Efficient Identification of the optimal dosing regimen with a nonparametric method

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BACKGROUND

- Dose Finding is the most relevant and visible task of pharmacometricians.
- “Open loop” dosing stands and falls with the ability to identify relevant covariates.
- In 2008, “clinical irrelevance criteria” have been suggested to limit the search space [1].
- In 2012 and 2017 a high dimensionality/brute force method (”full random effects model” (FREM)) has been advocated as the optimal solution to the covariate problem [2,3].
- Paradigms employed in anesthesia and “target concentration intervention” (former TDM) focus on dose finding, based on a target exposure. Dose can be a parameter.
- Why not combine these lines of thought? 1) parameter identification, 2) definition of target (exposure or PD), 3) estimation of corresponding dose, 4) covariate search on dose.

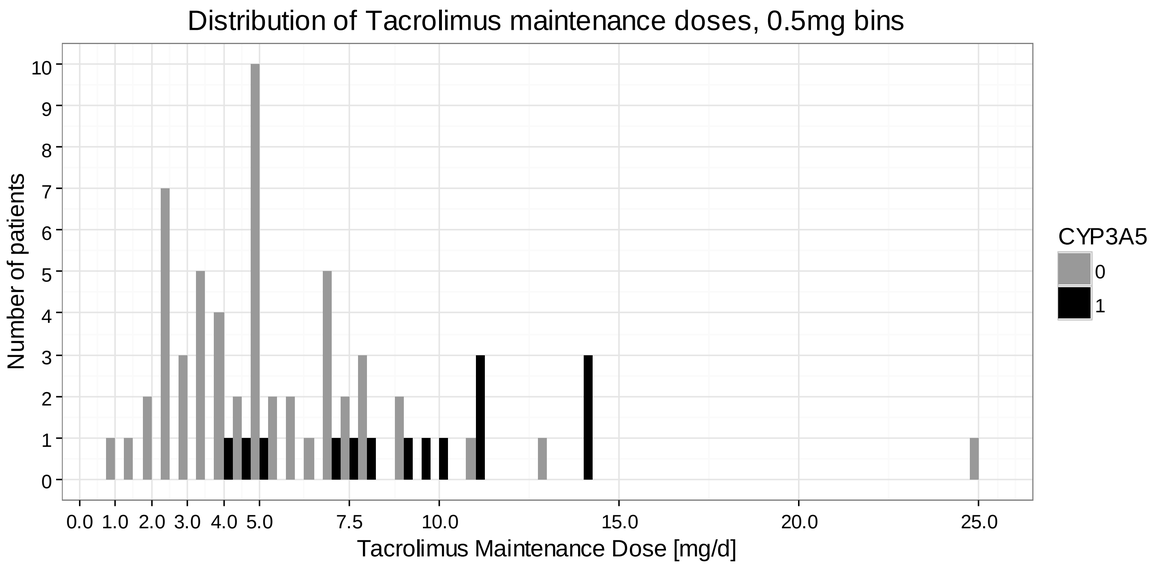
OBJECTIVES

- To suggest, formalize and demonstrate a therapy focused covariate search strategy.
- Question: Inclusion of which covariate into the dosing algorithm improves percent target attainment to which degree and how complex is the corresponding dosing regimen?

METHODS

- PK data from 70 adult patients (CYP3A5.0: n=55; CYP3A5.1: n=15) after renal transplantation, receiving tacrolimus once daily at steady state and undergoing TDM was used. TDM doses are informative regarding covariate effects to be expected. (**Fig. 1.**)
- PK parameter estimation was done nonparametrically (most accurate empirical Bayesian estimates (EBEs) of individual parameter vectors (IPV) (Pmetrics 1.5 (NPAG)[4])).
- A target for dosing (here: Css,min=8mcg/L, median in the population) and a dosing interval (24h) were specified.
- The dose for target attainment was determined using a fixed unit dose , IPVs and bioavailability as estimable parameter (cheap trick to be able to estimate dose).
- Comparison of the empirical cumulative distribution functions (ecdf’s) of support point (SPTPs) and IPV based doses (probability corrected): Quality control.
- Covariate exploration/search on IPV doses (unless nSPTP = nIndividuals, SPTPs do not directly relate to covariates): Weight, Hct, day after transplant, CYP3A5 expression.
- Selection of covariate candidates, which promise to improve target attainment to a clinically relevant degree (i.e. display a clear pattern vs. IPV doses (**Fig. 2.** Panel 1)).
- Rerun model with covariates included, obtain dose estimates by covariate level/value and compare objective function values to base model.
- Comparison of candidate regimens regarding exposure ranges in the population and complexity (here: Ideal (100% target attainment, fully individualized doses), TDM based, covariate adjusted open loop (n=2) and one size fits all (OSFA) dosing strategies.
- Decision for the regimen with both acceptable target attainment and practical feasibility.

