Quick Reference

Vancomyin

Developer

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Citation

S.G. Wicha, M.G. Kees, A. Solms, I.K. Minichmayr, A. Kratzer, C. Kloft TDMx – a novel web-based open-access support tool for optimising antimicrobial dosing regimens in clinical routine. Int. J. Antimicrob. Agents. 45: 442-444 (2015).

Disclaimer

TDMx has been created for personal use only. The use of any result generated by TDMx is in any case the sole risk and responsibility of the TDMx user. Therapeutic decision should not solely rely on TDMx as information provided by TDMx does not replace clinical judgement. Although TDMx has been validated carefully, there is no guarantee for the accuracy of the provided results. When using TDMx you automatically agree with this disclaimer and the legal notices.

Requirements

TDMx is fully tested on Google Chrome® and Mozilla Firefox® browsers.
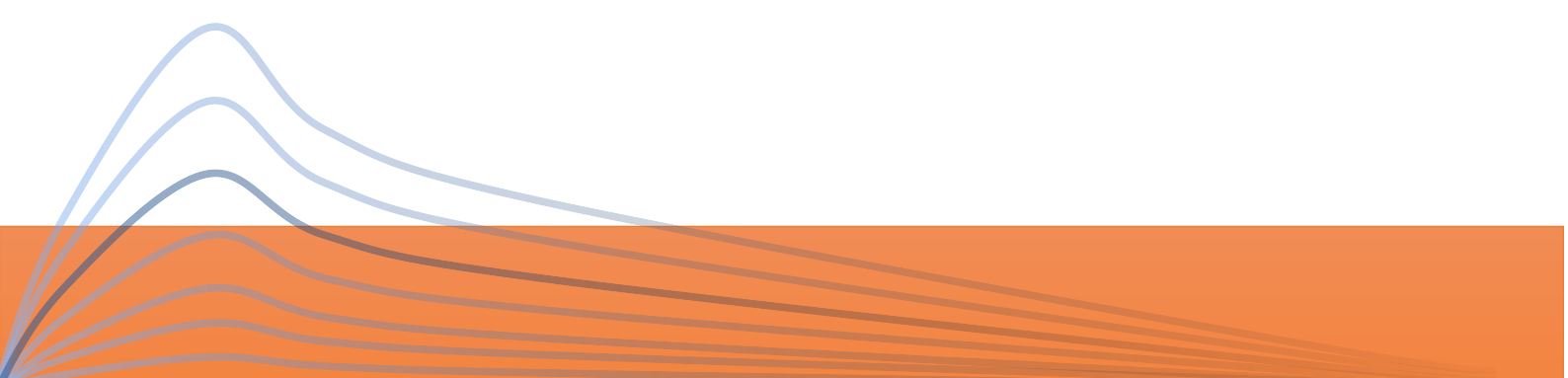
Introduction

TDMx is a web-based model-informed precision dosing (MIPD) software to perform dosing simulations to support **T**herapeutic **D**rug **M**onitoring (TDM) with pharmacometrics (x). TDMx was developed as an educational tool for healthcare professionals to demonstrate application of model-supported TDM in clinical practice as well as clinical research. Furthermore, TDMx is suitable for teaching TDM in undergraduate studies.

TDMx was developed using reactive programming with a server-client architecture: TDMx reactively visualizes your input such as dosing history, patient covariates or drug measurements. Thereby, TDMx provides quick answers to clinically relevant questions. TDMx does not require any software to be installed on your PC or tablet computer. Simply access TDMx through a generic web browser.

