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PARAMETER ESTIMATION IN HYPERTHERMIA *IN VITRO* EXPERIMENTS

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Abstract. *The aim of this work is to estimate parameters of a hyperthermia in vitro experiment with prostate cancer cells (DU145). The physical problem involves the laser heating of one well in a 96-well plate, during three minutes. Two mathematical models were proposed to represent the physical problem. In the complete model, natural convection due to the laser heating was considered and its solution was obtained numerically with the commercial software COMSOL Multiphysics®. The reduced model is given in terms of a lumped system with an analytic solution. The thermal damage caused in the cells was modeled by a first order reaction, with reaction rate given by an Arrhenius equation. A Bayesian approach was applied to estimate the parameters with the Markov Chain Monte Carlo (MCMC) method implemented via Metropolis-Hastings algorithm. A computational time reduction strategy for the MCMC was applied with the Approximation Error Model (AEM). The MCMC method with the AEM approach was able to estimate the parameters during simulated in-vitro hyperthermia experiments.*

Keywords: *Hyperthermia, Laser, Cancer Cell, Inverse Problems, Bayesian Inference*

1. INTRODUCTION

Hyperthermia for the treatment of cancer involves the heating of the tumor for a given period (Habash *et al.* Part.2, 2006; Mallory *et al.*, 2016). Generally, this therapy is applied together with other treatment modalities such as radiotherapy and chemotherapy (Hidelbrandt *et al*., 2002). Hyperthermia is not only applied to oncology, but also in other areas such as physiotherapy, urology, cardiology and ophthalmology (Habash *et al*. Part.1,2006).

Mathematical modeling is of major importance for the prognostics and planning of the cancer treatment (Quaranta *et al*., 2005). Unknown model parameters or functions can be estimated with the experimental responses of the system via inverse analysis (Ozisik and Orlande, 2000). Costa *et al.* (2018) used Approximate Bayesian Computation (ABC) to select a model and estimate parameters during *in-vitro* chemotherapy experiments of tumor (DU-145) and normal (macrophage RAW 264.7) with doxorubicin. The application of inverse analyses to cancer therapy problems can be found, for example, in (Varon *et al.*,2016; Lamien *et al.*, 2017).

Tang and McGoron (2009), with the objective to evaluate the cytotoxic effect of hyperthermia combined with chemotherapy, used a laser to heat cancer cells *in vitro*. They reported the positive adjuvant effects of the thermal therapy on the chemotherapy. Within this context, the objective of this work is to estimate the parameters of the hyperthermia *in-vitro* treatment by using inverse analysis, with simulated temperature measurements.

2. PHYSICAL PROBLEM AND MATHEMATICAL FORMULATIONS

The physical problem considered here is illustrated by figure 1. The lateral and bottom surfaces of the well were considered thermally insulated and the top surface exchanged heat with the surroundings by convection and linearized radiation. The cells inside the well were classified as alive or dead. Natural convection of the cell culture medium was modeled with Boussinesq´s approximation. The medium, which was considered homogeneous, was heated by a laser in the near-infrared range. The initial temperature of the medium was assumed uniform. Values assumed for several model parameters can also be found in figure 1.

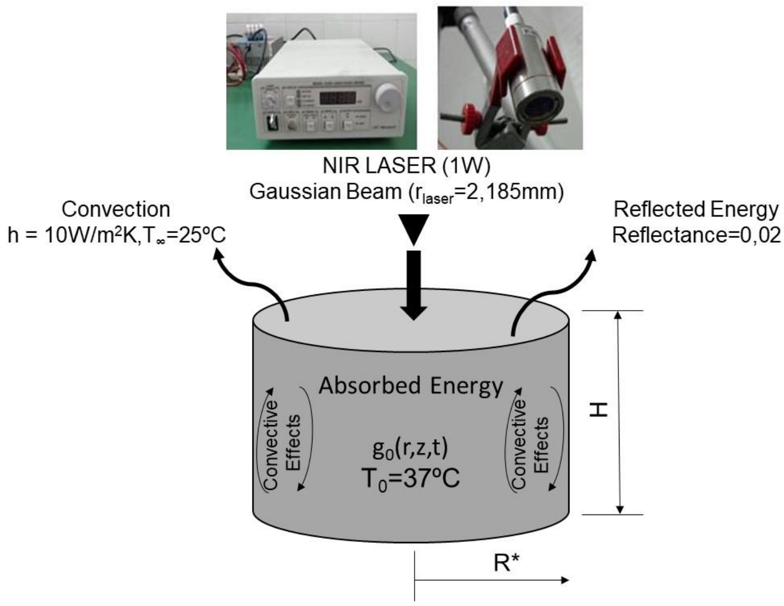


Figure 1. Physical problem - Hyperthermia *in-vitro* experiment with laser heating

