Supporting Information for Paper Entitled: Theoretical Insights Into the Retinal Dynamics of VEGF in Patients Treated with Ranibizumab, Based on an Ocular Pharmacokinetic/Pharmacodynamic Model

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CONTENTS

S1 ESTIMATION OF THE HYDRODYNAMIC RADII OF R, V, VR AND RVR SPECIES

The hydrodynamic radii (R_{h} values) of the VEGF dimer (V), Ranibizumab Fab (R), VR and RVR species were estimated by representing each species as a prolate ellipsoid and applying Perrin's formula (given below) [1]. The dimensions of the ellipsoid were estimated from Ferrara's structural representation of the RVR species [2], as follows.

Axial ratios of each species were first estimated by drawing lines corresponding to the apparent length and apparent width of each species and taking their ratio (width/length) as shown in Figure S1.

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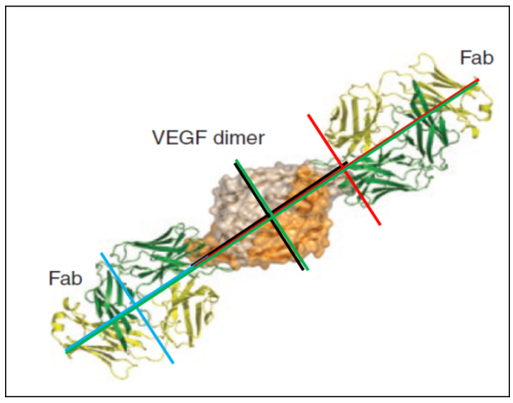


Figure S1: RVR structure taken from N. Ferrara [2]. Coloured line segments superimposed on figure were drawn by eye to estimate the apparent lengths (longer segments) and widths (shorter segments) of the different species: V (black), R (blue), VR (red) and RVR (green) species. The axial ratio (dimensionless) was taken as the ratio of the width/length.

The molecular weights (M_W) of the VEGF dimer and Ranibizumab were taken as 44000 and 48000 daltons, respectively, from literature values [3, 4] and the values of the VR and RVR species calculated additively. The volume of each species was computed from the corresponding molecular weight assuming a protein density of 1.33 g/mL [5] and was set equal to that of a prolate ellipsoid with semi-major axis a and semi-minor axis b, i.e. $V_{\text{prolate}} = (4/3)ab^2$. The values of a and b were computed from the volume and the previously estimated axial ratios (set equal to b/a).

Perrin's formula for prolate ellipsoids [1] was used to calculate R_h from the values of a and b.

$$R_h = \frac{a\sqrt{1-\left(\frac{b}{a}\right)^2}}{\log\left[\left\{1+\sqrt{1-\left(\frac{b}{a}\right)^2}\right\}\Big/\frac{b}{a}\right]} \tag{S.1}$$

The resulting R_h values and related parameters are given in Table S1.

	Units	**V**	**R**	**VR**	**RVR**
Molecular Weight	Da	44,000	48,000	92,000	140,000
Volume*	$10^4\times$Å	5.50	6.00	11.5	17.5
Axial ratio (b/a)	none	0.68	0.74	0.37	0.26
Semi-major axis (a)	Å	30.5	29.7	58.1	85.4
Semi-minor axis (b)	Å	20.7	22.0	21.7	22.1
Hydrodynamic radius (R_h)	nm	2.39	2.45	3.29	4.07

Table S1: Hydrodynamic radii of each species and related parameters used to calculate them. *Assumes protein density of 1.33 g/mL.

The estimated R_h for Ranibizumab (2.45 nm) is in excellent agreement with the experimental value (2.5 nm) for a Fab molecule determined from dynamic light scattering measurements by Shatz et al. [6]; while the R_h estimated for the RVR species (4.07 nm) is similar to the experimental value reported in [6] for an IgG molecule (4.9 nm), which has a comparable M_W.

S2 Vitreous-aqueous clearance parameter

The 3-compartment PK model, for a general intravitreally injected antibody, denoted in the retina, vitreous and aqueous, by $c_{\text{ret}}(t)$, $c_{\text{vit}}(t)$ and $c_{\text{aq}}(t)$, respectively (with units of pM), is given by the following equations

$$\frac{dc_{\text{ret}}}{dt} = -\left(\frac{S_{\text{ret}}}{V_{\text{ret}}}\right)\left[p_{\text{ILM}}+p_{\text{RPE}}\right]c_{\text{ret}} + \left(\frac{S_{\text{ret}}}{V_{\text{ret}}}\right)p_{\text{ILM}}c_{\text{vit}}, \tag{S.2}$$

$$\frac{dc_{\text{vit}}}{dt} = \left(\frac{S_{\text{ret}}}{V_{\text{vit}}}\right)p_{\text{ILM}}c_{\text{ret}} - \left[\left(\frac{S_{\text{ret}}}{V_{\text{vit}}}\right)p_{\text{ILM}}+k_{\text{el}}\right]c_{\text{vit}}, \tag{S.3}$$

$$\frac{dc_{\text{aq}}}{dt} = \left(\frac{V_{\text{vit}}}{V_{\text{aq}}}\right)k_{\text{el}}c_{\text{vit}} - \left(\frac{C_L}{V_{\text{aq}}}\right)c_{\text{aq}}, \tag{S.4}$$

where $c_{\text{ret}}(0) = c_{\text{aq}}(0) = 0$ and $c_{\text{vit}}(0) = c_0$ representing the initial concentration corresponding to the intravitreal injection. All parameter definitions can be found in Table 3 in the main text. As this is a linear ODE system with constant coefficients, it is readily solved to give:

$$c_{\text{ret}}(t) = \frac{c_0 p_{\text{ILM}}}{\lambda_2 - \lambda_1}\left(\frac{S_{\text{ret}}}{V_{\text{vit}}}\right) K_2 K_1 \left[e^{-\lambda_1 t} - e^{-\lambda_2 t}\right], \tag{S.5}$$

$$c_{\text{vit}}(t) = \frac{c_0 p_{\text{ILM}}}{\lambda_2 - \lambda_1}\left(\frac{S_{\text{ret}}}{V_{\text{vit}}}\right) \left[K_1 e^{-\lambda_2 t} + K_2 e^{-\lambda_1 t}\right], \tag{S.6}$$

$$c_{\text{aq}}(t) = \frac{c_0 p_{\text{ILM}} k_{\text{el}}}{\lambda_2 - \lambda_1}\left(\frac{S_{\text{ret}}}{V_{\text{aq}}}\right) \left[\frac{K_1}{\frac{C_{\text{L}}}{V_{\text{aq}}} - \lambda_2}\left(e^{-\lambda_2 t} - e^{-\left(\frac{C_{\text{L}}}{V_{\text{aq}}}\right)t}\right) + \frac{K_2}{\frac{C_{\text{L}}}{V_{\text{aq}}} - \lambda_1}\left(e^{-\lambda_1 t} - e^{-\left(\frac{C_{\text{L}}}{V_{\text{aq}}}\right)t}\right)\right], \tag{S.7}$$

where

$$K_1 = 1 + \left(\frac{V_{\text{vit}}}{S_{\text{ret}}}\right)\frac{k_{\text{el}} - \lambda_1}{p_{\text{ILM}}}, \quad K_2 = -1 + \left(\frac{V_{\text{vit}}}{S_{\text{ret}}}\right)\frac{\lambda_2 - k_{\text{el}}}{p_{\text{ILM}}}, \tag{S.8}$$

and $K_1, K_2, \lambda_1, \lambda_2 > 0$, and λ_1 and λ_2 are the absolute distinct real eigenvalues of M, the matrix defined as follows

$$M = \begin{pmatrix} -\frac{S_{\text{ret}}}{V_{\text{ret}}}\left(p_{\text{ILM}} + p_{\text{RPE}}\right) & \frac{S_{\text{ret}}}{V_{\text{ret}}} p_{\text{ILM}} \\ \frac{S_{\text{ret}}}{V_{\text{vit}}} p_{\text{ILM}} & -\left(\frac{S_{\text{ret}}}{V_{\text{vit}}} p_{\text{ILM}} + k_{\text{el}}\right) \end{pmatrix}, \tag{S.9}$$

which are the solutions of the following equation

$$\left(\frac{S_{\text{ret}}}{V_{\text{ret}}}\left(p_{\text{ILM}} + p_{\text{RPE}}\right) - \lambda\right)\left(\frac{S_{\text{ret}}}{V_{\text{vit}}} p_{\text{ILM}} + k_{\text{el}} - \lambda\right) - \frac{S_{\text{ret}}^2}{V_{\text{ret}} V_{\text{vit}}} p_{\text{ILM}}^2 = 0 \tag{S.10}$$

This equation can be rearranged to give k_{el}, in terms of λ_1, as

$$k_{\text{el}} = \lambda_1 - \frac{S_{\text{ret}}}{V_{\text{vit}}} p_{\text{ILM}} + \frac{\left(S_{\text{ret}} p_{\text{ILM}}\right)^2}{V_{\text{vit}} S_{\text{ret}}\left(p_{\text{ILM}} + p_{\text{RPE}}\right) - V_{\text{vit}} V_{\text{ret}} \lambda_1}. \tag{S.11}$$

For simplicity in the main text we refer to λ_1 as λ.

S3 Initial conditions

Initial conditions for VEGF can be derived from the steady state solution of Equations 9-20 in the main text, in the absence of ranibizumab, as follows:

$$\begin{pmatrix} \frac{S_{\text{ret}}}{V_{\text{ret}}}\left(p_{\text{ILM}}^{(v)} + p_{\text{RPE}}^{(v)}\right) & -\frac{S_{\text{ret}}}{V_{\text{ret}}} p_{\text{ILM}}^{(v)} \\ \frac{S_{\text{ret}}}{V_{\text{vit}}} p_{\text{ILM}}^{(v)} & -\left(\frac{S_{\text{ret}}}{V_{\text{vit}}} p_{\text{ILM}}^{(v)} + k_{\text{el}}^{(v)}\right) \end{pmatrix} \begin{pmatrix} v_{\text{ret}}(0) \\ v_{\text{vit}}(0) \end{pmatrix} = \begin{pmatrix} \frac{V_{\text{in}}}{V_{\text{ret}}} \\ 0 \end{pmatrix}, \tag{S.12}$$

$$v_{\text{aq}}(0) = \frac{V_{\text{vit}}}{C_{\text{L}}} k_{\text{el}}^{(v)} v_{\text{vit}}. \tag{S.13}$$

Therefore we find

$$\begin{pmatrix} v_{\text{ret}}(0) \\ v_{\text{vit}}(0) \\ v_{\text{aq}}(0) \end{pmatrix} = E_Q \begin{pmatrix} 1 + \frac{k_{\text{el}}^{(v)}}{\frac{S_{\text{ret}}}{V_{\text{vit}}} p_{\text{ILM}}^{(v)}} \\ 1 \\ \frac{V_{\text{vit}}}{C_{\text{L}}} k_{\text{el}}^{(v)} \end{pmatrix}, \tag{S.14}$$

where

$$E_Q = \frac{1}{V_{\text{vit}} k_{\text{el}}^{(v)}}\left(\frac{V_{\text{in}}}{\frac{S_{\text{ret}} p_{\text{RPE}}^{(v)}}{V_{\text{vit}} k_{\text{el}}^{(v)}} + 1 + \frac{p_{\text{RPE}}^{(v)}}{p_{\text{ILM}}^{(v)}}}\right). \tag{S.15}$$

Therefore we may write V_{in} as a function of $v_{\text{aq}}(0)$, as follows

$$v_{\text{aq}}(0) = E_Q \frac{V_{\text{vit}}}{C_{\text{L}}} k_{\text{el}}^{(v)} = \frac{1}{C_{\text{L}}}\left(\frac{V_{\text{in}}}{\frac{S_{\text{ret}} p_{\text{RPE}}^{(v)}}{V_{\text{vit}} k_{\text{el}}^{(v)}} + 1 + \frac{p_{\text{RPE}}^{(v)}}{p_{\text{ILM}}^{(v)}}}\right) \tag{S.16}$$

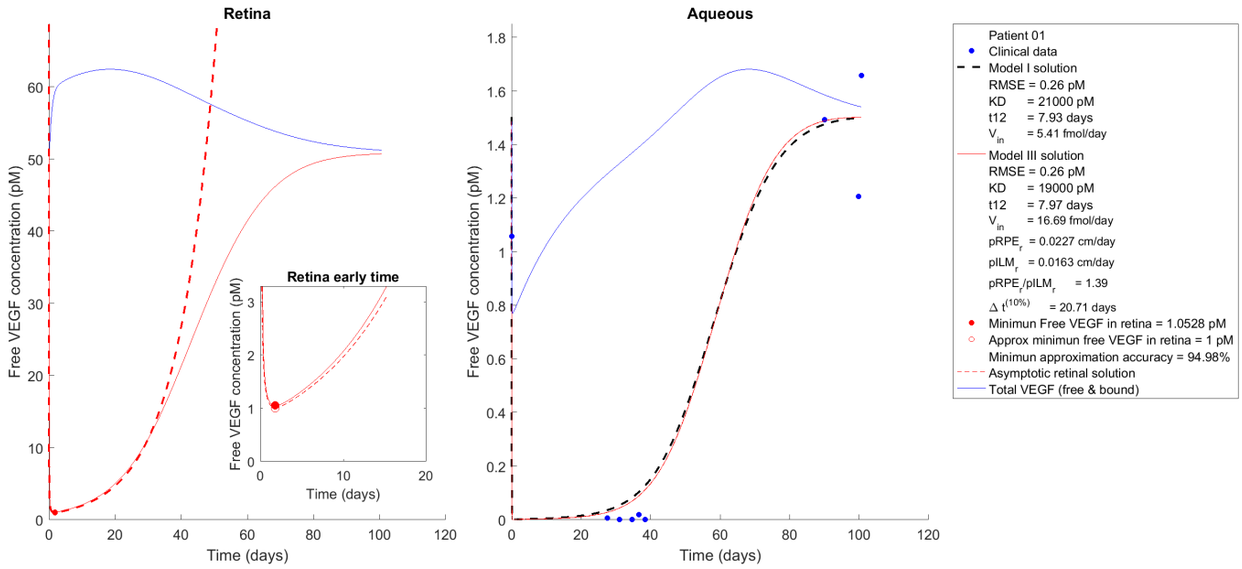
$$\Rightarrow \quad V_{\text{in}} = C_{\text{L}}\left(1 + \frac{S_{\text{ret}} p_{\text{RPE}}^{(v)}}{V_{\text{vit}} k_{\text{el}}^{(v)}} + \frac{p_{\text{RPE}}^{(v)}}{p_{\text{ILM}}^{(v)}}\right) v_{\text{aq}}(0). \tag{S.17}$$

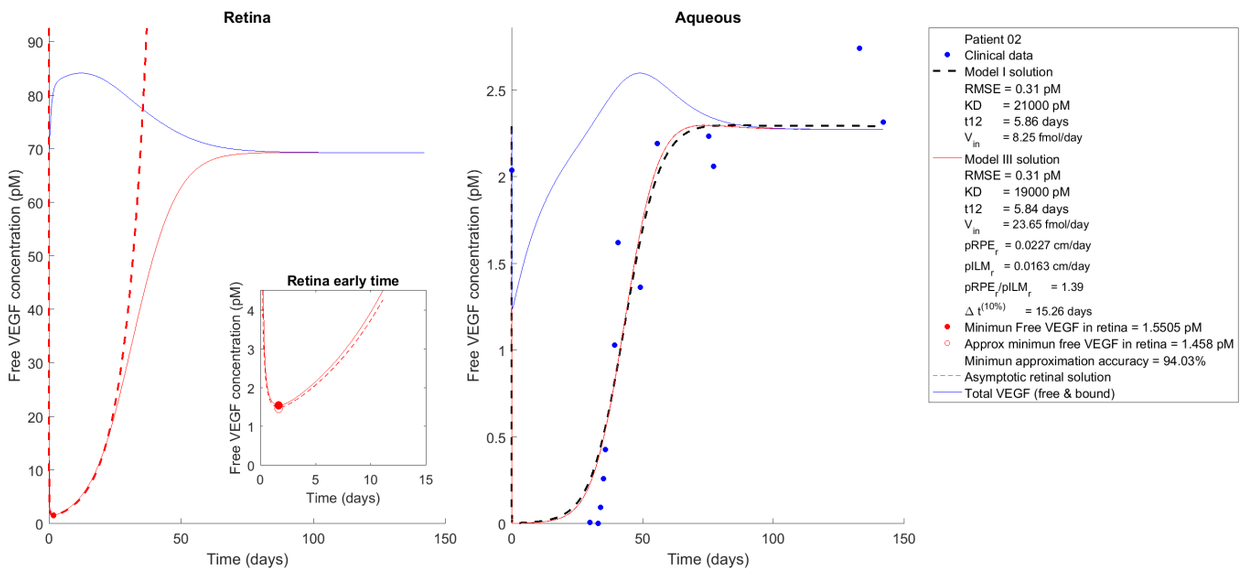
Additionally we note the analogue of this relationship derived from the 2-compartment equivalent of this model, presented in Hutton-Smith et al.2016 [7]. Notice, as defined by Equations 8-15 of [7], the relationship between V_{in} and $v_{\text{aq}}(0)$ differs to Equation S.17 in the two compartment model, instead being described by Equation S.18.

