

# A Diffuse Interface Framework for Modeling the Evolution of Multi-cell Aggregates as a Soft Packing Problem

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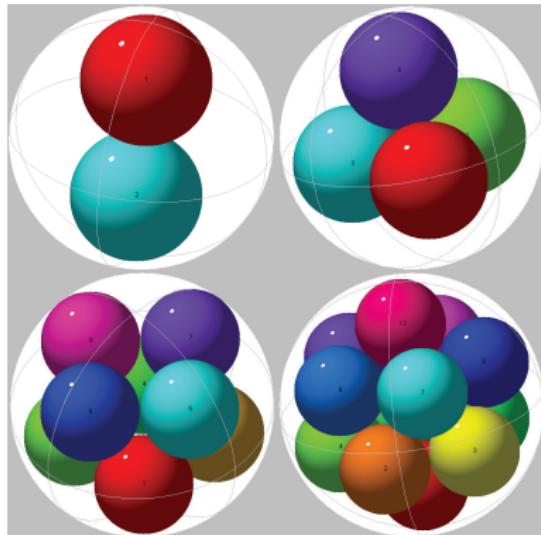
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## Soft packing of cells in cellular aggregates



Hard Packing of Spheres<sup>1</sup>



Soft Packing of Cells<sup>2</sup>

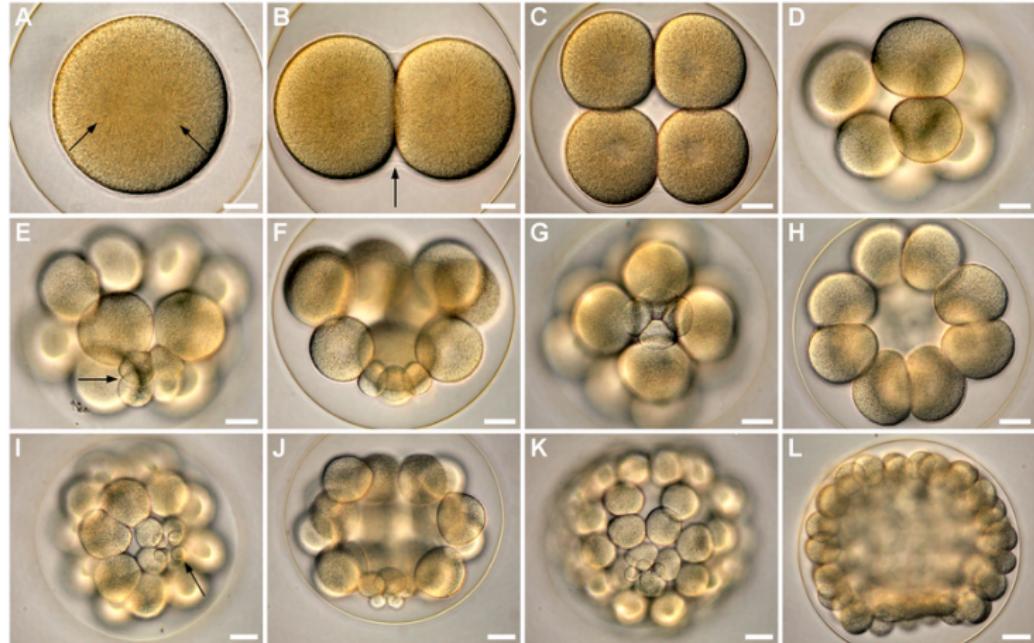
<sup>1</sup> <https://commons.wikimedia.org/w/index.php?curid=29251495>

<sup>2</sup> Embryo of *Echinaster brasiliensis* (A. E Migotto, Universidade de Sao Paulo)  
<https://www.cell.com/pictureshow/embryogenesis>

# Soft packing problem: Overview

- ▶ Motivation
  - ▶ Embroyogenesis
  - ▶ Tumor growth
- ▶ Relevant numerical models
  - ▶ Lattice (Cellular automata) and Off-Lattice (Vertex and cell based) models.
- ▶ Phase field formulation of soft packing
- ▶ Mechanics of soft packing
- ▶ Results
- ▶ Summary

