Quick Reference TDMx Tobramycin

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Application

TDMx Tobramycin

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).

Purpose

The TDMx Tobramycin software is intended for healthcare professionals to calculate individualized dosing regimens for the aminoglycoside antibiotic tobramycin, spanning paediatric and adult patients with or without cystic fibrosis. The software aims to address the problem of high inter-patient variability in tobramycin exposure achieved with standard dosing, which can result in concentrations that are not within the range needed to balance efficacy against nephro-/ototoxicity risk.

TDMx Tobramycin utilizes patient-specific data such as demographics, laboratory values (serum creatinine), and, if available, previous dosing records and measured tobramycin plasma concentrations, to determine individual pharmacokinetic parameters using the implemented population pharmacokinetic model (see Select a model). This computational task is designed to assist healthcare professionals in achieving a peak (Cmax/MIC) >10 and AUC24h/MIC >70 mg*h/L for efficacy, while keeping the trough (Cmin) below the safety threshold appropriate to the dosing strategy used (<1 mg/L for extended-interval, <2 mg/L for traditional multiple-daily dosing).

TDMx Tobramycin is intended for use in patients prescribed tobramycin who require dose individualization for enhanced safety and efficacy, including patients with cystic fibrosis. 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 Tobramycin should be healthcare facilities that have the capability to measure drug concentrations and monitor patient responses to antibiotic therapy.

TDMx Tobramycin 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 Tobramycin 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 model implemented in TDMx Tobramycin (see Select a model) was adapted from a published literature model (Hennig et al. 2007) spanning children through adults, with and without cystic fibrosis.

Launch TDMx from the web

Go to www.TDMx.eu

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

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.

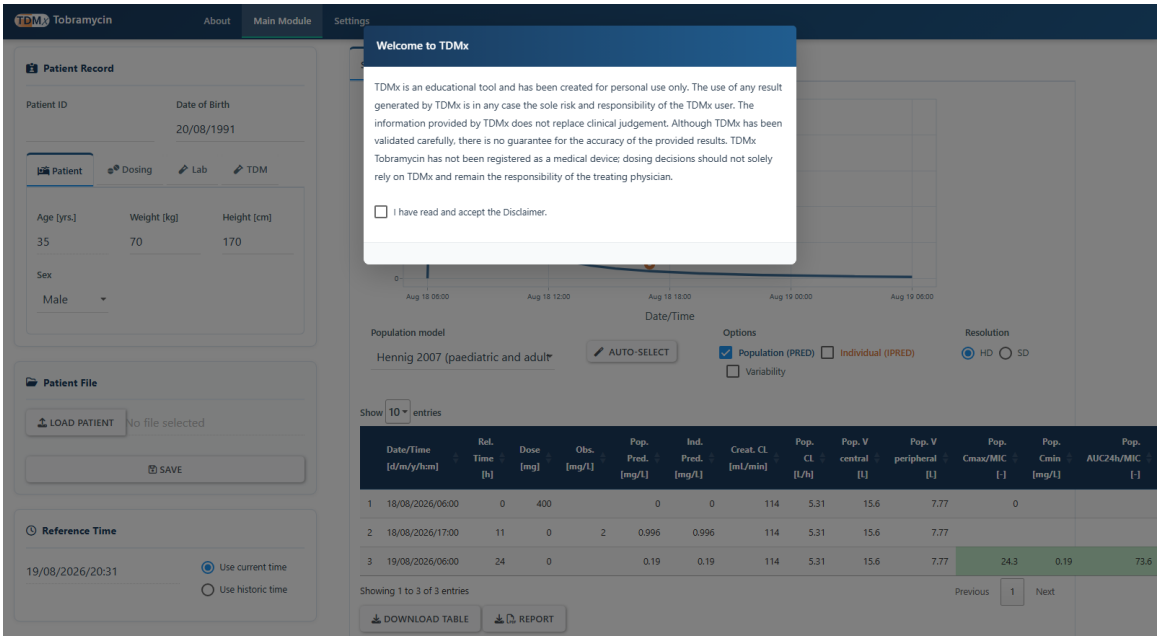

Figure 1: Startup dialog shown when launching TDMx Tobramycin.

