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

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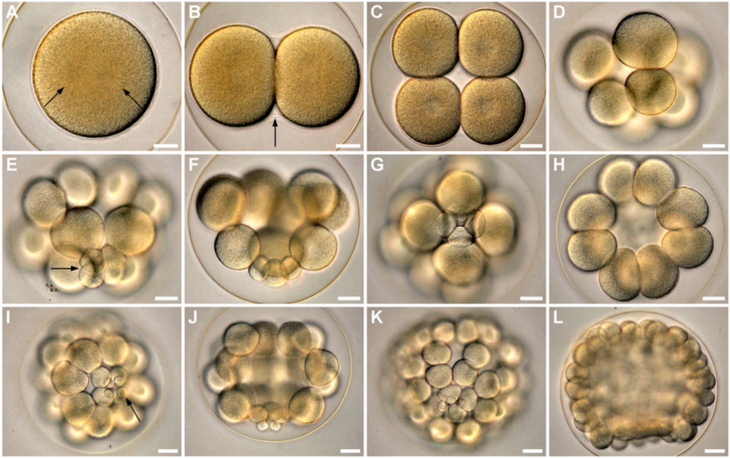
Soft packing problem: Overview

- Motivation
  - Embroyogenesis
  - Tumor growth
- Previous models
  - Vertex based, cell based, cellular automata.
- Phase field formulation of soft packing
- Mechanics of soft packing
- Material models
- Summary

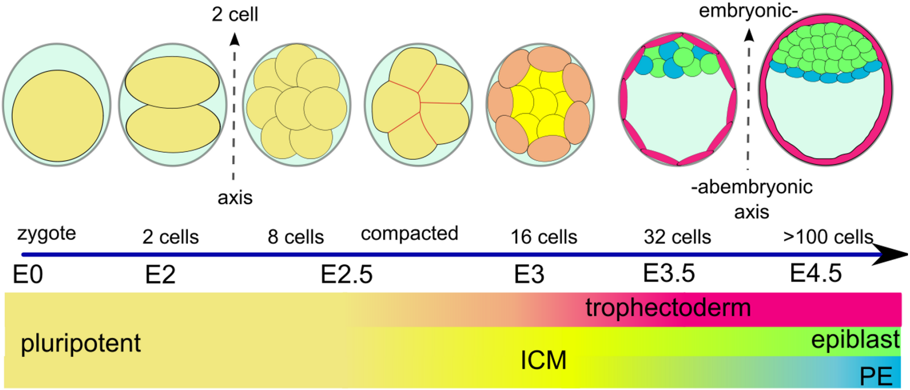
Motivation: Embroyogenesis



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

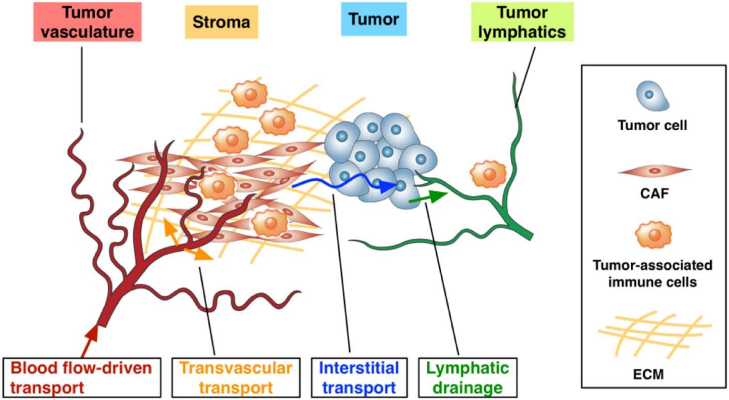
Embroyogenesis in C. subdepressus

Motivation: Embroyogenesis



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]

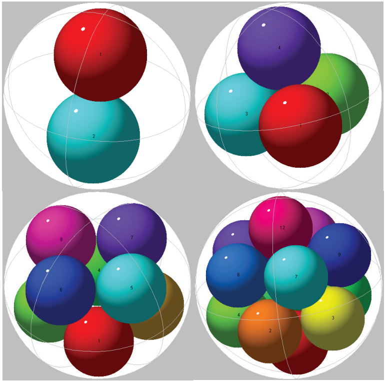
Motivation: Tumor growth



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

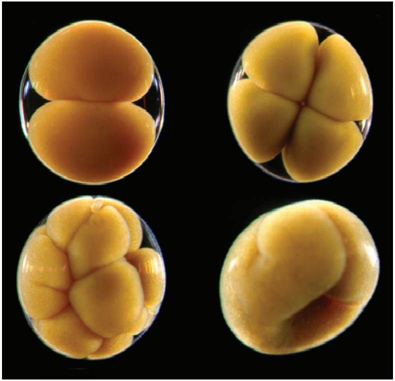
Cell packing in growing tumors [Reference: Mills Lab, RPI]

Soft packing of cells in cellular aggregates



Hard Packing of Spheres [1]

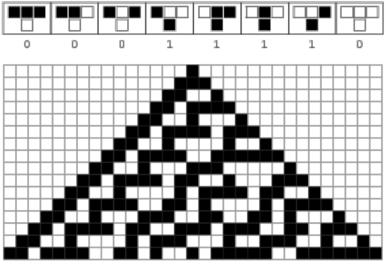
?



