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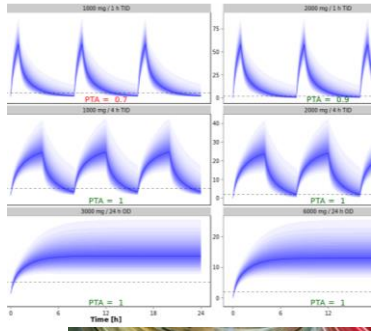

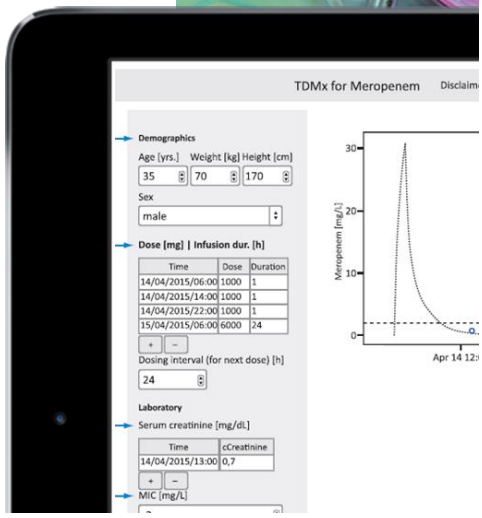

Bring your tablet – individualized antibiotic dosing with interactive case studies

Sebastian G. Wicha, Ph.D.

Junior Professor of Clinical Pharmacy
Department of Clinical Pharmacy
Institute of Pharmacy
University of Hamburg, Germany

ICID Congress
Buenos Aires, 3 March 2018

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Outline

- Introduction to
  - Therapeutic Drug Monitoring using Pharmacometrics
  - TDMx software as an example of a precision dosing tool

- Interactive case studies with
  - Piperacillin

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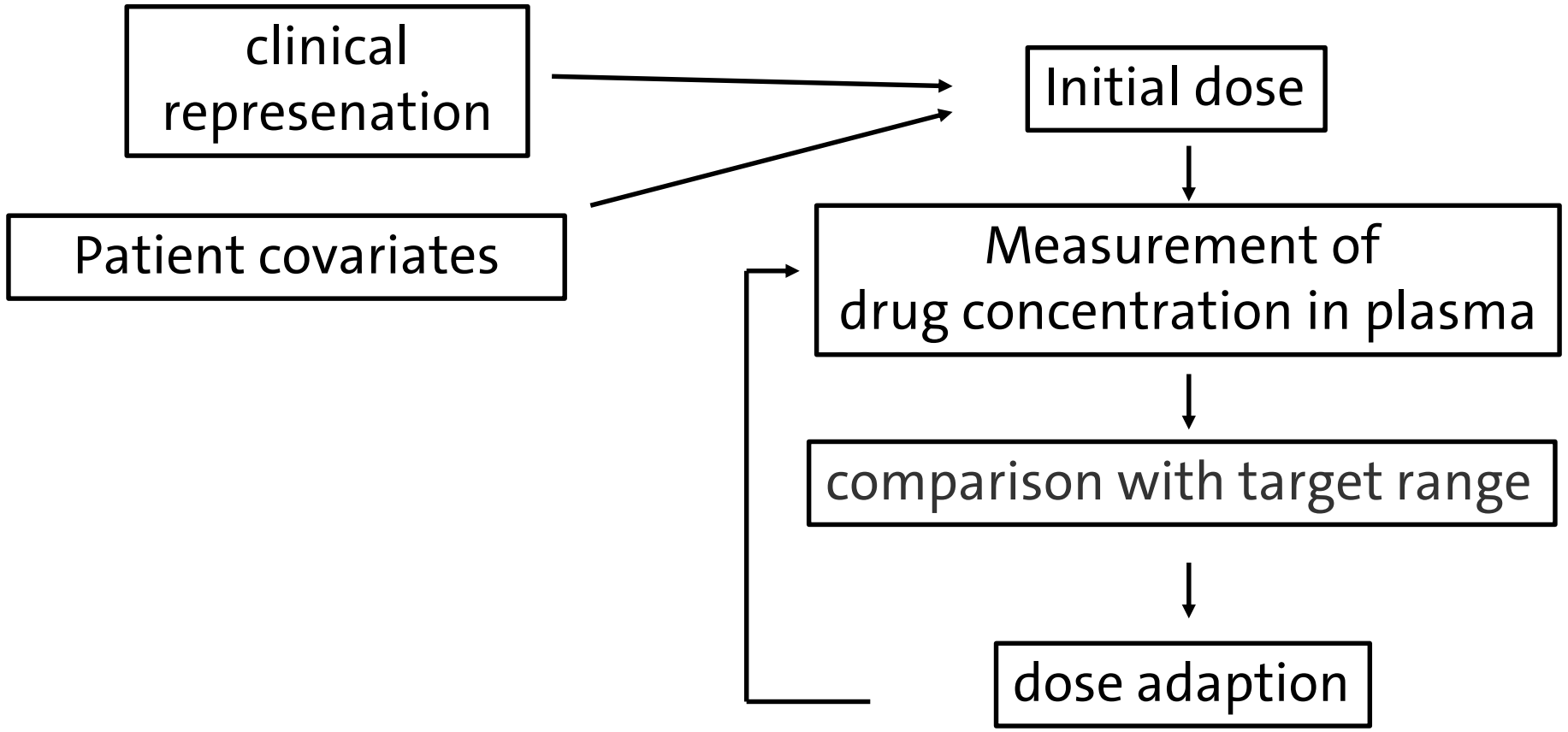
WiFi for interactive case studies

- Network: Sheraton Convention Center
- Password: ICID2018_guest

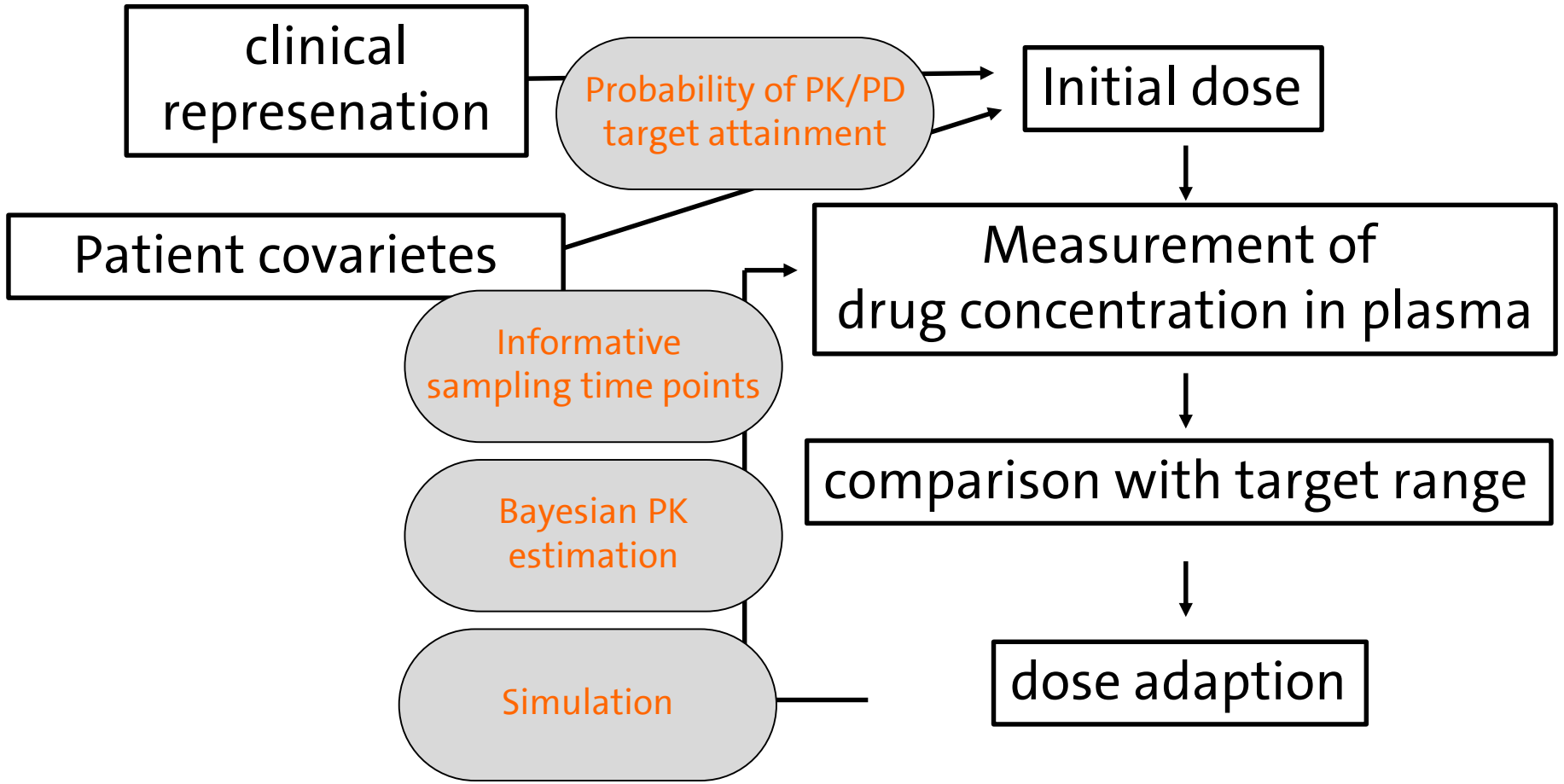
Therapeutic Drug Monitoring empowered by PharmacometrX

