

How can Mathematics help someone with Glioblastoma Multiforme?

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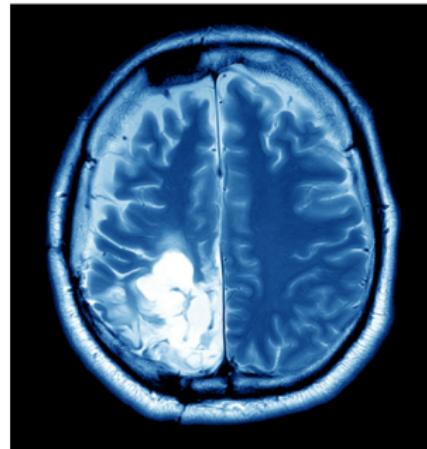
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GLIOBLASTOMA MULTIFORME (GBM)

- Brain tumor (grade IV)
- 3481 cases in 2018 (France)
- 5% of patients survive at least 5 years
- Treatments¹ = Surgery + Radiotherapy-Chemotherapy



¹R. Stupp et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med, 352:987–996, 2005. doi: 10.1056/NEJMoa043330.

WORK OBJECTIVES

Numerical modelling around
the behaviour of GBM

- Model based on tumour-induced angiogenesis
- Numerical schemes
- Numerical simulations

Combined state and parameter estimation

- Inverse problem formulation
- Inverse problem resolution
- Numerical resolution



GLIOBLASTOMA GROWTH MODEL

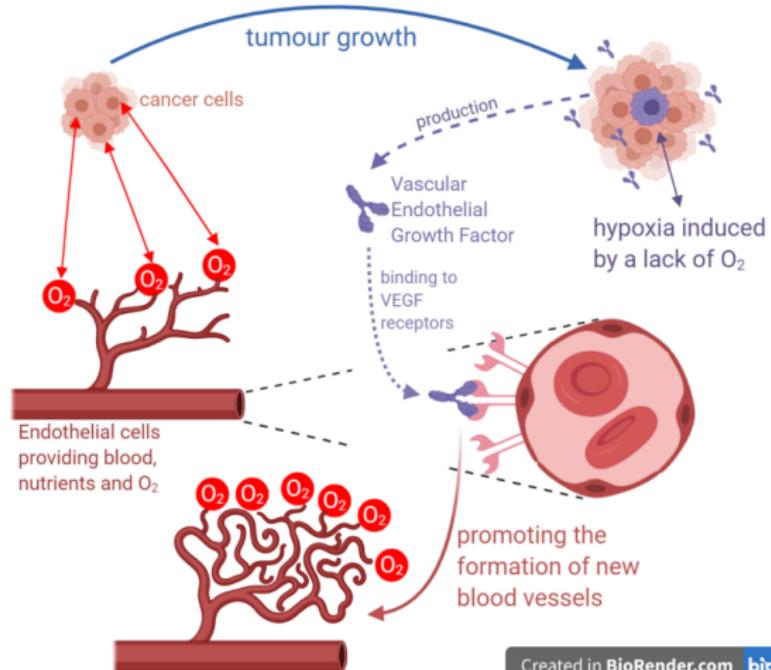
Numerical modelling around
the behaviour of GBM

