Information transfer in QT-RR dynamics: Towards a model-free QT correction method

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Abstract

Background. Heart dynamics is complex and results from interactions between various processes. The relation between the electrical properties of the heart and the beating rate is essential for the heart functioning. This relation is central when determining the corrected QT interval — an important measure of the risk for potentially lethal arrhythmias.

Methods. We use the transfer entropy method from information theory to quantitatively study the mutual dynamics of the ventricular action potential duration (the QT interval) and the length of the beat-to-beat (RR) interval. This method allows for quantifying *unidirectional* information flows between the coupled processes and, thus, for assessing the degree of inter-dependence in an empirical data-driven manner.

Results. We show that the QT and RR intervals are coupled in a *dynamical* fashion. In particular, for healthy individuals there is a strong asymmetry in the information transfer: the information flow *from RR to QT* dominates over the opposite flow (from QT to RR), i.e. QT depends on RR to a larger extent than RR on QT. Moreover, the *history* of the intervals has a strong effect on the information transfer. For example, at sufficiently long QT history length the information flow asymmetry inverts, that is, the QT-to-RR transfer becomes larger than RR-to-QT and the RR influence on QT dynamics weakens. Additionally, we observe a critical history length of RR (about 25 heart beats), after which the RR-to-QT transfer no longer changes. Finally, we examine how the QT correction affects the information flows between QT and RR. We demonstrate that the current QT correction methods cannot properly capture the changes in the information flows between the coupled QT and RR time series.

Conclusions. We conclude that our results obtained through a model-free information theory perspective can be directly utilized to significantly improve the present QT correction schemes in clinics.

1 Introduction

Heart dynamics is the result of complex interactions between various subsystems. The core of these interactions is the relation between the electrical properties of the heart and the overall cardiac response in the form of muscle contraction. To this end, studies of duration of the ventricular action potential and its relation to the heart rate have particular importance [1].

It is known that the QT interval of the electrocardiogram (ECG) recordings relates to the ventricular action potential duration and varies with the heart rate (HR) [1–4]. The relation between QT and HR has a practical importance as the assessment of the QT with respect to the HR values facilitates stratification of patients with increased risk of severe arrhythmias, including different ventricular arrhythmias and *torsades de pointes*, which may result in sudden cardiac death [1, 4–7]. Additionally, the QT values normalized according to the HR variability are used in assessment of adverse cardiac side effects of drugs in the context of diseases not directly related to the heart, as cancer and others [1, 8, 9].

Different formulas and methods to adjust the QT values according to the HR have been proposed.

The most frequently used ones are the formulas of Bazett and Fridericia [10, 11]. Although the formulas result from simple fitting procedures, they are still widely used in medical practice [3, 12, 13]. The formulas have been criticized due to their inability to universally capture the QT-HR relationship [14, 15], their subjective character [16, 17] and extreme simplicity [17–19]. Some other approaches exist too, including graphical procedures [20] and regression type corrections [1, 15].

Additionally, recent evidence demonstrates improvements in the QT correction procedures when a range of the past values of HR is taken into account [4, 21, 22]. The correction improvement is especially profound in patients with atrial fibrillation, where HR values are unpredictable [23, 24].

In this work, we analyze the coupled QT and beat-to-beat (RR) interval dynamics in terms of information flows. We use the transfer entropy method [25] which quantifies information transfer between two related processes. Specifically, we demonstrate asymmetry in the information flows between QT and RR time series of the same individual. Moreover, we show that the history length of the past values significantly affects the information flows, and the effect is opposite when QT and RR history lengths are varied independently. Additionally, the RR-QT reciprocal configuration, where QT interval may correspond to either the beginning of the related RR or its end, affects the information flow. Moreover, we demonstrate that the widely used QT correction formulas are not able to reduce the observed information transfers as stipulated by the correction procedures. Finally, the gender effects on the informational transfers are discussed.

2 Methods

Transfer entropy (TE) estimates information transfer (defined in Shannon terms) by calculating the amount of information that the *source* process provides about the next state of the *destination* process in the context of the destination's past [25]. Figure 1 schematically shows the effects of the history values on the next (i-th) value of a signal. For example, the RR→QT (green lines) information transfer is calculated by first taking only k QT history values and estimating their share in *predicting* the i-th QT value (dashed line) and, second, by considering both the share of k QT history values and the share of n RR history values in predicting the i-th QT value (solid line). Finally, the difference between the two estimations is directly related to the RR→QT transfer [25, 26].

