Trabajo Fin de Máster

Estimation of indices derived from electrocardiographic and blood pressure signals for the study of the autonomic regulation during hemodialysis and hypotension episodes prediction

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ABSTRACT

Hemodialysis is the main urea treatment due to kidney failure. During hemodialysis, the patients often suffer symptomatic hypotension episodes, together with nausea, vomiting, and sometimes syncope. Dialysis-induced hypotension is one of the main problems during hemodialysis, not only because of the discomfort of the patient and the decrease of the treatment effectiveness due to the interruptions, but also it has been reported that these events increase the patients' mortality. Therefore it is desirable to find methods to prevent these episodes, specially using noninvasive techniques which permit to identify which patients are prone to suffer hypotension.

One of the hypothesis of the dialysis-induced hypotension origin is a malfunction of the cardiovascular regulation of the autonomic nervous system. The analysis of heart rate variability is a noninvasive tool which allows to study the changes in that system activity, and it can be complemented with measures derived from blood pressure variability, such as baroreflex sensitivity.

Several clinic indices have been estimated from the heart rate variability, blood pressure variability and baroreflex sensitivity, in order to discriminate between hypotension-prone and hypotension-resistant patients. The database used in this work consists of electrocardiogram and blood pressure signals acquired simultaneously during hemodialysis in Lund (Sweden) and Copenhaguen (Denmark) and belonging to patients identified as prone or resistant to suffer hypotension events based on clinical history.

A classifier has been proposed to separate prone and resistant patients, and a feature selection have been performed to improve the classification, obtaining an accuracy (Acc) of 88.4%. Introducing the information about the diabetes state, the results have improved: Se=97.5%, Sp=72.7% and Acc=92.3%. This results have been improved further by balancing the two classes: Se=87.8%, Sp=100% and Acc=93.2%.

Lastly, the evolution of these features have been studied during the hemodialysis treatment. Results have shown that resistant patients show features similar as prone patients as the treatment goes on. This fact has also been shown in the resistant record who had an hypotension event, which is classified as prone in several segments, including those prior to the hypotension episode.

As a practical work for the master, some visits to hemodialysis sessions in Hospital Clínico Universitario Lozano Blesa have been conducted. There, the protocol used during the treatment was explained, as well as the dialyzer machine.

Obtención de índices derivados de la señal electrocardiográfica y de presión sanguínea para el estudio de la regulación autonómica durante hemodiálisis y predicción de episodios de hipotensión

RESUMEN

La hemodiálisis es el principal tratamiento de la uremia debida a una insuficiencia renal. Durante la hemodiálisis, el paciente sufre frecuentemente hipotensiones sintomáticas, seguidas de náuseas, vómitos y, en ocasiones, síncope. La hipotensión es una de las principales complicaciones de los pacientes de hemodiálisis, no sólo por la incomodidad del paciente y la pérdida de eficacia del tratamiento debido a las interrupciones, sino que ha sido demostrado que también incrementa la mortalidad de los pacientes que las sufren. Se busca por tanto desarrollar métodos para poder predecir y evitar estos episodios, en especial usando técnicas no invasivas que nos permitan además identificar a los pacientes con propensión a sufrir hipotensiones.

Una de las hipótesis respecto al origen de dichas hipotensiones es una alteración en la regulación cardiovascular del sistema nervioso autónomo. La variabilidad del ritmo cardiaco es una de las principales medidas no invasivas que se usa para medir la actividad de dicho sistema, que puede completarse con medidas obtenidas a partir de la variabilidad de la presión sanguínea, por ejemplo, la sensibilidad barorrefleja.

Se han obtenido diversos índices clínicos obtenidos a partir de la variabilidad del ritmo cardiaco, la variabilidad de la presión sanguínea, y la sensibilidad barorrefleja, capaces de distinguir entre pacientes propensos y resistentes a sufrir episodios de hipotensión. Como base de datos se han utilizado señales electrocardiográficas (ECG) y de presión sanguínea (BP) registradas simultáneamente durante hemodiálisis en Lund (Suecia) y Copenhague (Dinamarca) que pertenecen a sujetos de los cuales se sabe si son propensos o resistentes a sufrir hipotensiones.

Se ha propuesto un clasificador capaz de separar los distintos pacientes en propensos y resistentes, y se ha aplicado una selección de características para mejorar dicha clasificación, obteniendo una precisión (Acc) de 88.4%. Introduciendo la información del estado de diabetes de los pacientes, se ha conseguido mejorar el resultado consiguiendo una sensibilidad (Se) y una especificidad (Sp) de 97.5% y 72.7% respectivamente, y una Acc=92.3%. Este resultado se ha mejorado balanceando las dos clases consiguiendo Se=87.8%, Sp=100% y Acc=93.2%.

Por último, se ha estudiado cómo evolucionan dichas características a lo largo del tratamiento de hemodiálisis. Los resultados muestran que los pacientes resistentes presentan características similares a los pacientes propensos a lo largo del tratamiento, siendo más evidente en los casos de pacientes resistentes con episodios de hipotensión.

Como parte práctica del máster se ha asistido a varias sesiones de hemodiálisis en el Hospital Clínico Universitario Lozano Blesa donde se ha conocido el protocolo utilizado durante las sesiones, así como el funcionamiento de la máquina dializadora.

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Chapter 1

Introduction

1.1 Context

This work is supported by the Gobierno de Aragón, by project TEC-2010-21703-C03-02, by CIBER de Bioingeniería, Biomateriales y Nanomedicina through Instituto de Salud Carlos III and by Grupo Consolidado GTC from DGA which belongs to the Instituto de Investigación en Ingeniería de Aragón (I3A), University of Zaragoza.

1.2 Motivation

Hemodialysis is the main urea treatment due to kidney failure, and one of the biggest complications that occur during these treatments are hypotension. Hypotension events, which happens in about 30% of the hemodialysis sessions, are an important problem because they are the cause of circulatory collapse, leading to premature termination. The origin of these events is still not completely known, but it is clearly multifactorial, and may be dependent on factors like diabetes and overweight. It has also been reported that hypotension episodes carry on an increase in the mortality of the patients [1, 2]. These events are highly costly and more medical care is required, as well as the duration of patient rehabilitation. Despite the improvement of technology and research in this field, dialysis-induced hypotension is still one of the most common complication, and it is highly desirable to develop methods to prevent these events.

One of the hypothesis of the dialysis-induced hypotension origin is a malfunction of the cardiovascular regulation of the autonomic nervous system (ANS) [3]. The analysis of heart rate variability (HRV) is a noninvasive tool which allows to study the changes in the ANS activity. The blood pressure variability (BPV) is also used to check the changes in the blood pressure, and to obtain a measure of baroreflex sensitivity (BRS) [4], which measures changes in heart rate induced by changes in blood pressure, and it is considered another noninvasive measure of the ANS activity. The hypothesis of this work is that a patient which suffers hypotension episodes will experiment a sharp decrease of the blood pressure caused by the hemodialysis, non compensated by the ANS.

In this work the autonomic cardiovascular regulation is analyzed by the processing of HRV, BPV and BRS and a classifier is evaluated to study which indices are able to discriminate between hypotension–prone and hypotension–resistant patients. The diabetes state is also included in

the study to improve the results, since the clinic literature has reported an impairment of the ANS in diabetic patients. To achieve this, two databases will be analyzed, summing up to 52 records of electrocardiographic and blood pressure signals during hemodialysis treatment from 24 patients previously labeled as hypotension–prone or hypotension–resistant based on clinical history.

