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ADDING FURTHER CONFUSION TO 'TENSION' AS PROMISED OVER SLACK

COUPLING IN-PLANE TRANSPORT PHENOMENA AND MEMBRANE CURVATURE

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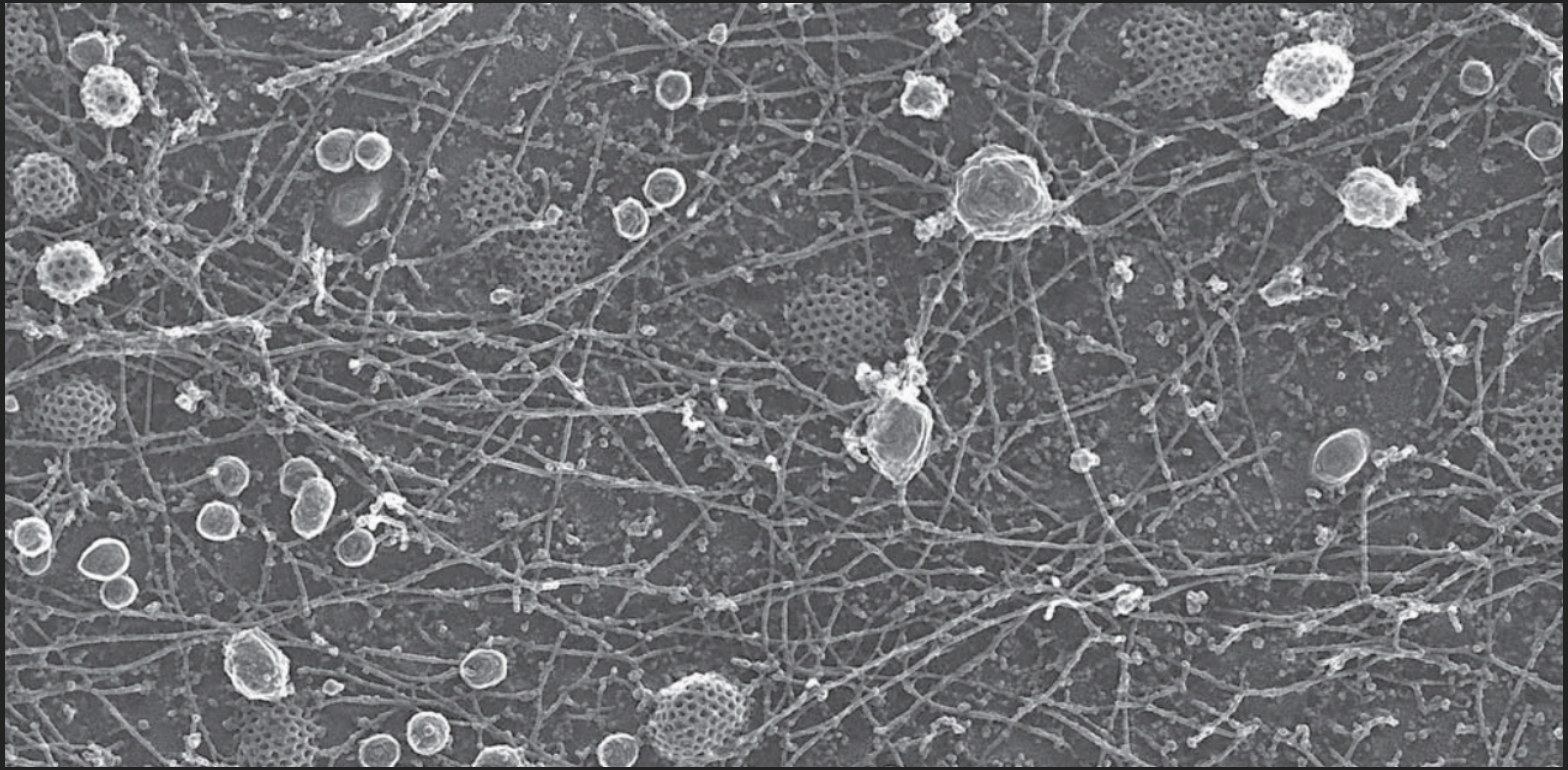
THE VALUE OF MODELS FOR MEMBRANE BUDDING

Lee et al, Curr. Opin. Cell. Biol. 2021

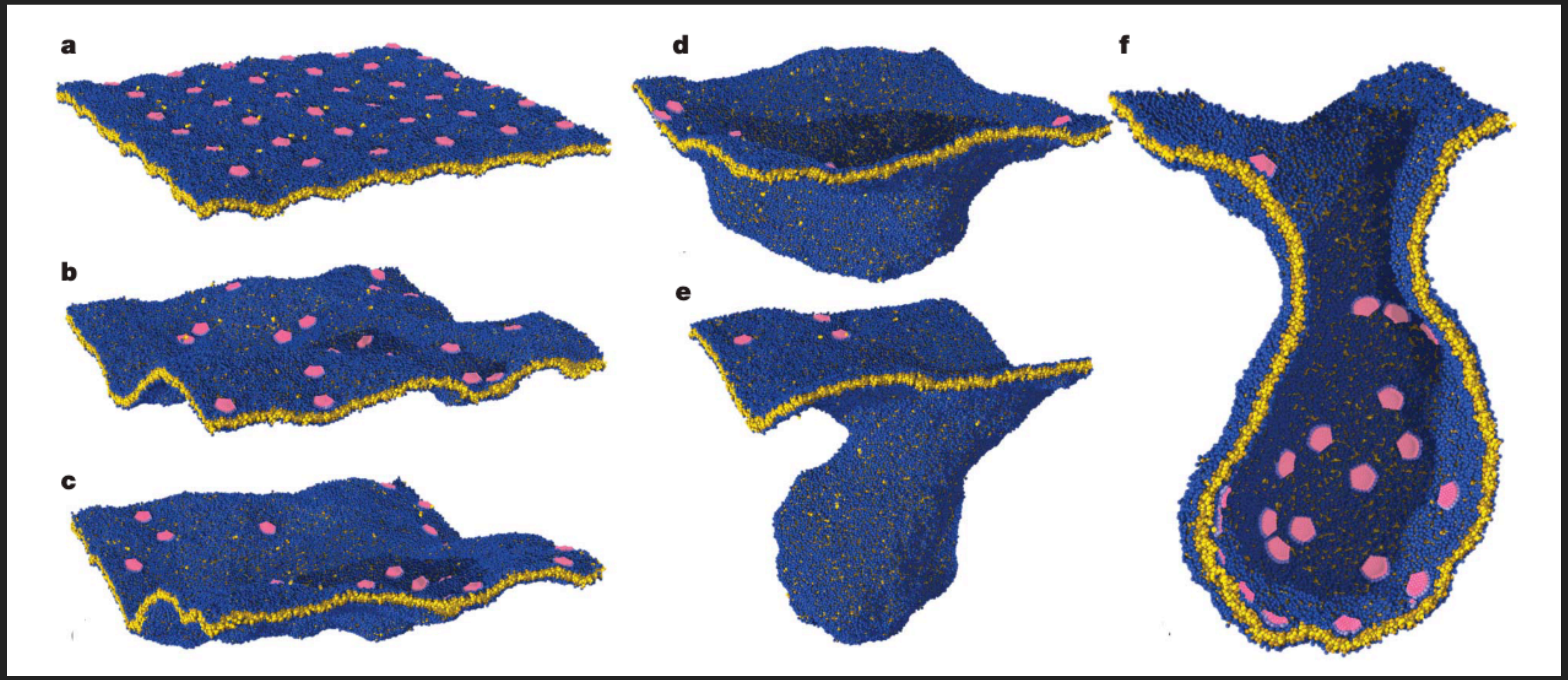
EXPERIMENTAL OBSERVATIONS OF CLATHRIN-COATED PITS



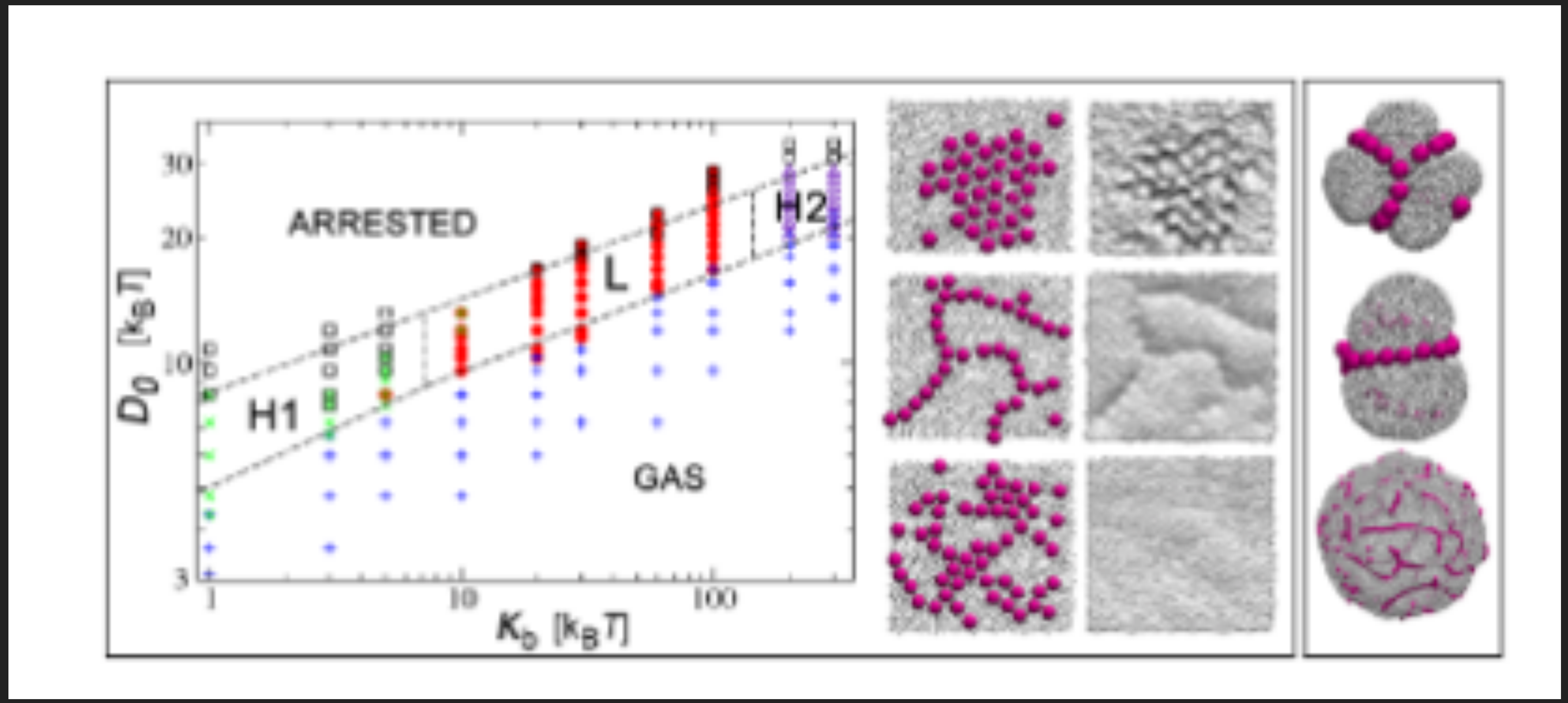
Heterogeneity along the membrane and aggregation of proteins are critical for formation of coated pits

