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Achieving Synchronization in Cardiac Oscillators with Suitable Neural Input

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***Abstract* -The normal cardiac rhythm is the result of collective, synchronized action of a large number of cardiac oscillators which play a crucial role in the determination of the sinus rhythm. The physiological function of the cardiovascular system is under the control of the autonomic nervous system (ANS). The two limbs of the ANS, sympathetic and parasympathetic, are critical in determining the oscillations within the heart. The pumping effectiveness of the heart is controlled by the sympathetic and parasympathetic nerves, which abundantly supply the heart that act in opposing ways. However, the two divisions act together to regulate the activity of the internal organs as per the needs of the body at any particular time. The cardiac centers in the central nervous system exert an influence on the heart's activity through sympathetic and parasympathetic nerves. This influence governs the rate of beat, the systolic contractile force and the velocity of atrioventricular conduction. The parasympathetic stimulation causes a decrease in heart rate whereas sympathetic stimulation increases it. The intrinsic cardiac nervous system is seen to play an active role in regulating cardiac function which consists of sympathetic and parasympathetic neurons and interconnecting local circuits. An appropriate mathematical model that describes the electrical activity and ion exchange in the sinoatrial node (SAN) is considered and the dynamical equations describing the behaviour of the chosen model are solved with the corresponding source code developed and implemented using Matlab.An Integrate and Fire Neuron (IFN) model is developed that mimics the role of ANS which acts as an external influence to the preferred SAN cell to in order to coax synchronization between the coupled cell pair. The influence of the suitable neuron model in effecting synchrony between the coupled SAN cell pair is demonstrated with the aid of simulation studies.**

Keywords: **Cardiac rhythm, autonomic nervous system, Integrate and Fire Neuron, Synchronization, sinoatrial node**

I. INTRODUCTION

In the normal cardiac excitation sequence the action potential (A.P) is initiated in the sino atrial (SA) node that travels through the atrial wall, the atrio ventricular (AV) node, the Purkinje system and the ventricular wall. The time course of the action potential (membrane potential as a function of time) is notably different in various regions of the heart. The autonomic nervous system (ANS) represents the principal regulatory route of internal bodily functions. The sympathetic and parasympathetic autonomic axes provide neural input into every major bodily system [1]. The sympathetic activity can be thought of as a complex output of the central nervous system providing subtle control over end organ function [2]. The sympathetic activity facilitates motor action, increasing the cardiac output by dilating vessels of the musculature (and reducing blood supply to the gut). In contrast, Parasympathetic activity promotes recuperative functions effecting heart rate reduction, lowering of blood pressure, and slowing of gut motility. The bodily states of arousal associated with survival (e.g., Fight and flight responses) are typically characterized by increased sympathetic activity and, usually, decreased parasympathetic activity [3, 4]. The heart is supplied with both sympathetic and parasympathetic (vagi) nerves. The parasympathetic nerves are distributed mainly to the SA and AtrioVentricular (AV) nodes, to a lesser extent to two atrial muscles, and very little to the ventricular muscle. The sympathetic nerves are equally distributed to all parts of the heart, strongly to the ventricular muscle as well as to all the other areas. The stimulation of the vagal nerves decreases the rate of rhythm of the sinus node, and decreases the excitability of the AV node, eventually slowing transmission of the cardiac impulse into the ventricles. Weak to moderate vagal stimulation slows down the rate of heart pumping and strong stimulation of the vagi can stop completely the rhythmical excitation by the sinus node from the atria into the ventricles through the AV mode [5]. The sympathetic nervous system plays a major role in the regulation of cardiovascular function over multiple time scales that are achieved through differential regulation of sympathetic outflow to a variety of organs [6]. A lot of experimentation studies support the contention that intrinsic cardiac neurons are involved in regulating cardiac function [7, 8] and these neurons interact via a number of synaptic mechanisms to maintain adequate cardiac output. The ability of a simple pump "heart" relates to a 'heart brain' and its extensive intrinsic nervous system consisting of sympathetic and parasympathetic neurons besides the interconnecting local circuits [8]. For the species 'Rabbit', the SA 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 with a varied range of firing frequencies (330-80 bpm) synchronize and beat at a common frequency corresponding to the normal cardiac rhythm. A pair of coupled cells takes longer time to approach the steady state common frequency if there is a higher difference in its intrinsic frequencies (i.e., time to approach steady state is high if the difference in frequency is high) [9]. The problem of rapid return to a stable state, if it occurs at all, is required to be more acute in a large network, like the rabbit heart, with a wide range of intrinsic frequencies (330-80 bpm). An integrate and fire neuron (IFN) model which is one of the most widely used models for analyzing the behaviour of neural systems is considered and the aim is to quantify that the externally applied neural input can better aid the coupled cell pair to undergo synchronization [10].

II. DETERMINATION OF IFN GAIN VALUES FOR SPECIFIED PARAMETER RANGES

A free adjustable parameter exists in the chosen model [11] dynamic equations, - the leakage conductance (conducting the "background" current) which helps to vary the frequency of oscillation. The variation of this parameter represented in micro Siemens (μS) reflects in the intrinsic frequency of the action potential generated. It is inferred that variations in the free parameter (hereinafter called 'Parameter') induces subsequent variations in the intrinsic rate of the SAN cell and is represented in Table I.

TABLE I 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

The IFN gain values are chosen such that the SA node cell oscillates at its least and utmost possible intrinsic frequencies by maintaining the Parameter (leakage conductance) value. The variations in the oscillatory rate of the SAN cell for different IFN gain values are computed and the determination of IFN gain values for specified parameter ranges obtained.

