Defining the Predictive Ceiling of Electrogram Features Alone for Predicting Outcomes From Atrial Fibrillation Ablation

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Abstract

The aim of this study is to improve the prediction of long-term outcomes in patients with atrial fibrillation solely using electrogram (EGM) features. We developed three distinct models based on data from a cohort of $N = 561$ patients, each targeting different aspects of EGM analysis:

- ***Principal Component Analysis (PCA):*** *We applied PCA to analyze the variances of eigenvectors projecting more than a fixed threshold of the overall variance (15%). To identify common projection axes among these eigenvectors, we employed the k-means algorithm for clustering.*
- ***Auto Regressive:*** *This technique involves applying a bijective transformation to the coefficients, which are subsequently used as input for various machine learning classifiers, including Random Forest or Support Vector Classifier.*
- ***Feature Engineering:*** *We performed feature engineering by extracting voltage, rate, and shape similarity metrics from raw EGM (Electrogram) data.*

1. Introduction

Prior studies [1] have sought to forecast long-term outcomes following atrial fibrillation (AF) ablation by incorporating clinical variables, structural data, and intracardiac electrograms (EGM), but with only modest success. Our aim was to ascertain the predictive capacity of global electrogram data exclusively in AF patients, particularly with respect to acute and procedural success after ablation.

2. First approach - EGM Variance through clustering

2.1. Hypothesis

We hypothesized that explainable machine learning – using principal component analysis (PCA) combined with unsupervised clustering of EGM may reveal novel features that predict arrhythmia freedom after AF ablation.

2.2. Method

We studied N=561 AF patients (65.0±10.4 yrs , 27.6% female) in whom unipolar EGM were recorded at 64-sites.

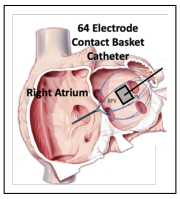

Figure 1. Basket Sensors to collect EGM

Our goal is to uncover concealed information within the variance of the Electrogram (EGM), which correlates with the long-term outcomes of patients. Throughout the remainder of this study, we will work with a set of $X_i \in R^{N\times T}$, where $N = 64$, and T denotes the number of data points in each time series for the i-th patient.

Initially, we analyze the patients independently to identify patterns (or deviations) in the variance of their data sets. Subsequently, by leveraging this knowledge, we seek linear projections that maximize (or minimize) the variance for one group in comparison to the other.

2.2.1. Standardizing the data and selecting the right frequency

To analyze the variance within patients' Electrogram (EGM) data, it is essential to standardize the dataset [2]. This is achieved through the following affine transformation:

$$\widetilde{X} = \frac{X - E[X]}{\sigma_X}$$

Once this standardization is completed, we observed that the sampling frequency significantly influences the analysis. We aimed to strike a balance between a high frequency (resulting in a large volume of data) and a low

frequency (resulting in a smaller volume of data). Consequently, for the remainder of our work, we opted for a frequency of 400 Hz, which represents a favorable compromise.

2.2.2. Singular Value Decomposition and Variance Selection

Various methods have been developed for studying dataset variance, with PCA [3] standing out as particularly efficient. Therefore, we decided to leverage the mathematical principles of PCA to serve our specific objectives. Our work commences with a Singular Value Decomposition (SVD) on the dataset:

$$X = USV^T$$

where $U^TU = I_N$, $V^TV = I_T$, $S \geq 0$, and $X \in R^{N\times T}$.

By definition, the columns of U are the output eigenvectors, and the columns of V are the input eigenvectors, with $S_{i,i}$ as the corresponding singular values.

In our specific case, we have $N = 64$ and $T = 400 \times 58$ (a frequency of 400 Hz for 58 seconds). Since our interest lies in forecasting the output, we will focus exclusively on the output eigenvectors, which are represented by U.