The mathematical formulation for the physical problem is given by:

$$\rho_{ref}\nabla.\mathbf{u} = 0 \qquad \text{for } 0 < r < R^*;\ 0 < z < H;\ t > 0 \qquad (1a)$$

$$\frac{\partial N_{alive}}{\partial t} - \mathcal{D}\nabla^2 N_{alive} + \mathbf{u}.\nabla N_{alive} = R_{alive} \qquad \text{for } 0 < r < R^*;\ 0 < z < H;\ t > 0 \qquad (1b)$$

$$\frac{\partial N_{dead}}{\partial t} - \mathcal{D}\nabla^2 N_{dead} + \mathbf{u}.\nabla N_{dead} = R_{dead} \qquad \text{for } 0 < r < R^*;\ 0 < z < H;\ t > 0 \qquad (1c)$$

$$N_{alive} \xrightarrow{k} N_{dead} \qquad \text{for } 0 < r < R^*;\ 0 < z < H;\ t > 0 \qquad (1d)$$

$$R_{alive} = \frac{dN_{alive}}{dt} = -kN_{alive} = R_{dead} \qquad \text{for } 0 < r < R^*;\ 0 < z < H;\ t > 0 \qquad (1e)$$

$$k = 10^{k_\alpha} e^{\left\{-\frac{E}{R_{gas}T}\right\}} \qquad \text{for } 0 < r < R^*;\ 0 < z < H;\ t > 0 \qquad (1f)$$

$$\rho_{ref}\left(\frac{\partial \boldsymbol{u}}{\partial t} + \mathbf{u}.\nabla\mathbf{u}\right) = -\nabla P + \mu\nabla^2\mathbf{u} - \rho_{ref}\left[1 - \beta\left(T - T_{ref}\right)\right]\mathbf{g} \qquad \text{for } 0 < r < R^*;\ 0 < z < H;\ t > 0 \qquad (1g)$$

$$\rho_{ref}C_p\left[\frac{\partial T}{\partial t} + (\mathbf{u}.\nabla T)\right] - K\nabla^2 T = [1 - R]F\mu_\alpha e^{[-\mu_\alpha(H-Z)]} e^{\left[-\frac{2r^2}{r_{laser}{}^2}\right]} \qquad \text{for } 0 < r < R^*;\ 0 < z < H;\ t > 0 \qquad (1h)$$

$$T = T_0;\ N = N_0; \qquad \text{for } 0 < r < R^*;\ 0 < z < H;\ t = 0 \qquad (1i)$$

where ρ_{ref} is the density, C_p is the specific heat, K is the thermal conductivity, R is the reflectance, r_{laser} is the laser beam, k is the reaction rate (Arrhenius), E is the activation energy, R_{gas} is the gas constant, μ is the dynamic viscosity, β is the coefficient of thermal expansion and $\mathcal{D}$ is the cell diffusion coefficient.

Since the laser beam is assumed co-axial with the well and the boundary conditions are axisymmetric, the problem can be written in terms of the coordinates *r* and *z*. Figure 2 presents the boundary conditions for the problem.

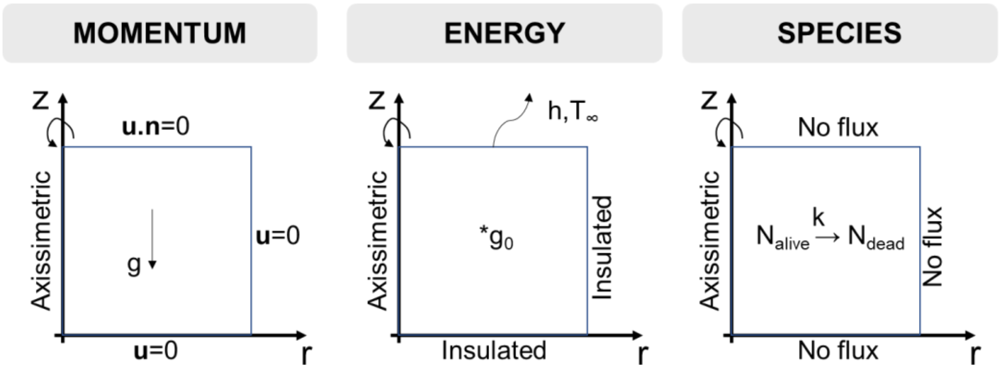


Figure 2. Boundary conditions of the complete model

The mathematical formulation given by equations (1a) to (1i) were considered here as a *complete model* for the problem, which is supposed to perfectly represent the phenomena taking place during the *in vitro* hyperthermia treatment. In order to expedite the numerical computations, a reduced model is now proposed. For the reduced model, the medium was assumed to be at a uniform temperature and natural convection effects were neglected. The mathematical formulation of the reduced model is thus given by:

$$\frac{dT}{dt} + \left[\frac{h}{\rho C_p H}\right] T = \left[\frac{S_{laser}}{\pi {R^*}^2 \rho C_p H}\right] + \left[\frac{h T_\infty}{\rho C_p H}\right] \qquad \text{for } t > 0 \qquad (2a)$$

$$\frac{dN_{alive}}{dt} = -\left\{10^{k_a} e^{\left\{-\frac{E}{RT}\right\}}\right\} N_{alive} \qquad \text{for } t > 0 \qquad (2b)$$

where

$$S_{laser} = [1-R] F \mu_\alpha 2\pi \left\{\left[\frac{1}{\mu_\alpha}\right] - \left[\frac{e^{(-\mu_\alpha H)}}{\mu_\alpha}\right]\right\} \left\{\left[\frac{{r_{laser}}^2}{4}\right] - \left[\left(\frac{{r_{laser}}^2}{4}\right) e^{\left(-\frac{2{R^*}^2}{{r_{laser}}^2}\right)}\right]\right\} \qquad (2c)$$

Equation (2a) was rewritten as:

$$\frac{dT}{dt} + \left[\frac{P_{hc}}{H}\right] T = \left[\frac{P_{sc}}{\pi {R^*}^2 H}\right] + \left[\frac{P_{hc} T_\infty}{H}\right] \qquad \text{for } t > 0 \qquad (3a)$$

where

$$P_{hc} = \frac{h}{\rho C_p} \qquad (3b)$$

$$P_{sc} = \frac{S_{laser}}{\rho C_p} \qquad (3c)$$

The analytical solution of the reduced model is given by:

$$T(t) = e^{(-At)} T_0 + \frac{B}{A}\left[1 - e^{(-At)}\right] \qquad (4a)$$

$$N_{alive}(t) = N_0 EXP\left\{-\int_{t'=0}^{t} 10^{k_a} EXP\left[-\frac{E}{R_{gas} T(t)}\right] dt'\right\} \qquad (4b)$$

where

$$A = \frac{P_{hc}}{H} \qquad (4c)$$

$$B = \left[\frac{P_{sc}}{\pi {R^*}^2 H} + \frac{P_{hc} T_\infty}{H}\right] \qquad (4d)$$

3. INVERSE PROBLEM

A Bayesian approach was applied to estimate the parameters in the problem formulation by implementing the Markov Chain Monte Carlo method (MCMC), via the Metropolis-Hastings algorithm (Kaipio and Somersalo, 2004).

The *a posteriori* probability distribution is obtained with Bayes' theorem as:

$$\pi(\mathbf{P}|\mathbf{Y}) = \frac{\pi(\mathbf{P})\pi(\boldsymbol{Y}|\mathbf{P})}{\pi(\mathbf{Y})} \tag{5}$$

where $\pi(\mathbf{Y}|\mathbf{P})$ is the likelihood function, which expresses the probability density of measurements $\mathbf{Y}$ with $\mathbf{P}$ given, $\pi(\mathbf{P})$ is the *a priori* density of the parameters before the measurements are taken and $\pi(\mathbf{Y})$ plays the role of a normalizing constant.

Thus, Bayes' Theorem can be written as:

$$\pi(\mathbf{P}|\mathbf{Y}) \propto \pi(\mathbf{P})\pi(\mathbf{Y}|\mathbf{P}) \tag{6}$$

The simulated measurements were assumed with normal distribution, zero means and known standard deviations. Thus, the likelihood function can be written as (Kaipio and Somersalo, 2004):

$$\pi(\mathbf{P}|\mathbf{Y}) = (2\pi)^{-D/2}|\mathbf{W}|^{-1/2}\exp\left\{-\frac{1}{2}[\mathbf{Y} - \mathrm{T}(\mathbf{P})]^{\mathrm{T}}\mathbf{W}^{-1}[\mathbf{Y} - \mathrm{T}(\mathbf{P})]\right\} \tag{7}$$

where D is the total number of measurements, $\mathrm{T}(\mathbf{P})$ is the solution of the complete model and $\mathbf{W}$ is covariance matrix of measurement errors. The parameters for the reduced model are given by:

$$\mathbf{P}^T = [T_0, T_\infty, P_{hc}, P_{sc}, N_0, E, k_a] \tag{8}$$

The prior densities for T_∞, P_{hc}, N_0, E and k_a were selected as truncated Gaussian priors, given for a general parameter P_j by:

$$\pi(P_j) = \begin{cases} \frac{1}{\sqrt{2\pi\sigma_j{}^2}} exp\left[-\frac{1}{2}\frac{(P_j-\mu_j)^2}{\sigma_j{}^2}\right]; a < P_j < b \\ 0; \qquad P_j \le a \ e \ P_j \ge b \end{cases} \tag{9}$$

while uniform distribution were used for the priors of T_0 and P_{hc}, that is,

$$\pi(\mathrm{P_j}) = \begin{cases} \frac{1}{(\mathrm{b-a})}; \mathrm{a} < \mathrm{P_j} < \mathrm{b} \\ 0; \mathrm{P_j} \le \mathrm{a \ e \ P_j} \ge \mathrm{b} \end{cases} \tag{10}$$

One disadvantage on the application of Monte Carlo methods is the large computational times required. On the other hand, the use of computationally fast reduced models for the physical problem can be appropriately accommodated within the Bayesian framework by using the Approximation Error Model – AEM (Kaipio and Somersalo, 2004).

Transient temperature measurements were simulated with the complete model, at the position $z = H$ and $r = 0$. The solution of the inverse problem was based on the reduced model and the Approximation Error Model approach, which is described next.

4. APPROXIMATION ERROR MODEL (AEM)

Kaipio and Somersalo (2004) presented the Approximation Error Model to reduce the computational cost associated with the solution of inverse problems by simulation methods within the Bayesian framework. In this approach, the reduced model is used in the solution of the inverse problem, and the errors related to the reduction of the model are added to the measurement model (Kaipio and Somersalo, 2004), that is,

$$\mathbf{Y} = \mathbf{T}_c(\mathbf{P}) + \boldsymbol{e} \tag{11}$$

where $\mathbf{T}_c(\mathbf{P})$ is the solution of the complete model.

By considering the solution of the reduced model, $\mathbf{T}_r(\mathbf{P})$, Eq. (11) becomes:

$$\mathbf{Y} = \mathbf{T}_c(\mathbf{P}) + \boldsymbol{e} + [\mathbf{T}_\mathrm{r}(\mathbf{P}) - \mathbf{T}_\mathrm{r}(\mathbf{P})] \tag{12}$$

or

$$\mathbf{Y} = \mathbf{T}_r(\mathbf{P}) + [\mathbf{T}_c(\mathbf{P}) - \mathbf{T}_r(\mathbf{P})] + \boldsymbol{e} \tag{13}$$

where the error between the complete and reduced model is given by:

$$\boldsymbol{\varepsilon}(\mathbf{P}) = [\mathbf{T}_c(\mathbf{P}) - \mathbf{T}_r(\mathbf{P})] \tag{14}$$

Eq. (13) can then be written as:

$$\mathbf{Y} = \mathbf{T}_r(\mathbf{P}) + \boldsymbol{\eta}(\mathbf{P}) \tag{15}$$

where

$$\boldsymbol{\eta}(\mathbf{P}) = \boldsymbol{\varepsilon}(\mathbf{P}) + \mathbf{e} \tag{16}$$

The most common approach to model the error $\boldsymbol{\eta}(\mathbf{P})$ is to consider it as a Gaussian random variable (Kaipio and Somersalo, 2004). Hence, the likelihood given by Eq. (7) is rewritten as:

$$\pi(\mathbf{P}|\mathbf{Y}) = (2\pi)^{-D/2}\left|\widetilde{\mathbf{W}}\right|^{-1/2}\exp\left\{-\frac{1}{2}[\mathbf{Y} - \mathbf{T}_\mathrm{r}(\mathbf{P}) - \overline{\boldsymbol{\eta}}]^\mathrm{T}\widetilde{\mathbf{W}}^{-1}[\mathbf{Y} - \mathbf{T}_\mathrm{r}(\mathbf{P}) - \overline{\boldsymbol{\eta}}]\right\} \tag{17}$$

where $\overline{\boldsymbol{\eta}}$ and $\widetilde{\mathbf{W}}$, is the mean and the covariance matrix that includes the statistics of the approximation errors and of the measurement errors. The so-called complete error model is given by:

$$\overline{\boldsymbol{\eta}} = \overline{\boldsymbol{\varepsilon}} + \overline{\mathbf{e}} + \boldsymbol{\Gamma}_{\boldsymbol{\eta}\mathbf{P}}\boldsymbol{\Gamma}_\mathbf{P}{}^{-1}(\mathbf{P} - \boldsymbol{\mu}) \tag{18}$$

