Evaluating the risks of arrhythmia through big data: automatic processing and neural networks to classify epicardial electrograms

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Abstract

Arrhythmic behaviors are a major risk to the population. These are diverse and can have their origin in cellular dynamics that affect the functioning of the heart. When trying to understand the mechanisms behind arrhythmogenesis the epicardial electrograms present themselves as a useful measurement because they reflect the electrical behavior of the cells surrounding the electrodes. Nevertheless, there is a lack of methods in the literature to automatically process and analyze these signals. In this paper, an algorithm to automatically detect the R, S and T wave peaks in epicardial electrogram signals is presented. This algorithm uses the derivative of the signal to find the activation and recovery times, and uses these as fiducial points to find the desired features. These features are then used as inputs to an artificial neural network, trained to classify individual beats into 'healthy' and 'pathological'. After optimization, both the detector and the neural network showed good performance in their tasks; furthermore, the robustness and amenability to real-time implementation of the methods here presented make them ideal for monitoring patients or experimental platforms when epicardial electrograms can be measured.

1. Introduction

Cardiovascular diseases (CVD) remain the number one cause of death in the world. Nowadays, the electrocardiogram (ECG) is the preferred method to assess the risk of a person suffering a heart-related disease. Notwithstanding, the ECG finds a limitation when trying to determine the cellular mechanisms that lead to CVDs because it sums the contributions from the electrical activity of the whole heart and provides no means of assessing the cellular causes for pathology. Studies that need a closer look at the cellular dynamics use cardiac surface electrograms, obtained by placing electrodes on the surface or inside the walls of the heart. This acquisition is preferred when monitoring open heart surgeries or *ex-vivo* experimental platforms because it is an indicator of the electrical activity of the cells that surround each one of the electrodes. By analyzing the morphology of the electrogram, one is capable of formulating hypotheses about what is happening at the cellular level that is producing a pathology at the organ level.

Previous studies have shown how pathological behaviors at a cellular level may lead to dangerous arrhythmic behaviors [1] and how these are reflected in the epicardial electrogram [2–6]. Authors have pointed out the importance and possible impact of performing automatic analyses of electrograms [7]; but surprisingly, there is, nowadays, a gap in the literature involving the automatic extraction of features from electrograms and their evaluation is usually done visually and manually. This paper proposes an algorithm to automatically detect the main waves observed in the epicardial electrograms: the R, S and T waves. The applicability of these measurements is proven by using the extracted features as inputs to an artificial neural network for beat classification.

2. Materials and Methods

2.1. Data acquisition

Unipolar epicardial electrograms (EGM) were acquired by means of a custom-made electrode grid placed on the left ventricle of a porcine heart during a Physioheart experiment. This is an *ex-vivo* experimental setup, developed by LifeTec Group (Eindhoven, Netherlands) [8], by means of which the physiology and pathology of a porcine heart may be studied under conditions that closely resemble those found *in-vivo* [9]. The grid contained 121 electrodes ordered in a 11x11 grid, and allowed the recording of the electrical activity of the epicardium during the experiment. Signals were acquired using a Biosemi Active Two acquisition and pre-processing system at a sampling frequency of 2048 Hz and the digitized signals – referred to as $s[n]$ from here onwards – were stored in a computer for further processing. A total of $B = 34765$ beats were recorded

from over an hour of the experiment duration. Many different morphologies can be found among the recorded beats, corresponding to both healthy and pathological states.

2.2. Signal conditioning

The acquired signals ($s[n]$) were digitally filtered using a high-pass, fourth order, Butterworth filter with cutoff frequency $f_c = 0.5$ Hz; this filter eliminated the baseline offset introduced by the acquisition system and the baseline wander caused by slow electrode movement. Afterwards, the time derivative of the signal was calculated as:

$$\frac{ds[n]}{dn} = s[n] - s[n-1], \quad n \in [2, N] \tag{1}$$

where N was the number of samples in the signal. In the derivative the pacing signal showed as an abnormally large deflection; this, along with an arbitrarily high threshold, was used to segment all the beats from $s[n]$, and all the following steps were performed on each individual beat ($b_i[n]$ with $i \in [1, B]$). The interest in processing each beat separately was in that such treatment is more easily translatable to a real-time application. Following segmentation, a digital low-pass, fourth order, Butterworth filter with cutoff frequency $f_c = 40$ Hz was applied to the segmented beats to eliminate the low amplitude, high frequency noise produced by the electrodes vibration. Observe that this filter would have eliminated the high frequency component that makes the pacing signal so visible in the derivative, this is why it was only applied after the beats had been segmented.

