Analysis of Heart Rate Variability in Preterm Neonates

Aidan O'Keeffe

UGS 320K: Undergraduate Research Experience

Dr. Joshua Chang

January 17, 2023

Introduction

Sepsis is one of the leading causes of death for preterm infants. Sepsis can progress from mild symptoms to death in as little as 12 hours (Ring, 2018). *Blood cultures* are the surest way to diagnose sepsis, yet, according to Alan Groves M.D. at Dell Medical School—a domain expert and a collaborator on this project—these tests require 2 to 4 hours to produce results, as well as expertise and laboratory resources to prepare. These hours can mean the difference between life and death, so oftentimes an attending physician will order antibiotic treatment as soon as they suspect spesis. This practice saves lives, but it carries all the costs associated with excess use of antibiotics.

This unsatisfactory situation has incentivized researchers to develop tools for the early diagnosis of sepsis based on vital sign measurements. A set of vital signs that have shown promise are metrics of *heart rate variability*: the beat to beat variation on heart rate. Heart rate variability is linked to the nervous system's control of heart rate, which in turn is related to immune response, so the hope has been that heart rate variability will indicate baterial presence in the blood well before the onset of symptoms (Fairchild and Aschner, 2012).

The most widely used tool in this field is the HeRO score, a proprietary algorithm which incorporates three heart rate variability metrics to produce a score from 0 to 5 for the risk of developing sepsis in the next 24 hours (Fairchild and Aschner, 2012). Despite its widespread use, the HeRO has not been found to predict sepsis to a satisfactory degree, so other researchers have continued attempting to solve the problem (Masino et al, 2019).

The guiding question of this study was: Do time series measurements of heart rate variability metrics show any indications of sepsis? To answer this question, preexisting ECG recordings for a small set (n=7) of infants s—some who developed sepsis, some who did

not—were pulled, a set of heart rate variability metrics were calculated, and these metrics were visualized.

The visualizations did not show any indicators, a result which is addressed in the Discussion section.

Materials

Programming Tools

This analysis was carried out in Python, making heavy use of the numpy, pandas, matplotlib, and waveform-database libraries. Code in the form of Jupyter Notebooks can be found online at https://github.com/aidanlokeeffe/nicu_hrv_analysis.

Data

The dataset for this study consisted of ECG recordings from 7 preterm infants, here termed infants for simplicity. 3 of the infants (1, 5, and 7) developed sepsis, and the other 4 (2, 3, 4, 6) did not. The septic infants were selected based on the criteria that their incidents of sepsis were “very severe” and that they did not experience other major issues during the recording period. The non-septic infants were selected based on the criteria that they were close in age to one of the septic infants and that they had “relatively uncomplicated” experiences during the recording period. These criteria were outlined by Dr. Groves. Table 1 provides a summary of the infants.

Table 1: Summary of Infants

Infant	*Became Septic*	*Gestational Age at Birth*	*Gestational Age at Start of Recording*
1	Yes	27w 4d	29w 1d
2	No	26w 0d	27w 4d
3	No	24w 5d	33w 4d
4	No	25w 1d	34w 0d
5	Yes	24w 6d	34w 5d
6	No	28w 0d	29w 4d
7	Yes	24w 0d	27w 5d

The data was originally collected for the purpose of monitoring the patients' status during their stays in the NICU at Dell Medical School. The data is now housed securely at Dell Medical School; only students, staff, and faculty associated with Dell Medical School are able to access this data. To protect the patients' privacy, the data was deidentified.

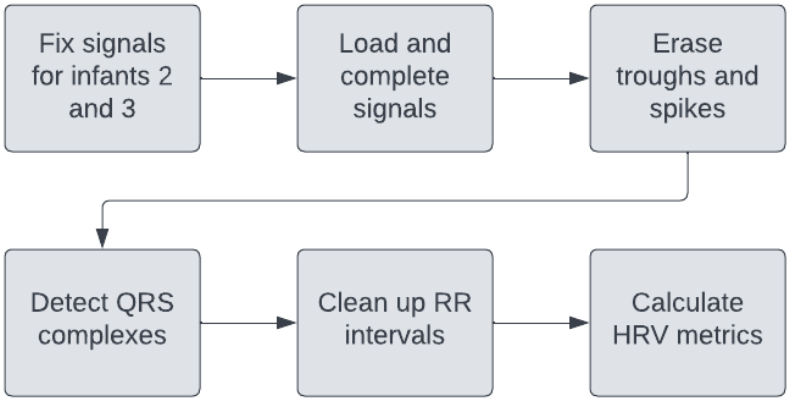
The dataset was pulled by Joshua Chang MD PhD, a neurologist at UT Austin and the supervisor for the course under which this project took place. The data itself consisted of approximately 2 weeks of vital sign recordings per infant stored in csv format, with the time of sepsis landing the middle for septic infants. The columns were: time, anywhere from 1 to 3 ECG signals (sampling frequency 250 Hz), respiratory impedance (125 Hz), and SPO2 (62.5 Hz). The

