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Selection between Michaelis–Menten and target-mediated drug disposition pharmacokinetic models

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Abstract

Target-mediated drug disposition (TMDD) models have been applied to describe the pharmacokinetics of drugs whose distribution and/or clearance are affected by its target due to high binding affinity and limited capacity. The Michaelis–Menten (M–M) model has also been frequently used to describe the pharmacokinetics of such drugs. The purpose of this study is to investigate conditions for equivalence between M–M and TMDD pharmacokinetic models and provide guidelines for selection between these two approaches. Theoretical derivations were used to determine conditions under which M–M and TMDD pharmacokinetic models are equivalent. Computer simulations and model fitting were conducted to demonstrate these conditions. Typical M–M and TMDD profiles were simulated based on literature data for an anti-CD4 monoclonal antibody (TRX1) and phenytoin administered intravenously. Both models were fitted to data and goodness of fit criteria were evaluated for model selection. A case study of recombinant human erythropoietin was conducted to qualify results. A rapid binding TMDD model is equivalent to the M–M model if total target density R_{tot} is constant, and $R_{tot}K_D/(K_D + C)^2 \ll 1$ where K_D represents the dissociation constant and C is the free drug concentration. Under these conditions, M–M parameters are defined as: $V_{max} = k_{int}R_{tot}V_c$ and $K_m = K_D$ where k_{int} represents an internalization rate constant, and V_c is the volume of the central compartment. R_{tot} is constant if and only if $k_{int} = k_{deg}$, where k_{deg} is a degradation rate constant. If the TMDD model predictions are not sensitive to k_{int} or k_{deg} parameters, the condition of $R_{tot}K_D/(K_D + C)^2 \ll 1$ alone can preserve the equivalence between rapid binding TMDD and M–M models. The model selection process for drugs that exhibit TMDD should involve a full mechanistic model as well as reduced models. The best model should adequately describe the data and have a minimal set of parameters estimated with acceptable precision.

Keywords

Michaels–Menten; Target-mediated drug disposition; Nonlinear pharmacokinetics; Erythropoietin

Introduction

Pharmacokinetics of drugs with saturable clearance is usually described by the Michaelis–Menten (M–M) equation [1, 2]. For cases where a saturable clearance and/or distribution process is controlled by the pharmacological target of the drug (e.g., enzymes or receptors), a mechanistic target-mediated drug disposition (TMDD) pharmacokinetic model has been developed [3]. The fundamental principle for both of these nonlinear processes is capacity limitation [4]. For M–M pharmacokinetics, capacity limitation can occur for many processes, including: hepatic metabolism, and renal and biliary excretion [5]. For TMDD, the limitation is due to the capacity of drug target [4]. Distinct from the M–M model, TMDD models can also account for the turnover of the capacity term and characterize the kinetics of drug target in a more mechanistic manner [4]. Experimental data for target kinetics are very useful when applying TMDD models; however, such information is usually difficult to obtain, and investigators often have access to only free or total drug concentrations in a biological fluid. Under such circumstances, the M–M model has been frequently applied. The M–M model has been shown to fit data from TMDD systems well (and sometimes preferred over TMDD models as demonstrated later), although a TMDD model can also be applied to estimate drug target associated parameters, albeit usually with less precision [6–8].

Monoclonal antibodies frequently present with properties of TMDD. Efalizumab is a humanized anti-CD11a monoclonal antibody, and the significance of target-mediated clearance has been demonstrated in both in vitro and in vivo systems [9, 10]. The M–M model has been successfully used to characterize the pharmacokinetics and pharmacodynamics of efalizumab in patients with psoriasis [6, 7]. In contrast, the pharmacokinetics of TRX1, an anti-CD4 monoclonal antibody that induces immune tolerance by blocking CD4-mediated functions, has been characterized by a TMDD model [11]. The CD4 receptor has been demonstrated to account for the target-mediated clearance of TRX1 [11]. Hematopoietic growth factors are classic examples of drugs that show TMDD properties. Erythropoietin (EPO) is a glycoprotein hormone that stimulates red blood cell production. Its nonlinear pharmacokinetics has been attributed to receptor-mediated endocytosis and lysosomal degradation in the bone marrow [12, 13]. The M–M model has been successfully applied to recombinant human EPO (rHuEPO) pharmacokinetic data in several species including human [8, 14, 15]. On considering a wider range of dose levels, Woo and colleagues developed a more mechanistic TMDD model for rHuEPO [16]. Granulocyte colony stimulating factor (G-CSF) is another drug which is eliminated by neutrophil G-CSF receptor-mediated endocytosis and renal clearance [17]. Thus far, the nonlinear pharmacokinetics of G-CSF has been only characterized by the M–M model. Selection between M–M and TMDD models can be challenging, and conditions under which these two models are equivalent (or different) might prove useful for pharmacokinetic analysis of such systems.

A rapid binding or quasi-equilibrium TMDD model has been developed [18], which is based on the assumption that the target-binding process is much faster than other processes in the system [18]. This assumption simplifies the full TMDD model by replacing the two microconstants of drug-target binding with the equilibrium dissociation rate constant. Gibiansky and co-workers have introduced a quasi-steady-state (QSS) approximation for the full TMDD model as well [19]. The QSS approximation assumes that the drug-target complex concentration changes more slowly than the binding and internalization processes. They also proposed a M–M approximation and further simulations showed that the pharmacokinetics of drugs with target-mediated disposition may be well described by the M–M model if drug concentrations are much higher than the total target concentration [19].

The aims of this work are to investigate conditions under which the M–M and the rapid binding TMDD models are equivalent, and to provide guidelines for model selection for drugs that have TMDD properties. Equations which define such equivalent conditions were derived. Computer simulations and model fitting were conducted to confirm and validate such conditions. Typical TMDD profiles were simulated based on literature data for TRX1, and M–M profiles were simulated based on literature data for the antiepileptic drug phenytoin, the clearance of which is controlled by saturable cytochrome P450 enzymes [20, 21]. Both the M–M and a series of TMDD models were fitted to simulated data, and a general framework was developed for the selection between M–M and TMDD pharmacokinetic models. A case study of rHuEPO was used to test the robustness of these results.

