QT prolongation assessment using model-averaging: a robust alternative for Thorough QT studies

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Summary

The proposed model-averaging method enables to assess QT prolongation with full pre-specification of the analysis and controls the type I error while providing satisfactory power.
It can be applied to the analysis of QT data from TQT studies as well as early clinical studies.

Background

- TQT studies are pivotal safety studies testing whether the drug-induced QT prolongation is equal to or greater than 10 ms.
- Model-based analysis could increase efficiency over the currently used intersection-union test.
- However, in pivotal settings the analysis is prespecified and robustness against model misspecification needs to be guaranteed.

Methods

- The proposed approach is based on exposure-response modeling using model-averaging between a parametric and a nonparametric model (Fig. 1)

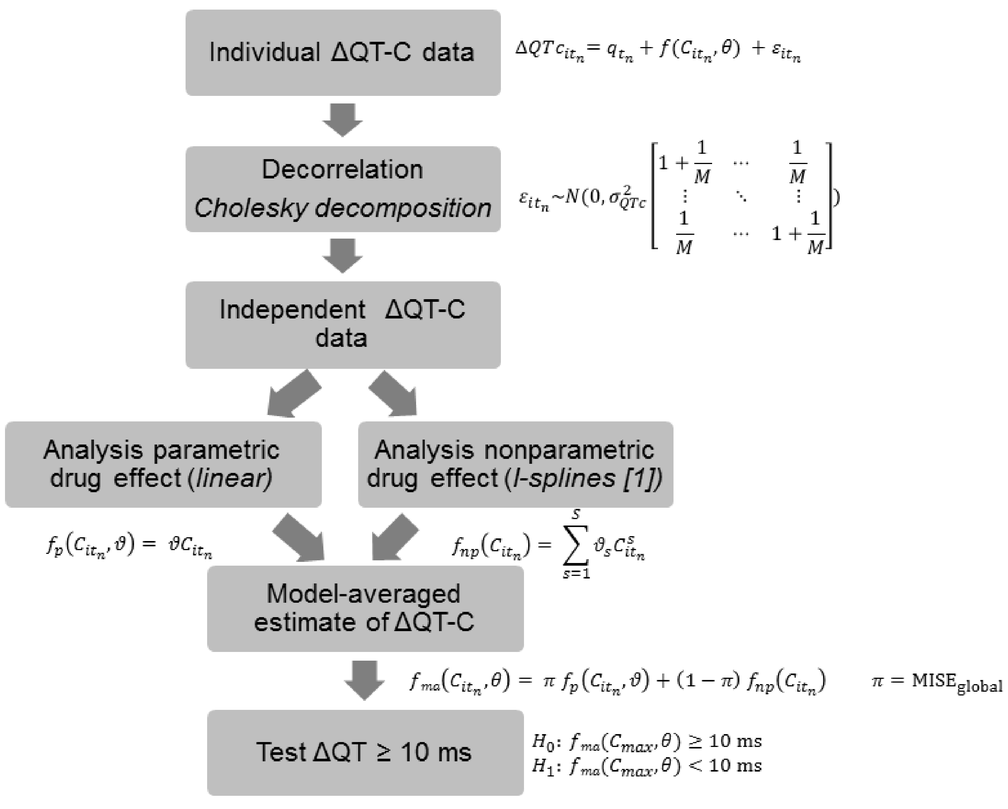

Figure 1. Summary of the model-averaged method

q_{t_n} is the diurnal variation at sampling time t_n, f is a function representing the concentration-response relationship, C_{it_n} is the observed drug concentration for patient i at time t_n, θ is a vector of drug effect parameters, ε_{it_n} is the residual error and M is the number of baseline measurements used in the computation of the individual baseline. where $f_{ma}(C_{it_n}, \theta)$ is a model-averaged estimator with parameters θ, $f_p(C_{it_n}, \vartheta)$ is a parametric estimator with parameter ϑ, $f_{np}(C_{it_n})$ is a non-parametric estimator based on monotonically increasing I-splines, π is the weight of the parametric estimator, $C^s_{it_n}$ is the s[th] element of the I-spline concentration vector and ϑ_s are the estimated slopes. $\mathrm{MISE}_{\mathrm{global}}$ are weights adapted from [2]. C_{max} is the geometric mean of the observed maximum individual concentrations of the high dose group. One-sided 95% confidence intervals were obtained via bootstrap (N=999).