$$\widetilde{\mathbf{W}} = \mathbf{W}_\varepsilon + \mathbf{W} - \boldsymbol{\Gamma}_{\boldsymbol{\eta}\mathbf{P}}\boldsymbol{\Gamma}_\mathbf{P}{}^{-1}\boldsymbol{\Gamma}_{\mathbf{P}\boldsymbol{\eta}} \tag{19}$$

where $\overline{\boldsymbol{\varepsilon}}$, $\overline{\mathbf{e}}$ and $\boldsymbol{\mu}$ are the means of $\boldsymbol{\varepsilon}$, $\mathbf{e}$ and $\mathbf{P}$, respectively, while $\mathbf{W}_\varepsilon$, $\boldsymbol{\Gamma}_{\boldsymbol{\eta}\mathbf{P}}$ and $\boldsymbol{\Gamma}_\mathbf{P}$ are the covariance matrices of $\boldsymbol{\varepsilon}$, $\boldsymbol{\eta}$ and $\mathbf{P}$, and $\mathbf{P}$, respectively. With the hypothesis of zero mean for the measurement errors, $\overline{\mathbf{e}} = 0$, and neglecting the linear dependence between $\boldsymbol{\eta}$ and $\mathbf{P}$, Eqs. (18,19) reduced to the so-called Enhanced Error Model (Kaipio and Somersalo, 2004), that is used in this work:

$$\overline{\boldsymbol{\eta}} \approx \overline{\boldsymbol{\varepsilon}} \tag{20}$$

$$\widetilde{\mathbf{W}} \approx \mathbf{W}_\varepsilon + \mathbf{W} \tag{21}$$

The statistics of the modeling errors are then estimated via Monte Carlo simulations as

$$\overline{\boldsymbol{\varepsilon}} = \frac{1}{\mathrm{N_s}}\sum_{\mathrm{n}=1}^{\mathrm{N_s}} \boldsymbol{\varepsilon}_n(\mathbf{P}) \tag{22}$$

$$\widetilde{\mathbf{W}} = \frac{1}{\mathrm{N_s} - 1}\sum_{\mathrm{n}=1}^{\mathrm{N_s}}[\boldsymbol{\varepsilon}_n(\mathbf{P}) - \overline{\boldsymbol{\varepsilon}}]\,[\boldsymbol{\varepsilon}_n(\mathbf{P}) - \overline{\boldsymbol{\varepsilon}}]^\mathrm{T} \tag{23}$$

The number of samples N_s, used in the Monte-Carlo simulations is chosen by verifying the convergence of covariance matrix $\widetilde{\mathbf{W}}$, which can be examined through its trace, such as in Lamien *et al.* (2017).

5. RESULTS

In this work, the physical properties, as well as other parameters used in the numerical simulations below, are: $T_\infty = 25$ ºC, $h = 10\ \mathrm{W/m^2k}$, $F = 67000\ \mathrm{W/m^2}$, $\mu_\alpha = 88.2\ \mathrm{m^{-1}}$, $R = 0.02$, $\mu = 0.8904 \times 10^{-3}$ Pas, $C_p = 4180{,}9$ J/kgK, $\rho = 997.07\ \mathrm{kg/m^3}$, $K = 0.6110$ W/mk, $\beta = 2.057\ \times 10^{-4}\ \mathrm{K^{-1}}$, $\mathcal{D} = 1.6667 \times 10^{-3}\ \mathrm{m^2s^{-1}}$, $N_0 = 13090$ cell/well, $E = 1.61 \times 10^5$ J/mol, $k_a = 22.89098$.

The reduced model was used to perform the verification of the complete model solution for a hyperthermia treatment of 3 minutes. A comparison of the two solutions exhibit excellent agreement, as shown by figure 3.

