

Development and implementation of drug-drug interaction mechanisms with target-mediated drug disposition

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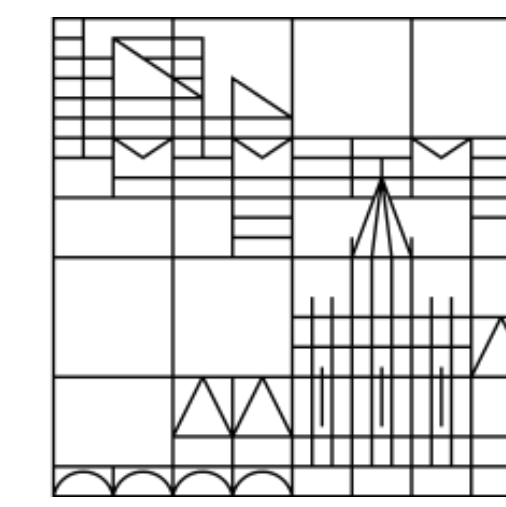
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Introduction and Objectives

Introduction

Drugs interact in many different ways with their targets. Some drug-drug interaction (DDI) mechanisms can be formulated by drug-receptor binding kinetics based on first principles, such as competitive, uncompetitive or non-competitive DDI [1].

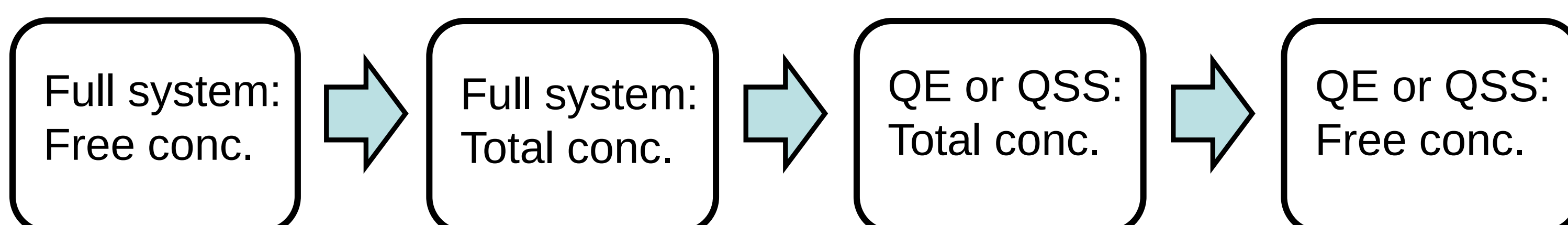
Target-mediated drug disposition (TMDD) describes drug binding with high affinity to a target such as a receptor [2]. Exemplarily, we consider the competitive DDI mechanism with TMDD behaviour [3]. Up to now, no straightforward representation of the quasi-equilibrium (QE) or quasi-steady state (QSS) form is available for implementation. We present a general method to construct an ODE formulation of the QE or QSS approximation in free concentration variables.

Objectives

- To present the **competitive** drug-drug interaction mechanism with **target mediated drug disposition** and with or without **endogenous baselines**
- To derive the **quasi-equilibrium** and **quasi-steady state** approximation for the competitive DDI mechanism
- To construct a QE or QSS formulation in **free concentration variables without solving any equation system** which can be directly implemented in any PKPD software

Methods

Construction principle of the QE or QSS approximation in original free variables



The QE or QSS assumption approximates rapid binding by an infinitely fast binding process.

QE or QSS total concentration formulation

The algebraic part (of the competitive DDI TMDD system) reads

$$K_{YA}(C_{totA} - C_A) = (R_{tot} - C_{totA} - C_{totB} + C_A + C_B)C_A$$

$$K_{YB}(C_{totB} - C_B) = (R_{tot} - C_{totA} - C_{totB} + C_A + C_B)C_B$$

but no explicit solution for C_A and C_B is known, compare [3].

→ **Reformulate the approximation in free concentrations!**

QE or QSS free concentration formulation

In the QE or QSS assumption one part of the i.v. bolus administered drug is infinitely fast bound to the receptor and the other part goes to the free drug concentrations. Hence, after an i.v. bolus the algebraic parts are no longer fulfilled and the new states of the free drug and the receptor concentrations need to be calculated again by solving another equation system.

→ **Mimic i.v. bolus by an i.v. short infusion to avoid solving of this equation system!**

References:

[1] Banks HT (1975) Modeling and control in biomedical sciences, Lecture notes in biomathematics, Springer

[2] Mager DE, Jusko WJ (2001) General pharmacokinetic model for drugs exhibiting target-mediated drug disposition. J Pharmacokinet Pharmacodyn 28(6):507-32

