

Beyond the linear model: fully automated concentration-QT analysis and reporting



SimulationsPlus

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INTRODUCTION

- QT interval prolongation assessment as a marker for risk of drug-induced arrhythmia is an integral part of drug development for small molecules.
- QT analysis may be carried out with concentration-QTc modeling based on entry-into-man (SAD and MAD studies) as an alternative to thorough QT (TQT) studies [1].
- The **scientific white paper** (Garnett et al. [2]) provides **guidance for performing and reporting** concentration-QT modeling to support regulatory submissions.
- The standard model is a **linear mixed-effects model**.

OBJECTIVE 1: Extend the linear model to nonlinear and delayed-effect models

OBJECTIVE 2: Automation of data preparation, model selection, and reporting

EXTENSIONS OF THE LINEAR MODEL

The white-paper linear model is defined as:

$$\Delta QT_{c_{i,j,k}} = (\Theta_0 + \eta_{0,i}) + \Theta_1 * TRT_j + (\Theta_2 + \eta_{2,i}) * C_{i,j,k} + \Theta_{3,k} * TIME_k + \Theta_4 * (QT_{c_{i,j,k}=0} - \text{mean}(QT_{c_{i,j,k}=0}))$$

The model is rewritten to have two components, a structural model and a statistical model (i.e., drug effect and inter-individual variability with random and covariate effects) [3]:

$$\text{Structural model: } \Delta QT_{c_{i,j,k}} = \Theta_{0,i} + \Theta_{2,i} * C_{i,j,k}$$

$$\text{Statistical model:}$$

$$\Theta_{0,i} = \Theta_{0,\text{pop}} + \eta_{0,i} + \Theta_1 * TRT_j + \Theta_4 * BL_{\text{cent},i,j} + \Theta_{3,T1} * I(\text{TIME}=T1) + \Theta_{3,T2} * I(\text{TIME}=T2) + \dots$$

$$\Theta_{2,i} = \Theta_{2,\text{pop}} + \eta_{2,i}$$

Considering that the structural model is expressed as a simple function of the concentration, other models are specified by defining the transformation of the concentration, $f(C_{i,j,k})$. The same applies when directly modeling $\Delta\Delta QT_c$.

$$\text{General structural model: } (\Delta)\Delta QT_{c_{i,j,k}} = \Theta_{0,i} + f(C_{i,j,k})$$

The following models can capture nonlinear conc- ΔQT_c relationships or a delayed effect between the concentration and ΔQT_c :

Table 1. Model alternatives for structural concentration-QT modeling

Model	Structural model	Parameters
No effect	$f(C_c) = 0$	
Linear	$f(C_c) = \text{slope} * C_c$	slope
Loglinear	$f(C_c) = p_1 * \log(1 + C_c/p_2)$	p_1, p_2
E_{max}	$f(C_c) = E_{\text{max}} * C_c / (C_c + EC_{50})$	E_{max}, EC_{50}
E_{max} with sigmoidicity	$f(C_c) = E_{\text{max}} * C_c^\gamma / (C_c^\gamma + EC_{50}^\gamma)$	$E_{\text{max}}, EC_{50}, \gamma$
Effect compartment (hysteresis)	$d/dt(C_e) = (1/\tau_0) * (C_c - C_e)$ $f(C_e) = \text{slope} * C_e$	τ_0 , slope

AUTOMATED CONCENTRATION-QT ANALYSIS

The **freely downloadable R scripts** automatically execute the analysis:

- data preparation:** triplicate averaging, baseline derivation, QTc calculation, and more.
- conc-(Δ) ΔQT_c analysis:** standard linear analysis or evaluation of alternative models.
- report generation:** as Word document including exploratory data analysis, assessment of key modeling assumptions, and results in figures and tables.

Case study

The dofetilide data (Johannesen et al. [4]) are analyzed. Single doses of 500 μg dofetilide or placebo were administered to 22 healthy subjects in a two-period crossover study. PK and QT data were collected at 16 matching time points of 24 h.

