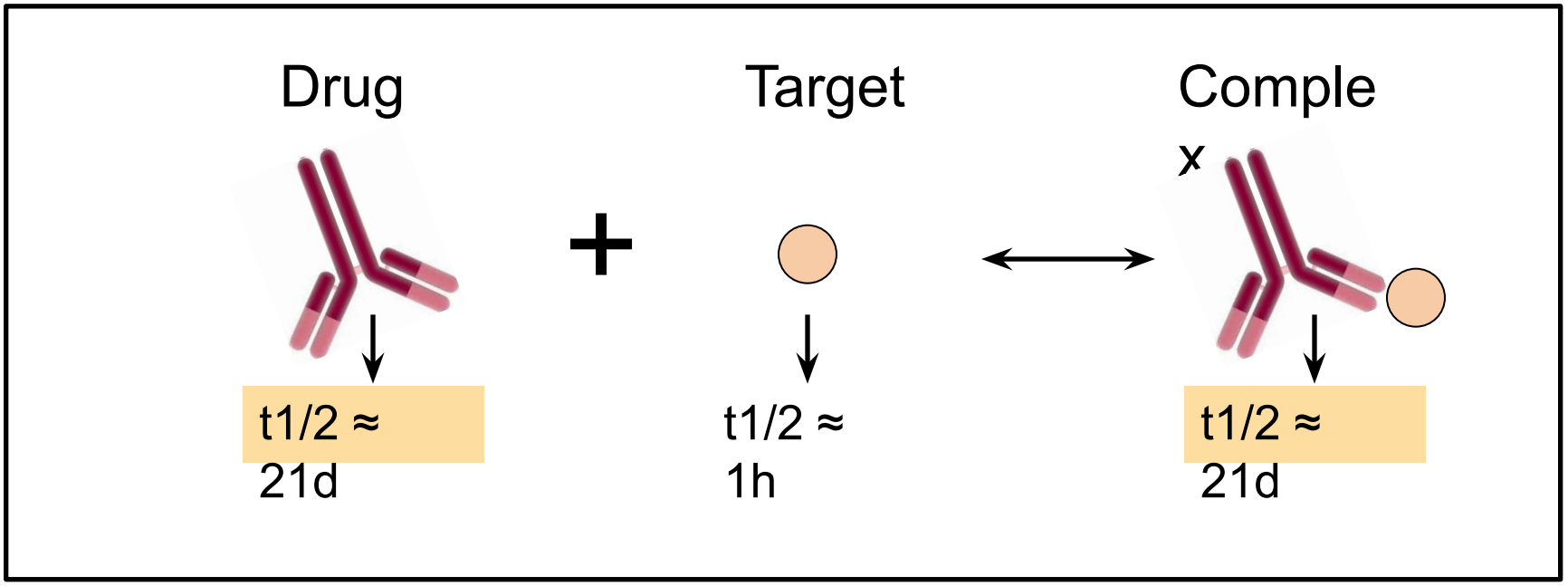

Assessing the Identifiability of Models for Monoclonal Antibody Target Mediated Drug Disposition Using a New Metric of Potency

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Pharmacometrics, Novartis - July 13, 2016

NOVARTIS

Overview

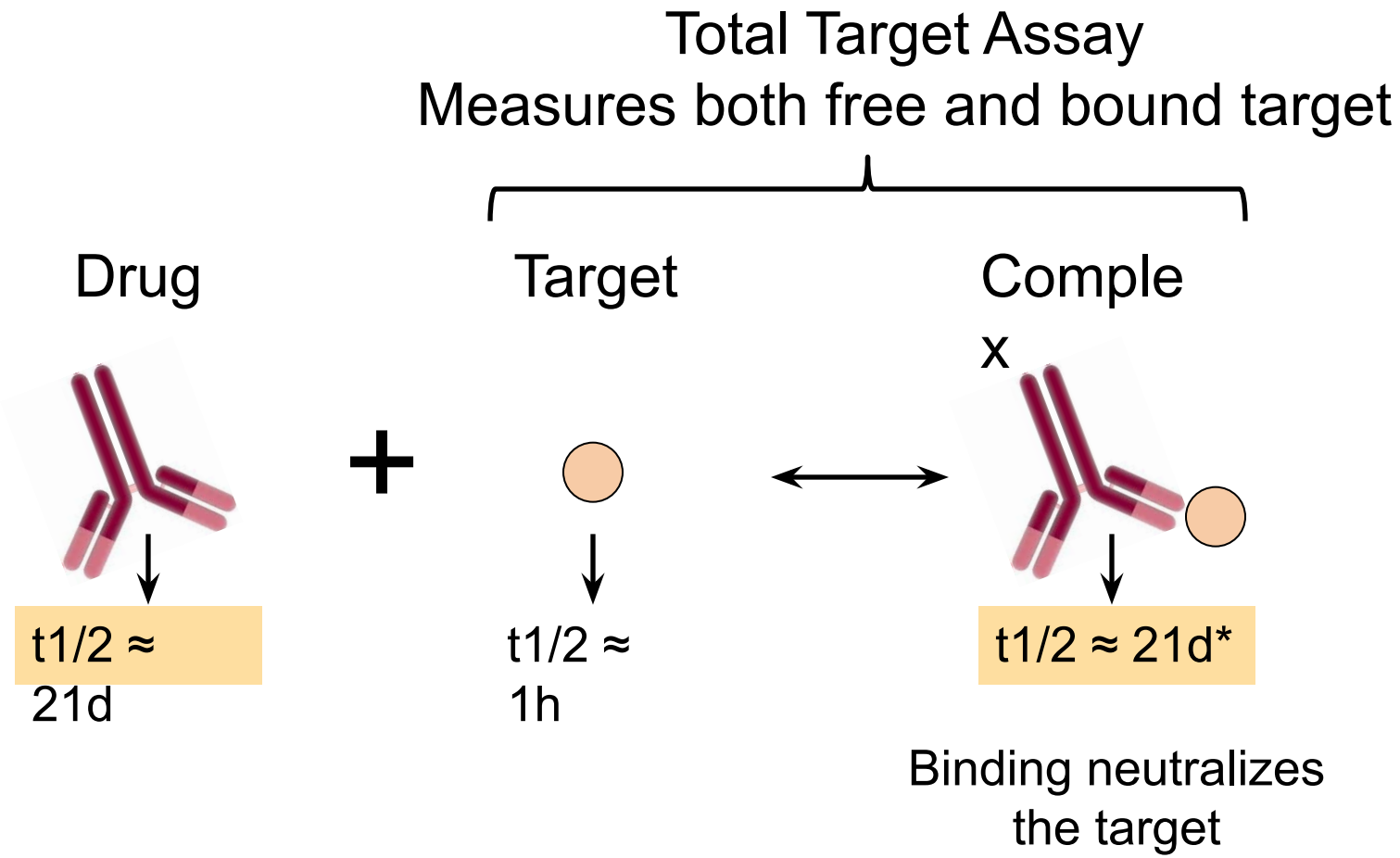
- Introduction to monoclonal antibody drugs.
- Present model for describing kinetics of monoclonal antibody drug and its target
- Analyze mathematical model to
  - 1) Identify nondimensional potency factor for target inhibition

$$\frac{\text{Free Target}}{\text{Baseline Target}} \approx \frac{K_d \cdot T_{acc}}{C_{avg}}$$

