30-NOV-2017

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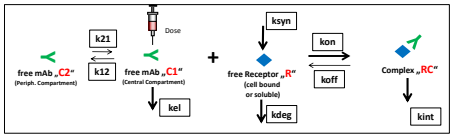
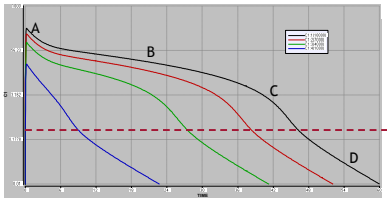
PML School: Target-mediated Drug Disposition (TMDD) Modeling Using the Quasi-equilibrium Assumption

TMDD Model



- Target Mediated Drug Disposition (TMDD) often plays a role in elimination of monoclonal antibodies (mAbs) or other biologics
- Published TMDD models usually have binding to target in Central Compartment
- Addition of peripheral („tissue") compartment frequently required, as most mAbs follow 2-compartment-model
- See PML school lesson 6: full TMDD model
  - Main assumptions of TMDD equations
  - Typical ranges of parameters
  - Usage of multiple „Observe" statements if Target or Complex data is available in addition to free mAb

TMDD Model - Challenges

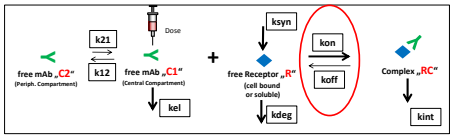


4 Phases of TMDD:
A): Rapid Decline
B): Target route saturated, slow 1st order disposition
C) Mixed order disposition
D) Low drug conc, koff and kint driven disposition

- Bioanalytical data is often not rich enough (e.g. not enough doses tested or time-conc traces „cut" by bioanalytical LLoQ) to allow reasonable estimation of all TMDD parameters
- A critical element is kint, the degradation rate of the complex. Can be in the range of kel (the free drug) if e.g. target is a small cytokine; or in the range of kdeg (the free receptor) if target is e.g. a membrane bound receptor; or „anything in-between".
- Potential instability of the model, long run times
- Especially, the binding constants kon (and koff) are often difficult to estimate from PK data
- Solutions:
  - Freeze (at least initially) one or more parameters (e.g. kon, koff,...) based on e.g. in vitro data
  - Use simplifications of the full TMDD model to reduce complexity

TMDD Model - QE Assumption

- QE model assumes equlibrium between Complex (RC) vs free Drug (C) and free Receptor (R):
  - KD = koff/kon = C * R / RC
- Reasonable assumption, as the binding processes are often faster than drug elimination or turnover of the free Receptor (R) or the Complex (RC)
  - In cases were kint is not << koff, the QE assumption may not hold and QSS (Quasi steady state) may be more approriate with Kss = (kint + koff)/kon
- For full mathematical derivation of ODEs see literature (backup slide)
- Plug in the code from reliable literature source into Phoenix using only the textual mode
  - Gibiansky L, Gibiansky E, Kakkar T, Ma P. Approximations of the target-mediated drug disposition model and identifiability of model parameters. J Pharmacokinet Pharmacodyn. 2008



TMDD Model - QE Approximation

$$\frac{dC_{tot}}{dt} = \frac{I(t)+k_a A_d}{V} - k_{el} C_{tot} - (k_{el}+k_{pt}-k_{tp})\,C + \frac{k_{tp} A_T}{V}; \quad (14)$$

```
deriv(Ctot = (-Kint*Ctot -((CL/V1)+(Q/V1)-Kint)*C1)*V1 + Q*C2) #Total amount of mAb. Left side Multiplied by V1 to have
↳Atot in pmol/kg because of dosing in pmol/kg
```

NB: written in Ctot = total drug = free + complex.
Move 1. from Conc in paper to Amount and 2. from parametrization in k to CL

$$\frac{dA_T}{dt} = k_{pt} C \cdot V - k_{tp} A_T; \quad (15)$$

```
deriv(A2 = Q*C1 - Q*C2)  #free mAb amount in peripheral compartment
C2 = A2/V2
```

$$\frac{dR_{tot}}{dt} = k_{syn} - k_{deg} R_{tot} - (k_{on} - k_{deg})\,(C_{tot} - C). \quad (16)$$

$$\bar{A}_d(0) = D_1;\ C(0) = D_2/V;\ A_T(0) = 0;\ R_{tot}(0) = k_{syn}/k_{deg}. \quad (17)$$

```
Ksyn = R0 * Kdeg
deriv(Rtot = Ksyn - Kdeg*Rtot-(Kint-Kdeg)*(Ctot-C1) )#Total receptor in nM
sequence(          #"sequence" defines initial conditions (t=0)
Rtot = R0
)
```

