Citation: CPT Pharmacometrics Syst. Pharmacol. (2015) 00, 00; doi:10.1002/psp4.41

TUTORIAL

A Tutorial on Target-Mediated Drug Disposition (TMDD) Models

P Dua[1]*, E Hawkins[1,2] and PH van der Graaf[3]

Target-mediated drug disposition (TMDD) is the phenomenon in which a drug binds with high affinity to its pharmacological target site (such as a receptor) to such an extent that this affects its pharmacokinetic characteristics.[1] The aim of this Tutorial is to provide an introductory guide to the mathematical aspects of TMDD models for pharmaceutical researchers. Examples of Berkeley Madonna[2] code for some models discussed in this Tutorial are provided in the Supplementary Materials.
CPT Pharmacometrics Syst. Pharmacol. (2015) **00**, 00; doi:10.1002/psp4.41; published online 00 Month 2015

BACKGROUND AND OVERVIEW OF TMDD MODELS

The Langmuir adsorption isotherm, defined by the chemist Irving Langmuir (1881-1957),[3] forms the basis for the most common classic models of ligand–receptor binding. Using pharmacological nomenclature, it relates the amount of drug–receptor complex (P) formed with the total number of receptors (R_0) and free drug (L) in the following manner, based on principles of the law of mass action[4]:

$$P = \frac{R_0 L}{K_D + L} \qquad \text{(II.1)}$$

where K_D is the equilibrium dissociation constant. This model is based on the assumption that the concentration of the ligand greatly exceeds that of the receptor and therefore is not affected by the formation of the ligand–receptor complex. For very potent, high-affinity compounds this assumption may not be valid, and under such conditions the concentration of unbound drug will be affected by its binding to the pharmacological target and the binding model becomes[3]:

$$P = \frac{1}{2}\left[K_D + L_0 + R_0 - \sqrt{(K_D + L_0 + R_0)^2 - 4L_0R_0}\right] \qquad \text{(II.2)}$$

where L_0 is the initial, total drug concentration.

Eq. II.2 only applies to steady-state conditions where the total amount of R_0 and L_0 remain constant, which rarely applies to *in vivo* conditions. Therefore, Levy (1994)[1] introduced the concept of TMDD for the phenomenon of drug distribution through binding to the pharmacological target in the context of pharmacokinetic-pharmacodynamic (PKPD) behavior, building on earlier studies on the interplay between capacity limitation and enzyme/receptor turnover in pharmacokinetics.[5,6] Although originally proposed to describe the effects of extensive ligand-target binding in tissues for small and large molecules, TMDD has featured most prominently in the literature as a saturable clearance mechanism for biologics, in particular peptides, proteins, and monoclonal antibodies (mAbs). In parallel with growing experimental evidence supporting the TMDD concept,[7] a large body of literature has developed over the last few years addressing the theoretical aspects, typically based on mathematical analysis and simulations.

The starting point for a basic TMDD model is the binding of a drug (represented by L) to a target (R) to produce a complex (P) in a reversible reaction. This second-order binding and first-order dissociation is represented by the rate constants k_{on} and k_{off}. The elimination of the drug, target, and complex by the body are modeled by first-order rate constants $k_{e(L)}$, k_{out}, and $k_{e(P)}$, respectively. The production of the target (k_{in}) is also included. The changes of the concentrations of the three compounds with time are modeled by ordinary differential equations (ODEs) with nonlinear binding terms.

Since the first TMDD model was proposed by Mager and Jusko in 2001,[8] more complex TMDD models have been developed. The development of these models is shown in **Figure 1** and described below.

There are several classes of drug that exhibit TMDD. The main class of these are biologics, which are products produced by cutting-edge biotechnology and they include mAbs,

ABBREVIATIONS: TMDD, Target mediated drug disposition; mAb, Monoclonal antibody; QE, Quasi-equilibrium; RB, Rapid binding; QSS, Quasi-steady state; MM, Michaelis–Menten; FcRn, Neonatal Fc receptor; PK, Pharmacokinetic; PD, Pharmacodynamic; FIH, First in human; c-Mpl, Human myeloproliferative leukemia virus oncogene; TPO, Thrombopoietin; DPP-4, Dipeptidyl peptidase-4; EPO(R), Erythropoietin (Receptor); rHuEPO, Recombinant human erythropoietin; GLP-1R, Glucagon-like peptide 1 receptor; IgE, Immunoglobulin E; IgG, Immunoglobulin G; IgM, Immunoglobulin M; DKK-1, Dickkopf-related protein 1; IFN(AR), Interferon (alpha/beta receptor); EGF(R), Epidermal growth factor (receptor); IL-1Interleukin 1; CRP, C-reactive protein; SAA, Serum amyloid A; RANKL, Receptor activator of nuclear factor κ-B ligand; LIF, Leukemia inhibitory factor; rhLIF, Recombinant human leukemia inhibitory factor; MTX, Methotrexate; NTX, N-terminal telopeptide; TPO, Thyroid peroxidase; PEG-TPOm, Pegylated thrombopoietin mimetic peptide; TNF, Tumor necrosis factor; VEGF, Vascular endothelial growth factor; GO, Gemtuzumab ozogamicin; AML, Acute myeloid leukemia; G-CSF, Granulocyte-colony stimulating factor; TrkB, Tyrosine receptor kinase-B; HSP90, Heat shock protein 90.

[1]Pharmatherapeutics Research Clinical Pharmacology, Pfizer Neusentis, Cambridge, UK; [2]Department of Mathematics, University of Surrey, Guildford, UK; [3]Leiden Academic Centre for Drug Research (LACDR), Systems Pharmacology, Leiden, The Netherlands. *Correspondence: P Dua (pinky.dua@pfizer.com)
Received 27 November 2013; accepted 7 April 2015; published online on 0 Month 2015. doi:10.1002/psp4.41

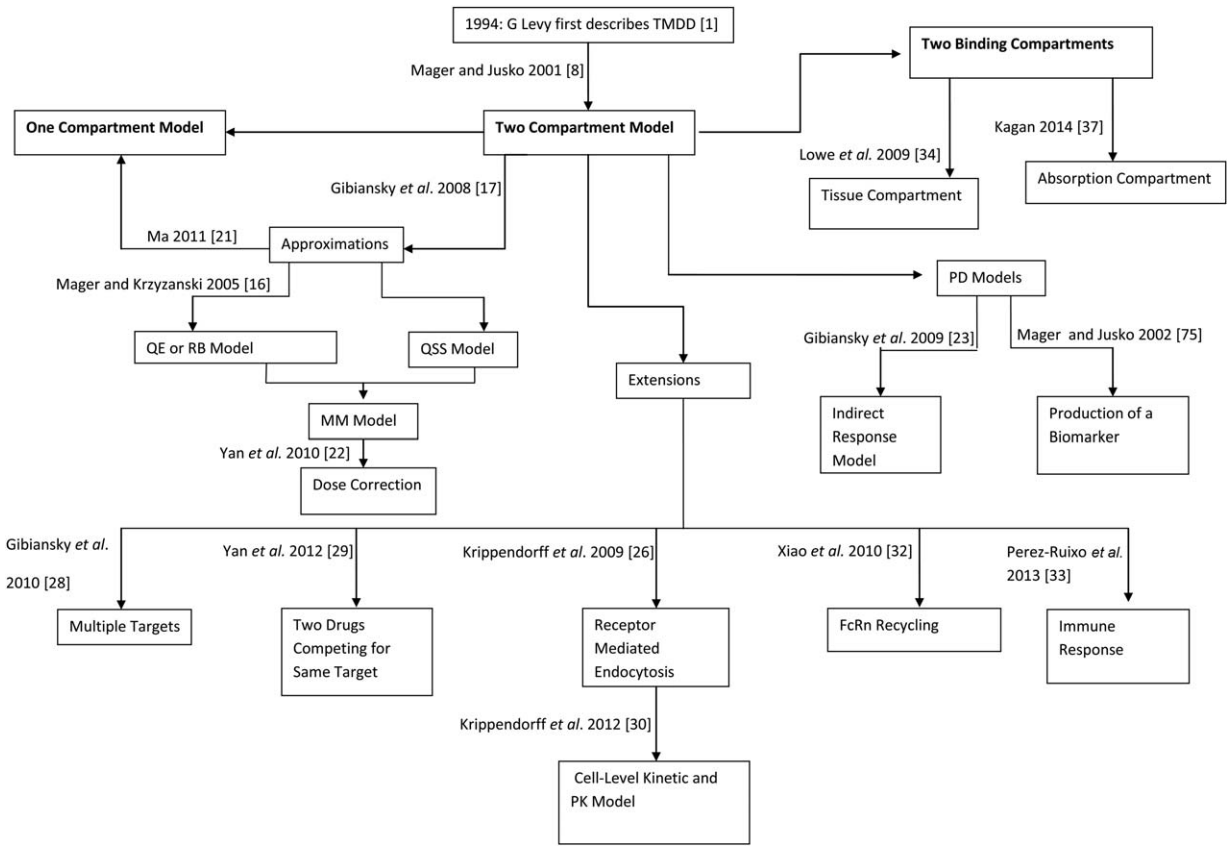

Figure 1 Flow chart showing the development of TMDD models. References alongside arrows indicate who developed the model (example models are provided in Berkeley Madonna code in the **Supplementary Material**).

cytokines, and growth factors.[9] Biologics differ from normal compounds because they are much larger, have slower absorption rates, confined distribution, and different elimination. They are designed for a specific target, typically found on the cell membrane which they bind to with high affinity.[10] Due to this high affinity, the binding to the target and subsequent turnover of the drug–target complex can contribute significantly to the disposition of biologics. However, this elimination by binding to a target is saturable because of the finite number of targets on the cell surface. This saturability causes the nonlinearity seen in TMDD models. Also, clearly some small molecules exhibit TMDD, as was the case for warfarin, the first drug to be described using TMDD by Levy in 1994.[1] Some examples of how TMDD models have been used to describe the PKPD of various drugs are provided in **Table 1**. Note that this is not a comprehensive review, which would be outside the scope of a tutorial. For a comprehensive overview of general aspects of TMDD and PKPD of biologicals, we refer to many excellent reviews in this area (see, for example, ref. 10 and references therein).