Launch TDMx from the web

Go to www.TDMx.eu

Navigate to the menu LAUNCH TDMX and select a suitable drug.
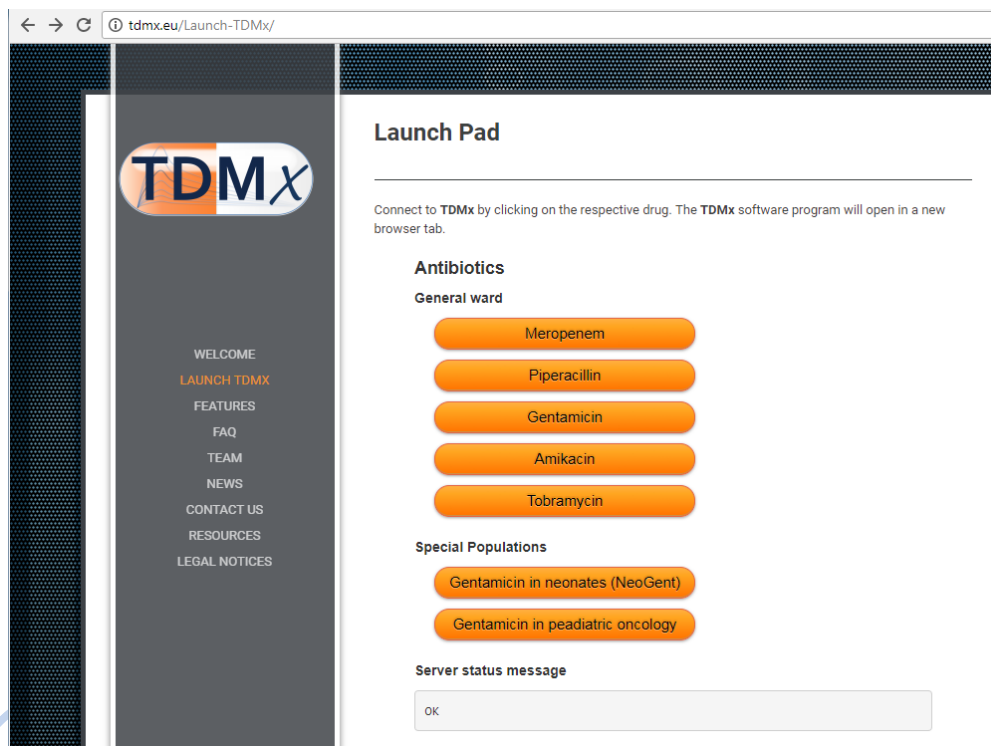
Main module

The main module consists of two panels: the patient panel (input) and the prediction/visualization panel (output) (Figure 1).
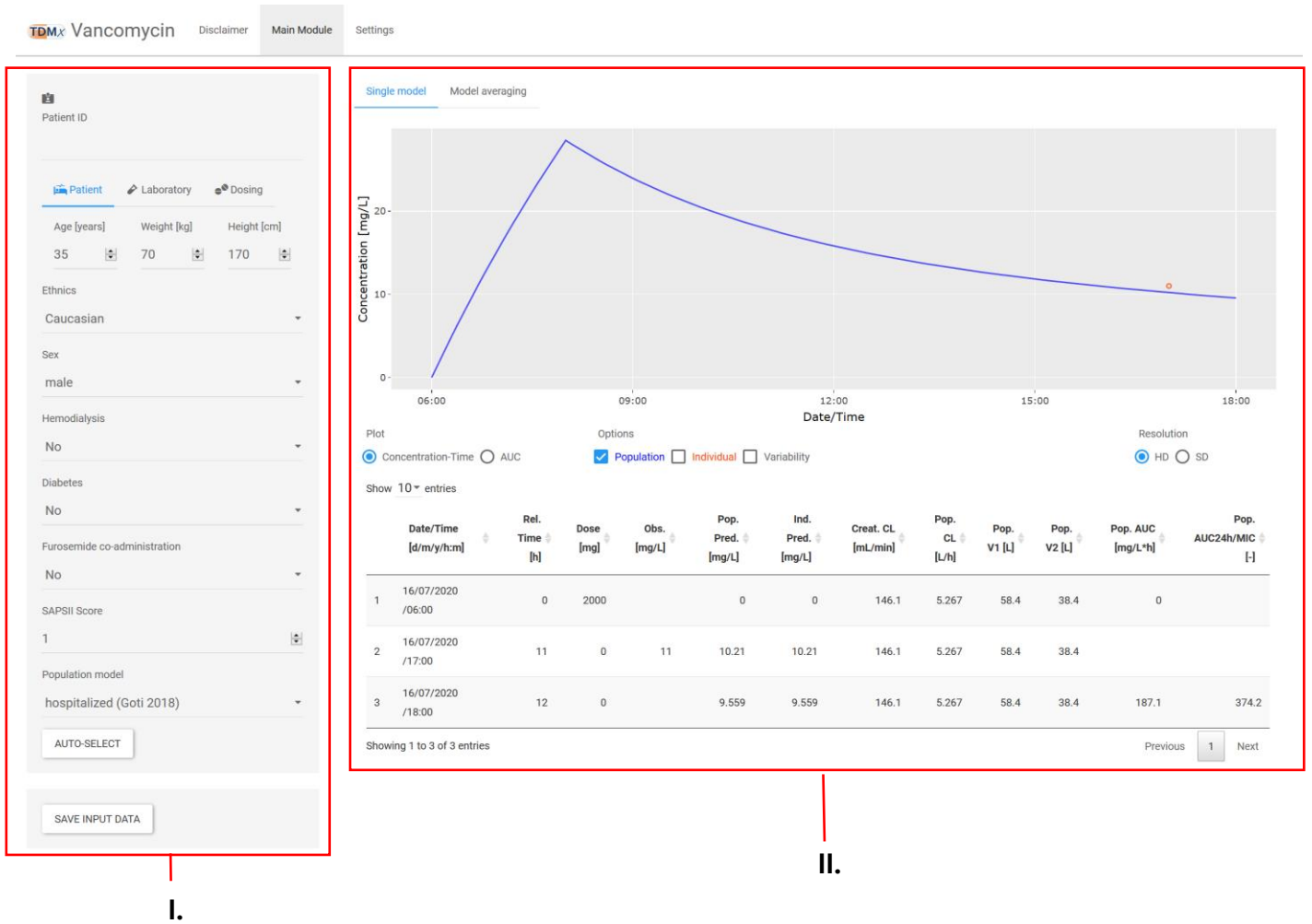

