DOI: 10.18605/2175-7275/cereus.v12n4p178-190

<< Recebido em: 30/11/2020 Aceito em: 13/12/2020. >>

ARTIGO ORIGINAL

REVISTA CEREUS ISSN: 2175-7275

Solution of an Inverse Heat Transfer Problem for Treatment of Tumors by Hyperthermia

Solução de um Problema de Transferência de Calor para o Tratamento de Tumores por Hipertermia

Bianca Duarte Oliveira[1], Fran Sérgio Lobato[2], Gustavo Barbosa Libotte[3], Gustavo Mendes Platt[4]

[1]Instituto de Ciências Agrárias

E-mail : bianca.duarte@ufu.br

[2]Faculdade de Engenharia Química, [1,2]Universidade Federal de Uberlândia, Brasil.

E-mail: fslobato@ufu.br

[3]Laboratório Nacional de Computação Científica, Brasil.

E-mail: glibotte@lncc.br

[4]Universidade Federal do Rio Grande, Brasil.

E-mail: gmplatt@furg.br

ABSTRACT

In the last decades, some treatments for different types of cancer have been proposed and studied. Among these, we can cite radiotherapy, chemotherapy, cryosurgery and hyperthermia. In general, hyperthermia is the heating of tumor region for a certain period of time so that healthy cells remain unchanged, while pathological cells are destroyed. From the mathematical point of view, the phenomenon of heat transfer in the region of interest can be represented by a partial differential equation that is dependent on characteristics related to the material used for heating and the cell properties where the carcinoma is located. This contribution aims to formulate and solve inverse problems for the determination of geometry and source term during the hyperthermia process. For this purpose, the direct problem is solved considering the Normal Collocation Method and the inverse problem is solved considering the Differential Evolution algorithm. The results obtained demonstrate that the proposed methodology is able to obtain good estimates in all the proposed case studies, proving to be an interesting alternative to solve this type of problem.

Keywords: Hyperthermia, Heat Transfer, Direct Problem, Inverse Problem, Differential Evolution.

RESUMO

Nas últimas décadas, inúmeros tratamentos para os diferentes tipos de câncer têm sido propostos e estudados. Dentre estes, pode-se destacar a radioterapia, a quimioterapia, a criocirurgia e a hipertermia. Especificamente em relação à hipertermia, o procedimento consiste no aquecimento da região do tumor durante um determinado intervalo de tempo de modo que as células normais tendem a permanecer inalteradas, enquanto as células patológicas são destruídas. Do ponto de vista matemático, o fenômeno de transferência de calor na região de interesse pode ser representado por uma equação diferencial parcial que é dependente das características do material utilizado para o aquecimento e das propriedades das células onde o carcinoma se localiza. A presente contribuição tem por objetivo formular e resolver problemas inversos para a determinação da geometria e do termo fonte durante o processo de hipertermia. Para essa finalidade, o problema direto é resolvido considerando o Método da Colocação Normal e o problema inverso é resolvido considerando o algoritmo de Evolução Diferencial. Os resultados obtidos demonstram que a metodologia proposta é capaz de obter boas estimativas em todos os estudos de caso propostos, configurando uma interessante alternativa para a resolução deste tipo de problema.

Palavras-chave: Hipertermia, Transferência de Calor, Problema Direto, Problema Inverso, Evolução Diferencial.

1. INTRODUCTION

Cancer is one of diseases that most attract the attention of scientific community due to large number of cases that arise every year, lethality rate and limited treatment options in some cases. In view of the types of cancerthat exist, several forms of treatment can be used, among them we can mention: surgical removal of the tumor, radiotherapy, chemotherapy, and drug administration (Hafid and Lacroix, 2017). These last three treatments have a particular characteristic, the side effects related to reduction of immunity (Singh and Kumar, 2014).