Sochacki, et al. bioRxiv 2020.07.18.207258

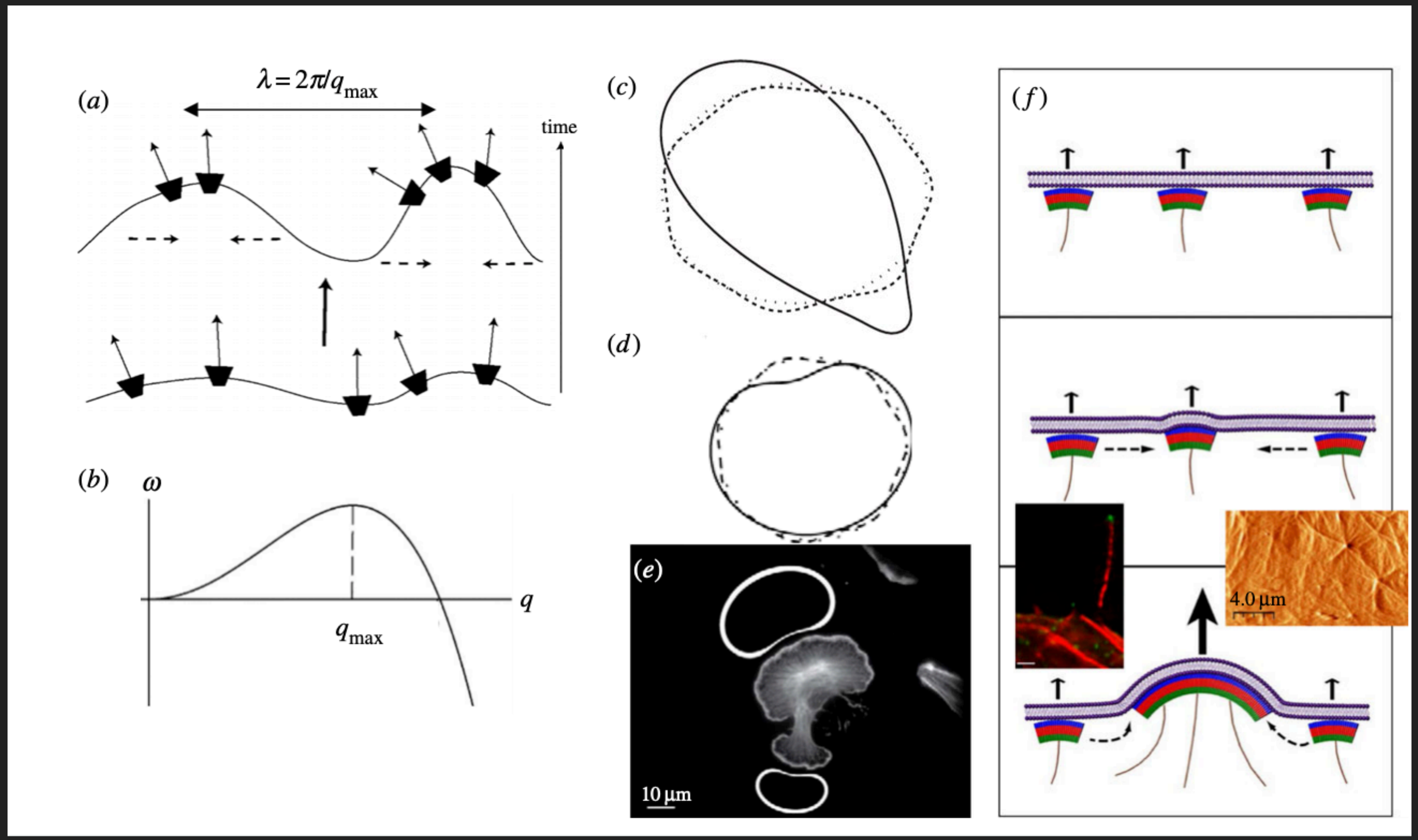
AGGREGATION OF PARTICLES AND INTERACTION WITH CURVATURE



Reynwar, et al. *Nature* 447 (7143): 461–64.



Sarić, Anđela, and Angelo Cacciuto. 2012. *Physical Review Letters* 108 (11): 118101.



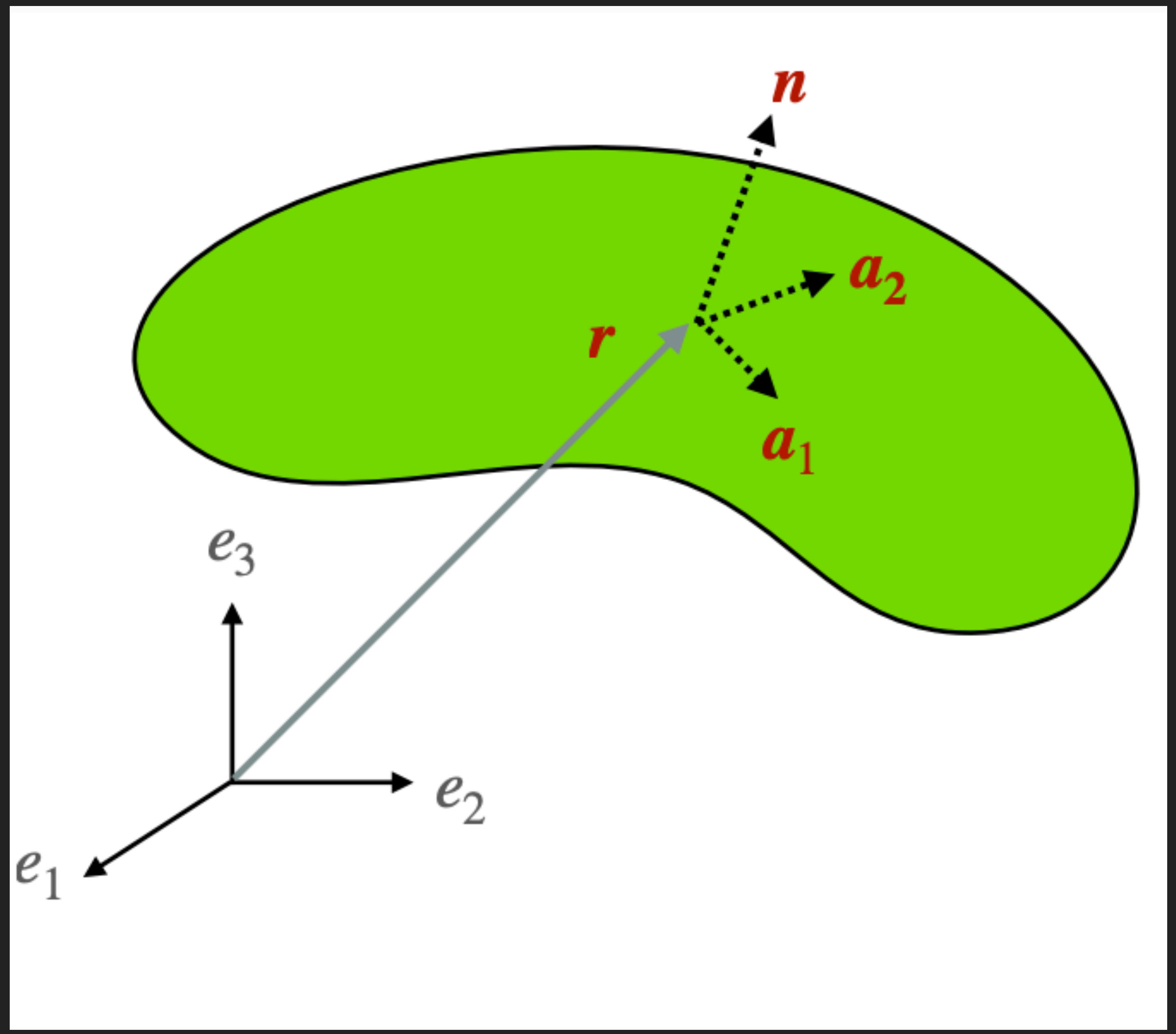
Gov, N. S. 2018. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 373 (1747): 20170115.

HOW CAN WE INCORPORATE MULTIPLE PHYSICS IN CONTINUUM MODELING?

- Goal: to access the heterogeneity that is associated with membrane-protein interactions in cells
- Bonus: can we get some insight into membrane tension and tie things back to the talks from week 1?
- Tools: continuum modeling

ELASTIC SURFACES — SOME PRELIMINARIES

- The equations of motion in the absence of inertia are simply the equations of mechanical equilibrium.
  - $\alpha \in \{1,2\}$ are surface coordinates
  - $\boldsymbol{\Sigma}^{\alpha}_{;\alpha} + p\boldsymbol{n} = \boldsymbol{0}$, where $\boldsymbol{\Sigma}$ is the stress tensor
  - $\boldsymbol{\Sigma}^{\alpha} = N^{\beta\alpha}\boldsymbol{a}_{\beta} + S^{\alpha}\boldsymbol{n}$ is the stress vector
  - $N^{\beta\alpha}$ has contributions from elastic and viscous stresses
  - $N^{\beta\alpha}$ and S^{α} can be calculated from the strain energy



See for detailed derivation: Steigmann, D. J. 1999. “Fluid Films with Curvature Elasticity.” *Archive for Rational Mechanics and Analysis* 150 (2): 127–52.

Gentler introduction: Deserno, Markus. 2015. “Fluid Lipid Membranes: From Differential Geometry to Curvature Stresses.” *Chemistry and Physics of Lipids* 185 (January): 11–45.

