AFIRT: A Dimensionless Potency Metric for Characterizing the Activity of Monoclonal Antibodies in Target Tissue

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Abstract

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Introduction

In the development of biologics, understanding target engagement at the site of action plays a critical role in dose regimen selection [1]. As measurements at the site of action are often impossible to obtain, model based predictions of target engagement are often used to help justify the dose selection. For example, 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 [2]. 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 observation 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.

$$RO = B \cdot C_\mathrm{min}/(B \cdot C_\mathrm{min} + K_\mathrm{d}) \tag{1}$$

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 however is that physiological models can be complex, making them difficult time consuming to develop and difficult 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, however, is that it is not obvious that Equation 1 is appropriate to the clinical scenario as this equation was derived for the in vitro setting [3] where the was no drug distribution, target distribution, receptor synthesis, or receptor turnover.

In this paper, an analysis of the target mediated drug distribution system is is performed with the goal of deriving a simple expression for target engagement in the clinical scenario. This work provides a simple expression for target engagement in the tissue of interest, extending previous work characterizing the Average Free target to Initial target Ratio (AFIR) at steady state in circulation [4].

Theory

The drug and target dynamics are modeled with the following system of ordinary differential equations. The model is shown in Figure 1. THOUGH THIS FIGURE PROBABLY NEEDS TO BE UPDATED.

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

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

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

$$\frac{dM_1}{dt} = k_{\text{syn}M1} - k_{\text{shed}M_1}M_1 - k_{13M}M_1 + \frac{V_{M_3}}{V_{M_1}}k_{31M}M_3 - k_{eM1}M_1$$
$$- k_{\text{on1}}D_1 \cdot M_1 + k_{\text{off1}}(DM_1) \tag{5}$$

$$\frac{dM_3}{dt} = k_{\text{syn3}} - k_{\text{shed}M_3}M_3 + \frac{V_{M_1}}{V_{M_3}}k_{13M}M_1 - k_{31M}M_3 - k_{eM3}M_3-$$
$$k_{\text{on3}}D_3 \cdot M_3 + k_{\text{off3}}(DM_3) \tag{6}$$

$$\frac{dS_1}{dt} = k_{\text{syn}S1} + k_{\text{shed}M_1}M_1 - k_{13S}S_1 + \frac{V_{S_3}}{V_{S_1}}k_{31S}S_3 - k_{eS1}S_1 - k_{\text{on1}}D_1 \cdot S_1$$
$$+ k_{\text{off1}}(DS_1) \tag{7}$$

$$\frac{dS_3}{dt} = k_{\text{syn}S3} + k_{\text{shed}M_3}M_3 - k_{31S}S_3 + \frac{V_{S_1}}{V_{S_3}}k_{13S}S_1 - k_{eS3}S_3 - k_{\text{on3}}D_3 \cdot S_3$$
$$+ k_{\text{off3}}(DS_3) \tag{8}$$

$$\frac{d(DM_1)}{dt} = -k_{\text{shed}DM_1}DM_1 - k_{13DM}(DM_1) + \frac{V_{DM_3}}{V_{DM_1}}k_{31DM}(DM_3) - k_{eDM1}DM_1$$
$$+ k_{\text{on1}}D_1 \cdot M_1 - k_{\text{off1}}(DM_1) \tag{9}$$

$$\frac{d(DM_3)}{dt} = -k_{\text{shed}DM_3}DM_3 - k_{31DM}(DM_3) + \frac{V_{DM_1}}{V_{DM_3}}k_{13DM}(DM_1) - k_{eDM3}DM_3$$
$$+ k_{\text{on3}}D_3 \cdot M_3 - k_{\text{off3}}(DM_3) \tag{10}$$

$$\frac{d(DS_1)}{dt} = -k_{\text{shed}DM_3}DS_1 - k_{13DS}DS_1 + \frac{V_{DS_3}}{V_{DS_1}}k_{31DS}DS_3 - k_{eDS1}(DS_1)$$
$$+ k_{\text{on1}}D_1 \cdot S_1 - k_{\text{off1}}(DS_1) \tag{11}$$

$$\frac{d(DS_3)}{dt} = -k_{\text{shed}DM_3}DS_3 - k_{31DS}DS_3 + \frac{V_{DS_1}}{V_{DS_3}}k_{13DS}DS_1 - k_{eDS3}(DS_3)$$
$$+ k_{\text{on3}}D_1 \cdot S_3 - k_{\text{off1}}(DS_3) \tag{12}$$

