Computational Cellular Model of Heart Rate Variability During Controlled Respiration

N. Sadowski and G. Drzewiecki

Department of Biomedical Engineering, Rutgers University, New Brunswick, New Jersey, 08901, USA
nicole.sadowski@rutgers.edu; garydrz@soe.rutgers.edu

The sinoatrial node (SAN), located in the right atrium wall, is the heart's biological pacemaker and determines heart rate due to the repetitive spontaneous action potentials for cardiac rhythmic contractions in the heart pacemaker cells. The funny current (I_f) and SAN, together with regulation by the sympathetic and parasympathetic nervous systems, modulate the frequency of the SAN action potential. The interaction of these systems is responsible for the rhythmic pacemaker activity, controlling heart rate, and abnormalities resulting in arrhythmias.

The Hodgkin-Huxley model was groundbreaking for research regarding biological modeling. Instead of using theoretical equations, it was the first model to use mathematical reconstructions of experimentally established kinetics of ion channel permeability and gating [1]. The Hodgkin-Huxley model also accurately predicted the shape of the action potential, coinciding with research conducted in other areas of biological modeling. The ideas proposed by the Noble model were based on the basic principles of the Hodgkin-Huxley model and described an electric circuit modeling the behavior of currents traveling through a membrane signified either by changing the membrane capacity or by the movement of ions through resistances in parallel with the membrane capacitance [2]. The Noble model was used to model a cardiac action potential, but required further modifications to represent a cardiac myocyte's highly complex electrical activity due to the heart's cardiac output fluctuations. The essential change to the Hodgkin-Huxley model was the addition of another potassium channel to represent the Purkinje fibres of the heart and contained both an inward rectifier and a delayed rectifier for potassium [1]. A representation of the circuit described in the Noble model is presented in Figure 1. These fluctuations allow the heart to compensate for sudden physical and physiological changes. The oscillations of a healthy heart are intricate and non-linear in nature, providing the flexibility for rapid adaptation to an uncertain and constantly fluctuating environment [3].

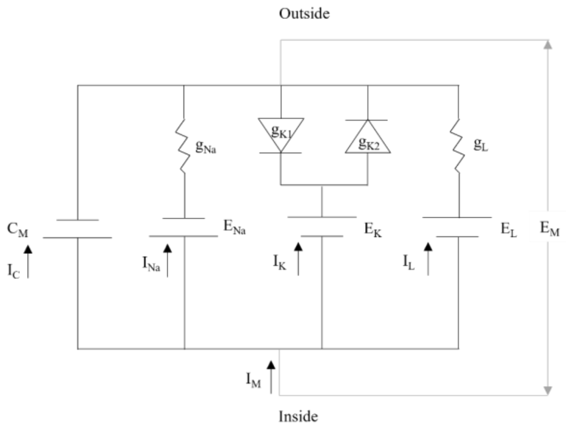

Figure 1. The representative circuit includes the Noble model's electrical activity and the Hodgkin-Huxley model's modifications.

A single cardiac pacemaker cell model was produced based on the alterations to the Noble model to represent cardiac electrophysiology parameter values of a cardiac myocyte and was modified to include a leak channel to account for the funny current and yield a continuously oscillating action potential [1]. The action potential's frequency depends on the voltage and conductance of the leak channel. A dual cardiac pacemaker cell model was produced with the addition of a coupling resistor, connecting two cells to one another for interaction, which allowed for the variation of one of the pacemaker cells to simulate various common types of arrhythmias. Once the dual cardiac pacemaker cell model was established and tested, controlled respiration was added to the model to produce a model that accurately depicted accurate human physiological processes [4]. For this to occur, a sine wave was added to the leak voltage channel of one of the cells. This allowed for the investigation of the addition of controlled respiration and its effects on the model. The electrical activity signals generated by the dual cardiac pacemaker cell model were analyzed using several methods, including heart rate variability (HRV) and acquired frequency spectrums. The

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determination of HRV plays a significant role in the early detection of cardiovascular diseases. It has often been seen that HRV is generally detected before a formal diagnosis. Using the generated action potentials produced by the dual cardiac pacemaker cell model, the time correlating to the R portion of the QRS complex was determined. HRV was calculated by taking the time difference between subsequent R peaks, and the mean HRV was determined from these values. The frequency spectrum of the obtained HRV plots were calculated using Fourier transform analysis by breaking down each signal into sinusoids at the various signals present in each signal [5]. Also, the fundamental frequency of each signal was determined by presenting a peak at the calculated value. To calculate the fundamental frequency and produce a representative plot of the Fourier transform analyses in MATLAB, the fft function was used. The fft function analyzes a specified signal in the time domain and converts that signal to the frequency domain.

