From cells to tumours: the case of invasive brain tumours

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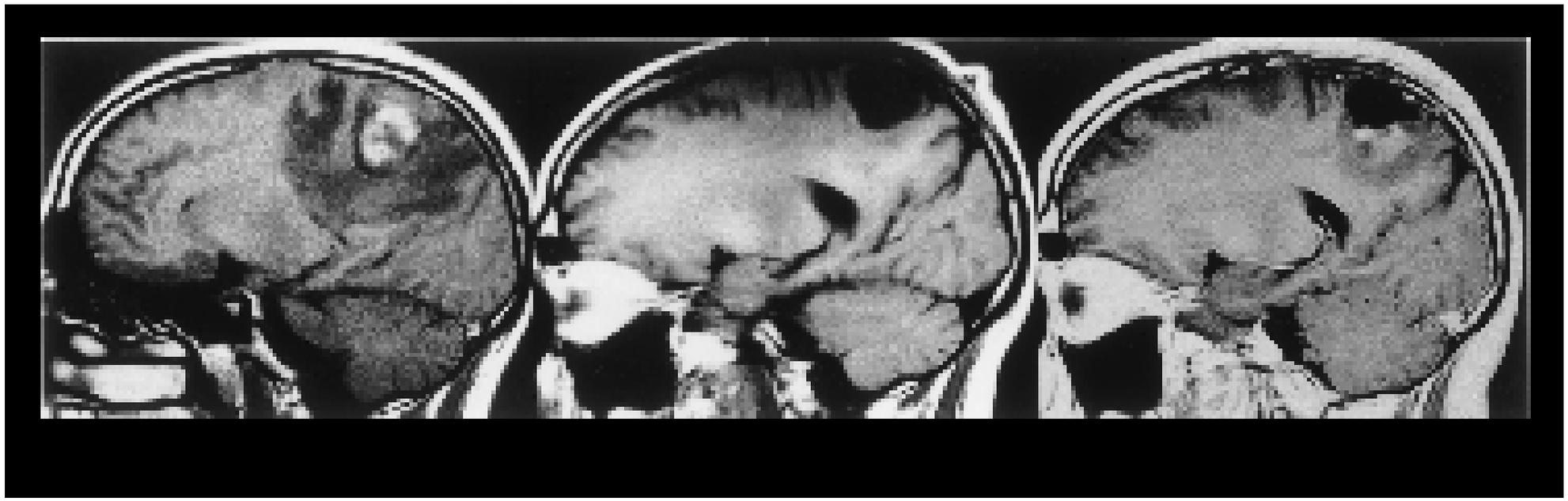
Brain tumours

1 person in 4 in France suffers from cancer over his/her lifespan

Brain tumours are rare (2 %)

However, this pathology cannot be cured

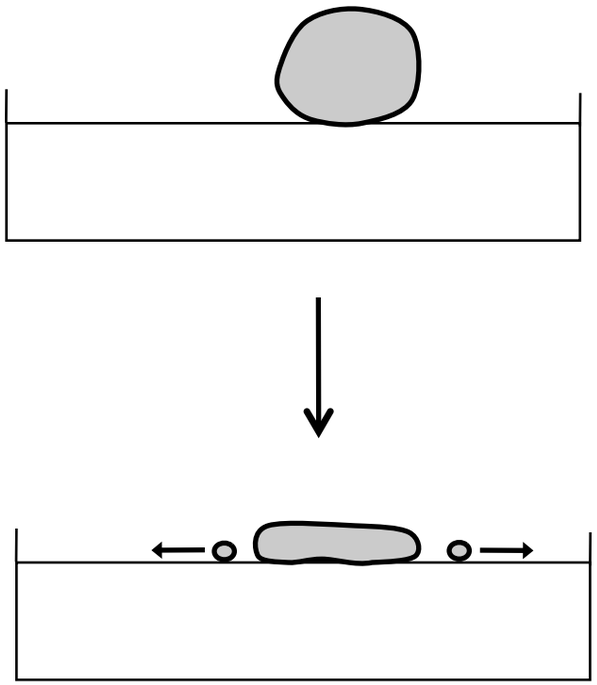


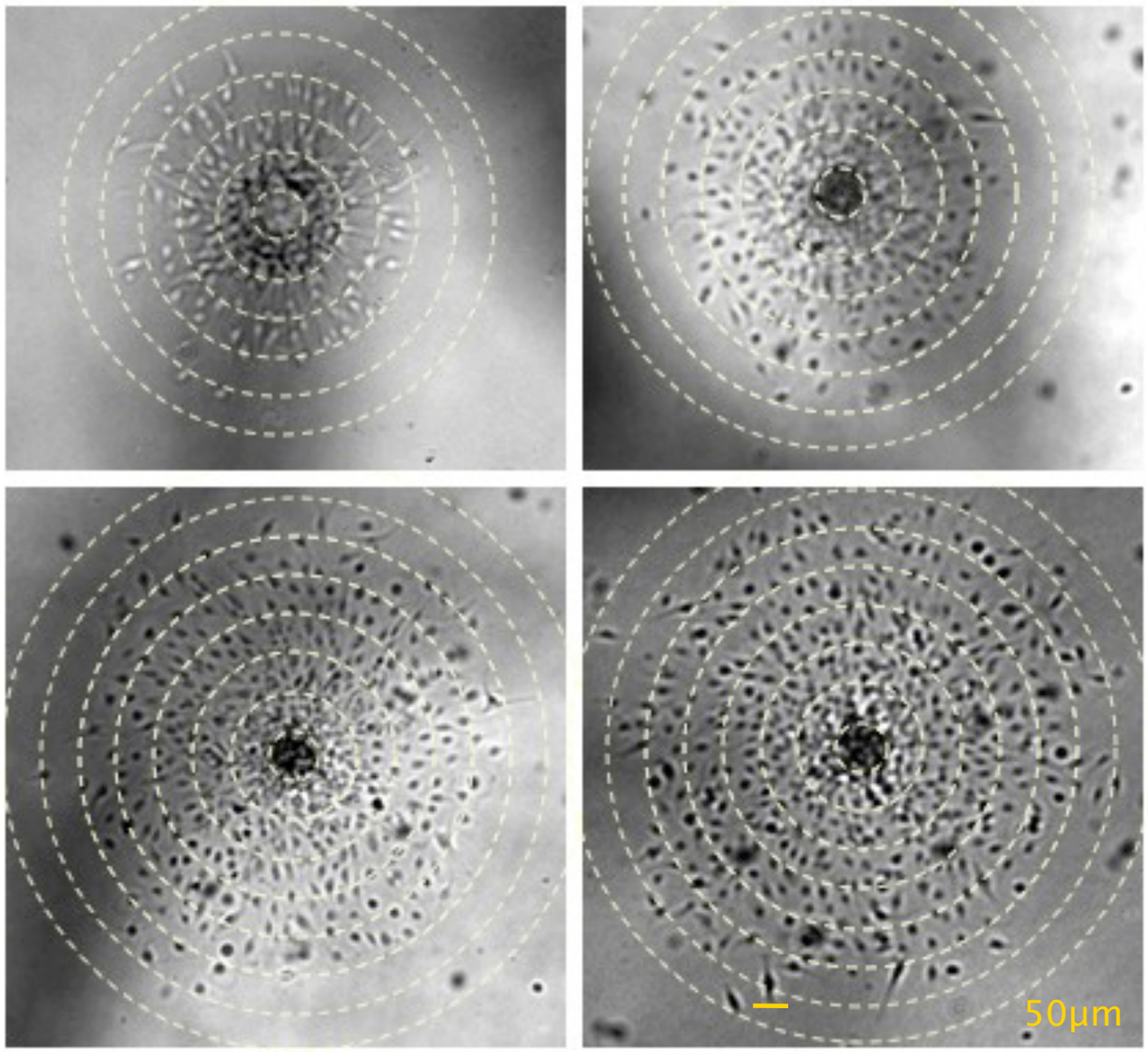
Recurrence after treatment

Cost of migration: invasion of malignant gliomas and implications for treatment, Giese A, Bjerkvig R, Berens ME, Westphal M..J Clin Oncol. 2003 8, 1624-36

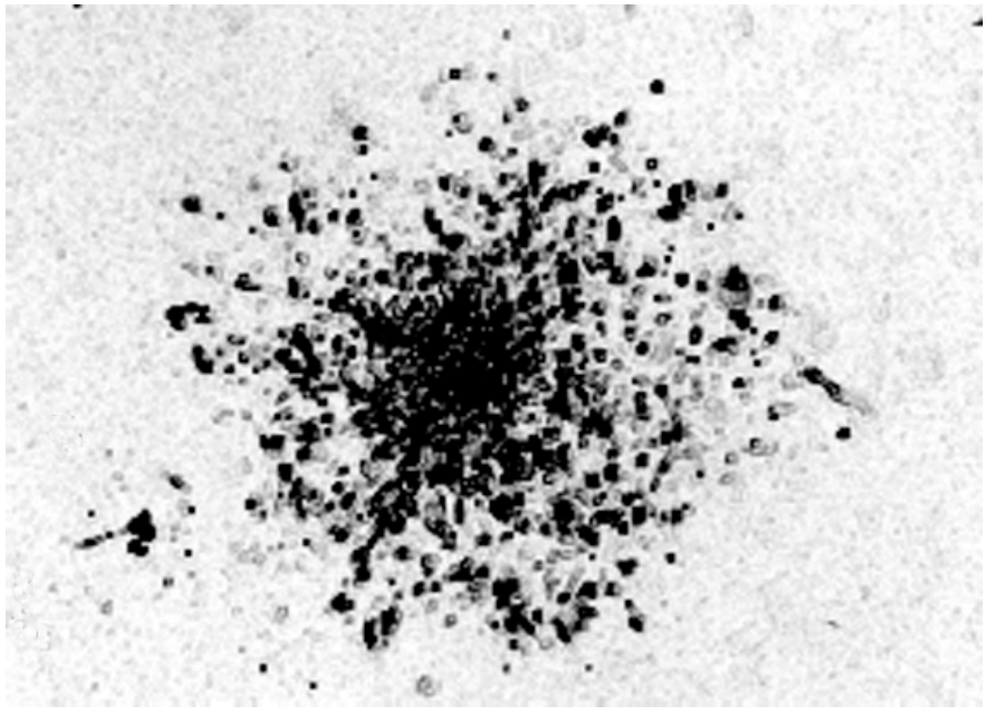
Migration of cancerous cells plays a key role in the poor outcome for patients

Experiments: spheroids

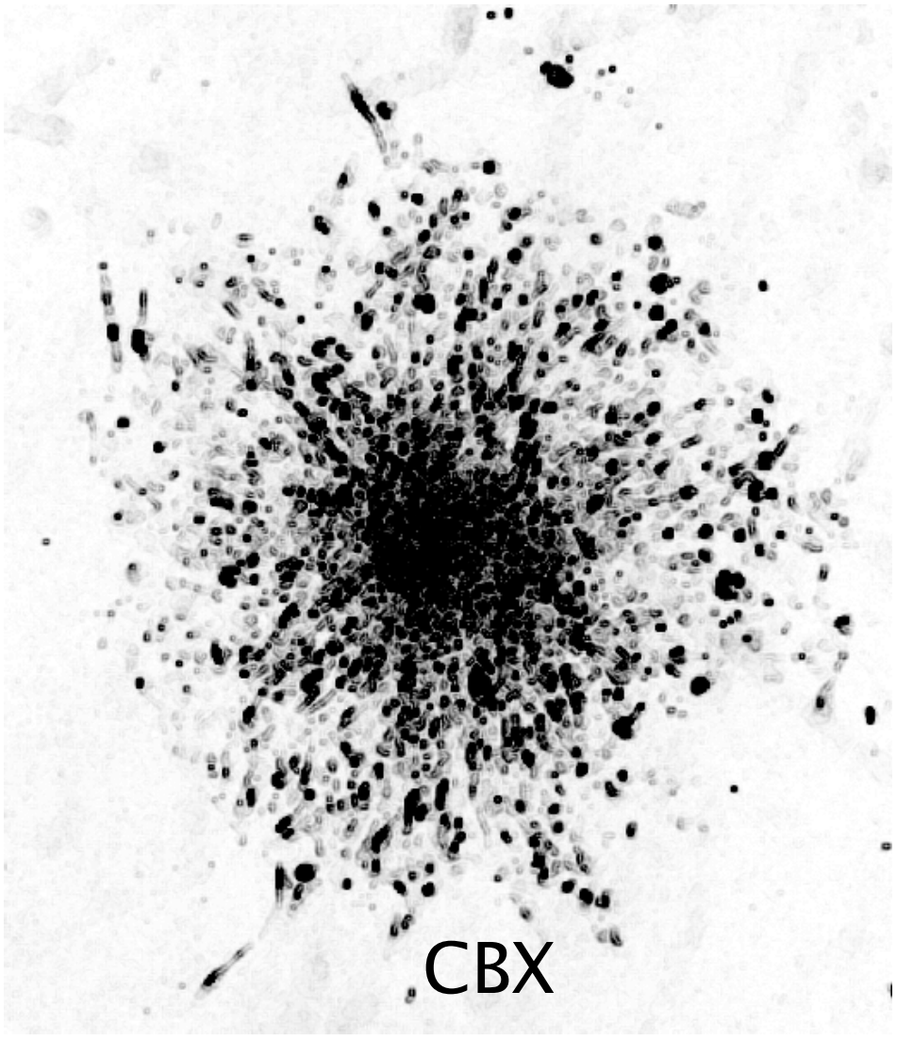




Experiments: inhibition of cell-cell interactions



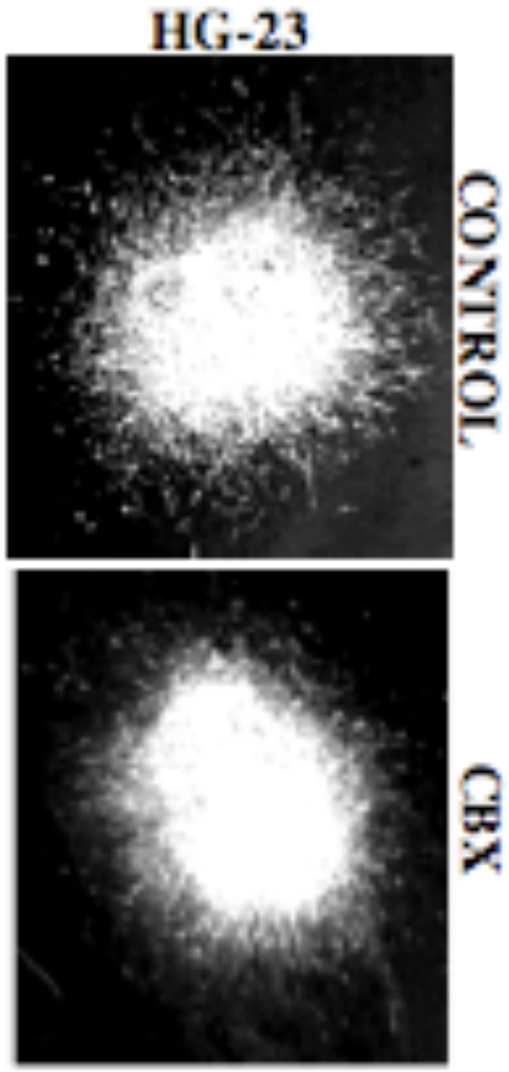
Control

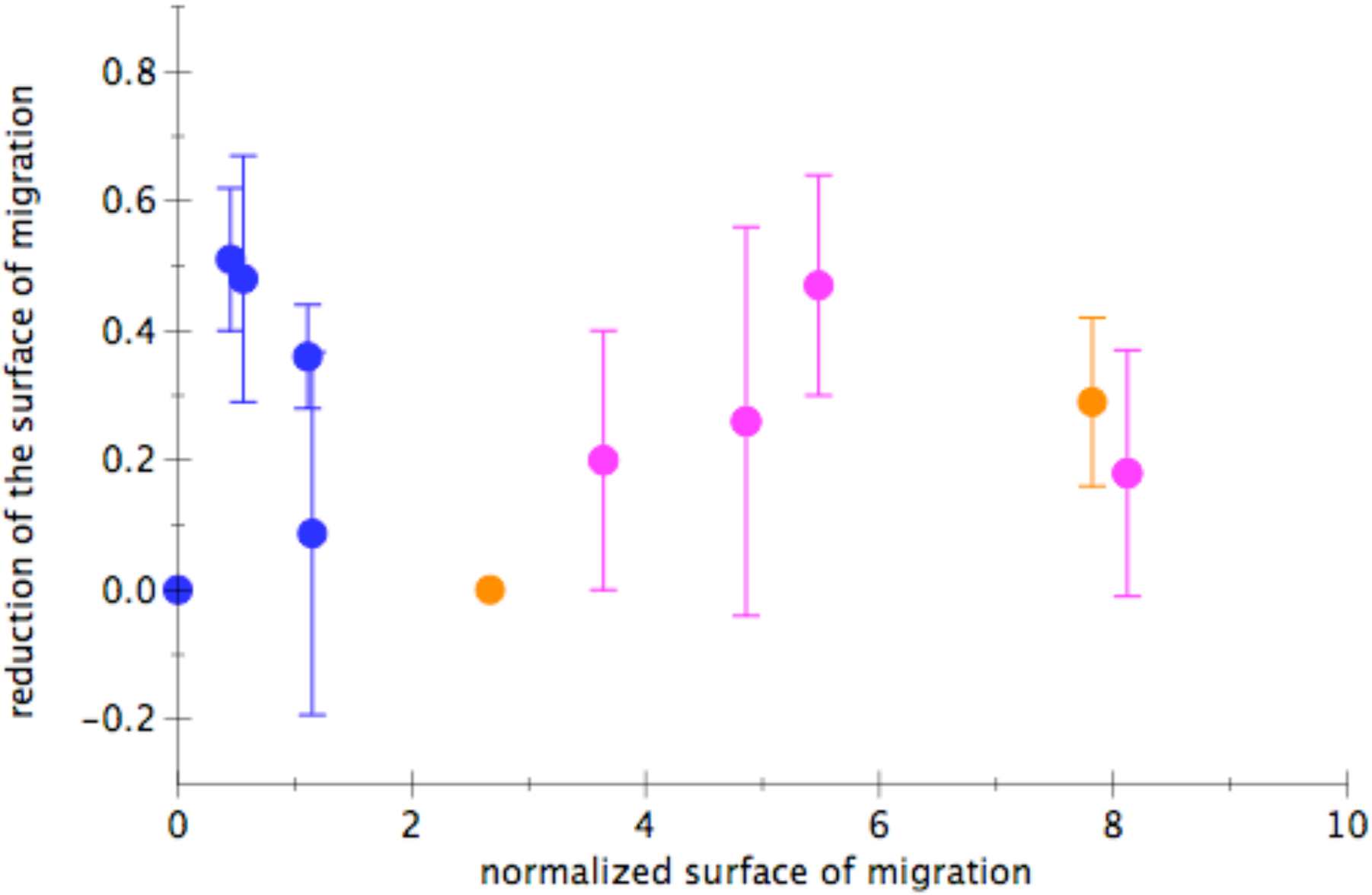


CBX

CBX-inhibited_surface/ control_surface>1

Experiments with brain slices





- Human glioma into brain slice
- Spheroids
- Human glioma into nude mice

Oliveira R, Christov C, Guillamo J S, de Bouard S, Palfi S, Venance L, Tardy M and Peschanski M, 2005, BMC Cell Biol., 6, 7.

