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A Bio-Physical Analysis of Extracellular Ion Mobility and Electric Field Stress

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Abstract

The electric field stress applied to the cell in the electric field will cause the biological effects of the cell on electromagnetic field. In this paper, the single-shell spherical cell is equated to dielectric spheres, and a biophysical method is used to solve the boundary value problem, and then Maxwell tensor analysis is used to discuss the electric field stresses affecting the applied electric field applied to the cells. The results of numerical analysis show that the ion mobility decreases nonlinearly with increasing frequency in the lower region of the applied electric field frequency, and increases with increasing equivalent dielectric constant at a certain frequency, and the magnitude of the electric field stress is almost independent of the frequency; as the frequency increases, the ion mobility tends to a minimum value and is almost independent of the equivalent dielectric constant, while the applied electric field frequency and the cell dielectric constant both affect the cell normal and the tangential stresses. Therefore, the frequency applied electric field and cell dielectric constant affect the extracellular ion mobility, electric field stress applied to the cell membrane by the electric field; the extracellular ion mobility caused by the electric field in the low frequency range is more pronounced than that in the high frequency, and electric field stress is the basic cause of cell deformation.

Keywords

Mobility, Electric Stress, Biological Effects of Electromagnetic Field

1. Introduction

Electric fields can regulate cell growth [1], cytoskeleton reorganization [2], activation of intracellular channels [3], protein secretion and gene expression [4] *et al.* Also experimental studies have revealed that changing electric fields can cause cell deformation, cell fusion, rotation, and cell damage [5]. These phenomena had triggered mechanistic studies on the biological effects of electric fields.

In the late 1950s, Schwan *et al.* [6] began a series of studies on the action of electric fields on biological cells, which viewed as simple geometric shells with electromagnetic properties. In the early 1970s [7], Helfrich added the theory of elasticity to the lipid layer to study the action of applied electric fields on phospholipid vesicles, and Peterlin *et al.*, in 2007, viewed the phospholipid layer as an anisotropic medium to discuss the mechanism of cellular deformation under the action of electric fields [8]. So far, the interaction of static fields, time-varying electric fields, and pulsed waves with biological cells has also been studied [9]-[16]. It is generally accepted that the additional electric fields generated by electric fields inside and outside the cell, the electric field forces exerted on the cell, and the changes induced in ion concentrations on both sides of the cell membrane are responsible for the biological effects of cellular electromagnetic fields.

Under the action of applied electric field, the analysis of the field in cell membrane, inside and outside the membrane is often assumed there is no free charge in the solution region, and the electric field is solved by the method of separation of variables. For the analysis of the forces exerted on the cell by external electric fields, the Maxwell stress tensor method is commonly used [11] [17]. These methods are based on the bio-electromagnetic theory and the model of the interaction between the electric field and the target body, by solving boundary value problem to obtain the electric field distribution in the study area, and then to analyze the stresses exerted on the cell by the stress tensor. This method can give the threshold value of the field intensity that causes the effects, but the limitation is that the influence of the thermal motion and the fact that there is a free charge in the study area are not considered.

Based on this, this paper uses the theory of bio-electromagnetism to discuss the factors that affect the ion mobility outside the cell membrane and the stress of the electric field applied to the cell membrane when an electric charge is present outside the spherical cell.

2. Model

The spherical cell is usually represented by the single-shell spherical model shown in **Figure 1(a)**, where R_0 is the outer radius of the cell membrane, d is the thickness of the cell membrane, ε_{m1}, ε_i, ε_e, σ_{m1}, σ_i and σ_e are the dielectric constant and conductivity of the cell membrane, the inner and outer medium of the cell membrane, respectively. Based on the bio-electromagnetic theory, the single-shelled spherical cell can be equated with a homogeneous media sphere with dielectric constant ε_p and conductivity σ_p as shown in **Figure 1(b)**, and there is a relationship as Equation (1) and (2) show [18] [19].

$$\varepsilon_p = \varepsilon_m \frac{R_0^3\left(\varepsilon_i + 2\varepsilon_{m1}\right) + 2a^3\left(\varepsilon_i - \varepsilon_{m1}\right)}{R_0^3\left(\varepsilon_i + 2\varepsilon_{m1}\right) - a^3\left(\varepsilon_i - \varepsilon_{m1}\right)}, \quad a = R_0 - d \tag{1}$$

