Open-Source Quantitative Modeling of Tuberculosis Drug-Induced Cardiac Risks

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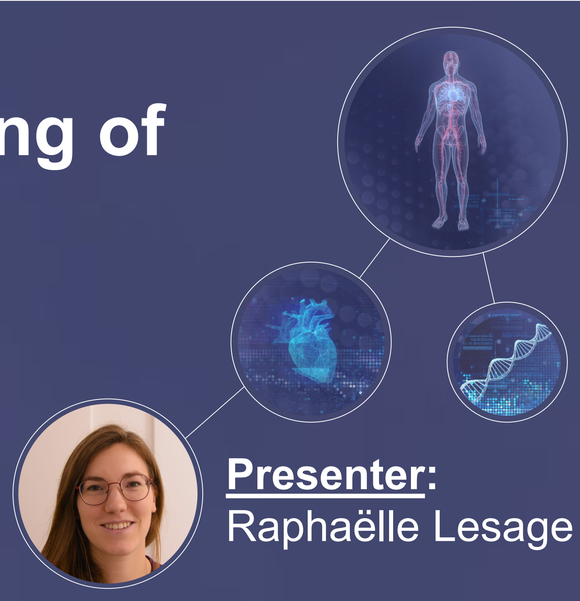

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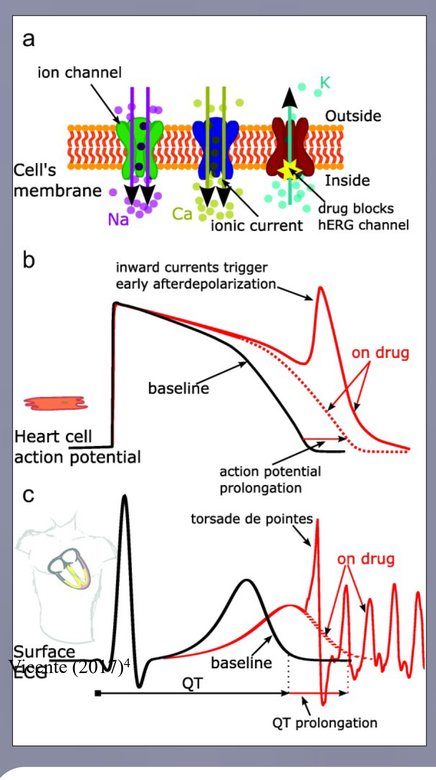
Intro

Some **anti-tuberculosis** (TB) drugs are associated with pro-arrhythmic risks[1]. In drug development, such a risk is assessed via the corrected QT (**QTc**) interval duration on the ECG. Drugs that Inhibit the cardiac ion channels may delay cardiac cells' **action potential** (**AP**), leading to QTc prolongation. The goals of this study were (1) to develop an **Open-Source QSP-PBPK** framework to predict the **cardiac risk of anti-TB drugs** and find **safe doses,** (2) to ensure broader access to these technological advancements.

PBPK models – TB drugs | **Data-driven QTc model** | **Action potential model**

Methods



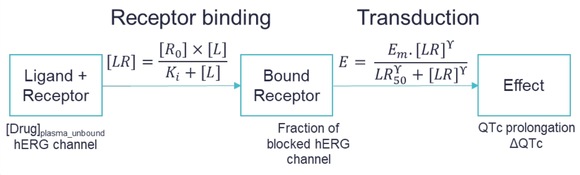
Vicente (2017)[4]

Anti-TB drug PBPK models were developed and made available in the latest OSPS v12.0, and validated with clinical data.

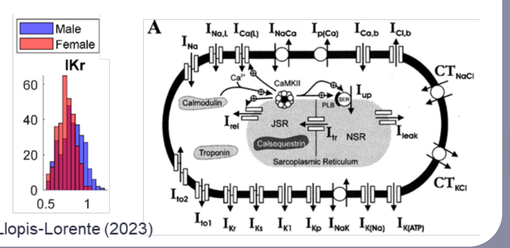
A data-driven QTc prolongation model was developed for Moxifloxacin and Bedaquilin, adapted from Gotta (2016)[2]. It utilizes *in vitro* ion channel binding data to quantify how hERG inhibition translates to QTc prolongation.

Then, a mechanistic cardiac electrophysiology model[3] including mixed-gender population variability was translated from MATLAB to R, validated against CiPA drugs[4], and applied to Moxifloxacin, a TB-drug with pro-arrhythmic risk. The input concentration was obtained from the PBPK model, ion channel inhibition potential was derived from patch clamp experiments[3]. Resulting drug effects on cardiomyocyte AP and duration at 90% repolarization (APD90) were computed.

