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NONNEGATIVE MATRIX FACTORIZATION FOR NONINVASIVE PREDICTION OF CATHETER ABLATION OUTCOME IN PERSISTENT ATRIAL FIBRILLATION

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ABSTRACT

Despite the increasing popularity of catheter ablation (CA) for treating atrial fibrillation (AF), the identification of patients who would actually benefit from the therapy remains a challenging open issue. This study aims at noninvasively predicting CA outcome by quantifying the spatio-temporal variability of the atrial activity (AA) signal measured on the standard 12-lead electrocardiogram. The normalized mean square error (NMSE) between consecutive atrial segments and their principal component approximations is computed for each lead, as a recent noninvasive index of AF organization. In the present work, the multilead NMSE array is decomposed by means of a nonnegative matrix factorization (NNMF) with two different initializations. The reconstruction error between the original NMSE matrix and its low-rank NNMF approximation is taken as a classification feature. A dataset of persistent AF patients undergoing CA reveals that the proposed feature is able to predict the therapy outcome with a notably higher level of statistical significance than recent single-lead indices.

Index Terms— Atrial fibrillation, catheter ablation, electrocardiogram, nonnegative matrix factorization, principal component analysis.

1. INTRODUCTION

Affecting up to 10% of the adult population over 80 years of age, atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice. Often referred to as "the last great frontier of cardiac electrophysiology", this supraventricular arrhythmia is characterized by the generation and propagation of irregular electrical activation patterns throughout the atrial myocardium, inducing an ineffective atrial contraction and an increased risk of stroke due to blood stagnation in the atria. Radiofrequency catheter ablation (CA) is becoming a first-line therapeutic option for persistent AF treatment, yet inconsistent success rates are reported by clinical centers [1]. This has motivated a number of attempts of an a priori selection of positive responders to CA, thus avoiding unnecessary and/or dangerous procedures.

Among the studies aiming at CA outcome prediction, special emphasis has been laid on the analysis of the 12-lead electrocardiogram (ECG), a standard noninvasive tool in clinical practice. The fibrillatory wave amplitude measured in one lead (V_1 or II) is a valid predicting feature [2] but, as shown in [3], its manual computation is prone to errors and lacks robustness to the intrinsic variability of the ECG signal across different leads. More recently, the AF spatio-temporal complexity measure proposed in [4] computes the normalized mean square error (NMSE) between the original ECG and its reduced rank approximation in one lead only. This single-lead index can noninvasively quantify the level of AF organization according to Konings' criteria for endocardial recordings [5], but is unable to distinguish successful from failing CA procedures [6].

This work takes a step forward in the noninvasive spatio-temporal analysis of AF and its relation with CA outcome by taking into account the variability of the atrial signal across ECG leads. To this end, the NMSE index data are stored in the form of a matrix with nonnegative elements, and subsequently approximated by a nonnegative matrix factorization (NNMF) with reduced rank. Experimental results on a database of persistent AF ECG recordings demonstrate that the reconstruction error of this approximation presents clinical value for patient selection, as it is able to successfully predict CA outcome before the procedure with a statistical significance level well over that of single-lead indices. NNMF has extensively been used in areas as diverse as text processing, data mining and image processing, among other application domains [7]. To our knowledge, the present work reports the first application of this matrix decomposition technique in ECG signal processing.

2. AF SPATIO-TEMPORAL COMPLEXITY

This section introduces the quantitative, noninvasive measure of AF spatio-temporal complexity proposed in [4]. The starting point of this measure is the segmentation, mean correction and concatenation of TQ intervals, thus isolating the atrial activity (AA) contribution to the standard ECG while neglecting other sources of interference, such as ventricular activity and noise (Fig. 1). We denote $y_\ell(t)$ the AA signal at sample instant t on lead ℓ, $1 \leq \ell \leq L$, with $L = 12$ the number of ECG leads. Thus, the resulting AA signal matrix is:

