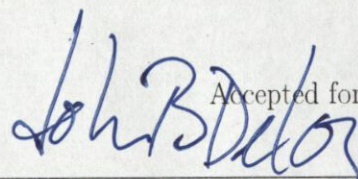# Examination of Noninvasive Alternatives to Blood Pressure Waveform Measurement in Preterm Infants
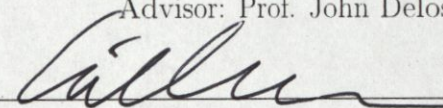
A thesis submitted in partial fulfillment of the requirement
for the degree of Bachelor of Science with Honors in
Physics from the College of William and Mary in Virginia,
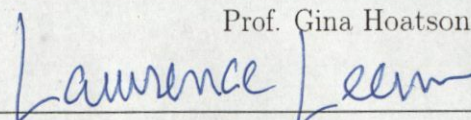
by

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Abstract

Preterm infants are at an elevated risk for a number of medical conditions including shock. Continuous monitoring of the blood pressure (BP) waveform can allow for early detection of such conditions. However, BP is monitored invasively using an arterial catheter. To examine possible non-invasive alternatives, we used ECG, SPO2, and BP data collected from 14 infants at the neonatal intensive care unit (NICU) in Veldhoven, Holland. One hour's worth of data was randomly selected to analyze from the second and penultimate days of each baby's stay. Using the BP waveform together with the ECG, we calculated the R-peak to BP-trough time (RTT), BP-trough-to-peak time (PW), and BP amplitude (A). Using the SPO2 and ECG data, which can be taken continuously and non-invasively, we calculated the corresponding quantities for the SPO2 waveform (sRTT, sPW, and sA). We then calculated the correlations between each pair of quantities and between each quantity and systolic, diastolic, and average BP. We observed little correlation between corresponding wave components and little consistent correlation between SPO2-derived variables and BP. However, sRTT showed a consistently strong negative correlation with A and PW over both hours analyzed. Because these correlations decreased consistently in absolute value over each babies stay, we they could be markers of illness. Despite this, the clinical significance of these correlations is limited, and future work will focus on searching for correlates of BP that are functions of multiple SPO2- and ECG-derived quantities.

Chapter 1

Introduction

1.1 The Blood Pressure Waveform

Preterm infants are at a higher risk than full-term infants for a number of medical conditions including septic shock, a state of insufficient blood flow to the tissues due to the activity of pathogens. The major clinical indicator of shock is a dangerously low blood pressure (BP). However, in the early stages of shock, vasoconstriction can compensate for reduced blood volume to maintain a stable blood pressure, and it may only become obvious that the patient is in shock after the patient's condition has become critical [3]. The blood pressure waveform, a continuous curve of BP vs. time for some position in the arterial tree, provides information on both blood pressure and vasoconstriction.

The relationship between the blood pressure waveform and vasoconstriction is due to the dynamics of blood flow. Each heartbeat produces a pressure pulse in the aorta which propagates down the arterial tree. The speed of the pressure pulse is determined by the distensibility of the artery, D, where

$$D = \text{(fractional change in volume)}/\text{(change in pressure)} = \frac{(dV/dP)}{V}. \qquad (1.1)$$

The velocity of the pressure wave, PWV, is then

$$PWV = \sqrt{\frac{V}{\rho}\frac{dP}{dV}} = \sqrt{\frac{1}{\rho D}} \quad , \tag{1.2}$$

where ρ is the density of the fluid, in the case blood, which is for all intents and purposes a constant [5].

Thus, the speed of the pressure wave is inversely related to distensibility. Over the short term, distensibility is primarily dependent on vasodilation and vasoconstriction. The BP waveform shows the pressure wave as it propagates past the arterial catheter used as a pressure detector. We denote this time as Pulse Width, PW.

$$PW = \text{time of BP peak} - \text{time of previous BP trough} \tag{1.3}$$

If we define the pulse length, λ, as the distance in space from the peak of the pressure pulse at a given time to the furthest location down the artery where any increase from baseline pressure is detectable, then we can write the Pulse Width as

$$PW = \frac{\lambda}{PWV} \tag{1.4}$$

Thus, we cannot calculate PWV from PW since we have no way of measuring λ.
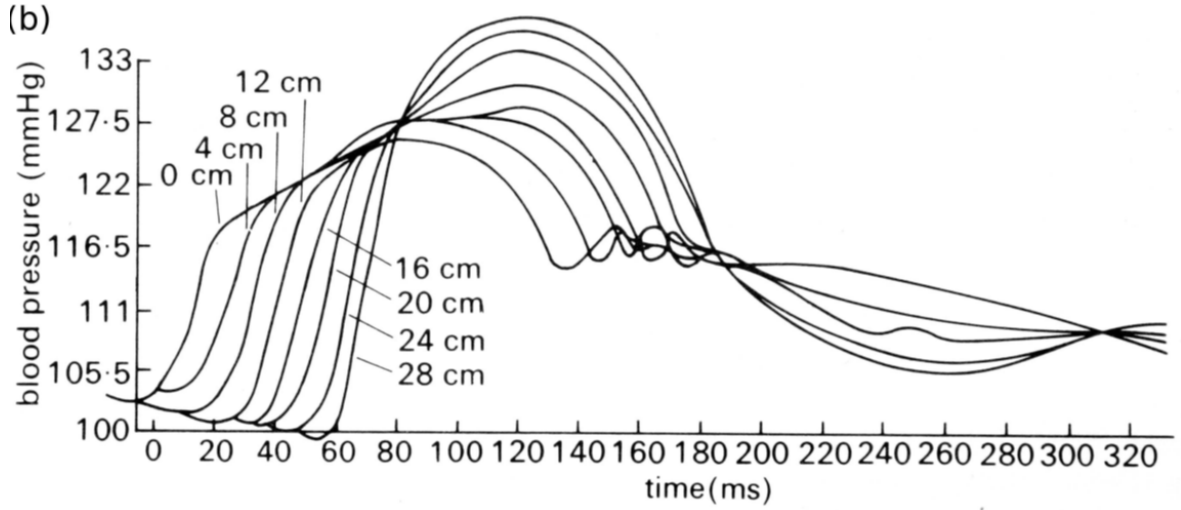
Figure 1.1: A plot of the blood pressure waveform as measured at various distances from the left ventricle. Note that both time and amplitude differences between the wave peak and trough vary considerably depending on location [1].

