Quick Reference

TDMx Factor VIII

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Application

TDMx Factor VIII

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 Factor VIII software is intended for healthcare professionals to calculate individualized replacement-therapy dosing regimens for Factor VIII concentrate in patients with haemophilia A. The software aims to address the problem of high inter-patient variability in Factor VIII activity achieved with standard dosing, which can result in trough activity levels that are insufficient to prevent spontaneous bleeding or to support surgical/peri-operative haemostasis.

TDMx Factor VIII utilizes patient-specific data such as demographics (age, weight, ethnicity), disease severity, the specific Factor VIII product and assay method used, inhibitor status and, if available, previous dosing records and measured Factor VIII activity levels, 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 trough Factor VIII activity appropriate to the clinical context — a conservative floor of ≥1 IU/dL to prevent spontaneous bleeding in severe haemophilia A, ≥3-5 IU/dL for standard prophylaxis, or substantially higher targets peri-operatively or during active bleeding.

TDMx Factor VIII is intended for use in patients prescribed Factor VIII replacement therapy 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 Factor VIII should be healthcare facilities that have the capability to measure Factor VIII activity levels and monitor patient responses to replacement therapy.

TDMx Factor VIII 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 Factor VIII 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 Factor VIII (see Select a model) was adapted from a published literature model (Abrantes et al. 2017) describing Factor VIII pharmacokinetics across a broad haemophilia A population, including paediatric patients.

Launch TDMx from the web

Go to www.TDMx.eu

Navigate to the menu LAUNCH TDMX and select the module for Factor VIII.

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.

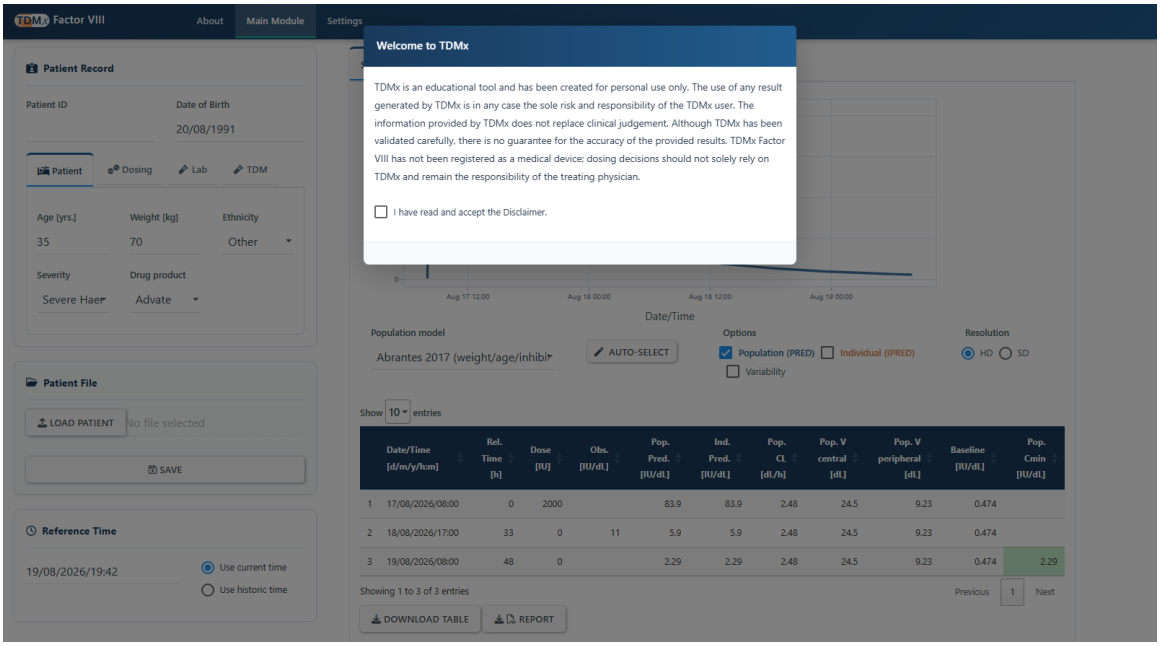

Figure 1: Startup dialog shown when launching TDMx Factor VIII.

