Modeling origin and natural evolution of low-grade gliomas

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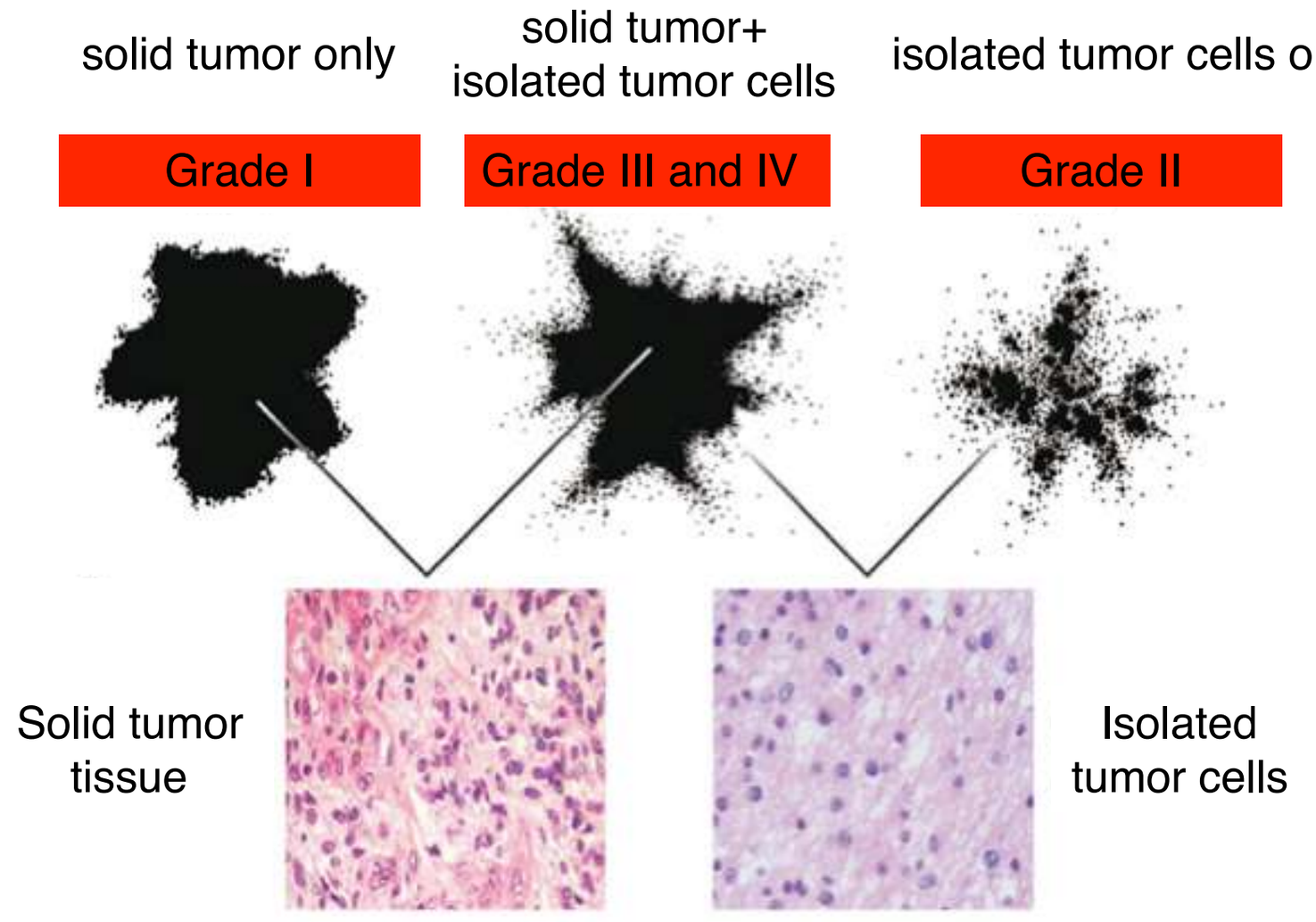
Paris Diderot University, IMNC lab

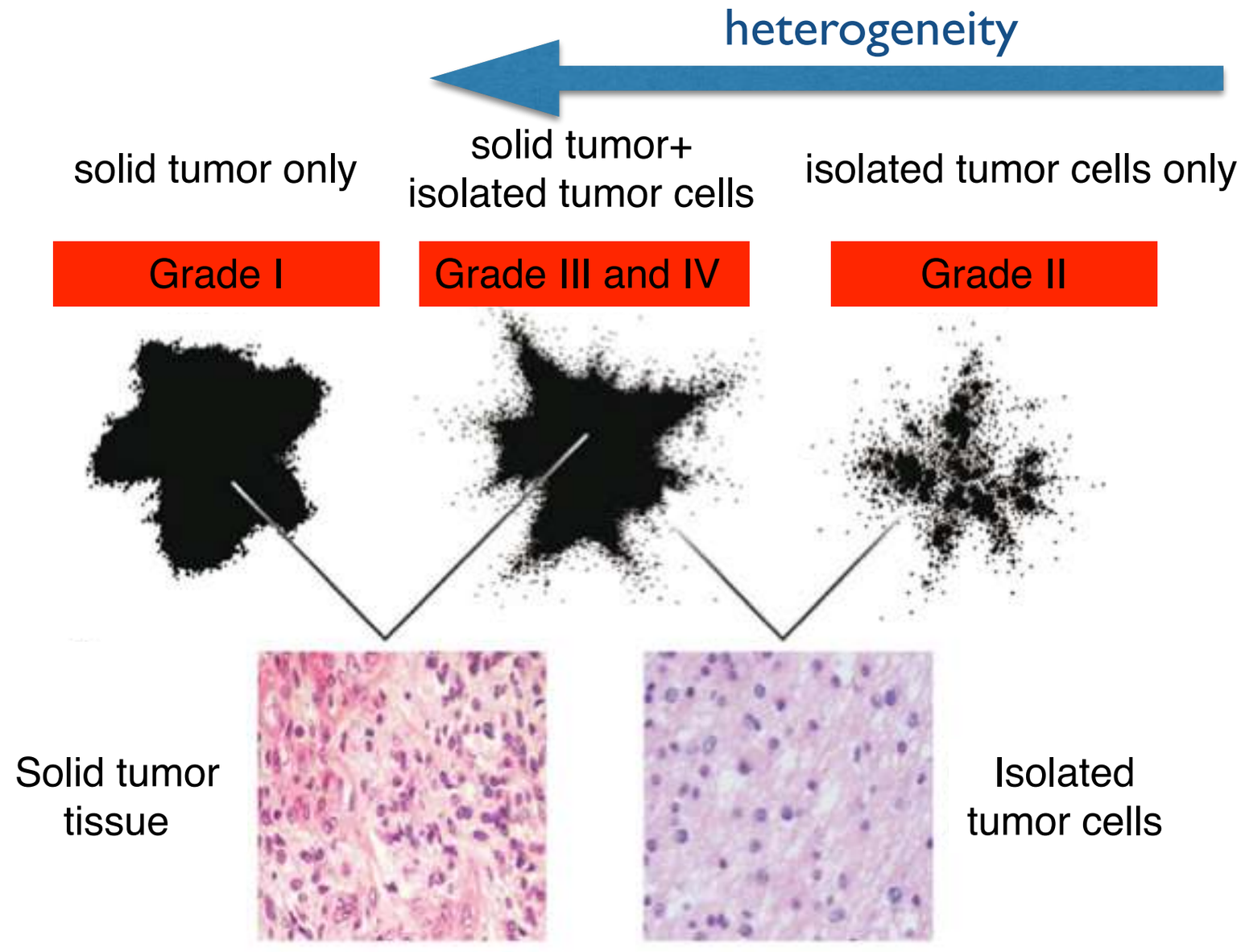
2nd HTE workshop: Mathematical & Computer Modeling to study tumors heterogeneity in its ecosystem, November 14th, 2018

Gliomas



Grade I: the grade I tumors may be curable by surgery
Grade II diffuse astrocytomas or oligodendrogliomas: evolve 7-8 years in anaplastic tumors
Grade III anaplastic gliomas: fatal evolution in 2 to 4 years.
Grade IV glioblastoma multiforme: Average survival of 6 months to 2 years (based on feasible treatment).

Gliomas



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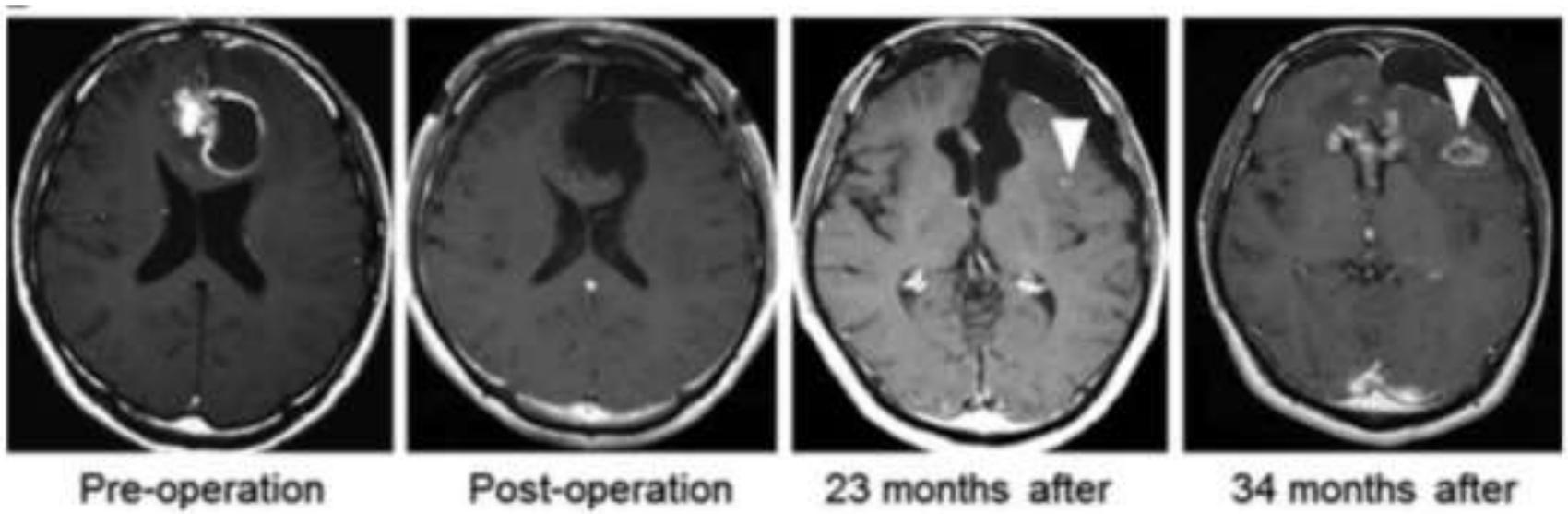
Diffuse low-grade gliomas: recurrence

Gliomas are rare tumors, but grade II (and more) gliomas cannot be cured

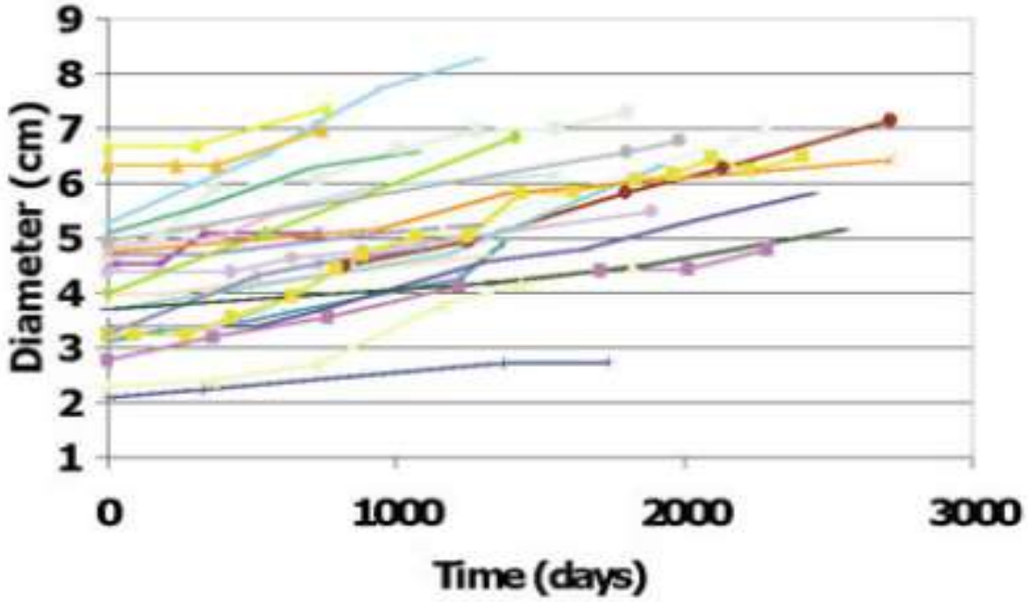


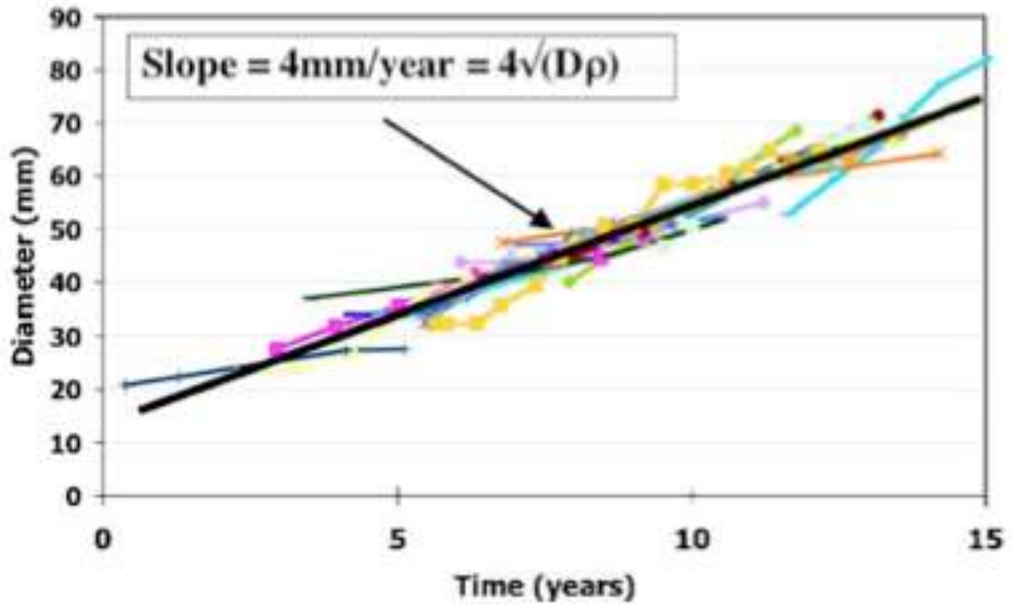
systematic recurrence, even after treatments

Glioma cells migrate normal surrounding tissue, causing recurrence of the tumor.
⇒ **Invasion plays a key role in the poor outcome of patients**

Shibahara, I et al (2015) Malignant clinical features of anaplastic gliomas without IDH mutation , *Neuro Oncol.,* **17**, 136-144.

A linear growth of the tumor radius





Mandonnet E et al (2003) Continuous growth of mean tumor diameter in a subset of grade II gliomas. *Ann Neurol* **53**, 524–528

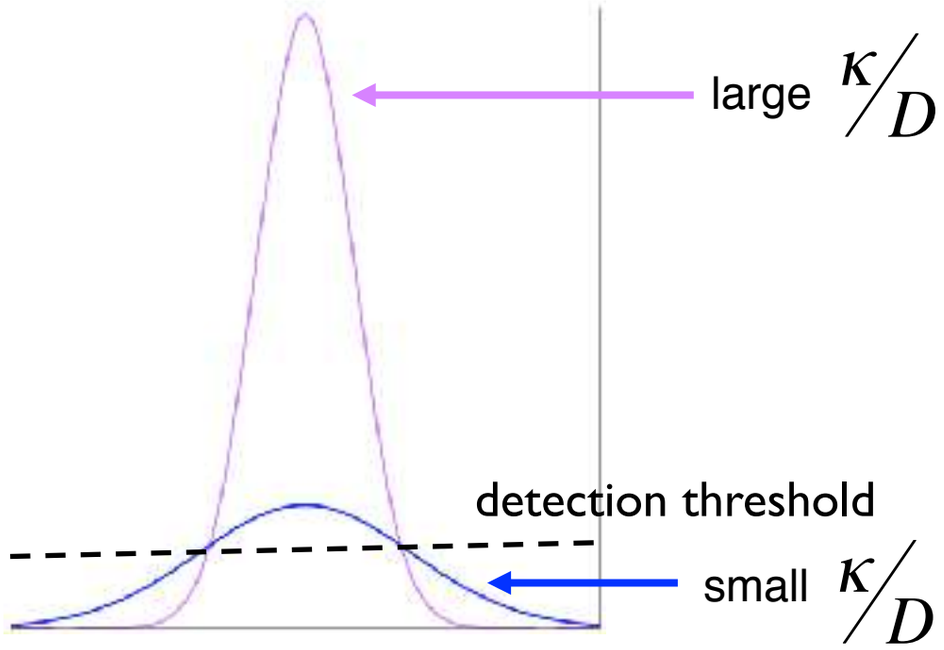
Modeling tumor growth

$$\frac{\partial C(\vec{r},t)}{\partial t} = \nabla(D(\vec{r},t)\nabla C(\vec{r},t)) + \kappa(\vec{r},t)C(\vec{r},t)$$

if D and κ are uniforms and constants

$$\frac{\partial C(r,t)}{\partial t} = D\nabla^2 C(r,t) + \kappa C(r,t)$$

Solution in 3D: $C(r,t) = \frac{N_0}{(4\pi Dt)^{3/2}} e^{\kappa t} e^{-r^2/4Dt}$



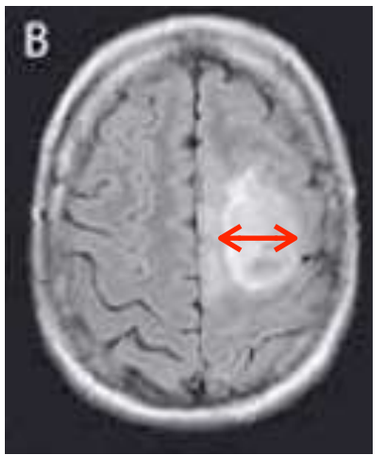
Assumption: diameter of the tumor on a MRI scan= iso cell density curve (C^*)