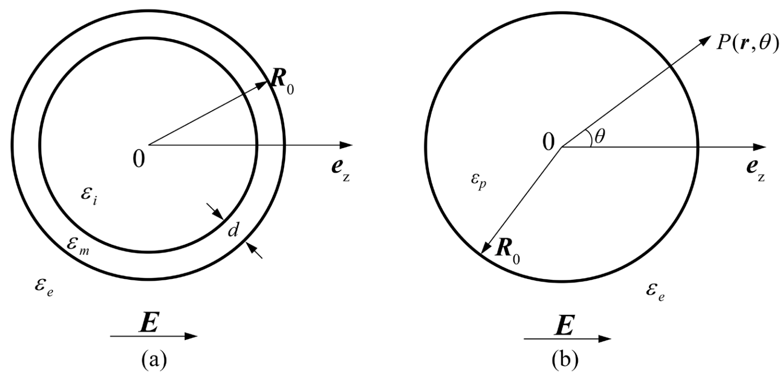


Figure 1. A physical model of the biological cell.

$$\sigma_p = \sigma_m \frac{2(1-v')\sigma_m + (1+2v')\sigma_i}{(2+v')\sigma_m + (1-v')\sigma_i}, \quad v' = \left(\frac{1-d}{R_0}\right)^3 \tag{2}$$

In this paper, the equivalent dielectric sphere is used as the study model, as shown in Figure 1(b). The spherical coordinate system is established with the center of the dielectric sphere as the coordinate origin and the direction of the external electric field as the *z*-direction, and the applied electric field is $\boldsymbol{E} = \boldsymbol{e}_z E_0 \exp(-i\omega t)$, where E_0, ω are the amplitude and frequency of the applied electric field, respectively. Assume that the ions in the extracellular medium is charged with $\pm e$, and their mobility is $\pm u$, and the average values of ion concentrations at zero field is $n^+ = n^- = n_0$.

3. Theoretical Analysis

3.1. Ion Mobility

If the external electric field acting on the cell is weak, according to the Poisson equation which the potential of the extracellular region satisfies and the continuity equation the ion density satisfies, the extracellular ion mobility u satisfies Equation (3):

$$\nabla^2 u(\boldsymbol{r}) = \gamma^2 u(\boldsymbol{r}) \tag{3}$$

where $u(\boldsymbol{r}) = u^+(\boldsymbol{r}) + u^-(\boldsymbol{r})$, $\gamma^2 = \frac{i\omega}{D} + \chi^2$, $\chi = \left(\frac{2n_0 e^2}{\varepsilon_0 \varepsilon_e KT}\right)^{1/2} = \left(\frac{\sigma_e}{\varepsilon_0 \varepsilon_e D}\right)^{1/2}$ is the reciprocal of the Debye shielding length, D is the ion diffusion coefficient, and the relationship D with the mobility u is: $Dq = uKT$.

The general solution of Equation (3) is dressed as Equation (4):

$$u(\boldsymbol{r},\theta) = B\exp(-\gamma r)\left(\frac{1}{\gamma r} + \frac{1}{(\gamma r)^2}\right)\cos\theta \tag{4}$$

where B is the coefficient to be determined.

3.2. The Field Distribution

Based on the electromagnetic field theory, suppose that the internal and external electrical potential values of the equivalent dielectric sphere are $\varphi_p(\boldsymbol{r},t)$ and $\varphi_e(\boldsymbol{r},t)$, respectively, then $\varphi_p(\boldsymbol{r},t)$ and $\varphi_e(\boldsymbol{r},t)$ satisfy Equation (5) and (6) [20]:

$$\nabla^2\varphi_e(\boldsymbol{r},t) = -\frac{e}{\varepsilon_0\varepsilon_e}\left[n^+(\boldsymbol{r},t) - n^-(\boldsymbol{r},t)\right],\quad r > R \tag{5}$$

$$\nabla^2\varphi_p(\boldsymbol{r},t) = 0,\quad r < R_0 \tag{6}$$

The $\varphi_p(\boldsymbol{r},t)$ and $\varphi_e(\boldsymbol{r},t)$ satisfies the boundary conditions as Equation (7):

$$\begin{cases} r = a: \quad \varphi_p = \varphi_e \\ \qquad\qquad \varepsilon_p\dfrac{\partial\varphi_p}{\partial r} = \varepsilon_e\dfrac{\partial\varphi_e}{\partial r} \\ \qquad\qquad \sigma_e\dfrac{\partial\varphi_e}{\partial r} + qD\dfrac{\partial u}{\partial r} = 0 \\ r \to \infty: \quad \boldsymbol{E}_e = \boldsymbol{E} \\ r \to 0: \quad \varphi_p \text{ is limited value} \end{cases} \tag{7}$$

