Quick Reference TDMx Vancomycin

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Author: Sebastian Wicha, Lead Developer

Application

TDMx Vancomycin

Developer

Prof. Dr. Sebastian G. Wicha Institute of Pharmacy University of Hamburg Germany email info (at) tdmx.eu

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).

Purpose

The TDMx Vancomycin software is intended for healthcare professionals to calculate individualized dosing regimens for the glycopeptide antibiotic vancomycin in adult patients, including hospitalised, critically-ill, obese and haematopoietic stem-cell transplant populations. The software aims to address the problem of high inter-patient variability in vancomycin exposure achieved with standard dosing, which can result in concentrations that fall outside the range needed to balance efficacy against nephrotoxicity risk.

TDMx Vancomycin utilizes patient-specific data such as demographics, laboratory values (including renal function markers) and, if available, previous dosing records and measured vancomycin plasma concentrations, to determine individual pharmacokinetic parameters using one of seven implemented population pharmacokinetic models (see Select a model). This computational task is designed to assist healthcare professionals in achieving an AUC24h/MIC of 400-600, the consensus target for balancing efficacy against nephrotoxicity risk (assuming a broth microdilution MIC; use MIC = 1 mg/L if unavailable), interpreted alongside a trough concentration of 10-20 mg/L.

TDMx Vancomycin is intended for use in patients prescribed vancomycin who require dose individualization for enhanced safety and efficacy. It is designed to be used in clinical settings where such individualized dosing can be monitored and managed.

Intended users of the software are healthcare professionals (medical doctors, clinical pharmacists) who have expertise or training in therapeutic drug monitoring and

pharmacokinetics. The operating environment for TDMx Vancomycin should be healthcare facilities that have the capability to measure drug concentrations and monitor patient responses to antibiotic therapy.

TDMx Vancomycin should not be used where it is not feasible to obtain the patient-specific data necessary for dose calculations, or where doing so would contravene the clinical judgement of the treating healthcare professional.

Disclaimer

TDMx is an educational tool and 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. The 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. TDMx Vancomycin has not been registered as a medical device; dosing decisions should not solely rely on TDMx and remain the responsibility of the treating physician.

Requirements

TDMx is fully tested on Google Chrome® and Mozilla Firefox® browsers. No installation is necessary — TDMx runs entirely in the browser.

Performance characteristics

TDMx was developed using reactive programming with a server-client architecture: TDMx reactively visualizes the user input such as dosing history, patient covariates or drug measurements. TDMx does not require any software to be installed locally.

The population pharmacokinetic models implemented in TDMx Vancomycin (see Select a model) were adapted from published literature models spanning hospitalised, critically-ill, obese and haematopoietic stem-cell transplant patient populations.

Launch TDMx from the web

Go to www.TDMx.eu

Navigate to the menu LAUNCH TDMX and select the module for vancomycin.

Startup and disclaimer

During startup of the TDMx app, a welcome dialog is shown with the disclaimer above. Tick “I have read and accept the Disclaimer” and click “Start TDMx” to proceed (Figure 1).

Loading a previously saved patient is done afterwards, directly in the main interface (see *Patient File*, below) — not as part of this startup step.

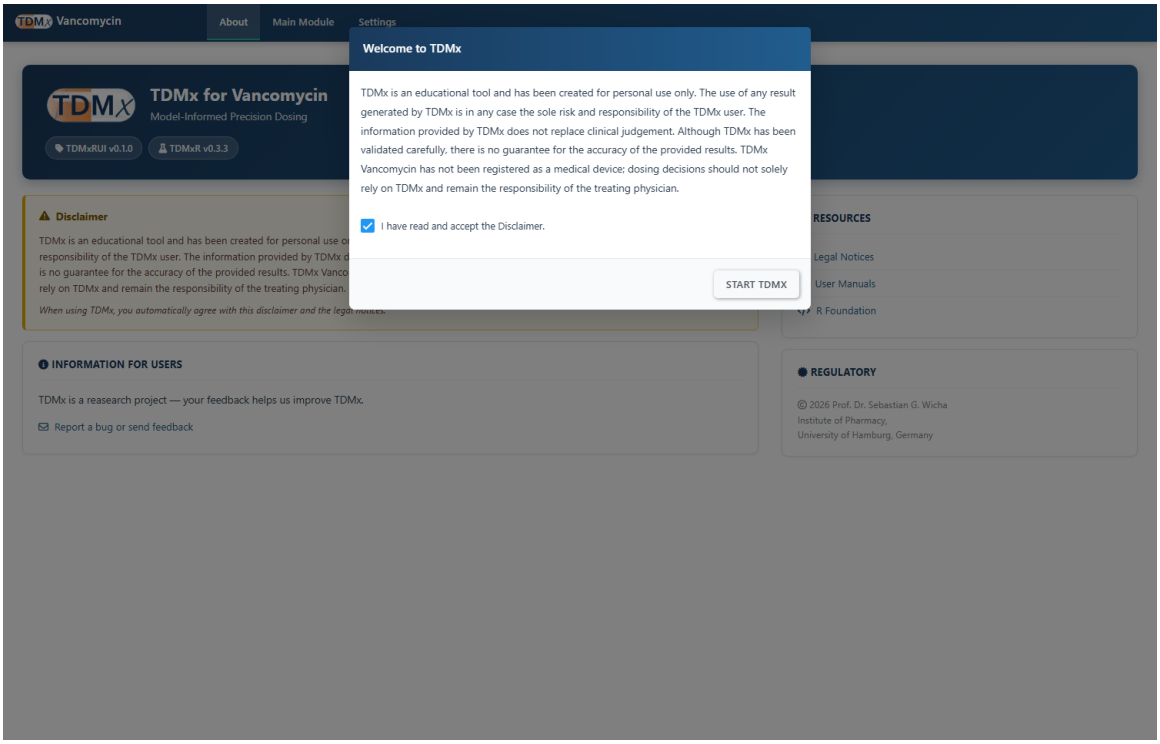

Figure 1: Startup dialog shown when launching TDMx Vancomycin.

