Approximate Equilibria for a T Cell and Treg Model

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Abstract: We analyse a model of immune response by T cells (CD4), where regulatory T cells (Tregs) act by inhibiting IL-2 secretion. We introduced an asymmetry reflecting that the difference between the growth and death rates can be higher for the active T cells and the active Tregs than for the inactive T cells and inactive Tregs. This asymmetry mimics the presence of memory T cells. In this paper we start by analysing the model in the absence of Tregs. We obtain an explicit formula that gives approximately the antigenic stimulation of T cells from the concentration of Tregs. Afterwards, we present an explicit formula that describes approximately the balance between the concentration of T cells and the concentration of Tregs; and an explicit formula that relates approximately the antigenic stimulation of T cells, the concentration of T cells and the concentration of Tregs. For our parameter values, the relation between the antigenic stimulation of T cells and the concentration of T cells is an hysteresis that is unfold when some of the parameters are changed. We also consider a linear tuning between the antigenic stimulation of T cells and the antigenic stimulation of Tregs. Again, we have obtained an explicit formula relating approximately the antigenic stimulation of T cells, the concentration of T cells and the concentration of Tregs. With it, we can explain the appearance of an isola and a transcritical bifurcation.

Keywords: Equilibria, hysteresis, bifurcation, ODE model, immunology, T cells, Tregs, asymmetry, death rates.

This paper is dedicated to the memory of Professor José Sousa Ramos.

1 Introduction

The immune system protects the host from pathogen invasion. During such an invasion, T cells specific to the antigen proliferate and act to remove the pathogen. However, the immune system can erroneously target self antigens (autoimmunity) and cause tissue damage and death. Regulatory T cells, or Tregs, are a fundamental component of the T cell repertoire, being generated in the thymus under positive selection by self peptides [6]. The Treg repertoire is as diverse as conventional T cells [6] and performs vital immune suppressive functions. Removal of Tregs, e.g. by (cell sorted) adoptive transfer experiments, causes a variety of autoimmune disorders in rodents, whilst many autoimmune diseases can be associated with a misregulation of Tregs, e.g. IPEX [12].

Under exposure to their specific antigen, conventional T cells are activated, leading to secretion of growth cytokines (predominantly interleukine 2, denoted IL-2), and expression of the interleukine 2 receptor which triggers cytokine driven proliferation. However, in the presence of active Tregs, the growth of conventional T cells is inhibited. Part of this growth inhibition is the inhibition of IL-2 secretion by T cells [13], [15]. Further, most studies indicate that regulation is not T cell specific, i.e. Tregs inhibit all conventional T cells independent of their antigen specificity [16], although a different report suggests the contrary [14]. Tregs clearly function to limit the autoimmune responses with a delicate balance between appropriate immune activation and immune response suppression being achieved.

How such a balance is established and controlled is the central focus of the papers [1], [2], [3], [4]. For a review see [10] and references within. We observe that T cell proliferation through cytokines already has a control structure: cytokine driven growth exhibits a quorum

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population size threshold [5]. For low antigenic stimulation b of T cells, only one stable equilibria is found characterized by low concentrations of T cells, thus corresponding to an controlled state. For high antigenic stimulation b of T cells, again only one stable equilibria is found, this time corresponding to an immune response state, since the concentration of T cells is high, close to the capacity of T cells. For intermediate values of the antigenic stimulation b of T cells, between two catastrophe points b_L and b_H, two stable equilibria are found, a controlled and an immune response state. Furthermore, an unstable equilibria is also present. If the antigenic stimulation rises above the threshold b_H, control is lost and autoimmunity arises. Note that even if the antigenic stimulation level b falls to the original value, at which control was originally achieved, control may not be reacquired. Control is only attained if stimulation falls below the second threshold b_L. This phenomena, termed hysteresis, is common in many physical and biological systems.

We propose in [1] that Tregs locally adjust these thresholds by inhibiting IL-2 secretion. The immune response-suppression axis is then a balance between the local numbers of activated T cells (e.g. from a pathogen encounter) and activated Tregs. In [4] we introduce an asymmetry reflecting that the difference between the growth and death rates can be higher for the active T cells and the active Tregs than for the inactive T cells and inactive Tregs. This asymmetry can be explained by the effect of memory T cells. The memory T cells last longer than the other T cells and react more promptly to their specific antigen [11]. This results in a positive correlation between the antigenic stimulation and the difference between the growth rate and the death rate of T cells. Hence, this asymmetry brings up the relevance of the antigenic stimulation of Tregs in the control of the local Treg population size [4]. As a result, under homeostasis, a larger antigenic stimulation of Tregs results in a larger Treg population size. We observe in [4] that there is a direct association between the antigenic stimulation of Tregs and the thresholds b_L and b_H of antigenic stimulation of T cells. Therefore, by adjusting the level of self-antigenic stimulation of T cells to different levels, organs can have different levels of protection against the development of an (auto-)immune response by T cells.

We will study the relation between the antigenic stimulation a of Tregs and the antigenic stimulation b of T cells, both being presented by antigen presenting cells (APC), such as dendritic cells [7]. For simplicity, we analyse a linear tuning between these stimuli as in [4], with the slope parameter modeling the effect of the antigen presenting cells (APC). Changing the slope parameter reveals the presence of an isola. Additionally, a transcritical bifurcation occurs when the isola merges with the hysteresis. [4]. This transcritical bifurcation may give rise to two alternative scenarios, depending on the rate of increase of the antigenic stimuli: in one case the appearance of autoimmune responses (fast increase) and

in another case the suppression of the immune responses (slow increase) [10].

