Cellular calcium concentration changes as a response to intercellular periodic signals and cell synchronization

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The biological effects of electromagnetic field are caused by the interactions between the electromagnetic field and the biologic system, which involves biological structure, function, and other aspects on different biological levels. The calcium is one of the second messengers which transmit physiological information, affect biological processes such as cell differentiation, maturation, and apoptosis through calcium oscillation, and result different bioeffects. In this study, cellular calcium concentration changes as a response to intercellular periodic signals were investigated. Based on the kinetic model of calcium oscillation in hepatocytes, the intercellular coupling factor was used as the influence factor to analyze the intracellular calcium oscillation pattern under single cell and coupled cells. The results showed that the responses of cellular calcium oscillation were different. In particular, the responses to periodical signals of different frequencies and magnitudes could be divided into two groups with one group having significant changes and the other not. The results also indicated that differences of cells lead to different intracellular calcium oscillation behaviors and the coupling coefficient between cells affects the synchronization of the calcium oscillation.

Keywords: cell; calcium concentration; periodical signals; synchronization; electromagnetic field.

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Introduction

Life on earth has evolved in the environment of natural electromagnetic fields (EMFs). Over the past century, this natural electromagnetic environment has been significantly changed by introducing and fast growing of vast spectrum of man-made electromagnetic fields, which has been assumed for decades that these changes are harmless to human health. However, the epidemiological studies in the past 35 years suggested a potential correlation between cancer induction and alternating extremely low frequency electromagnetic field exposure. The correlation between cancer induction in human being and EMFs exposure was first suggested by the study based on epidemiological findings of an excess leukemia incidence among children who lived in the vicinity of high-voltage wires [1]. Subsequent epidemiological studies by others conducted in several different countries provided supporting evidences linking EMFs to a variety of human malignancies including brain tumors and leukemia [2-4]. The consistency of the marginal findings over the time brings concerns from the general public, and therefore, the regulatory agencies must give the definitive answers.

The reactions caused by interactions between the electromagnetic field and the biological system are called the biological effects which can be divided into thermal reaction and non-thermal reaction groups. The thermal reaction is

that the temperature of organism will be increased after absorbing electromagnetic energy, which will lead the function changes of organism. The non-thermal reaction is that the organism does not have an obvious rise of temperature. However, many changes including physiological, biochemical, and the functional changes display the biology window effect [5, 6] in terms of selected EMFs frequency and power. Biology window effect is a typical non-thermal biological effect of electromagnetic fields with frequency window and intensity window. Thermal biological effect and its mechanism have been well studied. However, although there are several studies about non-thermal biological effect of electromagnetic fields [7-9], the following basic questions of non-thermal effect need to be further explored, which include (1) do electromagnetic fields act on different biological target sites with the common biological structure? (2) is there a relationship between frequency window and intensity window on the same biological target?

The weak electromagnetic fields with various frequency ranges cause significant modifications of physiological status of living systems [10-12]. Ca^{2+} ions are of importance in the biological effects of the EMFs [11, 13, 14]. Some biological effects of the EMFs are considered as a result of the influence on Ca^{2+} dependent intracellular signaling processes. It has been demonstrated that weak EMFs can affect processes of Ca^{2+} transport through plasma membrane [15, 16], modify activity of Ca^{2+} dependent membrane associated proteins [17, 18], induce Ca^{2+} mobilizations [19], change intracellular free calcium concentration ($[Ca^{2+}]_i$) [20, 21] and the affinity of intracellular proteins to Ca^{2+} [22]. The calcium ion oscillation was observed in 1986 [23]. Researches found that the formation of calcium ion oscillation was related to the concentration of IP_3. The calcium ion as the information carrier can be propagated from one cell to another in the process of the communication between cells. Because of the gap junctions among the cells, the calcium oscillation displays the synchronization in multi-cell system [24-26]. Many effective models of the mechanisms have been proposed based on experimental results and mathematical methods, such as single calcium store model [24], the dynamical model of intercellular calcium oscillations in hepatocytes [26], etc.