Figure 1 Main interface of the TDMx web-application

I.   Input panel: Here patient-related information, laboratory data and dosing records can be provided. For further details, please refer to *Create a patient*.

II. Output panel: This area contains graphical (e.g. the individual PK profile) and numerical output (e.g. the individual area-under-the-curve) based on the patient-individual predictions using the model specified under *Create a patient*.

After the user has entered patient-related information (e.g. covariates) and additionally, a dosing regimen of the drug of interest, the PK profile based on a (predefined) population PK model can be inspected in the output panel (blue line – 'Population'). To obtain the individual PK profile based on Bayesian feedback (orange line – 'Individual'), the user can specify historical laboratory data (e.g. drug plasma measurements).

If a different population PK model is preferred for simulations/predictions, a dropdown menu in the input panel contains a list of available models. Furthermore, the web-app can automatically select the model with the best fit for purpose or a weighted average of a set of models. Please refer to *Select a model* for further details.
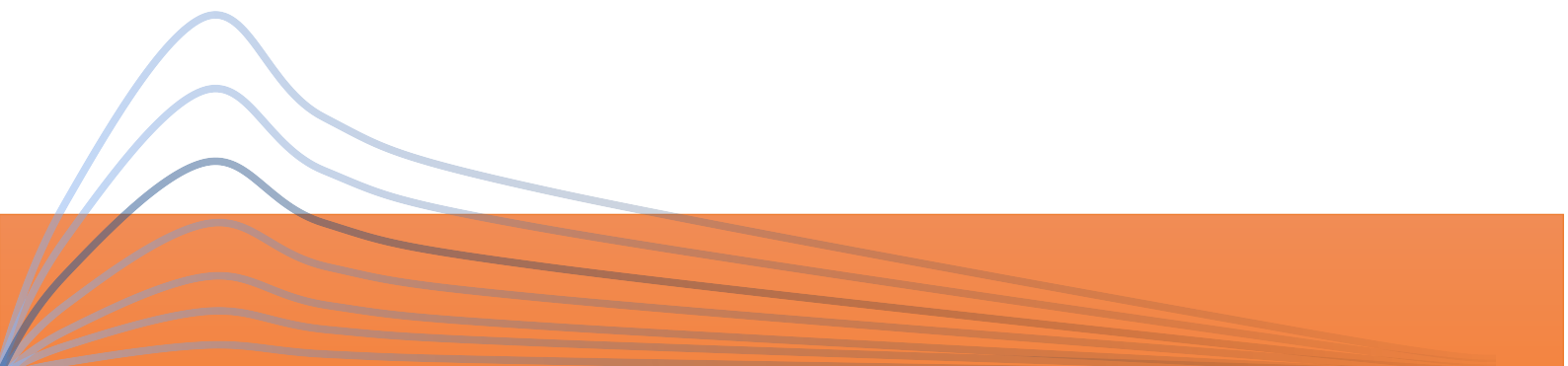
Create a patient

The user can save and load a patient profile including covariates, TDM related data and dosing history. To save the data click the 'SAVE INPUT DATA'-button (Figure 2, V.) in the patient panel.

