Target-Mediated Drug Disposition (TMDD) Equations and Approximations for Systems with 1:2 and 2:1 Drug-Target Binding Stoichiometry

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BACKGROUND

TMDD equations were initially written and are used assuming 1:1 stoichiometry of drug-target binding even though many biological systems do not conform to this assumption. Specifically, this assumption is violated for monoclonal antibodies that have two identical binding sites. Although standard TMDD equations provide excellent fit of the observed data, it is of interest to derive correct equations and approximations that assume truebinding stoichiometry between the drug and the target.

OBJECTIVES

To derive the TMDD model and its approximations for biological systems with 2:1 and 1:2 stoichiometry of drug-target binding.

METHODS/RESULTS

TMDD equations for systems with 2:1 and 1:2 drug target binding were formulated. Quasi-steady state (QSS) assumptions were applied to derive QSS approximations of these systems. QSS systems with zero internalization rate (k_{int}=0) or zero dissociation rate (k_{off}=0) correspond to quasi-equilibrium (QE) or irreversible binding (IB) approximations of the TMDD equations. Michaelis-Menten (MM) approximations were derived assuming that concentrations of the drug-target complexes are much smaller than concentrations of the free drug.

CONCLUSIONS

QSS, QE, IB, and MM approximations of the TMDD models with 1:2 and 2:1 binding were derived. They can be used to provide a more detailed and precise description of the TMDD systems with 1:2 and 2:1 binding stoichiometry than those of the standard TMDD model.

Drug has 2 binding sites Target has 1 binding site

$$\frac{dA_d}{dt} = -k_a A_d; \quad A_d(0) = D_1;$$
$$\frac{dC}{dt} = \frac{In(t) + F_{SC} k_a A_d + k_{tp} A_T}{V_c} - (k_{el} + k_{pt})C$$
$$-2k_{on} C \cdot R + k_{off} RC; \quad C(0) = D_2 / V_c;$$
$$\frac{dA_T}{dt} = k_{pt} C \cdot V_c - k_{tp} A_T; \quad A_T(0) = 0;$$
$$\frac{dR}{dt} = k_{syn} - k_{deg} R - 2k_{on} C \cdot R + 2k_{off} R_2 C$$
$$-k_{on} RC \cdot R + k_{off} RC; \quad R(0) = k_{syn} / k_{deg};$$
$$\frac{dRC}{dt} = 2k_{on} C \cdot R - (k_{int} + k_{off})RC - k_{on} R \cdot RC + 2k_{off} R_2 C;$$
$$\frac{dR_2 C}{dt} = k_{on} R \cdot RC - (k_{int} + 2k_{off})R_2 C; \quad RC(0) = RC_2(0) = 0.$$

Full model

C, **R**, **RC**, and **R_2C** are concentrations of free (unbound) drug, target, and drug complexes with one or two target molecules;
k_{el} is linear elimination rate constant,
k_{pt} and **k_{tp}** are inter-compartment rate constants,
k_{on}, **k_{off}**, and **k_{int}** are binding, dissociation, and internalization (elimination of the complex) rate constants;
k_{deg} and **k_{syn}** are degradation (elimination of the target) and target production rate constants;
V_C is central volume; **In(t)** is the infusion rate; **F_{SC}** is absolute subcutaneous bioavailability.
K_D $=k_{off}/k_{on}$; ***K_{IB}***$=k_{int}/k_{on}$

QSS assumptions:
$$2k_{on} C \cdot R - (k_{int} + k_{off})RC - k_{on} R \cdot RC + 2k_{off} R_2 C = 0;$$
$$k_{on} R \cdot RC - (k_{int} + 2k_{off})R_2 C = 0.$$

Equivalent to:
$$2 \cdot C \cdot R = (K_D + K_{IB})RC + K_{IB} R_2 C,$$
$$R \cdot RC = (2K_D + K_{IB})R_2 C$$

