Introduction
Detailed mechanistic models for determining pharmacokinetics / pharmacodynamics (PKPD) could be particularly attractive in the area of monoclonal antibodies (mAbs), since these therapeutic agents have certain tractable properties which make them more amenable to translation across the preclinical–clinical interface than traditional small molecules (see Agoram et al., 2007).

Inspired by recent examples of how a rigorous mathematical analysis of these models was done to aid the understanding of complex pharmacological systems and provide tools to predict essential PKPD properties of mAbs (Mager and Krzyzanski; 2005, Peletier and Gabrielson, 2009; Krippendorf et al., 2009), we explored the behaviour of a target-mediated drug disposition (TMDD) model to address two questions relevant to mAb discovery:

• What is the relationship between the target affinity of the antibody and its in vivo potency?

• Could rebound (i.e. antigen levels in excess of pre-dose baseline levels) occur once antibody dosing has been stopped?

Model
The model consists of a drug (antibody) called Ligand (L) binding reversibly with a target (antigen) called the Receptor (R) to form the Receptor-Ligand Complex (P).

\[ \frac{dL}{dt} = -k_{on} R \cdot L + k_{off} P \]
\[ \frac{dR}{dt} = k_{off} P - k_{on} R \cdot L + k_{o} L \]
\[ \frac{dP}{dt} = k_{o} L - k_{off} P - k_{o} P \]

with the following initial conditions: \( L(0) = L_0, R(0) = R_0, P(0) = 0 \).

The model parameters include:

• Binding rate constants \( k_{on} \) and \( k_{off} \).

• Receptor synthesis and elimination rates \( k_{o} \) and \( k_{el} \).

• Elimination rates of the Ligand and complex, \( k_{o} \) and \( k_{el} \).

• Initial amounts of the Ligand \( L_0 \) and Receptor \( R_0 \).

\[ k_{on} = \frac{k_{off}}{k_{o} + k_{off}} \]

Parameter values for mAb case study (Agoram et al.2007) were used for simulation and only single iv bolus dosing was considered.

Measurement of in vivo Potency
The in vivo potency is measured by the lowest concentration of the free receptor reduction achieved with a particular drug dose.

At the minimum value of the receptor concentration, \( R_{min} = R_{in} \). Using this and an analysis of the fast and slow manifolds of the concentration profiles gives,

\[ R_{min} = \frac{K_{on} K_{off}}{K_{on} + K_{off}} \]

In vivo potency can thus be measured quantitatively by \( R_{min} \).

How Can the Potency be Increased?

In vivo potency can be increased by decreasing \( R_{min} \). From the above formula, this can be done by:

• Increasing \( K_{on} \)

• Decreasing \( K_{off} \)

• Obviously, increasing \( L \) improves the potency too.

Changing \( k_{on} \) and \( k_{off} \) is equivalent to decreasing the equilibrium dissociation constant, \( K_{d} = \frac{k_{off}}{k_{on}} \).

The next question was whether changes in \( k_{on} \) and \( k_{off} \) manifest themselves in an inversely proportional manner.

Note: \( k_{on} \) and \( k_{off} \) are intrinsic properties of the system. They cannot be influenced!

Conclusions
• A mathematical analysis of the TMDD model can be used to address common issues that occur in monoclonal antibody drug discovery and development programs.

• Using this mathematical analysis in the IgE case study, it was shown that the in vivo potency of the drug can be enhanced most effectively by increasing the \( K_{d} \) (affinity constants) property of the Ligand.

• The unique condition for Receptor level to exceed the baseline concentration after stopping the Ligand administration was also found \( (K_{on}) > k_{off} \).

Future Work
Similar analysis of the TMDD model with additional mechanism such as feedback and internalisation of the complex will be done. It will also be extended to include multiple compartments.

References

Rebound
A situation whereby the Receptor (antigen) level exceeds the baseline concentration once the dosing is stopped (rebound) was investigated with the TMDD model by linearising the model about the steady state. Feedback mechanism such as internalisation of the complex are usually the source of rebound. However, without this source, the eigenvalues and the corresponding eigenvectors were determined to see the approximate solution around the steady state.

From the trajectories of the eigenvectors obtained, it was found that rebound can only occur when:

\[ k_{on} > k_{off} \]

That is, the elimination of the Ligand is greater than the elimination of the Complex. Following this result, the TMDD model was simulated with new values of parameters such that \( k_{on} > k_{off} \).

Note: Rebound: receptor concentration is seen to exceed the baseline.

The qualitative relationship between the magnitude of the rebound and the various system and drug parameters remains to be investigated.

Saturation Effect
Conditions that lead to a drug-agent complex excess of receptor level occur once the drug is dosed. These results show that a drug-discovery strategy that would increase \( K_{d} \) may be more effective than one focussed on decreasing \( k_{off} \) or simply \( K_{d} \).

Results

• Variation of \( R_{min} \) with \( k_{on} \) and \( k_{off} \) is shown below.

• With the values of the parameters of the IgE case, \( R_{min} = 0.574\text{mM} \) was achieved.

• Doubling \( k_{on} \) gives a new value of \( R_{min} = 0.299\text{mM} \) and halving \( k_{off} \) gives a new value of \( R_{min} = 0.424\text{mM} \).

• Clearly doubling \( k_{on} \) has had a much greater effect than halving \( k_{off} \), even though both have the effect of halving \( K_{d} = \frac{k_{off}}{k_{on}} \).