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ANGIOGENESIS IN BIOLOGY

Tumor-associated angiogenesis

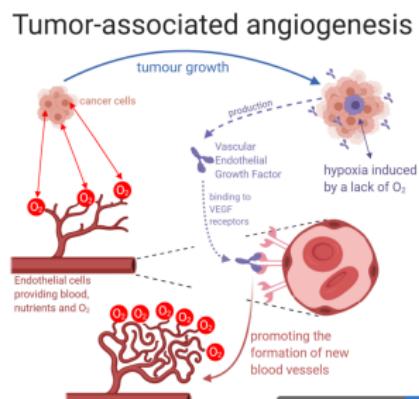


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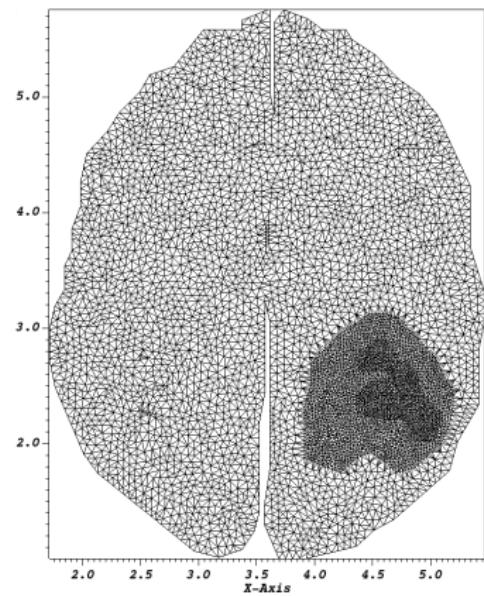
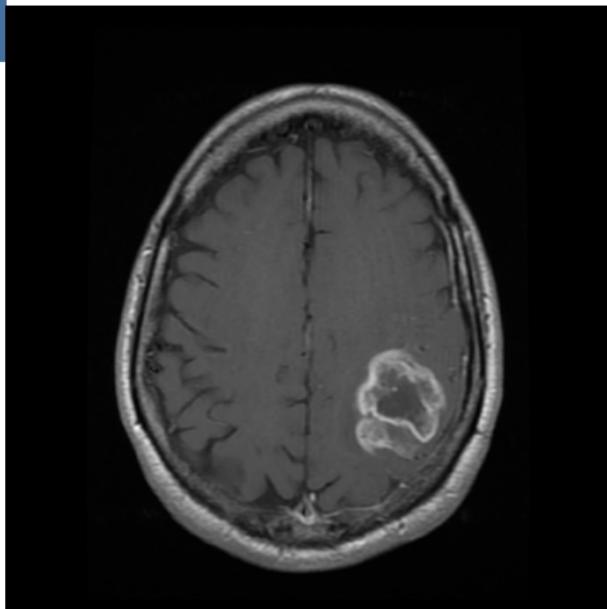
ANGIOGENESIS MODEL

