Use of the Heart Rate Variability as a Diagnostic Tool

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1 RESEARCH PROBLEM

The electrocardiographic signal represents the electrical activity of the heart. It has several nodes able to generate synchronized electrical impulses to sequentially activate its valves. All this impulses overlapped form the well-known QRS complex (Figure 1). Usually, the position of the R peak is taken as the instant in which the heartbeat has place. Thus, to determine the heart rate it is necessary to find all the R peaks present during the measurement of the ECG signal.

Heart Rate (HR) is controlled by the Autonomous Nervous System (ANS), which is composed by the Sympathetic Nervous System (SNS) and the Parasympathetic Nervous System (PNS). Both of them, SNS and PNS, respond to the necessities of the rest of physiologic systems (thermoregulatory, vasomotor, respiratory, central nervous, etc. systems) which make possible to correlate variations in the HR with the performance of all those systems. In short, due to the easiness with which is possible to obtain the ECG signal, and taking into consideration that is taken through a non-invasive measurement, several parameters of it have been studied for helping to the diagnosis of several diseases and as a tool to study the patients' fitness. However, to study carefully the performance of those physiological systems, in most of the cases it is not only enough to know just the HR, but also the Heart Rate Variability (HRV), which is the focus of the study carried out through this thesis.

HRV signal represents the variation of the heart rate beat-to-beat, i.e. represents all the durations of the intervals between adjacent R peaks, or RR intervals. Thus, it is extremely important to correctly detect all the R peaks. Most of the times, this is not a trivial task as some noises and artefacts that affect the ECG signal difficult that detections. The most important of those noises and artefacts are the electromyographic noise, produced by the activation of the thorax muscles, and the artefacts produced by the movement of the electrodes. There are more noises (respiration noise, 50/60 Hz noise, etc.) as is stated by Friesen et al in (G. M. Friesen et al., 1990), but the peaks produced but electromyogram and those produced by the movement (motion artefacts) are very similar to the R peaks, so their presence can provoke false detections. In general, to avoid those false detections, time constrains are used, setting an interval in which after an R peak detection, a new heartbeat cannot be produced (in this work, a minimum RR interval has been set to 300 ms. which corresponds to 300 bpm).

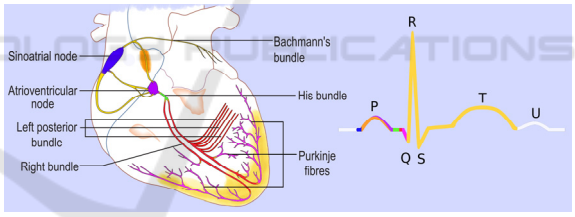

Figure 1: QRS complex peaks and segments and their correspondences with heart valves and muscles.

A great number of R peak detection algorithms have been proposed during the lasts 30 years. However, with the increasing computational capabilities of the computers, those algorithms tent to be more and more complex by using filters and tools with a large number of computations in order to avoid all the sources of noise and artefacts. Nevertheless, in the real-time monitoring area, in which portable devices are used, complex algorithms can not be used due to the fact that those portable devices must have a long life battery, and they have a limited number of resources. Also, R peak detections algorithms only show the position of the R peaks, but HRV signal must be analysed on one manner or another to study different kinds of factors, so the R peaks detection algorithm are the basis of other algorithms, and they must be implemented together with the main algorithm. That is why, in real-time monitoring applications, R peaks detections must be as simple as possible. For those reasons, a new R peaks detection algorithm is proposed in this thesis. This algorithm is able to work in real-time on reduced resources platforms obtaining a good performance in terms of sensitivity

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and positive predictivity.

Once we have the R detections problem solved, we can access to the HRV signal features which can be related to several physiological systems performance. For instance, as will be commented later on, the study of the respiration rate through the HRV signal has led to the study of the sleeping phases or to the development of several apnoea detectors; relationship between HRV signal and the Central Nervous System has been used to study the mental state in order to detect stressing situations or, even, to classify the mood of the subjects (anger, confusion, happiness, anxiety, etc.); in the neonatal context, this signal has been used to detect seizures, or pain episodes of new-born infants, or even, to perform an assessment of the foetal health state; etc.

In this thesis we study the relationship between changes on the HRV signal and the presence of allergic reactions to drugs or food. Today, there is a process called provocation test to detect this kind of allergies. The steps followed during this test are:

1. When the patient arrives to the hospital, his basal state is established by measuring blood pressure, heart rate, SpO2 and the volume of the expired air (peak flow).
2. The suspected allergen is divided into several doses of different sizes (the number of doses and their sizes depend on the allergen). The smallest dose is then administered to the subject.
3. After an observation period of 30 or 60 minutes (again, depending on the allergen) if the patient does not present any symptom, the next smallest dose is administered to him.

The process continue until all the doses are given to the subject. When the allergen is finished, there is an observation period of 120 minutes. If nothing happens to the subject, neither in the next 24 hours, it is classified as non-allergic. In the case in which any symptom appears during the tests, the symptoms are treated, and the patient is classified as allergic. Figure 2 summarizes a generic provocation test.

