Target-mediated drug disposition model for a bispecific antibody: full model and quasi-equilibrium approximation

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Introduction and Objectives

A bispecific antibody (bsAb) is an artificial protein that can simultenously bind to two different targets. BsAbs are considered as the next generation of targeted biologics for cancer therapy. In [1], [2] a mechanistic target-mediated drug disposition model (TMDD) for bsAbs was developed to investigate and simulate the binding behavior of this class of proteins. In the model the binding between the bsAb and its targets R_A and R_B was assumed to follow classical enzyme kinetic binding rules (see[3]) completed with processes of target synthesis and degradation as well as complex elimination. To reduce the number of model parameters we develop a rapid binding approximation of the bsAb TMDD model. This model will be derived by generalizing the quasi equilibrium / quasi steady state (QE/QSS) principles of Koch et al. [4] to bsAbs.

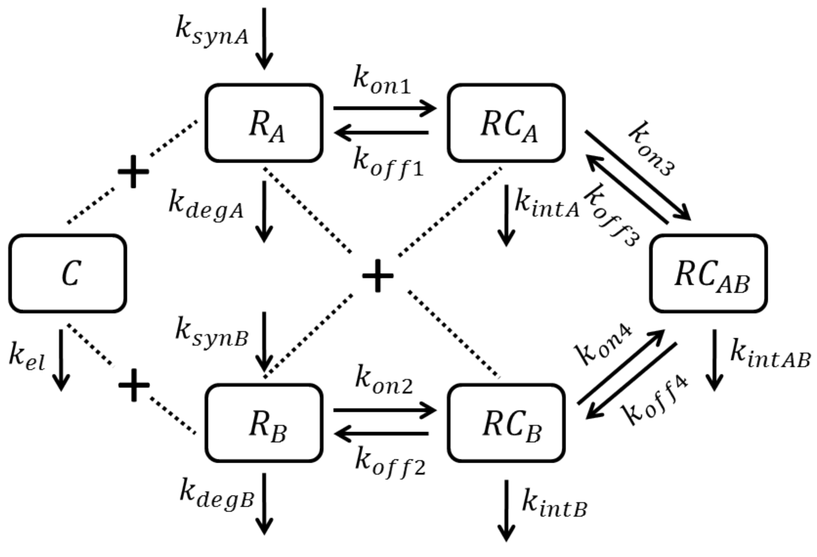
Objectives:

- To motivate a QE/QSS approximation of the general bsAb model to selectively reduce the number of usually not identifiable binding parameters.
- To reformulate the QE/QSS approximation into bsAb and target variables resulting in ordinary differential equations (ODEs) being suitable for an implementation in any standard PKPD software.

Methods

General construction principles of bsAb TMDD models with rapid binding (QE, QSS etc.) approximation:

1.) Develop the bsAb TMDD model in original variables, i.e. in the bsAb C, the targets R_A, R_B, binary complexes RC_A, RC_B and ternary complex RC_{AB}:



2.) Reformulate the bsAb TMDD system in total drug and total target concentrations.
3.) Apply the QE/QSS etc. approximation based on the corresponding rapid binding assumptions and eliminate the undesired parameters.
4.) Reformulate the QE/QSS etc. approximation in the original variables for the bsAb C and the targets R_A, R_B.

References:

[1] Hollander, N (2009) Bispecific antibodies for cancer therapy, Immunology 2:211-222.

[2] Li L, Gardner I, Gill K (2014) Modeling the binding kinetics of Bispecific Antibodies under the Framework of Minimal Human PBPK Model, AAPS NBC, poster T2056.

[3] Bisswanger, H (2008) Enzyme Kinetics: principles and methods, sec. ed., Wiley VCH.

[4] Koch G, Jusko WJ, Schropp J (2017) Target mediated drug disposition with drug drug interaction, Part II: competitive and uncompetitive cases, J. Pharmacokinet. Pharmacodyn. 44:27-42.

[5] Fenichel N (1979) Geometric singular perturbation theory for ordinary differential equations, J. Diff. equations 31:54-98.