as an example software for model-based TDM

Therapeutic drug monitoring



Therapeutic drug monitoring
enhanced by pharmacometrics



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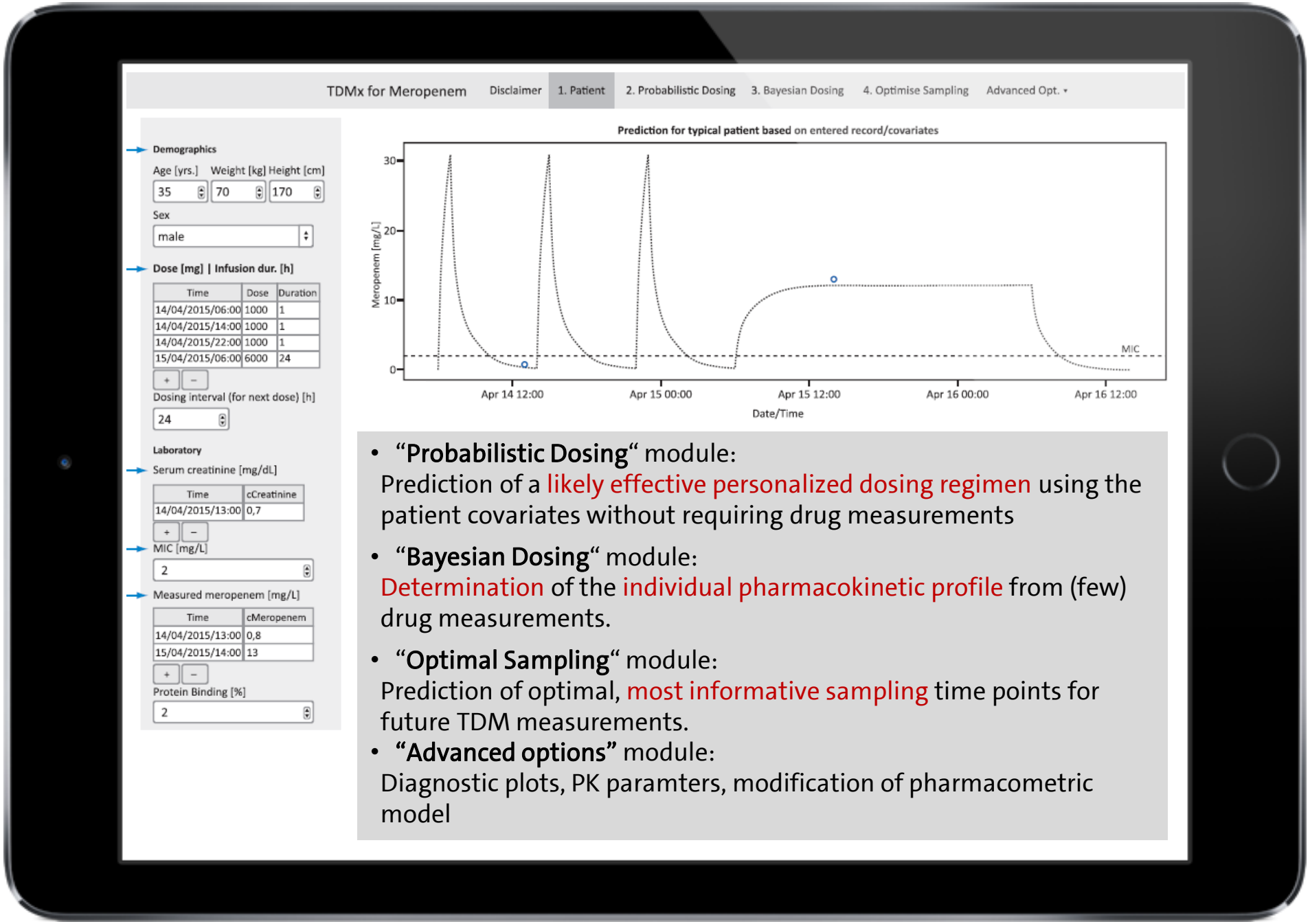

- "**Probabilistic Dosing**" module:
  Prediction of a likely effective personalized dosing regimen using the patient covariates without requiring drug measurements
- "**Bayesian Dosing**" module:
  Determination of the individual pharmacokinetic profile from (few) drug measurements.
- "**Optimal Sampling**" module:
  Prediction of optimal, most informative sampling time points for future TDM measurements.
- **"Advanced options"** module:
  Diagnostic plots, PK paramters, modification of pharmacometric model

Wicha SG et al. *Int J Antimicrob Agents*. 2015;45(4):442–444.

TDMx – workflow
exemplified by a patient

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TDMx – workflow: Probabilistic dosing
Determination of the initial dosing regimen

Patient:	H.S.
Age:	50 years
Weight:	100 kg
Height:	175 cm
Serum creatinine:	0.8 mg/dL
MIC of pathogen:	2 mg/L

Dose recommendation according to drug label: 1000 mg q8h (short-term infusion)

→ Evaluation by TDMx (”Probabilistic Dosing“)

TDMx – workflow: Probabilistic dosing
Determination of the initial dosing regimen

Demographics

Age [yrs.]	Weight [kg]	Height [cm]
50	100	175

Sex: male

Laboratory

Serum creatinine [mg/dL]

Time	cCreatinine
25/05/2015/13:00	0.8

+ -

MIC [mg/L]: 2

PK/PD Target (%fT>MIC)

TDMx – workflow: Probabilistic dosing

Determination of the initial dosing regimen

Demographics

Age [yrs.] 50 | Weight [kg] 100 | Height [cm] 175

Sex: male

Laboratory

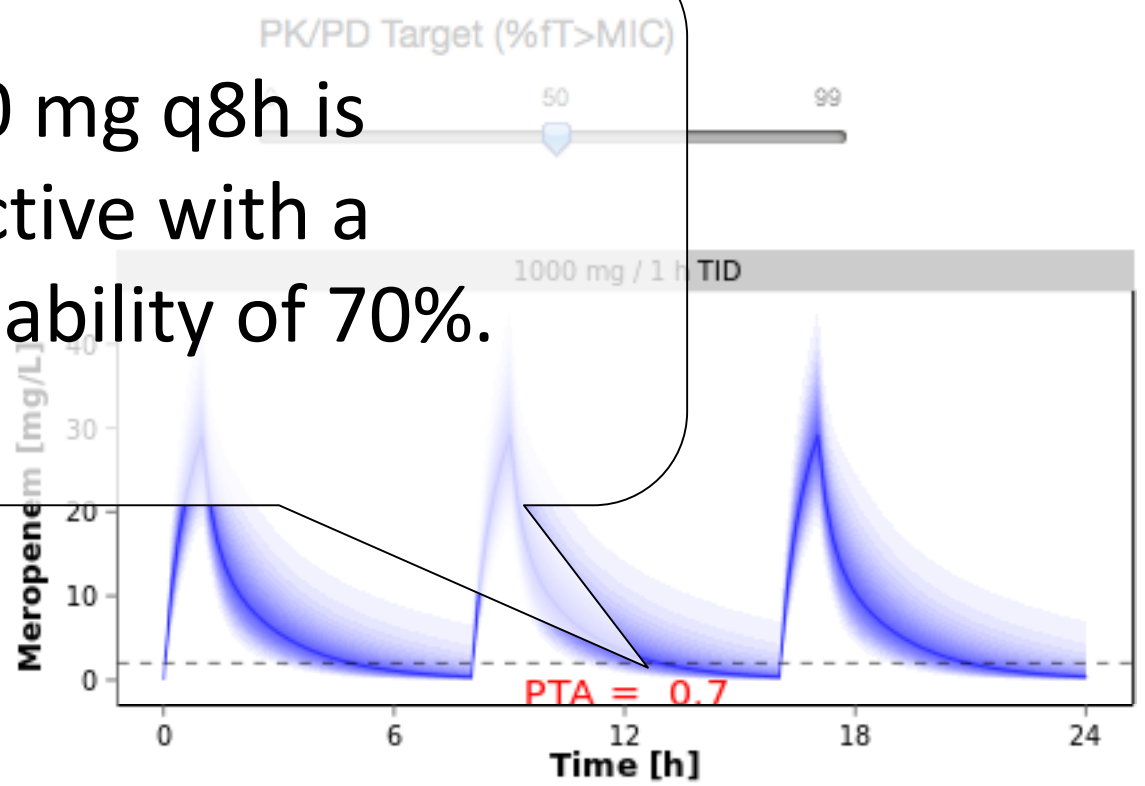
Serum creatinine [mg/dL]

Time	cCreatinine
25/05/2015/13:00	0.8

+ -

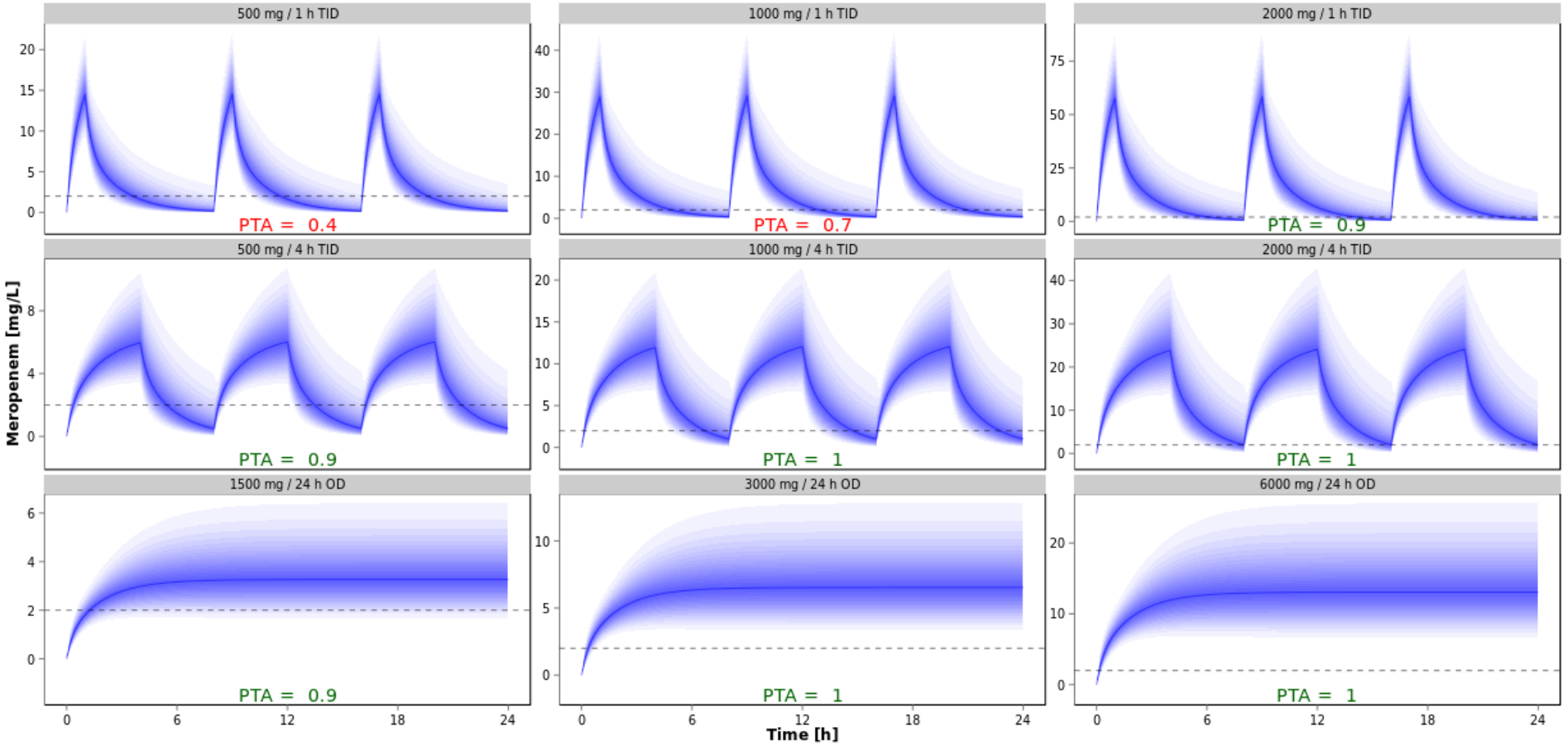
MIC [mg/L]: 2

1000 mg q8h is effective with a probability of 70%.



