

A diffuse interface framework for modelling the evolution of multi-cell aggregates as a soft packing problem driven by the growth and division of cells

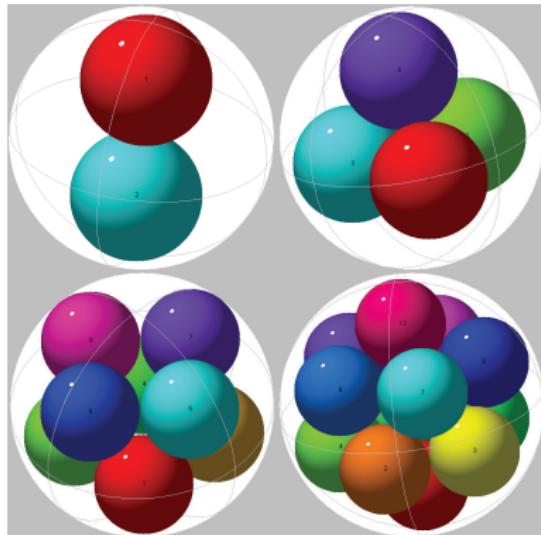
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15th US National Congress on Computational Mechanics (USNCCM)
Austin, TX July 29, 2019

Soft packing of cells in cellular aggregates



Hard Packing of Spheres¹



Soft Packing of Cells²

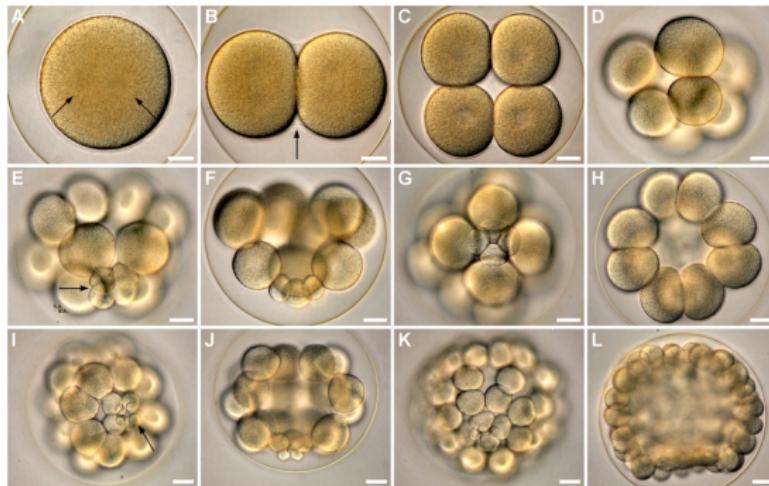
¹ <https://commons.wikimedia.org/w/index.php?curid=29251495>

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

Soft packing problem: Overview

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

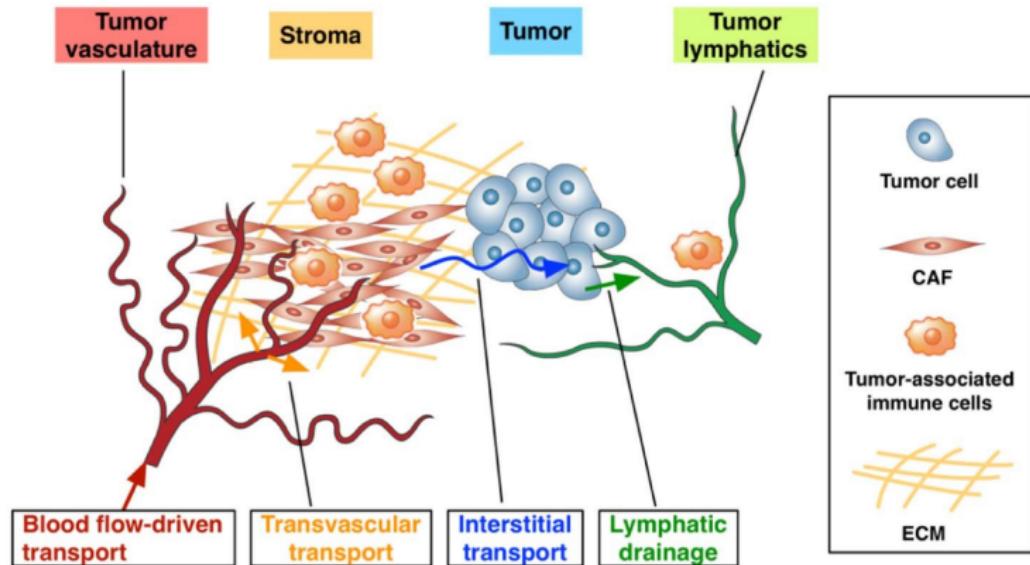
Motivation: Embryogenesis



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

Embryogenesis in *C. subdepressus* (sea urchin)