REVISITING THE GOVERNING EQUATIONS

Homogeneous membranes

$$W = kH^2 + \bar{k}K,$$

$$k[\Delta H + 2H(H^2 - K)] - 2\lambda H = p$$

$$\lambda_{,\gamma} = 0$$

Heterogeneous membranes

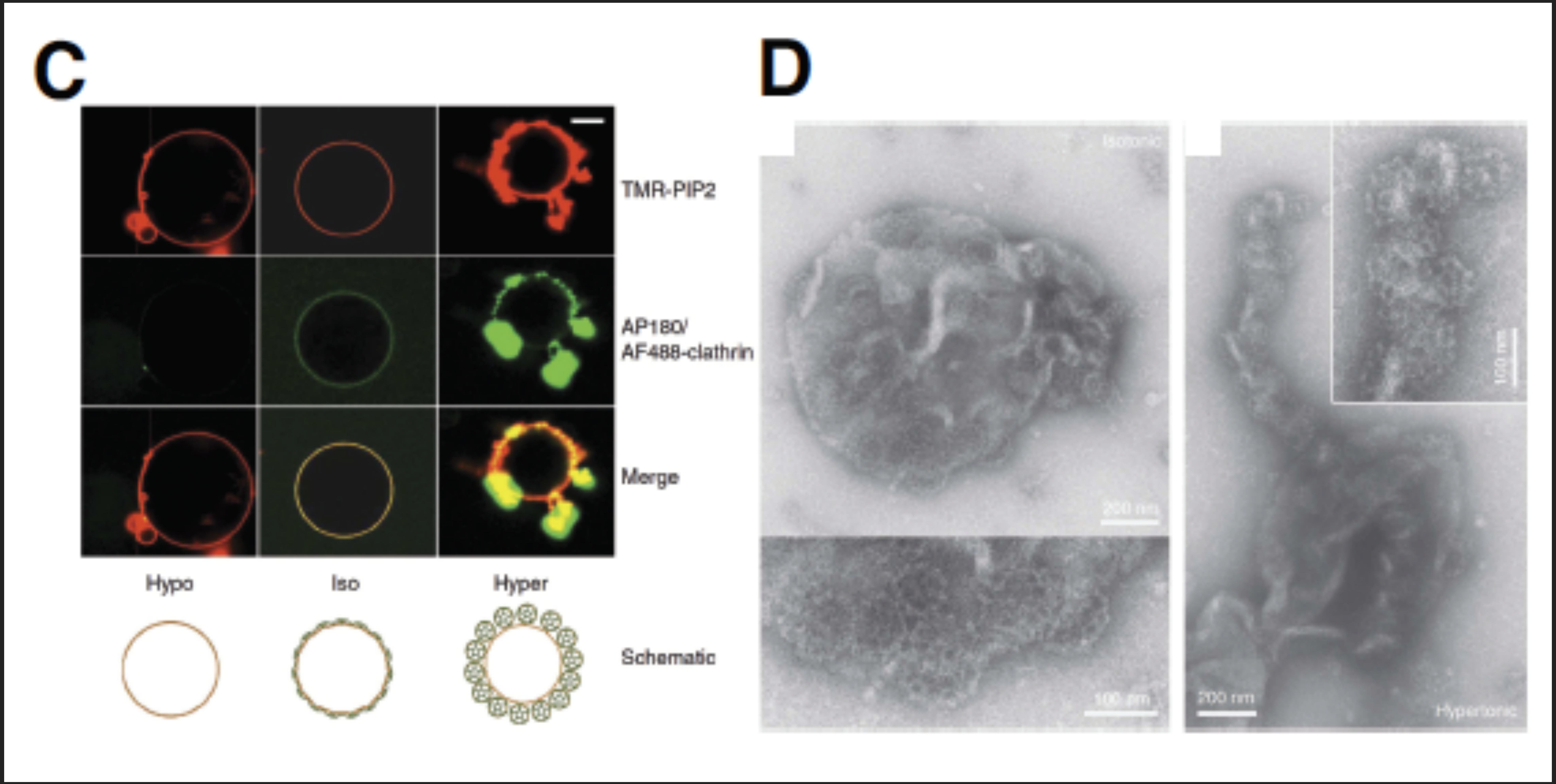
$$W = k(H - C)^2 + \bar{k}K,$$

$$k\left[\Delta(H - C) + 2(H - C)\left(H^2 + HC - K\right)\right] - 2\lambda H = p.$$

$$\lambda_{,\gamma} = -\frac{\partial W}{\partial x^\gamma}\bigg|_{\exp} = 2k(H - C)\frac{\partial C}{\partial x^\gamma},$$

Steigmann ARMA 1999
Jenkins SIAM J Appl Math 1977

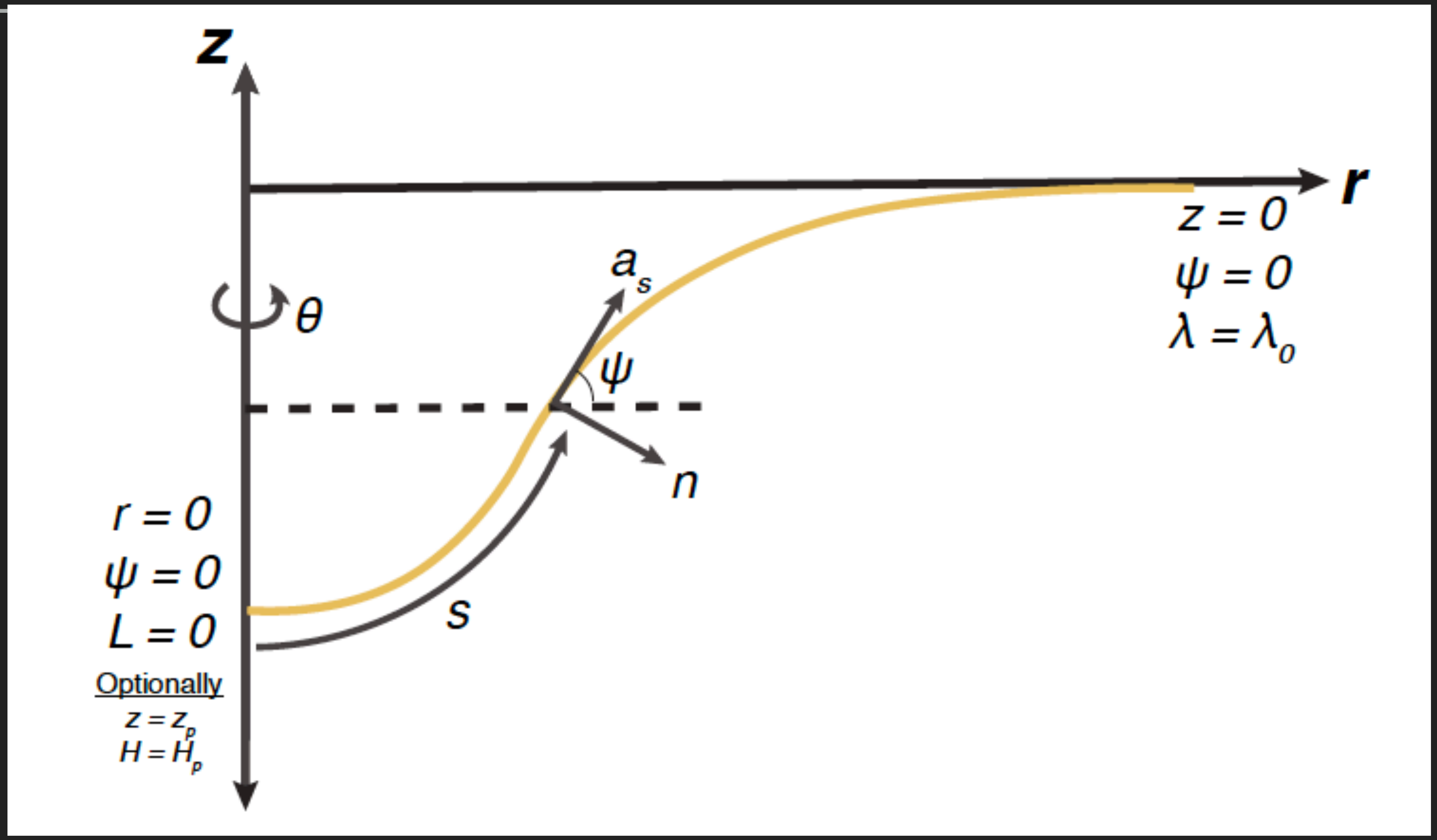
MEMBRANE TENSION INHIBITS BUD FORMATION IN VITRO



Saleem et al. Nature Comm. 2015

MEMBRANE MODEL FOR ENDOCYTOSIS

- Assume axisymmetric geometries
- Impose local incompressibility and carry out a force balance.



Helfrich energy:

$$W = k\left(H - C(\theta^1, \theta^2)\right)^2 + \bar{k}K$$

Shape equation:

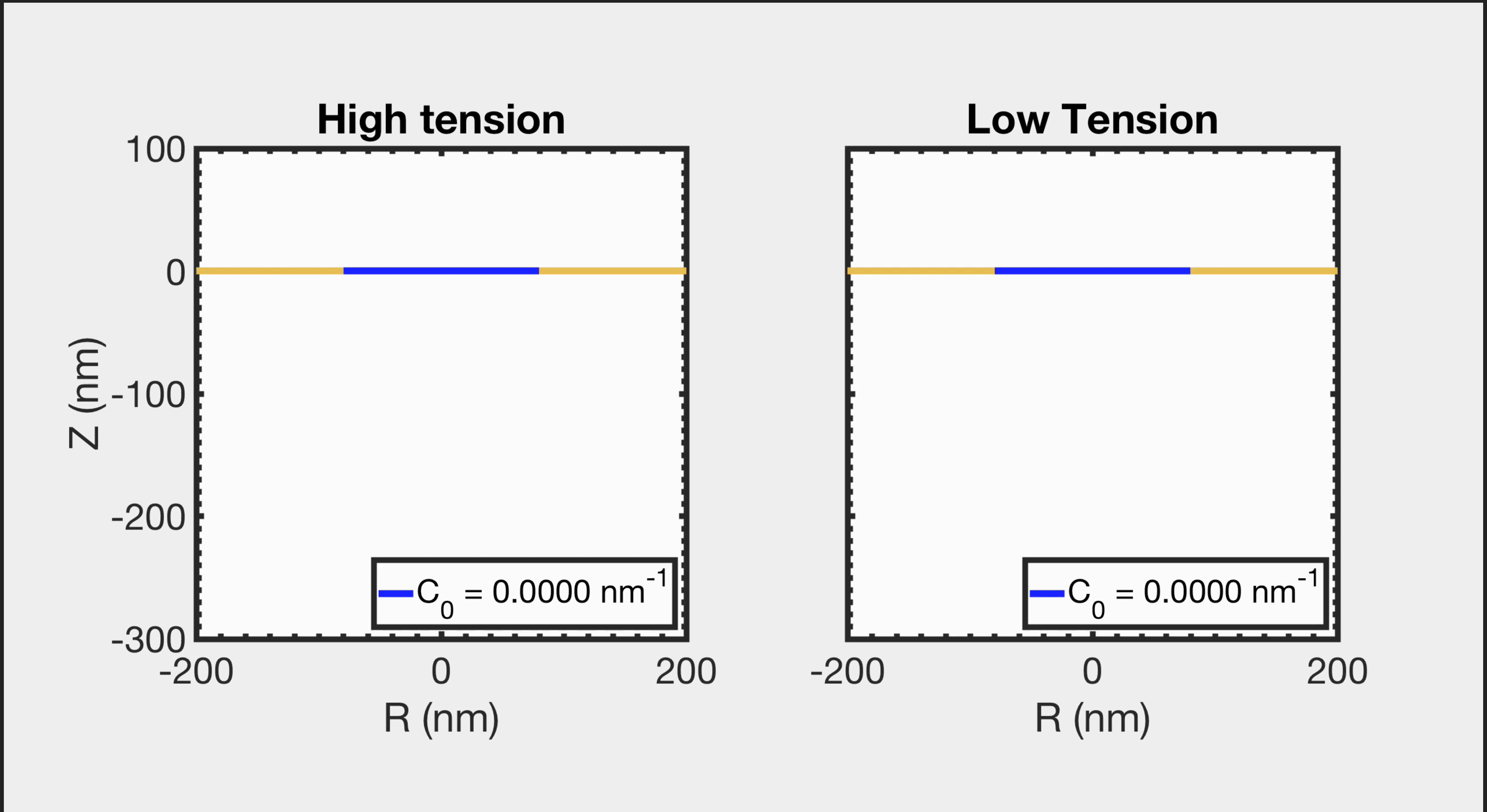
$$\underbrace{k[\Delta(H-C) + 2(H-C)(H^2 + HC - K)]}_{\text{Elastic Effects}} = \underbrace{p + 2\lambda H}_{\text{Capillary effects}} + \underbrace{\mathbf{f}\cdot\mathbf{n}}_{\text{Force due to actin}}$$

