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Heart Rate Variability in Preterm Infants

Final Report

ECSE 456 – DP #44

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Abstract

Extremely preterm infants, born with a gestational age of under 28 weeks, have underdeveloped respiratory systems and almost all require mechanical ventilation during their first days after birth [2]. However, the time at which the babies are extubated is critical, as removing the tube too soon ultimately leads to re-intubation which itself is associated with complications. On the other hand, prolonged MV is also associated with negative effects, risking permanent respiratory damage. The overall goal is to build a program, APEX, capable of collecting cardiorespiratory as well as clinical data and analyzing the signals using machine learning methods to predict extubation readiness. Our ECSE 456 project focuses on the analysis of heart rate and has for objectives to implement a noise-robust algorithm to detect the heart rate from ECG signals and provide a package for heart rate variability analysis. In this work, we developed a noise-robust, fully functional pipeline on MATLAB which takes as input any .mat electrocardiogram signal and outputs its heart rate. We tested our software on data collected by the APEX research team, as well as on annotated datasets, for which we obtained results of 95.92% Sensitivity, 99.91% Positive Predictivity and 95.83% Accuracy. Our entire source code has been open sourced on Github.

List of abbreviations:

- NICU: Neonatal Intensive Care Unit
- MV: Mechanical Ventilation
- GA: Gestational Age
- BPD: Bronchopulmonary Dysplasia
- APEX: Automated Predictor of Extubation Readiness
- ECG: Electrocardiogram
- HR: Heart Rate
- HRV: Heart Rate Variability
- IBI: Inter-Beat Interval
- BPM: Beats Per Minute
- P&T: Pan and Tompkins
- GUI: Graphical User Interface
- MAD: Median Absolute Deviation
- HRVAS: Heart Rate Variability Analysis Software

1 Introduction/Motivations

1.1 Preterm Infants & MV

Approximately 15,000 infants are admitted to neonatal intensive care units (NICU) in Canada each year, 11% of these infants are extremely preterm (≤ 28 weeks gestational age). Of the infants born with gestational age (GA) of 24 and 25 weeks, 99% and 95% respectively require mechanical ventilation (MV) [3]. Mechanical ventilation consists of a tube inserted in the trachea and a ventilator. The ventilator simulates natural airflow in order to provide air for the lungs, as shown in Figure 1. Although MV is lifesaving at first, prolonged MV has been correlated with numerous negative effects, including airway trauma, ventilator associated pneumonia, and bronchopulmonary dysplasia (BPD)[4]. BDP is the most serious morbidity as it is has been associated with long term respiratory damage and neurodevelopment impairment [5] and an important socio-economic burden [6]. The duration of MV strongly correlates with BPD risk; each additional week increases the odds of BDP by a factor of 2.7 [7]. For these reasons, clinicians attempt to minimize the length of MV as much as possible. However, extubating infants before they are ready is also harmful, as it leads to lung derecruitment and muscle fatigue, and ultimately reintubation. This is risky, as a recent study has shown that 40% of intubation were associated with adverse outcomes, such as injury to the upper airway and infection [8]. Extubation failure, defined as the need for reintubation, is the outcome for almost 50% of preterm infants requiring MV. As both prolonged MV and the need for reintubation are correlated with short and long-term damages, the overall goal is to reduce the time of MV while maximizing the chance of extubation success.

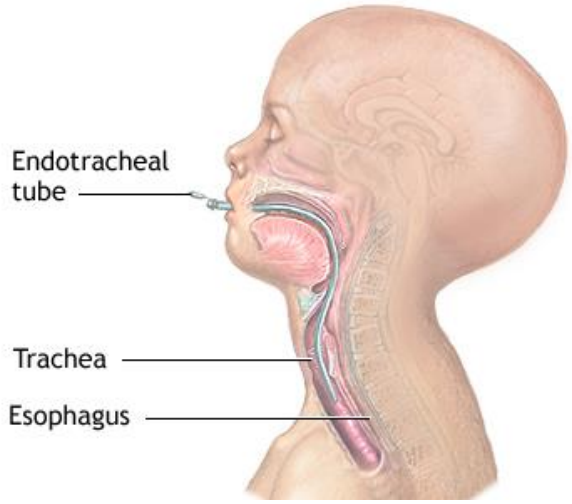


***Figure 1**: Schematic of endotracheal intubation. Mechanical ventilation involves inserting a tube down the patient's trachea to maintain adequate oxygenation and gas exchange. [9]*

Sections 1 to 5.1 are heavily based on material presented in last semester's report. We invite the interested reader to refer to it for further details on these sections. [10]

1.2 Current Procedures

The current procedures for determining extubation readiness are usually based on clinical judgement: personal experience and bedside observations of blood gases, oxygen requirements and ventilator settings [11]. There are significant practice variations as they are clinician-based instead of evidence based.

1.3 APEX

The overall goal of the project is to build a program, Automated Predictor of Extubation Readiness (APEX), to acquire cardiorespiratory and clinical data, and to perform data analysis using machine learning methods to predict extubation readiness.

A diagram of the process flow is shown in Figure 2. Cardiorespiratory data includes heart rate data, respiratory signals and pulse oximeter data. APEX will then classify the infants in three groups: success, failure, and uncertain.

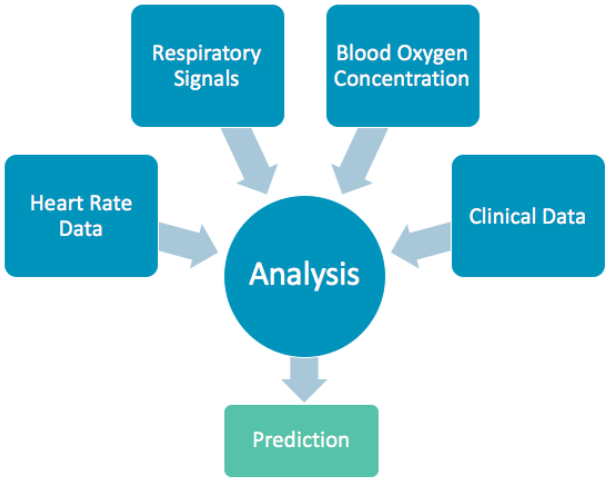


***Figure 2**: Representation of the APEX program, which collects cardiorespiratory and clinical data, analyzes them, and predicts extubation readiness.*

1.4 Our focus

The task that we are focused on in this overall project is the heart rate data. The goal of our project is to build a noise-robust algorithm capable of detecting the heart rate from electrocardiograms (ECG) signals of infants, to determine potential metrics to assess heart rate variability, and finally to evaluate those metrics as predictors for extubation readiness.

2 Background

2.1 Electrocardiograms

Electrocardiograms are a measure of the heart's electrical activity. As electrodes are placed on the patient's body, ECGs represent the depolarization and repolarization of the heart as it contracts to pump blood for the body. Three main events can be distinguished in a heartbeat: the P wave, the QRS complex (also called R wave), and the T wave, as shown in Figure 3 [12]. Due to their lower amplitude and lower signal to noise ratio (SNR), the detection of the P and T waves has not been as extensively investigated as the R peak. Our study therefore concentrates on detecting the R wave of ECG infants.

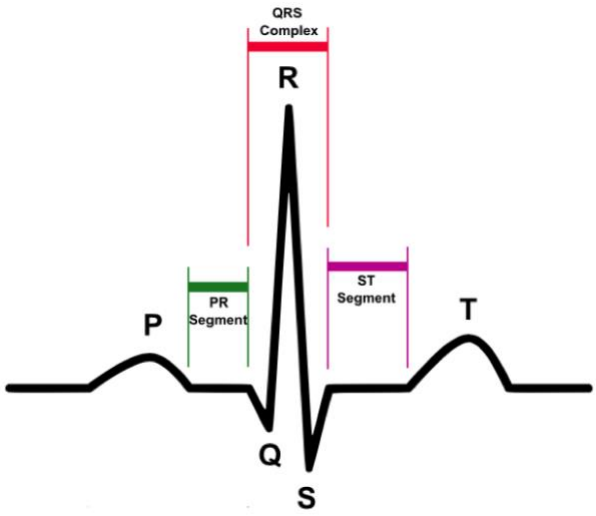


***Figure 3**: Electrocardiogram of a heartbeat, with the 3 main events (peaks): the P wave, the QRS complex, and the T wave. [1]*

2.2 Tachogram and Heart Rate Variability

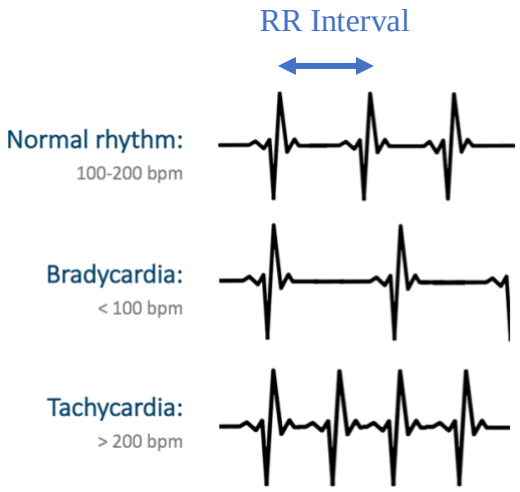


***Figure 4**: Heart rate comparing normal behavior and abnormal behavior (bradycardia and tachycardia), and their respective ranges in beats per minute.*

The collection of electrocardiogram signals is done by sampling the electrical potential between electrodes on the patient's chest at a frequency fs. The RR interval, or inter-beat interval (IBI), refers to the time interval between two successive R-peaks as a function of sample number. It is calculated as follows:

$$time\_interval[n] = Rtime\_sig[n+1] - Rtime\_sig[n], \quad (1)$$

where Rtime_$sig[n]$ corresponds to the time at the R_peak location at sample n. The time interval can be computed up to $n = length(sig) - 1$. The discrete heart rate (in beats per minute, or BPM) is calculated as follows:

$$heartRate[n] = 60 * \frac{fs}{interval[n]} \quad (2)$$

The tachogram corresponds to the continuous heart rate as a function of time, and it is thus inversely proportional to the RR interval (usually in milliseconds). An example of tachogram is shown in Figure 5. Here continuous refers to the fact that this is a signal with the same sampling frequency as the original collected signal. It is calculated by interpolating the heart rate values for all time points.

We used two main methods for interpolation:

- **Linear interpolation**: the values at each point are based on a linear interpolation of the values at the neighboring points in both directions.
- **Spline interpolation**: the values at each point are based on a cubic interpolation of the values at the neighboring points in both directions.

