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

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OBJECTIVES

TMDD equations [1] contain many assumptions that are unlikely to hold in real biological systems, such as:

- One-to-one 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_{syn}) and degradation rate (k_{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 the biological systems that violate the assumptions of TMDD equations.

METHODS

Dense population data, concentrations of the total drug (C_{tot}=C+RC) and the total target (R_{tot}=R+RC) were simulated for the following TMDD models:

M1: standard two-compartment TMDD model with target production, one-to-one binding, and elimination in the central compartment only [1];

M2: elimination from the central and peripheral compartments;

M3: elimination only from the peripheral compartment;

M4: R and RC diffusion to the peripheral compartment, and binding and internalization (k_{int}) in both compartments;

M5: k_{syn} dependent on C or R;

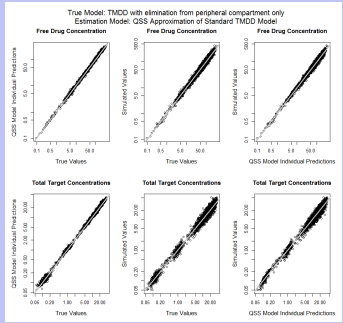
M6: Target production, binding and elimination from the peripheral compartment;

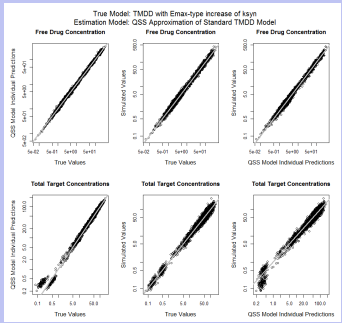
M7: Two drug binding sites with various combinations of binding parameters k_{on} and k_{off}.

The quasi-steady state (QSS) approximation of the standard TMDD model [2] 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 models M1-M7 except M5, where R_{tot} predictions were biased at low R_{tot} values.
- Most parameter estimates agreed with the true values. The exceptions were (> 25% bias):
  - Parameters of the peripheral compartment (Q,V_p) were under-estimated in M2 and M3;
  - Clearance (CL) was under-estimated in M3;
  - k_{int} was over-estimated in M4 and M6;
  - CL, Q, V_p, and k_{int} were biased in M5 but the fit was improved and bias eliminated when dependencies k_{syn}(C) or k_{syn}(R) were added.
- Investigation of the systems with 1:2 binding (antibody with two binding sites) indicated that the concentrations of the total drug and the total target were well described by the QSS approximation of the standard TMDD model;
- The parameter estimates of model M7 were unbiased with the exception of QSS constant K_{SS} that was in the range of 40%-103% of the true $(k_{off}+k_{int})/k_{on}$ value.





True values are simulated values without residual error; **Simulated Values** include residual error.

Parameter Estimates of the QSS Approximations of the Standard TMDD Model

The data were simulated from the full TMDD models M1-M6 and estimated using the QSS approximation of model M1. Red: bias exceeds 25%.

	True	M1	M2	M3	M4	M5a		M5b		M6
CL	0.3	0.296	0.231	0.118	0.150	0.429	0.268	0.235	0.323	0.162
V_c	3.0	2.92	2.91	2.90	3.12	2.83	2.89	2.84	2.94	3.05
Q	0.2	0.199	0.122	0.091	0.180	0.308	0.253	0.303	0.171	0.179
V_p	3.0	2.89	1.00	0.52	2.80	0.585	3.31	3.93	2.39	2.35
F_1	0.7	0.693	0.693	0.691	0.657	0.670	0.685	0.679	0.688	0.706
k_a	0.5	0.497	0.496	0.493	0.616	0.512	0.497	0.504	0.517	0.504
k_{int}	0.05	0.049	0.050	0.0485	0.073	0.0338	0.053	0.068	0.042	0.182
k_{syn}	1	0.994	1.00	1.00	0.903	8.08	1.39/10.3 k_{50}=21.3	4.61	5.60/0.48 k_{50}=0.005	0.566
k_{deg}	10	11.8	11.8	12.3	9.80	159	14.6	36.3	10.4	7.63
K_{ss}	0.015	0.0117	0.0101	0.0116	0.0142	0.0028	0.024	0.014	0.0067	0.032

k_{on}=10 and k_{off}=0.1 used for simulations.

Simulated models: **M1**: standard TMDD, **M2**: CL from both central and peripheral (P) compartments, **M3**: CL from only P, **M4**: R and RC diffusion to P, with same k_{on}, k_{off} and k_{int} in both compartments, **M5**: k_{syn}(C), **M6**: R and RC are only in P, C free is simulated and estimated.

True column = values used for simulations except the following: in **M2**, CL = 0.15 from both central and peripheral compartments; in **M4**, Q_{target} = 5, CL = 0.15; in **M5a**, k_{syn} changes from 1 to 10, k_{50}=10; in **M5b**, k_{syn} changes from 10 to 1, k_{50}=0.005; in **M6**, CL = 0.15.

In **M5a** and **M5b,** 1st/2d columns show the estimated values without/with accounting for k_{syn}(C).

CONCLUSIONS

- The QSS approximation of the standard TMDD model provides an excellent fit even when underlying assumptions are violated but the parameter estimates may not correspond to the true values. The fit was most sensitive to perturbations of the target production rate.
- Central compartment measurements do not allow to determine true structural model of the system with TMDD.

REFERENCES

[1] Mager DE, Jusko WJ (2001) General pharmacokinetic model for drugs exhibiting target-mediated drug disposition. J Pharmacokinet Pharmacodyn 28:507-532

[2] Gibiansky L, Gibiansky E, Kakkar T, Ma P (2008) Approximations of the target-mediated drug disposition model and identifiability of model parameters. J Pharmacokinet Pharmacodyn 35(5):573-91