Population Approach Group in Europe
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Modeling Drugs with Target-Mediated Disposition

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Introduction

Target-Mediated Drug Disposition:

- Binding to the target influences drug distribution and/or elimination;
- Most relevant for **biologics**;
- Many different classes of biologics are known to have TMDD:
  - monoclonal antibodies;
  - cytokines, growth factors;
  - fusion proteins;
  - antibody-small molecule drug conjugates;
  - hormones and metabolic factors;
- Most TMDD experience is with **monoclonal antibodies** (immunoglobulins).

Properties of Biologics that are Important for TMDD Modeling

Most biologics:

- Designed to be highly specific; act by binding to a specific target;
- PK is often influenced or even dominated by this binding;

Linear clearance of biologics:

- Dominant at high concentrations when the target-mediated pathway is saturated;
- Catabolism (for large molecules, e.g. whole IgG antibodies) or
- Renal filtration (for smaller molecules, e.g. antibody fragments);

Target-mediated clearance:

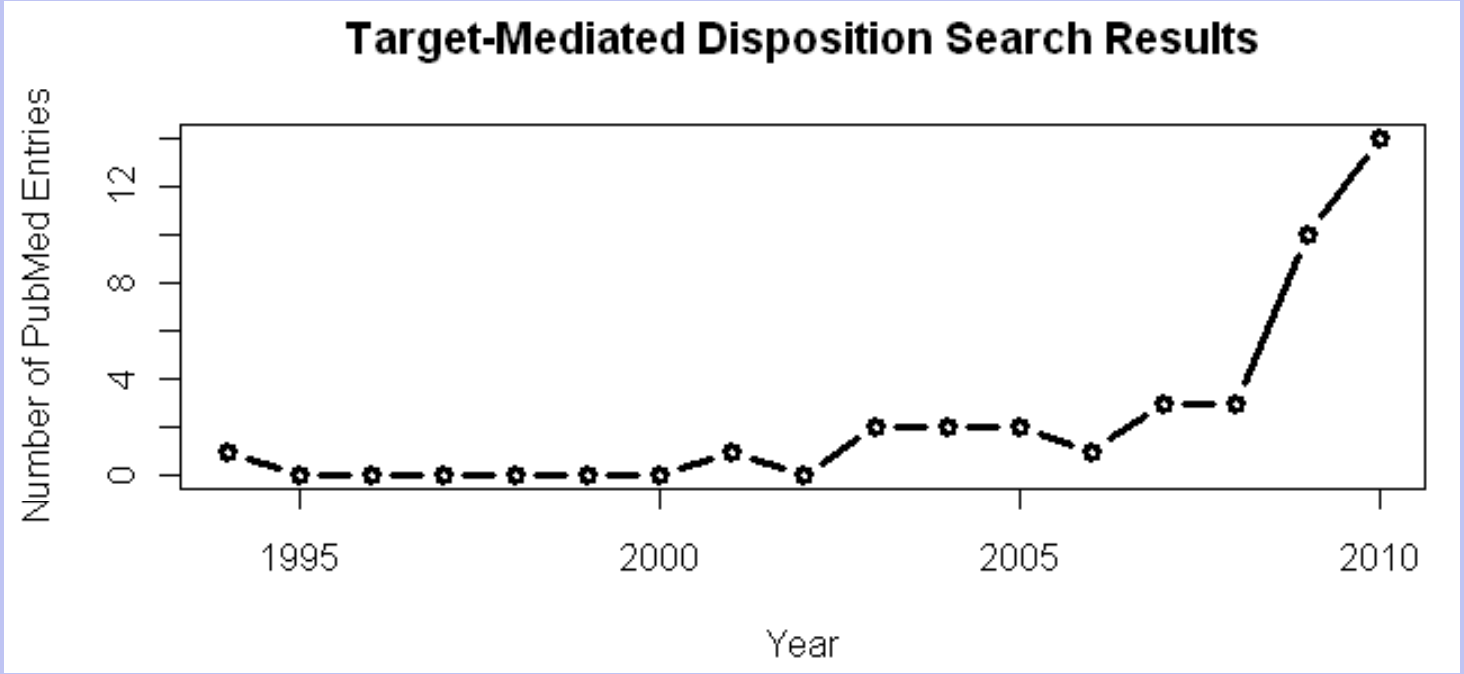
- Most visible at low concentrations;
- Results in faster than linear elimination;
- Internalization of cell surface receptors (for membrane-bound targets) followed by endocytosis;
- Catabolism (for soluble targets);
- Increases with increase of the endogenous target concentration.

TMDD Timeline

1994: TMDD idea/term was introduced by Gerhard Levy [Pharmacologic target-mediated drug disposition, Clinical Pharmacology & Therapeutics (1994) 56:248-252]

2001: TMDD equations were formulated by Don Mager and Bill Jusko [*JPP* (2001) 28: 507-532]

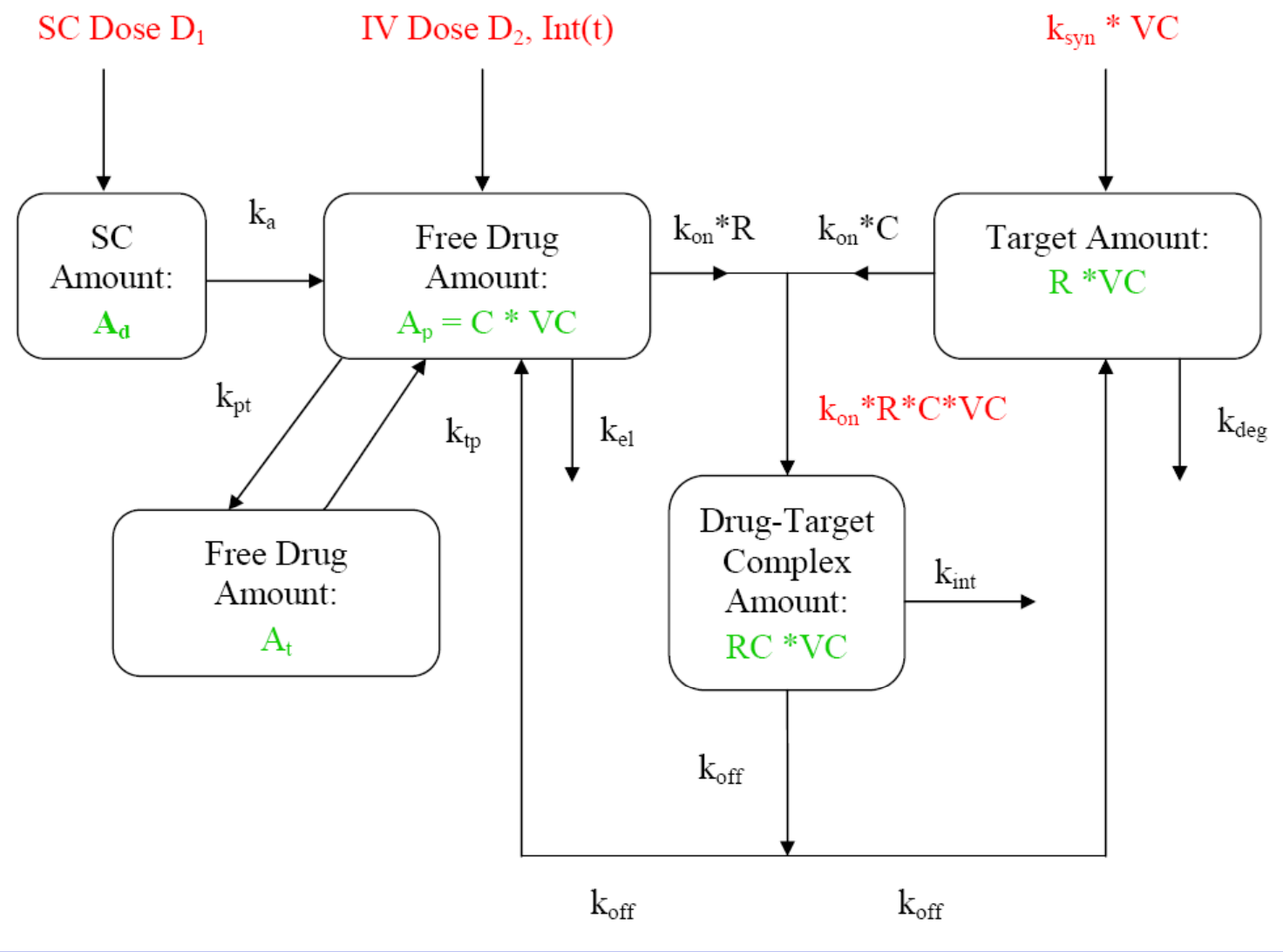
1994-2010:



2011: "Target-Mediated Drug Disposition" Session at PAGE

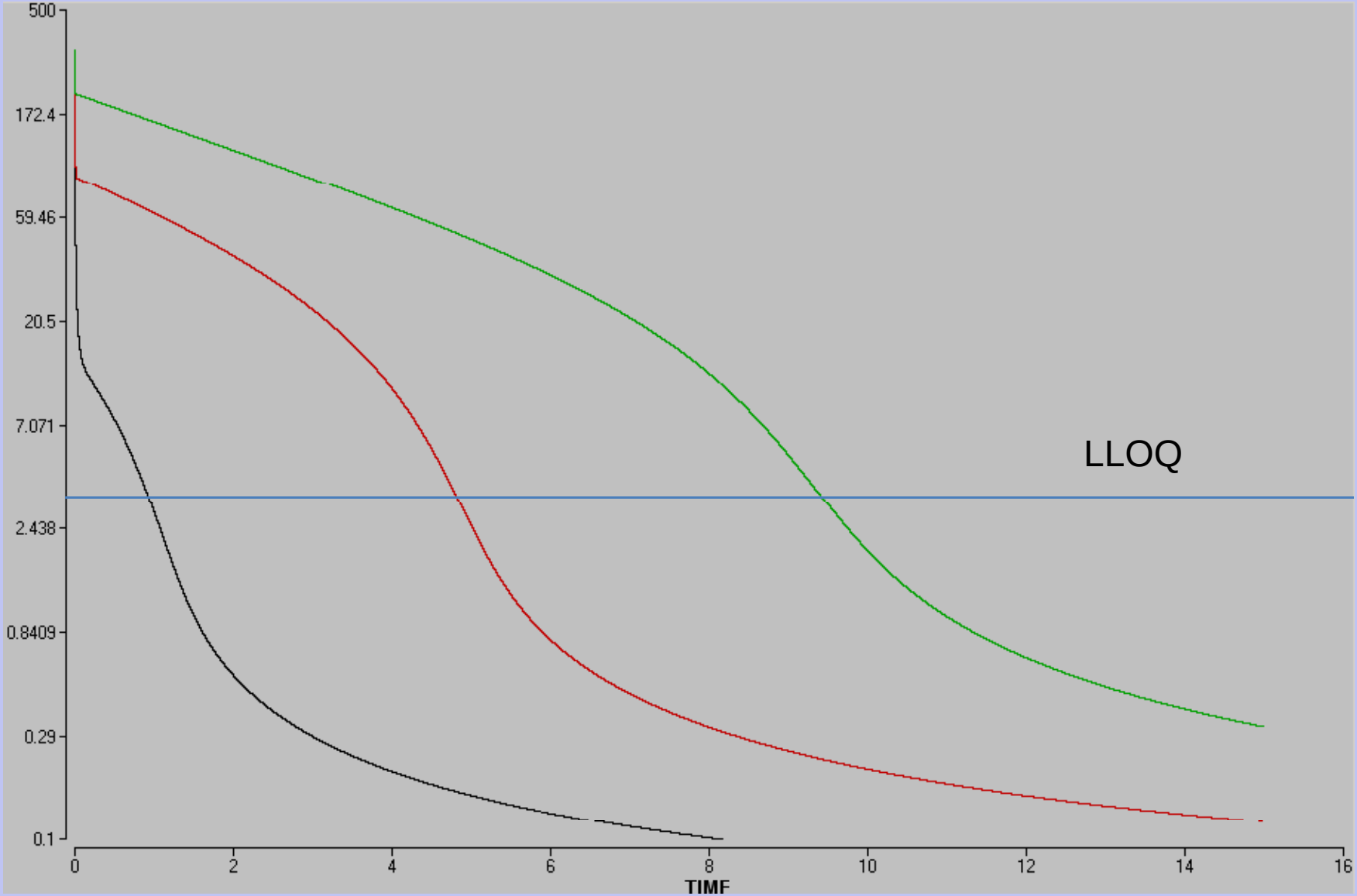
TMDD model

Red: input; Green: amount; Black: rate constants



Characteristic Concentration-Time Course Following IV bolus dose

Black: Dose=400; Red: Dose=650; Green: Dose = 1000.



