Irreversible Binding (IB) and Michaelis-Menten (MM) Approximations of the Target-Mediated Drug Disposition (TMDD) Model

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ABSTRACT

Purpose:

To derive the IB and MM approximations of the TMDD equations; to investigate parameter ranges where these approximations can be used for description of TMDD data and for estimation of target production rate and free target suppression.

Methods:

The IB approximation was derived assuming that the drug-target binding is irreversible. The MM approximation was derived assuming that the free target concentration is much smaller than the drug concentration. A population PK dataset (3355 observations from 224 subjects) was simulated using the TMDD model. The MM approximation was used to describe the simulated data. Predicted drug concentrations were compared with the true (simulated) values. Bias and precision of the parameter estimates were investigated.

Results:

The IB equations for a drug that is described by a two-compartment model and administered intravenously (D_2) and subcutaneously (D_1) are presented below:

$$\frac{dA_d}{dt} = -k_a A_d; \qquad C = \frac{1}{2}\left[C_{dif} - K_{IB} + \sqrt{(C_{dif} + K_{IB})^2 + 4R_0 K_{IB}}\right]$$

$$\frac{dC_{dif}}{dt} = \frac{In(t) + k_a A_d}{V} - (k_{el} + k_{pt})C - \frac{k_{syn} C}{K_{IB} + C} + k_{tp}\frac{A_T}{V}; \qquad K_{IB} = \frac{k_{deg}}{k_{on}};$$

$$\frac{dA_T}{dt} = k_{pt} C \cdot V - k_{tp} A_T; A_d(0) = D_1; C_{dif}(0) = D_2 / V - R_0; A_T(0) = 0.$$

Here C_{dif}=C – R; C and R are the concentrations of the free (unbound) drug and the target in the central compartment, k_{el} is the linear elimination rate, k_{on}, k_{deg}, k_{int}, k_{syn} are the binding, degradation, internalization, and the target production rate; V is the central compartment volume; R_0=k_{syn}/k_{deg} is the baseline target concentration.

The IB approximation is valid for high-affinity (large k_{on}) drugs in cases where the drug-target dissociation rate k_{off} is either small or much smaller than k_{int}. If R_0 << C, C_{dif}= C and the IB is described by the model with Michaelis-Menten elimination (V_{max}=k_{syn}, K_M=K_{IB}, R_0 =0). A discrepancy between the true and MM solutions does not exceed R_0. In the simulation study for a system with R_0 << C, the MM model precisely estimated all relevant TMDD parameters with less than 5% bias and less than 5% relative standard error, and provided unbiased population and individual predictions of the unbound drug concentrations C and the target production rate k_{syn}.

Conclusions:

The new IB and MM approximations of the TMDD equations were derived. The simulated examples demonstrated validity of these approximations and their ability to estimate the TMDD parameters. The results extend the parameter range where the Michaelis-Menten approximation can describe the TMDD data.

Irreversible Binding Equations

When binding is irreversible, k_{off}= 0. Then TMDD Eqs. [1] result in

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

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

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

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

Irreversible Binding Quasi-Steady-State Equations

When k_{on} is large and assuming quasi-steady-state:

$$k_{syn} - k_{deg} R - k_{on} C \cdot R = 0 \quad \text{or} \quad R = \frac{k_{syn}}{k_{deg} + k_{on} C}$$

Then

$$\frac{dC_{dif}}{dt} = \frac{In(t) + k_a A_d}{V} - (k_{el} + k_{pt})C - \left(k_{syn} - k_{deg} R\right) + k_{tp}\frac{A_T}{V};$$

$$C_{dif} = C - R = C - \frac{k_{syn}}{k_{deg} + k_{on} C};$$

After some straightforward manipulations one can arrive at:

$$\frac{dC_{dif}}{dt} = \frac{In(t) + k_a A_d}{V} - (k_{el} + k_{pt})C - \frac{k_{syn} C}{K_{IB} + C} + k_{tp}\frac{A_T}{V};$$

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

$$C = \frac{1}{2}\left[C_{dif} - K_{IB} + \sqrt{(C_{dif} + K_{IB})^2 + 4K_{IB} R_0}\right]; \qquad R = \frac{R_0 K_{IB}}{K_{IB} + C}$$

$$A_d(0) = D_1; C_{dif}(0) = D_2 / V - R_0; A_T(0) = 0.$$

$$R_0 = k_{syn} / k_{deg}; K_{IB} = k_{deg} / k_{on}.$$

Alternative form: time derivative of C_{dif} can be computed as:

$$\frac{dC_{dif}}{dt} = \frac{dC}{dt}\left(1 + \frac{R_0 K_{IB}}{(C + K_{IB})^2}\right)$$

Then:

$$\frac{dC}{dt} = \frac{\frac{In(t) + k_a A_d}{V} - (k_{el} + k_{pt})C - \frac{k_{syn} C}{K_{IB} + C} + k_{tp}\frac{A_T}{V}}{1 + \frac{R_0 K_{IB}}{(C + K_{IB})^2}}$$

Irreversible Binding Michaelis-Menten Equations

If

$$\frac{R_0 K_{IB}}{(C + K_{IB})^2} << 1$$

then

$$\frac{dC}{dt} = \frac{In(t) + k_a A_d}{V} - (k_{el} + k_{pt})C - \frac{k_{syn} C}{K_{IB} + C} + k_{tp}\frac{A_T}{V}$$

These coincide with the Michaelis-Menten equations where

$$V_{max} = k_{syn}, \qquad K_M = K_{IB}.$$

RESULTS: Simulated PK Study

Cases 1 and 2: Target concentration << drug concentration

- Single-subject and rich population PK data for 224 subjects were simulated from the TMDD model (Table 1: True);
- Single-subject simulations of the typical dosing regimens indicated that TMDD model and IB, QSS-IB and MM approximations would provide similar description of the PK data (Figure 1);
- Population PK model using QSS-IB approximation was able to recover the true model parameters (Table 1: QSS-IB) and correctly estimate the drug and target concentrations;
- Population PK model with Michaelis-Menten approximation was able to recover the true model parameters (Table 1: MM) and describe the individual free drug concentration-time profiles;
- Estimate of K_M parameter of the MM model was much closer to the irreversible binding constant K_{IB}=k_{deg}/k_{on} than to the dissociation constant K_D= k_{off}/k_{on} or quasi-steady-state constant K_{SS}= (k_{off} +k_{int})/k_{on} (Table 1 Case 1).