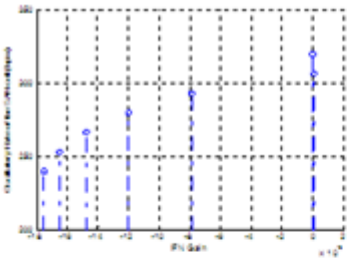

Fig.1. Parameter value ≥3.2488e-004 (μS)

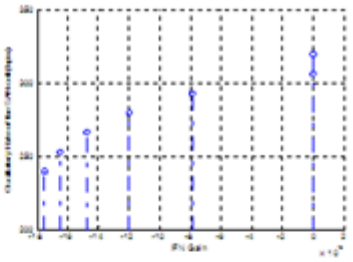

Fig.2. Parameter ≥2.4592e-004 to <3.2488e-004 (μS)

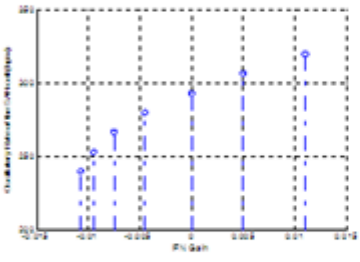

Fig.3. Parameter ≥1.9877e-004 to <2.4592e-004 (μS)

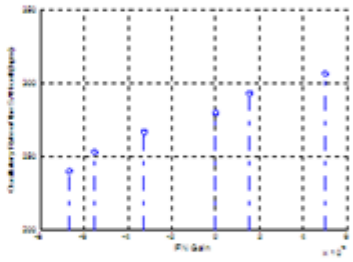

Fig.4. Parameter ≥1.6565e-004 to <1.9877e-004 (μS)

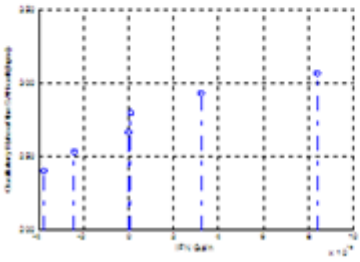

Fig.5. Parameter ≥1.4068e-004 to <1.6565e-004 (μS)

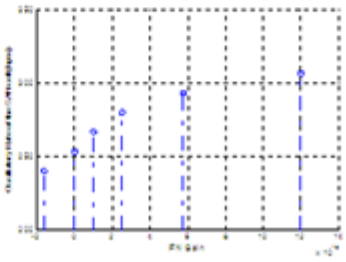

Fig.6. Parameter ≥1.23e-004 to < 1.4068e-004 (μS)

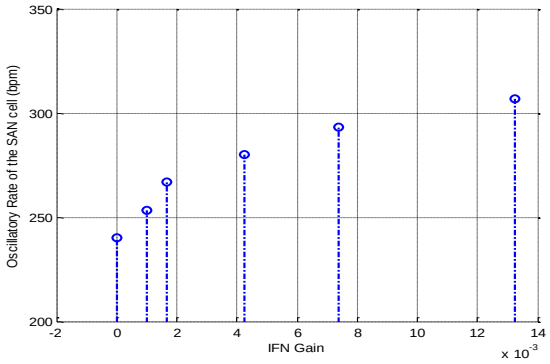

Fig.7Parameter value <1.23e-004 (µS)

For each and every Parameter (range of) values the integrate and fire neuron (IFN) model input is effected and the corresponding variations in the oscillatory rate of the SAN cell determined and depicted above. The resultant intrinsic frequencies obtained for all the IFN gain variations in both extremes are plotted in Fig.1-7.

III. SIMULATION STUDIES FOR SAN CELL PAIR WITH IFN

Two rabbit Sino Atrial Nodal cells of the chosen model under study [11] are coupled with one another by means of coupling conductance that resembles gap junction channels (GGJ) in real electrophysiology with a varying frequency gradient as depicted in Fig.8 below. When SAN Cell2 beats at a slower rate, the IFN, which monitors the difference of the activities of the two cardiac cells, stimulates that slower Cell2 until the two cells synchronize. It is significant to note that the converse is also true.The gap junction conductance (GGJ) is maintained at three different levels of coupling; weak (0.01µS), medium (0.1µS) and strong (1µS).

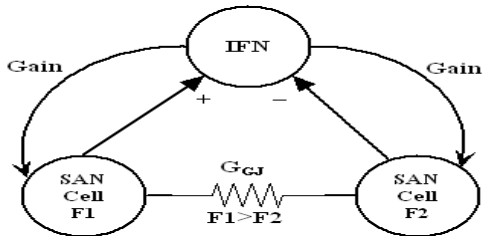

Fig.8 Coupled SAN cell pair

The integrate and fire neuron model (with a gain of proper magnitude) is initially provided as an external input for the coupled SAN cell pair that is not in synchrony so as to coax the cells in unison and the results obtained are presented below.

A. Case 1

Maintaining the Parameter value of the cells as given in column 3&4 of Table 2 the SAN cell1 is made to oscillate at an intrinsic frequency of 293bpm and cell 2 at 280 bpm respectively. When coupled the cells failed to synchronize.A positive gain value of the IFN model (as in column 5) is applied to the slowly paced SAN cell so as to induce an improved oscillatory rate. The set gain value is referred from Fig.1 as the case may be and as expected the external IFN gain value increase the oscillatory rate of the cell and eventually the cell pair regain synchronization with a common intrinsic frequency of 307 bpm as seen in Fig.9. On the contrary a negative IFN gain value provided to the faster cell reduces the oscillatory rate of the cell, with the Rabbit SAN (RSAN) cell pair eventually synchronizing to a common intrinsic frequency of 293 bpm as seen in Fig.10. In both the responses a huge phase difference between the action potentials of the cells can be observed and the gap junction conductance (GGJ) is maintained at a low value of 0.01µS.

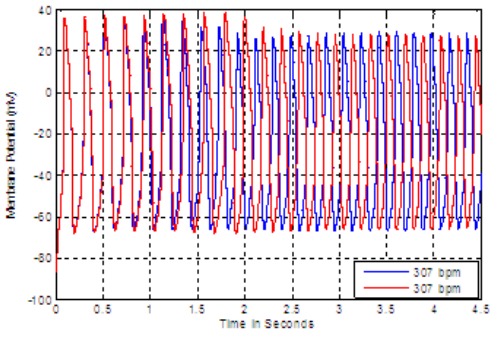

Fig.9 A.P of a RSAN cell pair with +ve IFN gain

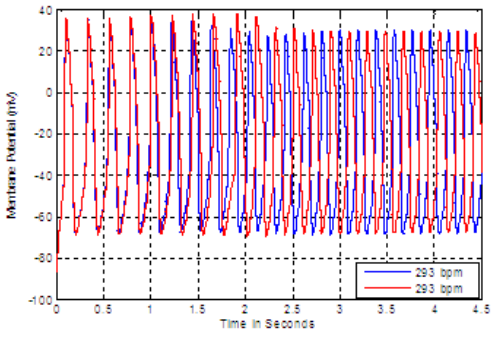

Fig.10 A.P of a RSAN cell pair with –ve IFN gain

The gap junction conductance (GGJ) alone is increased and now maintained at 0.1µS, and the influence of the IFN gain on the SAN cell pair is studied for the same Parameter settings. It is noted that again for a positive IFN gain applied to the slowly paced cell, the cell pair synchronizes to a common frequency of 293 bpm whereas for a negative gain fed to the faster cell, the oscillatory rate of the cell pair goes down and finally settles to an intrinsic frequency of 280 bpm. The responses obtained are given in Fig's.11 and 12 both possessing a small phase difference between the coupled cells.

