Tumor growth: from agent-based model to free-boundary problem

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Arizona State University

In collaboration with:

- *Pedro Lowenstein* (Michigan Univ.)
- *Diane Peurichard* (Univ. of Vienna, Austria)

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Center for Scientific Computations And Mathematical Modeling
University of Maryland

Outline

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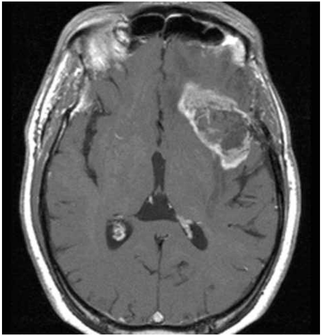
Brain cancer: Glioblastoma



Treatment

- surgery
- radiation therapy
- chemotherapy
- viral therapy

... but **15 – 21** months survival

$\Rightarrow$ *tumor recurrence*

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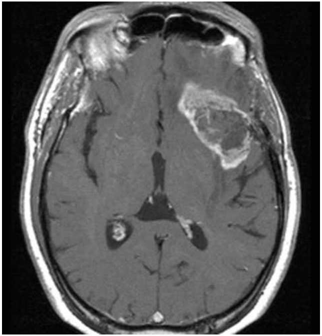

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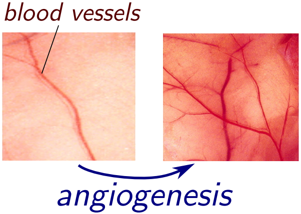
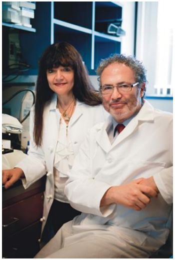


Another approach

blocking angiogenesis (VEGF)

Experiments in mice (Castro-Lowenstein lab)



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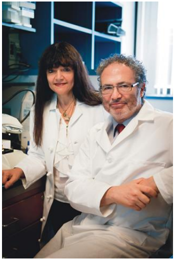

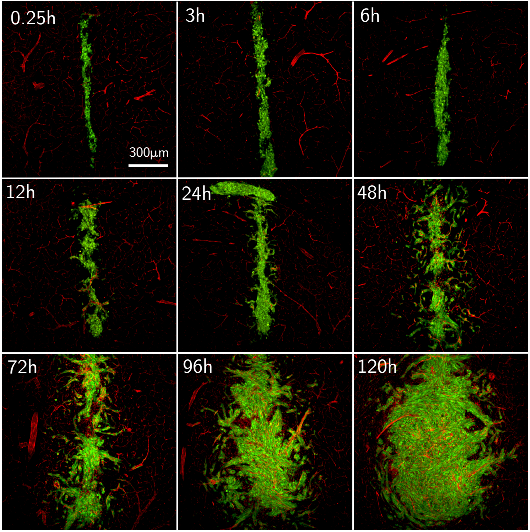

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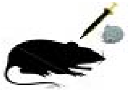
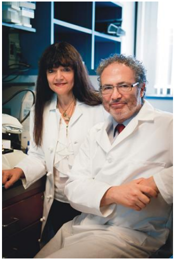
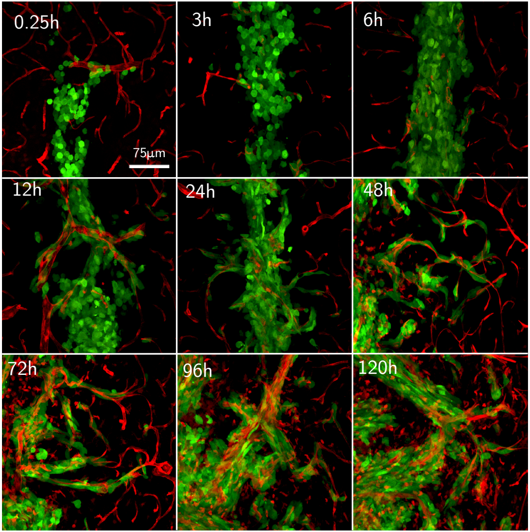
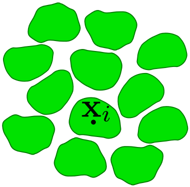






Mathematical Models

- **Agent-based models** (*micro*)
  Each cancer cell is represented: $\mathbf{x}_i \in \mathbb{R}^3$
  $\Rightarrow$ *(large) systems of interacting particles*
  Ref.: Byrne, Drasdo, Deutsch...