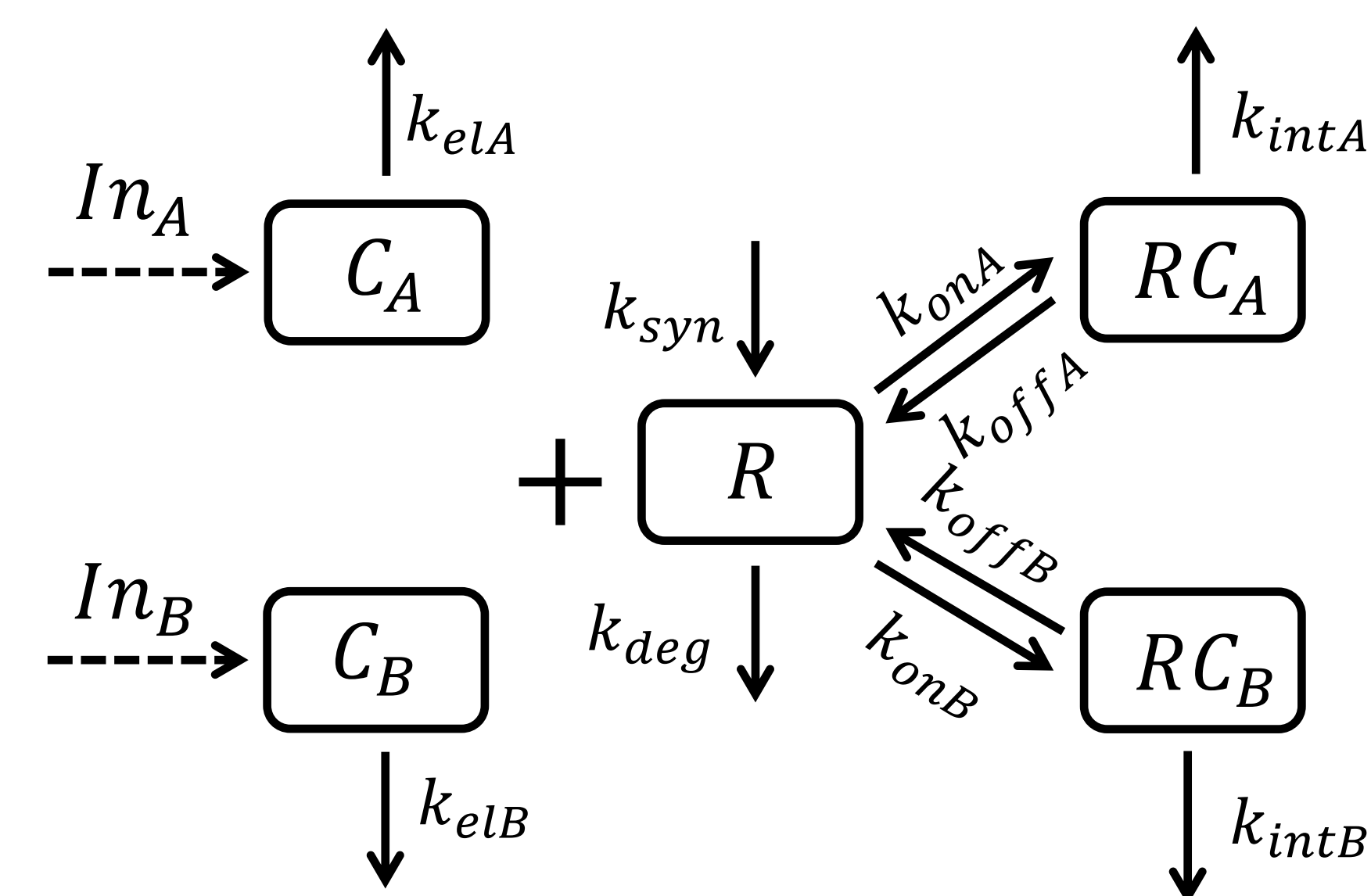
[3] Yan X, Chen Y, Krzyzanski W (2012) Methods to solving rapid binding target-mediated drug disposition model for two drugs competing for the same receptor. J Pharmacokinet Pharmacodyn 39(5):543-60

Results

Competitive DDI with TMDD

Both drugs compete for the same receptor, which is a common behaviour in several DDI scenarios. Often therapeutic antibodies and hematopoietic growth factors are agents competing for the same receptor with endogenous substances [3].

Competitive DDI in free variables with endogenous baselines $C_A^0, C_B^0 \geq 0$ based on TMDD drug-receptor binding kinetics:



Competitive DDI QE or QSS approximation in free variables:

The differential equations for the QE or QSS approximation are

$$\begin{pmatrix} \frac{d}{dt} C_A \\ \frac{d}{dt} C_B \\ \frac{d}{dt} R \end{pmatrix} = M_{Com}(C_A, C_B, R) \begin{pmatrix} In_A(t) - k_{elA}C_A - k_{intA} \frac{C_A R}{K_{YA}} \\ In_B(t) - k_{elB}C_B - k_{intB} \frac{C_B R}{K_{YB}} \\ k_{syn} - k_{deg}R - k_{intA} \frac{C_A R}{K_{YA}} - k_{intB} \frac{C_B R}{K_{YB}} \end{pmatrix}$$

where K_Y is either the dissociation K_D or steady state K_{SS} constant and M_{Com} a matrix. The baseline initial values are