Data-driven QTc prediction



Mechanistic AP prediction



Results

- PBPK models of 5 anti-TB drugs replicated dose-concentration relationships (e.g., isoniazid evaluated across 11 clinical studies in healthy and TB patients). They were made available in OSPS v12.0
- The data-driven QTc model predicts the dose-QTc relationship for Moxifloxacin at low doses and Bedaquilin metabolite at high doses
- The mechanistic AP model and the virtual population transferred to R successfully reproduce the effect of high-risk CiPA drugs on AP in male and female virtual populations.
- The model predicts that Moxifloxacine increases APD90 by 35ms under the tested clinical dose, in line with the reported ΔΔQTc of 29.9ms.
- A quantitative relationship between AP delay and QTc prolongation is necessary for quantitative validation.

Conclusion

PBPK models of TB drugs and QSP cardiac effect models have been implemented in an open-source framework to enhance dose testing and cardiac safety assessment in various populations. This ensures that technological advancements in TB-drug PK and PD assessment are accessible to a broader audience. The next steps involve further testing and validating the framework with new *in vitro* data for TB drugs.

Transfer to OSPS v12 and validate anti-TB drugs PBPK models

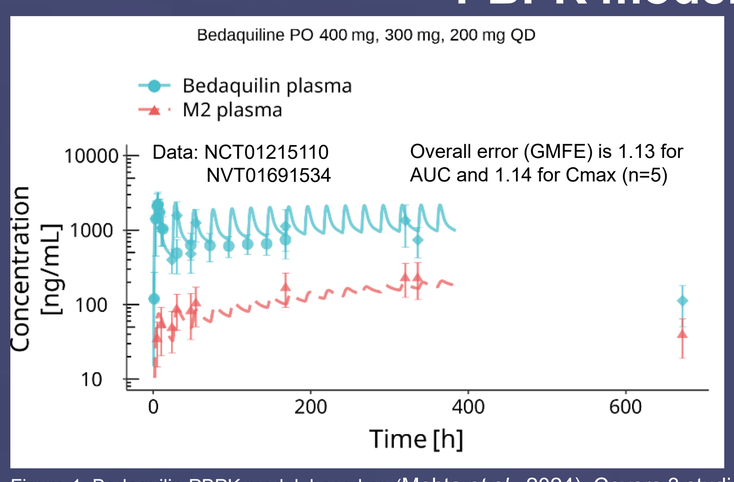


Figure 1: Bedaquilin PBPK model, based on (Mehta *et al.*, 2024). Covers 3 studies with Bedaquilin from po 200 to 700 mg.

PBPK models

GitHub

GitHub OSPS PBPK library[6]
- Bedaquilin
- Rifampicine
- Isoniazid
- Moxidectine
- Moxifloxacine

Data-driven QTc modelling

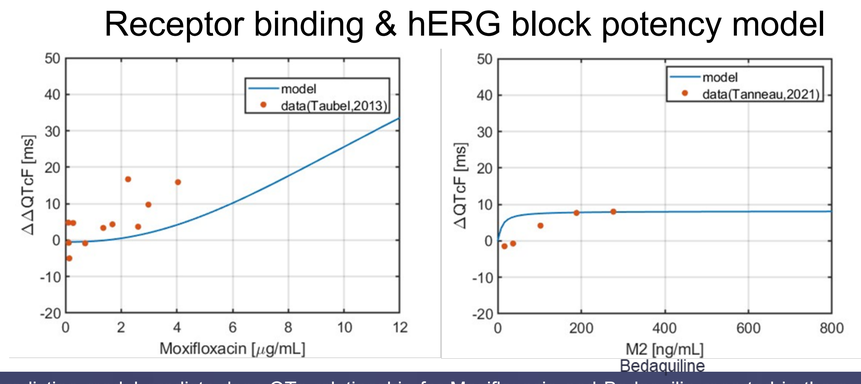


Figure 2: QTc prediction model predicts dose-QTc relationship for Moxifloxacin and Bedaquilin reported in thorough QT studies (Taubel, 2013 and Tanneau, 2021). Fridericia's correction was implemented using a resting heart rate of 75bpm. ΔQTcF for the placebo was assumed to be 0.5ms (reported as close to 0 in the literature).