In Section 2, we present our immune response model as a set of five ordinary differential equations. The approximate equilibria of the model are exhibited in Section 3, where we analyse the model in the absence of Tregs, presenting an explicit formula for the approximate value of the antigenic stimulation of T cells given the concentration of T cells. Furthermore, we analyse the model in the presence of Tregs and we show an approximate formula that yields the balance between the concentration of T cells and the concentration of Tregs. We also analyse how both concentrations are related to the approximate value of the antigenic stimulation of T cells. In Section 4, we consider a tuning between the antigenic stimuli and we obtain an analytic expression with the approximate relation between the antigenic stimulation of T cells, the concentration of T cells and the concentration of Tregs. We discuss the results in Section 5.

2 Theory

There are a number of different (CD4) T cell regulatory phenotypes reported; we use a model of Tregs that are currently identified as $CD25^+$ T cells, although this is not a definitive molecular marker. At a genetic level, these Tregs express Foxp3, a master regulator of the Treg phenotype inducing CD25, CTLA-4 and GITR expression, all correlating with a suppressive phenotype [12].
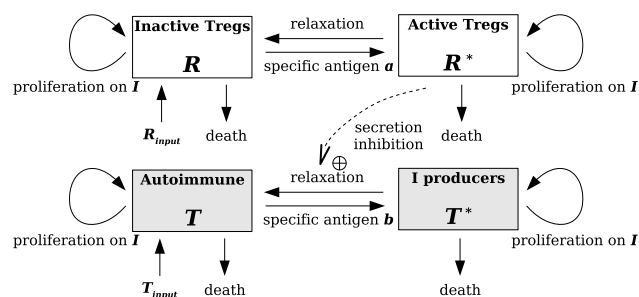

Fig. 1: Model schematic showing growth, death and phenotype transitions of the Treg populations R, R^*, and autoimmune T cell T, T^* populations. Cytokine dynamics are not shown: IL-2 is secreted by activated T cells T^* and adsorbed by all the T cell populations equally. Reproduced from [4].

Our model from [4] uses a population of Tregs and conventional T cells with processes shown schematically in Figure 1. Both populations require antigenic stimulation for activation. Levels of antigenic stimulation

are denoted a and b for Tregs and conventional T cells respectively. Tregs are activated by self antigens from an inactive state, denoted R, to an active state R^*. The IL-2 secreting T cells are denoted T^* and the non secreting T cells are denoted T. On activation conventional T cells secrete IL-2 and acquire proliferative capacity in the presence of IL-2. Tregs also proliferate in the presence of IL-2 although less efficiently than normal T cells [15], and they do not secrete IL-2. Finally, we include an influx of (auto) immune T cells into the tissue (T_{input}) and Tregs (R_{input}), which can represent T cell circulation or naive T cell input from the thymus.

The model consists of a set of five ordinary differential equations. We have a compartment for each T cell population (inactive Tregs R, active Tregs R^*, non secreting T cells T, secreting activated T cells T^*) and interleukine 2 density I:

$$\frac{dR}{dt} = (\varepsilon\rho I - \beta(R + R^* + T + T^*) - d_R)R$$
$$+\hat{k}(R^* - aR) + R_{input},$$

$$\frac{dR^*}{dt} = (\varepsilon\rho I - \beta(R + R^* + T + T^*) - d_{R^*})R^*$$
$$-\hat{k}(R^* - aR),$$

$$\frac{dT}{dt} = (\rho I - \beta(R + R^* + T + T^*) - d_T)T$$
$$+k(T^* - bT + \gamma R^* T^*) + T_{input},$$

$$\frac{dT^*}{dt} = (\rho I - \beta(R + R^* + T + T^*) - d_{T^*})T^*$$
$$-k(T^* - bT + \gamma R^* T^*),$$

$$\frac{dI}{dt} = \sigma(T^* - (\alpha(R + R^* + T + T^*) + \delta)I).$$

The new parameters are in Table 1 and the other ones are in [1].

The model studied in this paper keeps the basic properties of the immune response by T cells, controlled by Tregs, that were present in [1] and [2]. The main distinction of this model is the asymmetry in the difference between the growth and death rates modeled as in [3], [4] and [10]. With this kind of asymmetry present for the T cells, an increase in the antigenic stimulation of T cells results in an increase in the population of T cells caused both by the increase in cytokine secretion and by the decrease in the average death rate of T cells. Furthermore, the asymmetry improves the dynamic behaviour of the model (introduced in [1]), as shown previously in [3] and [4].

3 Equilibria of the model

In a ODE model, the equilibria, stable or unstable, is the set of points where all the derivatives vanish. When the Jacobian matrix of the steady state has all eigenvalues with negative real parts, we have a stable equilibria. If at

Table 1: New parameters of the model.

Parameter	Symbol	Range	Value
T cell T, T^*			
Death rate of inactive T cells (day^{-1})	d_T	$0.1 - 0.01$ [9]	0.1
Death rate ratio of active:inactive T cells	d_{T^*}/d_T	$0.01 - 100$	0.1
Input rate of inactive T cells (cells/ml/day)	T_{input}	$0 - 10^4$	100
Tregs R, R^*			
Death rate ratio of inactive Tregs : inactive T	d_R/d_T	$0.01 - 100$	1
Death rate relative ratio of Tregs : T	$\frac{d_{R^*}}{d_R} / \frac{d_{T^*}}{d_T}$	$0.01 - 100$	1
Input rate ratio of inactive Tregs : inactive T	R_{input}/T_{input}	$0.01 - 100$	1

least one eigenvalue has a positive real part, we are in the presence of an unstable equilibria.

