Learning-Based Approach to Predict Fatal Events in Brugada Syndrome

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Abstract Brugada Syndrome (BrS) is an arrhythmic disorder which increases the probability of developing arrhythmic events, even life-threatening ones, in young and otherwise healthy individuals. It accounts for 5-20% of sudden deaths in people with no structural cardiac abnormality. The first clinical manifestation of this syndrome is, usually, a cardiac arrest. A correct evaluation of the risk of developing an arrhythmic event could prevent premature deaths and unnecessary procedures. This paper focuses on the idea that analysis based on machine learning can extract some piece of information not visible to the human eye and, thus, forecast if a sudden death will occur or not. The study population comprises 209 electrocardiograms (ECGs) from Piedmont Brugada register, 41 of subjects who had an event, while the remaining 168 are used as controls; therefore, it is a binary classification problem. Cardiologists manually measured 24 features per ECG. Then, a multi-layer perceptron (MLP), a boosted decision tree (BDT) model, a decision tree, a Support Vector Machine (SVM), and a Naïve Bayes (NB) classifier were employed to classify the ECGs. All models show a high negative predictive value: a patient whose predicted class is negative is likely to remain asymptomatic. Since the positive predictive values of

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the MLP and NB are not sufficiently high, the opposite cannot be stated. Finally, F1-score shows BDT outperforms (0.67) all the other models.

Key words: Boosted Decision Tree; Brugada Syndrome; Electrocardiogram; Multilayer Perceptron; Risk Stratification; Shallow Learning; Sudden Cardiac Death.

1 Brief introduction to the Brugada Syndrome

Brugada syndrome (BrS) is a congenital, potentially life-threatening disease that affects the heart's electrical activity and predisposes to ventricular arrhythmias (ventricular tachycardia or fibrillation, VT, VF) and sudden cardiac death (SCD) [1]. It is an *inherited primary arrhythmia syndrome* [2], since it has a genetic basis without any heart structural anomaly.

BrS affects people, mainly males (around 8 times more than females), around 45 years old at diagnosis [3, 4]. BrS affects only 5 over 10 000 people [5] and its correlation with SCD is still under investigation.

Syncope occurs frequently, either at rest or during sleep, like ventricular tachycardia and SCD or aborted SCD. Drugs, alcohol, and fever, may increase the probability of arrhythmia and could unveil a BrS pattern in asymptomatic subjects [6, 7].

The syndrome causes are not yet clear. Several ideas have been proposed, as repolarization and depolarization anomalies [8, 9]. Different concauses can exist in the same person, while the same anomaly could not cause the syndrome in all patients.

BrS is diagnosed using an electrocardiogram (ECG), by recognizing a disease-specific pattern in the right precordial leads (see Fig. 1). These alterations may not be always present; however, the administration of particular drugs could force the appearance in the ECG signal of these disease-specific patterns when not spontaneously present.

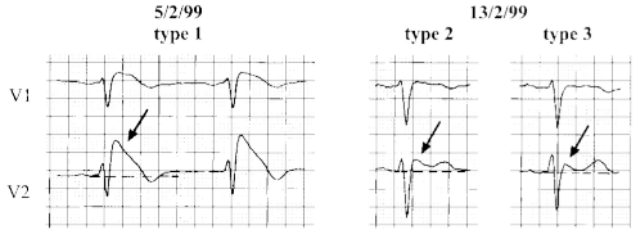

Fig. 1 Example of BrS patterns in precordial leads from different recordings of a single patient.

The implant of a cardioverter defibrillator (ICD) could be suggested for BrS patients at high risk of SCD, to prevent death in case of VF or VT.

1.1 Risk stratification

The implantable cardioverter defibrillator is the main therapeutical and prevention approach. In particular, if implanted in young patients, the percentage of complications rises to 0.5-1.5% per year [10]. Therefore, to prevent death, cardiologists need to clearly discriminate between patients who will develop dangerous arrhythmias, thus requiring specific treatment and/or ICD, from those who will remain asymptomatic. This issue is called *risk stratification* and our work tries to assess if a neural-based ECG analysis can be exploited as an additional tool for risk stratification.

