Computer Simulations of Heat Flow for Cancer Treatment

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July 07, 2023

Overview

1. Introduction
   - Motivation
   - Hyperthermia
2. First Study Case
   - Methods
   - Numerical Experiments
3. Second Study Case
   - Methods
   - Numerical Experiments
4. Conclusions and Future Works

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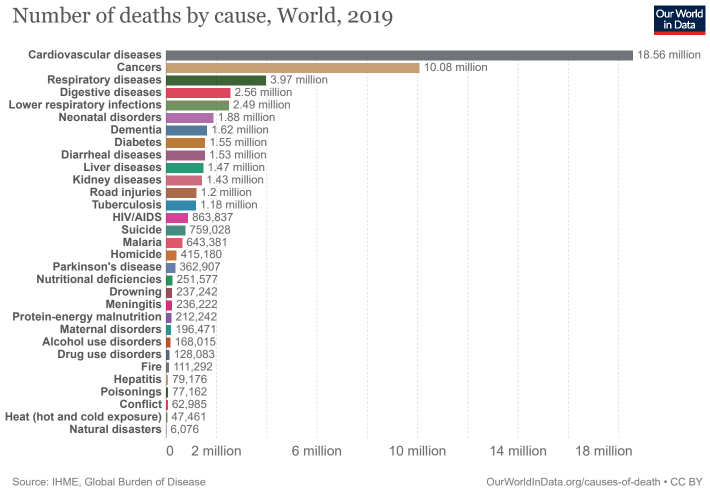
Motivation

The second biggest cause of death worldwide



Hyperthermia

- Overheat the tumour tissue
- Semi-invasive treatment
- Magnetic field using low frequency
- bioheat transfer using Pennes model

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Bioheat Model

We considers the following Pennes model for simulate the bioheat [1]

$$
\begin{cases}
\rho c \dfrac{\partial T}{\partial t} = \nabla \cdot k \nabla T + \omega_b \rho_b c_b (T_a - T) + Q_m + Q_r & \text{in } \Omega \times I \\
k \nabla T \cdot \vec{n} = 0 & \text{in } \partial\Omega \times I \\
T(\cdot, 0) = T_0 & \text{in } \Omega,
\end{cases}
$$

[1] Fatigate, G. R., Lobosco, M., and Reis, R. F. (2023). A 3D Approach Using a Control Algorithm to Minimize the Effects on the Healthy Tissue in the Hyperthermia for Cancer Treatment. Entropy, 25(4), 684.

Assumptions

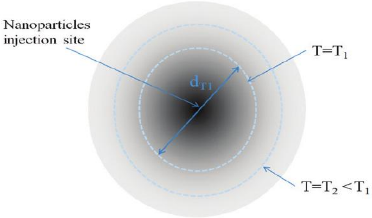
The following simplifications are considered when using Pennes' model:

- Equilibrium site: The heat transfer between blood and tissue occurs in capillaries;
- Blood perfusion: The blood flow in capillaries is considered isotropic;
- Vascular architecture: The local vascular geometry is not considered;
- Blood temperature: The body core temperature is the same as that reached by the capillaries.

Heat Source

The specific absorption rate (SAR) [2] around an injection site is approximated by:

$$Q_r = \sum_{i=1}^{N_p} A e^{-r(\vec{x})_i^2 / r_{0,i}^2}$$



where N_p is the number of nanoparticle injections into the tumor, A is the maximum heat generation rate, r is the distance to the injection point, and r_0 is the hyperthermia coverage radius.

[2] Salloum, M., Ma, R., and Zhu, L. (2009). Enhancement in treatment planning for magnetic nanoparticle hyperthermia: optimization of the heat absorption pattern. International Journal of Hyperthermia, 25(4), 309-321.

Finite Difference Method

Bidimensional domain

The solution was approximated using the FDM in a heterogeneous medium using a FTCS ...

$$T_{i,j}^{n+1} = \frac{h_t}{\rho c}\left(\varphi_{dif}(T^n) + \omega_b \rho_b c_b (T_a - T_{i,j}^n) + Q_m + Q_r\right) + T_{i,j}^n,$$

where

$$\varphi_{dif}(T^n) = \frac{\kappa_{i+1/2,j}(T_{i+1,j,k}^n - T_{i,j}^n) - \kappa_{i-1/2,j}(T_{i,j}^n - T_{i-1,j}^n)}{h^2} + \frac{\kappa_{i,j+1/2}(T_{i,j+1}^n - T_{i,j}^n) - \kappa_{i,j-1/2}(T_{i,j}^n - T_{i,j-1,k}^n)}{h^2}.$$

Finite Difference Method

Three-dimensional domain

The solution was approximated using the FDM in a heterogeneous medium using a FTCS ...

$$T^{n+1}_{i,j,k} = \frac{h_t}{\rho c}\left(\varphi_{dif}(T^n) + \omega_b \rho_b c_b (T_a - T^n_{i,j,k}) + Q_m + Q_r\right) + T^n_{i,j,k},$$

where

$$\begin{aligned}\varphi_{dif}(T^n) = & \frac{\kappa_{i+1/2,j,k}(T^n_{i+1,j,k} - T^n_{i,j,k}) - \kappa_{i-1/2,j,k}(T^n_{i,j,k} - T^n_{i-1,j,k})}{h^2} + \\ & \frac{\kappa_{i,j+1/2,k}(T^n_{i,j+1,k} - T^n_{i,j,k}) - \kappa_{i,j-1/2,k}(T^n_{i,j,k} - T^n_{i,j-1,k})}{h^2} + \\ & \frac{\kappa_{i,j,k+1/2}(T^n_{i,j,k+1} - T^n_{i,j,k}) - \kappa_{i,j,k-1/2}(T^n_{i,j,k} - T^n_{i,j,k-1})}{h^2},\end{aligned}$$

