

AFIRT: A parameter for predicting target inhibition in tissue in order to guide dose selection of biologics.

Abstract Word Count: XYZ

Body Word Count (including figure captions): XYZ

Number of Figures: XYZ

Number of Tables: XYZ

Keywords: monoclonal antibody | target mediated drug disposition | pharmacokinetics and pharmacodynamics | pharmacometrics

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Figure are in a separate file at the end of this document. They'll images themselves will need to be removed for CPT:PSP (06-Figures.tex).

Abstract

XYZ

1 Rough outline

In this paper we will:

- derive AFIRT
 - new result = AFIRT formula
 - new result = Kssd
- use sensitivity analysis to confirm AFIRT formula and show when it fails
 - large receptor concentration (herceptin = trastuzumab)
- specific practical results from AFIRT and sensitivity analysis
 - demonstrate the importance of understanding tissue-accumulation (bevacizumab)
 - explore how fast shed rate needs to be to limit inhibition
- discussion
 - practical value - don't need every microconstant, just a few lumped parameter estimates
 - don't need a complex physiological model, the simple formula can work well
 - essentially, Kssd should have been used for atezo instead of Kd

2 Introduction

During biologic drug development, prediction of target engagement at the site of action plays a critical role in dose regimen selection [?]. Because target engagement measurements at the site of action are often impossible to obtain, model based predictions of target engagement at the site of action are often used to help justify the dose regimen selection. The methods used to predict target engagement vary significantly in their level of complexity and assumptions and we briefly describe here both a simple and complex approach for two different immunotherapies: pembrolizumab and atezolizumab.

For the PD-1 inhibitor pembrolizumab, a physiologically based model for antibody distribution and target engagement was developed to predict the dose needed to achieve target engagement and tumor suppression [?]. This model made many detailed assumptions about many parameters in mouse and in how these parameters would scale to humans. For the PD-L1 inhibitor atezolizumab, a much simpler approach was taken to help justify the dose regimen, where a particular tumor biodistribution coefficient (B) and in vivo binding affinity (K_d) was assumed, the steady state trough concentration (C_{min}) was estimated from clinical observations, and then the receptor occupancy (RO) formula in Equation 1 was used to identify the dosing regimen that would provide the

drug concentration needed to achieve 95% target occupancy. Fewer assumptions about specific parameters are made with this simple model, but in choosing this simple model, many implicit assumptions are made, which were not all clearly stated.

$$RO = B \cdot C_{\min} / (B \cdot C_{\min} + K_d) \quad (1)$$

The advantage of using the complex, mechanistic model as done for pembrolizumab is that ideally, it captures all essential underlying physiology processes in making the dose regimen prediction. The disadvantage of this approach is that physiological models can be complex, making them time consuming to develop, difficult to estimate all model parameters, and challenging to explain to collaborators. The advantage using the simple RO formula as done for atezolizumab is that it is fast, easy to implement, and easy to explain to collaborators. The disadvantage is that it is not immediately obvious that Equation 1 is the appropriate equation to use to describe the clinical scenario as this equation was derived for the *in vitro* setting for chemical species[?] where there was no drug distribution, target distribution, receptor synthesis, or receptor internalization/shedding.

In this paper, a mathematical analysis of a physiologically-based model for drug distribution and target turnover is performed and a simple expression for predicting target engagement in the clinical scenario is derived. All assumptions made in deriving this formula are explicitly stated. This paper extends previous work that focused on target engagement in circulation, as characterized by the Average Free target to Initial target Ratio (AFIR) at steady state in circulation [?].

PROVIDE AN OUTLINE OF THE PAPER HERE

3 Theory

In this section, an expression for the average free target to initial target ratio in tissue (AFIRT) is derived for the model in Figure ??.

3.1 Model Description

The model in Figure ?? is based on the standard TMDD model [?, ?], where a drug (D) binds its target, but it has been extended to include the following processes:

- Shedding of the membrane bound target (M) into soluble target (S).
- The drug can bind both the soluble target and the membrane-bound target to form complexes DS and DM respectively.
- Both the soluble and membrane-bound target are present in both the central compartment (1) and a tissue compartment (3).
- Soluble target is able to distribute between the central and tissue compartment (e.g. passive diffusion of target molecules)

- Membrane-bound target is able to distribute between central and tissue compartment (e.g. active trafficking of immune cells expressing the membrane-bound target).

As with the standard TMDD model, the peripheral compartment (2) contains the drug only; it is included so that the two-compartment pharmacokinetics of the drug can be described. This model is more complex than most physiological models in the literature. Often, trafficking of the membrane-bound target is ignored and often, either the soluble or membrane-bound target is modeled but not both. In this paper, an analysis of this complete model is performed. The simpler scenarios can easily be represented using this model and setting the appropriate parameters to zero.

The ordinary differential equations for describing this system are summarized

below.

$$\begin{aligned} \frac{dD_1}{dt} = & \frac{1}{V_C} \text{Dose}_{iv}(t) - k_{12D} D_1 + \frac{V_{D_2}}{V_{D_1}} k_{21D} D_2 - k_{13D} D_1 + \frac{V_{D_3}}{V_{D_1}} k_{31D} D_3 \\ & - k_{eD1} D_1 - k_{on1} D_1 \cdot S_1 + k_{off1}(DS_1) - k_{on1} D_1 \cdot M_1 + k_{off1}(DM_1) \end{aligned} \quad (2)$$

$$\frac{dD_2}{dt} = k_{12D} \frac{V_{D_1}}{V_{D_2}} D_1 - k_{21D} D_2 \quad (3)$$

$$\begin{aligned} \frac{dD_3}{dt} = & \frac{V_{D_1}}{V_{D_3}} k_{13D} D_1 - k_{31D} D_3 - k_{eD3} D_3 - k_{on3} D_3 \cdot M_3 + k_{off3}(DM_3) \\ & - k_{on3} D_3 \cdot S_3 + k_{off3}(DS_3) \end{aligned} \quad (4)$$

$$\begin{aligned} \frac{dM_1}{dt} = & k_{synM1} - k_{shedM1} M_1 - k_{13M} M_1 + \frac{V_{M_3}}{V_{M_1}} k_{31M} M_3 - k_{eM1} M_1 \\ & - k_{on1} D_1 \cdot M_1 + k_{off1}(DM_1) \end{aligned} \quad (5)$$

$$\begin{aligned} \frac{dM_3}{dt} = & k_{syn3} - k_{shedM3} M_3 + \frac{V_{M_1}}{V_{M_3}} k_{13M} M_1 - k_{31M} M_3 - k_{eM3} M_3 - \\ & k_{on3} D_3 \cdot M_3 + k_{off3}(DM_3) \end{aligned} \quad (6)$$

