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Anti-receptor antibodies: is it better to displace the dummy ligand?

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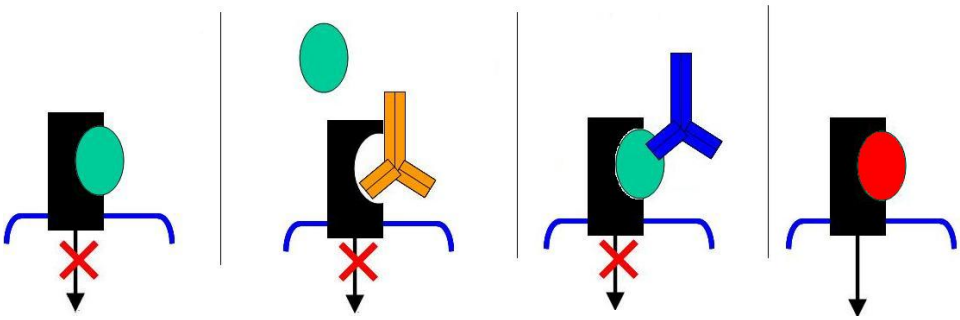

1 Introduction

In some biological systems, because the binding of certain ligands to tissue receptors results in an undesirable signal, false ligands are produced (in addition to ligands) which can also bind to receptors, thus blocking them and preventing signalling. To this system we may add a drug in the form of an antibody, which is also capable of binding to the receptor and blocking ligand binding. Of interest is the reduction in such bindings that can be achieved, in order to minimise the subsequent signalling. All the reactions are reversible, with the system potentially in a continuous state of flux.

The question we address here is whether it is beneficial for the antibody to block both ligand and false ligand binding, or whether it should allow false ligands to continue to bind. Type 2 antibodies (the second form of action) have the advantage that receptors may be blocked in two ways, with both the false ligand and the receptor binding needing to first be reversed before a ligand binding can take place. Type 1 antibodies (the first form of action) have the advantage that more false ligands are kept free in the system to bind to any remaining unbound receptors.

Given that the system is flooded with antibodies at treatment, the answer is fairly simple: all other dynamics being equal, the type 2 antibody which can also double bind will be better. If the two antibodies differ in other properties (such as affinities) as well, however, then there will be an interplay between factors so that the benefits of alternative antibodies are less clear. Here we focus on quantifying the effectiveness of the two antibody types in minimising the amount of ligand-bound receptor complex.

1.1 Notation

In our model we use the following notation for variables:

R	unbound receptor concentration
R_F	false ligand-bound receptor concentration
R_L	ligand-bound receptor concentration
L	ligand concentration
F	false ligand concentration
A	antibody concentration
R_2	complex of R & A concentration
R_3	complex of R & A & F concentration

and parameters:

μ_i	rate of production of substance i ($i = L, F, R$)
λ_i	decay rate of substance i ($i = L, F, R, A$) .

In practice only ligand, false ligands and unbound receptors are produced, with decay a result of degradation.

1.2 Orders of magnitude

The approximate ordering of the decay rates λ is as follows

$$\lambda_A \simeq \lambda_{R_2} \simeq \lambda_{R_3} \ll \lambda_R \approx \lambda_{R_F} \simeq \lambda_{R_L} \ll \lambda_F \simeq \lambda_L. \tag{1}$$

These values will be important in what follows in allowing us to make asymptotic approximations

2 Model

2.1 Reactions

The system consists of the following reactions:

$$R + F \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R_F, \tag{2}$$

$$R + L \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} R_L, \tag{3}$$

$$R + A \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} R_2, \tag{4}$$

$$R_2 + F \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} R_3, \tag{5}$$

$$R_F + A \underset{k_{-6}}{\overset{k_6}{\rightleftharpoons}} R_3. \tag{6}$$

The last two reactions are only relevant for the type 2 antibody. For antibodies of type 1, which prevent false ligand binding to the receptor and which do not bind to false-ligand-bound receptors, we have $k_5 = k_{-5} = k_6 = k_{-6} = 0$. For antibodies of type 2 these parameters will be nonzero, and relate to the binding rate of false ligand to antibody-bound-receptors and the binding of antibodies to false-ligand-bound-receptors respectively.

In what follows we may therefore analyse the dynamics of either antibody types by considering the full system.

2.2 Equations

We assume that each of the reactions (2)-(6) is governed by the Law of Mass Action, which leads to the following model describing the evolution of the concentration of each species:

$$\begin{aligned}
\frac{\mathrm{d}R}{\mathrm{d}t} &= \mu_R - \lambda_R R - k_{-1}(K_1 RF - R_F) - k_{-2}(K_2 LR - R_L) \\
&\quad -k_{-4}(K_4 AR - R_2), && (7)\\
\frac{\mathrm{d}F}{\mathrm{d}t} &= \mu_F - \lambda_F F - k_{-1}(K_1 RF - R_F) - k_{-5}(K_5 R_2 F - R_3) && (8)\\
\frac{\mathrm{d}R_F}{\mathrm{d}t} &= -\lambda_{R_F} R_F + k_{-1}(K_1 RF - R_F) - k_{-6}(K_6 AR_F - R_3), && (9)\\
\frac{\mathrm{d}L}{\mathrm{d}t} &= \mu_L - \lambda_L L - k_{-2}(K_2 LR - R_L) && (10)\\
\frac{\mathrm{d}R_L}{\mathrm{d}t} &= -\lambda_{R_L} R_L + k_{-2}(K_2 LR - R_L), && (11)\\
\frac{\mathrm{d}A}{\mathrm{d}t} &= -\lambda_A A - k_{-4}(K_4 AR - R_2) - k_{-6}(K_6 AR_F - R_3), && (12)\\
\frac{\mathrm{d}R_2}{\mathrm{d}t} &= -\lambda_{R_2} R_2 + k_{-4}(K_4 AR - R_2) - k_{-5}(K_5 R_2 F - R_3), && (13)\\
\frac{\mathrm{d}R_3}{\mathrm{d}t} &= -\lambda_{R_3} R_3 + k_{-6}(K_6 AR_F - R_3) + k_{-5}(K_5 FR_2 - R_3), && (14)
\end{aligned}$$

where $K_i = k_i/k_{-i}$ (equal to the inverse of the reaction affinity).

The parameters involved in the model are summarised in Table 1.

Parameter	Description	Value & units
μ_R	Production rate of new receptors	mol ml^{-1} s^{-1}
μ_F	Production rate of new false ligands	mol ml^{-1} s^{-1}
μ_L	Production rate of new ligands	mol ml^{-1} s^{-1}
λ_R	Decay rate of receptors	s^{-1}
λ_F	Decay rate of false ligands	s^{-1}
λ_L	decay rate of ligands	s^{-1}
λ_{RL}	decay rate of the RL-complex R_L	s^{-1}
λ_{RF}	decay rate of the RF-complex R_F	s^{-1}
λ_{R2}	decay rate of the RA-complex R_2	s^{-1}
λ_{R3}	decay rate of the RAF-complex R_3	s^{-1}
k_{-1}	Dissociation rate of the RF-complex R_F	s^{-1}
k_{-2}	Dissociation rate of the RL-complex R_L	s^{-1}
k_{-4}	Dissociation rate of the RA-complex R_A	s^{-1}
k_{-5}	Dissociation rate of the RAF-complex R_3 to $R_2 + F$	s^{-1}
k_{-6}	Dissociation rate of the RAF-complex R_3 to $R_F + A$	s^{-1}
K_1	Reaction constant for $R + F \rightleftharpoons R_F$	ml mol^{-1}
K_2	Reaction constant for $R + L \rightleftharpoons R_L$	ml mol^{-1}
K_4	Reaction constant for $R + A \rightleftharpoons R_2$	ml mol^{-1}
K_5	Reaction constant for $R_2 + F \rightleftharpoons R_3$	ml mol^{-1}
K_6	Reaction constant for $R_F + A \rightleftharpoons R_3$	ml mol^{-1}
k_1	Association rate of R & F	ml mol^{-1} s^{-1}
k_2	Association rate of R & L	ml mol^{-1} s^{-1}
k_4	Association rate of R & A	ml mol^{-1} s^{-1}
k_5	Association rate of R_2 & F	ml mol^{-1} s^{-1}
k_6	Association rate of R_F & A	ml mol^{-1} s^{-1}

Table 1: Dimensional parameter values.

2.3 Nondimensionalisation

We choose the following non-dimensionalisation for the system, scaling time with the ligand decay rate, since this is the time scale we are initially interested in. Each complex is scaled with its reaction constant so that all scaled variables are of order one

$$\begin{aligned} t &= \frac{1}{\lambda_L}\bar{t}, \qquad F = \frac{\mu_F}{\lambda_F}\bar{F}, \qquad L = \frac{\mu_L}{\lambda_L}\bar{L}, \qquad A = A^0\bar{A}, \\ R_F &= K_1\frac{\mu_R}{\lambda_R}\frac{\mu_F}{\lambda_F}\bar{R}_F, \qquad R_L = K_2\frac{\mu_R}{\lambda_R}\frac{\mu_L}{\lambda_L}\bar{R}_L, \\ R_2 &= K_4\frac{\mu_R}{\lambda_R}A^0\bar{R}_2, \qquad R_3 = K_{4,5}\frac{\mu_R}{\lambda_R}\frac{\mu_F}{\lambda_F}A^0\bar{R}_3, \qquad R = \frac{\mu_R}{\lambda_R}\bar{R}, \end{aligned}$$

where $K_{4,5} = K_4K_5$ for simplicity and where A^0 is the initial dose of antibody given at time $t = 0$.

Detailed balancing of the two mechanisms by which R_3 can be obtained from R (one via R_F, the other via R_2) implies

$$\frac{k_1 k_6}{k_{-1} k_{-6}} = \frac{k_4 k_5}{k_{-4} k_{-5}}, \tag{15}$$

which implies $K_1 K_6 = K_4 K_5$.