- Simulations were performed to investigate the properties of the proposed approach. They were based on a real TQT study (Fig. 2) and comprised following settings:

- 3 parallel arms (placebo, low dose, high dose) of 50 or 100 individuals
- 3 baseline and 8 post-dose QTcF and drug concentration measurements per individual
- drug concentrations simulated from the pharmacokinetic model of the real data, with observed concentrations driving the drug effect
- QT simulated from the placebo model of the real data, with varying noise levels and under 4 drug effect models

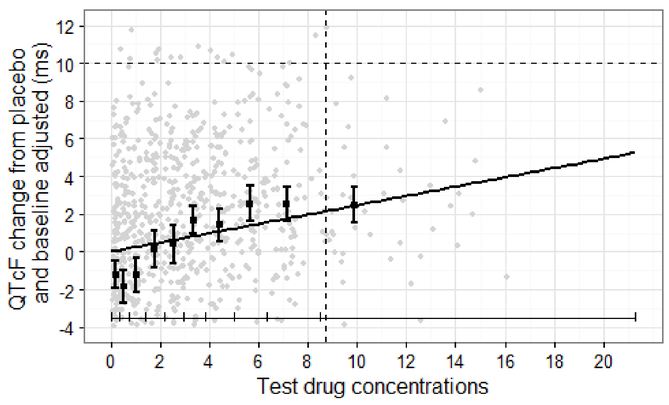

Figure 2. Concentration quantile – ΔΔQTCF plot of the real data example, with estimated QT prolongation using a linear estimator

Results

Type I error

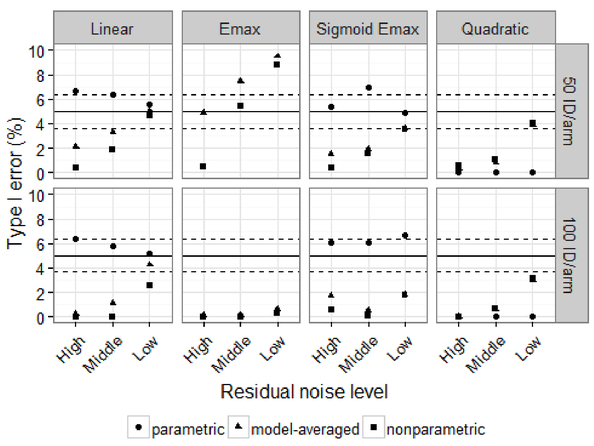

Figure 3. Type I error of the tests based on the parametric, model-averaged and nonparametric estimators

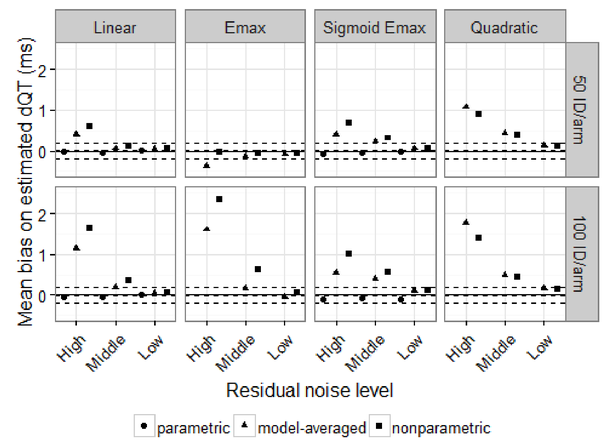

Figure 4. Mean bias on the estimated QT prolongation at C_{max} for the parametric, model-averaged and nonparametric estimators when the true drug effect is 10 ms

- The model-averaged method demonstrated satisfactory type I error in the investigated scenarios (Fig. 3). The type I errors in the Emax, 50 ID/arm scenario could be reduced to a value close to the nominal level by optimizing the nonparametric settings.
- The model-averaged method led to conservative upward bias below 0.5 ms, except under high noise scenarios where bias was higher (Fig. 4).