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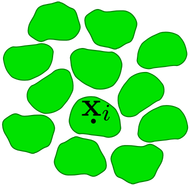

- **Partial Differential Equation** (*macro*)
  Cancer is described as a "mass": $\rho(\mathbf{x}, t)$
  $\Rightarrow$ *reaction-diffusion, hybrid multiscale model*
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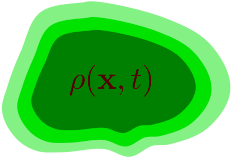

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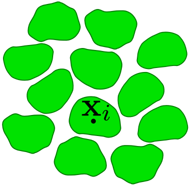

- **Kinetic model** (*mesoscopic*)

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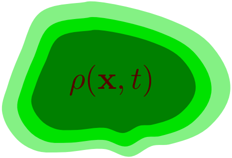
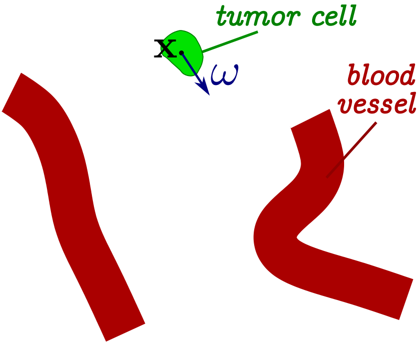


Kinetic model



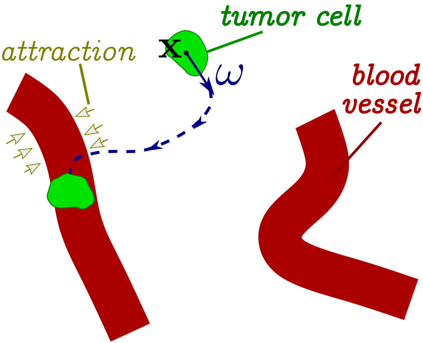
Dynamics:

$$\begin{cases} \mathbf{x}' = c(\mathbf{x})\omega \\ d\omega = \sigma dB_t \end{cases}$$

with V density of blood vessel and

$$c(\mathbf{x}) = \begin{cases} c_0 & \text{if } V(\mathbf{x}) > 0 \\ c_1 & \text{if } V(\mathbf{x}) = 0 \end{cases}$$

Kinetic model



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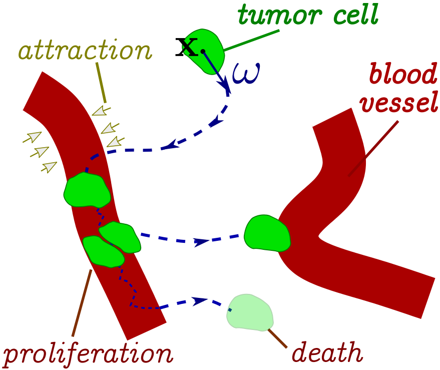

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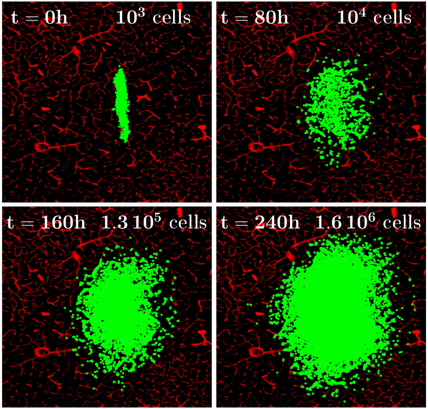
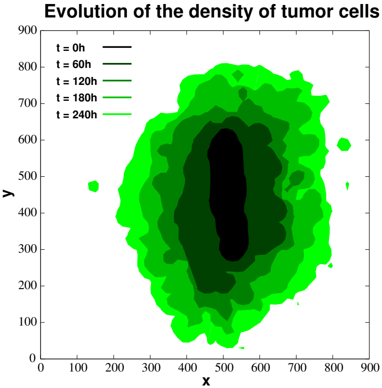
coupled with birth/death process

Kinetic model





Numerical and in vivo experiments show that brain-tumor spread **without** *angiogenesis.*

Outline

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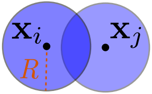
Cell represented by a position $\mathbf{x}_i \in \mathbb{R}^2$ and a fix radius $R > 0$.



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- cells are *pushing* each other:

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with $\phi_{ij} = \phi\left(\left|\frac{\mathbf{x}_j - \mathbf{x}_i}{2R}\right|^2\right)$.