Main module

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

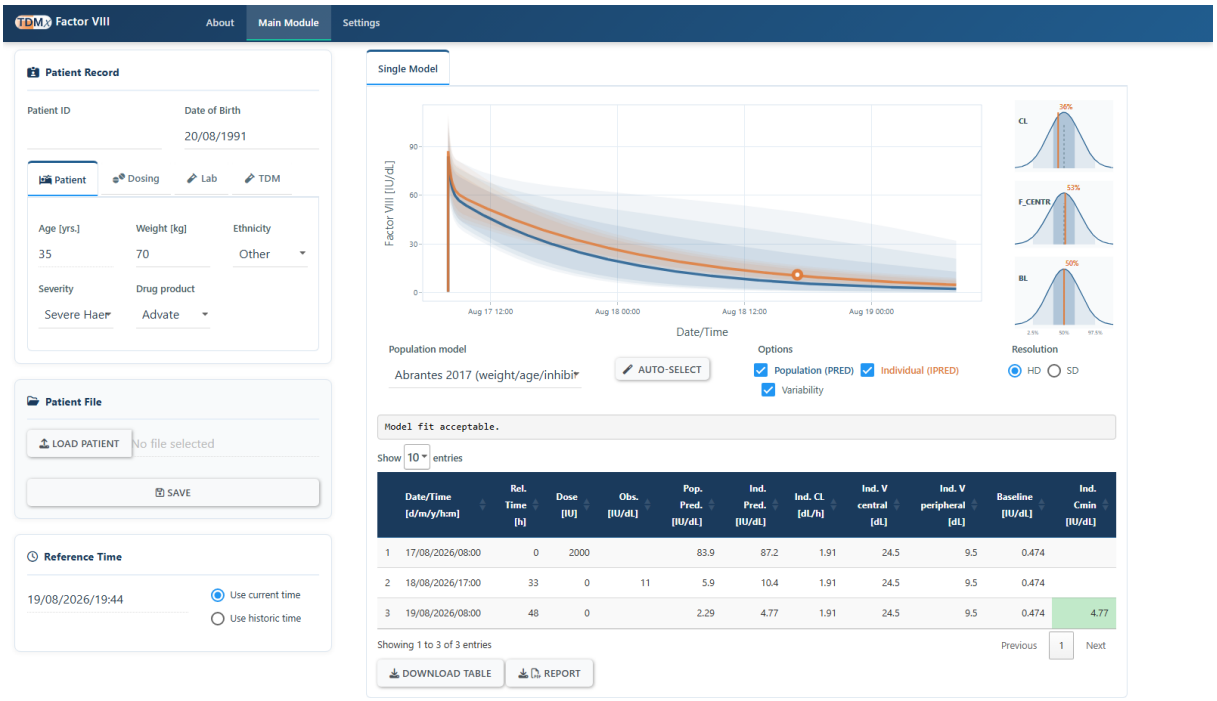

Figure 2: Main interface of the TDMx web-application, Patient tab, with Individual and Variability ticked.

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): only one population pharmacokinetic model is implemented for Factor VIII (see Select a model), so there is no separate Model averaging tab here (unlike some other TDMx modules).

Tick any combination of the three Options next to the plot:

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

- Individual (IPRED, orange): Individually-predicted Factor VIII activity-time data using the dosing record, patient covariates and the observed activity-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, F_CENTR, BL) 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 activity levels 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 [IU]
- Obs.: Observed Factor VIII activity [IU/dL]
- Pop./Ind. Pred.: Population- or individually-predicted Factor VIII activity, respectively

- Pop./Ind. CL: Clearance of the population or individual model [dL/h]
- Pop./Ind. V central/V peripheral: Volumes of distribution of the population or individual model [dL]
- Baseline: The patient's own endogenous Factor VIII activity [IU/dL] — a genuine non-zero floor that is added to the predicted activity even with no drug on board, depending on disease severity (see Patient below)
- Pop./Ind. Cmin: Population- or individually-predicted trough Factor VIII activity at the end of the current dosing interval

Note volumes are reported in dL (not L) and clearance in dL/h, matching how Factor VIII activity is conventionally reported (IU/dL).