The heart rate ranges from approximately 100 to 200 bpm for infants. Heart rate varies often. Changes includes low heart rates (≤ 100 bpm), called bradycardia, and high heart rates (≥ 200 bpm), called tachycardia, both illustrated in Figure 4. Heart rate variability (HRV) refers to variations of the RR-interval, that cannot always be seen in the tachogram. Metrics are used to quantify heart rate variability, which can be measured in different ways:

- **Time domain**: various time domain measures and statistical analyses can be conducted on the heart rate signal. Some examples are listed below [13](NN refers to the interval between two waves of the same type, such as RR):
  - **Mean NN**: The mean of all NN intervals
  - **SDNN**: Standard deviation of all NN intervals
  - **RMSSD**: The square root of the mean of the sum of the squares of differences between adjacent NN intervals

- **SDNNi**: Mean of the standard deviations of all NN intervals differing by more than 50 ms in the entire recording
- **NNx**: Number of pairs of adjacent NN intervals differing by more than x ms in the entire recording
- **pNNx**: NNx count divided by the total number of NN intervals

- **Frequency domain**: A times series is often visualized as a set of discrete values as a function of time. However, the Fourier transform allows us to visualize the signal as a spectrum: the amplitude as a function of frequency. [13] Under appropriate conditions, this transform, and its inverse do not destroy information. The frequency domain analysis uses the tachogram as it needs a signal with a high sampling frequency to be effective. Some examples include:
  - VLF: Power in VLF range ($f \leq 0.04$ Hz)
  - LF: Power in LF range ($0.04 \leq f \leq 0.15$ Hz)
  - HF: Power in HF range (0.15 Hz $\leq f \leq 0.04$ Hz)

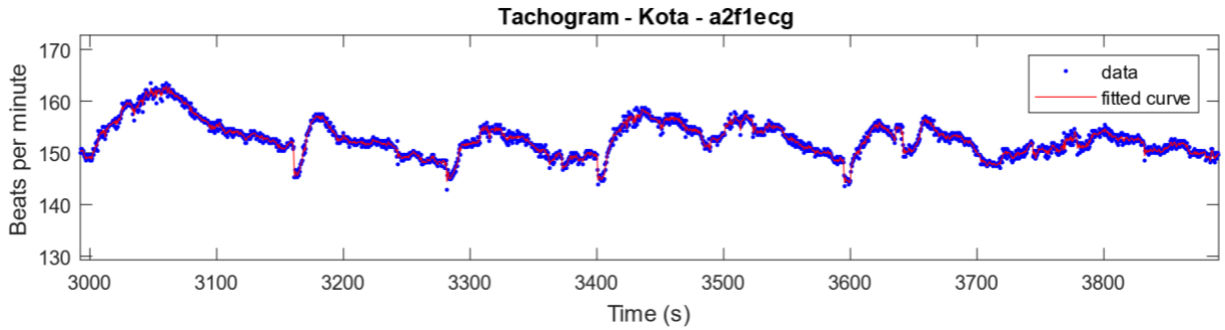
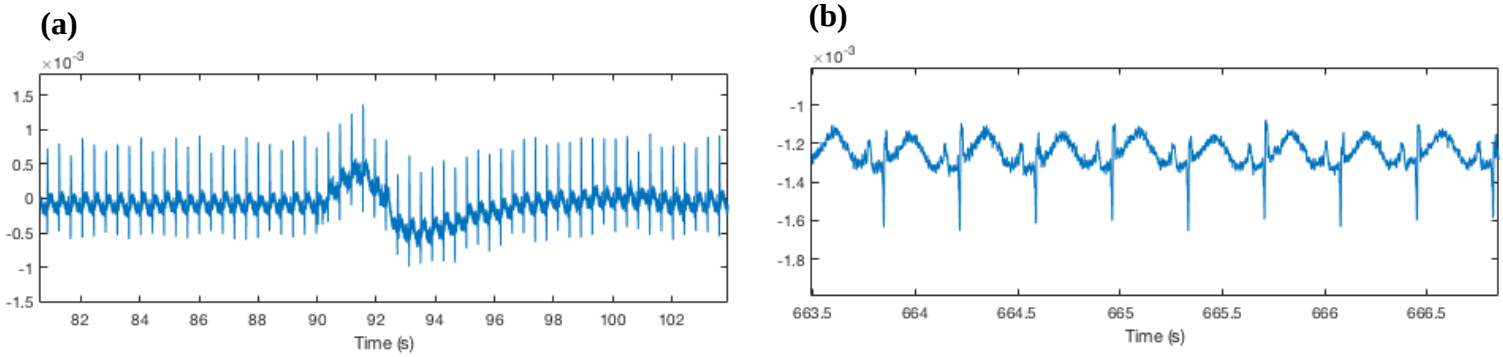


***Figure 5**: Example of a tachogram (heart rate) of an infant in beats per minute (bpm).*

2.3 Noise

Detecting the heart rate for preterm infants is significantly more difficult than for adults as the ECGs recorded in the NICU medical beds carry large amounts of noise from various sources. Common problems in NICUs consist of baseline drifts (see Figure 6a), and weak signals (b). In Figure 6b, the R peak is nearly the size of P-waves and large T-waves, adding a challenge for the detection of the R-peak. Cases of episodic noise may also occur, due to electrodes falling off (Figure 6c), phone interferences (d), handling of the baby (e), and other random noise (f).



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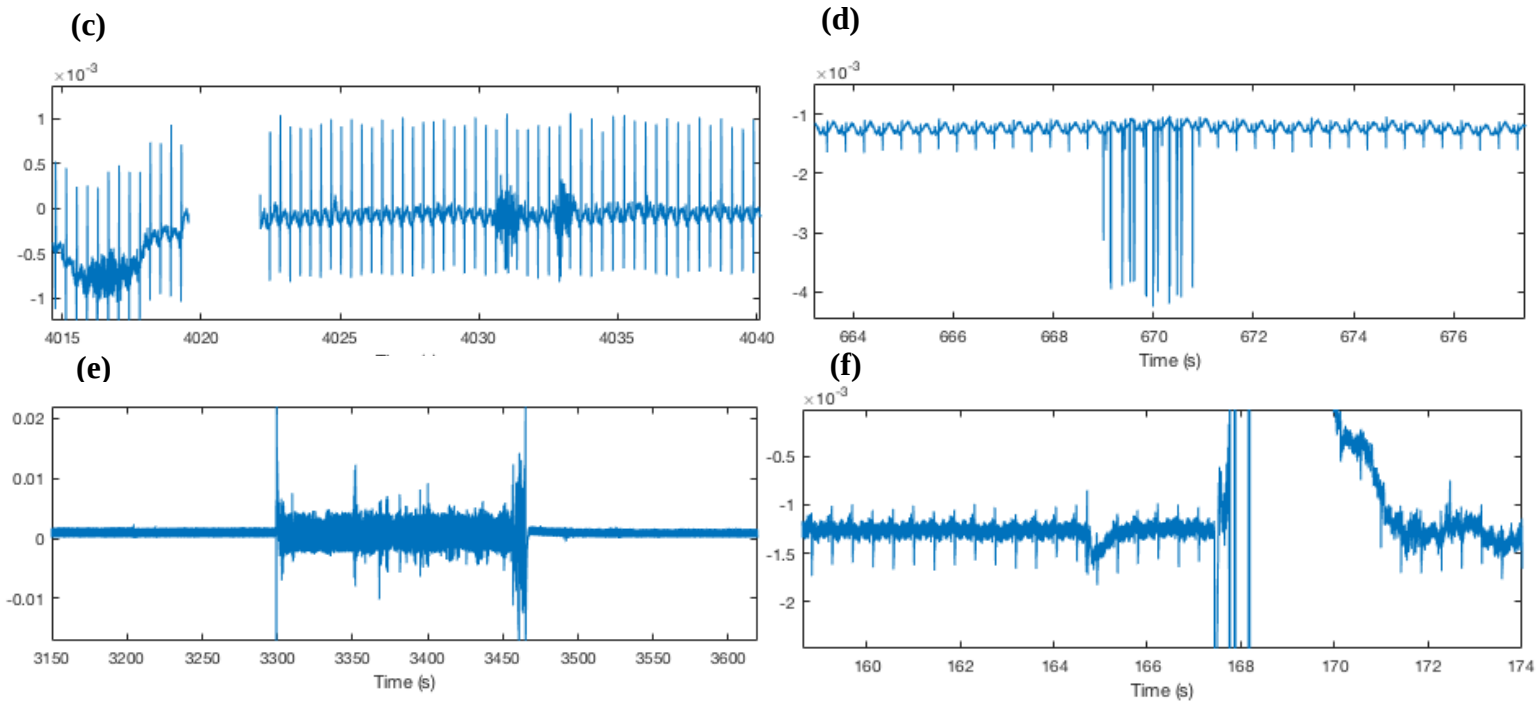

***Figure 6**: Examples of different sources of noise. Constant issues include as **a)** baseline drift and **b)** weak R peak. Intermittent sources include **c)** electrode falling off, **d)** phone interference, **e)** handling of the baby and **f)** other random noise.*

2.4 Handling missing and noisy data

It is rarely possible to obtain a recording with no noise or ectopic beats. Ectopic beats are occasional disturbances in the heart rate seen characterized by a missed or extra beat. While these noisy events can be excluded from the time domain analyses, they can introduce large artefacts in frequency analysis methods. Indeed, the missing discrete heart rate impulses correspond to broad-band noise in the frequency domain.

Various approaches can be used to deal with erroneous or missing data. The simplest one being to simply delete these periods and concatenate surrounding data. Long-term correlations in the time series can however be disturbed by this approach in the frequency domain.

Another method is to interpolate the signal at the noisy points based on the neighboring clean data. Different interpolation methods can be used such as spline or cubic interpolation. Some frequency domain analyses are also particularly suited for analyzing unevenly spaced measurements. In this way, no interpolation or deletion of time periods is made. The Lomb periodogram for example, allows for analysis even when there are very large gaps in the signal [14].