Theoretical

The structure of a M–M pharmacokinetic model is shown in Fig. 1a. Free Drug in the central compartment (C) is eliminated from the system by the combination of a first-order rate constant (k_{el}) and a saturable process described by the M–M equation. The model equations are as follows:

$$\frac{dC}{dt} = In(t) - \frac{(V_{max}/V_c)C}{K_m + C} - (k_{pt} + k_{el})C + k_{tp}A_T/V_c \quad (1)$$

$$\frac{dA_T}{dt} = k_{pt}CV_c - k_{tp}A_T \quad (2)$$

where V_c denotes the volume of distribution of the central compartment. $In(t)$ represents a function of drug input or endogenous substance production. Tissue distribution is characterized by the peripheral compartment (A_T), which is connected to the central compartment through two first-order rate constants (k_{pt} and k_{tp}). The initial conditions for this system following an intravenous (IV) bolus dose are defined by the steady-state (baseline) value:

$$C(0) = \frac{Dose}{V_c} + C_0; \quad A_T(0) = k_{pt}V_c C_0 / k_{tp} \quad (3a, b)$$

where C_0 is the concentration of endogenous substance. The endogenous substance production rate is defined by the steady-state (baseline) value:

$$In(0) = \frac{(V_{max}/V_c)C_0}{K_m + C_0} + k_{el}C_0 \quad (4)$$

The TMDD pharmacokinetic model has been described elsewhere [18], and is shown in Fig. 1b. Briefly, free drug in the central compartment (C) binds to its free target (R) at a second-order rate constant (k_{on}), forming a drug-target complex (RC). The RC complex can either dissociate at a first-order rate (k_{off}) or be internalized and degraded at a first-order rate (k_{int}). Free drug can also be removed from the central compartment by a first-order elimination process (k_{el}). Free targets are synthesized at a zero-order rate (k_{syn}) and degraded at a first-order rate (k_{deg}). The model equations are as follows:

$$\frac{dC}{dt} = In(t) - k_{on}R \cdot C + k_{off}RC - (k_{el} + k_{pt})C + k_{tp}A_T / V_c \quad (5)$$

$$\frac{dA_T}{dt} = k_{pt}V_cC - k_{tp}A_T \quad (6)$$

$$\frac{dR}{dt} = -k_{on}R \cdot C + k_{off}RC + k_{syn} - k_{deg}R \quad (7)$$

$$\frac{dRC}{dt} = k_{on}R \cdot C - k_{off}RC - k_{int}RC \quad (8)$$

The initial conditions for Eqs. 5–8 following an IV bolus dose are defined by the steady-state (baseline) value:

$$C(0) = \frac{Dose}{V_c} + C_0; \quad (9a)$$

$$A_T(0) = k_{pt}V_cC_0 / k_{tp}; \quad (9b)$$

$$R(0) = R_0; \quad (9c)$$

$$RC(0) = k_{on}R_0C_0 / (k_{int} + k_{off}); \quad (9d)$$

The endogenous substance production rate is also defined by the baseline value:

$$In(0) = k_{on}R_0C_0 + k_{off}k_{on}R_0C_0 / (k_{int} + k_{off}) + k_{el}C_0 \quad (10)$$

Under the rapid binding condition [22]:

$$\frac{R \cdot C}{RC} = \frac{k_{off}}{k_{on}} \equiv K_D \quad (11)$$

where K_D represents the equilibrium dissociation constant. On re-parameterizing the system in terms of total drug (C_{tot}) and target (R_{tot}) concentrations:

$$C_{tot} = RC + C; \quad R_{tot} = RC + R \quad (12a, b)$$

one can derive another set of equations [18]:

$$\frac{dC_{tot}}{dt} = In(t) - k_{int}(C_{tot} - C) - (k_{el} + k_{pt})C + k_{tp}A_T/V_c \quad (13)$$

$$\frac{dR_{tot}}{dt} = k_{syn} - (k_{int} - k_{deg})(C_{tot} - C) - k_{deg}R_{tot} \quad (14)$$

$$\frac{dA_T}{dt} = k_{pt}CV_c - k_{tp}A_T \quad (15)$$

$$C = \frac{1}{2} \left[(C_{tot} - R_{tot} - K_D) + \sqrt{(C_{tot} - R_{tot} - K_D)^2 + 4K_D C_{tot}} \right] \quad (16)$$

The initial conditions for Eqs. 13–16 following an IV bolus dose are:

$$C_{tot}(0) = \frac{Dose}{V_c} + \frac{R_{tot0}C_0}{K_D + C_0} + C_0; \quad (17a)$$

$$R_{tot}(0) = R_{tot0}; \quad (17b)$$

$$A_T(0) = k_{pt}V_cC_0/k_{tp} \quad (17c)$$

The endogenous substance production rate is defined by the steady-state (baseline) value:

$$In(0) = \frac{k_{int}R_{tot0}C_0}{K_D + C_0} + k_{el}C_0 \quad (18)$$

To investigate the conditions under which the M–M and the rapid binding TMDD models are equivalent, we have derived the differential form of Eq. 16. Our calculations followed an approach introduced by Wagner [2]. When R_{tot} is constant, the derivative of Eq. 16 is (see Appendix 1):

$$\frac{dC}{dt} = \frac{In(t) - \frac{k_{int}R_{tot}C}{K_D + C} - (k_{el} + k_{pt})C + k_{tp}A_T/V_c}{1 + \frac{R_{tot}K_D}{(K_D + C)^2}} \quad (19)$$

with an initial condition $C(0) = \frac{Dose}{V_c} + C_0$ assuming an IV bolus dose administration. If the ratio in the denominator of Eq. 19 is much smaller than 1, i.e.,

$$\frac{R_{tot}K_D}{(K_D + C)^2} \ll 1 \quad (20)$$

then Eq. 19 can be further reduced to:

$$\frac{dC}{dt} = In(t) - \frac{k_{int}R_{tot}C}{K_D + C} - (k_{el} + k_{pt})C + k_{ip}A_T/V_c \quad (21)$$

which is mathematically identical to Eq. 1 with $V_{max} = k_{int}R_{tot}V_c$ and $K_m = K_D$. Eq. 20 is satisfied for any concentration if

$$R_{tot} \ll K_D \quad (22)$$

or

$$R_{tot} \ll C \text{ and } K_D \ll C. \quad (23a, b)$$

Methods

Model simulations

Computer simulations of concentration versus time profiles for M–M and TMDD models and parameter estimations were conducted with Phoenix WinNonlin 6.0 (Pharsight Corporation, Cary, NC). All simulated data were checked for nonlinearity by plotting the dose-normalized concentration–time profiles, which do not superimpose for nonlinear data.

