A Machine Learning Approach for LQT1 *vs* LQT2 Discrimination

Rémi Dubois[1,4], Fabrice Extramiana[2], Isabelle Denjoy[2], Pierre Maison-Blanche[2],
Martino Vaglio[3], Pierre Roussel[4], Fabio Babilini[3], Antoine Leenhardt[2]

[1]LIRYC, Université de Bordeaux, France   [2] Hôpital Bichat, Paris,
France [3]Amps IIc, NewYork, NY, USA   [4]SIGMA lab, Paris, France

Abstract

Long QT syndrome (LQT) is a congenital disease caused by a mutation of genes that leads to a distortion and a prolongation of the T-wave on standard ECG.

The present study proposes an algorithm to automatically discriminate between patients with type 1 or type 2 LQT syndrom. The core of the method is the modeling of the T-wave recomputed on its principal lead by a single parameterized function named Bi-Gaussian Function (BGF). From all the features computed from this model, a statistical analysis was performed to select only the most relevant ones for the discrimination. A classifier was then designed through a Linear Discriminant Analysis (LDA).

A database composed of 410 LQTS patients whose genotype is known was used to train the classifier and evaluate its performances.

1. Introduction

Long QT syndrome (LQT) is a congenital disease characterized by an abnormal repolarization process. It is caused by the mutation of several genes, all of which encoding cardiac ion channels. 13 LQT types associated to different gene combinations were identified; all of them resulting in the distortion and the prolongation of the T-wave, as visualized on the body surface ECG. Type 1 and type 2 LQT are the most common forms and are respectively related to the slow and to the fast components of the delayed rectifier potassium current. Genotype has proved to be important for clinical management of LQTS patients [1]. However, the turnaround time may be long and T-wave morphology phenotyping remains critical at bedside to discriminate between LQTS types.

The present work aims at designing a classifier that automatically associates to LQT 12 lead ECG records the probability of belonging to type 1 or type 2. The proposed methodology is based on a machine learning approach to model the T-wave morphology, allowing the extraction of various features; a statistical analysis is then performed to select the most relevant finally used for the classification task.

2. Data

The database consists in 410 records of 12 lead ECGs, 266 carried out on type 1 LQT patients and 144 on type 2 LQT patients with genotype confirmed diagnostic. 196 records (124/72), randomly chosen, were picked up for the feature selection process and the classifier design both presented below. The remaining 214 records were used for the estimation of the performances.

3. Methods

Since LQT syndrome is associated to an abnormal repolarization process, the proposed study focuses on the T wave analysis: the first step, detailed in the next section, is the computation of features for its characterization. Then, a statistical analysis expounded in section 3.2 is performed to select the most relevant features for classification; and at last, the classifier (section 3.3) is designed with the selected features. The overall process from the feature extraction to the classifier design is illustrated on Figure 1.
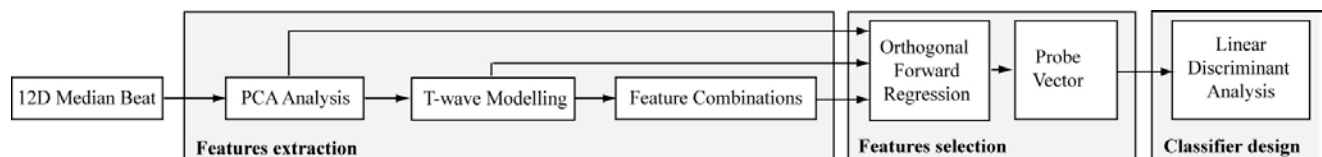

Figure 1. Overview of the classifier design. From a median beat, several features are computed on the T-wave from a PCA analysis and a parameterized model; then a statistical analysis is performed to select only the relevant features for the classifier designed.

