Towards Accurate and Model-Free QT Correction

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Abstract

In the electrocardiogram (ECG), the QT interval is an important metric of risk for various adverse cardiovascular events and a key measure in cardiotoxicology. The main challenge in the interpretation of the QT measurement is its dependence on the heart rate, i.e., the RR intervals. To correct the QT interval for heart rate, a multitude of approximative methods have been developed, e.g., the power-law formulas of Bazett and Fridericia that are still in clinical use. However, these methods are known to under- or overcorrect the QT intervals, and none of the methods developed to date are universally applicable to different conditions.

Here we present a QT correction method that is not based on models or empirical data, but directly utilizes information transfer between the RR and QT intervals during the measurement. The method dynamically adapts to a multitude of previous RR intervals and gives the QT correction as an output. We outline the essential principles of the method and provide a set of test results that demonstrate the stability of the corrected QT values in comparison with the conventional correction methods.

1. Introduction

The QT interval is the time measured from the beginning of the QRS complex to the end of the T wave in the electrocardiogram (ECG). It corresponds to the duration of the ventricular action potential, i.e., the time for the ventricles to depolarize and repolarize. Hence, the QT interval is a direct measure for ventricular arrythmias. In particular, QT prolongation is associated with numerous adverse cardiovascular diseases and events such as long QT syndrome, heart failure, coronary artery disease, *torsades de pointes*, and sudden cardiac death (see, e.g., Ref. [1]).

The QT interval is also a key metric in drug development [2]. QT prolongation has been the most common cause of the withdrawal or restriction of drugs on the market [3]. In 2005, a new guidance on the clinical assessment of drug-induced QT prolongation was adopted, and the "thorough QT/QTc study" became the standard part of drug development programs [4, 5].

The fundamental challenge in the interpretation of the QT interval is its dependence on the heart rate (HR). Typically, low HR, i.e., long RR intervals correspond to long QT intervals and vice versa. For this reason, the QT interval needs to be compensated for the HR to obtain the *corrected QT* (QTc) interval. The most commonly used correction formula is Bazett [6] developed through a simple fitting procedure in 1920. It is still widely used despite its known problems to under(over)correct at low (high) HR. Fridericia's correction [7] also from 1920 employs a similar model with a different fitting parameter, and it is currently the standard adopted by FDA [2], even though several alternative formulae have been suggested, e.g., the Hodges [8] and Framingham [9] corrections, and more recently the spline QTc method [10].

An alternative approach is the *individual* QT correction [11, 12] employing a fitting to the baseline RR-QT pairs of each individual. Even though this method performs well and suits to thorough QT/QTc studies, its applicability to clinical practice is challenging due to, e.g., the QT hysteresis [13, 14]. To account for hysteresis, a beat-to-beat method [15] that employs all raw QT-RR interval data instead of any QT correction, is an appealing alternative.

Here we employ information theory, particularly the properties of transfer entropy [16] for the RR-QT relationship [17] to properly remove the dependence of the QT interval on the RR interval. The resulting QT correction is completely free of models or empirical data. We demonstrate with a few examples that our correction method yields superior performance over the existing methods in terms of QTc stability at varying HR.

2. Methods

2.1. Transfer entropy

The essential building block in our QT correction method is *transfer entropy* (TE) introduced by Schreiber [16] and applied to the RR-QT relationship by some of the present authors [17]. We assume that the QT dependence on the HR is (largely) determined by the information flow from the time-dependent RR interval process

to the corresponding QT interval process. Thus, reducing this information flow by setting TE to zero can yield the (corrected) QT interval length.

TE estimates information transfer from the source to the destination process that we may now denote directly as RR(t) and and QT(t), respectively. In simple terms, adopting the terminology of Ref. [18], TE equals to information flow from RR to QT, which equals to information (or uncertainty) about future observation QT(t+1) gained from the past observations of QT **minus** information about future observation QT(t+1) gained from past observations of both RR and QT. Formally, we can express TE from RR to QT as [17]

$$\begin{aligned} \mathrm{TE}_{\mathrm{RR}\to\mathrm{QT}} &= \sum_i p\left(\mathrm{QT}_i, \mathrm{QT}_{i-1}^{(k)}, \mathrm{RR}_{i-1}^{(n)}\right) \\ &\times \log_2 \frac{p\left(\mathrm{QT}_i|\mathrm{QT}_{i-1}^{(k)}, \mathrm{RR}_{i-1}^{(n)}\right)}{p\left(\mathrm{QT}_i|\mathrm{QT}_{i-1}^{(k)}\right)}. \quad (1) \end{aligned}$$

Here $p(x)$ and $p(x|y)$ refer to probability distributions and conditional probability distributions. Then $\mathrm{QT}_{i-1}^{(k)}$ and $\mathrm{RR}_{i-1}^{(n)}$ are k and n preceding values, backwards from $i-1$, of QT and RR series, respectively. Previously, we have shown [17] that $\mathrm{TE}_{\mathrm{RR}\to\mathrm{QT}}$ profoundly dominates over $\mathrm{TE}_{\mathrm{QT}\to\mathrm{RR}}$, and that in the former case the RR history has a long-term effect, i.e., TE increases as a function of n and saturates at around $n \sim 10$. Hence, in the following we set QT history to $k = 1$ and vary the RR history in the range $n = 1 \ldots 50$.