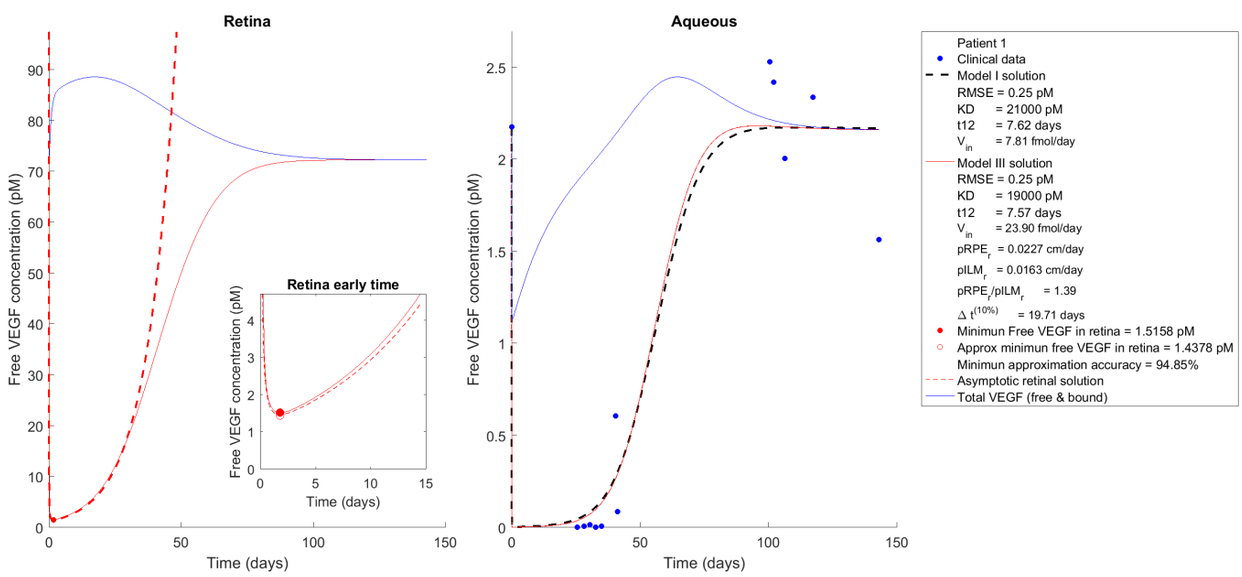
$$V_{\text{in}} = C_{\text{L}} v_{\text{aq}}(0). \tag{S.18}$$

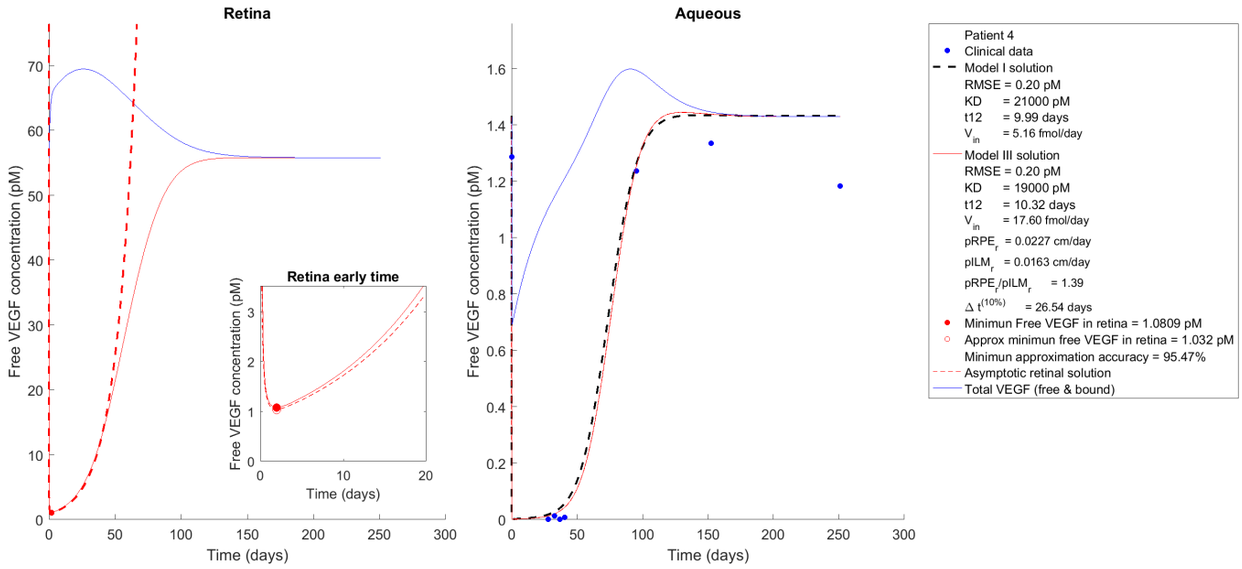
S4 INDIVIDUAL PATIENT PLOTS

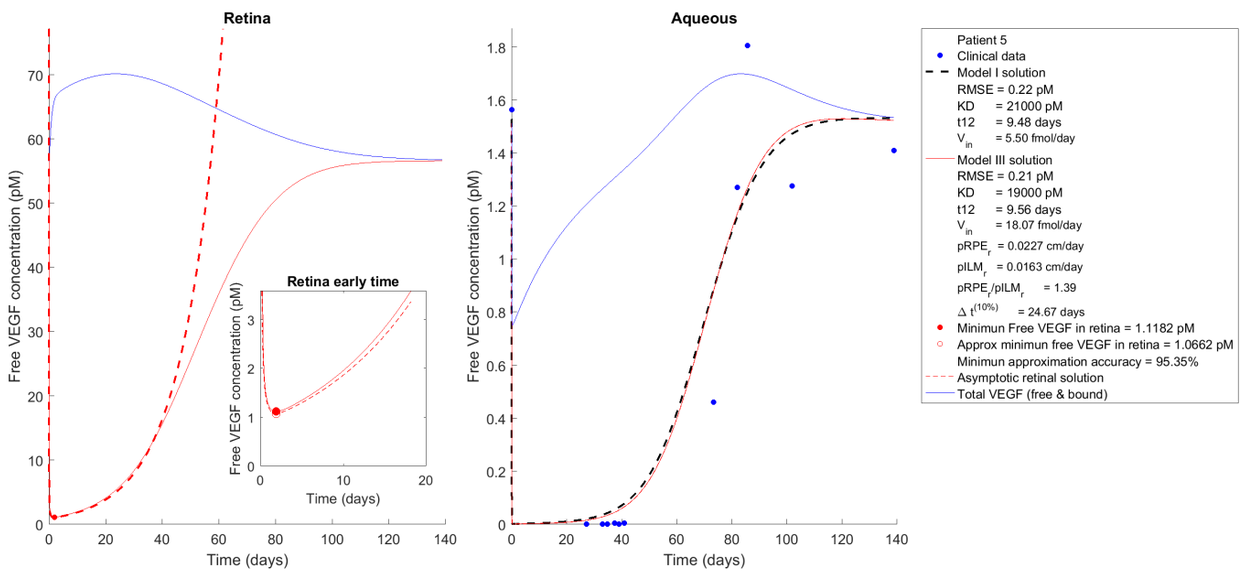
The following 31 figures show the individual plots for each patient in the retina and aqueous, the solid red lines represent the numerical solution for the 3-compartment PK/PD model presented in the main text (for K_D = 19,000), whereas the dashed black line in the aqueous shows the corresponding 2-compartment PK/PD fit, originally presented in Hutton-Smith et al 2016 [7]. All fit parameters for a specific patient can be found in the figure legend.

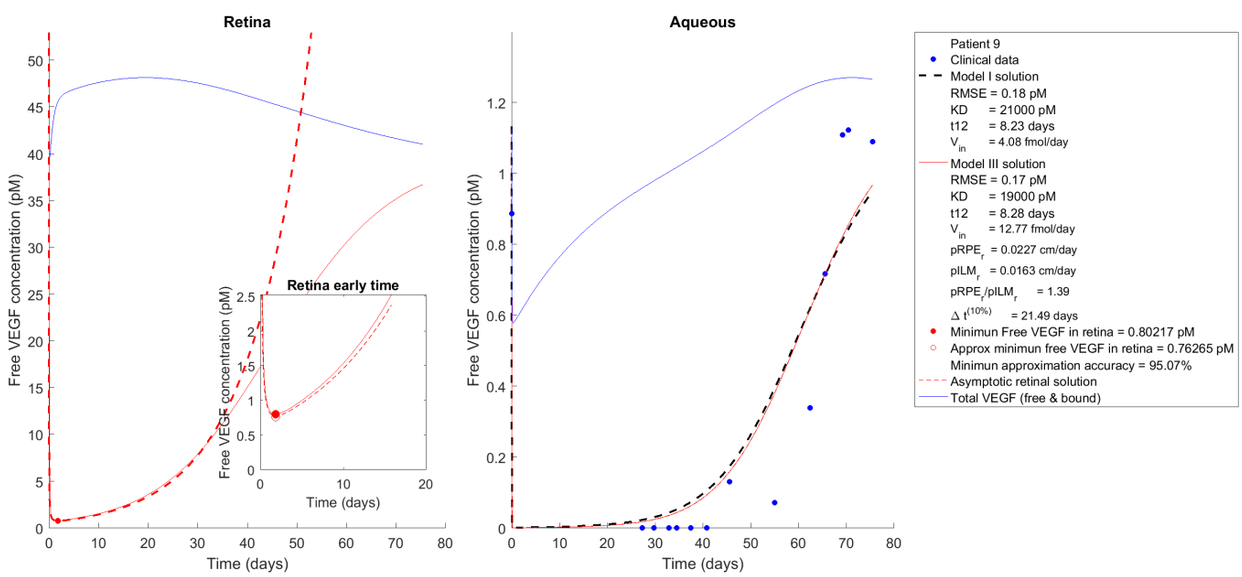


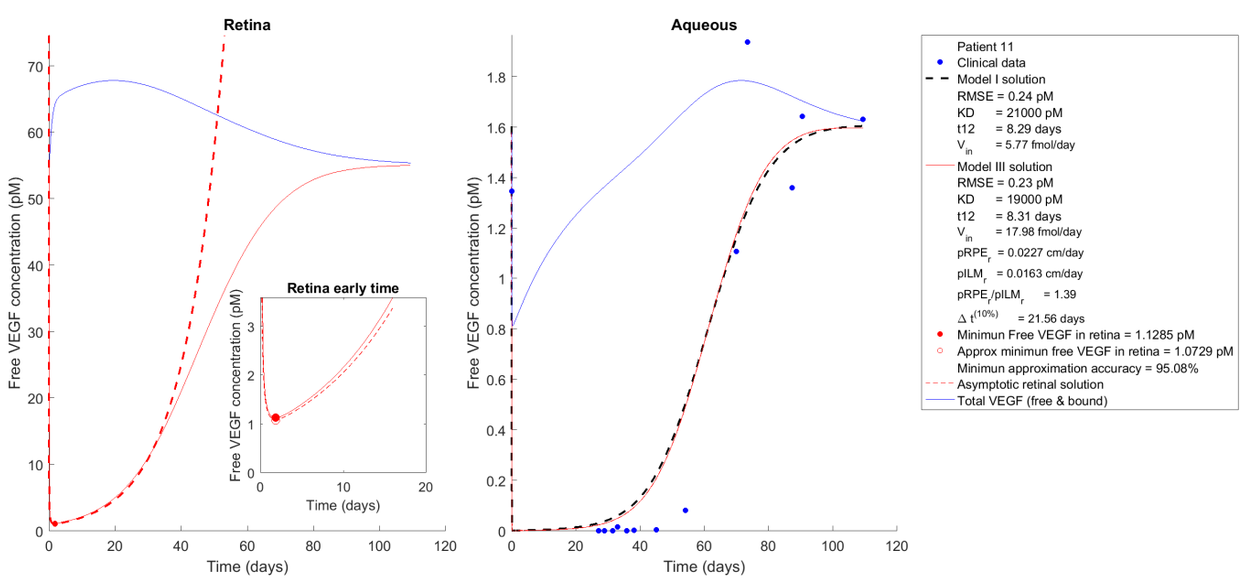


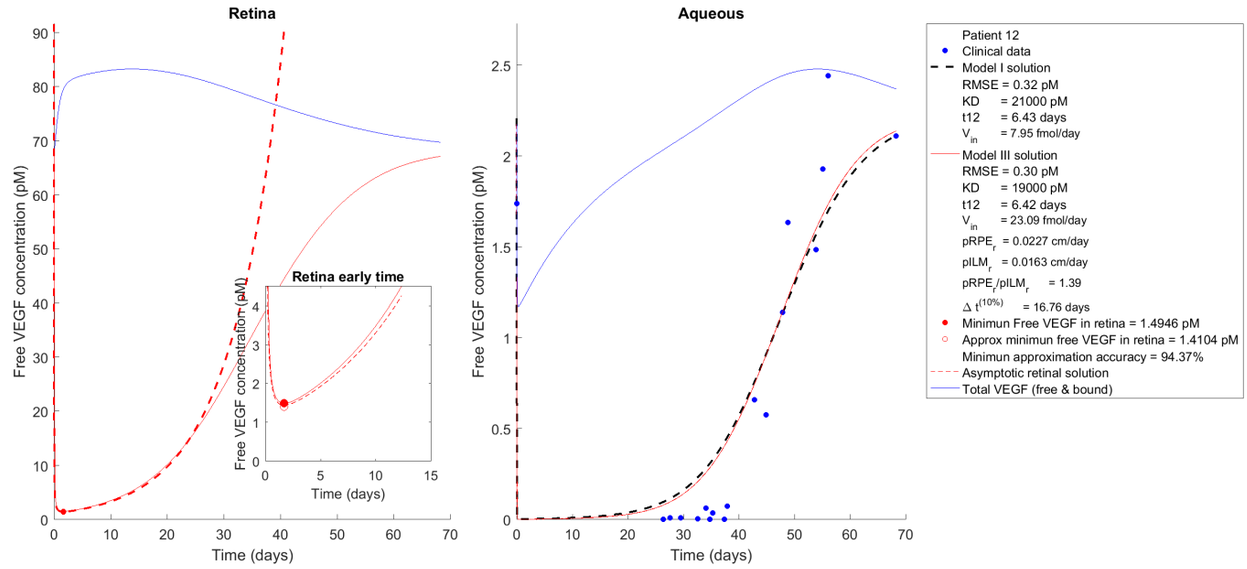


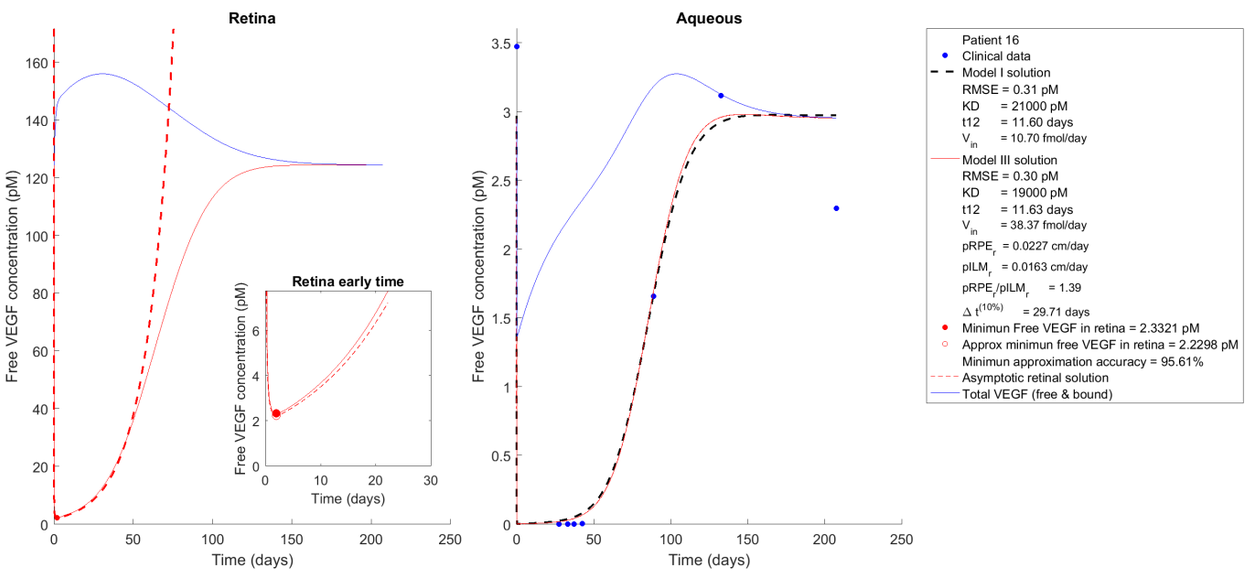

Retina
Aqueous
Retina early time
Free VEGF concentration (pM)
Time (days)
Patient 4
Clinical data
Model I solution
RMSE = 0.20 pM
KD = 21000 pM
t12 = 9.99 days
V_in = 5.16 fmol/day
Model III solution
RMSE = 0.20 pM
KD = 19000 pM
t12 = 10.32 days
V_in = 17.60 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t(10%) = 26.54 days
Minimun Free VEGF in retina = 1.0809 pM
Approx minimun free VEGF in retina = 1.032 pM
Minimun approximation accuracy = 95.47%
Asymptotic retinal solution
Total VEGF (free & bound)

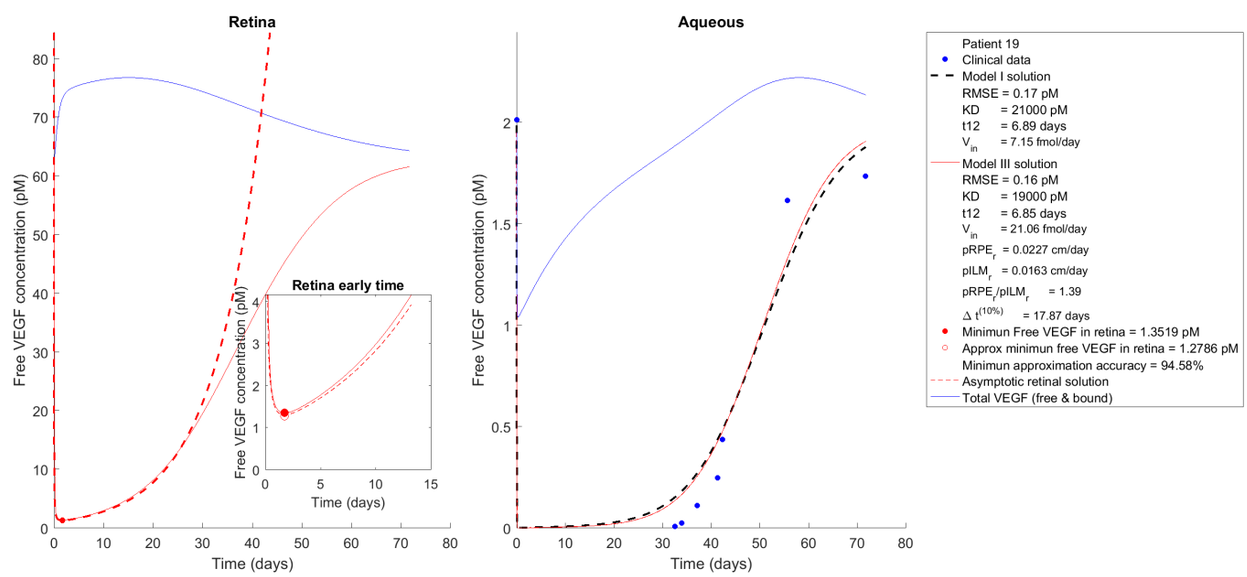

Retina
Aqueous
Retina early time
Free VEGF concentration (pM)
Time (days)
Patient 5
Clinical data
Model I solution
RMSE = 0.22 pM
KD = 21000 pM
t12 = 9.48 days
V_in = 5.50 fmol/day
Model III solution
RMSE = 0.21 pM
KD = 19000 pM
t12 = 9.56 days
V_in = 18.07 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t(10%) = 24.67 days
Minimun Free VEGF in retina = 1.1182 pM
Approx minimun free VEGF in retina = 1.0662 pM
Minimun approximation accuracy = 95.35%
Asymptotic retinal solution
Total VEGF (free & bound)