Let $x = T + T^*$ be the total concentration of T cells and $y = R + R^*$ be the total concentration of Tregs. When the system is at equilibrium we have that:

$$(\varepsilon\rho I - \beta(x + y) - d_R)R$$
$$+\hat{k}(R^* - aR) + R_{input} = 0 , \qquad (1)$$

$$(\varepsilon\rho I - \beta(x + y) - d_{R^*})R^*$$
$$-\hat{k}(R^* - aR) = 0 , \qquad (2)$$

$$(\rho I - \beta(x + y) - d_T)T$$
$$+k(T^* - bT + \gamma R^* T^*) + T_{input} = 0 , \qquad (3)$$

$$(\rho I - \beta(x + y) - d_{T^*})T^*$$
$$-k(T^* - bT + \gamma R^* T^*) = 0, \qquad (4)$$

$$\sigma(T^* - (\alpha(x + y) + \delta)I) = 0 . \qquad (5)$$

Let $\Delta_T = d_T - d_{T^*}$ and $\theta = k(1 + b) - \Delta_T$. When $\Delta_T \ll k$, the T, T^* balance is much faster than the T cell death rates. We can use this information to obtain an approximate expression of the relation between T^* and x.

Lemma 1. *When the system is at equilibrium (stable or unstable) and $\Delta_T \ll k$, the concentration of active T cells T^* is given approximately by*

$$T^* \approx \frac{kbx^2}{(\theta + k\gamma R^*)x + T_{input}} . \qquad (6)$$

Remark: For the default parameter values used in this paper, we observe that $\Delta_T = 0.099 \ll 2.4 = k$. We can observe in figure 2 that, for different values of y, the difference between the approximate value and the exact value of T^* is smaller than 1%.
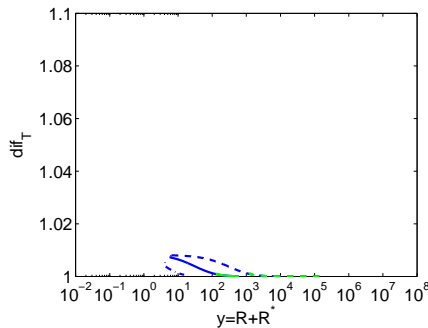

Fig. 2: Relative deviation $dif_T = T^*_{approx}/T^*_{exact}$ between the approximate value of T^* obtained from the Lemma 1 and the exact value.
$\frac{d_R}{d_T} = 0.1$ (dashes), 1 (solid), and 10 (dash-dot). The colors indicate when it is plotted the smallest root (green) or largest root (blue) of x from Theorem 2.

Proof of Lemma 1:

Adding (3) and (4), we obtain

$$\rho I - \beta(x+y) = \frac{d_T T + d_{T^*} T^* - T_{input}}{T + T^*} . \qquad (7)$$

Subtracting (4) from (3), we get

$$(\rho I - \beta(x+y))(T-T^*) - d_T T + d_{T^*} T^* \\ +2k(T^* - bT + \gamma R^* T^*) + T_{input} = 0 . \qquad (8)$$

Replacing (7) in (8) we get

$$\frac{T - T^*}{T + T^*}(d_T T + d_{T^*} T^* - T_{input}) - d_T T + d_{T^*} T^* \\ +2k(T^* - bT + \gamma R^* T^*) + T_{input} = 0 . \qquad (9)$$

Since $T = x - T^*$, we have that $\frac{T-T^*}{T+T^*} = 1 - \frac{2T^*}{x}$ and we obtain,

$$d_T(x - T^*) + d_{T^*} T^* - T_{input} \\ -\frac{2T^*}{x}(d_T(x - T^*) + d_{T^*} T^* - T_{input}) \\ -d_T(x - T^*) + d_{T^*} T^* \\ +2k(T^* - b(x - T^*) + \gamma R^* T^*) + T_{input} = 0 . \qquad (10)$$

Multiplying equation (10) by $x/2$, reordering the terms and substituting $\Delta_T = d_T - d_{T^*}$ and $\theta = k(1+b) - \Delta_T$, we get

$$\Delta_T(T^*)^2 + ((\theta + k\gamma R^*)x + T_{input})T^* - kbx^2 = 0 . \quad (11)$$

We have a polynomial of the second degree in T^*. By using $H(x, R^*) = (\theta + k\gamma R^*)x + T_{input}$, we get

$$T^* = \frac{-H \pm \sqrt{H^2 + 4\Delta_T kbx^2}}{2\Delta_T} . \qquad (12)$$

We must have $T^* > 0$, therefore we will only get the positive root.

By assuming that $\Delta_T \ll k$, we can make a first order Taylor expansion of the square root.