This model is considering three compartments like Model C but it is tak-

ing into account the possibility for the target to shad, i.e. the target in the previous models is always membrane-bound but in reality it can shad into the blood and into the tumor. We are also adding the lymphocyte trafficking (k_{13M} and k_{31M}). The analysis we are carrying out on this model is similar to the one done for model C with the required modification. 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 xxxxxxx (QSSD). The quasi-steady state approximation assumed that $-k_{\mathrm{shed}DM_3}DM_3 - k_{eDM3}DM_3 + k_{\mathrm{on3}}D_3 \cdot M_3 - k_{\mathrm{off3}}(DM_3) = 0$, similarly as before for k_d we define $k_{ss} = \frac{k_{\mathrm{shed}DM_3}+k_{eDM3}+k_{\mathrm{off3}}}{k_{\mathrm{on3}}}$. The quasi-steady state xxxxxxx approximation assumed that $-k_{\mathrm{shed}DM_3}DM_3 - k_{31DM}(DM_3) - k_{eDM3}DM_3 + k_{\mathrm{on3}}D_3 \cdot M_3 - k_{\mathrm{off3}}(DM_3) = 0$, we define $k_{ssd} = \frac{k_{\mathrm{shed}DM_3}+k_{31DM}+k_{eDM3}+k_{\mathrm{off3}}}{k_{\mathrm{on3}}}$. 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

$$\mathrm{AFIRT} \approx k_{ssd}\frac{M_{3\mathrm{tot,ss}}}{M_{3,0}}\frac{\mathrm{CL}\times\tau}{\mathrm{B}\times\mathrm{Dose}},$$

$$\mathrm{AFIRT} \approx k_{ss}\frac{M_{3\mathrm{tot,ss}}}{M_{3,0}}\frac{\mathrm{CL}\times\tau}{\mathrm{B}\times\mathrm{Dose}},$$

$$\mathrm{AFIRT} \approx k_{d}\frac{M_{3\mathrm{tot,ss}}}{M_{3,0}}\frac{\mathrm{CL}\times\tau}{\mathrm{B}\times\mathrm{Dose}},$$

where

$$M_{3\mathrm{tot,ss}} = \frac{k_{13DM}(V_C/V_T)k_{\mathrm{syn}M1} + (k_{eDM1} + k_{\mathrm{shed}DM_1} + k_{13DM})k_{\mathrm{syn}M3}}{(k_{eDM1} + k_{\mathrm{shed}DM_1} + k_{13DM})(k_{eDM3} + k_{\mathrm{shed}DM_3} + k_{31DM}) - k_{31DM}k_{13DM}},$$

$$M_{3,0} = \frac{k_{13M}(V_C/V_T)k_{\mathrm{syn}M1} + (k_{eM1} + k_{\mathrm{shed}M_1} + k_{13M})k_{\mathrm{syn}M3}}{(k_{eM1} + k_{\mathrm{shed}M_1} + k_{13M})(k_{eM3} + k_{\mathrm{shed}M_3} + k_{31M}) - k_{31M}k_{13M}},$$

$$\mathrm{B} = \frac{k_{13D}(V_C/V_T)}{k_{eD3} + k_{31D}}.$$

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

1 Soluble target at Initial State and Steady State

1.1 Some formulas

With the same notations as in the sections above.
At initial state, we have

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

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

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

(13)