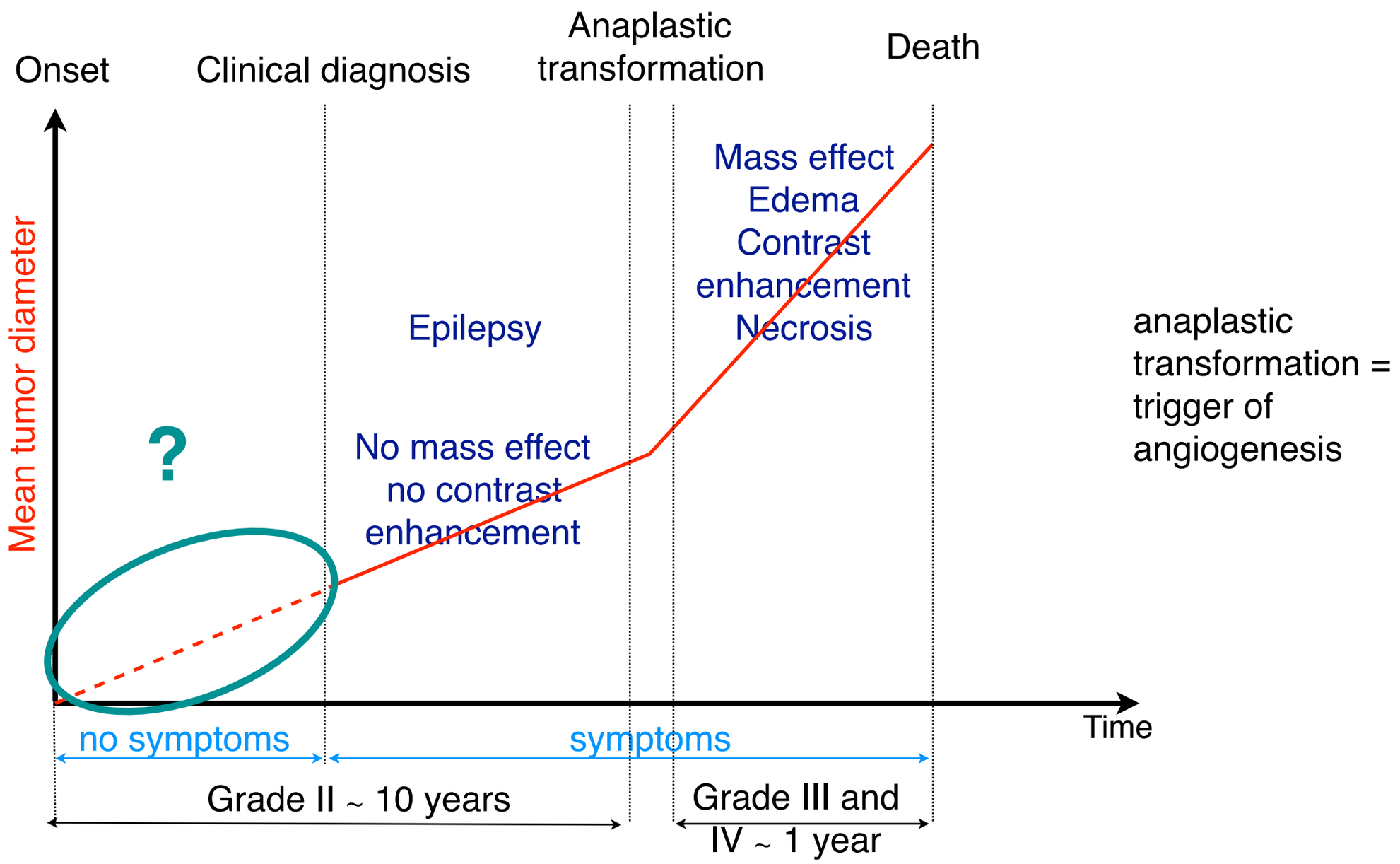
$$r(t) = \sqrt{4Dt(\kappa t + \ln(\frac{N_0}{C^*(4\pi Dt)^{3/2}}))} \qquad r(C^*, t \to \infty) = \sqrt{4D\kappa}t$$

- <v> = 2 mm/yr
- Linear evolution since r = 10 mm $\Longrightarrow$ for the model r_{min} = 15 mm

Cook J et al. (1995) Resection of gliomas and life expectancy, *J Neurooncol.* **24**, 131

The natural history of low grade gliomas





-Very invasive tumors but patients can live more than ten years after diagnosis

Pallud J et al, (2008) Les gliomes infiltrants de bas grade, REG, *Neurologies* **11**, 94-101

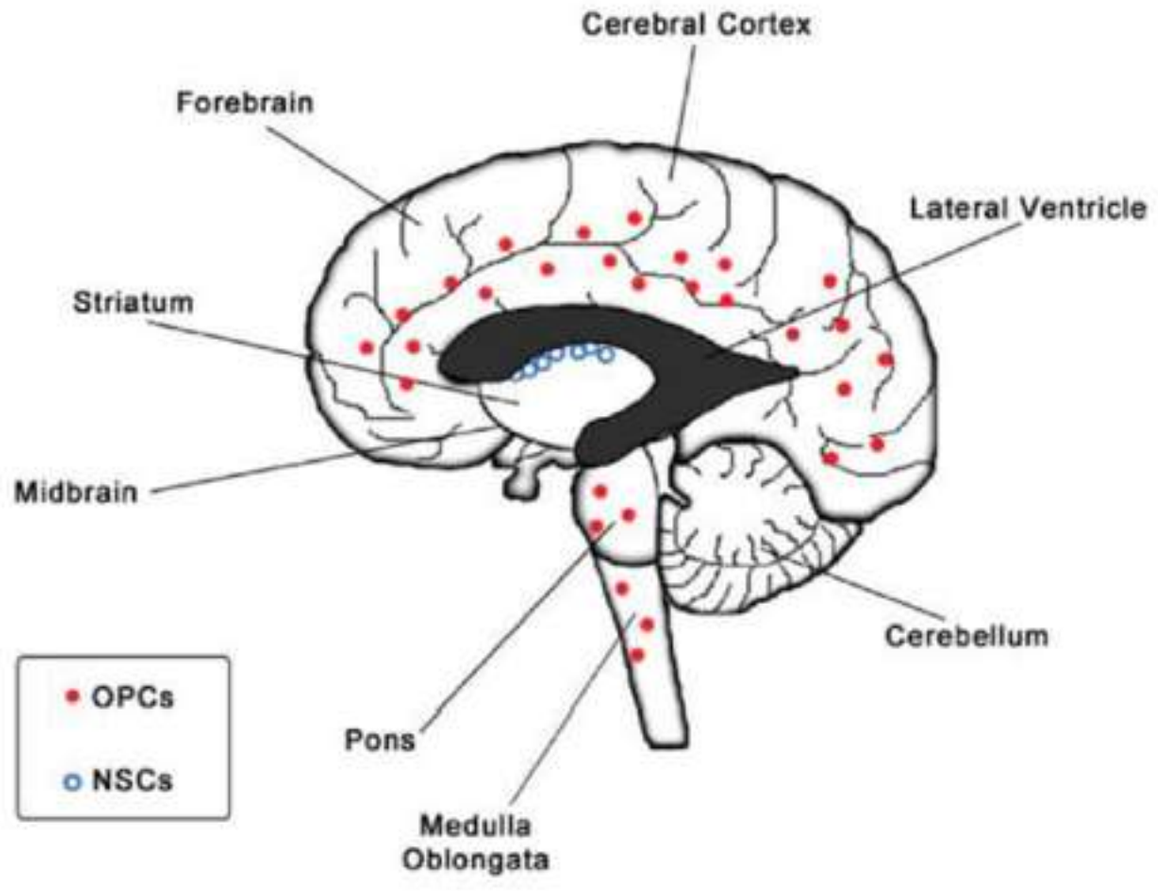
Oligodendrocyte precursor cells (OPCs)

➢ Cycling cells in the adult brain are mainly OPCs (NG2+ cells)

Geha S et al., (2010), NG2+/Olig2+ cells are the major cycle-related cell population of the adult human normal brain, *Brain Pathol.*, **20,** 399-411

➢ OPCs are the most widely distributed population of cycling cells in adult brain.
➢ In contrast, a small population of NSCs is found in the SVZ lining the lateral ventricles.

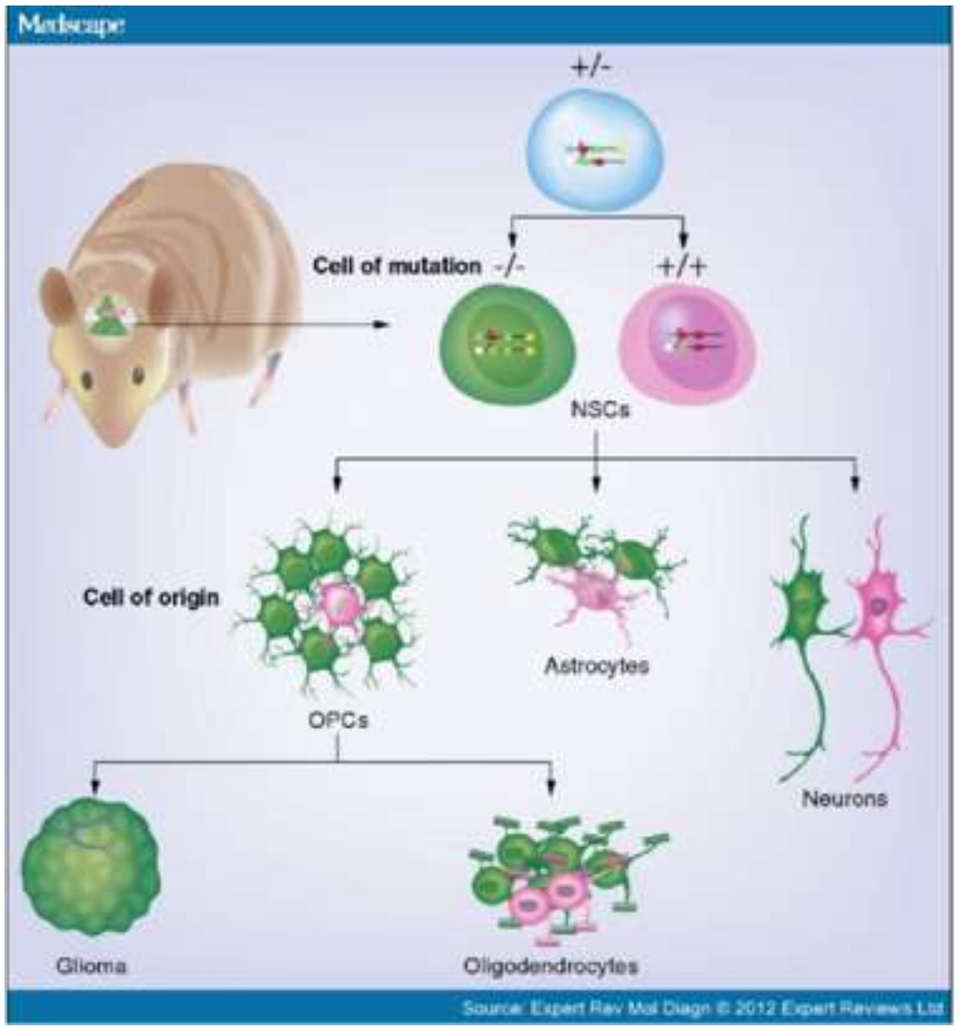
Ilkanizadeh S et al, (2014), Glial Progenitors as Targets for Transformation in Glioma, *Adv Cancer Res.*, **121**, 1–65.



OPCs at the origin of gliomas?

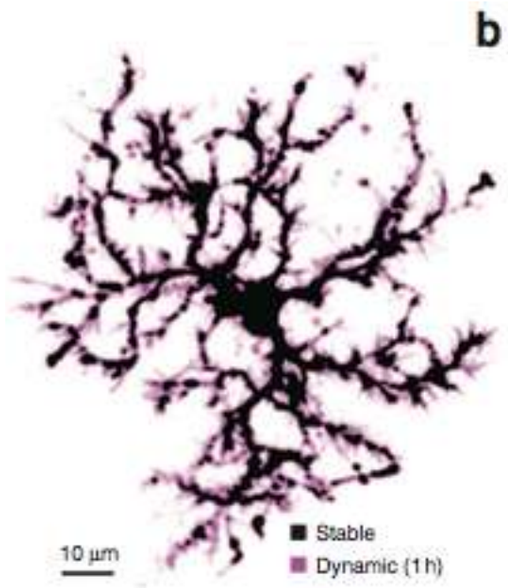
➢ Mutated OPCs trigger gliomas in mouse.

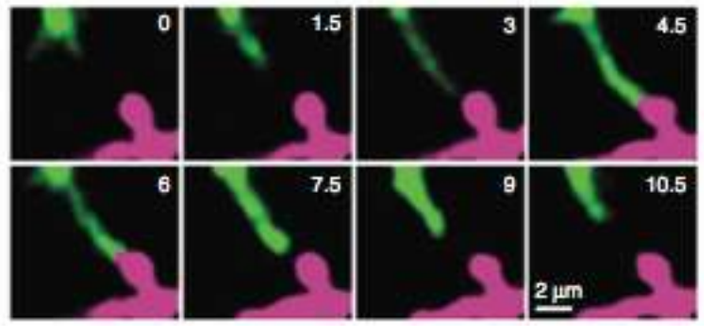
Zong H et al , (2012) The cellular origin for malignant glioma and prospects for clinical advancement, *Expert Rev Mol Diagn.*, **12**, 383-94

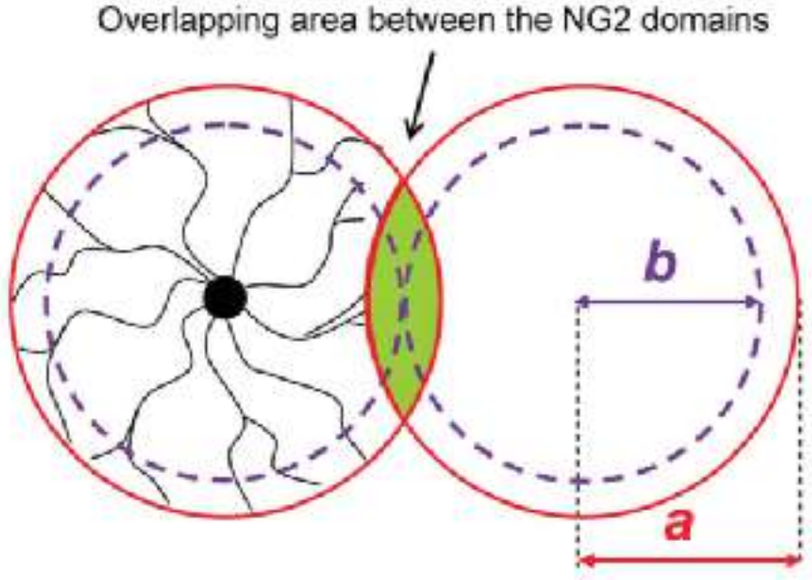


⇒ OPCs (Oligodendrocyte Precursor cells) are strongly suspected to be the cell of origin of some gliomas.

OPCs dynamics *in vivo*



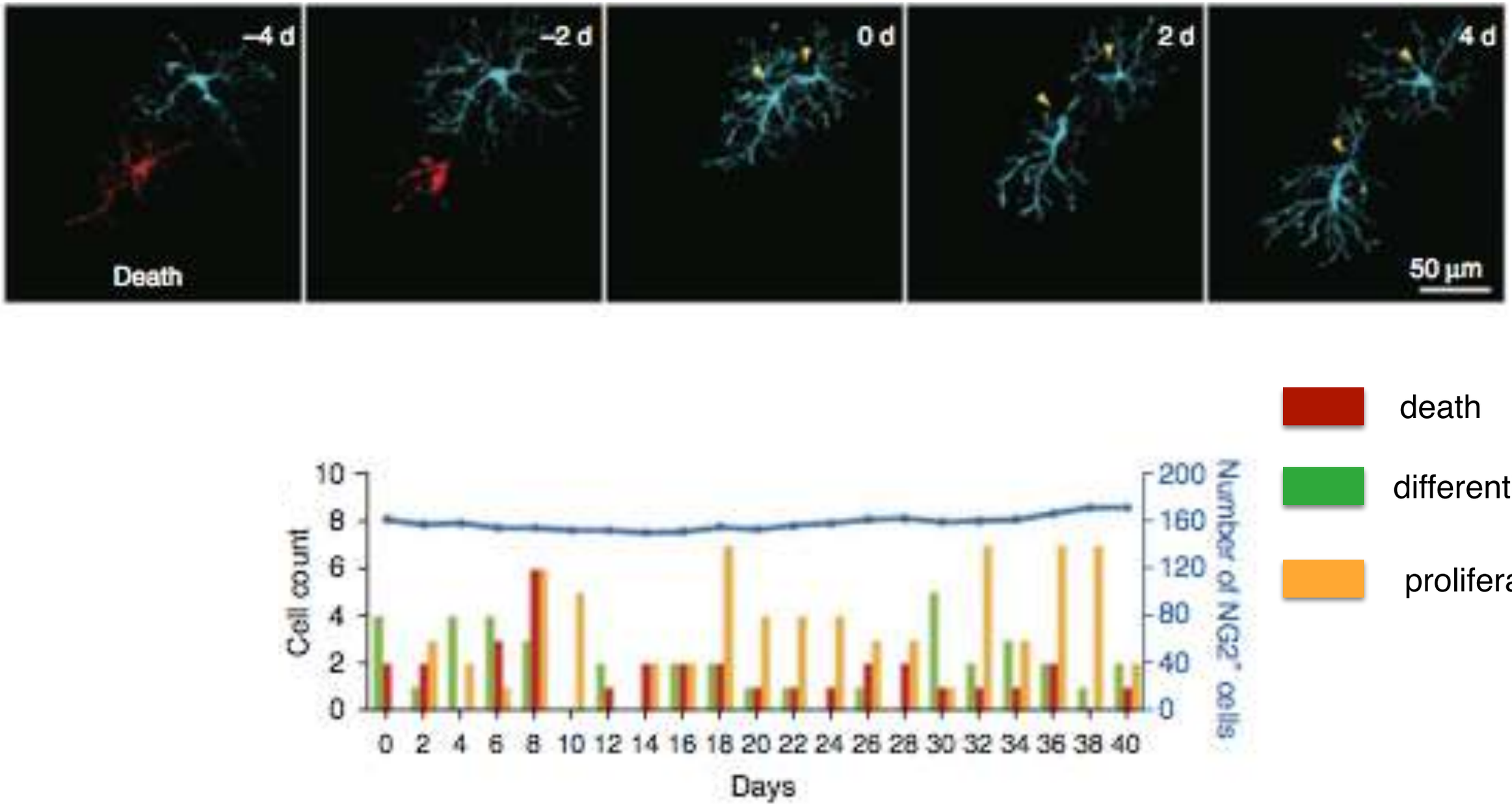




OPCs organize in a grid-like manner, with individual cells occupying almost non-overlapping domain

