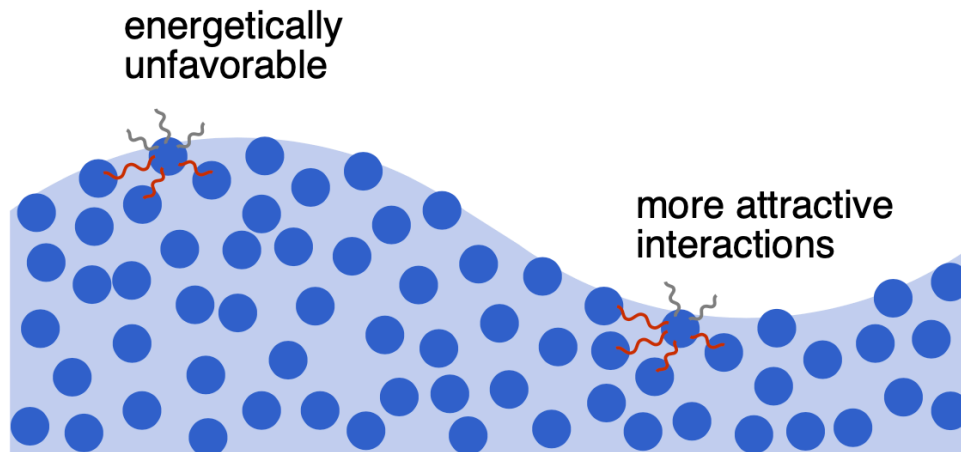
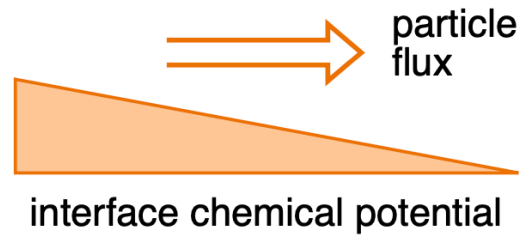
10 μ m

