High Specificity IEGM Beat Detection by Combining Morphological and Temporal Classification for a Cardiac Neuromodulation System

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Abstract

Elevated heart rate is known to be an independent risk factor for a higher overall mortality, especially for patients suffering from coronary artery disease, e.g. from heart failure. Since pharmacological approaches can not exclusively address heart rate, we investigated a cardiac neuromodulation technique lowering elevated heart rate by means of electrical neurostimulation. The idea is to exclusively modulate the parasympathetic tone in the sinoatrial node area to decrease heart rate. However, electrical stimulation of the heart may pose a specific risk as one temporally misplaced stimulation can cause atrial and especially ventricular fibrillation. Accordingly, we aimed to trigger on the intracardiac electrogram in the upper right atrium and present two algorithms satisfying the requirements of highly specific, secure real-time detection within one heart beat: Decision tree and neural network. Both algorithms were combined with a heart rate prediction estimating upcoming action potentials to maximize beat recognition against artifacts. The combined algorithms were validated on human intracardiac electrograms from electrophysiological examinations with promising results (specificity: 100 %, sensitivity$_{tree}$: 70.2 %, sensitivity$_{net}$: 87.3 %) for secure neurostimulation.

1. Introduction

Over the decades, long term and follow-up examinations have shown that heart rate itself is an autonomous risk factor for a higher overall mortality [1]. The risk prediction is independent of the existence or the extent of coronary diseases [2, 3]. The predictive value remains even after the adaption of further risk factors, e.g. left ventricular systolic dysfunction, arterial hypertension, smoking, age and diabetes mellitus [4–6]. Epidemiological data show a growing risk of mortality in heart rates greater than 60 beats per minute (bpm) [2,3]. Furthermore, for patients suffering from congestive heart failure based on coronary

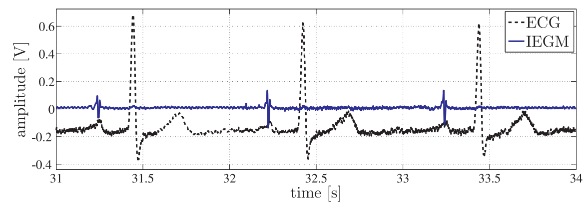

Figure 1. Sequence of an ECG (lead Einthoven I, black dashed) and corresponding IEGM (blue solid) taken in the upper right human atrium.

artery disease (CAD), treated with beta blockers, heart rate retains its prognostic importance: Patients having resting heart rates above 70 bpm show *inter alia* significantly increased cardiovascular mortality rates [7]. Beyond that, with each 5 % increase of heart rate, cardiovascular mortality increases by 8 % [7]. In this patient collective heart rate reduction by a selective sinoatrial node (SAN) blocker with i_f-channel inhibitors such as Ivabradine (by an average of 6 bpm) resulted in a decrease of hospitalization, but not in a reduction of the cardiovascular mortality rate [8]. Besides, the clinically achievable decrease of the SAN frequency is pharmacologically limited and rarely achieves more than $10 - 20$ bpm. Moreover, these medications are not able to exclusively modulate the SAN frequency but also have an impact on electrophysiological conditions in the atria or can rarely cause central nervous visual disorders [9]. This underlines that available pharmacological approaches are only of limited use for frequency reduction according to their inadequate maximum effectiveness, the extracardiac side effect profile and the insufficient compliance of medication intake.

We contrived a new technique called 'cardiac neuromodulation'. The fundamental idea behind this method is the reduction of heart rate by selective modulation of the parasympathetic tone to the SAN by electric neurostimulation. Electrical neurostimulation poses a localized therapy with maximum benefit with virtually no systemic side effects. Modulation is achieved by electric neurostimulation via an inserted catheter at the upper right atrium in the area of the SAN. The expected extent of rate reduction of this methodology is higher compared to medications. Additionally, a reversibly controllable frequency reduction in a dynamic range is a major advantage. We investigated the technique of cardiac neuromodulation in a clinical study which showed good results with a decrease of the initial heart rate by $20\,\%$ [10]. To determine optimal stimulation parameters for cardiac neuromodulation and functional characterization of the intracardiac nervous system, we developed a neurostimulator providing various stimulation patterns (monophasic, biphasic, sinusoids and damped sinusoidal oscillations) within a wide range of burst frequencies, voltage amplitude and duration of the burst cycle length [11]. Neuromodulation (or neurostimulation) itself is an upcoming technique under investigation and, to some extent, already in use in various medical research fields, e.g. spinal cord stimulation (SCS) for treatment of e.g. chronic pain and failed back surgery syndrome [12] and deep brain stimulation (DBS) for the alleviation of Parkinson's disease, Tourette syndrome or depression [13]. Initial experiences in human trials have shown promising results in ventricular frequency reduction in permanent atrial fibrillation by electrical neuromodulation of the parasympathetic tone to the atrio-ventricular node [14].