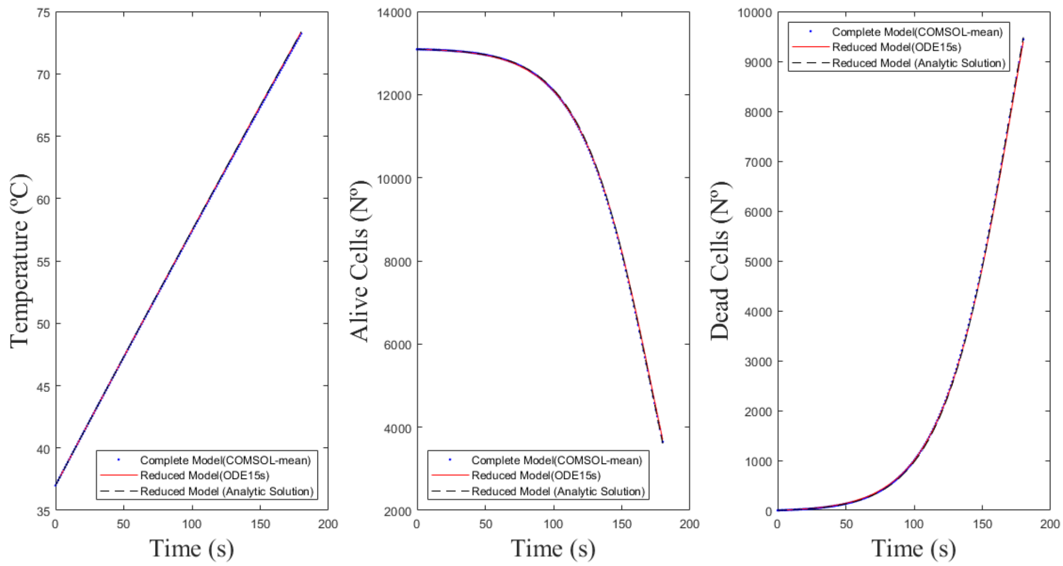
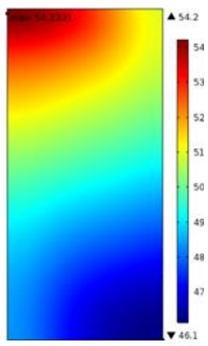
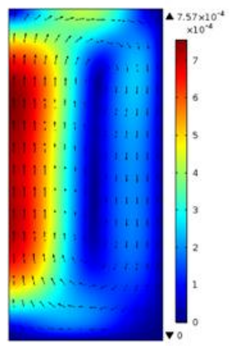
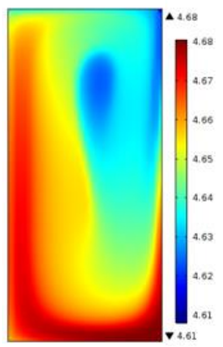
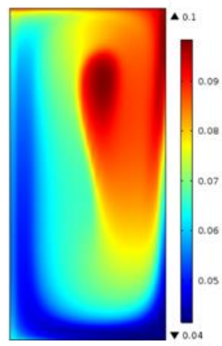
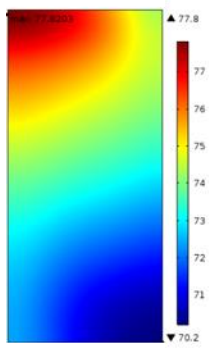
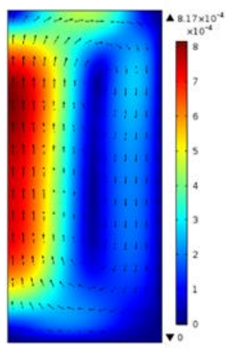
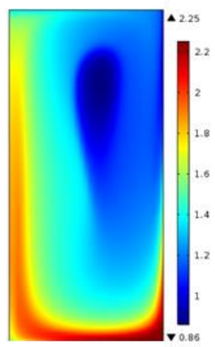
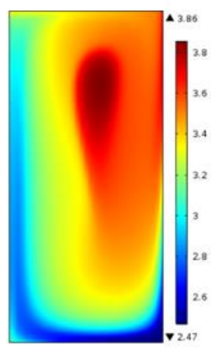


Figure 3. Verification of the direct problem

Table 2 shows the complete model solutions for temperature, velocity, number of alive cells and number of dead cells, respectively, for times 60 s and 180 s.

Table 2. Temperature, Velocity, Alive Cells and Dead Cells for times 60 s and 180 s - Complete Model.

Temperature (ºC)	Velocity (m/s)	Alive Cells (Nº)	Dead Cells (ºN)
			
			

In order to compute the statistics of modelling error, the samples for the time varying heat flux were obtained from random numbers with a normal distribution, with zero mean and standard deviation of 5 % of the exact flux value. The convergence of AEM means and covariance matrix trace is obtained with around 250 Monte Carlo simulations, as shown by figures 4a and 4b, respectively. Anyhow, the AEM statistics were computed in this work by using 500 samples.

