Characterization of bispecific antibodies and the ternary complex including an optimal dosing strategy

Johannes Schropp[1] and Gilbert Koch[2,3]

(1) Department of Mathematics and Statistics, University of Konstanz, Germany
(2) Pediatric Pharmacology and Pharmacometrics, University of Basel, Children's Hospital (UKBB), Basel, Switzerland
(3) Department of Pharmaceutical Sciences, The State University of New York at Buffalo, NY, USA

Introduction and Objectives

Bispecific monoclonal antibodies (BsMabs) are promising candidates in cancer immunotherapy. For example, BsMabs may simultaneously bind a T cell and a tumor cell. In general, a BsMab binds to two targets (e.g. receptors) forming two binary complexes. Both binary complexes further cross-bind with the same targets creating the ternary complex. Based on this binding kinetics modeled by the law of mass action, several mathematical models [1]-[2] were designed to guide the development of BsMabs. In this study the concentration of the ternary complex is considered as the produced effect of the BsMab drug and the behaviour of the ternary complex is investigated. A BsMab model [3] that incorporates linear elimination, internalization of the complexes and synthesis and degradation of the targets is applied. We are focused on modeling and simulation of the PK of a BsMab binding to cell membrane targets on different cells.

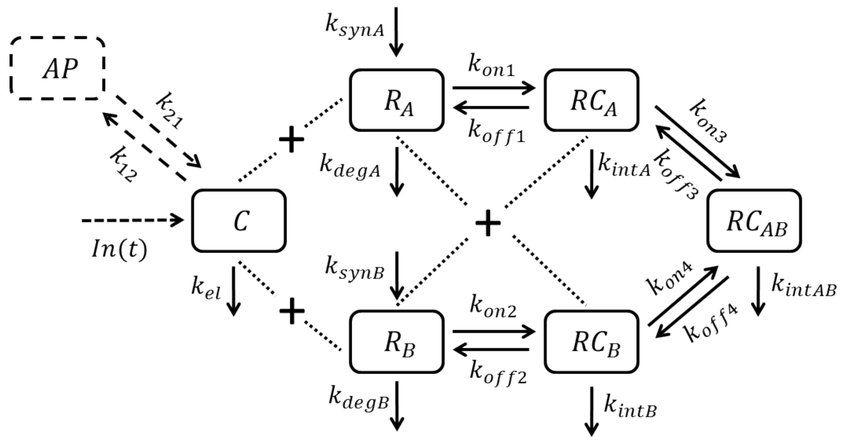
Objectives:

- To demonstrate that from the cross-binding structure the ternary complex inherits some PK uncommon features such as (i) for escalating BsMab doses the concentration of the ternary complex decreases and finally vanishes, and (ii) the ternary complex may be fully available although the BsMab concentration is already below the limit of quantification.
- To develop an optimal dosing strategy for a BsMab, i.e. ensuring maximal concentration of the ternary complex as long as possible.

Methods

The ternary complex concentration and optimal dosing:

1.) Substitute binding rates k_{onZ}, k_{offZ}, $Z = 1, \ldots, 4$ by their equilibrium constants, set the affinity constant α and replace the original BsMab TMDD model by its QE approximation (see [3] for equations):



2.) Derive the equilibrium binding relations of the binary and ternary complex with respect to the BSMab concentration in the QE model without synthesis, degradation, eliminination and internalization.
3.) Set up the dosing scheme depending on the time evolution of the total concentration of the BsMab, the targets R_A and R_B in the full model or its QE approximation and the equilibrium binding relations.

References:

[1] Rhoden JJ, Dyas GL, Wroblewskki VJA (2016) Modeling and Experimental Investigation of the Effects of Antigen Density, Binding Affinity and Antigen Expression Ratio on Bispecific Antibody Binding to Cell Surface Targets, J Biol Chem 291(21):11337-47.

[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] Schropp J, Koch G (2017) Target-mediated drug disposition model for a Bispecific Antibody: development of full model and quasi-equilibrium like approximation, PAGE Poster II-04.

