An asymptotic description of a basic FcRn-regulated clearance mechanism and its implications for PBPK modelling of large antibodies

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Objectives & Introduction

Objectives: **(1)** Perform a standard singular perturbation analysis (see e.g. Van Dyke, 1975; Lin and Segel, 1988) of the basic FcRn-regulated clearance mechanism outlined by Patsatzis et al. (2022) and thereby obtain a deeper understanding of it. **(2)** Compare the asymptotic clearance expression to that obtained from a full PBPK model (Shah and Betts, 2012)

Introduction:

- Physiology-based pharmacokinetic (PBPK) models are important tools for understanding the distribution and clearance of drugs in organisms.
- The long half life of antibody drugs is usually attributed to the Neonatal Fc Receptors (FcRn-s) which bind and save antibodies from degradation in the endosomal space of endothelial cells.
- A mechanistic formulation of the FcRn-regulated endosomal degradation has been proposed and employed successfully by several PBPK models found in the literature (Shah and Betts, 2012; Li and Shah, 2019; Glassman and Balthasar, 2019; Liu and Shah, 2023). However, due to the complexity of their formulation, a deeper understanding of how the parameters in the model affect clearance has so far remained elusive.
- A simpler form of the mechanism, consisting of a single plasma space and a single endosomal space, was studied by Patsatzis et al. (2022)–although for an unusually high dose–through the lens of a computational singular perturbation analysis.

Conclusions & Discussion

- A relatively simple equation relating clearance to physiological model parameters has been derived.
- The results should caution against estimating k_{deg} and $[\text{FcRn}]_0$ in a PBPK setting simultaneously (cf. Shah and Betts, 2012; Liu and Shah, 2023)
- For typical physiological parameters and 'high' antibody dose levels IgG elimination is akin to that for target mediated drug disposition, however, for low dose levels clearance is 'linear'.
- The dependence of clearance on the model parameters is well reflected in a full PBPK setting.

Problem Definition & Methods

Problem definition:

- Basic FcRn-regulated endosomal degradation mechanism from Patsatzis et al. (2022) (Figure below);
- The governing equations and initial conditions read

$$\frac{\mathrm{d}C_{\mathrm{p}}^{\mathrm{IgG}}}{\mathrm{d}t} = -\frac{\mathrm{CL_{up}}}{V_p}\cdot\left(s\cdot C_{\mathrm{p}}^{\mathrm{IgG}} - C_{\mathrm{e}}^{\mathrm{IgG.FcRn}}\right),$$
$$\frac{\mathrm{d}C_{\mathrm{e}}^{\mathrm{IgG}}}{\mathrm{d}t} = \frac{\mathrm{CL_{up}}}{V_e}\cdot s\cdot C_{\mathrm{p}}^{\mathrm{IgG}} + k_{\mathrm{off}}\cdot C_{\mathrm{e}}^{\mathrm{IgG.FcRn}} - \left(k_{\mathrm{deg}} + k_{\mathrm{on}}\cdot C_{\mathrm{e}}^{\mathrm{FcRn}}\right)\cdot C_{\mathrm{e}}^{\mathrm{IgG}},$$
$$\frac{\mathrm{d}C_{\mathrm{e}}^{\mathrm{FcRn}}}{\mathrm{d}t} = \left(\frac{\mathrm{CL_{up}}}{V_e} + k_{\mathrm{off}}\right)\cdot C_{\mathrm{e}}^{\mathrm{IgG.FcRn}} - k_{\mathrm{on}}\cdot C_{\mathrm{e}}^{\mathrm{IgG}}\cdot C_{\mathrm{e}}^{\mathrm{FcRn}},$$
$$\frac{\mathrm{d}C_{\mathrm{e}}^{\mathrm{IgG.FcRn}}}{\mathrm{d}t} = -\frac{\mathrm{d}C_{\mathrm{e}}^{\mathrm{FcRn}}}{\mathrm{d}t},$$

$$C_{\mathrm{p}}^{\mathrm{IgG}}(0) = \frac{\mathrm{Dose}}{V_p},\quad C_{\mathrm{e}}^{\mathrm{FcRn}}(0) = [\mathrm{FcRn}]_0,\quad C_{\mathrm{e}}^{\mathrm{IgG}}(0) = C_{\mathrm{e}}^{\mathrm{IgG.FcRn}}(0) = 0.$$