2.2. Probability distributions

ECG data with RR and QT intervals are used to estimate the probability distributions of observing QT interval values given two distinct historical contexts: (i) the QT history alone and (ii) the QT and RR history together. These probability distributions – corresponding to the denominator and then numerator in Eq. (1) – are conventionally called transition probabilities [16, 17]. To obtain smooth transition probabilities for proper interpolation of QT intervals we apply kernel density estimation (KDE) techniques. The idea is to account each data point contributing to the probability distribution as a *kernel* that has a predefined shape, e.g., a Gaussian function drawn around the given point with a specific width.

Using KDE with a Gaussian kernel we first estimate the joint probability distribution of events QT_i, QT_{i-1},...,QT_{i-k}, and, if RR history is included, RR_{i-1},...,RR_{i-n} for any given coupled series of RR and QT intervals. Next, for the given interval QT_i and its history $\mathrm{QT}_{i-1}^{(k)}$ and/or $\mathrm{RR}_{i-1}^{(n)}$ we take a slice of the joint distribution along the QT_i axis (see Fig. 1). This slice, appropriately normalized according to the chain rule, represents the one-dimensional (1D) conditional probability density $p\left(\mathrm{QT}_i|\mathrm{QT}_{i-1}^{(k)}, \mathrm{RR}_{i-1}^{(n)}\right)$ or $p\left(\mathrm{QT}_i|\mathrm{QT}_{i-1}^{(k)}\right)$ as a function of QT_i. Now, equality of these two 1D distributions warrants a zero TE from RR to QT intervals as $\log 1 = 0$ in Eq. (1). Thus, an appropriate QT value equating the two 1D distributions in the QT space is a *candidate* for QTc. In summary, the algorithm proceeds beat-by-beat drawing the two 1D distributions for every QT_i based on its history of QT and RR intervals and finding the proper intersection points of the distributions as demonstrated in Fig. 1.

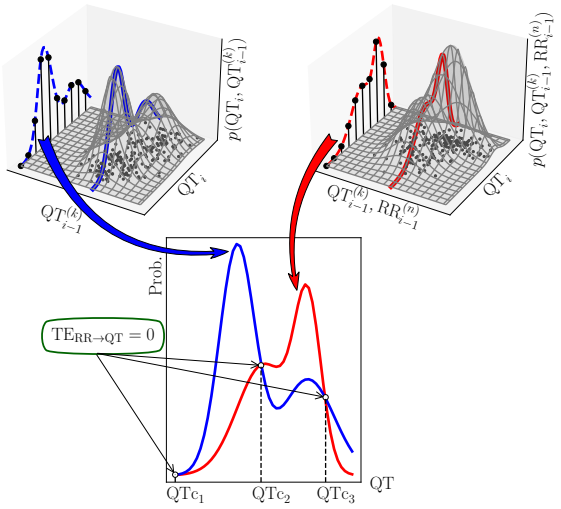

Figure 1. Estimation of the transition probabilities from the data points (black) according to Gaussian kernel density estimation. The intersection of the one-dimensional distributions as a function of QT_i yields zero transfer entropy and thus candidates for QTc.

2.3. QTc selection

Finally, we need to select the target QTc among multiple potential candidate QTc values corresponding to the intersection points of the two distributions. The bottom panel of Fig. 1 exemplifies this task with three possible candidates (QTc_1, QTc_2, QTc_3). The selection procedure is a complex task of its own, and we have several options – apart from the obvious exclusion of intersections in the tails of the distributions, e.g., QTc_1 in Fig. 1. Possible options include but are not limited to (i) maximum probability, i.e., the highest intersection point; (ii) minimum distance to QT_0, i.e., the QT value observed at 60 BPM (RR=1000 ms) according to the data; (iii) the mean of all the QTc candidates exceeding a minimum threshold. In the following we resort to option (ii) with a 2nd order polynomial fit to the RR-QT point cloud to determine QT_0.

3. Demonstration

To demonstrate the performance of the method we selected 15 out of 18 healthy subjects in PhysioNet [19] "MIT-BIH Normal Sinus Rhythm" database and 3 out of 7 healthy subjects in "MIT-BIH Long Term" database. The selection was made according to the optimal data quality for RR and QT intervals. The intervals were extracted using the the methods in Refs. [19–21].