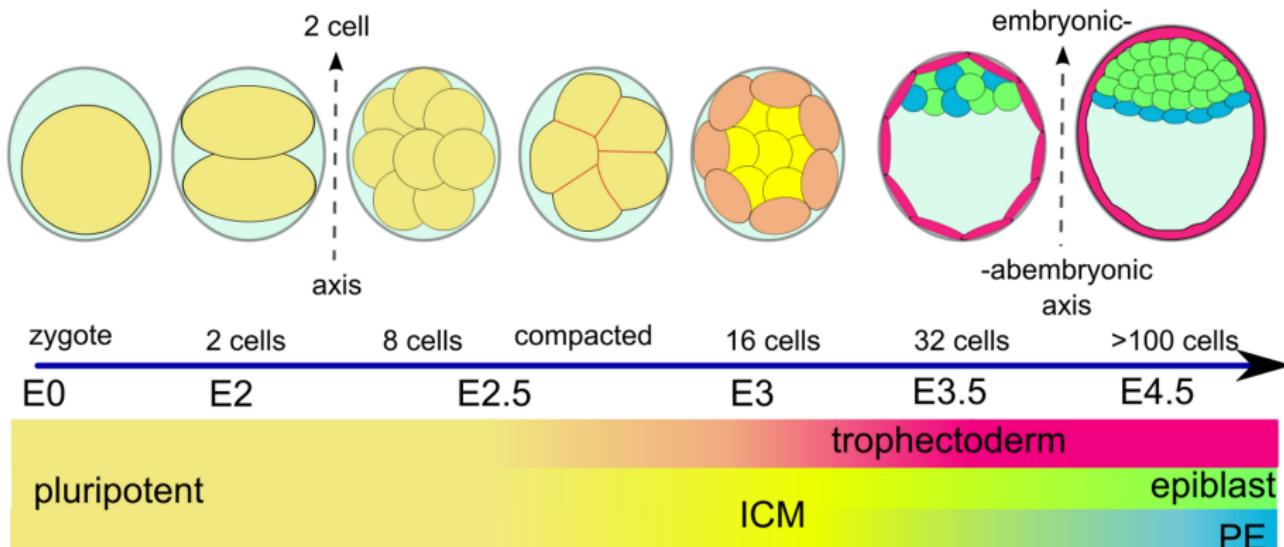
## Motivation: Embryogenesis



Early cleavages of *C. subdepressus* under light microscopy [Reference: B. C. Vellutini and A. E. Migotto, PLOS One, 2010]

Embryogenesis in *C. subdepressus*

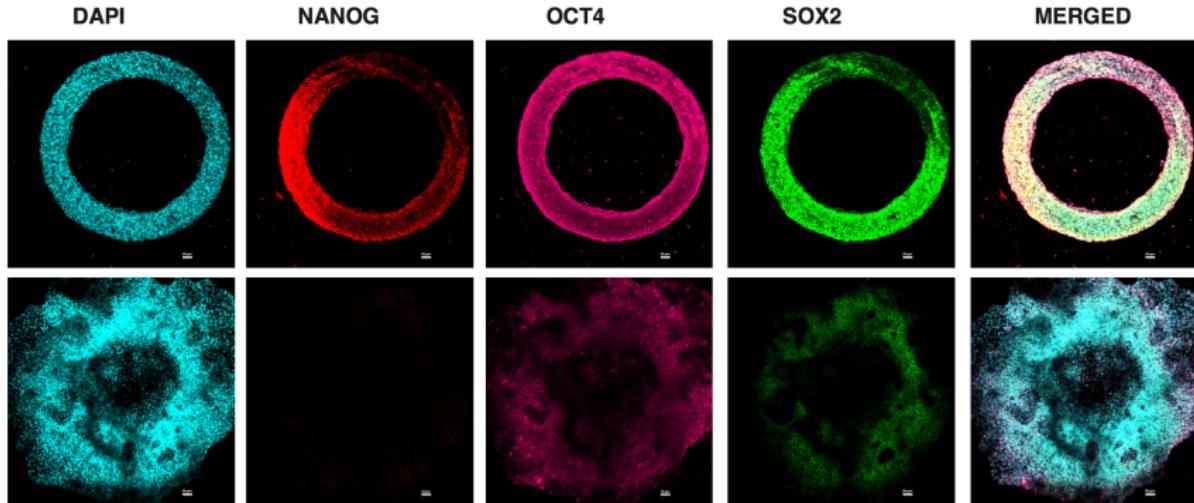
## Motivation: Embryogenesis



Schematic view of morphological and lineage specification steps during the early mouse embryonic development [Reference: Krupinski P, Chickarmane V, Peterson C (2011), PLoS Comput Biol 7(5): e1001128]

