

# Quick Reference





## **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.



## Introduction

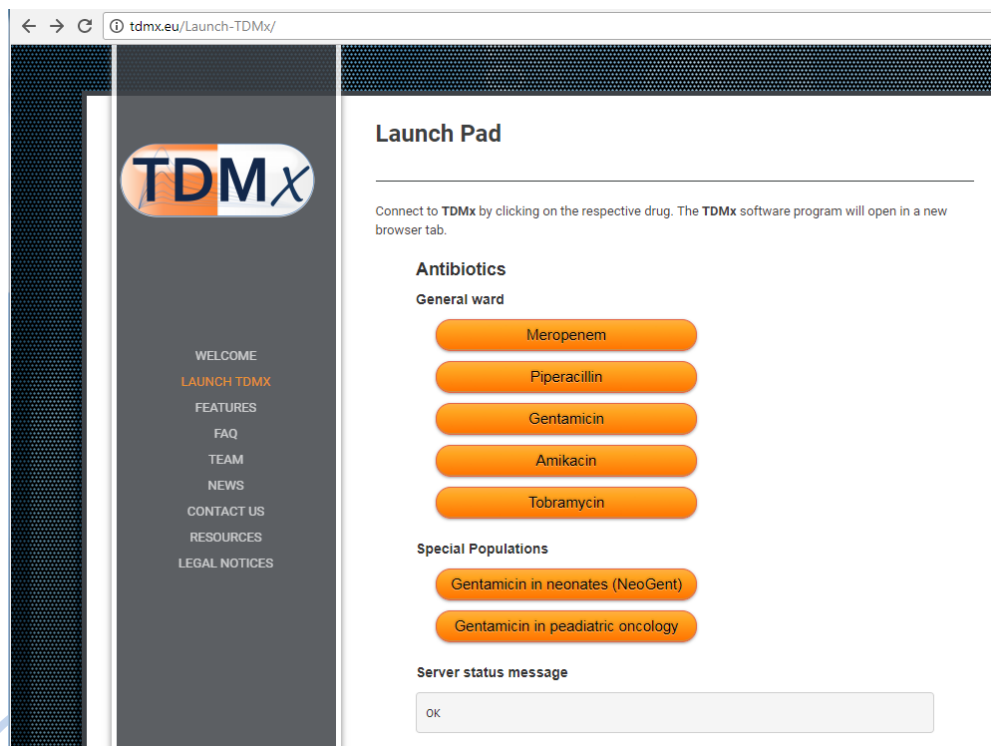
TDMx is a web-based software to perform dosing simulations to support **Therapeutic Drug Monitoring (TDM)** with pharmacometrics (x). TDMx was developed as an educational tool for healthcare professionals to demonstrate application of model-supported TDM in clinical practice as well as clinical research. Furthermore, TDMx is suitable for teaching TDM in undergraduate studies.

TDMx was developed using reactive programming with a server-client architecture: TDMx reactively visualises 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](http://www.TDMx.eu)

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



## Patient module

In the patient module, all patient-related information is provided such as patient covariates incl. the susceptibility of the target pathogen. With this basic information the user can already use the 'Probabilistic dosing' module of TDMx. Furthermore, the user can enter any dosing regimen of the drug of interest along with drug measurements to obtain the individual pharmacokinetic profile based on Bayesian feedback in the 'Bayesian dosing' module. Note that the precise appearance of the module is drug dependent.

TDMx for Meropenem

Disclaimer
1. Patient
2. Probabilistic Dosing
3. Bayesian Dosing
4. Optimise Sampling
Advanced Opt. ▾

**Demographics**

Age [yrs.]    Weight [kg]    Height [cm]

Sex

▾

Dose [mg] | Infusion dur. [h]

Time	Dose	Duration
09/11/2017/06:00	1000	1

+    -

Dosing interval (for next dose) [h]

**Laboratory**

Serum creatinine [mg/dL]

Time	cCreatinine
09/11/2017/13:00	0.7

+    -

MIC [mg/L]

