Uncertainty Quantification of Thermal Damage in Hyperthermia as a Cancer Therapy

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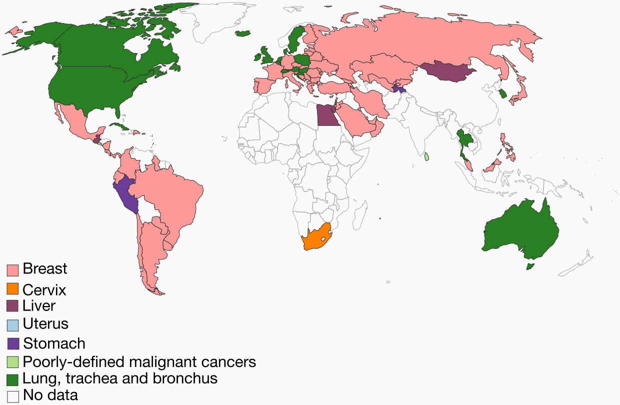
Overview

Introduction

Cancer

Cancer remains a major global health concern, with breast cancer being the leading cause of cancer-related death among women in many countries.



Hyperthermia

- Promising non-invasive cancer treatment;
- Heats the tumor region to induce necrosis;
- Hyperthermia is a complementary treatment to chemotherapy and radiotherapy;
- One strategy involves the use of a ferrofluid containing magnetic nanoparticles.

Matematical Model

Pennes' Model

The Pennes equation was considered to simulate bioheat transfer[1].

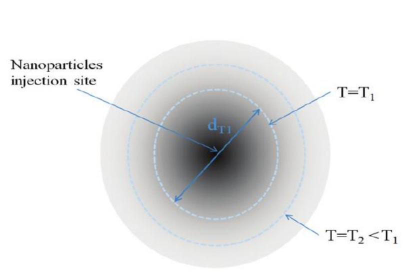
$$
\begin{cases}
\rho c \dfrac{\partial T}{\partial t} = \nabla \cdot k \nabla T + \omega_b \rho_b c_b (T_a - T) + Q_m + Q_r & \text{em } \Omega \times I \\
k \nabla T \cdot \vec{n} = 0 & \text{em } \partial\Omega \times I \\
T(\cdot, 0) = 37,0 & \text{em } \Omega
\end{cases}
\tag{1}
$$

[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.

Pennes' Model: Magnetic Nanoparticles

- Possibility of using high energy potential;
- Water-based, biocompatible ferrofluid solution;
- Injection of ferromagnetic fluid, *e.g.*, 0.1, 0.2, or 0.3 cc;
- SAR[2] is responsible for modeling the overheating caused by the injections.

$$Q_r = \sum_{i=1}^{N_p} A e^{-r_i^2/r_{0,i}^2},$$



[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.

Pennes' Model: Limitations

Simplifications adopted in the Pennes' model:

- Heat transfer is assumed to occur only through capillaries;
- Blood flow is considered isotropic;
- Vascular geometry is not taken into account;
- Capillary temperature is assumed to be equal to body temperature;

Numerical Scheme

Finite Difference Method

The solution was approximated using the Finite Difference Method (FDM) in a heterogeneous medium, applying the FTCS scheme.

$$
\begin{aligned}
T^{n+1}_{i,j,k} = \frac{h_t}{\rho c}\Bigg[& \frac{k_{i+1/2,j,k}(T^n_{i+1,j,k} - T^n_{i,j,k}) - k_{i-1/2,j,k}(T^n_{i,j,k} - T^n_{i-1,j,k})}{h^2} + \\
& \frac{k_{i,j+1/2,k}(T^n_{i,j+1,k} - T^n_{i,j,k}) - k_{i,j-1/2,k}(T^n_{i,j,k} - T^n_{i,j-1,k})}{h^2} + \\
& \frac{k_{i,j,k+1/2}(T^n_{i,j,k+1} - T^n_{i,j,k}) - k_{i,j,k-1/2}(T^n_{i,j,k} - T^n_{i,j,k-1})}{h^2} + \\
& \rho_b c_b \omega_b \left(T_a - T^n_{i,j,k}\right) + Q_m + Q_r \Bigg] + T^n_{i,j,k}
\end{aligned} \tag{2}
$$

