How can Mathematics help someone with Glioblastoma Multiforme?

Congrès d'Analyse Numérique pour les Jeunes - 2020

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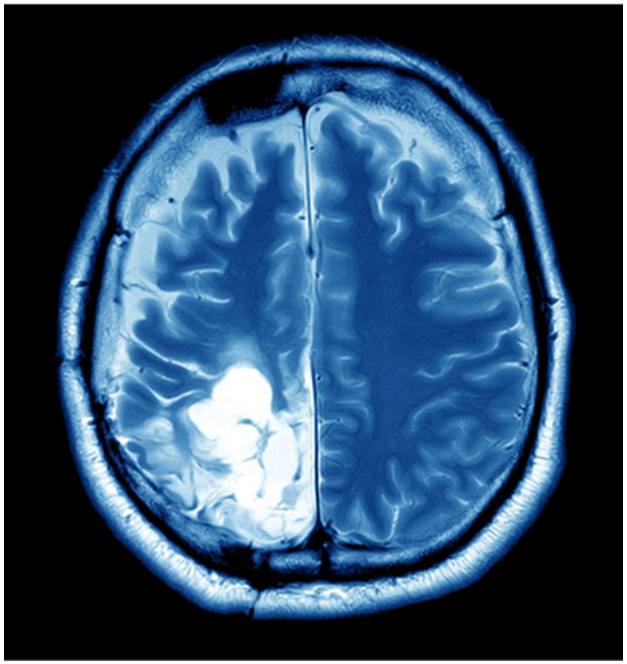
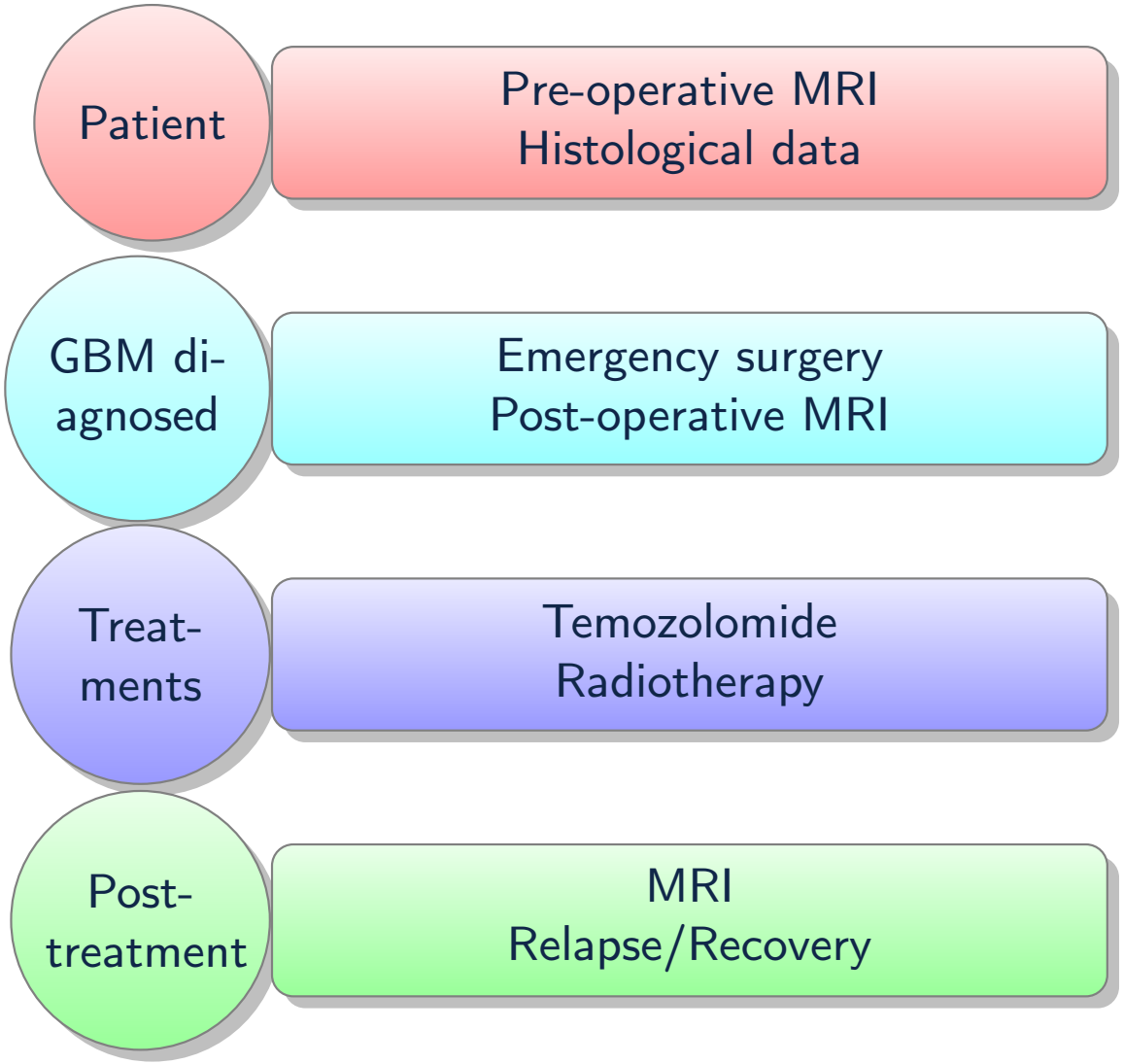
Glioblastoma Multiforme (GBM)

- Brain tumor (grade IV)
- 3481 cases in 2018 (France)
- Median age: 66
- 5% of patients survive at least 5 years
- High risk of relapse
- Tumor resistance against treatments



