A Multicentric Study of Long-term Rhythm Patterns in Heart Rate

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Abstract

Heart rate (HR) shows oscillations with different periods as a result of the sympatho-vagal balance. The most studied ones are short-period variations and the circadian pattern. However, the existence of rhythms of longer periods has not been systematically studied.

The aim of this work is to study HR long-period rhythms in a multicentric database including 336 patients in sinus rhythm, with implanted cardioverter defibrillator. We used two methodological approaches: First a rhythmometric procedure to automatically select the statistically significant rhythms present in the signal; Second, the LASSO path approach to analyze the order of activation of the rhythms, representing the importance of each rhythm.

Most of the population showed a significant annual rhythm (78% day/80% night). Weekly and quarterly rhythms were also present (weekly 26% /26% ; quarterly 22%/21%). Monthly rhythm was rarely present. Most present rhythm combinations were annual plus weekly (21%/21%) and annual plus quarterly (19%/18%). The order of activation given by the LASSO path was in agreement with the multicomponent rhythmometric model in the 86%/85% of the cases.

The unusual long monitoring period, and the high number of patients, represent an ideal scenario to robustly assess the existence of long-term rhythms.

1. Introduction

Physiological rhythms arise from stochastic, nonlinear biological mechanisms interacting with a fluctuating environment. Separation of dynamics due to intrinsic rather than extrinsic mechanisms is not possible. Several studies indicate rich dynamics with differences between normal individuals and patients. Therefore, disruption of the rhythmic processes beyond normal bounds or emergence of abnormal rhythms is associated with disease. A possible approach to study these dynamics is to analyze qualitative aspects of simplified mathematical models of physiological systems [1].

Most biological variables vary greatly along several time scales in health and disease [2]. Heart rate (HR) shows oscillations with different periods. The most studied ones are short-period variations (seconds, minutes) and the circadian pattern. However, there is little information about the existence of rhythms of longer periods and they have not been systematically studied. One reason is the difficulty to ensemble the appropriate dabatabases with a large number of subjects and sufficient monitoring periods.

A suitable hypothesis is that physiological mechanisms in healthy subjects are more adaptable to environmental changes than those in pathological subjects, and maybe with a progressive deterioration of this adaptability related to the severity of the pathological condition. Several stud-

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ies have shown blunted or altered circadian rhythms of different physiological variables [3–5].

The aim of this study is to assess the adaptation capabilities, the patients responses, to stimuli of longer time periods. To this end we assessed the long-term HR rhythms present in a multicentric database including 336 patients. The database was assembled from SCOOP platform, a repository conveying around 12000 intracardiac electrograms stored by implanted cardioverter defibrillators (ICDs). The analysis was performed by means of two methodological approaches: First a rhythmometric procedure to automatically select the statistically significant rhythms present in the signal; Second, the LASSO path approach to analyze the order of activation of the rhythms, representing the importance of each rhythm.

The structure of the paper is as follows. Section 2 describes the multicentric database and the data preprocessing. In Section 3, the two methodological approaches are presented. Section 4 depicts the results. Finally, the conclusions are outlined in Section 5.

2. Dataset

A multicentric database including 381 patients in sinus rhythm, was assembled from SCOOP platform. SCOOP is a Spanish platform developed by Medtronic Ibérica S.A., it represents a pioneer scientific repository system in the cloud involving 48 national hospitals and conveying around 12000 intracardiac electrograms stored by ICDs and subsequently labeled by a scientific committee of expert physicians.

Daily and nightly mean HR was extracted from each patient record for its analysis. The monitoring period varies between 382 and 2348 days. From this dataset, patients with more than 5% of atrial or ventricular pacing at any point during the monitoring period were discarded. Also, assuming that some of the subjects could have suffered atrial fibrillation (AF) episodes during the monitoring period, a signal preprocessing was designed trying to detect AF episodes. Namely, HR samples differing in more than 15% of the mean of the previous 5 days were discarded. In this case, if more than the 20% of the samples are discarded in one patient, the patient is discarded from the analysis. Finally 336 patients remained for the study.

3. Methods

Extensive and dense time series collected over several decades show that nearly all biological variables display some degree of more or less periodic behaviour. When statistical methods are involved in data analysis time-dependence must be taken into account. Hence, in many cases, is useful to look upon a measurement series as consisting on a deterministic part, which may have both rhythmic and arrhythmic systematic components, and a noise part [2]. We used a rhythmometric procedure based on a multicomponent COSINOR approach and a non-parametric statistic test to automatically select the statistically significant rhythms present in the HR signal. Furthermore, we used the LASSO path approach to analyze the order of activation of the rhythms, representing the importance of each rhythm.

