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Fate of mAbs and Target-Mediated Drug Disposition (TMDD)

PK27

Note: The exercise is based on exercise PK27 in the text: Gabrielsson, J. & Weiner, D.L. (5th ed., 2016). *Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications.* Swedish Pharmaceutical Press, Stockholm.

Main TMDD Assumptions

- The drug-target binding is a simple one-to-one binding process with only one type of drug-target complex produced
- The drug is highly specific and does not bind to any other target
- The drug-target binding occurs only in the central but not in the peripheral (tissue) or depot (lymphatic system) compartments
- Free drug distribution to tissues is linear and is described by intercompartmental rate constants
- Recycling of the target does not occur in the elimination process of the drug target complex
- Influence of the immune response (such as appearance of binding and/or neutralizing antibodies) is negligible
- Target production and degradation rates are constant and do not depend on the drug or target concentrations

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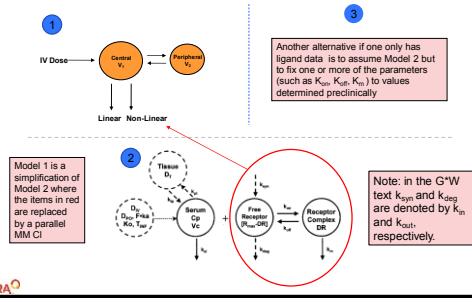
Fate of mAbs: TMDD Model Candidates



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Typical Ranges of Parameters for Therapeutic Monoclonal Antibodies

Parameter		Customary units	Re-normalized units	Conversion Factor
Dose		1-500 mg	10-3000 nmol	1 mg = 6.7 nmol
CL, Q		10-100 mL/hr	0.24-2.4 L/day	1 mL/hr=0.24 L/day
V_p, V_t			3-6 L	
F_{SC}			0.3-1	
k_a	sc		0.2-1.5 1/day	
t_{lag}	sc		1-8 days	
k_{on}		$10^4 - 10^8$ 1/(Ms)	1-100 1/(nmol/L)/day	10^3/(Ms) = 8.64 1/(nmol/L)/day
k_{off}		$10^{-6} - 10^{-3}$ 1/s	0.1-100 1/day	10^{-3} 1/s = 86.4 1/day
$K_D = k_{off}/k_{on}$			1-100 nmol/L	
k_{int}	soluble	similar to k_{el}	0.01-0.2 1/day	
	membrane	similar to k_{deg}	5-100 1/day	
k_{syn}			1-2 nmol/L/day	
k_{deg}			1-150 1/day	
$R_{max} = k_{syn} / k_{deg}$		1-10^4 pmol/L	10^{-3}-10 nmol/L	

Conversions assume 150 kDa molar weight. These may be useful for obtaining initial estimates.

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TeGenero Disaster – Lack of TMDD Understanding

WIKIPEDIA

The crucial pitfall to avoid when scaling protein drugs is target binding and receptor occupancy. A tragic example of this is the case of TGN1412, a monoclonal antibody directed against T lymphocytes, which produced multi-organ failure in six healthy volunteers (ESG, 2006); this serious outcome led to the introduction of the MABEL. The MRSD calculated by the conventional allometric approach was 0.1 mg·kg^{-1}. When receptor theory was used to investigate this dose, it was found that 0.1 mg·kg^{-1} would elicit greater than 90% receptor occupancy. In this situation, not only was the pharmacodynamic effect unacceptably high, producing a cytokine storm, **but the increased receptor occupancy could have altered the pharmacokinetics of the antibody by decreasing the clearance,** thereby further increasing the peak concentration of the antibody in the plasma and prolonging its effect. There are many lessons to be learned from this tragedy, but an important mechanistic lesson is that once receptor occupancy starts to increase, the pharmacodynamic and pharmacokinetic response to further dose escalations becomes non-linear; in this situation, allometric scaling, which was used for TGN1412, will not work. It is important to determine in preclinical studies whether target binding occurs and, if so, a MABEL must be derived by using models that account for target binding. The MABEL is useful for protein drugs because it defines a dose at which receptor occupancy is low.