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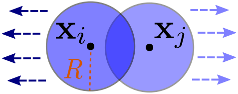

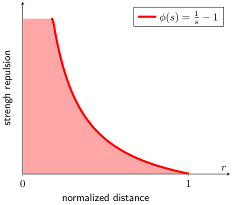

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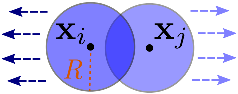

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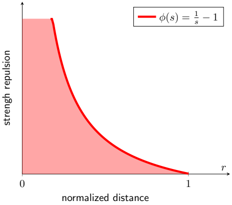

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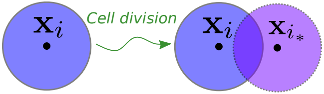
- cells *divide* at a rate $\mu > 0$ (Poisson process):

$$\mathbf{x}_i \rightsquigarrow (\mathbf{x}_i, \mathbf{x}_{i_*})$$



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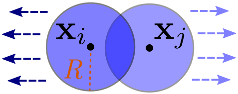

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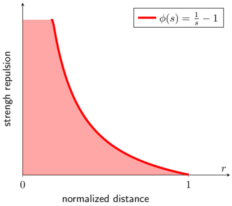

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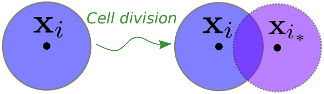

Goal: investigate the dynamics at a *macroscopic scale*.

Numerical experiments

We study three cases:

- **Case 1**: pushing, no cell division $\mu = 0$
- **Case 2**: pushing and cell division
- **Case 3**: *strong* pushing and cell division (repulsion $\phi \rightsquigarrow \frac{\phi}{\varepsilon}$ and $\varepsilon \to 0$)

Numerical experiments

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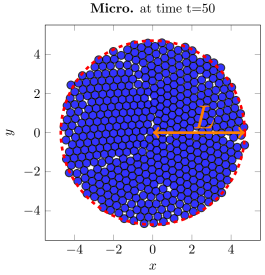
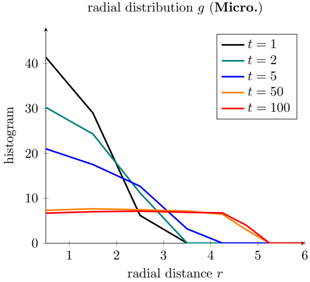
  $\Rightarrow$ *converges to* **compact** *config.*





Numerical experiments

- **Case 2**: pushing and cell division

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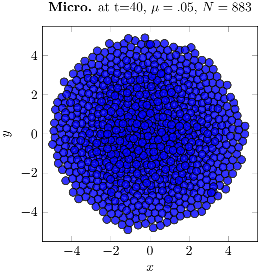
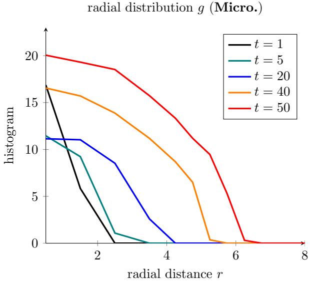
  $\Rightarrow$ *diffuses and growths*





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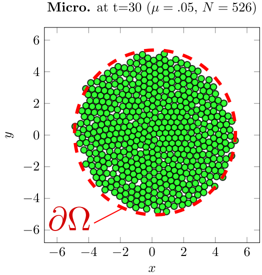
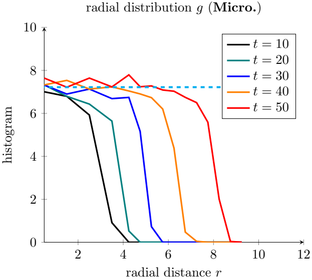
  $\Rightarrow$ *"free boundary problem"*





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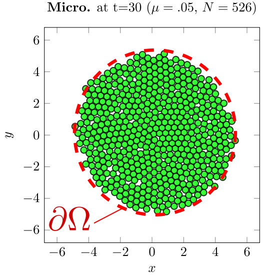

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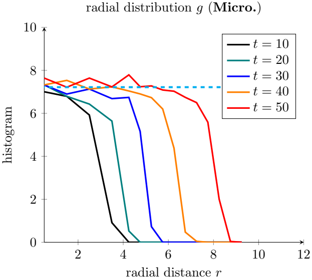