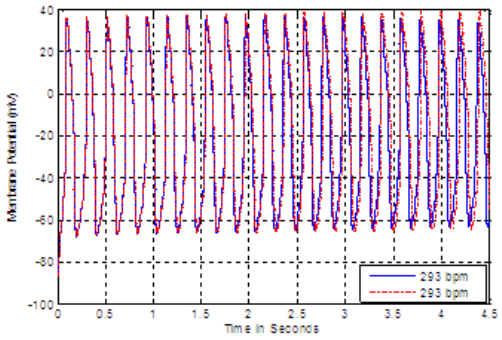

Fig.11. A.P of a RSAN cell pair with +ve IFN gain

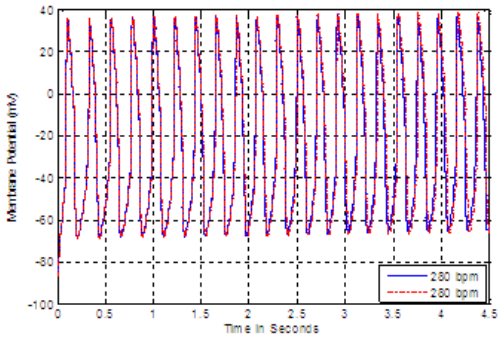

Fig.12. A.P of a RSAN cell pair with –ve IFN gain

Similar variation in the GGJ alone increased to 1µS also maintains synchrony, but the intrinsic frequency of the cell pair increases to 293 bpm for positive IFN gain and decreases to 280 bpm for negative gain values respectively.

The responses obtained are presented in Fig.'s 13 and 14 with the action potentials of the coupled SAN cells in phase with one another.

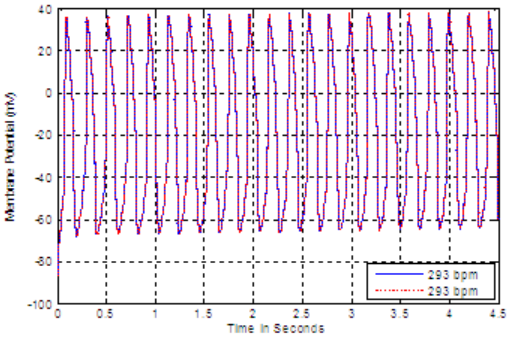

Fig.13. A.P of a RSAN cell pair with +ve IFN gain

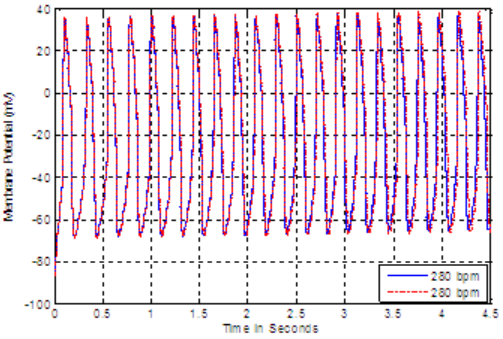

Fig.14. A.P of a RSAN cell pair with –ve IFN gain

The variations as well as the IFN gain values provided in case 1 are specified in Table II.

TABLE II PARAMETER SETTINGS, IFN GAIN VALUES AND OBSERVED PHENOMENA FOR CASE 1

S.No.	G_{GJ} value (µS)	Parameter for cell 1 & Oscillatory rate	Parameter for cell 2 & Oscillatory rate	IFN Gain Value	Observed Phenomena & Oscillatory rate of the cell pair
1	0.01	1.9877e-004 293 bpm	1.9717e-004 280 bpm	0.005	Synchronized 307 bpm
				−0.0025	293 bpm
2	0.1	1.9877e-004 293 bpm	1.9717e-004 280 bpm	0.005	Synchronized 293 bpm
				−0.0025	280 bpm
3	1	1.9877e-004 293 bpm	1.9717e-004 280 bpm	0.005	Synchronized 293 bpm
				−0.0025	280 bpm

B. Case 2

The Parameter settings as in Table 3 are provided with the GGJ maintained at 0.01µS and an attempt is made to synchronize the cell pair (which was otherwise not in synchrony) to a common frequency. A positive IFN gain applied to the slowly paced SAN cell synchronizes the cell pair to a common frequency of 293 bpm as seen in Fig.15 whereas a negative gain to the faster SAN cell value reduces the oscillatory rate, with the cell pair eventually attaining synchrony at 280 bpm as seen in Fig.16. In both the responses a huge phase difference exists between the cells.

The influence of the IFN gain on the SAN cell pair investigated for the same Parameter settings as before with the GGJ alone increased to 0.1µS. A positive gain to the slowly paced cell synchronizes the cell pair to a common frequency of 280 bpm and a negative gain to the faster cell reduce the oscillatory rate of the cell pair and eventually enables them to undergo synchronization to a common frequency of 253 bpm. The responses obtained are with a small phase difference between them and presented in Fig.17 and Fig.18.

