Building up a posteriori percentiles for Therapeutic Drug Monitoring

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Introduction

Population pharmacokinetic (PK) models can produce percentiles from the predictive distribution of drug plasma concentrations at a particular time point *t* (hereafter referred to as *a priori* percentiles), which depict the likelihood of observed concentrations at time *t* in a population of interest. These can be used in Therapeutic Drug Monitoring (TDM) to assess the adequacy and expectedness of concentration measurements in a patient when the drug features a high inter-individual kinetic variability coupled with tight therapeutic margins e.g. Voriconazole (VRC). When past concentration measurements are available on a patient, these can be used to compute *a posteriori* percentiles i.e. percentiles from the posterior predictive distribution of concentrations. Conceptually, the posterior predictive distribution refers to the expected distribution of concentrations at time *t* in a hypothetical sub-population of patients having the exact same vector of past observations (and covariate values) as that of the patient under monitoring. Consequently, *a posteriori* prediction intervals are narrower compared to their *a priori* counterparts, which possibly renders them more powerful for detecting changes in drug disposition and/or adherence issues for the patient being monitored.

Objectives

Using Monte Carlo (MC) simulations from the population PK model of VRC in [1], build *a posteriori* percentiles to:

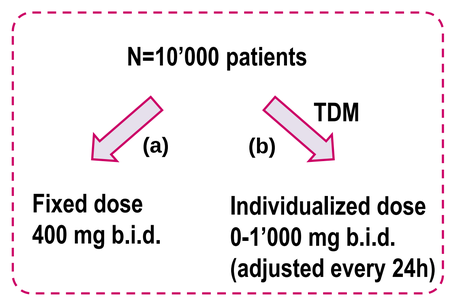
- Determine the probability that future VRC concentrations lie within a prespecified therapeutic interval under a fixed (400 mg b.i.d.) or an individualized dosing regimen for a simulated patient with normal hepatic function.
- Compare the power of both *a priori* and *a posteriori* 90% prediction intervals for detecting a change in drug disposition following e.g. the onset of severe hepatic cholestasis (SHC), or for the identification of treatment adherence issues (non-compliance).

Methods

Simulated trough concentrations for N=10'000 fictive patients with normal hepatic function and no co-medication were generated using the VRC population PK model developed in [1]. The simulation design considered the oral administration of VRC b.i.d. with plasma concentrations measured every 24 hours over a period of 10 days. Two situations were simulated:

(a) All patients receive a fixed oral dose of 400 mg VRC b.i.d.

(b) After two initial oral doses of 400 mg VRC, each patient receives an adjusted dose b.i.d. so that his/her predicted VRC trough concentration (*a posteriori*) at steady-state lies as close as possible to the center of the therapeutic interval, defined as the geometric mean of its limits (1.5-4.5 mg/mL as recommended in [1]). The optimal dose was selected on a grid ranging from 0 to 1'000 mg, with 50 mg increments (corresponding to the smallest oral VRC dose available on the market).



The proportion of patients with simulated VRC trough concentrations above / within / below the therapeutic interval was calculated under each design.

For a single patient, 90% prediction intervals for trough concentrations at the measurement occasions were calculated both *a priori* (i.e. using the patient's covariate information only) and *a posteriori* (i.e. using both the patient's covariate information and his/her past concentration measurements). The posterior distribution of random effects was sampled using the Sampling Importance Resampling (SIR) algorithm [2,3] while treating population parameters in the model as known.

SIR algorithm [2,3]

Bayes law:

$$h(\boldsymbol{\eta}_i) \equiv \pi_{\hat{\boldsymbol{\Theta}}}(\boldsymbol{\eta}_i|\boldsymbol{y}_i) \propto \pi_{\hat{\boldsymbol{\Theta}}}(\boldsymbol{y}_i|\boldsymbol{\eta}_i)\,\pi_{\hat{\boldsymbol{\Theta}}}(\boldsymbol{\eta}_i) = \pi^*_{\hat{\boldsymbol{\Theta}}}(\boldsymbol{\eta}_i|\boldsymbol{y}_i) \equiv h^*(\boldsymbol{\eta}_i)$$

