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## Statistical Analysis Of The Effects Of Atropine And Propranolol On The Inter-Beat Interval Of Rats

Abdud Dahian

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STATISTICAL ANALYSIS OF THE EFFECTS OF ATROPINE AND  
PROPRANOLOL ON THE INTER-BEAT INTERVAL OF RATS

By

Abdud Dahian

A Thesis  
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in the Department of Agricultural and Biological Engineering

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STATISTICAL ANALYSIS OF THE EFFECTS OF ATROPINE AND  
PROPRANOLOL ON THE INTER-BEAT INTERVAL OF RATS

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Heart rate variability (HRV) analysis has proved to be an important tool for assessing autonomic nervous system. For instance, it has been used during dipyridamole echocardiographic test to differentiate ischemic from nonischemic responses [6]. RR Interval analysis can provide additional information that can lead to early detection of a possible change in the activity of the autonomic nervous system. HRV analysis can be done using Wavelet Transform. This thesis presents a modification of an existing algorithm for extracting the R-R interval from EKG data sets and the use of wavelet transform (WT) technique to compute the time-frequency domain energy quantities. The project used data obtained previously from a study of the effects of two pharmacological agents, atropine and propranolol, on laboratory rats. Results showed that the ratio of high

frequency energy over the total energy (HF/total) of atropine treated rats was higher than baseline (control).

## DEDICATION

I would like to dedicate this thesis to my mother, Zainab Farzana.

## ACKNOWLEDGEMENTS

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# CHAPTER I

## INTRODUCTION

Heart rate variability (HRV) refers to the beat-to-beat timing variations of the EKG signal or the RR intervals.

A heartbeat consists of a rhythmic contraction (systole) and relaxation (diastole) of the heart muscle. The heartbeat starts with a signal from the sino-atrial (SA) node, followed by the depolarization of the atrium, and then the depolarization of the ventricles. This is expressed by the P, QRS, T complex in an electrocardiogram (Figure 1.1), The P section is the atrium contraction portion of the wave form, the QRS section, is the section when the atrium starts to relax and the ventricle starts to contract, and the T section, is the section when the ventricle starts to relax. The heart beat or the heart rate (HR) is partially regulated by the Autonomic Nervous System (ANS). The ANS consists of the sympathetic nervous system (SNS), which causes a faster depolarization of the ventricles causing the HR to increase, and the parasympathetic nervous system (PNS), which causes a slower depolarization of ventricles causing a decrease in the HR. The balance between the SNS and the PNS, also known as the sympathovagal balance determine the variability of the heartbeat. Some pharmacological agents are also known to affect the HR and HRV.

Heart rate variability (HRV) analysis has proven to be an important tool for assessing autonomic nervous system activity. For instance, it has been used during the dipyridamole echocardiographic test, to evaluate if spectral analysis of RR interval variability makes it possible to differentiate ischemic from nonischemic responses. In this test, the spectral components of HRV (total power, very low frequency power, low frequency power and high frequency power) were analyzed (during dipyridamole infusion in patients with coronary artery disease) just before and after the onset of ischemia-related events (peak dipyridamole effect) [6]. It has been used to study acute hypoxia in fetal lambs by investigating the changes in the power spectral pattern of HRV during acute hypoxia [8] and to study the onset of ventricular tachycardia in acute myocardial infarction by analyzing the power spectral components of HRV [5]. Although raw EKG signal does provide critical information, the inter-beat interval (R-R Interval) analysis can provide additional information that can lead to early detection of a possible change in the activity of the autonomic nervous system. HRV analysis can be performed using different tools, and Wavelet Transform (WT) is one such tool.

The WT is suitable for measuring non-stationary signals in which frequency changes with time [7]. Biological signals like HR are non-stationary in that the HR keeps changing because of a number of factors previously mentioned. Since WT can provide both the time and frequency information simultaneously, it has gained interest during the last decade in accurately predicting heart disease.

This project proposes to modify an existing algorithm for extracting the R-R interval from EKG data sets, validate it with the data sets from a given rats experiment and then use WT technique to compute the time-frequency domain energy quantities, which will then be statistically analyzed to quantify the HRV. This project will use the data obtained previously from the study of the effects of two pharmacological agents, atropine and propranolol, on laboratory rats as the basis for the analysis.

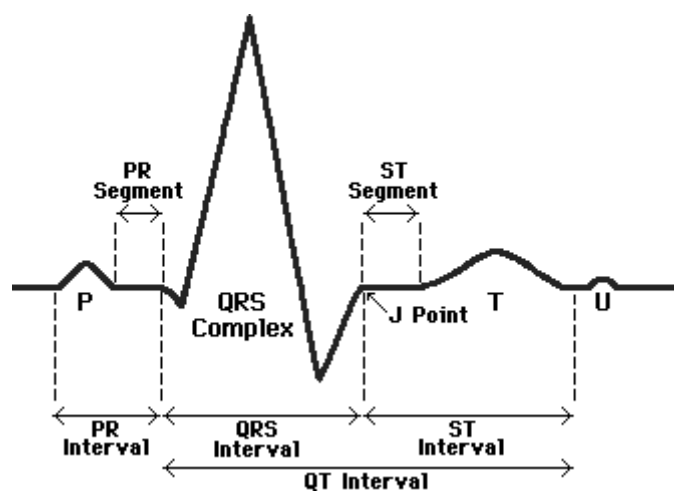


Figure 1.1 EKG Complex [16]

## CHAPTER II

### LITERATURE REVIEW

#### QRS Algorithm

Thompkins J et al. devised a real-time QRS detection algorithm in 1985. It was able to detect the QRS complexes based upon analysis of slope, amplitude and width. Their algorithm was able to detect about 99.3 percent of the QRS complexes. This algorithm is also known as the “Thompkins” method [12]. Another method of detecting QRS complexes, known as the “So and Chan” method, was devised in 1997. They used a first derivative approach to build a real-time ambulatory ECG monitor to detect the QRS complexes [10]. Recently in 2004, Timo Bragge et al. devised a high-resolution QRS detection algorithm for sparsely sampled ECG recordings. They reported that it accurately estimated the R-wave fiducial points from extremely low (sparsely) sampled ECG recordings, i.e., the ECG recordings that used a sampling frequency of less than 500 Hz. [13]. [3] used a steep slope method, which adaptively changes the threshold.

In general, the HRV analysis methods can be divided into time domain, frequency domain and non-linear method.



### **Time Domain Analysis Method of HRV Analysis**

Time domain analysis of HRV involves statistical analysis of various aspects of the R-R data. For example, [1] performed a time-domain analysis of HRV by computing the mean, standard deviation and also the root mean square of successive RR intervals (RMSSD).

Other time domain parameters that have been measured are:

SDANN – the standard deviation of the average NN (or RR) intervals. SDANN is said to reflect components of autonomic regulation largely related to sympathetic activation [15]. [15] proved that it might be an important prognostic factor in patients with severe circulatory failure and atrial fibrillation.

HRV triangular index – the integral of the density distribution (that is, the number of all NN intervals) divided by the maximum of the density distribution. This geometric measure is used for long-term analysis of HRV and hence is influenced by lower frequencies than the higher frequencies [9].

### **Frequency Domain Analysis Method**

[5] presented a study of the onset of ventricular tachycardia in acute myocardial infarction using frequency domain analysis. They found that the power spectral analysis of components of HRV had the potential to quantify the cardiac autonomic tone during ambulatory electrocardiograph recording. They analyzed the power spectral components of very low frequency power (VLF), which had the frequency range of 0.0033-0.04 Hz,

low frequency (LF) of frequency range 0.04-0.15 Hz and high frequency (HF) of frequency range of 0.15-0.4 Hz power. The areas under the curve were computed and it was found that the total power of HRV increased progressively before the onset of ventricular tachycardia episodes [4].

### **Non-linear Analysis Methods**

Some of the non-linear analysis methods include the Poincare plots, the chaos theory, and time-frequency analysis methods. The WT is considered a class of time-frequency transform, which include the Wigner-Ville and Gabor short-time Fourier transform (STFT). STFT had a problem with resolution; it was able to give a band of frequencies in a given time interval but not the exact time-frequency representation of a signal. Wavelet Transform uses the principle of Multi-Resolution Analysis in which the signal is analyzed at different frequencies and at different resolutions [8]. Wavelet transforms are currently being used more commonly, as they can provide information in the time-frequency domain. Some of the advantages using the time-frequency methods are the ability to identify which frequency occurs in what time and near perfect reconstruction of the signal back to its original form from the transform coefficients without the requirement for oversampling [5].

The continuous wavelet transform (CWT) was developed to overcome the problem of resolution in STFT. Similar to STFT in which a window function is

multiplied with the signal and integrated over all times, CWT used a mother wavelet, which is multiplied with the signal and integrated over all times [7].

The CWT is as defined by equation 4.1:

$$CWT_x^\psi(\tau, s) = \Psi_x^\psi(\tau, s) = \frac{1}{\sqrt{|s|}} \int x(t) \psi^* \left( \frac{t - \tau}{s} \right) dt \quad (4.1)$$

Here  $x(t)$  is the signal which is multiplied with a transforming function,  $\Psi(t)$ , also known as the mother wavelet. The transformed signal is a function of  $\tau$  and  $s$ , which are known as the translation and scale parameters. The term  $1/(\sqrt{s})$  is a constant to make the transformed signal to have the same energy at every scale. The translation parameter relates to the location of the window in time as the window is shifted through the signal [7].

The scale is defined as  $1/\text{frequency}$ . Hence, low frequencies (high scales) correspond to information of a signal which spans over (a larger time span) the entire signal and high frequency (low scale) corresponds to the detailed information that lasts a relatively short time. As a mathematical operation, scaling either dilates or compresses a signal, which means that, larger scales correspond with dilated or stretched out signal and smaller scales correspond with compressed signal [7].

The computation of CWT is as follows. Let  $x(t)$  be the signal to be analyzed. A mother wavelet is chosen which serves as a prototype for all windows in the process, hence the name mother wavelet. All windows that are used will be the dilated or compressed and shifted (translation) versions of the mother wavelet. Some of the

commonly used mother wavelets used are the Haar, Daubechies 4 and Morlet. Once the mother wavelet is chosen, the procedure starts with a scale  $s=1$ , for convenience, and increases i.e., starting for high frequencies to low frequencies. Hence  $s=1$  will correspond to the most compressed wavelet and as the value of  $s$  is increased the wavelet will dialate. Hence the first value will be calculated according to the equation 4.1 at  $\tau=0$  and  $s=1$ . The wavelet is the shifted by  $\tau$  amounts to a location  $t=\tau$ , and with the same scale  $s=1$ , the transform value is calculated. This is repeated until the wavelet reaches the end of the signal. Hence one row of values for the time-scale plane for  $s=1$  is calculated. Then,  $s$  is increased by a small amount and since this is a continuous transform, both the  $\tau$  and  $s$  need to be incremented continuously. This procedure is repeated for every value of  $s$  and once it is done for every required value of  $s$ , the computation of CWT is done. Figure 2.1 (Time (sec) along X-axis and Amplitude along Y-axis) shows the computation of CWT for  $s=1$  (high frequencies) at four different  $\tau$  values. The blue window should be as narrow as the highest frequency in the signal. Hence the signal is localized in time by shifting the wavelet in time, and it is localized in scale (frequency) by changing the value of  $s$  [7].

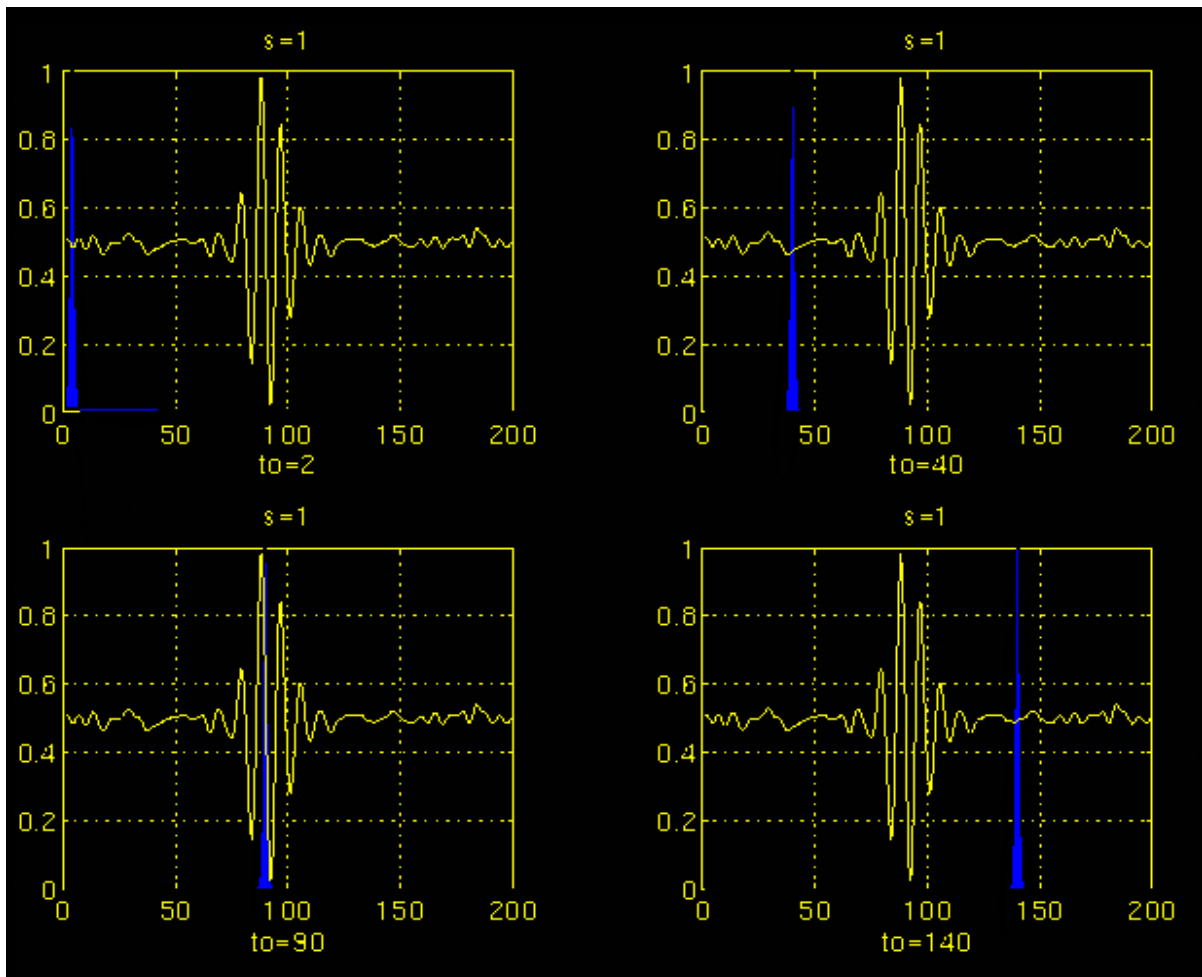


Figure 2.1 Signal and wavelet function with  $s=1$  [7]

If the signal has a spectral component that is the same as  $s$ , then the product of the wavelet with the signal at the location will be a large value, and at other times it will be either small, or zero. Hence at  $t=110\text{ms}$  and  $s=1$  as seen in Figure 2.1 (Time (sec) along X-axis and Amplitude along Y-axis), the CWT of the signal will be large.

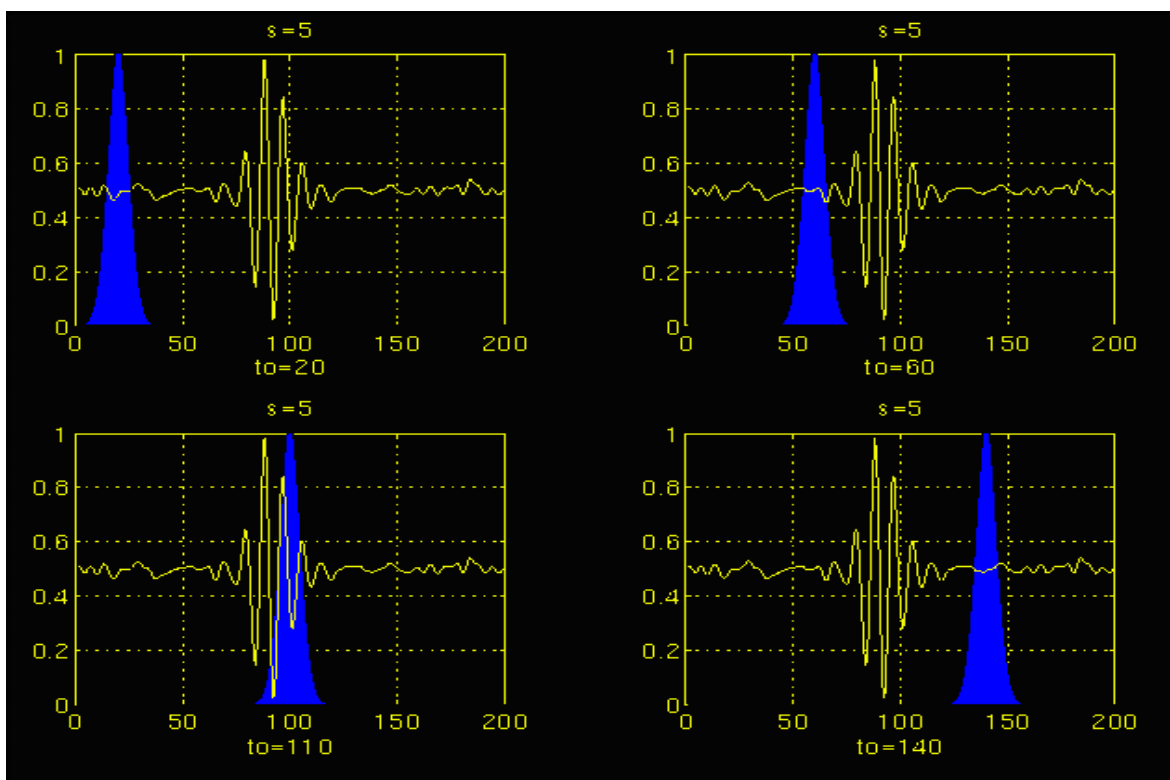


Figure 2.2 Signal and wavelet function with  $s=5$  [7]

