Title: Target-Mediated Drug Disposition Model for Drugs with Multiple Targets

Authors: Leonid Gibiansky*(1), Ekaterina Gibiansky (2)

Institutions: (1) QuantPharm LLC, North Potomac MD, US; (2) ICON Development Solutions, Ellicott City, MD, US

Objectives: To present the target-mediated drug disposition (TMDD) model for drugs that bind to more than one target; to derive the rapid binding (RB), quasi-steady-state (QSS) and Michaelis-Menten (MM) approximations of these equations; to investigate drug and target concentration-time profiles for these systems.

Methods: Equations that describe drugs with target-mediated drug disposition (TMDD) [1] were extended to describe drug interactions with more than one target. Approximations (RB, QSS and MM) [2, 3] of these equations were derived. Concentration-time profiles of the free drug, free and total target concentrations were simulated for a monoclonal antibody that can bind to two different targets.

Results: An example of the QSS equations for a drug that is described by a two-compartment model, binds to i=1, N targets with different affinities and different turnover characteristics, and is administered intravenously (IV bolus dose D_2) and subcutaneously (SC dose D_1) is presented below:

$$\frac{dA_d}{dt} = -k_a A_d; \qquad A_d(0) = F_1 D_1; \qquad C_{tot}(0) = \frac{D_2}{V};$$

$$\frac{dC_{tot}}{dt} = \frac{In(t) + k_a A_d + k_{tp} A_T}{V} - (k_{el} + k_{pt})C - \sum_{i=1}^{N} \frac{R^i{}_{tot} k^i{}_{\text{int}} C}{K^i{}_{SS} + C};$$

$$\frac{dA_T}{dt} = k_{pt} CV - k_{tp} A_T; \qquad A_T(0) = 0;$$

$$\frac{dR^i{}_{tot}}{dt} = k^i{}_{syn} - k^i{}_{\text{deg}} R^i{}_{tot} - (k^i{}_{\text{int}} - k^i{}_{\text{deg}}) \frac{R^i{}_{tot} C}{K^i{}_{SS} + C}; \quad R^i{}_{tot}(0) = \frac{k^i{}_{syn}}{k^i{}_{\text{deg}}}.$$

Here C, R^i, and R^iC are the concentrations of the free (unbound) drug, the free i^{th} target, and the complex of the drug with the i^{th} target in the central (serum) compartment, k_{el} is the linear elimination rate constant, k^i_{on}, k^i_{off}, and k^i_{int} are the binding, dissociation, and internalization (elimination of the complex) rate constants. k^i_{deg} and k^i_{syn} are the degeneration (elimination of the target) and target production rate constants; $K^i_{SS}=(k^i_{off}+k^i_{int})/k^i_{on}$ are the steady-state constants; V is the central compartment volume. $C_{tot} = C + \sum_{i=1}^{N} R^i C$ and $R^i_{tot}=R^i+R^iC$ are the total (free and bound) concentration of the drug in the central compartment and the total concentration of the i^{th} target that are related by the equations:

$$R^i C = \frac{R^i{}_{tot} C}{K^i{}_{SS} + C}; \quad R^i = \frac{R^i{}_{tot} K^i{}_{SS}}{K^i{}_{SS} + C}; \quad C_{tot} = C + \sum_{i=1}^{N} \frac{R^i{}_{tot} C}{K^i{}_{SS} + C}.$$

The RB approximation can be obtained by the formal substitution of the equilibrium dissociation constants $K^i_D= k^i_{off}/k^i_{on}$ in place of K^i_{SS} in the QSS equations. If the total concentration of any of the targets is constant (i.e. $k^i_{int} = k^i_{deg}$ for some i), than R^i_{tot} can be considered to be a constant parameter of the system for those targets. If the total concentration of any of the targets is small relative to the free drug concentrations, then this-target contribution to the total drug concentration is negligible, and the overall contribution of this target to the system is described by the Michaelis-Menten elimination term $V^i_{max}C/(K^i_{SS}+C)$ where $V^i_{max}=R^i_{tot}\, k^i_{int}$. Simulations of concentration-time profiles for a monoclonal antibody that binds 2 targets demonstrated that this binding can lead to unusual nonlinear drug behaviors not reminiscent of the TMDD behavior for drugs with one target. One of the examples (Figure 1) shows that interaction of the drug with 2 targets may lead to a rebound of the free target concentration for one of the targets above the pre-dose values, a phenomenon usually attributed to a feedback mechanism.

