Predicting Rebound for mAbs using the TMDD Model

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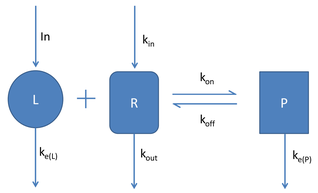
Introduction

Protein-therapeutic antibody interactions can change the distribution and clearance of the target protein. This can result in free target concentrations increasing above their baseline level, so-called antigen rebound. Here we present a systematic evaluation of the antigen/antibody PKPD properties that could result in antigen rebound for a target-mediated drug disposition (TMDD) model and for extensions that include feedback.

The basic model and antigen rebound

We consider a model involving an antibody (ligand L), an antigen/protein (receptor R), and an antibody-protein complex (P) [Levy, 1994; Mager & Jusko, 2001]:



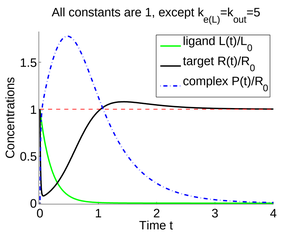
This system can be modelled by the ODE's

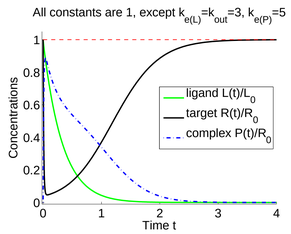
$$\frac{dL}{dt} = \mathrm{In} - k_{\mathrm{e(L)}}\,L - k_{\mathrm{on}}\,LR + k_{\mathrm{off}}\,P$$
$$\frac{dR}{dt} = k_{\mathrm{in}} - k_{\mathrm{out}}\,R - k_{\mathrm{on}}\,LR + k_{\mathrm{off}}\,P$$
$$\frac{dP}{dt} = -k_{\mathrm{e(P)}}\,P \quad + k_{\mathrm{on}}\,LR - k_{\mathrm{off}}\,P$$

- The baseline is $L = 0$, $R = R_0 = \frac{k_{\mathrm{in}}}{k_{\mathrm{out}}}$, $P = 0$, which is globally asymptotically stable.
- At time $t = 0$, a bolus dose L_0 is injected, thus we have initially

$$L = L_0, \quad R = R_0 = \frac{k_{\mathrm{in}}}{k_{\mathrm{out}}}, \quad P = 0.$$

Two typical simulations: on the left the protein level goes above baseline once the antibody runs out; on the right no rebound happens.

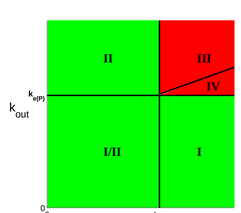




A mathematical analysis of the ligand-receptor-complex phase space shows that the presence or absence of rebound is fully determined by the elimination parameters:

Theorem 1 [Aston et al, 2013] *In the basic TMDD model, the free protein level rebounds, i.e., increases to values above the baseline, if and only if the elimination rate of the complex is slower than the elimination rate of both the antibody and the protein, i.e.,*

$$k_{\mathrm{e(P)}} < k_{\mathrm{e(L)}} \text{ and } k_{\mathrm{e(P)}} < k_{\mathrm{out}}.$$



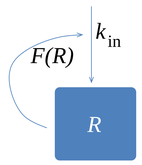
Green: no rebound
Red: rebound

This result also applies for multiple drug doses and the occurrance of rebound does not depend on the amount of drug injected.

Feedback control on endogenous production

In the basic version of the TMDD model, reduction of free target levels does not have any impact on the endogenous production or elimination rate of the free target. Such feedback may also be a reason for protein rebound, so below we describe how feedback influences rebound in the TMDD model.

Case 1: Direct feedback



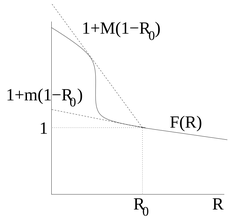
Feedback is modelled by modifying the protein turnover term k_{in} to $k_{\mathrm{in}}\,F(R)$, where $F(R)$ represents the feedback. Only the receptor equation is affected:

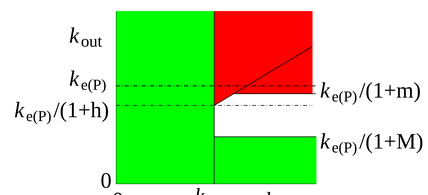
$$\frac{dR}{dt} = k_{\mathrm{in}}\,F(R) - k_{\mathrm{out}}\,R - k_{\mathrm{on}}\,LR + k_{\mathrm{off}}\,P$$

The feedback $F(R)$ decreases when R increases and $F(R_0) = 1$.

Theorem 2

- *The feedback does not induce protein rebound without the presence of the antibody.*
- *With one (or more) anti-body doses L_0 added, the rebound depends again on the elimination parameters. The rebound region has been expanded compared to the case without feedback, but there are still large regions without rebound.*



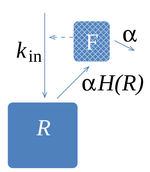


Sketch of a feedback function $F(R)$:

$$m = \min\left\{\tfrac{(F(R)-1)R_0}{R_0-R} \mid 0 < R < R_0\right\},$$
$$M = \max\left\{\tfrac{(F(R)-1)R_0}{R_0-R} \mid 0 < R < R_0\right\},$$
$$h = -F'(R_0)R_0.$$

Green: no rebound;
Red: rebound;
White: need more info about $F(R)$ (if F is linear, $m = M = h$ and no white region is present).