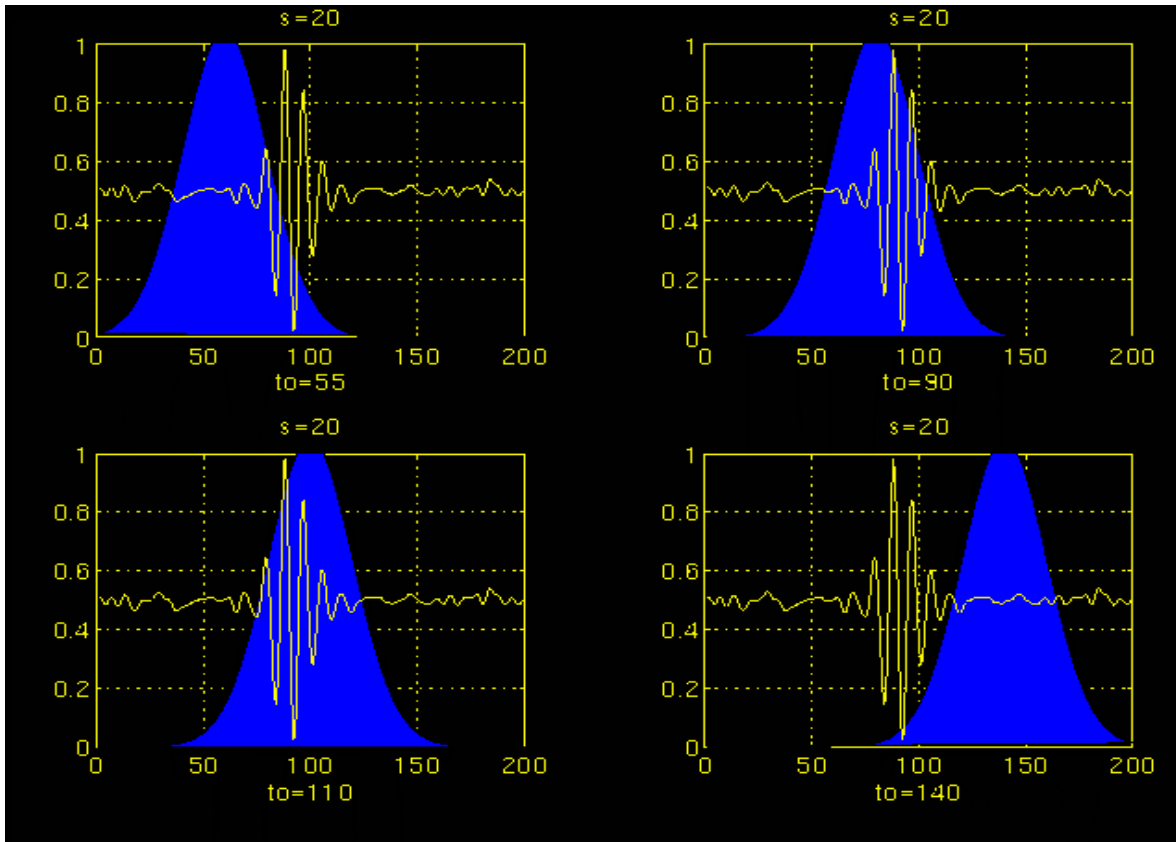


Figure 2.3 Signal and wavelet function with  $s=20$  [7]

Figure 2.2 (Time (sec) along X-axis and Amplitude along Y-axis) and Figure 2.3 (Time (sec) along X-axis and Amplitude along Y-axis) explain this process with  $s=5$  and  $s=20$ . As seen, the width of the window increases and the scale increases (frequency decreases). Hence as the scale increases the lower frequency components are detected [7].

The discrete wavelet transform (DWT) is computed with the main idea being the same as CWT, multiresolution analysis. DWT is important in that it provides coarse and detailed information by decomposing the signal. The detailed information is used to

calculate the variability power of high and low frequencies which, in our case, is needed to quantify the effects of atropine and propranolol. Hence, DWT is used in this study. Here digital filtering techniques are used to calculate the time-scale representation i.e., filters of different cutoff frequencies are used to analyze the signal at different scales. The signal is passed through a series of high pass filters to analyze the higher frequencies, and it is passed through a series of low pass filters to analyze the lower frequencies. In DWT, the scale is changed by upsampling (increasing) and downsampling (subsampling) operations. Downsampling corresponds to reducing the sampling rate or removing some of the samples of the signal. Downsampling by two refers to dropping every other sample of the signal. At higher scales (lower frequencies), the sampling rate can be decreased, according to Nyquist's rule, which states the sampling frequency to be twice that of the highest frequency present. The scale parameter  $s$  can be discretized on a logarithmic scale, and the time parameter is discretized with respect to the scale parameter, i.e., a different sampling rate is used for every scale (dyadic sampling grid). Hence the DWT uses a dyadic grid, with the logarithmic base of 2, in which case the scales 2, 4, 8, 16, ... are computed. Since the discrete scale changes by a factor of 2, the sampling rate is reduced for the time axis by a factor of 2 at every scale [7].

The procedure starts by passing the signal through a halfband low pass filter. Half of the samples can be eliminated according to the Nyquist's rule. Discarding every other sample will subsample the signal by two; the signal will have half the number of points. The scale of the signal is now doubled. The low pass filter removes the high frequency



information, but leaves the scale unchanged. Only the subsampling process will change the scale, i.e., the low pass filtering halves the frequencies, but leaves the scale unchanged. The signal is then subsampled by 2 since half the number of samples are redundant.

The DWT analyzes the signal at different scales by decomposing the signal into coarse approximation and detail information. Successive high pass and low pass filtering of the time domain signal results in the decomposition of the signal into different frequency bands. Hence the original signal is first passed through a halfband high pass filter and a low pass filter. After the filtering, half the samples can be eliminated according to Nyquist's rule. The signal can then be subsampled by 2, by discarding every other sample. This constitutes one level of decomposition. This procedure is repeated for further decomposition, and at every level, filtering and subsampling will result in half the number of samples (half the time resolution) and half the frequency band spanned (double the frequency resolution). Figure 2.5 explains this principle where  $x[n]$  is the original signal to be decomposed and  $h[n]$  and  $g[n]$  are low pass and high pass filters, respectively. The bandwidth of the signal at every level is denoted by ' $f$ ' [7].

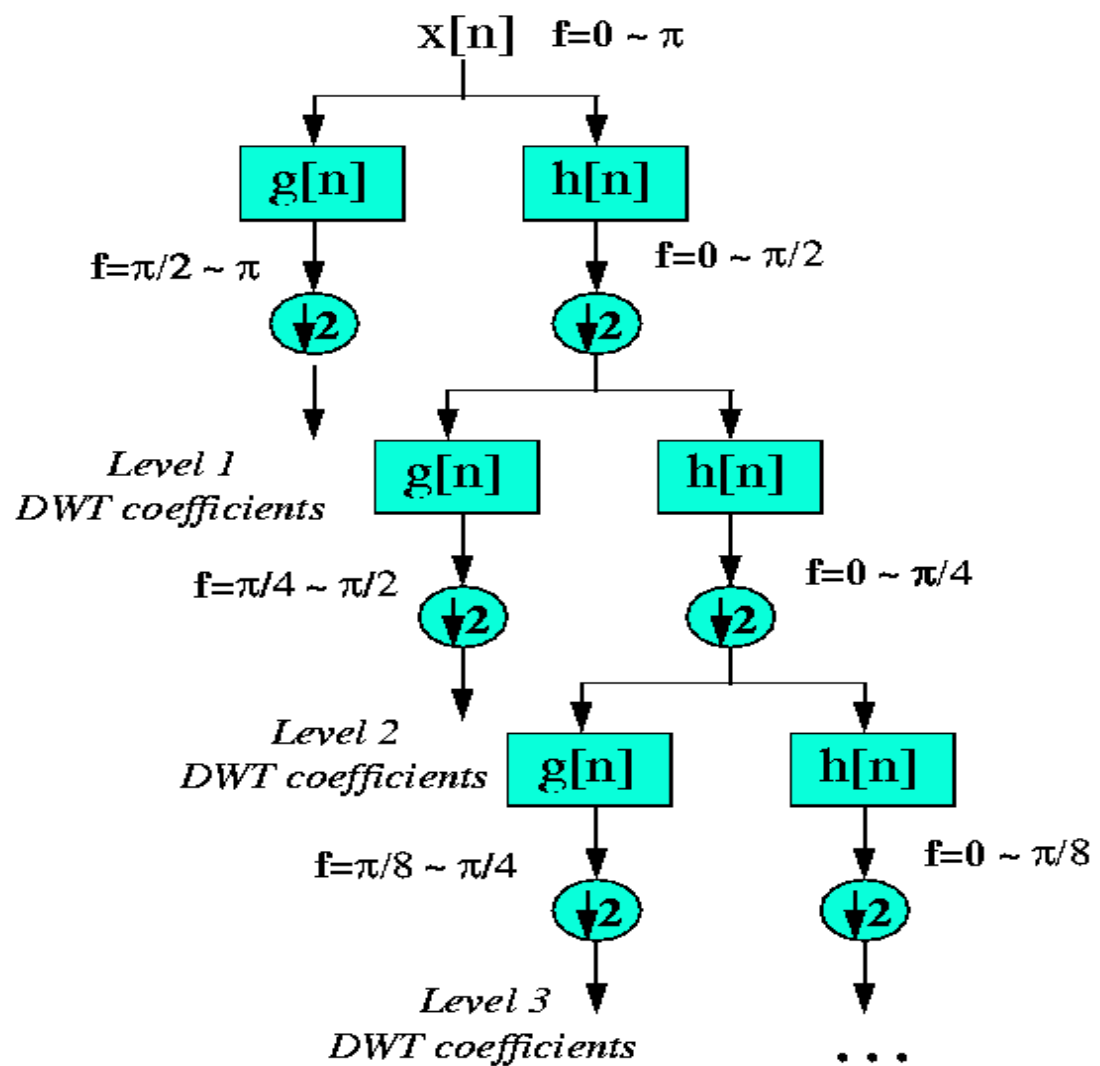


Figure 2.4: DWT algorithm [7]

[6] used WT during dipyridamole-induced myocardial ischemia. They assessed the spectral components of HRV using WT analysis for the last 5 min before the beginning of the test and for 5 min after the onset of ischemia-related events. They found a greater increase in LF power and in LF/HF ratio in patients with multivessel coronary artery disease than in those with less coronary involvement.

## CHAPTER III

### METHODOLOGY AND PROCEDURE

In this study, five different rats were used, and the baseline condition recordings were made prior to injecting the rats with atropine or propranolol. Each baseline, atropine treatment group and propranolol treatment group had nine segments of data, each segment being one-minute recordings. Short term data analysis was done by analyzing each segment of the recording, and longer term data analysis was done by concatenating the data segments in which the variability power was calculated in each section, and then the average of power was taken. The data was sampled at a rate of 5000 Hz.

The procedure in this study is listed as follows:

1. The text files were read, and graphs were generated for visual inspection.
2. A modification to [3] steep slope method is being tested. [2] found that digital filtering methods and first derivative methods for QRS (peak) detection gave good results. A first derivative algorithm specified by [2] was chosen for this study.
3. The fiducial points or the R-wave peaks of each heartbeat were extracted by calculating the slope of each waveform using the formula specified by [2]:  
$$\text{slope}(n) = -2*a(n-2)-a(n-1)+a(n+1)+2*a(n+2)$$
 where 'a(n)' represents the amplitude of the EKG data at discrete time n.

4. The steep slope method of QRS detection was used which is based on the comparison of an absolute value of slope ( $\text{abs}(S)$ ) of the EKG signal and a threshold value  $M$  (' $S$ ' is the slope). A QRS (peak) is detected if  $\text{abs}(S) \geq M$ . Initially, the threshold value  $M$  was set to  $0.6 * \text{abs}(S)$ . So when  $\text{abs}(S) > M$ , a QRS (peak) was detected. Now a maximum of the absolute value of slope was searched in an interval of 250ms, and that will now be used to calculate the next threshold value;  $M = 0.6 * \max(\text{abs}(S))$ .

5. The threshold value  $M$  was limited to 1.5 times its previous detected QRS peak in order to eliminate any extrasystoles or artifacts that might have been introduced during EKG recording.

6. Once all the absolute slope values were calculated, the resultant series were plotted again for inspection against the original EKG to check and see if any peaks had been missed.

7. R-wave peaks, i.e., maximum values within every 250 points were inspected, and their corresponding time values were obtained. Once the time of every R-wave peak was obtained, the RR interval was then calculated, which is the difference between the times of two successive R-wave peaks.

8. Once the RR interval was obtained, the mean RR value was also calculated and beats per minute was also calculated, which is  $\text{bpm} = 60 / (\text{time difference of two successive peaks})$ .

9. The RR tachogram was then obtained by plotting the RR interval against time.
10. The QRS algorithm was validated statistically by hand counting the number of R-wave peaks detected and checked for any missing peaks. The RR tachogram data was then resampled at 10 Hz, using linear interpolation, assuming that the maximum frequency contained in the data was less than 5 Hz. According to Shannon's sampling theorem, the sampling rate should be greater than twice the highest frequency of the signal. In this study, the maximum frequency of heart rate for rats is 5 Hz (420BPM). The high frequency ranged from 1.78 Hz to 3.5 Hz and the low frequency ranged from 0.4 Hz to 1.7 Hz. Hence 10 Hz sampling frequency is adequate.
11. Daubechies-2 and Daubechies-4 were used as mother wavelets for the wavelet transformation of the resampled data.
12. As mentioned above in the literature, CWT or DWT can be used for multiresolution analysis. In our case, since we needed to quantify the effects of atropine and propranolol, we needed to find the variability power of high frequency and low frequency present in the signal. This was obtained by DWT, in which, the signal was passed through a series of low pass and high pass filters, which decompose the signal into coarse information and detail information respectively. The variability power was obtained from the detail information.
13. Using DWT, the signal was decomposed into wavelet coefficients (coarse and detail coefficients). At the first level, the scaled wavelets compared to the length of two ( $2^1$ ) consecutive RR intervals and the level above it to a length of four ( $2^2$ ) consecutive

RR intervals. Hence the initial levels (2, 4, 8,...) have a smaller value of dilation factor, which represents high-frequency variations in the signal, and the higher levels (32, 64, 128,...) have a larger value of dilation factor, which would represent low-frequency variations in the signal. In this study, seven levels were examined and each level was labeled as 2, 4, 8, 16, 32, 64, and 128, with the numbers corresponding to the width of the wavelet with which the RR signal was compared. Table 3.1 lists the frequency range at each level and Figure 3.1 shows the shape of analyzing wavelet at each level.

14. Once the detailed coefficients was obtained for each level, the variability power was calculated to each level as the sum of squares of the coefficients at each level. The high frequency (HF) variability power was obtained from levels 2, 4, and 8 (1.78 Hz – 3.5 Hz) i.e., the energy stored in the detailed part of these three levels represents the HF energy. The low frequency (LF) variability power was obtained from levels 16, and 32 (0.4 Hz – 1.78 Hz) i.e., the energy stored in the detailed part of these two levels represents the LF energy. The square summation of the detailed coefficients at all levels was the total energy. Also calculated are values HF/total, LF/total and the ratio LF/HF.

Table 3.1

Frequency range at each level

Level	Frequency (Hz)
2	7.137-3.568
4	3.568-1.784
8	1.784-0.892
16	0.892-0.4461
32	0.446-0.223
64	0.223-0.111
128	0.111-0.041



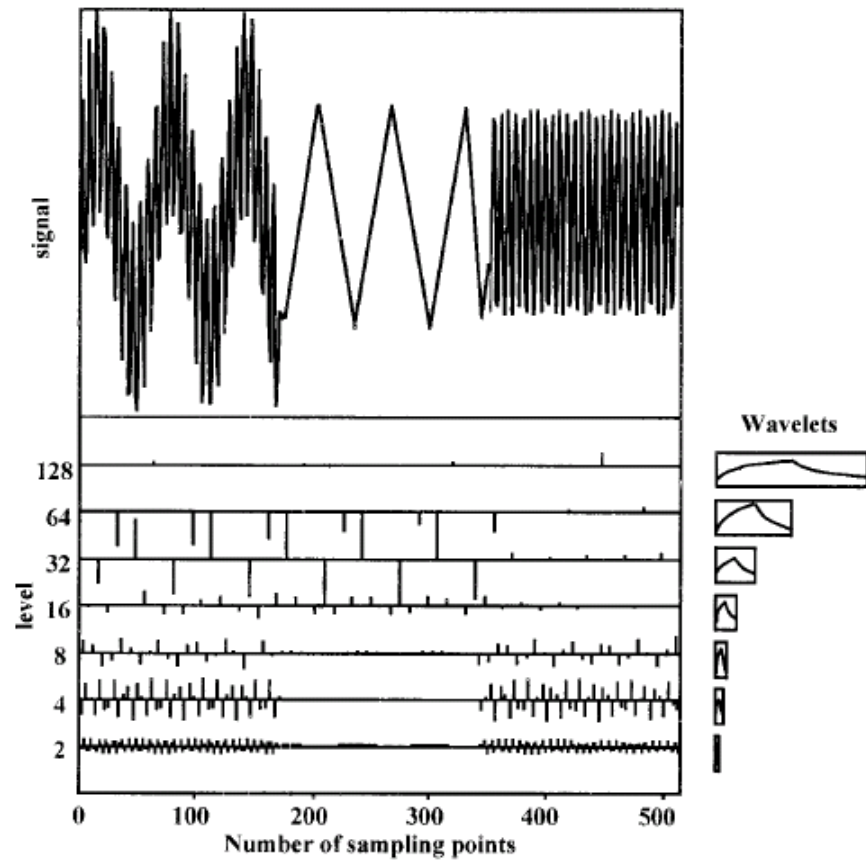


Figure 3.1 Example of the shape of analyzing wavelet at each level. [14]

15. Correlation between the baseline case and atropine and also for the baseline case and propranolol was calculated for each rat data to study if there was a steady correlation.

16. One way ANOVA was also performed on the data to show a significant difference ( $P < 0.05$ ) between the means of HF/total of baseline and atropine and also to see if there was a consistent difference among rats.

## CHAPTER IV

### STATISTICAL ANALYSIS RESULTS FOR HRV

A QRS algorithm was implemented in Matlab to extract the R-wave peaks and then to extract the RR intervals from the original EKG, and then HRV was analyzed using WT technique (source code is attached in Appendix A). First test was done to validate the QRS algorithm and RR interval, and the second test was done to statistically quantify the effects of atropine and propranolol. The results and the observations are summarized as follows:

#### **Validation of QRS Extraction Algorithm and RR Intervals**

Table 4.1 shows the validated results of the QRS algorithm and the RR intervals by checking the miss ratio in five different rats. This was done by hand counting the number of beats in random time periods (in 4 seconds, 5 seconds, 10 seconds out of the one minute segments) in the original EKG and comparing it with the number of R-wave peaks generated in the same time period. Similarly the RR intervals generated was found to be equal to one minus the number of beats. Appendix B contains the plots of the validated results for the QRS algorithm and the RR intervals.