ONE-COMPARTMENT MODEL

The one-compartment model, first described by Mager and Jusko in 2001[8] and then mathematically analyzed in detail by Aston *et al*. 2011,[11] is the simplest TMDD model (**Figure 2**). This model assumes a single bolus infusion of the drug (L_0) into the central compartment (represented in **Figure 2** by the zero-order rate constant, "In").

By assuming that all reactions occur in a single compartment, only a set of three ODEs is needed to fully describe the reaction mechanism:

$$\frac{dL}{dt} = -k_{e(L)}L - k_{on}LR + k_{off}P \qquad \text{(III.1)}$$

$$\frac{dR}{dt} = k_{in} - k_{out}R - k_{on}LR + k_{off}P \qquad \text{(III.2)}$$

$$\frac{dP}{dt} = k_{on}LR - k_{off}P - k_{e(P)}P \qquad \text{(III.3)}$$

$$L(0) = L_0, \quad R(0) = R_0 = \frac{k_{in}}{k_{out}}, \quad P(0) = 0. \qquad \text{(III.4)}$$

The Berkeley Madonna code for this base TMDD model is provided in the **Supplementary Materials** (Model 1) as well as a simulation showing the nonlinear (dose- and time-dependent) behavior of the pharmacokinetics of the ligand.

Parameters that affect potency

Aston *et al*.[11] mathematically analyzed this model to answer the question of which parameters affect the potency

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
Romiplostim	c-Mpl receptor	Two Compartment QE with Depot	Yes	Platelets from precursor cells	68
TPO	c-Mpl receptor	Two Compartment	No	N/A	70
Linagliptin	DPP-4	Binding in Two Compartments QE	Yes	N/A	35
Vildagliptin	DPP-4	Binding in Two Compartments QE	No	N/A	36
rHuEPO	EPOR	Two Compartment	No	N/A	48
rHuEPO	EPOR	Two Compartment (QE and full)	Yes	Process of erythropoiesis	55, 69
Epoetin-α HEXAL/ Binocrit(HX575), rHuEPO	EPOR	Two Compartment MM (full and RB also tested)	Yes	Red blood cell production	61
Exenatide	GLP-1R	Two Compartment	Yes	Insulin, glucose	57, 66
Exenatide	GLP-1R	Two Compartment with MM absorption from Depot	No	N/A	52
Abciximab	Glycoprotein IIb/IIIa	Two Compartment Wagner	No	N/A	74
ANG317 (human mAb)	IgE	Two Compartment QSS	Yes	IL-4Rα	46
Xolair	IgE	One Compartment with Depot	No	N/A	53
Fully human IgG2 mAb	ALK1	Two Compartment	No	N/A	42
Fully human IgG2 mAb	Hepcidin	FcRn Recycling	No	N/A	32
Anti-DKK-1 IgG2 antibody	DKK-1	Two Compartment	No	N/A	54
Rituximab	IgG	Three Compartment	No	N/A	27
Rituximab	IgG	FcRn Recycling	No	N/A	72
IFN-β	IFNAR	Two Compartment with Depot and Lymph	Yes	Neopterin	75, 76
IFN-β	IFNAR	Two Compartment RB	Yes	IP-10 mRNA	7
IFN-β	IFNAR	Two Compartment RB with Lymph	No	N/A	47
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
TRX 1	CD4 receptor	Two Compartment	No	N/A	79

Table 1. *cont.*

Ligand	Receptor	PK model used	PD model used	Biomarker	Reference
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

of the drug. In this context, potency was defined as the concentration (or amount) of drug needed to produce a defined response or effect.[12] In the analysis reported by Aston *et al.*,[11] potency was measured by calculating the minimum amount of target (R_{min}) observed after drug administration. The higher the potency of a given dose of the drug the smaller the value of R_{min}. Obviously, it was concluded that R_{min} was minimized when $K_D = \frac{k_{off}}{k_{on}}$ was reduced, i.e., when $k_{on} \to \infty$ and $k_{off} \to 0$. However, increasing k_{on} was found to be more effective than decreasing k_{off} as a saturation effect was observed, when $k_{off} \to 0$, R_{min} approached a positive limit. However, other measures of potency, such as area under the curve (AUC), were not considered to see whether increasing the binding rate resulted in increased potency in general.

Chimalakonda *et al.*[13] investigated the percentage inhibition of the receptor and confirmed that decreasing K_D by increasing k_{on} resulted in lowering the minimum concentration of the receptor and improving the duration of receptor inhibition. However, the maximum duration of receptor inhibition was found to be fixed for a particular antibody and dose, regardless of its binding rate. Therefore, improving the binding affinity beyond a certain value would not result in longer duration of inhibition. However, this result was found from simulations of receptor concentrations and as far as we know has not yet been confirmed using mathematical analysis.

Parameters that affect rebound

The parameters that affected rebound were also mathematically analyzed by Aston *et al.*[14] (see **Figure 6**). Rebound is the process that describes the postdose increase of free receptor concentrations to greater than the original free receptor baseline value. Rebound occurs for single and multiple doses if and only if the elimination rate of the product ($k_{e(P)}$) is slower than the elimination rates of the ligand ($k_{e(L)}$) and receptor (k_{out}). Very recently, this work has been extended by an analysis that takes into account feedback mechanisms.[15]

TWO-COMPARTMENT MODEL: BINDING IN THE CENTRAL COMPARTMENT

This model, first described by Mager and Jusko in 2001,[8] assumes that only unbound drug can distribute into a peripheral tissue compartment, while other ligands remain in the central compartment. The concentration of drug in the tissue compartment is given by L_T and the rate at which the drug is transferred between plasma and tissue is given by the first-order rate constants, k_{pt} and k_{tp}, respectively (**Figure 3**).

Since an extra compartment is added, another equation is added resulting in the following model:

$$\frac{dL_T}{dt} = k_{pt}L_C - k_{tp}L_T \tag{IV.1}$$

$$\frac{dL_C}{dt} = -k_{e(L)}L_C - k_{on}L_C R + k_{off}P - k_{pt}L_C + k_{tp}L_T \tag{IV.2}$$

$$\frac{dR}{dt} = k_{in} - k_{out}R - k_{on}L_C R + k_{off}P \tag{IV.3}$$

$$\frac{dP}{dt} = k_{on}L_C R - k_{off}P - k_{e(P)}P \tag{IV.4}$$

$$L_C(0) = L_{C0}, \quad L_T(0) = 0, \quad R(0) = R_0 = \frac{k_{in}}{k_{out}}, \quad P(0) = 0. \tag{IV.5}$$

An outline of the Berkeley Madonna code for this two-compartment TMDD model is provided in the **Supplementary Materials** (Model 2).

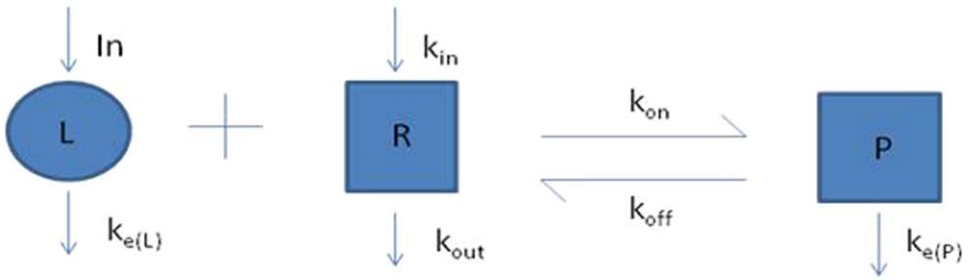

Figure 2 One-compartment TMDD model.

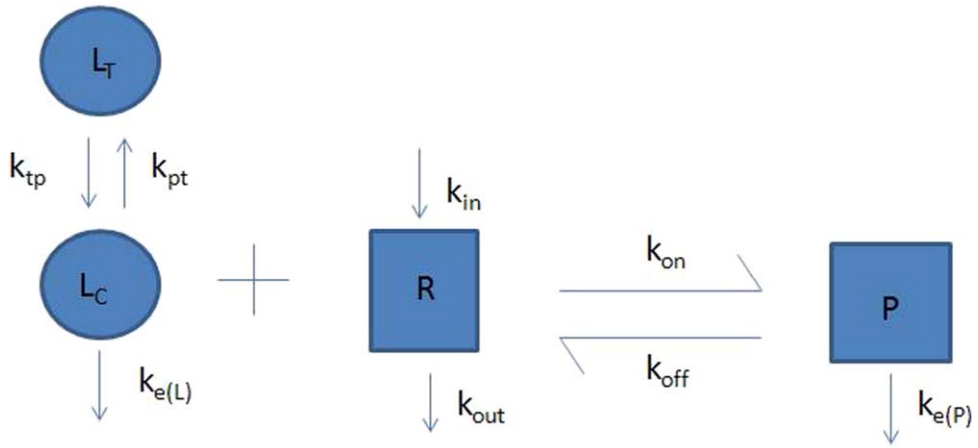

Figure 3 Two-compartment TMDD model, with binding in the central compartment.

Approximations to the model

Due to the increased number of parameters occurring in this model, simpler models based on approximations have been developed to enable fitting the model to data more feasible. The first of these models to be developed, by Mager and Krzyzanski in 2005,[16] was the quasi-equilibrium (QE) model (also known as the rapid binding model). Based on this work, Gibiansky *et al.*[17] developed more of these simpler models using alternative approximations. These new models are the quasi-steady state (QSS) model and the Michaelis–Menten (MM) model.