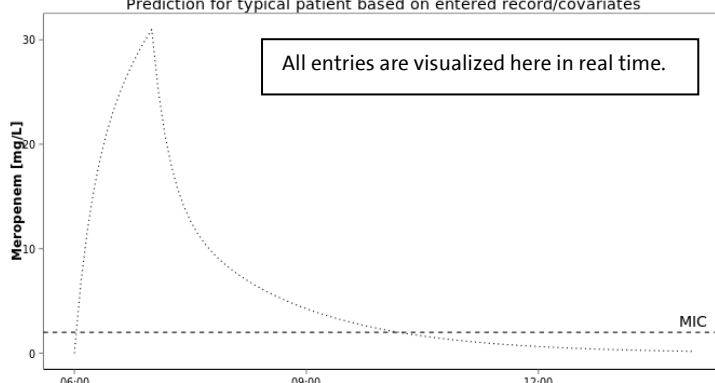
Measured meropenem [mg/L]

Time	cMeropenem
09/11/2017/13:00	

+    -

Protein Binding [%]

Prediction for typical patient based on entered record/covariates



Time [dd/mm/yyyy/hh:mm]

Dose [mg]

Infusion duration [h]

cMeropenem [mg/L]

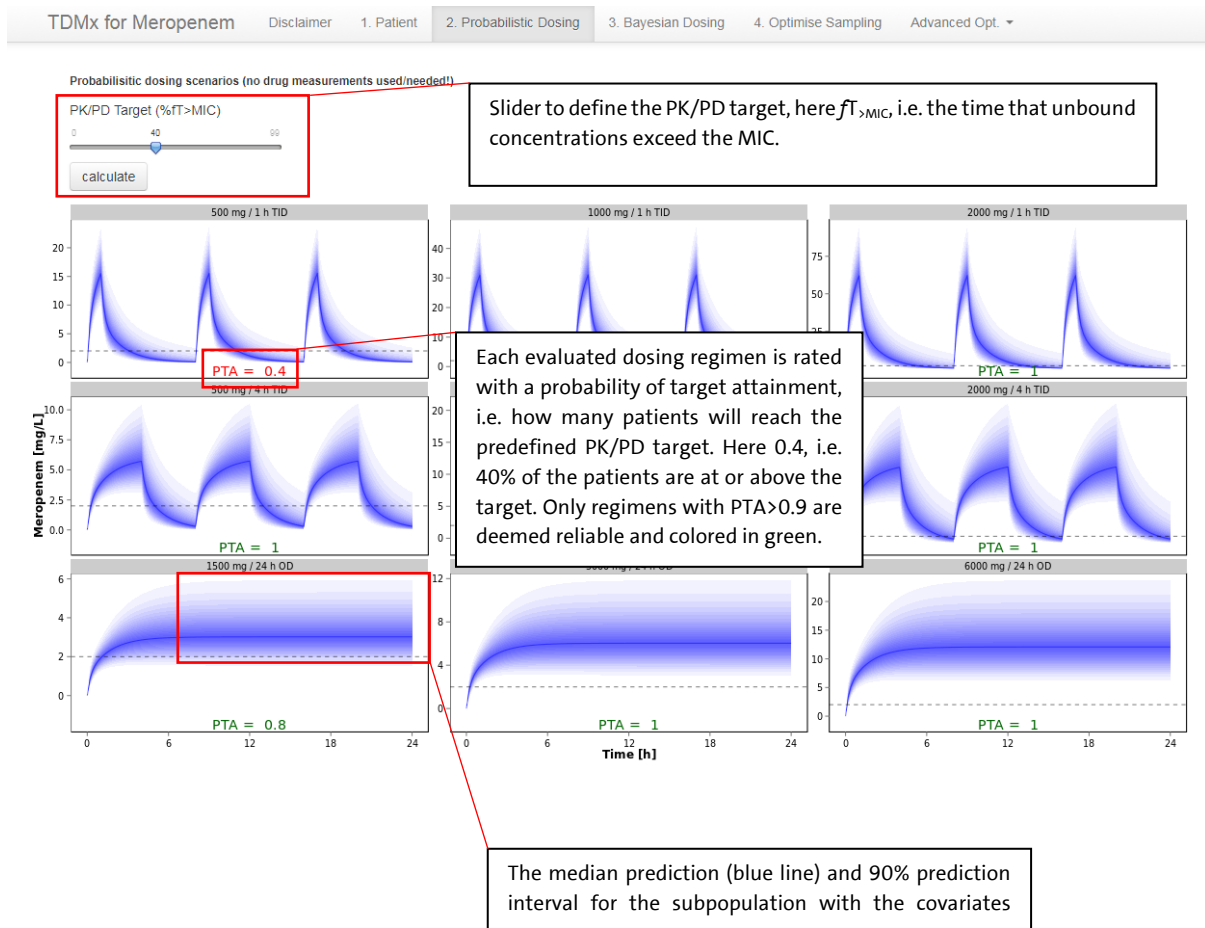
Patient data and dosing record. Entering a dosing record is only required for Bayesian Dosing. Further doses can be added by '+' and removed by '-'. The dosing interval field indicates when the next dose is added in relation to the last entry in the table. Any entry can be modified by typing into the respective field.