Spatial variation of membrane tension:

$$\underbrace{\lambda_{,\gamma}}_{\text{Gradient of surface pressure}} = \underbrace{-2k(H-C)\frac{\partial C}{\partial x^\gamma}}_{\text{protein-induced variation}} - \underbrace{\mathbf{f}\cdot\mathbf{a}_\gamma}_{\text{force induced variation}}$$

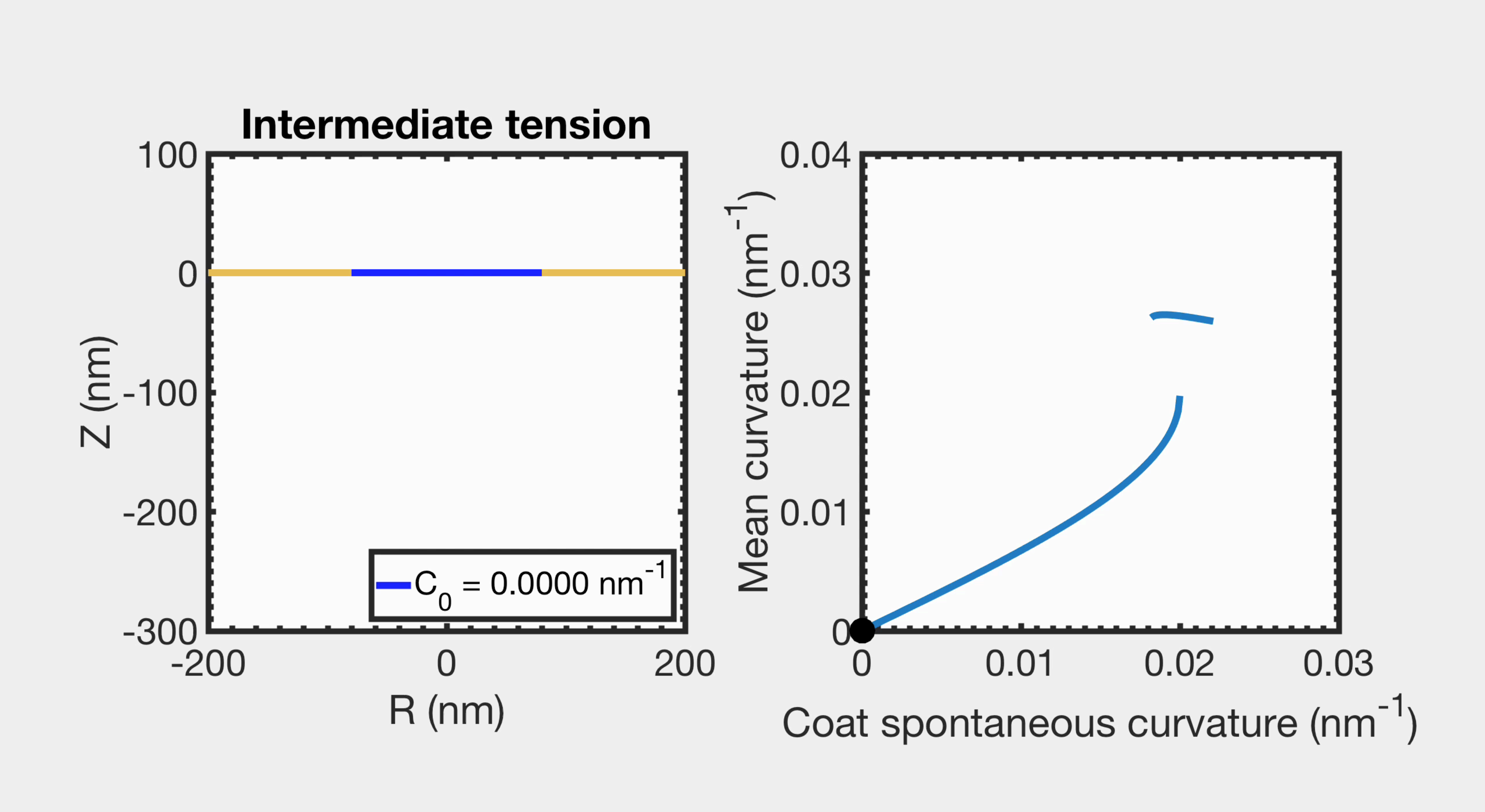
Hassinger et al, PNAS 2017

MEMBRANE TENSION INHIBITS BUD FORMATION FOR INCREASING SPONTANEOUS CURVATURE



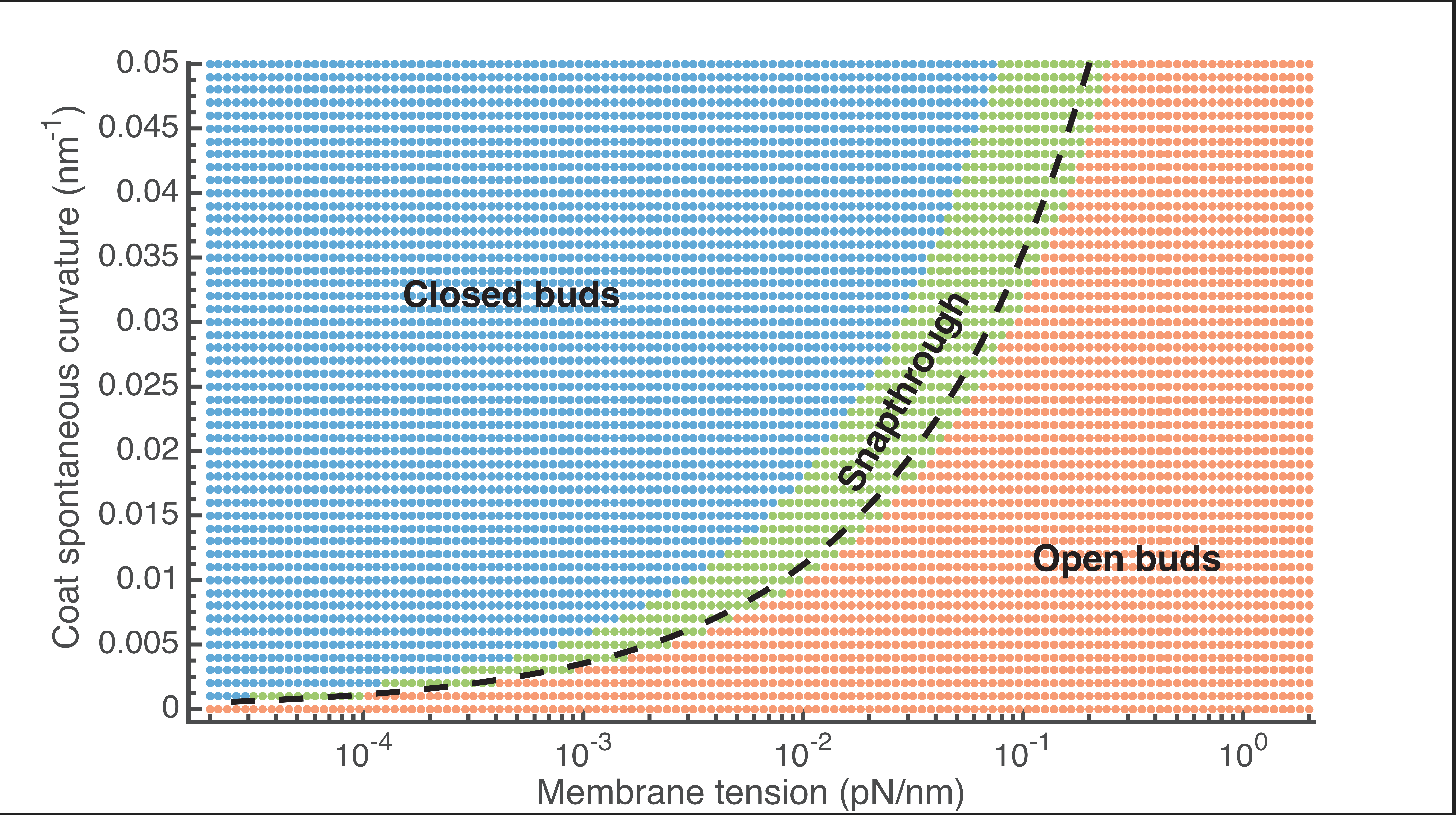
Hassinger et al, PNAS 2017

PHYSIOLOGICAL TENSION AND SNAP THROUGH INSTABILITY: EFFECT OF INCREASING SPONTANEOUS CURVATURE



Hassinger et al, PNAS 2017

SNAPTHROUGH INSTABILITY AND BUD FORMATION



Hassinger et al, PNAS 2017

VISCOUS STRESSES + INCOMPRESSIBILITY CONSTRAINT

- Goal: to accommodate intrasurface viscous flow; $\mathbf{v} = v^{\alpha}\mathbf{a}_{\alpha} + w\mathbf{n}$
  - Add a 2D analog of the conventional viscous stress to the elastic stress
  - With $\mathbf{v} = v^{\alpha}\mathbf{a}_{\alpha} + w\mathbf{n}$ representing the surface velocity, the incompressibility constraint becomes $v^{\alpha}_{;\alpha} = 2Hw$; H is the mean curvature and K is the Gaussian curvature
  - Viscous stress is given by $\pi^{\alpha\beta} = 2\nu\left[a^{\alpha\mu}a^{\beta\eta}d_{\mu\eta} - wb^{\alpha\beta}\right]$.
  - Here, $d_{\mu\eta} = \left(v_{\mu;\eta} + v_{\eta;\mu}\right)/2$ is the rate-of-strain tensor
  - $a_{\alpha\beta}$ is the first fundamental form and $b_{\alpha\beta}$ is the second fundamental form

COUPLED VISCOUS AND ELASTIC STRESSES ON A HOMOGENEOUS MEMBRANE

- The `shape equation' becomes

$$\underbrace{k[\Delta H + 2H(H^2 - K)]}_{elastic\ effects} + \underbrace{2\nu[b^{\alpha\beta}d_{\alpha\beta} - w(4H^2 - 2K)]}_{viscous\ effects} = p + 2\lambda H$$

