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Understanding the Signal Transduction Mechanism of Gap Junctions Using Computational Approach in Cardiac Cells

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Abstract

Gap junctions are important intercellular communication mechanisms in heart tissue, and their function is critical to maintaining normal cardiac electrical signals. Gap junctions allow direct electrical connectivity between cardiac myocytes with every beating, allowing for the fast and synchronized spread of cardiac excitement. Proper gap junction communication results in the relatively close start of all cardiomyocyte action potentials as well as an ordered contraction. Many types of cardiac illness cause changes in gap junction coupling. It is understood that the connexin (Cx) component of gap junctions has both direct and indirect functions in the transmission of electrical impulses from the cardiac pacemaker to functioning myocytes through the cardiac conduction system (CCS). In this work, the single cardiac cell of human Purkinjie Fibre and Ventricular Cells are modelled. The modelled cells are coupled via gap junction channels. The computational research intends to investigate the electrotonic function of gap junction conduits in the transmission of electrical impulses between heart cells. It is also studied the effect of the gap junction role between pairs of cells and extrapolate these findings at the tissue level.

Keywords: ***Cardiac cell model, Gap junction, Human ventricle cell model, Purkinje cell***

I. Introduction

The fundamental process which sustains human life is the control and coordination of electrical waves and impulses that are transmitted throughout the heart chambers. Cardiac conduction often gets obstructed under pathological conditions where it could result in arrhythmias and death sometimes when normal propagation is not restored properly [1]. In cardiac tissues, The quick flow of ions via the cytoplasm of cardiac cells facilitate the electrical communication at the subcellular level and the gap junctions made up by hemichannels of specialised proteins known as connexins included into the intercalated discs control and mediate the slow intracellular flow [2].

A variety of hexameric arrangements and connexin types are established to regulate the ionic flow through the gap junctions where a non-linear behaviour between transjunctional voltage and electrical conductance are observed as a result of dynamic conditions. This reveals a non-ohmic electrical behaviour [3]. Due to the gap junction channels, the cardiac myocytes present in the ventricular myocardium of mammals are considered to be a form of the functional syncytium. On a succinct note, Connexin in every single GJC is necessary for both metabolic and electrical communication between adjacent cells [4]. The role of particular connexin patterns in the control of GJC development in the heart was discussed in [5]. Cxs plays an indirect and a direct role in the transmission of electrical impulses from the cardiac pacemaker via the cardiac conduction system

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(CCS) to the working myocyte in the heart [6, 7]. The key determinants influencing the conduction characteristics of cardiac GJC are the specific connexin isoforms and their construction into homotypic, heterotypic, or heteromeric channels [8-10].

In mammals, The substantial expression of Cx43 throughout the chamber myocardium is thought to be distinctive [11] and maybe as an adaptation to allow fine and quick control [12, 13, and 14]. Cx43 is a dominant isoform expressed in the mammalian atrial and ventricular myocardium and post-translational modifications (de/phosphorylation) of the same, exhibit alterations in conducting properties [15-17].

Many pathophysiological conditions, such as ischemia [18, 19], hemodynamic overload [12, 20] and diabetes [21, 22] might also influence Cx43 phosphorylation and thus change its susceptibility to arrhythmias [17]. Apart from alterations in phosphorylation, a proarrhythmic potential could also be a result of impaired Cx43 expression, spatial distribution, and heterogeneity [23, 24]. Correspondingly, the role of Cx43 hemichannels in a pro-arrhythmic environment was recently reviewed in [25]. Similarly, the alteration in Cx40 is associated with certain types of arrhythmias [26, 27]. Unlike working myocardium, the Purkinje myocytes in the terminal part of the CCS express Cx40, as well as Cx43 [28, 29]. Comprehensive studies indicate the ability of the entire CCS to produce the first connexin to appear during cardiogenesis [30], Cx45 [31,32], throughout the myocardium in small amounts including the nodes [32], where Cx30 is also detected [33].

Further developments regarding Cx40, which is a marker of chamber myocardium differentiation and is said to allow for faster transmission of the electrical impulses [34, 35]. The existence of Purkinje-working myocardium coupling is traditionally described only in homoisotherms, as no evidence for the Purkinje fibres (PFs) was found in the poikilotherms [36,37]. During the embryonic development and early postnatal stages, The presence of negligible amounts of Cx40 in the compacted myocardium [38,39], makes Cx40 Purkinje-myocyte coupling possible. Whereas, With the help of Cx43, the mature heart establishes Purkinje-working myocardium junctional connections. [38,39]. These respective junctions and PFs render to be a common source for arrhythmias [40, 41].

