Mathematical Model for Rheumatoid Arthritis

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that manifests as a persistent inflammatory synovitis, which is when the synovial membrane (lining) of a joint becomes inflamed, and eventually destroys the joints. The origin of this disease is still unknown, but it is hypothesized it results from an abnormal immune response to contact with an infectious agent in an individual who has a genetic liability. In RA there is an abnormal activation of T-helper cells in the synovial membrane which causes the body to not familiarize its own antigens associated with synovium cells. In this disease, the division of cells known as cytokines has an important role in stimulating inflammation. Cytokines are proteins that function by merging with specific receptors on the target cells, leading to cellular survival, cellular differentiation, and cellular proliferation. Cytokines are important for accurate immune response integrity because an increase of proinflammatory cytokines causes an increase of soluble receptors and anti-inflammatory cytokines. After a short period of time, the system returns to stable bioactivity in the joints which we call an equilibrium. Inflammation occurs when there is a lack of balance between the pro-inflammatory cytokines and anti-inflammatory cytokines causing the joint to deteriorate. TNF-a inhibitors are treatments that help stop inflammation and are used worldwide to treat Rheumatoid Arthritis. They reduce inflammation and can stop disease progression by targeting an inflammation-causing substance called Tumor Necrosis Factor alpha TNF-α. The anti-TNF-α is based on the concept that the TNF-α becomes bioactive when it is bound to cell receptors in the receptor compartment. Therefore, the neutralization of this bioactivity suggests there is a failure of transduction of the inflammatory message. Thus, TNF-α is prevented from binding to TNF-α receptors blocking the inflammatory response and putting the disease into remission, even though this effect is not permanent. TNF-α inhibitors have been created in the form of soluble receptors such as Etanercept and sTNFR2 and in the form of therapeutic biological agents such as Infliximab. In 2005, a mathematical model was published in Rheumatology based on the role of TNF-α in the therapy of RA. It represents TNF-α dynamics in receptor compartment in presence of inhibitors, which are treatments, and it consists of four coupled ordinary differential equations. In the following sections, we analyze and solve the model by setting conditions such as initial conditions and fixing parameters to study the behavior of TNF-a and predict the effectiveness of naturally produced sTNFR2, and the effectiveness of Etanercept (Enbrel) and Infliximab (Remicade).

The Model

The mathematical model was developed to predict clinical benefit of the treatments: Etanercept, Infliximab and the naturally produced sTNFR2. The model represents TNF-α (Tumour Necrosis Factor alpha) behavior in the 'receptor compartment' which we define as the inflamed synovial joint within which locally produced TNF-α can bind to cell-surface receptors. In final, the following model is used to show the bioactivity of TNF-α in the body against three inhibitors.

$$\frac{dL}{dt} = \omega_1 + \nu R_{tot} r - k_1 R_{tot}(1 - r)L + k_{-1} R_{tot} r - k_a LA + k_{-a} C - \delta_1 L$$

$$\frac{dr}{dt} = k_1(1-r)L - k_{-1} r - \varepsilon r$$

$$\frac{dA}{dt} = \omega_a - k_a LA + k_{-a} C - \delta_a$$

$\frac{dC}{dt} = k_a LA - k_{-a} C - \delta_c C$

L is the receptor compartment concentration where TNF-α binds to cell surface receptors TNFR1 (the TNFR1 protein attaches (binds) to another protein called tumor necrosis factor (TNF)) with total density of Rtot to form receptor-ligand complexes and has a bound proportion of r. L is the representation of a non-zero concentration of free TNF- α. A is the receptor compartment concentrations to antibodies, meaning TNF-a can bind to antibodies to form antibody–antigen complexes with receptor compartment concentration C. We consider a receptor to be a region of tissue, or a molecule in a cell membrane, which responds specifically to a particular neurotransmitter, hormone, antigen, or other substance.