As can be deduced, this process is not risk free: even with the constant observation of the medical staff, the allergic reaction can be of different levels of dangerousness: from the appearance of hives, or conjunctivitis, to breathing difficulties or, even, anaphylaxis. It is neither possible to know which patient may suffer a more or less dangerous reaction, nor the kind of the reaction. So it is really a complex and dangerous process. Through a previous study carried out by the research group, we have concluded that there is a relationship between changes on several patients' HRV signal and a posterior occurrence of allergic reactions. Thus, the objective is to employ the measurement and analysis of the HRV signal to detect allergic reactions. In this way, it is possible, first of all, the automation of the process, so the medical staff could receive an alert as soon as the allergic reaction is detected by analysing the HRB; and, secondly, the number of doses needed during the test could be reduced. Due to the fact that the lasts doses are the biggest and more dangerous, we could reduce the risk to which patients are exposed during the provocation tests. The rest of this paper is organized as follows: Section 2 lists the main objectives of the presented thesis; Section 3 introduces the state of art regarding QRS complex detection algorithms and application fields of HRV as a diagnostic tool; Section 4 introduces the proposed algorithms; Section 5 explains the expected outcome and finally, Section 6 states the stay of the research.

2 OUTLINE OF OBJECTIVES

The main objective of this thesis is the study of the HRV signal to demonstrate its worth as an

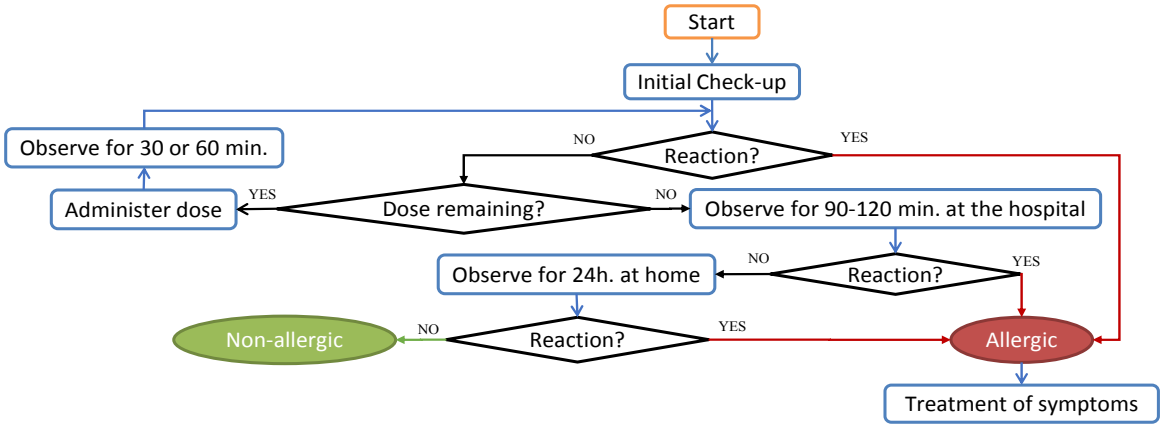

Figure 2: Provocation tests flowchart.

alternative or a helping tool to diagnose and control health problems of different natures. To reach this objective, it is necessary:

1. To design an R peak detection algorithm capable to work in real-time and to be implemented on low-cost devices.
2. To study the HRV of patients (allergic and non-allergic) during provocation tests.
3. To design an algorithm that, based on the HRV signal, detects the presence of allergic reactions before the appearance of physical symptoms.

Besides, it is planned to propose another interesting use of the HRV monitoring as a diagnostic tool for its use with diabetics

3 STATE OF THE ART

3.1 QRS Complex Detection

R peak detection algorithms can be divided into two stages (Figure 3). The first phase (pre-processing) processes the ECG signal in order to reduce or remove the most part of the artefacts and noises commented above. At the second stage, the ECG signal is analysed to find the R peaks.

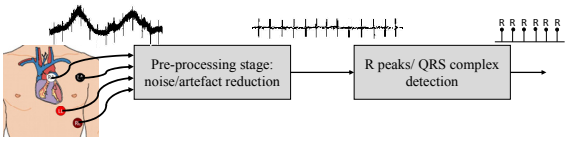

Figure 3: Typical structure of a QRS complex detection algorithm.

3.1.1 Pre-processing Stage

Some of the most common techniques used to pre-process an ECG signal are the following ones:

- Wavelet transform (M. W. Phyu et al., 2009; a. Ghaffari et al., 2008): Through this technique, ECG signal can be divided into a set of basic functions and the ones that do not provide valid information are removed.
- Hilbert transform (C. Xiaomeng, 2011; R. Rodriguez et al., 2013): An interesting property of this technique is that it produces a zero crossing every time there is an inflexion on the raw signal (as in the R peaks case). However the features of some artefacts are very similar to the R peaks detected in this way, so they can be misinterpreted.
- EMD (S. Pal and M. Mitra, 2012; S. Pal and M. Mitra, 2010): As wavelet, this is a decomposition technique in which ECG signal is divided into oscillatory functions (Intrinsic Mode Functions, IMF). Some authors combine EMD with Wavelet (M. K. Das et al., 2011; B. Khiari et al., 2013) as well as with Hilbert (S. Kouchaki et al., 2012; M. Zhang and C. Zhang, 2010) to improve the performance of the pre-processing stage.
- Differentiation based computations (J. Moraes et al., 2002; M. Adnane et al., 2009): These techniques are based on the well-known Pan and Tompkins (J. Pan and W. J. Tompkins, 1985) algorithm. Although these are the most efficient techniques from a power consumption and computational complexity point of view, they require a more complex detection stage.