Table 4.1

Validation results for QRS algorithm and RR intervals

Rat Number	Case	Time period checked at random (sec)	Number of beats in original EKG	Number of peaks detected	Number of RR intervals	Miss Ratio (%)
2	Baseline	24-28	21	21	20	0
2	Baseline	45-55	56	56	55	0
5	Baseline	10-15	28	28	27	0
5	Baseline	40-50	57	57	56	0
2	Atropine	6-10	32	32	31	0
2	Atropine	22-32	79	79	78	0
5	Propranolol	34-36	11	11	10	0
5	Propranolol	50-55	26	26	25	0

Figure 4.1 shows the original EKG and the detection of R-wave peaks in a baseline case. Figure 4.2 shows the RR tachogram and the beats per minute (BPM) Vs time for Rat 2. It was also seen from Figure 4.2 that the beats per minute of Rat 2 for baseline is averaged around 320BPM.

Figure 4.3 shows the original EKG and the R-wave peaks detected for Rat 2 injected with atropine. As seen in Figure 4.4, the beats per minute have increased to 475BPM. Figure 4.5 shows the original EKG and the R-wave peaks detected for Rat2 injected with propranolol, and Figure 4.6 shows the RR tachogram and the beats per minute, which are averaged at 315BPM. The same was observed in other rats. With the administration of atropine the heart rate increases, and with propranolol the heart rate decreases.

