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Research Article

Solution of a mathematical model for the treatment of rheumatoid arthritis

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Abstract

Rheumatoid arthritis is an autoimmune disease of unknown etiology that manifests as a persistent inflammatory synovitis and eventually destroys the joints. The immune system recognizes synovial cells as *not self* and consequently causes lymphocyte and antibody proliferation that is promoted by the pro-inflammatory cytokines, the most significant being tumor necrosis factor TNF-α. In the treatment of rheumatoid arthritis either monoclonal antibodies or soluble receptors are used to neutralize the TNF-α bioactivity, such as sTNFR2, Etanercept and Infliximab. In [M. Jit *et al.* Rheumatology 2005;44:323-331] a mathematical model that represents the TNF-α dynamics in the inflamed synovial joint within which locally produced TNF-α can bind to cell-surface receptors was proposed. It consists of four coupled ordinary differential equations, that were integrated numerically assuming a range of estimates of the key parameters. In this paper we complement the previous work by determining the general solution of those equations for specific conditions on the parameters. Then we characterize the behavior of TNF-α in the presence of different inhibitors and also evaluate the inhibitors effectiveness in the treatment of rheumatoid arthritis.

Keywords: `Rheumatoid arthritis treatment model, ordinary differential equations, general solution`

AMS subject classification: `92C50, 34A34, 34A05`

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that manifests as a persistent inflammatory synovitis and eventually destroys the joints. The cause of this disease is still unknown but it is hypothesized it results from an aberrant immune response to contact with an infectious agent in an individual who has a genetic predisposition. In RA there is an abnormal activation of T-helper cells in the synovial membrane which recognize antigens in association with synovium cells as *not self*. In this disease cytokines have a key role to promote inflammation. Cytokines are proteins that interact with specific receptors on target cells causing cellular proliferation, cellular survival, cellular differentiation [1]. When cytokine binds to a specific receptor it begins a signal transmission process within the target cell. This process is known as transduction. An increase of proinflammatory cytokines causes an increase of soluble receptors and anti-inflammatory cytokines so after a short period of time the system returns to equilibrium. Therefore in health conditions cytokines are important for the immune response integrity. In RA, the synovium has an increased number of T-helper lymphocytes $CD4+$ T_H1 and a diminished number of T-helper lymphocytes $CD4+$ T_H2. The inflammatory process is stimulated by the proinflammatory cytokines produced by T-helper lymphocytes T_H1. This effect is augmented by the inability of T-helper lymphocytes of type T_H2 to produce a sufficient quantity of anti-inflammatory cytokines. The resulting imbalance between pro-inflammatory cytokines and anti-inflammatory cytokines leads to a chronic inflammatory process that causes worsening serious joint damage [2]. The T-helper lymphocytes $CD4+$ T_H1 promote the proliferation of pro-inflammatory cytokines [3] such as tumor necrosis factor α (TNF-α) and interleukin 1 (IL-1). In RA it has been observed that the 40% of cells layer which covers synovial tissue expresses TNF-α and the 20% expresses IL-1 [4]. TNF-α is the major mechanism responsible for

the chronic inflammation, as evidenced by B cell proliferation with autoantibody[a] production. Thanks to molecular biotechnology, it has been possible to create in laboratory TNF-α inhibitors. The anti-TNF-α are based on the concept that the TNF-α becomes bioactive when it is bound to cell receptors in 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, although unfortunately this effect is not permanent.
The TNF-α inhibitors have been created in the form of soluble receptors such as Etanercept and sTNFR2 and in the form of chimeric monoclonal antibodies such as Infliximab. In 2005, a mathematical model was published in *Rheumatology* [5] based on the role of TNF-α in the therapy of RA. It represents TNF-α dynamics in receptor compartment in presence of inhibitors and it consists of four coupled ordinary differential equations that were integrated numerically assuming a range of estimates of the key parameters. In the present paper we analyse this model and solve it analytically for appropriate conditions on the parameters and initial conditions to study TNF-α behaviour and thus to predict the effectiveness of naturally produced sTNFR2, as well as two of the licensed treatments[b] Etanercept (Enbrel®) and Infliximab (Remicade®).
In Section 2 we describe the model and the qualitative analysis at equilibrium obtained by M. Jit *et al* in [5].
In Section 3 we describe in detail how to obtain the general solution of the system for specific conditions on the parameters.
In Section 4 we show the behavior of the obtained solution by using different values of the parameters, and different initial concentrations of free TNF-α.
The last Section contains some final remarks.