  - 2) Assess the identifiability of the model

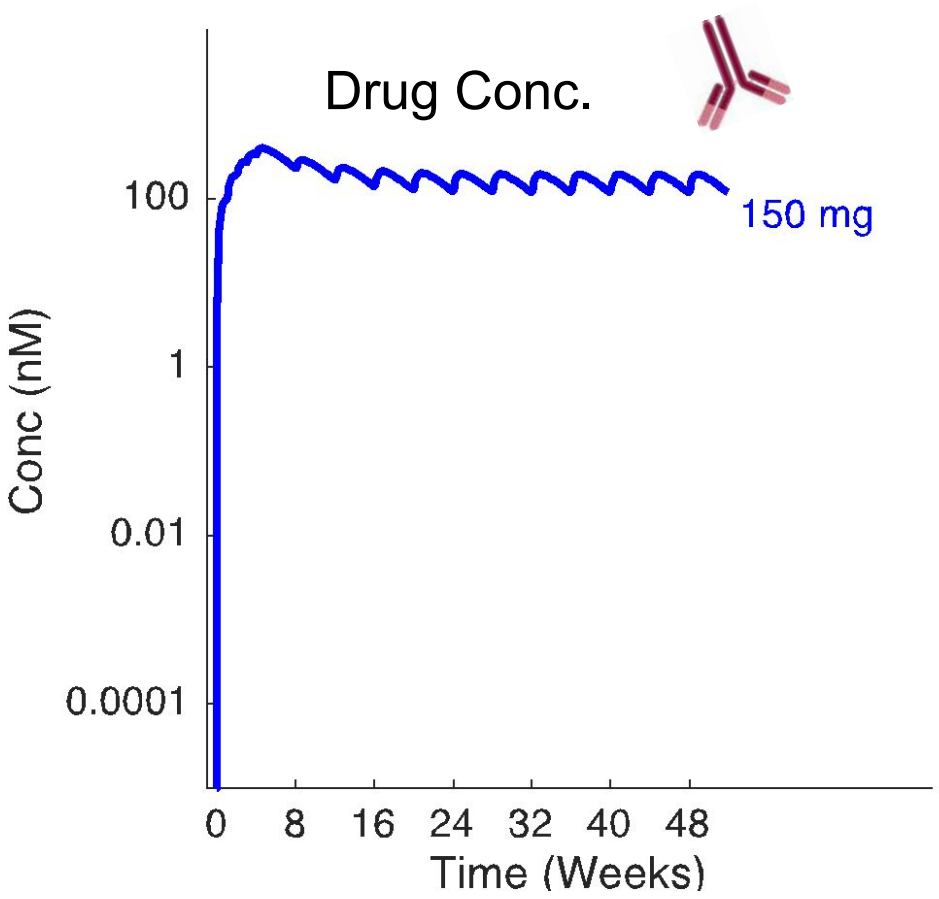
INTRODUCTION

Monoclonal Antibodies with Soluble Targets

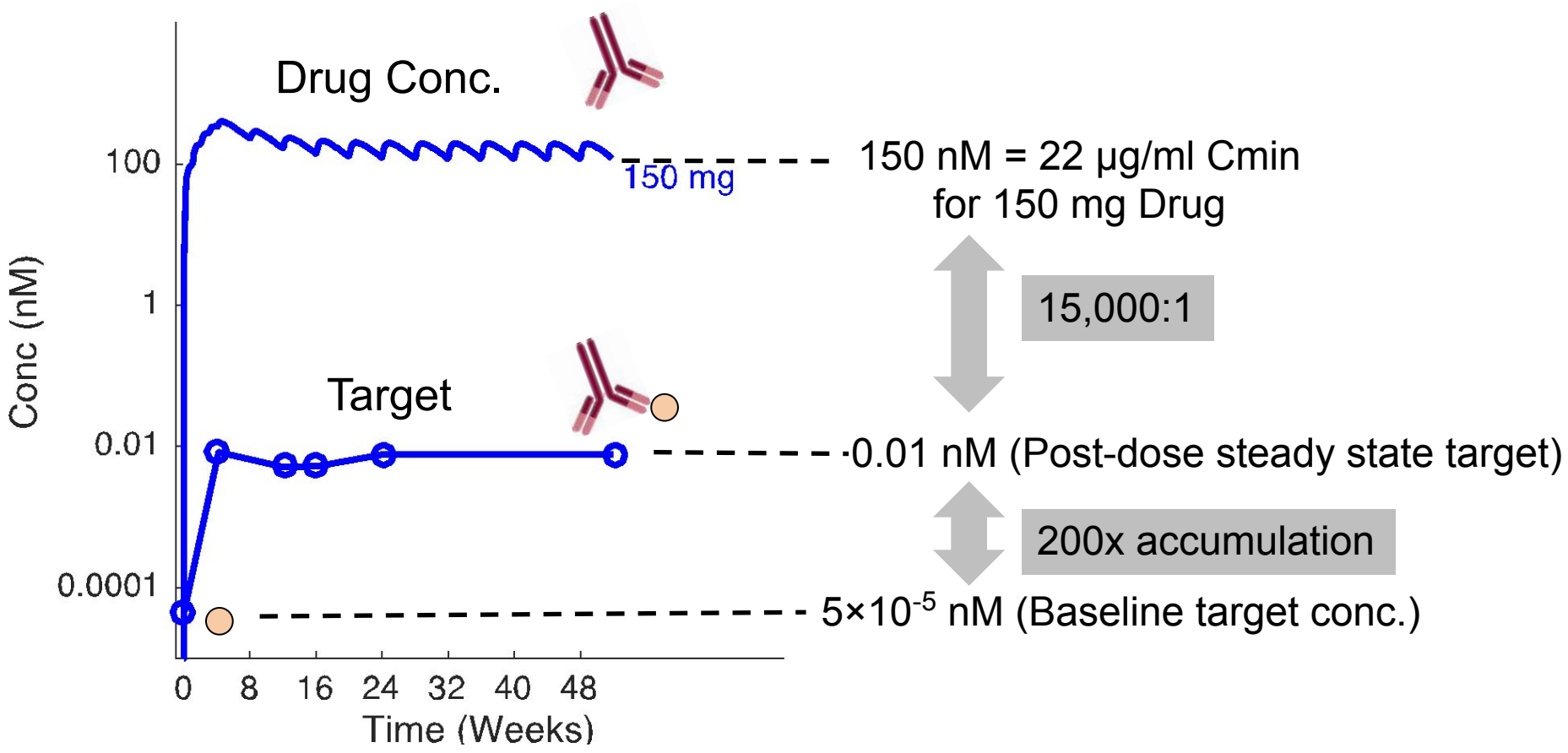


* Drug and complex do not necessarily have the same half-life

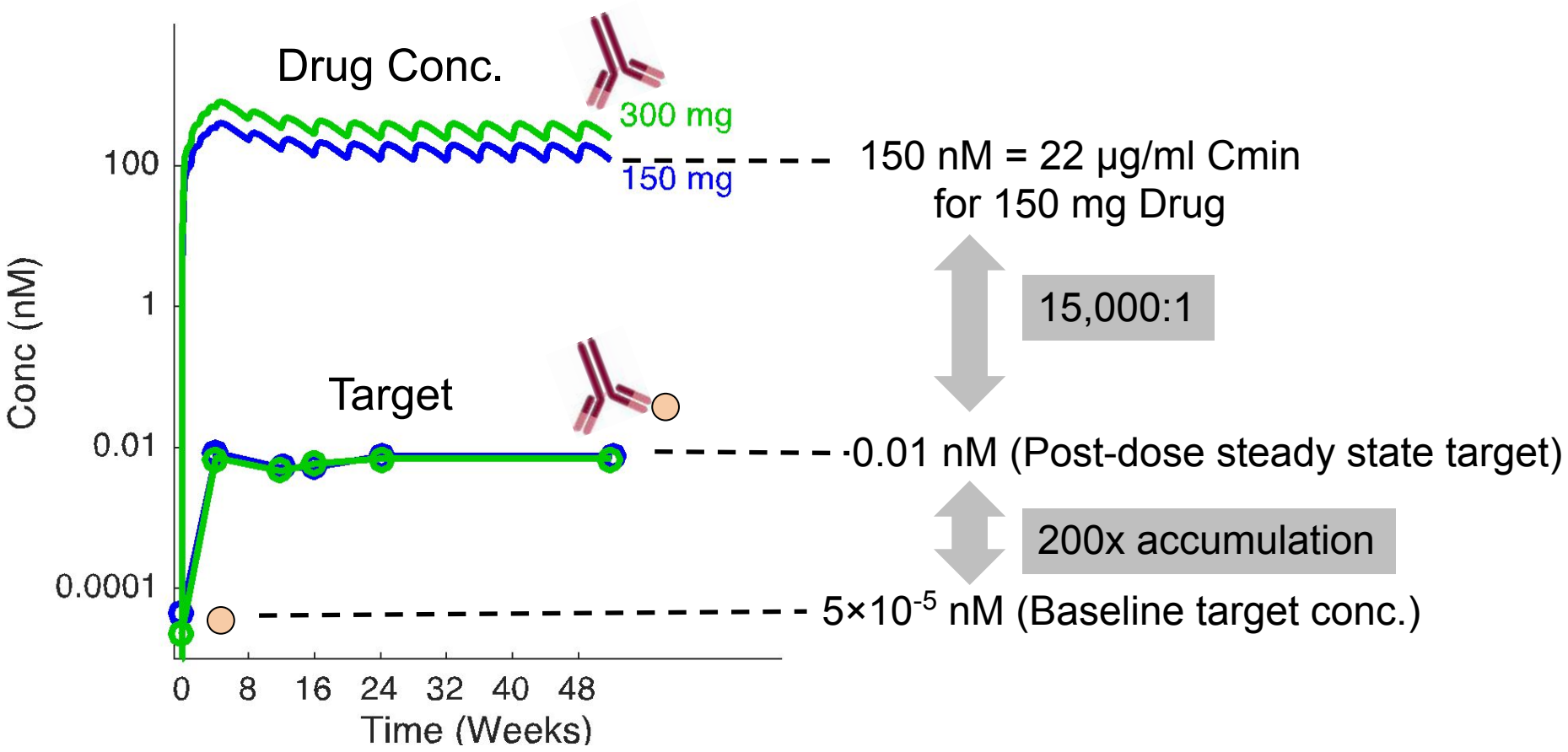