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

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

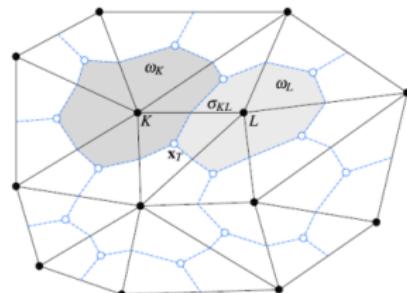


BUILDING A MESH BASED ON MRIs

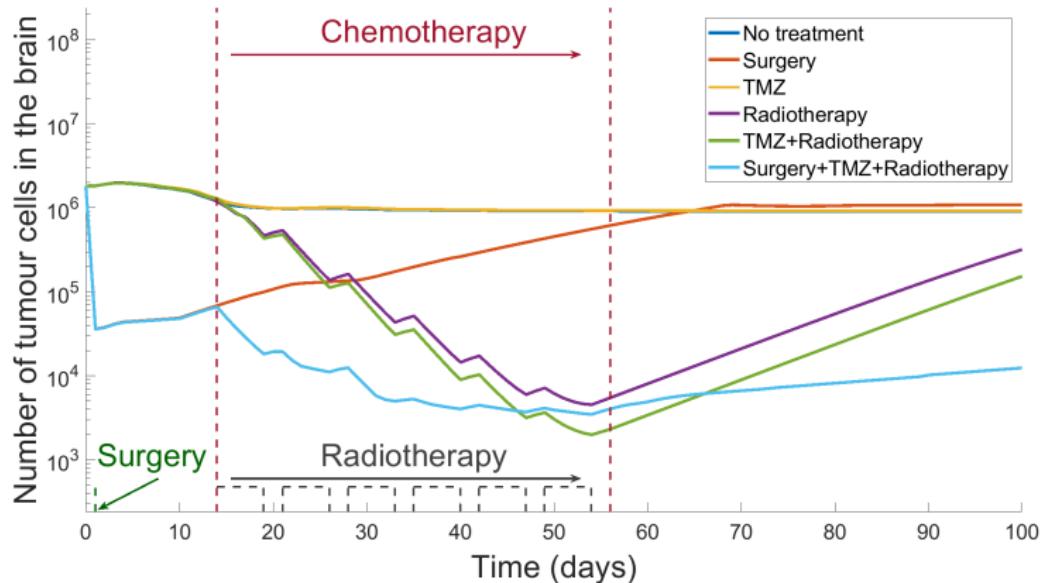


BUILDING A NUMERICAL SCHEME

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

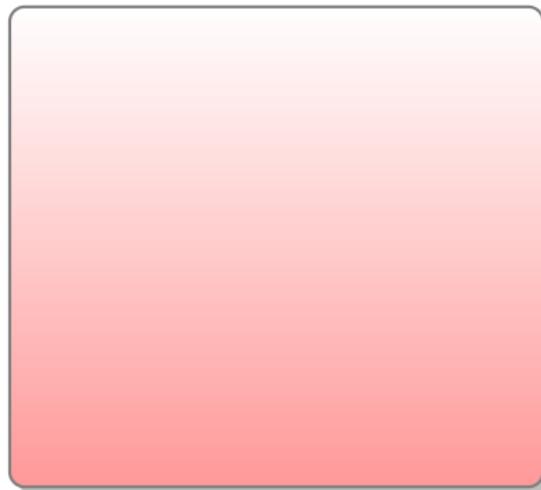


BEHAVIOUR OF THE TUMOUR DURING TREATMENTS



Alonso, F., Serandour, A.A. & Saad, M. Simulating the behaviour of glioblastoma multiforme based on patient MRI during treatments. J. Math. Biol. 84, 44 (2022). <https://doi.org/10.1007/s00285-022-01747-x>

PARAMETER ESTIMATION FOR GLIOBLASTOMA MULTIFORME



Combined state and parameter estimation

- Inverse problem formulation
- Inverse problem resolution
 - Numerical resolution

OUR INVERSE PROBLEM WITH GBM

Find $\theta = (\rho, \delta, \alpha, \beta, \gamma)$.

$$\begin{cases} \frac{\partial u}{\partial t} - \nabla \cdot (D_1 \nabla u) + \nabla \cdot (D_1 \chi u \nabla c) = g_1(u, c, \theta) = \rho u(1-u) - \delta u \\ \frac{\partial c}{\partial t} - \nabla \cdot (D_2 \nabla c) = g_2(u, c, \theta) = \alpha u - \beta c - \gamma u c \\ u(t=0, x) = u_0(x), c(t=0, x) = c_0(x) \\ D_1 \nabla u \cdot \vec{n} - D_1 \chi u \nabla c \cdot \vec{n} = 0, D_2 \nabla c \cdot \vec{n} = 0 \\ d_i = \mathcal{H}(u(t_i, \cdot), c(t_i, \cdot)) \end{cases}$$

Where are errors?

- Precision of the analytical model
- Estimation of the initial state
- Measurements precision

OUR INVERSE PROBLEM WITH GBM

$$\begin{cases} \frac{\partial u}{\partial t} - \nabla \cdot (D_1 \nabla u) + \nabla \cdot (D_1 \chi u \nabla c) = g_1(u, c, \theta) + q_1(t, x) \\ \frac{\partial c}{\partial t} - \nabla \cdot (D_2 \nabla c) = g_2(u, c, \theta) + q_2(t, x) \\ u(t=0, x) = u_0(x) + a_1(x), c(t=0, x) = c_0(x) + a_2(x) \\ D_1 \nabla u \cdot \vec{n} - D_1 \chi u \nabla c \cdot \vec{n} = 0, D_2 \nabla c \cdot \vec{n} = 0 \\ d_i = \mathcal{H}(u(t_i, \cdot), c(t_i, \cdot)) + \epsilon_i \end{cases}$$

Where are errors?

- Precision of the analytical model $\implies q_1(t, x), q_2(t, x) \sim \mathcal{N}(0_{\mathbb{R}^2}, K_{qq})$
- Estimation of the initial state $\implies a_1(t, x), a_2(t, x) \sim \mathcal{N}(0_{\mathbb{R}^2}, K_{aa})$
- Measurements precision $\implies (\epsilon_i)_{1 \leq i \leq N_{mea}} \sim \mathcal{N}(0_{\mathbb{R}^m}, \Sigma_{\epsilon\epsilon})$

Find θ minimizing $\mathcal{J}(u, c, \theta) = e_1(u, c, \theta) + e_2(u, c, \theta) + e_3(u, c, \theta)$.