2. The model

In [5] a mathematical model has been developed in order to predict short-term and long-term clinical benefit by the administration of Etanercept, Infliximab and the naturally produced sTNFR2, , i.e.:

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

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

$$\frac{dA}{dt} = \omega_a - k_a L A + k_{-a} C - \delta_a A, \tag{3}$$

$$\frac{dC}{dt} = k_a L A - k_{-a} C - \delta_c C. \tag{4}$$

It represents TNF-α dynamics in the receptor compartment within which locally produced TNF-α can bind to cell-surface receptors. In [5] it was assumed that free TNF-α, with receptor compartment concentration L, can bind to cell-surface receptors, TNFR1 of total density R_{tot}, to form receptor-ligand complexes or to antibodies, with receptor compartment concentration A, to form antibody-antigen complexes with receptor compartment concentration C. In the model, r is the bound proportion to form receptor-ligand complexes and $1-r$ the unbound proportion; 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, and k_{-a} is the ligand-inhibitor dissociation rate. Internalization of bound receptors occurs at rate ϵ and the total receptor density R_{tot} is assumed constant. The constant ω_1 represents the production rate of TNF-α which is the stimulus that maintains the inflammatory response, while ω_a represents the rate at which antibodies

[a] Autoantibody is an immunoglobulin that reacts against self antigens
[b] Etanercept and Infliximab were approved by the Food and Drug Administration in 1998, and the European Medicine Agency in 2000 and 1999, respectively [6].

are introduced into the receptor compartment. Clearance processes from the receptor compartment are assumed to be first-order with rates δ_1 for free TNF-α, δ_a for free antibody, and δ_c for antibody−antigen complexes. The constant ν measures the strength of a possible stimulated autocrine response which up-regulates 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. Thanks to this model it is possible to study the interactions between TNF-α and the specific ligand-binding inhibitor.
The steady state of the system is represented by a production of TNF- α equal to zero, which implies that when the exogenous production rate ω_1 is different from zero this is indicative of the disease state. 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.
This equilibrium is stable if the autocrine response is not too large, i.e. when: $\nu < \epsilon + \delta_1 K_1$ where $K_1 = \dfrac{k_{-1} + \epsilon}{R_{tot} k_1}$.
By using the following estimated parameters:

$$\omega_1^{eq} = 8 \times 10^{-15} M s^{-1},\ k_1 = 1.7 \times 10^{7} M s^{-1},\ k_{-1} = 5.5 \times 10^{-4} s^{-1},$$

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

in [5] it was proven that the zero state will be stable if $\nu \leq \epsilon$ 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 $\nu \geq \epsilon + \delta_1 K_1$, and in this case TNF-$\alpha$ production is maintained from autocrine action only.
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.
Moreover, in [5] it was found that all three inhibitors reduce the concentration of total bioactive TNF-α leading the system to a new lower equilibrium level if the following particular estimates of parameters are taken into consideration, namely

(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 synovial fluid, they immediately act on TNF-α 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 sequestred.
The bioactivity is different for the three inhibitors and it depends also on the period of time considered since administration.
The analyzed model contains certain assumptions which simplify it.
Repeated exposure to antibodies can program the body to produce endogenous neutralizing antibodies which lead to a decrease of the therapeutic activity after a certain period of time. When this develops, it is referred to as the anti-human chimeric response (HACA). This response has been observed with continued Infliximab therapy; however, as Infliximab is not a sole therapy, but combined with methotrexate, the HACA response is not considered clinically significant for this inhibitor. As regards the treatment with Etanercept, the HACA response occurs sporadically and for a small number of patients. Another simplification was to consider ω_a constant. This rate depends on the different concentrations between the serum and the receptor compartment which depends upon the pharmacokinetic properties of the in-

hibitors following their administration, but since the model is focused on the dynamics between receptor, ligand and inhibitor for a relatively short time, one may consider the distribution of the treatment in a nearly steady state, and thus assume ω_a constant. Another simplification is to ignore the dispersion of endogenous TNFR2 by monocytes. The body is capable of producing endogenous second type receptor for TNF-α, but the concentration in synovial fluid is two orders of magnitude less compared with exogenous therapeutic levels of anti-TNF-α concentrations, and therefore it is not considered in the model.