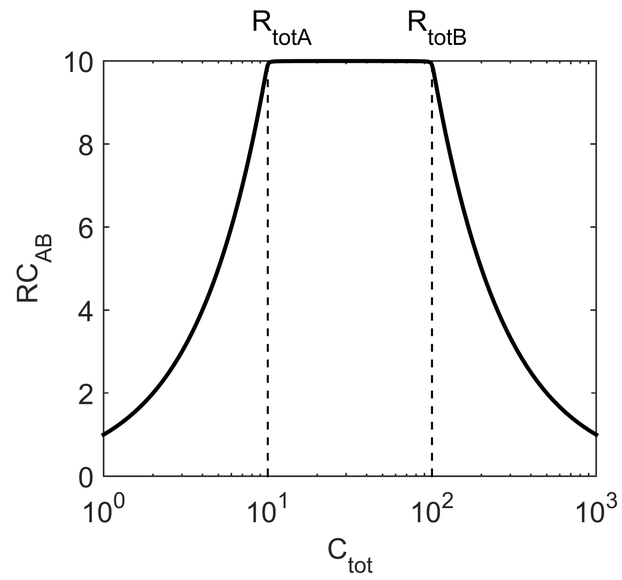
[4] Vasileva AB (1963) Asymptotic behaviour of solutions to certain problems involving nonlinear differential equations containing a small parameter multiplying the highest derivatives, Russ math Surv 18: 13-83.

Results

Equilibrium binding relations:
The concentration of the ternary complex with respect to the free BsMab concentration reads

$$RC_{AB}(C) = \frac{CR_A(C)R_B(C)}{\alpha KD_1 KD_2} \tag{1}$$

with $R_A(C)$, $R_B(C)$ describing the equilibrium relation between the free targets A and B and the BsMab. Due to Li et al [2] the optimal working area of the ternary complex becomes more visible in a $(C_{tot}(C), RC_{AB}(C))$, $C_{tot} = C + RC_A + RC_B + RC_{AB}$ diagram.



The diagram shows that i) the ternary complex concentration tends to zero for escalating BsMab doses and ii) the achieved ternary complex concentration is optimal, if

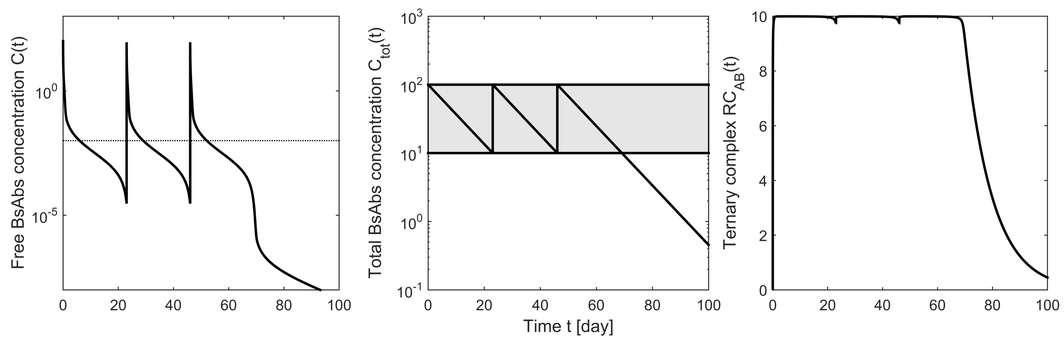
$$\min(R_{totA}, R_{totB}) \leq C_{tot} \leq \max(R_{totA}, R_{totB}). \tag{2}$$

Optimal dosing strategy:
In the full model or its QE approximation $C_{tot}, R_{totA}, R_{totB}$ evolve in time. But due to formula (2) and singular perturbation theory [4] an optimal dosing strategy has to satisfy

$$\min(R_{totA}(t), R_{totB}(t)) \leq C_{tot}(t) \leq \max(R_{totA}(t), R_{totB}(t))$$

for as many t values as possible. This leads to

- Initial dose $dose_{init} = \max(R^0_{totA}, R^0_{totB})V$.
- Next dosing point t_{next} is defined via $\min(R_{totA}(t_{next}), R_{totB}(t_{next})) = C_{tot}(t_{next})$.
- Optimal dose $dose_{next} = (\max(R_{totA}(t_{next}), R_{totB}(t_{next})) - \min(R_{totA}(t_{next}), R_{totB}(t_{next})))V$.



Simulations show the optimal dosing strategy for IV bolus administrations in case of constant total receptors. Note that the ternary complex concentration is optimal though the BsMab concentration is below the limit of quantification (indicated by the dashed line).

Conclusions

- Due to the crosslinking structure of the formed complexes the ternary complex shows different properties compared to the classical concentration effect terms.
- The presented model allows a characterization of the optimal working area of the BsMab. Using this characterization we showed how optimal re-dosing time points and doses can be obtained.
- The method has great potential to assist the modeling, simulation and drug dosing process in any kind of BsMabs studies.