C. elegans zygote

R. Geßele, J. Halatek, L. Würthner, and E. Frey, Nat. Comm. 11, 539 (2020)

Thermodynamic Systems

phase separation



Gibbs - Thomson Relation

$$\Delta\rho \cdot \delta\mu = -\sigma\kappa$$

Jump in the densities $\Delta\rho$

Chemical potential shift $\delta\mu$

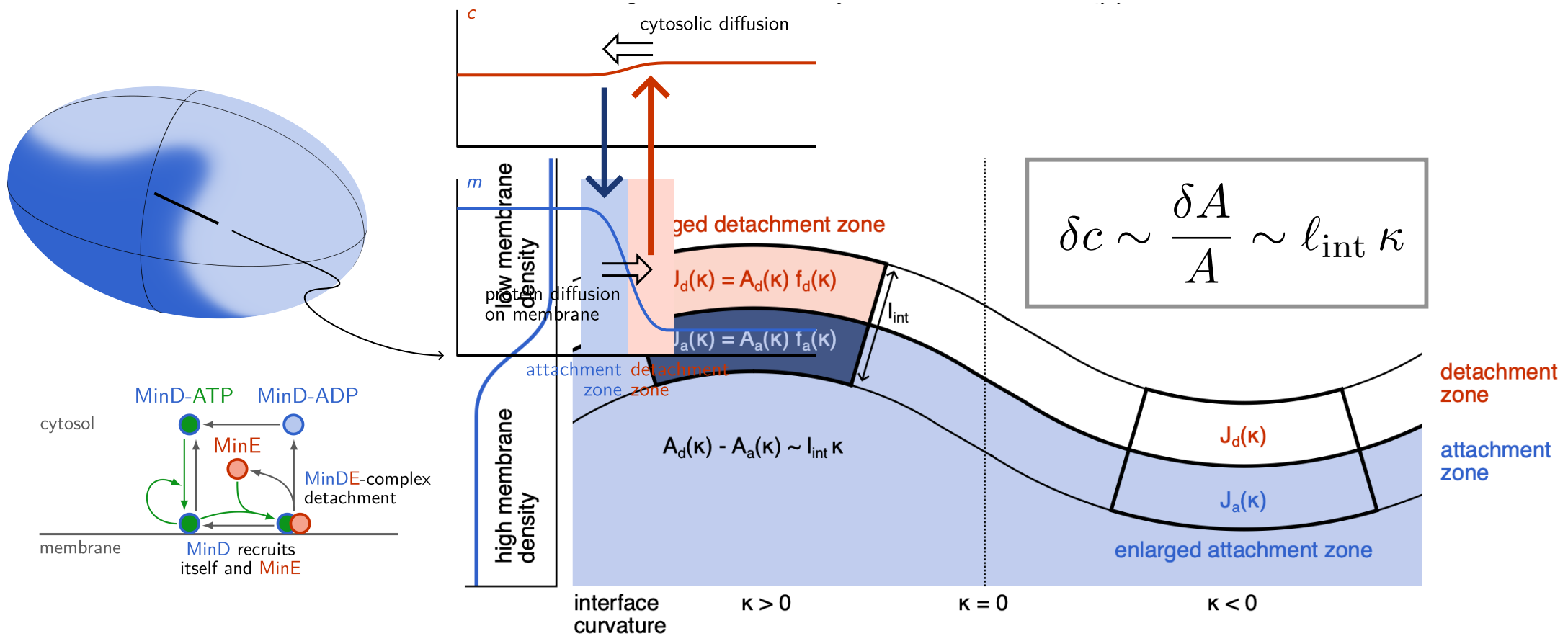
Surface tension σ

Curvature κ

Is there a concept analogous to
surface tension in pattern-forming systems?

Can non-equilibrium systems form
supramolecular structures like mixtures and foams?

Cyclic protein fluxes generate surface tension



Turing foam in the *in vitro* Min system

Stationary *in vitro* Min pattern

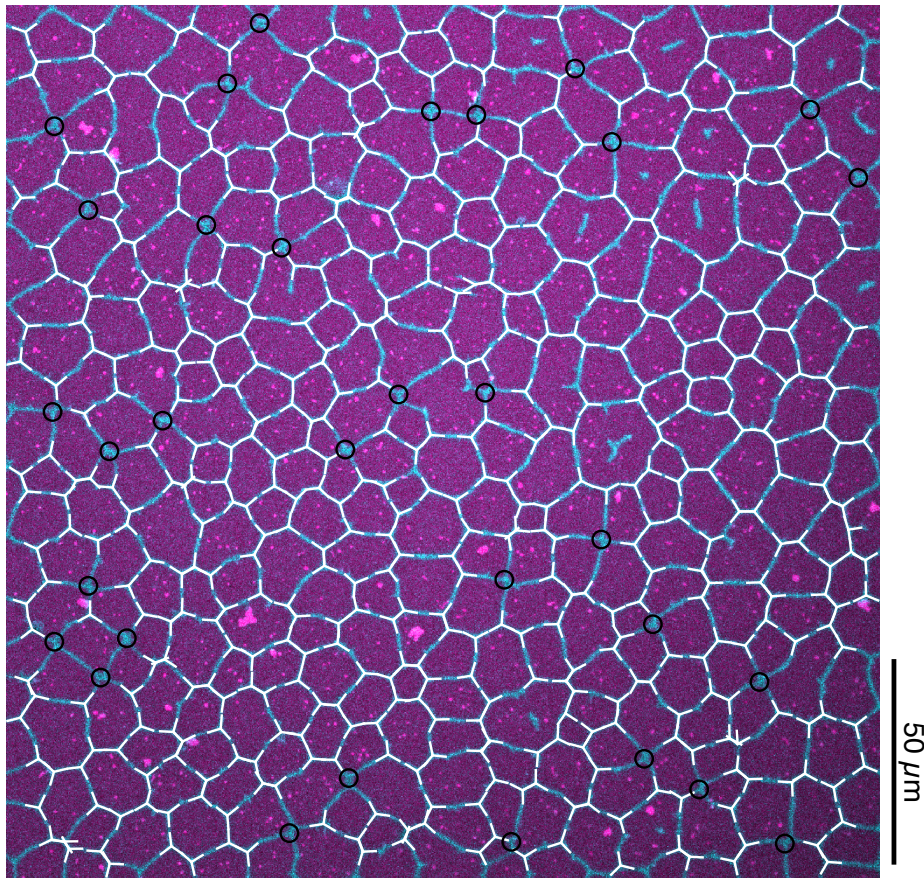


Glock et al., ACS Syn. Bio. 8(1), 148 (2019)

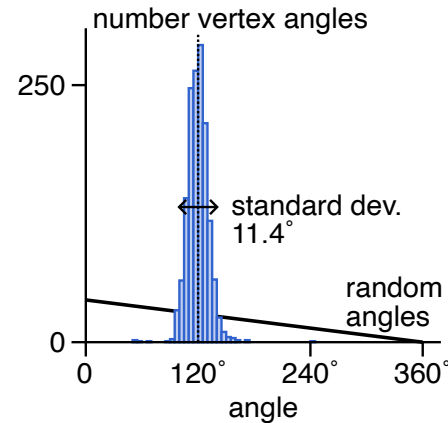
Turing foam in the *in vitro* Min system

Experiment: 94% triple vertices

MinD MinE



Glock et al., ACS Syn. Bio. 8(1), 148 (2019)