Differential Evolution

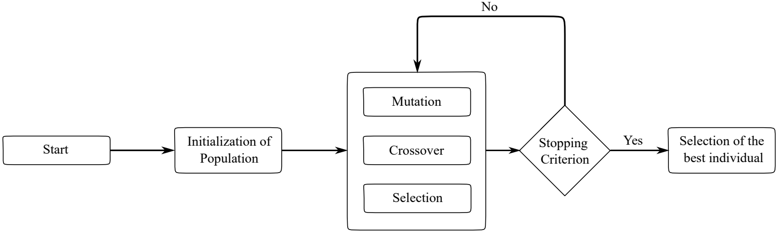


Figure 1: Differential Evolution Scheme

Bioheat

Ruy

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Differential Evolution

Minimization problem

$$\min O(p) = 300 - N_t - (100 - N_h) - 100\beta, \tag{1}$$

$$\beta = \begin{cases} 1, & \text{if } \; N_t = 100\% \\ 0, & \text{otherwise.} \end{cases} \tag{2}$$

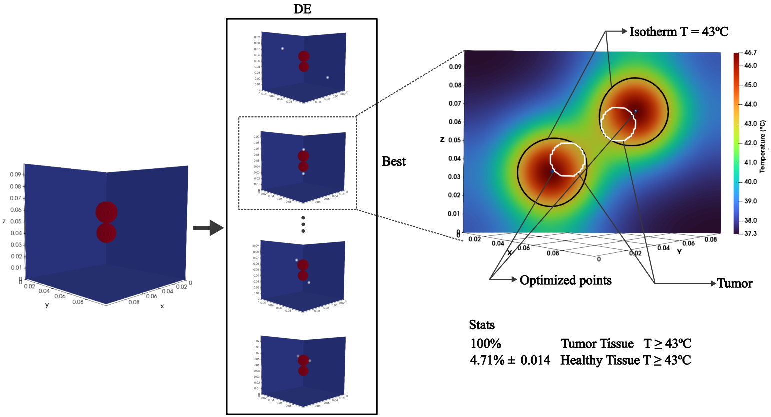
Mutation (best/1/bin)

$$X_p^{i+1} = X_{best}^i + F * (X_a^i - X_b^i). \tag{3}$$

Selection

$$U^{i+1} = \begin{cases} X_p^{i+1}, & \text{if } \; r_i \leq C \\ X_r^i, & \text{otherwise.} \end{cases} \tag{4}$$

Graphic Abstract



Two-dimensional

- The simulation scenario is a square domain
- Length equal $0.1m$
- All the tumor are circular
- Radius equal to $0.01m$
- Standard deviation smaller than 2%

Two-dimensional

First Scenario

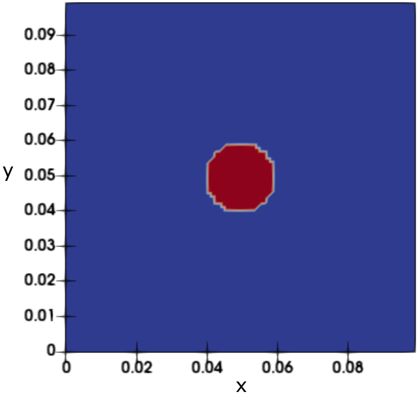


Figure 2: The tumor has a radius of 0.01m, and its center is positioned at (0.050, 0.050)

First Scenario

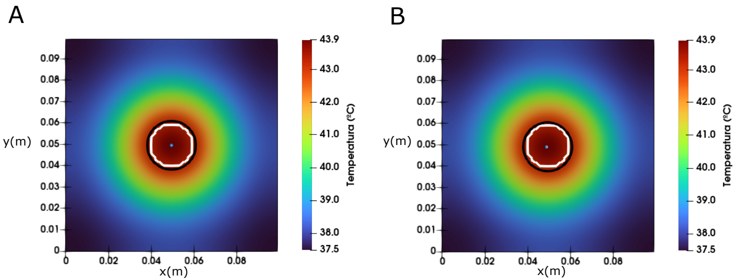


Figure 3: The healthy tissue affected by the treatment. Panel A is the naive solution, and Panel B is the DE answer.

First Scenario

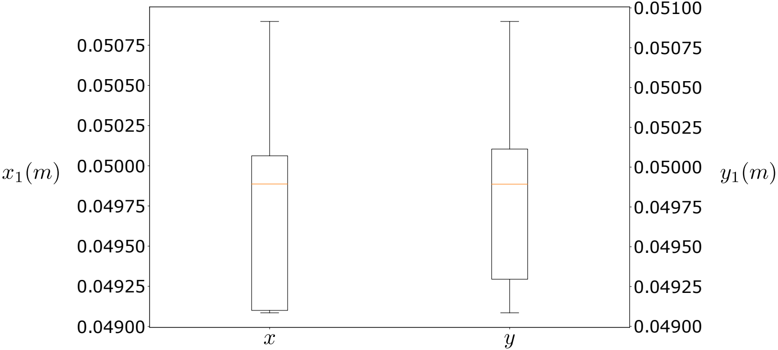


Figure 4: The boxplot presents the variation of 10 optimization processes for the first scenario

