TMDD Model Translated from NONMEM (NM-TRAN) to Phoenix NLME (PML)

Phoenix Modeling Language School

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Agenda

- TMDD Model: Brief Overview
- 1 compartment, A Single Dose IV Bolus Example:
  - ✓ NONMEM versus PHOENIX NLME
- Demonstration
- Questions and Answers

TMDD Model Selected Publications: Model Development and Applications

1. Mager, D.E. and Jusko, W.J. General pharmacokinetic model for drugs exhibiting target mediated drug disposition. J Pharmacokinet Pharmacodyn 28 (2001):507–32.

2. Mager, D.E. and Krzyzanski, W. Quasi-equilibrium pharmacokinetic model for drugs exhibiting target-mediated drug disposition. Pharm Res 22 (2005):1589–96.

3. **Gibiansky, L., Gibiansky**, E., Kakkar, T. and Ma, P. Approximations of the target mediated drug disposition model and identifiability of model parameters. J Pharmacokinet Pharmacodyn 35 (2008):573–91.A*

4. **Gibiansky, L. and 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 5 (2009):803–12.*

5. Yan, X., Mager, D.E. and Krzyzanski, W. Selection between michaelis-menten and target-mediated drug disposition pharmacokinetic models. J Pharmacokinet Pharmacodyn 37 (2010):25–47.

TMDD Model Selected Publications (continued)

6. P Dua, E Hawkins, PH van der Graaf. A Tutorial on Target-Mediated Drug Disposition (TMDD) Models CPT Pharmacometrics Syst Pharmacol. 2015 Jun; 4(6): 324–337. Published online 2015 Jun 15. doi: 10.1002/psp4.41 PMCID: PMC4505827

7. **Lambertus A. Peletier, Johan Gabrielsson** Dynamics of target-mediated drug disposition: characteristic profiles and parameter identification. J Pharmacokinet Pharmacodyn. 2012 Oct; 39(5): 429–451. Published online 2012 Aug 1. doi: 10.1007/s10928-012-9260-6 PMCID: PMC3446204

Additional Background on TMDD Model – Assumptions and Challenges:

- PML School: Target-mediated Drug Disposition (TMDD) Modeling Using the Quasi-equilibrium Assumption 30-NOV-2017 Frank Striebel – MorphoSys AG
- PML school lesson 6 : full TMDD model
- Metrum MI 212, lecture 4 and lab 4*

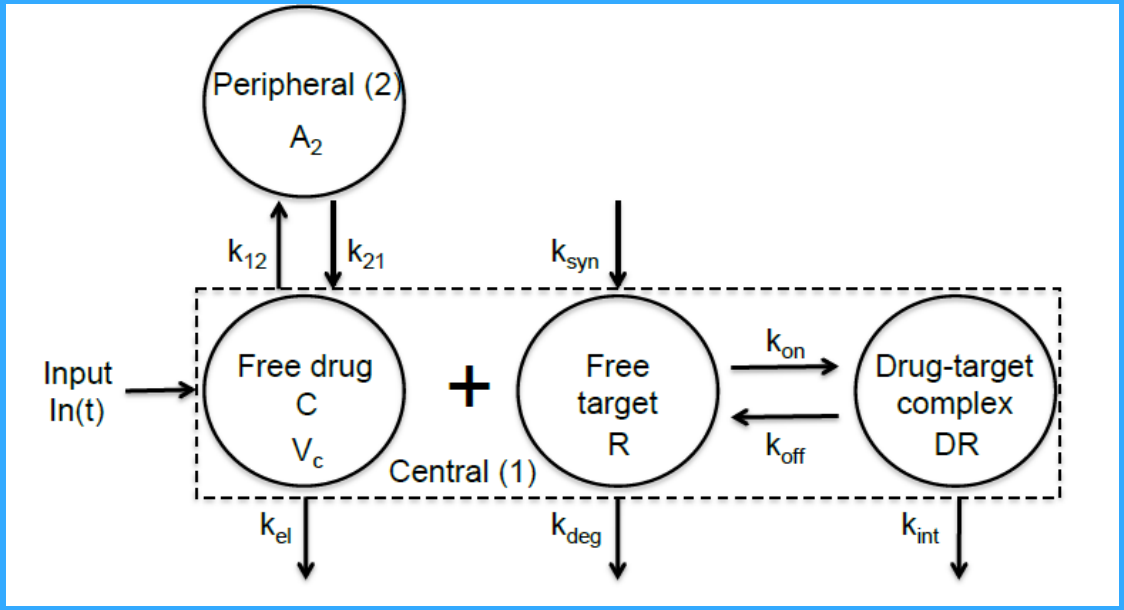
Exhibited TMDD Drugs

Table 1 Examples of the ligands and receptors exhibiting TMDD that have been modeled in the current literature