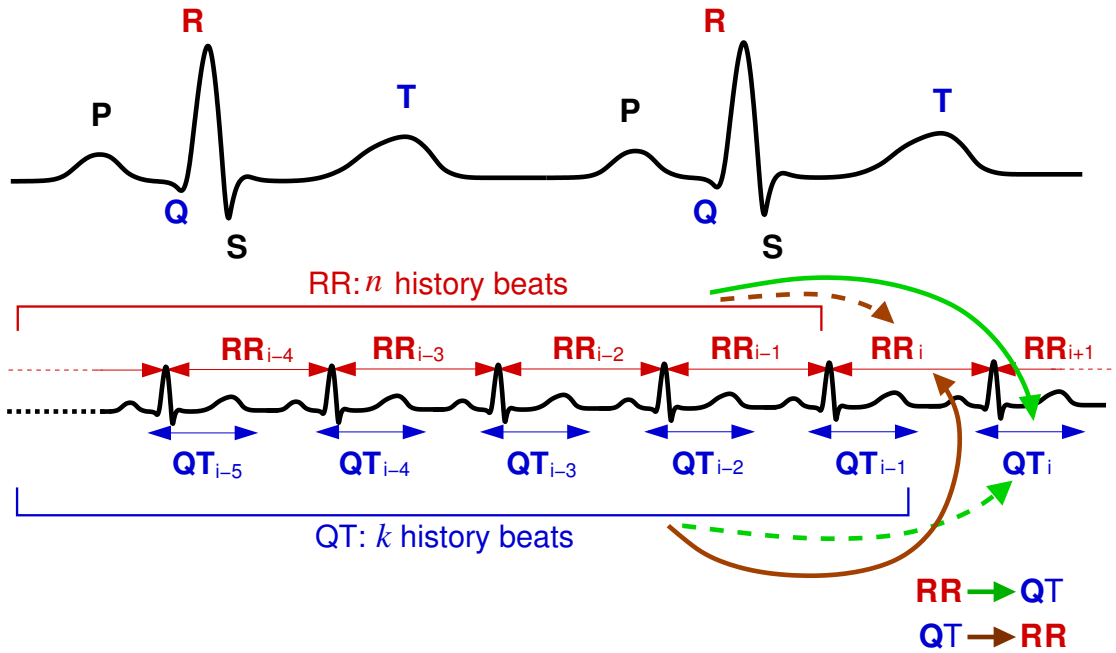

Figure 1: Information transfer between RR and QT series accounting for the past values (history). The two effects are compared when calculating TE: the history effect of the *destination* signal (**dashed** green/brown arrow) and that of the *source* signal in the context of the destination history (**solid** green/brown arrow).

The relation between history effects on predictions of the next value of, e.g., QT series in RR→QT transfer estimation is formally written as [25]:

$$\mathrm{TE}_{\mathrm{RR}\to\mathrm{QT}} = \sum_i p(\mathrm{QT}_i, \mathrm{QT}_{i-1}^{(k)}, \mathrm{RR}_{i-1}^{(n)}) \log_2 \frac{p(\mathrm{QT}_i|\mathrm{QT}_{i-1}^{(k)}, \mathrm{RR}_{i-1}^{(n)})}{p(\mathrm{QT}_i|\mathrm{QT}_{i-1}^{(k)})},$$

where $p(x)$ is a probability distribution, $p(x|y)$ is a conditional probability, $\mathrm{QT}_{i-1}^{(k)}$ and $\mathrm{RR}_{i-1}^{(n)}$ are k and n past values (from $i-1$ backwards) of QT and RR series, respectively. The sum is taken over all states i of the process. The resulting TE measure is in bits of information and is the average over the process realizations. In this study we vary RR history (n) and QT history (k) lengths separately. Unless specified otherwise, the history length is one heart beat.

We use Java Information Dynamics Toolkit (JIDT version 1.3.1) for TE calculations [26] with Kraskov-Stögbauer-Grassberger probability estimation [27], 4 nearest neighbors, and default values for other parameters.

3 Data

We downloaded raw ECG signals from PhysioNet [28] ("MIT-BIH Normal Sinus Rhythm" and "MIT-BIH Long Term" databases). Then, we extracted RR and QT intervals using the provided software [28–31] and discarded low quality signals. The final data set contains ECG recordings of 18 healthy individuals: 11 women (age from 20 to 45 years, mean 32), 7 men (age from 26 to 75 years, mean 46). Data were preprocessed to remove artifacts in the detected QT and RR values.

4 Results

First, we observe that the RR→QT transfer is larger than the opposite QT→RR transfer (Fig. 2). Since the TE algorithm adds a small amount of noise to the original data [26, 27], we run TE calculations for