Colour coding: the Ind. Cmin column is shaded green when the value falls at or above the target trough configured under Settings (1 IU/dL by default) and red otherwise — the same threshold used for the "PTA" column in the candidate-interval dosing dialog. 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).
- Age [yrs.] (computed automatically from the Date of Birth field) and Weight [kg].
- The categorical covariates Ethnicity, Severity and Drug product, each selected from a dropdown menu.
- The single implemented population model (Abrantes 2017), pre-selected — see Select a model.

Age is used for a maturation effect on clearance (most relevant in infants), and weight scales both clearance and the volumes of distribution allometrically. Severity distinguishes Severe Haemophilia A (baseline endogenous Factor VIII activity <1 IU/dL) from Moderate Haemophilia A (1-5 IU/dL) and sets the baseline (BL) value added to the predicted activity. Drug product only affects the prediction when set to Refacto AF *and*

the Assay method (Lab tab) is set to “One stage” — a measured assay-discrepancy effect specific to that combination; every other product/assay combination is treated identically.

Dosing

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

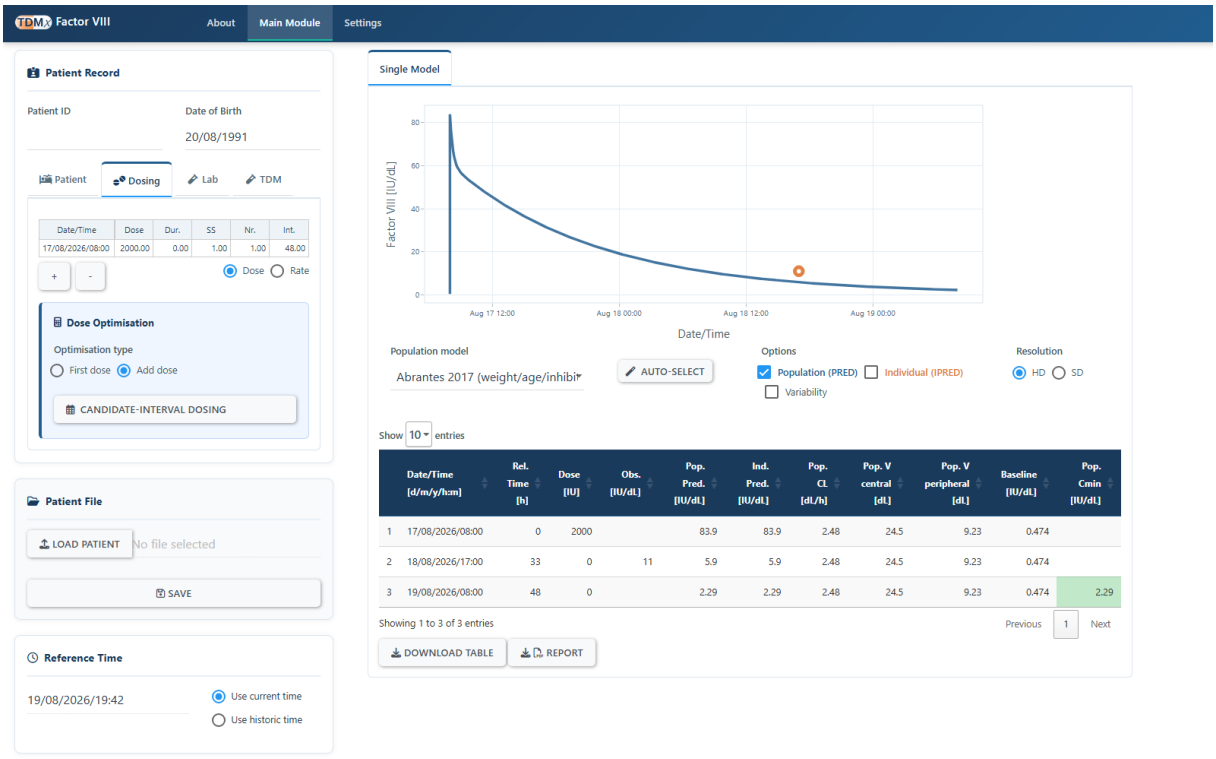