$$\mathbf{Y} = [\mathbf{y}(1), \mathbf{y}(2), \ldots, \mathbf{y}(N)] \tag{1}$$

where $\mathbf{y}(t) = [y_1(t), \ldots, y_L(t)]^{\mathrm{T}}$ and N denotes the number of samples in the concatenated TQ segments; $(\cdot)^{\mathrm{T}}$ is the transpose operator. The AF spatio-temporal organization measure put forward in [4] is based on the similarity between the principal subspaces of the AA signal along consecutive time intervals, and can be summarized as follows. Each row of $\mathbf{Y}$ is split into a fixed number S of equal-length segments. Every segment is composed of $N_S = [N/S]$ samples, so that $\mathbf{Y} = [\mathbf{Y}^{(1)}, \mathbf{Y}^{(2)}, \ldots, \mathbf{Y}^{(S)}]$, with $\mathbf{Y}^{(s)} = [\mathbf{y}((s-1)N_S+1), \mathbf{y}((s-1)N_S+2), \ldots, \mathbf{y}(sN_S)]$, $s = 1, \ldots, S$. Each segment is then decomposed by the principal component analysis (PCA) according to the linear model $\mathbf{Y}^{(s)} = \mathbf{M}^{(s)}\mathbf{X}^{(s)}$, $s = 1, 2, \ldots, S$. The principal components (PCs) $\mathbf{X}^{(s)}$ are stored in decreasing order of variance. The columns of the mixing matrix $\mathbf{M}^{(s)}$ represent the principal directions, and quantify the relative spatial contribution of the PCs to the ECG leads. The n dominant directions of a reference segment $\mathbf{Y}^{(r)}$ are stored in the first n columns

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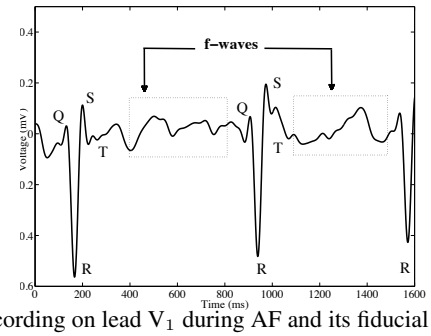

Fig. 1. ECG recording on lead V_1 during AF and its fiducial points. Dotted boxes highlight the TQ intervals whose concatenation forms the AA signal matrix $\mathbf{Y}$ in eqn. (1).

of matrix $\mathbf{M}_n^{(r)}$. The AA signal in segment $s \neq r$ is then projected onto the subspace spanned by $\mathbf{M}_n^{(r)}$, yielding:

$$\hat{\mathbf{Y}}_n^{(s,r)} = \mathbf{M}_n^{(r)}[\mathbf{M}_n^{(r)\mathrm{T}}\mathbf{M}_n^{(r)}]^{-1}\mathbf{M}_n^{(r)\mathrm{T}}\mathbf{Y}^{(s)}. \quad (2)$$

We can consider $\hat{\mathbf{Y}}_n^{(s,r)}$ as the estimation of the AA signal segment $\mathbf{Y}^{(s)}$ function of $\mathbf{Y}^{(r)}$. The normalized mean square error $\mathrm{NMSE}_{\ell,n}^{(s,r)}$ between the original sth-segment signal $y_\ell^{(s)}(t)$ and its reconstruction $\hat{y}_{\ell,n}^{(s,r)}(t)$ on the ℓth-lead is computed as:

$$\mathrm{NMSE}_{\ell,n}^{(s,r)} = \frac{\sum_{t=1}^{N_S}[y_\ell{}^{(s)}(t) - \hat{y}_{\ell,n}^{(s,r)}(t)]^2}{\sum_{t=1}^{N_S}[y_\ell^{(s)}(t)]^2}. \quad (3)$$

In [4], the average of $\mathrm{NMSE}_{\ell,n}^{(s,r)}$ values over all segments quantifies AF organization noninvasively in V_1 ($\ell = 7$), as it typically shows the best atrial-to-ventricular amplitude ratio. Interestingly, this single-lead index seemed to be closely related to Konings' criteria for AF complexity classification based on endocardial signals, but it did not provide a significant predictive value for CA outcome [6].

3. ANALYSIS OF THE NMSE MATRIX

The present work aims at a more elaborate analysis of the NMSE index defined in eqn. (3). Processing the NMSE data with more sophisticated techniques is expected to gather further subtle information about AF complexity that is otherwise neglected in the single-lead analysis. The key idea is to exploit the spatial diversity inherent to the multilead ECG recording. As a result of this diversity, NMSE indices of different leads are expected to share some common underlying factors that may be estimated by suitable signal decomposition techniques. The reconstruction error between the original NMSE indices and their truncated decomposition can be used as a measure of the overall complexity of the AA signal across the whole 12-lead ECG and not just for a single lead. Since, by definition, NMSE values cannot be negative, a nonnegative matrix factorization (NNMF) [8] appears as a natural choice for this particular scenario.