To investigate conditions under which R_{tot} is constant, R_{tot} vs. time profiles were simulated with varying k_{int} or k_{deg} values using the full TMDD model. Model parameter values were adopted from the anti-CD4 monoclonal antibody TRX1 which clearly demonstrates TMDD pharmacokinetics [11]. Simulations were conducted at a dose of 10 mg kg⁻¹.

To investigate equivalence between M–M and rapid binding TMDD models under the condition $R_{tot} \ll K_D$, TMDD drug concentration–time profiles were simulated based on TRX1 with the rapid binding TMDD model using the original R_0 value (54.9 nM) and a 100-fold smaller value (0.549 nM), resulting in R_0/K_D ratios of 2.8 and 0.028. For each R_0/K_D value, simulations were conducted with varying k_{int} or k_{deg} values. In either case, the k_{deg} or k_{int} value was fixed to 3.93 day⁻¹. Data were simulated for three single doses of 1, 5, and 10 mg kg⁻¹ administered as a 2-h IV infusion [11]. The limit of detection was 156 ng ml⁻¹ [11] and a total of 48 points were simulated from 0.02 to 36 h. The identical sampling schedule was used for all dose levels. Residual error was further introduced to the data using SAS 9.0 (SAS Institute Inc., Cary, NC) according to a proportional error model:

$$Y = \hat{Y}(1 + \varepsilon) \quad (24)$$

where Y denotes the simulated value, $\hat{Y}$ is the model predicted concentration and ε is the residual error, which is assumed to be normally distributed random variable with mean zero and standard deviation $\sigma = 0.05$. Simulated data were fitted with M–M and rapid binding TMDD models. The weighted sum of squared residuals (WSSR) from model fitting was plotted against k_{int} or k_{deg} as a measure of goodness of fit.

To provide guidance for selecting between TMDD and M–M models, two pharmacokinetic data sets were simulated based on the TMDD and M–M models with the addition of residual

error. These simulated data mimic the situation when nonlinearity is present, the mechanism of the nonlinearity is not fully understood and, most importantly, the “best” model is not known. Residual error was introduced to the simulated data as described by Eq. 24 with $\sigma = 0.15$. The M–M model structure was based on phenytoin pharmacokinetics, and parameters for simulation were obtained from a study in rats conducted by Della and colleagues [20]. Phenytoin concentration–time profiles were simulated for three single dose levels of 10, 40, and 100 mg kg⁻¹, which were administered as a 5-min IV infusion. A total of 36 time points was simulated to cover complete concentration–time profiles, and the limit of detection was 0.25 µg ml⁻¹ [20]. For the TMDD profile, data were simulated for three single doses of 1, 5, and 10 mg kg⁻¹ of TRX1 administered as a 2-h IV infusion [11]. A total of 34 time points was simulated, and the limit of detection was 156 ng ml⁻¹ [11].

Pharmacokinetic data for rHuEPO were simulated based on the rapid binding TMDD model and parameter values reported for humans [16]. To mimic experimental data, residual error was introduced to simulated data as described by Eq. 24 with $\sigma = 0.15$. The simulated concentrations were terminated at times when they reached values of 569, 300 and 157 mIU ml⁻¹ (i.e., concentrations where $R_{tot}K_D/(K_D + C)^2$ equals 0.01, 0.04 and 0.1). Thus, three data sets with increasing number of data points were generated for rHuEPO.

Model fitting

The simulated data with added random error for TRX1, phenytoin and rHuEPO were fitted with various models including the full and rapid binding TMDD, full and rapid binding TMDD with $k_{int} = k_{deg}$, and M–M models. The metrics of WSSR and Akaike Information Criterion (AIC) were used for model selection [23, 24]. Minimization was performed using Phoenix WinNonlin 6.0 (Pharsight Corporation, Cary, NC) with Gauss–Newton with Levenberg and Hartley minimization algorithms. The squared residuals were weighted by the inverse of squared model predicted values ($1/\hat{Y}^2$). For the model fitting of rHuEPO data, the endogenous EPO concentration (C_0) was fixed at 16.7 mIU ml⁻¹ according to the original publication [16]. The physiological parameters, k_{syn} and k_{epo} , which define endogenous EPO turnover, were coded as secondary parameters.

Results

Effect of k_{int} and k_{deg} on R_{tot}

The effect of k_{int} and k_{deg} on the total target density was studied by means of mathematical analysis and computer simulation. In Appendix 2, we show that R_{tot} is constant if and only if $k_{int} = k_{deg}$. This theorem is not affected by the presence of endogenous substance or the consideration of the rapid binding assumption. Figure 2 shows the effect of k_{int} and k_{deg} on R_{tot} through simulations of R_{tot} vs. time curves as a function of varying k_{int} and k_{deg} values. In panel A, where k_{int} is fixed at 3.93 day⁻¹, R_{tot} is decreased in the presence of drug when $k_{deg} < k_{int}$ and reaches a minimum followed by a plateau. Thereafter, R_{tot} gradually returns to baseline. Lower k_{deg} values correspond with a greater extent of R_{tot} decrease and a longer duration of the plateau phase. On the other hand, the condition of $k_{deg} > k_{int}$ leads to an increase of R_{tot} , which gradually returns to baseline after reaching the maximum value. Higher k_{deg} values correspond with a greater increase and a sharper peak in R_{tot} . If k_{deg} is equal to k_{int} , R_{tot} remains constant during the entire period. It should be noted that k_{syn} is coded as $R_0 \cdot k_{deg}$ in the model. The change of k_{deg} will lead to a proportional change of k_{syn} in order to conserve the R_0 value. In panel B, where k_{deg} is fixed at 0.69 day⁻¹, when $k_{int} > k_{deg}$, R_{tot} decreases in the presence of drug, reaches a plateau, and then returns to baseline. Greater k_{int} values correspond with a greater extent of decrease in R_{tot} and a longer plateau phase. When $k_{int} < k_{deg}$, R_{tot} is increased to a maximum value and returns to baseline. The lower k_{int} value corresponds to a greater increase and a sharper peak shape.

Overall, if k_{int} is greater than k_{deg} , R_{tot} will decrease, and if k_{int} is less than k_{deg} , R_{tot} will increase in the presence of drug. Physiologically, this observation indicates that if the elimination process of drug-target complex is slower than the degradation process of free target, the formation of drug-target complex will lead to an increase in the total target density. On the other hand, if the elimination process is faster, then the formation of the drug-target complex will accelerate total target elimination.