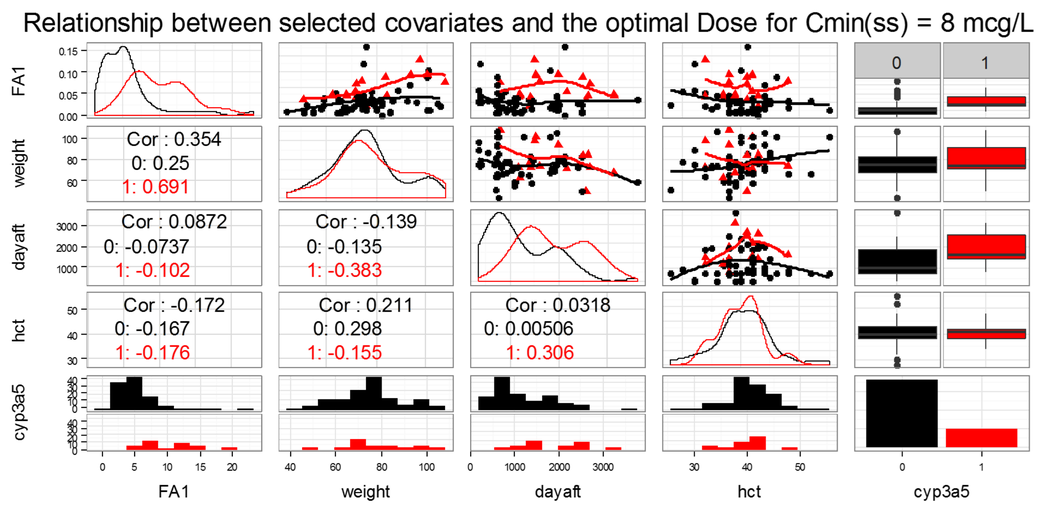
Fig. 1. Covariate expected to be identified: CYP3A5



