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Window Effect of Tumor Cell Induced by The Pulsed Electric Field*

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Abstract Based on the multilayer dielectric model, this paper presents an equivalent circuit model about pulsed electric field, which adapted to spherical bio-cells. In the same frequency domain, the variation tendency of intracellular membranes and epicyte are same, and spectral analysis shows that different frequency spectrum electric field can cause different biomedicine effect. This paper will introduce our work about how to calculate trans-membrane voltage and discuss the relationship among pulse, trans-membrane voltage and impedance, which indicates that different frequency domain and different duration have an effect on the selectivity of intracellular membranes and epicyte. Analysis of time domain and frequency domain shows that on the surface of the cell exists a window, when the duration is between 10^{-8}～10^{-6} s, and the voltage of intracellular membranes will exceed the epicyte's. The result also indicates as t increases, the outer and inner membrane field intensity decreases but bounce back when t is about 3.2×10^{-7}ns of parameters group, which means this is a minimum and is a very meaningful value for the following research. The Window Effect provides a research approach to accounts for biomedicine effect about electrical pulses.

Key words pulsed electric field (PEF), transmembrane potential, time-domain, frequency-domain, window effect
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Pulsed electric field has been widely studied in the past few years and gradually became the research hotspot of bioelectromagnetics, on account of its distinct biomedical effect and that provided a new probable therapy pathway with no need for medicine for the cancer treatment [1–4]. Plenty of experimental researches show that different parameter the PEF fetches different biomedical effect it will cause. A typical example is the microsecond PEF found by Weaver, many reversible aquaporin with radius about 20～110 nm will form in the cell's outer membranes, but there is no evident impact on intracellular membranes. This physical phenomenon is what we called electroporation[5–6], which makes cytomembrane becomes increasingly permeable to molecular drug, and has been successfully applied to oncotherapy.

Nevertheless, too long duration will give rise to heat effect, which will cause much pain to the patient and impact upon therapeutic effect. Schoenbach *et al*. discovered that if plasma membrane effects are delayed and become smaller as pulse duration is shortened, high pulsed electric fields such as ns-PEFs will target the nucleus and modify cellular functions but cell viability was not affected by these pulses[7–8]. Vernier *et al*. found real-time imaging of calcium bursts in human lymphocytes exposed to nanosecond, megavolt-per-meter pulsed electric fields. Ultra-short (less than 30 ns), high-field (greater than 1 MV/m), electric pulses induce increases in cytosolic calcium concentration and translocation of phosphatidylserine (PS) to the outer layer of the plasma membrane in Jurkat T-lymphoblasts[9–11].

Furthermore, Stacey *et al*. discovered that the electric tension increases to 10 kV/cm, the duration shortens to ns level, and it will lead to a series of cell reaction differing from electroporation effect[12–13]. This kind of ns level PEF can lead to organelle membrane

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electroporation, such as cell nucleus and mitochondria, but not epicyte's integrity, and can induce tumour cell apoptosis. This phenomenon is known as intracellular electro manipulation (IEM). Also, we need to take security of clinical application into consideration; too long or short duration and the voltage will cause irreversible damage to ambient healthy cells, and affect the therapeutic effect of patient. Therefore, the key is to precisely confirm its parameter in clinical application. Some researchers has put forward various kinds of spherical cellular structure to study the cell's transmembrane voltage. Joshi developed a distributed network model [14] and Schwan developed a classical electrostatics model [15-16]. Kontik and Damijan expanded Schwan's theory [17-19], introduced an universal analytical method, and Foster proposed a simplified method to calculate organelles potential[20].

There are many circuit expressions in double-shell model. For example, Joshi *et al*. [21] made cytomembrane and cell suspension equivalent to a parallel connection between capacitance and resistance, made cytochylema, contact and external wires equivalent to a resistor, lined up cytomembrane and cytochylema, then put it and cell suspension in parallel. Yao *et al*. [22] made cytomemebrane and karyolemma equivalent to a capacitance, cytoplasm and nuclear substance equivalent to a resistor. Lined up cytomembrane and cytoplasm, put it and a series branch compared of cell nucleus and nuclear substance, in parallel.

But we use an equivalent circuit model differs from above-mentioned. In comparison to Joshi *et al*, we pay attention to the impedance effects of cytoplasm and cell nucleus, taking more influence factors into consideration will make reckoning more precise. Better than Yao *et al*, whom used half-of the cell spherical shell as the equivalent model, we use the whole cell spherical shell as an intact circuit model, which is more reliable.