Figure 3: Input panel to edit dosing-related data.

A new dosing event can be added via “+”, while “-” removes the latest one. Specify the date (dd/mm/yyyy/hh:mm) and the dose in IU. Factor VIII is normally given as a slow intravenous push (bolus) — leave Dur. at 0 unless a genuine infusion was given. If a dose is repeated, the number of repeats and the dosing interval (in hours) can be specified via Nr. and Int., respectively.

SS (steady state): enter 1 if this dosing record represents an already-established, ongoing prophylaxis regimen rather than the patient’s literal first-ever Factor VIII dose, or 0 otherwise. With SS = 1, TDMx simulates that dose against the steady-state activity profile for repeated dosing at that amount and interval, instead of a naive single-dose decay from a drug-naive baseline — the appropriate assumption for most returning patients.

Newly added or computed doses (via “+” or the dosing dialog below) default to SS = 0, since they represent a dose being added on top of the existing record rather than a new steady-state anchor.

TDMx offers one dose-optimisation tool for Factor VIII; 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.

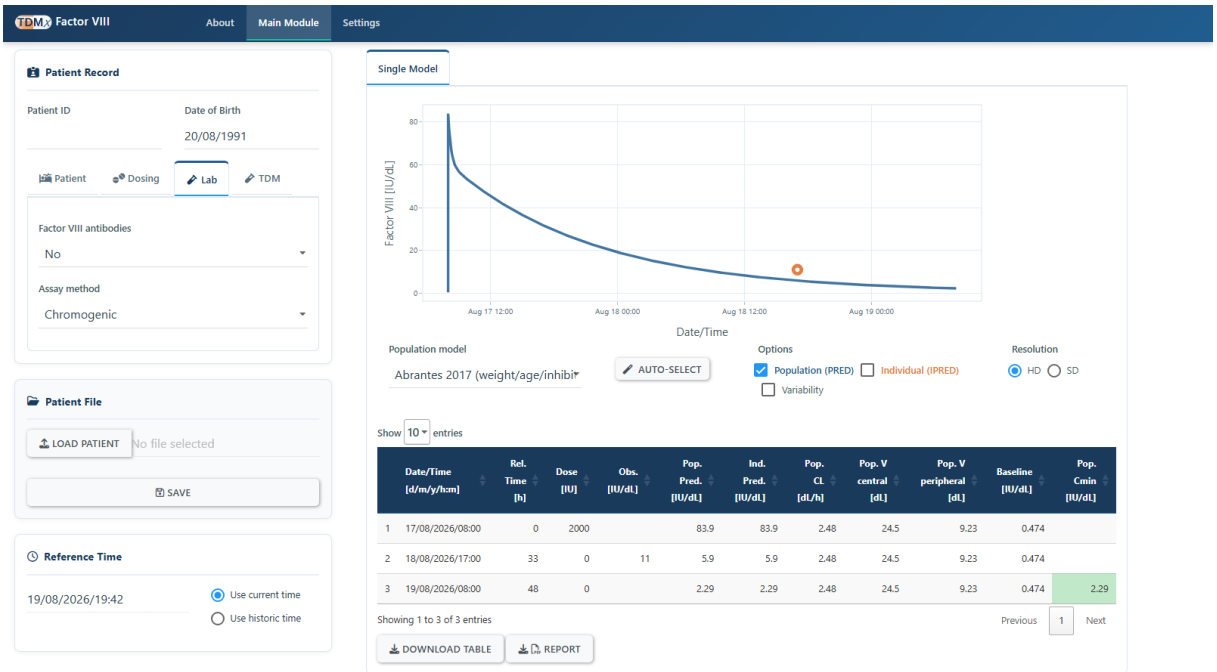

Figure 4: Input panel to enter laboratory data.

