Quick Reference TDMx Infliximab

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Author: Sebastian Wicha, Lead Developer

Application

TDMx Infliximab

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 Infliximab software is intended for healthcare professionals to calculate individualized maintenance dosing regimens for the anti-TNFα monoclonal antibody infliximab in patients with inflammatory bowel disease (Crohn's disease or Ulcerative Colitis). The software aims to address the problem of high inter-patient variability in infliximab exposure achieved with standard dosing, which can result in trough concentrations that are insufficient to maintain clinical remission.

TDMx Infliximab utilizes patient-specific data such as demographics, diagnosis, laboratory values (including albumin and faecal calprotectin), antibodies-to-infliximab (ATI) status and, if available, previous dosing records and measured infliximab plasma concentrations, to determine individual pharmacokinetic parameters using one of four implemented population pharmacokinetic models (see Select a model). This computational task is designed to assist healthcare professionals in achieving a maintenance-phase trough concentration of ≥5 mg/L (≥7-10 mg/L for refractory or perianal fistulising disease), the consensus target range for maintaining clinical response.

TDMx Infliximab is intended for use in patients prescribed infliximab 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 Infliximab should be healthcare facilities that have the capability to measure drug concentrations and monitor patient responses to therapy.

TDMx Infliximab 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 Infliximab 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 Infliximab (see Select a model) were adapted from published literature models describing infliximab pharmacokinetics in inflammatory bowel disease.

Note: unlike most other TDMx modules, TDMx Infliximab works on a **days** (not hours) time axis throughout — dosing intervals, resolution settings and the candidate-interval dosing dialog are all expressed in days. This matches infliximab's long elimination half-life and typical 4-8 week maintenance dosing interval.

Launch TDMx from the web

Go to www.TDMx.eu

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

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.

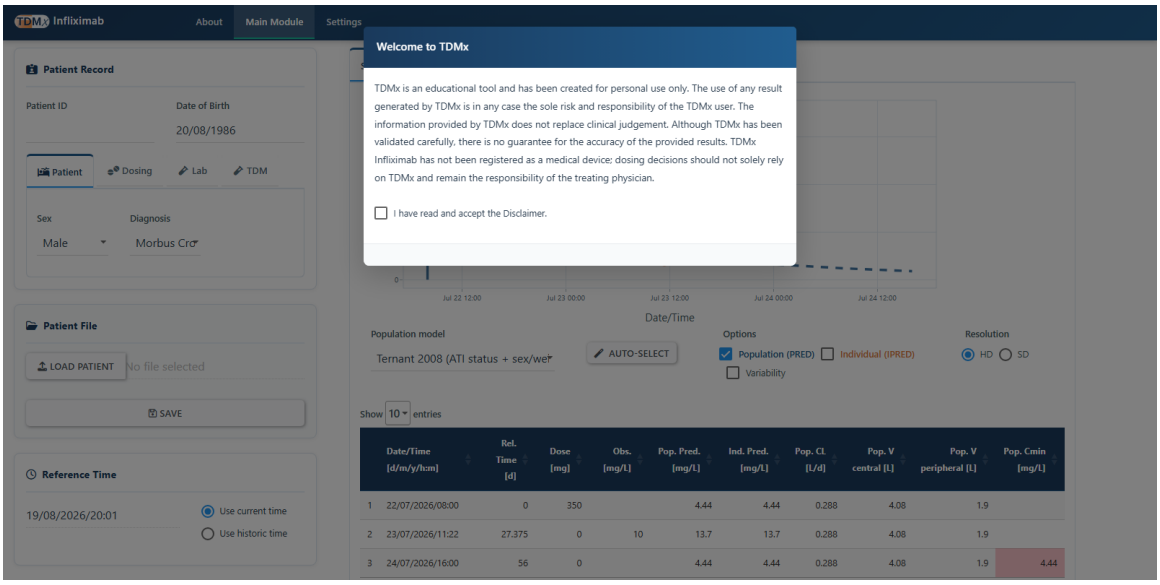

Figure 1: Startup dialog shown when launching TDMx Infliximab.