Treatments of Glioblastoma Multiforme



PhD objectives

Building a model around the behaviour of GBM

- Model consistent for Biology
- Model original for Mathematics

→

Getting simulations of GBM growth

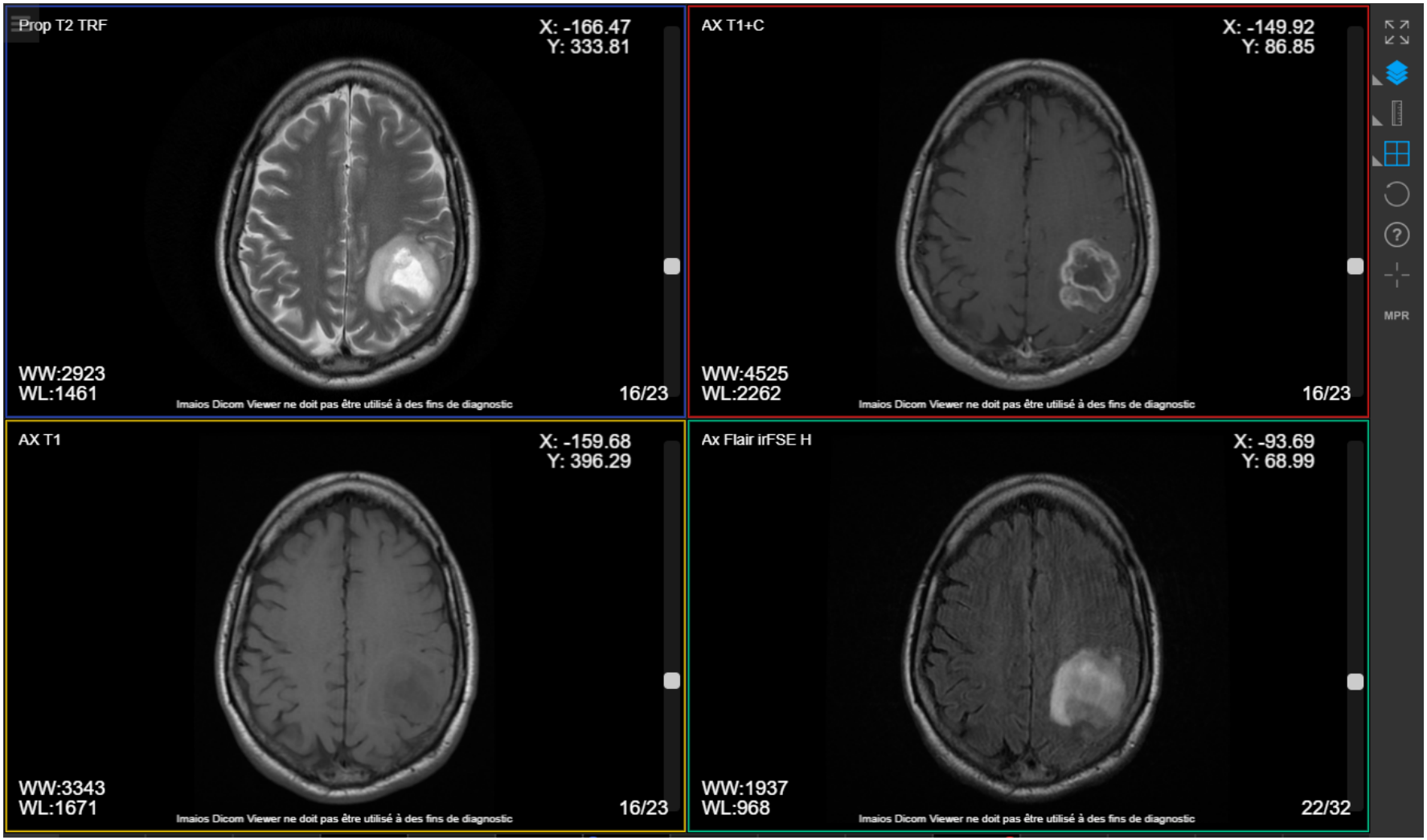
- Use MRIs for simulations
- Use an appropriate numerical method

→

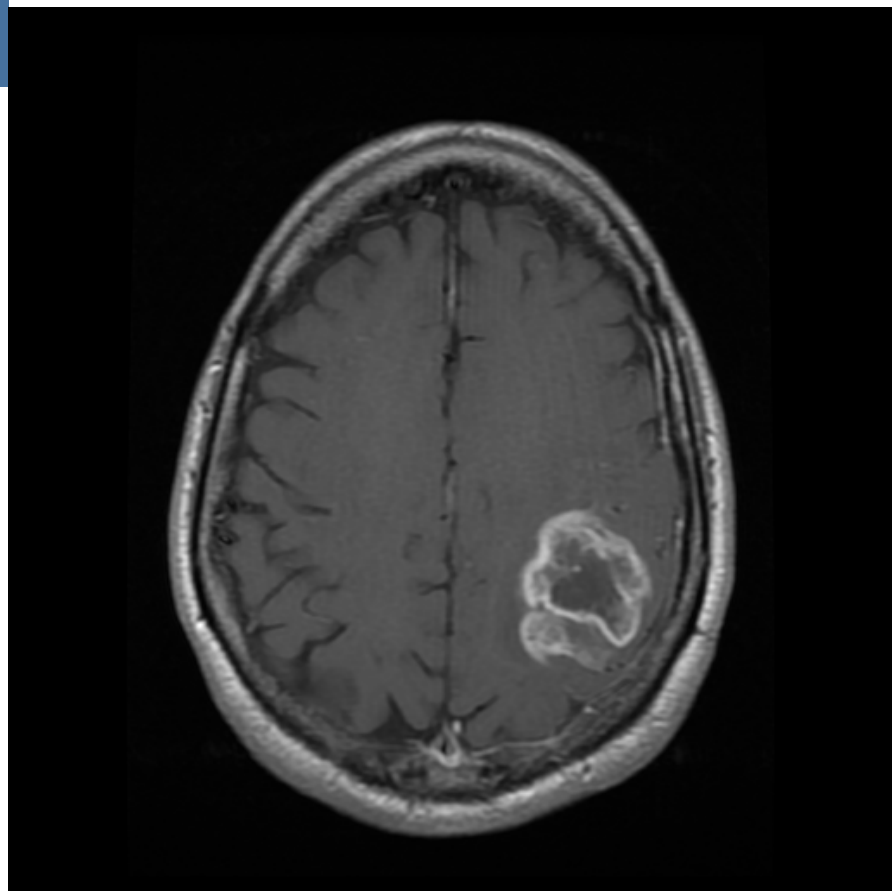
Confronting determinist model and patient data

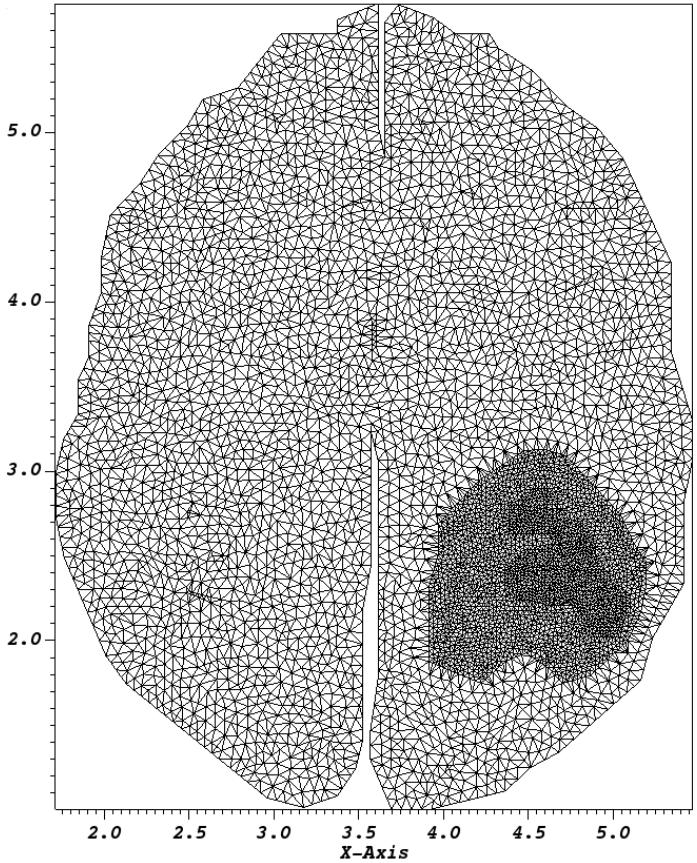
- Be able to have an adaptative model fitting individual data