The mechanism studies on biological effects of electromagnetic fields have been conducting in the aspects of cell membrane, signal channel, and gene expression [27-29]. The cell membrane has been proved the target site of electromagnetic fields [30]. The previous results also showed that the electromagnetic fields could not only directly act on the cell but also on the signal channel, and therefore, to affect the signal transduction and cause biological effects. This study focused on the changes of calcium oscillation inside of the cells with the addition of electromagnetic fields. Based on the kinetic model of calcium ion oscillation in hepatocytes, the intercellular coupling factor was applied as the influent factor to analyze the intracellular calcium oscillation pattern in the single cell and coupled multi-cells.

Materials and Methods

Preparation of cell samples

The human liver cancer (7721) cell line cultured in logarithmic growth phase was prepared as a monolayer suspension by conventional digestion with trypsin (Glorious Bioengineering Company, Wuhan, China). The cell survival rate was determined by using trypan blue exclusion. When the cell survival rate reached 95% and cell density reached 2×10^5 cells/mL, the monolayer suspension was inoculated into a special 50 mm culture dish with a small hole of 1 cm in diameter opened in the center of the dish bottom and covered by a coverslip. The inoculated dish was incubated at 37°C in a 5% CO_2 incubator for 24 h with RPMI Media 1640 (Thermo Fisher Scientific, Carlsbad, CA, USA) containing 10% calf serum (Sijiqing Bioengineering Materials Research Institute, Hangzhou, Zhejiang, China).

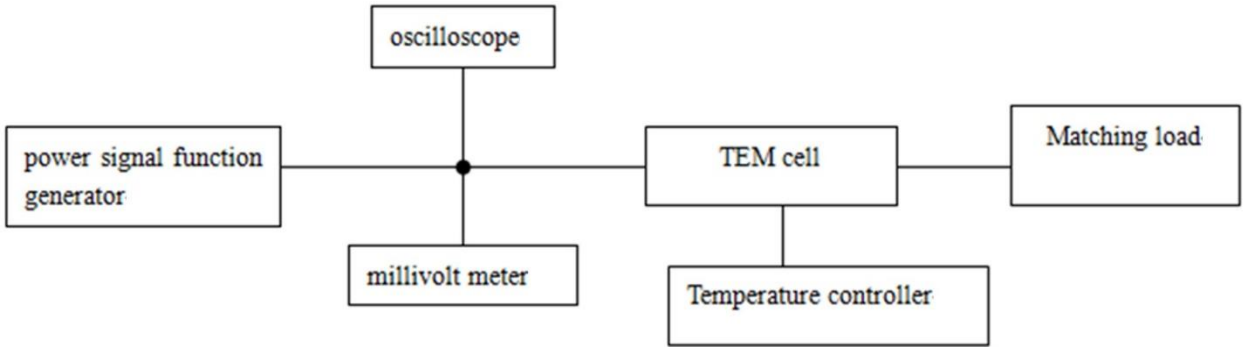

Figure 1. The schematic diagram of the experimental system.

The fluorescence load of cell samples

The fluorescence loading is a process to integrate pre-processed fluorescent probe with cell samples. Briefly, 50 µg of Fluo-3 fluorescent probe (Bio-Rad, Hercules, CA, USA) was dissolved in 50 µl of dimethyl sulfoxide (Coonit Chemical Technology, Suzhou, Jiangsu, China) for stock solution preparation. Two forms of Fluo-3 fluorescent probes, free Fluo-3 and Fluo-3/AM by combining Fluo-3 with Acetoxymethyl Esters [32], were employed in this study. After mixing 500 µl of Hank's solution (Zhen Shanghai and Shanghai Industrial Co., Ltd, shanghai, China) with 5 µl of stock solution, it was applied to wash the cell samples 2-3 times at 24-35°C. 100 µl of Fluo-3/AM was incubated with the cell samples for about 30 minutes in the dark. After the cells were concentrated in sufficiently high concentration of fluorescent probes, the cells were rinsed three times with Hank's solution (pH 7.0 ± 0.1) thoroughly.