Posterior — *Conditional likelihood* — *Prior* — *Non-normalized posterior*

$\pi_C(X)$: distribution of *X* with constant *C*

$\boldsymbol{y}_i$: vector of past concentrations for patient *i*

$\boldsymbol{\eta}_i$: vector of random effects for patient *i*

$\hat{\boldsymbol{\Theta}}$: vector of point estimates for population parameters

1) Calculate empirical Bayes estimates $\hat{\boldsymbol{\eta}} = \underset{\boldsymbol{\eta}_i}{\operatorname{argmax}}\ \log h^*(\boldsymbol{\eta}_i)$ and their variance $\hat{\boldsymbol{\Gamma}} = \operatorname{var}(\hat{\boldsymbol{\eta}}) = \left[-\frac{\partial^2}{\partial \boldsymbol{\eta}_i^2} \log h^*(\boldsymbol{\eta}_i)\Big|_{\boldsymbol{\eta}_i=\hat{\boldsymbol{\eta}}}\right]^{-1}$
2) Sample $\tilde{\boldsymbol{\eta}}_1, ..., \tilde{\boldsymbol{\eta}}_M$ from $g(\boldsymbol{\eta}_i) \equiv \text{Student-}t\left(\hat{\boldsymbol{\eta}}_i, \hat{\boldsymbol{\Gamma}}, \nu\right)$ with e.g. $\nu = 2$ degrees of freedom
3) Calculate $r_j = h^*(\tilde{\boldsymbol{\eta}}_j)\,/g(\tilde{\boldsymbol{\eta}}_j)$ for $j = 1, ..., M$
4) Calculate $w_j = r_j / \sum_{k=1}^{M} r_k$
5) Resample $\boldsymbol{\eta}_1, ..., \boldsymbol{\eta}_N$ with $N << M$ from $\tilde{\boldsymbol{\eta}}_1, ..., \tilde{\boldsymbol{\eta}}_M$ using unequal inclusion probabilities $w_1, ..., w_M$ ($M = 10N$ was used here)

The simulation design was slightly altered to estimate the power of detecting a possible change in drug disposition or a treatment adherence issue. The onset of SHC (that corresponds to a drop of 55% in VRC clearance according to [1]) was simulated from day-7 of therapy (starting at *t*=160 hours). Treatment non-compliance was simulated by a single missing dose at *t*=156 hours (i.e. 2nd dose in day-7 of therapy). SHC onset and treatment non-compliance were simulated separately. Under both settings, all patients (restricted to N=2'000 for computational reasons) received an individualized dosage with adaptation every 24 hours (according to design b above) while assuming a normal hepatic function and full treatment adherence.

The power to detect the effect of such change was calculated as the (one-sided) probability for an observed concentration to lie above the 95% percentile (SHC onset) or below the 5% percentile (treatment non-compliance) of the predictive distribution, both *a priori* or *a posteriori*.

Remark: although the model in [1] was fitted to observational data, the simulation design considered above implicitly assumes the dose and covariate effects estimated in model [1] to be causal (e.g. we assume that study [1] did not suffer from residual confounding and/or counfounding-by-indication).

Conclusions

When past concentration measurements are available for a patient under monitoring, *a posteriori* percentiles:

- **depict the likelihood of future observed concentrations in the patient**, under the current or an adapted dosing regimen, assuming that the patient's condition remains stable.
- **become narrower** (asymptotically bounded by the intra-individual variability) as more past observations are considered, since an increasing part of the inter-individual variability is explained by the patient's history.
- **increase the chance of detecting major changes** in drug disposition and/or treatment adherence issues compared to the prior predictive distribution (although power remains globally weak in our example).
- **can be graphically communicated to the attending physician**, who can then judge whether a measured concentration is both expected and appropriate for his/her patient.

Results

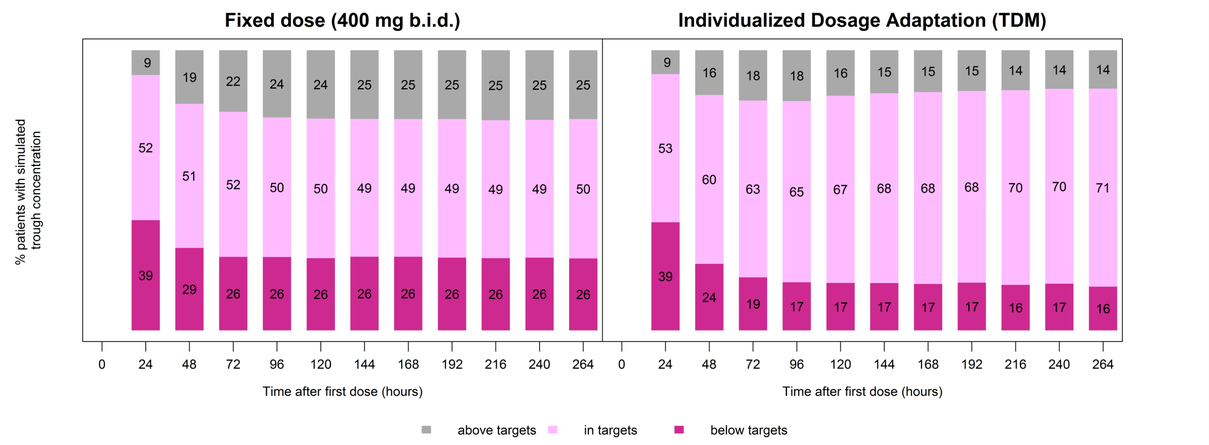


Figure 1: Proportion of patients (N=10'000) with trough concentration above / within / below the therapeutic interval proposed in [1] (1.5-4.5 mg/L) under a fixed dosing regimen (400 mg b.i.d.) or using TDM with individualized bayesian dosage adaptation.

