Investigation of methods to assess the individual relationship between the RR and QT interval of the ECG

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GMDS 2006

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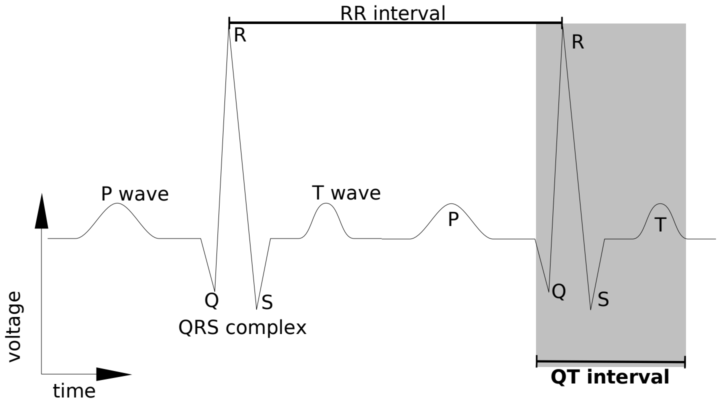
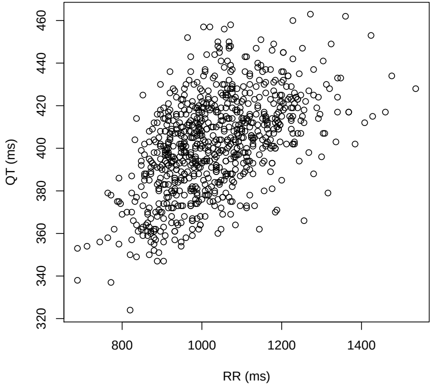
ECG Wave Form

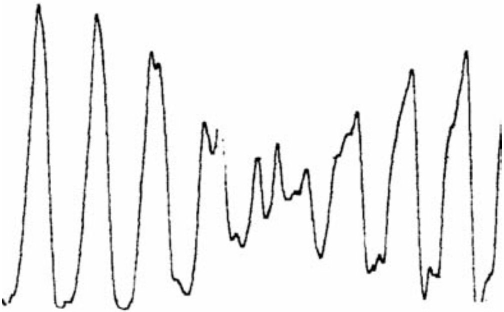


Scatter Plot of RR/QT Intervals



Scatter plot of a subsample of the study data set, including observations of several subjects

Torsade de Pointes — "Twisting of the points"



(Horacek T. (1998): Der EKG-Trainer. Thieme, Stuttgart)

- Special case of ventricular tachycardy
- Typical "twisted" appearance in the ECG

Torsade de Pointes 2

- Can lead to arrythmia and death
- Can be caused by insufficient repolarisation in heart cells
- Several pharmaceutic agents are known to make TdP more likely
- Relative prolongation of the QT interval can be used as a surrogate endpoint

Problems

- QT length depends on RR (= 1 / Heart Rate)
- Change of heart rate causes QT effect even if repolarisation is not affected
- No simple linear relationship
- Dependence appears to be individual

Aim: a *corrected* QT interval which can be interpreted independently of the heart rate

Classic Approaches

Simple, generally applicable formula?

- Fridericia (1920): $QTcF = \frac{RR}{\sqrt[3]{QT}}$
- Bazett (1920): $QTcB = \frac{RR}{\sqrt{QT}}$

- $+$ easy to calculate
- $+$ depends only on actual RR and QT
- - imprecise: often high correlation between RR and QTc, known miscorrection
- - does not account for individual characteristics

QTcB and QTcF

Both Fridericia and Bazett imply the same principle:

$$QT = a \cdot RR^b \quad \Leftrightarrow \ln QT = \ln a + b \cdot \ln RR \quad \text{(parabolic)}$$

Alternatives:

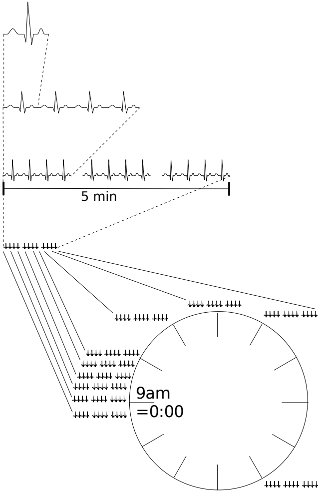
$$QT = a + b \cdot RR \quad \text{(linear)}$$

$$QT = \exp(a + b \cdot RR) \quad \Leftrightarrow \ln QT = a + b \cdot RR \quad \text{(log/linear)}$$

