ASSESSMENT OF GAP JUNCTIONAL CONDUCTANCE MAGNITUDE IN CARDIAC SYNCHRONIZATION - A COMPUTATIONAL STUDY

[1]T S Murugesh

[1]Assistant Professor

[1] Department of Electronics and Instrumentation Engineering, Faculty of Engineering and Technology

[1]Annamalai University, Annamalai Nagar, 608002. India

Abstract : Auto rhythmic cells refer to the cardiac muscle cells responsible for synchronizing the contractile cells to coordinate a heart contraction. The normal pace making in the heart depends on the coordinated discharge frequency of thousands of pacemaker cells comprising the sinoatrial (SA) region. The SA node, that serves as the normal pacemaker of the heart comprises of thousands of cells whose intrinsic frequencies are not identical. The electrical activities of the various SA node cells coordinate to give rise to a single impulse by means of a complex mechanism during each cardiac cycle. The propagation of excitation within the heart involves action potential (A.P) generation by cardiac cells and its propagation in the multicellular tissue. The most contributing factor towards cardiac communication is the gap junction (GJ) where GJ conduction occurs by direct movement of ions between cells. GJs permit large areas of cardiac tissue to contract as a single unit, a functional syncytium, by synchronizing oscillations of large number of cells. It is seen that, when aggregates with different spontaneous frequencies are brought into close opposition, their activities synchronize to a common frequency. In cardiac cells many different kinds of ions interact to generate action potential that go through the heart and cause a synchronized normal contraction. The action potential from the model of a cardiac cell, specifically auto rhythmic cells of a species (rabbit) is obtained and the influence of model parameters on the intrinsic frequency of the specified auto rhythmic cell is investigated. A cell pair is formulated by coupling the SA node cells using gap junctional conductance channels with a varying frequency gradient. The synchronization issues in the cell pair are analyzed and the influence of GJ conductance magnitude in coaxing synchronization between the coupled cell pair is assessed with the aid of simulation studies.

Index Terms **– Cardiac cells, pacemaker, Synchronization, gap junction conductance, action potential, sinoatrial node.**

I. INTRODUCTION

The cardiac myocyte is the most physically energetic cell in the body, contracting constantly, without tiring, 3 billion times or more in an average human lifespan. By coordinating its beating activity with that of its 3 billion neighbours in the main pump of the human heart, over 7,000 liters of blood is pumped per day, without conscious effort, along 100,000 miles of blood vessels [1]. The electrical excitation originating in specialized regions of the cardiac muscle spreads over the myocardium to activate muscular contraction, all of these under feedback control regulating the cardiac output [2]. The auto rhythmic excitation in the cardiac muscle is driven by the sino atrial (SA) node, the natural pacemaker of the heart. Biological rhythms, like the cardiac rhythm are generated by large populations of mutually interacting cellular oscillators where the individual oscillators inherit intrinsic frequencies with significant dispersion. The normal cardiac rhythm is the result of collective, synchronized action of a large number of cardiac pacemakers/oscillators. In the normal cardiac excitation sequence the action potential initiated in the sino atrial (SA) node travels through the atrial wall, the atrio ventricular (AV) node, the Purkinje system and the ventricular wall. The change in electrical potential associated with the passage of an impulse along the cell membrane is action potential. The conduction of Action Potential is the outcome of complex interactions between cellular electrical activity, electrical cell-to-cell communication as well as the cardiac tissue structure [3]. From the electro physiology point of view and from the literature studies it can be perceived that the role of gap junctions are important in cardiac muscle; the signal to contract is passed efficiently through gap junctions allowing the heart muscle cells to contract in tandem. On considering the species 'Rabbit', the Sino Atrial nodal cells exhibit an intrinsic frequency of about 170 beats per minute (bpm), followed by AV nodal cells at 120-330 bpm, and Purkinje fibers at 80-140 bpm. Such a network of cardiac oscillators/pacemakers with a varied range of firing frequencies (330-80 bpm) synchronize and beat at a common frequency corresponding to the normal cardiac rhythm. The entrainment of cardiac pacemakers at a rate different from their intrinsic frequency leads to changes in the intrinsic beating frequency [4, 5]. Frequency entrainment is an important phenomenon, from a practical standpoint, as it forms the basis on which heart pacemakers' work. The work aims to analyze and investigate the varied intrinsic frequencies of the cardiac pacemakers and the mechanism behind the mutual entrainment among them. The focus is also on the influence of the extent of gap junctional conductance magnitude on the intrinsic frequencies of the cardiac system and by which synchronization can be accomplished within it.