During startup of the TDMx app, it is possible to upload a previously saved patient click 'BROWSE' and select the previously saved patient-file (*.tdmx).

The input panel consists of three tabs: Patient, Laboratory and Dosing. The tabs are described in the following:
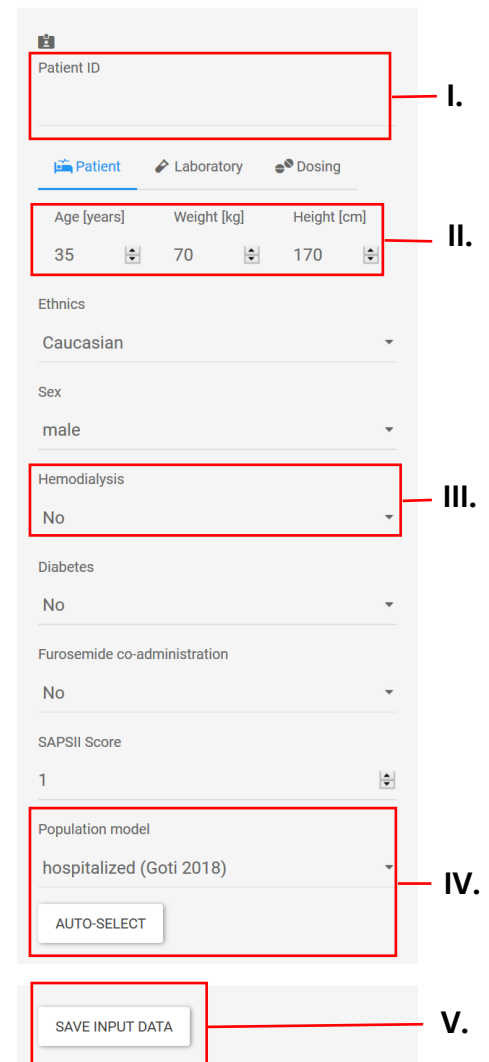
Patient

In this tab the user can specify the following:

I.   Determine a name/identifier for this patient.
II.   Specify continuous covariates by either typing the value (without units) or click the up/down button.
III.   Categorical covariates can be selected by clicking on the dropdown menu in the respective box.

> **Note:** Some covariates are used by selected models only. Hover over the covariate to see, which model accounts for this covariate, respectively.

IV.   Select a model for predictions/simulations. Please refer to *Select a model* for further details.
V.   Save and export patient data.

Figure 2 Input panel to edit patient-related data

Laboratory

In the laboratory-tab, the user can specify data obtained during therapeutic drug monitoring (e.g. drug plasma concentrations, serum creatinine, ...). These values will be directly used as covariates in the population PK model and improve the prediction.

Figure 3 Input panel to edit laboratory data

I.   A new drug plasma concentration can be added via the '+', while a click on '-' will remove the latest measurement. Please specify the date (dd/mm/yyyy/hh:mm) of the measurement and enter the concentration in mg/L.

II. Further clinically relevant parameters can be added at the respective position. Please specify the date of the measurement as dd/mm/yyyy/hh:mm, and enter the concentration in the stated unit. In the case of no measurement being available for this patient, the user is asked to leave the respective box as is.

III. If the underlying model might use one or more of the laboratory markers for predictions/simulations and one of them is not available, it will automatically use a predefined population value, which will cancel the influence of the respective marker out.

III. Some laboratory markers can be entered in different units. TDMx will automatically convert all entered measurements.

IV. The vancomycin minimial inhibitory concentration (MIC) is specified here. Provide an educated guess or assume a worst-case scenario if not (yet) available.

Dosing

Via the dosing-tab the user can define all dosing events. The tab further contains a panel for optimized Bayesian dosing.

I.   A new dosing event can be added via the '+', while a click on '-' will remove the latest dosing. Please specify the date (dd/mm/yyyy/hh:mm), the amount (Dose) in mg and the infusion duration (Dur) in hours. If a dosing is reoccurring, the number of repetitive dosings and the corresponding time interval (in hours) can be specified via Nr. and Int., respectively.

II. TDMx can automatically optimize either the first dosing or the next dose to meet a specified target. Therefore, the user needs to specify the desired target, the time of the next dose (dd/mm/yyyy/hh:mm) and which dose shall be optimized.

Note: Please refer to *Bayesian dosing* for more details.