This paper used multi-layered media transmitting model, which is appropriate for quantitative and quanlitative analysis. Its main theory is that intracellular membranes and epicyte are sensitive to different PEF parameter; cytomembrane will be staved when transmembrane voltage reaches to a specified value(1V). Although equivalent circuit analysis cannot describe the microcosmic dynamical mechanism of intracellular electromanipulation, time-domain analysis cannot provide calculated clear physical image, it is still a straightforward procedure to research Window Effect parameter. Based on a multilayered medium equivalent circuit model, this paper studied the varying tendency with the time of each cytomembrane's transmembrane voltage under various kinds of pulse, discussed the transmembrane potential's response to pulse under time and frequency domain, and finally confirm the parameter of window effect. As a monocyclic pulse, one given pulse duration corresponds to one center frequency, the main energy of which is concentrated upon center frequency. Therefore, we can simply use harmonic function with different center frequency to solve equivalent circuit equation of transmembrane potential induced by different MEP duration.

1 Model

As shown in Figure 1, the multilayer dielectric model and its equivalent circuit indicates that the functions of cell cytoplasm, nuclear cytoplasm and extracellular medium can be regarded as a resistive load (R_4, R_5, R_6), and the functions of external and inner membrane can be regarded as a parallel connection of a resistive and a capacitive load (R_1, C_1; R_2, C_2), respectively. It is easy to understand that the value of R_6 does not affect the transmembrane potential of cell membrane and nuclear membrane. So the equivalent circuit can be simplified as Figure 1c with $R_5=2R_3+R_4$.

According Ohm's law and the method to calculate the capacity of parallel plate capacitor, the value of R_i, C_i can be calculated as following formula

$$R_1=\frac{d_1}{\sigma_1 s},\ R_2=\frac{d_2}{\sigma_2 s},\ R_3=\frac{2r_2}{\sigma_4 s},\ R_4=\frac{r_1-r_2}{\sigma_5 s} \tag{1}$$

$$R_5=2R_4+R_3=\frac{2r_2}{\sigma_4 s}+\frac{2(r_1-r_2)}{\sigma_5 s}=\frac{2\sigma_5 r_2+2\sigma_4(r_1-r_2)}{\sigma_4\sigma_5 s} \tag{2}$$

$$C_1=\frac{\varepsilon_0\varepsilon_{r1}s}{d_1},\ C_2=\frac{\varepsilon_0\varepsilon_{r2}s}{d_2} \tag{3}$$

Where σ_i, d_i, ε_{ri}, r_i is the conductivity, thickness of external and inner membranes, relative permittivity and radius of cell and nuclear. The parameter "s" is the equivalence value of cross-sectional area of current. It is assumed the same value to each multilayer dielectric model just because the calculation convenience in this paper.

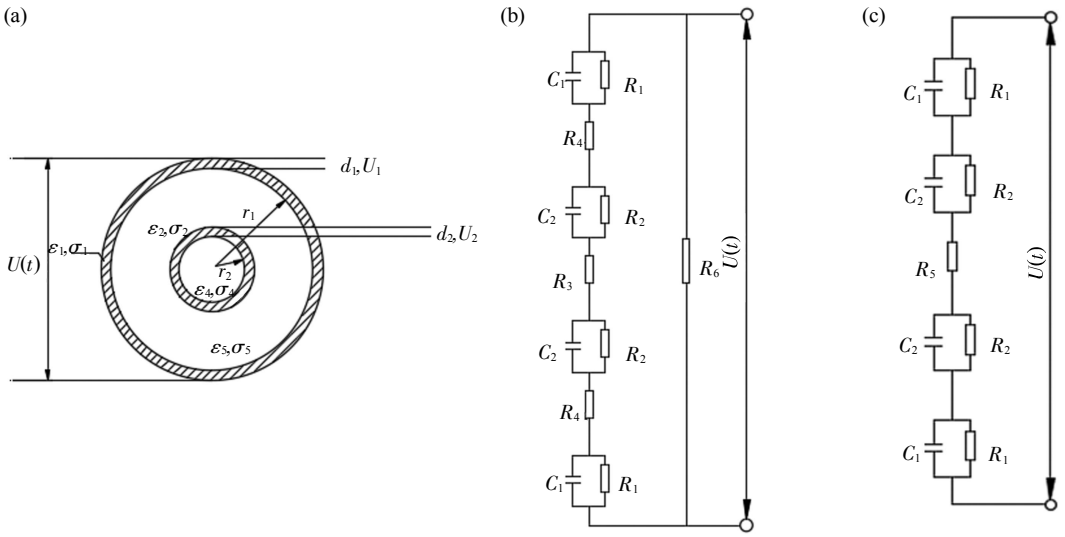

Fig. 1　Multilayer dielectric model of spherical cell and its equivalent circuits

(a) Multilayer dielectric model of spherical cell. (b) Equivalent circuit of cell subjected to PEF. (c) Simplified equivalent circuit of cell subjected to PEF.