The addition of the sine wave signifying controlled respiration caused an alteration in the uniform rate of oscillation of the action potential of the given cell. The rate of oscillation of the action potential of the given cell increased as the voltage of the leak channel increased. A representative figure of the effects of controlled respiration on the action potential of a given cell is presented in Figure 2. The generated model consisted of a cell driven by the voltage of the leak channel with the addition of a sine wave to represent controlled respiration, as well as a second cell driven by the first cell through the use of a coupling resistor. This allowed for the investigation of the addition of controlled respiration and its effects on the model and it was determined that as the voltage of the leak channel increases, the rate of oscillation of the action potential, or voltage membrane, of the cell increases. The electrical activity signals generated by the dual cardiac pacemaker cell model were analyzed using several methods, including heart rate variability (HRV) and acquired frequency spectrums. The HRV plot of the dual cardiac pacemaker cell model with controlled respiration is portrayed in Figure 3. The frequency spectrum of the obtained HRV plots were calculated using Fourier transform and the fundamental frequency was calculated to be 0.0429 Hz for the dual cardiac pacemaker cell model with controlled respiration. To verify that the results of this experiment were accurate, a controlled respiration experiment was conducted with the use of the ECG recording feature on the Apple Watch. Controlled respiration was performed by the subject to which they inhaled for 5 seconds (s), then exhaled for 5 s. This method was performed for the duration of the ECG recording, approximately 30 s. Once a desirable ECG recording was achieved, the experiment was repeated for non-controlled (normal) breathing, meaning that the subject recorded the ECG with a normal respiration rate.

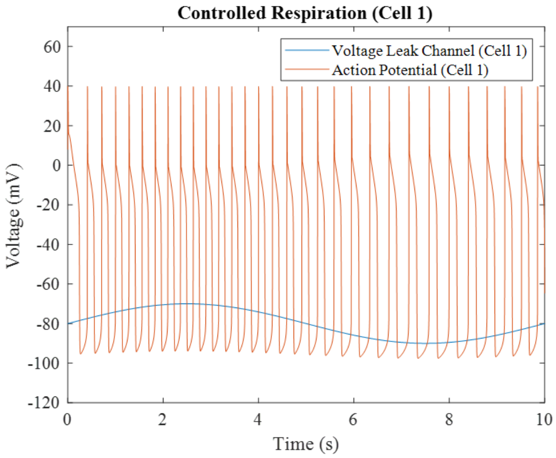

Figure 3. Representation of the addition of a controlled breathing sine wave to the voltage leak channel upon the action potential of a single cell.

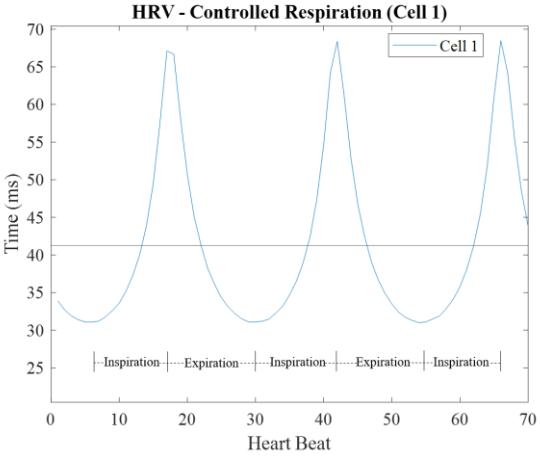

Figure 2. Representation of HRV of the dual cardiac pacemaker cell model with controlled respiration. Mean HRV for this model was calculated to be 41.2 ms.

The output information was analyzed using an application from the Apple App Store called Analyzer and the calculation of the measured period between the R-R wave peaks was performed. This information was used to calculate the HRV, and subsequent plots were generated. Visual representations of the computed HRV for controlled and non-controlled respiration experiments are portrayed in Figure 4 and Figure 5, respectively. The controlled respiration experiment determined that the R-R period was shorter during air intake and longer during exhalation. Therefore, the rate of oscillation was greater during intake than during exhalation, mimicking the results of the dual cardiac pacemaker cell model with the addition of controlled respiration. These results were also confirmed with a non-controlled respiration ECG recording. The fundamental frequencies and generated frequency spectrum were also produced for controlled and non-controlled respiration experiments. These results were compared to the outputted results of the controlled respiration dual cardiac pacemaker cell model for accuracy. The mean HRV was also calculated and determined to be 23.1 milliseconds (ms) and 17.1 ms for the controlled and non-controlled respiration experiments, respectively.

The HRV data obtained from the dual cardiac pacemaker cell model with the addition of controlled respiration was compared to the HRV data obtained by the controlled respiration experiment performed with the Apple Watch. It was determined that the fundamental frequency, determined by presenting a peak at the calculated value, was calculated to be 0.067 Hz and 0.098 Hz for the dual cardiac pacemaker cell model with the addition of controlled respiration and the controlled respiration experiment, respectively. These two fundamental frequency values were similar to one another when compared to the non-controlled respiration experiment in which the fundamental frequency values were determined to be 0.18, 0.21, 0.38, and 0.45 Hz.