1.3 Hemodialysis

Blood is in charge of substances distribution, such as nutrients and oxygen, to all the cells in the body, and the removal of waste products and fluids. For this reason, it is essential for the blood to remain clean and maintain the correct balance and levels of the substances which circulate through it. This balance is controlled by the kidney, and when it stops working, a kidney transplant is needed. This solution is not always possible since the main problem is to find an appropriate kidney which will be accepted by the patient body.

The goal of dialysis is to replace the ill kidney of a patient. The hemodialysis is a process which lets the blood flow outside the patient body through an artificial kidney (dialyzer), and this process is repeated from 2 to 4 times a week, lasting each session between 2 and 5 hours, being the duration and the frequency of the treatment very dependant of each patient.

The process consists of pumping, on the one hand, the patient's blood, and on the other hand, the dialysis fluids, both in opposite directions through the dialyzer. This two channels are separated by a semi permeable membrane which allows to filter the harmful substances in the blood. It is essential to maintain the appropriate pressure to assure the membrane filtration is performed.

The hemodialysis treatment can generate several complications, being hypotension events the main problem. A blood pressure level too low makes the blood not able to reach appropriately all the parts in the body through the arteries, and it causes symptoms such as dizziness and vertigo. Not only that, but it has also been reported an increase of mortality in these patients [1, 2]. That is the reason why it is very desirable to be able to predict these events, as well as patients hypotension–prone, through the study of the patient's physiological signals.

1.4 Physiological signals

In this section, the physiological signals will be presented. They will be used to estimate the heart rate and the blood pressure variability signals.

1.4.1 ECG

The electrocardiogram (ECG) describes the electrical activity of the heart and provides, in a non invasive way, information about the cardiac muscle activity allowing the evaluation and diagnosis of cardiovascular diseases.

In Figure 1.1, it can be seen the main waves and intervals of the ECG signal, which are repeated periodically with each beat [5]. The P wave is the start of the beat, while T wave

marks the end. Q, R and S waves forms the QRS complex. The RR interval is defined as the distance between two consecutive R waves, and it is used to measure the heart rate.

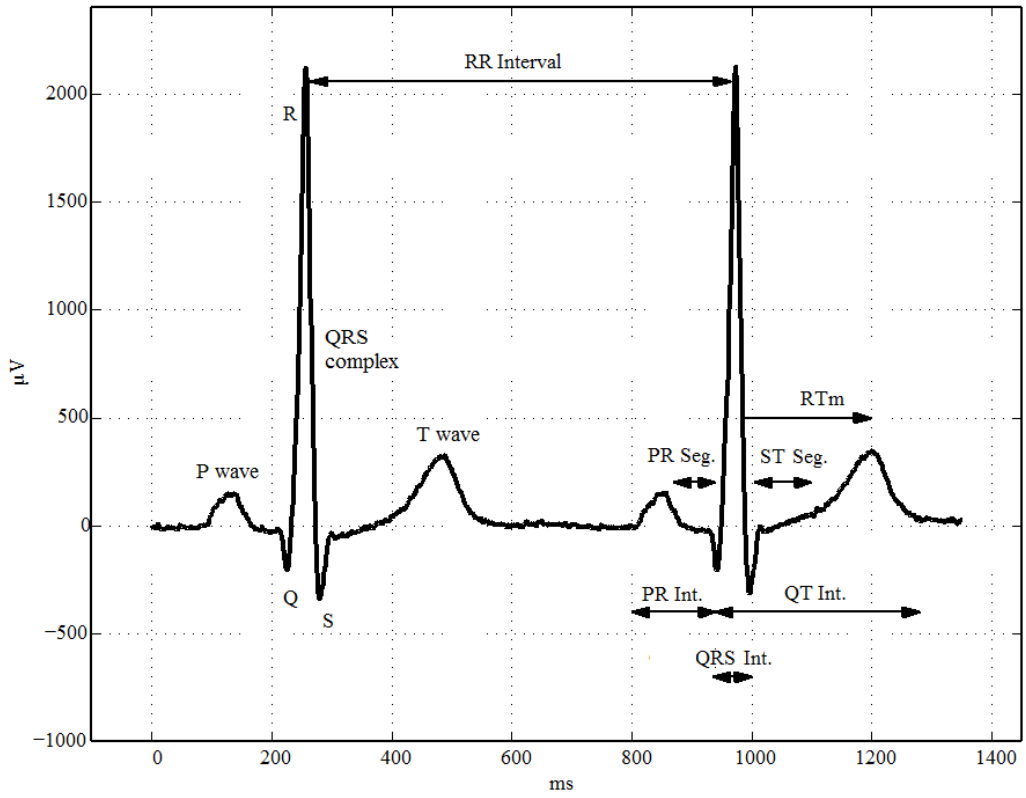

Figure 1.1: ECG signal with the most important waves and intervals.

Several electrodes localized in the skin of the patient monitor the space-temporal variations of the electric field generated by the heart, which leads to the ECG signal. The voltage difference between two electrodes is called lead, and each lead provides a different point of view of the same information.

There are three bipolar leads, called I, II and III, and they are calculated as (1.1), and they are shown in Figure 1.2:

$$\begin{aligned} I &= V_{\mathrm{LA}} - V_{\mathrm{RA}} \\ II &= V_{\mathrm{LL}} - V_{\mathrm{RA}} \\ III &= V_{\mathrm{LL}} - V_{\mathrm{LA}} \end{aligned} \tag{1.1}$$

where V_{LA}, V_{RA} and V_{LL} are the voltages measured in left arm, right arm and left leg, respectively. There are also the precordial leads: V1, V2. V3, V4, V5 and V6, which are unipolar leads.

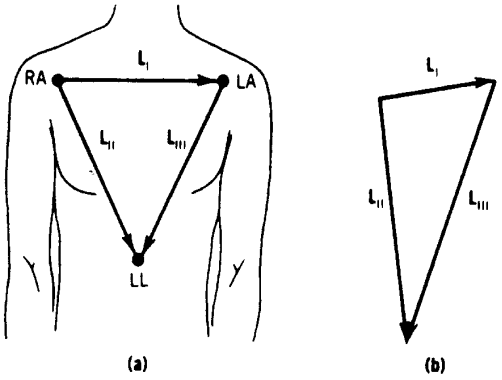

Figure 1.2: Bipolar leads.

1.4.2 Heart rate variability (HRV)

The origin of the heart rate variability lies in the electrical impulses which are generated in the sinoatrial node. The heart rate varies beat-to-beat with small variations around the mean, and these variations are controlled by the autonomic nervous system (ANS). The ANS is composed of two branches: sympathetic system and parasympathetic or vagal system. Generally speaking, sympathetic system is the responsible of increasing the heart rate while the parasympathetic system decreases it. The interaction between both systems is the origin of the HRV.

The Integral Pulse Frequency Modulation model, or IPFM model, can explain the influence of the ANS in the HRV. This model is based on the hypothesis that the sympathetic and parasympathetic systems activity can be represented as a modulating signal with zero mean, which is added to a DC level, and is integrated up to a threshold, defined by the mean cardiac period. In that time, a beat is produced and the integrator is reset, starting the process again [6].