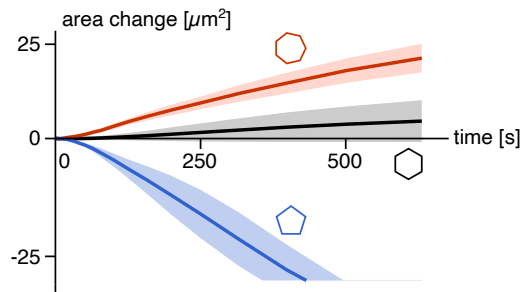
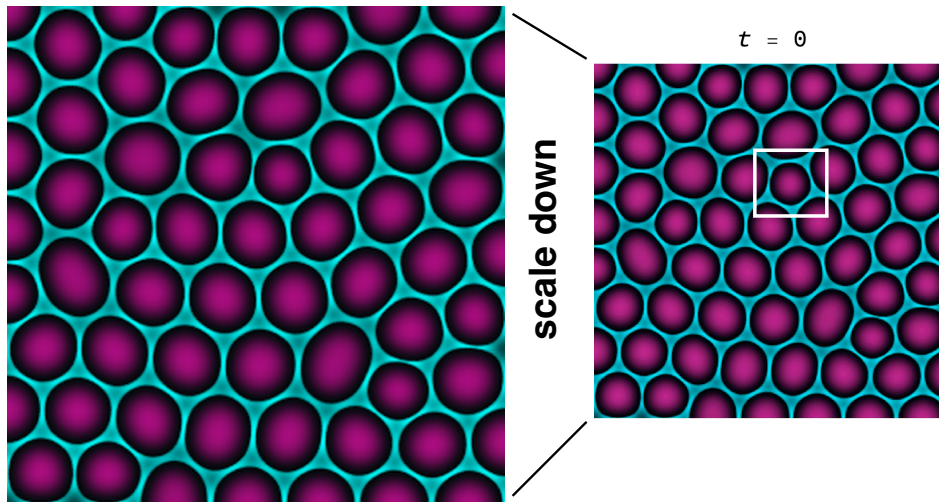
Plateau vertex conditions of
2D liquid foams:

- triple vertices
- 120° vertex angles

Can not occur in liquid foams!
Intrinsic pattern wavelength

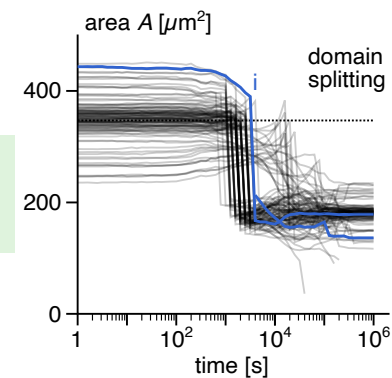
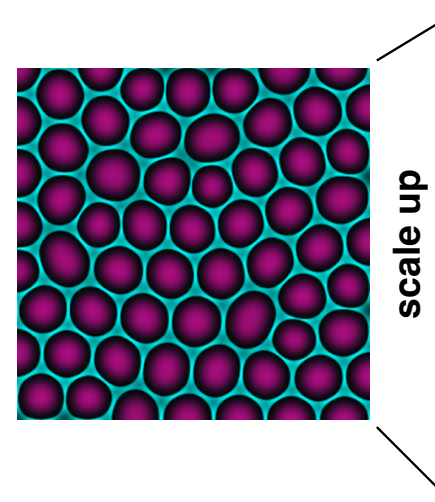
Domain coarsening and domain splitting

Coarsening at small length scales



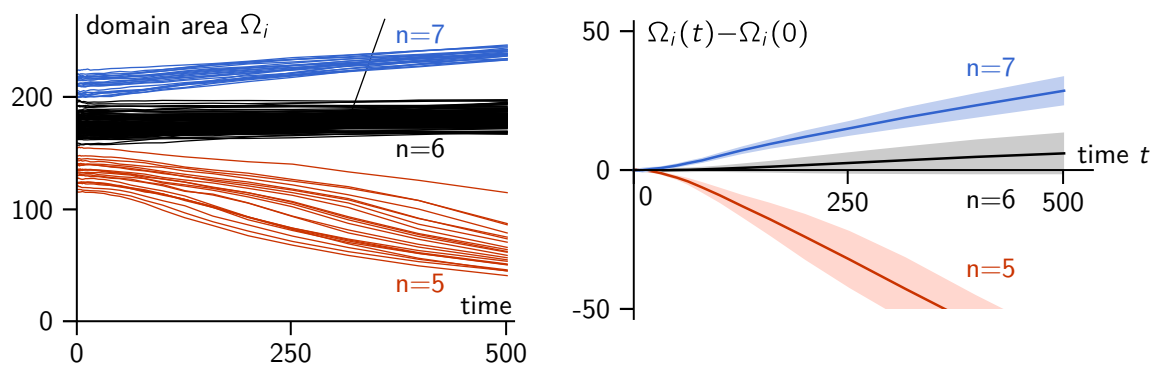
Von Neumann's law!
Analogous to liquid foams.

Splitting of large domains



Topological transitions
causing domain splitting.