Mechanistic AP model in R - Validation

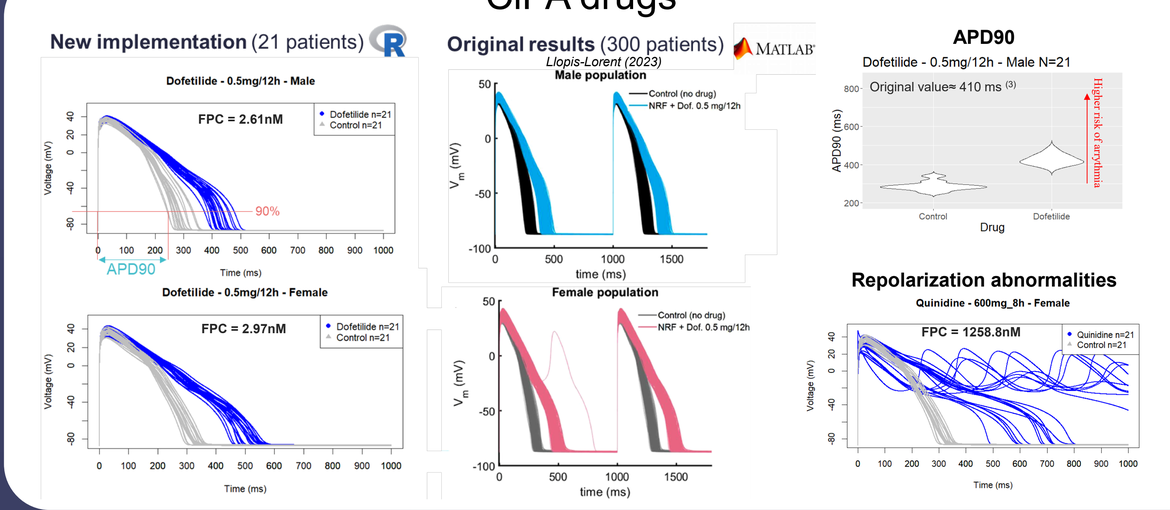


Figure 3: R implementation validation with benchmark CiPA drugs. AP predictions was reproduced in R compared to the original paper. Dofetilide was modelled with $IC_{50}^{hERG} = 1.47nM, hKr = 0.63$ and high IC_{50} for other channels. 'FPC'= free plasma concentration. The APD90 was increased under Dofetilide, in line with known pro-arrhythmic risks. Expected repolarization abnormalities are also reproduced.

Cardiac effect of TB-drug Moxifloxacin

Input definition

Moxi PBPK (iv infusion)
60min: 5.63mg/h/kg
30min: 0.26mg/h/kg
Johannesen L, et al. (2016)[5]

PBPK model

$C_{max-Moxi}^{unbound} = 8.4\mu M$

$C_{max-M2}^{unbound} = 5.8\mu M\ (40\%\ of\ parent, 5\%\ bound)$

hERG

Moxifloxacin	hERG
IC50 (μM)	94.4
hill	0.65

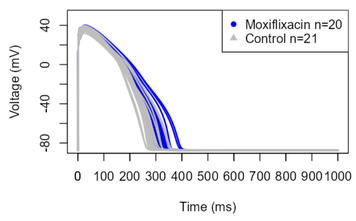
Data source: patch-clamp assay[5]

Inhibition
Moxi. [μM]

Cardiac electrophysiology model output

	Gender	FPC (nM)	IC50IKr (nM)	hIKr	IC50INa (nM)	hINa	IC50INaL (nM)	hINaL	IC50ICaL (nM	hICaL
M_iv_infusion_Mox_M2	1	14200	94400	0.65	1.00E+08	1	2.88E+05	1.08	1.50E+06	1.9

Moxi iv 5.63mg/h/kg (1h) + iv 0.26mg/h/kg (0.5h) with M2 - Male



Action potential delay

➔ The cardiac AP is delayed by 35ms under the effect of circulating Moxifloxacin and M2 metabolite.

Observed ΔΔQTc
29.9 ms
Johannesen L, et al. (2016) [5]

Figure 4: Simulating the effect of Moxifloxacin and its metabolite (M2) on the cardiomyocyte action potential. Input parameters (IC50, hill coef.) obtained from fitting a non-linear model with *in vitro* patch clamp data. Free plasma concentration of Moxi. and M2 were obtained from simulating the dosing of a published clinical trial[5] with the PBPK model. Moxifloxacin treatment induces a significant delay in the action potential compared to control in the male population (t-test). The observed effect in the original clinical trial

References

[1] J. Brust. et al. (2021) Effectiveness and Cardiac Safety of Bedaquiline-Based Therapy for Drug-Resistant Tuberculosis: A Prospective Cohort Study.

[2] V. Gotta et al. (2016) Application of a systems pharmacology model for translational prediction of hERG-mediated QTc prolongation

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[4] J. Vincente (2017) Mechanistic Model-Informed Proarrhythmic Risk Assessment of Drugs: Review of the "CiPA" Initiative and Design of a Prospective Clinical Validation Study.

[5] Johannesen L, et al. (2016). Late sodium current block for drug-induced long QT syndrome: Results from a prospective clinical trial. Clin Pharmacol Ther.

[6] https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library

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