Thermal Damage

Thermal Damage: Arrhenius

Thermal damage was evaluated using the Arrhenius model in both tumor and healthy tissue regions.

$$\Omega(x, y, z, t) = \ln\left(\frac{C(0)}{C(t)}\right) = \int_0^t A e^{\frac{-E_a}{R_u T(x,y,z,\tau)}}\, d\tau, \tag{3}$$

- If the computed damage parameter $\Omega(x, y, z, t)$ reaches 1.0, approximately 63.2% of the cells are considered to be dead;
- An Arrhenius damage parameter of 4 indicates nearly 98.2% cellular death;
- Omega values in the range $4 \leq \Omega \leq 10$ are considered indicative of complete tumor ablation.

Uncertainty Quantification

Uncertainty Quantification

Monte Carlo simulations with 1,000 samples were performed to quantify the uncertainties associated with two correlated parameters in the Arrhenius model: the frequency factor A and the activation energy E_a.

$$E_a \approx 2.63 \times 10^3 \ln(A) + 2.46 \times 10^4 \begin{cases} E_{a_u} & = W \sim U(E_{a_{\min}}, E_{a_{\max}}), \\ A & = e^{3.832 \times 10^{-4} E_a - 10.042}, \end{cases}$$

$$\ln(A) = 3.832 \times 10^{-4} E_a - 10.042 \begin{cases} A_u & = W \sim U(A_{\min}, A_{\max}), \\ E_a & = 2.63 \times 10^3 \ln(A_u) + 2.46 \times 10^4 \end{cases}$$

Results

Execution Environment

- Implemented in C;
- AMD® EPYC$^{\text{TM}}$ 7713 CPU;
- NVIDIA A100 GPU (for CUDA parallelization);
- Single-core execution;
- Results visualized using ParaView;
- Execution parameters and domain taken from the literature.

Simulated Scenario

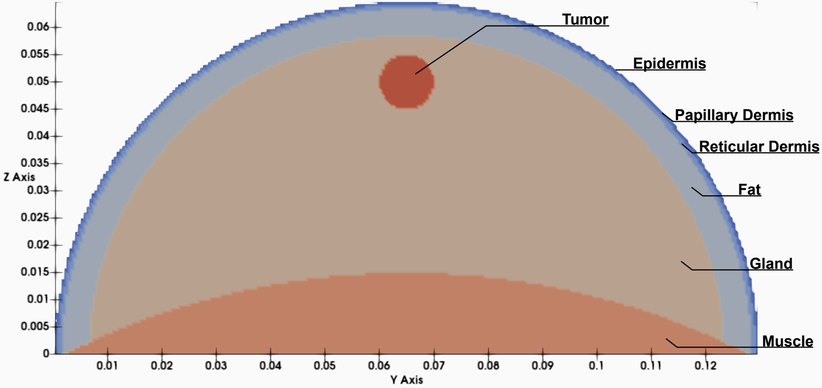


Figure 1: Simulated breast tumor

Heat Spread

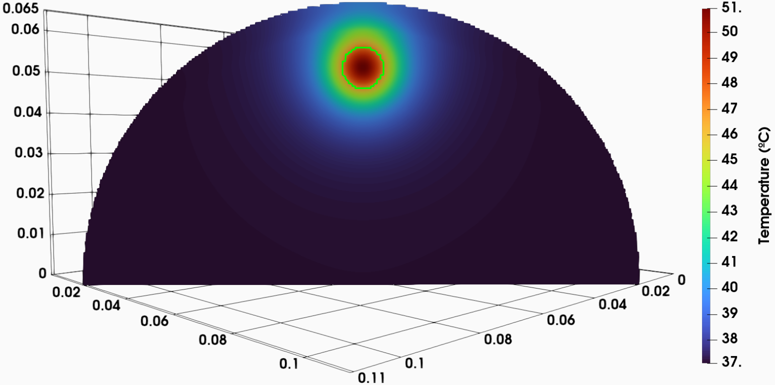


Figure 2: Temperature distribution computed from the bioheat equation at $t = 50\,\mathrm{min}$.