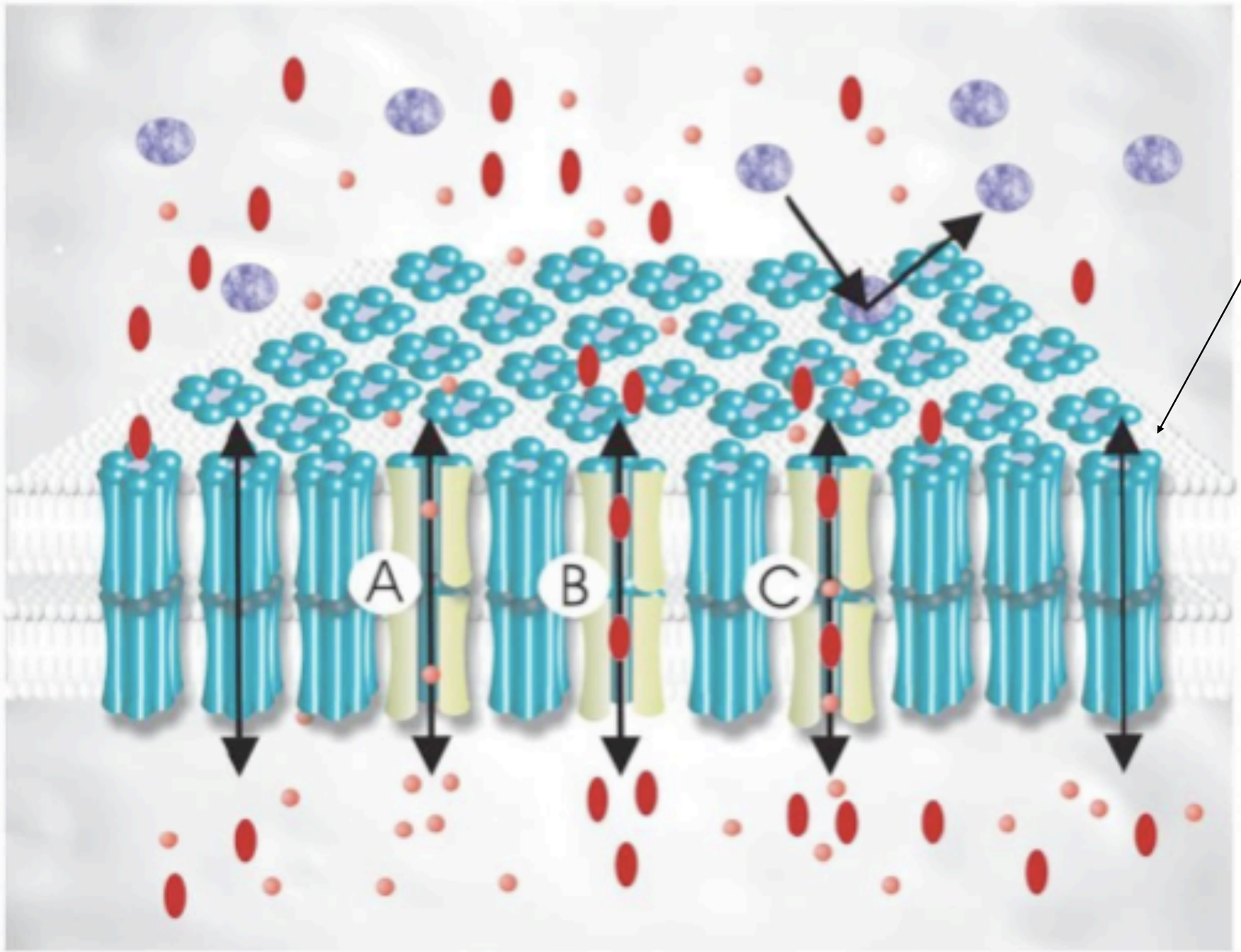
Some questions

1. On a substrate of collagen: how do cells migrate? Do they diffuse?

2. Why does migration increase when cell interactions are inhibited?

3. Why does migration decrease on a more complex substrate?

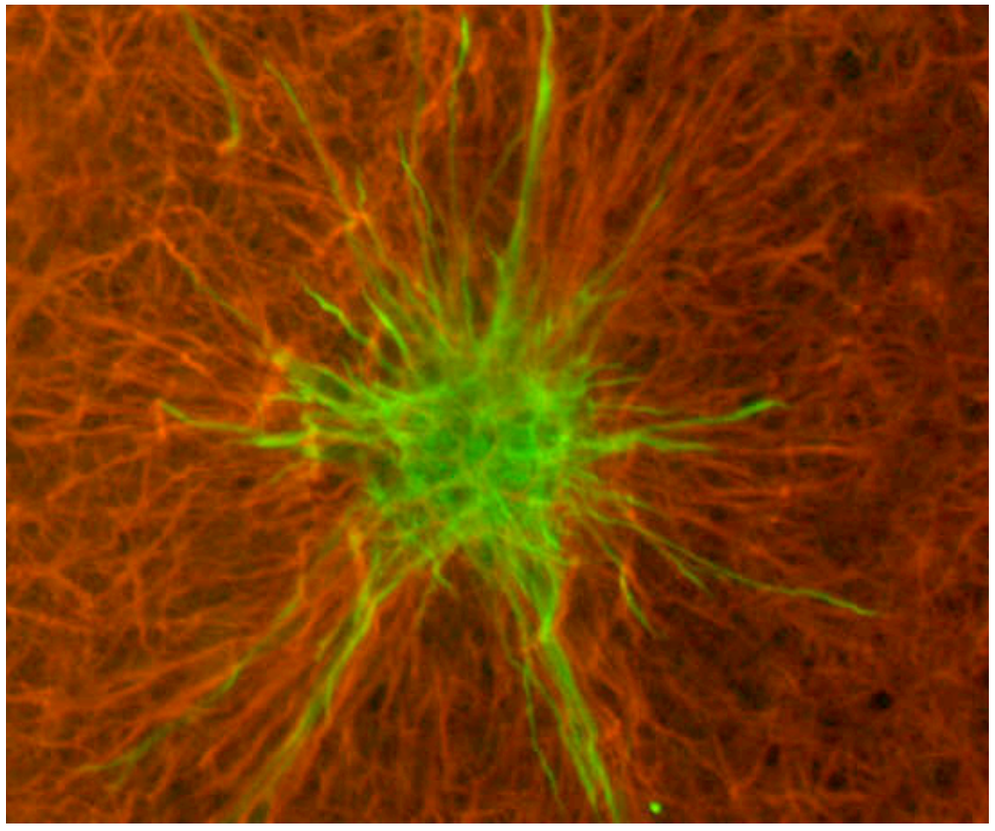
Gap junctions

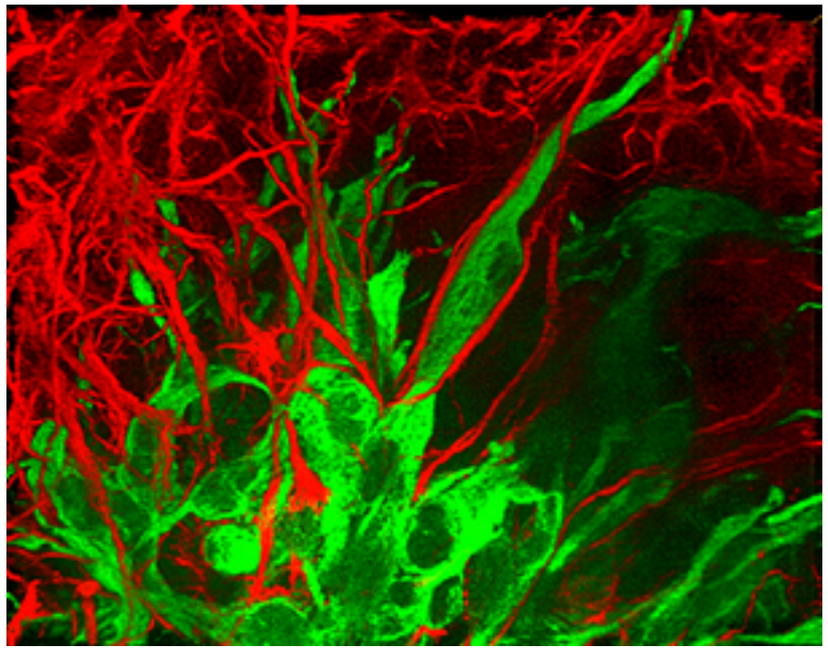


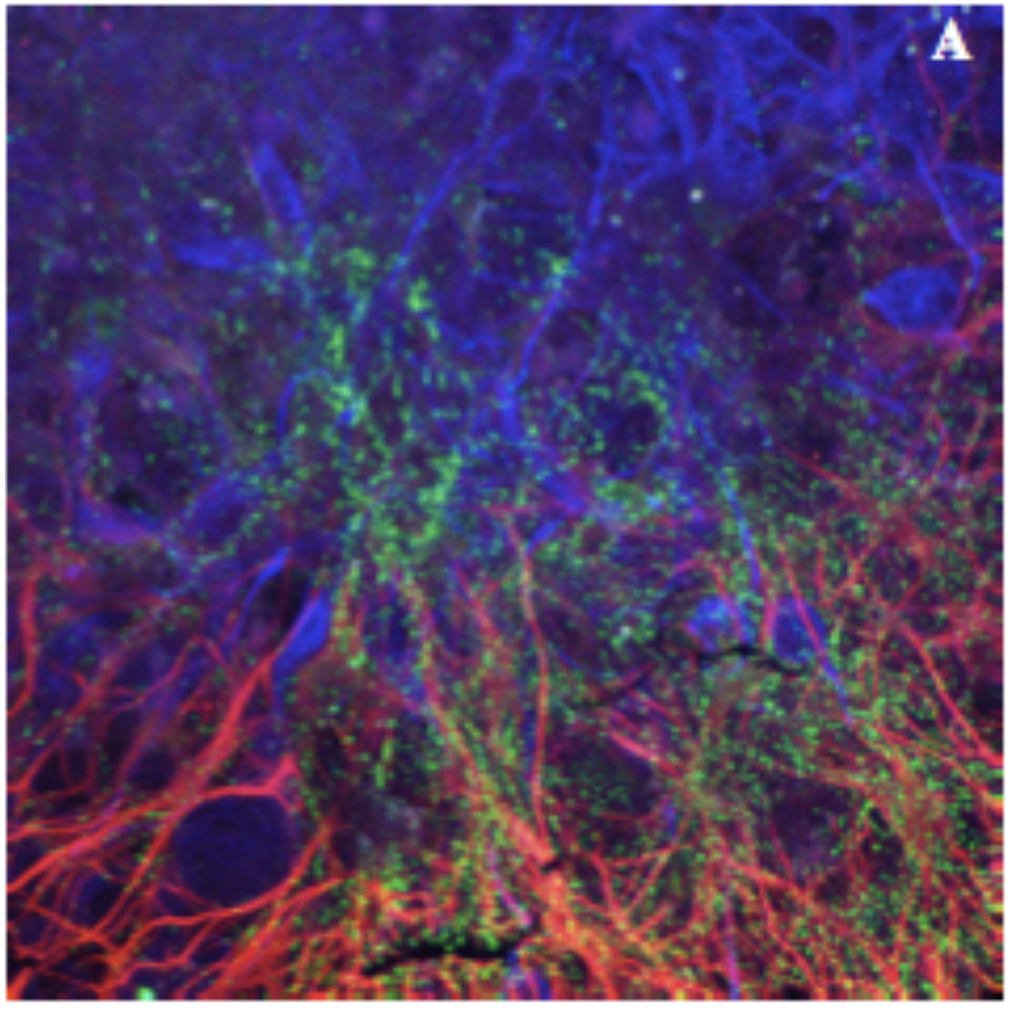
Connexin

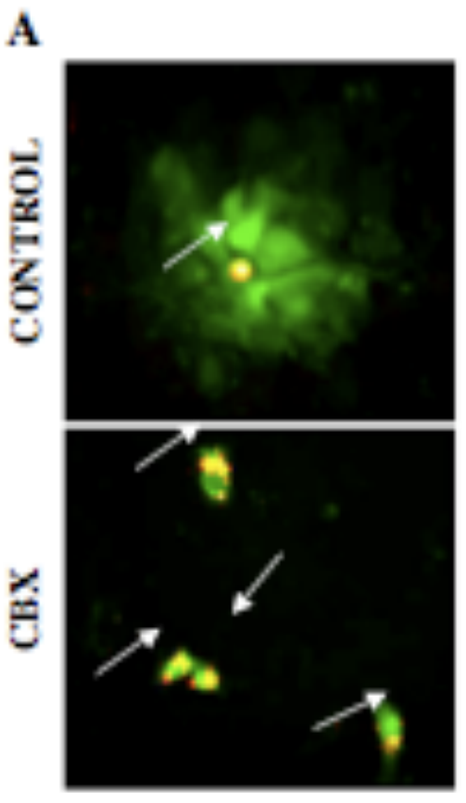
-electrical signals
-small molecules <1kDa (glucose, ATP, Ca2+, amino acids…)

Interactions between tumour astrocytes and normal ones









Oliveira R, Christov C, Guillamo J S, de Bouard S, Palfi S, Venance L, Tardy M and Peschanski M, 2005, BMC Cell Biol., 6, 7.

