Transfer Entropy for Linear QT Correction Under Stationary and Gaussian Assumptions of the QT/RR Probability Distribution

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Abstract

Recently, Transfer Entropy (TE) was proposed as a new approach to correct the QT interval by setting TE(RR→QT) equal to 0. In the first part of the study, we provided a closed-form solution for the coefficient of a linear correction formula according to TE=0, when the random process QT/RR is stationary and normally distributed. When the QT/RR history is neglected, the obtained coefficient is equivalent to the slope of the QT/RR relationship obtained by minimum mean square error (MMSE). When the history is instead considered, the optimal coefficient takes a different expression. Also, we found that TE=0 cannot always be set. Therefore, we introduced a new QT correction paradigm according to minimum transfer entropy (MTE). In the second part of the study, we computed the correction formulas according to both MMSE and MTE, from QT/RR series extracted from 25 Holter ECG recordings available on Physionet. The MTE approach considered individual Pearson's correlation coefficients between previous QT interval and RR value, which was found statistically different than 0, i.e., 0.70 ± 0.31 *(*$p < 0.01$*). The individual coefficients obtained with both approaches were: MMSE=*0.143 ± 0.061 *vs MTE=*0.101 ± 0.052 *(*$p < 0.05$*), with the latter resulting in an average reduction of about 27%. The study suggested that the use of QT/RR history significantly changes the value of the optimal coefficient.*

1. Introduction

The relationship between QT and RR intervals has been extensively investigated for i) reaching a better understanding of the interaction between autonomic nervous system and ventricular repolarization; and ii) its practical role in determining the cardiac risk for drug safety testing.

The problem of comparing QT intervals measured at different heart rates has been under investigation for more than 100 years. Different correction schemes were widely studied to reduce the effect of the heart rate on the measured QT interval. For example, Bazett's, Fridericia's and Framingham's correction formulas are among the most widely used for quantifying the corrected QT interval (QTc). Such formulas are based on the instantaneous RR value and its corresponding QT interval. Although these formulas make the computation of QTc feasible in short ECG recordings, it is well known that that QT/RR relationship presents a hysteresis, that makes the QT interval dependent on a history of previous RR values, up to 2 preceding minutes [1]. In addition, formulas were found having different performance for risk stratification [2]. These limitations still encourage investigations for alternative QT correction schemes.

The classic approach used to correct the QT interval is to propose a parametric correction formula of QTc and to fit its parameters in such a way to set the correlation between QTc and RR equal to 0. For a linear correction formula of the form $\mathrm{QTc} = \mathrm{QT} + \alpha(1 - \mathrm{RR})$, this is equivalent to find α that minimizes the covariance between QTc and RR or, alternatively, the mean square error between QT and $\alpha\mathrm{RR}$ after removing their mean values. Here, we defined this approach as correction according to minimum mean square error (MMSE).

Recently, Transfer Entropy (TE) has been evaluated to assess the inter-relationship between the RR and QT interval series at different history lengths and was proposed as a new approach for correcting the QT interval by setting TE equal to 0 [3]. The objective of this study was to shed light on how much different the introduced correction scheme is from MMSE. With this aim in mind, in the first part of the study, we investigated on closed-form solutions for the parameter α of a linear correction formula when the bivariate random process formed by QT/RR is stationary and normally distributed. In the second part of the study, we compared the parameter α computed using both schemes on Holter ECG recordings.

2. Methods

2.1. The QT/RR model

Let us assume that the RR and QT series are realizations of a stationary, multivariate and normally-distributed random process. In this scenario, any subset of the random variables composing the process is distributed as a multivariate Normal distribution. Hence, the random vector composed by consecutive variables can be defined as

$$\begin{bmatrix}\mathbf{q}_k \\ \mathbf{r}_k\end{bmatrix} \sim N(\mu, \Sigma) \tag{1}$$

with

$$\begin{aligned}\mathbf{q}_k &= \begin{bmatrix}\mathrm{QT}_k & \mathrm{QT}_{k-1} & \cdots & \mathrm{QT}_{k-(n_{\mathrm{QT}}-1)}\end{bmatrix}^\intercal \\ \mathbf{r}_k &= \begin{bmatrix}\mathrm{RR}_k & \mathrm{RR}_{k-1} & \cdots & \mathrm{RR}_{k-(n_{\mathrm{RR}}-1)}\end{bmatrix}^\intercal\end{aligned} \tag{2}$$

where n_{RR} and n_{QT} represent the number of RR and QT values considered and k is the beat index, whereas μ and Σ are the constant-in-time mean vector and covariance matrix of the random process.

