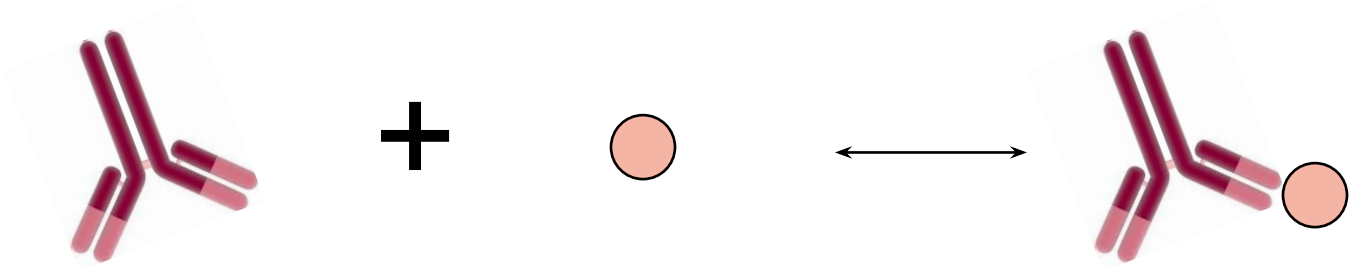


Two new parameters for characterizing ligand binding systems.

Andrew Stein
October 17, 2017
ACoP8 – Mathematical Pharmacology

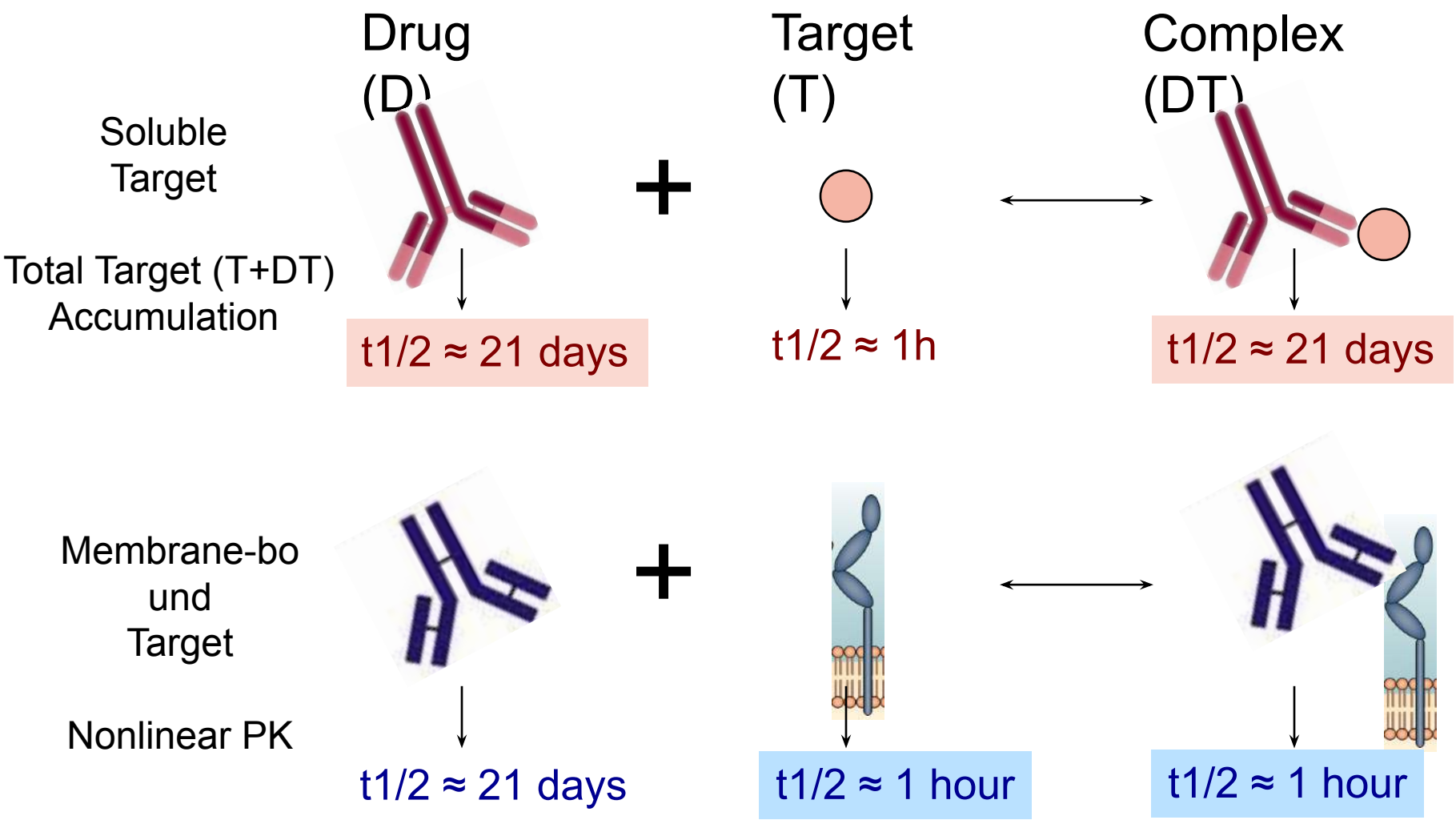
Overview

- Onset of PK nonlinearity: $C_{crit} = \frac{V_m}{CL}$
- Average target inhibition: $AFIR = \frac{K_d \cdot T_{acc}}{C_{avg}}$
- These simple expressions allow us to:
  - Predict doses needed for target inhibition
  - Understand sensitivity to model parameters
  - Understand which model parameters are identifiable
  - Interpret total target kinetics data
  - Rapidly benchmark compounds

Differences between small molecules and monoclonal antibodies

Property	Small Molecules	Monoclonal Antibodies (IgG1)
Molecular Weight	500 Da	150,000 Da
Half-Life (human)	minutes - hours	3 weeks
Affinity for target	Moderate to high	Very high