Defining C_{tot} and R_{tot} as
$$C_{tot} = R + RC + R_2 C \qquad R_{tot} = R + RC + 2R_2 C$$

results in:
$$C = C_{tot} \frac{(K_D + K_{IB})(K_D + K_{IB}/2) + K_{IB} R/2}{(K_D + K_{IB} + R)(K_D + K_{IB}/2 + R)};$$
$$RC = C_{tot} \frac{R(2K_D + K_{IB})}{(K_D + K_{IB} + R)(K_D + K_{IB}/2 + R)};$$
$$R_2 C = C_{tot} \frac{R^2}{(K_D + K_{IB} + R)(K_D + K_{IB}/2 + R)}.$$

$$R = \frac{1}{2}\left[-(2C_{tot} + K_D + K_{IB} - R_{tot}) + \sqrt{(2C_{tot} + K_D + K_{IB} - R_{tot})^2 + 4(K_D + K_{IB})R_{tot}}\right]$$

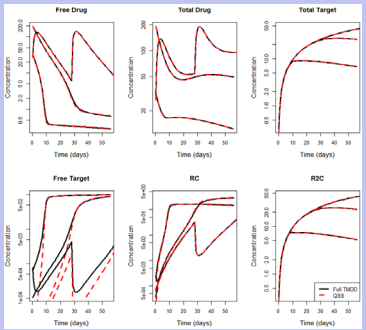
QSS approximation

$$\frac{dA_d}{dt} = -k_a A_d;$$
$$\frac{dC_{tot}}{dt} = \frac{In(t) + F_{SC} k_a A_d + k_{tp} A_T}{V_c} - (k_{el} + k_{pt})C$$
$$-k_{int} C_{tot} \frac{R \cdot (2K_D + K_{IB} + R)}{(K_D + K_{IB} + R)(K_D + K_{IB}/2 + R)};$$
$$\frac{dA_T}{dt} = k_{pt} C \cdot V_c - k_{tp} A_T;$$
$$\frac{dR_{tot}}{dt} = k_{syn} - k_{deg} R_{tot} - (k_{int} - k_{deg}) \cdot C_{tot} \cdot \frac{2R}{K_D + K_{IB} + R};$$
$$A_d(0) = D_1; \quad C_{tot}(0) = D_2 / V_c; \quad A_T(0) = 0; \quad R_{tot}(0) = k_{syn} / k_{deg}.$$

MM approximation

$$\frac{dA_d}{dt} = -k_a A_d;$$
$$\frac{dC}{dt} = \frac{In(t) + F_{SC} k_a A_d + k_{tp} A_T}{V_c} - (k_{el} + k_{pt})C$$
$$-k_{int} \frac{R_{tot} \cdot C}{(K_D + K_{IB})/2 + C};$$
$$\frac{dA_T}{dt} = k_{pt} C \cdot V_c - k_{tp} A_T;$$
$$\frac{dR_{tot}}{dt} = k_{syn} - k_{deg} R_{tot} - (k_{int} - k_{deg}) \cdot \frac{R_{tot} \cdot C}{(K_D + K_{IB})/2 + C};$$

Simulations: Concentration-time profiles from the full TMDD model and the corresponding QSS approximation were simulated for 3 dosing regimens: 100 mg IV, 600 mg IV, and 100 mg SC (2 doses).
CL=0.3; V_C=3; V_P=3; Q=0.2; k_a=0.5; F_{SC}=0.7; k_{on}=25; k_{off}=1; ; k_{int}=0.01; k_{syn}=1; k_{deg}=10.
Simulations demonstrated a good agreement between exact and approximate equations, except for free target at very low concentrations. Additional investigations are planned to investigate applicability of this approximation across the range of system parameters.