II. SPECIES & MODEL CONSIDERED

Due to a large volume of experimental data relating to the behaviour of a number of different cells within the rabbit, the same species is chosen as the focus for this work. While differences between the rabbit and human heart do exist, including differences in size, 300grams in humans [6] versus 30grams in rabbit [7], and resting heart rate, 70 beats per minute in humans [8] versus 260 beats

per minute in the rabbit [9], rabbit hearts are shown to be remarkably close to human hearts in terms of electrophysiological activity [10]. In particular, rabbits are shown to match very closely with humans with respect to certain types of heart failure [11]. With these similarities in cardiac behaviour, coupled with a lack of electrophysiological data available for humans and abundance for rabbits, an appropriate rabbit model that fits the scope of this research work is considered.

Several mathematical models are available that describe the electrical activity and ion exchange in the sinoatrial node (SAN). In cardiac cells many different kinds of ions interact to generate action potential that go through the heart and cause a synchronized normal contraction. Differential equations are developed to define the movement of each ion in the dynamic cardiac environment. The chosen model must provide acceptable fits to voltage clamp and action potential data and can be used to seek biophysically based explanations of the electrophysiological activity in the rabbit sinoatrial node cell. One such model is the Demir single sino atrial node cell model [12] and the dynamical equations describing its behaviour are solved and the corresponding source code is developed and implemented using Matlab. The results obtained from the previous work carried out [13, 14] has shown that the parameter (the leakage conductance) variations of a cardiac cell induced proportionate changes in its intrinsic frequency, but coaxed the cells to oscillate only for a specified range. The variations in the leakage conductance (hereinafter called 'Parameter') induce subsequent variations in the intrinsic rate of the SAN cell and is represented in Fig.1.

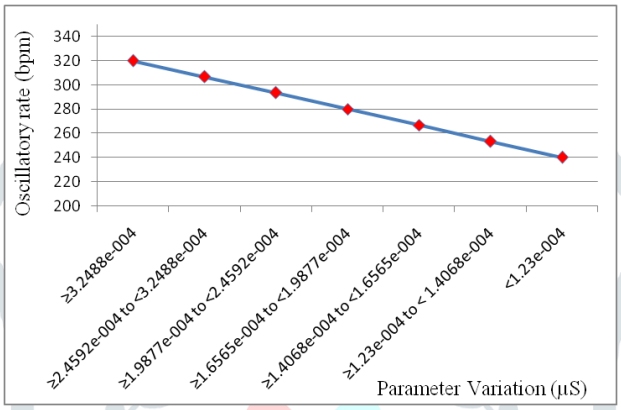

Fig.1. Parameter variation Vs Oscillatory rate of the SAN cell

The parameter variations represented in micro Siemens (µS) effected in obtaining the varied oscillatory rates in beats per minute (bpm) of the rabbit sino atrial node cell of Fig.1 is tabulated in Table 1.

Table 1. Parameter variation Vs Oscillatory Rate of the SAN cell

S.No	Parameter value (µS)	Oscillatory Rate (bpm)
1	≥3.2488e-004	320
2	≥2.4592e-004 to <3.2488e-004	307
3	≥1.9877e-004 to <2.4592e-004	293
4	≥1.6565e-004 to <1.9877e-004	280
5	≥1.4068e-004 to <1.6565e-004	267
6	≥1.23e-004 to < 1.4068e-004	253
7	<1.23e-004	240

III. SIMULATION STUDIES FOR RABBIT SAN CELL PAIR MODEL

Two Sino Atrial Nodal cells are coupled with one another by means of coupling conductance that resembled gap junction channels (GJ) in real electrophysiology. The gap junction conductance (GGJ) is maintained at three different levels of coupling; weak (0.01µS), medium (0.1µS) and strong (1µS).

3.1 Case 1

A weak coupling between the cells is initially provided with GGJ of 0.01µS. The simulation is carried out by varying the individual parameter value of the cells and the impact of these changes on the synchronization among the cell pair analyzed. For the cell 1 the parameter value to oscillate at 293 bpm is assigned whereas the parameter of cell 2 maintained at a value to make it oscillate at 280 bpm. Upon simulation it is seen that the cell pair failed to synchronize with the intrinsic frequencies of the cells being at 307 bpm and 293 bpm respectively with the action potentials (A.P) of the cell pair out of phase with one another as seen in Fig.2.

Maintaining the parameter changes for the cells as before but by increasing the GGJ to 0.1µS, it is seen that the cell pair synchronized to a common frequency of 293 bpm but with a small phase difference between them. The response obtained is shown in Fig.3.

On further increase in the GGJ alone to 1µS, it is observed that the cell pair again synchronized to a common frequency of 280 bpm with both the cells in phase with each other as in Fig.4.

The changes effected in this case 1 as well as the observed phenomena are consolidated in Table 2.