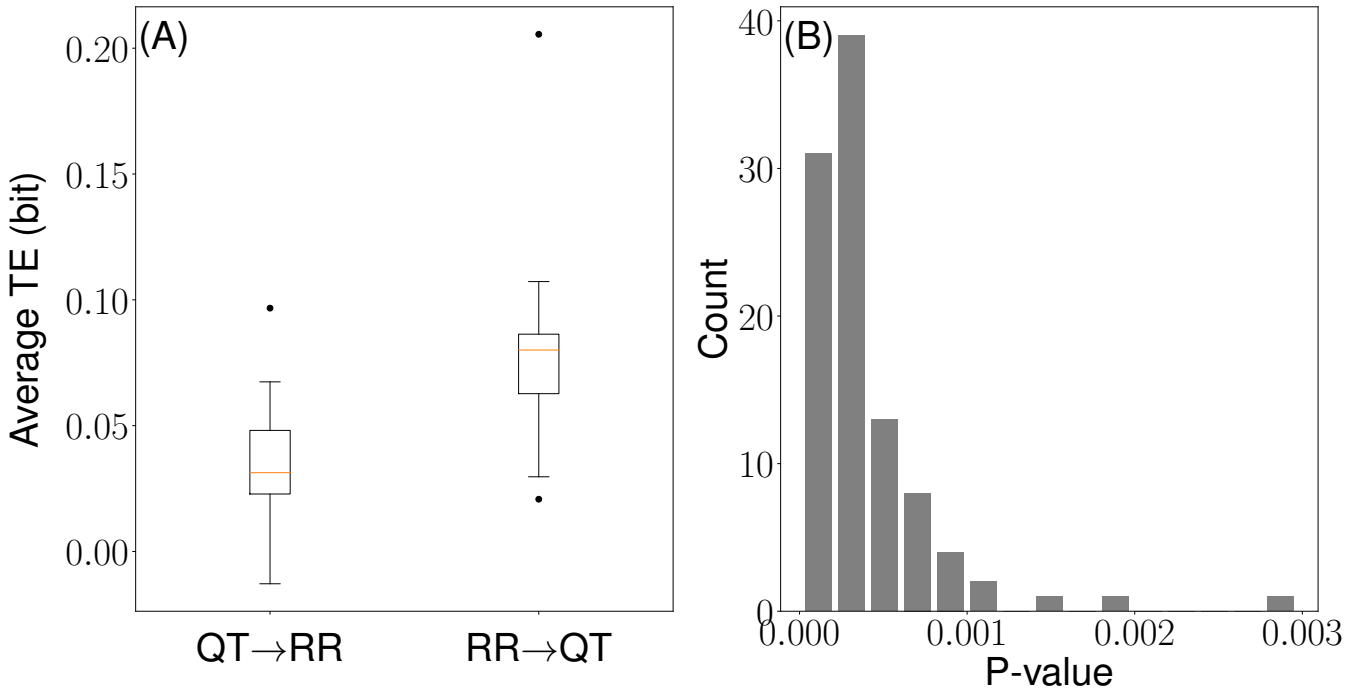

Figure 2: RR→QT information transfer is larger than that of QT→RR. (A) Distribution of TE averages. The red lines show the median of the distributions. The upper and lower boundaries of the box depict the 1st and the 3rd quartiles of the distributions. The lines extend further to cover additional 1.5 of the interquartile range (length of the box). Circles (•) depict outliers (i.e. points beyond the covered ranges). (B) Individual comparisons (paired two-sided t-test) between TE distributions.

100 times, each time taking the average from 18 coupled time series in order to estimate the true mean value of the subject group. The resulting average TE distributions for the two information transfers are shown in Fig. 2A. The distributions are significantly ($P < 0.0006$ unpaired two-sided t-test) different. Moreover, the individual comparisons between 100 TE distributions with paired two-sided t-test result in the P-value distribution shown in Fig. 2B, which also confirms the significance.

The inequality $\mathrm{TE}_{\mathrm{RR}\to\mathrm{QT}} > \mathrm{TE}_{\mathrm{QT}\to\mathrm{RR}}$ suggests that there is an implicit asymmetry in these otherwise equally important subprocesses in the context of the normal heart functioning. As $\mathrm{TE}_{\mathrm{X}\to\mathrm{Y}}$ quantifies the degree of a dependency $Y = f(X)$, the larger value of $\mathrm{TE}_{\mathrm{RR}\to\mathrm{QT}}$, compared to $\mathrm{TE}_{\mathrm{QT}\to\mathrm{RR}}$, indicates that the QT interval is more dependent on RR interval values, while RR depends on QT to a significantly less extent.

Heartbeat history. Next, we consider effects of the history length of the RR/QT series on TE. For this, we vary the history length of each series (RR or QT) separately, while keeping the history length of the other signal minimal, i.e., one heart beat.

Figure 3 demonstrates that with increasing history length the initial gap between RR→QT and