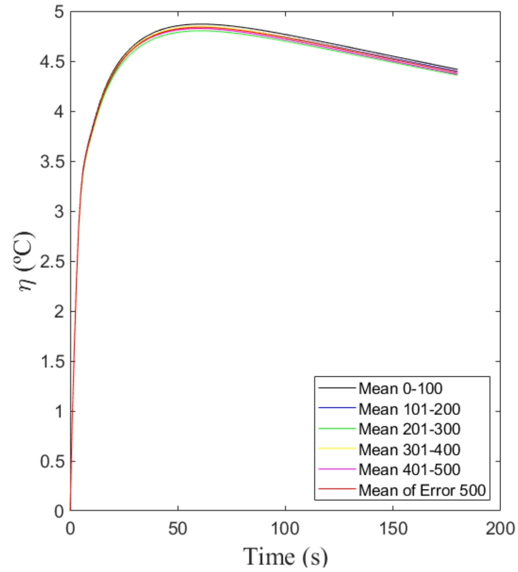


Figure 4.a: Difference between mean of error

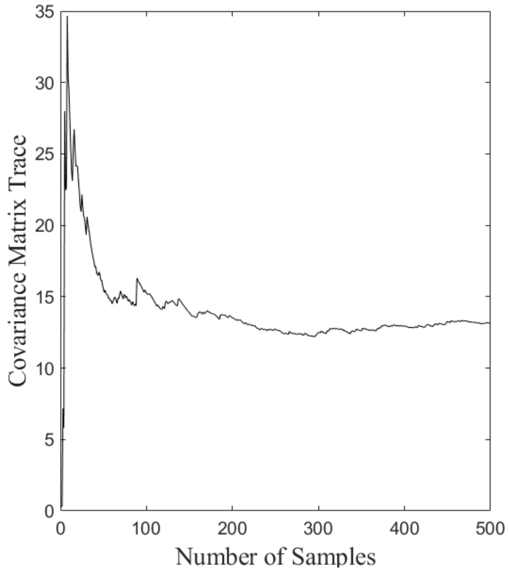
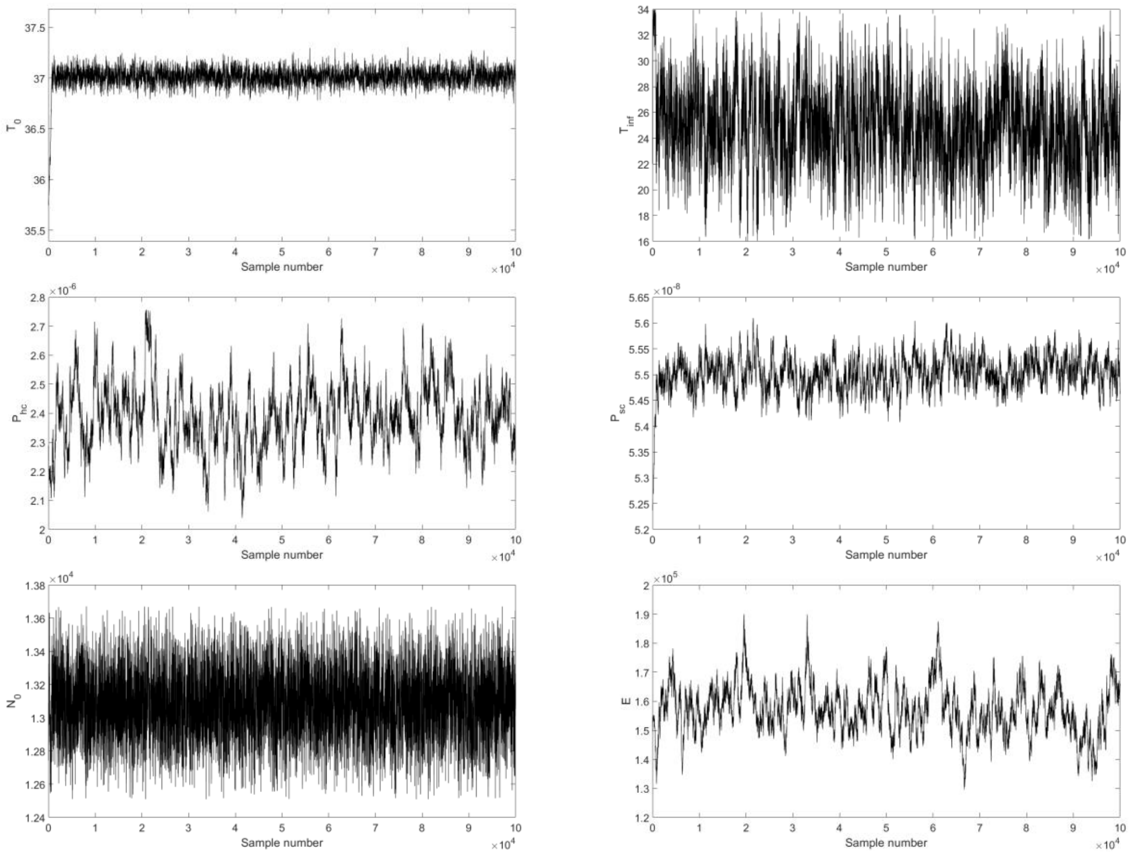


Figure 4.b: Convergence covariance matrix trace

Figure 5 shows the evolutions of the Markov chains for the model parameters, where the burn-in period can be characterized by a number of states ranging from 10000 to 30000. Thus, the equilibrium distributions were considered after 30000 states, when the statistics of the marginal posteriors were computed with the samples of the Markov chains. The acceptance ratio was 34.06 %.