The parameters of the system are defined below,

r is the bound proportion to form receptor-ligand complexes

$1 - r$ the unbound proportion to form receptor-ligand complexes

k_1 is the TNF-α receptor association rate

k_{-1} is the TNF-α receptor dissociation rate

k_a is the ligand-inhibitor association rate

k_{-a} is the ligand-inhibitor dissociation rate

ε is the rate of internalization of bound receptors occurs

R_{tot} is the total receptor density, assumed constant

ω_1 the constant that represents the production rate of TNF-α which is the stimulus that maintains the inflammatory response

ω_a represents the rate at which antibodies are introduced into the receptor compartment.

We assume that the clearance processes from the receptor compartment are first order with rates δ_1 for free TNF-α, δ_a for free antibody, and δ_c for antibody−antigen complexes.

ν is a constant that measures the strength of a possible stimulated autocrine response which upregulates TNF-α production in response to the density of bound receptors, and it is assumed to be in linear form since this response is not quantified. When ν is zero it means that there is no stimulatory response.

The steady state equilibrium of the system is represented by a production of TNF- α equal to zero (when $\omega_1 = 0$), which implies that when the uncentered production rate ω_1 is different from zero there is a disease state equilibrium. This means that the production of TNF- α, which is represented as ω_1, controls the result of either a disease-free equilibrium or an equilibrium where the disease takes over. When $\omega_1 = 0$, and in absence of treatment of antibody ($\omega_a = 0$), the state in which all variables in the system take the value zero (zero state of the system) is the equilibrium state. When $\omega_1 > 0$ and $\omega_a \geq 0$ there is a unique

non-zero stable equilibrium in which the equilibrium TNF-α level is an increasing function of both ω_1 and ν and the equilibrium TNF-α level is a decreasing function of ω_a. Thanks to this model it is possible to study the interactions between TNF-α and the specific ligand-binding inhibitor. The equilibrium is stable if the autocrine response is not too large. Meaning there is minimal bioactivity when $\nu < \varepsilon + \delta_1 K_1$

Where ki = $\frac{k-1+\varepsilon}{Rtotk1}$

Simulating with estimated parameters:

$\omega^{eq} = 8 \times 10^{-15} Ms^{-1}$, $k_1 = 1.7 \times 10^{7} Ms^{-1}$, $k_{-1} = 5.5 \times 10^{-4} s^{-1}$, 1

$R_{tot} = 1.5 \times 10^{-10} M$, $\varepsilon = 6 \times 10^{-4} s^{-1}$, $\delta_1 = 10^{-5} s^{-1}$,

it was proven that the zero state will be stable if $\nu \leq \varepsilon$ when the stimulated endocytosis rate ε has order $10^{-4} s^{-1}$ and $\delta_1 K_1$ has order $10^{-6} s^{-1}$. The zero state becomes unstable when $\nu \geq \varepsilon + \delta_1 K_1$, and in this case TNF-α production is maintained from autocrine action only. All three inhibitors reduce the concentration of total bioactive TNF-α leading the system to a new lower equilibrium level if the following estimates of parameters are taken into consideration,

(A) $k_a = 1.9 \times 10^{7} M^{-1} s^{-1}$, $k_{-a} = 5.8 \times 10^{-3} s^{-1}$, $\delta_c = 2.3 \times 10^{-5} s^{-1}$, $\delta_a = 2.3 \times 10^{-5} s^{-1}$, in the case of naturally produced sTNFR2;

(B)$k_a = 7 \times 10^{8} M^{-1} s^{-1}$, $k_{-a} = 7 \times 10^{-4} s^{-1}$, $\delta_c = 1.7 \times 10^{-6} s^{-1}$, $\delta_a = 0 - 1.7 \times 10^{-6} s^{-1}$, in the case of administration of Etanercept;

(C) $k_a = 10^{6} M^{-1} s^{-1}$, $k_{-a} = 10^{-4} s^{-1}$, $\delta_c = 8.5 \times 10^{-7} s^{-1}$, $\delta_a = 0 - 8.5 \times 10^{-7} s^{-1}$, in the case of administration of Infliximab.

