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Sensitivity of thermophysiological models of cryoablation to the thermal and biophysical properties of tissues

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ABSTRACT

Advancement in biomedical simulation and imaging modality have catalysed the development of in silico predictive models for cryoablation. However, one of the main challenges in ensuring the accuracy of the model prediction is the use of proper thermal and biophysical properties of the patient. These properties are difficult to measure clinically and thus, represent significant uncertainty that can affect the model prediction. Motivated by this, a sensitivity analysis is carried out to identify the model parameters that have the most significant impact on the lesion size during cryoablation. The study is initially carried out using the Morris method to screen for the most dominant parameters. Once determined, analysis of variance (ANOVA) is performed to quantitatively rank the order of importance of each parameter and their interactions. Results from the sensitivity analysis revealed that blood perfusion, water transport and ice nucleation parameters are critical in predicting the lesion size, suggesting that the acquisition of these parameters should be prioritised to ensure the accuracy of the model prediction.

1. Introduction

Cryoablation is a minimally invasive cancer treatment that is used primarily for treating renal tumors. The treatment destroys tumor tissue by applying extremely low temperatures delivered via a cryoprobe, while sparing the neighboring healthy tissue. One of the main challenges in designing a successful cryoablation treatment is its dependency on various factors such as the tissue properties and their response to cold, the anatomical structure of the organ, the protocol of the cryoablation treatment and the experience of the interventional radiologist administering the treatment. The advancement in biomedical simulation and imaging modality in recent years have catalysed the development of in silico predictive models for cryoablation [55–57]; [51]). These models can predict not only the transient temperature distribution inside the tissue, but also the formation of intracellular ice that is responsible for cell death. This has allowed clinicians to better visualize the iceball and the tissue temperature profile, and use these information to plan and decide the appropriate cryosurgical protocol to improve the success rate and to reduce the risks of the treatment.

The mechanism of cell destruction during freezing can be primarily attributed to direct cell injury, which encompasses cell dehydration and intracellular ice formation (IIF) [43]. These thermophysiological processes need to be properly addressed to accurately model the cryoablation process. Nevertheless, this can be a challenge due to the difficulty in prescribing appropriate thermal and biophysical properties to represent the tissue. In current clinical practice, there is still a lack of practical approach in measuring these properties, particularly parameters pertaining to cellular water transport and IIF. Although literature values are often adopted in the modelling process, they are often cited with significant uncertainties and may compromise the accuracy of the model prediction. This can be problematic when comparing simulation results with experimental and clinical studies. Furthermore, implementation of cryoablation models is often limited by the computational resources and time available. A model that can account for the variation and temperature dependencies of all the factors is impractical, while a highly simplified model can lead to inaccurate results. Hence, there is a need to strike a balance between a model that is computationally feasible and one that is within acceptable level of accuracy.

Motivated by this, the present study aims to establish a multiscale mathematical model of renal tissue cryoablation based on a coupled phase change bioheat transfer, cellular dehydration and IIF models. A sensitivity analysis is carried out using the developed

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model to identify the parameters and their interactions that have significant effect on the lesion size. Due to the large number of parameters involved, a global screening exercise is first executed using the Morris method, followed by a quantitative analysis using Analysis of Variance (ANOVA) to rank the model parameters in the order of their importance. Parameters that have the strongest impact on the lesion size can be isolated and be given priority during the acquisition of information. On the other hand, less important parameters can be given more leeway in terms of its accuracy in the confidence that the accuracy of the numerical predictions will not be significantly affected.

2. Materials and methods

2.1. Morris method

The Morris method is a randomized, one-factor-at-a-time global screening technique used to shortlist and identify the input parameters that are considered to have dominant effect on the output [49]. The technique can characterize the relative importance of input parameters and distinguish among those that have negligible effect, linear and additive effect, as well as non-linear effect or interaction with other parameters [58]. Morris method is ideal for models with large number of input variables or those that demand high computational effort. For this reason, it is chosen in this study as an initial screening exercise to separate the parameters that are significant from those that are less significant.

