# Modelisation and optimal control for tumor growth models


**Hussein RAAD**

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# Outline

- Introduction
- Motivation and Objectives
- Theoretical Results
- Numerical Results
- Conclusion and perspective

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- ◇ Lactate is considered an important hallmark of glioma development.

- Related Literature (tumor growth):
  - Math modeling of tumor growth (glioma) : P. Tracqui (1995), K.R. Swanson, J.D. Murray, E.C. Alvord, E. Mandonnet, R. Guillevin, ...
  - Math modeling of tumor growth and chemotherapy: J.D. Murray, E.C. Alvord, K.R. Swanson, G. Powathil, M. Kohandel, V. Calvez, E. Grenier, H. Garcke, K. Lam, E. Rocca...

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- Proposed model:

$$\partial_t \varphi + \alpha \Delta^2 \varphi - \Delta f(\varphi) + (1-\omega)\frac{k(u)\varphi}{k' + |\varphi|} = J(u) \quad (1)$$

$$\partial_t u - div(D(x)\nabla u) = (a(\varphi) - v)u(1 - \frac{u}{N}) - uP(\varphi) \quad (2)$$

where $\varphi$ is the lactate concentration, $u$ is the tumor density, $\omega$ and $v$ represent treatments (chemotherapy).

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- ◇ Compare and calibrate the mathematical model to medical data.
- ◇ Simulate the evolution of the tumor and lactates and optimize the dose of treatments to be administered to the patient to reduce them.
- ◇ Utilization of the lactate equation:

$$\partial_t \varphi + \alpha \Delta^2 \varphi - \Delta f(\varphi) + (1-\omega)\frac{k\varphi}{k' + |\varphi|} = J \quad \text{in}\, \Omega \times (0, T], \tag{3}$$

$$\frac{\partial \varphi}{\partial \nu} = \frac{\partial \Delta \varphi}{\partial \nu} = 0 \qquad \text{on} \quad \partial\Omega \tag{4}$$

$$\varphi|_{t=0} = \varphi_0 \tag{5}$$

H.Raad, L.Cherfils, C.Allery, R. Guillevin. Optimal control of a model for brain lactate kinetics, Asymptotic Analysis, pp. 1–32, 2023.

◇ Insertion of the following functional:

$$\mathcal{J}(\varphi,\omega) = \frac{1}{2}\int_0^T \int_\Omega \left(\varphi - \widehat{\varphi}\right)^2 dxdt + \frac{1}{2}\int_\Omega \left(\varphi(T) - \widehat{\varphi}(T)\right)^2 dx + \frac{\beta}{2}\int_0^T \int_\Omega \omega^2 dxdt.$$

where $\widehat{\varphi}$ is the piecewise continuous target function.

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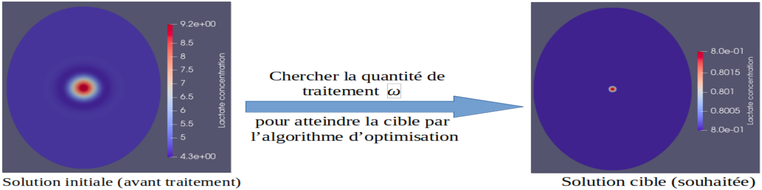


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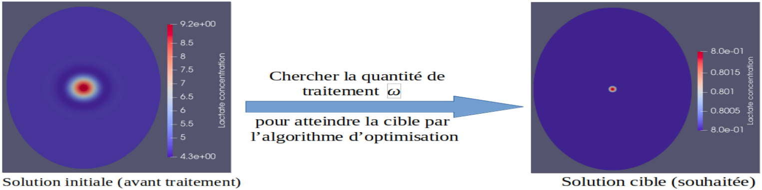


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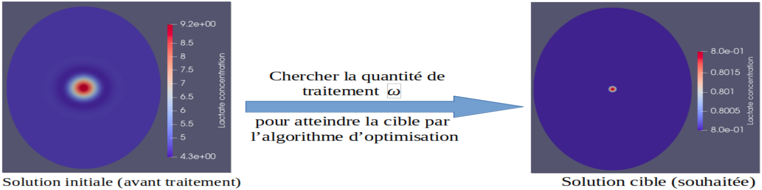


