Modelling tumour cell migration: from microscopic to macroscopic

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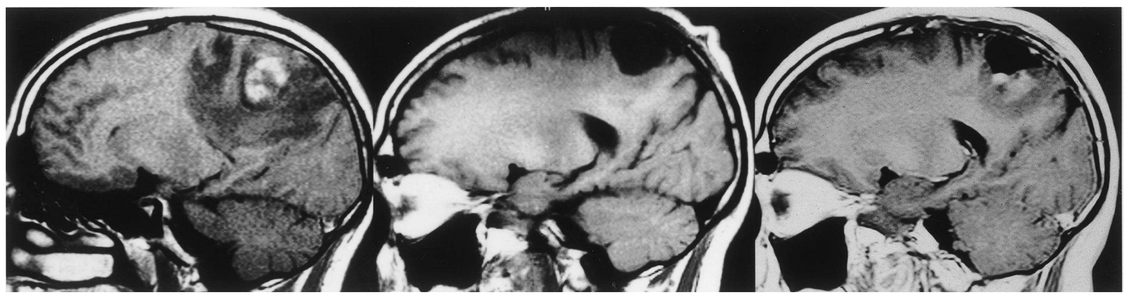
Background

Glioblastoma are aggressive brain tumors — the survival expectation after diagnosis is only a few months.

Because cancer cells (astrocytes) migrate into the neighbouring parts of the brain, the tumor is diffuse. It appears only partially on MRIs. A surgeon cannot see (and remove) all cancer cells → after resection, the tumor recurs and patients die.

Picture below [1]: before surgery, immediately after surgery, 12 month after surgery and X-ray.



- Migration of cells plays a key role in these tumors
- In absence of efficient treatment, modelization could help

[1] A. Giese, R. Bjerkvig, M.E. Berens, and M. Westphal, *Journal of Clinical Oncology* **21** 1624 (2003).

Modeling cancer cell migration

Two kinds of models in literature:

Cellular automata

Space is discretized. Cells are small boxes on a lattice. Cells evolve according to stochastic rules.
Pros: rather intuitive (if not realistic), easy to take interactions between cells or between cells and substrate into account.
Cons: no analytic results (simulations needed), number of cells in the model restricted by computer power, many simulations needed since model is stochastic.

[2] A.R. Kansal, S. Torquato, G.R. Harsh IV, E.A. Chiocca, and T.S. Deisboeck, *J. Theor. Biol.* **203** 367 (2000).
[3] S. Dormann and A. Deutsch, *in Silico Biol.* **2** 35 (2002).
[4] D. Drasdo and S Hoehme, *Phys. Biol.* **2** 133 (2005).

Partial Differential Equations (PDE)

Space is continous. Cells are dealt with indirectly through their density ρ. We solve for ρ a PDE like

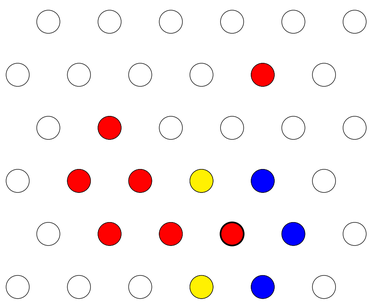
$$\frac{\partial \rho(\vec{r},t)}{\partial t} = D\nabla^2\rho(\vec{r},t). \qquad (1)$$

Pros: We can get analytic results, exploit ready-to-use PDE-solving software, deterministic model (no randomness, no noise), no limit on system size if ρ is a smooth function.
Cons: What should the PDE for ρ be? Is ρ smooth and well-defined?

[5] P. Tracqui, *Acta Biotheoretica* **43** 443 (1995).
[6] P. Tracqui, G.C. Cruywagen, D.E. Woodward, G.T. Bartoo, J.D. Murray, and E.C. Alvord Jr, *Cell Prolif.* **28** 17 (1995).
[7] P.K. Burgess, P.M. Kulesa, J.D. Murray, and E.C. Alvord Jr, *J. Neuropathol. Exp. Neurol.* **56** 704 (1997).
[8] K.R. Swanson, C. Bridge, J.D. Murray and E.C. Alvord Jr, *J. Neurol. Sci.* **216** 1 (2003).

We provide a simple, reusable way to derive a (macroscopic, deterministic) PDE from a (microscopic, stochastic) cellular automaton.

The cellular automaton of M. Aubert *et al.* [9,10]



Cancer cells live on the sites (nodes) of a hexagonal tiling. At each time step, each cell attempts to jump to each neighbouring empty site with rate:
p if, after this move, it would stay in contact with at least one cell with which it was already in contact,
$1-p$ if, after this move, it would have broken all contacts with previously neighbouring cells.

Parameter p parametrizes interaction: $p > 1/2$ favors attraction, $p = 1/2$ is similar to diffusion of non-interacting particles.

[9] M. Aubert, M. Badoual, S. Féreol, C. Christov, and B. Grammaticos, *Phys. Biol.* **3** 93 (2006).
[10] M. Aubert, M. Badoual, C. Christov, and B. Grammaticos, *J. R. Soc. Interface* **5** 75 (2008).

The hydrodynamic limit

Procedure (very close to the so-called *hydrodynamic limit* well known in physics):
1. For convenience, write the stochastic rules of the cellular automaton with linear operators.
2. Introduce the occupation probability ρ of the lattice sites. Write down its evolution equation assuming there is no correlation between neighbouring sites (mean field-like approximation).
3. Postulate that ρ has a continuation to continuous space and use a Taylor expansion to get a PDE from the equations for discrete space.

For the cellular automaton of [9], we get:

$$\frac{\partial \rho(\vec{r},t)}{\partial t} = \mathrm{div}[D(\rho)\vec{\nabla}\rho] \qquad \text{with} \qquad D(\rho) = (1-p)/4 + (2p-1)\rho(1-\rho/2)/2. \qquad (2)$$

Should be exact if correlations of site occupation probabilities are negligible.