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

(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

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

$$S_{3tot,ss} = \frac{\frac{V_C}{V_T} k_{13DS} \cdot (k_{synS1} + k_{shedDM1} M_{1tot,ss}) + (k_{13DS} + k_{eDS1})(k_{synS3} + k_{shedDM3} M_{3tot3,ss})}{(k_{13DS} + k_{eDS1})(k_{31DS} + k_{eDS3}) - k_{13DS} k_{31DS}}$$

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

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

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

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

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

1.2 Pseudo-Code for extending the core functions

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

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

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

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

$$\tag{18}$$

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

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

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

$$\text{Kd.S} = \frac{k_{off3}}{k_{on3}} \tag{21}$$

$$\tag{22}$$

Finally,

$$\text{Tacc.tum.S} = \text{S3tot.ss}/\text{S30} \tag{23}$$

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

2 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

$$\frac{dD_1}{dt} = \frac{1}{V_1}\text{Dose}_{iv}(t) - k_{12D}D_1 + \frac{V_3}{V_1}k_{21D}D_2 - k_{13D}D_1$$
$$+ \frac{V_2}{V_1}k_{31D}D_3 - k_{\text{on}1}D_1 \cdot M_1 + k_{\text{off}1}(DM_1) - k_{eD1}D_1 \tag{24}$$

$$\frac{dD_2}{dt} = k_{12D}\frac{V_1}{V_3}D_1 - k_{21D}D_2 \tag{25}$$

$$\frac{dD_3}{dt} = \frac{V_1}{V_2}k_{13D}D_1 - k_{31D}D_3 - k_{\text{on}3}D_3 \cdot M_3 + k_{\text{off}3}(DM_3) - k_{eD3}D_3 \tag{26}$$

$$\frac{dM_1}{dt} = k_{\text{syn}1} - k_{13M}M_1 + \frac{V_2}{V_1}k_{31M}M_3 - k_{\text{on}1}D_1 \cdot M_1 + k_{\text{off}1}(DM_1)$$
$$- k_{eM1}M_1 \tag{27}$$

$$\frac{dM_3}{dt} = k_{\text{syn}3} + \frac{V_1}{V_2}k_{13M}M_1 - k_{31M}M_3 - k_{\text{on}3}D_3 \cdot M_3 + k_{\text{off}3}(DM_3)$$
$$- k_{eM3}M_3 \tag{28}$$

$$\frac{d(DM_1)}{dt} = -k_{13DM}(DM_1) + \frac{V_2}{V_1}k_{31DM}(DM_3) + k_{\text{on}1}D_1 \cdot M_1 - k_{\text{off}1}(DM_1)$$
$$- k_{eDM1}(DM_1) \tag{29}$$

$$\frac{d(DM_3)}{dt} = \frac{V_1}{V_2}k_{13DM}(DM_1) - k_{31DM}(DM_3) + k_{\text{on}3}D_3 \cdot M_3 - k_{\text{off}3}(DM_3)$$
$$- k_{eDM3}(DM_3) \tag{30}$$

$$\tag{31}$$

We will calculate $D_{\text{tot,avg3}}$, which is the average drug concentration at steady state in the tissue. We have $D_{\text{tot,avg3}} = B \cdot D_{\text{tot,avg1}}$, where $D_{\text{tot,avg1}}$ 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 $D_{\text{tot,avg1}} = \text{Dose}/(CL \cdot \tau)$, 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

$$\frac{d\mathbf{D}}{dt} = A \cdot \mathbf{D}(t) + B \cdot Dose_{iv}(t), \tag{32}$$

with measurement

$$\mathbf{m}(t) = C \cdot \mathbf{D}(t), \tag{33}$$

where

$$\mathbf{D} = \begin{pmatrix} D_1 \\ D_2 \\ D_3 \end{pmatrix}, \tag{34}$$

$$A = \begin{pmatrix} -(k_{13D} + k_{12D} + k_{eD1}) & \dfrac{V_3}{V_1}k_{21D} & \dfrac{V_2}{V_1}k_{31D} \\ \dfrac{V_1}{V_3}k_{12D} & -k_{21D} & 0 \\ \dfrac{V_1}{V_2}k_{13D} & 0 & -(k_{31D} + k_{eD3}) \end{pmatrix}, \tag{35}$$

$$B = \begin{pmatrix} \dfrac{1}{V_1} \\ 0 \\ 0 \end{pmatrix}, \tag{36}$$

$$C = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & 1 \end{pmatrix}. \tag{37}$$