Figure 4 Input panel to edit dosing-related data

Select a model

Model selection (manually)

For all predictions and simulations, a predefined model, the model from Goti *et al.*[1] [REF] is selected. This model has been externally validated in a clinical dataset of hospitalized patients undergoing vancomycin TDM and also provided a good predictive performance in ICU patients.[2] [3]

If the user aims to use a different model for a specific patient population, a dropdown menu in the patient model (Figure 2) contains a list of models developed in a different patient population (e.g. extreme obese, critically ill, etc.).

Model selection (automatically)

TDMx includes an algorithm, which selects the best fitting model for an individual patient automatically (Figure 2, AUTO-SELECT).[4]

After clicking on the AUTO SELECT − button, the algorithm internally compares the predictions with the entered TDM data and selects the model with the best fit. The selected model will be mentioned in the pop-up window on the right. For further details on the algorithms, please refer to the publication by Uster *et al.* [4]

Model averaging (automatically)

Relying on more than one model simultaneously, can be beneficial as shown by Uster *et al.*[4] Therefore, TDMx also includes a model averaging algorithm, which includes the collective information of multiple population models. This algorithm automatically compares the individual model predictions with the entered TDM data. But instead of selecting the best-fitting model, the algorithm weights the model predictions relative to the others and averages the predictions according to the determined weights.

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[1] Goti, V., Chaturvedula, A., Fossler, M. J., Mok, S. & Jacob, J. T. Hospitalized Patients With and Without Hemodialysis Have Markedly Different Vancomycin Pharmacokinetics. Ther. Drug Monit. 40, 212–221 (2018).

[2] Broeker, A. *et al.* Towards precision dosing of vancomycin: a systematic evaluation of pharmacometric models for Bayesian forecasting. *Clin. Microbiol. Infect.* **25**, 1286.e1-1286.e7 (2019).

[3] Cunio, C. B. et al. Towards precision dosing of vancomycin in critically ill patients: an evaluation of the predictive performance of pharmacometric models in ICU patients. Clin. Microbiol. Infect. XX, XX–XX (2020).

[4] Uster et al. A model averaging/selection approach improves the predictive performance of model-informed precision dosing: vancomycin as a case study. Clin. Pharmacol. Ther. XX, XXX–XXX (2020).

To choose the model averaging approach in TDMx click on the 'Model average' tab above the output window. TDMx will automatically start the averaging and present the results in the output panel.
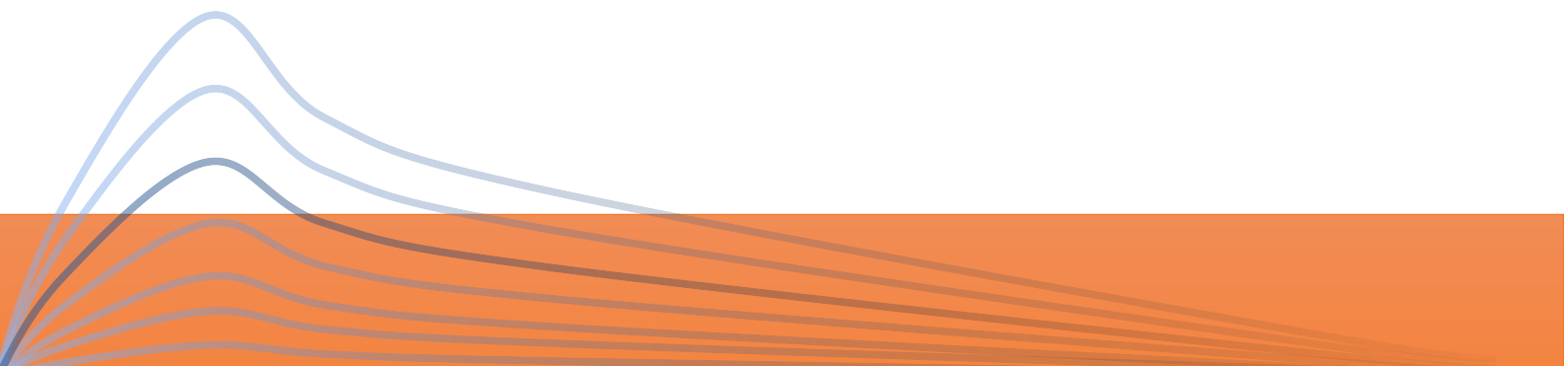
Output panel

Graphical and numerical results are presented in the output panel. The PK profile based on a predefined population PK model can be inspected in the output panel (blue line – 'Population'). The individual PK profile based on Bayesian feedback is available, if (historical) TDM data (e.g. drug plasma measurements, surrogate marker) was supplied (orange line – 'Individual').