Main module

The main module consists of two panels: the patient panel (input, left) and the prediction/visualization panel (output, right) (Figure 2).

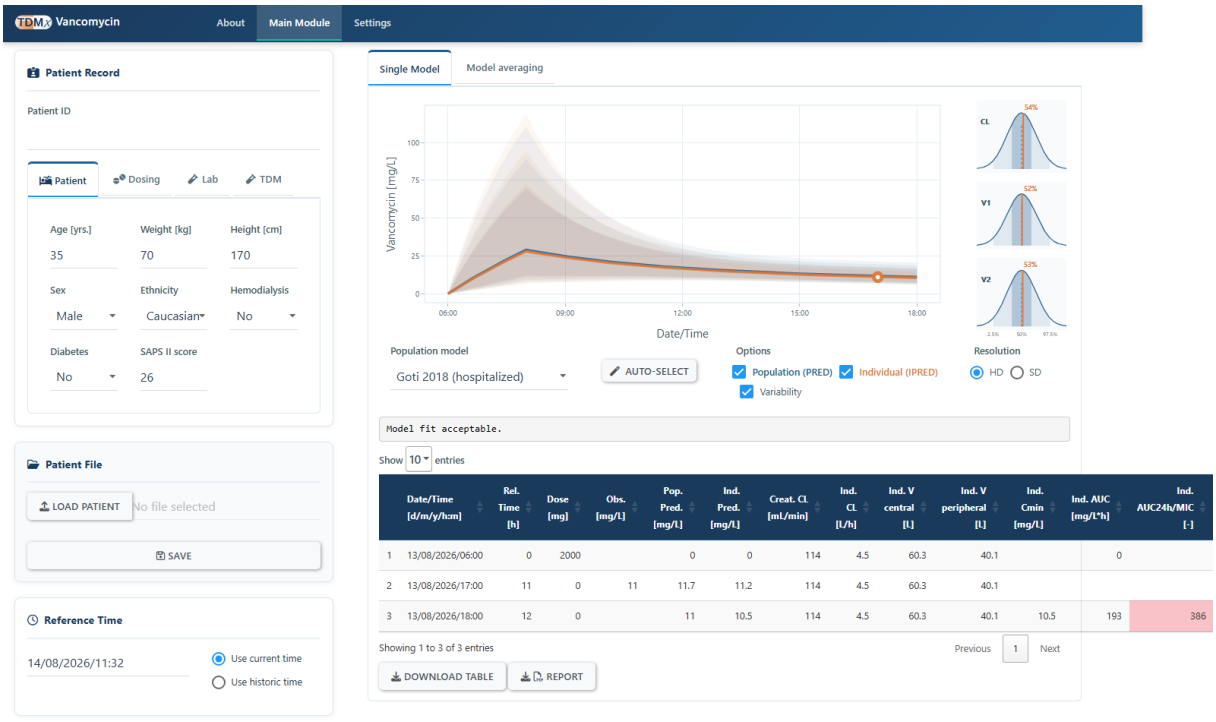

Figure 2: Main interface of the TDMx web-application, Patient tab, with Individual and Variability ticked.

Input panel (left column): contains three wells — *Patient Record* (patient ID and the Patient/Dosing/Lab/TDM tabs, described below), *Patient File* and *Reference Time*.

- *Patient File*: "LOAD PATIENT" opens a previously saved *.tdmx file directly into the current session; "SAVE" downloads the current patient's full record as a* .tdmx file.
- *Reference Time*: the date/time TDMx treats as "now". Switch to "Use historic time" to backdate a prediction, e.g. when reviewing a case retrospectively.

Output panel (right column): contains graphical and numerical output using the information provided in the input panel, under two tabs — *Single Model* (one selected population PK model, described here) and *Model averaging* (a weighted ensemble of models, see Model averaging).

In the Single Model tab, tick any combination of the three Options next to the plot:

- Population (PRED, blue): Population-predicted concentration-time data using the dosing record and patient covariates. Observed concentration-time data are not used.

- Individual (IPRED, orange): Individually-predicted concentration-time data using the dosing record, patient covariates and the observed concentration-time data, via Bayesian estimation. Requires at least one TDM measurement.
- Variability: adds shaded prediction-interval bands (up to 95%) around the ticked Population and/or Individual line(s).

PK parameter density plot: whenever "Individual" is ticked and TDM data are available, a small panel of density curves (one per estimated PK parameter, e.g. CL, V1, V2) appears to the right of the main plot. Each curve is the population distribution of that parameter; the shaded band marks the 2.5th–97.5th percentile range and the vertical line marks where this patient's individually estimated parameter falls, labelled with its percentile. A value near 50% indicates a typical patient; a value near the extremes (close to 2.5% or 97.5%) flags a potential outlier worth a closer look.

Model fit message: also shown once "Individual" is ticked, directly above the numerical table, is a one-line fit message:

- "Model fit acceptable." (black) — both checks below passed.
- "Poor model fit." (red) — the relative prediction error between observed and individually-predicted concentrations exceeds the configured threshold (default 40%).
- "...Patient parameters outside population distribution." (appended, red) — one or more of this patient's estimated PK parameters falls outside the model's expected population range (outside its 95% interval by default).

The message turns red if either check fails, so it can also read "Model fit acceptable. Patient parameters outside population distribution." — treat any red message as a prompt to inspect the fit and parameters carefully rather than accepting the prediction at face value.

