



Methods of Solving Rapid Binding Target-Mediated Drug Disposition Model for Two Drugs Competing for the Same Receptor

Wojciech Krzyzanski, Xiaoyu Yan, Yang Chen

Department of Pharmaceutical Sciences, University at Buffalo, State University New York

Objectives

The target mediated drug disposition (TMDD) model [1] has been adopted to describe pharmacokinetics for two drugs competing for the same receptor. A rapid binding assumption introduces total receptor and total drug concentrations while free drug concentrations C_A and C_B are calculated from the equilibrium (Gaddum) equations [2]. The Gaddum equations are polynomials in C_A and C_B of second degree that have explicit solutions involving complex numbers. The aim of this study was to develop numerical methods to solve the rapid binding TMDD model for two drugs competing for the same receptor that can be implemented in pharmacokinetic software.

Methods

The target mediated drug disposition model (TMDD) for two drugs two molecular species (C_A and C_B) competitively bind to the same receptor (R) is shown in Fig. 1.

TMDD Model

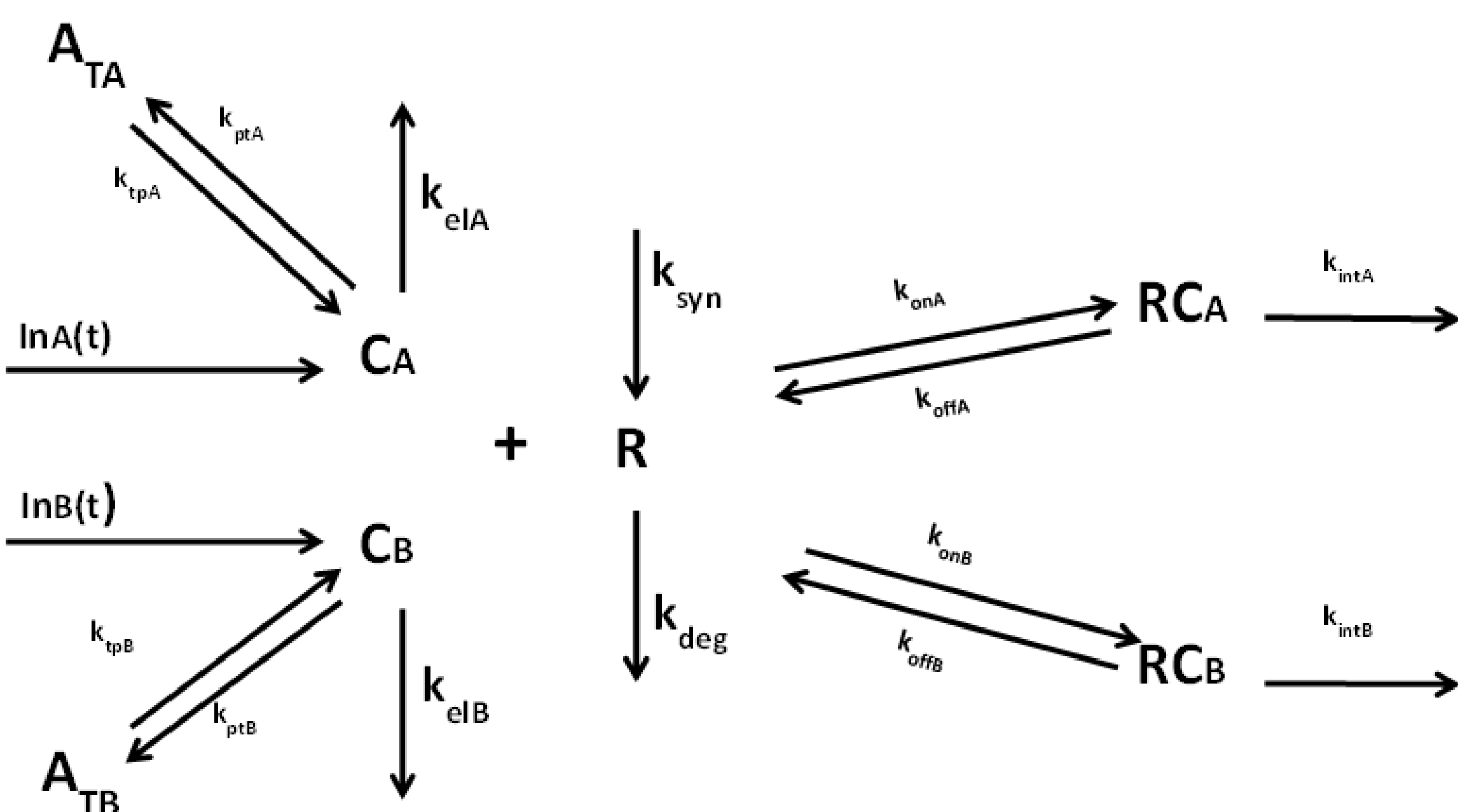


Fig. 1. Schematic representation of TMDD model. Free drugs in the central compartment (C_A and C_B) bind to the free receptor (R) at the second-order rate (k_{onA} and k_{onB}) to form drug-receptor complexes (RC_A and RC_B). The drug-receptor complexes (RC_A and RC_B) can either be dissociated at the first-order rate (k_{offA} and k_{offB}) or be internalized and degraded at the first-order rate (k_{intA} and k_{intB}). Free drugs (C_A and C_B) can also be removed from the central compartment by the first-order elimination process (k_{elA} and k_{elB}) or be distributed to the tissue compartment at the first-order rate (k_{tpA} , k_{tpB} , k_{ptA} , k_{ptB}). Free receptors (R) are synthesized at the zero-order rate (k_{syn}) and degraded at the first-order rate (k_{deg}). The input rates $In_A(t)$ and $In_B(t)$ can account for any process (zero-order infusion, first-order absorption, etc.) except for intravenous (IV) bolus that may require additional model components.

