

## **Title: Why Standard Target-Mediated Drug Disposition (TMDD) Models Describe Observed Data: Testing Sensitivity to Model Assumptions**

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**Purpose:** TMDD equations contain many assumptions that are unlikely to hold in real biological systems, such as: 1-to-1 drug-target binding; binding and elimination occur only in the central compartment; free target (R) and drug-target complex (RC) do not diffuse to the peripheral compartment; target production rate ( $k_{\text{syn}}$ ) and degradation rate ( $k_{\text{deg}}$ ) do not depend on the drug (C) or target concentrations. Yet TMDD approximations often provide an excellent fit of observed data. We aim to investigate whether the classical TMDD model can describe the data simulated from biological systems that violate assumptions of TMDD equations.

**Methods:** Dense population concentrations of total drug ( $C_{\text{tot}}=C+RC$ ) and total target ( $R_{\text{tot}}=R+RC$ ) were simulated for the following TMDD models: standard (M1); elimination from central and peripheral compartments (M2); elimination only from peripheral compartment (M3); R and RC diffusion to peripheral compartment, and binding and internalization ( $k_{\text{int}}$ ) in both compartments (M4);  $k_{\text{syn}}$  dependent on C or R (M5); target production, binding and elimination from peripheral compartment (M6); 2 drug binding sites with various combinations of binding parameters  $k_{\text{on}}$  and  $k_{\text{off}}$  (M7). The quasi-steady state (QSS) approximation of the standard TMDD model was used to fit the data. Model predictions and parameter estimates were compared with true values.

**Results:** The QSS approximation provided an excellent fit of the data for all models except M5, where  $R_{\text{tot}}$  predictions were biased at low  $R_{\text{tot}}$  values. Most parameter estimates agreed with the true values. The exceptions were (> 25% bias): parameters of peripheral compartment ( $Q, V_2$ ) were under-estimated in M2 and M3; clearance (CL) was under-estimated in M3;  $k_{\text{int}}$  was over-estimated in M4 and M6. CL, Q,  $V_2$ , and  $k_{\text{int}}$  were biased in M5 but the fit was improved and bias eliminated when dependencies  $k_{\text{syn}}(C)$  or  $k_{\text{syn}}(R)$  were added. QSS constant  $K_{\text{SS}}$  was in the range of 40%-103% of the true  $(k_{\text{off}}+k_{\text{int}})/k_{\text{on}}$  value in M7.

**Conclusions:** The QSS approximation of the standard TMDD model provides an excellent fit even when underlying assumptions are violated, but the parameters may not correspond to the true values. The fit was most sensitive to perturbations of the target production rate.