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Cell-Cell Coupling And Cell Hubness Make a Cell More Resistant Against Low-Frequency Electromagnetic Stress: A Computational Modeling Study

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Abstract**—**In this study, a computational framework was used to check out how cell physical connections to neighboring cells and the hubness property of a cell affect its response to environmental stress such as extremely low-frequency electromagnetic (ELF-EMF) intervention. For this purpose, a mathematical model of a special kind of excitable cells, i.e. human pancreatic beta-cell was incorporated. The connection between cell models was also formulated by a mathematical expression. Furthermore, by changing the characteristics of the model toward increasing calcium dynamics, the hubness property was assigned to the cell model. Using this mathematical model the effect of ELF-EMF was investigated. The simulation results indicated that the physical connection of a cell to its neighbor cells enhanced its potential to tolerate ELF-EMF stresses, possibly via channel sharing or via perturbing ELF-EMF field. Also, when a cell possessed the hubness property, it showed higher resistance against ELF-EMF interventions, possibly due to different calcium dynamics compared with non-hub cells.

Keywords— Computational modeling, Electromagnetic, Cell coupling, Hub-cell

I. INTRODUCTION

Interaction between extremely low-frequency electromagnetic fields (ELF-EMF) and biological systems has been the center of attention during several past decades [1]. Electromagnetic fields are capable to affect ionic displacement through the membrane[2], the enzymatic reactions inside the cell [3] and also DNA structure[4]. Following the change in structural or functional properties of a cell by electromagnetic radiation, the behavior and usual treat of the cell might be altered. In this regard, many researches have been performed so far to understand how electromagnetic waves alter cellular functions. In spite of extensive conducted researches, due to the very complex nature of biological systems, many questions regarding the effect of electromagnetic fields on these systems remained unanswered. One of the open questions is about the role of cellular physical connections to neighboring cells in their response to environmental electromagnetic exposures.

Cellular connections are very important for many natural functions in the body. In stem cells, cell-to-cell connection determines a balance between proliferation, differentiation or quiescence condition[5]. In cancer development, the interaction between adjacent cells is essential for tumor growth[6] and deficient cell-cell coupling in the heart might cause the malignant arrhythmias[7]. It was shown that coupling between cells had remarkable effects on the ensemble behavior of cellular systems. In the islet of Langerhans, isolated β-cells exhibited irregular spiking[8], whereas the coupled cells exhibited more regular bursting electrical oscillations[9]. Any change in cell connections might cause the pathological condition and triggers the disease. In spite of the importance of coupling cells in physiological functions, it is not clear how it affects cellular responses to environmental stresses like electromagnetic interventions. In the present work, using a computational approach and a mathematical model of excited cells, it was evaluated that how cell-cell coupling might change the response of a cell to the exposed ELF-EMFs. Mathematical models, provided that they simulate the real condition with high enough accuracy, are useful tools for testing the new hypothesis. Here, a mathematical model of human pancreatic beta cells[10], the insulin secretion units, that follows well the experimental observations about these cells was incorporated to investigate the effect of cell-cell coupling on electromagnetic responsiveness of cells. This model is a set of differential equations for modeling the voltage-current relationship of different types of ion channels (including calcium, potassium, sodium, chloride and TRPM channels) and the glycolytic pathway (for details see[10], [11]). For coupling adjacent cell models, the gap junction coupling model was used[12].

Another important issue that affects the coupling of a cell to its neighbors is the special role that the cell might pose in a group of cells. In different organs in human body, special kinds of cells with relatively higher connections to neighboring cells are observed that act as central information transferring and processing nodes. Such kinds of cells are called hub and exist in the brain, heart and pancreas as pace-makers. For example, recently Johnston et al. showed that in the islet of Langerhans a few numbers of highly connected cells with more metabolic activity compared with other cells existed[13]. These cells play important roles in the rhythmic activity of the islet of Langerhans. The hub failure in diabetic rodents implies the possible role of these cells in diabetes disease [13]. Using the computational approach, it was shown that hub cells might show different calcium dynamics compared with non-hub cells, especially due to higher expression of P/Q and T-type calcium channels[12]. Here, enhancing the mathematical model of beta cells (by increasing the conductance of P/Q- and T-type calcium channels from base value), the hub cell was simulated and the effect of ELF-EMFs on hub-cells was compared with non-hub cells. Due to the importance of hub cells in the correct functioning of body, it is hypothesized that hub cells might be equipped with mechanisms to be protected against external stresses. Furthermore, as other natural communities, it is supposed that the connected population of cells are more resistant against external invasions. In the present work, these hypotheses were tested using computational approaches while the targeted sample was chosen to be pancreatic beta cells.