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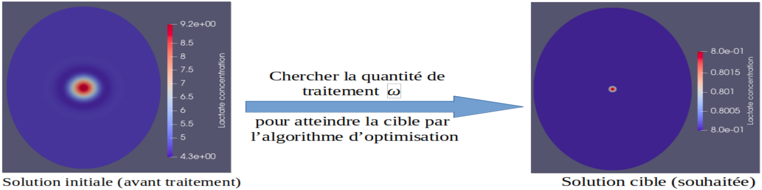


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◇ This work consists in two parts:

- ◇ Theoretical part: propose a model and study the well-posed character of the equations.
- ◇ Numerical part: identify for each patient the parameters $(k, k', J...)$ involved in the equations and optimize the treatment parameters $\omega$ and $v$.

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# Notations

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◇ The constants $k, k', \alpha$ and $J$ are positive.

◇ Existence and uniqueness of the Cahn-Hilliard problem.

### Theorem

*We assume that* $\varphi_0$ *is given such that* $\varphi_0 \in H^1(\Omega)$*.*
*Then* (3)-(5) *has a unique weak solution* $\varphi$*, such that*
$\varphi \in L^\infty([0,T], H^1(\Omega)) \cap C([0,T]; H^1(\Omega)) \cap L^2(0,T; H^3(\Omega))$ *and*
$\frac{\partial \varphi}{\partial t} \in L^2([0,T], H^{-1}(\Omega))\ \forall T > 0$.

**Remark:**

◇ We can rewrite (3)-(5) in the equivalent form

$$\partial_t \varphi - \Delta\mu + (1-\omega) g(\varphi) = J \qquad \text{in } \Omega \times (0,T], \tag{6}$$

$$\mu = -\alpha\Delta\varphi + f(\varphi) \quad \text{in } \Omega \times (0,T], \tag{7}$$

$$\frac{\partial\varphi}{\partial\nu} = \frac{\partial\mu}{\partial\nu} = 0 \quad \text{on } \partial\Omega \times (0,T] \tag{8}$$

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◇ Let us define the control-to-state operator $S$:

$$\omega \in \mathcal{U}_{ad} \mapsto S(\omega) = (\varphi, \mu)$$

where $(\varphi, \mu)$ is the unique weak solution to the equivalent form with initial data ($\varphi_0$ and parameter $\omega$) over $[0, T]$.

- Existence and uniqueness of the linearized problem and the adjoint problem.

## Theorem

*For any $\omega \in \mathcal{U}_{ad}$, there exists a unique $(\xi, \pi)$ associated to $S(\omega) = (\varphi, \mu)$ solution of the adjoint problem with*

$\xi \in L^2(0, \tau^*; H^2(\Omega)) \cap H^1(0, \tau^*; (H^2(\Omega))') \cap C^0([0, \tau^*]; L^2(\Omega))$

$\pi \in L^2(0, \tau^*; L^2(\Omega))$

*satisfying*

$$-\langle \partial_t \xi, p \rangle_{H^{-2}, H^2} + \alpha \int_\Omega \pi \Delta p \, dx + (1 - \omega^*) g'(\varphi^*) \xi p \, dx$$

$$- \int_\Omega \left( f'(\varphi^*) \pi p + (\varphi^* - \hat{\varphi}) p + \frac{1}{r} \chi_{[\tau^* - r, \tau^*]}(t) (\varphi^* - \hat{\varphi}) p \right) dx = 0$$

$$\int_\Omega \pi q dx + \int_\Omega \nabla \xi \nabla q dx = 0$$

*for a.e. $t \in (0, \tau^*)$ and $\forall q \in H^1(\Omega)$ and $p \in H^2(\Omega)$.*

◇ Existence of a minimizer for the objective functional.

**Theorem**

*Let* $\omega \in \mathcal{U}_{ad}$ *and* $\tau \in (0, T]$ *and let* $\varphi$ *be a solution of* (3) *corresponding to* $\omega$.