Furthermore, neither λ nor distensibility and thus PWV are constant throughout the arterial tree. The larger arteries closer to the heart have much higher distensibility and thus lower speeds. In fact, in adults "the velocity of pressure pulse transmission in the normal aorta is 3 to 5 m/sec; in the large arterial branches, 7 to 10 m/sec; and in the small arteries, 15 to 35 m/sec" [4]. The shape of the pressure pulse varies as well, as shown in Figure 1.1. Therefore, to get a measure of total arterial stiffness, we must use the pulse transit time, the time taken between the generation of the pulse at the heart and the time of the trough of the BP waveform, which corresponds to the arrival of the pressure wave at the measurement site.
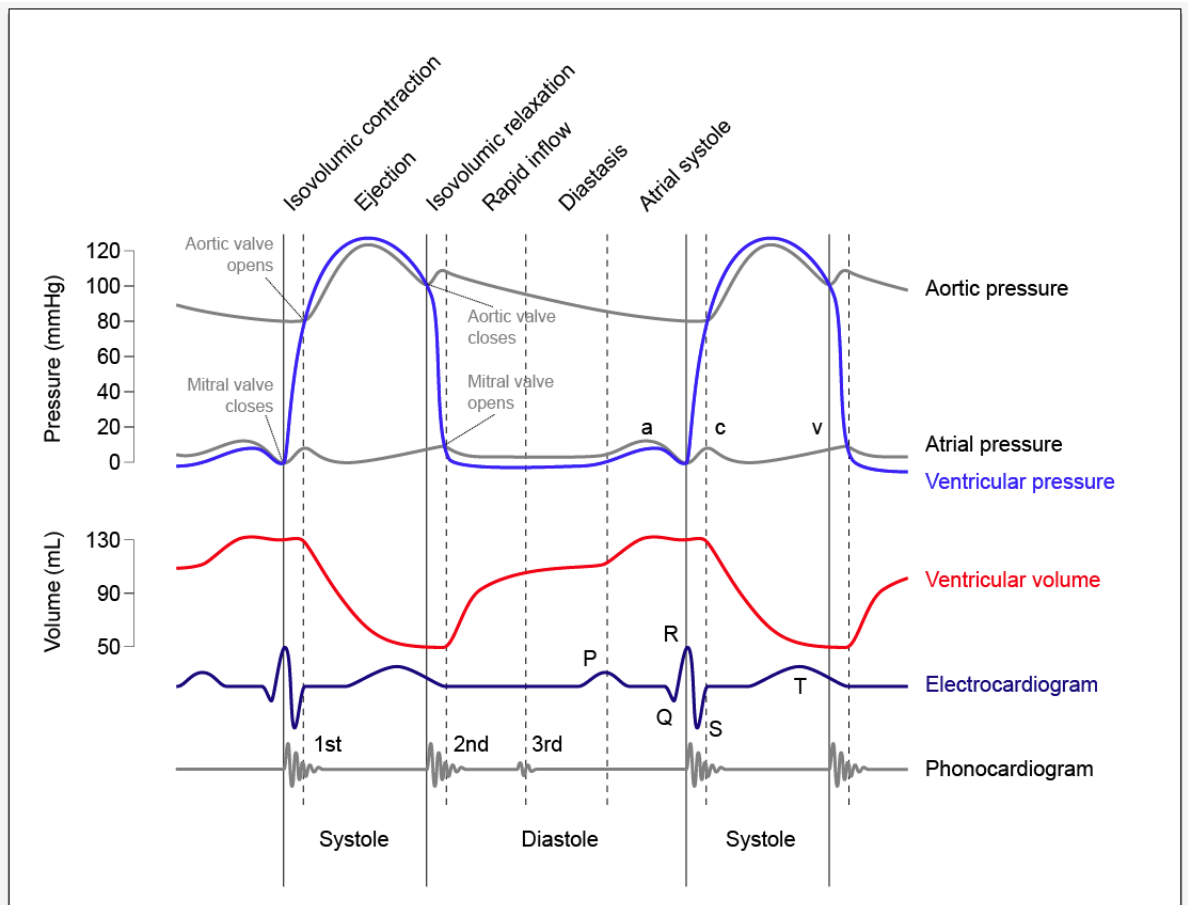
Figure 1.2: A diagram of the cardiac cycle showing aortic and ventricular pressure and electrocardiogram waves. Note the time delay between the R-peak of the ECG and the trough of the aortic pressure wave. This pre-ejection period corresponds to the isovolumetric contraction of the left ventricle. [4]

Figure 1.2 shows that the trough of the pressure pulse in the aorta occurs when the aortic valve is opened after isovolumetric contraction of the heart. This occurs shortly after the appearance of the R-wave in the ECG which marks the beginning of cardiac contraction. The time between the R-wave and the beginning of the pressure pulse is the Pre-Ejection Period, which lasts for about 100 ms in adults [8]. Since the Pre-Ejection period is short, we can thus estimate the actual pulse transit time by the time between the arrival of the pulse at the catheter and the previous R-peak of the ECG. We denote this as R Transit Time, RTT.

$$RTT = \text{time of BP trough} - \text{time of previous R-peak in the ECG} \quad (1.5)$$

However, it is important to keep in mind that RTT is only an estimate of the actual transit time due to the addition of the pre-ejection period. One study in adults has noted that the time contribution of pre-ejection period to RTT accounted for a substantial and variable (12-35%) portion of RTT [8]. Thus, we expect our inability to account for pre-ejection period may be a potential source of failure to finding consistent correlations between RTT and other markers of vasoconstriction.

Vasoconstriction causes an increase in average blood pressure, which suggests that it should correlate positively with blood pressure. Average blood pressure can be calculated from the BP waveform by averaging it over the course of a heartbeat, which we define as the interval between two R-peaks. Just as clinically important are the diastolic and systolic blood pressures, which correspond to the trough and peak values of the BP waveform. We will refer to difference between these values as the Amplitude, A, of the BP waveform.

$$A = \text{BP peak pressure} - \text{previous BP trough pressure} \quad (1.6)$$

Thus, the BP waveform provides useful information about both blood pressure and degree of arterial vasoconstriction. Unfortunately, in the setting of the neonatal

intensive care unit (NICU) continuous monitoring of blood pressure is impractical. It requires insertion of a catheter into the artery, which is highly invasive and undesirable for healthy infants. A noninvasive method for estimating blood pressure and arterial rigidity is therefore desirable for use in cases where catheterization is inappropriate. We consider such an alternative using the peripheral capillary oxygen saturation (SPO2) in the blood.

1.2   The SPO2 Waveform

SPO2 is continuously monitored in the NICU using a pulse oximeter attached to the hand or foot. It is measured using a photoplethysmometer which shines a beam of light onto the wrist, and measures the absorption spectrum of the reflected beam. Because the spectrum of the blood in the arteries is the only part of the signal that changes rhythmically with each heartbeat, the contributions of the surrounding tissue can be filtered out. Oxygenated and deoxygenated hemoglobin emit different frequencies of light, so the ratio of oxygenated to deoxygenated hemoglobin in the arterial blood can be calculated. This ratio gives the peripheral oxygen saturation in the arterial capillaries (SPO2).

The SPO2 waveform rises and falls as each volume pulse of oxygenated arterial blood enters the peripheral arteries. Thus, SPO2 is a measure of the blood volume wave, the peaks and troughs of which correspond to the peaks and troughs in the blood pressure waveform in the peripheral arteries where the SPO2 is taken. This raises the possibility that we can use the SPO2 waveform as a substitute for the BP waveform for estimation of blood pressure and arterial stiffness. For each of the quantities defined above for the BP waveform, Pulse Width, R Transit Time, and Amplitude (PW, RTT, and A), we define a corresponding quantity for the SPO2

waveform (sPW, sRTT, and sA).

$$sPW = \text{time of SPO2 peak} - \text{time of previous SPO2 trough} \qquad (1.7)$$

$$sRTT = \text{time of SPO2 trough} - \text{time of previous R-peak in the ECG} \qquad (1.8)$$

$$sA = \text{SPO2 peak value} - \text{SPO2 trough value} \qquad (1.9)$$

Of course, since SPO2 measures oxygen saturation, its magnitude depends on the degree of ventilation, which is not taken into account by the blood pressure waveform. Therefore, we do not expect the absolute magnitude of the SPO2 to be related to blood pressure. In addition, while the BP waveform is measured in a single artery, the SPO2 is an average over however many peripheral arteries fall within the beam of the pulse oximeter. Since the SPO2 and BP waveform are taken at different points in the arterial tree, the relation between BP and SPO2 waveforms will also depend on the relation between the true blood pressures at the respective points. For example, if blood were redirected into the trunk at the expense of the extremities, SPO2 measured in the periphery would show a negative relation to BP measured in the aorta even assuming a perfect correspondence between SPO2 and BP locally.

Despite this, we will test the hypothesis that the SPO2 waveform can correlate with BP by examining the correlation between the sPW, sRTT, and sA with the corresponding features of the blood pressure waveform. An example heartbeat showing these variables is given in Figure 1.3. Since the correspondence is not exact, the correlation of different features of different waves will be considered. In addition, we will examine correlations between features of each individual wave and whether these correlations are similar for the SPO2 and BP waves. Most importantly, we consider whether any elements of the SPO2 correlate with blood pressure.