TMDD equations

Formulated by Mager and Jusko [*JPP* (2001) 28: 507-532]

$$\frac{dA_d}{dt} = -k_a A_d;$$

$$\frac{dC}{dt} = \frac{In(t) + k_a A_d}{V} - (k_{el} + k_{pt})C - k_{on} C \cdot R + k_{off} RC + k_{tp} \frac{A_T}{V};$$

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

$$\frac{dR}{dt} = k_{syn} - k_{\deg} R - k_{on} C \cdot R + k_{off} RC;$$

$$\frac{dRC}{dt} = k_{on} C \cdot R - (k_{\text{int}} + k_{off})RC.$$

Initial conditions:

$$A_d(0) = F_{SC} D_1; C(0) = D_2 / V_C; A_T(0) = 0; RC(0) = 0; R(0) = k_{syn} / k_{\deg}.$$

Main assumptions

- The drug-target binding is a simple (not cooperative or allosteric) 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 inter-compartment rate constants;
- Target and drug-target complex do not diffuse to the peripheral compartment;
- 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.

Typical ranges of parameters for therapeutic monoclonal antibodies

Conversions assume 150 kDa molar weight. Information concerning target parameters (k_{deg}, k_{int}, k_{syn}, R_{max}) is difficult to find, sparse and not very reliable. The table contains approximate ranges cited in the literature.

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=0.024 L/day
V_p, V_t			3-6 L	
F_{SC}			0.3-1	
k_a			0.2-1.5 1/day	
t_{max}^{SC}			1-8 days	
k_{on}		$10^4 – 10^6$ 1/(Ms)	1-100 1/(nmol/L)/day	10^5/(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	

Problems with the TMDD equations

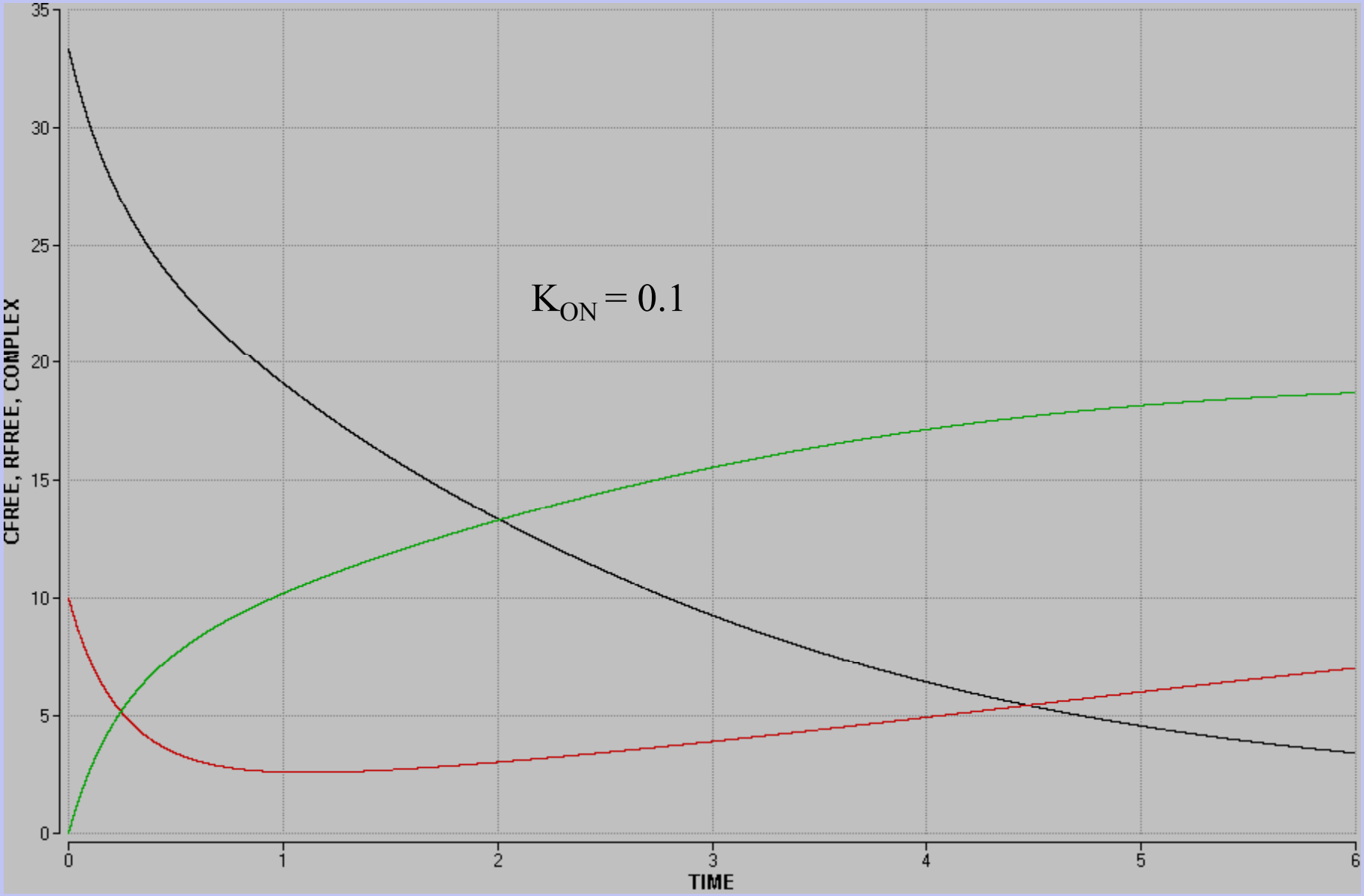
- Include processes of very different scales: binding (minutes to an hour), target-turnover (hours), elimination (days to weeks);
- Binding is much faster than the other processes: k_{on} is very large relative to the other rate constants;
- Stiff differential equations;

- Typical sampling schedules do not provide enough information to estimate binding parameters;
- Imprecise parameter estimates, especially for binding and target turnover parameters;
- Instability of the model (dependence on initial conditions);

- Long run time (weeks for a reasonable-size data set).

Concentration-time course following IV bolus dose

Black: Free Drug (C) Red: Free Target (R) Green: Complex (RC)



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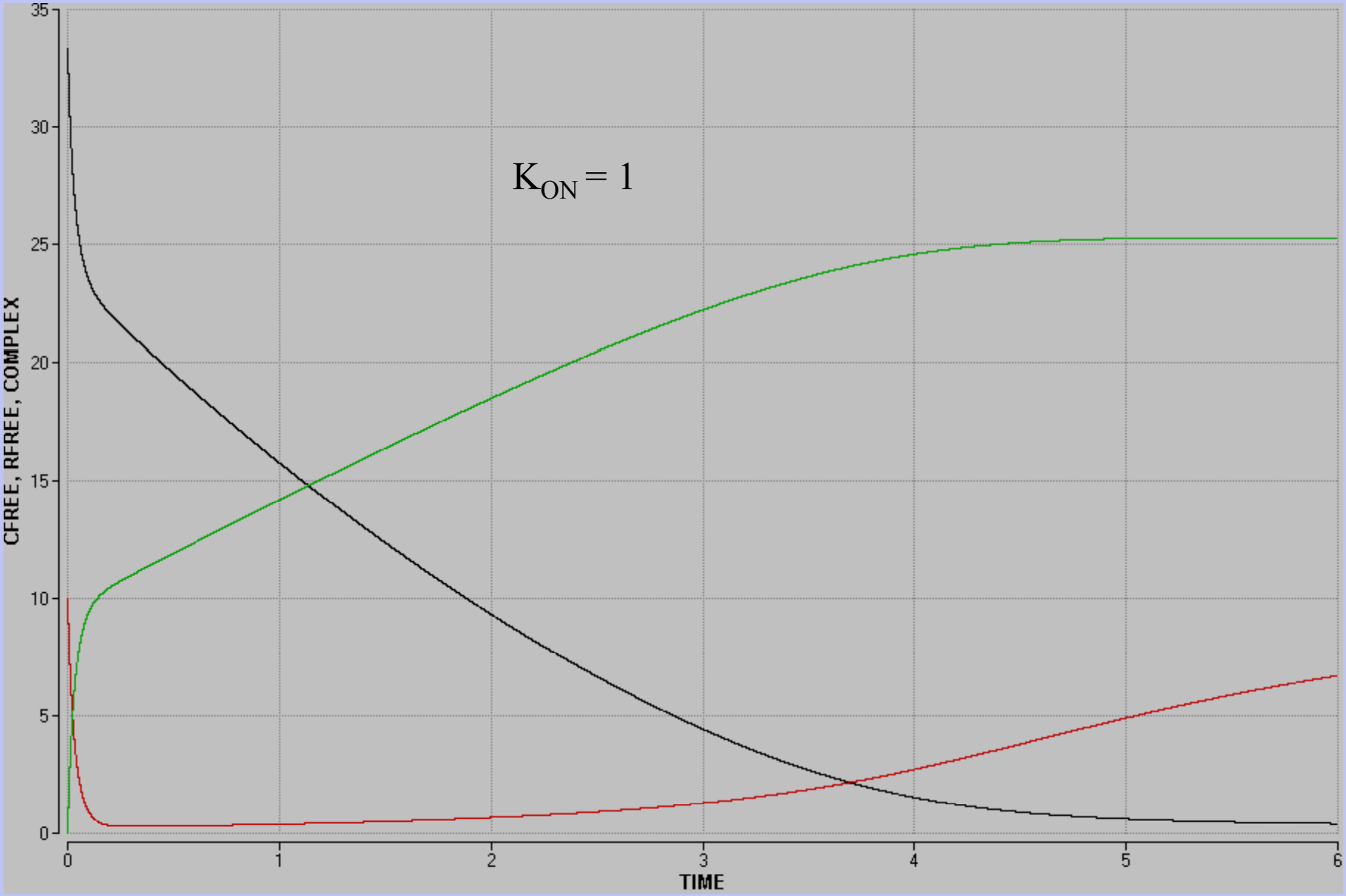