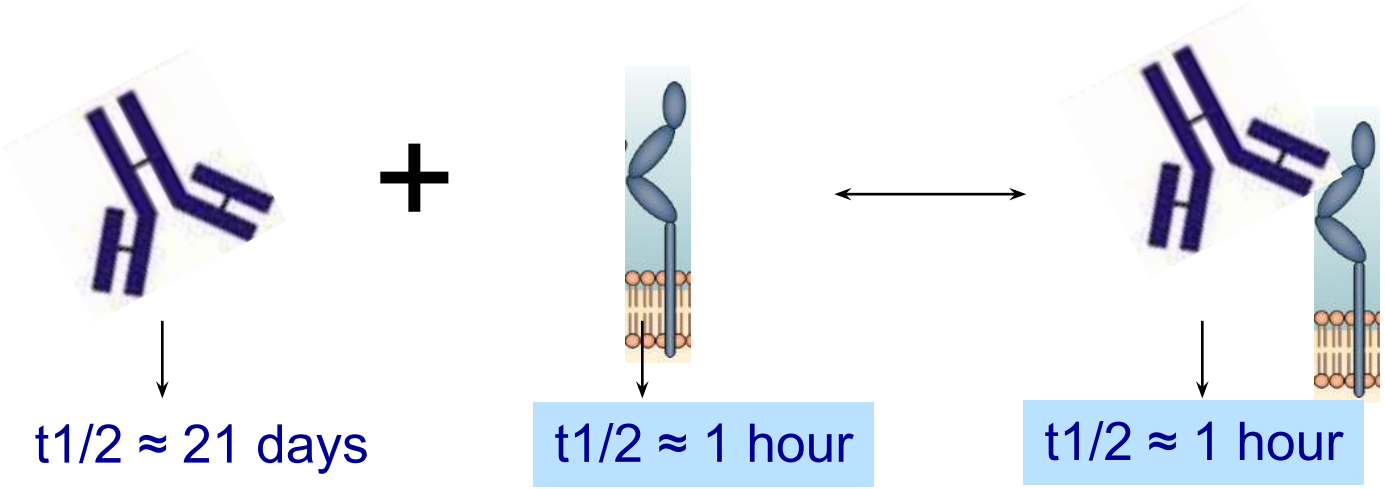
Soluble vs Membrane-Bound Targets



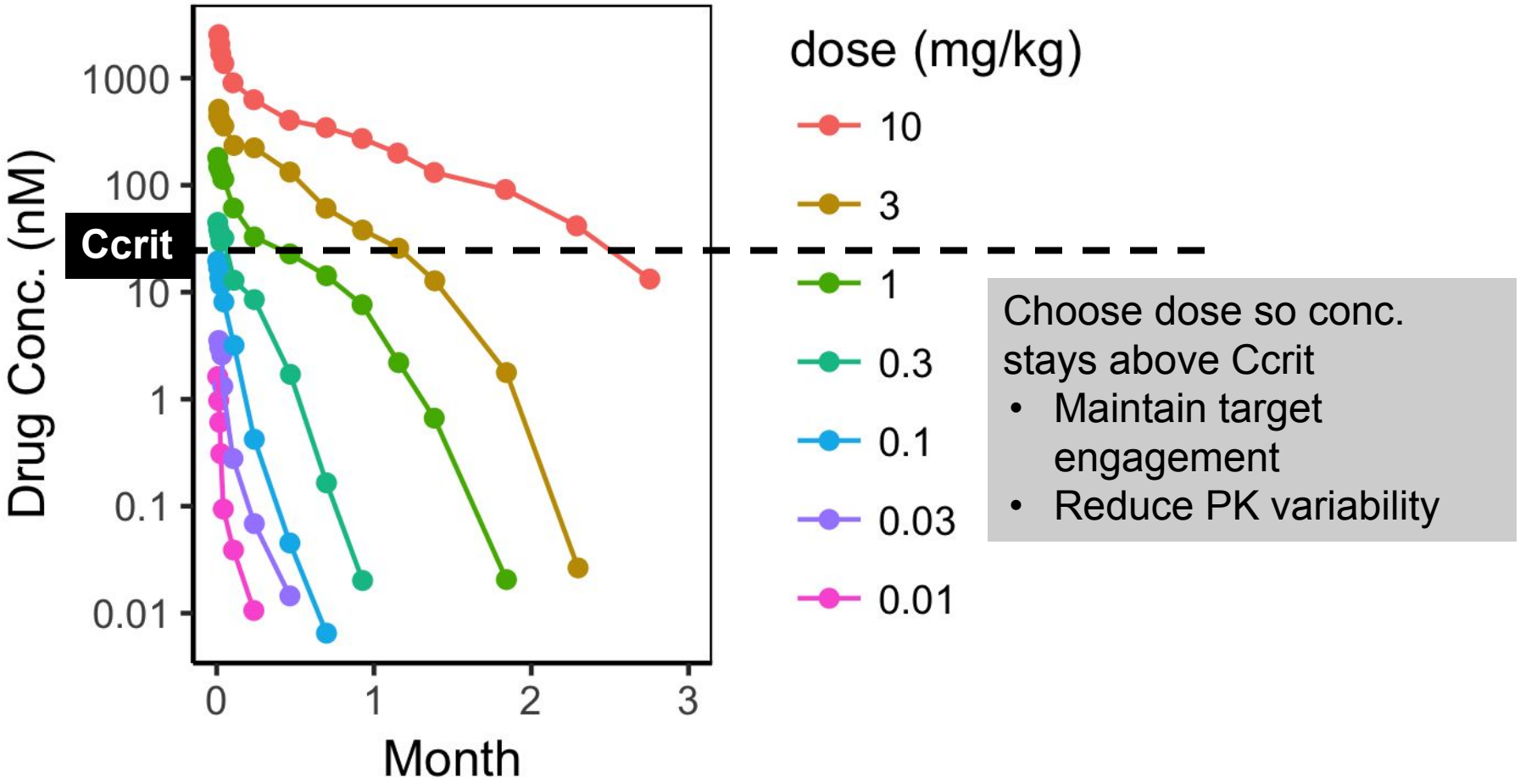
Characterizing onset of PK nonlinearity for membrane-bound targets

In collaboration with Bert Peletier at Leiden University in The Netherlands

Manuscript in progress. Contact andrew.stein@novartis.com if interested in further details.



