On the coupling between a basic FcRn mechanism and target-mediated drug disposition of antibodies—an asymptotic analysis in the high binding affinity limit

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Objectives & Introduction

Objectives:
(1) Develop a combined FcRn–TMDD model and examine its behaviour in various relevant parameter regimes. **(2)** Develop an asymptotic framework in the high binding-affinity limit to describe the characteristic phases of the combined model. **(3)** Derive relevant pharmacometric expressions for the problems, and thereby obtain a deeper understanding of the dynamics governing an FcRn–TMDD system.

Introduction:

- Antibody pharmacokinetics (PK) is typically governed by two key mechanisms: non-specific endosomal clearance modulated by neonatal Fc receptors (FcRn) and target-mediated drug disposition (TMDD). Usually the former is incorporated in a similar manner in many of the physiology-based pharmacokinetic (PBPK) models presented in the literature; see e.g. Willmann et al. (2003); Garg and Balthasar (2007); Shah and Betts (2012); Niederalt et al. (2018).
- TMDD is incorporated in PBPK models to address the effects of 'high-affinity–low-capacity' binding sites on antibody PK and thereby account for target-mediated (specific) clearance. While the two mechanisms have been studied thoroughly and independently through minimal models, e.g. by Peletier and Gabrielsson (2012) and Kristiansen (2019), and by Kátai et al. (2024), respectively, their coupling and interaction remains to be explored to that level of detail.
- One of the simplest combined models can be constructed by including target receptors in the plasma space of the basic FcRn model explored in Kátai et al. (2024).
- An important aspect to consider is the magnitudes of the parameters involved. If there is a significant time scale gap between the two clearance processes, one or the other will dominate antibody clearance. Hence, the most relevant parameter regimes are likely those that result in both clearance mechanisms coming into play over the same time scale.

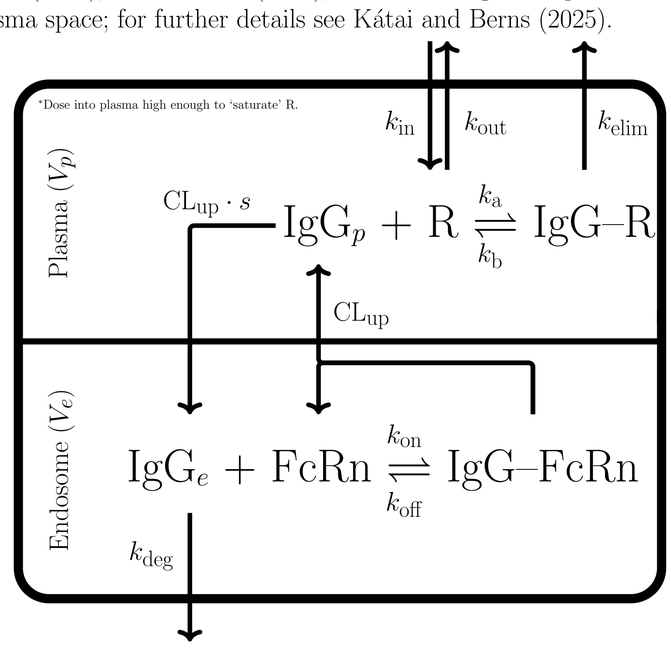
Conclusions & Discussion

- Constructed a combined FcRn–TMDD model based on the FcRn-model of Kátai et al. (2024) by including target binding in the plasma space.
- The three-tiered scaling framework of Kátai et al. (2024) was used to rank the parameters corresponding to the TMDD-submodel; the key consideration was that both the specific (TMDD) and the non-specific (FcRn) elimination processes were required to appear over the same time scale.
- Accurate asymptotic expressions were obtained for each characteristic phase of the problems that provide valuable insight for future PBPK as well as standard PK-PD modelling efforts.
- The results may also be utilised to assess the validity of various quasi-equilibrium, quasi-steady state and Michaelis–Menten assumptions, but also to address parameter (non)identifiability (Peletier and Gabrielsson, 2012; Kristiansen, 2019).