Patients having suffered from aborted SCD or ventricular arrhythmias are easily identified as patients at highest risk. On the contrary, it is much more difficult to recognize asymptomatic patients at risk.

The majority of researches were not able to assess the role of positive genetic testing or family history of SCD in risk stratification [3, 11].

The primary ECG markers recognized in various statistical analyses to have a prognostic value in outcome prediction are listed below [12]:

- Spontaneous type 1 pattern
- QRS axis left deviation
- PR interval
- Fragmented QRS complex
- QRS duration
- R wave in lead aVR
- R wave in lateral leads (I, aVL)
- Early repolarization pattern: J point elevation with concave ST-segment elevation and prominent T wave in at least two consecutive leads
- QT dispersion

Artificial intelligence applied to the problem of predicting the outcome associated with a BrS patient yields a more reliable estimation of the diagnostic markers but paves also the way to diagnose the disease, even when the BrS pattern is either partially expressed or completely absent in the ECG trace.

The AI applications to BrS range from automatic BrS diagnose to completely avoiding drug administration to unveil hidden Brugada markers. Finally, the scarce amount of visually interpretable ECG markers strongly affects risk stratification; in this sense, neural-based techniques may recognize novel ECG markers, which have not been yet detected [13, 14, 15, 16, 17].

2 Database description

The database for the risk stratification was extracted from Piedmont Brugada regist[8] and contains features drawn from 209 12-lead ECG traces: 41 belonging to patients who developed an *event*, while the remaining 168 are used as *controls*. The

latter class is made of people with a diagnosed Brugada syndrome who did not develop a major cardiac event.

Event class comprises SCD and VT. Syncope was not included into this group because of the complexity to discriminate between arrhythmogenic syncope, which could be caused by BrS, and neutrally mediated syncope, which is not related to Brugada syndrome. ECGs were acquired from patients not underlying any pharmacological therapy nor drug inoculation.

ECG features were chosen in compliance to the risk stratification guidelines for BrS and were measured manually by cardiologists. The list below summarizes the collected features:

1. Age
2. Sex
3. Cardiac Frequency
4. PR interval
5. QRS axis
6. QRS duration in DI
7. QRS duration in DII
8. QRS duration in V1
9. QRS duration in V2
10. QRS duration in V6
11. QT interval in V5
12. QT interval in V2
13. Corrected QT interval in V5
14. Corrected QT interval in V2
15. T-peak T-end in V2
16. J T-end in V2
17. J elevation in V1
18. J elevation in V2
19. S duration in DI
20. S amplitude in DI
21. R duration in aVR
22. R amplitude in aVR
23. BrS Type 1 in any peripheral lead
24. QRS fragmentation

3 Learning architectures

Since Brugada is a relatively novel cardiac syndrome, few works are present in literature using machine learning. Indeed, the main focus has been the identification of type 1 Brugada pattern [13, 14, 15]. In this paper, instead, a novel approach based on physician-engineered features is proposed for performing BrS risk stratification.

To this aim, two models were built: a multi-layer perceptron (MLP) neural network [18] and a boosted decision tree (BDT) [19]. Then, they were compared with a naïve Bayes classifier, and a support vector machine (SVM), and a simple decision tree (DT).

MLP is an artificial neural network where multiple artificial neurons are connected to each other in a specific structure in order to learn complex, non-linear relationships between input and output data [20].

BDT exploits ensemble learning, based on multiple decision trees. A DT has a graph architecture, whose nodes perform a test on each single feature, by comparing it with a threshold. A sequence of tests ends to a terminal node (*leaf*), which represents a class label. The classification rules are given by the paths found in the tree.

4 BDT and MLP experiments

For training and assessing the quality of the proposed models, the database was randomly divided into two sets (training and test). The training set is required for the model parameter estimation. In order to evaluate the generalization properties, an independent set (test set) is needed, which means data of a single patient were used either during training or for testing. The algorithms were developed using Python.