The nondimensional governing equations are

$$\begin{aligned}
\frac{\mathrm{d}\bar{L}}{\mathrm{d}\bar{t}} &= 1 - \bar{L} - q_2(\bar{L}\bar{R} - \bar{R}_L), && (16)\\
\frac{\mathrm{d}\bar{F}}{\mathrm{d}\bar{t}} &= \bar{\lambda}_F(1 - \bar{F}) - q_1(\bar{R}\bar{F} - \bar{R}_F) - q_4 q_5(\bar{R}_2\bar{F} - \bar{R}_3), && (17)\\
\frac{\mathrm{d}\bar{R}}{\mathrm{d}\bar{t}} &= \bar{\lambda}_R(1 - \bar{R}) - q_0(\bar{R}\bar{F} - \bar{R}_F) - q_L(\bar{L}\bar{R} - \bar{R}_L) - q_4(\bar{R}\bar{A} - \bar{R}_2), && (18)\\
\frac{\mathrm{d}\bar{R}_L}{\mathrm{d}\bar{t}} &= -\bar{\lambda}_{RL}\bar{R}_L + p_2(\bar{R}\bar{L} - \bar{R}_L), && (19)\\
\frac{\mathrm{d}\bar{R}_F}{\mathrm{d}\bar{t}} &= -\bar{\lambda}_{RF}\bar{R}_F + p_1(\bar{F}\bar{R} - \bar{R}_F) - p_0(\bar{R}_F\bar{A} - \bar{R}_3), && (20)\\
\frac{\mathrm{d}\bar{R}_2}{\mathrm{d}\bar{t}} &= -\bar{\lambda}_{R2}\bar{R}_2 + p_4(\bar{A}\bar{R} - \bar{R}_2) - p_F(\bar{F}\bar{R}_2 - \bar{R}_3), && (21)\\
\frac{\mathrm{d}\bar{R}_3}{\mathrm{d}\bar{t}} &= -\bar{\lambda}_{R3}\bar{R}_3 + p_5(\bar{R}_2\bar{F} - \bar{R}_3) + p_6(\bar{R}_F\bar{A} - \bar{R}_3), && (22)\\
\frac{\mathrm{d}\bar{A}}{\mathrm{d}\bar{t}} &= -\bar{\lambda}_A A - q_A(\bar{R}\bar{A} - \bar{R}_2) - p_A(\bar{R}_F\bar{A} - \bar{R}_3), && (23)
\end{aligned}$$

where the new nondimensional parameters are defined by

$$\begin{gathered}
\bar{\lambda}_F = \frac{\lambda_F}{\lambda_L}, \qquad \bar{\lambda}_R = \frac{\lambda_R}{\lambda_L}, \qquad \bar{\lambda}_A = \frac{\lambda_A}{\lambda_L}, \qquad \bar{\lambda}_{RF} = \frac{\lambda_{RF}}{\lambda_L}, \qquad \bar{\lambda}_{RL} = \frac{\lambda_{RL}}{\lambda_L},\\
\bar{\lambda}_{R2} = \frac{\lambda_{R2}}{\lambda_L}, \qquad \bar{\lambda}_{R3} = \frac{\lambda_{R3}}{\lambda_L}, \qquad q_0 = \frac{k_1}{\lambda_L}\frac{\mu_F}{\lambda_F}, \qquad q_L = \frac{k_2}{\lambda_L}\frac{\mu_L}{\lambda_L},\\
q_1 = \frac{k_1}{\lambda_L}\frac{\mu_R}{\lambda_R}, \qquad q_2 = \frac{k_2}{\lambda_L}\frac{\mu_R}{\lambda_R}, \qquad q_4 = \frac{k_4 A^0}{\lambda_L}, \qquad q_5 = \frac{k_5}{\lambda_L}\frac{\mu_R}{\lambda_R},\\
p_1 = \frac{k_{-1}}{\lambda_L}, \qquad p_2 = \frac{k_{-2}}{\lambda_L}, \qquad p_4 = \frac{k_{-4}}{\lambda_L}, \qquad p_5 = \frac{k_{-5}}{\lambda_L}, \qquad p_6 = \frac{k_{-6}}{\lambda_L},\\
p_A = \frac{k_{-6}}{\lambda_L}\frac{\mu_R}{\lambda_R}\frac{\mu_F}{\lambda_F}K_{4,5}, \qquad q_A = \frac{k_4}{\lambda_L}\frac{\mu_R}{\lambda_R}.
\end{gathered} \tag{24}$$

For simplicity, we additionally define p_0 by

$$p_0 = \frac{k_6 A^0}{\lambda_L}$$

and note the two identical identities

$$p_F = \frac{k_5}{\lambda_L}\frac{\mu_F}{\lambda_F} = \frac{q_0 q_5}{q_1}, \quad \frac{p_0 q_1}{p_6 p_1} = \frac{q_4 q_5}{p_4 p_5} = \frac{K_{45} A^0 \mu_R}{\lambda_R}, \tag{25}$$

the latter being a consequence of detailed balancing (15). The parameters appearing the nondimensional equations are summarised in Table 2.

