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A Short Review of Applications of inverse heat equation in medical sciences

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Abstract : The models which take spatial effects into consideration are expressed in terms of partial differential equations (PDEs), and in the field of medical they also need to take into account the fact that the tumor region is changing in time; in fact, the tumor region and its boundary $\Gamma(t)$, are unknown in advance. Thus one needs to determine both the unknown "free boundary" $\Gamma(t)$ together with the solution of the PDEs in the tumor region. This type of problem is called a *free boundary problem*. The models described in this chapter are free boundary problems. The main concern is the spatial/geometric features of the free boundary. This paper is to present some results of various researchers and mathematicians on mathematical modeling, analysis, and numerical simulations of cancer treatment and diagnosis in Hyperthermia, ductal carcinoma in situ and Infrared Thermography. In particular, we formulate a number of inverse problems for the well-posed free boundary valued problem related to clinical diagnose of cancer.

Keywords : Inverse Heat Equation, DCIS, Hyperthermia, Infrared Thermography, Penne's bio heat model, Bio- heat transfer equation.

1. INTRODUCTION

Inverse heat equations find their use in various fields of medical sciences. At present, modern surgery has at its disposal a great variety of different surgical techniques for heating biological tissue in a localized and safe way. All these techniques are based on specific applicators, *i.e*. devices which extract (cryosurgery) or introduce heat (laser, radiofrequency current, microwave or ultrasound treatments). The present section deals with parabolic partial differential equation (PDE) models arising in medicine (example: cancer therapy hyperthermia, DCIS, Thermography.) .In this type of application the 3D geometry – say, of human patients – motivates the choice of *tetrahedral* finite element methods (FEM). The clinical setting requires the robust computational solution of problems to prescribed accuracy at highest possible speed on local workstations. Reliability plays the dominant role in medicine, which is a nice parallelism with the intentions of mathematics. Numerical speed is required to permit a fast simulation of different scenarios for different patients. In other words: the situation both requires and deserves the construction of highly efficient algorithms, numerical software, and visualization tools. Before moving ahead a brief introduction of these medical terms has been given below.

1.1. Cancer

Cancer is a class of diseases or disorders characterized by uncontrolled division of cells and the ability of these cells to spread, either by direct growth into adjacent tissue through invasion, or by implantation into distant sites by metastasis. Transportation of cancerous cells to distant sites is done through the bloodstream or lymphatic system. Cancer may affect people at all ages, but risk tends to increase with age. It is one of the principal causes of death in developed countries.

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Cancer may attack any organ, *e.g*. liver, lung, breast etc. while the severity of disease depends on various parameters such as the site and character of the malignancy and the presence/absence of metastasis. Despite of the fact that modern medicine and medical research and technology made significant progress on the last decades, still a definitive cancer diagnosis usually requires the histological examination of tissue by a pathologist. This tissue is obtained by an invasive procedure as biopsy or surgery. Most cancer types can be treated and some cured, depending on the specific type, location, and stage.

Once diagnosed, cancer treatment usually involves a combination of surgery, chemotherapy and radiotherapy. In cases of late detection or no treatment, cancers may eventually cause illness and death, though this is not always the case.

Cancer can also occur solely in young children and adolescents.

1.2. Hyperthermia

The objective of application of oncology is indisputable: to destroy selectively - if possible – the malignant cells, to eliminate the tumor by heat [1]. The deep-heat targeting and control of noninvasive transfer of energy are major problems of oncological hyperthermia. The theoretical discussion and strict biophysical examination of the actually used, mainly experimentally introduced, control parameters and dose concepts are vital in any serious investigation.