Main module

The main module consists of two panels: the patient panel (input, left) and the prediction/visualization panel (output, right) (Figure 2). Only one population pharmacokinetic model is implemented for tobramycin (see Select a model), so there is no separate Model averaging tab here (unlike some other TDMx modules).

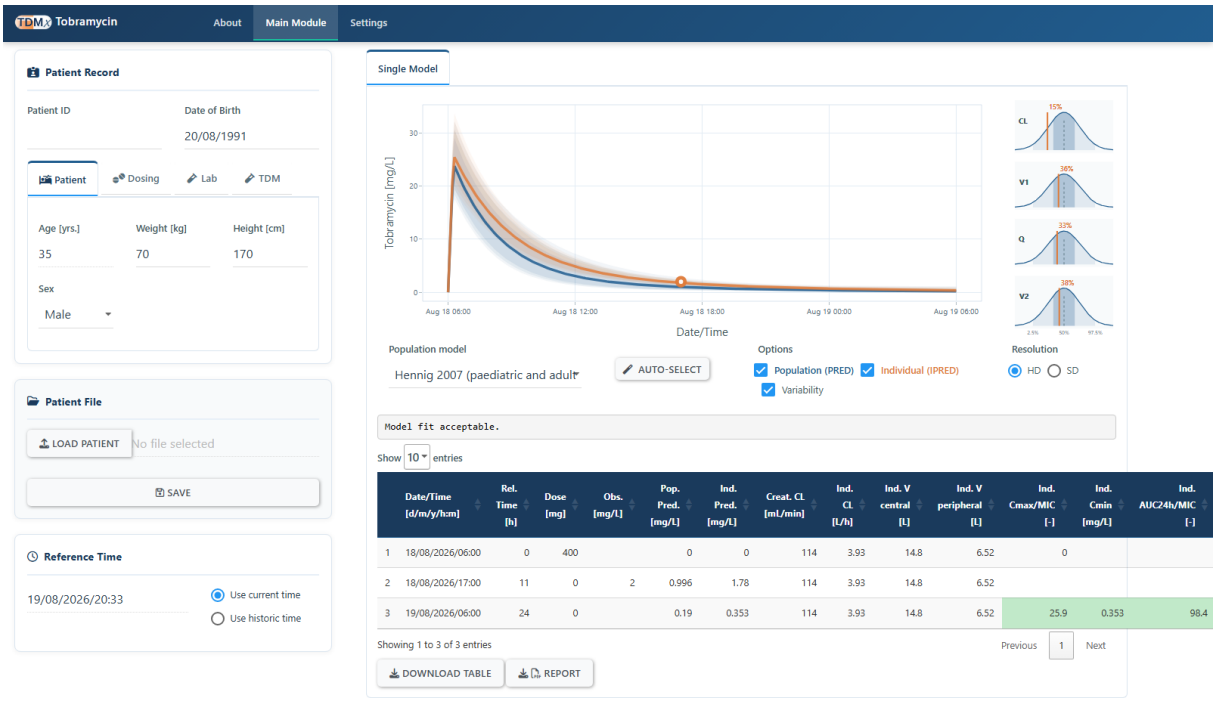

Figure 2: Main interface of the TDMx web-application, Patient tab, with Individual and Variability ticked.

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.

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, Q, 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 [mg]
- Obs.: Observed concentration-time data [mg/L]
- Pop./Ind. Pred.: Population- or individually-predicted concentration-time data, respectively
- Creat. CL: Cockcroft-Gault creatinine clearance (a display-only estimate — the structural model itself scales renal function from lean body mass, age and a creatinine ratio term, not directly from this value)

- 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)
- Pop./Ind. Cmax/MIC, Cmin, AUC24h/MIC: Population- or individually-predicted peak-to-MIC ratio, trough concentration and 24-hour AUC-to-MIC ratio, shown for dosing rows only (MIC entered under the Lab tab)

Colour coding: the Cmax/MIC, Cmin and AUC24h/MIC columns are each shaded green when within the target range configured under Settings and red otherwise — the same colours and thresholds used for the results table in the "Conventional Dosing (Cmax-Cmin)" modal. This is a quick visual check, not a substitute for clinical judgement — always inspect the actual numbers.