3. Resolution of the model

The non-linear model (1)-(4) consists of four first-order ordinary differential equations. Through algebraic manipulations and with appropriate conditions on the parameters we reduce the system to a system of linear equations. Since the non-linear term LA appears in (3) and (4), by adding (3) and (4) we obtain the following differential equation :

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

where there are linear terms only. By introducing a new variable:

$$u_1 = A + C,$$

and by replacing

$$C = u_1 - A, \tag{6}$$

into equation (5) we obtain the following differential equation:

$$-\frac{du_1}{dt} - \delta_a A - \delta_c u_1 + \delta_c A + \omega_a = 0. \tag{7}$$

By imposing the following conditions on the parameters (c.p):
(c.p.1)

$$\delta_a = \delta_c,$$

and replacing them into equation (7), we obtain the following linear differential equation:

$$\frac{du_1}{dt} = -\delta_c u_1 + \omega_a, \tag{8}$$

and by integrating it we obtain:

$$u_1 = \frac{\omega_a}{\delta_c} + A_1 e^{-\delta_c t}, \tag{9}$$

where A_1 is a constant which depends on the initial conditions[c]. Then we multiply equation (2) by R_{tot}, adding equation (1) in order to obtain the following equation:

$$-\frac{dL}{dt} - \frac{dr}{dt}R_{tot} - \delta_1 L - \epsilon R_{tot} r - k_a LA + k_{-a} u_1 - k_{-a} A + \nu R_{tot} r + \omega_1 = 0, \tag{10}$$

where the non-linear term LA appears. Combining (3) with (10) yields the following differential equation:

$$-\frac{dL}{dt} - \frac{dr}{dt}R_{tot} + \frac{dA}{dt} - \delta_1 L + \delta_c A - \epsilon R_{tot} r + \nu R_{tot} r + \omega_1 - \omega_a = 0, \tag{11}$$

[c] $A_1 = u_1(0) - \frac{\omega_a}{\delta_c}$.

without non-linear terms. By introducing a new variable:

$$u_3 = A - R_{tot}r - L,$$

and by replacing:

$$A = u_3 + R_{tot}r + L, \tag{12}$$

into equation (11) we obtain the following differential equation:

$$\frac{du_3}{dt} - \delta_1 L + \delta_c u_3 + \delta_c R_{tot} r + \delta_c L - \epsilon R_{tot} r + \nu R_{tot} r + \omega_1 - \omega_a = 0. \tag{13}$$

By imposing the following conditions on the parameters:
(c.p.2)

$$\epsilon = \delta_c + \nu,$$

we obtain a differential equation where r does not appear:

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

Through a further condition:
(c.p.3)

$$\delta_1 = \delta_c,$$

we obtain the following linear differential equation:

$$\frac{du_3}{dt} + \delta_c u_3 + \omega_1 - \omega_a = 0, \tag{14}$$

and can integrate it, i.e.:

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

where A_2 is a constant which depends on initial conditions[d]. We remark that the condition **(c.p.3)** implies that $\delta_1 = \delta_a$. The substitutions (6) and (12) into equation (1) yield the following equation:

$$-\frac{dL}{dt} - \delta_c L + k_1 R_{tot} L r - k_1 R_{tot} L - k_a u_3 L - k_a R_{tot} L r - k_a L^2 - k_{-a} L +$$

$$+ k_{-1} R_{tot} r - k_{-a} u_3 + k_{-a} u_1 - k_{-a} R_{tot} r + \nu R_{tot} r + \omega_1 = 0,$$

where the non-linear terms Lr and L^2 appear. By imposing the following condition on the parameters:
(c.p.4)

$$k_1 = k_a,$$

we eliminate the non-linear term Lr, i.e.:

$$-\frac{dL}{dt} - \delta_c L - k_a u_3 L - k_a R_{tot} L - k_a L^2 - k_{-a} L + + k_{-1} R_{tot} r - k_{-a} u_3 + k_{-a} u_1 - k_{-a} R_{tot} r + \nu R_{tot} r + \omega_1 = 0,$$

and by imposing a further condition:
(c.p.5)

$$\nu = k_{-a} - k_{-1},$$

[d] $A_2 = u_3(0) - \frac{\omega_a - \omega_1}{\delta_c}$.

we eliminate the dependence from r:

$$-\frac{dL}{dt} - \delta_c L - k_a u_3 L - k_a R_{tot} L - k_a L^2 - k_{-a} L - k_{-a} u_3 + k_{-a} u_1 + \omega_1 = 0. \tag{16}$$

The equation obtained is a Riccati equation. By the transformation which linearizes it ie:

$$L = \frac{1}{k_a u_4} \frac{du_4}{dt}, \tag{17}$$

the equation (16) and (2) become the following:

$$\frac{d^2 u_4}{dt^2} + \frac{du_4}{dt}(\delta_c + k_a u_3 + k_a R_{tot} + k_{-a}) + k_a u_4 (k_{-a} u_3 - k_{-a} u_1 - \omega_1) = 0, \tag{18}$$

$$\frac{1-r}{u_4} \frac{du_4}{dt} - \frac{dr}{dt} - (\delta_c + k_{-a}) r = 0. \tag{19}$$