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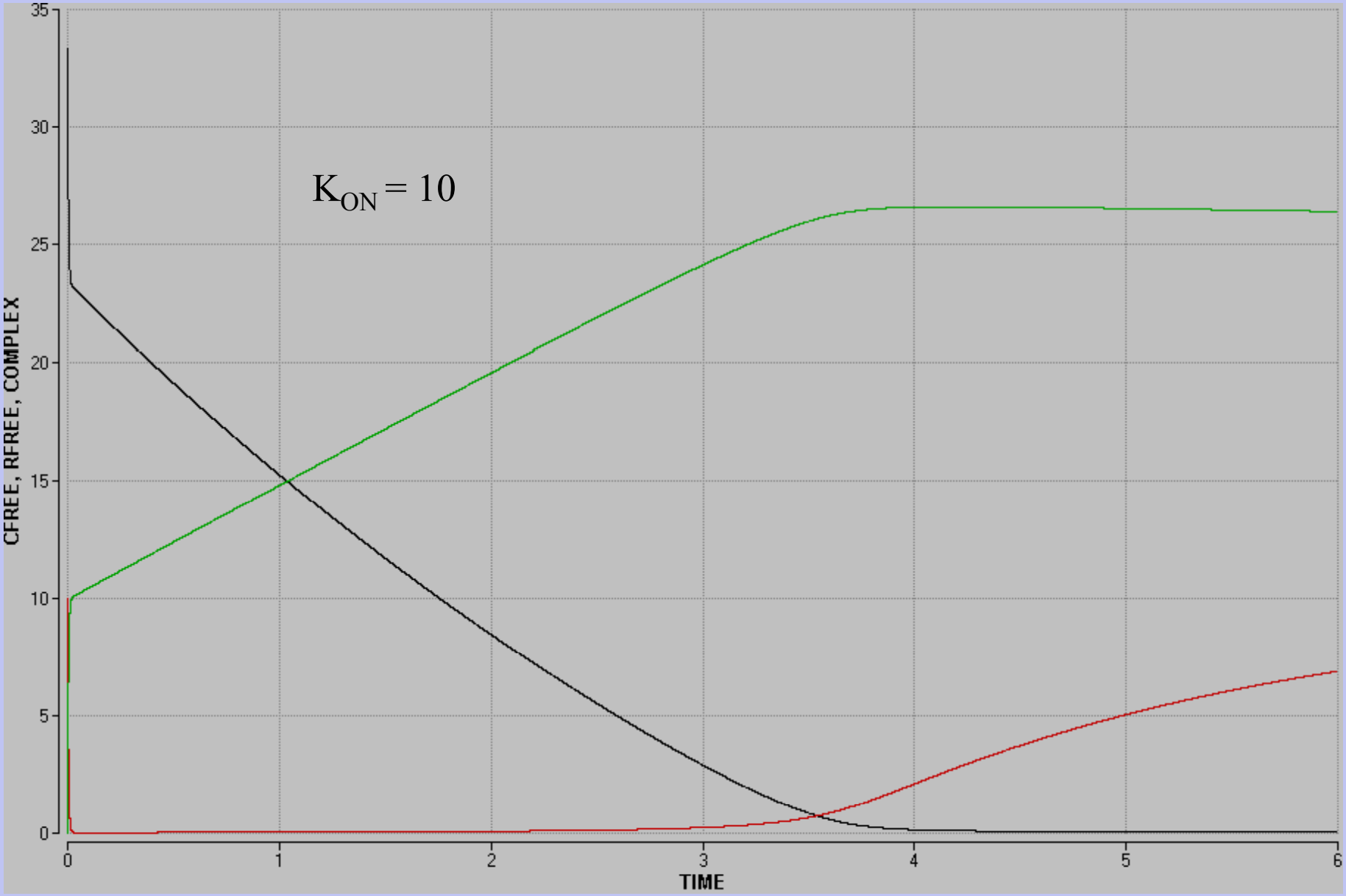
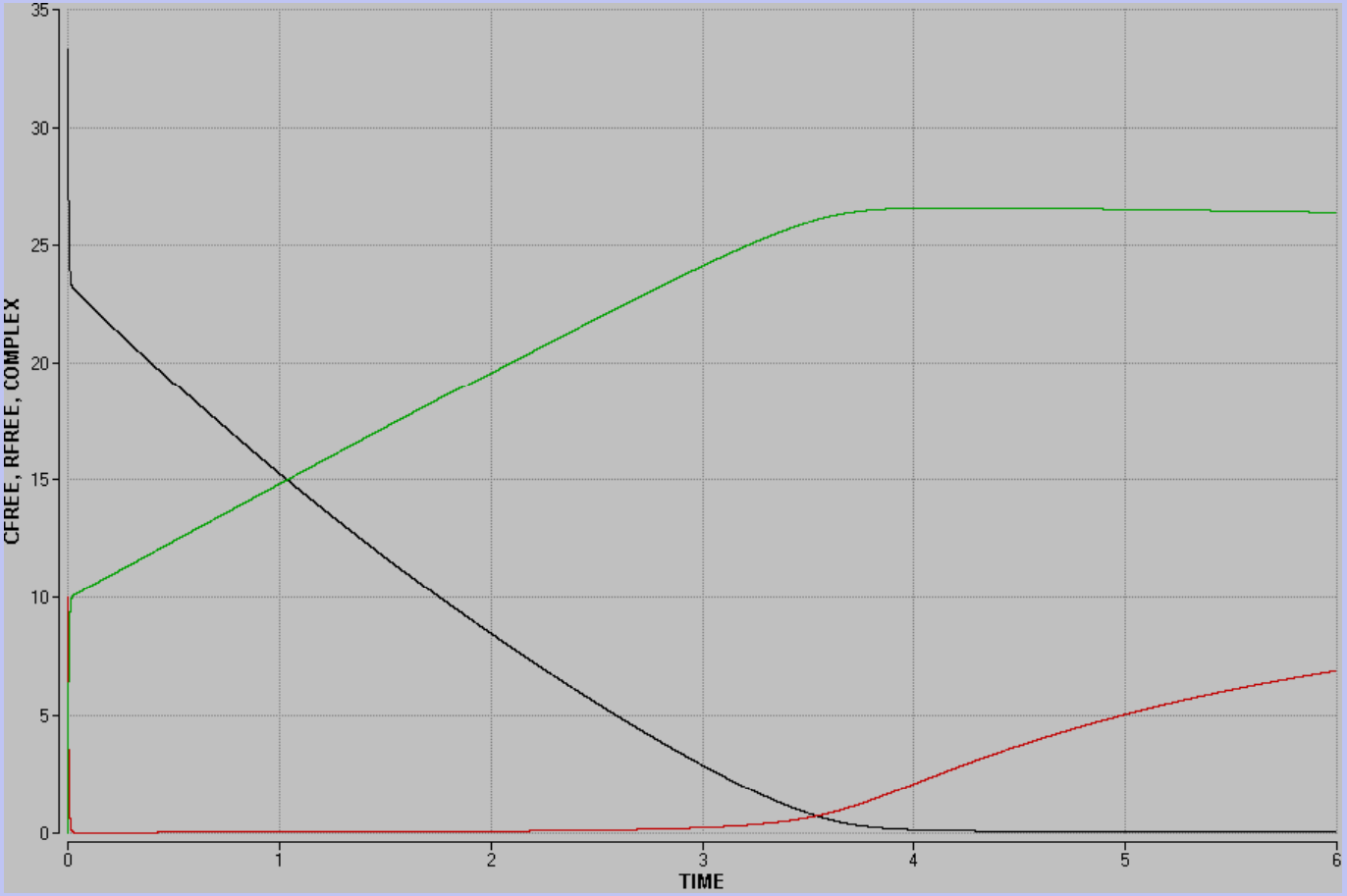


Possible solution:

Assume instantaneous binding to derive approximations that describe clinically relevant (slowly changing) processes



How to derive approximations?

Equations contain the same term $k_{on}C \bullet R$, the only large term on the right-hand side:

$$\frac{dC}{dt} = \frac{In(t) + k_a A_d}{V} - (k_{el} + k_{pt})C - k_{on}C \cdot R + k_{off} RC + k_{tp} \frac{A_T}{V};$$

$$\frac{dR}{dt} = k_{syn} - k_{\deg} R - k_{on}C \cdot R + k_{off} RC;$$

$$\frac{dRC}{dt} = k_{on}C \cdot R - (k_{\text{int}} + k_{off})RC.$$

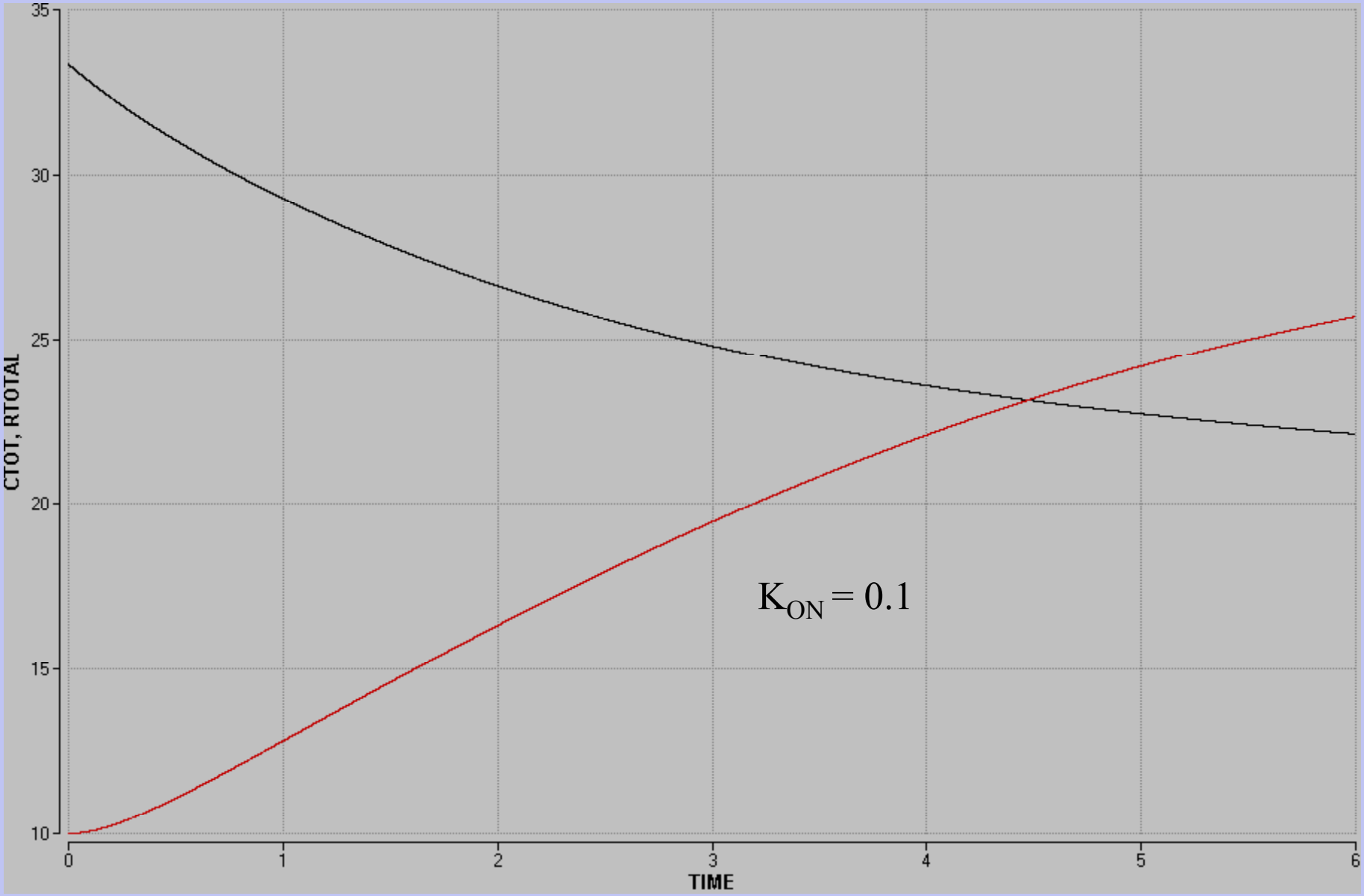
Sums of equations (1)+(3) and (2)+(3) do not contain $k_{on}C \bullet R$:

$$\frac{d(C + RC)}{dt} = \frac{In(t) + k_a A_d}{V} - (k_{el} + k_{pt})C + k_{tp} \frac{A_T}{V} - k_{\text{int}} RC;$$