3.1. Nonnegative Factorization of the NMSE Matrix

More specifically, the NMSE values can be arranged into an $\big(L \times \beta\big)$ matrix $\mathbf{A}$, where $\beta = S(S-1)$, with nonnegative elements by storing $\mathrm{NMSE}_{\ell,n}^{(s,r)}$ in entry $[\mathbf{A}]_{\ell,(r-1)(S-1)+(s-1)}$ if $r < s$ or in entry $[\mathbf{A}]_{\ell,(r-1)S+(s-1)}$ if $r > s$, for $r, s = 1, 2, \ldots, S$, $s \neq r$. Matrix $\mathbf{A}$ contains the NMSE for all leads over all segments, using consecutively every segment as a reference. To approximate these multilead data via low-rank subspace decompositions while preserving nonnegativity, we resort to a NNMF, which yields the approximate rank-R factorization:

$$\mathbf{A} \approx \mathbf{WH} \quad (4)$$

where $\mathbf{W}$ and $\mathbf{H}$ with size $(L \times R)$ and $\big(R \times \beta\big)$, respectively, are the nonnegative factors, i.e., matrices with nonnegative entries. These can be computed as the minimizers of the objective function:

$$\Psi(\mathbf{W}, \mathbf{H}) = \|\mathbf{A} - \mathbf{WH}\|_{\mathrm{F}}^2 \quad (5)$$

where $\|\cdot\|_{\mathrm{F}}$ stands for the Frobenius norm. This minimization can be carried out through an alternating least squares (ALS) algorithm [8]. Criterion (5) is also a measure of approximation performance. Thus, the root mean square residual (RMSR) between $\mathbf{A}$ and its low-rank approximation (4), defined as:

$$\mathrm{RMSR} = \sqrt{\frac{\Psi(\mathbf{WH})}{L\beta}} \quad (6)$$

can naturally be introduced as a multilead measure of the AA spatio-temporal complexity as reflected on the NMSE array.

3.2. NNMF Rank Selection

Some issues must carefully be taken into account before applying NNMF, namely, the choice of the approximation rank R and the initialization of the nonnegative factors $\mathbf{W}$ and $\mathbf{H}$. An appropriate decision on R is critical in practice, and it is very often problem-dependent [8]. In our study, as we can think about $\mathbf{WH}$ as a compressed form of $\mathbf{A}$, we have decided to strongly reduce $\mathbf{A}$ dimensionality and perform a rank-2 approximation. Indeed, the decomposition has been computed for every value of R ranging from 1 to $(L-1)$ for both initializations explained in the sequel. Experimental evidence reveals that $R = 2$ is the minimum rank value such that statistically significant differences between the categories examined can be observed; hence, the choice of this value to carry out data decomposition.

3.3. NNMF Initialization

Another important point is that NNMF methods are iterative, and thus sensitive to initialization of $\mathbf{W}$ and $\mathbf{H}$. Nearly all NNMF algorithms use random initializations that are simple but often provide unsatisfactory performance. A good initialization can improve their speed and accuracy, as it can sidestep some of the problems linked to convergence to spurious local minima [7]. Our investigation has considered two algorithms returning the initial matrices $\mathbf{W}_0$ and $\mathbf{H}_0$ as outputs. The first algorithm searches for the two leads (rows) characterized by the maximum mean square value (MSV) of the NMSE index in $\mathbf{A}$. This choice is somewhat inspired by the maximum-variance formulation of PCA. Just as PCA achieves the best rank-R subspace approximation by maximizing the variance of the principal components, one could expect that the rows of $\mathbf{A}$ with maximal MSV may lie not too far from the NNMF components in $\mathbf{H}$ minimizing the objective (5). Under these assumptions, such rows have been selected from $\mathbf{A}$ to form $\mathbf{H}_0$. Then, the initial value of the factor $\mathbf{W}$ is returned by the ALS algorithm under the positivity constraint as:

$$\mathbf{W}_0 = \mathbf{A}\mathbf{H}_0^{\mathrm{T}}\big(\mathbf{H}_0\mathbf{H}_0^{\mathrm{T}}\big)^{-1} \quad (7)$$

and then setting all $\mathbf{W}_0$ nonnegative elements to zero.