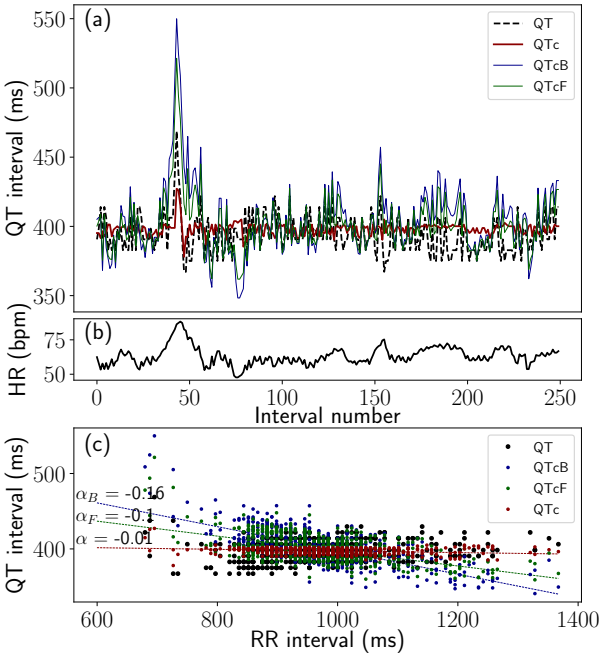

Figure 2. (a) Example of QT(c) values for a healthy subject as a function of time. (b) Corresponding heart rate during the measurement. (c) RR-QT point cloud during the measurement.

In Fig. 2(a) we show a representative example of a continuous segment of 250 QT intervals (dashed line), together with the QTc values computed with our method and with the Bazett (QTcB) and Fridericia (QTcF) formulae. Figure 2(b) shows the corresponding HR computed as the inverse of the RR intervals. The erroneous correction of both QTcB and QTcF (here mainly undercorrection) is clearly visible at HRs that are considerably below or above 60 BPM. For example, the increase in HR at 40-50 beats leads to a significant increase in both QTcB and QTcF – beyond the normal range – whereas our method shows only a moderate and short perturbation, which is preceded and followed by stable behavior. Overall, the standard deviation of our QTc values throughout the segment is only a fraction of that of QTcB and QTcF.

Figure 2(c) shows the RR-QT(c) point clouds of the same segment, together with linear fits to the data. First, it is noteworthy that the raw QT values are widely distributed, i.e., the variance of QT values is large at a fixed RR range. Secondly, the undercorrection of Bazett and Fridericia formulae is clearly visible as the points follow a trend with slopes $\alpha_{\mathrm{B}} = -0.16$ and $\alpha_{\mathrm{F}} = -0.1$, respectively. In contrast, our method yields a nearly horizontal line with $\alpha = -0.01$. Thus, there is practically no under- or overcorrection in the QT values. In addition, all the QTc points are densely distributed along this horizontal line.

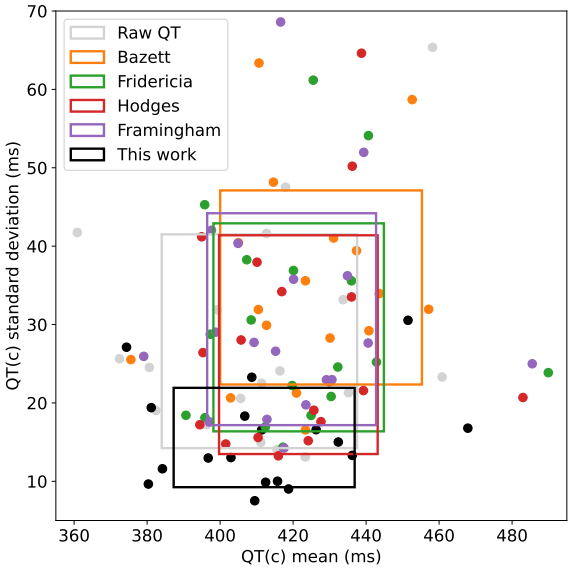

Figure 3. (a) Mean and standard deviation (SD) of QT(c) values over the full measurement for all the 18 subjects, respectively (points). The color of the points indicate the method (raw QT in gray). The rectangles visualize the method-specific distributions of each point cloud (see text).

In Fig. 3 we demonstrate the overall performance of our QTc method for all the 18 subjects under study. Each point shows the subject-specific mean QT(c) over the measurement (x axis) together with the standard deviation (SD). The rectangles show the method-specific distributions over all the subjects. Here the width and height of each rectangle is twice the SD of the points in x and y direction, respectively. There are significant individual differences in the *mean* QTc regardless of the method as demonstrated by the widths of the rectangles. Importantly, however, the SD(QTc) of every subject is significantly reduced with our method. For example, the SD's of Bazett are focused in the range $25 - 45$ ms, whereas the corresponding range in our method is only $10 - 20$ ms. We are currently performing further analysis of RR-QTc behavior, including larger sets of data.

4. Summary

In this work we have first introduced the relevance of the QT interval and the challenges in its interpretation, especially to correct for the heart rate, and outlined the present approaches to QT correction. Then we have presented a QT correction method that stems from information transfer from RR to QT intervals. We have demonstrated with a few examples of normal subjects that our method outperforms the conventional methods in stability at varying heart rate. Our QTc method is currently being validated for large datasets, and we foresee extensive use for the method both in academic and clinical studies, as well as in drug development in the future.

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