It seems to be of vital importance the definition of hyperthermia object function in oncology. Hyperthermia (also called **thermal** therapy or thermotherapy) is a type of **cancer treatment** in which body tissue is exposed to high temperatures (up to 113°F). Research has shown that high temperatures can damage and kill **cancer** cells, usually **with** minimal injury to normal tissues (1) At present this therapy is applied in combination with chemotherapy or radiotherapy. The idea is that heated tumor cells are more sensitive to extinction by either rays or drugs. For the medical treatment, the cancer patient is put into an applicator, which essentially consists of a set of 83 (old) or 24 (new) radiofrequency antennas and a water bolus to allow for a low reflection passage of the radio waves into the body. [1]

The antennas emit radiation at a frequency of about 100 MHz corresponding to a wave length in water of about 30 cm, which – physically speaking – means that *wave optics* and interference phenomena rather than ray optics must be modelled. Heat within the body is produced by absorption of the radio waves and distributed by blood circulation in the tumor as well as in sane tissue. Mathematically speaking, the whole system (*patient, water bolus, applicator, surrounding air*) is modeled by the time harmonic Maxwell's equations in inhomogeneous media and a so– called bio–heat transfer (BHT) partial differential equation describing the heat distribution in the body. The task is to tune the set of radiofrequency antennas optimally such that the heat will concentrate within the tumor of a patient, but not at any hot spots elsewhere.

1.3. Ductal carcinoma in situ (DCIS)

Breast cancer is the most common cancer in women, among whom it is the second leading cause of cancer death. Ductal carcinoma in situ (DCIS) refers to a specific diagnosis of cancer that is isolated within the breast duct, and has not spread to other parts of the breast. At this stage, the tumor is noninvasive, being confined by the basement membrane of the duct. However, if left untreated, it is thought to then invade the breast stromal tissue surrounding the ducts, and become life threatening. The duct is made up of a central region of lumen (extracellular fluid), lined by a thin layer of epithelial cells, a layer of myo-epithelial cells and an outer basement membrane (the duct wall) comprising a meshwork of proteins. Ducts in the healthy breast have an average diameter of 0.2 mm and are surrounded by stroma (connective tissue). DCIS occurs when there is a proliferation of epithelial cells that have undergone a malignant transformation (usually originating from a single mutant cell). DCIS is characterized according

to the appearance of the tumor cells proliferating within the duct and the broadest classification subdivides them into two types: high (comedo) and low grade (non-comedo) DCIS [15]. Low grade DCIS is well differentiated, the non-comedo type DCIS tends to be less aggressive than the comedo types of DCIS. The most common non-comedo types of DCIS are: (1) Solid DCIS: cancer cells completely fill the affected breast ducts. (2) Crib form DCIS: cancer cells do not completely fill the affected breast ducts; there are gaps between the cells. (3) Papillary DCIS: the cancer cells arrange themselves in a fern-like pattern within the affected breast ducts.

1.4. Thermography

Medical infrared thermography is non-invasive, non-contact and functional imaging method that measures the radiation emitted from the skin surface and provides information about subtle temperature changes in it. The different patterns of temperature not only depend on physical parameters such as the tissue sensitivity coefficient, but also in the physiology associated to the homeostatic and metabolic processes and the structure and dynamics of the vascular, tissular and nervous systems.

Medical applications of infrared thermography are not a recent phenomenon. However, in the past years their success was rather limited mainly due to the complexity, high cost and poor sensitivity provided by the generation of infrared cameras that were available at that time. Nowadays, advances in the infrared technology have again promoted its medical application as a promising non-invasive tool for imaging the functionality of superficial layers of tissues and the influence of vascular, neurogenic and metabolic process that affect them. In [7] Santa Cruz et al. have investigated by means of thermography the correlation, in patients treated with boron neutron capture therapy (BNCT), between the spatial extension of the acute skin reaction and the superficial dose distribution, in order to better determine tolerance doses and therefore to optimize the BNCT treatment. Also they conclude that given the capacity of thermography to observe the functional aspects of tissues, the technique can help to locate abnormally high temperature regions as well as melanoma nodules that are virtually invisible in CT images.