MINIMIZE $\mathcal{J} \implies$ BAYESIAN APPROACH

$$\begin{aligned}\mathcal{J}(u, c, \theta) &\equiv e_1(u, c, \theta) + e_2(u, c, \theta) + e_3(u, c, \theta) \\&= \iiint_I \int_{\Omega} \mathcal{E}(u, c, \theta)^T(t, x) W_{qq}(t, x, s, y) \mathcal{E}(u, c, \theta)(s, y) dx dy dt ds \\&\quad + \iint_{\Omega} (\Psi_0 - \Phi_0)^T(x) W_{aa}(x, y) (\Psi_0 - \Phi_0)(y) dx dy \\&\quad + \sum_{i=1}^{N_{mea}} (d_i - \mathcal{H}(u(t_i, \cdot), c(t_i, \cdot)))^T W_{\epsilon\epsilon} (d_i - \mathcal{H}(u(t_i, \cdot), c(t_i, \cdot)))\end{aligned}$$

With

$$\mathcal{E}(u, c, \theta) = \begin{pmatrix} \frac{\partial u}{\partial t} - \nabla \cdot (D_1 \nabla u) + \nabla \cdot (D_1 \chi u \nabla c) - g_1(u, c, \theta) \\ \frac{\partial c}{\partial t} - \nabla \cdot (D_2 \nabla c) - g_2(u, c, \theta) \end{pmatrix}$$

$$\Psi_0 = (u(t=0), c(t=0)), \quad \Phi_0 = (u_0, c_0)$$

$$\int_I \int_{\Omega} W_{qq}(t_1, s, x_1, u) \cdot K_{qq}(s, t_2, u, x_2) du ds = \delta(t_1 - t_2) \delta(x_1 - x_2) \mathbb{I}_2$$

HOW TO MINIMIZE \mathcal{J} ?

A minimum (u^*, c^*, θ^*) of \mathcal{J} on E follows

$$d\mathcal{J}(u^*, c^*, \theta^*) \cdot (\delta u, \delta c, \delta \theta) = 0, \text{ for all directions } (\delta u, \delta c, \delta \theta) \in E.$$

In our case, the differential of \mathcal{J} is

$$\begin{aligned} & d\mathcal{J}(u^*, c^*, \theta^*) \cdot (\delta u, \delta c, \delta \theta) \\ &= de_1 + de_2 + de_3 \\ &= d\mathcal{E}^T(u^*, c^*, \theta^*) \cdot (\delta u, \delta c, \delta \theta) \circ W_{qq} \circ \mathcal{E}(u^*, c^*, \theta^*) \\ &+ \delta \Psi_0^T \star W_{aa} \star (\Psi_0^* - \Phi_0) \\ &+ d\mathcal{H}(u^*, c^*) \cdot (\delta u, \delta c)^T W_{\epsilon\epsilon} (d - \mathcal{H}(u^*, c^*)). \end{aligned}$$

$$\circ \equiv \int_I \int_{\Omega} \cdot dx dt, \quad \star \equiv \int_{\Omega} \cdot dx$$

THIS IS HOW TO MINIMIZE \mathcal{J}

We define the variable λ as

$$\begin{aligned}\lambda : (t, x) \in I \times \Omega &\mapsto W_{qq}(t, \cdot, x, \cdot) \circ \mathcal{E}(\Psi, \eta), \\ &= \begin{bmatrix} \lambda_1(t, x) \\ \lambda_2(t, x). \end{bmatrix}\end{aligned}$$

The differential of \mathcal{J} becomes

$$d\mathcal{J}(u^*, c^*, \theta^*) \cdot (\delta u, \delta c, \delta \theta) = d\mathcal{E}^T(u^*, c^*, \theta^*) \cdot (\delta u, \delta c, \delta \theta) \circ \lambda + de_2 + de_3$$

Moreover,

$$\begin{aligned}K_{qq}(t, \cdot, x, \cdot) \circ \lambda &= \begin{bmatrix} (K_{qq}\lambda)_1 \\ (K_{qq}\lambda)_2 \end{bmatrix} = \mathcal{E}(\Psi, \eta)(t, x) \\ \implies \begin{cases} \frac{\partial u}{\partial t} - \nabla \cdot (D_1 \nabla u) + \nabla \cdot (D_1 \chi u \nabla c) = g_1(u, c, \theta) + (K_{qq}\lambda)_1 \\ \frac{\partial c}{\partial t} - \nabla \cdot (D_2 \nabla c) = g_2(u, c, \theta) + (K_{qq}\lambda)_2 \end{cases}\end{aligned}$$