This manuscript was organized as follows. Section 2 described the mathematical model for pancreatic beta cells and the way that the effect of electromagnetic fields was incorporated in the model. Furthermore in this section, the hubness of a pancreatic beta-cell was described. The obtained results and related discussions were given in sections 3 and 4, respectively.

II. RELATED WORKS

Li et al. developed a mathematical model for investigating the effect of electromagnetic fields on neurons. The results showed electromagnetics could suppress the electrical activities of a single neuron. Furthermore, in a neuronal network the electromagnetic field could suppress the spatiotemporal propagation 14]. It was shown that low-frequency electromagnetic fields in pulsed form changed processing activity of neurons[15]. Farashi et al. used mathematical modelling for the effect of temperature variation on beta cells[11]. Temperature change might probably occur during electromagnetic stresses. Furthermore, using the mathematical modelling the author previously investigated the parameter optimization for finding the ranges of parameters for the significant influence of electromagnetic radiations on beta-cells [16]. To the best of the author's knowledge, there is no computational related study to search how coupling in a network of cells might affect electromagnetic responses of the cells.

III. METHODOLOGY

In this study, the mathematical model for human pancreatic beta cells was used as the benchmark for testing the effect of cell coupling and hubness on ELF-EMF effects. The mathematical description for this model is as follows.

Mathematical Model of β-cells

The open or close probability of voltage-dependent ion channels of a pancreatic β-cell can be modeled with a first-order differential equation, where the steady-state condition follows a Boltzmann function[10]. The current-voltage relationship for each ion channel(X) can be simply described using Ohm's law as (1).

$$I_X = g_X(v - V_X) \quad (1)$$

In which, v is the transmembrabe voltage, V_X is the voltage for half-maximal activation and g_X is the conductance of ion channel which is voltage-sensitive for voltage-dependent channels, depends on the ligand (for example for GABA receptor channels) or depends on the calcium concentration for calcium-dependent channels (see [10]). The overall voltage-current relationship for β-cell is described according to (2).

$$\frac{dv}{dt} = -I_{ion} \quad (2)$$

In (2), I_{ion} is the overall current of ion channels.
The influence of an external field (E_{ext}) on β-cell electrical activity can be included in the model by displacement current (I_D) [16] as follows.

$$J_D = \frac{\partial D}{\partial t} = \varepsilon \frac{\partial E_{ext}}{\partial t} \quad (3)$$

$$I_D = SJ_D = \varepsilon S \frac{\partial E_{ext}}{\partial t} = dC_m \frac{\partial E_{ext}}{\partial t} \quad (4)$$

In (3) and (4), ε is the permittivity of the membrane, S is the surface of membrane, d is the thickness of membrane, C_m is the capacitance for membrane ($C_m = \varepsilon S/d$) and D describes the electric flux density. Due to the fact that diameter is relatively larger than membrane thickness, the membrane capacitance property was modelled by a flat capacitor. Displacement current is added to (1) as follows.

$$\frac{dv}{dt} = -I_{ion} + I_D \quad (5)$$

Even though evidences confirmed that cells responded to environmental electromagnetic stresses[1], it seems that such response is highly dependent on the characteristic features (such as intensity and frequency) of the exposed field[16]. In this regard, the parameters were adjusted according to the previous author's work [16] to have the highest interaction between beta-cell and electromagnetic wave.

Model for cell-cell coupling

The purpose of this study was to investigate the way that cell coupling might affect the response of cells to electromagnetic fields. In this regard, it was necessary to use a model for coupling beta-cells. There are two known mechanisms for gating hemichannels of a gap junction that consist of Vj-gating and loop-gating mechanisms. Vj-gating is related to the fast transition between open and subconductance state of the channel and the loop-gating exhibits the step-wise gating of the channel[17]. The time-constant for loop-gating is relatively larger than Vj-gating. It is supposed that channel gating is getting started with Vj-gating and is completed by loop-gating [17]. For completing the gait process, it was suggested that at least four channel subunits were necessary [18]. These descriptions were converted to mathematical expression as the following formulas.

$$P_{open}=h^4m \qquad (6)$$

In which *h* and *m* showed the probability for loop-gating and Vj-gating mechanisms, respectively. It should be noted that these two gating mechanisms were considered to be independent. For a gap junction channel consists of two independent hemi-channel (for example connexin36 in human beta-cells), channel opening status or conductivity (with maximum conductivity of g_{max}) can be expressed as Eq (7).

$$G= g_{max}\, P_{open1}\, P_{open2} \qquad (7)$$

The details of the proposed voltage-dependent mathematical model for β-cells coupling via connexin36 (CX36) channels and the parameters can be found elsewhere[12].

