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# Spectroscopic imaging of a dilute cell suspension ☆

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ABSTRACT

The paper aims at analytically exhibiting for the first time the fundamental mechanisms underlying the fact that effective biological tissue electrical properties and their frequency dependence reflect the tissue composition and physiology. For doing so, a homogenization theory is derived to describe the effective admittivity of cell suspensions. A new formula is reported for dilute cases that gives the frequency-dependent effective admittivity with respect to the membrane polarization. Different microstructures are shown to be distinguishable via spectroscopic measurements of the overall admittivity using the spectral properties of the membrane polarization. The Debye relaxation times associated with the membrane polarization tensor are shown to be able to give the microscopic structure of the medium. A natural measure of the admittivity anisotropy is introduced and its dependence on the frequency of applied current is derived. A Maxwell–Wagner–Fricke formula is given for concentric circular cells, and the results can be extended to the random cases. A randomly deformed periodic medium is also considered and a new formula is derived for the overall admittivity of a dilute suspension of randomly deformed cells.



RÉSUMÉ

Dans cet article, on introduit une approche spectroscopique afin d'imager les propriétés électriques d'un tissu biologique. On construit un dévéloppement asymptotique de l'admittivité effective du tissu en fonction de la fraction volumique des cellules et du tenseur de polarisation de la membrane cellulaire. On étudie les propriétés de ce tenseur et on introduit le concept de temps de relaxation pour des géométries de cellules quelconques. Ce concept permet de distinguer

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différentes organisations cellulaires du tissu à partir de mesures spectroscopiques de l'admittivité effective.



## 1. Introduction

The electric behavior of biological tissue under the influence of an electric field at frequency $\omega$ can be characterized by its frequency-dependent effective admittivity $k_{ef} := \sigma_{ef}(\omega) + i\omega\epsilon_{ef}(\omega)$, where $\sigma_{ef}$ and $\varepsilon_{ef}$ are respectively its effective conductivity and permittivity. Electrical impedance spectroscopy assesses the frequency dependence of the effective admittivity by measuring it across a range of frequencies from a few Hz to hundreds of MHz. Effective admittivity of biological tissues and its frequency dependence vary with tissue composition, membrane characteristics, intra- and extra-cellular fluids and other factors. Hence, the admittance spectroscopy provides information about the microscopic structure of the medium and physiological and pathological conditions of the tissue.

The determination of the effective, or macroscopic, property of a suspension is an enduring problem in physics [44]. It has been studied by many distinguished scientists, including Maxwell, Poisson [52], Faraday, Rayleigh [54], Fricke [31], Lorentz, Debye, and Einstein [26]. Many studies have been conducted on approximate analytic expressions for overall admittivity of a cell suspension from the knowledge of pointwise conductivity distribution, and these studies were mostly restricted to the simplified model of a strongly dilute suspension of spherical or ellipsoidal cells.

In this paper, we consider a periodic suspension of identical cells of arbitrary shape. We apply at the boundary of the medium an electric field of frequency $\omega$. The medium outside the cells has an admittivity of $k_0 := \sigma_0 + i\omega\epsilon_0$. Each cell is composed of an isotropic homogeneous core of admittivity $k_0$ and a thin membrane of constant thickness $\delta$ and admittivity $k_m := \sigma_m + i\omega\epsilon_m$. The thickness $\delta$ is considered to be very small relative to the typical cell size and the membrane is considered very resistive, *i.e.*, $\sigma_m \ll \sigma_0$. In this context, the potential in the medium passes an effective discontinuity over the cell boundary; the jump is proportional to its normal derivative with a coefficient of the effective thickness, given by $\delta k_0 / k_m$. The normal derivative of the potential is continuous across the cell boundaries.

We use homogenization techniques with asymptotic expansions to derive a homogenized problem and to define an effective admittivity of the medium. We prove a rigorous convergence of the original problem to the homogenized problem via two-scale convergence. For dilute cell suspensions, we use layer potential techniques to expand the effective admittivity in terms of cell volume fraction. Through the effective thickness, $\delta\, k_0/k_m$, the first-order term in this expansion can be expressed in terms of a membrane polarization tensor, $M$, that depends on the operating frequency $\omega$. We retrieve the Maxwell–Wagner–Fricke formula for concentric circular-shaped cells. This explicit formula has been generalized in many directions: in three dimension for concentric spherical cells; to include higher power terms of the volume fraction for concentric circular and spherical cells; and to include various shapes such as concentric, confocal ellipses and ellipsoids; see [14,15,28–30,43,55–57].

The imaginary part of $M$ is positive for $\delta$ small enough. Its two eigenvalues are maximal for frequencies $1/\tau_i, i = 1, 2$, of order of a few MHz with physically plausible parameters values. This dispersion phenomenon well known by the biologists is referred to as the $\beta$-dispersion. The associated characteristic times $\tau_i$ correspond to Debye relaxation times. Given this, we show that different microscopic organizations of the medium can be distinguished via $\tau_i, i = 1, 2$, alone. The relaxation times $\tau_i$ are computed numerically for different configurations: one circular or elliptic cell, two or three cells in close proximity. The obtained results illustrate the viability of imaging cell suspensions using the spectral properties of the membrane polarization. The Debye relaxation times are shown to be able to give the microscopic structure of the medium.