NB: written in Rtot = total receptor = free + complex. Initialize Rtot = R0 via „sequence" statement. The other initial conditions (C, RC,...) do not need to be initialized in Phoenix as all 0.

$$C = \frac{1}{2}\left[(C_{tot} - R_{tot} - K_D) + \sqrt{(C_{tot} - R_{tot} - K_D)^2 + 4K_D C_{tot}}\right]; \quad (11)$$

$$RC = \frac{R_{tot} C}{K_D + C}. \quad (12)$$

QE assumption

```
C1 = 1/2*((Ctot-Rtot-KD)+sqrt((Ctot-Rtot-KD)^2+4*KD*Ctot))  #free mAb in central compartment in nM
Complex = Rtot*C1/(KD+C1)#Complex in central compartment in nM
```

- Furthermore, add „standard" PML elements: observe statement + error model, structural parameters, fixed (and random) effects. Full model code see Phoenix file / text file in Forum.

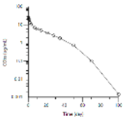
Gibiansky L, Gibiansky E, Kakkar T, Ma P. Approximations of the target-mediated drug disposition model and identifiability of model parameters. J Pharmacokinet Pharmacodyn. 2008

Demo

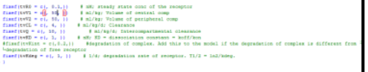
1. Fit TMDD data example with QE approximation
2. Use QE approximation to simulate Receptor Occupancy at different KD, R0

Demo I
Fit TMDD data example with QE approximation

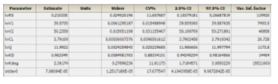
1. Plot example dataset, Dose =1 mg/kg:



2. Find reasonable initial estimates, execute model



3 Results



Although apparently reasonable %CV calculated, results are dependent on initial estimates for kdeg and R0 in this hypothetical example. Freezing KD to 1 nM alleviates this issue.

Demo II
Use QE approximation to simulate Receptor Occupancy at different KD, R0

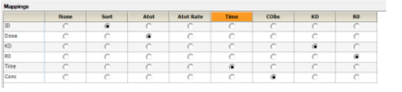
1. Generate „Simulation Matrix“
   - Example: Different KDs and R0

ID	Dose	KD	R0	Time	Conc
1	6700	0.05	0.01	0	0
2	6700	0.1	0.01	0	0
3	6700	0.5	0.01	0	0
4	6700	1	0.01	0	0
5	6700	5	0.01	0	0
6	6700	0.05	0.1	0	0
7	6700	0.1	0.1	0	0
8	6700	0.5	0.1	0	0
9	6700	1	0.1	0	0
10	6700	5	0.1	0	0

2. Copy QE model. Remove (e.g. by #) the KD and R0 from stparm and fixef. Add instead covariate statements to read in KD and R0 from Simulation Matrix.

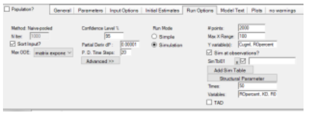
```
#stparm(KD = tvKD)          #fixef(tvKD = c(, 1, ))
#stparm(Kint = tvKint)      #fixef(tvKint = c(,0.2,))

covariate(KD)
covariate(R0)
```

3. Mapping

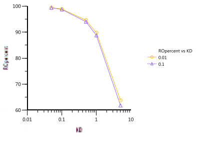


Demo II
Use QE approximation to simulate Receptor Occupancy at different KD, R0

4. Run Simulation. Ask for Sim Table giving Receptor Occupancy (ROpercent) at Day 50



4. Plot SimTable01.



- In this hypothetical example using this model, Receptor Occupancy at Day 50 is
  - largely independent of initial Receptor Conc R0 between 0.1 and 0.01 nM
  - dependent on KD
- For affinity considerations of mAbs, see also Tiwari et al 2017 (use full TMDD model)