Case 2: Moderated feedback



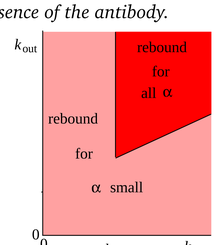
Feedback is modelled via a moderator F, giving an extra ODE for the moderator and a modified receptor equation:

$$\frac{dR}{dt} = k_{\mathrm{in}}\,F - k_{\mathrm{out}}\,R - k_{\mathrm{on}}\,LR + k_{\mathrm{off}}\,P$$
$$\frac{dF}{dt} = \alpha\,(H(R) - F),$$

here α represents the feedback response speed.

Theorem 3

- *For any $\alpha > 0$, the feedback can induce protein rebound in absence of the antibody.*
- *For any $\alpha > 0$, if the elimination rate of the antibody is faster than the elimination rate of the complex ($k_{\mathrm{e(L)}} > k_{\mathrm{e(P)}}$) and the elimination rate of the protein is sufficiently fast, then protein rebound will occur after adding an antibody dose L_0 to the baseline state (red region).*
- *If the feedback is slow to respond (α is small), then the addition of a dose of the antibody will always result in protein rebound, whatever the elimination rates are (pink region).*



Generalisation

Our analysis can also be applied to other models with moderator feedback, e.g with multiple compartments or different antibody-protein interactions. With all antibody variables in a vector $\mathbf{X}$ and R a protein related variable, consider models that can be written as:

$$\frac{d\mathbf{X}}{dt} = G_1(\mathbf{X}, R)$$
$$\frac{dR}{dt} = k_{\mathrm{out}}(R_0\,F - R) + g_2(\mathbf{X}, R)$$
$$\frac{dF}{dt} = \alpha(H(R) - F)$$

Assumptions

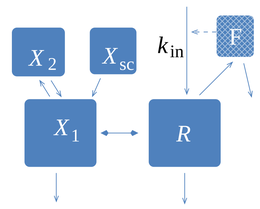
- There exist stable baseline state $(\mathbf{X}_0, R_0, 1)$.
- $\frac{\partial G_1}{\partial R}(\mathbf{X}_0, R_0) = 0 = \frac{\partial g_2}{\partial R}(\mathbf{X}_0, R_0)$.
- An inital dose $\mathbf{X}_1$ is given to the baseline state and $g_2(\mathbf{X}_1, R_0) < 0$.

Theorem 4 *There is an α_0 such that for all $0 < \alpha < \alpha_0$ there will be rebound.*

Application: An efficacy model for efalizumab

In [Ng et al, 2005], a more compartment model with feedback was developed to analyse the efficacy of efalizumab on patients with psoriasis:

$$\frac{dX_{\mathrm{sc}}}{dt} = -k_a X_{\mathrm{sc}},$$
$$\frac{dX_1}{dt} = -(k_{10} + k_{12})X_1 + k_{21}X_2 - \frac{V_{\mathrm{m}}X_1}{K_{\mathrm{mc}}V_{\mathrm{c}} + X_1} + F_{\mathrm{a}}k_{\mathrm{a}}X_{\mathrm{sc}},$$
$$\frac{dX_2}{dt} = k_{12}X_1 - k_{21}X_2,$$
$$\frac{dR}{dt} = k_{03\max}F - k_{30}R - \frac{V_{\mathrm{m2}}RX_1}{K_{\mathrm{mc}}V_{\mathrm{c}} + X_1},$$
$$\frac{dF}{dt} = k_{\mathrm{off}}\left[\left(\frac{K_{\mathrm{mc03}}}{K_{\mathrm{mc03}} + R}\right) - F\right],$$



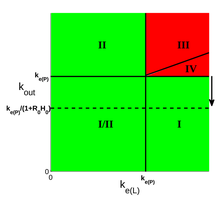
where $\mathbf{X} = (X_{\mathrm{sc}}, X_1, X_2)$ are the amounts of efalizumab in the depot, central and peripheral compartments respectively, R is the total %CD11a on the surface of each T cell and F is the production rate of %CD11a to the T cell surface.

Observation The feedback rate $\alpha = \frac{k_{\mathrm{off}}}{V_{\mathrm{m2}}} = 7.1 \times 10^{-4}$ is under $\alpha_0 = 8.9 \times 10^{-2}$, hence rebound can be expected and is observed in patients [Ng et al, 2005].

Conclusions and discussion

We have shown

- The basic TMDD model without feedback will lead to rebound if the elimination rates of the protein and antibody are faster than the elimination rate of the complex.
- If direct linear feedback is added to the basic TMDD model, then the rebound region will be enlarged to include some elimination rates of the protein that are smaller than the complex. No rebound can happen for elimination rates of the complex that are larger than the elimination rates of the drug.
- Slow feedback via a moderator will lead to rebound, whatever the eliminations rates are.



Open question Is it possible to have no rebound with fast feedback via a moderator?

References

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4. C.M. Ng, A. Joshi, R.L. Dedrick, M.V.Garovoy and R.J. Bauer, 2005. Pharmacokinetic-pharmacodynamic-efficacy analysis of efalizumab in patients with moderate to severe psoriasis. *Pharma. Res.*, **22**: 1088–1100.