Most of this techniques are sometimes combined with different kinds of high and low pass filters, not without a level of complexity.

3.1.2 Detection Stage

Regarding the detection stage, most of the algorithms use one or more fixed thresholds to detect the R peaks. This is a good technique only if the processed ECG signal is very clear, without noise or. However, this is not the most common situation so, usually, this threshold or thresholds have to be adaptive i.e. their amplitude should change depending on the features of the ECG signal. Furthermore, time intervals are usually employed for which it has to be considered the maximum and minimum possible heart rates (usually 220 – 40 bpm), and the minimum and maximum RR intervals. Another technique used to detect the R peaks, is the analysis of the QRS complex morphology (slopes analysis, position of the peaks and intervals, etc.); nevertheless the morphology of a QRS complex depends on the position of the electrodes and, mainly, on each person. Actually, the morphology of a person's QRS complex can change during a measurement, what invalidates this technique.

As is commented below, in most of the proposed R peak detection algorithms, the main concern of the authors is the completely removal of all the noises, without taking into account the computational complexity. That fact, make most of them unable to be implemented on battery-driven devices. In the area in which this research is carried out it is extremely important to reach a trade-off between performance and computational efficiency.

3.2 HRV Study Applications

The use of the HRV signal to study some diseases or

the analysis of the health state of a person is being used more and more lately. The main reason is the previously mentioned relationship between this signal and almost all the physiologic systems, through the ANS. The next selection of works represents the use of the HRV signal in different areas:

- The most direct use of the HRV signal is to optimize high performance trainings or to analyse the state of subjects during stress tests (R. Bailón et al., 2013: R. Bailón et al., 2011). Through the HRV it is possible to obtain information related to the effort made, energy expenditure, the oxygen, fat and carbohydrates consumption, or the recover ability of each individual. So, a physical trainer is able to adjust each training session in a personalized way, obtaining the best results from each participant.
- Another important application can be found on the study of people's mood trough HRV signal (M. Kumar et al., 2007; P.-Y. Hsieh and C.-L. Chin, 2011). Due to the relationship between the HRV and the CNS, it is possible to infer if a person is stressed, relaxed, happy, depressed, etc. This can be used to improve the quality of life of all the workers in an office and, thus, their throughput.
- A novel and very interesting application of the HRV signal is the detection of pain episodes (J. De Jonckheere et al., 2011; A. Fanelli et al., 2013) and seizures (M. B. Malarvili and M. Mesbah, 2009) of neonatal and, even, foetal patients. In this way, just measuring and analysing their ECG signal, it is possible to reduce their mortality.
- Due to the relation between the HRV signal and the respiration rate, it is possible to automatically detect apnea episodes (J. Hayano, et al., 2011; E. Gil et al., 2009) or analyse the quality of the sleeping phase (S. Eyal et al., 2012).

4 METHODOLOGY

As is commented above, the main objective is to analyse the HRV signal in order to relate its changes with an abnormality, as can be the presence of an allergic reaction. Another constrain is the realisation of this analysis in real-time. For that reasons, one of the basis of this thesis is the design of a real-time R peaks detection algorithm capable to work on portable devices. Once we are able to obtain the positions of all the heartbeats, the next steps will consists in the study of the relationship between the changes on the HRV signal and the situations at which the subjects are exposed.

4.1 QRS Complex Detection Algorithm

Each of the stages of the designed algorithm have been optimized to reach the "low-cost" requirements. Figure 4 shows the block diagram of the proposed R peak detection algorithm.

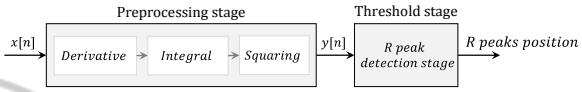

Figure 4: R peaks detection algorithm's blocks diagram.

This algorithm is based on the Pan & Tompkins algorithm, mainly the pre-processing stage. The first stage processes the ECG signal as follow: First, raw ECG signal is derived by using (1). This operation reduces the low frequency noises (as the one produced by the respiration). Then an integration window (2) is used to reduce the high frequency artefacts; and, finally, all the samples are squared (3) in order to empathize the R peaks, while reducing the noise peaks. Results of the pre-processing stage are shown in Figure 5.

$$y_0[n] = x[n] - x[n - N_d] \quad (1)$$

$$\text{with } N_d = round\left(\frac{3F_S}{128}\right)$$

$$y_1[n] = \sum_{k=0}^{N-1} y_0[n-k] \quad (2)$$

$$\text{with } N = round\left(\frac{3F_S}{128}\right) - 1$$

$$y[n] = \left(y_1[n]\right)^2 \quad (3)$$

Once the noises and artefacts have been reduced, next steps consist in detecting the positions of the R peaks. The output of the last stage is a positive signal that has two high-amplitude peaks corresponding to each QRS complex. At the detection stage, the objective is to detect one of these peaks. However, some noise peaks could appear due to electromyographic noises that produce the same high amplitude peaks. To avoid the generation of false positives (i.e. noise peaks classified as R peaks), we use a dynamic threshold controlled by the state machine of Figure 6. The value of the threshold changes with each new sample as follows:

State 1: During interval RR_{min} + QRS_{int} (minimum

possible RR interval + standard QRS duration), a maximum is searched. When this interval finishes, the maximum found is taken as an R peak, and the threshold value is set to the median value of all the detected R peaks.

