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Diaphragm electromyography post processing with Simulink as a means of guiding weaning from ventilation in preterm infants

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TU Delft

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by

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TU Delft

Abstract

The problem of premature births is widespread throughout the world affecting 41000 newborns daily; the issues that follow, often related to breathing, require the use of mechanical ventilation to compensate for the poor compliance of the respiratory muscles of newborns. However, side effects associated with artificial ventilation, including atrophy, require a cyclic interruption of automatic ventilation so that infants can develop and train their respiratory muscles (the so-called weaning from ventilation). However, the criteria for judging the readiness and progression of the detachment from ventilation are unsatisfactory since they rely on the subjective judgments of the clinicians. As a consequence, a research project in collaboration between TU Delft, the DEMCON BV (a Dutch mechatronics engineering company) and the Erasmus Medical Center of Rotterdam was carried out to look for an objective measure, provided with visual feedback, to give indications of the respiratory fatigue of newborns to the clinicians, also referred as work of breathing (WOB). This research revealed that the analysis of the diaphragmatic electromyography (dEMG) is a non-invasive tool that can be used to measure the WOB. As a result, three WOB detection algorithms named peak-to-peak (P2P), differential-peak-to-peak (DP2P) and area-under-the-curve (AUC) were developed. The relevance of these algorithms consists in extracting the WOB information from the dEMG and giving direct visual feedback to the clinicians. Moreover, since often weaning from ventilation is impaired by the advent of adverse events such as apnea and brachicardia, two algorithms were implemented to detect such complications as well.

Before starting the actual research, some background work was carried out for the DEMCON BV. DEMCON BV deals with the acquisition and processing of dEMG utilising a Software called Polybench. The first part of the background work was to write a Simulink program which has the same functionality as Polybench. The relevance of this work consists in allowing better communication between DEMCON and anyother professional who wants to collaborate with them since Simulink is a popular software while Polybench is not. The second part of the background work was to create a Simulink block-chain that given a raw dEMG signal can extract the breathing envelope from it.

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Preface

The following thesis is addressed to all those who are interested in the field of neonatology and more precisely, in weaning from automatic ventilation applied in the neonatology field.
Chapter 1 introduces the reader to the general aspects of the premature birth, the dEMG, the instrumentation used in the project, and the proposed methodology together with the aim and objectives.
The **Chapter 2** introduces the reader to the actors and tool that played an important role in this thesis, i.e. Demcon (a Dutch company that deals with bio-signals, including dEMG) and Polybench (an EMG extraction and post-processing software). Furthermore, it explains why Demcon decided to switch from Polybench to Simulink. Those interested in knowing in detail what Polybench does and how it was translated into Simulink can find an exhaustive explanation in the **Appendix**.
Due to contamination of various nature of the dEMG, it is possible to have a clear of information out of it only after an appropriate "cleaning" session. Therefore, the **Chapter 3** describes the techniques used to clean the electromyographic signal to extract only the information related to breathing.
The **Chapter 4** deals with the algorithms implemented to extract in real time the respiratory effort of the newborns. The **Chapter 5** introduces the reader to the concepts of apnea and brachicardia and elucidates the algorithms implemented to detect such negative events.
The results and the discussions are presented in **Chapter 6** and **Chapter 7** respectively. Conclusions are in **Chapter 8**, acknowledgment are in **Chapter 9**. Finally, the Polybench blocks and the functions of the blocks used in Simulink are available at the end in the **Appendix**.

Delft, February 19, 2019

1

Introduction

1.1. Premature birth

Premature birth is the one that takes place before the 37th gestational week: the number of premature births amounts to 41000 per day [3]. Premature birth is a significant cause of morbidity, and infant mortality [4] and is the second leading cause of mortality in children under five years [5]. Premature birth is subdivided according to the gestational age:

Table 1.1: Table of prematurity. Source: [4]

Label	Definition (week's completed gestation)
Extremely Preterm	<28
Very Preterm	28 to <32
Moderate Preterm	32 to <34
Late Preterm	34 to <37
Early-Term	37 to <39
Term	38 to <41
Post-Term	>42

The more significant problems that occur concurrently with premature births are the respiratory ones [6]; premature infants are at risk of developing both infectious and non-infectious respiratory diseases, and 40% of survivors are affected by bronchopulmonary dysplasia (BPD) [7].
Strategies to cope with BPD are both medical (such as the usage of antenatal steroids and surfactant) and mechanical (mechanical ventilation) [8]. Unfortunately, mechanical ventilation, if done invasively, leads to ventilator lung injury (VLI); consequently, over the years there has been a shift towards non-invasive ventilation. [9]. However, non-invasive mechanical ventilation unloads the diaphragm and alters its structure and function, thus does not allow it to develop correctly, leading to muscular atrophy [10].
As a result, the neonatologists tend to limit the exposure time of the newborns to mechanical ventilation (the so-called weaning from ventilation) to allow them to attempt autonomous breathing (the so-called spontaneous breathing trial, or SBT) to train the respiratory muscles. [11].
Nowadays, weaning procedures are scarce and lack objectivity; in fact, they rely on the personal judgment of the clinicians. [11]. The majority of the clinicians use the trial and error strategy to assess the weaning outcomes [12, 13]: basically, they wean the infants if their clinical conditions are stable and they reintubate them in case their status deteriorate. However, the trial and error method leads either to overtreatment or undertreatment and the need for a more objective parameter arise; the EMG (more precisely, the dEMG) could be a possible solution [1], as it is discussed in the next section.

1.2. Surface electromyography

1.2.1. EMG introduction

To guide clinicians during weaning from ventilation, it is necessary to provide them with a measure that asses the fatigue to which the newborn is subjected during breathing, the so-called work of breathing (WOB). Surface electromyography is an exciting candidate in measuring the WOB in real time as it is both a non-invasive technique and it also closely related to muscle fatigue.

Surface electromyography is recorded by non-invasive electrodes placed on top of the skin overlying a muscle. The electrodes measure the potential difference generated by the action potential travelling towards the electrodes pair. Since each motor unit (i.e. the combination of the motor neuron and the skeletal muscle) is made up of several muscle fibres, the EMG measures the sum of all the muscle fibres action potentials that are part of the same motor unit. The magnitude and density of the EMG are mainly related to the motor units action potential recruitment and their firing frequency.

1.2.2. EMG contamination

Various types of noises contaminate the EMG signal, therefore analysing the EMG pattern can be very difficult especially when EMG motions occur [14].

The primary noise sources of the EMG are:

- **Tissue Characteristic**
  The thickness and composition of skin underneath the electrodes influence the EMG detection [15]; thicker skin layer can significantly reduce the EMG amplitude due to the considerable distance of the electrodes and the muscle fibres [16].

- **Cross-talk**
  The cross-talk refers to the detection of the electrical activity of the muscles adjacent to the one clinicians are interested in [17].

- **Changes in the geometry between muscle belly and the electrode site**
  During muscle contraction, the distance between the muscle belly and the electrodes changes; consequently also the distance between the electrodes changes, thus altering the EMG.

- **Inherent noise**
  All kinds of electronics generate electrical noise, also known as “inherent noise," whose frequency spectrum ranges from 0 Hz to several thousand Hz [18].

- **Inherent instability of the signal**
  The magnitude of the EMG is quasi-random due to the quasi-random nature of the firing rate of the motor unit; such firing rate affects mostly the frequencies in the 0-20 Hz range [18].

- **Movements artifacts**
  Unwanted noise such as movement artefacts noise can come up during EMG measurements [19]. Whenever a muscle moves underneath the skin or when a force causes movements at the electrode-skin interface, movements artefacts arise; accelerometers attached nearby the electrodes monitors such situations [19]. Due to the different nature of the muscles among different subjects, the same movement artefact can generate different EMG noise across different individuals [19].

- **Electrocardiographic artifacts**
  The electrical activity of the heart is by far the most influential source of noise during EMG measurements [20], especially when dealing with the trunk EMG [21]. The ECG magnitude is orders of magnitude higher than the EMG. Unfortunately, its centre frequency is around 80 Hz, so it is close to the peak power region of the EMG frequency spectrum. Avoiding to place the electrodes on the central axis of the heart is the first way to reduce the ECG contamination [22]. In case the QRS complex is visible in the EMG, it can be isolated and subtracted from the EMG record leaving the rest of the waveforms unaffected [21].

1.3. Diaphragm electromyography in newborns

1.3.1. dEMG introduction

The diaphragm EMG (otherwise known as dEMG) measures the electrical activity of the phrenic nerve, which is essential for breathing, as it sends motor information to the diaphragm and receives sensory information from it [23]. Therefore, the dEMG measures the diaphragm activity [24] and monitors the respiration of the newborns [25], and its change in magnitude is related to the WOB [26, 27].

1.3.2. Measurements procedure

The amplitude of the dEMG in the preterm infants is very low; therefore the electrodes should be placed at the minimal muscle-skin distance [28]. As a consequence, the clinicians place the electrodes in the zone of apposition [28]. Accordingly, the clinicians place the electrodes in the right six and the seventh interspace between the midclavicular and midaxillary lines [29] (see figure 1.1). Since the infants are moving a lot during the wake phase and create several movement artefacts, the measurements need to be performed during the sleeping phase [25].

Figure 1.1: Electrodes placements in neonates example, source: [1]

1.3.3. dEMG relation with the work of breathing

The usefulness of the dEMG is strictly related to the fact that it gives information on the WOB. Research by Maaesingh et al. [30] showed a correlation between the logarithm of the dEMG and the severity of asthma, showing that dEMG decreases when the asthma level decreases, thus demonstrating that asthma causes the diaphragm to work more than during the usual conditions. Research by Sprikkelman et al. [31] corroborates the idea that increases in dEMG indicate difficulty in respiration, by demonstrating that the dEMG in children increases upon histamine-induced bronchoconstriction. Research by Stein et al. [32] also link the dEMG with the increase in the respiratory effort. Research by Kraaijenga et al. [1] demonstrated that the dEMG level in infants who fail weaning from ventilation is higher than those who succeeded. Based on the previous considerations, the dEMG reveals as a suitable tool to investigate the work of breathing during the weaning from mechanical ventilation.

1.3.4. Diaphragm-Abdomen electrical activity relation

Diaphragms electrical activity travels through the body; this is why it is possible to measure it at the abdomen. Indeed, since the abdomen motion reflects diaphragm contributions to breathing [33], we can state that the abdomen electrical activity indicates the diaphragm one because when the sleeping patient contracts and relaxes the diaphragm, the abdomen contracts and relaxes in turn. However, abdominal muscles contribute significantly to postural control [34], have an essential role in the control and movement of the lumbar spine and pelvis [35], participate in a wide range of postural adjustments in response to external bio-mechanical perturbations [35] and can also be activated to compensate predictable movement-related postural disturbances [36]. As a result, when the patient is not at rest, the abdominal electrical activity deviates from the diaphragmatic activity. Consequently, in the analysis of the dEMG, it is essential to distinguish when the signal refers to respiration (undisturbed dEMG) and when it refers to movements (disturbed dEMG). This concept is fundamental in the WOB detection; distinguishing undisturbed from disturbed dEMG is the basis on which the WOB algorithms rely.

1.4. dEMG data acquisition

The dEMGs have been extracted according to the procedures shown in section 1.3.2. However, apart from it, only the abdominal electrodes were used, but not the intercostal electrodes. The collection and transmission of the electromyographic signals during the thesis project have been enabled by the Dipha®16 device (specifications are available at the following link: http://www.macawi.com/wp-content/uploads/2015/10/Dipha.pdf).

Figure 1.2: Dipha®16

The Dipha ®16 allows the data acquisition and pre-processing to take place in a lightweight, smartphone-sized, battery-powered measurement box. Measurement data is transmitted with low power from the Dipha ®device to a transceiver USB stick connected to a Personal Computer or Notebook placed at a distance of up to 10 meters.
Dipha ®16 consists of surfaces electrodes (non-invasive measurements), it does not require skin preparation or impedance check and has a battery autonomy of 24 hours. The Dipha amplifier is equipped with shielded electrodes cables that reduce cables capacitance and cross-talk and prevents electrical contamination by main interference. Dipha device comes together with an easy to move around trolley which carries a touch screen PC on which online and real-time data analysis is displayed.

1.5. Thesis Aim and Objectives

1.5.1. Aim

This thesis aims to develop an effective and intuitive tool to assist clinicians during the process of weaning from ventilation by letting them know how the trend of respiratory fatigue of newborns is evolving through time. Such a tool should be a real-time trend which declines, maintains stable or increases according to the newborn's difficulty of respiration. Moreover, such a device is to be insensitive to contamination artefacts (mainly ECG and movements noise) and should be provided as well with additional options that reveal the occurrence of adverse events such as apnea and-or brachicardia.

