Domain Heterogeneity in Radiofrequency Therapies

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The objective of this research work was to study the differences between the predicted ablation volume in homogeneous and heterogeneous models of typical radiofrequency (RF) procedures for pain relief. A three-dimensional computational domain comprising of the realistic anatomy of the target tissue was considered in this study. A comparative analysis was conducted for three different scenarios: (a) a completely homogeneous domain comprising of only muscle tissue, (b) a heterogeneous domain comprising of nerve and muscle tissues, and (c) a heterogeneous domain comprising of bone, nerve and muscle tissues. Finite-element-based simulations were performed to compute the temperature and electrical field distribution during conventional RF procedures for treating pain, and exemplified here for the continuous case. The predicted results reveal that the consideration of heterogeneity within the computational domain results in distorted electric field distribution and leads to a significant reduction in the attained ablation volume during the continuous RF application for pain relief. The findings of this study could provide first-hand quantitative information to clinical practitioners about the impact of such heterogeneities on the efficacy of RF procedures, thereby assisting them in developing standardized optimal protocols for different cases of interest.

Keywords: radiofrequency therapies ; pain relief ; bioheat transfer ; coupled thermo-electric analysis ; multiscale models for biological tissues ; feedback control systems ; AI and machine learning algorithms ; finite element method ; coupled mathematical models ; clinical applicat

1. Introduction

Globally, pain management is an enormous challenge that places significant physical, social and economic burdens on society. In accordance with the International Association for the Study of Pain (IASP), pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” Furthermore, pain is always a highly subjective and integrative experience that is associated with biological, psychological, and social factors. This complex definition of pain continues to evolve with advancements in medical science and technology [1]. As per the current definition of pain, a plethora of pain and pain states exist, such as nociceptive pain, neuropathic pain, acute pain, chronic pain, etc. Developing an effective treatment option for tackling acute and chronic pain is the main focus of pain management therapists, owing to the significant effects they have on the quality of life of patients, including disability, mood swings, anxiety, and overuse of medicine, to name a few [2]. Notably, acute pain lasts for less than three days and tends to diminish afterward with the passage of time as healing occurs, whereas chronic pain is the extension of acute pain that can go well beyond the expected healing duration post-injury or surgery and typically lasts for more than three months, and in some cases may last indefinitely [1][2]. A multitude of drug-based and non-drug based options exists for the management of pain, which often utilizes multimodal and multidisciplinary approaches, viz., pharmaceutical, physical therapy, rehabilitation and surgery [1][2][3][4].

Chronic pain is one of the major public health problems affecting billions of people all around the world. In Canada, for example, chronic pain imposes a significant burden on healthcare resources, accounting for approximately $7.2 billion annually [5][6]. There has been widespread reliance on the usage of opioids as a pain medication for mitigating chronic pain, which can do more harm than good [7]. Several inexpensive alternative treatment options have also been explored in clinical practices for mitigating chronic pain and minimizing the usage of opioids. Among the available treatment modalities for chronic pain relief, minimally invasive radiofrequency ablation offers several advantages, such as it is precise, reproducible, cheap and highly effective [8][9]. The application of radiofrequency (RF) has been growing rapidly and increasing in popularity for treating different types of pain, such as in the management of low back pain, knee pain, hip pain, migraine, etc. [10][11][12][13][14][15][16][17]. Generally, the power delivery during such pain management procedures is done using either a continuous or a pulsed mode [14]. In the conventional continuous power delivery mode, RF currents applied between the electrode (accurately placed on the target nerve) and the dispersive ground electrode (placed on the patient’s skin) results in temperatures above 50 °C. The high temperature obtained during the continuous RF procedure results in coagulative necrosis of the neural tissue that further leads to protein denaturation and axon destruction, which ultimately stops the transmission of nociceptive signals from the periphery, thereby mitigating pain. In contrast to the continuous RF mode, which relies on the high temperature to cause neural ablation, the pulsed delivery mode utilizes the application of short pulses of RF current to the neural tissue from the RF generator that is followed by silent phases to allow time for heat dissemination [14][18][19]. The electric field generated due to these applied pulses disrupts the functioning of neuronal membrane, along with genetic changes that affect cytokine release [8]. Thus, the mechanism of action of both these modes is quite different. Importantly, the pulsed mode is a theoretically nonablative procedure, since the maximum temperature during such procedures is usually not allowed to exceed 42 °C, thus making it less destructive in comparison to the continuous RF. Although the exact explanation of the complete mechanisms of action involved during the pulsed RF procedure for treating chronic pain remains elusive, extensive research is being undertaken to quantify its associated effects [13][20]. Despite the increasing use of various radiofrequency therapies in clinical practices for treating pain, controversy still exists over their efficacy and treatment outcomes [6].