State 2: Taking *d* as the difference between the position of the last peak and the ending of State 1, this state waits during $RR_{min} - d$. This avoids the detection of large T waves and artefact as a new R peak.

State 3: Threshold level decreases following (4) until its value reaches again the processed ECG signal.

$$th[n] = Pth * th[n-1] \tag{4}$$

$$\text{with } Pth = \frac{0.7 * F_s}{128} + 4.7$$

Figure 7 represents the correspondence between the State and the value of the threshold.

Parameters that depend on the frequency have been chosen by evaluating the performance of the algorithm over 90 signals of different frequencies and different features (Table 1). First database is the MIT Arrhythmia database (MITDB), composed by 48 signals of patients with different kinds of arrhythmias; second one is Normal Sinus Rhythm Database (NSRDB), its 18 ECG signals corresponds to healthy adults; and, finally, Allergy database (ADB) is composed by 24 ECG signals of children (aged 7 months to 10 years) exposed to provocation test at the Paediatrics section of the University Cork Hospital. 2100 combinations of the 3 parameters were tested: 10 values of *N* (1 to 10), 10 values of *Nd* (1 to 10), and 21 values of *Pth* (4.5 to 6.5 in steps of 0.1). Table 1 summarizes the overall performance of the algorithm on each database. Metrics used are:

- Sensitivity: $Se = \frac{TP}{TP + FN}$ (5)

- Positive predictivity: $+P = \frac{TP}{TP + FP}$ (6)

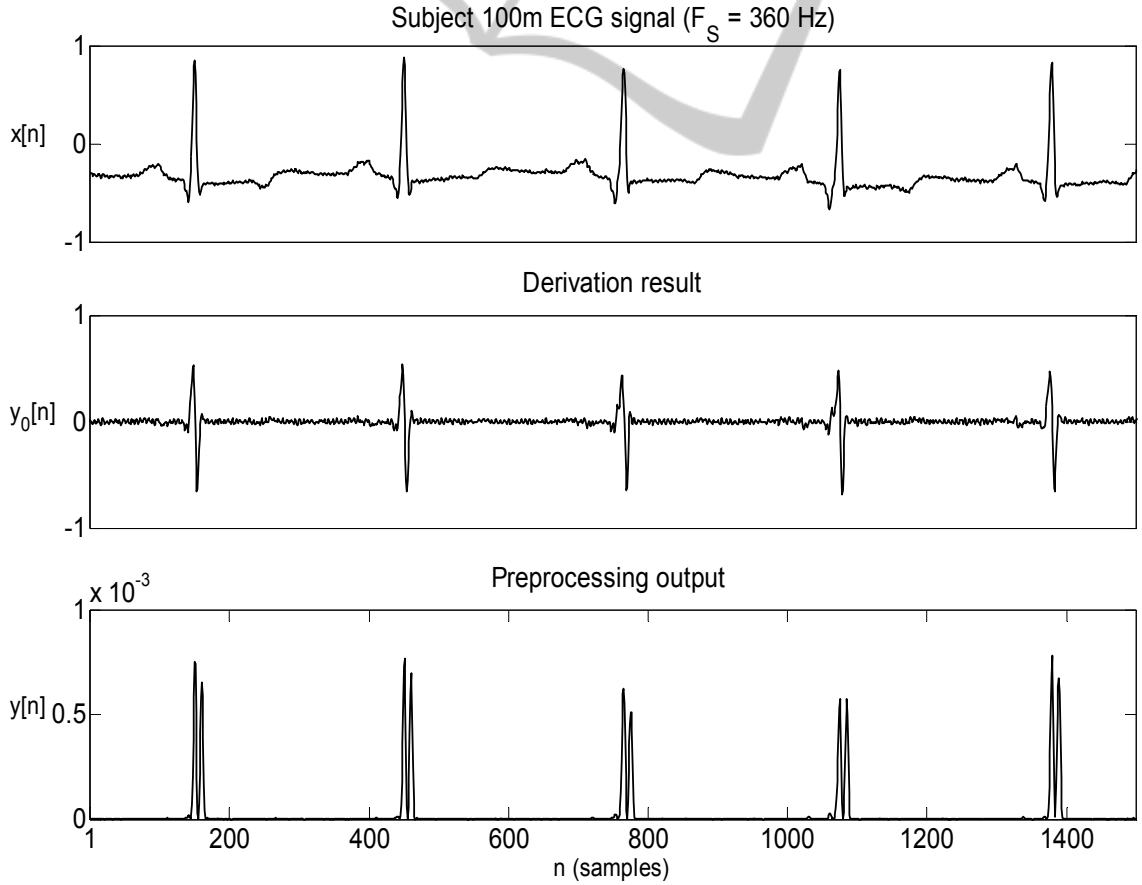

Figure 5: Pre-processing stage results.