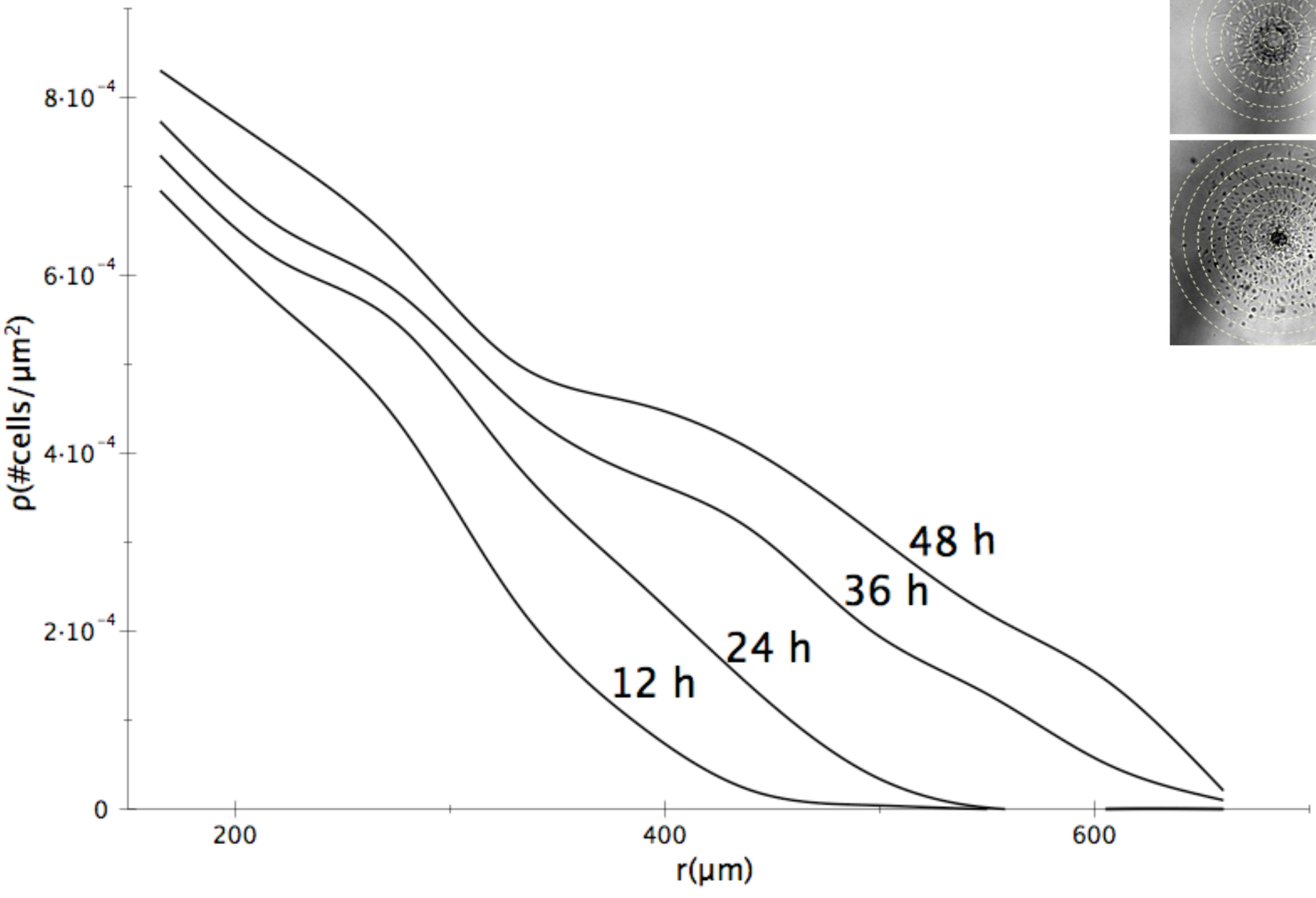
Towards a model

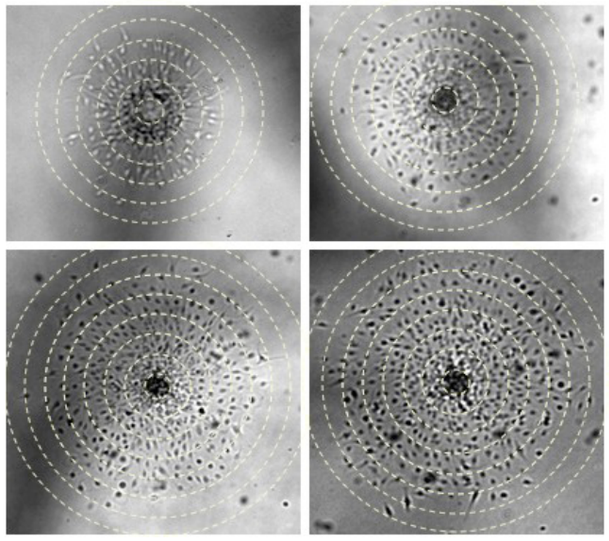
Two types of interactions

1. Homotypic interactions (only between tumour cells):
migration on a substrate of collagen

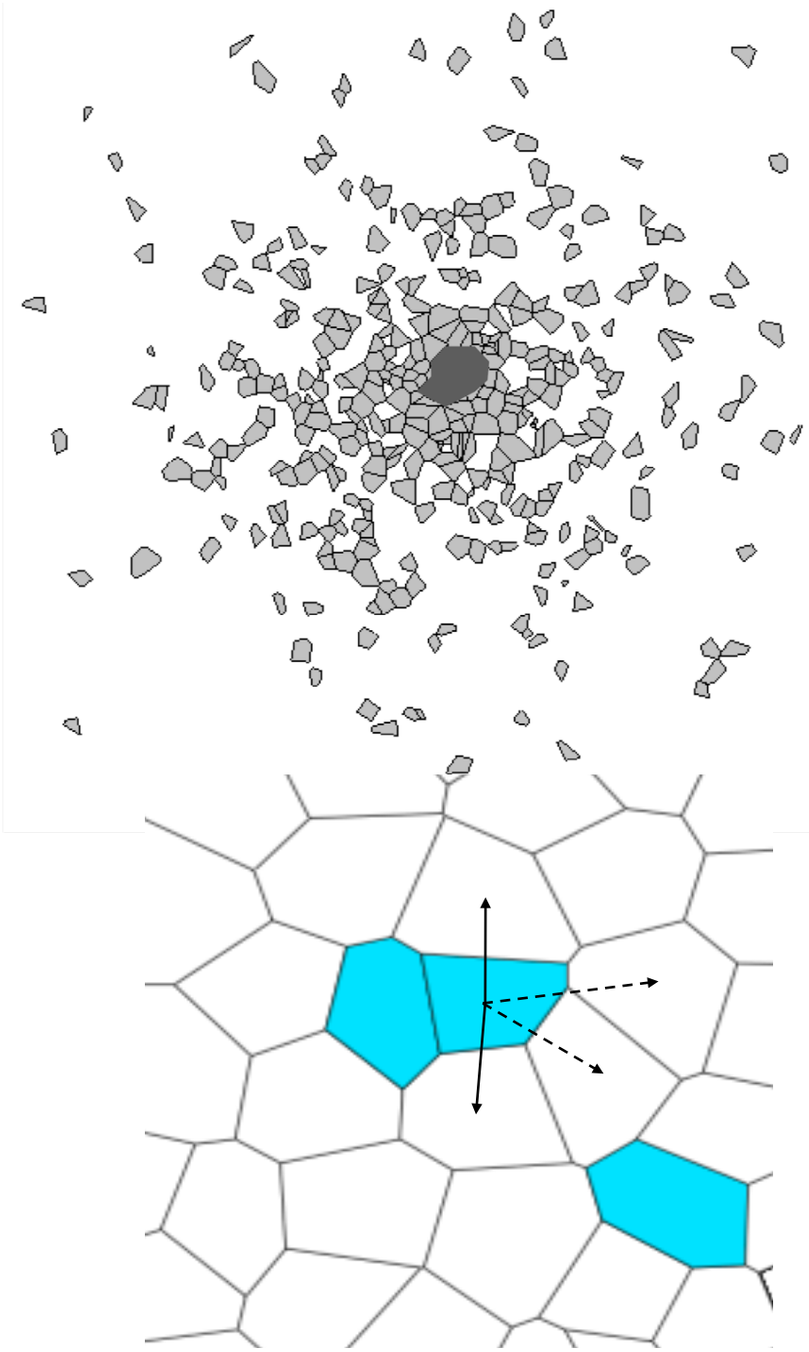
2. Homotypic and heterotypic interactions (also between tumour cells and astrocytes):
migration on a substrate of brain slices

Experiments: density profiles





A cellular automaton model



Cellular automaton:

A stochastic model that can be used for a moderate number of cells

Geometry: regular or quasi-random grid

Each site can be either empty or occupied by one cell

A center of fixed size exists. We assume that it can eject a large number of cells

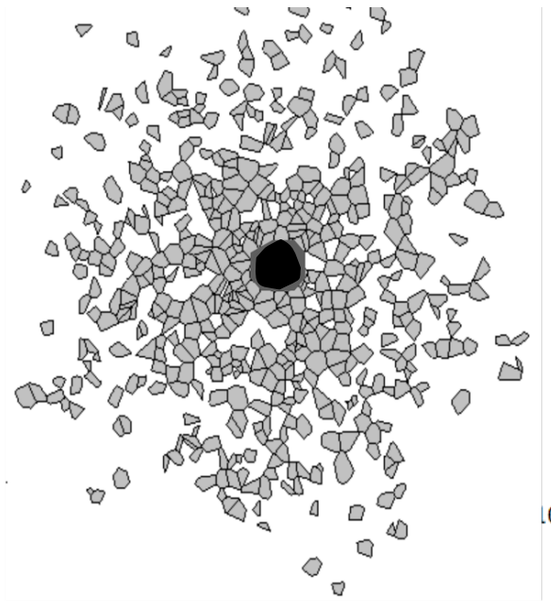
We study only migration. The net proliferation is negligible (5% prolif, 3% apoptosis)

Rule of motion:

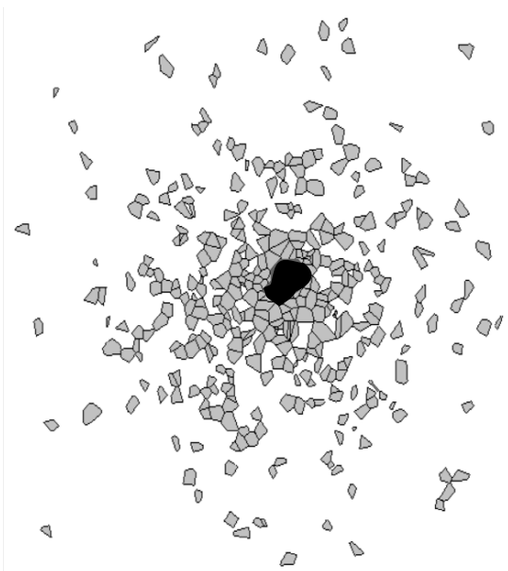
at each step, a cell has a probability p to stay in contact with neighbouring cells