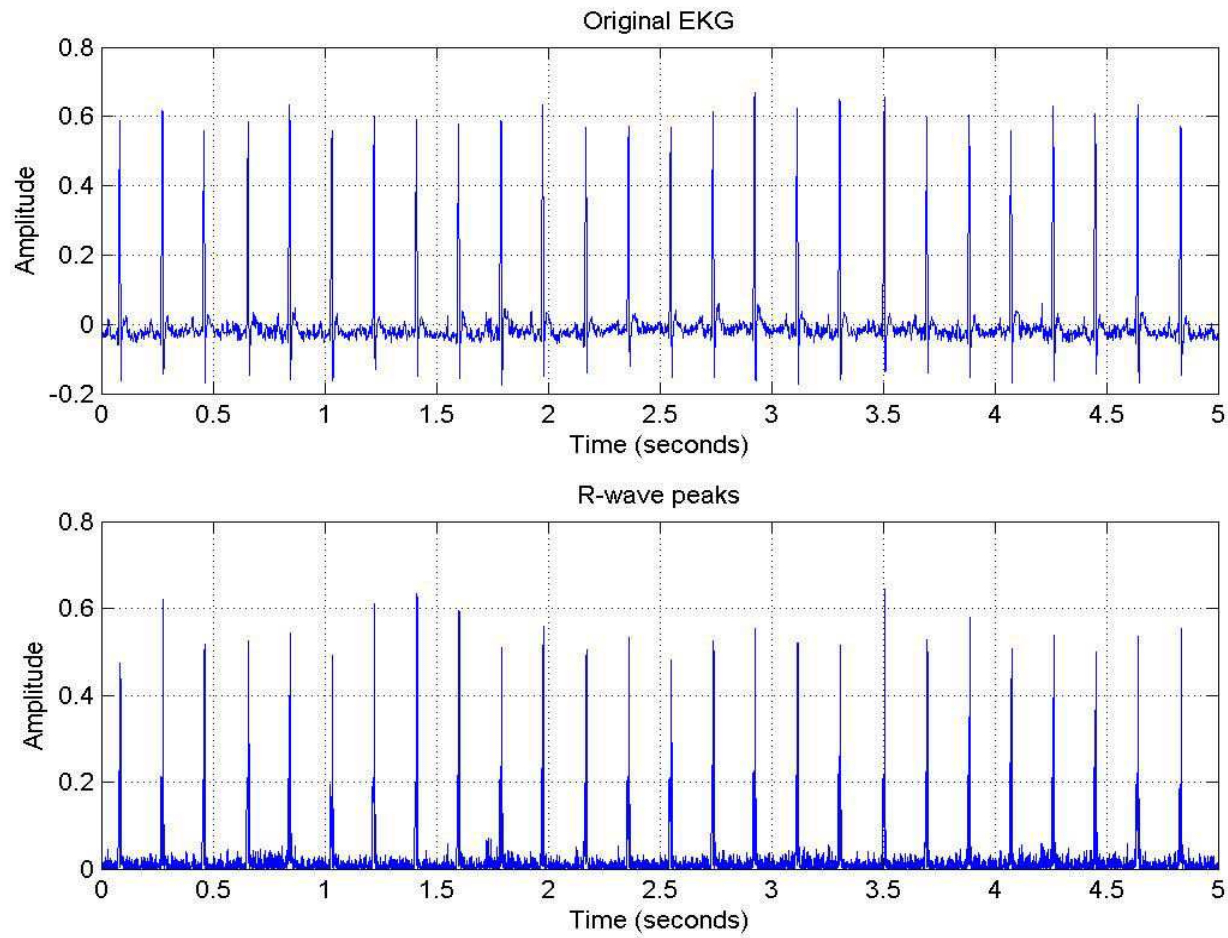


Figure 4.1: Original EKG and R-wave peaks of Rat 2 for baseline case

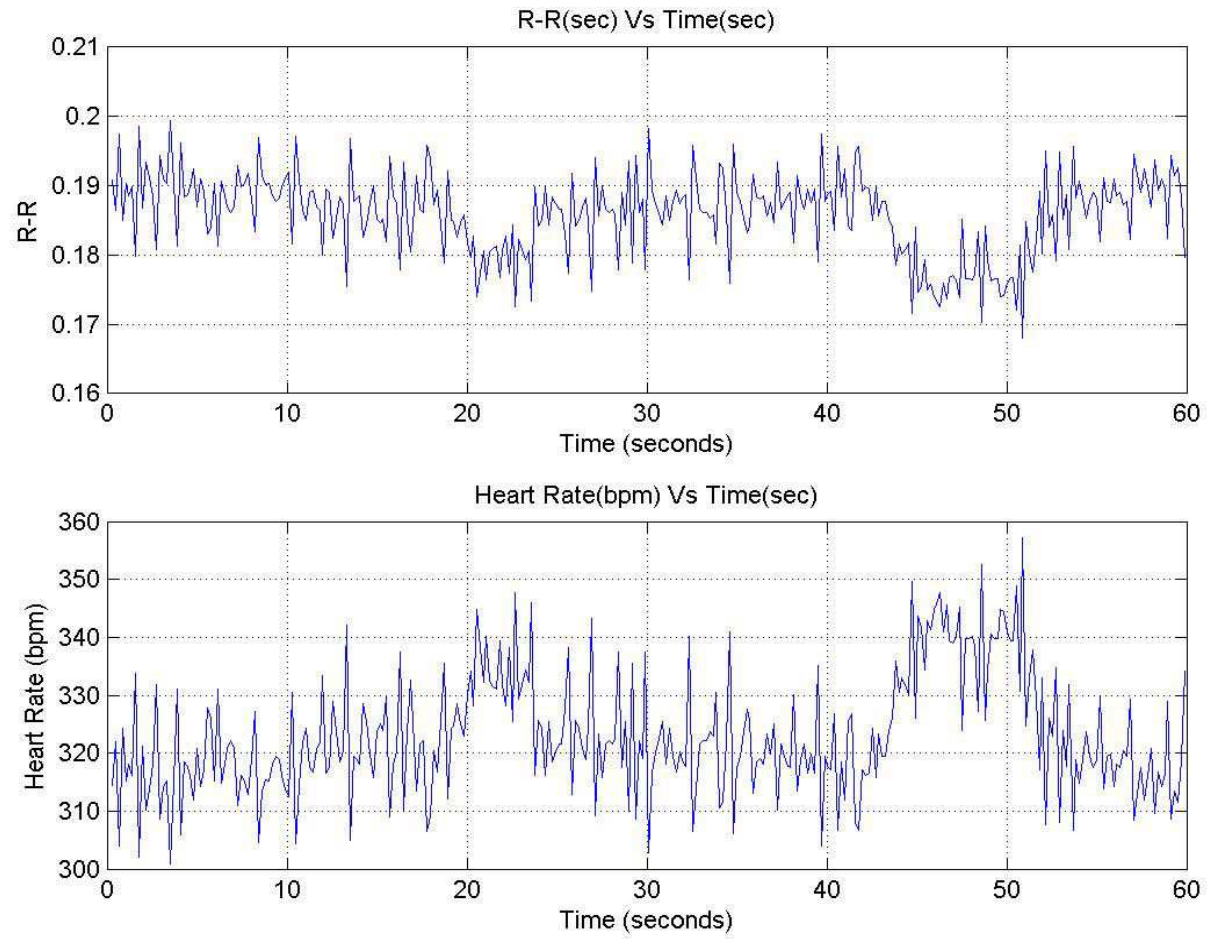


Figure 4.2: RR tachogram and Heart rate of Rat 2 for baseline case

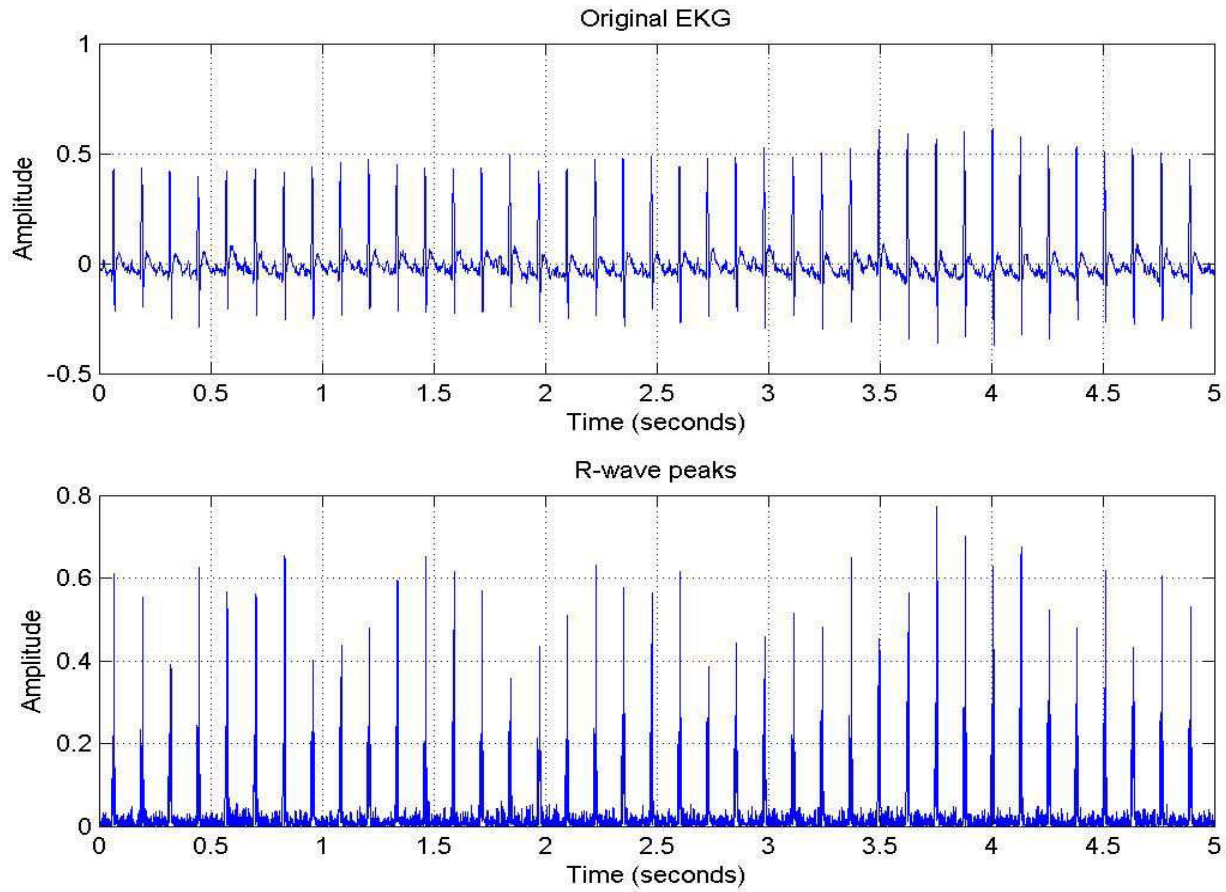


Figure 4.3: Original EKG and R-wave peaks of Rat 2 for atropine case

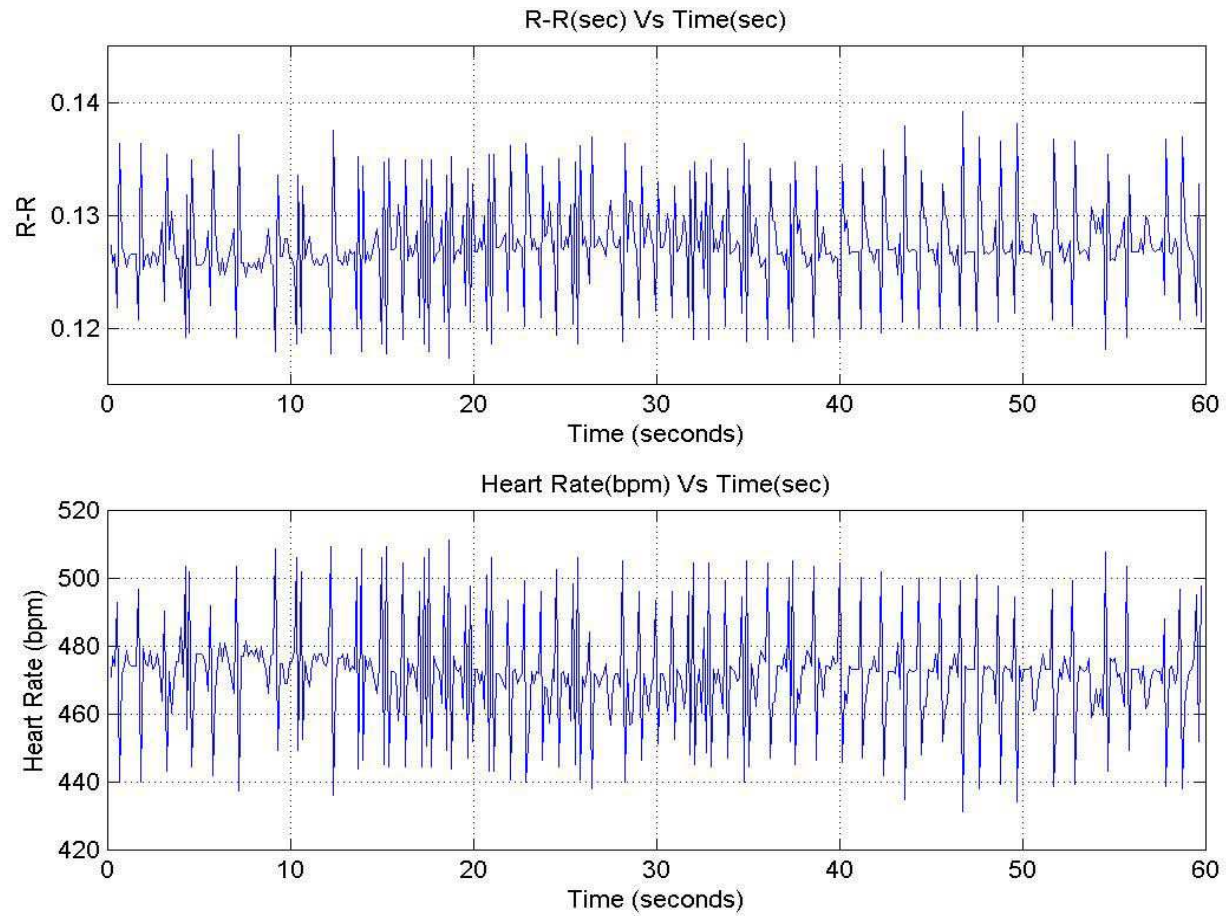


Figure 4.4: RR tachogram and Heart rate of Rat 2 for atropine case



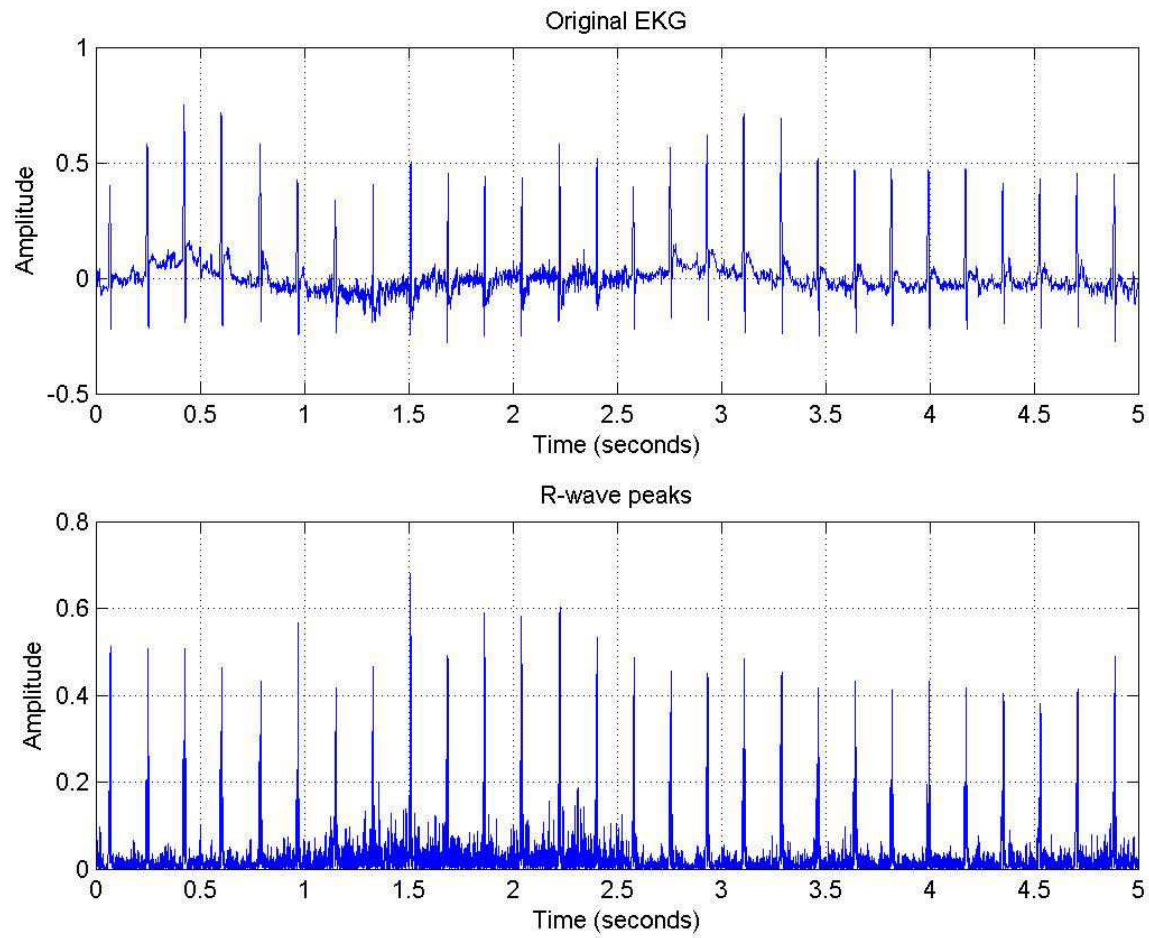


Figure 4.5: Original EKG and R-wave peaks of Rat 5 for propranolol case

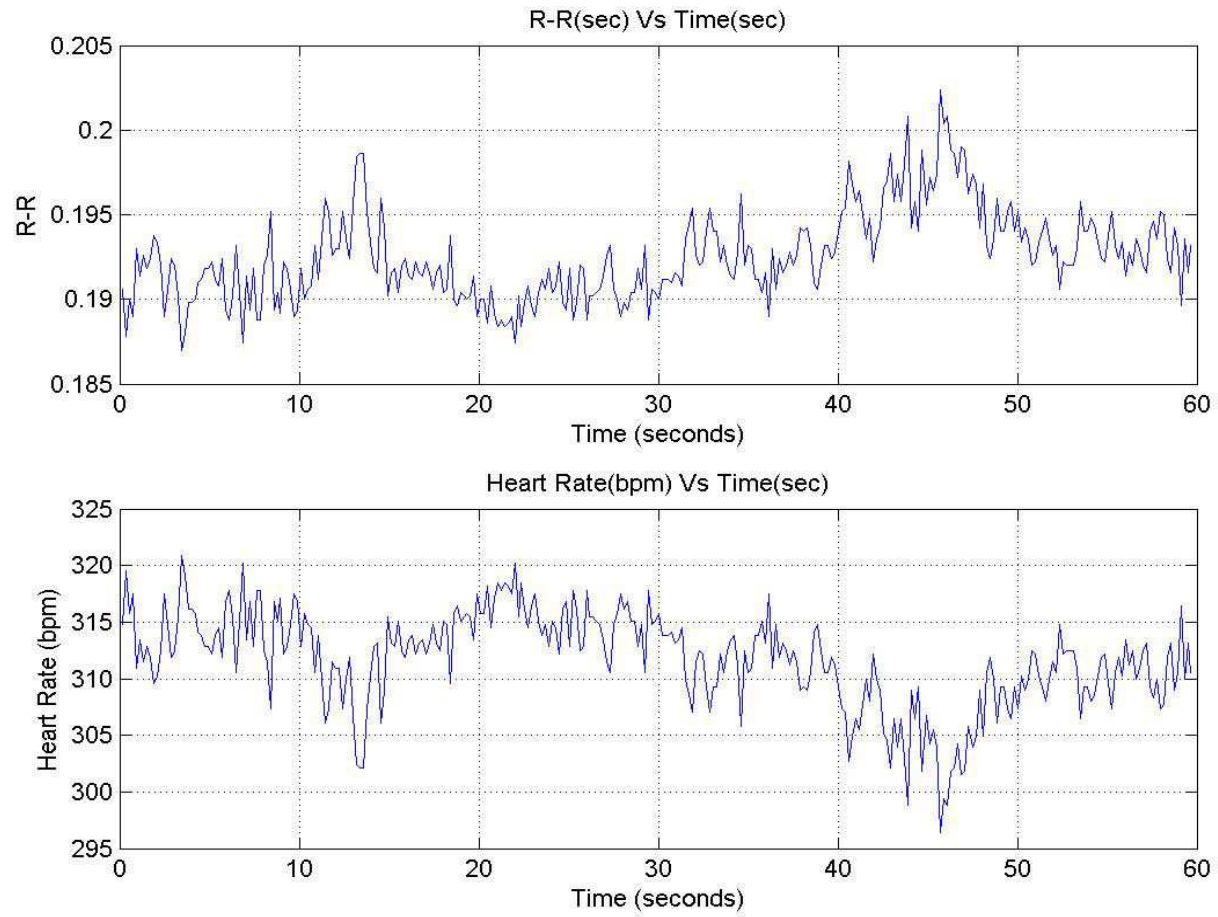


Figure 4.6: RR tachogram and Heart rate of Rat 5 for propranolol case

### Statistical Analysis of HRV

Correlation between baseline and atropine and also between baseline and propranolol was evaluated by performing statistical analysis in SAS. The ANOVA between baseline and atropine and also between baseline and propranolol was calculated for the same rat, and also the variance among different rats was calculated to see if there was a consistent difference across different rats.

Table 4.2 shows the results of HF/total for baseline and atropine, and Table 4.3 shows the HF/total for baseline and propranolol. Table 4.3 shows the correlation and variance between baseline and atropine and between baseline and propranolol. In Tables 4.2 and 4.3, column 1 is the rat number, column 2 is the type of mother wavelet (Daubechies-2 or Daubechies-4), column 3 is the mean HF/total value for baseline from nine segments and column 4 is the mean HF/total for atropine or propranolol from the nine segments for each rat. In Table 4.4, column 1 is the rat number, column 2 is the correlation and variance for each rat, column3 is the relation between baseline and atropine and column 4 is the relation between baseline and propranolol.

Table 4.2.

HF/total for baseline and atropine using Daubechies2 and Daubechies4 as wavelets

Rat Number	Wavelet	HF/total (Baseline)		HF/total (Atropine)	
		Mean	Std Dev	Mean	Std Dev
2	Daubechies4	0.43122	0.18480	0.76309	0.05275
	Daubechies2	0.54072	0.13792	0.81061	0.05105
5	Daubechies4	0.51609	0.11595	0.74657	0.09974
	Daubechies2	0.56950	0.16517	0.58938	0.39419
122	Daubechies4	0.50578	0.08087	0.75191	0.06326
	Daubechies2	0.56928	0.10534	0.77141	0.06323
123	Daubechies4	0.53627	0.11366	0.59377	0.17563
	Daubechies2	0.66371	0.14666	0.62317	0.20103
124	Daubechies4	0.54882	0.21180	0.69168	0.21791
	Daubechies2	0.61066	0.17843	0.64256	0.14914

Table 4.3.

HF/total for baseline and propranolol using Daubechies2 and Daubechies4 as wavelets

Rat Number	Wavelet	HF/total (Baseline)		HF/total (Propranolol)	
		Mean	Std Dev	Mean	Std Dev
2	Daubechies4	0.43122	0.18480	0.53070	0.17108
	Daubechies2	0.54072	0.13792	0.55420	0.20674
5	Daubechies4	0.51609	0.115950	0.53101	0.15810
	Daubechies2	0.56950	0.16517	0.61502	0.14983
122	Daubechies4	0.50578	0.08087	0.64341	0.20094
	Daubechies2	0.56928	0.10534	0.61563	0.22317
123	Daubechies4	0.57627	0.11366	0.48867	0.09974
	Daubechies2	0.66371	0.14666	0.51414	0.08264
124	Daubechies4	0.54882	0.21180	0.66535	0.15710
	Daubechies2	0.61066	0.17843	0.73043	0.15811

Table 4.4

Relation between baseline and atropine and between baseline and propranolol

Rat Number	Correlation or Variance	Between baseline & atropine		Between baseline & propranolol	
		*D4	**D2	D4	D2
2	Correlation	0.17313	-0.21133	-0.00633	-0.12267
	ANOVA(P value)	0.000	0.000	0.0081	0.0560
5	Correlation	0.49957	0.53790	-0.06864	0.25970
	ANOVA(P value)	0.001	0.7446	0.0519	0.0303
122	Correlation	0.18942	-0.01243	-0.23193	-0.61837
	ANOVA(P value)	0.0005	0.0002	0.0238	0.0039
123	Correlation	0.60163	0.40121	0.03469	0.23799
	ANOVA(P value)	0.8380	0.2323	0.0458	0.0058
124	Correlation	0.07127	0.26587	0.45260	0.17362
	ANOVA(P value)	0.0417	0.0229	0.0078	0.0116

\*D4: Daubechies 4 wavelet

\*\*D2: Daubechies 2 wavelet

As can be seen from Table 4.2 and Table 4.3, the mean energy distribution in the high frequency part for baseline is below 0.56, while that of atropine is greater than 0.6. Atropine causes an increase in the sympathetic nervous system activity thus causing the heart rate to increase. For some rats with propranolol, the mean energy distribution in the high frequency part is above 0.56, and for some it is below 0.56; in general they are close to the baseline value. At first propranolol causes an increase in the heart rate, but later it decreases to a value close to the baseline value.

Table 4.4 shows a positive correlation between baseline and atropine for the different rats using Daubechies 4 as mother wavelet. Rats 2, 5 and 122 seem to have a negative correlation, and rats 123 and 124 seem to have a positive correlation between baseline and propranolol using Daubechies 4. This positive correlation for rats 123 and 124 mean that there is not much decrease in the heart rate i.e., not much variability in the heart rate when propranolol was injected, and the heart rate was close to the baseline case.

One-way ANOVA was performed using Splus, and it can be seen from Table 4.3 that the P value for baseline and atropine is 0 for Rat 2, 0.001 for Rat 5, 0.0005 for Rat 122, 0.838 for Rat 123 and 0.0417 for Rat 124. P value for baseline and propranolol is 0.0081 for Rat 2, 0.0519 for Rat 5, 0.0238 for Rat 122, 0.0458 for Rat 123 and 0.0078 for Rat 124. All these values are observed for Daubechies 4 wavelet.

Correlation and variance among rats was observed to see if there was a consistent difference among different rats. Table 4.4 shows this observation. In table 4.4, column 1 is the rat number, column 2 shows the relation among rats with baselines, column 3 shows the relation among rats injected with atropine and column 4 shows the relation among rats injected with propranolol.

Table 4.5

## Correlation and variance among rats

Rat Number	Comparing baselines of two rats		Comparing atropine effects of two rats		Comparing propranolol effects of two rats	
	Corr	P value	Corr	P value	Corr	P value
2 & 122	0.08	0.816	-0.38	0.005	-0.17	0.036
5 & 124	-0.55	0.005	NA	NA	NA	NA
2 & 123	0.09	0.901	0.45	0.487	-0.05	0.005
2 & 124	-0.66	0.04	NA	NA	NA	NA
2 & 5	0.43	0.23	0.23	0.52	0.32	0.38
5 & 123	-0.03	0.921	NA	NA	NA	NA
5 & 122	0.12	0.73	0.30	0.391	-0.006	0.98

To determine if there is a consistent difference between two rats, one has to first check if their baselines are correlated. If the baselines are not correlated then there is no point in checking to see if there is a consistent difference between their atropine and propranolol readings. As seen in Table 4.5, the baselines of Rat 2 and Rat 122 have a positive correlation of 0.08 and a P value of 0.816. But there seemed to be a negative correlation between their atropine and propranolol values. The baselines of Rat 2 and Rat 123 showed a positive correlation, but their propranolol readings were negatively correlated. The baselines of Rat 2 and Rat 5 showed positive correlation and so did their

atropine and propranolol readings. The baselines of Rat 5 and Rat 124 have a negative correlation of -0.55. The baselines of Rat 2 and Rat 124 were negatively correlated with -0.66. The baselines of Rat 5 and Rat 123 were negatively correlated with -0.03.



## CHAPTER V

### CONCLUSION AND DISCUSSION

In this study, previously collected data were used to quantify the effects of pharmacological agents atropine and propranolol on five laboratory rats. A QRS detection algorithm using steep slope method was modified and validated. The RR intervals obtained from this algorithm were used to analyze HRV using WT technique. Results showed that the ratio of high frequency energy over the total energy (HF/total) had a positive correlation for baseline and atropine. Most rats showed a negative correlation for baseline and propranolol, and a couple of rats showed a positive correlation close to zero, showing that the heart rate reduced close to the baseline case, i.e., the heart rates were almost similar.

#### Conclusion

1. Validation of QRS detection algorithm was done statistically by hand counting the number of peaks and checking for any misses. The use of Menard et al. first derivative algorithm with Christov et al. steep slope method showed good results. There was no loss in QRS peak detection. The plots of validated results are as shown in Appendix B.

2. Heart rate for baseline case of rats was observed at 320 BPM and for atropine case it was observed at 475BPM, validating the fact that atropine causes the heart rate to increase. The propranolol case was observed at 315BPM, which showed that by administration of propranolol the heart beats decreased and were close to the baseline case.
3. HF/total showed a positive correlation for baseline and atropine case and a negative correlation for baseline and propranolol case using Daubechies 4 as mother wavelet.
4. There is a significant difference between the means of HF/total of baseline and HF/total of atropine while the means of HF/total of baseline and propranolol were not significantly different.
5. Haar wavelet and Daubechies 4 wavelets are used most of the time as mother wavelets and considered to be well suited for analysis of HRV. In this study Daubechies 2 wavelet was used to check the correlation. Although some results were quite close, but still Daubechies 2 wavelet did not show good results for HRV analysis. Out of the five rats, two showed a negative correlation between baseline and atropine. Also three rats out of the five showed a positive correlation between baseline and propranolol.

6. Correlation coefficient and analysis of variance were performed on individual rats, and they showed consistent difference for rats injected with atropine and propranolol. The results also showed that it was difficult to observe a consistent difference across rats. Among the seven sets of rats studied, only one set showed a consistent difference. This shows that the effects of atropine and propranolol depend on individual rats and hence cannot be generalized among rats.

### **Discussion and Future Work**

1. Mean HF/total

The mean HF/total for the baseline case was below 0.56 for all rats while that for atropine case was above 0.6 for four of the five rats using Daubechies 4 wavelet. This is because the high frequency energy is higher for atropine case, which results in faster heart rate. For propranolol, some rats had below 0.56 while some rats had above 0.56. They are close to the baseline case as propranolol activates the parasympathetic nervous system, which causes the heart rate to decrease and stay close to the baseline case.

2. Missing heart beats

It has been seen in rats that sometimes there is no heart beat for a few seconds. Figure 5.3 shows the original EKG and R-wave peaks and Figure 5.4 shows the RR tachogram, and the heart rate for Rat 5. It can be seen that for a period

of 5 seconds there is no heartbeat, and this can be seen as a big spike in the RR tachogram. Further study needs to be done to exactly quantify this effect.

3. Although it should be expected that the high frequency energy for a rat injected with atropine should be higher compared to that of a baseline case, which reflects as an increased heart rate, Rat 123 did not show this difference as seen in Figure 5.1 (Rats numbered 1 through 5 are Rat 2, Rat 5, Rat 122, Rat 123 and Rat 124 respectively). The P value (0.8385) confirmed that there was no significant difference between the means of HF/total of baseline case and atropine case. This could perhaps be because of a lag in the recording times of when the rat was injected with atropine and when the actual recording of EKG took place. Figure 5.2 shows the variability power of baseline and propranolol in different rats. Rat numbers 1 through 5 are Rat 2, Rat 5, Rat 122, Rat 123 and Rat 124 respectively).