Numerical output table:

- Date/Time: Time stamp of the event
- Dose: Administered dose
- Obs.: Observed concentration-time data
- Pop. Pred: Population-predicted concentration-time data using the dosing record and patient covariates. Observed concentration-time data are not used.

- Ind. Pred: Individually-predicted concentration-time data using the dosing record, patient covariates and the observed concentration-time data using Bayesian estimation.
- Creat. Clearance: Creatinine Clearance estimated using the appropriate equation as specified in each implemented population pharmacokinetic model.
- Pop./Ind. CL/V central/V peripheral: Pharmacokinetic parameters of the population or individual model, respectively, considering patient covariates (and, for the individual parameters, the observed concentration-time data). Individual parameters are displayed if "Individual" is selected.
- Pop./Ind. Cmin: Population- or individually-predicted trough concentration at the end of the current dosing interval.
- Pop./Ind. AUC/AUC24h-MIC: Population- or individually-predicted area-under-the-concentration-time curve over 24 h, and that value divided by the MIC.

Colour coding: the Ind. AUC24h/MIC column is shaded green when the value falls within the target range configured under Dose optimisation (400-600 by default) and red otherwise — the same colours and threshold used for the "PTA AUC24h/MIC" column in the dose-optimisation tables. This is a quick visual check, not a substitute for clinical judgement — always inspect the actual numbers, including the trough concentration.

Input panel

The input panel consists of four tabs: Patient, Dosing, Lab and TDM.

Patient

In this tab the user can specify the following (Figure 2):

- A name/identifier for this patient (Patient ID, above the tabs).
- Continuous covariates (Age, Weight, Height, SAPS II score) by either typing the value or using the up/down stepper.
- The categorical covariates Sex, Ethnicity, Hemodialysis and Diabetes, each selected from a dropdown menu.
- A population model for predictions/simulations, or AUTO-SELECT to let TDMx pick the best-fitting model automatically. See Select a model for details.

Note: not every covariate is used by every model. Hover over a covariate's label to see a tooltip listing which model(s) actually use it for that patient's prediction — a covariate can still be entered even if the currently selected model ignores it.

Covariate	Goti 2018	Thomson 2009	Adane 2015	Revilla 2010	Roberts 2011	Mangin 2014	Okada 2018
Age	used (creatinine clearance)	used (creatinine clearance)	used (creatinine clearance)	used (creatinine clearance)	used (creatinine clearance)	not used	used (creatinine clearance)
Weight	used (creatinine clearance & central volume)	used (creatinine clearance & volumes)	used (creatinine clearance, body surface area, central volume)	used (clearance & central volume)	used (creatinine clearance, body surface area, central volume)	used (clearance & volumes, allometric)	used (creatinine clearance, body surface area, central volume)
Height	not used	not used	used (body surface area)	not used	used (body surface area)	not used	used (body surface area)
Sex	used (creatinine clearance)	used (creatinine clearance)	used (creatinine clearance)	used (creatinine clearance)	used (creatinine clearance)	used (clearance)	used (creatinine clearance)
Ethnicity	not used	not used	not used	used (creatinine	not used	not used	not used

Covariate	Goti 2018	Thomson 2009	Adane 2015	Revilla 2010	Roberts 2011	Mangin 2014	Okada 2018
				clearance)			
Serum creatinine	used (creatinine clearance)	used (creatinine clearance)	used (creatinine clearance)	used (creatinine clearance)	used (creatinine clearance)	used directly (clearance)	used (creatinine clearance)
Albumin	not used	not used	not used	used (creatinine clearance)	not used	not used	not used
Serum urea nitrogen	not used	not used	not used	used (creatinine clearance)	not used	not used	not used
Hemodialysis	used (clearance & central volume)	not used	not used	not used	not used	not used	not used
Diabetes	n/a	n/a	n/a	n/a	n/a	used (reduces inter-compartmental	n/a

Covariate	Goti 2018	Thomson 2009	Adane 2015	Revilla 2010	Roberts 2011	Mangin 2014	Okada 2018
						clearance)	
SAPS II score	n/a	n/a	n/a	n/a	not used	used (clearance)	n/a

Dosing

Via the Dosing tab (Figure 3) the user can define all dosing events, and launch dose optimisation.

