Modeling the migration of cancer cells: from microscopic to macroscopic models

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Overview

Glioblastoma multiforme

Modeling cell diffusion — why? how?

Some in vitro experiments

“Microscopic” and “macroscopic” models with 1-site cells

“Microscopic” and “macroscopic” models with 2-site cells

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Glioblastoma multiforme

- Brain is made essentially of neurons, astrocytes and oligodendrocytes.
- Glioblastoma = one of the brain tumors, made of astrocytes. Represents 52% of primary brain cancers.
- Life expectation after discovery, untreated: 3 months; after 5 years, treated: 10%
Glioblastoma multiforme

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Migration ⇝ recurrence

A. Giese et al. (2003)
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Modeling glioblastoma / cell diffusion (1)

► Why?
To get a quantitative tool at the scale of the brain → predictions about efficiency of treatment, most probable location of recurrences, ...

► How?
Essentially two kinds of models (which may be mixed):

► stochastic, discrete, microscopic models (cellular automata, cell- or individual-based models, ...)

► deterministic, continuous space, macroscopic models: Partial Differential Equations (PDE)
Modeling glioblastoma / cell diffusion (2)

Advantages of a PDE for clinical predictions:

- There are ready-to-use softwares to solve PDEs.
- No need to average over the stochastic noise (one simulation is enough).
- Reduced number of space discretization steps (no need of one lattice step per cell).
- Easier to get analytical results / predict the effect of parameter changes.

But: how to establish a PDE for cell diffusion?
Modeling glioblastoma / cell diffusion (3)

How to establish a PDE for cell diffusion?

Easy answer: don’t establish, assume that the standard heat equation is valid for the density $\rho$ of cancer cells.

$$\frac{\partial \rho(x, y, z, t)}{\partial t} = \nabla \cdot [D(x, y, z)\nabla \rho] + \lambda \rho$$

K. Swanson et al., 2000-2008
Modeling glioblastoma / cell diffusion (3)

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Is enough until we get detailed, quantitative data about the tumor.
Modeling glioblastoma / cell diffusion (4)

How to establish a PDE for cell diffusion?

More complicated answer: establish a “microscopic” model for the behaviour of single cells (e.g. a cellular automaton), then derive a PDE from this microscopic model — this talk.
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In vitro, 2D, diffusion experiments

A spheroid (ball) of cancerous astrocytes is put on a 2D collagen surface; cells diffuse out. Negligible proliferation and apoptosis.
Experiments → importance of cell-cell interactions (1)

Cancer cells are seen to interact to get out of the spheroid (healthy astrocytes rearrange to facilitate migration).
Experiments → importance of cell-cell interactions (2)

Inhibition of cell-cell interactions (gap junctions) with a drug enhances migration

Normal (cells interact)

With drug (reduced interaction)
**In vitro, 2D, diffusion experiments**

Spheroids of GL15 cells (model cancerous astrocytes) are put on a 2D collagen surface; cells diffuse out.
Outcome of experiments: time-dependent density curves

M. Aubert et al. (2006)
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A cellular automaton for GL15 cells

M. Aubert et al. (2006)

Space is discretized as a hexagonal tiling (less anisotropic than square lattice). At most one (cancer) cell per site.

Rules for the motion of cancer cells:

- $p$ is fixed, between 0 and 1.
- A cell goes to a neighbouring empty site...
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Rules for the motion of cancer cells:

- $p$ is fixed, between 0 and 1.
- A cell goes to a neighbouring empty site...
- ...with rate $p$ if, doing so, it stays in contact with at least one former neighbour...
- ...with rate $1 - p$ if, doing so, it breaks all contacts with former neighbours

$p = 1/2 \leftrightarrow$ indifferent diffusion
Cellular automaton vs. experiments

M. Aubert et al. (2006)
Going to a PDE: the hydrodynamic limit

Idea: replace description of actual configuration (site 1 is empty, site 2 is full, ...) with the local density of cells.

\[ n(x, y, t) \rightarrow \rho(x, y, t) \]

Occupation number of site \(x, y, n(x, y, t)\), is an integer (0 or 1) that fluctuates (has a probability distribution) Local density \(\rho(x, y, t)\) is a real number; \(\rho\) is a smooth function (one can write a PDE for \(\rho\))
Going to a PDE: the hydrodynamic limit

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Local density \( \rho(x, y, t) \) is a real number; \( \rho \) is a smooth function (one can write a PDE for \( \rho \))

The idea is not new (several reviews and books since the 80’s) and there are several techniques to derive a PDE (Green-Kubo formula, Chapman-Enskog, continuous space limit of the master equation, ...).