Treatment with these drugs is rapidly effective because as soon as they reach the joint lining, they immediately act to reduce TNF-α bioactivity and establish a new equilibrium. Studying the concentrations of free TNF-α inhibitor-linked it was seen that all three inhibitors act as slow-release reservoirs. At first a decrease of TNF-α concentrations is observed but then, once these levels are reduced by the clearance, the effect is the release of TNF-α previously sequestered. The bioactivity is different for the three inhibitors, and it depends also on the period considered since administration. In the next section we will discuss the simplification of the model that is done by keeping ωa constant because to study the bioactivity of TNF- α there needs to be a steady state.

Resolution of the Model

Here we reduce and find the solution of our model.

The non-linear model (1)-(4) consists of four first-order ordinary differential equations. This mathematical model was developed to predict the short-term and long-term benefits of using Etanercept, Infliximab, and naturally produced sTNFR2.

(1) $$\frac{dL}{dt} = \omega_1 + vR_{tot}r - k_1 R_{tot}(1-r)L + k_{-1}R_{tot}r - k_a LA + k_{-a}C - \delta_1 L$$

(2) $$\frac{dr}{dt} = k_1(1-r)L - k_{-1}r - \varepsilon r$$

(3) $$\frac{dA}{dt} = \omega_a - k_a LA + k_{-a}C - \delta_a A$$

(4) $$\frac{dC}{dt} = k_a LA - k_{-a}C - \delta_c C$$

Through algebraic manipulation and by placing conditions on the parameters, we can reduce the above system of equations to a system of linear equations.
By adding equations (3) and (4), we obtain the following differential equation:

(5) $$-\frac{dA}{dt} - \frac{dC}{dt} - \delta_a A - \delta_c C + \omega_a = 0$$

Equation (5) is the linear model since it has only linear terms.

Now we introduce a new variable:

$$U_1 = A + C$$

$$\downarrow$$

(6) $$C = U_1 - A$$

By substituting (6) into equation (5), we get:

(7) $$-\frac{dU_1}{dt} - \delta_a A - \delta_c U_1 + \delta_c A + \omega_a = 0$$

Placing the condition $\delta_a = \delta_c$ on the parameters and substituting into equation (7), we obtain the following linear differential equation:

(8) $$\frac{dU_1}{dt} = -\delta_c U_1 + \omega_a$$

Now we place the following condition on the parameters:

$$\mathcal{E} = \delta_c + v$$

By substitution, we get:

$$\frac{du_3}{dt} - \delta_1 L + \delta_c u_3 + \delta_c R_{tot} r + \delta_c L - (\delta_c + v) R_{tot} r + v R_{tot} r + \omega_1 - \omega_a = 0$$

$$\frac{du_3}{dt} - \delta_1 L + \delta_c u_3 + \delta_c R_{tot} r + \delta_c L - \delta_c R_{tot} r - v R_{tot} r + v R_{tot} r + \omega_1 - \omega_a = 0$$

$$\frac{du_3}{dt} - \delta_1 L + \delta_c u_3 + \delta_c L + \omega_1 - \omega_a = 0$$

By placing the condition $\delta_1 = \delta_c$ on the equation above, we get:

(14) $$\frac{du_3}{dt} + \delta_1 u_3 + \omega_1 - \omega_a = 0$$

By integrating equation (14), we obtain:

(15) $$u_3 = e^{-\delta_c t} A_2 - \frac{(\omega_1 - \omega_a)}{\delta_c}$$

$A_2 = u_3(0) - \frac{\omega_a - \omega_1}{\delta_c}$. A_2 is a constant that depends on initial conditions.

The condition $\delta_1 = \delta_c$ we placed earlier implies $\delta_1 = \delta_a$.