Quasi-equilibrium (QE) model. The QE model assumes that equilibrium between the binding and dissociation of the complex has been achieved, ($k_{on}L_CR = k_{off}P$). This equilibrium assumption is plausible because these two rates are often of several magnitudes faster than the other processes. The model simplifies the full TMDD model by introducing the equilibrium constant ($K_D = \frac{k_{off}}{k_{on}} = \frac{L_CR}{P}$), the total concentration of drug in the central compartment ($L_{tot} = L_C + P$), and the total concentration of receptor ($R_{tot} = R + P$) into the model.

$$\frac{dL_T}{dt} = k_{pt}L_C - k_{tp}L_T \tag{IV.6}$$

$$\frac{dL_{tot}}{dt} = -(k_{e(L)} + k_{pt})L_C - \frac{R_{tot}k_{e(P)}L_C}{K_D + L_C} + k_{tp}L_T \tag{IV.7}$$

$$\frac{dR_{tot}}{dt} = k_{in} - k_{out}R_{tot} - (k_{e(P)} - k_{out})\frac{R_{tot}L_C}{K_D + L_C} \tag{IV.8}$$

$$L_C = \frac{1}{2}\left[(L_{tot} - R_{tot} - K_D) + \sqrt{(L_{tot} - R_{tot} - K_D)^2 + 4K_DL_{tot}}\right] \tag{IV.9}$$

$$L_{tot}(0) = L_{C0}, \quad R_{tot}(0) = R_0 = \frac{k_{in}}{k_{out}}, \quad L_T(0) = 0. \tag{IV.10}$$

An outline of the Berkeley Madonna code for the QE model is provided in the **Supplementary Materials** (Model 3).

This model is very useful as it accurately predicts the linear terminal phase of the drug concentration–time graph.[18] Thus, if the researcher wanted to accurately find the terminal half-life of the drug, this model could be used instead of fitting the more complicated full TMDD model. The QE model also accurately predicts the clearance of the drug at high doses.[19] However, the QE model may not predict the initial rapid decline in receptor concentrations or the initial increase in the amount of the complex. Therefore, the model may not be suitable to fit to an experiment that takes place over a short time interval. Also, if this reduction in the receptor is not as rapid then the QE model would not be appropriate to use.

From ref. 17 it can also be concluded that the accuracy of the QE model is dependent on the rate of elimination of the complex. If this rate is much larger than the rate of dissociation of the complex, i.e., $k_{e(P)} \gg k_{off}$, then the QE model is inaccurate and should not be used. However, if the rate of elimination of the complex is small, then this assumption can be used to get accurate PK results. Finally, while this model can be used to adequately describe total drug concentrations and total receptor concentrations, it has been found to overpredict the concentration of receptor.[20] Since these concentrations cannot typically be measured experimentally and are an important indication of the potency of a drug, clinicians need to be confident that they can be predicted accurately and, as such, should not rely on results obtained from fitting a QE model only.

Quasi-steady-state (QSS) model. The QSS model assumes that the binding rate is balanced by the sum of the dissociation and internalization rates ($k_{on}L_CR = (k_{off} + k_{e(P)})P$). The only difference between this model and the QE model is that now the equilibrium constant is $K_{SS} = K_D + \frac{k_{e(P)}}{k_{on}}$. This model produces a more accurate result than the QE model when $k_{e(P)} \gg k_{off}$. Unlike the QE model, the QSS model accurately predicts the phase when the amount of receptor is approximately zero.[18] For a potent drug this phase may represent the majority of the experiment, since in theory the aim of the drug is to bind to the receptor and keep it bound for as long as possible. Thus, the QSS model may fit the majority of data points in this case and give a good approximation. An outline of the

Berkeley Madonna code for the QSS model is provided in the **Supplementary Materials** (Model 4). Also provided in the **Supplementary Materials** is a full example of implementing the QSS model using the parameter values for denosumab, Gibiansky *et al.*[63] (Model 8).

In ref. 21, the QSS model was mathematically analyzed for the particular case where R_{tot} was assumed to be constant and there was no flow of drug to the tissue. The analysis concluded that the QSS model was a good predictor when

$$\frac{\max(k_{e(L)}, k_{e(P)} - k_{e(L)})}{k_{off} + k_{e(P)} + k_{on}(L_{C0} + R_{tot})} \ll 1 \qquad \text{(IV.11)}$$

Thus, the QSS model provides a good approximation to the parameters when k_{on} is large. Large k_{on} results in $R_{min} \approx 0$,[11] which further proves that the QSS model is accurate during the phase when the amount of receptor is approximately zero.

However, the QSS model does not accurately predict the initial fast phase or terminal phase,[18] so should not be used to calculate terminal half-life of the drug. If an accurate terminal half-life needs to be calculated, the QE model should be used.

Michaelis–Menten (MM) model. The MM model is derived from the Michaelis–Menten equation for enzyme kinetics, which relates reaction rate to concentration. This equation states that reaction rate $= \frac{V_{max}\text{Conc}}{K_m + \text{Conc}}$. For $V_{max} = R_{tot}k_{e(P)}$, $K_m = K_{SS}$ and $\text{Conc} = L_C$. For the MM model to hold either a QE or QSS assumption is necessary, so the MM model is a special case of the QE and QSS models. The MM and QE models are equivalent when $K_M = K_D$ and when the inequality $\frac{R_{tot}K_D}{(K_D + L_{C0})^2} \ll 1$ holds.[22] Also, in this model it is assumed that the target concentration is small relative to the free drug concentration. Finally, unless the condition $R_{tot} = R_0$ constant is applied, this model is mathematically equivalent to the QSS model. Thus, V_{max} is a model parameter to be determined by data fitting. The model is defined by the following equations:

$$\frac{dL_T}{dt} = k_{pt}L_C - k_{tp}L_T \qquad \text{(IV.12)}$$

$$\frac{dL_C}{dt} = -(k_{e(L)} + k_{pt})L_C - \frac{V_{max}L_C}{K_m + L_C} + k_{tp}L_T \qquad \text{(IV.13)}$$

$$L_C(0) = L_{C0}, \quad R_{tot} = R_0 = \frac{k_{in}}{k_{out}}, \quad L_T(0) = 0. \qquad \text{(IV.14)}$$

An outline of the Berkeley Madonna code for the MM model is provided in the **Supplementary Materials** (Model 5).

In this model, the target is assumed to be fully saturated, thus it follows that it would be a good approximation to the full model when there is a large initial concentration of the drug (i.e., when a high dose is given). This was mathematically proven[21] for the case where the amount of receptor is assumed to be constant (sometimes referred to as the Wagner assumption) and when there is no movement of drug into the tissue. However, it may take some time for the target to become fully saturated, especially if the drug is given subcutaneously and has to travel to the plasma. It was also proven in ref. 21 that the MM model provides an accurate approximation when $\frac{k_{e(L)} + R_{tot}k_{on}}{(K_M + L_{C0})k_{on}} \ll 1$.

The MM model is also accurate at predicting the phase when the amount of receptor is approximately zero and the next phase where it increases before the terminal phase is reached.[17] Thus, it seems to provide a wider range of good approximations than the QE model. Also, it is recommended that the MM model be used when the data provided by the experiment are incomplete (i.e., when not all concentrations to the variables can be found or insufficient timepoints were taken).[22]

However, for the MM model to be accurate for all doses, the rate of elimination of the complex needs to be high.[17] If this rate is low, then only concentrations for high-dose levels can be found using this model.

Effect of administration: route and scheme

In the models described above, a single bolus injection has been assumed to have been injected straight into the central compartment. If, however, a subcutaneous (or other extra vascular) dose ($D1$) is administered, this is not the case. Instead, another compartment, a depot, is added to the full model to represent the time taken for the drug to reach the central compartment with a constant absorption rate constant (k_a). Therefore, $L_C(0) = 0$ as at time $t = 0$ all the drug would be in the depot. The concentration of drug in the depot is represented by the variable L_D. The additions to the two-compartment model are given below and all other equations and initial conditions remain the same.

$$\frac{dL_D}{dt} = -k_aL_D; \quad L_D(0) = D_1 \qquad \text{(IV.15)}$$

$$\frac{dL_C}{dt} = k_aL_D - (k_{e(L)} + k_{pt})L_C - k_{on}L_CR + k_{off}P + k_{tp}L_T \qquad \text{(IV.16)}$$

Also, the drug could be administered *via* a constant rate intravenous infusion. In this case an infusion rate (k_f) is then added into the equation for $\frac{dL_C}{dt}$ to represent the continuous supply of the drug intravenously.

Correction to the initial conditions for MM model. In all the above models, even though the equations have been simplified and equilibriums have assumed to have been reached, the initial conditions of the models remain the same as they were for the full TMDD model. However, Yan *et al.*[24] showed that this may not be the case. In the time taken for the system to reach equilibrium some of the injected drug would bind to the target and so this should be taken into account. In the study, a corrected initial condition for the MM model was given:

$$L_{Ccorr}(0) = \frac{1}{2}\left[\left(\frac{\text{Dose}}{V} - \frac{V_{max}}{k_{e(P)}V} - K_m\right) + \sqrt{\left(\frac{\text{Dose}}{V} - \frac{V_{max}}{k_{e(P)}V} - K_m\right)^2 + 4\frac{K_m\text{Dose}}{V}}\right] \qquad \text{(IV.17)}$$

This dose correction introduced one more parameter, $k_{e(P)}$, into the model structure, thus allowing it to be identified.

The study in ref. 24, which tested the dose correction using parameters obtained from the TMDD PK model for romiplostim in humans, found that the corrected initial condition improved the model. The corrected model was able to accurately estimate all the parameters except K_m, whereas in the original MM model all the estimated parameters were substantially biased. In particular, the new model provided a better estimate to $k_{e(L)}$ and provided a more accurate estimate for the volume of distribution and for the clearance.

Further investigation needs to be done to see if this particular dose correction would improve the other models that are based on equilibrium approximations and whether this correction would work for different routes of administration or for different administration schemes. A dose correction was successfully used by Olsson-Gisleskog *et al*. to model lower doses of rHuEPO in human subjects, but in this case a different correction to Eq. IV.17 was used.[25] Also, the correction assumed that only a single dose was administered and additional studies need to be done to see what the correction would be for multiple doses and whether this correction would be a necessary improvement to a multiple dosing model.