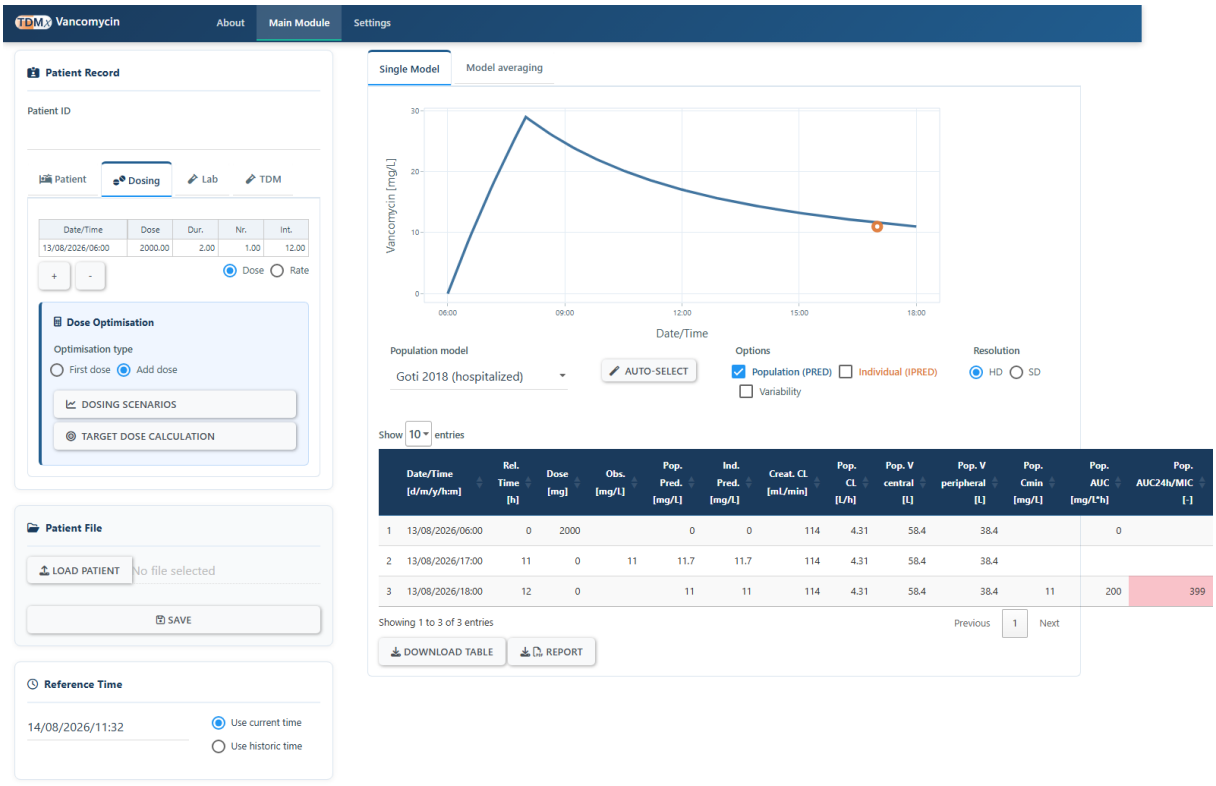

Figure 3: Input panel to edit dosing-related data.

A new dosing event can be added via “+”, while “-” removes the latest one. Specify the date (dd/mm/yyyy/hh:mm), the dose in mg (or, if switched to “Rate”, the infusion rate in mg/h) and the infusion duration (Dur.) in hours — vancomycin is dosed intravenously

into the central compartment only. If a dose is repeated, the number of repeats and the dosing interval (in hours) can be specified via Nr. and Int., respectively.

TDMx offers two dose-optimisation tools; see Dose optimisation below.

Lab

In the Lab tab (Figure 4), the user can specify laboratory data obtained from the patient. These values are used directly as covariates in the population PK model and improve the prediction.

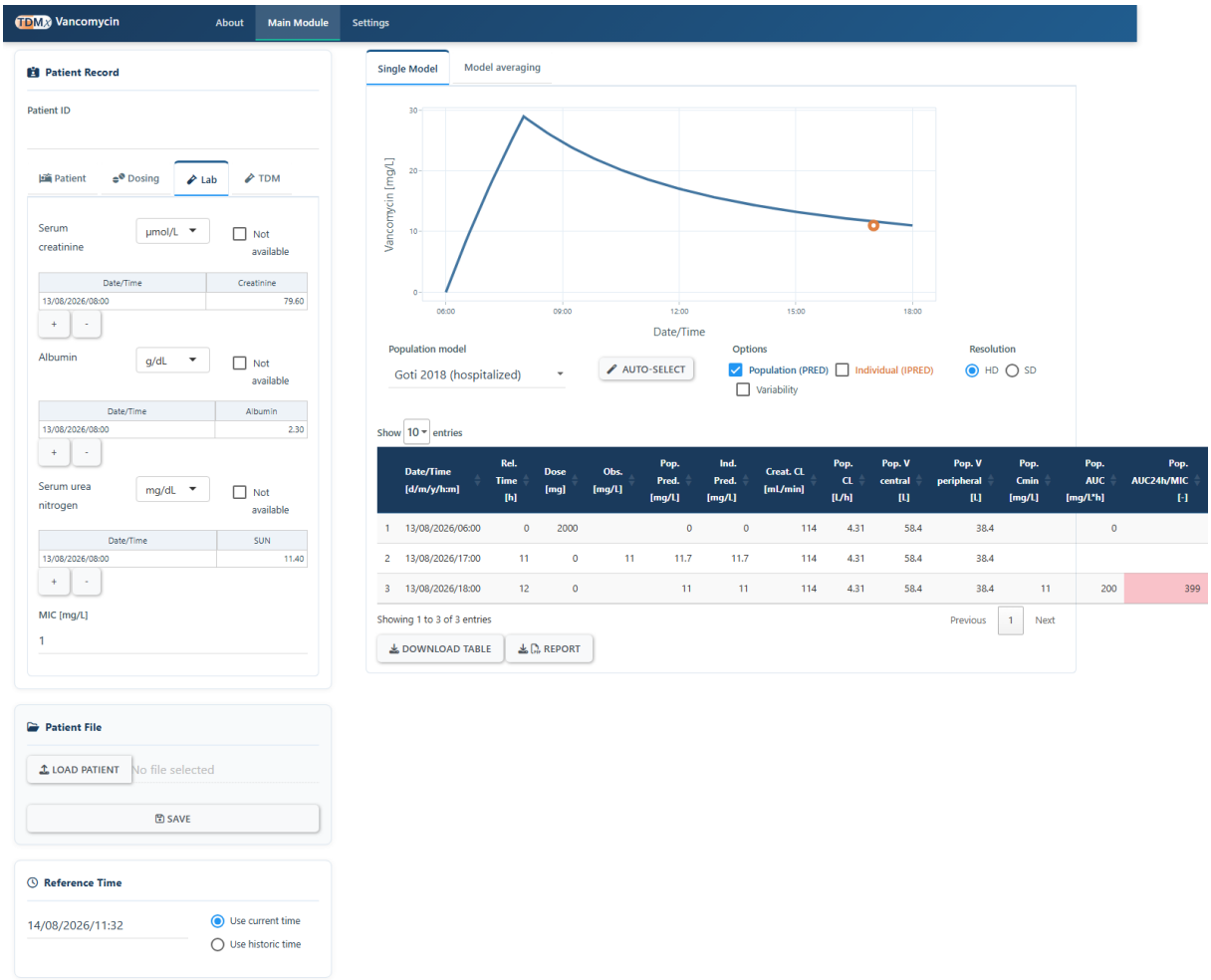

Figure 4: Input panel to enter laboratory data.