Equivalence between M–M and rapid binding TMDD models

Given the condition described by Eq. 20, Eq. 19 is equivalent to the M–M model shown in Eq. 1. In particular, if $R_{tot} \ll K_D$ (Eq. 22), Eq. 20 is satisfied. It can be concluded that if $R_{tot} \ll K_D$ and $k_{int} = k_{deg}$, the rapid binding TMDD model is equivalent to the M–M model. The above conclusion is illustrated in Fig. 3, where the simulated data based on the rapid binding TMDD model were refitted with both M–M and rapid binding TMDD models for varying values of k_{deg} or k_{int} . Comparing panels a and b in Fig. 3 reveals that as the R_0/K_D ratio decreases from 2.8 to 0.028, the WSSR values from both models become similar. The same trend in the change of WSSR is observed on comparing panels c and d, where simulations were conducted for various k_{int} values. It would be expected that when $k_{int} \neq k_{deg}$ and R_{tot} is not constant, the rapid binding TMDD profile may not be well characterized by the M–M model. Especially when $k_{int} < k_{deg}$, R_{tot} increases (Fig. 2) and the condition $R_{tot} \ll K_D$ might be challenged. But, the WSSR values from the rapid binding TMDD and M–M model fittings were demonstrated to be very similar over a wide range of k_{int} and k_{deg} (from 0.4 to 50). This reflects a previous finding that simulated TMDD signature profiles are not sensitive to changes in k_{int} or k_{deg} at early sampling times [25]. With a relative small total target baseline, $k_{int} < k_{deg}$ will likely result in only a moderate increase in R_{tot} . Under this condition, Eq. 20 may still hold for relatively high concentrations. In light of the proportional residual error with $\sigma = 0.05$ that was introduced to the simulated data, the M–M and TMDD models capture such profiles equally well.

Model selection

TRX1 and phenytoin concentration–time profiles were generated by simulation, based on previously published models [11, 20], and residual error was added as described in the methods. The M–M and a series of TMDD models were fitted to the data, and parameter estimates and model fitting criteria (WSSR and AIC) are reported in Tables 1 and 2. The TRX1 data and model-predicted profiles from fitting the M–M and rapid binding TMDD models are shown in Fig. 4 (the rapid binding TMDD model had the lowest AIC listed in Table 1). Whereas the TMDD model well described the data, the M–M model was only able to capture data for higher dose levels (5 and 10 mg kg⁻¹) (Fig. 4). The lower dose data (1 mg kg⁻¹) were clearly over predicted. Interestingly, the TRX1 data were simulated using the full TMDD model. The values of $Dose/V_c \cdot k_{on}$ and k_{off} are greater than the other rate constants and serve to explain the better performance of the rapid binding TMDD model [18]. Consequently, k_{on} and k_{off} parameters were estimated with poor precision using the full TMDD model (Table 1).

The phenytoin data and model-predicted profiles from the M–M model and the rapid binding TMDD model with $k_{int} = k_{deg}$ are shown in Fig. 5. Among the tested TMDD models, the rapid binding model with $k_{int} = k_{deg}$ had the lowest AIC value with the best precision of parameter estimates (Table 2). However, the model with the lowest AIC value across all models was the M–M model. The model predictions from the M–M and the rapid binding TMDD model with $k_{int} = k_{deg}$ almost completely overlapped and both models fitted the data well (Fig. 5). Accordingly, the WSSR values were also similar (0.742 and 0.741, Table 2). Since the TMDD model has more parameters than the M–M model, CV% values for some parameters would be expected to be greater for the TMDD model, which is clearly

demonstrated in Table 2. In addition, parameter estimates for the rapid binding TMDD model with $k_{int} = k_{deg}$ show that the $R_0 \ll K_D$. This is the condition under which this model is equivalent to the M–M model as described previously. Calculating the product of $k_{int}R_{tot}V_c$ gives $979 \text{ nmol kg}^{-1} \text{ min}^{-1}$, which is very close to the V_{max} value estimated by the M–M model. The K_D is also similar to the estimated K_m value. These observations support the concept that the rapid binding TMDD model with $k_{int} = k_{deg}$ is equivalent to the M–M model.

M–M and TMDD models for rHuEPO

A case study of recombinant human EPO was employed to test the condition $R_{tot} \ll C$ and $K_D \ll C$ (Eq. 23) and confirm the consistency of AIC during model selection. Recombinant human EPO data were simulated using the rapid binding TMDD model [16]. Data were truncated at concentrations of 569, 300, and 157 mIU ml⁻¹ after incorporation of residual error. Their respective molar concentrations are 0.117, 0.0617, and 0.0323 nM. These thresholds were chosen to highlight the condition described by Eq. 23 and resulted in values of 0.01, 0.04 and 0.1 for $R_{tot}K_D/(K_D + C)^2$. Figure 6 shows the truncated data at the threshold of 157 mIU ml⁻¹ and model-predicted profiles from the rapid binding TMDD and M–M models. Only the threshold of 157 mIU ml⁻¹ yielded at least one model with CV% less than 100% for all parameter estimates. The AIC values clearly show that the rapid binding TMDD model is superior to the M–M model for the selected data (Table 3), and the M–M model tends to over predict the simulated data for the low dose (Fig. 6). However, due to overparameterization, the CV% values for k_{int} , k_{deg} , K_D , and R_{tot} are high (>100) for the rapid binding TMDD model. The M–M model exhibited better precision of parameter estimates. As the values of $R_{tot}K_D/(K_D + C)^2$ decrease to 0.04 and 0.01, AIC clearly favored the M–M model (data not shown), but the CV% for V_{max} , K_m , k_{int} , k_{deg} , R_0/R_{tot} , and K_D were increased due to insufficient low concentration data points (data not shown).

These results show that even though the pharmacokinetics of a drug follows TMDD properties, this might not be discernable from concentration–time profiles based on AIC and precision metric, unless the limit of detection allows for the measurement of low concentrations and/or a sufficient dose-ranging study is conducted. Under such limiting conditions, precise parameter estimates might not be achievable with a TMDD model, and the M–M model would be preferred as mentioned earlier. Accordingly, for TMDD profiles at high drug concentrations, the M–M model might perform better than TMDD models, regardless of the presence of target turnover processes.