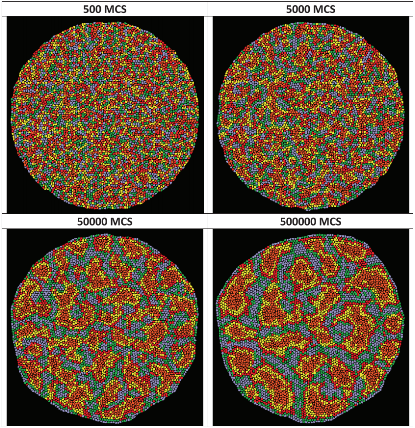
Soft Packing of Cells [2]

[1] https://commons.wikimedia.org/w/index.php?curid=29251495
[2] Embryo of Echinaster brasiliensis (A. E Migotto, Universidade de Sao Paulo)
https://www.cell.com/pictureshow/embryogenesis

Relevant numerical models: Cellular automata / High-Q Potts models



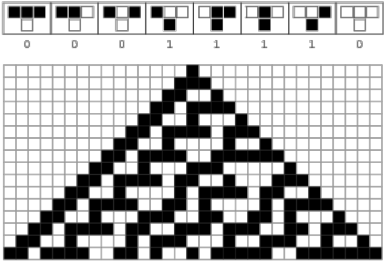
Cellular automata rules[1]



Clustering dynamics using CA models[2]

[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: Cell and vertex based models



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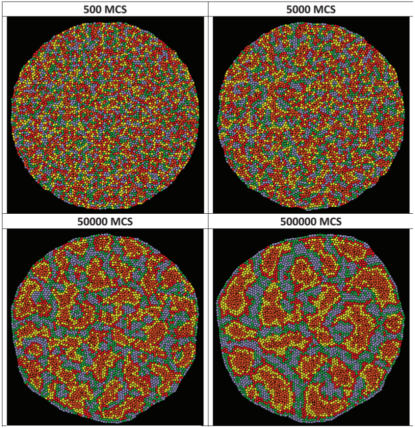

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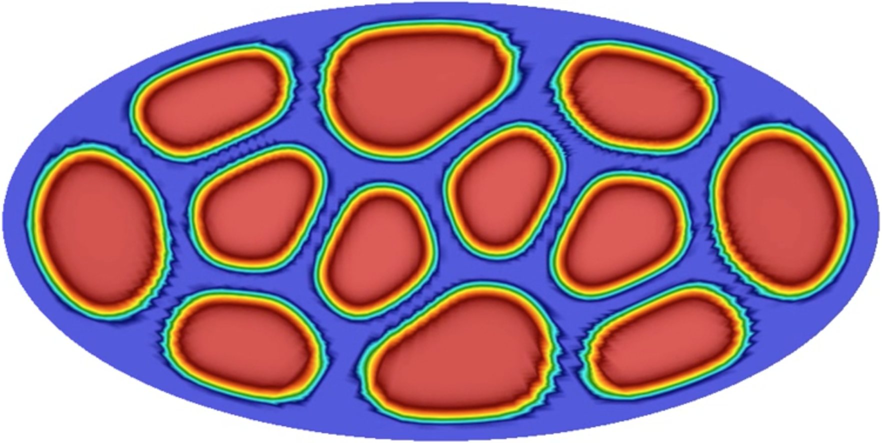
Soft packing: A novel phase field approach



Phase field simulation of soft packing

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:

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

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

Allen-Cahn dynamics

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

Chemical potential:

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

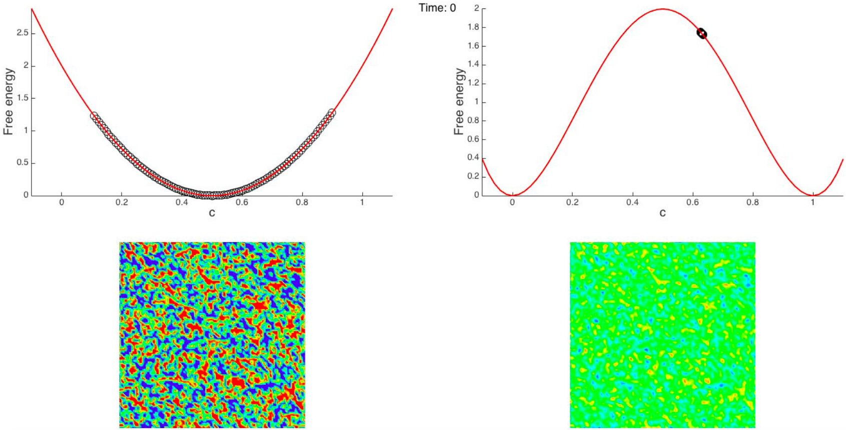
Kinetics:

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

- 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

Phase field modeling



Comparison of Fickian diffusion and higher order diffusion

Soft packing: A novel phase field approach

Let $\Omega \in \mathbb{R}^2$ with a smooth boundary $\partial\Omega$. Scalar fields c_k, $k = 1, \ldots, N$ 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 $\omega_k = \{\boldsymbol{X} \in \Omega | c_k(\boldsymbol{X}) = 1\}$. The exterior is $\Omega \backslash \omega_k$. The free energy density function is built up beginning with the following form:

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

where the double-well term, $f(c_k) = \alpha c_k^2 (c_k - 1)^2$, enforces segregation into ω_k and $\Omega \backslash \omega_k$.

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

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

Here, $\boldsymbol{c} = \{c_1, \ldots, c_N\}$, and λ is a penalty coefficient that enforces repulsion between any two cells k, l thus modelling cell contact.

Soft packing: A novel phase field approach

Taking the variational derivative with respect to c_k in Equation (**??**) yields

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

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

where $\boldsymbol{n}$ is the unit outward normal vector to $\partial\Omega$. The chemical potential of the k^{th} cell is identified as,

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

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

Numerical implementation

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

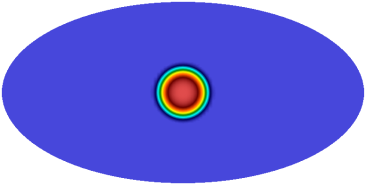
$$\text{where} \quad \mu_k^{n+1} = f'^{\,n+1}(c_k) - \kappa \Delta c_k^{n+1} + \sum_{l \neq k} 2\lambda c_k^{n+1} {c_l^{n+1}}^2$$

The weak form of the problem is: Find $c_k^{n+1} \in \mathscr{S} = \{c \in \mathscr{H}^1(\Omega) | c = 0 \text{ and } \nabla c \cdot \boldsymbol{n} = 0 \text{ on } \partial\Omega\}$ such that for any arbitrary variation $w \in \mathscr{V} = \{w \in \mathscr{H}^1(\Omega) | w = 0 \text{ and } \nabla w \cdot \boldsymbol{n} = 0 \text{ on } \partial\Omega\}$ on c_k, the following residual equations are satisfied:

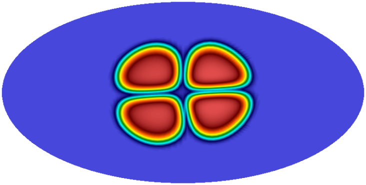
$$\int_\Omega w c_k^{n+1}\, \mathrm{d}V = \int_\Omega (w c_k^n - \boldsymbol{\nabla} w \cdot \Delta t M \boldsymbol{\nabla} \mu_k^{n+1} + w \Delta t s_k\, \mathrm{d}V$$

$$\int_\Omega w \mu_k^{n+1}\, \mathrm{d}V = \int_\Omega (w f'^{\,n+1}(c_k) + \boldsymbol{\nabla} w \cdot \kappa \boldsymbol{\nabla} c_k^{n+1}\ dV + \int_\Omega w \sum_{l \neq k} 2\lambda c_k^{n+1} {c_l^{n+1}}^2)\, \mathrm{d}V$$

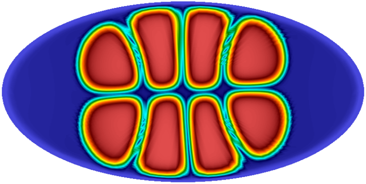
Shape model: Results



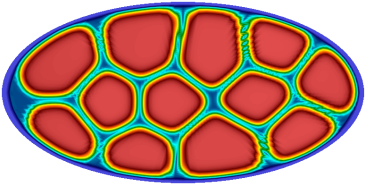
(a) Initial single circular cell



(b) Progression to four cells



(c) Progression to eight cells



(d) Progression to twelve cells.

Shape model: Results

Shape model: Extension to material models

Soft packing: Connection to embroyogenesis

Soft packing: Connection to tumor growth

Summary and ongoing work

Thanks!!!