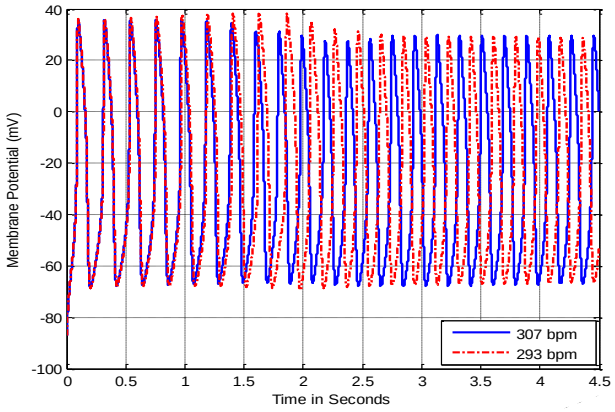

Fig.2. A.P of a Rabbit SAN cell pair for GGJ at 0.01µS (Case 1)

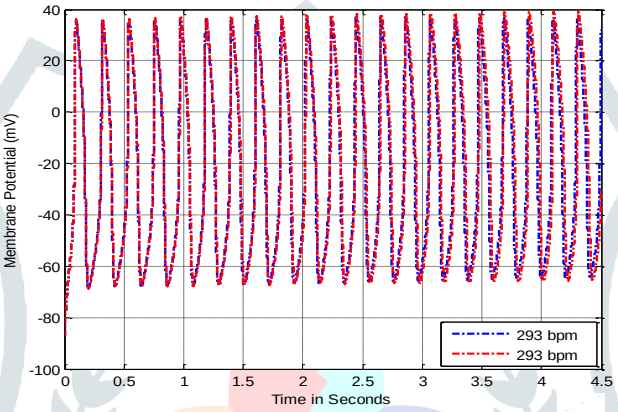

Fig.3. A.P of a Rabbit SAN cell pair for GGJ at 0.1µS (Case 1)

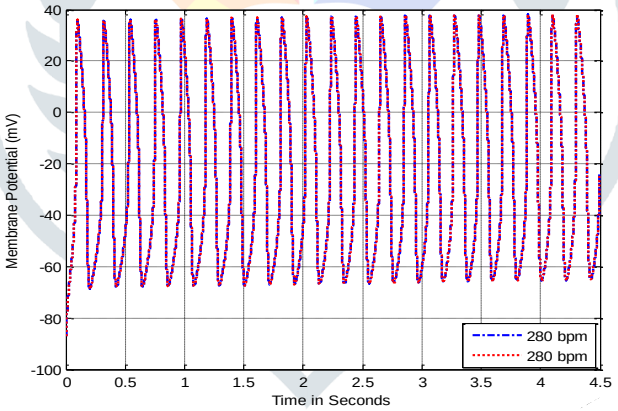

Fig.4. A.P of a Rabbit SAN cell pair for GGJ at 1µS (Case 1)

Table 2. Parameter settings and observed phenomena for Case 1.

S.No.	G_{GJ} value (µS)	Parameter for cell 1 & Oscillatory rate	Parameter for cell 2 & Oscillatory rate	Observed Phenomena & Oscillatory rate of the cell pair
1	0.01	1.9877e-004 293 bpm	1.9717e-004 280 bpm	Not Synchronized 307 bpm; 293 bpm
2	0.1	1.9877e-004 293 bpm	1.9717e-004 280 bpm	Synchronized 293 bpm
3	1	1.9877e-004 293 bpm	1.9717e-004 280 bpm	Synchronized 280 bpm

3.2 Case 2

Now the parameter values are selected so as to make the SAN cells oscillate with intrinsic frequencies of 267 bpm and 253 bpm respectively. Similar to the previous case the GGJ is maintained at 0.01µS and upon simulation the cell pair does not synchronize with differed intrinsic frequencies of 293 bpm and 280 bpm respectively. Besides a huge phase difference between them is observed as shown in Fig.5.

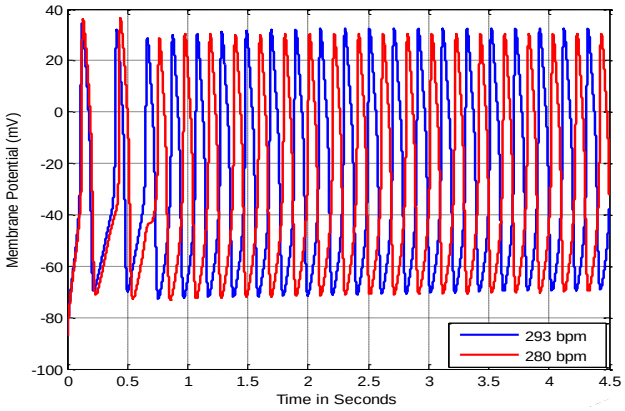

Fig.5. A.P of a Rabbit SAN cell pair for GGJ at 0.01µS (Case 2)

Maintaining the parameter changes for the cells as before but by increasing the GGJ to 0.1µS, the cell pair synchronizes to a common frequency of 253 bpm. However small phase difference exists between them and the response obtained is shown in Fig.6.