reason there is a varying number of ECG signals is that the bedside monitor has 3 electrodes, and only one of the signals was recorded at any given time. The original files were too large to be stored in memory, so Dr. Chang split each of them into 5 files labeled by infant number and letter; for example, one such files was “raw_waves_data_1a.csv”. The files were each about 3.5 GB in size. The files were then stored on Box, which is how they could be accessed for this project.

It should be noted that this dataset is too small to justify making any inferences, but that is acceptable in this instance because this project’s aim was only to see if visual indicators of sepsis could be seen in the data.

Methods

Figure 1: Data Pipeline

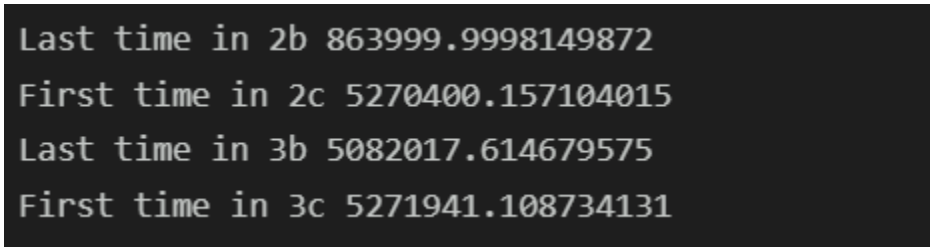


In order to calculate heart rate variability (HRV) metrics, one first needs to extract the heartbeats from the ECG signal; recall that herat rate variability is the beat to beat variation in heart rate. To do this, one needs a clean, complete ECG signal, and a QRS detector. Additionally, QRS detectors are not perfect tools, so some additional cleaning of the resulting data is required.

Only after this process can heart rate variability metrics be calculated. This is a complicated process, but details will be provided as each step of the pipeline is presented.

Step 1: Fix signals for infants 2 and 3

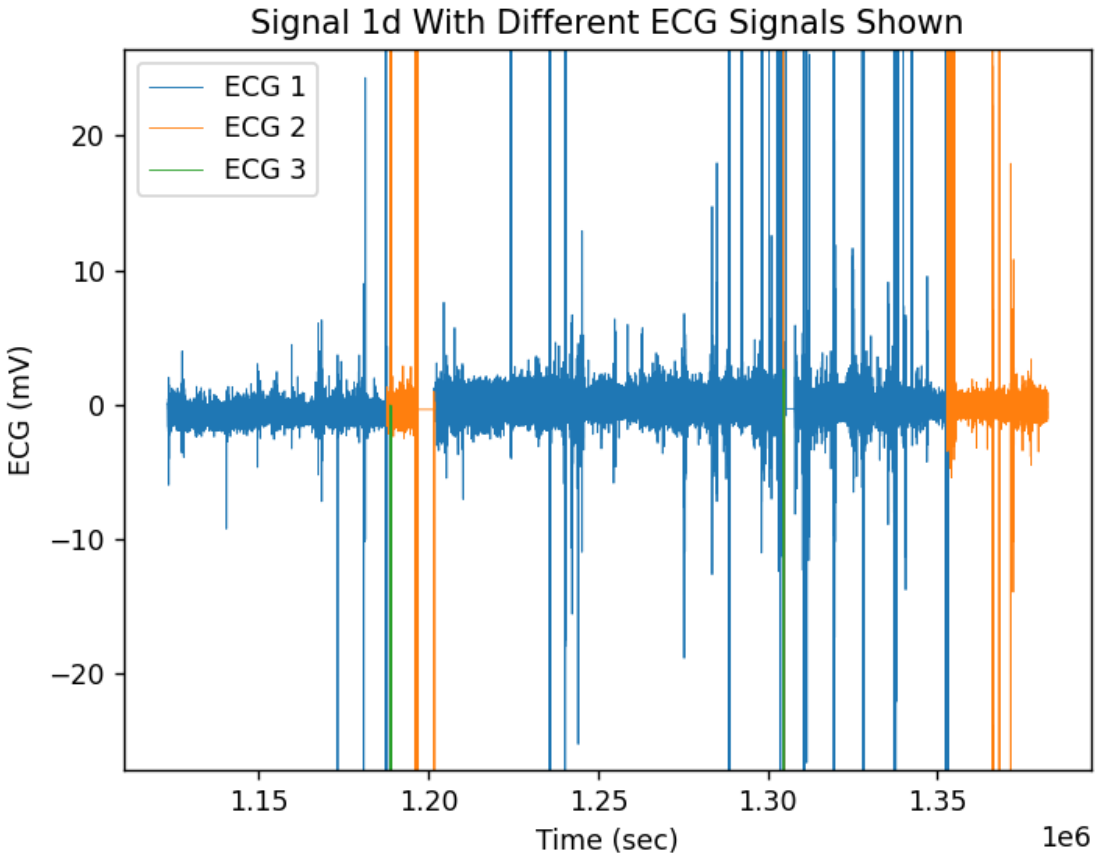
Figure 2: Proof of Discontinuous Time Index for Infants 2 and 3



