Nonparametric Modeling and Population Approach to the Individualized Heart Rate Correction of the QT Interval

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INTRODUCTION

The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. Drug-induced ventricular arrhythmia associated with QT prolongation is a well-recognized form of drug toxicity. It is widely recognized [1] that the QT interval be dependent on the heart rate and has to be adjusted to aid interpretation. Existing correction formulas rely on parametric models estimated from pooled population data. Herein, a more flexible model-free nonparametric approach and a parametric population model for individualized correction formulas are investigated.

MATERIALS

Both approaches were evaluated using QT-RR data obtained in dogs from 24h ambulatory electrocardiograms. Empirical Bayes estimation of the nonparametric correction formula was performed. The population modeling method was evaluated in poor sampling scenarios. Differently from [4], where a power model is used, a linear mixed effect model in the logarithmic scale was here adopted.

NONPARAMETRIC INDIVIDUALIZED APPROACH

A novel nonparametric approach (Regularization) is proposed which exploits individual data to obtain regressions for each subject.

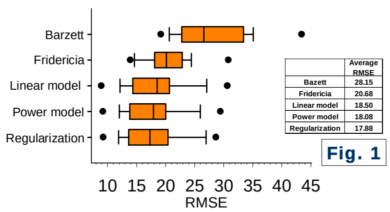
$$QT_k = f(RR_k) + \varepsilon_k$$

$$\hat{f}_\gamma = \arg\min_f \sum (y_k - f(x_k))^2 + \gamma \int (f''(x))^2 dx$$

γ is tuned automatically using Generalized Cross Validation method

The fitted curve is flexible in that it smoothly adapts itself to data, with smoothness being mathematically characterized in terms of second derivative magnitude.

The superiority of the new method over traditional parametric alternatives is assessed in terms of Root Mean Square Error (RMSE) using pooled regression, i.e. fitting the model to the whole data pool (**Fig. 1**).



	Average RMSE
Bazett	28.15
Fridericia	20.68
Linear model	18.50
Power model	18.08
Regularization	17.88

Fig. 1

Our model-free regression is apparently unbiased, unlike, for example, Fridericia's method (**Fig. 2**).

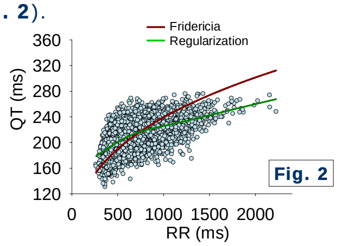


Fig. 2

Further improvement in fitting individual data is obtained by resorting to an individualized approach. The improvement in individual RMSE over the pooled approach is apparent: **Fig.3** depicts the pooled and individualized regressions for a given study subject, whereas **Fig. 4** shows individual RMSE distributions as box plots, both for the individualized and the pooled approach.

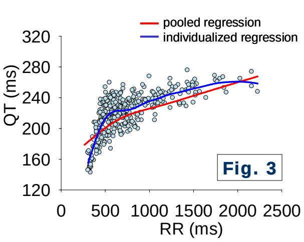
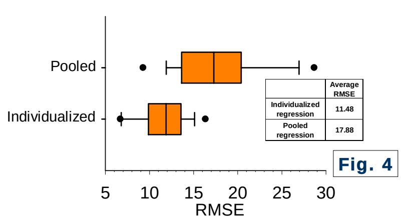


Fig. 3



	Average RMSE
Individualized regression	11.48
Pooled regression	17.88

Fig. 4

Fig. 5 displays a goodness-of-fit plot for the two methods.

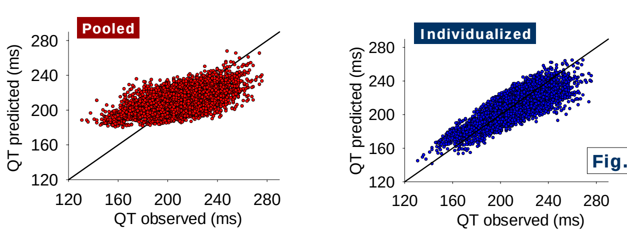


Fig. 5

PARAMETRIC POPULATION APPROACH

A Bayesian population model is introduced which jointly models the population QT-RR relationship and the individual ones, therefore exploiting other subjects' information to learn individual parameters. Such approach results in robust estimation also when a particular subject is poorly sampled.

A parametric linear mixed effects model based on the power regression is here exploited. Our population method was tested in a realistic small-sample scenario by uniformly under-sampling each individual's dataset (60 to 100 data points per subject).

$$QT = a\ RR^b \xrightarrow{\text{Linearized power model}} \ln QT = \ln a + b\ \ln RR$$

For each i-th subject ($i = 1, \ldots, m$) and j-th observation ($j = 1, \ldots, n_i$):

$$\ln QT_{ij} = \ln a_i + b_i \ln RR_{ij}$$

Population model

$$y_{ij} = \Phi_1 + \Phi_2 g_{ij} + \phi_{1,i} + \phi_{2,i}\, g_{ij} + \varepsilon_{ij}$$

$$y_{ij} := \ln QT_{ij}$$

$$g_{ij} := \ln RR_{ij}$$

Additionally, each subject's data was partitioned into three portions of RR: one of them, assigned randomly to each subject, was used for estimating the model, while the other two were served as a validation dataset. This reflects the fact that, in practical studies, a particular subject may be sampled only at certain hours of the day, in which the variability of heart rate is small.

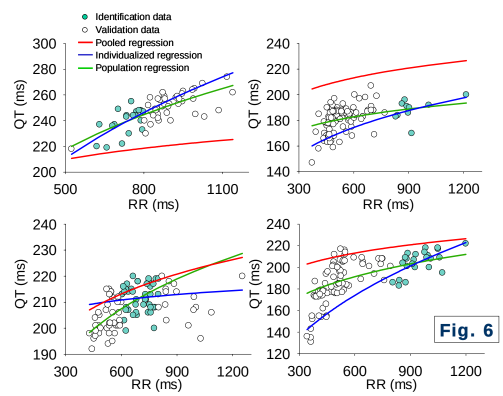


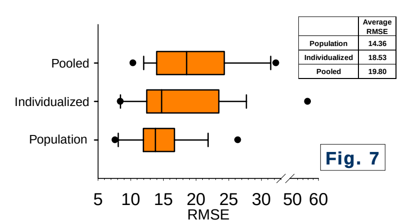
Fig. 6

As an example, the individual regressions obtained with the population and individualized methods, together with the pooled regression, are shown in **Fig. 6** for 4 different subjects.

Their validation data points are shown together with the identification ones.

The robustness of the population regressions is apparent when compared to the individualized ones, even in such small-sample scenario.

As a quantitative performance measure of the population, individualized and pooled approaches, the distribution of individual validatory RMSEs is shown as boxplots for all the three methods (**Fig. 7**).



	Average RMSE
Population	14.36
Individualized	18.53
Pooled	19.80

Fig. 7

CONCLUSIONS

Individualized regression yields a significant improvement over pooled methods, especially in the nonparametric case, which proved superior to all traditional parametric formulas. The adoption of individualized QT correction is therefore advised, in accordance with [1] as well as with [2-4]. Moreover, individualized correction by means of a population model provides robust correction formulas even when subjects are scarcely sampled, or when data is only available in certain RR regions.

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