Second Scenario

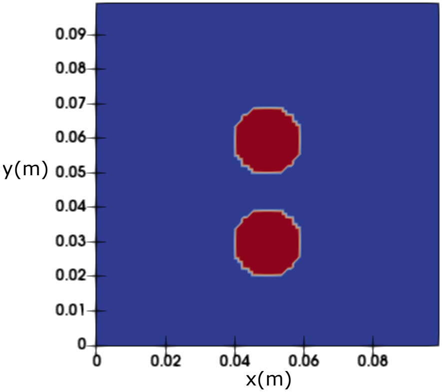


Figure 5: The tumors have a radius of 0.01m each and their centers are positioned at (0.050, 0.030), and (0.050, 0.060)

Second Scenario

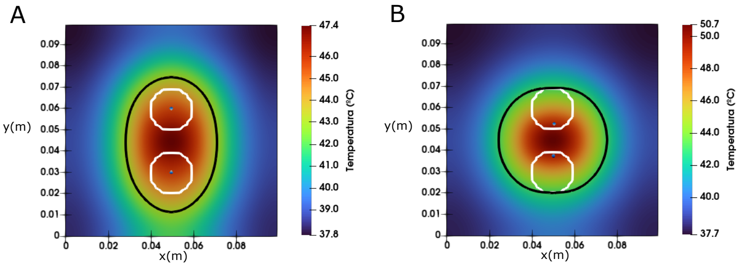


Figure 6: The healthy tissue affected by the treatment is reduced from 16.51% to 15.18%

Second Scenario

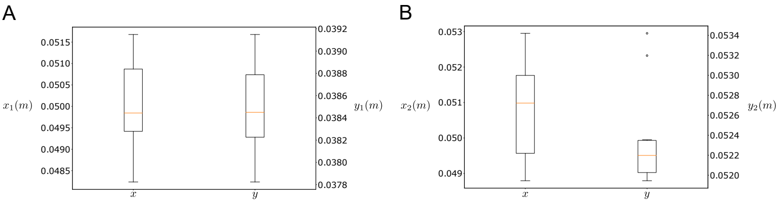


Figure 7: The boxplot presents the variation of 10 optimization processes for the second scenario

Third Scenario

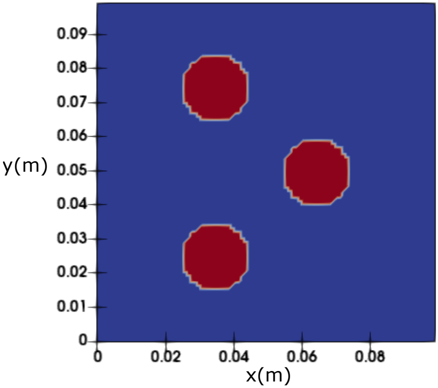


Figure 8: The tumors have a radius of 0.01m each and their centers are positioned at (0.035, 0.025), (0.065, 0.050) and (0.035, 0.075)

Third Scenario

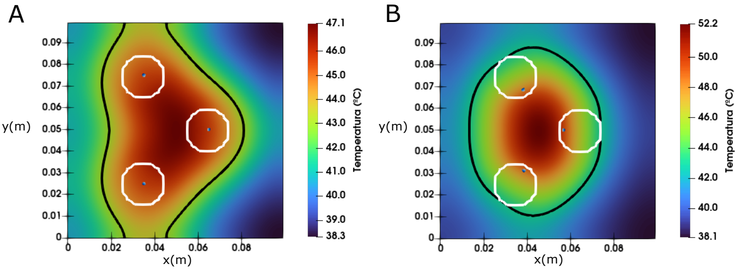


Figure 9: The healthy tissue affected by the treatment is reduced from 40% to 30%

Third Scenario

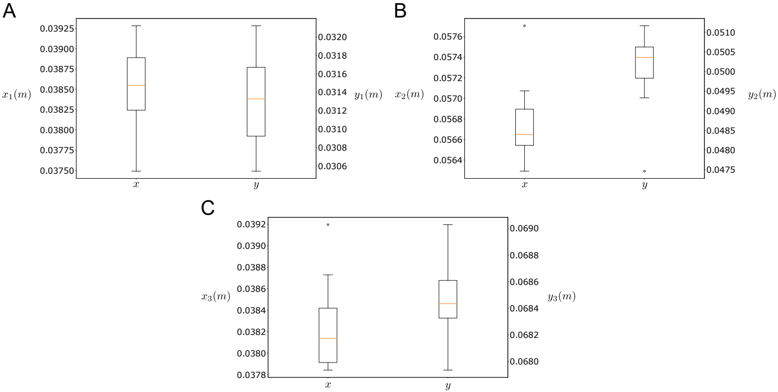


Figure 10: The boxplot presents the variation of 10 optimization processes for the third scenario

Three-dimensional

Three-dimensional

- The simulation scenario is a cube domain
- Length equal $0.1m$
- All the tumors are spherical
- Radius equal to $0.01m$
- Standard deviation smaller than 10^{-2}