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:

$$r = 1 + \frac{u_2}{u_4} \tag{20}$$

where u_2 is a new dependent variable of time t. By applying the transformation (20) to equation (19), we obtain:

$$\frac{du_2}{dt} = -(\delta_c + k_{-a})(u_2 + u_4), \tag{21}$$

that, once the general solution of (18) is determined, can be integrated as:

$$u_2 = \left(A_3 - (\delta_c + k_{-a}) \int e^{(\delta_c + k_{-a})t} u_4 \, dt \right) e^{-(\delta_c + k_{-a})t}, \tag{22}$$

where A_3 is a constant which depends on initial conditions[e]. Thanks to transformation (17) the equation (18) is linear and with the aid of MAPLE 16 we obtain its general solution to be:

$$u_4 = e^{\frac{Pt}{2\delta_c}} (C_1 M_{k,m}(z) + C_2 U_{k,m}(z)) \tag{23}$$

where $M_{k,m}(z)$ e $U_{k,m}(z)$ are KummerM and KummerU functions[f], respectively, C_1 e C_2 are constants which depends on initial conditions[g], and in particular:

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

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

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

[e] $A_3 = u_2(0)$.

[f] More information about those functions can be found in classical textbooks, e.g., [8] and [9].

[g] Replacing the solution (23) in (17), the two constants C_1 e C_2 reduce to one, say $C_1 = 1$, $C_2 = A_4$.

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

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

Summarizing:

$$u_1(t) = \frac{\omega_a}{\delta_c} - \frac{\omega_a - u_1(0)\delta_c}{\delta_c}e^{-\delta_c t}, \tag{24}$$

$$u_2(t) = \left(u_2(0) - (\delta_c + k_{-a})\int_0^t e^{(\delta_c + k_{-a})t}u_4(t)\,\mathrm{d}t\right)e^{-(\delta_c + k_{-a})t}, \tag{25}$$

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

$$u_4(t) = e^{\frac{Pt}{2\delta_c}}(C_1M_{k,m}(z) + C_2U_{k,m}(z)). \tag{27}$$

By replacing (27) in (17) we obtain L, by replacing (27) and (25) in (20) we obtain r, by replacing (17), (20) and (26) in (12) we obtain A, and finally by replacing (24) in (6) we obtain C.

4. The behaviour of TNF-α

To determine the effectiveness of three inhibitors to reduce the concentration of bioactive TNF-α, we analyzed the behaviour of L in the case of naturally produced sTNFR2, the administration of Infliximab and that of Etanercept.
A non-zero concentration of free TNF-α is indicative of the disease state and it is represented by the indicator L.
In RA there are increased levels of TNF-α causing synovial inflammation and joint destruction. We assume that at time $t = 0$ the concentration of free TNF-α is higher than zero. In presence of inhibition the rates ω_1 and ω_a are higher than zero, and the initial condition $L(0)$ is higher than zero.
In the following Figures and Tables, time t is represented in hours h, and L is expressed in molarity M. We use the same values of some of the parameters given in [5], i.e.:

$$R_{tot} = 1.5 \times 10^{-10}M, \omega_1 = 8 \times 10^{-15}Ms^{-1}, \omega_a = 10\omega_1.$$

In the case of the soluble receptor sTNFR2, by assuming the following values of the parameters:

$$k_{-a} = 5.8 \times 10^{-3}s^{-1}, \delta_c = 2.3 \times 10^{-5}s^{-1}, k_{-1} = 5.5 \times 10^{-4}s^{-1}, k_a = 1.9 \times 10^{-4}M^{-1}s^{-1},$$

and by imposing the following initial conditions **(i.c.1)**:

$$u_1(0) = 0.003162277660, u_3(0) = 0.002511886432, L(0) = 0.0006503257844,$$

we obtain a decrease of L from an original value of 0.0006503257844 M. As we observe from Table 1, a decrease of L corresponds to an increase on the proportion of TNF-α, which binds to form the receptor-ligand complexes, namely the increasing trend of r assures the ability of sTNFR2 receptor to bind free TNF-α. In fact, as seen in Table 1, after 3 hours about 72.8 % of free TNF-α is bound to form the receptor-ligand complexes.