Model selection

The user can switch between a concentration-time-profile or the AUC over time, select/deselect the respective predictions and switch between two resolutions (defined under *Settings*).

Furthermore, the table below the graph contains numerical information regarding the predicted PK parameters, plasma concentrations and pharmacokinetic/pharmacodynamic (PK/PD) targets at the respective time-point (Figure 5).
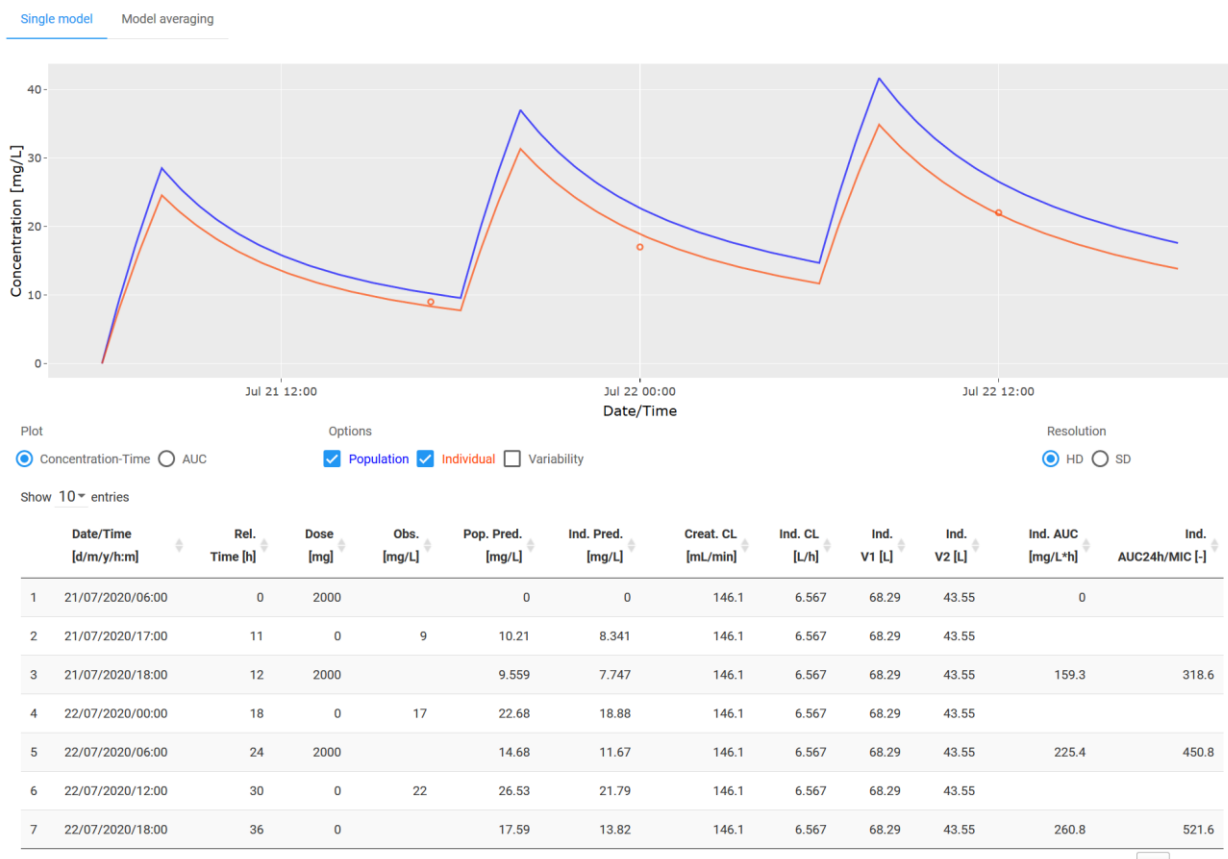