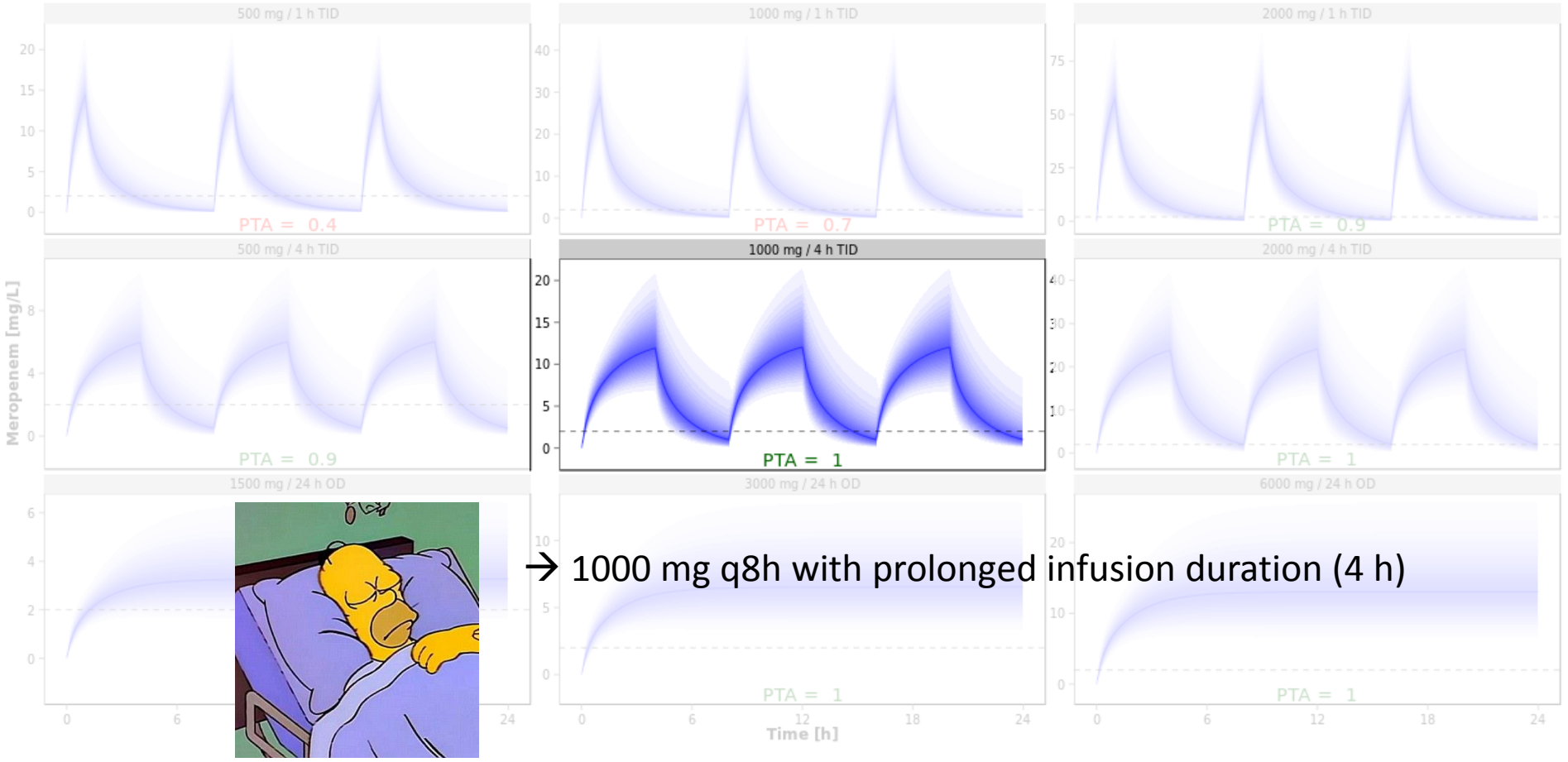
TDMx – workflow: Probabilistic dosing

Determination of the initial dosing regimen



Daily dose: 1500 mg 3000 mg 6000 mg

TDMx – workflow: Probabilistic dosing
Determination of the initial dosing regimen



→ 1000 mg q8h with prolonged infusion duration (4 h)

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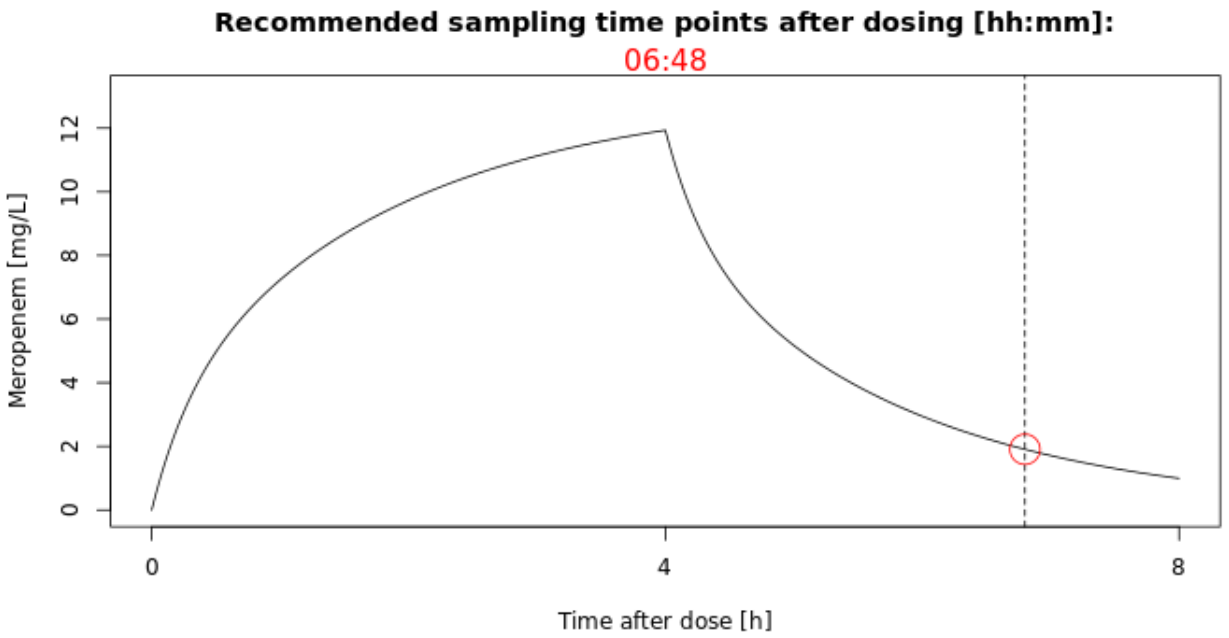
TDMx – workflow: Optimal sampling
Determination of $T_{>MIC}$

