Pharmacodynamic Modeling of Biologics with Target-Mediated Drug Disposition: TMDD Approximations, Relation to Indirect-Response Models, and Application to Population PK-PD Analyses

 # 125

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OBJECTIVES

- To investigate the rapid binding (RB), quasi-steady-state (QSS) and Michaelis-Menten (MM) approximations [2,3] of the TMDD model [1] as applied to the pharmacodynamic (PD) data;
- To derive relationships between the parameters of the TMDD and indirect response models;
- To investigate and compare applicability of the TMDD approximations in cases when the drug-target complex is eliminated faster or slower than the free target;
- To test the identifiability analysis algorithm [3] on the example of the simulated population PK-PD data.

METHODS

- TMDD equations and its approximations were reviewed and compared with the indirect-response model equations.
- For several combinations of model parameters, concentrations of the drug, target, and drug-target complex were simulated from the TMDD model and the corresponding RB, QSS, and MM approximations. Simulated concentration-time profiles were compared to investigate the ability of the approximations to describe the TMMD model predictions.
- The population PK-PD dataset that included the data from two studies was simulated. The first study imitated the fist-in-man, dose-escalation, rich sampling study with 4 cohorts of six subjects administered single dose of 100, 300, 1000, or 3000 nmol. The second study imitated a phase 2 study with 2 arms of 100 subjects administered three doses of 1000 or 3000 nmol with 4 week intervals. Free drug concentrations and total target concentrations were measured. Identifiability of the TMDD model parameters and ability of the approximations to describe the simulated data, to estimate the TMDD model parameters, and to predict unobservable free target concentrations were investigated.

RESULTS: Comparison with Indirect Response Models

QSS equation for the total target concentration

$$\frac{dR_{tot}}{dt} = k_{syn} - k_{\deg} R_{tot} - (k_{\text{int}} - k_{\deg}) \frac{R_{tot} C}{K_{SS} + C}; \qquad R_{tot}(0) = k_{syn} / k_{\deg}$$

can be rewritten in two equivalent forms

$$\frac{dR_{tot}}{dt} = k_{syn} - k_{\deg} R_{tot} \left(1 + E_{\max} \frac{C}{K_{SS} + C}\right); \qquad E_{\max} = \frac{k_{\text{int}}}{k_{\deg}} - 1;$$

$$\frac{dR_{tot}}{dt} = k_{syn} - k_{\deg} R_{tot} \left(1 - E_{\max} \frac{C}{K_{SS} + C}\right); \qquad E_{\max} = 1 - \frac{k_{\text{int}}}{k_{\deg}}.$$

Thus, QSS approximation of the TMDD model can be interpreted as the indirect response model with stimulation or inhibition of elimination depending on whether internalization rate constant k_{int} is larger or smaller than the target degradation rate k_{deg}.

Drug-target complex (RC) and free target (R) concentrations are expressed as:

$$RC = \frac{R_{tot} C}{K_{SS} + C}, \qquad R = \frac{R_{tot} K_{SS}}{K_{SS} + C}$$