Another initial condition that can be improved is that of the baseline concentration of a receptor. In some cases the initial concentrations of the target receptor vary throughout the day and as such should be modeled using an initial condition that varies with time. For example, endogenous erythropoietin was found to vary diurnally and as such in this case the MM model was improved by modeling its baseline concentration using the sum of two cosine functions.[25]

EXTENSIONS TO TWO-COMPARTMENT MODEL

Many research articles have built upon the two-compartment model to incorporate different phenomena that may affect the PK properties of a specific drug. In this section an overview of these more complicated models based on the two-compartment model will be given, outlining the benefits and drawbacks of each.

Adding additional nonbinding compartments

The simplest way to extend the two-compartment model is to add another compartment to the model which the compound, typically the drug, can flow into and out of with time-invariant constants. These compartments can either be added into the model to represent processes that occur before or after binding takes place in the central compartment.

An example of adding another compartment before the binding process is adding a depot to the model. This extension to the model has already been analyzed in this article in *Effect of Administration: Route and Scheme*. Unlike other compartments, the drug can only flow out of the depot. In addition to the depot, a lymph compartment can be added to the model. The drug flows into the lymph compartment from the depot and then out of the lymph compartment into the central compartment. The drug cannot flow in the opposite direction. This additional compartment needs to be incorporated into the model if a large time delay between the dose being administered and the drug reaching the central compartment is observed, and if this time delay cannot completely be explained by incorporating a depot. For examples of the types of drugs modeled using a lymph compartment, see **Table 1**.

Additional compartments can also be added to represent processes that occur after the binding process in the central compartment. For example, an endogenous compartment can be added in which either the receptor and the complex can flow into, or the drug and complex can. This compartment is used to represent the additional process where the receptor and complex are recycled inside the cell,[26] or to represent the process where the drug and complex are recycled by binding to FcRn receptor.[27] Both of these models will be considered in more depth in the sections about receptor-mediated endocytosis and FcRn-mediated recycling.

Multiple targets

Some drugs have the ability to bind to multiple targets in one cell; for example, they could bind to both cell membrane (M) and soluble (S) targets. This was investigated[28] and a full TMDD model for a drug binding to N different targets was developed. In an attempt to address issues related to overparameterization, the article further developed and tested an approximated model for the two targets (S and M) case. This model was based on the QSS model but a MM term was used to estimate the M-target parameters. This MM term, $V^M_{\max}$, is a model parameter that needs to be found by data fitting but can be interpreted by using $V^M_{\max} = R^M_0 k^M_{e(P)}$. The model used the assumption that enough free drug was present to ensure that the targets did not compete with each other. Since the M-target and the drug-M-target complex are located on the cell surface, they can rarely be measured, and the model also assumes that the total concentration of M-target was constant ($R^M_{tot} = R^M_0$). Thus, R^M_0 could be considered a parameter of the system. Finally, it was assumed that the total concentration of the M target, R^M_{tot}, was small relative to the free drug concentrations, L_C and L_T. The final model is given below:

$$\frac{dL_D}{dt} = -k_a L_D; \quad L_D(0) = D_1 \tag{V.1}$$

$$\frac{dL_T}{dt} = k_{pt} L_C - k_{tp} L_T \tag{V.2}$$

$$\frac{dL_{tot}}{dt} = k_f L_D + k_{tp} L_T - (k_{e(L)} + k_{pt}) L_C - \frac{R^S_{tot} k^S_{e(P)} L_C}{K^S_{SS} + L_C} - \frac{V^M_{\max} L_C}{K^M_{SS} + L_C} \tag{V.3}$$

$$\frac{dR^S_{tot}}{dt} = k^S_{in} - k^S_{out} R^S_{tot} - (k^S_{e(P)} - k^S_{out}) \frac{R^S_{tot} L_C}{K_S S^S + L_C} \tag{V.4}$$

$$L_C = \frac{1}{2}\left[(L_{tot} - R^S_{tot} - K^S_{SS}) + \sqrt{(L_{tot} - R^S_{tot} - K^S_{SS})^2 + 4K^S_{SS} L_{tot}}\right] \tag{V.5}$$

$$L_{tot}(0) = \frac{D_2}{V}, \quad R^S_{tot}(0) = R^S_0 = \frac{k^S_{in}}{k^S_{out}}, \quad L_T(0) = 0 \tag{V.6}$$

An outline of the Berkeley Madonna code for this multiple targets model is provided in the **Supplementary Materials** (Model 6). When fitted to the data, the model provided

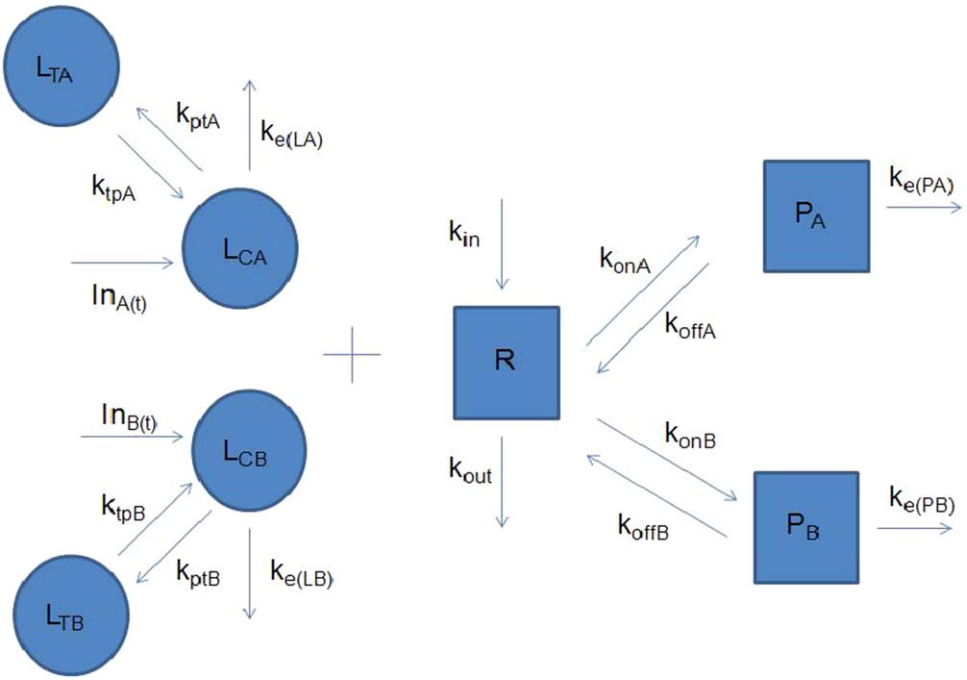

Figure 4 Model with two drugs binding to the same target.

unbiased estimates of all the parameters except for K_{SS}^{S}, which was underestimated by 29%.[28] It was also able to accurately predict the reduction in the amount of the unbound M-target. However, the model was only tested on high doses of the drug, since it was assumed in the model that both targets were saturated. Also, the model assumes that the drug binds to only one target at a time, which may not be the case. This is certainly not the case when a chimeric ligand binds to two targets at once. However, a full TMDD model would need to be developed to describe chimeric ligands.

Two drugs competing for the same target

In ref. 29, the situation where two drugs (drug *A* and drug *B*) bind to the same target to get two different complexes was investigated, see **Figure 4**. This model can also be applied to a drug competing with an endogenous species for the same target.

The model consists of a system of ODEs that are used to find total receptor ($Rtot = R + P_A + P_B$) and total free drug concentrations ($L_{Atot} = L_{CA} + P_A$, $L_{Btot} = L_{CB} + P_B$). The initial conditions used were defined by the steady states of the equations and by IV bolus doses of drug *A*, Dose_A, and of drug *B;* Dose_B. $L_{Atot}(0)$, $L_{Btot}(0)$, and $R_{tot}(0)$ are the baseline plasma concentrations. The rapid binding assumption was used to create the system.

$$\frac{dL_{Atot}}{dt} = In_A(t) - (k_{e(L_A)} + k_{ptA})L_{CA} + k_{tpA}L_{TA} - k_{e(P_A)}(L_{Atot} - L_{CA}) \quad \text{(V.7)}$$

$$\frac{dL_{TA}}{dt} = k_{ptA}L_{CA} - k_{tpA}L_{TA} \quad \text{(V.8)}$$

$$\frac{dL_{Btot}}{dt} = In_B(t) - (k_{e(L_B)} + k_{ptB})L_{CB} + k_{tpB}L_{TB} - k_{e(P_B)}(L_{Btot} - L_{CB}) \quad \text{(V.9)}$$

$$\frac{dL_{TB}}{dt} = k_{ptB}L_{CB} - k_{tpB}L_{TB} \quad \text{(V.10)}$$

$$\frac{dR_{tot}}{dt} = k_{in} - k_{out}R_{tot} - (k_{e(P_A)} - k_{out})(L_{Atot} - L_{CA}) - (k_{e(P_B)} - k_{out})(L_{Btot} - L_{CB}) \quad \text{(V.11)}$$

$$L_{Atot}(0) = \frac{\text{Dose}_A}{V_C} - L_{Atot0} \quad L_{TA}(0) = \frac{k_{ptA}L_{A0}}{k_{tpA}} \quad L_{Btot}(0) = \frac{\text{Dose}_B}{V_C} - L_{Btot0} \quad \text{(V.12)}$$

$$L_{TB}(0) = \frac{k_{ptB}L_{B0}}{k_{tpB}} \quad R_{tot}(0) = R_{tot0} \quad \text{(V.13)}$$

To get drug concentrations in the plasma (L_{CA} and L_{CB}) the equilibrium equations below are required to be numerically solved. These are known in pharmacology as the Gaddum equations.

$$(R_{tot} - L_{Atot} - L_{Btot} + L_{CA} + L_{CB})L_{CA} = K_{DA}(L_{Atot} - L_{CA}) \quad \text{(V.14)}$$

$$(R_{tot} - L_{Atot} - L_{Btot} + L_{CA} + L_{CB})L_{CB} = K_{DB}(L_{Btot} - L_{CB}) \quad \text{(V.15)}$$

The model was used in ref. 29 to simulate the concentration–time profiles of immunoglobulin, IgG, using published parameter values. However, since the equilibrium equations could not be solved analytically, the model was not fitted to any data due to the limitations of the software available.