1.5.2. Objectives

- **Objective 1: Translate Polybench into Simulink**
  This thesis is carried on in collaboration with DEMCON BV. DEMCON BV is a med-tech company which, among its range of competences, deals with surface dEMG acquisition and analysis as well. DEMCON uses a software named Polybench to perform such analysis; however, they recently expressed the need to have a Simulink program which has the same functionality that Polybench has. Therefore the first aim to accomplish was to create a Simulink file that did exactly what Polybench does. The reason for this is explained in **Chapter 2**. It is essential to specify that the Polybench software to which the thesis refers was written empirically.

- **Objective 2: Extracting the respiratory envelope from the raw diaphragm EMG measurements**
  As pointed out previously, the dEMG is polluted by several factors. Therefore, cleaning the dEMG and extracting only the relevant information is a must. Polybench has already an embedded feature that

extracts the respiratory envelope from the Raw dEMG, however, as suggested by Tom Goos (scientific researcher at Erasmus MC Rotterdam), developing a further breathing envelope extraction technique would be beneficial. The main reason for this is that forming a new method that gives results comparable to the Polybench embedded one would corroborate its efficiency and correctness. Furthermore, it is worth doing it from a scientific point of view in general.

- **Objective 3: Creating a WOB detection algorithm and adverse events detection**
  Such an objective is the core of the thesis. Such an algorithm, named peak-to-peak (P2P), was thought to display the WOB real time as a means of the difference between consecutive positive-negative peak distances arising in the breathing envelope (such a concept would be explained in **Chapter 4**). The P2P algorithm was designed to analyse only the breathing envelope segments which are free from artefacts, i.e. the undisturbed dEMG, thus discarding those who are polluted, i.e. the disturbed dEMG. Two other WOB detection algorithms were created as well to allow comparison.
  Moreover, apnea and brachicardia detection algorithms were developed as well since in case such events frequently occur during weaning, clinicians might consider interrupting it.

1.6. Methodology

Extensive bibliographic research before the thesis start revealed that there is no clear definition of how to calculate the WOB. As a consequence, the scarcity of scientific literature concerning the goal of this thesis does not allow to apply a recognised or traditional methodology. Therefore, the methodology used is purely empirical, and only its corroboration by other researchers and scientists will fully confirm its veracity.

During the translation from Polybench to Simulink phase, each Polybench block functionality was analysed by reading its description in the Polybench instruction manual. Then, a Simulink block with that same functionality was created in Simulink. Finally, the Simulink block was given a test function as input: if the output was matching the feature of the Polybench block, then such block was considered as correct. Once that all the Polybench blocks were translated into Simulink, they were finally assembled all together.

As for the respiration envelope extraction, findings from the scientific literature were gathered together to post-process the Raw dEMG by employing appropriate filtering techniques. New features such as the signal reconstruction and the outliers removal were added as well. The Raw dEMG data were gathered from 3 EMG measurements in the NICU performed as previously described in section 1.3.2

As for the WOB algorithm, it was designed to analyse only the respiratory segments of the respiration envelope (thus avoiding artefacts). Therefore, the main problem was to check that such an algorithm was able to distinguish what was respiration from what was artefacts. Consequently, I asked and obtained the permission to assist into 3 EMG measurements in the NICU in the Erasmus MC Rotterdam; I carefully observed the children behaviour by registering in which time frame they were moving or swallowing. Then, those measurements were analysed offline to check whether the algorithm was ignoring the segments of dEMG where artefacts were occurring. Finally, two other WOB algorithms were to created to allow comparison with the first one.

2
DEMCON and Polybench

The current section introduces the reader to DEMCON, that is the company to which this thesis is addressed, and Polybench, that is the software with which this company deals with analyzing and post-processing the EMG.

2.1. DEMCON

DEMCON is a high-end technology supplier of products and systems, focusing on high-tech, industrial systems and vision, embedded, optomechatronic and medical systems. DEMCON is a company that supports clients with a wide range of competencies. As a system supplier, DEMCON can cover the entire needs of the customer, from proof-of-principle, prototype and pre-production to serial production.
The role of the DEMCON in this thesis is crucial as it is both the subject who proposed the thesis project and is the one to whom the thesis files and algorithms will be sent for the final check and further investigation.

2.2. Polybench

Polybench is the software used by DEMCON to analyse the EMG and extract information from it. During the thesis project, it was installed (licensed) on a computer in my office in the Erasmus MC Rotterdam. Polybench working flow has been carefully analysed to allow it to be translated into Simulink.

Polybench is a software designed to process electrical signals of human nature, allowing both the analysis of signals in real time and post processing offline. Polybench can easily handle multichannel data (example: EEG and EMG) thus allowing the comparison among data coming from different sources.
The Polybench operating system is inspired by the block system: mathematical operator symbols of basic, or complex mathematical functions are placed on a drawing area, and then connected by arrows. The arrow flow is coherent with the signal flow, thus allowing the user to easily follow the signal and see how it changes along the way as well.
By clicking the blocks the user can easily visualize and modify its properties if needed. In order to help the user to understand their working principle, the blocks refer to extensive descriptions, tutorials and examples. The effect of the parameter setting can be noticed immediately since the analysis is performed on-line, therefore the blocks can be added and modified while the system is running.
Processing errors inside the blocks are detected by the system which displays a red color (either on the blocks and/or on the arrows) thus stating an error message.

2.2.1. Moving to Simulink

Although Polybench performs correctly its functions in the diagnostic field and is intuitive and easy to use, its diffusion is not widespread and its usage is not free (license is required).
It is also true that software such as Matlab (and consequently Simulink) also need the license, but this license is granted free of charge to students of technical universities of a certain level (such as the TU Delft) and are often already installed in the computers of libraries of such universities. As a consequence, the use of software such as Simulink allows a better collaboration between DEMCON and any student, researcher, professional,

etc. It is therefore no coincidence that DEMCON has expressed the need to implement a program in Simulink that has the same functionality as Polybench concerning the analysis of diaphragmatic electromyography. Moreover, the Polybench software has not been certified yet, and a software written within it is complicated to get CE certification as it needs to be reviewed and updated when it becomes part of a medical device. The methodology involved in the translation phase is previously explained in the section 1.6.

An exhaustive explanation of what Polybench does and how it was translated into Simulink is available in the **Appendix** section.

3
Extracting the breathing envelope

The following section elucidates the technique I used to process the raw dEMG acquired and extract the breathing information from it. This technique consists mainly in the identification and later elimination of the ECG artefact. As a result of this technique, we expect to see the dEMG transformed into a sort of sine wave with a period consistent with the respiratory frequency of a premature baby. The results presented in this section are based on a Simulink simulation. At section 3.3, the overview of the program is presented, to help the reader to follow the signal flow.

3.1. Purpose

The diaphragmatic electromyogram resulting from the measurements alone is not useful on its own because it is severely polluted by various sources of external noise, especially the electrocardiogram. Polybench already has an internal system that extracts the breathing envelope. However, it was decided to find a parallel method to obtain the breathing envelope to either improve the Polybench algorithm or to corroborate what Polybench already does and then prove its veracity.

3.2. Method

3.2.1. Extracting QRS complex

Although analyzing non-invasively the respiratory fatigue through electrodes is an exciting and non-risky technique, we have to deal with the interference caused by ECG waves (also defined as QRS complex) due to electrodes placement [25].The proximity of the electrodes to the heart muscle causes the diaphragmatic electromyogram actually to appear like an electrocardiogram, as shown in figure 3.1.

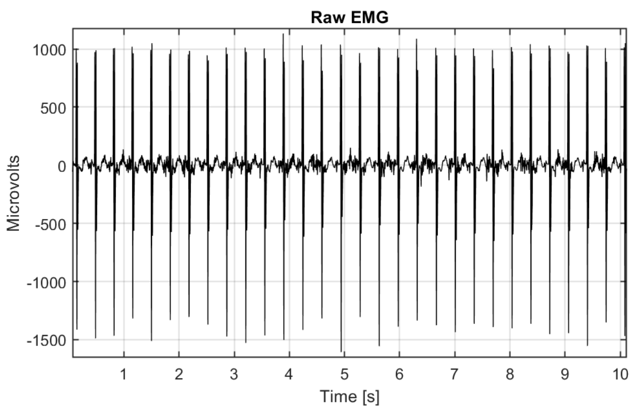

Figure 3.1: RAW dEMG

Before proceeding with the identification of the QRS complex, it was necessary to clean the signal from the contaminations at high frequencies. Since the sampling frequency is 500 Hz, the signal contains relevant frequencies up to 250 Hz according to the Nyquist theorem. As a result, the signal was filtered with a cutoff frequency of 250 Hz. Since the QRS complex occurs in a 9-20 Hz frequency range, the signal was bandpass-filtered in such range, thus extracting the QRS waves (figure 3.2).

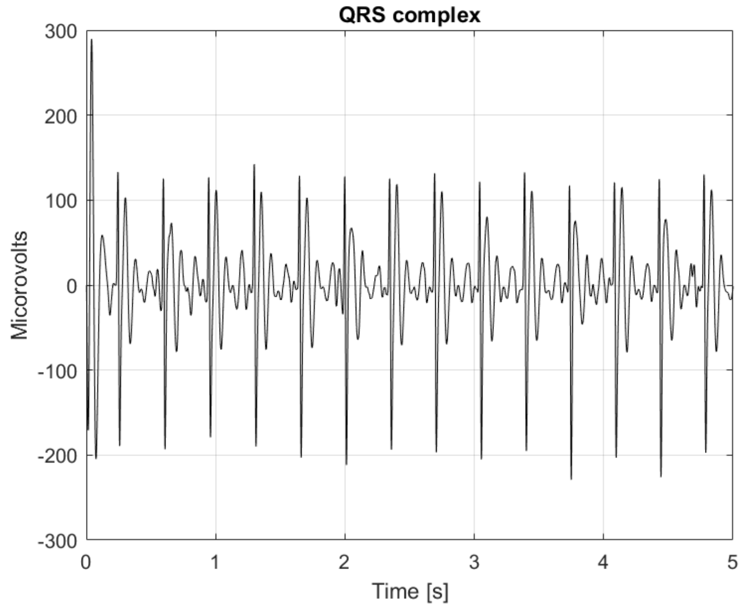

Figure 3.2: QRS complex

3.2.2. Pulse Generator

Subsequently, the signal entered a pulse generator block. The pulse generator is a function that I designed which, by identifying the QRS complex, generates unit pulses where the QRS waves are not present and null pulses when the QRS waves they are present (as shown in figure 3.3).

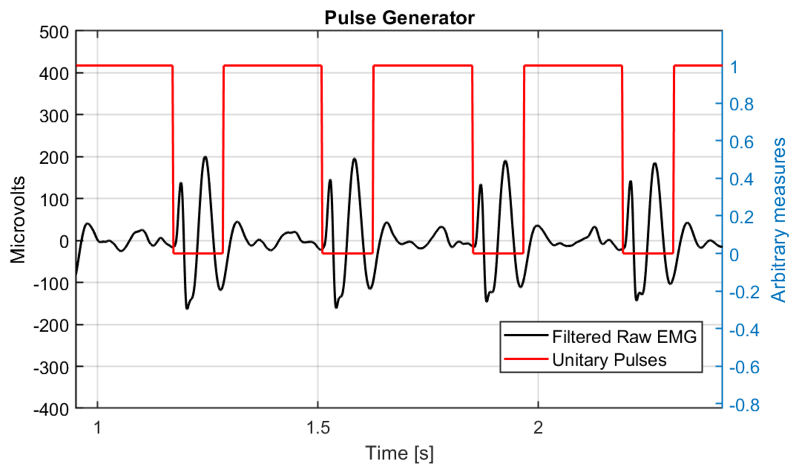

Figure 3.3: Unitary pulse generator

The usefulness of the unitary pulses consists in the fact that if they are multiplied by the original signal, they leave unchanged the parts in which the electrocardiography interference are absent, thus eliminating only the elements polluted by the QRS.

3.2.3. Extracting Respiratory Pattern

Due to the spectral components of the QRS complex, there are interference in the 70-300 Hz [2]. Therefore, the original signal, after being low pass-filtered with a cut off frequency of 250 Hz, was bandpass filtered in the 70-250 Hz range [2]. As one can see in the figure 3.4, the filtered signal seems to be unchanged from the raw one shown in figure 3.1, but if we take a look at the QRS amplitude spike ranges, we can see that they are considerably reduced (changing from [-1000, 1000] microvolts to [-400, 400] microvolts).