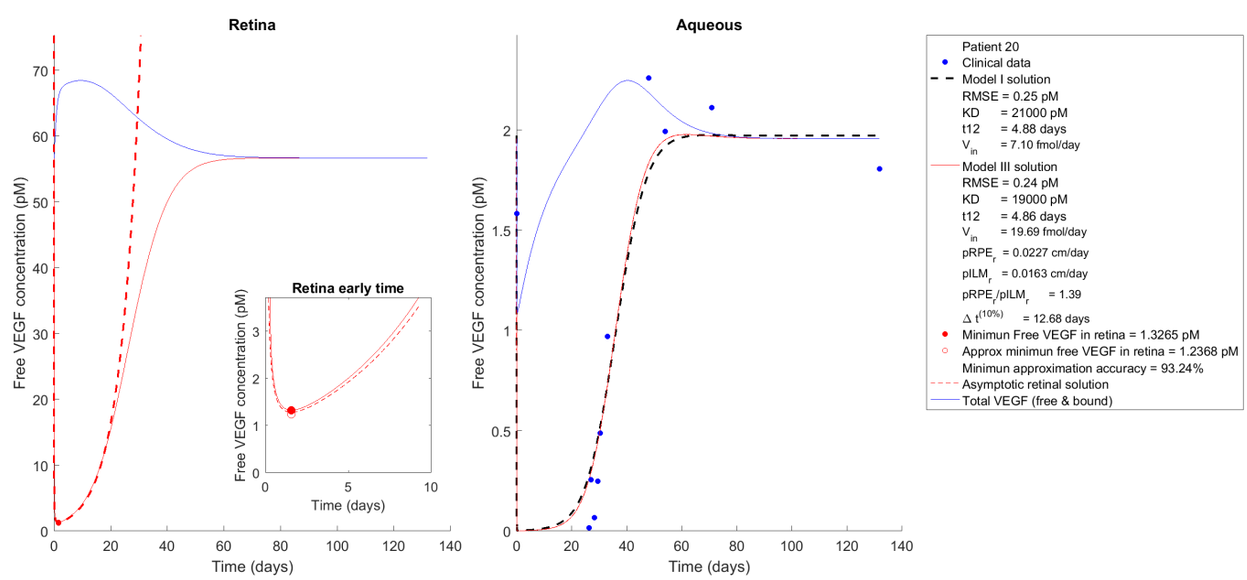

Retina
Aqueous
Retina early time
Free VEGF concentration (pM)
Time (days)
Patient 9
Clinical data
Model I solution
RMSE = 0.18 pM
KD = 21000 pM
t12 = 8.23 days
V_in = 4.08 fmol/day
Model III solution
RMSE = 0.17 pM
KD = 19000 pM
t12 = 8.28 days
V_in = 12.77 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t(10%) = 21.49 days
Minimun Free VEGF in retina = 0.80217 pM
Approx minimun free VEGF in retina = 0.76265 pM
Minimun approximation accuracy = 95.07%
Asymptotic retinal solution
Total VEGF (free & bound)

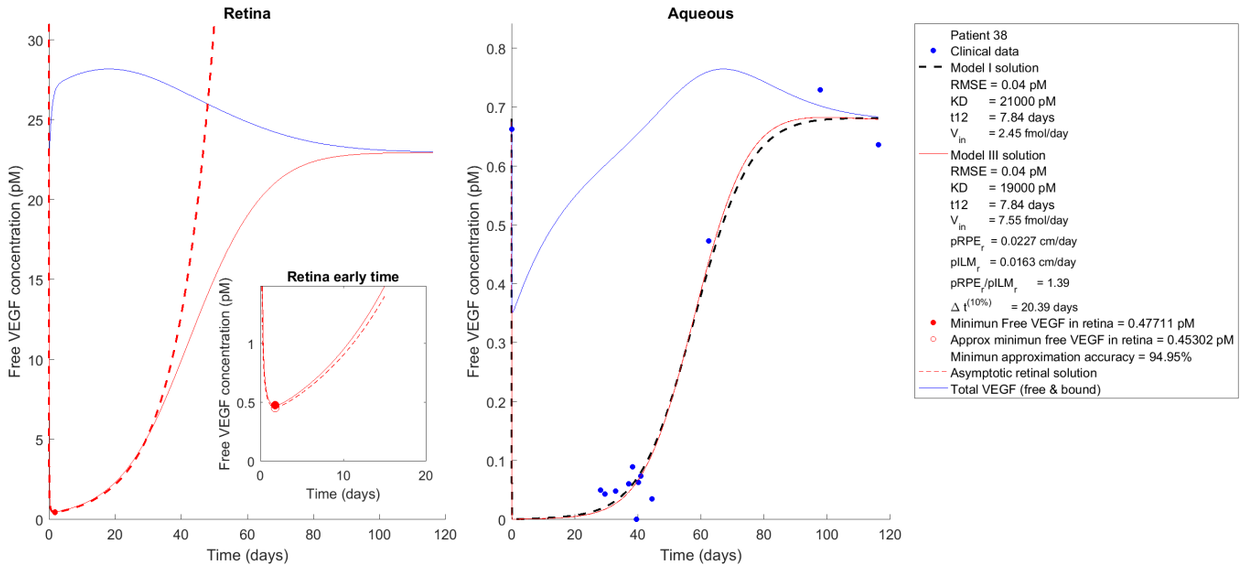

Retina
Aqueous
Retina early time
Free VEGF concentration (pM)
Time (days)
Patient 11
Clinical data
Model I solution
RMSE = 0.24 pM
KD = 21000 pM
t12 = 8.29 days
V_in = 5.77 fmol/day
Model III solution
RMSE = 0.23 pM
KD = 19000 pM
t12 = 8.31 days
V_in = 17.98 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t(10%) = 21.56 days
Minimun Free VEGF in retina = 1.1285 pM
Approx minimun free VEGF in retina = 1.0729 pM
Minimun approximation accuracy = 95.08%
Asymptotic retinal solution
Total VEGF (free & bound)

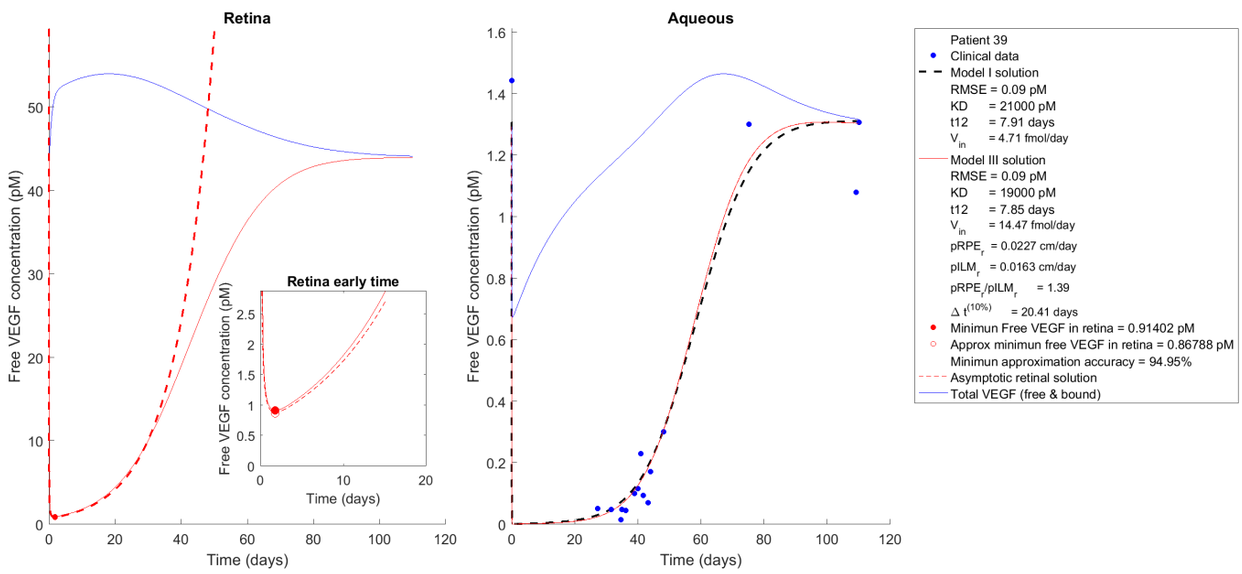

Retina
Retina early time
Free VEGF concentration (pM)
Time (days)
Aqueous
Free VEGF concentration (pM)
Time (days)
Patient 12
Clinical data
Model I solution
RMSE = 0.32 pM
KD = 21000 pM
t12 = 6.43 days
V_in = 7.95 fmol/day
Model III solution
RMSE = 0.30 pM
KD = 19000 pM
t12 = 6.42 days
V_in = 23.09 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t(10%) = 16.76 days
Minimun Free VEGF in retina = 1.4946 pM
Approx minimun free VEGF in retina = 1.4104 pM
Minimun approximation accuracy = 94.37%
Asymptotic retinal solution
Total VEGF (free & bound)

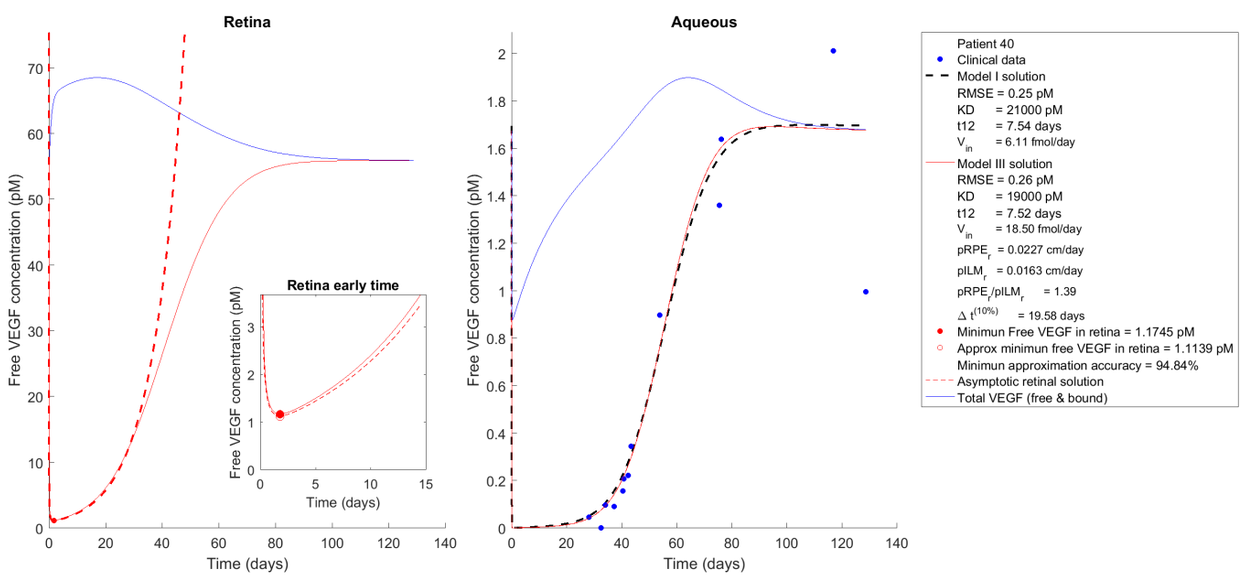

Retina
Retina early time
Free VEGF concentration (pM)
Time (days)
Aqueous
Free VEGF concentration (pM)
Time (days)
Patient 16
Clinical data
Model I solution
RMSE = 0.31 pM
KD = 21000 pM
t12 = 11.60 days
V_in = 10.70 fmol/day
Model III solution
RMSE = 0.30 pM
KD = 19000 pM
t12 = 11.63 days
V_in = 38.37 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t(10%) = 29.71 days
Minimun Free VEGF in retina = 2.3321 pM
Approx minimun free VEGF in retina = 2.2298 pM
Minimun approximation accuracy = 95.61%
Asymptotic retinal solution
Total VEGF (free & bound)

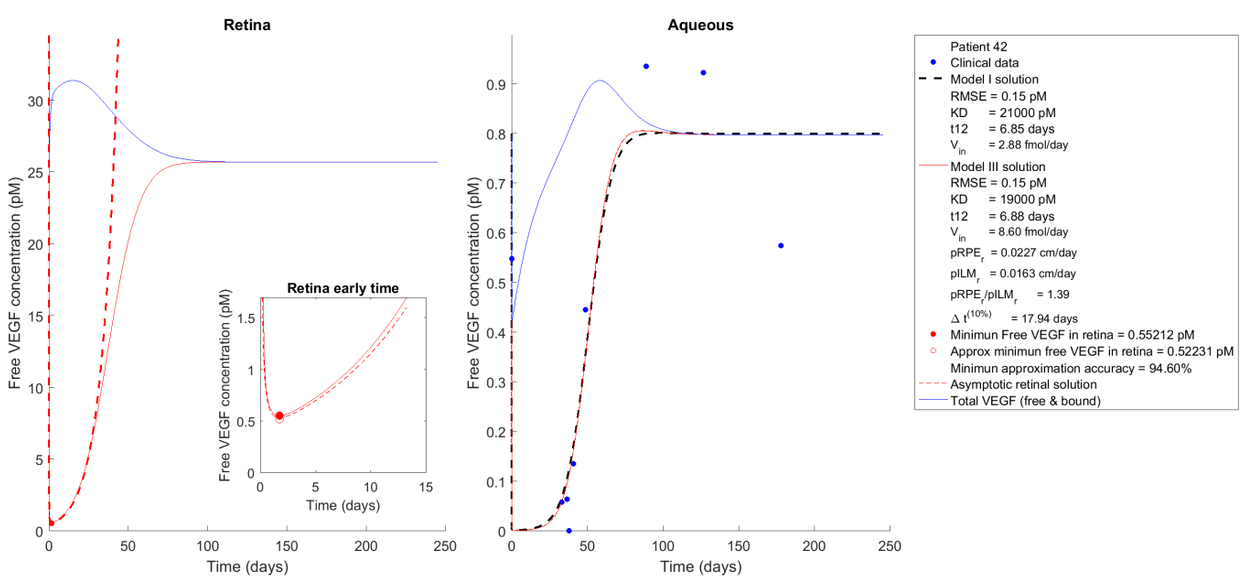

Retina
Retina early time
Free VEGF concentration (pM)
Time (days)
Aqueous
Free VEGF concentration (pM)
Time (days)
Patient 19
Clinical data
Model I solution
RMSE = 0.17 pM
KD = 21000 pM
t12 = 6.89 days
V_in = 7.15 fmol/day
Model III solution
RMSE = 0.16 pM
KD = 19000 pM
t12 = 6.85 days
V_in = 21.06 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t(10%) = 17.87 days
Minimun Free VEGF in retina = 1.3519 pM
Approx minimun free VEGF in retina = 1.2786 pM
Minimun approximation accuracy = 94.58%
Asymptotic retinal solution
Total VEGF (free & bound)

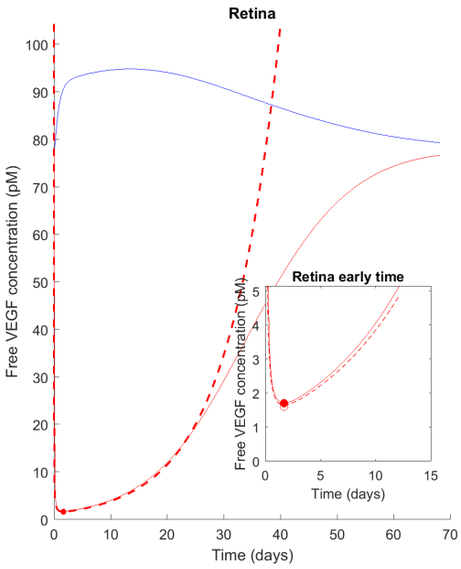

Retina
Retina early time
Free VEGF concentration (pM)
Time (days)
Aqueous
Free VEGF concentration (pM)
Time (days)
Patient 20
Clinical data
Model I solution
RMSE = 0.25 pM
KD = 21000 pM
t12 = 4.88 days
V_in = 7.10 fmol/day
Model III solution
RMSE = 0.24 pM
KD = 19000 pM
t12 = 4.86 days
V_in = 19.69 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t(10%) = 12.68 days
Minimun Free VEGF in retina = 1.3265 pM
Approx minimun free VEGF in retina = 1.2368 pM
Minimun approximation accuracy = 93.24%
Asymptotic retinal solution
Total VEGF (free & bound)

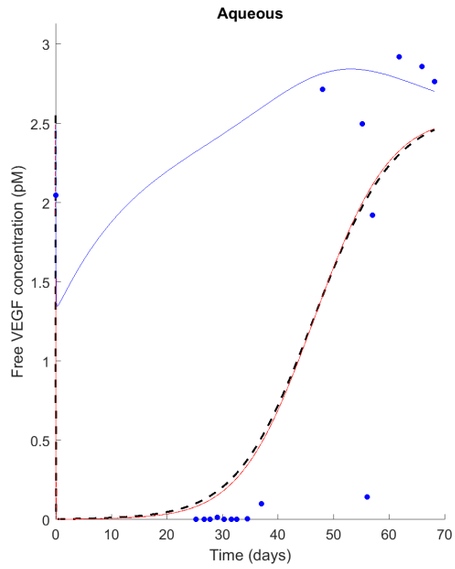

Retina
Aqueous
Retina early time
Free VEGF concentration (pM)
Time (days)
Patient 38
Clinical data
Model I solution
RMSE = 0.04 pM
KD = 21000 pM
t12 = 7.84 days
V_in = 2.45 fmol/day
Model III solution
RMSE = 0.04 pM
KD = 19000 pM
t12 = 7.84 days
V_in = 7.55 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t(10%) = 20.39 days
Minimun Free VEGF in retina = 0.47711 pM
Approx minimun free VEGF in retina = 0.45302 pM
Minimun approximation accuracy = 94.95%
Asymptotic retinal solution
Total VEGF (free & bound)


Retina
Aqueous
Retina early time
Free VEGF concentration (pM)
Time (days)
Patient 39
Clinical data
Model I solution
RMSE = 0.09 pM
KD = 21000 pM
t12 = 7.91 days
V_in = 4.71 fmol/day
Model III solution
RMSE = 0.09 pM
KD = 19000 pM
t12 = 7.85 days
V_in = 14.47 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t(10%) = 20.41 days
Minimun Free VEGF in retina = 0.91402 pM
Approx minimun free VEGF in retina = 0.86788 pM
Minimun approximation accuracy = 94.95%
Asymptotic retinal solution
Total VEGF (free & bound)