As an alternative, both cryotherapy and hyperthermia procedures have been considered as treatment of certain cancer types, such as in the liver, lung and breast (Singh and Kumar, 2014).The cryotherapy consists of freezing diseased tissue in order to promote the reduction of cellular activity and, consequently, the elimination of cancer cells. On the other hand, the hyperthermia is theprocedure of increasing tumor temperature to stimulate blood flow, increase oxygenation and render tumor cells more sensitive to radiation, i.e., this approach aims the elimination of tumor cells by heating the region of interest (Suleman et al. 2020). Both approaches are minimally invasive procedures, i.e., damage to the surrounding healthy tissue and side effects can be minimized (Hafid and Lacroix, 2017).In general, these two procedures are performed by inserting a device into the tissue to be frozen or heated. For each type of device, a particular approach can be employed. For example, cryosurgery uses a gas, usually nitrogen, to cool the region of interest (Singh and Kumar, 2014). On the other hand, in hyperthermia, a conductive material is generally used to heat the region of interest (Andra et al., 1999).

In relation to heating process of human body, it is known that the increase in temperature stimulates the immune system and, consequently, helps to eliminate unwanted organisms (Pennes, 1948). In the case of tumor treatment, when the affected area is heated, cancer cells deteriorate while healthy ones can be preserved, i.e., depending on the exposure time of the tissue and the temperature (usually between 40 and 45 ^{o}C), healthy cells remain unchanged, while tumor cells tend to be destroyed. Temperatures up to 45–50 ^{o}C induce necrosis and contribute to the elimination of cancer tissue due to dehydration, thickening, and denaturation of intracellular proteins, as well as destroying cell membranes. Finally, temperatures between 50 and 100 ^{o}C causes coagulation necrosis. (Olayiwola et al. 2012).

During the hyperthermia process, itis very important to control the temperature in the region of interest, in order to minimize possible damage to healthy tissues. In this case, to evaluate the effective destruction of a tissue, the integralof Arrhenius(Connors, 1990) must be computed. This allows to measure, indirectly, the level of cell destruction during this process (Behrouzkia et al. 2016).

The hyperthermia procedure is indicated for carcinomas at initial stage, which can be associated with other types of treatment in order to increase the effectiveness and guarantee the total elimination of tumor (Zhu et al. 2012). For example, hyperthermia can be associated with radiotherapy to improve the control of the tumor sizewhile minimizing damage to healthy tissue (Jha et al. 2016). In addition, for certaincancer drugs, the hyperthermia treatment can be used to improve the absorptionand to accelerate chemical reactions in chemotherapy, i.e., this treatment becomes more effective and less toxic (Jha et al. 2016).As mentioned by Wust et al. (2002), the main side effects observed in hyperthermia are: pain at target site, bleeding, blood clots, infection, swelling, burns, blistering, and also cause damage to skin, nerves and muscles around the treated area.

Among the different cancer treatments, hyperthermia seems to be the least employed in clinical practice (Coleman et al. 2009). One reason for this may be the difficulty in directing sufficient amounts of heat only to tumor tissue (Olayiwola et al. 2012). In practice, the effectiveness of this type of treatment depends on several factors, such as the maximum temperature reached, the total heating time and the tumor tissue properties (Coleman et al. 2009).

The efficiency of tumors treatment by hyperthermia requires the knowledge of temperature distribution in order to minimize the side effects. In this context, due to the complexity of tissue structure and its high heterogeneity, the use of numerical models arises as a powerful tool for the prediction and control of temperature distribution in treatments for hyperthermia (Lamien, 2015).

In this contribution, the objectiveis to formulate and solve inverse problems for the determination of geometry and source term during the hyperthermia process. The proposed methodology consists of associatingthe Normal Collocation Method (NCM), used to solve the direct problem, with the Differential Evolution (DE) algorithm, considered to solve the inverse problem. This work is structured as follows. In Section 2, the mathematical model that represents the process of interest is presented, as well as a brief description of the NCM. In Section 3, the DE algorithm is presented. The main steps of the proposed methodology are presented in Section 4. The results obtained with the solutionof three case studies considering real experimental points are presented in Section 5. The conclusions are drawn in the last section.

2. MATHEMATICAL MODELING

Consider a heat source *P* concentrated within a small sphere of radius *R,* surrounded by a homogeneous medium, according to Fig. 1. Two regions of interest are depicted: (1) represents the interior of the sphere with radius $r \leq R$, and (2) is defined by the homogeneous material outside of the sphere, given by$R < r \leq R_{max}$, where R_{max} is the total size of the domain.In turn, the temperature sensors are defined at specific points in theradial domain.