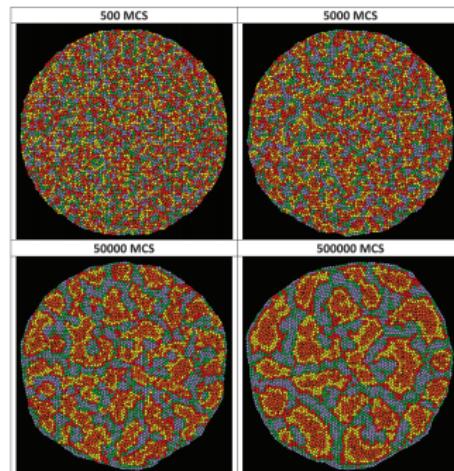
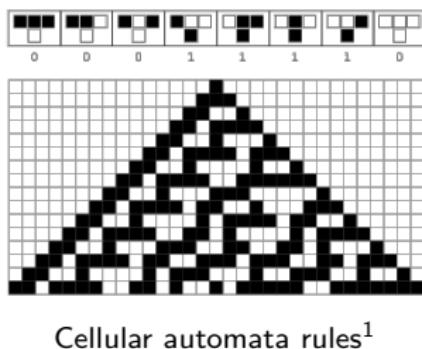
Motivation: Tumor growth



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

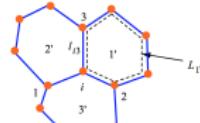
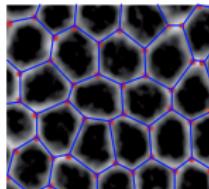
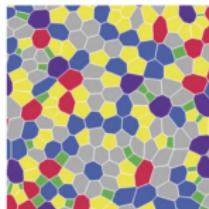
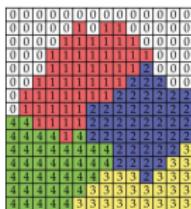


Clustering dynamics using CA models²

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

² 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 models¹

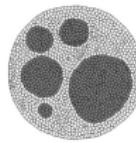
Illustration of vertex dynamics
models²



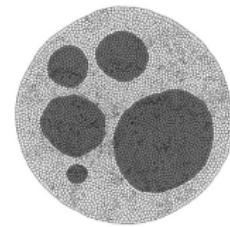
(a) $t = 0$



(b) $t = 20$



(c) $t = 50$



(d) $t = 70$

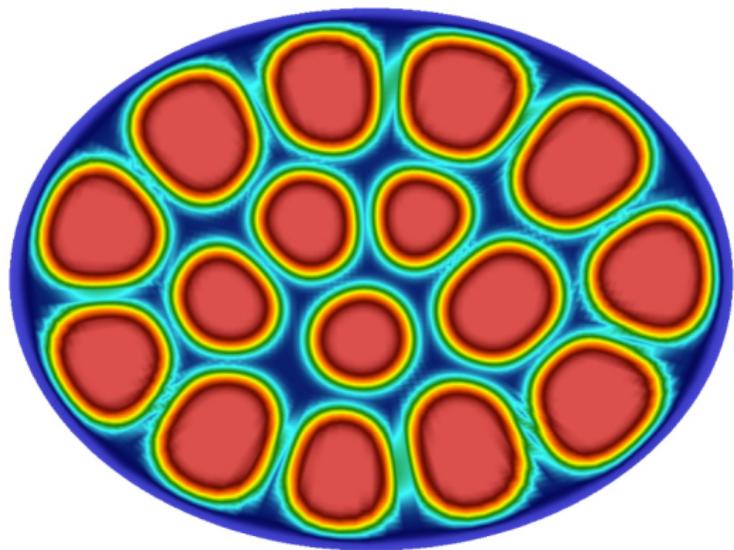
Simulation of cell sorting using the Nagai-Honda vertex dynamics model³

¹ P.J. Albert, Cell Adhesion & Migration, 10, 2016

² G.K. Xu et al., Journal of Biomechanics, 49, 2016

³ 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

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:

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

- ▶ 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:

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

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

van der Waals, Verhandel. Konink. Akad. Wetsten. 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

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

The chemical potential of the k^{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:

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

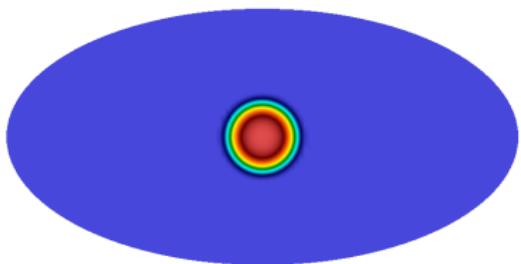
where $\mu_k^{n+1} = f'^{n+1}(c_k) - \kappa \Delta c_k^{n+1} + \sum_{l \neq k} 2\lambda c_k^{n+1} c_l^{n+1^2}$