Since $kb \lesssim \theta$ and $\Delta_T \ll \theta$, we have that

$$\Delta_T kbx^2 \lesssim \Delta_T \theta x^2 \ll \theta^2 x^2 < H^2 . \qquad (13)$$

Therefore,

$$\sqrt{H^2 + 4\Delta_T kbx^2} = \sqrt{\left(1 + \frac{4\Delta_T kbx^2}{H^2}\right)H^2}$$

$$\approx \left(1 + \frac{2\Delta_T kbx^2}{H^2}\right)H + \mathcal{O}(2) . \qquad (14)$$

From (12) and (14) we get

$$T^* = \frac{-H + \left(1 + \frac{2\Delta_T kbx^2}{H^2}\right)H}{2\Delta_T} + \mathcal{O}(2) . \qquad (15)$$

Simplifying this equation and using the expression of $H(x, R^*)$, we obtain (6).

$\square$

3.1 Equilibria in the absence of the Tregs

Here, we consider the simplified model of the immune response by T cells in the absence of Tregs, by assuming that $R = R^* = 0$, thus eliminating equations (1) and (2):

$$\frac{dT}{dt} = (\rho I - \beta(T + T^*) - d_T)T + k(T^* - bT) + T_{input} ,$$

$$\frac{dT^*}{dt} = (\rho I - \beta(T + T^*) - d_{T^*})T^* - k(T^* - bT) ,$$

$$\frac{dI}{dt} = \sigma(T^* - (\alpha(T + T^*) + \delta)I) .$$

Let

$$\Delta_T = d_T - d_{T^*}, \qquad (16)$$
$$E(x) = (\alpha x + \delta)(d_T x - T_{input} + \beta x^2), \qquad (17)$$
$$F(x) = \rho x + \Delta_T(\alpha x + \delta) . \qquad (18)$$

Theorem 1. *Let $b_0(x)$ be the antigen function in the absence of Tregs. The level of antigenic stimulation of T cells is given approximately by $b_0(x)$, when the simplified system in the absence of Tregs is at equilibrium (stable or unstable).*

$$b_0(x) = \frac{(x(k - \Delta_T) + T_{input})E}{kx(xF - E)} . \qquad (19)$$

Conversely, given an antigenic stimulation level b_0 of T cells, the approximate concentration x of T cells is a zero of a fourth order polynomial that can be explicitly constructed.

Remark: Both the numerator and the denominator of $b_0(x)$ are polynomials of degree four in x.

Proof of Theorem 1:

When the system is at equilibrium we have that:

$$(\rho I - \beta x - d_T)T + k(T^* - bT) + T_{input} = 0 , \tag{20}$$
$$(\rho I - \beta x - d_{T^*})T^* - k(T^* - bT) = 0 , \tag{21}$$
$$\sigma(T^* - (\alpha x + \delta)I) = 0 . \tag{22}$$

Solving (22) for T^* gives

$$T^* = I(\alpha x + \delta) . \tag{23}$$

Adding (20) and (21), we obtain

$$(\rho I - \beta x - d_T)T + (\rho I - \beta x - d_{T^*})T^* + T_{input} = 0 . \tag{24}$$

Reordering the terms gives

$$(\rho I - \beta x)(T + T^*) - d_T T - d_{T^*}T^* + T_{input} = 0 . \tag{25}$$

Isolating $\rho I - \beta x$ we get

$$\rho I - \beta x = \frac{d_T T + d_{T^*}T^* - T_{input}}{T + T^*} . \tag{26}$$

Replacing (23) in (26) and using $T = x - T^*$ we get,

$$\left(\rho\left(\frac{T^*}{\alpha x + \delta}\right) - \beta x\right)(x - T^* + T^*)$$
$$= d_T(x - T^*) + d_{T^*}T^* - T_{input} . \tag{27}$$

Using $\Delta_T = d_T - d_{T^*}$ we have,

$$\rho\left(\frac{T^*}{\alpha x + \delta}\right)x - \beta x^2 = d_T x - \Delta_T T^* - T_{input} . \tag{28}$$

Multiplying both sides by $\alpha x + \delta$

$$\rho x T^* - (\alpha x + \delta)\beta x^2$$
$$= (\alpha x + \delta)(d_T x - \Delta_T T^* - T_{input}) . \tag{29}$$

Isolating the terms with T^* gives

$$(\rho x + \Delta_T(\alpha x + \delta))T^*$$
$$= (\alpha x + \delta)(d_T x - T_{input}) + (\alpha x + \delta)\beta x^2 . \tag{30}$$

Using $E(x) = (\alpha x + \delta)(d_T x - T_{input} + \beta x^2)$ and $F(x) = \rho x + \Delta_T(\alpha x + \delta)$, results in

$$T^*F = E . \tag{31}$$

Applying Lemma 1 we get,

$$\left(\frac{kbx^2}{\theta x + T_{input}}\right)F = E . \tag{32}$$

Since $\theta = k(1 + b) - \Delta_T = k + kb - \Delta_T$, we obtain

$$kbx^2 F = (k + kb - \Delta_T)xE + T_{input}E . \tag{33}$$

Moving the terms with b to the left side of the equation, we get

$$b(kx^2 F - xkE) = x(k - \Delta_T)E + T_{input}E . \tag{34}$$

By solving equation (34) for b we obtain (19).

$\square$

3.2 Equilibria in the presence of the Tregs

We now study the full model, with both the T cells and the Tregs. Let $\Delta_R = d_R - d_{R^*}$ and $\lambda = \hat{k}(1 + a) - \Delta_R$. Similarly to what is observed for the T cells, when $\Delta_R \ll \hat{k}$, the R, R^* balance is much faster than the Treg death rates. Once more, we can use this information to obtain an approximate expression of the relation between R^* and y.