$$\begin{aligned} \frac{dS_1}{dt} = & k_{synS1} + k_{shedM1} M_1 - k_{13S} S_1 + \frac{V_{S_3}}{V_{S_1}} k_{31S} S_3 - k_{eS1} S_1 - k_{on1} D_1 \cdot S_1 \\ & + k_{off1}(DS_1) \end{aligned} \quad (7)$$

$$\begin{aligned} \frac{dS_3}{dt} = & k_{synS3} + k_{shedM3} M_3 - k_{31S} S_3 + \frac{V_{S_1}}{V_{S_3}} k_{13S} S_1 - k_{eS3} S_3 - k_{on3} D_3 \cdot S_3 \\ & + k_{off3}(DS_3) \end{aligned} \quad (8)$$

$$\begin{aligned} \frac{d(DM_1)}{dt} = & -k_{shedDM1} DM_1 - k_{13DM}(DM_1) + \frac{V_{DM_3}}{V_{DM_1}} k_{31DM}(DM_3) - k_{eDM1} DM_1 \\ & + k_{on1} D_1 \cdot M_1 - k_{off1}(DM_1) \end{aligned} \quad (9)$$

$$\begin{aligned} \frac{d(DM_3)}{dt} = & -k_{shedDM3} DM_3 - k_{31DM}(DM_3) + \frac{V_{DM_1}}{V_{DM_3}} k_{13DM}(DM_1) - k_{eDM3} DM_3 \\ & + k_{on3} D_3 \cdot M_3 - k_{off3}(DM_3) \end{aligned} \quad (10)$$

$$\begin{aligned} \frac{d(DS_1)}{dt} = & -k_{shedDM3} DS_1 - k_{13DS} DS_1 + \frac{V_{DS_3}}{V_{DS_1}} k_{31DS} DS_3 - k_{eDS1}(DS_1) \\ & + k_{on1} D_1 \cdot S_1 - k_{off1}(DS_1) \end{aligned} \quad (11)$$

$$\begin{aligned} \frac{d(DS_3)}{dt} = & -k_{shedDM3} DS_3 - k_{31DS} DS_3 + \frac{V_{DS_1}}{V_{DS_3}} k_{13DS} DS_1 - k_{eDS3}(DS_3) \\ & + k_{on3} D_1 \cdot S_3 - k_{off1}(DS_3) \end{aligned} \quad (12)$$

For the first time we are calculating the AFIRT using an alternative approximations to the quasi-equilibrium (QE), the quasi-steady state (QSS) and the quasi-steady state xxxxxxxx (QSSD). The quasi-steady state approximation assumed that $-k_{shedDM3} DM_3 - k_{eDM3} DM_3 + k_{on3} D_3 \cdot M_3 - k_{off3}(DM_3) = 0$, similarly as before for k_d we define $k_{ss} = \frac{k_{shedDM3} + k_{eDM3} + k_{off3}}{k_{on3}}$.

DESCRIBE THE INITIAL CONDITIONS OF THE MODEL

3.2 AFIRT derivation

The general form of AFIRT is the following

$$\text{AFIRT} = \text{Free Fraction Coefficient} \times \text{Target Accumulation Rate} \times \frac{CL \times \tau}{B \times \text{Dose}}$$

Depending on particular drug, the target can be membrane-bound or soluable. Free Fraction Coefficient(FCC) measures how fast drug-target complex unbinds

$$\text{FCC} = \frac{DT_3}{D_3 \cdot T_3}$$

Target Accumulation Rate (T_{acc}) measures free target to initial target ratio at steady state.

$$T_{\text{acc}} = \frac{T_{\text{ss}}}{T_{\text{in}}}$$

The calculation of FCC will depend on how fast various processes are assumed to be. For membrane-bound target, the following three FCC will be used for AFIRT

$$\begin{aligned} K_{\text{ssd}} &= \frac{k_{\text{off}3} + k_{e\text{DM}3} + k_{\text{shedDM}3} + k_{31\text{DM}}}{k_{\text{on}3}} \\ K_{\text{ss}} &= \frac{k_{\text{off}3} + k_{e\text{DM}3} + k_{\text{shedDM}3}}{k_{\text{on}3}} \\ K_{\text{d}} &= \frac{k_{\text{off}3}}{k_{\text{on}3}} \end{aligned}$$

Likewise, the following three FCC will be used for soluable target

$$\begin{aligned} K_{\text{ssd}} &= \frac{k_{\text{off}3} + k_{e\text{DS}3} + k_{31\text{DS}}}{k_{\text{on}3}} \\ K_{\text{ss}} &= \frac{k_{\text{off}3} + k_{e\text{DS}3}}{k_{\text{on}3}} \\ K_{\text{d}} &= \frac{k_{\text{off}3}}{k_{\text{on}3}} \end{aligned}$$

Their derivation can be found in the appendix.

For membrane-bound target, the target accumulation rate can be computed as

$$T_{\text{acc}} = \frac{T_{\text{tot,ss}}}{T_{30}}$$

where $T_{\text{tot,ss}}$ means drug-target complex concentration at steady state, and T_{30} means target concentration at the initial state. At the initial state, the change of target in D_1 and D_3 are both zero. Therefore, to solve T_{10} and T_{30} , one can set equation 5 and 6 (resp, 7 and 8 for soluable target) to be zero and solve the

linear system. At the steady state, targets in both D_1 and D_3 are in the form of complexes, and the change of complex concentration is zero. Therefore, to solve $T_{1\text{tot},ss}$ and $T_{3\text{tot},ss}$, one can set equation 9 and 10 (resp, 11 and 12 for soluable target) to be zero, and solve the linear system.

$$M_{30} = \frac{\frac{V_C}{V_T} k_{13M} k_{synM1} + (k_{shedM1} + k_{13M} + k_{eM1}) k_{synM1}}{(k_{shedM1} + k_{13M} + k_{eM1})(k_{shedM3} + k_{31M} + k_{eM3}) - k_{13M} k_{31M}}$$

$$M_{3\text{tot},ss} = \frac{\frac{V_C}{V_T} k_{13DM} k_{synM1} + (k_{shedDM1} + k_{13DM} + k_{eDM1}) k_{synM1}}{(k_{shedDM1} + k_{13DM} + k_{eDM1})(k_{shedDM3} + k_{31DM} + k_{eDM3})}$$

$$S_{30} = \frac{\frac{V_C}{V_T} \cdot k_{13S} \cdot (k_{synS1} + k_{shedM1} M_{10}) + (k_{13S} + k_{eS1})(k_{synS3} + k_{shedM3} M_{30})}{(k_{13S} + k_{eS1})(k_{31S} + k_{eS3}) - k_{13S} k_{31S}}$$

$$S_{3\text{tot},ss} = \frac{\frac{V_C}{V_T} k_{13DS} \cdot (k_{synS1} + k_{shedDM1} M_{1\text{tot},ss}) + (k_{13DS} + k_{eDS1})(k_{synS3} + k_{shedDM3} M_{3\text{tot},ss})}{(k_{13DS} + k_{eDS1})(k_{31DS} + k_{eDS3}) - k_{13DS} k_{31DS}}$$

Their derivation can be found in the appendix.