	Date/Time [d/m/y/h:m]	Rel. Time [h]	Dose [mg]	Obs. [mg/L]	Pop. Pred. [mg/L]	Ind. Pred. [mg/L]	Creat. CL [mL/min]	Ind. CL [L/h]	Ind. V1 [L]	Ind. V2 [L]	Ind. AUC [mg/L*h]	Ind. AUC24h/MIC [-]
1	21/07/2020/06:00	0	2000		0	0	146.1	6.567	68.29	43.55	0	
2	21/07/2020/17:00	11	0	9	10.21	8.341	146.1	6.567	68.29	43.55		
3	21/07/2020/18:00	12	2000		9.559	7.747	146.1	6.567	68.29	43.55	159.3	318.6
4	22/07/2020/00:00	18	0	17	22.68	18.88	146.1	6.567	68.29	43.55		
5	22/07/2020/06:00	24	2000		14.68	11.67	146.1	6.567	68.29	43.55	225.4	450.8
6	22/07/2020/12:00	30	0	22	26.53	21.79	146.1	6.567	68.29	43.55		
7	22/07/2020/18:00	36	0		17.59	13.82	146.1	6.567	68.29	43.55	260.8	521.6

Figure 5 Output panel of the single model prediction

Model averaging

The graphical output of the model averaging is following the style of the single-model output (Figure 6). The user can switch between a graphical presentation of the concentration-time profile or the AUC over time and inspect numerical results of the predictions and the PK/PD target.

The black line represents the PK profile utilizing the model averaging algorithm, while the colored lines represent the single-model predictions, respectively. Additionally, a bar plot indicates the weight (i.e. influence) of each single-model in the averaging. Hover above the element of interest to obtain more information.
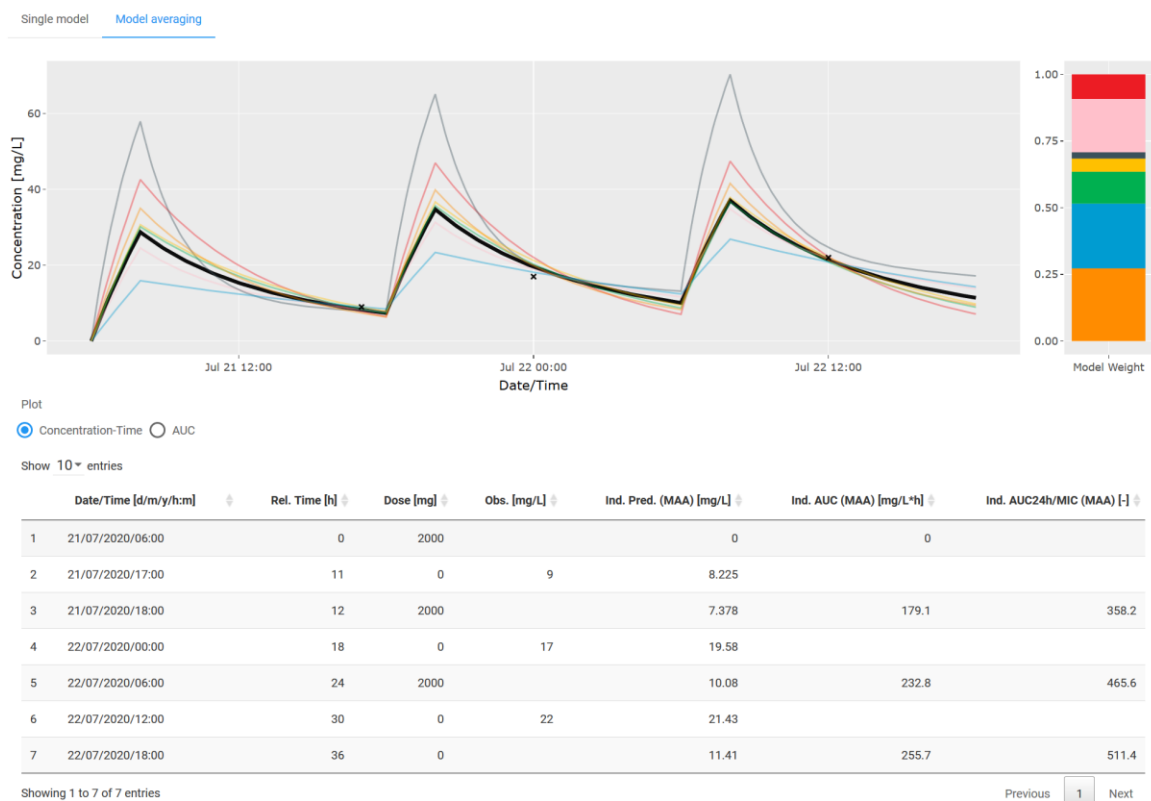

Figure 6 Output panel of the averaged predictions

Bayesian dosing

TDMx can predict an optimal dosing to meet a user-defined PK/PD target. The predictions are thereby based on the selected model, the patient covariates and/or pathogen data either with or without requiring drug measurement. The optimization without requiring drug measurements is potentially useful to guide therapeutic decisions already before initiating treatment or if no drug measurements are available, while the optimization with drug measurements (Bayesian dosing) can support the ongoing therapy.