Lemma 2. *When the system is at equilibrium (stable or unstable) and $\Delta_R \ll \hat{k}$, the concentration of active Tregs R^* is given approximately by*

$$R^* \approx \frac{\hat{k}ay^2}{\lambda y + R_{input}} . \tag{35}$$

Remark: For the default parameter values used in this paper, we observe that $\Delta_R = 0.099 \ll 2.4 = \hat{k}$. We can observe in figure 3 that, for different values of y, the relative difference between the approximate value and the exact value of R^* is smaller than 10%.
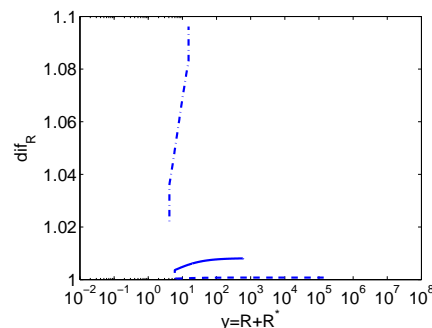

Fig. 3: Relative deviation $dif_R = R^*_{approx}/R^*_{exact}$ between the approximate value of R^* obtained from the Lemma 2 and the exact value.
$\frac{d_R}{d_T} = 0.1$ (dashes), 1 (solid), and 10 (dash-dot).

Proof of Lemma 2:

Adding (1) and (2), we obtain

$$\varepsilon \rho I - \beta(x+y) = \frac{d_R R + d_{R^*} R^* - R_{input}}{R + R^*} . \qquad (36)$$

Subtracting (2) from (1), we get

$$(\varepsilon \rho I - \beta(x+y))(R - R^*) - d_R R + d_{R^*} R^*$$
$$+ 2\hat{k}(R^* - aR) + R_{input} = 0 . \qquad (37)$$

Replacing (36) in (37) we get

$$\frac{R - R^*}{R + R^*}(d_R R + d_{R^*} R^* - R_{input}) - d_R R + d_{R^*} R^*$$
$$+ 2\hat{k}(R^* - aR) + R_{input} = 0 . \qquad (38)$$

Since $R = y - R^*$, we have that $\frac{R - R^*}{R + R^*} = 1 - \frac{2R^*}{y}$. Hence we obtain,

$$d_R(y - R^*) + d_{R^*} R^* - R_{input}$$
$$- \frac{2R^*}{y}(d_R(y - R^*) + d_{R^*} R^* - R_{input})$$
$$- d_R(y - R^*) + d_{R^*} R^*$$
$$+ 2\hat{k}(R^* - a(y - R^*)) + R_{input} = 0 . \qquad (39)$$

Multiplying equation (39) by $y/2$, reordering the terms and using $\lambda = \hat{k}(1+a) - \Delta_R$, we obtain

$$\Delta_R (R^*)^2 + (\lambda y + R_{input}) R^* - \hat{k} a y^2 = 0 . \qquad (40)$$

The above is polynomial of the second degree in R^*. By substituting $L(y) = \lambda y + R_{input}$, we get

$$R^* = \frac{-L \pm \sqrt{L^2 + 4\Delta_R \hat{k} a y^2}}{2\Delta_R} . \qquad (41)$$

We must have $R^* > 0$, therefore we will only get the positive root.

By assuming that $\Delta_R \ll \hat{k}$, we can make a first order Taylor expansion of the square root.

Since $\hat{k} a \lesssim \lambda$ and $\Delta_R \ll \lambda$, we have that

$$\Delta_R \hat{k} a y^2 \lesssim \Delta_R \lambda y^2 \ll \lambda^2 y^2 < L^2 . \qquad (42)$$

Therefore

$$\sqrt{L^2 + 4\Delta_R \hat{k} a y^2} = \sqrt{\left(1 + \frac{4\Delta_R \hat{k} a y^2}{L^2}\right) L^2}$$
$$\approx \left(1 + \frac{2\Delta_R \hat{k} a y^2}{L^2}\right) L + \mathcal{O}(2) . \qquad (43)$$

From (41) and (43) we get

$$R^* = \frac{-L + \left(1 + \frac{2\Delta_R \hat{k} a y^2}{L^2}\right) L}{2\Delta_R} + \mathcal{O}(2) . \qquad (44)$$

Simplifying this equation and using the expression of $L(y)$ we obtain (35).

□

Using Lemma 2, we can obtain a polynomial that gives the balance between the concentration of T cells $x = T + T^*$ and the concentration of Tregs $y = R + R^*$ (see Figure 4).

Let

$$P_{22} = \beta \lambda (\alpha \Delta_T + \rho(1 - \varepsilon))$$
$$P_{21} = \beta R_{input} (\alpha \Delta_T + \rho(1 - \varepsilon))$$
$$P_{13} = \beta \lambda (2\alpha \Delta_T + \rho(1 - \varepsilon))$$
$$P_{12} = \beta R_{input} (2\alpha \Delta_T + \rho(1 - \varepsilon)) - \hat{k} a \Delta_R (\rho + \alpha \Delta_T)$$
$$\qquad + \lambda (\rho(d_R - \varepsilon d_T) + \Delta_T(\alpha d_R + \beta \delta))$$
$$P_{11} = R_{input}(\rho(d_R - \varepsilon d_T) + \Delta_T(\alpha d_R + \beta \delta))$$
$$\qquad - R_{input} \lambda (\rho + \alpha \Delta_T)$$
$$P_{10} = -R_{input}^2 (\rho + \alpha \Delta_T) \qquad (45)$$
$$P_{04} = \alpha \beta \lambda \Delta_T$$
$$P_{03} = \Delta_T (\alpha \beta R_{input} + \lambda(\alpha d_R + \beta \delta) - \alpha \hat{k} a \Delta_R)$$
$$P_{02} = \Delta_T R_{input}(\alpha d_R + \beta \delta) - \delta \hat{k} a \Delta_T \Delta_R$$
$$\qquad + \lambda(\varepsilon \rho T_{input} - \alpha \Delta_T R_{input} + \delta \Delta_T d_R)$$
$$P_{01} = R_{input}(\varepsilon \rho T_{input} - \alpha \Delta_T R_{input} + \delta \Delta_T(d_R - \lambda))$$
$$P_{00} = -\delta \Delta_T R_{input}^2 .$$