To compare the time it takes for the BP pulse wave to arrive at the site of the BP catheter vs the site of the pulse oximeter, we also measure the Peak Time Difference, PTD and Trough Time Difference, TTD.

$$PTD = \text{(time of SPO2 peak)} - \text{(time of BP peak)} \tag{1.10}$$

$$TTD = \text{(time of SPO2 trough)} - \text{(time of BP trough)} \tag{1.11}$$

Fluctuations in these quantities give information about the pressure pulse wave velocity between these two sites, if they occur along the same branch of the arterial tree, or about differences in PWV across different branches of the arterial system, if the two sites are located along separate branches.
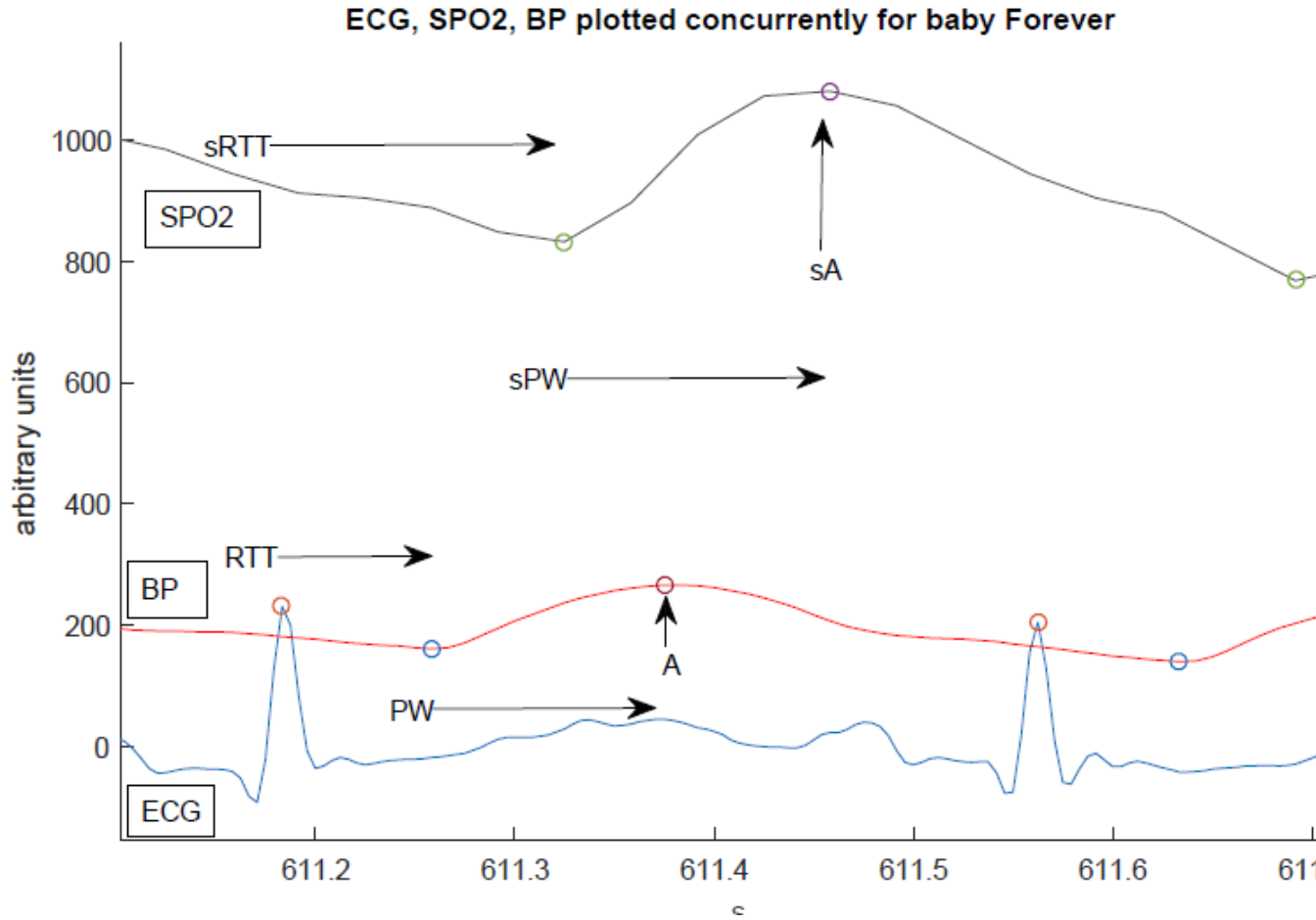
Figure 1.3: An example R-to-R interval taken from the baby Forever with some of the quantities we calculated displayed. From top to bottom the peripheral oxygen saturation, SPO2, blood pressure (BP), and electrocardiogram (ECG) waveforms are displayed.The three quantities measured from the SPO2 are sRTT (R-peak to SPO2 trough), sPW (SPO2 trough to SPO2 peak), and sA (amplitude of SPO2 waveform). RTT, PW, and A are defined similarly for the blood pressure (BP) wave.

Chapter 2

Data

The anonymized data used were collected in 2008 from the Veldhoven NICU in Holland, with approval from the ethical board. Each record consisted of data from a single baby monitor recorded over one hour. ECG data was collected from three leads at 240 Hz (240 times per second). SPO2 data was collected at 60 Hz and given in arbitrary units. Systolic, diastolic, and average blood pressure measurements in mmHg were taken at two-second intervals. A continuous blood pressure wave form was collected at 120 Hz from a catheter inserted into an artery. The location of this catheter may have varied with the patient. At this moment we do not have the exact locations. Dr. Peter Andriessen, who was involved in collecting the data, mentioned that possible locations included near or in the aorta, the radial artery in the arm, or the tibial artery in the leg.

Data was collected continuously over each baby's stay in the NICU. Stays varied from as little as two days to over a week. For each infant, we analyzed a randomly selected hour's worth of data from the second day and the same hour of the penultimate day in the NICU. Not all babies had sufficiently long stays or sufficiently good data for this procedure, so for two of the infants we analyzed the first and last days instead. If no good data was available during the second or penultimate, the third or third to last days were used instead and so on. This information is given in the Table

Baby	Total	Days Before 1st	After 2nd	Interval
Forever	6	1	1	3
Gracious	6	1	1	3
Handsome	2	0	0	1
Heard	2	0	0	1
Honeybee	6	1	1	3
Laurels	10	1	5	3
Lifegiving	8	1	3	3
Log	6	1	1	3
Meadow	10	1	1	7
Pleasant	11	1	2	7
Steadfast	7	2	1	3
Wiseone	9	1	1	6
Wisetwo	8	1	1	5
Yourhonor	6	1	1	3
Youthful	6	1	2	2

Table 2.1: Days spent in the NICU. Total gives the total number of days the baby spent in the NICU (or at least those for which data was recorded), Before 1st gives the number of days spent in the NICU before the first day chosen for analysis, After 2nd gives the number of days in the NICU after the second day chosen for analysis, and Interval gives the number of days between the two hours analyzed.

2.1. In the future, this analysis could be expanded to encompass the data from the entire duration of each baby's stay.

Chapter 3

Data Analysis Procedure

3.1 Data Extraction

We used MATLAB to analyze the NICU data. A major part of this work was data cleaning. In order to find the R-Peaks of the ECG we used an implementation of the Pan-Tompkins algorithm provided by William and Mary graduate student Denise McKaig. The algorithm's peak detection ability varied based on the ECG lead. Thus, to choose the best ECG lead for each hour, the peaks for each lead were calculated and the lead with the lowest standard deviation of peak-to-peak interval time was chosen, provided it had over 1,000 peaks and thus was not just failing to register much of anything. ECG traces from two example leads are shown in Figures 3.1 and 3.2.

In the SPO2 data, a step-like artifact was observed, with SPO2 flat-lining between every other pair of points. Since we would expect blood oxygen to increase smoothly, the data were corrected by taking a moving average over each two points. This removed the artifact, and had the advantage that the result contained only one fewer point than the original data and was symmetric as opposed to left or right shifted. Figure 3.3 gives an example of this process.