By substituting equations (6) and (12) into equation (1), we obtain:

$$-\frac{dL}{dt} - \delta_c L + K_1 R_{tot} Lr - K_1 R_{tot} L - K_a u_3 L - K_a R_{tot} Lr - K_a L^2 - K_{-a} L + K_{-1} R_{tot} r - K_{-a} u_3 + K_{-a} u_1 - K_{-a} R_{tot} r + v R_{tot} r + \omega_1 = 0$$

which yields the non-linear terms Lr and L^2. By placing the condition $K_1 = K_a$ on the parameters we can eliminate Lr.

$$-\frac{dL}{dt} - \delta_c L - K_a u_3 L - K_a R_{tot} L - K_a L^2 - K_{-a} L + K_{-1} R_{tot} r - K_{-a} u_3 + K_{-a} u_1 - K_{-a} R_{tot} r + v R_{tot} r + \omega_1 = 0$$

By placing the condition $v = K_{-a} - K_{-1}$ and substituting into the equation above, we get:

(16) $$-\frac{dL}{dt} - \delta_c L - K_a u_3 L - K_a R_{tot} L - K_a L^2 - K_{-a} L - K_{-a} u_3 + K_{-a} u_1 + \omega_1 = 0$$

By integrating equation (8), we obtain:

$$(9) \quad U_1 = \frac{\omega_a}{\delta_c} + A_1 e^{-\delta_c t}$$

$A_1 = U_1(0) - \frac{\omega_a}{\delta_c}$. A_1 is a constant that depends on the initial conditions.

Now, we multiply equation (2) by R_{tot} and add the product to equation (1):

$$R_{tot}\left(\frac{dr}{dt}\right) = (k_1(1-r)L - k_{-1}r - \varepsilon r)\, R_{tot}$$

$$+$$

$$\frac{dL}{dt} = \omega_1 + \nu R_{tot} r - k_1 R_{tot}(1-r)L + k_{-1} R_{tot} r - k_a LA + k_{-a} C - \delta_1 L$$

$$(10) \quad -\frac{dL}{dt} - \frac{dr}{dt} R_{tot} - \delta_1 L - \varepsilon R_{tot} r - k_a LA + k_{-a} U_1 - k_{-a} A + \nu R_{tot} r + \omega_1 = 0$$

Equation (10) gives us the non-linear term LA. Adding equation (3) and (10), we get:

$$-\frac{dL}{dt} - \frac{dr}{dt} R_{tot} - \delta_1 L - \varepsilon R_{tot} r - k_a LA + k_{-a} U_1 - k_{-a} A + \nu R_{tot} r + \omega_1 = 0$$

$$+$$

$$\frac{dA}{dt} = \omega_a - k_a LA + k_{-a} C - \delta_a A$$

$$(11) \quad -\frac{dL}{dt} - \frac{dr}{dt} R_{tot} + \frac{dA}{dt} - \delta_1 L + \delta_c A - \varepsilon R_{tot} r + \nu R_{tot} r + \omega_1 - \omega_a = 0$$

Now we have only linear terms because we eliminated the term LA.
Now, we introduce a new variable:

$$U_3 = A - R_{tot} r - L$$

$$\downarrow$$

$$(12) \quad A = U_3 + R_{tot} r + L$$

By substituting variable (12) into equation (11), we get:

$$(13) \quad \frac{du_3}{dt} - \delta_1 L + \delta_c U_3 + \delta_c R_{tot} r + \delta_c L - \varepsilon R_{tot} r + \nu R_{tot} r + \omega_1 - \omega_a = 0$$

The equation that we obtain is a Ricatti equation. By using the following transformation, we can linearize equation (16).

$$L = \frac{1}{K_a U_4} \frac{dU_4}{dt} \tag{17}$$

Equations (16) and (2) then become:

$$\frac{d^2U_4}{dt^2} + \frac{dU_4}{dt}\left(\delta_c + K_a U_3 + K_a R_{tot} + K_{-a}\right) + K_a U_4\left(K_{-a}U_3 - K_{-a}U_1 - \omega_1\right) = 0 \tag{18}$$

$$\frac{1-r}{U_4} - \frac{dU_4}{dt} - \frac{dr}{dt} - \left(\delta_c + K_{-a}\right)r = 0 \tag{19}$$