Conclusions: Equations of the target-mediated drug disposition model and its approximations were derived for the drug that binds to two or more different targets. Simulated examples demonstrated validity of the quasi-steady-state approximation of this system. Simulations for a monoclonal antibody that binds two targets revealed unusual kinetic properties of the drug and the targets, including possible rebound of one of the targets above the baseline level.

References:

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

[2] Mager DE, Krzyzanski W. Quasi-equilibrium pharmacokinetic model for drugs exhibiting target-mediated drug disposition. Pharmaceutical Research, (2005) 22 (10): 1589-1596.

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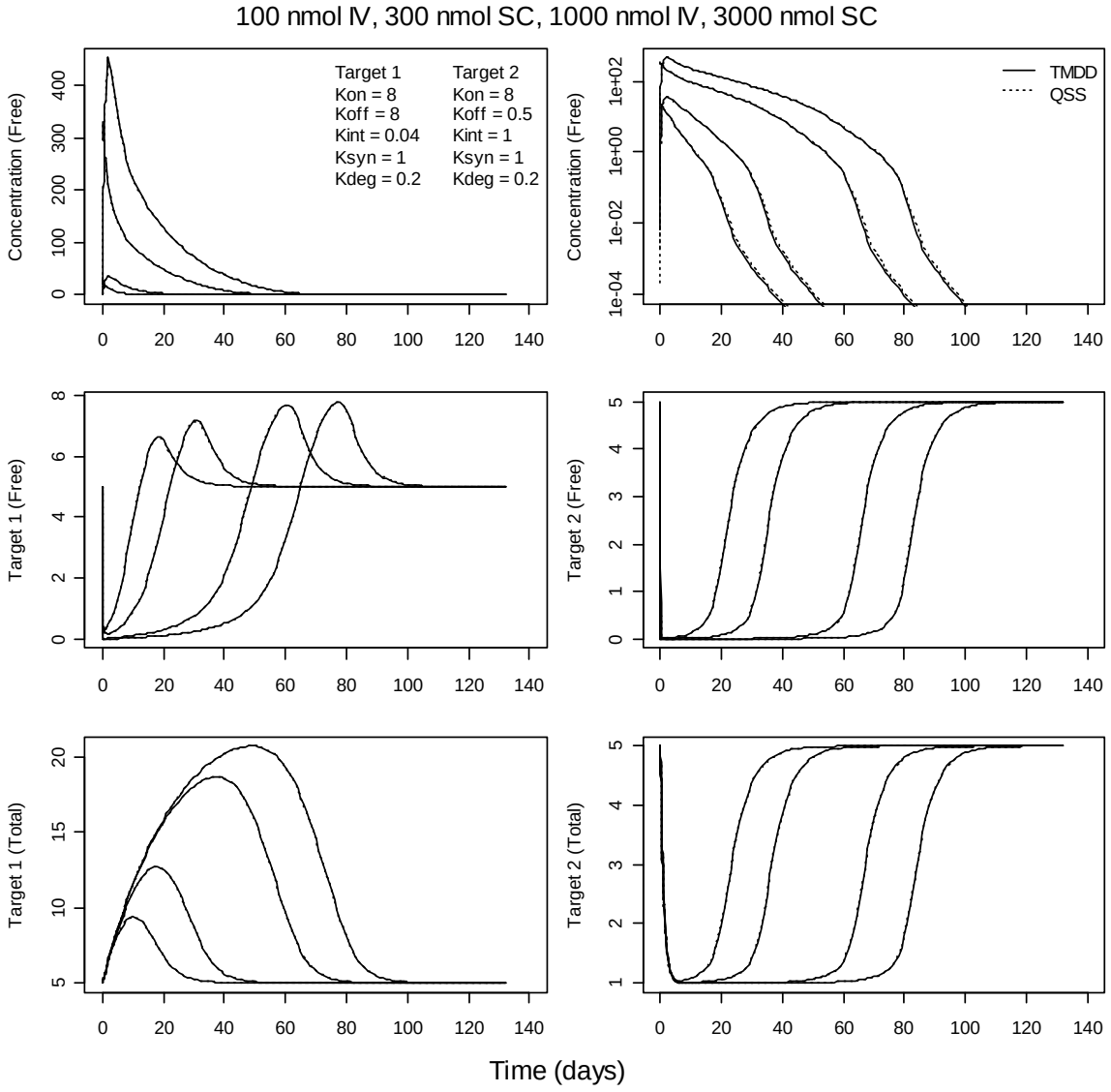
Figure 1: **Predictions from the TMDD and QSS Models for a Drug That Binds to Two Targets**



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