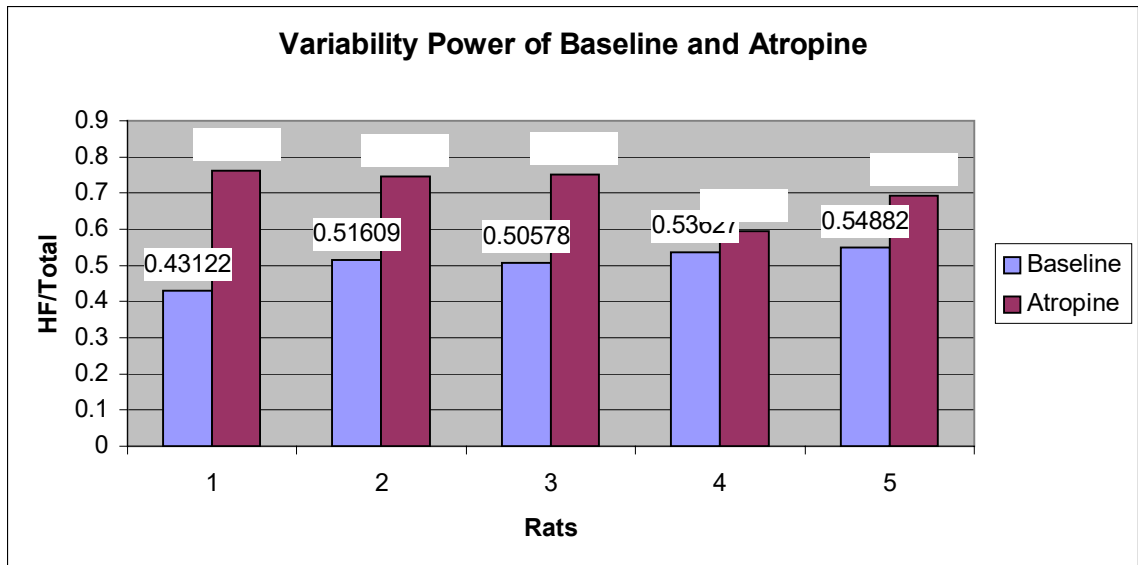


Figure 5.1 Variability power of baseline and atropine in different rats

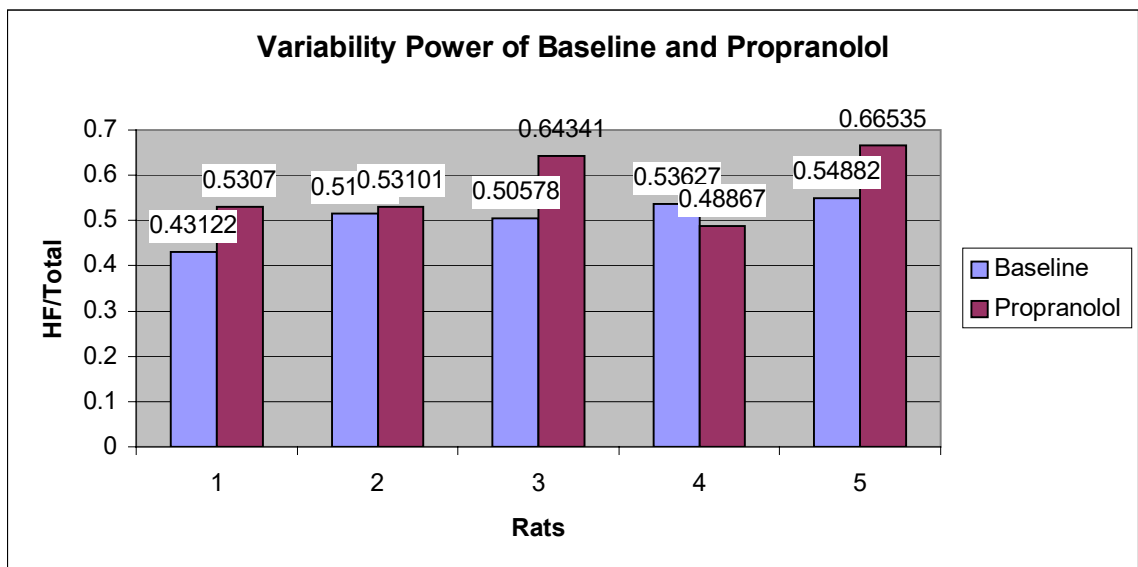


Figure 5.2 Variability power of baseline and propranolol in different rats

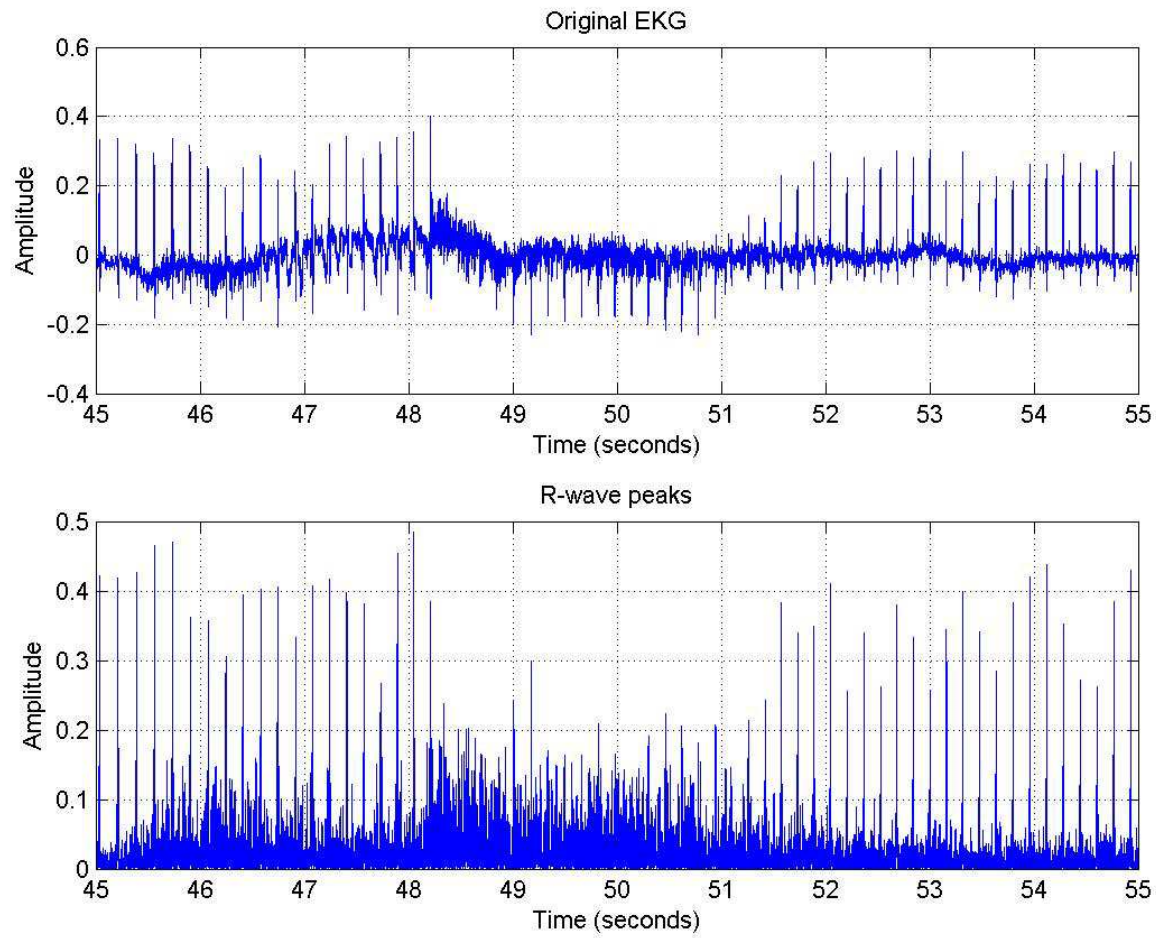


Figure 5.3: Original EKG and R-wave peaks of Rat 5 for baseline case with missing heart beats.

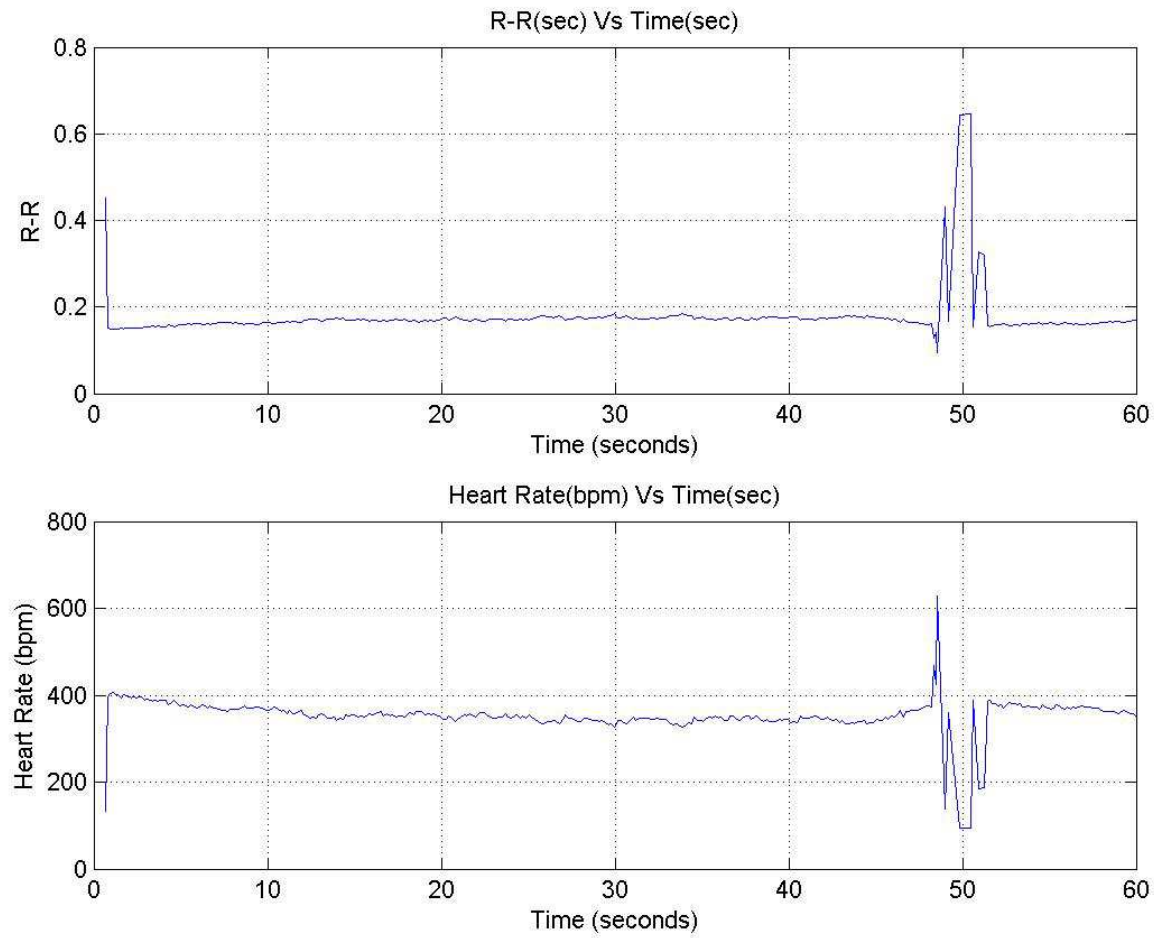


Figure 5.4: RR tachogram and Heart rate of Rat 2 for baseline case with missing heart beats.

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APPENDIX A

QRS DETECTION ALGORITHM IMPLEMENTED IN

MATLAB

```
M = dlmread('c:\data\Rat5\atrop+prop\Rat 5 EKG atro 9Feb04\Rat 5 EKG atro 9Feb04
seg00.txt','');

len_M = length(M);

t1 = [M(1):0.0002:M(len_M)];

t = t1';

a = M(:,2);

%Plotting the original ECG

figure(1);set(1,'Name','Original EKG & R Peaks');

subplot(2,1,1);plot(t,a);

xlabel('Time (seconds)')      % Label x-axis

ylabel('Amplitude')          % Label y-axis

grid

limit = (length(a));

len = limit-4;
```

```
for b = 1:len
    s1(b)=0;
end
s=s1';

s(1) = -2*a(1)-a(2)+a(4)+2*a(5);

sth_temp = 0.6 * abs(s);
sth = sth_temp(1);

max_count=1;
count_s=1;
count=0;
i=3;
while i <= len
    if abs(s(i-2)) > sth
        for j = i:i+7
            s(j-1) = -2*a(j-2)-a(j-1)+a(j+1)+2*a(j+2);
            temp_s(count_s) = s(j-1);
```

```

    count_s = count_s+1;
end

maxi_temp(max_count) = max(abs(temp_s));
max_count = max_count+1;

for zerotemp_s = 1:count_s-1
    temp_s(zerotemp_s)=0;
end

i=j+1;
maxi (max_count) = max(abs(s));
temp1 = 0.6 * maxi (max_count);
if temp1 > 1.5 * maxi(max_count-1)
    sth = 1.5 * maxi(max_count-1);
else
    sth = 0.6 * temp1;
end

els

s(i-1) = -2*a(i-1)-a(i)+a(i+2)+2*a(i+3);

```

```
        i=i+1;
    end
end

%Finding max every 250 points.
k3=1;
k4=1;
index1=1;
count_s=1;
while k3 < length(s)
    for k4 = k3:k3+249
        if k4 > length(s),break,end
        temp_s1(count_s) = abs(s(k4));
        count_s=count_s+1;
    end
    k3=k4;
    maxi_temp3(index1) = max(temp_s1);

    if maxi_temp3(index1) < 0.2
```

```
    maxi_temp3(index1) = 0;
else
    maxi_temp4(index1) = maxi_temp3(index1);
    index1=index1+1;
end

for zerotemp_s = 1:count_s-1
    temp_s1(zerotemp_s)=0;
end

count_s=1;
end

len_t2 = length(t);
temp_lim = t(len_t2)-0.0008;

t2=[M(1):0.0002:temp_lim];
t3 = t2';

len_s = length(s);
```

```
len_t3 = length(t3);

if len_t3 < len_s
    d1 = len_s - len_t3;
    start = M(1) - (0.0002 * d1);
elseif len_t3 > len_s
    d1 = len_t3 - len_s;
    start = M(1) + (0.0002 * d1);
else
    start = M(1);
end

t4=[start:0.0002:temp_lim];
t5 = t4';

subplot(2,1,2);
plot(t5,abs(s));
xlabel('Time (seconds)')      % Label x-axis

ylabel('Amplitude')         % Label y-axis
```



```
grid
```

```
cout=1;
```

```
coutl=1;
```

```
i1=1;
```

```
i2=1;
```

```
j1=1;
```

```
time=0;
```

```
dtloop=1;
```

```
dt=1;
```

```
dttemp=1;
```

```
dttempl=1;
```

```
s_max=abs(s);
```

```
s_maxl=s_max';
```

```
len_maxitemp4=length(maxi_temp4);
```

```
disp(len_maxitemp4);
```

```
while i1 < len_maxitemp4
```

```
if dtloop > len_s,break,end
if i1 > len_maxitemp4,break,end
if s_max1(dtloop) == maxi_temp4(i1)
    cout=cout+1;
    j1=j1+1;
    time(j1) = t5(dtloop);
    i1=i1+1;
    dttemp(i1) = time(j1) - time(j1-1);

    if dttemp(i1) < 0.0700
        cout1=cout1+1;
        dttemp(i1)=0;
        time(j1)=time(j1-1);
    else
        dttemp1(i2) = dttemp(i1);
        i2=i2+1;
        t6(j1) = time(j1);
    end
end
dtloop = dtloop+1;
```

```
end
```

```
%dt has just the RR values.
```

```
for i2 = 2:length(dttemp1)
```

```
    dt(i2-1) = dttemp1(i2);
```

```
    bpm(i2-1) = 60/dt(i2-1);
```

```
end
```

```
%Mean RR
```

```
mu_dt = mean(dt);
```

```
disp('Mean RR');
```

```
disp(mu_dt);
```

```
i2=1;
```

```
for i1 = 3:length(t6)
```

```
    if t6(i1) == 0
```

```
        %t6(i1) = t6(i1);
```

```
    else
```

```
        t7(i2) = t6(i1);
```

```
        i2=i2+1;
```

```

    end
end

len_t7=length(t7);
len_dt=length(dt);
t10=len_t7-1;
dt2=len_dt-1;
check1=0;

%Plotting the RR Tachogram
if length(t7) > length(dt)
    check1=1;
    t9=t7(1:t10);
    figure(2);set(2,'Name','RR & BPM');
    subplot(2,1,1);plot(t9,dt);
    xlabel('Time (seconds)')      % Label x-axis
    ylabel('R-R')                % Label y-axis
    grid
elseif length(dt)>length(t7)
    dt1=dt(1:dt2);

```

```

figure(2);set(2,'Name','RR & BPM');

subplot(2,1,1);plot(t9,dt1);

xlabel('Time (seconds)')      % Label x-axis
ylabel('R-R')                % Label y-axis

grid

else

%Plotting the RR Tachogram

figure(2);set(2,'Name','RR & BPM');

subplot(2,1,1);plot(t7,dt);

xlabel('Time (seconds)')      % Label x-axis
ylabel('R-R')                % Label y-axis

grid

end

%BPM plot

if length(t7) > length(bpm)

subplot(2,1,2);plot(t9,bpm);

xlabel('Time (seconds)')      % Label x-axis
ylabel('Heart Rate (bpm)')    % Label y-axis

```

```

    grid
else
    subplot(2,1,2);plot(t7,bpm);
    xlabel('Time (seconds)')      % Label x-axis
    ylabel('Heart Rate (bpm)')    % Label y-axis
    grid;
end

%Sampling the RR Tachogram data with Linear Interpolation
len_t7 = length(t7);

t8 = t7;

if check1==1
    t11 = t9;

    interp1(t11,dt,t9(t10)-0.3);
    x=t9(1):0.1:t9(t10)+0.1;
    y=interp1(t11,dt,x,'linear');
else

```

```

    interp1(t8,dt,t7(len_t7)-0.3);
    x=t7(1):0.1:t7(len_t7)+0.1;
    y=interp1(t8,dt,x,'linear');
end

%Applying Discrete Wavelet Transform using DAUBECHIES 4 as Mother Wavelet.
[cA,cD] = dwt(y,'db4');

l_a = length(a);

A1 = upcoef('a',cA,'db4',1,l_a);
D1 = upcoef('a',cD,'db4',1,l_a);

%subplot(5,1,2); plot(A1); title('Approximation A1');

%subplot(5,1,3); plot(D1); title('Detail D1');

%Decomposing the R-R at level 7.
[C,L] = wavedec(y,7,'db4');

```

```
cA7 = appcoef(C,L,'db4',7);
```

```
[cD1,cD2,cD3,cD4,cD5,cD6,cD7] = detcoef(C,L,[1,2,3,4,5,6,7]);
```

```
check1=0;
```

```
cD11=cD1(1:(length(cD1)-7));
```

```
cD12=cD11';
```

```
cD13=cD11*cD12;
```

```
cD21=cD2(1:(length(cD2)-7));
```

```
cD22=cD21';
```

```
cD23=cD21*cD22;
```

```
cD31=cD3(1:(length(cD3)-7));
```

```
cD32=cD31';
```

```
cD33=cD31*cD32;
```

```
cD41=cD4(1:(length(cD4)-7));
```

```
cD42=cD41';
```



```
cD43=cD41*cD42;
```

```
cD51=cD5(1:(length(cD5)-7));
```

```
cD52=cD51';
```

```
cD53=cD51*cD52;
```

```
cD61=cD6(1:(length(cD6)-7));
```

```
cD62=cD61';
```

```
cD63=cD61*cD62;
```

```
cD71=cD7(1:(length(cD7)-7));
```

```
cD72=cD71';
```

```
cD73=cD71*cD72;
```

```
var_test = isnan(cD13);
```

```
if var_test==1
```

```
    cD13=0;
```

```
end
```

```
var_test = isnan(cD23);
```

```
if var_test==1
    cD23=0;
end
var_test = isnan(cD33);
if var_test==1
    cD33=0;
end
var_test = isnan(cD43);
if var_test==1
    cD43=0;
end
var_test = isnan(cD53);
if var_test==1
    cD53=0;
end
var_test = isnan(cD63);
if var_test==1
    cD63=0;
end
var_test = isnan(cD73);
```

```

if var_test==1
    cD73=0;
end

high_var_power = cD13+cD23+cD33;
low_var_power = cD43+cD53+cD63;
total_var_power = cD13+cD23+cD33+cD43+cD53+cD63+cD73;
ratio_high = high_var_power/total_var_power;
ratio_low = low_var_power/total_var_power;

dlmwrite('c:\MATLAB6p5\work\Results\Rat5\atropop\9Feb04\mean_RR.xls',mu_dt);
dlmwrite('c:\MATLAB6p5\work\Results\Rat5\atropop\9Feb04\result_high.xls',high_var_
_power);

dlmwrite('c:\MATLAB6p5\work\Results\Rat5\atropop\9Feb04\result_low.xls',low_var_
power);

dlmwrite('c:\MATLAB6p5\work\Results\Rat5\atropop\9Feb04\result_total.xls',total_var_
_power);

dlmwrite('c:\MATLAB6p5\work\Results\Rat5\atropop\9Feb04\result_ratio_high.xls',rati
o_high);