Ligand	Receptor	PK model used	PD model used	Biomarker	Reference
Gemtuzumab ozogamicin	CD33 antigen	One Compartment Cell Level Kinetic	No	N/A	31
Type 1 IFN	IFNAR1 or IFNAR2	Two Compartment Ctot and Rtot	No	N/A	41
Canakinumab	IL-1β	Binding in Two Compartments QSS	No	N/A	60
Canakinumab	IL-1β	Binding in Two Compartments	Yes	CRP and SAA	62
Tocilizumab	IL-6R (soluble)	Two Compartment QSS with MM elimination	Yes	Neutrophil, platelets	64
rhLIF	LIF receptor	Two Compartment with 2 Depots	No	N/A	73
Anti-MTX mAb	MTX	Two Compartment	No	N/A	65
Denosumab	RANKL	One Compartment QE with constant Rtot	Yes	Serum NTX	71
Denosumab	RANKL	Two Compartment QSS with Depot	No	N/A	63
PEG-TPOm	TPO	One Compartment	Yes	Platelets from precursor cells	56
Infliximab	TNFα	One Compartment with Depot	No	N/A	53
Aflibercept (VEGF-Trap)	VEGF	Two Compartment MM	No	N/A	67
rhVEGF	VEGF receptors	Two Compartment with constant R	No	N/A	77
Filgrastim	G-CSF receptor	One Compartment with Depot	No	N/A	78
Anti-CD81 mAb	CD81	One Compartment QE	No	N/A	80
TAM-163	TrkB	Two Compartment with Depot	No	N/A	81
HSP90 Inhibitors	HSP90	Both Two Compartment and One Compartment RB	No	N/A	82
AMG-811	IFN-γ	One Compartment QSS	No	N/A	44

Reproduced from Dua et al, *A Tutorial on Target-Mediated Drug Disposition (TMDD) Models* 2015CPT Pharmacometrics Syst. Pharmacol. (2015) 4, 324–337