Main module

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

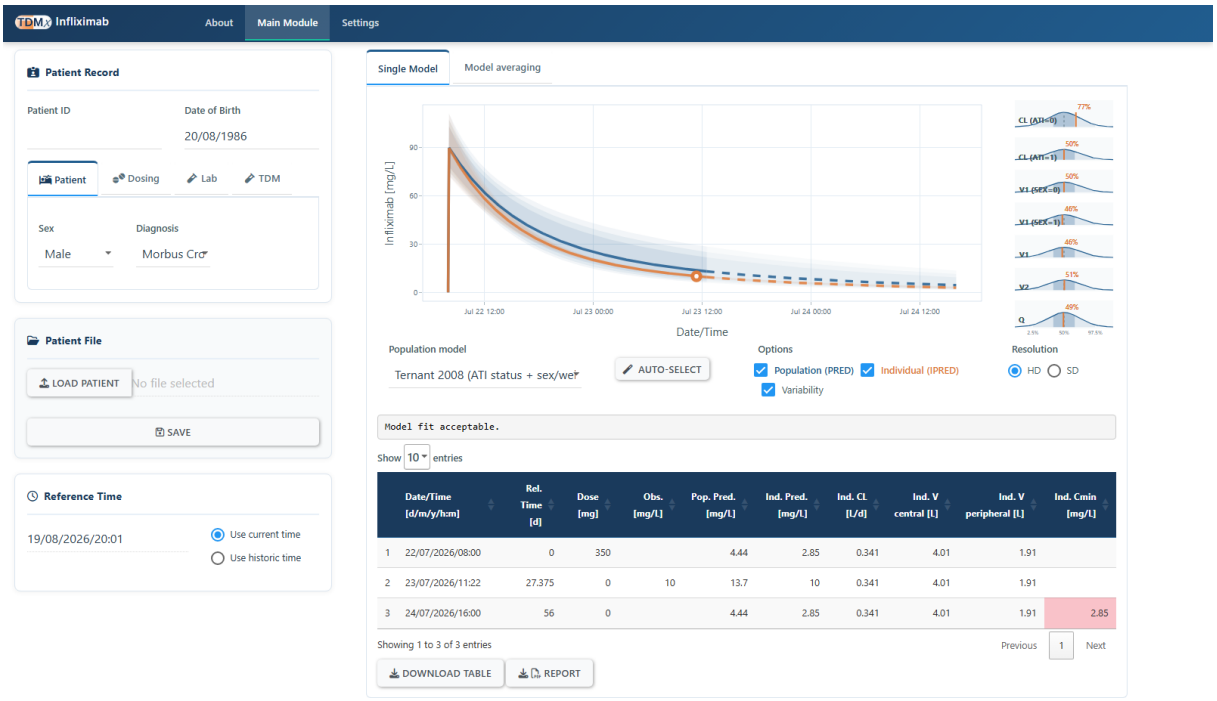

Figure 2: Main interface of the TDMx web-application, Patient tab, with Individual and Variability ticked.

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) appears to the right of the main plot. For the Ternant 2008 model, the ATI-status- and sex-dependent parameters (CL, V1) each get their own curve per covariate branch (e.g. "CL (ATI=0)" and "CL (ATI=1)"). 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
- Rel. Time: Time relative to the first dose, **in days**
- Dose: Administered dose [mg]

- Obs.: Observed concentration-time data [mg/L]
- Pop./Ind. Pred.: Population- or individually-predicted concentration-time data, respectively
- 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

Colour coding: the Ind. Cmin column is shaded green when the value falls at or above the target trough configured under Settings (5 mg/L 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).
- The categorical covariates Sex and Diagnosis (Morbus Crohn / Colitis Ulcerosa), 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: Age and Height are not requested — none of the four implemented models use them. 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.

Covariate	Ternant 2008	Aubourg 2015	Passot 2016	Dreesen 2020
Sex	used (CL, V1)	used (CL, V1)	used (CL, V1)	not used

Covariate	Ternant 2008	Aubourg 2015	Passot 2016	Dreesen 2020
Weight	used (CL, V1), time-varying	used (CL, V1), time-varying	used (CL, V1), time-varying	not used
Diagnosis	not used	not used	used (CL, V1)	not used
Albumin	not used	not used	not used	used (CL)
Faecal calprotectin	not used	not used	not used	used (CL)
Antibodies to infliximab (ATI)	used (CL), time-varying	not used	not used	used (CL), time-varying
CD Activity Index	not used	not used	not used	used (CL)