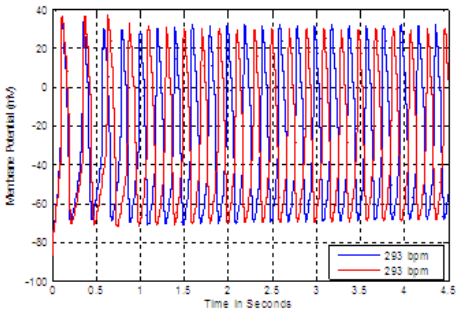

Fig.15. A.P of a RSAN cell pair with +ve IFN gain

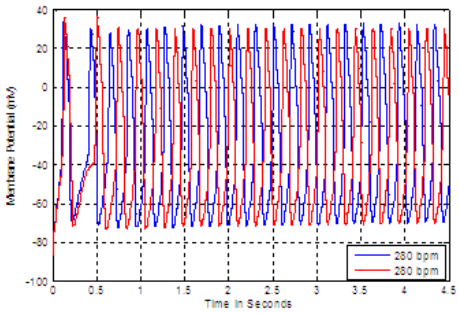

Fig.16. A.P of a RSAN cell pair with –ve IFN gain

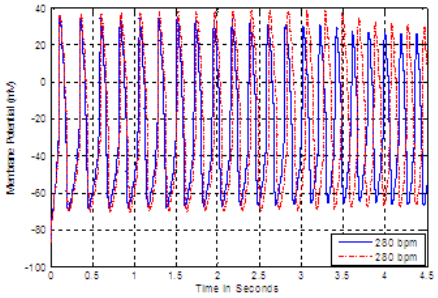

Fig.17. A.P of a RSAN cell pair with +ve IFN gain

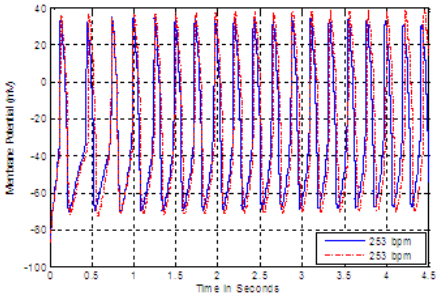

Fig.18. A.P of a RSAN cell pair with –ve IFN gain

On increasing the GGJ alone to 1µS, the synchrony prevails but with the intrinsic frequency of the cell pair being increased to 267 bpm for positive IFN gain with both the generated action potentials of the cell pair in phase with each other as seen in Fig.19 and the oscillatory rate is maintained at 253 bpm for a negative IFN gain value as shown in Fig.20.

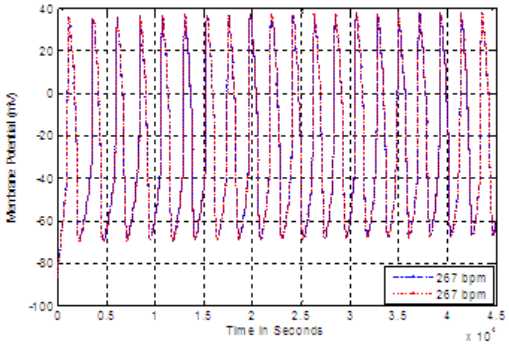

Fig.19. A.P of a RSAN cell pair with +ve IFN gain

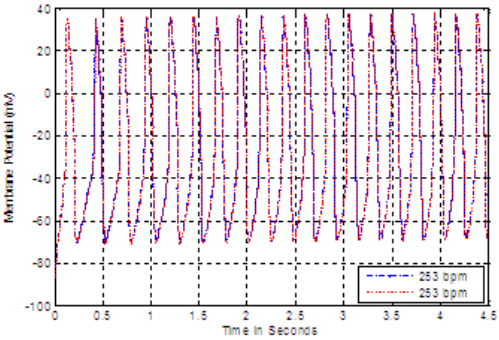

Fig.20. A.P of a RSAN cell pair with –ve IFN gain

The below Table III recapitulates all the variations made in this case.

TABLE III 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	IFN Gain Value	Observed Phenomena & Oscillatory rate of the cell pair
1	0.01	1.4068e-004 267 bpm	1.23e-004 253 bpm	0.005	Synchronized 293 bpm
				−0.001	280 bpm
2	0.1	1.4068e-004 267 bpm	1.23e-004 253 bpm	0.005	Synchronized 280 bpm
				−0.001	253 bpm
3	1	1.4068e-004 267 bpm	1.23e-004 253 bpm	0.005	Synchronized 267 bpm
				−0.001	253 bpm

C. Case 3

The Parameter settings as in Table 4 are adopted with the GGJ at 0.01µS and it is seen that the coupled cells fail to synchronize and an effort is initiated to synchronize the coupled cell pair. With a positive IFN gain applied to the slower cell, the cell pair synchronizes to a common frequency of 307 bpm as seen in Fig.21 and a negative IFN gain to the faster cell again synchronizes the SAN cell pair to a common frequency of 280 bpm. The response of the same is presented in Fig. 22. In both the responses a huge phase difference between the action potentials generated in the coupled cell pair is observed.

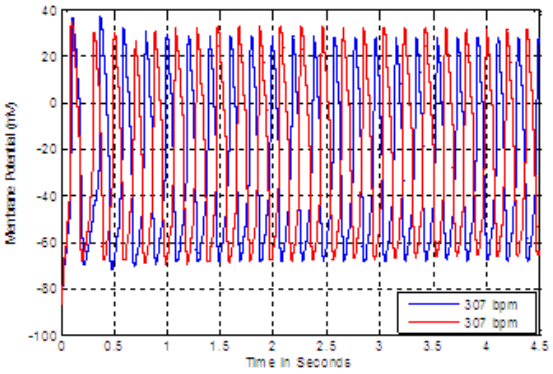

Fig.21. A.P of a RSAN cell pair with +ve IFN gain

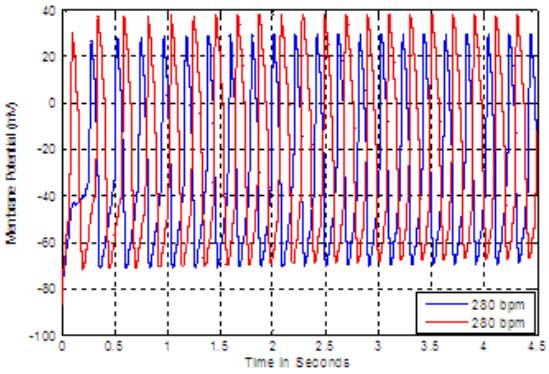

Fig.22. A.P of a RSAN cell pair with –ve IFN gain

When the GGJ alone is increased to 0.1µS with the other Parameters being maintained constant the coupled cell pair is not in synchronization with the intrinsic frequencies of the cells being 280 bpm and 307 respectively as shown in Fig.23.