By using the method of the characteristic curves (7) in the equation (19) to eliminate the term with the derivative of U_4, we obtain the transformation:

$$r = 1 + \frac{U_2}{U_4} \tag{20}$$

U_2 is a new dependent variable of time t. By applying the transformation (20) to equation (19) we obtain:

$$\frac{dU_2}{dt} = -\left(\delta_c + K_{-a}\right)\left(U_2 + U_4\right) \tag{21}$$

Once the general solution of equation (18) is determined, equation (21) can be integrated as:

$$U_2 = \left(A_3 - \left(\delta_c + K_{-a}\right)\int e^{\left(\delta_c + K_{-a}\right)t} U_4\, dt\right) e^{-\left(\delta_c + K_{-a}\right)t} \tag{22}$$

$A_3 = U_2(0)$. A_3 is a constant which depends on initial conditions.
By transformation (17), equation (18) is linearized. By applying MAPLE 16, the general solution is obtained as:

$$U_4 = e^{\frac{Pt}{2\delta_c}}\left(C_1 M_{K,m}(z) + C_2 U_{K,m}(z)\right)$$

and

$M_{K,m}(z)$ $U_{K,m}(z)$ are KummerM and KummerU functions.

C_1 and C_2 are constants which depend on initial conditions.

$$P = k_a(\omega_1 - \omega_a - R_{tot}\delta_c) - \delta_c(k_{-a} + \delta_c) - N^{\frac{1}{2}}$$

$$K = \frac{1}{2\delta_c^2}N^{\frac{1}{2}} + \frac{1}{2\delta_c^2(\omega_1 - \omega_a + u_3(0)\delta_c}\Big[(\delta_c^3 - (k_{-a} - k_a R_{tot})\delta_c^2 - k_a(\omega_1 - \omega_a)\delta_c)u_3(0)$$
$$+(\omega_1 - \omega_a + 2k_{-a}u_1(0))\delta_c^2 + ((k_a R_{tot} - k_{-a})\omega_1 - (k_a R_{tot} + k_{-a})\omega_a)\delta_c - k_a(\omega_1 - \omega_a)^2\Big]$$

$$m = 1 + \frac{N^{\frac{1}{2}}}{\delta_c^2}$$

$$N = \delta_c^4 + (2k_a R_{tot} + 2k_{-a})\delta_c^3 + (k_a^2 R_{tot}^2 + (2k_{-a}R_{tot} + 2\omega_1 + 2\omega_a)k_a + k_{-a}^2)\delta_c^2$$
$$-2k_a(R_{tot}(\omega_1 - \omega_a) - k_{-a}(\omega_1 + \omega_a))\delta_c + k_a^2(\omega_1 - \omega_a)^2$$

$$z = \frac{k_a}{\delta_c^2}(\omega_1 - \omega_a + u_3(0)\delta_c)e^{-\delta_c t}$$

(24) $$u_1(t) = \frac{\omega_a}{\delta_c} - \frac{\omega_a - u_1(0)\delta_c t}{\delta_c}$$

(26) $$u_2(t) = \left(u_2(0) - (\delta_c + k_{-a})\int_0^t e^{(\delta_c + k_{-a})t}u_4(t)dt\right)e^{-(\delta_c + k_{-a})t}$$

(26) $$u_3(t) = \frac{\omega_a - \omega_1}{\delta_c} + \frac{\omega_1 - \omega_a + u_3(0)\delta_c}{\delta_c}e^{-\delta_c t}$$

(27) $$u_4(t) = e^{\frac{P_t}{2\delta_c}}(C_1 M_{k,m}(z) + C_2 U_{k,m}(z))$$

By substituting equation (27) in (17) we obtain L.
By substituting equations (27) and (25) in (20) we obtain r.
By substituting equations (17), (20), and (26) in (12) we obtain A.
By substituting equation (24) in (6) we obtain C.