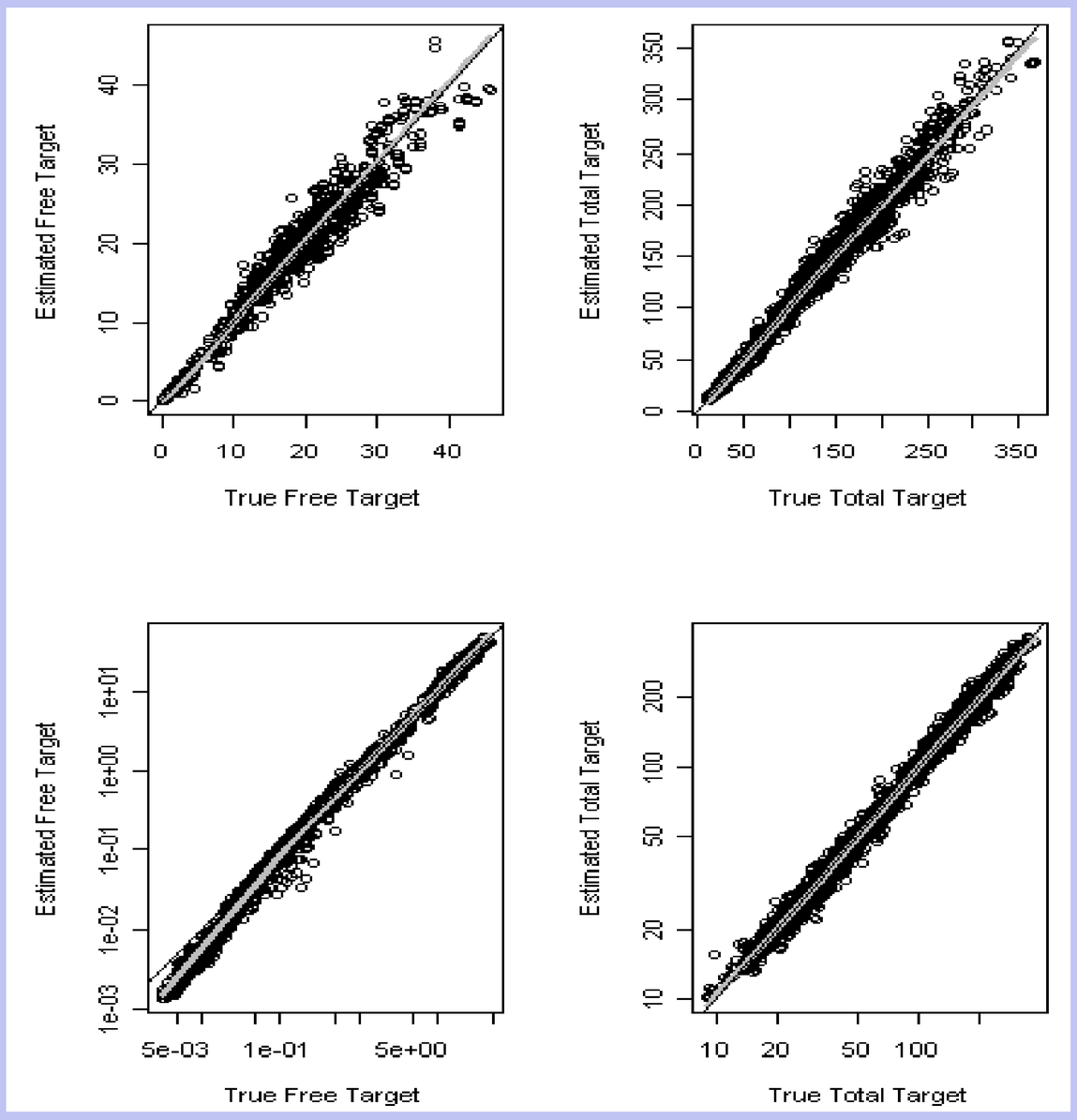
RESULTS: Comparison between Approximations

For the investigated range of parameters, the RB and QSS approximations provided an adequate description of the data simulated from the TMDD model. The MM approximation was applicable when the degradation rate of the drug-target complex exceeded the degradation rate of the free target, and was not appropriate otherwise.

RESULTS: Simulated PK-PD Study

- TMDD model was able to estimate all model parameters except the binding constants.
- The RB and QSS approximations were able to recover the true model parameters and estimate the drug, target, and complex concentrations correctly.
- The indirect-response PK-PD model (using individual predictions of drug concentrations) precisely estimated the relevant TMDD model parameters, providing unbiased population and individual predictions of the total and free target concentrations (**Figure 1**).

Figure 1: Free and Total Target Concentrations Predicted using Indirect Response Model versus True Values (Simulated from the TMDD Model)



CONCLUSIONS

- RB and QSS approximations provided excellent description of the PK and PD data simulated from the TMDD model;
- Equation for the total target concentration derived based on these approximations coincides with the indirect-response model;
- The simulated population PK-PD study demonstrated that for drugs with TMDD, parameters of the indirect response models can be used to estimate unobservable free target concentrations that are important for pharmacodynamic modeling.

REFERENCES:

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