```

```
dlmwrite('c:\MATLAB6p5\work\Results\Rat5\atropop\9Feb04\result_ratio_low.xls',ratio_low);
```

```
%Applying Discrete Wavelet Transform using DAUBECHIES 2 as mother wavelet.
```

```
[cAA,cDD] = dwt(y,'db2');
```

```
l_a = length(a);
```

```
AA1 = upcoef('a',cAA,'db2',1,l_a);
```

```
DD1 = upcoef('a',cDD,'db2',1,l_a);
```

```
%Decomposing the R-R at level 7.
```

```
[C1,L1] = wavedec(y,7,'db2');
```

```
cAA7 = appcoef(C1,L1,'db2',7);
```

```
[cDD1,cDD2,cDD3,cDD4,cDD5,cDD6,cDD7] = detcoef(C1,L1,[1,2,3,4,5,6,7]);
```

```
check1=0;
```

```
cDD11=cDD1(1:(length(cDD1)-7));
```

cDD12=cDD11';

cDD13=cDD11\*cDD12;

cDD21=cDD2(1:(length(cDD2)-7));

cDD22=cDD21';

cDD23=cDD21\*cDD22;

cDD31=cDD3(1:(length(cDD3)-7));

cDD32=cDD31';

cDD33=cDD31\*cDD32;

cDD41=cDD4(1:(length(cDD4)-7));

cDD42=cDD41';

cDD43=cDD41\*cDD42;

cDD51=cDD5(1:(length(cDD5)-7));

cDD52=cDD51';

cDD53=cDD51\*cDD52;

```
cDD61=cDD6(1:(length(cDD6)-7));
```

```
cDD62=cDD61';
```

```
cDD63=cDD61*cDD62;
```

```
cDD71=cDD7(1:(length(cDD7)-7));
```

```
cDD72=cDD71';
```

```
cDD73=cDD71*cDD72;
```

```
var_test = isnan(cDD13);
```

```
if var_test==1
```

```
    cDD13=0;
```

```
end
```

```
var_test = isnan(cDD23);
```

```
if var_test==1
```

```
    cDD23=0;
```

```
end
```

```
var_test = isnan(cDD33);
```

```
if var_test==1
```

```
    cDD33=0;
```

end

var\_test = isnan(cDD43);

if var\_test==1

    cDD43=0;

end

var\_test = isnan(cDD53);

if var\_test==1

    cDD53=0;

end

var\_test = isnan(cDD63);

if var\_test==1

    cDD63=0;

end

var\_test = isnan(cDD73);

if var\_test==1

    cDD73=0;

end

high\_var\_power = cDD13+cDD23+cDD33;

```

low_var_power = cDD43+cDD53+cDD63;
total_var_power = cDD13+cDD23+cDD33+cDD43+cDD53+cDD63+cDD73;
ratio_high = high_var_power/total_var_power;
ratio_low = low_var_power/total_var_power;

%dlmwrite('c:\MATLAB6p5\work\Results\Rat2\baseline\3Feb04\mean_RR1.xls',mu_dt)
;
dlmwrite('c:\MATLAB6p5\work\Results\Rat5\atroprop\9Feb04\result_high1.xls',high_var_power);
dlmwrite('c:\MATLAB6p5\work\Results\Rat5\atroprop\9Feb04\result_low1.xls',low_var_power);
dlmwrite('c:\MATLAB6p5\work\Results\Rat5\atroprop\9Feb04\result_total1.xls',total_var_power);
dlmwrite('c:\MATLAB6p5\work\Results\Rat5\atroprop\9Feb04\result_ratio_high1.xls',ratio_high);
dlmwrite('c:\MATLAB6p5\work\Results\Rat5\atroprop\9Feb04\result_ratio_low1.xls',ratio_low);