Other than in SCS and DBS, the cardiac neuromodulation has one major challenge: Electrical stimulation in the heart in general poses the danger of producing arrhythmia. Therefore, calculated triggering of electrical impulses is essential. For this purpose, the electrode catheter, used for sensing and stimulation, accesses the intracardiac electrogram (IEGM) in the SAN area. To ensure safe stimulation of the parasympathetic nerve, we provided stimulation in the absolute refractory period of the atrial myocardium. Hence, exact datection of IEGM beats is indispensable. A typical IEGM from the SAN can be seen in Fig. 1. The IEGM (blue solid) presented here in concordance to the ECG (Einthoven I, black dashed) has been recorded in the upper right atrium beginning with the onset of P-wave. It can be seen that the amplitude and shape of the IEGM beats may vary. In this paper, we present a comparison of two algorithms to investigate how IEGM triggered cardiac neuromodulation can be implemented in a secure way, operating in real-time in order to decrease high resting heart rates.

2. Methodology

The developed neurostimulation system is going to be used in animal experiments investigating the optimal stimulation patterns and maximum achievable, physiologically sensible decrease in heart rate. To avoid side effects caused by erroneous electrical stimulation, a bipolar electrode catheter will tap the IEGM, which is in use for both sensing and stimulation. Algorithms for this application have very specific requirements:

- specificity of the algorithm is most important due to possible effects of one incorrect stimulation
- robustness and real-time capability must be provided to allow neurostimulation within one heart beat cycle in the refractory period of heart muscle cells
- simple implementation on a microcontroller, as the neurostimulator device is based on a MSP430 from Texas Instruments.

Specificity or true negative rate (TNR) is defined as:

$$TNR = \frac{TN}{TN + FP} \tag{1}$$

with TN as the number of true negatives and FP as the number of false positives. In most medical engineering application such as ECG monitoring, an attempt is made to increase the sensitivity. Sensitivity or true positive rate (TPR) is defined as:

$$TPR = \frac{TP}{TP + FN} \tag{2}$$

with TP as the number of true positives and FN as the number of false negatives.

For testing and evaluation of the algorithms, a dataset of 604 IEGM beats with an overall duration of about eight minutes with a sampling rate of 977 samples/s is available. These signals have been recorded during sinus rhythm of standard catheter ablation with ECG leads Einthoven I, II, and III and several IEGM signals in the right atrium of six patients (male and female). All recorded signals have been separated with Matlab into sequences of 32 samples with an overlap of 16 samples. IEGM classification was carried out in correlation to the ECG signals and marked whether or not an IEGM beat is correctly detected. According to the circumstance of the signal recording during this standard procedure, we found the signal shape varying both interindividual and intraindividual. Nevertheless, this scenario allows controlled *in silico* testing.

We here compare two algorithms that satisfy the above mentioned requirements combining morphological and temporal classification. First, we use a binary decision tree with four features: skewness, change of skewness, standard deviation and variation of the standard deviation. We established this feature combination having the advantage of only calculating two features in each step, storing in a variable and calling from there, sustaining real-time operation. In this case, the specificity of the binary decision tree achieved $99.27\,\%$ and a sensitivity of $63.87\,\%$ [15]. As we found that according to the varying IEGM beat shape and possible artifacts in between two IEGM misclassifications are inevitable, we here combine the decision tree with a

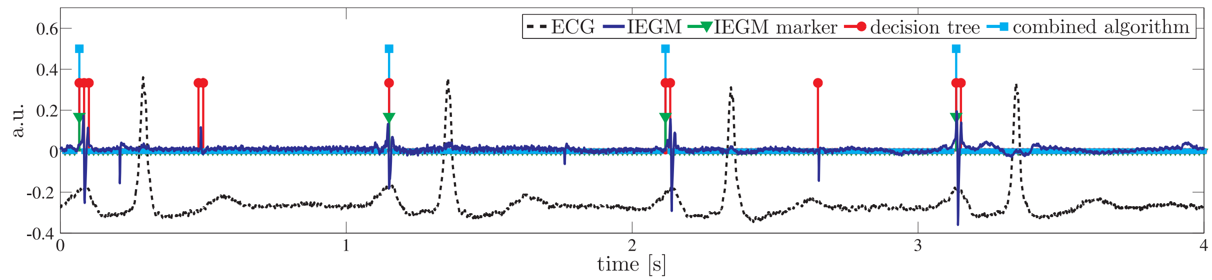

Figure 2. Sequence with ECG (black dashed), IEGM (blue solid), manual IEGM beat marker (green ▼), decision tree marker (red ●) and the combination of decision tree and heart rate prediction (turquoise ■). High levels of markers represent detected IEGM beats.

heart rate prediction:

$$T_{10}(t > t_0) = \frac{1}{10} \sum_{i=0}^{i=9} T_{10}(t_{-i}). \qquad (3)$$

Averaging over the last ten recognized heart cycles and thereby calculating the average cycle length duration T_{10} allows an estimation of the upcoming IEGM beat under the assumption of a symmetric distribution and not taking into account differences in standard deviation. This prediction leads to a certain window function by which the morphological classifications are mashed with variable threshold.