$$\frac{d(R + RC)}{dt} = k_{syn} - k_{\deg} R - k_{\text{int}} RC$$

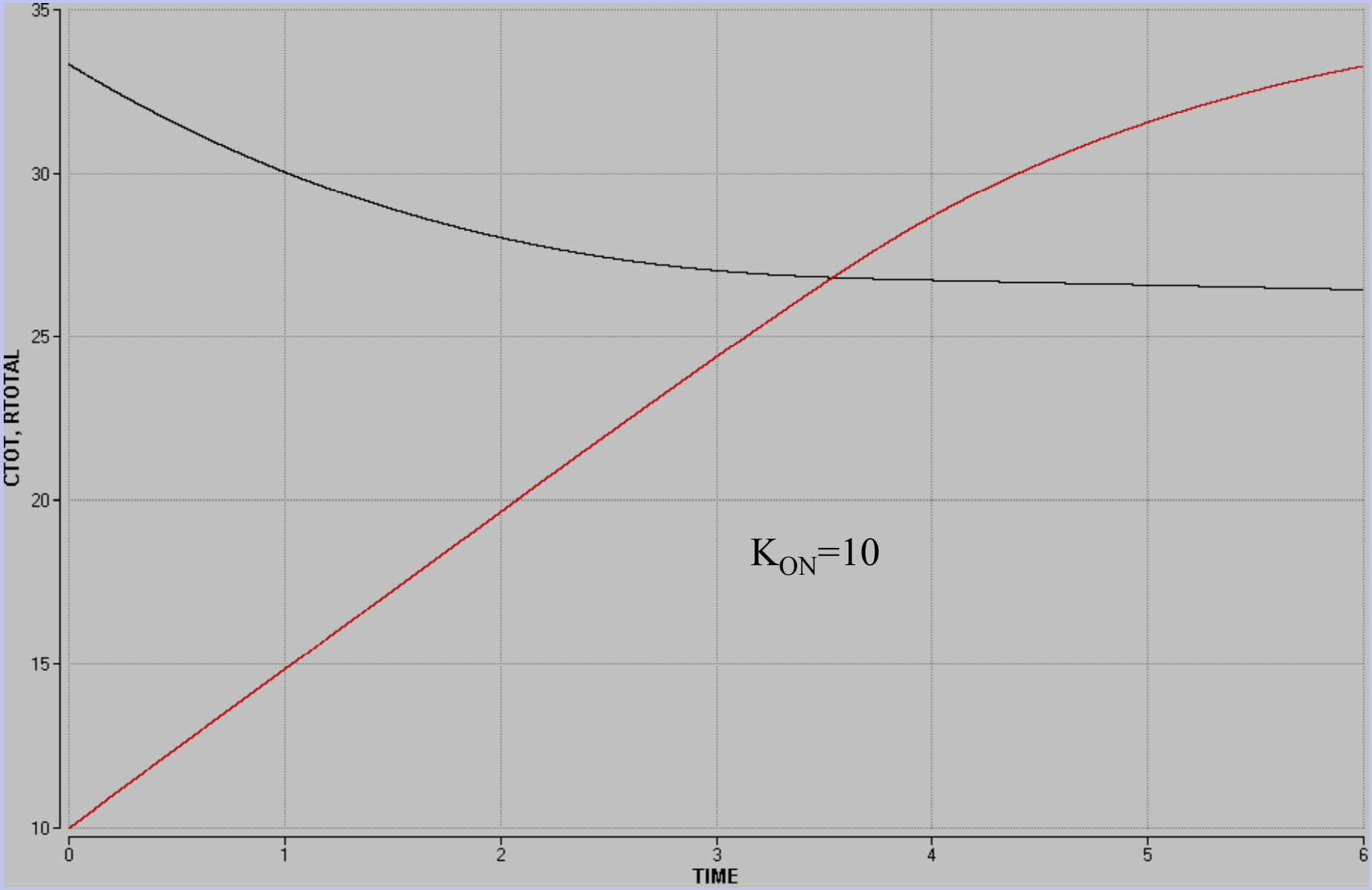
Concentration-time course following IV bolus dose

Black: Total Drug (C_{tot} = C + RC); Red: Total Target (R_{tot} = R + RC).



Concentration-time course following IV bolus dose

Black: Total Drug (C_{tot} = C + RC); Red: Total Target (R_{tot} = R + RC).



One can use "slow" differential equations for C_{tot} and R_{tot}

3 quantities (C, R, RC) enter the equations; need to be expressed via C_{tot} and R_{tot}

Two relations: $C_{tot} = C + RC$; $R_{tot} = R + RC$; one more equation is needed.

Assume that one of the "fast" equations is at quasi-steady-state (QSS).

A: Free target is at QSS:

$$\frac{dR}{dt} = k_{syn} - k_{\deg} R - k_{on} C \cdot R + k_{off} RC = 0;$$

When k_{on} and k_{off} are large, the first two terms can be neglected, resulting in quasi-equilibrium (QE) conditions:

$$0 = -k_{on} C \cdot R + k_{off} RC; \qquad \frac{C \cdot R}{RC} = \frac{k_{off}}{k_{on}} = K_D$$

B: Drug-target complex is at QSS:

$$\frac{dRC}{dt} = k_{on} C \cdot R - (k_{\text{int}} + k_{off})RC = 0;$$

$$\frac{C \cdot R}{RC} = \frac{k_{off} + k_{\text{int}}}{k_{on}} = K_{SS}.$$

If we assume that $k_{int} << k_{off}$, then $K_D = K_{SS}$

Two slow equations + Assumptions = TMDD Approximations

Approximations of the TMDD model

Quasi-Equilibrium (Rapid Binding; QE): $\frac{C \cdot R}{RC} = K_D$

Mager and Krzyzanski [*Pharm Res* (2005) 22(10): 1589-1596]

Quasi-Steady-State (QSS): $\frac{C \cdot R}{RC} = K_{SS}$

Gibiansky, Gibiansky, Kakkar, Ma [*JPP* (2008) 35(5):573-91]

Irreversible binding (IB): $k_{\text{int}} >> k_{off}; \quad R = \frac{k_{syn}}{k_{\text{deg}} + k_{on}C}$

Gibiansky, Gibiansky [PAGE 2010, abstract 1728]

TMDD and Michaelis-Menten Equations

- PK of monoclonal antibodies is often described by the two-compartment model with parallel linear and Michaelis-Menten (MM) elimination (V_{max}, K_M);
- Can we derive MM equations from the TMDD equations? YES:
- Each of the TMDD approximations can be further simplified to arrive at the Michaelis-Menten equations:

When C >> RC, QSS (QE) is equivalent to

MM **Approximation** where $V_{max}(t) = \mathbf{R_{tot}(t)}\, k_{int}$; $K_M = K_{SS}$ (K_D);

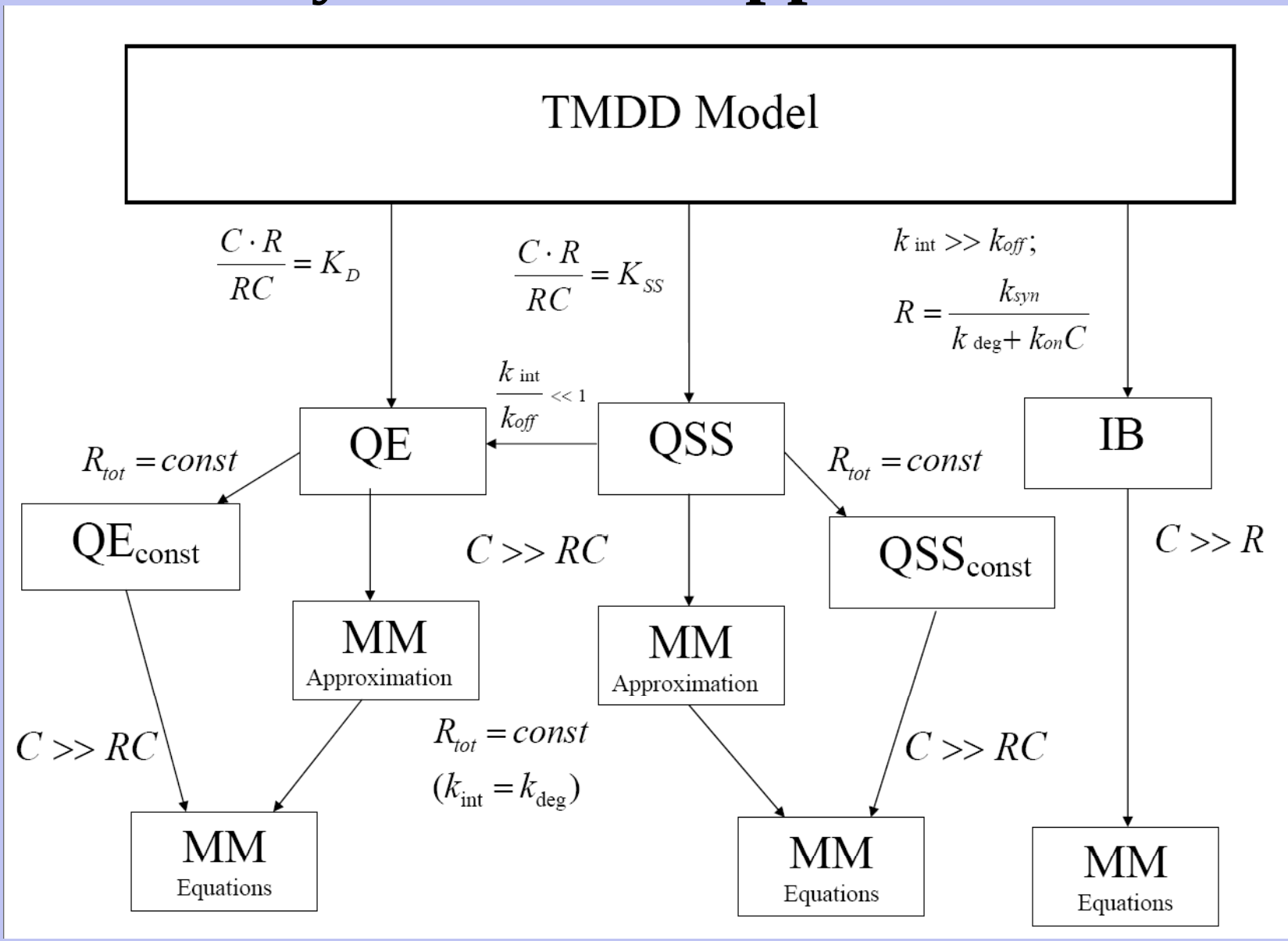
When C >> RC **and** R_{tot} = constant, QSS (QE) is equivalent to

MM **Equations** where $V_{max} = \mathbf{R_{tot}}\, k_{int} = k_{syn}$; $K_M = K_{SS}$ (K_D);

When C >> R, IB is equivalent to

MM **Equations** where $V_{max} = k_{syn}$; $K_M = k_{deg}/k_{on}$.

Hierarchy of TMDD Approximations



Identifiability of Model Parameters

The main reasons to use approximations:

- Poor identifiability of the full TMDD model parameters given the data;
- Long run time of the full TMDD model

Detailed discussion of identifiability of TMDD model parameters:

Gibiansky, Gibiansky, Kakkar, Ma: Approximations of the target-mediated drug disposition model and identifiability of model parameters. JPP (2008) 35(5):573-91.

Modeling Drugs with TMDD

The analysis of any specific drug should always start with the investigation of the underlying biological processes. When the standard assumptions do not hold, the equations should be modified to reflect mechanistic understanding of the system.

Practical considerations

- All equations are in molar form;
- AMT and DV should be converted to molar units, or conversion should be done in the Nonmem control stream (via F_i and S_i parameters);
- Nonmem usually operates in amounts while TMDD system is usually written in concentrations; one should be careful not to mix these quantities;
- It is often difficult to understand what is measured: free or total drug concentrations. Assay properties need to be understood before start of modeling.

Data

Soluble target:

- Usually, total drug concentration C_{tot} is available;
- Sometimes, both free and total drug concentrations are available;
- Sometimes, total target concentration R_{tot} is available;
- Free target concentration R is rarely available (except at baseline).

Membrane-bound target:

- Usually, only free drug concentration C is available
- Sometimes, target occupancy R/R_{tot} is available.

Quantities of interest for PK and PK-PD
(to compute in the control stream)

- Free drug concentration (C)
- Free target concentration (R)
- Drug-target complex concentration (RC)
- Total drug concentration ($C_{tot} = C+RC$)
- Total target concentration ($R_{tot} = R+RC$)
- Target occupancy (R/R_{tot})
- Ratio of free target to the baseline value (R/R_0, $R_0=k_{syn}/k_{deg}$)

How to select correct approximation?

<u>Approach 1</u>

Move from the bottom to the top, based on the model fit:

- Start with the linear model;
- Apply linear model with parallel linear and Michaelis-Menten elimination;
- Apply QSS approximation;
- Increase the complexity while checking the model fit and relative standard errors of the parameter estimates;

- We have not seen any data where the full TMDD model was needed (and/or well-estimated);
- Simulations from the full TMDD model indicate that PK of mABs with TMDD and clinically relevant PK sampling can always be described by QSS equations.

How to select correct approximation?

Useful diagnostic tools:

- Individual plots:
  - increase of elimination (slope on the semi-log-plots) at low concentrations and/or at low doses indicates non-linearity;
- Plots of random effects versus dose: consistent trends indicate that the more complex model is needed;
- Goodness of fit plots stratified by dose: dose-dependent bias indicates that the more complex model is needed;
- Precision of parameter estimates: large RSE may indicate over-parameterization;
- Consistence of the results with the model assumptions and biology.

How to select correct approximation?

Approach 2

Select approximation based on biology (properties of the drug and the target):

- Soluble or membrane target?
- Rapid or slow elimination of the drug-target complex?