Acquiring a patient data

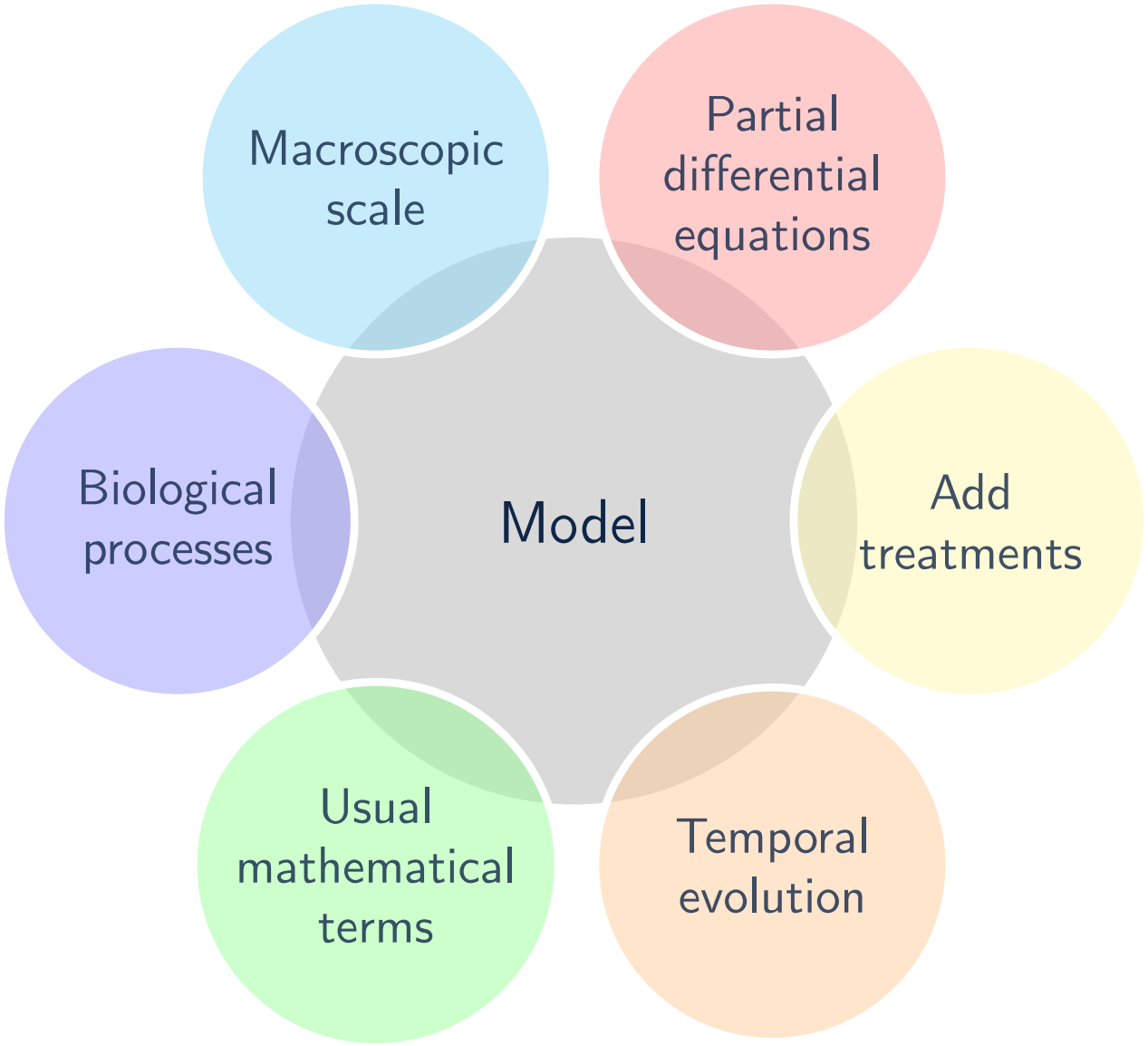


Building a mesh based on MRIs

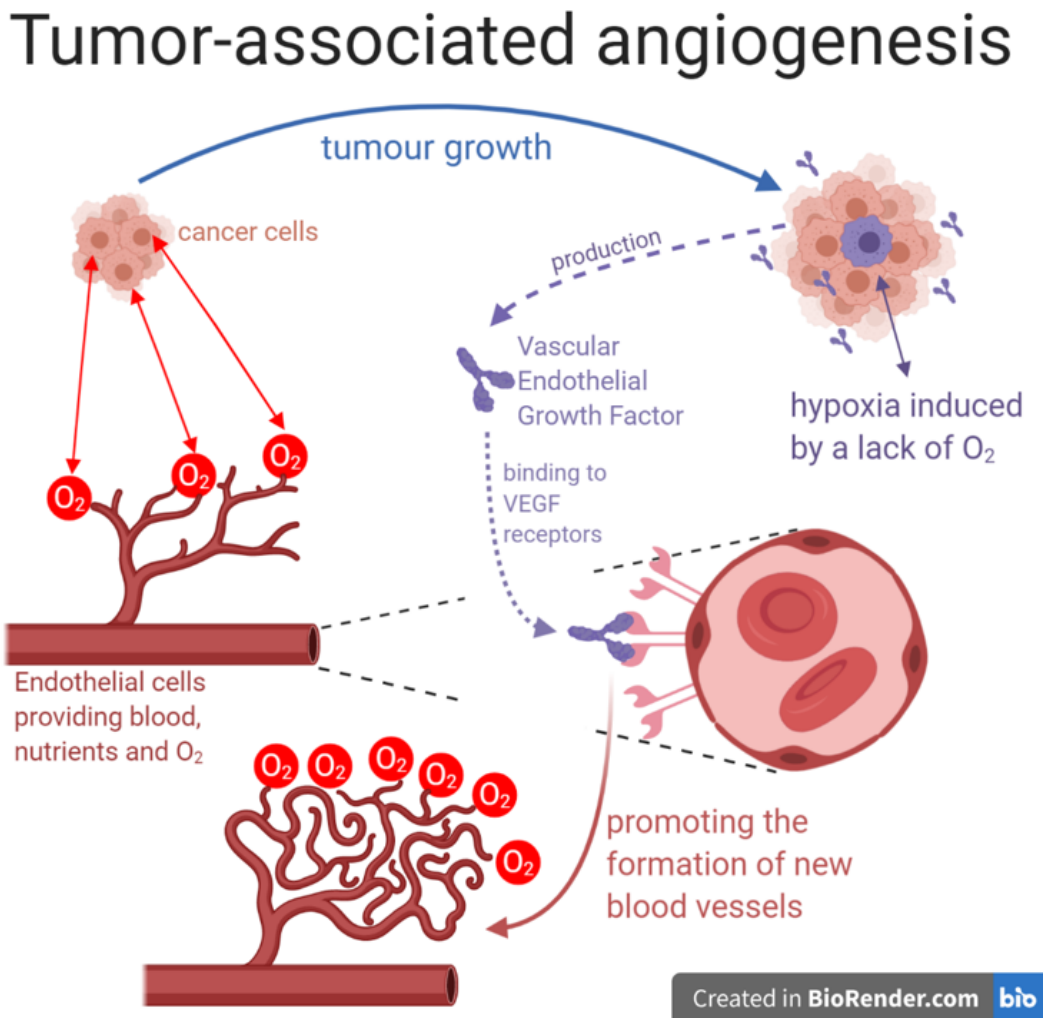




Building a model



Angiogenesis in Biology



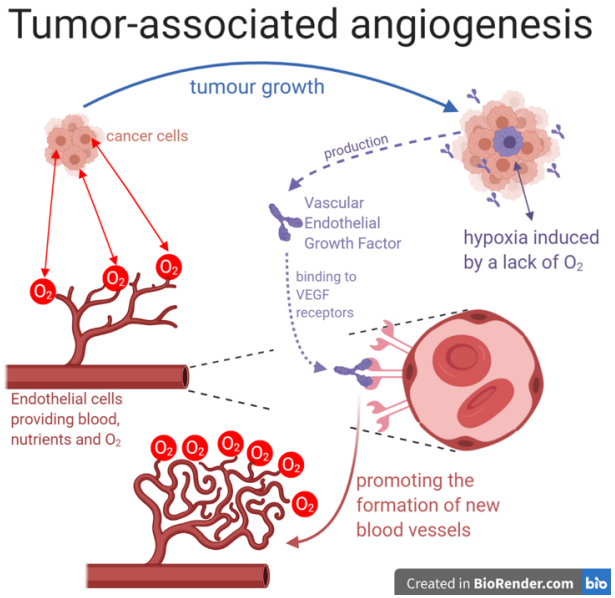
Angiogenesis in Mathematics

1. $\frac{\partial u}{\partial t}$ — Temporal evolution
2. $-\nabla.(\Lambda(x)a(u)\nabla u)$ — Random diffusion/migration
3. $+\nabla.(\Lambda(x)\chi(u)\nabla c)$ — Convection/Chemotaxis/Haptotaxis
4. $\rho_1 u(1-u-u_e)$ — Reproduction/Mitosis
5. $-\beta_1 u$ — Degradation/Apoptosis/Necrosis
6. $-\gamma_2 uc$ — Consumption