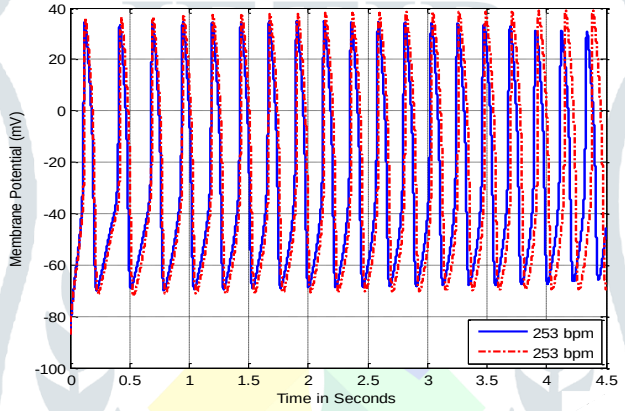

Fig.6. A.P of a Rabbit SAN cell pair for GGJ at 0.1µS (Case 2)

On further increase in the GGJ alone to 1µS, the cell pair synchronizes to a common frequency of 253 bpm with both the SAN cells in phase with each other as seen in Fig.7.

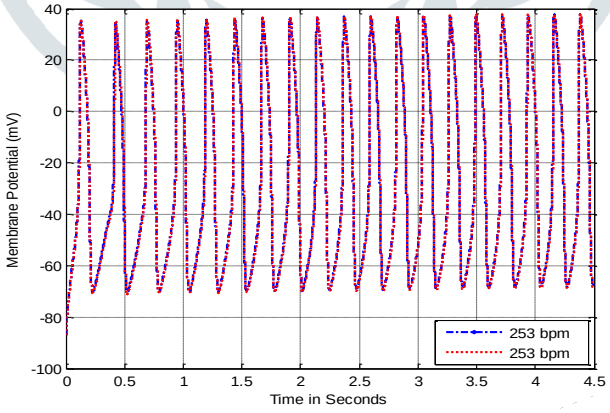

Fig.7. A.P of a Rabbit SAN cell pair for GGJ at 1µS (Case 2)

The Table 3 recapitulates all the variations made in this case.

Table 3. Parameter settings and observed phenomena for Case 2.

S.No.	G_{GJ} value (µS)	Parameter for cell 1 & Oscillatory rate	Parameter for cell 2 & Oscillatory rate	Observed Phenomena & Oscillatory rate of the cell pair
1	0.01	1.4106e-004	1.2343e-004	Not Synchronized

		267 bpm	253 bpm	293 bpm; 280 bpm
2	0.1	1.4106e-004 267 bpm	1.2343e-004 253 bpm	Synchronized 253 bpm
3	1	1.4106e-004 267 bpm	1.2343e-004 253 bpm	Synchronized 253 bpm

3.3 Case 3

Now the parameter values are selected so as to introduce large variations in the individual oscillatory rate of the SAN cells and for the given parameter values the cells oscillated with intrinsic frequencies of 240 bpm and 280 bpm respectively. Similar to the previous case the GGJ is maintained initially at 0.01µS. It is seen that the cell pair failed to synchronize with their intrinsic frequencies at 280 bpm and 293 bpm respectively, also with a huge phase difference between them as seen in Fig.8.

When the GGJ is increased to 0.1µS with the other parameters maintained constant, the cells again do not synchronize with their intrinsic frequencies at 280 bpm and 307 bpm respectively, with a phase difference among them as depicted in Fig.9.

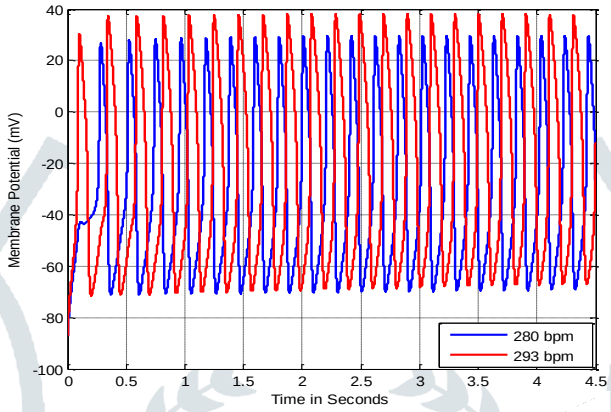

Fig.8. A.P of a Rabbit SAN cell pair for GGJ at 0.01µS (Case 3)