Discussion

There has been an increasing interest in TMDD models due to the development of more potent and target specific drugs. The binding between such high affinity drugs and their targets (relative to dose) has a significant effect on pharmacokinetic profiles [26]. The similarity between M–M and TMDD models is due to capacity limitation in elimination processes. Therefore, they share some similarities at high doses, where both systems are saturated. However, there is a striking difference between M–M and TMDD models at low doses or concentrations [26]. The M–M model exhibits linear parallel decay for low doses. On the other hand, there is a very rapid drop and a long terminal phase for TMDD systems. Accordingly, the M–M model can over predict low dose data, as shown for both TRX1 and rHuEPO [8]. When the low dose data for rHuEPO are excluded, the M–M model fits the data perfectly well (Fig. 6). The rapid decrease in drug concentrations for low doses reflects the depletion of drug by rapid target binding. In addition, the relatively long terminal phase is one of hallmark features of TMDD profiles and its slope is controlled by several parameters including k_{tp} , k_{pt} , R_0 , K_D , k_{el} and k_{int} [25]. Binding processes are usually very rapid and difficult to capture by normal sampling regimens in pharmacokinetic studies.

Although the terminal phase should be easier to capture than binding processes in terms of time, the long terminal phase usually occurs at concentrations that are too low to be determined or below the range of clinical interest. Thus, the M–M model might be sufficient to characterize such profiles and outperform the TMDD model.

Typical TMDD and M–M profiles were simulated based on literature data for TRX1 and phenytoin. However, these data contained residual errors and were used to mimic the situation when the “best” model is not known. Under such circumstances, various TMDD and M–M models were fitted to the data and tested. The array of models are not nested and they are constructed based on different assumptions. Therefore, the model with more parameters does not guarantee a better fit than the model with less parameters. Comparison of models 2 and 3 for TRX1 (Table 1), models 3 and 5 for phenytoin (Table 2) and models 2 and 3 for rHuEPO (Table 3) demonstrate that the model with more parameters may result in higher WSSR values. This necessitates the individual assessment of these different models. The AIC has long been used as an informative metric for selection among models which are not nested. For the TRX1 data, AIC values suggest that the TMDD model is superior to the M–M model, whereas the opposite is true for phenytoin. The values of WSSR and parameter estimates, in contrast, imply that the rapid binding TMDD model with $k_{int} = k_{deg}$ is equivalent to the M–M model. Therefore, in this study, AIC indicates the “best” model. For rHuEPO, although AIC was lowest for the rapid binding TMDD model, only the M–M model resulted in the acceptable precision of parameter estimates ($CV\% < 100\%$).

We have established equivalency between the M–M and rapid binding TMDD models if R_{tot} is constant and Eq. 20 is satisfied. The case for rHuEPO suggests that these two models can describe the data equally well, even if R_{tot} changes with time ($k_{int} \neq k_{deg}$), as long as the condition defined by Eq. 20 holds. This can be explained by our findings that if the TMDD model predictions are not sensitive to k_{int} or k_{deg} parameters, the changes in R_{tot} are not relevant. Such conditions typically exist for higher drug concentrations relative to target density (i.e., saturation) as described by Eq. 23a, b. This conclusion was also implied in Fig. 3, where the condition $R_{tot} \ll K_D$ (Eq. 22) was assumed. It shows that the M–M model is equivalent to the rapid binding TMDD model over a wide range of different k_{int} and k_{deg} values. The condition $R_{tot} \ll K_D$ is not only mathematically interesting, but also of practical importance. C.E.R.A., a continuous erythropoietin (EPO) receptor activator, was developed such that its K_D value is 50–100 fold higher than that of Epoetin- β [27]. Based on previous parameter estimates from the rapid binding TMDD model (Table 3) [16], R_{tot}/K_D of C.E.R.A. would be 0.013–0.026. This might serve to explain the good simultaneous fit of the M–M model to plasma concentration data from both low and high IV bolus doses of C.E.R.A [28], whereas the M–M model over predicts low dose data for rHuEPO [8]. The reduced receptor-mediated elimination results in a reduced clearance of C.E.R.A compared with Epoetin- β [28] and enables a once-monthly dosing regimen.

Based on above findings, standard modeling-fitting criteria [24] may be used to guide model development for drugs with TMDD properties:

1. Pharmacokinetic data should be fitted with an array of models including the full TMDD model, the M–M model, and a number of reduced approximate TMDD models (e.g., rapid binding or QSS TMDD models).
2. The parameter estimates, standard errors (CV%) and statistics describing goodness of fit such as AIC should be recorded.
3. These metrics calculated from fitting different models should be directly compared. The models yielding parameter estimates with acceptable precision and with the lowest AIC values should be selected.

These guidelines are simpler than an algorithm proposed by Gibiansky and colleagues [19], in which estimated full TMDD model parameters are used to obtain parameters for various approximations and decisions are made after comparison of model predictions. Instead of evaluating various approximations, our approach attempts to select the best model based on quantitative criteria and suggests that observing the principle of parsimony should be sufficient. For the full TMDD model that yields parameters with poor estimates of precision or does not converge at all (which usually occurs for population analysis), various reduced model should be tested.

If the M–M model emerges as superior, then this may imply that the data do not contain enough information for the target-mediated clearance process to be identified by a TMDD model. However, if target dynamics or pharmacodynamic data are available, then joint modeling of pharmacokinetic and pharmacodynamic data may infer binding kinetics, warranting a mechanism based TMDD model [4]. Although the pharmacological effect may be used to regulate drug clearance in an empirical manner [17], a TMDD model provides a natural framework for integrating exposure–response relationships when pharmacodynamics influences drug disposition.

Our findings apply to single dose data with IV input, and such information is typically recommended, even for drugs that will eventually be administered extravascularly (e.g., orally or subcutaneously), to best understand the disposition of the drug. An absorption process might contribute to nonlinear pharmacokinetic behavior (e.g., dose dependent bioavailability) and drug disposition can also be biased by flip-flop kinetics. Recombinant human EPO has been reported to exhibit both of these phenomena [8]. Theoretically, these findings should apply to multiple dose pharmacokinetic data, assuming system parameters are time-invariant.

We analyzed approximations of the TMDD model based on the rapid binding or quasi-equilibrium assumption [18]. Other approximations have been reported in the literature that leads to analogous conclusions. Gibiansky and colleagues [19, 29] assumed a quasi-steady-state. Mathematically, this reduces the full model to the form equivalent to the rapid binding TMDD model with K_D replaced with $K_{ss} = (k_{off} + k_{int})/k_{on}$. Consequently, most of our conclusions reporting equivalence and selection between the rapid binding TMDD and M–M models will also apply to the QSS TMDD model. Discrepancies between the QSS and rapid binding TMDD models would be reflective of varying k_{int} values.