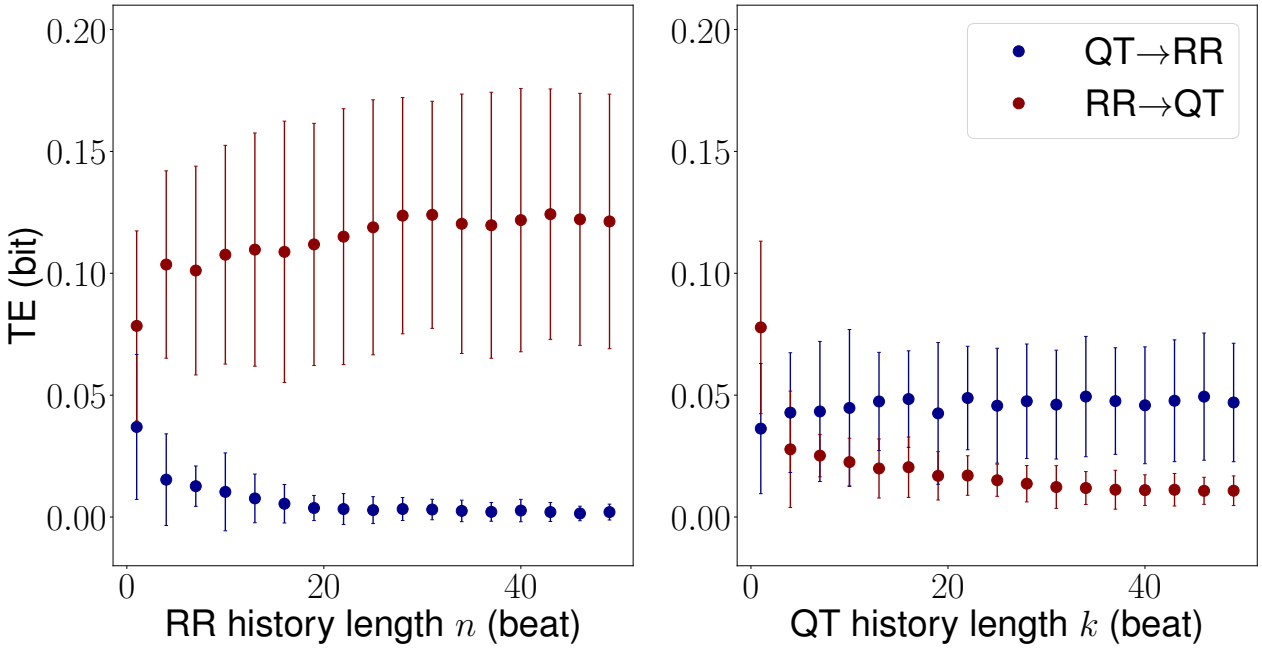

Figure 3: History length effect on information transfers. Dots (•) represent mean values, whereas the error bars standard deviations.

QT→RR transfers increases further. However, as RR history length n becomes longer, $\mathrm{TE}_{\mathrm{RR}\to\mathrm{QT}}$ starts dominating over the opposite transfer; while as QT history length k increases, $\mathrm{TE}_{\mathrm{QT}\to\mathrm{RR}}$ becomes larger than the opposite transfer. Note that $\mathrm{TE}_{\mathrm{RR}\to\mathrm{QT}}$ at large n is still larger than $\mathrm{TE}_{\mathrm{QT}\to\mathrm{RR}}$ at large k (Fig. 3). Additionally, $\mathrm{TE}_{\mathrm{QT}\to\mathrm{RR}}(n)$ reaches zero after 20...25 beats, while $\mathrm{TE}_{\mathrm{RR}\to\mathrm{QT}}(k)$ is not effectively zero at the farthest point considered ($k = 50$). These results indicate that the RR time series have a strong influence on the QT series as well as a larger informational content.

Finally, in Fig. 3 we can also determine the *critical* history length after which the information transfers remain constant. Thus, for example, $\mathrm{TE}_{\mathrm{RR}\to\mathrm{QT}}$ reaches a plateau at around 20...30 beats of RR history. This critical value reveals a characteristic length of the RR history which is able to explain the QT variability that can be explained by RR.

In order to verify that the history dependence in fact takes place as shown in Fig. 3, we conduct a permutation test, where QT and RR series from different individuals are mixed to form new unrelated coupled time series. Here, we use 10 permutations, resulting in 180 coupled QT/RR series. We calculate the TE distributions over different RR and QT history lengths and then compare them to the original