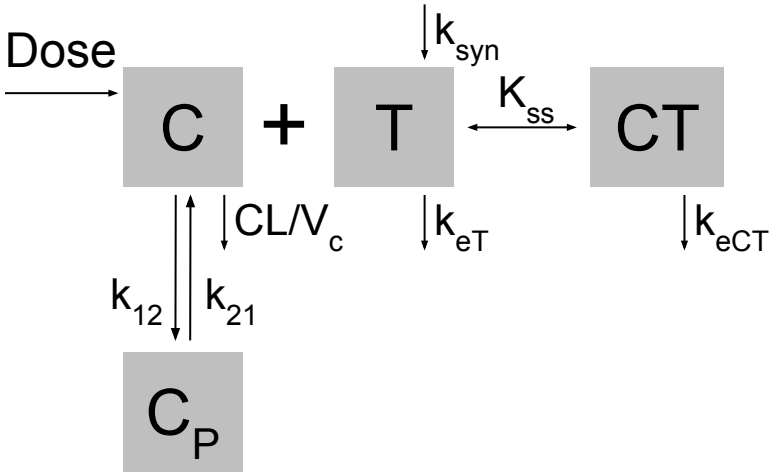
Nonlinear pharmacokinetics occurs at "critical concentration" = C_{crit}



Burmester, G. R. et al. Mavrilimumab, a human monoclonal antibody targeting gm-csf receptor-α, in subjects with rheumatoid arthritis: a randomised, double-blind, placebo- controlled, phase I first-in-human study. Annals of the rheumatic diseases 70, 1542–1549 (2011).

Michaelis-Menten approximation of ligand binding model

Ligand Binding Model (Membrane-Bound)



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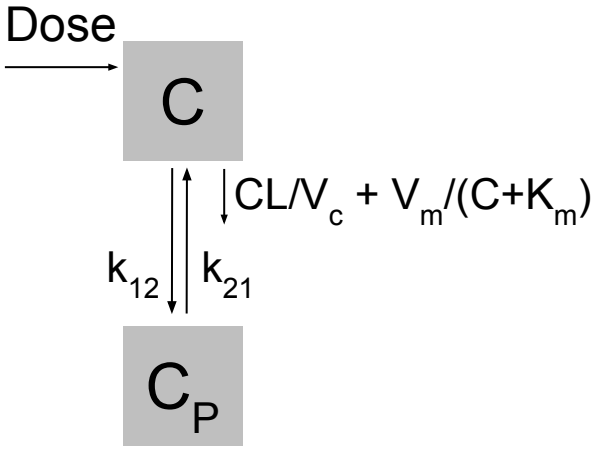
Michaelis-Menten Model



$$K_{ss} = \frac{k_{off} + k_{eDT}}{k_{on}}$$

$V_m = k_{syn} \cdot V_c$
$K_m = K_{ss}$

Approximation derived in: Ma, Peiming. "Theoretical considerations of target-mediated drug disposition models: simplifications and approximations." *Pharmaceutical research* 29.3 (2012): 866-882.

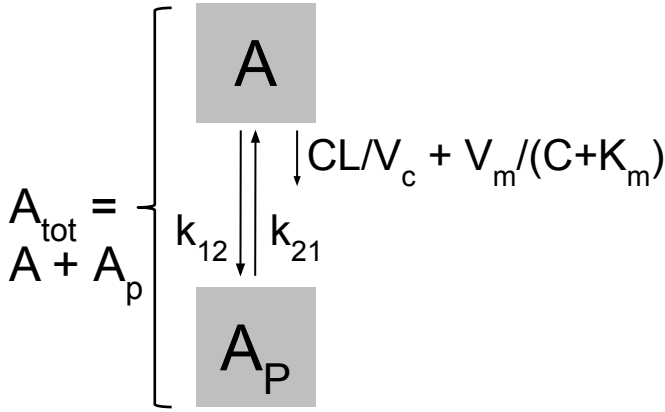
“Derivation” for C_{crit}

$A = C \cdot V_c \quad A_p = C_p \cdot V_p$

$$\frac{dA}{dt} = -k_{12}A + k_{21}A_p - CL \cdot C - \frac{V_m C}{C + K_m}$$

$$+ \quad \frac{dA_p}{dt} = k_{12}A - k_{21}A_p$$

$$\frac{dA_{tot}}{dt} = -CL \cdot C - \frac{V_m C}{C + K_m};$$



For large doses (and concentrations), $C \gg K_m$

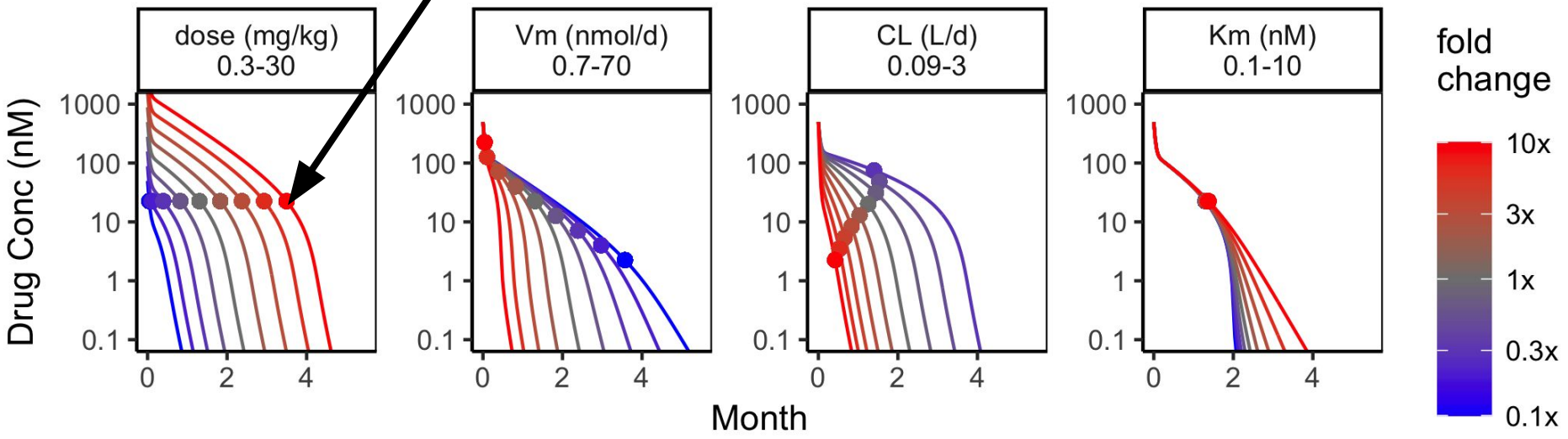
$$\frac{dA_{tot}}{dt} \approx -CL \cdot C - V_m$$