Three-dimensional study of the activation sequence of the ventricular myocardium is quite challenging. From the electrocardiogram, It is concluded that transmural stimulation proceeds from the endocardium to the epicardium (which contains the PFs). Epicardial optical mapping demonstrates apex-to-base activation, with the earliest active patches around ventricular apices [39, 42, 43], similar to bundle branch terminations.

II. Cardiac models

1. The model

The dynamics of the membrane potential in a cardiac cell is described by the differential equation (1):

$$C\frac{dV_m}{dt} = I^{ion} + I_{stim} \qquad (1)$$

Where, C is the membrane capacitance; Vm is the membrane potential; t is the time; I^{ion} is the summation of Ionic currents in transmembrane, and I_{stim} is a stimulus current applied externally (Hodgkin & Huxley 1952) [44]. Many biophysically comprehensive descriptions of I^{ion} have previously been generated for a wide range of cardiac tissue types and species.

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A gap junction conductance channel links the cells together as depicted in Figure 1. The gap junction channel replicates the Cx 43 channel in the electrophysiology of the heart.

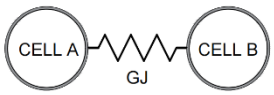

Figure 1 Gap junction conductance of two adjacent cells

When a cardiac cells pair are connected by a GJ conductance, gj, Figure 1. The voltage dynamics of coupled cell pair is stated as:

$$C_1 \frac{dV_1}{dt} = I_1^{ionkin} + g_j(V_2 - V_1) \qquad (2)$$

$$C_2 \frac{dV_2}{dt} = I_2^{ionkin} + g_j(V_1 - V_2) \qquad (3)$$

Where *V*1 and *V*2 are the voltage across a membrane of cells A and B, respectively; C_1 and C_2 are the membrane capacitances of cells A and B, respectively; I_1 ^{ionkin} and I_2 ^{ionkin} indicates the total ion channel currents in cells A and B.; *gj* represents the conductance of the GJ connecting the two cells.

III. Proposed Cardiac Models

In this work, the following two human cardiac cells models namely Purkinje and Ventricular cells were identified to carry out the computational study on cardiac intercell communications.

a. Human Purkinje cell model (2009)

The recent human Purkinje cell model of Philip Stewart (2009) was used. Based on the human endocardial cell model created by ten Tusscher et al. (2004)[46] and ten Tusscher & Panfilov (2006)[47], Philip Stewart et al [45] created a description of I_{ion} for the human PF cell. They altered their model in response to experimental findings from Han et al. (2002) [48] detailing the characteristics of potassium currents in human PF cells. As seen in the equation, their explanation of I_{ion} involves the inclusion of two currents: a hyperpolarization-activated current, If, and a sustained potassium current, I_{sus}, for a total of 14 ionic currents (4). The total ionic current of equation (4) was replaced in equation (1) for simulating the human Purkinje cell model.

$$I_{ion} = I_{Kr} + I_{Ks} + I_{K1} + I_{to} + I_{sus} + I_{Na} + I_{b,Na} + I_{Ca,L} + I_{b,Ca} + I_{NaK} + I_{NaCa} + I_{p,Ca} + I_{p,K} + I_f \quad (4)$$

The dynamics of this PF cell was simulated using MATLAB and the response of the PF single cell is plotted in Figure 2. The result obtained is well-matched with that of the Philip Stewart model. The action potential parameters are well matched.