According to the stationary model, the means, variances, autocorrelation coefficients and Pearson's correlation coefficients for two random variables X and Y can be defined as follows

$$\begin{aligned}\mu_X &= E[X] \\ \sigma_X^2 &= E[(X-\mu_X)^2] \\ \rho_X[\tau] &= \frac{E[(X_{k+|\tau|}-\mu_X)(X_k-\mu_X)]}{\sigma_X^2} \\ \rho_{X,Y}[\tau] &= \frac{E[(X_{k+\tau}-\mu_X)(Y_k-\mu_Y)]}{\sigma_X\sigma_Y}.\end{aligned} \tag{3}$$

To improve readability, in the rest of the paper, we used $\rho_X = \rho_X[1]$ and $\rho_{X,Y} = \rho_{X,Y}[0]$ for these two coefficients.

2.2. Linear correction formula and transfer entropy

In this study, we employed TE to determine the optimal linear correction formula, *i.e.*, finding the optimal α value of

$$\mathrm{QTc}_k = \mathrm{QT}_k + \alpha(1-\mathrm{RR}_k) \tag{4}$$

such that TE between RR and QTc is zero.

As reported in [3], the main concept for optimal correction according to TE was that past samples should not change the entropy value of the corrected random variable. If this holds then these samples do not affect the corrected value because they turn out to be statistical independent. The TE from RR to QTc can be written as

$$\begin{aligned}T_{\mathrm{RR}\to\mathrm{QTc}} = {} & h(\mathrm{QTc}_k|\mathbf{Q}\mathbf{q}_k) \\ & - h(\mathrm{QTc}_k|\mathbf{Q}\mathbf{q}_k, \mathrm{RR}_k, \mathbf{R}\mathbf{r}_k)\end{aligned} \tag{5}$$

where $h(X|C)$ is the Conditional Differential Entropy of the random variable X conditioned on all values of C, and $\mathbf{Q}$ and $\mathbf{R}$ are matrices selecting the history of $\mathbf{q}_k$ and $\mathbf{r}_k$ to condition upon, but excluding QT_k and RR_k (the matrices contained only 0 and 1, and their first entry is 0).

In order to compute the TE, we relied on well-known results about the entropy of a multivariate Gaussian variable that, for a variable X with d dimensions and covariance matrix Σ_X, is

$$h(X) = \frac{d}{2} + \frac{d}{2}\log(2\pi) + \frac{1}{2}\log(|\Sigma_X|) \tag{6}$$

where $|\Sigma_X|$ represents the determinant of Σ_X.

The conditional entropy of two variable is

$$h(Y|X) = h(X,Y) - h(X), \tag{7}$$

and, when (X,Y) is normally distributed, the marginal distribution of X can be obtained by removing the rows and columns related to the random variable Y from the covariance matrix.

Using (4), (6) and (7), the optimal value of α, according to $\mathrm{TE}=0$, was obtained by solving the equation[1]

$$|\Sigma_{(\mathrm{QTc}(\alpha),\mathbf{Q}\mathbf{q}_k)}| = \frac{|\Sigma_{(\mathrm{QT}_k,\mathbf{Q}\mathbf{q}_k,\mathrm{RR}_k,\mathbf{R}\mathbf{r}_k)}||\Sigma_{(\mathbf{Q}\mathbf{q}_k)}|}{|\Sigma_{(\mathbf{Q}\mathbf{q}_k,\mathrm{RR}_k,\mathbf{R}\mathbf{r}_k)}|} \tag{8}$$

where the notation of $\Sigma_{(X_i)_{i\in\mathbb{N}}}$ defines the covariance matrix built with the ordered sequence of random variables $(X_i)_{i\in\mathbb{N}}$. In case the matrix $\mathbf{Q}$ does not select any variable on the right-hand side of (8), the determinant of $\Sigma_{(\mathbf{Q}\mathbf{q}_k)}$ is set to 1.