2. Clinical Applications, Future Outlook and Model Developments

2.1. Heterogeneous Surroundings and Clinical Trials

Radiofrequency ablation has been used for pain management since the mid-1970s [20] and has significantly evolved from a therapy that was mainly employed for mitigating neuropathic pain to one of the most promising and frequently applied techniques in clinical practices for alleviating axial spine and musculoskeletal pain [1][16]. Today, the application of RFA in treating pain has steadily expanded and accepted for the treatment of facet joint, sacroiliac joint dysfunction and osteoarthritis [8][9][10][11][12][13][14][15][16][17][18][19][21]. However, there are significant contradictions and inconsistencies in the reported clinical results on the efficacy of RF procedures. Most of the clinical studies available in the literature are retrospective studies or case studies limited to reporting high-quality randomized controlled trials [22][23][24][25][26][27][28][29][30]. Furthermore, inappropriate selection criteria and treatment parameters could result in poor treatment outcomes, whereas anatomical variations, which are still not well-established, could limit the accurate interpretation of the obtained results. Thus, additional large-scale clinical studies of RF application in pain management are needed with longer follow-up periods to demonstrate its efficacy along with quantification of associated long-term adverse effects.

There has been continuous development in RF delivery systems and protocols in the quest to increase the ablation volume, which will lead to enhanced efficacy of the RF procedure. Continuous RF is the conventional form of energy delivery, and it causes a decline in the transmission of pain signals by damaging both sensory and motor nerve fibers [1][19]. Three different types of electrodes are typically utilized for delivery of RF energy to the target neural tissue, viz., monopolar, bipolar and cooled RF electrodes (arranged in ascending order of ablation volume generation). Another mechanism of RF energy delivery to the target nerve is the pulsed RF procedure. As mentioned earlier, contrary to the continuous RF that causes tissue destruction by heat, the pulsed RF is virtually painless and does not lead to any neural coagulation and irreversible tissue damage. Instead, it leads to an alteration in the pain signal transduction of the nerve fibers [1,19]. Although the efficacy of pulsed RF has been well-documented, the exact mechanism of action in the mitigation of pain is not fully understood yet [14][18][29][30][31][32][33][34]. Pulsed RF has shown promise in treating neuropathic pain and certain other clinical conditions where continuous RF is potentially hazardous, such as radicular pain, headaches, chronic shoulder pain, knee and hip pain, axial low back pain, and peripheral nerve pain [18][31][32]. However, further clinical studies are required to quantify the exact mechanism responsible for pain mitigation and broaden the clinical utility of these interventional pain procedures.

2.2. Multiscale Models for Biological Tissues

In order to capture the nuances of the biological cells/tissues exposed to external forces, a multiscale modeling approach provides an efficient and cost-effective alternative for bridging the different scales during the computational analysis [35][36][37][38]. Thus, further refinements in the proposed pain management models can be attained by using multiscale modeling approaches, whereby the damage caused due to RF currents can be quantified at a cellular level. This can be accomplished by coupling predominant phenomena during RF procedures that occur at different scales. Such multiscale models would not only assist in a better understanding of the pre-existing bio-physical behavior during pain management therapy, but also help in predicting the mechanisms that remain elusive to date and in generating new hypotheses for quantifying small-scale effects. Furthermore, while dealing with the small-scale effects of biological cells exposed to RF currents, the development and usage of stochastic models is practically unavoidable [37][39][40]. Moreover, bones in general, and cortical bones in particular, are biological tissues considered as part of our computational domain in the present study. They may exhibit additional effects, based on coupled phenomena, that would be useful to incorporate in further developments of the presented model. Among these, piezoelectricity plays a special role (e.g., [41]). For example, for cortical bones, piezoelectric properties are often responsible for the coupling between macroscopic and micro/nanoscopic scales, which may provide additional insight into certain dysfunctions and diseases [41]. Such properties also provide a foundation for wider usage of these biomaterials in tissue engineering [42]. In describing piezoelectricity, we couple electrical and mechanical fields. The well-posedness of such models of coupled piezoelectricity, along with rigorous energy bounds, were derived by one of us in a series of earlier papers, e.g., [43]. This was done for the first time in a general, dynamic setting through the application of the Faedo–Galerkin procedure and generalized solution technique. Coupled electro-mechanical models have been developed and used in a wide range of applications [44][45][46][47][48][49][50][51][52].