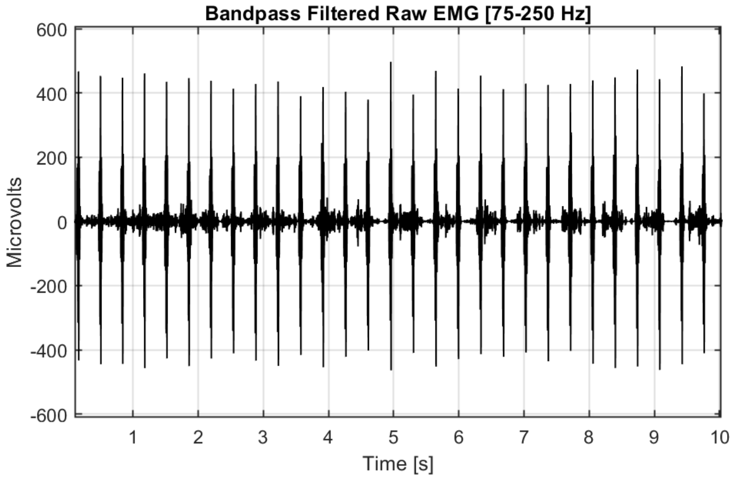

Figure 3.4: Butterworth Filtered [75-250 Hz] EMG signal

Subsequently, the signal was multiplied with the pulse generated by the pulse generator to mask the QRS complex. However, this multiplication leads to a loss of part of the signal.
The figure 3.5 clearly shows that the segments where the QRS was present are now clamped to 0.

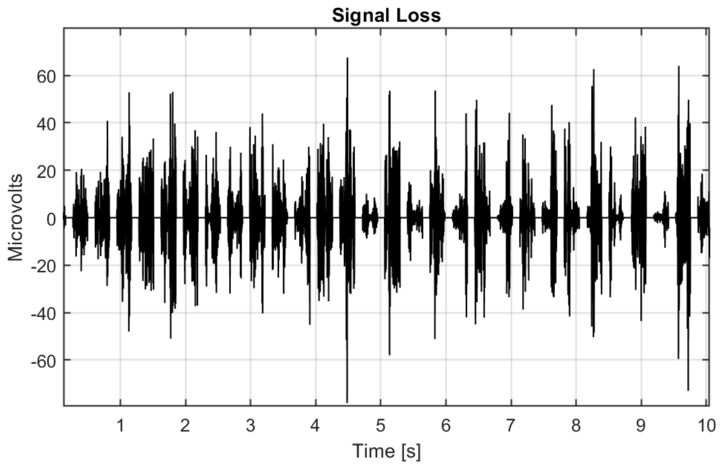

Figure 3.5: Butterworth Filtered [75-250 Hz] EMG multiplied times the pulse generator output

Consequently, I decided to artificially remove some outliers that were still present by creating an outlier removal block that eliminates the parts of the signals that exceed a certain threshold (in this case, the threshold was set to 35 μv). Then, I decided to reconstruct the signal in the masked zones using the segments that have not been masked by the pulse generator (see signal reconstruction block in figure 3.9). The principle of signal reconstruction is based on the fact that, as I empirically noticed through the measurements, every 0.3 seconds a QRS complex occurs. As a result, I decided to compare the signal shown in the figure 3.5 with its delayed version of 0.3 seconds. When the signal had a value of 0, the value of its delayed version was then assigned to it.

Figure 3.6 shows the reconstructed signal. Reconstruction was not perfect since some null segments were still present, but they were considerably reduced with respect to the previous signal shown in figure 3.5.

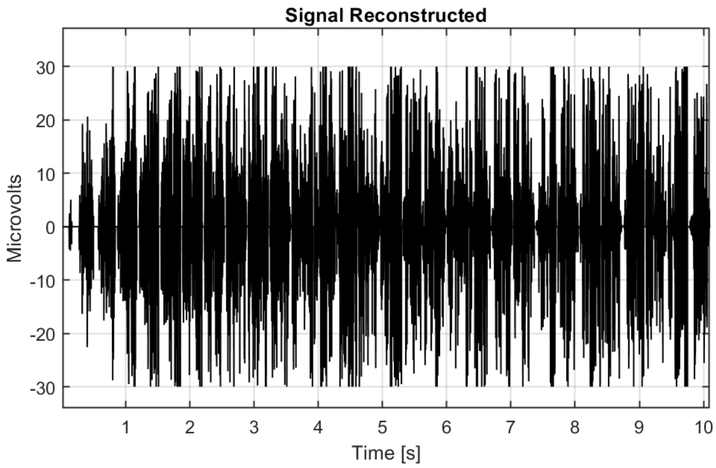

Figure 3.6: Signal Reconstructed

Finally, the signal was full-wave rectified (see figure 3.7) and low-pass filtered according to the low-frequency respiration rate ($freq < 1Hz$) of the preterm infants [2], and the respiration envelope was extracted (see figure 3.8).
In figure 3.9 you can see the sequence of blocks that transform the raw dEMG into a breathing envelope.

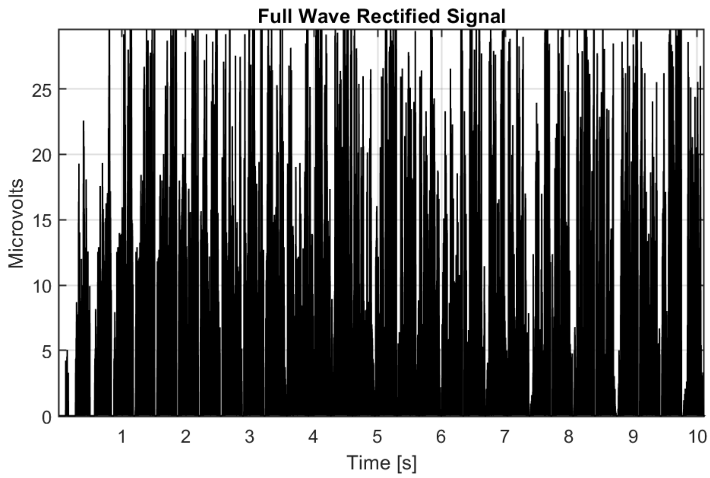

Figure 3.7: Full Wave Rectified Signal

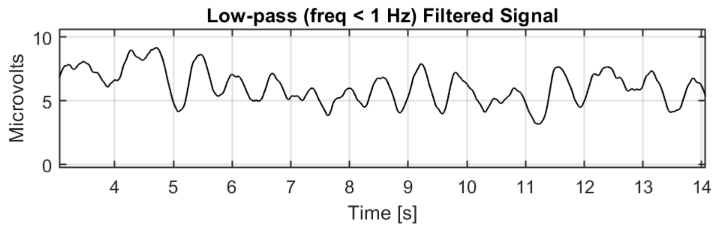

Figure 3.8: Respiration Envelope extraction example

3.3. Overview

The Raw EMG signal enters a second order band pass filter with 1-250 Hz frequency range, then enters a 9-20 Hz second order band pass filter with 9-20 Hz frequency range, enters a 30 step tapped delay and goes inside the pulse generator. The output of the pulse generator is a signal which has a value of 1 when the ECG wave in the raw signal are absent and 0 when they are present.

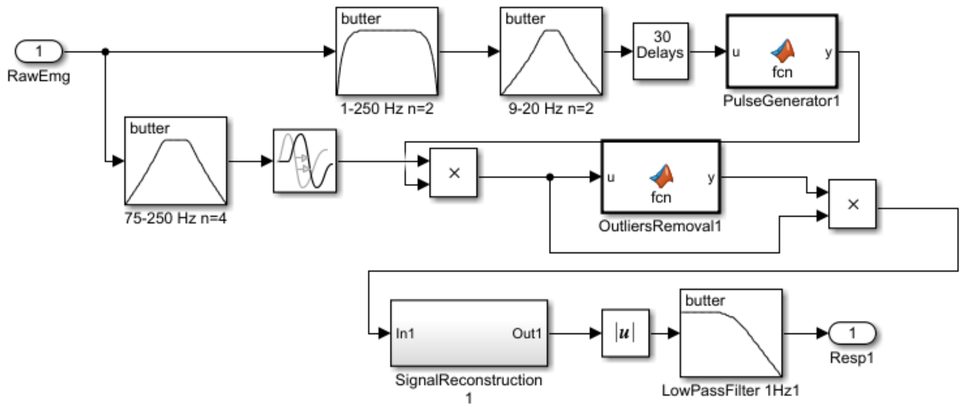

Figure 3.9: Extracting breathing envelope Simulink blocks

Consecutively, the Raw EMG enters a fourth order bands pass filter with 75-250 Hz frequency range, is delayed of 30 time steps and finally is multiplied times the output of the pulse generator in order to get rid of the QRS complex. Since outliers are still present, the signal enters an outliers removal which generates a value of 1 when outliers are absent and 0 when they are present. The output of the outliers removal is then multiplied times the previous signal so that outliers are finally removed. To cope with the loss of signal caused by the pulse generator, the signal enters the signal reconstruction block that reconstructs the signal where it was clamped to 0 by the pulse generator block. Finally the signal is rectified and low pass filtered with 1 Hz cut off frequency.

3.4. Results

In this section, I will present the results of my envelope compared to the DEMCON one, together with their correlation coefficient, for each of the three patients. For ease of visualisation, the results are reported on a 30 seconds time span.

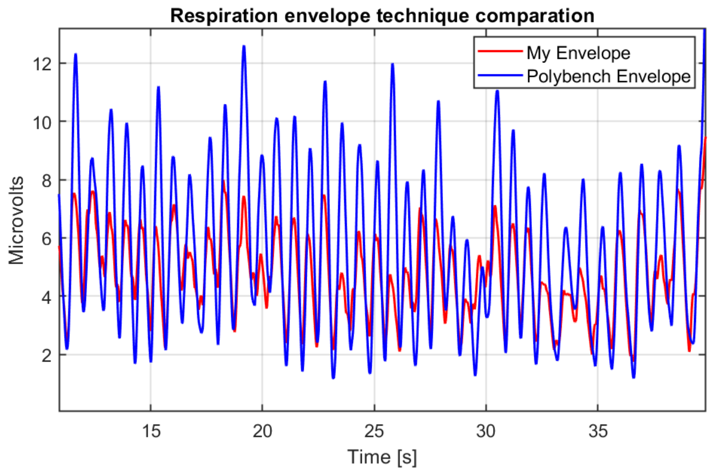

Figure 3.10: Respiration envelope comparison patient 1

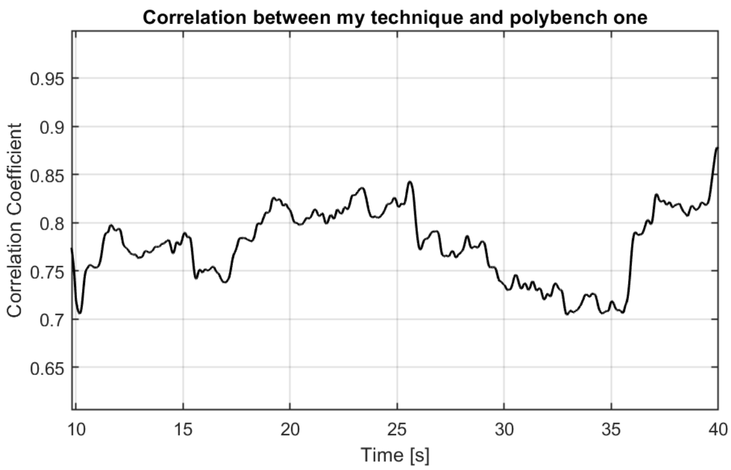

Figure 3.11: Respiration envelope correlation patient 1

Figure 3.10 shows the comparison between my envelope and the Polybench one in the first patient. As we can see, they are not the same in terms of magnitude, but their correlation coefficient in figure 3.11 shows that they are medium correlated (i.e. correlation coefficient >0.7). Figure 3.12 shows the comparison between my envelope and the Polybench one in the second patient. As we can see, also in this case they are not the same in terms of magnitude, but their correlation coefficient in figure 3.13 shows that they are highly correlated (i.e. correlation coefficient >0.8) for more than 50% of the time, while the rest of the time keep being medium correlated. Figure 3.14 shows the comparison in the third patient. In this case, instead, they are very similar in terms of magnitude, and their correlation coefficient in figure 3.15 shows that they are always highly correlated, with an average on the correlation coefficient of 0.9.