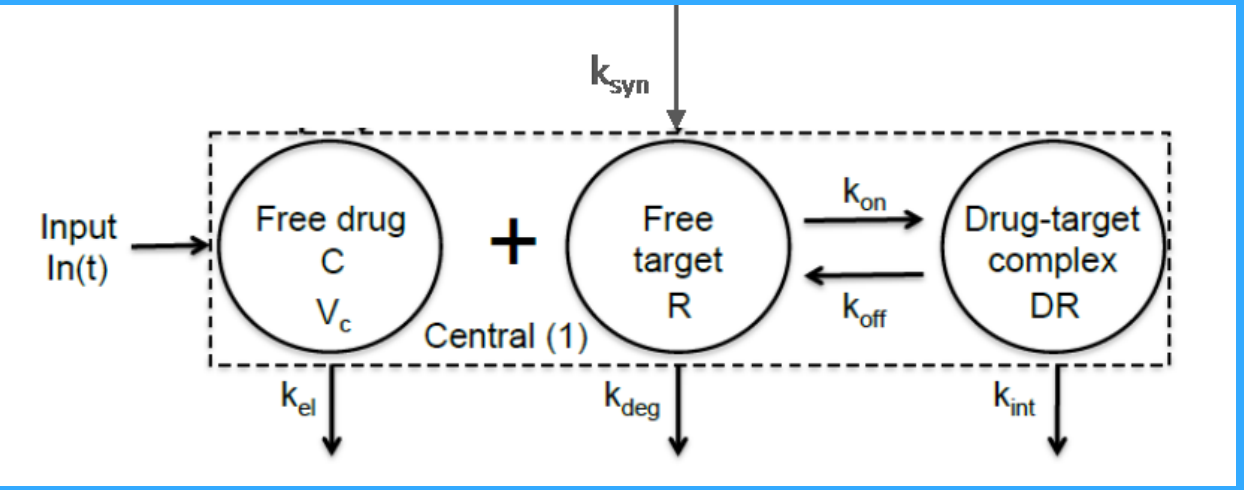
TMDD 2 Compartmental Model Overview



Reproduced from Mager DE and Krzyzanski W, 2005

- C, R, DR (RC): Molar concentrations of free (unbound) drug, free target, and drug-target complex in the central compartment, respectively
- Aa: amount of drug (moles) in the peripheral compartment
- In(t) is a function of drug input or endogenous substance production
- Vc (V) is the central compartment volume
- Kel, K12,and K21 are the linear elimination, central to peripheral, and peripheral to central rate constants, respectively, for the drug
- Ksyn and Kdeg are the target synthesis and degradation rate constants, respectively