The SPO2 signal fluctuated roughly sinusoidally with a period of about 0.4 seconds
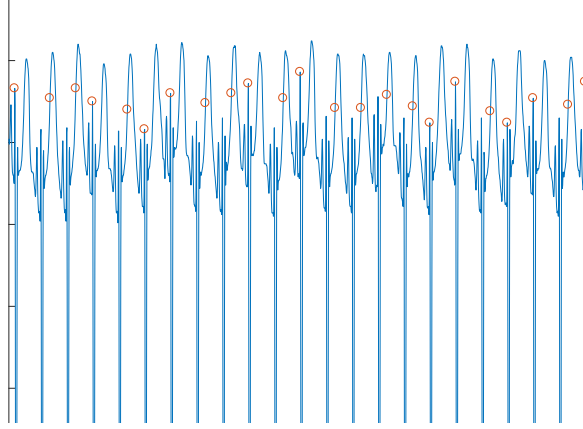
Figure 3.1: The ECG I lead for one of the babies. Red circles show the peaks found by the algorithm. Because of artifacts, the algorithm does not consistently recognize peaks, resulting in a poor signal. The bad signal quality results in high variance in the length of R-to-R intervals, so the algorithm rejects the signal in favor of an alternative ECG lead.
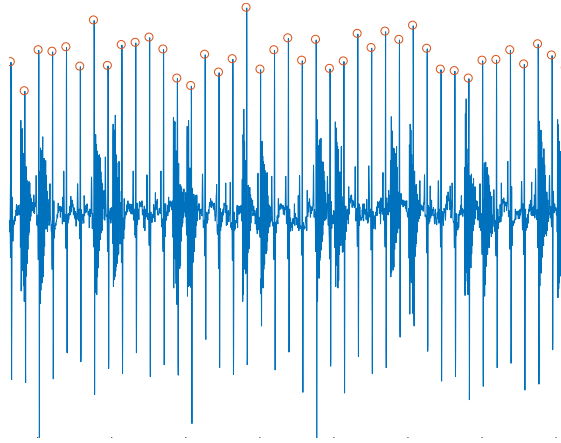
Figure 3.2: The ECG II lead for the same baby. Red circles show the peaks found by the algorithm. Since the algorithm successfully and consistently finds peaks in this signal, R-to-R peak spacing is relatively constant and the algorithm chooses this lead to analyze, unless the ECG III lead is better.

(2.5 Hz), although multiple peaks and troughs occurred in periods of noise. Figure 3.4 shows that the SPO2, ECG, and BP waveforms share the same period, with an SPO2 trough typically occurring shortly after each ECG peak.

In theory, the trough of the SPO2 waveform should always follow the R-peak of the
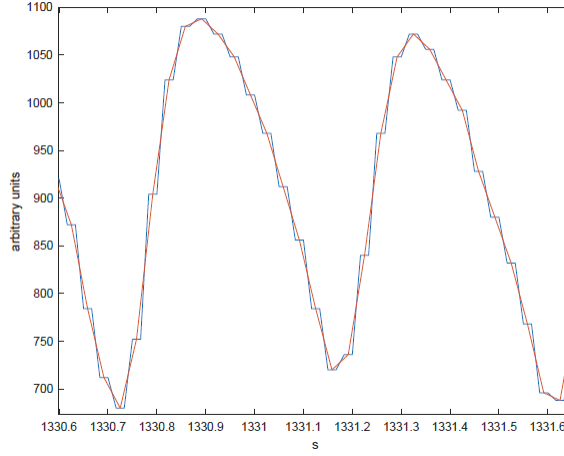
Figure 3.3: The stair step discontinuities of the original SPO2 (blue) corrected by calculating a new SPO2 (red).

ECG, since blood oxygen content in the capillary bed and thus SPO2 cannot increase until the pulse of freshly oxygenated blood arrives from the heart. However, we found that the relative position of the SPO2 waveform with respect to the ECG waveform varied throughout the hour, occasionally resulting in SPO2 troughs occurring before the peaks of the ECG waveform. In these cases, the relation between the SPO2 and ECG is unclear, so we have excluded them from our study by removing SPO2 waves in which the peak precedes the trough after the R-wave.

The blood pressure waveform is also coupled with the ECG, with each R-R ECG interval corresponding to a blood pressure trough followed by a peak. This synchronization of SPO2 and blood pressure with the cardiac cycle made it convenient for us to calculate quantities and take averages on a per heartbeat basis
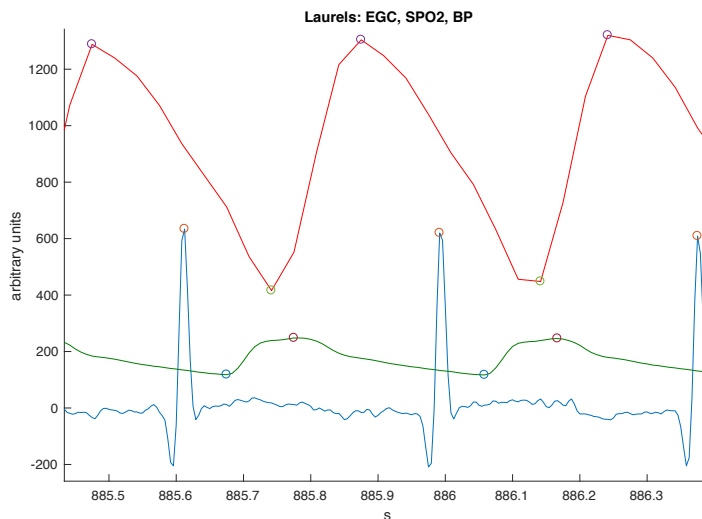
Figure 3.4: SPO2 (red), ECG(blue), and BP (green), shown on the same time scale for the second hour analyzed from the baby Laurels.

3.2 Data Filtering

We observed artifacts and noise in ECG, SPO2, and BP data. However, since the interval between R-peaks in the ECG was largely unaffected by noise, we chose to filter only the SPO2 and BP waveforms. Each section of the SPO2 and BP waveforms lying between R-peaks was considered independently for acceptance or rejection. Preliminary peaks for the two waveforms were found using the MATLAB function 'findpeaks()'. We observed that while good SPO2 waveforms had only one peak, good BP waveforms often had a shoulder lagging the main peak, sometimes resulting in a secondary peak and trough. This shoulder is the dicrotic notch, which occurs normally and corresponds to the closure of the aortic valve [6]. Thus, while we chose to exclude intervals of SPO2 with more than one peak per cardiac cycle, we accepted multiply peaked BP intervals, choosing to use the highest peak and lowest trough for our calculations. Intervals with extreme values for blood pressure or SPO2 or

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peak-to-trough heights outside of the normal range were also filtered out using the parameters for blood pressure and SPO2 given in Table 3.1.

Due to the periodic nature of the SPO2 and BP waveforms, with consistent frequencies of around 2.5 Hz, we also filtered based on the Fast Fourier Transforms (FFT) of the portion of the SPO2 and BP waveforms on the R-R interval. Because of the small number of sample points for each heartbeat, most good waveforms had nearly all of their power in the second point. Thus we chose to define the power ratio of a waveform over a given heartbeat as the square of the second point of the FFT divided by the sum of the squares of all points. We filtered out all points with power ratios below a certain cutoff level, which was determined by comparing this ratio for a number of heartbeats with both good and bad waveforms. The cutoff is given in Table 3.1. Examples of good and bad FFT's are given in Figures 3.5 and 3.6.

Discard If	BP	SPO2
Any point <	0.7x(median trough height)	400
Any point >	1.5x(median peak height)	1500
# Peaks/Troughs >	NA	1
Power Ratio <	0.8	0.5
Trough to Peak Height <	1	0.7x(median peak to trough height)
Trough to Peak Height >	250	2x(median peak to trough height)

Table 3.1: Filter criteria for SPO2 and BP. The units are those used in the raw data files.

Using the filtered SPO2 and BP waveforms, peaks, and troughs, along with the ECG R-peak locations, we calculated all other quantities (RTT, average BP, sPW, A etc) for each heartbeat. A given quantity was only calculated if all the waveforms on which it depended had good filtered data on that interval.

To compare two calculated quantities, we first removed all heartbeats where one or both quantity lacked filtered data. We then found the Pearson correlation for
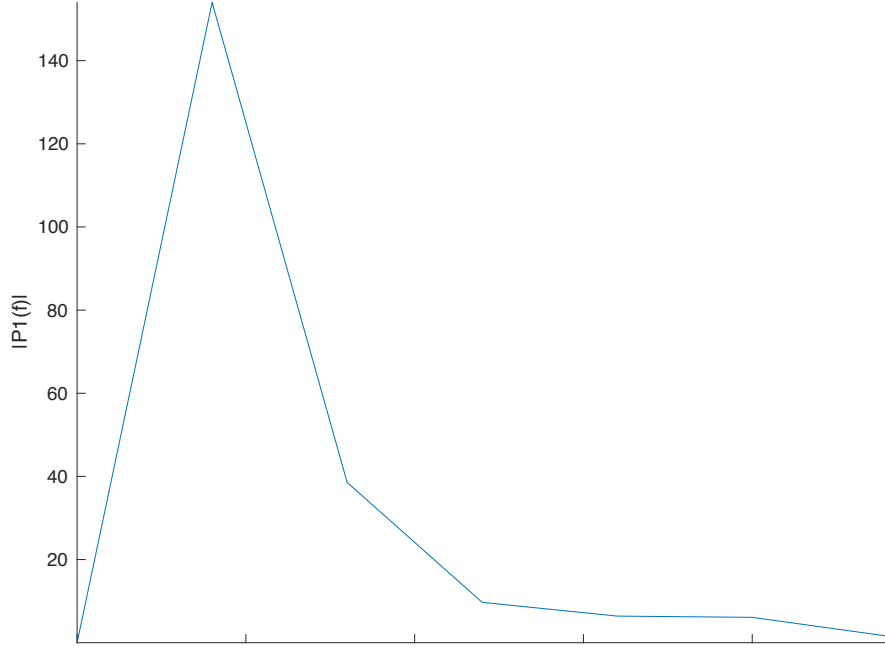
Figure 3.5: A Fourier transform from the baby Youthful taken over the SPO2 points between two R-peaks in the ECG during an interval of good data. Given the small number of points, it is sharply peaked around 2.5 Hz, which corresponds to the second point, and thus has a power ratio above the cutoff level