Dosing

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

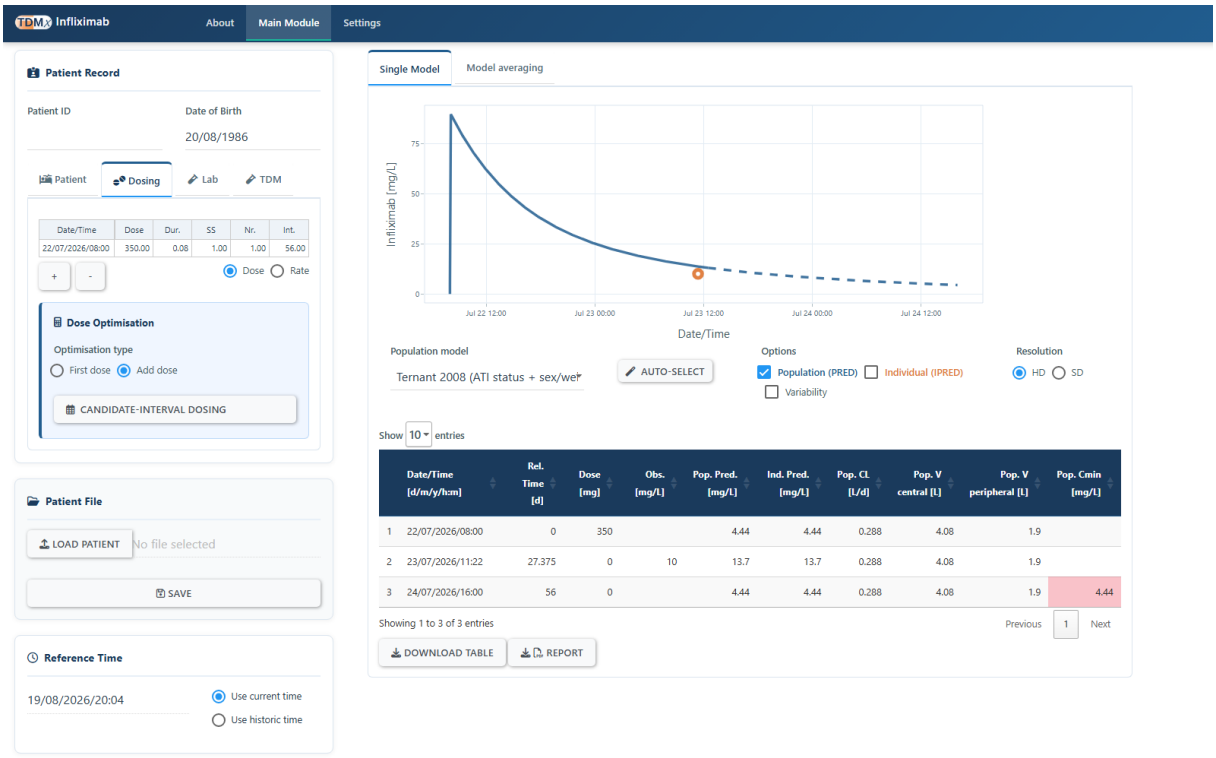

Figure 3: Input panel to edit dosing-related data.

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/day) and the infusion duration (Dur.) **in days** (e.g. a typical ~2 h infusion = 0.083 d) — infliximab is dosed intravenously into the central compartment only. If a dose is repeated, the number of repeats and the dosing interval (in days) can be specified via Nr. and Int., respectively.

SS (steady state): enter 1 if this dosing record represents an already-established, ongoing maintenance regimen rather than the patient's literal first-ever infusion, or 0 otherwise. With SS = 1, TDMx simulates that dose against the steady-state concentration 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, since infliximab therapy typically spans months to years. 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 infliximab; see Dose optimisation below.

In the Lab tab (Figure 4), the user can specify laboratory data obtained from the patient. Weight, Albumin, Faecal calprotectin and Antibodies to infliximab (ATI) status are tracked **over time** (unlike most other TDMx modules, which use single constant values) — infliximab therapy typically spans months to years, over which these can change meaningfully. CD Activity Index (CDAI) is entered as a single constant value.