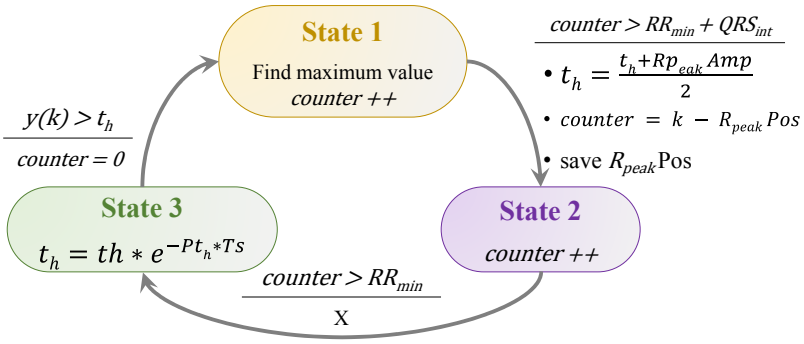

Figure 6: Threshold value setting finite state machine.

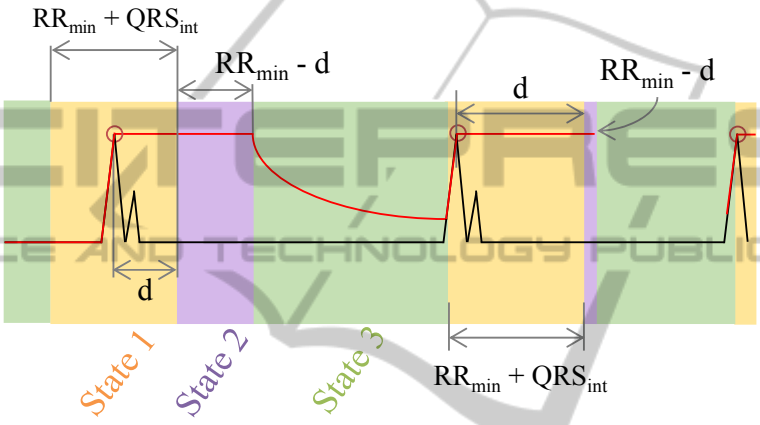

Figure 7: Correspondence between the states of the FSM and the value of the threshold.

Table 2: Features and Overall Performance of the R Peaks Detection Algorithm over the Used Databases.

Database	# of subjects	F_s (Hz)	Length	TP	FN	FP	Se (%)	+P (%)
MITDB	48	360	24 h	109107	308	295	99.719	99.730
NSRDB	18	128	15 h	195846	60	11	99.969	99.994
ADB	24	256	10 h	195872	1137	1396	99.423	99.292

4.2 Allergy Detection Algorithm

Thanks to the studies about the HRV signal and its relation with most of the physiological systems of the body, some works have been published on how to obtain a great number of its features and the meaning of their variations. Depending on the final application, it would be necessary to select one HRV feature of a group of them.

In a previous work, 18 features of the HRV were selected to study the heart performance during an allergic reaction. These features were obtained using 60 seconds windows with 1 second shift: mean of all the RR intervals within the window; standard deviation (STD); coefficient of variation: STD/mean; RMS of differences between adjacent RR intervals; number of pairs of adjacent RR intervals differing by more than 50 ms, NN50.; pNN50, pNN25: NN50/NN25 divided by the total of RR intervals; positive and negative sequential trend: percentage of consecutive RR increasing/decreasing pairs; cardiac sympathetic/vagal indexes and their relations (CSI, CVI, CSI*CVI and CSI/CVI); histogram index; very low, low and high frequency power: total power of the HRV spectrum in the VLF band (0 to 0.04 Hz), LF band (0.04 to 0.15 Hz) and HF band (0.15 to 0.4 Hz); ratio LFHF.

The process needed to obtain all these features and detect an allergic reaction has a very high computational cost. Another objective of this thesis consists in reducing this group in order to be able to perform the allergy detection in real-time. Through the analysis of a previous obtained database (ADB), we can study all these features on 24 subjects

exposed to provocation tests: 15 of them allergic, and 9 non-allergic. Table 3 summarizes the features of each test.

Table 3: ADB features.