> *What equation governs the motion of the boundary $\partial\Omega$?*

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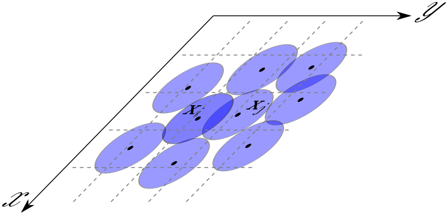
Empirical distribution

- **Repulsion dynamics**: let $\{\mathbf{x}_i(t)\}_{i=1..N}$ solution **micro.**



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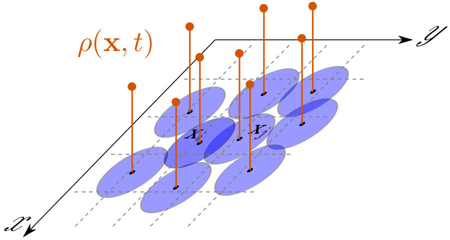

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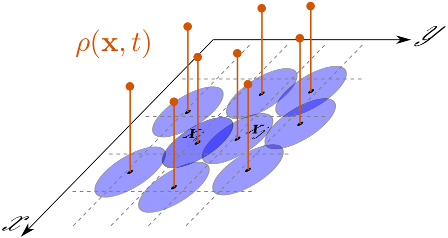
$$G[\rho](\mathbf{x}) = -\int_{\mathbf{y}} \phi\left(\left|\frac{\mathbf{x}-\mathbf{y}}{2R}\right|^2\right)(\mathbf{y}-\mathbf{x})\rho(\mathbf{y})\,\mathrm{d}\mathbf{y}.$$



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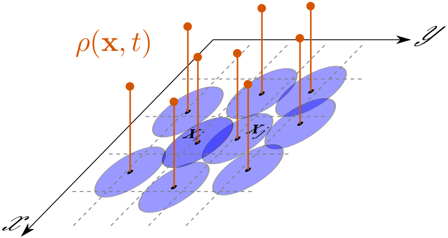

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- **Repulsion dynamics** + **cell division**:

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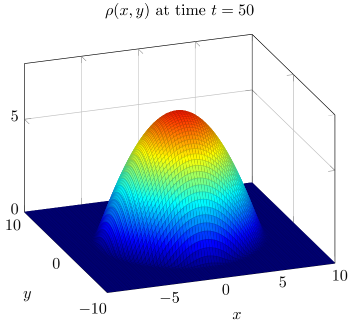

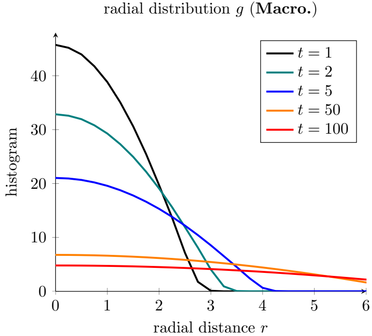

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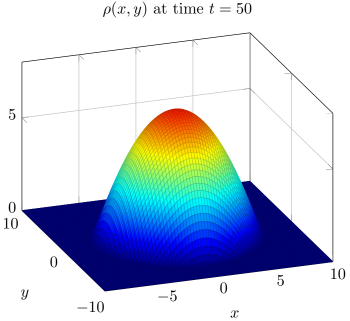

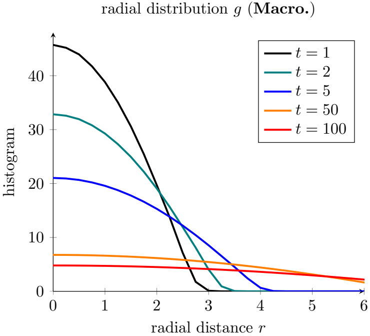

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Explanation: Dirac distributions are *unstable* (weak) solutions.

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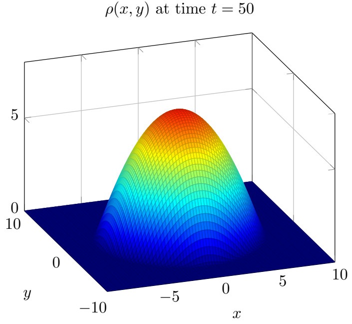

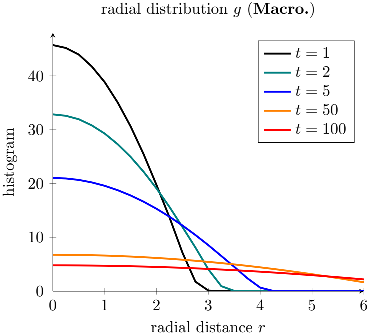

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Fix: introduce a **density threshold** for the interaction