## Motivation: Embryogenesis

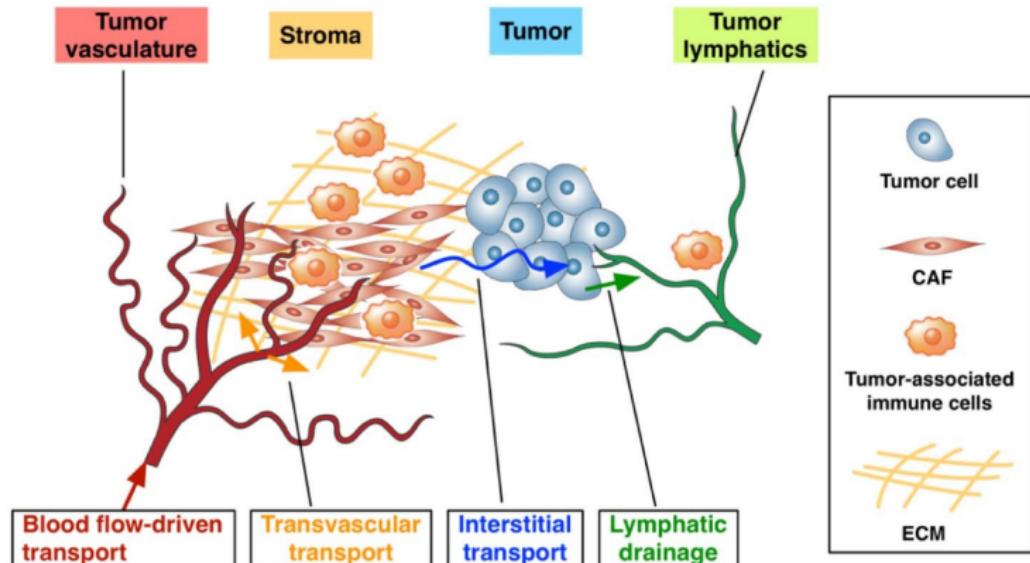
-BMP4



+BMP4

Expression of various transcription factors under different BMP4 concentrations and domain geometries. [Experiments by Tugba Topal, University of Michigan.]

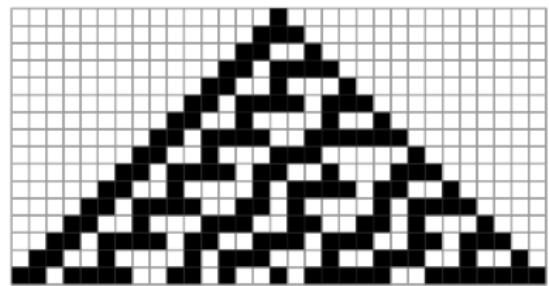
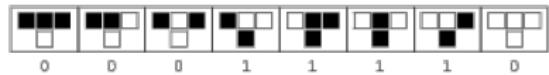
## Motivation: Tumor growth



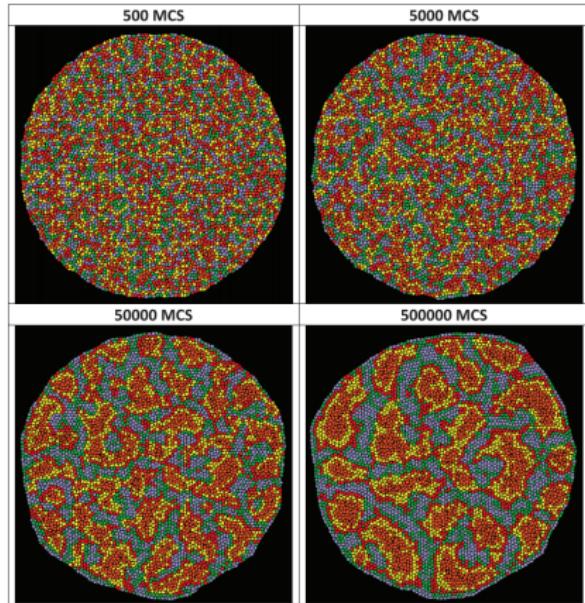
Complexity of the tumor microenvironment [Reference: Bumsoo Han et al., Cancer Letters, Vol. 380: 1, 2016]

Cell packing in growing tumors [Reference: Kristen Mills Lab, RPI]

## Relevant numerical models: On-Lattice (Cellular automata / High-Q Potts) models



Cellular automata rules<sup>1</sup>

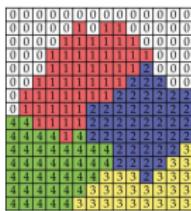


Clustering dynamics using CA models<sup>2</sup>

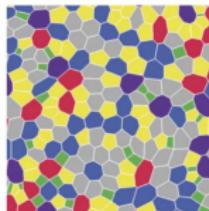
<sup>1</sup> <http://mathworld.wolfram.com/CellularAutomaton.html>

<sup>2</sup> Y. Zhang et al., PLoS ONE 6(10): e24999. doi:10.1371/journal.pone.0024999, 2011

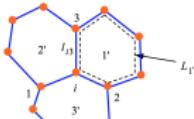
Relevant numerical models: Off-lattice (Vertex and Cell based) models