Weak formulation:

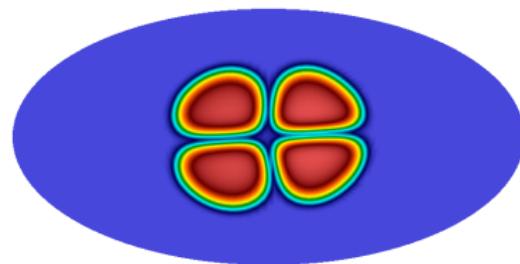
$$\int_{\Omega} w c_k^{n+1} \, dV = \int_{\Omega} (w c_k^n - \nabla w \cdot \Delta t M \nabla \mu_k^{n+1} + w \Delta t s_k) \, dV$$
$$\int_{\Omega} w \mu_k^{n+1} \, dV = \int_{\Omega} (w f'^{n+1}(c_k) + \nabla w \cdot \kappa \nabla c_k^{n+1}) \, dV + \int_{\Omega} w \sum_{l \neq k} 2\lambda c_k^{n+1}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

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

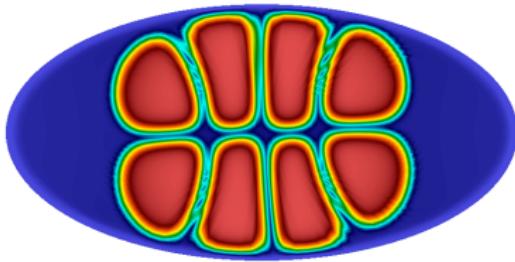
Results: Cell divisions and soft packing - Increasing Volume



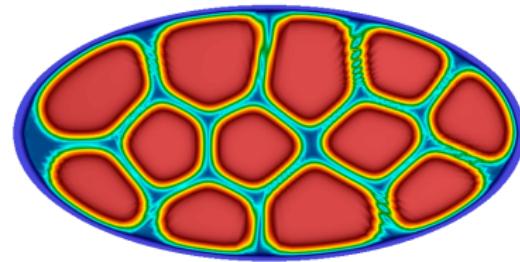
Initial single circular cell



Progression to four cells



Progression to eight cells

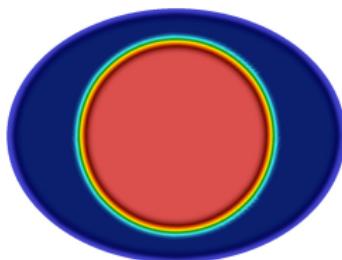


Progression to twelve cells.

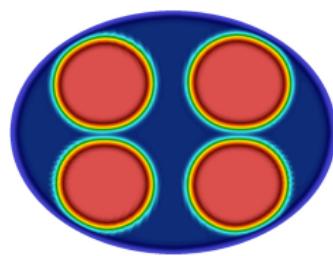
Second division of cells.

Progression of cell division and packing with 12 cells.

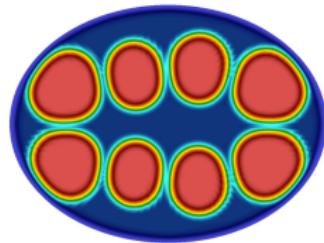
Results: Cell divisions and soft packing - Constant Volume