Define C_{crit} to be where the linear ($CL \cdot C$) and nonlinear (V_m) components contribute equally to total elimination

$$CL \cdot C_{crit} = V_m \rightarrow \boxed{C_{crit} = \frac{V_m}{CL}}$$

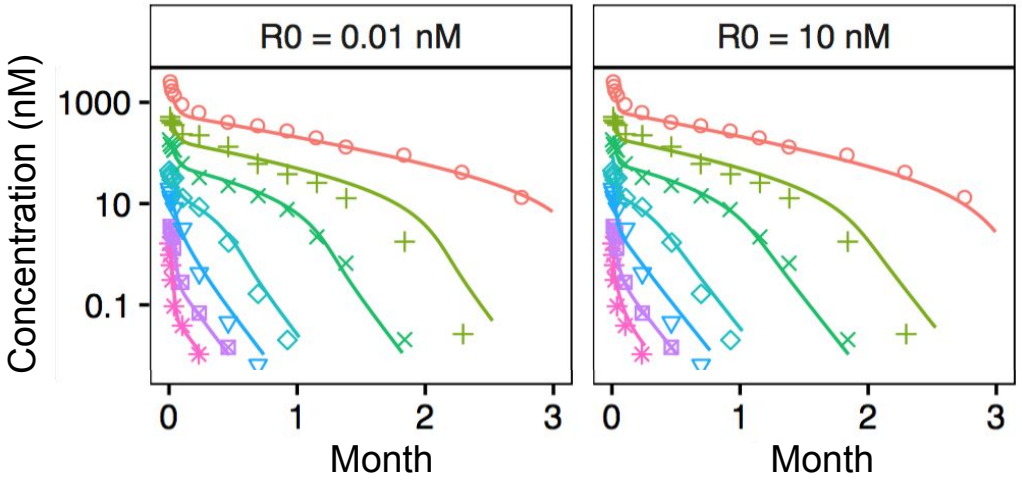
Sensitivity analysis for Ccrit

$$C_{crit} = \frac{V_m}{CL}$$



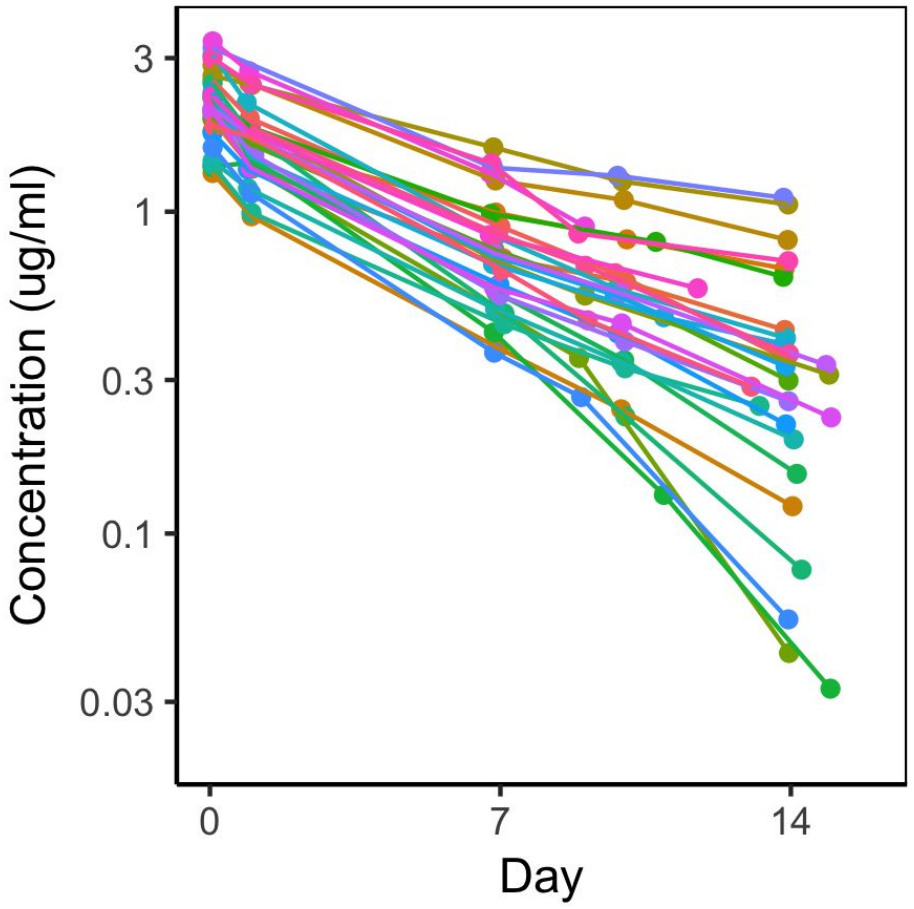
Ccrit helps in understanding parameter identifiability

- Deriving initial parameter estimates: $V_m = C_{crit} \cdot CL_{from\ NCA}$
- Understanding which model parameters are identifiable
  - **Vm** = ksyn·Vc is often easiest "TMDD" parameter to estimate from nonlin. PK
  - **Km** (from steep elimination phase) can be more difficult to identify
  - **R_0** (receptor density) is often impossible to estimate from PK alone [1]



1. Stein, Andrew. "Practical unidentifiability of receptor density in target mediated drug disposition models can lead to over-interpretation of drug concentration data." *bioRxiv* (2017): 123240.

Random effect on Vm is important for describing variable Ccrit.

