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Model-based Estimators of QT Series Time Delay in Following Heart-Rate Changes

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***Abstract*— Sudden cardiac death is the leading cause of death among cardiovascular diseases. Markers for patient risk stratification focusing on QT-interval dynamics in response to heart-rate (HR) changes can be characterized in terms of parametric QT to RR dependence and QT/RR hysteresis. The QT/RR hysteresis can be quantified by the time delay the QT interval takes to accommodate for the HR changes. The exercise stress test has been proposed as a proper test, with large HR dynamics, to evaluate the QT/RR hysteresis. The present study aims at evaluating several time-delay estimators based on noise statistic (Gaussian or Laplacian) and HR changes profile at stress test (gradual transition change). The estimator's performance was assessed on a simulated QT transition contaminated by noise and in a clinical study including patients affected by coronary arteries disease (CAD). As expected, the Laplacian and Gaussian estimators yield the best results when noise follows the respective distribution. Further, the Laplacian estimator showed greater discriminative power in classifying different levels of cardiac risk in CAD patients, suggesting that real data fit better the Laplacian distribution than the Gaussian one. The Laplacian estimator appears to be the choice for time-delay estimation of QT/RR hysteresis lag in response to HR changes in stress test.**

***Clinical Relevance*—The proposed time-delay estimator of QT/RR hysteresis lag improves its significance as biomarkers for coronary artery diseases risk stratification.**

I. INTRODUCTION

Sudden cardiac death (SCD) is the leading cause of death with an incidence of 15%-20% among all deaths in Western societies [1]. Elevated repolarization heterogeneity in the ventricular myocardium can promote ventricular arrhythmias which are strongly associated to SCD [3]. Particularly, during exercise, ventricular repolarization dispersion can be exacerbated in response to abrupt changes in heart rate (HR) due to the different repolarization adaptation to HR changes shown by distinct ventricular cells [3]. Ventricular repolarization is reflected by the T wave in the electrocardiogram (ECG) from which the QT interval can be measured. QT-interval duration characterizes repolarization dynamics. The time delay of QT interval in accommodating to HR changes (QT/RR hysteresis) has been shown to be a marker for SCD risk stratification [2], [3], [4], [5]. The relation between HR changes and their induced QT changes has been modeled with a non-linear part, representing the stationary relation of QT with RR, plus a first order linear system representing the system memory [6]. This allows to measure the QT time lag in respose to any RR change and was particularly applied to compute the time the QT series takes to follow a step-like HR change [2], [6]. However, step-like maneuvers are uncommon and difficult to provoke leading to a recent proposal to measure the QT time lag during stress test maneuvers [3], [7]. Since HR varies almost linearly in stress test, the QT series should then follow the HR changes with other linear trend delayed by the time lag under estimation [3]. This method was evaluated in patients with suspected cardiovascular disease, to characterize arrhythmias and SCD risk [3]. The time delay of QT series in following changes in the HR series was computed as the time lag between the observed QT series and an expected instantaneous memoryless HR-dependent QT series, derived from the HR and a patient specific estimate of the stationary QT to RR dependence [3]. The computation of the time lag between the two series can be formulated as a two-channel time-delay estimation, which, under the hypothesis of series contaminated by Gaussian noise, is well known to reduce to the least square (LS) estimation which, under conditions of finite support, results in the maximization of the cross-correlation between the two channels [8], but that here, the increasing or decreasing abrupt changes do not satisfy this condition, preventing the use of the cross-correlation. In addition, features derived from the ECG typically present a heavy-tailed distribution, better represented by a Laplacian, rather than by a Gaussian [9]. In the case of the QT interval, it results from a QRS onset and T-wave end identifications, which are largely subject to outliers, then better represented by a Laplacian distribution. The aim of this study is to derive a Laplacian-based time-delay estimator and test it in simulation and clinical practice.

II. MATERIALS AND METHODS

A QRS detector, identifying QRS-complex occurrence time and an ECG wave delineator, identifying the QRS onset and the T-wave end for each beat are required to generate the HR and QT series [10]. These series typically follow approximately linear transitions during stress test which also include some measurement noise and constitute the basis for the time delay detector derivation.