Target Type: Soluble versus Membrane

What to expect for soluble low-molecular-weight target

- Likely accumulation of the drug-target complex;
- Free and/or total drug concentration is available;
- Total target or drug-target complex concentration is often available;
- The QSS approximation is the expected model.

What to expect for membrane target with fast target turn-over

- Total target concentration is likely to be small;
- Only free drug concentration is available;
- Target measurements are rarely available;
- The MM approximation (or equations) is the expected model

Each rule has exceptions !!!

Covariates that may influence PK

Covariate	Parameter	Comment
Weight	Clearance, volume	Usually, close to allometric scaling; often, CL exponent is closer to 1 rather than to 0.75
Age	Absorption rate	k_a may decline with age ~ $(AGE/AGE_{ref})^{-0.5}$; possible explanation: lymphatic transport is passive, and it may depend on skin properties and level of physical activity. Both may change/decline with age.
Disease state	Clearance	Target concentration (that may depend on disease state) may influence the target-mediated clearance. However, in several examples, disease state was seen influencing linear rather than target-mediated part of clearance.
Baseline target concentration		
Liver function, kidney function	Clearance	Usually, no effect is observed + no biological reasons to believe that liver, kidney function or gender should influence PK of mABs. For smaller biologics, kidney function may influence clearance.
Gender		

Covariates that may influence PK

Covariate	Parameter	Comment
SC Formulation	Bioavailability, absorption rate	Proteins are very sensitive to changes in formulation, even to change in solution strength (viscosity, aggregation)
SC injection dose	Absorption rate, bioavailability	Absorption may be permeation-limited and decrease with increase of volume of drug in injection
HAHA (human-anti-human antibodies) or ADA (anti-drug antibodies)	Clearance	HAHA formation may increase clearance. Often, HAHA can be measured (due to assay properties) only at low drug concentrations, for subjects with high clearance, thus confounding the censoring of observations effect and possible HAHA-induced increase of clearance.

Case study

Dosing and Sampling Scheme in the Population PK-PD Simulations

Study	N	Dosing	Sampling
1	6	Single dose, IV, 100 nmol	30 min (only IV), 6, 12, 24 hrs; then 7, 14, 28, 42, 56, 72, 86, 100, 114, 128, 132 days
	6	Single dose, SC, 300 nmol	
	6	Single dose, IV, 1000 nmol	
	6	Single dose, SC, 3000 nmol	
2	100	Three doses at 0, 28 and 56 days, SC, 1000 nmol	4, 12, 24 hrs; then 7, 28, 42, 56, 63, 70, 77, 91, 105, 119, 133, 147, 161, 175, 189 days
	100	Three doses at 0, 28 and 56 days, IV, 1000 nmol	

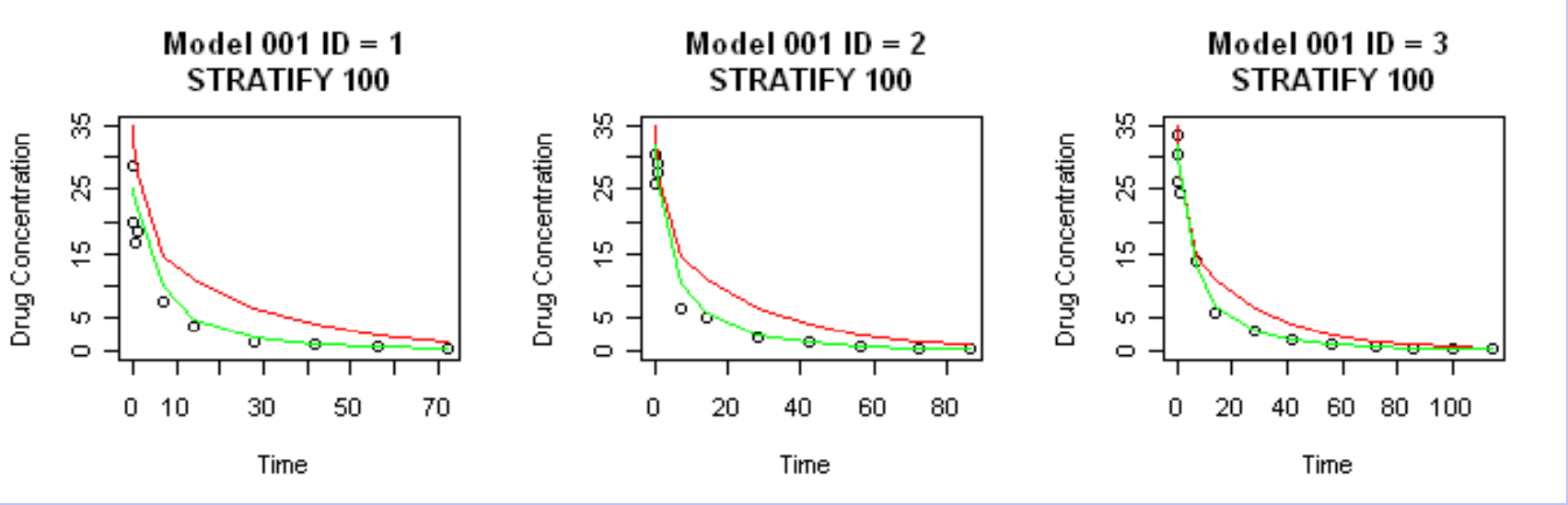
Free drug concentrations are measured

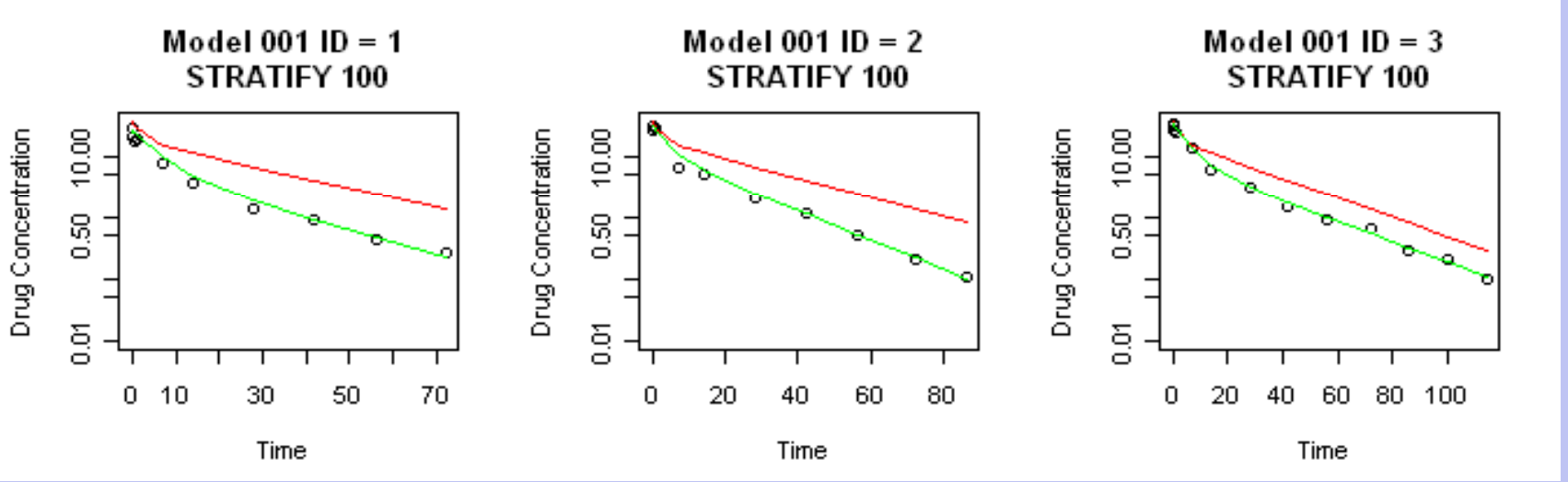
Parameters of the "True" model

Parameter	Definition	True Values
CL (L/day)	Linear clearance	0.15
V_c (L)	Central volume	3.00
Q (L/day)	Inter-compartment clearance	0.45
V_p (L)	Peripheral volume	3.0
F_1	Bioavailability	0.6
k_a (day^{-1})	Absorption rate	1.0
k_{on} $(nmol/L)^{-1}/day$	Association rate	8.0
k_{off} (day^{-1})	Dissociation rate	8.0
k_{int} (day^{-1})	Internalization rate	0.04
k_{syn} (nmol/day)	Target production rate	1
k_{deg} (day^{-1})	Degradation rate	0.2
σ^2_{conc}	Variances of the exponential residual errors	0.0225
σ^2_{target}		0.04
$R_0 = k_{syn}/k_{deg}$ (nmol/L)	Baseline target concentration	5.0
$K_{SS}=(k_{int}+k_{off})/k_{on}$ (nmol/L)	QSS constant	1.0