The rapid binding TMDD model is mathematically equivalent to the M–M model under the conditions that R_{tot} is constant and Eq. 20 is satisfied. The M–M model parameters (e.g., V_{max} and K_m) estimated under these conditions are demonstrated to be very close to their counterparts in the rapid binding TMDD model (Table 2). We further demonstrate that the M–M model can perform better than TMDD models even if R_{tot} is not constant. Eq. 19 and the conditions under which R_{tot} is constant were presented previously by Yan et al. [30]. A similar equation under the QSS assumption was provided by Gibiansky and colleagues [29]. Peletier and colleagues have derived a proof of a theorem for the sufficient condition when R_{tot} is constant ($k_{int} = k_{deg}$) [31]. A derivation for both necessary and sufficient conditions is provided in Appendix 2.

Model selection depends on many factors, and in this study, the only uncertainty in the data was a modest residual error. Sampling times were selected to ensure sufficient information about drug pharmacokinetics. Further studies are necessary to address the impact of the experimental design on model selection. Similarly, our objectives preclude analysis of inter-subject variability and covariate effects on the selection between the TMDD and M–M models. The quality of data is critical for discerning the difference between M–M and

TMDD profiles. Residual error was added to simulated data based on a proportional error model with $\sigma = 0.05$ or 0.15 . Greater noise in the data should make it more difficult to select the “true” model; however, it seems that AIC is still indicative for model selection for data containing random proportional error with $\sigma = 0.15$.

The linear elimination in TRX1 was relatively small compared with the nonlinear elimination pathway and phenytoin did not exhibit linear elimination. The influence of linear clearance to our current findings was evaluated by escalating constant values of linear clearance (data not shown). The results suggest that AIC is still useful for selecting the “best” model between TMDD and M–M systems. However, the identifiability of parameters associated with nonlinear pathways might be compromised. The difference between V_{max} estimated from the M–M model and $R_{tot}k_{int}V_c$ from the rapid binding TMDD model was increased. A similar trend was observed for K_m and K_D . However, all of these terms were still proximal.

In summary, the rapid binding TMDD model is equivalent to the M–M model when R_{tot} is constant ($k_{int} = k_{deg}$) and the condition of Eq. 20 is satisfied. Furthermore, these two models differ for concentrations sensitive to k_{int} or k_{deg} parameters. If the condition described by Eq. 20 alone is satisfied for target-mediated data, the M–M model might still perform better than TMDD models for high concentration or censored data. These findings might be applicable for other types of approximations of TMDD models other than the rapid binding approximation. Simple model selection guidelines for drugs with TMDD properties are also provided.

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Appendix 1

Derivation of Wagner equation (Eq. 19)

The Eq. 12a, b can be rearranged to the following form:

$$C_{tot} = C + \frac{R_{tot}C}{K_D + C} \quad (A1)$$

Differentiating both sides of Eq. A1 gives:

$$\frac{dC_{tot}}{dt} = \frac{dC}{dt} + \frac{d}{dt} \left(\frac{R_{tot}C}{K_D + C} \right) = \frac{dC}{dt} + \frac{R_{tot}K_D}{(K_D + C)^2} \frac{dC}{dt} + \frac{C}{K_D + C} \frac{dR_{tot}}{dt} \quad (A2)$$

Solving above equation for dC/dt results in:

$$\frac{dC}{dt} = \frac{\frac{dC_{tot}}{dt} - \frac{C}{K_D + C} \frac{dR_{tot}}{dt}}{1 + \frac{R_{tot}K_D}{(K_D + C)^2}} \quad (A3)$$

Substitution of dC_{tot}/dt from Eq. 13 into Eq. A3 and further replacement of C_{tot} with Eq. A1 yield:

$$\frac{dC}{dt} = \frac{\ln(t) - \frac{(k_{int}R_{tot} + \frac{dR_{tot}}{dt})C}{K_D + C} - (k_{el} + k_{pt})C + k_{tp}A_T/V_c}{1 + \frac{R_{tot}K_D}{(K_D + C)^2}} \quad (A4)$$

If R_{tot} is constant, then $dR_{tot}/dt = 0$, and one obtains Eq. 19.

Appendix 2

Theorem: for the TMDD model, R_{tot} is constant if and only if $k_{int} = k_{deg}$

Proof

(a) Proof of the sufficient condition

At steady state, from Eq. 14 it can be reached:

$$k_{syn} - k_{deg}R_0 - k_{int}RC_0 = 0 \quad (A5)$$

Hence,

$$k_{syn}=k_{deg}R_0+k_{int}RC_0 \quad (A6)$$

If R_{tot} is constant, Eq. 14 implies:

$$k_{syn} - k_{deg}R - k_{int}RC=0 \quad (A7)$$

Replacing k_{syn} with Eq. A6, one can obtain:

$$k_{deg}(R_0 - R)+k_{int}(RC_0 - RC)=0 \quad (A8)$$

From Eq. 12a, b, it can be concluded:

$$R_{tot}=RC+R; R_{tot0}=RC_0+R_0 \quad (A9,10)$$

That R_{tot} is constant implies:

$$R_{tot}=R_{tot0} \quad (A11)$$

Substitution of R_{tot} and R_{tot0} from Eqs. A9 and A10 to Eq. A11 results in:

$$RC+R=RC_0+R_0 \quad (A12)$$

Rearrangement of Eq. A12 gives:

$$R_0 - R=RC - RC_0 \quad (A13)$$

Replacing R_0-R in Eq. A8 with Eq. A13 yields:

$$(k_{deg} - k_{int})(RC_0 - RC)=0 \quad (A14)$$

Since $RC_0 - RC \neq 0$ after drug administration, the Eq. A14 implies:

$$k_{int}=k_{deg} \quad (A15)$$

(b) Proof of the necessary condition

If $k_{int} = k_{deg}$, then Eq. 14 implies:

$$\frac{dR_{tot}}{dt} = -k_{deg}R_{tot}+k_{syn} \quad (A16)$$

Replacing k_{syn} in Eq. A16 with Eq. A6 yields:

$$\frac{dR_{tot}}{dt} = -k_{deg}R_{tot}+k_{deg}R_0+k_{int}RC_0 \quad (A17)$$

Substitution of k_{int} with k_{deg} gives:

$$\frac{dR_{tot}}{dt} = -k_{deg}R_{tot} + k_{deg}(R_0 + RC_0) \quad (A18)$$

Given $R_{tot0} = RC_0 + R_0$, Eq. A18 reduces to:

$$\frac{dR_{tot}}{dt} = -k_{deg}R_{tot} + k_{deg}R_{tot0} \quad (A19)$$

Since Eq. A19 starts from initial condition, it can be concluded that:

$$\frac{dR_{tot}}{dt} = 0 \quad (A20)$$

End of proof.