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A. Modeling of QT ramp-like transition at stress test

The QT series, resampled at 4 Hz, $d_{\mathrm{QT}}(n)$, and the expected instantaneous memoryless, HR-dependent QT series, $d^i_{\mathrm{QT}}(n)$, were modeled as a gradual step-like transition $s(n)$ plus added uncorrelated white noises $v_2(n)$, $v_1(n)$, respectively (either Gaussian or Laplacian) with equal variance σ_v^2 and a time lag, τ, between the two series:

$$\left.\begin{array}{l} d^i_{\mathrm{QT}}(n) = x_1(n) = s(n) + v_1(n) \\ d_{\mathrm{QT}}(n) = x_2(n) = s(n-\tau) + v_2(n) \end{array}\right\} n = 0,...,N-1, \quad (1)$$

where N is the length of the observed window. For simplicity we assimilate $d^i_{\mathrm{QT}}(n)$ and $d_{\mathrm{QT}}(n)$ to $x_1(n)$ and $x_2(n)$, respectively.

B. Time delay estimators

The τ parameter in (1) influences the observed data $d_{\mathrm{QT}}(n)$, which follows a certain probability distribution. This parameter, when data follows an assumed probability distribution, can be estimated by maximum likelihood (ML) estimation. To derive the ML estimator of τ between $d_{\mathrm{QT}}(n) \equiv x_2(n)$ and $d^i_{\mathrm{QT}}(n) \equiv x_1(n)$, we depart from the two-channel model [8] in (1). It is assumed that the QT trend $s(n)$ has stationary behaviour at both ends of the observation window, for a duration guaranteeing that delaying by τ the series, it still has the same stationary value at end samples (transition much shorter than the observation interval). The optimal ML estimate of τ depends on the assumed distribution of the noise contaminating the series.

1) Gaussian: The probability density function (PDF) characterizing the observation $\mathbf{x}_1 = \left[x_1(0)\cdots x_1(N-1)\right]^T$ and $\mathbf{x}_2 = \left[x_2(0)\cdots x_2(N-1)\right]^T$, with $\mathbf{s} = \left[s(0)\cdots s(N-1)\right]^T$, results for Gaussian noise in:

$$p_v(\mathbf{x}_1,\mathbf{x}_2;\tau,\mathbf{s}) = \prod_{n=0}^{N-1} \frac{1}{2\pi\sigma_v^2} \exp\left[-\frac{\left((x_1(n)-s(n))^2+(x_2(n)-s(n-\tau))^2\right)}{2\sigma_v^2}\right]. \quad (2)$$

Taking the logarithm and grouping factors independent of τ or $\mathbf{s}$, we obtain:

$$\ln p_v(\mathbf{x}_1,\mathbf{x}_2;\tau,\mathbf{s}) = \text{Constant} + -\tfrac{1}{2\sigma_v^2} \sum_{n=0}^{N-1} \left((x_1(n)-s(n))^2+(x_2(n)-s(n-\tau))^2\right). \quad (3)$$

Maximization of the log-likelihood function in (3) is done by first deriving with respect to $s(n)$ for a given τ:

$$\frac{\partial \ln p_v(\mathbf{x}_1,\mathbf{x}_2;\tau,\mathbf{s})}{\partial s(n)} = \frac{1}{2\sigma_v^2}\left(2x_1(n)+2x_2(n+\tau)-2s(n)-2s(n)\right), \quad (4)$$

which when set to zero, results in the following estimator:

$$\hat{s}(n;\tau) = \frac{x_1(n)+x_2(n+\tau)}{2}. \quad (5)$$

Inserting $\hat{s}(n;\tau)$ into the log-likelihood function in (3) and maximizing with respect to the other parameter τ, we obtain:

$$\begin{aligned} \hat{\tau} &= \arg\min_\tau \left(\sum_{n=0}^{N-1} (x_1(n)-x_2(n+\tau))^2 + (x_2(n)-x_1(n-\tau))^2 \right) \\ &= \arg\max_\tau \left(\frac{1}{2} \sum_{n=0}^{N-1} x_1(n)x_2(n+\tau) + x_2(n)x_1(n-\tau) - \frac{E_x(\tau)}{4} \right), \\ &\text{with } E_x(\tau) = \sum_{n=0}^{N-1} \left(x_1^2(n)+x_2^2(n)+x_1^2(n-\tau)+x_2^2(n+\tau)\right). \end{aligned} \quad (6)$$