Cellular automaton results

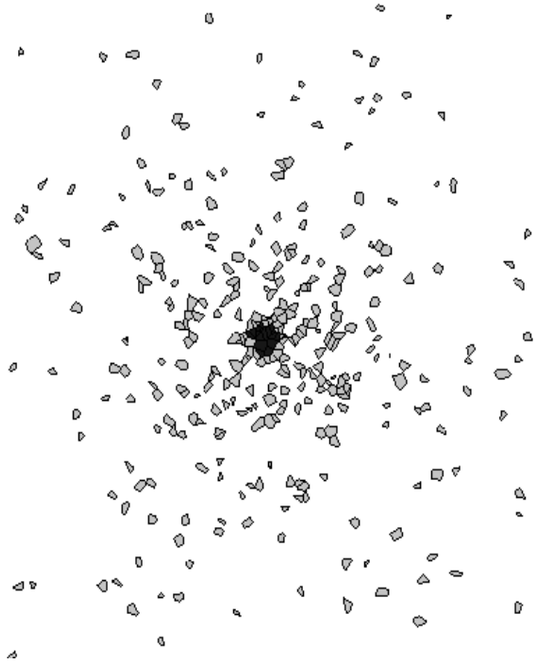
p=1

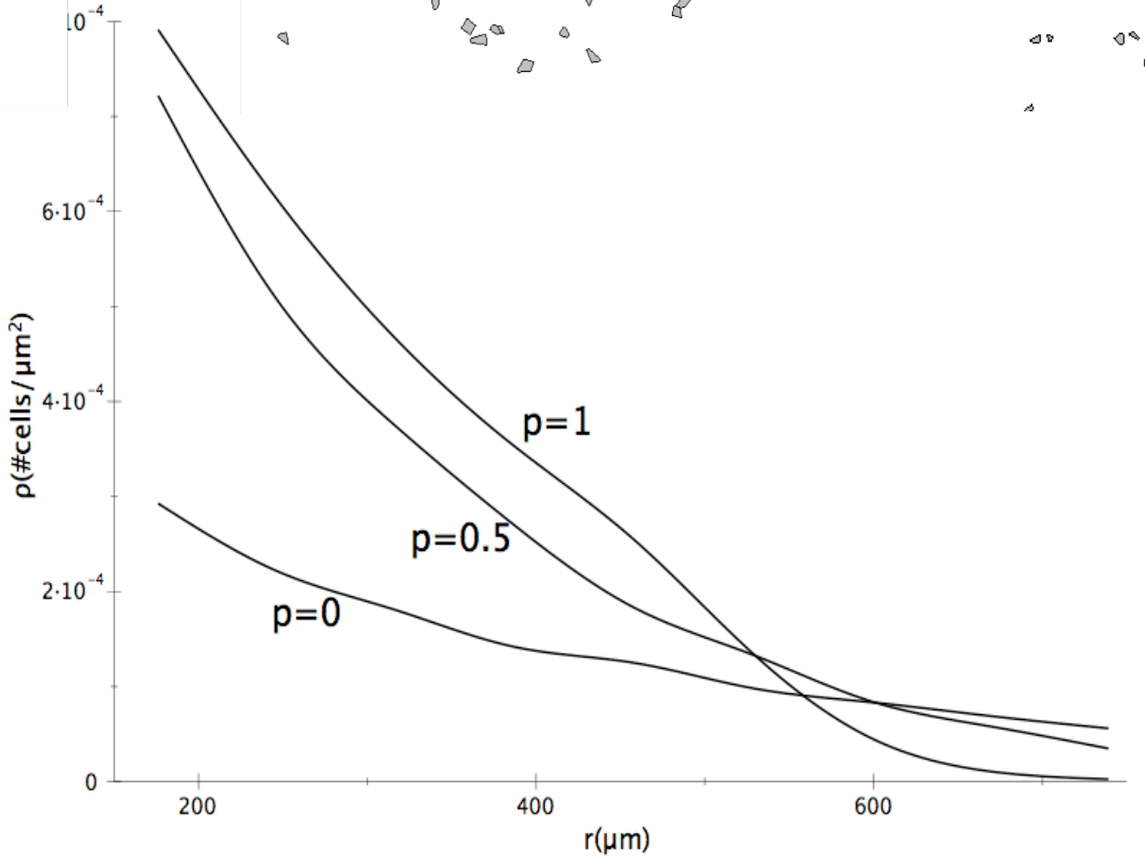


p=0.5 diffusion

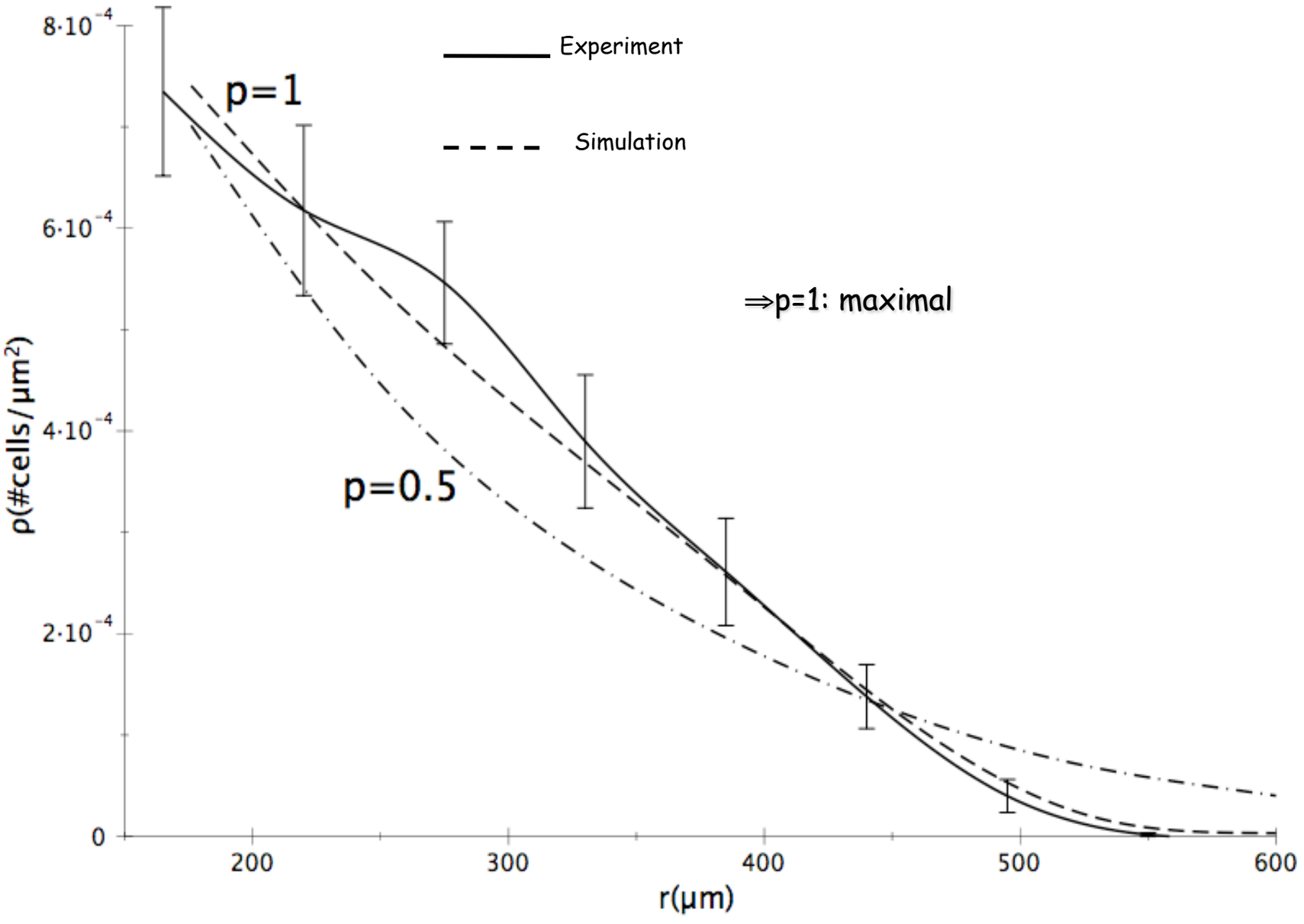


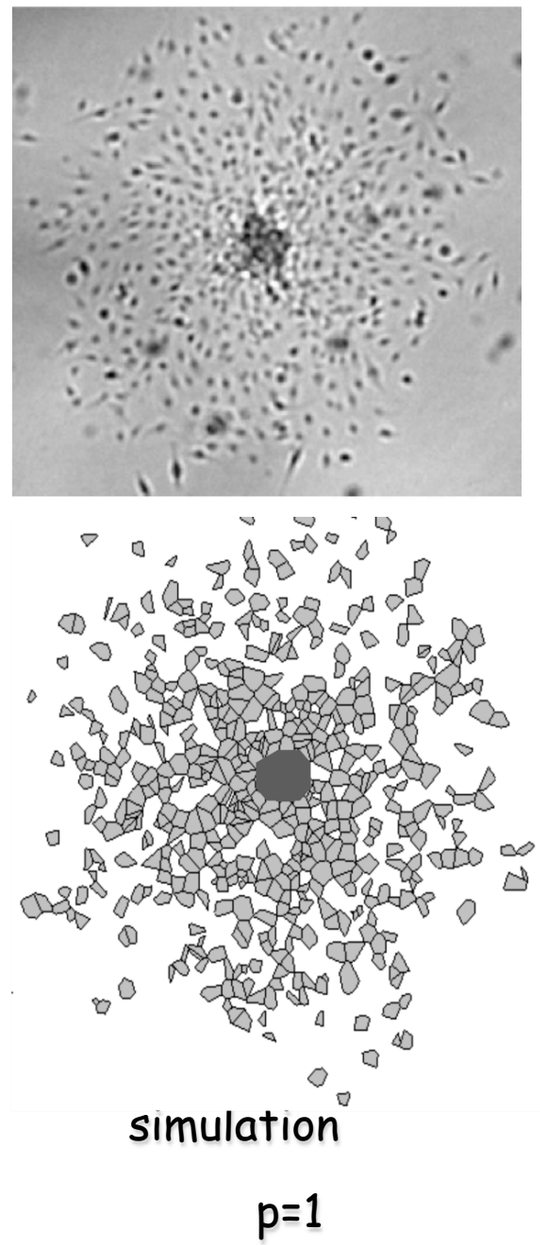
p=0





Cellular automaton results





M. Aubert, M. Badoual, S. Féréol, C. Christov, B. Grammaticos, A cellular automaton model for the migration of glioma cells, Phys. Biol. 3 (2006) 93.

Are cells diffusing?

Stochastic model (microscopic)

Cellular automaton

Continuous limit

Deterministic model (macroscopic)

Diffusion PDE

$$\Rightarrow \frac{\partial \rho}{\partial t} = \vec{\nabla}(D(\rho)\vec{\nabla}\rho)$$

Nonlinear diffusion

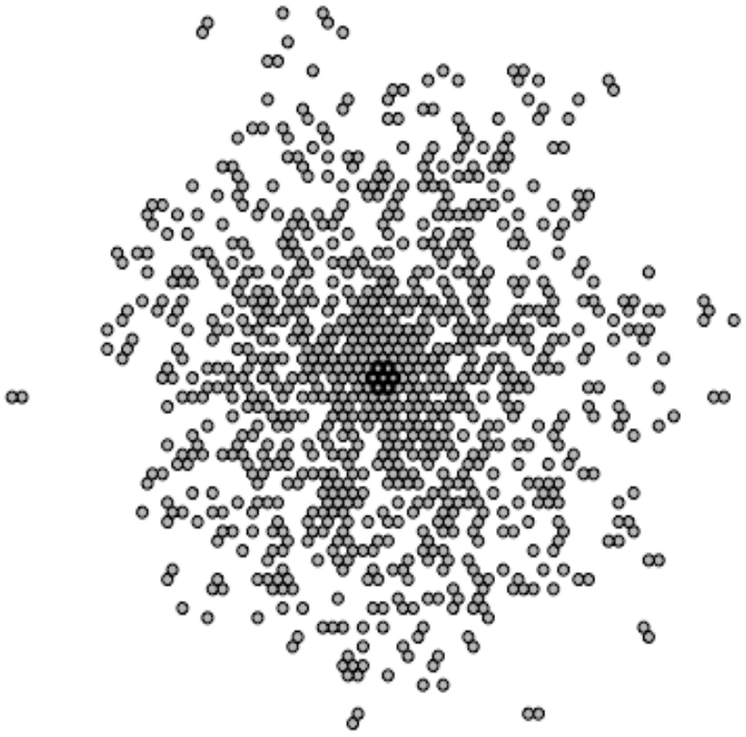
$$D(\rho) = 2D_0(1 - p + (2p - 1)\rho(2 - \rho))$$

ρ: cell density
p: probability to stay in contact with neighbouring cells

C. Deroulers, M. Aubert, M. Badoual, B. Grammaticos, Modelling tumour cell migration: from microscopic to macroscopic, Phys. Rev. E 79 (2009) 031917

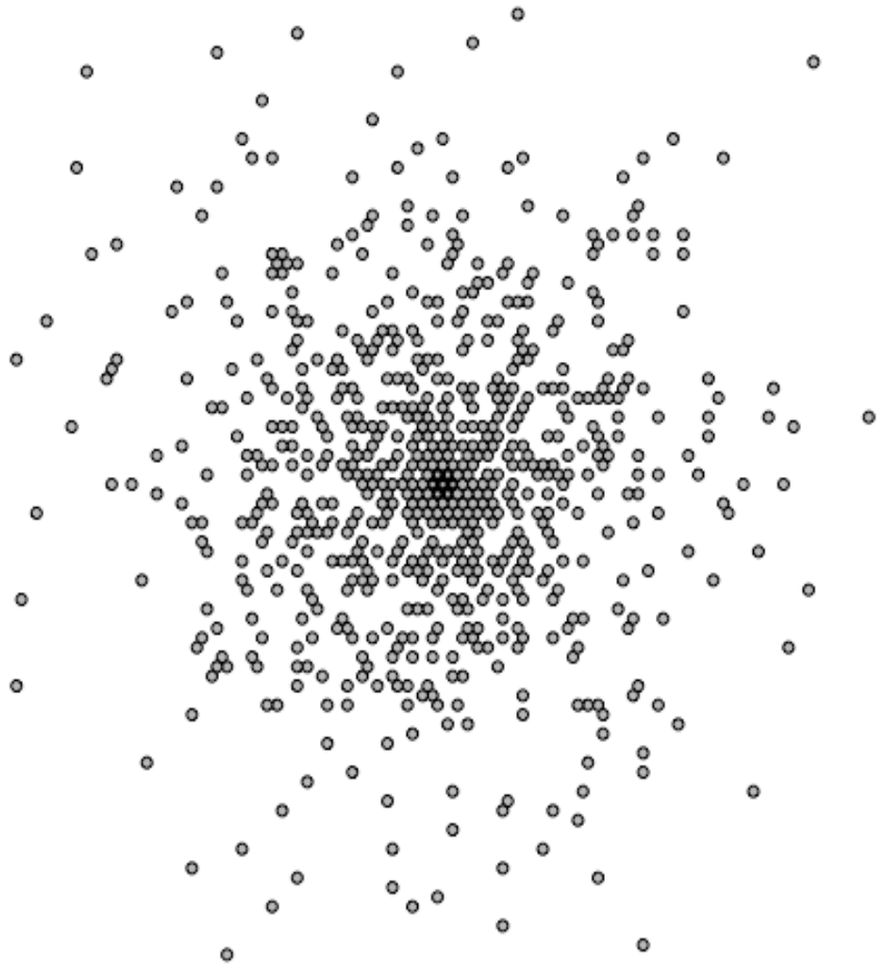
Inhibition of cell-cell interactions

p=1 ⇔ control



p=0.5

(corresponds to the situation where GJ are inhibited)