Construction of experimental system

The schematic diagram of the experimental system is shown in Figure 1. The system is composed by following instruments including YB1561 power signal function generator and YB2172 AC millivolt meter (Yangzhong Electronic Instrument, Jiangsu, China), V-252 oscilloscope (Hong Kong, China), TEM cell (Xidian University, Xi'an, Shaanxi, China), SWK-1 temperature controller (Sinan Instrument, Beijing, China), and MC Digital Thermometer (Dahua Instrument, Shanghai, China). The temperature of the whole experimental process was maintained at 35 ± 0.2°C. The electromagnetic field strength was 1.78×10^{-7} T. The matching load was set as 50 ohms.

Acquisition of experimental data

After the cell samples were fluorescently loaded, the fluorescence intensity was measured immediately by using laser confocal scanning microscopy. The control sample group data were recorded as the cytoplasm fluorescence intensity minus the background fluorescence intensity. The cell samples were then placed in the exposed chamber with the preset extremely low frequency (ELF) electromagnetic parameters for 20 min. The intracellular and background fluorescence intensities were measured again. The exposed group data were recorded as the cytoplasm fluorescence intensity minus the background fluorescence intensity. The data collected from both control and exposed groups were subjected to statistical analysis.

Numerically model

Dynamical model of intercellular calcium oscillations was applied to analyze the synchronization between cells [26]. For the multi-cell system, Hofer described the following relationship:

$$\frac{dx_j}{dt} = \rho_j(v_0 + v_c\frac{p_j}{K_0 + p_j} - v_4\frac{x_j^2}{K_4^2 + x_j^2} + \frac{\alpha_j k_r(x_x, p_j)}{\beta_j}(z_j - (1+\beta_j)x_j) - \alpha_j v_3\frac{x_j^2}{K_3^2 + x_j^2}) + \gamma(x_i - x_j) \quad (1)$$

$$\frac{dz_j}{dt} = \rho_j(v_0 + v_c \frac{p_j}{K_0 + p_j} - v_4 \frac{x_j^2}{K_4^2 + x_j^2}) + \gamma(x_i - x_j) \quad (2)$$

where x_j and z_j denote the cytoplasm calcium concentration and the free calcium content in cell j, respectively. x_i is the cytosolic calcium concentration in cell i. p_j is the IP_3 concentration in cell j. The parameter v_0 describes the background calcium leakage; v_c is the rate of IP_3-induced calcium leakage; v_3 is the maximum rate of calcium rise in endoplasmic reticulum, and v_4 is the maximum rate of calcium extrusion through the plasma membrane. γ is a relative coupling coefficient and is proportional to the gap junctional permeability. The IP_3 release function $k_r(x_j, p_j)$ is:

$$k_r(x_j, p_j) = k_1\left[\frac{d_2(d_1 + p_j)p_j x_j}{(d_p + p_j)(d_a + x_j)(d_2(d_1 + p_j) + x_j(d_3 + p_j))}\right]^3 + k_2 \quad (3)$$

where p_j, α_j, and β_j are the construction parameters in cell j while $\alpha_j = A_{ER} / A_{PM}$, $\beta_j = C_{ER} / C_{CR}$. The A_{ER}, A_{PM}, C_{ER}, and C_{CR} are the areas of endoplasmic reticulum and plasma membrane, the effective volumes of endoplasmic reticulum and the cytoplasm of cell j, respectively.

Model parameters

In this study, we considered three linear spherical cells as described in Figure 2 with x_0 = 0, z_0 = 0, x_4 = 0, and z_4 = 0. Among them, cell 1 and cell 4 were the boundary cells in the model while v_0 = 0.2 μM/s, v_c = 4.0 μM/s, v_3 = 9.0 μM/s, v_4 = 3.6 μM/s, K_0 = 4.0 μM, K_3 = 0.12 μM, K_4 = 0.12 μM, d_1 = 0.3 μM, d_2 = 0.4 μM, d_3 = 0.2 μM, d_p = 0.2 μM, k_1 = 40.0/s, k_2 = 0.02/s, $p_{i,j}$ = 0.02/μM.

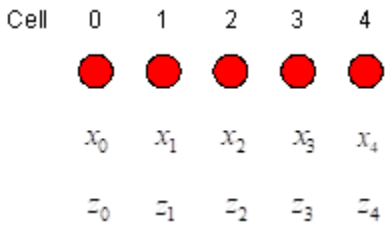

Figure 2. Linear cell model.