All laboratory information is gathered here. While serum creatinine, a (guesstimate) MIC and protein binding is required in any case, the measured drug concentration is only required for Bayesian Dosing.

## Probabilistic Dosing module

TDMx can predict a likely successful *a priori* dosing regimen solely based on patient covariates and/or pathogen data without requiring drug measurements. This probability of target attainment analysis is potentially useful to guide therapeutic decisions already before initiating treatment or if no drug measurements are available.

This module is also drug specific. For beta-lactams, it looks as follows (or similar).



For aminoglycosides, the Probabilistic Dosing module looks as follows:

TDMx for Gentamicin
Disclaimer
1. Patient

PK/PD target for efficacy (Cmax/MIC) and safety (Cmin). AUC<sub>24h</sub>/MIC as alternative target is presented in the plot.

PK/PD target(Cmax/MIC)  
20

PK/Tox target(Cmin) [mg/L]  
1

Date/time for next dose  
10/11/2017/08:00

Infusion duration [h]  
0.05

Minimum dose [mg/kg]  
3

Feasible dosing intervals [h]  
q24

Algorithm  
Median (recommended)

Calculate

---

Format/Unit

Time [dd/mm/yyyy/hh:mm]

Cmax/MIC [-]

Cmin [mg/L]

Infusion duration [h]

Probabilistic dosing scenarios (no drug measurements used/needed!)

Dosing interval: q 24 h / Target concentrations reached!

The median prediction (blue line) and 90% prediction interval for the subpopulation with the covariates specified in the patient module are simulated.

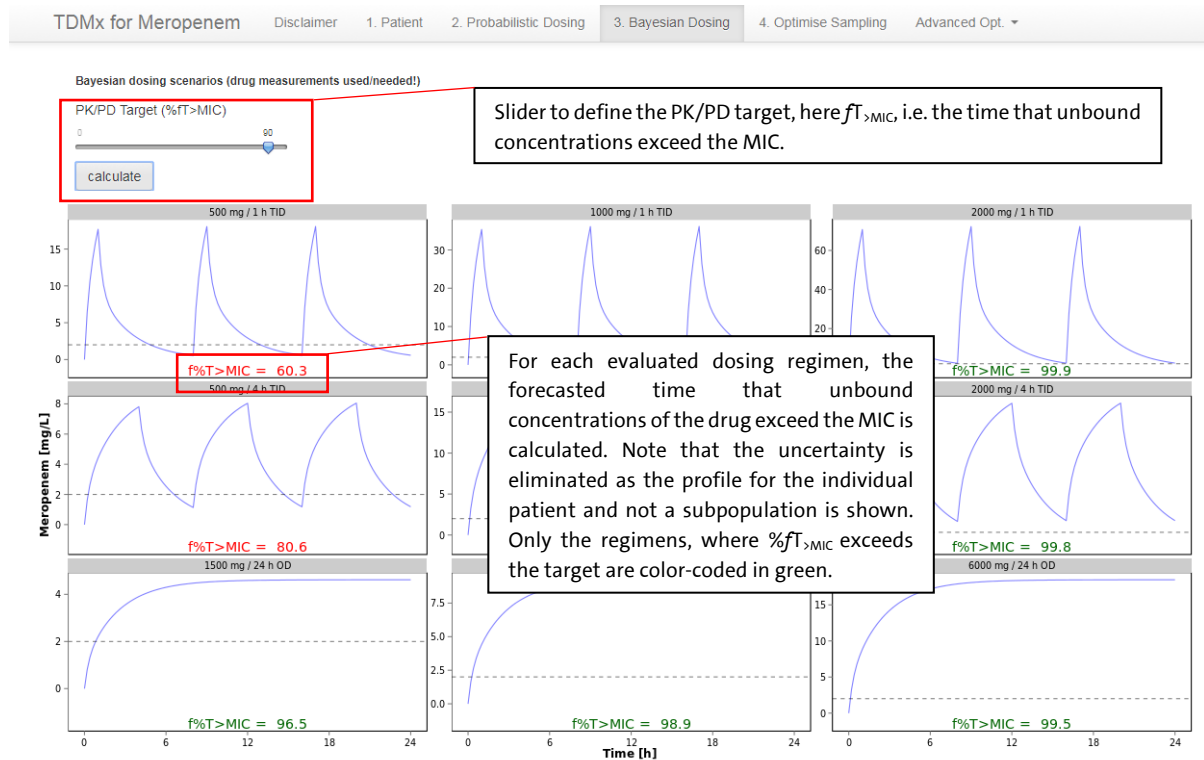
Read carefully and check if the targets have been reached with the selections made