→ „Optimal Sampling“-Module




http://www.tu-pc.com/fondos/media/3482.jpg

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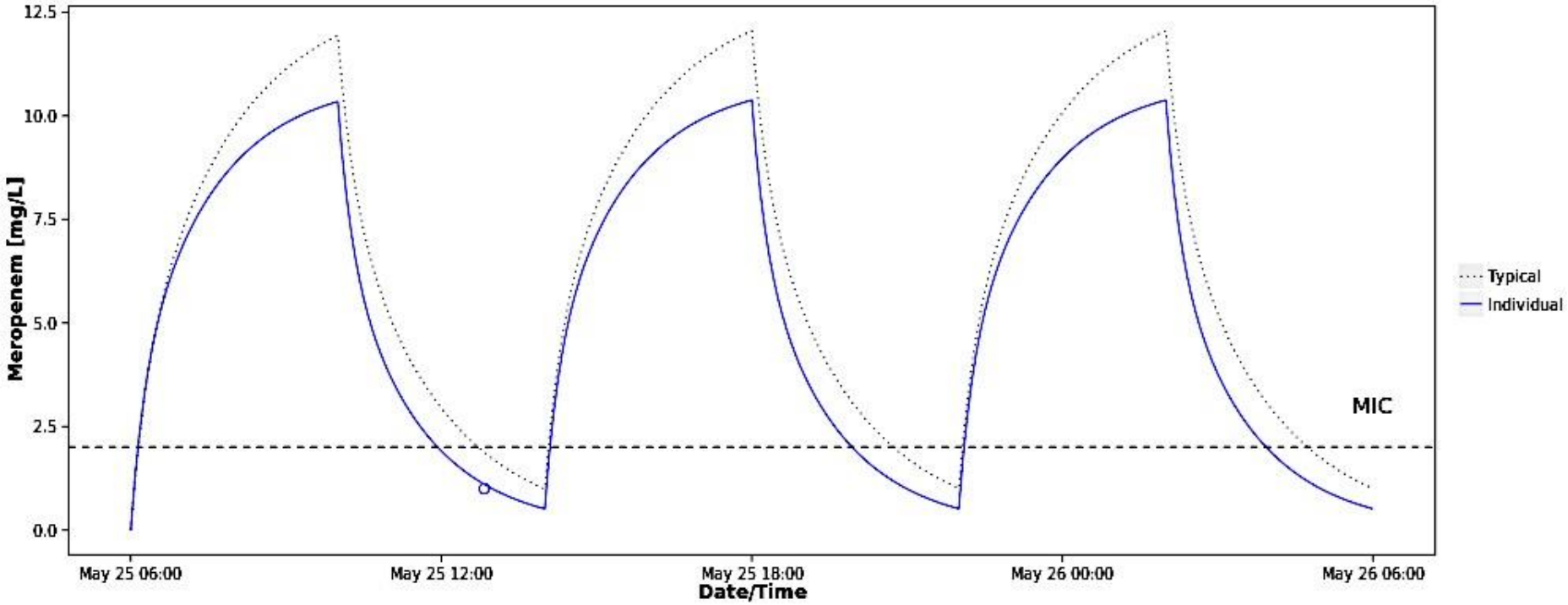
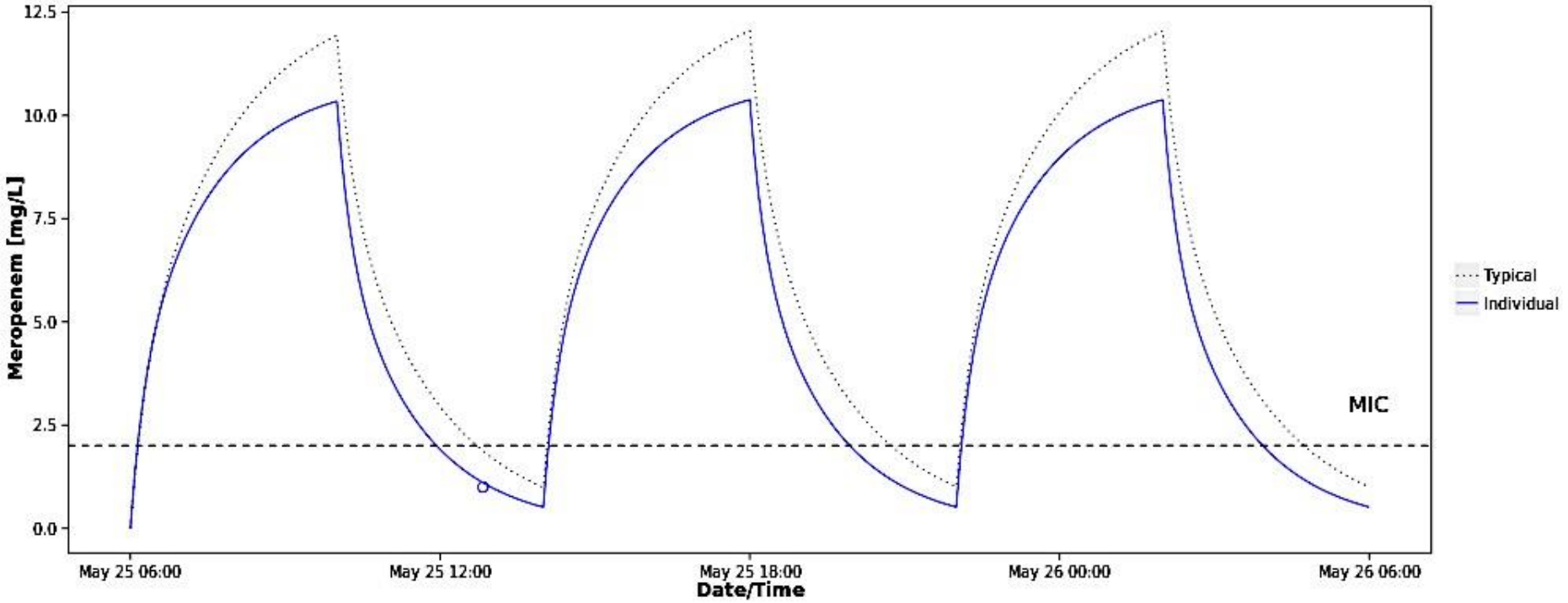
TDMx – workflow: Bayesian Dosing
Determination of the individual PK



	Parameter	Unit	Description	Typical	Individual
1	CL	[L/h]	Drug Clearance	19.10	22.90
2	V1	[L]	Central Volume of Distribution	15.40	14.40
3	Q	[L/h]	Intercompartimental Clearance	18.60	18.80
4	V2	[L]	Peripheral Volume of Distribution	12.60	11.90
5	%fT>MIC	[%]	Percentage of observation period that unbound drug concentrations exceeds the MIC		72.40

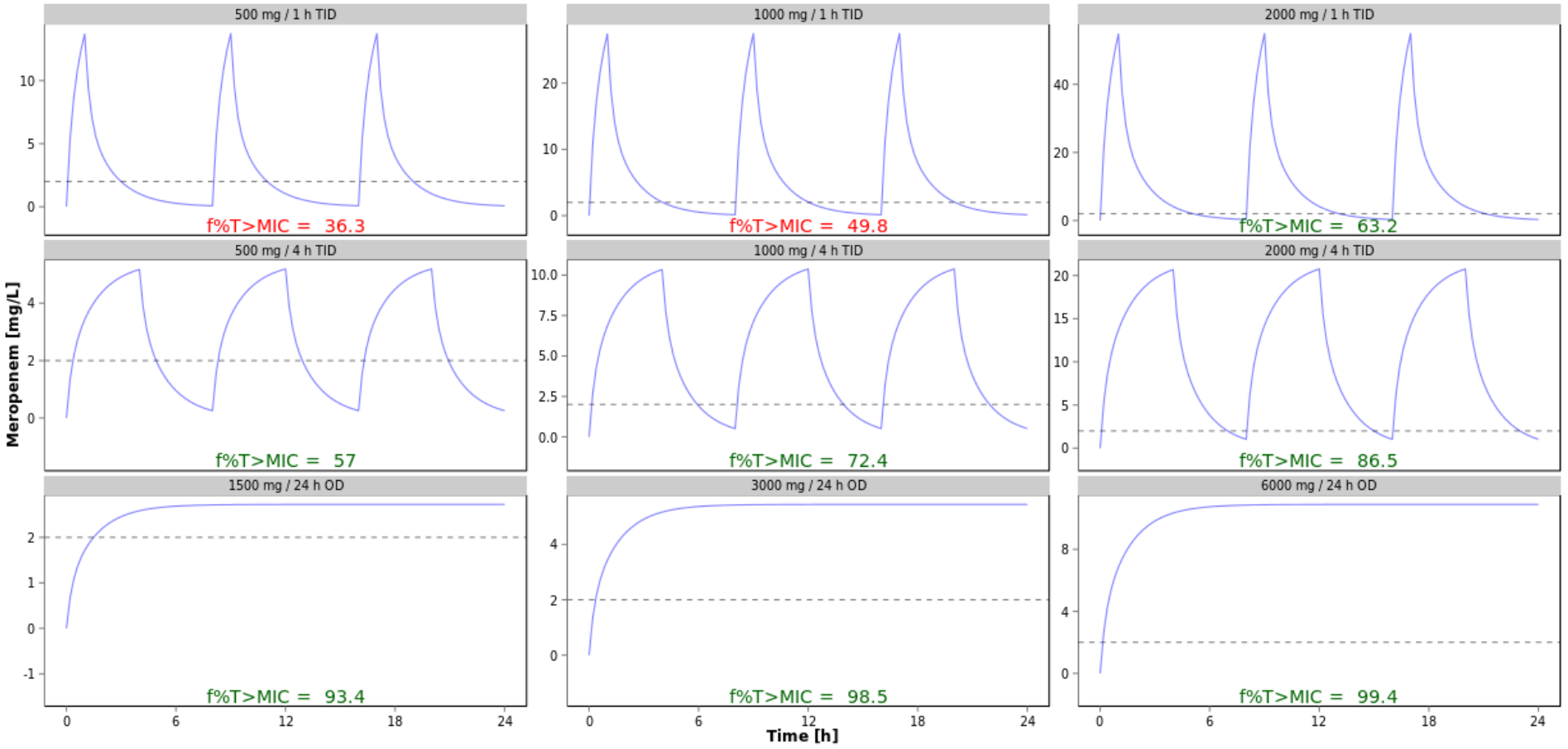
TDMx – workflow: Bayesian Dosing
Determination of the individual PK



	Parameter	Unit	Description	Typical	Individual
1	CL	[L/h]	Drug Clearance	19.10	22.90
2	V1	[L]	Central Volume of Distribution	15.40	14.40
3	Q	[L/h]	Intercompartimental Clearance	18.60	18.80
4	V2	[L]	Peripheral Volume of Distribution	12.60	11.90
5	%fT>MIC	[%]	Percentage of observation period that unbound drug concentrations exceeds the MIC		72.40

TDMx – workflow: Bayesian Dosing
Evaluation of alternative dosages

→ „Bayesian-Dosing“-Module



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Patient Case Work
Piperacillin

Piperacillin

Journal of Antimicrobial Chemotherapy (2005) **56**, 388–395
doi:10.1093/jac/dki243
Advance Access publication 7 July 2005

JAC

Population pharmacokinetics and pharmacodynamics of piperacillin/tazobactam in patients with complicated intra-abdominal infection

Chonghua Li[1], Joseph L. Kuti[1], Charles H. Nightingale[1], Debra L. Mansfield[2], Adrian Dana[2] and David P. Nicolau[1]*

[1]*Center for Anti-Infective Research and Development, Hartford Hospital, 80 Seymour Street, Hartford, CT 06102, USA;* [2]*Wyeth Pharmaceuticals, Collegeville, PA 19426, USA*

Explore the impact of the patient covariates on PK

→ Creatinine Clearance (CL_{CR})

→ Body weight

Table 2. Piperacillin final population model parameter estimates

	Pharmacokinetic structural model[a]		
Parameter	Population estimate	SE[b]	RSE (%)[c]
Clearance (L/h)	$CL = \theta_1 + \theta_2 \times CL_{CR}/89$		
θ_1	5.05	1.24	24.55
θ_2	9.60	1.67	17.40
interindividual variability	27.7%	0.0169	21.98
Volume of distribution (L)	$V = \theta_3 \times WT/81.8$		
θ_3	22.3	1.57	7.04
interindividual variability	25.2%	0.0329	51.65
Residual error model			
proportional	18.5%	0.0126	36.73
additive	1.77 mg/L	3.01	96.17

[a]AIC value of the final model was 993.04.
[b]SE, standard error of θ_1, θ_2 and θ_3; and standard error of the variance of the interindividual variability and residual errors.
[c]RSE, relative standard error.

www.tdmx.eu

TDMx

WELCOME | LAUNCH TDMX | FEATURES | FAQ | TEAM | NEWS | CONTACT US | RESOURCES | LEGAL NOTICES

Therapeutic Drug Monitoring
empowered by PharmacometrX

Launch Pad

Connect to **TDMx** by clicking on the respective drug. The **TDMx** software program will open in a new browser tab.

Antibiotics

General ward

- Meropenem
- Piperacillin
- Gentamicin
- Amikacin
- Tobramycin

Special Populations

- Gentamicin in neonates (NeoGent)
- Gentamicin in peadiatric oncology

Server status message

OK

EVENTS

November 2017

TDMx at "CRE reduce - dose optimization workshop" in Sydney, November 15 2017. See you there!

March 2018

TDMx at the ICID congress in Buenos Aires, Argentina on March 3, 2018. See you there! More info.

