# Mechanistic Interpretation of Indirect-Response Models for Drugs with Target-Mediated Disposition

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## OBJECTIVES

- To derive indirect response models (IRM) from the target-mediated drug disposition (TMDD) equations [1-4]
- To demonstrate (on the example of the simulated PK-PD data ) that IRM can be used to estimate TMDD parameters and unobservable unbound target concentrations.

## METHODS

- TMDD equations and its quasi-steady-state (QSS) approximation were used to derive the IRM equations for total target concentrations.
- The ability of IRM to estimate the TMDD parameters and predict unobservable unbound target concentrations were investigated using population PK-PD simulations in NONMEM.
  - ✓ The simulated dataset included rich data from two studies. Study 1 included 4 cohorts of six subjects administered single 100 nmol IV, 300 nmol SC, 1000 nmol IV, or 3000 nmol SC doses. Study 2 included two 100-subject arms administered multiple 1000 or 3000 nmol SC doses at 4 week intervals.
  - ✓ PK parameters of the simulation model were typical of monoclonal antibodies.
  - ✓ TMDD binding and target turnover parameters were similar to those estimated for omalizumab [5,6] with the elimination rate of the drug-target complex ($k_{int}$) 5 times lower than the elimination rate of the unbound target ($k_{deg}$).
  - ✓ The unbound drug and total target concentrations were simulated from the TMDD model.
  - ✓ The QSS approximation and IRM were used for estimation.

## RESULTS

### Comparison with Indirect Response Models

Direct correspondence between the parameters of the TMDD (QSS) equation for the total target concentration

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

and IRM was established:

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

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

This correspondence allows estimating TMDD parameters (production rate $k_{syn}$ of the unbound target, degradation rate $k_{deg}$ of the unbound target, quasi-steady state constant $K_{SS}$, and degradation rate of the drug-target complex $k_{int}$). Then, the drug-target complex concentration RC and the unobservable unbound target concentration R can be computed as

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

In the simulation study, IRM (that utilized individual predictions of the free drug concentrations provided by the empirical PK model) precisely estimated the TMDD population parameters with less than 7% bias and less than 5% relative standard error, and provided unbiased and precise population and individual predictions of the total and unbound target concentrations.

### Generalization to TMDD systems with cooperative or allosteric binding

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

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

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

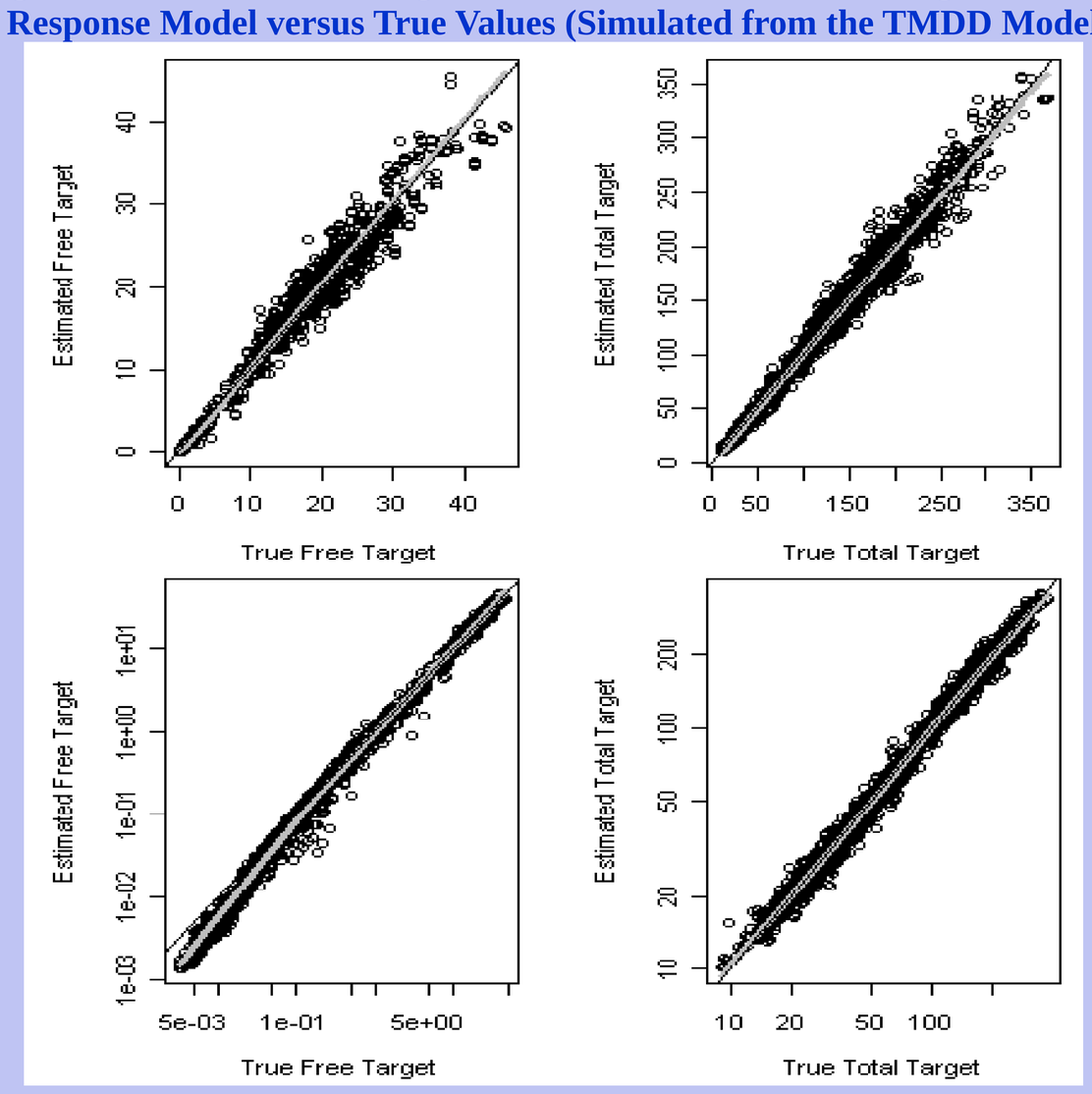
Then, the drug-target complex concentration RC and the unobservable unbound target concentrations R can be computed as

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

### Simulated PK-PD Study

- PK and PD data were simulated using the TMDD model;
- The QSS approximation was able to recover the true model parameters and estimate the drug, target, and complex concentrations correctly;
- An empirical PK model with Michaelis-Menten elimination was able to describe individual concentration-time profiles, but parameter estimates and population predictions were strongly biased and dose-dependent;
- The indirect-response PK-PD model (that used the individual predictions of drug concentrations) precisely estimated the relevant TMDD model parameters and provided 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

- The equation for the total target concentration of the QSS approximation coincides with the indirect-response models with inhibition (when $k_{int} < k_{deg}$) or stimulation (when $k_{int} > kd_{eg}$) of elimination.
- For drugs with TMDD, Indirect Response Models are in fact mechanistic models that can be used to estimate the TMDD model parameters and the unobservable unbound target concentrations that are important for pharmacodynamic modeling.

## REFERENCES

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