The influence of the coupling on the calcium concentration was numerically analyzed by the second order Runge-kutta method based on the dynamical model of intercellular calcium oscillations.

Results

Measurement of calcium concentration

The data of the calcium ion concentration before and after the EMFs exposure were shown in table 1. In order to intuitively observe the change of calcium ion concentration before and after radiated by different electromagnetic fields, we turn the value from time domain to time-frequency domain through map function. The map function used in this study was described as follow [31]:

$$PHM_x(t, v) = \int_{-\infty}^{\infty} \frac{h(\tau)}{2}[x(t+\tau)x*(t) + x(t)x*(t-\tau)]e^{-j2\pi v\tau}d\tau \quad (4)$$

where $x(t)$ is the change of calcium ion concentration with time. $PHM_x(t, v)$ is the distribution of calcium ion concentration at (t, v) with t as time and v as frequency. In this study, only the contour maps that f = 16 Hz, Ep = 53 V/m (Figure 3), and f = 16 Hz, Ep = 26 V/m (Figure 4) were applied, while Ep was the peak value of electronic field.

Numerically analysis

Figure 5 showed the time evolution of the cytoplasm calcium concentration x in the absence an external EMF, while cell 1 demonstrated α_1 = 2.0, β_1 = 0.1; cell 2 demonstrated α_2 = 1.5, β_2 = 0.2; and cell 3 showed α_3 = 1.8, β_3 = 0.15.

Discussion

Calcium ion, as a second messenger, is a basic element that maintains the normal metabolism and physiology of cells. It acts as an important regulator to control many subcellular processes and control cellular biophysical and biochemical

Table 1. The effect of ELF electromagnetic field on the concentration of intracellular cytosolic Ca^{2+}.

f (Hz)	Peak value of electric field (V/m)	The serial number of samples						*P* value
			1	2	3	4	5	
16	53	s	3.35	2.35	2.32	2.40	3.62	< 0.001
		t	6.34	7.86	8.38	6.22	7.08	
32	53	s	2.43	3.16	3.28	2.94	3.07	> 0.10
		t	2.62	3.02	2.89	2.20	2.77	
45	53	s	0.66	3.15	2.85	2.94	2.50	< 0.005
		t	3.50	6.91	4.33	7.76	6.31	
60	53	s	2.67	3.11	3.71	4.42	3.70	> 0.05
		t	2.43	3.52	1.69	2.47	2.75	
16	26	s	3.21	4.07	2.62	2.87	4.22	> 0.10
		t	2.14	3.59	2.19	3.42	3.12	
16	80	s	2.46	1.42	1.16	2.41	1.35	< 0.001
		t	3.09	4.03	3.50	3.41	3.38	
16	87	s	4.53	2.15	5.97	3.78	1.76	> 0.10
		t	4.91	4.47	4.98	2.15	4.79	

Notes: s: experimental group, t: matched group, p: reliability coefficient.