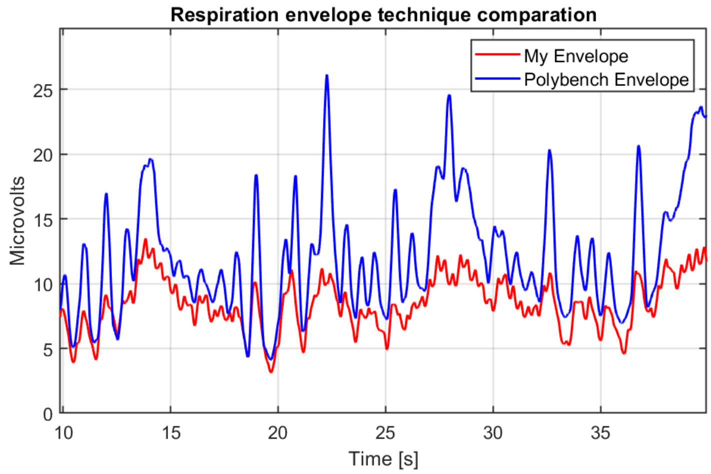

Figure 3.12: Respiration envelope comparison patient 2

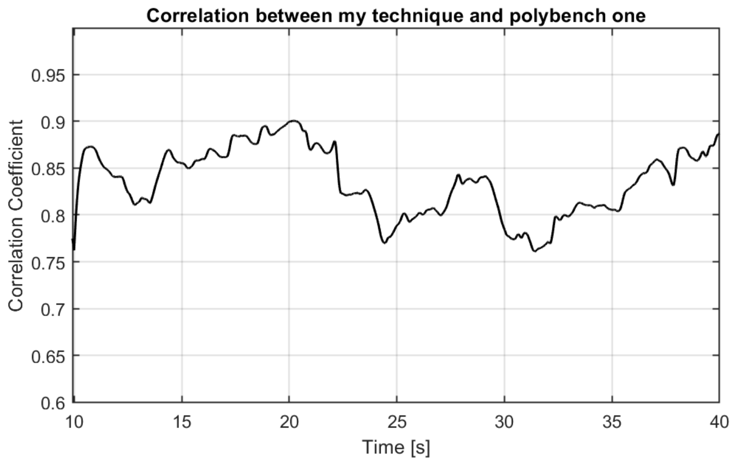

Figure 3.13: Respiration envelope correlation patient 2

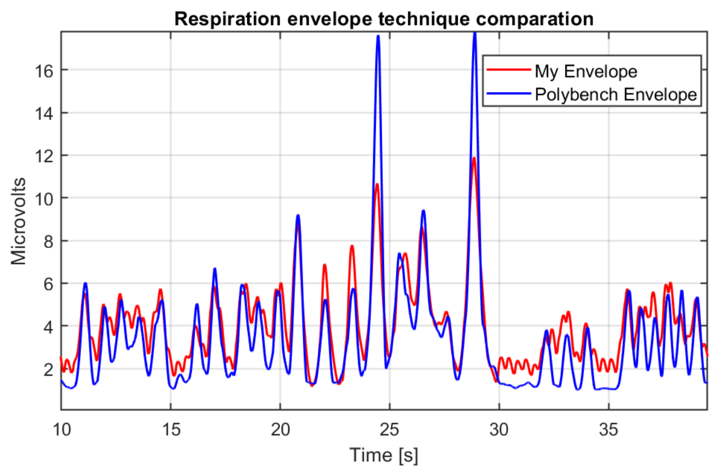

Figure 3.14: Respiration envelope comparison patient 3

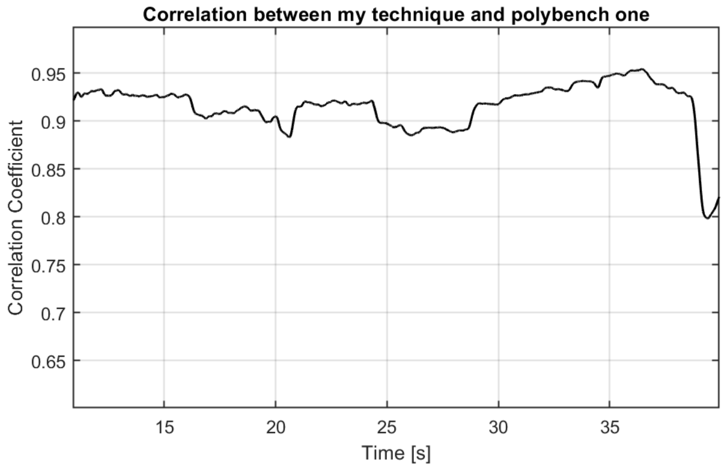

Figure 3.15: Respiration envelope correlation patient 3

The results reported up to now are based on a outlier removal value of 35 μv, which means that part of signal exceeding that value are manually clamped to 0. This value was chosen empirically because it gave the best behavior performance in terms of correlation both for the first and the third patient. But regarding the second patient, something different happened. In the second patient, the more I raised the outlier removal value, the better the correlation was, as shown in the figure 3.16 and 3.17.

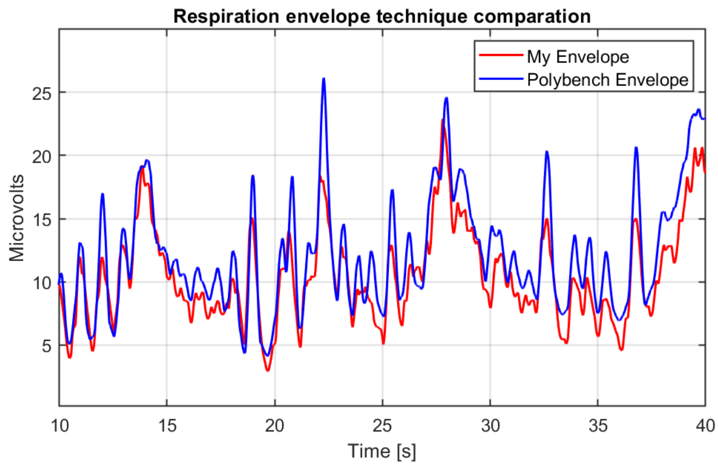

Figure 3.16: Respiration envelope comparison patient 2, with outlier removal value of 100 μv.

At this point, some questions arise. Why is the magnitude of my breathing envelope different from the Polybench one? Why, even if their magnitude are different, do they seem to oscillate with the same frequency? Why is my magnitude lower than the Polybench one? Why is the outlier removal value of 35 optimal for the patient 1 and 3, but not for the patient 2? Those questions are discussed in the comments section.

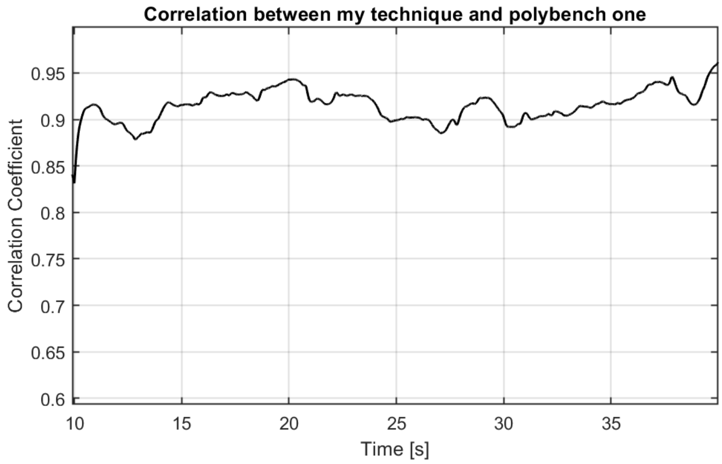

Figure 3.17: Respiration envelope correlation patient 2, with outlier removal value of 100 μv.

3.5. Comments

The following section is based on the assumption that the Polybench respiration envelope is correct, or at least is better than the mine, for the simple fact that it was developed by a recognised mechatronics company such as DEMCON.
The reason why the two envelopes are different and give different magnitudes is basically that they are extracted with two different techniques. However, those techniques cannot be compared. In fact, while my technique is known and explained before, the Polybench technique is not known but is a kind of black box which only display the result.
The fact that, even if their magnitude is different, both envelopes oscillate with same frequency is probably a good sign that indicates that the filters used in my technique are correct, especially regarding the final low-pass filter of 1 Hz.

If we take a look at the previous figures, we notice that the magnitude of my respiration envelope is lower than the Polybench one. The reason of this can be due to three factors. The first one is that the signal reconstruction is not perfect, therefore signal loss is still present. As a consequence, the 1 Hz low pass filter needs the final signal to be at least undisturbed for 1 second in order to be correctly detected. However, signal loss occurs at time step lower than 1 second. The second reason can lie in the fact that the outlier removal removes part of the original signal, which contributes to an additional signal loss. The third factor is due to the fact that the QRS complex is not filtered perfectly. In fact, the QRS pulses is based on a threshold system. When the signal overcomes a certain threshold, it is considered to be an ECG and therefore it is eliminated. However, the ECG wave does not begin and ends at a threshold level, but actually begins and ends at 0 levels, so part of the ECG is still present in the signal even after the ECG removal.

Finally, the reason why the respiration envelope correlation in patient 2 is affected differently by the outlier removal value from patient 1 and 3 can be found in the outlier removal block itself. As we said before, the outlier removal removes not only outliers, but also useful signal. If we take a look at patient 2, we see that his magnitude is greater than the other two patients. Therefore, probably increasing the level of outliers removal (up to 100 in our case) allows more original signal to enter inside the filter. Since the magnitude of the patient 2 is the greatest of the three patients, probably the magnitude of the outliers is needed by the filter to recognize the respiratory wave. On the other hand, the patient 3, who has the lowest magnitude, has a lot of useless information in the outliers, so setting an outlier removal level of 35 is needed actually to remove those useless information. The patient 1, whose magnitude is higher than patient 3 and lower than patient 2, is in an intermediate situation. In his case, setting a too high outlier removal value would allow a too much useless signal to pass. On the other hand, setting a too low level of outlier removal value would cause too much signal loss.
Those thing being said, I consider that my technique reveals successful for patient 2 in terms of correlation (when outlier removal is set to 100) and for patient 3 both for correlation and the magnitude (outlier removal

value of 35). However, it reveals mediocre when dealing with patient 1. For those reasons, I consider that my technique needs further investigation before being used since gives different results based on different patients, and therefore it is not ready to be used. On the other hand, the fact that in two cases out of three it correlates very highly with the DEMCON technique can be considered beneficial in confirming the DEMCON technique validity.

4

Work of breathing extraction algorithms

The current chapter is the core of the thesis. First of all, it guides the reader to recognise the characteristics related to both the undisturbed and disturbed breathing pattern (sections 4.1 and 4.2.1). Consequently, it gives the guidelines to define an undisturbed breathing wave (section 4.3). Such instructions do not derive from any previous literature findings, but they are entirely empirical and derive from the intuition I developed after having observed real-time EMG measurements for several times.
Then, the reader is introduced to the peak-to-peak (P2P) algorithm, which is the algorithm I developed to extract the WOB. The P2P is named this way because it calculates the difference between consecutive positive-negative peaks that occur during the EMG measurements. During the P2P testing phase, two main problems arose but were successfully solved (section 4.4.1 and 4.4.2).
Since the P2P could not be compared to any other algorithm in the literature, two new algorithms named differential peak-to-peak (DP2P) and area-under-the-curve (AUC) were developed. Section 4.5 explains the importance of visualising the trend of the WOB changing over time. Section 4.6 points out the problem of defining the percentage of the respiratory fragment that was actually used in the WOB analysis (this concept becomes clear later). The last section is dedicated to the discussions.

The algorithms that are explained in the chapter are applied to breathing envelope dEMG embedded in Polybench. As mentioned before, I could also have chosen the EMG breathing envelope extracted with my technique explained in the previous chapter, but I preferred to use the Demcon breathing envelope dEMG as it presents less random oscillations and therefore it is more convenient to analyse. As we will see in the chapter, in fact, the random oscillations of the breathing envelope are an obstacle to the algorithm that must be overcome. Moreover, as explained before, my technique lacks in robustness and needs further work prior being accepted.

4.1. Undisturbed breathing pattern characteristics

The only parts of the diaphragm electromyography that are relevant to the research are those referred solely to the respiration. Therefore it is necessary to define, at least qualitatively, how an undisturbed breathing envelope looks.
Understanding the qualitative trend of the breathing envelope is a crucial step to establish the rules that define which parts of the dEMG refer to the breathing, excluding anything that has nothing to do with breath, such as movements artifacts, coughing, apneic episodes, etc. Figure 4.1 is an example of the typical trend of a breathing envelope undisturbed from any kind of noise.

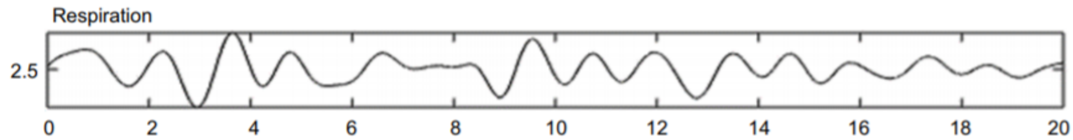

Figure 4.1: Breathing envelope extraction, source: [2]

By observing the signal, it comes up that:

- The signal oscillates around a mean value (2.5 in the example).
- The signal amplitude remains inside a lower and upper boundary.
- The tonic level oscillations do not exceed the 1.5 microvolts range.
- The signal period T (where $T = \frac{1}{freq}$) seems to be around 1 second according to the infants respiration frequency $freq = 1Hz$.
- The signal has a "smooth" shape: it recalls a sine wave, there are no angular points, and there are no abrupt changes in the slope. That means that the function is monotonically increasing when traveling from a local minimum to a local maximum and monotonically decreasing as it travels from a local maximum to a local minimum.

If the breathing envelopes were always like this, it would be straightforward to develop an algorithm that calculates the peak-to-peak difference: it would be sufficient to recognize each time a local minimum and maximum point and make their difference. Actually, for the sake of precision, considering the signal waves as parabolas pointing upwards, you should calculate a local minimum point first, a maximum point later, and finally another local minimum point and make the difference between that point of maximum and the average of the two points of minimum calculated previously. Figure 4.2 helps to clarify this concept.