Solving the above boundary value problem, then we get Equation (8):

$$\begin{cases} \varphi_e(\boldsymbol{r},\theta) = \left\{-E_0 r + \dfrac{A}{r^2} - \dfrac{qB}{\varepsilon_0\varepsilon_e\gamma^2}\exp(-\gamma r)\left(\dfrac{1}{\gamma r} + \dfrac{1}{(\gamma r)^2}\right)\right\}\cos\theta \\ \varphi_p(\boldsymbol{r},\theta) = -Cr\cos\theta \end{cases} \tag{8}$$

where

$$\begin{cases} A = \dfrac{\varepsilon_p - (\varepsilon_{ge} + \varepsilon_p R)}{\varepsilon_p + 2(\varepsilon_{ge} + \varepsilon_p R)} R_0^3 E_0 \\ B = \dfrac{-3\varepsilon_p R}{\varepsilon_p + 2(\varepsilon_{ge} + \varepsilon_p R)} \cdot \dfrac{\gamma^2 R_0 \varepsilon_0 \varepsilon_e}{e} E_0 R_0^3 \exp(\gamma R_0)\left(\dfrac{1}{\gamma R_0} + \dfrac{1}{(\gamma R_0)^2}\right)^{-1} \\ C = -\dfrac{3\varepsilon_{ge}}{\varepsilon_p + 2(\varepsilon_{ge} + \varepsilon_p R)} E_0 \end{cases} \tag{9}$$

$$\varepsilon_{ge} = \varepsilon_e + \frac{\sigma_e}{i\omega\varepsilon_0},\quad R = \frac{\sigma_e}{i\omega\varepsilon_0\varepsilon_e}\frac{\gamma R_0 + 1}{(\gamma R_0)^2 + 2(\gamma R_0 + 1)}.$$

3.3. The Electric Field and the Electrical Stress on the Cell Membrane

From the relationship $\boldsymbol{E} = -\nabla\varphi$, the electric field strength $\boldsymbol{E}_e$ outside the equivalent medium sphere (cell) is $\boldsymbol{E}_e = E_r\boldsymbol{e}_r + E_t\boldsymbol{e}_t$, where $\boldsymbol{e}_r$, $\boldsymbol{e}_t$ denote the unit vector in the normal and tangential directions of the cell membrane surface, respectively, and we have Equation (10):

$$\begin{cases} E_r = \left[E_0 + \dfrac{2A}{r^3} - \dfrac{e}{\varepsilon_0\varepsilon_e}\dfrac{B}{\gamma^2 r}\exp(-\gamma r)\left(1 + \dfrac{2}{\gamma r} + \dfrac{2}{\gamma^2 r^2}\right)\right]\cos\theta \\ E_t = \left[-E_0 + \dfrac{A}{r^3} - \dfrac{e}{\varepsilon_0\varepsilon_e}\dfrac{B}{\gamma^2 r}\exp(-\gamma r)\left(\dfrac{1}{\gamma r} + \dfrac{1}{\gamma^2 r^2}\right)\right]\sin\theta \end{cases} \tag{10}$$

Since the electromagnetic wave has momentum, it is incident on the equivalent medium sphere (cell surface) and exerts a certain pressure on the cell. From electromagnetic field theory, the momentum flow density tensor is shown as Equation (11):

$$\vec{T} = -\boldsymbol{ED} - \boldsymbol{BH} + \frac{1}{2}\vec{I}\left(\boldsymbol{E}\cdot\boldsymbol{D} + \boldsymbol{B}\cdot\boldsymbol{H}\right) \tag{11}$$

where $\boldsymbol{E}$, $\boldsymbol{H}$ denote the electric field and the magnetic field exposed to cell, respectively. If only the electric field effect is considered, the average value of the electric field stress applied to the unit area outside the cell membrane for a varying electric field is calculated as Equation (12):