Drug Pharmacokinetics for 150 mg monthly subcutaneous dosing



Target accumulation is 200x and drug is in vast excess to its target.



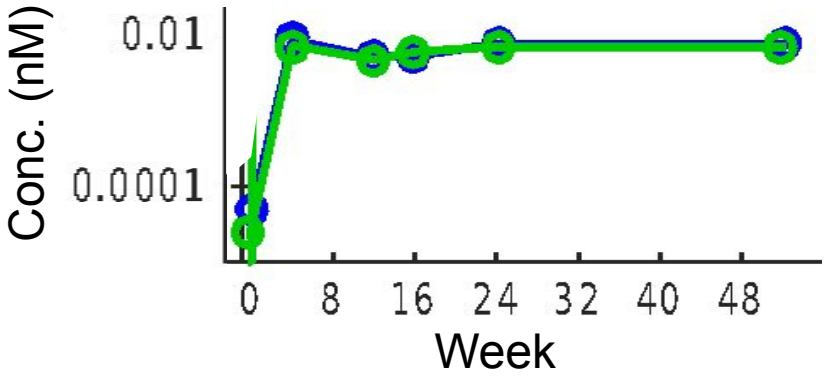
Target accumulation is similar for both 150 mg and 300 mg



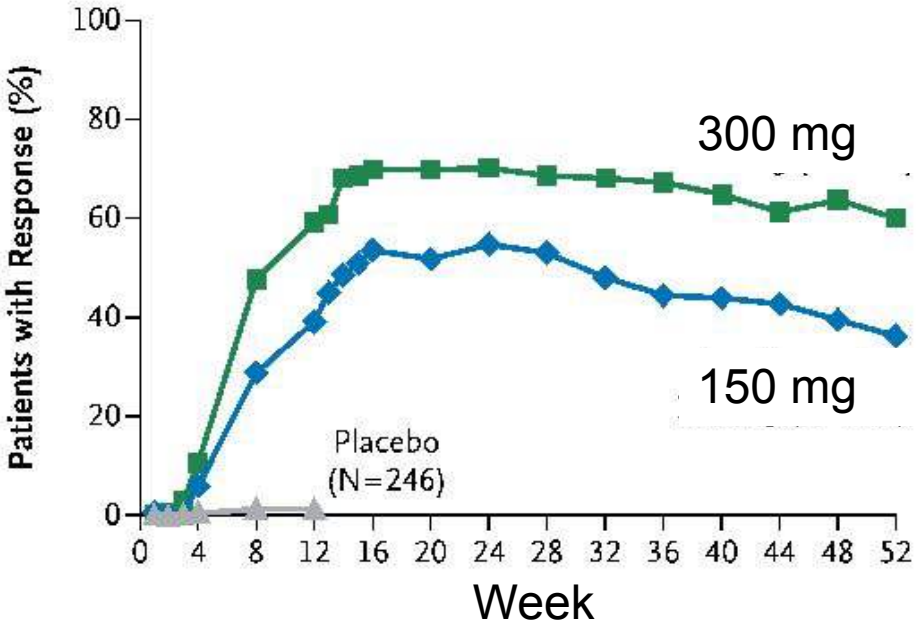
Question: What would you predict for efficacy?