2　Theoretical analysis

2.1　Power spectrum analysis of typical pulse

Gaussian-type PEFs generated by conventional electronic devices can be described as a Gaussian pulse, a monocycle and a quasi-rectangular pulse shown in Figure 2, which are usually used in IEM and electroporation effects.

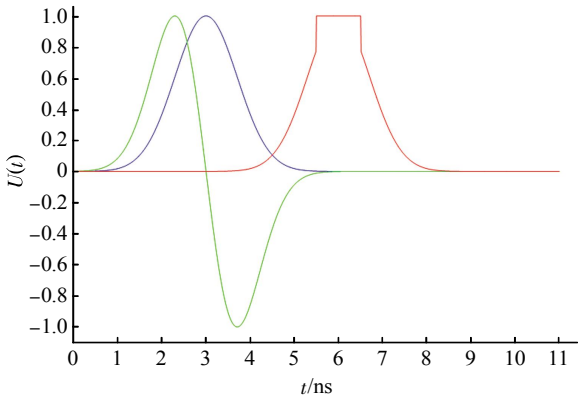

Fig. 2　Gaussian-type PEFs used in IEM and electroporation effects

—— : Generator 1; —— : Generator 2; —— : Generator 3.

Gaussian function $U_1(t)$ with FWHM T can be written as

$$U_1(t)=U_0\exp(-\alpha t^2) \tag{4}$$

Where $$\alpha=\frac{4\ln 2}{T^2} \tag{5}$$

Corresponding to $U_1(t)$, a monocycle function $U_2(t)$ can be written as

$$U_2(t)=-\sqrt{2\alpha}\,\mathrm{e}^{1/2}U_0 \cdot t\exp(-\alpha t^2) \tag{6}$$

And a quasi-rectangular pulse can be written as

$$U_3(t)=\begin{cases} U_0\exp(-\alpha t^2) & t<-\tau_0/2,\ t>\tau_0/2 \\ U_0 & -\tau_0/2<t<\tau_0/2 \end{cases} \tag{7}$$

According to Fourier integral transform, the power spectrum of $U_i(t)$ can be written as

$$\begin{cases} P_1(\omega)=\dfrac{U_0^2}{4\alpha\pi}\mathrm{e}^{-\omega^2/(2\alpha)} \\ P_2(\omega)=\dfrac{U_0^2}{4\alpha\pi}\cdot\omega^2\mathrm{e}^{-\omega^2/(2\alpha)} \\ P_3(\omega)=\dfrac{U_0^2}{4\pi^2}\left[\sqrt{\dfrac{\pi}{\alpha}}\,\mathrm{e}^{-\omega^2/(4\alpha)}+\dfrac{2}{\omega}\sin\dfrac{\tau_0\omega}{2}\right]^2 \end{cases} \tag{8}$$

Eq.(8) indicates that $P_1(\omega)$ and $P_3(\omega)$ are the same function when ω>>1. The extreme condition and the maximum values of $P_2(\omega)$ are

$$\begin{cases} \omega_0=\sqrt{2\alpha}=\dfrac{2\sqrt{2\ln 2}}{T} \\ P_2(\omega_0)=\dfrac{\mathrm{e}^{-1}U_0^2}{2\pi}=8.858\times10^{-2}U_0^2 \end{cases} \tag{9}$$

As $\omega=\gamma\omega_0$, solving simultaneous Eq.(8) and Eq.(9) gets

$$\frac{P_2(\gamma\omega)}{P_2(\omega_0)}=\gamma^2\exp(-\gamma^2+1) \tag{10}$$

Eq. (10) indicates the value of $P_2(\gamma\omega)/P_2(\omega_0)$ is constant for a given γ. In combination of Eq. (9), it is clear that the curve of $P_2(\omega)$ will moves to higher frequency as a whole as the pulse durations decrease.

Figure 3 shows the curve of $P_2(\omega)$ under different pulse durations. It suggested that the transmembrane voltage induced by a monocycle could be regarded as the effects carried out by a harmonic sine function with a certain frequency, such as ω_0. Taking $P_2(\omega_0)/2$ as a reference, the band of the power spectrum ranges from 0.481 ω_0 to 1.634 ω_0.

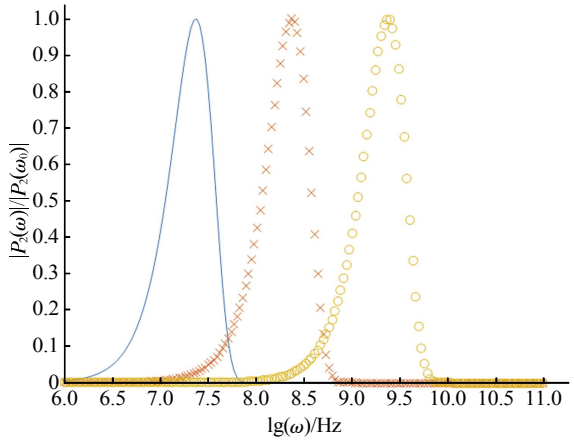

Fig. 3 The power spectrum of the first-order Gaussian function

—: T=100 ns; ×: T=10 ns; ○: T=1 ns.