First Scenario

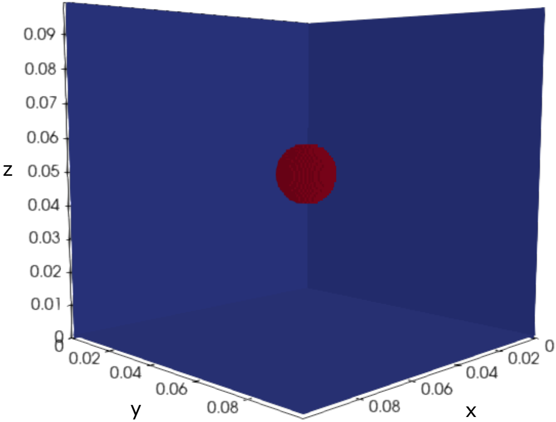
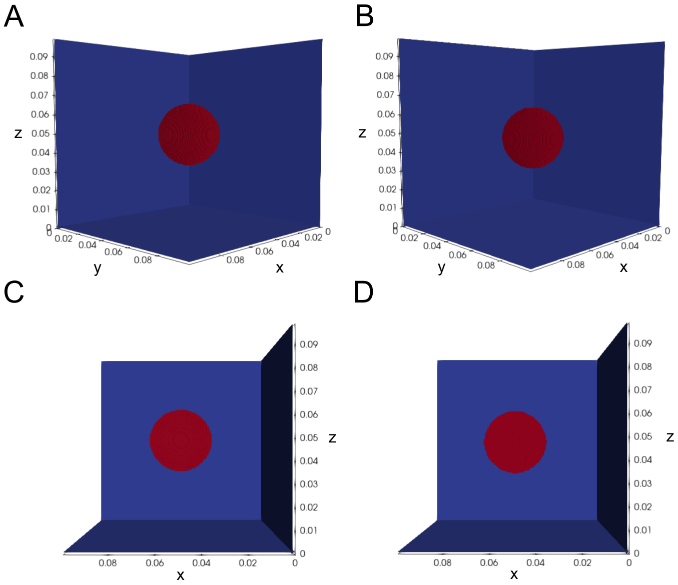
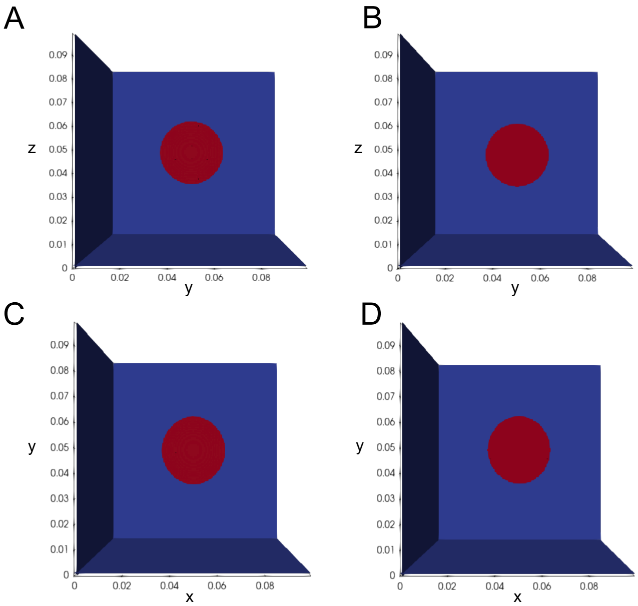


Figure 11: The tumor has a radius of 0.01m, and its center is positioned at (0.050, 0.050, 0.050)

First Scenario



First Scenario



First Scenario

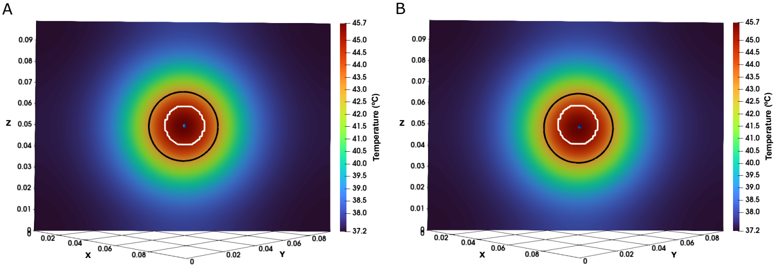


Figure 12: In both cases, the total tissue damage of the tumor was observed, and 1.53% of healthy tissue was damaged.

Second Scenario

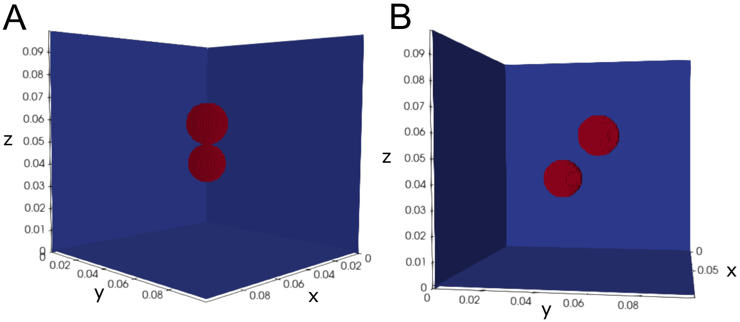
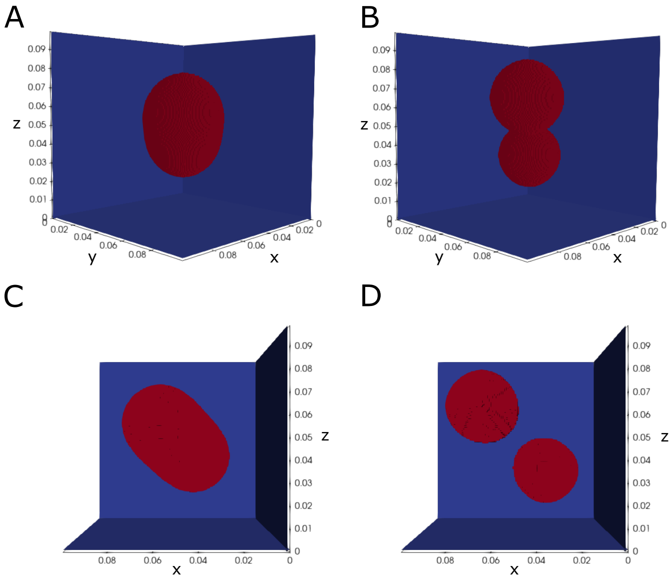
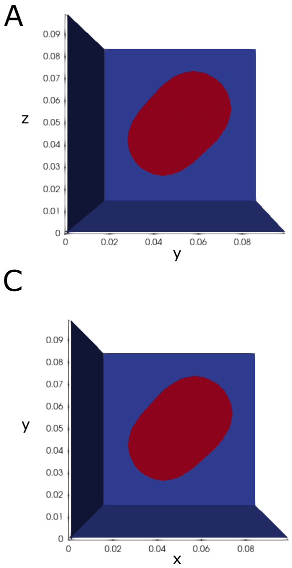