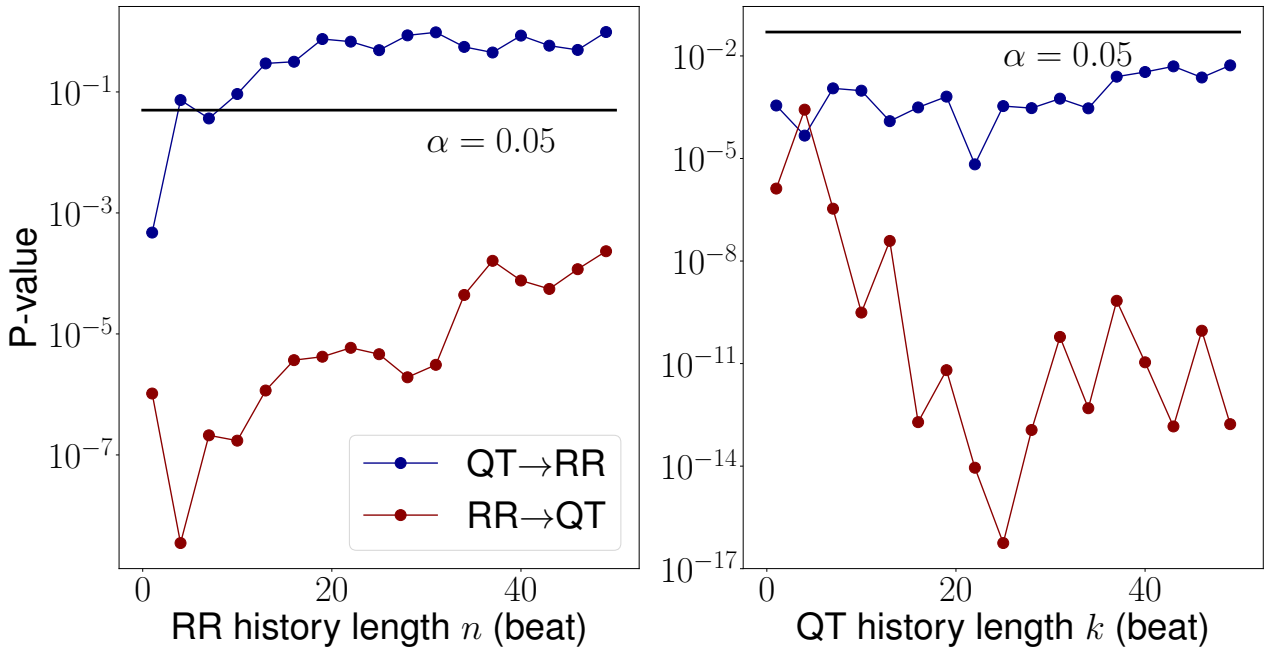

Figure 4: P-values resulting from (unpaired) t-test comparisons between 18 true and 180 permutation distributions for each history length value (cf. Fig. 3). Solid black line denotes the false discovery rate $\alpha = 0.05$.

distributions corresponding to Fig. 3. The comparison in the form of P-values (unpaired t-test) is shown in Fig. 4. The results confirm that all transfers arise from the genuine QT/RR relationship in the individuals, that is, the original transfers are significantly different from the surrogate permuted QT and RR sequences. The QT→RR transfer might look as an exception to the rule; however, $\mathrm{TE}_{\mathrm{QT}\to\mathrm{RR}}$ becomes apparently zero after several beats of history n (Fig. 3). Thus, in the case of QT→RR, there are no statistically significant differences between the original and surrogate data, as no information transfer exists.

QTstart and QTend configurations. A coupled QT/RR process can assume two configurations in regards to how the QT interval is selected. The QT interval may be coupled with the RR interval *starting* at the R-wave immediately following the Q-wave. This configuration is here referred to as "QTstart" (Fig. 5). However, the most common choice of the heart research community (see, e.g., [32]) is the configuration, where the QT interval is coupled with the RR interval *ending* at the R-wave immediately following the Q-wave ("QTend", Fig. 1). All results reported above have been obtained using the QTend configuration. Next, we study whether the configuration itself can cause differences in the information transfers between RR and QT.

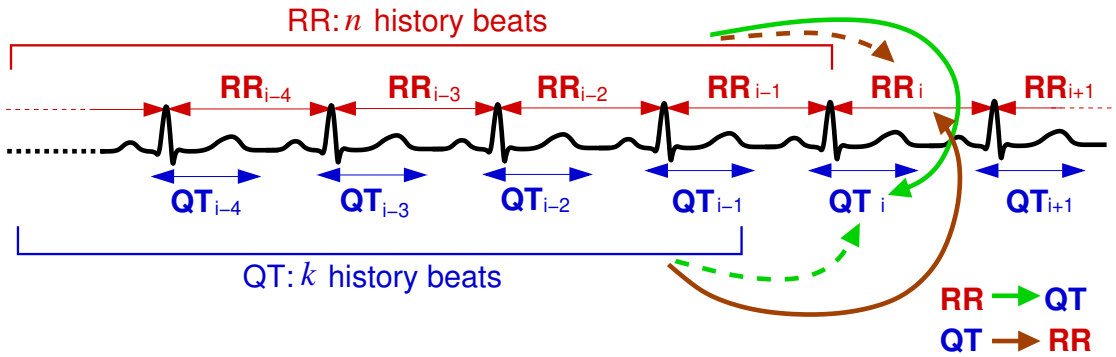

Figure 5: QTstart configuration. The QT interval can be taken to occur at the *end* of the corresponding RR interval (**QTend**, cf. Fig. 1) or at the *beginning* of it (**QTstart**).

We take the individual QT/RR series in their QTend configuration and transform them into the corresponding QTstart configuration. Then, we calculate TE distributions over the RR/QT history length and compare the two results in Fig. 6.