Theorem 2. *When the system is at equilibrium (stable or unstable) and $\Delta_R \ll \hat{k}$, the approximate concentration of T cells $x = T + T^*$ is given implicitly as function of the concentration of Tregs $y = R + R^*$ by the zeros of the second degree polynomial in x:*

$$P_{22}x^2 y^2 + P_{21}x^2 y + P_{13}xy^3 + P_{12}xy^2 + P_{11}xy + P_{10}x$$
$$+ P_{04}y^4 + P_{03}y^3 + P_{02}y^2 + P_{01}y + P_{00} = 0 . \qquad (46)$$

Conversely, the approximate concentration y of Tregs is given implicitly as a function of the concentration x of T cells by the zeros of the above fourth order polynomial in y.

Proof of Theorem 2:
Isolating ρI from (7) gives:

$$\rho I = \frac{d_T T + d_{T^*} T^* - T_{input}}{T + T^*} + \beta(x + y) . \qquad (47)$$

By replacing (47) in (36) we obtain

$$\varepsilon \left(\frac{d_T T + d_{T^*} T^* - T_{input}}{T + T^*} + \beta(x + y)\right) - \beta(x + y)$$
$$= \frac{d_R R + d_{R^*} R^* - R_{input}}{R + R^*} . \qquad (48)$$

Since $T = x - T^*$ and $R = y - R^*$, and multiplying (48) by xy results in

$$((\varepsilon d_T - d_R) - \beta(1 - \varepsilon)(x + y))xy$$
$$- ((d_{T^*} - d_T)T^* - T_{input})\varepsilon y$$
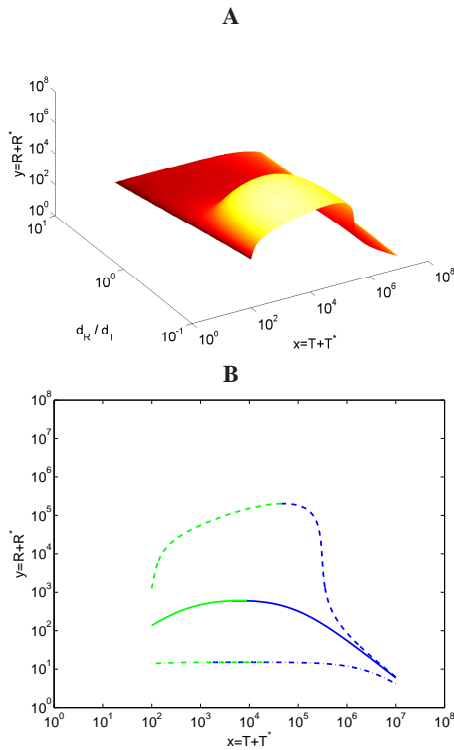$$- ((d_{R^*} - d_R)R^* - R_{input})x = 0 . \qquad (49)$$

A

B

Fig. 4: Relation between the concentration of T cells $x = T + T^*$ and the concentration of Tregs $y = R + R^*$, from Theorem 2.
A: Horizontal axis: $x = T + T^*$; "away axis": $\frac{d_R}{d_T}$; vertical axis: $y = R + R^*$. Low values of b are darker and higher values are lighter.
B: Cross sections of the equilibria manifold in figure A for $\frac{d_R}{d_T} = 0.1$ (dashes), 1 (solid), and 10 (dash-dot). The horizontal axis is the total concentration $x = T + T^*$ of T cells, and the vertical axis is the total concentration $y = R + R^*$ of Tregs. The colors indicate when it is plotted the smallest root (green) or largest root (blue) of x from Theorem 2.

Using $C(x,y) = ((\varepsilon d_T - d_R) - \beta(1-\varepsilon)(x+y))xy$, $\Delta_T = d_T - d_{T^*}$ and $\Delta_R = d_R - d_{R^*}$ gives

$$C - (\Delta_T T^* + T_{input})\varepsilon y + (\Delta_R R^* + R_{input})x = 0 . \quad (50)$$

Multiplying (7) by x and using $T = x - T^*$, we obtain

$$\rho I x - \beta(x+y)x = d_T(x - T^*) + d_{T^*}T^* - T_{input} . \quad (51)$$

Reordering the terms of the previous expression and using $\Delta_T = d_T - d_{T^*}$ we have

$$\rho I x + \Delta_T T^* = \beta(x+y)x + d_T x - T_{input} . \quad (52)$$

Solving (5) for I we get

$$I = \frac{T^*}{\alpha(x+y) + \delta} . \quad (53)$$

Replacing (53) in (52) we get

$$\frac{\rho x}{\alpha(x+y) + \delta}T^* + \Delta_T T^* = \beta(x+y)x + d_T x - T_{input} . \quad (54)$$