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

$$A' := TAT^{-1} \qquad B' := TB \qquad C' := CT^{-1}, \tag{38}$$

for some transformation matrix

$$T = \begin{pmatrix} t_{11} & t_{12} & t_{13} \\ t_{21} & t_{22} & t_{23} \\ t_{31} & t_{32} & t_{33} \end{pmatrix} \qquad T^{-1} = \begin{pmatrix} \hat{t}_{11} & \hat{t}_{12} & \hat{t}_{13} \\ \hat{t}_{21} & \hat{t}_{22} & \hat{t}_{23} \\ \hat{t}_{31} & \hat{t}_{32} & \hat{t}_{33} \end{pmatrix}. \tag{39}$$

Alternatively, one can get this similarity transform with the change of variables $\mathbf{D} = T^{-1}\mathbf{D}'$. Then from (32) and (33) we have

$$\frac{d(T^{-1}\mathbf{D}')}{dt} = A \cdot (T^{-1}\mathbf{D}')(t) + B \cdot Dose_{iv}(t), \qquad \mathbf{m}(t) = C \cdot (T^{-1}\mathbf{D}')(t). \tag{40}$$

Multiplying the first equation in (40) on the left by T yields

$$\frac{d\mathbf{D}'}{dt} = TAT^{-1} \cdot \mathbf{D}'(t) + TB \cdot Dose_{iv}(t). \tag{41}$$

Then we have the new model equation and measurement

$$\frac{d\mathbf{D}'}{dt} = A' \cdot \mathbf{D}'(t) + B' \cdot Dose_{iv}(t), \qquad \mathbf{m}(t) = C' \cdot \mathbf{D}'(t), \tag{42}$$

where A', B', and C' are given by (38).

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

$$B' = B. \tag{43}$$

From this and (38) 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,

$$C' = C. \tag{44}$$

From this and (38) 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

$$T^{-1} = \frac{1}{\det T} \begin{pmatrix} t_{22}t_{33} - t_{23}t_{32} & t_{13}t_{32} - t_{12}t_{33} & t_{12}t_{23} - t_{13}t_{22} \\ t_{23}t_{31} - t_{21}t_{33} & t_{11}t_{33} - t_{13}t_{31} & t_{13}t_{21} - t_{11}t_{23} \\ t_{21}t_{32} - t_{22}t_{31} & t_{12}t_{31} - t_{11}t_{32} & t_{11}t_{22} - t_{12}t_{21} \end{pmatrix}, \tag{45}$$

with the determinant given by

$$\det T = t_{11}(t_{22}t_{33} - t_{23}t_{32}) - t_{12}(t_{21}t_{33} - t_{23}t_{31}) + t_{13}(t_{21}t_{32} - t_{22}t_{31}). \tag{46}$$

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

$$T = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & t_{23} \\ 0 & 0 & 1 \end{pmatrix} \qquad T^{-1} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & -t_{23} \\ 0 & 0 & 1 \end{pmatrix}. \tag{47}$$

Putting this into (38) yields

$$A' = \begin{pmatrix} -(k_{13D} + k_{12D} + k_{eD1}) & \dfrac{V_3}{V_1}k_{21D} & -\dfrac{V_3}{V_1}k_{21D}t_{23} + \dfrac{V_2}{V_1}k_{31D} \\ \dfrac{V_1}{V_3}k_{12D} + \dfrac{V_1}{V_2}k_{13D}t_{23} & -k_{21D} & (k_{21D} - k_{31D} - k_{eD3})t_{23} \\ \dfrac{V_1}{V_2}k_{13D} & 0 & -(k_{31D} + k_{eD3}) \end{pmatrix}. \tag{48}$$

