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Intelligent non-invasive modeling of ultrasound-induced temperature in tissue phantoms

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ABSTRACT

Raising temperature of human cells (hyperthermia) is an ancient tool for tumor masses reduction and extinction, actually even before the existence of a molecular understanding of cancer cells. Hyperthermia is being increasingly used for patients' rehabilitation and oncological diseases' treatment but still constitutes a major driver for researching more efficient and reliable therapeutic usage aiming at outstanding patients wellbeing and socio-economic benefits. Efficient hyperthermia practice demands knowledge about the exact amount of heating required at a particular tissue location, as well as information concerning the spatial heating distribution. Both of these processes require accurate characterization. Until now, ultrasound heating treatments are being monitored by magnetic resonance imaging (MRI), recognized as being capable of achieving a 0.5 °C/cm^3 temperature resolution [1], thereby imposing a gold standard in this field. However, one can notice that MRI-based techniques, besides the inconvenient instrumental cost, obliges the presence of a team of expert clinicians and limits the hyperthermia ultrasound treatment area due to the space restrictions of an MRI examination procedure. This article introduces a novel non-invasive modelling approach of ultrasound-induced temperature propagation in tissues, to be used as a cost effective alternative to MRI monitoring of ultrasound therapeutic techniques, achieving a maximum temperature resolution of 0.26 °C/cm^3, clearly inferior to the MRI gold standard resolution of 0.5 °C/cm^3. In order to derive the model, and avoiding painful invasive in-vivo sampling, a phantom was employed, whose composition respects the human tissues' reaction to ultrasound beams. In contrast with previous works of the authors, in the present paper we study the possibility of using b-spline neural networks (BSNN) as reliable noninvasive estimator of temperature propagation in phantoms [2,3]. The proposed methodology achieves better results than previous approaches, does not require the use of an Imaging Ultrasound transducer and, as the proposed models are piecewise polynomial models, they can be easily inverted and used in closed-loop control of therapeutic ultrasound instruments.

1. Introduction

A thermal therapy is generically defined as a session where the temperature of the patient's tissue is deliberately varied, in a *controlled* way, in order to treat some illness. The time that a cell can be exposed to a certain temperature before it dies, defines its *thermotolerance*, a characteristic exploited in hyperthermic therapy. Normal and cancer cells exhibit different thermotolerance values, thus indicating the possibility of killing cancerous cells while leaving the normal ones alive [4]. In a general way, cancerous cells do not tolerate high temperatures for the same amount of time as the normal ones do. However, even if this premise is right, exploiting the thermotolerance discrepancy detected among these cells would constitute in a highly sensitive process. Such a process would require to be fully controlled to limit its effects on healthy cells. The challenge consists on finding the appropriate balance of temperature and duration that allows for the desired cancer cell death, whilst maintaining the toxicity of healthy cells under acceptable, unharmful levels. Consequently, these therapies are highly limited by the safety and effectiveness of the tissue heating process, which ideally should allow a perfect control over the space

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and time dimensions, i.e. we need to be able to accurately control the temperature of the cells and the duration that the cells are exposed to a specific temperature. Furthermore the heating process should restrict the therapy to a specific region, in order to not damage the surrounding areas. Certainly these requirements raise massive technical challenges.

The biological complexity inherent to human tissue results in a media with highly volatile characteristics, giving shape to the dynamics involved in the temperature propagation process. One should expect slightly distinct behaviours as a response to changes with respect to different body parts, gender, age group and general environment conditions. The hypothesis selected to approximate the real temperature propagation function should be robust enough to contemplate this variability, and be capable of capturing temperature dynamics in terms of space and time dimensions.

Different approaches have been proposed for non-invasive temperature estimation. These techniques are based on electrical impedance tomography (EIT) [5], microwave thermometry [6], magnetic resonance imaging [7], and backscattered ultrasound (BSU) [8]. More specifically, focusing on ultrasound based temperature estimators, several methods have been reported, based on the extraction of temporal-echo shifts [9,10], frequency shifts [11,12], and changes on the attenuation coefficient [13]. Regardless of the arguable value of these approaches, they often require various assumptions to be made, which in turn requires a high level of parametrization, e.g. the average scatterer spacing [14], the speed of sound of the media [15] or even its variation with respect to temperature [16].