First, while inspecting the data, it was noticed that the time index was discontinuous from file “raw_waves_data_2b.csv” to file “raw_waves_data_2c.csv”, as well as from file “raw_waves_data_3b.csv” to file “raw_waves_data_3c.csv”, as is demonstrated in Figure 2. To resolve this, the time indices for files 2a and 2b were shifted up to align with 2c, and likewise for files 3a and 3b.

Step 2: Load and complete signals

Figure 3: Example of the Multiple ECG Signals



Recall that each file could contain anywhere from 1 to 3 ECG signals. These signals ranged between similar values and were not shifted with respect to each other, so it was decided to merge the signals together. First, we took ECG 1. ECG 2 and then ECG 3 were used to fill in missing data.

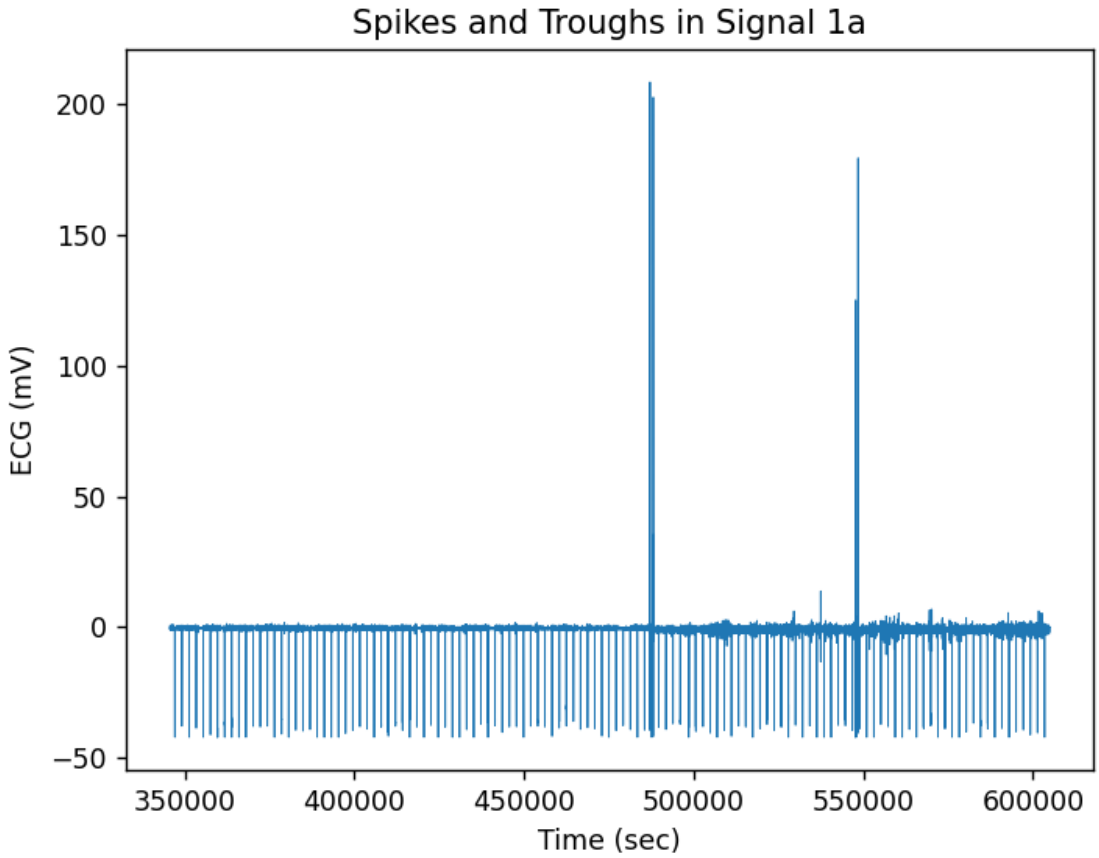
Figure 4 shows signal 1d before the three signals were combined. ECG 1 is recorded most of the time, ECG 2 the second most often, and ECG is recorded so rarely that it is barely visible. There is still some missing data, but the amount is so small that it is invisible at this scale. (Talk more about the scale).