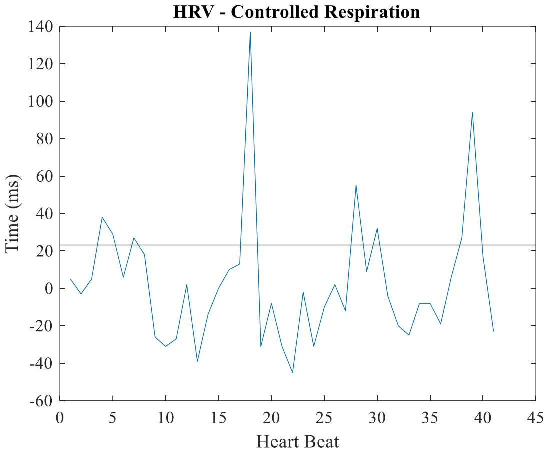

Figure 5. Representation of HRV of the controlled respiration experiment conducted with the ECG feature of the Apple Watch. The mean HRV for this experiment was calculated to be 23.1 ms.

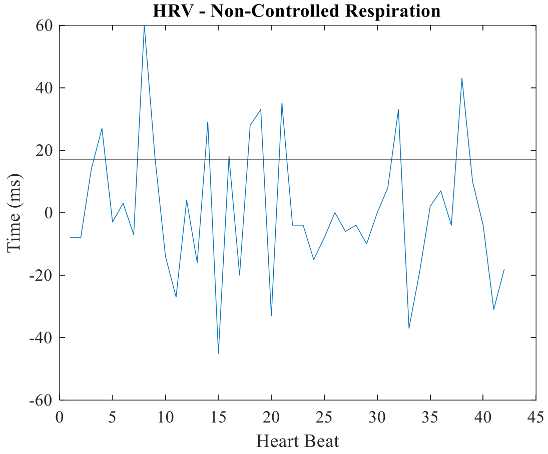

Figure 4. Representation of HRV of the non-controlled respiration experiment conducted with the ECG feature of the Apple Watch. The mean HRV for this experiment was calculated to be 17.1 ms.

The results of this study were compared to the results of previous work. Specifically, a study by Aysin and Aysin compared the results of controlled respiration and normal or non-controlled respiration. The conclusions of this study indicated that during controlled respiration, the calculated fundamental frequency, based upon HRV, was calculated to be 0.085 Hz, and the peak of the frequency spectrum was located in the lower frequency range [6]. These results were anticipated since the parasympathetic nervous system activity is facilitated by respiration and the respiration rate is lower in controlled breathing compared to normal breathing [6]. Therefore, when compared to the results of similar prior works, the fundamental frequency value of the dual cardiac pacemaker cell model with respiration and the controlled respiration experiment validates the HRV model for controlled and non-controlled respiration conditions. Additionally, it was determined that the addition of the controlled respiration sine wave to the voltage leak channel of the first cell directly affected the rate of oscillation of the action potential of that cell as well as the second cell when it was added to the model through the use of coupling resistor. Similarly, a study performed by Ben-Tal et al. concluded similar results and established a relationship between the cardiac vagal nerve and respiratory output [7]. It was concluded that the output of the respiratory rhythm generating signal, similar to the sine wave used in this experiment, was primarily responsible for controlling the cardiac output signal [7].

Noble has developed a cellular model for a single cardiac pacemaker cell. While the Noble model successfully modeled pacemaker activity, it does not model HRV. HRV is of recent interest for its possible value as a diagnostic indicator of the cardiac system. In this article, a dual cardiac pacemaker cell model was created using MATLAB to model both common arrhythmias and HRV. This model was then evaluated for its ability to provide normal HRV measurements and frequency spectrum analysis. HRV data was further collected by performing an experiment via Apple Watch ECG recording for controlled and non-controlled (normal) respiration. This research validates the HRV model for both controlled and non-controlled respiration conditions.