Available markers are Serum creatinine, Albumin, Serum urea nitrogen and the vancomycin minimal inhibitory concentration (MIC). Specify the date of measurement as dd/mm/yyyy/hh:mm and the value in the stated (or an alternative) unit — TDMx automatically converts entered measurements between units. If no measurement is

available, leave the field at its default value; if the selected model uses that marker, TDMx substitutes a predefined population value which cancels out its influence. For the MIC, provide an educated guess (default: broth microdilution MIC = 1 mg/L) if not (yet) available.

TDM

A new drug plasma concentration can be added via "+", while "-" removes the latest measurement. Specify the date (dd/mm/yyyy/hh:mm) and the concentration in mg/L (Figure 5). Untick "Include" to exclude a sample from the Bayesian estimation without removing it from the plot.

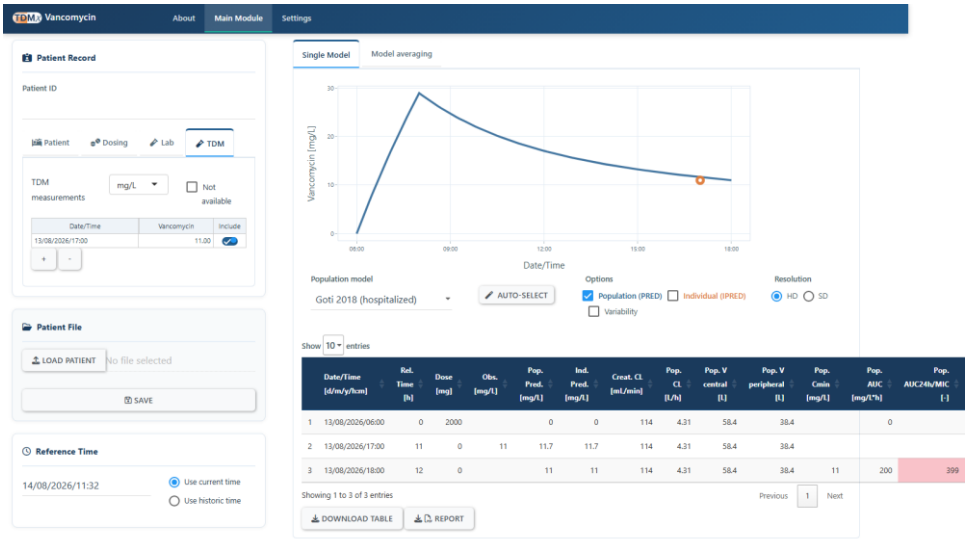

Figure 5: Input panel to enter TDM data.

Dose optimisation

Both tools are opened from the Dosing tab and use the selected model, the patient's covariates and pathogen data (measured or assumed MIC), either with or without drug measurements. Optimising without drug measurements is useful to guide dosing before treatment starts or when no measurements are available; optimising with measurements supports ongoing therapy and is more precise, since individual PK parameters are used.

Note: if "First dose" is selected as the optimisation type, all previous dosing and TDM data will be removed. A warning is shown; accept it only if this is intended.

Dosing Scenarios

Clicking “DOSING SCENARIOS” opens the Dose Optimisation dialog (Figure 6), which evaluates a table of candidate doses (500, 750, 1000, 1250, 1500 and 2000 mg by default, at a 12 h interval) against a target AUC24h/MIC of 400-600. Dose levels, durations and intervals can be edited directly in the table. Click “CALCULATE” to fill in the predicted AUC24h/MIC and probability of target attainment (PTA) for each row, select the most suitable row, and click “ACCEPT DOSE” to add it to the patient’s dosing record.