Results

Total concentration formulation:
BsAb TMDD model in total drug $C_{tot} = C + RC_A + RC_B + RC_{AB}$ and total target $R_{totX} = R_X + RC_X + RC_{AB}$ concentration, $X = A, B$, reads

$$\frac{d}{dt}C_{tot} = In(t) - k_{el}C - k_{intA}RC_A - k_{intB}RC_B - k_{intAB}RC_{AB} \quad (1)$$
$$\frac{d}{dt}R_{totA} = k_{synA} - k_{degA}R_A - k_{intA}RC_A - k_{intAB}RC_{AB} \quad (2)$$
$$\frac{d}{dt}R_{totB} = k_{synB} - k_{degB}R_B - k_{intB}RC_B - k_{intAB}RC_{AB} \quad (3)$$
$$\frac{d}{dt}RC_A = k_{on1}R_AC - (k_{off1} + k_{intA})RC_A - k_{on4}R_B\,RC_A + k_{off4}RC_{AB} \quad (4)$$
$$\frac{d}{dt}RC_B = k_{on2}R_BC - (k_{off2} + k_{intB})RC_B - k_{on3}R_A\,RC_B + k_{off3}RC_{AB} \quad (5)$$
$$\frac{d}{dt}RC_{AB} = k_{on3}R_ARC_B + k_{on4}R_BRC_A - (k_{off3} + k_{off4} + k_{intAB})RC_{AB} \quad (6)$$

completed with baseline initial values.

QE approximation:
The QE approximation based on the theory of Fenichel [5] allows selective acceleration of binding rates. This gives

$$0 = R_AC - K_{D1}RC_A, \quad 0 = R_BC - K_{D2}RC_B \quad (7)$$
$$0 = R_ARC_B + R_BRC_A - \alpha(K_{D1} + K_{D2})RC_{AB} \quad (8)$$

with $K_{Di} = k_{offi}/k_{oni}$, $i = 1, 2, 3, 4$ and $\alpha = (K_{D3} + K_{D4})/(K_{D1} + K_{D2})$ denoting the affinity ratio between C and R_B for target A or C and R_A for target B. The QE approximation system is then (1)-(3), (7)-(8) and initial values in baseline.

Reformulation of the approximation in original variables:
Reformulation of (1)-(3) in the original variables C, R_A and R_B yields

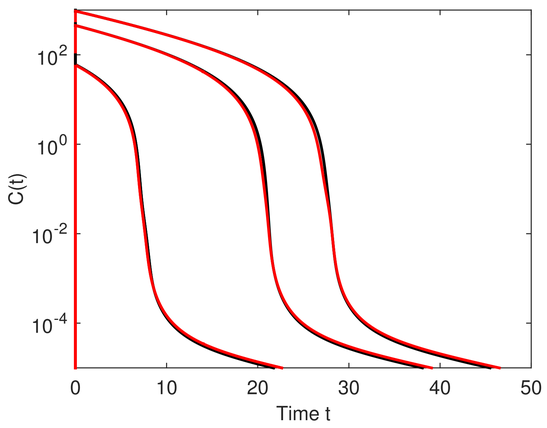
$$\begin{pmatrix} \frac{d}{dt}C \\ \frac{d}{dt}R_A \\ \frac{d}{dt}R_B \end{pmatrix} = M_{bsAb}(C, R_A, R_B) \cdot g_{bsAb}(C, R_A, R_B) \quad (9)$$

with a (3×3) matrix $M_{bsAb}(C, R_A, R_B)$ with long and tedious entries (usually stored in the model library of the PKPD software) and

$$g_{bsAb}(C, R_A, R_B) = \begin{pmatrix} In(t) - k_{el}C - k_{intA}RC_A - k_{intB}RC_B - k_{intAB}RC_{AB} \\ k_{synA} - k_{degA}R_A - k_{intA}RC_A - k_{intAB}RC_{AB} \\ k_{synB} - k_{degB}R_B - k_{intB}RC_B - k_{intAB}RC_{AB} \end{pmatrix}.$$

Remark: We mimic IV bolus administration by short infusion. No non-linear equation system has to be solved. Equation (9) can simply be implemented in any PKPD software.

Approximation quality:
Parameters were set to typical values. All internalization rates and all binding parameters kon_X, k_{offX} were set different. BsAb concentration C from full model (black line) and from QE approximation (red line) is shown.



Conclusions

- Using the design principles of Koch et al. [4] a QE approximation of the bsAb TMDD model was established, which retains nearly the full information of the original model.
- The bsAb QE approximation is superior to the original model due to the less number of usually unidentifiable parameter.
- The method has great potential to assist the modeling and simulation process in any kind of bsAbs studies.