Tiwari A, Abraham AK, Harrold JM, Zutshi A, Singh P. Optimal Affinity of a Monoclonal Antibody: Guiding Principles Using Mechanistic Modeling. AAPS J. 2017 Mar;19(2):510-519. doi: 10.1208/s12248-016-0004-1

Conclusions

- The textual input mode of Phoenix is very versatile and allows input of user-defined custom models
  - Potentially challenge published models / adapt to your specific case
- TMDD models (full model and to a lesser extent also approximations) rely on rich data.
  - Appropriate dose range studied
  - Bioanalytics: Does the PK assay measure free or total drug?
  - Ideally additional bioanalytical data available on Receptor/Complex/Receptor Occupancy
- The Quasi-Equilibrium (QE) model is one useful simplification of the full TMDD model.
  - QE model assumes equlibrium between Complex (RC) vs free Drug (C) and free Receptor (R)
  - Full TMDD model and other simplifications (e.g. QSS, MM) should also be explored.

Backup

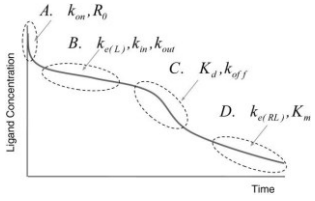
Literature

TMDD

- Gibiansky L, Gibiansky E, Kakkar T, Ma P. Approximations of the target-mediated drug disposition model and identifiability of model parameters. J Pharmacokinet Pharmacodyn. 2008 Oct;35(5):573-91. doi: 10.1007/s10928-008-9102-8. Epub 2008 Nov 13.
- Gibiansky L, Gibiansky E. Target-mediated drug disposition model: approximations, identifiability of model parameters and applications to the population pharmacokinetic-pharmacodynamic modeling of biologics. Expert Opin Drug Metab Toxicol. 2009 Jul;5(7):803-12. doi: 10.1517/17425250902992901. Review.
- Mager DE, Jusko WJ. General pharmacokinetic model for drugs exhibiting target-mediated drug disposition. J Pharmacokinet Pharmacodyn. 2001 Dec;28(6):507-32.
- Dua P, Hawkins E, van der Graaf PH. A Tutorial on Target-Mediated Drug Disposition (TMDD) Models CPT Pharmacometrics Syst Pharmacol. 2015 Jun;4(6):324-37. doi: 10.1002/psp4.41. Epub 2015 Jun 15.
- Peletier LA, Gabrielsson J. Dynamics of target-mediated drug disposition: characteristic profiles and parameter identification. J Pharmacokinet Pharmacodyn. 2012 Oct;39(5):429-51. doi: 10.1007/s10928-012-9260-6. Epub 2012 Aug 1.

Affinity Considerations mAbs

- Tiwari A, Abraham AK, Harrold JM, Zutshi A, Singh P. Optimal Affinity of a Monoclonal Antibody: Guiding Principles Using Mechanistic Modeling. AAPS J. 2017 Mar;19(2):510-519. doi: 10.1208/s12248-016-0004-1



Schematic representation of how the parameters may be derived from properties of the four phases. In *Phase A* ligand binds to the receptor (k_{on}), during *Phase B* ligand is primarily eliminated directly ($k_{el(L)}$); time of termination yields information about k_{in}. In *Phase C* the saturation term is important (K_d), and in *Phase D* ligand elimination proceeds mainly though the receptor ($k_{el(RL)}$)

Reproduced from: Peletier LA, Gabrielsson J. Dynamics of target-mediated drug disposition: characteristic profiles and parameter identification. J Pharmacokinet Pharmacodyn. 2012 Oct;39(5):429-51. doi: 10.1007/s10928-012-9260-6. Epub 2012 Aug 1.

Questions?

Coming up…

Adaptive Simulations: Extending PML to Trial Simulations
A pre-clinical example to simulate a desired outcome
December 14, 2017 | 10am EST
Presenter: Bernd Wendt

Topics for 2018: NONMEM to PML Comparisons

- Popular Models using NONMEM software
  - 1:1 translation into Phoenix Modeling Language
  - Setup and run NONMEM models in Phoenix
  - Setup and Run same model in Phoenix NLME
  - Compare Results

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