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A comprehensive theoretical study of thermal relations in plant tissue following electroporation

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ABSTRACT

Electroporation is the application of electric pulses of sufficient amplitude to target tissue, which entails not only permeabilization of cell membranes, but also heat generation and dissipation. Noticeable rises in temperature have been observed in a number of electroporation applications. These temperature rises are a potential source of alteration of thermodynamic properties of tissue wherein mass transport is occurring. Transport parameters are temperature-dependent, as they relate to thermodynamic processes.

This paper presents a theoretical study of thermal relations in tissue immediately following electroporation. An analysis of thermal transfer characteristics of tissue based on available data from literature is performed, and a model of heat transfer in tissue is presented. The tissue is modelled as a porous medium, and the chosen model for analysis, which we call the dual-porosity model, is a two-temperature model developed for heterogeneous porous materials. The dual-porosity model in its given form is a particular example of a LaLoThEq (Lack of Local Thermal Eqilibrium) model. This model is used to evaluate the potential for any significant alteration of cell membrane's thermal conductivity due to electroporation, and examines whether electroporation thus directly influences heat redistribution in tissue.

The main result is an in-depth theoretical analysis on the potential influence of electroporation on heat transfer characteristics of tissue via any direct influence of the treatment to the cell membrane. Findings of the study indicate that, on the contrary to the effects of electroporation on mass transport in tissue, the treatment would appear to exert a negligible influence on heat redistribution, at least due to its direct impact on the cell membrane. Other impacts of electroporation that could potentially result in a heterogeneous heat (re)distribution in tissue are briefly discussed, albeit not the subject of this study.

1. Introduction

An electric field of sufficient strength can cause an increase of conductivity and permeability of cell membrane. The effect is known as electroporation and is attributed to creation of aqueous pathways in the membrane [40]. Electroporation is essentially the application of electric pulses of sufficient amplitude to cells or target tissue, with the purpose of achieving the permeabilised state of the cell's lipid bilayer membrane.

Quantifying mass transport and heat transfer (both transmembrane and in bulk tissue) in connection with electroporation of biological tissues is an important research objective. The ability to fully comprehend transport processes has ramifications in all applications of electroporation. Understanding mass transport is particularly important, in example, for improving juice extraction and facilitating selective extraction/introduction of compounds from/into plant cells [27,47], introducing new electroporation-based technologies and medical treatments [14,31], and solving environmental challenges via use of the so-called "green" biorefinery [13,21]. Since heat generation (Joule heating) is unavoidably associated with electroporation, either as an undesired side effect [11] or an effect that is actively exploited in applications of thermal tissue ablation and ohmic heating [17,25,32], it is important to understand heat transfer in electroporation applications as well.

While electroporation continues to be intensively investigated, there is a persisting lack of models that can be used to model heat transfer and mass transport in complex structures such as biological tissues with relation to electroporation at the macro scale. This paper presents an attempt at extending an existing theoretical mathematical description – the "dual-porosity" model – for studying mass transport in electroporated tissue. The model is adapted to the problem of heat transfer in order to elucidate whether the

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cell membrane presents a significant barrier to heat transfer in tissue, and to answer the question of whether electroporation alters this barrier, if at all present, through its effect on the membrane.

A model, called the dual-porosity model, was recently adapted for the field of electroporation research [6,29,30] employing mass conservation and transport laws that enables coupling effects of electroporation to the membrane of individual cells with the resulting mass transport (and, by extension through analogy, transmembrane heat transfer and heat transfer in tissue). The model leans strongly upon firmly established approaches presented in previous works that are devoted to similar oft-encountered problems in chemical engineering [15,24]. These approaches in studying mass transport all benefit from a well-known mathematical analogy of heat and mass transfer, and consequently, the developed dual-porosity model is a special case of the classical LaLoThEq (Lack of Local Thermal Equilibrium) model for porous media [35, 39,43,44], which has long been present in literature on heat transfer. An analytical solution has been found for the presented dual-porosity model formulation, however, the model can (and should, through further development) easily be extended with additional dependencies to account for heterogeneities in tissue and temporal component of electroporation, and then solved numerically.

Due to the finite resistance of biological tissue, electroporation unavoidably entails the flow of an electric current through the tissue. This current through, what is electrically an ohmic load, results in heat generation and dissipation. This means that thermal effects are necessarily integrally and inseparably associated with electroporation. Noticeable rises in temperature have been noted in a number of electroporation applications [1,18,19]. These temperature rises are a potential source of alteration of the thermodynamic properties of the material where mass transport is occurring. Parameters such as viscosity, diffusion rate coefficient, and the rate of chemical reactions and changes are known to be strongly dependent on temperature, since they are fundamentally related to thermodynamic processes.