Figure 13: The tumor has a radius of 0.01m, and its centers are positioned at (0.040, 0.040, 0.040) and (0.060, 0.060, 0.060

Second Scenario



Second Scenario



Second Scenario

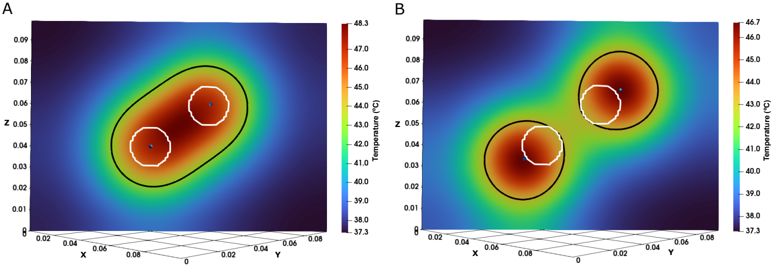


Figure 14: The naive version resulted in 7.03% of healthy tissue damage, while the optimized version resulted in 4.71% of damage

Third Scenario

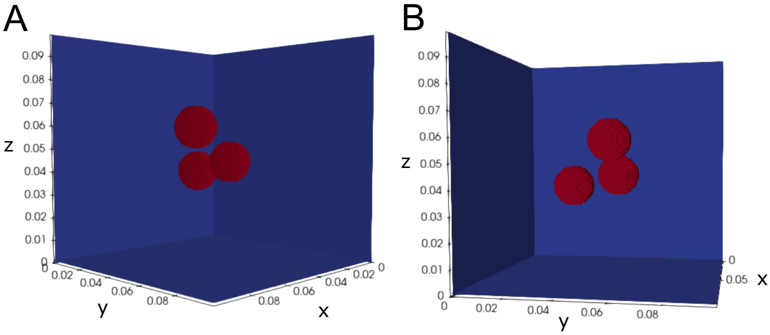
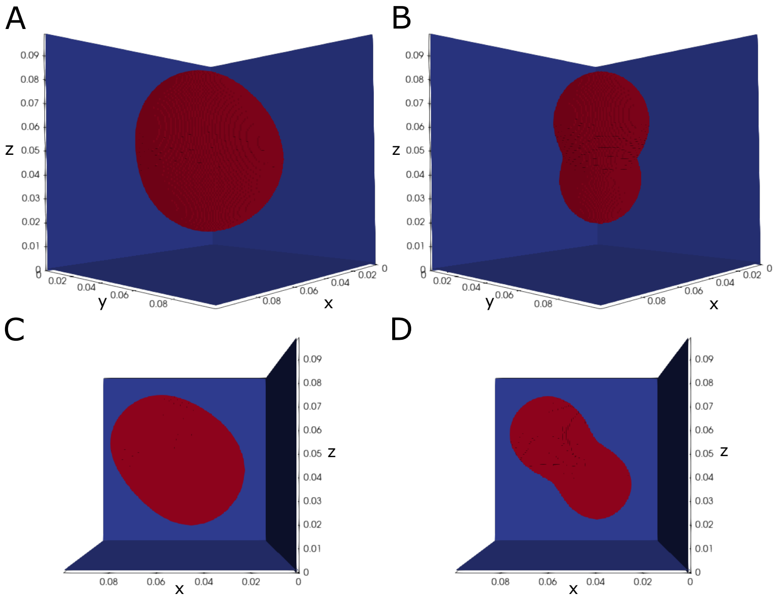
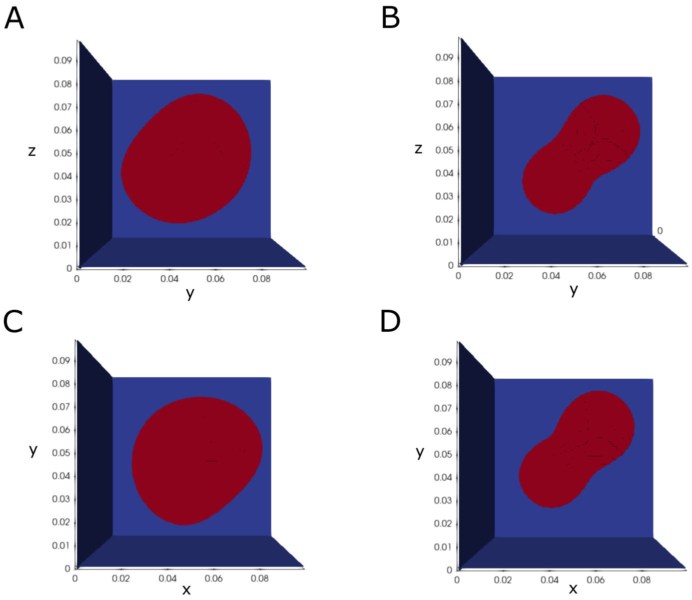


Figure 15: The tumor has a radius of 0.01m, and its centers are positioned at (0.045, 0.035, 0.040), (0.045, 0.055, 0.045), and (0.065, 0.055, 0.060)