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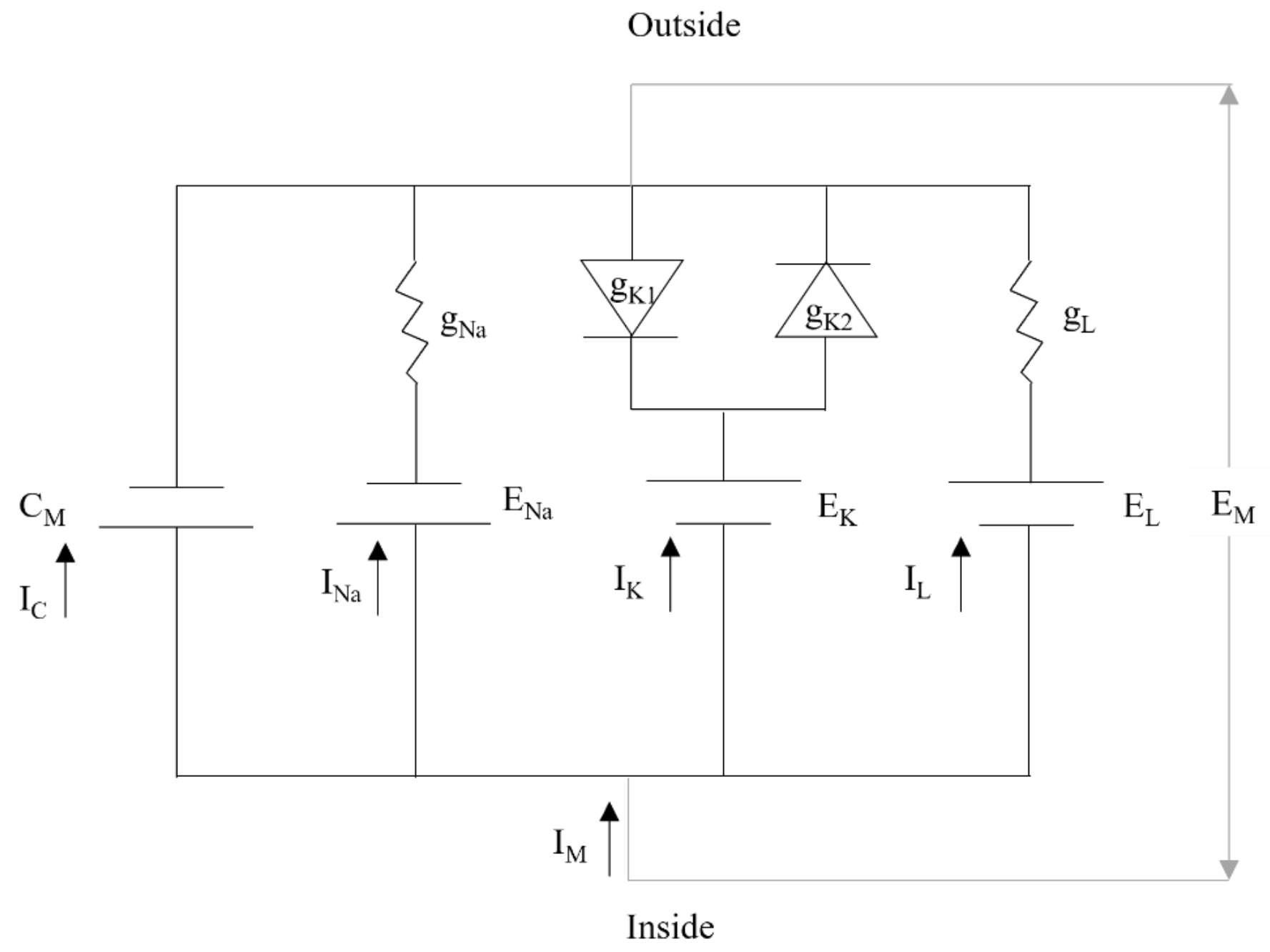
N. Sadowski and Dr. G. Drzewiecki
Department of Biomedical Engineering, Rutgers, The State University of New Jersey
nicole.sadowski@rutgers.edu; garydrz@soe.rutgers.edu

Abstract

- The funny current (I_f) and the sinoatrial node (SAN) modulate the frequency of the SAN action potential. The interaction of these systems is responsible for the rhythmic pacemaker activity, controlling heart rate, and abnormalities resulting in arrhythmias.
- A cellular model for a single cardiac pacemaker cell has been developed by Noble. While the Noble model successfully modeled pacemaker activity, it does not model heart rate variability (HRV).
- HRV is of recent interest for its possible value as a diagnostic indicator of the cardiac system.
- A dual cardiac pacemaker cell model was created using MATLAB to model both common arrhythmias and HRV.
- HRV data was further collected by performing an experiment via Apple Watch ECG recording for controlled and non-controlled (normal) respiration.

Overview of the Noble Model

- The Hodgkin-Huxley model was the first model to use mathematical reconstructions of experimentally established kinetics of ion channel permeability and gating [1]. It also accurately predicted the shape of the action potential.
- The ideas proposed by the Noble model were based on the basic principles of the Hodgkin-Huxley model and was used to model a cardiac action potential, but required further modifications to account for fluctuations in cardiac output.
- The essential change to the Hodgkin-Huxley model was the addition of another potassium channel to represent the Purkinje fibres of the heart and contained both an inward rectifier and a delayed rectifier for potassium [1].
- The oscillations of a healthy heart are intricate and non-linear in nature, providing the flexibility for rapid adaptation to an uncertain and constantly fluctuating environment [2].
- Representation of the Noble model circuit:

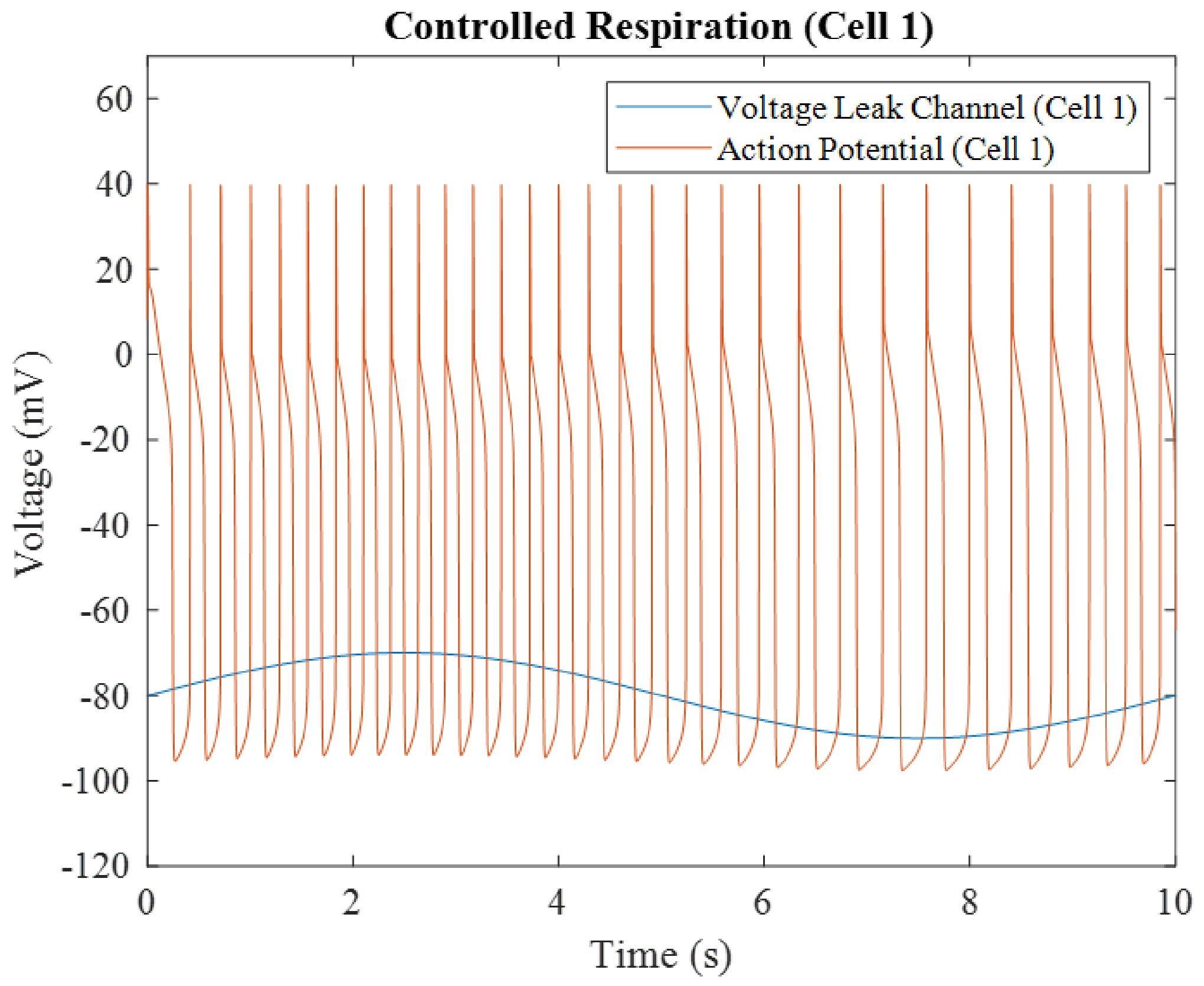


Cardiac Pacemaker Cell Model

- A single cardiac pacemaker cell model was produced based on the Noble model and was modified to include a leak channel to account for the funny current and yield a continuously oscillating action potential [1].
- The action potential's frequency depends on the voltage and conductance of the leak channel.
- A dual cardiac pacemaker cell model was produced with the addition of a coupling resistor, connecting two cells to one another for interaction.
- The dual cardiac pacemaker cell model had several capabilities, including simulating various common types of arrhythmias (tachycardia, bradycardia, and partial block arrhythmias) and calculating HRV [3].