ABOUT λ

Let's rewrite that at (u^*, c^*, θ^*) , for all direction $(\delta u, \delta c, \delta \theta)$

$$d\mathcal{E}^T \circ \lambda^* + \delta \Psi_0^T \star W_{aa} \star (\Psi_0^* - \Phi_0) + d\mathcal{H}^T W_{\epsilon\epsilon} (d - \mathcal{H}(u^*, c^*)) = 0$$

- Develop expressions with the integrals over space and time.
- Perform integration by part to factorize everything by $\delta \Psi = (\delta u, \delta c)$ or $\delta \theta$.

$$\int_{\Omega} \delta \Psi(t_f)^T \lambda^*(t_f) = 0 \quad (1)$$

$$\int_{\Omega} \delta \Psi_0^T (W_{aa} \star (\Psi_0^* - \Phi_0) - \lambda^*(t_0)) = 0 \quad (2)$$

$$\oint_{\partial\Omega} \int_I \delta u^T \cdot ((D_1 \nabla \lambda_1 - D_1 \chi \lambda_1 \nabla c) \cdot \vec{n}) = 0 \quad (3)$$

$$\oint_{\partial\Omega} \int_I \delta c^T \cdot ((D_2 \nabla \lambda_2 - D_1 \chi u \nabla \lambda_1) \cdot \vec{n}) = 0 \quad (4)$$

$$(5)$$

ABOUT λ

Let's rewrite that at (u^*, c^*, θ^*) , for all direction $(\delta u, \delta c, \delta \theta)$

$$d\mathcal{E}^T \circ \lambda^* + \delta \Psi_0^T \star W_{aa} \star (\Psi_0^* - \Phi_0) + d\mathcal{H}^T W_{\epsilon\epsilon} (d - \mathcal{H}(u^*, c^*)) = 0$$

$$\begin{aligned} \int_I \int_{\Omega} \delta u^T \cdot & \left(\frac{\partial \lambda_1}{\partial t} - \nabla \cdot (D_1 \nabla \lambda_1) - D_1 \chi \nabla c \nabla \lambda_1 \right. \\ & \left. + \frac{\partial g_1}{\partial u} \lambda_1 + \frac{\partial g_1}{\partial c} \lambda_2 + \mathcal{C}(u, c)_1 \right) = 0 \quad (6) \end{aligned}$$

$$\begin{aligned} \int_I \int_{\Omega} \delta c^T \cdot & \left(\frac{\partial \lambda_2}{\partial t} - \nabla \cdot (D_2 \nabla \lambda_2) + \nabla \cdot (D_1 \chi u \nabla \lambda_1) \right. \\ & \left. + \frac{\partial g_2}{\partial u} \lambda_1 + \frac{\partial g_2}{\partial c} \lambda_2 + \mathcal{C}(u, c)_2 \right) = 0 \quad (7) \end{aligned}$$

$$\delta \theta^T \left(\int_I \int_{\Omega} \begin{bmatrix} \frac{\partial g_1}{\partial \rho} & \frac{\partial g_1}{\partial \delta} & \frac{\partial g_1}{\partial \alpha} & \frac{\partial g_1}{\partial \beta} & \frac{\partial g_1}{\partial \gamma} \\ \frac{\partial g_2}{\partial \rho} & \frac{\partial g_2}{\partial \delta} & \frac{\partial g_2}{\partial \alpha} & \frac{\partial g_2}{\partial \beta} & \frac{\partial g_2}{\partial \gamma} \end{bmatrix}^T \cdot \begin{bmatrix} \lambda_1 \\ \lambda_2 \end{bmatrix} dt dx \right) = \delta \theta^T \mathcal{G}(\theta, u, c, \lambda) = 0 \quad (8)$$