Problem Definition & Methods

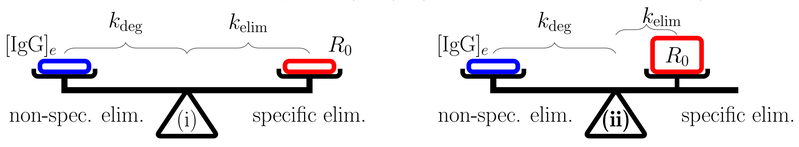
Problem definition

- Basic FcRn-modulated endosomal degradation mechanism based on Patsatzis et al. (2022); Kátai et al. (2024), but with target receptor binding in the plasma space; for further details see Kátai and Berns (2025).



Methods–three-tiered scaling framework

- Extend three-tiered scaling setup of Kátai et al. (2024) with the parameters pertaining to TMDD (see below); use the baseline FcRn concentration (F_0) and $(k_{on} \cdot F_0)^{-1}$ as the reference concentration and time scales, respectively.
- Examine two parameter regimes (i, **ii**); (baseline receptor level R_0).



- Analyse problems using the method of matched asymptotic expansions, with the small parameter $\epsilon = \frac{k_{off}}{k_{on}F_0} \ll 1$; for further details see e.g. the textbooks by Van Dyke (1975) or Kuehn et al. (2015).

Time scales

$O(\epsilon^{-2})$ **Overall elimination:**
⇒ non-specific elimination ($k_{deg}[IgG]_e$);
⇒ specific elimination ($k_{elim}[IgG–R]$);
maximum turnover ($k_{out}R_0$)

{ (i) k_{out} & k_{elim} are intermediate, R_0 is much lower than F_0
(ii) k_{out} & k_{elim} are low, R_0 is comparable to F_0

$O(\epsilon^{-1})$ **Intermediate processes:**
⇒ pinocytic uptake & recycling (CL_{up});
⇒ FcRn dissociation (k_{off});
⇒ 'Intrinsic' degradation (k_{deg});
⇒ IgG–R dissociation (k_b);

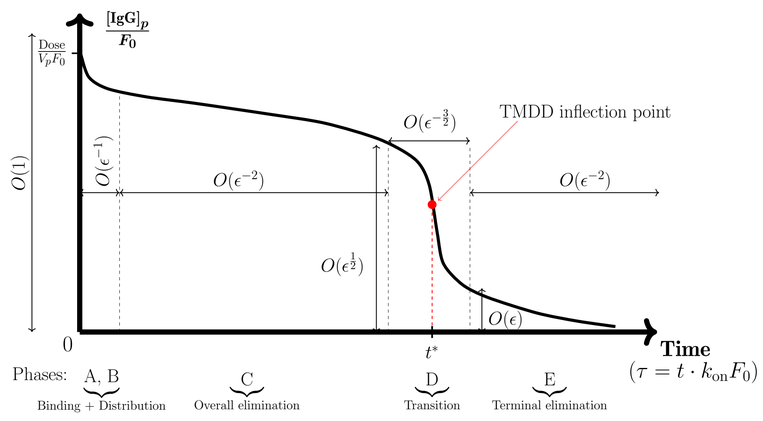
$O(1)$ **Binding:**
⇒ FcRn binding (k_{on});
⇒ R binding (k_a);

*TMDD parameter magnitudes motivated by Zasedateleva et al. (2024).

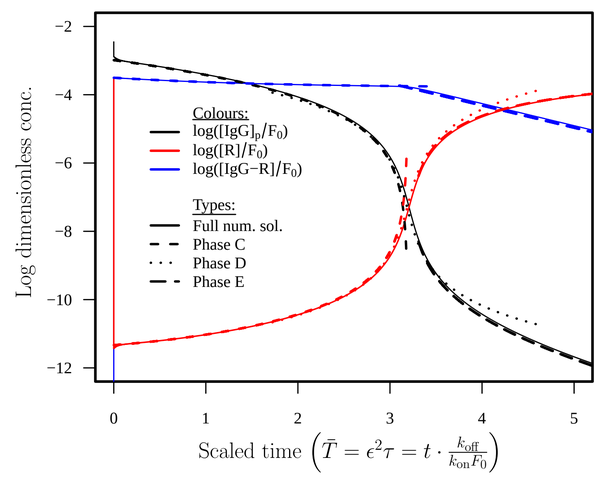
Results

Low elim. rate constant case (ii)–the solution structure & accurate theory

- Illustration of the solution structure for case **(ii)**:



- Derived accurate asymptotic approximations valid in each characteristic phase; see Kátai and Berns (2025) for further details.
- A comparison between the asymptotic theory and the full solution to the system:



The TMDD inflection point–start of receptor 'desaturation'

- TMDD inflection point in the log($[IgG]_p$) versus time curve†:

$$t^* \approx \frac{k_{on}F_0(sV_e + V_p)}{k_{deg}\left(\frac{CL_{up}}{V_e} + k_{off}\right)sV_e} \log\left(\frac{\mathbf{Dose} - R_0V_p}{V_pF_0} \cdot \frac{k_{deg}\left(\frac{CL_{up}}{V_e} + k_{off}\right)sV_e}{k_{out}R_0k_{on}(sV_e + V_p)} + 1\right).$$

- Conc. of IgG_p at the inflection point and where $K_D = k_b/k_a$:

$$[IgG]_p\Big|_{t^*} \sim \sqrt{\frac{R_0K_DV_p}{sV_e + V_p}\left[\frac{k_{out}}{k_{elim}} + \left(1 - \frac{k_{out}}{k_{elim}}\right)e^{-k_{elim}t^*}\right]}.$$

- Product and ratio of IgG_p and the normalised free receptor conc. at the inflection point:

$$\left([IgG]_p\frac{[R]}{R_0}\right)\Big|_{t^*} \sim K_D\left[\frac{k_{out}}{k_{elim}} + \left(1 - \frac{k_{out}}{k_{elim}}\right)e^{-k_{elim}t^*}\right],$$

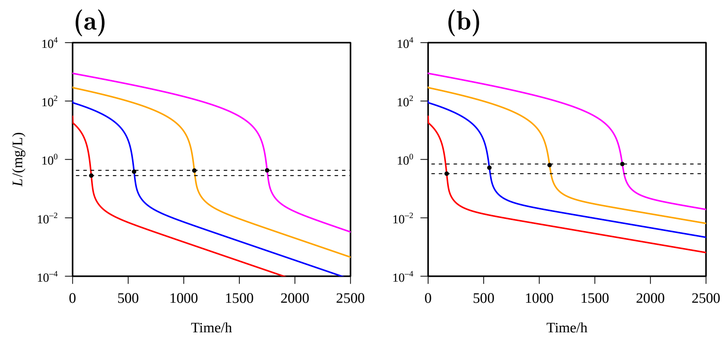
$$\left([IgG]_p\frac{R_0}{[R]}\right)\Big|_{t^*} \sim \frac{R_0V_p}{sV_e + V_p}.$$

†The expression shown is a simplified version, for the more accurate formula see Kátai and Berns (2025).

- In general, the dose affects the conc. at the inflection point by an $O(1)$ factor via t^*; this is due to the turnover and drug-target complex elim. occurring on the long elim. time scale, hence, the corresponding modes are not necessarily exhausted within a 'finite' time t^*.
- Often $k_{out} \approx k_{elim}$ or t^* is sufficiently large, in which case the dose has negligible effect on the concentrations at the inflection point.

The dose can affect the TMDD inflection point

- Clearly the dose may impact the TMDD inflection point for the case (ii).
- Contrary to previous belief, the dose in the classic TMDD system (Peletier and Gabrielsson, 2012) generally affects the conc. at the TMDD inflection point, which can be easily shown from the theory presented by Kristiansen (2019), but also from numerical calculations.
- Solved numerically the governing equations in Peletier and Gabrielsson (2012) for different doses (30-900 mg/L intitial IgG concentration; different coloured lines) using their reference parameter values **(a)**, and when the rate constant corresponding to the elimination of IgG–R is halved **(b)**; L is the ligand (IgG) concentration.
- If the gap between k_{out} and k_{elim} is increased **(a → b)**, the effect of dose on the conc. at the inflection point (filled circles) becomes more pronounced.



- In practice the effect of dose on the TMDD inflection point is virtually impossible to detect:
  1. Insufficient number of data points available at and in the neighbourhood of the inflection point;
  2. The 'small' $O(1)$ fold-change is not as apparent in the logarithmic plot; $[IgG]_p/F_0$ decreases from $O(1)$ in phases A, B & C to $O(\epsilon^{\frac{1}{2}})$ and $O(\epsilon)$ in phases D & E, respectively.

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