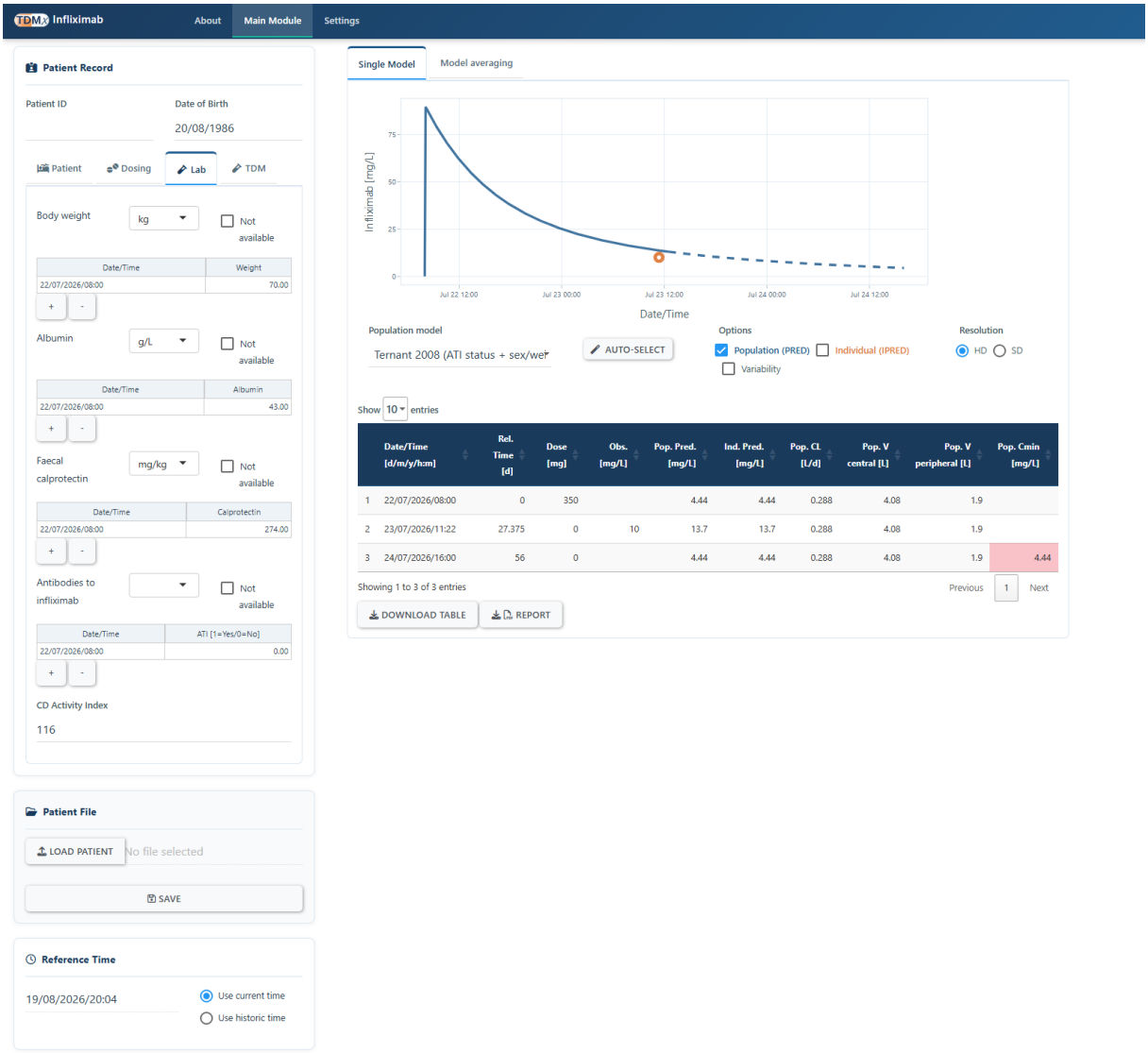

Figure 4: Input panel to enter laboratory data.

Specify the date of each 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 or tick

"Not available"; if the selected model uses that marker, TDMx substitutes a predefined population value which cancels out its influence.

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.