- Kon and koff are the binding and dissociation rate constants, respectively
- Kint is the elimination rate constant for the drug-target complex

TMDD 1 Compartmental Model Overview



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- Kel, is the linear elimination rate constant, respectively, for the drug
- Ksyn and Kdeg are the target synthesis and degradation rate constants, respectively
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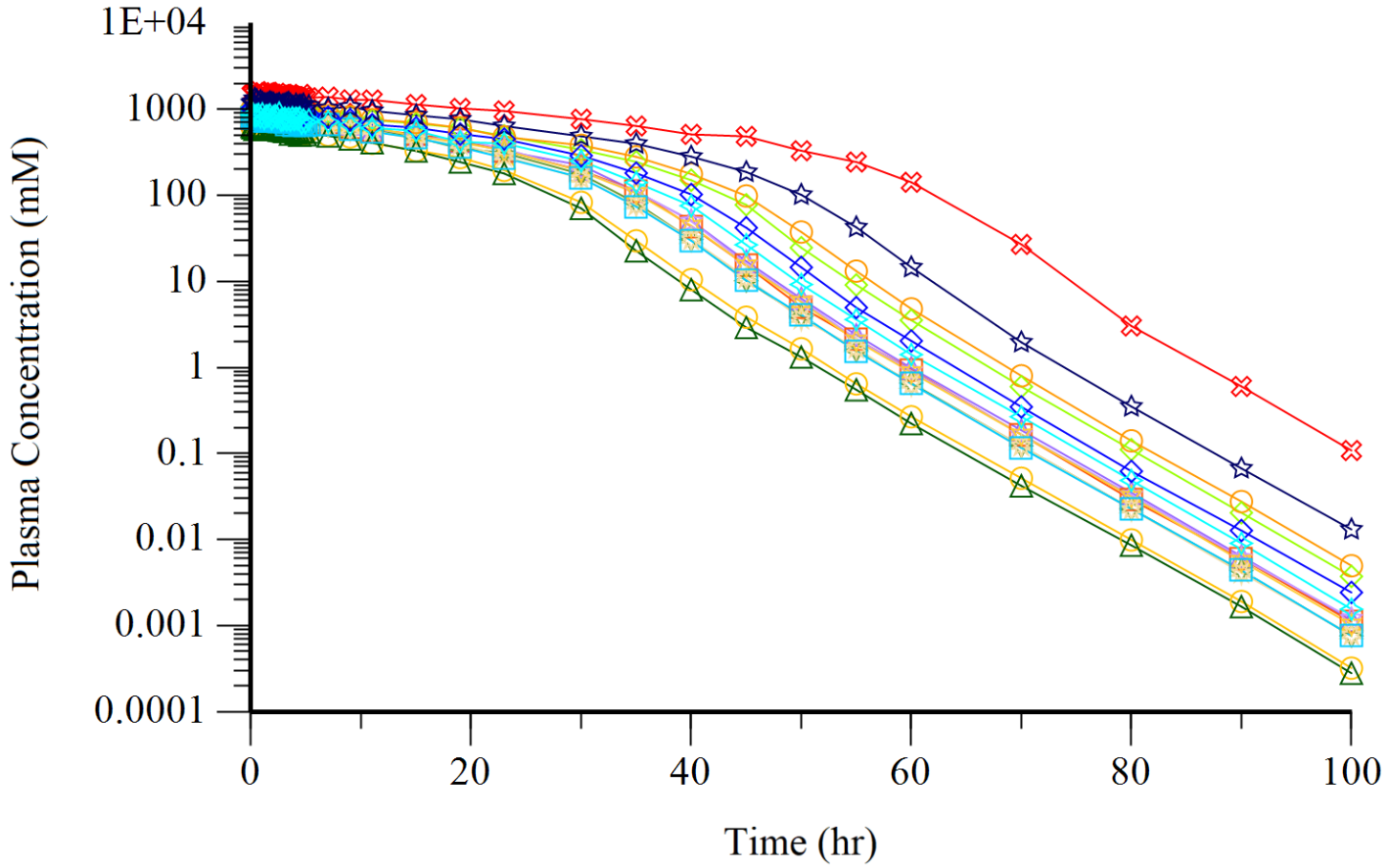
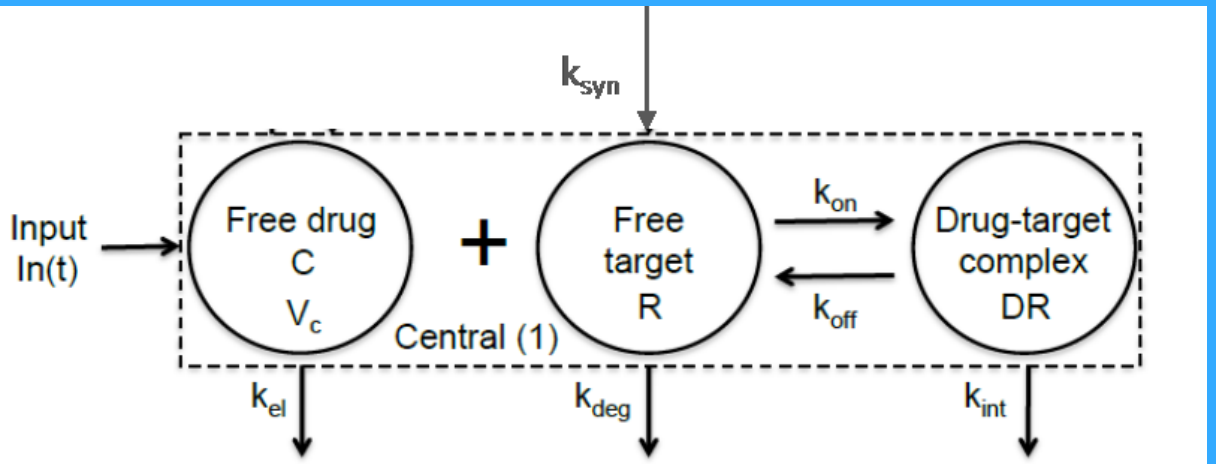
- Kint is the elimination rate constant for the drug-target complex