Specify date/time for the probabilistic dose, the infusion duration, a minimum dose and select feasible dosing intervals that shall be evaluated. TDMx will report the shortest possible dosing regimen amongst the evaluated ones that meet the PK/PD and PK/Tox target.



## Bayesian Dosing module

If one or multiple drug measurements are available, TDMx uses Bayesian forecasting to calculate the pharmacokinetic parameters of your individual patient in order to simulate deterministically a tailored dosing regimen.



For aminoglycosides, the Bayesian Dosing module looks as follows:

TDMx for Gentamicin
Disclaimer
1. Patient

PK/PD target for efficacy (Cmax/MIC) and safety (Cmin). AUC<sub>24h</sub>/MIC as alternative target is presented in the plot.

Prediction of next dose based on individual patient (using Bayesian estimates)

AUC<sub>24h</sub>/MIC: 70.4

The solid line represents the estimated pharmacokinetic profile from the drug measurements (dots) and the dashed line the forecasted profile with the calculated doses at the reported dosing times.

Read carefully and check if the targets have been reached with the selections made.

Dosing interval: q 36 h / Target concentrations reached!

Specify date/time for the Bayesian forecasted dose, the infusion duration, a minimum dose and select feasible dosing intervals that shall be evaluated. TDMx will report the shortest possible dosing regimen amongst the evaluated ones that meet the PK/PD and PK/Tox target.

PK/PD target(Cmax/MIC)

PK/Tox target(Cmin) [mg/L]

Date/time for next dose

Infusion duration [h]

Minimum dose [mg/kg]

Feasible dosing intervals [h]

Format/Unit

Time [dd/mm/yyyy/hh:mm]

Cmax/MIC [-]

Cmin [mg/L]

Infusion duration [h]





## Optimal Sampling module

TDMx tells you which sampling time points are most informative to describe the individual pharmacokinetics based on D-optimal design theory. Currently, the optimal design module can predict the most informative sampling time points for PK/PD relationships or even for the full pharmacokinetic profile.

TDMx for Meropenem    Disclaimer    1. Patient    2. Probabilistic Dosing    3. Bayesian Dosing    4. Optimise Sampling    Advanced Opt. ▾

Optimise sampling for PK of  
 Typical patient ▾

Optimise for  
 Full PK ▾

Sampling after  
 Steady state ▾

Dose [mg]  
 1500

Infusion duration [h]  
 4

Dosing interval for steady state designs [h]  
 8

Observation period [h]  
 8

Calculate

**Recommended sampling time points after dosing [hh:mm]:**  
 00:06 00:36 03:42 06:54

Meropenem [mg/L]

Time after dose [h]

Select if the optimal sampling design shall be calculated for the typical patient (if not drug measurements are available) or for the individual patient (if measurements are available). Select if you want to optimize to determine the full pharmacokinetic profile or for the PK/PD target only (e.g.  $T > MIC$ ).