Angiogenesis model

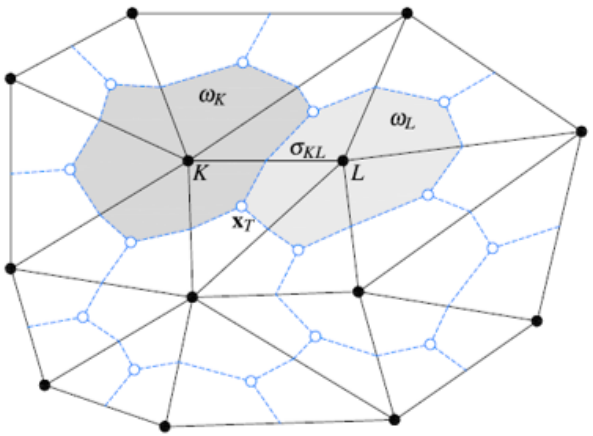
$$\begin{cases} \partial_t u - \nabla.(\Lambda(x)a(u)\nabla u) + \nabla.(\Lambda(x)\chi(u)\nabla c) = \rho_1 f_{u_e}(u) - \beta_1 u - T(t,u) \\ \partial_t c - \nabla.(D_2\nabla c) = \alpha_2 u_e - \beta_2 c - \gamma_2 u.c \\ \partial_t u_e - \nabla.(\Lambda(x)a(u_e)\nabla u_e) + \nabla.(\Lambda(x)\chi(u_e)\nabla V) = \rho_3 f_u(u_e) - \beta_3 u_e \\ \partial_t V - \nabla.(D_4\nabla V) = \alpha_4 g(c) - \beta_4 V - \gamma_4 u_e V \end{cases}$$

- $\Lambda(x)$: medium dependant diffusion matrix
- D_2 and D_4: Isotropic diffusion matrix
- $a(.)$: cell-dependant diffusion function
- $\chi(.)$: cell-dependant chemotaxis function
- $f_.(.)$: cell-dependant reproduction function
- $T(.)$: treatment function
- $g(.)$: O_2-dependant production under hypoxia



Building a numerical scheme

- Positivity of all quantities
- Upper-boundedness of cell quantities
- Use Finite-Volume for numerical flux conservation
- No constraints on the mesh needed



Usual numerical problem 1

- Diffusion term: $-\nabla.(\Lambda(x)a(u)\nabla u)$
  - Finite-Volume approximation:

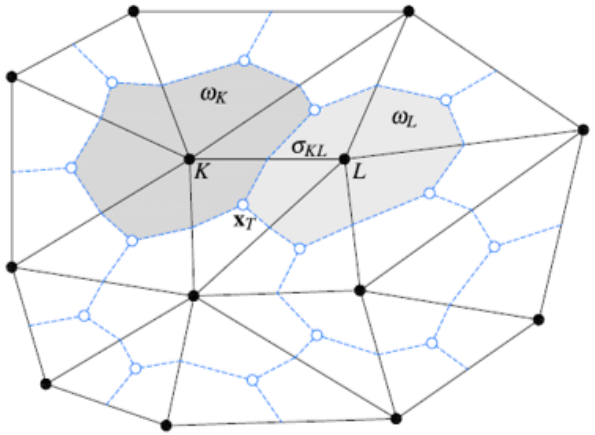
$$-\int_{\omega_K} \nabla.(\Lambda(x)a(u)\nabla u)dx = -\int_{\partial\omega_K} \Lambda(x)a(u)\nabla u.\vec{n}$$
$$= -\sum_{\sigma_{KL}\in\varepsilon_K} \int_{\sigma_{KL}} \Lambda(x)a(u)\nabla u.\vec{n_{\sigma_{KL}}}$$

  - Without mesh constraints there is no Finite Volume approximation ensuring positivity of quantities
- Approximate the Diffusion Matrix on σ_{KL} using Finite-Element approximation:

$$\Lambda_{KL} = \int_\Omega -\Lambda(x).\nabla\Phi_K(x).\nabla\Phi_L(x)dx$$

Usual numerical problem 2

- How to get bounded quantities: $0 \leq u(t,x) \leq u_{max}$
- Without constraints, no feasible for no degenerative problems
- Degenerate problem:
  - Adding terms with support functions $\subset [0, u_{max}]$
  - $a(u), \chi(u), f_{u_e}(u) \sim \mathbb{1}_{[0,u_{max}]}(u)$



Numerical scheme

$$\begin{cases} \partial_t u - \nabla.(\Lambda(x)a(u)\nabla u) + \nabla.(\Lambda(x)\chi(u)\nabla c) = \rho_1 f_{u_e}(u) - \beta_1 u - T(t,u) \\ \partial_t c - \nabla.(D_2\nabla c) = \alpha_2 u_e - \beta_2 c - \gamma_2 u.c \\ \partial_t u_e - \nabla.(\Lambda(x)a(u_e)\nabla u_e) + \nabla.(\Lambda(x)\chi(u_e)\nabla V) = \rho_3 f_u(u_e) - \beta_3 u_e \\ \partial_t V - \nabla.(D_4\nabla V) = \alpha_4 g(c) - \beta_4 V - \gamma_4 u_e V \end{cases}$$

$$\begin{aligned} &\circ \frac{m_K}{\delta t}(u_K^{n+1} - u_K^n) + \sum_{\sigma_{KL}\in\mathscr{E}_K} \Lambda_{KL}.a_{KL}^{n+1}.(u_K^{n+1} - u_L^{n+1}) \\ &- \sum_{\sigma_{KL}\in\mathscr{E}_K} \Lambda_{KL}.a_{KL}^{n+1}.\mu_{KL}^{n+1}.(c_K^{n+1} - c_L^{n+1}) \\ &= m_K\rho_1 f_{u_{e_K}^{n+1}}(u_K^{n+1}) - m_K\beta_1 u_K^{n+1} - m_K T(u_K^{n+1}) \\ &\circ \frac{m_K}{\delta t}(c_K^{n+1} - c_K^n) + \sum_{\sigma_{KL}\in\mathscr{E}_K} D_{KL}^{(2)}\eta_{KL}^{n+1}(p(c_K^{n+1}) - p(c_L^{n+1})) \\ &= m_K\alpha_2 u_{e_K}^{n+1} - m_K\beta_2 c_K^{n+1} - \gamma_2 u_K^{n+1} c_K^{n+1} \end{aligned}$$