Rapid Binding TMDD Model

$$\begin{aligned} \frac{dC_{A_{tot}}}{dt} &= In_A(t) - (k_{elA} + k_{ptA})C_A + k_{tpA}A_{TA}/V_c - k_{intA}(C_{A_{tot}} - C_A) \\ \frac{dA_{TA}}{dt} &= k_{ptA}V_cC_A - k_{tpA}A_{TA} \\ \frac{dC_{B_{tot}}}{dt} &= In_B(t) - (k_{elB} + k_{ptB})C_B + k_{tpB}A_{TB}/V_c - k_{intB}(C_{B_{tot}} - C_B) \\ \frac{dA_{TB}}{dt} &= k_{ptB}V_cC_B - k_{tpB}A_{TB} \\ \frac{dR_{tot}}{dt} &= k_{syn} - k_{deg}R_{tot} - (k_{intA} - k_{deg})(C_{A_{tot}} - C_A) - (k_{intB} - k_{deg})(C_{B_{tot}} - C_B) \end{aligned}$$

$$\begin{aligned} C_{A_{tot}}(0) &= \frac{Dose_A}{V_c} + C_{A_{tot}0} \\ A_{TA}(0) &= k_{ptA}V_cC_{A0}/k_{tpA} \\ C_{B_{tot}}(0) &= \frac{Dose_B}{V_c} + C_{B_{tot}0} \\ A_{TB}(0) &= k_{ptB}V_cC_{B0}/k_{tpB} \\ R_{tot}(0) &= R_{tot0} \end{aligned}$$

Equilibrium equations:

$$(R_{tot} - C_{A_{tot}} - C_{B_{tot}} + C_A + C_B)C_A = K_{DA}(C_{A_{tot}} - C_A) \quad (R_{tot} - C_{A_{tot}} - C_{B_{tot}} + C_A + C_B)C_B = K_{DB}(C_{B_{tot}} - C_B)$$

Baseline conditions:

$$k_{syn} = k_{deg}(R_{tot0} - RC_{A0} - RC_{B0}) + k_{intA}RC_{A0} + k_{intB}RC_{B0}$$

$$In_{A0} = k_{elA}C_{A0} + k_{intA}RC_{A0}$$

$$In_{B0} = k_{elB}C_{B0} + k_{intB}RC_{B0}$$

Gaddum equations:

$$RC_A = \frac{R_{tot}C_A/K_{DA}}{1 + C_A/K_{DA} + C_B/K_{DB}} \quad RC_B = \frac{R_{tot}C_B/K_{DB}}{1 + C_A/K_{DA} + C_B/K_{DB}}$$

Results

Algebraic solution of equilibrium equations

$$C_A = \frac{C_{A_{tot}}K_{DA}}{K_{DA} + R_{tot}(1-z)} \quad C_B = \frac{C_{B_{tot}}K_{DB}}{K_{DB} + R_{tot}(1-z)}$$

$$0 < z < a_A + a_B \quad \text{and} \quad z < 1$$

$$a_A = \frac{C_{A_{tot}}}{R_{tot}} \quad a_B = \frac{C_{B_{tot}}}{R_{tot}} \quad k_A = \frac{K_{DA}}{R_{tot}} \quad k_B = \frac{K_{DB}}{R_{tot}}$$

$$K_{DA} \neq K_{DB} \quad z^3 + bz^2 + cz + d = 0 \quad K_{DA} = K_{DB} \quad z^2 + bz + c = 0$$

$$b = -(2 + k_A + k_B + a_A + a_B) \quad b = -(1 + a_A + a_B + k_A)$$

$$c = 1 + 2a_A + 2a_B + k_A + k_B + k_Ba_A + k_Aa_B + k_Ak_B \quad c = a_A + a_B$$

$$d = -(k_Ba_A + k_Aa_B + a_A + a_B)$$

The roots of the cubic equation are given by explicit formulas involving complex numbers.