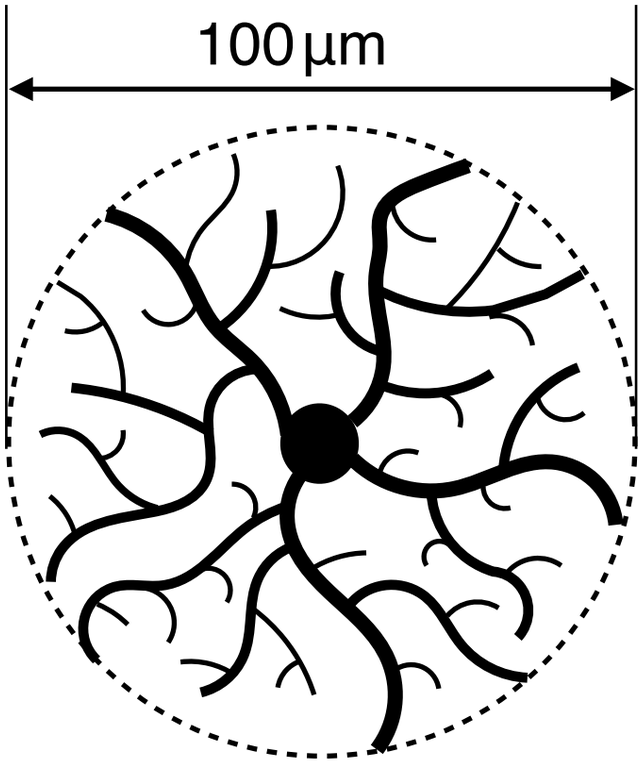
Xu G et al, (2014), Spatial organization of NG2 glial cells and astrocytes in rat hippocampal CA1 region, *Hippocampus*, **24**, 383-95

OPCs maintain a constant density *in vivo*



Hughes EG et al, (2013), Oligodendrocyte progenitors balance growth with self-repulsion to achieve homeostasis in the adult brain, *Nat Neurosci.*, **16**, 668-76.

Modeling OPCs dynamics



Model: a cellular automaton without lattice (continuous space)

Rules

A cell can:

1. proliferate (⇒ proliferation rule)
2. migrate (⇒ migration rule)
3. and disappear (differentiate or die) (differentiation rule)

The formation of a glioma: different scenarios

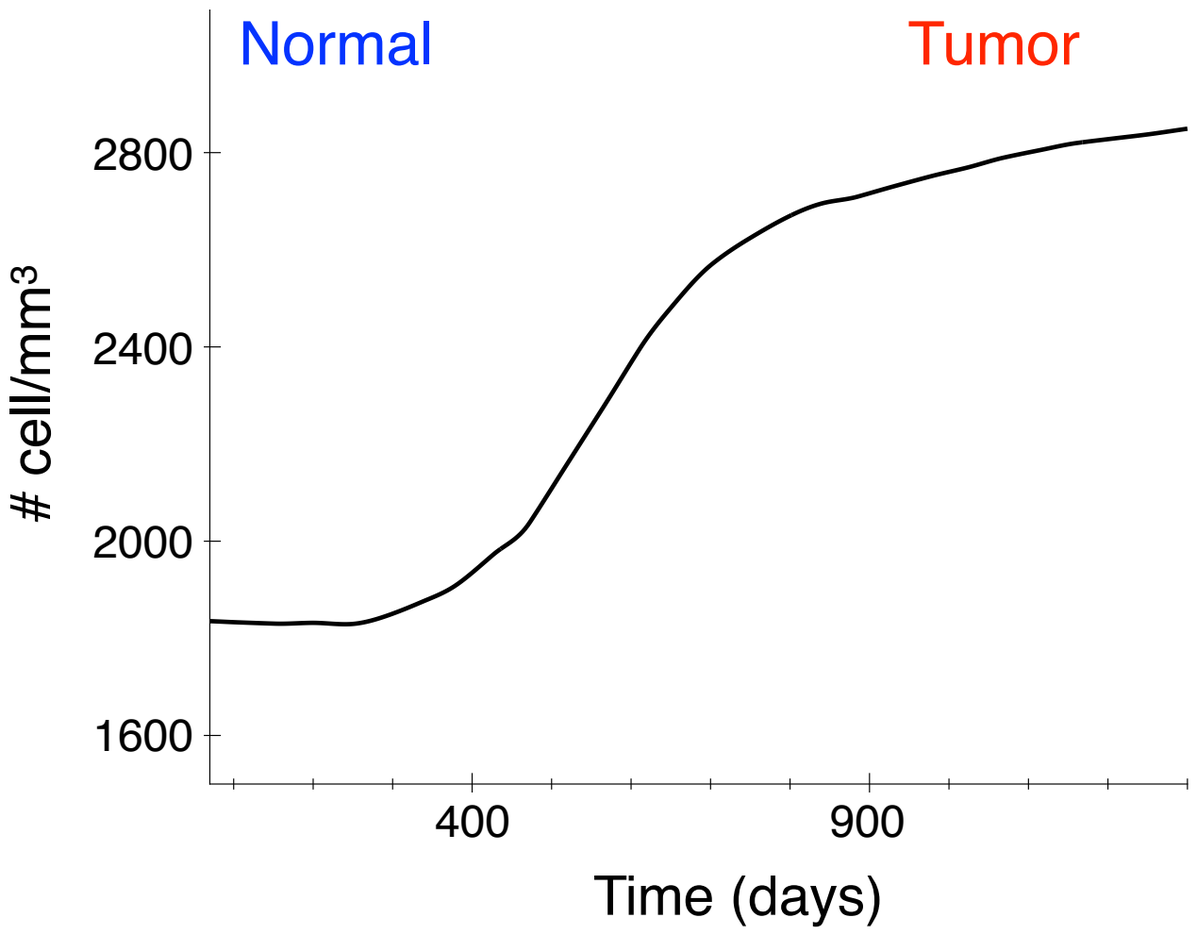
- Apparition of an immortal cell.
- Apparition of a cell that has lost its contact inhibition.
- Apparition of a highly proliferative cell.

The daughter cells have the same proliferative properties than the mother cells.

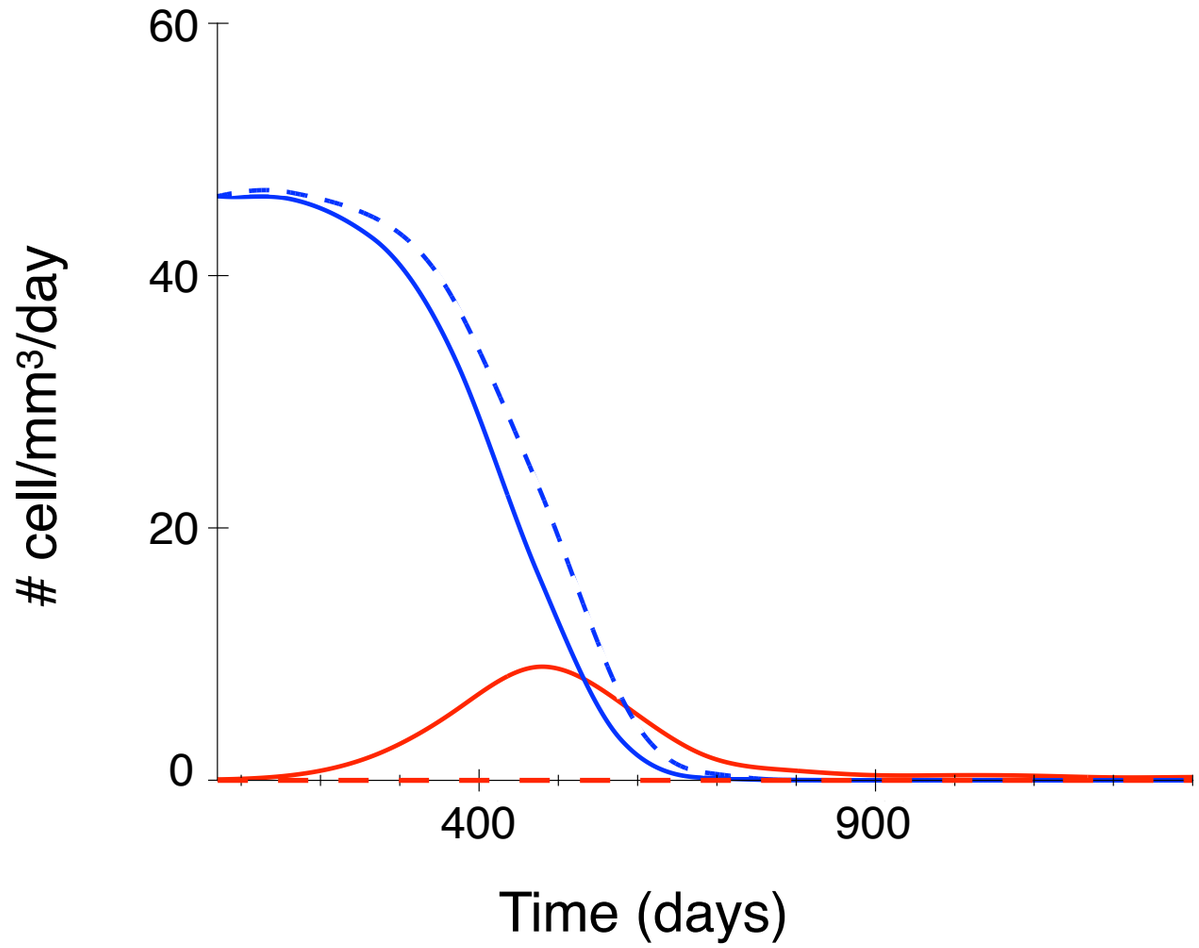
The formation of a glioma: different scenarios

First scenario: Apparition of an immortal cell

Cell density in a 1mm³ volume



Proliferative cell density



The formation of a glioma: different scenarios

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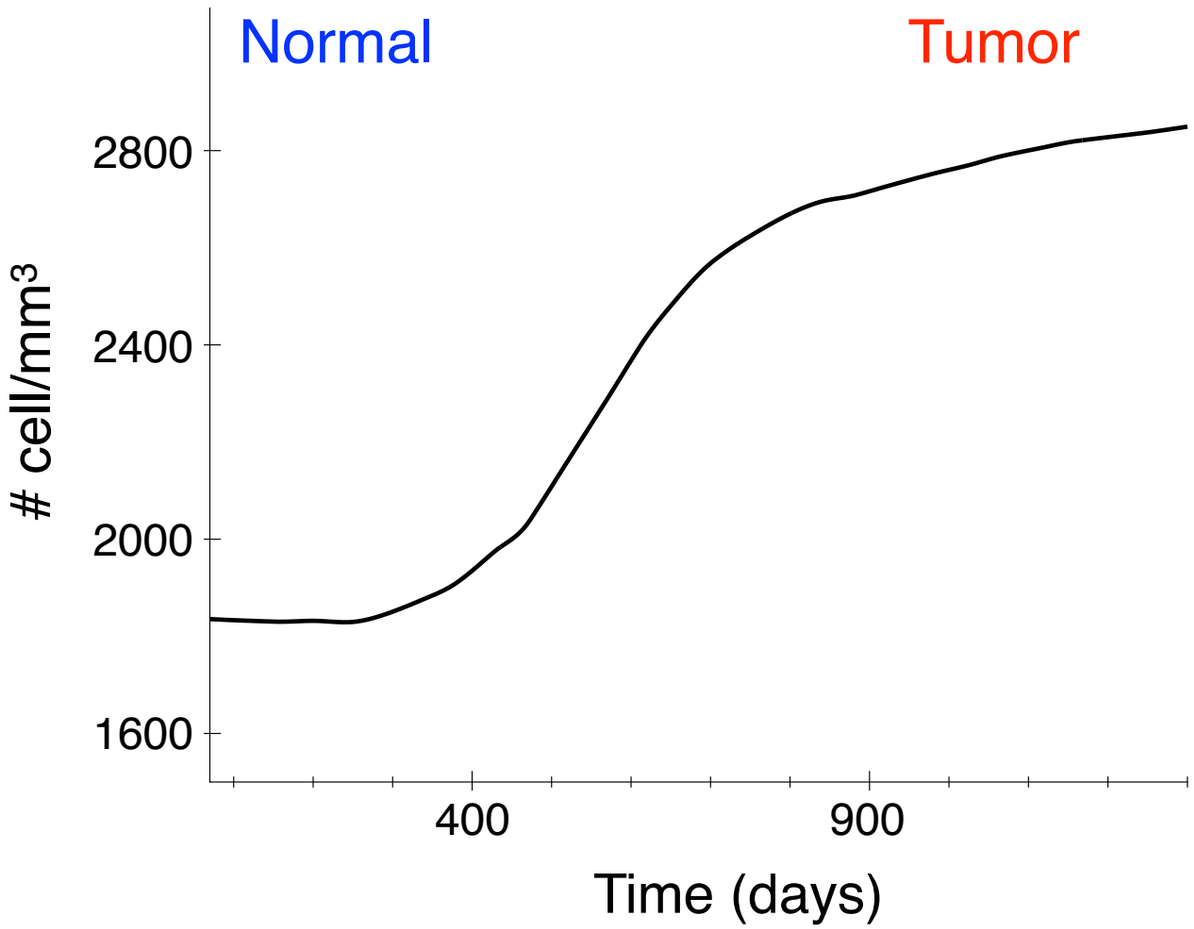

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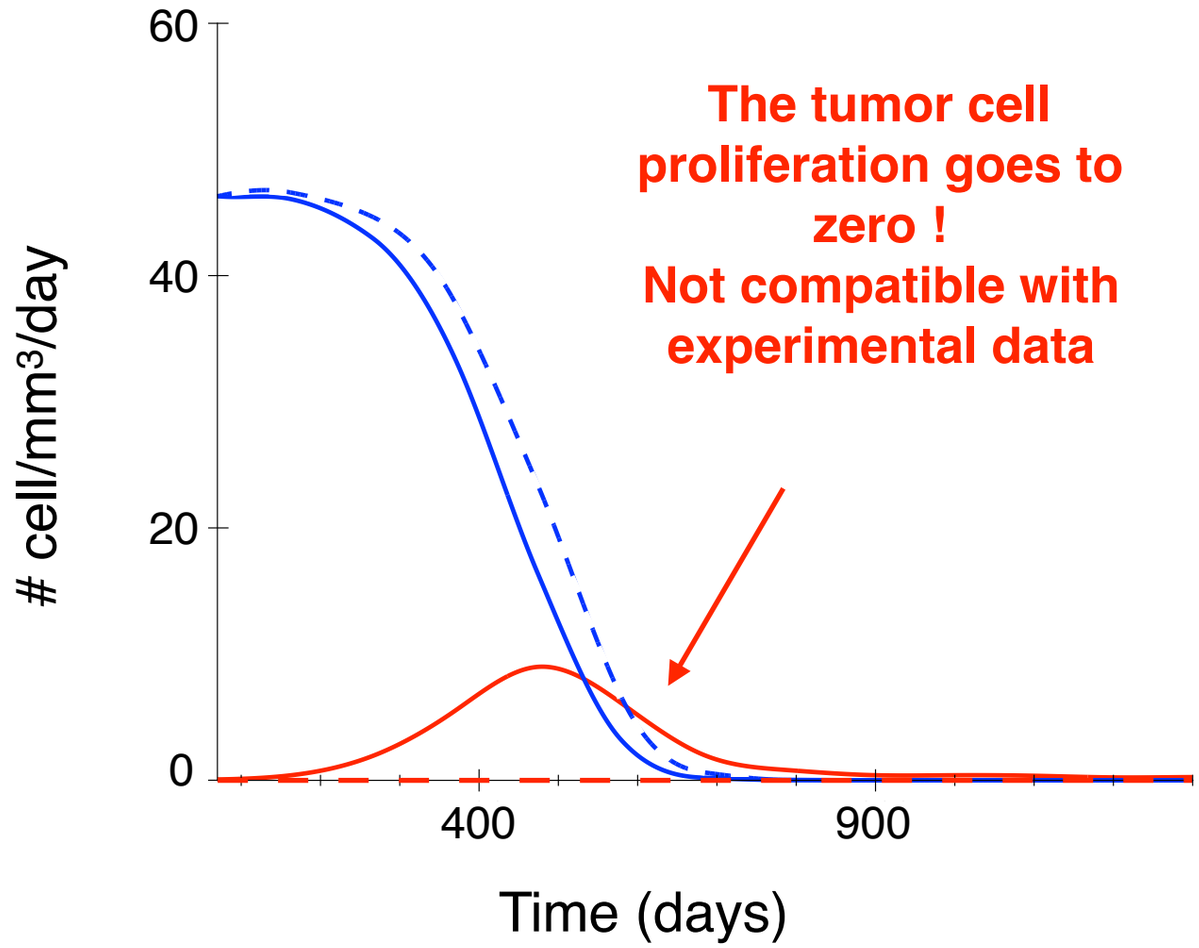
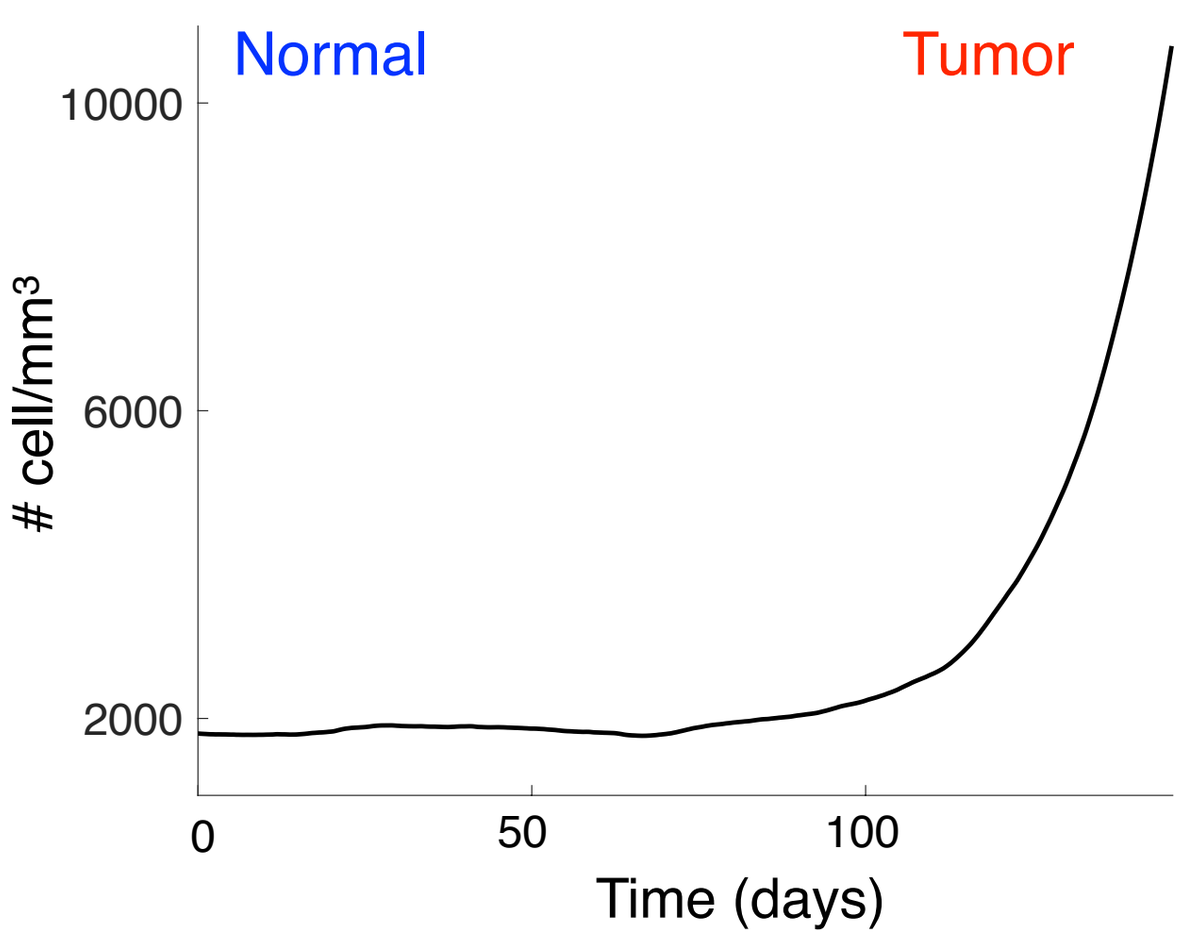