- **Factor VIII antibodies**: whether Factor VIII inhibitory antibodies have been detected (Yes/No).
- **Assay method**: One stage or Chromogenic — only affects the prediction in combination with Refacto AF as the drug product (see Patient above).

TDM

A new Factor VIII activity measurement can be added via “+”, while “-” removes the latest one. Specify the date (dd/mm/yyyy/hh:mm) and the activity in IU/dL (Figure 5). Untick

“Include” to exclude a sample from the Bayesian estimation without removing it from the plot.

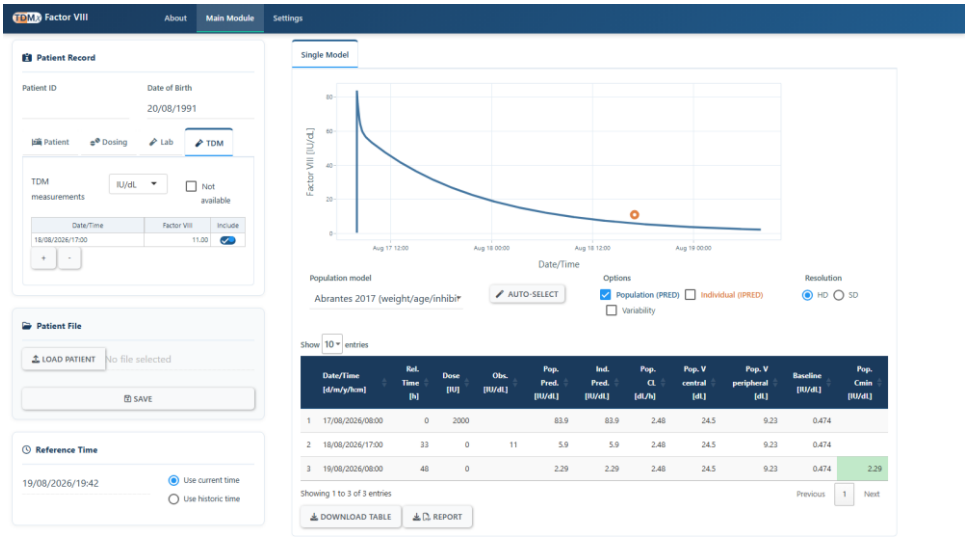

Figure 5: Input panel to enter TDM data.

Dose optimisation

The Candidate-Interval Dosing dialog is opened from the Dosing tab and uses the selected model, the patient’s covariates and (if available) measured Factor VIII activity levels. Optimising without 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.

Clicking “CANDIDATE-INTERVAL DOSING” opens the dialog (Figure 6):