3.1. Rhythmometric Analysis

A data sequence can be represented by a temporal regression model known as the cosinor model [2], defined by

$$y_n = M + A_0 \cos(2\pi f_0 t_n + \phi_0) + e_n,\ n = 1, \ldots, N, \quad (1)$$

where M denotes the rhythm-adjusted mean or MESOR (midline estimating statistic of rhythm), A_0 the amplitude, f_0 the fundamental frequency, ϕ_0 the acrophase (i.e., the lag from a defined reference time point to the crest time in the cosine curve fitted to the data), and N the signal length. The random variable e_n corresponds to the difference between the observed sample y_n and the value provided by the estimated regression model $\hat{y}_n$. The least squares (LS) method is applied to determine the regression parameters.

Joint characterization of a set of rhythms is provided by a multiple components model [2], which extends the regression model in (1) to become

$$y_n = M + \sum_i A_i \cos(2\pi f_i t_n + \phi_i) + e_n, \quad (2)$$

Where f_i, A_i and ϕ_i are the frequency, the amplitude and the acrophase corresponding to each considered rhythm.

In the present study, weekly, monthly, quarterly and annual rhythms are considered, since those where the rhythms of interest selected by the cardiologist.

The LS method is used to find the regression parameters in (2). Next, the rhythmometric method leans toward a bootstrap hypothesis test [6] to select the rhythm components with statistical relevance in (2). The MESOR component is used as the starting rhythmometric model. In order to construct the final model, the method iteratively adds to the previous model the sinusoidal component in (2) with the highest amplitude. The mean square error (MSE) between the signal and each model (E_k) is computed to obtain the difference between the residuals of the two models ($\Delta E_k = E_{k-1} - E_k$). The statistical relevance of each model versus the previous one is assessed by using a paired bootstrap hypothesis test. A number of B random resamplings with replacement of residuals E_k are made to obtain ΔE_k for each resampling ($B = 2500$). A suitable statistical hypothesis test is to contrast the null hypothesis that the models have the same unexplained variance

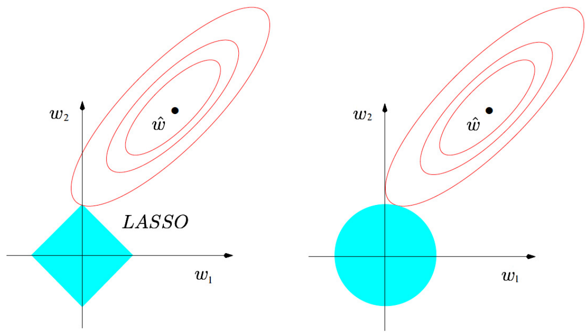

Figure 1. Comparison of estimation weights constraints between LASSO (left) and regularized regression (right). Adapted from [9].

($\Delta E_k = 0$) against the alternative hypothesis that both models have different unexplained variance ($\Delta E_k \pm 0$). The paired bootstrap hypothesis test determines that the addition of a new sinusoidal component is relevant when at least 97.5% of the B values, for the estimated probability density function of ΔE_k, are on the right-hand side of zero; a detailed explanation is found in [7].

3.2. LASSO Path

We propose, in this work, to use a differente approach to select rhythm components based on regularization techniques. As an alternative to the previous method, we can fit the complete rhythmometric model and constraint the coefficients associated to each component. We propose to use $L1 - norm$ penalization which has the effect of forcing some of the coefficient estimates to be exactly equal to zero, yielding to sparse models [8].