Since the signal $s(n)$ is assumed to have constant value in an interval larger than τ at the extremes, the estimator in (6), from first equality, is just the LS estimate by varying τ:

$$\hat{\tau}_{\mathrm{LS}} = \arg\min_\tau \sum_{n=0}^{N-1} (x_1(n)-x_2(n+\tau))^2; \quad \tau \in \{-I,...,I\}, \quad (7)$$

with I representing the plausible range of values for τ.

Alternatively, when $s(n)$ is of finite support and contained in the observation interval, E_x becomes independent of τ and the ML estimate of τ, from second equality in (6), results in the value of τ maximizing the cross-correlation between $x_1(n)$ and $x_2(n+\tau)$ [8]. However, since here $s(n)$ is not zero at the interval extremes and, in addition, their values can differ from one end to the other, $E_x(\tau)$ does depend on τ, making the ML estimate resulting from (6) non-interpretable as a cross-correlation maximization. If we rather modify the signals $x_1(n)$ and $x_2(n)$ by adding a constant value b, such that the mean values at the extremes of the new signals, $\tilde{x}_i(n) = x_i(n) - b_i$, i=1,2, have the same module a and reverted sign, $E_{\tilde{x}}$ becomes independent of τ and the cross-correlation ML estimate could be used based on the modified signal $\tilde{x}_i(n)$. A reasonable estimation of b_i is

$$\hat{b}_i = \frac{\mathrm{med}\{x_i(0),...,x_i(I-1)\} + \mathrm{med}\{x_i(N-I),...,x_i(N-1)\}}{2}, \quad (8)$$

with the I samples at observation interval onset and end where we have guaranties the HR is stationary. The ML estimate is then the one that maximizes the cross-correlation function between the biased modified observations (BCC):

$$\hat{\tau}_{\mathrm{BCC}} = \arg\max_\tau \left(\sum_{n=0}^{N-1} \tilde{x}_1(n)\tilde{x}_2(n-\tau) \right); \quad \tau \in \{-I,...,I\}. \quad (9)$$

If we assume that the transition always occurs at the center of the observation interval, the estimation of the bias b_i can just be avoided by zero-meaning the observed signals, guaranteeing the same absolute mean value at the series extremes. Thus, the estimate in (9) can be used with the cross-correlation of the zero-meaned (ZCC) observation signals $\tilde{x}_1(n) = x_1(n) - \mathrm{mean}\{\mathbf{x}_1\}$ and $\tilde{x}_2(n) = x_2(n) - \mathrm{mean}\{\mathbf{x}_2\}$, resulting in the $\hat{\tau}_{\mathrm{ZCC}}$ estimator.

2) Laplacian: To derive the ML time delay estimation under Laplacian noise distribution we depart from the same signal model, but with Laplacian noise distribution resulting

in the following observation signal PDF:

$$p_v(\mathbf{x}_1,\mathbf{x}_2;\tau,\mathbf{s}) = \prod_{n=0}^{N-1}\frac{1}{2\sigma_v^2}\exp\left[-\frac{\sqrt{2}}{\sigma_v}(|x_1(n)-s(n)|+|x_2(n)-s(n-\tau)|)\right]. \quad (10)$$

Taking again the logarithm and grouping factors independent of τ or $\mathbf{s}$, we obtain:

$$\ln p_v(\mathbf{x}_1,\mathbf{x}_2;\tau,\mathbf{s}) = \text{Constant} + -\frac{\sqrt{2}}{\sigma_v}\sum_{n=0}^{N-1}(|x_1(n)-s(n)|+|x_2(n)-s(n-\tau)|). \quad (11)$$

