TDMx: A web application for bedside model-supported therapeutic drug monitoring to improve antibiotic therapy

Sebastian G. Wicha (1), Martin G. Kees (1,2), Alexander Solms (3), Iris K. Minichmayr (1), Alexander Kratzer (4), Charlotte Kloft (1)

[1]Dept. of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Germany
[2]Dept. of Anaesthesiology and Intensive Care, Charité Universitätsmedizin Berlin - Campus Benjamin Franklin, Berlin, Germany
[3]Institute of Mathematics, University of Potsdam, Germany
[4]Hospital Pharmacy, University Hospital Regensburg, Germany

Background and Objectives

- **Pharmacokinetic (PK) variability** can negatively affect the **effectiveness** and **safety** of **antibiotic treatment**.
- **Pharmacometric models** have evolved as useful tools to **quantify** and **explain** PK variability between patients and to explore the pharmacodynamic (PD) consequences of this variability on therapy outcomes. Although manifold predictive pharmacometric models and PK/PD relationships have been published over the years, the application of these mathematical models in therapeutic drug monitoring (TDM) is yet limited, as available professional software is mostly difficult to use and more simple software often lacks profound functionality.
- Hence, we aimed to develop '**TDMx**' (speak: 'TDMetrics'), an **easy-to-use**, but **powerful modular software** tool for **bedside dosing decisions**, making use of **state-of-the-art pharmacometric** techniques such as
  - **(i) Probabilistic dosing**/probability of target attainment (PTA) analysis **without requiring drug measurements**,
  - **(ii) Bayesian dosing** with PK estimation and definite PK/PD target attainment analysis **if drug measurements are available** and
  - **(iii) (Adaptive) optimal design** module to **sample** at the **most informative time points**.

Methods

- RStudio (RStudio Inc., with 'R' version 3.1.1 [1]) was utilised as IT framework.
- The 'R' package 'shiny' (version 0.10.2.1) was employed for programming the user-interface.
- Peer-reviewed, published PK models were selected and encoded into 'TDMx'. Sub-modules were created to satisfy the objectives (i)-(iii).
- 'TDMx' was validated against NONMEM™ (version 7.3 [2]) as the gold-standard software in pharmacometrics.

Results

The first release of 'TDMx' [3] comprises instances tailored to support TDM of aminoglycosides (**amikacin** [4], **gentamicin** [5]) and beta-lactams (**meropenem** [6], **piperacillin** [7]). A typical 'TDMx' workflow for model-supported TDM is illustrated in Fig. 1.

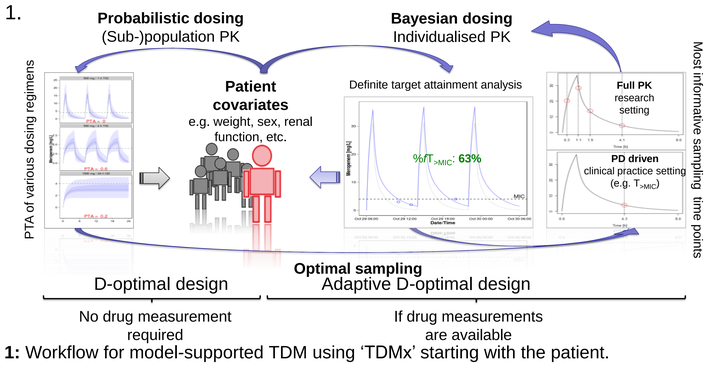

Fig. 1: Workflow for model-supported TDM using 'TDMx' starting with the patient.

Results

Validation against NONMEM™:

The simulation and estimation algorithms of 'TDMx' were **successfully validated** against **NONMEM™** and **identical results** were obtained for PK parameters (3 sig. digits) and PK profiles.

Modules:

Patient module: Input module for all available patient data (e.g. demographics, laboratory measurements) as well as for the dosing schedule (Fig. 2).

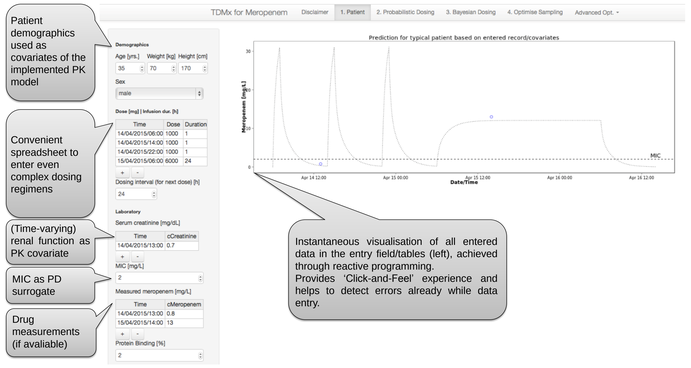

Fig. 2: Screenshot of the 'Patient module' of 'TDMx'.

Probabilistic dosing module: Computes based on the selected PK/PD target the PTA to select **a likely effective dosing regimen** solely using patient covariates, e.g. to initiate empiric therapy, or to guide institutions where **no drug measurements** are available (Fig. 3).