Parameter	Description	Value
$\bar{\lambda}_F$	Equilibration rate of false ligands	$\mathcal{O}(1)$
$\bar{\lambda}_R$	Equilibration rate of receptors	small
$\bar{\lambda}_{RF}$	Rate of decay of RF complex	small
$\bar{\lambda}_{RL}$	Rate of decay of RL complex	small
$\bar{\lambda}_A$	Rate of decay of antibodies/drug	very small
$\bar{\lambda}_{R2}$	Rate of decay of RA complex	very small
$\bar{\lambda}_{R3}$	Rate of decay of RAF complex	very small
p_1	Rate of formation of R_F	
p_2	Rate of formation of R_L	
p_4	Rate of formation of R_2	
p_5	Rate of formation of R_3 from $R_2 + F$	
p_6	Rate of formation of R_3 from $R_F + A$	
p_0	Disociation rate of $R_3 \to R_F + A$	
p_F	Rate at which R_2 binds to F	
p_A	Rate at which drug A binds to R_F	
q_1	Rate of loss of F due to binding to R	
q_2	Rate of loss of L due to binding to R	
q_4	Rate of loss of receptors due to A-binding	
q_5	Rate of loss of F due to binding to R_2	
q_0	Rate of loss of receptors due to F-binding	
q_L	Rate of loss of receptors due to L-binding	
q_A	Rate at which drug A is bound to R	

Table 2: Parameters involved in the nondimensional model. Magnitudes of the λ_* parameters have been determined using (1). We assume that all the other parameters are large, since chemical binding/unbinding reactions occur on a faster timescale than receptor or ligand production and destruction.

2.4 Alternative formulation

We wish to reformulate this problem and consider the total number of receptors, ligands and false ligands: let us write these as R_0, L_0, F_0 respectively. We nondimensionalise by writing

$$R_0 = \frac{\mu_R \bar{R}_0}{\lambda_R}, \qquad L_0 = \frac{\mu_L \bar{L}_0}{\lambda_L}, \qquad F_0 = \frac{\mu_F \bar{F}_0}{\lambda_F}, \tag{26}$$

then conservation of the total amount of receptors, ligands, false ligands and antibodies becomes:

$$\bar{L}_0 = \bar{L} + \frac{q_2}{p_2}\bar{R}_L, \tag{27}$$

$$\bar{F}_0 = \bar{F} + \frac{q_1}{p_1}\bar{R}_F + \frac{q_1 p_0}{p_1 p_6}\bar{R}_3, \tag{28}$$

$$\bar{R}_0 = \bar{R} + \frac{q_L}{p_2}\bar{R}_L + \frac{q_0}{p_1}\bar{R}_F + \frac{q_4}{p_4}\bar{R}_2 + \frac{q_0 p_0}{p_1 p_6}\bar{R}_3, \tag{29}$$

$$1 = \bar{A} + \frac{q_A}{p_4}\bar{R}_2 + \frac{q_A p_F}{p_4 p_5}\bar{R}_3. \tag{30}$$

Let the solution of (49)–(52) for R – equivalently rewriting (48) as a cubic in R – be $R = R^0$: then the total amount of ligand (L_0), false ligand (F_0) and receptors (R_0) in the

drug-free case ($R_2 = 0 = R_3$) are given by

$$\bar{L}_0 = \bar{L} + \frac{q_2}{p_2}\bar{R}_L = \frac{(p_2 + \bar{\lambda}_{RL} + q_2\bar{R}^0)}{p_2 + \bar{\lambda}_{RL} + q_2\bar{\lambda}_{RL}\bar{R}^0}, \tag{31}$$

$$\bar{F}_0 = \bar{F} + \frac{q_1}{p_1}\bar{R}_F = \frac{\bar{\lambda}_F(p_1 + \bar{\lambda}_{RF} + q_1\bar{R}_0)}{p_1 + \bar{\lambda}_{RF} + q_1\bar{\lambda}_{RF}\bar{R}_0}, \tag{32}$$

$$\bar{R}_0 = \bar{R} + \frac{q_0}{p_1}\bar{R}_F + \frac{q_L}{p_2}\bar{R}_L = \bar{R}^0\left(1 + \frac{q_L}{p_2+\bar{\lambda}_{RL}+q_2\bar{\lambda}_{RL}\bar{R}_0} + \frac{q_0\bar{\lambda}_F}{p_1+\bar{\lambda}_{RF}+q_1\bar{\lambda}_{RF}R^0}\right). \tag{33}$$

Now we express the number of free ligands, and free false ligands, in terms of the total numbers of ligands and free receptors, using (27)–(28), which implies

$$\bar{L} = \frac{p_2\bar{L}_0}{p_2 + q_2\bar{R}}, \qquad \bar{F} = \frac{p_1\bar{F}_0}{p_1 + q_1\bar{R}}. \tag{34}$$

The number of free receptors is then given by solving (29), namely

$$\bar{R}_0 = \bar{R}\left(1 + \frac{q_L L_0}{p_2 + q_2\bar{R}} + \frac{q_0 F_0}{p_1 + q_1\bar{R}}\right), \tag{35}$$

which is in effect a cubic.