Figure 4: Heartbeat Detection Around a Segment of Flat Data

After combining the signals, there was often still some missing data. The heartbeat detector—a tool to be covered in more detail under Step 4—failed to detect any heartbeats after even one missing data point, so the remaining missing data had to be filled in somehow. It was decided to use fill-forward—where the most recent data point is written over missing data—because the heartbeat detector was able to detect heartbeats after flat segments while also recognizing that no beats were contained in the missing segment, as shown in Figure 4.

Step 3: Erase troughs and spikes

Figure 5: A Signal with Troughs and Spikes



In Figure 5, observe that the majority of the signal remains around a baseline near 0 mV, but that there are major deviations from this baseline. Some of these deviations are sporadically placed, such as the sharp positive deviations in Figure 5; these types of deviations were termed spikes. Other deviations were placed periodically, each reaching down to about -50 mV; these kinds of deviations were termed troughs. In Figure 5, throughs look similar to the teeth of a comb. These deviations were only present in files 1a and 1b; their cause remains unknown. Nonetheless, they interrupted heartbeat detection in a similar fashion to missing data, so they had to be eliminated.

Figure 6: Zoomed in View of a Trough

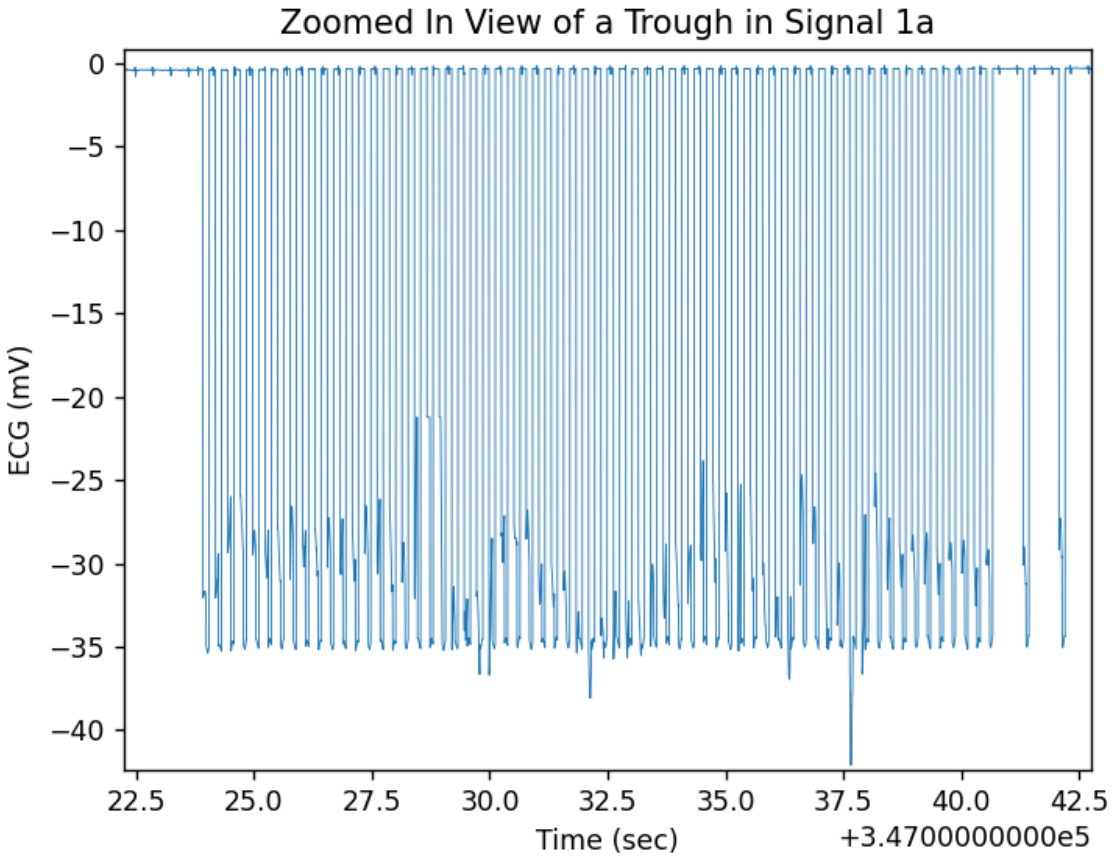
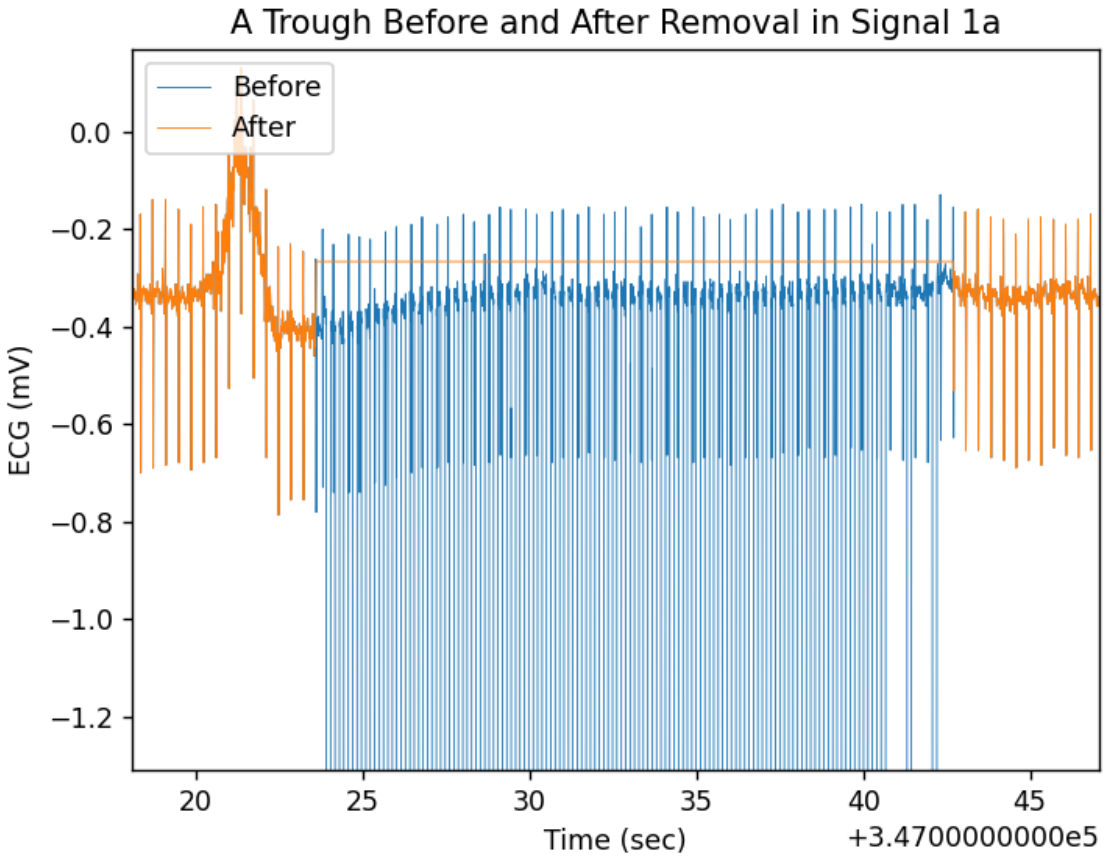