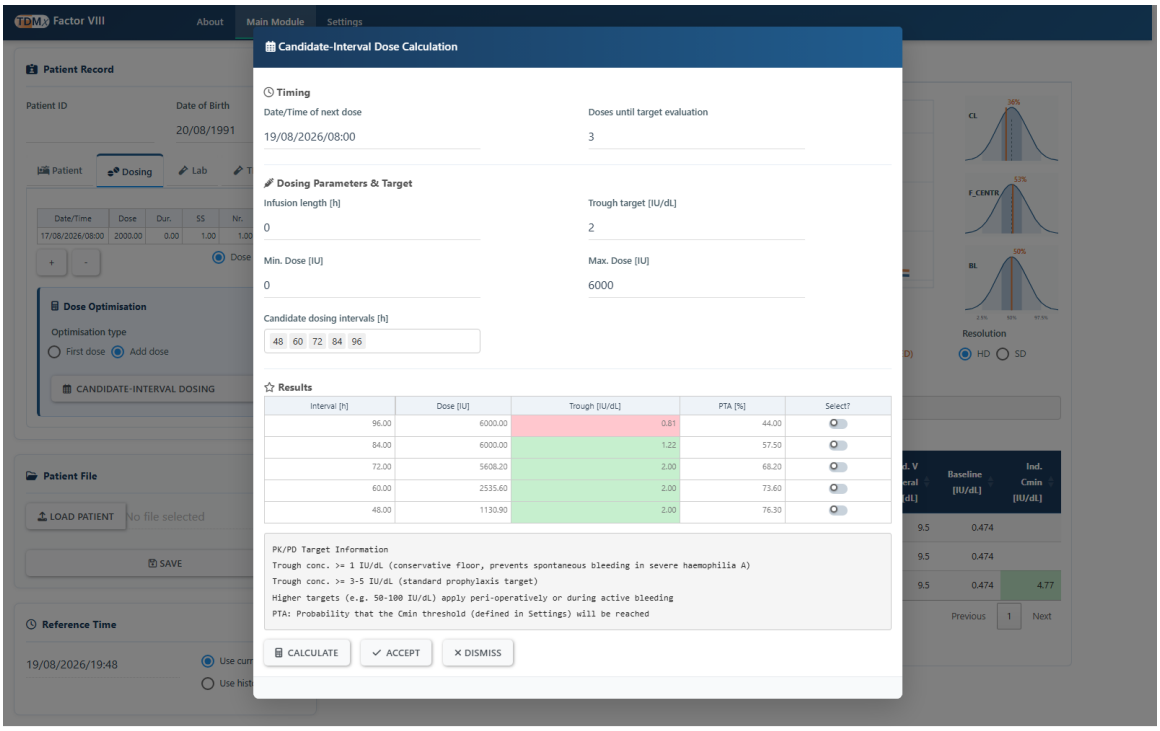

Figure 6: Candidate-Interval Dose Calculation dialog.

- **Timing**: the date/time of the next dose, and *Doses until target evaluation* — the number of identical, repeated doses to give at each candidate interval before the trough is checked (default 3 for Factor VIII, reflecting its comparatively fast elimination relative to typical prophylaxis intervals; higher values move the calculation closer to true steady state).
- **Dosing Parameters & Target**: Infusion length (0 for a bolus, the norm for Factor VIII), the trough target in IU/dL, and the Min./Max. Dose bounds (IU) for the optimisation.
- **Candidate dosing intervals**: one or more intervals (in hours) to evaluate side by side. Type a value and press enter to add a custom interval.
- **Results**: click “CALCULATE” to solve, for each candidate interval, the dose that reaches the target trough after the configured number of doses. The Trough column is colour-coded the same way as the main PK table (green = at/above target, red = below); PTA is the probability of actually reaching the target given population/residual variability, computed in the background once the doses/troughs are shown. Select the most suitable row and click “ACCEPT” to add it to the patient’s dosing record — the accepted row’s Nr. is set to match *Doses*

until target evaluation, so the record itself reflects the same repeated-dose course that was solved for.

Select a model

Only one population pharmacokinetic model is currently implemented for Factor VIII:

Model	Population	Key covariates used
Abrantes 2017	Broad haemophilia A population, including paediatric patients	Weight, Age, Ethnicity, Severity, Inhibitor status, Drug product × Assay method