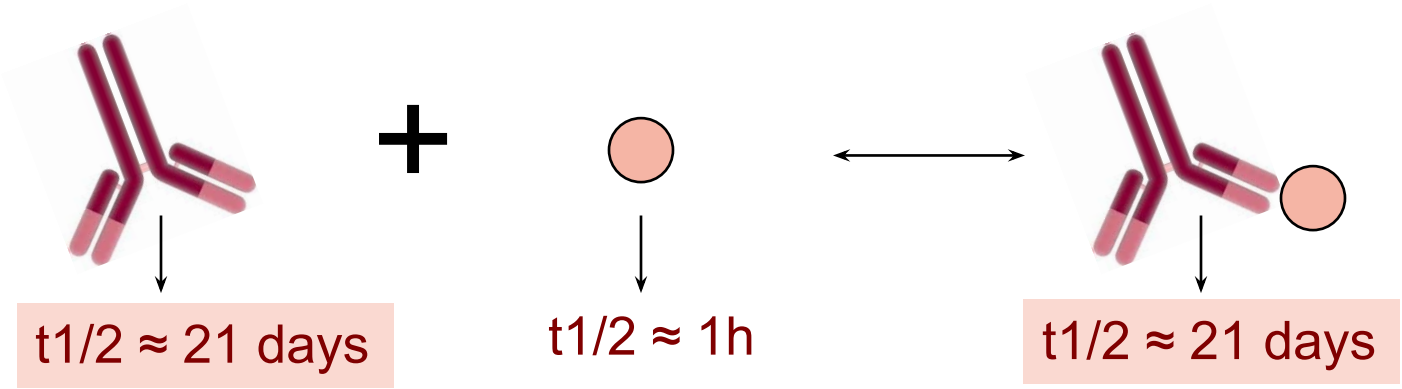


- Some pts exhibited MM kinetics while others appear linear.
- Ccrit varied between patients.
- PopPK required random effect on Vm to characterize this heterogeneity

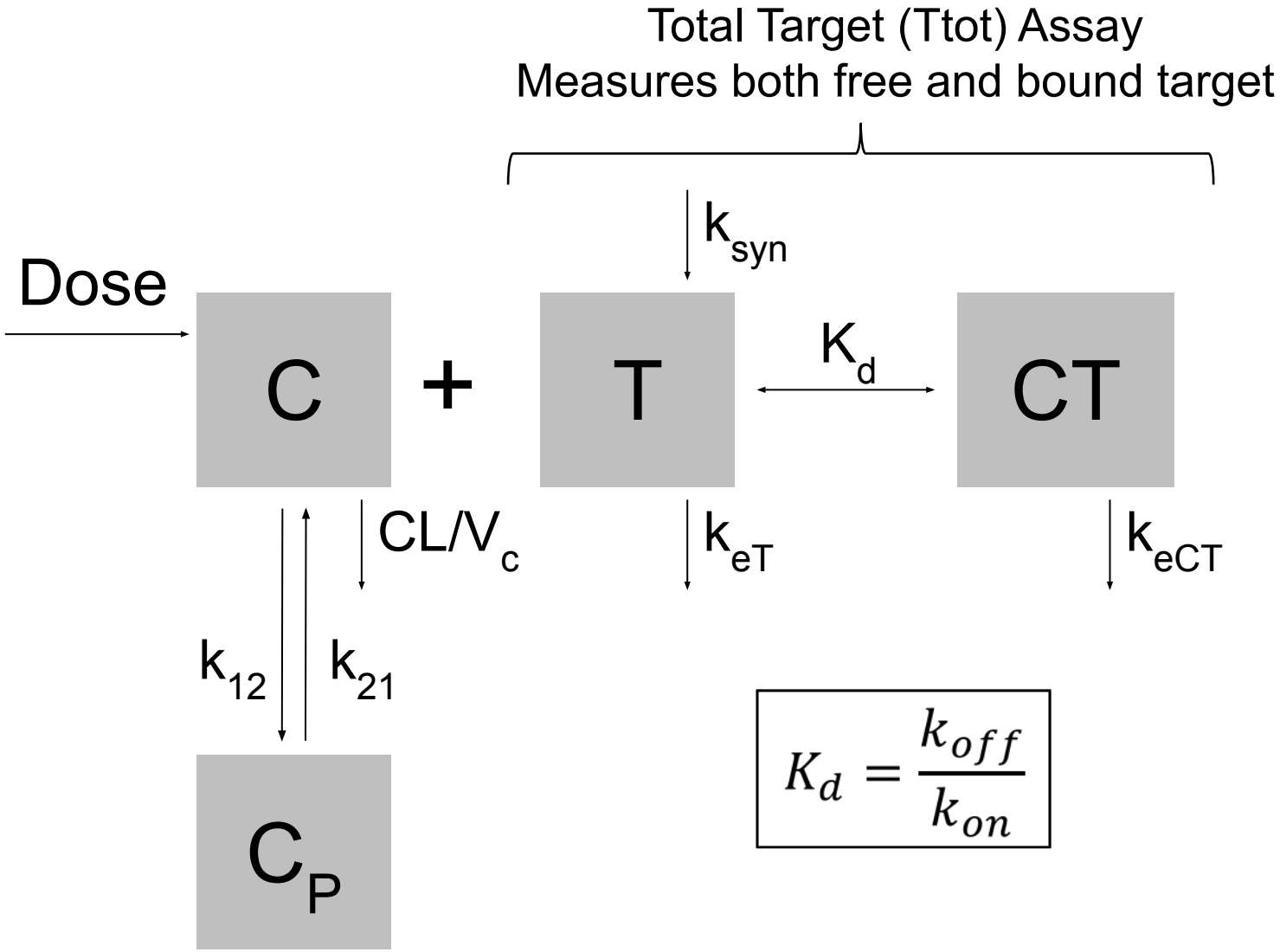
Characterizing soluble target inhibition

Stein, A. M., and Ramprasad Ramakrishna. "AFIR: A dimensionless potency metric for characterizing the activity of monoclonal antibodies." *CPT: pharmacometrics & systems pharmacology* 6.4 (2017): 258-266.

Additional work done at 2017 Math-to-Industry Bootcamp at the Institute of Mathematics and its Applications at University of Minnesota by Sameed Ahmed, Miandra Ellis, Ngartelbaye Guerngar, Hongshan Li, Luca Pallucchini

