

Model-based reproduction of receptor-targeting antibody pharmacodynamics allows to identify ligand turnover parameters

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Introduction

- Early biologics discovery is hampered by the scarcity of data on novel targets, particularly when target-mediated drug disposition is expected to affect clinical pharmacokinetics (PK), delaying dose-to-man predictions.
- Binding kinetics for the novel target and its receptor in signalling pathways may be available before phase 1 studies.
- We propose using binding kinetics data early to model ligand and receptor turnover, which would accelerate drug discovery and guide preclinical studies.
- The model can be augmented to account for soluble receptor and downstream ligand-receptor interactions.

Methods

- A two-compartment model was used to describe antibody PK, with target-mediated clearance parametrized by association and dissociation rates (based on surface plasmon resonance measurements).
- An ordinary differential equations-based model that accounts for synthesis and degradation of ligand, membrane-bound receptor and soluble-bound receptor was successfully developed in MATLAB R2023b.
- The model was calibrated based on a synthetic dataset comprised of receptor-targeting antibody concentration, receptor occupancy, total ligand concentration and total soluble receptor concentration.
- Parameter estimations were run for N = 100 individuals with body weights and synthesis rates sampled from independent lognormal distributions, and intercompartmental and elimination clearances were scaled allometrically with body weight (exponent 0.9).

Results

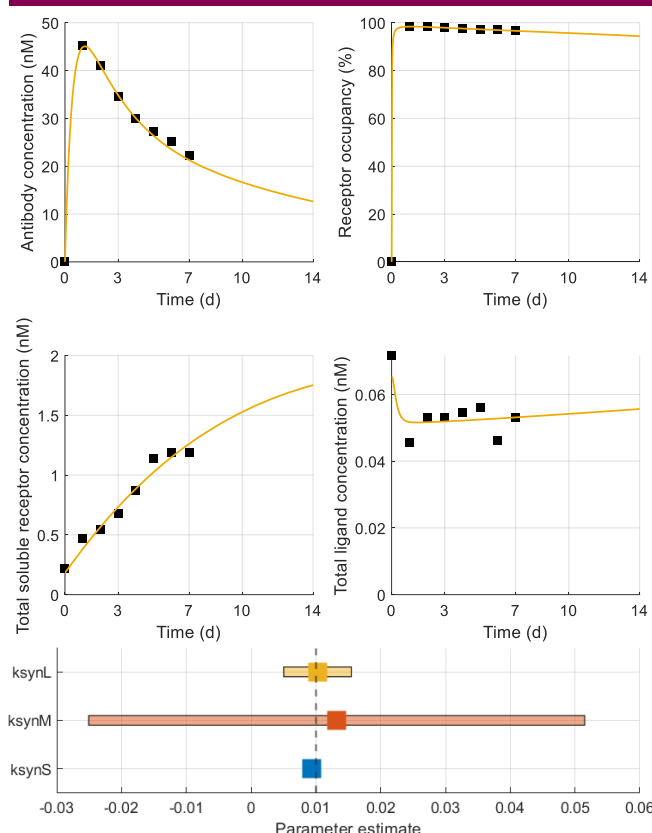


Figure 2. Example of a fit to a synthetic dataset

A simulation based on the point estimates of three synthesis rates is overlaid on top of the example dataset. Each point in the dataset was generated from a distinct random individual to mimic the preclinical studies. The point estimates of synthesis rates were 0.0094; 0.0132; 0.0103 nM/h with coefficients of variation (CV) of 1.62%, 148% and 26.0%. In the bottom panel, point estimates and 95% confidence intervals are shown against the ground truth values.

Model parameter	ksynS	ksynM	ksynL
Ground truth value (nM/h)	0.01	0.01	0.01
CV from parameter estimation with no inter-individual variability (%)	0.0036	0.17	0.058
Median CV across 1000 simulations with 0.1 inter-individual variability on body weight and synthesis rates	1.84	144.6	31.1

Estimates of the synthesis rates are useful to predict the PKPD of a potential ligand-targeting antibody before any *in vivo* data.