The second initialization strategy stems from the "concept vector" notion proposed in [9]. The idea is to compress the data by partitioning them into clusters and use their centroids to form the unknown matrices. This approach becomes quite time-consuming when processing high-dimensional data, which has led to several

clustering variants looking for a trade-off between compression and preservation of the most essential data. In keeping with [10], we exploit the singular value decomposition (SVD) of $\mathbf{A}$, given by $\mathbf{A} = \mathbf{USV}^{\mathrm{T}}$, to form R-dimensional centroid basis vectors. In particular, we apply the Euclidean k-means algorithm on the β vectors of the first R orthogonal right-singular vectors in $\mathbf{V}$ and we identify R bi-dimensional clusters. Such a strategy allows a considerable reduction in complexity as a lower dimensional matrix is processed and successive operations are computationally less expensive. Finally, we locate columns of $\mathbf{A}$ corresponding to clusters of $\mathbf{V}$ and determine their centroids, which then form the columns of $\mathbf{W}_0$. Thanks to this grouping action, a sort of temporal quantization of AF information carried by every segment is fulfilled, unlike the first initialization proposed above, in which a spatial selection of ECG leads is accomplished instead. Matrix $\mathbf{H}_0$ is finally output as:

$$\mathbf{H}_0 = \left(\mathbf{W}_0^{\mathrm{T}}\mathbf{W}_0\right)^{-1}\mathbf{W}_0^{\mathrm{T}}\mathbf{A}. \tag{8}$$

4. EXPERIMENTAL ASSESSMENT

4.1. Experimental Protocol and ECG Preprocessing

This study examines 21 persistent AF patients treated by CA at the Cardiology Department of Princess Grace Hospital in Monaco. Preprocedural standard 12-lead ECGs were acquired at a 1-kHz sampling rate with the aid of Prucka Cardiolab$^{\mathrm{TM}}$ and Biosense CARTO$^{\mathrm{TM}}$ electrophysiological measurement systems. AF procedural termination was defined as the conversion either directly to sinus rhythm or intermediate tachyarrhythmia, directly by ablation or by CA followed by electrical cardioversion. Postoperative outcome was observed within a 3-month blanking period. According to this short-term criterion, 17 successful procedures were accomplished. For every patient, the ECG recording is first processed by a fourth-order zero-phase Chebyshev bandpass filter with -3-dB cutoff frequencies of 0.5 Hz and 30 Hz to suppress baseline wander and high frequency noise (e.g., power line interference, myoelectric artifacts) outside the AF dominant frequency range. Then, R-peak time instants are estimated on V_1 by Pan-Tompkins' algorithm; an improved version of Woody's method allows detection of Q wave onset and T wave offset, from which TQ segments are concatenated giving rise to the AA signal matrix defined in Sec. 2.

4.2. Statistical Analysis and Results

Output parameters are computed using $S = 4$ segments, and PCA approximation has been performed by retaining the first spatial topography ($n = 1$). They are expressed as mean $\pm$ standard deviation for each of the two patient classes in the database; these classes are referred to as "AF termination" and "non AF termination" by CA according to the above protocol. After testing normal distribution by Lilliefors' test, differences between the two groups of patients are statistically validated by an unpaired Student's t-test if data follow a Gaussian distribution, a two-sample Kolmogorov-Smirnov test otherwise, under a confidence level $\alpha = 0.05$. Such results are shown in Table 1, besides p values of each unpaired test. Classification performance is quantified by the receiver operating characteristic (ROC) curve parameters, namely, the area under curve (AUC) and the related p-value, based on the maximization of sensitivity and specificity, i.e., the rate of true positives and true negatives, respectively. The AUC index quantifies the overall ability of the parameter under test to discriminate between the classes examined: the closer to unity its value, the more accurate its predictive power. All values are reported in Table 3, assuming again a confidence level $\alpha = 0.05$. Evaluation indices are computed for both NNMF initialization methods described in Sec. 3.3, yielding $(\mathrm{RMSR})_{\mathrm{MSV}}$ and $(\mathrm{RMSR})_{\mathrm{SVD}}$, respectively. Tables 1 and 3 also draw a comparison with previous studies. Special attention is paid to the single-lead descriptor of AF organization developed in [6, 11], i.e., the average NMSE on lead V_1 as summarized at the end of Sec. 2. Moreover, the f-wave amplitude, originally proposed as a CA-outcome predicting feature but obtained manually in [2], is automatically computed as in [3] both on V_1 ($D(\mathrm{V}_1)$) and from all standard ECG leads ($\overline{D}_{12}$). The inter-lead weighted mean $\overline{\mu_1}$ proposed in [11] is also compared with our parameter with respect to its accuracy in classifying patients and characterizing AF. Finally, NNMF is evaluated by comparing its performance with PCA rank-2 decomposition of the same input matrix and subsequent estimation evaluation by NMSE ($(\mathrm{NMSE})_{\mathrm{PCA}}$).