An attempt to enforce synchronization between the cell pair with a positive IFN gain appropriately fed to the slower cell eventually synchronizes it to a common frequency of 320 bpm as in Fig.24, whereas a negative IFN gain to the faster cell synchronizes it to a common frequency of 280 bpm as in Fig.25.

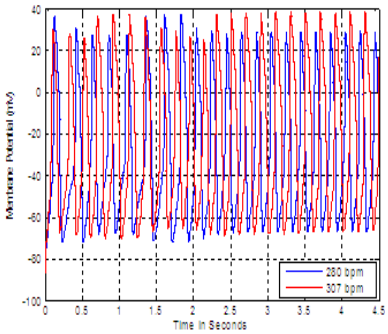

Fig.23. A.P of a RSAN coupled cell pair for GGJ at 0.1µS not in synchrony (Case 3)

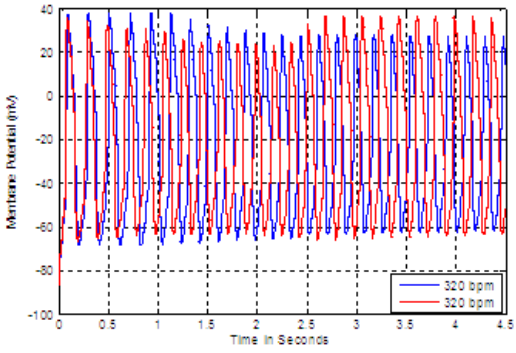

Fig.24. A.P of a RSAN cell pair with +ve IFN gain

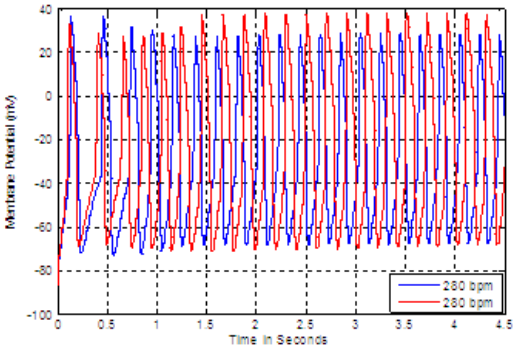

Fig.25. A.P of a RSAN cell pair with –ve IFN gain

For a strong couplingstrength of 1µS, by maintaining the Parameters it is noticed that the cell pair is already in synchronization at a common frequency of 267 bpm. The oscillatory rate of the cell pair is seen to increase bypreserving synchrony even for varying IFN gains. An IFN input with an apt positive gain to the slower cell increases the oscillatory rate to 280 bpm whereas the oscillatory rate reduces to 253 bpm for a proper negative gain value fed to the faster cell eventually maintaining synchrony. The responses obtained in which both the cells are in phase with each other are presented in Fig.26 and Fig.27.The Parameter variations made in case 3 as well as the IFN gain values provided are given in Table 4.

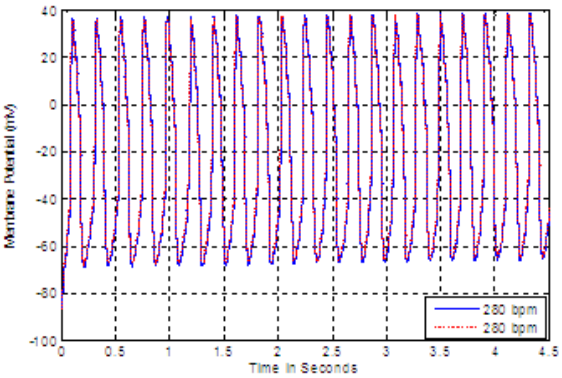

Fig.26. A.P of a RSAN cell pair with +ve IFN gain

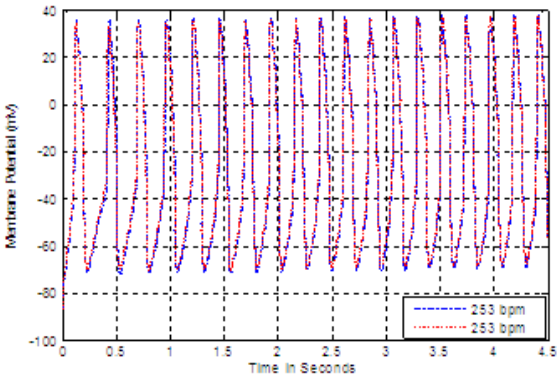

Fig.27. A.P of a RSAN cell pair with –ve IFN gain

TABLE IV PARAMETER SETTINGS, IFN GAIN VALUES AND OBSERVED PHENOMENA FOR CASE 3

S.No.	G_{GJ} value (µS)	Parameter for cell 1 & Oscillatory rate	Parameter for cell 2 & Oscillatory rate	IFN Gain Value	Observed Phenomena & Oscillatory rate of the cell pair
1	0.01	1.229e-004 240 bpm	1.6565e-004 280 bpm	0.01	Synchronized 307 bpm
				−0.0061	280 bpm
2	0.1	1.229e-004 240 bpm	1.6565e-004 280 bpm	0.02	Synchronized 320 bpm
				−0.00261	280 bpm
3	1	1.229e-004 240 bpm	1.6565e-004 280 bpm	0.01	Synchronized 280 bpm
				−0.00261	253 bpm

D. Case 4

By maintaining the Parameter changes as in Table 5, the GGJ coupling is maintained at 0.01µS for which the cell pair does not synchronize with the intrinsic frequencies being 293 bpm and 307 bpm respectively as shown in Fig.28. An external IFN input induces synchronization among the cell pair with a suitable positive gain applied to the slowly paced cell, maintaining synchrony at a common frequency of 333 bpm as shown in Fig.29. A proper negative IFN gain applied to the faster paced cell decreases the oscillatory rate of the SAN cell pair and in the end the cell pair synchronizes to a common frequency of 307 bpm as in Fig.30. Both the responses obtained are seen to exhibit a huge phase difference in their generated action potential waveforms.