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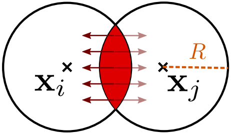

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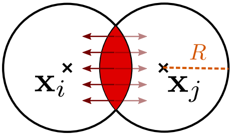

We modify the transport equation:

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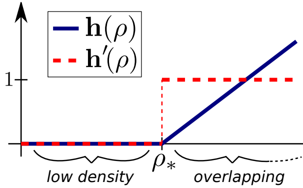
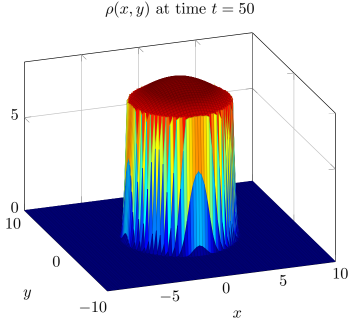
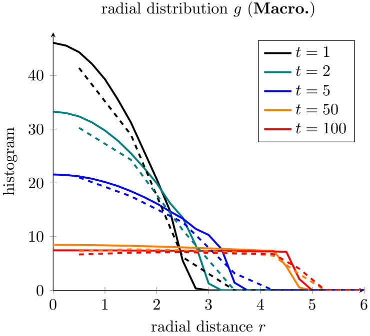
and $\mathbf{h}(\rho) = \rho - \rho_*$ for $\rho \geq \rho_*$.



Case 1: no cell-division

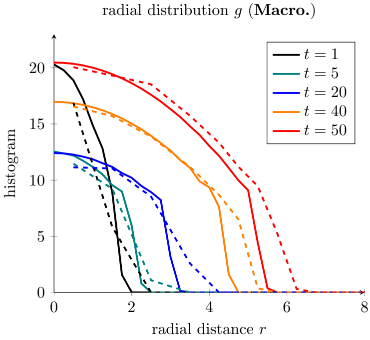
Using the **threshold** $\rho_* = \frac{1}{\pi R^2}$:





Case 2: with cell-division

Using the **threshold** $\rho_* = \frac{1}{\pi R^2}$:



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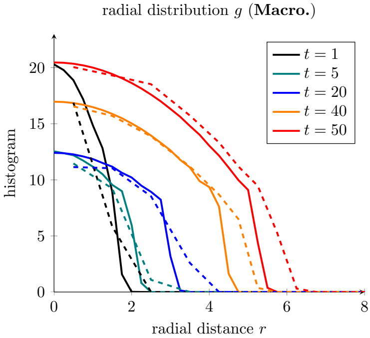
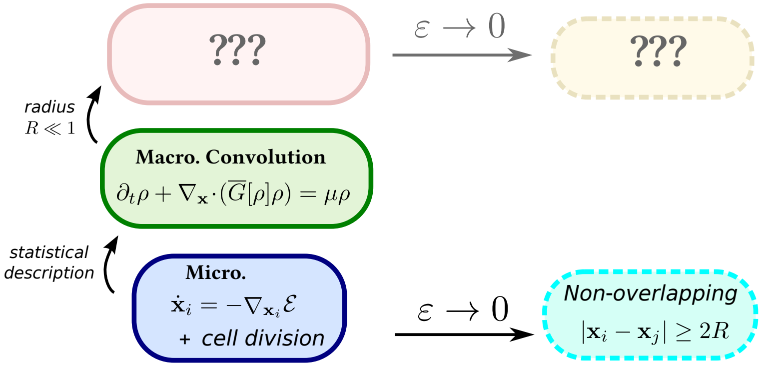


Question: How about case 3 (non-overlapping with $\varepsilon \to 0$)?