Maximization of the log-likelihood function in (11) by first differentiating with respect to $s(n)$ for a given τ:

$$\frac{\partial \ln p_v(\mathbf{x}_1,\mathbf{x}_2;\tau,\mathbf{s})}{\partial s(n)} = -\frac{\sqrt{2}}{\sigma_v}\left(\frac{x_1(n)-s(n)}{|x_1(n)-s(n)|}+\frac{x_2(n+\tau)-s(n)}{|x_2(n+\tau)-s(n)|}\right) = -\frac{\sqrt{2}}{\sigma_v}\left[\text{sgn}(x_1(n)-s(n))+\text{sgn}(x_2(n+\tau)-s(n))\right], \quad (12)$$

and setting to zero, results in the following estimator:

$$\hat{s}(n;\tau) = \text{med}\{x_1(n),x_2(n+\tau)\} = \frac{x_1(n)+x_2(n+\tau)}{2}. \quad (13)$$

Inserting $\hat{s}(n;\tau)$ into the log-likelihood function in (11) and maximizing with respect to the other parameter τ, we obtain:

$$\hat{\tau} = \arg\min_{\tau}\sum_{n=0}^{N-1}\left(\frac{|x_1(n)-x_2(n+\tau)|}{2}+\frac{|x_2(n)-x_1(n-\tau)|}{2}\right). \quad (14)$$

Making use of the assumption that $s(n)$ has constant value at the extremes of the observation interval for a period larger than τ, the Laplacian estimator (LE) of τ can be written as:

$$\hat{\tau}_{\text{LE}} = \arg\min_{\tau}\sum_{n=0}^{N-1}|x_1(n)-x_2(n+\tau)|; \quad \tau\in\{-I,...,I\}. \quad (15)$$

C. Simulation

To assess the time delay estimator in a controlled scenario, we simulate an HR acceleration (negative slope transition in $d_{\text{QT}}(n)$ series) as a gradual step-like transition as:

$$s(n) = \begin{cases} a+b, & n = 0,...,\frac{N-T}{2}-1 \\ a\left(1-\frac{2}{T+1}(n-\frac{N-T-2}{2})\right)+b & n = \frac{N-T}{2},...,\frac{N+T}{2}-1 \\ -a+b, & n = \frac{N+T}{2},...,N-1 \end{cases} \quad (16)$$

where T models the duration of QT transitions between two assumed flat areas taking values from a uniform random distribution between 10 and 70 s. The amplitude of the step is $2a$ and $b+a$ indicates the departing level of the step (Fig.1). In case of HR deceleration (positive slope transition in $d_{\text{QT}}(n)$) the step like transition has the form $-s(n)$. Observation signal length N is taken as 1000 s. Added white noise $v_i(n)$ was scaled to better match the variability of the real series with a factor taken randomly between 0.010 and 0.50 s. The transition ramp $2a$ amplitude was chosen to match the amplitude range of real QT transitions. The mean stationary QT value at higher HR, $b-a$, was generated randomly between 0.23 and 0.30 s, and at lower HR, $b+a$, between 0.33 and 0.40 s. The simulated time lag τ was also randomly selected and ranged between 0 and 70 s. In total, 800 series realizations, sampled at 4 Hz, were generated, which were the result of summing up 200 realizations from each combination of negative/positive slope transition with Gaussian/Laplacian added noise. Ranges of parameters were chosen based on real QT changes in stress test [3].

To evaluate the time-delay estimator's performance, the error, ε, between the true τ introduced at the simulation and the estimated one, $\hat{\tau}$, was computed as $\varepsilon = \hat{\tau}-\tau$.