3 Requirements

3.1 Constraints

Since 2013, a study is being run in five tertiary level NICUs in North America [2]. The ECG signals from 250 extremely preterm infants were collected for 1 hour prior to extubation. The extubation outcome is recorded after 72h, then again after 14 days. We therefore have access to a labelled dataset with, for each recording, the outcome of the extubation. The final goal is to build an algorithm capable of estimating the probability of extubation success from

the raw ECG recording. The raw ECG recording is composed of 1 hour of monitoring with normal ventilator settings, followed by 10 minutes of SBT (Spontaneous Breathing Trial). This is a phase in which the ventilator settings are turned to minimal to see how the infants react when needing to breath on their own. The algorithm should output a probability of extubation success, along with a measure of confidence. To ensure that it is useful to the rest of the research team and can be reused and integrated into other projects, documentation should be as extensive as possible and easily accessible.

3.2 Previous Semester Accomplishments

Last semester, we built an algorithm capable of detecting the heart rate from the raw ECG data, to recover as much data as possible from the signal while removing or correcting erroneous values. We initially validated our function. manually by inspecting the tachogram visually.

3.3 Current Semester Goals

The goal of this semester was to build a fully functional pipeline, usable by the APEX team. The pipeline should take in the raw recording file from the APEX database, process the signal with the toolkit built last semester and compute time and frequency domain metrics for heart rate variability. To be usable, the pipeline needs to be tested and validated, and the impact of the various filters on the final signal should be measured.

4 Heart Rate Detection

4.1 Algorithm

The function steps are shown in the figure below.

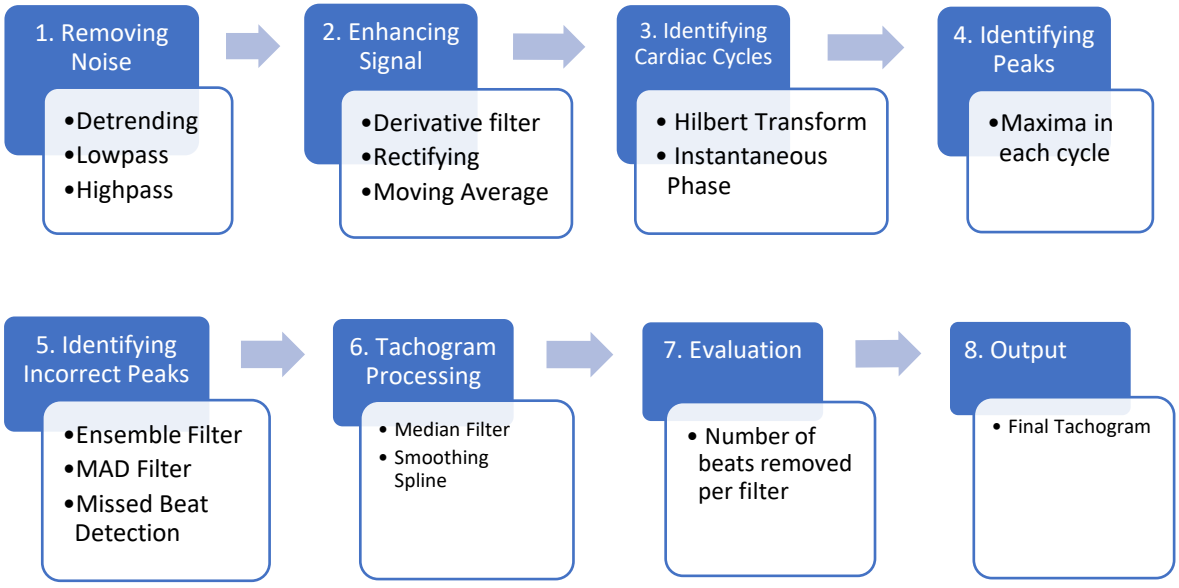

***Figure 7**: Fully functional pipeline steps, from detection of beats (1-4), to post-processing stages (5-6), and output evaluation and generation.*

Steps 1-4:
Raw ECG

The algorithm takes as an input the raw ECG signal, as shown in Figure 8, as well as its sampling frequency. In our case, the sampling frequency is always 1000 Hz.

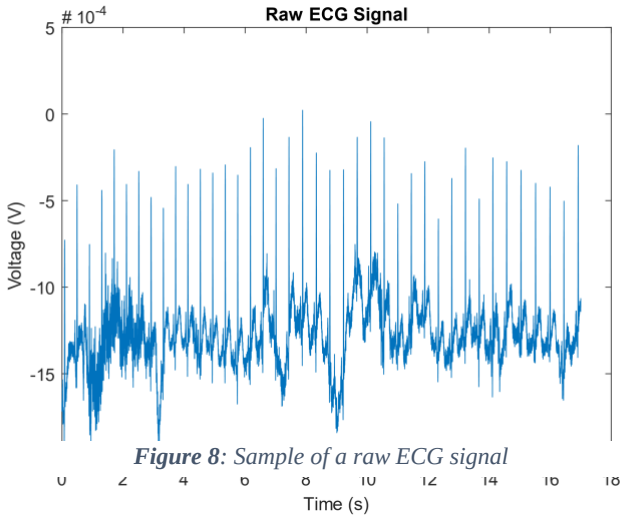

***Figure 8**: Sample of a raw ECG signal*

Removing Amplitude Variations

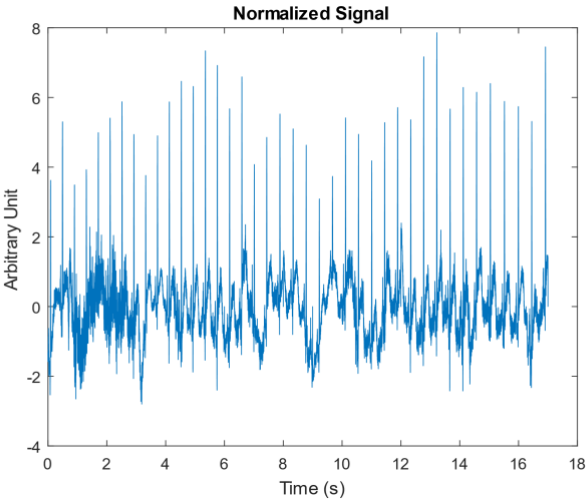

***Figure 9**: Processed ECG Signal*

We first iterate over the signal and for each 1 second period, we remove the mean from each data point divide each point by the standard deviation of the signal in that second. This allows us to have comparable values throughout the signal, independent of amplitude modulations, as shown in Figure 9. The next step in the process is to remove as much noise as possible. This is done by using bandpass filters. We used the same filters as in the Kota algorithm: A High-Pass filter with a frequency cut-off of 16 Hz, to remove baseline wander and a Low-Pass filter with a frequency cut-off of 26 Hz to remove high frequency noise.

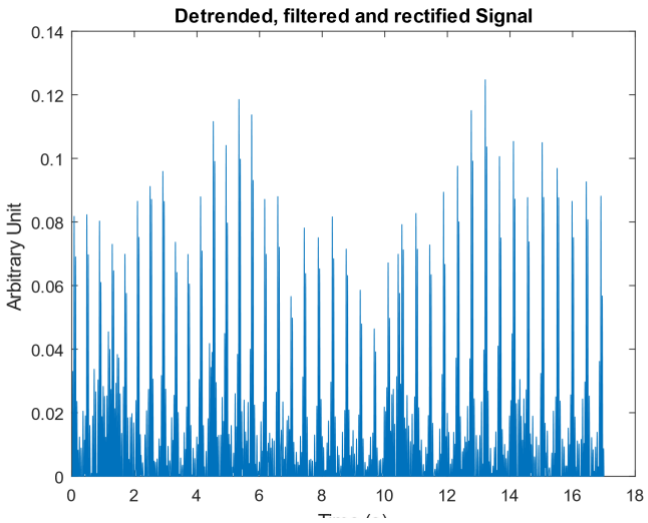

***Figure 10**: Rectified Signal*

Enhancing the signal

To enhance the QRS complex, the difference between successive samples of the signal is taken. This is similar to a high-pass filter and allows us to enhance the characteristic shape of the R-Peak. We then rectify the signal by setting the negative data points to 0, as shown in Figure 10.

We then compute a 150ms running average of the rectified data. At this stage, the signal shows clear peaks centered on the QRS complex of the original ECG.

Identifying Cardiac Cycles

Up to this point, the algorithm is like Pan & Tompkins. Their algorithm would now try find peaks directly. However, this is sensitive to changes in amplitude, as explained in section 5.2.1. Instead, we first identify the cardiac cycles using the Hilbert Transform. The Hilbert transform, calculated for a function f(t) as the convolution: $\frac{1}{\pi t} * f(t)$. It allows us to compute the instantaneous phase of the signal, as shown in Figure 11. The Hilbert transform can be more easily represented in the frequency domain: it imparts a phase shift of 90° to every Fourier component of a function [15].

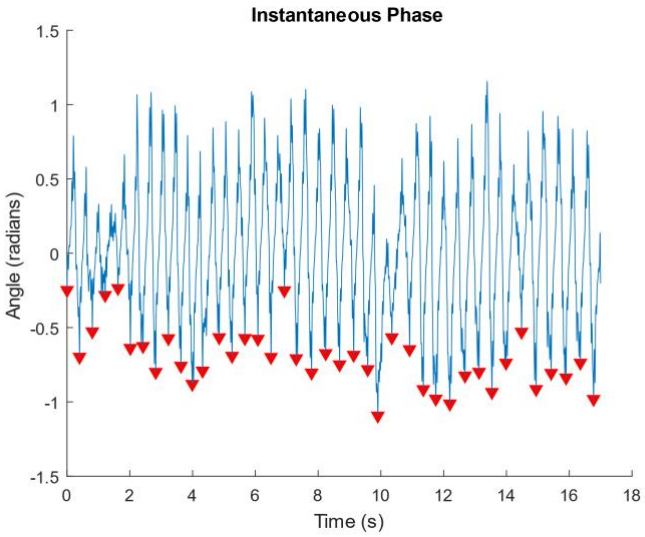

***Figure 11**: Instantaneous Phase of the Signal*

Previous research has shown that the instantaneous phase of the signal exhibits phase slips when the signal passes through a minimum. Since the processed signal shows clears minima between each R-Peak, we can find the minima to determine the onset and end of the cardiac cycle, as shown in Figure 11 [16].

Finding the R-Peaks

Once we know the beginning and end of cardiac cycles, we simply look for the point with the maximum amplitude in each cycle. In their paper, Kota & Al look for peaks directly in the raw signal. This enables them to avoid any latencies introduced by the filter stages. During our validation (see section 6), we found that we had better results in searching for peaks in the normalized signal. This has the advantage of not introducing any latencies, compared to other filtering techniques, while reducing the susceptibility to noise. The ECG with marked beaks is shown in Figure 12.