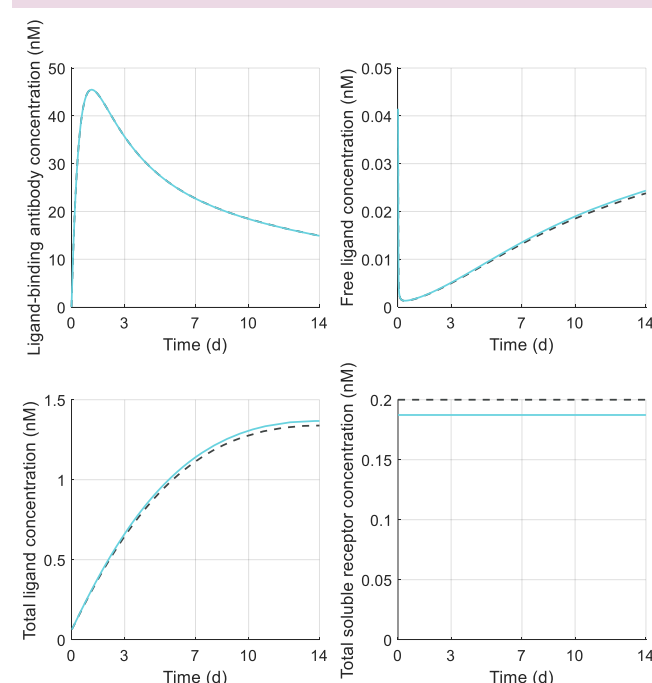


Figure 3. Predicted ligand turnover based on estimated synthesis rates and ground truth simulations. Dashed line shows the ground truth simulation with synthesis rates of 0.01 nM/h.

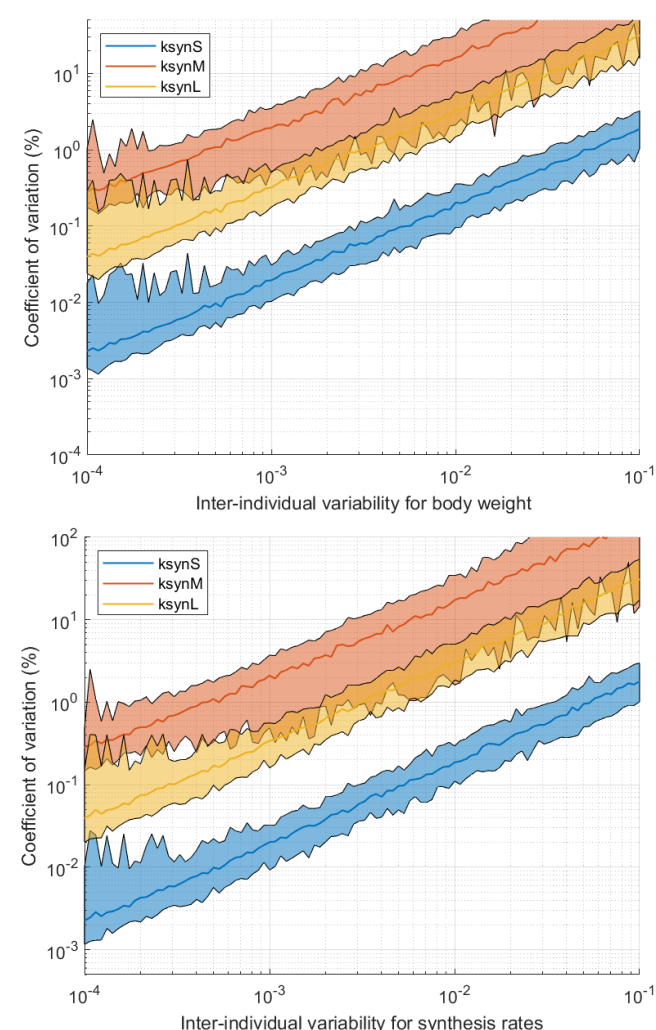


Figure 4. CV from parameter estimates with different values of inter-individual variability. For N = 100 individuals, 5% and 95% quantiles are plotted.