TMDD Model: Example



- A single dose intravenous bolus administration: 1000 unit dose
- 15 subjects
- 100 hr sampling time points
- Only individual drug plasma concentration vs. time profiles are available

TMDD with QE Approximation- 1 Compartmental Model



Assumptions:

$$k_{on} C \cdot R - k_{off} RC = 0;$$

$$\frac{C \cdot R}{RC} = \frac{k_{off}}{k_{on}} = K_D,$$

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

$$RC = \frac{R_{tot} C}{K_D + C},$$

- Kd: equilibrium dissociation constant
- Ctot and Rtot: total (free and bound) concentration of the drug in the central compartment and the total concentration of the Receptor
- Ctot = C + RC
- Rtot = R + RC

*Gibiansky, L., Gibiansky, E., Kakkar, T. and Ma, P. Approximations of the target mediated drug disposition model and identifiability of model parameters. J Pharmacokinet Pharmacodyn 35 (2008):573–91.A**

NLME Code: TMDD_QE Approximation; 1 Compartment

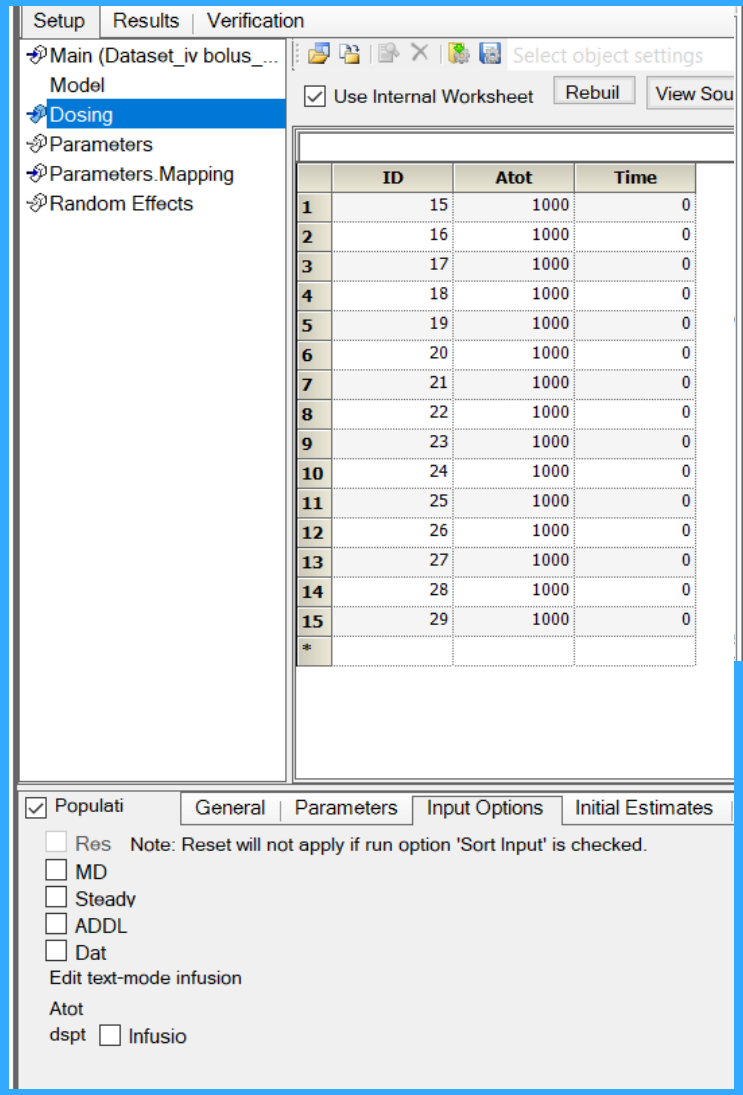
Derivative Equations	Phoenix NLME
#Total drug concentration DCtot/dt= Dose- kint*Ctot - (kel - kint)*C) ; (modified Eq14) Ctot = Atot/V KD = koff/kon #Free drug in central compartment C = 1/2*((Ctot-Rtot-KD)+sqrt((Ctot-Rtot-KD)^2+4*KD*Ctot)) RC = Rtot*C/(KD + C) R = Rtot - RC	 deriv(Atot = - kint*V*Ctot - (kel - kint)*C*V) Ctot = Atot/V KD = koff/kon C = 1/2*((Ctot-Rtot-KD)+sqrt((Ctot-Rtot-KD)^2+4*KD*Ctot)) RC = Rtot*C/(KD + C) R = Rtot - RC

*Gibiansky, L., Gibiansky, E., Kakkar, T. and Ma, P. Approximations of the target mediated drug disposition model and identifiability of model parameters. J Pharmacokinet Pharmacodyn 35 (2008):573–91.A**