*Then, there exists* $\omega^* \in \mathcal{U}_{ad}$ *and* $\tau^* \in (0, T]$ *such that:*

$$\inf_{(\omega,\tau)\in\mathcal{U}_{ad}\times(0,T]} \mathcal{J}(\varphi,\omega,\tau) = \mathcal{J}(\varphi^*,\omega^*,\tau^*)$$

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◇ Fréchet differentiability of the functional with respect to time.

◇ Simplification of the first-order optimality condition.

**Remark:** We could also have put the control function on $J$ instead of $k$, meaning this time that the treatment inhibits the lactate production in the tumor cells.

The equation then reads:

$$\partial_t \varphi + \alpha \Delta^2 \varphi - \Delta f(\varphi) + g(\varphi) = (1-\omega)J \quad \text{in}\, \Omega \times (0, T],$$

$$\frac{\partial \varphi}{\partial \nu} = \frac{\partial \Delta \varphi}{\partial \nu} = 0 \qquad \text{on} \quad \partial \Omega$$

$$\varphi_{|t=0} = \varphi_0$$

We can prove similar results with minor modifications.

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- ◇ we aimed to identify the patient parameters $k, k'$ and $J$ from the medical data.

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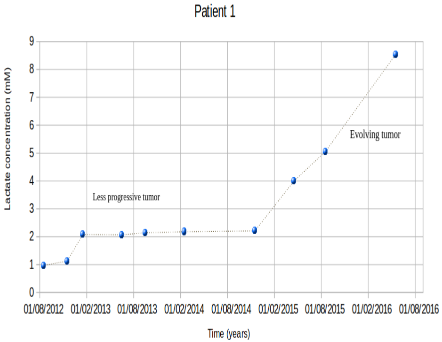
- we used the following ordinary differential equation:

$$\partial_t \varphi + \frac{k\varphi}{k' + \varphi} = J$$

$\varphi$: the concentration of lactate
$k$ : the maximum transport speed between blood and cell.
$k'$ : the modified positive Michaelis-Menten constant.
$J$ : the phenomena of lactate production and consumption.

The evolution of lactate levels over the years.



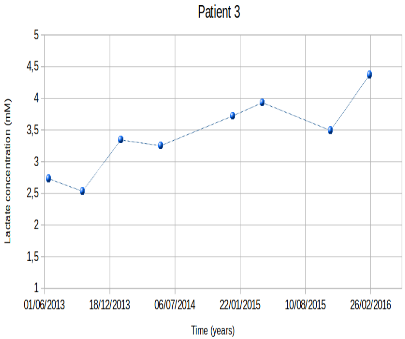




Fig.2 : Medical data from the University Hospital of Poitiers

The parameters of these two patients were identified for the both phases.

**Patient 1:**
For the stable tumor phase we obtained $J_1 = 0.726\ mM/month$, $k_1 = 1,122\ mM/month$ and $k' = 1.31\ mM$.
For the evolving tumor phase we obtained $J_2 = 2.05$, $k_2 = 2.097$ and $k' = 1.31$.

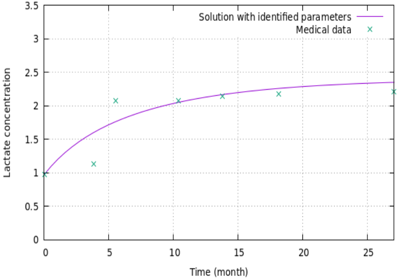



Fig.3a : Stable tumor phase.

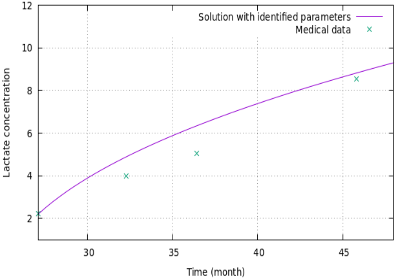



Fig.3b : Evolving tumor phase.

**Patient 3:**
For the stable tumor phase we obtained $J_1 = 2.034\ mM/month$, $k_1 = 2.292\ mM/month$ and $k' = 0.515\ mM$.
For the evolving tumor phase we obtained $J_2 = 3.44$, $k_2 = 3.87$ and $k' = 0.515$.