A non-equilibrium von Neumann law



Analogous to the von-Neumann law
for coarsening of 2D foams

Interfaces driven by curvature

$$v_{\perp} \sim \kappa$$

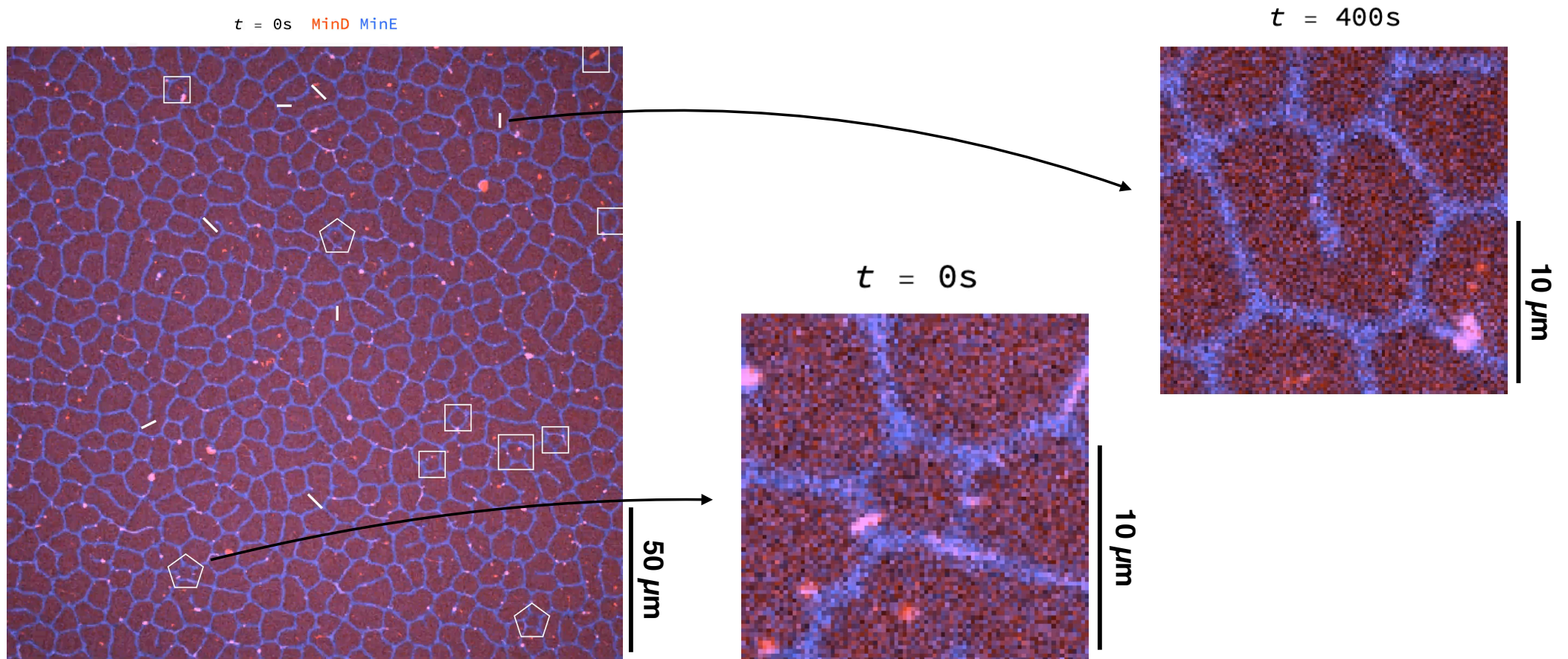
Evolution of domain areas

$$\partial_t |\Omega_i| = \int_{\partial\Omega_i} ds v_{\perp} \sim \int_{\partial\Omega_i} ds \kappa$$