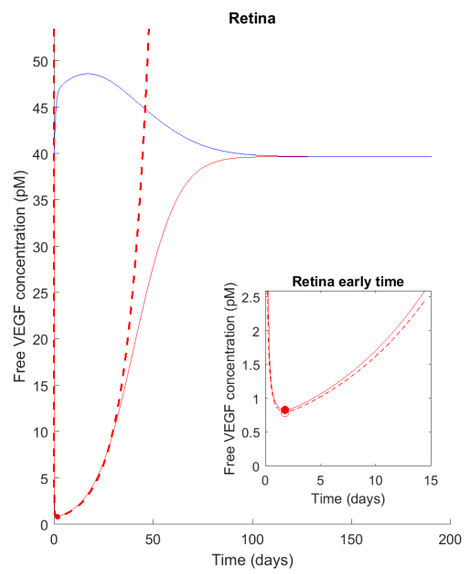

Retina
Aqueous
Retina early time
Free VEGF concentration (pM)
Time (days)
Patient 40
Clinical data
Model I solution
RMSE = 0.25 pM
KD = 21000 pM
t12 = 7.54 days
V_in = 6.11 fmol/day
Model III solution
RMSE = 0.26 pM
KD = 19000 pM
t12 = 7.52 days
V_in = 18.50 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t(10%) = 19.58 days
Minimun Free VEGF in retina = 1.1745 pM
Approx minimun free VEGF in retina = 1.1139 pM
Minimun approximation accuracy = 94.84%
Asymptotic retinal solution
Total VEGF (free & bound)

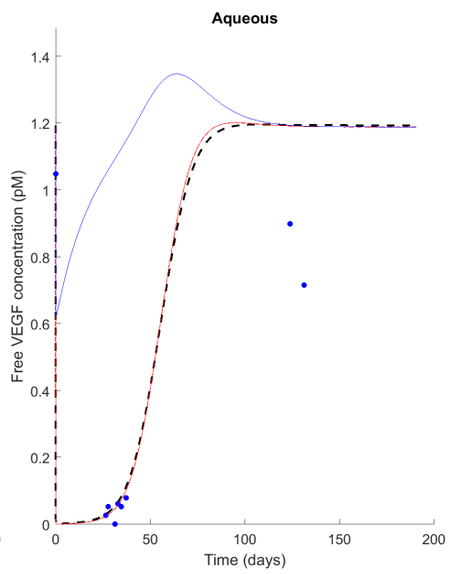

Retina
Aqueous
Retina early time
Free VEGF concentration (pM)
Time (days)
Patient 42
Clinical data
Model I solution
RMSE = 0.15 pM
KD = 21000 pM
t12 = 6.85 days
V_in = 2.88 fmol/day
Model III solution
RMSE = 0.15 pM
KD = 19000 pM
t12 = 6.88 days
V_in = 8.60 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t(10%) = 17.94 days
Minimun Free VEGF in retina = 0.55212 pM
Approx minimun free VEGF in retina = 0.52231 pM
Minimun approximation accuracy = 94.60%
Asymptotic retinal solution
Total VEGF (free & bound)



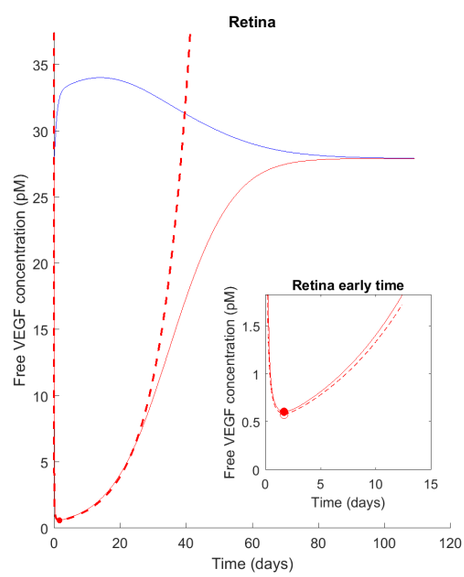


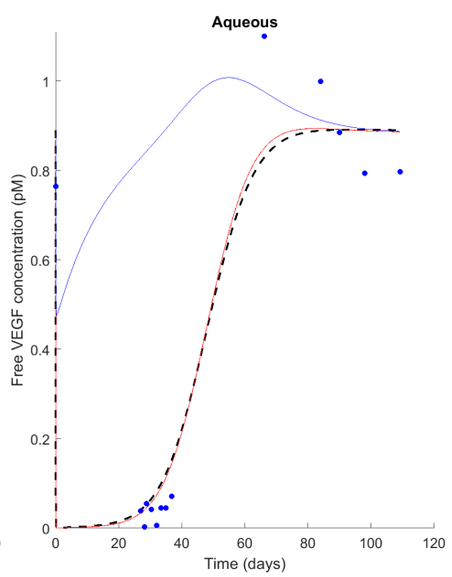
Patient 47
Clinical data
Model I solution
RMSE = 0.65 pM
KD = 21000 pM
t12 = 6.30 days
V_{in} = 9.18 fmol/day
Model III solution
RMSE = 0.64 pM
KD = 19000 pM
t12 = 6.30 days
V_{in} = 26.36 fmol/day
$pRPE_r$ = 0.0227 cm/day
$pILM_r$ = 0.0163 cm/day
$pRPE_r/pILM_r$ = 1.39
$\Delta t^{(10\%)}$ = 16.46 days
Minimun Free VEGF in retina = 1.7106 pM
Approx minimun free VEGF in retina = 1.6132 pM
Minimun approximation accuracy = 94.31%
Asymptotic retinal solution
Total VEGF (free & bound)



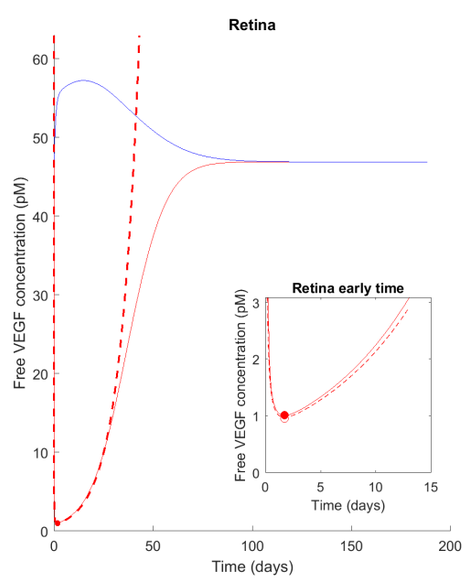


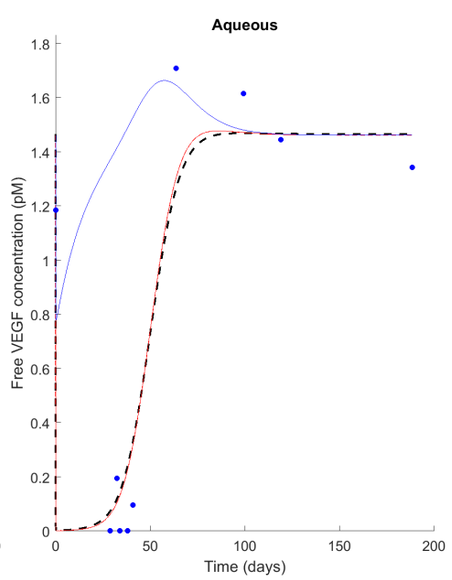
Patient 53
Clinical data
Model I solution
RMSE = 0.27 pM
KD = 21000 pM
t12 = 7.50 days
V_{in} = 4.30 fmol/day
Model III solution
RMSE = 0.26 pM
KD = 19000 pM
t12 = 7.51 days
V_{in} = 13.13 fmol/day
$pRPE_r$ = 0.0227 cm/day
$pILM_r$ = 0.0163 cm/day
$pRPE_r/pILM_r$ = 1.39
$\Delta t^{(10\%)}$ = 19.56 days
Minimun Free VEGF in retina = 0.83351 pM
Approx minimun free VEGF in retina = 0.79051 pM
Minimun approximation accuracy = 94.84%
Asymptotic retinal solution
Total VEGF (free & bound)



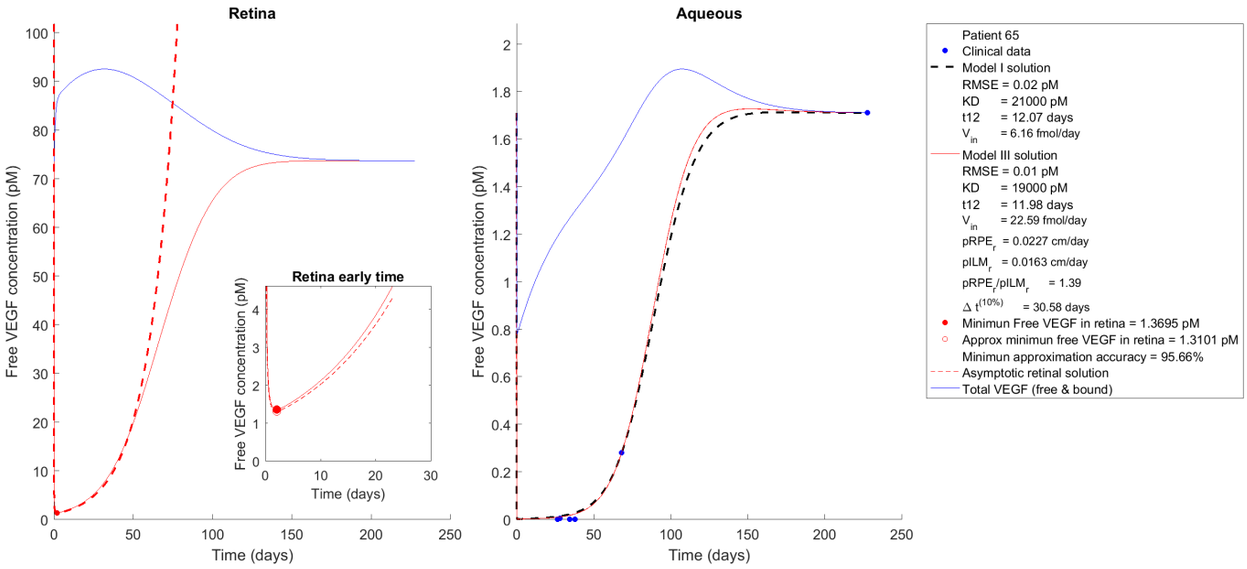


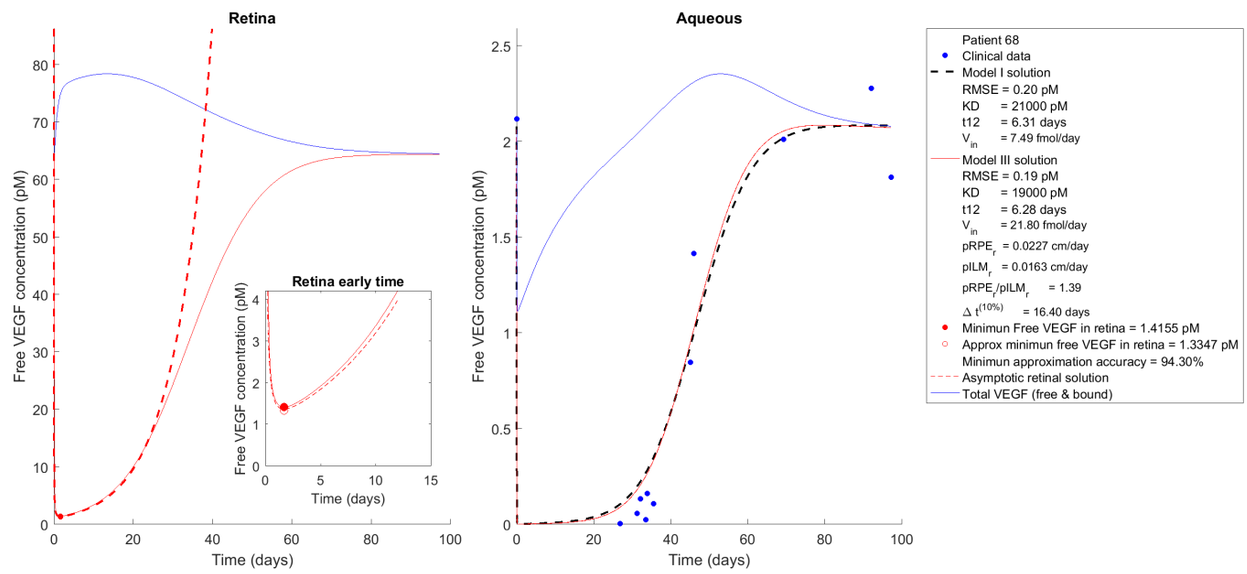
Patient 54
Clinical data
Model I solution
RMSE = 0.10 pM
KD = 21000 pM
t12 = 6.50 days
V_{in} = 3.20 fmol/day
Model III solution
RMSE = 0.09 pM
KD = 19000 pM
t12 = 6.49 days
V_{in} = 9.41 fmol/day
$pRPE_r$ = 0.0227 cm/day
$pILM_r$ = 0.0163 cm/day
$pRPE_r/pILM_r$ = 1.39
$\Delta t^{(10\%)}$ = 16.95 days
Minimun Free VEGF in retina = 0.60853 pM
Approx minimun free VEGF in retina = 0.57456 pM
Minimun approximation accuracy = 94.42%
Asymptotic retinal solution
Total VEGF (free & bound)

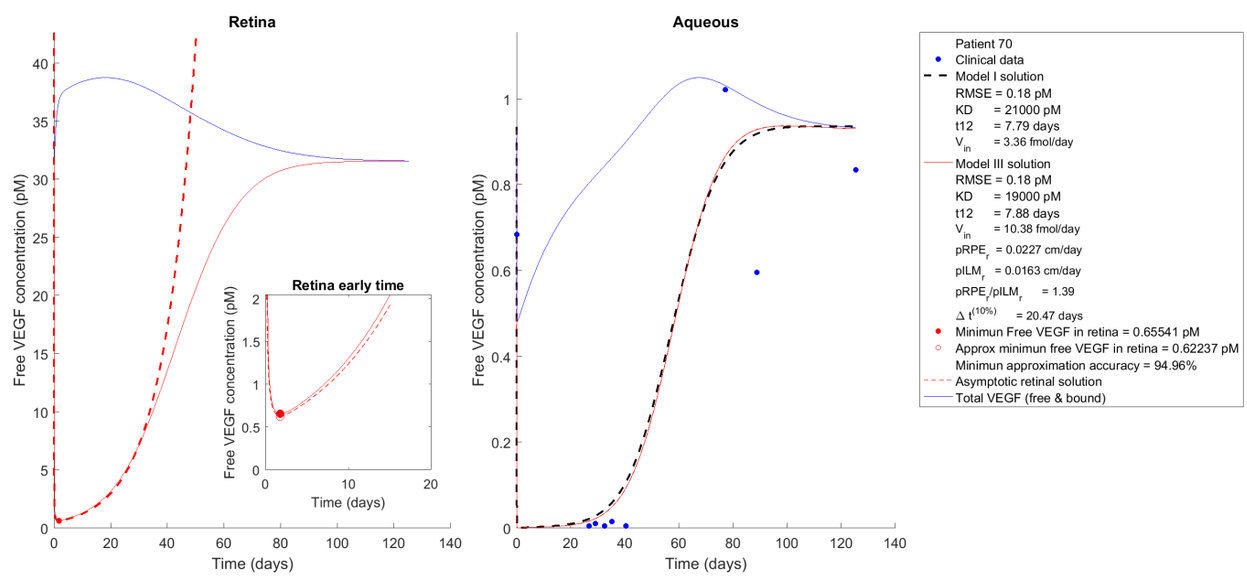


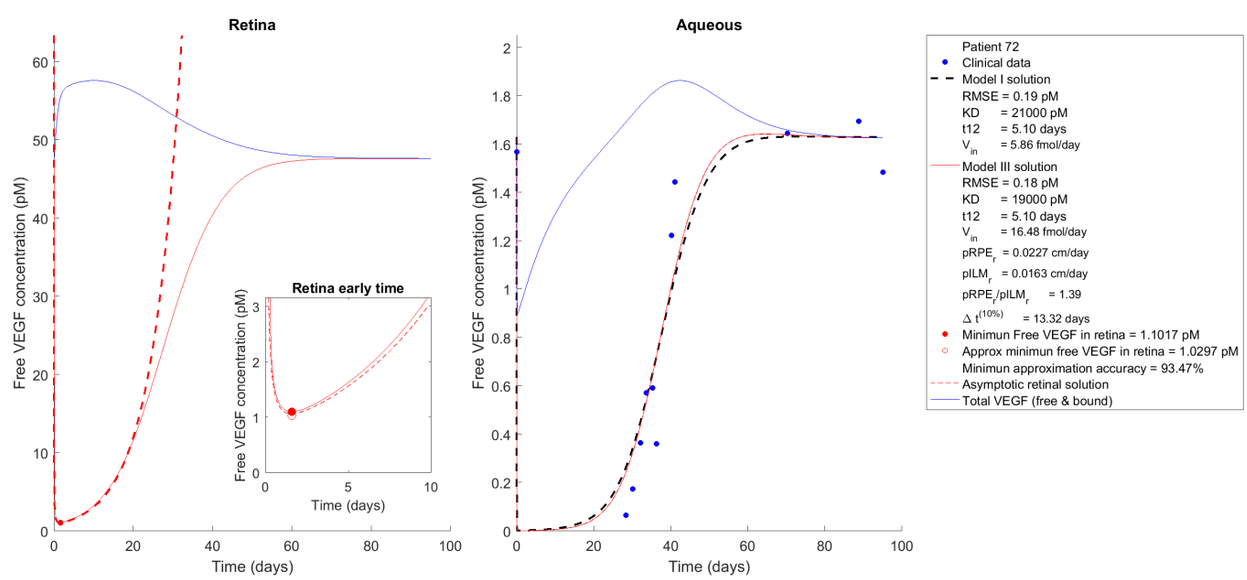


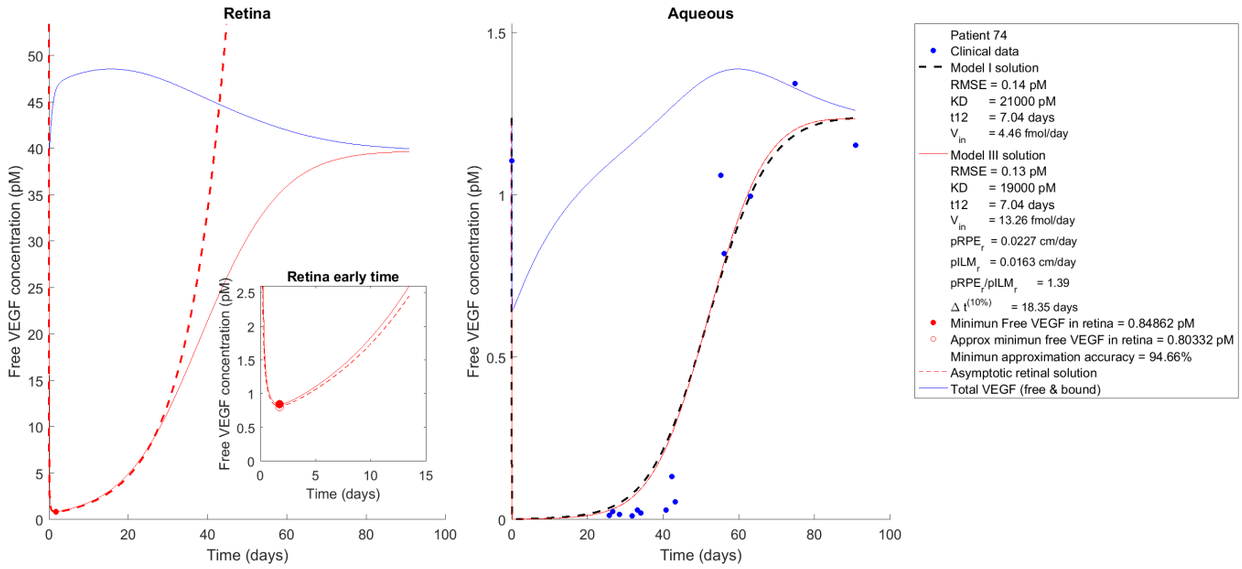
Patient 55
Clinical data
Model I solution
RMSE = 0.21 pM
KD = 21000 pM
t12 = 6.78 days
V_{in} = 5.28 fmol/day
Model III solution
RMSE = 0.20 pM
KD = 19000 pM
t12 = 6.78 days
V_{in} = 15.72 fmol/day
$pRPE_r$ = 0.0227 cm/day
$pILM_r$ = 0.0163 cm/day
$pRPE_r/pILM_r$ = 1.39
$\Delta t^{(10\%)}$ = 17.70 days
Minimun Free VEGF in retina = 1.0108 pM
Approx minimun free VEGF in retina = 0.95571 pM
Minimun approximation accuracy = 94.55%
Asymptotic retinal solution
Total VEGF (free & bound)

