

Target-mediated drug disposition of monoclonal antibody binding to plasma soluble target

Some insights from PBPK/PD and popPK/PD approaches

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Introduction

Target-mediated drug disposition (TMDD) models play an important role in elucidating non-linear pharmacokinetics (PK) of monoclonal antibodies (mAbs), incorporating complexities arising from processes such as non-specific clearance, target turnover, target binding and target-drug internalization giving rise to non-linear and dose-dependent PK of mAbs [1,2,3]. When mAb targets soluble proteins, the formation of circulating Ab-target complexes introduces a challenge in characterizing kinetics and dynamics of both free Ab and target molecules. In some cases, no assays are available to measure free drug and target, further complicating the interpretation of the PK. This becomes even more relevant, when elimination characteristics of drug-target complexes masks the PK of free Ab. We developed a physiologically based pharmacokinetic (PBPK) model for a plasma soluble target to perform a simulation study to characterize and understand the drivers of non-linear PK and pharmacodynamics (PD) behaviors. Learnings from a mechanistic and bottom-up approach like PBPK were used to generate structural models and parameter ranges for PopPK/PD models which in turn provide mechanistic insights.

Methods

Modeling and simulation for PBPK model were performed with PK-Sim, MoBi and opsuite-R package belonging to Open Systems Pharmacology available as freeware under the GPLv2 License [4] and the adult model was built according to Kuepfer et al. [5]. The PBPK model included binding to the plasma soluble target with single binding site. Target turnover (target synthesis and degradation) was also considered. We investigated two scenarios: 1) mAb can bind to a single target generating 1-to-1 complex and 2) mAb can bind to two targets in a two-step fashion generating 1-to-1 and 1-to-2 complexes. The target, Ab and complexes are allowed to distribute in plasma and interstitial spaces with different volume of distribution due to different molecular weights. The Ab and complexes are eliminated via endosomal clearance and protected from endosomal clearance by FcRn mediated recycling [6]. Clearance differences of complexes in comparison to Ab were considered.