Figure 1 shows a decrease of free TNF-α concentration L from an original value of 0.0006503257844 M to a value of 0.0005072829288 M in the time-interval of 3 hours.
In the case of treatment with Infliximab, by assuming the following values of the parameters:

$$k_{-a} = 10^{-4}s^{-1}, \delta_c = 8.5 \times 10^{-7}s^{-1}, k_{-1} = 5.5 \times 10^{-5}s^{-1}, k_a = 10^{-2}M^{-1}s^{-1},$$

Table 1. L, r, A, and C in the first 3 hours of naturally produced sTNFR2 with **(i.c.1)**.

t(h)	L	r	A	C
0	0.0006503257844	0	0.003162212217	0.000000065443
0.1	0.0006449626238	0.0016224270	0.003136136531	0.0000000656
0.2	0.0006396352483	0.0071973274	0.003110267422	0.000000074195
0.3	0.0006343792099	0.0162816543	0.003084639035	0.000000055308
0.4	0.0006291265219	0.0287207100	0.003059181985	0.000000076567
0.5	0.0006239503538	0.0443694710	0.003033968058	0.000000064442
0.6	0.0006188115818	0.0630175213	0.003008956753	0.000000057705
0.7	0.0006136799027	0.0844088194	0.002984116408	0.000000086301
0.8	0.0006086498612	0.1082578305	0.002959540214	0.00000005534
0.9	0.0006036311065	0.1342592855	0.002935136482	0.000000054822
1	0.0005986468766	0.1620971497	0.002910927120	0.000000061168
1.1	0.0005937006246	0.1914516552	0.002886914263	0.000000070582
1.2	0.0005888062827	0.2220070039	0.002863110535	0.000000068795
1.3	0.0005839660073	0.2534565945	0.002839516798	0.000000053313
1.4	0.0005791243625	0.2855087181	0.002816076329	0.000000079241
1.5	0.0005743580597	0.3178903427	0.002792864566	0.000000069534
1.6	0.0005696277675	0.3503502206	0.002769840909	0.000000063201
1.7	0.0005649373705	0.3826608159	0.002747007991	0.00000005603
1.8	0.0005602507946	0.4146195437	0.002724328496	0.000000083771
1.9	0.0005556243561	0.4460488508	0.002701857504	0.000000089792
2	0.0005510533202	0.4767964193	0.002679589057	0.00000007851
2.1	0.0005465318725	0.5067339724	0.002657516128	0.000000055424
2.2	0.0005420263670	0.5357558385	0.002635603867	0.00000005387
2.3	0.0005375639572	0.5637779766	0.002613878235	0.000000046384
2.4	0.0005331128105	0.5907358050	0.002592306215	0.000000064493
2.5	0.0005287364613	0.6165823180	0.002570950167	0.000000044360
2.6	0.0005243601906	0.6412865098	0.002549734211	0.000000060399
2.7	0.0005200508984	0.6648314673	0.002528724088	0.000000045415
2.8	0.0005157498543	0.6872121419	0.002507859926	0.000000057840
2.9	0.0005115396198	0.7084342107	0.002487223150	0.000000014818
3	0.0005072829288	0.7285119747	0.002466675367	0.000000053325

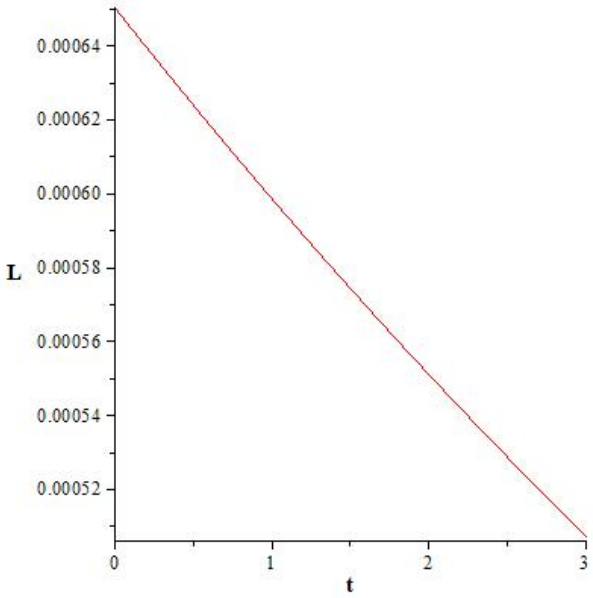

Figure 1. (sTNFR2) For $0 \leq t \leq 3$ h, L decreases.

and by imposing the following initial conditions **(i.c.2)**:

$$u_1(0) = 0.00002511886432, u_3(0) = 0.00001995262315, L(0) = 0.0000051468753,$$

we obtain different inhibition levels as it is shown in Table 2.