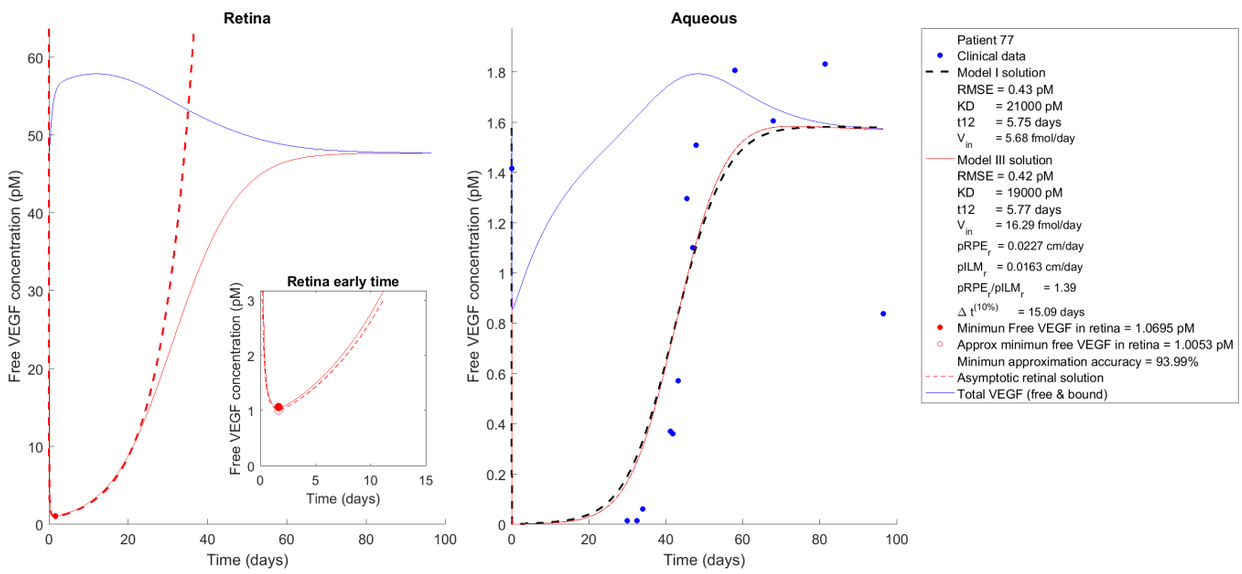

Retina
Retina early time
Free VEGF concentration (pM)
Time (days)
Aqueous
Free VEGF concentration (pM)
Time (days)
Patient 65
Clinical data
Model I solution
RMSE = 0.02 pM
KD = 21000 pM
t12 = 12.07 days
V_in = 6.16 fmol/day
Model III solution
RMSE = 0.01 pM
KD = 19000 pM
t12 = 11.98 days
V_in = 22.59 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t^(10%) = 30.58 days
Minimun Free VEGF in retina = 1.3695 pM
Approx minimun free VEGF in retina = 1.3101 pM
Minimun approximation accuracy = 95.66%
Asymptotic retinal solution
Total VEGF (free & bound)

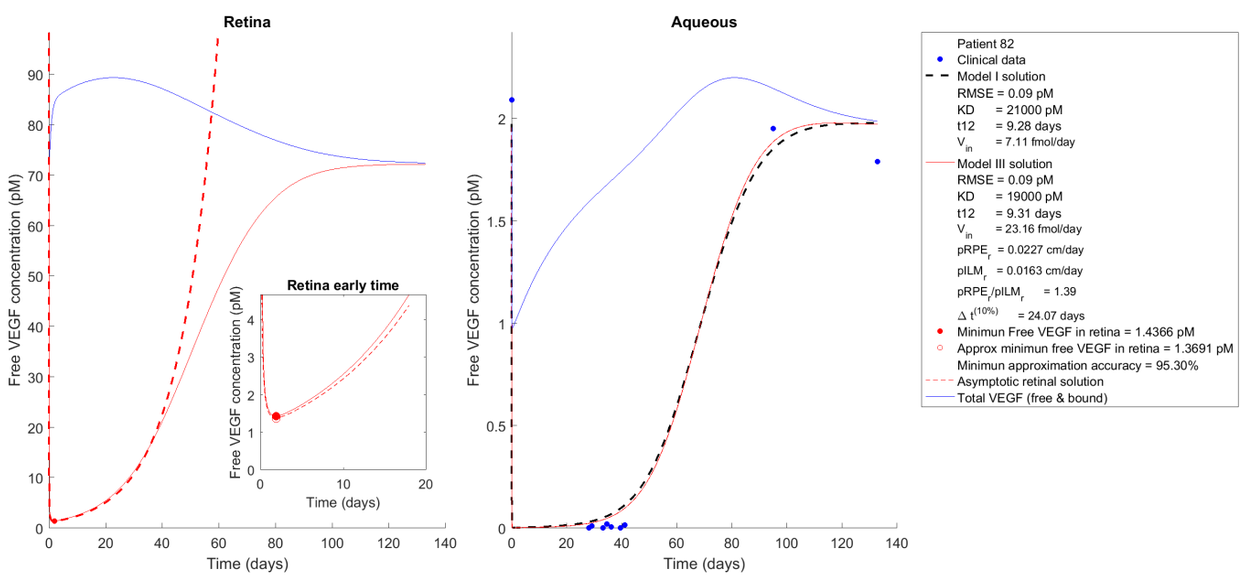

Retina
Retina early time
Free VEGF concentration (pM)
Time (days)
Aqueous
Free VEGF concentration (pM)
Time (days)
Patient 68
Clinical data
Model I solution
RMSE = 0.20 pM
KD = 21000 pM
t12 = 6.31 days
V_in = 7.49 fmol/day
Model III solution
RMSE = 0.19 pM
KD = 19000 pM
t12 = 6.28 days
V_in = 21.80 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t^(10%) = 16.40 days
Minimun Free VEGF in retina = 1.4155 pM
Approx minimun free VEGF in retina = 1.3347 pM
Minimun approximation accuracy = 94.30%
Asymptotic retinal solution
Total VEGF (free & bound)

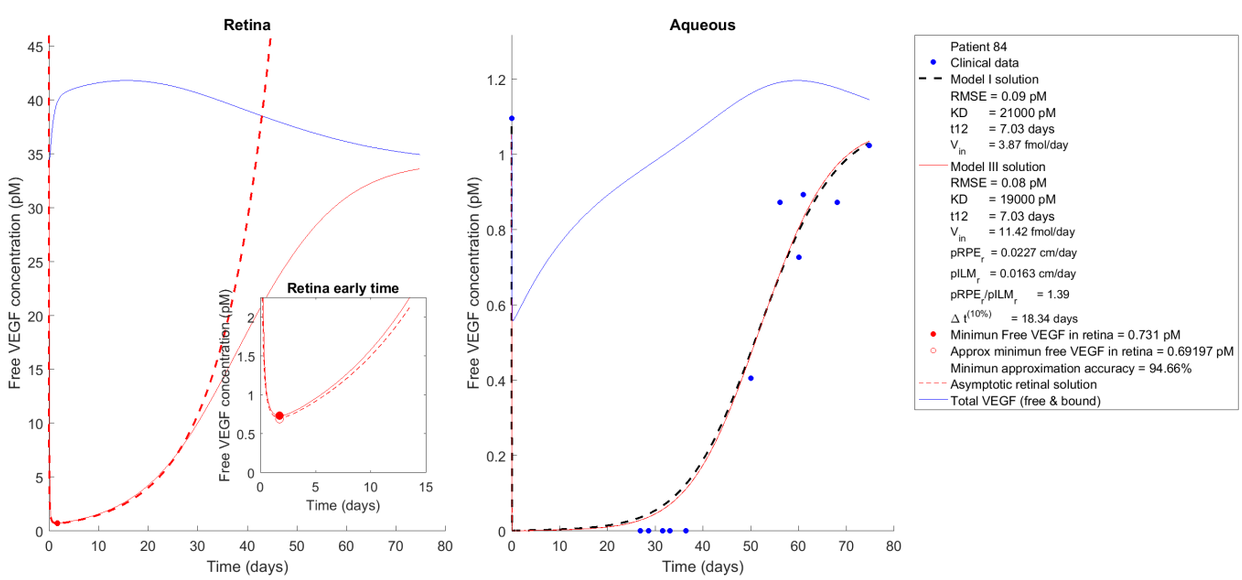

Retina
Retina early time
Free VEGF concentration (pM)
Time (days)
Aqueous
Free VEGF concentration (pM)
Time (days)
Patient 70
Clinical data
Model I solution
RMSE = 0.18 pM
KD = 21000 pM
t12 = 7.79 days
V_in = 3.36 fmol/day
Model III solution
RMSE = 0.18 pM
KD = 19000 pM
t12 = 7.88 days
V_in = 10.38 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t^(10%) = 20.47 days
Minimun Free VEGF in retina = 0.65541 pM
Approx minimun free VEGF in retina = 0.62237 pM
Minimun approximation accuracy = 94.96%
Asymptotic retinal solution
Total VEGF (free & bound)

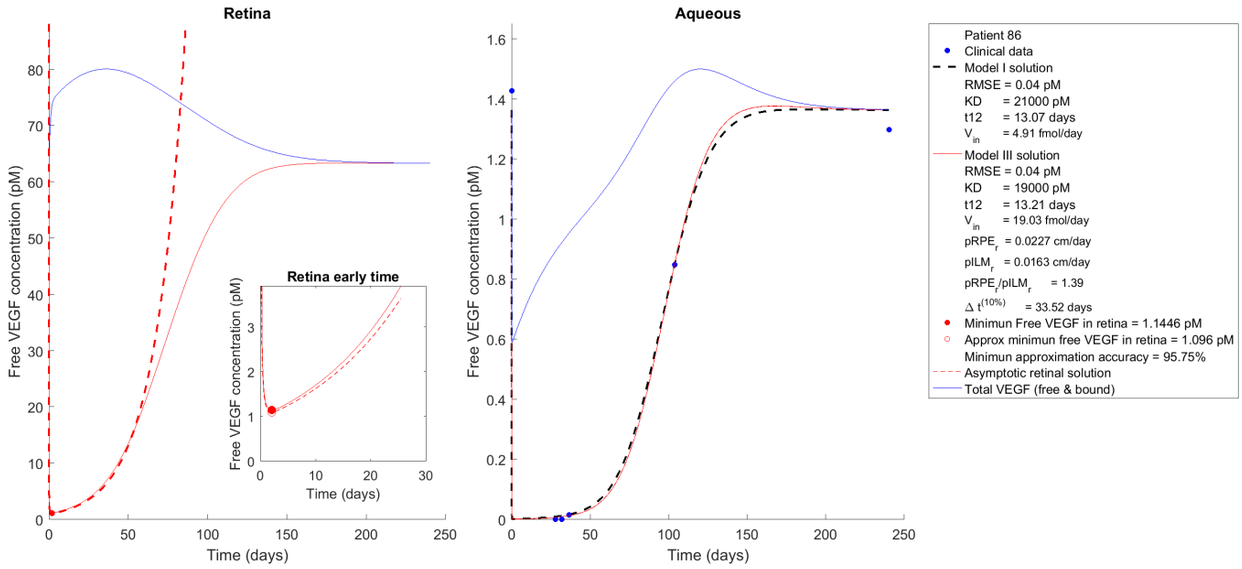

Retina
Retina early time
Free VEGF concentration (pM)
Time (days)
Aqueous
Free VEGF concentration (pM)
Time (days)
Patient 72
Clinical data
Model I solution
RMSE = 0.19 pM
KD = 21000 pM
t12 = 5.10 days
V_in = 5.86 fmol/day
Model III solution
RMSE = 0.18 pM
KD = 19000 pM
t12 = 5.10 days
V_in = 16.48 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t^(10%) = 13.32 days
Minimun Free VEGF in retina = 1.1017 pM
Approx minimun free VEGF in retina = 1.0297 pM
Minimun approximation accuracy = 93.47%
Asymptotic retinal solution
Total VEGF (free & bound)

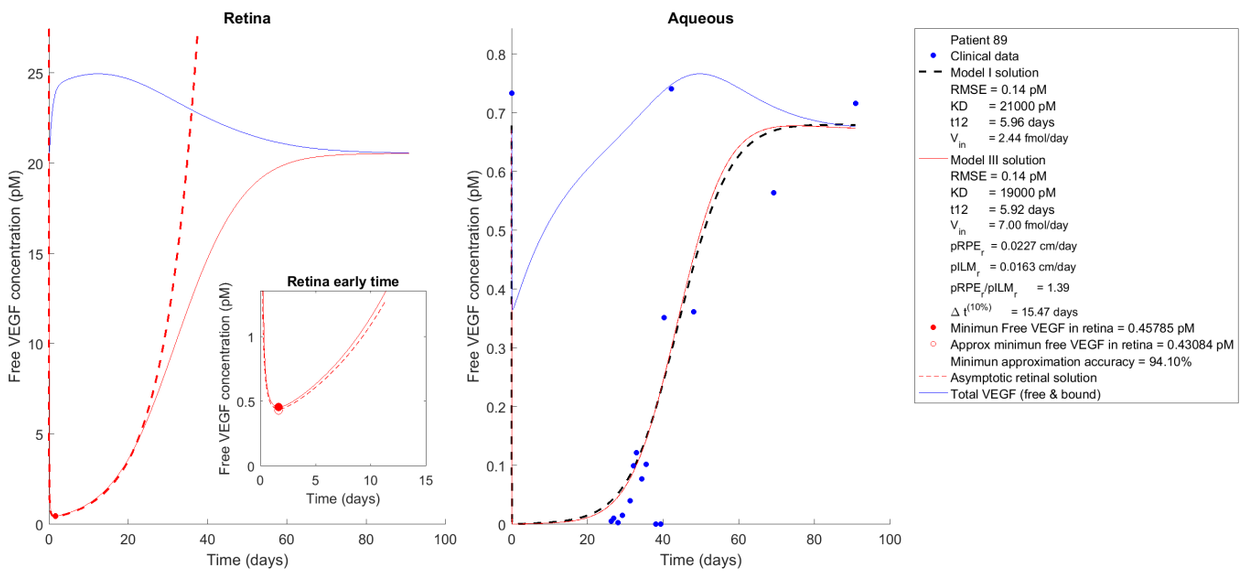

Retina
Aqueous
Retina early time
Free VEGF concentration (pM)
Time (days)
Patient 74
Clinical data
Model I solution
RMSE = 0.14 pM
KD = 21000 pM
t12 = 7.04 days
V_in = 4.46 fmol/day
Model III solution
RMSE = 0.13 pM
KD = 19000 pM
t12 = 7.04 days
V_in = 13.26 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t(10%) = 18.35 days
Minimun Free VEGF in retina = 0.84862 pM
Approx minimun free VEGF in retina = 0.80332 pM
Minimun approximation accuracy = 94.66%
Asymptotic retinal solution
Total VEGF (free & bound)