The XGBoost library has been used for the BDT implementation. The best set of hyperparameters has required a five-fold cross-validation grid search (max tree depth equal to 3, and learning rate equal to 0.1. To avoid overfitting, at each iteration, the complexity of the model (i.e. the number of trees) is controlled by using the *early stopping*. This technique tracks the generalization error on an independent set, called *validation*, and stops the training when the performance on this set worsens for a predefined amount of iterations (here equal to 10). The validation set is made of samples drawn from 20% of the training set. Hence, both validation and test sets are not used for training. However, for determining the generalization properties, only the test is taken into account, because the validation set influences training, by deciding when to stop it. In order to evaluate the performance, the ROC AUC metric has been selected. This approach has determined the need for three estimators. Due to the hierarchical structure of the BDT algorithm, it was necessary to randomly select a great amount (80%) of the overall dataset for training, while the remaining 20% was used for testing purposes. Otherwise, the BDT model was not able to converge to a meaningful representation of the input space. Therefore, the training set was composed of 167 examples, and each test set was made of 42 samples.

The scikit-learn library has used for the MLP. The best set of hyperparameters was determined by a grid search based on a seven-fold cross-validation. Training exploited the Adam optimizer with an *adaptive* learning rate equal to 0.001, and a regularization term of 0.01. The database for the MLP model was normalized to zero-mean unit-variance (*z-score*) in order to avoid the impact of scaling on training. The final architecture is given by a single hidden layer composed of 50 neurons with ReLU activation functions. For sake of comparison, the same split into training and testing sets used for the BDT model (i.e. 80%-20%) was performed. Unfortunately, given the reduced amount of samples in the overall dataset, a so large percentage of samples in the training set was leading the model to overfitting data. Therefore, to overcome this problem, only 60% of the database was used for training. It gave a training set of only 125 samples.

All *NaN* values in the pre-processing phase were substituted with the feature median value. Also, the feature correlation matrix was computed to prune (redundant) features with an high correlation (> 0.9). However, no feature was pruned. It can be noted that data are more correlated in the *event* class than in the *control* class (see Fig. 2).

The classification quality was measured using the ROC and the Precision-Recall curves [21, 22], since using only accuracy could strongly bias the performance assessment. Indeed, in a class unbalanced scenario, as per the proposed database, a global high accuracy score could be reached even with a bad classification per-

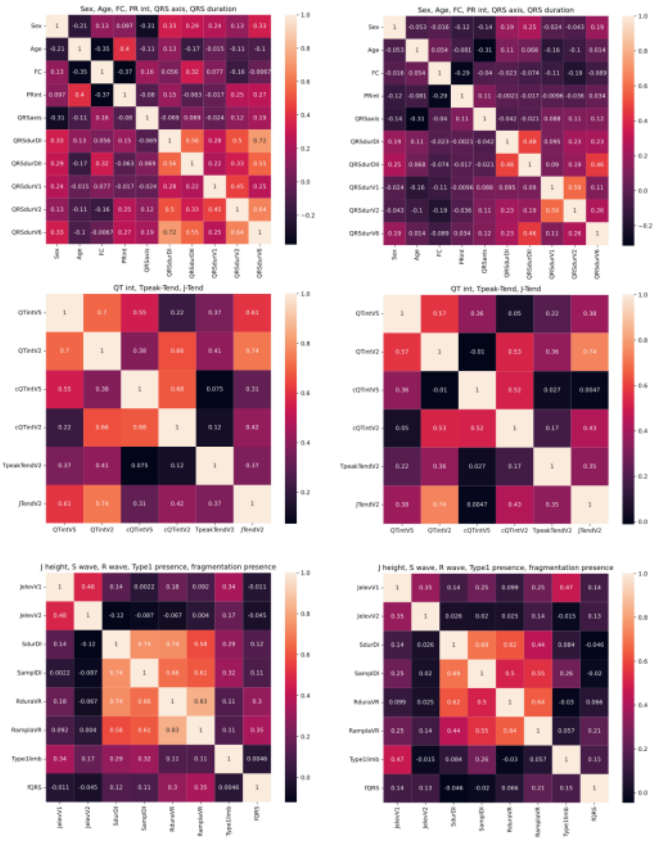

Fig. 2 Features correlation matrices for *event* (left) and *control* classes (right).

formance on the less numerous class. To this purpose, both positive and negative predictive values (PPV and NPV) , and F1-score were employed:

$$PPV = \frac{TruePositives}{TruePositives + FalsePositives} \tag{1}$$

$$NPV = \frac{TrueNegatives}{TrueNegatives + FalseNegatives} \tag{2}$$

$$F1 = \frac{TruePositives}{TruePositives + \frac{FalseNegatives+FalsePositives}{2}} \tag{3}$$

where the *Positive* and *Negative* refers to *event* and *control* classes, respectively.

