

Target-mediated drug disposition for soluble targets: what can we trust in early feasibility simulations?

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Abstract

Target-mediated drug disposition (TMDD) models are widely used to describe the pharmacokinetics of monoclonal antibodies, target engagement, and free target suppression^{2,3}. For antibodies directed against soluble targets, these models are also used in early discovery to assess target tractability, required affinity, and feasible dose regimens^{1,4,5}. However, early feasibility simulations often rely on uncertain biological parameters, including baseline target concentration, target turnover, binding affinity, and the elimination or internalization rate of the drug-target complex. This work synthesized reported TMDD parameter values for antibodies against soluble targets and evaluated how assay sensitivity and common model assumptions influence parameter estimation and biological inference¹.

Background

Soluble ligands, including cytokines, chemokines, growth factors, enzymes, and extracellular signaling proteins, are an important class of therapeutic targets for monoclonal antibodies¹. Antibody binding can alter both antibody disposition and the apparent kinetics of the target⁴. TMDD models are therefore useful because they connect antibody pharmacokinetics, target binding, target turnover, drug-target complex elimination, and free target suppression within a single mechanistic framework^{2,3}. However, early feasibility simulations are often performed before rich clinical or nonclinical target data are available. As a result, key parameters must be assumed, including baseline target concentration, target degradation, binding affinity, and complex elimination^{1,5}. For soluble targets, this is especially challenging because baseline concentrations are often low, sometimes close to or below assay LLOQ. Loss of low-concentration target data can limit information on the true baseline and the late recovery phase after target engagement^{1,6}. One particularly important uncertainty is the internalization or elimination rate of the drug-target complex, k_{int} . Although k_{int} is often fixed to the antibody elimination rate, published case studies show that this assumption is not always valid¹. Since total target accumulation and free target suppression are strongly influenced by k_{int} , incorrect assumptions can bias estimates of in vivo affinity and lead to misleading target-engagement predictions¹.

Methods

Published case studies of monoclonal antibodies directed against soluble targets were reviewed to extract TMDD-relevant parameters, including baseline target concentration, target degradation rate, complex internalization or elimination rate, binding affinity, antibody clearance, and antibody half-life¹. Extracted parameters were explored graphically to assess whether simple biological descriptors could support early feasibility assumptions. Relationships of particular interest included target molecular weight versus target half-life, baseline target concentration, and complex internalization rate^{1,5}. A full two-compartment TMDD model with subcutaneous absorption was then used to generate synthetic concentration-time data. The model included antibody distribution, linear antibody clearance, reversible target binding, endogenous target synthesis and degradation, and elimination of the drug-target complex^{1,3}. Simulated observations included total antibody and total target concentrations, reflecting assay outputs commonly used for quantitative interpretation of soluble-target TMDD systems^{1,6}. The dataset included four dose groups, three replicate subjects per dose group, rich sampling from 0 to 32 days, and proportional residual error. The synthetic data were refitted under three main scenarios: all parameters estimated, progressive truncation of total target data to mimic increasing assay LLOQ, and fixed k_{int} where the true data-generating value differed from the assumed antibody elimination rate¹.

Results

TMDD modeling reports were identified for 14 soluble targets. Baseline target concentrations were typically low, often in the pM range, but varied widely across targets, disease settings, and assay contexts¹. The literature-derived parameter landscape is summarized in Figure 1. Target molecular weight provided partial information for target half-life, but did not reliably predict baseline target concentration or complex internalization, k_{int} ^{1,5}. Thus, simple biological descriptors may support early assumptions for k_{deg} , but not for all key TMDD parameters. Across reported examples, complex elimination was often similar to antibody elimination, although important deviations were observed. Therefore, fixing $k_{\text{int}} = k_{\text{el}}$ may be useful as a pragmatic starting point, but should not be interpreted as a biological rule¹. In simulations, increasing total-target LLOQ reduced informative target data and biased recovery of R_0 and k_D , as shown in Figure 2. This indicates that assay sensitivity can directly affect apparent target baseline and in vivo affinity estimates. Fixing k_{int} incorrectly led to compensatory changes in estimated affinity, while antibody clearance and absorption remained comparatively stable¹. The fitted profiles in Figure 3 illustrate that antibody PK can remain visually acceptable even when total-target behavior and inferred affinity are biased. Together, these results show that acceptable antibody PK fits may still mask biased inference for target accumulation, in vivo affinity, and free target suppression¹.

Discussion and practical recommendations

Soluble-target TMDD models can support early feasibility assessment, affinity requirements, and translational dose selection, but their outputs are sensitive to target baseline and assay performance^{1,5,6}.

Practical message: a good antibody PK fit does not necessarily imply reliable target-engagement inference¹.