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 and Height, by either typing the value or using the up/down stepper.
- The categorical covariate Sex, selected from a dropdown menu.

All four covariates (Age, Weight, Height, Sex) are used by the Hennig 2007 model, which computes renal function from lean body mass, age and serum creatinine relative to an age/sex-typical reference value.

Dosing

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

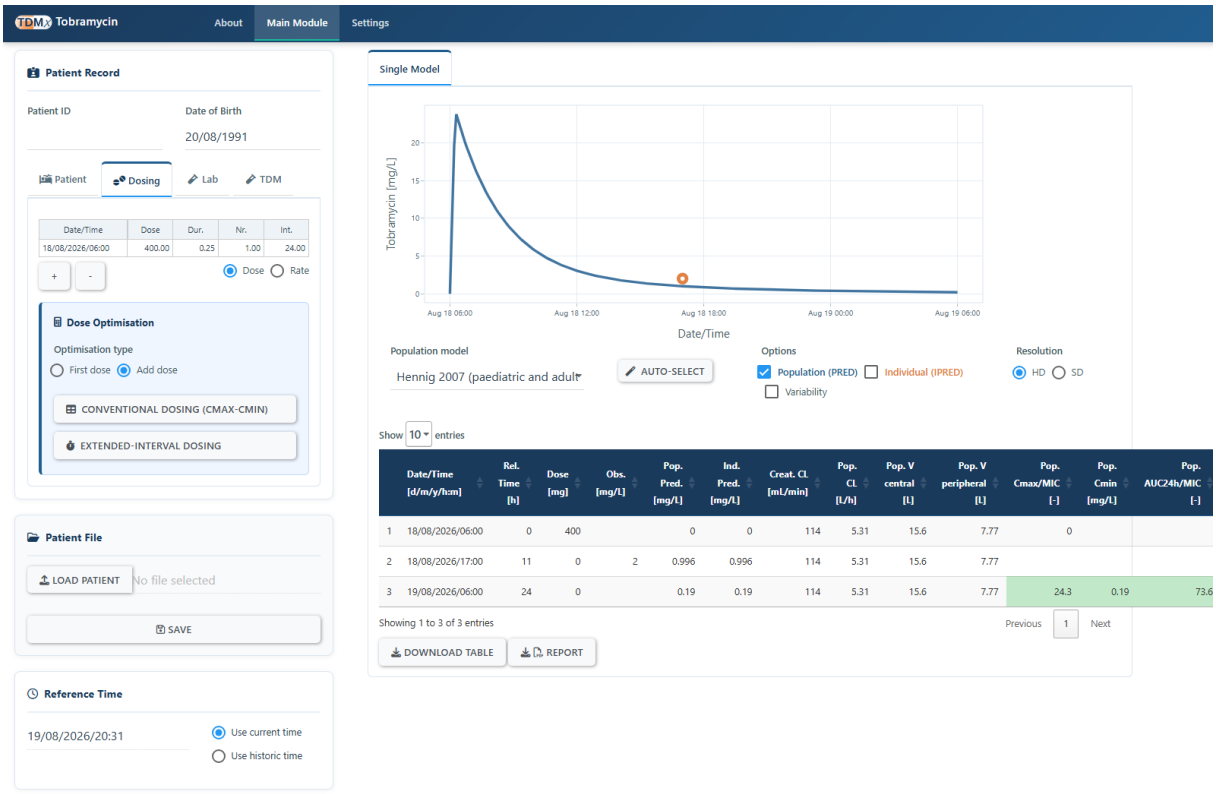

Figure 3: Input panel to edit dosing-related data.

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 — tobramycin 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 for tobramycin; 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.