```



APPENDIX B  
PLOTS FOR VERIFYING THE QRS ALGORITHM AND RR  
INTERVALS

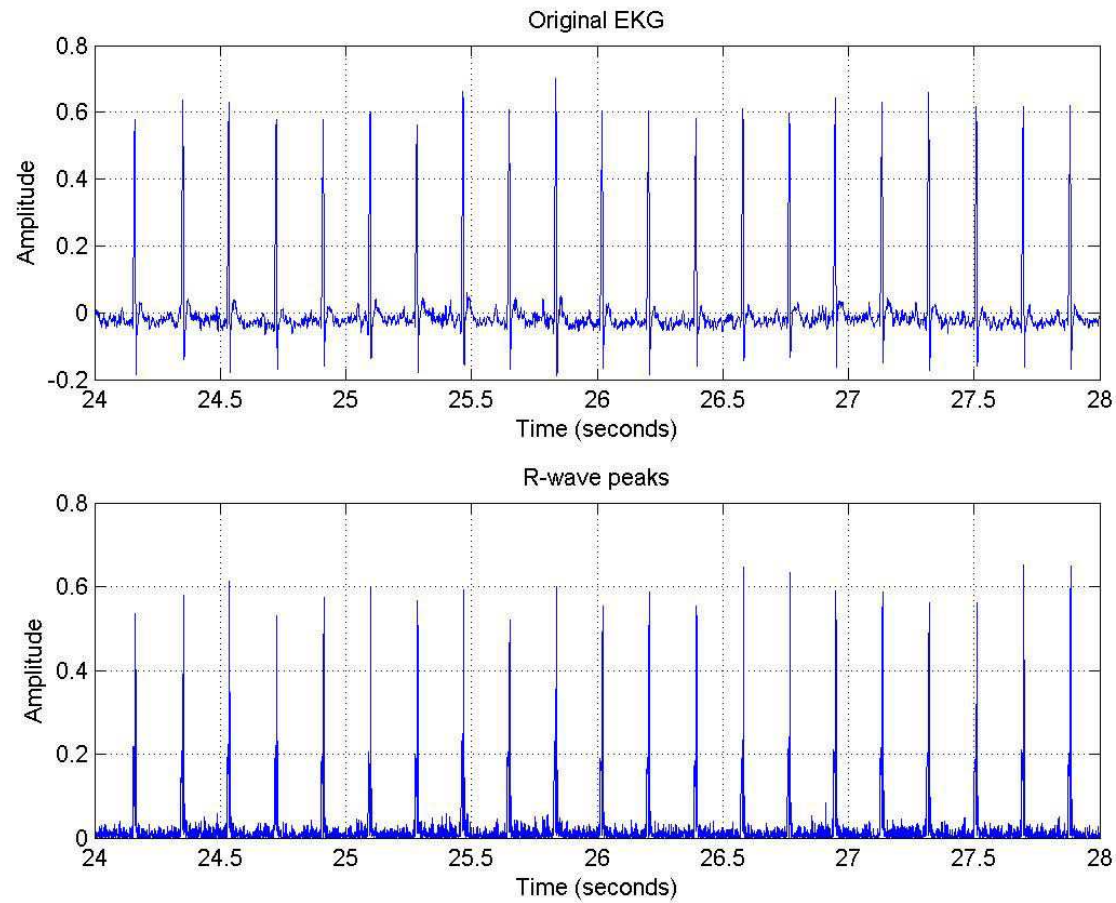


Figure B.1: Original EKG and R-wave peaks of Rat 2 for baseline case

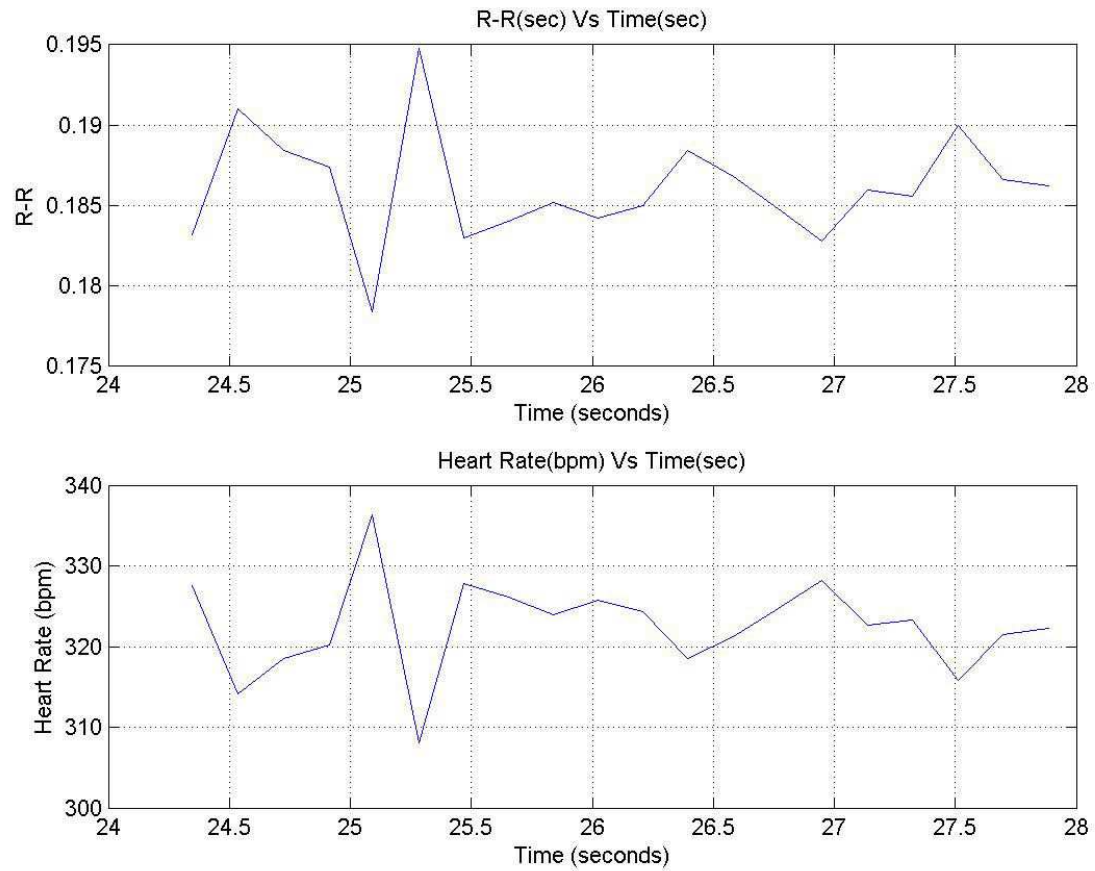


Figure B.2: RR tachogram and Heart rate of Rat 6 for baseline case

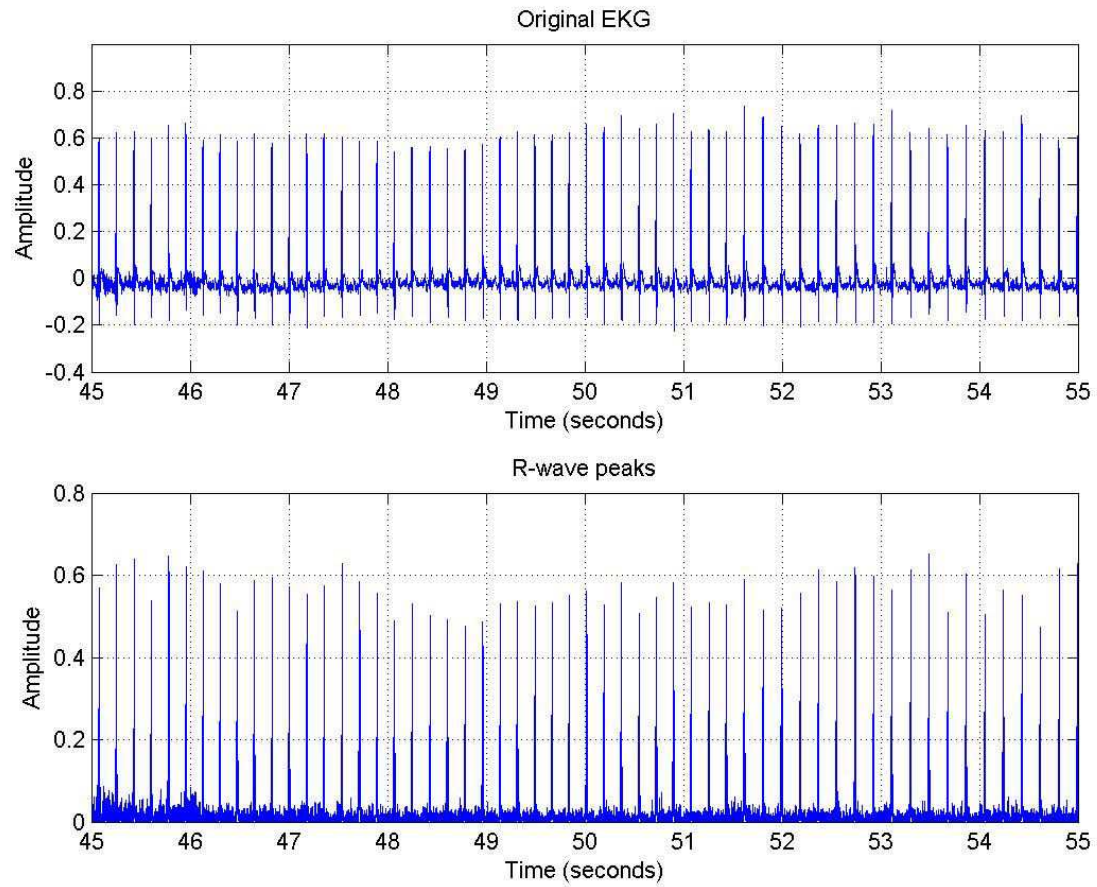


Figure B.3: Original EKG and R-wave peaks of Rat 2 for baseline case

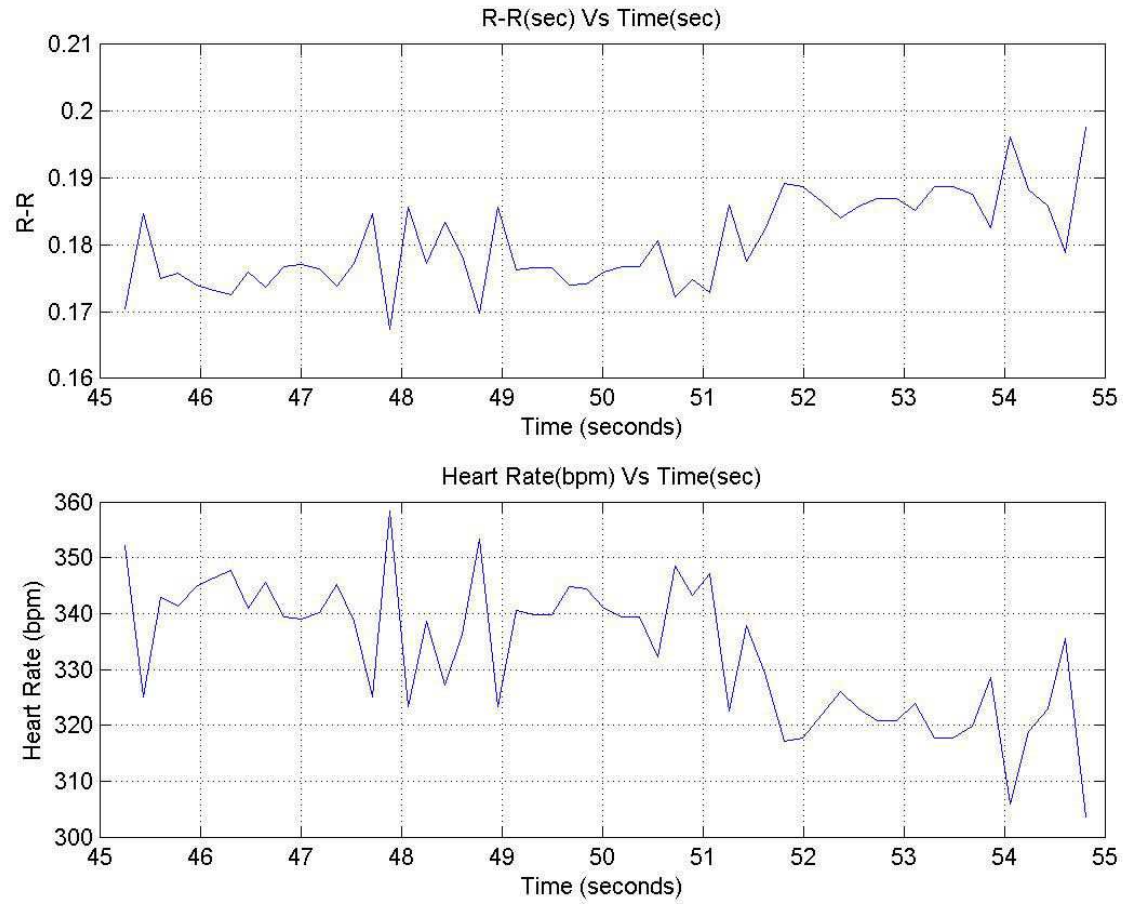


Figure B.4: RR tachogram and Heart rate of Rat 2 for baseline case

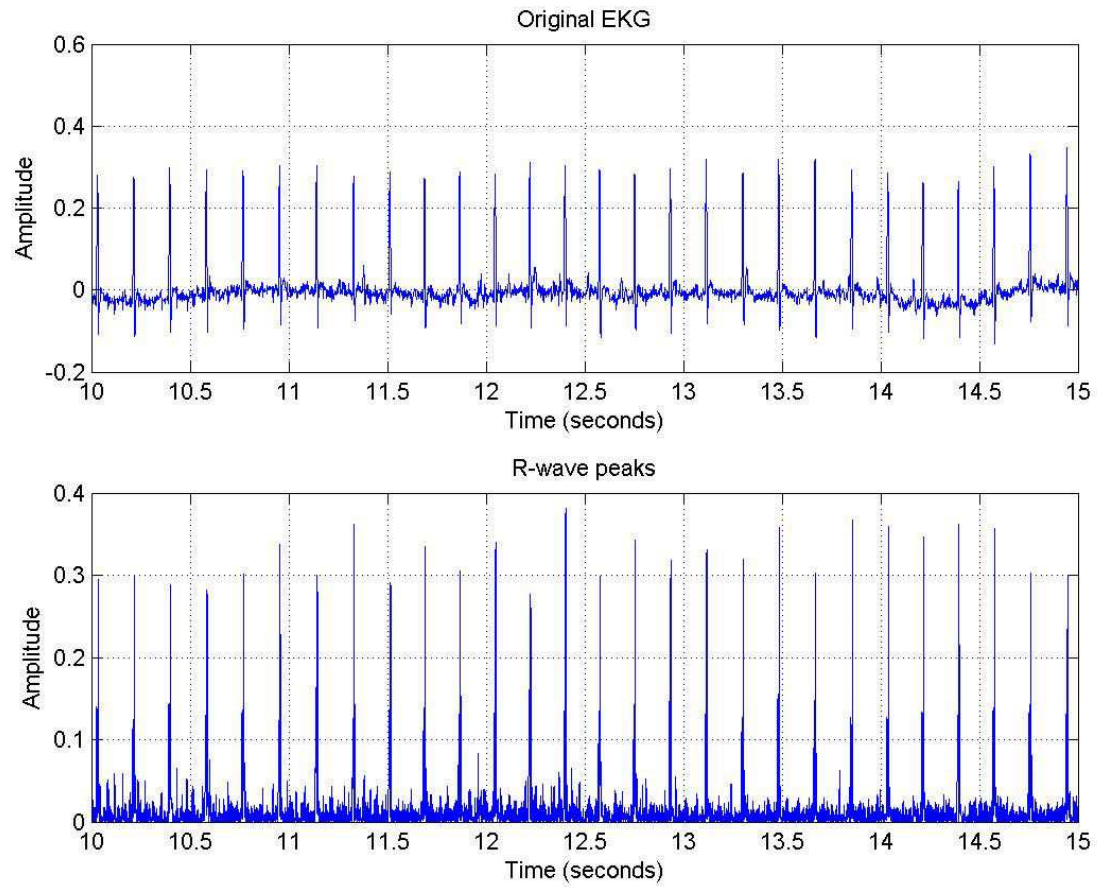


Figure B.5: Original EKG and R-wave peaks of Rat 2 for baseline case

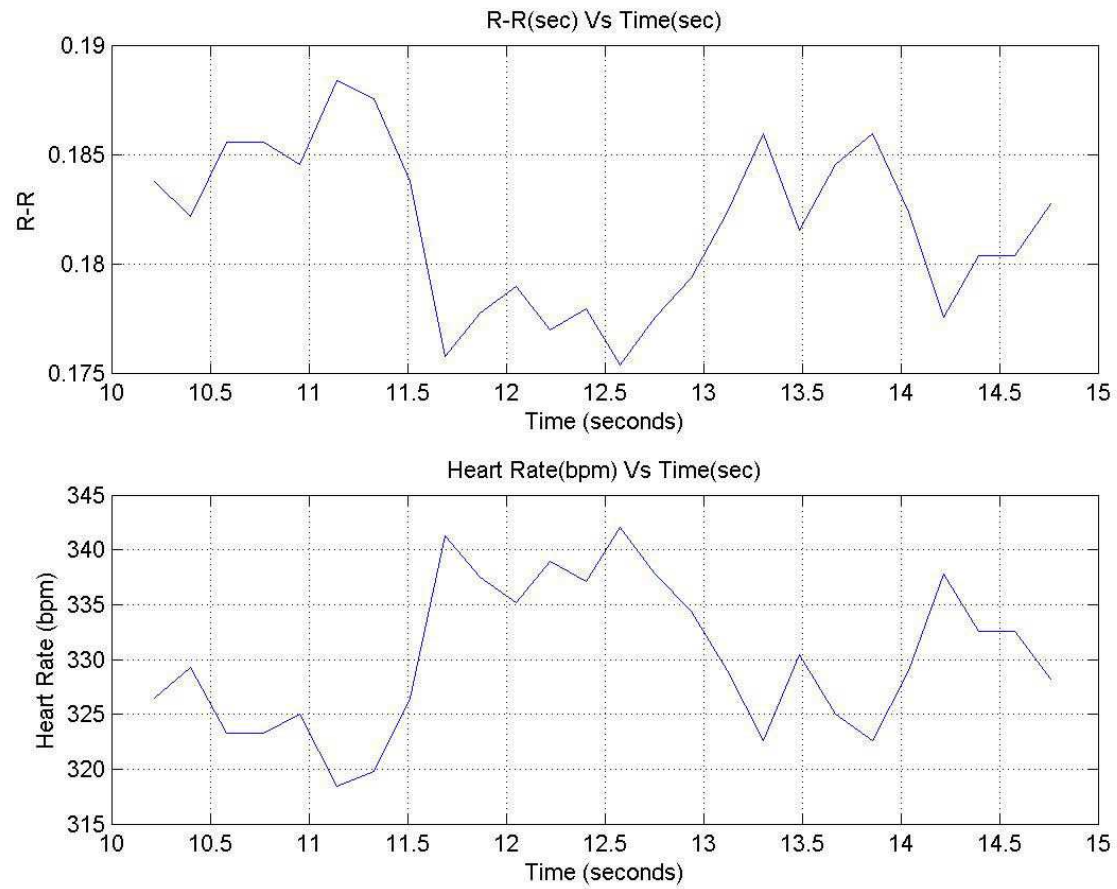


Figure B.6: RR tachogram and Heart rate of Rat 2 for baseline case



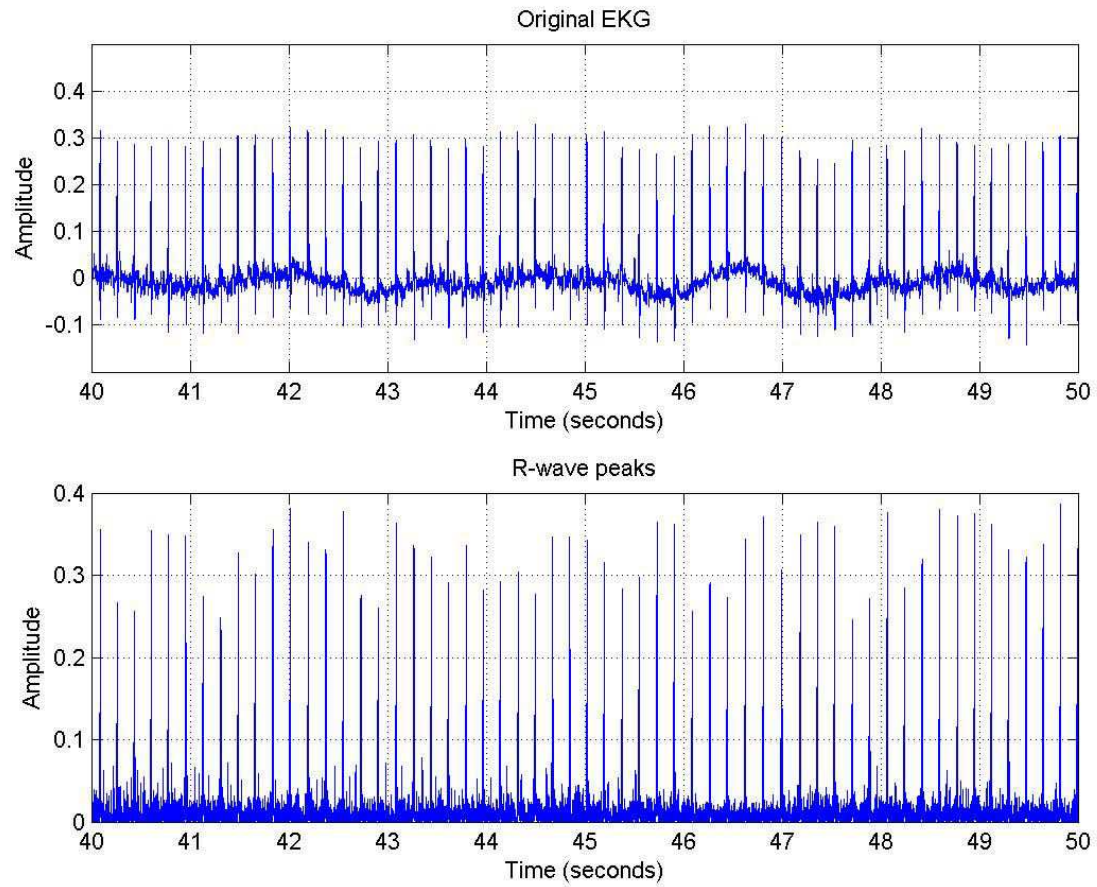


Figure B.7: Original EKG and R-wave peaks of Rat 2 for baseline case



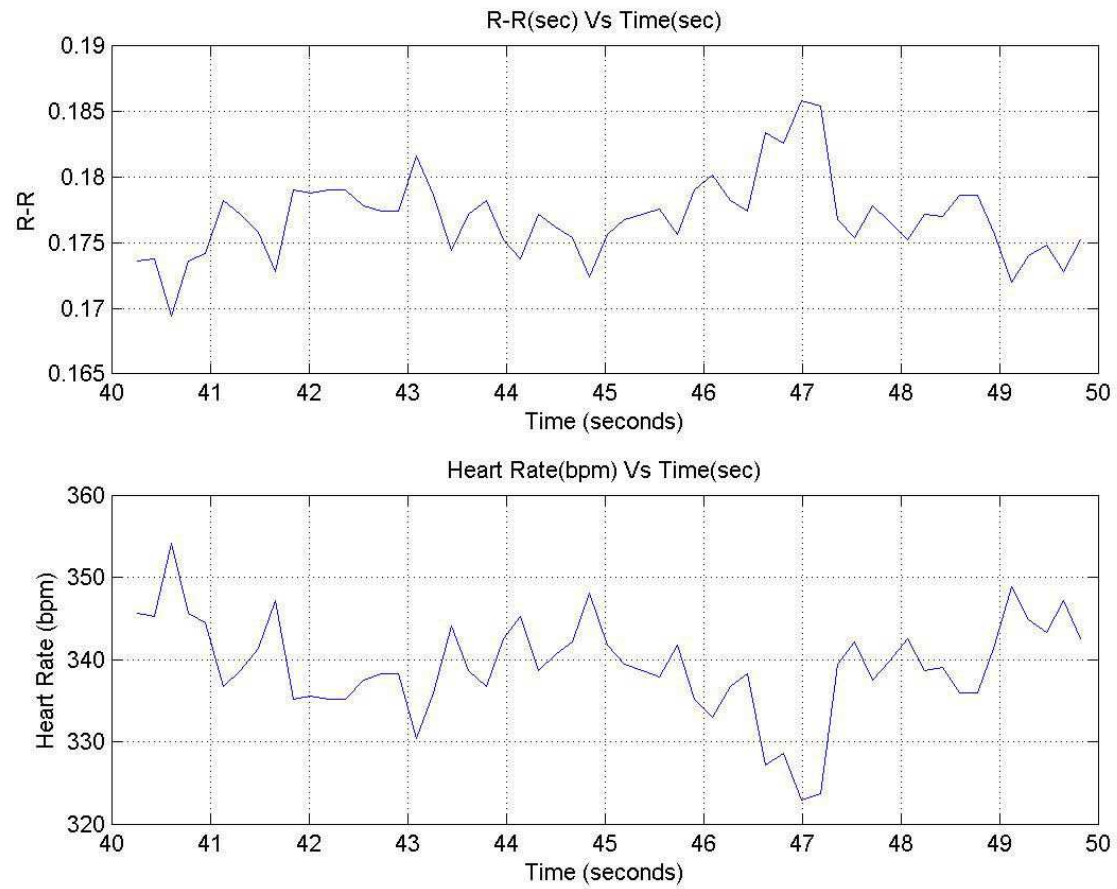


Figure B.8: RR tachogram and Heart rate of Rat 2 for baseline case