2.3. ARI-based detector

One of the most important features of the EGM is the activation-recovery interval (ARI), which reflects the action potential duration of the cells surrounding the electrode [2]. The activation time can always be found as the point where the derivative of the signal is minimal, and the recovery time as the point where the derivative of the signal is maximal during the T wave [4]. The derivative of each filtered beat ($db_i[n]/dt$) was calculated as shown in Eq. 1 and the activation (At) and recovery (Rt) times were found as:

$$At_i = \arg\min_n \left(\frac{db_i[n]}{dn} \right), n \in [1, SW_{At}] \tag{2a}$$

$$Rt_i = \arg\max_n \left(\frac{db_i[n]}{dn} \right), n \in [At_i{+}n_1, At_i{+}n_2] \tag{2b}$$

with $n_1 = 100$ ms and $n_2 = 400$ ms – the minimum and maximum possible phyisiological values for the activation-recovery interval, respectively – and SW_{At} was a search window, optimized as explained in Section 2.5. The activation and recovery times, them being the easiest to find, were then used as reference points to search for the features of each beat of the epicardial electrogram. The R, S and T waves' peaks were found by looking for zero crosssings (ZC) in the derivative of each beat as follows:

Table 1. Values taken by n_3 and n_4.

Feature	n_3	n_4
R_i	$At_i - SW_R$	At_i
S_i	At_i	$At_i + SW_S$
T_{pre_i}	$Rt_i - SW_{T_{pre}}$	Rt_i
T_{post_i}	Rt_i	$Rt_i + SW_{T_{post}}$

$$ZC_i = \{n \in [n_3, n_4] \mid sign\left(\frac{db_i[n]}{dn}\right) \neq sign\left(\frac{db_i[n+1]}{dn}\right)\} \tag{3}$$

were, n_3 and n_4 define the limits of the signal intervals where zero crossings were looked for when detecting each of the features; these values are defined in Table 1, where SW_x were search windows, optimized as specified in Section 2.5.

Special consideration has to be given to the T wave since, as shown by Potse et al. [5], it can be either positive, negative or biphasic. A T-wave peak occurring before the recovery time will always be negative, whereas a peak after the recovery time will always be positive, regradless of the morphology of the T wave. This is why two thresholds were defined:

$$\gamma_{T_{pre}} = -\gamma_1 max(|b_i[n]|) \quad n \in [n_3, n_4] \tag{4a}$$

$$\gamma_{T_{post}} = \gamma_2 max(|b_i[n]|) \quad n \in [n_3, n_4] \tag{4b}$$

and zero crossings in the derivative before the recovery time were only considered T wave peaks if the signal amplitude at that point was less or equal to $\gamma_{T_{pre}}$ and those after the recovery time were only kept if the amplitude of the signal was greater or equal to $\gamma_{T_{post}}$, both thresholds were optimized as will be later explained.

Finally, to avoid signaling false peaks due to noise, the R peak was chosen as the zero crossing in which the signal ($b_i[n]$) had the largest amplitude and the S peak where the signal was at it's lowest amplitude among the zero crossings within their respective search windows. For the T wave a similar method is applied; if looking before the recovery point the zero crossing where the signal was minimal was chosen, if looking after the recovery point the the zero crossing where the signal was maximal was chosen.

2.4. Performance evaluation

Automatic detections were compared to manually made annotations of the peaks; a detection was considered to be a true positive if the automatic mark happened within 10 ms of the manual annotation, it was considered a false positive if it happened with no manual mark within 10 ms and a false negative was considered when no automatic mark was within 10 ms of a manual annotation. The detection of each of the peaks was evaluated using the sensitivity (Se) and positive predictive value (P^+) of the automatic detections, calculated as:

$$Se = TP/(TP + FN) * 100 \tag{5a}$$

$$P^+ = TP/(TP + FP) * 100 \tag{5b}$$

where TP is the sum of all true positives, FP the sum of all false positives and FN the sum of all false negatives.

2.5. Detection optimization

To accurately estimate the generalization error and to avoid overfitting in the optimization of the parameters a cross-validation approach was used [10]. A 10-fold cross-validation algorithm was performed on 75% of the available beats, randomly sampled with a uniform distribution, to decide which combination of parameters produced the best results. During the cross validation, *receiver operating characteristic* (ROC) curves were used to measure the error in the detections as a function of the sensitivity and the positive predictive value. A set of parameters was considered better if the distance of it's point on the ROC curve was closer, in an Eucledian sense, to perfect detection ($Se = 100\%$, $100 - P^+ = 0$). The parameters that performed best in the cross validation were then tested on the remaining 25% of the data to report the final Se and P^+. This was repeated 10 times, and the performance of the delineator, later reported, is the best Se and P^+ obtained over the ten iterations.