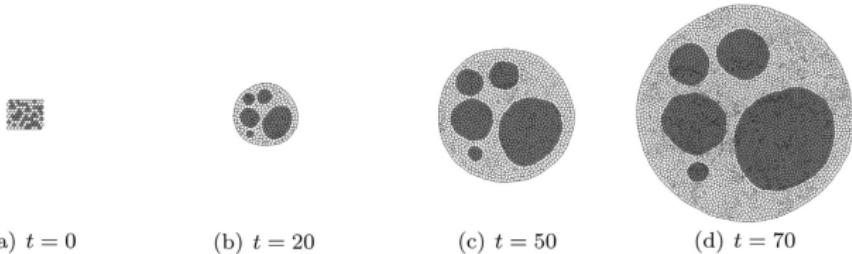
## Comparison of lattice based and off-lattice models<sup>1</sup>



A hexagonal lattice structure composed of black hexagons. The boundaries between the hexagons are highlighted with a combination of red and blue lines, creating a pattern of alternating colored segments along the edges.



## Illustration of vertex dynamics models<sup>2</sup>



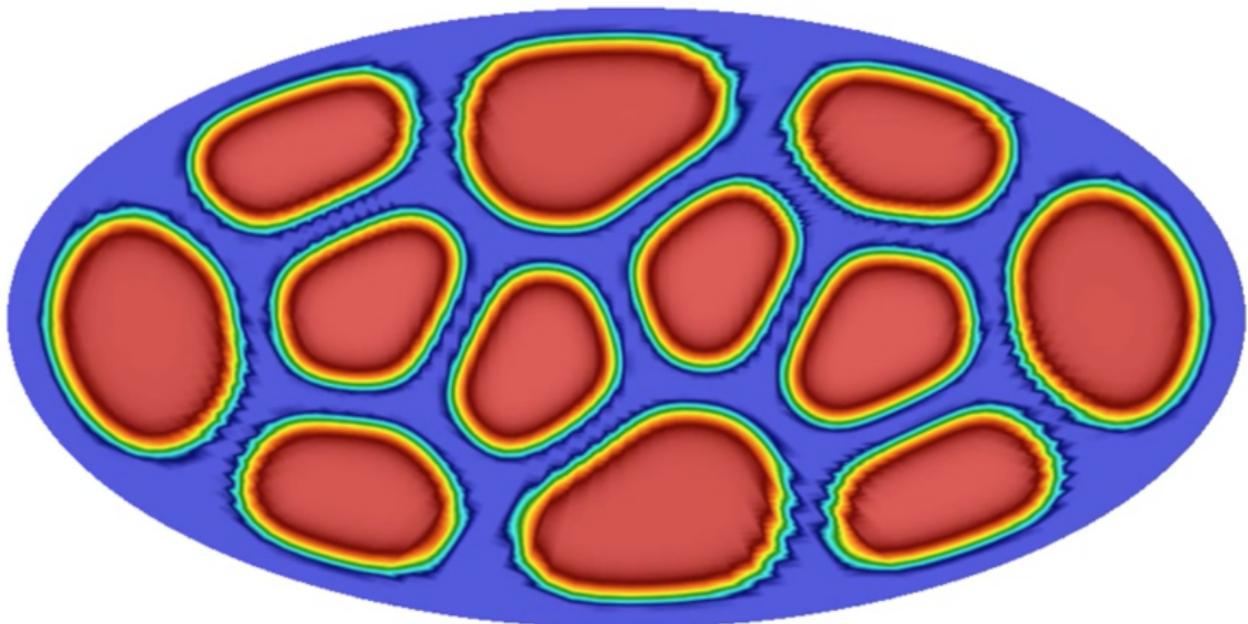
## Simulation of cell sorting using the Nagai-Honda vertex dynamics model<sup>3</sup>