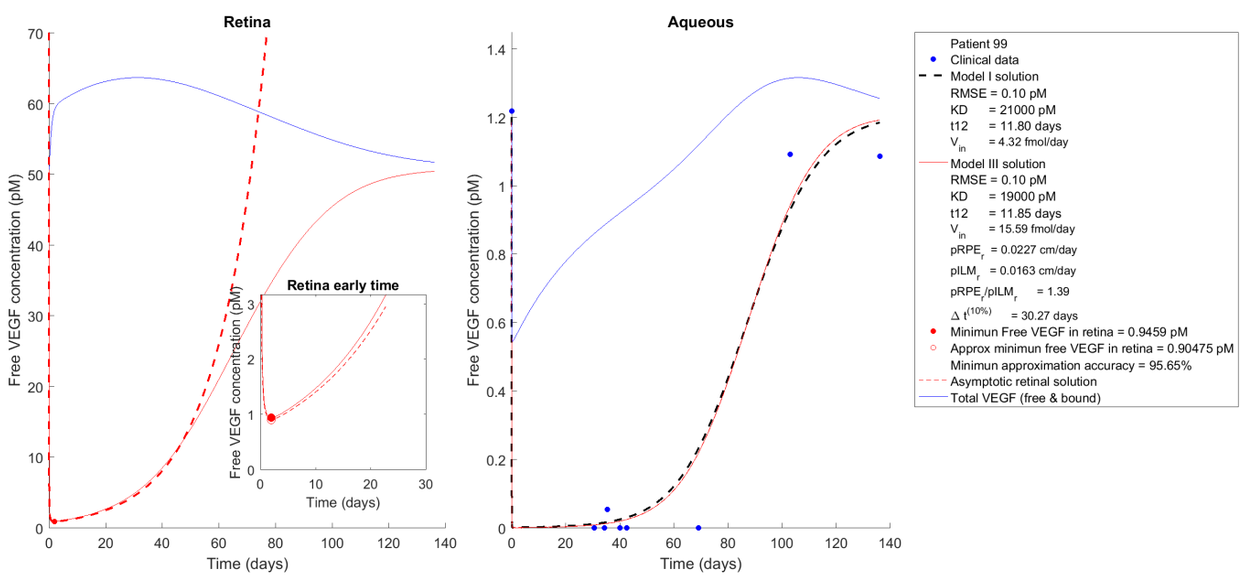

Retina
Aqueous
Retina early time
Free VEGF concentration (pM)
Time (days)
Patient 77
Clinical data
Model I solution
RMSE = 0.43 pM
KD = 21000 pM
t12 = 5.75 days
V_in = 5.68 fmol/day
Model III solution
RMSE = 0.42 pM
KD = 19000 pM
t12 = 5.77 days
V_in = 16.29 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t(10%) = 15.09 days
Minimun Free VEGF in retina = 1.0695 pM
Approx minimun free VEGF in retina = 1.0053 pM
Minimun approximation accuracy = 93.99%
Asymptotic retinal solution
Total VEGF (free & bound)

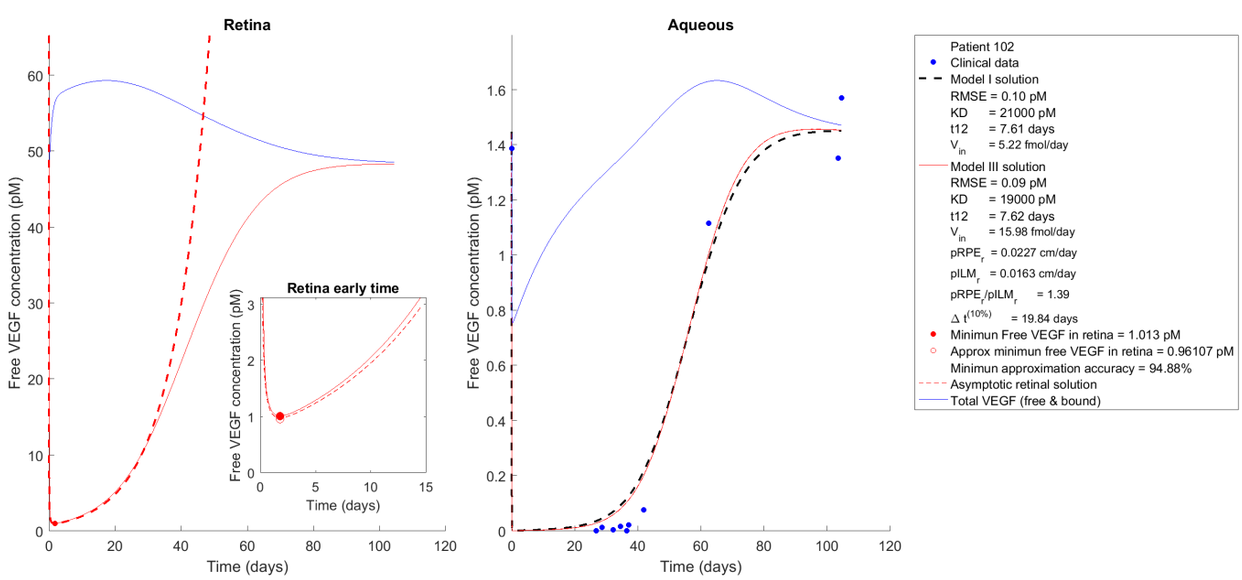

Retina
Aqueous
Retina early time
Free VEGF concentration (pM)
Time (days)
Patient 82
Clinical data
Model I solution
RMSE = 0.09 pM
KD = 21000 pM
t12 = 9.28 days
V_in = 7.11 fmol/day
Model III solution
RMSE = 0.09 pM
KD = 19000 pM
t12 = 9.31 days
V_in = 23.16 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t(10%) = 24.07 days
Minimun Free VEGF in retina = 1.4366 pM
Approx minimun free VEGF in retina = 1.3691 pM
Minimun approximation accuracy = 95.30%
Asymptotic retinal solution
Total VEGF (free & bound)


Retina
Aqueous
Retina early time
Free VEGF concentration (pM)
Time (days)
Patient 84
Clinical data
Model I solution
RMSE = 0.09 pM
KD = 21000 pM
t12 = 7.03 days
V_in = 3.87 fmol/day
Model III solution
RMSE = 0.08 pM
KD = 19000 pM
t12 = 7.03 days
V_in = 11.42 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t(10%) = 18.34 days
Minimun Free VEGF in retina = 0.731 pM
Approx minimun free VEGF in retina = 0.69197 pM
Minimun approximation accuracy = 94.66%
Asymptotic retinal solution
Total VEGF (free & bound)


Retina
Aqueous
Retina early time
Free VEGF concentration (pM)
Time (days)
Patient 86
Clinical data
Model I solution
RMSE = 0.04 pM
KD = 21000 pM
t12 = 13.07 days
V_in = 4.91 fmol/day
Model III solution
RMSE = 0.04 pM
KD = 19000 pM
t12 = 13.21 days
V_in = 19.03 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t(10%) = 33.52 days
Minimun Free VEGF in retina = 1.1446 pM
Approx minimun free VEGF in retina = 1.096 pM
Minimun approximation accuracy = 95.75%
Asymptotic retinal solution
Total VEGF (free & bound)


Retina
Aqueous
Retina early time
Free VEGF concentration (pM)
Time (days)
Patient 89
Clinical data
Model I solution
RMSE = 0.14 pM
KD = 21000 pM
t12 = 5.96 days
V_in = 2.44 fmol/day
Model III solution
RMSE = 0.14 pM
KD = 19000 pM
t12 = 5.92 days
V_in = 7.00 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t(10%) = 15.47 days
Minimun Free VEGF in retina = 0.45785 pM
Approx minimun free VEGF in retina = 0.43084 pM
Minimun approximation accuracy = 94.10%
Asymptotic retinal solution
Total VEGF (free & bound)


Retina
Aqueous
Retina early time
Free VEGF concentration (pM)
Time (days)
Patient 99
Clinical data
Model I solution
RMSE = 0.10 pM
KD = 21000 pM
t12 = 11.80 days
V_in = 4.32 fmol/day
Model III solution
RMSE = 0.10 pM
KD = 19000 pM
t12 = 11.85 days
V_in = 15.59 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t(10%) = 30.27 days
Minimun Free VEGF in retina = 0.9459 pM
Approx minimun free VEGF in retina = 0.90475 pM
Minimun approximation accuracy = 95.65%
Asymptotic retinal solution
Total VEGF (free & bound)


Retina
Aqueous
Retina early time
Free VEGF concentration (pM)
Time (days)
Patient 102
Clinical data
Model I solution
RMSE = 0.10 pM
KD = 21000 pM
t12 = 7.61 days
V_in = 5.22 fmol/day
Model III solution
RMSE = 0.09 pM
KD = 19000 pM
t12 = 7.62 days
V_in = 15.98 fmol/day
pRPE_r = 0.0227 cm/day
pILM_r = 0.0163 cm/day
pRPE_r/pILM_r = 1.39
Δ t(10%) = 19.84 days
Minimun Free VEGF in retina = 1.013 pM
Approx minimun free VEGF in retina = 0.96107 pM
Minimun approximation accuracy = 94.88%
Asymptotic retinal solution
Total VEGF (free & bound)

In order to illustrate the dynamics of total VEGF in the retina and aqueous humour, we present Figure S2 for patient 40, identical to the above figures, with the addition of VR and RVR concentration profiles. As drug permeates into the retina and binds VEGF the elimination of total VEGF will decrease due to the smaller permeability of the VEGF-drug complexes. This leads to a transient increase in the total VEGF concentration in the retina, given the constant production of VEGF. In the aqueous humour, which reflects the vitreous, the initial rate of VEGF influx will decrease correspondingly and the total concentration will show a transient fall.

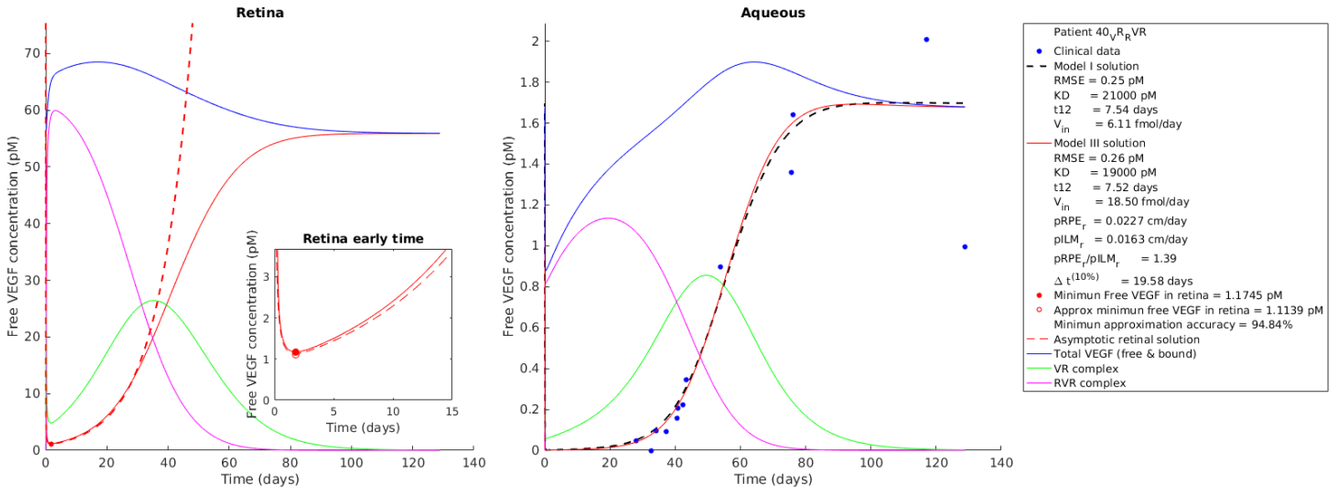


Figure S2: Patient 40, as in the above plots, with the addition of VEGF-ranibizumab (VR) and ranibizumab-VEGF-ranibizumab (RVR), profiles.

S5 Relationship between $t_{1/2}^{(r)}$ and K_D

The distribution of predicted $t_{1/2}^{(r)}$ values across patients, for values of K_D in the range 50-50,000 pM, can be seen in Figure S3 of the main text. For a value of K_D, the mean predicted value of $t_{1/2}^{(r)}$ is shown by the solid blue line, while the solid grey region denotes ±SD from the mean. As in Hutton-Smith et. al [7] we used the mean experimental value of $t_{1/2}^{(r)}$, 7.9 (±1.74) days, shown respectively by the solid red and dashed lines, to estimate the *in vivo* value for K_D, giving 19,000 pM (16,000-25,000 pM) , as is shown graphically in Figure S3. The dashed blue line denotes the mean $t_{1/2}^{(r)}$, over patients, resulting the analysis performed in [7], using an analogous two-compartment PK/PD model to analyse the Saunders et. al. dataset [8], which predicted an *in vivo* value for K_D of 21,000 pM (18,000-27,000 pM).

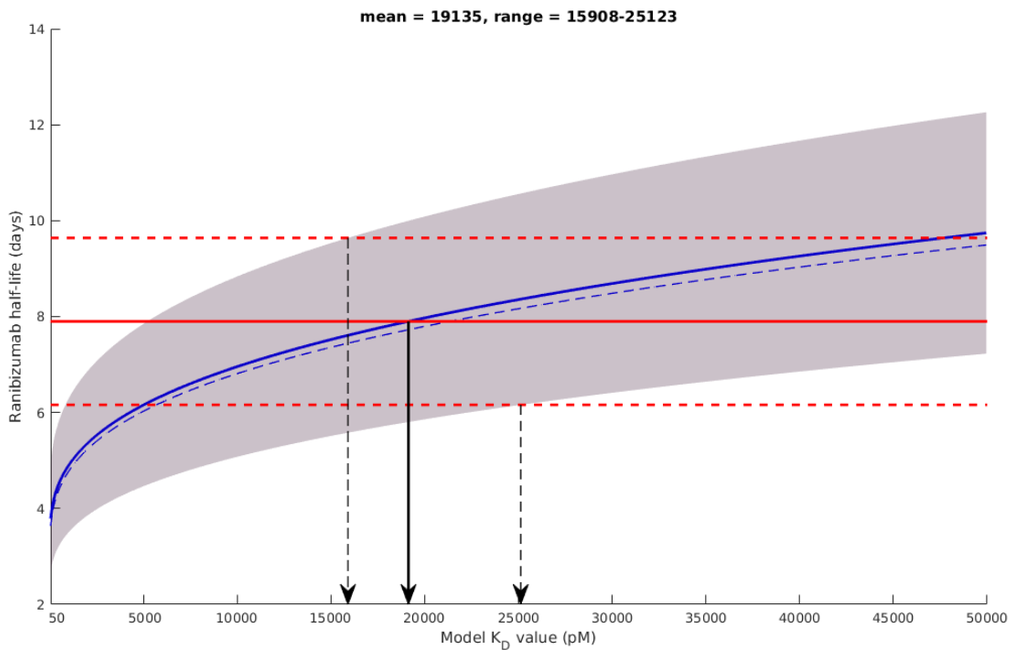


Figure S3: Distribution of predicted $t_{1/2}^{(r)}$ values, generated over the prescribed range of K_D values (50-50,000 pM) for all 31 patients. The mean patient predicted $t_{1/2}^{(r)}$ value is shown by the solid blue line, with the grey region denoting ±SD. The solid red line shows the experimental mean value of $t_{1/2}^{(r)}$, 7.9 days, with the dashed red line showing ±SD, 1.74 days. The analogous two-compartment mean for $t_{1/2}^{(r)}$, with respect to K_D, is shown by the dashed blue line, taken from [7].

S6 Asymptotic analysis

S6.1 Non-dimensionalisation

Let

$$v_{\text{ret}}(0) = v_0, \quad r_{\text{ret}}(0) = 0, \quad c_{\text{ret}}(0) = 0, \quad h_{\text{ret}}(0) = 0, \tag{S.19}$$
$$v_{\text{vit}}(0) = u_0, \quad r_{\text{vit}}(0) = r_0, \quad c_{\text{vit}}(0) = 0, \quad h_{\text{vit}}(0) = 0. \tag{S.20}$$

Now let us non-dimensionalise the vitreous and retinal system equations, using the following non-dimensionalisation

$$v_{\text{ret}} = v_0 x_{\text{ret}}, \quad r_{\text{ret}} = r_0 y_{\text{ret}}, \quad c_{\text{ret}} = v_0 z_{\text{ret}}, \quad h_{\text{ret}} = v_0 w_{\text{ret}}, \tag{S.21}$$
$$v_{\text{vit}} = v_0 x_{\text{vit}}, \quad r_{\text{vit}} = r_0 y_{\text{vit}}, \quad c_{\text{vit}} = v_0 z_{\text{vit}}, \quad h_{\text{vit}} = v_0 w_{\text{vit}}. \tag{S.22}$$

Therefore

$$x_{\text{ret}}(0) = 1, \quad y_{\text{ret}}(0) = 0, \quad z_{\text{ret}}(0) = 0, \quad w_{\text{ret}}(0) = 0, \tag{S.23}$$
$$x_{\text{vit}}(0) = u_0/v_0, \quad y_{\text{vit}}(0) = 1, \quad z_{\text{vit}}(0) = 0, \quad w_{\text{vit}}(0) = 0, \tag{S.24}$$

and

$$t = \frac{1}{k_{\text{off}}}\tau. \tag{S.25}$$

This gives

Retina

$$\frac{\mathrm{d}x_{\mathrm{ret}}}{\mathrm{d}\tau} = \left(z_{\mathrm{ret}} - 2\frac{r_0}{K_D}x_{\mathrm{ret}}y_{\mathrm{ret}}\right) + Q^{(v)}x_{\mathrm{vit}} - E^{(v)}x_{\mathrm{ret}} + V, \tag{S.26}$$

$$\frac{\mathrm{d}y_{\mathrm{ret}}}{\mathrm{d}\tau} = \left(\frac{v_0}{r_0}z_{\mathrm{ret}} - 2\frac{v_0}{K_D}x_{\mathrm{ret}}y_{\mathrm{ret}}\right) + \left(2\frac{v_0}{r_0}w_{\mathrm{ret}} - \frac{v_0}{K_D}y_{\mathrm{ret}}z_{\mathrm{ret}}\right) + Q^{(r)}y_{\mathrm{vit}} - E^{(r)}y_{\mathrm{ret}}, \tag{S.27}$$

$$\frac{\mathrm{d}z_{\mathrm{ret}}}{\mathrm{d}\tau} = -\left(z_{\mathrm{ret}} - 2\frac{r_0}{K_D}x_{\mathrm{ret}}y_{\mathrm{ret}}\right) + \left(2w_{\mathrm{ret}} - \frac{r_0}{K_D}y_{\mathrm{ret}}z_{\mathrm{ret}}\right) + Q^{(c)}z_{\mathrm{vit}} - E^{(c)}z_{\mathrm{ret}}, \tag{S.28}$$

$$\frac{\mathrm{d}w_{\mathrm{ret}}}{\mathrm{d}\tau} = -\left(2w_{\mathrm{ret}} - \frac{r_0}{K_D}y_{\mathrm{ret}}z_{\mathrm{ret}}\right) + Q^{(h)}w_{\mathrm{vit}} - E^{(h)}w_{\mathrm{ret}}, \tag{S.29}$$