I PROPOSE THAT THIS SECTION START WITH A HIGH LEVEL OVERVIEW OF THE STEPS TO CALCULATE AFIRT. THEN, THESE STEPS CAN EITHER BE REPRODUCED IN THE MAIN BODY OR IN THE APPENDIX.

KEY STEPS

- Focus on steady state for a constant infusion.
- Assume the drug concentration is very large
- Calculate drug concentration in tissue at steady state $D_{\text{tot,avg3,ss}} = C_{\text{avg3,ss}} = B \cdot C_{\text{avg1,ss}} = D_{\text{tot,avg1,ss}}$.
 - For large drug concentration, target kinetics can be ignored.
 - Use the similarity transform to remove k_{eD3} .
 - This gives us a simple expression for $C_{\text{avg1}} = D_{\text{tot,avg1}}$ as a function of CL .
 - This also gives us an expression for B such that $C_{\text{avg3}} = D_{\text{tot,avg3}} = B \cdot C_{\text{avg1}}$.
- Calculate target concentration in tissue at steady state.
 - For large drug concentration, drug kinetics can be ignored.
 - Do the small matrix algebra inversion to calculate M_{30} and $M_{3\text{tot},ss}$.
 - Calculate accumulation factor
- Calculate the free fraction by assuming various processes are slow/fast.
 - K_d
 - K_{ss}

– K_{ssd}

- Putting this all together gives $AFIRT_M$.
- A similar process can be followed for $AFIRT_S$.

3.2.1 Membrane-bound Target

The quasi-steady state approximation assumed that $-k_{shedDM_3}DM_3 - k_{31DM}(DM_3) - k_{eDM3}DM_3 + k_{on3}D_3 \cdot M_3 - k_{off3}(DM_3) = 0$, we define $k_{ssd} = \frac{k_{shedDM_3} + k_{31DM} + k_{eDM3} + k_{off3}}{k_{on3}}$. These approximations are obtained from equation (16) at steady state, i.e. $\frac{d(DM_3)}{dt} = 0$, and assuming the terms $\frac{V_{DM_1}}{V_{DM_3}}k_{13DM}(DM_1)$ and $k_{31DM}(DM_3)$ are negligible for the QSS. We assume that only $\frac{V_{DM_1}}{V_{DM_3}}k_{13DM}(DM_1)$ is negligible for the QSSD.

We obtain the following approximations

$$\begin{aligned} AFIRT &\approx k_{ssd} \frac{M_{3tot,ss}}{M_{3,0}} \frac{CL \times \tau}{B \times Dose}, \\ AFIRT &\approx k_{ss} \frac{M_{3tot,ss}}{M_{3,0}} \frac{CL \times \tau}{B \times Dose}, \\ AFIRT &\approx k_d \frac{M_{3tot,ss}}{M_{3,0}} \frac{CL \times \tau}{B \times Dose}, \end{aligned}$$

where

$$\begin{aligned} M_{3tot,ss} &= \frac{k_{13DM}(V_C/V_T)k_{synM1} + (k_{eDM1} + k_{shedDM1} + k_{13DM})k_{synM3}}{(k_{eDM1} + k_{shedDM1} + k_{13DM})(k_{eDM3} + k_{shedDM3} + k_{31DM}) - k_{31DM}k_{13DM}}, \\ M_{3,0} &= \frac{k_{13M}(V_C/V_T)k_{synM1} + (k_{eM1} + k_{shedM1} + k_{13M})k_{synM3}}{(k_{eM1} + k_{shedM1} + k_{13M})(k_{eM3} + k_{shedM3} + k_{31M}) - k_{31M}k_{13M}}, \\ B &= \frac{k_{13D}(V_C/V_T)}{k_{eD3} + k_{31D}}. \end{aligned}$$

We can notice from the picture below that the approximation obtained using the (QSS) hypothesis gives better results than the one using (QE).

3.2.2 Soluble target at Initial State and Steady State

With the same notations as in the sections above.

At initial state, we have

$$\begin{aligned}\frac{dS_1}{dt} &= 0 \\ \frac{dS_3}{dt} &= 0 \\ M_1 &= M_{10} \\ M_3 &= M_{30} \\ D_1 &= 0 \\ D_3 &= 0 \\ DS_1 &= 0 \\ DS_3 &= 0\end{aligned}$$

So ODE 13 and 14 give us the following linear system

$$\begin{bmatrix} -(k_{13S} + k_{eS1}) & \frac{V_T}{V_C} k_{31S} \\ \frac{V_C}{V_T} k_{13S} & -(k_{31S} + k_{eS3}) \end{bmatrix} \cdot \begin{bmatrix} S_1 \\ S_3 \end{bmatrix}_0 = \begin{bmatrix} -k_{synS1} - k_{shedM1} M_{10} \\ -k_{synS3} - k_{shedM3} M_{30} \end{bmatrix}.$$

So the initial soluble target concentration in the central and tumor compartment is

$$S_{10} = \frac{(k_{31S} + k_{eS3}) \cdot (k_{synS1} + k_{shedM1} M_{10}) + \frac{V_T}{V_C} k_{31S} (k_{synS3} + k_{shedM3} M_{30})}{(k_{13S} + k_{eS1})(k_{31S} + k_{eS3}) - k_{13S} k_{31S}} \quad (13)$$

$$S_{30} = \frac{\frac{V_C}{V_T} \cdot k_{13S} \cdot (k_{synS1} + k_{shedM1} M_{10}) + (k_{13S} + k_{eS1})(k_{synS3} + k_{shedM3} M_{30})}{(k_{13S} + k_{eS1})(k_{31S} + k_{eS3}) - k_{13S} k_{31S}}. \quad (14)$$

At steady state, we assume that all soluble target are in the form of bounded complex. By the symmetry of our model, we have

$$\begin{aligned}S_{1tot,ss} &= \frac{(k_{31DS} + k_{eDS3}) \cdot (k_{synS1} + k_{shedDM1} M_{1tot,ss}) + \frac{V_T}{V_C} k_{31DS} (k_{synS3} + k_{shedDM3} M_{3tot,ss})}{(k_{13DS} + k_{eDS1})(k_{31DS} + k_{eDS3}) - k_{13DS} k_{31DS}} \\ S_{3tot,ss} &= \frac{\frac{V_C}{V_T} k_{13DS} \cdot (k_{synS1} + k_{shedDM1} M_{1tot,ss}) + (k_{13DS} + k_{eDS1})(k_{synS3} + k_{shedDM3} M_{3tot,ss})}{(k_{13DS} + k_{eDS1})(k_{31DS} + k_{eDS3}) - k_{13DS} k_{31DS}}\end{aligned}$$