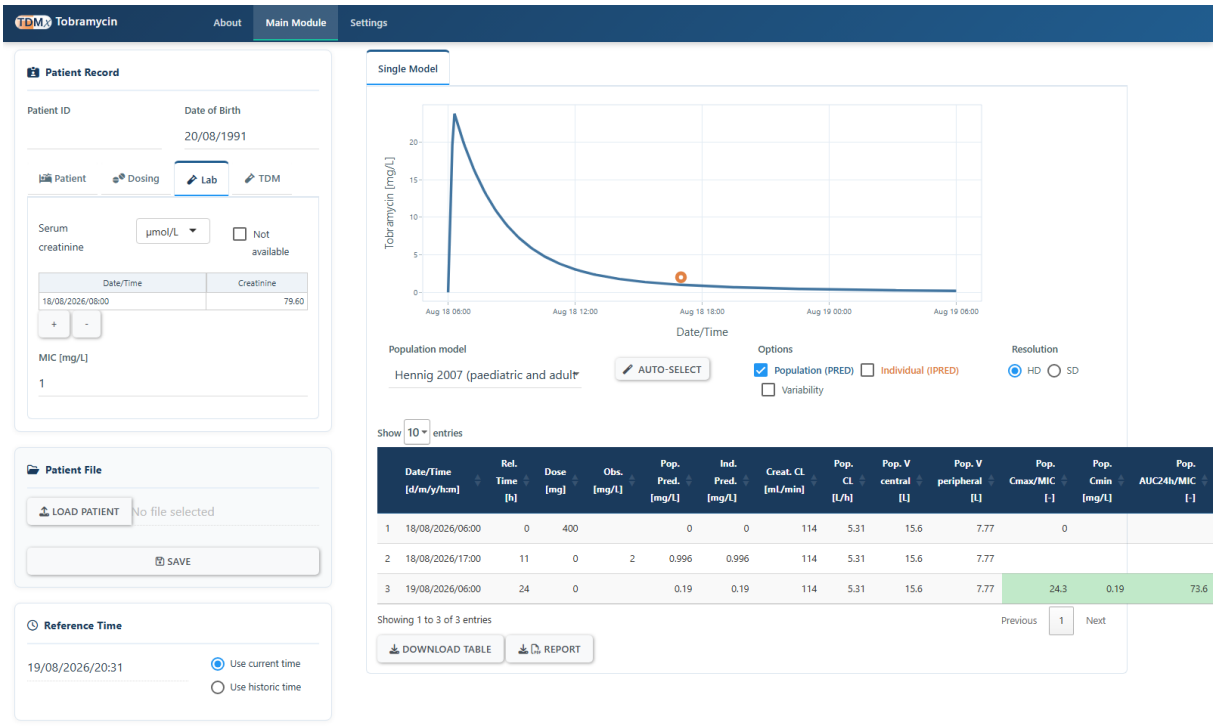

Figure 4: Input panel to enter laboratory data.

Available markers are Serum creatinine and the tobramycin 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. For the MIC, provide an educated guess (default: 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.

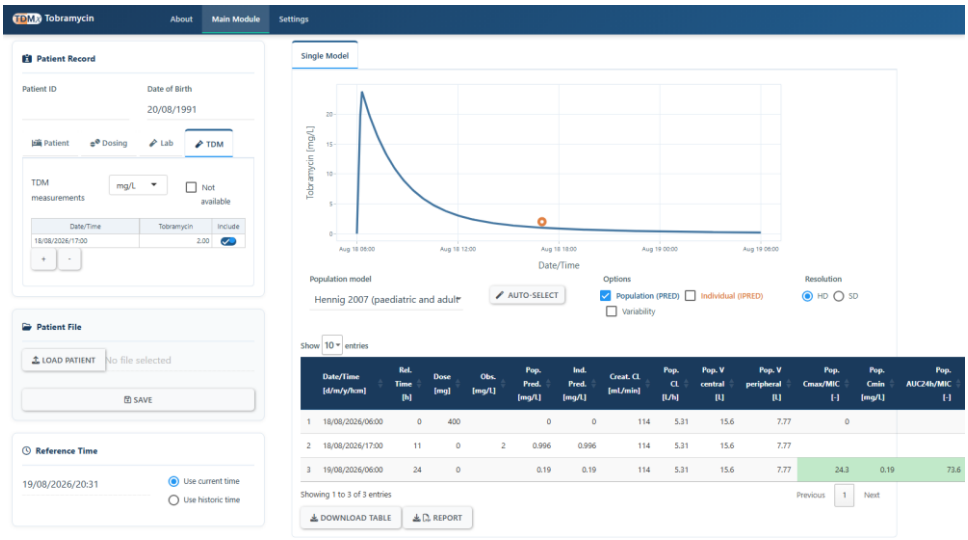

Figure 5: Input panel to enter TDM data.