Pancreatic hub cells

Using a computational framework, the author investigated the role of different ion channels on the capability of a β-cell to control the electrical activity of its connected cells[12]. Since hub cells control the rhythmic activity of connected β-cells, the synchronized electrical activity of connected cells should follow the hub cell. According to the results proposed by Johnston et al. [13], the author concluded that the hub cells might be distinct from non-hub cells due to the higher expression of P/Q and T-type calcium channels[12]. This was simulated by enhancing the conductance of T-type and P/Q calcium channels in the model (see [12]).

Evaluation of the effect of the electromagnetic field and statistical analysis

The output of the model is the time-series for membrane electrical activity. Like the experimental evidences[10] in which reported that beta-cell electrical activity showed spiking or bursting patterns, the model also enables to produce such patterns. For assessing the effect of ELF-EMFs on cell electrical activity, inter-burst-interval (IBI), spike amplitude, burst duration (BD) and inter-spike-interval (ISI) were used as criteria. An automatic algorithm for calculating these measures by a thresholding strategy was used. The statistical analysis for investigating the sensible effects of low-frequency electromagnetic fields was performed using student t-test. All simulations consist of model implementation, calculation of measures and statistical analyses were performed in Matlab 2017.

IV. RESULTS AND DISCUSSION

According to the mathematical model of β-cells, a target cell was coupled to different numbers of neighboring cells where the coupling strength was determined using the gap-junction model[12]. Fig. 1 showed the effect of the external electric field with different frequency, amplitude and wave shapes on ISI of the exposed cell (with different coupled neighbors), when compared with the similar control (unexposed) case. The model parameter set for exposed and unexposed cases was the same. In another study, the author showed that, in order to produce sensible effects, the local electric field amplitude should cross a threshold value (E_{ext}>10 kV/m). Furthermore, it was shown that the pulsed and continuous excitations changed the attribute of the electrical activity in different ways. Also, there should be characteristic frequencies in extremely low-frequency region (f<300 Hz) for β-cells[16]. When the ISI ratio was closer to 1, it implied that the external electric field had a smaller effect on the electrical activity of the system. It is worth noting that the membrane electrical activity of beta-cells is correlated with insulin secretion[19]. The results of Fig. 1 showed that the change of ISI for different field intensities, frequencies and wave shapes was smaller when the targeted cell coupled to its neighbors (i.e. when the number of the connected cell to the target cell was 1 or 8) compared with the isolated cell (i.e. the cell with zero connected cells). In order to consider beta-cell heterogeneity, the parameters of the targeted and neighbors were perturbed around the reported values from literature(Table 1 in [10]) and the simulation was repeated. The ISI ratios in Fig. 1 was the average value for several simulations (n=24).

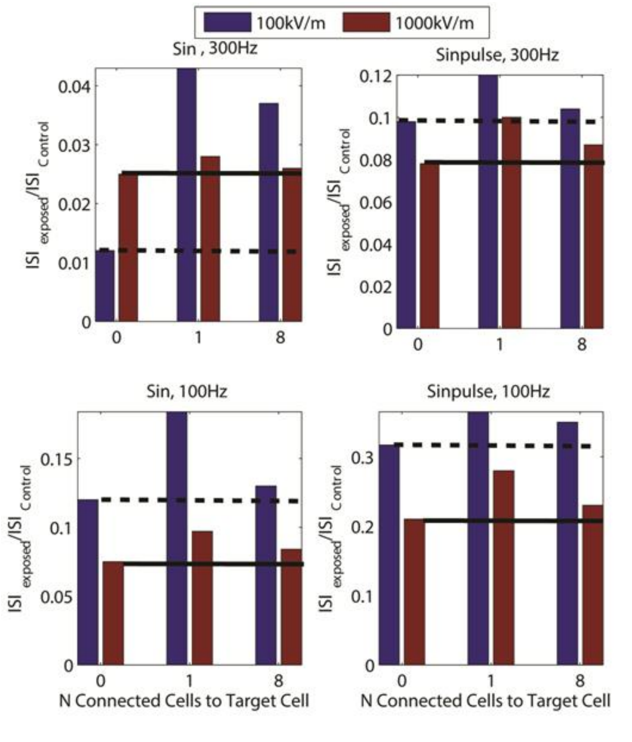

Fig. 1 Effect of cell coupling on the influence of external electric field on beta-cell electrical activity.