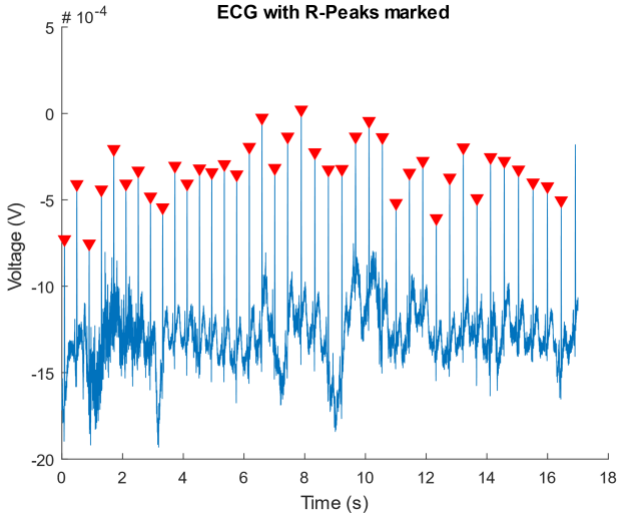

***Figure 12**: Raw ECG with marked beats*

Step 5: Identifying Incorrect Peaks

After the heart rate detection algorithm, three different beat processing functions are used to flag peaks deemed invalid, which are not interpolated for the extraction of the tachogram.

The **Ensemble Filter** computes the static correlation of each heart beat with respect to the average heartbeat over the entire ECG signal. This function is used for continuous parts of the signal that do not correlate with the average heartbeat. The correlation coefficient is computed between the QRS (QRS centered at a given heartbeat i) and the $AvgQRS$ (average QRS of the whole signal), such that:

$$\rho(QRS, Avg\_QRS) = \frac{1}{N-1}\sum_{k=1}^{N}\left(\overline{\frac{QRS_k - \mu_{QRS}}{\sigma_{QRS}}}\right)\left(\overline{\frac{Avg\_QRS_k - \mu_{Avg\_QRS}}{\sigma_{Avg\_QRS}}}\right), \quad (3)$$

where μ_{QRS} and σ_{QRS} are the mean and standard deviation of the ith QRS signal, and μ_{Avg_QRS} and σ_{Avg_QRS} are the mean and standard deviation of the average QRS signal [17]. The minimum static correlation ranges from 0 (low correlation) to 1 (high correlation).

The **MAD** function, or Median Absolute Deviation, computes the statistical dispersion of the signal. It is used to eliminate the extreme outliers, often with random and sudden occurrence. The following equation is computed:

$$D(n) = \frac{|x(n) - x_m|}{1.483 med\{|x(n) - x_m|\}}, \quad (4)$$

where x_m is the median value over the entire record, $x_m = med\{x(n)\}$ [18].

A threshold $\boldsymbol{\tau}$ is used such that all samples for which $D(n) < \tau$ are not taken into account in the generation of the tachogram.

The **Missed Beats Detection** filter catches overlooked beats by comparing its corresponding RR intervals to the sum of its neighboring ones. The deviation tolerance tol can be adjusted accordingly such that:

$$RR(i)_{error} = \big(RR(i-1) + RR(i+1)\big) \pm tol \quad (5)$$

The power of using such beat processing functions allows to remove as many incorrectly detected beats. The figure below shows a tachogram after steps 1-4 (left), and the tachogram after beat processing (right), which has interpolated data in red. It can be seen that many invalid spikes have been removed.

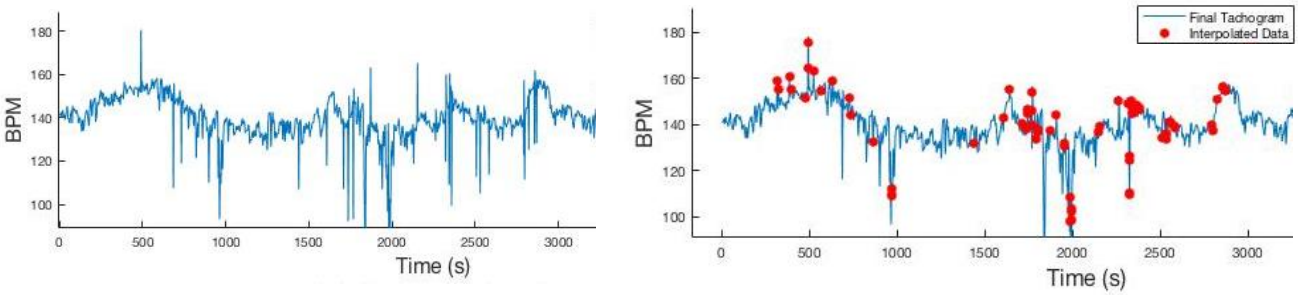

***Figure 13**: Effect of beat processing parameters: the tachogram on the left is generated after steps 1-4. The tachogram on the right is after step 5, in which many beats deemed invalid have been interpolated.*

Step 6: Tachogram Generation

This section controls how the beats are connected from one another, to go from the equation (2), which is the discrete computation of heart rate from the RR intervals, to continuous time.

The interpolation is done either **directly** (straight line between each sample), or using a **Smoothing Spline**, which fits the points with respect to a smoothing coefficient p. The smoothing spline s minimizes [19]:

$$p\sum_i \left(y_i - s(x_i)\right)^2 + (1-p)\int \left(\frac{d^2s}{dx^2}\right)^2 dx \qquad (6)$$

The smoothing coefficient p can be varied from 0 (high smoothing) to 1 (no smoothing).

Tachogram Processing

A simple **Median Filter** can be used to smoothen and filter out all remaining false beats. The filter is run of the entire signal and each point is replaced by the median of itself and its two neighbors. The default window size value of 3 allows to eliminate only the extrema (which in general correspond to incorrectly detected beats) from the final tachogram.

Step 7-8: Evaluation & Output

The function then computes the number of beats removed per filter, and generates the different outputs, including the final tachogram and the location of the R-peaks. The various outputs, including the evaluation measures can be seen in Tables 1 and 2 below.

-

Table 1: Evaluation measures of function

Name	Type	Description
totalNumBeats	Int	Total number of detected R-Peaks
percentInvalid	Double	Percentage of beats that were determined invalid.
splinesRSquare	Double	R-Square value if the spline smoothing method was chosen. Otherwise 0.
numRemovedEnsemble	Int	Number of beats removed by the ensemble filter
numRemovedMAD	Int	Number of beats removed by the MAD filter
missedBeatsNum	Int	Number of missed beats removed

Table 2: Main outputs (step 8) of the full pipeline

Name	Type	Description
tachogram	Double Array	Series of RR intervals as a function of beat number. in samples (ms)
r_locs	Int Array	Location of the R-peaks. Unit: Sample point corresponding to the R-Peak.
heartRate	Double Array	Interpolation of the tachogram as a function of time. Unit: BPM?
interpolatedFlag	Boolean Array	Boolean array of the same length as the heart rate array. Indicates which samples were interpolated where R-Peaks where determined invalid.
evaluation	Struct	Evaluation measures. See details below.

4.2 Graphical User Interface (GUI)

We computed a graphical user interface in order to allow a simple visualization of the function and the effect of parameters on the output (Figure 14). The filter parameters and tachogram generation can be selected on the left column. The right column displays the electrocardiogram with flagged beats, and the corresponding tachograms with beats removed by each filter.

A user's guide is included in the Appendix, which explains each GUI section in more detail.

a) **b)**

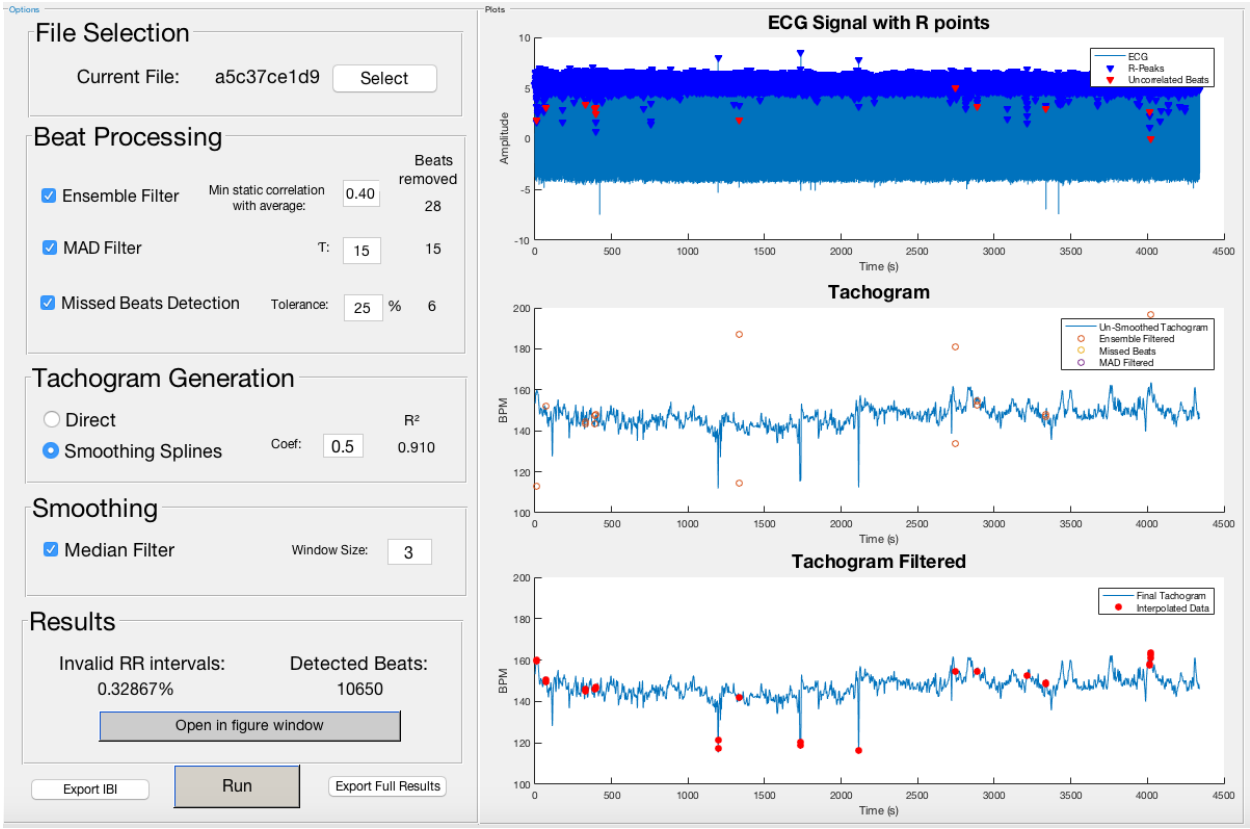

***Figure 14**: User Interface. The left column* **a)** *allows the selection of the ECG file and of the beat processing parameters (Ensemble, MAD, Missed Beats Detection, and Median), as well as direct or smoothing spline generation of the tachogram. The right column* **b)** *displays the ECG signal with the R-Peaks detected (1st graph), the tachogram with invalid beats detected per filter (2nd graph), and the final tachogram with interpolated beats (3rd graph).*

5 Validation

5.1 Validation on Physionet ECGs

To validate our beat-extraction algorithm, we used a database from Physionet [20], a website holding large amounts of physiological signals, including electrocardiograms for which valid beats have formerly been marked by physicians.
To validate on signals resembling as much as possible to our APEX ECGs, we ran our function on the picsdb, the preterm infants electrocardiogram database.
The physionet data was processed and enhanced during its collection, allowing us to get extremely good results over hundreds of hours of recording.