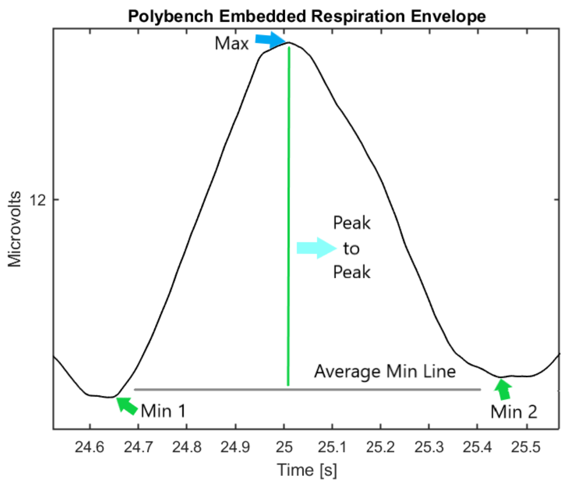

Figure 4.2: Peak to peak detection visualization

4.2. Disturbed dEMG signal and respiration pattern recognition

4.2.1. Contaminated breathing envelope

Unfortunately, the diaphragmatic electromyography signal resembles the previous example only in case the infant is stable and at rest. If the newborn is unstable and often moves, the electromyography signal behaves as shown in the figure 4.3.

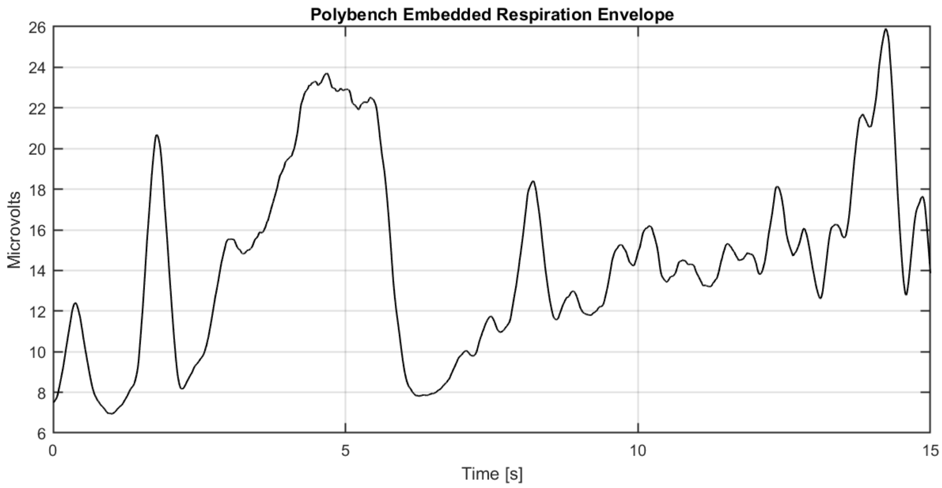

Figure 4.3: Disturbed breathing envelope

By performing a qualitative analysis of the signal, it is clear that:

- The signal does not oscillate around a fixed value.
- The signal does not have a "smooth" shape; each wave of the signal seems to be different from one another, the wave shape does not recall a sinusoid, local maxima and minima are often very close to each other and do not necessarily refer to the maxima and minima we are interested.
- Some waves have a monotonically increasing and decreasing trend when they travel from a local minimum to a local maximum and from a local maximum to a local minimum respectively.
- Some waves have a period much longer than 1 second, so they are not consistent with the respiratory frequency of the newborn.

4.2.2. Breathing pattern recognition

As mentioned previously, the dEMG is often affected by various artifacts, and it is necessary to distinguish which is breathing from what is not. Methods to judge whether or not the signal refers to respiration are based on the empirical observation of prematurely born patients in the neonatal department at the Erasmus Medical Center in Rotterdam. During measurements taken on 3 premature babies in the Erasmus MC NICU, I carefully and simultaneously observed both the patient and the Polybench monitor, and I understood how the signal behaved when the patient was visibly quiet or agitated. I found out that:

- If the patient is at rest, the signal often recalls the shapes shown previously in the figure 4.1.
- Sometimes though, even if there is no movement, the shape of the signal deviates from the ideal shape shown in the figure 4.1 and behaves more crudely. The performance of the function is not monotonous between a minimum and a maximum and between a maximum and a minimum, the difference between two minima of the same wave is excessive, the tonic level of the dEMG changes visibly within a few seconds.
- If the patient is agitated, the signal cannot be traced back to a sinusoid or a disturbed sinusoid, and it assumes an irregular and unidentifiable pattern.
- If the magnitude of the signal is drastically reduced (slightly higher or even lower than the tonic level) concurrently with the reduction of the oxygen saturation level below 90%, apnea is occurring.

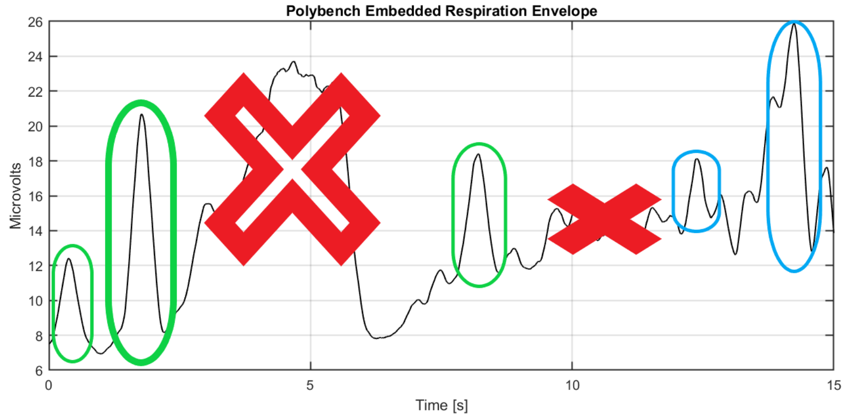

Figure 4.4: Recognizing respiratory segments from disturbed EMG

The figure 4.4 shows an extraction of 15 seconds of a real measurement example. The segments that inevitably refer to breathing are highlighted in green, the more "rough" segments still referring to breathing are highlighted in blue, finally a red cross eliminates what does not refer to breathing.

Strictly speaking, the peak-to-peak detection algorithm must recognize the segments highlighted in green and blue and discard the rest, then it must calculate the actual peak-to-peak value.

4.3. Breathing wave detection guidelines

For the signal to be considered related only to breathing, it is necessary that the following conditions occur:

- The time distance between two consecutive minima is to be lower than a certain threshold (1.3 s in our case).
- The magnitude distance between the maximum and both the minima should be greater than a fixed threshold of 2μv.
- The magnitude distance the two consecutive minima should be less than a fixed threshold of 2μv.

4.4. Implementing the P2P algorithm

In this section, the peak-to-peak algorithm will be explained step-by-step. The algorithm would perform real-time the following instructions

- Looking for a first local minimum point.
- Looking for a maximum point.
- Looking for a second minimum point .
- Determining if such minimum point is a false minimum (this concept would be elucidated later).
- In case the minimum detected is a false one; the algorithm would ignore it and keep looking for the second minimum.
- In case another maximum greater than the previous one is found, the current found maximum takes the place of the previous one. Then, it keeps looking for the second minimum.
- Once the second minimum is detected, the time interval between the two minima is calculated.
- The magnitude difference between the maximum and both minima is calculated.
- If the time interval between the two minimum is lower than 1.3 seconds, the difference between the maximum and the minima is higher than 2μv, and the difference between the current and previous minimum is less than 2μv (the concept of distance between consecutive minima is elucidated later in

section 4.4.2), the peaks distance is calculated by subtracting the magnitude of the maximum to the average of the two minima. The average of the minima is stored in an array that keeps track of the tonic level of the diaphragm. In case such conditions are not respected, the segment is discarded.

- The cycle starts again

4.4.1. False minimum

The figure 4.5 elucidates the false minimum problem. In case a minimum point is detected almost right after the maximum point detection and-or the magnitude of the minimum is very close to that of the maximum, it is almost sure that such minimum point is not a "true" one but it is a consequence of the random fluctuations of the function.

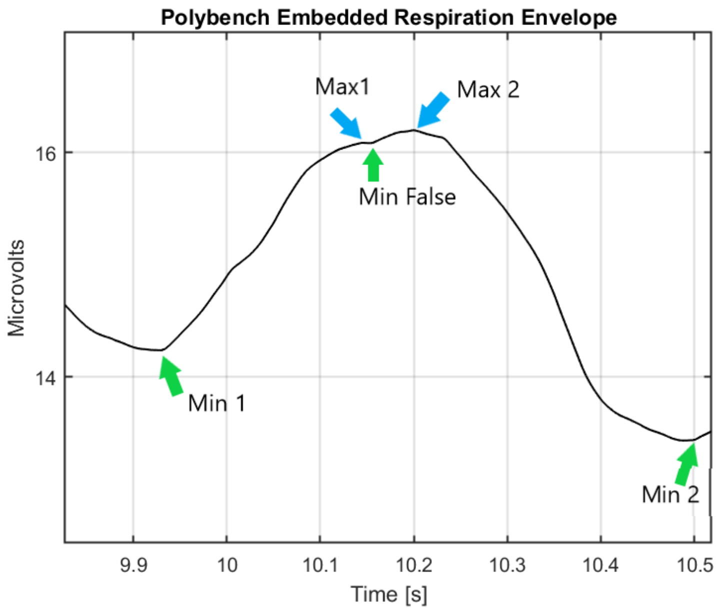

Figure 4.5: False minimum

Therefore, in case of the example in 4.5, during the simulation running, the algorithm detects the local minimum Min 1, then the local maximum Max 1, then the other local minimum Min False, it ignores it and detects another local maximum Max 2, and then detects the local minimum Min 2. Finally, it chooses the greatest value between Max 1 and Max 2 and subtracts the average between Min 1 and Min 2 from it (provided that the previously explained rules are respected).

4.4.2. Maximum distance between two consecutive minima

It has been noticed, through several qualitative dEMG analysis, that an excellent undisturbed dEMG respiratory envelope usually has a very low variation between two consecutive minima. Figure 4.6 represents an undisturbed portion of dEMG; as you can see, the difference in micro-volts between two successive minima is low ($< 2\mu v$).

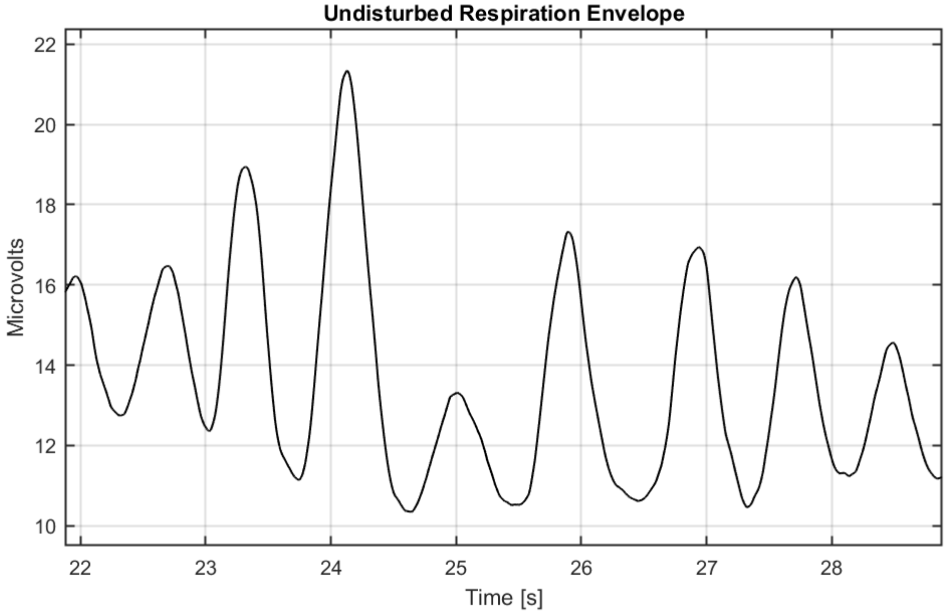

Figure 4.6: dEMG undisturbed segment

On the other hand, when movements are occurring, usually it is possible to recognize some smooth signals that, if it weren't for the difference in magnitude between the minima, they would be considered as breathing portions. Figure 4.7 shows the previous dEMG few seconds before when movements were occurring; the time distance between MIN1 and MIN2, and between MIN2 and MIN3 is in the acceptable range, as well as the magnitude distance between MIN1 and MAX1, MAX1 and MIN2, MIN2 and MAX2, MAX2 and MIN3.