Formulas for computing membrane target at initial and steady state can be found in *Model F Appendix*, for convenience, we include them below

$$M_{10} = \frac{(k_{shedM3} + k_{31M} + k_{eM3})k_{synM1} + \frac{V_T}{V_C}k_{31M}k_{synM3}}{(k_{shedM1} + k_{13M} + k_{eM1})(k_{shedM3} + k_{31M} + k_{eM3}) - k_{13M}k_{31M}}$$

$$M_{30} = \frac{\frac{V_C}{V_T}k_{13M}k_{synM1} + (k_{shedM1} + k_{13M} + k_{eM1})k_{synM1}}{(k_{shedM1} + k_{13M} + k_{eM1})(k_{shedM3} + k_{31M} + k_{eM3}) - k_{13M}k_{31M}}$$

$$M_{1tot,ss} = \frac{(k_{shedDM3} + k_{31DM} + k_{eDM3})k_{synM1} + \frac{V_T}{V_C}k_{31DM}k_{synM3}}{(k_{shedDM1} + k_{13DM} + k_{eDM1})(k_{shedDM3} + k_{31DM} + k_{eDM3})}$$

$$M_{3tot,ss} = \frac{\frac{V_C}{V_T}k_{13DM}k_{synM1} + (k_{shedDM1} + k_{13DM} + k_{eDM1})k_{synM1}}{(k_{shedDM1} + k_{13DM} + k_{eDM1})(k_{shedDM3} + k_{31DM} + k_{eDM3})}$$

The formulas to compute various AFIRTS for soluble targets in the tumor compartment are

$$\text{AFIRTS.Kssd} = \text{Kssd.S} \times \frac{\text{Tacc.tum.S}}{B \times C_{avg1}} \quad (15)$$

$$\text{AFIRTS.Kss} = \text{Kss.S} \times \frac{\text{Tacc.tum.S}}{B \times C_{avg1}} \quad (16)$$

$$\text{AFIRTS.Kd} = \text{Kd.S} \times \frac{\text{Tacc.tum.S}}{B \times C_{avg1}} \quad (17)$$

(18)

Where Kssd.S, Kss.S and Kd.S

$$\text{Kssd.S} = \frac{k_{shedDM3} + k_{31DS} + k_{eDS} + k_{off3}}{k_{on3}} \quad (19)$$

$$\text{Kss.S} = \frac{k_{shedDM3} + k_{eDS} + k_{off3}}{k_{on3}} \quad (20)$$

$$\text{Kd.S} = \frac{k_{off3}}{k_{on3}} \quad (21)$$

(22)

Finally,

$$\text{Tacc.tum.S} = \text{S3tot.ss}/\text{S30} \quad (23)$$

To compute AFIRT for soluable target from simulation, do

1. compute Sfree.pct := $\frac{S_3}{S_{30}}$
2. take the average of Sfree.pct in the steady steady state
3. return the result from step 2

4 Methods and Results

5 Discussion

The key insight from this work is that under many clinically relevant scenarios, AFIRT can be estimated using four parameters: a binding constant (K_{eq}), the target accumulation ratio (T_{acc}), the average drug concentration in circulation (C_{avg}) and the biodistribution coefficient for the drug to the tissue of interest (B)

$$\text{AFIRT} = \frac{K_{\text{eq}} \cdot T_{\text{acc}}}{B \cdot C_{\text{avg}}} \quad (24)$$

The binding constant (K_{eq}) above depends on the nature of the target of interest.

- For soluble targets, a surface plasmon resonance estimate for K_d may be sufficient. It should be noted that there have been scenarios where the estimate for the in vitro and in vivo K_d differed by 1000-fold (e.g. TNF- α [?, Figure 8]).
- For membrane-bound targets on cells where trafficking between tissue and circulation is negligible, K_{ss} can be estimated by a cell-based assay.
- For membrane-bound targets on cells where trafficking between tissue and circulation is rapid, K_{ssd} may be needed. As it is not clear how to directly estimate this parameter, one solution is to adjust a cell-based estimate for K_{ss} by a "safety factor."
- Key Insight = AFIRT
 - Just need a few terms, don't need a big mechanistic model
 - Mention effect of doubling dose, halving K_{ss} etc.
But halving K_{ss} is different from halving K_d .
- Review Assumptions needed for AFIRT to hold
 - large drug concentration
 - distribution of drug-target complex out of tissue can be ignored
 - fluctuations during dosing interval can be ignored
 - others?
- Importance of using K_{ss} or even K_{ssd} from cell based assays instead of K_d . The more realistic the preclinical system, the better.
- Things that are ignored
 - Feedback, though this would be easy to include. Just need to have different ksyn for initial condition and steady state.

- Low-Intermediate concentrations, especially relevant for ADCs and bispecifics.
- Competition for target binding sites between drug and endogenous ligand.

- Applications
 - Can rapidly assess new drugs
 - Can help inform dose finding

Also mention connection with L50 from [?]

6 Conclusion

7 Appendix

7.1 Predicting drug concentration in tissue ($D_{\text{tot,avg3}}$)

Ignoring target, then at steady state

$$\begin{aligned} - \begin{pmatrix} k_{\text{inf}} \\ 0 \\ 0 \end{pmatrix} &= \frac{d}{dt} \begin{pmatrix} D_1 \\ D_2 \\ D_3 \end{pmatrix} = \begin{pmatrix} -(k_e D_1 + k_{12D} + k_{13D}) & (V_P/V_C)k_{21D} & (V_T/V_C)k_{31D} \\ (V_C/V_P)k_{12D} & -k_{21D} & 0 \\ (V_C/V_T)k_{13D} & 0 & -(k_e D_3 + k_{31D}) \end{pmatrix} \cdot \begin{pmatrix} D_1 \\ D_2 \\ D_3 \end{pmatrix} \\ &= A \cdot \begin{pmatrix} D_1 \\ D_2 \\ D_3 \end{pmatrix} \end{aligned}$$

B is given by the ratio of $D_{3,ss}/D_{1,ss}$ at steady state.

$$\begin{aligned} \begin{pmatrix} D_1 \\ D_2 \\ D_3 \end{pmatrix}_{ss} &= A^{-1} \cdot \begin{pmatrix} -k_{\text{inf}} \\ 0 \\ 0 \end{pmatrix} \\ \begin{pmatrix} D_1 \\ D_2 \\ D_3 \end{pmatrix}_{ss} &= \frac{-k_{\text{inf}}}{\det A} \begin{pmatrix} a_{22}a_{33} - a_{23}a_{32} \\ a_{23}a_{31} - a_{21}a_{33} \\ a_{21}a_{32} - a_{22}a_{31} \end{pmatrix} = \begin{pmatrix} k_{21D}(k_e D_3 + k_{31D}) \\ k_{21D}(V_P/V_C)(k_e D_3 + k_{31D}) \\ k_{21D}(V_C/V_T)k_{13D} \end{pmatrix} \end{aligned}$$