NEWS

September 2017

New model: Gentamicin in pediatric oncology patients. For more news, see here.

Demographics

Age [yrs.] 35

Weight [kg] 50

Height [cm] 170

Sex

male

Dose [mg] | Infusion dur. [h]

Time	Dose	Duration
25/02/2018/06:00	4000	0.5

\+ -

Dosing interval (for next dose) [h]

8

Laboratory

Serum creatinine [mg/dL]

Time	cCreatinine
25/02/2018/13:00	0.7

\+ -

MIC [mg/L]

2

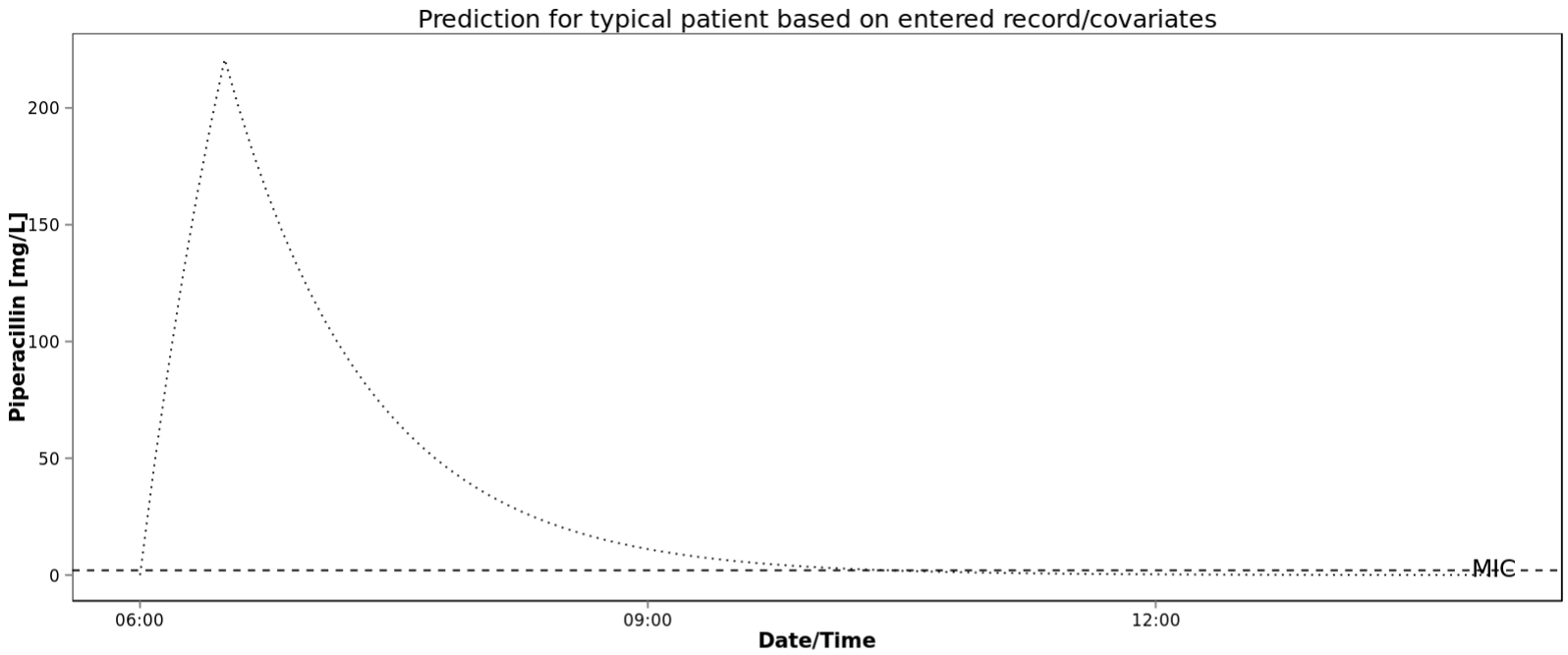
Measured piperacillin [mg/L]

Time	cPiperacillin
25/02/2018/13:00	

\+ -

Protein Binding [%]

20



Demographics

Age [yrs.] 35

Weight [kg] 100

Height [cm] 170

Sex

male

Dose [mg] | Infusion dur. [h]

Time	Dose	Duration
25/02/2018/06:00	4000	0.5

\+ -

Dosing interval (for next dose) [h]

8

Laboratory

Serum creatinine [mg/dL]

Time	cCreatinine
25/02/2018/13:00	0.7

\+ -

MIC [mg/L]

2

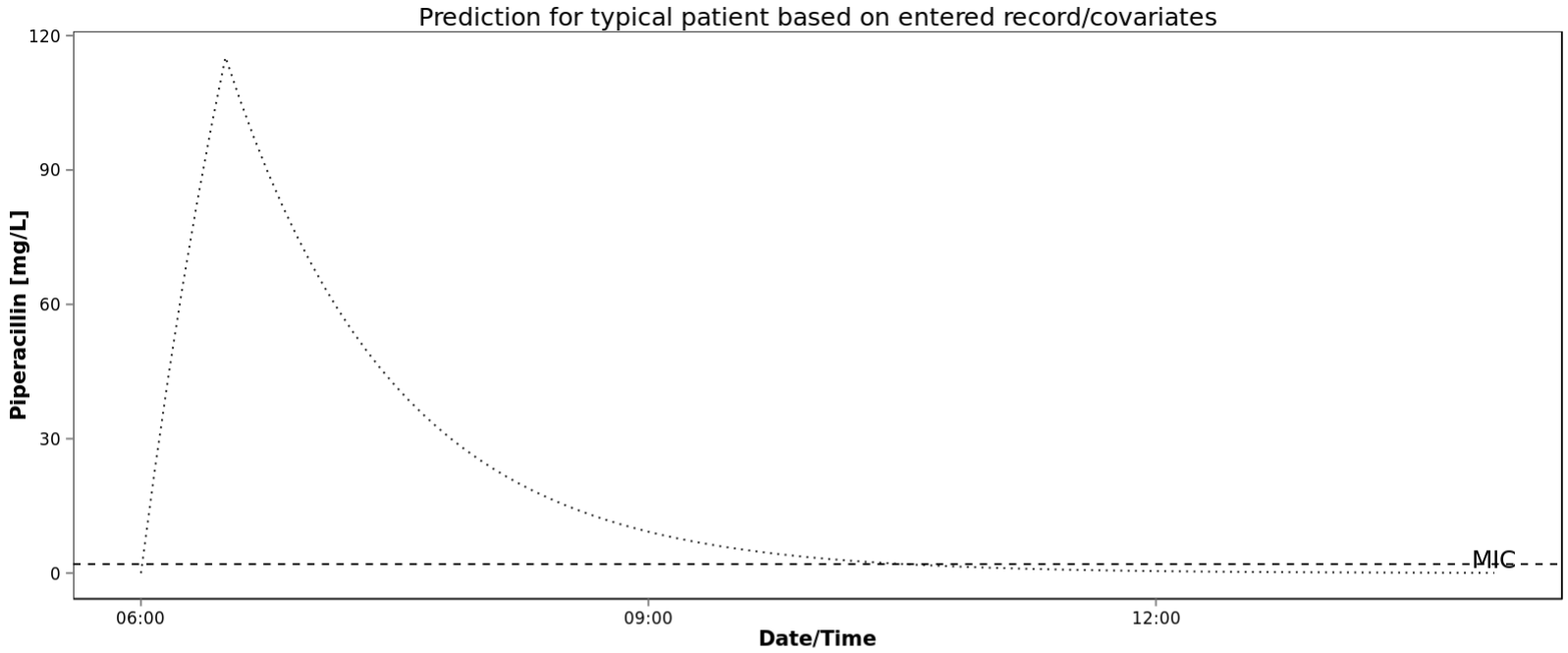
Measured piperacillin [mg/L]

Time	cPiperacillin
25/02/2018/13:00	

\+ -

Protein Binding [%]

20



Demographics

Age [yrs.] 35

Weight [kg] 70

Height [cm] 170

Sex: male

Dose [mg] | Infusion dur. [h]

Time	Dose	Duration
25/02/2018/06:00	4000	0.5

\+ -

Dosing interval (for next dose) [h]: 8

Laboratory

Serum creatinine [mg/dL]

Time	cCreatinine
25/02/2018/13:00	0.7

\+ -

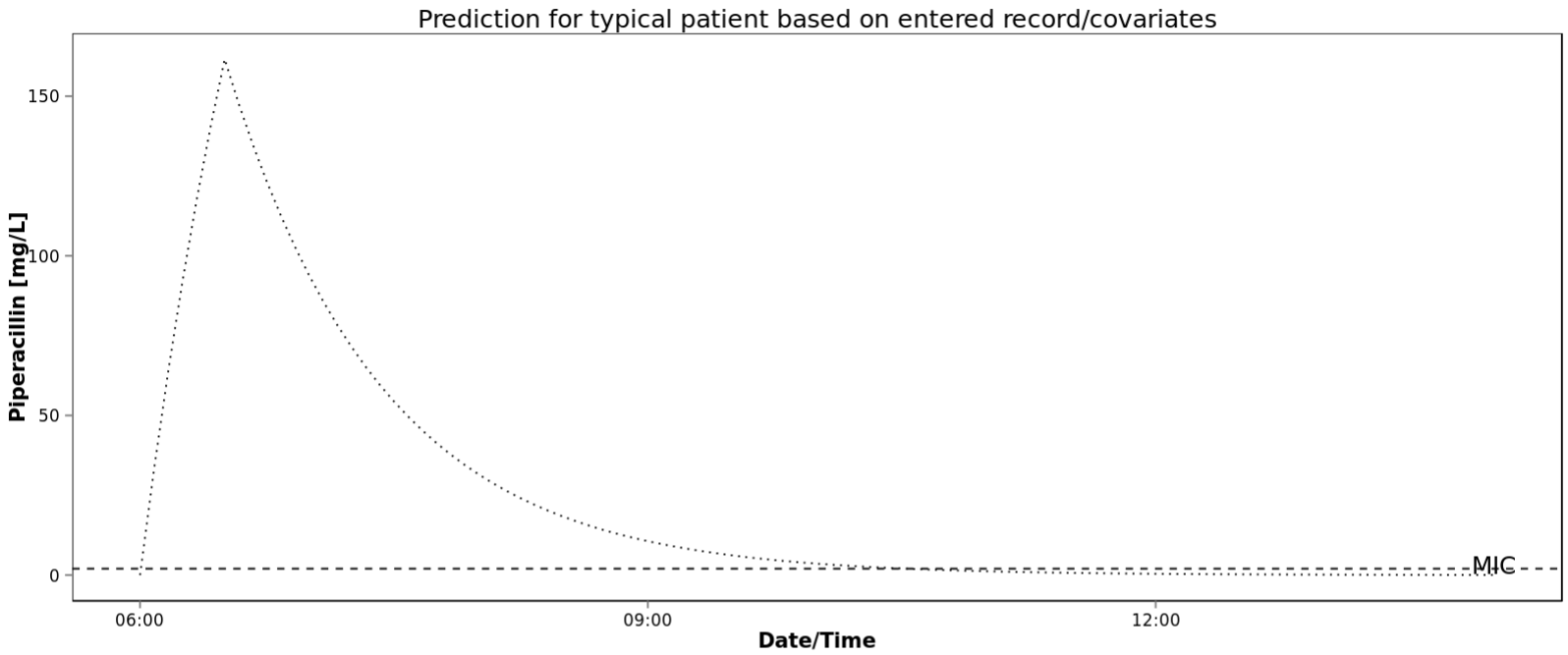
MIC [mg/L]: 2

Measured piperacillin [mg/L]