Greater efficacy is observed at 300 mg vs 150 mg Why?

Total Target Data
Similar for 150 mg and 300 mg

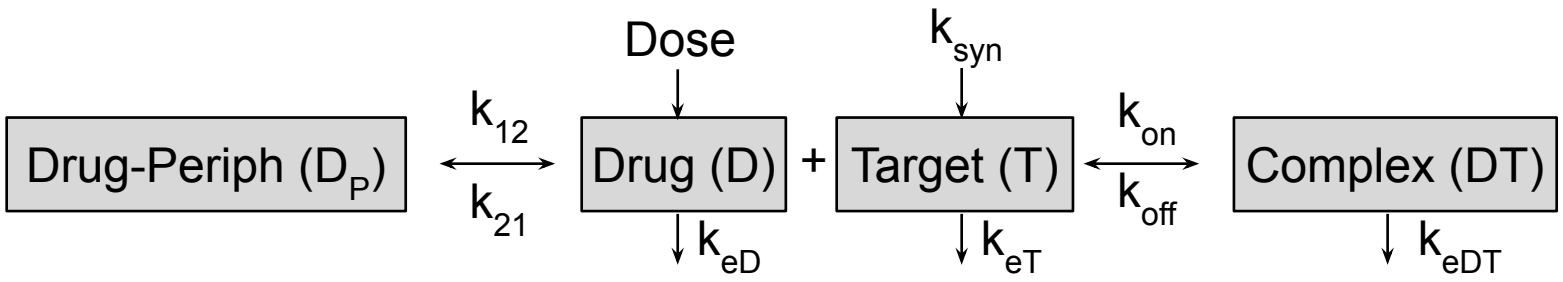


PASI^2 90 Efficacy Metric
Superior for 300 mg



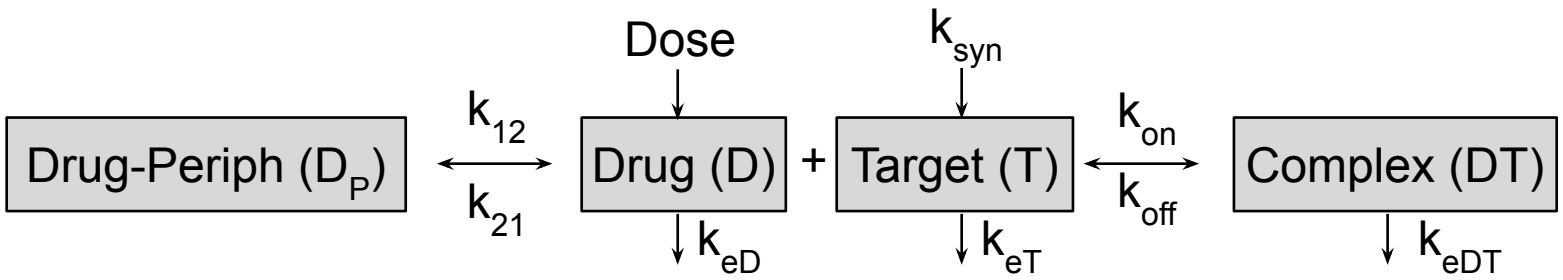
MATHEMATICAL MODEL OF DRUG-TARGET BINDING

The PK-binding model



- **Assumption:** Target binding and synthesis in the peripheral compartment.
  - This assumption is made out of convenience: data is not rich enough to identify additional peripheral parameters.

The PK-binding model equations



Dose or Synthesis | Elimination | Binding | Distribution

$$
\begin{aligned}
dD/dt &= \text{Dose Input} - k_{eD}D - k_{\text{on}}D\cdot T + k_{\text{off}}(DT) - k_{12}D + k_{21}D_P \\
dT/dt &= k_{\text{syn}T} - k_{eT}T - k_{\text{on}}D\cdot T + k_{\text{off}}(DT) \\
d(DT)/dt &= -k_{eDT}(DT) + k_{\text{on}}D\cdot T - k_{\text{off}}(DT) \\
dD_P/dt &= k_{12}D - k_{21}D_P
\end{aligned}
$$

- Not all parameters of this model are identifiable.
- We only measure total target, which is the sum: $T_{tot} = T + DT$

The Quasi-Equilibrium Assumption

- **Assumption:** binding is rapid such that drug, target, and complex stay in equilibrium.

$$k_{\text{on}} D \cdot T = k_{\text{off}}(DT)$$

$$\frac{D \cdot T}{(DT)} = \frac{k_{\text{off}}}{k_{\text{on}}} = K_d$$

- This assumption allows us to reduce number of state variables from four [D, T, DT, D_P] to three [D_{tot}, T_{tot}, D_P] plus an algebraic set of equations

$$D_{\text{tot}} = D + (DT)$$

$$T_{\text{tot}} = T + (DT)$$

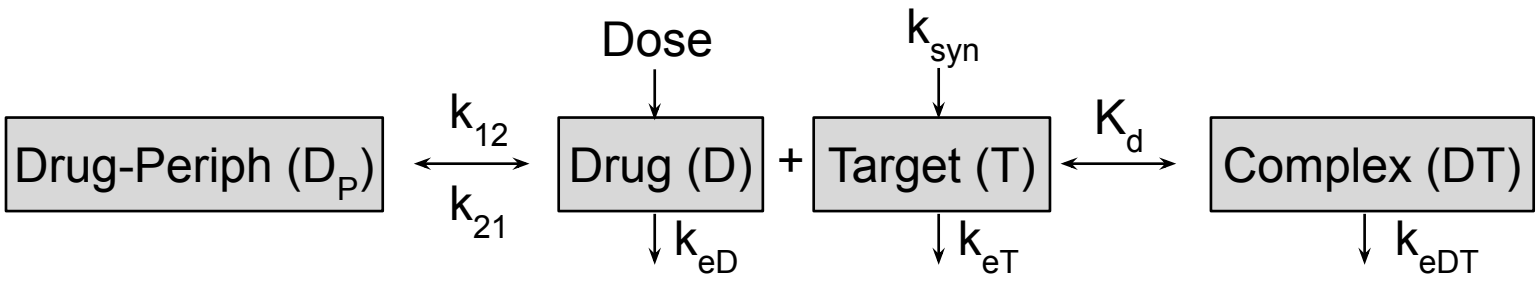
$$B = D_{\text{tot}} - T_{\text{tot}} - K_d$$

$$D = \frac{1}{2}\left(B + \sqrt{B^2 + 4 \cdot K_d \cdot D_{\text{tot}}}\right)$$

$$(DT) = \frac{D \cdot T_{\text{tot}}}{K_d + D}$$

The Quasi-Equilibrium Model

Binding only occurs in central compartment



Dose or Synthesis | Elimination | Distribution

$$dD_{tot}/dt = \text{Dose Input} - k_{eD}D - k_{eDT}(DT) - k_{12}D + k_{21}D_P$$