Linear model fit

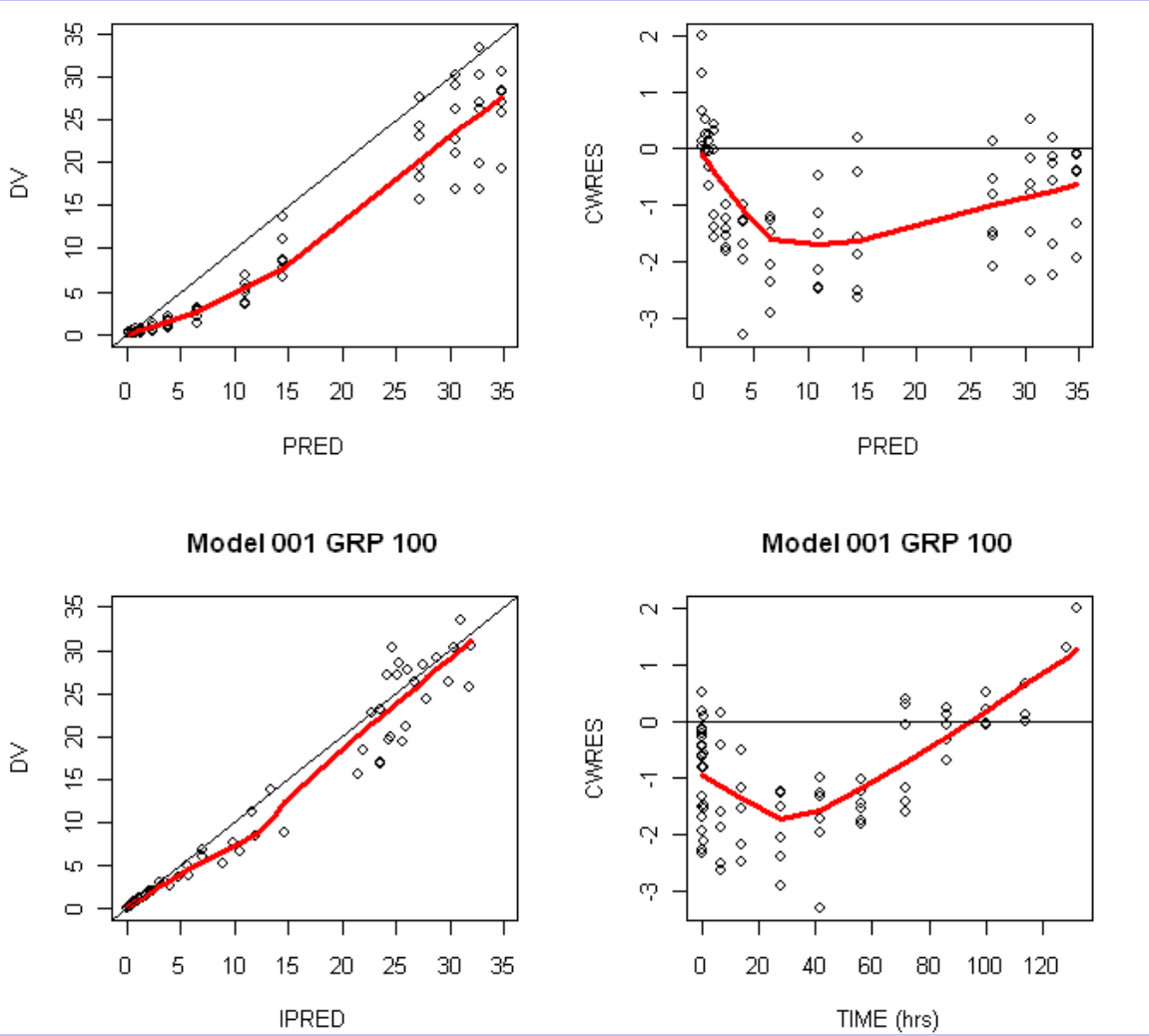
Individual plots, the lowest dose





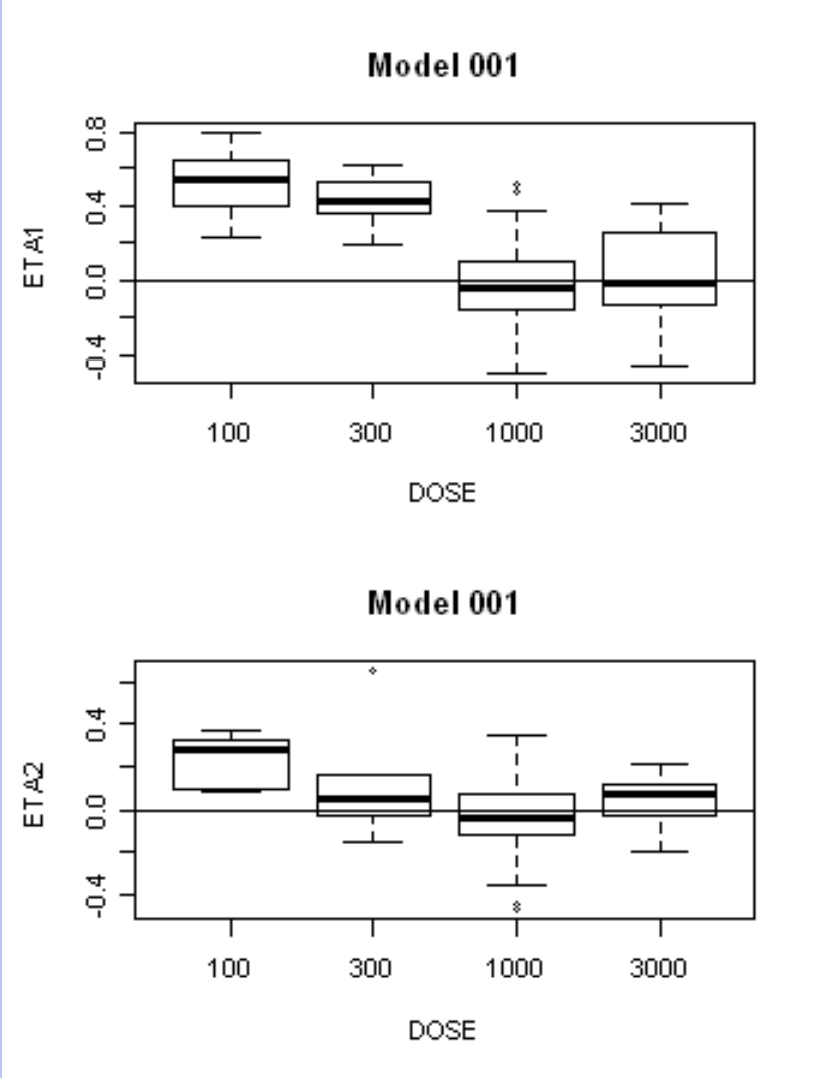
Linear model fit

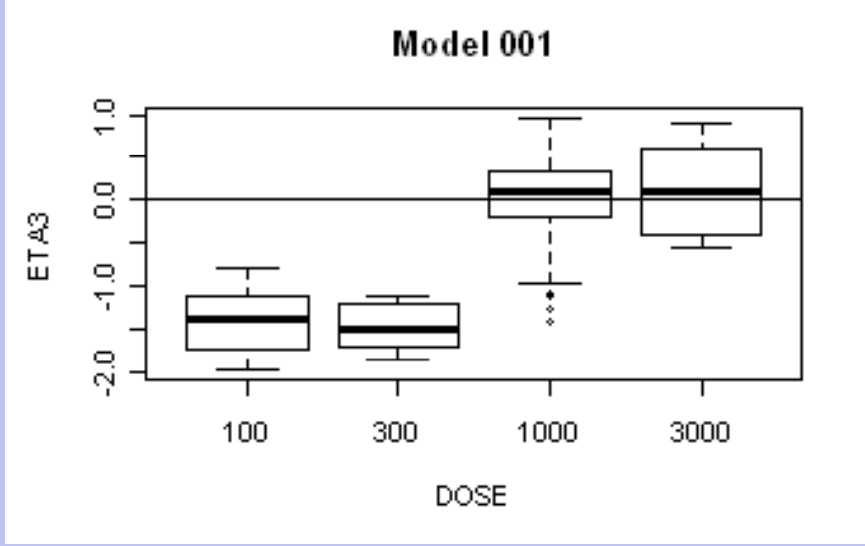
Basic diagnostic plots, the lowest dose



Linear model fit

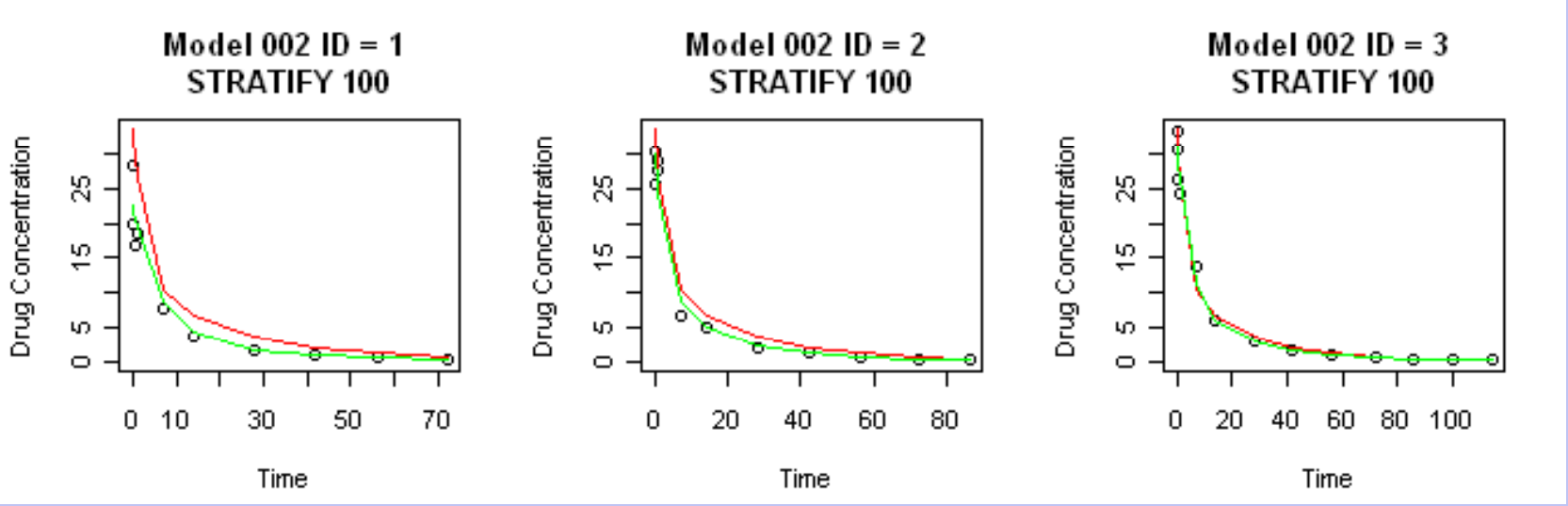
Random effects versus dose (ETA1: CL, ETA2: V_C, ETA3: Q)

