TDMx – a web-based paradigm for model-supported personalised therapeutic drug monitoring

Sebastian G. Wicha

Dept. of Clinical Pharmacy and Biochemistry
Institute of Pharmacy
Freie Universität Berlin

PKUK, Chester, UK
November 19, 2015
Therapeutic Drug Monitoring empowered by Pharmacometrix

pronounced: ‘TDMetrics’
Therapeutic drug monitoring

1. Initial dose
2. Measurement of drug concentration in plasma
3. Comparison with target range
4. Dose adaption

- Clinical representation
- Patient covariates
The population approach

http://feelgrafix.com/data_images/out/26/953258-simpsons.jpg
The population approach
The population approach

drug concentration

http://feelgrafix.com/data_images/out/26/953258-simpsons.jpg
http://images.clipartpanda.com/needle-clipart-hypodermic-needle.gif

Typical patient
The population approach

typical patient interindividual variability
The population approach

typical patient
interindividual variability
residual variability
The population approach

Impact of Patient covariates
Body weight, renal function, ...

typical patient
interindividual variability
residual variability

http://feelgrafix.com/data_images/out/26/953258-simpsons.jpg
http://images.clipartpanda.com/needle-clipart-hypodermic-needle.gif
The population approach

Numerous population PK models are available for antibiotics:

→ **135** PubMed hits within 2005-2015!*

→ How to better exploit this knowledge?

* (population pharmacokinetics[Title/Abstract]) AND antibiotics[MeSH Terms]
  search date: 20.5.2015
Therapeutic drug monitoring enhanced by pharmacometrics

Clinical representation

Patient covariates

Initial dose

Measurement of drug concentration in plasma

Comparison with target range

Dose adaption

Probability of PK/PD target attainment

Informative sampling time points

Bayesian PK estimation

Simulation
TDMx – modules

- **Patient** module:
  Data entry (patient covariates, laboratory, dosing record)

- **Probabilistic Dosing** module:
  Prediction of a likely effective dosing regimen without requiring drug measurements

- **Bayesian Dosing** module:
  Determination of the entire pharmacokinetic profile from (few) drug measurements by means of Bayesian techniques for performance of deterministic dosing simulations.

- **Optimal Sampling** module:
  Prediction of optimal, most informative sampling time points for future TDM measurements.
TDMx core simulation function

Analytical solutions for linear PK models

- 1 and 2 compartment models
- Multiple dosing by superposition allowing for
  - date / time input
  - flexible dosing regimes
TDMx core simulation function

**Analytical solutions** for linear PK models
- 1 and 2 compartment models
- Multiple dosing by superposition allowing for
  - date / time input
  - flexible dosing regimes

Fallback to **differential equation systems**
- Time-varying covariates
- AUC calculations
- Allows for inclusion of non-linear PK models
TDMx – workflow exemplified by a patient
TDMx – workflow

Patient:  
H.S.  
Age:  
50 years  
Weight:  
100 kg  
Height:  
175 cm  
Serum creatinine:  
0.8 mg/dL
TDMx – workflow

→ Suspected nosocomial pneumonia
→ Therapy with meropenem
→ Assumption of a pathogen with MIC 2 mg/L

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

<table>
<thead>
<tr>
<th>Age [yrs.]</th>
<th>Weight [kg]</th>
<th>Height [cm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>100</td>
<td>175</td>
</tr>
</tbody>
</table>

Sex

male

Laboratory

Serum creatinine [mg/dL]

<table>
<thead>
<tr>
<th>Time</th>
<th>cCreatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>25/05/2015/13:00</td>
<td>0.8</td>
</tr>
</tbody>
</table>

MIC [mg/L]

2
TDMx – workflow: Probabilistic dosing determination of the initial dosing regimen

**Demographics**

<table>
<thead>
<tr>
<th>Age [yrs.]</th>
<th>Weight [kg]</th>
<th>Height [cm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>100</td>
<td>175</td>
</tr>
</tbody>
</table>