the two quantities averaged over 1, 5 and 10 filtered heartbeats. For the 5 and 10 heartbeat averages, there was the possibility that, due to a long stretch of bad data, filtered heartbeats a long time apart would be included together in the same average. Thus, only heartbeats within the 0.5 seconds times the number of heart beats being averaged over were included in any given average, and if the end of the interval was reached before the given number of heartbeats, the first heartbeat to fall outside the interval was used as a starting point for taking the next average.

In order to take into account the possibility of changes in blood pressure lagging or leading changes in APPPT, DPO, or some other calculated quantity, we used the normalized cross correlation to find the lag at which the absolute value of the Pearson correlation coefficient was greatest. We then calculated the Pearson correlations,
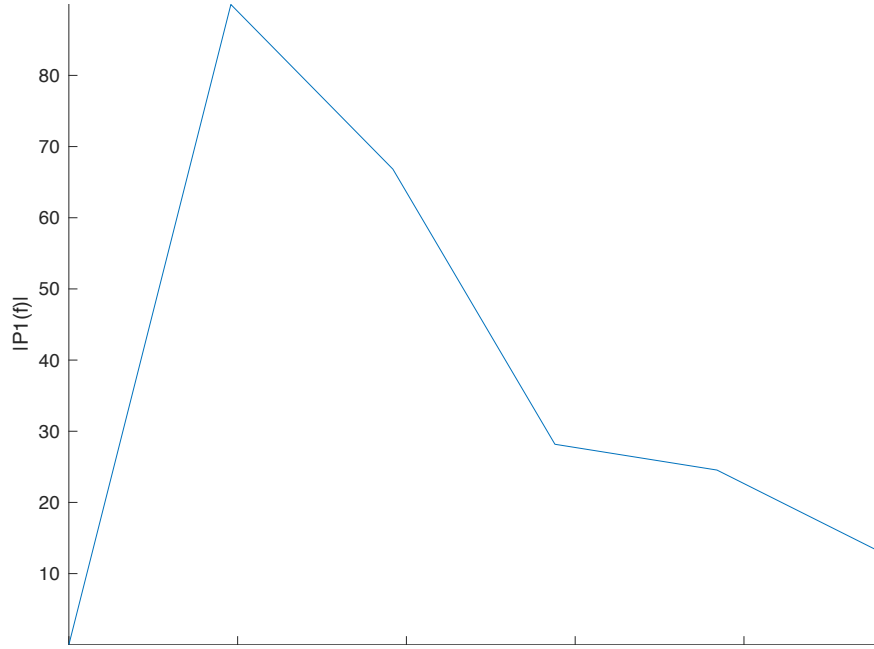
Figure 3.6: A Fourier transform from the baby Youthful taken over the SPO2 points between two R-peaks in the ECG during an interval of noisy data. The peak is much less sharp and there is much more power at higher frequencies, corresponding to points after the second point, leading to a power ratio below the cutoff level.

linear models, and R-squared values for each pair of quantities, averaged over the given number of heartbeats.

Chapter 4

Results

4.1 Overview of Correlations

For the quantities calculated, we found that the maximum absolute value of the normalized cross correlation tended to occur at either zero lag, or at a lag on the order of hundreds of heartbeats which is much too long to be physiologically plausible. These large lags are mathematical artifacts of the cross-correlation function which occur when the data contains a roughly equal number of regions of both positive and negative correlation. Since such lags don't represent any real attunement of the data, we conclude that correlations between all quantities should be calculated with no lag. This suggests that if there is any causal relation between the quantities calculated, it occurs on the timescale of the single heartbeat.

Comparing the correlations of quantities averaged over 1, 5, and 10 heartbeats, we found that there was a consistent small increase in the absolute value of the correlations found, especially for correlations already above 0.1, as data was averaged over longer intervals. This is confirmation that the filtering process is functioning well, since if correlations were caused by large localized spikes due to noisy data, we would expect them to decrease when these spikes were averaged with the surrounding values. Since this is not the case, the physiological processes linking the SPO2, ECG,

	avgBP	diasBP	sysBP	A	PW	RTT	sA	sPW	sRTT
avgBP		0.9±0	0.9±0.1	0.1±0.4	0.3±0.3	0.2±0.3	-0.1±0.2	0.1±0.1	0±0.2
diasBP			0.8±0.2	-0.1±0.4	0.2±0.3	0.2±0.3	-0.1±0.2	0.1±0.1	0.1±0.2
sysBP				0.5±0.3	0.3±0.3	0.2±0.3	-0.1±0.2	0.1±0.2	-0.2±0.2
A					0.3±0.5	0±0.3	0±0.2	0.1±0.2	-0.4±0.2
PW						-0.1±0.4	0.1±0.3	0.2±0.2	-0.4±0.3
RTT							-0.1±0.2	0.1±0.1	0.1±0.3
sA								0.1±0.2	-0.1±0.3
sPW									-0.3±0.4
sRTT									

Table 4.1: Average correlation between each pair of calculated quantities plus or minus standard deviation for a randomly selected hour on the second day of the NICU stay for all 14 babies. All quantities are averaged over 10 filtered heartbeats.

	avgBP	diasBP	sysBP	A	PW	RTT	sA	sPW	sRTT
avgBP		1±0	1±0	0.5±0.2	0.2±0.3	0.3±0.2	-0.1±0.4	0.1±0.2	0.1±0.3
diasBP			0.9±0.1	0.2±0.3	0±0.3	0.3±0.2	-0.2±0.4	0±0.2	0.2±0.3
sysBP				0.7±0.2	0.3±0.3	0.2±0.2	-0.1±0.4	0.1±0.2	0±0.3
A					0.6±0.4	0±0.1	0.2±0.3	0±0.2	-0.2±0.2
PW						-0.1±0.2	0.3±0.2	0.1±0.2	-0.3±0.2
RTT							-0.1±0.2	0±0.1	-0.1±0.2
sA								0.1±0.3	-0.3±0.2
sPW									-0.2±0.3
sRTT									

Table 4.2: Average correlation between each pair of calculated quantities plus or minus standard deviation for the same hour on the penultimate day of the NICU stay for all 14 babies. All quantities are averaged over 10 filtered heartbeats

and BP signals must operate continuously and over multiple heartbeats corresponding to time periods of at least two-three seconds. Thus, in the following discussion, we will consider the correlations found between variables averaged over 10 heartbeats, the longest time scale used.

The two large tables (4.1 and 4.2) give the average correlations across all 14 infants

for each pair of the variables calculated along with the associated standard deviations. The first table is calculated using random hours from the second day in each infants stay in the NICU, and the second table is calculated from the the same hours on the penultimate day (for precise details of stay length and number of intervening days see Table 2.1). The three largest correlations in each table, in the upper left hand corner are merely correlations of the BP with itself and therefore expected. More interesting is the fact that the amplitude, A, and Pulse Width, PW, are substantially positively correlated both with each other and with the systolic BP and much less correlated with average and diastolic BP. The estimated transit time, RTT, also shows a weak but consistent positive correlation with systolic, but not diastolic or average, BP. Thus, increasing systolic pressure tends to decrease the speed of pulse propagation. This is the opposite result from the strong negative correlation between systolic BP and RTT that has been observed in previous studies on adults [7]. From Equation 1.3, $PW = \frac{\lambda}{PWV}$, so it is likely that the similar increase in PW is also due mostly to increased PWV as opposed to lengthening of the pressure pulse.