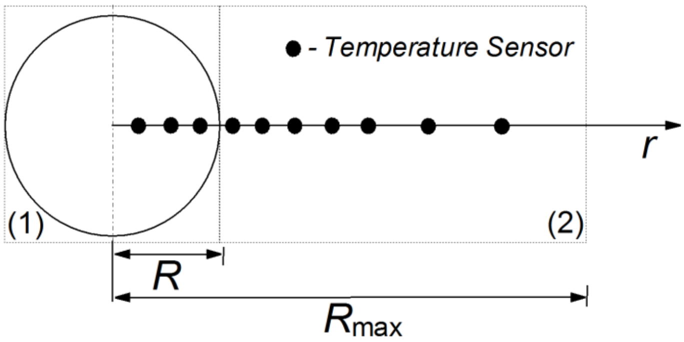


Figure 1. Schematic representation of the domain considered (Adapted from Andra et al. (1999)).

The material used for heating (region 1) and the surrounding environment (region 2) are characterized by values of respective heat conductivities (*λ*), by their specific capacities (*c*) and densities (*ρ*).Due to the symmetryin relation to the center of the sphere, the temperature profile (*T*) can be assumed to be dependent only ontime (*t*) and radial position (*r*), i.e., the temperature is denoted by *T*(*t*,*r*). Considering that the surrounding environment represents a region with small size and homogeneity, with negligiblemetabolic generation and blood perfusion rate, this process can be modeled by the classical heat conduction equation. Mathematically, this process is represented, in spherical coordinates, by the following differential equations (Andra et al., 1999):

$$\rho_1 c_1 \frac{\partial T_1}{\partial t} = \frac{\lambda_1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial T_1}{\partial r}\right) + P, \quad 0 \leq r \leq R \tag{1}$$

$$\rho_2 c_2 \frac{\partial T_2}{\partial t} = \frac{\lambda_2}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial T_2}{\partial r}\right), \quad R < r \leq R_{max} \tag{2}$$

where subscripts 1 and 2 represent regions (1) and (2), respectively, as shown in Fig. 1, valid for all $t \geq 0$.

To evaluate this model, it is considered that the initial temperature (t=0) for all spatial domain is equal to T_0, i.e.:

$$T_1(0,r) = T_0, \quad 0 \le r \le R \tag{3}$$

$$T_2(0,r) = T_0, \quad R < r \le R_{max} \tag{4}$$

Due to the symmetry, the temperature in the center of the sphere (r = 0) is finite. Mathematically, this condition can be represented as:

$$\frac{\partial T_1(t,0)}{\partial r} = 0, \quad t \ge 0 \tag{5}$$

For r□ R_{max}we consider that the temperature is nearly equal to initial temperature of the process, i.e.:

$$T_2(t,R_{max}) = T_0, \quad t \ge 0 \tag{6}$$

Since the domain of this problem is characterized by two regions, the continuity for temperature and heat flow must be guaranteed at$r$ equal to R, i.e.:

$$T_1(t,R) = T_2(t,R), \quad t \ge 0 \tag{7}$$

$$\lambda_1 \frac{\partial T_1(t,R)}{\partial r} = \lambda_2 \frac{\partial T_2(t,R)}{\partial r}, \quad t \ge 0 \tag{8}$$

To solve the forward problem, the Normal Collocation Method (NCM) is considered. In general, it is based on the definition of a surrogate function (generally a polynomial function), in which its numerical solution is evaluated by considering an arbitrary number of points (Villadsen and Stewart, 1967). For this purpose, the original equation must satisfy the approximation function at the points considered, as well as the initial and boundary conditions (if the test case is aboundary value problem). Thus, once the polynomial is defined, it is replaced in the original model, obtaining residuals for each point considered. Such residuals must be minimized. The algebraic system coming from this operation must be solved taking an appropriate numerical technique. The main steps for application of this approach are presented below (Laranjeira and Pinto, 2001):

- Define the input parameters: mathematical model, initial-boundary conditions, and order (N) of the approximation (the polynomial has N+1 coefficients);
- Define the collocation points (generally, these points are equally spaced);

- Replace the approximation function in the original differential model. Thus it is converted into an equivalent nonlinear equation. The approximation function mustbe satisfied according to the boundary conditions;
- The resulting nonlinear model is solved by using, for example, the Newton Method;
- Verify if the obtained solution is sensitive in relation to theincrease of the degree of approximation.