A lot of works have demonstrated the existence of three components in the HRV [7]: a very low frequency component (VLF) whose oscillatory frequency is between 0 to 0.04 Hz, a low frequency component (LF) with frequencies ranged between 0.04 to 0.15 Hz, and a high frequency component (HF) with frequencies between 0.15 to 0.4 Hz. These bands can be seen in Figure 1.3.

The LF component is considered to be a measure of the sympathetic branch activity, at least when its power is expressed in normalized units with regard to the total power in HRV, taking VLF component apart [8, 9]. The HF component is considered a measure of the parasympathetic activity, due to the respiratory sinus arrhythmia, which causes an increase of the heart rate during the inspiratory phase, and a decrease during the expiratory phase [9]. A quantitative measure of the interaction between the two systems, that is, the sympathovagal balance, can be measured as the ratio of the LF power to the HF power [8, 9].

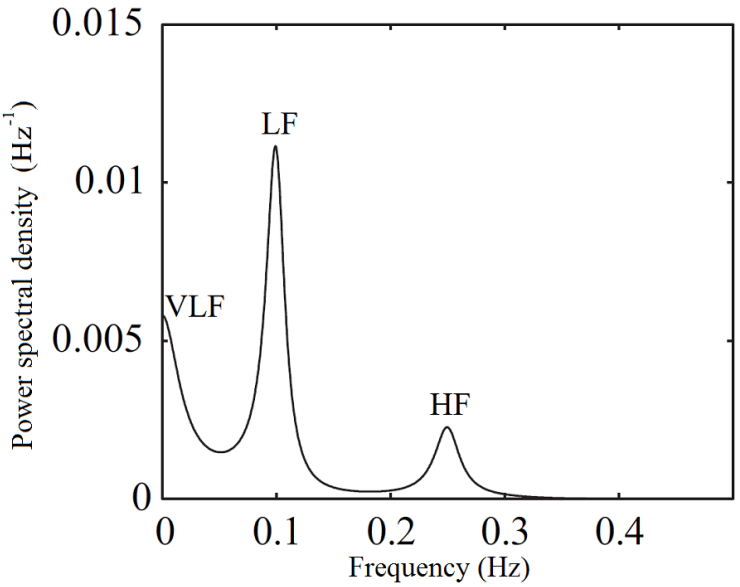

Figure 1.3: Frequency bands.

1.4.3 Blood pressure (BP)

Blood pressure is defined as the pressure exerted by circulating blood upon the walls of blood vessels (arteries, arterioles, veins and capillaries), although it generally means arterial pressure. Together with respiratory frequency, heart rate and thermoregulation, it is the most common measured parameter.

It is closely related to the cardiac cycle and for each beat, it can be seen a systolic pressure, defined as the peak of the pressure wave in the arteries, and a diastolic pressure, defined as the minimum of the wave. Systolic pressure occurs during the ventricular contraction or systole, while diastolic pressure coincides with the ventricular relaxation or diastole. An example of the BP signal can be seen in Figure 1.4.

The typical blood pressure values for an adult, healthy, rested person are approximately 120 mmHg for systolic and 80 mmHg for diastolic pressure. A general classification can be seen in Table 1.4.3.

CATEGORY	Systolic pressure (mmHg)	Diastolic pressure (mmHg)
Hypotension	< 90	< 60
Optimal	90 - 119	60 - 79
Normal	120 - 129	80 - 84
Normal high	130 - 139	85 - 89
Hypertension grade 1	140 - 159	90 - 99
Hypertension grade 2	160 - 179	100 - 109
Hypertension grade 3	≥ 180	≥ 120

Table 1.1: Classification of blood pressure for adult people

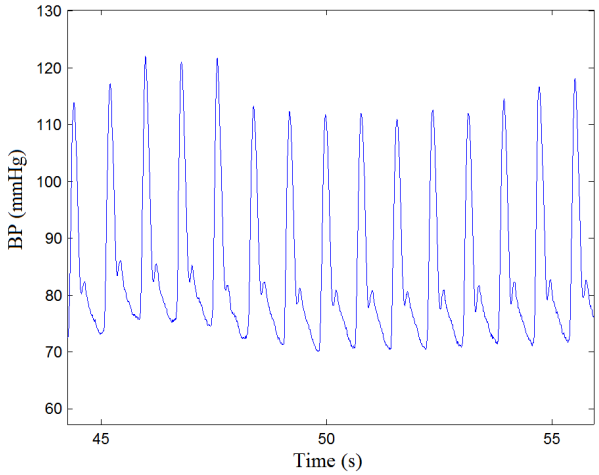

Figure 1.4: Blood pressure signal.

However, systolic and diastolic pressure levels are not constant and they experiment beat-to-beat natural variations, and there are large variations among different patients. It also varies in stressful situations or due to nutritional factors, illnesses or exercise. During an hemodialysis treatment it is essential to monitor this signal due to the risk of hypotension events.

In any patient, a blood pressure drop of 30 mmHg related to his normal pressure, or a systolic pressure below 90 mmHg can be diagnosed as an hypotension episode. These episodes often happen together with symptoms such as dizziness, nausea, vomiting or syncope.

Using blood pressure variability (BPV) [10] and HRV, it is possible to study the baroreflex sensitivity (BRS) [11]. The BRS is a marker of the reflex vagal activity in the cardiac level, which represents the variation in the RR interval induced by a unitary variation in the blood pressure level.

1.5 Goals

The goal of this TFM is the analysis of the cardiovascular autonomic regulation during hemodialysis. Three aims are proposed:

- Estimation of the HRV and BPV from the ECG and BP signals.
- Estimation of the indices which mark the ANS activity, and selection of the best indices to discriminate between hypotension–prone and hypotension–resistant patients.
- Development of a linear classifier with the selected features.
- Study the behaviour of the features in hypotension events.

1.6 Structure

The following chapters are briefly described below:

- **Chapter 2**: The database used in this project is described.
- **Chapter 3**: Explanation of the methods for:
  - HRV estimation
  - BPV estimation
  - Spectral analysis
  - BRS estimation
  - Features derivation
  - Features selection
  - Prone versus resistant classification
- **Chapter 4**: The results of the features selection and the performance of the classifier are shown.
- **Chapter 5**: The results of the features selection and the performance of the classifier are discussed.
- **Chapter 6**: The conclusions and future expansion of the work are presented.

Chapter 2

Study population

In this work, 2 databases have been used which consist of the ECG and BP signals from patients with end–stage renal failure who attended to regular sessions of hemodialysis treatment, lasting between 2 and 5 hours, 3 times a week.

Sweden database

This database consists of 28 records from 15 different patients adquired in Park Dialys, Lund, Sweden, and Helsingborg Hospital, Helsingborg, Sweden.

The ECG signal was recorded using a standard 12–lead configuration, and digitalized at a sampling rate of 1000 Hz and amplitude resolution of 0.06 μV (Siemens-Elema AB, Sweden); the blood pressure signal was measured in the finger using a Finapres (Ohmeda, Netherlands) and sampled at a rate of 200 Hz with a MP100 data acquisition system (Biopac, USA).