<sup>1</sup> P.J. Albert, Cell Adhesion & Migration, 10, 2016

<sup>2</sup> GK. Xu et al., Journal of Biomechanics, 49, 2016

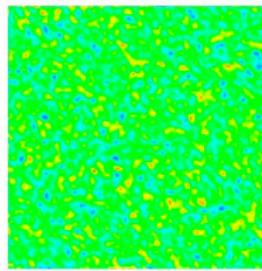
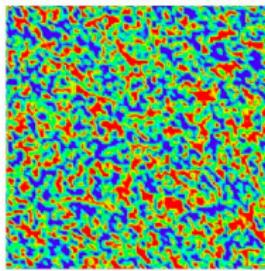
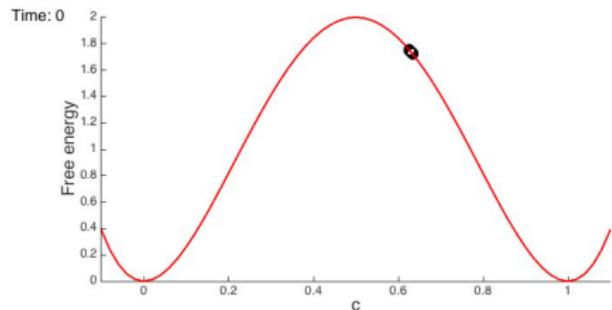
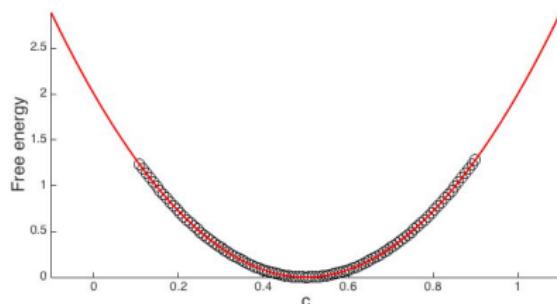
<sup>3</sup> A. G. Fletcher et al., Progress in Biophysics and Molecular Biology, 113, 2013

## Soft packing: A novel phase field approach



Phase field simulation of soft packing  
<https://arxiv.org/abs/1806.01410>

## Phase field modeling



Comparison of Fickian diffusion and higher order diffusion

## Phase field modeling

Cahn-Hilliard dynamics

$$\Pi(c, \nabla c) = \int_{\Omega} [f(c) + \nabla c \cdot \kappa(\nabla c) \nabla c] dV$$

Chemical potential:

$$\mu = \delta_c \Pi(c, \nabla c)$$

Kinetics:

$$\frac{\partial c}{\partial t} = \nabla \cdot (-\mathbf{L}(\nabla c) \nabla \mu)$$

- ▶ Models evolution of conserved fields like composition.
- ▶ Fourth order PDE with complex anisotropic dependencies.

Allen-Cahn dynamics

$$\Pi(\eta_i, \nabla \eta_i) = \int_{\Omega} [f(\eta_i) + \nabla \eta_i \cdot \kappa(\nabla \eta_i) \nabla \eta_i] dV$$

Chemical potential:

$$\mu = \delta_{\eta_i} \Pi(\eta_i, \nabla \eta_i)$$

Kinetics:

$$\frac{\partial \eta_i}{\partial t} = -(\mathbf{L}(\nabla \eta_i) \mu)$$

- ▶ Models evolution of non-conserved fields like structural order parameters.
- ▶ System of highly coupled second order PDE's.

van der Waals, Verhandel. Konink. Akad. Westen. Amsterdam, 1893  
Cahn & Hilliard, J. Chem. Phys., 1958

## Soft packing: A novel phase field approach

Let  $\Omega \in \mathbb{R}^2$  with a smooth boundary  $\partial\Omega$ . Scalar fields  $c_k$ ,  $k = 1, \dots, N$  with  $c_k \in [0, 1]$  serve to delineate the interior and exterior of the cell numbered  $k$ . Here, the interior of cell  $k$  is  $\omega_k \subset \Omega$ , where  $\omega_k = \{\mathbf{X} \in \Omega | c_k(\mathbf{X}) = 1\}$ . The exterior is  $\Omega \setminus \omega_k$ . The free energy density function is built up beginning with the following form:

$$\psi_1(c_k) = \alpha c_k^2 (c_k - 1)^2 + \frac{\kappa}{2} |\nabla c_k|^2$$

The total free energy of the multi-cell aggregate is a functional  $\Pi[\mathbf{c}]$ , defined as

$$\begin{aligned}\Pi[\mathbf{c}] &:= \int_{\Omega} \psi(\mathbf{c}, \nabla \mathbf{c}) \, dV \\ &= \int_{\Omega} \left( \sum_{k=1}^N f(c_k) + \sum_{k=1}^N \frac{\kappa}{2} |\nabla c_k|^2 + \sum_{l \neq k} \sum_{k=1}^N \lambda c_k^2 c_l^2 \right) \, dV.\end{aligned}$$

## Variational formulation

Taking the variational derivative with respect to  $c_k$  yields

$$\begin{aligned}\delta\Pi_k[\mathbf{c}; w] &= \frac{d}{d\epsilon} \int_{\Omega} \sum_{k=1}^N \left( f(c_k + \epsilon w) + \frac{\kappa}{2} |\nabla(c_k + \epsilon w)|^2 + \sum_{l \neq k} \lambda(c_k + \epsilon w)^2 c_l^2 \right) dV \Big|_{\epsilon=0} \\ &= \int_{\Omega} w \left( f'(c_k) - \kappa \Delta c_k + \sum_{l \neq k} 2\lambda c_k c_l^2 \right) dV + \int_{\partial\Omega} w \kappa \nabla c_k \cdot \mathbf{n} dS\end{aligned}$$