SOLUTION OF THE INVERSE PROBLEM

$$\begin{cases} \frac{\partial u}{\partial t} - \nabla \cdot (D_1 \nabla u) + \nabla \cdot (D_1 \chi u \nabla c) = g_1(u, c, \theta) + (K_{qq} \lambda)_1, \\ \frac{\partial c}{\partial t} - \nabla \cdot (D_2 \nabla c) = g_2(u, c, \theta) + (K_{qq} \lambda)_2, \\ u(t=0, x) = u_0(x) + (K_{aa} \lambda^0)_1, c(t=0, x) = c_0(x) + (K_{aa} \lambda^0)_2, \\ D_1 \nabla u \cdot \vec{n} - D_1 \chi u \nabla c \cdot \vec{n} = 0, D_2 \nabla c \cdot \vec{n} = 0, \end{cases} \quad (\text{KS 1})$$

$$\begin{cases} \frac{\partial \lambda_1}{\partial t} - \nabla \cdot (D_1 \nabla \lambda_1) - D_1 \chi \nabla c \cdot \nabla \lambda_1 = -\frac{\partial g_1}{\partial u} \lambda_1 - \frac{\partial g_1}{\partial c} \lambda_2 - \mathcal{C}(u, c)_1, \\ \frac{\partial \lambda_2}{\partial t} - \nabla \cdot (D_2 \nabla \lambda_2) + \nabla \cdot (D_1 \chi u \nabla \lambda_1) = -\frac{\partial g_2}{\partial u} \lambda_1 - \frac{\partial g_2}{\partial c} \lambda_2 - \mathcal{C}(u, c)_2, \\ \lambda(t=t_f, x) = 0, \\ (D_1 \nabla \lambda_1 - D_1 \chi \lambda_1 \nabla c) \cdot \vec{n} = (D_2 \nabla \lambda_2 - D_1 \chi u \nabla \lambda_1) \cdot \vec{n} = 0, \end{cases} \quad (\text{KS 2})$$

$$\mathcal{G}(\theta, u, c, \lambda) = \int_I \int_{\Omega} \begin{bmatrix} \frac{\partial g_1}{\partial \rho} & \frac{\partial g_1}{\partial \delta} & \frac{\partial g_1}{\partial \alpha} & \frac{\partial g_1}{\partial \beta} & \frac{\partial g_1}{\partial \gamma} \\ \frac{\partial g_2}{\partial \rho} & \frac{\partial g_2}{\partial \delta} & \frac{\partial g_2}{\partial \alpha} & \frac{\partial g_2}{\partial \beta} & \frac{\partial g_2}{\partial \gamma} \end{bmatrix}^T \cdot \begin{bmatrix} \lambda_1 \\ \lambda_2 \end{bmatrix} dt dx = 0_{\mathbb{R}^5}, \quad (\text{KS 3})$$

NUMERICAL RESOLUTION

- Let's fix a value of θ^k .
- We find the associated value of $u^k(\theta^k)$, $c^k(\theta^k)$ and $\lambda^k(\theta^k)$.
- Find a better value of θ trying to get $\mathcal{G}(\theta, u, c, \lambda) = 0_{\mathbb{R}^5}$
- $\theta^{k+1} \leftarrow$ Newton-Raphson method to cancel out $\theta \mapsto \mathcal{G}(\theta, u^k, c^k, \lambda^k)$