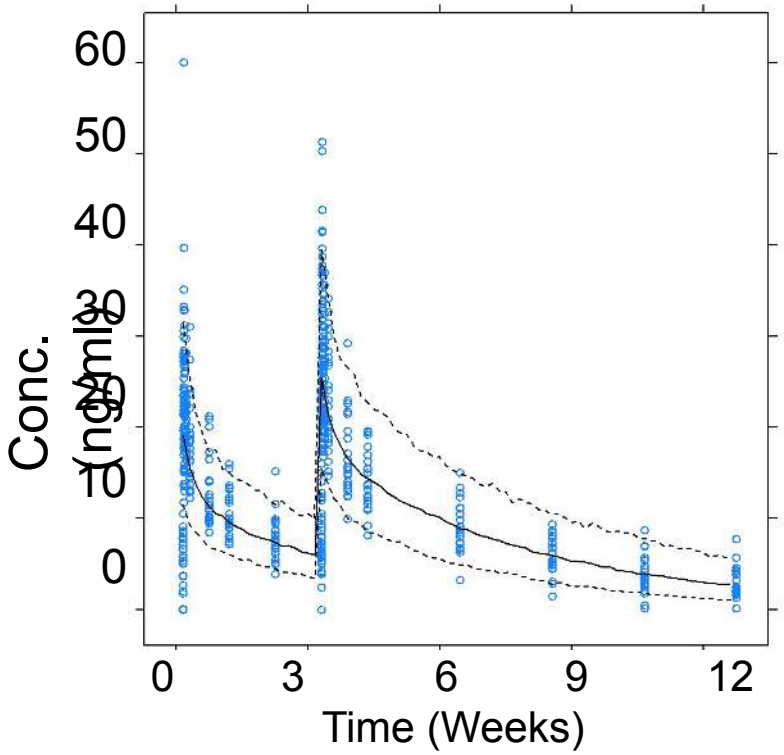
$$dT_{tot}/dt = k_{syn}T - k_{eT}T - k_{eDT}(DT)$$

$$dD_P/dt = k_{12}D - k_{21}D_P$$

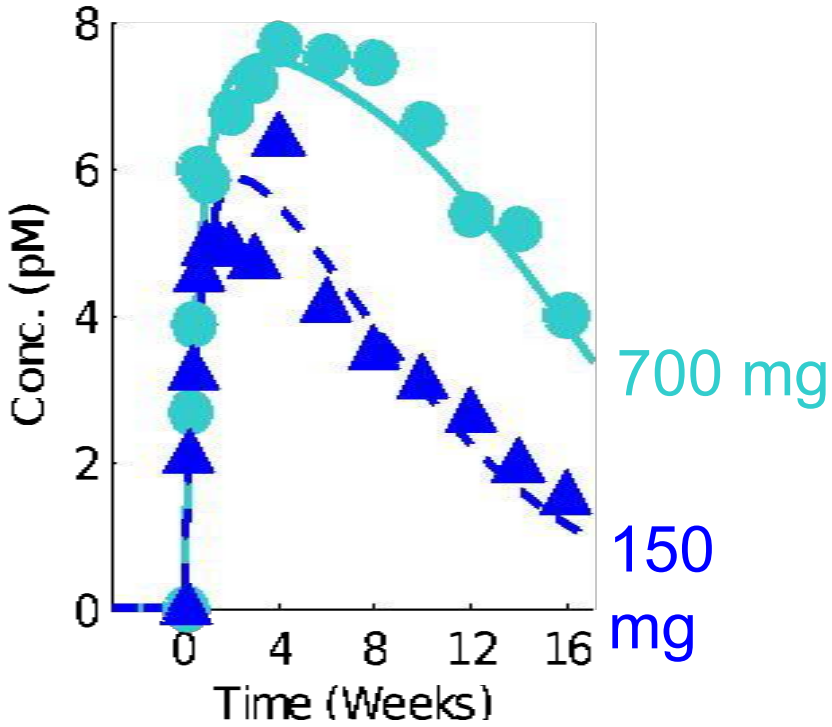
Concentrations D, T, and DT are solved for using algebraic binding equations

Model fit to drug PK and target accumulation data

Drug Concentration
(700 mg iv dosing)



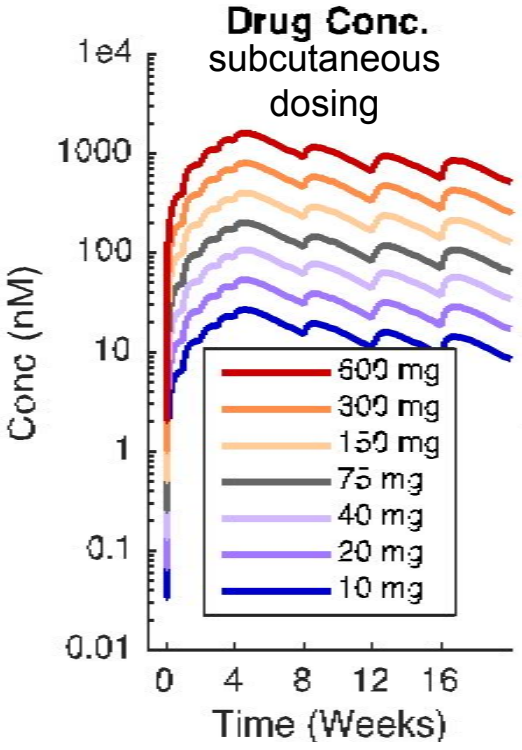
Total Target Concentration
(subcutaneous dosing)