Thermal field treatment requires special attention for problems like those considered in this study. Notably, the thermal effects in this study were quantified considering the classical Fourier's law of heat conduction with the Pennes bioheat equation as presented in Equation (5), which assumes the infinite speed of heat propagation. However, in biological tissues that have non-homogenous inner structures, accounting for a finite speed of thermal disturbances becomes important, suggesting the existence of non-Fourier conduction with a delay ranging from 10 to 20 s [53]. Several studies have been reported providing a way to incorporate such non-Fourier heat transfer behaviors in their computational models, e.g., [54][55][56][57]. Moreover, the attainment of elevated temperatures during RF procedures can also result in thermo-elastic deformation, including thermal expansion and tissue shrinkage, which is interlinked with many complex small-scale effects, such as protein denaturation, collagen contraction and dehydration. Again, the exact mechanism of such associated effects at an elevated temperature within the biological tissue during thermal therapies are not completely elucidated yet, but significant recent developments have been devoted to this area of research utilizing both experimental and computational studies [53]. From a computational perspective, the coupling between thermal and mechanical fields, e.g., for elastic tissues such as muscles, etc., can be done by the development of coupled models of thermoelasticity, as well as efficient numerical methods for their solution, e.g., [58][59][60][61][62][63][64][65][66][67][68][69][70]. Moreover, the development of such models also includes complex nonlinear cases where numerous advances have been made in the improvement of numerical methodologies, e.g., [71][72][73][74]. The coupling of the thermoelasticity and piezoelectric model, as is the case for bone tissues, can be done by the development of piezothermoeleastic models [75][76][77]. This could lead to the development of fully coupled thermo-electro-mechanical models of thermal therapies [23]. Also, the development of such models is relevant to other areas of application, as well as in the development of new methods [78][79]. Furthermore, the proposed model of RF application for mitigating pain presented in this study assumed the quasi-static approximation of Maxwell's equations (see Equation (1)), whereby the extent of variation of electric and magnetic fields is negligible. Consequently, the electromagnetic field is modeled only by considering the electric field component (neglecting the magnetic field effects) because the wavelength of the electromagnetic field at RF frequency of around 500 kHz is several orders of magnitude larger than the size of the active electrode. However, models exist in the literature that consistently include the magnetic field effects, e.g., [78]. The electrode-tissue and plastic-tissue interfaces (as presented in Figure 1) can be more rigorously modeled by incorporating electrode-tissue contact force [80][81][82][83][84], as well as other non-trivial effects, e.g., thermal degradation, spiking, etc., in polymeric materials [85][86][87].

Several studies have been reported in the literature for modeling blood perfusion within biological tissues, at both micro- and macro-vascular levels [88][89][90][91][92][93][94]. Notably, micro-vascular perfusion refers to the perfusion at a capillary (or small-scale) level while macro-vascular perfusion is associated with the heat-sink effect caused by large blood vessels [95]. The blood flow at a micro-vascular level within the biological tissue is typically modeled by utilizing the porous media theory, whereby the tissue is assumed to be comprised of two phases: the solid phase comprising of cells and the extracellular space, and the fluid phase comprising of capillary size blood vessels [93][94][96][97][98]. The blood flow within the large blood vessels (2 mm in diameter) is modeled by additional coupling of the fluid flow model with the proposed thermo-electric model presented in this study, whereby the geometry of the blood vessel within the computational domain can be incorporated either by including a cylinder or a vascular tree [88][89][90][91][92][99][100]. It is expected that further refinement of the model can be done by deriving the computational domain from actual patient-specific data, which will provide more rigorous analysis and would help medical practitioners to obtain more accurate and precise predictions of the treatment outcomes during the RF application in pain management. Thus, the coupled multiscale framework could assist us in quantifying the unknown biologically-relevant phenomena occurring at cellular and sub-cellular scales and lead to a better understanding of the associated intricacies of RF application in pain management.

2.3. Coupling Frameworks and Pain Relief Models

The application of machine learning has been growing rapidly in the biological, biomedical and behavioral sciences. Importantly, both machine learning and multiscale modeling complement each other in creating more robust predictive models in the current field of research [101][102]. Recently, several studies have been reported in the literature that have explored the application of AI and machine learning algorithms in the field of thermal therapies [103][104][105][106][107][108][109][110][111]. The integration of machine learning with the coupled models could play a vital role in decision-making processes and the treatment planning stage of such procedures, e.g., by providing a priori information about electrode placement for enhancing treatment efficacy or by the real-time monitoring of the damage to the target tissue and other critical structures. Furthermore, a general framework of incorporating human factors into mathematical models of complex systems with control has been provided in [112][113]. This can be useful in the context of AI and the machine learning algorithms mentioned earlier in Section 2. Moreover, there has been a surge in the development of neural tissue models for capturing the transduction, transmission, perception and modulation of pain at molecular, cellular and neuron networks levels [114][115][116][117][118]. The aforementioned coupled multiscale thermo-electro-mechanical model can be readily integrated with the Hodgkin–Huxley neural model for predicting the treatment outcomes in terms of decline in the actual pain signals that can be coupled with the damage model presented in Equation (7). Such coupling of the neuronal models with the proposed model would assist in our better understanding of the molecular changes affecting the neuronal behavior, such as in quantifying the exact damage to the axons during the application of RF procedures for treating pain. Future studies can be conducted by incorporating the actual physiological neuronal geometries and modeling of biophysical phenomena at sub-cellular scale, viz., accounting for changes in the concentrations of potassium, sodium, calcium and magnesium at the membrane layer [119][120][121][122][123]. Such multiscale, multiphysics and fully coupled models will provide a better understanding of the molecular changes affecting the neuronal behavior, along with quantification of the mitigation of actual pain signals during RF procedures.

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