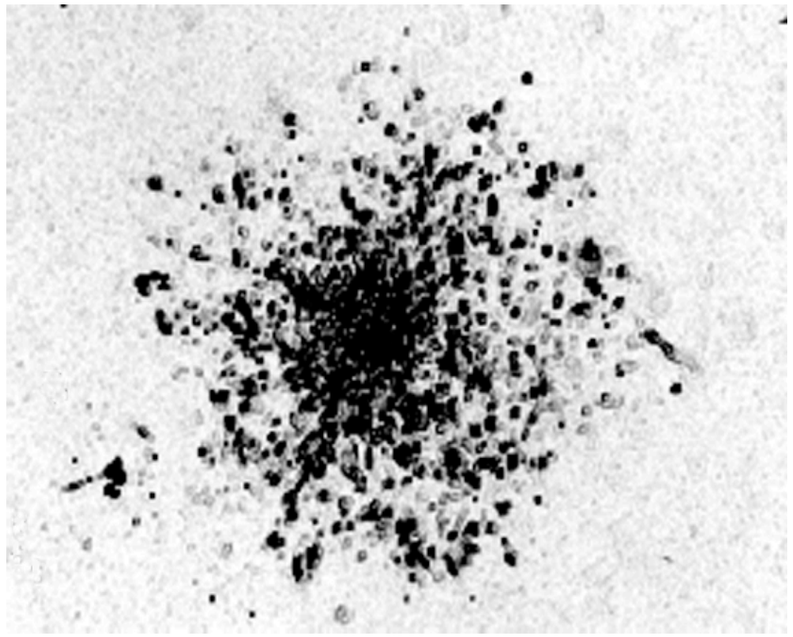
Decreasing p ⇒ decreases interaction

⇒ Enhanced migration

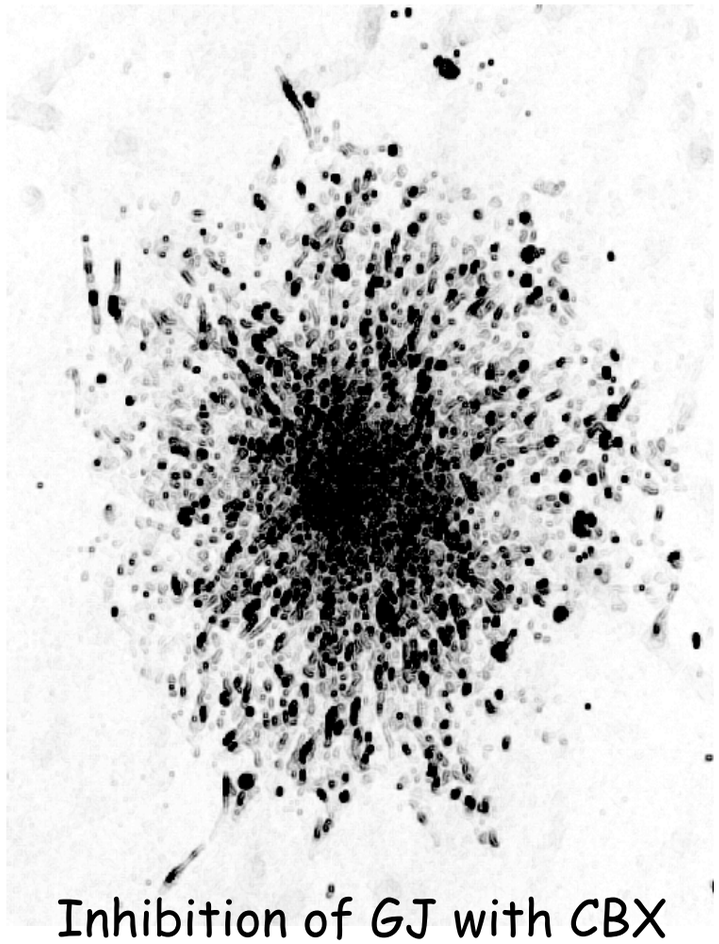
Inhibition of cell-cell interactions

Experiments

48h



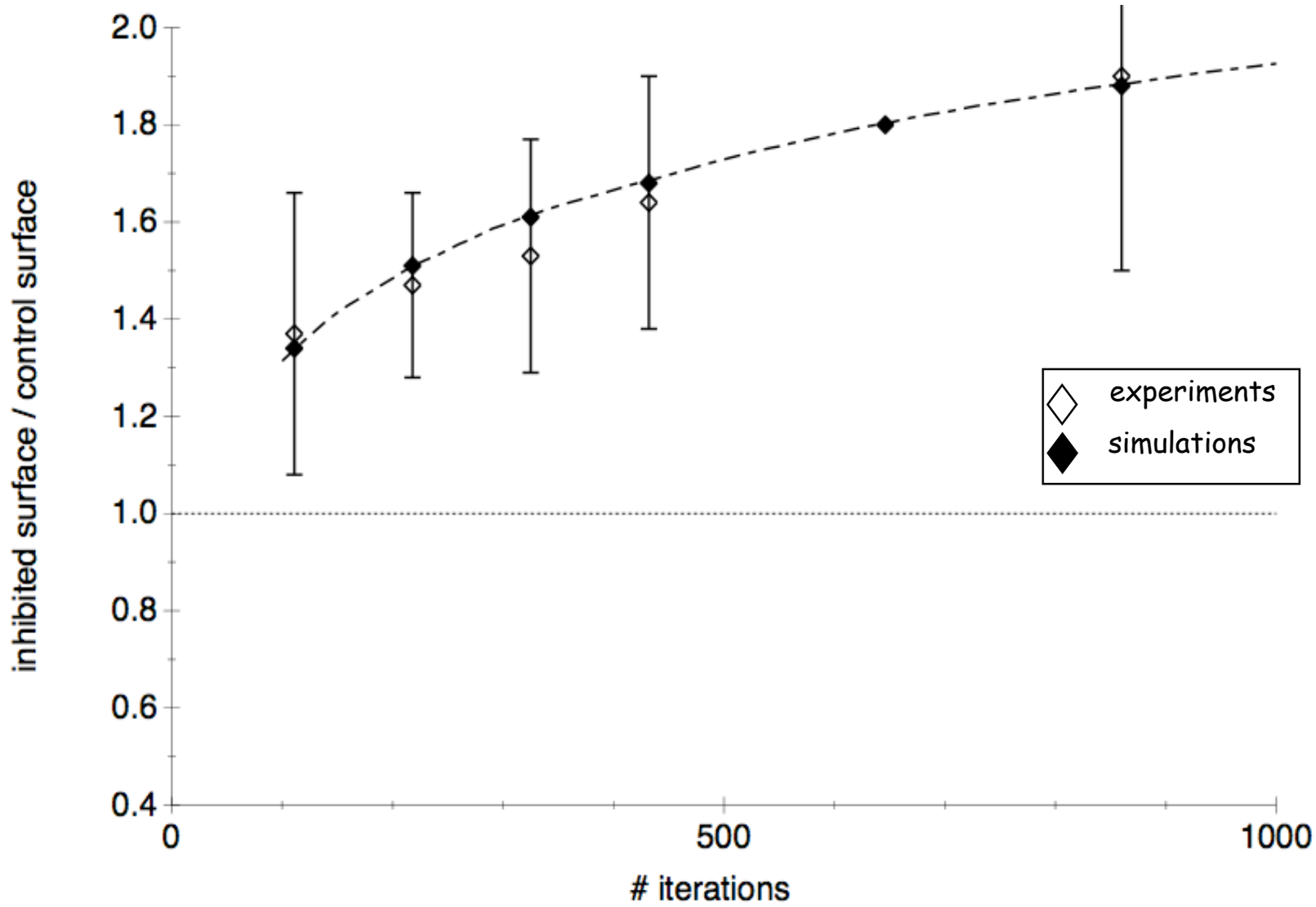
Control



Inhibition of GJ with CBX

Surface_CBX/ surface_control > 1 ⇒ cells with inhibited GJ migrate more

A quantitative comparison

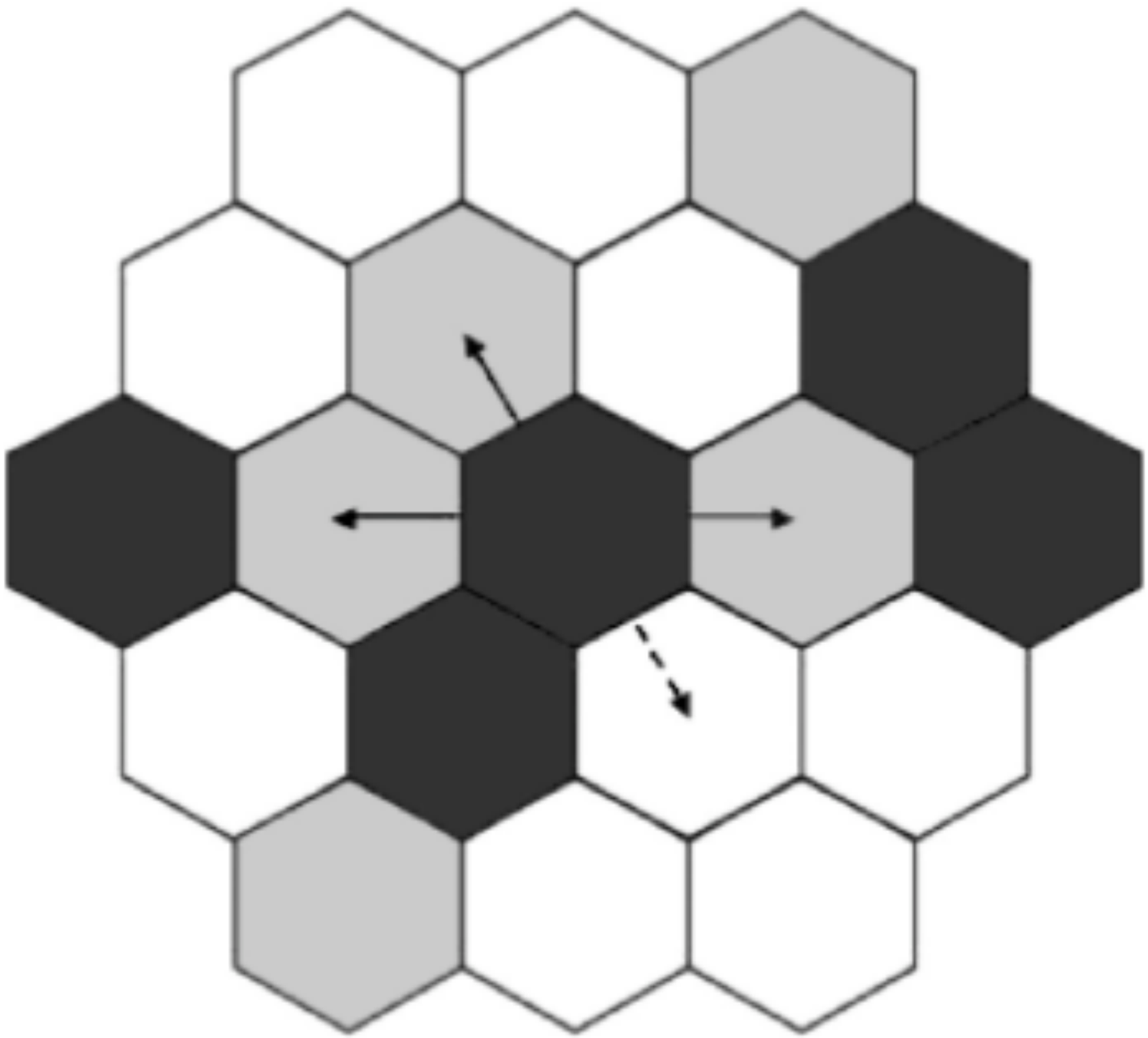


⇒ enhanced migration when GJ are inhibited

⇒ good agreement between experiments and simulations

M. Aubert, M. Badoual, C. Christov, B. Grammaticos, A model for glioma cell migration on collagen and astrocytes, Proc. Roy. Soc. Interface 5 (2008) 7586.

Cellular automaton for migration on astrocytes



δ: density of normal astrocytes

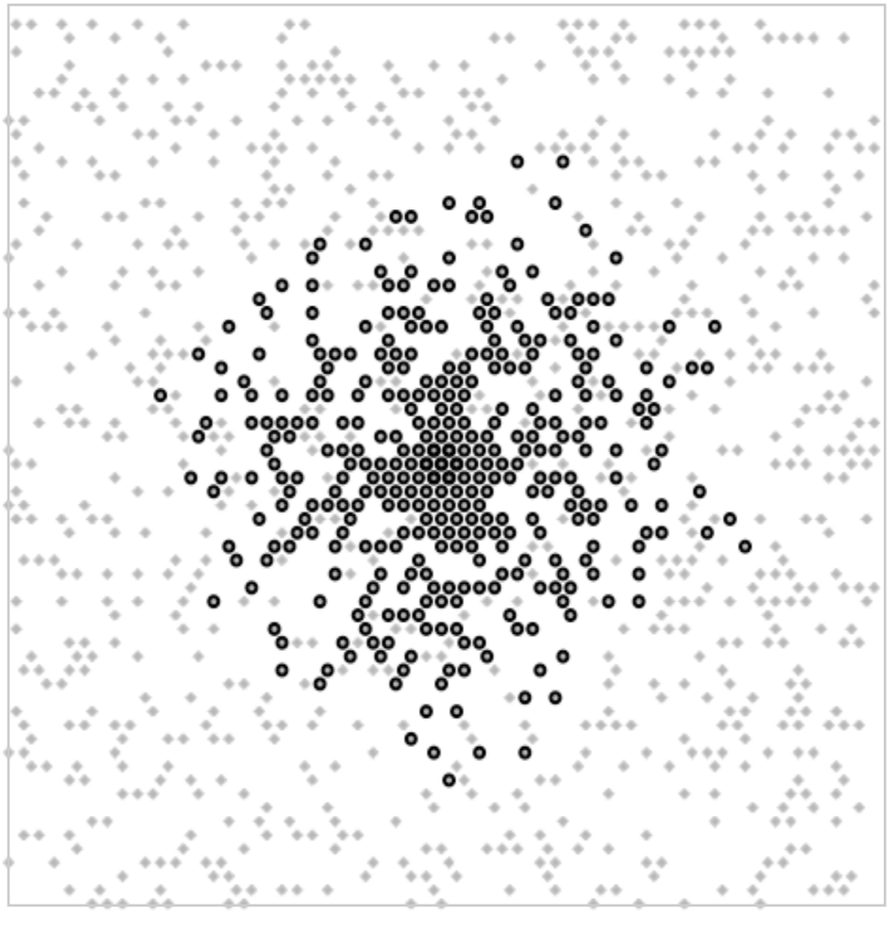
p: probability to stay in contact with neighbouring cells

q: probability to go on a site occupied by an astrocyte

Inhibition of cell-cell interactions

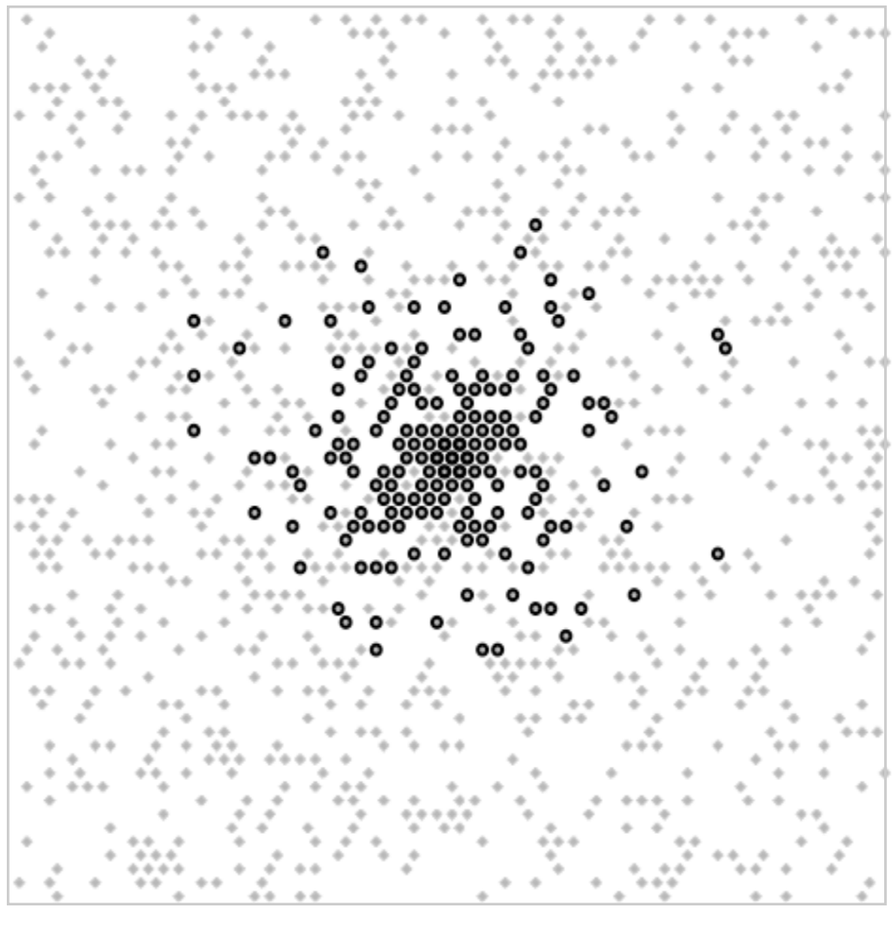
control

(p=1, q=1)



With gap junctions inhibited

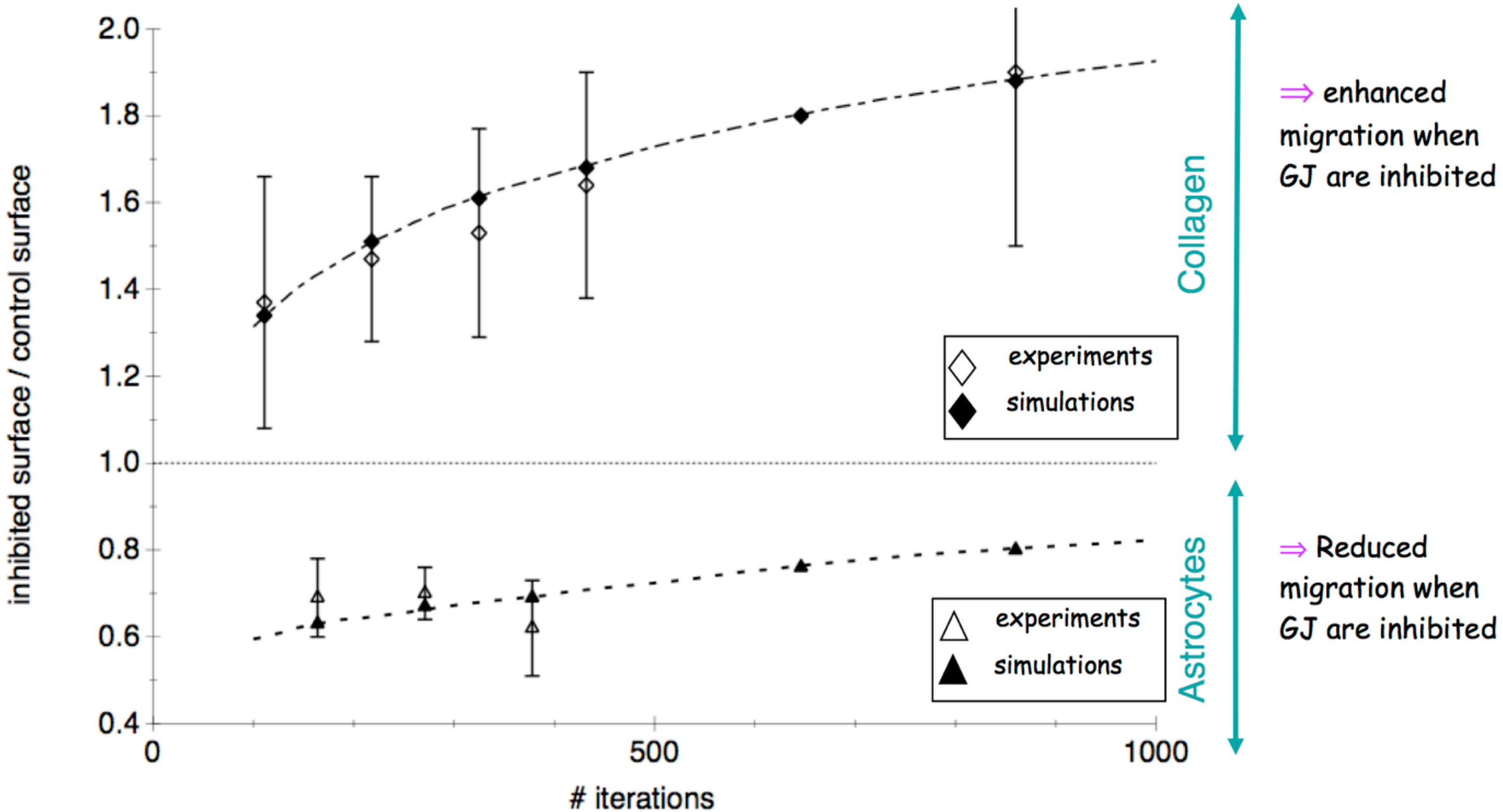
(p=0.5, q=0)



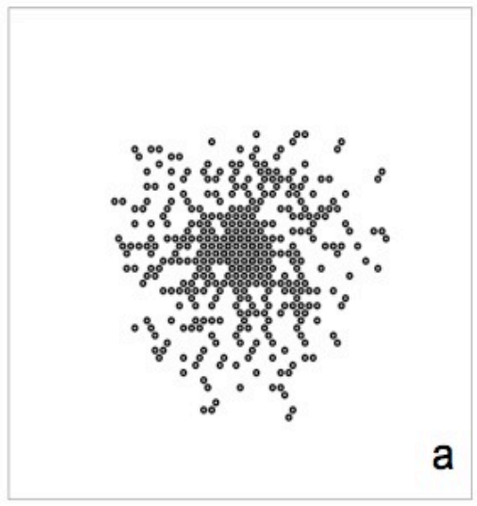
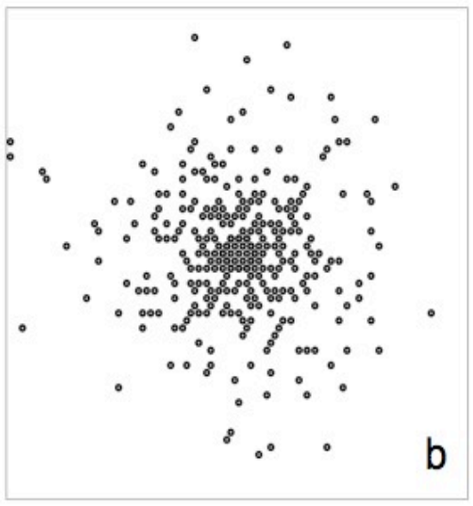
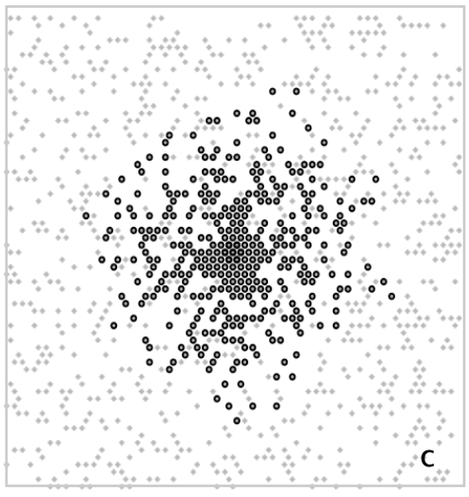
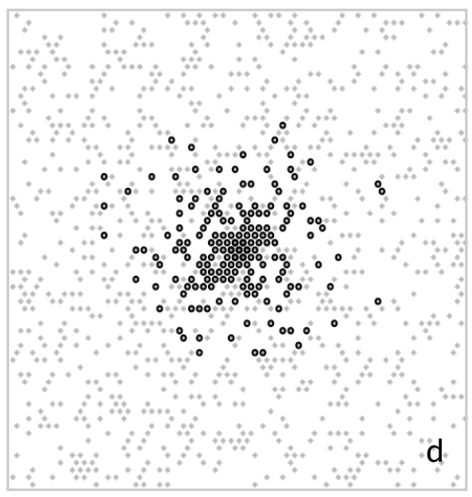
Monolayer of astrocytes (30%)