Numerical scheme

$$\circ \frac{m_K}{\delta t}(u_K^{n+1} - u_K^n) + \sum_{\sigma_{KL} \in \mathscr{E}_K} \Lambda_{KL}.a_{KL}^{n+1}.(u_K^{n+1} - u_L^{n+1})$$

$$- \sum_{\sigma_{KL} \in \mathscr{E}_K} \Lambda_{KL}.a_{KL}^{n+1}.\mu_{KL}^{n+1}.(c_K^{n+1} - c_L^{n+1}) = m_K F(u_K^{n+1})$$

$$a_{KL}^{n+1} = \begin{cases} \max\limits_{s \in \mathscr{I}_{KL}^{n+1}} a(s), & \text{if } \Lambda_{KL} \geq 0 \\ \min\limits_{s \in \mathscr{I}_{KL}^{n+1}} a(s), & \text{if } \Lambda_{KL} < 0 \end{cases}$$

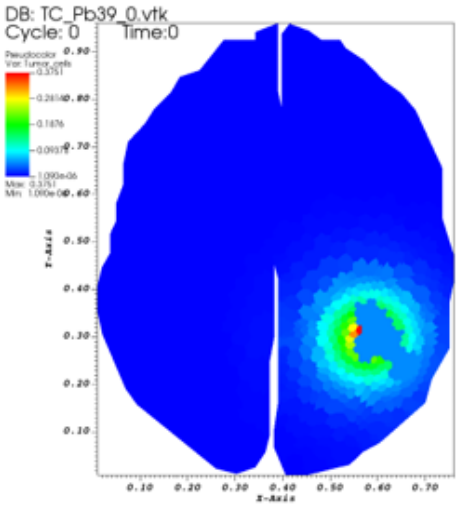
$$\mathscr{I}_{KL}^{n+1} = [\min(u_K^{n+1}, u_L^{n+1}), \max(u_K^{n+1}, u_L^{n+1})]$$

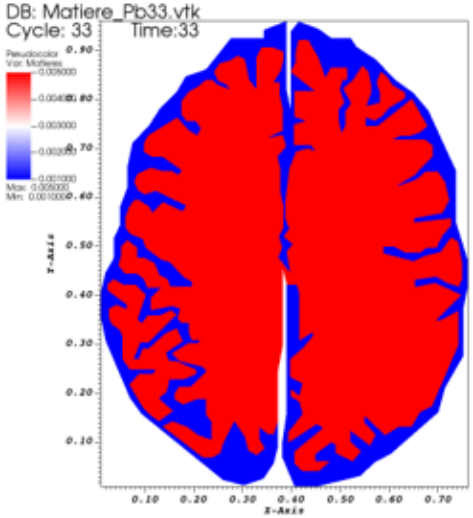
$$\mu_{KL}^{n+1} = \begin{cases} \mu_\downarrow(u_K^{n+1}) + \mu_\uparrow(u_L^{n+1}), & \text{if } \Lambda_{KL}(c_K^{n+1} - c_L^{n+1}) \geq 0 \\ \mu_\uparrow(u_K^{n+1}) + \mu_\downarrow(u_L^{n+1}), & \text{if } \Lambda_{KL}(c_K^{n+1} - c_L^{n+1}) < 0 \end{cases}$$

$$\mu_\uparrow(z) = \int_0^z (\mu'(y))^+ dy \qquad \mu_\downarrow(z) = -\int_0^z (\mu'(y))^- dy$$