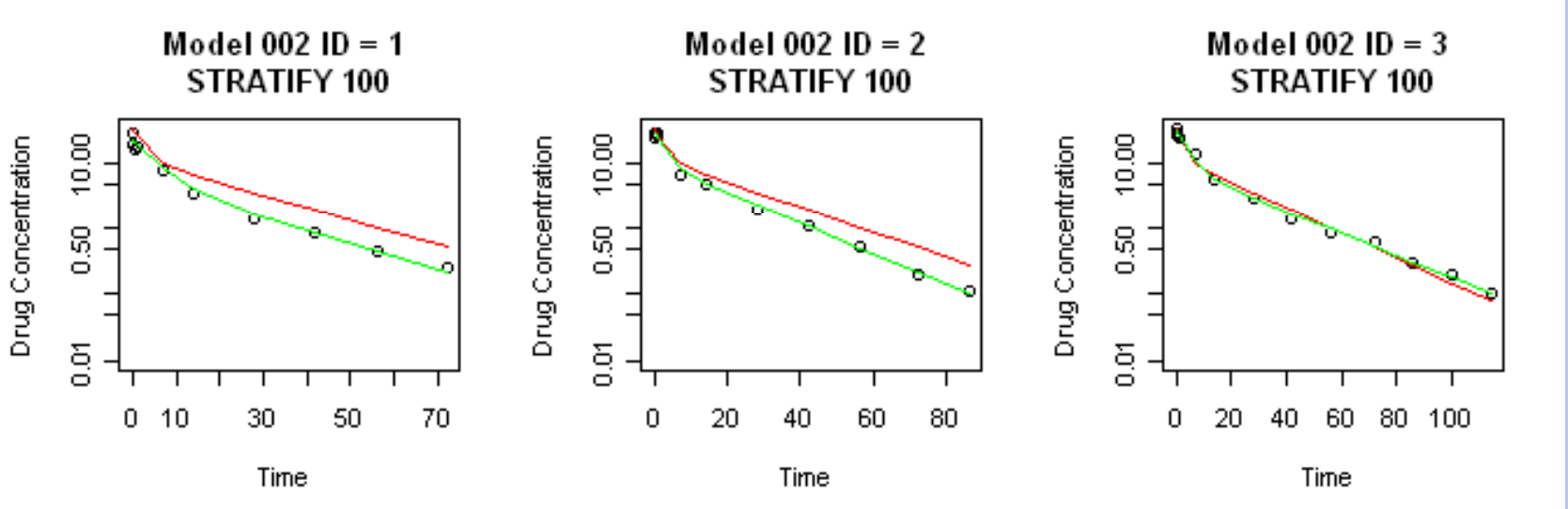




Linear + MM model fit

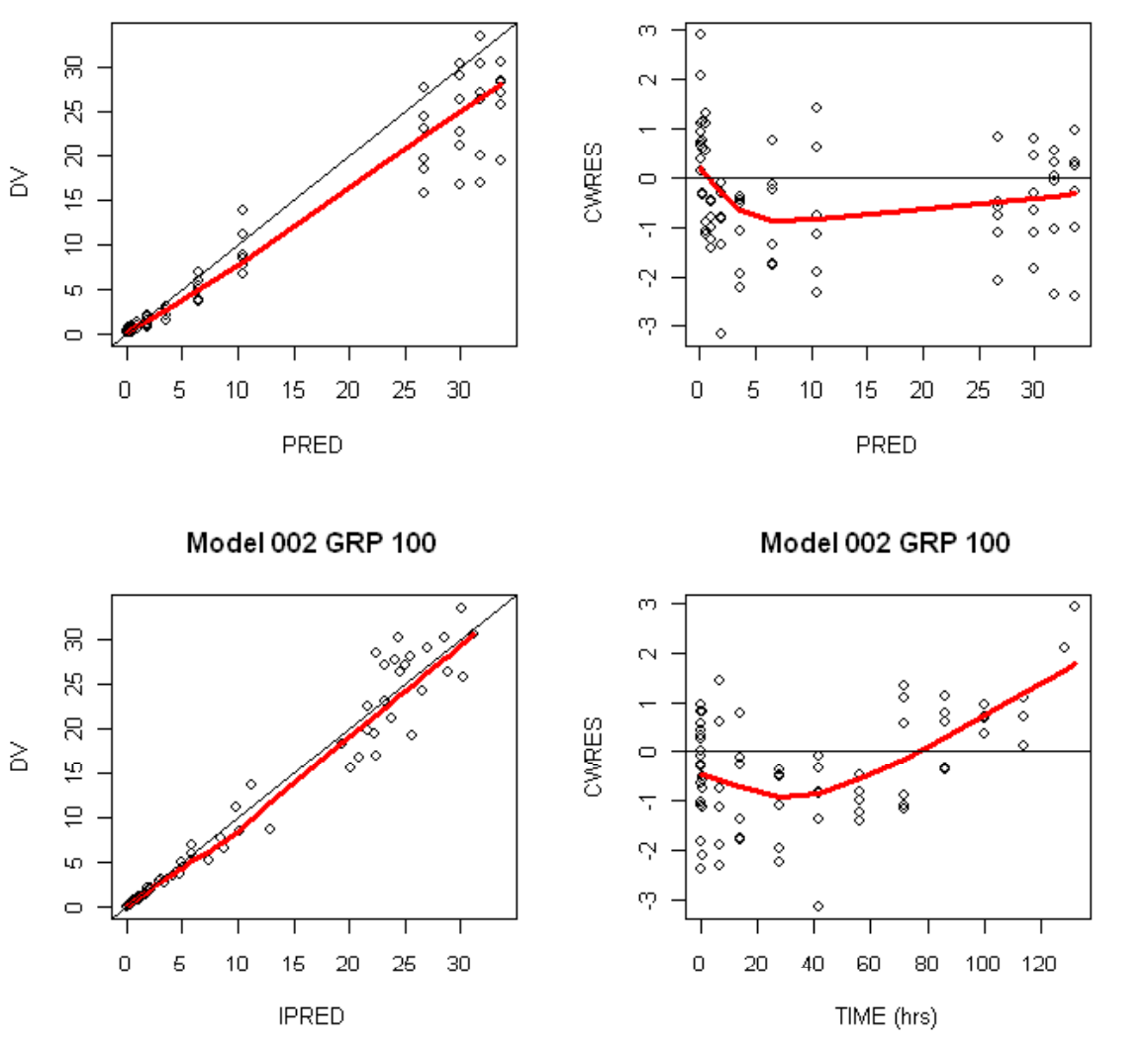
Individual plots, the lowest dose





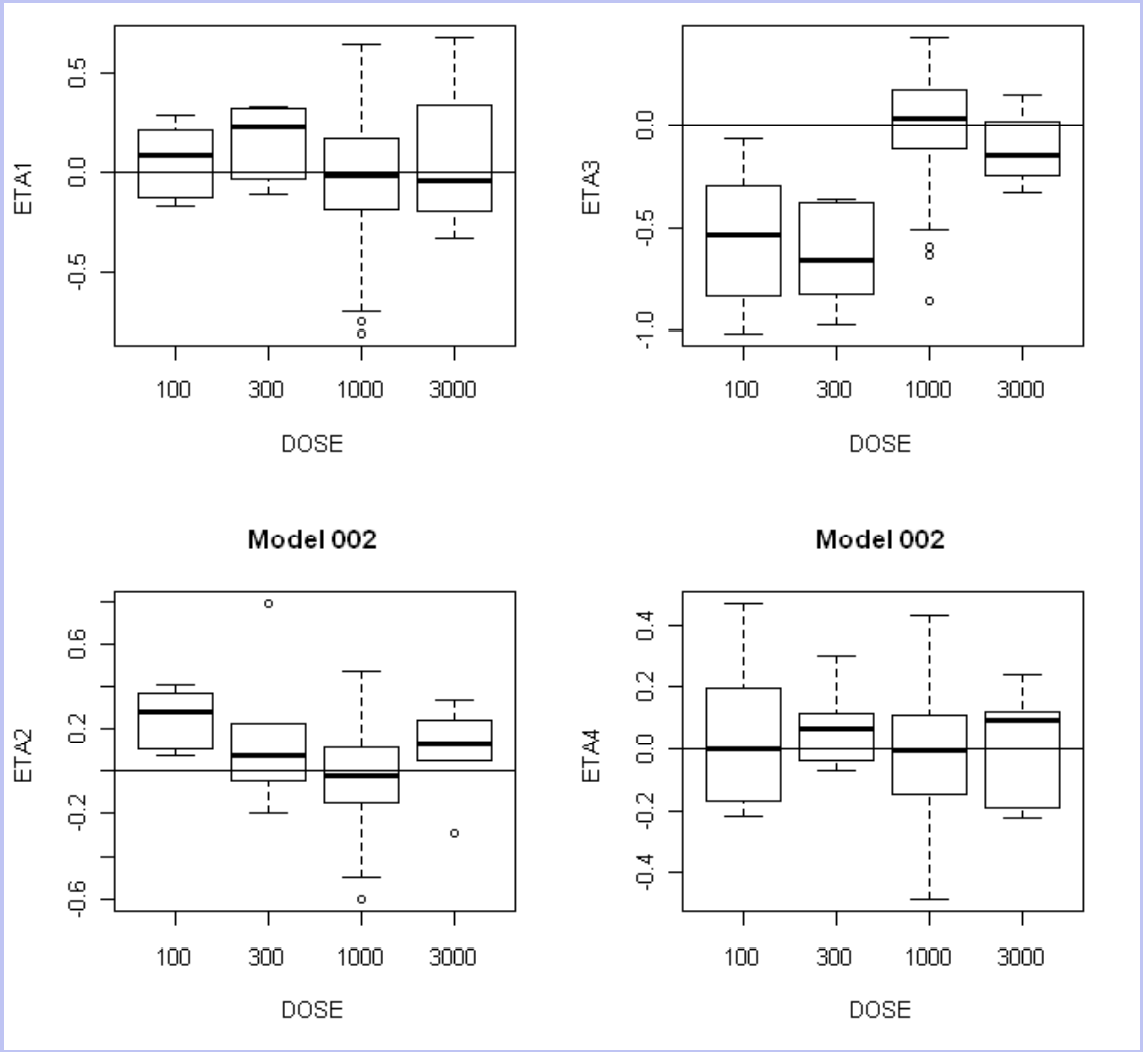
Linear + MM model fit

Basic diagnostic plots, the lowest dose



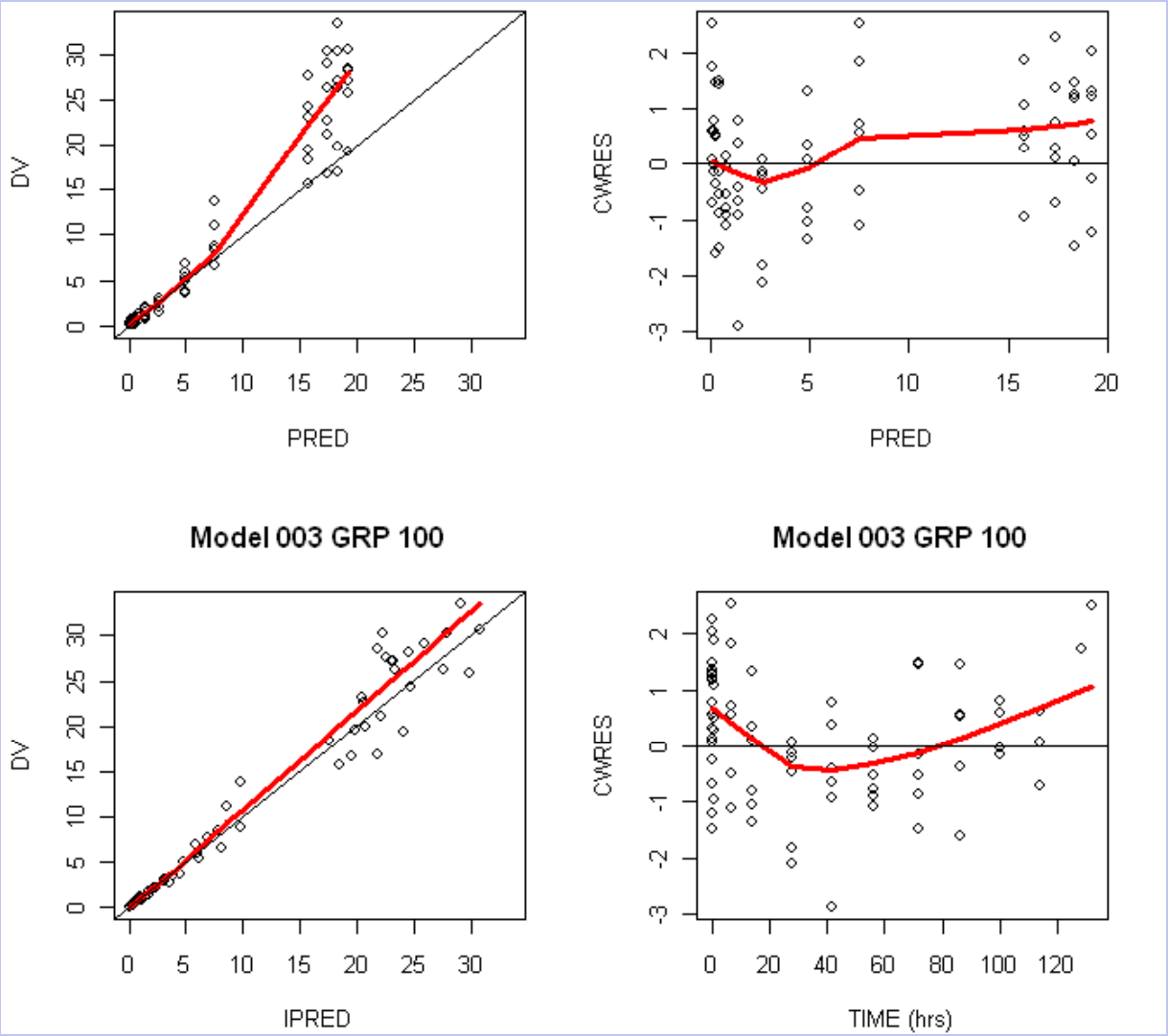
Linear + MM model fit

Random effects versus dose (ETA1: CL, ETA2: V_C , ETA3: Q , ETA4: K_{SS})