Thermal effects associated with electromagnetic fields are of high importance in biomedical applications, such as electrochemotherapy and tissue ablation by irreversible electroporation [8,9,16,50], gene transfer [23,41], or radiofrequency ablation [49]. In medical treatments, much attention is dedicated to ensuring that the damage to healthy tissue, which would ideally be left unaltered by the treatment, is under control and kept at the lowest possible extent, and various modelling techniques have been employed to evaluate Joule heating and subsequent thermal generation and dissipation. Numerical finite element models are often employed due to the complexity of the system (tissue heterogeneities and anisotropy) and the relatively complex form of the Pennes bioheat equation [36] that is habitually used to describe thermal relations in perfused tissues.

Thermal relations in biological material treated with electromagnetic fields have been studied extensively across a range of applications and on multiple scales by using various approaches, ranging from pure *in silico* molecular dynamics studies and theoretical non-equilibrium thermodynamics models to *in vivo* studies on model animal tissues. An early consideration of the effects of Joule heating associated with electroporation is presented in e.g. [20]. The authors present an account of model development, whereby a theoretical model was developed to estimate the power dissipation in individual cells during electroporation. They concluded that although heating that may be considered as insignificant at the macroscopic level of a cell suspension or tissue, may actually be substantial on the level of the cell membrane. This supposed rise in temperature could be responsible for a lowering of the threshold required for electroporation, as thermal energy is additionally raising the energy level of the bilayer. This has recently been re-evaluated and examined in a study presenting an analytical model for calculating the cell membrane temperature gradient [12]. The authors of the study show that electric field generates cell membrane temperature gradients, particularly during sequential pulsing over a sustained period of time. They conjecture that thermal gradients may contribute to electroporation through induced transmembrane voltages.

A recent study in molecular dynamics simulations [34] shed more light on the heat conduction characteristics of the cell membrane itself, by studying heat conduction characteristics of a DPPC lipid bilayer. Thermal conductivity of the lipid bilayer that was evaluated in this molecular dynamics simulation was found to be anisotropic, and lower than that of bulk water. This is thought to be mainly due to the lipid composition at the centre of the bilayer, where acyl chains of lipid molecules face each other due to a loss of the covalent-bond and low number density, and thermal conductivity is the lowest. Even lower than thermal conductivity across the bilayer was found to be the thermal conductivity along the bilayer, meaning the bilayer exhibits a strong anisotropic behaviour in terms of heat conduction.

Another field of electroporation applications that has received considerable attention in studying and modelling thermal effects with and without relation to mass transport is skin electroporation, where electric fields are used for breaching the impermeable stratum corneum for topical drug or gene delivery. The reader is referred to Ref. [5] in particular for a thermal study, or [38] for a more comprehensive review. Modelling thermal relations in skin electroporation is a challenging task, mainly due to highly variable properties between various layers of skin [4,37]. A recent study [42] presents the development of a complex analytical bioheat model for studying temperature increases in electroporation of a subcutaneous tumour, accounting for the multi-layer heterogeneous structure of the skin.

Very different considerations and approaches as compared to the field of biomedical applications can be found in the food processing and other industrial applications of electroporation. In these application areas, it is not a rarity to find treatment protocols delivering high energies to target biological material, and high currents that are present in tissues during long treatment times can cause a substantial rise in temperature due to ohmic heating [47]. Ohmic heating using lower voltages for longer periods of time can, with or without electroporation, also be intentionally used as mild treatment of raw material to increase the rate of mass transfer within tissue [25,48]. Modelling with the purpose of studying thermal effects in this field is mainly limited to various models dealing with the generation and distribution of heat in continuous-flow treatment chambers [26,22], with the purpose of optimising their design, thus avoiding hot spots that can otherwise cause electrode material degradation or treatment chamber deterioration. Theoretical studies relating thermal relations in electroporated plant tissue in industrial applications focusing on enhancing mass transport are virtually non-existent, and presently studies mainly comprise phenomenological models relating electrical or thermal damage to tissue with treatment parameters.

The title of this paper title bears no mention of mass transport, however, we wish to emphasize the inseparable connection between electroporation, the thermal effects that are associated with it, and mass transport processes in tissue. The relations between these (all fundamentally thermodynamic) processes are complex and interdependent. Recent research has shown [12] that thermal gradients across the plasma membrane can result in the differences in *electric potential* on either side of the membrane, meaning that there seems to exist a positive feedback connection whereby thermal gradients resulting from electroporation can alter electric relations on the membrane, thus affecting electroporation, heat, and mass transfer directly.