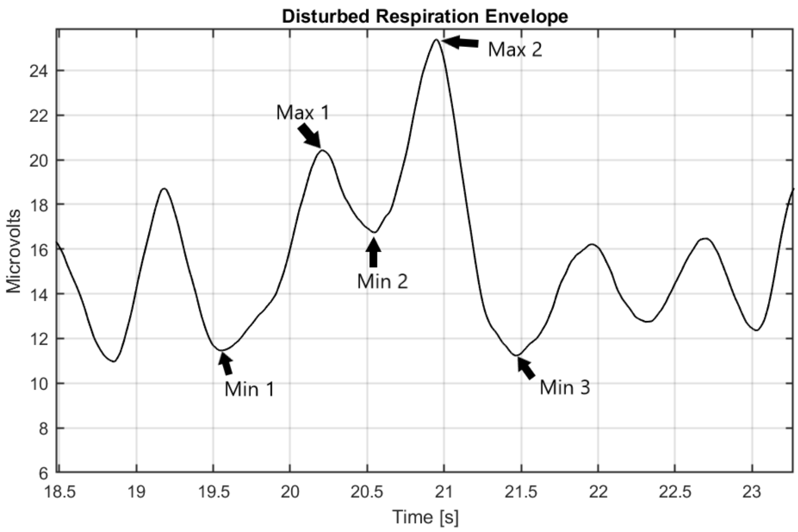

Figure 4.7: dEMG disturbed segment

However, the difference in magnitude between MIN1 and MIN2, and MIN2 and MIN3 is too large ($> 2\mu v$); this frequently happens during movements artifacts. Therefore the previous dEMG segment is discarded.

4.5. Peak-to-peak trend

As pointed out by the specialized nurse Bas Bol, the interest in the peak-to-peak does not necessarily refer to the instant peak-to-peak values, but more precisely to how they change over time. As a result, the peak-to-peak values are collected and averaged every 30 seconds (see figure 4.8). There is no specific reason for the choice of 30 seconds as an average time, however you can change it at any time by changing the tapped delay options in Simulink.

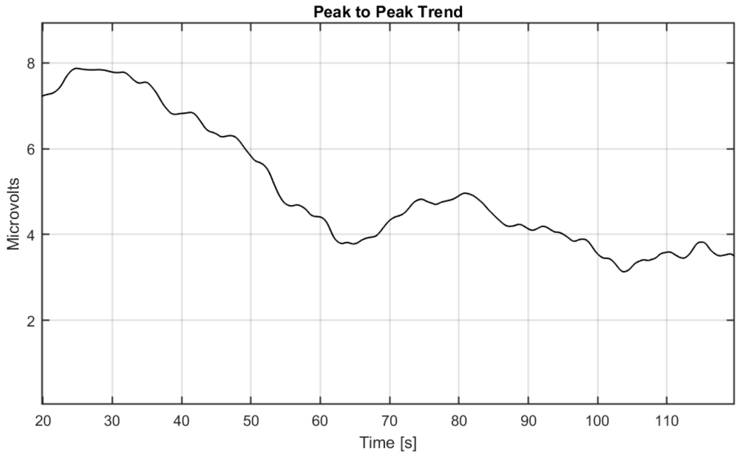

Figure 4.8: Peak-to-peak trend averaged over 30 seconds time span

This curve can be used in conjunction with clinical observation to establish the threshold level beyond which the patient's respiratory fatigue becomes excessive and prevents weaning.

4.6. Percentage of respiratory fragments

As mentioned earlier, it is necessary to separate into the respiration envelope what is respiration from what is not. In cases of stable and quite patients, it is merely a matter of eliminating some sporadic movement from an almost clear and uncontaminated dEMG. But in more complicated cases like the patient mentioned above, removing artifacts is something that happens frequently. Therefore it is necessary to have a parameter that indicates how much the measurements are disturbed or not; as a consequence, a simple function is included into the Simulink program that shows in a graph the percentage of dEMG segments that refer solely to the respiration. This graph is useful because it is possible to establish a threshold below which the patient is considered excessively agitated and consequently not ready for weaning. Moreover, it might also be possible to set a safety threshold above which the patient can be considered to be likely to be stable and ready for weaning.

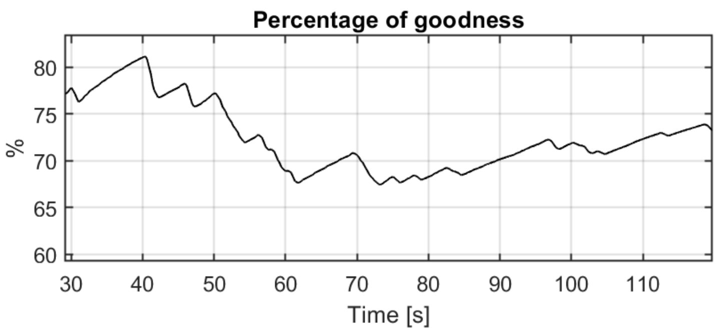

Figure 4.9: Percentage of respiration fragments of dEMG

4.7. AUC

Although P2P detection is an adequate tool to measure the respiratory fatigue, it has a pitfall; it does not take into account the diaphragmatic tonic level. As a result, if the patient triplicates his tonic level for any reason but continues to breathe with the same pattern of peaks, for P2P algorithm it makes no difference. This problem could be remedied by integrating the P2P trend with the tonic level one, but this would make it difficult to read on the screen. Therefore, it is useful to implement a function that calculates the AUC of the segments that refer to the breathing. By doing so, you also take into account the tonic level.
The algorithm for the AUC is straightforward and is as follows:

- Looking for a first minimum point.
- Once the algorithm finds it, the function starts to add the value of the function multiplied by the time step (0.002 s).
- Looking for a maximum point.
- If while searching the maximum point a new minimum comes up, the function resets the value of the area under the curve to 0 and starts calculating it again.
- Looking for the second minimum.
- In case the analyzed segment refers to the breathing, the function outputs the final value of the area under the curve, finally resets the value of it to 0, and the cycle starts again.
- Otherwise, the function directly outputs a value of 0 and the cycle starts again.

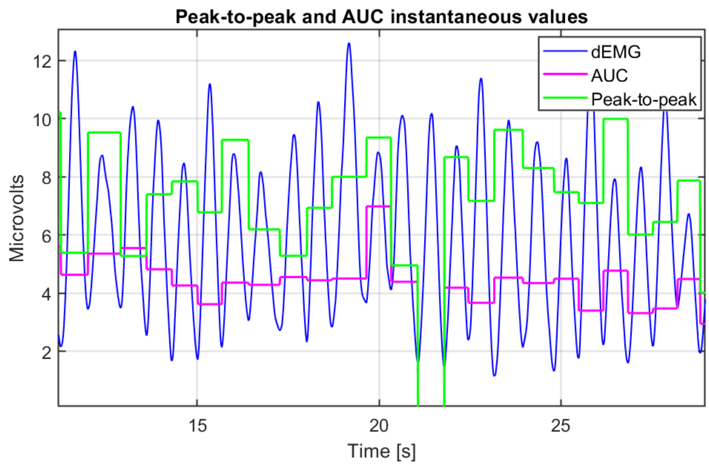

Figure 4.10: Area under to curve and peak-to-peak detection instant values

In the figure 4.10 we see an example the area under the curve compared to P2P instantaneous value during real time analysis. Figure 4.11 shows an example of the trend of the area under curve over time.

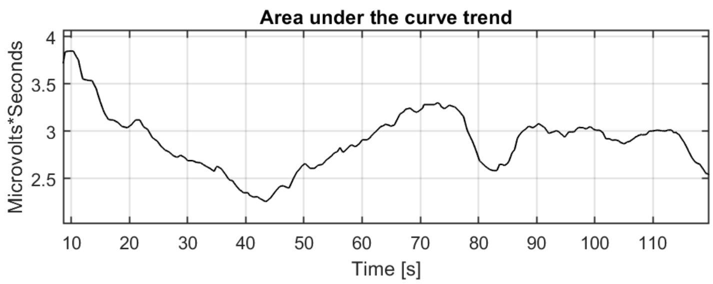

Figure 4.11: Area under the curve trend

4.7.1. AUC and P2P comparison

The AUC and P2P algorithm do not reveal a high correlation. The reason for this is related to the difference between the two algorithms. To make the explanation clearer, we could think about a respiratory wave as a triangle, where the base is the time distance between two consecutive minima and the height is the magnitude distance between the maximum and the average minima line. Figure 4.12 helps to visualise the concept.

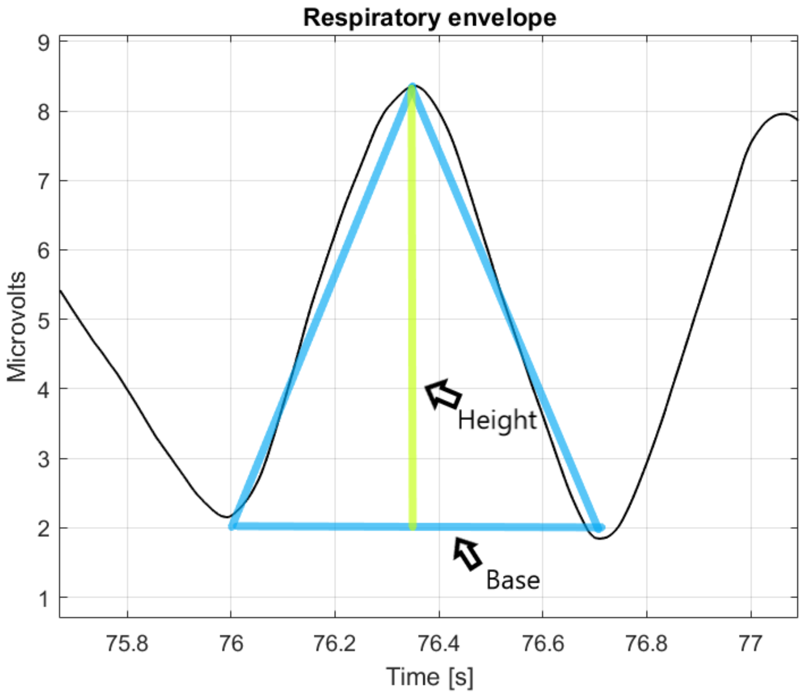

Figure 4.12: Breathing wave as triangle example

We can think about the P2P algorithm as a function that keeps tracks of the heights and the AUC as a function that holds records of the product of the heights times the bases. As a consequence, the two algorithms can be correlated only when the base changes proportionally to the height. Such lack of correlation then could be a sign that the patient diaphragm muscle activity (i.e. the height) does not grow or decline proportionally to the time of air intake and exhale (i.e. the base). However, this does not mean that one of the two algorithms is wrong, since basically, even if they refer to the same EMG envelope, they express two different measures.

To be more in-depth about their difference, if we make an analogy between volts and newtons, we can state that the P2P represents the instantaneous force of the breathing, while the AUC represents its momentum. This fact could induce to think that AUC is better than P2P. However, since the definition of momentum as the "intrinsic power" that a moving object carries refers to mechanics, not electronics. So, the fact that AUC measures the momentum doesn't seem enough to convince that it is better than the P2P.

4.8. DP2P

Although the P2P detection based on the previous algorithm seems to be interesting, it is always good to corroborate its effectiveness with a method that performs the same function but in a different way. The DP2P relies on the principle that to identify the maxima and minima points of the breathing envelope it is sufficient to observe its derivative; when the latter crosses the axis of the abscissas, a minimum or maximum point has been detected. By combining the information of the breathing envelope and its derivative, it is possible to extract the peaks difference value referring exclusively to the breathing.
The DP2P is explained here step by step.

- The DP2P function receives as input both the respiration envelope and its derivative.

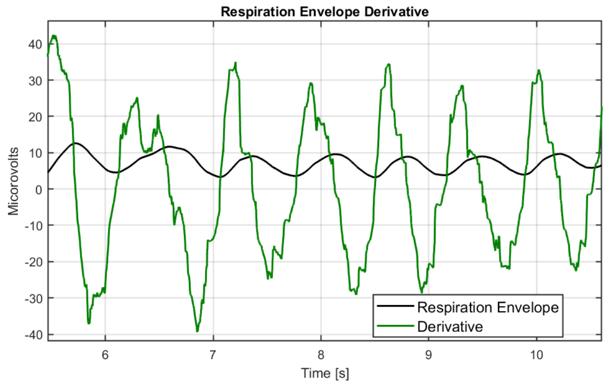

Figure 4.13: Respiration Envelope (in black) vs its derivative (in green)

- The function analyzes the difference in time between two consecutive times in which the derivative crosses the abscissa line.
- In case the time distance is "too short" ($\Delta T < 0.3$) or "too long" ($\Delta T > 0.8$) , the correspondent EMG envelope segment is discarded.
- In case of such time distance is in the security range and the envelope EMG value is not "too low" ($< 2\mu$v) or "too large" ($> 30\mu$v) the function calculates the absolute value of the difference between the EMG values related to their 0 derivatives. The reason why the absolute value is used is that when the derivative is 0, we know that we found a stationary point regardless if it is minimum or maximum (unless we decide to use the second derivative).

The DP2P trend is very similar to that calculated with the P2P as can be seen in the figure 4.14, where the Person's r correlation test reveals a correlation higher than 0.8 for more than 80% of the time.