To identify significant eigenvectors, we examine the variance of the i-th eigenvector of U, denoted as $\Sigma_{i,i}$, and select only those with a substantial variance exceeding a threshold of 15% of the total variance:

$$J(X) = \{i \in N \,|\, \Sigma_{i,i} > 0.15\, V\}$$

where $V = \sum_j \Sigma_{j,j}$ represents the total variance.

Finally, for a patient with EGM X, we define the set of eigenvectors with significant explanatory power as:

$$\text{Eig}(X) = \{U_i \,|\, i \in J(X)\}$$

Each U_i represents an axis of projection where the variance along it is $\Sigma_{i,i}$. For instance, if we have:

$$X = \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_N \end{bmatrix} \quad U_i = \begin{bmatrix} u_{1,i} \\ u_{2,i} \\ \vdots \\ u_{N,i} \end{bmatrix}$$

Then the linear projection along the axis U_i is given by:

$$U_i^T X = \sum_{j=1}^{N} u_{j,i} x_j$$

Here, x_j represents an EGM time series, and by performing this linear combination using U_i, we create a new representation that captures strong explanatory power in terms of variance.

2.2.3. K-means Algorithm for the Eigenvectors

After computing $\text{Eig}(X)$ for each patient, we aggregate all the eigenvectors into two primary sets: $K_{\text{Recurrence}}$ and $K_{\text{Non Recurrence}}$.

$$K_{\text{Recurrence}} = \bigcup_{X \text{ patients recurrence}} \text{Eig}(X)$$

$$K_{\text{Non Recurrence}} = \bigcup_{X \text{ patients non recurrence}} \text{Eig}(X)$$

The subsequent step is quite intuitive: we aim to identify common directions within each set to distinguish projected variance based on group characteristics.

Given that we are working in high dimensions ($N = 64$), we sought an effective algorithm that converges quickly. The widely recognized K-means algorithm [4] emerged as a robust method for this purpose:

Algorithm 1 k-means

procedure KMEANS($(\vec{x_1}, ..., \vec{x_N}), K$)
  $(\vec{s_1}, ..., \vec{s_K}) \leftarrow SelectRandomSeeds((\vec{x_1}, ..., \vec{x_N}), K)$
for $k \leftarrow 1$ **to** K
do $\vec{\mu_k} \leftarrow \vec{s_k}$
  while stopping criterion has not been met **do for** $k \leftarrow 1$ **to** K
    for $n \leftarrow 1$ **to** K
    do $j \leftarrow$ **argmin** $\|\vec{\mu_i} - \vec{x_n}\|$
      $w_j \leftarrow w_j \cup \{\vec{x_n}\}$
    for $k \leftarrow 1$ **to** K **do**
      $\vec{\mu_k} \leftarrow \frac{1}{|w_k|} \sum_{\vec{x} \in \omega_k} \vec{x}$

return $\{\vec{\mu_1}, ..., \vec{\mu_K}\}$

2.2.4. Centroid Selection for Discrimination

After applying the K-means algorithm to the two data sets, $K_{\text{Recurrence}}$ and $K_{\text{Non Recurrence}}$, we obtain two sets of centroids: $C_{\text{Recurrence}}$ and $C_{\text{Non Recurrence}}$. These sets contain the common axes of projection for the two categories.

To determine which centroids discriminate the most from the others, we define a loss function for a given direction μ as follows:

$$L(\mu, X) = E\big[\mu^T\, XX^T\, \mu\big] + 2\, V\big[\mu^T\, XX^T\, \mu\big]$$

This function was designed to weigh both the expected value of the projected variance and the standard variation of it, with weights $(\frac{1}{3}, \frac{2}{3})$. Therefore, for a centroid $\mu \in C$,

we aim to maximize or minimize the following quantity:

$$L(\mu) = L(\mu, X_{\text{Recurrence}}) - L(\mu, X_{\text{Non Recurrence}})$$

Using the training sets $C_{\text{TRAIN Recurrence}}$ and $C_{\text{TRAIN Non Recurrence}}$, we define the Monte Carlo estimator

$$\hat{L}(\mu) = \hat{L}(\mu, X_{\text{Recurrence}}) - \hat{L}(\mu, X_{\text{Non Recurrence}})$$

with

$$\hat{L}(\mu, X_R) = \frac{1}{m} \sum_{X_R} \mu^T X X^T \mu + \frac{2}{m-1} \sum_{X_R} \left(\mu^T X X^T \mu - \overline{X_n}\right)^2$$