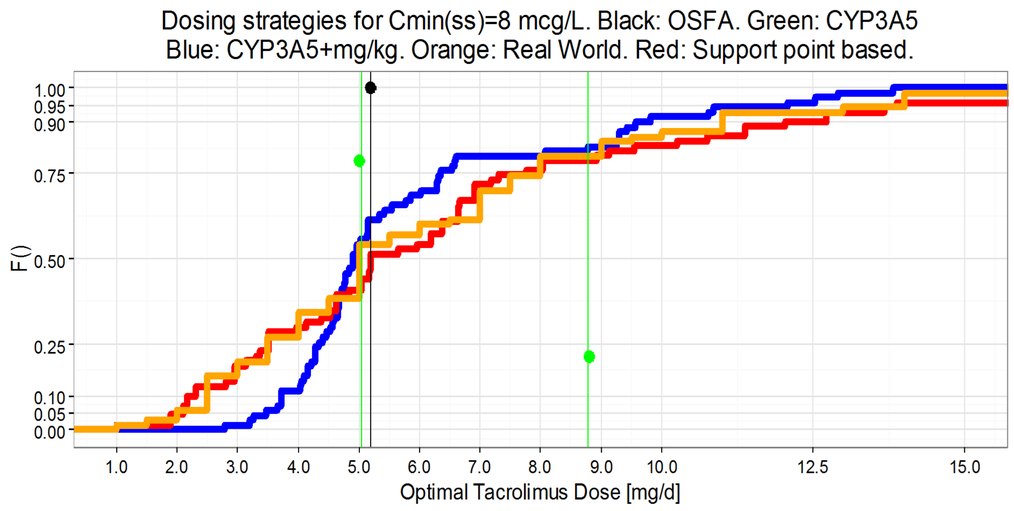
RESULTS

- A 2 compartment model with first order input adequately described the PK of tacrolimus. Although this type of model can be solved analytically for the optimal dose, the "dose estimation" approach was favored in order to demonstrate applicability to more complex systems (e.g. transit compartment PK models, indirect response models…).
- As expected, the ecdf of dose using the IPVs was virtually identical to that of the support points, justifying the use of individual dose vs. covariate plots.
- CYP3A5 expression was the only covariate identified and decreased -2LL by 50 compared to unique dose, the only other open loop scenario explored.
- Rounded Dose(s) were 2-13 mg/d (Q5-Q95) for TDM based, 5 and 9 mg/d (95% CI: 4.3-6.1; 8.0-11.2 mg/d) for CYP3A5 based, 3.5-11 mg/d (Q5-Q95) for CYP3A5+weight based (mg/kg) and 5 mg/d (95% CI: 4.7-6.8 mg/d) for unique dose.
- TDM based dosing achieved Cmin,ss concentrations between 5-11 mcg/L in 95% of the investigated patient population. The respective values for CYP3A5 based, CYP3A5+weight based and unique dose are 65%, 65% and 50%.
- As expected, CYP3A5 is relevant for target attainment of tacrolimus, but not sufficient to replace TDM adjusted dosing. Weight correction only adds complexity, not precision.
- The method will be explored further regarding its usefulness for rapid and to the point dose finding and communication (**Fig. 2.** Panels 2 and 3).

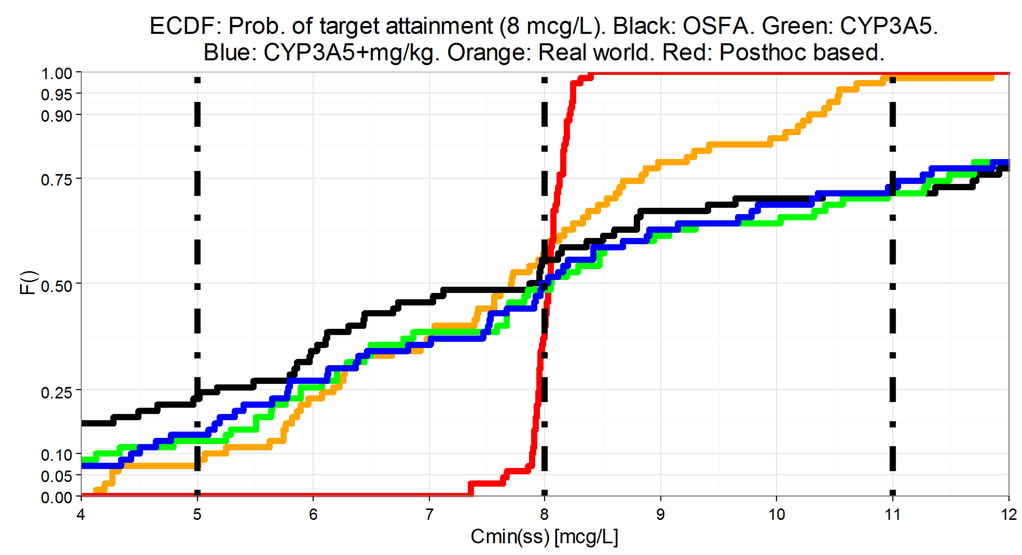
Figure 2.
Panel 1: Covariates vs. Dose (Dose is FA1, “bioavailability” in Pmetrics). Red: CYP3A5 expressors.



Panel 2a: Dose distribution belonging to the different strategies: The flatter, the more complex.



Panel 2b: Corresponding distribution of Css,min: The flatter, the less precise. Note the difference between the orange (real world) and the red line (theoretical performance of TDM): Intraindividual variability is not accounted for by TDM, physicians target a range (therapeutic window).



CONCLUSIONS

- An almost trivial solution to the covariate selection and identification problem has been formalized and demonstrated. Gain: Reduced dimensionality during calculation steps. Drawback: Specification of target (exposure or PD) prior to covariate search.
- Using empirical distribution functions, the tradeoff between complexity of dosing and precision of target attainment can be assessed and communicated simultaneously.
- Since Dose is the only parameter to be estimated during the covariate search, a brute force approach, if selected, will be much more efficient than using the “full model”.

[1] Tunblad K, Lindbom L, McFadyen L, Jonsson EN, Marshall S, Karlsson MO. The use of clinical irrelevance criteria in covariate model building with application to dofetilide pharmacokinetic data. J Pharmacokinet Pharmacodyn. 2008 Oct;35(5):503-26
[2] PAGE 21 (2012) Abstr 2455 [www.page-meeting.org/?abstract=2455]
[3] PAGE 26 (2017) Abstr 7365 [www.page-meeting.org/?abstract=7365]
[4] Neely MN, van Guilder MG, Yamada WM, Schumitzky A, Jelliffe RW. Accurate detection of outliers and subpopulations with Pmetrics, a nonparametric and parametric pharmacometric modeling and simulation package for R. Ther Drug Monit. 2012 Aug;34(4):467-76