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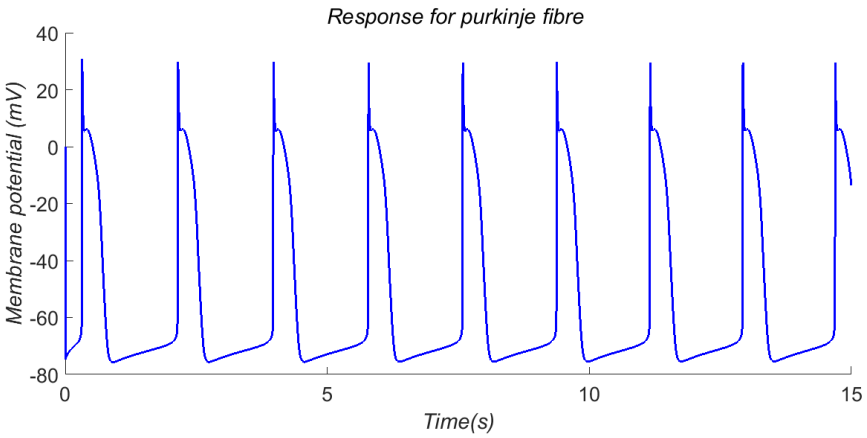

Figure. 2 Single-cell response of human Purkinje cell

b. Human ventricular cell model (2019)

Tomek *et.al* (49) developed a human ventricle cell model. This recently developed one is taken into account for the computational study of ventricular myocardium cells. The model is highly complex and incorporates all ventricle dynamics. The ionic current dynamics of the Tomek model is given in equation (5).

$$Iion = -\frac{1}{1} * (INa + INaL + Ito + ICaL + ICaNa + ICaK + IKr + IKs + IK1 + INaCa_i + INaCa_{ss} + INaK + INab + IKb + IpCa + ICab + IC1Ca + IC1b + Ikatp + Istim) \quad (5)$$

The dynamics of this model is also developed using MATLAB; the response of the single cell is depicted in Figure 3 and the response is highly matched with that original model.

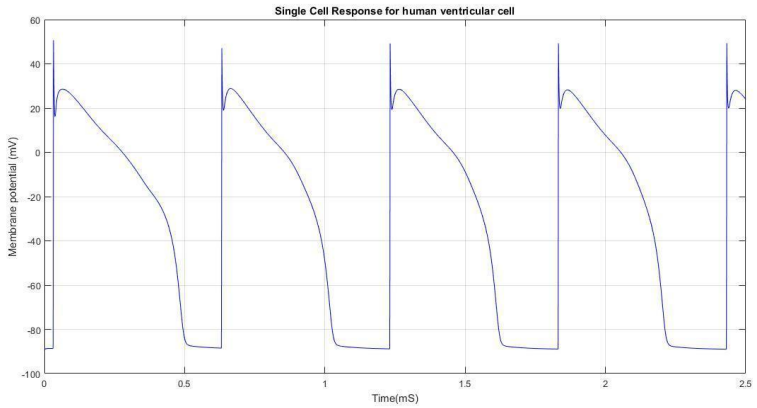

Figure. 3 Single-cell response of human ventricle cell

IV. Cardiac Cell Pair

The response of single cardiac Purkinje and Ventricle cells is highly encouraging. After the single-cell model study, it is planned to connect two cells discretely through electrical conductance which resembles the gap junction conductance channel in cardiac electrophysiology. The gap junction

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conductance value is selected in the range of 140 – 165 pS which is the same as that of Cx 40 connexin in Purkinje fibre of human heart in the range of around 155 – 160 pS. Similarly, human ventricle cells are coupled through electrical conductance in the range of 70-80 pS which resembles real ventricle connexin Cx 43 in the range of 60- 100 pS. The two cells are coupled as shown in Figure 1.

Case 1: Purkinje cell Pair.

In this two PF cells are coupled through a conductance value of 150 pS. The intrinsic frequency of the two cells is selected as 35 bpm and 40 bpm. The cells pair response is depicted in Figure 4. It is observed from the figure that the cells are well synchronized to a common frequency of 36 bpm. It indicates that proper gap junction conductance value brings the two cells in sync. The same concept if expanded to large groups of cells i.e. tissue will propagate the action potential in a well-synchronized way.