General Information about the Study

- EKG data of a Thorough QT Study performed at Boehringer Ingelheim (see poster BM-17 for details)
- Baseline days of each of the four crossover cycles
- 96 or 144 RR/QT pairs per day and person
- 56 subjects, $\approx$ 29.000 wave forms overall

Structure of ECG Recordings



One ECG wave

Four successive ECG waves

Three sequences within
a five minute interval

8 – 12 intervals throughout
one day, at different distances

Measurement time points
(relative to drug application
on the next day):

–0:10	0:40	4:00
0:05	1:00	8:00
0:10	2:00	12:00
0:20	3:00	23:50

Modeling

Find useful models for RR/QT dependence incorporating

1. Individual effects
2. Temporal correlation of measurements
3. Circadian effects

→ Linear Mixed Effects Model including

1. Random effects (intercept and slope) per subject
2. Temporal correlation of residuals
3. Cosinusoidal representation of time

Models

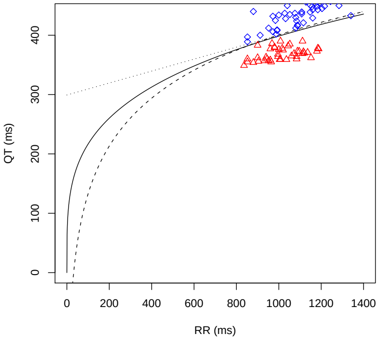
Transformation 1 (log/log)
$x_{ijkl} = \ln RR_{ijkl}$
$y_{ijkl} = \ln QT_{ijkl}$

Transformation 2 (linear)
$x_{ijkl} = RR_{ijkl}$
$y_{ijkl} = QT_{ijkl}$

Transformation 3 (log/linear)
$x_{ijkl} = RR_{ijkl}$
$y_{ijkl} = \ln QT_{ijkl}$

- i: index of subject
- j: index of period (day)
- k: index of time point within day
- l: index of repetition within time point
- $t_{ijkl} = t_l$ relative time of observation (x_{ijkl}, y_{ijkl})

Models



solid line: Transformation 1 (log/log), dotted line: Transformation 2 (linear)

dashed line: Transformation 3 (log/linear) blue rhombes/red triangles: data of two individuals

Model without Circadian Effect

$$y_{ijkl} = (a + \alpha_i) + (b + \beta_i) \cdot x_{ijkl} + \epsilon_{ijkl}$$

$(\alpha_i, \beta_i,)^T \sim N(0, \Sigma), \Sigma$ positive definite
$\epsilon_{ij} \sim N(0, R)$ i.i.d. (vector of all observations of subject i in day j)

- $R_{uncorrelated} = \sigma^2 I$
- $R_{exp} = \sigma^2 \exp\left(\frac{-d_{l_q l_r}}{\rho}\right),\ d_{l_q l_r} = \left|t_{l_q} - t_{l_r}\right|$
- $R_{Gauss} = \sigma^2 \exp\left(\frac{-d^2_{l_q l_r}}{\rho^2}\right),\ d_{l_q l_r} = \left|t_{l_q} - t_{l_r}\right|$

Model with Circadian Effect

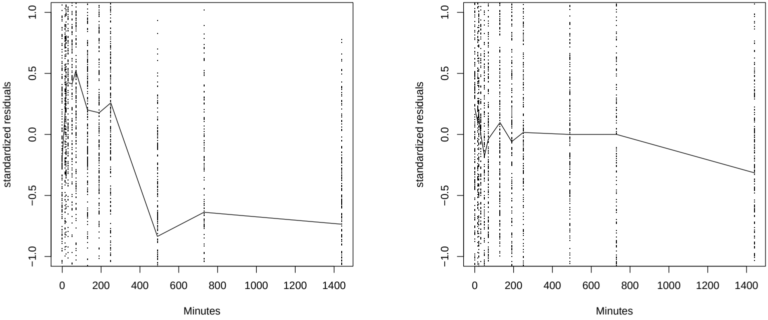
$$
\begin{aligned}
y_{ijkl} &= (a+\alpha_i) + (b+\beta_i)\cdot x_{ijkl} + \\
&+ \sum_{p=1}^{m}\left((c_p+\gamma_{pi})\cdot \cos\frac{p\cdot t_{ijkl}}{1440} + (d_p+\delta_{pi})\cdot \sin\frac{p\cdot t_{ijkl}}{1440}\right) + \epsilon_{ijkl}
\end{aligned}
$$