Fig. 1. Schematic representation of the **a** M-M and **b** TMDD pharmacokinetic models. *Symbols* are defined in theoretical

Fig. 2.

Simulations of the effect of k_{int} and k_{deg} on total target-time profile in the target-mediated drug disposition model. Simulations were performed with TRX1 parameter values from Ng et al. [11] with varying k_{deg} or k_{int} value at dose of 10 mg kg^{-1} . **a** Data were simulated with following parameter values: $k_{int} = 3.93$, $k_{deg} = 0.69, 1.7, 2.8, 3.93, 5.0, 7.8, 11.7$. **b** Data were simulated with following parameter values: $k_{deg} = 0.69$, $k_{int} = 0.17, 0.35, 0.52, 0.69, 1.7, 2.8, 3.93$. Other parameter values were $k_{el} = 0.078$, $k_{pt} = 0.649$, $k_{tp} = 0.874$, $V_c = 41.7$, $k_{on} = 0.753$, $k_{off} = 14.6$, $R_0 = 54.9$. Parameter units are specified in Table 1

Fig. 3.

WSSR values from fitting the M–M and rapid binding TMDD model to data simulated by the rapid binding TMDD model with varying k_{deg} or k_{int} values. The residual error was introduced to simulated data using a proportional error model with $\sigma = 0.05$. **a** Data were simulated with the following parameter values: $k_{el} = 0.078$, $k_{pt} = 0.649$, $k_{tp} = 0.874$, $V_c = 41.7$, $K_D = 19.4$, $k_{int} = 3.93$, $R_0 = 54.9$, $k_{deg} = 0.4, 0.7, 1.2, 1.7, 2.8, 3.93, 5.0, 6.0, 7.8, 9.8, 11.8, 15.0, 19.7, 25, 30, 40, 50$. **b** Data were simulated using the same parameter values in Panel A except for $R_0 = 0.549$. **c** Data were simulated with the following parameter values: $k_{el} = 0.078$, $k_{pt} = 0.649$, $k_{tp} = 0.874$, $V_c = 41.7$, $k_{deg} = 3.93$, $K_D = 19.4$, $R_0 = 54.9$, $k_{int} = 0.4, 0.7, 1.2, 1.7, 2.8, 3.93, 5.0, 6.0, 7.8, 9.8, 11.8, 15.0, 19.7, 25, 30, 40, 50$. **d** Data were simulated using the same parameter values in Panel C except for $R_0 = 0.549$. WSSR values are shown for the M–M (solid triangles) and rapid binding TMDD model (open triangles). Parameter units are specified in Table 1

Fig. 4.

Simulated TRX1 data fitted with the rapid binding TMDD and M-M models. Symbols represent simulated data and correspond to TRX1 doses of 1 (*filled circle*), 5 (*open circle*), and 10 (*filled inverted triangle*) mg kg^{-1} . Data were created by simulations using TRX1 parameters from Ng et al. [11] and residual error was added using a proportional error model with $\sigma = 0.15$. Parameter values for simulation and model estimates are listed in Table 1. Model predictions are shown for the M-M (*dashed lines*) and rapid binding TMDD (*solid lines*) models

Fig. 5. Simulated phenytoin data fitted with the M–M model and rapid binding TMDD model with $k_{int} = k_{deg}$. Symbols represent simulated data and correspond to phenytoin doses of 10 (*filled circle*), 40 (*open circle*), and 100 (*filled inverted triangle*) mg kg^{-1} . Data were created by simulations using phenytoin parameters from Della et al. [20] and residual error was added using a proportional error model with $\sigma = 0.15$. Parameter values for simulation and model estimates are listed in Table 2. Model predictions are shown for the M–M model (*solid lines*) and rapid binding TMDD model with $k_{int} = k_{deg}$ (*dashed lines*)

Fig. 6.

Simulated rHuEPO data fitted with both M–M and rapid binding TMDD models. Symbols represent simulated data and correspond to doses of 100 (*filled circle*), 150 (*open circle*), 300 (*filled inverted triangle*), and 500 (*open triangle*) IU/kg in man. Data were created by simulations using a TMDD model and parameters from Woo et al. [16] and residual error was added using a proportional error model with $\sigma = 0.15$. Parameter values for simulation and model estimates are listed in Table 3. Model predictions are shown for the M–M (*dashed lines*) and rapid binding TMDD (*solid lines*) models

Table 1

Parameter estimates and diagnostics for fitting simulated TRX1 data

Parameter	Estimates (CV%)					
	0	1	2	3	4	5
k_{el} (day ⁻¹)	0.078	0.0805 (9.3)	0.0825 (7.7)	0.0792 (7.9)	0.0796 (10.6)	0.0676 (14.5)
k_{pr} (day ⁻¹)	0.649	0.737 (28.4)	0.768 (25.1)	0.718 (23.5)	0.814 (25.7)	0.621 (31.5)
k_{ip} (day ⁻¹)	0.874	0.935 (17.3)	0.964 (18.4)	0.933 (16.1)	0.873 (19.3)	0.740 (19.9)
V_c (ml kg ⁻¹)	41.7	40.7 (7.5)	41.2 (5.3)	41.3 (5.8)	42.9 (7.8)	48.6 (7.7)
k_{deg} (day ⁻¹)	0.694	0.674 (12.9)	0.779 (12.4)	0.676 (12.7)	1.78 (19.8)	N/A
K_D (nM)	N/A	N/A	N/A	59.3 (48.3)	3.06 (21.7)	N/A
k_{on} (nM ⁻¹ day ⁻¹)	0.753	2.10 (> 100)	1.66 (34.0)	N/A	N/A	N/A
k_{off} (day ⁻¹)	14.6	66.2 (> 100)	2.94 (41.9)	N/A	N/A	N/A
k_{int} (day ⁻¹)	3.93	5.38 (79.3)	0.779 (12.4)	8.50 (41.3)	1.78 (19.8)	N/A
R_0 (nM)	54.9	57.7 (14.2)	47.9 (12.9)	57.3 (14.2)	21.5 (22.9)	N/A
V_{max} (pmol kg ⁻¹ day ⁻¹)	N/A	N/A	N/A	N/A	N/A	1770.0 (5.6)
K_m (nM)	N/A	N/A	N/A	N/A	N/A	5.47 (23.3)
WSSR	N/A	0.403	0.423	0.405	0.779	1.33
AIC	N/A	-12.9	-13.3	-14.8	5.50	21.6