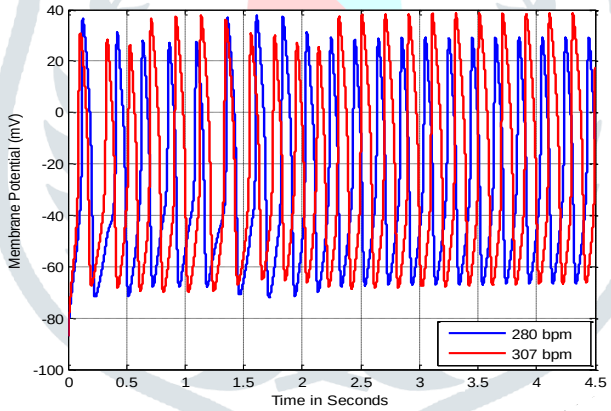

Fig.9. A.P of a Rabbit SAN cell pair for GGJ at 0.1µS (Case 3)

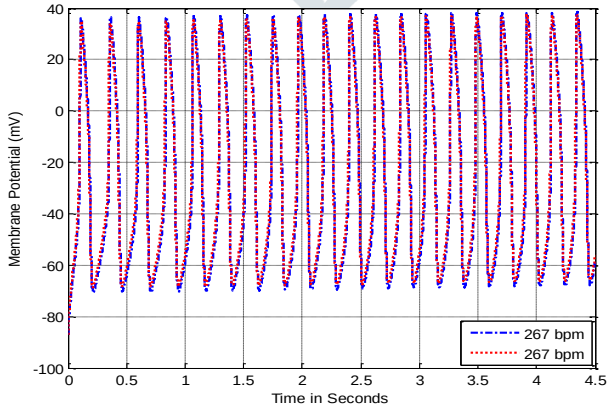

Fig.10. A.P of a Rabbit SAN cell pair for GGJ at 1µS (Case 3)

A further increase of the GGJ value alone to 1µS made the cells to synchronize to a common frequency of 267 bpm with the cells in phase with each other as seen in Fig.10. The simulation effected with all the parameter variations made is presented in Table 4.

Table 4. Parameter settings and observed phenomena for Case 3.

S.No.	G_{GJ} value (µS)	Parameter for cell 1 & Oscillatory rate	Parameter for cell 2 & Oscillatory rate	Observed Phenomena & Oscillatory rate of the cell pair
1	0.01	1.2022e-004 240 bpm	1.9717e-004 280 bpm	Not Synchronized 280 bpm; 293 bpm
2	0.1	1.2022e-004 240 bpm	1.9717e-004 280 bpm	Not Synchronized 280 bpm; 307 bpm
3	1	1.2022e-004 240 bpm	1.9717e-004 280 bpm	Synchronized 267 bpm

3.4 Case 4

Now the parameter values are selected to provide variations in the higher oscillatory range of the cells. The SAN cells for the given parameters oscillated with intrinsic frequencies of 307 bpm and 280 bpm respectively. Similar to the previous case the GGJ is maintained at 0.01µS, for which the cell pair evades to synchronize with their intrinsic frequencies at 293 bpm and 307 bpm respectively along with a huge phase difference among them as seen in Fig.11.

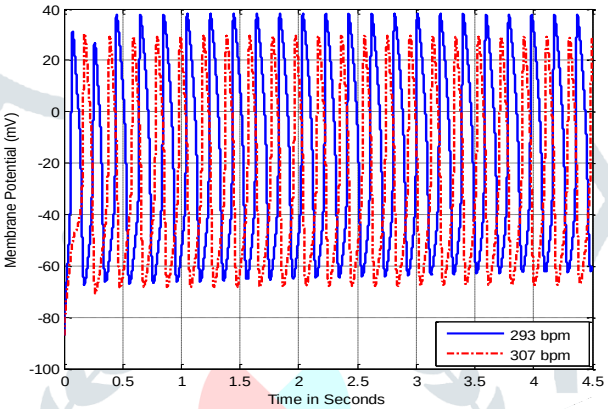

Fig.11. A.P of a Rabbit SAN cell pair for GGJ at 0.01µS (Case 4)

By maintaining the parameters, an increase in the GGJ to 0.1µS is seen to keep the cells out of synchronization with the intrinsic frequencies of the cell pair being 320 bpm and 293 bpm respectively as given in Fig.12 with a phase difference.