Numerical solution of equilibrium equations

$$f(z) = z^3 + bz^2 + cz + d$$

The real roots of the cubic equation are found by the bisection method applied to the function $f(z)$.

Differential solution of equilibrium equations

$$\frac{dC_A}{dt} = \frac{K_{DA}C_{A_{tot}}F - C_A F(RP_{tot} - CP_{A_{tot}} - CP_{B_{tot}}) + K_{DA}C_B CP_{A_{tot}} - K_{DB}C_A CP_{B_{tot}}}{EF + FC_A + EC_B}$$

$$\frac{dC_B}{dt} = \frac{K_{DB}C_{B_{tot}}E - C_B E(RP_{tot} - CP_{A_{tot}} - CP_{B_{tot}}) + K_{DB}C_A CP_{B_{tot}} - K_{DA}C_B CP_{A_{tot}}}{EF + FC_A + EC_B}$$

$$\begin{aligned} E &= R_{tot} - C_{A_{tot}} - C_{B_{tot}} + C_A + C_B + K_{DA} \\ F &= R_{tot} - C_{A_{tot}} - C_{B_{tot}} + C_A + C_B + K_{DB} \\ CP_{A_{tot}} &= In_A(t) - (k_{elA} + k_{ptA})C_A + k_{tpA}A_{TA}/V_c - k_{intA}(C_{A_{tot}} - C_A) \\ CP_{B_{tot}} &= In_B(t) - (k_{elB} + k_{ptB})C_B + k_{tpB}A_{TB}/V_c - k_{intB}(C_{B_{tot}} - C_B) \\ RP_{tot} &= k_{syn} - k_{deg}R_{tot} - (k_{intA} - k_{deg})(C_{A_{tot}} - C_A) - (k_{intB} - k_{deg})(C_{B_{tot}} - C_B) \end{aligned}$$

Example 1: Exogenous and endogenous IgG competing for FcRn receptor

A previously published model by Hansen et al. [3] has been adopted to account for the competitive interaction between endogenous IgG (A) and exogenous IgG (B) and FcRn receptor.