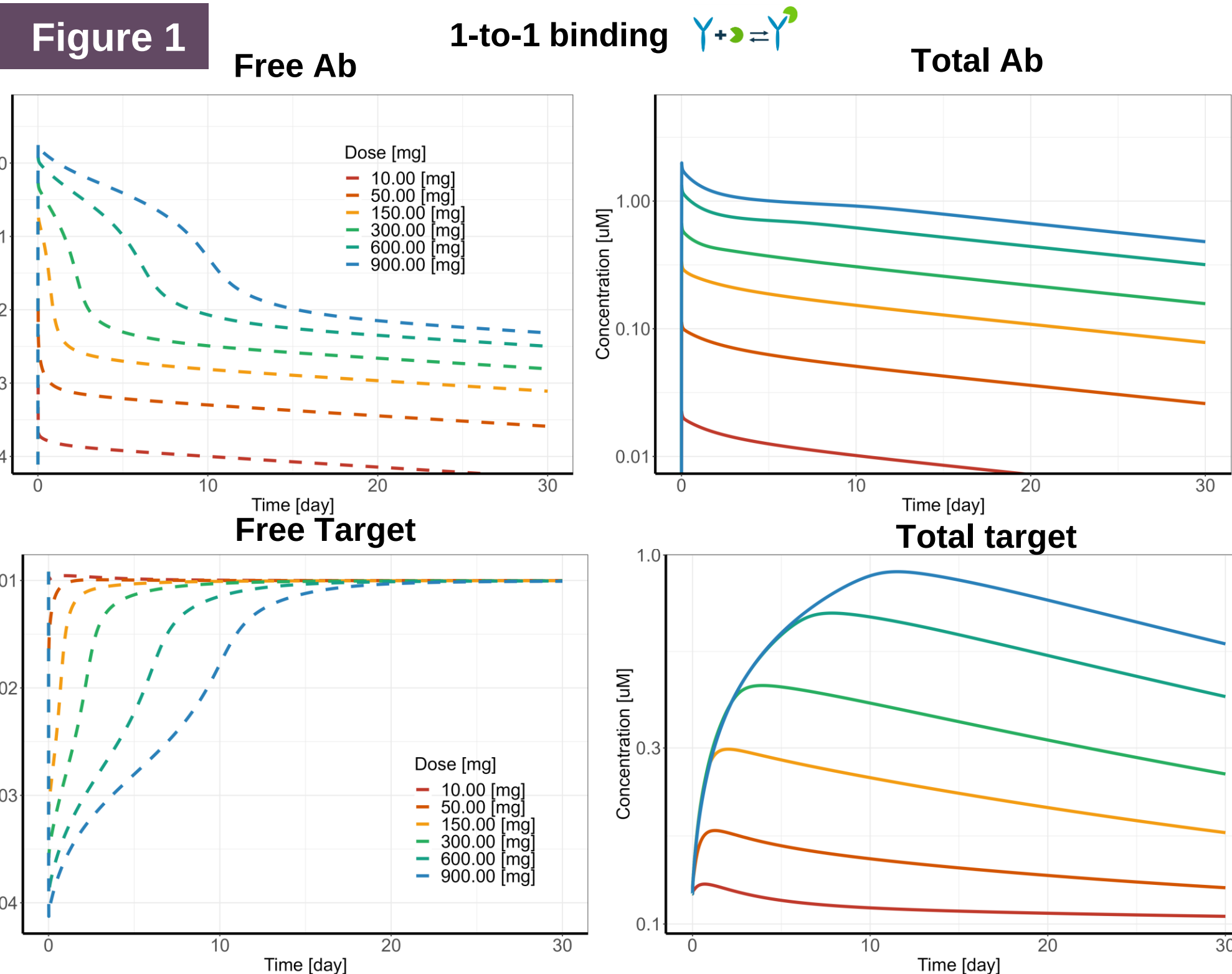


Figure 1 Time profiles of various species circulating in plasma for 1-to-1 binding for different antibody doses: Upper left, upper right, lower left and lower right depict time profiles for free antibody, total antibody, free target and total target respectively. Total antibody is a sum of free antibody and 1-to-1 complex, whereas total target is a sum of free target and 1-to-1 complex.