We ran the function on 5 different picsdb files and got the following results:

Parameters:	Results:			
Ensemble function = 0.1	**Total Beats**:	803272	**Sensitivity**:	95.92%
MAD window size = 20	**TP (valid)**:	768820	**P+ Predictivity**:	99.91%
Missed Beat Tolerance = 20%	**FN (missed)**:	34452	**Accuracy:**	95.83%
Median filter window size = 3	**FP (extra)**:	600		

where Sensitivity (Se), positive predictivity (+P) and accuracy (Acc) were calculated using the following equations:

$$Se = \frac{TP}{TP+FN} \times 100\% \quad (7)$$

$$+P = \frac{TP}{TP+FP} \times 100\% \quad (8)$$

$$Acc = \frac{TP}{TP+FP+FN} \times 100\% \quad (9)$$

However, as the Physionet database is extremely reduced in noise, we made our Ensemble Function parameter loose (0.1) in order to avoid removing any valid data.

5.2 Validation on APEX

In order to ensure our beat processing parameters were adapted for the unprocessed APEX data, we visually assessed the effects of the parameters on the tachogram, as well as quantitavely with the heart rate variability metrics (see section 5.3).
To decide on appropriate parameters, we ran our function on noisy ECGs, resulting in noisy tachograms with large numbers of unrealistic spikes, as well as clean electrocardiograms, for which all variations in the tachogram (bradycardia or tachycardia) represent real physiological data. It was expected that our function removes little to no beats in the clean electrocardiogram, and many falsely detected peaks in the noisy electrocardiogram. The chosen parameters were the following:

Ensemble function $= 0.2$
MAD window size $= 20$
Missed Beat Tolerance $= 25\%$
Median filter window size $= 3$

Testing on typical signals:

A tachogram ("a5c37ce1d999") showing both clean and noisy parts is shown in Figure 15 below. Four main spikes in the tachogram are visible: at 1200s (a), 1750s (b), 2100s (c) and 4000s (d). By zooming in, spikes a), b) and c) represent real bradycardias, as shown in the close-up figures, are expected to stay intact. Spike d) is noise from the ECG which does not represent real data, as can be seen from the flat line at 4020s, and should be removed.

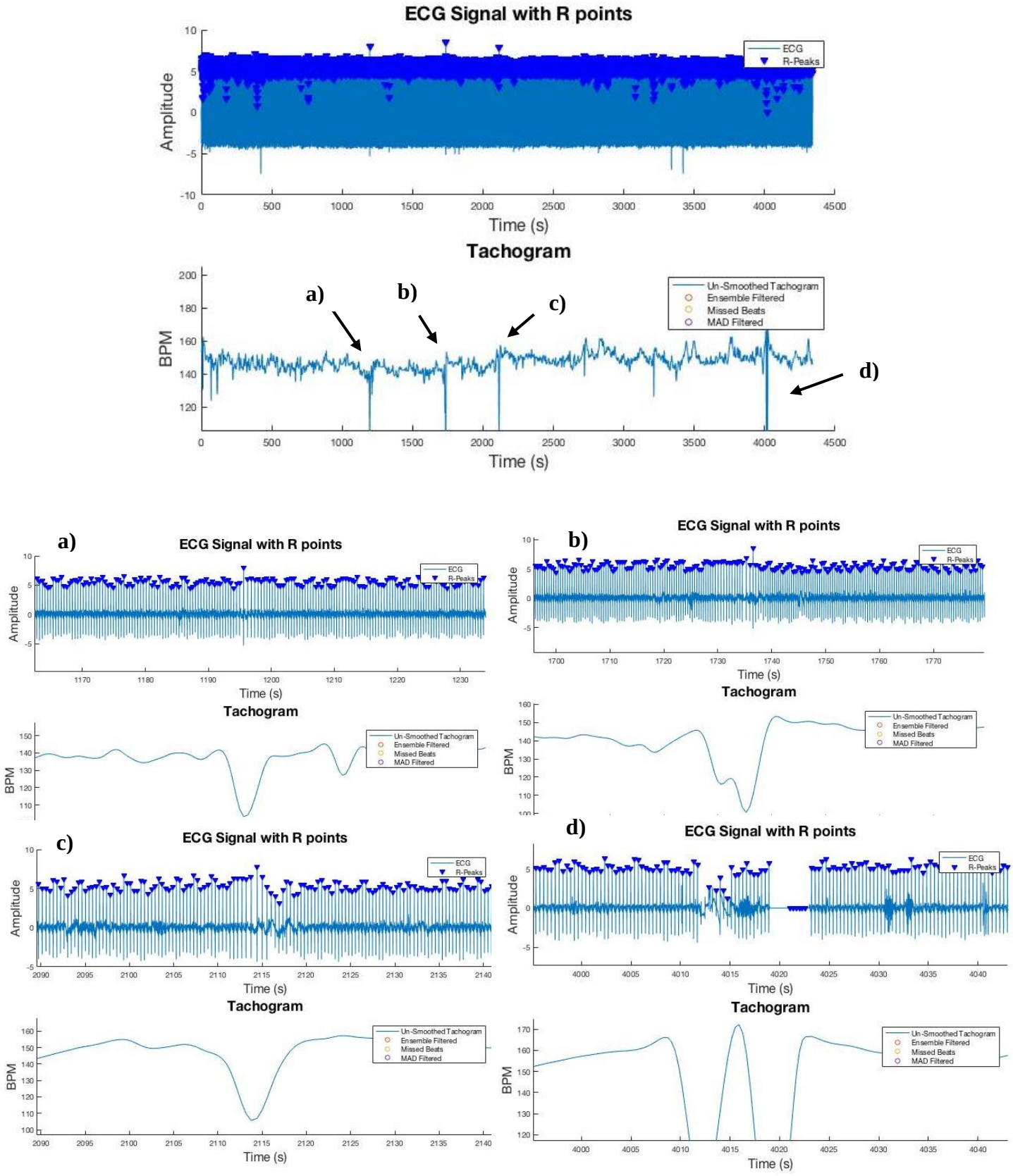

***Figure 15**: ECG signal "a5c37ce1d999" with detected R-Peaks and generated tachogram after steps 1-4 (top graph). The four bottom graphs are close-up electrocardiograms and corresponding tachograms of the four labeled spikes a), b), c) and d) of the top figure. Only spike d) should be removed by the beat processing function.*

The results are shown in Figure 16 below. Spikes a), b) and c) are still almost intact, although there are still a few beat removals. The parameters properly remove spike d) which should not be taken into account during the extraction of the filter.

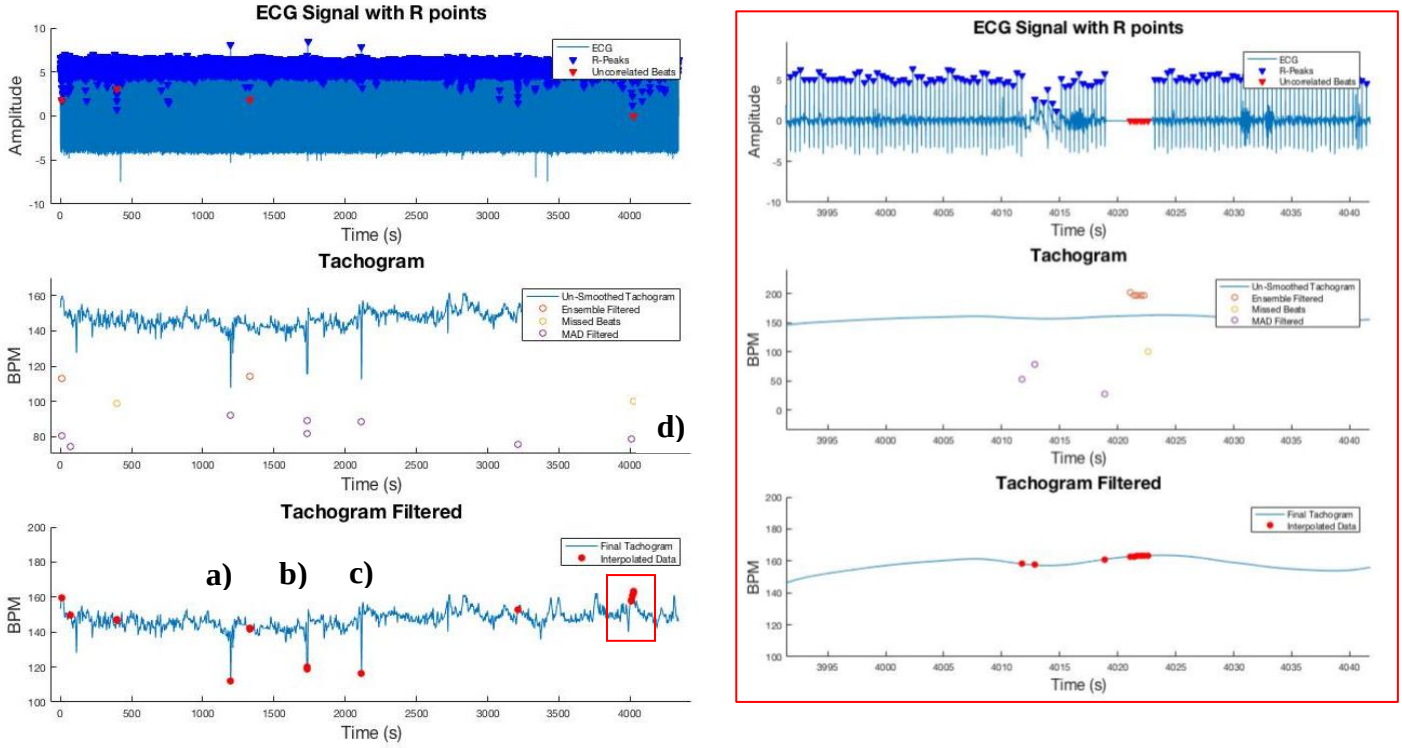

***Figure 16**: Tachogram after running the beat processing functions. Spikes a) b) and c) (left) are practically intact while spike d) (right) is completely removed.*

<u>Testing on clean signals:</u>

Another example of our function parameters is shown below. The electrocardiogram chosen ("c1f6f1d2676e") is clean, and we verified manually that the variations seen in the tachogram were real. It was thus expected that our function parameters were appropriate and did not remove noise.