Drug has 1 binding site Target has 2 binding sites

$$\frac{dA_d}{dt} = -k_a A_d; \quad A_d(0) = D_1;$$
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$$-2k_{on} C \cdot R + k_{off} RC - k_{on} C \cdot RC + 2k_{off} RC_2; \quad C(0) = D_2 / V_c;$$
$$\frac{dA_T}{dt} = k_{pt} C V_c - k_{tp} A_T; \quad A_T(0) = 0;$$
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$$\frac{dRC_2}{dt} = k_{on} C \cdot RC - (k_{int} + 2k_{off})RC_2; \quad RC(0) = RC_2(0) = 0.$$

Full model

C, **R**, **RC**, and **RC_2** are concentrations of free (unbound) drug, target, and target complexes with one or two drug molecules;
k_{el} is linear elimination rate constant,
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K_D $=k_{off}/k_{on}$; ***K_{IB}***$=k_{int}/k_{on}$

QSS assumptions:
$$2k_{on} C \cdot R - (k_{int} + k_{off})RC - k_{on} C \cdot RC + 2k_{off} RC_2 = 0,$$
$$k_{on} C \cdot RC - (k_{int} + 2k_{off})RC_2 = 0.$$

Equivalent to:
$$C \cdot R = (K_D + K_{IB})RC/2 + K_{IB} RC_2/2,$$
$$C \cdot RC = (2K_D + K_{IB})RC_2.$$

Defining C_{tot} and R_{tot} as
$$R_{tot} = R + RC + RC_2 \qquad C_{tot} = C + RC + 2RC_2$$

results in:
$$R = R_{tot} \frac{(K_D + K_{IB})(K_D + K_{IB}/2) + K_{IB} C/2}{(K_D + K_{IB} + C)(K_D + K_{IB}/2 + C)};$$
$$RC = R_{tot} \frac{C(2K_D + K_{IB})}{(K_D + K_{IB} + C)(K_D + K_{IB}/2 + C)};$$
$$RC_2 = R_{tot} \frac{C^2}{(K_D + K_{IB} + C)(K_D + K_{IB}/2 + C)}.$$

$$C = \frac{1}{2}\left[(C_{tot} - 2R_{tot} - K_D - K_{IB}) + \sqrt{(C_{tot} - 2R_{tot} - K_D - K_{IB})^2 + 4(K_D + K_{IB})C_{tot}}\right]$$

QSS approximation

$$\frac{dA_d}{dt} = -k_a A_d;$$
$$\frac{dC_{tot}}{dt} = \frac{In(t) + F_{SC} k_a A_d + k_{tp} A_T}{V_c} - (k_{el} + k_{pt})C - k_{int} \frac{2R_{tot} C}{K_D + K_{IB} + C};$$
$$\frac{dA_T}{dt} = k_{pt} C \cdot V_c - k_{tp} A_T;$$
$$\frac{dR_{tot}}{dt} = k_{syn} - k_{deg} R_{tot} - (k_{int} - k_{deg}) \cdot R_{tot} \cdot \frac{C \cdot (2K_D + K_{IB} + C)}{(K_D + K_{IB} + C)(K_D + K_{IB}/2 + C)};$$
$$A_d(0) = D_1; \quad C(0) = D_2 / V_c; \quad A_T(0) = 0; \quad R_{tot}(0) = k_{syn} / k_{deg}.$$

MM approximation is obvious, C_{tot}= C, and not shown

Simulations: Concentration-time profiles from the full TMDD model and the corresponding QSS approximation were simulated for 3 dosing regimens: 100 mg IV, 600 mg IV, and 100 mg SC (2 doses).
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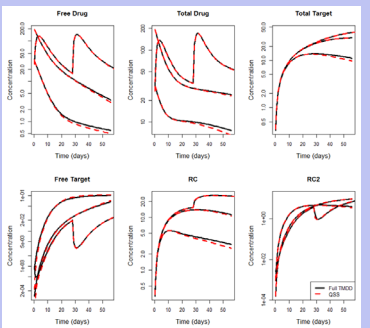

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