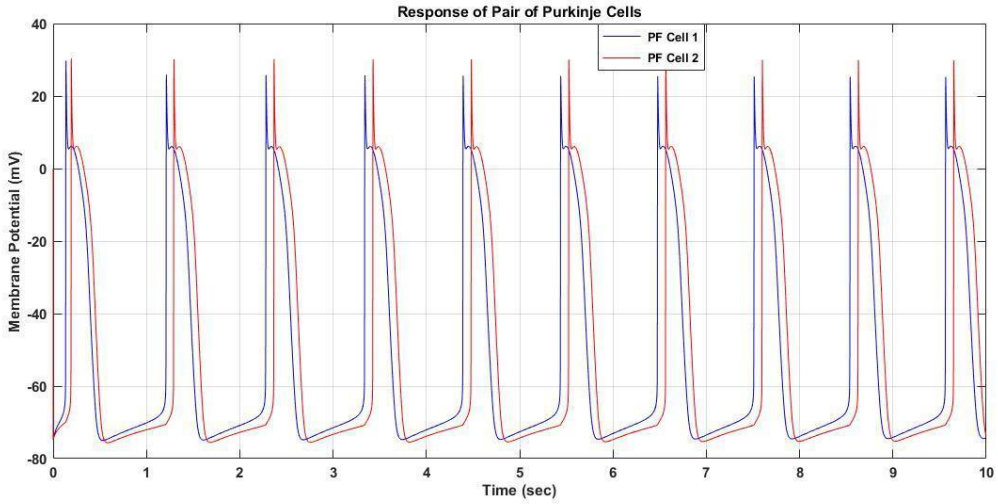

Figure. 4 Cell pair response of human Purkinje cell with Gjc of 150 pS

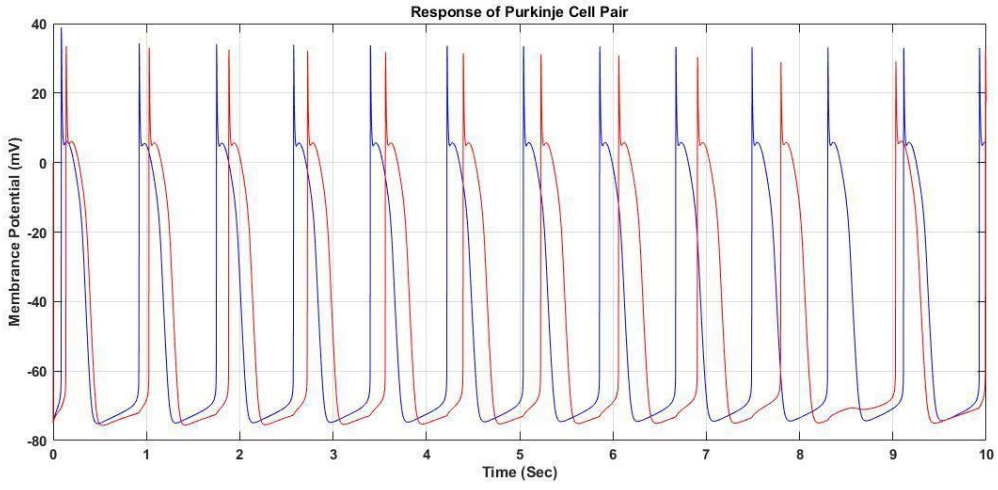

Figure. 5 Cell pair response of human Purkinje cell with Gjc of 160 pS

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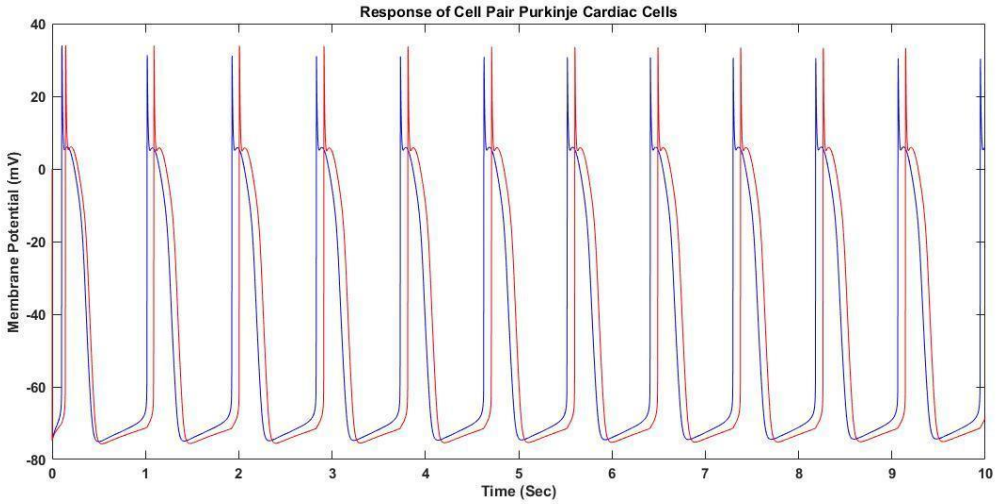