$$\begin{aligned}\boldsymbol{P} &= \left\langle -\boldsymbol{e}_r \cdot \vec{T}_e \right\rangle = \frac{1}{4} Re\left(\varepsilon_e \boldsymbol{E}_r \cdot \boldsymbol{E}_r^* - \varepsilon_e \boldsymbol{E}_t \cdot \boldsymbol{E}_t^*\right)\boldsymbol{e}_r + \frac{1}{4} Re\left(\varepsilon_e \boldsymbol{E}_r \cdot \boldsymbol{E}_t^*\right)\boldsymbol{e}_t \\ &= P_r \boldsymbol{e}_r + P_t \boldsymbol{e}_t\end{aligned} \tag{12}$$

In the above equation, $\vec{T}_e = -\varepsilon_e \boldsymbol{EE} + \frac{1}{2}\vec{I}\varepsilon_e\left(\boldsymbol{E}\cdot\boldsymbol{E}\right)$, $\langle\cdots\rangle$ represents the average value in one cycle.

4. Numerical Analysis and Discussion

In the analysis of the mechanism of the bio-effects of electromagnetic fields, the typical values of the cell geometric and the electrical parameters are often used: $R_0 = 10\ \mu\text{m}$, $d = 5\ \text{nm}$, $\varepsilon_m = 4.4\times10^{-11}\ \text{F}\cdot\text{m}^{-1}$, $\varepsilon_i = 6.4\times10^{-10}\ \text{F}\cdot\text{m}^{-1}$, $\varepsilon_e = 6.4\times10^{-10}\ \text{F}\cdot\text{m}^{-1}$, $\sigma_m = 3\times10^{-7}\ \text{S}\cdot\text{m}^{-1}$, $\sigma_i = 0.3\ \text{S}\cdot\text{m}^{-1}$, $\sigma_e = 1.2\ \text{S}\cdot\text{m}^{-1}$. From the equivalent Equations (1), (2), the typical parameter values correspond to $\varepsilon_p = 6.35\times10^{-10}\ \text{F}\cdot\text{m}^{-1}$ and $\sigma_p = 0.0018\ \text{S}\cdot\text{m}^{-1}$, respectively. In the following numerical analysis, the equivalent permittivity of the dielectric sphere is taken around the values of these parameters. Consider that for small ions, the diffusion coefficient D is taken as $2 \times 10^9\ \text{m}^2/\text{s}$ [21] and the Debye length x is taken as $10^8\ \text{m}^{-1}$ [20].

4.1. Effect of the Frequency and the Equivalent Permittivity on Extracellular Ion Mobility

Figure 2 shows the relationship between the ionic mobility of cell membrane surface and the frequency of external electric field, where $\theta = 0.5$, the curves of data1, data2 and data are corresponding to $\varepsilon_p = 0.5$, $6.4 \times 10^{-11}\ \text{Fm}^{-1}$, $6.35 \times 10^{-11}\ \text{Fm}^{-1}$ and $9.6 \times 10^{-11}\ \text{Fm}^{-1}$, respectively. **Figure 2** shows that the ion mobility decreases nonlinearly with increasing frequency in the region of lower frequency of the applied electric field (e.g., frequency less than 5×10^6 Hz) and increases with the increasing of the equivalent permittivity at a certain frequency; With the increasing of the frequency, the ion mobility tends to a minimum value and is almost independent of the equivalent permittivity.

The diffusion coefficient D is a physical quantity that indicates how fast the ions move by diffusion from a high concentration to a low concentration, driven by a concentration gradient. The ion mobility u characterizes how fast the ions