Gauß–Bonnet, 120° vertex angles

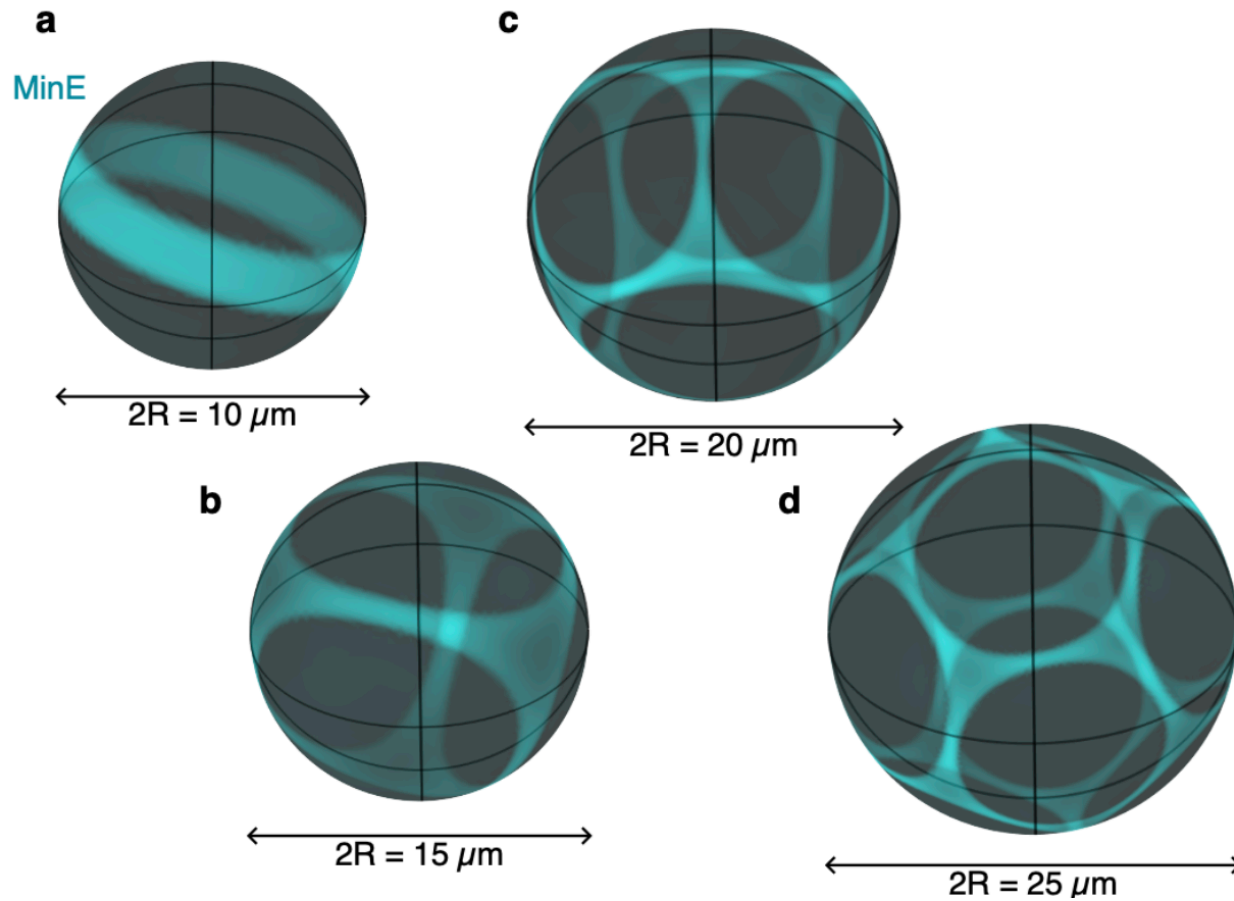
$$\partial_t |\Omega_i| \sim (n_i - 6)$$

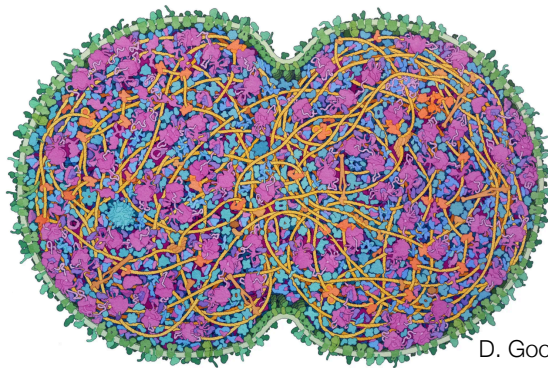
Domain evolution in the *in vitro* Min Turing foam



H. Weyer , T. A. Roth & E. Frey [arXiv:2409.20070]; data from Schwille lab (MPI Biochemistry, Munich)

Polyhedral MinE meshes





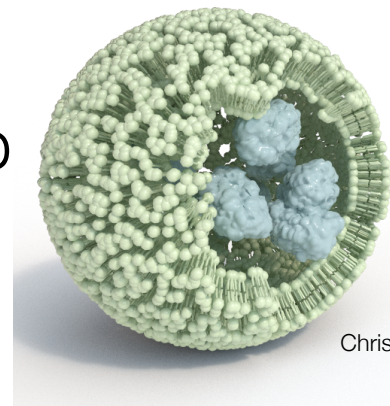
D. Goodsell

Biological cell

"What I cannot create, I do not understand."