Figure. 6 Cell pair response of human Purkinje cell synchronized

A similar study has been performed with a higher value of gap junction conductance (165 pS) and response is demonstrated in Figure 5. The figure reveals that two cells are trying to come to synchronization and could not. Hence, both the cells are now oscillating at a new different frequency and which could not bring proper heart action potential propagation in the cardiac conduction system. Further, it has been studied by varying the value of gap junction conductance and found that both cells are well synchronized to a new BPM and the response was shown in Figure 6.

Case 2: Ventricle Cell Pair.

A similar study has been carried out for a pair of ventricle cells. It is noted from the study that proper selection of gap junction conductance establishes proper synchronization among the cells. The two cases are depicted in Figure 7 and 8. In the first figure, both cells are propagating the action potential whereas in the second figure the action potential propagation is not proper among the two cells.

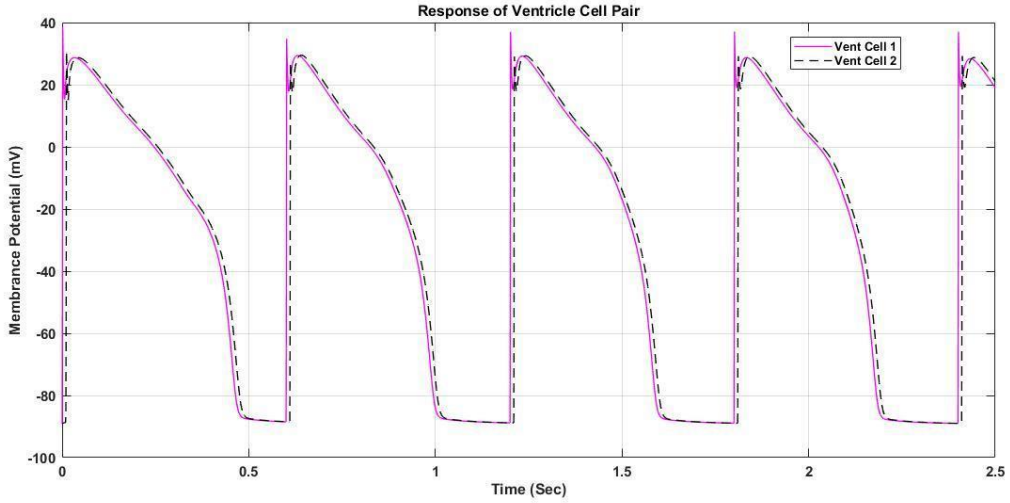

Figure. 7 Cell pair response of human ventricular cell with proper propagation

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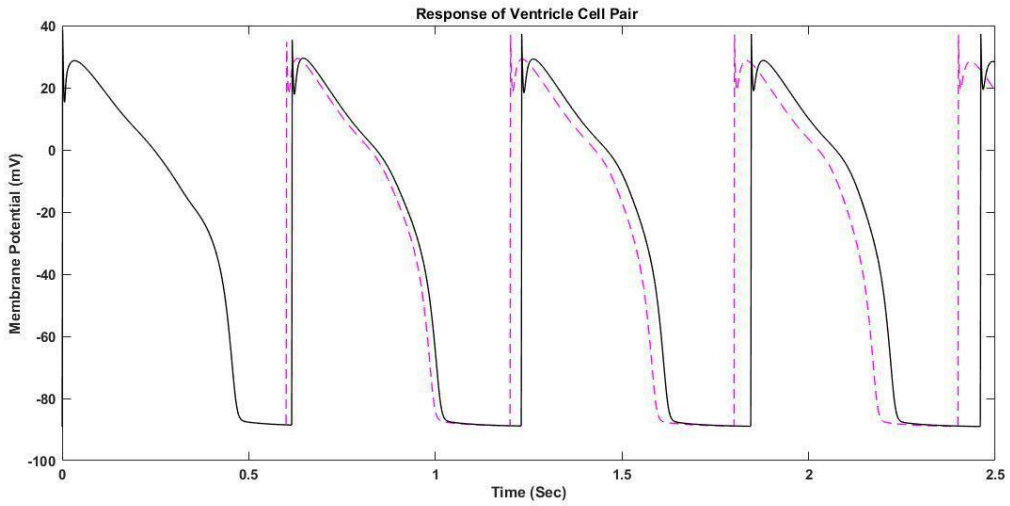

Figure. 8 Cell pair response of human ventricular cell with improper propagation

Case 3: Purkinje – Ventricle Cell Pair.