2.2 Transmembrane potential and window effect

For simplicity, assuming the sine function with a center frequency ω_0, that is

$$U(t)=U_0\sin(\omega_0 t) \tag{11}$$

The circuit equations shown in Figure 1 are

$$\begin{cases} U_{C_1}(t)=\dfrac{Z_1}{2Z_1+2Z_2+R_5}U(t) \\ U_{C_2}(t)=\dfrac{Z_2}{2Z_1+2Z_2+R_5}U(t) \\ U_{R_5}(t)=\dfrac{R_5}{2Z_1+2Z_2+R_5}U(t) \\ U_{C_3}(t)=\dfrac{Z_1}{2Z_1+2Z_2+R_5}U(t) \\ U_{C_4}(t)=\dfrac{Z_2}{2Z_1+2Z_2+R_5}U(t) \end{cases} \tag{12}$$

$$\text{Where}\begin{cases} \dfrac{1}{Z_1}=\dfrac{1}{Z_{C_1}}+\dfrac{1}{Z_{R_1}}=i\omega_0 C_1+\dfrac{1}{R_1} \\ \dfrac{1}{Z_2}=\dfrac{1}{Z_{C_2}}+\dfrac{1}{Z_{R_2}}=i\omega_0 C_2+\dfrac{1}{R_2} \end{cases} \tag{13}$$

and ‘i’ is the imaginary unit.

According to Eq. (12) and Eq. (13), it is suggested that the U of t of second order differential equations as follows

$$\begin{aligned} &R_5C_1C_2\frac{\partial^2}{\partial t^2}U_{C_1}(t)+(2C_2+2C_1+\frac{R_5C_1}{R_2}+\frac{R_5C_2}{R_1})\frac{\partial U_{C_1}(t)}{\partial t} \\ &-C_2\frac{\partial U(t)}{\partial t}+(\frac{2}{R_2}+\frac{2}{R_1}+\frac{R_5}{R_1R_2})U_{C_1}(t)-\frac{U(t)}{R_2}=0 \end{aligned} \tag{14}$$

$$\begin{aligned} &R_5C_1C_2\frac{\partial^2}{\partial t^2}U_{C_2}(t)+(2C_1+2C_2+\frac{R_5C_1}{R_2}+\frac{R_5C_2}{R_1})\frac{\partial U_{C_2}(t)}{\partial t} \\ &-C_1\frac{\partial U(t)}{\partial t}+(\frac{2}{R_1}+\frac{2}{R_2}+\frac{R_5}{R_1R_2})U_{C_2}(t)-\frac{U(t)}{R_1}=0 \end{aligned} \tag{15}$$

$$\begin{aligned} &R_5C_1C_2\frac{\partial^2}{\partial t^2}\ (U_{R_5}(t)-U(t))+(\frac{R_5C_1}{R_2}+\frac{R_5C_2}{R_1} \\ &+2C_1+2C_2)\frac{\partial}{\partial t}U_{R_5}(t)-(\frac{R_5C_1}{R_2}+\frac{R_5C_2}{R_1})\frac{\partial}{\partial t}U(t) \\ &+(\frac{2}{R_1}+\frac{2}{R_2}+\frac{R_5}{R_1R_2})U_{R_5}(t)-\frac{R_5}{R_1R_2})U(t)=0 \end{aligned} \tag{16}$$

Solutions of equations under three different excitation source Eq.(14)–Eq.(16). We can get a cell’s outer membrane of transmembrane potential U_{c_1}, transmembrane potential U_{c_2} cell membrane, cytoplasm transmembrane potential U_{R_5} under different excitation source along with the change of time t. We also found that when the equivalent circuit of capacitance value change and delayed effect of the circuit will change too. In order to research of variation of delayed effect, we expand the initial capacitive load of external and inner membrane (C_1, C_2) to 50 and 100 times.

From the Figures 4a, 5a and 6a, it indicates that when a pulse voltage are added to the cells, the difference of capacitance in circuit among inner and outer membrane and cytoplasm makes a delayed effect. Meanwhile, the delay time has nothing to do with the excitation source while the change trend of voltage is consistent with the excitation source. We know when C_1, C_2 are different value, the delayed effect is different, when capacitance increase gradually, the delay of circuit also gets longer. However, we cannot find the window effects of circuit and consider looking for window effect from frequency domain by studying relationship between U and ω to confirm the window effect.