⇒ Reduced migration when GJ are inhibited

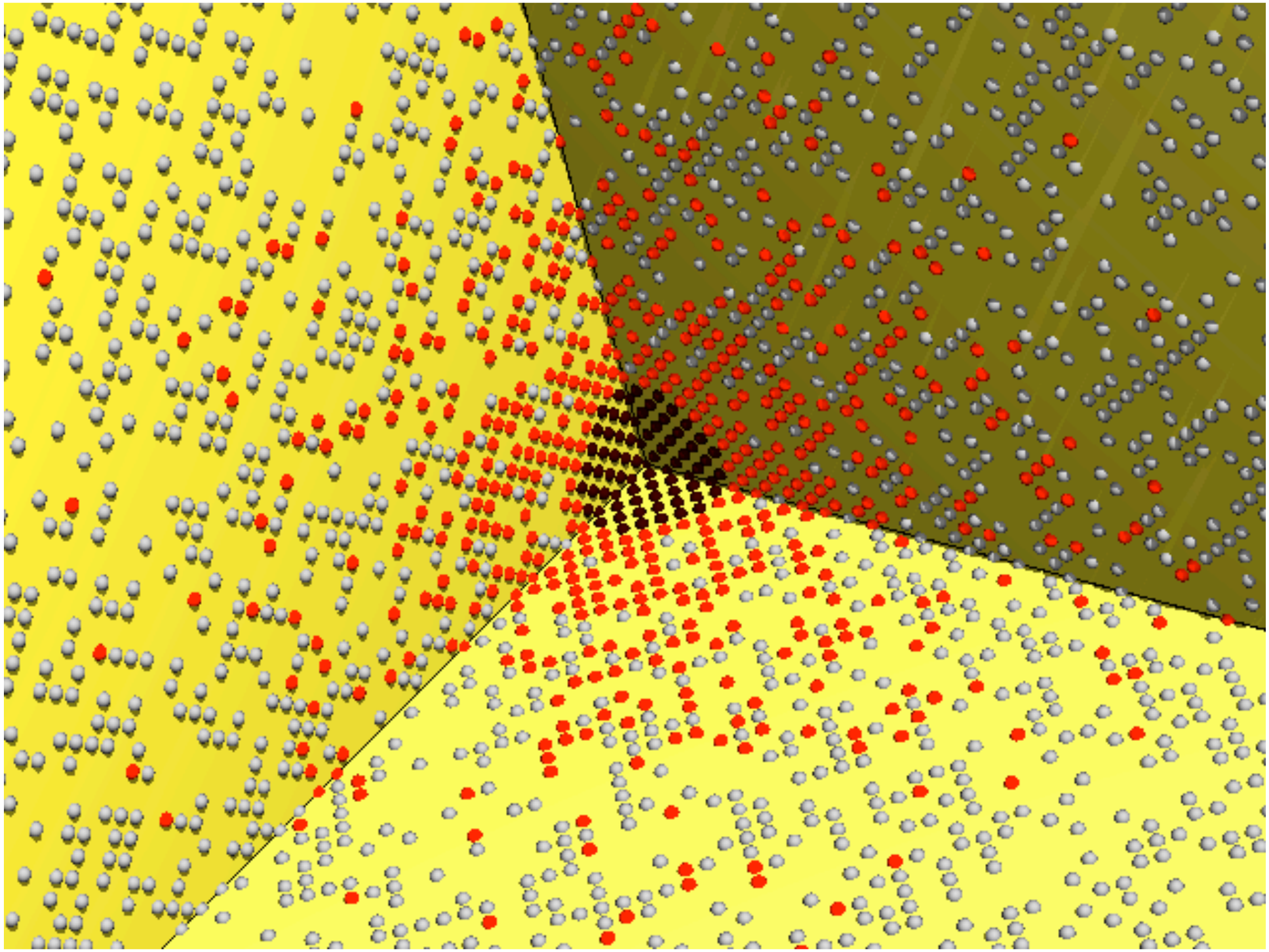
A quantitative comparison (again)



Summary

	control (p=1, q=1)	GJ inhibition (p=0.5, q=0)	
collagen			⇒ Enhanced migration
Monolayer of astrocytes			⇒ Reduced migration 30% of normal astrocytes

Example of a 3D evolution



The diffusion coefficient

Stochastic model (microscopic)

Cellular automaton

Continuous limit

Deterministic model (macroscopic)

Diffusion PDE

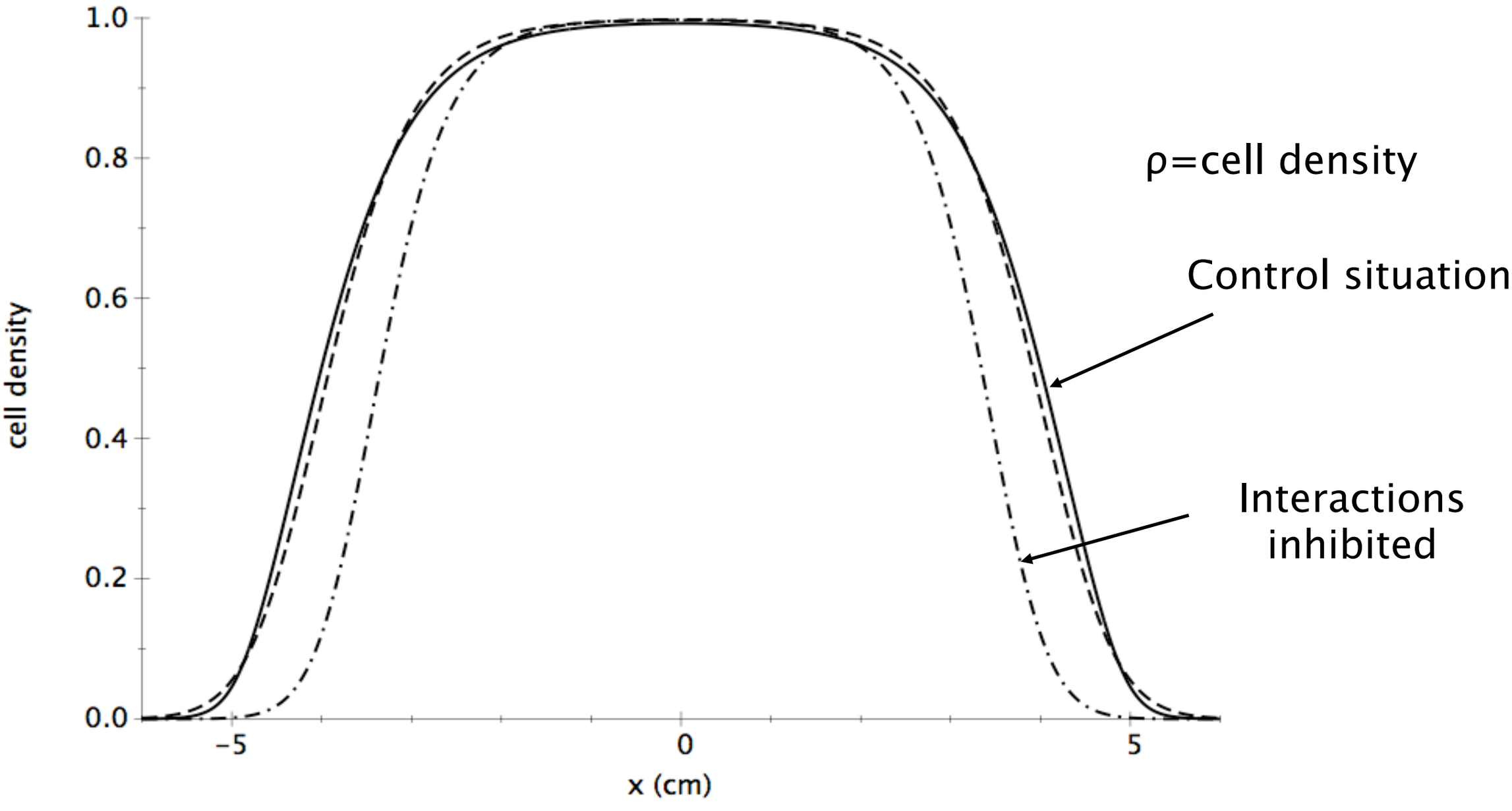
$$\Rightarrow \frac{\partial \rho}{\partial t} = \vec{\nabla}(D(\rho)\vec{\nabla}\rho)$$

$$D(\rho) = 2D_0(\delta q + (1-\delta)(1-p+(2p-1)\rho(2-\rho)))$$

δ : density of normal astrocytes
p: probability to stay in contact with neighbouring cells
q: probability to go on a site occupied by a normal astrocyte

M. Badoual, C. Deroulers, M. Aubert, B. Grammaticos, Modelling intercellular communication and its effects on tumour invasion, Phys. Biol. 7 (2010) 046013

Application to “real” tumours



20 % increase of the life expectancy
2 months for high grade gliomas and 2 years for low grade gliomas

Conclusion

- The model has been validated by comparison with experiments.
- Answer to the biological question concerning migration
Cell-cell interactions involve some cell adhesion.
When the adhesion is removed, cell migrate further on a acellular substrate.
But when the adhesion to the substrate is removed, cells cannot migrate easily and migration is reduced.

- An interesting off-shoot: nonlinear diffusion.

- Predictions of the model
If GJ communications are inhibited in a tumour, the invasion will decrease, leading to an increase in the lifetime of the patient of 20%.
Glioblastoma: typical survival time, 1 year. Expected gain: 2 months.
Low grade gliomas: typical survival time, 10 years. Expected gain: 2 years.

But we are still far from the clinical applications!
- What drug?
- How to inject this drug only in the tumour?
- Side effects?

A study of the evolution of real tumours

Low grade gliomas (grade II)

- Very invasive tumours that cannot be cured.
- However patients can live more than ten years after diagnosis.

Three phases in the evolution of low grade gliomas

- The first phase is a “silent period” before clinical revelation.
- The second phase (symptomatic period) is characterized by a linear evolution of the radius of the tumour (typical value 2mm/yr).
- In the third phase, the tumour undergoes an anaplastic transformation leading to neurological deficit and ultimately death.

Linear evolution of the tumour radius

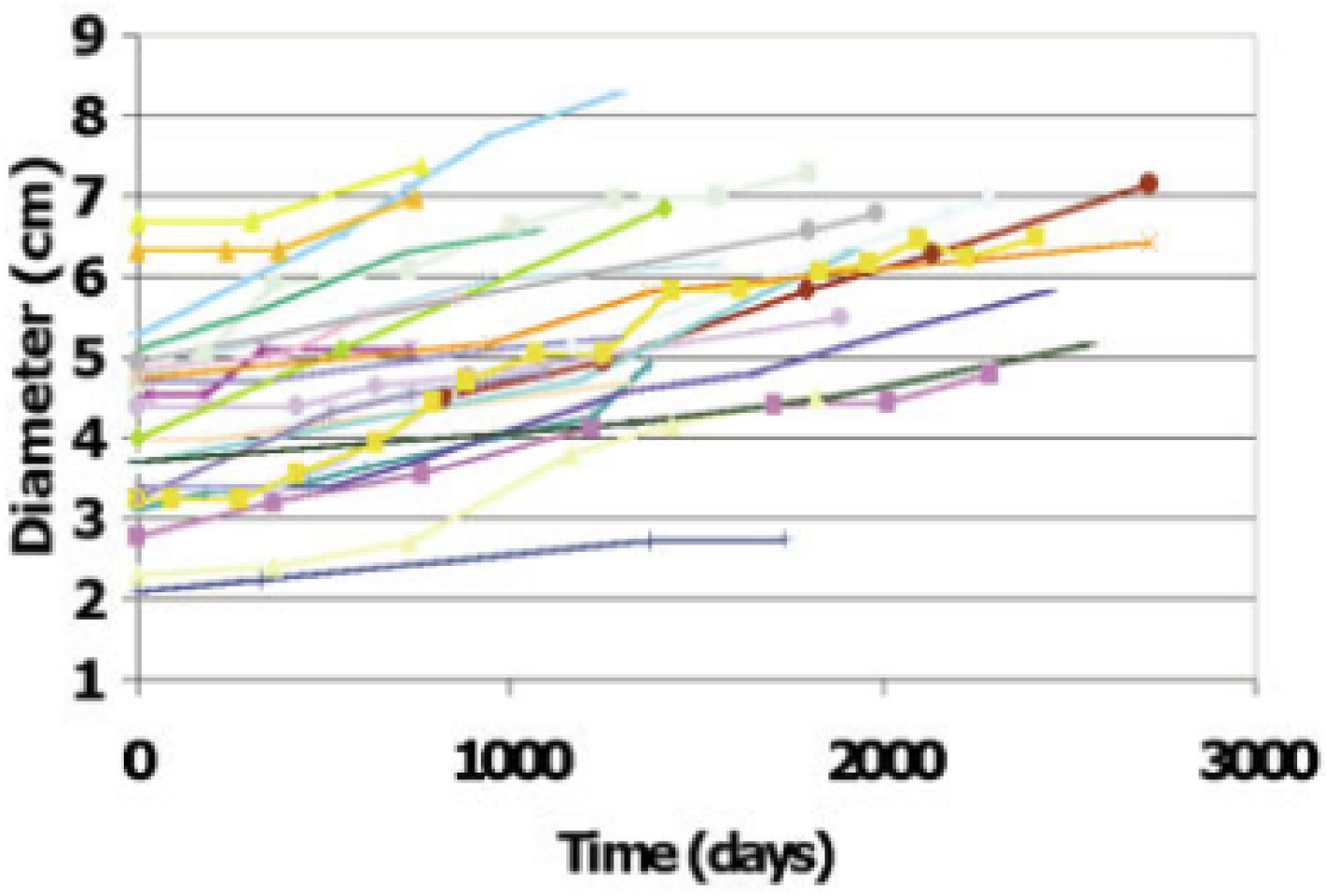


Fig 2. Evolution of the mean tumor diameters over time in the 27 patients. Each curve starts at the first magnetic resonance image (MRI) obtained at diagnosis and ends at the last follow-up MRI (or last MRI before anaplastic transformation).

Mandonnet E, Delattre JY, Tanguy ML, Swanson KR, Carpentier AF, Duffau H, Cornu P, van Effenterre R, Alvord EC Jr, Capelle L (2003), Ann Neurol 53:524–528

The model used for tumour evolution

$$\frac{\partial C}{\partial t} = \nabla(D\nabla C) + \kappa C(1 - C/C_0)$$

diffusion

proliferation (logistic growth)

$$\rho = \frac{C}{C_0} \qquad \text{cell density}$$

$$\frac{\partial \rho}{\partial t} = \nabla(D\nabla \rho) + \kappa \rho(1 - \rho)$$

Swanson KR, Bridge C, Murray JD, Alvord EC Jr. J Neurol Sci. (2003) 216(1), p.1

Linear evolution of radius at large time

We solve numerically the diffusion-proliferation equation in 3D
Initial condition: one cell,
i.e. density of gaussian form with volume of a sphere of radius r_0=0.02 mm)

$$\rho(r,t) = \left(\frac{t_0}{t+t_0}\right)^{3/2} \exp\left(-\frac{r^2}{4D(t+t_0)} + \kappa t\right)$$

with $t_0 = \frac{r_0^2}{4D}$

Radius of the tumour on a MRI examination:

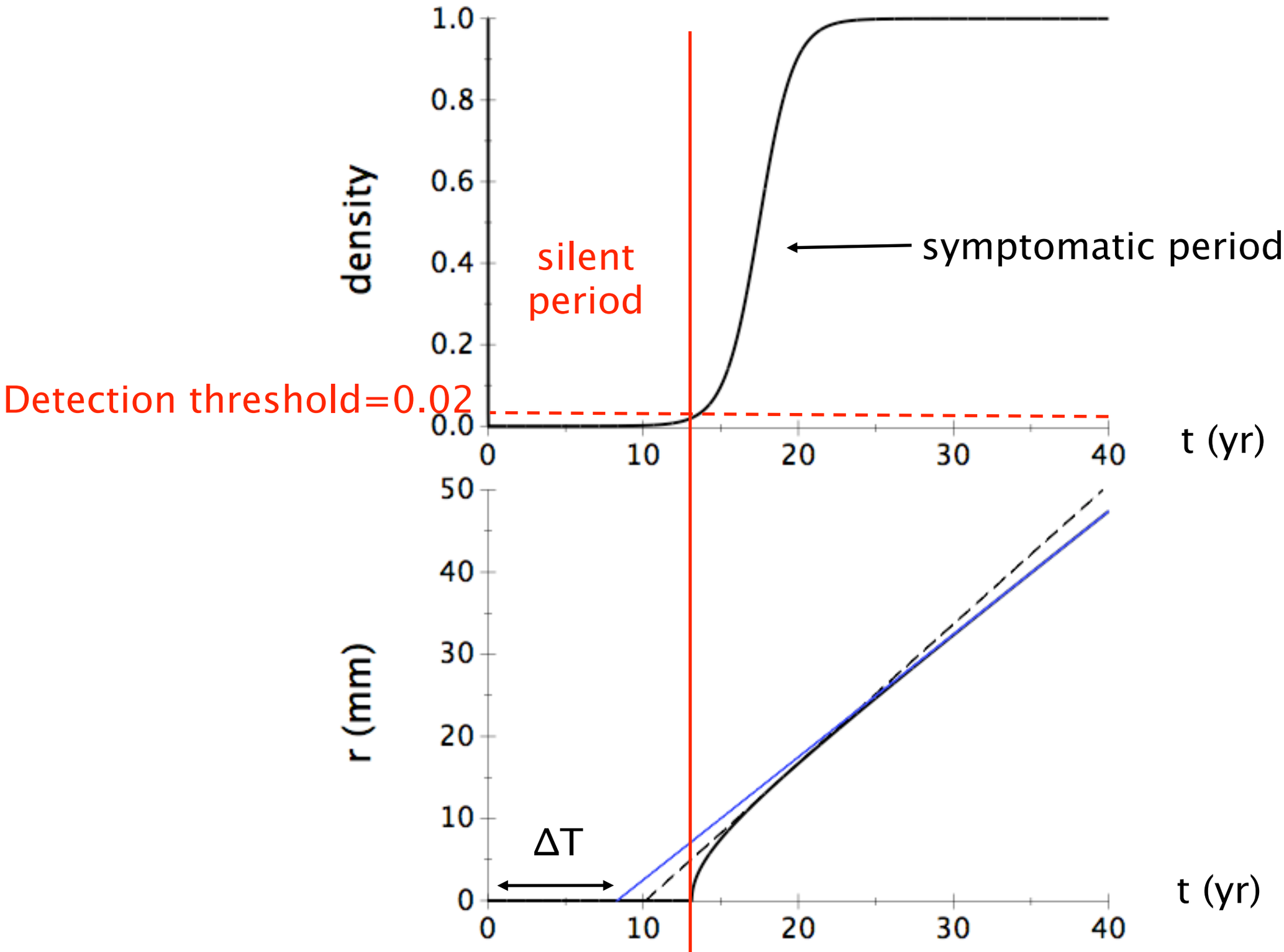
Introduce a threshold ρ^*

Find asymptotically

$$t \to \infty \;\Rightarrow\; r(\rho^*, t) \sim \sqrt{4D\kappa}t$$

Constant radial growth velocity

The two phases



Application to real patients

204 patients with the radial velocity v estimated from MRI and a measure of the radius of the tumour at a given time ($0.5<v<4$ mm.yr^{-1})