- Use literature-derived or molecular-weight-informed k_{deg} values as starting points, not fixed truths.
- Do not fix $k_{\text{int}} = k_{\text{el}}$ without sensitivity analysis.
- Prioritize total-target assays with LLOQ below expected baseline where possible.
- Treat in vivo k_D estimates cautiously when target data are truncated.
- Interpret antibody PK fits together with target profiles, not in isolation.

References

- Nasim A, Fairman D, Nixon E, Jagdale P, Cui Z, Mohan K, Yates JWT. TMDD modeling for antibodies directed against soluble targets: parameter values for de novo modeling and simulation from experimental data. *Clin Pharmacol Ther*. 2026;119:1440–1459.
- Gibiansky L, Gibiansky E, Kakkar T, Ma P. Approximations of the target-mediated drug disposition model and identifiability of model parameters. *J Pharmacokinet Pharmacodyn*. 2008;35:573–591.
- Dua P, Hawkins E, van der Graaf PH. A tutorial on target-mediated drug disposition models. *CPT Pharmacometrics Syst Pharmacol*. 2015;4:324–337.
- David JP, Hansen RJ. Properties of a general PK/PD model of antibody-ligand interactions for therapeutic antibodies that bind to soluble endogenous targets. *mAbs*. 2010;2:576–588.
- Muliaditan M, Sepp A. Application of quantitative protein mass spectrometric data in the early predictive analysis of target engagement by monoclonal antibodies. *Clin Transl Sci*. 2022;15:1634–1643.
- Fairman D, Tang H. Best practices in mAb and soluble target assay selection for quantitative modelling and qualitative interpretation. *AAPS J*. 2023.