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NCA, PK, and TMDD Approaches – Pros and Cons

1- Non-compartmental analysis (NCA)
- Model independent (i.e., not mechanistic)

2- Compartmental analysis & Population PK/PD analysis
- PK drives PD
- Ability to simulate within the dose levels already tested
- A simplified biological model

3- Target-Mediated Drug Disposition (TMDD)
- PK drives PD
- and PD drives PK by integrating key biological information in model such as:
  - Receptor occupancy data
  - Relevant in vitro binding data (eg., drug-receptor complex)
  - Feedback mechanism
- Ability to better simulate PK and PD to ultimately support dose decision during drug development process

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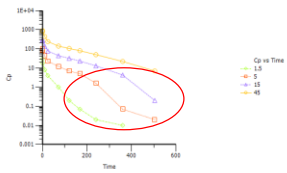
PK27 - Plot of the Data



- The area circled in red where the curves bend down and then back up is a classical TMDD profile.
- To improve one's ability to successfully fit a TMDD model to data, one should target doses to identify this trend if at all possible.
- Note that this aspect of the profile occurs at lower / intermediate doses and not at higher ones
- Getting the correct dose range to see this aspect of the curve can be difficult

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PK27 – Overview Steps

- **Plot Data**
- **Perform NCA on the ligand data**
- **Fit two standard PK models to the ligand data**
  1. **A model with MM clearance**
  2. **A model with parallel linear and MM clearance**
- **Fit three TMDDs model to the data**
  1. **Ligand only**
  2. **Ligand plus receptor**
  3. **Ligand plus receptor and ligand-receptor complex**
- **Examine the output – note how the precision of k_{on}, k_{off} and k_{eRL} improve with the simultaneous model fitting**
- **Compare the fit of the ligand only to a PK model with parallel linear and MM elimination**

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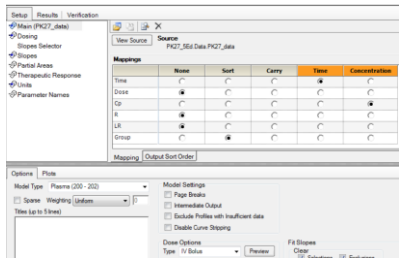
NCA Setup and Results



Dosing data

	Group	Dose	Time of Dose
1	1.5	1.5	0
2	5	5	0
3	15	15	0
4	45	45	0

NCA Results

Group	Cl_pred	AUCINF_D_pred
2	0.00389	257.00
5	0.00165	606.94
15	0.00121	825.90
45	0.00105	951.64

Note how clearance decreases and dose adjusted AUC increases with increasing dose

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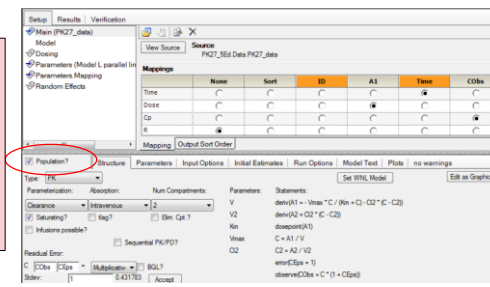
Basic PK Model – Use 1st Order Elimination

All of these models require Population mode due to simultaneous fitting of multiple dose levels. However we will use the naïve pooled mode as we only have 1 subject per dose.



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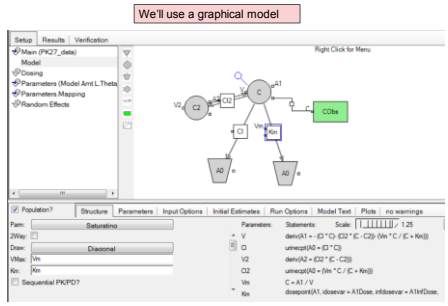
Alternative PK Model – Use Parallel 1st Order & MM Elimination

We'll use a graphical model



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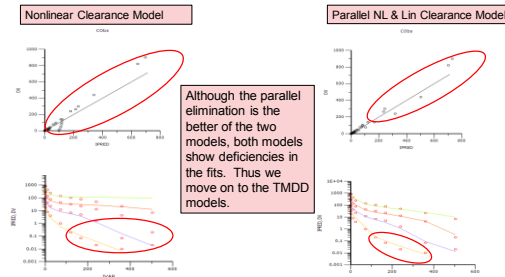
Results of Fitting Ligand Data to Linear and Nonlinear Clearance Models

Nonlinear Clearance Model

Parallel NL & Lin Clearance Model

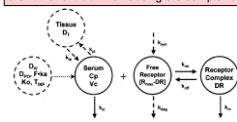


Although the parallel elimination is the better of the two models, both models show deficiencies in the fits. Thus we move on to the TMDD models.