Table 2. L, r, A, and C in the first 3 hours since the administration of Infliximab with **(i.c.2)**.

t(h)	L	r	A	C
0	0.000005146875300	0	0.00002509949845	0.00000001936587
0.1	0.000005145302446	0.0000182549	0.00002509184695	0.00000001936097
0.2	0.000005143730223	0.0000359090	0.00002508419793	0.00000001935593
0.3	0.000005142167698	0.0000532412	0.00002507656048	0.00000001934166
0.4	0.000005140590593	0.0000702170	0.00002506891030	0.00000001934247
0.5	0.000005139030144	0.0000870523	0.00002506127863	0.00000001932710
0.6	0.000005137464484	0.0001037944	0.00002505364362	0.00000001931742
0.7	0.000005135894744	0.0001205959	0.00002504600638	0.00000001931230
0.8	0.000005134336395	0.0001374904	0.00002503838238	0.00000001929628
0.9	0.000005132757054	0.0001546109	0.00002503073925	0.00000001930173
1	0.000005131197826	0.0001720343	0.00002502311811	0.00000001928753
1.1	0.000005129626867	0.0001898363	0.00002501548707	0.00000001928556
1.2	0.000005128070813	0.0002080288	0.00002500787278	0.00000001926917
1.3	0.000005126507102	0.0002267821	0.00002500025270	0.00000001926092
1.4	0.000005124940206	0.0002460353	0.00002499263130	0.00000001925631
1.5	0.000005123373556	0.0002659645	0.00002498501198	0.00000001925196
1.6	0.000005121811298	0.0002864920	0.00002497739890	0.00000001924370
1.7	0.000005120255935	0.0003077783	0.00002496979459	0.00000001922901
1.8	0.000005118690798	0.0003298036	0.00002496218234	0.00000001922458
1.9	0.000005117129944	0.0003526624	0.00002495457621	0.00000001921637
2	0.000005115564003	0.0003762839	0.00002494696687	0.00000001921369
2.1	0.000005114009980	0.0004008639	0.00002493937128	0.00000001919959
2.2	0.000005112449221	0.0004263138	0.00002493177081	0.00000001919270
2.3	0.000005110882715	0.0004526532	0.00002492416645	0.00000001919203
2.4	0.000005109327717	0.0004799796	0.00002491657543	0.00000001918035
2.5	0.000005107770519	0.0005082899	0.00002490898406	0.00000001917134
2.6	0.000005106214185	0.0005376177	0.00002490139540	0.00000001916195
2.7	0.000005104653360	0.0005679707	0.00002489380410	0.00000001915752
2.8	0.000005103097009	0.0005993194	0.00002488621911	0.00000001914910
2.9	0.000005101538985	0.0006317739	0.00002487863429	0.00000001914284
3	0.000005099981816	0.0006652506	0.00002487105219	0.00000001913619

Figure 2 shows a decrease of free TNF-α concentration L from an original value of 0.0000051468753 M to a value of 0.000005099981816 M.
After 3 hours, about 0.07% of free TNF-α is bound to form the receptor-ligand complexes.
Figure 3 shows a decrease of L from an original value of 0.0000051468753 M to a value of 0.000002474282538 M after ten days, while about 88.8% of free TNF-α is bound to form the receptor-ligand complexes.

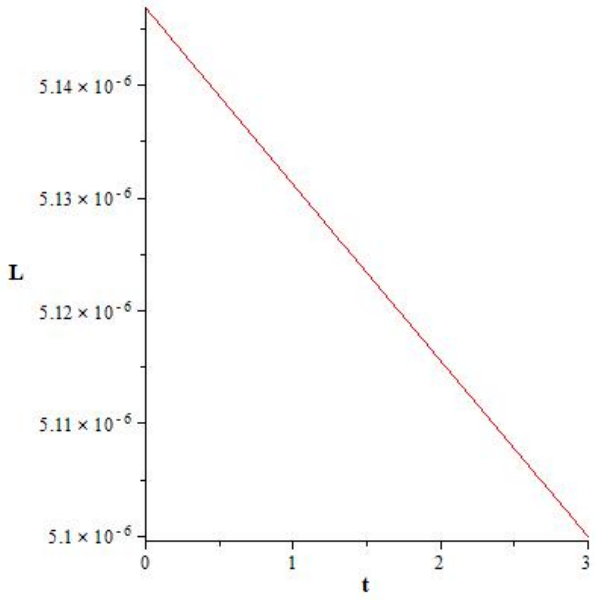

Figure 2. (Infliximab) In the time-interval $0 \leq t \leq 3$ h, L decreases.

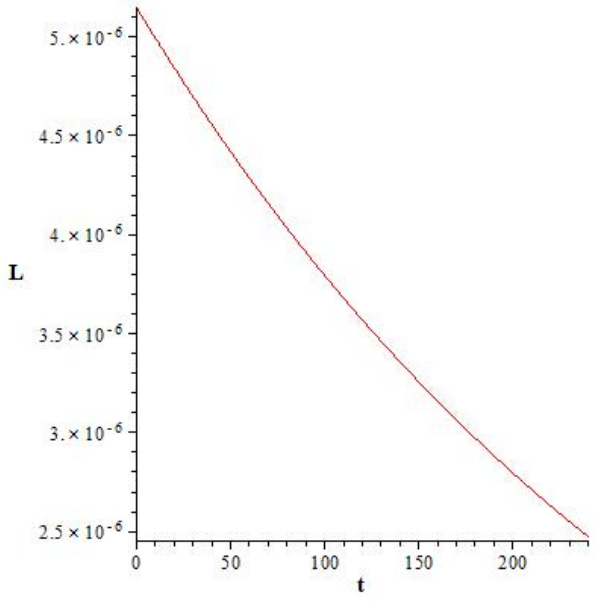

Figure 3. (Infliximab) In the time-interval of ten days, L decreases.