D. Clinical significance

To evaluate the significance of different estimators in clinical practice, we considered LS and LE estimators, since they were the ones showing the best performance in simulation, see section III. A total of 448 ECGs recorded from patients undergoing exercise stress testing at Tampere University Hospital in Finland [11] were analyzed. Patients were classified into four groups according to their likelihood of suffering from coronary artery disease (CAD). The low risk (LR) ECG group (ECG-LR) consists of patients determined as of LR just with information from clinical history and the ECG, without subsequent coronary angiography (COR). The remaining patients, who underwent a COR, were classified depending on whether they presented less than 50% (COR-LR), between 50 and 75% (COR-MR), or more than 75% (COR-HR) of luminal narrowing of the diameter of at least one major epicardial coronary artery or main branches. LR, MR, and HR refer to Low, Mild and High Risk, respectively. There were 213, 59, 24 and 152 subjects in ECG-LR, COR-LR, COR-MR and COR-HR groups, respectively.

Uniformly sampled $d_{\text{RR}}(n)$ and $d_{\text{QT}}(n)$ series were computed after applying a signal processing filtering pipeline to the ECG [3]. Then, the instantaneous memory-less, HR-dependent QT interval, $d^i_{\text{QT}}(n)$, was computed. This series follows the temporal variation of $d_{\text{RR}}(n)$ within the amplitude range of $d_{\text{QT}}(n)$. The $d^i_{\text{QT}}(n)$ series represents the QT value that would correspond to each $d_{\text{RR}}(n)$ value, provided they would have come from a stationary condition. Therefore, $d^i_{\text{QT}}(n)$ is supposed to be a memory-less version of the observed QT series, $d_{\text{QT}}(n+\tau)$. An automatic procedure was applied to each signal to delimit exercise and recovery observation ramps [3]. The observation interval is considered to begin at sample n_o, taken I samples before the start of the $d^i_{\text{QT}}(n)$ change. A similar procedure is done for the end of the observation interval n_e, selected I samples after the time when $d^i_{\text{QT}}(n)$ change finishes. The exercise ramp is a case of negative slope and the recovery, a case of positive slope, as introduced in section II-A. The delay in exercise and recovery ramps, τ_e and τ_r, and their difference, $\Delta\tau = \tau_r - \tau_e$, were computed for each subject. The results are comparatively evaluated for the four patient groups.

III. RESULTS

An example of simulated QT transitions is shown in Fig 1. Table I contains the distribution, mean±standard deviation (SD), of $\hat{\tau}$ and relative errors ε in simulation for the different estimators under test. Fig. 2 shows box plots with the performance of LS (top row) and LE (bottom row) estimators in the clinical study, for different risk groups.

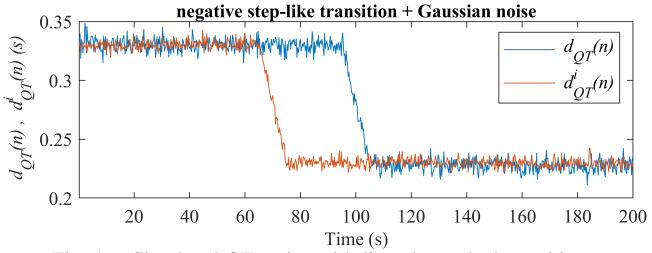

Fig. 1. Simulated QT series with linearly gradual transitions.

TABLE I

SIMULATION RESULTS: DISTRIBUTIONS OF THE ESTIMATED DELAY $\hat{\tau}$ AND OF THE CORRESPONDING ERROR ε, REPORTED AS MEAN $\pm$ SD (S)

Noise PDF	Gaussian	Laplacian
$\tau(s)$	21.47 ± 16.27	
$\hat{\tau}_{\mathrm{ZCC}}(s)$	21.52 ± 16.20	21.50 ± 16.21
$\varepsilon_{\mathrm{ZCC}}(s)$	0.05 ± 1.31	0.03 ± 1.22
$\hat{\tau}_{\mathrm{BCC}}(s)$	21.53 ± 16.21	21.50 ± 16.21
$\varepsilon_{\mathrm{BCC}}(s)$	0.06 ± 1.34	0.03 ± 1.22
$\hat{\tau}_{\mathrm{LS}}(s)$	21.54 ± 16.26	21.50 ± 16.29
$\varepsilon_{\mathrm{LS}}(s)$	0.07 ± 1.20	0.02 ± 1.01
$\hat{\tau}_{\mathrm{LE}}(s)$	21.55 ± 16.18	21.48 ± 16.29
$\varepsilon_{\mathrm{LE}}(s)$	0.08 ± 1.20	0.01 ± 0.90