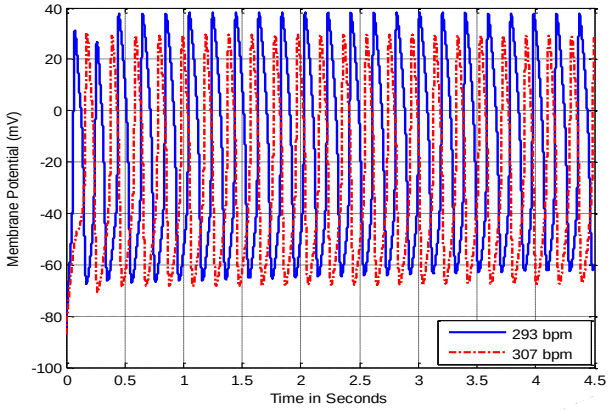

Fig.28. A.P of a Rabbit SAN coupled cell pair for GGJ at 0.01µS not in synchrony (Case 4)

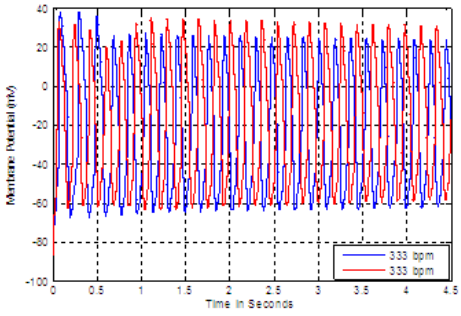

Fig.29. A.P of a RSAN cell pair with +ve IFN gain

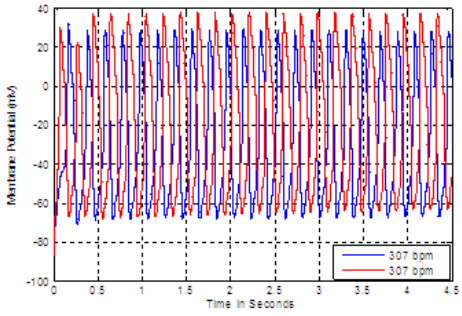

Fig.30. A.P of a RSAN cell pair with –ve IFN gain

The coupling strength is increased to 0.1µS while maintaining the Parameters and it is seen that the SAN cell pair is not in synchrony with the intrinsic frequencies of the cell pair being 320 and 293 bpm respectively as in Fig.31.

Efforts are made to attain synchrony among the cell pair. An appropriately fed positive IFN gain synchronizes the cell pair to a common frequency of 320 bpm as in Fig.32 but with a phase difference. On the contrary an apt negative IFN gain input synchronizes the coupled cell pair with an initial phase difference to a reduced oscillatory rate of 293 bpm as given in Fig.33.

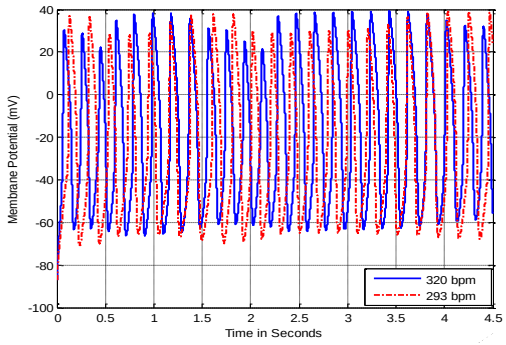

Fig.31. A.P of a Rabbit SAN coupled cell pair for GGJ at 0.1µS not in synchrony (Case 4)

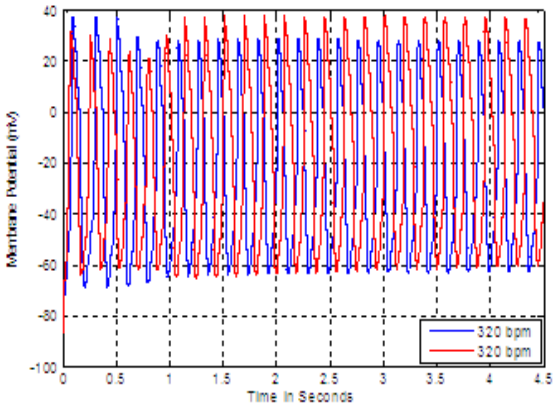

Fig.32. A.P of a RSAN cell pair with +ve IFN gain

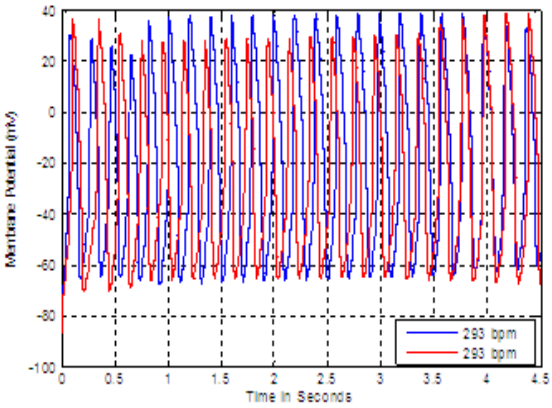

Fig.33. A.P of a RSAN cell pair with –ve IFN gain

A strong coupling level in the order of 1µS establishes synchrony among the cell pair resulting in a higher oscillatory rate of 320 bpm for a proper positive IFN gain whereas the oscillatory rate is lesser at 293 bpm for an apt negative gain value. In the responses the action potentials of the cells obtained are in phase with each other as in Fig.34 and 35.

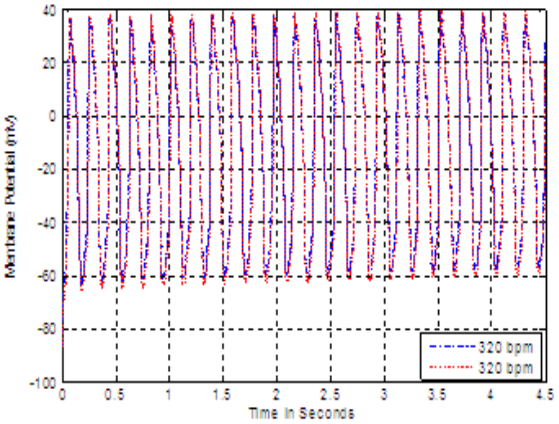

Fig.34. A.P of a RSAN cell pair with +ve IFN gain

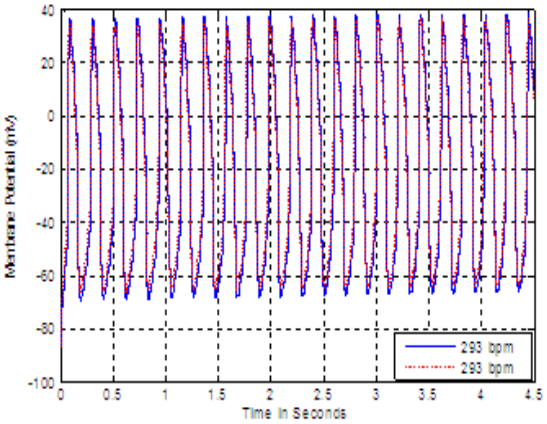

Fig.35. A.P of a RSAN cell pair with –ve IFN gain

All the variations made and provided IFN gains in case 4 are presented in Table 5.