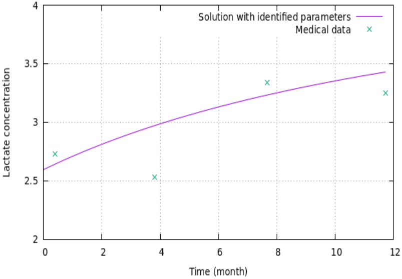



Fig.4a : Stable tumor phase.

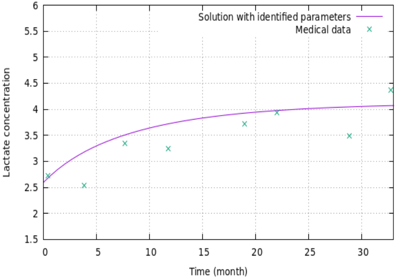
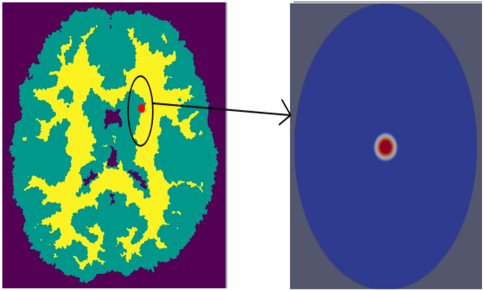



Fig.4b : Evolving tumor phase.

## Treatment optimization



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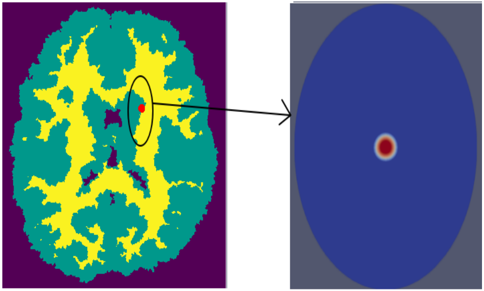

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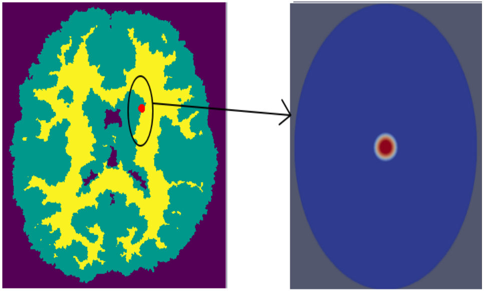

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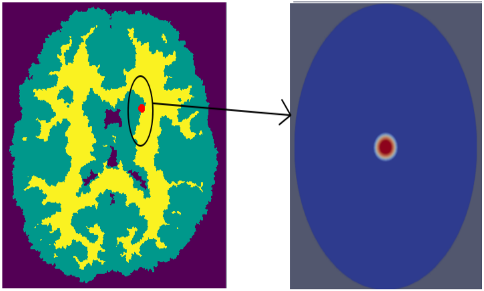

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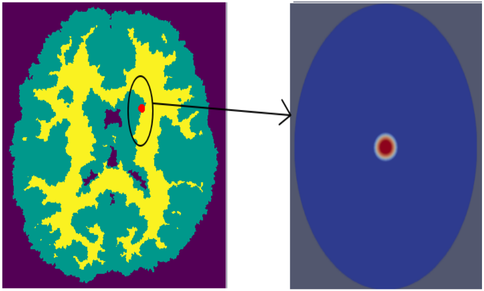


- $\Omega$ is an ellipse parametrized by $x = 6cos\theta$ and $y = 8sin\theta$, with $\theta \in [0, 2\pi]$
- The initial tumor area is delimited by a circle of radius $r = 0.8$.
- The target value of the lactate concentration is taken as $\hat{\varphi} = 0.8$ mM.
- $\alpha = 0.01$ and the potential $f(\varphi) = 0.002\varphi(\varphi - 5)(\varphi - 10)$.

◇ With the algorithm we obtain $\omega^* = 0.804$ (patient 1).