- Incompressibility condition

$$\underbrace{v^{\alpha}_{;\alpha}}_{divergence\ of\ velocity} = 2wH$$

- Gradient of surface pressure

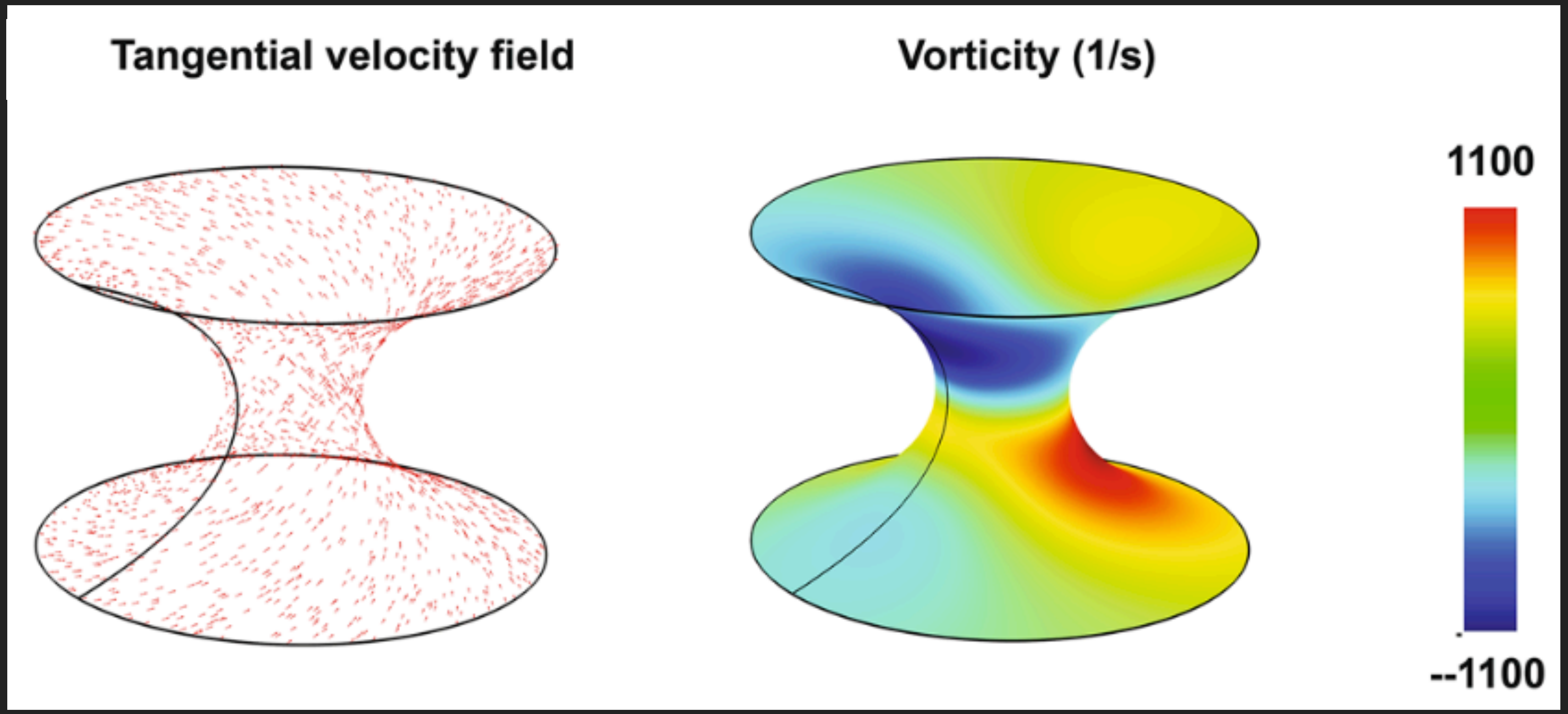
$$\lambda_{,\gamma} - 4\nu w H_{,\gamma} + 2\nu(a^{\alpha\mu}d_{\gamma\mu;\alpha} - w_{,\alpha}b^{\alpha}_{\gamma}) = 0$$

STOKES FLOW ON MINIMAL SURFACES TO BUILD INTUITION ABOUT λ

- On a plane

$$\underbrace{v^{\alpha}_{;\alpha}}_{\textit{divergence of velocity}} = 0 \quad \text{and} \quad \lambda_{,\gamma} + \nu \nabla^2 v_{\gamma} = 0$$

- Can also analyze on catenoids and helicoids – flow fields are Killing vector fields. See Bahmani et al. Cont Mech. Thermo. 2015



ADDING VISCOUS STRESSES FOR A HETEROGENEOUS MEMBRANE

$$\underbrace{k\left[\Delta(H-C)+2(H-C)\left(H^2+HC-K\right)\right]-2\lambda H}_{\text{Elastic contribution}}+\underbrace{2\nu\left[b^{\alpha\beta}d_{\alpha\beta}-w\left(4H^2-2K\right)\right]}_{\text{Viscous contribution}}=p.$$

Elastic contribution

Viscous contribution

$$\underbrace{\lambda_{,\gamma}-4\nu wH_{,\gamma}+2\nu\left(a^{\alpha\mu}d_{\gamma\mu;\alpha}-w_{,\alpha}b^{\alpha}_{\gamma}\right)=2k(H-C)\frac{\partial C}{\partial x^{\gamma}}.}$$

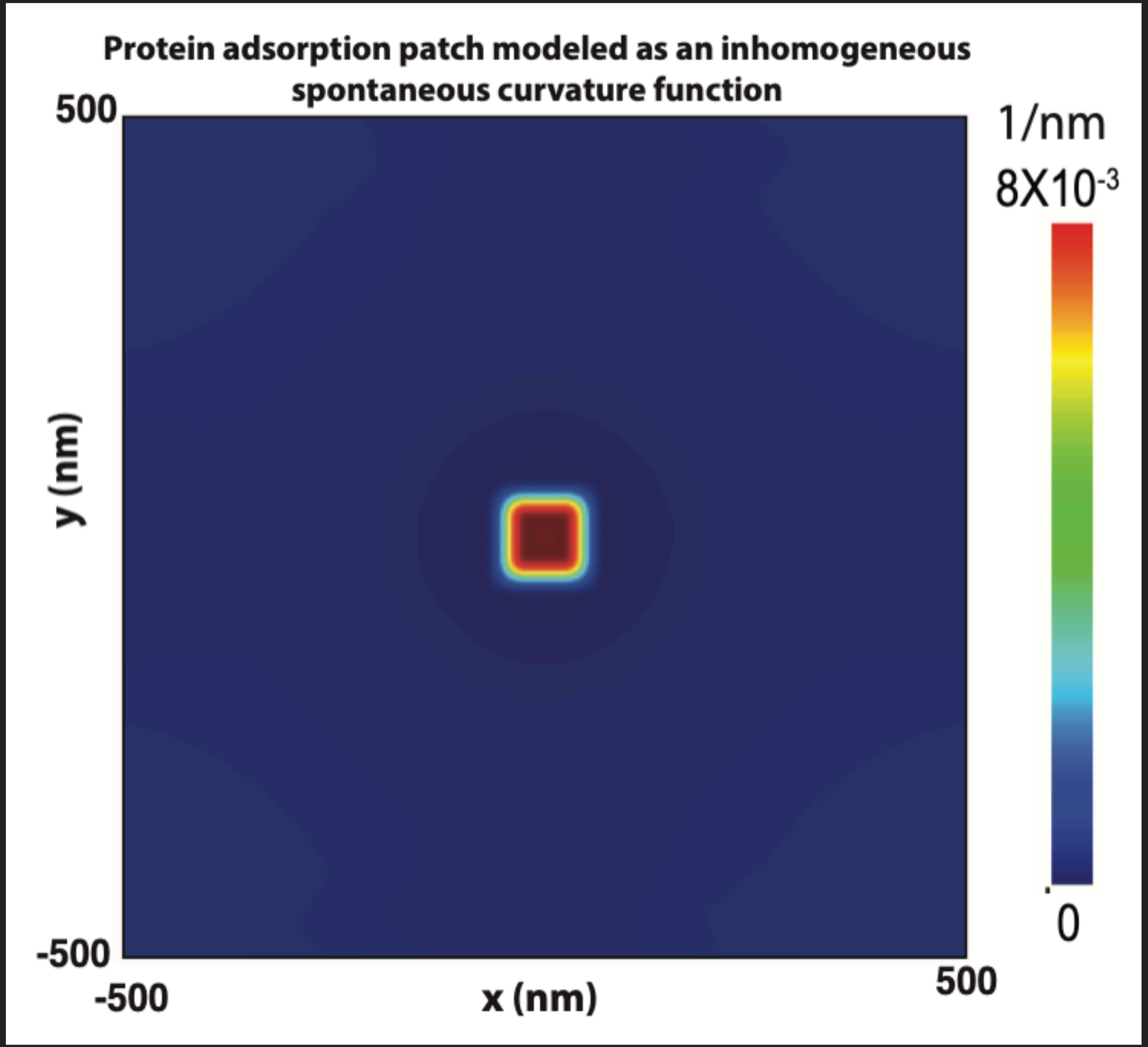
Equations for 2D surface flow with changing shape