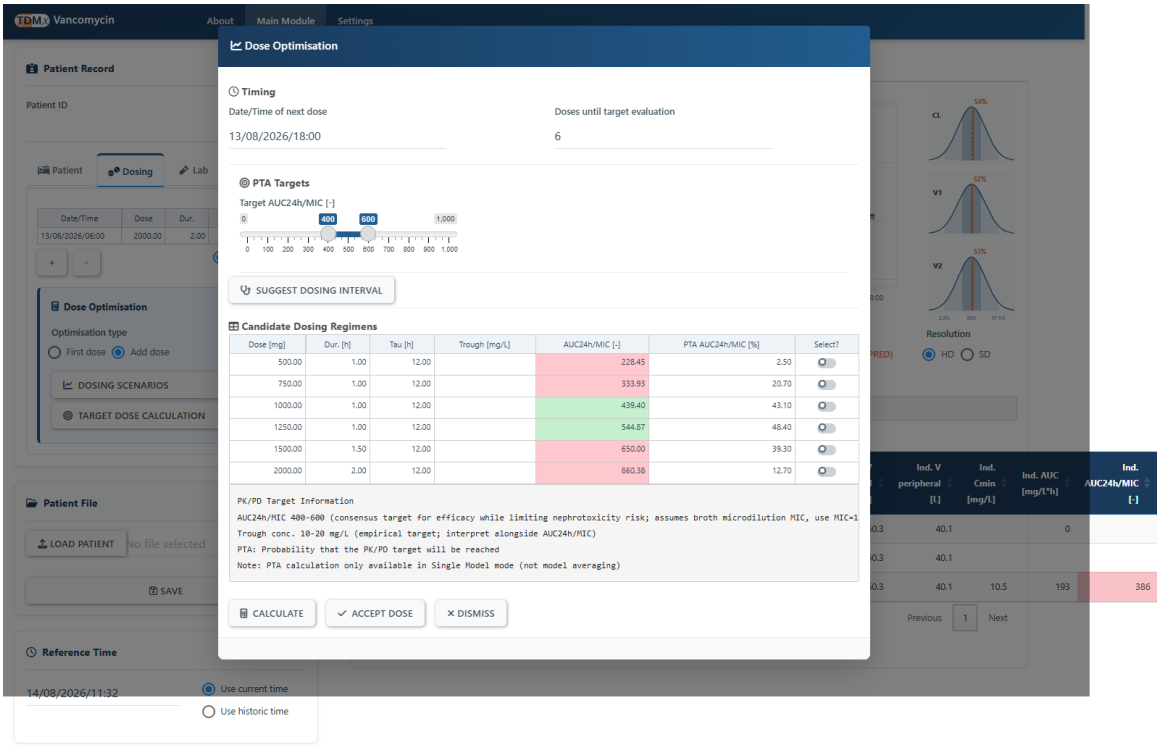

Figure 6: Dose Optimisation dialog (Dosing Scenarios).

Target Dose Calculation

Clicking “TARGET DOSE CALCULATION” opens the Exact Dose Calculation dialog (Figure 7), which searches for a single dose — within a Min./Max. Dose range (0-2500 mg by default) — that hits one exact target value, either an AUC24h/MIC (default target 500) or a trough concentration (Cmin, default target 15 mg/L), at a given dosing interval and infusion length. Next to the dosing interval field, “Suggest dosing interval” fills in a renal-function-based starting interval from the patient’s estimated creatinine clearance (≥100 mL/min: 8 h; 50–100: 12 h; 30–50: 24 h; <30: 48 h) — adjust manually if needed. Click “CALCULATE” to compute the optimised dose, then “ACCEPT” to add it to the patient’s dosing record.

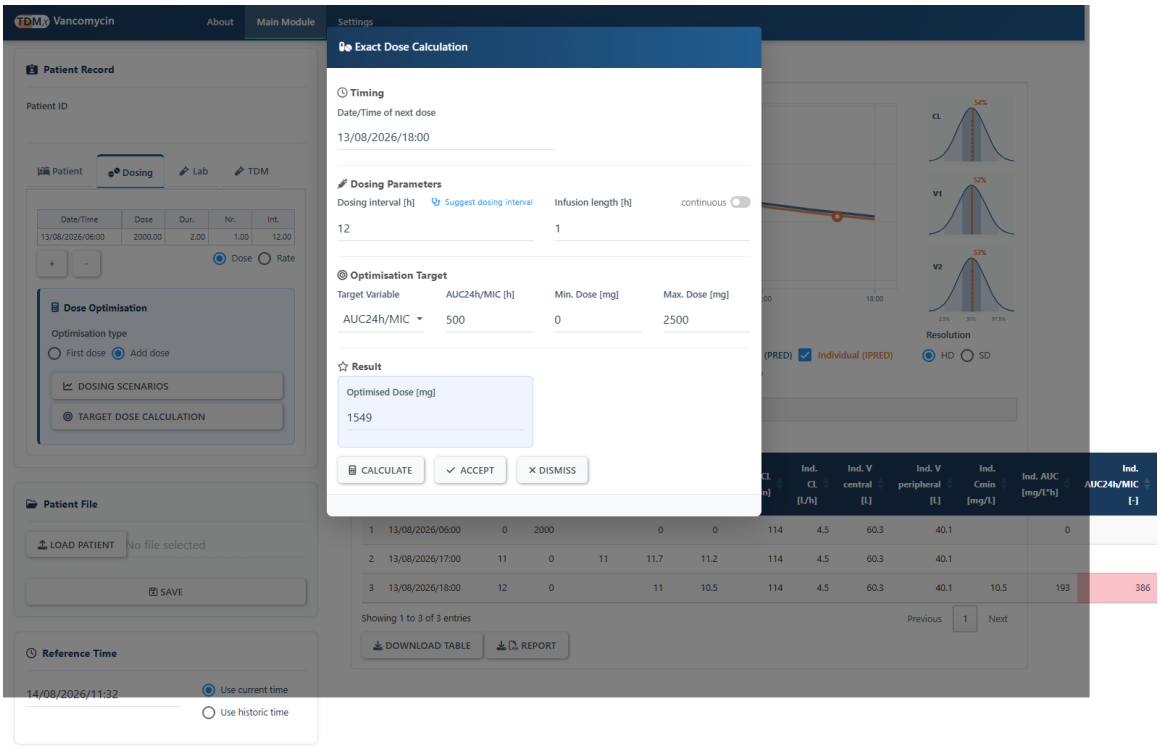

Figure 7: Exact Dose Calculation dialog (Target Dose Calculation).

Model averaging

Instead of relying on a single population model, the *Model averaging* output tab (Figure 8) combines the predictions of several models into one weighted, individually-estimated prediction — useful when no single model clearly fits best, or to hedge against any one model's misspecification.