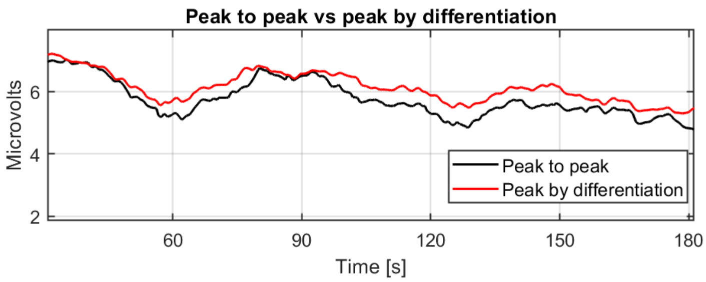

Figure 4.14: Peak to peak trend vs peak to peak by differentiation trend.

As can be seen, this algorithm, with respect to the P2P, does not perform any control over the distance between two consecutive minima. In fact, unlike the P2P, this algorithm does not analyze the respiratory wave in its entirety but only analyzes half of it. The reason for this lies in the fact that sometimes when breathing becomes more disturbed, the respiratory wave deviates from what can be called correct breathing, and behaves singularly. In fact, it assumes a form that does not remember a proper respiratory wave because of the excessive distance between its minima; at the same time, however, if such a wave was split in two, the resulting halves, analysed individually, have the characteristics of a proper respiratory wave cut in half. This behaviour could mean that it is probably not a non-respiratory segment, but rather a respiratory portion that indicates a moment of abrupt changes in the intensity of breathing, but that still refers to breathing. It must be said that such a type of waves can occur either right before or after a movement occurs and during normal breathing when no movement is detected.

4.9. P2P compared to DP2P

The P2P and the DP2P algorithm are highly correlated (i.e. their correlation coefficient >0.8) for 80% of the time.

If we keep in mind the triangle example explained in section 4.12, we see that both algorithms rely on the same measurements, i.e. the heights, therefore the high correlation can confirm the robustness of both methods since they measure the same thing. The reason why their correlation drops below the high level in a certain period is due to the difference in the way they calculate the heights. The P2P algorithm calculates the heights as a difference in magnitude between the maximum point and the average of the two minimum points. However, if the magnitude difference between the two minima exceeds a certain threshold, the measurements are discarded. On the other hand, the DP2P does not make any restriction on the distance between two consecutive minima, since it doesn't analyse the whole respiratory wave, but its half (see figure 4.15).

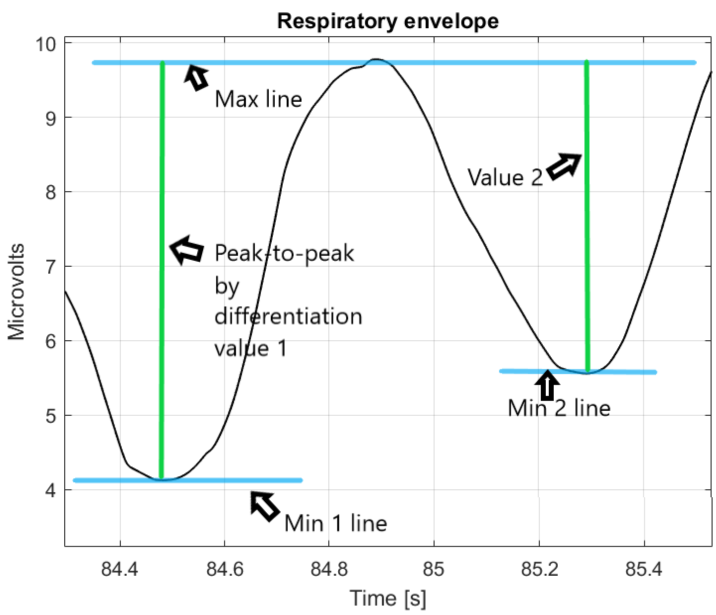

Figure 4.15: Peak to peak by differentiation visualization

The high correlation between the two different methods can be due to the fact that sudden movements and abrupt changes in the intensity of breathing are not frequent.

4.10. Discussions

The P2P, which is the core of the thesis, is based upon the constraints that define what is a respiration pattern from what is not. However, since such constraints are not taken from the scientific literature, such values are determined empirically after carefully observing the real-time measurements in the hospital. For example, the reason why I chose that the distance in magnitude between two consecutive minima should not exceed 2 microvolts is that I noticed, after several minutes of observing the measurements, that good respiration waves often begin in a minimum point and end up in a minimum point value which has a value close to the previous one (i.e. less than 2 microvolts). On the other hand, I noticed that when such a distance exceeds the value of 2 microvolts, the respiration fragment is likely to be a non-respiratory one. The same reasoning holds for the other constraints. Moreover, it must be pointed out that the constraints that I figured out in my research are based on a few samples of 3 patients. This means that future research done on a much greater sample could reveal that such constraints values can change within patients according to their weight, congenital conditions etc..

It must be also pointed out that there is no specific reason why I average the results of the trends over a period of time of 30 seconds. The time span of 30 seconds is chosen as an example to show to the reader that the results are not presented instantaneously but averaged over time. The value of averaging is to be chosen by clinicians according to their experience and expectations.

Furthermore, it is worth knowing that it is up to the choice of the clinicians to choose whether to utilize the P2P/DP2P or the area AUC. In case they prefer to have a measure of the peaks fluctuations, they will use the P2P/DP2P algorithm. On the other hand, if they feel they need to take into account the tonic level in their measurements, they would use the AUC method. In any of those case, they could rely on the percentage of good measurements trend to check whether the measurements performed are severe, medium or seldom polluted.

5

Adverse events detection

The following chapter is dedicated to the detection of the apnea and the brachicardia. Those issues are not strictly related to the WOB analysis, however, in case they occur they could indicate danger, and therefore the WOB analysis would no longer be reliable.

5.1. Apnea detection

During the first days of their life, premature infants often encounter difficulty in the control of respiration [37]; apnea is one of the major problems and can be an indication of weaning failure and need of re-intubation.
Apnea of prematurity is defined as a cessation of breathing for more than 15-20 seconds often accompanied by oxygen desaturation or brachicardia [38].
EMG of the diaphragm is an adequate technique to detect airway obstruction [39], therefore implementing an apnea detection function can be an indication of weaning outcomes predictions.
The function for the detection of apnea is straightforward. It is only necessary to select a threshold below which, if the signal remains there for a fixed period, the event is considered apneic.

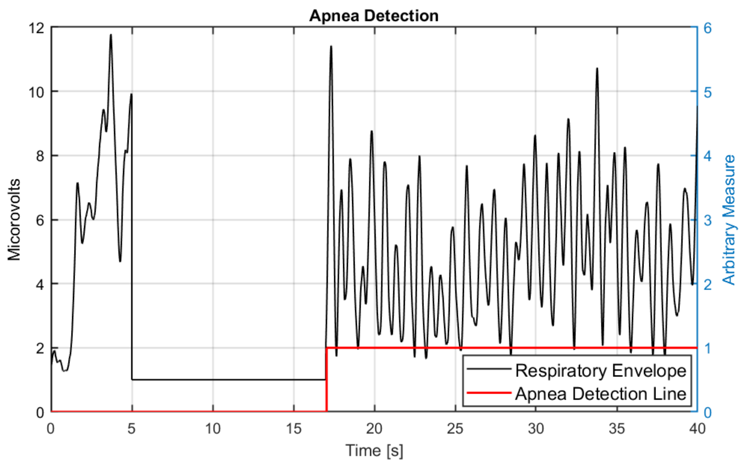

Figure 5.1: Apnea detection

In figure 5.1 we observe a ceased breathing activity in the period between 5 and 17 seconds. The function recognizes that the signal has been below the prefixed level (in this case the tonic level) for the fixed period (in this case 10 seconds) and moves the apnea line from level 0 to level 1. In case another apnea episode would happen, the apnea line would move from 1 to 2, then from 2 to 3 and so on.
The reason why I chose 10 seconds as a warning time is just for showing how the detection works, but the actual time is to be chosen by the clinicians.

5.2. Heart Rate and Brachicardia Detection

Apnea of prematurity is often accompanied by episodes of brachicardia (heart rate $<\frac{2}{3}$ average Hear Rate for a period longer than 4 seconds)[40]. Therefore it may be useful to develop a function that calculates in real time the heartbeat both instantaneous and mediated over a certain period and then compares them to detect any episodes of bradycardia.

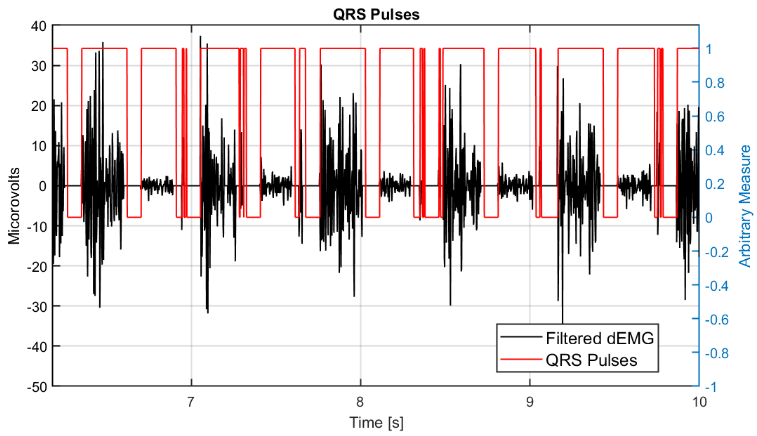

Figure 5.2: QRS and masked dEMG

By observing the figure 5.2 we can see the QRS pulses from the blocks of the Polybench file called QRS-detection (check appendix at the section A.2 to see what QRS pulses are). As we can see, the QRS pulses are null when the signal is masked and not null when the signal is not masked. To be precise, sometimes it happens that the QRS pulses are null even when the signal is not masked. Whenever the signal is masked, a heartbeat is occurring. Since the number of times that the signal is masked is equal to that of the times that is not masked, it is sufficient to count the number of the QRS pulses and divide them by the time to know the heart rate. However, since the QRS pulses are not continuous but have interruptions, they are considered continuous if their discontinuities are small (less than 0.05 seconds).

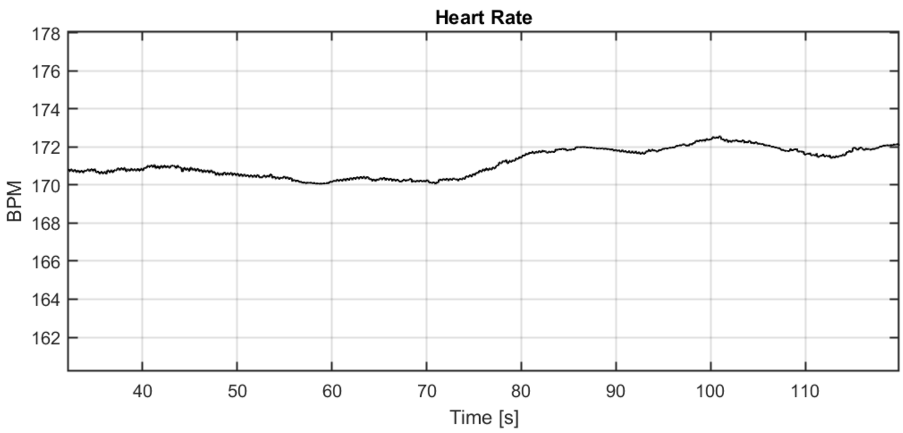

Figure 5.3: Heart Rate detection (Beats per minute)

Figure 5.3 represents the trend of the heartbeat averaged over a time period of 30 seconds. Figure 5.4 instead represents the brachicardia detection. The heart rate (in black) has been modified to a drastically low level in the time range from 100 to 110 seconds. After 10 seconds since the beginning of the brachicardia, the brachicardia line is activated to level 1. As in the case of apnea, if other episodes of brachicardia would happen its level would raise to 2, then 3 and so on.