Outline

Outline derivation



Porous media equation

Asymptotic $R \ll 1$

$$\overline{G}[\rho](\mathbf{x}) = -\int_{\mathbf{y}} \phi\left(\left|\frac{\mathbf{x}-\mathbf{y}}{2R}\right|^2\right)(\mathbf{y}-\mathbf{x})\mathbf{h}(\rho(\mathbf{y}))\,\mathrm{d}\mathbf{y}$$

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$$= (2R)^3 \int_{\mathbf{z}} \phi(|\mathbf{z}|^2)\,\mathbf{z}\,\mathbf{h}(\rho(\mathbf{x}-2R\mathbf{z}))\,\mathrm{d}\mathbf{z}$$

Porous media equation

Asymptotic $R \ll 1$

$$\begin{aligned}\overline{G}[\rho](\mathbf{x}) &= -\int_{\mathbf{y}} \phi\left(\left|\frac{\mathbf{x}-\mathbf{y}}{2R}\right|^2\right)(\mathbf{y}-\mathbf{x})\mathbf{h}(\rho(\mathbf{y}))\,\mathrm{d}\mathbf{y} \\ &= (2R)^3 \int_{\mathbf{z}} \phi(|\mathbf{z}|^2)\,\mathbf{z}\,\mathbf{h}(\rho(\mathbf{x}-2R\mathbf{z}))\,\mathrm{d}\mathbf{z} \\ &= -\alpha_R\,\mathbf{h}'(\rho(\mathbf{x}))\nabla_{\mathbf{x}}\rho(\mathbf{x}) + \mathcal{O}(R^5)\end{aligned}$$

with α_R constant.

Porous media equation

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with α_R constant. Neglecting high order term leads to a **porous media** equation:

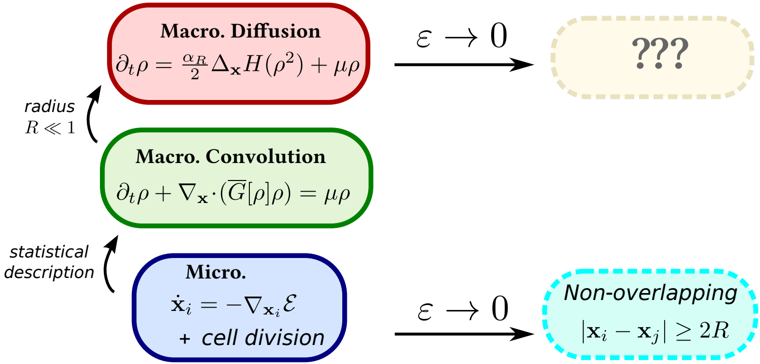
$$\partial_t\rho = \alpha_R\nabla_{\mathbf{x}}\cdot\left(\mathbf{h}'(\rho(\mathbf{x}))\rho\nabla_{\mathbf{x}}\rho\right) + \mu\rho,$$

or:

$$\partial_t\rho = \frac{\alpha_R}{2}\Delta_{\mathbf{x}}H(\rho^2) + \mu\rho$$

with $H(s) = (s-\rho_*^2)^+$.

Outline derivation



Free-boundary problem (Hele-Shaw)

Asymptotic $\phi \rightsquigarrow \frac{\phi}{\varepsilon}$ and $\varepsilon \to 0$ (*no-overlapping*)

$$\partial_t \rho_\varepsilon = \frac{\alpha_R}{2\varepsilon} \Delta_{\mathbf{x}} H(\rho_\varepsilon^2) + \mu \rho_\varepsilon.$$

Question: is there a limit equation as $\varepsilon \to 0$?

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Suppose: $\rho_\varepsilon \xrightarrow{\varepsilon \to 0} \rho_\infty$.

- $\mathcal{O}(\varepsilon^{-1})$: $\Delta_{\mathbf{x}} H(\rho_\infty^2) = 0 \Rightarrow \rho_\infty(\mathbf{x}) \leq \rho_*$.

  Denote $\Omega(t) = \{\rho_\infty(\mathbf{x}, t) = \rho_*\}$.

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  Denote $\Omega(t) = \{\rho_\infty(\mathbf{x}, t) = \rho_*\}$.
- $\mathcal{O}(\varepsilon^0)$: perturbation analysis $\rho_\varepsilon = \rho_\infty + \varepsilon \rho_1 + \mathcal{O}(\varepsilon^2)$

$$\begin{array}{rcl} \partial_t \rho_\varepsilon & = & \alpha_R \rho_\infty \Delta_{\mathbf{x}} \rho_1 + \mu \rho_\varepsilon + \mathcal{O}(\varepsilon) \\ & \downarrow & \\ 0 & = & \alpha_R \Delta_{\mathbf{x}} \rho_1 + \mu \qquad \text{on } \Omega(t). \end{array}$$

Free-boundary problem (Hele-Shaw)