This contradicts our hypothesis that the RTT is determined primarily by arterial rigidity and thus degree of vasoconstriction. In that case, since vasoconstriction both decreases distensibility and raises BP, we expect a faster PWV and thus a shorter RTT. A possible explanation is that the correlation between BP and and RTT is the result of increased heart rate. If the heart beats faster and harder, blood pressure will increase. However, especially in the circulatory system of the preterm infant which is still adjusting in the wake of birth, increased heart-rate could result in a more turbulent blood flow, or greater interference from the reflected wave. If these slowed the pressure pulse down sufficiently to counteract the effect of vasoconstriction, a positive correlation such as that observed could result.

Comparing the correlation of the BP waveform to the correlations between the

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corresponding quantities from the SPO2 waveform (sA and sPW) and systolic blood pressure, we fail to find a corresponding relation. On both the second and penultimate days, the Pulse Width and Amplitude of the SPO2 have average correlations with absolute values of 0.1 or less with the systolic BP with a standard deviation of over twice the average value. The inconsistency in the case of the amplitude is likely due to the dependence of blood oxygen saturation on air intake via the lungs, which is not captured by BP variation. The cause of the lack of correlation between systolic BP and sPW is less obvious. Since the BP at the site of SPO2 measurement (either the hand or the foot) is not known, it is unclear whether this lack of correlation means that the SPO2 Pulse Width is insensitive to BP locally or merely that, due to reflection and disorderly propagation down the arterial tree, the systolic pressure pulse as measured in the catheterized artery is unrelated to the systolic pressure in the peripheral arteries.

The most potentially useful correlations are those between sRTT, the estimated pulse transit time for the SPO2, and A and PW from the BP waveform. These correlations are consistently negative, greater than 0.1, and over one standard deviation away from zero across both days. Notably, both correlations decrease in absolute value from the second to the penultimate day, suggesting that this negative correlation could be associated with illness. Despite the strong correlations between A and PW and the systolic blood pressure, sRTT and systolic BP are only weakly negatively correlated.

These correlations tell us that the time it takes the blood pressure pulse to arrive at the peripheral capillary bed decreases as PW and A of the BP pulse in the artery increases. Interestingly, there is no consistent correlation between RTT and sRTT. The physical meaning of these correlations is dependent on the location of the intra-arterial catheter used to measure the BP waveform. Since SPO2 is taken in the

peripheral arteries in the hand or foot, no intra-arterial catheter can be placed at a point further along the arterial tree than the SPO2 is monitored at.

Thus, the arterial catheter may be either located directly "upstream" of the pulse oximeter, or it may be located in a different branch of the circulatory system entirely, for example in the tibial artery of the leg if the SPO2 cuff is placed around the hand. In the first case, the same pressure pulse propagates sequentially past both devices, so

$$sRTT = RTT + \text{pulse transit time from catheter to oximeter site} \qquad (4.1)$$

This would imply that the Trough Time Difference, TTD, defined as SPO2 trough time minus BP trough time is always positive. However, the calculated TTD values from all babies contain a considerable number of points with negative values. Therefore, unless all of these points are in error, we can conclude that the BP catheter was placed in an artery in a different branch of the arterial tree than wherever the SPO2 was monitored.

In this case, the lack of substantial correlation between RTT and sRTT is reasonable. To explain the strong negative correlations between sRTT, A and PW we consider the implications of the changing shape of the pressure pulse from Figure 1.1, which is redrawn in the accompanying figure. The BP pressure pulse begins in the aorta as a relatively shallow wave with a trough near the end. However, as the wave propagates down the arterial tree, reflections from curves in the arteries and bifurcations oppose the progress of the pressure wave. This results in a "crumpling" of the front section of the wave and the increase in amplitude of the peak. The crumpling causes the trough of the wave to move backwards in time. Since we measure sRTT from the trough of the SPO2 wave, which should correspond roughly with the trough of the BP wave, waves that experience greater crumpling should have longer sRTT's.
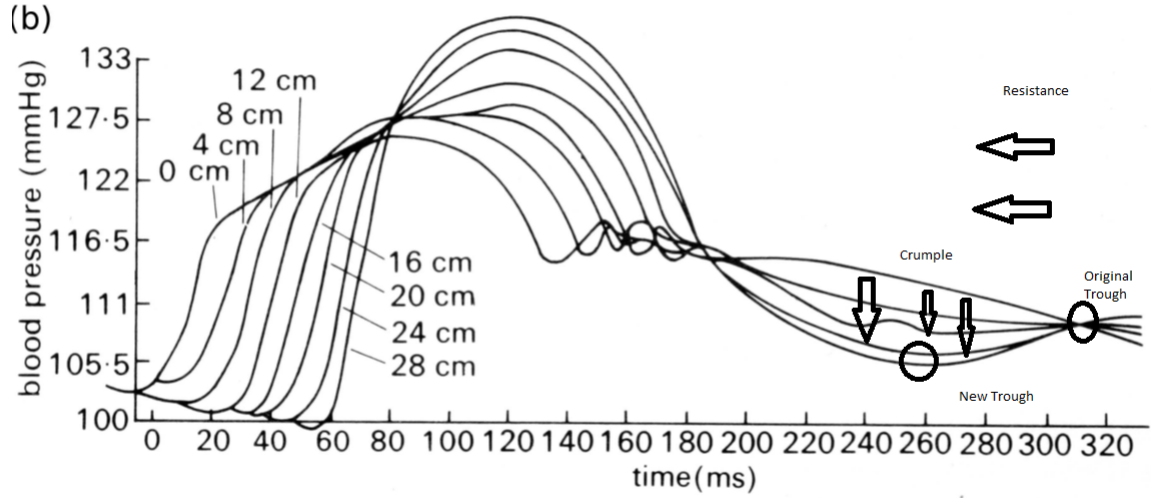
Figure 4.1: The BP pressure pulse experiences "crumpling" as it moves down the arterial tree, causing its trough to appear earlier in time.

Increasing the amplitude of the wave, A, or increasing the length of the pulse, λ, increases the area of the pressure pulse, and thus the area that the "crumpling forces" need to crumple in order to move the trough back by the same amount of time. Therefore, if the crumpling force that a pressure pulse experiences is constant or depends increases less than linearly with λ, the trough will occur earlier, decreasing sRTT and resulting in a negative correlation between sRTT and λ and A. Since PW is directly proportional to λ from Equation 1.3, this could explain the otherwise counterintuitive negative correlation between PW and sRTT. In addition, because crumpling increases with distance from the heart, we would expect that the anti-crumpling influence of A and PW are much less important for RTT. This would explain the lack of correspondingly strong negative correlations between RTT and A and PW.

4.2 Alteration of Correlations over NICU Stay

The unexpected correlations between sRTT, A, and PW (average -0.4 for sRTT vs PW and sRTT vs A on the second day and -0.2 and -0.3 respectively on the penultimate day) is especially significant because it relates two variables that must be derived from the invasive measurement of the BP waveform to a quantity that can be calculated from noninvasive ECG and SPO2 measurements. We now consider how the relationship between these quantities changes over each infant's stay. As in the previous section, all data is averaged over 10-heartbeat intervals.

To determine if the A vs sRTT and PW vs sRTT distributions remained constant for a given baby over time, we calculated a linear regression model for the combined data from second and penultimate days, then computed the residuals corresponding to each day and used a two-sample-Kolmgorov-Smirnov test to determine the p-value for the two samples coming from the same population. For both A vs sRTT and PW vs sRTT, we reject the null hypothesis (the residuals are distributed the same for both days) in favor of the alternative hypothesis (the residuals are distributed differently) for all 14 babies at a significance level of p =0.01. Figure 4.2 shows an example of the distribution shift for A and sRTT.

To clarify how the A vs sRTT and PW vs sRTT distributions change over time, we plot the coefficients of linear regressions calculated for each of these two quantities for both the second and penultimate day of each infants stay in the NICU. Black lines connecting the pairs of points mean that both baby-hours are taken from the same infant.