⇒ *nonlinear* diffusion if cancer cells interact ($p \neq 1/2$) instead of the often assumed linear diffusion (1).

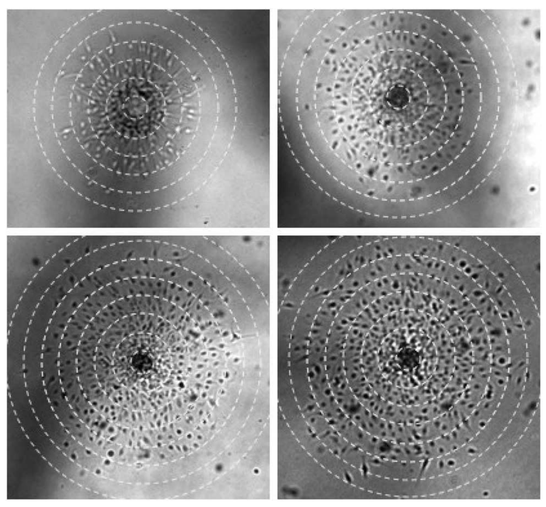
3D generalization can be computed; *e. g.* on the f.c.c. lattice:

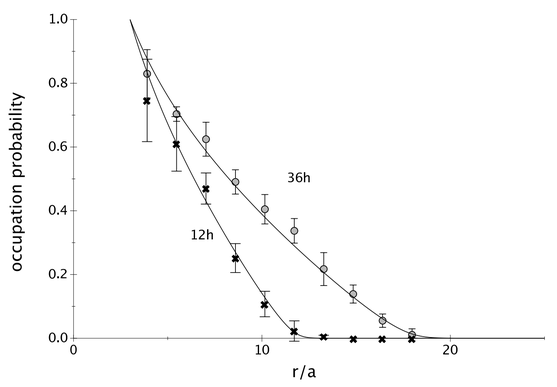
$$D_{3\mathrm{D}}(\rho) = (1-p)/6 + (2p-1)\rho(4 - 6\rho + 4\rho^2 - \rho^3)/6. \qquad (3)$$

[11] C. Deroulers, M. Aubert, M .Badoual and B. Grammaticos, *submitted* (2008).

Comparing with *in vitro* experiments

Migration assay of cancer cells out of a spheroid on a 2D collagen substrate [9] (performed by C. Christov, Henri Mondor Hospital, Créteil, France): photographs taken 12h, 24h, 36h and 48h after the spheroid was placed on collagen. Proliferation and apoptosis of cells are seldom and nearly compensate → there is only cell migration.
M. Aubert *et al.* showed [9] that the cellular automaton can reproduce the experimental results if the interaction parameter p is close to 1, and that usual diffusion ($p = 1/2$) is excluded.

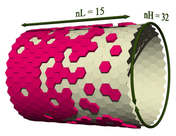




Cell density as a function of the distance to the spheroid. Dots: experiments. Solid lines: results from the PDE (2) with $p = 0.95$.

→ Our PDE with p close to 1 is equally able to reproduce the outcome of experiments.

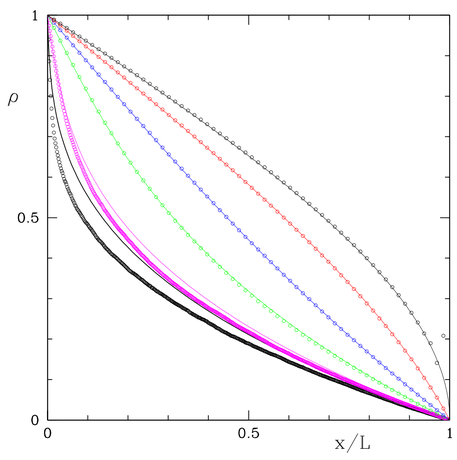
Are correlations always negligible?



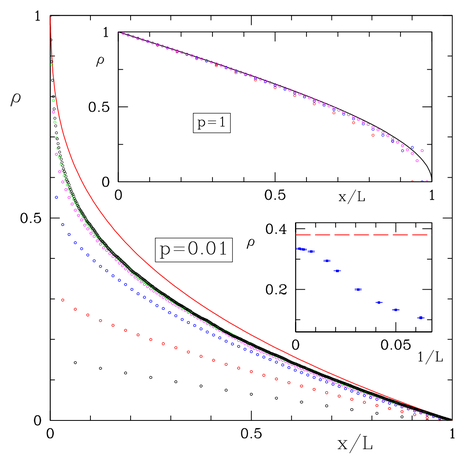
(typical configuration for $p = 0.8$)

We simulate the cellular automaton in the steady state between a reservoir full of cancer cells and an empty reservoir. We compare, for several values of p, the observed stationary density $\rho(x)$ of cells with the prediction from Eq. (2).
Small discrepancy observed on the boundary of the empty reservoir for p close to 1 ↔ dynamically induced correlations (see cartoon on the right: cells that are alone stay longer, hence a negative correlation of site occupation probabilities).

More serious discrepancies observed for p close to 0 ↔ for $p = 0$, the model is a cooperative kinetically constrained model of glass forming liquids where motion of individual cells involve collective rearrangements [12], hence correlations develop. But p close to 0 is not relevant for our biological problem.



$\rho(x)$ for $p = 0.01, 0.05, 0.2, 0.4, 0.7$ and 1.



p is fixed; sizes $n_L = 15, 31, 63, 127, 255$ and 511.

[12] A.C. Pan, J.P. Garrahan, and D. Chandler, *Phys. Rev. E* **72** 041106 (2005).