The third graph of Figure 17 has 3 red dots, meaning that only 3 beats were deemed incorrect from the function. We see from the GUI screenshot that the Ensemble Function and MAD function did not remove any beats, confirming that the chosen parameters were not too harsh. By checking visually for each beat on the ECG signal directly, we verified that the 3 beats were indeed incorrectly detected. This shows that the parameters chosen are not too harsh for clean APEX data.

<u>Testing on noisy signals:</u>

Finally, we also tested our function on noisy signals to ensure that our parameters were not too loose and removed all noise. An example is shown in Figure 18, for signal "c2da36316597."

As expected, almost all noise is removed from the tachogram (Figure 19). Particularly noisy parts of the signal, as outlined by the red square, is not taken into account for the interpolation of the tachogram.

Clean ECG (“c1f6f1d2676e”):

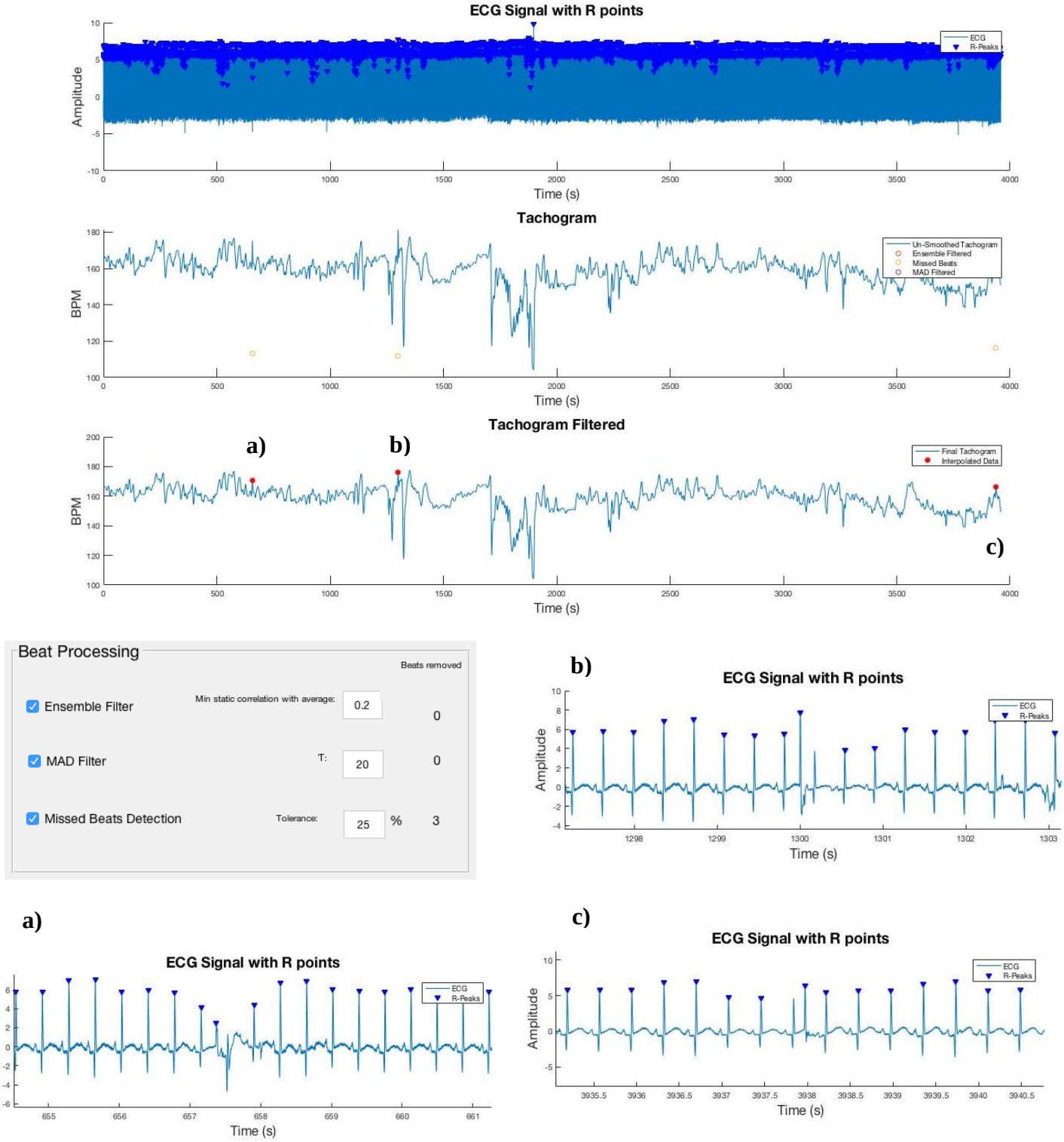

Figure 17: Clean electrocardiogram for which all main spikes represent real data. The beat processing function only removes 3 beats over the entire signal. The three removed beats a), b) and c) are correctly removed as shown from the three close-up graphs.

Noisy ECG (“c2da36316597”):

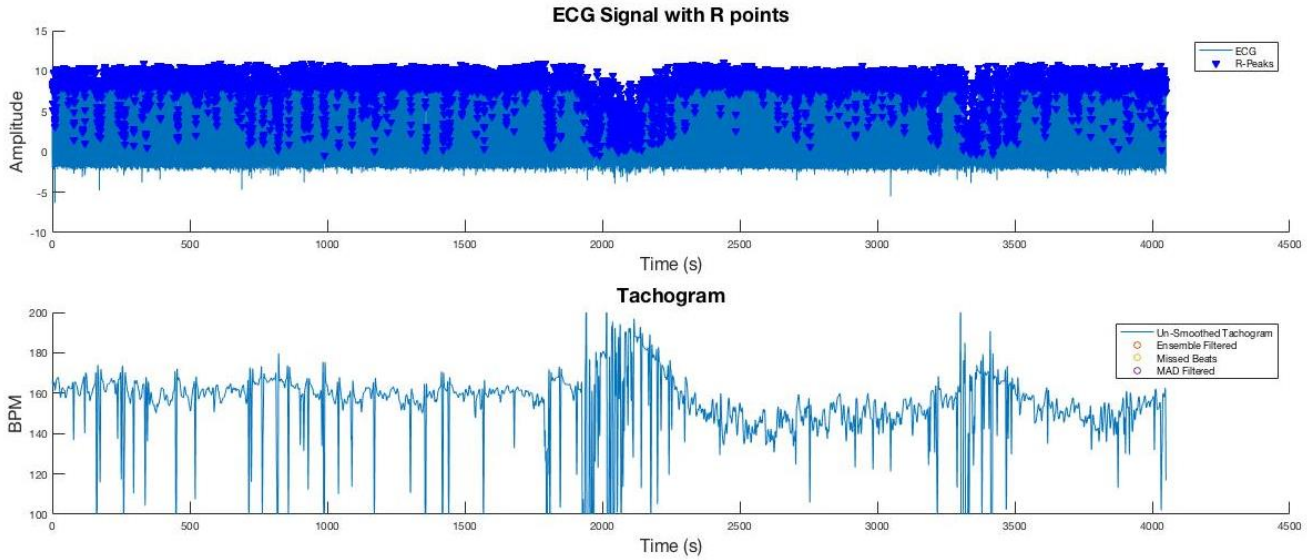

Figure 18: Example of a noisy electrocardiogram signal and tachogram (after steps 1-4 of our function).