Frequency Factor A Scenario

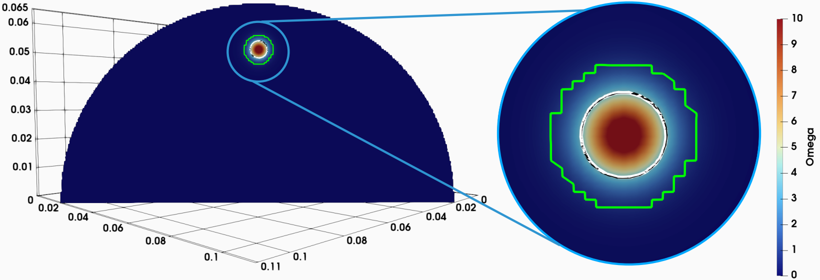


Figure 3: Simulation results for the scenario with uncertainty in the frequency factor A at $t = 5\,\text{min}$.

Frequency Factor A Scenario

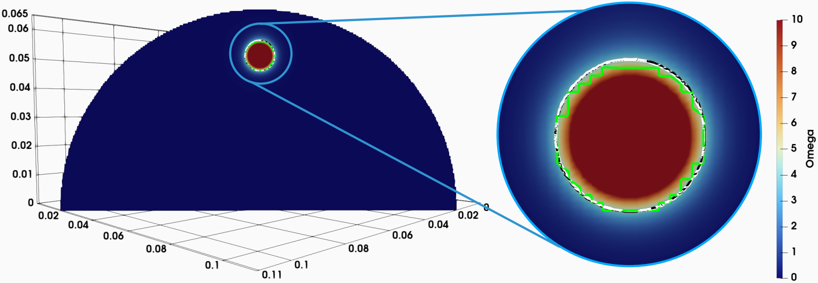


Figure 4: Simulation results for the scenario with uncertainty in the frequency factor A at $t = 10\,\text{min}$.

Frequency Factor A Scenario

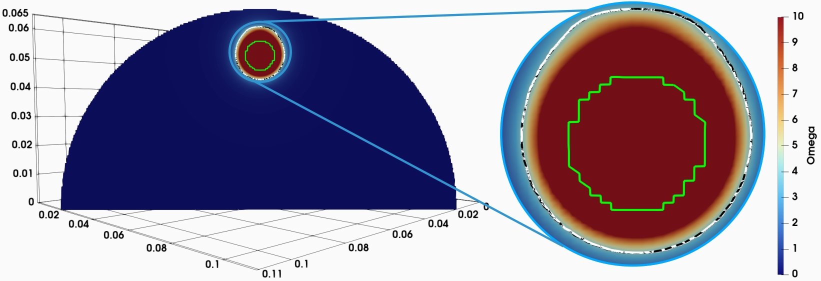


Figure 5: Simulation results for the scenario with uncertainty in the frequency factor A at $t = 50$ min.

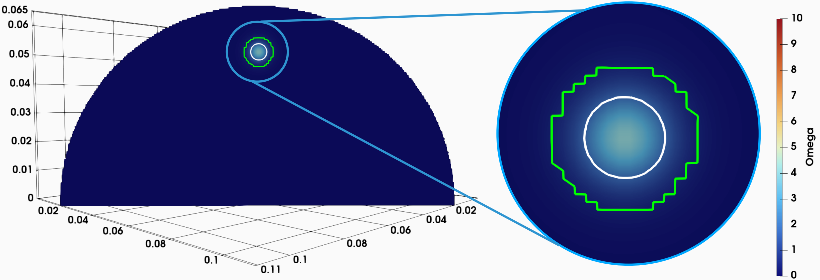


Figure 6: Simulation results for the scenario with uncertainty in the activation energy E_a at $t = 5\,\text{min}$.