It is worth mentioning that the quality of the obtained results depends both on the approximation function considered and the number of collocation points. In this case, by increasing the number of collocation points does not necessarily imply the improvementof the obtained results. According to Villadsen and Michelsen (1978), this methodology is easy to be implemented even for highly nonlinear problems.

3. INVERSE PROBLEM

In order to solve the inverse problem, we consider the DE algorithm, proposed by StornandPrice (1995), to solve unconstrained single-objective optimization problems. In general, this heuristic approach is based on vector operations (addition and subtraction) to generate a potential candidate for solving general optimization problems. The procedure proposed in this algorithm consists of the following steps (Price et al. 2005):

- Characterization of problem: objective function andconstraints (in this case, a penalization strategy is used to lead with this type of case study), vector of design variables and search space (domain of the problem);
- DE parameters: population size (*NP*), number of generations, crossover probability (*CR*), perturbation rate (*F*) and a particular strategy considered for generation of mutant vector;
- An initial population is randomly generatedwith *NP* candidates, ensuring that all individuals are within the feasible domain;
- Each individual is evaluated according to objective function. The best candidate, in terms of value of this function, is taken to bethe current optimal solution;
- While the number of generations is not met, three individuals(chosen randomly in the population) are selected (one is selected to be replaced and two other individuals to perform the vector subtraction). The difference between these two individuals is added to the third individual, weighted by a perturbation rate *F*. This procedure

representsthe mutation operator, and is repeated until a new population, with size *NP* is generated;

- The crossover operator combines the characteristics of individuals from the original population of a given generation, with individuals resulting from the mutation. For each coordinate of the mutant vector, if a normally distributed random number in the range [0, 1] is less than *CR*, or if a particular coordinate of the mutant vector is selected at random, the corresponding coordinate is replaced in the individual of the original population.
- In the selection step, the individuals resulting from the mutation and crossover operations are compared one by one with the individuals of the original population, in terms of the value of the objective function, in order to define the members of the next generation.
- These proceduresare repeated until a stopping criterion (generally the number of generations) is satisfied.

StornandPrice (1995) suggest a set of default parameters for initializing this algorithm. Typically, *NP* should be between 5 and 10 times the dimension of the problem to be solved. The perturbation rate *F* must be chosen in the range [0, 2] (a good initial value for this parameter is 0.5). The crossover probability *CR* should be a value close to one (0.8 may be a good initial choice). For the generation of potential candidates, StornandPrice (1995) proposed 10 strategies. Some of them are presented below:

- rand/1: $X = X_{\kappa_1} + F(X_{\kappa_2} - X_{\kappa_3})$;
- rand/2: $X = X_{\kappa_1} + F(X_{\kappa_2} - X_{\kappa_3} + X_{\kappa_4} - X_{\kappa_5})$;
- best/1: $X = X_{best} + F(X_{\kappa_2} - X_{\kappa_3})$;
- best/2: $X = X_{best} + F(X_{\kappa_2} - X_{\kappa_3} + X_{\kappa_4} - X_{\kappa_5})$;

where κ_i (i = 1, 2, ..., 5) represents the *i*-th position of the population (chosen randomly from [1, NP], all of which must be different from each other), and X_{best} is the best solution in the current generation. In these relations, the kind of process may berandom or not (in this last case, the approach is called*best*), and 1 or 2 represents the number of pairs considered for the generation of a potential candidate. The complete description of all steps of the DE algorithm can be found in Storn and Price (1995)

4. METHODOLOGY

The methodology proposed in this work consists of the following steps:

- To solve the direct problem, a polynomial approximation with a degree equal to 10 in the NCMisconsidered. In this case, 250 and 300 pointsequally spacedin radial and temporal directionsare used;
- Three inverse problems (IP) are proposed: i) determination of the source term P(IP$_1$); ii) determination of the radius R (IP$_2$); and iii) determination of the source term P and radius R (IP$_3$). For each problem, the following objective functions (OF) are defined:

$$\mathrm{PI}_1 \to \min_{P} FO_1 \equiv \sum_{i=1}^{N_1}\sum_{j=1}^{N_2}\left(T^{\exp}\left(t_i,r_j\right)-T^{cal}\left(t_i,r_j\right)\right)^2 \tag{9}$$

$$\mathrm{PI}_2 \to \min_{R} FO_2 \equiv \sum_{i=1}^{N_1}\sum_{j=1}^{N_2}\left(T^{\exp}\left(t_i,r_j\right)-T^{cal}\left(t_i,r_j\right)\right)^2 \tag{10}$$

$$\mathrm{PI}_3 \to \min_{P,R} FO_3 \equiv \sum_{i=1}^{N_1}\sum_{j=1}^{N_2}\left(T^{\exp}\left(t_i,r_j\right)-T^{cal}\left(t_i,r_j\right)\right)^2 \tag{11}$$

where $T^{exp}(t_i,r_j)$ and $T^{cal}(t_i,r_j)$ represent the experimental and calculated (simulated) temperature distributions at the coordinate points (t_i,r_j), respectively. N_1 and N_2 represent the number of experimental points in temporal and radial directions, respectively. In each problem, the system of equations defined by Eqs. (1)-(8) is evaluated to obtain the temperature profiles;

- For IP$_1$, $0 \le P \le 10$ (W/cm^3) and R equal to 0.315 (cm) are considered. For IP$_2$, $0.01 \le R \le 1$ (cm) and P is equals to 6.15 (W/cm^3). Finally, for IP$_3$, both P and R are not known, i.e., $0 \le P \le 10$ (W/cm^3) and $0.01 \le R \le 1$ (cm);
- In all applications, additional parameters are considered (Andra et al., 1999): T_0 = 0 ^{o}C, ρ_1= 1.66 (g/cm^3), c_1 = 2.54 (J/(g K)), $\lambda_1 = 0.778\times10^{-2}$(W/(K m)), ρ_2 = 1 (g/cm^3), c_2 = 3.72 (J/(g K)), $\lambda_2 = 0.642\times10^{-2}$ (W/(K m)), R_{max} = 1.5 (cm), and $0 \le t \le 300$ (s);
- The experimental points, required to formulate each IP, are taken fromAndra et al. (1999). These authors describe the experimental procedure used to heata region of a muscle tissue considered to represent small carcinomas in breast. To evaluate each of objective function, two sets of experimental pointsare considered. In the first,the

temperature sensors are located at *r*= (0.20475 0.3465 0.43785 0.5292 0.6237) (cm) and in the second,the temperature sensors are located at *t* = (6 22 45 101 196) (s);

- DE Parameters: population size *NP* = 20, maximum number of generations equal to 50, crossover probability *CR* = 0.8, perturbation rate *F* = 0.8, rand/1/bin strategy (Storn and Price, 1995), and maximum number of generations as a stopping criterion. The DE algorithm is executed 20 times considering different initial seeds in random number generator. In each run, the number of objective function evaluations is 20+20×50.

5. RESULTS AND DISCUSSIONS

Table 1 presents the results obtained considering the proposed methodology for each inverse problem. At first, it is observed that DE, for the parameters defined in the previous section, is able to find good estimates for the design variables in all runs for each problem, given the value of the standard deviation obtained, i.e., the DE algorithm always converged to nearly the same point.

Table 1. Results obtained for each inverse problem.

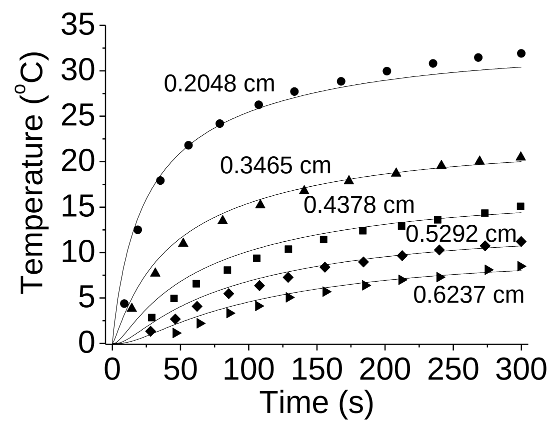
		P (W/cm^3)	*R* (cm)	*OF* (^{o}C^2)
IP$_1$	Best	6.0515	-	58.6299
	Standard Deviation	3.0767×10^{-4}	-	1,3205×10^{-4}
IP$_2$	Best	-	0.3149	62.9705
	Standard Deviation	-	1.4196×10^{-4}	8.7028×10^{-5}
IP$_3$	Best	5.6763	0.3281	51.4430
	Standard Deviation	1.0824×10^{-3}	1.3012×10^{-4}	1.9776×10^{-3}