From Figure 4.3, the most obvious trend in the A vs sRTT regression is the increase in the value of the intercept. This is unsurprising since infants are sick when they are admitted to the NICU and are thus likely to have weaker hearts that
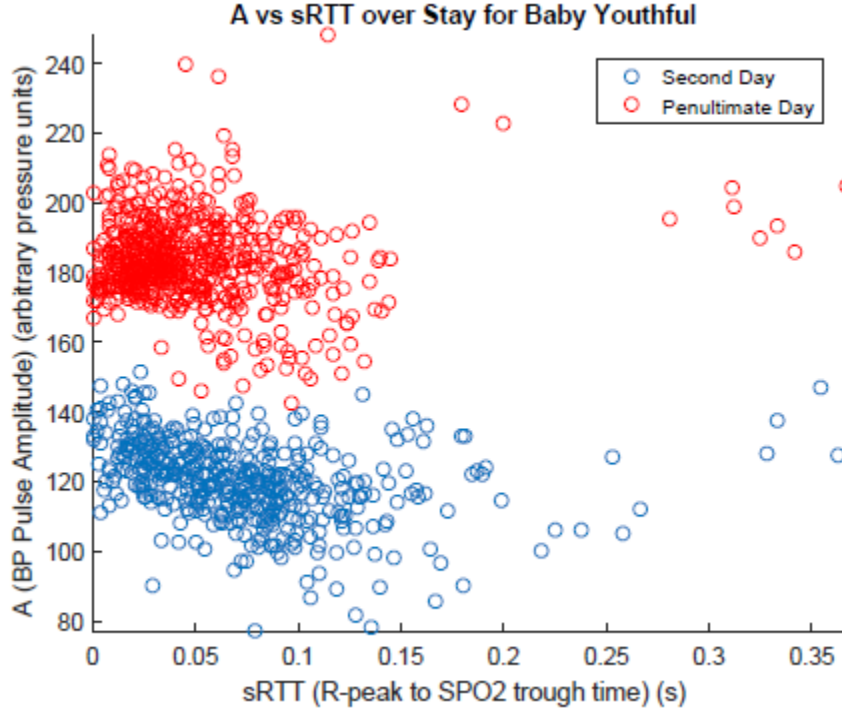
Figure 4.2: Comparison of A vs sRTT from the second and penultimate days of the bay alias Youthful's stay in the NICU. The distribution has clearly shifted. In this case, while the negative slope is still similar, A has nearly doubled over the intervening period.

generate pressure waves of smaller amplitude. As they recover, the power of their hearts and the amplitude of the resulting pressure pulses generated ought to increase. Also apparent is an equalizing tendency in the slope. Babies that had large negative slopes, and thus correlations, between A and sRTT, on the second day of their stay experience an increase in slope by the penultimate day, and vice versa, although the average change in correlation is positive Thus, it is possible that the relation between A and sRTT returns to some normal homeostatic level after a shift toward greater negative correlation during illness.

Figure 4.4 shows that the absolute value of both the slope and intercept of the
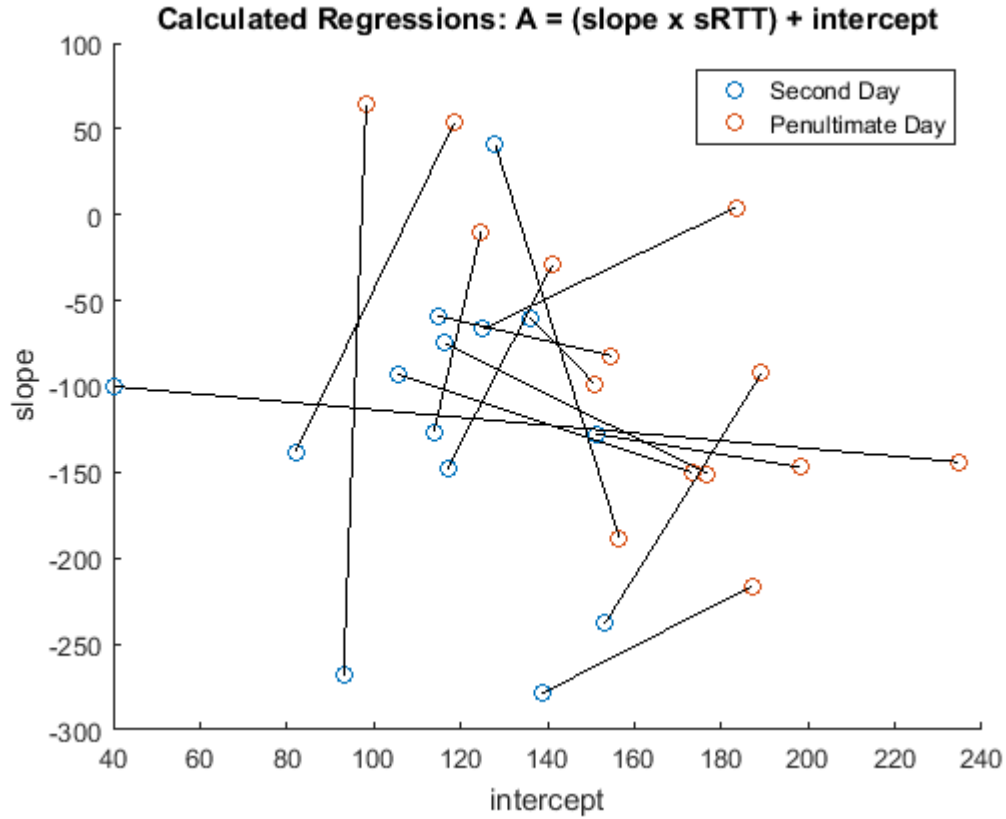
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Figure 4.3: Scatter of A vs sRTT linear regression coefficients for second and penultimate days of all 14 infants. Black lines connect hours from the same baby.

PW vs sRTT regression decrease consistently over the course of treatment. It seems likely that in the healthy infant, PW and sRTT would be completely uncorrelated or even have a positive correlation.

Not only are the A and PW themselves positively correlated, the changes in their correlations with sRTT over the course of treatment in the NICU are also strongly positively correlated. This is evidenced in the linear appearance of the scatterplot in Figure 4.5. The outlying point in the bottom left corresponds to the baby Heard who has extremely noisy data on the second day of his stay, making the unusually large negative A and PW vs sRTT correlations calculated that day for him suspect. Excepting that point, nearly all infants see an increase (corresponding to a decrease
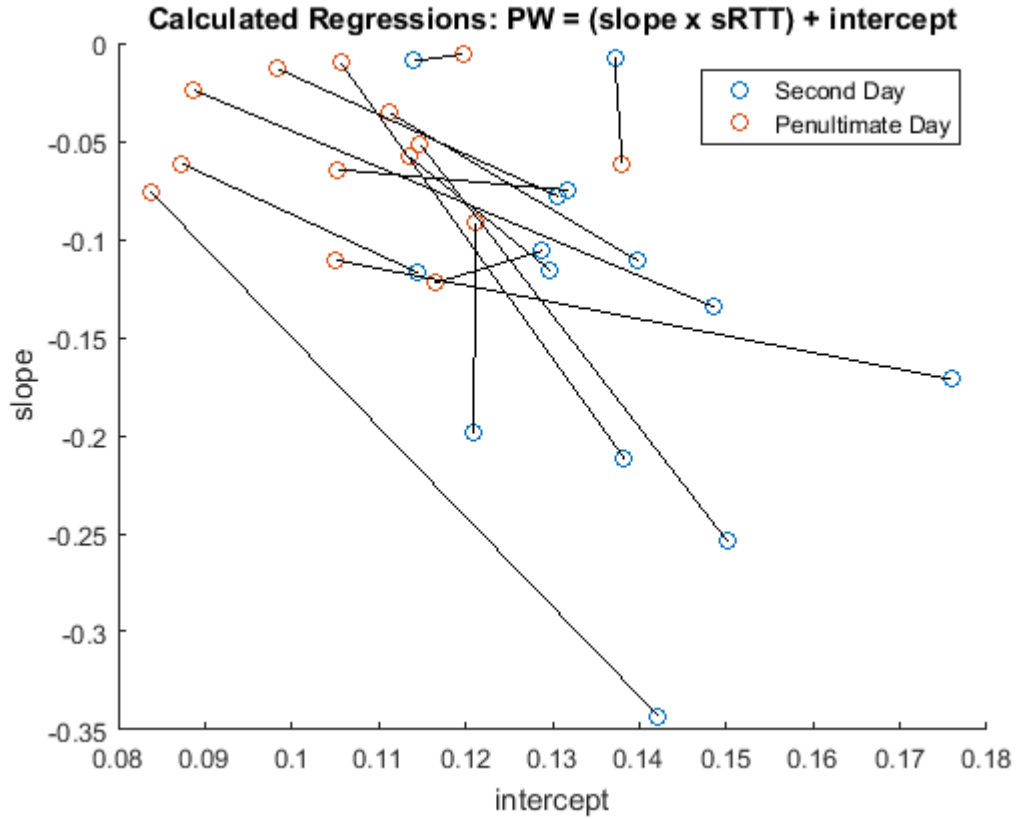
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Figure 4.4: Scatter of PW vs sRTT linear regression coefficients for second and penultimate days of all 14 infants. Black lines connect hours from the same baby.

in absolute value) in both correlations over their NICU stays.