Time	cPiperacillin
25/02/2018/13:00	

\+ -

Protein Binding [%]: 20



= Creatinine Clearance of 146 mL/min

Demographics

Age [yrs.] 35

Weight [kg] 70

Height [cm] 170

Sex: male

Dose [mg] | Infusion dur. [h]

Time	Dose	Duration
25/02/2018/06:00	4000	0.5

\+ -

Dosing interval (for next dose) [h]: 8

Laboratory

Serum creatinine [mg/dL]

Time	cCreatinine
25/02/2018/13:00	2.2

\+ -

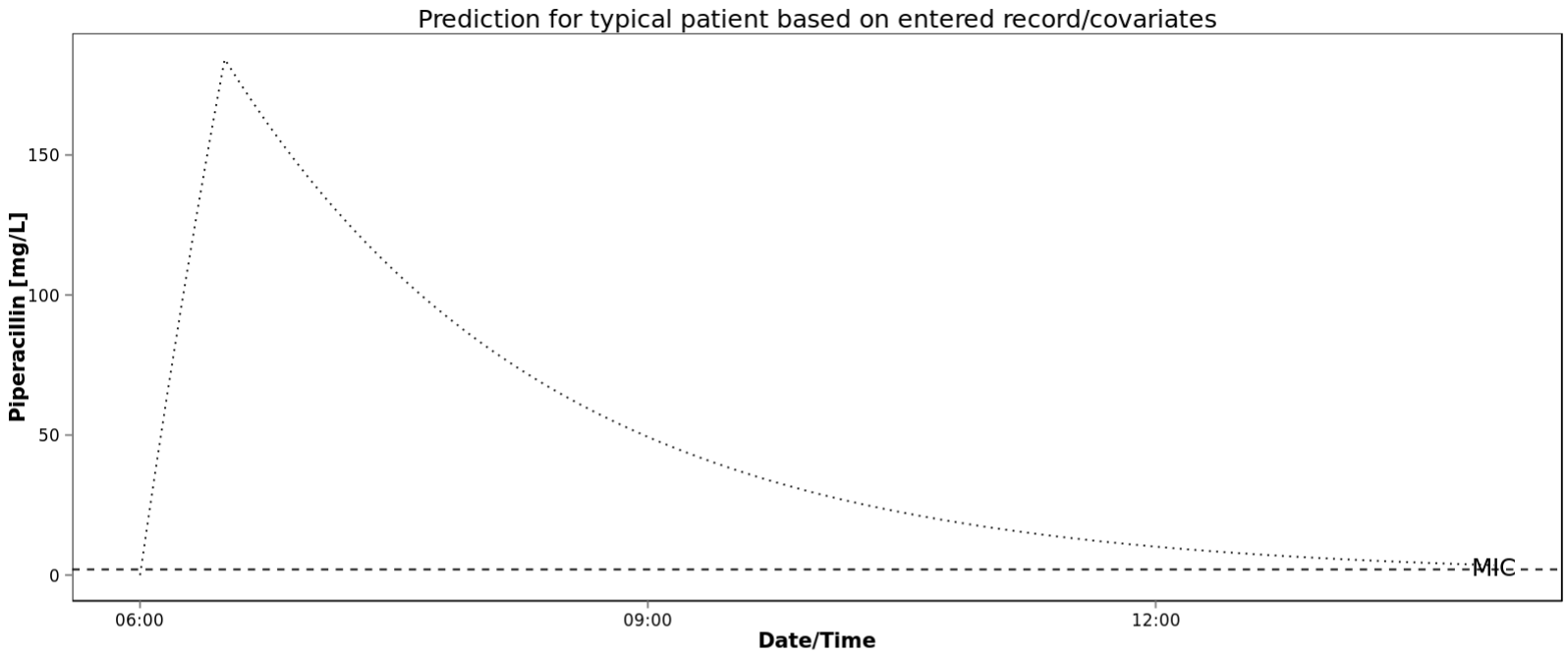
MIC [mg/L]: 2

Measured piperacillin [mg/L]

Time	cPiperacillin
25/02/2018/13:00	

\+ -

Protein Binding [%]: 20



= Creatinine Clearance of 46 mL/min

Patient Case I
Piperacillin

A male patient (56 yrs., body weight 85 kg, body height 182 cm) is hospitalized due to a severe hospital-acquired pneumonia and treatment with 'the standard' 4 g piperacillin/0.5 g tazobactam administered as 30 min intravenous infusion every 8 h is planned. Clinical chemistry at admission confirms inflammation (CRP 281 mg/dL) and the serum creatinine level was determined to 0.78 mg/dL.

- Evaluate the standard dosing regimen with TDMx using 'Probabilistic Dosing' and the pre-defined MIC of 2 mg/L!
  - Explore different target values
    - Conservative $fT_{>MIC}$: 40%
    - Intermediate $fT_{>MIC}$: 80%
    - Aggressive: $fT_{>MIC}$: 99%

Demographics

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

56 85 182

Sex

male

Dose [mg] | Infusion dur. [h]

Time	Dose	Duration
03/03/2018/06:00	4000	0.5

+ -

Dosing interval (for next dose) [h]

8

Laboratory

Serum creatinine [mg/dL]

Time	cCreatinine
03/03/2018/13:00	0.7

+ -

MIC [mg/L]

2

Measured piperacillin [mg/L]

Time	cPiperacillin
03/03/2018/13:00	

+ -

Protein Binding [%]

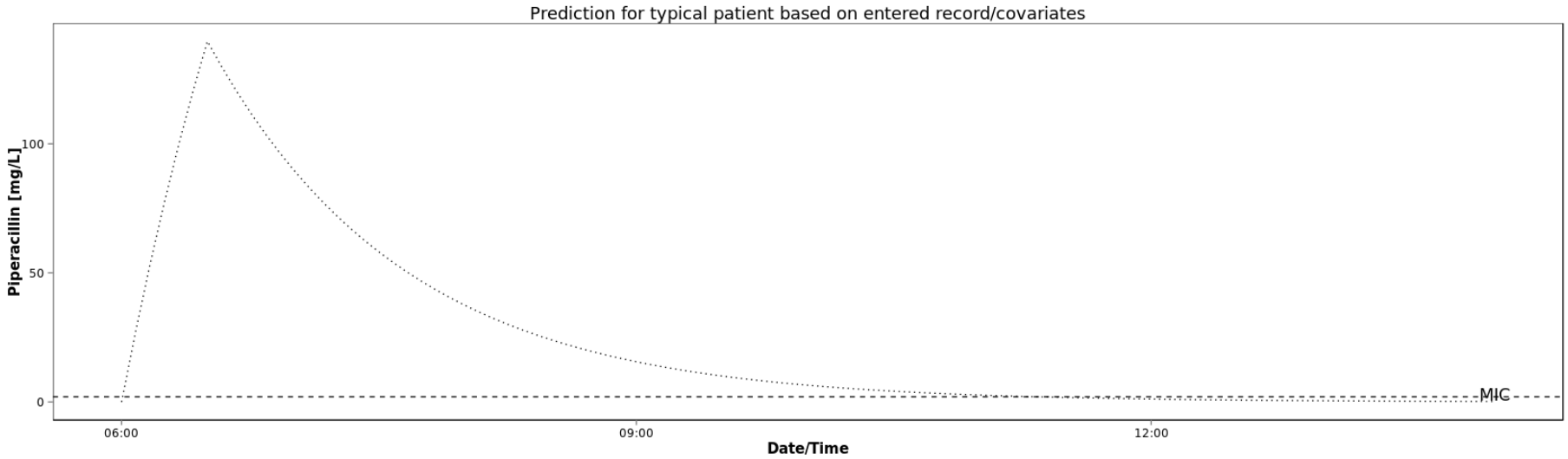
20

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

Dose [mg]

Infusion duration [h]

cPiperacillin [mg/L]



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

PK/PD Target (%fT>MIC)

0 40 99

calculate

Select dosing regimens to be evaluated by probabilistic dosing:

BID scenarios

4 g / 0.5 h BID | 4 g / 6 h BID

TID scenarios

4 g / 0.5 h TID | 4 g / 4 h TID

QID scenarios

4 g / 0.5 h QID | 4 g / 3 h QID

Continuous scenarios

8 g / 24 h SID | 12 g / 24 h SID | 16 g / 24 h SID

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

PK/PD Target (%fT>MIC)

0 40 99

calculate

Select dosing regimens to be evaluated by probabilistic dosing:

BID scenarios

TID scenarios

4 g / 0.5 h TID

QID scenarios

Continuous scenarios

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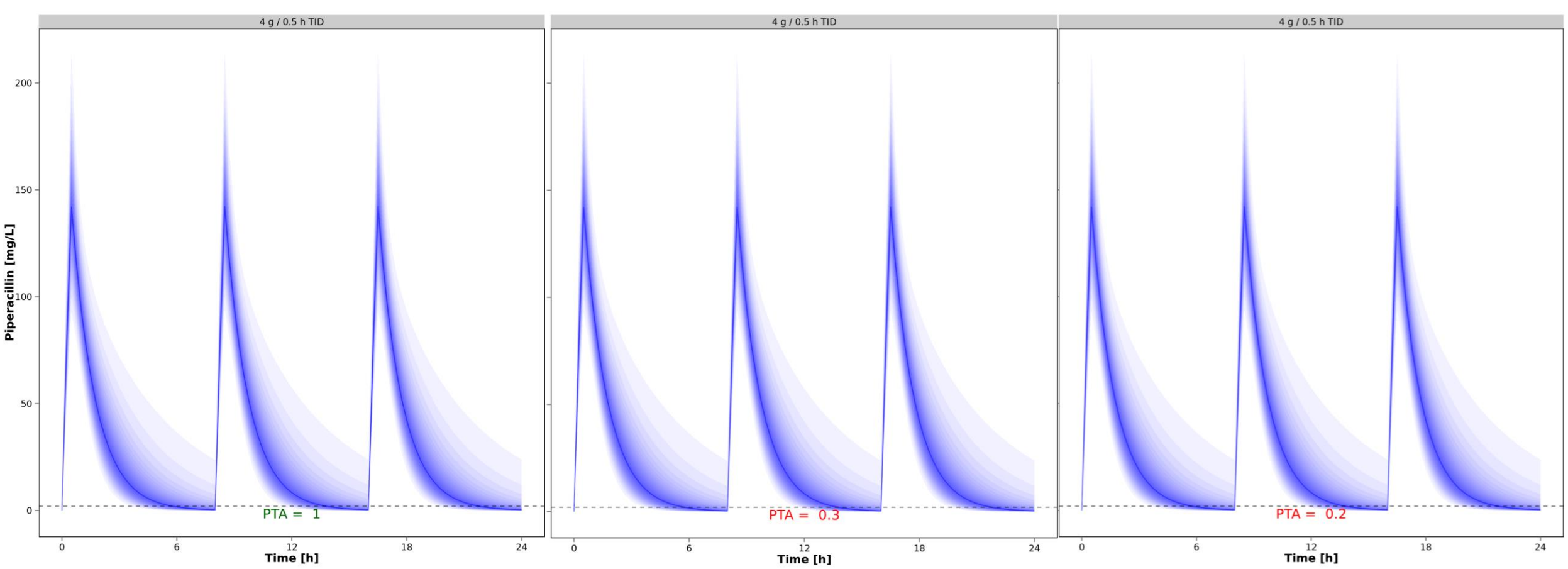
Patient Case I
Piperacillin

$fT_{>MIC}$: 40%

$fT_{>MIC}$: 80%

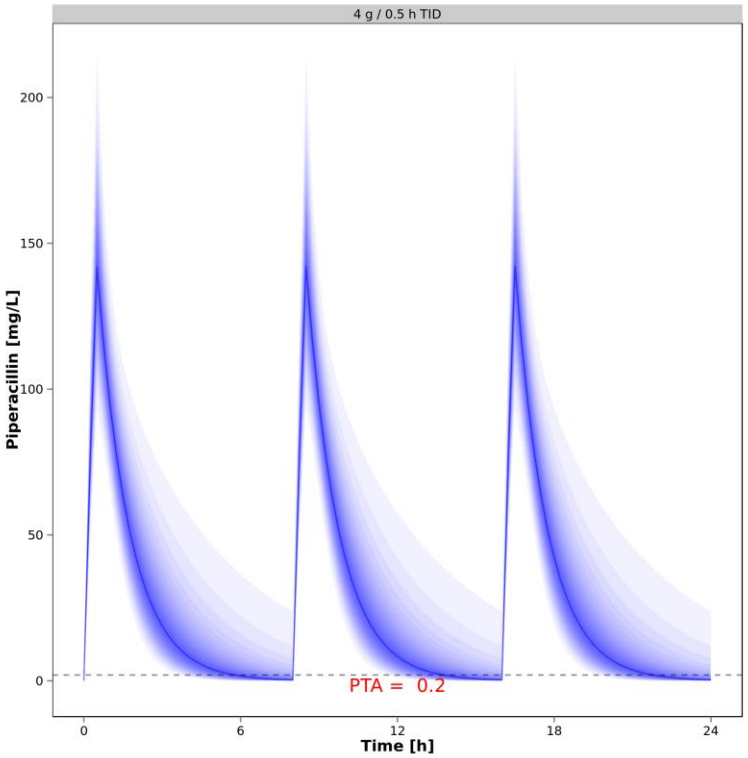
$fT_{>MIC}$: 99%



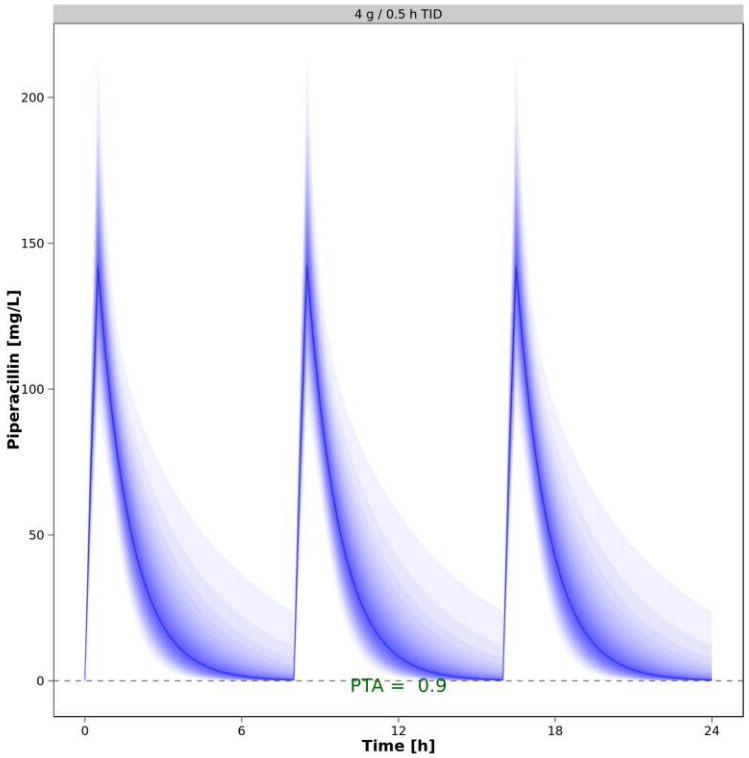
Patient Case I
Piperacillin

- Explore the impact of MIC on the attainment of the aggressive target. At which MIC value does therapy become likely effective (i.e. PTA >0.9)

MIC: 2 mg/L



MIC: 0.016 mg/L



Patient Case I
Piperacillin

- Therapy was initiated with 4g q8h regimen as follows

Dosing time	Dose (mg)	Infusion duration (h)
03/03/2018/06:05	4000	0.5
03/03/2018/14:10	4000	0.5
03/03/2018/22:08	4000	0.5

- The following piperacillin concentration were determined

Sampling time	Piperacillin (mg/L)
03/03/2018/15:05	100.9
03/03/2018/16:55	11.4
03/03/2018/18:20	3.8

- MIC of a P. aeruginosa isolate was 1.0 mg/L

Demographics

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

56 85 182

Sex

male

Dose [mg] | Infusion dur. [h]

Time	Dose	Duration
03/03/2018/06:05	4000	0.5
03/03/2018/14:10	4000	0.5
03/03/2018/22:08	4000	0.5

\+ -

Dosing interval (for next dose) [h]

8

Laboratory

Serum creatinine [mg/dL]

Time	cCreatinine
03/03/2018/13:00	0.78

\+ -

MIC [mg/L]

1

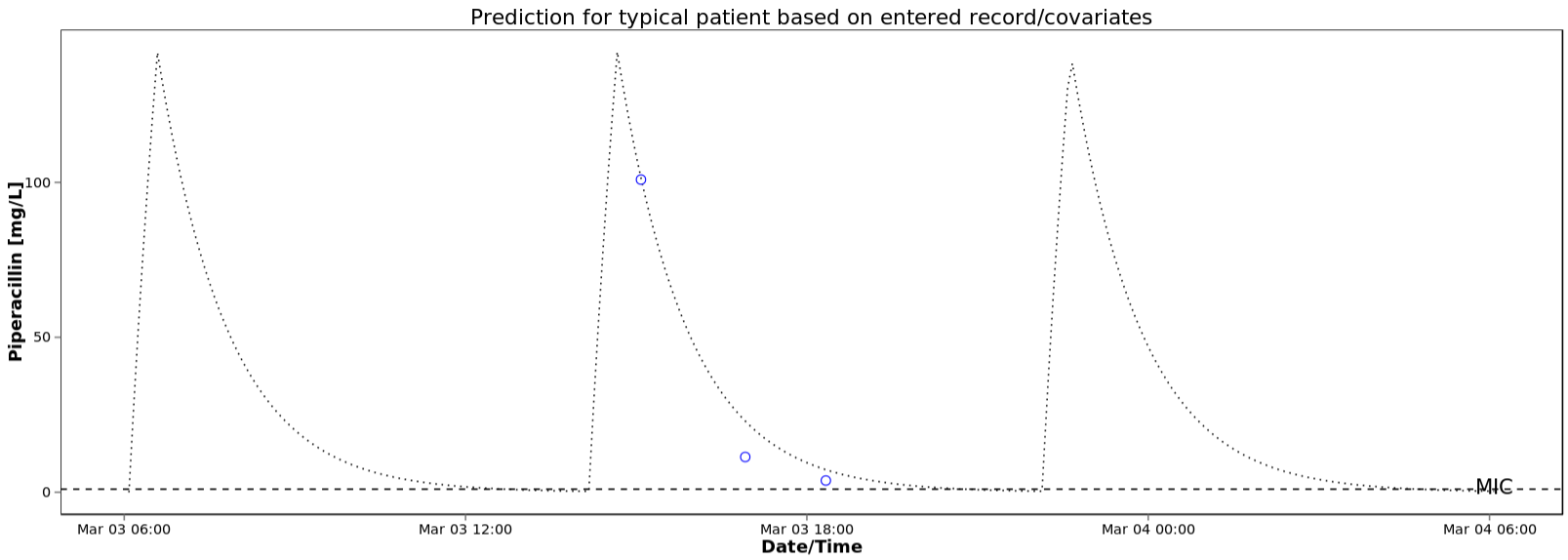
Measured piperacillin [mg/L]

Time	cPiperacillin
03/03/2018/15:05	100.9
03/03/2018/16:55	11.4
03/03/2018/18:20	3.8