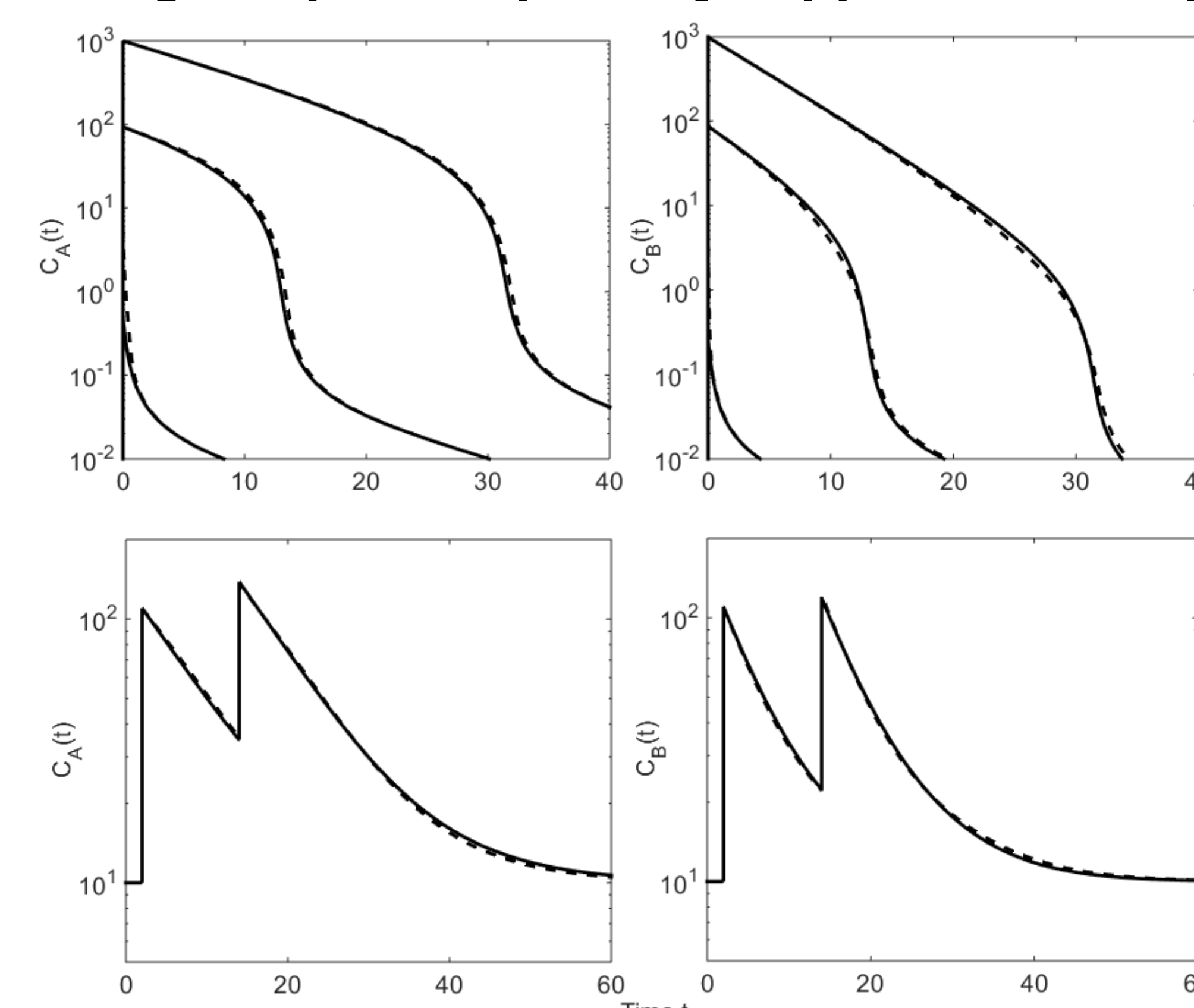
$$C_A(0) = C_A^0, \quad C_B(0) = C_B^0, \quad R(0) = R^0 = \frac{k_{syn}}{k_{deg} + k_{intA} \frac{C_A^0}{K_{YA}} + k_{intB} \frac{C_B^0}{K_{YB}}}$$

and the input function

$$In_X(t) = k_{elX}C_X^0 + k_{intX} \frac{C_X^0 R^0}{K_{YX}} + In_{AdX}(t), \quad X \in \{A, B\}$$

where drug administration is described by $In_{AdX}(t)$. The complexes can be recovered from $RC_X = \frac{C_X R}{K_{YX}}$.

Original (dashed) and QE approximation (solid) comparison



Without baseline
Escalating doses
10,100 and 1000
administered at $t = 0$

With baseline
Baseline $C_A^0 = C_B^0 = 10$
and dose $d_A = d_B = 100$ with multiple
administration at $t = 2$
and 14

Conclusions

- We developed an ODE formulation in **free variables without any equation system** which can be applied to DDI mechanisms based on drug-receptor binding kinetics, such as **competitive**, **uncompetitive** or **non-competitive**
- Presented formulation can be **straightforward implemented** in any PKPD software