As an alternative to the decision tree, we implemented a feed forward neuronal network with one hidden layer consisting of three neurons. Decision tree and neural network operate on the same features, while for the latter they are normalized first. Training is provided using the backpropagation algorithm for weight adaptation. As optimization Levenberg-Marquardt is used, which minimizes the mean squared error. Positive and negative classes are weighted differently for training: According to their differing samples quantities, we normalized by a factor of $1/\text{number}$. To ensure high specificity rates, the neural network is also combined with the window function of the heart rate prediction of eq. 3.

3. Results

To achieve reliable values for the quality of both algorithms, we used the leave-one-out cross validation for examination with k subsamples. For k times the cross validation is repeated with one subsample for testing and the remaining $(k-1)$ subsamples as the training data. The results of all k folds are than averaged and analyzed. Validation of both algorithms were performed with Matlab for detailed analysis of the classification results. Fig. 2 shows an example of a typical signal sequence: For verification reasons the ECG Einthoven lead I (black dashed) is plotted in addition to the IEGM signal (blue solid). IEGM markers (green ▼) show the manual decision in correlation to ECG for an underlying IEGM beat. Decision tree markers (red ●) show decision of the tree itself, and combined algorithm markers (turquoise ■) show the overall decision of the tree combined with the heart rate prediction algorithm. It can be seen that artifacts that morphologically resemble the IEGM can be eliminated according to the additional temporal classification.

The binary decision tree combined with heart rate prediction showed best performance with a signal tolerance of 0.17 mean cycle length as heart rate variability of the recorded signals is in a normal range. Furthermore, as within neurostimulation periods heart rate is decreasing from beat to beat, the window function must not be set too narrow. The neural network showed best performance with scaling with shifted and scaled features as input around the mean value.

Detailed results of the algorithms are summarized in Tab. 1. Both algorithms show very high specificity TNR of almost $100\,\%$ which is of major importance for cardiac neuromodulation. The sensitivity TNR of the neural network with $87.3\,\%$ is higher than the one of the decision tree ($70.2\,\%$). Nevertheless, during stimulation period 3 of 4 IEGM beats would be supported with the decision tree,

Table 1. Results of the leave-one-out cross validation process on decision tree and neural network classification both combined with heart rate prediction algorithm (rounded values).

	Decision tree	Neural network
Specificity TNR	$100\,\%$	$100\,\%$
Sensitivity TPR	$70.2\,\%$	$87.3\,\%$
False negative rate	$29.8\,\%$	$12.8\,\%$
False positive rate	$3.69 \cdot 10^{-05}\%$	$3.69 \cdot 10^{-05}\,\%$
Pos. pred. value	$99.8\,\%$	$99.8\,\%$
Neg. pred. value	$99.3\,\%$	$99.7\,\%$
Correct rate	$99.4\,\%$	$99.7\,\%$
Error rate	$0.7\,\%$	$0.3\,\%$

which is assumed to be sufficient to lower high heart rate and keep it on a low level. The high results of positive predictive value PPV and negative predictive value NPV in both cases, show the high accuracy of both combined algorithms. Correct rate and error rate are both extremely good, those of the neural network being slightly better.

4. Discussion and Conclusion

Cardiac neuromodulation is a new approach to lower pathologically high resting heart rates by means of electrical stimulation. To provide secure stimulation without unacceptable side effects, such as atrial fibrillation, triggering on the IEGM is mandatory. For the investigation of optimal stimulation parameters, the developed neurostimulator is going to be used in animal experiments. In addition to the high demands on specificity and robust IEGM detection also the real-time capability and simple implementation is of significant importance. There is no problem if not every IEGM beat is supported by cardiac neuromodulation, but it must not be stimulated incorrectly or too late. According to the requirements, a binary decision tree and a neural network have been implemented in Matlab. Both have been combined with a heart rate prediction algorithm. The testing dataset consists of human IEGM signals recorded during standard ablation procedure and has been manually analyzed regarding IEGM depolarizations. Validation was carried out with a leave-one-out cross validation process.

Both, decision tree and neural network, show very high performance when combined with a heart rate prediction algorithm based on the average of the last ten cycle length durations. The specificity of both is extremely high (almost $100\,\%$) on this dataset, sensitivity of the neural network is higher than the one of the decision tree. Nevertheless, as both combined algorithms remain real-time capable, they will be implemented on the neurostimulator device and proved in a hardware-in-the-loop system on more datasets before experimental setup.

Acknowledgements

The authors would like to thank the German Research Foundation (DFG) supporting this project (DFG LE 817/10-1 and SCHA 790/3-1).

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