\+ -

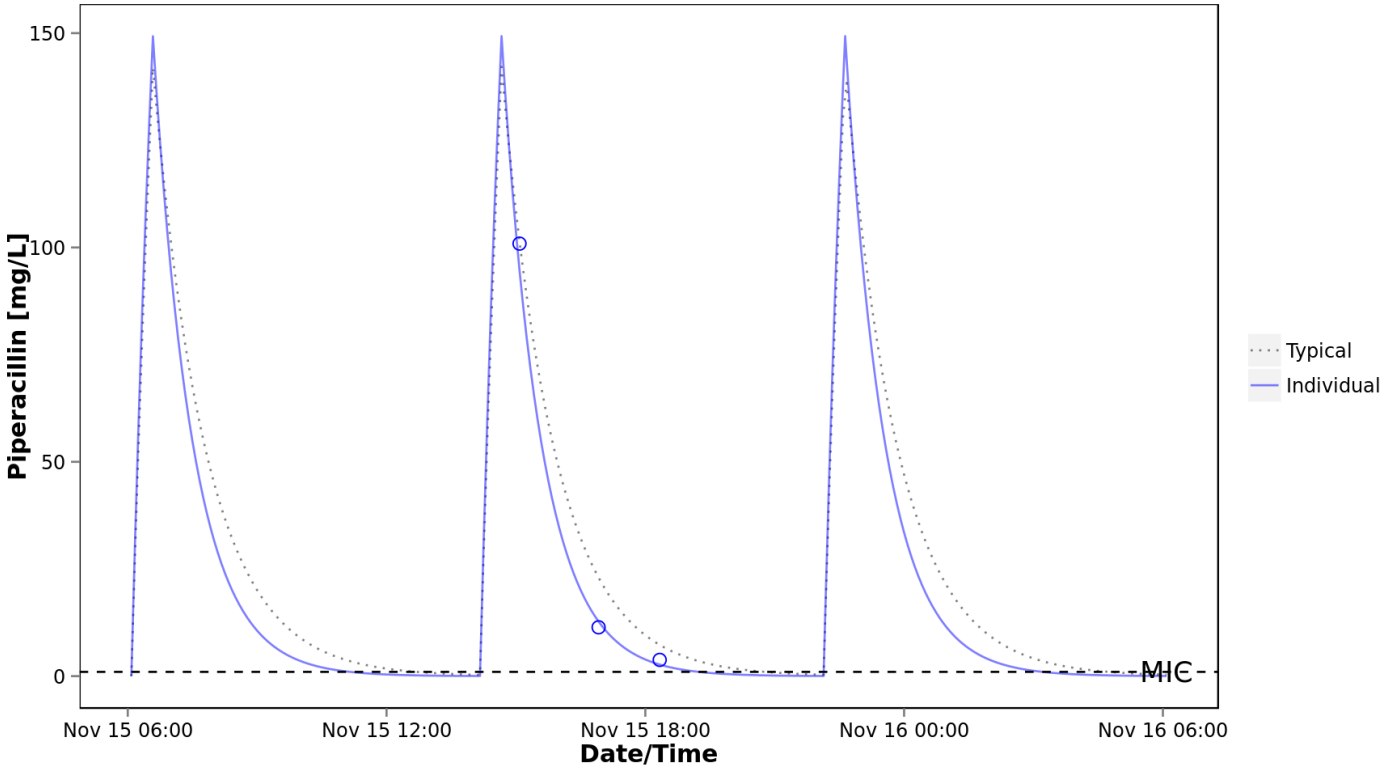
Protein Binding [%]

20



Patient Case I
Piperacillin

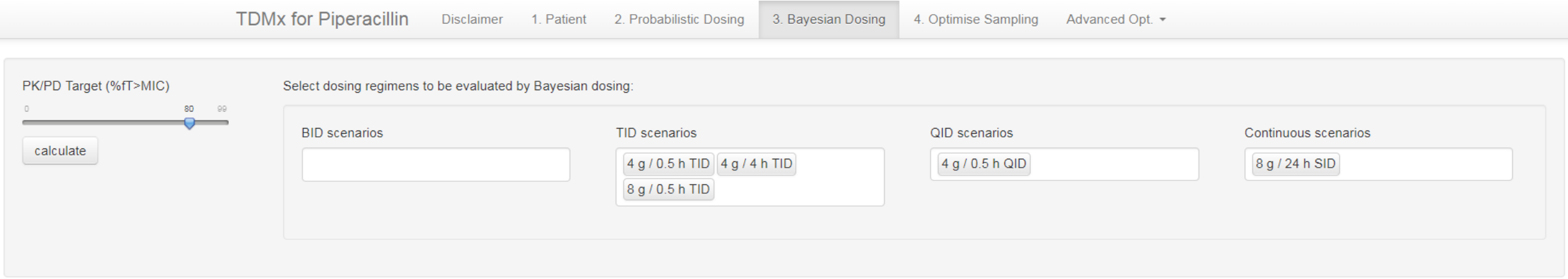
- Advanced users: Inspect the results of the Bayesian estimation



	Parameter	Unit	Description	Typical	Individual
1	CL	[L/h]	Drug Clearance	18.80	22.60
2	V1	[L]	Central Volume of Distribution	23.20	20.60
3	Half-life	[h]	Elimination half-life	0.86	0.63
4	%fT>MIC	[%]	Percentage of observation period that unbound drug concentrations exceed the MIC		60.90

Patient Case I Piperacillin

- Which regimen provides the highest %T>MIC?
  - 4g infused over 0.5 h three times daily (TID) (total daily dose: 12 g)
  - 4 g infused over 4 h three times daily (TID) (total daily dose: 12 g)
  - 8g infused over 0.5 h three times daily (TID) (total daily dose: 24 g)
  - 4g infused over 0.5 h four times daily (QID) (total daily dose: 16 g)
  - 8 g infused over 24 h once daily (SID) (total daily dose: 8 g)


TDMx for Piperacillin
Disclaimer
1. Patient
2. Probabilistic Dosing
3. Bayesian Dosing
4. Optimise Sampling
Advanced Opt.
PK/PD Target (%fT>MIC)
0
80
99
calculate
Select dosing regimens to be evaluated by Bayesian dosing:
BID scenarios
TID scenarios
4 g / 0.5 h TID
4 g / 4 h TID
8 g / 0.5 h TID
QID scenarios
4 g / 0.5 h QID
Continuous scenarios
8 g / 24 h SID

PK/PD Target (%fT>MIC)

0 80 99

calculate

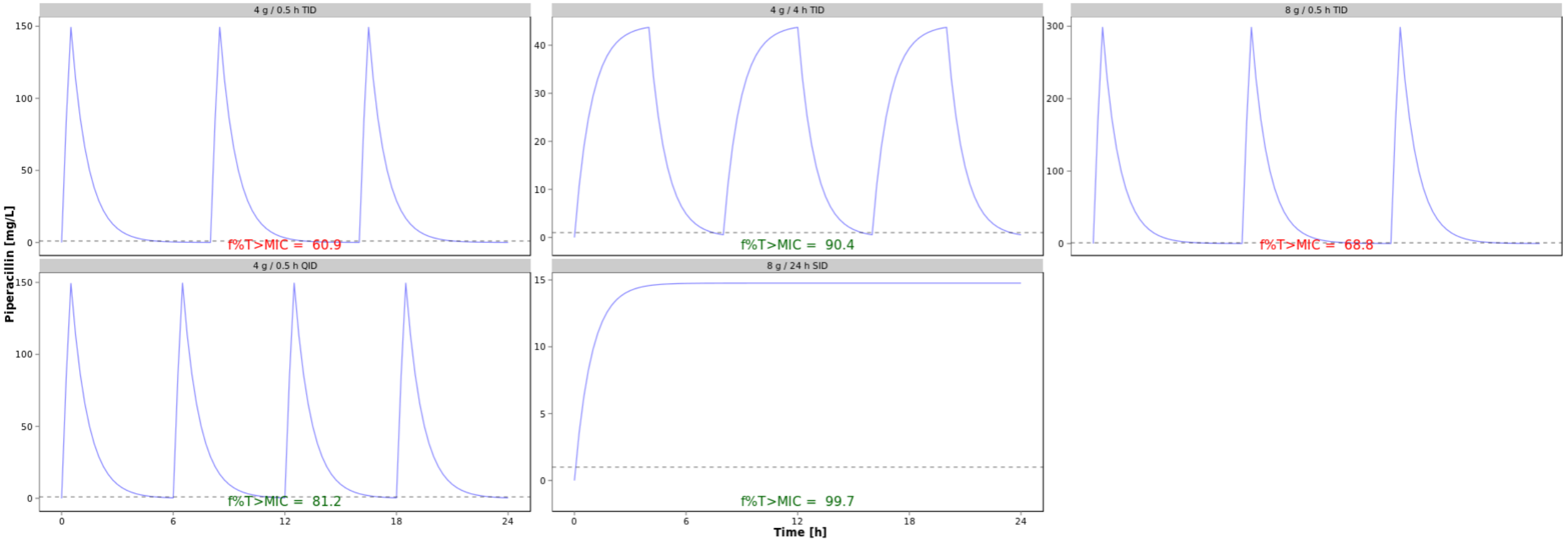
Select dosing regimens to be evaluated by Bayesian dosing:

BID scenarios

TID scenarios: 4 g / 0.5 h TID | 4 g / 4 h TID | 8 g / 0.5 h TID

QID scenarios: 4 g / 0.5 h QID

Continuous scenarios: 8 g / 24 h SID



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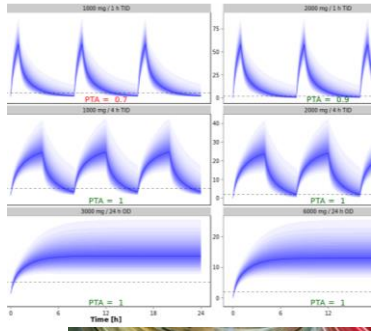
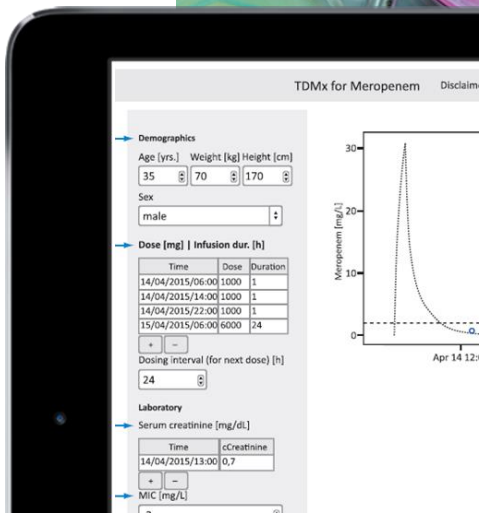
Conclusion





- Pharmacometrics is the method of choice to build quantitative relationships between pharmacokinetics and pharmacodynamics
- Pharmacometric techniques can enhance therapeutic drug monitoring and ease dose adjustment
  - No need to wait for steady state
  - More precise dose adjustments than conventional methods
- Consider TDM in
  - Critically-ill/trauma patients
  - Risk settings for high MIC values
- Easy to use software to facilitate bedsite dose adjustments is available