The sampling strategy of Morris method involves the discretization of the experimentation region into a p-level grid; each Δx apart, such that $\Delta x = 1/(p-1)$. The input parameters x_i, selected from their respective range, are normalized to be between 0 and 1, such that $x_i = \{0, 1/(p-1), 2/(p-1), \ldots, 1\}$. The experimentation region thus represents a k-dimensional, p-level grid hypercube from where the input parameters are randomly sampled. The method starts by randomly selecting a starting point for a given set of input parameters x with output $y(x)$. The set of input parameters is then randomly varied by Δx in a single orientation x_i to generate a new set of parameters. The elementary effect E_i due to the change in the ith input factor can be expressed as:

$$E_i(x) = \frac{y(x_1, x_2, \ldots, x_i + \Delta x, \ldots, x_k) - y(x)}{\triangle x}. \quad (1)$$

This step is repeated for the remaining input factors until all the inputs have been varied within the experimentation region.

For k input parameters, $k+1$ computational runs are required to compute all the elementary effects as the calculation of E_i necessitates the evaluation of the output twice. The entire process is repeated for the specified number of orientation r, thus giving a total of $r(k+1)$ experimental run, with each input parameter having r elementary effects. The random variations of each of the input factor for each orientation can be visualized as a set of parameter trajectories traced out in the experimentation region. These trajectories are shown in Fig. 1 for a computational experiment with three input parameters and three random orientations.

To gauge the significance of each input parameter, the mean μ of the elementary effects, which estimates the overall effect of the input factor on the model output; and the standard deviation σ, which estimates the non-linear effects, such as second order and higher order effects, and interaction effects among the input parameters, are calculated:

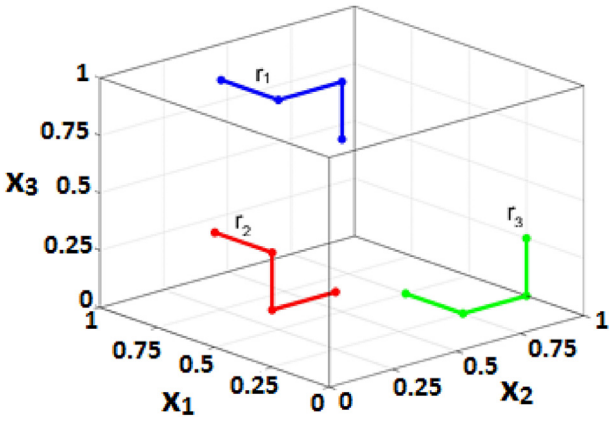

Fig. 1. Parameter trajectories in the Morris method with k=3 and r=3.

$$\mu = \sum_{i=1}^{r} \frac{E_i}{r}, \quad (2)$$

$$\sigma = \sqrt{\frac{\sum_{i=1}^{r}(E_i - \mu)^2}{r}}. \quad (3)$$

Generally, a large measure of μ indicates that the particular input parameter has profound effect on the output. On the other hand, a large measure of σ translates to a high degree of spread, signaling the potential nonlinear or interaction effect among the input parameters [49]. For more details on the Morris method, one may refer to the papers by Campolongo et al. [8,9].

2.2. Analysis of variance

Analysis of variance (ANOVA) is a statistical analysis commonly used in the design of experiments [47]. The objective of ANOVA is to determine which input parameters or their interactions have significant effect on the model response. Unlike the Morris method, ANOVA is able to distinguish the interaction effects among the various model inputs and rank them based on their order of importance. ANOVA may be carried out using two- or three-level factorial design. Three-level factorial design, also denoted by 3^k, is often preferred since it is able to address the presence of curvature in the response function. This permits nonlinear relationships between the model response and each parameter to be captured accordingly.

In the interest of brevity, details on the implementation of ANOVA will not be presented. Readers may consult textbooks by Montgomery [47] and Saltelli et al. [58] for a complete description of ANOVA. The general steps in implementing ANOVA include: (a) identify the input factors and their numerical ranges, (b) decide the level of factorial design, (c) perform the experiment and collect output data, (d) calculate sum of square (SS), (e) determine the degree of freedom (DOF), (f) Compute mean square (MS), (g) calculate the test ratio F_o and (h) draw conclusion. The input factors and their interactions are ranked according to their test ratio F_o based on a specified confidence level α. For instance, if the value of F_o calculated for a particular input parameter is greater than the critical F_o at a given α, it can be concluded that the input parameter has a significant effect on the model output. Else, the input parameter has negligible effect.