Prerequisites

R and MonolixSuite 2024 with the R API lixoftConnectors.
Execution of the following R code:

```
source("../_mlxQTcTools/mlxQTcTools.R")
library(lixoftConnectors)
initQTc(path="C:/Program Files/Lixoft/MonolixSuite2024R1")
```

STEP 1: DATA PREPARATION

The R function **process_QTcData()** computes additional variables for the analysis data set:

- QTc** computation by applying the heart-rate correction, e.g., using Fridericia's formula.
- Averaging of triplicate** QTc for each time point.
- ΔQT_c** (baseline-corrected QTc) computation
- $\Delta\Delta QT_c$** (baseline and placebo-corrected QT) derivation (if cross-over setup).
- ΔHR** and **$\Delta\Delta HR$** computation for exploratory data visualization.
- Covariate** derivation: centered QTc baseline, placebo-adjusted centered baseline (for $\Delta\Delta QT_c$), time as categorical factor, drug concentration, and RR interval duration.

RANDID	EXTRT	EXDOSE	TPT	BASELINE	PCSTRESN	RR	PR	QT	QRS
1001	Dofetilide	500	-0.5	Y	.	908	141	370	95
1001	Dofetilide	500	-0.5	Y	.	901	143	372	100
1001	Dofetilide	500	0.5	N	120	899	142	369	95
1001	Dofetilide	500	0.5	N	120	1057	126	380	95
1001	Dofetilide	500	0.5	N	120	902	131	369	97
1001	Dofetilide	500	1	N	1610	907	147	389	93
1001	Dofetilide	500	1	N	1610	949	139	392	94
1001	Dofetilide	500	1	N	1610	979	144	395	96
1001	Dofetilide	500	1.5	N	1930	896	158	425	92
1001	Dofetilide	500	1.5	N	1930	946	144	435	96
1001	Dofetilide	500	1.5	N	1930	958	138	436	95

```
process_QTcData(data="Dofetilide_data.csv",
  QTname = "QT", RRname = "RR", CONCname = "PCSTRESN",
  TRTname = "EXTRT", IDname = "RANDID", TIMEname = "TPT",
  bComputeQTc = TRUE, correctionMethod = "Fridericia",
  bComputeBaseline = TRUE, BLFLAGname = "BASELINE",
  stepOrder = "FirstCorrectThenAverage",
  outName = "Dofetilide_formatted.csv", silent=FALSE)
```

RANDID	EXTRT	EXDOSE	TPT	BASELINE	CONC	RR	PR	QT	QRS	HR	QTc	BLQTc	BLHR	dQTc	dHR	BLQTc.cent	BLQTc.centAdjPR	ddQTc	ddHR	Cc_reg	RR_reg	TIME_cat
1001	Dofetilide	500	-0.5	Y	0	915.667	141	369.667	96	65.546	380.722	380.722	65.546	0	0	-14.202	-10.788	0	0	0	915.667	-0.5
1001	Dofetilide	500	0.5	N	120	952.667	142	372.667	95	63.341	379.094	380.722	65.546	-1.628	-2.205	-14.202	-10.788	4.371	6.311	120	952.667	0.5
1001	Dofetilide	500	1	N	1610	945	147	392	93	63.555	399.523	380.722	65.546	18.802	1.991	-14.202	-10.788	18.948	3.259	1610	945	1
1001	Dofetilide	500	1.5	N	1930	933.333	158	432	92	64.34	442.083	380.722	65.546	61.362	-1.206	-14.202	-10.788	63.409	0.844	1930	933.333	1.5
1001	Dofetilide	500	2	N	2430	939.667	136	442	97	63.941	451.355	380.722	65.546	70.633	-1.605	-14.202	-10.788	68.143	0.584	2430	939.667	2
1001	Dofetilide	500	2.5	N	2900	970.333	129	441.667	97	61.847	446.142	380.722	65.546	65.421	-3.699	-14.202	-10.788	66.689	-7.137	2900	970.333	2.5
1001	Dofetilide	500	3	N	2940	917.333	138	433.333	97	65.441	446.032	380.722	65.546	65.31	-0.105	-14.202	-10.788	72.46	-6.739	2940	917.333	3
1001	Dofetilide	500	3.5	N	2500	946.667	146	416.667	95	63.39	424.359	380.722	65.546	43.638	-2.156	-14.202	-10.788	50.43	-4.78	2500	946.667	3.5
1001	Dofetilide	500	4	N	2560	924.667	138	426	95	64.904	437.284	380.722	65.546	56.562	-0.642	-14.202	-10.788	61.864	-7.167	2560	924.667	4
1001	Dofetilide	500	5	N	2120	925	145	409.333	96	64.918	420.194	380.722	65.546	39.473	-0.63	-14.202	-10.788	39.467	-6.659	2120	925	5

The process_QTcData() function is flexible and adapts to the columns already present in the dataset. Several options are available for heart-rate correction and baseline calculation.

