Predicting rebound for mAbs using the TMDD model

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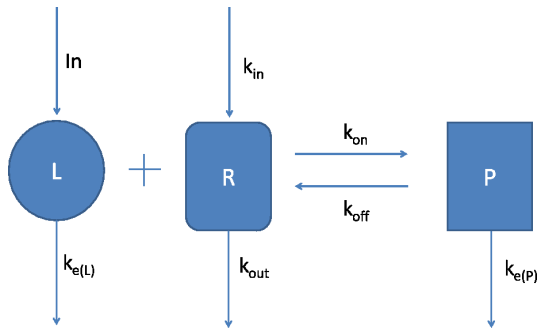
An interesting property of protein-therapeutic antibody interactions is the potential of the therapeutic antibody to change the distribution and clearance pathways of the target protein. This could, in turn, result in modified concentrations of the target protein in blood and in other organs. For example, binding and neutralisation of cytokines such as interleukins by blocking/neutralising antibodies causes an increase in the total levels of the cytokine [6]. This increase is due to the blockade of the clearance pathways for the cytokine - the large drug-target complex cannot be cleared through the kidneys and since the complex cannot bind to the target, target-mediated clearance is also impaired. This complexation process may also have other less well-understood consequences such as the potential for release of the target from the complex at a later time, and distribution of the target to tissues and organs due to the longer plasma half-life and potential release of target in the tissues.

The consequent increase of the antigen - "antigen rebound" - has been sparsely studied and only anecdotal reports exist in the literature. For example, rebound symptoms have been reported on cessation of anti-tumour necrosis factor (TNF) therapies [2] and a corresponding increase in TNF levels have been demonstrated to occur in patients [1]. Similarly, treatment with an anti-IL6 antibody has also been shown to increase total IL6 activity [4] and an increase in tumour size on cessation of VEGF treatment has also been reported [3]. Apart from the pharmacokinetic (PK) interaction described previously, there might be multiple other reasons for the rebound in target levels after cessation of treatment with an antibody - an increase in the production rate of the target antigen due to homeostatic feedback and residual bio-activity of the antibody-target complex magnified by the vastly higher levels of the complex are two apparent reasons.

The potential for PK interaction between the target protein and antibody to result in rebound in free antigen levels is only now being appreciated [8]. However, a systematic evaluation of the physiological conditions and target/antibody PKPD properties that could result in its occurrence is not yet available. Such analysis could be critical in designing antibody therapies that are unlikely to result in antigen rebound and, therefore, maximise the therapeutic potential of the target.



$$\frac{dL}{dt} = -k_{e(L)}L - k_{on}LR + k_{off}P \quad (1)$$

$$\frac{dR}{dt} = k_{in} - k_{out}R - k_{on}LR + k_{off}P \quad (2)$$

$$\frac{dP}{dt} = k_{on}LR - k_{off}P - k_{e(P)}P \quad (3)$$

Figure 1: The TMDD reaction mechanism.

We consider when a simple protein-antibody interaction results in rebound in protein levels in a target-

mediated drug disposition (TMDD) model, based on Levy [5] where the antibody (ligand) L binds reversibly with the protein (receptor) R to form a protein-antibody complex P as shown in Figure 1. The TMDD model assumes a mechanism-based reaction to explain the drug-target interaction. The parameters of the model are the binding rate constants k_{on} and k_{off}, the protein turnover and elimination rates k_{in} and k_{out}, and the elimination rates of the antibody and complex $k_{\text{e(L)}}$ and $k_{\text{e(P)}}$. The system is assumed to be initially at baseline state, into which single or multiple bolus infusions of the antibody are made (represented in Figure 1 by 'In'). The infusions decrease the free protein level, but after the injections are stopped, it goes up again and returns to its baseline value. By a mathematical analysis of the (L, R, P)-phase plane we show that, in this model, the presence or absence of rebound is fully determined by the elimination parameters.

Theorem 1 *In basic TMDD model (1)-(3), the free protein level R rebounds, i.e., increases to values above the baseline, if and only if if the elimination rate of the complex is slower than the elimination rate of both the antibody and the protein, i.e., $k_{\text{e(P)}} < k_{\text{e(L)}}$ and $k_{\text{e(P)}} < k_{\text{out}}$.*

Two typical illustrations of this theorem are depicted in Figure 2. On the left, the elimination rate of the complex is significantly slower than the elimination rate of both the antibody and the protein and the rebound of the protein levels to above its baseline (indicated by the red dashed line) can be observed. On the right, the elimination rate of the complex is larger than the elimination rate of both the antibody and the protein and the protein levels stay below baseline.