In physiological organs like the brain, heart and pancreas, hub cells are responsible for the main connections between cells. For evaluating the way that such cells respond to the external electromagnetic interventions another simulation was performed. Fig. 2 showed the effect of external electric fields on the main characteristic features of membrane electrical activity of hub and non-hub beta-cells. The excitation contained the continuous (Sin) and pulsed sinusoidal (SinPulse) waveforms. Each panel showed the difference between the features of electrical activities of the exposed cell (hub or non-hub) and the control (unexposed) cell, both with the same parameter set. When the electrical activity of the exposed and unexposed cells were similar (i.e. the difference was closer to zero), it might imply that the cell was more resistant against exposure. According to Fig. 2, both continuous and pulsed electric fields had sensible effects on the electrical activity of hub and non-hub beta-cells, however, the electrical activity of exposed hub cell compared with its control showed smaller deviation when compared with non-hub cell. It should be noted that due to the heterogeneity of pancreatic beta-cells, the simulation has been repeated (n=15) for different parameter sets of β-cell model (i.e. different conductance for ion channels), where the reported parameters of control beta-cell (Table. 1 in Riz et al.,(2014)) were multiplied by a constant value that was drawn from a normal distribution. The standard deviation of such normal distribution was supposed to be relatively small(σ=0.05). The mean difference values and the standard deviation of these values were shown in Fig. 2.

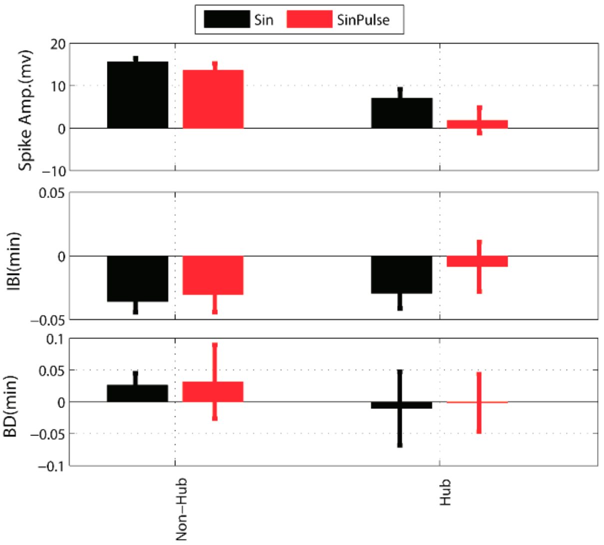

Fig. 2 Comparison between hub and non-hub beta-cell's electrical activity in response to an external electric field (local electric field amplitude: 100kV/m, f=300 Hz, PRF=50 Hz, exposure time=60s).

V. DISCUSSION

The result of this study implied that coupling between cells made them more robust against an electromagnetic perturbation (Fig. 1). It seems that the coupled cells can mitigate the effect of electromagnetic interventions via possibly channel sharing[20]. Coupling a cell to its neighbor through gap junctions is also necessary for a pancreas to secret insulin in a bursting mode[21]. Connected cells are also more potent to perturb the local distribution of the external field and in this way make this external intervention inefficacious. Furthermore, results of Fig. 1 indicated that such higher resistance of coupled cells against external electric fields was satisfied for different frequencies, wave shapes and field intensities for the applied field. The simulation results reported by Fig. 2 indicated that when a cell was hub, it was less affected by an external stress. This is an important outcome, since hub cells govern the rhythmicity of the population and play pivotal roles for information transfer in the system. Any failure of these cells might collapse the network and triggers the disease. In this regard, the higher resistance of such cells against external electromagnetic interventions should preserve the cellular networks from the hazardous effect of intervention. Such higher resistance of hub cells against ELF-EMF could be searched in higher calcium dynamics of these cells. Interestingly, Pall[22] via reviewing several papers reported that voltage-gated calcium channels were important elements for cell responses to ELF-EMF. The stimulation of nitric oxide-cGMP-protein kinase G pathway by increasing level of Ca^{2+} upon EMF excitation[23] was reported as the regulatory pathway for electromagnetic effects [22]. As the author showed using a computational simulation, hub cell showed higher expression of Ca2+ ion channels and therefore different calcium dynamics. However, the role of calcium dynamics in hub cells for higher level of resistance against external electromagnetic fields needs more in-depth investigation. This should be stick in mind that hub cells are highly connected cells, therefore besides the help of higher calcium dynamics, they can mediate the effect of ELF-EMF through their connection to neighboring cells.

V. CONCLUSION AND FUTURE SCOPE

Pancreatic beta cells are very important units in the pancreas. The glucose concentration is regulated by insulin secreted by these cells. It is of special interest to investigate how environmental factors affect beta cell activity. In this study, using a computational modeling approach, it was revealed that physical connectivity between cells makes them more resistant against environmental stress like ELF-EMF radiation. Connected cells might suppress the effect of external ELF-EMF fields by channel sharing in a way that through shared channels the metabolite perturbations caused by external stimuli are compensated. Also, it was shown that when a cell acts as a hub, it had the potential to tolerate an ELF-EMF compared with its non-hub counterpart. It should be concluded that even though these results were obtained for a special type of cells (i.e. human pancreatic beta cells), they can possibly be generalized to other types of excitable cells such as neurons and heart pacemakers. Furthermore, these outcomes were obtained in a computational framework and can be considered as a starting hypothesis for experimental investigations.

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