After a thorough analysis of the Purkinje pair and ventricle pair of cells, the next investigation focused on creating a PF and Ventricle cell pair that are connected as depicted in Figure 9. Initially, the study was performed using multiple values of gap junction conductance and the same study was repeated for a fixed set of values, where the latter demonstrated a better synchronization and propagation of action potential from PF to ventricle cells. Astonishingly, the ventricle and PF cells were found to work at a concordant frequency (Figure 10). Whereas, the resultant alterations in action potential propagation caused by variations in gap junction conductance values are illustrated in (Figure 11). Further studies on this model by coupling 2 PF cells along with a ventricle cell, displayed an apt action potential propagation in the presence of a suitable GJ conductance value (Figure 12).

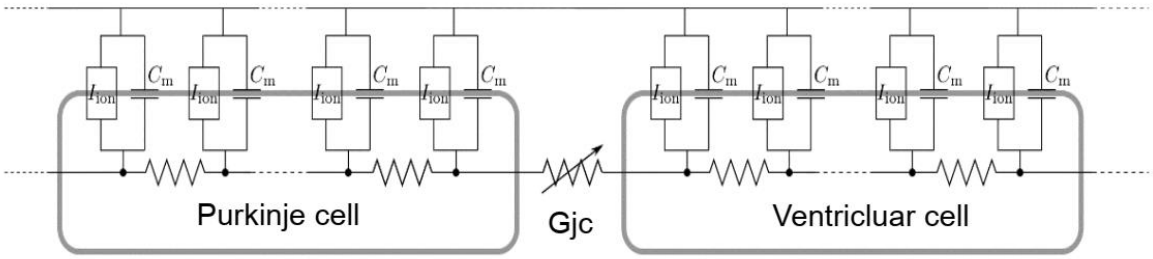

Figure. 9 The electrical circuit representation for the cellular models of pair of Purkinje and ventricular cells connected with gap junction conductance (Gjc)

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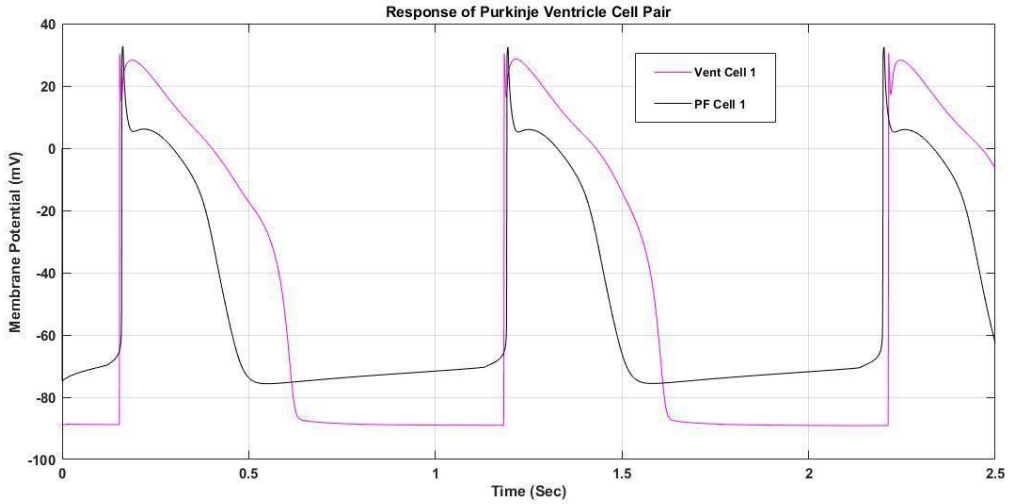

Figure. 10 Cell pair response of human Purkinje-ventricular cell with proper propagation