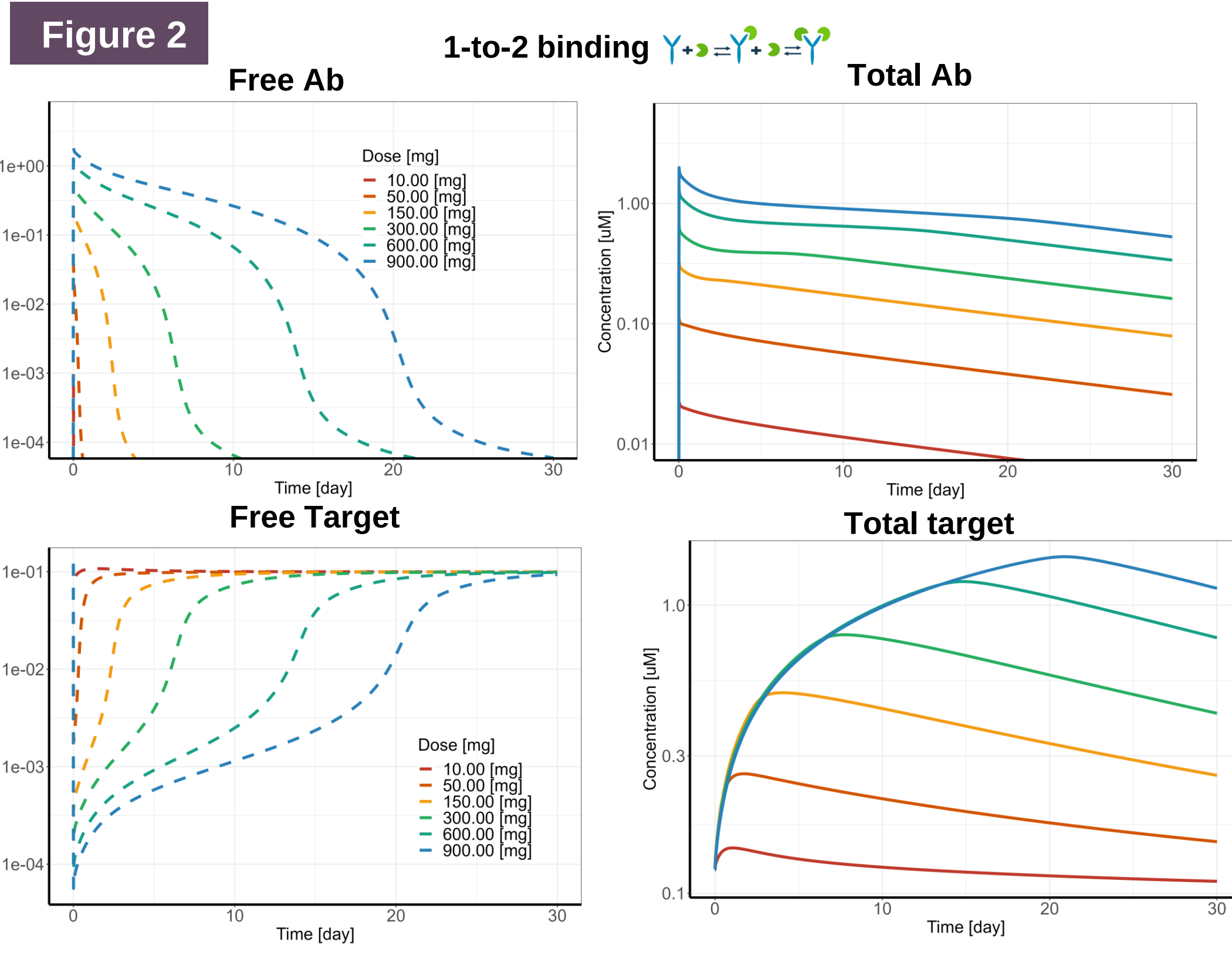


Figure 2 Time profiles of various species circulating in plasma for 1-to-2 binding for different antibody doses: Upper left, upper right, lower left and lower right depicts time profiles for free antibody, total antibody, free target and total target respectively. Total antibody is a sum of free antibody, 1-to-2 and 1-to-1 complexes, whereas total target is a sum of free target and 1-to-1 and 2 times 1-to-2 complexes.