Activation Energy E_a Scenario

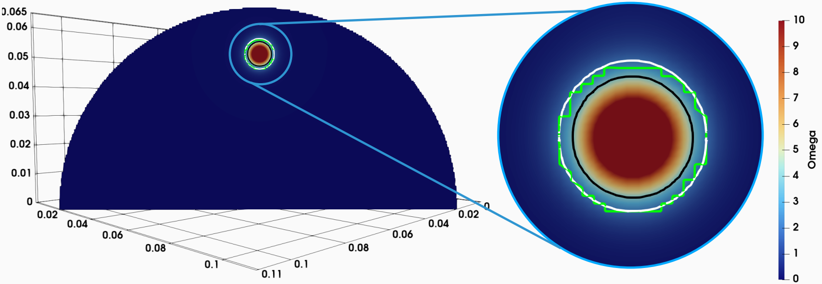


Figure 7: Simulation results for the scenario with uncertainty in the activation energy E_a at $t = 10\,\text{min}$.

Activation Energy E_a Scenario

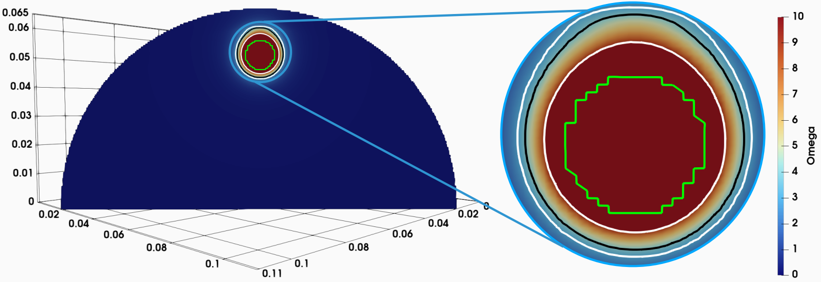


Figure 8: Simulation results for the scenario with uncertainty in the activation energy E_a at $t = 50\,\text{min}$.

Uncertainty Quantification Results

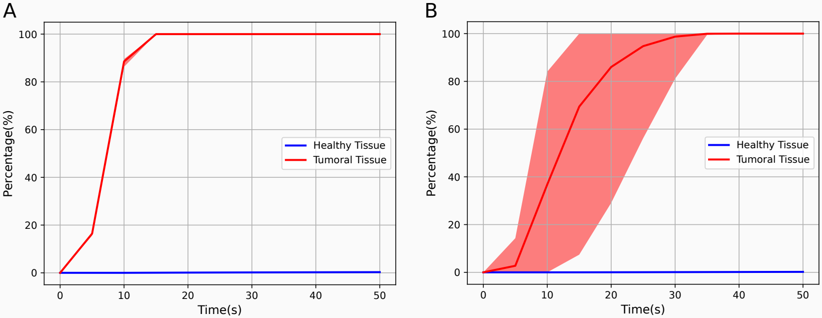


Figure 9: Results of the uncertainty quantification due to variations in A and E_a for assessing tumor damage during hyperthermia treatment.

Conclusion and Future Works

Conclusion and Future Works

- Variations in the frequency factor A have a minor influence on tissue damage predictions, even when A spans from $A_{\text{min}} = 7.39 \times 10^{39}$ to $A_{\text{max}} = 3.10 \times 10^{98}$.
- In contrast, variations in the activation energy E_a significantly affect the outcomes, with E_a ranging from $E_{a_{\text{min}}} = 2.577 \times 10^5$ J/mol to $E_{a_{\text{max}}} = 6.030 \times 10^5$ J/mol.
- The confidence intervals observed in the thermal damage suggest that uncertainty in E_a leads to a critical damage threshold ($\Omega \geq 4$) being reached between 15 and 35 minutes.

Conclusion and Future Works

- In future work, we plan to study different tissue layers in the human body using realistic tumor and tissue geometries;
- Incorporate Multilevel Monte Carlo (MLMC) methods to accelerate simulations and improve computational efficiency;
- Finally, we intend to validate the model results using clinical or experimental data.

Acknowledgements

Obrigado!

Thanks!

CNPq [3] CAPES FAPEMIG [4]

[3] 423278/2021-5

[4] APQ-01226-21