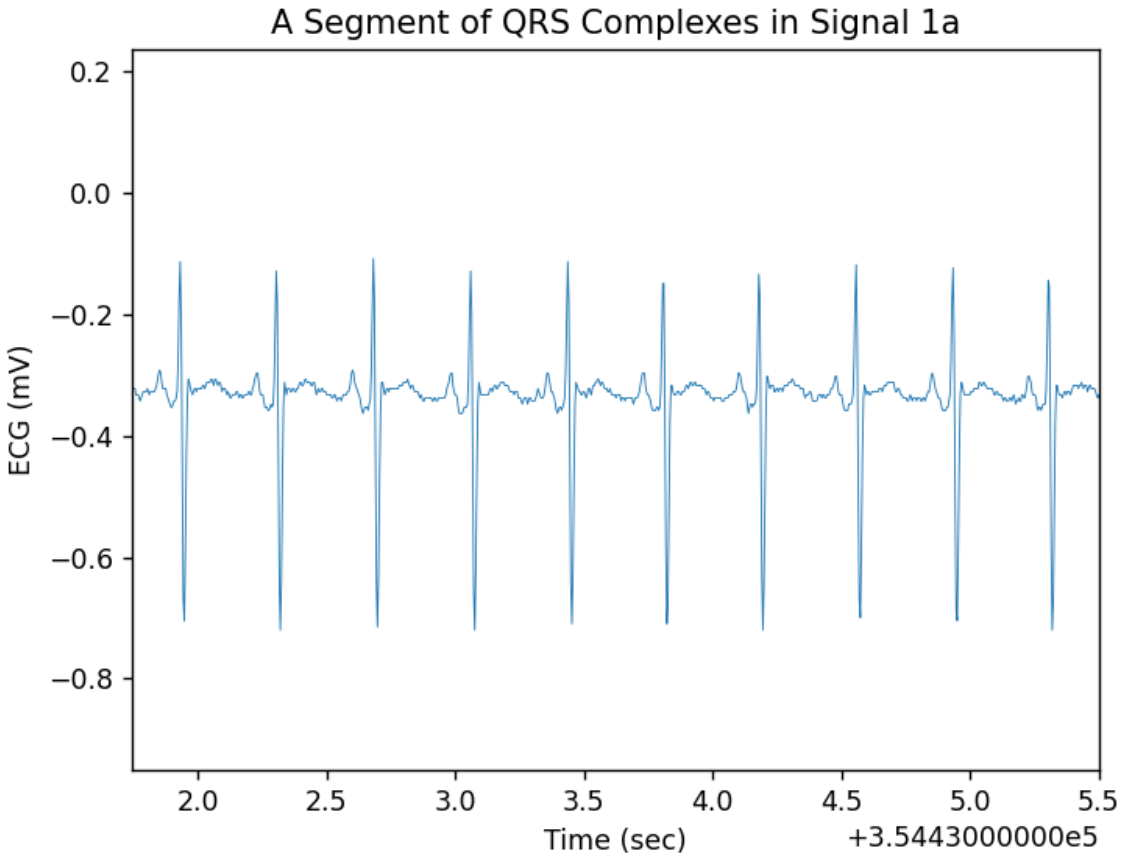
Figure 6 shows a zoomed in view of a through. Observe how the signal rapidly oscillates between baseline and -50 mV. The most expedient way to clean out troughs was to erase them entirely and then use fill-forward on the newly missing segments. This was done in such aa way that the signal outside of the trough was minimally disturbed, as in Figure 7.

Figure 7: Signal Before and After Trough Erasure



Step 4: Detect QRS complexes

Figure 8: A Segment of QRS Complexes



Finally, the signal is clean enough for the heartbeat detector to work.

The proper name for a heartbeat in an ECG signal is a QRS complex; likewise, a heartbeat detector is really called a QRS detector. Figure 8 shows a segment of QRS complexes as they appear in these ECG signals. Note that these are of a different shape than the typical QRS complex of which you may find images online.

Labeling all of the QRS complexes by hand in this amount of data would be an impossible task, so a QRS detector was required. There are many QRS detectors available. For this study, it was decided that XQRS would be used. The reasons for this are:

1. One study found that XQRS can place QRS complexes accurately in time while also keeping other types of error low (Eilers, Chromik, and Arnrich, 2021), and