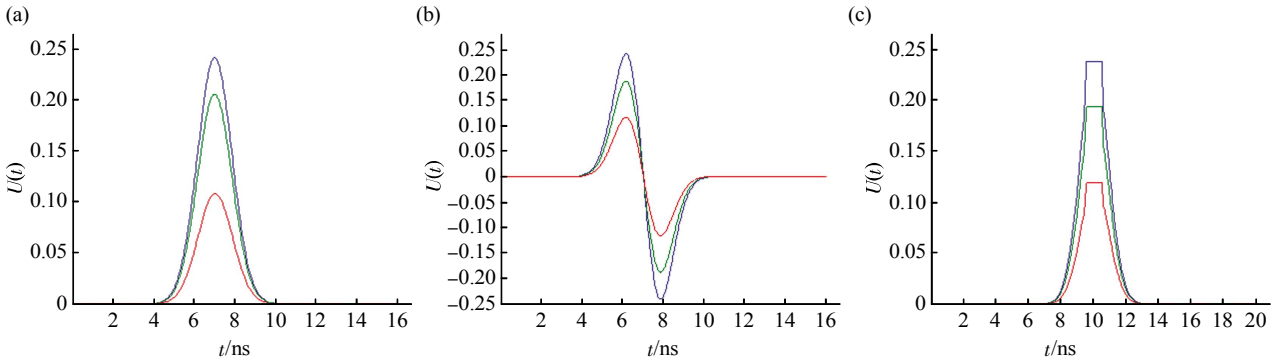

Fig. 4　The membrane potential changes vs time

Three types of excitation source with capacitive of external and inner membrane C_1 and C_2. —: U_{C_1}; —: U_{C_2}; —: U_{R_5}.

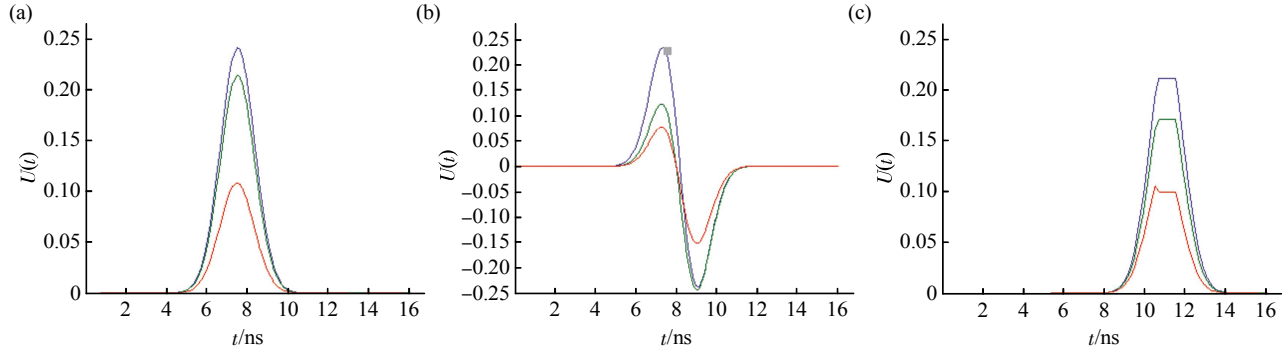

Fig. 5　The membrane potential changes vs time

Three types of excitation source with capacitive of external and inner membrane $50C_1$ and $50C_2$. —: U_{C_1}; —: U_{C_2}; —: U_{R_5}.

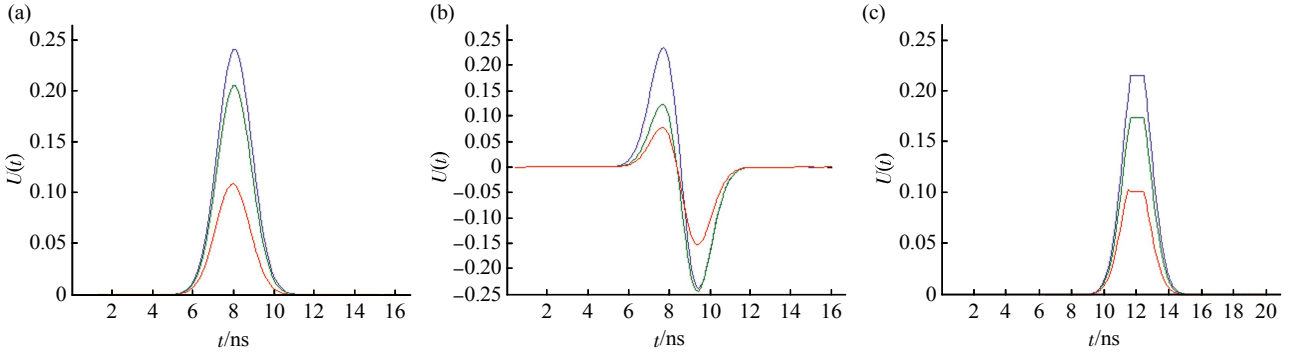

Fig. 6　The membrane potential changes vs time

Three types of excitation source with capacitive of external and inner membrane $100C_1$ and $100C_2$. —: U_{C_1}; —: U_{C_2}; —: U_{R_5}.