In case of Etanercept administration, by assuming the following values of the parameters:

$$k_{-a} = 7 \times 10^{-4} s^{-1}, \delta_c = 1.7 \times 10^{-6} s^{-1}, k_{-1} = 5.5 \times 10^{-4} s^{-1}, k_a = 7 \times 10^{-2} M^{-1} s^{-1},$$

and by imposing the following initial conditions **(i.c.3)**:

$$u_1(0) = 0.000005011872336, u_3(0) = 0.000003981071706, L(0) = 0.000001030284012,$$

a decrease of free TNF-α concentration is observed as it results from Table 3 and Table 4.

Figure 4 shows a decrease of free TNF-α concentration L from an original value of 0.000001030284012 M to a value of 0.0000010116367 M. After 3 hours, about 2.4% of free TNF-α is bound to form the receptor-ligand complexes. After four days since administration of Etanercept, about 99.99% of free TNF-α is bound to form the receptor-ligand complexes, and L decreases from an original value of 0.000001030284012 M to a value of 0.0000005747512787 M.

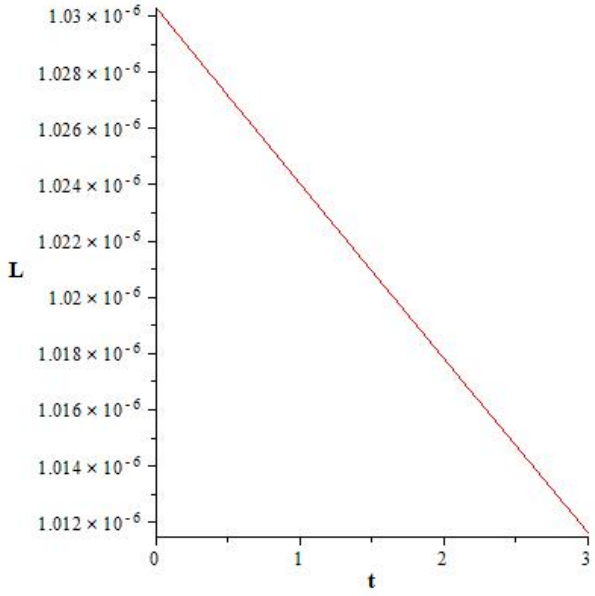

Figure 4. (Etanercept) For $1 \leq t \leq 3$ h, L decreases.

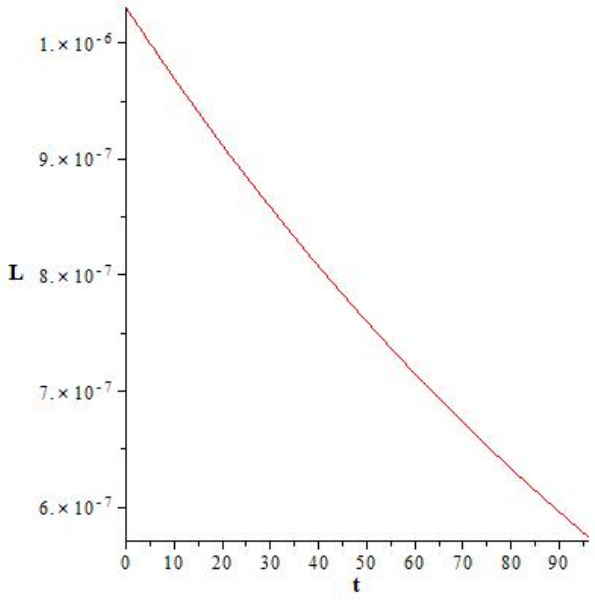

Figure 5. (Etanercept) In the time-interval of four days, L decreases.