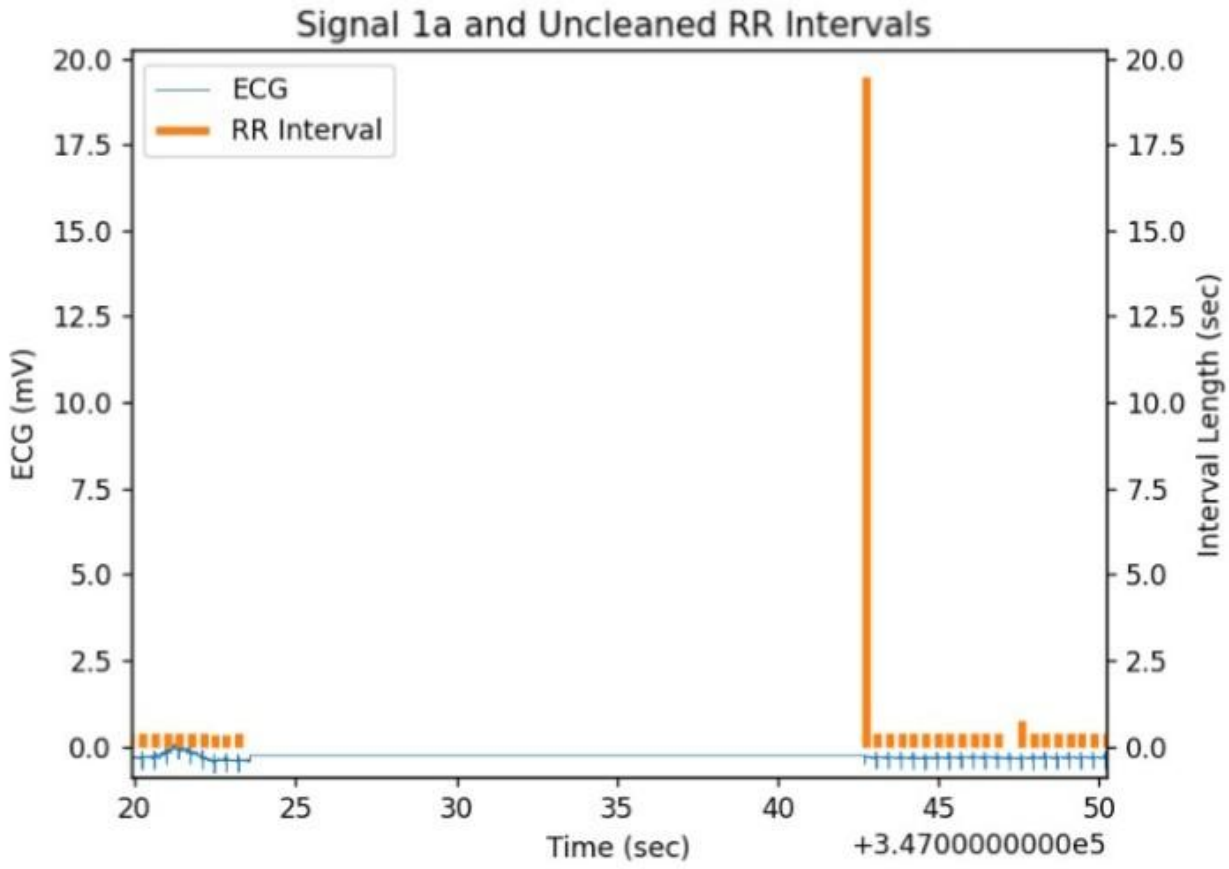
2. XQRS comes with the waveform-database library, so it was readily available.

It was found that XQRS was unacceptably slow if it was fed the whole signal at a time, but was fast if it was fed the signal in chunks, so the signal was broken up into chunks of 10,000 measurements, QRS complexes were detected in each of these, and then the results were combined and stored.

Step 5: Clean up RR intervals

A point of terminology first: the highest point of a QRS complex is called the R peak, and usually this is marked as the location of the beat. An RR interval is then the length of time that passes between each R peak. Most heart rate variability metrics are defined as statistics of the RR intervals.