QSS - constant R_{tot} model fit

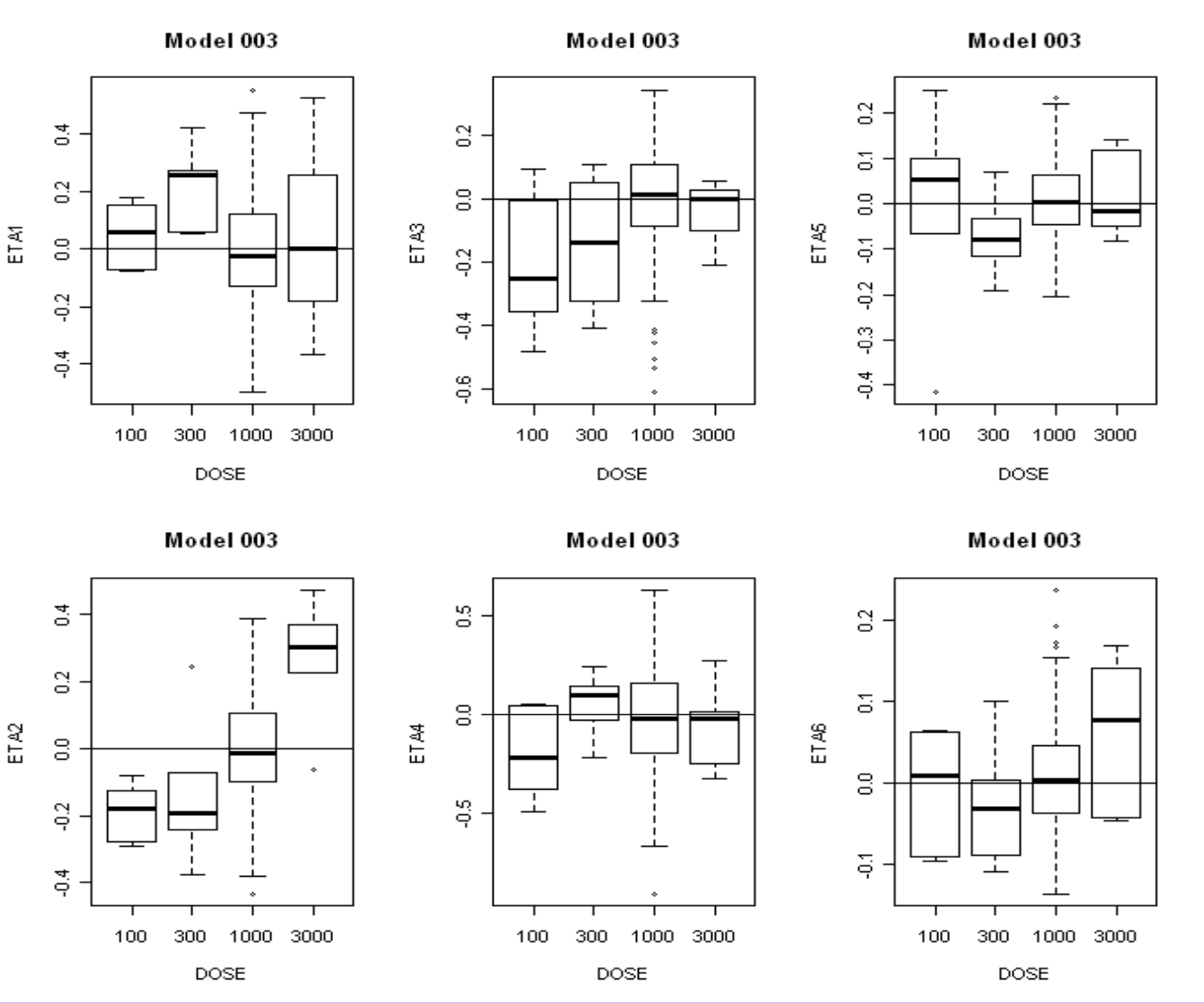
Basic diagnostic plots, the lowest dose



QSS - constant R_{tot} model fit

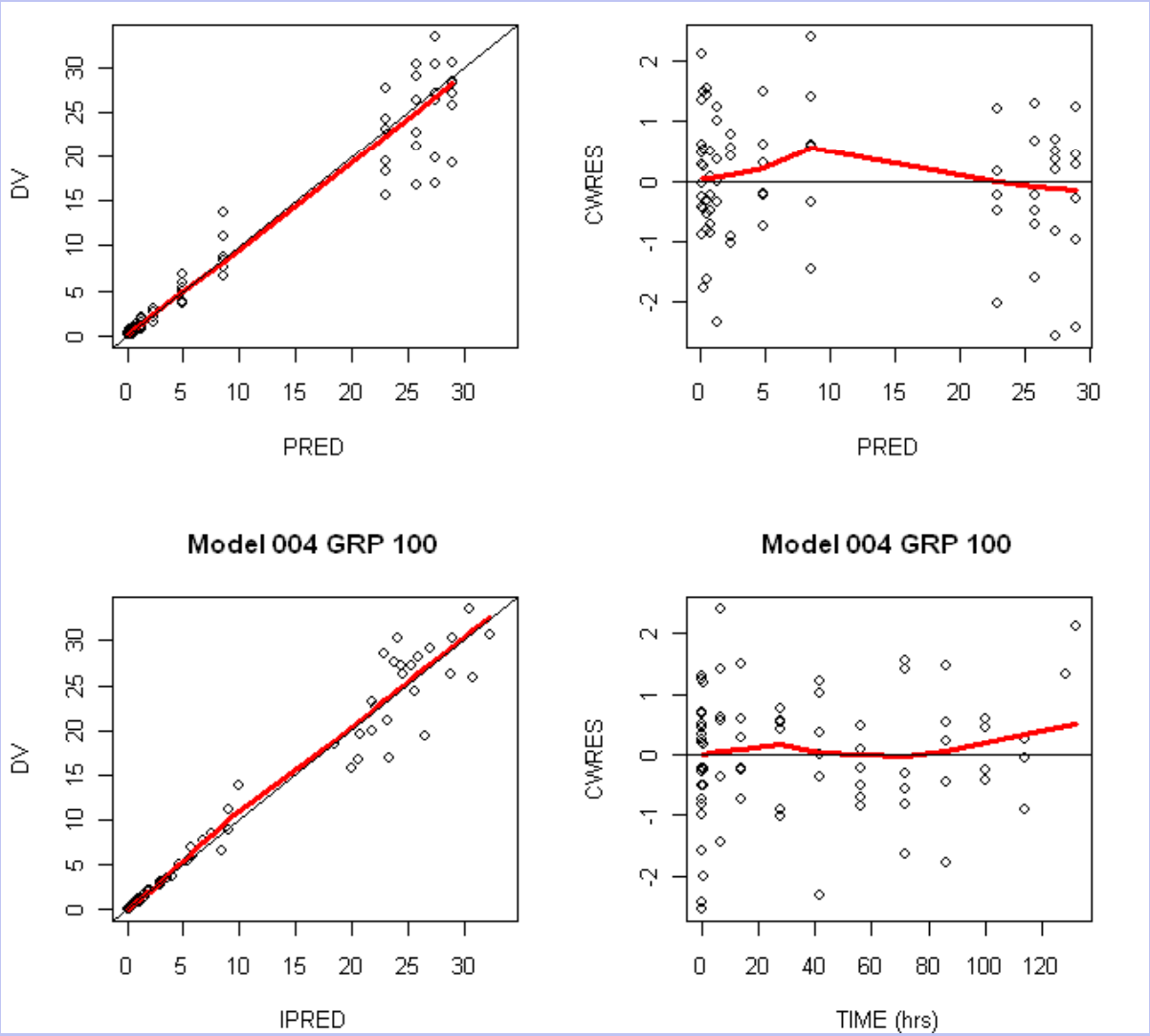
Random effects versus dose

(ETA1: CL, ETA2: V_C , ETA3: Q , ETA4: K_{SS} , ETA5: K_{INT}, ETA6: R_{TOT})



QSS model fit

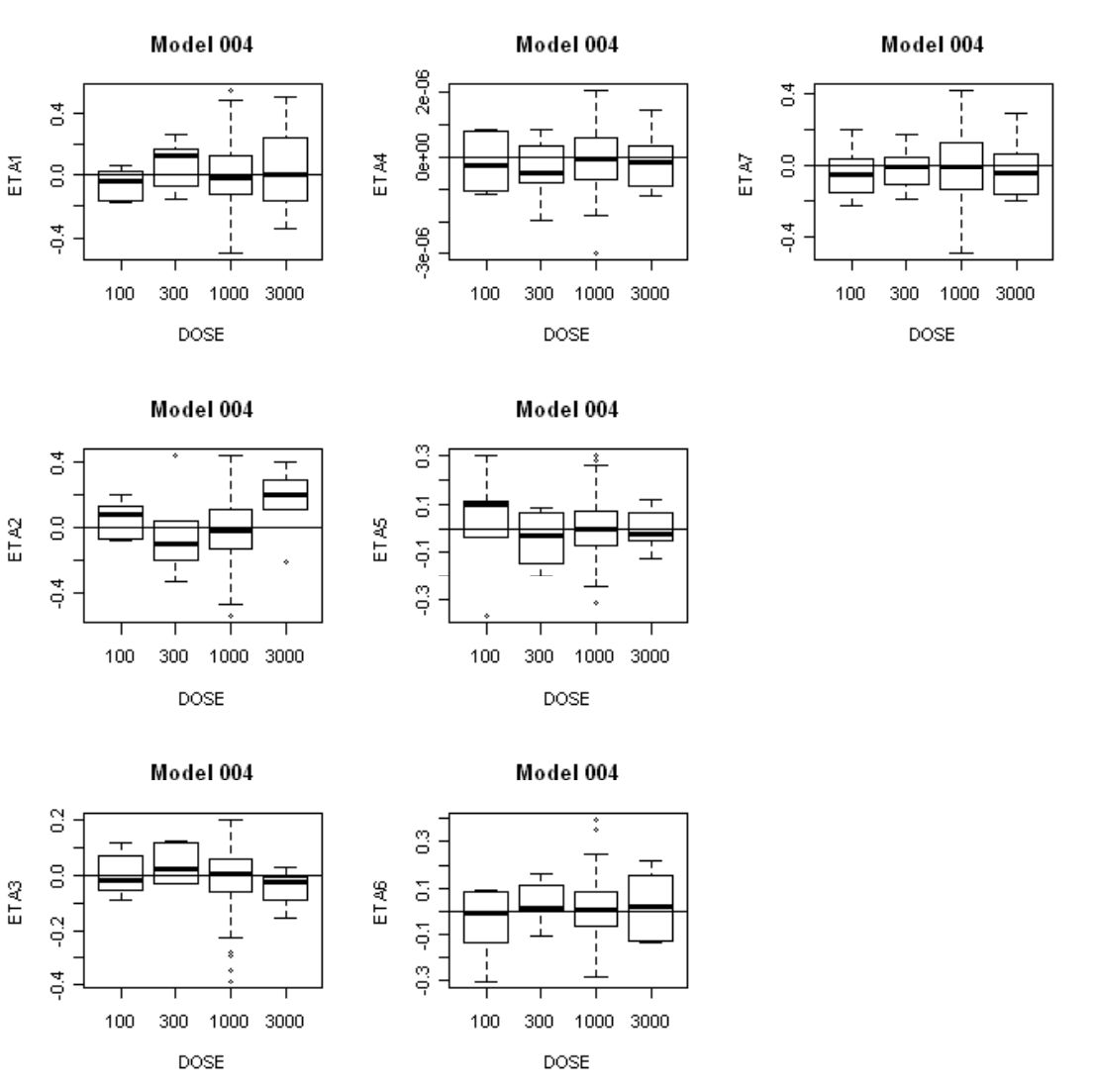
Basic diagnostic plots, the lowest dose



QSS model fit

Random effects versus dose

(ETA1: CL, ETA2: V_C, ETA3: Q, ETA4: KSS, ETA5: K_{INT}, ETA6: K_{SYN}, ETA7: K_{DEG})



Parameters of the "true", linear, MM and QSS models

Parameter	Definition	True Value	Linear	MM Model	QSS RTOT	QSS PK
CL (L/day)	Linear clearance	**0.15**	**0.189**	**0.121**	**0.163**	**0.153**
V_c (L)	Central volume	**3.00**	**2.86**	**2.96**	**2.92**	**2.92**
Q (L/day)	Inter-compartment clearance	**0.45**	**0.641**	**0.482**	**0.454**	**0.486**
V_p (L)	Peripheral volume	**3.0**	**2.03**	**3.26**	**2.60**	**2.99**
F_1	Bioavailability	**0.6**	**0.569**	**0.608**	**0.595**	**0.593**
k_a (1/day)	Absorption rate	**1.0**	**0.865**	**0.831**	**1.3**	**0.981**
k_{on}(nmol/L)$^{-1}$/day	Association rate	**8.0**				
k_{off} (1/day)	Dissociation rate	**8.0**				
k_{int} (1/day)	Internalization rate	**0.04**			**0.0362**	**0.0405**
k_{syn} (nmol/L/day)	Target production rate	**1.0**				**0.986**
k_{deg}(1/day)	Degradation rate	**0.2**				**0.185**
σ^2_{conc}	Variances of the exponential residual errors	**0.0225**	**0.0413**	**0.0257**	**0.0239**	**0.0223**
σ^2_{target}		**0.04**				
$R_0 = k_{syn}/k_{deg}$ (nmol/L)	Baseline target concentration	**5.0**			**17.3**	**5.32**
$K_{SS}=(k_{int}+k_{off})/k_{on}$ (nmol/L)	Steady-state constant	**1.0**		**45.1**	**3.05**	**1.13**
V_{max} (nmol/L/day)				**3.29**		
MVOF	Objective Function	**-8990**	**-7007**	**-8501**	**-8742**	**-9001**

Summary

- TMDD equations provide useful framework to describe drug and target concentrations for biologics;
- TMDD equations are based on many implicit and explicit assumptions; validity of these assumption should be evaluated on a case by case basis;
- Full TMDD model is rarely identifiable given the clinical data; appropriate approximations can (or even should) be used;
- TMDD model approximations provide robust, identifiable models that describe all TMDD features;
- Selection of the most suitable approximation should be guided by biological considerations and confirmed by the model diagnostics;
- Dose-dependencies of diagnostic plots and random effects can be used to identify model deficiencies and guide TMDD model development;
- Availability of data following administration of wide range of doses is important for unbiased and precise estimation of the TMDD model parameters;
- Use of incorrect approximations may result in biased parameter estimates.

Results presented in the talk were obtained in collaboration with Ekaterina Gibiansky
Additional references on the original papers will be included in the online version of the slides

THANK YOU FOR YOUR ATTENTION

Questions?

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