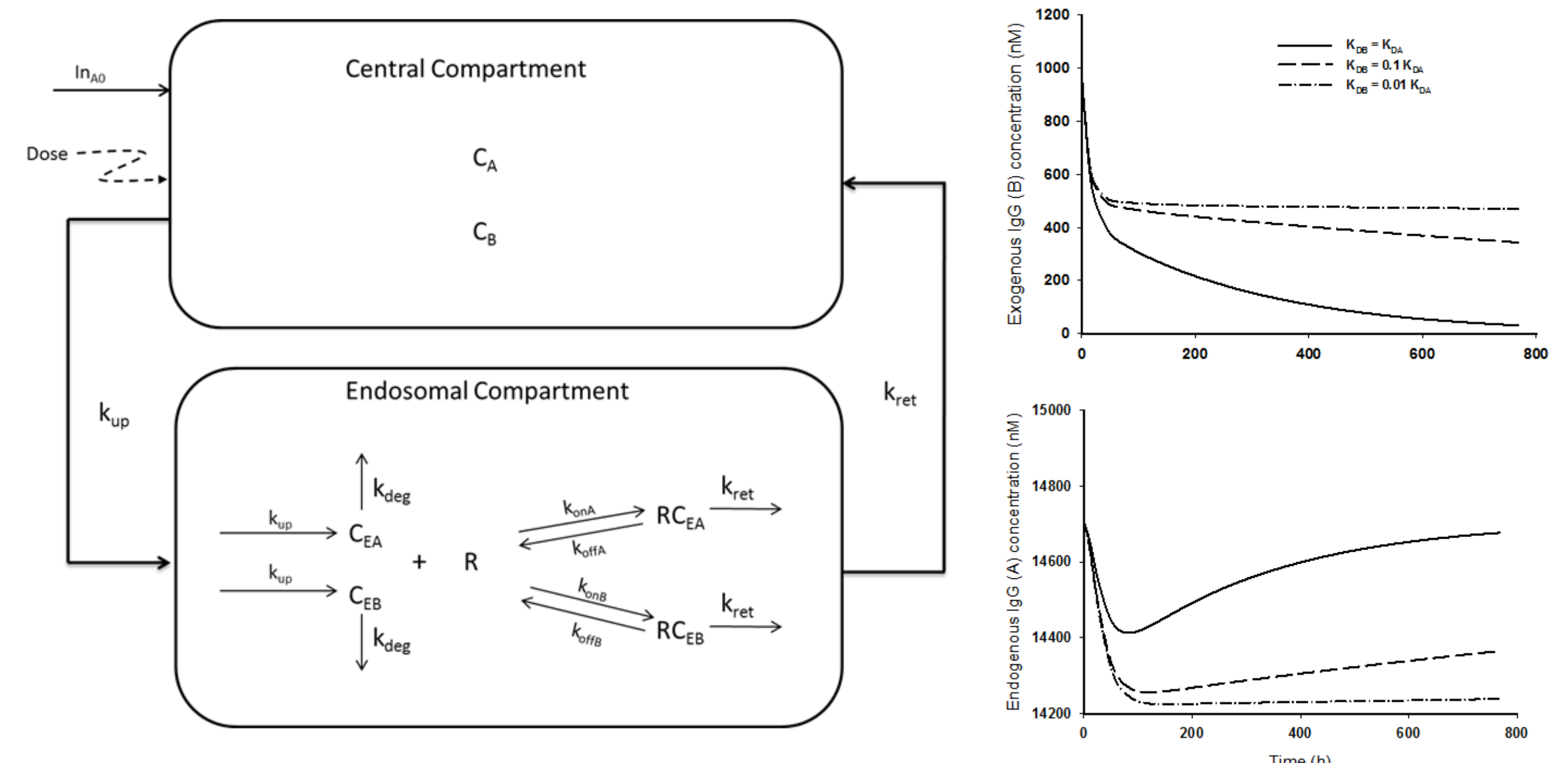


Fig. 2. This model is based on the protection of IgG catabolism by the FcRn receptor. IgGs in the blood central compartment (C_A , C_B) are taken up into endosomal compartment by fluid phase endocytosis, represented by a first-order process (k_{up}). Once inside the endosome, free IgGs (C_{EA} , C_{EB}) can bind to FcRn receptor to form IgG/receptor complexes (RC_{EA} , RC_{EB}). Bound IgGs are recycled and returned to the central compartment by a first-order process k_{ret} , while unbound IgGs (C_{EA} , C_{EB}) proceed to the lysosomes and undergo degradation by a first-order process k_{deg} .

Fig. 3. Endogenous IgG plasma concentration profiles (upper panel) and exogenous plasma concentration profiles (lower panel) after administration of 10 mg/kg (6.67 nmole/kg) exogenous IgG the equilibrium dissociation constant $K_{DB} = K_{DA}$, $0.1K_{DA}$, and $0.01K_{DA}$. The equilibrium equations were solved using differential equations implemented in ADAPT 5 (BMSR, USC LA). The parameter values were $k_{ret} = k_{up} = 1.03 \text{ day}^{-1}$, $k_{deg} = 0.43 \text{ day}^{-1}$, $R_{tot} = 1.22 \text{ nM}$, $V_E = V_c = 66.9 \text{ mL kg}^{-1}$, $C_{A0} = 14700 \text{ nM}$, $K_{DA} = 4.8 \text{ nM}$, $In_{A0} = 108 \text{ nMh}^{-1}$.

Example 2: Recombinant human EPO analogue and endogenous EPO competing for EPOR

A previously published TMDD model for EPO by Woo et al. [4] was adopted and competitive interaction between endogenous EPO and exogenous ESA was further introduced. The model structure is presented in in Fig. 1 with $In_A(t) = k_{EPO}$ representing the zero-order production rate for the endogenous EPO, and $In_B(t) = 0$. Darbepoetin (DA) was employed as exogenous ESA in the model. The endogenous EPO (C_A) and exogenous DA (C_B) competitively bind to the EPOR (R), forming drug-receptor complexes (RC_A and RC_B). The drug-receptor complexes are internalized through the same first-order process $k_{int} = k_{intA} = k_{intB}$.