Addition of Controlled Respiration to the Cardiac Pacemaker Cell Model

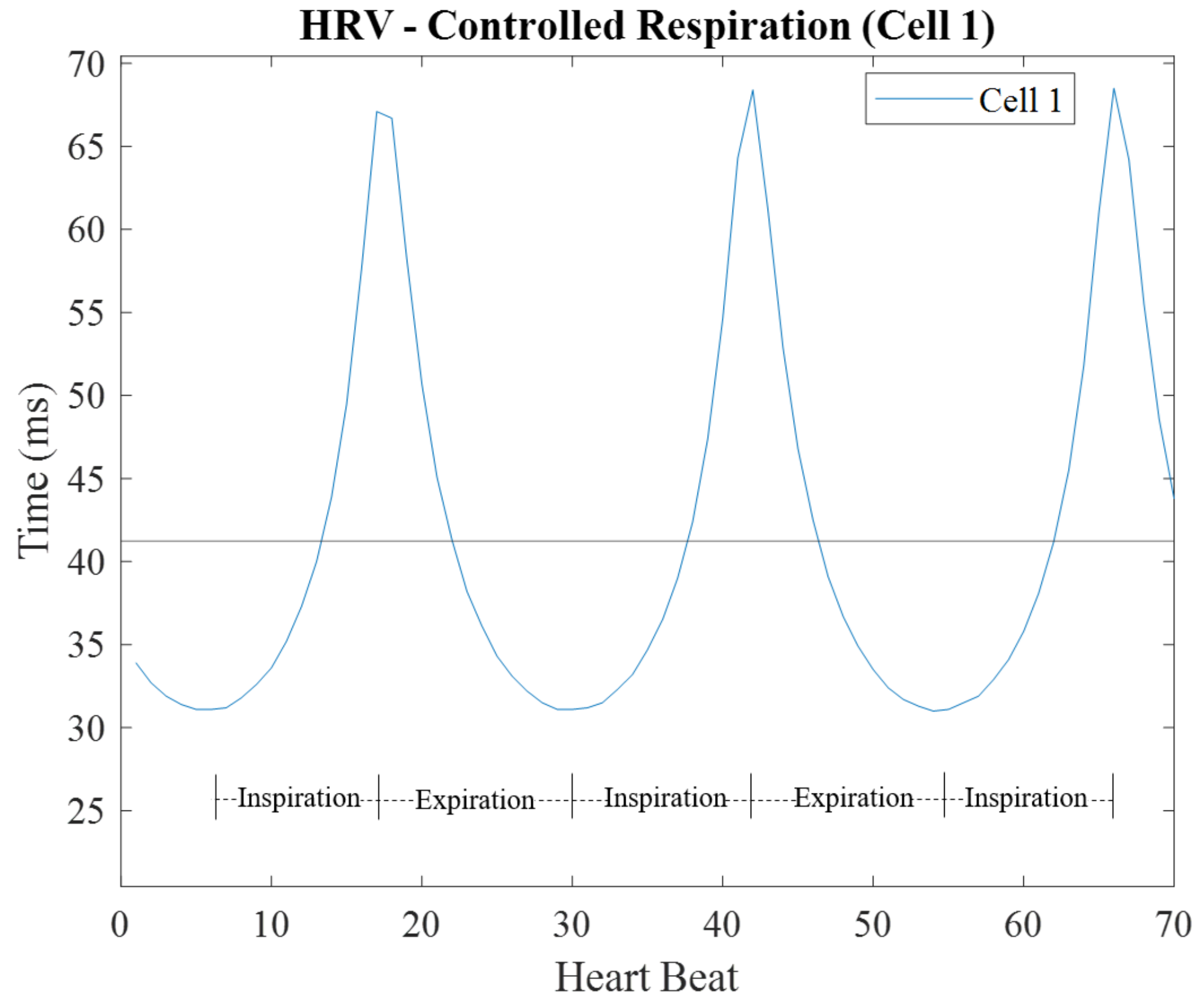
- Controlled respiration was added to the dual cardiac pacemaker cell model to accurately depicted accurate human physiological processes.
- The rate of oscillation of the action potential of the given cell increased as the voltage of the leak channel increased.
- Effects of controlled respiration on the action potential of a given cell



- The dual cardiac pacemaker cell model consisted of a cell driven by the voltage of the leak channel with the addition of a sine wave to represent controlled respiration, as well as a second cell driven by the first cell through the use of a coupling resistor.
- It was determined that as the voltage of the leak channel increases, the rate of oscillation of the action potential, or voltage membrane, of the cell increases.