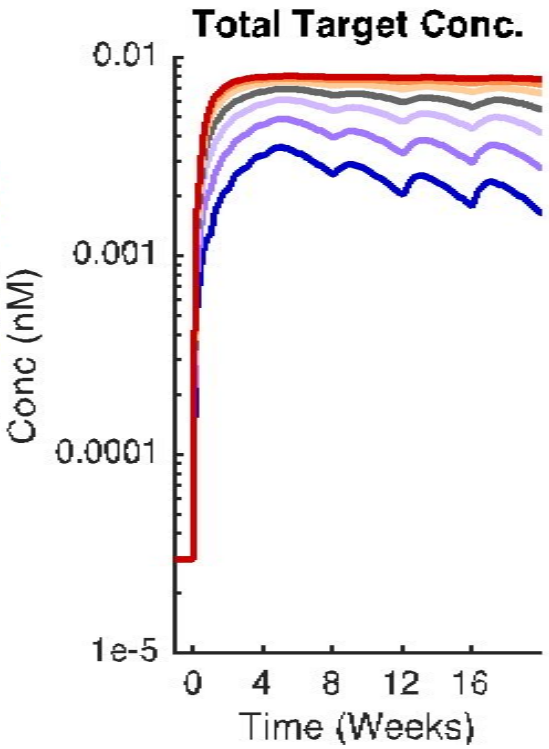


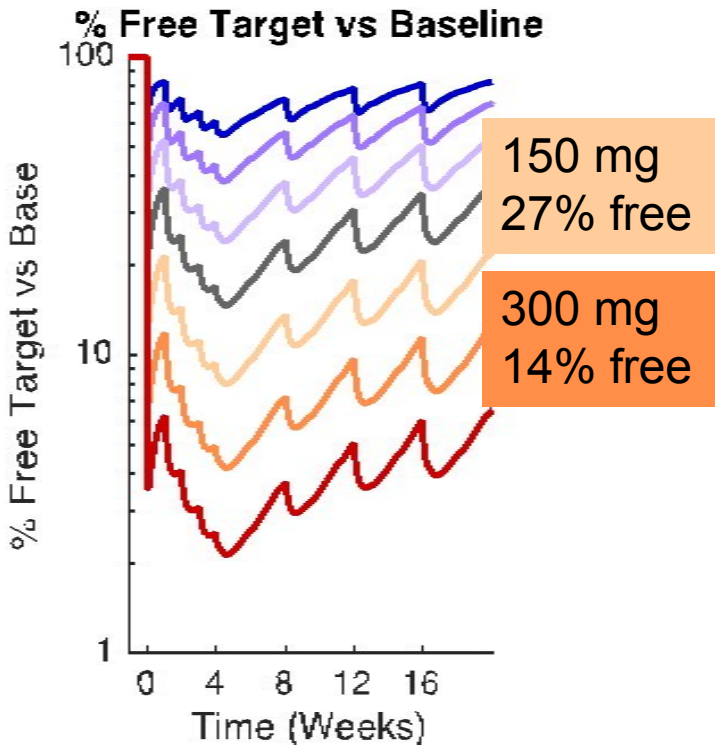
Model can be used to:

1) Describe available PK and total target data.
2) Predict free target concentration

Sensitivity analysis: total target plateaus, but free target continues to decline with dose







2 compartment linear PK with subcutaneous absorption

Above 150 mg, total target concentration plateaus **(measurable)**

Above 150 mg, every 2x dose increase leads to 2x free target decrease **(predicted)**

MATHEMATICAL ANALYSIS OF DRUG-TARGET MODEL

Key Quantity of Interest: Free Target vs Baseline

$$\frac{\text{Free Target}}{\text{Baseline Target}} = \frac{T}{T_0} = \left(\frac{T}{T_{\text{tot,ss}}}\right)\left(\frac{T_{\text{tot,ss}}}{T_0}\right)$$

1) Free Target vs Total Target

2) Total Target Accumulation

Calculating Free Target vs Total Target

- Algebraic manipulation of quasi-equilibrium equation

$$\text{Binding Equation} : (D)(T) = K_d(DT)$$

$$\text{Replace with } T_{tot} : (D)(T) = K_d(T_{tot} - T)$$

$$\text{Rearrange terms} : (D)(T) = K_d T_{tot} - K_d T$$

$$: (D + K_d)(T) = K_d T_{tot}$$

$$: T = \frac{K_d T_{tot}}{D + K_d}$$

$$\frac{\text{Free Target}}{\text{Total Target}} : \frac{T}{T_{tot}} = \frac{K_d}{D + K_d} \approx \frac{K_d}{D} \approx \frac{K_d}{D_{tot}}$$

When Dtot >> Ttot, Kd

Analysis of total target dynamics before dosing

Before Dose, DT=0

$$\text{Recall} \quad : \quad dT_{tot}/dt = k_{synT} - k_{eT}T - k_{eDT}DT$$

At steady state: $dT_{tot}/dt = 0$

$$T_0 = k_{synT}/k_{eT}$$

Analysis of total target dynamics after dosing

2) Total Target accumulation

For large drug conc., most target is bound, $T \approx 0$, and $DT \approx T_{tot}$

$$\text{Recall} \quad : \quad dT_{tot}/dt = k_{synT} - k_{eT}T - k_{eDT}DT$$

At steady state: $dT_{tot}/dt = 0$

$$T_{tot,ss} = k_{synT}/k_{eDT}$$

$$\text{Accumulation ratio} \quad : \quad T_{ac} = \frac{T_{tot,ss}}{T_0} = \frac{k_{synT}/k_{eDT}}{k_{synT}/k_{eT}} = \frac{k_{eT}}{k_{eDT}}$$

c

Estimating the free target compared to baseline

$$\frac{\text{Free Target}}{\text{Baseline Target}} = \frac{T}{T_0} = \left(\frac{T}{T_{\text{tot,ss}}}\right)\left(\frac{T_{\text{tot,ss}}}{T_0}\right)$$

$$= \left(\frac{K_d}{D}\right) \cdot (T_{acc})$$

$$\frac{\text{Average Free Target}}{\text{Baseline Target}} \approx \left(\frac{K_d}{C_{ava}}\right) \cdot (T_{acc})$$

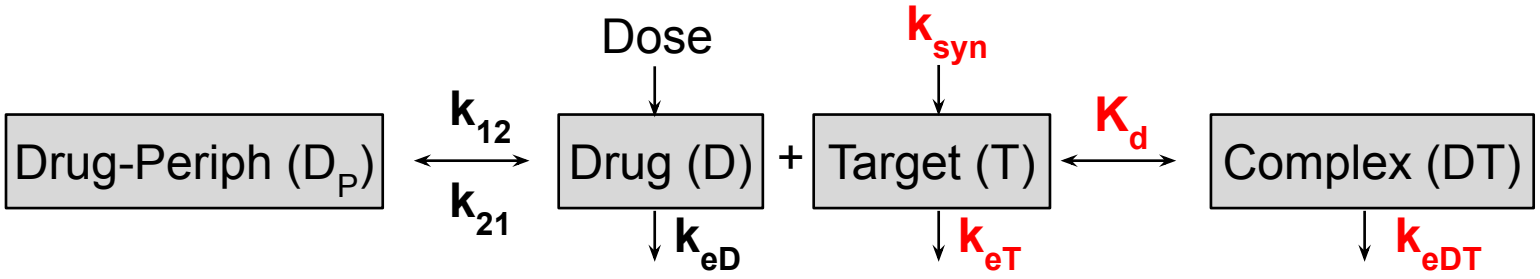
Summary

$$\frac{\text{Free Target}}{\text{Baseline Target}} \approx \frac{K_d \cdot T_{acc}}{C_{avg}}$$