R. Feynman

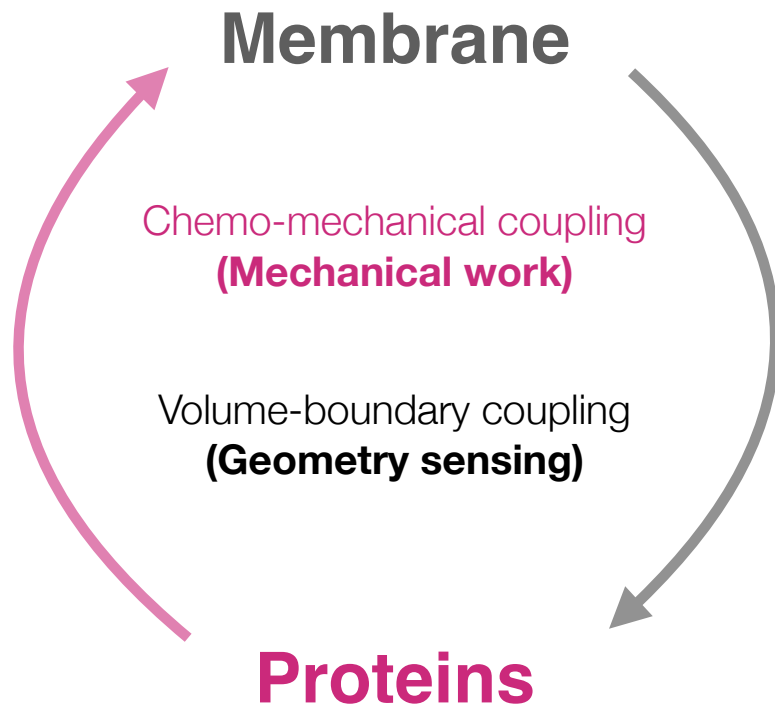
life-like system from the b
Theorie



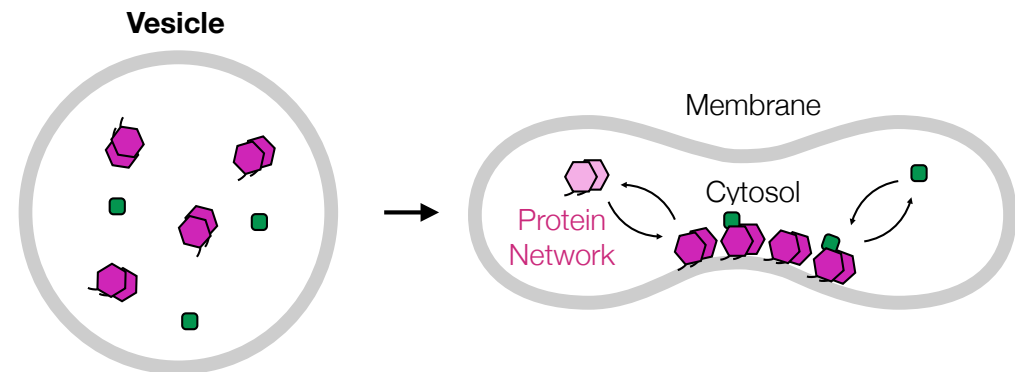
Chris Hohmann

Synthetic cell