Receptor-mediated endocytosis

Receptor-mediated endocytosis (RME) describes the process whereby the receptor and complex are internalized

into the cell from the cell surface where they are either degraded or recycled back to the cell surface. A TMDD model incorporating this process was developed by Krippendorff *et al.*[26] An RME model based on the full two-compartment model was developed as well as simplified models based on the QSS model. The model was then used to successfully model the behavior of therapeutic protein drugs binding to the epidermal growth factor receptor (EGFR). The article also concluded that the impact of RME varied for drugs with the same K_D value but different k_{off} values.

Cell-level kinetic and PK model

The cell-level kinetic and PK model is another example of an extension to the two-compartment TMDD model. This model, developed by Krippendorff *et al.*,[30] incorporates aspects of the RME model and the two drugs competing for the same receptor model. This model represents a drug binding to a receptor at the cell level to prevent receptor–ligand complexes being formed that initiate signaling downstream. Thus, either the drug or ligand already present can bind by TMDD to the same receptor. This receptor can undergo the process of RME. This model is useful when a drug inhibits the actions of another ligand already present at the cell level. Since it is used predominantly to model cancer drugs, two models have been developed for modeling the behavior of normal and tumor cells.

This model was also analyzed mathematically, and an integral of inhibition was used to investigate which parameters influenced the extent of receptor inhibition. Using linear analysis, it was found that there was a "plateau" of effect independent of parameter values, indicating that the receptor can only be inhibited by a finite amount.

The cell-level kinetic model can also be applied to a one-compartment TMDD model. In this model only the central and cell-level compartments are considered. This model, developed by Jager *et al.*,[31] was successfully used to model the monoclonal antibody GO, which binds to a receptor called CD33. This drug is used to treat acute myeloid leukemia (AML) and as such a cell-level kinetic model was used to show how much of the drug entered the cells and how this affected the number of leukemia blast cells. The model successfully did so, fitting both PK blood data and the data on the amount of free and bound CD33 following drug administration. Finally, the data fitting reproduced published values for the initial number of leukemia blast cells. No mathematical analysis of this model was done, however.

FcRn recycling

Xiao *et al.*[32] extended the QE two-compartment model with a depot to include the process of FcRn-mediated endosomal recycling. This improvement to the model was needed to account for the increased elimination of the drug and complex at higher concentrations (in this case 300 mg/kg). In this process the drug and complex distribute from the central compartment into the endosomal space where they bind to the FcRn receptor to form two FcRn-complexes. These FcRn-complexes are then broken down into the drug and original complex in a recycling process that feeds back into the central compartment. This process inherently leads to an increased rate of elimination of the drug and complex. To simplify the model the number of FcRn receptors was considered to be constant and the same binding and dissociation rate constants were used for both the FcRn receptor binding to the drug and for the FcRn receptor binding to the complex. Also, $k_{e(L_C)} = k_{e(P_C)}$ and both FcRn complexes were recycled with the same rates. An outline of the Berkeley Madonna code for this model is provided in the **Supplementary Materials** (Model 7).

Immune response

An extension of the one-compartment TMDD model was created by Perez-Ruixo *et al.*[33] to incorporate adaptive immune response (cellular and humoral). When a drug is injected, in certain cases antidrug antibodies are produced as an immune response. This response alters the pharmacokinetics of the drug and may lead to a loss of therapeutic effect. However, this response is complicated to model, as it differs from patient to patient depending on the drug administered, the dosing regime, and genetic factors. In the model, two stages of immune response are taken into account. In the first stage the drug stimulates B cells to produce IgM, which does not directly bind to the drug but affects its clearance. In the second stage, after a period of time, IgG is produced, which binds to the drug to form an additional complex, which is an additional elimination pathway for the drug. This model is in its early development stages; the authors only carried out simulations of the model and did not fit the model to actual data.

MODEL WITH BINDING IN OTHER COMPARTMENTS THAN THE CENTRAL COMPARTMENT

All the models that have been described in this article so far have assumed that the binding of the drug to the target to form a drug target complex and its dissociation only occurs in the central compartment. However, this may not be the case, especially if both the drug and its target are able to distribute into the tissue, if the target naturally occurs in multiple compartments, or if the target can be absorbed into the lymphatic system following subcutaneous injection. Thus, binding can occur in the tissue compartment and can occur in the absorption compartment. These two cases will be considered in turn.

Binding in the tissue compartment

In the first case binding can occur in both the tissue and central compartments, see **Figure 5**.

While this phenomenon has not been explored in detail mathematically (**Figure 6**), Lowe *et al.*,[34] Retlich *et al.*,[35] and Landersdorfer *et al.*[36] developed TMDD models to represent binding occurring in both the tissue and central compartments.

The model exhibiting binding in two compartments was developed by Lowe *et al.*[34] and based on a QE assumption to model the behavior of any antisoluble ligand antibody. Equations for the total drug amounts and the total target amounts in each compartment were given, since experimentally the amount of the free target on its own cannot be measured. This model made the assumption that the

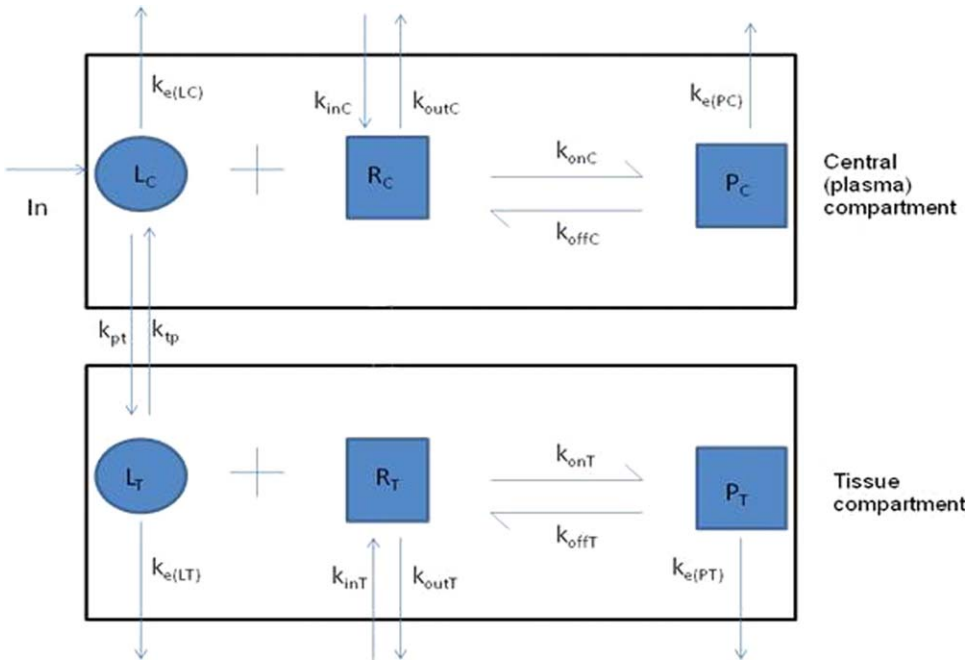

Figure 5 Two-compartment TMDD model with binding in both tissue and central compartments.

elimination rate of the complex was the same for both compartments, but further assumed that this was also the case for the elimination rate of the drug and free target.

The model was tested [34] using data from two studies giving doses of an antisoluble ligand antibody to cynomolgus monkeys. The antibody was not disclosed in the article.

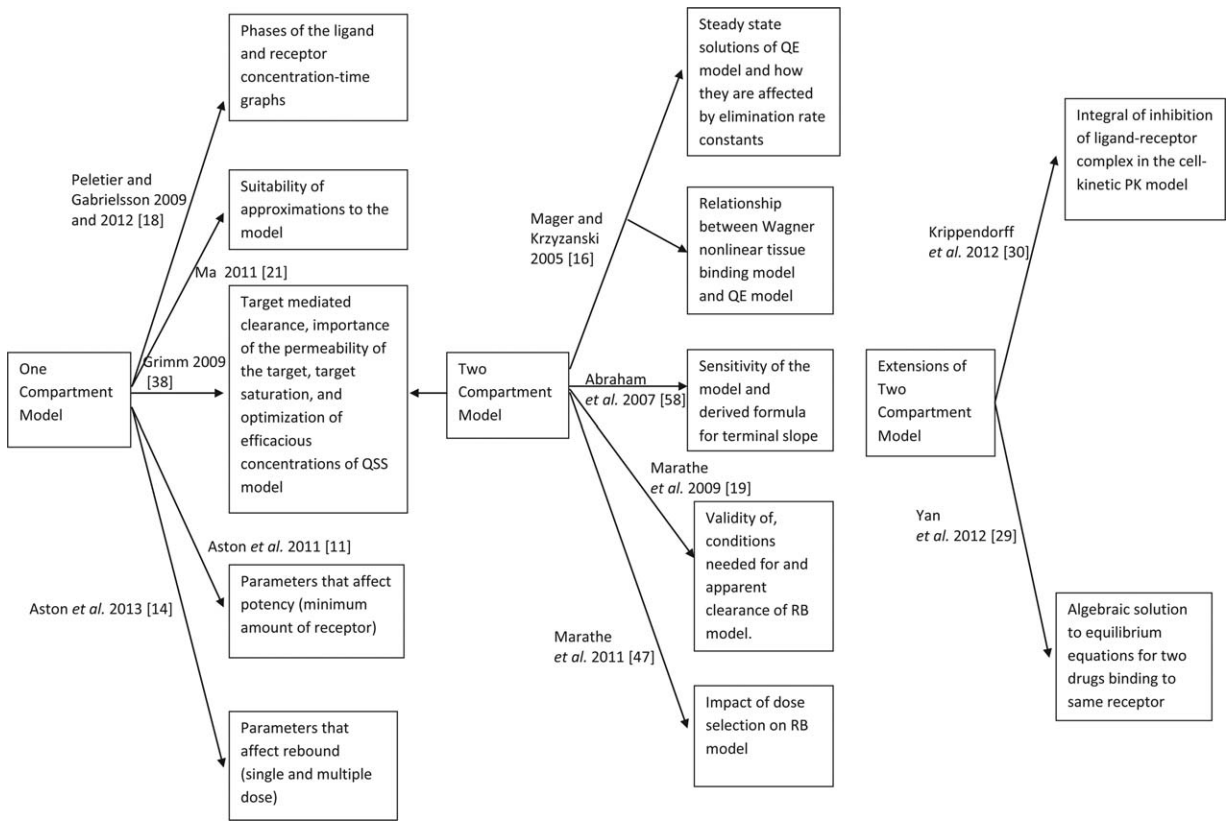

Figure 6 Flow chart showing the mathematical investigations completed on TMDD models in the current literature.