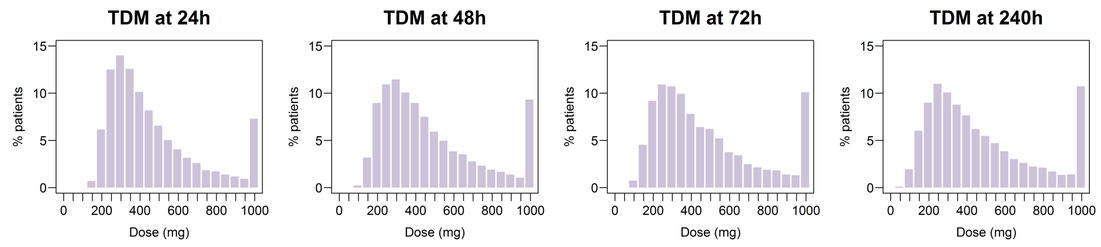


Figure 2: Distribution of adjusted doses at various time points when simulated patients are undergoing TDM (N=10'000).

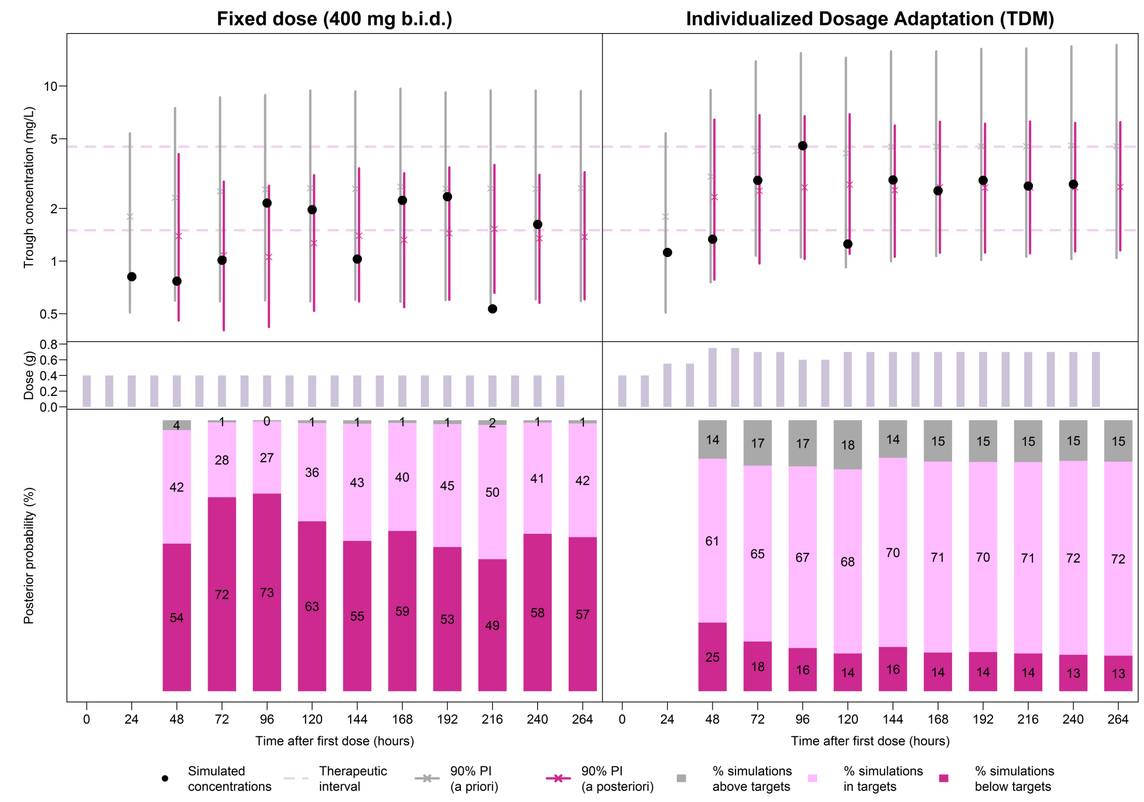


Figure 3: Simulated trough concentrations for one illustrative patient under either a fixed dosing regimen (400 mg b.i.d.) or an individualized dosing regimen using TDM, with *a priori* and *a posteriori* 90% prediction intervals (PI) for trough concentrations, and *a posteriori* probabilities for future trough concentrations to lie above / within / below the therapeutic interval (N=10'000 simulations).