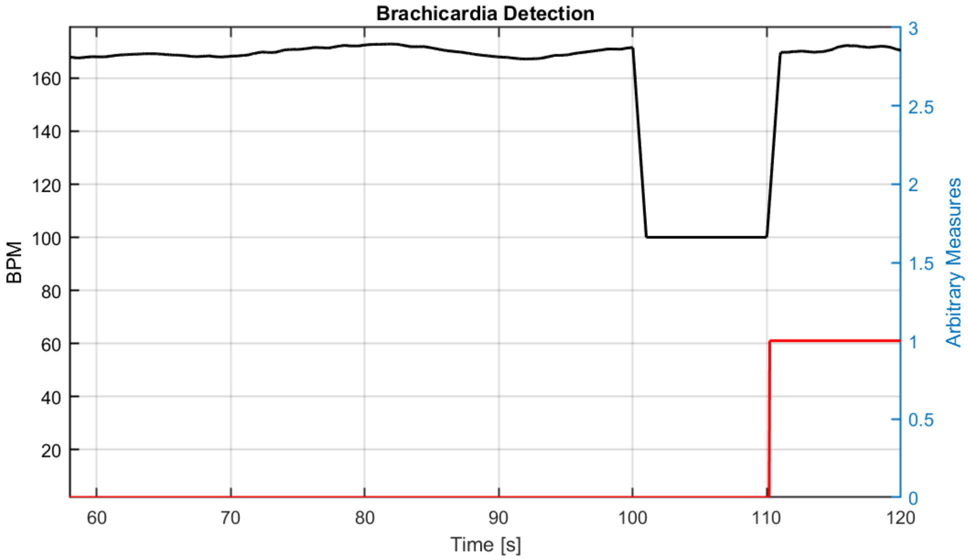

Figure 5.4: Brachicardia Detection

5.2.1. Heart rate detection function validity

It was decided to implement another method and compare the results to corroborate the idea that the heart rate detection is correct. As a consequence, it was thought to insert the raw EMG into a level detector ($S = 1000, R = 900$) that detects the heart waves directly according to the amplitude of the EMG (to see what a level detector is, check the Appendix at the section A.1.3). Afterward, a frequency detection function counts the unitary pulses of the level detector and divides the total by the time. The results of both methods are shown in the figure 5.5. They are equal.

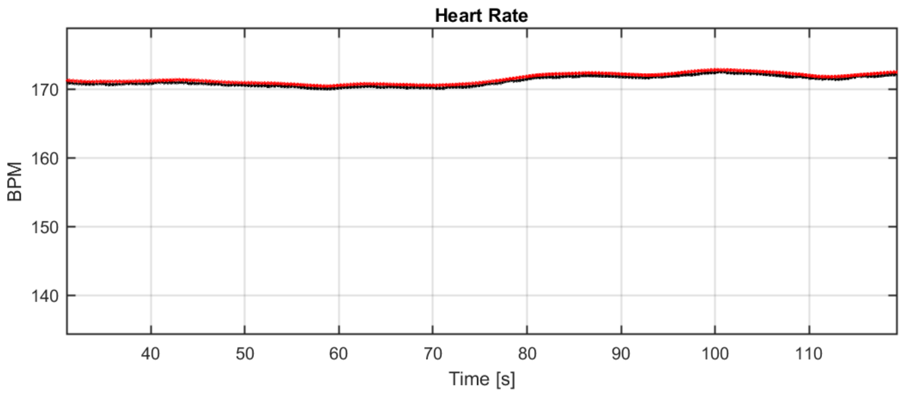

Figure 5.5: Heart rate detection comparison between the two methods (in red and black respectively)

5.3. Discussion

The apnea detection algorithm is based on the principle that if the respiration envelope signal value remains below the tonic level one for a specified amount of time (15-20 seconds), apnea is occurring. The reason why I chose to set the tonic level as a threshold is that I observed that when the dEMG value was below the tonic level for a period of time greater than 10 seconds, the oxygen saturation level dropped below the 90%, therefore apnea was occurring. However, since such an assumption relies on a sample of only three patients, further research could determine that the threshold value under which apnea occurs can differ.

The brachicardia detection algorithm compares the instantaneous heart rate to the average one. It must be pointed out that there is no specific reason why I chose 30 seconds to be time for averaging the heart rate; it is just an example to show how the algorithm works. The clinicians can choose the time they prefer based on their knowledge. It is worth knowing an instantaneous measurement does not exist per se, therefore when I refer to the instantaneous heart rate I actually refer to the heart rate averaged on a time span which is considered negligible with respect to the total time of the measurements. In this case, I chose such average time to be of 5 seconds, but of course, clinicians can choose to modify it.

Furthermore, it is worth noting that clinicians might not be interested in the total number of adverse events per se, but their number over a specified amount of time. This is why the apnea and brachicardia detection Simulink blocks have been provided with a feature that, in case clinicians want, can calculate the number of their occurrence over time.

6
Results

The DEMCON Polybench software has been transcribed in Simulink, so any engineer with Matlab skills can contribute to it. Small inaccuracies in the software have been corrected as well. It is remarkable that the breathing envelope embedded in Polybench has been corroborated by the fact that it is highly correlated (Pearson's r coefficient >0.8) to a breathing envelope coming from a method based on previous scientific research with the addition of my personal features like signal reconstruction, outliers removal and pulse generator. Although both techniques give interesting results, the one embedded in Polybench is more comfortable to analyze because of its greater "smoothness." Smooth functions, in fact, are more convenient to investigate when dealing with maxima and minima points research. An algorithm based on the analysis of the breathing envelope was developed to extract the work of breathing through peak-to-peak analysis. This algorithm allows to eliminate data related to movements artifacts and to consider only those related to breathing. The algorithm, in short, tries to recognize the "beauty" of the electromyographic wave; if the wave shape results to be consistent with a respiratory wave, the signal is analyzed, otherwise, it is discarded. Although the algorithm is very efficient in discarding movement artifacts, it is also true that some respiratory waves are incorrectly rejected (around 15%, sometimes 20%). However, this is not a serious problem; in fact, the crucial point of the analysis of the breathing envelope is to get rid of the artifacts movements as they would introduce incorrect data into the work of breathing analysis. On the other hand, if you do not detect a respiratory wave, it does not seriously affect the WOB analysis as it is not the instant WOB that matters but is its average over time. Thus, assuming that the undetected waves do not deviate excessively from those previously detected, one can afford to ignore their contribution. In addition to the WOB trend, the detection of apnea and bradycardia have been developed to provide additional measures to clinicians as well. Unfortunately, due to the high computational time required by Simulink to perform a simulation, it was not possible to analyze the whole set of data. For further research, having a computer with great computational speed would be beneficial since it could be possible to simulate real weaning from ventilation situation based on hours of measurements instead of making trials on a few minutes of data.

7
Discussions

In this chapter, the results come together, and it is elucidated how they will present themselves to the clinicians. First of all, they will see on the screen the trend of the WOBs that they prefer, be it the P2P, the AUC or DP2P. At the same time, it will be joined with the percentage of goodness trend, the graph of apnea and that of brachicardia.
Finally, a question arises: how do clinicians use it? The analysis of the WOB trend over time could be used by clinicians as follows:

- The WOB trend and the percentage of goodness line should be carefully observed in conjunction with the newborn's clinical condition.
- At the time when the newborn seems unstable, and intubation is deemed necessary, a threshold line must be drawn on both trend chart.
- This experiment must be repeated several times so that it can be deduced if a threshold line actually exists (i.e. if its value is not changing drastically among different measurements).
- In case a threshold end exists, but varies from patient to patient, it is necessary to identify the reasons for this variation in order to normalize the results. These variations could be related to the weight of the newborn, to its d-EMG tonic, etc.
- During the weaning process, clinicians should always keep an eye on the brachicardia and apnea charts. When the values of one of the latter are considered excessive, the weaning is interrupted.

Here is an example to clarify what was explained before. In figure 7.1 we see the WOB trend and a red line, which represents the threshold line. When the value of the trend WOB exceeds this line, the weaning is interrupted.
In figure 7.2 we see the trend of the percentage of goodness and the threshold line. If the trend value goes below this line, weaning is interrupted.
In figure 7.3 one can see the apnea event chart with the threshold line. In case the apnea line overcomes such threshold line, the weaning is interrupted. Please notice that the number of events can eighter refer to total number of events or to their occurrence over a certain amount of time, according to the clinicians need. The example of the chart for the brachicardia events is not represented since it is the same as the one of the apnea.

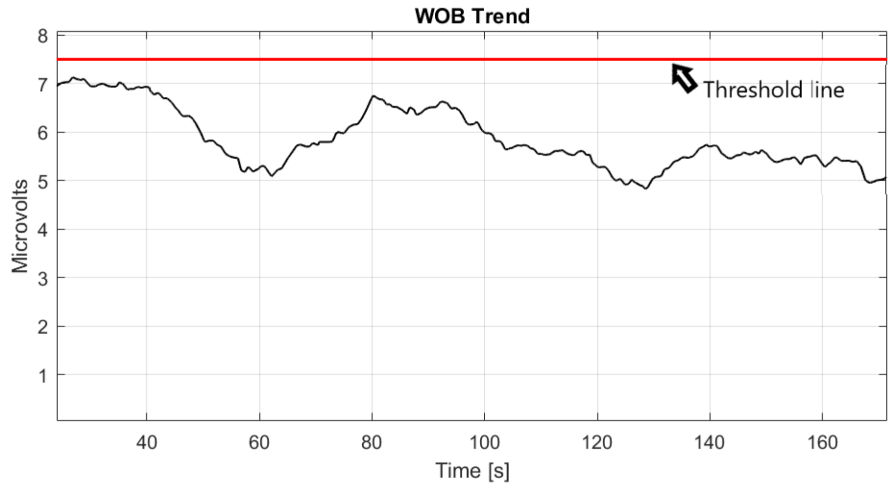

Figure 7.1: WOB trend with threshold line

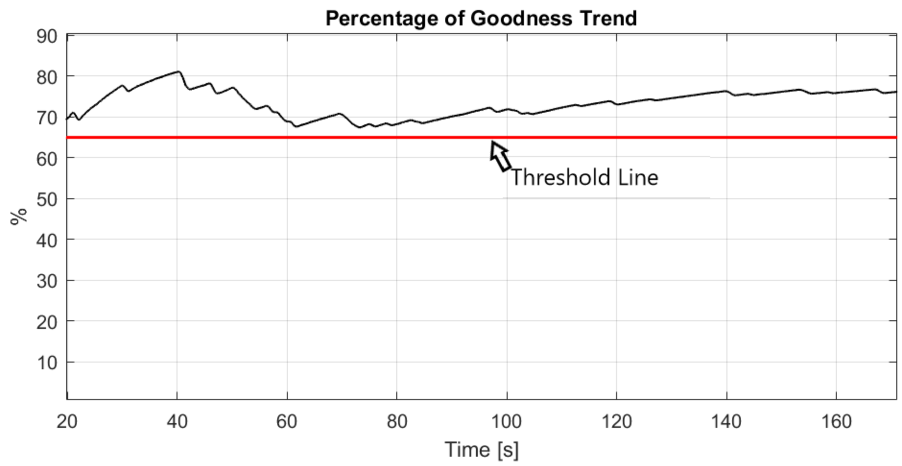

Figure 7.2: Percentage of goodness trend with the threshold line

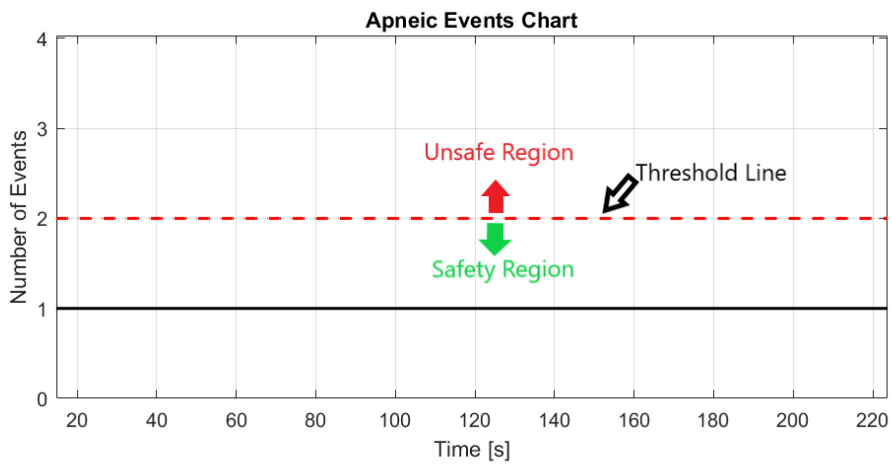

Figure 7.3: Apneic events chart with threshold line.

8 Conclusions

As future research, I would suggest as a future work to relate the diaphragm EMG with the intercostal EMG to find any correlation. In fact, Hawkes et al. [41] revealed in their research that when respiratory muscle fatigue occurs, intercostal and diaphragmatic muscle try to work in synergy to overcome the effort, thus increasing their correlation.

These things being said, it must be pointed out the fact that the topic of weaning from ventilation is little discussed and requires greater attention from the scientific community, referring to both clinicians and biomedical engineers. Therefore, this thesis project should not be meant as a point of arrival but more than anything else as a starting point from which, clinicians and above all engineers can take inspiration for future research. It would be interesting if to intensify the collaboration between the hospitals and the universities of engineering so that we can create different teams of engineers, each of which deals with a different category of patients (referred to their weight, age, and congenital conditions). Having a multitude of students working on postprocessing of the electromyograms on newborns could make significant improvements to the algorithms described in the thesis and above all could give relevance to the scientific research due to a large number of analyses carried out. Finally, the collaboration between clinicians and engineers must always be present as they can achieve results that, if they were alone, could not even have imagined.

9 Acknowledgments

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A
Appendix

The appendix has been removed for copyright reasons.