ID	Age	Gender	Allergen	OFC length	Total doses	Result
1	18 months	M	Wheat	0h. 14min.	1	
2	6 years	M	Peanut	1h. 40min.	5	
3	9 years	M	Egg	1h. 34min.	5	
4	12 months	M	Milk	1h. 44min.	4	
5	8 years	M	Peanut	2h. 13min.	7	
6	9 years	F	Peanut	0h. 36min.	1	
7	6 years	M	Soy	0h. 57min.	3	
8	5 years	M	Peanut	1h. 45min.	5	Fail
9	8 years	F	Egg	0h. 50min.	2	
10	3 years	M	Milk	1h. 23min.	3	
11	6 years	F	Peanut	1h. 25min.	5	
12	5 years	F	Milk	0h. 41min.	2	
13	3 years	F	Milk	1h. 46min.	5	
18	8 years	M	Soy	0h. 33min.	1	
21	9 years	F	Wheat	1h. 37min.	7	
14	12 months	M	Milk	2h. 10min.	4	
15	6 years	M	Egg	1h. 42min.	5	
16	10 years	M	Egg	2h. 09min.	9	
17	4 years	F	Soy	2h. 11min.	8	
19	6 years	M	Peanut	1h. 51min.	8	Pass
20	7 months	F	Milk	0h. 56min.	2	
22	4 years	F	Wheat	1h. 29min.	6	
23	2 years	M	Peanut	1h. 03min.	4	
24	18 months	F	Milk	1h. 33min.	6	
Mean	4 years 9 months	--	--	1h. 15 min.	4.5	---

The diagnostic ability of each feature can be obtained by analysing its Area under the ROC curve (AUC). Sensitivity (7) and Specifity (8) for each value of each feature's standard deviation is represented.

$$Se = \frac{\#\ ofAllergicSubjectsCorrectlyClassified}{\#\ ofAllergicSubjects} \quad (7)$$

$$Sp = \frac{\#\ ofNonAllergicSubjectsCorrectlyClassified}{\#\ ofNonAllergicSubjects} \quad (8)$$

If the AUC is 50% (the lowest possible value), the result of the classification is random; above this value, the greater the AUC value is, the better the diagnostic ability is. Also, computational time employed by Matlab to obtain each feature has been obtained. These two values are represented in Figure 8. Best AUC is obtained by using mean feature (94.07 %), while worst one (50.7 %) was obtained with CSI feature.

Due to the fact that with the mean, the best result is obtained and the computational load needed to compute it is low, this was the selected feature to detect the allergic reactions. The next step involves the analysis of this feature during all the provocation tests, in order to establish the differences between allergic and non-allergic subjects.

Black line of Figure 9 shows the mean of the HRV, MRR, (computed in windows of 60 seconds with 1 second shift) of an allergic subject and Figure 10, of a non-allergic subject. First grey area represents the interval until the patients gets the first dose, information during this interval will be used as patients' background. Next grey areas represent the intervals in which they get the next doses. During these intervals, MRR signal will not be analysed because patients are having the allergen, medical staff could be taken measurements, or even, reallocating the electrodes, etc., so, ECG signal could being corrupted, and a false positive can be produced.

There is a clear difference between these two signals: the elevations produced on the subject 7 MRR are not present on the other one. It has been observed that this kind of elevations appears (more or less clearly) in all the allergic subjects, while they are not on the non-allergic ones. Another interesting thing is that they appear, in most of the cases, several minutes before the tests ended (i.e. the instant in which the allergic subjects manifested symptoms). The allergy detection process consists, thus, in modelling them and detect these peaks.

Normal HRV of a subject depends on his/her age, sex, health state, weight, etc. so, it is necessary to normalize the MRR signal. Due to the fact that the algorithm does not know these features, it is necessary to normalize each signal depending on its own features. First grey area (background interval) has been used to compute the mean MRR of each subject, as during this time, they are in a "normal" situation. Once they take the first dose, the value of the mean is subtracted from the MRR signal (red line of the figures 9 and 10), the value of the mean is recomputed each time the subjects have a new dose.

The new mean's value is computed with the MRR values from the last time the subjects ate a dose, to the instant in which they had a new one. As we are looking for positive peaks (HR increases), if the MRR decreases, it will not represent an allergic reaction so, values lower than zero are removed, obtaining what we call normalized MRR signal (NMRR). NMRR represent how the MRR signal moves away from its mean normal value.

Finally, the mean value of all the peaks within the NMRR signal are computed as follows: a threshold called *ParamZero* has been established. The mean of all the consecutive values higher than this threshold is obtained. If this value is higher than *allergy_threshold*, the peak represents an allergic reaction. To set the *allergy_threshold*, the maximum value of all the peaks present on the NMRR signal has been computed for each subject. As Figure 11 shows, there is a clear difference between allergic subject's maximum peak value (green bars); and non-allergic's ones (orange bars). Finally, several

values of *ParamZero* have been tested, obtained performances to those values are plotted on Figure 12. The selected value of these two parameters allow us to correctly detect 14 of 15 allergic subjects (all except for the number 18), and none of the non-allergic subjects are misclassified as allergic. Also, the detection of the allergic subjects occur in an average time of 42 minutes before they are detected by the medical staff (mean provocation tests length: 79 min.). This time reduction implies also a reduction of the number of doses needed from 3.93 to 1.5 (mean value).