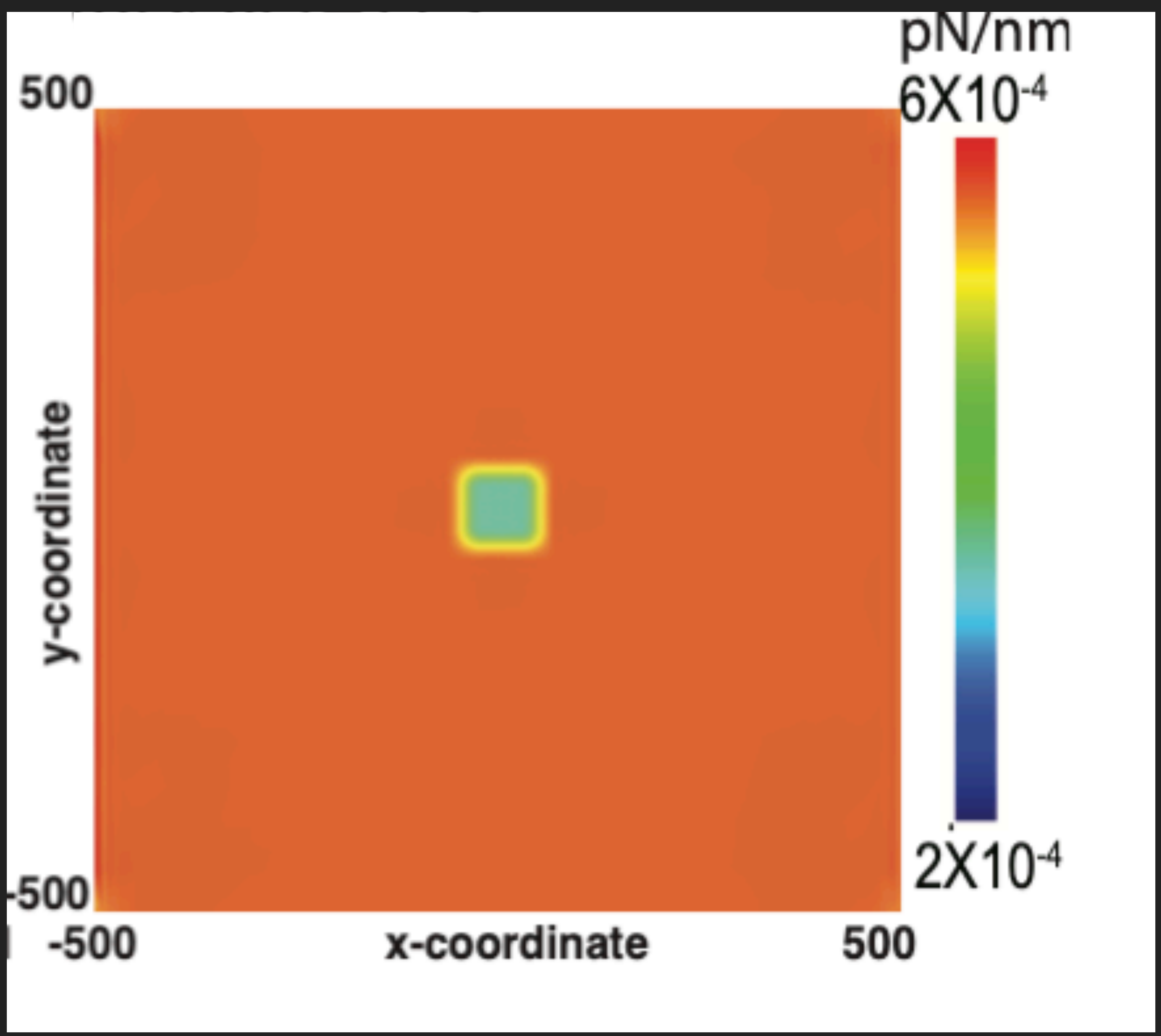
$$\underbrace{v^{\alpha}_{;\alpha}-2wH=0}$$

Constraint implementing 2D incompressibility

Rangamani et al BMMB 2013
Rangamani et al. Biophys J 2014
Rahimi and Arroyo, Phys Rev E 2013

THINK OF λ AS A SURFACE PRESSURE RATHER THAN MEMBRANE TENSION



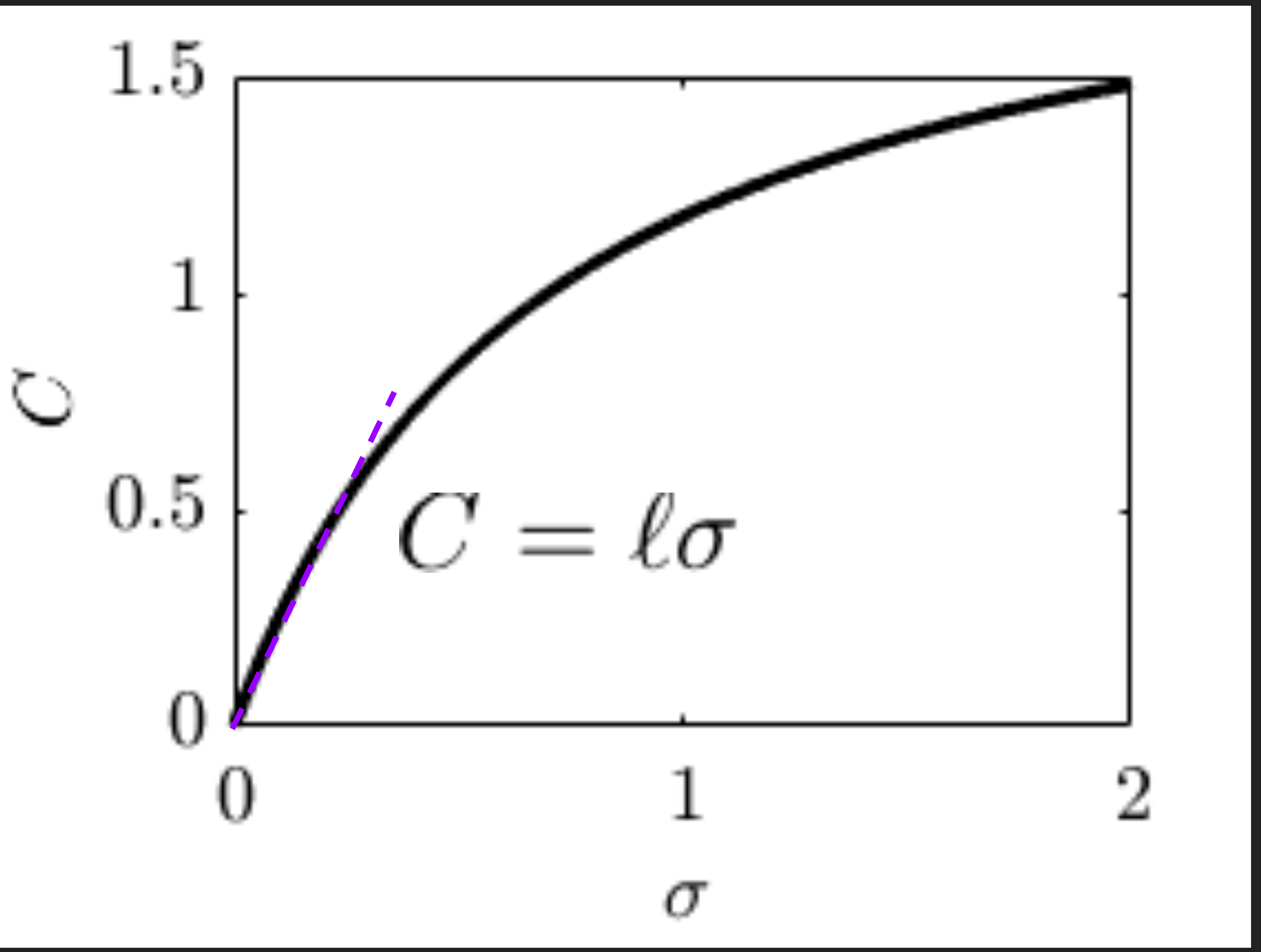


Rangamani et al BMMB 2013
Rangamani et al. Biophys J 2014
See also Lipowsky, Reinhard. 2013. "Spontaneous Tubulation of Membranes and Vesicles Reveals Membrane Tension Generated by Spontaneous Curvature." Faraday Discussions 161 (0): 305–31.

ADDING DIFFUSION AND AGGREGATION OF PROTEINS IN THE PLANE OF THE MEMBRANE

- Protein density (σ) is dilute and therefore C varies linearly with σ : $C = \ell\sigma$
- Membrane is still incompressible and ϕ is the area fraction of σ
- Membrane energy density becomes

$$W = \underbrace{k_B T \sigma_s \left[\phi \log \phi + (1-\phi)\log\left(1-\phi\right)\right]}_{entropic\ interactions} + \underbrace{\frac{\gamma\sigma_s}{2}\phi(1-\phi) + \frac{\gamma}{4}|\nabla\phi|^2}_{aggregation} + \underbrace{\kappa(H-\ell\sigma)^2 + \bar{\kappa}K}_{bending\ energy}.$$



Agrawal and Steigmann, ZAMP, 2011
Mahapatra et al. JFM 2020
Mahapatra et al. arXiv 2021
See also Noguchi, arXiv 2021 for binding contribution

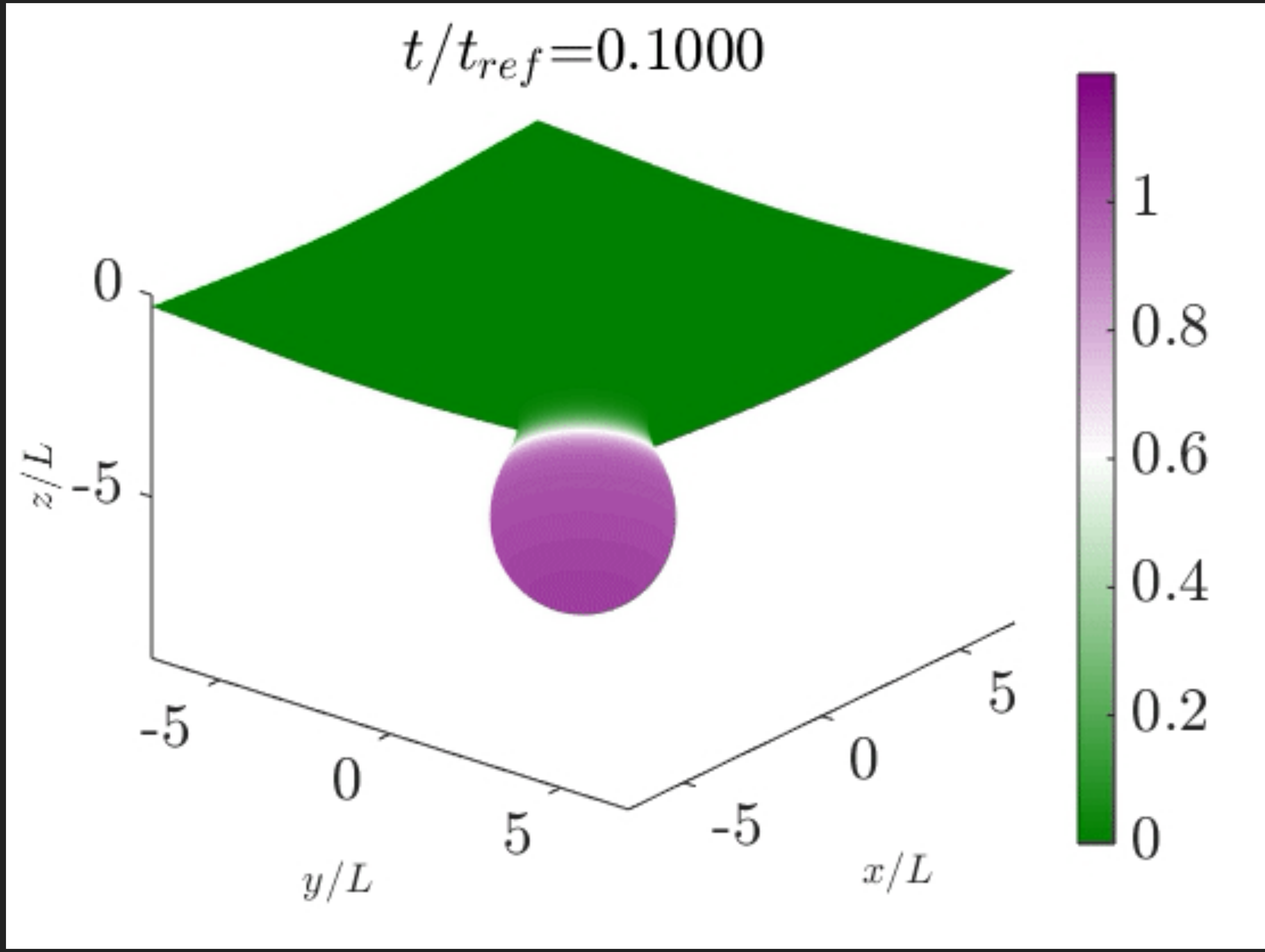
DYNAMICS OF PROTEIN DIFFUSION + AGGREGATION COUPLED WITH BENDING

$$\phi_t + Pe\,\nabla\cdot(\boldsymbol{v}\phi) = \nabla^2\phi\left[\frac{1}{1-\phi} + \frac{2\hat{L}^2\hat{S}}{\hat{B}}\phi - \hat{A}\phi\right] - \phi\left[\frac{2\hat{L}}{\hat{B}}\nabla^2 H + \frac{\hat{A}}{2\hat{S}}\nabla^4\phi\right]$$
$$+\nabla\phi\cdot\left[\nabla\phi\left(\frac{1}{(1-\phi)^2} + \frac{2\hat{L}^2\hat{S}}{\hat{B}} - \hat{A}\right) - \frac{2\hat{L}}{\hat{B}}\nabla H - \frac{\hat{A}}{2\hat{S}}\nabla(\nabla^2\phi)\right].$$