In case of the IP$_1$, the value of the source term *P* estimated (*P* = 6.0515 W/cm^3) agrees with that adopted by Andra et al. (1999) (which is *P* = 6.15 W/cm^3) for the generation of temperature profiles during the treatment. Regarding the second inverse problem, the estimated radius (*R* = 0.3149 cm) is also in agreement with that used by Andra et al. (1999) (*R* = 0.315 cm). Finally, for the last IP, the results obtained by the proposed methodology (*P* = 5.6763 W/cm^3 and *R* = 0.3281 cm) are also close to those adopted by Andra et al. (1999) (*P* = 6.15 W/cm^3 and *R* = 0.315 cm). For the last case, greater distances between the values are observed,in comparison to the first two IPs. This is due to need for simultaneous adjustment of the models to the experimental points and, regarding the inherent errorof the process, both the parameters P and R suffer small deviations when compared to individual adjustments. However, it is important to note that, as expected, the increase in the number of design variables in the last IP reduces the value of *OF* in comparison to the first two cases. This is due to the fact that the number of degrees of freedomhas increased, which allows, in practice, the best concordance between experimental and simulated profiles.

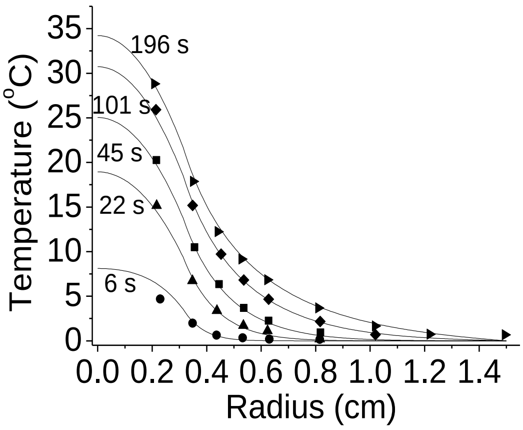
Figures 2(a), 2(c) and 2(e) present the temperature profiles as a function of time, according to the sensors located at r = [0.20475 0.3465 0.43785 0.5292 0.6237] (cm). Figures 2(b), 2(d) 2(f) present the temperature profiles as a function of radius considering some time instants t = [6 22 45 101 196] (s). For each IP, a good agreement between experimental and simulated profiles is observed. This demonstrates that the proposed methodology is able to find a set of parameters for the purpose of minimizing each objective function. From the physical point of view, it can be seen in Fig. 2(a) that close to the center of the sphere, the temperature increases with time. On the other hand, for points located above the radius of the sphere (R = 0.315 cm), as the source term is equals to zero, the temperature is close to the boundary condition, i.e., $T_0 = 0$ ^oC. The same behavior can be observed for Figs. 2(c) and 2(e). In Fig. 2(d) it is clear that the boundary conditions are met, i.e., at $r = 0$ cm, the heat flow is equal to zero (symmetry condition) and for $r = R_{max}$ cm, we have $T_0 = 0$ ^oC. For a given radial position, when the time increases, the temperature also increases, indicating that the system is being heated. In this case, the system is heated in the domain defined between $0 \leq r \leq R_{max}$ (region (1)) and the tissue (region (2)), thus simulating the process of hyperthermia.