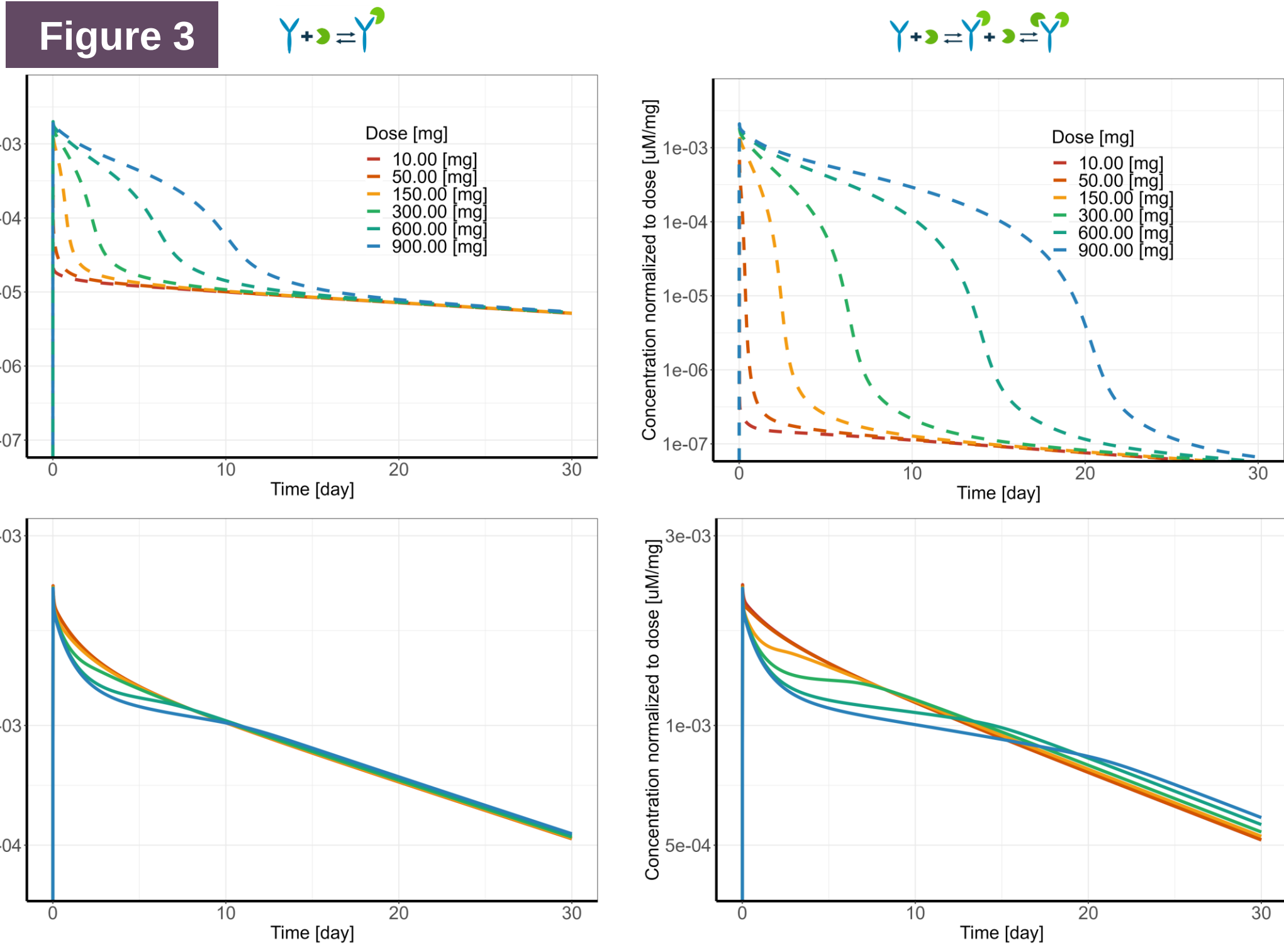


Figure 3 Dose normalised time profiles of free and total antibody for 1-to-1 and 1-to-2 binding: Upper left and lower left panel depict free and total antibody time profile respectively. Upper right and lower right panels depict free and total antibody time profile respectively.