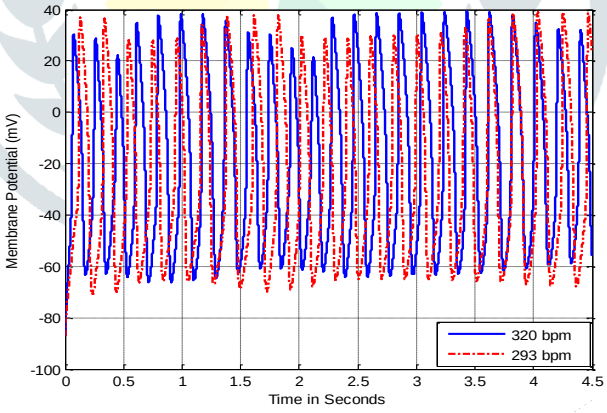

Fig.12. A.P of a Rabbit SAN cell pair for GGJ at 0.1µS (Case 4)

A further increase of the GGJ value alone to 1µS forces the cell pair to synchronize to a common frequency of 307 bpm with zero phase difference between them as seen in Fig.13. The variations effected in accordance with the simulation for case 4 are provided in Table 5.

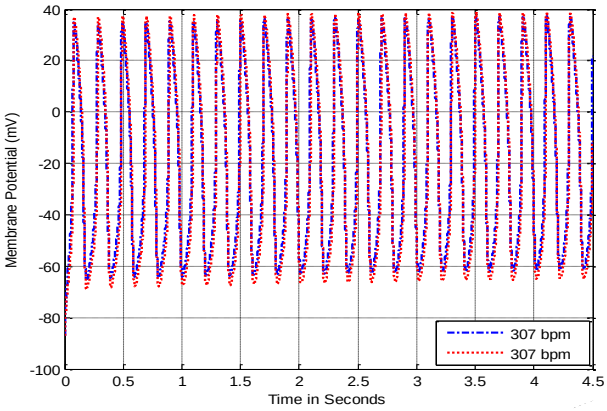

Fig.13. A.P of a Rabbit SAN cell pair for GGJ at 1µS (Case 4)

Table 5. Parameter settings and observed phenomena for Case 4.

S.No.	G_{GJ} value (µS)	Parameter for cell 1 & Oscillatory rate	Parameter for cell 2 & Oscillatory rate	Observed Phenomena & Oscillatory rate of the cell pair
1	0.01	3.2381e-004 307 bpm	1.6575e-004 280 bpm	Not Synchronized 293 bpm; 307 bpm
2	0.1	3.2381e-004 307 bpm	1.6575e-004 280 bpm	Not Synchronized 320 bpm; 293 bpm
3	1	3.2381e-004 307 bpm	1.6575e-004 280 bpm	Synchronized 307 bpm

3.5 Case 5

Now the parameter values to the SAN cell pair is provided so as to have an utmost difference in their individual intrinsic rates. The aim is to couple the two SAN cells with the individual intrinsic frequencies at 240 and 320 bpm respectively and upon maintaining the GGJ at 0.01µS the cell pair exhibited a large phase difference among them and eventually failed to synchronize with their intrinsic frequencies at 267 and 307 bpm respectively. The response obtained is shown in Fig.14.

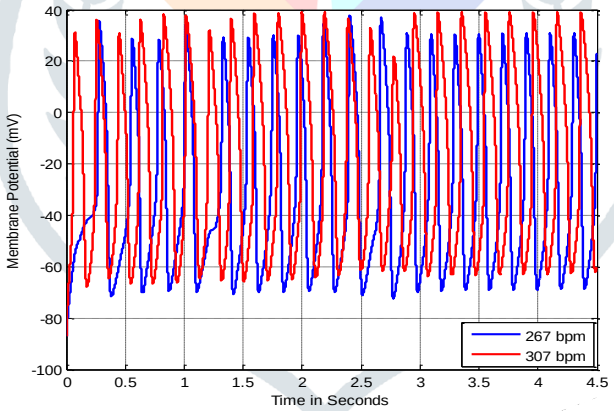

Fig.14. A.P of a Rabbit SAN cell pair for GGJ at 0.01µS (Case 5)

Increasing the GGJ alone to 0.1µS still does not synchronize the cell pair, exhibiting a phase difference and the intrinsic frequencies of the cells being at 267 and 320 bpm respectively. The response obtained is shown in Fig.15.

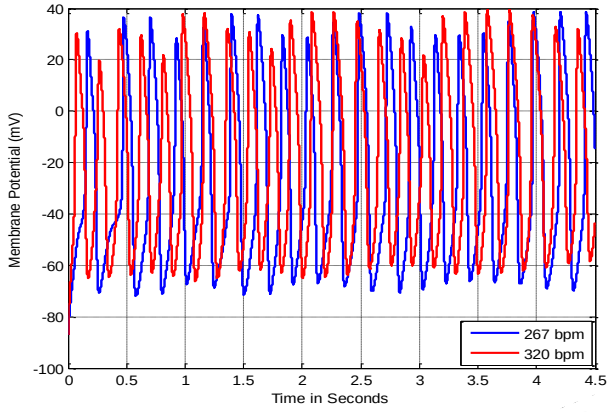

Fig.15. A.P of a Rabbit SAN cell pair for GGJ at 0.1µS (Case 5)

A further increase in the GGJ alone to 1µS finally synchronizes the cell pair to a common frequency of 293 bpm as seen in Fig.16, with both the cells in phase with one another. All the variations made in this case 5 are given in Table 6.