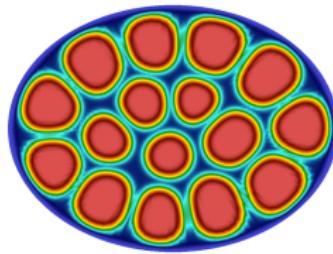
Initial single circular cell



Progression to four cells



Progression to eight cells

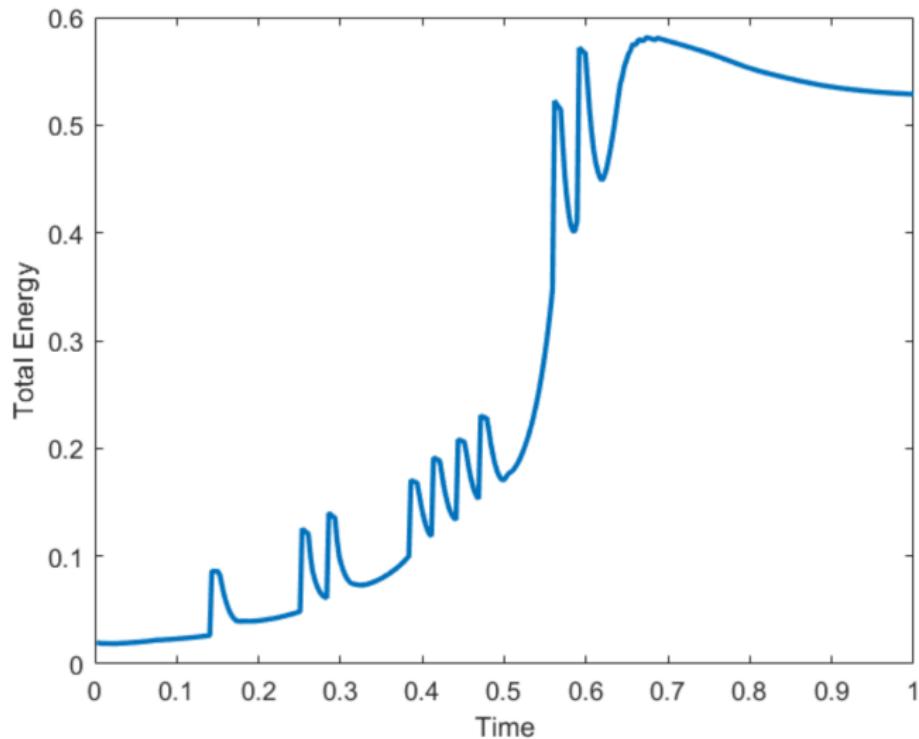


Progression to sixteen cells.

Progression of cell division and packing with 16 cells.

Results: Cell divisions and soft packing

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



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:

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

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

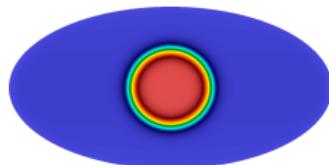
$$I[c] = \begin{bmatrix} I_{11}[c] & I_{12}[c] \\ I_{21}[c] & I_{22}[c] \end{bmatrix} = \begin{bmatrix} \int c \bar{X}_1^2 dV & \int c \bar{X}_1 \bar{X}_2 dV \\ \int c \bar{X}_1 \bar{X}_2 dV & \int c \bar{X}_2^2 dV \end{bmatrix}$$

Modified free energy functional:

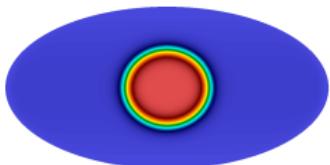
$$\begin{aligned} \Pi[c, \nabla c] := & \int_{\Omega} \left(\sum_{k=1}^N f(c_k) + \sum_{k=1}^N \frac{\kappa}{2} |\nabla c_k|^2 + \sum_{l \neq k} \sum_{k=1}^N \lambda c_k^2 c_l^2 \right) dV \\ & + \sum_{k=1}^N \sum_{i=1}^{\dim} \delta_k^i (I_i^{k\text{ref}} - I_i^k)^2 \end{aligned} \quad (1)$$

Results: Cell divisions and soft packing

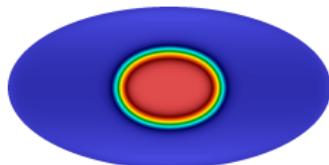
Equilibrium shapes controlled by the shape parameters:



$$\delta_2 = 50000$$

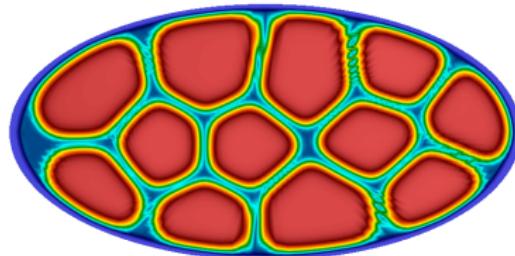


$$\delta_2 = 100000$$

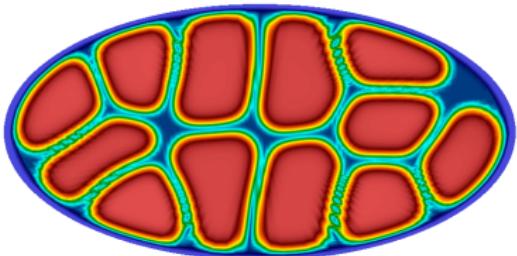


$$\delta_2 = 200000$$

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



Phase only model



Phase+Shape model

Progression of cell division and packing with 12 cells.

Summary and look ahead

- ▶ Demonstrated a diffused interface based numerical framework for modeling growth and packing of cell aggregates. This work is now published and referenced as:
J. Jiang, K. Garikipati, S. Rudraraju "A diffuse interface framework for modelling the evolution of multi-cell aggregates as a soft packing problem due to growth and division of cells", Bulletin of Mathematical Biology , 2019.
- ▶ 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.
 - ▶ Many arbitrary cell shape can be represented without being limited to polygonal shapes or a jagged representation of the cell boundary.
- ▶ 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.