2.5 Reduced system

The *nondimensionalised* equations (16)–(23) may be combined to produce 4 equations (in 8 unknowns) devoid of the fast reactions:

$$\frac{\mathrm{d}}{\mathrm{d}\bar{t}}(\bar{F} + K_1\frac{\mu_R}{\lambda_R}\bar{R}_F + K_{4,5}A^0\frac{\mu_R}{\lambda_R}\bar{R}_3) = \frac{\lambda_F}{\lambda_L}(1-\bar{F}) - \frac{\lambda_{R_F}}{\lambda_L}\frac{\mu_R}{\lambda_R}K_1\bar{R}_F - \frac{\lambda_{R_3}}{\lambda_L}K_{4,5}A^0\frac{\mu_R}{\lambda_R}\bar{R}_3, \tag{36}$$

$$\frac{\mathrm{d}}{\mathrm{d}\bar{t}}(\bar{A} + K_4\frac{\mu_R}{\lambda_R}\bar{R}_2 + K_{4,5}\frac{\mu_R}{\lambda_R}\frac{\mu_F}{\lambda_F}\bar{R}_3) = -\frac{\lambda_A}{\lambda_L}\bar{A} - \frac{\lambda_{R_2}}{\lambda_L}K_4\frac{\mu_R}{\lambda_R}\bar{R}_2 - \frac{\lambda_{R_3}}{\lambda_L}K_{4,5}\frac{\mu_R}{\lambda_R}\frac{\mu_F}{\lambda_F}\bar{R}_3 \tag{37}$$

$$\frac{\mathrm{d}}{\mathrm{d}\bar{t}}(\bar{L} + K_2\frac{\mu_R}{\lambda_R}\bar{R}_L) = 1 - \bar{L} - \frac{\lambda_{R_L}}{\lambda_L}K_2\frac{\mu_R}{\lambda_R}\bar{R}_L \tag{38}$$

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}\bar{t}}(\bar{R} + K_1\frac{\mu_F}{\lambda_F}\bar{R}_F + K_2\frac{\mu_L}{\lambda_L}\bar{R}_L + K_4A^0\bar{R}_2 + K_{4,5}A^0\frac{\mu_F}{\lambda_F}\bar{R}_3) &= \\ \tfrac{\lambda_R}{\lambda_L}(1-\bar{R}) - \tfrac{\lambda_{R_2}}{\lambda_L}K_4A^0\bar{R}_2 - \tfrac{\lambda_{R_3}}{\lambda_L}K_{4,5}A^0\tfrac{\mu_F}{\lambda_F}\bar{R}_3 - \tfrac{\lambda_{R_F}}{\lambda_L}K_1\tfrac{\mu_F}{\lambda_F}\bar{R}_F - \tfrac{\lambda_{R_L}}{\lambda_L}K_2\tfrac{\mu_L}{\lambda_L}\bar{R}_L\end{aligned} \tag{39}$$

3 Drug-free system

In the absence of antibodies we first look at the steady state of system (36)-(39): using the nondimensional parameter definitions of (24) and dropping bars for simplicity we have:

$$1 - R = \frac{q_0}{\lambda_R}(RF - R_F) + \frac{q_L}{\lambda_R}(RL - R_L), \tag{40}$$

$$1 - L = q_2(LR - R_L), \tag{41}$$

$$1 - F = \frac{q_1}{\lambda_F}(RF - R_F), \tag{42}$$

$$R_F = \frac{p_1}{\lambda_{RF}}(RF - R_F), \tag{43}$$

$$R_L = \frac{p_2}{\lambda_{RL}}(RL - R_L). \tag{44}$$

Solving in reverse order, we find

$$R_L = \frac{p_2 RL}{p_2 + \lambda_{RL}}, \qquad R_F = \frac{p_1 RF}{p_1 + \lambda_{RF}}, \tag{45}$$

and hence

$$L = \frac{p_2 + \lambda_{RL}}{p_2 + \lambda_{RL} + q_2\lambda_{RL}R}, \qquad F = \frac{\lambda_F(p_1 + \lambda_{RF})}{p_1 + \lambda_{RF} + q_1\lambda_{RF}R}, \tag{46}$$

$$R_L = \frac{p_2 R}{p_2 + \lambda_{RL} + q_2\lambda_{RL}R}, \qquad R_F = \frac{p_1\lambda_F R}{p_1 + \lambda_{RF} + q_1\lambda_{RF}R}, \tag{47}$$

where R is given by solving

$$\lambda_R(1-R) = \frac{q_0\lambda_F R}{p_1 + \lambda_{RF} + q_1\lambda_{RF}R} + \frac{q_L\lambda_{RL}R}{p_2 + \lambda_{RL} + q_2\lambda_{RL}R}. \tag{48}$$

This clearly has a unique solution in $0 < R < 1$, (since LHS $>$ RHS at $R = 0$, and as R increases, LHS decreases monotonically and RHS increases monotonically, and at $R = 1$, we have LHS $<$ RHS). Obtaining the root of (48) requires solution of the cubic

$$aR^3 + bR^2 + cR - d = 0, \tag{49}$$

with

$$a = q_1 q_2 \lambda_{RF}\lambda_{RL}, \qquad d = \lambda_F(p_1 + \lambda_{RF})(p_2 + \lambda_{RL}), \tag{50}$$

$$b = \lambda_{RF}\lambda_{RL}q_1 q_1 \left[\frac{q_L}{\lambda_R q_2} + \frac{\lambda_F q_0}{\lambda_R q_1} + \frac{1}{q_2} + \frac{\lambda_F}{q_1} + \frac{p_2}{\lambda_{RL}q_2} + \frac{\lambda_F p_1}{\lambda_{RF}q_1} - 1\right], \tag{51}$$

$$c = (p_1 + \lambda_{RF})(p_2 + \lambda_{RL})\left[1 + \frac{\lambda_{RF}(q_0\lambda_F - q_1\lambda_R)}{\lambda_R\lambda_F(p_1 + \lambda_{RF})} + \frac{\lambda_{RL}(q_L - q_2\lambda_R)}{\lambda_R(p_2 + \lambda_{RL})}\right]. \tag{52}$$