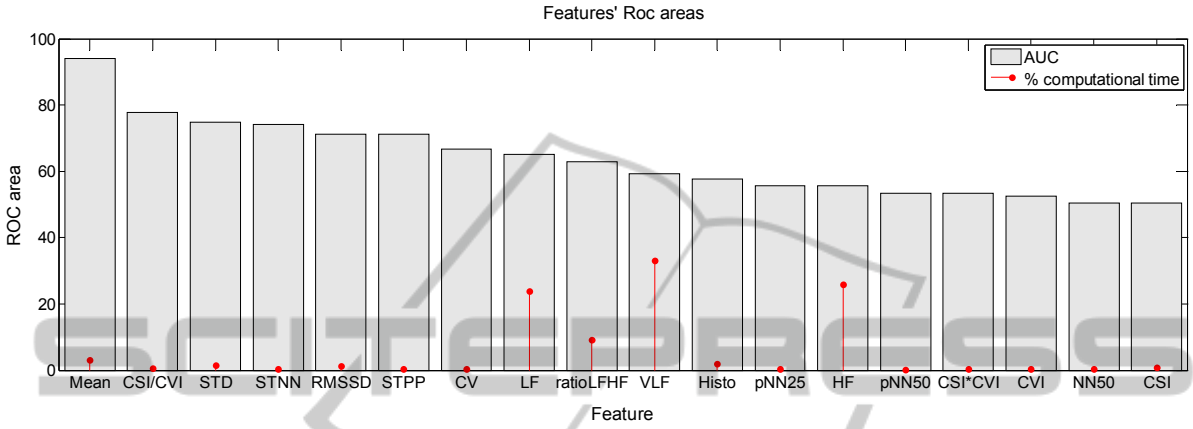

Figure 8: AUC vs. computational time of each feature.

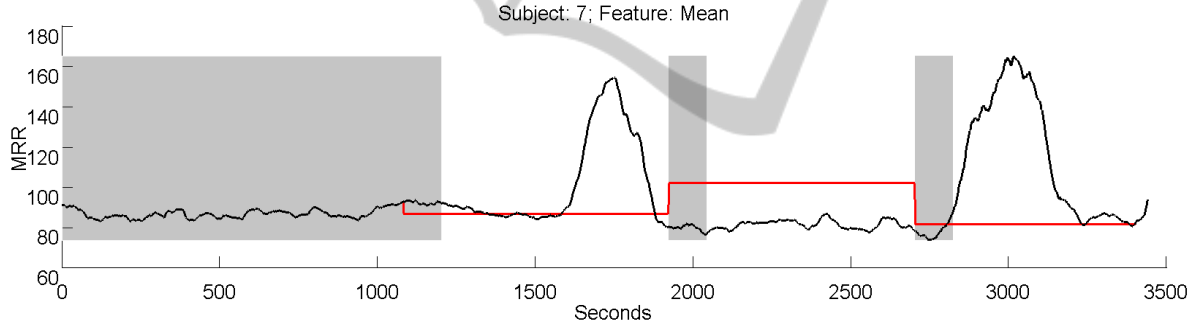

Figure 9: Mean of the HRV of an allergic subject.

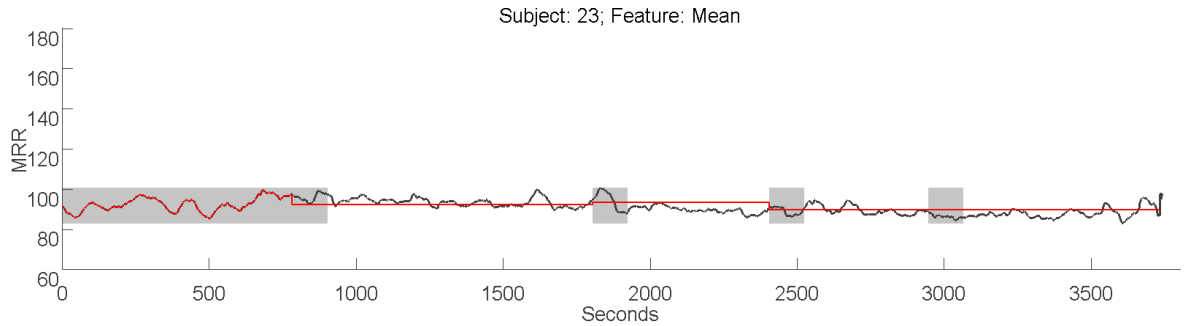

Figure 10: Mean of the HRV of a non-allergic subject.