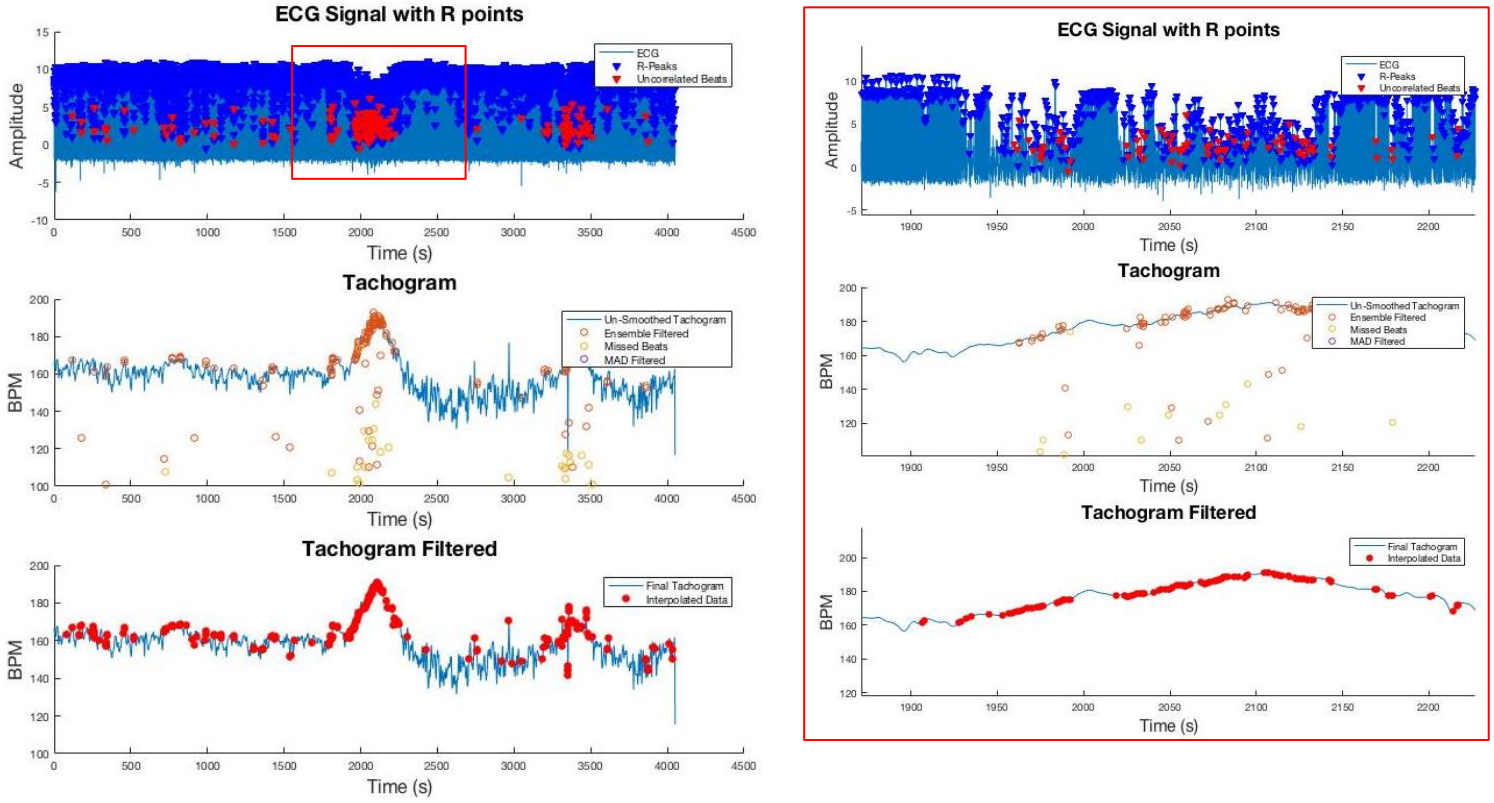

***Figure 19**: Noisy signal after beat processing functions and median filter applied (step 5-6): almost all spikes have been removed in noisy areas (left graph). The right graph is a close up of a particularly noisy part (red rectangular outline), which is successfully removed by the post-processing function.*

5.3 Effect of filtering parameters on Metrics

Different parameters were selected in order to evaluate their effects on the HRV metrics: Ensemble Function (**EF**), **MAD**, Missed Beats (**MB**), Smoothing Spline (**SS**), and median filter (**Med**). Metrics were most sensible to variations in the Ensemble and MAD functions, in particular the SDNN and RMSDD in time domain.

Table 3 shows the effect of the beat processing parameters when one is varied at a time for the signal showing both clean and noisy sections ("a5c37ce1d999"). It can be seen that changing the smoothing spline to direct, and adding the median filter have no effect on the metrics.

***Table 3**: Effects of beat processing parameters (Ensemble Function (**EF**), **MAD**, Missed Beats (**MB**), Smoothing Spline (**SS**), and median filter (**Med**)) on HRV metrics for the ECG signal "a5c3ecg".*

EF Parameter	MAD Parameter	MB Parameter	SS	Med	mean (ms)	SDNN (ms)	NNx (count)	pNNx (%)	RMSSD (ms)	SDNNi (ms)
x	x	x	Yes	x	407.6	25.9	53	0.5	30.3	48.9
0.2	x	x	Yes	x	407.1	18.8	41	0.4	15.4	48.9
x	20	x	Yes	x	407.4	24	45	0.4	27.6	48.9
x	x	25	Yes	x	407.4	24	45	0.3	27.6	48.9
x	x	x	No	x	407.6	25.9	53	0.5	30.3	48.9
x	x	x	Yes	3	407.6	25.9	53	0.5	30.3	48.9

In order to assess in more detail the effects of the Ensemble and MAD function parameters, we varied their values on the three signals used in the previous section (5.2). The results are shown in Tables 4 (change in Ensemble) and 5 (change in MAD). Recall that the smaller the MAD parameter is, the harsher the removal of beats (opposite to the Ensemble Function).

Most metrics do not vary significantly with changing parameters, except for SDNNi which can be multiplied or divided by 2-3 with harsher parameters (see values in red). This let us to keep relatively loose parameters (MAD = 20 and EF = 0.2) to avoid removing too much valuable data.

Table 4: Change of time domain metrics with respect to the Ensemble Function on 3 different signals. The constant parameters are the following: MAD 20, MB 25, Smoothing Spline and Median 3.

HRV Variable	EF	ibi	mean	SDNN	NNx	pNNx	RMSSD	SDNNi
Subject	Parameter	(count)	(ms)	(ms)	(count)	(%)	(ms)	(ms)
a5c37ce1d999	0.2	10627	407.2	15	28	0.3	7.7	48.9
a5c37ce1d999	0.4	10615	407.2	14.9	25	0.2	7.6	48.9
a5c37ce1d999	0.5	10600	407.2	14.9	25	0.2	7.6	10.7
c1f6f1d2676e	0.2	10472	377.8	21.4	11	0.1	5.2	17
c1f6f1d2676e	0.4	10469	377.8	21.4	9	0.1	4.7	16.9
c1f6f1d2676e	0.5	10467	377.8	21.4	9	0.1	4.7	16.9
c2da36316597	0.2	10008	380	22.9	22	0.2	9.3	51.5
c2da36316597	0.4	9769	380.6	22.1	9	0.1	6.3	19.3
c2da36316597	0.5	9596	381	21.8	4	0	5.9	18.9

Table 5: Change of time domain metrics with respect to the MAD Function on 3 different signals. The constant parameters are the following: EF = 0.2, MB 25, Smoothing Spline and Median 3.

HRV Variable	MAD	ibi	mean	SDNN	NNx	pNNx	RMSSD	SDNNi
Subject	Parameter	(count)	(ms)	(ms)	(count)	(%)	(ms)	(ms)
a5c37ce1d999	20	10626	407.2	15	28	0.3	7.7	48.9
a5c37ce1d999	15	10626	407.2	14.8	27	0.3	7.6	48.9
a5c37ce1d999	10	10614	407	14	20	0.2	7	48.8
c1f6f1d2676e	20	10471	377.8	21.4	11	0.1	5.2	17
c1f6f1d2676e	15	10471	377.8	21.3	9	0.1	5.1	16.9
c1f6f1d2676e	10	10451	377.5	19.8	3	0	3.7	49.2
c2da36316597	20	10008	380	22.9	22	0.2	9.3	51.5
c2da36316597	15	10008	379.9	22.5	19	0.2	7.3	51.5
c2da36316597	10	10006	380	22.3	15	0.1	6	51.5

6 Heart Rate Variability Analysis Software (HRVAS)

Heart Rate Variability Analysis Software (HRVAS) is a package allowing the computation of time domain, frequency domain, and nonlinear HRV metrics which we integrated directly with our beat-extraction toolbox. It was chosen for its robust design, open source availability and completeness. Developed by John T. Ramshur, PhD and is well documented [21]
Built entirely in MATLAB, it is easily extendable and customizable. We added an export function in our algorithm to save results in the correct format for HRVAS. Having a GUI, shown in Figure 20, as well as a batch programmatic mode allows the entire pipeline to be used at various stages of development: from data exploration using the GUI to high volume processing using the command line.

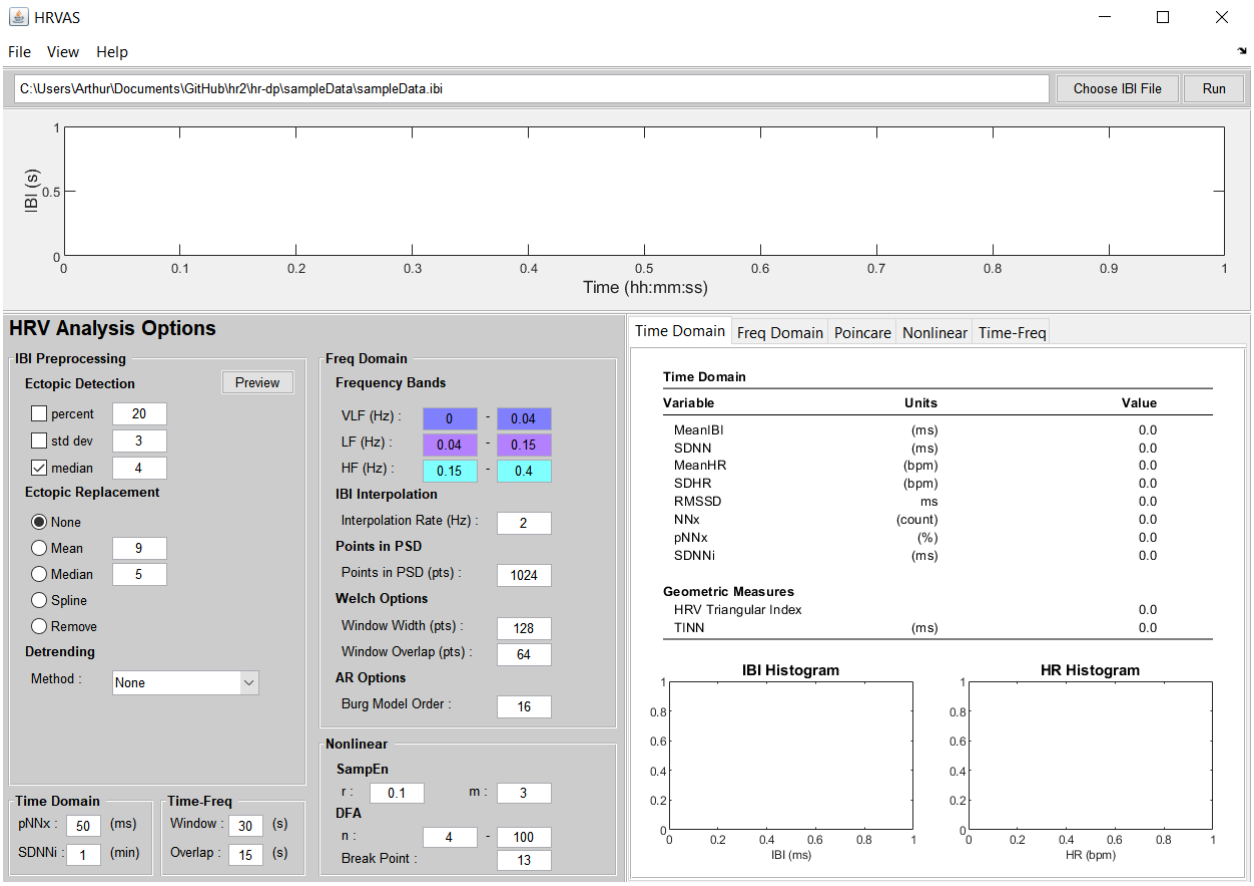

***Figure 20**: HRVAS Software interface.*

7 Documentation and Software Package

To ensure that the tools that we developed are useful and benefit the most people, the entire source code has been Open Sourced on github:
https://github.com/arthurkuhn/hrvtoolkit

A website has been set-up to host documentation and other relevant information:
http://hrvtoolkit.com.