On the one hand, $\mathrm{TE}_{\mathrm{RR}\to\mathrm{QT}}$ significantly differs between the two configurations at small n and k

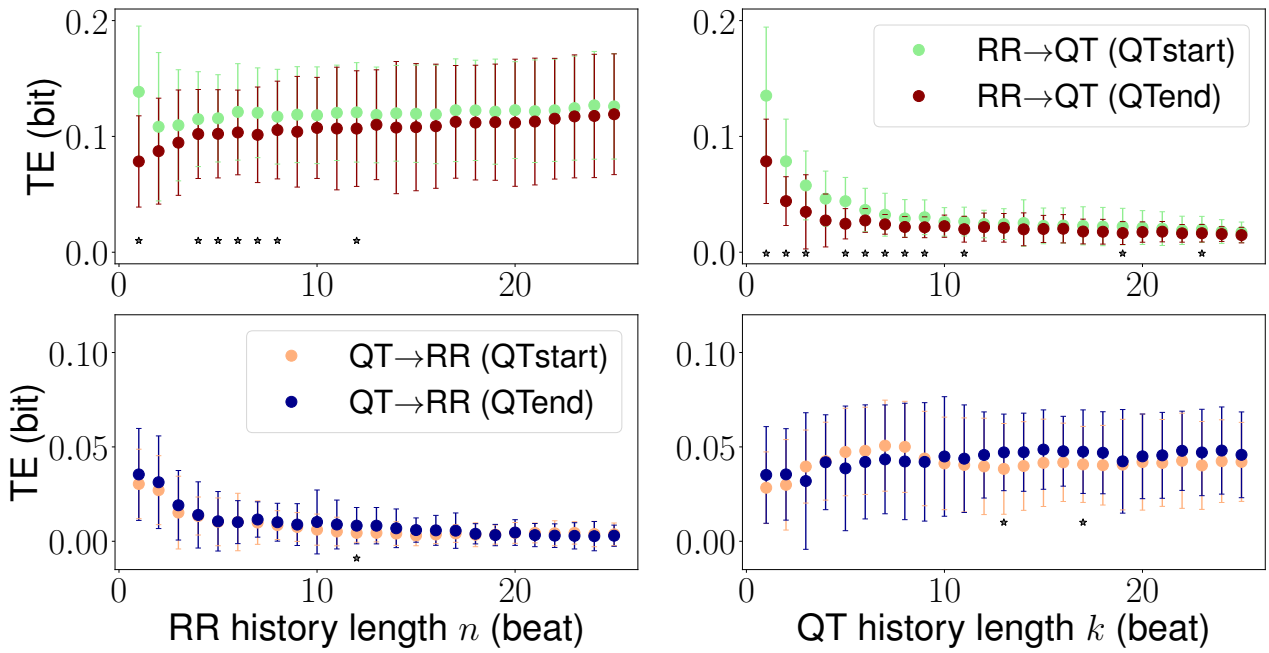

Figure 6: QTstart vs. QTend configuration (format: mean ± standard deviation). Stars show significant differences between distributions ($P \leq 0.05$, paired t-test).

with the mean QTstart-transfer being larger than the mean QTend-transfer. The effect is especially pronounced for several first beats of the history (Fig. 6). On the other hand, $\mathrm{TE}_{\mathrm{QT}\to\mathrm{RR}}$ does not reveal such tendencies, although occasionally TE distributions at some history lengths seem to be significantly different (Fig. 6).

The RR→QT transfer, being a direct measure of QT dependence on RR, is affected by the mutual QT/RR configuration. The QT correction schemes must account for this, especially if the procedure is based on the previous beats as in Refs. [4, 21] and given that the effect is not uniform along the history length.

Information transfer and QT correction. The QT interval correction is a known technique for normalizing the QT interval duration for different patients in order to be able to compare them at different heart rates and to determine whether there are signs for the increased risk of potentially lethal arrhythmias [1].

Here, we correct the observed QT time series using the Fridericia and Bazett correction formulas [10, 11] and calculate the TE distributions at various history lengths for the corrected QT/RR time series.

Then, we compare them with the original distributions in Fig. 7. Here, only the Fridericia correction is shown. We find that all transfers are significantly different at $n, k = 1$ (the same result holds for Bazett correction, data not shown). Only the corrected RR→QT transfer deviates systematically from the original transfer at $n, k > 10 \ldots 12$ beats (the systematic deviations were not observed for Bazett correction, data not shown). The corrected QT→RR transfer is statistically similar to the original transfer at most of the history lengths (both n and k).