**Sex**

male

**Laboratory**

<table>
<thead>
<tr>
<th>Serum creatinine [mg/dL]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
</tr>
<tr>
<td>25/05/2015/13:00</td>
</tr>
</tbody>
</table>

**PK/PD Target (%fT>MIC)**

0 50 99
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]: 0.8
- MIC [mg/L]: 2

**TDMx – workflow:** Probabilistic dosing

**Determination of the initial dosing regimen**

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

---

**Demographics**

<table>
<thead>
<tr>
<th>Age [yrs.]</th>
<th>Weight [kg]</th>
<th>Height [cm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>100</td>
<td>175</td>
</tr>
</tbody>
</table>

**Laboratory**

<table>
<thead>
<tr>
<th>Time</th>
<th>cCreatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>25/05/2015/13:00</td>
<td>0.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MIC [mg/L]</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
TDMx – workflow: Probabilistic dosing
Determination of the initial dosing regimen
### TDMx – workflow: Probabilistic dosing determination of the initial dosing regimen

<table>
<thead>
<tr>
<th>Daily dose</th>
<th>500 mg / 1 h TID</th>
<th>1000 mg / 1 h TID</th>
<th>2000 mg / 1 h TID</th>
</tr>
</thead>
<tbody>
<tr>
<td>1500 mg</td>
<td>PTA = 0.4</td>
<td>PTA = 0.7</td>
<td>PTA = 0.9</td>
</tr>
<tr>
<td>3000 mg</td>
<td></td>
<td></td>
<td>PTA = 1</td>
</tr>
<tr>
<td>6000 mg</td>
<td></td>
<td></td>
<td>PTA = 1</td>
</tr>
</tbody>
</table>

**Graphs**

- **500 mg / 1 h TID**
- **1000 mg / 1 h TID**
- **2000 mg / 1 h TID**
- **500 mg / 4 h TID**
- **1000 mg / 4 h TID**
- **2000 mg / 4 h TID**
- **1500 mg / 24 h OD**
- **3000 mg / 24 h OD**
- **6000 mg / 24 h OD**

**Time [h]**

- 0  6  12  18  24

**Concentration [mg/L]**

- 0  5  10  15  20  25  30  35  40  45  50  55  60

**PTA**

- 0.4
- 0.7
- 0.9
- 1
Algorithm for probabilistic dosing in TDMx

Conventional approach:
Monte-Carlo Simulation (MCS)
- n=1000 stochastic simulations
- for 9 scenarios: ca. 3 min.

TDMx approach:
Approximation by delta-method (DM)
- \( \text{var}(f(\theta, t)) \approx \text{diag} | J\{f(\theta, t)\} \ast \Omega \ast J\{f(\theta, t)\}^T | \)
- for 9 scenarios < 10 sec.

\( \theta \) PK parameter
\( J \) Jacobian matrix w.r.t PK parameter \( \theta \)
\( \Omega \) Variance-covariance matrix

Wicha et al. PAGE 24 Abstr 3445
Algorithm for probabilistic dosing in TDMx

Conventional approach:
Monte-Carlo Simulation (MCS)
n=1000 stochastic simulations

TDMx approach:
Approximation by delta-method (DM)
\[ \text{var}(f(\theta,t)) \approx \text{diag} \left| \nabla f(\theta,t) \right|^T \Omega \nabla f(\theta,t) \]

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

→ 1000 mg q8h with prolonged infusion duration (4 h)
TDMx – workflow: Optimal sampling
Determination of $T_{>MIC}$

→ ”Optimal Sampling“-Module

**Recommended sampling time points after dosing [hh:mm]:**

06:48

![Graph showing recommended sampling time points for Meropenem concentration over time after dose.](http://www.tu-pc.com/fondos/media/3482.jpg)
TDMx – workflow: Optimal sampling
Determination of entire PK profile

→ „Optimal Sampling“-Module

Recommended sampling time points after dosing [hh:mm]:
00:18 01:00 04:00 06:48
TDMx optimal sampling module