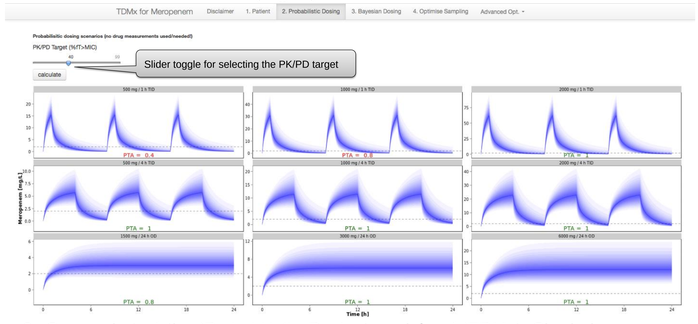

Fig. 3: Screenshot of the 'Probabilistic Dosing' module of 'TDMx'. Shaded area represents anticipated (un-)certainty of the PK profile (2.5th – 97.5th percentile) due to interindividual variability of the (sub-)population. PTAs of the respective dosing regimens are indicated in green if favourable (i.e. > 0.9) or in red if insufficient.

Results (cont'd.)

Bayesian dosing module: Estimates individual PK parameters for **definite target attainment** analyses if **drug measurements** are available (Fig. 4).

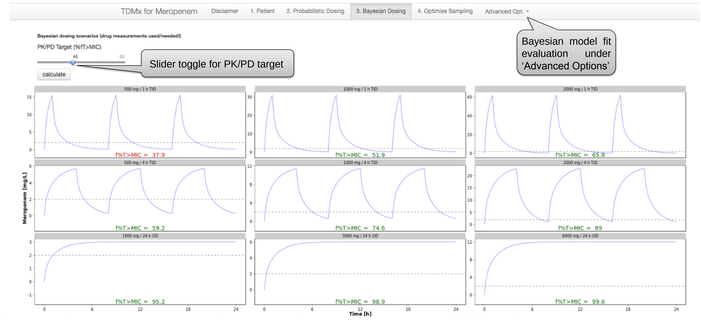

Fig. 4: Screenshot of the 'Bayesian Dosing' module of 'TDMx'. Regimens that provide reliable target attainment are indicated in green, unfavourable regimens are highlighted in red.

Optimal design module: Predicts the **most informative sampling time points** for the precise estimation of either **PK parameters** (e.g. in a research setting) or **PD surrogates** (e.g. $T_{>MIC}$ as a relevant PK/PD index in clinical routine) (Fig. 5).

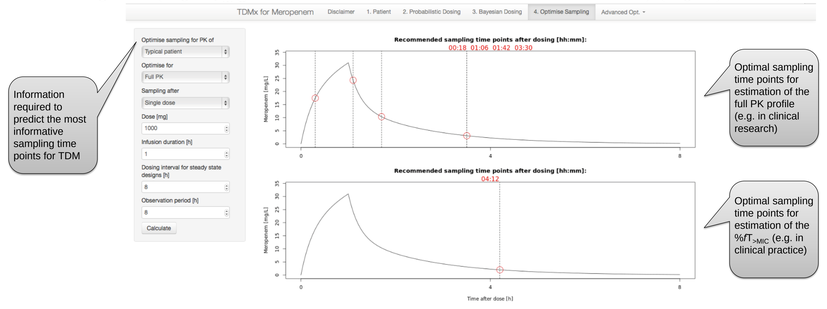

Fig. 5: Screenshot of the 'Optimal sampling' module of 'TDMx'.

Conclusions

- With 'TDMx', we provide an **easy-to-use, flexible and powerful web-application,** making use of state-of-the art pharmacometric techniques to support **bedside drug dosing decision-making**.
- In comparison to other available tools, 'TDMx' offers broader functionality and can entirely be used in a **web browser**, also on various (mobile) devices. Even complex dosing regimens can be analysed by use of convenient spreadsheet functionalities.
- 'TDMx' is **freely available** online under: **www.tdmx.eu**.

References

[1] R Core Team. R. A language and Environment for Statistical Computing. R Foundation for Statistical Computing, R 3.1.1, Vienna, Austria (2015).
[2] S. Beal, L.B. Sheiner, A. Boeckmann, *et al.* NONMEM 7.3 Icon Development Solutions, Ellicott City, MD, USA (2013).
[3] S.G. Wicha, M.G. Kees, A. Solms, *et al. Int. J. Antimicrob. Agents*, 45: 442–444 (2015).
[4] S. Romano, M. Del Mar Fdez de Gatta, V. Calvo, *et al. Clin. Drug Investig.*, 15: 435–44 (1998).
[5] D. Xuan, D.P. Nicolau, C.H. Nightingale. *Int. J. Antimicrob. Agents*, 23: 291–295 (2004).
[6] C. Li, J.L. Kuti, C.H. Nightingale, *et al. J. Clin. Pharmacol.*, 46: 1171–8 (2006).
[7] C. Li, J.L. Kuti, C.H. Nightingale, *et al. J. Antimicrob. Chemother.*, 56: 388–95 (2005).

For additional information, please contact
Sebastian G. Wicha
sebastian.wicha@fu-berlin.de