Conclusions

- Model-based simulations of ligand turnover, suppression, and accumulation can serve as an early-stage guideline for target validation, antibody engineering, or preclinical study design.
- Model-based approach can be useful to extract baseline free ligand concentration and baseline free receptor concentration values that would otherwise be obscured.
- For ligands that have soluble receptors acting as a potential drug sink, this approach allows one to identify baseline free soluble receptor concentration separately.
- Better parameter estimates can come from more frequent sampling, from data on additional downstream protein ligands and receptors that form the same signalling pathway, and from data on changes in protein ligand concentrations caused by disease progression.
- Modelling ligand concentration changes under antibody treatment can be used as a guide for disease-modifying properties of a drug and for dose setting in preclinical and clinical studies.

References

1. Betts A, Keunecke A, van Steeg TJ, van der Graaf PH, Avery LB, Jones H, Berkhout J. Linear pharmacokinetic parameters for monoclonal antibodies are similar within a species and across different pharmacological targets: A comparison between human, cynomolgus monkey and hFcRn Tg32 transgenic mouse using a population-modeling approach. *MAbs*. 2018 Jul;10(5):751-764. doi: 10.1080/19420862.2018.1462429. Epub 2018 May 14. PMID: 29634430; PMCID: PMC6150614.
2. Hearty S, Leonard P, O'Kennedy R. Measuring antibody-antigen binding kinetics using surface plasmon resonance. *Methods Mol Biol*. 2012;907:411-42. doi: 10.1007/978-1-61779-974-7_24. PMID: 22907366.

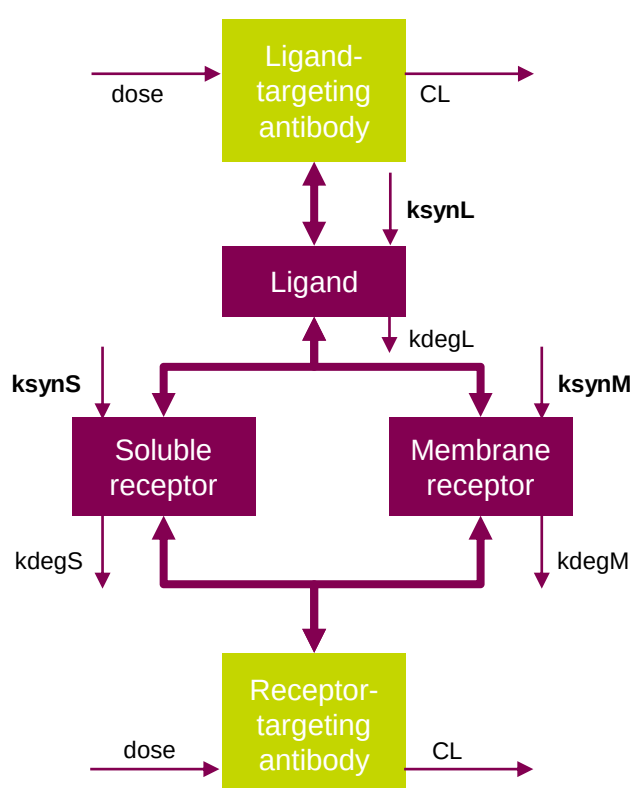


Figure 1. Model scheme

The model accounts for the binding between the ligand and the receptor, between the ligand and its antibody, and between the receptor and its antibody. The synthesis rates for the ligand (ksynL), the soluble receptor (ksynS) and the membrane-bound receptor (ksynM) are optimized during the model calibration.