Each patient has been classified as being hypotension–resistant (R) or hypotension–prone (P) based on their previous clinical history. Besides, they have also been classified as being diabetic (D) or non-diabetic (ND) patients.

Symptomatic hypotension occurred in 4 of the 28 sessions (one in the resistant group and the others in the prone group), of which 1 was acute (systolic blood pressure fall larger than 30 mmHg per 10 minutes prior to hypotension).

Denmark database

A second database is used in this work, consisting of 29 sessions from 11 patients. These patients underwent hemodialysis treatments in Copenhague, Denmark. Due to the poor quality of the BP signal, 5 sessions were rejected from this work and only 24 sessions from 9 patients were used.

Both ECG and BP signal were adquired simultaneously using a Biopac MP150 data acquisition system (BIOPAC Systems, Inc., USA) at a 1000 Hz sampling rate. The ECG signal was recorded using a 6-lead configuration, and the blood pressure was measured with a Finapres.

All patients are classified as being hypotension–prone, and they have also been classified as being diabetic or non-diabetic patients. Symptomatic hypotension occurred in 5 of the 24

sessions, and all of them were acute.

Global database

In total, a sum of 52 records from 24 patients were used in this work. A brief summary of the database can be seen in Table 2.

Characteristic	Resistant (R)	Prone (P)
# Patients	7	17
# Measurements	11	41
D / ND (patients)	3/4	7/10
D / ND (measurements)	4/7	17/24
Acute hipotension episodes	1	6

Table 2.1: Study population characteristics

Chapter 3

Methods

In this chapter, the methods used in this work to estimate the heart rate variability, blood pressure variability and baroreflex sensitivity will be described. The feature selection will be explained, as well as the classification framework.

The ECG and BP signals have been registered during several hours, coinciding with the duration of the hemodialysis session. It has been decided to segment the variability signals associated to ECG and BP signals in 5 minutes segments with overlap of 1 minute, where stationarity has been assumed.

3.1 Heart rate variability

The HRV signal can be estimated by using the beat occurrence instants t_k, which are detected from the ECG signal. For the Sweden database, the detection marks were obtained by ARISTOTLE [12] using a rule based on the QRS complex centre of gravity.

For the Copenhagen database, another QRS detector had already been used, which belongs to the toolbox for biological signal analysis from Lund University. This detector previously decimated the signal by 10, that means, it only worked with 1 every 10 samples in the signal, the rest were rejected. The main source of noise in HRV signal is the error in heart beat detection or jitter. Therefore it is important to increase the detection accuracy and a second search was performed in the signal sampled at 1000 Hz to find the QRS complex peaks.

The HRV signal is derived from these QRS marks, following a method based on the integral pulse frequency modulation (IPFM) model, whose block diagram can be seen in Figure 3.1. This model assumes that the activity of the ANS can be modelled by a modulating signal $m(t)$ which, together to a DC level, is accumulated up to a threshold T, and in that instant t_k a beat is generated and the whole process is repeated.

From the occurrence instants t_k, the instantaneous heart rate is obtained $d_{\mathrm{HR}}(n)$, as described in [13], and following the algorithms described in [14].

As the very low frequency components can mask the low frequency band, a low-pass filter with a cut-off frequency of 0.03 Hz is used to obtain the filtered signal $d_{\mathrm{HRM}}(n)$ which correspond to the VLF band (0–0.04 Hz). Finally, the signal $d_{\mathrm{HRV}}(n)$ is calculated as:

$$d_{\mathrm{HRV}}(n) = d_{\mathrm{HR}}(n) - d_{\mathrm{HRM}}(n) \tag{3.1}$$

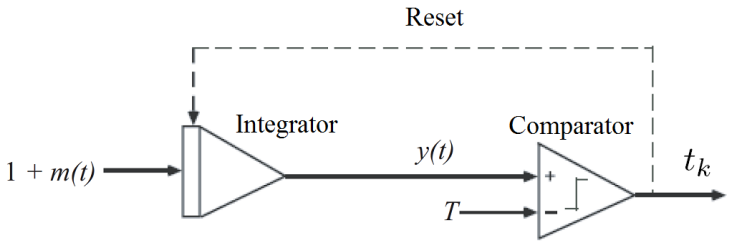

Figure 3.1: IPFM block diagram.

3.2 Blood pressure variability

In a similar way, the blood pressure variability can be estimated. As explained in [13], the blood pressure is preprocessed to remove the noise and find the peaks of the signal using a time–varying threshold, which correspond to the systolic blood pressure.

Once the peaks associated to the systolic blood pressure are detected (Figure 3.2), they are interpolated using cubic splines and generating the blood pressure variability signal $d_{\mathrm{BP}}(n)$.

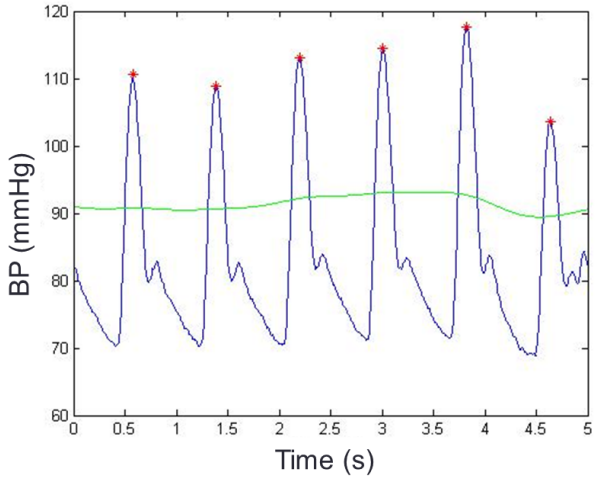

Figure 3.2: Blood pressure signal, threshold and peaks (systolic blood pressure).

In a similar way to HRV, $d_{\mathrm{BP}}(n)$ is filtered to obtain $d_{\mathrm{BPM}}(n)$ and then $d_{\mathrm{BPV}}(n)$ is calculated as:

$$d_{\mathrm{BPV}}(n) = d_{\mathrm{BP}}(n) - d_{\mathrm{BPM}}(n) \tag{3.2}$$

3.3 Spectral analysis

Spectral density estimation is a basic tool in signal processing which provides very useful information in the field of biological signals. The spectral density of a signal, or spectrum, indicates how is the power of the signal distributed in the frequency domain.

In this work, the Welch periodogram [15] has been chosen as a non parametric method of spectral estimation. With this method, the signal $x(n)$ is segmented in K segments of length L samples. Then, the modified periodogram is estimated in each segment (with a possible overlap D) and the average is calculated:

$$\hat{S}_{\mathrm{x}}(f) = \frac{1}{K} \sum_{i=0}^{K-1} \hat{S}_{\mathrm{M}}^{(i)}(f), \tag{3.3}$$

where $\hat{S}_{\mathrm{M}}^{(i)}(f)$ is the modified periodogram of the i-th segment, defined as:

$$\hat{S}_{\mathrm{M}}^{(i)}(f) = \frac{1}{LU} \sum_{n=0}^{L-1} |x^{(i)}(n) w(n) e^{-j2\pi f n}|^2, \tag{3.4}$$

being $x^{(i)}(n)$ the i-th segment of $x(n)$, $w(n)$ the L samples-length window, and U a normalization factor to compensate the window power:

$$U = \frac{1}{L} \sum_{n=0}^{L-1} |w(n)|^2, \tag{3.5}$$

In this work, this method have been applied to the segments of both heart rate and blood pressure variability signals. A Hamming window has been used, and the following values have been used: L=2 minutes and D=1 minute.