3.1. ECG processing, feature extraction

Time averaging and lead reduction

A standard 12D ECG record usually encompasses a long strip of data. In order to gather the information onto a minimal representation, both the number of beats (usually several tens) and the number of leads (12 leads) are reduced. To that end, a median beat on each lead is computed (CalECG, Amps llc, NY, US). Then, the spatial reduction from 12 leads to 1 is performed using a vectorcardiographic analysis of the T wave [2, 3]. In vectorcardiography, the T-wave is represented in the 8-dimensional space in which each dimension corresponds to one independent lead (I, II, V1 to V6). The 'principal axis' of the T wave is computed using Principal Component Analysis (PCA) and is used as a virtual lead onto which the T-wave representation is projected to obtain a 1-D signal (Figure 2).
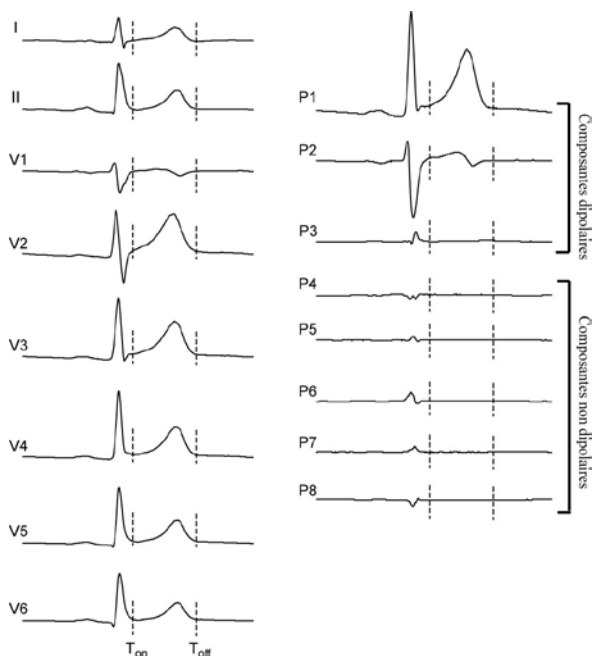

Figure 2. The Principal Component Analysis of the T wave leads to a representation in a 8 dimension space derived from the 8 independent leads. The first component (P1) is holding the maximum amount of variability and it is used as a virtual lead for the T wave representation for modeling.

The Principal Component Analysis (PCA) of the T wave leads to eight eigenvalues ($\lambda_1 > ... > \lambda_8$) and to the corresponding eigenvectors. Each eigenvalue represents the amount of energy of the T-wave on the corresponding eigenvector; the sum of all the eigenvalues represents the total power of the T wave [4]. The eigenvector associated to the largest eigenvalue λ_1 (ie associated to the maximum of energy) is the principal axis of the Twave.

Features extracted from the PCA analysis

Three features were evaluated from the PCA decomposition of the T wave. Several studies have shown that the T-wave representation lies preferably in the 2D space based on the first two eigen vectors, and that the components outside the 3D space, called the non-dipolar components, may be associated to regional ventricular repolarization heterogeneities [5, 6]. These characteristics are associated with two features that can be estimated from the eigenvalues as follows:

$$T_{2D} = \frac{\sum_{i=1\_2} \lambda_i}{\sum_{i=1\_8} \lambda_i} \quad \text{and} \quad T_{3D} = \frac{\sum_{i=1\_3} \lambda_i}{\sum_{i=1\_8} \lambda_i}$$

A third feature is related to the symmetry of the representation in the 2D plane and is estimated by:

$$T_{WL} = \sqrt{\frac{\lambda_2}{\lambda_1}}$$

T-wave modeling

The projection of the T-wave on the principal axis is then modeled by a five-parameter function composed of two half-gaussian functions with different amplitudes named Bi-Gaussian function (BGF) [7] (Figure 3). Three measures can assess the quality of the modeling: the mean error ε, the mean square error *EQM*, and the correlation coefficient R^2:

$$\varepsilon = \frac{1}{N}\sum_i \left(y(i) - \hat{y}(i)\right)$$

$$EQM = \frac{1}{N}\sum_i \left(y(i) - \hat{y}(i)\right)^2$$

$$R^2 = \frac{\sum_i \left(y(i) - \bar{y}\right)\left(\hat{y}(i) - \bar{\hat{y}}\right)}{\sqrt{\sum_i \left(y(i) - \bar{y}\right)^2 \sum_i \left(\hat{y}(i) - \bar{\hat{y}}\right)^2}}$$

where *y* is the T-wave signal, $\bar{y}$ the mean value of *y*, $\hat{y}$ the BGF model and *N* the number of samples.

Then, the five parameters of the T-wave model are used to compute surrogates of several standard repolarization features (Table I line 5 to 13).

3.2. Feature selection

Due to the small size of the available database, the number of features must be reduced in order to prevent overfitting when training the classifier and to obtain a good generalization. We use here a forward feature selection process associated to a random probe method [8]. This method is twofold: First, the candidate features are ranked according to their relevance for the discrimination task; and, second, each feature is assigned a number that estimates its relevance by the use of a 'probe' random vector. This section briefly reviews the methodology and its mathematical basis.

Table 1.
Candidate features for the classification process.