STEP 2: CONCENTRATION-QTc ANALYSIS

The function **generateAllQTcProjects()** creates and executes Monolix conc-QT projects.

- A **library of models** is provided (all models in Table 1).
- Choice of modeling ΔQT_c or $\Delta\Delta QT_c$ directly.
- Choice of running the standard linear model only or assessing alternatives
- If alternatives are chosen to be considered:
 - The best-fitting model is automatically selected based on the BICc.
 - Results for the best-fitting model are reported.
 - The best-fitting model is compared to the linear model.
 - A delayed effect is detected, warning that a full pop PK/PD model is suggested.

```
generateAllQTcProjects(
  dataSet="Dofetilide_formatted.csv",
  IDname="RANDID", TIMEname="TPT", TRTname="EXTRT",
  CONCname="CONC", placeboName = "Placebo",
  modelFolder="._/mlxQTcTools/models/ddQTcModels",
  projectFolder="._/mlx_runs",
  isddQTc = T,
  bRun = T)
```

Population parameter estimates				
	VALUE	S.E.	LINEARIZATION	
Fixed Effects				
sdQTc_pop	1.254	31.7	-0.754	-0.243
base_dQTc0_BLQTc.centAdjPR	-10.468	0.304	22.17	-10.477
slope_pop	0.0279	0.00143	5.12	0.0281
Standard Deviation of the Random Effects				
omega_slope	0.00571	20.444	0.00044	16.5
Error Model Parameters				
addQTc	11.748	0.457	3.09	10.894

The Monolix projects generated can be opened in the GUI and explored or further modified (e.g., covariates can be added).

STEP 3: REPORTING

A customizable **Quarto template** is used to create a standard report in Word.

The report includes:

- Exploratory data analysis:** data summary, QT/QTc, RR correction, baseline QTc, ΔQT_c , $\Delta\Delta QT_c$ and concentration-time.
- Model assumption validation:** heart-rate independence from drug concentration, QTc independence from heart rate, linearity of the concentration-QTc relationship, immediate effect of concentration change on (Δ) ΔQT_c change.
- Modeling results:** model comparison, model fit, parameter estimates, goodness of fit.
- $\Delta\Delta QT_c$ prediction intervals:** derivation and assessment of the 10-ms threshold.

```
quarto_render(input = "._/mlxQTcTools/QTc_quarto_allModels.qmd",
  output_file = "Dofetilide_dQTc_report.docx",
  execute_params = list(folderName = "._/mlx_runs",
    compoundName = "Dofetilide",
    CONCname = "CONC",
    placeboName = "Placebo",
    studyType = "dQTc",
    concentrationUnit = "pg/mL",
    nBins = 10,
    orderTRT = c("Placebo", "Dofetilide"),
    threshBICc = 0))
```

Concentration- ΔQT_c analysis of Dofetilide (preliminary report)

[...]

4.2 Assumption 2: QTc interval duration is independent of RR interval duration.

A scatter plot of QTc interval duration vs RR interval duration, stratified by treatment, is provided in Figure 15.

Figure 15: QTc interval duration vs RR, overall (A) and by treatment (B).

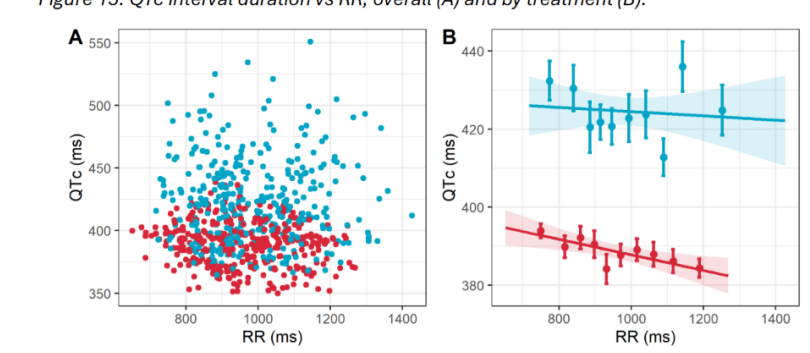


Table 1: Slope estimates, confidence intervals, and p-values of the linear regression for each treatment to numerically assess the assumption.

REFERENCES

- [1] ICH E14 Guideline: Q&A (2015)
- [2] Garnett et al., *JKPD* (2018)
- [3] Celliere et al., *JKPD* (2025)
- [4] Johannesen et al., *CPT* (2014)

Download
the R functions and
examples here!



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