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

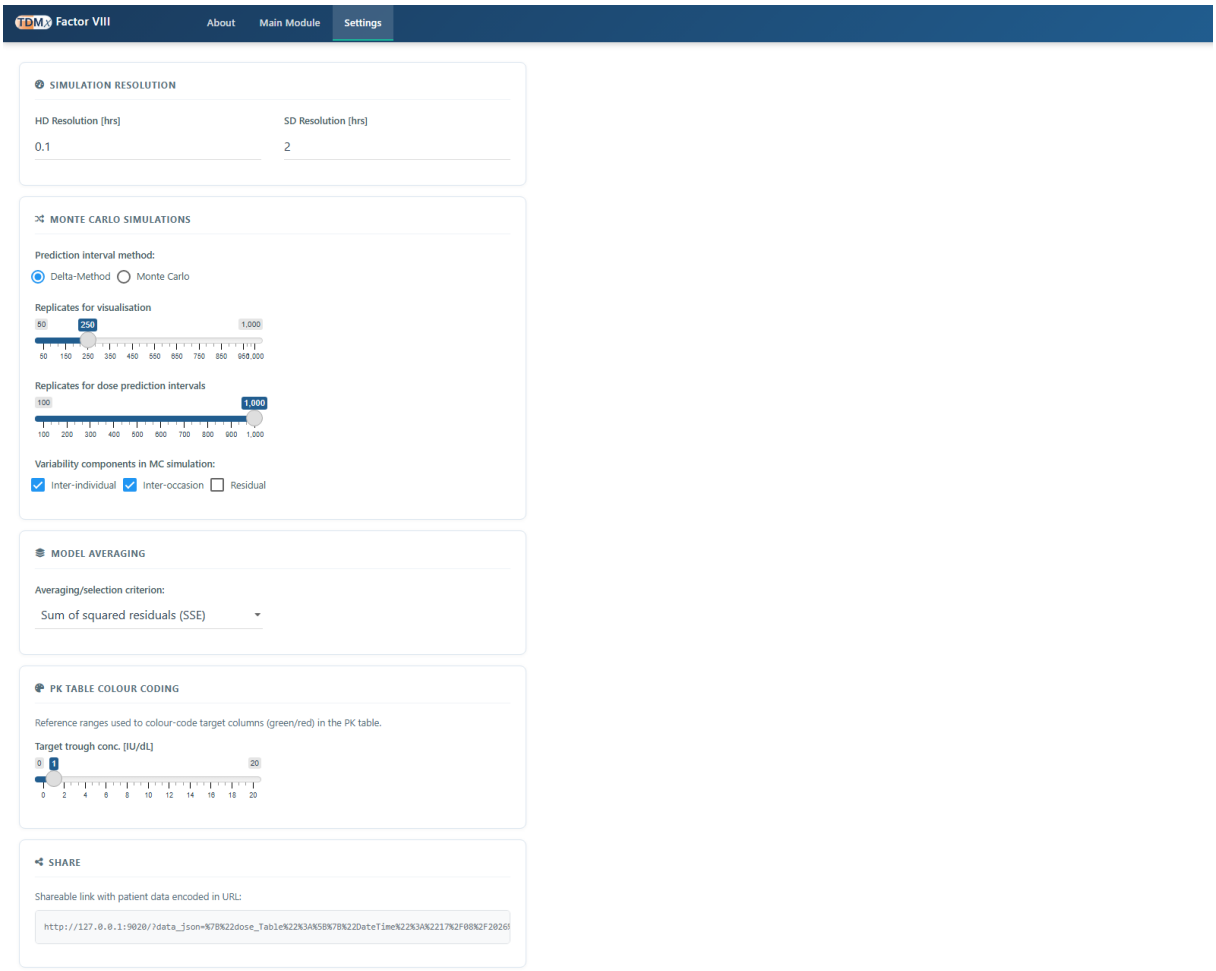

Figure 7: Settings tab.

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 trough concentration (default 1 IU/dL) used to colour-code the Ind. Cmin column in the main PK table and the PTA calculation in the candidate-interval dosing dialog.
- **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 Factor VIII activity
TDM	Therapeutic drug monitoring
CL	Clearance
BL	Baseline (endogenous Factor VIII activity)
SS	Steady state
Cmin	Trough concentration
PTA	Probability of target attainment