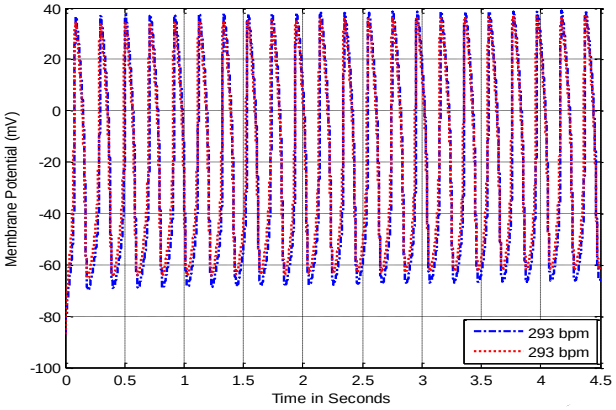

Fig.16. A.P of a Rabbit SAN cell pair for GGJ at 1µS (Case 5)

Table 6. Parameter settings and observed phenomena for Case 5.

S.No.	G_{GJ} value (µS)	Parameter for cell 1 & Oscillatory rate	Parameter for cell 2 & Oscillatory rate	Observed Phenomena & Oscillatory rate of the cell pair
1	0.01	1.229e-004 240 bpm	3.2488e-004 320 bpm	Not Synchronized 267 bpm; 307 bpm
2	0.1	1.229e-004 240 bpm	3.2488e-004 320 bpm	Not Synchronized 267 bpm; 320 bpm
3	1	1.229e-004 240 bpm	3.2488e-004 320 bpm	Synchronized 293 bpm

IV. RESULTS AND DISCUSSION

It is inferred from the above simulation studies that when two cells are coupled (in auto rhythmic mode) the cell pair synchronize only when the intrinsic frequencies of the two cells are sufficiently close, and the coupling conductance (GGJ) also sufficiently high.

It is further inferred that when the cells synchronize to a common frequency the phase difference between the cells decreases with increasing gap junction conductance (GGJ).

Five different cases are considered. In cases 1 and 2, for a medium coupling range (0.1 µS), the cell pair synchronize as there exist only a small difference in their individual intrinsic frequencies (Fig.3 and Fig.6).

In cases 3, 4 and 5, the cell pair failed to synchronize for the same medium range of coupling conductance (0.1 µS) as the difference between their intrinsic frequencies are sufficiently large (Fig's. 9, 12 and 15) which additionally conveyed that increasing intercellular resistance (GGJ) might lead to a complete loss of synchrony.

The intrinsic frequencies of the individual SAN cells in case 1 and case 2 are purposefully chosen such that the difference between their intrinsic frequencies (13 bpm in case 1; 14 bpm in case 2) are small when compared to case 3 and case 4 which is considerably larger than the first two cases (40 bpm in case 3; 27 bpm in case 4).

From the simulation study the following observations are made.

With weak coupling (0.01 µS), the cell pair failed to synchronize for all the cases and the cells continued to beat at different intrinsic frequencies with a large phase difference.

With medium coupling (0.1 µS), the cells beat at a common frequency (with constraints imposed on the frequency gradient) exhibiting a small phase difference but the synchronization is dependent on the difference between the intrinsic frequencies of the cells being small or large.

With strong coupling (1 µS), the cell pair synchronized with the action potentials of both the cells in phase with one another. When a pair of cardiac cells do entrain (synchronize) with sufficiently strong coupling, provided their difference in intrinsic frequencies is also large (case 3, Fig.10, case 4, Fig.13 and case 5, Fig.16) and they do so at a common frequency closer to (or) to the intrinsic frequency of the faster cell, which therefore seems to "set the pace" for the cell pair. On the contrary when the difference in intrinsic frequencies is small (case 1, Fig.4 and case 2, Fig.7) the pair of cells entrained to a common frequency closer to the intrinsic frequency of the slower cell. This underlies the fact that coupling conductance magnitude is a major determinant in the dynamics of the coupled SA node cells.

It is observed that as long as the provided electrical coupling (with their coupling strengths) paved way for sufficient interaction between the cells, the pair of cells with different intrinsic frequencies can mutually entrain to a common period. Nevertheless, while the resulting pattern of activity indicated that both the cells were discharging at the same frequency, their activation time is usually not concurrent. From the predictions of the oscillator theory and from the studies on biological oscillators and cardiac pacemaker activity, it can be seen that the process of mutual entrainment required that there be some phase difference between the oscillators for proper coordination to be maintained.