6. CONCLUSIONS

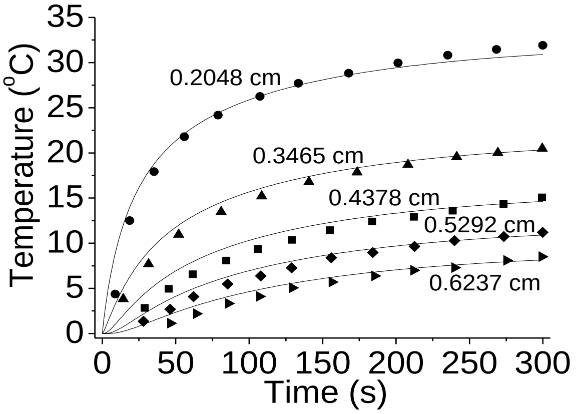
The present work aimed to formulate and solve inverse problems to represent the hyperthermia process considering a spherical heat source. For this purpose, three case studies were defined. The first was proposed to determine the source term, the second to determine the radius and the third to determine both source term and geometry. For the solution of the direct problem, the Normal Collocation Method was considered. In the case of the inverse problem, the Differential Evolution algorithm was used. From the obtained results it was possible to verify that the proposed methodology was able to obtain good estimates in all the proposed inverse problems, considering the good adjustment between the experimental and simulated profiles.



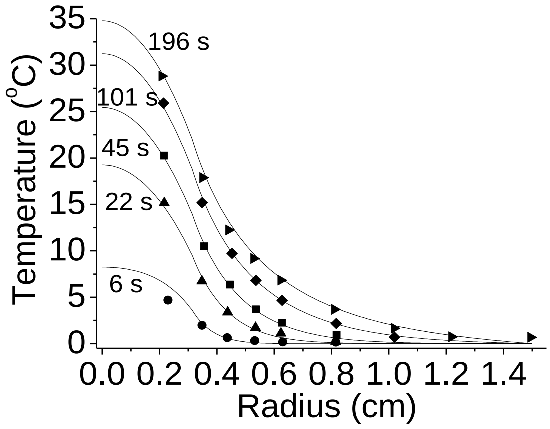
(a) Time Profile for the IP_1.



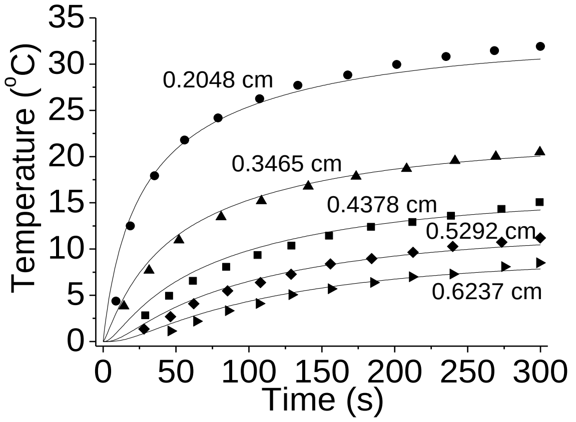
(b) Radial Profile for the IP_1.



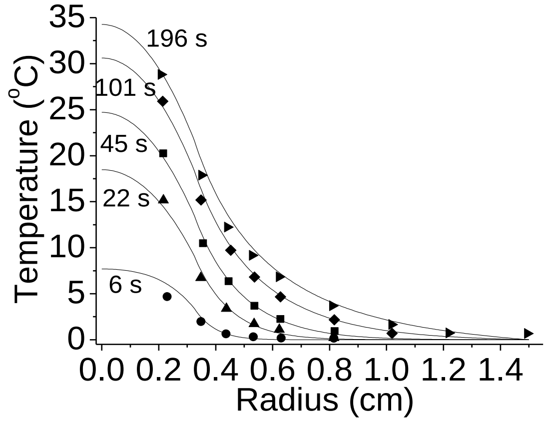
(c) Time Profile for the IP_2.



(d) Radial Profile for the IP_2.



(e) Time Profile for the IP_3.



(f) Radial Profile for the IP_3.

Figure 2. Experimental and calculated temperature distributions for IP_1, IP_2 and IP_3.

It is important to note that the formulation and solution of this type of inverse problem allows obtaining parameters used for the study of hyperthermia process. In this case, establishing these parameters and the mathematical model, it is possible to simulate different conditions in order to evaluate different strategies for tissue heating, as well as this can be coupled with other mathematical models for the characterization of thermal damage, and to formulate design problems to determine the time operation required to heat the tumor region.