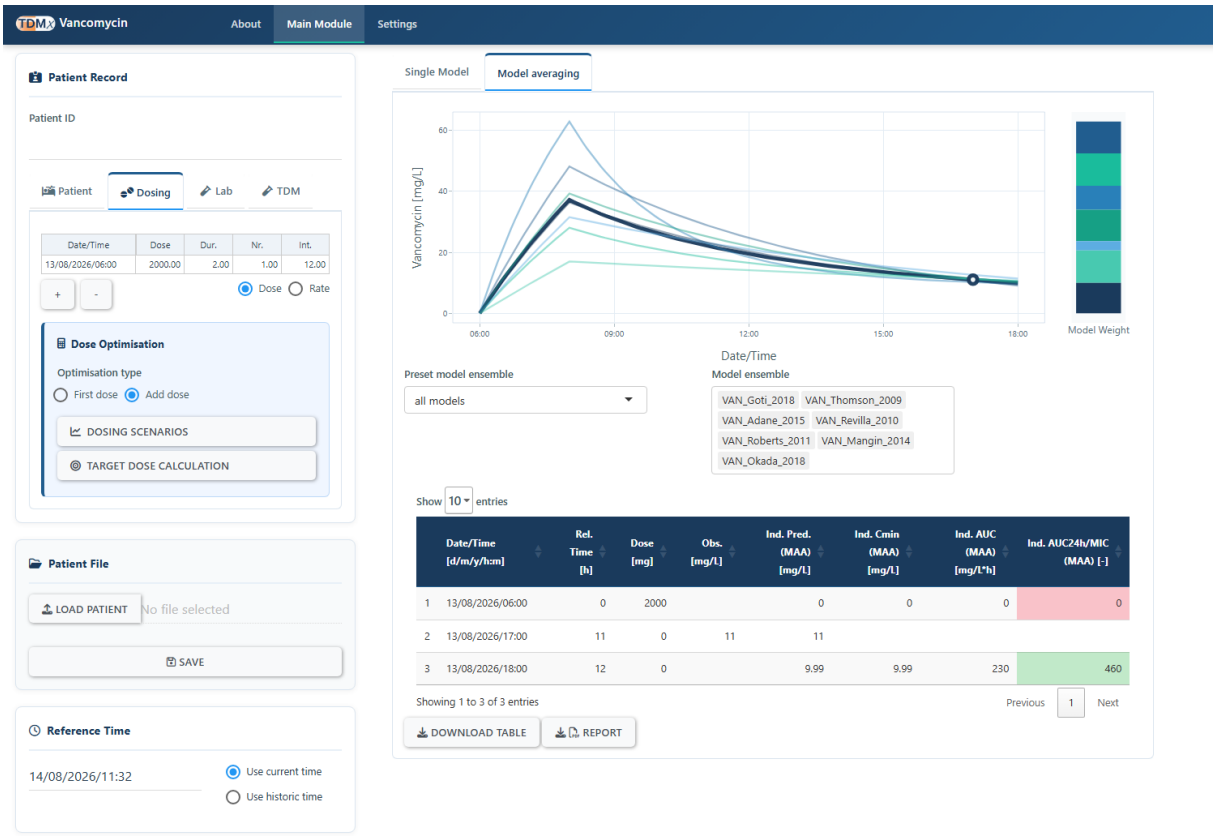

Figure 8: Model averaging tab — model-averaged prediction, per-model contributions and model weights.

- **Preset model ensemble**: a dropdown of predefined sets of candidate models — “all models” (all seven VAN_* models, the default) or “one model” (Goti 2018 only, matching the Single Model default).
- **Model ensemble**: the actual list of models included, pre-filled from the preset above but editable — add or remove individual models as needed.
- **Plot**: the thick navy line is the weighted, model-averaged individual prediction; the thin coloured lines are each candidate model’s own individual prediction (same colours as its slice of the “Model Weight” bar on the right). Weights are estimated from how well each model fits this patient’s TDM data.
- **Table**: Ind. Pred./Cmin/AUC/AUC24h-MIC (MAA) columns show the model-averaged individual prediction, colour-coded the same way as the Single Model table (see Main module).

The weighting criterion (sum of squared residuals by default, or the objective function value) can be changed under Settings. PTA calculation is only available in Single Model mode, not in Model averaging.

Select a model

Model selection (manually)

For all predictions and simulations, a predefined default model — Goti 2018 (hospitalised) — is selected. If a different model is more appropriate for a specific patient population, the "Population model" dropdown on the Patient tab lists all seven models:

Model	Population	Key covariates used
Goti 2018	Hospitalised patients	Weight, Age, Sex, Serum creatinine, Hemodialysis
Thomson 2009	Hospitalised patients	Weight, Age, Sex, Serum creatinine
Adane 2015	Obese patients	Weight, Height, Age, Sex, Serum creatinine
Revilla 2010	ICU patients	Weight, Age, Sex, Serum creatinine, Ethnicity, Albumin, Serum urea nitrogen
Roberts 2011	Critically-ill patients	Weight, Height, Age, Sex, Serum creatinine
Mangin 2014	Critically-ill patients	Weight, Sex, Serum creatinine, Diabetes, SAPS II score
Okada 2018	Haematopoietic stem-cell transplant patients	Weight, Height, Age, Sex, Serum creatinine

Model selection (automatically)

TDMx includes an algorithm that automatically selects the best-fitting model for an individual patient. After clicking “AUTO-SELECT”, the algorithm internally compares the predictions of all listed models with the entered TDM data and selects the model with the best fit. The selected model is shown in a pop-up window. For further details on the algorithm, refer to the publication by Uster et al.

Model fit warnings

TDMx continuously checks the fit between the individual prediction and the entered TDM data against two thresholds, and reports the result as the fit message described under Main module (“Model fit acceptable.” / “Poor model fit.” / “...Patient parameters outside population distribution.”):

- **Residual check**: flags a poor fit if the relative prediction error, |predicted – observed| / mean(predicted, observed), exceeds 40% for any TDM sample (configurable).
- **Parameter check**: flags an outlier patient if any individually estimated PK parameter falls outside the 95% interval of that parameter’s population distribution (configurable), i.e. the same percentile shown by the PK parameter density plot.