Individual D-optimal design

$$OBJ(x_i \mid \theta_j) = \det |\Sigma(J_{ij}^*J_{ij}^T)|^{-1}$$

- $x_i$: Sampling time point $i$
- $\theta_j$: PK parameter $j$
- $J_{ij}$: Jacobian matrix w.r.t PK parameter $\theta_j$ at time point $i$
TDMx – workflow: Bayesian Dosing Determination of the individual PK

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Description</th>
<th>Typical</th>
<th>Individual</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 CL</td>
<td>L/h</td>
<td>Drug Clearance</td>
<td>19.10</td>
<td>22.90</td>
</tr>
<tr>
<td>2 V1</td>
<td>L</td>
<td>Central Volume of Distribution</td>
<td>15.40</td>
<td>14.40</td>
</tr>
<tr>
<td>3 Q</td>
<td>L/h</td>
<td>Intercompartmental Clearance</td>
<td>18.60</td>
<td>18.80</td>
</tr>
<tr>
<td>4 V2</td>
<td>L</td>
<td>Peripheral Volume of Distribution</td>
<td>12.60</td>
<td>11.90</td>
</tr>
<tr>
<td>5 %fT&gt;MIC</td>
<td>%</td>
<td>Percentage of observation period that unbound drug concentrations exceeds the MIC</td>
<td></td>
<td>72.40</td>
</tr>
</tbody>
</table>
TDMx – workflow: Bayesian Dosing Determination of the individual PK

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Description</th>
<th>Typical</th>
<th>Individual</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 CL</td>
<td>[L/h]</td>
<td>Drug Clearance</td>
<td>19.10</td>
<td>22.90</td>
</tr>
<tr>
<td>2 V1</td>
<td>[L]</td>
<td>Central Volume of Distribution</td>
<td>15.40</td>
<td>14.40</td>
</tr>
<tr>
<td>3 Q</td>
<td>[L/h]</td>
<td>Intercompartmental Clearance</td>
<td>18.60</td>
<td>18.80</td>
</tr>
<tr>
<td>4 V2</td>
<td>[L]</td>
<td>Peripheral Volume of Distribution</td>
<td>12.60</td>
<td>11.90</td>
</tr>
<tr>
<td>5 %fT&gt;MIC</td>
<td>[%]</td>
<td>Percentage of observation period that unbound drug concentrations exceeds the MIC</td>
<td>72.40</td>
<td></td>
</tr>
</tbody>
</table>
TDMx Bayesian PK estimation

Maximum \textit{a posteriori} estimation based upon parametric population PK models

\[
OBJ(x_i \mid \theta_j) = \sum\left(\frac{(y_i - f(x_i))^2}{\sigma_i^2} + \log \sigma_i^2\right) + \sum\left(\eta_j^2/\omega_j^2\right)
\]

- \(x_i\): Sampling time point \(i\)
- \(\theta_j\): PK parameter \(j\)
- \(y_i\): Observed concentration at time point \(i\)
- \(f(x_i)\): Predicted concentration at time point \(i\)
- \(\sigma_i^2\): Residual variance at time point \(i\)
- \(\eta_j\): Deviation of PK parameter \(j\) from population mean
- \(\omega_j\): Variance of PK parameter \(j\)
TDMx – Bayesian PK estimation
Validation vs. NONMEM™: Meropenem
Customisation of the population PK model

PK/Covariate model:

Clearance (CL) [L/h] =
\[14.6 \times (\text{CLCR}_i \times \text{t}/83)^{0.62} \times (\text{AGE}_i/35)^{-0.34}\]

Intercompartmental Clearance (Q) [L/h] =
18.6

Central volume of distribution (V1) [L] =
\[10.8 \times (\text{WT}_i/70)^{0.99}\]

Peripheral volume of distribution (V2) [L] =
12.6

Interindividual variability of PK parameters:

\%CV(\text{CL}) = 34.35

\%CV(\text{Q}) = 53.85

\%CV(\text{V1}) = 37.82

\%CV(\text{V2}) = 31.94
TDMx – workflow: Bayesian Dosing Evaluation of alternative dosages

→ „Bayesian-Dosing“-Module
Patient characteristics
e.g. body weight, renal function, etc.
Probabilistic dosing
(Sub-)population PK

Patient characteristics
e.g. body weight, renal function, etc.
Optimal sampling
Highly informative sampling time points

Does not require measurements of drug concentration

If measurement of drug concentration available

Probabilistic dosing
(Sub-)population PK

Patient characteristics
e.g. body weight, renal function, etc.