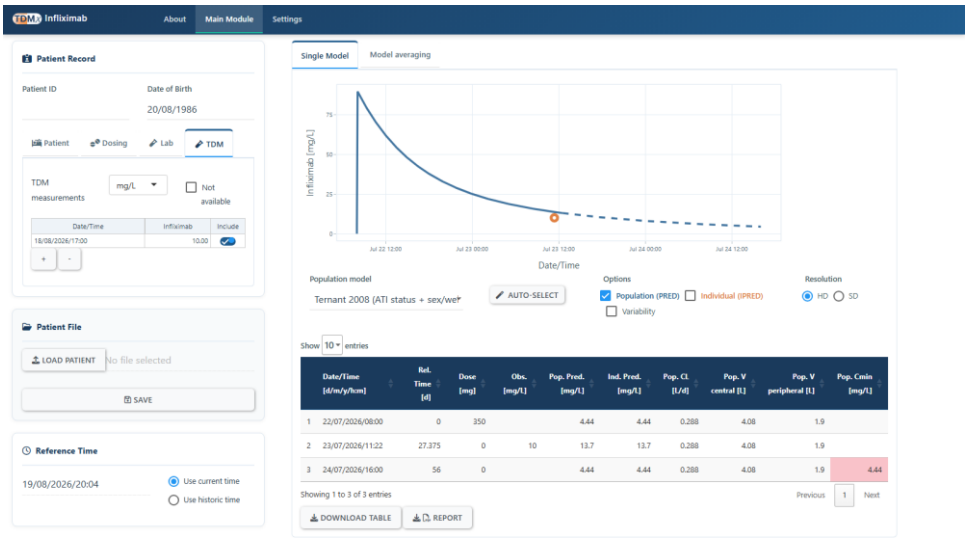

Figure 5: Input panel to enter TDM data.

Dose optimisation

The Candidate-Interval Dosing dialog is opened from the Dosing tab and uses the selected model, the patient's covariates and (if available) measured infliximab concentrations. 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):

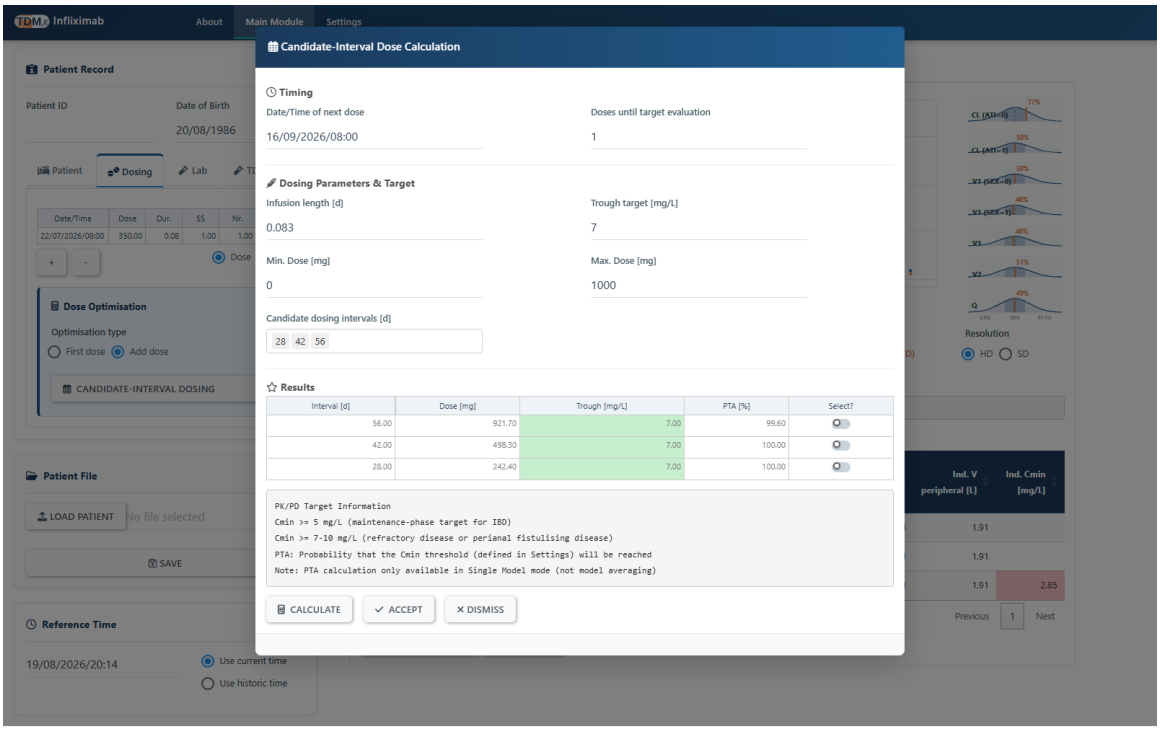

Figure 6: Candidate-Interval Dose Calculation dialog.

- **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 1 for infliximab, since its long elimination half-life relative to the typical 4-8 week maintenance interval means accumulation beyond the first dose is comparatively small; increase it to move the calculation closer to true steady state).

- **Dosing Parameters & Target**: Infusion length in days (e.g. a typical ~2 h infusion = 0.083 d), the trough target in mg/L, and the Min./Max. Dose bounds (mg) for the optimisation.