Table 1 shows the accuracy, NPV, PPV, and F1-score relative to:

- The main model architectures trained on the original dataset.
- MLP with the optimized threshold.
- The main model architectures trained on a dataset where the *control* class samples were pruned to reach the same size of the positive class (reduction scenario).
- The main model architectures trained on a dataset where the *event* class examples were repeated to pair the size of the negative class (replica scenario).

Table 1 BDT and MLP performance comparison on different datasets

	Accuracy	NPV	PPV	F1-Score
BDT	0.9048	0.8947	1.00	0.67
MLP	0.8095	0.8333	0.50	0.27
MLP opt. threshold	0.6547	0.8979	0.3143	0.43
BDT reduced	0.5294	0.50	0.5384	0.64
MLP reduced	0.5757	0.60	0.5556	0.59
BDT replicated	0.5151	0.5238	0.50	0.43
MLP replicated	0.5909	0.5745	0.6316	0.47

4.1 Supplementary experiments

The previous models were also compared with a simple Decision Tree (DT), a Naïve Bayes (NB) classifier and a Support Vector Machine (SVM); Table 2 yields the results with regard to the evaluation metrics. The Bayesian optimization algorithm was used to find the best performing set of hyperparameters.

The DT, Naïve Bayes, and SVM accuracies were 84.2%, 82.3%, and 82.3%, respectively, without *z-score* normalization. Indeed, their accuracies are similar to the MLP (80.9%), but much worse than BDT performance (90.4%). On the contrary, the SVM F1-score got the minimum value of 0.18, which means the accuracy value cannot be trusted.

Table 2 Supplementary experiment performance

	Accuracy	NPV	PPV	F1-Score
DT	0.8420	0.8390	0.90	0.35
NB	0.8230	0.8570	0.5770	0.45
SVM	0.8230	0.8190	1.00	0.18

5 Discussion

Experiments have shown a high NPV, which is very important for the cardiologist since it means that a patient classified as negative (non-event) is likely to remain asymptomatic, i.e. not requiring an ICD implantation.

The BDT overwhelms the MLP neural network and non-neural approaches like the Naïve Bayes classifier, the SVM and the simple DT, whose F1-score is very low; indeed, it reached an accuracy of 90.4% and a F1-score value of 0.67. Also, BDT correctly classified all the *event* class examples (PPV = 100.0 %). All the dataset manipulation techniques worsened the classification. In general, the *control* class was almost perfectly learned in the case of the BDT model and of the MLPs trained on the original dataset. Change of the classification threshold in favor of the positive class did not yield an improvement in the positive predictive value but an increase in the negative predictive value, and an overall worsening in the classifier performance, as the predictive performance on the positive class cannot be considered reliable. Similar consideration can be performed for the models trained on the manipulated datasets, either the *replicated* or *reduced* ones.

The difference in the learning capabilities regarding the two classes could be correlated with the dataset class imbalance and the insufficient representation of the positive class, but could also be caused by the irrelevance of the measured features. Therefore, future steps in this analysis could be to change the features measured on the available ECG traces. Finally, the role and importance of each feature in classifying between *event* and *non-event* will be deepened in a future study.

The approach used in this work is based on feature engineering [23]. Future works will deal with deep learning techniques [24], like the convolutional neural networks [25], which only require raw inputs, e.g. ECG scans, because they implicitly extract features [26]. Their outcomes can be either directly classified or fed to more sophisticated neural networks for classification such as the Transformers [27]. Another matter of interest regards the use of a digitization algorithm to extract numerical signals from ECG scans for time-series analysis [28]. The feature-engineered approach, here proposed, can be considered as a baseline for the future comparison with more advanced techniques [29].

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