Figures

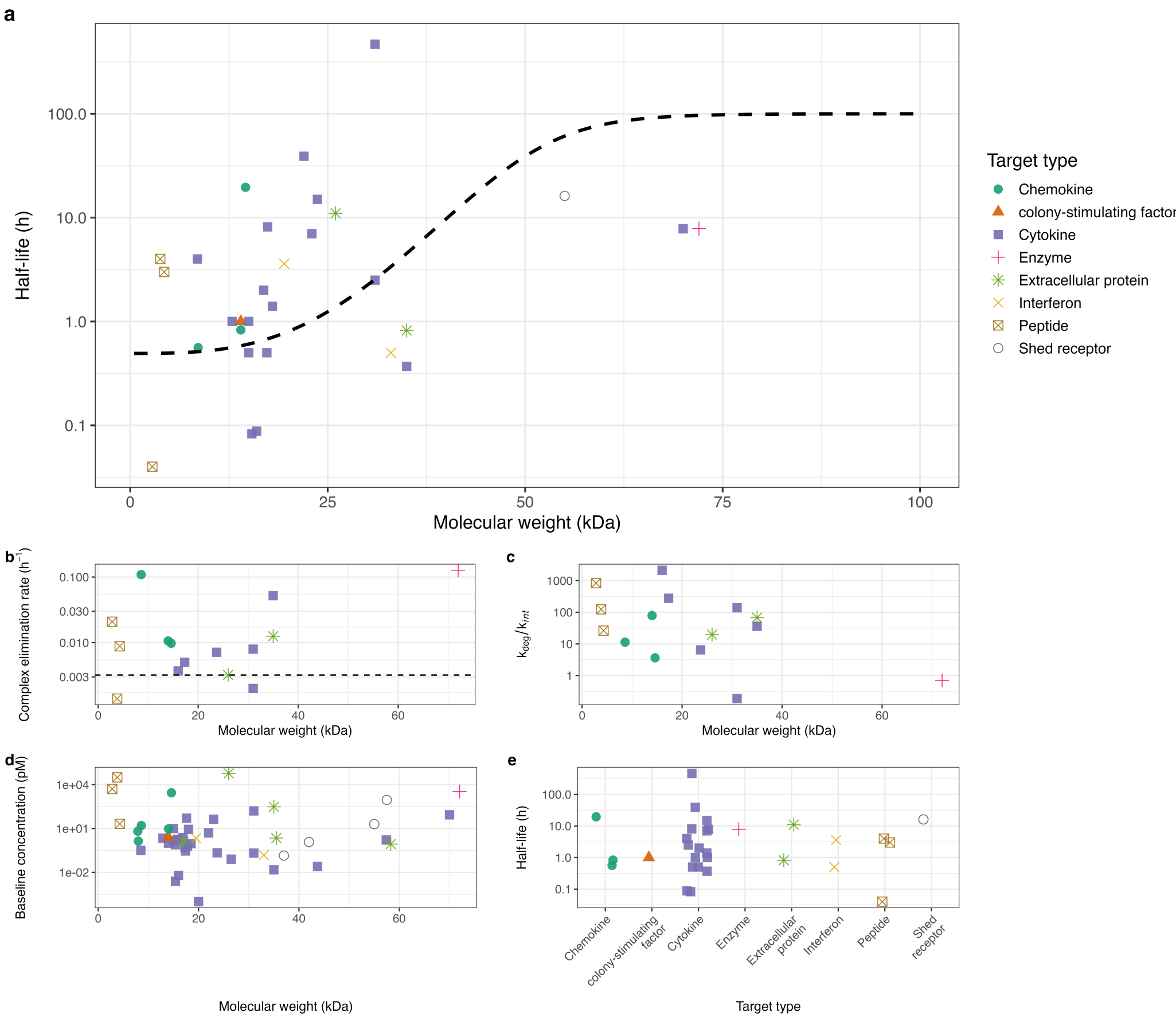


Figure 1. Literature-derived soluble-target TMDD parameter landscape. Reported soluble-target TMDD parameters span wide ranges across targets and target classes. Molecular weight provides partial information for target half-life, but does not reliably predict complex internalization, $k_{\text{deg}}/k_{\text{int}}$, or baseline target concentration.

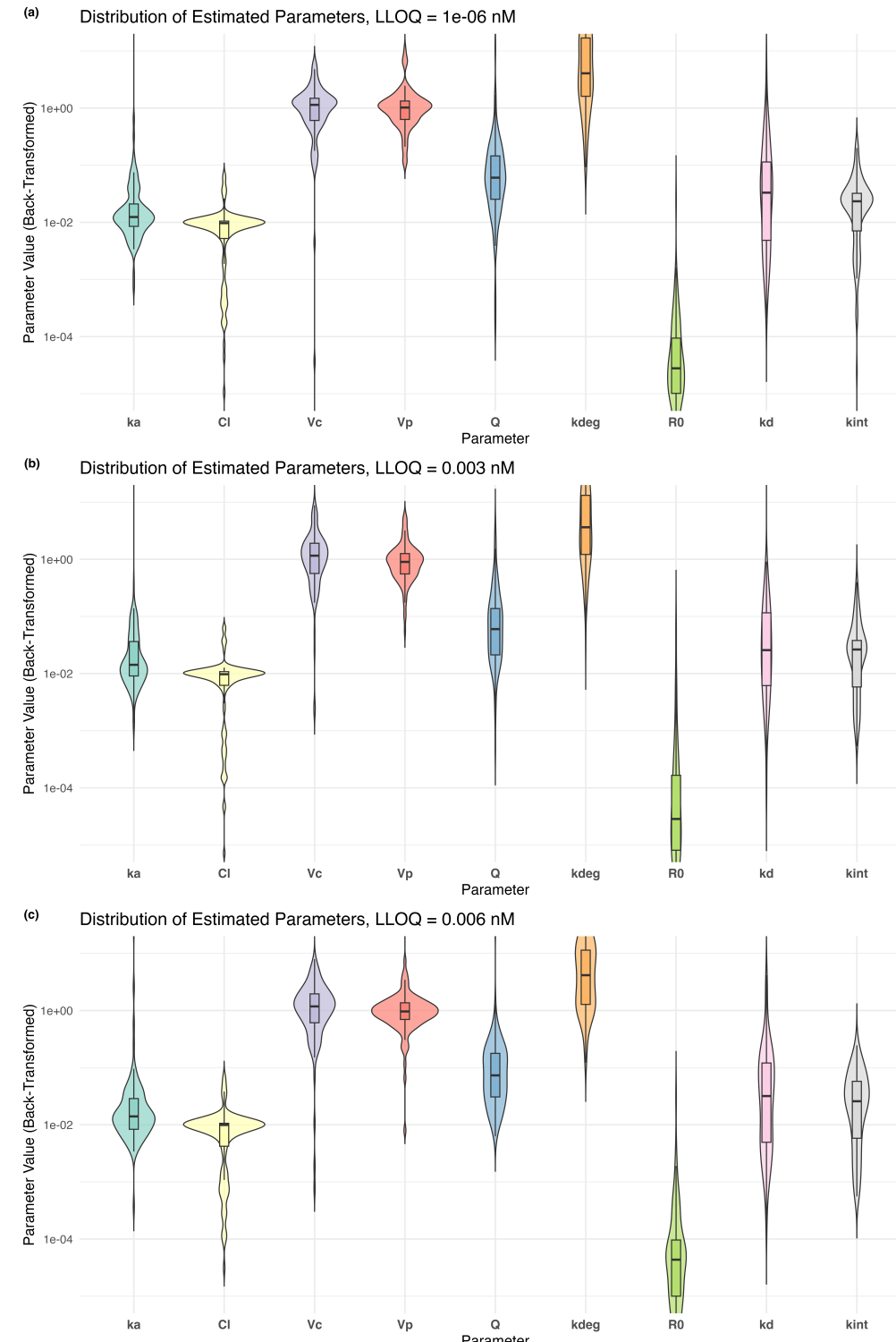


Figure 2. Impact of total-target assay LLOQ on parameter recovery. Increasing total-target LLOQ removes informative low-concentration total target data and increases bias and variability in recovered TMDD parameters, particularly R_0 and k_D .