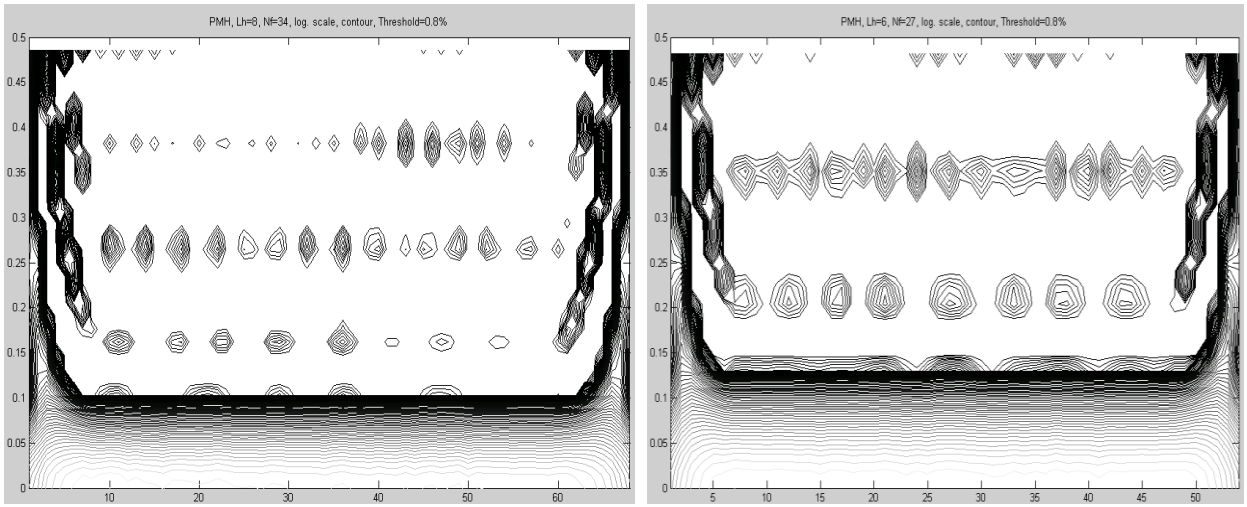

Figure 3. The $PHM_x(t, v)$ isolines before (a) and after (b) the exposure of electromagnetic field of f = 16 Hz, Ep = 53 V/m.

information processes. In the cell signaling system, the mechanisms by which different types of cells transmit signals may vary greatly. There are several kinds of paracrine signals and cross-linkers. When one cell receives a calcium signal to stimulate the secretion of adenosine triphosphate (ATP), it can in turn induce calcium signals in adjacent cells. Therefore, a calcium signal field is transmitted in the organ tissue composed of multiple cells. This study found that the information process of cells could be amplified and optimized by noise, and the disturbance in the nonlinear system environment could induce the serious phenomenon in the system [5, 33, 34].

It can be seen in table 1 that electromagnetic field (Ep = 53 V/m, f = 16 Hz or 45 Hz) made the cytoplasm calcium level increasing significantly ($P < 0.05$), while the adjacent electromagnetic

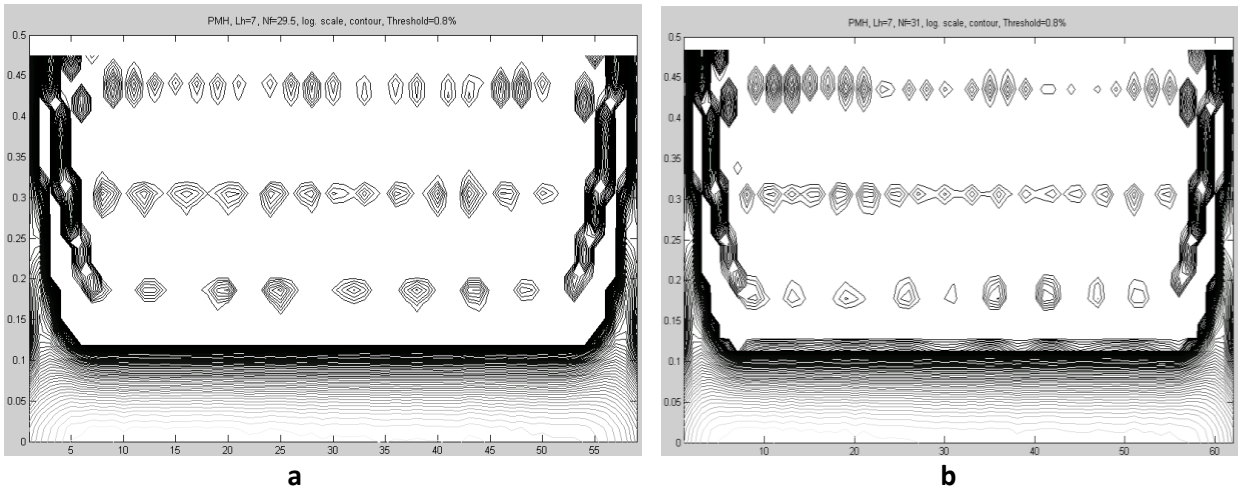

Figure 4. The $PHM_x(t, v)$ isolines before (a) and after (b) the exposure of electromagnetic field of f = 16 Hz, Ep = 26 V/m.