Solving simultaneous Eq. (12) and Eq. (13), we can obtain

$$\begin{cases} \left|\dfrac{U_{C_1}(t)}{U(t)}\right| = R_1\sqrt{\dfrac{1+(\omega_0\tau_2)^2}{U_{k1}^2+U_{k2}^2}} \\ \left|\dfrac{U_{C_2}(t)}{U(t)}\right| = R_2\sqrt{\dfrac{1+(\omega_0\tau_1)^2}{U_{k1}^2+U_{k2}^2}} \\ \left|\dfrac{U_{R_5}(t)}{U(t)}\right| = R_5\sqrt{\dfrac{(1-\omega_0^2\tau_1\tau_2)^2+\omega_0^2(\tau_1+\tau_2)^2}{U_{k1}^2+U_{k2}^2}} \end{cases} \tag{17}$$

Where

$$\begin{cases} U_{k1}=2(R_1+R_2)+R_5(1-\omega_0^2\tau_1\tau_2) \\ U_{k2}=\omega_0[2R_1\tau_2+2R_2\tau_1+R_5(\tau_1+\tau_2)] \\ \tau_1=R_1C_1=\varepsilon_0\varepsilon_{r1}/\sigma_1 \\ \tau_2=R_2C_2=\varepsilon_0\varepsilon_{r2}/\sigma_2 \end{cases} \tag{18}$$

The transmembrane potential of the external and inner membranes calculated by Eq.(1)–Eq.(2), Eq.(9) and Eq.(17)–Eq.(18) are shown in Figure 4, where cell parameters used in calculation are shown in Table 1. In consideration of the distinction of tumour cell and

normal cell and lager volume and poor conductivity of tumor cell than general cells, Table 1 is introduced from the relative parameters about Farage cell (Human blood B lymphocytes) by Ermolina *et al*.[23]

Table 1 Simulating parameters of cell

Parameter	Cell component	Group
Conductivity/(S•m^{-1})	Cell membrane σ_1	9.1×10^{-6}
	Cell cytoplasm σ_4	0.48
	Nuclear membrane σ_2	4.4×10^{-3}
	Nuclear cytoplasm σ_5	1.07
Relative permittivity	Cell membrane ε_{r1}	9.8
	Cell cytoplasm ε_{r4}	60
	Nuclear membrane ε_{r2}	60.3
	Nuclear cytoplasm ε_{r5}	120
Geometry parameter/(μm)	Cell radius r_1	5.2
	Cell membrane thickness d_1	0.007
	Nuclear radius r^2	4.4
	Nuclear membrane thickness d^2	0.04

The calculations indicate the external and inner transmembrane voltages are closely related to the PEF durations. If the pulse duration is longer than few microseconds, Figure 4a shows the bias voltage is mainly applied to the external membrane. Figure 4b shows $|Z_1/R_5| \approx |Zc_1/R_5| \approx R_1/R_5 >> 1$ and $|Z_2/R_5| \approx R_2/R_5 \sim 1$

$$|U_{C_1}(t)| = \left|\frac{Z_1}{2Z_1+2Z_2+R_5}\right| |U(t)| \approx \frac{R_1}{2R_1+2R_2+R_5}|U(t)| \quad (19)$$

So the value of U_{C_1} is determined by the ratio of R_1 and $2R_1+2R_2+R_5$. That is to say, the transmembrane potentials are mainly determined by the conductivity parameters of multilayer dielectric. On the other hand, if the pulse duration is shorter than dozen nanoseconds or even to nanosecond, Figure 4a shows the bias voltage is mainly applied to R_5. Figure 4b shows $|Z_1/R_5| \approx |Zc_1/R_5| << 1$ and $|Z_2/R_5| \approx |Zc_2/R_5| << 1$, so the value of U_{R_5} is determined by the ratio of R_1 and $2Zc_1+2Zc_2+R_5$.

$$|U_{R_5}(t)| = \left|\frac{R_5}{2Z_1+2Z_2+R_5}\right| |U(t)| \approx \left|\frac{R_5}{2Zc_1+2Zc_2+R_5}\right| |U(t)| \approx |U(t)| \quad (20)$$

That is to say, it is the relative permittivity parameters of external and inner membranes mainly determine the pulse duration by which the bias voltage is only applied on the R_5. However, if the pulse duration is between dozen nanoseconds and few micro-seconds, Figure 4a shows the bias voltage is mainly applied to the inner membrane and R_5. Figure 4b shows $|Z_1/R_5| \approx |Zc_1/R_5|$ decreasing rapidly and $|Z_2/R_5| \approx |Zc_2/R_5| \sim 1$. That is to say only when the pulse duration takes certain values, it has the value of Zc_1 or Zc_2 equivalent to R_5, the potential of inner membrane can up to its maximum values. This phenomenon is termed the window effect.