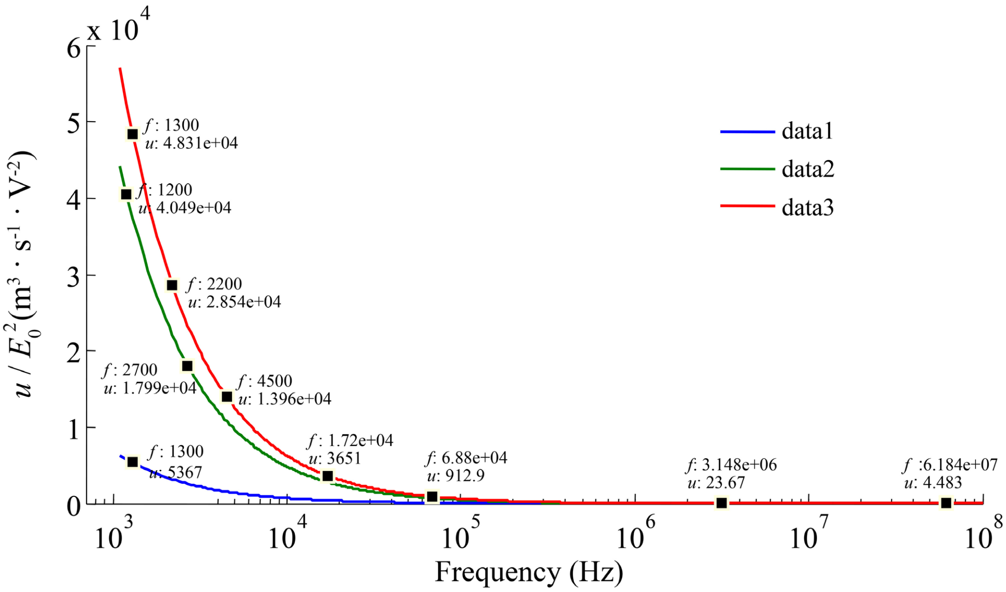


Figure 2. Ion mobility varies with frequency.

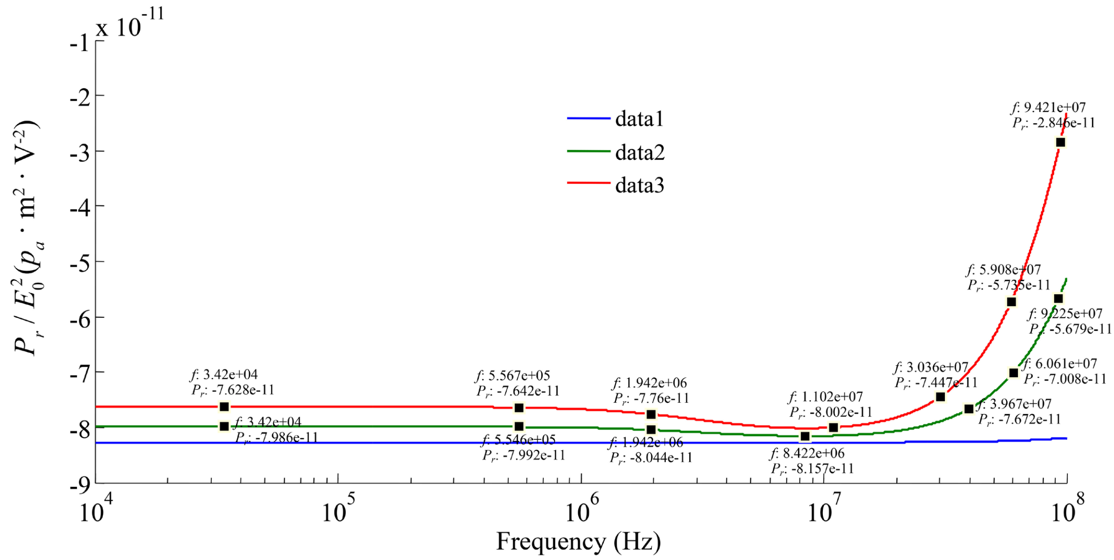
move under the action of an electric field and it is equal to the drift velocity per unit electric field. From Einstein's relation, a larger ion mobility u corresponds to a larger diffusion rate of ions from higher to lower concentrations. From Figure 2, it can also be concluded that, under the action of external electric field, in the lower frequency region, the larger the equivalent permittivity, the faster the ion diffusion rate from high to low concentration; The higher the frequency, the less the effect of the equivalent permittivity and the frequency on the ion mobility.

In biological cells, there is a defined concentration relationship inside and outside the cell membrane, and the ion migration across the membrane modulated by the external electric field will affect the physiological and living state of the cell. Figure 2 also illustrates that low frequency electric fields will cause strong biological effects on cells compare to high frequency electric fields.