In this context, the left-hand side of (8) is a polynomial function of order 2 with respect to α. In addition, considering that $\mathrm{TE} \geq 0$, the solution of (8) might not exist. Here, we proposed that QT correction has to be performed under a new paradigm that can be defined as minimum transfer entropy (MTE). Such minimum value can be found by

$$\frac{d|\Sigma_{(\mathrm{QTc}(\alpha),\mathbf{Q}\mathbf{q}_k)}|}{d\alpha} = 0. \tag{9}$$

In the next sections, we investigated on three different cases for QT correction according to MTE. The appendix reports the mathematical derivation for each case.

2.2.1. Case 1

In the first case, we considered only the use of $\mathrm{QT}_k/\mathrm{RR}_k$ pair to perform the correction according to MTE. In other words, no histories of QT and RR were considered. The first optimal α value was found by setting

$$T_{\mathrm{RR}\to\mathrm{QTc}} = h(\mathrm{QTc}_k) - h(\mathrm{QTc}_k|\mathrm{RR}_k) = 0. \tag{10}$$

By solving (8), it was possible to show that

$$\alpha = \rho_{\mathrm{QT,RR}}\frac{\sigma_{\mathrm{QT}}}{\sigma_{\mathrm{RR}}}, \tag{11}$$

that is equal to the $\mathrm{QT}_k/\mathrm{RR}_k$ slope according to MMSE.

[1]Note that $|\Sigma_{(\mathrm{QTc}(\alpha),\mathbf{Q}\mathbf{q}_k,\mathrm{RR}_k\mathbf{R}\mathbf{r}_k)}| = |\Sigma_{(\mathrm{QT}_k,\mathbf{Q}\mathbf{q}_k,\mathrm{RR}_k,\mathbf{R}\mathbf{r}_k)}|$, which does not depend on α, when the correction formula in (4) is used.

2.2.2. Case 2

In the second case, we wanted to verify what value of α would set $\mathrm{TE} = 0$ when one previous RR value is added in the framework. This is equivalent to assume a non-zero correlation between QT_k and RR_{k-1}. The TE formulation was the following

$$T_{\mathrm{RR}\to\mathrm{QTc}} = h(\mathrm{QTc}_k) - h(\mathrm{QTc}_k|\mathrm{RR}_k, \mathrm{RR}_{k-1}) = 0 \tag{12}$$

which differed from 0 for any value of α. However, the MTE solution was still located at $\alpha = \rho_{\mathrm{QT,RR}}\sigma_{\mathrm{QT}}/\sigma_{\mathrm{RR}}$.

2.2.3. Case 3

In the third case, we considered the current RR value and the previous QT interval in the correction scheme. In particular, the TE was

$$\begin{aligned} T_{\mathrm{RR}\to\mathrm{QTc}} = {} & h(\mathrm{QTc}_k|\mathrm{QT}_{k-1}) \\ & - h(\mathrm{QTc}_k|\mathrm{QT}_{k-1}\mathrm{RR}_k) = 0. \end{aligned} \tag{13}$$

Here, it was possible to show that

$$\alpha = \left(\frac{\rho_{\mathrm{QT,RR}} - \rho_{\mathrm{QT,RR}}[-1]\rho_{\mathrm{QT}}}{1 - \rho_{\mathrm{QT,RR}}[-1]^2} \right) \frac{\sigma_{\mathrm{QT}}}{\sigma_{\mathrm{RR}}}. \tag{14}$$

2.3. Experiment and statistical analyses

Comparing the α parameter found through MMSE in (11) and the one with MTE in (14), it is clear that the auto- and cross-correlation coefficients at lag 0 and 1 play a role in the correction formula. However, it is not clear whether the contribution of these coefficients become significantly relevant on real data. In order to verify so, we analyzed QT/RR profiles extracted from Holter ECG recordings and computed the individual parameter α for each subject and for the two schemes.

One-sample Kolmogorov-Smirnov test was employed to test whether data come from a Gaussian distribution. A paired t-test was used to compare the α values of MMSE vs MTE. One-sample t-test was instead used to verify whether i) the α parameter was different from Framingham's coefficient (*i.e.*, 0.154); and ii) the auto- and cross-correlation coefficients differed from 0. Significance levels were set at 0.05.

2.4. Dataset and QT/RR extraction

Similarly to [3], we employed two datasets freely available on Physionet [4], *i.e.*, "MIT-BIH Normal Sinus Rhythm Database" and "MIT-BIH Long-Term ECG Database", with a total of 25 subjects from which a 24h Holter ECG recording was collected.