As Figure 7(a) shown, when T is between $10^{-8} \sim 3.2\times10^{-7}$ s, the voltage on the cell mainly acts on inner membrane, and the voltage of external membrane is very small. This can cause intracellular membranes staved while there is no obvious effect on epicyte. Meanwhile this will keep completeness of cells, which means the time window effect that abnormal cell apoptosis without leak of potassium and calcium ion. That avoid side effect such as inflammation and infection, which increase treatment efficiency 2 which

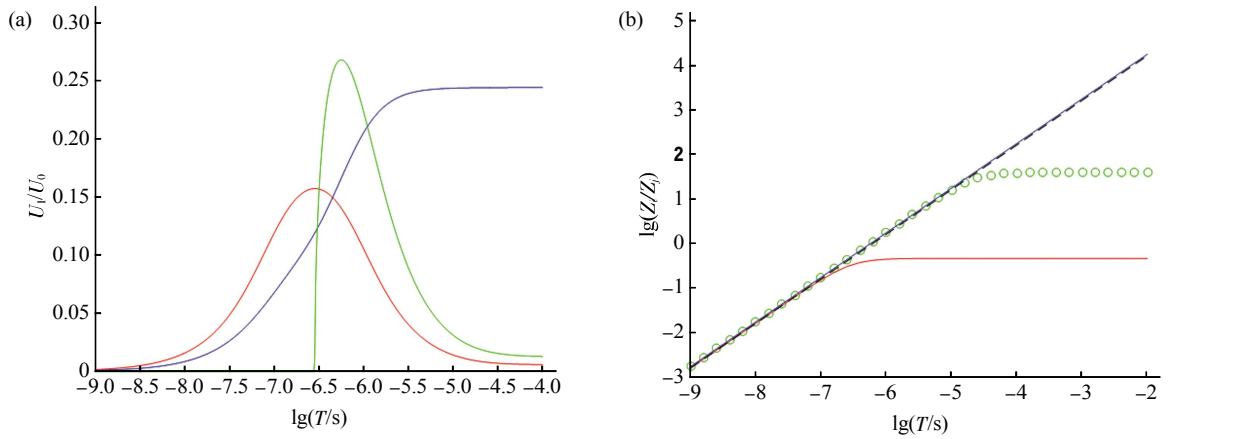

Fig. 7 The transmembrane voltages vs pulse durations

(a) The transmembrane voltages changes with the pulse duration. —: U_{C_1}; —: U_{C_2}; —: U_{R5}. (b) Z_i/Z_j *vs* pulse duration. ○: $|Z_1/R_5|$; —: $|Z_2/R_5|$; —: $|Zc_1/R_5|$; - - -: $|Zc_2/R_5|$.

means the time window effect. It also indicates the pulse duration corresponding to window effect may be written as

$$|Zc_1| \leqslant R_3 \leqslant |Zc_2| \tag{21}$$

Solving simultaneous Eq. (1), Eq. (2) and Eq. (8) gets

$$\frac{k_1\varepsilon_{r2}}{d_2} \leqslant T \leqslant \frac{k_1\varepsilon_{r1}}{d_1} \tag{22}$$

Where $$k_1=\frac{2\sqrt{2\ln 2}\,\varepsilon_0[\sigma_4(r_1-r_2)+2\sigma_5 r_2]}{\sigma_4\sigma_5} \tag{23}$$

As for a certain tumour cell, Eq.(22) and Eq.(23) show the parameters and pulse duration how to affect the window effect. It is easy to understand the importance that different waveform should be adopt to different tumour cells.

2.3 The threshold parameters of biomedical effects

Assuming that the external and inner membranes should be breakdown when the transmembrane voltages are up to the given value U_{k1} and U_{k2}, respectively, the electric filed intensity threshold of E_{k1} and E_{k2} under a PEF with pulse duration T can be carried out based on the calculations of the transmembrane voltage as follows

$$E_{k1} \geqslant \frac{U_{k1}}{2r_1}\frac{U_0}{U_{C_1}},\ E_{k2} \geqslant \frac{U_{k2}}{2r_2}\frac{U_0}{U_{C_2}} \tag{24}$$

Window effect is sensitive to the cell's parameters. Figure 8 shows the E of cell under cell's parameters. As t increases, the outer and inner membrane field intensity decreases but bounce back when t is about 3.2×10^{-7} ns of parameters group, which means this is a minimum and is a very meaningful value for the following research. It means that the pulse duration and the waveform of PEF should be precisely designed in order to have its main energy is concentrated on the area which can make sure the window effect occurred effectively.