Multiplying both sides of (54) by $\alpha(x+y) + \delta$ and solving for T^* we obtain

$$T^* = \frac{(\alpha(x+y) + \delta)(\beta(x+y)x + d_T x - T_{input})}{\rho x + \Delta_T(\alpha(x+y) + \delta)} . \quad (55)$$

Replacing (55) in (50), reordering the terms and using $G(x,y) = \rho x + \Delta_T(\alpha(x+y) + \delta)$, we get

$$C - \frac{(\alpha(x+y) + \delta)(\beta(x+y)x + d_T x - T_{input})}{G}\Delta_T \varepsilon y$$
$$-T_{input}\varepsilon y + (\Delta_R R^* + R_{input})x = 0 . \quad (56)$$

Applying Lemma 2 and using $L(y) = \lambda y + R_{input}$ we have

$$C - \frac{(\alpha(x+y) + \delta)(\beta(x+y)x + d_T x - T_{input})}{G}\Delta_T \varepsilon y$$
$$-T_{input}\Delta_T \varepsilon y + x\left(\Delta_R \frac{\hat{k}a y^2}{L} + R_{input}\right) = 0 . \quad (57)$$

Multiplying by $G(x,y)L(y)$ we obtain

$$CGL - (\alpha(x+y) + \delta)(\beta(x+y)x + d_T x - T_{input})\Delta_T \varepsilon y L$$
$$-T_{input}\varepsilon y G L + x\left(\Delta_R \hat{k}a y^2 + R_{input}L\right)G = 0 . \quad (58)$$

Expanding the previous expression and reordering the terms, we obtain the polynomial in (46). We note that $C(x,y)$, $G(x,y)$ and $L(y)$ are polynomials.

$\square$

From the results above, we are able to build the *antigen function* that relates the concentration of T cells $x = T + T^*$ and the concentration of Tregs $y = R + R^*$ with the level of the antigenic stimulation of T cells b. Let

$$\lambda = \hat{k}(1+a) - \Delta_R$$
$$\theta = k(1+b) - \Delta_T$$
$$L(y) = \lambda y + R_{input}$$
$$C(x,y) = ((\varepsilon d_T - d_R) - \beta(1-\varepsilon)(x+y))xy$$
$$M(x,y) = C(x,y) - T_{input}\varepsilon y + R_{input}x \quad (59)$$
$$N(x,y) = M(x,y)L(y) + \Delta_R a\hat{k}xy^2$$
$$Q(x,y) = ak\hat{k}\gamma xy^2 + T_{input}L(y)$$
$$J(x,y) = \varepsilon \Delta_T kxyL(y) .$$

Theorem 3. *Let $b(x,y)$ be the antigen function, and let $x(y)$ (or $y(x)$) be as in Theorem 2. The level of the antigenic stimulation of T cells is given approximately by $b(x,y)$, when the system is at equilibrium (stable or unstable).*

$$b(x,y) = \frac{((k - \Delta_T)xL + Q)N}{(J - kN))xL} . \quad (60)$$

Conversely, given an antigenic stimulation level b of T cells, the approximate concentration x of T cells and the approximate concentration y of Tregs are zeros of polynomials that can be explicitly constructed.
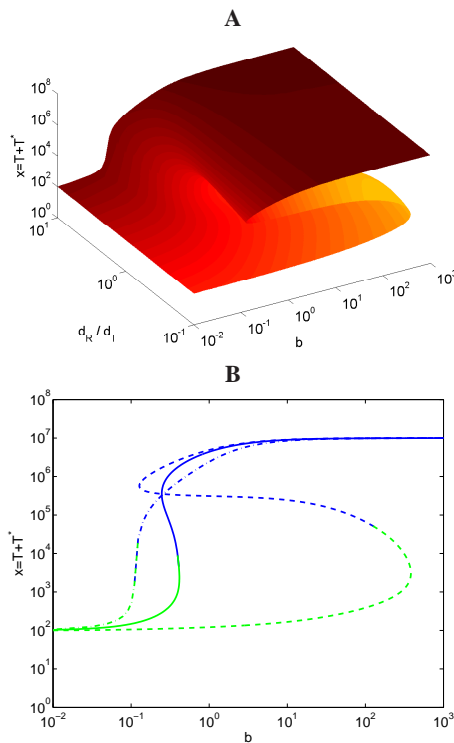
Fig. 5: Relation between antigenic stimulation b of T cells, the concentration of T cells $x = T + T^*$ and the relation $\frac{d_R}{d_T}$.