The tumor cell proliferation goes to zero !
Not compatible with experimental data

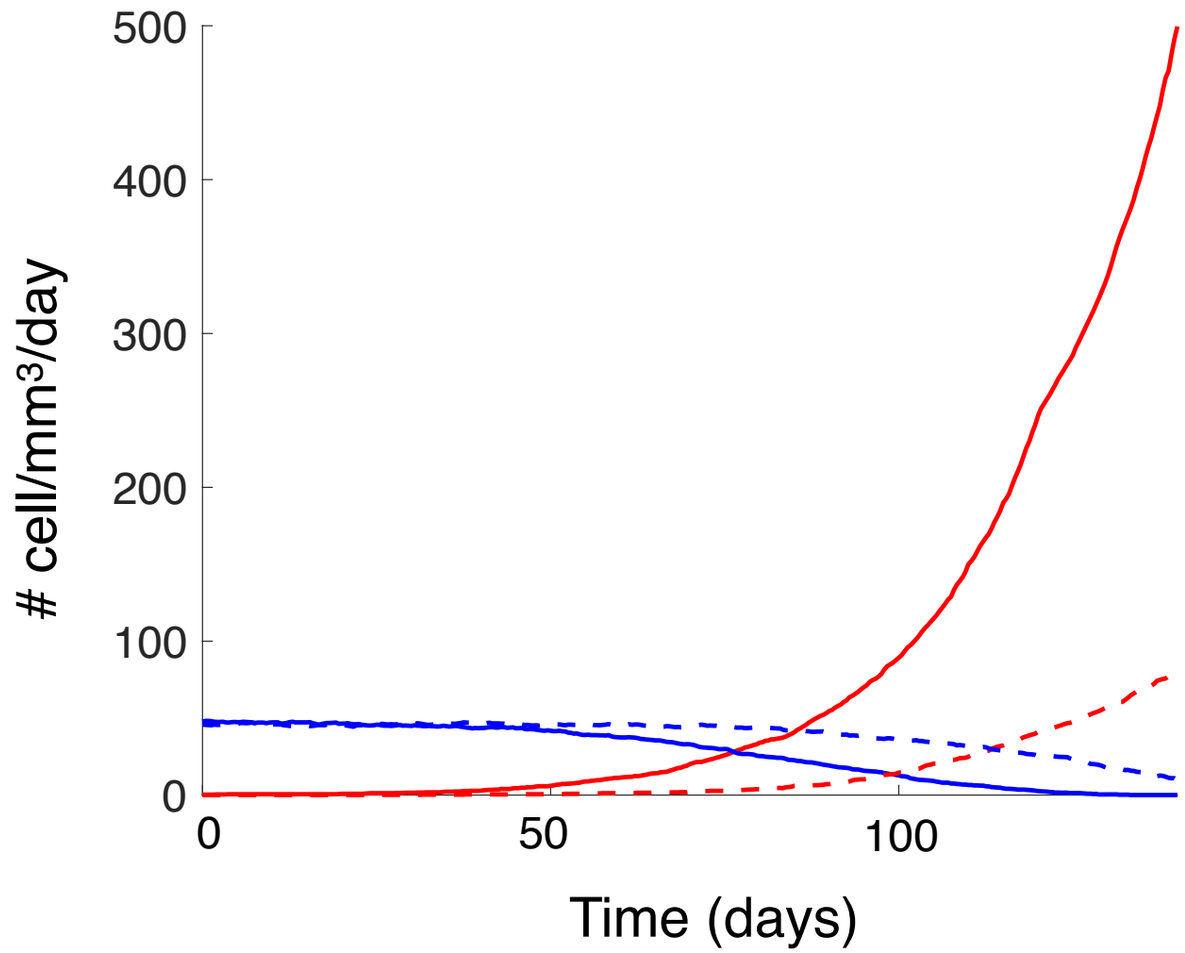
The formation of a glioma: different scenarios

Second scenario: Apparition of a cell without contact inhibition

Cell density in a 1mm³ volume



Proliferative cell density



The formation of a glioma: different scenarios

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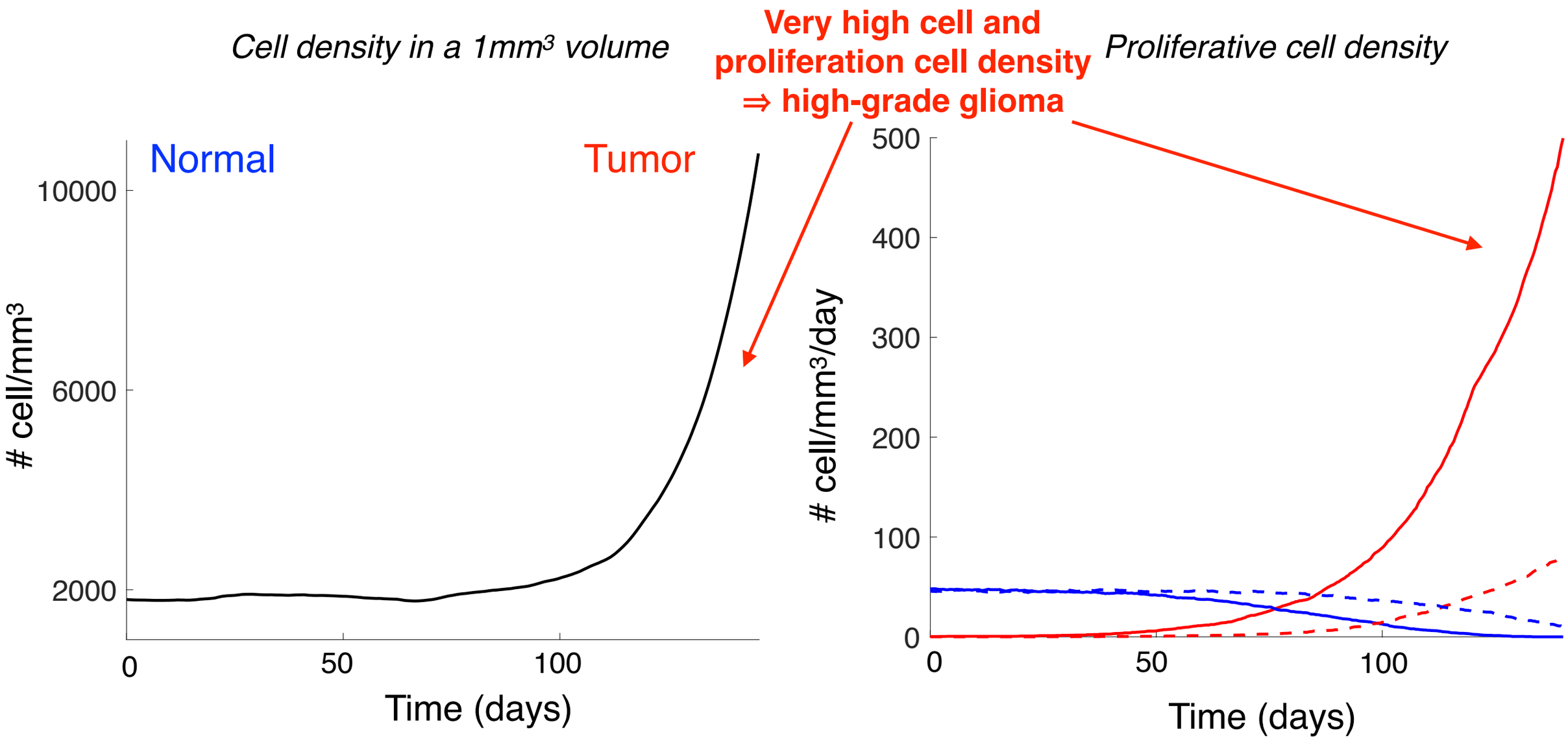


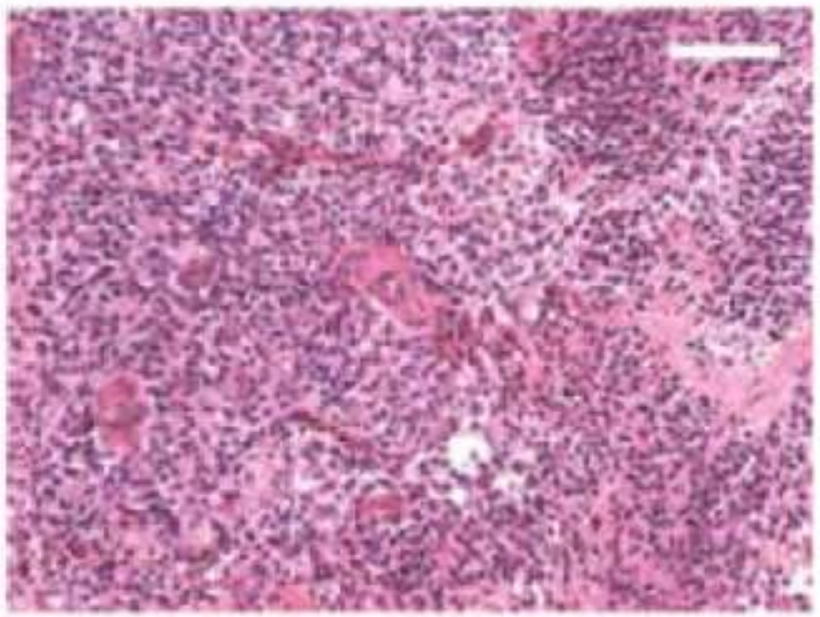
High-grade vs low-grade glioma

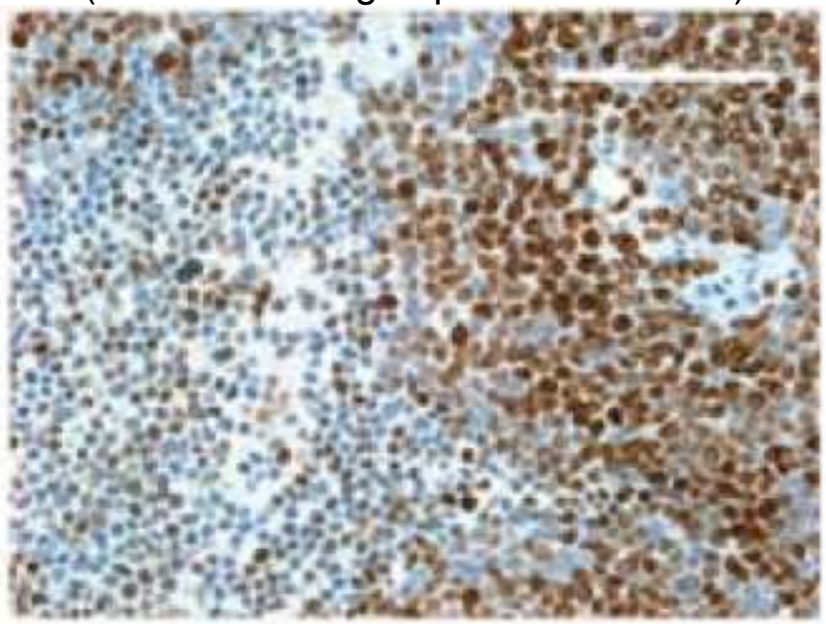
H & E

MIB-1

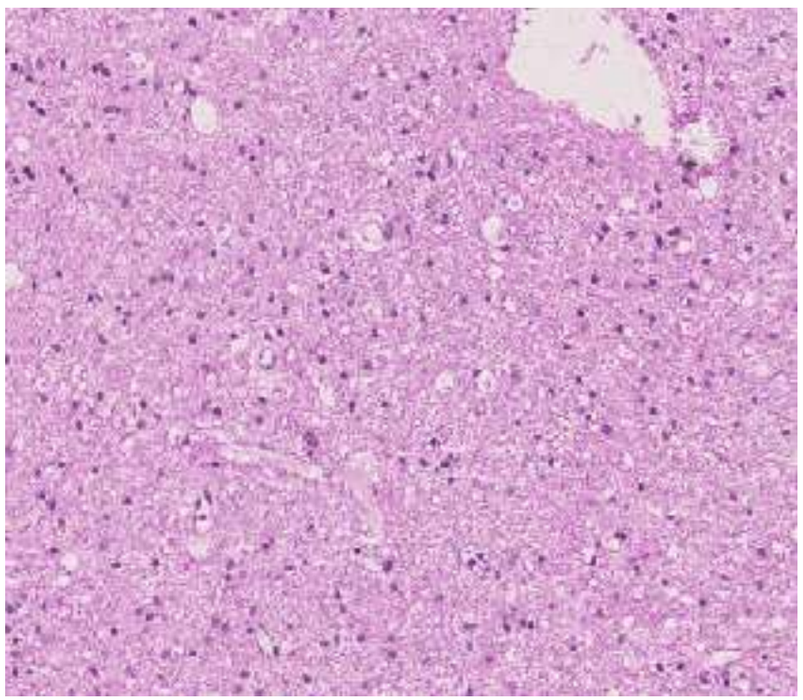
(immunostaining of proliferative cells)