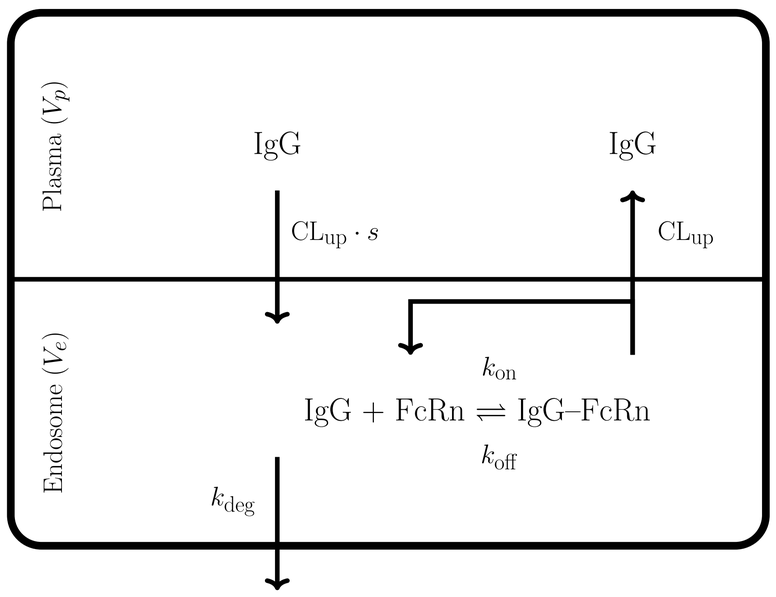


Fig.: Basic FcRn model scheme from Patsatzis et al. (2022) with modulated pinocytic uptake.

Methods:

- The system is non-dimensionalised using $[\text{FcRn}]_0$ and $(k_{\text{on}}\cdot[\text{FcRn}]_0)^{-1}$ as the reference concentration and time scales, respectively;
- The order of magnitudes of the following dimensionless groups are assumed to be

$$\epsilon \equiv \frac{k_{\mathrm{off}}}{k_{\mathrm{on}}\cdot[\mathrm{FcRn}]_0} \ll 1,\quad \frac{\mathrm{CL_{up}}/V_e}{k_{\mathrm{on}}\cdot[\mathrm{FcRn}]_0} = O(\epsilon),\quad \frac{k_{\mathrm{deg}}}{k_{\mathrm{on}}\cdot[\mathrm{FcRn}]_0} = O(\epsilon);$$

- Series solutions for $\epsilon \ll 1$ are sought over each characteristic time scale and matched using the so-called matched asymptotic expansions technique.
- The solution structure for low, intermediate and high doses were sought corresponding to cases when the FcRn is under-, 'exactly'- and over-saturated, respectively.
- For further technical details see Kátai et al. (2024).

Results

High doses: $\frac{\mathrm{Dose}}{V_p[\mathrm{FcRn}]_0} - \frac{sV_e+V_p}{sV_p} \gg \epsilon^{1/2}$

- FcRn 'over-saturated';
- Characteristic phases:
  - A: Binding,
  - B: Transport,
  - B_1: Rapid transition,
  - B_2: Rapid build-up & elim.,
  - B_3: Slow transition,
  - $\tilde{\mathrm{C}}$: Overall elimination.