Figure 9: Examples of Lengthy RR intervals

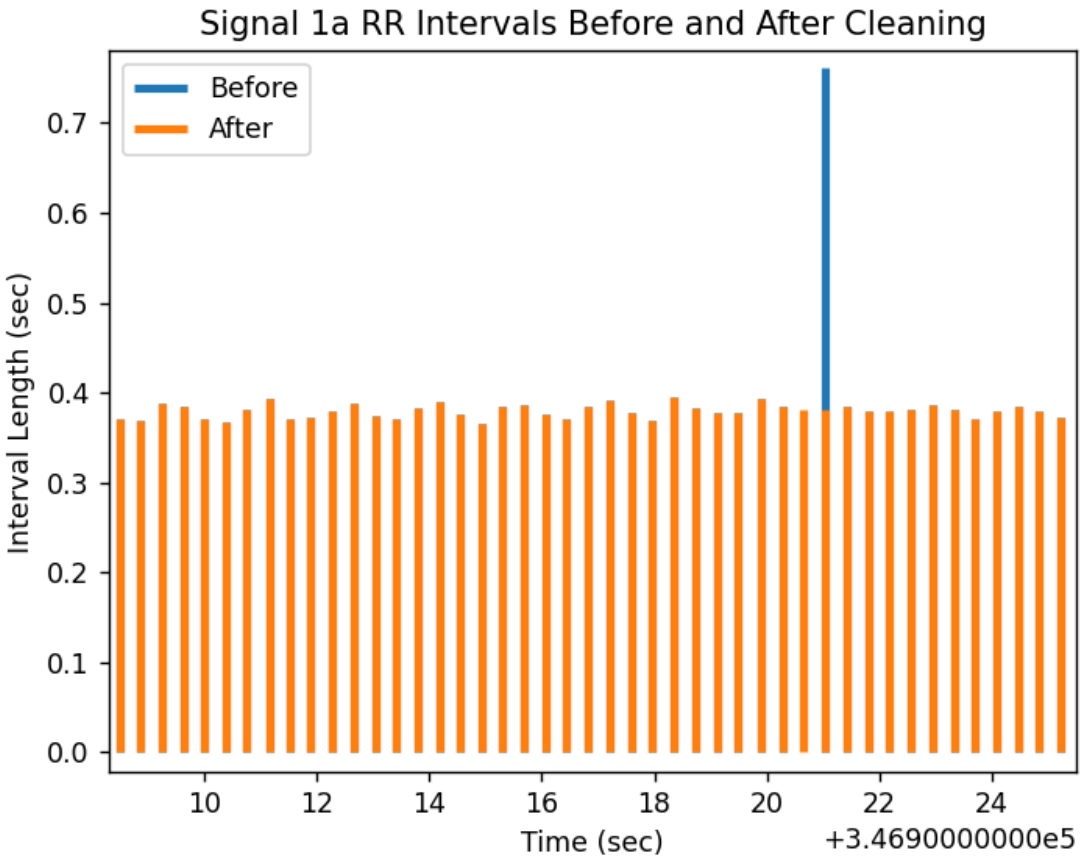


Now, after extracting the R peaks from the ECG, the RR intervals were calculated. It was found that some RR intervals were unrealistically short or unrealistically long, two cases of the latter of which are shown in Figure 9. Dr. Groves suggested that RR intervals shorter than 0.25 seconds be disregarded as physiologically unrealistic. The case of RR intervals that were too long was not as easy to address; as shown in Figure 9, lengthy RR intervals could be due to undetected beats or missing data.

It would be undesirable to throw out every RR interval that was too long, so a suboptimal solution was implemented. First, any RR interval longer than 5 seconds was assumed to be due to missing data (despite some instances were this was false), and was thrown out. Any lengthy RR interval shorter than 5 seconds was assumed to be due to undetected beats (again despite

evidence to the contrary), and was split into a number of equally sized pieces based on the length of the previous interval. The results of this operation are shown in Figure 10, although it is readily admitted that this approach has flaws.

Figure 10: RR Intervals After Lengthy Interval Reduction



Step 6: Calculate heart rate variability metrics

Finally, the data was in a form from which heart rate variability metrics could be calculated. The mean RR interval, *meanRR*, was calculated; this is not a heart rate variability metric, but it was so easy to compute that it was included. Dr. Groves was interested in seeing

four heart rate variability metrics: the standard deviation of the RR intervals, the root mean square of successive differences, the probability ot two consecutive RR intervals differing by more than 50 ms, and the probability of two consecutive RR intervals differing by more than 20 ms, abbreviated as *SDRR*, *RMSSD*, *pNN50*, and *pNN20*, respectively. Detailed discussions of these metrics' definitions and their relation to the nervous system can be found in work by Shaffer and Ginsberg (2017).

These statistics were calculated in a rolling window of 12 hours in length, so that for each of the plots below, for each point in time, the value of the metric at that time point is the metric calculated over the previous 12 hours.

Results

Discussion

Conclusion

Acknowledgements

I would like to give thanks to Dr. Alan Groves for sharing his high level view of this project, and to Joshua Chang for providing programming guidance and mentorship throughout this project.

Glossary

- Blood culture: A test where a sample of blood is incubated to show the presence of bacteria.

- Heart rate variability: The beat to beat variation of heart rate.
- Sepsis: Bacterial infection of the blood stream.

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