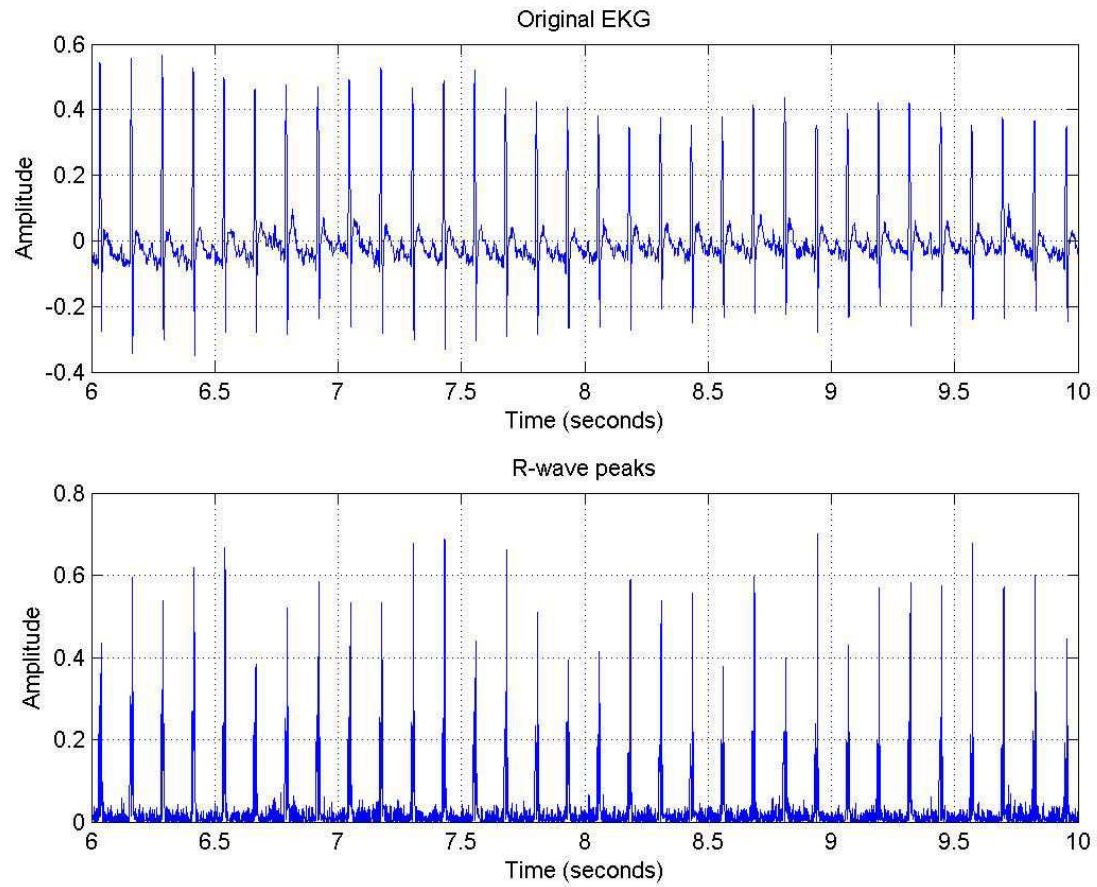


Figure B.9: Original EKG and R-wave peaks of Rat 2 for atropine case

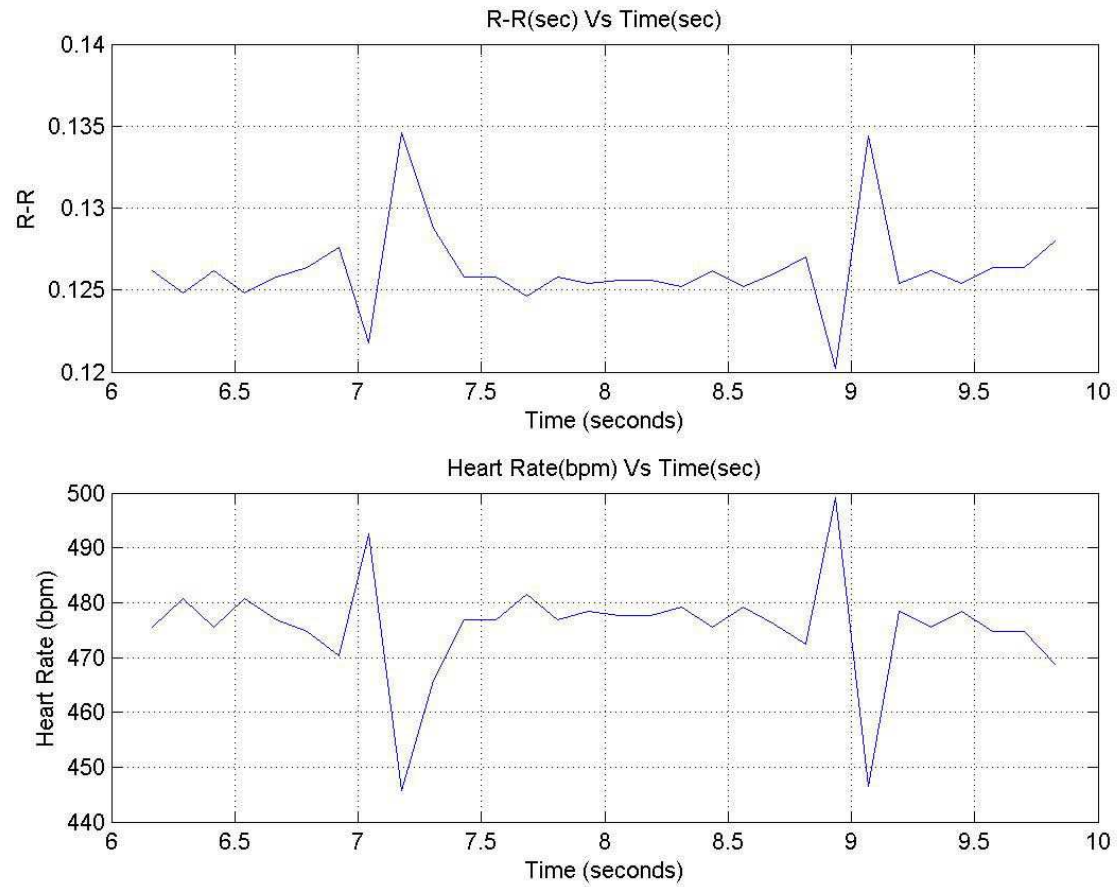


Figure B.10: RR tachogram and Heart rate of Rat 2 for atropine case

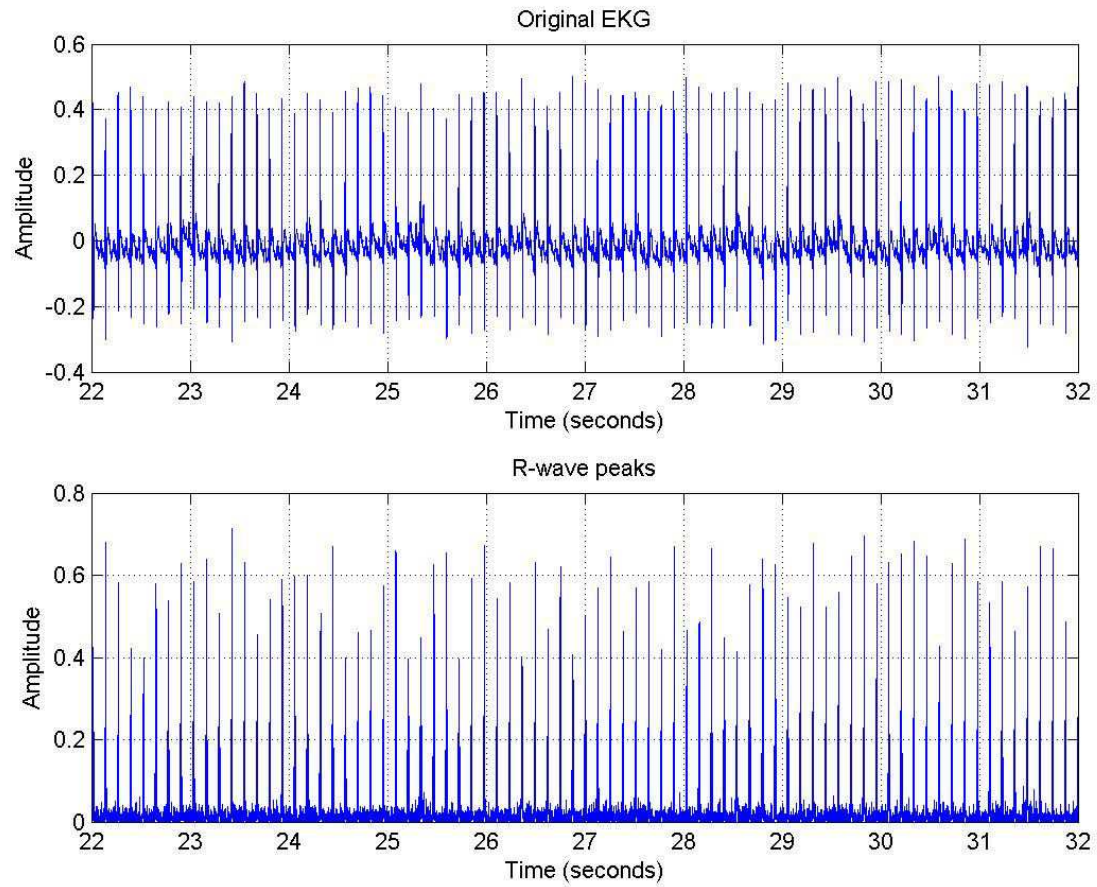


Figure B.11: Original EKG and R-wave peaks of Rat 2 for atropine case

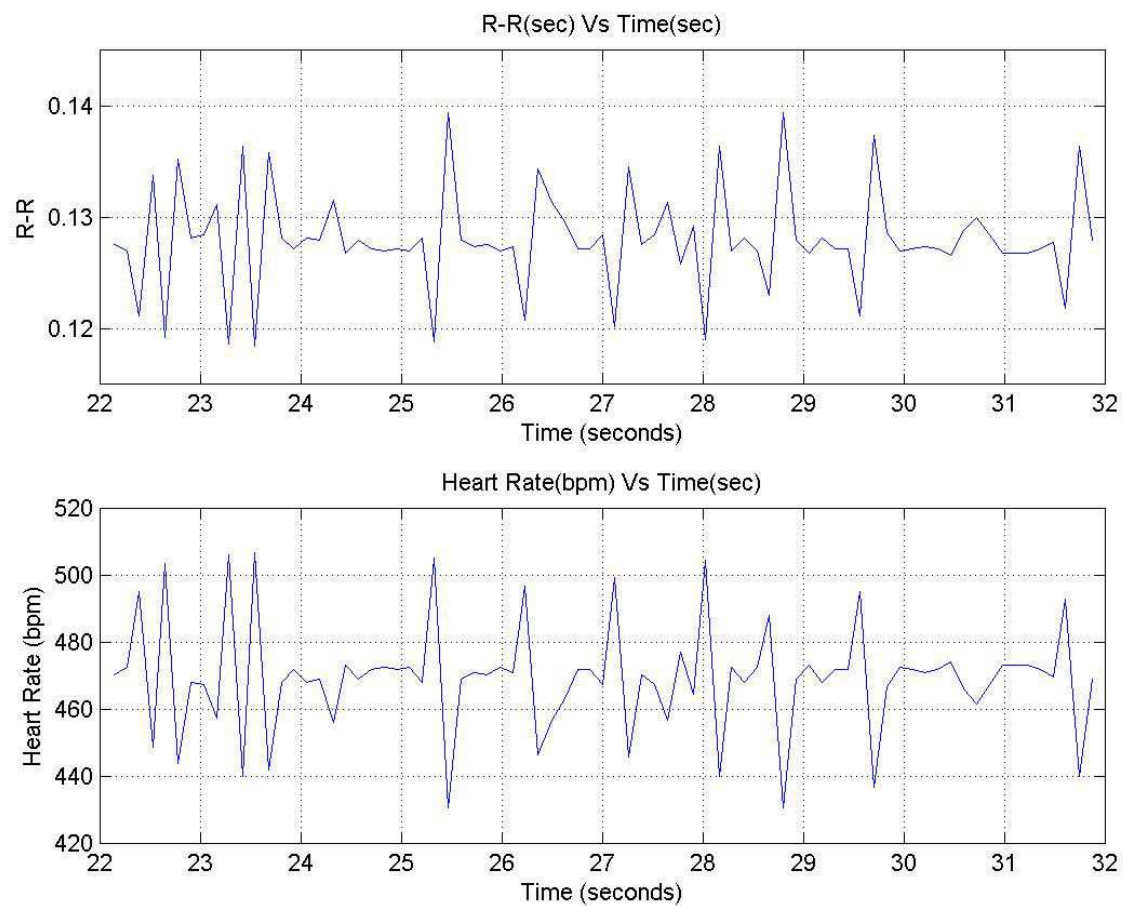


Figure B.12: RR tachogram and Heart rate of Rat 2 for atropine case

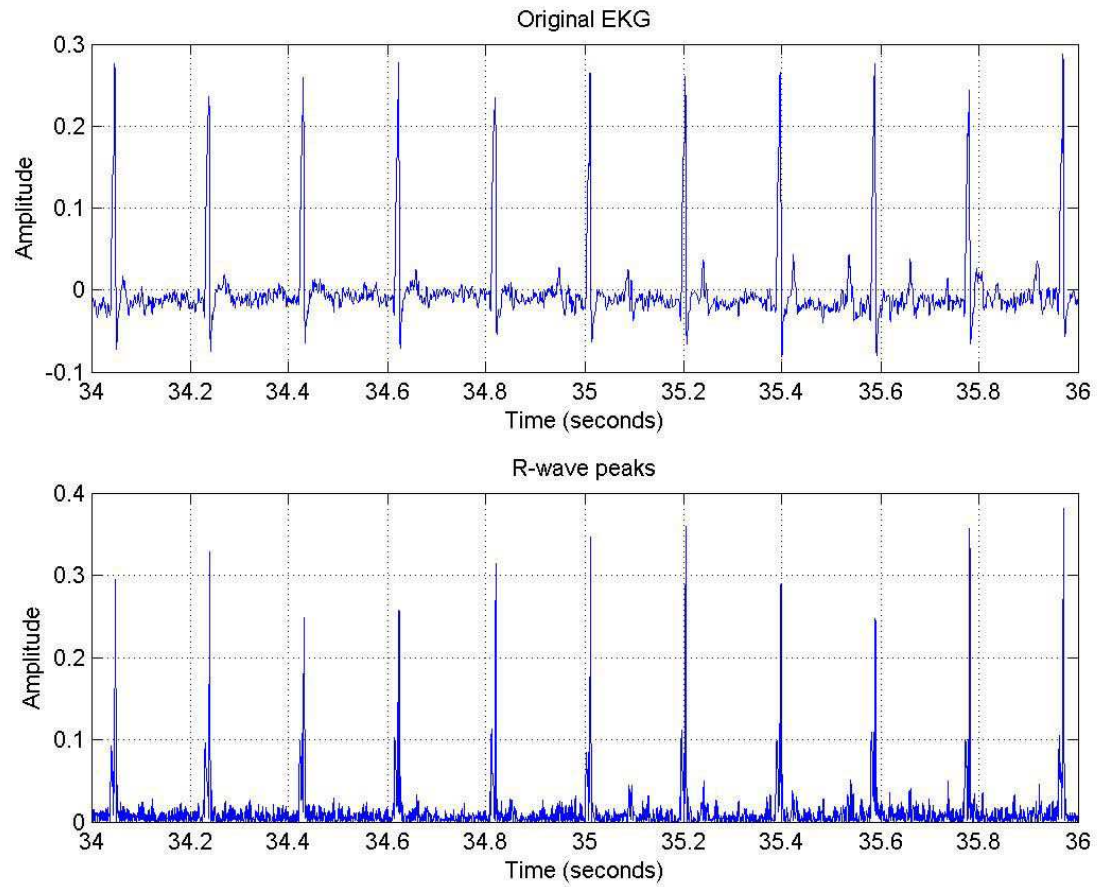


Figure B.13: Original EKG and R-wave peaks of Rat 5 for propranolol case



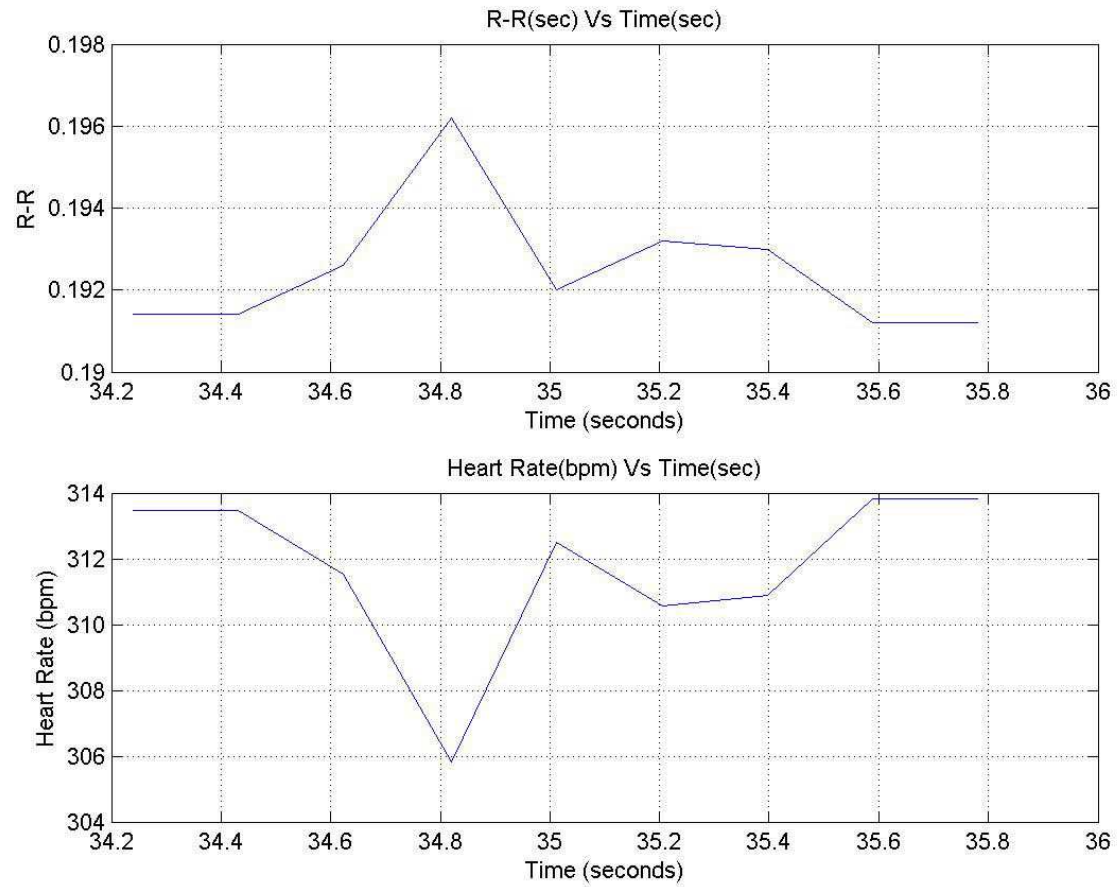


Figure B.14: RR tachogram and Heart rate of Rat 5 for propranolol case

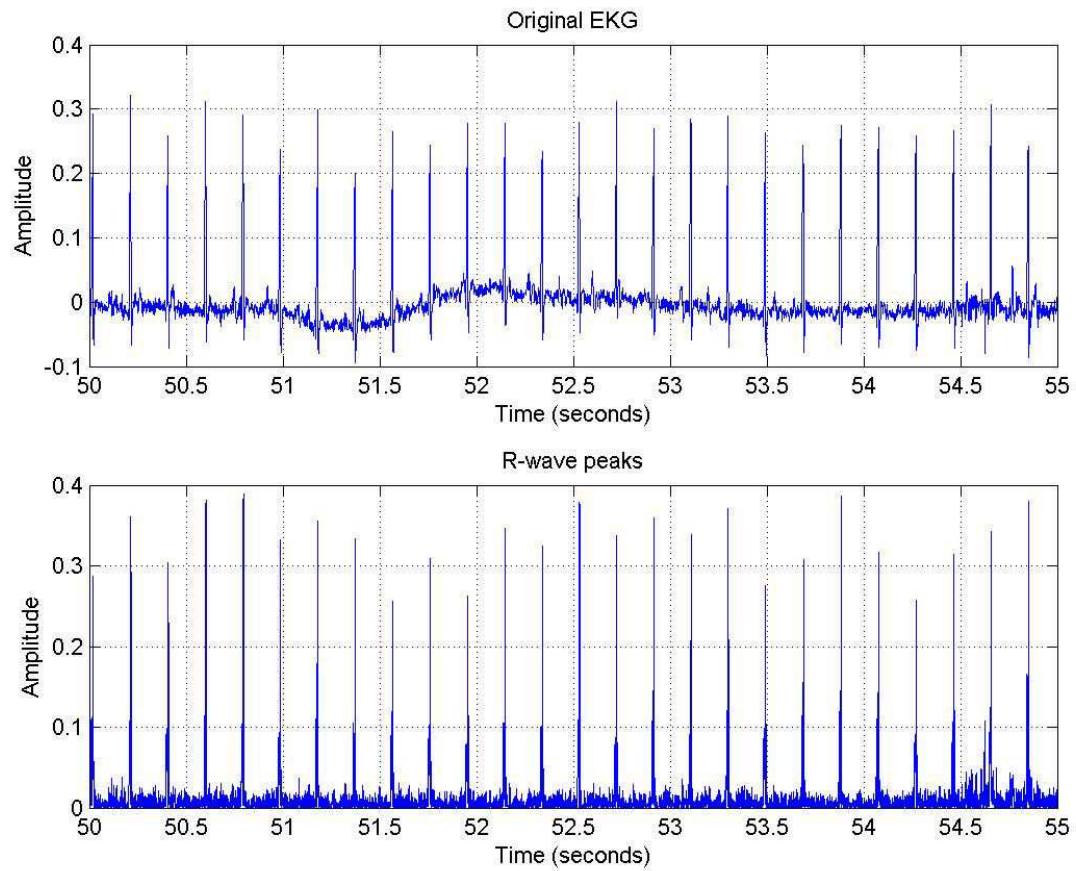


Figure B.15: Original EKG and R-wave peaks of Rat 5 for propranolol case



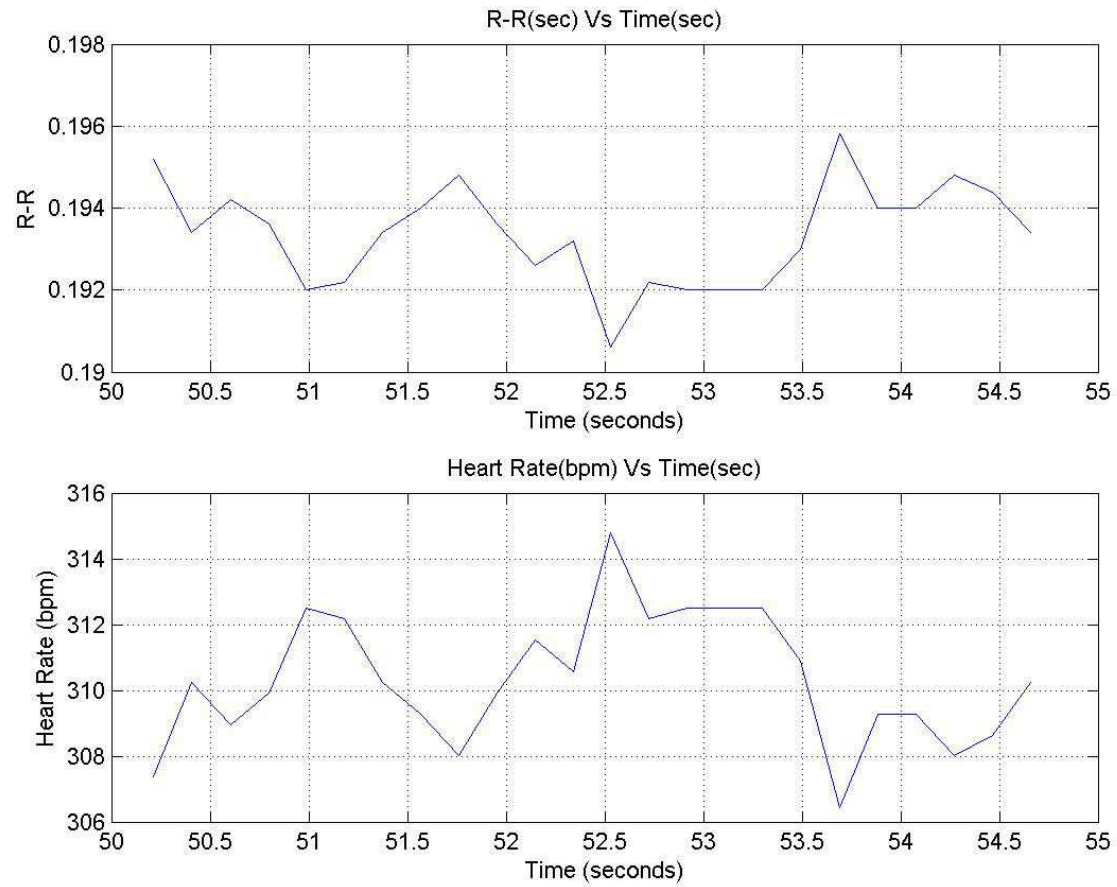


Figure B.16: RR tachogram and Heart rate of Rat 5 for propranolol case