Simulations

The behavior of L allows us to determine the effectiveness of the three inhibitors to reduce the concentration of bioactive TNF-α. We study the behavior of L in the case of the three inhibitors: sTNFR2, Infliximab and Etanercept (Enbrel). When L represents the non-zero concentration of free TNF-α that is present at the state of disease progression. Increasing levels of TNF-α causes synovial inflammation and joint destruction. In our simulations, we assume that at time t=0, the concentration of free TNF-α is higher than zero. This means rates ω_1 and ω_a are higher than zero, and the initial condition L(0) is higher than zero. When looking at the models, we must keep in mind that we must use certain parameters for the models to work, namely:

$$\omega_1 = 8x10^{-15}, k_1 = 1.7x10^{7}, k_{-1} = 5.5x10^{-4}, R_{tot} = 1.5x10^{-10}, \epsilon = 6x10^{-4}, \delta_1 = 10^{-5}$$

STNFR-2

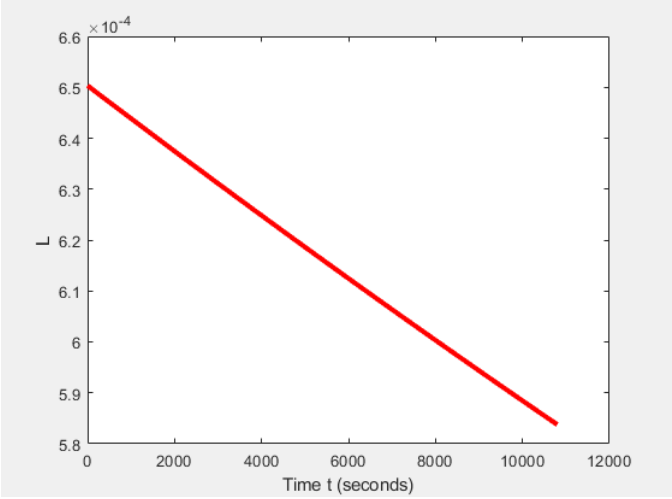
When looking at the sTNFR-2 treatment model, we must use the following parameters:

$$k_{-a} = 5.8x10^{-3}, \delta c = 2.3x10^{-5}, k_{-1} = 5.5x10^{-4}, k_a = 1.9x10^{4}$$

with initial conditions

L(0) = 0.0006503257844 , r(0) = 0 , A(0) = 0.003162212217, C(0)= 0.000000065443.

We see from our model that we have linear regression from our initial condition of just over $6.5x10^{-4}$, where over the course of 3 hours, the level of free TNF-α concentration decays (denoted L in the model) to just over $5.8x10^{-4}$.



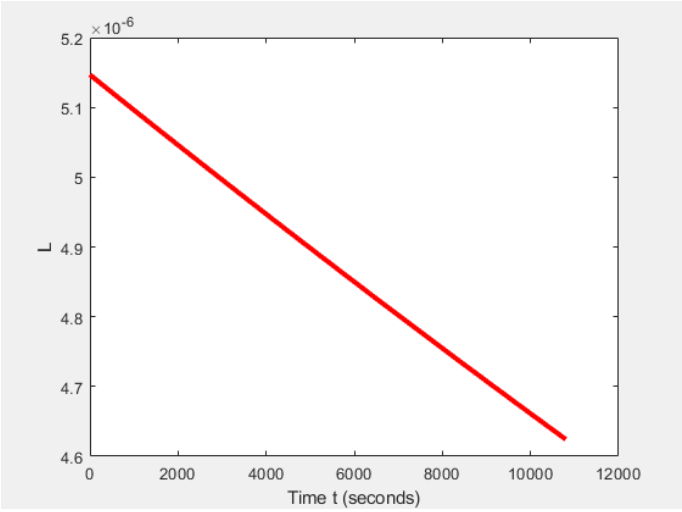
Infliximab

Similarly, if we look at the Infliximab treatment model, we must use the parameters:

$k_{-a} = 10^{-4}, \delta c = 8.5x10^{-7}, k_{-1} = 5.5x10^{-5}, k_a = 10^{-2}$ With initial conditions

L(0) = 0.000005146875300 , r(0) = 0 , A(0) = 0.00002509949845, C(0)= 0.00000001936587.