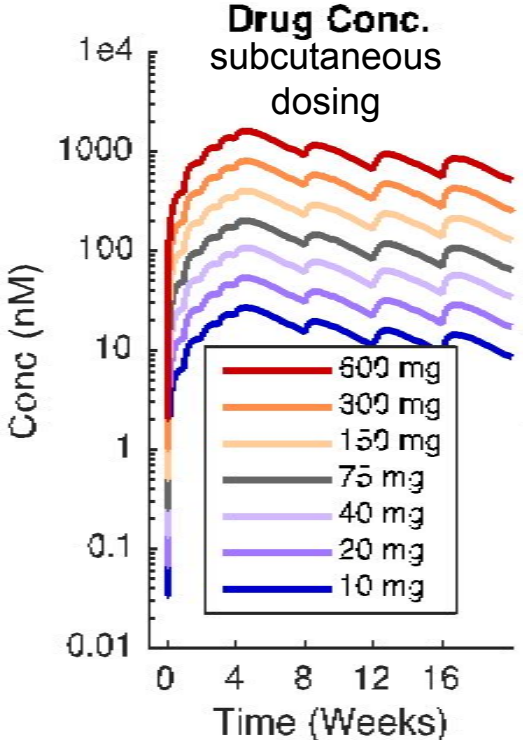


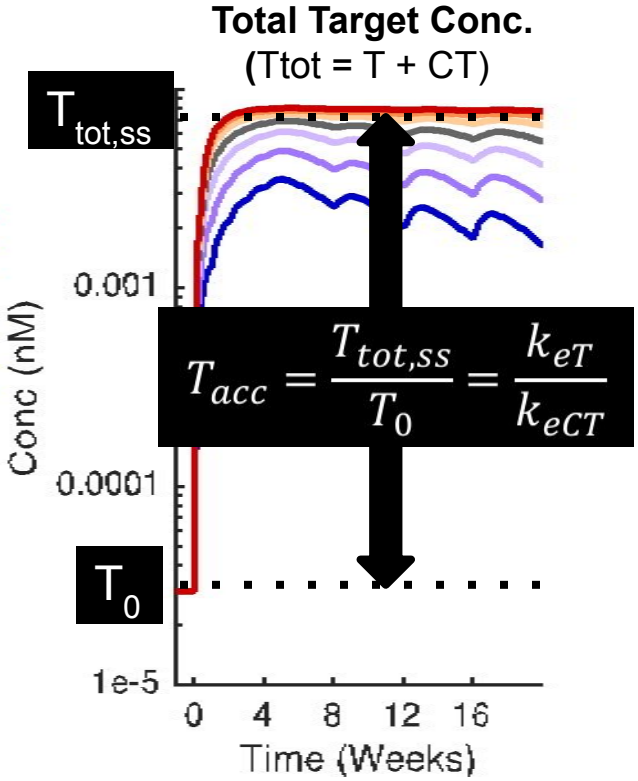
Ligand binding model (soluble target)

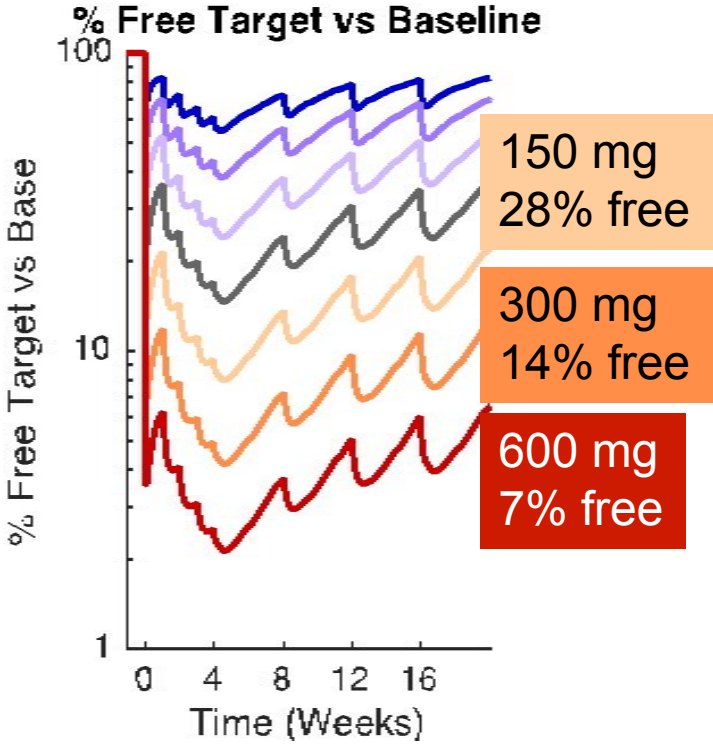


$$K_d = \frac{k_{off}}{k_{on}}$$

Sensitivity analysis. How does inhibition relate to parameters?







Above 150 mg, total target conc. plateaus

Above 150 mg, doubling dose halves the free target conc.

Estimating the free target compared to baseline

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

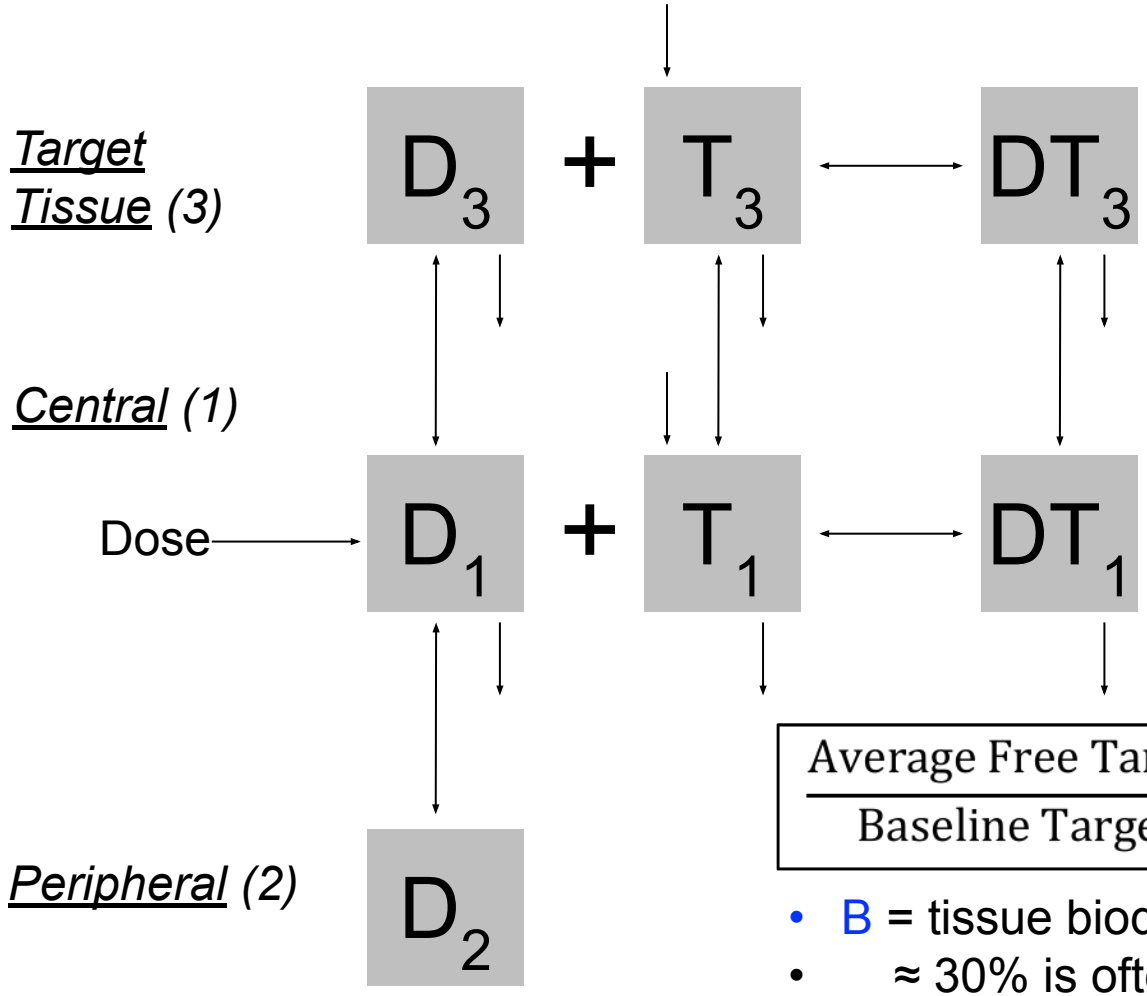
$$\approx \left(\frac{K_d}{C_{avg}}\right) \quad (T_{acc})$$