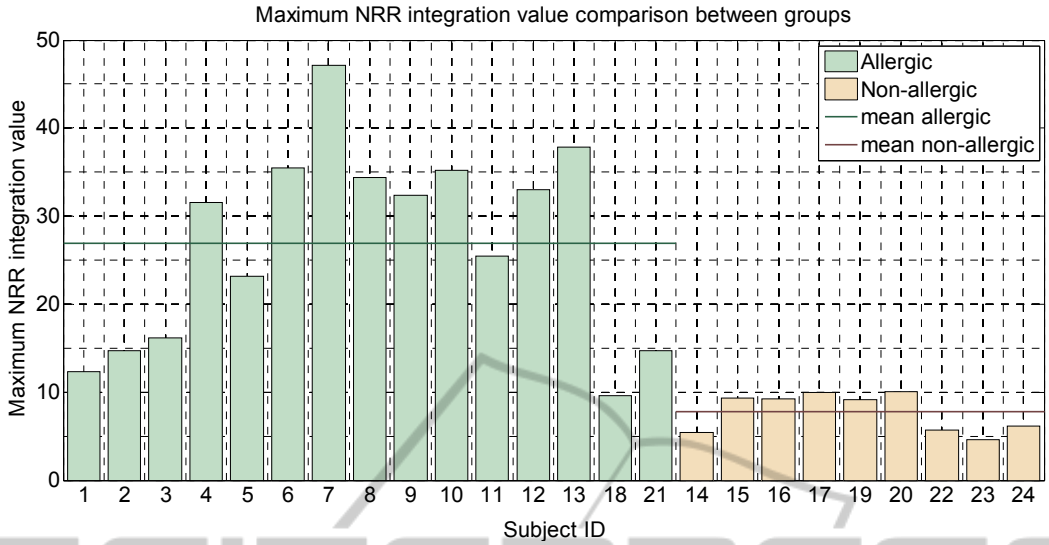

Figure 11: Maximum peak value for all the subjects.

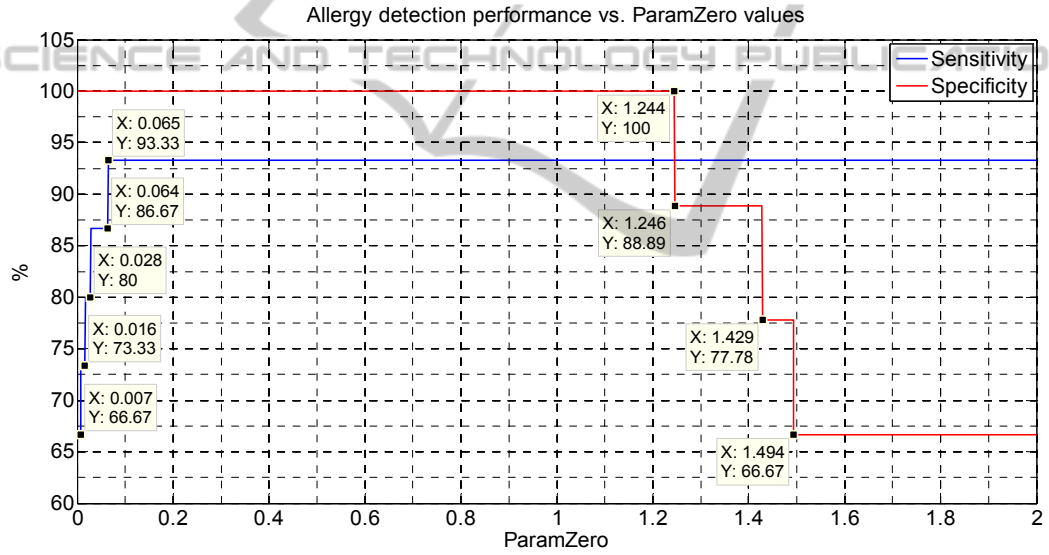

Figure 12: ParamZero values vs. Se and Sp.

5 EXPECTED OUTCOME

Among all objectives, this thesis pretends to demonstrate the utility of the analysis of the HRV to the early detection of allergic reactions. For that, the main objective is the design of a system composed by a local positioning system, a host and multiple devices to analyse continuously and remotely all the subjects' HRV present in the same room.

In the case of an allergic reaction is detected, the system will alert the personal staff, reporting the name or ID of the patient, as well as his/her location.

6 STAGE OF THE RESEARCH

During the realization of this thesis, two algorithms have been designed. The first algorithm, the QRS detector, have been tested thanks to the existence of a great number of annotated ECG databases.

However, as there is no preceding studies showing the relationship between the ECG signal and the allergies, there are no databases that the authors could use to test the allergic reactions detection algorithm. For that reason, and due to the fact that the available database (allergy database) is

composed only by 24 subjects (15 allergic), the author is nowadays carrying out a collection process at allergy section of the Guadalajara University Hospital (Spain). Subjects of this database are adults and children exposed to allergy provocation test involving drugs and food.

Nevertheless, only 2 of 11 subjects that come up are allergic and not all of them could be detected due to several circumstances.

Moreover, another application for the use of the HRV signal is just starting: the detection of hypoglycaemia in diabetic patients. At present, if a diabetic patient believes he is in a state of hypoglycaemia, he needs to do himself a blood analysis or carry continuously a device that measures the glucose level on the interstitial tissue. This devices are carried inserted, and apart from they affect the comfort of the patients, they are very expensive. Besides, this devices have a big delay on the level of glucose measurement on situations of abrupt changes: immediately after a big meal or during the realisation of physical activity.

It has been studied that, during a hypoglycaemia, the body generates adrenaline (like during a stress situation), which provokes a HR elevation (O. Hamdy et al., 2014). In this case, what makes difficult the detection of this situations are the daily activities that also elevate the HR, like the realization of physical activity. In this way, it is planned to study the HR and the movement (by using inertial sensors) of a series of diabetic subjects to establish the differences between normal HR elevations and those produced during normal situations.

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