And finally, the biodistribution coefficient for tissue 3 is given by:

$$B = \left(\frac{D_3}{D_1} \right)_{ss} = \frac{k_{21D}(V_C/V_T)k_{13D}}{k_{21D}(k_e D_3 + k_{31D})} = \frac{V_C}{V_T} \cdot \frac{k_{13D}}{(k_e D_3 + k_{31D})}$$

Thus in the limits prescribed above, where target expression does not effect drug distribution, we have:

$$D_{\text{tot,avg3}} = B \cdot D_{\text{tot,avg1}}$$

7.2 Predicting Target accumulation in Target Tissue ($M_{\text{acc}3}$)

Before the drug is given, the initial steady state target levels can be computed by solving the system below:

$$\begin{pmatrix} 0 \\ 0 \end{pmatrix} = \frac{d}{dt} \begin{pmatrix} M_1 \\ M_3 \end{pmatrix} = \begin{pmatrix} -(k_{eM1} + k_{13M} + k_{\text{shed}M_1}) & (V_T/V_C)k_{31M} \\ (V_C/V_T)k_{13T} & -(k_{eM3} + k_{31M} + k_{\text{shed}M_3}) \end{pmatrix} \begin{pmatrix} M_1 \\ M_3 \end{pmatrix}_0 + \begin{pmatrix} k_{\text{syn}1} \\ k_{\text{syn}3} \end{pmatrix}$$

$$\begin{pmatrix} k_{\text{syn}1} \\ k_{\text{syn}3} \end{pmatrix} = \begin{pmatrix} (k_{eM1} + k_{13M} + k_{\text{shed}M_1}) & -(V_T/V_C)k_{31M} \\ -(V_C/V_T)k_{13M} & (k_{eM3} + k_{31M} + k_{\text{shed}M_3}) \end{pmatrix} \begin{pmatrix} M_1 \\ M_3 \end{pmatrix}_0$$

Then, using the formula for inverting a 2d matrix gives

$$\begin{pmatrix} M_1 \\ M_3 \end{pmatrix}_0 = \frac{1}{((k_{eM3} + k_{31M} + k_{\text{shed}M_3})(k_{eM1} + k_{13M} + k_{\text{shed}M_1}) - k_{13T}k_{31T})} \times$$

$$\begin{pmatrix} (k_{eM3} + k_{31M} + k_{\text{shed}M_3}) & (V_T/V_C)k_{31M} \\ (V_C/V_T)k_{13M} & (k_{eM1} + k_{13M} + k_{\text{shed}M_1}) \end{pmatrix} \begin{pmatrix} k_{\text{syn}1} \\ k_{\text{syn}3} \end{pmatrix}$$

The key parameter of interest is the target expression in the tissue of interest:

$$M_{3,0} = \frac{k_{13M}(V_C/V_T)k_{\text{syn}M1} + (k_{eM1} + k_{\text{shed}M_1} + k_{13M})k_{\text{syn}3}}{(k_{eM1} + k_{\text{shed}M_1} + k_{13M})(k_{eM3} + k_{\text{shed}M_3} + k_{31M}) - k_{31M}k_{13M}}$$

If we assume that the drug is in vast excess to the amount of target and that almost all the target is present as bound to drug, then the total target kinetics can be described by the same set of equations above, but replacing all M terms with DM terms, giving

$$M_{3\text{tot},ss} = \frac{k_{13DM}(V_C/V_T)k_{\text{syn}M1} + (k_{eDM1} + k_{\text{shed}DM_1} + k_{13DM})k_{\text{syn}3}}{(k_{eDM1} + k_{\text{shed}DM_1} + k_{13DM})(k_{eDM3} + k_{\text{shed}DM_3} + k_{31DM}) - k_{31DM}k_{13DM}}$$

Then, to compute $M_{\text{acc}3}$ just take the ratio of $M_{\text{tot}3}/M_{03}$

$$M_{\text{acc}3} = \frac{M_{\text{tot}3}}{M_{03}} = \frac{k_{13DM}(V_C/V_T)k_{\text{syn}M1} + (k_{eDM1} + k_{\text{shed}DM_1} + k_{13DM})k_{\text{syn}3}}{(k_{eDM1} + k_{\text{shed}DM_1} + k_{13DM})(k_{eDM3} + k_{\text{shed}DM_3} + k_{31DM}) - k_{31DM}k_{13DM}} \times$$

$$\frac{(k_{eM1} + k_{\text{shed}M_1} + k_{13M})(k_{eM3} + k_{\text{shed}M_3} + k_{31M}) - k_{31M}k_{13M}}{k_{13M}(V_C/V_T)k_{\text{syn}M1} + (k_{eM1} + k_{\text{shed}M_1} + k_{13M})k_{\text{syn}3}}$$

7.3 Similarity Transform

We consider the model in Figure 1. A drug (D) binds to its target (M) to form a complex (DM). It has three compartments, central, tissue, and peripheral.

The drug and target dynamics are modeled with the following system of

ordinary differential equations

$$\begin{aligned} \frac{dD_1}{dt} &= \frac{1}{V_1} \text{Dose}_{iv}(t) - k_{12D} D_1 + \frac{V_3}{V_1} k_{21D} D_2 - k_{13D} D_1 \\ &\quad + \frac{V_2}{V_1} k_{31D} D_3 - k_{on1} D_1 \cdot M_1 + k_{off1}(DM_1) - k_{eD1} D_1 \end{aligned} \quad (25)$$

$$\frac{dD_2}{dt} = k_{12D} \frac{V_1}{V_3} D_1 - k_{21D} D_2 \quad (26)$$

$$\frac{dD_3}{dt} = \frac{V_1}{V_2} k_{13D} D_1 - k_{31D} D_3 - k_{on3} D_3 \cdot M_3 + k_{off3}(DM_3) - k_{eD3} D_3 \quad (27)$$

$$\begin{aligned} \frac{dM_1}{dt} &= k_{syn1} - k_{13M} M_1 + \frac{V_2}{V_1} k_{31M} M_3 - k_{on1} D_1 \cdot M_1 + k_{off1}(DM_1) \\ &\quad - k_{eM1} M_1 \end{aligned} \quad (28)$$

$$\begin{aligned} \frac{dM_3}{dt} &= k_{syn3} + \frac{V_1}{V_2} k_{13M} M_1 - k_{31M} M_3 - k_{on3} D_3 \cdot M_3 + k_{off3}(DM_3) \\ &\quad - k_{eM3} M_3 \end{aligned} \quad (29)$$

$$\begin{aligned} \frac{d(DM_1)}{dt} &= -k_{13DM}(DM_1) + \frac{V_2}{V_1} k_{31DM}(DM_3) + k_{on1} D_1 \cdot M_1 - k_{off1}(DM_1) \\ &\quad - k_{eDM1}(DM_1) \end{aligned} \quad (30)$$

$$\begin{aligned} \frac{d(DM_3)}{dt} &= \frac{V_1}{V_2} k_{13DM}(DM_1) - k_{31DM}(DM_3) + k_{on3} D_3 \cdot M_3 - k_{off3}(DM_3) \\ &\quad - k_{eDM3}(DM_3) \end{aligned} \quad (31)$$