As a proposal for future work, an inverse problem described by fractional differential equations and considering terms related to metabolic generation rate and blood perfusion will be studied. In addition, the Arrhenius model for calculating thermal damagewill also be incorporated to the proposed model.

REFERENCES

ANDRA, W., D'AMBLY, C. G., HERGT, R., HILGER, I., KAISER, W. A.**Temperature Distribution as Function of Time Around a Small Spherical Heat Source of Local Magnetic Hyperthermia**. Journal of Magnetism and Magnetic Materials, 194, 197-203, 1999.

BEHROUZKIA, Z., JOVEINI, Z., KESHAVARZI, B., EYVAZZADEH, N., AHGDAM, R. Z. **Hyperthermia: How Can It Be Used?**. Oman Medical Journal, 31, 89-97, 2016.

COLEMAN. A., AUGUSTINE, C. K., BEASLEY, G., SANDERS, G., TYLER, D. **Optimizing Regional Infusion Treatment Strategies for Melanoma of the Extremities**. Expert Rev. Anticancer Ther, 9, 1599-1609, 2009.

CONNORS, KENNETH A. **Chemical kinetics: the study of reaction rates in solution**. New York, VCH, 1990.

HAFID, M. AND LACROIX, M. **An Inverse Heat Transfer Algorithm for Predicting the Thermal Properties of Tumors during Cryosurgery**. International Journal of Biomedical and Biological Engineering, 11(6), 352-360, 2017.

JHA, S., SHARMA, P. K., MALVIYA, R. **Hyperthermia: Role and Risk Factor for Cancer Treatment**. Achievements in the Life Sciences, 10(2), 161-167, 2016.

LAMIEN, B. **Problema de Estimativa de Estado no Tratamento de Câncer por Hipertermia com Aquecimento por Laser Diodo na Faixa do Infravermelho Próximo**. Tese de Doutorado, Engenharia Mecânica - COPPE, Universidade Federal do Rio de Janeiro, 2015.

LARANJEIRA, P., PINTO, J.C. **Métodos Numéricos em Problemas de Engenharia Química**, Editora E-Papers, 316, ISBN 85-87922-11-4, 1º ed., 2001.

OLAYIWOLA, R. O., OLABIYISI, S. O., ODEBIYI, O. A., NDANUSA, A., MOMOH, R. M.. **Modeling and Simulation of Hyperthermia as Cancer Treatment**. International Journal of Science and Technology, 2, 590-595, 2012.

PENNES, H. H. **Analysis of Tissue and Arterial Blood Temperatures in the Resting Human Forearm**. Journal of Applied Physiology, 1(2), 93-122, 1948.

PRICE, K. V., STORN, R. M., LAMPINEN, J. A. **Differential Evolution: A Practical Approach to Global Optimization**, Springer Berlin Heidelberg, Berlin, Heidelberg, 2005.

SINGH, S. AND KUMAR, S. **Numerical Study on Triple Layer Skin Tissue Freezing using Dual Phase Lag Bio-Heat Model**. International Journal of Thermal Sciences, 86, 12-20, 2014.

STORN, R. M., PRICE, K. V. **Differential Evolution - A Simple and Efficient Heuristic for Global Optimization over Continuous Spaces**, Journal of Global Optimization, 11, 341-359, 1995.

SULEMAN, M., RIAZ, S., JALIL, R., **A Mathematical Modeling Approach Toward Magnetic Fluid Hyperthermia of Cancer and Unfolding Heating Mechanism**. Journal of Thermal Analysis and Calorimetry, 1, 1-27, 2020.

VILLADSEN, J., MICHELSEN, M.L. **Solution of Differential Equation Models by Polynomial Approximation**. Prentice-Hall, Inc., Englewood Cliffs, N.J., 1978.

WUST, P., HILDEBRANDT, B., SREENIVASA, G. **Hyperthermia in Combined Treatment of Cancer,** Lancet Oncol., 3 (8), 487-497, 2002.

ZHU, Q., ZHANG, A., LIU, P., XU, L. X. **Study of Tumor Growth under Hyperthermia Condition**. Computational and Mathematical Methods in Medicine, 198145-198154, 2012.