TABLE V PARAMETER SETTINGS, IFN GAIN VALUES AND OBSERVED PHENOMENA FOR CASE 4

S.No.	G_{GJ} value (μS)	Parameter for cell 1 & Oscillatory rate	Parameter for cell 2 & Oscillatory rate	IFN Gain Value	Observed Phenomena & Oscillatory rate of the cell pair
1	0.01	3.2487e-004 307 bpm	1.9876e-004 280 bpm	0.01	Synchronized 333 bpm
				−0.0005	307 bpm
2	0.1	3.2487e-004 307 bpm	1.9876e-004 280 bpm	0.005	Synchronized 320 bpm
				−0.00041	293 bpm
3	1	3.2487e-004 307 bpm	1.9876e-004 280 bpm	0.019	Synchronized 320 bpm
				−0.01	293 bpm

E. Case 5

The intrinsic frequencies of the SAN cells that constitute the cell pair are maintained at a finite oscillatory rate with the corresponding Parameter values as provided in Table 6. It is seen that the cell pair failed to be in synchrony with the intrinsic frequencies of the cells being 267 and 307 bpm respectively for a weak coupling strength of 0.01μS as seen in Fig.36. On applying an appropriate positive IFN gain value, the oscillatory rate of the cell pair increases, eventually synchronizing to a common frequency of 320 bpm whereas for a proper negative gain the cell pair synchronize to a common frequency of 293 bpm. Both the responses reveal a large phase difference in the action potential waveforms as seen in Fig's.37 and 38.

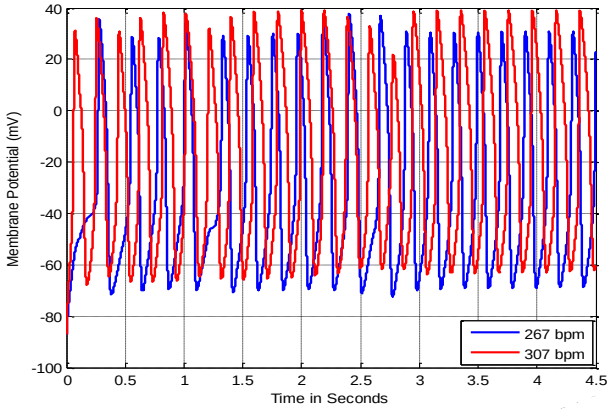

Fig.36. A.P of a Rabbit SAN cell pair with +ve& –ve IFN gain for GGJ at 0.01μS (Case 5)

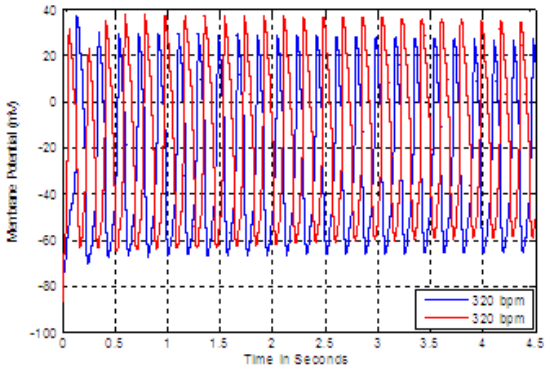

Fig.37. A.P of a RSAN cell pair with +ve IFN gain

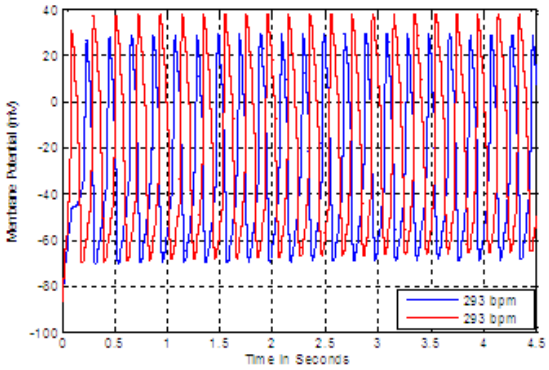

Fig.38. A.P of a RSAN cell pair with –ve IFN gain

With the efficacy of coupling increased to 0.1μS, various IFN gain values are tried so as to enable the cell pair attain synchrony. A positive IFN gain value properly applied in the end, synchronizes the cell pair to a common frequency of 320 bpm as in Fig.39 and an apt negative IFN gain too synchronizes the cell pair to a common frequency of 307 bpm as in Fig.40. In both the responses a moderate phase difference can be noticed among the resulting action potentials of the coupled SAN cells.

With a strong coupling strength of 1μS it can be seen that the cell pair is indeed in synchrony at a common frequency of 293 bpm. In order to further increase the oscillatory rate an appropriate positive IFN gain value applied finally synchronizes the cell pair to an increased common frequency of 307 bpm as in Fig.41. On the contrary an apt negative gain decreases the oscillatory rate and synchronizes the cell pair to a common frequency of 293 bpm as in Fig.42. In both the responses the action potentials of the coupled cell pair are in phase with each other.