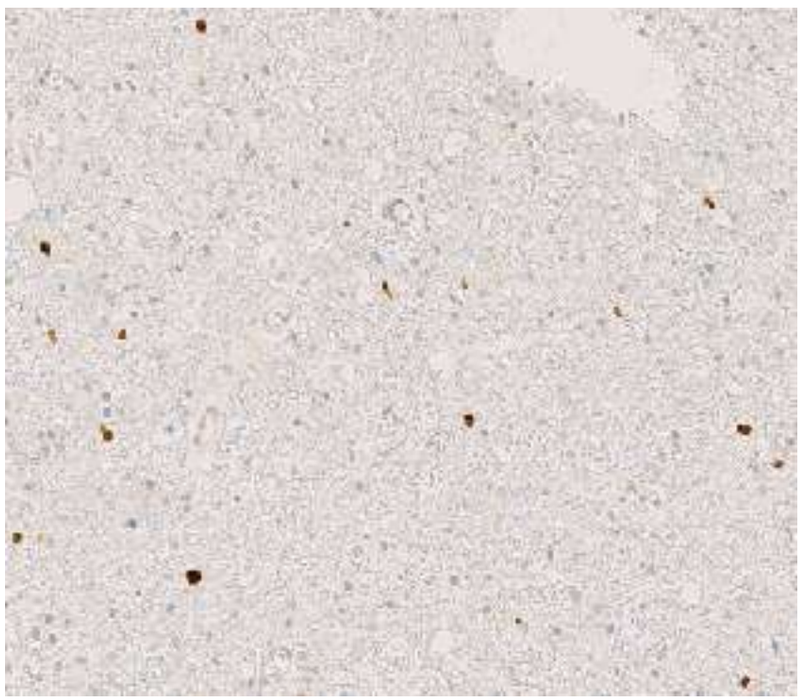
High grade





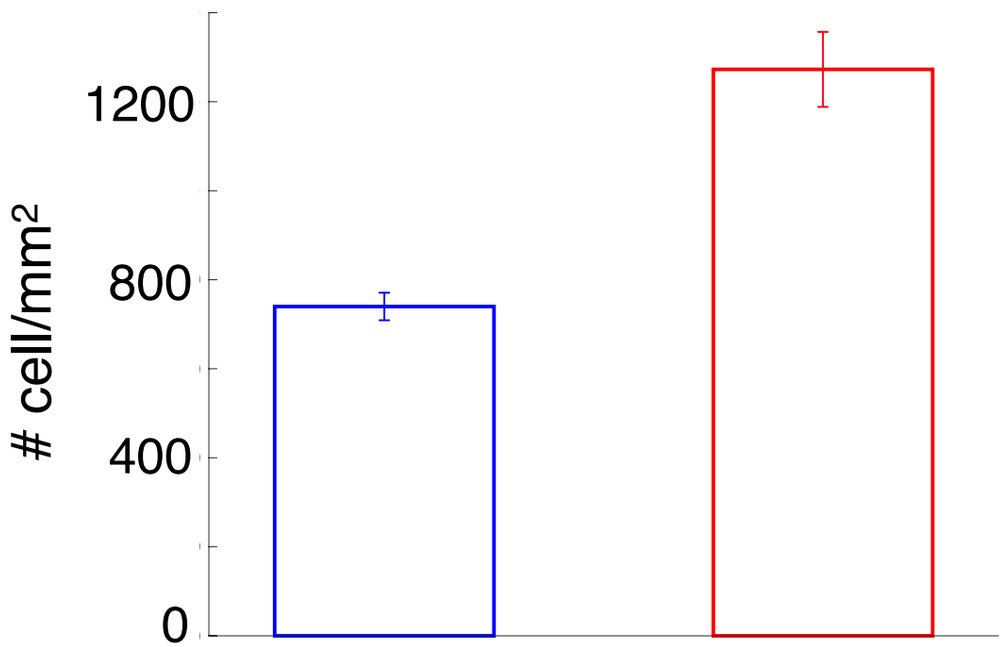
Low grade

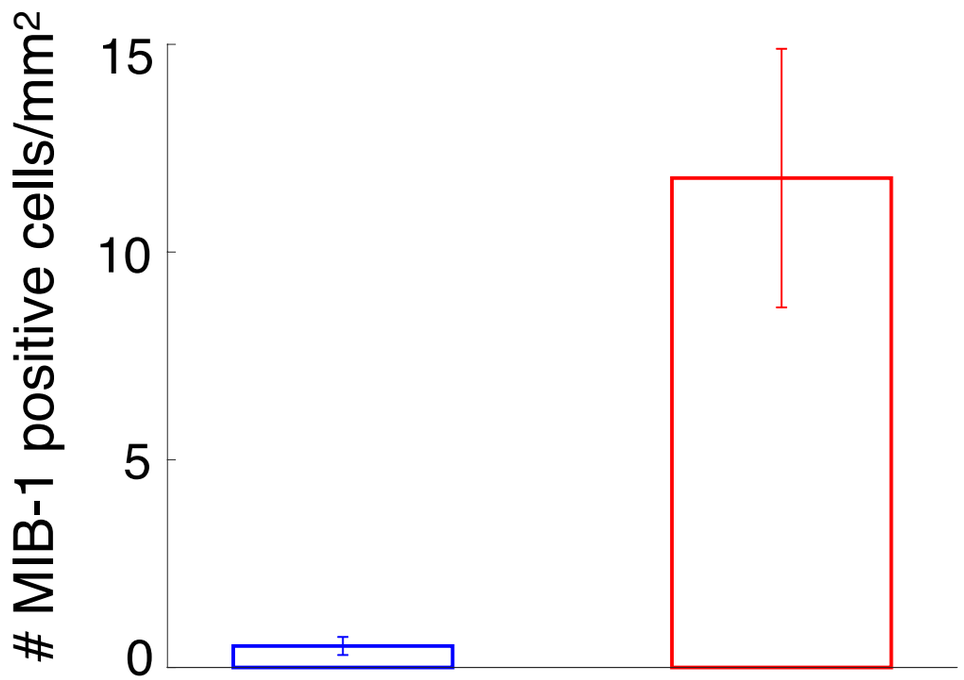




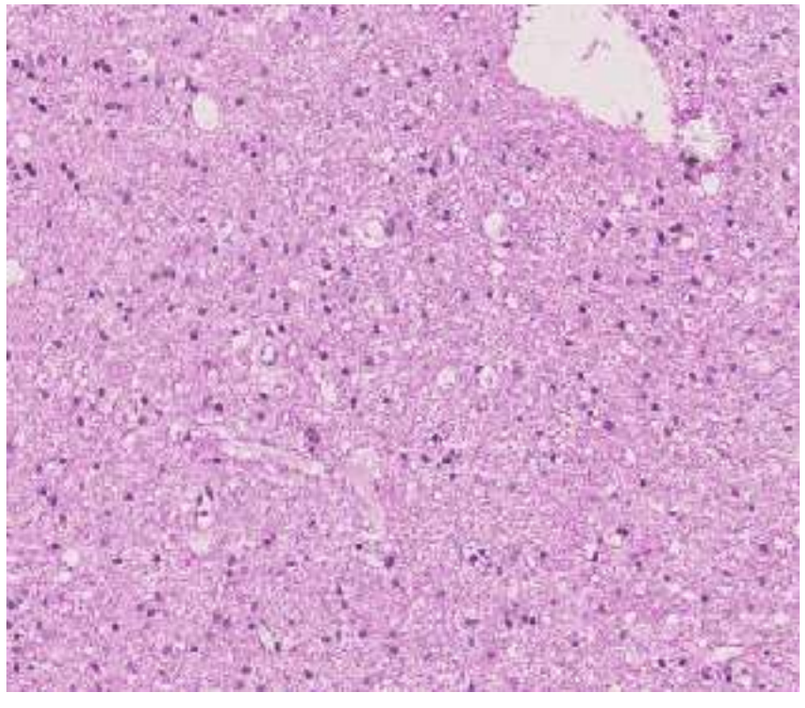
Singh SK et al (2004), Identification of human brain tumour initiating cells, *Nature*, **432**, 396-401.

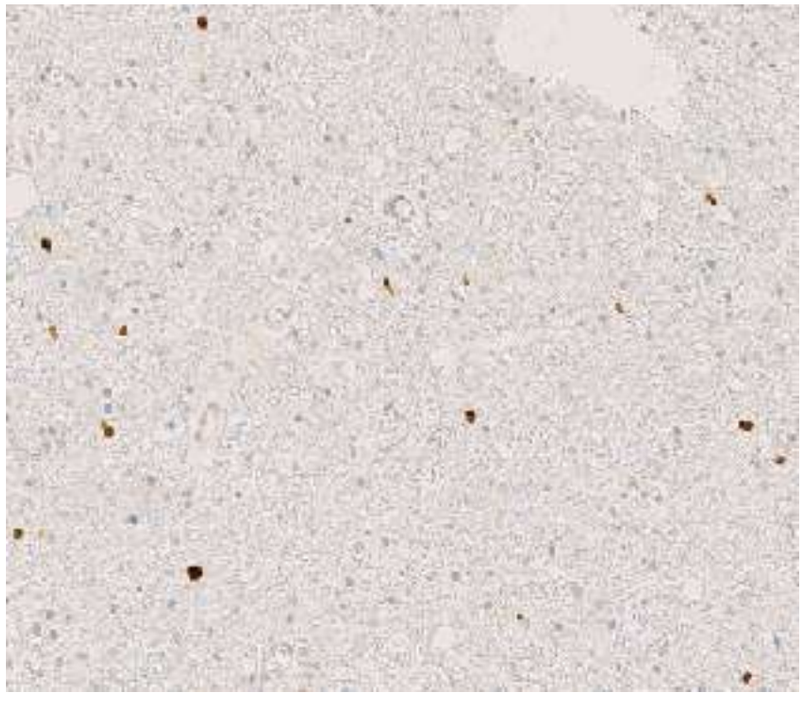
Low-grade glioma





H&E staining of a tumor tissue



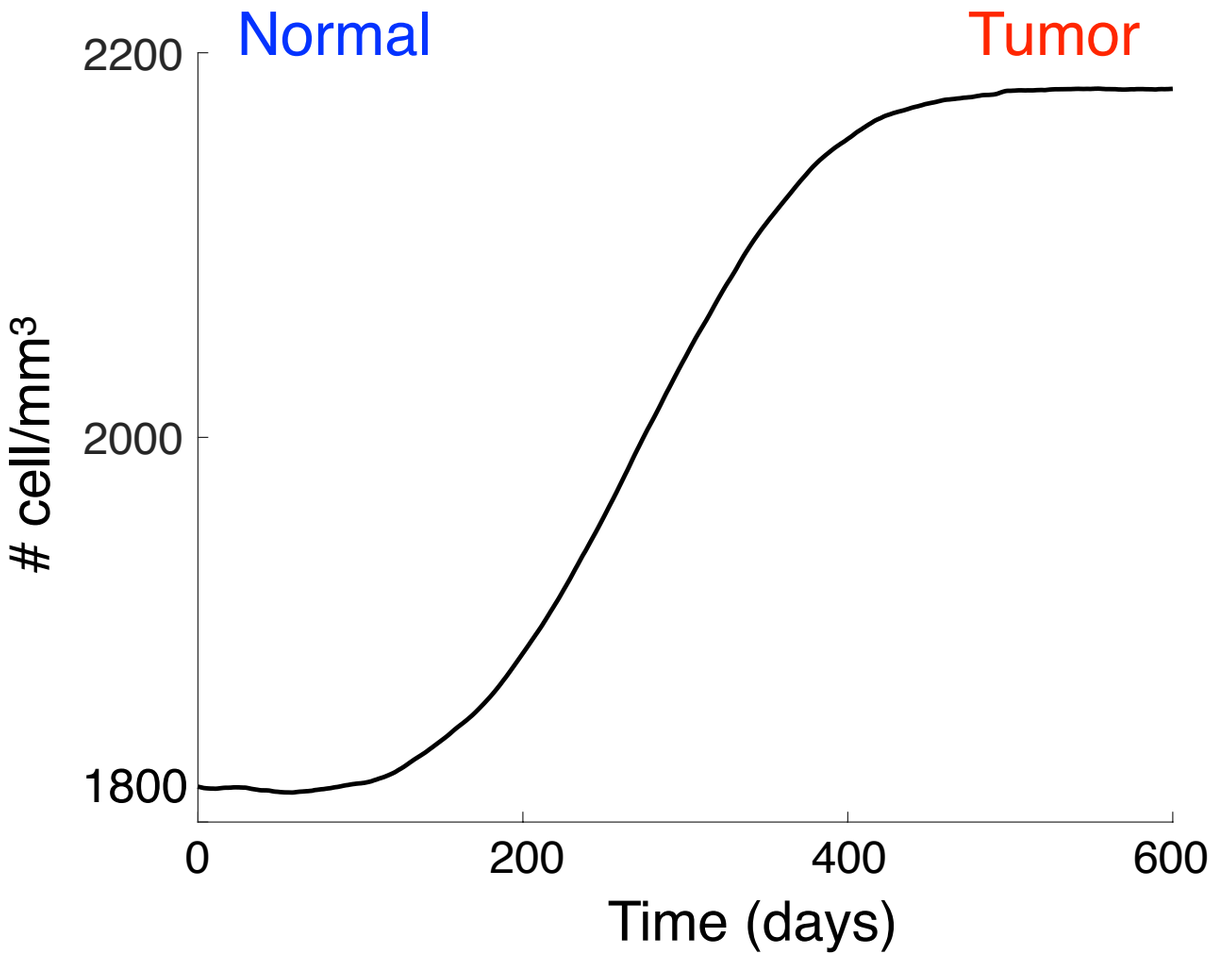


MIB1 immuno staining

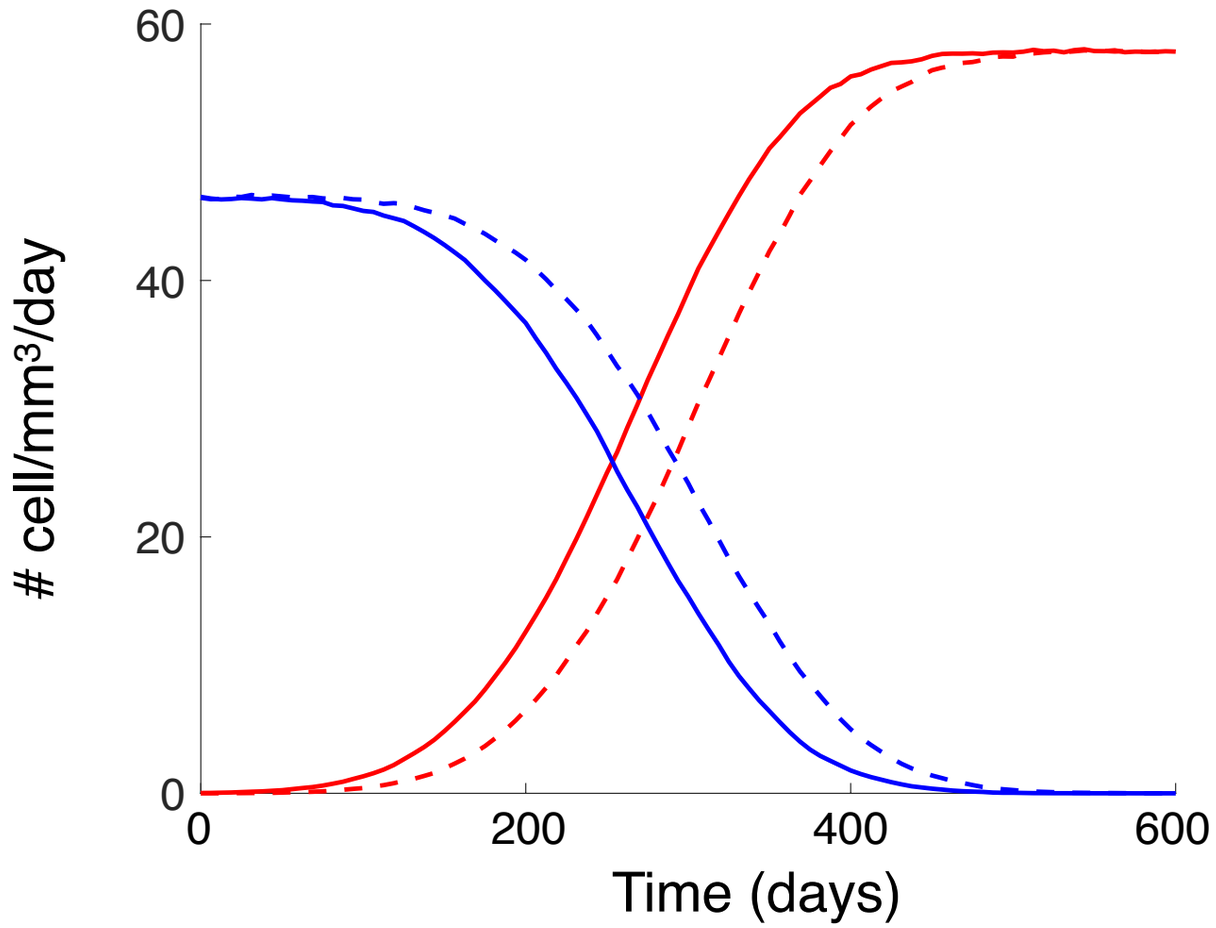
The formation of a glioma: different scenarios