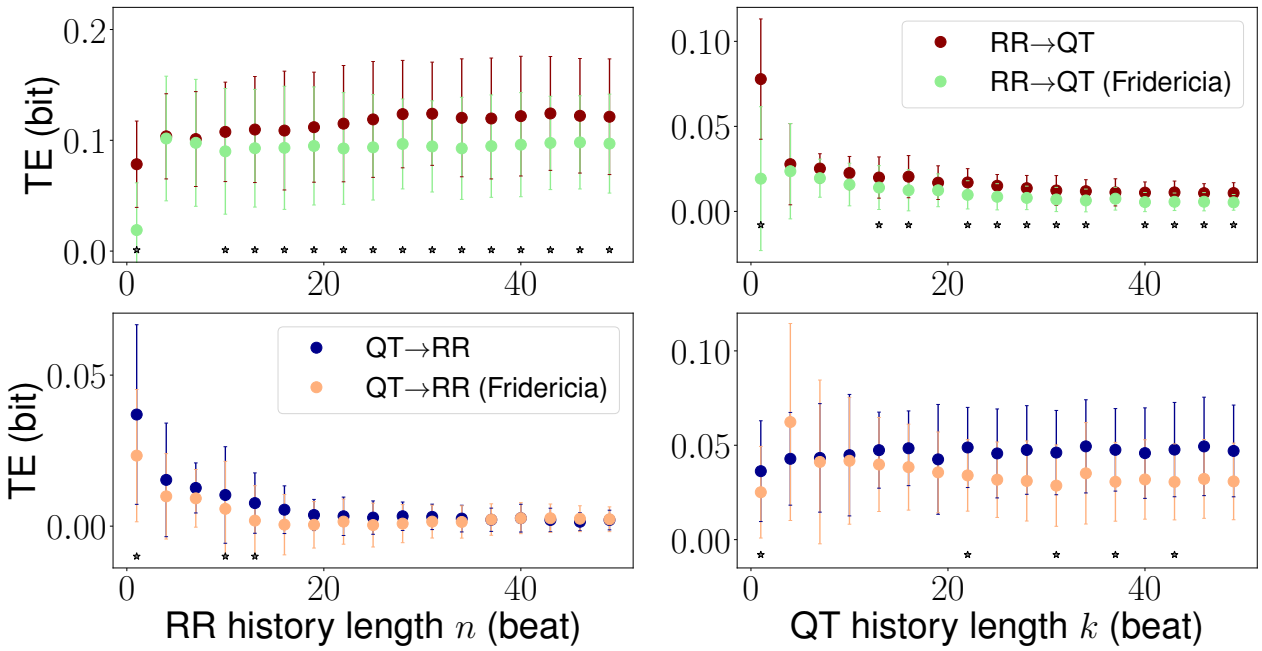

Figure 7: The effect of the QT correction (Fridericia formula) on the information flows. The stars show significant ($P \leq 0.05$, paired t-test) differences between TE distributions of the original and corrected signals. Data in the format mean ± standard deviation.

We note that the purpose of the QT correction procedures is to eliminate the dependence of QT on RR. Thus, the corrected values of QT should ideally show no inter-dependency with RR. Hence, information transfers must be equal to zero.

However, in Fig. 7 we observe significant non-zero transfer for the QT corrected series (both Fridericia and Bazett, the latter is not shown), though the tendency towards zero is evident in the case of the Fridericia-corrected RR→QT transfer with growing history length. Such a tendency is absent in the case of the Bazett correction, where all transfers are almost always statistically similar, except at $n, k = 1$ (data not shown). This result emphasizes the importance of the history of the heartbeat dynamics in

the context of the QT correction.

Gender effects. It is known that women have longer QT than men [33–35]. We have selected male and female subgroups from the studied cohort and calculated the TE distributions for different history lengths. The results are presented in Fig. 8. Although we do not find any significantly persistent discrepancies between the transfers, the $\mathrm{TE}_{\mathrm{RR}\to\mathrm{QT}}$ distributions over n demonstrate systematic deviations. Namely, the $\mathrm{TE}_{\mathrm{RR}\to\mathrm{QT}}$ mean value is persistently higher for males than for females at all n shown (Fig. 8, top left). We emphasize that our findings are based on a small sample of 7 men and 11 women. Therefore, further studies with a larger sample size might be needed.