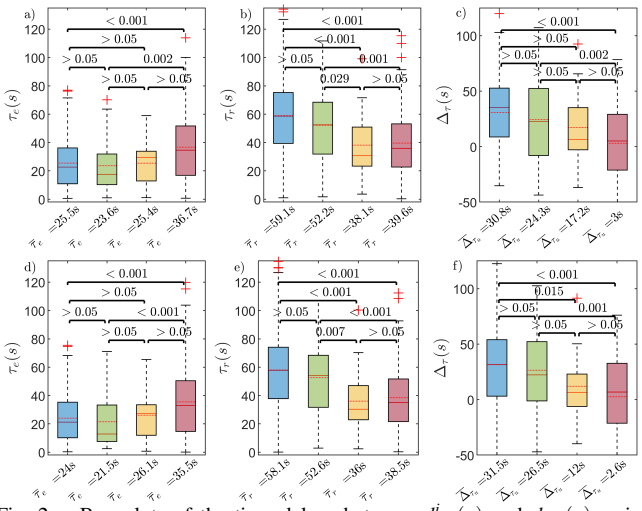

Fig. 2. Box plots of the time delays between $d^i_{\mathrm{QT}}(n)$ and $d_{\mathrm{QT}}(n)$ series for the four patient groups. a) and d) during exercise, τ_e, b) and e) during recovery, τ_r, and c) and f) the difference between recovery and exercise, Δ_τ. The red dotted and continuous lines correspond to the mean and median values, respectively. First row shows results for the Gaussian estimator $\hat{\tau}_{\mathrm{LS}}$; second row shows results for the Laplacian estimator, $\hat{\tau}_{\mathrm{LE}}$. Blue box: ECG-LR, green box: COR-LR, yellow box: COR-MR and red box: COR-HR. Overlined variables denote patient group means. Delay significance, p-values, in separating patient groups are plotted above box plot pairs.

IV. DISCUSSION

The aim of this study was to evaluate different estimators of the time delay in the response of QT interval to HR changes. Both Gaussian and Laplacian noise distribution based estimators slightly overestimate τ in case both of Gaussian noise and of Laplacian noise (Table I). In the case of Gaussian noise, the best-performing estimator is LS, with an error SD of $\varepsilon_{\mathrm{LS}}$ of 1.20 s while BCC gives the highest SD of $\varepsilon_{\mathrm{BCC}}$ of 1.34 s. The lower performance of BCC and ZCC could be a result of the extra variance added by the estimation of extra parameters: the bias value $\hat{b}_i$ at both sides of the transition and/or the mean value, respectively. In case of Laplacian noise, the best-performing estimator is LE with SD of $\varepsilon_{\mathrm{LE}}$ of 0.90 s (Table I). From the evaluation of $\hat{\tau}_{\mathrm{LS}}$ and $\hat{\tau}_{\mathrm{LE}}$ in clinical practice, it can be observed (Fig. 2) that the time delay estimated as $\hat{\tau}_{\mathrm{LE}}$ discriminates more significantly between Low, Mild and High risk CAD subjects. The more noticeable difference in results with respect to previous study [3], where the LS estimator was used (top row in Fig. 2) is that $\Delta\tau$ becomes significantly different between COR-MR and ECG-LR risk groups when delays are computed with $\hat{\tau}_{\mathrm{LE}}$ (third column, bottom row of Fig. 2).

V. CONCLUSIONS

Results, both in simulation and real data, show that the LE time-delay estimator, derived from Laplacian noise assumptions and consisting in minimizing the sum of the absolute differences between the two delayed series, is the best-performing estimator when computing delays between QT series trends in response to HR changes, as cardiac biomarkers for CAD risk stratification.

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