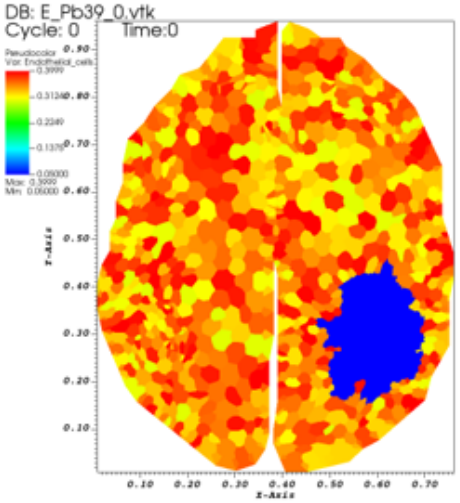
Add initial conditions

tumor cells

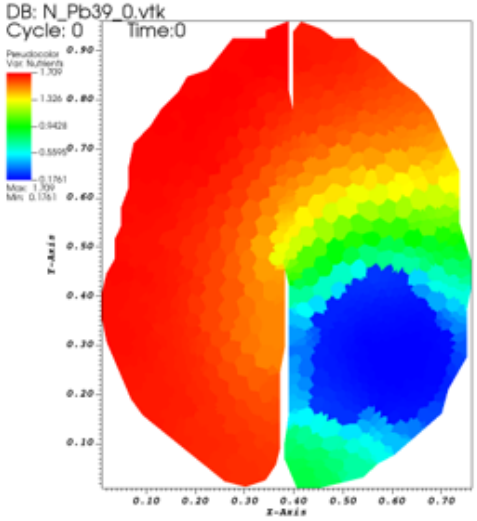




white and grey matters

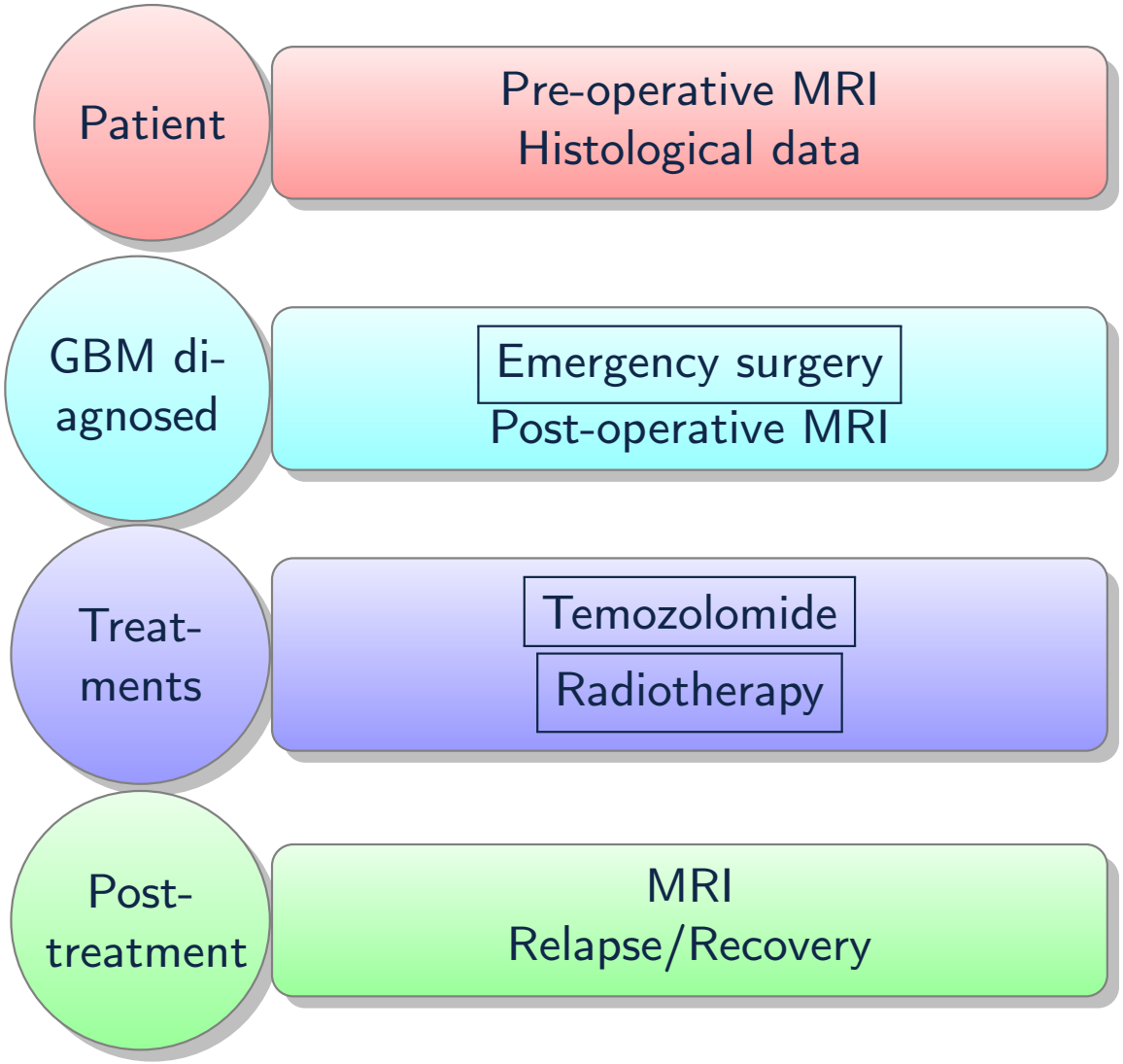


endothelial cells



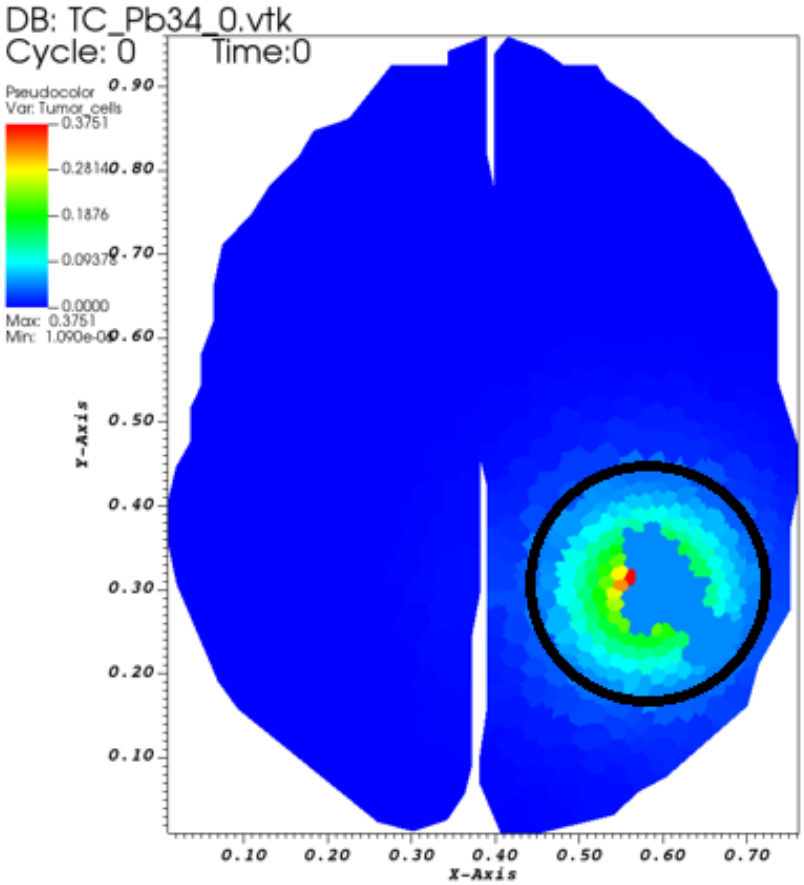
dioxygen

Treatments of Glioblastoma Multiforme

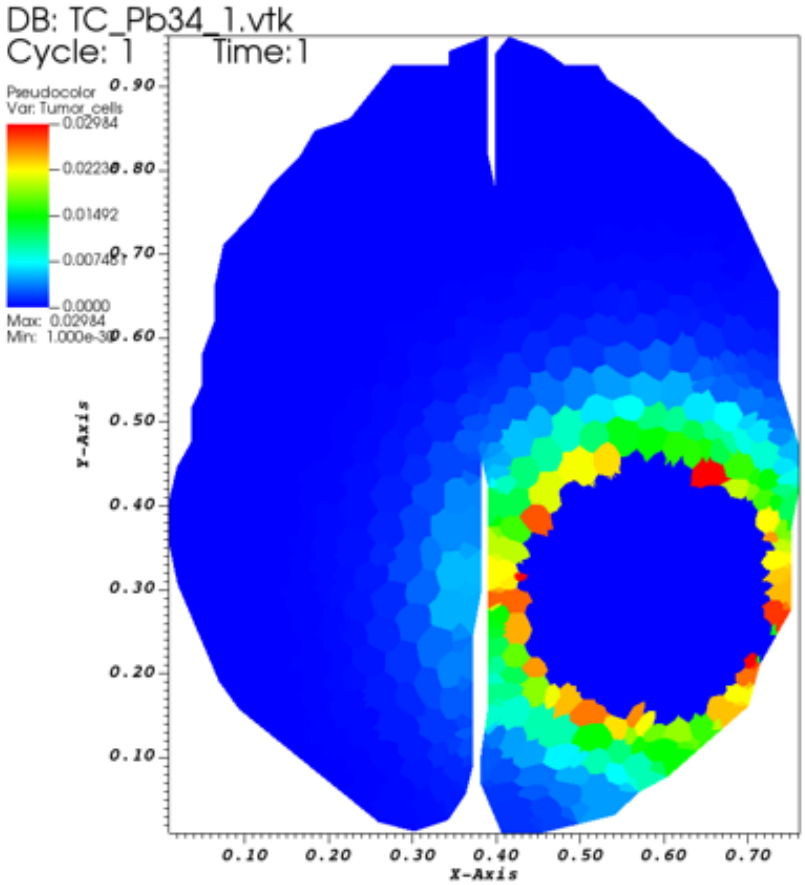


Modeling surgery

Before surgery

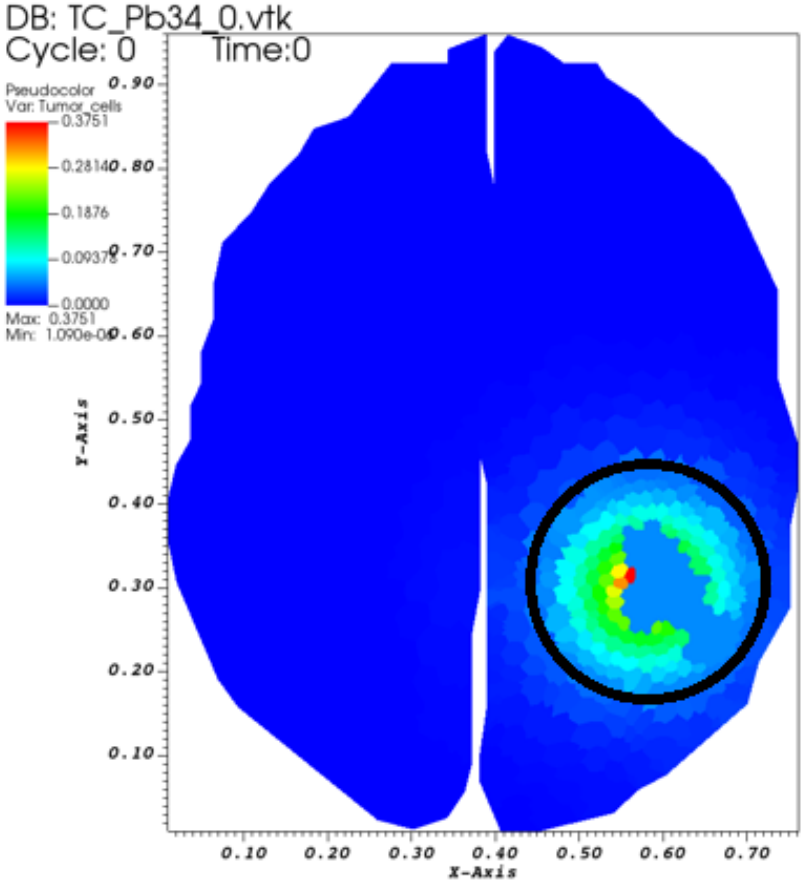


After surgery



Above a threshold ϵ, all quantities are set to 0.