DATASET COMPARISION: NONMEM vs Phoenix NLME

NONNEM → **Phoenix NLME**

	ID	GROUP	TIME	AMT	DV	RCCOM	EVID	CMT
2	15	1000	0	1000	.	.	1	1
3	15	1000	0.083	.	620.125	97.1072	0	1
4	15	1000	0.17	.	678.832	97.022	0	1
5	15	1000	0.34	.	721.162	97.2952	0	1
6	15	1000	0.51	.	653.176	97.9945	0	1
7	15	1000	0.68	.	622.716	95.8917	0	1
8	15	1000	0.85	.	639.29	96.6203	0	1
9	15	1000	1.02	.	627.767	96.595	0	1
10	15	1000	1.19	.	640.363	96.7894	0	1
11	15	1000	1.36	.	604.657	95.156	0	1
12	15	1000	1.53	.	630.046	96.7902	0	1
13	15	1000	1.7	.	609.257	96.7488	0	1
14	15	1000	1.87	.	683.129	96.1019	0	1
15	15	1000	2.04	.	587.367	96.5451	0	1
16	15	1000	2.21	.	596.947	97.0301	0	1
17	15	1000	2.38	.	601.644	95.8112	0	1
18	15	1000	2.55	.	633.344	95.1978	0	1
19	15	1000	2.72	.	594.672	98.787	0	1
20	15	1000	2.89	.	596.945	96.6141	0	1
21	15	1000	3.06	.	557.761	96.1893	0	1
22	15	1000	3.23	.	596.611	97.2165	0	1
23	15	1000	3.4	.	608.57	96.9831	0	1
24	15	1000	3.57	.	596.294	97.2227	0	1
25	15	1000	3.74	.	566.753	96.4092	0	1
26	15	1000	3.91	.	567.779	98.1996	0	1
27	15	1000	4.08	.	571.532	96.0171	0	1
28	15	1000	4.25	.	576.881	96.164	0	1
29	15	1000	4.42	.	545.807	96.2196	0	1
30	15	1000	4.59	.	565.442	95.2916	0	1



	ID	Atot	Time
1	15	1000	0
2	16	1000	0
3	17	1000	0
4	18	1000	0
5	19	1000	0
6	20	1000	0
7	21	1000	0
8	22	1000	0
9	23	1000	0
10	24	1000	0
11	25	1000	0
12	26	1000	0
13	27	1000	0
14	28	1000	0
15	29	1000	0
*			

	ID	dose	time	Cfree
1	15	1000	0.083	620.125
2	15	1000	0.17	678.832
3	15	1000	0.34	721.162
4	15	1000	0.51	653.176
5	15	1000	0.68	622.716
6	15	1000	0.85	639.29
7	15	1000	1.02	627.767
8	15	1000	1.19	640.363
9	15	1000	1.36	604.657
10	15	1000	1.53	630.046
11	15	1000	1.7	609.257
12	15	1000	1.87	683.129
13	15	1000	2.04	587.367
14	15	1000	2.21	596.947
15	15	1000	2.38	601.644
16	15	1000	2.55	633.344
17	15	1000	2.72	594.672
18	15	1000	2.89	596.945

TMDD_QE NONMEM vs. Phoenix NLME

```
$PROB TMDD_QE DATA
$INPUT ID GROUP TIME AMT DV RCCOM EVID CMT
$DATA DATA1000.csv IGNORE=C
$SUBROUTINE ADVAN6 TOL = 6
$MODEL
COMP(1) ; 1 CMT

 $PK
 KEL  = THETA(1)*EXP(ETA(1)) ; KEL for free drug
 V1   = THETA(2)*EXP(ETA(2))  ; V1 for free drug
 RTOT = THETA(3)  ; total of free receptor
 KON  = THETA(4)  ; binding rate constant
 KOFF = THETA(5)  ; dissociation rate constant
KINT = THETA(6)  ; elimination rate constant for drug-receptor
complex
```

```
test(){
dosepoint(Atot); dose in 1000 mM, IV bolus; Volume in L, time
in hr

#The posthoc parameters are defined in the form of PML in
stparm statements. tvKel and tvV are fixed effects, and nKel and
nV are random effects
stparm(kel = tvkel*exp(nKel))
stparm(V = tvV*exp(nV))
stparm(Rtot = tvRtot)
stparm(kon = tvkon)
stparm(koff = tvkoff)
stparm(kint = tvkint)
```

TMDD_QE NONMEM vs Phoenix NLME

#Adapted from Gibiansky et al. 2008 Journal of Pharmacokinetics and Pharmacodynamics".