Third scenario: Apparition of a highly proliferative cell

Cell density in a 1mm³ volume



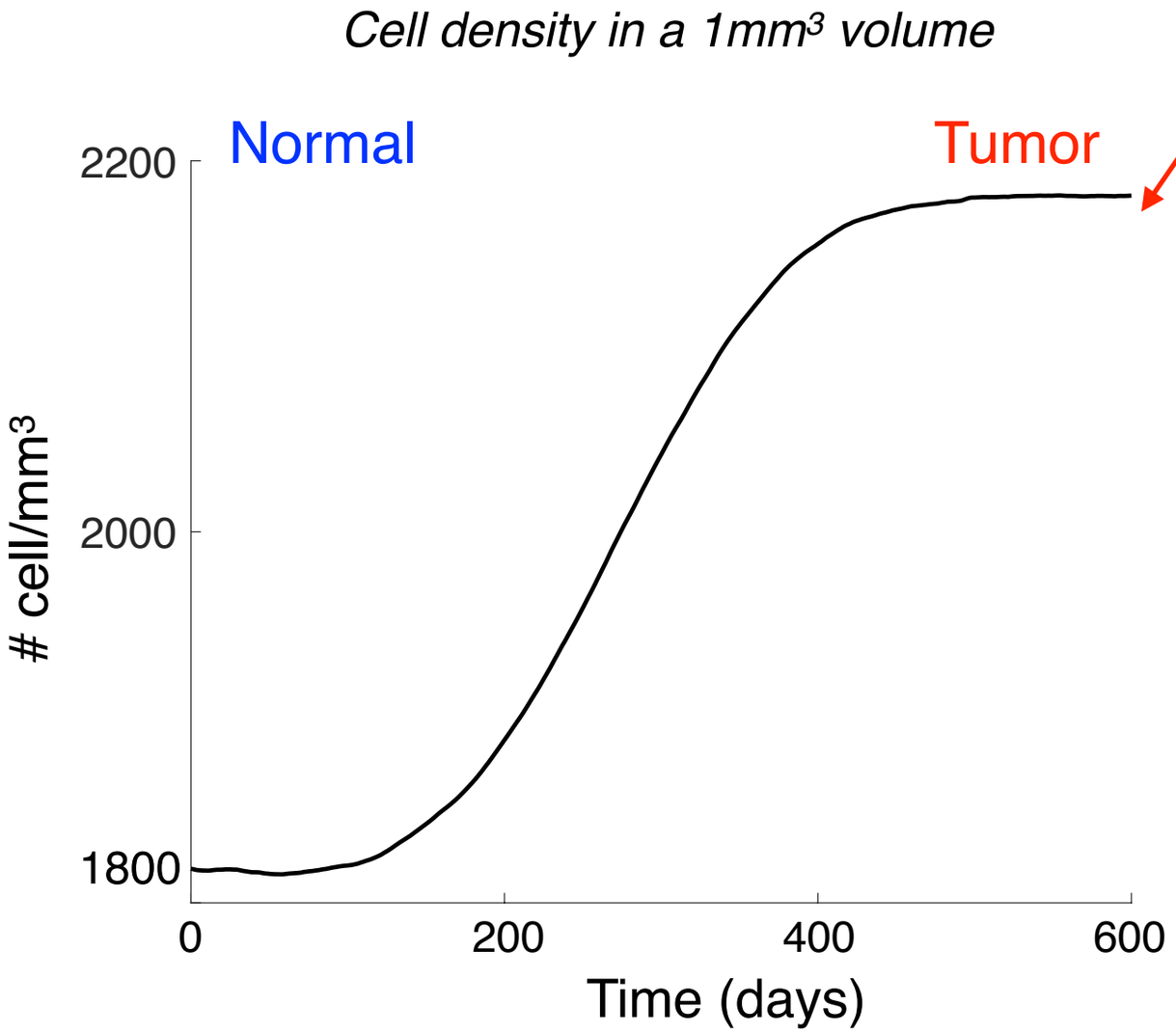
Proliferative cell density

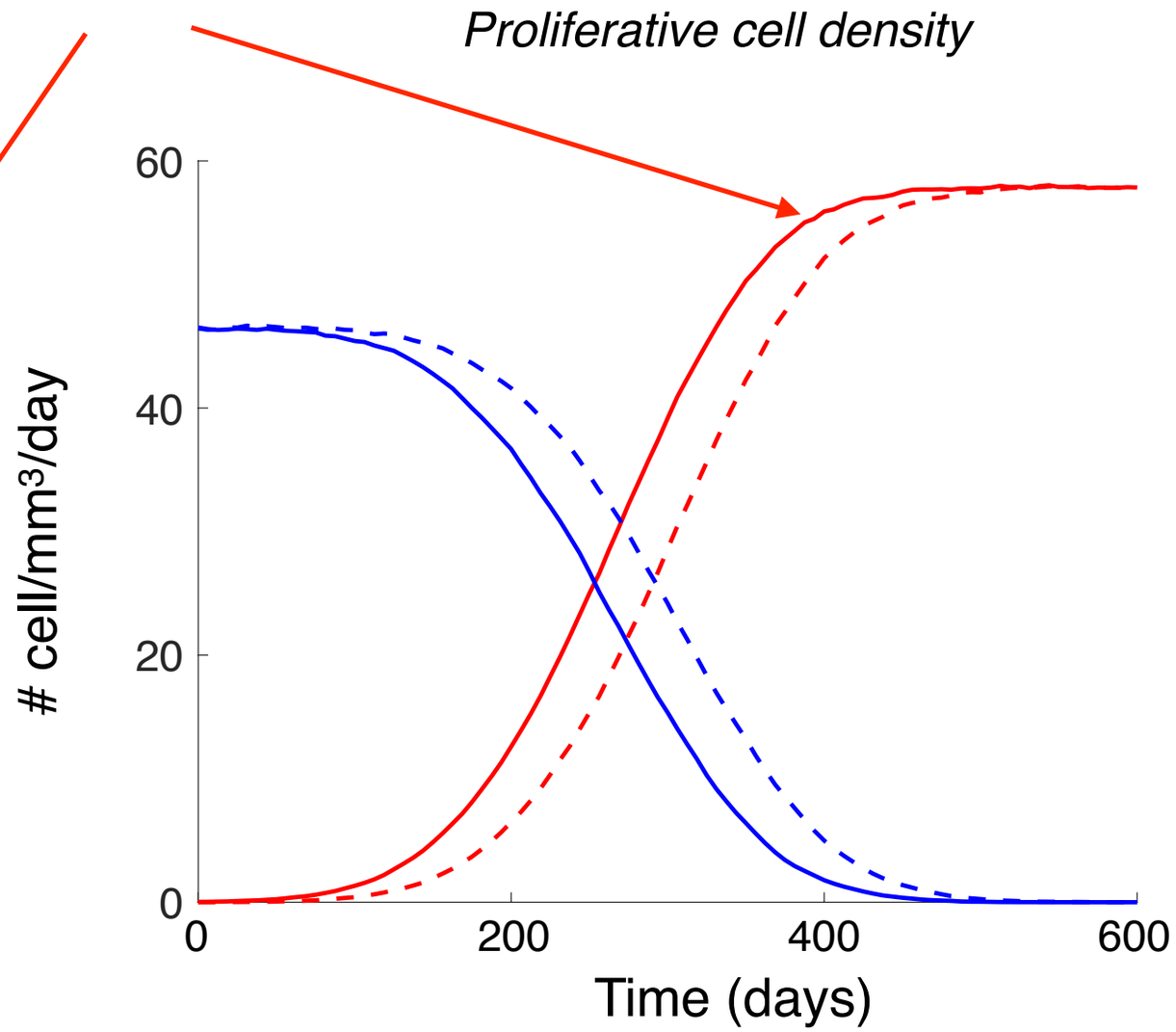


The formation of a glioma: different scenarios

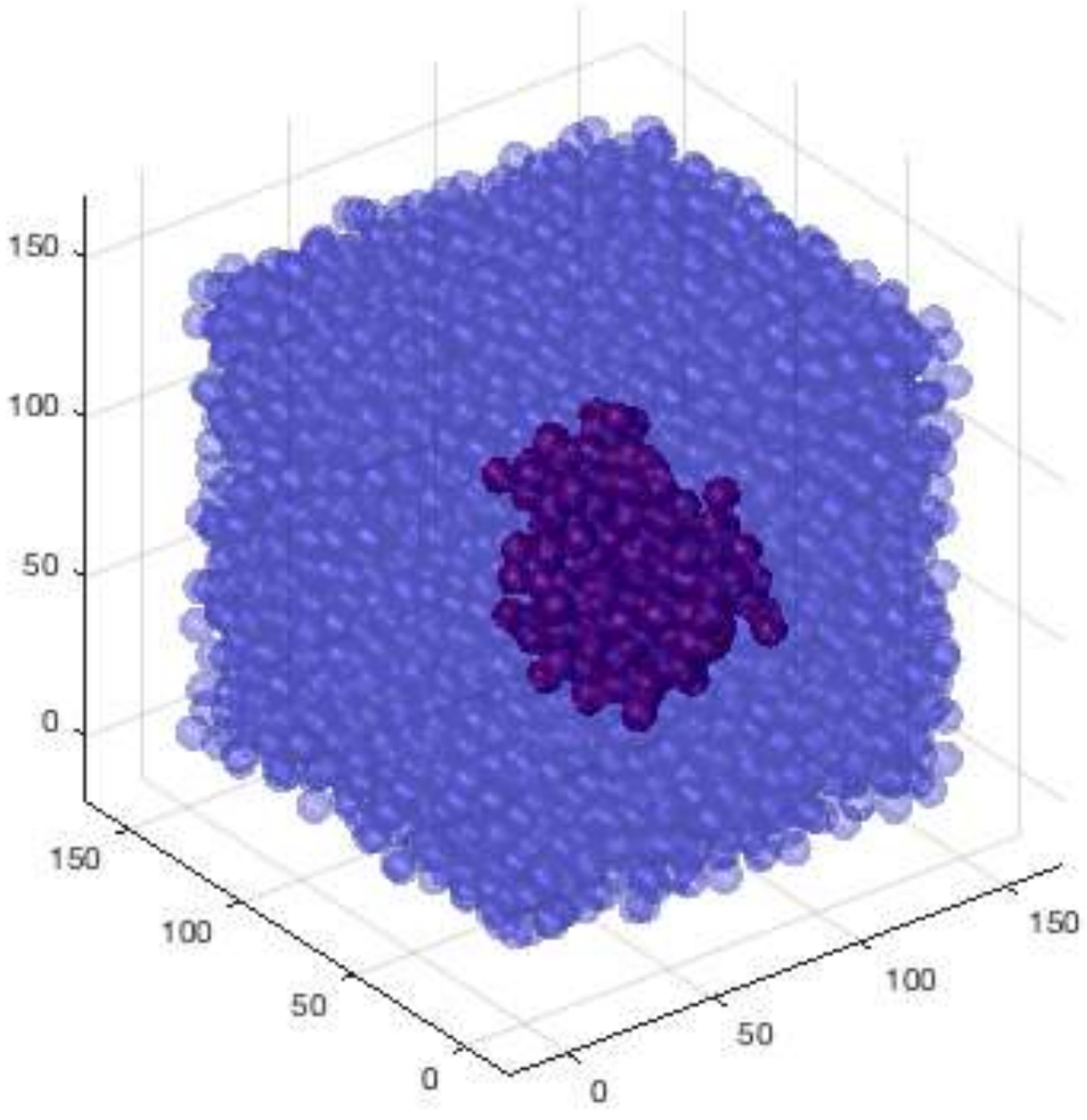
Third scenario: Apparition of a highly proliferative cell

Higher cell and proliferation cell density inside the tumor but not too high (a new equilibrium)
⇒ low-grade glioma



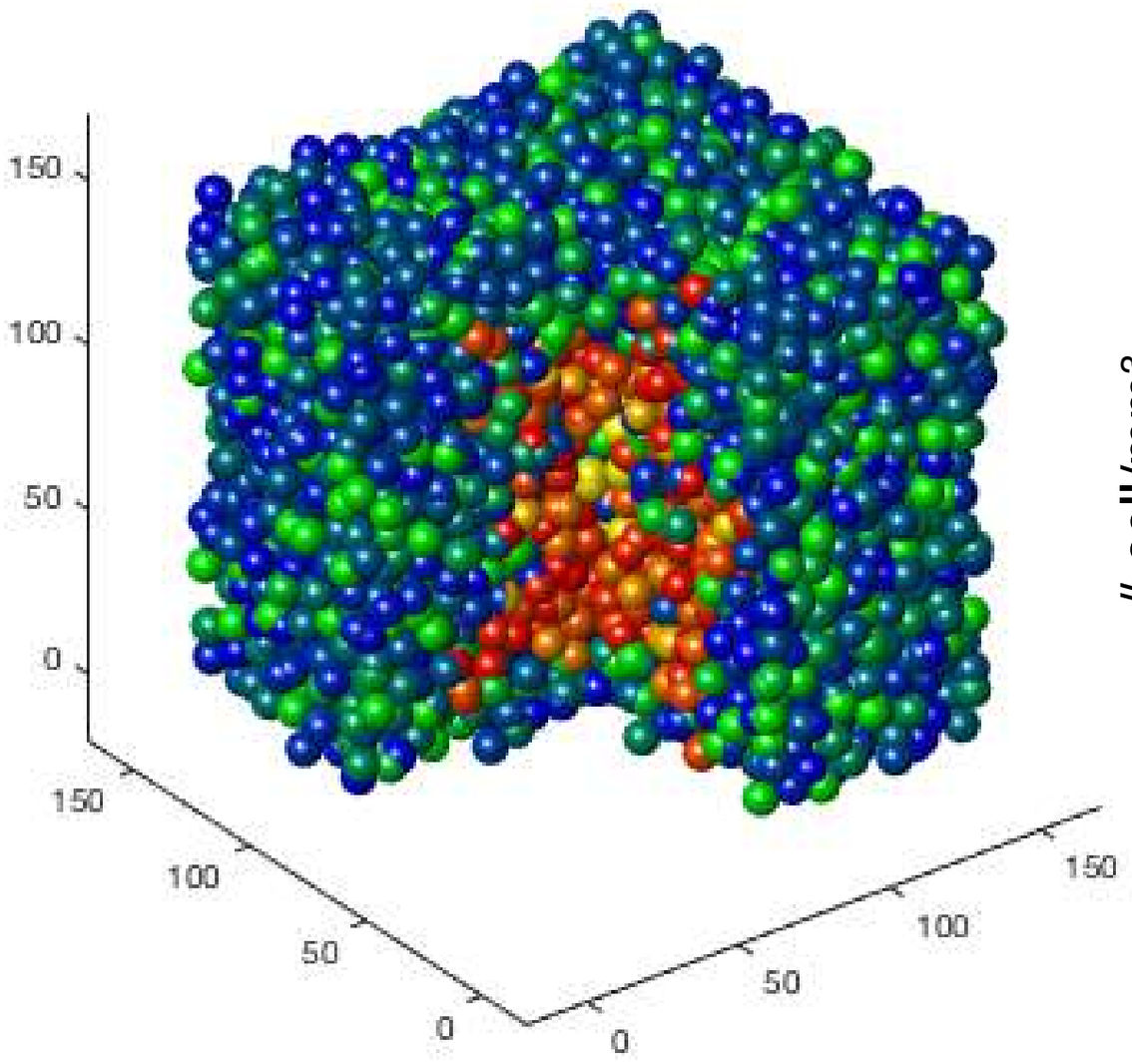


A highly proliferative cell at the origin of low-grade glioma

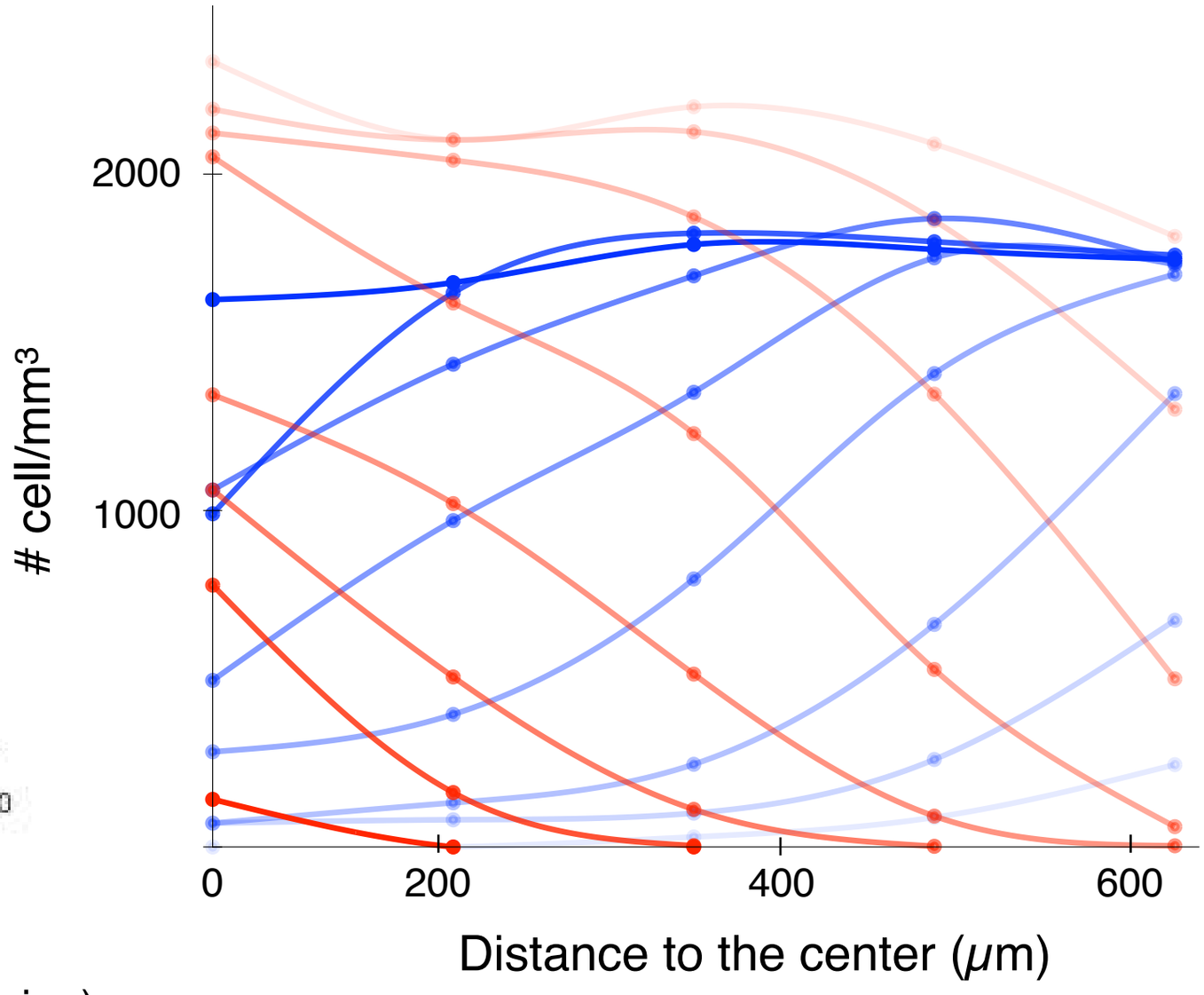


A very proliferative cell in red
Normal OPCs are in blue

Modeling the formation of a glioma



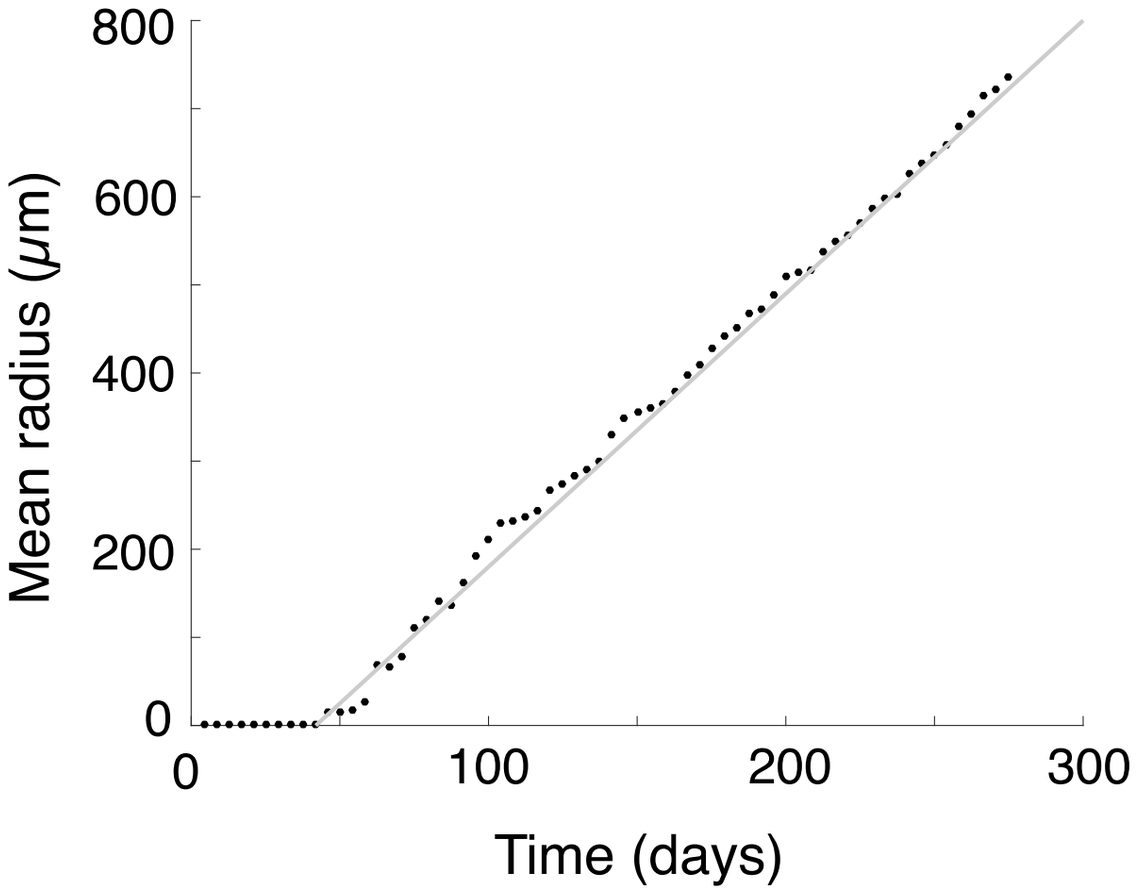
Tumor cells are yellow to red (cell clock increasing)
Normal OPCs are in blue to green (cell clock increasing)