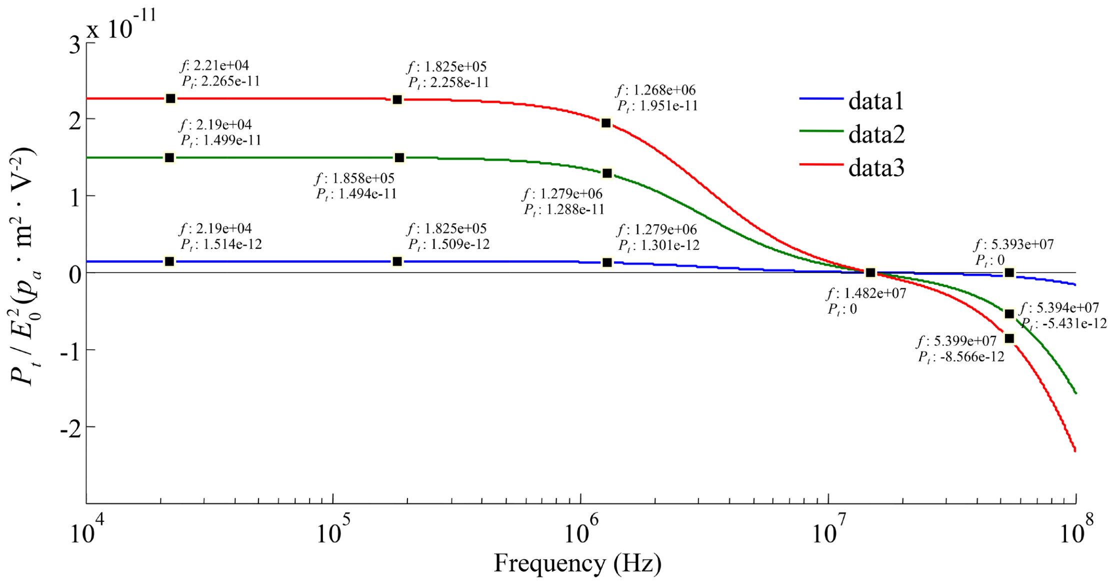
4.2. Electric Field Stress on the Cell

4.2.1. Effect of the Frequency and the Equivalent Permittivity on the Electric Field Stress

Figure 3(a) and Figure 3(b) give the curves of the normal force P_n, tangential force P_t (tangential force along the cell surface) versus the applied electric field frequency at $\theta = 0.5$, respectively, where $R_0 = 10^{-5}$ m, the curves data1, data2 and data3 are corresponding to $\varepsilon_p = 6.4\times10^{-11}\ \mathrm{F\cdot m^{-1}}$, $\varepsilon_p = 6.35\times10^{-10}\ \mathrm{F\cdot m^{-1}}$ and $\varepsilon_p = 9.6\times10^{-10}\ \mathrm{F\cdot m^{-1}}$, respectively. Figure 3 shows that at a certain position on the cell surface ($\theta = 0.5$) and within a certain frequency range (e.g., frequency less than 5×10^6 Hz), the normal and tangential forces acting on the cell surface hardly change with the increasing frequency; With further increase in frequency, the normal force on the cell decreases slowly, and when the frequency reaches a certain value, e.g., the frequency is 8.41×10^6 Hz, the normal force



(a)



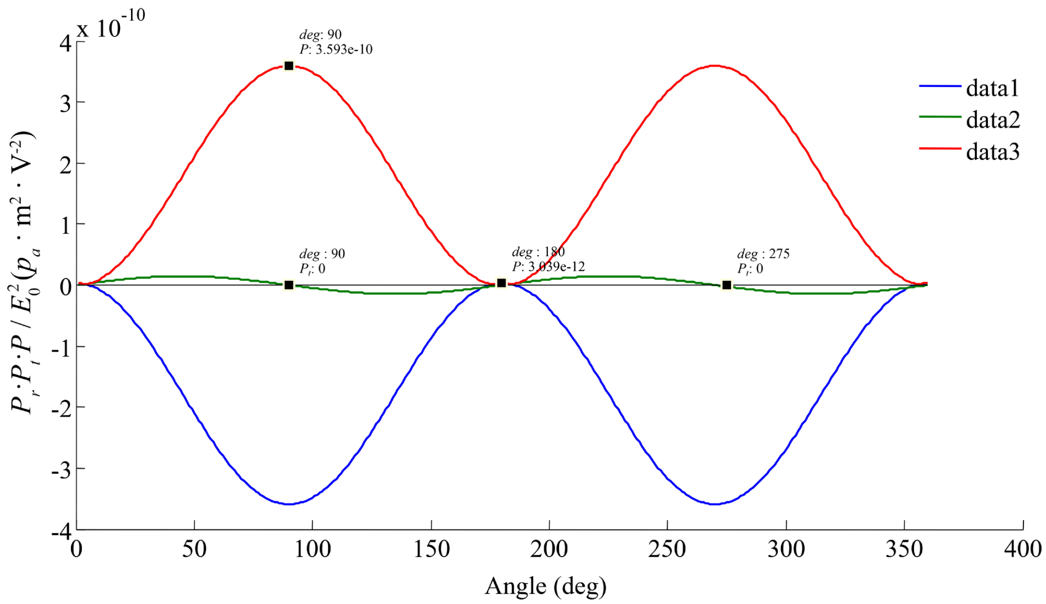
(b)