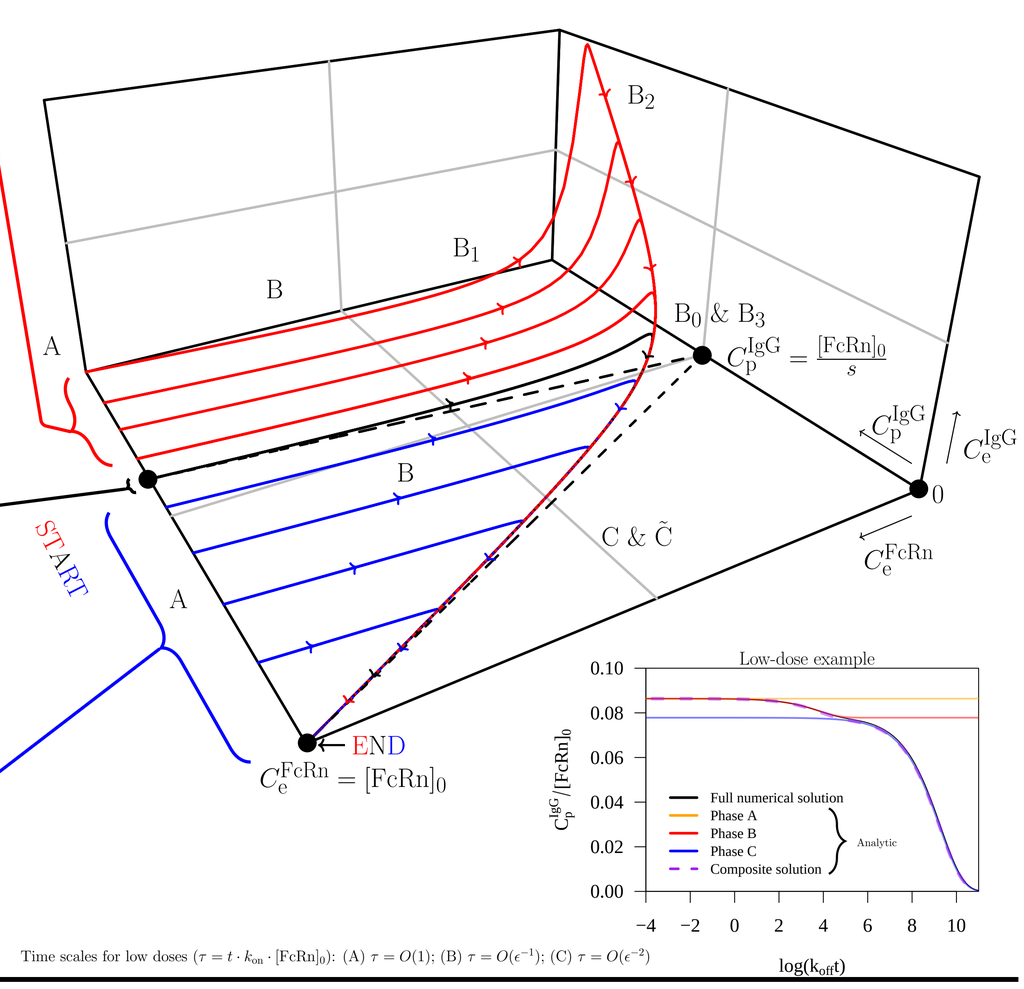
Intermediate doses: : $\frac{\mathrm{Dose}}{V_p[\mathrm{FcRn}]_0} \approx \frac{V_e}{V_p} + \frac{1}{s}$

- 'Exact' saturation of FcRn;
- Characteristic phases:
  - A: Binding,
  - B: Transport & equilibration,
  - B_0: Small build-up & elimination,
  - $\tilde{\mathrm{C}}$: Overall elimination.

Low doses : $-\frac{\mathrm{Dose}}{V_p[\mathrm{FcRn}]_0} + \frac{sV_e+V_p}{sV_p} \gg \epsilon^{1/2}$

- FcRn not saturated;
- Characteristic phases:
  - A: Binding,
  - B: Transport & equilibration,
  - C: Overall elimination.

Solution trajectories in phase space:



Time scales for low doses ($\tau = t\cdot k_{\text{on}}\cdot[\text{FcRn}]_0$): (A) $\tau = O(1)$; (B) $\tau = O(\epsilon^{-1})$; (C) $\tau = O(\epsilon^{-2})$

Clearance expression in the basic FcRn model:

- If clearance, CL, is defined through **(a)**, then in the terminal phase (C & $\tilde{\mathrm{C}}$) for all doses CL behaves as in **(b)**:

$$\textbf{(a)}\quad V_p\cdot\frac{\mathrm{d}C_{\mathrm{p}}^{\mathrm{IgG}}}{\mathrm{d}t} = -\mathrm{CL}\cdot C_{\mathrm{p}}^{\mathrm{IgG}},\qquad \textbf{(b)}\quad \mathrm{CL} \sim \underbrace{\frac{s\cdot V_e\cdot V_p}{s\cdot V_e + V_p}\cdot\frac{k_{\mathrm{deg}}}{k_{\mathrm{on}}\cdot[\mathrm{FcRn}]_0}\cdot\left(k_{\mathrm{off}} + \frac{\mathrm{CL_{up}}}{V_e}\right)}_{\text{constant}}\cdot\underbrace{\frac{[\mathrm{FcRn}]_0}{[\mathrm{FcRn}]_0 - C_{\mathrm{p}}^{\mathrm{IgG}}}}_{\approx 1 \text{ for typical doses}}.$$

Effect of parameters on CL in a full PBPK model:

† In-house model of PD-value based on Shah and Betts (2012).

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