Again, from our initial condition of just under $5.15x10^{-6}$ for L (again, defined as the level of free TNF-α concentration), over the course of 3 hours we see linear decay towards a little over $4.6x10^{-6}$.

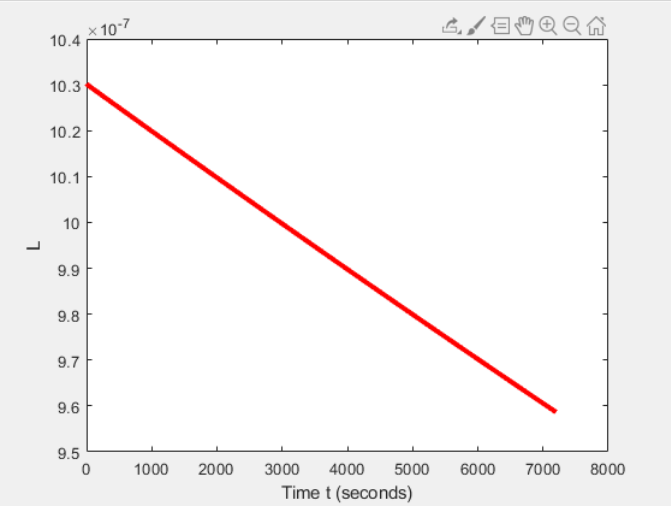


Etanercept

However, when we look at the Etanercept/Enbrel treatment model, we see something very unique, as we plot this over the course of 2 hours. This is because in the third hour the TNF-α forms receptor-ligand complexes. Our parameters are different as well, as we use
$k_{-a} = 7x10^{-4}, \delta c = 1.7x10^{-6}, k_{-1} = 5.5x10^{-4}, k_a = 7x10^{-2}$, with initial conditions:

L(0) = 0.000001030284012 , r(0) = 0 , A(0) = 0.000005011355717, C(0)= 0.000000000516620

Where our initial condition of $10.3x10^{-7}$ gradually declines towards a bit over $9.5x10^{-7}$, when regarding L.



Conclusion

Based on the three models that were presented above, we observed that the TNF-α levels uniquely decrease with each treatment. We found that from the three models, the sTNFR2 model decreases at the fastest rate compared to the other two models, where the sTNFR2 and Infliximab were plotted over the course of three hours. While the Etanercept (Enbrel) was plotted over the course of two hours. The effectiveness of the inhibitors towards the bioactivity of TNF-α, which demonstrates how it works to reduce and establish a new equilibrium, is on display here. Thus, with the new equilibria, the effects of RA are reduced. We note that inflammation and stiffness have a reduced progression until the treatments subside. Ultimately, the solution of our model is dependent on the initial conditions and conditions placed on our parameters to analyze the behavior of functions L(t), r(t), A(t), C(t).

Appendex

Attached are examples of the code we used, to make it work for all 3 models we simply have to change the initial conditions in y0, our time (in tspan), as well as the parameters we discussed in the report.