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.

Extended-Interval Dosing

Clicking "EXTENDED-INTERVAL DOSING" opens the Hartford-nomogram-style dialog (Figure 6): a fixed, weight-based dose (default 7 mg/kg, editable) is given, and TDMx solves for the shortest dosing interval that keeps the predicted trough at or below the target (default 2 mg/L, editable) after the given number of repeated doses (*Doses until target evaluation*, default 3 — accounts for accumulation across repeated dosing rather than just after a single dose). The continuously-solved interval is rounded up to the shortest of the standard intervals selected that still reaches the target; if none do, the longest is used and a warning is shown. Click "CALCULATE" to solve, then "ACCEPT" to add the resulting dose and interval to the patient's dosing record — both the Dose and Suggested interval fields can be manually overridden before accepting.

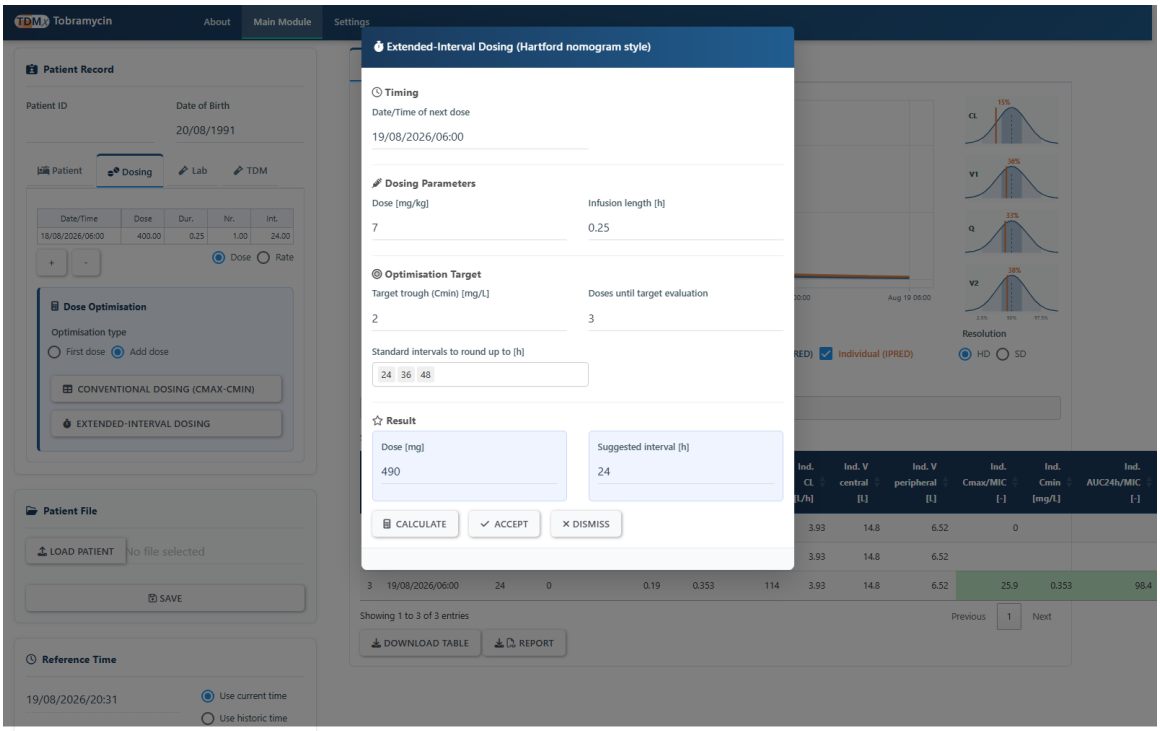

Figure 6: Extended-Interval Dosing dialog (Hartford nomogram style).