2. HEAT TRANSFER MODEL

Our present model for the dissipation of heat in the human body (*cf*. Pennes [4]) assumes potential flow for the blood within the various tissues including the tumor. This leads to the so–called *bio–heat transfer equation* (BHT)

$$\rho_t c_t \frac{\partial T}{\partial x^2} = k \frac{\partial^2 T}{\partial x^2} - W \rho_t \rho_b c_b (T - T_a) + Q,$$

$$Q = \frac{\sigma}{2} |E|^2 \tag{2.1}$$

Herein ρ_t, ρ_b denotes the density of tissue and blood, c_t, c_b the specific heat of tissue and blood, T, T_a the temperature of tissue and arterial blood, *k* the thermal conductivity of tissue, W the blood perfusion, Q the power deposition within the tissue, and σ the electric conductivity. The thermal effects of *strong* blood vessels are excluded in this simplified model.

The three dimensional Pennes' equation corresponding to practical situation is given by

$$\rho_t c_t \frac{dT}{dt} = k\left(\frac{d^2T}{dx^2} + \frac{d^2T}{dy^2} + \frac{d^2T}{dz^2}\right) - W\rho_t\rho_b c_b (T - T_a) + Q(x, y, z) \tag{2.1}$$

This energy balance equation is rewritten with temperature as the independent variable. To start with the energy storage term is represented in terms of its thermal capacitance and a first order derivative of temperature with time as $\rho c \frac{\partial T}{\partial t}$. The heat generation term is given as Qa. The remaining two terms on the right hand side are the conductive or convective heat transfer either into or out of the control volume. W_{cb} is proportionality constant and this relates the amount of perfusion induced convective cooling to the magnitude of temperature difference (T-Ta).

2.1. Optimal control problems on temperature distribution of the tumor embedded inside the biological tissue in hyperthermia

In hyperthermia treatment, the tumor cells inside the tissue are heated to a beneficial therapeutic temperature so as to kill the tumor cells by avoiding the damage of the healthy tissue [14]. In the last two decades, the conjugate gradient method coupled with ad joint equation approach has been extensively used in the resolution of general inverse heat transform problems [9]. The conjugate gradient method devices the basis from the variational principle and transforms the original direct problem to the solution of two sub problems, namely, the direct problem in variation and the adjoint problem [14].

In this method, a system of adjoint function and the condition of optimality of the control variables are obtained with the aid of calculus of variation [14]. The optimal values of control variables, thus, can be obtained from the optimality condition of the controls by means of computer simulations [2].

In course of analytical investigation of optimal control problems in multilayered biological tissue, the methodology generally adopted is the usual 'Maximal Principle' with a suitably constructed Hamiltonian followed by the use of a variant of finite difference method [13,11].

Some analytical investigations of optimal control problems on temperature distribution described by bio-heat transfer equation in multi-layered biological tissue have been carried out in different articles on the basis of Penne's bio-heat model [13].

In order to raise the temperature of the tumor inside the tissue to its beneficial therapeutic value, heat is generated in the tissue by microwave, laser and ultrasound which are most commonly used heating methods. Considering Penne's bio-heat model, analytical investigations on this aspect of temperature distribution in the tissue by controlling heating power have been studied in different articles [9, 10].

3. FREE BOUNDARY PROBLEM MODEL OF DCIS

Based on the ways they access the DCIS, they have posed different inverse problems for the free boundary model. In their paper they formulated four different inverse problems but we are taking only two inverse problems relevant to present scenario. One typical type of DCIS is that cancer cells completely fill the affected breast duct (solid type). We describe the solid type of DCIS by an one dimensional model.

We assume the tumor to be within the interval $[-s(t)/2,\ s(t)/2]$ at each time t; the growing boundary of the tumor is given by $x = -s(t)/2$ and $x = s(t)/2$, where $x = S(t)$ is an unknown function. As tumor growth strongly depends upon the availability of nutrients, its diffusion through the growing material is introduced in the description of model. We model tumor growth, using dimensionless nutrient concentration $C(x,t)$ which satisfies a reaction-diffusion equation. In the one-dimensional case, the model is simplified to-

$$\frac{\partial C}{\partial t} = \frac{\partial^2 C}{\partial x^2} - \lambda(x)C, \quad \text{in } B(t),\ t > 0 \tag{3.1}$$

$$C(-s(t)/2,\ t) = C_1, \qquad t > 0 \tag{3.2}$$

$$C(s)(t)/2,\ t) = C_1, \qquad t > 0 \tag{3.3}$$

$$C(x,\ 0) = C_0(x), \quad \text{in } B(0) \tag{3.4}$$

$$\frac{\partial s}{\partial t} = \mu \int_{-s(t)/2}^{s(t)/2} (C - \tilde{C})dx, \quad s(0) = s_0 \tag{3.5}$$