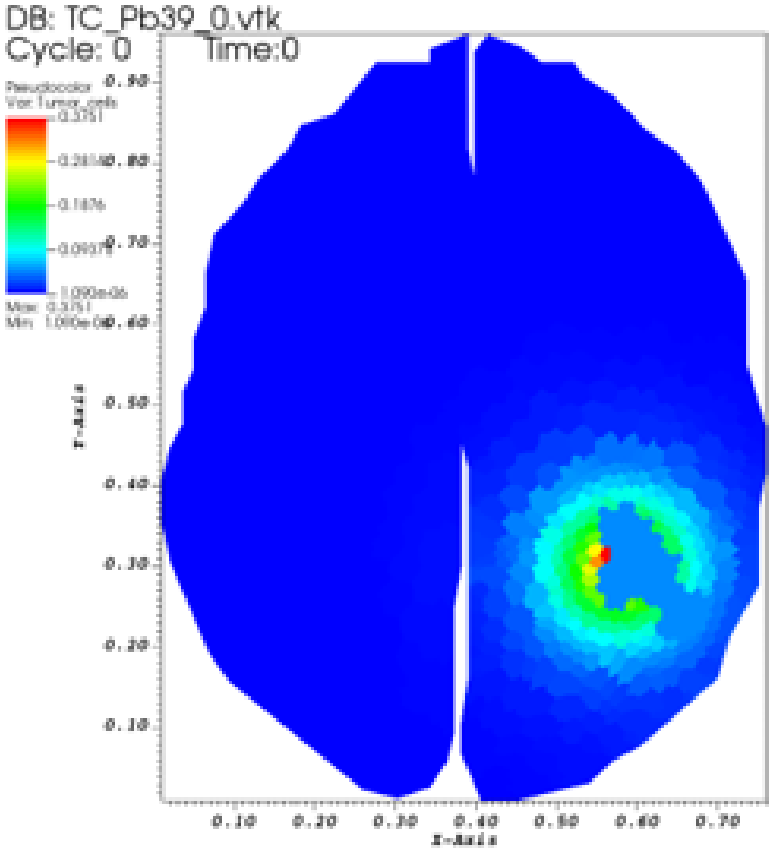
Modeling radiotherapy



- Adding the term: $-R_{eff}.k(t).u(t,x)$
- $R_{eff} = \alpha nd + \beta nd^2 f(\mu, \tau, \Delta\tau, n)$

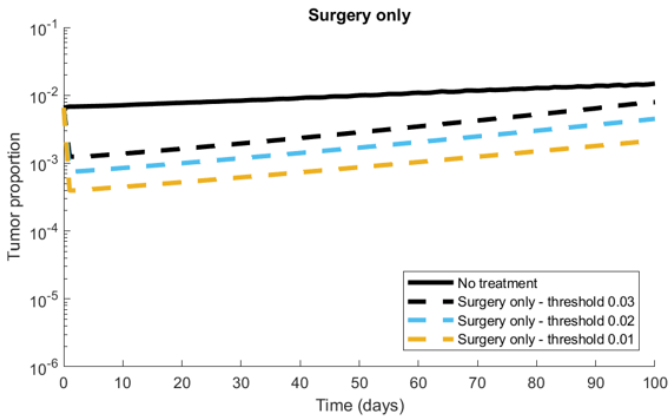
- Number of fractions per day (n)
- Individual dose in G_γ (d)
- Irradiation duration (τ)
- Time between irradiations ($\Delta\tau$)
- DNA damage rate (μ)
- Sensibility parameters (α, β)

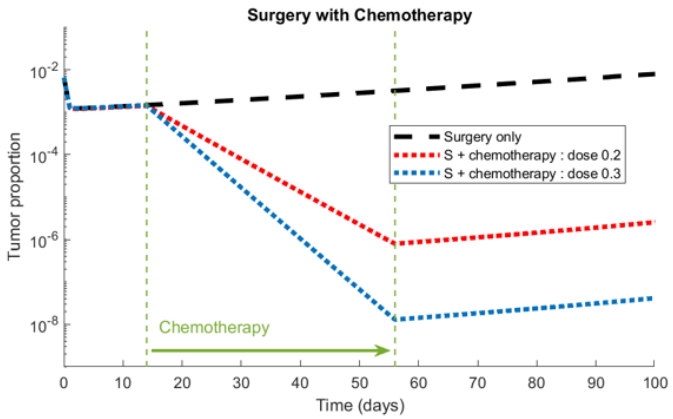
Modeling chemotherapy

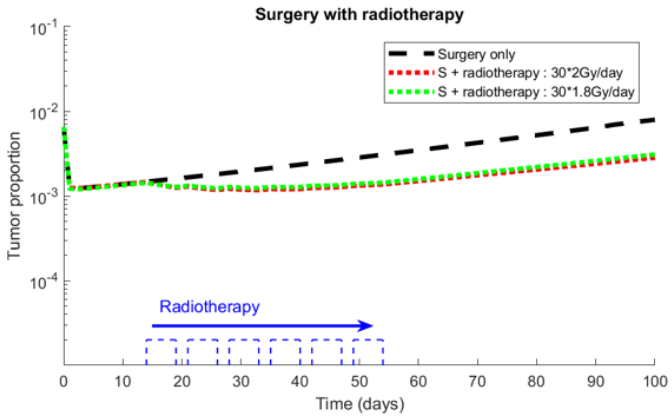


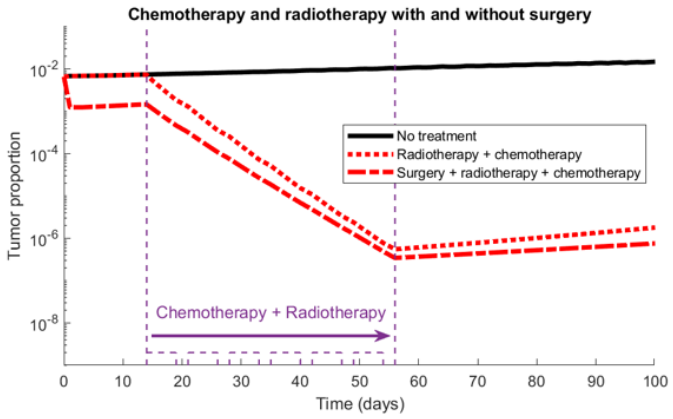
- Adding the term: $-Dose.k(t).u(t,x)$
- Temozolomide impacts all cells in the brain
- Possible existence of mutated tumor cells that aren't affected by the drug