Conventional Dosing (Cmax-Cmin)

Clicking “CONVENTIONAL DOSING (CMAX-CMIN)” opens the dialog (Figure 7), which solves, for every one of a fixed set of candidate dosing intervals (8, 12, 18, 24, 36 and 48 h by default — always evaluated), the dose that reaches a target Cmax/MIC ratio (default 10, editable). The resulting Cmax/MIC, Cmin and AUC24h/MIC are read back and colour-coded against the Settings-tab thresholds. Click “CALCULATE” to solve every interval, select the most suitable row, and click “ACCEPT” to add it to the patient’s dosing record.

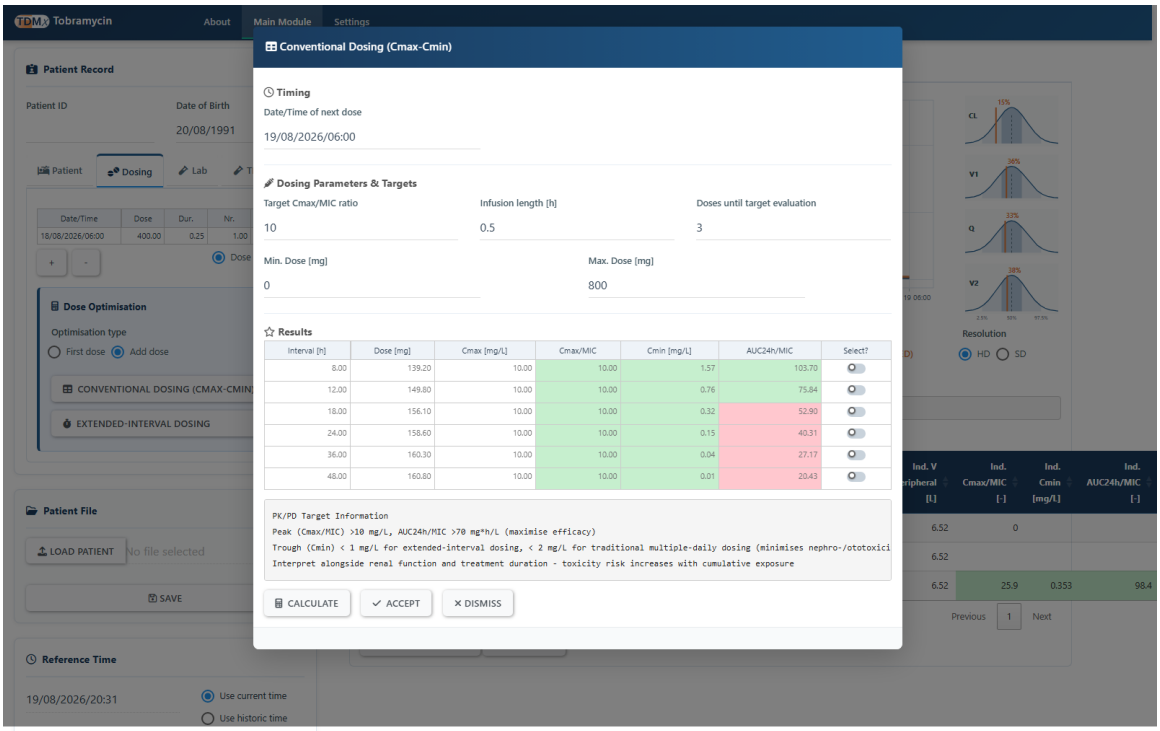

Figure 7: Conventional Dosing (Cmax-Cmin) dialog.

Both dialogs share a *Doses until target evaluation* field: the number of identical, repeated doses given (at the interval being solved, or at each candidate interval) before the trough/Cmax-Cmin/AUC24h-MIC is checked — accounts for accumulation across repeated dosing (higher = closer to steady state).

Select a model

Only one population pharmacokinetic model is currently implemented for tobramycin:

Model	Population	Key covariates used
Hennig 2007	Paediatric and adult, with and without cystic fibrosis, 0-85 yrs.	Weight, Height, Age, Sex, Serum creatinine

The “AUTO-SELECT” control next to the Population model field has no effect while only one model is implemented — it exists for consistency with other TDMx modules that offer several candidate models.