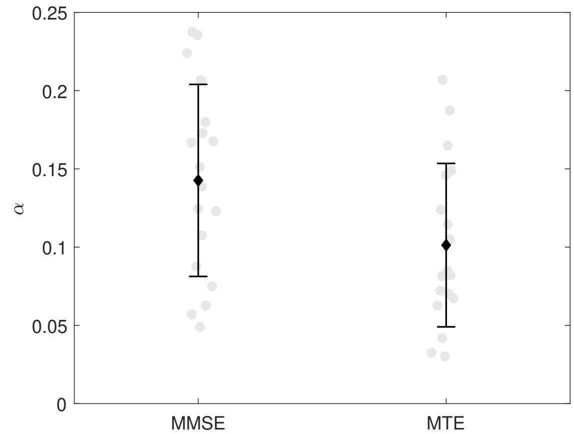

Figure 1. Errorbars for the individual parameters α computed using the MMSE and MTE schemes. Gray circles represent the computed values.

A standard ECG processing pipeline was performed on consecutive windows of 10 minutes. In each window, a Butterworth filter (3rd order, 0.5-40 Hz, zero phase) was applied to remove baseline wandering and high frequency noise. The isoelectric line of each ECG lead was then set back to 0 mV by subtracting the mode of the amplitude distribution from the ECG. Beats were detected using a modified version of Pan and Tompkins's algorithm [5]. The quality of each ECG lead was assessed by means of a correlation-based algorithm. In particular, the average QRS complex was first calculated and Pearson's correlation coefficients between each QRS complex and the average one was computed. The lead was considered of sufficient quality only if the average correlation across beats was higher than 0.9. Only segments with all good quality leads were further considered in the pipeline.

ECG beats were assigned to specific bins using RR-binning (minimum and maximum RR values were 500 ms and 1200 ms, bin size was 50 ms). The beats within each bin were then processed to create an average QRST template using Woody's algorithm [6]. Templates were built on the vector magnitude. The Q point and the end of T-wave were located on the template for each RR bin. The latter was found using the well-known T-wave slope method [7]. In order to build the correspondence with QT_k, the RR interval at beat k was defined as the difference between the time instant of the R peak at beat k and that one at beat $k-1$. The output of this phase was the QT/RR profile for each subject.

3. Results

Both α computed using the two schemes were found normally distributed ($p > 0.05$). The mean α values of the two schemes were found statistically significantly different between each other (mean $\pm$ standard deviation across subjects; MMSE: 0.143 ± 0.061 vs MTE: 0.101 ± 0.052; $p < 0.05$). The average MTE percent reduction of α, with respect to MMSE, was -27.54%. Figure 1 reports the errorbars of the individual parameters α for the two correction schemes.

The mean of the α value for MMSE was not statistically significantly different from Framingham's coefficient ($p > 0.05$), while it was for MTE ($p < 0.05$).

The average values of ρ_{QT}, $\rho_{\mathrm{QT,RR}}$, $\rho_{\mathrm{QT,RR}}[-1]$ were all statistically significantly different from 0 (0.82 ± 0.20, 0.83 ± 0.28, 0.70 ± 0.31, respectively; $p < 0.05$).

4. Discussion and conclusions

In this study, we found that the α coefficient calculated with $\mathrm{TE} = 0$ is equivalent to that one obtained by MMSE when considering: i) RR and QT series as stationary Gaussian processes; ii) no histories of QT and RR; and iii) a linear correction formula. In addition, we proved that TE cannot be set to 0 for any QT/RR history. Hence, we proposed a generalization of the correction scheme that considers the MTE instead of setting $\mathrm{TE} = 0$.

On real data, we found that Framingham's coefficient was higher than the α value computed according to MTE. This result can be explained by the fact that the QT history is considered in the new correction scheme, which is neglected by Framingham's formula. Despite its different value, the assessment of the effectiveness the new coefficient for drug safety testing is left to future works.

In [3], authors also proposed to perform the correction dynamically, *i.e.*, one sample at a time, by finding the QT interval that would set $\mathrm{TE} = 0$ considering the QT/RR history. This approach is substantially different from the traditional correction scheme in which the formula is selected beforehand, its parameters estimated and then used in applications. Attention should be payed in applying such correction approach since correcting under effects of drugs that alter the heart rate too can be misleading [8].