Vitreous

$$\frac{\mathrm{d}x_{\mathrm{vit}}}{\mathrm{d}\tau} = \left(z_{\mathrm{vit}} - 2\frac{r_0}{K_D}x_{\mathrm{vit}}y_{\mathrm{vit}}\right) + T^{(v)}x_{\mathrm{ret}} - K^{(v)}x_{\mathrm{vit}}, \tag{S.30}$$

$$\frac{\mathrm{d}y_{\mathrm{vit}}}{\mathrm{d}\tau} = \left(\frac{v_0}{r_0}z_{\mathrm{vit}} - 2\frac{v_0}{K_D}x_{\mathrm{vit}}y_{\mathrm{vit}}\right) + \left(2\frac{v_0}{r_0}w_{\mathrm{vit}} - \frac{v_0}{K_D}y_{\mathrm{vit}}z_{\mathrm{vit}}\right) + T^{(r)}y_{\mathrm{ret}} - K^{(r)}y_{\mathrm{vit}}, \tag{S.31}$$

$$\frac{\mathrm{d}z_{\mathrm{vit}}}{\mathrm{d}\tau} = -\left(z_{\mathrm{vit}} - 2\frac{r_0}{K_D}x_{\mathrm{vit}}y_{\mathrm{vit}}\right) + \left(2w_{\mathrm{vit}} - \frac{r_0}{K_D}y_{\mathrm{vit}}z_{\mathrm{vit}}\right) + T^{(c)}z_{\mathrm{ret}} - K^{(c)}z_{\mathrm{vit}}, \tag{S.32}$$

$$\frac{\mathrm{d}w_{\mathrm{vit}}}{\mathrm{d}\tau} = -\left(2w_{\mathrm{vit}} - \frac{r_0}{K_D}y_{\mathrm{vit}}z_{\mathrm{vit}}\right) + T^{(h)}w_{\mathrm{ret}} - K^{(h)}w_{\mathrm{vit}}, \tag{S.33}$$

where

$$Q^{(i)} = \frac{1}{k_{\mathrm{off}}}\frac{S_{\mathrm{ret}}}{V_{\mathrm{ret}}}p^{(i)}_{\mathrm{ILM}}, \quad E^{(i)} = \frac{1}{k_{\mathrm{off}}}\frac{S_{\mathrm{ret}}}{V_{\mathrm{ret}}}p^{(i)}_{\mathrm{RPE}} + Q^{(i)} \quad T^{(i)} = \frac{1}{k_{\mathrm{off}}}\frac{S_{\mathrm{ret}}}{V_{\mathrm{vit}}}p^{(i)}_{\mathrm{ILM}}, \tag{S.34}$$

$$K^{(i)} = \frac{k^{(i)}_{\mathrm{el}}}{k_{\mathrm{off}}} + T^{(i)}, \quad H^{(i)} = \frac{k^{(i)}_{\mathrm{el}}V_{\mathrm{vit}}}{k_{\mathrm{off}}V_{\mathrm{aq}}}, \quad V = \frac{V_{\mathrm{in}}}{v_0 k_{\mathrm{off}}V_{\mathrm{ret}}}. \tag{S.35}$$

Let

$$\omega = \frac{v_0}{r_0}, \quad \delta = \frac{v_0}{K_D}, \tag{S.36}$$

(S.37)

where

$$\omega \ll \delta \ll 1, \tag{S.38}$$

and all other parameters are $O(1)$, as can be calculated from their values as given in Table 2 of the main text and individual parameters listed in Section S4. Note this also implies that:

$$\varepsilon := \frac{\omega}{\delta} = \frac{K_D}{r_0} \ll 1. \tag{S.39}$$

Therefore our system of equations becomes:

Retina

$$\varepsilon\frac{\mathrm{d}x_{\mathrm{ret}}}{\mathrm{d}\tau} = \left(\varepsilon z_{\mathrm{ret}} - 2x_{\mathrm{ret}}y_{\mathrm{ret}}\right) + \varepsilon Q^{(v)}x_{\mathrm{vit}} - \varepsilon E^{(v)}x_{\mathrm{ret}} + \varepsilon V, \tag{S.40}$$

$$\frac{\mathrm{d}y_{\mathrm{ret}}}{\mathrm{d}\tau} = \delta\left[\left(\varepsilon z_{\mathrm{ret}} - 2x_{\mathrm{ret}}y_{\mathrm{ret}}\right) + \left(2\varepsilon w_{\mathrm{ret}} - y_{\mathrm{ret}}z_{\mathrm{ret}}\right)\right] + Q^{(r)}y_{\mathrm{vit}} - E^{(r)}y_{\mathrm{ret}}, \tag{S.41}$$

$$\varepsilon\frac{\mathrm{d}z_{\mathrm{ret}}}{\mathrm{d}\tau} = -\left(\varepsilon z_{\mathrm{ret}} - 2x_{\mathrm{ret}}y_{\mathrm{ret}}\right) + \left(2\varepsilon w_{\mathrm{ret}} - y_{\mathrm{ret}}z_{\mathrm{ret}}\right) + \varepsilon Q^{(c)}z_{\mathrm{vit}} - \varepsilon E^{(c)}z_{\mathrm{ret}}, \tag{S.42}$$

$$\varepsilon\frac{\mathrm{d}w_{\mathrm{ret}}}{\mathrm{d}\tau} = -\left(2\varepsilon w_{\mathrm{ret}} - y_{\mathrm{ret}}z_{\mathrm{ret}}\right) + \varepsilon Q^{(h)}w_{\mathrm{vit}} - \varepsilon E^{(h)}w_{\mathrm{ret}}, \tag{S.43}$$

Vitreous

$$\varepsilon\frac{\mathrm{d}x_{\mathrm{vit}}}{\mathrm{d}\tau} = \left(\varepsilon z_{\mathrm{vit}} - 2x_{\mathrm{vit}}y_{\mathrm{vit}}\right) + \varepsilon T^{(v)}x_{\mathrm{ret}} - \varepsilon K^{(v)}x_{\mathrm{vit}}, \tag{S.44}$$

$$\frac{\mathrm{d}y_{\mathrm{vit}}}{\mathrm{d}\tau} = \delta\left[\left(\varepsilon z_{\mathrm{vit}} - 2x_{\mathrm{vit}}y_{\mathrm{vit}}\right) + \left(2\varepsilon w_{\mathrm{vit}} - y_{\mathrm{vit}}z_{\mathrm{vit}}\right)\right] + T^{(r)}y_{\mathrm{ret}} - K^{(r)}y_{\mathrm{vit}}, \tag{S.45}$$

$$\varepsilon\frac{\mathrm{d}z_{\mathrm{vit}}}{\mathrm{d}\tau} = -\left(\varepsilon z_{\mathrm{vit}} - 2x_{\mathrm{vit}}y_{\mathrm{vit}}\right) + \left(2\varepsilon w_{\mathrm{vit}} - y_{\mathrm{vit}}z_{\mathrm{vit}}\right) + \varepsilon T^{(c)}z_{\mathrm{ret}} - \varepsilon K^{(c)}z_{\mathrm{vit}}, \tag{S.46}$$

$$\varepsilon\frac{\mathrm{d}w_{\mathrm{vit}}}{\mathrm{d}\tau} = -\left(2\varepsilon w_{\mathrm{vit}} - y_{\mathrm{vit}}z_{\mathrm{vit}}\right) + \varepsilon T^{(h)}w_{\mathrm{ret}} - \varepsilon K^{(h)}w_{\mathrm{vit}}, \tag{S.47}$$

S6.2 Asymptotic solution in y

Notice, by taking the following

$$y_{\text{ret}} = y_{\text{ret}}^{(0)} + \delta y_{\text{ret}}^{(1)} + O(\delta^2), \tag{S.48}$$
$$y_{\text{vit}} = y_{\text{vit}}^{(0)} + \delta y_{\text{vit}}^{(1)} + O(\delta^2), \tag{S.49}$$
$$y_{\text{aq}} = y_{\text{aq}}^{(0)} + \delta y_{\text{aq}}^{(1)} + O(\delta^2), \tag{S.50}$$

that, to $O(1)$, we have the system:

$$\frac{\mathrm{d}y_{\text{ret}}^{(0)}}{\mathrm{d}\tau} = -E^{(r)} y_{\text{ret}}^{(0)} + Q^{(r)} y_{\text{vit}}^{(0)}, \tag{S.51}$$
$$\frac{\mathrm{d}y_{\text{vit}}^{(0)}}{\mathrm{d}\tau} = T^{(r)} y_{\text{ret}}^{(0)} - K^{(r)} y_{\text{vit}}^{(0)}, \tag{S.52}$$

giving the following solution:

$$y_{\text{ret}}^{(0)}(\tau) = \frac{K_1 K_2}{K_1 + K_2}\left[e^{-\bar{\lambda_1}\tau} - e^{-\bar{\lambda_2}\tau}\right], \tag{S.53}$$
$$y_{\text{vit}}^{(0)}(\tau) = \frac{1}{K_1 + K_2}\left[K_2 e^{-\bar{\lambda_1}\tau} + K_1 e^{-\bar{\lambda_2}\tau}\right], \tag{S.54}$$

where

$$\bar{\lambda_1} \simeq K^{(r)} - \frac{Q^{(r)} T^{(r)}}{E^{(r)} - K^{(r)}}, \qquad \bar{\lambda_2} \simeq E^{(r)} + \frac{Q^{(r)} T^{(r)}}{E^{(r)} - K^{(r)}}, \tag{S.55}$$

$$K_1 = \frac{K^{(r)} - \bar{\lambda_1}}{T^{(r)}} = \frac{Q^{(r)}}{E^{(r)} - \lambda_1}, \tag{S.56}$$

$$K_2 = \frac{\bar{\lambda_2} - K^{(r)}}{T^{(r)}} = \frac{Q^{(r)}}{\bar{\lambda_2} - E^{(r)}}. \tag{S.57}$$

Also noting:

$$K_1 \simeq \frac{Q^{(r)}}{E^{(r)} - K^{(r)}}, \quad K_2 \simeq \frac{E^{(r)} - K^{(r)}}{T^{(r)}} \quad \Rightarrow \quad K_1 K_2 \simeq \frac{Q^{(r)}}{T^{(r)}} = \frac{V_{\text{vit}}}{V_{\text{ret}}}, \tag{S.58}$$

we may express the non-dimensional model decay rates via the following approximations:

$$\bar{\lambda_1} = \frac{1}{k_{\text{off}}}\lambda_1 \simeq \frac{1}{k_{\text{off}}}\left[k_{\text{el}}^{(r)} + \left(\frac{S_{\text{ret}}}{V_{\text{vit}}}\right) p_{\text{ILM}}^{(r)} - \left(\frac{S_{\text{ret}} p_{\text{ILM}}^{(r)}}{V_{\text{vit}}}\right) \frac{1}{\left[\left(1 + \frac{p_{\text{RPE}}^{(r)}}{p_{\text{ILM}}^{(r)}}\right) - \frac{V_{\text{ret}}}{V_{\text{vit}}}\left(1 + \frac{V_{\text{vit}} k_{\text{el}}}{S_{\text{ret}} p_{\text{ILM}}^{(r)}}\right)\right]}\right], \tag{S.59}$$
$$\bar{\lambda_2} = \frac{1}{k_{\text{off}}}\lambda_2 \simeq \frac{1}{k_{\text{off}}}\left[\frac{S_{\text{ret}} p_{\text{ILM}}^{(r)}}{V_{\text{ret}}}\left(1 + \frac{p_{\text{RPE}}^{(r)}}{p_{\text{ILM}}^{(r)}}\right)\right]. \tag{S.60}$$

Let us consider the ratio

$$\frac{\bar{\lambda_1}}{\bar{\lambda_2}} = \frac{\lambda_1}{\lambda_2} \simeq \frac{k_{\text{el}}^{(r)} + \left(\frac{S_{\text{ret}}}{V_{\text{vit}}}\right) p_{\text{ILM}}^{(r)} - \left(\frac{S_{\text{ret}} p_{\text{ILM}}^{(r)}}{V_{\text{vit}}}\right) \frac{1}{\left[\left(1+\frac{p_{\text{RPE}}^{(r)}}{p_{\text{ILM}}^{(r)}}\right) - \frac{V_{\text{ret}}}{V_{\text{vit}}}\left(1+\frac{V_{\text{vit}} k_{\text{el}}}{S_{\text{ret}} p_{\text{ILM}}^{(r)}}\right)\right]}}{\frac{S_{\text{ret}} p_{\text{ILM}}^{(r)}}{V_{\text{ret}}}\left(1+\frac{p_{\text{RPE}}^{(r)}}{p_{\text{ILM}}^{(r)}}\right)} \tag{S.61}$$

$$= \frac{k_{\text{el}}^{(r)}}{\frac{S_{\text{ret}} p_{\text{ILM}}^{(r)}}{V_{\text{ret}}}\left(1+\frac{p_{\text{RPE}}^{(r)}}{p_{\text{ILM}}^{(r)}}\right)} + \frac{\left(\frac{S_{\text{ret}}}{V_{\text{vit}}}\right) p_{\text{ILM}}^{(r)}}{\frac{S_{\text{ret}} p_{\text{ILM}}^{(r)}}{V_{\text{ret}}}\left(1+\frac{p_{\text{RPE}}^{(r)}}{p_{\text{ILM}}^{(r)}}\right)} - \frac{\left(\frac{S_{\text{ret}} p_{\text{ILM}}^{(r)}}{V_{\text{vit}}}\right) \frac{1}{\left[\left(1+\frac{p_{\text{RPE}}^{(r)}}{p_{\text{ILM}}^{(r)}}\right) - \frac{V_{\text{ret}}}{V_{\text{vit}}}\left(1+\frac{V_{\text{vit}} k_{\text{el}}}{S_{\text{ret}} p_{\text{ILM}}^{(r)}}\right)\right]}}{\frac{S_{\text{ret}} p_{\text{ILM}}^{(r)}}{V_{\text{ret}}}\left(1+\frac{p_{\text{RPE}}^{(r)}}{p_{\text{ILM}}^{(r)}}\right)} \tag{S.62}$$

$$= \frac{1}{1+\frac{p_{\text{RPE}}^{(r)}}{p_{\text{ILM}}^{(r)}}} \left\{ \frac{\left(\frac{S_{\text{ret}}}{V_{\text{vit}}}\right) p_{\text{ILM}}^{(r)}}{\frac{S_{\text{ret}} p_{\text{ILM}}^{(r)}}{V_{\text{ret}}}} + \frac{k_{\text{el}}^{(r)}}{\frac{S_{\text{ret}} p_{\text{ILM}}^{(r)}}{V_{\text{ret}}}} - \frac{\left(\frac{S_{\text{ret}} p_{\text{ILM}}^{(r)}}{V_{\text{vit}}}\right) \frac{1}{\left[\left(1+\frac{p_{\text{RPE}}^{(r)}}{p_{\text{ILM}}^{(r)}}\right) - \frac{V_{\text{ret}}}{V_{\text{vit}}}\left(1+\frac{V_{\text{vit}} k_{\text{el}}}{S_{\text{ret}} p_{\text{ILM}}^{(r)}}\right)\right]}}{\frac{S_{\text{ret}} p_{\text{ILM}}^{(r)}}{V_{\text{ret}}}} \right\} \tag{S.63}$$

$$= \underbrace{\frac{V_{\text{ret}}/V_{\text{vit}}}{1+\frac{p_{\text{RPE}}^{(r)}}{p_{\text{ILM}}^{(r)}}}}_{(1)} \left\{ 1 + \underbrace{\frac{V_{\text{vit}} k_{\text{el}}^{(r)}}{S_{\text{ret}} p_{\text{ILM}}^{(r)}}}_{(2)} - \underbrace{\frac{1}{\left(1+\frac{p_{\text{RPE}}^{(r)}}{p_{\text{ILM}}^{(r)}}\right) - \frac{V_{\text{ret}}}{V_{\text{vit}}}\left(1+\frac{V_{\text{vit}} k_{\text{el}}}{S_{\text{ret}} p_{\text{ILM}}^{(r)}}\right)}}_{(3)} \right\}. \tag{S.64}$$

The typical magnitudes of (1),(2) and (3) are $10^{-2}, 10^{0}$ and 10^{-1}, respectively, hence the ratio $\lambda_1/\lambda_2 \sim O(10^{-2})$. We also note this implies that $\lambda_1 \ll \lambda_2$.

Therefore in summary

$$\lambda_1 \simeq k_{\text{el}}^{(r)} + \left(\frac{S_{\text{ret}}}{V_{\text{vit}}}\right) p_{\text{ILM}}^{(r)} - \left(\frac{S_{\text{ret}} p_{\text{ILM}}^{(r)}}{V_{\text{vit}}}\right) \frac{1}{\left[\left(1+\frac{p_{\text{RPE}}^{(r)}}{p_{\text{ILM}}^{(r)}}\right) - \frac{V_{\text{ret}}}{V_{\text{vit}}}\left(1+\frac{V_{\text{vit}} k_{\text{el}}}{S_{\text{ret}} p_{\text{ILM}}^{(r)}}\right)\right]}, \tag{S.65}$$

$$\lambda_2 \simeq \frac{S_{\text{ret}} p_{\text{ILM}}^{(r)}}{V_{\text{ret}}}\left(1+\frac{p_{\text{RPE}}^{(r)}}{p_{\text{ILM}}^{(r)}}\right), \tag{S.66}$$

$$\frac{\lambda_1}{\lambda_2} \simeq \frac{V_{\text{ret}}/V_{\text{vit}}}{1+\frac{p_{\text{RPE}}^{(r)}}{p_{\text{ILM}}^{(r)}}} \left\{ 1 + \frac{V_{\text{vit}} k_{\text{el}}^{(r)}}{S_{\text{ret}} p_{\text{ILM}}^{(r)}} - \frac{1}{\left(1+\frac{p_{\text{RPE}}^{(r)}}{p_{\text{ILM}}^{(r)}}\right) - \frac{V_{\text{ret}}}{V_{\text{vit}}}\left(1+\frac{V_{\text{vit}} k_{\text{el}}}{S_{\text{ret}} p_{\text{ILM}}^{(r)}}\right)} \right\}. \tag{S.67}$$

S6.3 Initial asymptotic solution for x_{RET}

Let us consider the governing equation for x_{ret}

$$\varepsilon \frac{\mathrm{d}x_{\text{ret}}}{\mathrm{d}\tau} = \left(\varepsilon z_{\text{ret}} - 2x_{\text{ret}} y_{\text{ret}}\right) + \varepsilon Q^{(v)} x_{\text{vit}} - \varepsilon E^{(v)} x_{\text{ret}} + \varepsilon V. \tag{S.68}$$