Third Scenario

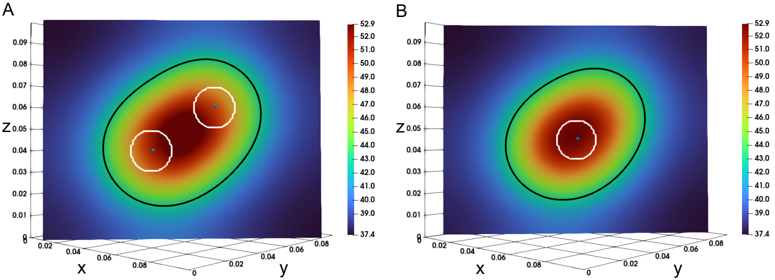


Third Scenario



Third Scenario

Naive



Third Scenario

Optimized

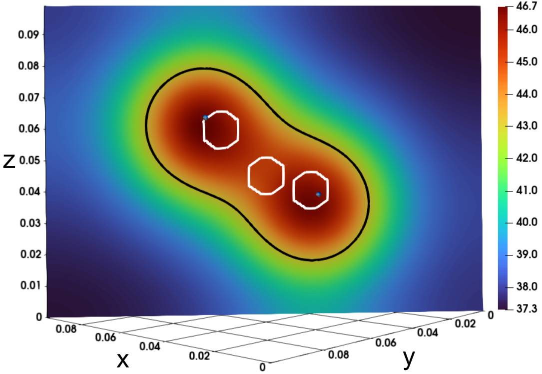


Figure 16: The naive version resulted in 14.05% of healthy tissue damage, while the optimized version resulted in 5.78% of damage

GPU Performance Evaluation

Table 1: The reported execution times are the mean for 10 executions, with a confidence interval of 95%.

Mesh ($N_x \times N_y \times N_z$)	**CPU time (s)**	**GPU time (s)**	**Speedup**
$64 \times 64 \times 64$	90.7 ± 0.55	1.1 ± 0.002	82.5
$128 \times 128 \times 128$	759.2 ± 2.38	9.0 ± 0.04	84.4
$256 \times 256 \times 256$	$5{,}998.96 \pm 22.60$	72.1 ± 0.05	83.2

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Porous Medium Model

On the other hand, considering the following porous medium model for simulate bioheat [3]

$$\begin{cases} \sigma \dfrac{\partial T}{\partial t} + \varepsilon(\rho c_p)_b \mathbf{u}_b \cdot \nabla T = \nabla\left(\kappa \cdot \nabla T\right) + (1-\varepsilon)\left(Q_m + Q_r\right) & \text{in } \Omega \times I, \\ T(.,0) = 37 & \text{on } \partial\Omega \times I, \\ \kappa \nabla T \cdot \vec{n} = 0 & \text{in } \Omega, \end{cases}$$

where $\sigma = [\rho c_p(1-\varepsilon) + \rho_b c_{pb}\varepsilon]$, $\kappa = (1-\varepsilon)k_t + \varepsilon k_b$.

[3] Esteves, A. M. B., Fatigate, G. R., Lobosco, M., and Reis, R. F. (2023, June). Influence of the Capillaries Bed in Hyperthermia for Cancer Treatment. In International Conference on Computational Science (pp. 623-637). Cham: Springer Nature Switzerland.

Finite Difference Method

The solution was approximated using the FDM in a heterogeneous porous medium using a FTCS ...

$$T_{i,j}^{n+1} = \frac{h_t}{\sigma}\left(\varphi_{dif}(T^n) - \varphi_{adv}(T^n) + (1-\varepsilon)Q_m + Q_r\right) + T_{i,j}^n,$$

where

$$\varphi_{dif}(T^n) = \frac{\kappa_{i+1/2,j}(T_{i+1,j}^n - T_{i,j}^n) - \kappa_{i-1/2,j}(T_{i,j}^n - T_{i-1,j}^n)}{h^2} + \frac{\kappa_{i,j+1/2}(T_{i,j+1}^n - T_{i,j}^n) - \kappa_{i,j-1/2}(T_{i,j}^n - T_{i,j-1,k}^n)}{h^2},$$

Upwind Scheme

... along with an upwind scheme:

$$\varphi_{adv}(T^n) = \varepsilon(\rho c_p)_b \mathbf{u}_{b_{i,j}} \cdot \left(\begin{cases} \dfrac{\left(u^n_{i,j} - u^n_{i-1,j}\right)}{h} & \text{for } u_{b_x} > 0 \\ \dfrac{\left(u^n_{i+1,j} - u^n_{i,j}\right)}{h} & \text{for } u_{b_x} < 0 \end{cases} \\ \begin{cases} \dfrac{\left(u^n_{i,j} - u^n_{i,j-1}\right)}{h} & \text{for } u_{b_y} > 0 \\ \dfrac{\left(u^n_{i,j+1} - u^n_{i,j}\right)}{h} & \text{for } u_{b_y} < 0 \end{cases} \right)$$

where $\mathbf{u}_b = \begin{pmatrix} u_{b_x} \\ u_{b_y} \end{pmatrix}$

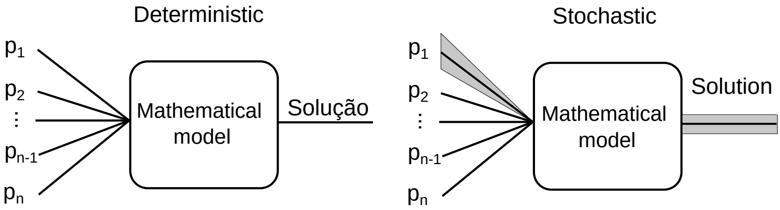
Uncertainty Quantification

Monte Carlo method

We employ the Monte Carlo method to quantify two uncertainty scenarios:

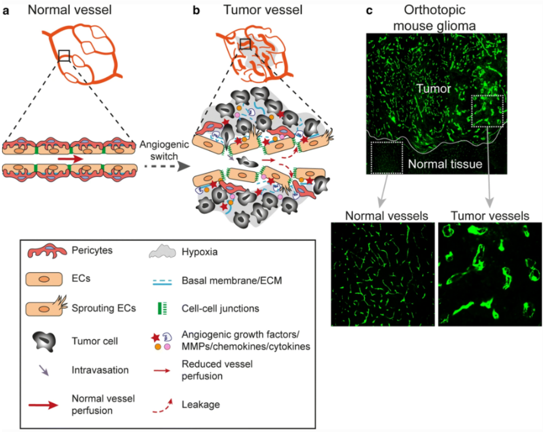
a) the influence of the capillaries architecture

b) the influence of the blood velocity



Capillaries Architecture

It is know that tumor growth induces angiogenesis [4]



[4] Lugano, R., Ramachandran, M., and Dimberg, A. (2020). Tumor angiogenesis: causes, consequences, challenges and opportunities. Cellular and Molecular Life Sciences, 77, 1745-1770.

Capillaries Architecture

For the capillaries architecture scenario, we analyze the influence of the number of capillaries:

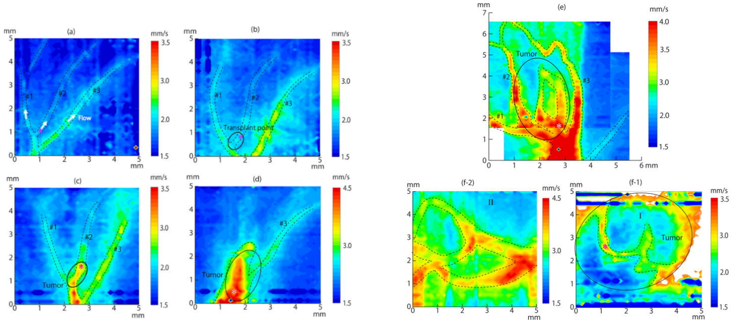
$$N_c = \begin{cases} 70 \times X \sim U(0.7, 1.3) & \text{for the tumor tissue,} \\ 50 \times X \sim U(0.7, 1.3) & \text{otherwise,} \end{cases}$$

and the angle of the capillaries.

$$\theta_c = \theta \times X \sim U(0.7, 1.3).$$

Blood Velocity

On the other hand, tumor growth also changes the blood flow [5]



[5] Ishida, H., Hachiga, T., Andoh, T., and Akiguchi, S. (2012). *In-vivo* visualization of melanoma tumor microvessels and blood flow velocity changes accompanying tumor growth. Journal of Applied Physics, 112(10), 104703.

Blood Velocity

In the blood velocity scenario, we analyze the influence of the blood velocity:

$$|\mathbf{u_{b_c}}| = |\mathbf{u_b}| \times X \sim U(0.5, 1.5),$$

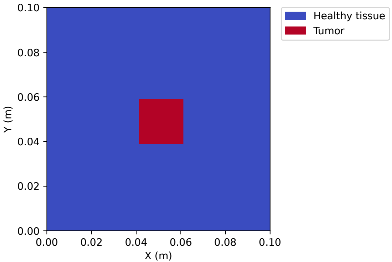
Parallel Stragegy

Algorithm 1: Pseudocode of Monte Carlo implementation using *OpenMP*

begin
    # pragma omp parallel
    foreach *Monte Carlo Sample* **do**
        foreach $t_n; n = 0, 1, \cdots, N_t$ **do**
            #pragma omp for
            foreach $(x_i, y_j); i = 0, 1, \cdots, N_x; j = 0, 1, \cdots, N_y$ **do**
                evaluate T_{ij}^{n+1}
            end foreach
        end foreach
    end foreach
end

Simulations Setups

- We consider squared tumor seated in $(x, y) \in [0.04, 0.06] \times [0.04, 0.06]$.
- For all Monte Carlo simulation we drew 10,000 samples



Influence capillaries architecture

Number of capillaries

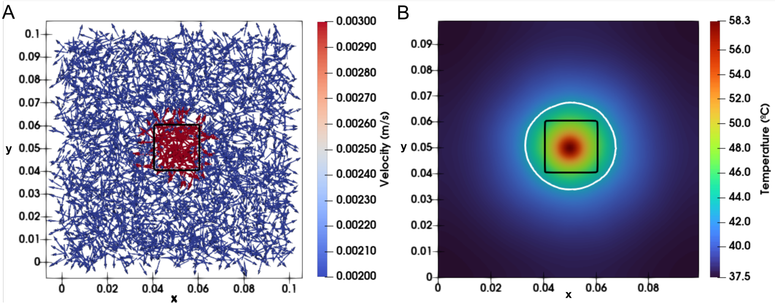


Figure 17: **A)** Base velocity field considering tumor tissue with 70% of capillaries terminals and the healthy tissue with 50% of capillaries terminals and **B)** Temperature distribution at $t = 50min$

Influence capillaries architecture

Number of capillaries

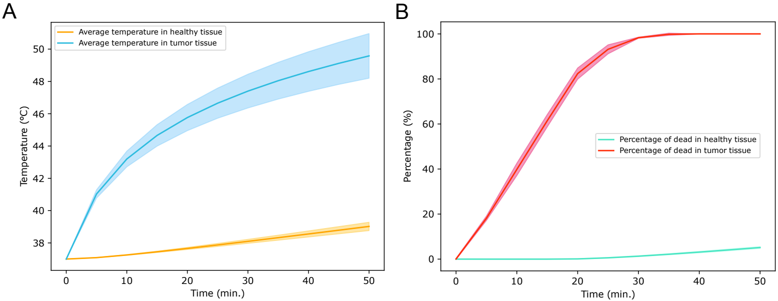


Figure 18: **A)** Evolution of temperature and **B)** Percentage of tumor and healthy tissues with $T \geq 43^o$C. Furthermore, only 5.2% of the healthy tissue reached a temperature of $43^o C$