Figure 3. The electric stress varies with the frequency.

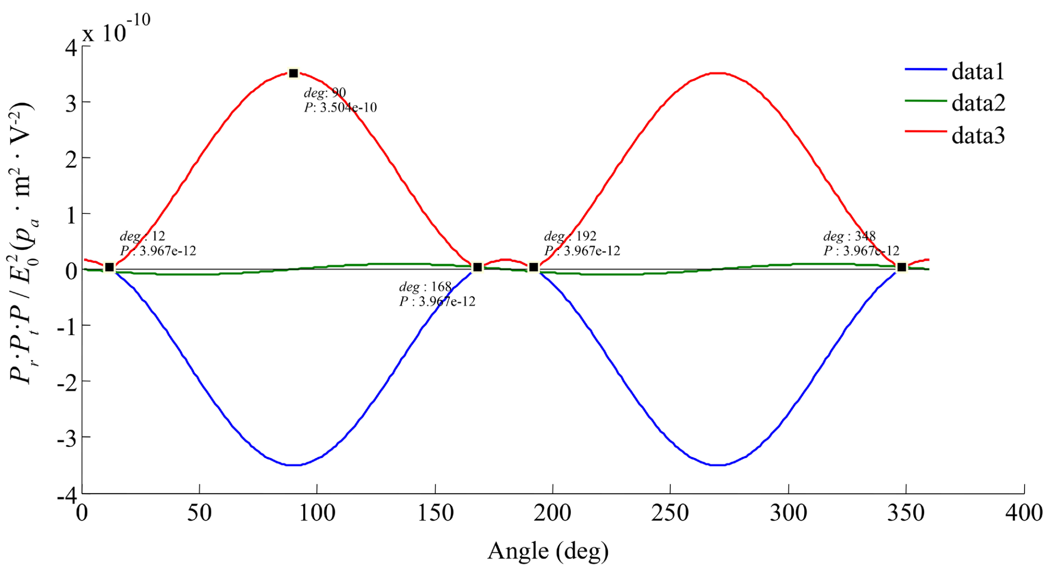
starts to increase, and the normal force is always expressed as pressure on the cell in the whole frequency range; For a certain frequency, the size of the normal force decreases and the size of the tangential force increases with the increase of the equivalent dielectric constant; For the cells with different equivalent permittivity, the threshold value of the change of the direction of the tangential force acting on the cell membrane surface is at same value, such as the frequency is 1.48×10^7 Hz.