The model was found to fit the data, giving relatively precise estimates to the parameters. The highest residual standard error (RSE) was associated with K_D (79%).

Retlich *et al*. developed a similar model to predict the behavior of the drug linagliptin. Although no reference was made to the earlier general model developed by Lowe *et al*.,[62] their later model was a simplified version of the earlier model. When developing the model, Retlich *et al*.[35] only considered differential equations for the amounts of the drug in the two compartments and the depot. The receptor concentrations were found using a pharmacodynamic E_{max} model and then these values were substituted into the differential equations for the drug concentrations. The rationale for utilizing a hybrid of two different models is unclear.

Landersdorfer *et al*.[36] produced a model predicting the behavior of the drug vildagliptin, based on the MM approximation. Vildagliptin is a novel antidiabetic agent that acts by binding to and therefore inhibiting dipeptidyl peptidase IV (DPP-4). The majority of DPP-4 naturally resides in the tissue, not in the central compartment. It was decided to base the model for vildagliptin on Retlich *et al*.'s model, since that model explained the nonlinearity of vildagliptin PK and the two-compartment TMDD model did not.

The model was fitted to one case study of 13 subjects, in which three doses and a placebo were investigated. The model adequately predicted the drug concentrations and effects of vildagliptin on DPP-4. The proposed mechanism was also compared with the findings of an *in vitro* microsomal and an *in vivo* metabolism study in rats, and it was found that these findings supported the model.

From these three models a more general model for any ligand can be developed, giving all the equations for the concentrations of the drug, target, and complex in both compartments. Once mathematically analyzed, this will give a greater understanding of the behavior of each of the variables. Also, this more general model will need to be fitted to other case studies of drugs potentially exhibiting this behavior, to see if this model is more effective than the previous TMDD model.

Binding in the absorption compartment

Following subcutaneous (SC) injection, where the drug is injected into the hypodermis, the drug reaches systematic circulation through both the blood and the lymphatic system, thus creating two absorption pathways. The mechanisms of this absorption are not fully understood. Previously, these two absorption pathways have been taken into account by adding a depot compartment which could represent the lymph (see *Adding Additional Nonbinding Compartments*, above). However, this does not directly assess the lymphatic compartment and does not allow for the fact that the drug may bind to its receptor while in the lymphatic system. Recently Kagan[37] developed a TMDD model that has incorporated this binding into the absorption compartment. In this absorption compartment the drug can transfer into the central compartment as before, but is also eliminated in the compartment and can bind to its receptor in the compartment. The full TMDD model has yet to be developed; a QE model of the absorption compartment was developed considering only total levels of bound and unbound drug at the absorption site and concentration of free drug in the central compartment. However, this model was used to successfully capture the observed dose-dependent bioavailability of rituximab. More research needs to be carried out to create and analyze a full model to see what additional insights this model creates compared to using a standard model with a depot compartment.

USES FOR TMDD MODELS

Once the chosen TMDD model has been fitted to the data for a specific drug, the estimated parameters can be used to calculate a PK profile and parameters for the drug at different doses including clearance, AUC, terminal slope, etc. This process has been applied to a variety of drugs including mAbs and proteins. **Table 1** outlines what models have been fitted to different drugs and their receptors in the current literature.

Grimm[38] calculated general formulas for the maximum target-mediated clearance for the three different models. The first was a one-compartment QSS model assuming that the target molecule was recycled (i.e., R is constant). The second model was the one-compartment model in equilibrium and the third was the two-compartment model with binding occurring in one compartment (the target site). For the third model, Grimm introduced a new parameter, "hermeticity," to measure the importance of the accessibility of the target site. This new parameter models the drug's ability to reach an inaccessible tumor. These formulas for clearance suggest a method for identifying a minimal dose required for efficacy.[38]

TMDD models can also be used to infer and predict human PK characteristics of a drug from animal studies. This allows for greater understanding of factors such as dose selection before a first-in-human (FIH) clinical trial.[39] A suitable TMDD model is fitted to the data from the animal trial. Then we use the following power law equation to calculate the human parameters:[40]

$$P = a\left(\frac{BW_h}{BW_a}\right)^b$$

Here P is the human parameter, a is the animal parameter, BW_h is the human bodyweight, BW_a is the animal bodyweight, and b is the power coefficient. If the animal parameters are expressed per unit weight, then we can set $BW_a = 1$. Kagan *et al*.[41] successfully used this method to predict the PK of interferon in rodents from human and monkey studies. The experimental data were for rodents, so the article worked backwards from human PK data to investigate whether the scaling worked. Luu *et al*.[42] predicted the human PK of a monoclonal antibody from a clinical trial in monkeys. When compared to experimental data from a human clinical trial, the model was found to correctly predict clearance, C_{max}, and AUC but underpredicted half-life and V_D for lower doses. Also, all the experimental PK profiles fell within the predicted PK population spread.

More complex models have also been used to find the starting dose for an FIH study from animal data. The model for binding in two compartments was used on data from cynomolgus monkeys to calculate the suppression in the concentration of the free target that could not be measured experimentally for each dose.[34]

Traditionally E_{max} was calculated by fitting an indirect response model but Gibiansky *et al*. showed that this model can be directly derived from the QSS model. It gives the equation for total target concentration only, which can be fitted to data only if the total target concentration is known. This equation is interesting because all the parameters of the full TMDD model can be calculated from it.

$$\frac{dR_{tot}}{dt} = k_{in} - k_{out} R_{tot}\left(1 + E_{max}\frac{L_C}{K_{SS}+L_C}\right); \quad E_{max} = \frac{k_{e(P)}}{k_{out}} - 1$$

This shows that the E_{max} of a drug can be found directly from fitting any two-compartment TMDD model to the drug's data and finding $k_{e(P)}$ and k_{out}.

As far as we know, Abraham *et al*.[7] provided the first experimental evidence of TMDD for biologics using interferon receptor knockout mice. The combined model was used to investigate interspecies scaling of PK and PD properties of type 1 interferon,[41] and was found to provide a reasonable description of the experimental data for humans and monkeys. The integrated PK/PD model was also used to successfully assess the receptor-mediated disposition and dynamics of interferon-β in mice.[7]

TYPICAL ISSUES ARISING FROM USING TMDD MODELS

Working with TMDD models can sometimes be complex and issues arise when using them to model actual data. One of these is that it may not be possible to measure all the concentrations needed in the model. For example, in reality it may not be possible to separate the bound and unbound receptor or drug. Thus, the total concentration equations ($L_{tot} = L + P$ or $R_{tot} = R + P$) may need to be used in conjunction with other equations in the model to arrive at values for the parameters. Another issue that may arise is that only the ligand data are available. Then these data can be used in conjunction with a QE or QSS model to estimate the values of K_D, K_{SS}, and R_{tot} by fitting the ligand equation to the data. From these values, the potency of the drug can be inferred. Also, these values can be compared with existing literature values (if available). However, using the TMDD models, estimated K_D values can differ from *in vitro* K_D values. This can occur for various reasons, which we will not discuss here but which can be found in the literature. Also, the estimated K_D is typically greater than the EC_{50} calculated from downstream biomarkers. Another, seemingly trivial, practical issue, that in our experience can easily lead to erroneous results, is the appropriate conversion between amounts and concentrations for drugs and system species and associated rate constants. An elegant example of how to implement this in model code is provided in ref. 43. Finally, the TMDD concept does not imply that the drug has nonlinear pharmacokinetics. In some cases the nonlinearity can be removed from the TMDD model if the total drug concentration is found to be equal to the free drug concentration in the central compartment. This removes the second-order term from the total drug concentration differential equation. Chen *et al*.[44] found this to be the case when modeling an antibody binding to the interferon-gamma (IFN-γ) receptor, since the free receptor concentration was negligible compared with the free drug concentration. In this case the antibody exhibited linear PK.

CONCLUSION

A variety of mathematical models have been developed to represent the TMDD of several drugs. This review has given a general description of the most-used models. The one-compartment model has started to be mathematically analyzed by Aston *et al*.,[11] but further analysis can still be done, especially in the area of relating various measures of *in vivo* potency and efficacy to drug and system properties. The two-compartment model with binding in the central compartment has been developed and analyzed. This model has been approximated and the occasions where each approximation should be used have been evaluated. Extensions to the model have been fully developed to include modeling multiple targets for the same drug, modeling multiple drugs competing for the same target, and modeling the inclusion of a PD model. Wang *et al*.[68] presented a particular case of the TMDD model, the pharmacodynamics-mediated drug disposition model (PDMDD), in which time dependency is added to the concentration-dependent clearance of the TMDD model. This may be important, for example, for growth factors such as erythropoietins. Finally, models have started to be developed to include binding between the drug and receptor in both the central and tissue compartments, and binding in the absorption compartment. These models are in their early developmental stages; a general model for any ligand still needs to be developed that includes all relevant rate constants. One area that has not been considered at all yet is the area of dimerization. Dimerization refers to the process whereby a drug–target complex can bind with another molecule to produce a dimer. This may be a relevant step to include in the TMDD model to fully predict the PK of a drug that can produce a dimer, for example in the area of neurotrophins. Another area that has not been fully developed is to apply TMDD to a minimal physiologically based pharmacokinetic model (MPBPK), thus incorporating physiological elements into a TMDD model. While this has not been attempted yet, Cao and Jusko[45] have concluded that the MPBPK model can be extended to handle TMDD and its dynamics.