(32)

We will calculate $D_{tot,avg3}$, which is the average drug concentration at steady state in the tissue. We have $D_{tot,avg3} = B \cdot D_{tot,avg1}$, where $D_{tot,avg1}$ is the average drug concentration at steady state in the central, and B is the antibody biodistribution coefficient. Assume that drug elimination only occurs in the central compartment, i.e., $k_{eD3} = 0$. Then for drugs dosed with linear PK at regular intervals and concentration much larger than target concentration, we have $D_{tot,avg1} = \text{Dose}/(CL \cdot \tau)$, where $CL = k_{eD1} \cdot V_1$ is the drug clearance [CITE REFERENCE 25 FROM AFIR ARTICLE].

For the model with drug elimination in both the central and tissue compartments, we will derive an alternative model with $k_{eD3} = 0$ that is indistinguishable from the existing model by using the similarity transform technique [CITE GODFREY 1989]. We consider drug concentration large enough that target binding does not affect drug distribution. Then the model equations for the drug can be written as

$$\frac{d\mathbf{D}}{dt} = A \cdot \mathbf{D}(t) + B \cdot \text{Dose}_{iv}(t), \quad (33)$$

with measurement

$$\mathbf{m}(t) = C \cdot \mathbf{D}(t), \quad (34)$$

where

$$\mathbf{D} = \begin{pmatrix} D_1 \\ D_2 \\ D_3 \end{pmatrix}, \quad (35)$$

$$A = \begin{pmatrix} -(k_{13D} + k_{12D} + k_{eD1}) & \frac{V_3}{V_1} k_{21D} & \frac{V_2}{V_1} k_{31D} \\ \frac{V_1}{V_3} k_{12D} & -k_{21D} & 0 \\ \frac{V_1}{V_2} k_{13D} & 0 & -(k_{31D} + k_{eD3}) \end{pmatrix}, \quad (36)$$

$$B = \begin{pmatrix} \frac{1}{V_1} \\ 0 \\ 0 \end{pmatrix}, \quad (37)$$

$$C = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & 1 \end{pmatrix}. \quad (38)$$

We transform this model into an indistinguishable model with coefficient matrices A' , B' , and C' such that $k'_{eD3} = 0$. This is accomplished with the similarity transform

$$A' := TAT^{-1} \quad B' := TB \quad C' := CT^{-1}, \quad (39)$$

for some transformation matrix

$$T = \begin{pmatrix} t_{11} & t_{12} & t_{13} \\ t_{21} & t_{22} & t_{23} \\ t_{31} & t_{32} & t_{33} \end{pmatrix} \quad T^{-1} = \begin{pmatrix} \hat{t}_{11} & \hat{t}_{12} & \hat{t}_{13} \\ \hat{t}_{21} & \hat{t}_{22} & \hat{t}_{23} \\ \hat{t}_{31} & \hat{t}_{32} & \hat{t}_{33} \end{pmatrix}. \quad (40)$$

Alternatively, one can get this similarity transform with the change of variables $\mathbf{D} = T^{-1}\mathbf{D}'$. Then from (??) and (??) we have

$$\frac{d(T^{-1}\mathbf{D}')}{dt} = A \cdot (T^{-1}\mathbf{D}')(t) + B \cdot Dose_{iv}(t), \quad \mathbf{m}(t) = C \cdot (T^{-1}\mathbf{D}')(t). \quad (41)$$

Multiplying the first equation in (??) on the left by T yields

$$\frac{d\mathbf{D}'}{dt} = TAT^{-1} \cdot \mathbf{D}'(t) + TB \cdot Dose_{iv}(t). \quad (42)$$

Then we have the new model equation and measurement

$$\frac{d\mathbf{D}'}{dt} = A' \cdot \mathbf{D}'(t) + B' \cdot Dose_{iv}(t), \quad \mathbf{m}(t) = C' \cdot \mathbf{D}'(t), \quad (43)$$

where A' , B' , and C' are given by (??).

Regardless of model formulation, the same dose is given to D_1 , that is,

$$B' = B. \quad (44)$$

From this and (??) we get $t_{11} = 1$, $t_{21} = 0$, and $t_{31} = 0$. Regardless of model formulation, we measure D_1 and D_3 , that is,

$$C' = C. \quad (45)$$

From this and (??) we get $\hat{t}_{11} = 1$, $\hat{t}_{12} = 0$, $\hat{t}_{13} = 0$, $\hat{t}_{31} = 0$, $\hat{t}_{32} = 0$, and $\hat{t}_{33} = 1$. For a 3×3 matrix, the inverse is given by

$$T^{-1} = \frac{1}{\det T} \begin{pmatrix} t_{22}t_{33} - t_{23}t_{32} & t_{13}t_{32} - t_{12}t_{33} & t_{12}t_{23} - t_{13}t_{22} \\ t_{23}t_{31} - t_{21}t_{33} & t_{11}t_{33} - t_{13}t_{31} & t_{13}t_{21} - t_{11}t_{23} \\ t_{21}t_{32} - t_{22}t_{31} & t_{12}t_{31} - t_{11}t_{32} & t_{11}t_{22} - t_{12}t_{21} \end{pmatrix}, \quad (46)$$

with the determinant given by

$$\det T = t_{11}(t_{22}t_{33} - t_{23}t_{32}) - t_{12}(t_{21}t_{33} - t_{23}t_{31}) + t_{13}(t_{21}t_{32} - t_{22}t_{31}). \quad (47)$$

Putting the above findings into T^{-1} yields $t_{12} = 0$, $t_{13} = 0$, $t_{32} = 0$, and $t_{33} = 1$. From $TT^{-1} = I$, we get $t_{22} = 1$. Then we have

$$T = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & t_{23} \\ 0 & 0 & 1 \end{pmatrix} \quad T^{-1} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & -t_{23} \\ 0 & 0 & 1 \end{pmatrix}. \quad (48)$$

Putting this into (??) yields

$$A' = \begin{pmatrix} -(k_{13D} + k_{12D} + k_{eD1}) & \frac{V_3}{V_1}k_{21D} & -\frac{V_3}{V_1}k_{21D}t_{23} + \frac{V_2}{V_1}k_{31D} \\ \frac{V_1}{V_3}k_{12D} + \frac{V_1}{V_2}k_{13D}t_{23} & -k_{21D} & (k_{21D} - k_{31D} - k_{eD3})t_{23} \\ \frac{V_1}{V_2}k_{13D} & 0 & -(k_{31D} + k_{eD3}) \end{pmatrix}. \quad (49)$$