It is assessed from the simulation results that higher the gap junction conductance and lesser the difference between the intrinsic frequencies of the pair of cells, better are the chances in improving synchronization. It is noticed that even upon adjusting the parameter values the pair of cells failed to synchronize as it undergoes an unbounded phase difference. From the electrophysiology point of view it shows that the extent of the gap junction conductance can influence the cells to synchronize only for a restricted range.

The simulation results of the SAN cell pair infer that whilst the efficacy of gap junction coupling is the major determinant in synchronization of these cells, other factors can also play a key role. These may include electrical field effects, neural influences and the effect of a shared interstitial space between the cells [15]. The connection of two SA node cells through gap junction conductance and the behavior of coupled cell pair with varying junctional conductance are explored. The interpretations regarding the functional role of gap junction channels in establishing synchronization between the coupled cell pair is given.

V. CONCLUSION

The variations in the Parameter applied to a single sino atrial node cell model and the relationship between its oscillatory rate has been postulated. Two rabbit SAN cells have been coupled by means of gap junction conductances and for various coupling strengths the synchronization phenomena between a pair of coupled SAN cells and the likelihood of the same in effecting entrainment between them investigated. With the aid of five case studies, the influence of gap junction channel magnitude on the intrinsic frequencies of the coupled SAN cells with varying frequency gradients have been analyzed and the simulated results presented.

REFERENCES

[1] Severs N J (2000), The cardiac muscle cell. Bioessays Vol.22, No.2: 188-199.

[**2**] Glass L, Hunter P and Mcculloch A (1991), Theory of Heart: Biomechanics, Biophysics and Nonlinear Dynamics of Cardiac Function. No. CONF-8907244--. New York, NY (USA); Springer-Verlag New York, Inc.

[**3**] Kleber A G and Rudy Y (2004), Basic Mechanisms of Cardiac Impulse Propagation and Associated Arrhythmias. Physiological reviews Vol.84, No.2: 431-488.

[**4**] Zeng W, Glass L and Shrier A (1991), Evolution of rhythms during periodic stimulation of embryonic chick heart cell aggregates. Circulation research Vol.69, No.4: 1022-1033.

[**5**] Kunysz A, Glass L and Shrier A (1995), Overdrive suppression of spontaneously beating chick heart cell aggregates: Experiment and theory. American Journal of Physiology-Heart and Circulatory Physiology Vol.269, No.3: H1153-H1164.

[**6**] Wong A K, Osborn T G, Miller J G, and Wickline S A (1993), Quantification of ventricular remodeling in the tight-skin mouse cardiomyopathy with acoustic microscopy. Ultrasound in medicine & biology Vol.19, No.5: 365-374.

[**7**] Corretti M C, Koretsune Y, Kusuoka H, Chacko V P, Zweier J L and Marban E (1991), Glycolytic inhibition and calcium overload as consequences of exogenously generated free radicals in rabbit hearts. Journal of Clinical Investigation Vol.88, No.3: 1014.

[**8**] Guyton A C and Hall J E (2007), *Textbook of Medical Physiology*. Eleventh Edition, Elsevier.

[**9**] Mischke K, Zarse M, Knackstedt C and Schauerte P (2011), Rate control in atrial fibrillation by cooling: effect of temperature on dromotropy in perfused rabbit hearts. *Cardiology research and practice*: 162984.

[**10**] Verkerk A O and Wilders R (2010), Relative importance of funny current in human versus rabbit sinoatrial node. *Journal of molecular and cellular cardiology* Vol.48, No.4: 799-801.

[**11**] Panfilov A V (2006), Is heart size a factor in ventricular fibrillation? Or how close are rabbit and human hearts? Heart Rhythm Vol.3, No.7: 862-864.

[**12**] Demir S S, Clark J W, Murphey C R and Giles W R (1994), A mathematical model of a rabbit sinoatrial node cell; Modeling in Physiology. American Journal of Physiology-Cell Physiology Vol.266, No.3: C832-C852.

[**13**] Murugesh T S, Krishnan J and Malathi R (2013), Certain investigations on the gap junction conductance in synchronization issues. *International Journal of Research and Reviews in Applied Sciences* Vol.15, Issue 3, pp. 312-321.

[**14**] Murugesh T S, Krishnan J and Malathi R (2013), Investigations on the intrinsic frequency of the cardiac cells in effecting synchronization. *International Journal of Current Research* Vol.5, Issue 10, pp. 3140-3148.

[**15**] Krishnan J, Chakravathy V S, Radhakrishnan S, Nayak V and Victor S (2005), Neural Influence is essential for synchronizing cardiac oscillators: A computational model. Indian Journal of Thoracic and Cardiovascular Surgery Vol.21, No.4: 262-268.