field (Ep = 53 V/m, f = 32 Hz or 60 Hz) did not. Therefore, 16 Hz and 45 Hz were selected as the frequency window respectively. When the frequency was 16 Hz, the ELF electromagnetic field with an electric field peak of 80 V/m made the cytosolic Ca^{2+} concentration increasing significantly ($P < 0.01$) comparing to that of the adjacent 26 V/m and 87 V/m. So that the peak value of 80 V/m was set as intensity window. The change of cytosolic Ca^{2+} concentration before and after expose to ELF electromagnetic field with different frequencies and intensities can also be reflected from the spectral variation of the time-frequency distribution function $PHM_x(t, v)$ contour. Taking Figure 3 as an example, the spectrum of cytosolic Ca^{2+} concentration was divided into two categories as continuum and discrete spectrum. After being irradiated by ELF electromagnetic field, the spectrum showed the following changes. First, the range of the continuum spectrum changed from 0 to 0.15 Hz (Figure 3a) and 0 to 0.1 Hz (Figure 3b). Second, the discrete spectrum also showed obvious changes from two discrete spectra before exposure to three discrete spectra after exposure. The spectral center frequency of the first discrete spectrum changed from 0.22 Hz before exposure to 0.17 Hz after exposure (shown as the nearest discrete closed curve from the continuous curve in Figure 3a and 3b, respectively). The center frequency of the second discrete spectrum before exposure was 0.35 Hz and was 0.27 Hz after exposure. The center frequency of the third discrete spectrum after exposure was 0.38 Hz while there was no third discrete spectrum before exposure. The results suggested that the continuum spectrum was narrowed, and the high-energy spectrum component in the continuum spectrum was suppressed, while the number of discrete spectra and the corresponding frequency center were changed. According to the results, the ELF electromagnetic field with f = 16 Hz and Ep = 53 V/m played a positive role in the change of Ca^{2+} concentration and produced a biological effect. Meanwhile, a similar analysis of Figure 4 showed the continuum distribution range of the time-frequency distribution function contour line corresponding to the cytosolic Ca^{2+} concentration and the corresponding frequency of the discrete spectrum before and after the exposure of f = 16 Hz and Ep = 26 V/m ELF electromagnetic field. The ELF electromagnetic field of f = 16 Hz and Ep = 26 V/m did not have a significant effect on the cytosolic Ca^{2+} concentration as the center did not change, which indicated that no biological effects had been produced. In this study, only a small frequency band and different intensity of ELF electromagnetic fields were used to exposure the cytosolic Ca^{2+}. It can be expected that other biological effects may occur in a wider range of