Independent MATLAB modules were documented separately, and all documentation will be made online.

8 Future Work

Our algorithm works efficiently on a wide set of inputs, however, the filters still need to be adjusted depending on the signal. An important improvement would be to make the process entirely automatic. In our current algorithm, beats that are deemed noisy are completely removed from the following steps of the pipeline. Ideally, to be able to explore long-term trends, we would like to be able to interpolate these missing values before the next preprocessing steps.

The next steps would be to find the correlation between the HRV metrics and the clinical outcome extubation, using machine learning methods. This would contribute to the APEX project to predict extubation readiness from different types of data, including electrocardiograms.

9 Social and Environmental Impact

9.1 Environmental Impact

This is a software project and there are almost no non-renewable resources are used both during development and during the life of the application. However, this project has the potential to have a large environmental impact. Reducing extubation failure, as well as minimizing intubation time could reduce morbidity and hospitalization times. This would free up beds and resources for other patients.
This also has the potential to reduce medical expenses. Stays in the NICU (Neonatal intensive cate unit) are extremely expensive. Currently, a day in the NICU can cost more than $10 000. This is not only an important burden for the families, but also for the healthcare system. The Total cost of medical care services due to preterm birth was estimated to be $16.9 billion in 2005 [22]. These costs are especially high for extremely preterm infants. For babies born at 24 weeks or before, median hospital costs are more than $200 000 for the duration of their stay. Between 25 and 28 weeks, median costs reach $120 000 [23]. Any reduction in these amounts could free up resources to be used elsewhere.

9.2 Social Impact

Evidently, the social impact of this project could be significant. The ability to correctly predict extubation time could limit the short and long-term damages caused by reintubations and prolonged MV, and therefore reduce associated morbidities and could in some cases, save lives. There will nonetheless still be risks associated to this project, as there are many, sometimes unpredictable clinical factors associated with extubation success. However, as the current extubation failure rate is 45%, and preliminary studies have shown encouraging results, we hope that our work will help improve the success rate. Since current practices are based on clinical judgment, a program taking into account large amounts of cardiorespiratory and clinical data and based on statistical measures could improve this outcome. This project is also beneficial for society as it contributes to research advancement in the clinical domain and is an example electrical and software engineering applied in the biomedical field.

10 Teamwork

We are both taking a 3-credit course. We both participated in all steps of the process: literature review, implementation of algorithms, and reports. In the first semester Arthur fully implemented the Kota peak detection algorithm and the confidence level measurement and Clara implemented the pre and post-processing stages (noise detection algorithms, median and pattern matching filtering), and manually validated Kota. In the second semester, Arthur implemented the GUI, pipeline and test code and Clara performed the different types of validation and HRV metric analysis.

11 Conclusion

In conclusion, this year we have designed and built a fully functional pipeline to go from raw ECG recordings into fully analysed signals. This semester, we concentrated on integrating the heart rate variability analysis package, as well as validating the function on a wide range of signals. We also focused on documenting our progress and setting-up proper help resources so that future users of the package can get set-up quickly. Finally, we open-sourced all the code and set-up resources to facilitate future collaboration. We both learned a lot throughout this project. We learned about all the medical issues that preterm infants face and the difficulties associated to record cardiorespiratory data, as well as the composition of electrocardiograms. As this is a medical project, a lot of "human" features factor in, creating an additional dimension to the challenge, such as noisy ECG signals. Validation was very time consuming but allowed us to get a clear understanding of the benefits and limitations of our package. Overall, this was an extremely stimulating and enriching project. This package will be presented to the rest of the APEX research team to be used to evaluate how the heart rate variability metrics that we calculated correlate with extubation outcome. We hope that it will be useful, and that it will be used by the medical research community in the future.

12 Acknowledgements

We thank Professor Robert E. Kearney and MD. Samantha Latremouille for their continuous guidance and support throughout this project. Their expert guidance steered us in the right direction and made the completion of this project possible.

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Appendix

Function parameters:

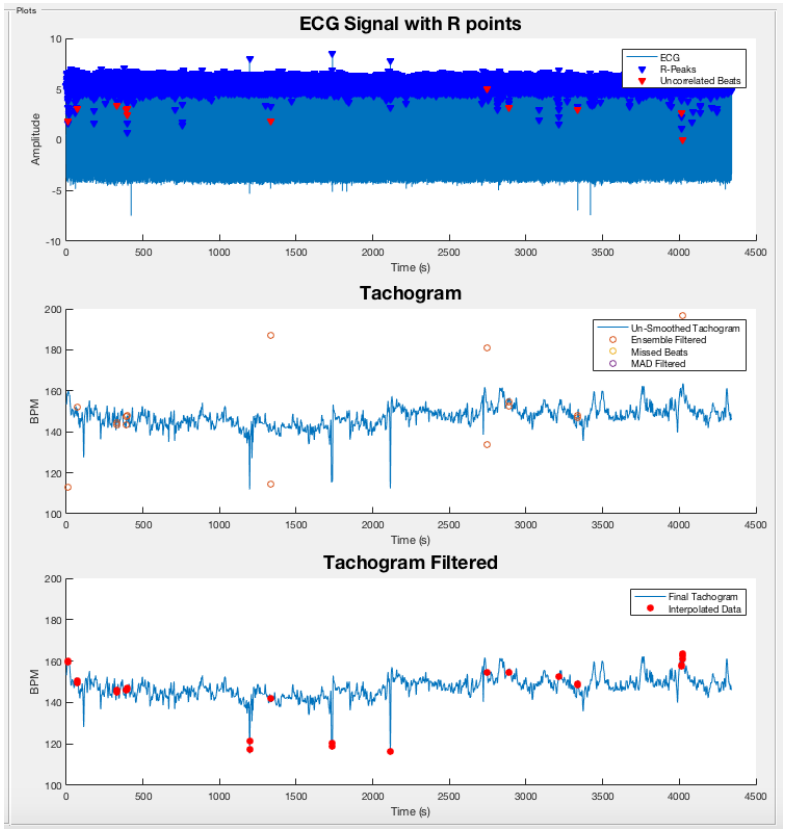
n_sample_start	Sample number where analysis will start	1	Sample number
n_sample_end	Sample number where the analysis will end	end	Sample number
ensemble_filter_threshold	Ensemble Filter Correlation Threshold	Off	
ensemble_filter_window	Ensemble filter window	200	Samples
mad_filter_threshold	Mad Filter Threshold	Off	
missed_beats_tolerance_percent	Tolerance in beat-to-beat variation	Off	Percent
median_filter_window	Median Filter Window Size	Off	Samples
Interpolation Method (spline or linear)	'Interpolation Method (spline or linear)	spline	String
smoothing_spline_coef	Smoothing Spline Coefficient	0.5	0 to 1
eval_type	Evaluation type (short, full, default none)	Off	String
directory	Directory where the file is located (if not on path)	''	String

GUI User Manual (right column):

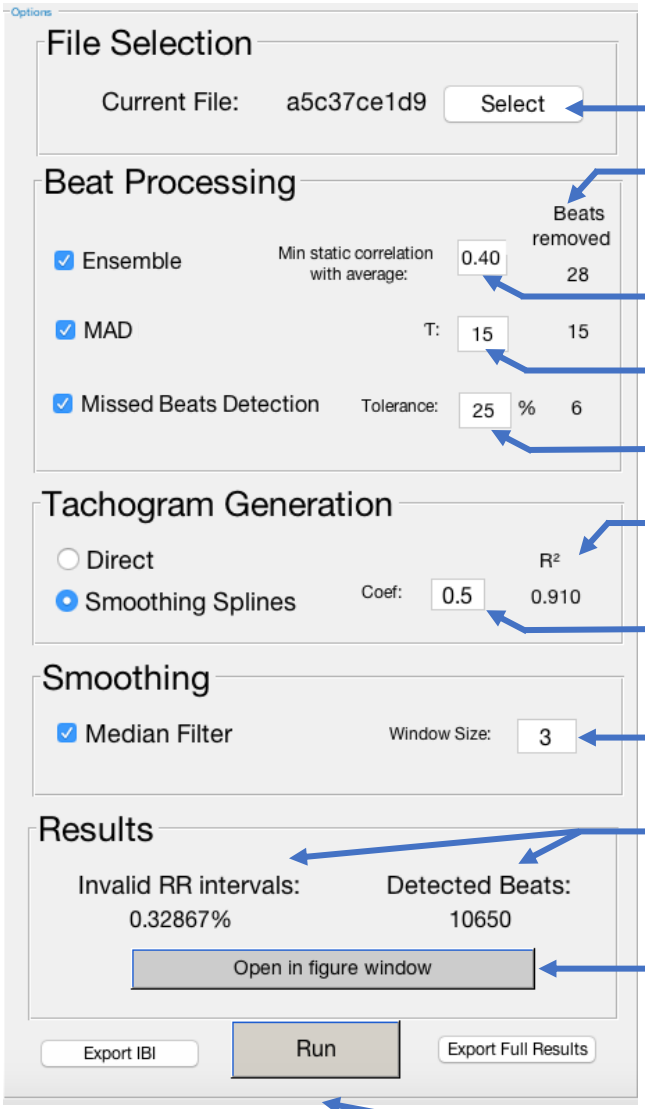
ECG with detected beats: in red are those deemed invalid by the ensemble beat processing method

The tachogram with beats deemed invalid by each processing function (different color for each) is displayed in this graph.

Final tachogram: all beats deemed invalid have been interpolated (in red), either directly or from the smoothing spline function.



GUI User Manual (left column):



Select any .mat

The number of beats removed by each beat processing method is displayed in this column

The user may type in any value ranging from 0-1 for minimum static correlation

Window size for

Tolerance for missed beat detection

Coefficient of determination R^2 for smoothing spline displayed here

Curve fitting coefficient (0-1) for smoothing spline

The user may enter the window size for the median filter

The percentage of invalid RR intervals over the whole ECG signal is displayed, along with the total number of detected beats

The user can open the figures on the right in a new window, allowing more flexibility (to zoom in, compare signals, etc.)

Once the user has selected his parameters, he can select run to apply changes.
The IBI files with chosen parameters can be saved for HRV analysis.
The full results can also be saved.