Red curves: tumor cells; blue curves: normal cells

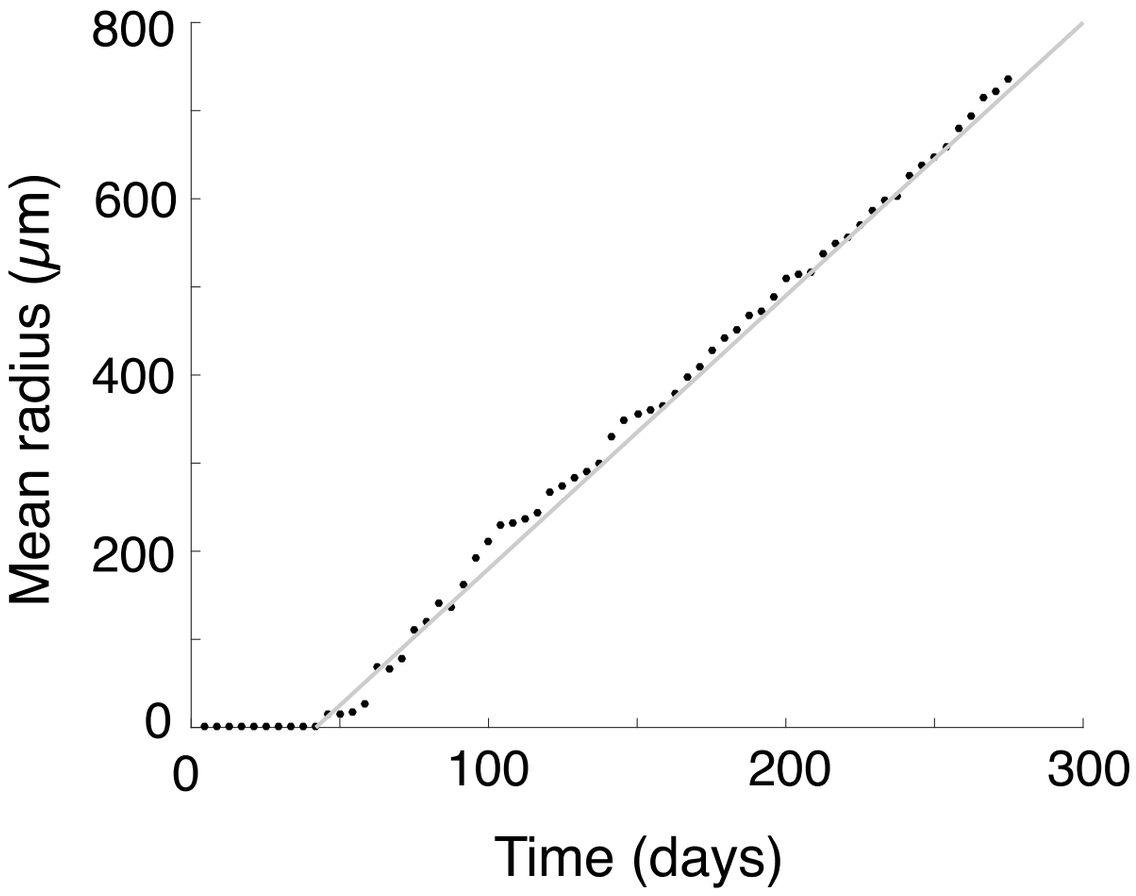
Dufour A et al, (2018), Modeling the dynamics of oligodendrocyte precursor cells and the genesis of gliomas, *PLoS Comput Biol.*, **14**, e1005977.

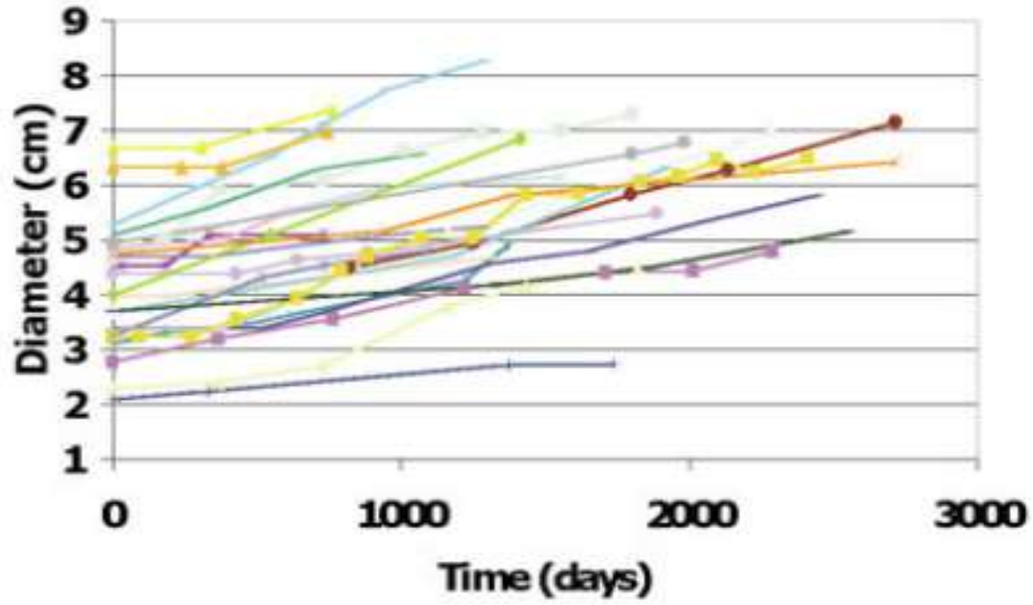
Modeling the formation of a glioma

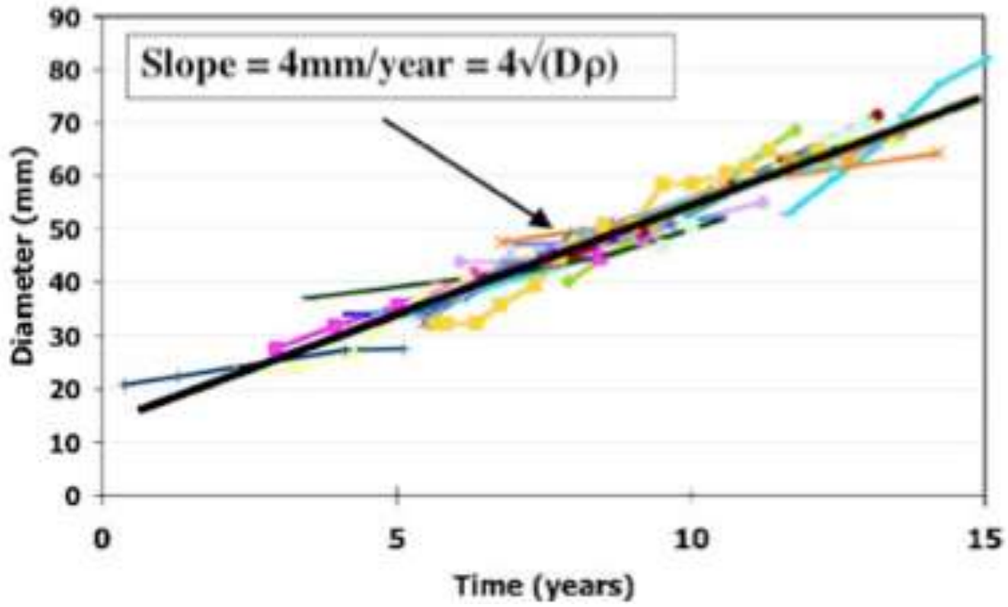


With reasonable parameters, v ≈ 1 mm/yr

Modeling the formation of a glioma







With reasonable parameters, v ≃ 1 mm/yr ⇒ consistent with clinical data

Mandonnet E et al (2003) Continuous growth of mean tumor diameter in a subset of grade II gliomas. *Ann Neurol,* **53**, 524–528

First step of formation of a glioma

OPC: oligodendrocyte precursor cell.

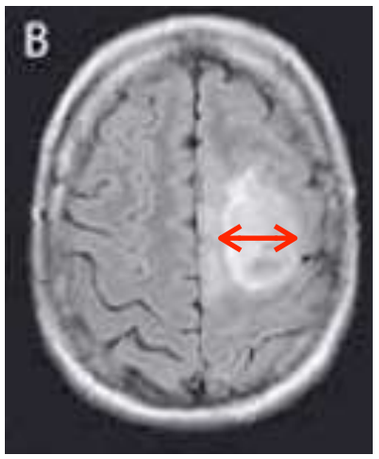
The appearance of a highly proliferative OPC among normal OPCs leads to the formation of a glioma-like tumor:

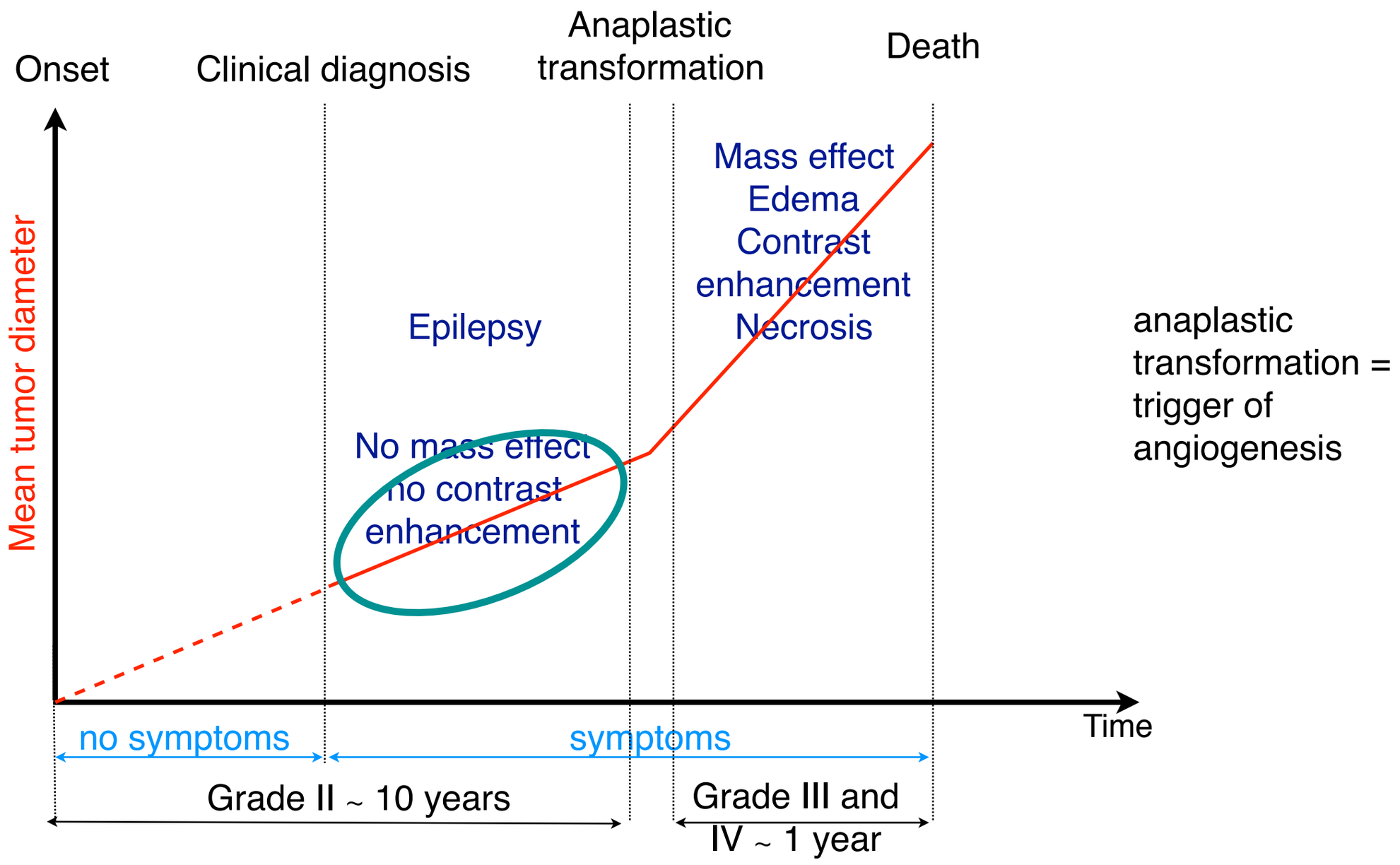
- invasive
- slow linear increase of the radius, compatible with clinical data

⇒ first step of heterogeneity: mixture and competition between normal and cancer cells

Dufour A et al, (2018), Modeling the dynamics of oligodendrocyte precursor cells and the genesis of gliomas, *PLoS Comput Biol.*, **14**, e1005977.

Increasing heterogeneity



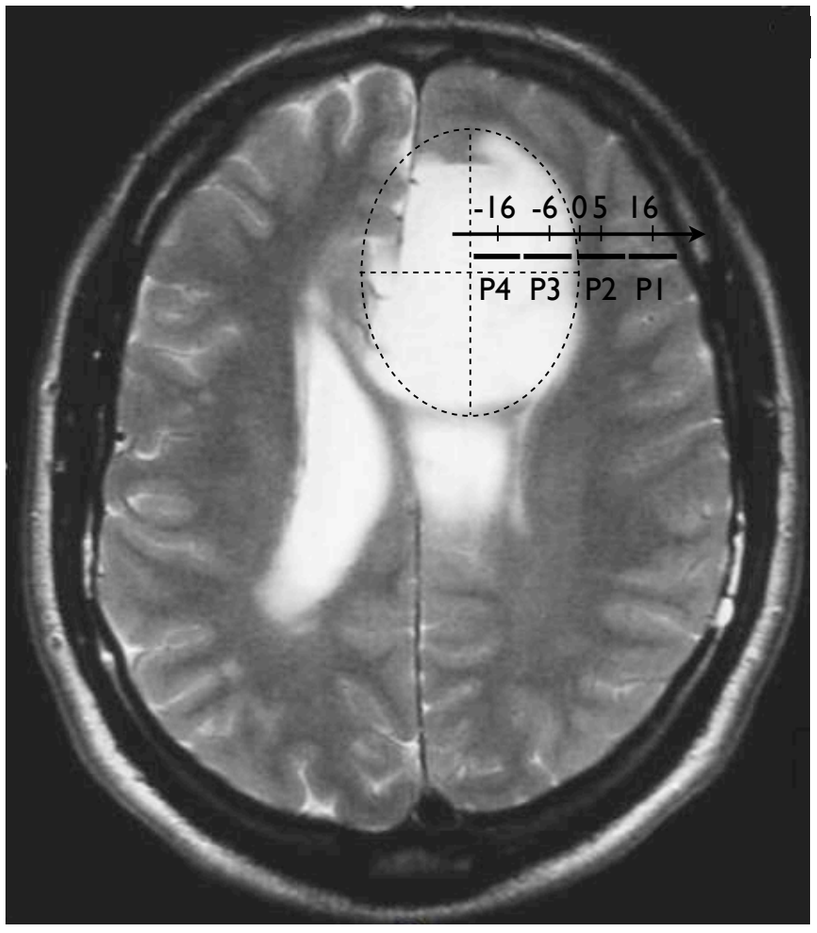


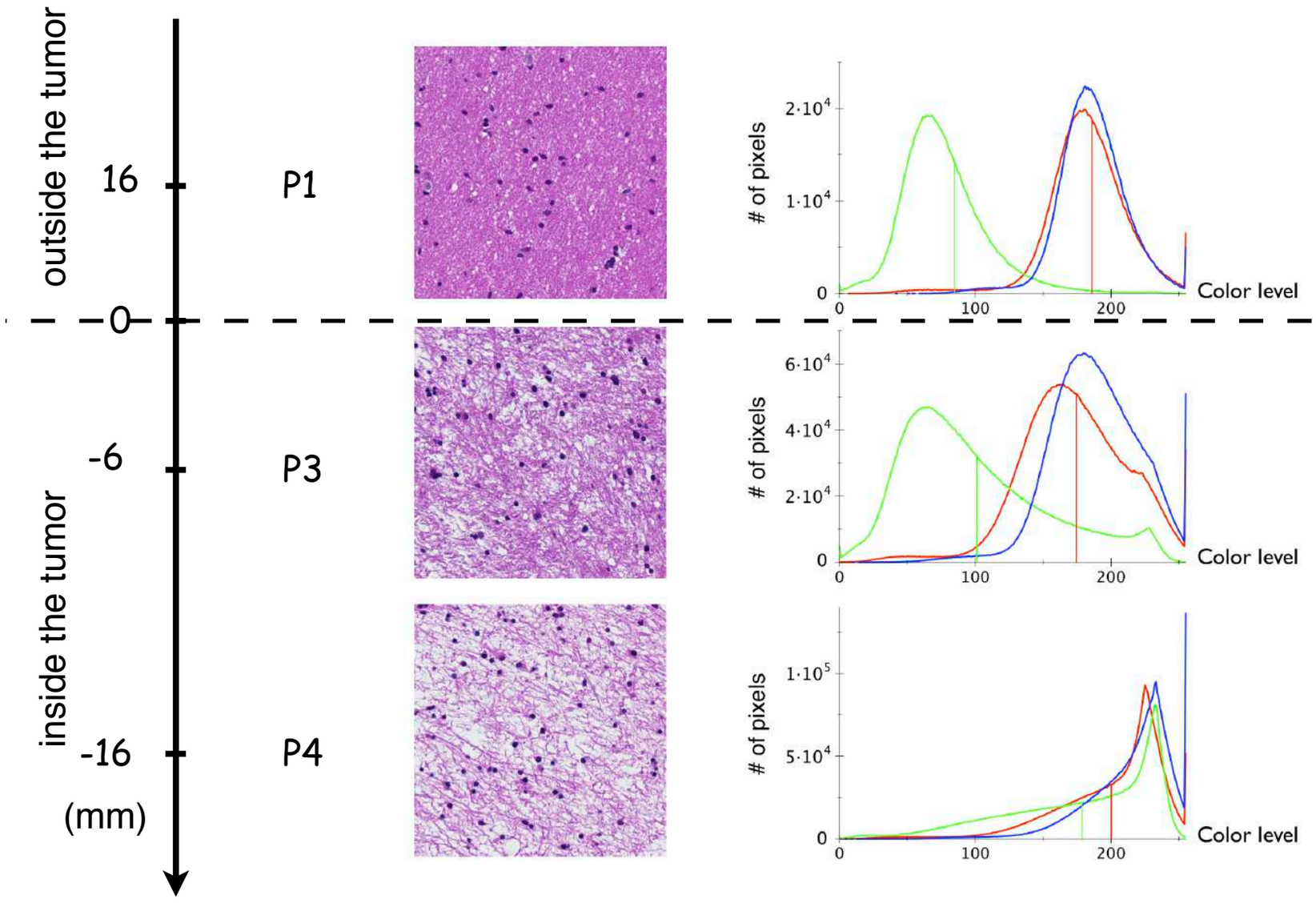
-Very invasive tumors but patients can live more than ten years after diagnosis

Pallud J et al, (2008) Les gliomes infiltrants de bas grade, REG, *Neurologies,* **11**, 94-101

Quantification of edema

Tumor tissue: normal cells + tumor cells + edema + ECM +….