Once the spectrum is estimated, the power of each frequency band are calculated [16]. In each band the following indices have been computed: $P_{\mathrm{VLF}}^{\mathrm{X}}$, $P_{\mathrm{LF}}^{\mathrm{X}}$ y $P_{\mathrm{HF}}^{\mathrm{X}}$.

$$P_{\mathrm{VLF}}^{\mathrm{X}} = \int_{f_{\mathrm{VLF}}^{i}}^{f_{\mathrm{VLF}}^{f}} \hat{S}_{\mathrm{X,M}}(f) df \tag{3.6}$$

$$P_{\mathrm{LF}}^{\mathrm{X}} = \int_{f_{\mathrm{LF}}^{i}}^{f_{\mathrm{LF}}^{f}} \hat{S}_{\mathrm{X,V}}(f) df \tag{3.7}$$

$$P_{\mathrm{HF}}^{\mathrm{X}} = \int_{f_{\mathrm{HF}}^{i}}^{f_{\mathrm{HF}}^{f}} \hat{S}_{\mathrm{X,V}}(f) df \tag{3.8}$$

where f^i y f^f are the initial and end frequency of each band. The superindex $^{\mathrm{X}}$ indicates if the signal is the heart rate or blood pressure variability. $\hat{S}_{\mathrm{X,M}}(f)$ and $\hat{S}_{\mathrm{X,V}}(f)$ are the spectrum of $d_{\mathrm{HRM}}(n)$ or $d_{\mathrm{SBPM}}(n)$, and $d_{\mathrm{HRV}}(n)$ or $d_{\mathrm{SBPV}}(n)$ respectively.

3.4 Baroreflex sensitivity

A BRS coefficient is established for each frequency band [17, 18]:

$$\begin{aligned} \alpha_{\mathrm{VLF}} &= \sqrt{\frac{P^{\mathrm{HR}}_{\mathrm{VLF}}}{P^{\mathrm{BP}}_{\mathrm{VLF}}}} \\ \alpha_{\mathrm{LF}} &= \sqrt{\frac{P^{\mathrm{HR}}_{\mathrm{LF}}}{P^{\mathrm{BP}}_{\mathrm{LF}}}} \\ \alpha_{\mathrm{HF}} &= \sqrt{\frac{P^{\mathrm{HR}}_{\mathrm{HF}}}{P^{\mathrm{BP}}_{\mathrm{HF}}}} \end{aligned} \tag{3.9}$$

where P^{HR} y P^{BP} are the power of heart rate and blood pressure variability, respectively. The subindex indicates the frequency band where it is measured.

3.5 Estimation of indices related to the ANS activity

The indices we have used in this work have been calculated in each segment for each record, and then the median have been used in the first 5 segments to get a unique feature for each record.

Heart rate variability

For the HRV features, the power in each frequency band are selected, as explained in Section 2.2: $P^{\mathrm{HR}}_{\mathrm{VLF}}$, $P^{\mathrm{HR}}_{\mathrm{LF}}$ and $P^{\mathrm{HR}}_{\mathrm{HF}}$.

It has been also calculated the normalized very low, low and high frequency power, defined as:

$$P^{\mathrm{HR}}_{\mathrm{VLFn}} = \frac{P^{\mathrm{HR}}_{\mathrm{VLF}}}{P^{\mathrm{HR}}_{\mathrm{LF}} + P^{\mathrm{HR}}_{\mathrm{HF}}} \tag{3.10}$$

$$P^{\mathrm{HR}}_{\mathrm{LFn}} = \frac{P^{\mathrm{HR}}_{\mathrm{LF}}}{P^{\mathrm{HR}}_{\mathrm{LF}} + P^{\mathrm{HR}}_{\mathrm{HF}}} \tag{3.11}$$

$$P^{\mathrm{HR}}_{\mathrm{HFn}} = \frac{P^{\mathrm{HR}}_{\mathrm{HF}}}{P^{\mathrm{HR}}_{\mathrm{LF}} + P^{\mathrm{HR}}_{\mathrm{HF}}} \tag{3.12}$$

The ratio between low and high frequency powers has also been calculated, denoted as $R^{\mathrm{HR}}_{\mathrm{LFHF}}$:

$$R^{\mathrm{HR}}_{\mathrm{LFHF}} = \frac{P^{\mathrm{HR}}_{\mathrm{LF}}}{P^{\mathrm{HR}}_{\mathrm{HF}}} \tag{3.13}$$

Lastly, the ratio variance within the 5 segments is also calculated, denoted as $V^{\mathrm{HR}}_{\mathrm{LFHF}}$.

Blood pressure variability

The same features were extracted for the blood pressure variability: $P^{\mathrm{BP}}_{\mathrm{VLF}}$, $P^{\mathrm{BP}}_{\mathrm{LF}}$, $P^{\mathrm{BP}}_{\mathrm{HF}}$, $P^{\mathrm{BP}}_{\mathrm{VLFn}}$, $P^{\mathrm{BP}}_{\mathrm{LFn}}$, $P^{\mathrm{BP}}_{\mathrm{HFn}}$, $R^{\mathrm{BP}}_{\mathrm{LFHF}}$ and $V^{\mathrm{BP}}_{\mathrm{LFHF}}$.

Baroreflex sensitivity

For the BRS, the features correspond to the indices associated to each frequency band: α_{VLF}, α_{LF} and α_{HF}, following the definition in (3.9).

3.6 Features selection

Feature selection is a process commonly used when there are a lot of features and not all of them are important. This process consists of selecting a subset that performs the best under some classification system. There are several methods to do this, and in particular, the sequential methods begin with a previous subset and iteratively add or remove features until some termination criterion is met. The drawback of these methods is that they are not guaranteed to produce the optimal result.

There are two main subgroups: sequential forward selection and sequential backward selection. The former starts with no features and adds them one at each step, adding the one that decreases the error the most, and it stops when any addition does not decrease significantly that error. The latter starts with the full set of features and in each step, the feature whose removal decrease the most the error is removed, until any further removal increases the error significantly. To reduce overfitting, this error is validated in a different set than training set.

The sequential floating selection method is a combination of both groups, and it is able to remove features which become obsolete with the addition of new ones, or reevaluate features that had been previously removed. In this work, the Sequential Floating Forward Selection (SFFS) method has been used, which consist of applying one forward step following several conditional backward steps as long as the error decreases [19], as follows:

1. Start with the empty set $Y = \{\emptyset\}$
2. Select the best feature
   $x^+ = \underset{x \notin Y_k}{\operatorname{argmax}}[J(Y_k + x)]$
   $Y_k = Y_k + x^+;\ k = k + 1$
3. Select the worst feature
   $x^+ = \underset{x \in Y_k}{\operatorname{argmax}}[J(Y_k - x)]$
4. If $J(Y_k - x^-) > J(Y_k)$ then
   $Y_{k-1} = Y_k - x;\ k = k - 1$
   go to Step 3
   else
   go to Step 2

being Y_k the pool of the k selected feature indices, J the criterion function to maximize and x the feature set. In Fig. 3.3 it can be seen the flow diagram followed by this method for the feature selection among d features.