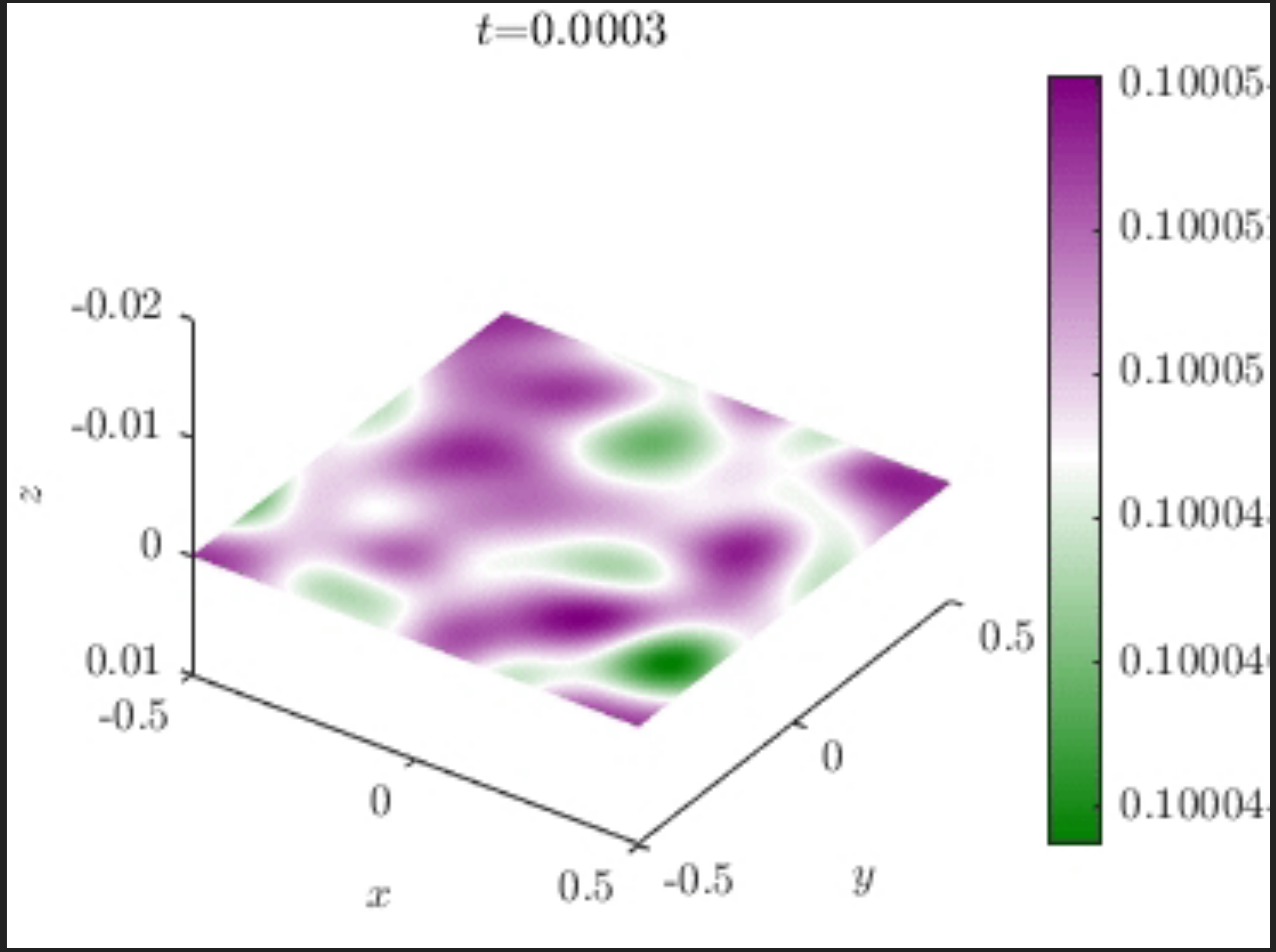
Dimensionless Number	Expression	Physical interpretation
$\hat{B}$	$\frac{k_B T}{\kappa}$	$\frac{\text{Thermal energy}}{\text{Bending energy}}$
$\hat{L}$	$\frac{\ell}{L}$	$\frac{\text{Spontaneous curvature length}}{\text{Domain length}}$
$\hat{A}$	$\frac{\gamma}{k_B T}$	$\frac{\text{Aggregation coefficient}}{\text{Diffusion coefficient}}$
$\hat{S}$	$\sigma_s L^2$	$\frac{\text{Domain area}}{\text{Protein footprint}}$
$\hat{T}$	$\frac{2L^2\lambda_0}{\kappa}$	$\frac{\text{Membrane tension energy}}{\text{Bending energy}}$
Pe	$\frac{\lambda_0 L^2}{\nu D}$	$\frac{\text{Advection strength}}{\text{Diffusion strength}}$

DYNAMICS OF THE COUPLED SYSTEM

No aggregation; diffusion of preformed patch; axisymmetry



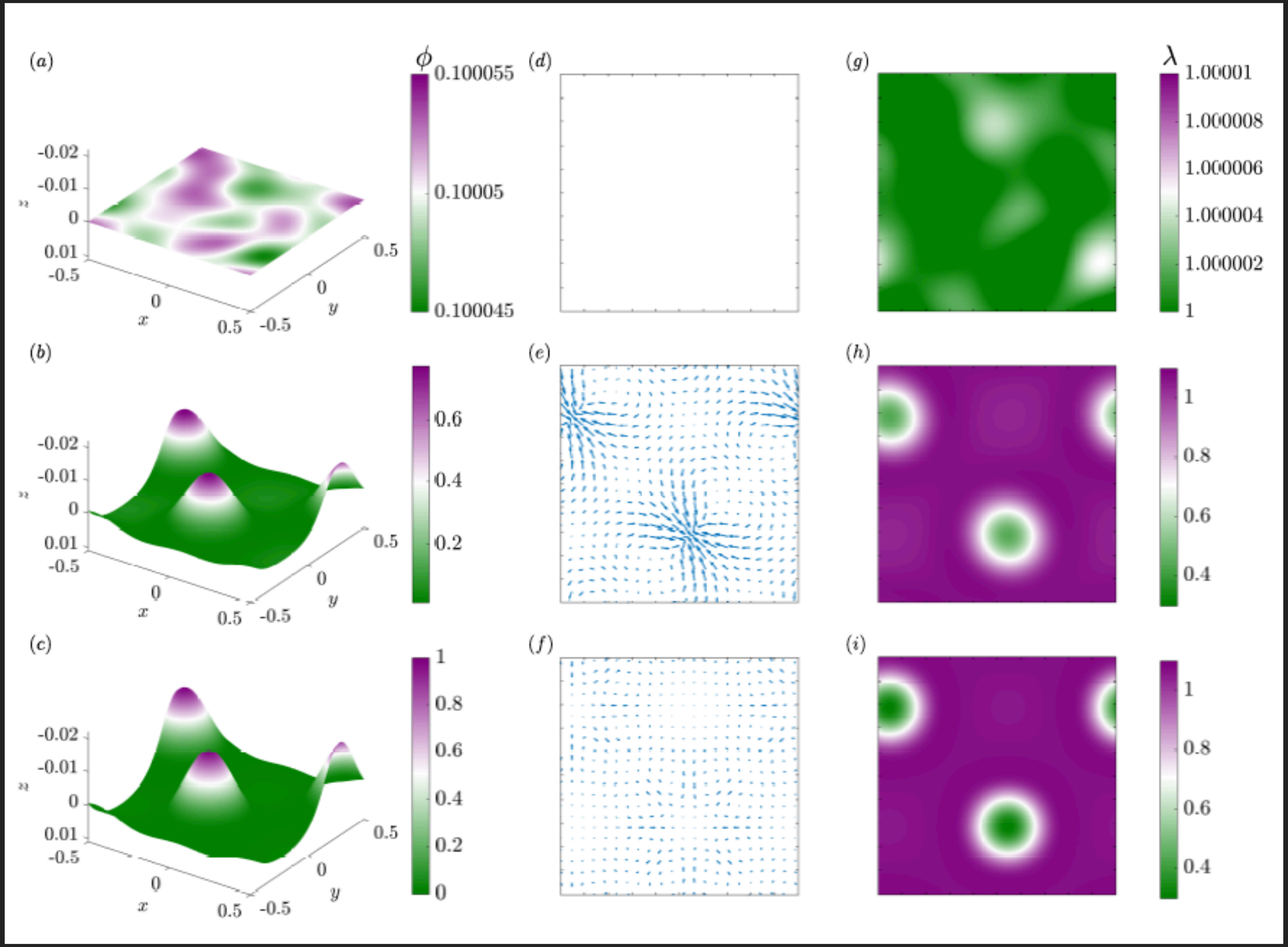
Coupled aggregation and diffusion; linearized Monge



