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

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INTRODUCTION

- QT interval prolongation assessment as a marker for risk of drug-induced arrythmia 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:

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

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

Structural model: $\Delta QTc_{i,j,k} = \Theta_{0,i} + \Theta_{2,i}*C_{i,j,k}$
Statistical model:

$$\Theta_{0,i} = \Theta_{0,pop} + \eta_{0,i} + \Theta_1*TRT_j + \Theta_4*BL_{cent,i,j} + \Theta_{3,T1}*I(TIME=T1) + \Theta_{3,T2}*I(TIME=T2) + \dots$$
$$\Theta_{2,i} = \Theta_{2,pop} + \eta_{2,i}$$

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 ΔΔQTc.

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

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

Table 1. Model alternatives for structural concentration-QT modeling

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

AUTOMATED CONCENTRATION-QT ANALYSIS

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

1. **data preparation:** triplicate averaging, baseline derivation, QTc calculation, and more.
2. **conc-(Δ)ΔQTc analysis:** standard linear analysis or evaluation of alternative models.
3. **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.
- **ΔQTc** (baseline-corrected QTc) computation
- **ΔΔQTc** (baseline and placebo-corrected QT) derivation (if cross-over setup).
- **ΔHR** and **ΔΔHR** computation for exploratory data visualization.
- **Covariate** derivation: centered QTc baseline, placebo-adjusted centered baseline (for ΔΔQTc), 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	96
1001	Dofetilide	500	-0.5	Y	.	938	135	367	93
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_centAdjPl	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	-1.844	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	-5.739	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	64.916	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 ΔQTc or ΔΔQTc 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.

RANDID	EXTRT	EXDOSE	TPT	BASELINE	CONC	RR	PR	QT	QRS	HR	QTc	BLQTc	BLHR	dQTc	dHR	BLQTc_cent	BLQTc_centAdjPl	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
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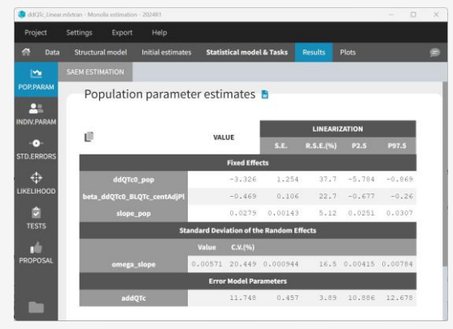
1001	Dofetilide	500	5	N	2120	925	145	409.333	96	64.916	420.194	380.722	65.546	39.473	-0.63	-14.202	-10.788	39.467	-6.659	2120	925	5

```
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)
```



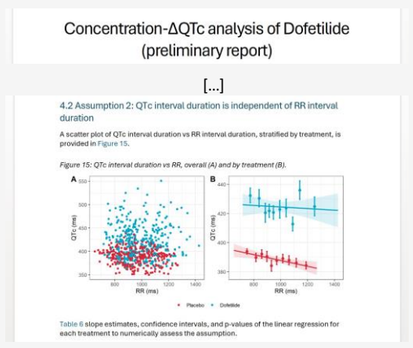
The Monolix projects generated can be opened in the GUI and explored or further modified (e.g., covariates can be added).

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, HR correction, baseline QTc, ΔQTc, ΔΔQTc 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)ΔQTc change.
- **Modeling results:** model comparison, model fit, parameter estimates, goodness of fit.
- **ΔΔQTc 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"),
                         thresBICc = 0))
```


Concentration-ΔQTc 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 6 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., *JPKPD* (2018)
[3] Celliere et al., *JPKPD* (2025)
[4] Johannesen et al., *CPT* (2014)

Download the R functions and examples here!

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