Now we impose

$$k'_{eD3} := -a'_{33} - \frac{V_1}{V_2}a'_{13} = 0, \quad (50)$$

from which we get $t_{23} = -(V_2/V_3)(k_{eD3}/k_{21D})$. After putting this last piece into A' , we get k'_{eD1} from

$$\begin{aligned} k'_{eD1} &= -a'_{11} - \frac{V_3}{V_1}a'_{21} - \frac{V_2}{V_1}a'_{31} \\ &= k_{eD1} - \frac{k_{13D} \cdot k_{eD3}}{k_{21D}}. \end{aligned} \quad (51)$$

Thus $CL' = k'_{eD1} \cdot V_1$, with k'_{eD1} given by (??). And finally we get $D_{\text{tot,avg1}} = \text{Dose}/(CL' \cdot \tau)$, and $D_{\text{tot,avg3}} = B \cdot D_{\text{tot,avg1}}$.

Remark: In the similarity transform, we measure D_1 and D_3 , which is indicated by C . As a result of imposing $C' = C$, the original model and the transformed model output the same values for these variables. D'_2 , however, differs from D_2 .

Study Highlights

What is the current knowledge on the topic? XYZ

What question did this study address? XYZ

What this study adds to our knowledge? XYZ

How might this change drug discovery, development and/or therapeutics? XYZ

Acknowledgements

The authors would like to thank the IMA as the Math-to-Industry bootcamp was where this work began. We'd also like to thank Ngartelbaye Guerngar who was also a member of the bootcamp team. Finally, we'd like to thank Eduardo Sontag and Greg Thurber for many helpful discussions.

Conflict of Interest

Andrew Stein is employed by Novartis Institute for BioMedical Research

Author Contributions

XYZ analyzed the data, XYZ performed the research, XYZ wrote the manuscript.

8 Figures and Tables

There is a limit of 6 tables and figures in the paper.

Drug	Trastuzumab	Pembrolizumab	Atezolizumab	Bevacizumab
Target Type	Membrane-Bound	Membrane-Bound	Membrane-Bound	Soluble
Target	HER2	PD-1	PD-L1	VEGF
Baseline Target (nM)	X	Y	Z	A
Other info?				

Table 1: Summary of drugs in this analysis. Listing all the parameters is probably a bit nuts. I'd rather refer the reader to teh spreadsheet and also in the appendix or supplementary material we can give more information.

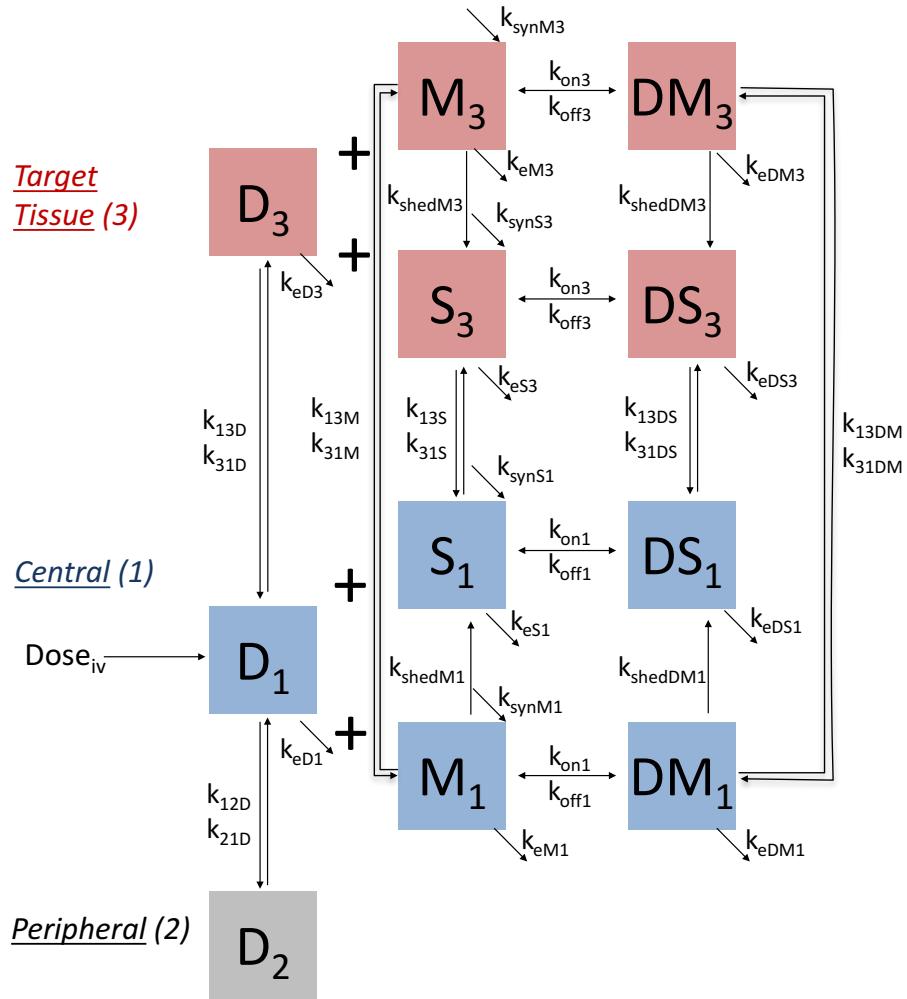


Figure 1: The extended target mediated drug disposition model. Vertical arrows represent distribution, horizontal arrows represent dosing and binding, and diagonal arrows represent synthesis and elimination.

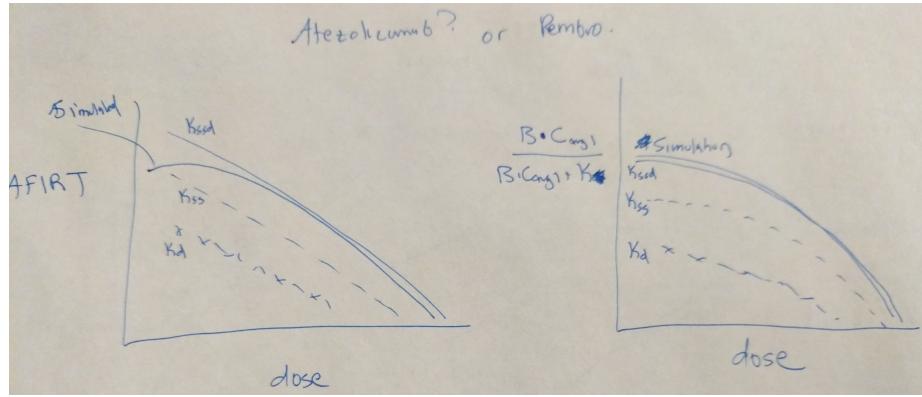


Figure 2: Here we show K_d , K_{ss} , K_{ssd} and that K_{ssd} is superior for describing the data. Might want to show for all four drugs and that K_{ssd} will be superior for atezo and pembro, though maybe all will be terrible for herceptin.