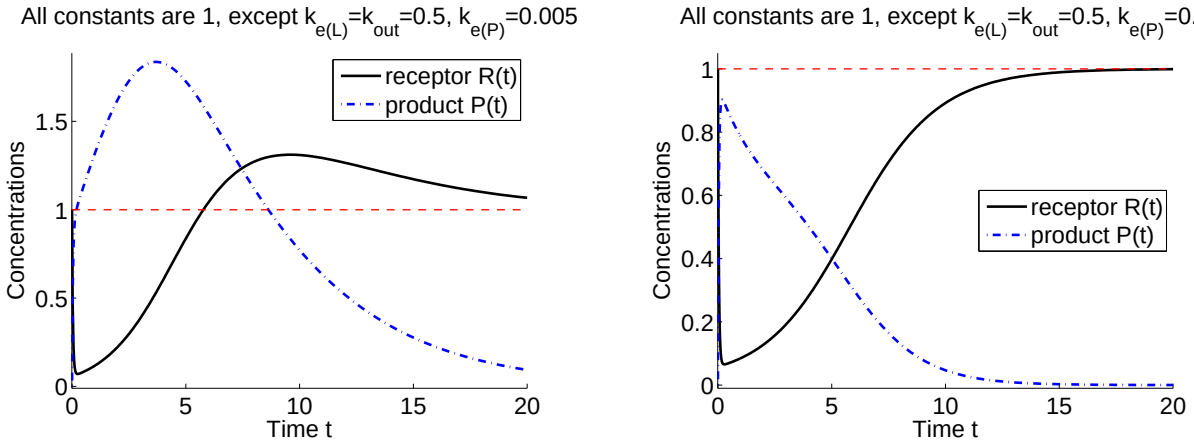


Figure 2: Time course of the protein (R) and complex (P) levels. On the left, $k_{\text{e(P)}} < k_{\text{e(L)}}$ and $k_{\text{e(P)}} < k_{\text{out}}$ and protein rebound occurs. On the right, $k_{\text{e(P)}} > k_{\text{e(L)}}$ and $k_{\text{e(P)}} > k_{\text{out}}$ and the protein levels stay below the baseline value.

Feedback in the production of the target protein is often quoted as a reason for protein rebound, so next we investigate how feedback influences rebound in the TMDD model. We model feedback by modifying the production term "k_{in}" to "$k_{\text{in}}\, F$", where F represents the feedback and it modelled by either

(F1) an algebraic term: $F = H(R)$, or

(F2) a dynamics process: $\dfrac{dF}{dt} = \alpha(H(R) - F)$.

The response function H is such that when the protein levels are reduced, the production rate increases and visa versa. Explicitly, H is a differentiable function with the property that $H(R_0) = 1$; $H(R) > 1$ when $0 \le R < R_0$; and $0 < H(R) < 1$ when $R > R_0$, where R_0 is the protein baseline value.

Such feedback mechanism is more likely to produce the rebound effect, however, the type of feedback strongly influences the rebound region:

- An algebraic feedback relation (F1) doesn't lead to rebound if no antibody is present; if the antibody is present, the rebound region will increase compared to the case without feedback, but there is still a large region when there is no rebound (including, but not restricted to the region where the elimination rate of the antibody is slower than the elimination rate of the protein). This result is obtained by a similar phase plane analysis as in the case without feedback.

- If the feedback is generated by a dynamic process (F2), then for any $\alpha > 0$ there is rebound in the protein levels if no anti-body is present, whatever the elimination rates are. If the anti-body is present, then the rebound depends on the responsiveness of the feedback. If it is slow to respond (α is small), then the presence of the anti-body can not prevent rebound. However, if the feedback responds very fast, then the presence of the anti-body can prevent rebound, depending on the elimination parameters, similar to the algebraic case. To show this transition, we use that if the dynamics process is very fast (α large), then the effect of the dynamics process is approximated by the algebraic term.

The result about the presence of rebound in systems with slow feedback can be generalised to TMDD type models with more compartments. This generalisation provides a context for the rebound observed in the treatment of patients with psoriasis using efalizumab [7] as the dynamic feedback mechanism in this model is very slow.

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