NUMERICAL RESOLUTION

$$\theta = [0.2, 0.1, 0.1, 0.03, 0.08]$$

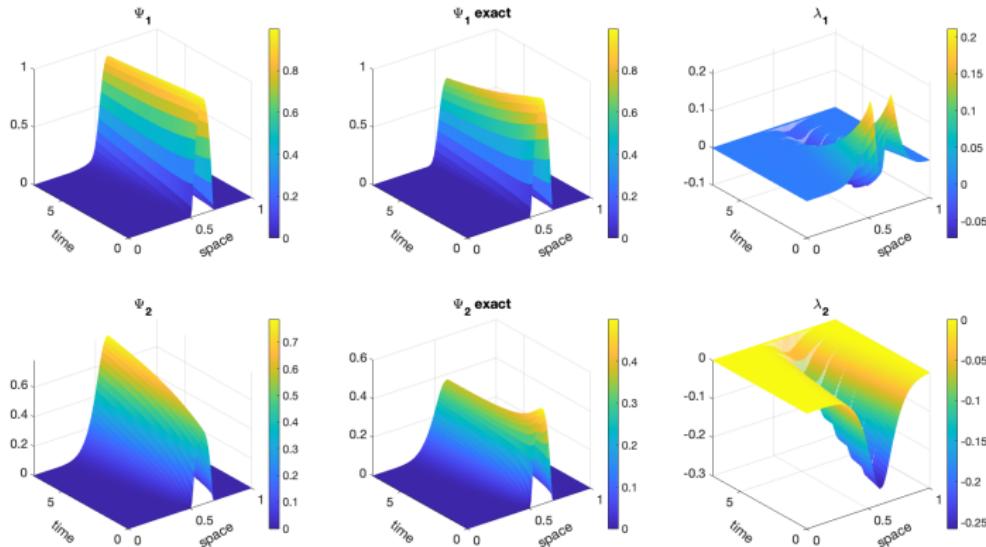


Figure: $\theta^0 \approx [0.2864, 0.0647, 0.3075, 0.0529, 0.1281]$

NUMERICAL RESOLUTION

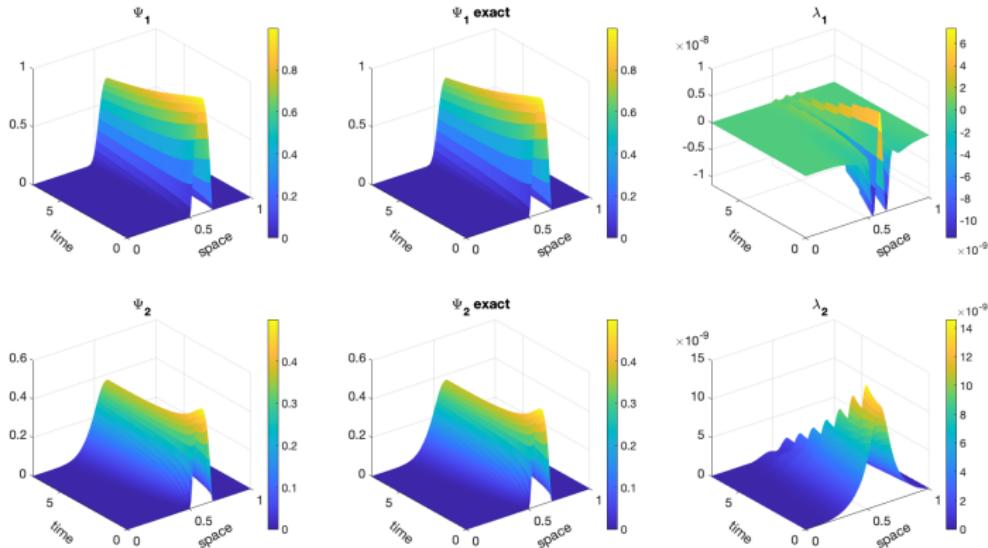


Figure: Final decision

NUMERICAL RESOLUTION

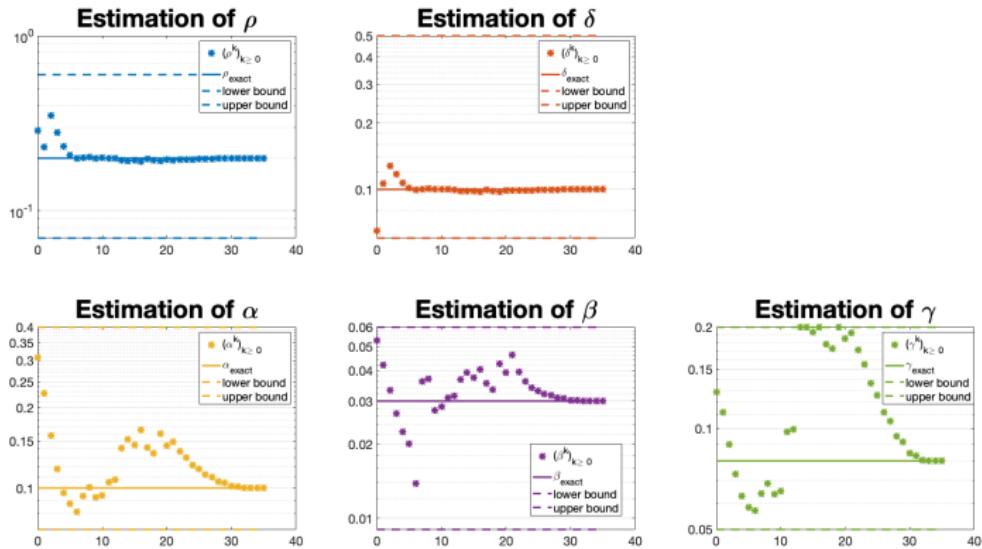


Figure: Iteration of θ^k

THANK YOU FOR YOUR ATTENTION