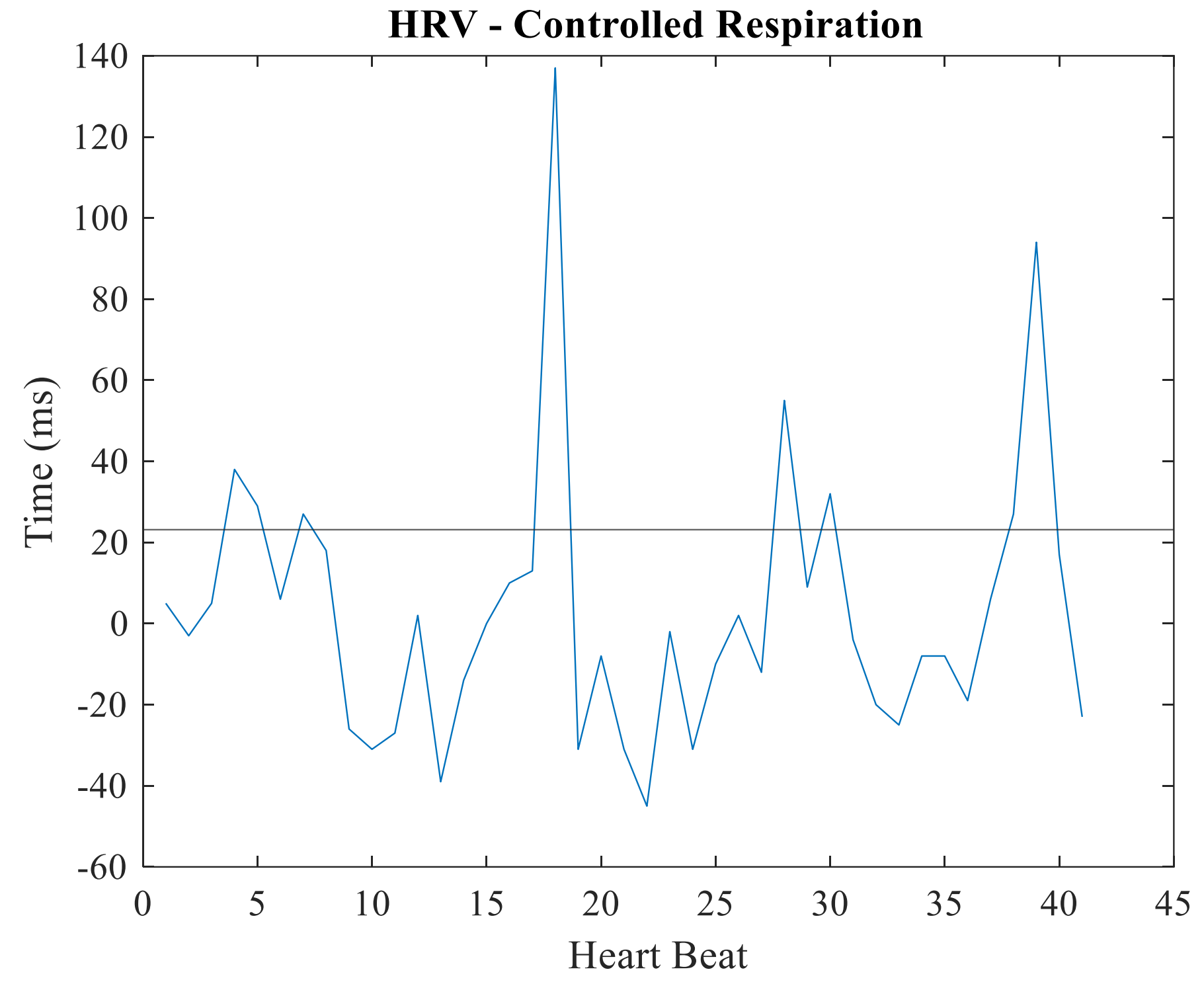
Analysis of the Cardiac Pacemaker Cell Model with Controlled Respiration

- The electrical activity signals generated by the dual cardiac pacemaker cell model were analyzed using several methods, including heart rate variability (HRV) and acquired frequency spectrums.
- HRV plot of the dual cardiac pacemaker cell model with controlled respiration.