Now we impose

$$k'_{eD3} := -a'_{33} - \frac{V_1}{V_2}a'_{13} = 0, \tag{49}$$

9

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

$$k'_{eD1} = -a'_{11} - \frac{V_3}{V_1}a'_{21} - \frac{V_2}{V_1}a'_{31}$$

$$= k_{eD1} - \frac{k_{13D} \cdot k_{eD3}}{k_{21D}}. \tag{50}$$

Thus $CL' = k'_{eD1} \cdot V_1$, with k'_{eD1} given by (50). 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.

Methods and Results

Discussion

Conclusion

Appendix

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

Ignoring target, then at steady state

$$-\begin{pmatrix} k_{\text{inf}} \\ 0 \\ 0 \end{pmatrix} = \frac{d}{dt}\begin{pmatrix} D_1 \\ D_2 \\ D_3 \end{pmatrix} = \begin{pmatrix} -(k_{eD1} + k_{12D} + k_{13D}) & (V_P/V_C)k_{21D} & (V_T/V_C)k_{31D} \\ (V_C/V_P)k_{12D} & -k_{21D} & 0 \\ (V_C/V_T)k_{13D} & 0 & -(k_{eD3} + k_{31D}) \end{pmatrix} \cdot \begin{pmatrix} D_1 \\ D_2 \\ D_3 \end{pmatrix}$$

$$= A \cdot \begin{pmatrix} D_1 \\ D_2 \\ D_3 \end{pmatrix}$$

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

$$\begin{pmatrix} D_1 \\ D_2 \\ D_3 \end{pmatrix}_{ss} = A^{-1} \cdot \begin{pmatrix} -k_{\text{inf}} \\ 0 \\ 0 \end{pmatrix}$$

$$\begin{pmatrix} D_1 \\ D_2 \\ D_3 \end{pmatrix}_{ss} = \frac{-k_{\text{inf}}}{\det A}\begin{pmatrix} a_{22}a_{33} - a_{23}a_{32} \\ a_{23}a_{31} - a_{21}a_{33} \\ a_{21}a_{32} - a_{22}a_{31} \end{pmatrix} = \begin{pmatrix} k_{21D}(k_{eD3} + k_{31D}) \\ k_{21D}(V_P/V_C)(k_{eD3} + k_{31D}) \\ k_{21D}(V_C/V_T)k_{13D} \end{pmatrix}$$

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

$$B = \left(\frac{D_3}{D_1}\right)_{ss} = \frac{k_{21D}(V_C/V_T)k_{13D}}{k_{21D}(k_{eD3} + k_{31D})} = \frac{V_C}{V_T} \cdot \frac{k_{13D}}{(k_{eD3} + k_{31D})}$$

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

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

2.2   Predicting Target accumulation in Target Tissue (M_{acc3})

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

$$\begin{pmatrix} 0 \\ 0 \end{pmatrix} = \frac{d}{dt}\begin{pmatrix} M_1 \\ M_3 \end{pmatrix} = \begin{pmatrix} -(k_{eM1} + k_{13M} + k_{\text{shed}M_1}) & (V_T/V_C)k_{31M} \\ (V_C/V_T)k_{13T} & -(k_{eM3} + k_{31M} + k_{\text{shed}M_3}) \end{pmatrix}\begin{pmatrix} M_1 \\ M_3 \end{pmatrix}_0 + \begin{pmatrix} k_{\text{syn1}} \\ k_{\text{syn3}} \end{pmatrix}$$

$$\begin{pmatrix} k_{\text{syn1}} \\ k_{\text{syn3}} \end{pmatrix} = \begin{pmatrix} (k_{eM1} + k_{13M} + k_{\text{shed}M_1}) & -(V_T/V_C)k_{31M} \\ -(V_C/V_T)k_{13M} & (k_{eM3} + k_{31M} + k_{\text{shed}M_3}) \end{pmatrix}\begin{pmatrix} M_1 \\ M_3 \end{pmatrix}_0$$