To conclude, this tutorial has provided an overview of the development and application of TMDD models since the original framework was proposed by Mager and Jusko.[8] It is expected that over the coming years more insights will be obtained into the behavior of these complex nonlinear models through systematic mathematical analysis of the important emerging properties and that extended TMDD

models will be developed that incorporate new biological processes to account for new emerging experimental data.

Conflict of Interest. As Editor-in-Chief for CPT:PSP, Piet H. van der Graaf was not involved in the review or decision process for this article.

1. Levy, G. Pharmacologic target-mediated drug disposition. *Clin. Pharmacol. Ther.* **56**, 248–252 (1994).
2. Krause, A. & Lowe, P.J. Visualization and communication of pharmacometric models with Berkeley Madonna. *CPT Pharmacometrics Syst. Pharmacol.* **3**, 1–20 (2014).
3. Kenakin, T. *A Pharmacology Primer: Theory, Application, and Methods* (Elsevier Academic Press, San Diego & London, 2004).
4. Lauffenburger, D.A. & Linderman J.J. *Receptor: Models for Binding, Trafficking, and Signalling* (Oxford University Press, New York, 1996).
5. Wagner, J.G. *Biopharmaceutics and Relevant Pharmacokinetics (*Drug Intelligence Publications, Hamilton Press, Fernandina Beach, FL, 1972).
6. Sugiyama, Y. & Hanano, M. Receptor-mediated transport of peptide hormones and its importance in the overall hormone disposition in the body. *Pharm. Res.* **6** 192–202 (1989).
7. Abraham, A.K., Kagan, L., Kumar, S. & Mager, D.E. Type 1 interferon receptor is a primary regulator of target-mediated drug disposition of interferon-β in mice. *JPET* **334**, 327–332 (2010).
8. Mager, D. & Jusko, W. General pharmacokinetic model for drugs exhibiting target-mediated drug disposition. *J. Pharmacokinet. Pharmacodyn.* **28**, 507–532 (2001).
9. Zhao, L. *et al.* Application of pharmacokinetics-pharmacodynamics/clinical response modeling and simulation for biologics drug development. *J. Pharm. Sci.* **101**, 4367–4382 (2012).
10. Dostalek, M. *et al.* Pharmacokinetics, pharmacodynamics and physiologically-based pharmacokinetic modeling of monoclonal antibodies. *Clin. Pharmacokinet.* **52**, 83–124 (2013).
11. Aston, P.J., Derks, G., Raji, A., Agoram B.M. & van der Graaf P.H. Mathematical analysis of the pharmokinetic-pharmacodynamic (PKPD) behaviour of monoclonal antibodies: predicting in vivo potency. *J. Theor. Biol.* **281**, 113–121 (2011).
12. Kenakin, T.P. *Pharmacology in Drug Discovery: Understanding Drug Response* (Elsevier Academic Press, London, Waltham, MA, & San Diego, 2012).
13. Chimalakonda, A.P. *et al.* Factors influencing magnitude and duration of target inhibition following antibody therapy: implications in drug discovery and development. *AAPS J.* **15**, 717–727 (2013).
14. Aston, P.J. *et al.* A mathematical analysis of rebound in a target-mediated drug disposition model: I. Without feedback. *J. Math. Biol.*; e-pub ahead of print 2013.
15. Derks, G., Aston, P., Agoram, B. & van der Graaf, P. Predicting rebound for MABs using the TMDD model. 7th Noordwijkerhout Symposium on Pharmacokinetics, Pharmacodynamics and Systems Pharmacology, Netherlands (2014).
16. Mager, D.E. & Krzyzanski, W. Quasi-equilibrium pharmacokinetic model for drugs exhibiting target-mediated drug disposition. *Pharm. Res.* **22**, 1589–1596 (2005).
17. Gibiansky, L., Gibiansky, E., Kakkar, T. & Ma, P. Approximations of the target-mediated drug disposition model and identifiability of model parameters. *J. Pharmacokinet. Pharmacodyn.* **35**, 573–591 (2008).
18. Peletier, L.A. & Gabrielsson, J. Dynamics of target-mediated drug disposition: characteristic profiles and parameter identification. *J. Pharmacokinet. Pharmacodyn.* **39**, 429–451 (2012).
19. Marathe, A., Krzyzanski, W. & Mager, D.E. Numerical validation and properties of a rapid binding approximation of a target-mediated drug disposition pharmacokinetic model. *J. Pharmacokinet. Pharmacodyn.* **36**, 199–219 (2009).
20. Davda, J.P. & Hansen, R.J. Properties of a general PK/PD model of antibody-ligand interactions for therapeutic antibodies that bind to soluble endogenous targets. *mAbs* **2**, 576–588 (2010).
21. Ma, P. Theoretical considerations of target-mediated drug disposition models: simplifications and approximations. *Pharm. Res.* **29**, 866–882 (2011).
22. Yan, X., Mager, D.E., & Krzyzanski, W. Selection between Michaelis-Menten and target-mediated drug disposition pharmacokinetic models. *J. Pharmacokinet. Pharmacodyn.* **37**, 25–47 (2010).
23. Gibiansky, L. & Gibiansky, E. Target-mediated drug disposition model: relationships with indirect response models and application to population PK-PD analysis. *J. Pharmacokinet. Pharmacodyn.* **36**, 341–351 (2009).
24. Yan, X. & Krzyzanski, W. Dose correction for the Michaelis-Menten approximation of the target-mediated drug disposition model. *J. Pharmacokinet. Pharmacodyn.* **39**, 141–146 (2012).
25. Olsson-Gisleskog *et al.* Population pharmacokinetics meta-analysis of recombinant human erythropoietin in healthy subjects. *Clin. Pharmacokinet.* **46**, 159–173 (2007).
26. Krippendorff, B.F. *et al.* Nonlinear pharmacokinetics of therapeutic proteins resulting from receptor mediated endocytosis. *J. Pharmacokinet. Pharmacodyn.* **36**, 239–260 (2009).
27. Kagan, L. *et al.* Subcutaneous absorption of monoclonal antibodies: role of dose, site of injection, and injection volume on rituximab pharmacokinetics in rats. *Pharm. Res.* **29**, 490–499 (2012).
28. Gibiansky, L. & Gibiansky, E. Target-mediated drug disposition model for drugs that bind to more than one target. *J. Pharmacokinet. Pharmacodyn.* **37**, 323–346 (2010).
29. Yan, X., Chen, Y. & Krzyzanski, W. Methods of solving rapid binding target-mediated drug disposition model for two drugs competing for the same receptor. *J. Pharmacokinet. Pharmacodyn.* **39**, 543–560 (2012).
30. Krippendorff, B.F., Oyarzún, D.A. & Huisinga, W. Predicting the F(ab)-mediated effect of monoclonal antibodies in vivo by combining cell-level kinetic and pharmacokinetic modeling. *J. Pharmacokinet. Pharmacodyn.* **39**, 125–139 (2012).
31. Jager, E. *et al.* Targeted drug delivery by gemtuzumab ozogamicin: mechanism-based mathematical model for treatment strategy improvement and therapy individualization. *PLoS One* **6**, e24265 (2011).
32. Xiao, J.J., *et al.* Pharmacokinetics of anti-hepcidin monoclonal antibody Ab 12B9m and hepcidin in cynomolgus monkeys. *AAPS J.* **12**, 646–657 (2010).
33. Perez Ruixo, J.J., Ma, P. & Chow, A.T. The utility of modeling and simulation approaches to evaluate immunogenicity effect on therapeutic protein pharmacokinetics. *AAPS J.* **15**, 172–182 (2013).
34. Lowe, P.J., Tannenbaum, S., Wu, K., Lloyd, P. & Sims, J. On setting the first dose in man: quantitating biotherapeutic drug-target binding through pharmacokinetic and pharmacodynamic models. *Basic Clin. Pharmacol. Toxicol.* **106**, 195–209 (2009).
35. Retlich, S. *et al.* Impact of target-mediated drug disposition on linagliptin pharmacokinetics and DPP-4 inhibition in type 2 diabetic patients. *J. Clin. Pharmacol.* **50**, 873–885 (2010).
36. Landersdorfer, C.B., He, Y.L. & Jusko, W.J. Mechanism-based population pharmacokinetic modeling in diabetes: vildagliptin as a tight binding inhibitor and substrate of dipeptidyl peptidase IV. *Br. J. Clin. Pharmacol.* **73**, 391–401 (2011).
37. Kagan, L. Pharmacokinetic modeling of the subcutaneous absorption of therapeutic proteins. *Drug Metab. Dispos.*; e-pub ahead of print 2014.
38. Grimm, H.P. Gaining insights into the consequences of target-mediated drug disposition of monoclonal antibodies using quasi-steady-state approximations. *J. Pharmacokinet. Pharmacodyn.* **36**, 407–420 (2009).
39. Agoram, B.M. Use of pharmacokinetic/pharmacodynamic modeling for starting dose selection in first-in-human trials of high-risk biologics. *Br. J. Clin. Pharmacol.* **67**, 153–160 (2008).
40. Mahmood, I. Pharmacokinetic allometric scaling of antibodies: application to the first-in-human dose estimation. *J. Pharm. Sci.* **98**, 3850–3861 (2009).
41. Kagan, L., Abraham, A.K., Harrold, J.M. & Mager, D.E. Interspecies scaling of receptor-mediated pharmacokinetics and pharmacodynamics of type 1 interferons. *Pharm. Res.* **27**, 920–932 (2010).
42. Luu, K.T., Bergqvist, S., Chen, E., Hu-Lowe, D. & Kraynov, E. A model-based approach to predicting the human pharmacokinetics of a monoclonal antibody exhibiting target-mediated drug disposition. *JPET* **341**, 702–708 (2012).
43. Yu, J. *et al.* From target selection to the minimum acceptable biological effect level for human study: use of mechanism-based PK/PD modeling to design safe and efficacious biologics. *AAPS J.* **13**, 169 (2011).
44. Chen, P. *et al.* Pharmacokinetic and pharmacodynamic relationship of AMG 811, an anti-IFN-γ IgG1 monoclonal antibody, in patients with systemic lupus erythematosus. *Pharm. Res.*; e-pub ahead of print 2014.
45. Cao, Y. & Jusko, W.J. Survey of monoclonal antibody disposition in man utilizing a minimal physiologically-based pharmacokinetic model. *J. Pharmacokinet. Pharmacodyn.*; e-pub ahead of print 2014.
46. Kakkar, T. *et al.* Population PK and IgE pharmacodynamic analysis of a fully human monoclonal antibody against IL4 receptor. *Pharm. Res.* **28**, 2530–2542 (2011).
47. Marathe, A., Van Wart, S. & Mager, D.E. Impact of dose selection on parameter estimation using a rapid binding approximation model of target-mediated drug disposition. *J. Pharmacokinet. Pharmacodyn.* **38**, 223–235 (2011).
48. Krzyzanski, W. & Wyska, E. Pharmacokinetics and pharmacodynamics of erythropoietin receptor in healthy volunteers. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **377**, 637–645 (2008).
49. Tang, C. & Prueksaritanont, T. Theoretical analysis of interplay of therapeutic protein drug and circulating soluble target: temporal profiles of "free" and "total" drug and target. *Pharm. Res.* **28**, 2447–2457 (2011).
50. Mager, D.E. Target-mediated drug disposition and dynamics. *Biochem. Pharmacol.* **72**, 1–10 (2006).
51. Peletier, L.A. & Gabrielsson, J. Dynamics of target-mediated drug disposition. *Eur. J. Pharm. Sci.* **38**, 445–464 (2009).
52. Chen, T., Mager, D.E. & Kagan, L. Interspecies modeling and prediction of human exenatide pharmacokinetics. *Pharm. Res.* **30**, 751–760 (2013).
53. Meno-Tetang, G.M. & Lowe, P.J. On the prediction of the human response: a recycled mechanistic pharmacokinetic/pharmacodynamic approach. *Basic Clin. Pharmacol. Toxicol.* **96**, 182–192 (2005).
54. Betts, A.M. *et al.* The application of target information and preclinical pharmacokinetic/pharmacodynamic modeling in predicting clinical doses of a Dickkopf-1 antibody for osteoporosis. *JPET* **333**, 2–13 (2010).