- **Candidate dosing intervals**: one or more intervals (in days) to evaluate side by side — by default 28, 42 and 56 days (4/6/8 weeks). 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 — PTA is only calculated in Single Model mode. 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.

Model averaging

Instead of relying on a single population model, the *Model averaging* output tab (Figure 7) 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.

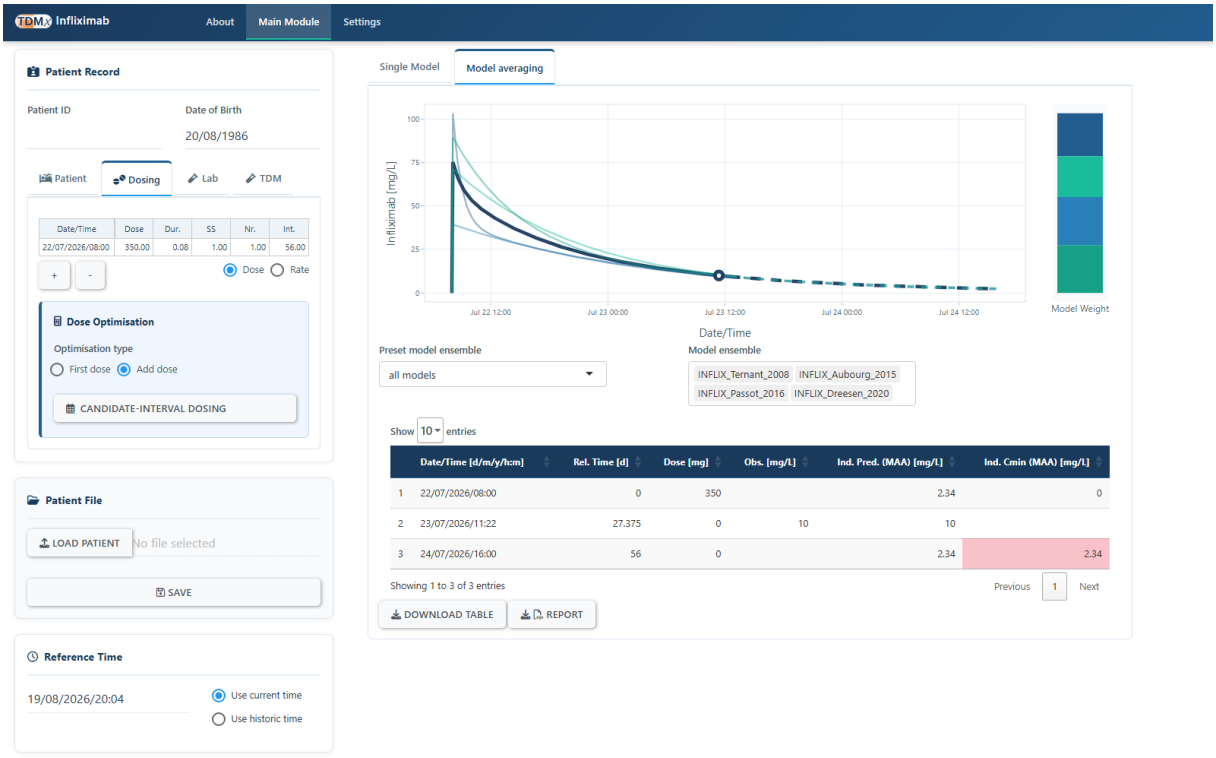

Figure 7: Model averaging tab — model-averaged prediction, per-model contributions and model weights.

- **Preset model ensemble**: a dropdown of predefined sets of candidate models — “all models” (all four INFLIX_* models, the default) or “one model” (Ternant 2008 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 (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 — Ternant 2008 — is selected. If a different model is more appropriate for a specific patient, the "Population model" dropdown on the Patient tab lists all four models:

Model	Key covariates used
Ternant 2008	Sex, Weight (time-varying), Antibodies to infliximab (time-varying) on CL/V1
Aubourg 2015	Sex, Weight (time-varying) on CL/V1
Passot 2016	Sex, Weight (time-varying), Diagnosis on CL/V1
Dreesen 2020	Albumin, Antibodies to infliximab (time-varying), Faecal calprotectin, CD Activity Index on CL