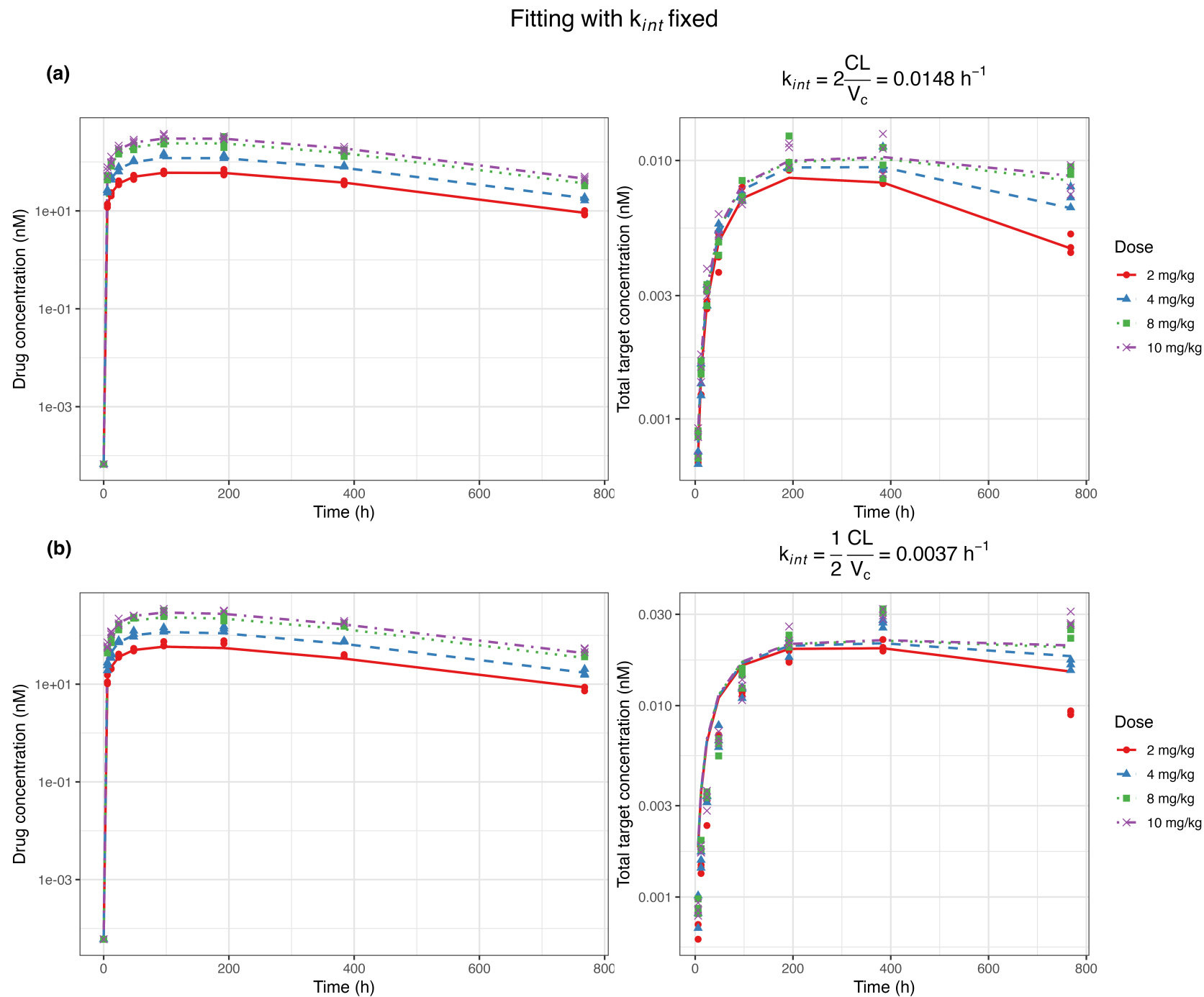


Figure 3. Consequence of fixing k_{int} incorrectly. When true complex internalization differs from the fixed model value, antibody PK may remain visually acceptable while total-target fits and inferred affinity are biased.



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