5. Final remarks

From an initial condition $L(0) = 0.0006503257844$ M, and with appropriate conditions on the parameters we have shown the effectiveness of inhibitors sTNFR2 to bind free TNF-α. After three hours, the free TNF-α reaches a level equal to approximately 0.0005072829288 M. This prove the effectiveness of this inhibitor to bind free TNF-α and therefore to reduce the inflammation. The inflammatory process causing damage to the synovial cells is halted once the free TNF-α level is reduced.
In the case of treatment with Infliximab for an initial condition $L(0) = 0.0000051468753$ M and appropriate conditions on the parameters we obtain a decrease of free TNF-α. After 3 hours, L is about equal to 0.000005099981816 M and after ten days is more than halved. This prove the effectiveness of this inhibitor to reduce the inflammation.
In the case of treatment with Etanercept for an initial condition $L(0) = 0.000001030284012$ M and appro-

Table 3. L, r, A, and C in the first 2 hours since the administration of Etanercept with **(i.c.3)**.

t(h)	L	r	A	C
0	0.000001030284012	0	0.000005011355717	0.000000000516620
0.1	0.000001029649833	0.0000290073	0.000005008311783	0.000000000523018
0.2	0.000001029024336	0.0000829492	0.000005005278011	0.000000000521112
0.3	0.000001028403282	0.0001817970	0.000005002250161	0.000000000515141
0.4	0.000001027775598	0.0003357788	0.000004999217162	0.000000000516176
0.5	0.000001027151445	0.0005500969	0.000004996189175	0.000000000514053
0.6	0.000001026523863	0.0008265374	0.000004993159238	0.000000000515734
0.7	0.000001025899711	0.0011648176	0.000004990134211	0.000000000514358
0.8	0.000001025275625	0.0015633417	0.000004987110728	0.000000000513291
0.9	0.000001024651517	0.0020212561	0.000004984088699	0.000000000512618
1	0.000001024030922	0.0025361637	0.000004981071659	0.000000000508807
1.1	0.000001023409083	0.0031068307	0.000004978054850	0.000000000506612
1.2	0.000001022773922	0.0037318869	0.000004975026193	0.000000000518113
1.3	0.000001022157669	0.0044103031	0.000004972017916	0.000000000511080
1.4	0.000001021532492	0.0051410043	0.000004969002185	0.000000000513345
1.5	0.000001020918190	0.0059231658	0.000004965998801	0.000000000505108
1.6	0.000001020296307	0.0067563093	0.000004962989305	0.000000000504824
1.7	0.000001019670685	0.0076400858	0.000004959977538	0.000000000508653
1.8	0.000001019051121	0.0085741432	0.000004956973297	0.000000000506797
1.9	0.000001018426057	0.0095578397	0.000004953965023	0.000000000510812
2	0.000001017809555	0.0105916184	0.000004950966776	0.000000000506639

Table 4. L, r, A, and C from 2 to 3 hours since the administration of Etanercept with **(i.c.3)**.

t(h)	L	r	A	C
2.1	0.000001017196455	0.0116746734	0.000004947973395	0.000000000499437
2.2	0.000001016567171	0.0128072989	0.000004944965295	0.000000000508789
2.3	0.000001015951386	0.0139891429	0.000004941972156	0.000000000505015
2.4	0.000001015332513	0.0152198975	0.000004938977392	0.000000000504700
2.5	0.000001014717770	0.0164998435	0.000004935988218	0.000000000500626
2.6	0.000001014101366	0.0178285302	0.000004932998843	0.000000000498586
2.7	0.000001013484031	0.0192055075	0.000004930009997	0.000000000497846
2.8	0.000001012867765	0.0206310236	0.000004927023679	0.000000000496408
2.9	0.000001012250497	0.0221048864	0.000004924037815	0.000000000496343
3	0.000001011636700	0.0236262714	0.000004921056879	0.000000000493178

priate conditions on the parameters we obtain a decrease of free TNF-α from its original value confirming the effectiveness of this inhibitor. After four days L reaches a value of 0.0000005747512787 M, about the half of its original value.
A decrease of L corresponds to an increase of the bound proportion r. The increasing trend of r assures the ability of sTNFR2 receptor to bind free TNF-α to form the receptor-ligand complexes.

We note that the model exhibits the following simplifications:

1) The human anti-chimeric antibody (HACA) response that cause a reduction on effectiveness of the inhibitors is not considered [10], [11].

2) The effects known as adverse reactions such as tuberculosis due to the use of TNF-α inhibitors is not considered.

3) The behaviour of TNF-α is isolated from other cytokines because TNF-α is prevalent in the inflammatory response.

Finding an analytic solution for the model which describes the dynamics of TNF-α in receptor com-

partment (1)-(4) allowed us to analyze the behavior of functions $L(t)$, $r(t)$, $A(t)$, $C(t)$ at different initial conditions and for specific conditions on the parameters.

It is important to remark that the solution depends on initial conditions.
The resolution of the model confirmed the results on effectiveness of inhibitors sTNFR2, Etanercept and Infliximab in the neutralization of the proinflammatory action exerted by the TNF-α in the treatment of RA.

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