The construction of accurate analytical models that incorporate such a wide amount of (physical) parameters is undoubtedly an arduous task. Also we would prefer non-invasive and painless methods, so, no biopsies of patients tissue is required. Instead of working on complex physical equations that govern such system, we propose a different modeling paradigm, namely the construction of *data-driven* models. The difference, despite simple, dramatically changes the whole modeling process. Physical models are represented by the analytical solutions found to satisfy a set of differential equations, i.e. an explicit time varying function that evolves through time in the same (approximate) way as the real temperature propagation we intend to model. Antagonistically, a data-driven model makes no assumptions about the physical laws that govern the process. Instead, a suitable mathematical structure incurs into a learning process, where the parameters of these structures are adapted (learned) from the knowledge that the learning process is capable of extracting from the data set available. This data set should represent the process under analysis and we construct an hypothesis that best explains it. Once finished the training phase, the model should be able to accurately respond to *new* situations, generalizing the knowledge acquired with the training set to out-of-sample inputs.

Learning how the temperature is propagated during an ultrasound hyperthermia session can be seen as a regression problem. Neural networks (NN) are cognitive computational metaphors, inspired by studies of the brain nervous system in biological organisms, and were chosen as our general hypothesis set to model the process, due to their interpolation ability [17], which makes these structures suitable to solve regression problems. Having selected our general model structure, we are then faced with two objectives: to approximate the real function $f(.)$ and to prevent model overfitting, i.e. avoid fitting the noise. A more elaborate analysis of this problem reveals that actually these two objectives tend to be contradictory, which may not seem intuitive at first glance, but it actually is once we notice that: (1) we only have available a finite realization of the target function, the training set D; and (2) the data set will most certainly be noisy since any physical sensor is limited to have a finite precision. Therefore a proper compromise between approximating and learning (preventing overfitting) must be found, within an hypothesis set, given the resources we have available, which are characterized by the quality and extension of the data set. An analysis of these characteristics tells us the model complexity we can afford.

In fact, the data used to construct the models was captured in a *invasive* way, forming a high quality data set. However we propose the use of a contaminated data set, by deliberately passing it through a Gaussian contamination process. Besides contemplating possible patient-dependant variabilities, this contaminated version can be seen as a simulated non-invasive data set, as if it was acquired by a non-invasive temperature estimation method, whose error can be approximated by the standard deviation σ that parameterizes the Gaussian distribution. The assessment of our approach has revealed itself as a promising cost-effective alternative to MRI, exhibiting surprising performance and scalability indicators. This means that a reliable temperature estimation method can be used to extract a complete set of non-invasive data that would be used in the construction of reliable models that are able to control a hyperthermia session, guaranteeing accuracy and safety concerns.

Table 1
Composition of the constructed homogeneous solution used to resemble human tissue.

Material	% Composition
Water	86.5
Glycerol	11.0
Agar	02.5

2. Materials and methods

2.1. Materials

The performance of data-driven models is highly dependent on the quality of the captured data. Notice that a highly contaminated data set ends up by restricting the complexity of the hypothesis we can afford, otherwise the model would invariably try to explain the dynamics of the noise, since the complexity allowed in the chosen hypothesis set $\mathcal{H}$ is such that it can fit the noise. Furthermore the data should be representative of the whole domain of the process intended to be modeled. It is generally difficult to incorporate prior knowledge into a neural network, therefore the network can only be as accurate as the data used to train the network.

In order to simulate human tissue, an artificial tissue studied in [18] was used. These mimicking materials are named *phantoms* as they intend to exhibit similar physical characteristics to the ones found in human tissues when subject to specific radiation. In the case of ultrasound therapy the basic composition of the phantom is presented in Table 1.

In order to adjust the attenuation coefficient, graphite powder was added, in this experiments 0.5% graphite was added proportionally reducing the water percentage. The homogeneous medium was designed to respect the biologic tissue properties of sound speed, acoustic impedance and attenuation coefficient.

For the localized heating of the phantoms, a therapeutic ultrasound device (TUS), *Sonopulse Generation 2000 Ibramed*, was used. The transducer's device presented a 3.5 cm^2 effective radiation area. The TUS may operate at 1 MHz or 3 MHz. Experiences hereby reported were performed at 1 MHz to enable higher wavelength i.e. deeper penetration on tissue also taking into account that higher emitting frequencies waves suffer from higher attenuation effects. A *pulsed* operation mode was chosen in order to mitigate possible interferences between both ultrasound transducers, the therapeutic and the imaging one; this procedure requires a perfect instrumental set-up matching so that the ultrasound echoes arrive