The chemical potential of the  $k^{\text{th}}$  cell is identified as,

$$\mu_k = f'(c_k) - \kappa \Delta c_k + \sum_{l \neq k} 2\lambda c_k c_l^2$$

Resulting kinetics:

$$\frac{\partial c_k}{\partial t} = - \nabla \cdot (-M \nabla \mu_k) + s_k$$

## Variational formulation

Time discretization:

$$c_k^{n+1} = c_k^n + \Delta t(M \nabla \cdot (\nabla \mu_k^{n+1}) + s_k)$$

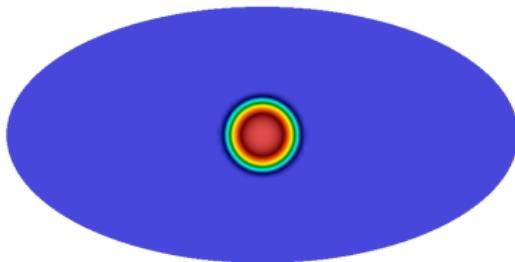
where  $\mu_k^{n+1} = f'^{n+1}(c_k) - \kappa \Delta c_k^{n+1} + \sum_{l \neq k} 2\lambda c_k^{n+1} c_l^{n+1^2}$

Weak formulation:

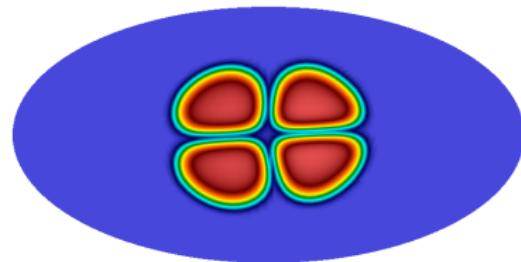
$$\int_{\Omega} w c_k^{n+1} \, dV = \int_{\Omega} (w c_k^n - \nabla w \cdot \Delta t M \nabla \mu_k^{n+1} + w \Delta t s_k) \, dV$$
$$\int_{\Omega} w \mu_k^{n+1} \, dV = \int_{\Omega} (w f'^{n+1}(c_k) + \nabla w \cdot \kappa \nabla c_k^{n+1}) \, dV + \int_{\Omega} w \sum_{l \neq k} 2\lambda c_k^{n+1} c_l^{n+1^2} \, dV$$

Implemented in the *deal.II* finite element framework.

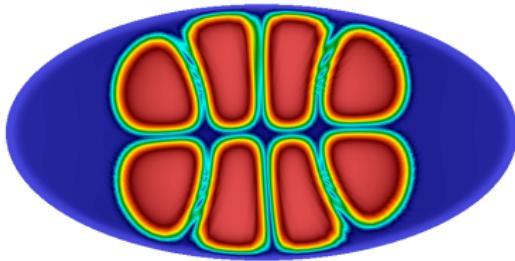
## Results: Cell divisions and soft packing



