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

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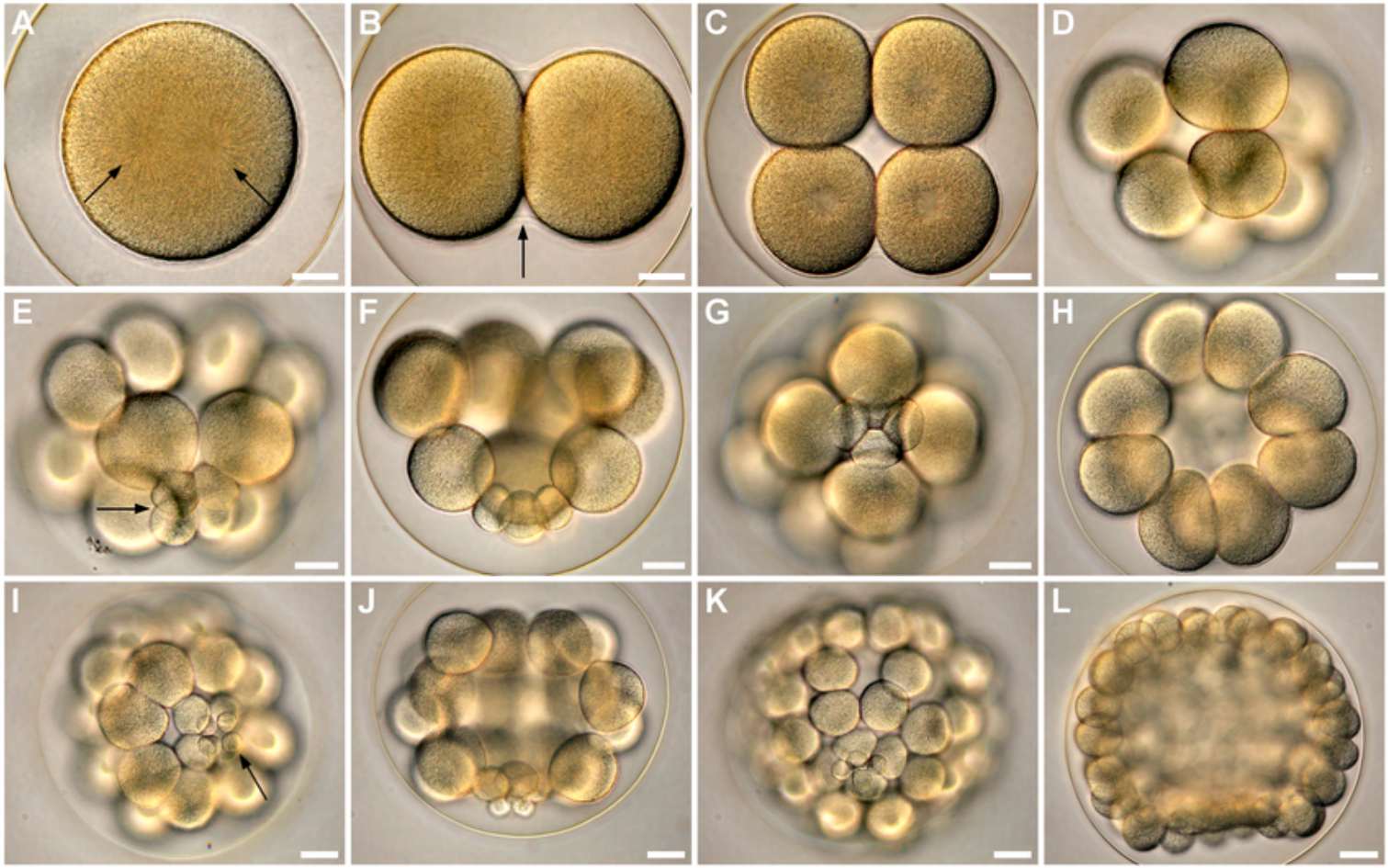
Motivation: Embroyogenesis



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

Embroyogenesis in C. subdepressus

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

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

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

Variational formulation

Taking the variational derivative with respect to c_k yields

$$\delta\Pi_k[\mathbf{c}; w] = \frac{\mathrm{d}}{\mathrm{d}\epsilon} \int_\Omega \sum_{k=1}^{N} \left(f(c_k + \epsilon w) + \frac{\kappa}{2} |\boldsymbol{\nabla}(c_k + \epsilon w)|^2 + \sum_{l \neq k} \lambda (c_k + \epsilon w)^2 c_l^2 \right) \mathrm{d}V \Bigg|_{\epsilon=0}$$

$$= \int_\Omega w \left(f'(c_k) - \kappa \Delta c_k + \sum_{l \neq k} 2\lambda c_k c_l^2 \right) dV + \int_{\partial\Omega} w \kappa \boldsymbol{\nabla} c_k \cdot \mathbf{n} \, dS$$

The chemical potential of the k^{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:

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

Variational formulation

Time discretization:

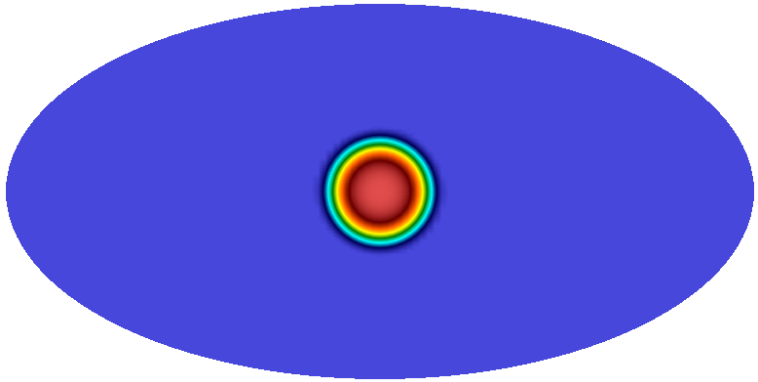
$$c_k^{n+1} = c_k^n + \Delta t(M\ \nabla \cdot (\nabla \mu_k^{n+1}) + s_k)$$
$$\text{where} \quad \mu_k^{n+1} = f'^{n+1}(c_k) - \kappa \Delta c_k^{n+1} + \sum_{l \neq k} 2\lambda c_k^{n+1} {c_l^{n+1}}^2$$

Weak formulation:

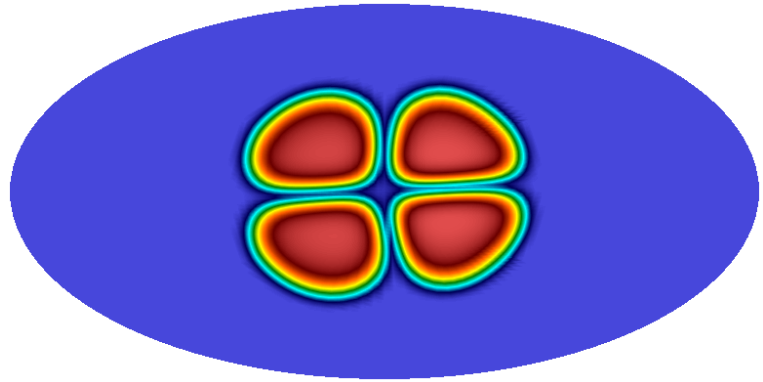
$$\int_\Omega w c_k^{n+1}\ \mathrm{d}V = \int_\Omega (w c_k^n - \nabla w \cdot \Delta t M \nabla \mu_k^{n+1} + w \Delta t s_k)\ \mathrm{d}V$$
$$\int_\Omega w \mu_k^{n+1}\ \mathrm{d}V = \int_\Omega (w f'^{n+1}(c_k) + \nabla w \cdot \kappa \nabla c_k^{n+1}\ dV + \int_\Omega w \sum_{l \neq k} 2\lambda c_k^{n+1}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

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

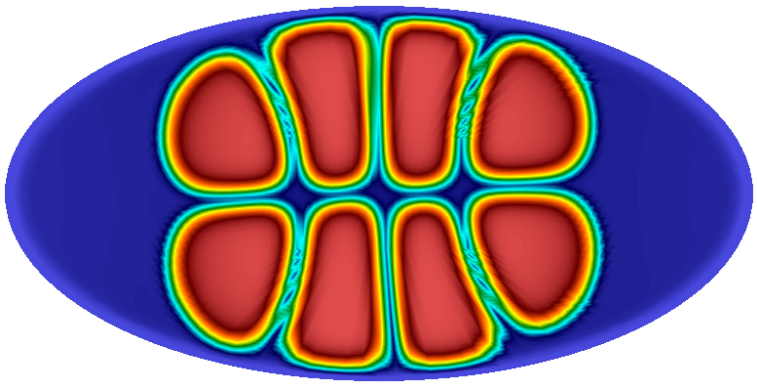
Results: Cell divisions and soft packing