$(\alpha_i, \beta_i, \gamma_{1i}, \ldots, \gamma_{mi}, \delta_{1i}, \ldots, \delta_{mi})^T \sim N(0, \Sigma), \Sigma$ positive definite
$\epsilon_{ij} \sim N(0, R)$ i.i.d. (vector of all observations of subject i in day j)

Residuals by Time

Residuals of all subjects and days, split to time points

m=0 (no cosinusoid) m=3

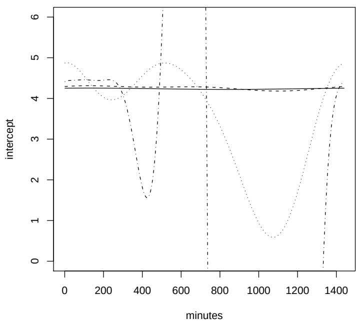


line: mean values per time point

line: mean values per time point

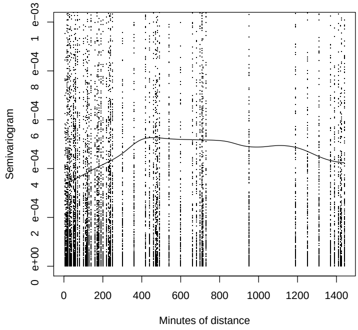
Cosinusoidal component and semivariogram

cosinusoidal curves



line:m=1 dashed:m=2 dotted:m=3 dot/dash:m=4

semivariogram for m=3, $R = \sigma^2 I$



"raw" residuals; line: Nadaraya-Watson estimate

Model Selection: Akaike Information Criterion

$AIC = -2l + 2d$ (smaller is better)

- l: Maximum log likelihood
- d: Dimension of the model

	Trans-formation 1 (log/log)	Trans-formation 2 (linear)	Trans-formation 3 (log/linear)
m=0, $R = \sigma^2 I$	-10138	18212	18155
m=1, $R = \sigma^2 I$	-10325	17999	17954
m=2, $R = \sigma^2 I$	-10451	17849	17806
m=3, $R = \sigma^2 I$	-10590	17687	17646
m=3, $R = R_{exp}$	**-10904**	**17366**	**17311**
m=3, $R = R_{Gauß}$	-10588	17689	17555

External Validation: Test with Placebo Data

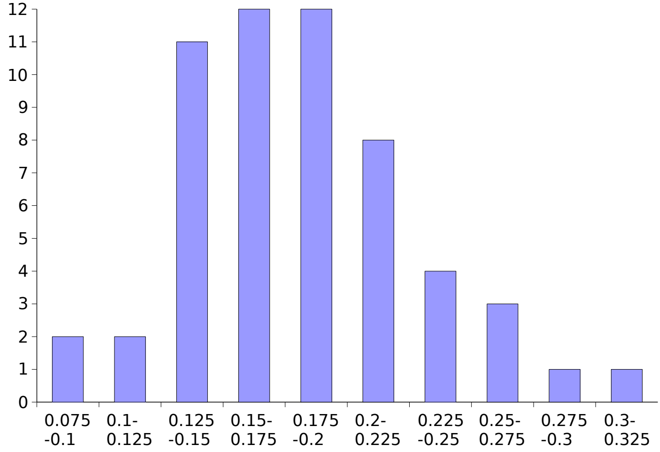
Comparison of Transformations by estimating QT intervals of observations not included in model building

Model: m=3, $R = R_{exp}$

	Transformation 1 (log/log)	Transformation 2 (linear)	Transformation 3 (log/linear)
$\sum(\widehat{QT} - QT)^2$	**673.026**	691.531	680.424

$\Rightarrow$ Transformation 1 performs best

Individual slopes per subject



Comparison of Aggregation Methods

Analysis of:

- Full data set (all wave forms)
- One randomly or systematically selected wave form per time point
- Mean values of all wave forms per time point

Estimations of the slope based on the first two methods are similar, while they differ substantially when mean values are used.

Discussion

- Parabolic dependence appears to be superior
- Respecting temporal correlation of residuals resonably increases the fit
- Circadian variability can be accounted for by a cosinusoid of third degree for twelve measurement time points in this special configuration

References

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