- Three key parameters determine target inhibition when there is a large excess of drug relative to target at steady state.
  - Binding affinity (K_d)
  - Target accumulation factor (T_{acc})
  - Drug concentration (C_{avg})
- In these circumstances, doubling dose, halving dosing interval, or halving K_d reduces free target by 50%
- At high doses, total target reaches plateau.
  This does not mean target inhibition has reached plateau

ANALYSIS OF TOTAL TARGET KINETICS

Target dynamics is characterized by 4 parameters



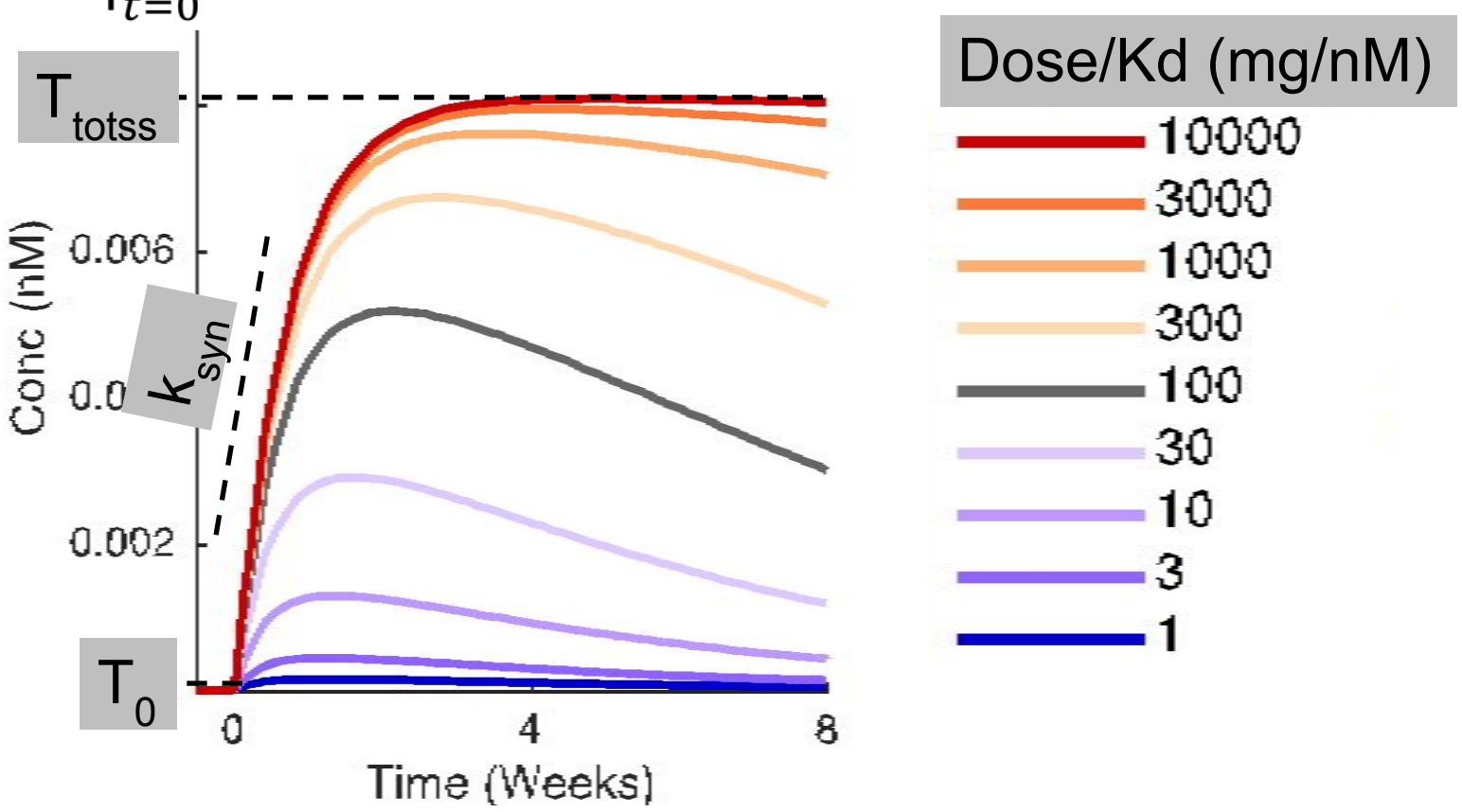
- To understand identifiability, it's useful to reparameterize:
  - $T_0 = k_{syn}/k_{eT}$
  - $T_{totss} = k_{syn}/k_{eDT}$
  - k_{eDT}
  - K_d

$dT_{tot}/dt \approx k_{syn} - k_{eDT} \cdot T_{tot}$ ⇒ $T_{tot} \approx T_0 + (T_{tot,ss} - T_0) \cdot \exp[-k_{eDT} \cdot$ for large drug concentrations

Understanding the total target dynamics

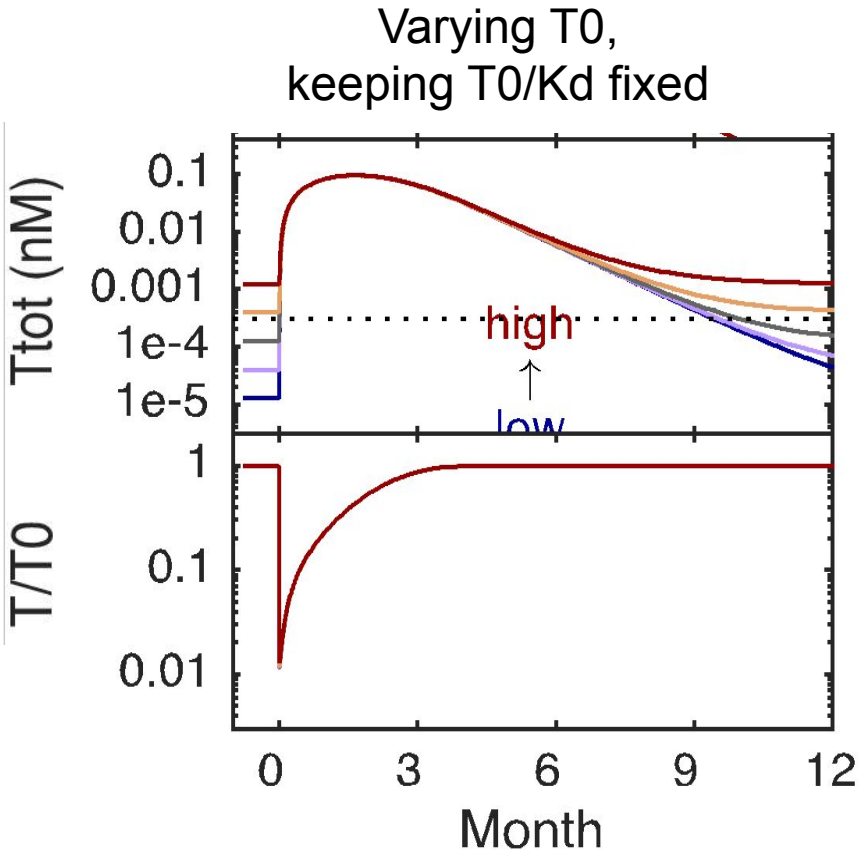
$$T_{tot} \approx T_{tot,ss} + (T_0 - T_{tot,ss}) \cdot \exp[-k_{eDT} \cdot t], \text{ for large drug conc.}$$

$$\left.\frac{dT_{tot}}{dt}\right|_{t=0} \approx (-T_{tot,ss}) \cdot (-k_{eDT}) = k_{syn}$$