CV/% = percent coefficient of variation, N/A = not applicable

TRX1 data were simulated using parameter values from Ng et al. [11] and residual error was added using a proportional error model with $\sigma = 0.15$. Simulated data were fitted with various TMDD models and the M-M model. Parameter values, WSSR and AIC from different model fitting were reported. The lowest AIC value was bold. Different models were represented by numbers as follows: 0 Original value used for simulation, 1 TMDD full model, 2 TMDD model with $k_{int} = k_{deg}$, 3 rapid binding TMDD model, 4 rapid binding TMDD model with $k_{int} = k_{deg}$, 5 M-M model

Table 2

Parameter estimates and diagnostics for fitting simulated phenytoin data

Parameter	Estimates (CV%)					
	0	1	2	3	4	5
k_{pt} (min ⁻¹)	0.197	0.230 (20.2)	0.231 (20.2)	0.234 (20.0)	0.231 (19.3)	0.220 (16.2)
k_{ep} (min ⁻¹)	0.060	0.0669 (12.8)	0.0678 (12.3)	0.0680 (12.7)	0.0675 (11.7)	0.0676 (11.4)
V_c (ml kg ⁻¹)	406.0	367.0 (15.1)	369.0 (14.5)	363.0 (14.1)	368.0 (12.8)	381.0 (8.7)
k_{deg} (min ⁻¹)	N/A	0.397 (> 100)	0.545 (> 100)	0.307 (> 100)	0.760 (> 100)	N/A
K_D (nM)	N/A	N/A	N/A	73800.0 (> 100)	21900.0 (7.6)	N/A
k_{on} (min ⁻¹ nM ⁻¹)	N/A	0.000076 (> 1000)	0.000057 (> 100)	N/A	N/A	N/A
k_{off} (min ⁻¹)	N/A	2.58 (> 1000)	0.723 (> 1000)	N/A	N/A	N/A
k_{int} (min ⁻¹)	N/A	0.807 (> 1000)	0.545 (> 100)	1.02 (> 100)	0.760 (> 100)	N/A
R_0 (nM)	N/A	6720.0 (> 100)	4880.0 (> 100)	8770.0 (> 100)	3500.0 (> 100)	N/A
V_{max} (pmol kg ⁻¹ min ⁻¹)	992000.0	N/A	N/A	N/A	N/A	980000.0 (2.6)
K_m (nM)	21100.0	N/A	N/A	N/A	N/A	21900.0 (7.3)
WSSR	N/A	0.748	0.744	0.752	0.741	0.742
AIC	N/A	5.56	3.34	3.73	1.20	-0.721

CV% = percent coefficient of variation, N/A = not applicable

Phenytoin data were simulated using parameter values from Della et al. [20] and residual error was added using a proportional error model with $\sigma = 0.15$. Simulated data were fitted with various TMDD models and the M-M model. Parameter values, WSSR and AIC from different model fitting were reported. The lowest AIC value was bold. Different models were represented by numbers as follows: 0 original value used for simulation, 1 TMDD full model, 2 TMDD model with $k_{int} = k_{deg}$, 3 rapid binding TMDD model, 4 rapid binding TMDD model with $k_{int} = k_{deg}$, 5 M-M model

Table 3

Parameter estimates and diagnostics for fitting simulated rHuEPO data

Parameter	Estimates (CV%)					
	0	1	2	3	4	5
V_c (ml kg ⁻¹)	47.0	47.2 (4.0)	41.3 (7.9)	46.1 (6.5)	45.2 (6.2)	49.4 (3.0)
k_{el} (h ⁻¹)	0.0949	0.0508 (43.6)	0 ^a	0.0767 (24.3)	0.0798 (24.2)	0 ^a
k_{pr} (h ⁻¹)	0.0359	0.0555 (34.4)	0.186 (25.8)	0.0364 (29.6)	0.0433 (23.7)	0.0930 (19.7)
k_{ip} (h ⁻¹)	0.115	0.0882 (50.2)	0.569 (19.6)	0.0801 (52.3)	0.0896 (38.8)	0.00833 (21.4)
k_{int} (h ⁻¹)	0.222	0.0872 (> 100)	0.000085 (> 1000)	0.154 (> 100)	0.623 (> 100)	N/A
k_{deg} (h ⁻¹)	0.897	3.74 (> 100)	0.000085 (> 1000)	1.38 (> 100)	0.623 (> 100)	N/A
K_D (nM)	0.0123	N/A	N/A	0.0102 (> 100)	0.111 (> 100)	N/A
k_{on} (nM ⁻¹ h ⁻¹)	N/A	32.4 (> 100)	94.8 (> 100)	N/A	N/A	N/A
k_{off} (h ⁻¹)	N/A	0.0496 (> 100)	0.0113 (> 100)	N/A	N/A	N/A
R_0 (nM)	0.0136	0.00849 (> 100)	0.116 (40.0)	N/A	N/A	N/A
R_{int0} (nM)	0.0162	N/A	N/A	0.0234 (> 100)	0.0421 (> 100)	N/A
C_0 (mIU ml ⁻¹) ^a	16.7	16.7	16.7	16.7	16.7	16.7
V_{max} (pmol kg ⁻¹ h ⁻¹)	N/A	N/A	N/A	N/A	N/A	0.0292 (71.9)
K_m (nM)	N/A	N/A	N/A	N/A	N/A	0.184 (98.8)
WSSR	N/A	0.929	2.04	0.915	0.960	1.12
AIC	N/A	14.0	52.6	11.2	11.8	15.9

^aFixed parameter or value. Fixation of k_{el} was based on F -test at $\alpha = 0.05$; CV% = percent coefficient of variation, N/A = not applicable

The rHuEPO data were simulated using parameter values from Woo et al. [16] and residual error was added using a proportional error model with $\sigma = 0.15$. Simulated data were truncated at concentration of 157 mIU ml⁻¹, which yields $R_{int0}KD/(KD + C)^2 = 0.1$. Truncated data were fitted with various TMDD models and the M-M model. Parameter values, WSSR and AIC from different model fitting were reported. The lowest AIC value was highlighted. Different models are represented by numbers as follows: 0 original value used for simulation, 1 TMDD full model, 2 TMDD model with $k_{int} = k_{deg}$, 3 rapid binding TMDD model, 4 rapid binding TMDD model with $k_{int} = k_{deg}$, 5 M-M model