$DES *; Adapted from Gibiansky et al. 2008 Journal of Pharmacokinetics and Pharmacodynamics* DADT(1) = - KINT*A(1) - (KEL - KINT)*CFREE*V1; C1 or Ctotal; C1 = A(1)/V1 ; KD = KOFF/KON ; CFREE = 1/2*((C1 - RTOT - KD) + SQRT((C1 - RTOT - KD)**2 + 4*KD*C1)) ; RC = RTOT*CFREE/(KD + CFREE) ; RFREE = RTOT - RC ;	# DE for the total drug amount in central compartment deriv(Atot = - kint*V*Ctot - (kel - kint)*C*V) #Total drug concentration Ctot = Atot/V #equilibrium dissociation constant KD = koff/kon #free drug concentration in central compartment C = 1/2*((Ctot-Rtot-KD)+sqrt((Ctot-Rtot-KD)^2+4*KD*Ctot) #complex concentration RC = Rtot*C/(KD + C) #free receptor concentration R = Rtot - RC

TMDD_QE NONMEM vs Phoenix NLME

```
$THETA
 (0, 0.005)     ; 1 KEL
 (0, 1)         ; 2 V1
 (100 FIXED)    ; 3 RTOT
 (0.1 FIXED)    ; 4 KON
 (0, 3)         ; 5 KOFF
 (0, 0.2)       ; 6 KINT

$ERROR
CALLFL=0; Call with every observation record
KD2 = KOFF/KON; redefine Kd
IPRED= 1/2*((A(1)/V1 - RTOT - KD2) + SQRT((A(1)/V1 - RTOT -
KD2)**2 + 4*KD2*A(1)/V1)); redefine CFree;
 Y=IPRED*(1 + EPS(1));  individual predicted value in model
 IRES = DV - IPRED; individual residual observed-predicted
IWRES = IRES/SQRT(IPRED**2*SIGMA(1,1)); proportional error
model
```

```
#Fixed effects;  initial estimate; parameters to
be estimated#
fixef(tvkel= c(, 0.006, ))
fixef(tvV = c(, 1, ))
fixef(tvRtot = c(, 100,))
fixef(tvkon = c(, 0.1, ))
fixef(tvkoff = c(, 3, ))
fixef(tvkint = c(,0.3,))


observe(CObs = C*(1 + eps1)) # free drug in
central compartment; multiplicative error
model

}
```

TMDD_QE NONMEM vs Phoenix NLME

```
$OMEGA
 0.02    0.02 ; BSV KEL AND V1
$SIGMA
 0.02          ; variance of epsilon one



$ESTIMATION METHOD=1 INTER NOABORT
MAXEVAL=999999 PRINT=10 ; FOCE
 NSIG = 4 SIGL = 6
$COV SIGL = 6 TOL = 6
$TABLE ID TIME DV PRED IPRED RES IRES WRES
IWRES CWRES NOAPPEND NOPRINT ONEHEADER
FILE = SDTAB
$TABLE ID KEL V1 RTOT KON KOFF KINT ETA1 ETA2
NOAPPEND NOPRINT ONEHEADER FIRSTONLY FILE =
PATAB
```

```
#random effect; within subject variability

ranef(diag(nV,nKel)=c(0.02,0.02))
#Initial estimate of the standard deviation for the
residual error#
error(eps1 = 0.1414) ;
```

Demo

Summary

- Set up and run NONMEM and PHOENIX NLME Model:
  - Population PK Modeling for TMDD_QE Approximation
  - Single Dose IV Bolus Injection; 15 Subjects
- FOCE Interaction vs. FOCE ELS

- Similar Results Between NONMEM and PHOENIX NLME Model

Questions?

Schedule for Q2

Date	Series	Topic
19-Apr	NONMEM-2-NLME	Nonlinear Elimination and Model Validation I: Bootstrap
3-May	NONMEM-2-NLME	Mixed Absorption and Model Validation II: VPC
17-May	NONMEM-2-NLME	Running NONMEM and Phoenix NLME in the Cloud
31-May	NONMEM-2-NLME	PD Emax inhibitory with baseline and shape factor
14-Jun	NONMEM-2-NLME	PD Indirect Response with IV Bolus Dosing
28-Jun	NONMEM-2-NLME	PKPD 1 Compartment-IV Infusion - Emax with Baseline, Shape and Effect

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Coming up…

NONMEM-2-NLME

Nonlinear elimination and model validation I: Bootstrap

April 19, 2018 | 10am EST

Presenter: Bernd Wendt

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