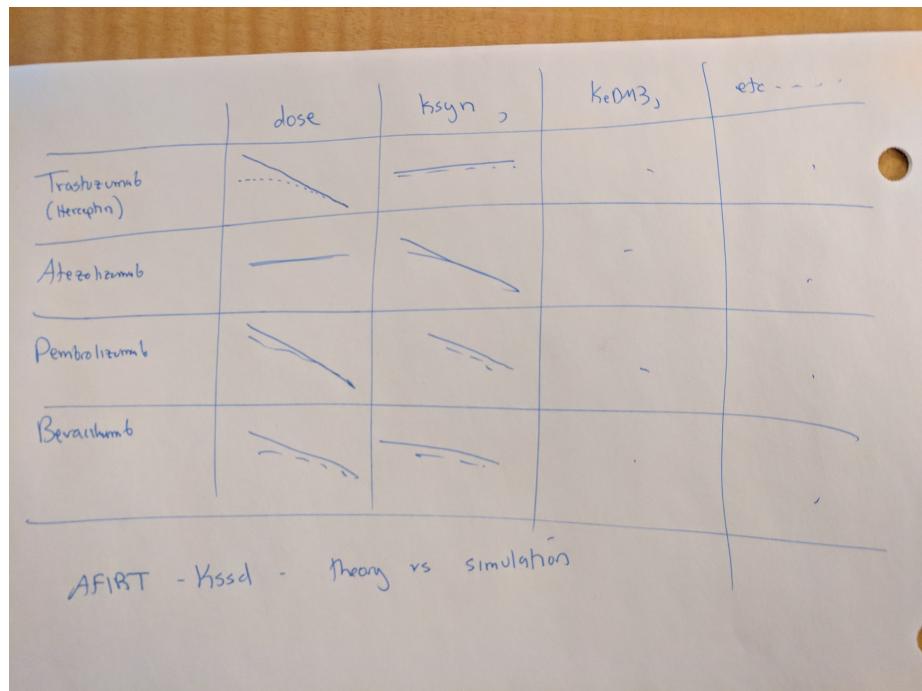


Figure 3: Sensitivity analysis that Sameed is currently working on (building off Hongshan's initial code). This will show the accuracy of the AFIRT (or lack thereof) over a wide range of scenarios)

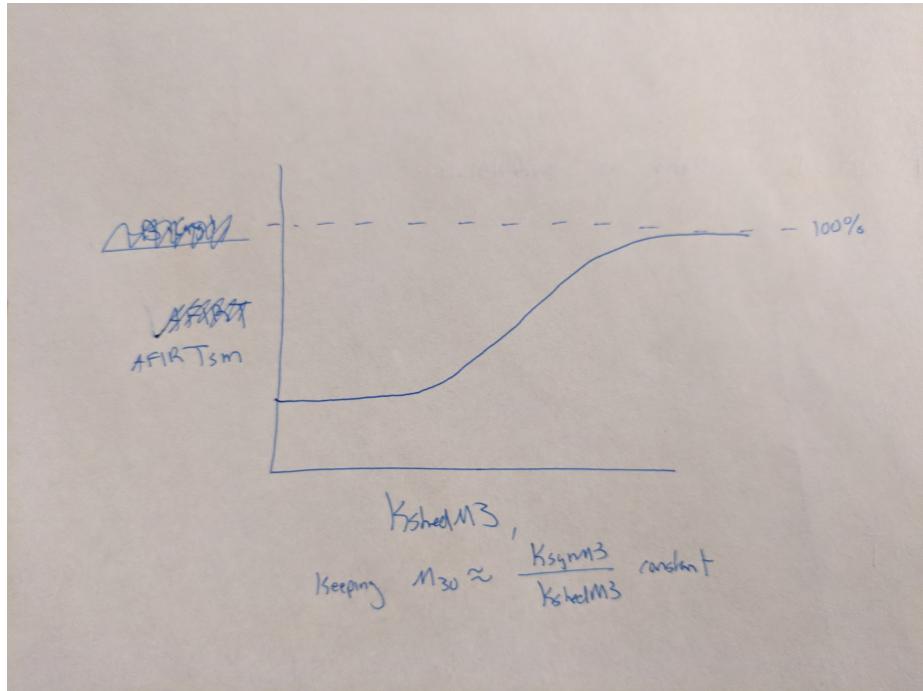


Figure 4: This will show that if the shedding is super fast, inhibiting the target is impossible. This can also I think readily be seen from the Kssd equation.

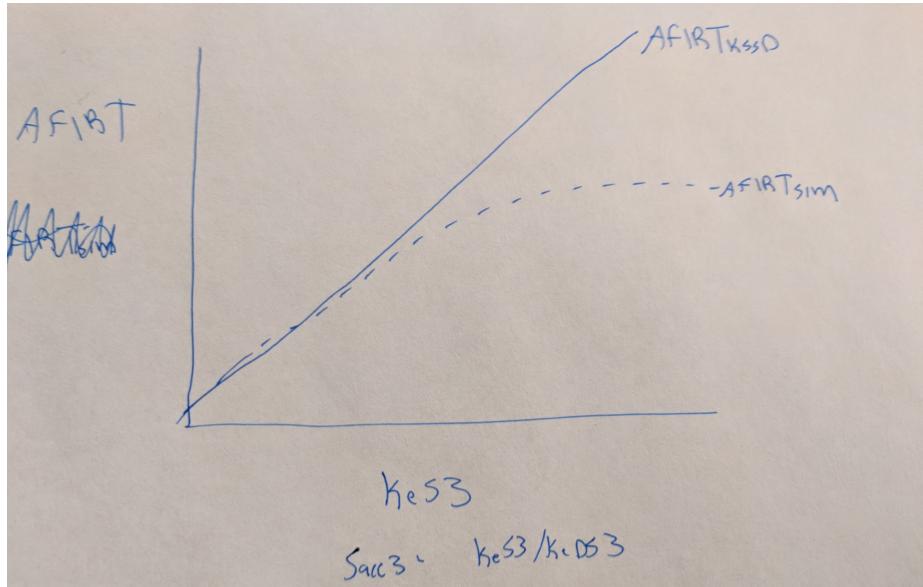


Figure 5: This will show that understanding the accumulation of the target in the tissue is critical. But this is often not measured.

WE MIGHT WANT ONE MORE FIGURE LOOKING AT THE ACCURACY OF K_{ssd} AS THE DISTRIBUTION BECOMES SLOW OR FAST.