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Statistical modeling of electrode based thermal therapy with Taguchi based multiple regression

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ABSTRACT

In this research the effect of physical predictors for the electrode based thermal therapy were considered and their effect on the final achieved temperature was quantified. For this purpose 6 predictors that may affect the temperature were studied. Knowledge of temperature inside the domain determines the extent of thermal damage in the domain. For the particular case of electrode based thermal therapy, a prediction model based on the regression analysis can be of immense importance in providing a quick and cost effective way to predict approximate temperature that would be achieved inside the computational domain. The regression model based on the physical predictors in an ideal situation can eradicate the need to solve complex electro-thermal equations for the prediction of temperature. In the first phase, a multiple regression model assuming a linear relationship between six independent variables and maximum achieved temperature as dependent variable or response was considered to best fit the observed values. A dummy variable was incorporated in the model to categorize the data for tissue and tumor. It was observed that multiple linear regression model could explain 82% of the variation in the observed data. In order to obtain a better prediction model, regression diagnostics were carried out and a modified model was obtained catering to the inherent nonlinear dependence of response variable on some variables. It was concluded that for electrode based thermal therapy improved regression model provided a marked improvement in terms of reliability of prediction over the original multiple linear regression model. Modified model was able to explain approximately 90% of the variation in observed data compared to 82% variation in data explained by the original model. Finally, it was revealed that as opposed to simulation software, the proposed regression model presents itself as being cheap, economical and quick alternative which can provide an estimate of the maximum temperature achievable inside the biological tissue.

1. Introduction

Cancer has been the leading cause of the mortality in the world and with each passing day its occurrence is increasing. Any treatment with minimum side effects can make a huge difference to the lives of patients suffering from cancer. There have been many modalities developed for the treatment of cancer. Thermal therapies have been developed which make use of the hyperthermic effects incurred by tissues by raising the temperature above 42 °C. In electrode based thermal therapy the electrodes are capacitively coupled and heating energy to the affected area is supplied by the resistance losses incurred in tissue by applying the electric potential across the electrodes. For thermal therapies the information about the temperature field inside the biological tissues is vital which shows the extent of thermal damage which is a function of temperature.

For temperature calculation inside the tissue various thermal models have been presented which differ in level of complexity and each one possessing different pros and cons [1,2] but Pennes bioheat model [3] is the most used model with many advantages like ease of implementation and effectiveness. The heat transfer inside the tissue can be represented by Pennes Equation [3]:

$$\rho c \frac{\partial T(X,t)}{\partial t} = \nabla.[k(X)\nabla T(X,t)] + \rho_b c_b \omega_b [T_a - T(X,t)] + Q(X,t) X \in \Omega \quad (1)$$

where $Q(X,t)$ includes the heat generated by external electromagnetic field $Q_r(X,t)$ and metabolic heat $Q_{met}(X,t)$ generated by natural mechanisms of the body.

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Pennes model has been extensively used for the heat transfer in biological simulations [2,4–10]. Charny et al. used Pennes bioheat equation for the simulation of limb heating [11]. Morose et al. computed the temperature distribution in muscle tissue and showed excellent agreement with the experimental results [12]. Tompkins et al. simulated the heat distribution in prostate cancer surrounded by normal tissue [13]. Yeh et al. simulated the bioheat transfer in intracavity applications and obtained a good correlation with the experimental results [14]. Hirate et al. used bioheat equation to simulate the heat transfer in human eye [15]. Ng et al. used two dimensional axisymmetric model of skin to simulate the skin burn injuries [16]. Deng et al. simulated the effect of large blood vessels on the temperature profile during cryosurgery [17]. Ooi et al. numerically investigated the effect of tumor on the temperature distribution in the eye [18]. Liu et al. simulated the bioheat transfer behind ribs utilizing the Pennes bioheat transfer which was validated with in vivo experiments in porcine liver [19].

Temperature plays an important role in hyperthermia therapy [4,20,21] and an elevated temperature can result in sudden death of the cell [20,22,23]. Based on the previous studies it is a well known fact now that maximum achieved temperature plays a vital part in the outcome of the treatment. Various studies quantifying the lethal effects of temperature on the tissues have been carried out and many thermal models have been proposed [24–27].