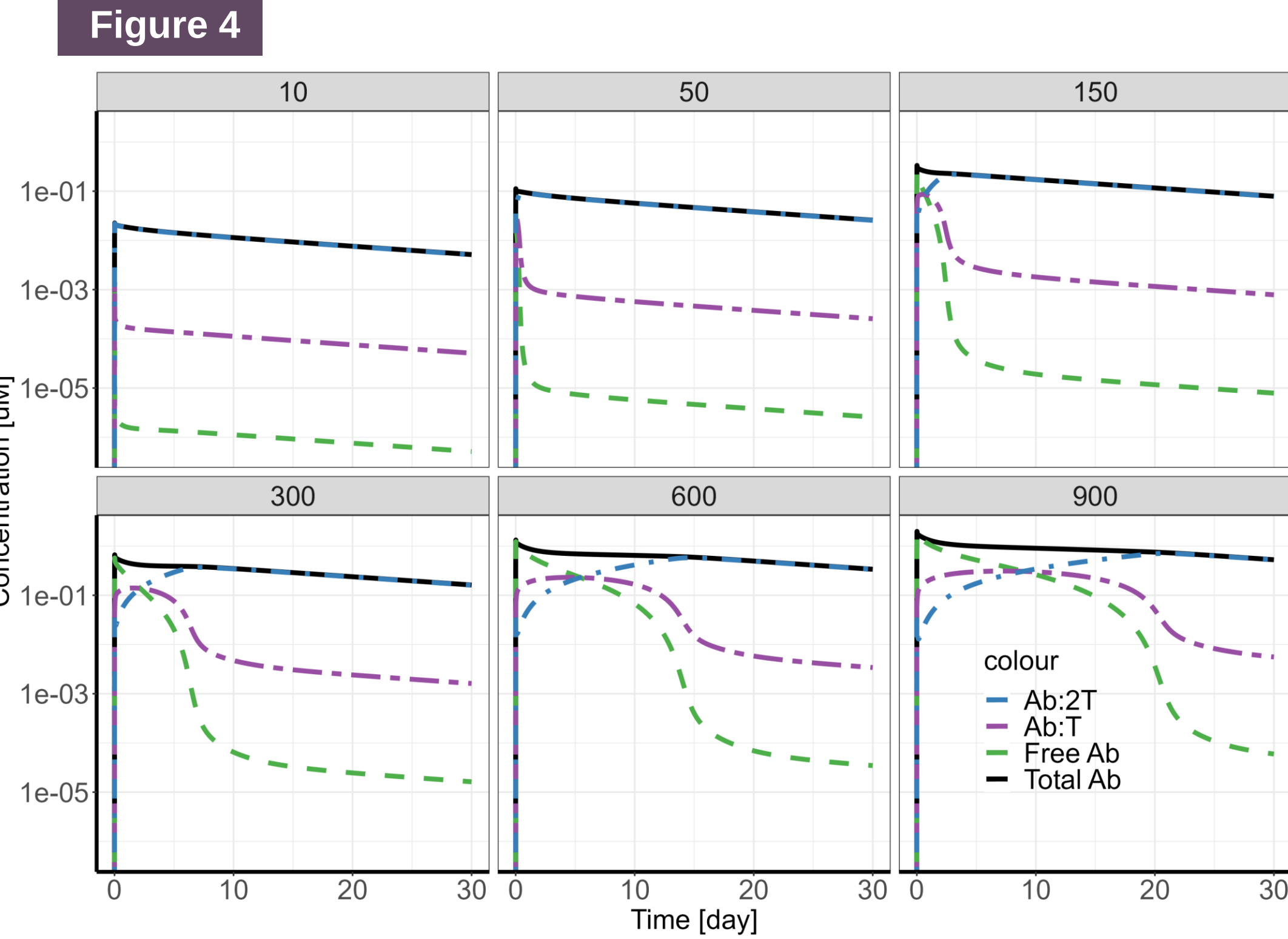


Figure 4 Breakdown of total Ab time profiles into free, 1-to-1 and 1-to-2 complexes considering 1-to-2 binding for different doses. Black line represents the total Ab time profile for a dose, whereas green, purple and blue lines represent corresponding free, 1-to-1 and 1-to-2 complexes time profile respectively.