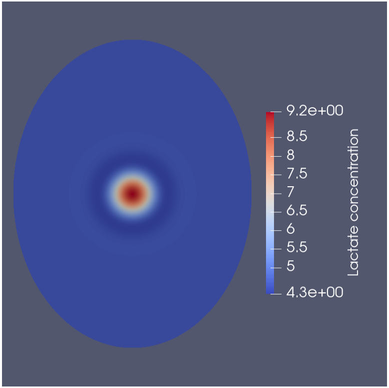



Fig.5a : Spatial distribution of lactate levels without treatment at T=6 months.

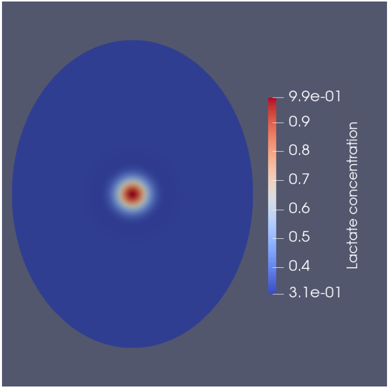
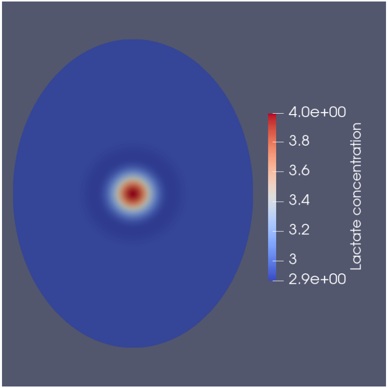



Fig.5b : Spatial distribution of lactate levels with treatment at T=6 months.

◇ With the algorithm we obtain $\omega^* = 0.322$ (patient 3).

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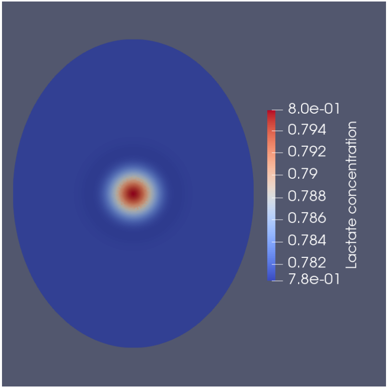


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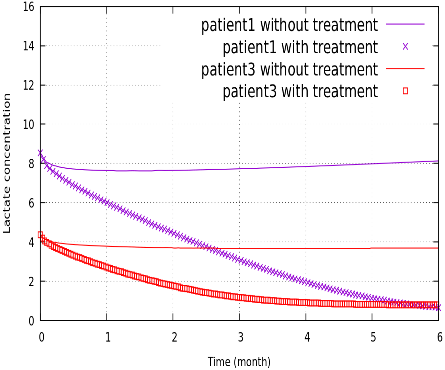


Fig.7 : Temporal evolution of lactate levels in the tumor area.

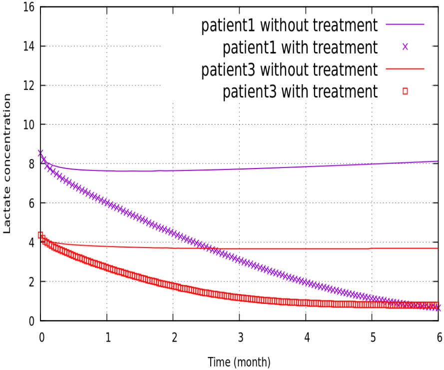


Fig.7 : Temporal evolution of lactate levels in the tumor area.

If we compare the lactate level inside the tumor area, we see that it decreased with treatment while it increased without treatment.

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- Conclusion and perspective

# Conclusion and perspective

◇ The mathematical modeling and the results are encouraging and consistent with the medical knowledge.

# Conclusion and perspective

- The mathematical modeling and the results are encouraging and consistent with the medical knowledge.

- Our aim now is to study the coupling with the tumor equation (2) :

$$\begin{cases} \partial_t \varphi + \alpha \Delta^2 \varphi - \Delta f(\varphi) + \dfrac{k(u)\varphi}{k' + |\varphi|} = (1-\omega) J(u) \\ \\ \partial_t u - div(D(x)\nabla u) = (a(\varphi) - v) u (1 - \frac{u}{N}) - u P(\varphi) \end{cases}$$

Thank you for your attention