Etanercept/Enbrel

```
function ratsystem_sol
clear all
clc
tic
tspan = [0 7200];
y0 = [0.000001030284012 0 0.000005011355717 0.000000000516620]
[t,y] = ode45(@ratsystem, tspan, y0);
plot(t, y(:,1), 'r', 'Linewidth', 3)
xlabel('Time t (seconds)')
ylabel('L')
toc
function dydt = ratsystem(t,y)
dydt = zeros(4,1);
w1= 8*10^(-15);
Rtot = 1.5*10^(-10);
k1 = 1.7*10^7;
kneg1 = 5.5*10^(-4);
ka = 7*10^(-2);
knega = 7*10^(-4);
delta1 = 10^(-5);
epsilon = 6*10^(-4);
deltaa = -1.7*10^(-6);
wa = 10*w1;
deltac = 1.7*10^(-6);
v = epsilon - deltac;
dydt(1) = w1+(v*Rtot*y(2))-(k1*Rtot*(1-y(2))*y(1))+(kneg1*Rtot*y(2))-
(ka*y(1)*y(3))+(knega*y(4))-(delta1*y(1));
```

```
dydt(2) = (k1*(1-y(2))*y(1))-(kneg1*y(2))-(epsilon*y(2));
dydt(3) = wa-(ka*y(1)*y(3))+(knega*y(4))-(deltaa*y(3));
dydt(4) = (ka*y(1)*y(3)) - (knega*y(4)) - (deltac*y(4));
end
End
```

sTNFR2

```
function ratsystem_sol
clear all
clc
tic
tspan = [0 10800];
y0 = [0.0006503257844 0 0.003162212217, 0.000000065443]
[t,y] = ode45(@ratsystem, tspan, y0);
plot(t, y(:,1), 'r', 'Linewidth', 3)
xlabel('Time t (seconds)')
ylabel('L')
toc
function dydt = ratsystem(t,y)
dydt = zeros(4,1);
w1= 8*10^(-15);
Rtot = 1.5*10^(-10);
k1 = 1.7*10^7;
kneg1 = 5.5*10^(-4);
ka = 1.9*10^(4);
knega = 5.8*10^(-3);
delta1 = 10^(-5);
epsilon = 6*10^(-4);
deltaa = -1.7*10^(-6);
wa = 10*w1;
deltac = 2.3*10^(-5);
v = epsilon - deltac;
dydt(1) = w1+(v*Rtot*y(2))-(k1*Rtot*(1-y(2))*y(1))+(kneg1*Rtot*y(2))-
(ka*y(1)*y(3))+(knega*y(4))-(delta1*y(1));
dydt(2) = (k1*(1-y(2))*y(1))-(kneg1*y(2))-(epsilon*y(2));
dydt(3) = wa-(ka*y(1)*y(3))+(knega*y(4))-(deltaa*y(3));
dydt(4) = (ka*y(1)*y(3)) - (knega*y(4)) - (deltac*y(4));
end
end
```

Infliximab

```
function ratsystem_sol
clear all
clc
tic
tspan = [0 10800];
```

```
y0 = [0.000005146875300 0 0.00002509949845, 0.00000001936587]
[t,y] = ode45(@ratsystem, tspan, y0);
plot(t, y(:,1), 'r', 'Linewidth', 3)
xlabel('Time t (seconds)')
ylabel('L')
toc
function dydt = ratsystem(t,y)
dydt = zeros(4,1);
w1= 8*10^(-15);
Rtot = 1.5*10^(-10);
k1 = 1.7*10^7;
kneg1 = 5.5*10^(-5);
ka = 10^(-2);
knega = 10^(-4);
delta1 = 10^(-5);
epsilon = 6*10^(-4);
deltaa = -1.7*10^(-6);
wa = 10*w1;
deltac = 8.5*10^(-7);
v = epsilon - deltac;
dydt(1) = w1+(v*Rtot*y(2))-(k1*Rtot*(1-y(2))*y(1))+(kneg1*Rtot*y(2))-
(ka*y(1)*y(3))+(knega*y(4))-(delta1*y(1));
dydt(2) = (k1*(1-y(2))*y(1))-(kneg1*y(2))-(epsilon*y(2));
dydt(3) = wa-(ka*y(1)*y(3))+(knega*y(4))-(deltaa*y(3));
dydt(4) = (ka*y(1)*y(3)) - (knega*y(4)) - (deltac*y(4));
end
end
```

Reference

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[3] L. Matteucci, M. C. Nucci, Solution of a mathematical model for the treatment of rheumatoid arthritis, (2018)