Figure 7 Dose optimization in the dosing panel

If the user has specified the PK/PD target, the date of the next dose (if applicable) and which dose shall be optimized (First dose/Next dose), a new window opens (Figure 8).
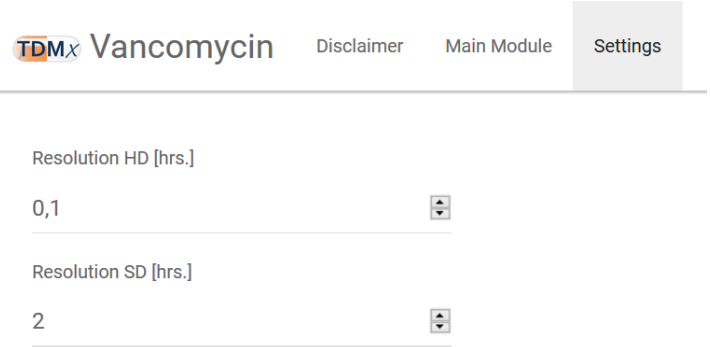
Note: If *First dose* is selected, all previous TDM data will be removed. Please, accept the warning, if intended.

I.   The user is asked to define a dosing interval in hours either empirically or as suggested based on the creatinine clearance.

II.   Furthermore, the infusion duration and the range of potential amount can be defined in the respective box.

III. By clicking the 'CALCULATE'-button the predicted new dose will appear in the New dose-box and can be rounded and/or added to the patient data.

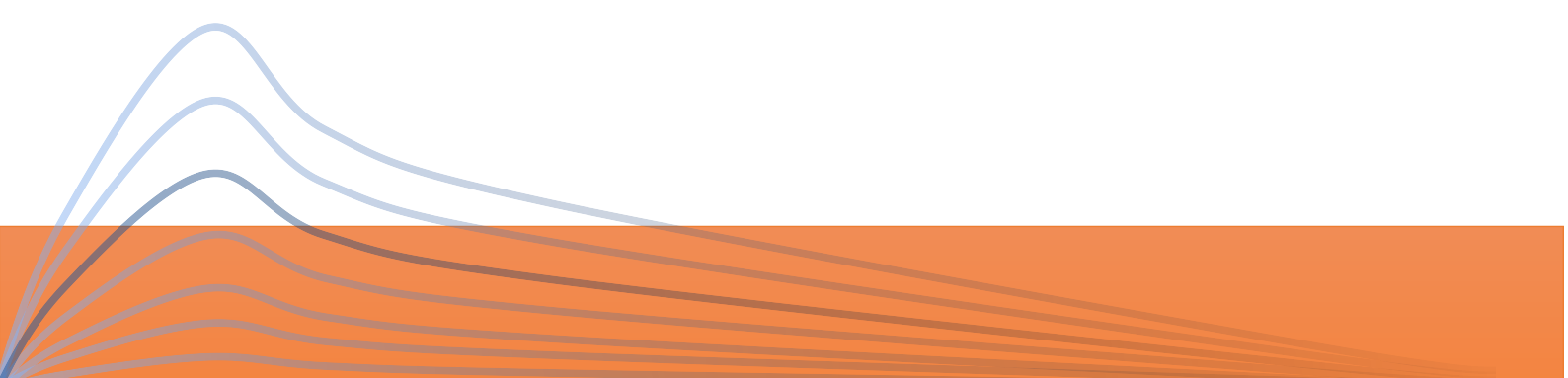*Figure 8 Dose optimization - window*

Settings

To optimize the speed/performance of TDMx the user can adjust the resolution of the output panel.

Figure 9 Module of the settings

Abbreviations

AUC	–	Area under the curve
CL	–	Clearance
HD	–	High definition
ICU	–	Intensive care unit
Ind.	–	Individual
MIC	–	Minimum inhibitory concentration
Obs.	–	Observed plasma concentration
PK	–	Pharmacokinetics
Pred.	–	Prediction(s)
TDM	–	Therapeutic drug monitoring
Vx	–	Volume of dristribution (1 = central, 2 = peripheral