Table 1. Interpatient statistical analysis

	AF termination	Non AF termination	p-value
$(\mathrm{RMSR})_{MSV}$	4.84 ± 5.13	6.54 ± 3.17	0.040
$(\mathrm{RMSR})_{SVD}$	4.83 ± 5.13	6.54 ± 3.17	0.040
$(\mathrm{NMSE})_{\mathrm{V}_1}$	82.7 ± 22.4	77.1 ± 33.7	0.683
$\overline{D}_{12}$	0.035 ± 0.016	0.018 ± 0.010	0.034
$\overline{\mu_1}$	61.59 ± 16.52	83.86 ± 14.27	0.040
$(\mathrm{NMSE})_{\mathrm{PCA}}$	99.4 ± 0.728	98.8 ± 0.756	0.350
$D(\mathrm{V}_1)$	0.072 ± 0.021	0.053 ± 0.021	0.128

4.3. Discussion

The results reported above prove that both RMSR-based classifiers are effectively capable of discriminating between the two categories of patients before ablation. Table 1 shows that higher index values are correlated with a lower probability of a successful procedure, in the same way as the multilead NMSE-based classifiers of [11]. By contrast, the AF complexity as measured by the single-lead NMSE of [4] (recalled in Sec. 2) does not seem to be linked to CA outcome, as already observed in [6]. These results also demonstrate the superiority of the proposed multilead index over single-lead approaches. Differences in CA outcome are statistically significant and p value is comparable with that of index $\overline{D}_{12}$. However, unlike our RMSR-based descriptors, there is no evidence of its ability to characterize AF organization by exploiting f-waves properties. As far as $(\mathrm{NMSE})_{\mathrm{PCA}}$ is concerned, we can remark that AA estimation by PCA does not help retrieving significant differences between the two classes, and data nonnegativity is not preserved at all in our specific application, in contrast with NMSE definition.

NNMF has proved to be a suitable tool for the compression of the input matrix, as only ECG electrodes which can actually help patients' classification have been selected during the initialization step. If we look at $\mathbf{W}_0$ as the set of nonnegative bases where to project our data and $\mathbf{H}_0$ as the corresponding coefficients, we can study directions of interaction of $\mathbf{W}_0$ factors with the ECG observations through matrix $\mathbf{B} = \left(\mathbf{W}_0^{\mathrm{T}}\mathbf{W}_0\right)^{-1}\mathbf{W}_0^{\mathrm{T}}$ in eqn. (8), whose elements $(b_{ij}), i = 1, \ldots, R, j = 1, \ldots, L$ are not necessarily positive and weigh the influence of the jth lead over the ith nonnegative factor; large positive values denote a more significant contribution over the leads of interest. To this aim, such matrix has been computed for each patient and the number of occurrences of (b_{ij}) having positive values per class has been analyzed, as shown in Table 2. The higher the numerical entry in Table 2, the higher the number of patients whose AF pattern is better characterized by the nonnegative factor on the lead associated with the entry itself. Subscripts SUCC and FAIL refer to successful and failing procedures respectively, whereas MSV and SVD refer to NNMF initialization methods. NF_1 and NF_2 represent the nonegative factors output by the decomposition, namely, the first and the second row of $\mathbf{B}$. Their relation with the observations is quantified by the parameter ϵ in Ta-