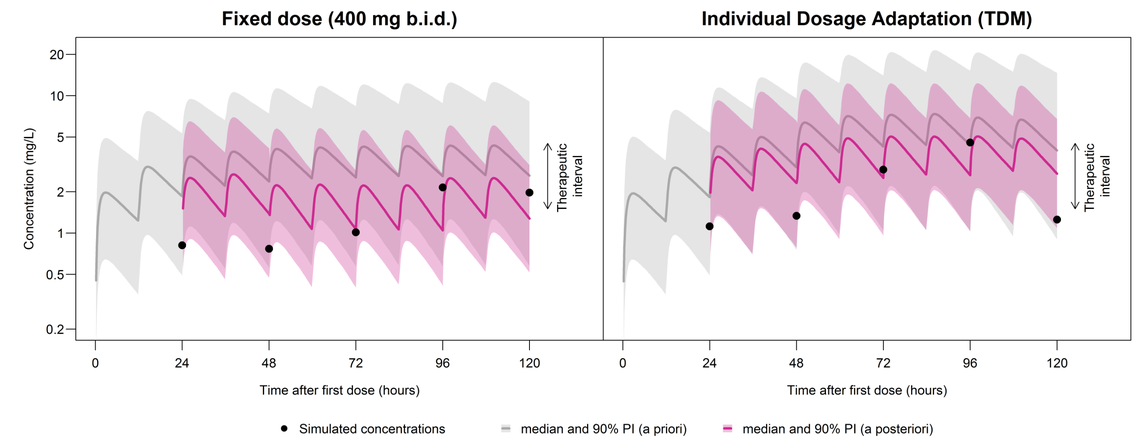


Figure 4: 90% prediction intervals (PI) with median *a priori* and *a posteriori* when considering incrementally the first five simulated concentrations of the illustrative patient in figure 3 under each dosing regimen (N=10'000 simulations). The vertical arrow refers to the therapeutic interval proposed in [1] (1.5-4.5 mg/L).

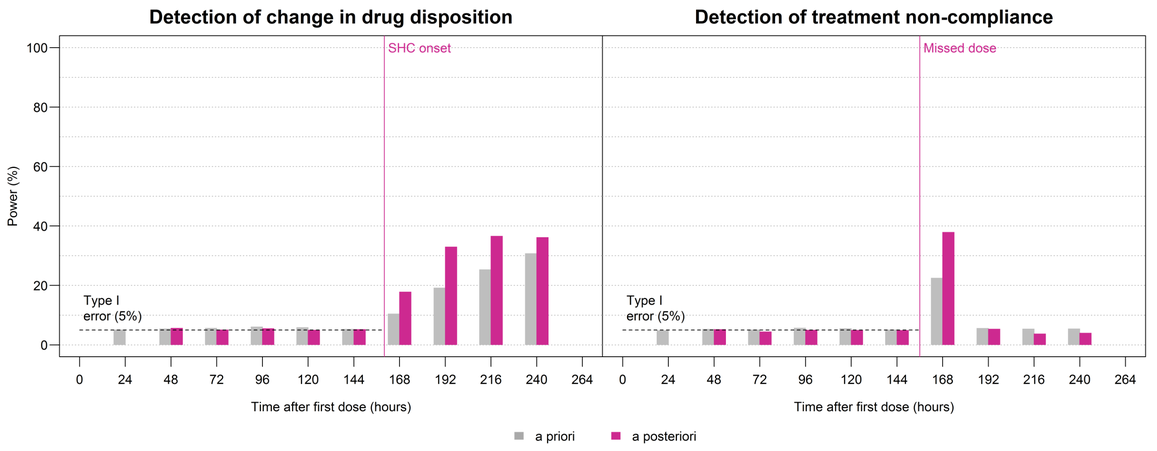


Figure 5: Statistical power i.e. probability to detect a change in drug disposition due to SHC occuring at *t*=160 hours (left panel) or due to a missed dose at *t*=156 hours (right panel) using both *a priori* and *a posteriori* 90% prediction intervals when patients undergo TDM with individualized dosage adaptation (N=2'000 simulations). The power corresponds to a one-sided test where each simulated concentration is labelled as atypical if it falls above the 95% percentile (left) or below the 5% percentile (right) of the predictive distribution.

References

[1] Pascual, A. et al. (2012) Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety: population pharmacokinetics-based analysis of adult patients with invasive fungal infections. Clin Infect Dis, 55(3):381-390

[2] Rubin, D.B. (1988) Using the SIR algorithm to simulate posterior distributions. In Bayesian Statistics 3, eds, M. H. Bernardo, K. M. DeGroot, D. V. Lindley, and A. F. M. Smith, Cambridge, MA: Oxford University Press, 395-402

[3] Smith, A.F.M. and Gelfand, A.E. (1992) Bayesian statistics without tears: A sampling resampling perspective. The American Statistician, 46(2):84-88