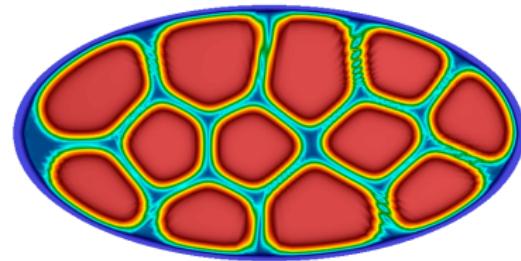
Initial single circular cell



Progression to four cells



Progression to eight cells



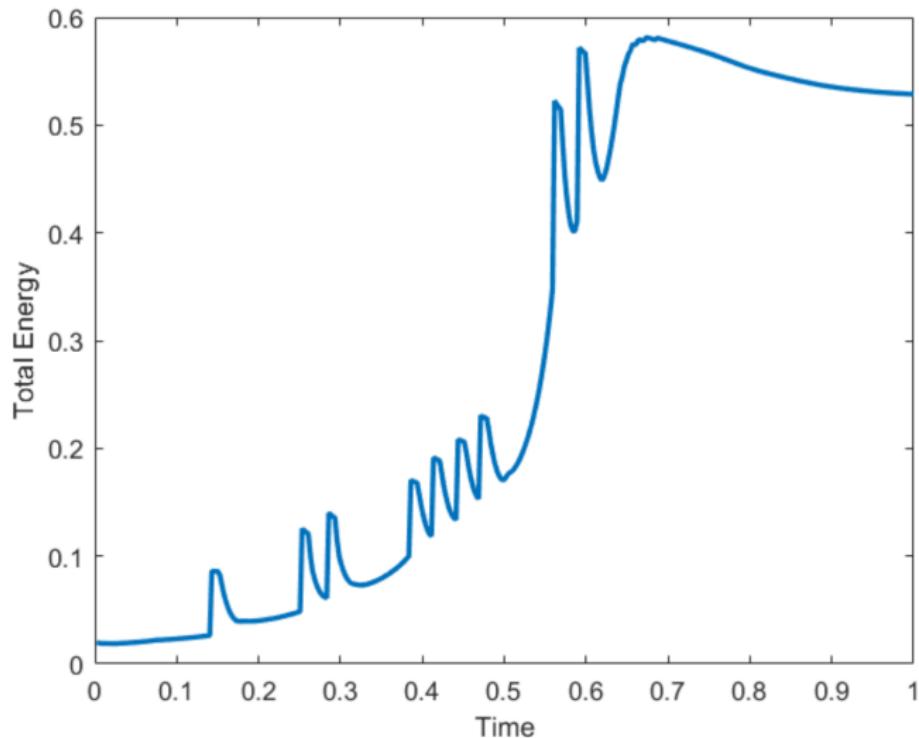
Progression to twelve cells.

Second division of cells.

Progression of cell division and packing with 12 cells.

## Results: Cell divisions and soft packing

Evolution of the phase field energy due to the division and packing processes.



## Observations

Highlights of the phase-only representation of soft packing:

- ▶ Natural representation for cell-cell interactions like cell division, cell-cell contact and cell-cell adhesion\*.
- ▶ No need for explicit topology tracking and topology changes, and model identical in 2D/3D.
- ▶ Diffusion provides a good presentation for cell mobility. Optimal packing solutions depend on the initial conditions and cell mobilities.

Limitations:

- ▶ Lacks explicit representation for mechanics. No underlying material model to represent the cytoskeletal mechanics or cell-cell interactions.
- ▶ Problem size scales with the number of cell considered.
- ▶ Phase field related length and time scales limit space and time discretization.

<https://arxiv.org/abs/1806.01410>

## Phase and Shape model: Basic treatment of mechanics

Shape changes of a cell determined through the changes to the principle moment of inertia ( $I^1, I^2$ ) of the cell:

$$\Pi_{\text{MI}} = \sum_{i=1}^{\text{dim}} \delta^i (I_i^{\text{ref}} - I_i)^2$$

where  $I_1$  and  $I_2$  are obtained from the Moment of Inertia tensor:

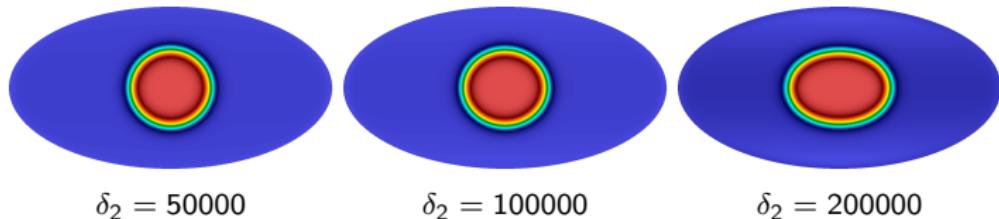
$$\mathbf{I}[c] = \begin{bmatrix} I_{11}[c] & I_{12}[c] \\ I_{21}[c] & I_{22}[c] \end{bmatrix} = \begin{bmatrix} \int c \bar{X}_1^2 dV & \int c \bar{X}_1 \bar{X}_2 dV \\ \int c \bar{X}_1 \bar{X}_2 dV & \int c \bar{X}_2^2 dV \end{bmatrix}$$

Modified free energy functional:

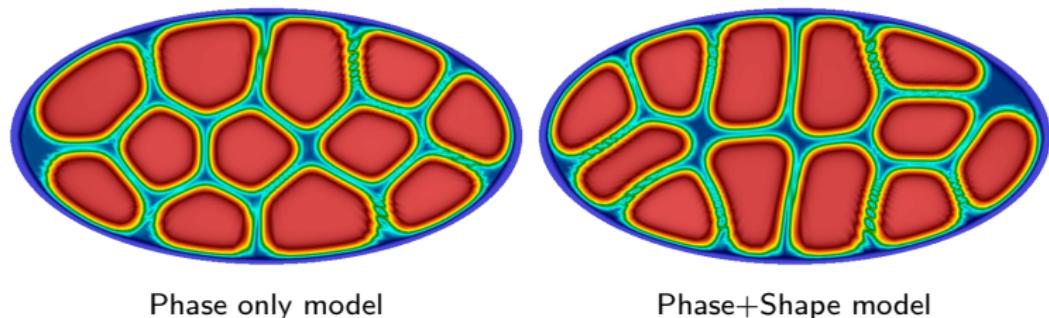
$$\begin{aligned} \Pi[\mathbf{c}, \nabla \mathbf{c}] := & \int_{\Omega} \left( \sum_{k=1}^N f(c_k) + \sum_{k=1}^N \frac{\kappa}{2} |\nabla c_k|^2 + \sum_{l \neq k} \sum_{k=1}^N \lambda c_k^2 c_l^2 \right) dV \\ & + \sum_{k=1}^N \sum_{i=1}^{\text{dim}} \delta_k^i (I_i^{k \text{ref}} - I_i^k)^2 \end{aligned} \quad (1)$$

## Results: Cell divisions and soft packing

Equilibrium shapes controlled by the shape parameters:



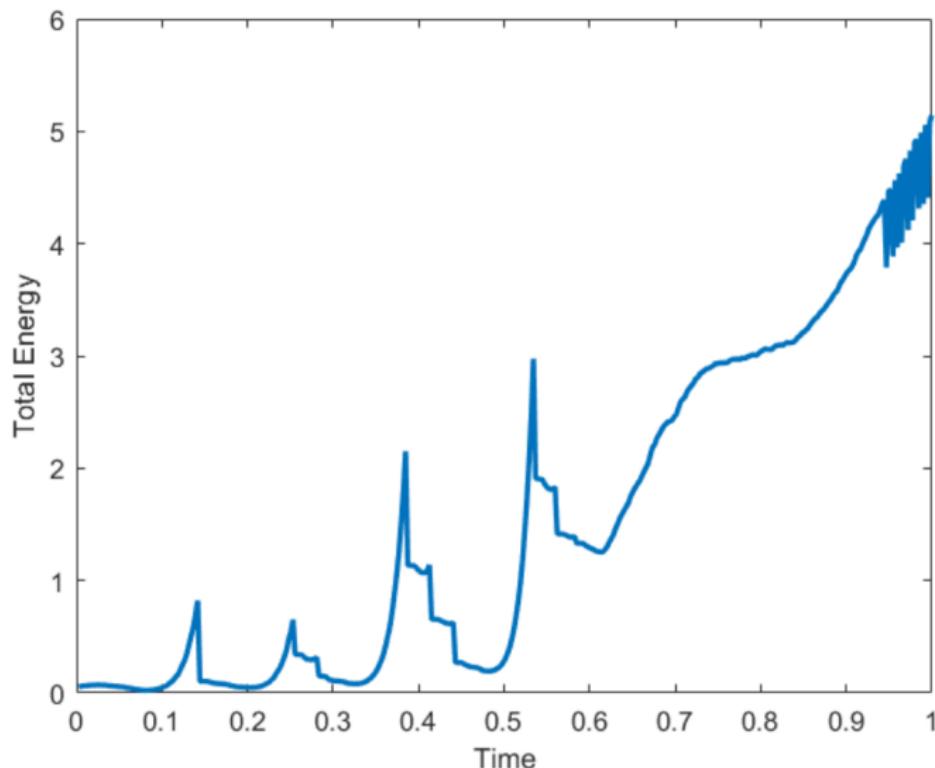
Comparison of phase only model with the phase and shape model:



Progression of cell division and packing with 12 cells.

## Results: Cell divisions and soft packing

Evolution of the phase field energy due to the division and packing processes.



## Summary and look ahead

- ▶ Developed a diffused interface based numerical framework for modeling growth and packing of cell aggregates. Salient features:
  - ▶ No discrete interface evolving mechanisms like those employed in lattice, cell-centric and vertex dynamics models needed.
  - ▶ Time evolution occurs at realistic time scales controlled by the growth rate, or doubling time of the cells, and does not need equilibrations needed by other discrete models.
  - ▶ Any arbitrary cell shape can be represented without being limited to polygonal shapes or a jagged representation of the cell boundary.
  - ▶ Basic model for incorporating mechanics and material models of the underlying cytoskeletal network.
- ▶ Ongoing numerical work on incorporating (1) A material model in place of the shape model, (2) Active parameter tracking to allow for scaling independent of the number of cells.
- ▶ Key applications: (1) Soft packing in cells, (2) Patterning in embryogenesis, (3) Other problems involving cell aggregates like collective cell motion.

Thanks!!!

Questions ?