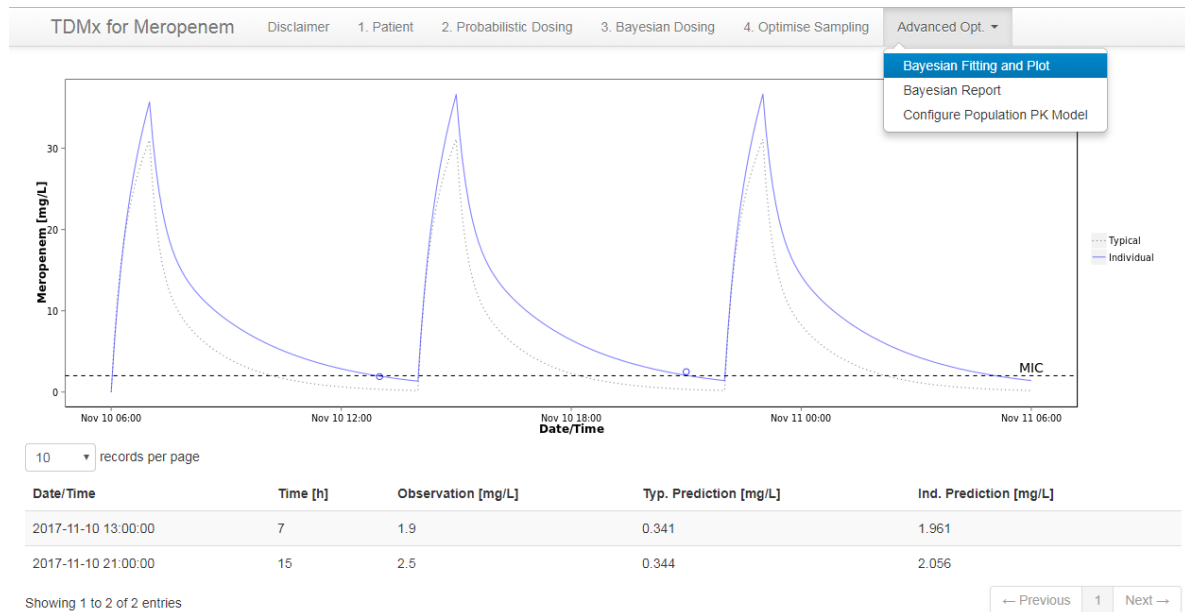
Specify for which dose/dosing schedule the design will be calculated.



## Advanced options

In this menu, more advanced options are presented.

In Bayesian Fitting and Plot, the result of the Bayesian estimation as well as the observed data, typical (grey dotted line) and individual predictions (blue solid line) are presented. The black horizontal dashed line indicates the MIC.



In the Bayesian Report, the typical and individual pharmacokinetic parameters can be retrieved. The PK/PD parameter is calculated for the entire therapy range that is displayed in the viewport in the Patient module or in the Bayesian Plot, visualized above.

Parameter	Unit	Description	Typical	Individual
1 CL	[L/h]	Drug Clearance	20.70	12.90
2 V1	[L]	Central Volume of Distribution	10.80	12.50
3 Q	[L/h]	Intercompartmental Clearance	18.60	17.90
4 V2	[L]	Peripheral Volume of Distribution	12.60	14.80
5 %fT>MIC	[%]	Percentage of observation period that unbound drug concentrations exceeds the MIC		87.10

Under Configure Population PK Model, the underlying population PK model can be modified (a reference to each original model is provided in under Disclaimer in each drug module). Changes are for recommended for research purposes only! This module is not available for all implemented drugs.

TDMx for Meropenem    Disclaimer    1. Patient    2. Probabilistic Dosing    3. Bayesian Dosing    4. Optimise Sampling    Advanced Opt. ▾

PK model  
 2 compartment IV infusion

**Warning: Modification of PK model recommended for research purposes only!**

**Available covariates:**  
 SEX\_i: Sex (male=0, female=1)  
 WT\_i: Weight (kg)  
 HT\_i: Height (cm)  
 AGE\_i: Age (yrs.)  
 CLCR\_i\_t: Creatinine Clearance (ml/min) (time-dependent)  
 SCR\_i\_t: Serum creatinine (mg/dL) (time-dependent)

**PK/Covariate model:**

Clearance (CL) [L/h] =

Intercompartmental Clearance (Q) [L/h] =

Central volume of distribution (V1) [L] =

Peripheral volume of distribution (V2) [L] =

**Interindividual variability of PK parameters:**

%CV(CL) =

%CV(Q) =

%CV(V1) =

%CV(V2) =

**Residual unexplained variability (RUV):**

Proportional RUV (%CV) =

Additive RUV [mg/L] =

Bayesian Fitting and Plot  
 Bayesian Report  
**Configure Population PK Model**

Here, the definitions of the pharmacokinetic parameter-covariate relationships are presented. The equations can be modified using the available covariates above.

Here, the values of the interindividual variability of the pharmacokinetic parameters are defined.

Here, the values of the intraindividual variability of the predicted vs. observed concentrations in an individual are defined.