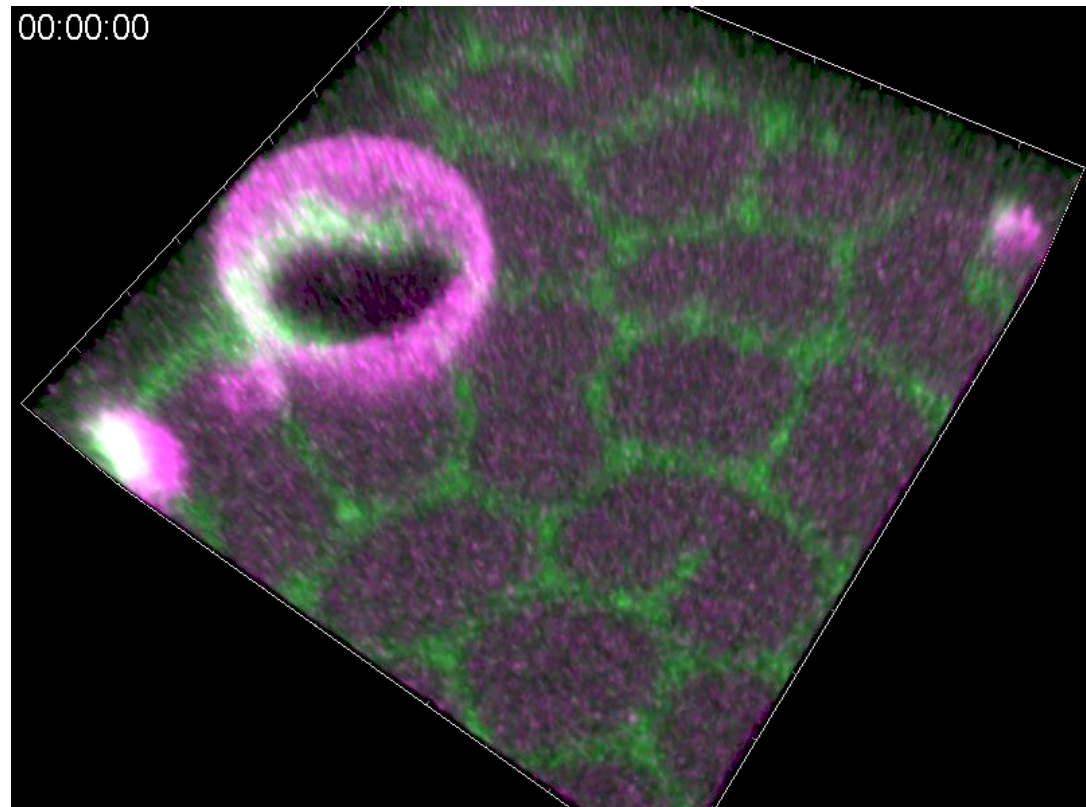
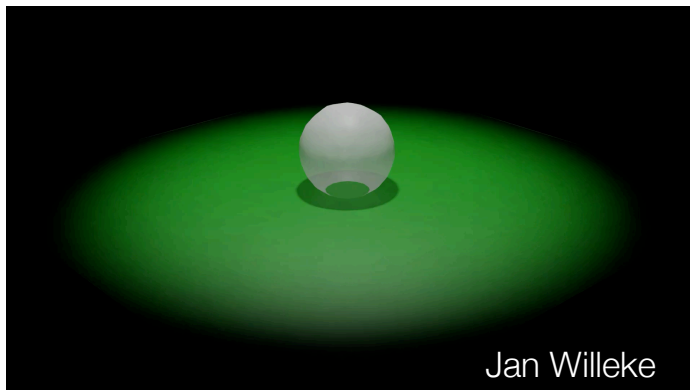
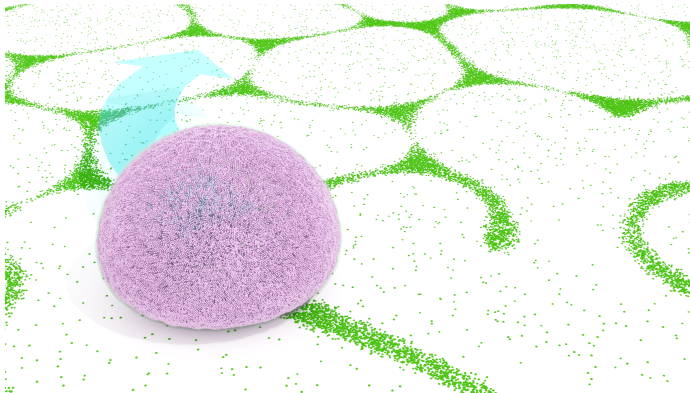
The most promising minimal system is ...