$$AFIR = \frac{\text{Average Free Target}}{\text{Baseline Target}} \approx \frac{K_d \cdot T_{acc}}{C_{avg}} = \frac{L_{50}^*}{C_{avg}}$$

- Three key parameters that determine target inhibition
  - **Kd:** Binding affinity (Kd)
  - **Tacc:** Target accumulation at steady state
  - **Cavg:** Average drug concentration at steady state
- Doubling dose or halving Kd reduces free target by 50%

* L_{50} was recently derived in: Gabrielsson et al., Pharmacology & Therapeutics, https://doi.org/10.1016/j.pharmthera.2017.10.011

AFIR can also be applied to a target tissue (in progress)



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

- B = tissue biodistribution coefficient,
- ≈ 30% is often assumed
- Target accumulation (Tacc) in tissue is difficult to measure. Often assumed = 1

Using AFIR, sensitivity to assumptions is easy to report

- Often, we select dose so that AFIR = $\frac{K_d \cdot T_{acc}}{C_{avg}} = 5\%$
  (e.g. 95% target coverage)
- What if 90% target coverage is sufficient (10% free)?
  - Then half the dose can be given
- What if 99% target coverage is needed (1% free)?
  - Then 5x higher dose is needed

Development of oral drug with same target as subcutaneous biologic

- Challenges
  - Oral biologics denatured in stomach
  - Small molecules will have poorer affinity (Kd) and higher elimination (CL)
- How will new drug compare to first generation drug?

Applying AFIR to 2nd generation drugs

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

Kd	Binding Affinity
T_{acc}	Target Accumulation
C_{avg}	Avg. Free Drug Conc.

+

$$C_{avg} \approx \frac{F \cdot f_u \cdot Dose}{CL \cdot \tau}$$

F	Bioavailability
fu	Fraction Unbound (small molecule)
CL	Clearance
τ	Dosing Interval

⇩

$$\frac{\text{Average Free Target}}{\text{Baseline Target}} \approx \frac{K_d \cdot T_{acc} \cdot CL \cdot \tau}{F \cdot f_u \cdot Dose}$$

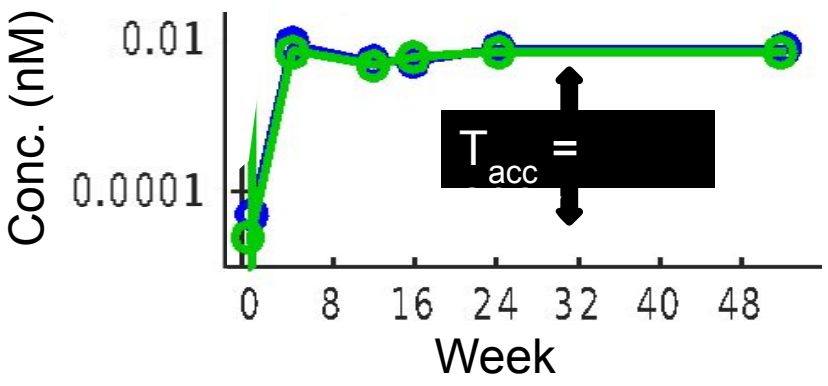
Using AFIR, other drug candidates can be rapidly assessed

$$AFIR = \frac{K_d \cdot T_{acc} \cdot CL \cdot \tau}{F \cdot f_u \cdot Dose}$$

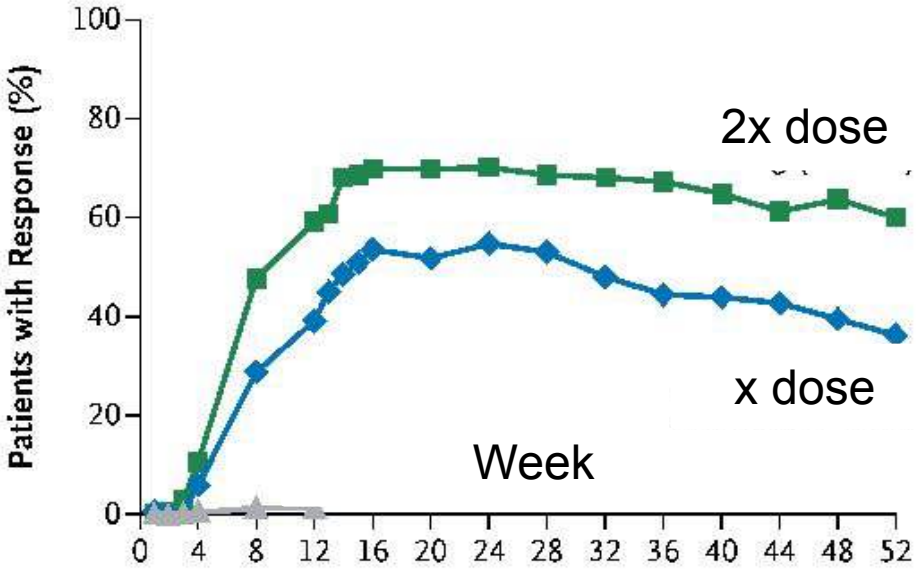
			subcutaneous mAb (150 kDa)
Affinity	Kd	nM	0.2
Accumulation	Tacc	-	200
Clearance	CL	L/day	0.17
Dose Interval	τ	day	30
Bioavailability	F	-	0.76
Free fraction	fu	-	1
Dose at 300 mg	Dose	nmol	2000
AFIR		-	14%

Greater efficacy is observed at 2x dose, even though total target has plateaued.