Following this procedure, we select the two centroids that maximize and minimize L:

$$\mu_{\text{Recurrence}} = \underset{\mu \in C_{\text{TRAIN Recurrence}}}{\text{argmax}} \quad L(\mu)$$

$$\mu_{\text{Non Recurrence}} = \underset{\mu \in C_{\text{TRAIN Non Recurrence}}}{\text{argmin}} \quad L(\mu)$$

Finally, we construct two directions where the projected variance should be maximal (resp. minimal) for the Recurrence Group vs. the Non Recurrent one.

2.3. First Results

A total of $N = 390$ patients experienced freedom from arrhythmia (AF and AT) for less than one year after the blanking period, constituting the "Freedom" group. Additionally, $N = 171$ patients had a recurrence, forming the "Recurrence" group.

We then computed and plotted the projected variance from Principal Component Analysis (PCA) of AF EGM in both the recurrence and freedom groups. This analysis allows us to evaluate the discriminatory power of one group versus the other.

When examining the projected variance for the "Freedom" group (see Figure 2), we observe that it serves as an effective means of classifying patients based on their labels. Notably, the variance was higher in the "Recurrence" group compared to the "Freedom" group ($\mu = 37.1\% \pm 21.3\%$ vs. $\mu = 29.5\% \pm 15.9\%$ of the global variance, median p-value = 0.21 for the Kolmogorov-Smirnov test) when considering the average distribution across 50 independent training/testing iterations.

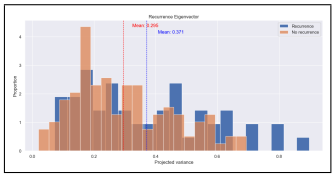

Figure 2. Proportion of the projected variance for an eigenvector of the Recurrence group

The analysis of the projected variance distribution revealed the presence of small clusters among patients in the "Recurrence" and "Freedom" groups. These clusters represent potential patterns that can be leveraged as relevant inputs for a neural network aimed at predicting a patient's state.

2.4. Conclusion for Variance Clustering

In summary, the application of PCA and unsupervised machine learning techniques provided valuable insights into the characteristics that can predict outcomes following AF ablation. These methods shed light on how Electrogram (EGM) data carry patient-specific information.

However, it's important to note that the projected variance along eigenvectors, while informative, may not provide a robust and efficient means of forecasting recurrence one year post-ablation. As a next step, we propose the exploration of more elaborate non-linear classifiers, coupled with feature engineering, to enhance the accuracy of long-term outcome predictions. Specifically, we intend to investigate Auto-Regressive models in combination with complex classifiers.

This path represents a promising direction for further research and may offer more accurate forecasts of patient outcomes following AF ablation.

3. A More Standard Approach - ML Classifier

3.1. Hypothesis

Our hypothesis is that employing explainable machine learning, using standard classifiers combined with auto-regressive models and handcrafted features extracted from EGM data, can provide additional information to complement PCA-based predictions, enhancing the ability to predict arrhythmia freedom following AF ablation.

3.2. General Classifiers

A variety of classifier types can be employed for this type of feature set, including ensemble learning methods, linear classifications, binary classifications, and more. We have explored multiple classifier types, including Random Forest, Support Vector Machine (SVM), Adaboost, Naive Bayes, and Logistic Regression. Among these, we aim to identify the most robust classifier based on the Area Under the Curve (AUC) score metric.