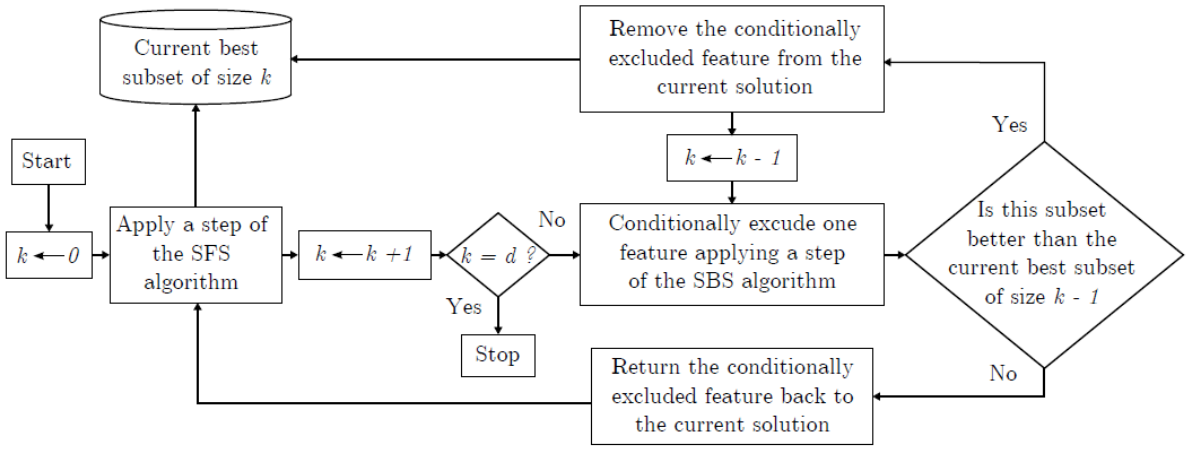

Figure 3.3: Flow diagram followed by this method for the feature selection among d features.

In this work, the idea of the leave–one–out method, which will be explained in the next section, is used in the features selection: the search is performed in all the observation but one, and the search is repeated until every observation has been left out once. In this way, in a database with N observations, $N - 1$ different feature subsets are obtained. The most K repeated features are selected for the final model.

Regarding the value of K, a commonly used rule is not to use more than $\sqrt{n_k}$ features, being n_k the number of observations which belong to the smallest group. As mentioned in Section 2.1, the database used in this work consist of 41 records from 17 prone patients, and 11 records from 7 resistant patients. Since the resistant group is the smaller one, it determines the upper limit for K, whose value in this work is $K = 2$.

3.7 Classifier

Linear Discriminant Classifier

The linear discriminant analysis method consists of searching some linear combinations of the selected features which provide the best separation between the considered classes. These different combinations are called discriminant functions [20]. This analysis assumes normal densities with equal covariance matrices in the classes.

Let $\mathbf{x}$ be a n length vector of new observations:

$$\mathbf{x} = \begin{bmatrix} \mathbf{x}_1 & \mathbf{x}_2 & \dots & \mathbf{x}_n \end{bmatrix}^T \tag{3.14}$$

the discriminant function associated to the class k, assuming all classes equiprobable, is defined as:

$$\delta_k(\mathbf{x}_i) = \mathbf{x}_i^T \Sigma^{-1} \mu_k - \frac{1}{2} \mu_k^T \Sigma^{-1} \mu_k, \qquad i = 1, \ldots, n, \quad k = 1, \ldots, C \tag{3.15}$$

where $\mathbf{x}_i$ is the new observation, the superindex ^{T} represents the transpose, C is the number of classes, μ_k is the vector of means of the class k and Σ is the joint covariance matrix. The parameters μ_k and Σ must be obtained previously from a training data set.

Then the output of the classifier will be:

$$\hat{G}(\mathbf{x_i}) = \underset{\mathbf{k}}{\operatorname{argmax}}[\delta_{\mathbf{k}}(\mathbf{x_i})] \tag{3.16}$$

Classifier evaluation

The optimal framework in classification is determining two non-overlapping groups: one training group for selecting the optimal features and training the classifier, and a validation group for testing the classifier. Unfortunately, not always is possible to have two different groups due to the low number of data, since the feature selection and classifier training would be overfitted to the training data, which may not be representative enough, and the classifier would not work properly for the validation data and, consequently, for additional databases. However, using all the observations for the training group and then for the evaluation group would give biased results, since the features and the classifier would be optimal only for that data and would not be general.

One of the most common approaches to solve this problem is the leave–one–out method [21]. For classifier training, this method uses all observations to train the classifier but one, which is used for evaluation, and process is repeated such that each observation in the database is used once as the validation data.

The leave–one–out method works with observations, which in this work is the same as records. A patient can have 1, 2, 3 or even 4 different records, corresponding to different days. A second alternative is considered, where the classifier works with patients instead of records: both feature selection and classifier training are performed with all the records from all patients but one, being the records from this patient left out, repeating the process with all the patients.

The framework in this project is as follows:

- The whole database is used for feature selection, following the leave–one–out record/patient method. The criterion used for the features search is to minimize the error of the classifier, which is the same to maximize the accuracy of the classifier.

- Once the features set is determined, a linear classifier is trained and evaluated using the leave–one–out method. The performance of the classifier is measured with sensitivity (Se), specificity (Sp), positive predictive value ($+PV$), negative predictive value ($-PV$) and accuracy (Acc), defined as:

$$
\begin{aligned}
Se &= \frac{TP}{TP + FN} \\
Sp &= \frac{TN}{TN + FP} \\
+PV &= \frac{TP}{TP + FP} \\
-PV &= \frac{TN}{TN + FN} \\
Acc &= \frac{TP + TN}{TP + TN + FP + FN}
\end{aligned}
\tag{3.17}
$$

with TP, TN, FP and FN being the number of true positives, true negatives, false positives and false negatives respectively. In this work, prone patients are classified as positive while being a resistant patient is classified as being negative.

Chapter 4

Results

4.1 Prone versus Resistant

Feature selection using the leave–one–out method with all records leads to $P^{\mathrm{BP}}_{\mathrm{VLF}}$, $V^{\mathrm{HR}}_{\mathrm{LFHF}}$, $P^{\mathrm{HR}}_{\mathrm{LF}}$ and $P^{\mathrm{HR}}_{\mathrm{HF}}$, but only the 2 first features are used in the analysis. The performance of the classifier can be seen in Table 4.1, where it can be seen the high sensitivity (Se=97.5%) but a null specificity. This means that the classifier classifies all resistant records as prone records, and the cause may be that the P and R groups in the database are strongly unbalanced (41P and 11R).

Using the leave–one–out patient method, it can be seen that specificity increases (Sp=54.5%) without affecting sensitivity. The accuracy also increases (Acc=88.4%). In this case, the features from feature selection are $P^{\mathrm{HR}}_{\mathrm{HFn}}$, $P^{\mathrm{BP}}_{\mathrm{VLF}}$, $V^{\mathrm{HR}}_{\mathrm{LFHF}}$ and $P^{\mathrm{HR}}_{\mathrm{HF}}$, but, again, only the first 2 features are used. The results are shown in Table 4.1.