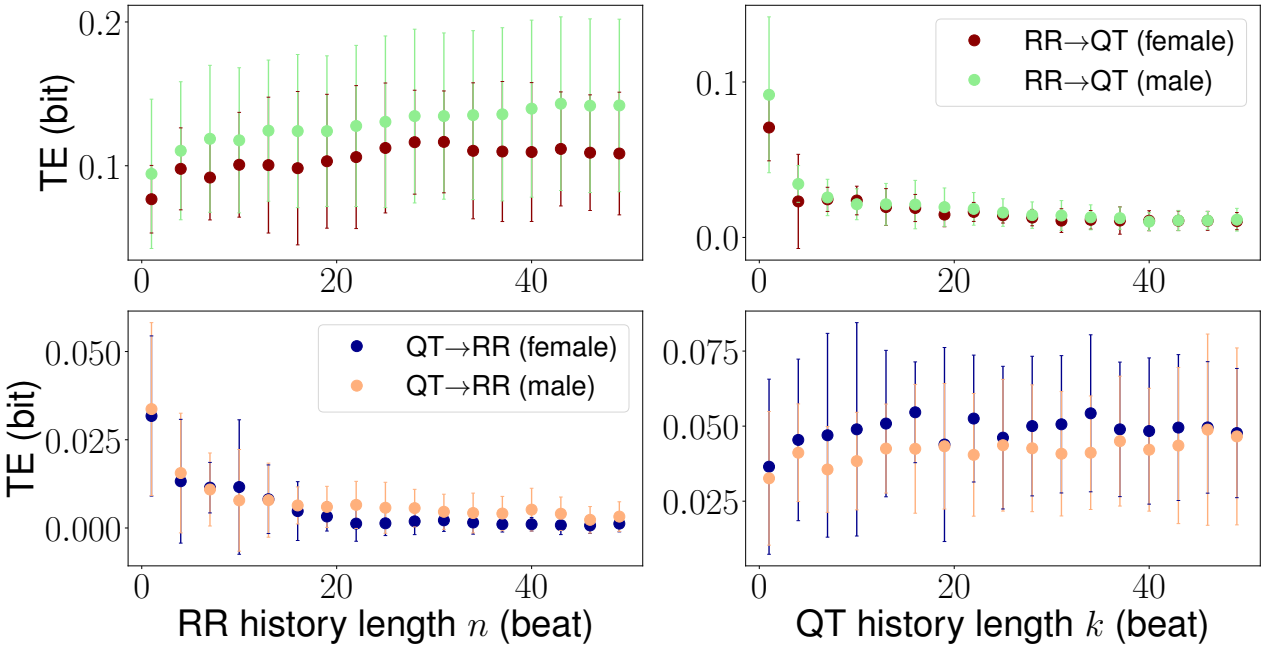

Figure 8: Gender effect on information transfer. The stars show significant ($P \leq 0.05$, unpaired t-test) differences between TE distributions for female and male subjects from the population studied. Data in the format mean ± standard deviation.

5 Discussion

In this work we have considered the transfer of information between coupled RR and QT interval dynamics of healthy individuals. We used the transfer entropy (TE) method for this purpose [25]. An important application of the analysis is the QT correction, which is a standard tool for diagnostic

purposes of potentially lethal arrhythmias [1, 2]. To the best of our knowledge, this study is the first attempt to establish a firm information theory approach to this clinical problem.

We have shown that the information transfer from RR to QT is larger than the transfer from QT to RR in the simplest case of accounting only for the effect of one previous beat of history. Thus, there is a hidden asymmetry of the information flow between RR and QT time series. Moreover, the inequality indicates that the QT interval is more dependent on RR interval values than RR on QT. The former is implicitly entailed by numerous studies on the QT interval correction; see, e.g., Refs. [1–4, 10, 11] and references therein.

The aforementioned asymmetry of the information flow becomes more profound as more RR past values are taken into account. This finding is in agreement with the recent studies suggesting that the longer RR history can improve the QT correction [21, 22]. Namely, the increase in the RR→QT information flow with the RR history length indicates a stronger ability of the RR history to explain the variability in QT, hence stronger QT dependence on RR. However, if longer QT history is considered the information flows reverse, indicating the strong RR dependence on QT. This result emphasizes the importance of comprehensive analysis of the mutual QT/RR dynamics, considering, for example, the QT history as well. However, this is usually neglected in the QT correction studies.

There is a characteristic history length n_{crit}, such that for history lengths longer than n_{crit} the QT correction based on the RR history should not produce any improved outcome. That is, the RR intervals of the past beyond n_{crit} are no more able to explain the variability in QT since the RR→QT transfer reaches the steady state.

In the literature, other attempts have been made to quantify the dynamic QT-RR coupling [4, 22, 36–38]. These approaches rely on statistical models of the given form and, thus, have assumptions behind the models. For example, in Ref. [4] the authors proposed to use the weighted average of the preceding RR intervals to account for the RR history effect on QT. They found that on average 150 preceding beats are enough to model QT accurately. Unlike these approaches transfer entropy accounts for the history *unconditionally*. Perhaps, this could be a reason for the lower estimation of the effective RR history ($n_{crit} \sim 20 \ldots 30$ heart beats).

We have shown that the mutual configuration (QTstart or QTend) of the coupling between QT and

RR intervals has a significant quantitative effect on the RR→QT transfer. Namely, the information flow RR→QT in the QTstart configuration is larger than the same transfer in the QTend configuration. Since this transfer reflects the degree of dependence of QT on RR, one would expect that the choice of the mutual configuration will quantitatively affect the relevant QT correction procedures. However, so far this distinction was not brought to attention in the studies pertaining to the subject of the QT correction (the usual choice of the research community is QTend, see, e.g., [32]).

Additionally, we have estimated the effects of the QT correction on the information transfer between QT and RR. For this, the widely used QT correction formulas (Fridericia [11] and Bazett [10]) were analyzed. We conclude that the most commonly used QT correction formulas cannot provide for the proper informational reduction in the corrected QT/RR time series for all lengths of the heartbeat history.

The gender differences were considered as it is known that females have longer QT intervals than males [33–35]. We have not found any statistically significant differences between the subgroups, although for our sample the mean RR→QT transfer was systematically larger for males than for females.

Finally, this purely empirical theory-free probabilistic approach to the QT correction problem might prove to be more effective in the medical context than the conventional "best-fit" formulae, as it establishes quantitative measures, uses probabilistic features, and does not have any constraining presumptions of the model itself.

Acknowledgments. We are specially thankful for useful discussions to Joseph Lizier and Jason Lloyd-Price. This work was supported by Academy of Finland, Key Project Funding.

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