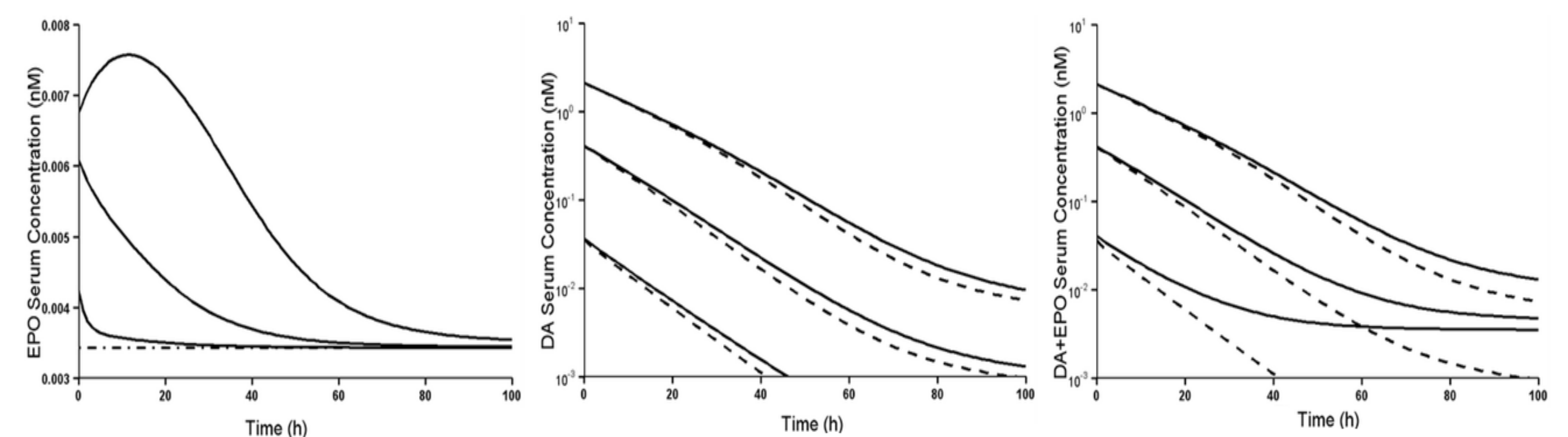


Fig. 4. Simulated concentration-time profiles for escalating IV bolus doses (0.1, 0.02, 0.002 nmol/kg) of darbepoetin (DA). Left panel: concentration-time profiles of endogenous EPO. Dash-dot line represents the baseline EPO level. Middle panel: concentration-time profiles of darbepoetin. Right panel: concentration-time profile of the sum of DA and EPO. Solid lines represent these profiles when $k_{EPO} = 0$. Other parameters for simulation were $V_c = 47.0 \text{ mL kg}^{-1}$, $k_{daA} = 0.095 \text{ h}^{-1}$, $k_{paA} = 0.036 \text{ h}^{-1}$, $k_{intA} = 0.222 \text{ h}^{-1}$, $k_{deg} = 0.897 \text{ h}^{-1}$, $K_{DA} = 0.0123 \text{ nM}$, $R_0 = 0.0162 \text{ nM}$, $C_{A0} = 0.00343 \text{ nM}$, $k_{elB} = 0.0413 \text{ h}^{-1}$, $k_{ptB} = 0.0047 \text{ h}^{-1}$, $k_{tpB} = 0.0067 \text{ h}^{-1}$, $K_{DB} = 0.053 \text{ nM}$. Equilibrium equations were solved using the bisection method in Phoenix WinNonlin 6.0 (Pharsight Corporation, Cary, NC).

Conclusions

• The explicit solutions to the equilibrium equations employ complex numbers, which cannot be easily solved by pharmacokinetic software.

• Both the bisection method and differential equations method of solving the equilibrium equations are readily implementable in pharmacokinetic software.

• Ignoring endogenous hormones competing for the same receptor might lead to inadequate model predictions for lower concentrations as well as biased parameter estimates.

References

- [1] Mager DE, Jusko WJ. General pharmacokinetic model for drugs exhibiting target-mediated drug disposition. J Pharmacokinet Pharmacodyn. 28:507-532 (2001).
- [2] Kenakin TP. A pharmacology primer: theory, application and methods: Elsevier Academic; 2009.
- [3] Hansen RJ, Baltasar JP. Pharmacokinetic/pharmacodynamic modeling of the effects of intravenous immunoglobulin on the disposition of antiplatelet antibodies in a rat model of immune thrombocytopenia. J Pharm Sci 92: 1206-1215 (2003).
- [4] Woo S, Krzyzanski W, Jusko WJ. Target-mediated pharmacokinetic and pharmacodynamic model of recombinant human erythropoietin (rHuEPO). J Pharmacokinet Pharmacodyn 34: 849-868 (2007).

Acknowledgment

This study was supported by the National Institute of General Medical Sciences, National Institutes of Health Grant GM 57980.