PERFORMANCE (%)	Se	Sp	+PV	-PV	Acc
Records	97.5	0	78.4	0	76.9
Patients	97.5	54.5	88.8	85.7	88.4

Table 4.1: Classifier performance for records and patients

4.2 Division into diabetic and non diabetic subgroups

The dataset is divided into diabetic and nondiabetic subgroups due to the fact that the diabetes state in patients may leads to an impairment in the ANS activity. In this scenario, two classifiers are trained, one for the diabetic subgroup, and another for the non diabetic subgroup. In this case, it is decided to work only with records, due to the low number of patients in each subgroup. In this way, the diabetic group consists of 21 records, of which 17 are hypotension–prone, while the non diabetic group consists of 31 records, of which 24 are hypotension–prone.

In each subgroup, feature selection is repeated and the classifier is trained and evaluated, as explained in Section 3.7. Results can be seen in Table 4.2. For the diabetic group, the selected features are $P^{\mathrm{HR}}_{\mathrm{HF}}$ and $P^{\mathrm{HR}}_{\mathrm{VLFn}}$, while for the non diabetic group the features are $P^{\mathrm{HR}}_{\mathrm{VLFn}}$ and α_{LF}.

Although they are two different classifiers, they can be seen as a decision tree where the diabetes variable decides which branch is activated. This way it can be considered as a global classifier whose performance can also be seen in Table 4.2. This Table shows how the performance improves significantly by splitting diabetic and non diabetic records (Acc=92.3%).

PERFORMANCE (%)	Se	Sp	+PV	-PV	Acc
Diabetic	94.1	50.0	88.8	66.6	85.7
Non diabetic	100	85.7	96.0	100	96.7
Global	97.5	72.7	93.0	88.8	92.3

Table 4.2: Classifier performance for diabetic and non diabetic groups and global performance

4.3 Group balance

The next step is to balance the P and R groups, by replicating each resistant record two times. The goal is to minimize the effect of being the prone group much bigger than the resistant one, leading to a bias in the performance. The new database consists of 41 P records and 33 R records.

The classification is repeated, with both the record and patient approach, and results can be seen in Table 4.3. In the record approach, the selected features are $R^{\mathrm{HR}}_{\mathrm{LFHF}}$, α_{HF}, α_{VlF}, α_{LF} and $V^{\mathrm{HR}}_{\mathrm{LFHF}}$, although only the first twoare used, and the results are better in specificity (Sp=63.6%), although the sensitivity decreases (Se=87.8%), as expected. The accuracy is slightly better (Acc=77.0%).

In the patient approach, the selected features are α_{VLF}, α_{HF}, α_{LF}, $P^{\mathrm{BP}}_{\mathrm{HF}}$ and $R^{\mathrm{HR}}_{\mathrm{LFHF}}$ (only used the first two). In this case the performance is worse (Acc=70.2%), as it can be seen in Table 4.3.

PERFORMANCE (%)	Se	Sp	+PV	-PV	Acc
Records	87.8	63.6	75.0	80.7	77.0
Patients	90.2	45.4	67.2	78.9	70.2

Table 4.3: Classifier performance for records and patients after group balance

Besides, the data set is again separated into diabetic and non diabetic records. In this case, the diabetic group consists of 29 records (17 P) and the non diabetic group consists of 45 records (24 P).

The new selected features for the diabetic group are α_{VLF}, $P^{\mathrm{BP}}_{\mathrm{HF}}$, $P^{\mathrm{HR}}_{\mathrm{LF}}$, $P^{\mathrm{HR}}_{\mathrm{LFn}}$ and $P^{\mathrm{HR}}_{\mathrm{HF}}$ (only used the first two); and for the non diabetic group the selected features are only $P^{\mathrm{BP}}_{\mathrm{VLF}}$ and $P^{\mathrm{HR}}_{\mathrm{LFn}}$. In Table 4.3 it can be seen the performance of both classifiers, as well as the global classifier. Sensitivity is decreased as a result of the balance (Se=87%), but the general results are better (Acc=93.2%).

PERFORMANCE (%)	Se	Sp	+PV	-PV	Acc
Diabetic	76.4	100	100	80.0	87.8
Non diabetic	95.8	100	100	94.4	97.5
Global	87.8	100	100	86.8	93.2

Table 4.4: Classifier performance for diabetic and non diabetic groups and global performance after group balance

4.4 Evolution of the performance

Indices used for feature selection have been calculated as the median of the first 5 segments of the records, in the beginning of the treatment. It is proposed to repeat the classifier performance but extracting those indices not only from the beginning, but also during the rest of the session.

The chosen features to train the classifier are the same as used in the previous section, when the search was performed only in the first 5 segments, and they are used in all the intervals. Then, in each interval, those features are extracted and used in classifier training and evaluation, using the leave–one–method.

Six intervals are proposed: segments 1-5, segments 6-10, segments 11-15, segments 16-20, segments 21-25 and segments 26-30, which correspond to minutes 0-21, 20-41, 40-61, 60-81, 80-101 and 100-121, respectively. The goal is to study the evolution of the performance of the classifier during the hemodialysis.

In Figure 4.1 it can be seen the evolution of sensitivity, specificity and accuracy for the global classifier in the D/ND scenario. The groups are balanced as explained in Section 4.3 and the selected features remain the same for every interval.

4.5 Hypotension events

Another scenario is proposed to study hypotension events. There are 7 episodes of hypotension, of which 6 are prone and 1 resistant. For each record with an hypotension event, the classifier is trained in every segment using all the records except the one being analyzed. The features used to train the classifier are the same as in the previous sections. The goal in this case is not to evaluate the classifier, but to analyze the values of each discriminant function and their evolution in time.

The 6 prone records do not show any significant change prior to the hypotension event, but the resistant record does actually show several drops in the resistant discriminant value, even being classified as prone in some segments. As explained in Section 3.7, the linear discriminant analysis uses two discriminant functions, associated with the prone and resistant groups. In Figure 4.2, it is represented the evolution of the normalized values of those functions for the resistant record. The largest drop occurs before the hypotension episode, marked with a black line.

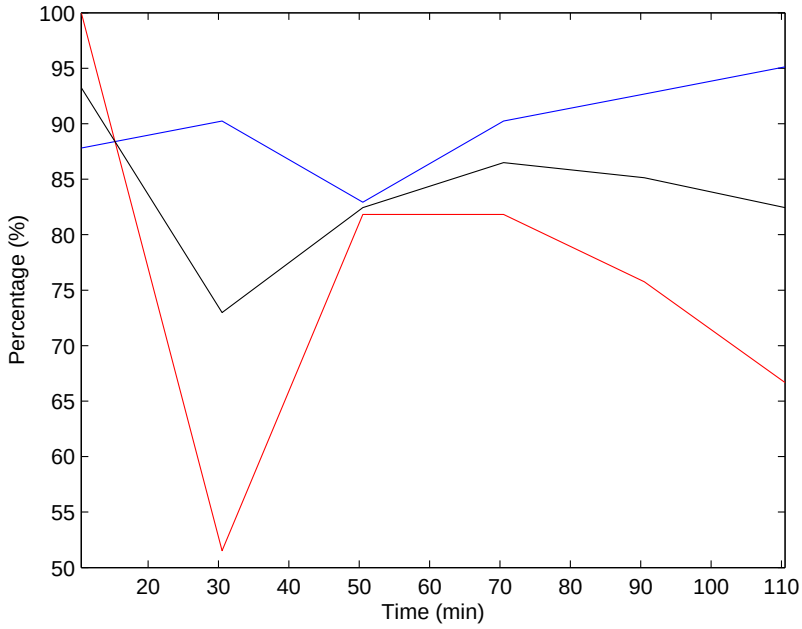

Figure 4.1: Sensitivity (blue), specificity (red) and accuracy (black) evolution in the global classifier.