In order to use this approach, we need to reformulate the rhythmometric model as a linear one, rewriting 2 as

$$y_n = M + \sum_i \alpha_i \cos(2\pi f_i t_n) + \beta_i \sin(2\pi f_i t_n) + e_n, \quad (3)$$

where $\alpha_i = A_i \cos(2\pi\phi_i)$ and $\beta_i = -A_i \sin(2\pi\phi_i)$. Collecting all the coefficients in a vector of weights $\boldsymbol{w} = [1, \alpha_1, \ldots, \alpha_k, \beta_1, \ldots, \beta_k]$, where k is the number of rhythm components. Using a matrix X to collect all the components and the MESOR, the rhythmometric model can be compactly written as

$$\boldsymbol{y} = X\boldsymbol{w} + \boldsymbol{e} \quad (4)$$

Weights of the model, $\boldsymbol{w}$, can be estimated using LS including a regularization term:

$$\hat{\boldsymbol{w}}_{L_2} = \underset{\boldsymbol{w}}{\operatorname{argmin}} \, \|\boldsymbol{y} - X\boldsymbol{w}\|_2^2 + \lambda\|\boldsymbol{w}\|_2^2 \quad (5)$$

The LASSO approach is shrinkage method like the previous one, but substituing L_2 norm in the regularization penalty on weights by L_1 norm [9]:

$$\hat{\boldsymbol{w}}_{L_1} = \underset{\boldsymbol{w}}{\operatorname{argmin}} \|\boldsymbol{y} - X\boldsymbol{w}\|_2^2 + \lambda\|\boldsymbol{w}\|_1 \quad (6)$$

where $\|\boldsymbol{w}\|_1 = \sum_{j=1}^{2k+1} |w_j|$.

The nature of LASSO constraint allows to control the number of weights actives ($w_i \neq 0$), so that, making λ sufficiently large will cause some of the weights to be exactly zero, see Figure 1.

Linear models penalized with the L_1 norm have sparse solutions, so that many of their estimated weights are zero. Accordingly, it is possible to use LASSO regression models to report the more important variables (features) of the model in the sense of mean squared error [10].

It is possible to perform a search on the regularization parameter λ. This is the so called LASSO path, in which starting at high values of λ assures that all weights are equal to zero. Then we give smaller values for λ up to zero. The idea is to register the event when a weight actives, that is, when $w_i \neq 0$, meaning that the associated rhythm component represent an important variable to explain the HR signal in the sense of minimum squared error [9]. We performed a complete LASSO path analysis in order to evaluate the activation dynamic of the rhythm components assuming that the first activated component represents the most relevant physiological rhythm.

Table 1. Percentage of patients showing each rhythm in the different time periods: Day, night and in both day and night.

Rhythm	Day (%)	Night (%)	Both (%)
Annual	72	80	66
Quarterly	22	21	12
Monthly	3	3	1.5
weekly	26	26	12

4. Results

Table 1 shows that most of the patients showed a significant annual rhythm, either in the daily mean HR, or in the nightly mean HR, and in many cases in both time periods. Weekly and quarterly rhythms were also present, whereas monthly rhythm was rarely present. Most usual rhythm combinations were annual plus weekly and annual plus quarterly (see Tab. 2). Figure 2 shows an example of a HR signal and the fitted model where the annual and weekly rhythms were significant according to the procedure in Sec. 3.1.

The order of activation given by the LASSO path was in agreement with the rhythmometric model (Sec. 3.1) in the 86% day/85% night of the patients.

Table 2. Percentage of patients showing each rhythm combination in the different time periods.

Rhythm combination	Day (%)	Night (%)	Both (%)
Annual+weekly	21	21	8
Annual+Quarterly	19	18	8
Annual+Monthly	1.5	2.7	1
Ann.+Quart.+week.	5	4	1

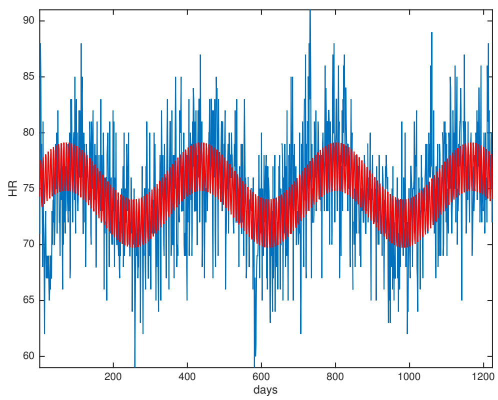

Figure 2. Example of mean HR evolution and fitted rhythmometric model. A combination of annual and weekly rhythms were significant for this signal.

5. Conclusions

The unusual long monitoring period, and the high number of patients in the database, represent an ideal scenario to robustly assess the existence of long-term rhythms.

In this study two technical approaches were in agreement in most cases, being the LASSO path used for the first time in rhythmometric analysis. The annual rhythm was by far the most significant one in the studied population.

Further studies will be devoted to assess the relation of the rhythm presence and the patient clinical data.

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