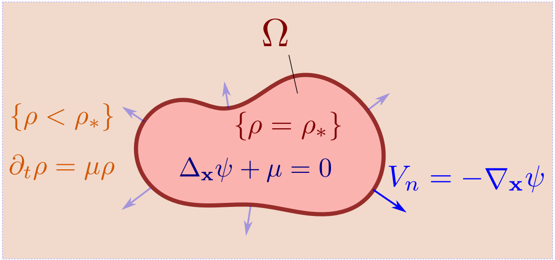
The **limit distribution** ρ_∞ satisfies

$$\begin{cases} \partial_t \rho_\infty = \mu \rho_\infty & \text{on } \mathbb{R}^2/\Omega \\ \rho_\infty = \rho_* & \text{on } \Omega \end{cases}$$

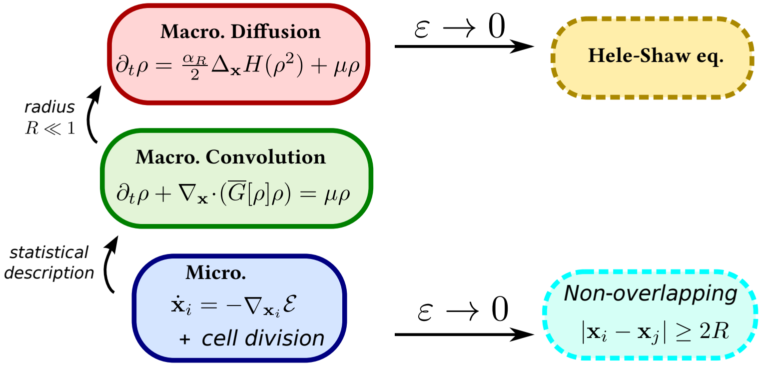
where $\Omega(t)$ is governed by a Laplace equation: let ψ solution to:

$$\begin{cases} \Delta_{\mathbf{x}} \psi + \mu = 0 & \text{on } \Omega \\ \psi = 0 & \text{on } \partial\Omega \end{cases}$$

the velocity of the boundary $\partial\Omega$ is $V_n = -\nabla_{\mathbf{x}} \psi$.



Outline derivation



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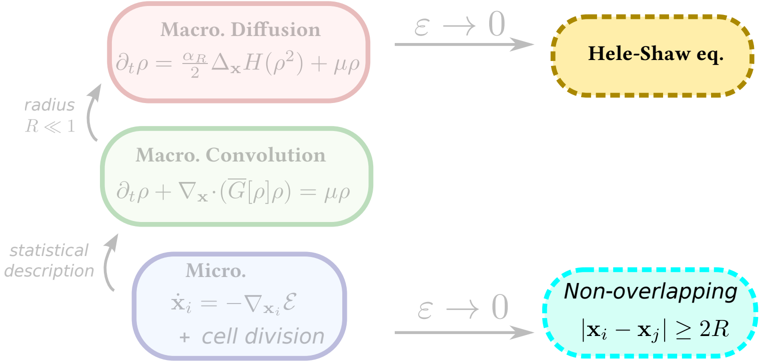
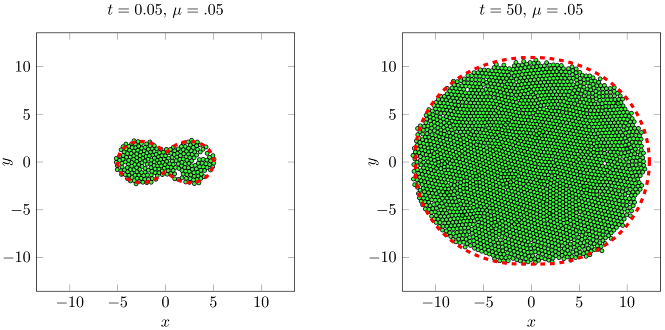


Case 3: non-overlapping



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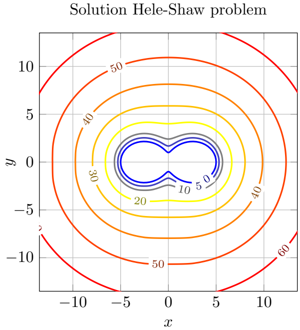
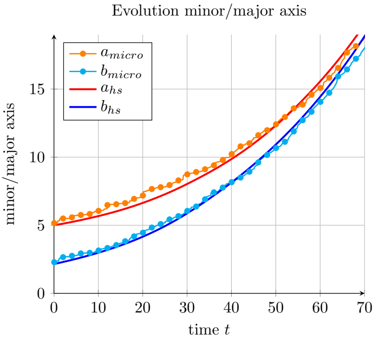
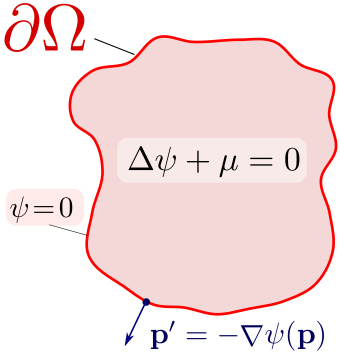