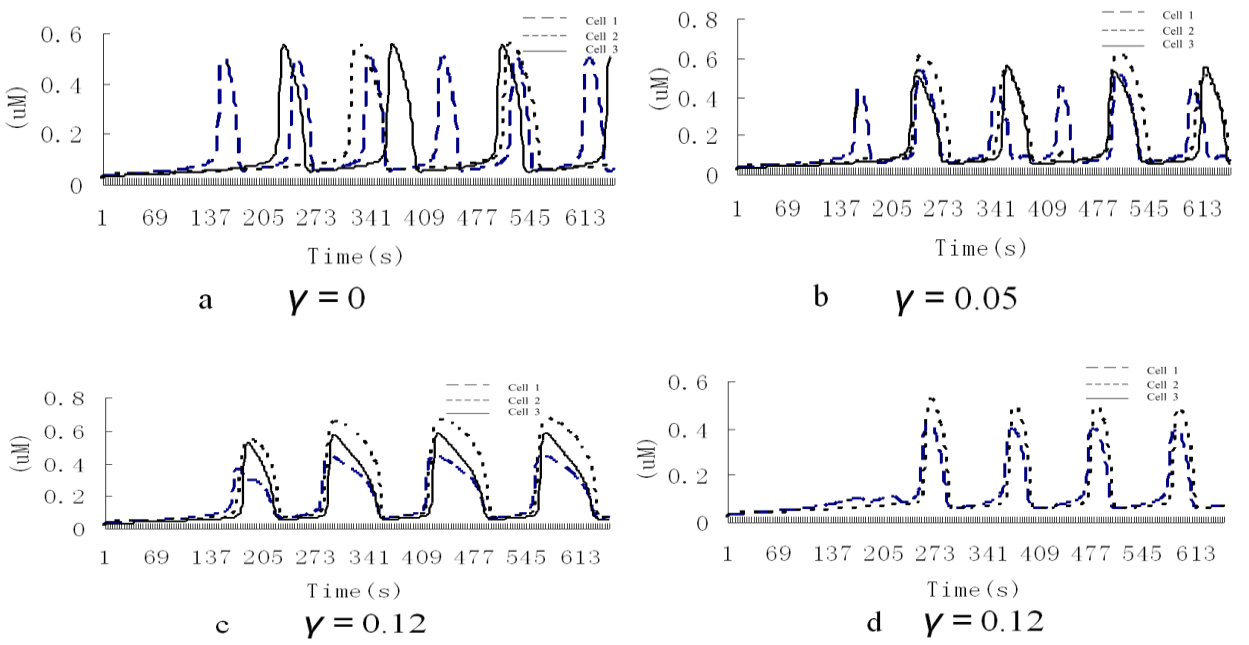

Figure 5. The time evolution of the intracellular calcium concentration affected by other cells.

frequencies and electromagnetic field strengths.

There were many studies at the cellular level that indicated that addition of an electromagnetic field might cause a change in the amount of calcium ions that migrated across the cell membrane and resulted in a biological non-thermal effect of the electromagnetic field [7]. It is undoubtedly of great significance to study the effect of time-varying electromagnetic fields on cell receptors and to study the effects of intracellular calcium oscillations.

In order to intuitively reflect the role of intracellular coupling imposed on calcium oscillation in cytosolic, the numerical results were summarized in Figure 5, where 5a to 5c showed a computed solution for p = 2 μM with the different coupling coefficient γ = 0, 0.05, and 0.12. Figure 5a showed that the amplitudes and the periods of cell 1, cell 2, and cell 3 were 0.5032 μM, 0.5611 μM, 0.554 μM, 92.8 s, 192.57 s, 138.6 s, respectively, which suggested that different structure of cells had different calcium oscillation under the condition without coupling. The time evolution of the intracellular calcium oscillation to cell 1, cell 2, and cell 3 under the conditions of γ = 0.05 and 0.12 was shown in Figure 5b and 5c. The amplitudes and the periods of cells were affected by the intercellular coupling which led to the calcium oscillation synchronization. In order to compare the synchronization of multi-cell system which has two or three cells under the same coupling coefficient condition, the curve of calcium oscillation under the coupling coefficient γ = 0.12 of cell 1 and cell 2 was shown in Figure 5d. The calcium oscillation was synchronized under this coefficient. Although the period was also 107.36 s, the amplitude showed difference with cell 1 as 0.3965 μM and cell 2 as 0.4940 μM, which suggested that the period of calcium oscillation of multi-cell system and the amplitude of calcium concentration were determined by the cell number.

Conclusion

The changes in calcium ion concentration in the cytoplasm of cells varied in response to periodic signals of different frequencies and intensities.

For some periodic signals (f = 16 Hz, Ep = 53 V/m; and f = 16 Hz, Ep = 80 V/m), the Ca^{2+} concentration in the cytoplasm produced significant changes and, therefore, produced biological effects, while the other periodic signals (f = 16 Hz, Ep = 26 V/m, and f = 32 Hz, Ep = 53 V/m) showed no biological effects. The results also showed that the difference in cells could lead to different calcium oscillations, which suggested that cell variability could lead to differences in cellular calcium oscillations. The intercellular coupling coefficient affected the synchrony of multicellular calcium oscillations with the different coupling coefficient caused different calcium oscillation amplitudes in different cells. Under the condition of a certain coupling coefficient, the calcium oscillation tended to be synchronized with time. The frequency of synchronous oscillations was consistent with the oscillation frequency of the cells with the fastest oscillation frequency in multiple cells. Therefore, calcium oscillation can be used as the detection index because the influence of electromagnetic field on the multi-cell calcium oscillation system is more reasonable as the basic mechanism of electromagnetic field biological frequency and intensity windows.

Acknowledgement

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