These expressions suggest that $b, c > 0$ (in addition to $a, d > 0$). Descartes rule of signs ensures that the equation has a unique positive root R^0, and for biologically relevant parameters this will yield the unique natural equilibrium of the system $(R^0, L^0, F^0, R_L^0, R_F^0)$. These values are considered the natural initial conditions for the drug-treated system i.e. we set:

$$R(0) = R^0,\ L(0) = L^0,\ F(0) = F^0,\ A(0) = A0,\ R_L(0) = R_L^0,\ R_F(0) = R_F^0,\ R_2(0) = 0,\ R_3(0) = 0.$$

4 Drug-treated system

We consider the system over a number of different timescales. The first timescale is given by $\hat{t} = \frac{\bar{t}}{k_1}$ and represents the period in which the antigen binds to the unbound receptors: the system quickly settles down following an initial steep drop in unbound receptor numbers. After the reactions have reached equilibrium there follows a period during which the ligand and false ligand converge to near steady values – we consider this to be the most important time for determining the quantity of ligand bound receptor as the relevant timescale most closely represents the treatment phase. Following this there is a long period of gradual antibody decay – over a timescale $\tilde{t} = \frac{\bar{t}}{\lambda_A}$ – during which the system returns to the natural drug-free steady state.

4.1 Binding phase: short term dynamics

As the drug A is introduced at $t = 0$ it very quickly binds to unbound receptors, with the system quickly attaining new ratios of R, R_L and R_F. However, over such short times, there is negligible creation or destruction of ligands, false ligands and receptors, and similalrly negligible decay of antibody (so that $A \approx A^0$). We therefore seek a solution to the generalised system which, over the timescale $\hat{t} = \frac{\bar{t}}{k_1}$, reduces to:

$$\begin{aligned} \bar{R}_F &= \bar{R}\bar{F}, && (53)\\ \bar{R}_L &= \bar{R}\bar{L}, && (54)\\ \bar{R}_2 &= \bar{A}\bar{R}, && (55)\\ \bar{R}_3 &= \bar{A}\bar{R}\bar{F} && (56) \end{aligned}$$

subject to

$$\begin{aligned} L_0 &= L + \frac{q_2}{p_2}R_L, & F_0 &= F + \frac{q_1}{p_1}R_F + \frac{q_1 p_0}{p_1 p_6}R_3,\\ 1 &= A + \frac{q_A}{p_4}R_2 + \frac{q_A p_F}{p_4 p_5}R_3, & R_0 &= R + \frac{q_L}{p_2}R_L + \frac{q_0}{p_1}R_F + \frac{q_4}{p_4}R_2 + \frac{q_0 p_0}{p_1 p_6}R_3. \end{aligned} \quad (57)$$

We thus obtain the solutions

$$L = \frac{p_2 L_0}{p_2 + q_2 R}, \qquad F = \frac{p_1 F_0}{p_1 + q_1 R(1 + p_0 A/p_6)}, \quad (58)$$

where R satisfies

$$R_0 = R\left[1 + \frac{q_L L_0}{p_2 + q_2 R} + \frac{q_4}{p_4}A + \frac{q_0(p_0 A + p_6)F_0}{p_1 p_6 + q_1(p_0 A + p_6)R}\right], \quad (59)$$

which is in effect a cubic for R. Our aim is thus to investigate the effect of A on the positive real solution for R. The signal, or response of the body which we are trying to prevent is caused by the ligand L binding to a receptor R, hence the complex $R_L = RL$ is a measure of the effectiveness of the drug A.

In the limit of the drug having a small influence on the system ($A \ll 1$) the expressions for L, F, R should be small perturbations of the solution (35). That is, $R = R^0(1 - AR_1)$ where

$$R_1 = \frac{1 + F_0 + R_0 + R^0(1 + R_0 - F_0 - L_0)}{1 + F_0 + L_0 + R_0 + R^0}(1 + R_0 - F_0 - L - 0). \quad (60)$$

This means that a low dose of drug will cause a small reduction in the number of free receptors, and consequently a small reduction in R_L too.

However, we typically expect the amount of drug to be vastly in excess of the number of receptors, ligands or false ligands, meaning that we can assume that $\bar{A} \simeq 1$ from (30).

In the limit of large A^0, the cubic (59) reduces to

$$R \sim R^* = \frac{R_0 p_4}{A q_4}, \qquad \text{hence} \qquad R_L \sim \frac{p_2 p_4 R_0 L_0}{p_4 q_2 R_0 + p_2 q_4 A}. \quad (61)$$

This value R^* provides, for biologically relevant parameters, a unique solution:

$$\left(\bar{R}^*, \bar{L}^*(\bar{R}^*), \bar{F}^*(\bar{R}^*), 1\right); \quad (62)$$

this is the solution we match to in the next time scale.

4.2 Ligand convergence phase

Over longer timescales, the production and decay of the various ligands and receptors, and receptor-ligand complexes will become significant, and lead to variations in the total number of ligands and receptors in the system. Over such timescales, totals L_0, R_0 and F_0 are not constant, and instead we will consider the concentrations of each complex and each free species (R, F, L, A, R_F, R_L, R_2, R_3).