Table 2. Occurrences of $\mathbf{B}$ positive weights

		I	II	III	aV_R	aV_L	aV_F	V_1	V_2	V_3	V_4	V_5	V_6	ϵ
$(\mathbf{B}_{\mathrm{MSV}})_{\mathrm{SUCC}}$	NF_1	9	9	8	7	8	9	9	8	5	5	7	6	12/8
	NF_2	7	6	8	7	7	6	9	9	9	9	9	9	12/8
$(\mathbf{B}_{\mathrm{MSV}})_{\mathrm{FAIL}}$	NF_1	0	1	2	0	2	2	3	1	2	1	0	1	9/1
	NF_2	4	4	2	4	3	4	2	3	3	3	4	4	12/3
$(\mathbf{B}_{\mathrm{SVD}})_{\mathrm{SUCC}}$	NF_1	10	6	8	9	8	6	4	8	6	7	9	8	12/7
	NF_2	4	9	11	9	10	11	11	12	10	10	7	10	12/10
$(\mathbf{B}_{\mathrm{SVD}})_{\mathrm{FAIL}}$	NF_1	0	0	2	0	2	1	3	2	2	1	1	0	8/1
	NF_2	4	4	2	4	3	3	1	2	2	4	4	4	12/3

ble 2, defined as the ratio between the number of leads with at least one positive weight and the average value of all occurrences over the row considered. Its value ranges between 0 (there are no leads presenting (b_{ij}) positive values) and ϵ^*, which equals the ratio between L and the number of patients per class, namely, $12/14$ if CA is successful, $12/7$ otherwise (all coefficients associated with each lead are positive in each patient). It is worth noting that several leads recur in almost all patients experiencing AF termination by CA, and there is no preferential influence by any of the nonnegative components over ECG observations. This results in ϵ values close to unity, as the high average number of positive weights' occurrences is balanced by a fairly uniform contribution to all leads from each basis factor. On the other hand, failing procedures are generally depicted by NF_1 through fewer leads, as some of them do not participate at all to CA outcome prediction (e.g., I,II, aV_R), regardless of the initialization modalities. On the contrary, NF_2 always contributes to some leads in all patients, for instance, I,II, aV_F, V_5, V_6. This result demonstrates that AF dynamics in ineffective procedures can be described by a smaller subset of leads, and it is confirmed by higher ϵ values. Some electrodes probably have a more important role in the description of AF maintenance thanks to their proximity to the sources of asynchronous rhythm, which are still active in patients not effectively treated by CA. This experiment points out the improvement made by NNMF not only on standard PCA, but also on $\overline{\mu_1}$. Indeed, our initialization methods enable an a priori selection of data to be processed, discarding all redundant and noisy elements deriving from inter-lead relationships or misleading contributions due to incorrect ECG acquisition (e.g., loose or disconnected leads). Actually, a spatial prefiltering process is performed, in contrast with $\overline{\mu_1}$, whose leveraging coefficients rather quantify AF temporal dispersion along the recording on each lead, regardless of their location. Finally, concerning $D(\mathrm{V}_1)$, even if numerical results are consistent with those reported in previous works using manual measures [2], they are not statistically significant, and the spatial variability typical of multilead ECG recordings is neglected as well. AUC values in Table 3 underline the ability of our RMRS-dependent descriptors to distinguish between successful and failing procedures, with a performance comparable with that of classical CA outcome predictors.

Table 3. CA outcome classification prediction performance

	AUC	p-value
$(\mathrm{RMSR})_{\mathrm{MSV}}$	0.79	$4 \cdot 10^{-3}$
$(\mathrm{RMSR})_{\mathrm{SVD}}$	0.79	$4 \cdot 10^{-3}$
$(\mathrm{NMSE})_{\mathrm{V_1}}$	0.48	$5 \cdot 10^{-1}$
$\overline{D_{12}}$	0.84	$4 \cdot 10^{-4}$
$(\mathrm{NMSE})_{\mathrm{PCA}}$	0.75	$2 \cdot 10^{-2}$
$\overline{\mu_1}$	0.86	$7 \cdot 10^{-5}$
$D(\mathrm{V}_1)$	0.75	$2 \cdot 10^{-2}$

5. CONCLUSIONS AND FURTHER WORK

This work has put forward a more elaborate analysis of AF spatio-temporal complexity through the NNMF of the NMSE array. Such a decomposition explicitly takes into account mutual correlations between ECG leads and identifies the most essential components of the data while preserving their nonnegativity. The reconstruction error of the low-rank NNMF approximation can successfully perform the noninvasive prediction of CA outcome before ablation, thus establishing the clinical value of this surface measure of AF organization as a therapy outcome predictor. Interesting open questions concern the rank selection for the NNMF decomposition and the links of the proposed predictor with recent indices exploiting the ECG multilead character, as well as the application of our method to further ECG-derived features (e.g., AA amplitude).

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