At early time we expect to see x_{ret} and z_{ret} to be small relative to y_{ret}, due to the large influx of drug into the retina. Any VEGF (x_{ret}) will be bound, and subsequently the VEGF-ranibizumab (z_{ret}) complex will then be bound again to form an RVR complex. As VEGF is produced within the retina we also expect $x_{\text{vit}} \ll x_{\text{ret}}$. Therefore if we take

$$x_{\text{ret}} = \delta_1 X_{\text{ret}}, \qquad z_{\text{ret}} = \delta_2 Z_{\text{ret}}, \qquad x_{\text{vit}} = \delta_3 X_{\text{vit}}, \tag{S.69}$$

where we assume that

$$\delta_1,\, \delta_2 \ll 1, \qquad \delta_3 \ll \delta_1,\, \delta_2 \tag{S.70}$$

then, upon substitution into Equation S.68, we may write the following

$$\varepsilon\delta_1 \frac{\mathrm{d}X_{\text{ret}}}{\mathrm{d}\tau} = \left(\varepsilon\delta_2 Z_{\text{ret}} - 2\delta_1 X_{\text{ret}} y_{\text{ret}}\right) + \varepsilon\delta_3 Q^{(v)} X_{\text{vit}} - \varepsilon\delta_1 E^{(v)} X_{\text{ret}} + \varepsilon V, \tag{S.71}$$

$$\Rightarrow \quad \varepsilon \frac{\mathrm{d}X_{\text{ret}}}{\mathrm{d}\tau} = \left(\frac{\varepsilon\delta_2}{\delta_1} Z_{\text{ret}} - 2X_{\text{ret}} y_{\text{ret}}\right) + \frac{\varepsilon\delta_3}{\delta_1} Q^{(v)} X_{\text{vit}} - \varepsilon E^{(v)} X_{\text{ret}} + \frac{\varepsilon}{\delta_1} V, \tag{S.72}$$

$$\Rightarrow \quad \underbrace{2X_{\text{ret}} y_{\text{ret}}}_{(1)} + \underbrace{\varepsilon\left(\frac{\mathrm{d}X_{\text{ret}}}{\mathrm{d}\tau} + E^{(v)} X_{\text{ret}}\right)}_{(2)} = \underbrace{\frac{\varepsilon\delta_3}{\delta_1} Q^{(v)} X_{\text{vit}}}_{(3)} + \underbrace{\frac{\varepsilon}{\delta_1} V}_{(4)}, + \underbrace{\frac{\varepsilon\delta_2}{\delta_1} Z_{\text{ret}}}_{(5)}. \tag{S.73}$$

Now, we note the magnitude of the terms in Equation S.73:

$$\underset{\sim O(1)}{(1)} \quad \underset{\sim O(\varepsilon)}{(2)} \quad \underset{\sim O\left(\frac{\varepsilon\delta_3}{\delta_1}\right)}{(3)} \quad \underset{\sim O\left(\frac{\varepsilon}{\delta_1}\right)}{(4)} \quad \underset{\sim O\left(\frac{\varepsilon\delta_2}{\delta_1}\right)}{(5)}, \tag{S.74}$$

As $\delta_3 \ll \delta_1$ term (3) is sub-dominant to (1), (2), (4) and (5), and as δ_2 and δ_1 are both $\ll 1$ we can take (5) $\ll$ (4) (due to the additional factor of δ_2 in (5)). This leaves us with the dominant balance (1) ~ (4), (2), (3), (5) $\ll$ (1), (4), giving us $\delta_1 = \varepsilon$. Therefore taking the following expansion: Therefore taking

$$X_{\text{ret}} = X_{\text{ret}}^{(0)} + \varepsilon X_{\text{ret}}^{(1)} + O(\varepsilon^2) \tag{S.75}$$

we find to $O(1)$ that

$$X_{\text{ret}}^{(0)} = \frac{V}{2y_{\text{ret}}} \tag{S.76}$$

$$\Rightarrow \quad v_{\text{ret}}(t) = \frac{\varepsilon v_0 V}{2y_{\text{ret}}(t)} \tag{S.77}$$

$$= \frac{\varepsilon v_0 V}{2}\left(\frac{K_1+K_2}{K_1K_2}\right)\left[\frac{1}{e^{-\lambda_1 t} - e^{-\lambda_2 t}}\right] \tag{S.78}$$

noting the following

$$K_1 + K_2 = \frac{\bar{\lambda_2} - \bar{\lambda_2}}{T^{(r)}} = \frac{V_{\text{vit}}}{S_{\text{ret}} p_{\text{ILM}}^{(r)}}(\lambda_2 - \lambda_1), \qquad K_1K_2 \simeq \frac{Q^{(r)}}{T^{(r)}} = \frac{V_{\text{vit}}}{V_{\text{ret}}}, \qquad \lambda_1 \ll \lambda_2 \tag{S.79}$$

therefore

$$\Rightarrow \quad \left(\frac{K_1+K_2}{K_1K_2}\right) \simeq \frac{V_{\text{ret}}}{S_{\text{ret}} p_{\text{ILM}}^{(r)}}(\lambda_2 - \lambda_1) \tag{S.80}$$

$$\tag{S.81}$$

Also noting

$$V = \frac{V_{\text{in}}}{v_0 k_{\text{off}} V_{\text{ret}}}, \quad \varepsilon = \frac{K_D}{r_0}, \tag{S.82}$$

we may write

$$\frac{\varepsilon v_0 V}{2} = \frac{K_D v_0 V_{\text{in}}}{2 r_0 v_0 k_{\text{off}} V_{\text{ret}}} \tag{S.83}$$

$$= \frac{1}{2}\frac{V_{\text{in}}}{r_0 k_{\text{on}} V_{\text{ret}}}, \tag{S.84}$$

Therefore we find an intermediate ~ $O(1)$ asymptotic solution for $v_{\text{ret}}(t)$ as follows

$$v_{\text{ret}}(t) = \frac{1}{2}\left\{\frac{V_{\text{in}}}{r_0 k_{\text{on}}}\right\}\left[\frac{(\lambda_2 - \lambda_1)/S_{\text{ret}} p_{\text{ILM}}^{(r)}}{e^{-\lambda_1 t} - e^{-\lambda_2 t}}\right] \tag{S.85}$$

$$\simeq \frac{1}{2}\left\{\frac{V_{\text{in}}}{r_0 k_{\text{on}}}\right\}\left[\frac{\lambda_2 - \lambda_1}{S_{\text{ret}} p_{\text{ILM}}^{(r)}}\right] e^{\lambda_1 t} \tag{S.86}$$

S6.4 Maximum suppression of VEGF in the retina

Therefore our approximation of v_{ret} is minimised when y_{ret} is maximised, which occurs at $t_{\min}$ when

$$-\lambda_1 e^{-\lambda_1 t_{\min}} + \lambda_2 e^{-\lambda_2 t_{\min}} = 0, \tag{S.87}$$

giving $t_{\min}$

$$t_{\min} = \frac{1}{\lambda_2 - \lambda_1}\log\left(\frac{\lambda_2}{\lambda_1}\right). \tag{S.88}$$

Notice, from these results we can see that

$$e^{-\lambda_1 t_{\min}} = \left(\frac{\lambda_2}{\lambda_1}\right)e^{-\lambda_2 t_{\min}} \quad \Rightarrow \quad e^{-\lambda_1 t_{\min}} - e^{-\lambda_2 t_{\min}} = \left(\frac{\lambda_2}{\lambda_1}\right)e^{-\lambda_2 t_{\min}} - e^{-\lambda_2 t_{\min}} \tag{S.89}$$

$$= \left(\frac{\lambda_2 - \lambda_1}{\lambda_1}\right)e^{-\lambda_2 t_{\min}}, \tag{S.90}$$

$$\tag{S.91}$$

therefore

$$\Rightarrow \quad v_{\text{ret}}(t_{\min}) = \frac{1}{2}\frac{V_{\text{in}}}{r_0 k_{\text{on}} S_{\text{ret}} p_{\text{ILM}}^{(r)}}\left[\frac{\lambda_2-\lambda_1}{e^{-\lambda_1 t_{\min}} - e^{-\lambda_2 t_{\min}}}\right] \tag{S.92}$$

$$= \left(\frac{1}{2}\frac{V_{\text{in}}}{r_0 S_{\text{ret}} p_{\text{ILM}}^{(r)} k_{\text{on}}}\right)\lambda_1 e^{\lambda_2 t_{\min}}. \tag{S.93}$$

Note now that

$$e^{\lambda_2 t_{\min}} = e^{\frac{\lambda_2}{\lambda_2-\lambda_1}\log\left(\frac{\lambda_2}{\lambda_1}\right)} = \left(\frac{\lambda_2}{\lambda_1}\right)^{\frac{\lambda_2}{\lambda_2-\lambda_1}} = \left(\frac{1}{\lambda_1/\lambda_2}\right)^{\frac{1}{1-\lambda_1/\lambda_2}}. \tag{S.94}$$

Now, letting $\alpha = \lambda_1/\lambda_2 \ll 1$, then if we take:

$$x := \left(\frac{1}{\alpha}\right)^{\frac{1}{1-\alpha}} \tag{S.95}$$

we find

$$x = \left(\frac{1}{\alpha}\right)^{\frac{1}{1-\alpha}} \tag{S.96}$$

$$= \left(\frac{1}{\alpha}\right)\left(\frac{1}{\alpha}\right)^{\frac{\alpha}{1-\alpha}} \tag{S.97}$$

$$= \frac{1}{\alpha}\exp\left\{\left(-\frac{\alpha}{1-\alpha}\right)\log\alpha\right\} \tag{S.98}$$

$$= \frac{1}{\alpha}\left[1 - \frac{\alpha}{1-\alpha}\log\alpha + O\left(\frac{\alpha^2}{2(1-\alpha)^2}\log^2\alpha\right)\right] \qquad \text{as } \alpha \to 0 \tag{S.99}$$

$$= \frac{1}{\alpha} - \frac{}{1-\alpha}\log\alpha + O\left(\frac{\alpha}{2(1-\alpha)^2}\log^2\alpha\right) \qquad \text{as } \alpha \to 0 \tag{S.100}$$

$$\simeq \frac{1}{\alpha} - \log\alpha + O\left(\frac{\alpha}{2}\log^2\alpha\right) \qquad \text{as } \alpha \to 0. \tag{S.101}$$

Notice that the error term tends to zero as $\alpha \searrow 0$, by setting $\alpha = \beta^2$ we find

$$\lim_{\alpha\to 0}\left(\frac{\alpha}{2}\log^2\alpha\right) = \frac{1}{2}\lim_{\beta\to 0}\left(\beta^2\log^2\beta^2\right) \tag{S.102}$$

$$= 2\lim_{\beta\to 0}\left(\beta\log\beta\right)^2 \tag{S.103}$$

$$= 0 \tag{S.104}$$

Therefore, using this result we may write

$$e^{\lambda_2 t_{\min}} = \left(\frac{1}{\lambda_1/\lambda_2}\right)^{\frac{1}{1-\lambda_1/\lambda_2}} \simeq \frac{\lambda_2}{\lambda_1} - \log\left(\frac{\lambda_1}{\lambda_2}\right) + O\left(\frac{\lambda_1}{2\lambda_2}\log^2\left(\frac{\lambda_1}{\lambda_2}\right)\right) \tag{S.105}$$

$$\Rightarrow \quad \lambda_1 e^{\lambda_2 t_{\min}} \simeq \lambda_2 - \lambda_1\log\left(\frac{\lambda_1}{\lambda_2}\right) + O\left(\frac{\lambda_1^2}{2\lambda_2}\log^2\left(\frac{\lambda_1}{\lambda_2}\right)\right) \tag{S.106}$$

where we note that the error is $O(10^{-2})$. Therefore, recalling the approximations for λ_1 and λ_2 we may write

$$v_{\text{ret}}(t_{\min}) = \left(\frac{1}{2}\frac{V_{\text{in}}}{r_0 S_{\text{ret}} p_{\text{ILM}}^{(r)} k_{\text{on}}}\right)\lambda_1 e^{\lambda_2 t_{\min}} \tag{S.107}$$

Therefore we have

$$v_{\text{ret}}(t_{\min}) = \frac{1}{2}\left\{\frac{V_{\text{in}}}{r_0 k_{\text{on}}}\right\}\left[\frac{\lambda_2 + \lambda_1\log\left(\frac{\lambda_2}{\lambda_1}\right) + O\left(\frac{\lambda_1^2}{2\lambda_2}\log^2\left(\frac{\lambda_1}{\lambda_2}\right)\right)}{S_{\text{ret}} p_{\text{ILM}}^{(r)}}\right]. \tag{S.108}$$

Figure S4 shows the early time free VEGF concentration profile, the numerical solution is shown in solid red, the full two exponential asymptotic solution is shown in dashed red, and the single exponential asymptotic simplification in dotted red.

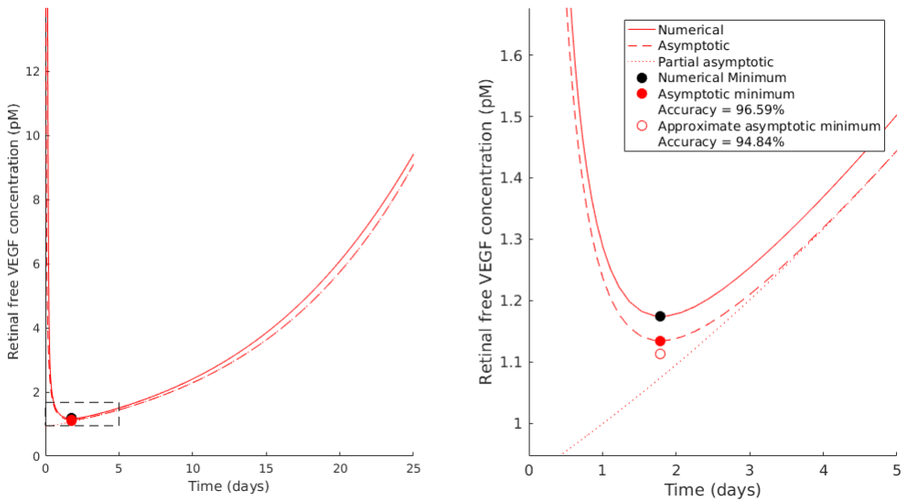


Figure S4: Initial free VEGF concentration in the retina, the dashed box in the left-hand panel is the region shown in the right-hand panel. The solid, dashed and dotted red lines denote the numerical, asymptotic (Equation S.85) and partial asymptotic (Equation S.86) solutions, respectively, for patient 40 at $K_{\mathrm{D}} = 19,000$ pM and $t_{12}^{(r)} = 7.9$ days. The solid red dot shows the minimum free VEGF concentration, the red circle shows the approximate form of the minimum free VEGF, presented in Equation S.108, the accuracy of which is given in the figure legend.

We also note that Equation S.108 may be approximated by the following

$$v_{\mathrm{ret}}(t_{\mathrm{min}}) \simeq \frac{1}{2}\left\{\frac{V_{\mathrm{in}}}{r_0 k_{\mathrm{on}}}\right\}\left[\frac{\lambda_2 - \lambda_1 \log\left(\frac{\lambda_1}{\lambda_2}\right)}{S_{\mathrm{ret}} p_{\mathrm{ILM}}^{(r)}}\right] \tag{S.109}$$

$$\simeq \frac{1}{2}\left\{\frac{V_{\mathrm{in}}}{r_0 k_{\mathrm{on}}}\right\}\left[\frac{\lambda_2 - \lambda_1}{S_{\mathrm{ret}} p_{\mathrm{ILM}}^{(r)}}\right], \tag{S.110}$$

therefore Equation S.86 may be written in terms of $v_{\mathrm{ret}}(t_{\mathrm{min}})$

$$v_{\mathrm{ret}}(t) \simeq \frac{1}{2}\left\{\frac{V_{\mathrm{in}}}{r_0 k_{\mathrm{on}}}\right\}\left[\frac{\lambda_2 - \lambda_1}{S_{\mathrm{ret}} p_{\mathrm{ILM}}^{(r)}}\right] e^{\lambda_1 t} \tag{S.111}$$

$$\simeq v_{\mathrm{ret}}(t_{\mathrm{min}}) e^{\lambda_1 t}. \tag{S.112}$$

S6.5 Drug retinal impermeability case study

Suppose that the retina is impermeable to ranibizumab and all VEGF-ranibizumab complexes. Then, this would cause the non-dimensional equation for retinal free VEGF to reduce to the following equation:

$$\frac{\mathrm{d}x_{\mathrm{ret}}}{\mathrm{d}\tau} = Q^{(v)} x_{\mathrm{vit}} - E^{(v)} x_{\mathrm{ret}} + V \tag{S.113}$$

If we assume that the system is in quasi steady-state, we may write:

$$x_{\mathrm{ret}} = \frac{1}{E^{(v)}}\left(Q^{(v)} x_{\mathrm{vit}} + V\right). \tag{S.114}$$

Therefore, as we expect x_{vit} to be very small post IVT injection, we may approximate x_{ret} to be (initially) equal to a constant, as follows:

$$x_{\mathrm{ret}} \simeq \frac{V}{E^{(v)}} \tag{S.115}$$

$$\Rightarrow \quad v_{\mathrm{ret}} \simeq \frac{V_{\mathrm{in}}}{S_{\mathrm{ret}}\left(p_{\mathrm{ILM}}^{(v)} + p_{\mathrm{RPE}}^{(v)}\right)}. \tag{S.116}$$

This approximation is shown, alongside the exact solution, in Figure S5. As can be seen from Figure S5 this approximation gives a very accurate value for initial reduction in free VEGF concentration.

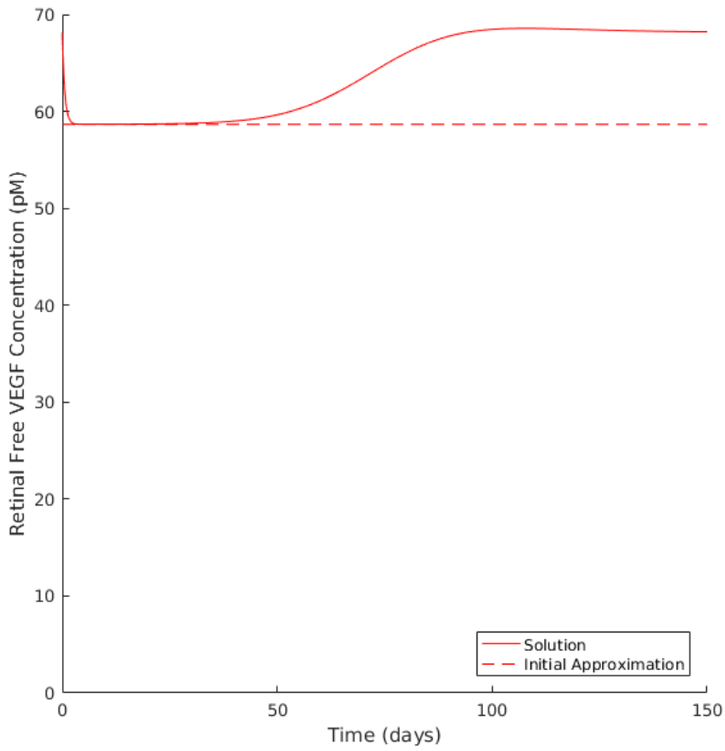


Figure S5: Dimensional solution for retinal free VEGF in the absence of drug (or drug-VEGF complex) retinal penetration

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