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

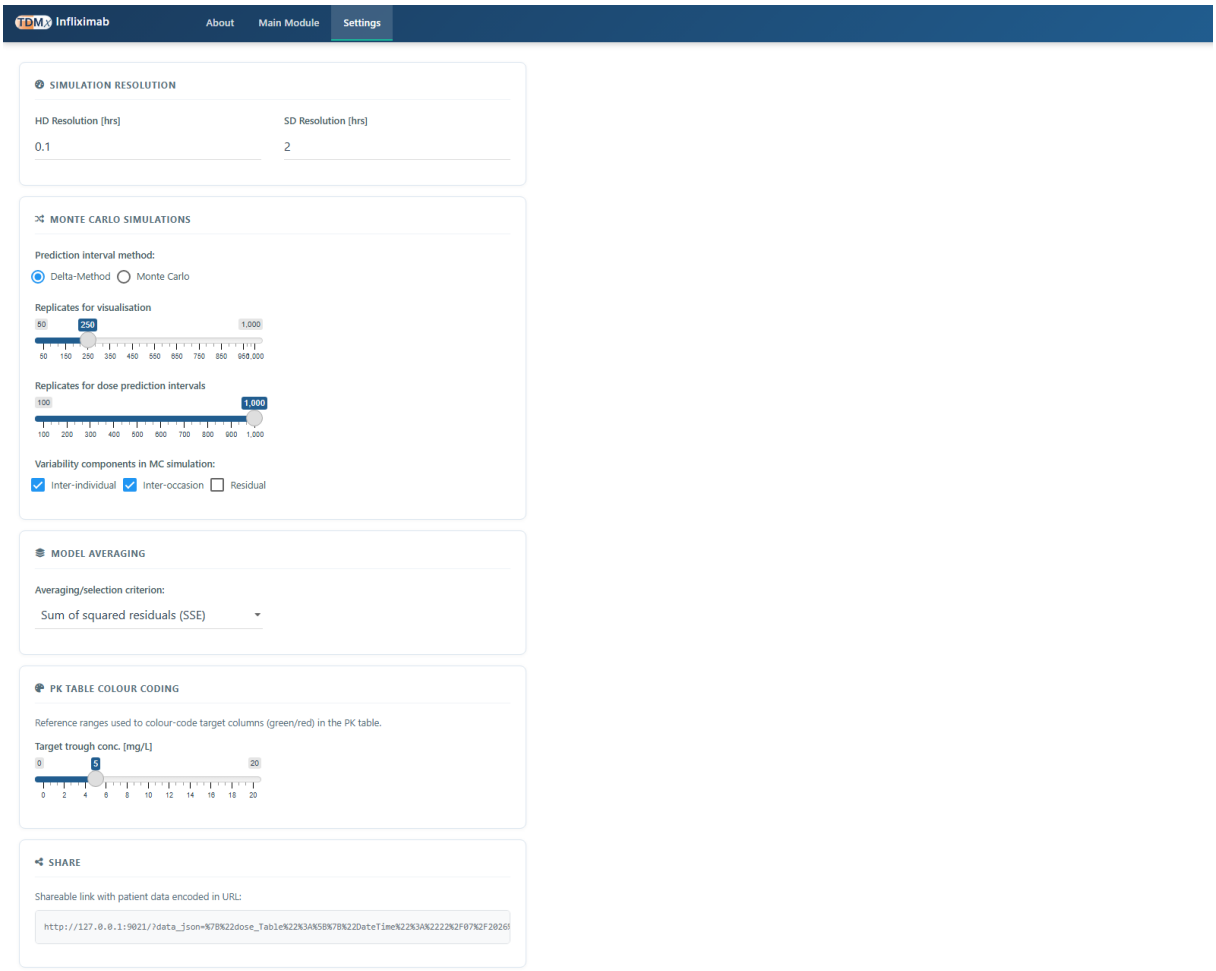

Figure 8: Settings tab.

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. Note these remain hour-based even though the rest of TDMx Infliximab works in days.
- **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.
- **PK Table Colour Coding**: the target trough concentration (default 5 mg/L) 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 plasma concentration
TDM	Therapeutic drug monitoring
CL	Clearance
Vx	Volume of distribution (1 = central, 2 = peripheral)
ATI	Antibodies to infliximab
CDAI	Crohn's Disease Activity Index
SS	Steady state

Abbreviation	Meaning
Cmin	Trough concentration
PTA	Probability of target attainment
MAA	Model-averaged (Model Averaging Approach)