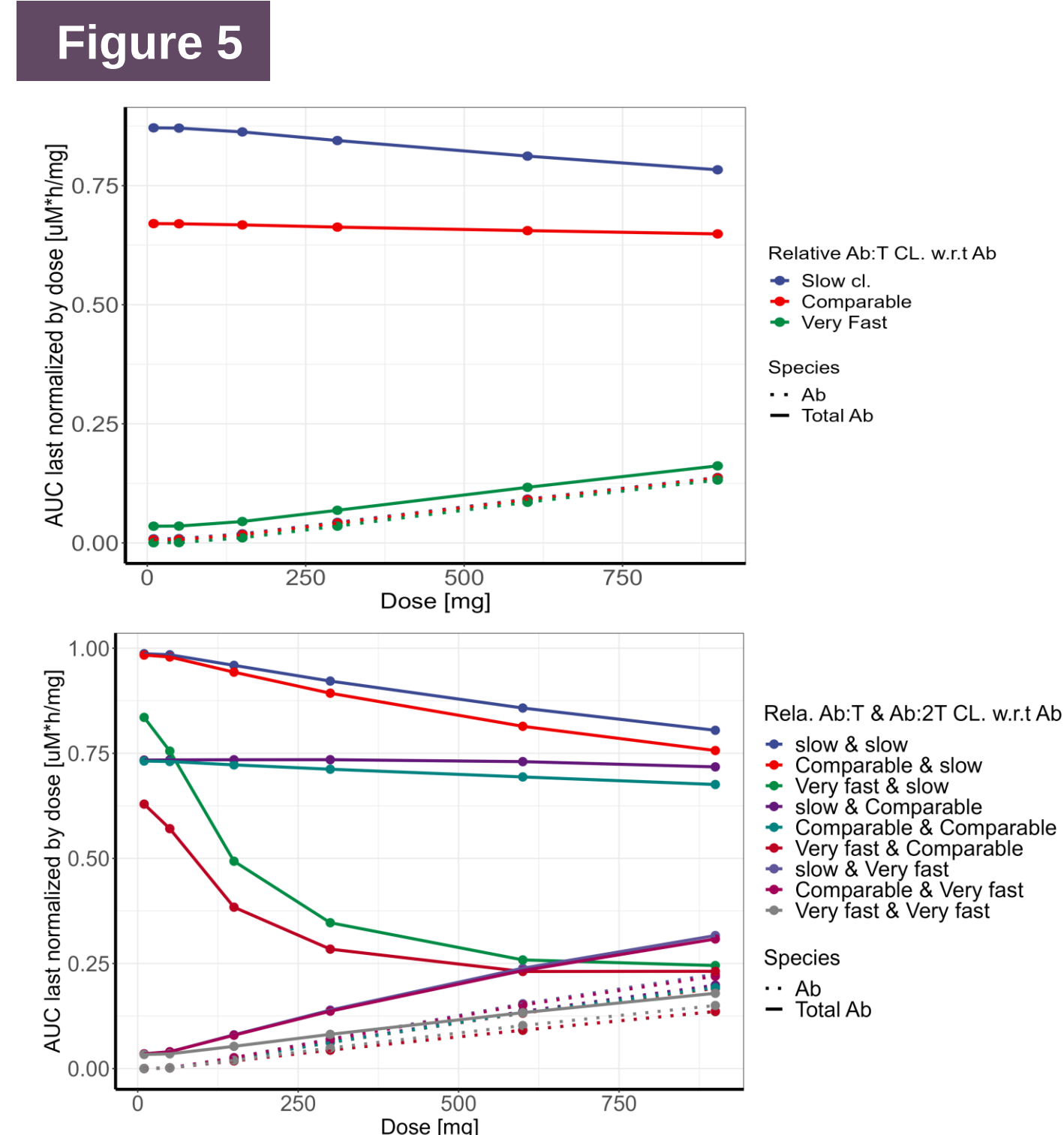


Figure 5 AUC last normalized by dose for 1-to-1 and 1-to-2 binding considering various clearance scenarios for complex: Upper and lower panel belong to 1-to-2 binding respectively.

Results

PK of mAbs for membrane bound target can indicate the duration and extend of target saturation, however, PK of total mAbs for plasma soluble targets can lead to misinterpretation. Unlike time profiles of free antibody which can show up to four different phases due to TMDD leading to dose over-proportional increase in AUC last, the time profile of total antibody depending on the possible stoichiometry, difference of volume of distribution, binding affinity and clearance of complexes relative to free antibody can mask underlying TMDD and display dose dependent non-linearity not readily associated with TMDD. In case of complexes having relatively smaller volume of distribution and comparable clearance relative to antibody, increasing doses can produce mono- or biphasic time profile for lower doses which transitions to multiphasic time profile for higher with a pronounced shouldering. These non-linearity of total antibody time profile can be strengthened or weakened for e.g. due to different clearance of complexes.

Conclusions

For mAb targeting plasma soluble proteins, masking of underlying TMDD by different complexes can lead to misinterpretation. Building PopPK/PD model is particularly challenging in absence of free target and antibody time profiles and benefit from mechanistic and bottom-up approach from PBPK to generate structural models, generate hypothesis and identify drivers of PK and PD.

References

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