Substituting equalities (53)–(56) into equations (36)–(39) we obtain:

$$\frac{\mathrm{d}}{\mathrm{d}\bar{t}}\left(\bar{F}\left(1+(K_1+K_{4,5}A^0\bar{A})\bar{R}\frac{\mu_R}{\lambda_R}\right)\right) = \frac{\lambda_F}{\lambda_L}(1-\bar{F}) - \left(\frac{\lambda_{R_F}}{\lambda_L}K_1 + \frac{\lambda_{R_3}}{\lambda_L}K_{4,5}A^0\bar{A}\right)\frac{\mu_R}{\lambda_R}RF \quad (63)$$

$$\frac{\mathrm{d}}{\mathrm{d}\bar{t}}(\bar{A}(1+\left(K_4+K_{4,5}\frac{\mu_F}{\lambda_F}\bar{F}\right)\bar{R}\frac{\mu_R}{\lambda_R})) = -\frac{\lambda_A}{\lambda_L}\bar{A} - \left(\frac{\lambda_{R_2}}{\lambda_L}K_4\bar{A} + \frac{\lambda_{R_3}}{\lambda_L}K_{4,5}\bar{A}\frac{\mu_F}{\lambda_F}\bar{F}\right)\bar{R}\frac{\mu_R}{\lambda_R} \quad (64)$$

$$\frac{\mathrm{d}}{\mathrm{d}\bar{t}}(\bar{L}(1+K_2\frac{\mu_R}{\lambda_R}\bar{R})) = 1-\bar{L} - \frac{\lambda_{R_L}}{\lambda_L}K_2\frac{\mu_R}{\lambda_R}\bar{R}\bar{L} \quad (65)$$

$$\frac{\mathrm{d}}{\mathrm{d}\bar{t}}\left(\left(1+K_1\frac{\mu_F}{\lambda_F}\bar{F}+K_2\frac{\mu_L}{\lambda_L}\bar{L}+\left(K_4+K_{4,5}\bar{F}\frac{\mu_F}{\lambda_F}\right)A^0\bar{A}\right)\bar{R}\right) = \frac{\lambda_R}{\lambda_L}\left(1-\bar{R}\right) - \left(\frac{\lambda_{R_F}}{\lambda_L}K_1\frac{\mu_F}{\lambda_F}\bar{F} + \frac{\lambda_{R_L}}{\lambda_L}K_2\frac{\mu_L}{\lambda_L}\bar{L} + \left(\frac{\lambda_{R_2}}{\lambda_L}K_4 + \frac{\lambda_{R_3}}{\lambda_L}K_{4,5}\bar{F}\frac{\mu_F}{\lambda_F}\right)A^0\bar{A}\right)\bar{R} \quad (66)$$

which are valid for all time scales beyond the initial binding phase described above. For solutions on a dimensional timescale of $1/\lambda_R$ we may use initial conditions given by matching to the solution (62) above. Assuming $\mu_R \ll \lambda_R$ and recalling that $\lambda_A \ll \lambda_R \ll \lambda_L$ our first three equations reduce to:

$$\frac{d\bar{A}}{d\bar{t}} = 0,\ \frac{d\bar{F}}{d\bar{t}} = \frac{\lambda_F}{\lambda_L}(1-\bar{F}),\ \frac{d\bar{L}}{d\bar{t}} = 1-\bar{L},$$

i.e.

$$\bar{A} = 1,\ \bar{F} = 1+(\bar{F}^*-1)e^{-\lambda_F\bar{t}/(\lambda_R\lambda_L)},\ \bar{L} = 1+(\bar{L}^*-1)e^{-\bar{t}/\lambda_R},$$

We may assume that $A^0 \gg 1$, in which case the final equation becomes

$$\frac{d}{d\bar{t}}\left(\bar{R}\bar{A}\left(K_4+K_{4,5}\bar{F}\frac{\mu_F}{\lambda_F}\right)\right) = \frac{\lambda_R}{A^0\lambda_L} - \bar{R}\bar{A}\left(\frac{\lambda_{R_2}}{\lambda_L}K_4 + \frac{\lambda_{R_3}}{\lambda_L}K_{4,5}\bar{F}\frac{\mu_F}{\lambda_F}\right), \quad (67)$$

where we have used the fact that the terms $\bar{R}_2 = \bar{R}\bar{A}$ and $\bar{R}_3 = \bar{R}\bar{A}\bar{F}$ dominate.

We first consider antibody 1, that is we take $K_{4,5} = 0$. Our differential equation is then reduced to

$$\frac{d}{dt}\left(\bar{R}\bar{A}\right) = \frac{\lambda_R}{A^0K_4\lambda_L} - \bar{R}\bar{A}\lambda_{R_2\lambda_L}, \quad (68)$$

which has the solution

$$\bar{R} = \frac{1}{\bar{A}}\left(\frac{\lambda_R}{A^0K_4\lambda_{R_2}} + C\mathrm{e}^{-\lambda_{R_2}t/\lambda_L}\right) \quad (69)$$

$$= \frac{1}{\bar{A}}\frac{\lambda_R}{\lambda_{R_2}A^0K_4} + \frac{1}{\bar{A}}\left(R^* - \frac{\lambda_R}{\lambda_{R_2}A^0K_4}\right)\mathrm{e}^{-\lambda_{R_2}\bar{t}/\lambda_L}. \quad (70)$$

Thus, in the presence of antibody 1,

$$\bar{R} \to \frac{\lambda_R}{A^0K_4\lambda_{R_2}} \quad (71)$$

for the time scale prior to the decay of the antibodies.