Turner et al. (2003) and ref. therein, Alber et al. (2007)
A toy model: Simple Symmetric Exclusion Process in 1D

For the average occupation number of site $i$, $\langle n_i \rangle$:

$$\frac{d\langle n_i \rangle}{dt} = -\langle n_i(t)[1 - n_{i+1}(t)] \rangle - \langle n_i(t)[1 - n_{i-1}(t)] \rangle + \langle [1 - n_i(t)]n_{i-1}(t) \rangle + \langle [1 - n_i(t)]n_{i+1}(t) \rangle$$

Neglect correlations: $\langle n_i n_j \rangle \approx \langle n_i \rangle \langle n_j \rangle$ then let $n_i(t) = \rho(ia, t)$:

$$\frac{d\langle n_i \rangle}{dt} \approx \langle n_{i+1}(t) \rangle + \langle n_{i-1}(t) \rangle - 2\langle n_i(t) \rangle$$

Taylor expansion for $a \ll 1$ $\rightarrow \frac{\partial \rho}{\partial t} = \frac{\partial^2 \rho}{\partial x^2} + O(a^2)$
Hydrodynamic limit for the GL15 cells

\[
\frac{\partial \rho(\vec{r}, t)}{\partial t} = \vec{\nabla} \cdot \left[ D(\rho) \vec{\nabla} \rho(\vec{r}, t) \right]
\]

with

\[
D(\rho) = \frac{(1 - p)}{4} + \frac{(2p - 1)\rho(1 - \rho/2)}{2}
\]

(hexagonal tiling in 2D) or

\[
D(\rho) = \frac{(1 - p)}{6} + \frac{(2p - 1)\rho(4 - 6\rho + 4\rho^2 - \rho^3)}{6}
\]

(f.c.c. lattice in 3D).
Hydrodynamic limit: remarks

- The existence of $\rho$ and the PDE can be rigorously justified for many models — those “that mix particles well”.


- One can set up a framework for a systematic expansion in powers of $1/D$ where the first order yields a PDE (correlations neglected) but successive corrections, which take correlations into account, yield integro-differential equations.


- For more complicated particle evolution rules, using a computer algebra software may help.
Hydrodynamic limit for the GL15 cells: numerical test

Stationary density profile between two reservoirs
Hydrodynamic limit for the GL15 cells vs. experiments
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# Plan
Glioblastoma
Modeling
Experiments
Micro→macro 1
Micro→macro 2
Conclusion

## Extended cells

![Extended cells image]
A 1D toy model

\[
\frac{\partial \rho}{\partial t} = \frac{\partial}{\partial x} \left[ (1 + 2\rho) \frac{\partial \rho}{\partial x} \right]
\]
2-sites cells model: rules

Rotation probability $r$ is a fixed number in $[0, 1]$.

With probability $r$: one of the four allowed rotations is made.

With probability $1 - r$: one of the two allowed translations is made.
2-sites cells model: simulations between two reservoirs

Rotation probability at each step:
- 0.9
- 0.5
- 0.25
- 0.1
- 0.01

2-sites cells
Stationary density profile
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When *in vivo* precise data will be available, it might be important to pick up the right PDE — the one which takes interactions (both biological and geometrical) between cells into account.

There are simple available techniques to derive PDEs as long as correlations are weak.

Simple diffusion experiments and simple microscopic models can lead to very interesting collective behaviour.
When *in vivo* precise data will be available, it might be important to pick up the right PDE — the one which takes interactions (both biological and geometrical) between cells into account.

- There are simple available techniques to derive PDEs as long as correlations are weak.
- Simple diffusion experiments and simple microscopic models can lead to very interesting collective behaviour.

Thank you for your attention! Please bare with us for the talk of Mathilde Badoual!
Appendices