4.2.2. Distribution of Electric Field Stress on the Cell Membrane Surface

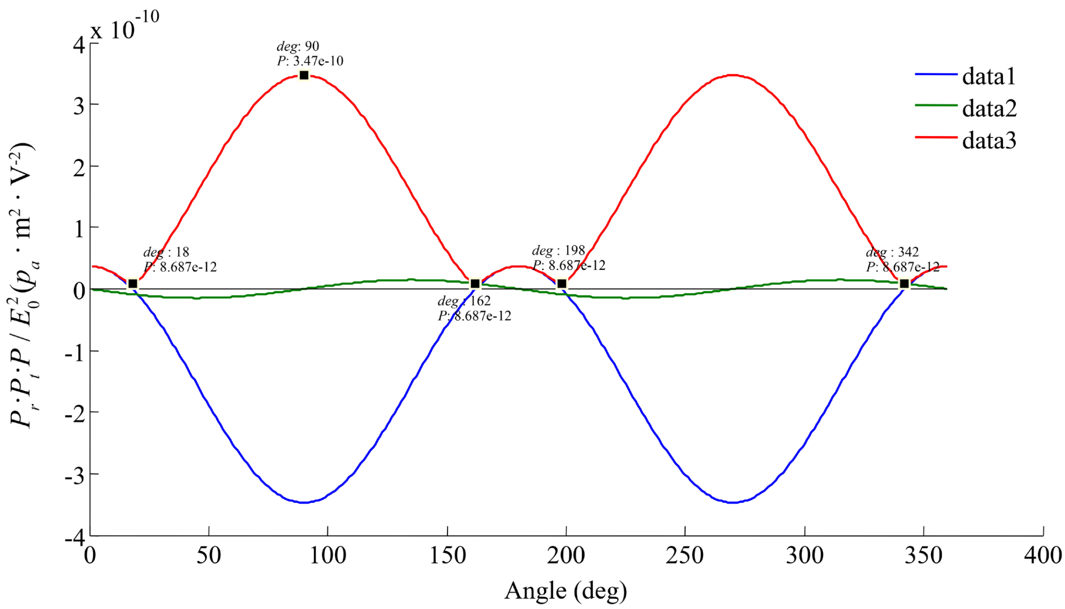
To analyze the effect of the frequency on the electric field stress distribution acting on the cell surface, Figure 4(a) and Figure 4(b) give the electric field stress distribution on the intersection formed the spherical cell surface and the *x-o-z* plane, where $\varepsilon_p = 6.35\times10^{-10}\ \mathrm{F\cdot m^{-1}}$, the curves of data1, data2 and data3 is the P_r, P_t and P, respectively. The frequency of applied electric field in **Figure 4(a)** and **Figure 4(b)** is 1.5 × 10⁶ Hz and 6.7 × 10⁷ Hz, respectively. It is show that the normal and tangential electric field stresses are smaller near the same direction as the external electric field, *i.e.* near $\theta = 0^\circ, 180^\circ$; Near the vertical direction, the maximum normal force and the minimum tangential force are exhibited, and the maximum value of the tangential force is approximately near $\theta = 45^\circ$ and -45°; Within a certain angle range, the electric field stresses are exhibited as the pull force on the cell membrane, *i.e.* for the frequency is 6.7 × 10⁷ Hz, when $-12^\circ < \Delta\theta < 12^\circ$ and $168^\circ < \Delta\theta < 192^\circ$, then $P_r > 0$.



(a)



(b)



(c)

Figure 4. The electric stress varies with the polar angle.

Figure 4(c) shows the variation of P_r, P_t and P with θ, where the external field frequency is 6.7 × 10^7 Hz and $\varepsilon_p = 9.6 \times 10^{-10}\ \mathrm{F \cdot m^{-1}}$. Comparing **Figure 4(b)** and **Figure 4(c)**, it can be seen that with the increase of ε_p, the maximum value of P_r, P is in decreases, but the value of $\Delta\theta$ is increases gradually.

The force exerted by the electric field on the cell membrane is decomposed into normal force perpendicular to the membrane surface (pressure or tension) and tangential force along the surface. The action of electric field force can cause the cell deformation. The frequency of the applied electric field and the change of the cell electrical parameters will lead to the cell deformation.

5. Conclusions

1) In a certain frequency range, the changes in frequency and cellular electrical parameters affect the extracellular ion mobility. In the lower frequency range (e.g., less than 5 × 10^6 Hz), the ion mobility decreases rapidly with the increasing frequency; At the same frequency, the mobility increases with increasing equivalent dielectric constant; With further increase of external electric field frequency, the ion mobility tends to the minimum value and is almost independent of the dielectric constant. It can be seen that the ion mobility caused by high equivalent permittivity in the low frequency electric field region is more pronounced compared to the lower equivalent permittivity and the high frequency region.

2) The electric fields exert the electric field forces on the cell surface. In the small frequency range, the frequency hardly affects the magnitude of electric field stress; With the increase of frequency, the frequency and the changes of the cell equivalent dielectric constant will affect the electric field stress applied to the cell. The electric field stress is the fundamental cause of the cell deformation.

The study of the biological effects of electromagnetic fields has always been a hot topic in bio-electromagnetics research. The content of this paper can be used as the basic analysis theory of the biological effects of the electromagnetic field.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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