Table 1. Cases 1 and 2: Parameters of the true TMDD model and parameter estimates of the QSS-IB and MM approximations

Values in round and square brackets indicate percent relative standard error and percent bias of the parameter estimates, respectively.

	Case 1: k_{on}=5, k_{off}=0.1, k_{int}=5, k_{syn}=1, k_{deg}=1			Case 2: k_{on}=5, k_{off}=1, k_{int}=10, k_{syn}=2, k_{deg}=1		
	True	QSS-IB	MM	True	QSS-IB	MM
CL	0.3	0.296 (2) [1]	0.299 (2) [0]	0.3	0.299 (2) [0]	0.306 (2) [2]
V_1	3.0	3.04 (2) [1]	3.02 (2) [1]	3.0	3.01 (2) [0]	2.97 (2) [1]
Q	0.2	0.197 (3) [1]	0.201 (2) [0]	0.2	0.201 (2) [0]	0.207 (2) [3]
V_2	3.0	2.97 (2) [1]	2.99 (2) [0]	3.0	3.01 (1) [0]	3.07 (1) [2]
F_{SC}	0.6	0.597 (2) [1]	0.598 (2) [0]	0.6	0.598 (1) [0]	0.602 (1) [0]
k_a	1.0	1.08 (3) [8]	0.975 (2) [3]	1.0	1.04 (3) [4]	0.891 (2) [11]
R_0	1.0	0.91 (19) [9]	-	2.0	1.34 (11) [33]	-
k_{syn}	1.0	1.01 (2) [1]	1 (2) [0]	2.0	2.01 (2) [0]	2.0 (2) [0]
K_{IB}	0.2	0.185 (4) [7]	0.206 (4) [3]	0.2	0.205 (2) [3]	0.215 (2) [7]
K_D	0.02			0.2		
K_{SS}	1.02			2.2		

Figure 1: Free drug and target concentrations: Case 1

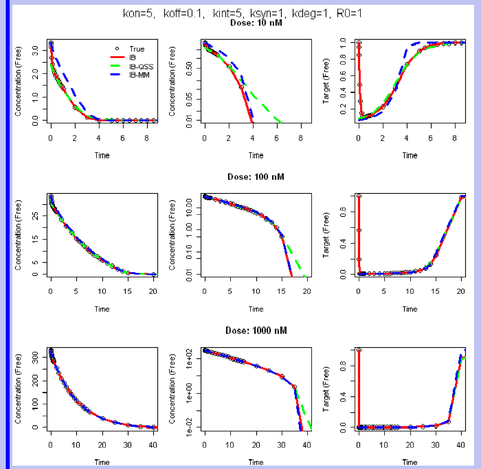
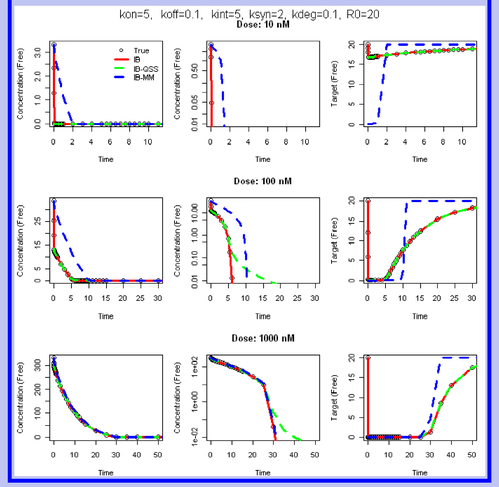


Figure 2: Free drug and target concentrations: Case 3



Cases 3: Drug and baseline target concentrations are comparable

Single-subject simulations of the typical dosing regimens (Figure 2) indicated that:

- TMDD and IB models provided identical description of the PK data;
- IB-QSS diverged from TMDD only at the very low concentrations;
- IB-MM may diverge from TMDD when the drug and baseline target concentration are comparable.

Population simulation study indicated that IB-QSS approximation correctly estimated model parameters while MM model parameter estimates were strongly biased.

DISCUSSION

TMDD equations [1] and its approximations [2-4] were investigated. Important case of irreversible binding was considered. IB-QSS approximation was obtained using QSS condition of the equation that describe free (rather than total as in [3-4]) target concentrations. Obtained IB-MM approximation is in agreement with the results discussed in [5].

CONCLUSIONS

- Irreversible binding limit of TMDD equations has been suggested. It is valid when the drug-target binding is irreversible, or when the internalization rate constant is much larger than the dissociation rate constant.
- The quasi-steady-state approximation of the irreversible binding equations has been suggested. It is valid when target concentration is at steady-state.
- It is shown that the Michaelis-Menten equation can be derived as an approximation of the irreversible binding equations. It is valid when the baseline target concentration is much smaller than the drug concentration.
- Relation between irreversible binding and Michaelis-Menten equations explains why Michaelis-Menten equations are often sufficient to describe pharmacokinetics of therapeutic monoclonal antibodies.

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