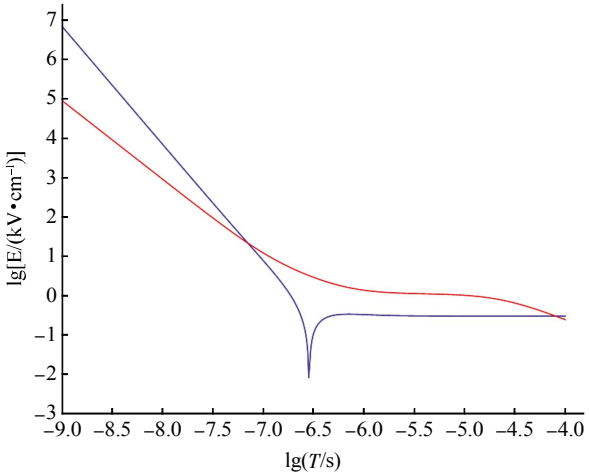

Fig. 8 The threshold relationship between the breakdown filed intensity and the pulse durations cell

—— : E_{k1}; —— : E_{k2}.

If the pulse duration is longer than few microseconds, the external membrane should be breakdown under lower field intensity about 1 kV/cm while the inner membrane needs 10 kV/cm. On the other hand, if the pulse duration is shorter than dozens of nanoseconds, both of the external and of inner membrane should be breakdown only when the field intensity is more than 10 000 kV/cm. However, if the pulse duration is determined by Eq. (22), the inner membrane should be breakdown under a lower field intensity about 100 kV/cm while the external membrane needs 1 000 kV/cm. Therefore，intracellular membranes staved while there is no obvious effect on epicyte kept completeness，when duration is less than about 10 ns and intensity about 100 kV/cm.

It is easy to explain that the external and the inner membranes should be breakdown at the same time under the conditions that the filed intensity is about 100 kV/cm and the pulse duration is about 0.01 μs –0.1 μs, because the transmembrane voltages applied to the two membranes are all lager than the threshold intensity.

2.4 A biomedical effect of unipolar and bipolar PEF

Vernier *et al* [24] reported an experiment which shown the difference between unipolar and biopolar PEFs. In contrast to unipolar pulses, which perturb membrane phospholipid order, tracked with FM1-43 fluorescence, only at the anode side of the cell, bipolar pulses redistribute phospholipids at both the anode and cathode poles, consistent with migration of the anionic PS head group in the transmembrane field. Although the equivalent circuit model could not describe the micro-dynamic mechanism concisely now, but it is sure that the bipolar PEF can induce more effective electroporation.

3 Conclusion

Because of the advantages of concentrating energy of PEF in certain band width, a simple analytical method, by which the analysis is instead by a harmonic function with a certain center frequency, is offered and it can describe the window effect and explain many phenomena of IEM and electroporation concisely in contrast to the complexion of the frequency domain analysis. There are different

phenomena in external and inner membranes under different PEF's parameters, which delay time change with the variation of membranes' parameters. When time of duration is shorter than 10 ns, the voltage of inner cells are greater than the cell's outer membrane voltage, by which PEF will have window effect on the cell membrane. Compared with the phenomenon of electroporation, window effect of short duration, will not produce too much heat effect, thus has better treatment effect. We believe in the future in tumor treatment, the window effect of PEF on further theoretical and experimental research are useful. Now, there are still many unsolved problems such as the non-liner and dynamic changes in transmembrane potential after poration, the ideal number of pulse in practical application, and influence of resting potential. All these still need further researches.

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脉冲电场下肿瘤细胞的窗口效应 *

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摘要　基于多层电介质模型，对于适应于球形生物细胞的脉冲电场，提出了一种等效电路模型，在相同频域下，内膜和外膜的变化趋势相同，频域分析表明，不同频谱场将引起不同的生物医学效应．我们针对癌症细胞计算了跨膜电压，并讨论了脉冲和跨膜电压以及阻抗的关系．结果表明不同的频域和不同的持续时间对细胞的内膜和外膜有选择性的影响，时域和频域的分析显示，在细胞上有一个窗口，当持续时间在 10^{-8}～10^{-6} s 之间，细胞内膜的电压将高于细胞外膜的电压．窗口效应为解释生物细胞的脉冲电学效应提供了一种参考思路．

关键词　脉冲电场(PEF)，跨膜电位，时域，频域，窗口效应

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