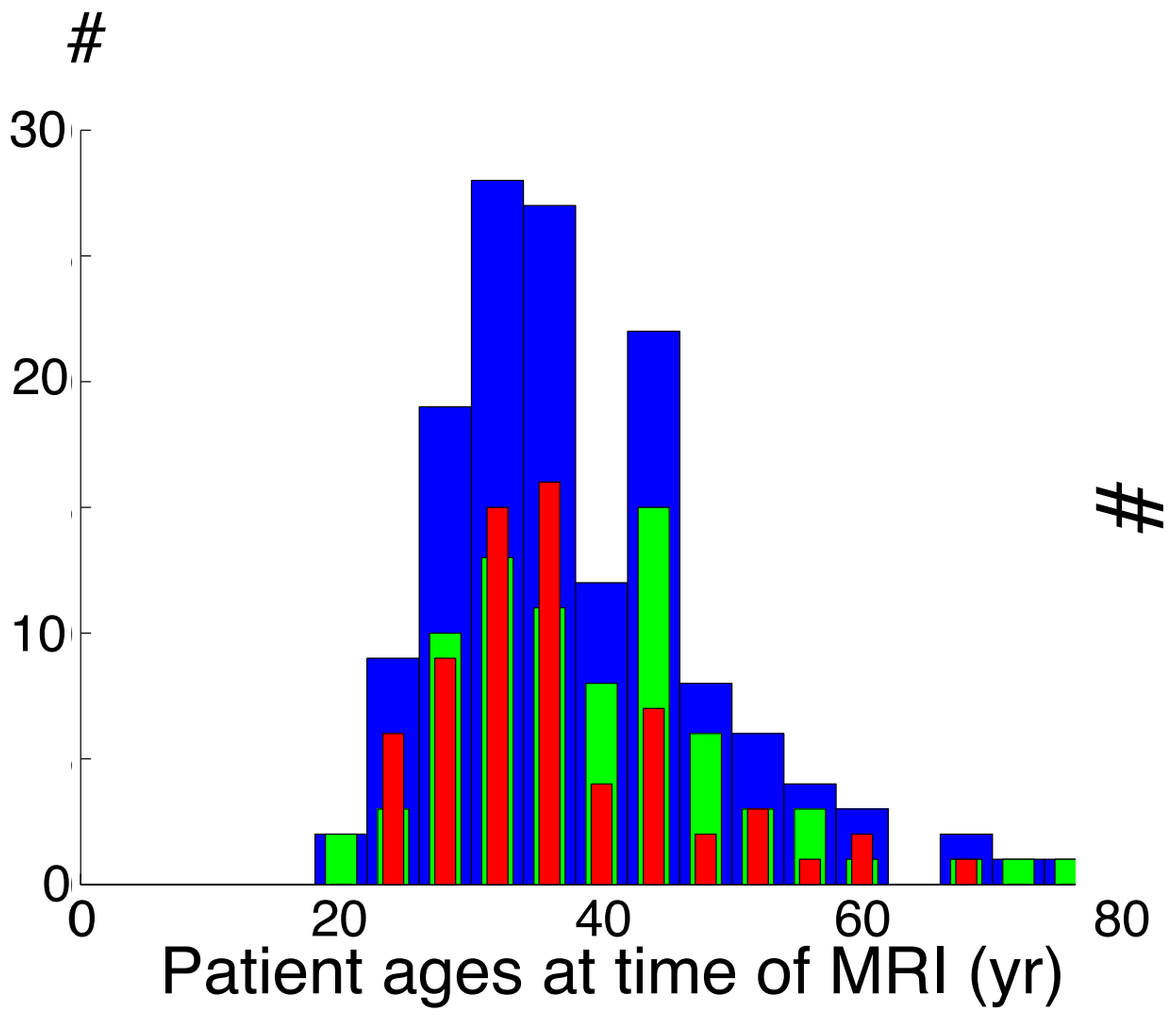
For each patient, ten values of κ in the range (0.1–10) yr^{-1} are used to solve the model equation and for each value of κ, the date of the genesis of the tumour is calculated.

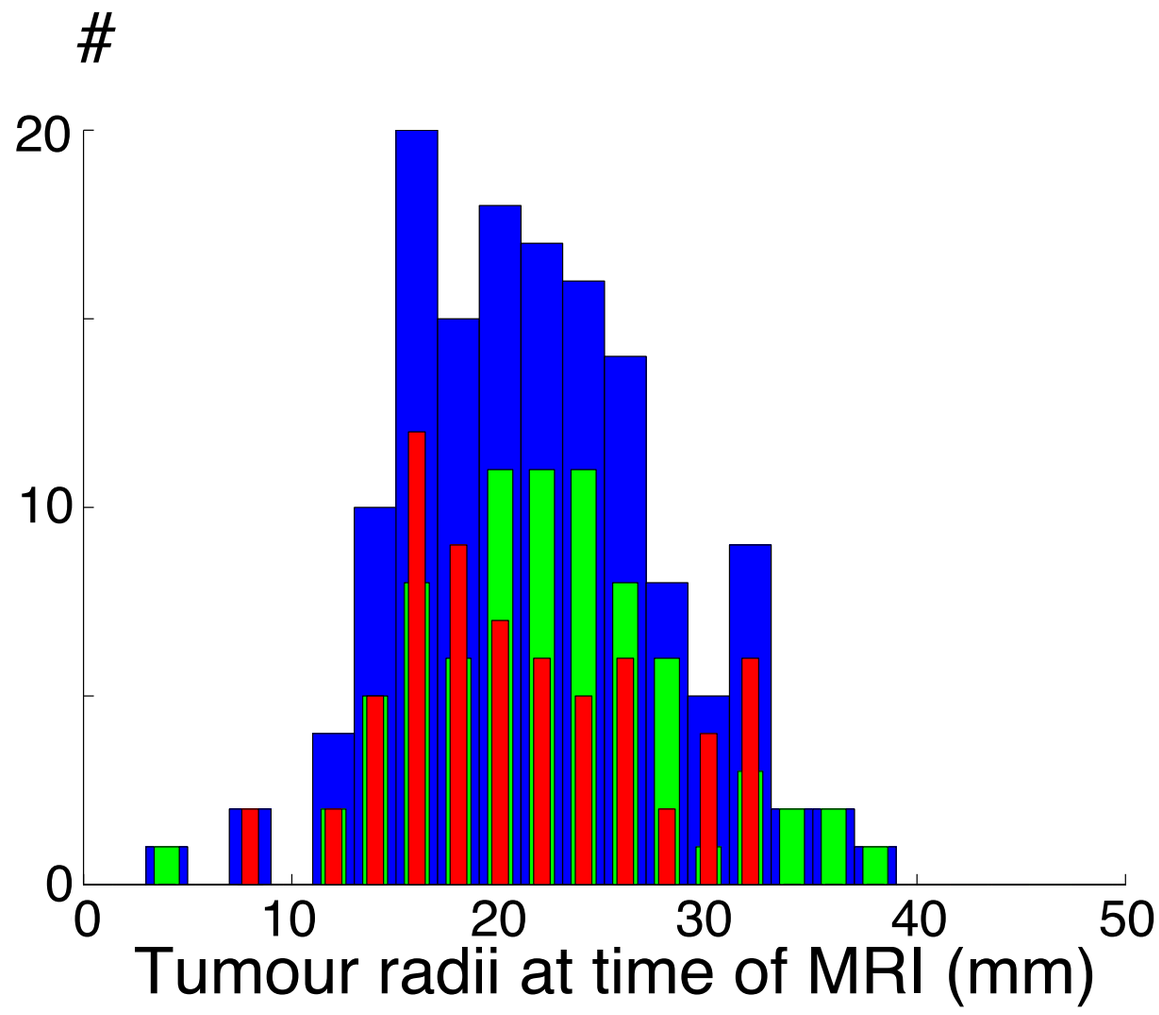
Constraints:

- Older than 18 year-old
- Linearity for r=15mm
- The “age” of the tumour should not be larger than the age of the patient himself
- The density at the centre should not be saturated for more than 5 years before the MRIs (low grade)

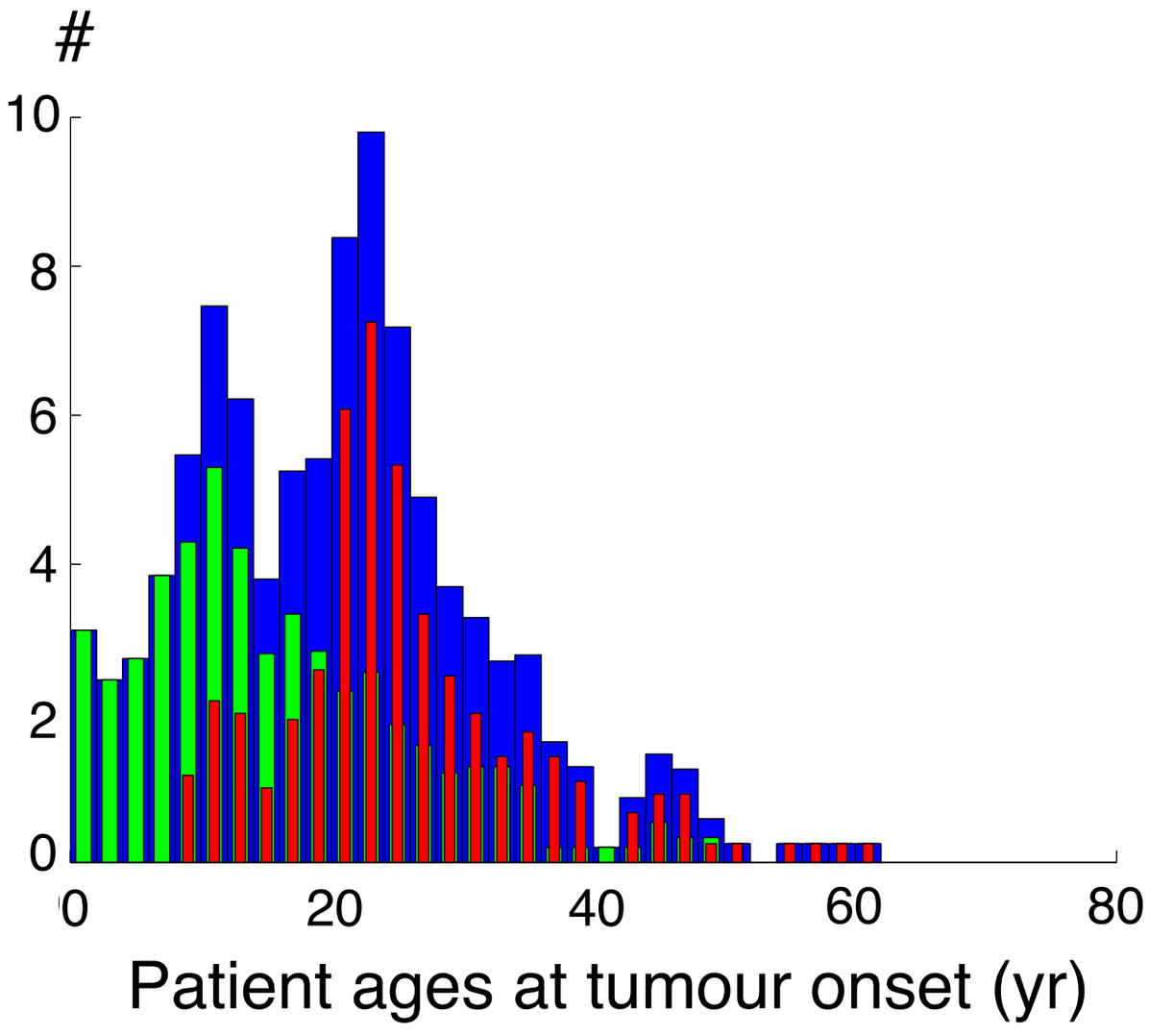
Improving the time-machine: estimating the date of birth of grade II gliomas, C. Gerin, J. Pallud, B. Grammaticos, E. Mandonnet, C. Deroulers, P. Varlet, L. Capelle, L. Taillandier, L. Bauchet, H. Duffau, M. Badoual to appear in Cell Prolif.