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

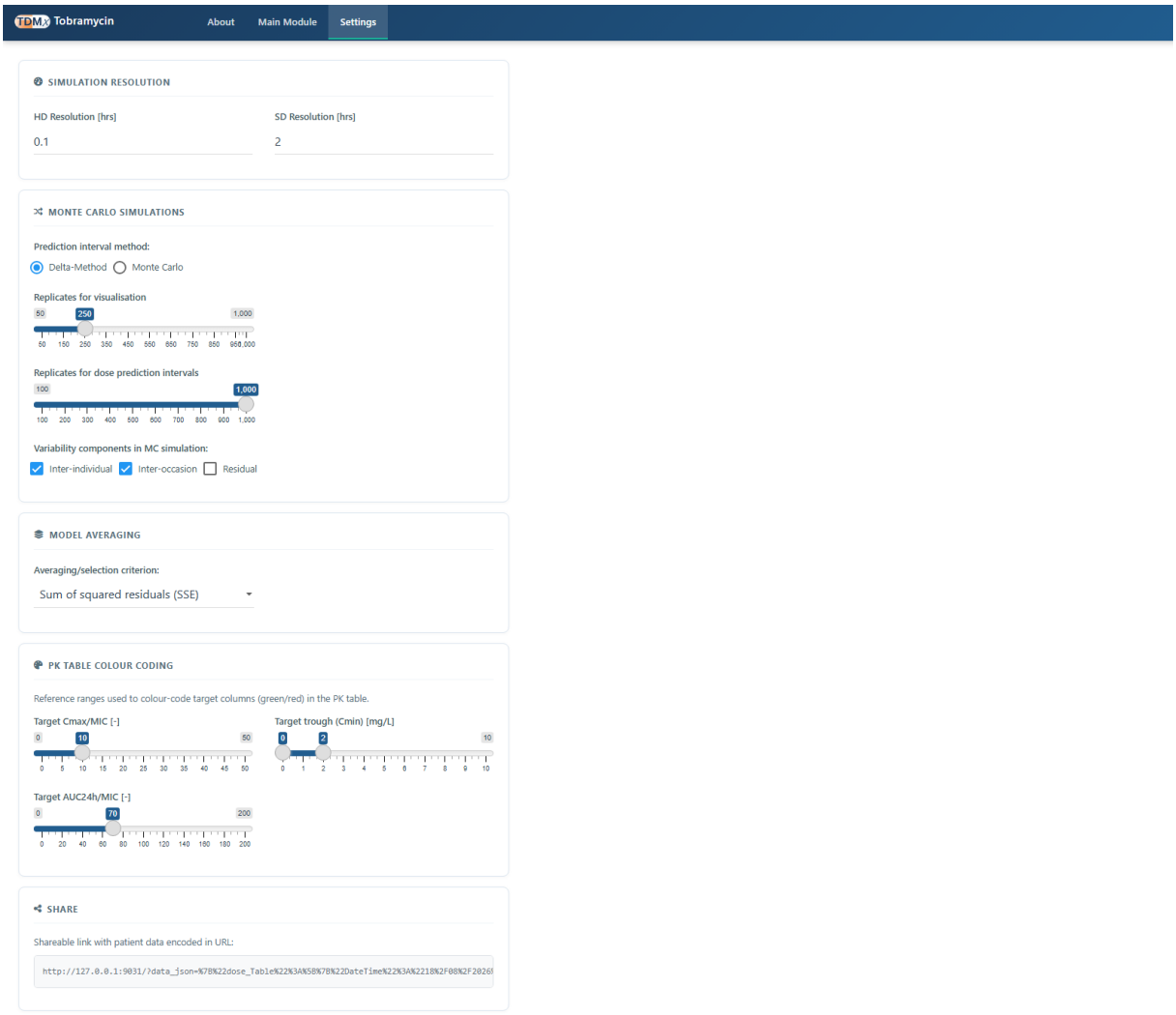

Figure 8: Settings tab.

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.

- **PK Table Colour Coding**: the target Cmax/MIC ratio (default 10), target trough (Cmin, default 2 mg/L) and target AUC24h/MIC (default 70) used to colour-code the main PK table and the "Conventional Dosing (Cmax-Cmin)" results table.
- **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
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
CRCL	Creatinine clearance
CF	Cystic fibrosis
Cmax	Peak concentration
Cmin	Trough concentration
AUC	Area under the curve
MIC	Minimum inhibitory concentration