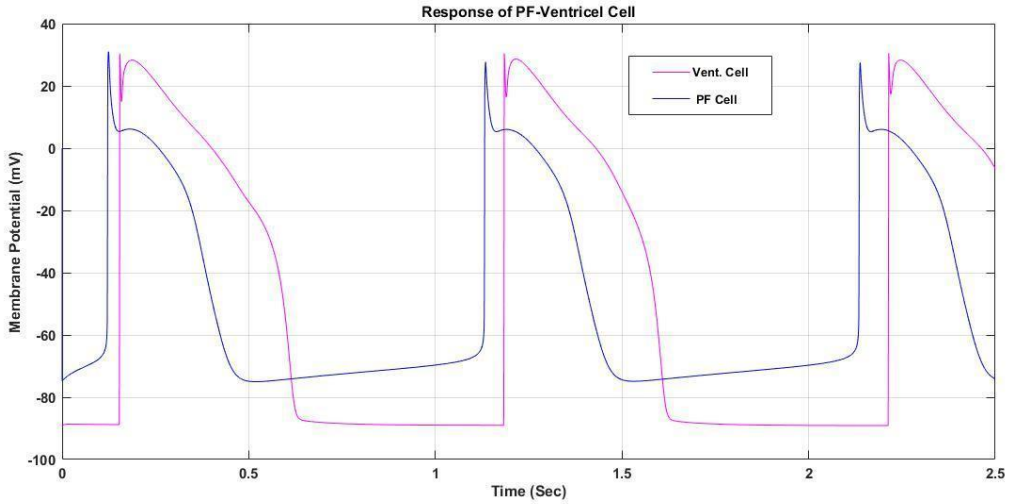

Figure. 11 Cell pair response of human Purkinje-ventricular cell with improper propagation

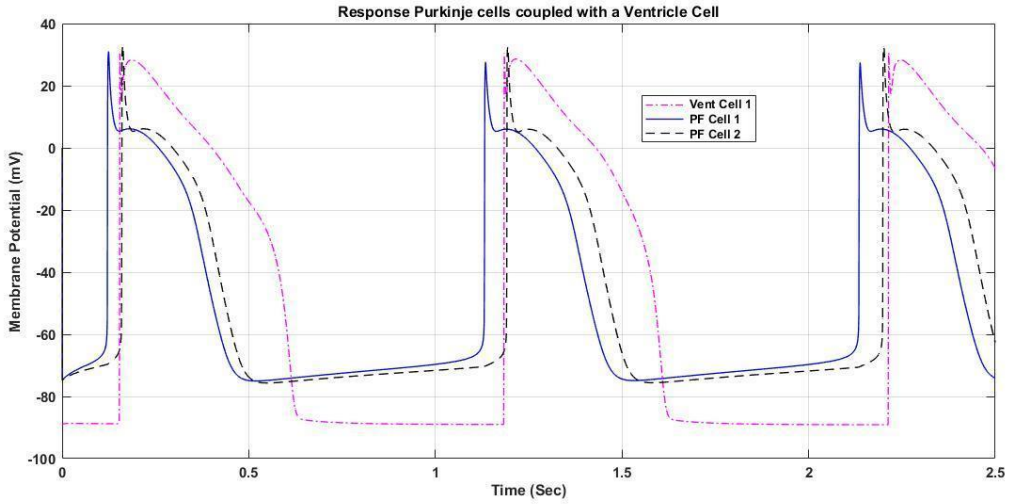

Figure. 12 Response of two PF cell and one ventricle cell with proper propagation

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V. Discussion:

The model of both human PF and Ventricle cells demonstrated contemporary working only under proper gap junction conductance values. In this study coupling of cells was made in a discrete manner which enabled the selection of GJ conductance values among every connection to be assigned. Despite successive shifts in synchronization amidst the same pair of cells, the cells only depicted negligible disturbances in action potential propagation caused by varying GJ conductance values. Our findings contradicted this model, where 2 different cells (PF and V) showed varied synchronizations for varying GJ conductance values disturbing the action potential propagation. This analysis emphasised that proper coupling through gap junction conductance play a vital role in cardiac electrical propagation among cardiac tissue. This cellular level study paves a way to understand the role of gap junction channels in cardiac conduction systems. Thereby, answering various unresolved complexities related to cardiac memory and causes leading to cardiac abnormalities like cardiac arrhythmia, myocardial infarction.

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