Influence capillaries architecture

Angles of capillaries

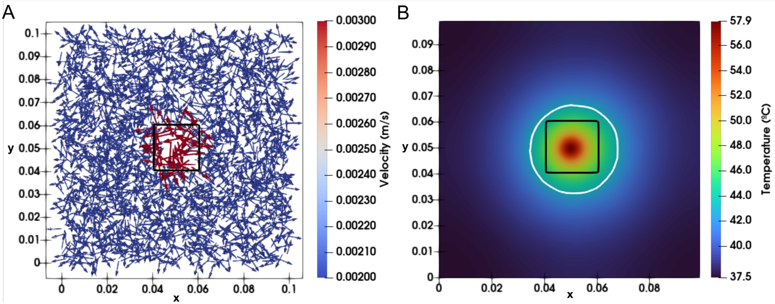


Figure 19: **A)** Base velocity field considering tumor tissue with 70% of capillaries terminals and the healthy tissue with 50% of capillaries terminals and **B)** Temperature distribution at $t = 50min$

Influence capillaries architecture

Angles of capillaries

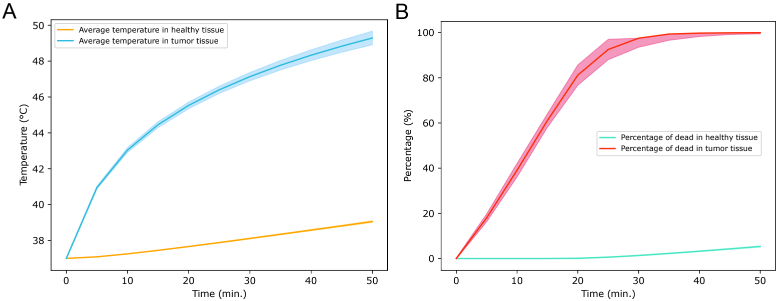


Figure 20: **A)** Evolution of temperature and **B)** Percentage of tumor and healthy tissues with $T \geq 43^o$C. Furthermore, only 5.3% of healthy tissue reached a temperature of $43^o C$ or higher

Influence of the blood velocity

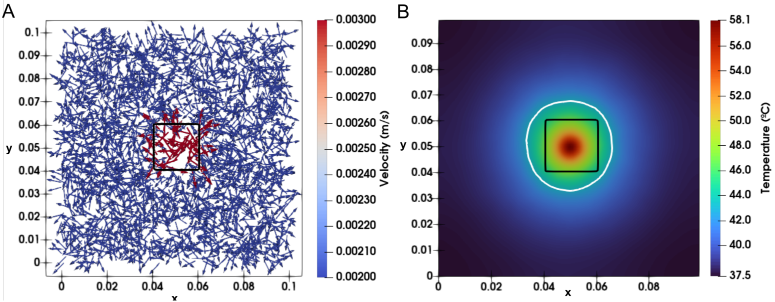


Figure 21: **A)** Base velocity field considering tumor tissue with 70% of capillaries terminals and the healthy tissue with 50% of capillaries terminals and **B)** Temperature distribution at $t = 50min$

Influence of the blood velocity

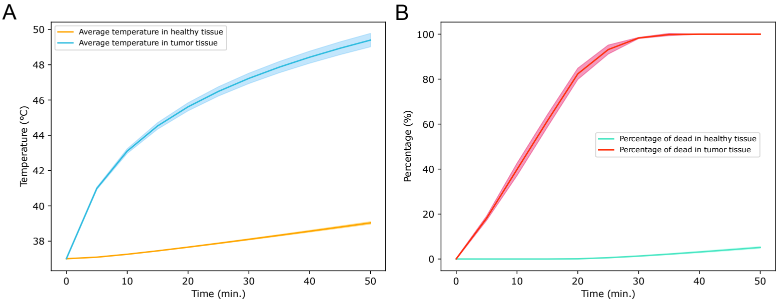


Figure 22: **A)** Evolution of temperature and **B)** Percentage of tumor and healthy tissues with $T \geq 43^oC$. Furthermore, only 5.1% of healthy tissue reached a temperature of $43^o C$ or higher

Overview

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   - Hyperthermia
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   - Numerical Experiments
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4. Conclusions and Future Works

Conclusions

- Possible to find optimal locations for injecting the nanoparticles
- Non-trivial location
- Strategy reduced healthy tissue damage by up to 59%
- CUDA improved performance up to 84 times

Conclusions

- The results presented in this study suggest that the capillaries bed architecture significantly influences temperature evolution in the simulated tissue
- Uncertainty analysis can be a powerful tool for treatment planning once it allows the possibility to perform several *in silico* trials and analyze the best option
- The results of this studies reinforce that *in silico* medicine might reduce the need for clinical trials with animals and cohort studies with humans

Future Works

- Consider the study of different tissue layers in the human body, such as skin, muscle, and fat, along with realistic tumor and tissue shapes
- Use more precise ways to quantify tumor ablation, such as the Arrhenius models
- Determine the uncertain parameters' best probability density function
- Search for the necessary number of injections
- Use Multi-GPU to speedup the implementation.

Acknowledgements

Danke Shön!

Obrigado!

Thanks!

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[6] 423278/2021-5

[7] APQ-01226-21

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Questions

Feel free to ask me!