Mahapatra et al. arXiv 2021

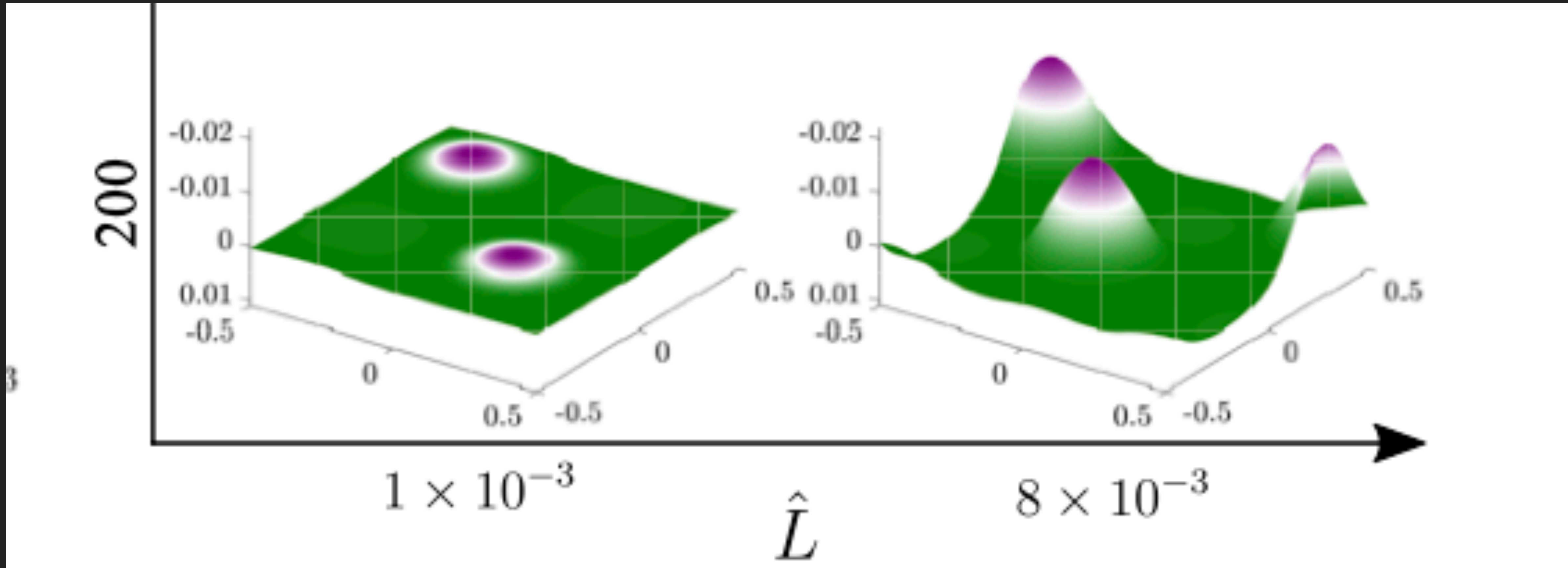
DYNAMICS OF THE COUPLED SYSTEM

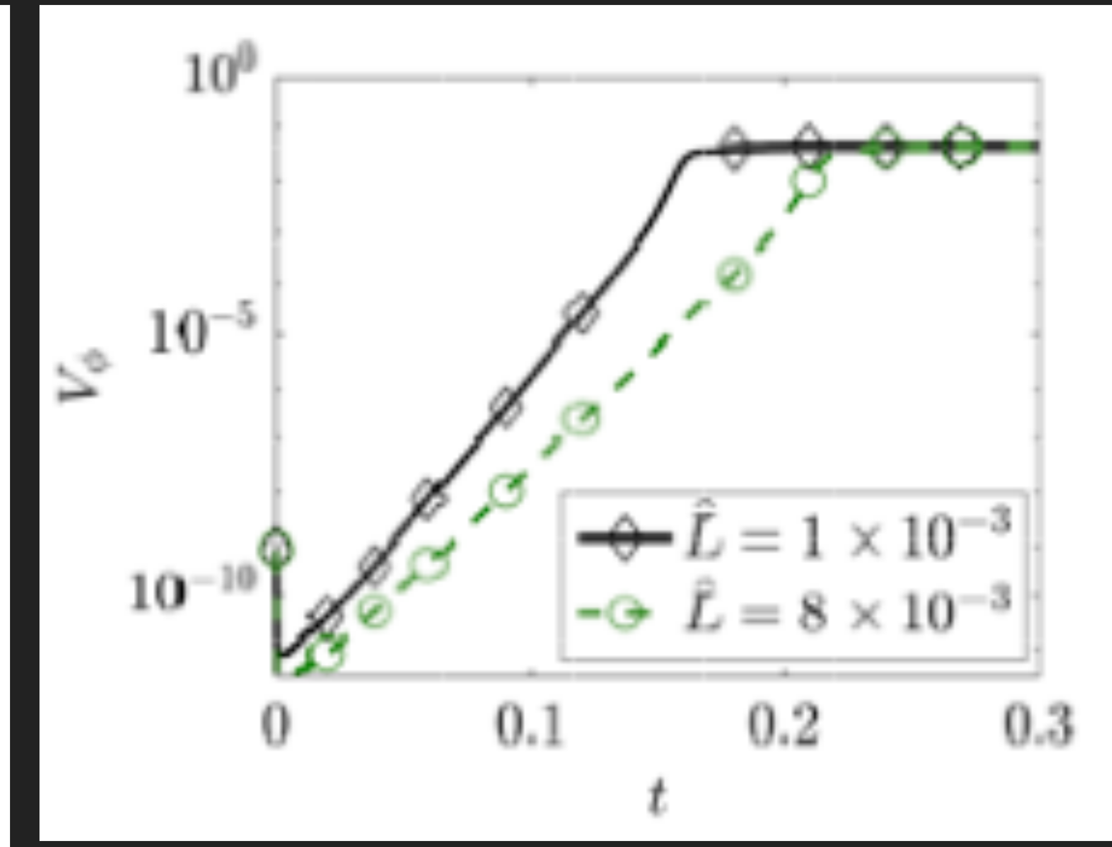
Time



Mahapatra et al. arXiv 2021

PHASE SPACE FOR CURVATURE-COUPLED DOMAIN FORMATION





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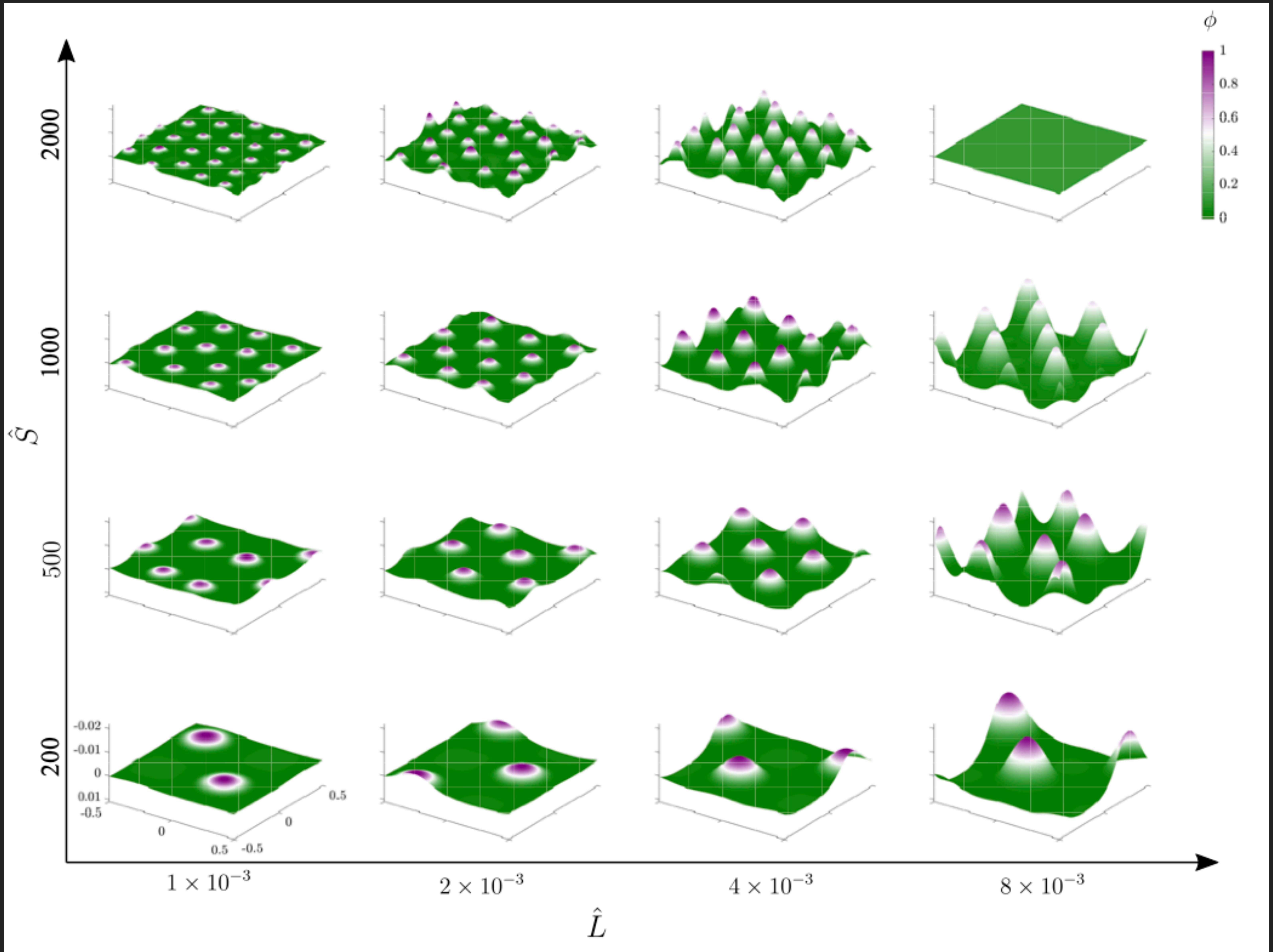
$\hat{T}$	$\frac{2L^2\lambda_0}{\kappa}$	Membrane tension energy / Bending energy
Pe	$\frac{\lambda_0 L^2}{\nu D}$	Advection strength / Diffusion strength

Mahapatra et al. arXiv 2021

CURVATURE-MEDIATED FEEDBACK ON AGGREGATION CAN BE BOTH POSITIVE AND NEGATIVE



Mahapatra et al. arXiv 2021

SUMMARY

- Considerations of heterogeneity are important for membrane-protein interactions
  - Models of increasing complexity help build intuition
  - Coupling of these models with other signaling events brings us closer to mechanochemical coupling for specific cellular processes at different scales

    - Tenner, Brian, Michael Getz, Brian Ross, Donya Ohadi, Christopher H. Bohrer, Eric Greenwald, Sohum Mehta, Jie Xiao, Padmini Rangamani, and Jin Zhang. 2020. "Spatially Compartmentalized Phase Regulation of a Ca2+-cAMP-PKA Oscillatory Circuit." *eLife* 9 (November). https://doi.org/10.7554/eLife.55013.
    - Denk, Jonas, Simon Kretschmer, Jacob Halatek, Caroline Hartl, Petra Schwille, and Erwin Frey. 2018. "MinE Conformational Switching Confers Robustness on Self-Organized Min Protein Patterns." *Proceedings of the National Academy of Sciences* 115 (18): 4553–58.
    - Frey, Erwin, Jacob Halatek, Simon Kretschmer, and Petra Schwille. 2018. "Protein Pattern Formation." In *Physics of Biological Membranes*, 229–60. Springer.
    - Thalmeier, Dominik, Jacob Halatek, and Erwin Frey. 2016. "Geometry-Induced Protein Pattern Formation." *Proceedings of the National Academy of Sciences* 113 (3): 548–53.

OPEN QUESTIONS

- How can we accommodate multiple families of proteins?
  - Particularly in the crowded regime that is closer to cellular membranes?
- What about binding of proteins to the membrane?
  - When do non-linearity and thickness effects start to matter?
- Multiple timescales involved with surface reactions complicate matters?

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