PK Profile
Clinical research

Prediction of optimal sampling time points

‘only’ PD
Clinical practice (e.g. $T_{>MIC}$)
Bayesian dosing
(Individual PK)
Evaluation of dosing in individual patients

Patient characteristics
e.g. body weight, renal function, etc.

Probabilistic dosing
(Sub-)population PK
Prediction of dosing regimen

Optimal sampling
Highly informative sampling time points

Does not require measurements of drug concentration
If measurement of drug concentration available

PK Profile
Clinical research

'Only' PD
Clinical practice (e.g. T_{>MIC})
TDMx infrastructure

• Web-based, open-access www.TDMx.eu

• No installation required

• Designed to work with
  • Laptops and desktop PCs
  • Tablets
  • (Smartphones) → big screens required!
TDMx infrastructure

**Server-side** (Linux webserver)
- Computation on computer cluster
- Results converted to HTML5 user interface
  (Framework: shiny for ‘R’/RStudio)

**Client-side** (web browser)
- Data entry (patient covariates, clinical chemistry, drug measurements)
- Results viewing
- No software apart from browser!
TDMx infrastructure

- TDMx is hosted at Amazon web services (AWS)

- AWS resources used by TDMx
  - **Elastic Cloud Computing (EC2)**
    Linux webserver with various container sizes
  
  - **Cloud Watch**
    Monitoring EC2 server resources (CPU load, memory, disk)

  - **Auto Scaling**
    Launches and terminates additional server instances

  - **Elastic Load Balancing**
    Distributes incoming traffic on servers
TDMx infrastructure

Problem with load balancing: ‘R’ is single threaded!

→ Load balancing on different levels

Server level:
- Assign users to separate instances of the same TDMx app on the same server.
- managed by TDMx load balancer on the website

Cloud level:
- Assign users to separate instances of the same TDMx app on a different servers.
- managed by AWS Elastic Load Balancer
Challenges in potential clinical use

- Availability of population PK models in special patient populations
- Prospective validation of clinical benefit of model-supported TDM
- Stand-alone software vs. interfacing with medical record system
- Personal use claim vs. medical product evaluation
TDMx - Summary

• TDMx can support TDM with pharmacometric techniques to foster model-informed patient care.

• TDMx is not a commercial product, but a scientific research project.

• Applications:
  • Teaching TDM (students of pharmacy and medicine)
  • Clinical research and patient care

• Implemented drugs:
  • Beta-lactams: meropenem, piperacillin
  • Aminoglycosides: gentamicin, amikacin
  • more will follow…

• TDMx is in open beta-testing:
We are happy about feedback!

TDMx Core Team

Sebastian G. Wicha
Lead Developer

Prof. Dr. Charlotte Kloft
Scientific Advisor

Martin Kees, M.D.
Medical Advisor

Alexander Solms, M.Sc.
Statistical Advisor

Iris Minichmayr, M.Sc.
Validation Advisor
Therapeutic Drug Monitoring empowered by PharmacometrX

TDMx (speak 'TDMetrics') is a research project to develop, maintain and advance a versatile web application to foster model-supported Therapeutic Drug Monitoring (TDM).

TDMx is easy to use!

TDMx brings state-of-the-art pharmacometrics to Therapeutic Drug Monitoring, thereby being very user-friendly. No technical pharmacometrics or modeling skills are required to use TDMx. We have developed TDMx as a showcase for a support tool with potential application in (i) clinical practice as well as (ii) clinical research. Furthermore, TDMx is suitable for (iii) teaching TDM in undergraduate studies. Learn more on how you can benefit from using TDMx in your specific setting!

TDMx is freely available online. Try now!