Behaviour of the tumor during treatments

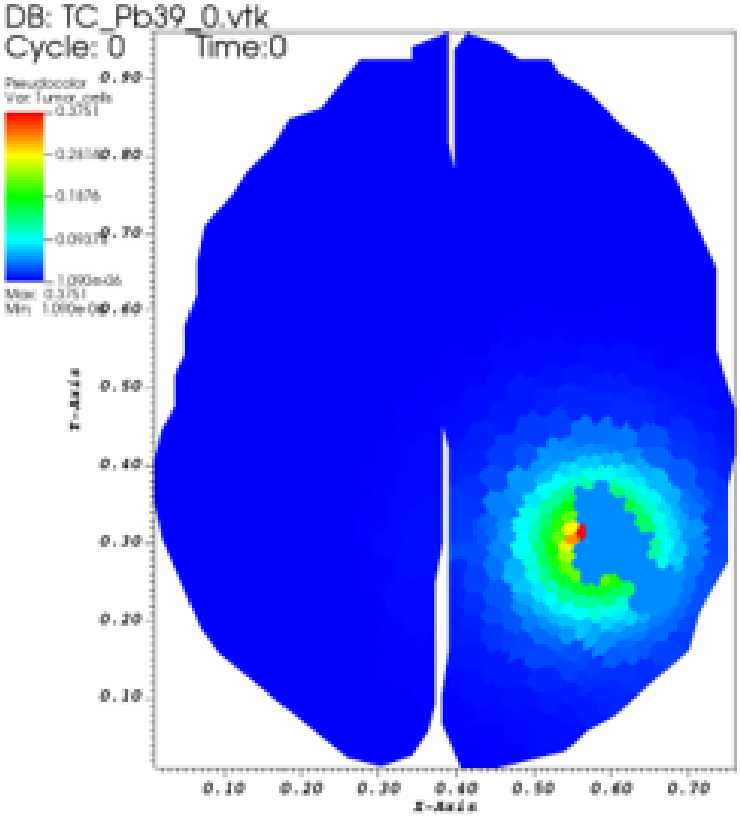




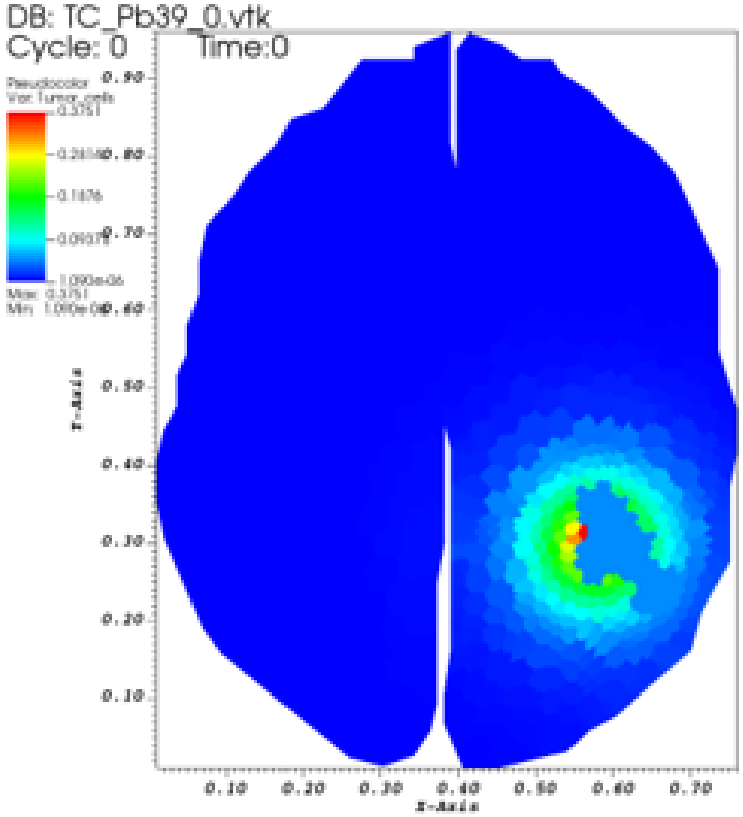




Behaviour of the tumor during treatments

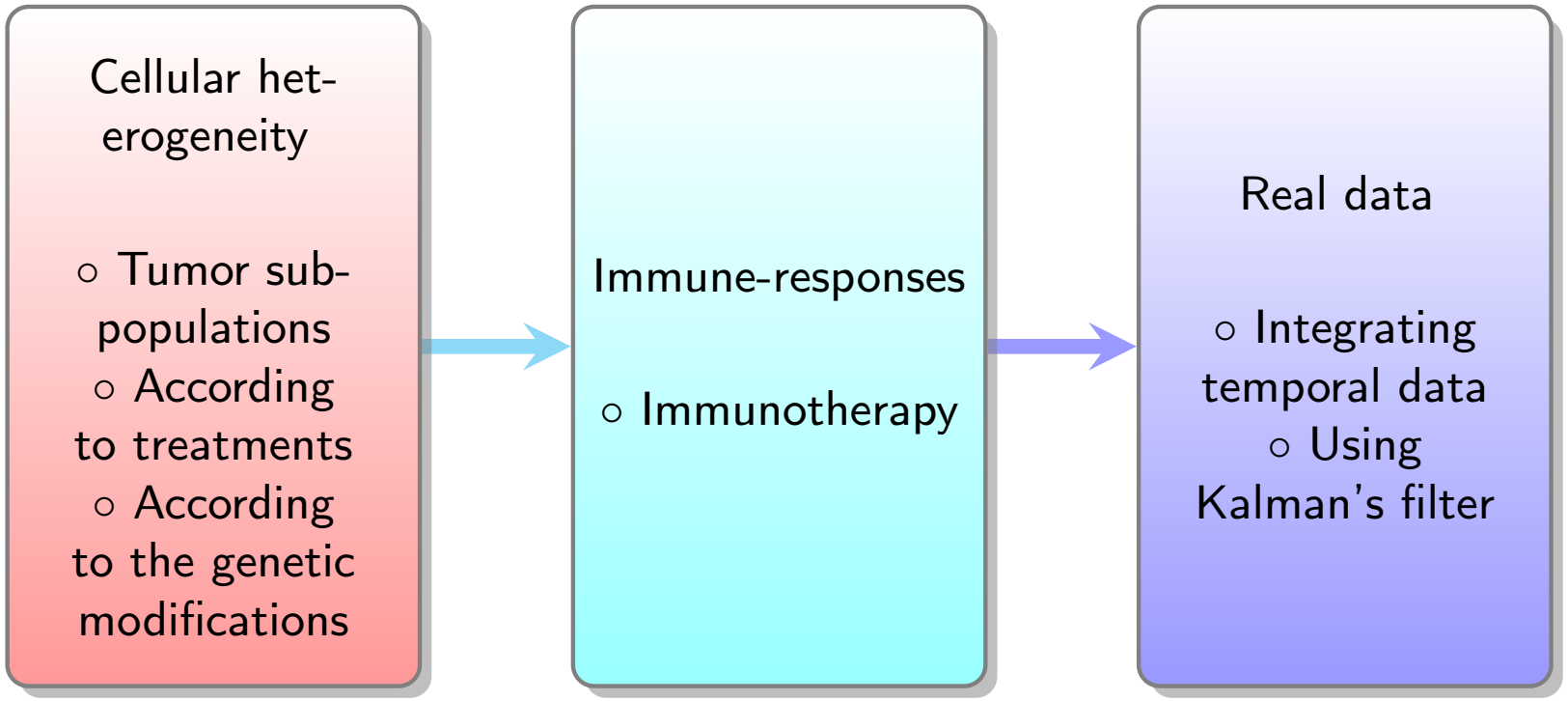


Without treatment



With treatments

Enhance the level of the model



Thank you for your attention