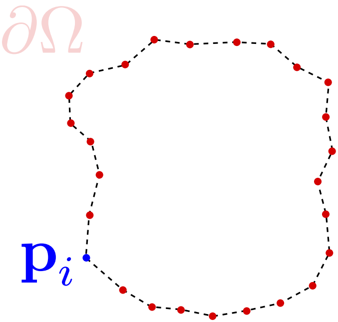


Numerical scheme for Hele-Shaw



Numerical scheme for Hele-Shaw

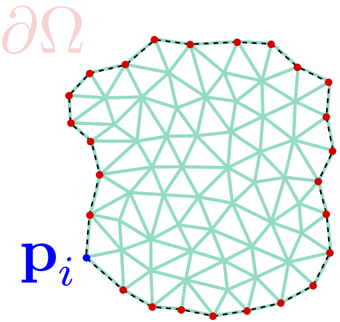
1) sample the boundary $\partial\Omega$: $\{\mathbf{p}_i\}_i$



Numerical scheme for Hele-Shaw

1) sample the boundary $\partial\Omega$: $\{\mathbf{p}_i\}_i$
2) find ψ solving the Elliptic problem:

$$\begin{cases} \Delta_{\mathbf{x}}\psi + \mu = 0 & \text{on } \Omega \\ \psi = 0 & \text{on } \partial\Omega \end{cases}$$



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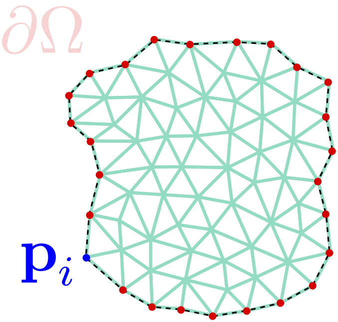

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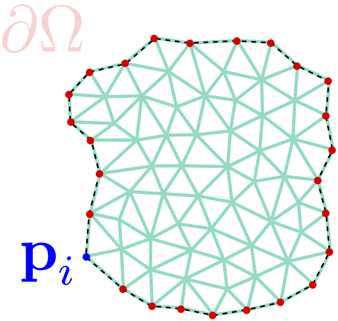

Triangulation:

× update grid each Δt

× accuracy $\nabla\psi$?

Numerical scheme for Hele-Shaw

1) sample the boundary $\partial\Omega$: $\{\mathbf{p}_i\}_i$
2) find $u = \psi + g$ solving:

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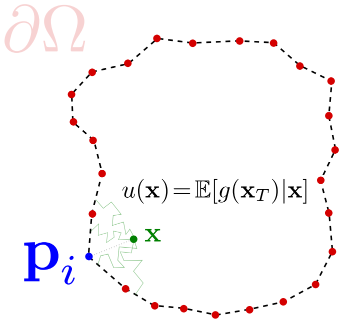

Dynkin's formula:

✓ grid free

✓ high accuracy ψ near $\partial\Omega$

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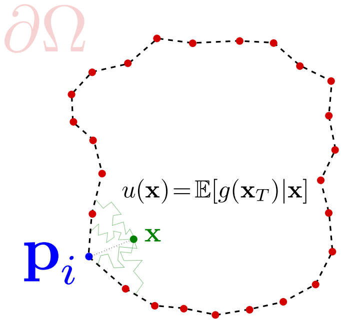
4) update the boundary points:

$$\mathbf{p}_i' = -\nabla\psi(\mathbf{p}_i)$$



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Outline

Summary

- include threshold ρ_* to match agent-based model/PDE
- derivation free-boundary problem for $\Omega(t)$
- develop a numerical scheme to solve the Hele-Shaw equation

Perspectives

- rigorous proof for the derivation
  Ref.: A. Mellet, B. Perthame, F. Quiros
- develop a faster method for the constraint dynamics:
  $\Rightarrow$ *P. Degond, M. Ferreira*
- different behavior for the cells: $\Rightarrow$ *D. Weser*