Mechanics & Geometry

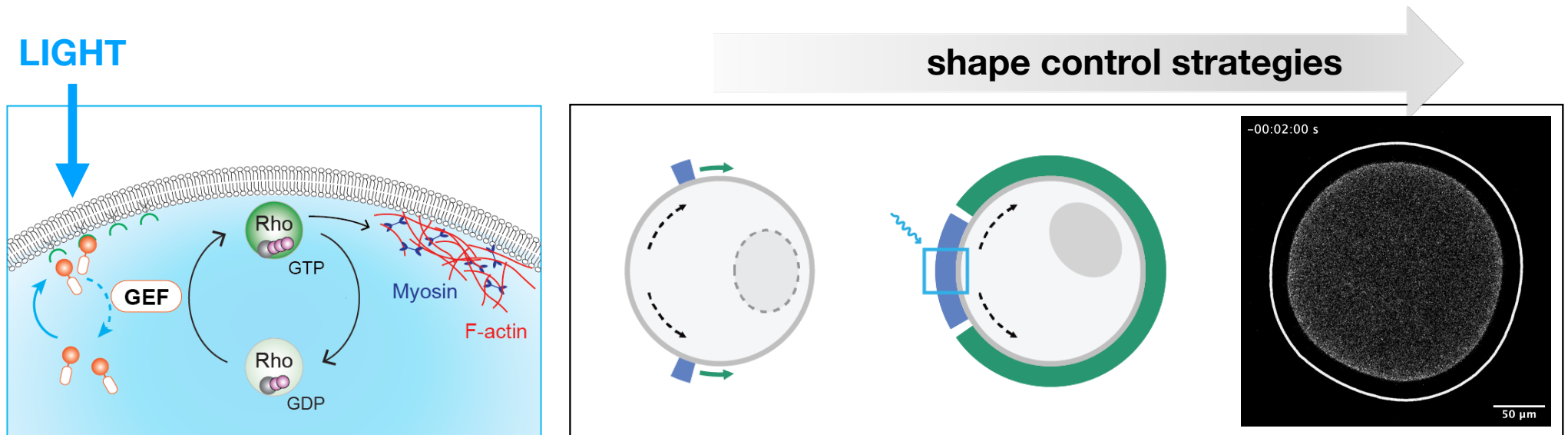


Patterns can drive cell-like motion



Meifang Fu*, Tom Burkart*, ... E. Frey & P. Schille, Nature Physics 2023

Shaping the shape of cells with light



Optogenetic tool allows real-time modulation of Rho cortical excitability

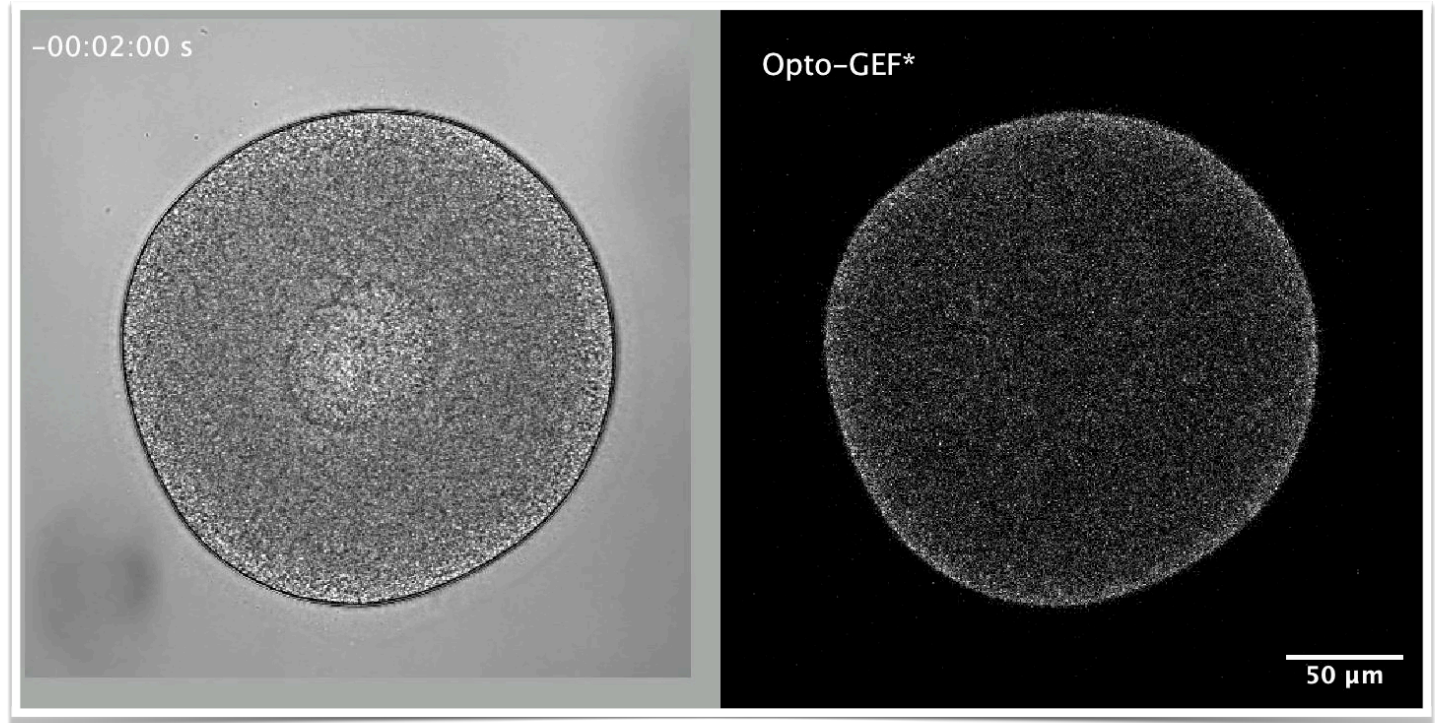
Selective triggering distinct mechanisms of surface excitations

Can achieve a broad range of cell shapes by optical control

Optical control of an excitable enzyme circuit for engineering dynamical cell shapes

Light-switchable enzymes can mediate molecular activations in living cells, yet their full potential in realizing versatile controls in nonlinear networks remains unexplored. We demonstrate optical control over a key enzyme for animal cell division to achieve a plethora of dynamical cell shapes, by biochemically hacking an endogenous signaling circuit.

nature portfolio



J. Liu, T. Burkart, ... E. Frey & N. Fakhri, Nature Physics (2025).

Emergence and Self-Organisation in Biological Systems

- ❑ **Rethinking pattern formation**

Local equilibria theory & mass-redistribution instability

- ❑ **Protein pattern formation**

From in vivo patterns to Turing foams & cell-like motion

- ❑ **Quo vadis?**

Dynamic manifolds & mechano-chemical coupling

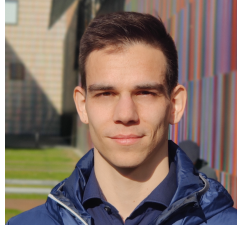
Life-like systems & synthetic cells & cell control



thanks to Master & PhD students



Henrik Weyer
LMU->KITP



Tom Burkart
LMU->MIT



Laeschkir Würthner
EMBL



Manon Wigbers
Certara



Tobias Roth
LMU



Jan Willeke
LMU



Fridtjof Brauns
KITP



Jacob Halatek
Bioleap

and our experimental collaboration partners



Petra Schwillle
MPI for Biochemistry



Nikta Fakhri
MIT



Cees Dekker
TU Delft



Suckjoon Jun
UCSD



Liedewij Laan
TU Delft

DFG

**MAX
PLANCK
SCHOOLS**

Matter to Life