PK27 – Initial parameter estimates and PML code for the full TMDD model

```
test(){
  deriv(A1 = (-Cl*C -Cld*(C-C2) -(kon*C*R -koff*LR)*V))
  deriv(A2 = Cld * (C-C2))
  deriv(R = kin -kout*R -kon*C*R + koff*LR)
  deriv(LR = kon*C*R - koff*LR - keRL*LR)
  C = A1/V
  C2 = A2/Vt
  kin = R0*kout
  dosepoint(A1)
  sequence{R = R0}
  error(CEps = 0.1)
  error(REps = 0.1)
  error(LREps = 0.1)
  observe(CObs = C + C*CEps)
  observe(RObs = R + R*REps)
  observe(LRObs = LR + LR*LREps)
  fixef(V = c(, 0.05, ), Vt = c(, 0.1, ), Cl = c(, .001, ), Cld = c(, 0.003, ), R0 = c(, 12, ))
  fixef(kon = c(, 0.091, ), koff = c(, 0.0011, ), kout = c(, 0.0089, ), keRL = c(, .003, ))
  secondary(Kd = koff / kon, Km = (koff + keRL)/kon)
}
```

Here I started with a basic 2 compartment bolus IV model, converted it to a textual model and edited it as follows. Statements in black are for modeling ligand only. Add the **blue** for adding the receptor data and the **red** and **blue** when adding the complex as well.



Note: in the G*W text k_{syn} and k_{deg} are denoted by k_{in} and k_{out}, respectively.

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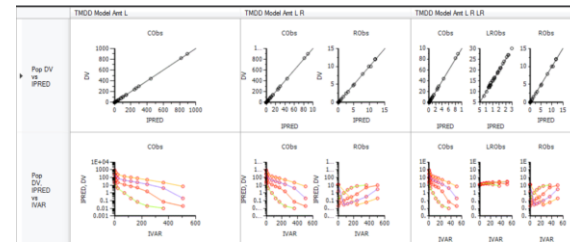
The Model Compare Object Displays Cross-Model Results (will demo)

Note the improvement in the Obs. vs. Predicted Values vs. the PK Models



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Estimated Thetas for the Three Models

Note how the precision for parameters involving the receptor improve as additional data (R and LR) are included in the model

	Name					
	Model Amt L		Model Amt L R		Model Amt L R LR	
Parameter	Estimate	CV%	Estimate	CV%	Estimate	CV%
V	0.0503	1.59	0.0506	1.08	0.0512	0.85
Vt	0.101	2.19	0.102	1.46	0.101	1.57
Cl	0.00101	1.09	0.00101	0.87	0.000999	0.96
Cld	0.00290	3.44	0.00287	2.95	0.00291	3.39
kon	0.101	17.84	0.0927	1.65	0.0968	1.59
koff	0.000895	29.78	0.000763	12.52	0.00124	4.15
keRL	0.00187	26.18	0.00169	20.60	0.00311	1.64
R0	11.9	4.09	11.9	1.80	11.8	0.62
kout	0.00890	5.46	0.00900	2.60	0.00910	1.57
stdev0	0.0422	11.36	0.0429	11.53	0.0499	11.52
stdev1			0.0519	13.44	0.0552	14.12
stdev2					0.0212	12.83

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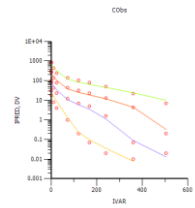
A Note on the PK Model for Ligand Only – parallel 1st order and MM Cl



Parameter	Estimate	CV%
tvV	0.0617	3.77
tvVt	0.109	21.86
tvCl	0.000992	1.50
tvCld	0.00138	15.47
tvVm	0.00666	9.99
tvKm	0.289	26.39
stdev0	0.275	14.80

Note that this model mimics the trends in the data but not as well as the TMDD model. Caution should be used if trying to use this model to extrapolate to other doses.

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Conclusions

- Due to identifiability problems one cannot estimate all of the TMDD parameters with adequate precision with only ligand data
- One should try to determine the dose range that enables one to see the distinctive TMDD profile (bending down and then back)
- Although not attempted here, If one only has ligand data another alternative is to fit the TMDD model but fixing one or more of the parameters (such as k_{on}, k_{off}, k_m) to estimates derived from preclinical data

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