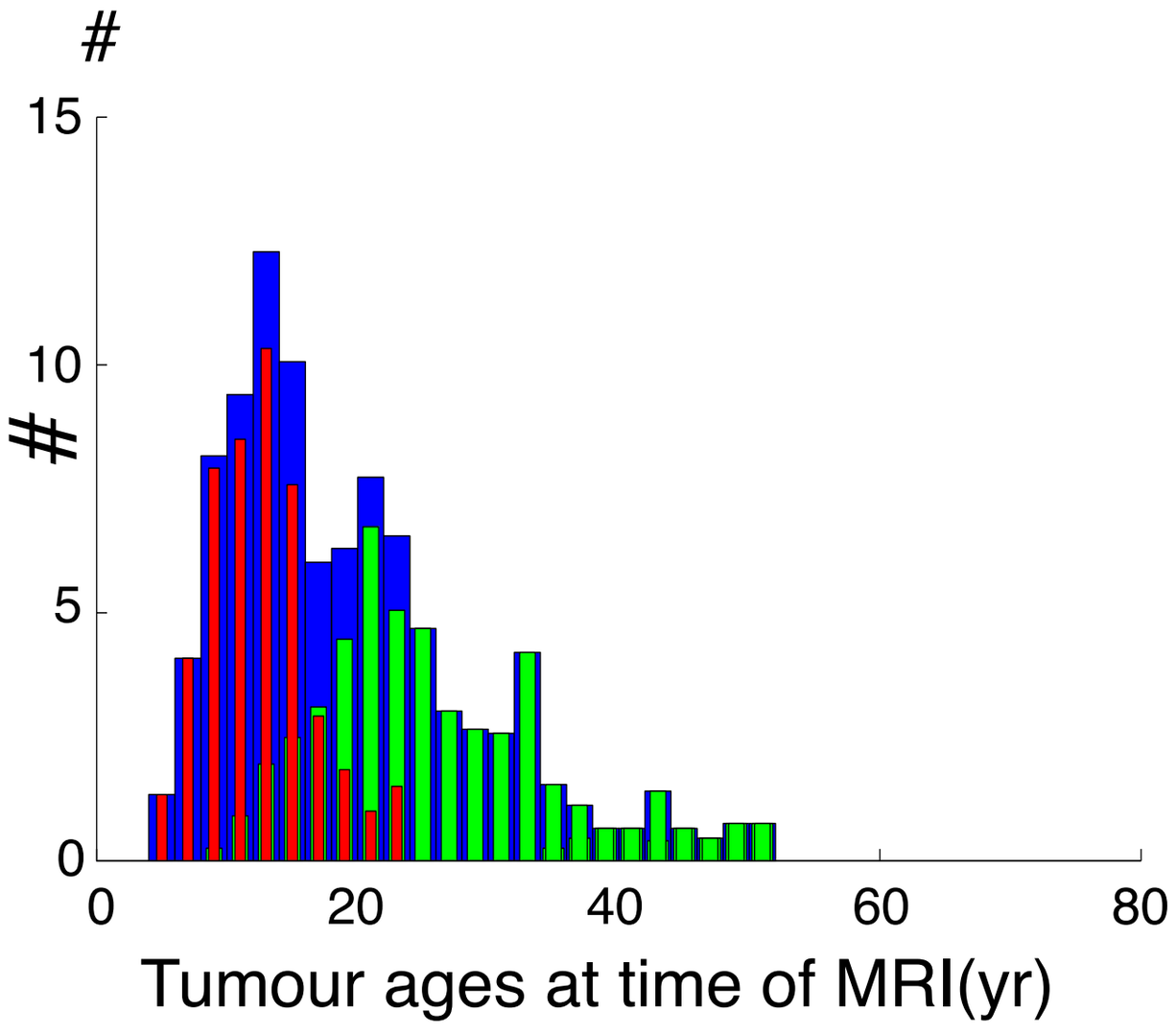
Distribution of patients' population



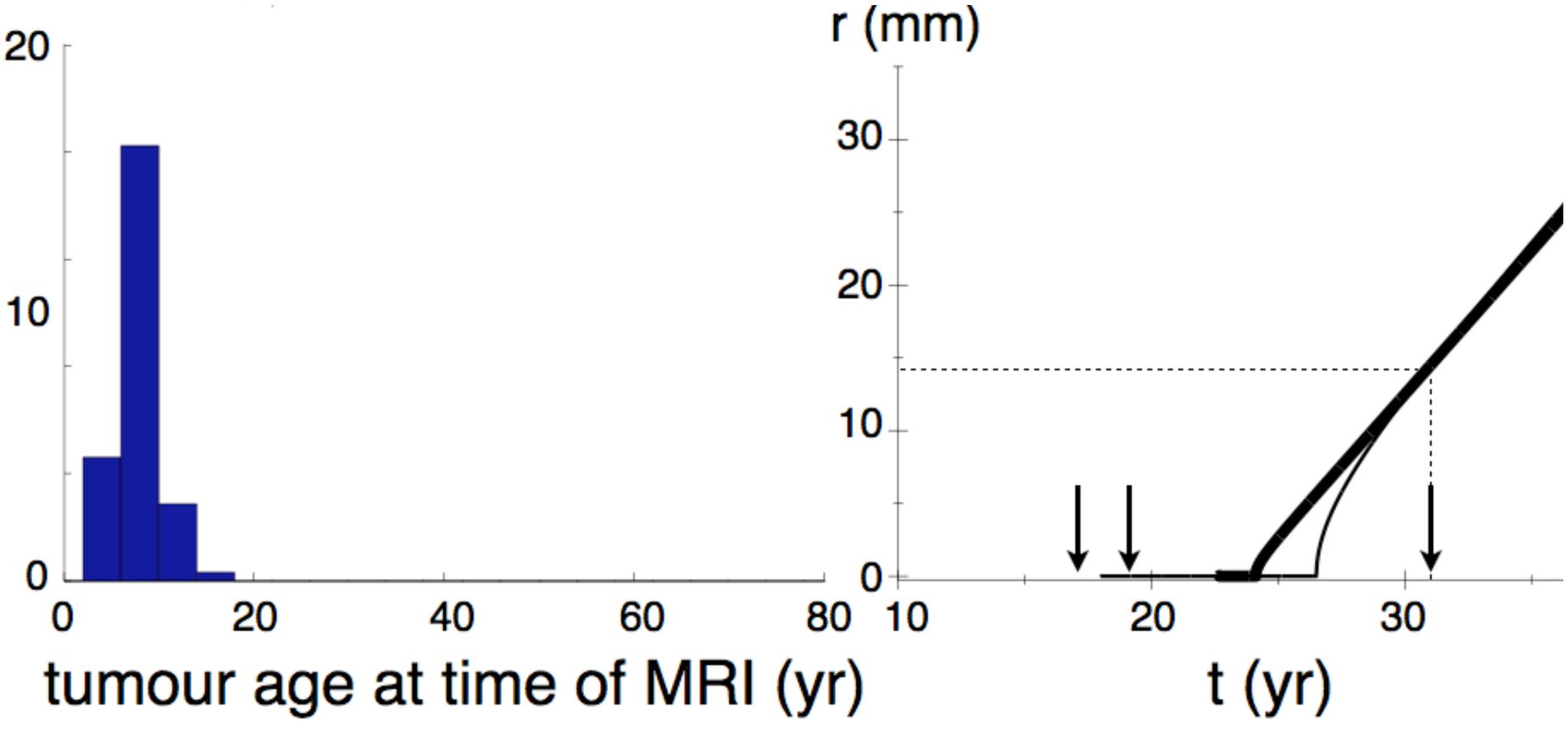


Distribution of patients' population





Asymptomatic patients



$\langle t_{MRI} \rangle \approx 8$ yr

Conclusion

- The model is consistent with the clinical data.

- Provides a (broad) estimate for the coefficients D and κ.

- Low grade gliomas are not congenital lesions but appear on average around 24 years of age.

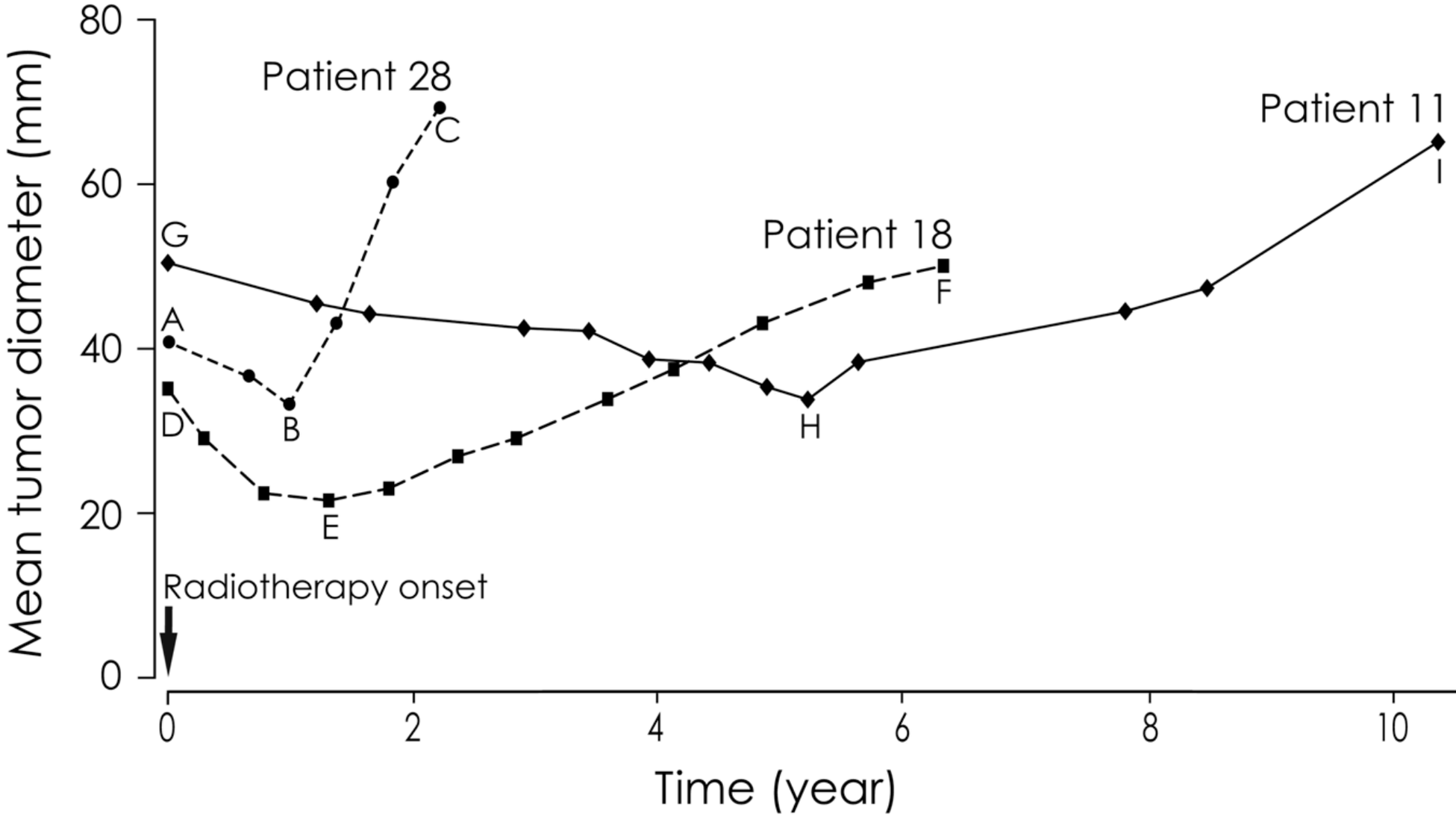
- At the time of diagnosis, the tumour has been growing for 11 years on average.

Open questions

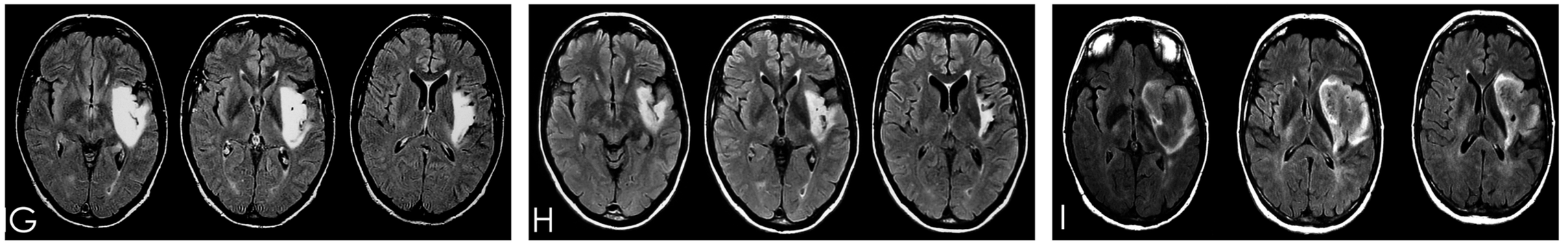
- What about patients with $v<2$ mm yr^{-1}?
- Some of them do not have any solution.
- $\langle t_0 \rangle = 14$ years for these patients. Is it a pedatric tumour?

- What determines the threshold? Oedema? Cell density?

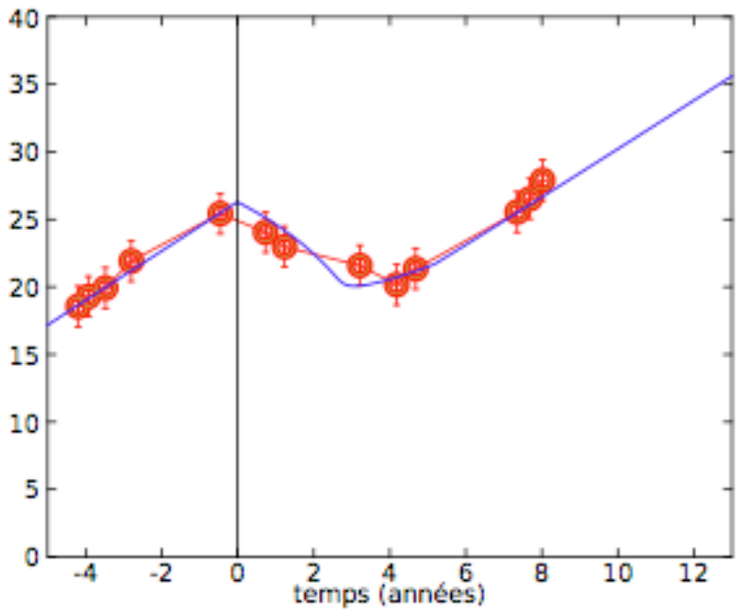
Envoi: an application to radiotherapy



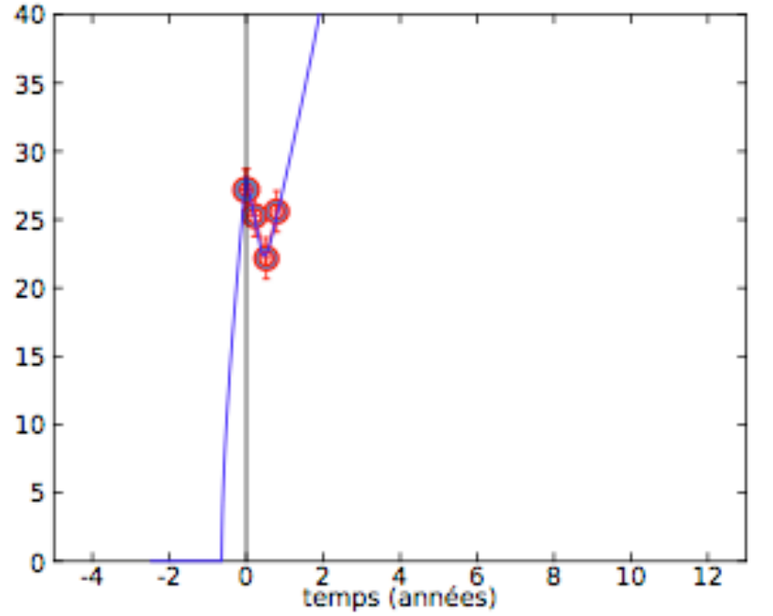
Patient 11



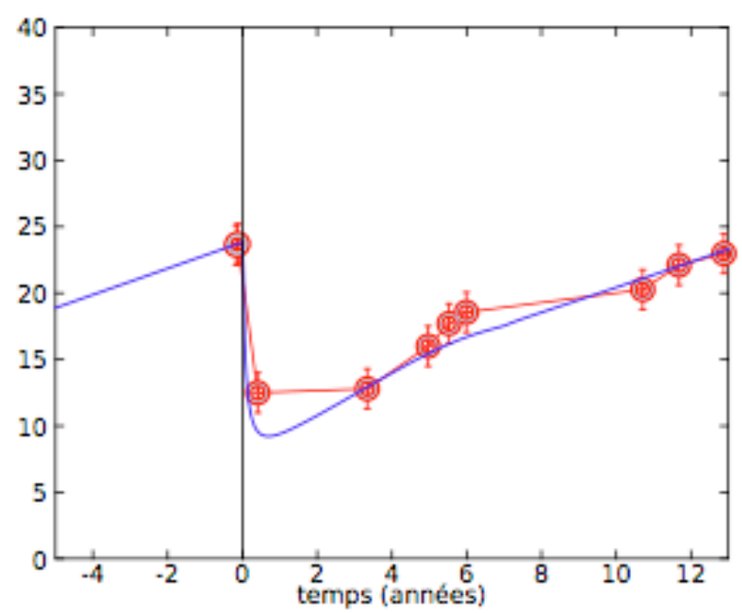
Radiotherapy: some model results



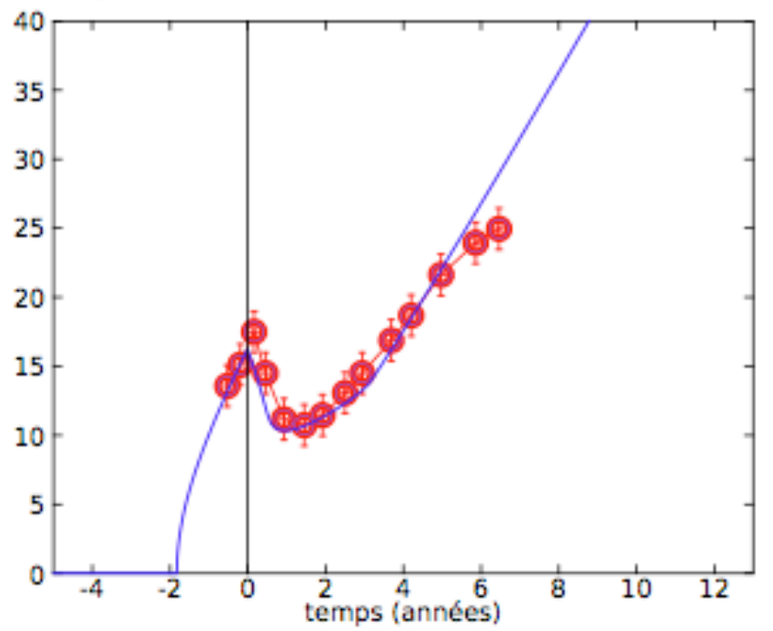
(a) κ=4,0/an, D=0,21mm^2/an, $r_0 = 0,64$, $\mu = 0,10$/an



(b) κ=20/an, D=11mm^2/an, $r_0 = 0,50$, $\mu = 0,066$/an



(c) κ=4,0/an, D=0,06mm^2/an, $r_0 = 0,75$, $\mu = 0,22$/an



(d) κ=4,0/an, D=1,56mm^2/an, $r_0 = 0,65$, $\mu = 0,13$/an

General conclusion

- Mathematical models can say something about tumours

- A study of tumour cell migration indicates the existence of cell attraction

- The reduced migration due to cell communication inhibition does not have a great practical usefulness

- For low-grade gliomas the model indicates a tumour genesis prior to what obtained by a rough, “linear extrapolation”, estimate

- Moreover the two-peaked patient population distribution may hint at the existence of tumours of different origin

- The application of the model to radiotherapy allows to assess some of the practitioners beliefs