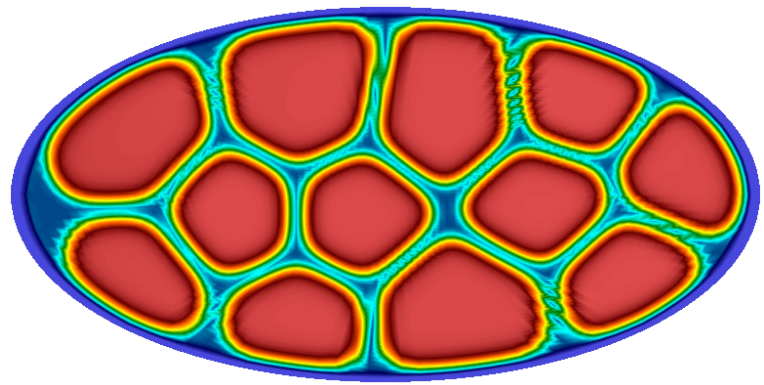
Initial single circular cell



Progression to four cells



Progression to eight cells

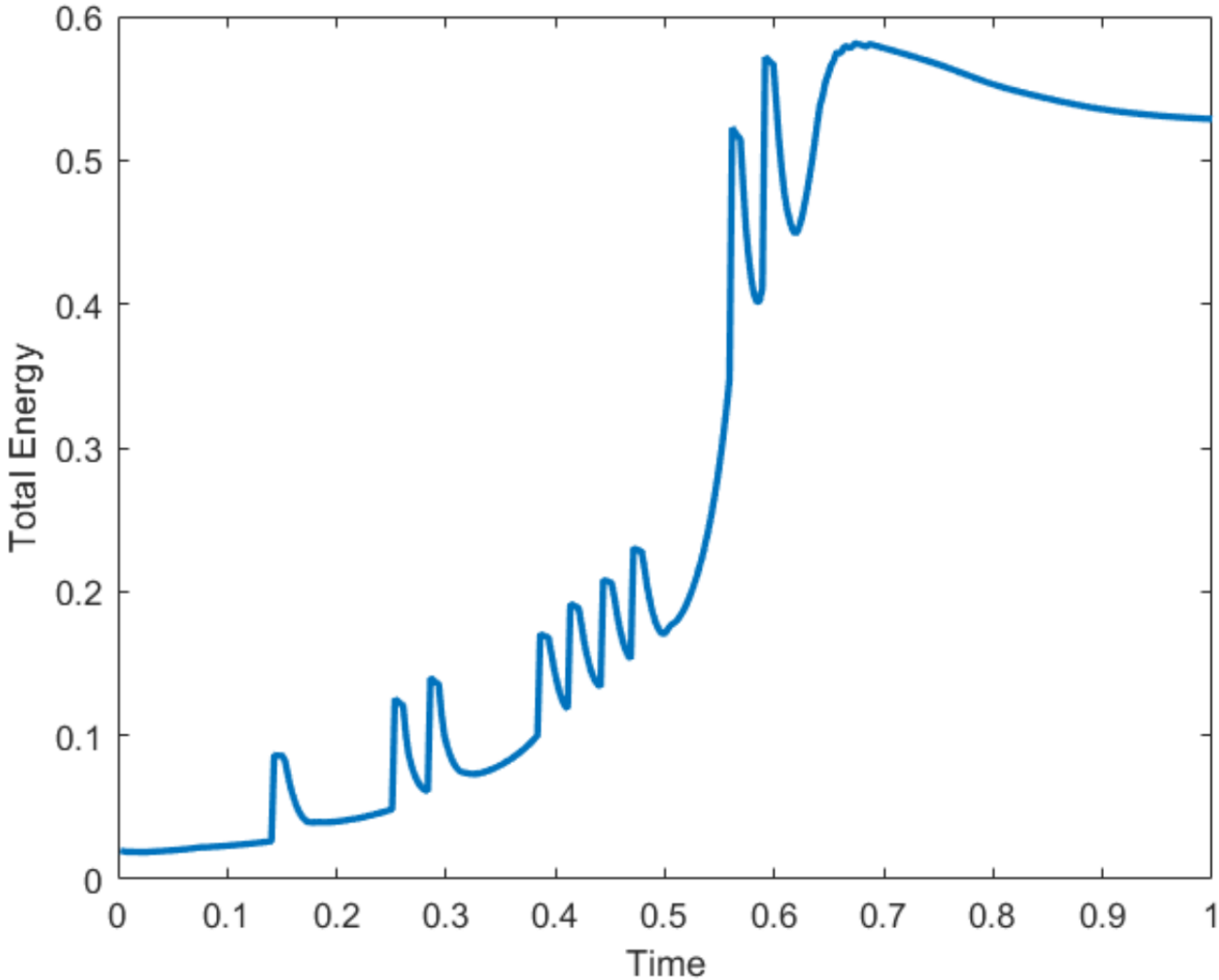


Progression to twelve cells.

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.



Scutoids as a possible geometric solution to three dimensional epithelial cell packing

- Scutoids develop because the apical and basal surface have different neighbours.Changes in cellular aspect ratio promote cellular rearrangements, and coupling between geometrical changes due to bending and line tension energy drives scutoid formation
- Appearance of scutoids is a general feature of the epithelial architecture and is directly affected by surface ratio anisotropy.
- It is significant in its study as experiments reveal a considerable minimization in tissue energy and stabilize soft tissue packing.
- Mathematical modeling and analysis of these complex geometrical shapes is executed using the Voronoi diagram on the plane of the epithelium.
- It is often assumed that this cellular architecture is driven by the cell organization in apical cells.

Summary and look ahead

- Developed a diffused interface based numerical framework for modeling growth and packing of cell aggregates. Salient features:
  - No discreet 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.