Power

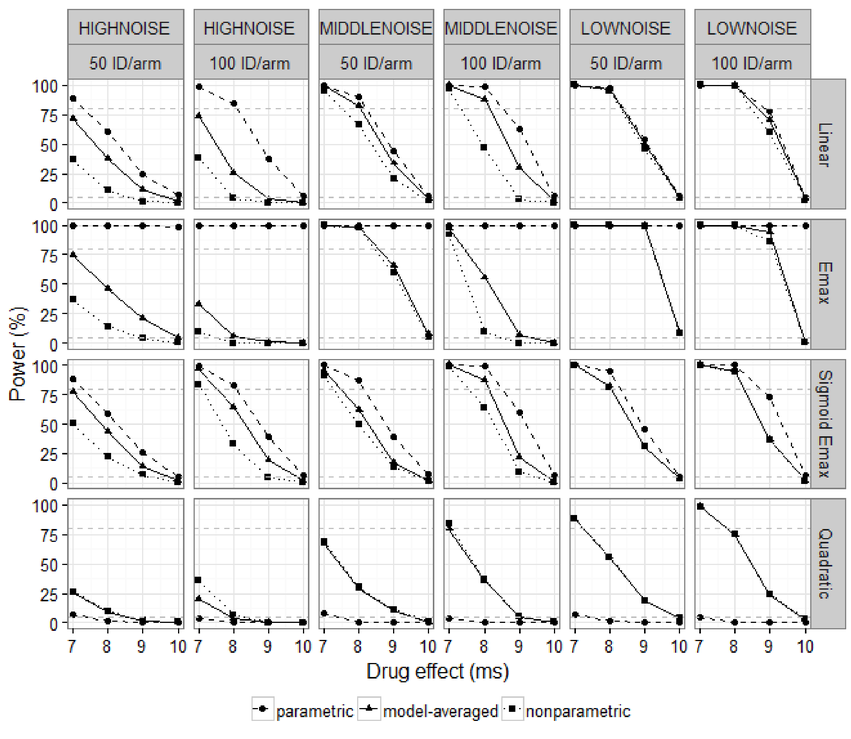

Figure 5. Power of the tests based on the parametric, model-averaged, and nonparametric estimators

- The power of the model-averaged test was at least as high as the power of the nonparametric test. In some scenarios it was markedly higher (Fig. 5).

Weights

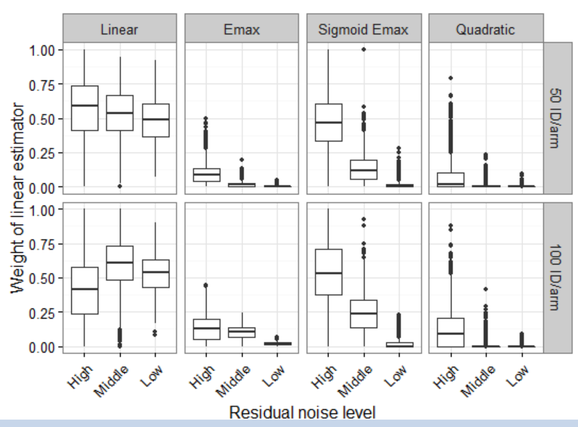

Figure 6. Distribution of MISE global weights of the parametric estimator for the high dose group when the true drug effect is 10 ms

- MISE weights followed the expected behavior of converging to 1 under the linear simulation model, and to 0 otherwise (Fig. 6).
- Median weights were around 0.6 across all linear scenarios.

Discussion

- Potential improvement of model-averaged procedure: automation of I-splines settings (knot selection), faster converging weights
- Application possible to QT data outside of TQT studies, and to other pivotal studies in general (bioequivalence for example)

[1] Yuan Y, Yin G, *Dose-Response Curve Estimation: A Semiparametric Mixture Approach*. Biometrics, 2011. 67: p. 1543–1554. [2] Ramsay JO, *Monotone Regression Splines in Action*. Statistical Science, 1988. 4(5):p. 421-465.

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The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115156, resources of which are composed of financial contributions from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution. The DDMoRe project is also supported by financial contribution from Academic and SME partners. This work does not necessarily represent the view of all DDMoRe partners.