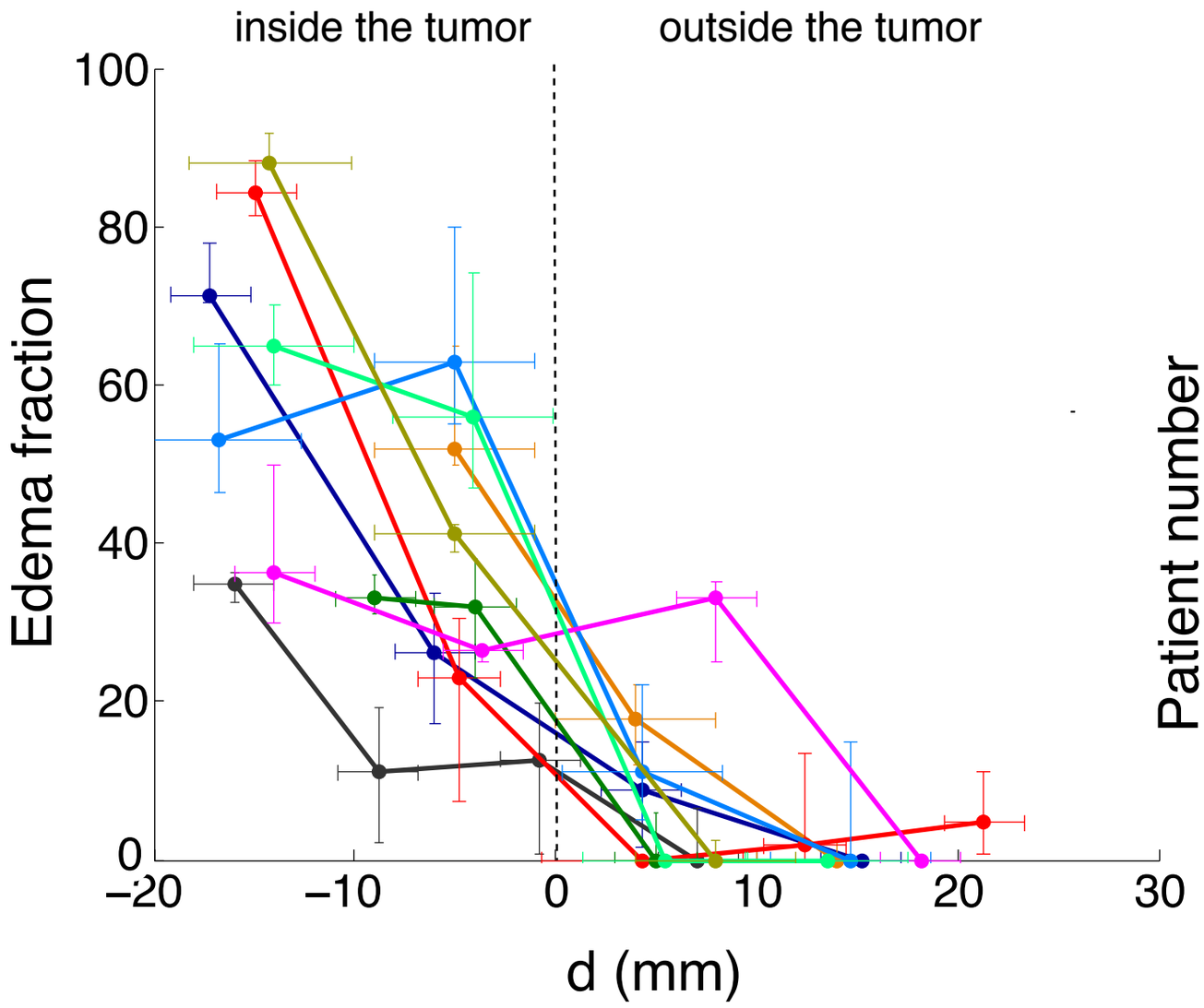


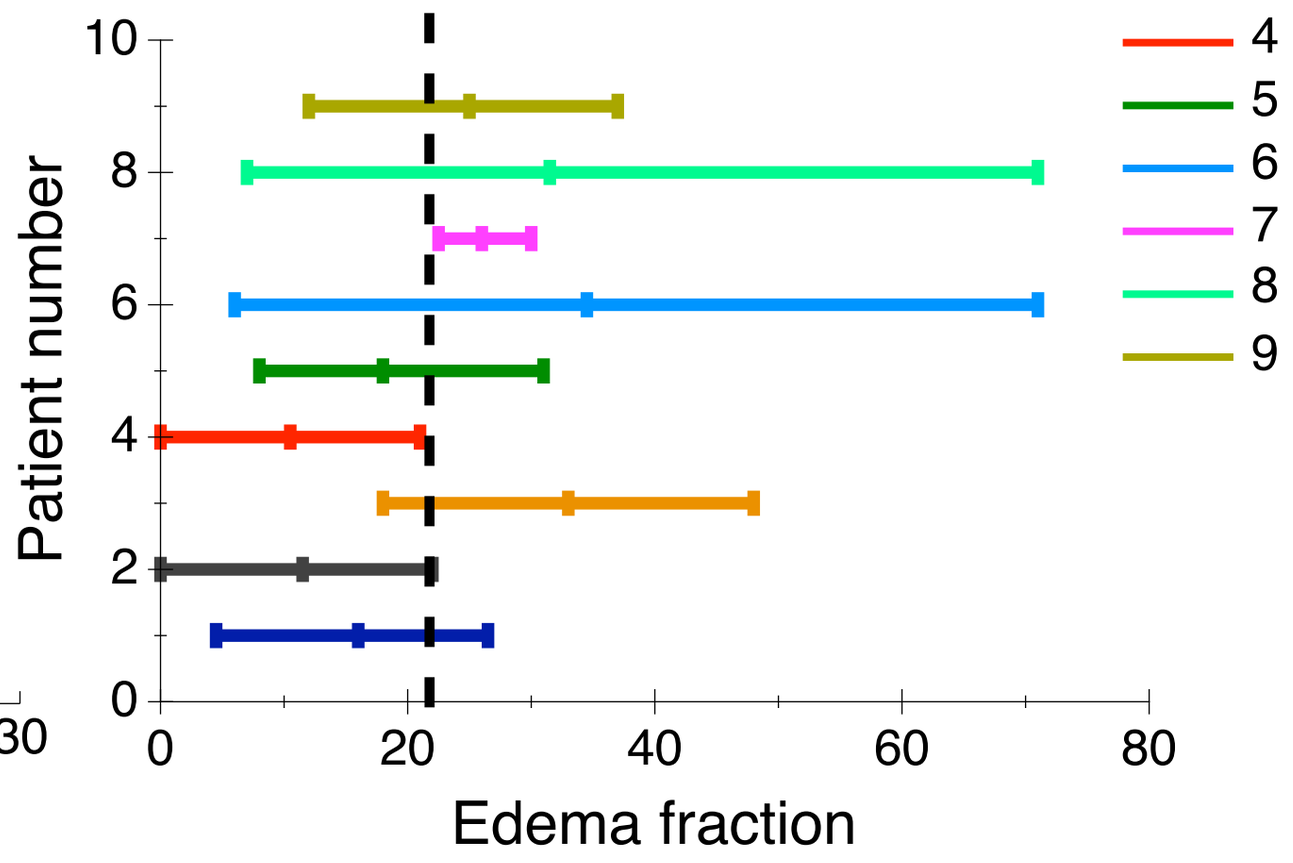


$$\xi = 0.92(1.01 - 10^{-2}(R_e - G_e))$$

ξ : area fraction of edema

Edema/border of the tumor





Gerin C, et al (2013) Quantitative characterization of the imaging limits of diffuse low-grade oligodendrogliomas, *Neuro-Oncology*, **15**, 1379.

A model with edema

Equation for the cell density evolution:

$$\frac{\partial \rho}{\partial t} = D\nabla^2\rho + \kappa\rho(1-\rho)$$

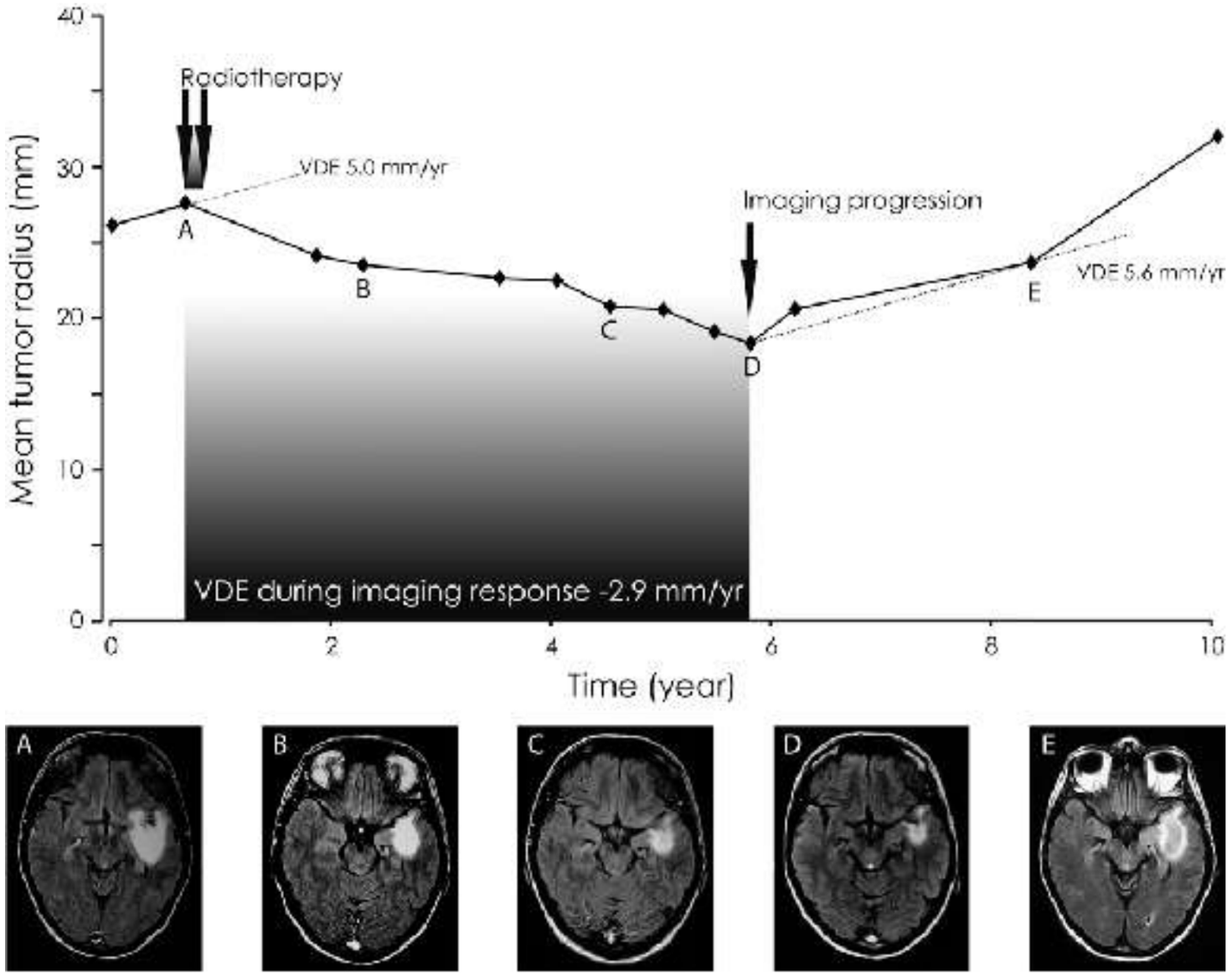
ρ: tumor cell density
ξ: edema fraction
κ: proliferation
D: diffusion
λ: edema production
μ: edema clearance

Equation for the edema fraction evolution:

$$\frac{\partial \xi}{\partial t} = \lambda\rho(1-\xi) - \mu\xi^{\nu}$$

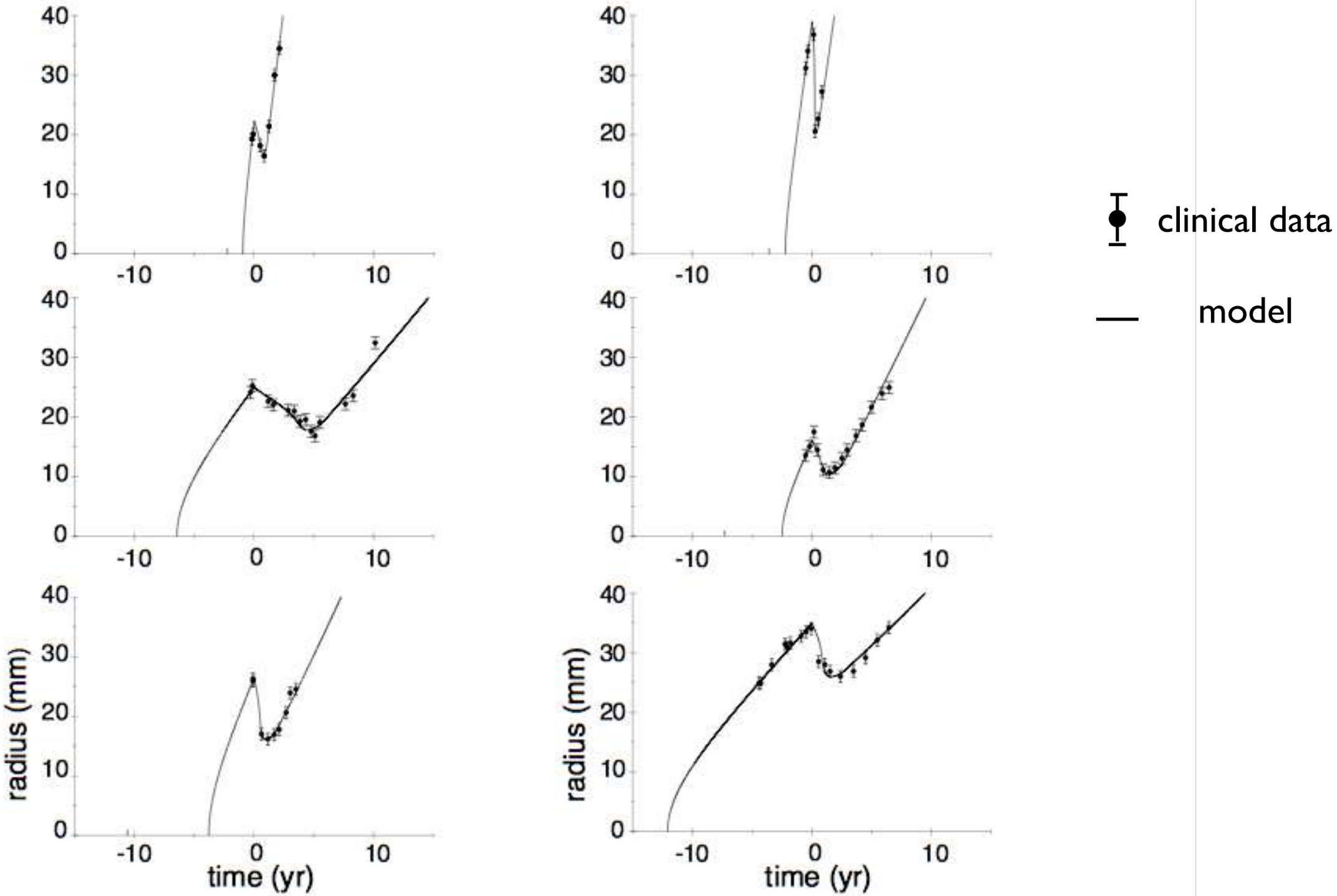
At the center, when ρ=1, ξ reaches its maximum value that verifies: $1 - \xi_e = \frac{\lambda}{\mu}{\xi_e}^{\nu}$

Low-grade gliomas and radiotherapy



Delay between the end of the radiotherapy and the regrowth of the tumor: Why?

Fit of clinical data



Badoual M, et al (2014) An oedema-based model for diffuse low-grade gliomas: application to clinical cases under radiotherapy, *Cell Prolif*, **47**, 369

Conclusion

➢ When the tumor grows the heterogeneity increases.

➢ In low-grade gliomas, the heterogeneity is still low: easier for modeling. Two models, with increased heterogeneity, corresponding to different stages of evolution of a glioma.

➢ Next step: study of the apparition of heterogeneity between tumor cells (hypoxia)

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Thank you for your attention !