First, SW_{At} and SW_R were simultaneously optimized in order to maximize the performance in the R peak detection. Afterwards, and using the previously optimized parameters for R peak detection, SW_S was found to optimize the detection of the S peak. Finally, the T wave peak detection was optimized by looking for the combination of $SW_{T_{pre}}$, $SW_{T_{post}}$, $\gamma_{T_{pre}}$ and $\gamma_{T_{post}}$ that produced the closest-to-perfect detection.

2.6. Automatic classification

As an example of the utility of these features, they were used as inputs to a fully-connected multi-layer perceptron, called artificial neural network (ANN), which was trained to classify the signals between 'healthy' and 'pathological'. The signals were manually annotated and the ANN was trained following established practices to avoid bias and variance [10]. Additionally, for three different ANN depths (2, 3 and 4 hidden layers) the number of hidden units per layer (constant along layers) was varied to find the optimal topology. The ANN was implemented using Theano (0.9.0) on Python (3.6.1). The performance of the network was measured using the Se and P^+ performance metrics from Eq. 5.

Table 2. Optimized parameters and detection performance.

Feature	Optimized Parameters	$\overline{Se}$	$\overline{P^+}$
R peak	$SW_{At} = 210$ ms $SW_R = 25$ ms	99.98%	99.98%
S peak	$SW_S = 45$ ms	99.50%	99.50%
T peak	$SW_{T_{pre}} = 100$ ms $SW_{T_{post}} = 50$ ms $\gamma_1 = 0.45$ $\gamma_2 = 0.35$	97.98%	98.21%

Table 3. Neural network performance for three network topologies.

Hidden layers	Hidden neurons	P^+	Se
2	12	97.9%	94.6%
3	13	98.7%	93.6%
4	23	94.4%	98.1%

3. Results

Table 2 shows the performance of the detection system after optimizing the parameters. The detector proved to be efficient in detecting the three desired features. The R and S peak detections showed the highest performances, them being over 99% in both Se and P^+. Also the T peak, which is the smallest deflection and the most susceptible to noise, was detected with high performance, showing Se and P^+ close to 98%.

Table 3 shows the best performance for each of the ANN depths after training. Results show that as the depth of the network increased so did the number of hidden neurons required per layer needed to achieve the same performance. Also, Table 3 shows that the increase in performance is small as the complexity of the network (i.e. more fully connected neurons) is increased.

4. Discussion

The algorithm presented in this paper can be used as a first step in the automatic processing and analysis of the EGM. The results shown in Table 2 suggest that the optimization process worked correctly, since the choice of parameters resulted in high performance values when tested on data not used for training. The use of ROC curves to pick the best parameters for the detector ensured that the amount of false positives and false negatives was minimized when the detector was applied to 'unseen' data, this guaranteed the best possible balance between Se and P^+ in the detections. These optimal features were then used as inputs to an ANN; one can observe that increasing the number of layers in the network did not translate into a significant improvement in performance. Using two hidden layers already provided good performance in classification, and the use of few layers, and thus neurons, is preferable in monitoring applications because it reduces the time required to process the inputs. Hence, the use of the detection algorithm along with a trained ANN with two hidden layers and 12 neurons per layer proved to be optimal for the classification of the beats.

A distinct advantage of these methods is that they require no further information than that contained in each beat to perform the detection of the features and classification of the beat. Furthermore, the use of computationally inexpensive techniques allow the extraction of features and further classification before the next beat is acquired. The ability to analyze cardiac electrograms in real-time would enable the development of a variety of tools for diagnostic and intervention, these tools require fully automated algorithms with minimal human input [7]; the methods presented here fit those requirements and they provide a template for the automatic analysis of EGM.

5. Conclusions

An algorithm to detect the peaks of the main waves of beats segmented from left ventricular unipolar epicardial electrograms and then classify the beats into 'healthy' or 'pathological' has been presented. The optimized detection algorithm achieved high Se and P^+ values in the detection of all wave peaks, which were used as input to a neural network that successfully classified the beats. This work sets a framework for the use of unipolar electrograms and machine learning techniques as a means to quantify the risk of suffering from pathological behaviors that may lead to arrhythmias.

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