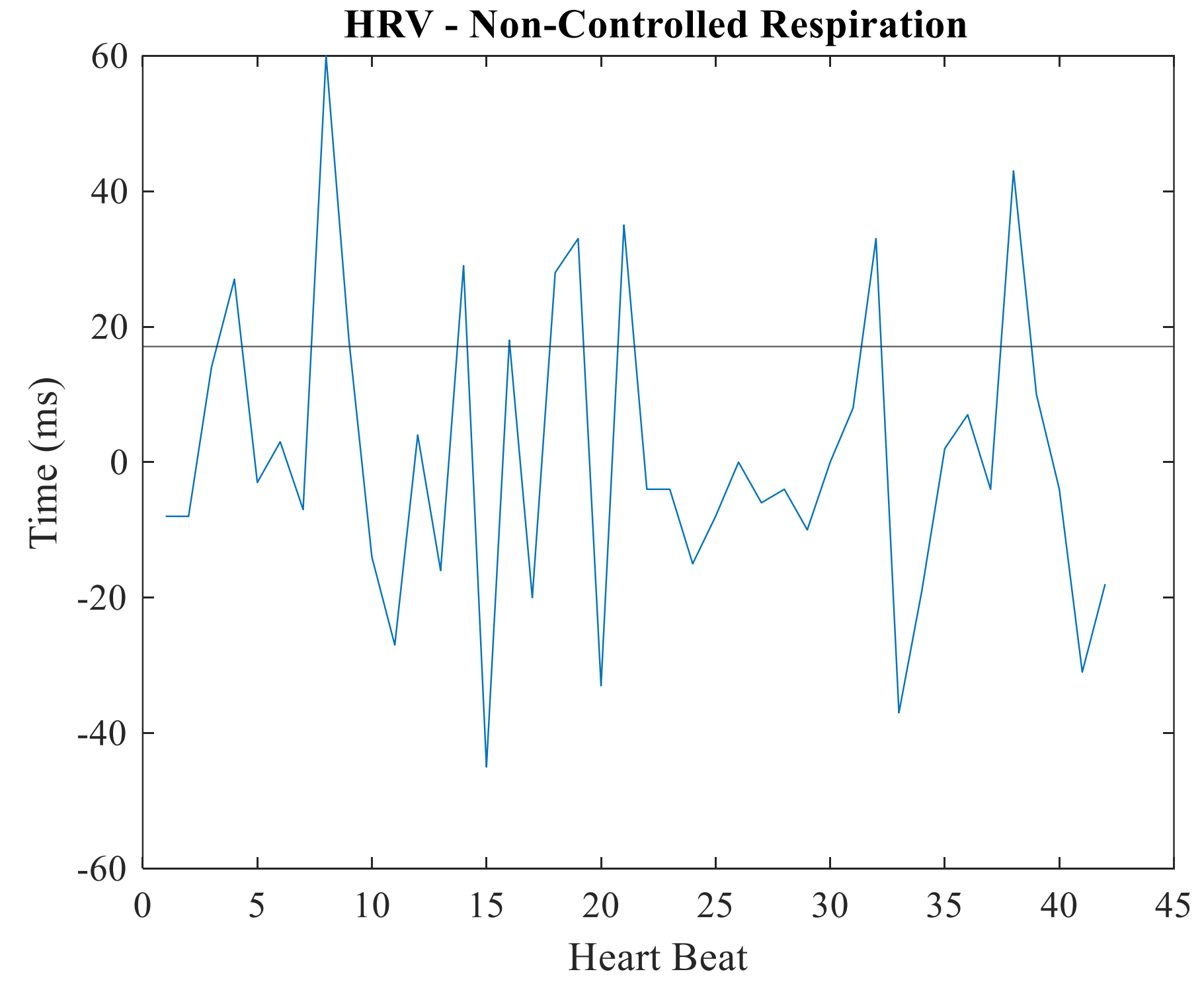


ECG Experimental Model

- To verify that the results of this experiment were accurate, a controlled respiration experiment was conducted with the use of the ECG recording feature on the Apple Watch.
- Controlled respiration was performed by the subject to which they inhaled for 5 seconds (s), then exhaled for 5 s. This method was performed for the duration of the ECG recording, for approximately 30 s.
- The experiment was repeated for non-controlled (normal) breathing, meaning that the subject recorded the ECG with a normal respiration rate.
- The output information was analyzed using an application from the Apple App Store called Analyzer and the calculation of the measured period between the R-R wave peaks was performed to calculate HRV.
- Representation of the computed HRV for controlled respiration experiment.



- Representation of the computed HRV for non-controlled respiration experiment



- The controlled respiration experiment determined that the R-R period was shorter during air intake and longer during exhalation.
- The rate of oscillation was greater during intake than during exhalation, mimicking the results of the dual cardiac pacemaker cell model with the addition of controlled respiration. These results were also confirmed with a non-controlled respiration ECG recording.
- The fundamental frequencies and frequency spectrums were also produced for controlled and non-controlled respiration experiments. These results were compared to the outputted results of the controlled respiration dual cardiac pacemaker cell model for accuracy.

ECG Experimental Model *(Continued)*

- The HRV data obtained from the dual cardiac pacemaker cell model with the addition of controlled respiration was compared to the HRV data obtained by the controlled respiration experiment performed with the Apple Watch.
- It was determined that the fundamental frequencies for the dual cardiac pacemaker cell model with the addition of controlled respiration and the controlled respiration experiment were similar to one another.

Comparison to Previous Works

- During controlled respiration the peak of the frequency spectrum was located in the lower frequency range [4]. These results were anticipated since the parasympathetic nervous system activity is facilitated by respiration and the respiration rate is lower in controlled breathing compared to normal breathing [4].
- When compared to the results of similar prior works, the fundamental frequency value of the dual cardiac pacemaker cell model with respiration and the controlled respiration experiment validated the HRV model for controlled and non-controlled respiration conditions.
- Additionally, it was determined that the addition of the controlled respiration sine wave to the voltage leak channel directly affected the rate of oscillation of the action potential of both cells in the dual cardiac pacemaker cell model.
- It was concluded that the output of the respiratory rhythm generating signal, similar to the sine wave used in this experiment, was primarily responsible for controlling the cardiac output signal [5].

Summary

- Noble has developed a cellular model for a single cardiac pacemaker cell but, it does not model HRV.
- HRV is of recent interest for its possible value as a diagnostic indicator of the cardiac system.
- In this article, a dual cardiac pacemaker cell model was created using MATLAB to model both common arrhythmias and HRV.
- The dual cardiac pacemaker cell model was then evaluated for its ability to provide normal HRV measurements and frequency spectrum analysis.
- HRV data was further collected by performing an experiment via Apple Watch ECG recording for controlled and non-controlled (normal) respiration.
- This research validates the HRV model for both controlled and non-controlled respiration conditions.

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