Total Target Data
Similar for X mg and 2X mg



Efficacy Metric
Superior for 2X dosing



AFIR goes from 28% to 14% after doubling dose.
It is the 200x accumulation of target (T_{acc}) that necessitates high doses

Identifiability –target inhibition can be estimated without baseline levels

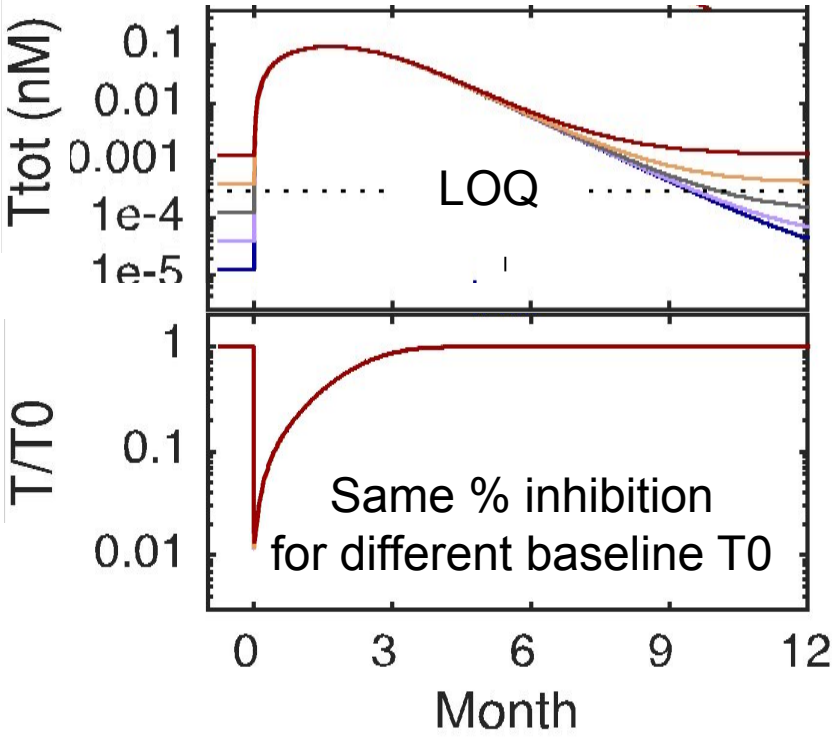
- Assay may not be sensitive enough to measure T_0.
- In that case, only three parameters may be identifiable:
  - k_{syn}, $T_{tot,ss}$, and T_0/K_d
- For free target inhibition, (T_0/K_d) is all that is needed

$$\frac{T(t)}{T_0} = \frac{K_d \cdot T_{acc}}{C(t)}$$

$$= \frac{K_d}{C(t)} \cdot \frac{T_{tot,ss}}{T_0}$$

$$= \left(\frac{T_{tot,ss}}{C(t)}\right)\left(\frac{T_0}{K_d}\right)$$

Varying T0,
keeping T0/Kd fixed



See poster T-087 for application to 4 compounds

Two new parameters for characterizing ligand binding systems

- Onset of PK nonlinearity: $C_{crit} = \frac{V_m}{CL}$
- Average target inhibition: $AFIR = \frac{K_d \cdot T_{acc}}{C_{avg}}$
- These simple expressions allow us to:
  - Predict doses needed for target inhibition
  - Understand sensitivity to model parameters
  - Understand which model parameters are identifiable
  - Interpret total target kinetics data
  - Rapidly benchmark compounds

Acknowledgements

- Mick Looby
- Bert Peletier
- Prasad Ramakrishna
- Henning Schmidt
- Jean-Louis Steimer
- Phil Lowe
- Karthik Subramanian
- Bruce Gomes
- Wenping Wang
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- Siyan Xu
- Brian Stoll
- Gerard Bruin
- Irina Koroleva
- Frank Kolbinger
- Max Woisetschlaeger

Backups

Calculating Free Target vs Total Target

- Algebraic manipulation of quasi-equilibrium equation

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

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

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

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

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

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

When Dtot >> Ttot, Kd

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

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

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

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

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

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

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 $DT \approx T_{tot}$

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

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

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

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

c

Is there an optimal Kd? It depends on definition of “optimal”

- Abhinav Tiwari et al. [1] report that an optimal Kd is when Kd ≈ 10% baseline target levels.
- AFIR analysis predicts that at large doses, reducing Kd by 50% will reduce the free target by 50%.
  - $\text{AFIR} = \frac{K_d \cdot T_{acc}}{C_{avg}}$
- Why do these two results seem to differ?

1. Tiwari, Abhinav, et al. "Optimal Affinity of a Monoclonal Antibody: Guiding Principles Using Mechanistic Modeling." The AAPS journal 19.2 (2017): 510-519.

Tiwari defines “optimal” Kd with respect to dose reduction

- Tiwari definition: Kd is at optimum when reducing Kd does not allow one to lower the dose and achieve comparable inhibition.
- AFIR equation gives:
  - AFIR $= \frac{K_d \cdot T_{acc}}{C_{avg}} = \frac{K_d \cdot T_{acc} \cdot CL \cdot \tau}{Dose \cdot F} = \left(\frac{K_d}{Dose}\right) \cdot \frac{T_{acc} \cdot CL \cdot \tau}{F}$
  - Reducing Kd always reduces inhibition
  - Why do these two analyses differ?
- AFIR approximation requires drug in excess to target.
- If dose is so low that [Target] $\gg$ [Drug], there are not enough drug molecules to bind target. Kd is irrelevant

Questions for TMDD models

- What % of drug gets into the tumor (B)?
- Can soluble targets accumulate in tumor? Or other tissue?
- Future research
  - Account for both membrane-bound and soluble ligands + shedding
  - Account for competitive endogenous ligand
  - Account for spatial heterogeneity in the tumor