#	Quantity	Description
1	T_{3D}	Proportion of the T wave in a 3D space
2	T_{WR}	T wave residuum (=1- T_{3D})
3	T_{2D}	Proportion of the T wave in a 2D space
4	T_{WL}	Shape of the T-wave loop
5	μ	QT_{peak} interval
6	σ_1	Ascending slope of the T wave
7	σ_2	Descending slope of the T wave
8	A_1	T wave amplitude on the right side
9	A_2	T wave amplitude on the left side
10	$A_1^- A_2$	ST segment elevation
11	$\mu+2\sigma_2$	QT interval
12	σ_1/σ_2	T-wave symmetry ratio
13	$2\sigma_1+2\sigma_2$	T-wave width
14	ε	Error for the T-wave modeling
15	EQM	Mean square error of the model
16	R^2	Correlation coefficient between the model and the T wave

Orthogonal Forward Regression

Let us consider a two-class discrimination task in a space X of dimension q. When the discriminant function is linear, the classification design aims at finding the values of the coefficients w_j such that:

$$y^i = sign\left(\sum_{j\in Q_p} w_j x_j^i\right)$$

for all the examples $\mathbf{x}^i=[x_1^i, x_2^i, ..., x_q^i]$ of the training set, where Q_p is a subset of p features from the q available ones ($p\leq q$), and y^i the label of $\mathbf{x}^i$.

The Orthogonal Forward Regression (OFR) procedure is an iterative process that searches for a subset Q_p to design the classifier without exploring the $p!/(q!(n-p)!)$ possible combinations of features.

Let $\mathbf{d_k}$ be the standardized vector of the kth feature for the N points of the training set: $\mathbf{d_k} = [x_k^1, x_k^2, ..., x_k^N]^T$. The first iteration of the OFR procedure consists in selecting the feature that best explains the labels ie that has the minimum angle with the standardized label vector $\mathbf{y}=[y_1, ..., y_N]^T$. Thus, the following quantity is computed for each feature k:

$$\cos^2(\mathbf{d_k}, \mathbf{y}) = \frac{\mathbf{d_k^T y}}{(\mathbf{d_k^T d_k})(\mathbf{y^T y})}$$

The feature vector with the largest value is selected.

Then, the remaining feature vectors, as well as the label vector, are projected orthogonally to the selected feature vector. In this subspace, the process is iterated and the next most relevant feature vector is selected according to the same rule. The procedure ends when the p features are ranked or if a stop criterion is met. The efficiency and the quality of the OFR procedure has been shown for linear models by Chen et al. in [9] and [10] and also for non-linear modeling by [11], and [12]
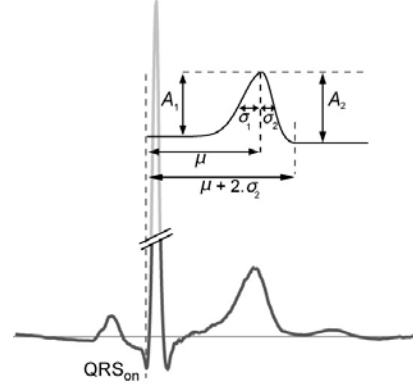

Fig. 3. Bi-Gaussian function modeling of a T-wave. Several features can be computed from the 5 parameters of the model (Line 5 to 13 table 1).

Probe Vector

The probe vector methodology allows to stop the OFR procedure without setting *a priori* a value to *p*. A random vector – the 'probe'- is generated and appended to the set of feature vectors. The feature vectors and the probe are ranked in decreasing relevance order by the OFR orthogonalization process. This process is repeated for a number of probe vectors and the probability distribution function of the rank of the probe vectors is estimated. The probe vectors are not relevant for the discrimination task, and the features ranked after the random probe with a probability larger than a given threshold are rejected. More details on the random probe method can be found in [8] [13].
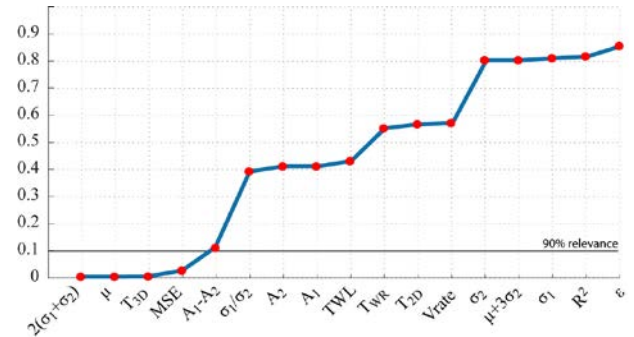

Fig. 4. Probability distribution function of the rank of the probe vector. Each feature is associated to its probability to be irrelevant for the classification task. The threshold is set to 10 % leading to select the 4 features.

Figure 4 shows the results of the ranking process for the fifteen features on the LQT discrimination task. Setting a threshold value of 10%, this graph shows that four features meet the requirement and are thus selected as inputs for the classifier.

3.3. Classification

The aim of the classifier design is to delineate the input space into two parts: one associated with the LQT_1 and

Table 2.
Results over the test database.