For electrode based thermal therapy, the energy is delivered by means of external electromagnetic field and maximum achieved temperature depends on the electric field strength inside the biological material. For the frequencies used in the electrode based thermal therapies, electric field strength inside the tissue can be calculated by simplified Maxwell's equations utilizing quasi static approximation. Kroeze et al. used the quasi static approximation at 13.56 MHz for the calculation of electromagnetic field inside the phantom and showed that the approximation was valid [28]. Liu et al. calculated the electromagnetic heating caused inside the biological tissues by utilizing quasi static approach and obtained the electromagnetic field utilizing Monte Carlo method [7]. D'Ambrosio et al. simulated the heating of deep seated pelvic tumors using the simplified Maxwell equations [29]. Ewa et al. discretized the final quasi static equation using boundary element method to obtain the induced electromagnetic field inside the biological tissue [9]. Jamil et al. simulated the electromagnetic heating phenomenon inside the biological tissues using finite element method and based his analysis on the quasi static approach [30].

By utilizing the quasi static approach, the time varying components of complex Maxwell's equations are eliminated and the electromagnetic field strength inside the tissue in a cartesian domain X, can be obtained by evaluating the scalar potential inside the tissue which uniquely represents an irrotational electric field intensity [7,9] i.e.,

$$\nabla.[\varepsilon(X).\nabla\varphi(X)] = 0 \tag{2}$$

where ε represents permittivity of the material which has unit of $C^2/N.m^2$.

Electric field strength E can be found using the following equation.

$$E(X) = -\nabla\varphi(X) \tag{3}$$

The volumetric heat generation as a result of electric field inside the biological tissue can be calculated using:

$$Q_r(X,t) = \frac{\sigma|E(X)|^2}{2} = \frac{\sigma\left[|E_x|^2 + |E_y|^2 + |E_z|^2\right]}{2} \tag{4}$$

where σ represents the electrical conductivity of the tissue which is measured in S/m. For further details of the electrode based thermal therapy readers are referred to refs.[7,9,30].

The purpose of this research is to devise a multiple linear regression model for capacitive type electrode based thermal therapy. In this research maximum temperature has been identified as the response variable and a particular emphasis here is to quantify the cumulative effect of physical and tunable independent variables on the outcome of the therapy. This effect was quantitatively expressed by utilizing multiple linear regression model. Organization of this paper is as follows. Next section describes the multiple regression concepts. Details of experimental setup used in the electrode based thermal therapy are provided in Section 3. Section 4 gives details about Taguchi's experimental design followed by Section 5 in which results and discussions are presented. Finally the results of the research have been summarized in the last section.

2. Multiple regression analysis

Success of a research depends on gathering and analysis of data which collectively provide the basis to achieve the ultimate goals of the research. With the advent of modern equipment and ever increasing computational resources at researcher's disposal, huge amount of data can be collected in short amount of time. Keeping in view the objectives of research and experimental design, a set of data is collected at the end of the measurement. Regression is a statistical tool used to describe the experimental data with set of parameters by establishing a certain relationship between dependent and independent variables. Dependent variable also known as response variable is the variable whose value is to be found. Independent variable also known as predictor variable is the one whose value is varied in order to find out its functional relationship with the dependent variable. The choice of independent variables and their respective levels is made by the researcher in the experimental design stage.

Regression analysis has previously been applied in biochemistry [31,32], biology [33,34], environmental science [35,36], and nanomedicine [37,38] etc. As can be seen from Eqs. (1)–(4), in order to find out the maximum temperature inside the tissue, complex mathematical equations need to be solved which requires personal effort as well as computational resources. In this scenario, multiple regression analysis can prove to be of great value if it can be used to predict the maximum temperature inside the tissue rendering itself as an easy and inexpensive alternative to the complex and time consuming numerical simulations.

In linear regression model, linear relationship is assumed between the predictors and the response. The mathematical equation that best describes the obtained data is known as regression equation or fitting function. The aim is to select the model that best fits the data between response and predictors. The functional relationship between the dependent and independent variables is established mathematically by employing the parameters in the regression equation. Parameters are the coefficients of independent variables in the regression equation and have same values at each data point. If the regression equation involves only one independent variable, the analysis is called simple regression. Regression involving more than one independent variable is known as multiple regression.

Regression is said to be linear if the parameters in the regression equation are linear and equation needs not be linear in terms of independent variables. The linear model can be described by following equation.

$$\widehat{T} = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots\ldots\ldots\ldots\ldots\ldots\ldots\beta_k X_k \tag{5}$$

where hat "^" on T indicates that it is a predicted value of T and Xs are the predictors or regressors, β represents the regression