If either check fails, treat the prediction with extra caution: inspect the plot and PK parameters carefully, and consider that a dosing regimen based on clinical judgement alone might be more appropriate for this patient than the one calculated by TDMx.

Settings

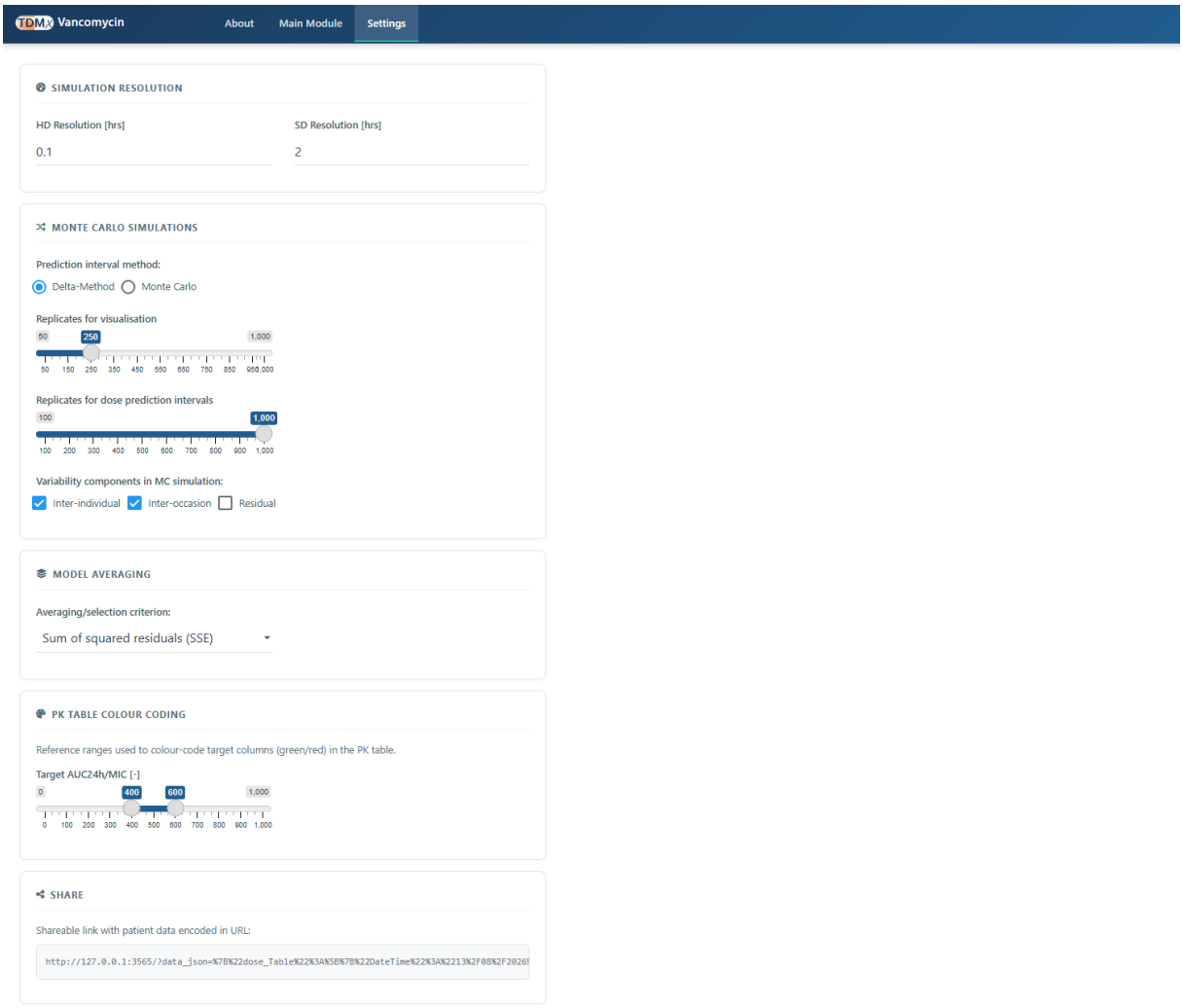

Figure 9: Settings tab.

To adjust the speed/performance and behaviour of TDMx:

- **Simulation Resolution**: separate time resolutions (in hours) for the high-definition (HD) and standard-definition (SD) plot/table output.
- **Monte Carlo Simulations**: choose the prediction-interval method — Delta-Method (fast, analytical approximation, default) or Monte Carlo (simulation-based) — and, for the latter, the number of replicates used for visualisation and for dose prediction intervals respectively. Variability components (Inter-individual, Inter-occasion, Residual) can be included or excluded from the simulation individually.

- **Model averaging**: the criterion used to weight/select models in Model averaging mode can be changed from the sum of squared residuals (SSE, default) to the objective function value.
- **Share**: generates a shareable link with the current patient's data encoded directly in the URL. This lets a colleague open the same patient record in their own browser session without needing to exchange a *.tdmx file.

Abbreviations

Abbreviation	Meaning
ICU	Intensive care unit
Ind.	Individual
HD	High definition
SD	Standard definition (lower time resolution)
PK	Pharmacokinetics
Pred.	Prediction(s)
Obs.	Observed plasma concentration
TDM	Therapeutic drug monitoring
CL	Clearance
Vx	Volume of distribution (1 = central, 2 = peripheral)
CRCL	Creatinine clearance
AUC	Area under the curve
Cmin	Trough concentration
MIC	Minimum inhibitory concentration

Abbreviation	Meaning
PTA	Probability of target attainment
SAPS II	Simplified Acute Physiology Score II