Where

$$B(t) = \left\{ x \mid \frac{s(t)}{2} < x < \frac{s(t)}{2} \right\},$$

$$B(t_0) = (-s_0/2,\ s_0/2).$$

Here $\lambda(x)\,C(x, t)$ is the nutrient consumption rate at the location x at time t. μ, C_1, $\widetilde{C}$ and s_0 are known constants. $C_0(x)$ and $\lambda(x) \geq 0$ the initial data, are given. The free boundary problem is to determine $(C(x,t), s(t))$ for given $\lambda(x)$, $C_0(x)$, μ, C_1, $\widetilde{C}$ and s_0.

3.1. Inverse problems related to cancer diagnose

There is a number of inverse problems motivated by cancer diagnosis.

3.1.1. Clinical data is obtained by one incisional biopsy. [17]

When noticing possible breast cancer, one opts to do an incisional biopsy to find out the DCIS pattern along with the changing rate at the moment. Since no information is available before, we can assume no initial data given, instead we assume that two conditions are given at terminal time $t = T$.

The problem is as follows: find $C(x, t)$, $s(t)$,. $\lambda(x)$ Such that

$$\frac{\partial C}{\partial t} = \frac{\partial^2 C}{\partial x^2} - \lambda(x)C, \quad \text{inB}(t),\ 0 < t < T \tag{3.6}$$

$$C(-s(t)/2, t) = C_1, \quad 0 < t < T \tag{3.7}$$

$$C(s(t)/2, t) = C_1, \quad 0 < t < T \tag{3.8}$$

$$C(x, T) = C_T(x), \quad -\frac{s(t)}{2} < x < \frac{s(t)}{2} \tag{3.9}$$

$$\frac{\partial s}{\partial t} = \mu \int_{-s(t)/2}^{s(t)/2} (C - \widetilde{C})dx, \quad s(T) = s_T \tag{3.10}$$

Where $$C_T(x, T) = \left\{ \omega_T(x) \,|\, -\frac{s(t)}{2} < x < \frac{s(t)}{2} \right\}$$

3.1.2. Clinical data is obtained by a sequence of needle biopsy.

When noticing a possible breast tumor, it may be benign; therefore one opts to do a sequence of needle biopsies over a time interval to find out the DCIS pattern change in the time interval. In this case we assume that we know initial data, and data at an internal point over time interval [0, T].[17]

The problem is as follows: find $C(x, t)$, $s(t)$,. $\lambda(x)$ Such that

$$\frac{\partial C}{\partial t} = \frac{\partial^2 C}{\partial x^2} - \lambda(x)C, \quad \text{inB}(t),\ 0 < t < T \tag{3.11}$$

$$C(-s(t)/2, t) = C_1, \quad 0 < t < T \tag{3.12}$$

$$C(s(t)/2, t) = C_1, \quad 0 < t < T \tag{3.13}$$

$$C(x, 0) = C_0(x), \quad -\frac{s(t)}{2} < x < \frac{s(t)}{2} \tag{3.14}$$

$$C(x_0, t) = C_2(t), \quad 0 < t < T \tag{3.15}$$

$$\frac{\partial s}{\partial t} = \mu \int_{-s(t)/2}^{s(t)/2} (C - \widetilde{C})dx, \quad s(0) = s_0 \tag{3.16}$$

4. MATHEMATICAL MODEL OF INFRARED THERMOGRAPHY

A number of bioheat transfer equations for living tissues have been proposed since the landmark paper by Pennes appeared in 1948. His main theoretical contribution was the suggestion that the rate of heat transfer between the blood and tissue is proportional to the product of the volumetric perfusion rate and the difference between the arterial blood temperature and the local tissue temperature.