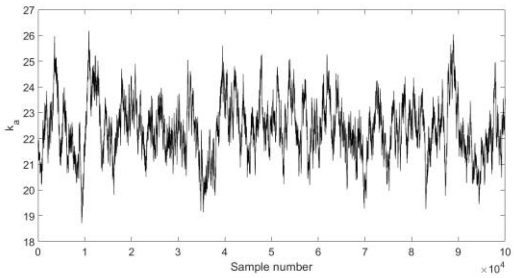


Figure 5. States of the Markov Chain

Figure 6 shows the exact temperatures at the measurement position (z = H, r = 0) obtained with the complete model, as well as the simulated measurements. The estimated temperatures, obtained with the estimated parameters by using the MCMC method with the reduced model and the AEM approach, are also shown in this figure. The agreement between estimated and exact temperatures is excellent.

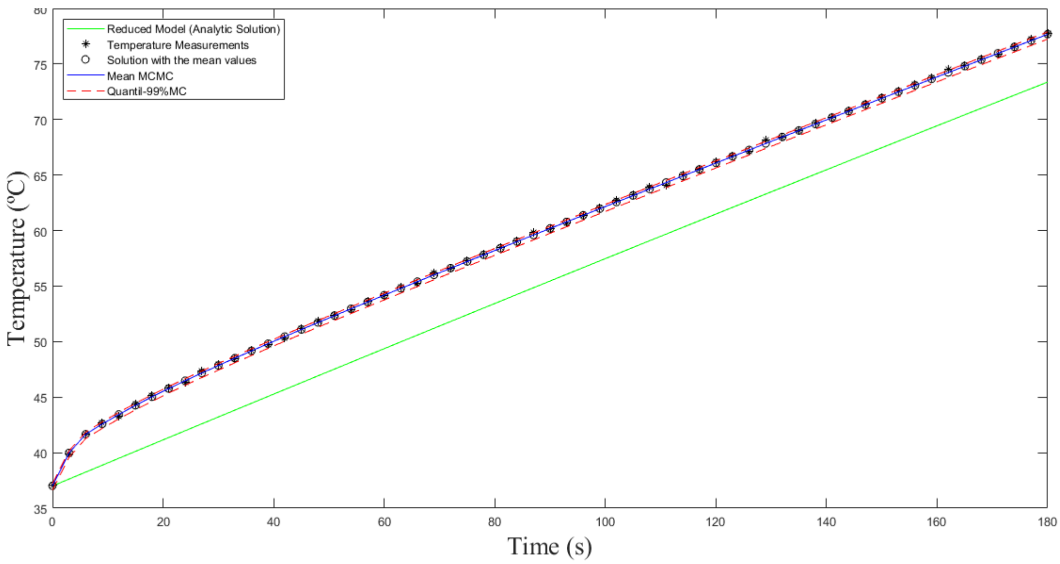


Figure 6. Solution of reduced model, complete model at z = H and r = 0, simulated measurements and estimated temperatures.

The prior distribution and results obtained for estimates of the posterior distribution are presented in Table 3.

Table 3. Prior distribution and inverse problem solution

Prior Distribution	**Posterior Distribution (MCMC)**
$T_0 \sim U[35.5; 38.5]$	$T_0 \sim N[37.00965;\ 0.07149]$
$T_\infty \sim N[25; 3]$	$T_\infty \sim N[24.93595;\ 2.95611]$
$P_{hc} \sim N[2.39885x10^{-6}; 5\ \%]$	$P_{hc} \sim N[2.38x10^{-6}; 1.06x10^{-7}]$
$P_{sc} \sim U[22.06x10^{-9}; 88.23x10^{-9}]$	$P_{sc} \sim N[5.5x10^{-8};\ 3.02x10^{-10}]$
$N_0 \sim N[13090; 195]$	$N_0 \sim N[13083;\ 193]$
$E \sim N[161000; 5\ \%]$	$E \sim N[159674.47;\ 7150.0525]$
$k_a \sim N[22.89098; 5\ \%]$	$k_a \sim N[22.79715; 1.24625]$

6. CONCLUSIONS

This study aimed at estimating the parameters of a hyperthermia *in-vitro* experiment with laser heating, through the Markov Chain Monte Carlo method. A reduced model and the Approximation Error Model approach were used in the inverse analysis. The results obtained here reveal the accuracy of the MCMC method with the AEM approach.

7. ACKNOWLEDGEMENTS

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