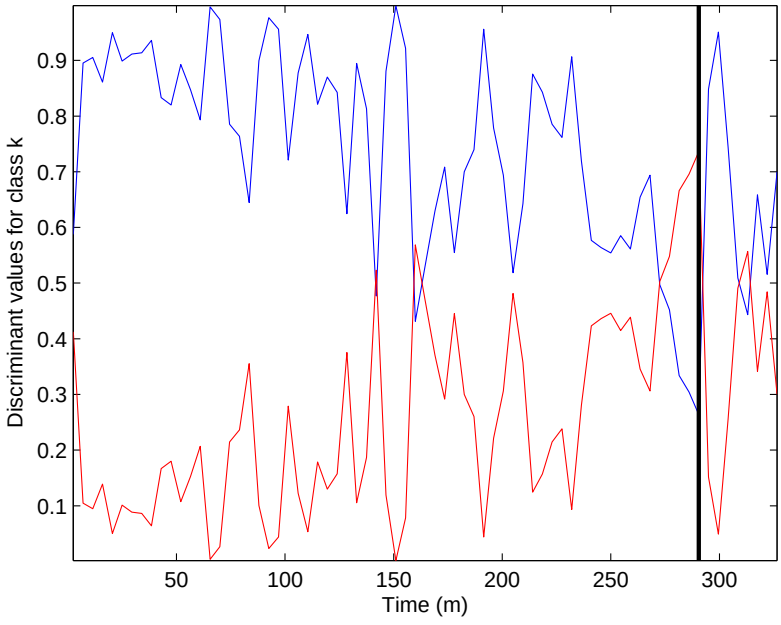

Figure 4.2: Normalized values of the discriminant functions for the resistant record: resistant (blue) and prone (red).

Chapter 5

Discussion

The main limitation of this work is the small size of the data set. While trying to make two different groups, one for training and another for evaluating, it became clear that it was very sensitive to the election of the records in each group, therefore it was needed to use a leave–one–out technique and use the whole data set for feature selection and classifier training.

The use of a linear classifier which is based in LDA makes results not optimal, since the features do not follow the assumption of normality and they are not independent. However, the data distribution is not known, and using any other non parametric method to estimate that distribution from the data may imply a risk of overfitting which could lead to a positive bias of the result. In this case, that risk is high due to the reduced number of patients.

If the patient approach is chosen, the classifier performance is improved in spite of reducing the cases in each group. When working with records, the classifier gives more importance to those patients with more records, and therefore the results are being biased. This may mean that the records from a single patients are not independent, and both HRV and BPV does not change significantly in different sessions for the same patient.

The division between diabetic and non diabetic patients deserves special attention. The results are significantly better after the division, which is a result that agrees with the hypothesis that the activity of the ANS in diabetic patients is affected. This means that the diabetes state should be used as another feature to train the classifier to improve the classification performance.

The balance of the groups is performed to avoid the bias in the results due to the different number of cases in each class. In this way, there is an increase in the specificity at the expense of the sensitivity, but the accuracy increases in all scenarios except when working with patients. The goal of replicating the resistant group is to give the same importance to both groups. The replicated data has been assumed to be representative enough of the resistant group.

Studying the evolution of the classifier performance, it can be seen that it is variable during the treatment. In the segments 6-10 (20-40 min) there is a drop in the specificity and, although it recovers from the drop, the Sp slowly decreases. The explanation may lie in the fact that resistant patients show, as the hemodialysis treatment progresses, similar features as prone patients, becoming easier to mix up prone and resistant patients. It is important to remark that the changes in prone patients are not as big as in the resistant group, otherwise the performance of the classifier would not decrease, since in each interval the classifier is trained and it would be able to separate both classes like in the beginning of the treatment.

In the case of the resistant patient who suffered an hypotension event, this effect becomes stronger. Changes in the features lead to a wrong classification, as it has been shown in that record. Prior to the hypotension, the discriminant value for the resistant class drops abruptly, since the patient present prone features. This could be used as a possible tool to predict hypotension events. Unfortunately, there is only one case of these characteristics in the database.

More interesting is to predict hypotension in prone patients, but there have not been any significantly changes in any prone records with these events. One of the possible explanations may be that the selected features to classify prone and resistant patients are not the most appropriate to describe the changes in prone patients who suffer hypotension episodes.

Regarding the selected features, they change in every scenario, which may indicate that the relevant information in HRV for classification in hypotension–prone and hypotension–resistant lies in different indices. Several papers show that the ratio between low and high frequency of the HRV is able to discriminate between P and R patients [22]. In some scenarios in this work, $R^{\mathrm{HR}}_{\mathrm{LFHF}}$ and $V^{\mathrm{HR}}_{\mathrm{LFHF}}$ have been selected, as well as $P^{\mathrm{HR}}_{\mathrm{LFn}}$ or $P^{\mathrm{HR}}_{\mathrm{HFn}}$, which are compatible with those results. Other features, as the BRS related, appear in some scenarios, which means the baroreflex does not work in the same way for prone and resistant patients, being able to explain the higher incidence of hypotension events in prone people. This does not agree with other studies which states that the BRS works correctly during hypotension episodes [23], but suggests that failure of the BRS is likely to be one of the factors which is responsible for suffering hypotension.

Chapter 6

Conclusion and future work

The first part in this work has included the study and analysis of the heart rate variability, blood pressure variability and baroreflex sensitivity in several patients from two databases. Several indices have been extracted in order to study if they are able to discriminate between being hypotension–prone or hypotension–resistant.

The second part in this work has focused in the selection of the best features for the classification, and the evaluation of a linear classifier. A leave–one–out technique has been applied due to the small size of the database. Two alternatives have been proposed: working with records or with patients, being the latter a better option (Acc=88.4%). A division into diabetic and non diabetic subgroups has been proved to improve the results, leading to a global classifier with Acc=92.3%.

Balancing the groups to avoid biased results has also improved the results in every scenario except one. The global classifier after making diabetic and non diabetic subgroups has the best result (Acc=93.2%).

The last part has studied the evolution of the classifier performance during the hemodialysis treatment. The results have shown that resistant patients show features similar as prone patients as the treatment goes on. This fact has also been shown in the resistant record who had an hypotension event, which is classified as prone in several segments, including those prior to the hypotension episode.

These results have been presented to the CASEIB 2012 conference. The full text can be read in Appendix C.

Since the main limitation of this work is the small size of the database, it is proposed for a future work to repeat this analysis with a bigger data set. The use of other classifiers, such as quadratic classifiers or neural networks, could also improve the results [24].

Besides, it is proposed to use other features, derived from the photoplethysmographic (PPG) signal [25], heart rate turbulence signal [25], or short term variability of oxygen saturation [26]. With more hypotension events, a feature selection could be performed to detect hypotension events.

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