The equation includes the heat transfer by conduction through the tissue, the volumetric metabolic heat generation of the tissue and a term including the volumetric perfusion rate and the difference between the arterial blood temperature and the local tissue temperature, where the arterial temperature is approximated to the core temperature of the body. The Penne's bioheat transfer equation is widely used to solve the temperature distribution for thermal therapy. In most of the works related with this topic the following steady-state Penne's equation is considered;

$$\lambda_e \nabla^2 T_e(x) + k_0[T_b - T_e(x)] + Q_{me} = 0, \quad x \in R^n, \ \eta = 2, 3.$$

where the subscripts $e = 1, 2$ identify the sub domains of healthy tissue and tumor respectively (Fig. 1)λ_e, is the thermal conductivity, $k_e = G_b C_b$ is the perfusion coefficient (is the blood perfusion rate, is the volumetric specific heat blood, is the metabolic heat source and T_b is the constant blood temperature.

4.1. Inverse problem and results

According to them, the presence of a highly vascularized tumor can lead to the increase of local blood perfusion and the capacity of metabolic heat source and therefore this causes an increase of temperature at the skin surface. Then, the idea is to use the abnormal temperature at skin surface in order to predict the location, size and thermal parameters of the tumor; this has been done considering two different inverse problems. The first problem concerns in the localization; depth, width and size of the tumor, assuming that all others parameters are known. The second one, is related with the estimation of the metabolic heat source intensity inside the tumor region being. In both cases we used the same methodology. Given temperature profiles obtained from the simulations, these were used as the clinical data. Then the Pattern Search method [20, 23], was used to estimate the tumor parameters by minimizing a fitness function. The fitness function relates the given data to the temperature profile for a given set of estimated parameters.

The results obtained by them show that for the two-dimensional case, as well as for the three-dimensional case, it is possible to determine the required parameters from the surface temperature data. Moreover when 5% and 10% of random noise was added to the input data the results obtained were very good. In the case when the input data were contaminated with 15% of random noise the results obtained were good enough. In all cases the values of the known parameters and the dimensions of the domain were the same.

5. CONCLUSIONS

5.1. Hyperthermia

On the background of dual-phase-lag heat conduction model, mentioned in equations 2.1 and 2.2, the optimal control problems can well be studied which may focus a modern guideline on the aspect of hyperthermia treatment. Further, analytical and numerical studies on the optimization problems to determine the optimum heating pattern, induced by magnetic particle injections in the tumor models with irregular structures, can also be developed which will give a good insight on the strategy of modern hyperthermia treatment.

5.2. DCIS

Their analysis shows that if we have information of the tumor pattern, and some information related to its growth rate with time, which may be obtained through an incisional biopsy and sequence of needle biopsy, then we can use a regularized minimization method to determine the coefficient function of the free boundary problem model of DCIS, hence to estimate the growth tendency of the tumor.

Since this is a rather simple model that neglects accounting for some important factors such as tumor cell density, etc., further study is necessary. Nevertheless, this result shows a way to use mathematical model in the diagnostic process of the growth tendency of DCIS.

5.3. infrared Thermography

A simple methodology was developed for the estimation of thermo physical or geometrical parameters of a tumor region using the temperature profile on the skin surface that may be obtained by infrared thermography. These inverse problems have been solved using a second order finite difference scheme coupled with the Pattern Search algorithm. The presented results demonstrate the feasibility of the proposed methodology. Even in the case when 5% and 10% of noise was added to the input data the methodology estimates the different parameters with very good accuracy for the 2D case as well as for the 3D case.

The good results obtained are largely due to the strong restrictions imposed to class of functions allowed for the thermal coefficients and the metabolic heat source.

According to the results, this methodology can help to locate tumor regions, like melanoma nodules, as well as to estimate parameters related with them that could be useful and important to study the tumor evolution after a treatment procedure

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