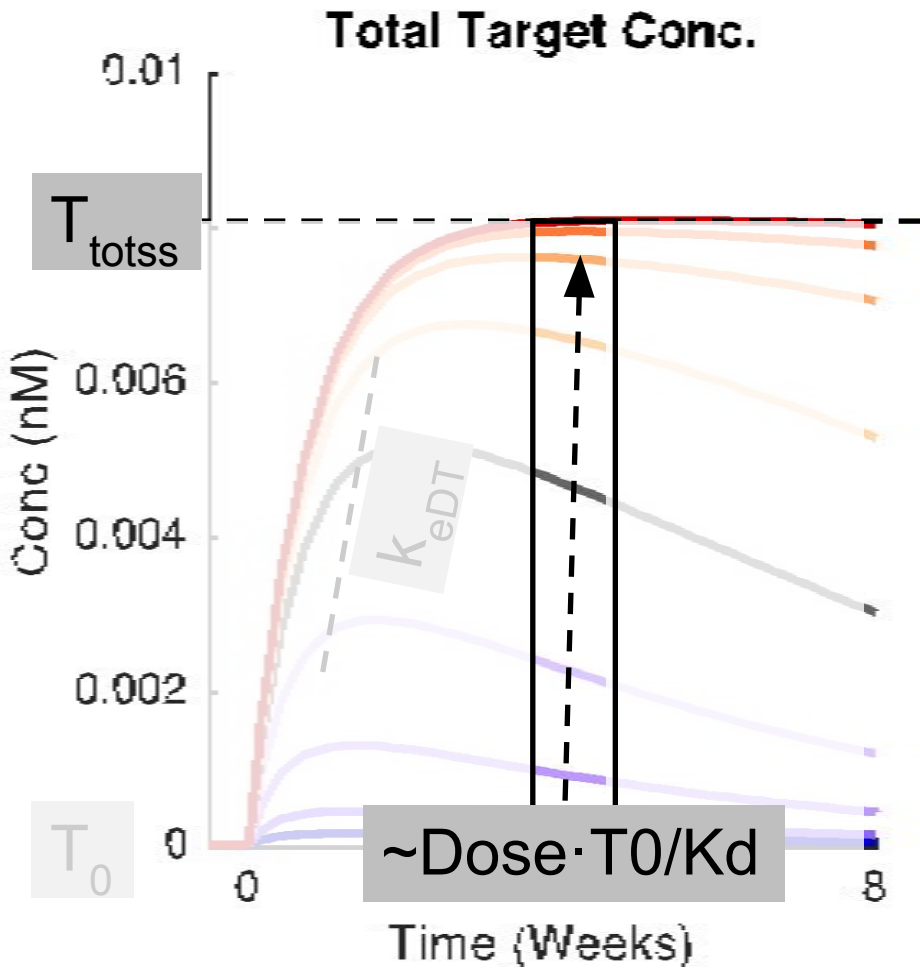
Identifiability – free target inhibition can be predicted even if baseline target is not measurable

- Assay may not be sensitive enough to measure T0.
- In that case, only three parameters may be identifiable:
  - k_{eDT}, T_{totss}, and T_0/K_d
- Note that free target inhibition (T/T_0) depends on the ratio T_0/K_d
  - $T/T_0 = K_d \cdot T_{acc}/C_{avg}$
  - $= (K_d/T_0) \cdot T_{totss}/C_{avg}$



Free target inhibition can be predicted even if complex elimination (keDT) is not identifiable

- k_{eDT} is also not identifiable if sufficient samples are not taken.
- But T/T_0 can still be estimated
  - $T/T_0 = K_d \cdot T_{acc}/C_{avg}$
  - $= (K_d/T_0) \cdot T_{totss}/C_{avg}$



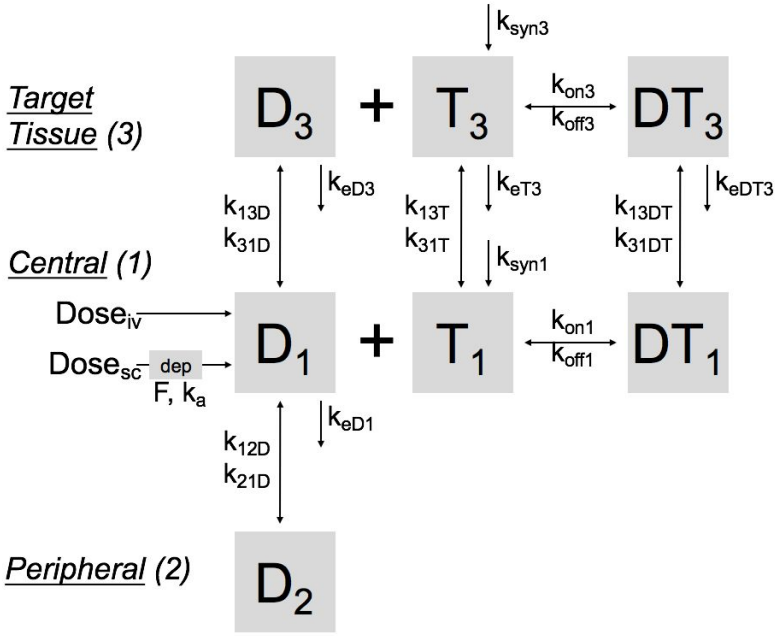
Summary

$$\frac{\text{Free Target}}{\text{Baseline Target}} \approx \frac{K_d \cdot T_{acc}}{C_{avg}}$$

- Three key parameters determine target inhibition when there is a large excess of drug relative to target at steady state.
  - Binding affinity (K_d)
  - Target accumulation factor (T_{acc})
  - Drug concentration (C_{avg})
- In these circumstances, doubling dose, halving dosing interval, or halving Kd reduces free target by 50%
- At high doses, total target reaches plateau.
  This does not mean target inhibition has reached plateau
- Free target inhibition is estimable even when baseline target (T_0) or rate of complex elimination (k_{eDT}) are not estimable.

Limitations

- This analysis focused on inhibition in blood. Inhibition in tissue is more challenging to measure and predict.



- This analysis only applies when drug is in vast excess to target (not applicable for anti-C5, where C5 ≈ 500 nM)

Acknowledgements

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