55. Woo, S., Krzyzanski, W. & Jusko, W.J. Target-mediated pharmacokinetic and pharmacodynamic model of recombinant human erythropoietin (rHuEPO). *J. Pharmacokinet. Pharmacodyn.* **34**, 849–868 (2007).
56. Samtani, M.N. *et al.* Pharmacokinetic and pharmacodynamic modeling of pegylated thrombopoietin mimetic peptide (PEG-TPOm) after single intravenous dose administration in healthy subjects. *J. Clin. Pharmacol.* **49**, 336–350 (2009).
57. Gao, W. & Jusko, W.J. Pharmacokinetic and pharmacodynamic modeling of exendin-4 in type 2 diabetic Goto-Kakizaki rats. *JPET* **336**, 881–890 (2011).
58. Abraham, A.K., Krzyzanski, W. & Mager, D.E. Partial derivative-based sensitivity analysis of models describing target-mediated drug disposition. *AAPS J.* **9**, Article 20 (2007).
59. Agoram, B.M., Martin, S.M. & van der Graaf, P.H. The role of mechanism-based pharmacokinetic-pharmacodynamic (PK-PD) modeling in translational research of biologics. *Drug Discov. Today* **12**, 1018–1024 (2007).
60. Chakraborty, A. *et al.* Pharmacokinetic and pharmacodynamic properties of canakinumab, a human anti-interleukin-1β monoclonal antibody. *Clin. Pharmacokinet.* **51**, e1–e18 (2012).
61. Yan, X. *et al.* Population pharmacokinetic and pharmacodynamic model-based comparability assessment of a recombinant human epoetin alfa and the Biosimilar HX575. *J. Clin. Pharmacol.* **52**, 1624–1644 (2012).
62. Lowe, P.J. Applying physiological and biochemical concepts to optimize biological drug development. *Clin. Pharmacol. Ther.* **87**, 492–496 (2010).
63. Gibiansky, L. *et al.* Population pharmacokinetic analysis of denosumab in patients with bone metastases from solid tumours. *Clin. Pharmacokinet* **51**, 247–260 (2012).
64. Gibiansky, L. & Frey, N. Linking interleukin-6 receptor blockade with tocilizumab and its hematological effects using a modeling approach. *J. Pharmacokinet. Pharmacodyn.* **39**, 5–16 (2012).
65. Lobo, E.D., Soda, D.M. & Balthasar, J.P. Application of pharmacokinetic/pharmacodynamic modeling to predict the kinetic and dynamic effects of anti-methotrexate antibodies in mice. *J. Pharm. Sci.* **92**(8), 1665–1676 (2003).
66. Gao, W. & Jusko, W.J. Target-mediated pharmacokinetic and pharmacodynamic model of exendin-4 in rats, monkeys, and humans. *Drug Metab. Dispos.* **40**, 990–997 (2012).
67. Thai, H.T. *et al.* A mechanism-based model for the population pharmacokinetics of free and bound aflibercept in healthy subjects. *Br. J. Clin. Pharmacol.* **72**(3), 402–414 (2011).
68. Wang, Y.M. *et al.* Pharmacodynamics-mediated drug disposition (PDMDD) and precursor pool lifespan model for single dose of romiplostim in healthy subjects. *AAPS J.* **12**, 729–740 (2010).
69. Ait-Oudia, S., Scherrmann, J.M. & Krzyzanski, W. Simultaneous pharmacokinetics/pharmacodynamics modeling of recombinant human erythropoietin upon multiple intravenous dosing in rats. *J. Pharmacol. Exp. Ther.* **334**, 897–910 (2010).
70. Jin, F. & Krzyzanski, W. Pharmacokinetic model of target-mediated disposition of thrombopoietin. *AAPS Pharm. Sci.* **6**, Article 9 (2004).
71. Marathe, A., Peterson, M.C. & Mager, D.E. Integrated cellular bone homeostasis model for denosumab pharmacodynamics in multiple myeloma patients. *J. Pharmacol. Exp. Ther.* **326**, 555–562 (2008).
72. Kagan, L. & Mager, D.E. Mechanisms of subcutaneous absorption of rituximab in rats. *Drug Metab. Dispos.* **41**, 248–255 (2013).
73. Segrave, A.M. *et al.* Pharmacokinetics of recombinant human leukemia inhibitory factor in sheep. *J. Pharmacol. Exp. Ther.* **309**, 1083–1092 (2004).
74. Mager, D.E. *et al.* Simultaneous modeling of abciximab plasma concentrations and ex vivo pharmacodynamics in patients undergoing coronary angioplasty. *J. Pharmacol. Exp. Ther.* **307**, 969–976 (2003).
75. Mager, D.E. & Jusko, W.J. Receptor-mediated pharmacokinetic/pharmacodynamic model of interferon-β 1a in humans. *Pharm. Res.* **19**, 1537–1543 (2002).
76. Mager, D.E. *et al.* Receptor-mediated pharmacokinetics and pharmacodynamics of interferon-β 1a in monkeys. *J. Pharmacol. Exp. Ther.* **306**, 262–270 (2003).
77. Eppler, S.M. *et al.* A target-mediated model to describe the pharmacokinetics and hemodynamic effects of recombinant human vascular endothelial growth factor in humans. *Clin. Pharmacol. Ther.* **72**, 20–32 (2002).
78. Wiczling, P. *et al.* Population pharmacokinetic modeling of filgrastim in healthy adults following intravenous and subcutaneous administrations. *Clin. Pharmacokinet.* **48**, 817–826 (2009).
79. Ng, C.M. *et al.* Pharmacokinetics/pharmacodynamics of nondepleting anti-CD4 monoclonal antibody (TRX1) in healthy human volunteers. *Pharm. Res.* **23**, 95–103 (2006).
80. Vexler, V. *et al.* Target-mediated drug disposition and prolonged liver accumulation of a novel humanized anti-CD81 monoclonal antibody in cynomolgus monkeys. *mAbs* **5**, 776–786 (2013).
81. Vugmeyster, Y. *et al.* Agonistic TAM-163 antibody targeting tyrosine kinase receptor-B. Applying mechanistic modeling to enable preclinical to clinical translation and guide clinical trial design. *mAbs* **5**, 373–383 (2013).
82. Yamazaki, S. *et al.* Application of target-mediated drug disposition model to small molecule heat shock protein 90 inhibitors. *Drug Metab. Dispos.* **41**, 1285–1294 (2013).
83. McNamara, P.J. *et al.* Effect of plasma protein and tissue binding on the time course of drug concentration in plasma. *J. Pharmacokinet. Biopharm.* **7**, 195–206 (1979).
84. Oie, S. *et al.* Effect of saturable binding on the pharmacokinetics of drugs: a simulation. *J. Pharm. Pharmacol.* **32**, 471–477 (1980).

Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website *(http://www.wileyonlinelibrary/psp4)*