Appendix

Results for the case 1 can be obtained by

$$\begin{aligned}
|\Sigma_{(\mathrm{QTc}_k(\alpha))}| &= \sigma^2_{\mathrm{RR}}\alpha^2 - 2\rho_{\mathrm{QT,RR}}\sigma_{\mathrm{QT}}\sigma_{\mathrm{RR}}\alpha + \sigma^2_{\mathrm{QT}} \\
|\Sigma_{(\mathrm{QT}_k,\mathrm{RR}_k)}| &= \sigma^2_{\mathrm{QT}}\sigma^2_{\mathrm{RR}}(1-\rho^2_{\mathrm{QT,RR}}) \\
|\Sigma_{(\mathrm{RR}_k)}| &= \sigma^2_{\mathrm{RR}}.
\end{aligned}$$

Results for the case 2 can be obtained by

$$\begin{aligned}
|\Sigma_{(\mathrm{QTc}_k(\alpha))}| &= \sigma^2_{\mathrm{RR}}\alpha^2 - 2\rho_{\mathrm{QT,RR}}\sigma_{\mathrm{QT}}\sigma_{\mathrm{RR}}\alpha + \sigma^2_{\mathrm{QT}} \\
|\Sigma_{(\mathrm{QT}_k,\mathrm{RR}_k,\mathrm{RR}_{k-1})}| &= \sigma^2_{\mathrm{QT}}\sigma^4_{\mathrm{RR}}\left(1-\rho^2_{\mathrm{QT,RR}} - \rho_{\mathrm{QT,RR}}[1]^2\right. \\
&\quad \left. -\rho^2_{\mathrm{RR}} + 2\rho_{\mathrm{QT,RR}}\rho_{\mathrm{QT,RR}}[1]\rho_{\mathrm{RR}}\right) \\
|\Sigma_{(\mathrm{RR}_k,\mathrm{RR}_{k-1})}| &= \sigma^4_{\mathrm{RR}}(1-\rho^2_{\mathrm{RR}}).
\end{aligned}$$

The discriminant of the quadratic formula for the roots of (8) is

$$-\frac{4\sigma^2_{\mathrm{QT}}\sigma^2_{\mathrm{RR}}(\rho_{\mathrm{QT,RR}}[-1] - \rho_{\mathrm{QT,RR}}\rho_{\mathrm{RR}})^2}{1-\rho^2_{\mathrm{RR}}}$$

which is 0 only if $\rho_{\mathrm{QT,RR}}[-1] - \rho_{\mathrm{QT,RR}}\rho_{\mathrm{RR}} = 0$, or negative otherwise.

Results for the case 3 can be obtained by

$$\begin{aligned}
|\Sigma_{(\mathrm{QTc}_k(\alpha),\mathrm{QT}_{k-1})}| &= \sigma^2_{\mathrm{QT}}\left(\alpha^2\sigma^2_{\mathrm{RR}}(1-\rho_{\mathrm{QT,RR}}[-1]^2)\right. \\
&\quad -2\alpha\sigma_{\mathrm{QT}}\sigma_{\mathrm{RR}}(\rho_{\mathrm{QT,RR}} - \rho_{\mathrm{QT,RR}}[-1]\rho_{\mathrm{QT}}) \\
&\quad \left. +\sigma^2_{\mathrm{QT}}(1-\rho^2_{\mathrm{QT}})\right) \\
|\Sigma_{(\mathrm{QT}_k,\mathrm{QT}_{k-1}\mathrm{RR}_k)}| &= \sigma^4_{\mathrm{QT}}\sigma^2_{\mathrm{RR}}\left(1-\rho^2_{\mathrm{QT,RR}} - \rho_{\mathrm{QT,RR}}[-1]^2\right. \\
&\quad \left. -\rho^2_{\mathrm{QT}} + 2\rho_{\mathrm{QT,RR}}\rho_{\mathrm{QT,RR}}[-1]\rho_{\mathrm{QT}}\right) \\
|\Sigma_{(\mathrm{QT}_{k-1})}| &= \sigma^2_{\mathrm{QT}} \\
|\Sigma_{(\mathrm{QT}_{k-1},\mathrm{RR}_k)}| &= \sigma^2_{\mathrm{QT}}\sigma^2_{\mathrm{RR}}(1-\rho_{\mathrm{QT,RR}}[-1]^2).
\end{aligned}$$

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