For antibody 2 we need to consider $K_{4,5} \neq 0$ and make use of the approximation $\lambda_{R_2} \approx \lambda_{R_3}$. The differential equation then has the solution

$$\bar{R} = \frac{1}{\bar{A}\left(K_4 + K_{4,5}\bar{F}\frac{\mu_F}{\lambda_F}\right)}\left(\frac{\lambda_R}{A^0\lambda_{R_2}} + C\mathrm{e}^{-\lambda_{R_2}\bar{t}/\lambda_L}\right) \tag{72}$$

Thus, in the presence of antibody 2,

$$\bar{R} \to \frac{\lambda_R}{A^0\left(K_4 + K_{4,5}\frac{\mu_F}{\lambda_F}\right)\lambda_{R_2}} \tag{73}$$

for the time scale prior to the decay of the antibodies.

4.3 Antibody decay phase

The final phase of the system is that in which it returns to the untreated state as a result of the drug leaving the body. For $\tilde{t} = \bar{t}/\lambda_A$ the first three equations of our system reduces to

$$\frac{dA}{d\tilde{t}} = -A,\ \frac{dF}{d\tilde{t}} = 0,\ \frac{dL}{d\tilde{t}} = 0,$$

i.e.

$$A = e^{-\lambda_A\bar{t}},\ F = 1,\ L = 1,$$

by matching from the previous solution, and R may be solved for as before if required. As the amount of antibody decays to zero, our solutions return to the drug-free state $(R^0, L^0, F^0, 0)$.

5 Antibody comparison

Consider the quasi-equilbrium to which R converges to in the intermediate phase at the end of the ligand convergence phase and the start of the antibody decay phase. We treat this as a measure of treatment success, since the number of ligand bound receptors is proportional to R: of interest is the effect of $K_{4,5}$ since this differentiates the behaviour of the two antibodies.

From (71) and (73) we have, in dimensional variables, that

$$R_L \to \frac{1}{A^0}\frac{K_2}{K_4}\frac{\mu_R}{\lambda_{R_2}}\frac{\mu_L}{\lambda_L} \qquad \text{with type 1 antibodies;}$$

$$R_L \to \frac{1}{A^0}\frac{K_2}{K_4 + K_{4,5}\frac{\mu_F}{\lambda_F}}\frac{\mu_R}{\lambda_{R_2}}\frac{\mu_L}{\lambda_L} \quad \text{with type 2 antibodies;}$$

respectively, prior to the phase of antibody decay. Assuming that body parameters not associated with antibody dynamics (such as λ_R) remain the same in the presence of either antibody, we may conclude that a measure of the effectiveness of antibodies of type 1 is:

$$\lambda_{R_2}^{(1)} K_4^{(1)} A^{0(1)} \tag{74}$$

and that a comparable measure for antibodies of type 2 is:

$$\lambda_{R_2}^{(2)} K_4^{(2)}\left(1 + K_5^{(2)}\frac{\mu_F}{\lambda_F}\right) A^{0(2)} \tag{75}$$

where the superscripts refer to the relevant antibodies.

6 Conclusions

Results confirm what we expect intuitively, that in a system flooded with antibodies, those antibodies able to bind to receptors which are already bound with false ligands (thus "'double locking"' these receptors from potential ligand binding) will perform better than those which will not, unless there is a significantly larger amount of the other antibody or there is a significant difference in the antibody performance. Explicitly, an antibody will perform better if the affinity of the antibody and receptor ($1/K_4$) or the decay rate of antibody bound receptor λ_{R_2} are large. Since the latter is assumed to be similar to the antibodies intrinsic decay rate, however, and is the timescale upon which solutions R converge, a significant difference in λ_{R_2} may be an inappropriate target. The quantity of antibodies that could be provided in a dose, A^0, is also not considered to be restricted and would thus be similar for each antibody type.

Expressions (74) and (75) therefore quantify the necessary difference between the affinity of the second antibody and receptor $1/K_4^{(2)}$, the affinity of the false ligand and antibody-bound-receptors $1/K_5^{(2)}$ (or alternatively the affinity of the antibody and the false-ligand-bound-receptor $1/K_6^{(2)} \approx 1/K_{4,5}^{(2)}$) and the affinity of the first antibody and receptor $1/K_4^{(1)}$ so that the better antibody can be identified i.e. a simpler antibody of type 1 is better only if

$$\lambda_{R_2}^{(1)} K_4^{(1)} \;>\; \lambda_{R_2}^{(2)} K_4^{(2)} \left(1 + K_5^{(2)} \frac{\mu_F}{\lambda_F}\right). \tag{76}$$

Appendix

Numerical solvers for the full system were developed during the study group in Matlab but for meaningful simulations require more accurate parameter values than we managed to estimate at the time: this is work in progress.