3.3. Method

Utilizing the same dataset (with $N = 561$ patients), we aim to construct a robust classifier capable of predicting long-term outcomes using auto regressive models. Although the majority of patients have EGM data from the left atrium ($N_{LA} = 517$), there are $N_{RA} = 39$ patients

with EGM data exclusively from the right atrium. To account for this variation, we introduce an additional categorical column to the $64 \times (\alpha_1, \alpha_2, \sigma^2)$ dataset, with values in $\{0, 1\}$ indicating the atrium area from which the EGM data originate.

With our dataset prepared and classifier models selected, we proceed to determine the optimal set of hyperparameters for each model. This is achieved through a Grid Search Cross-Validation approach, which combines grid search with cross-validation to ensure robust hyperparameter selection.

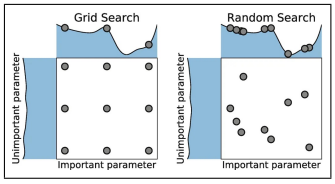

Figure 3. Grid Search Representation in a 2D space

3.4. Results

The initial phase involves the selection of the "best" model, based solely on the training set. To determine the relative robustness of one classifier over another, we implement a training-validation strategy utilizing the first training set. The results, in terms of the Area Under the Curve (AUC) metric for hyperparameters fitted using a grid search cross-validation approach, are presented in Figure 4.

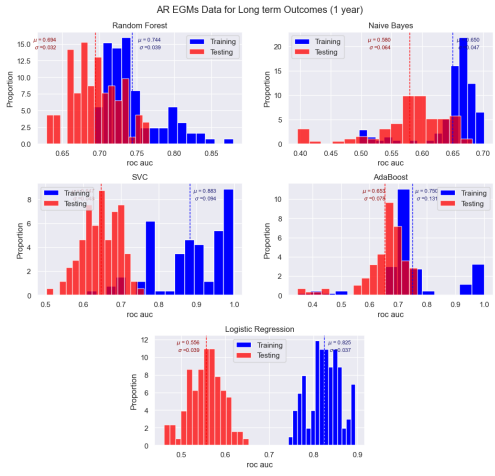

Figure 4. Comparison of the different classifiers in term of AUC-metric

Following the results presented in Figure 4, it is evident that the Random Forest Algorithm emerges as the most robust classifier among the five considered, yielding an average Area Under the Curve (AUC) of $AUC_{\text{average}} = 66.8\%$. Surprisingly, the Support Vector Machine Classifier, a relatively simple linear classifier, ranks second in terms of AUC, nearly matching the performance of the Naive Bayes classifier.

However, it is noteworthy that even with the Random Forest being the best-performing classifier, the AUC remains relatively low and falls short of our initial expectations based on the hypothesis.

With the training set learned, we proceed to calculate the results for the Holdout set with all classifiers, even though we have already chosen the Random Forest as our preferred classifier.

AR Scores for Long Term Outcomes (1y)					
Classifier	RF	SVC	NB	Boost	LR
AUC	0.71	0.63	0.55	0.62	0.53
Feature Engineering					
AUC	0.72	0.6	0.49	0.33	0.51

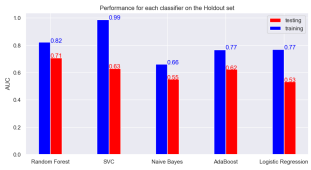

Figure 5. Holdout results in term of AUC-metric

An Area Under the Curve (AUC) of 0.71 achieved by the Random Forest classifier indicates that the model has indeed captured characteristic information within the Electrogram (EGM) data. However, it falls short of achieving perfect classification of patients with recurrence.

3.5. Conclusion

In conclusion, our exhaustive analysis of electrogram data in patients with atrial fibrillation (AF) provides limited predictive value for outcomes following AF ablation. The application of PCA-Clustering and AR-Classifier revealed features that could predict AF ablation outcomes with only modest success. This study sets a certain ceiling for electrographic predictors, suggesting that either sophisticated feature engineering or the incorporation of alternative data sources is necessary to improve prediction.

References

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