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

$$\begin{pmatrix} M_1 \\ M_3 \end{pmatrix}_0 = \frac{1}{((k_{eM3} + k_{31M} + k_{\text{shed}M_3})(k_{eM1} + k_{13M} + k_{\text{shed}M_1}) - k_{13T}k_{31T})} \times$$
$$\begin{pmatrix} (k_{eM3} + k_{31M} + k_{\text{shed}M_3}) & (V_T/V_C)k_{31M} \\ (V_C/V_T)k_{13M} & (k_{eM1} + k_{13M} + k_{\text{shed}M_1}) \end{pmatrix}\begin{pmatrix} k_{\text{syn1}} \\ k_{\text{syn3}} \end{pmatrix}$$

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

$$M_{3,0} = \frac{k_{13M}(V_C/V_T)k_{\text{syn}M1} + (k_{eM1} + k_{\text{shed}M_1} + k_{13M})k_{\text{syn3}}}{(k_{eM1} + k_{\text{shed}M_1} + k_{13M})(k_{eM3} + k_{\text{shed}M_3} + k_{31M}) - k_{31M}k_{13M}}$$

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

$$M_{3\text{tot,ss}} = \frac{k_{13DM}(V_C/V_T)k_{\text{syn}M1} + (k_{eDM1} + k_{\text{shed}DM_1} + k_{13DM})k_{\text{syn3}}}{(k_{eDM1} + k_{\text{shed}DM_1} + k_{13DM})(k_{eDM3} + k_{\text{shed}DM_3} + k_{31DM}) - k_{31DM}k_{13DM}}$$

Then, to compute M_{acc3} just take the ratio of M_{tot3}/M_{03}

$$M_{\text{acc3}} = \frac{M_{\text{tot3}}}{M_{03}} = \frac{k_{13DM}(V_C/V_T)k_{\text{syn}M1} + (k_{eDM1} + k_{\text{shed}DM_1} + k_{13DM})k_{\text{syn3}}}{(k_{eDM1} + k_{\text{shed}DM_1} + k_{13DM})(k_{eDM3} + k_{\text{shed}DM_3} + k_{31DM}) - k_{31DM}k_{13DM}} \times$$
$$\frac{(k_{eM1} + k_{\text{shed}M_1} + k_{13M})(k_{eM3} + k_{\text{shed}M_3} + k_{31M}) - k_{31M}k_{13M}}{k_{13M}(V_C/V_T)k_{\text{syn}M1} + (k_{eM1} + k_{\text{shed}M_1} + k_{13M})k_{\text{syn3}}}$$
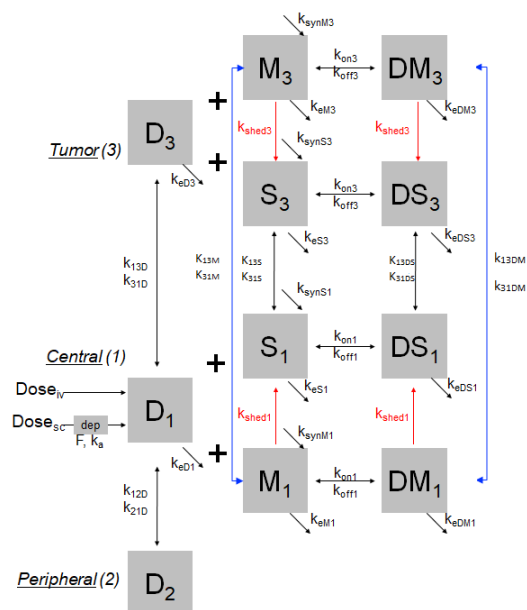
11

Figure 1: Model. TO BE UPDATED
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Figures

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

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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.

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