This suggests that both of these correlations are often signs of underlying ill health. The data is consistent with the crumple hypothesis, since we expect additional pressure wave amplitude and PW to make the greatest relative contribution to the crumple zone and thus the sRTT when baseline A and PWV are small. It seems that such a situation would necessarily result in a low systolic blood pressure. However, systolic BP only has a correlation of 0.17 with the correlation between A and sRTT and 0.20 with the correlation between PW and sRTT. This lack of correlation could be due to compensatory vasoconstriction keeping blood pressure in a reasonable range despite a weak pressure pulse.
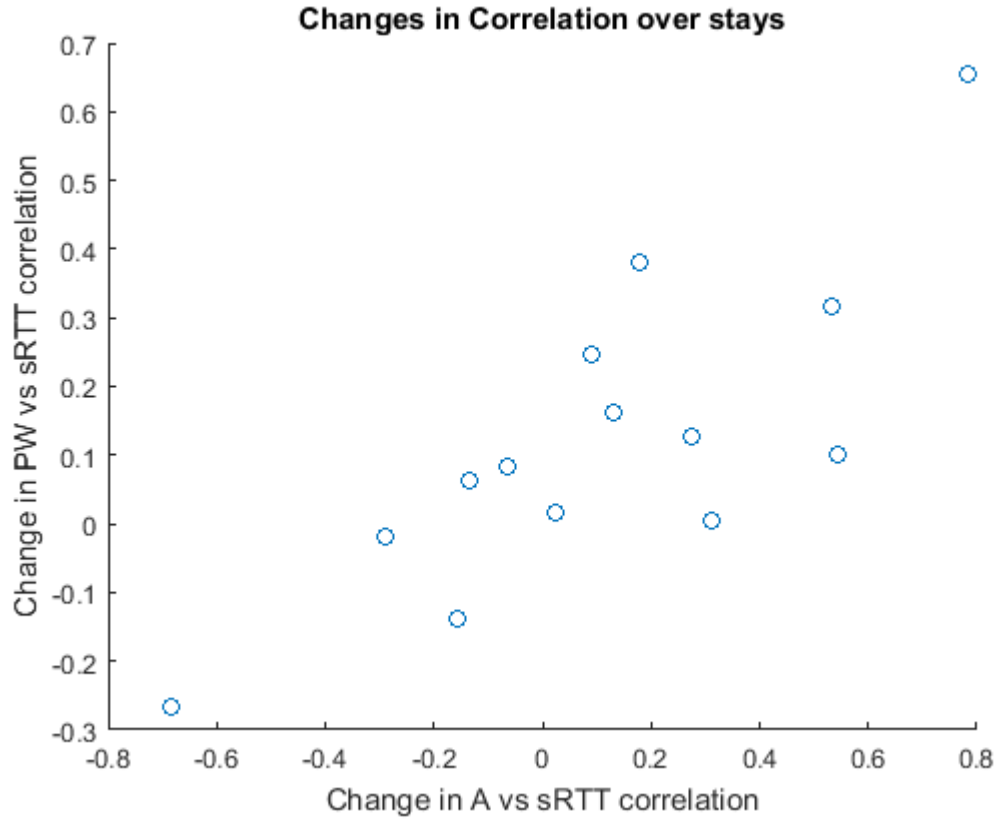
Figure 4.5: The change from the second to the penultimate day in the PW vs sRTT correlation vs the change in the A vs sRTT correlation for each of the 14 babies.

The correlations we have considered thus provide us with a noninvasive window into the BP waveform without revealing much about the BP itself. Pressure Pulse Width and Amplitude can be clinically useful in themselves, however, so it would be a plus to estimate them without the downsides of invasive measurement. The difficulty in this case, is the apparent dependence of the correlation on illness. Using it as a form of illness detection is impractical because collecting the A and PW data required to measure the correlation requires invasive catheterization that would generally not be performed unless the infant were already ill. On the other hand, using sRTT as an estimator of A and PW only during an illness limits its usefulness. Additionally, until we have better understanding of the underlying physiological mechanisms, we

have no way of knowing which specific types of illnesses this correlation holds for.

Chapter 5

Ongoing and Future Work

With the creation of a MATLAB algorithm that can automatically filter raw ECG, SPO2, and BP data and use it to calculate a wide range of statistics, we are now able to consider analysis of all hours over all days of the data provided. This could be accomplished quickly by implementing a parallel version of the algorithm on the William and Mary Sciclone supercomputer, which currently houses the Veldhoven NICU data. It would have the advantage of giving a continuous picture of the evolution of quantities over time. Notably, using only second and penultimate days of stays, we were unable discover a consistent relation between BP and any of the SPO2-derived quantities measured. Since it is clear that the correlations we are interested in vary over time, analysis of these correlations at some intermediate period might reveal stronger correlations that could point us to potential correlates with BP.

So far, we have merely considered correlations between pairs of quantities. However, our failure to find many strong or useful correlations in this way suggests BP would be better modeled using some function of two or more of the SPO2-derived variables we calculated. Potential methods for finding an appropriate function include canonical correlation analysis and machine learning.

Chapter 6

Conclusion

Using BP, SPO2, and ECG data taken from 14 babies from one hour from their second and penultimate days of their stays in the Veldhoven NICU, we calculated the quantities RTT (R Transit Time), Amplitude (A), and Pulse Width (PW) for the BP waveform and the corresponding quantities (sRTT, sA, and sPW) for the SPO2 waveform. Data was first prepared by selecting the best ECG lead, which was chosen by taking the lead with the smallest standard deviation in the intervals between the R-peaks found using a Pan-Tompkins algorithm. The SPO2 and BP waveforms were then filtered to remove noise, removing all intervals of these waveforms that contained values higher or lower than certain cutoffs, had more than one peak or trough or peaks before troughs (only for SPO2), had peak and trough values that were too close together or too far apart, or had associated Fourier transforms with too much power in higher frequencies inconsistent with the 2.5 hz period of the heartbeat. These variables were then averaged over 1, 5, and 10 heartbeats, and their Pearson correlations with each other and with systolic, diastolic, and average BP were calculated. Linear models were constructed in cases where scatterplots of the data showed evidence of linearity.

In general, no time lag was observed between any pair of quantities and averaging over more heartbeats was found to slightly increase correlations between variables.

This suggests that the underlying physiological causes of the correlations varied gradually on a time scale of at least 3 seconds, or roughly 10 heartbeats, the longest timescale averaged over.

We found that PW and A were both strongly correlated with systolic BP, with weaker correlations to diastolic and average BP. RTT was also found to be positively correlated with BP, which contradicted the negative correlation we expected to find due to vasoconstriction. We theorize that this was due to high BP corresponding to a faster and more erratic heartbeat. There were no significant correlations between the corresponding parts of BP and SPO2 waves. On both days a substantial negative correlation between sRTT and A and PW was observed, which is theorized to be a result of A and PW providing a protective function against "crumpling" of the pressure pulse as it moves down the artery.

Linear regressions were calculated for A vs sRTT and PW vs SRTT, and their slopes were found to tend towards zero together over each infant's stay. Since these correlations also correlated with each other, it seemed likely that they were associated with illness. Only a small correlation was found between these correlations and BP.

Future work will focus on filtering and computing these quantities for all hours in order to get a complete and continuous picture of how their relationships vary with time. In addition, it is clear that the relationships between the quantities derived from the ECG, SPO2, and BP waveforms are more complex than simple correlations between pairs of variables, and further work is needed to uncover what those relationships might be.

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