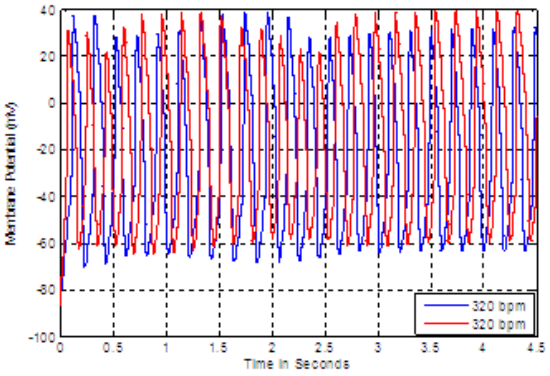

Fig.39. A.P of a RSAN cell pair with +ve IFN gain

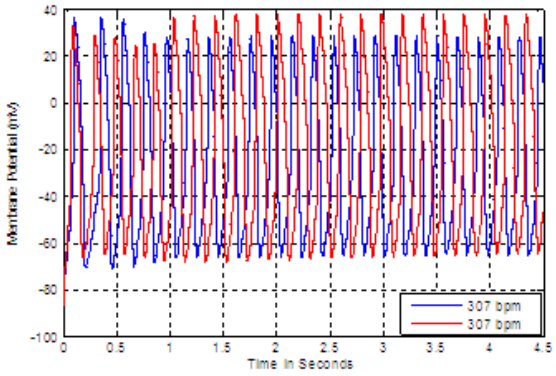

Fig.40. A.P of a RSAN cell pair with –ve IFN gain

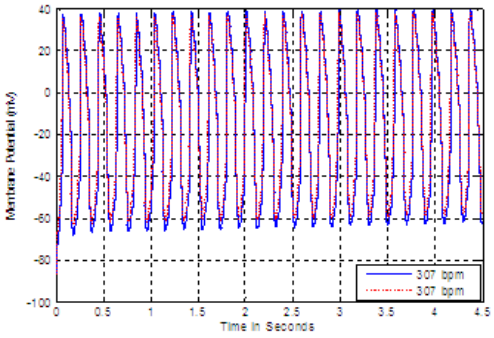

Fig.41. A.P of a RSAN cell pair with +ve IFN gain

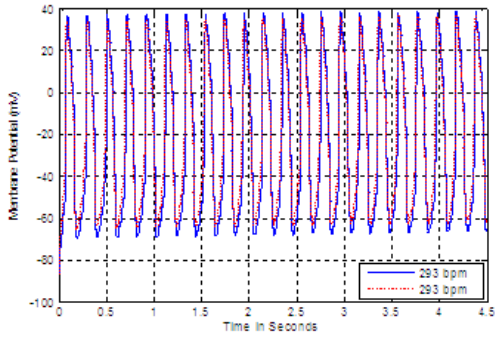

Fig.42. A.P of a RSAN cell pair with –ve IFN gain

The Parameter variations made and the IFN gain values provided to enable synchronization among the cell pair in this case is presented in Table 6.

TABLE VI PARAMETER SETTINGS, IFN GAIN VALUES AND OBSERVED PHENOMENA FOR CASE 5

S.No.	G_{GJ} value (µS)	Parameter for cell 1 & Oscillatory rate	Parameter for cell 2 & Oscillatory rate	IFN Gain Value	Observed Phenomena & Oscillatory rate of the cell pair
1	0.01	1.229e-004 240 bpm	3.2488e-004 320 bpm	0.0175	Synchronized 320 bpm
				−0.000265	293 bpm
2	0.1	1.229e-004 240 bpm	3.2488e-004 320 bpm	0.01375	Synchronized 320 bpm
				−0. 00055	307 bpm
3	1	1.229e-004 240 bpm	3.2488e-004 320 bpm	0.0175	Synchronized 307 bpm
				−0.0002	293 bpm

IV. RESULTS AND DISCUSSION

Generally, a group of oscillators is said to be synchronized when each oscillator's frequency has locked onto the same value as all the others [12]. Entrainment is a property of coupled oscillators and the simplest case occurs when the coupling is only one way; the frequency of one oscillator is constant and entrainment occurs when the other matches this frequency.

In a coupled SAN cell pair when the cardiac cells beat at different rates (no synchronization), a simple integrate and fire neuron model input is applied which activates either the slower cell or inhibits the faster cell to establish mutual consensus between them, for varied coupling conductances. The applied external neural input is multiplied by a "gain of proper magnitude" before being applied to the slower/faster cardiac cell.

Five cases are studied where the SAN cells are made to oscillate with the same values (or) in the similar range of values without differing in their individual intrinsic frequencies. It is inferred from the simulation studies that the oscillatory rate of the synchronized cell pair increased/decreased by appropriate variations in the applied IFN gain magnitude. In the simulations carried out the

magnitude of the gain is kept mostly the same for all the neurons, with the results indicating that an inhomogeneous gain yields faster synchronization for various frequency gradients.

It is further observed that the magnitude of gain applied to the integrate and fire neuron model goes high for higher frequency gradients whereas a much lower gain only is needed for cells with low frequency gradients. It is again observed that the process of mutual entrainment (synchronization) requires that there be some phase difference between the cardiac cells/oscillators for proper coordination to be maintained.

The coupled SAN cell pair failed to synchronize despite the coupling efficacy being weak (0.01 µS) Fig's.28 and 36or medium (0.1 µS) as evident from Fig's.23 and 31 which signifies that the value of gap junction conductance (GGJ) can coax the coupled cells to synchronize only to a certain extent [13].

It is observed that the SAN cell pair which fails to synchronize otherwise (Fig's.23,28, 31 and 36) is made to attain synchrony with the additional input applied from the integrate and fire neuron model (Fig's.24, 25,29, 30, 32, 33, 37and 38), regardless of the coupling strength being weak (0.01 µS), medium (0.1 µS) or strong (1 µS).
The simulation results quantify that the adjustable gain value of the externally applied IFN input can better aid the cells to undergo synchronization within the cardiac system. With proper value of gain it is shown that the coupled SAN cells quickly synchronize.

It is thus inferred that for a coupled pair of SAN cells/oscillators, even for sufficiently large differences in their individual intrinsic frequencies regardless of the coupling strength, the external IFN input can coax the cells into synchrony.

V. CONCLUSION

The neuron model considered which when applied appropriately is shown to restore entrainment between the pair of cells regardless of the efficacy of coupling. The results of these simulation studies show that the pair of coupled cardiac cells that otherwise do not synchronize are made to synchronize with suitable neural input and the simulated results presented.The work can be extended to a multitude of SA nodal cells that constitute a one dimensional array with the corresponding IFN input applied.

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