	Total database			Reliable labels only			
	Correct classification	*Sensibility LQT type 1*	*Sensibility LQT type 2*	*Correct classification*	*# Classified data*	*Sensibility LQT type 1*	*Sensibility LQT type 2*
2-Dimensional input space							
Learning Set	**83.2**	94.4	63.9	**86.3**	102 / 196	94.9	74.4
Validation Set	**79.4**	90.8	56.9	**87.8**	115 / 214	93.8	74.3
4-Dimensional input space							
Learning Set	**82.7**	91.9	66.7	**85.4**	130 / 196	90.2	77.1
Validation Set	**79.0**	85.2	66.7	**86.5**	138 / 214	90.6	73.6

the other with LQT_2. Here, a Linear Discriminant analysis (LDA) was performed on the data, and the separating hyperplan was defined as the location where the probabilities are equal to 0.5.

The input space is in turn the 4-dimensional space spanned by the 4 selected features; and the 2-dimensional subspace spanned by the two best one. The output is the probability of belonging to class 1 or class 2 given the following property:

$$P(LQT_1 | \mathbf{x}) = 1 - P(LQT_2 | \mathbf{x})$$

where $\mathbf{x}$ is a vector in the input space. The label assigned to any vector $\mathbf{x}$ is LQT_1 if $P(LQT_1/\mathbf{x}) > 0.5$, LQT_2 otherwise.

Moreover, a 'unlabeled' label can be assigned to the data for which the probability of being of type 1 or of type 2 is not high enough. We set this confidence threshold to 0.66: if $0.66 > P(LQT_i/\mathbf{x}) > 0.5$ (i=1 or 2), $\mathbf{x}$ is unlabeled.

4.   Results and discussions

The performances of the method were assessed on the validation set and are presented in Table II in both cases: for an input space of 2 dimensions and an input space of 4 dimensions. The left part of the table presents the results obtained over the entire databases (training and validation sets); whereas the right part shows the results only for reliable results that represent a subgroup of the dataset (see '# classified data' column).

These results suggest that, when using 2 features, the classifier is able to provide a correct diagnosis in about 88% of the classified examples if we accept no decision for 47% of the data. The unlabel group can be decreased to 35% by adding two more features in the input space.

In order to estimate the performances of the proposed method in a clinical context, a validation against manual annotations from cardiologist could be the next step.

Acknowledgements

References

[1] Tester DJ, Ackerman MJ. Genetic testing for potentially lethal, highly treatable inherited cardiomyopathies/channelopathies in clinical practice. Circulation. [Review]. 2011;123(9):1021-37.

[2] Damen AA, van der Kam J. The use of the singular value decomposition in electrocardiography. Med Biol Eng Comput. 1982;20(4):473-82.

[3] Extramiana F, Haggui A, Maison-Blanche P, Dubois R, Takatsuki S, Beaufils P, et al. T-wave morphology parameters based on principal component analysis reproducibility and dependence on T-offset position. Annals of Noninvasive Electrocardiology 2007;12(4):354-63.

[4] Rubel P, Fayn J, Mohsen N. Analyse Comparative des ECG/VCG Successifs d'un meme Patient. Mises à jour Cardiologiques 1988;17(6):179-87.

[5] Okin P, Devereux R, Fabsitz R, Lee E, Galloway J, Howard B. Principal Component Analysis of the T Wave and Prediction of cardiovascular Mortality in American Indians - The strong heart study. Circulation 2002;105:714-9.

[6] Fayn J, Rubel P. CAVIAR: a serial ECG processing system for the comparative analysis of VCGs and their interpretation with auto-reference to the patient. J Electrocardiol 1988;21 Suppl:S173-6.

[7] Dubois R, Roussel P, Vaglio M, Extramiana F, Badilini F, Maison-Blanche P, et al. Efficient Modeling of ECG Waves for Morphology Tracking. IEEE Proc Computers in Cardiology 2009;36:313-6.

[8] Stoppiglia H, Dreyfus G, Dubois R, Oussar Y. Ranking a Random Feature for Variable and Feature Selection. Journal of Machine Learning Research 2003;3:1399-414.

[9] Chen S, Cowan CFN, Grant PM. Orthogonal Least Square Learning Algorithm for Radial Basis Function Networks. IEEE Transactions on Neural Networks 1991;2(2):302-9.

[10] Chen S, Hong X, Luk BL, Harris CJ. Orthogonal-least-squares regression: A unified approach for data modelling. Neurocomputing 2009;72(10-12):2670-81.

[11] Urbani D, Roussel P, Parsonnaz L, Dreyfus G. The selection of neural models of non- linear dynamical systems by statistical tests. In: J. Vlontzos JH, and E. Wilson, editor. Neural Networks for Signal Processing IV 1993:229-37.

[12] Dubois R, Quenet B, Faisandier Y, Dreyfus G. Building meaningful representations for nonlinear modeling of 1d- and 2d-signals: applications to biomedical signals. Neurocomputing 2006;69(16-18):2180-92.

[13] Dreyfus G. Neural Networks, Methodology and Applications: Springer; 2005.

Address for correspondence
Rémi Dubois, remi.dubois@espci.fr