A: Horizontal axis: b; "away axis": $\frac{d_R}{d_T}$; vertical axis: $x = T + T^*$. Low values of $y = R + R^*$ are darker and higher values are lighter.
B: Cross sections of the equilibria manifold in figure A for $\frac{d_R}{d_T} = 0.1$ (dashes), 1 (solid), and 10 (dash-dot). The horizontal axis is the antigenic stimulation b of T cells, and the vertical axis is the total concentration $x = T + T^*$ of T cells. The colors indicate when it is plotted the smallest root (green) or largest root (blue) of x from Theorem 2.
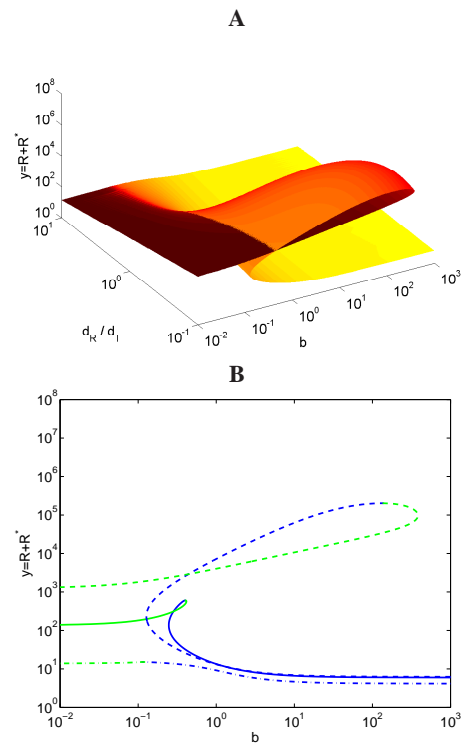
Fig. 6: Relation between antigenic stimulation b of T cells, the concentration of T cells $x = T + T^*$ and the relation $\frac{d_R}{d_T}$.

A: Horizontal axis: b; "away axis": $\frac{d_R}{d_T}$; vertical axis: $y = R + R^*$. Low values of $x = T + T^*$ are darker and higher values are lighter.
B: Cross sections of the equilibria manifold in figure A for $\frac{d_R}{d_T} = 0.1$ (dashes), 1 (solid), and 10 (dash-dot). The horizontal axis is the antigenic stimulation b of T cells and the vertical axis is the total concentration $y = R + R^*$ of Tregs. The colors indicate when it is plotted the smallest root (green) or largest root (blue) of x from Theorem 2.

Remark: The numerator of $b(x,y)$ is a polynomial of degree three in x and degree five in y and the denominator of $b(x,y)$ is a polynomial of degree three in x and degree four in y.

Proof of Theorem 3:
Isolating the T^* term in (50) gives

$$\varepsilon \Delta_T y T^* = C - T_{input} \varepsilon y + (\Delta_R R^* + R_{input}) x . \quad (61)$$

Replacing T^* by the expression from Lemma 1, multiplying both sides of (61) by $(\theta + k\gamma R^*)x + T_{input}$ and using the definition of $M(x,y)$ from (59), results in

$$\varepsilon \Delta_T k b x^2 y = (M + \Delta_R R^* x)\big((\theta + k\gamma R^*)x + T_{input}\big) . \quad (62)$$

Applying Lemma 2 to obtain an expression for R^* and multiplying both sides of (62) by $L^2(y)$ from (59), we get

$$\varepsilon \Delta_T k b x^2 y L^2 = (ML + \Delta_R \hat{k} a x y^2)\big((\theta L + k\gamma \hat{k} a y^2)x + T_{input}L\big) . \quad (63)$$

Using the definitions of $J(x,y)$, $N(x,y)$, $Q(x,y)$ and θ from (59), we obtain

$$b x J L = N\big((k(1+b) - \Delta_T)xL + Q\big) . \quad (64)$$

Moving the terms with b to the left side of the equation, we get

$$b x J L - b k x L N = \big((k - \Delta_T)xL + Q\big)N . \quad (65)$$

Solving the last expression for b gives us (60).

$\square$

For the default values of our parameters, the antigen function determines that the relation between the concentration x of T cells and the antigenic stimulation b of T cells is an hysteresis (see Figure 5). For low antigenic values of the antigenic stimulation b of T cells there is only one stable equilibria - a controlled state characterized by low concentrations x of T cells. Initial

conditions (at least those that are biologically plausible) converge over time to that stable state. For high antigenic values of the antigenic stimulation b of T cells there is also only one stable equilibria - an immune response state characterized by high concentrations x of T cells. For some values of the parameters (for instance, when $\frac{d_R}{d_T}$ is near 1), we observe two catastrophe points b_L and b_H of antigenic stimulation of T cells. For intermediate values of the antigenic stimulation b of T cells, between these two points, (for instance for $b \approx 0.5$), we observe that, there are two stable equilibria and one unstable equilibria. Hence, b_L and b_H bound the bistability region. Different initial conditions converge to either one of these two stable equilibria, defining two basins of attraction divided by a separatrix that contains the unstable equilibria.

The relation $\frac{d_R}{d_T}$, between the death rates of Tregs and T cells, affects the bistability region of the hysteresis. It also affects the concentration of Tregs. The distance between the thresholds b_L and b_H is very large for low values of $\frac{d_R}{d_T}$. When this relation is increased, the distance between b_L and b_H is reduced and the hysteresis is unfold for $\frac{d_R}{d_T} \approx 1.23...$ (see Figures 5 and 6). The concentration of Tregs is negatively correlated with $\frac{d_R}{d_T}$ (see Figure 4).

4 Tuning between the antigenic stimuli

The antigen presenting cells (APC), such as dendritic cells, present both self and non self antigens [8]. Therefore, there is a positive correlation between the levels of antigen stimulation a of the Tregs and the levels of antigen stimulation b of the T cells. For simplicity, we study a linear tuning between these stimuli in the form:

$$a(b) = a_0 + mb, \tag{66}$$

with a_0 as in [4] and $m \geq 0$. If the levels of antigenic stimulation a of Tregs and the levels of antigen stimulation b of the T cells are independent, the slope m is equal to zero.

Using this linear tuning, we can expand the result from Theorem 3. Let

$$
\begin{aligned}
\hat{\lambda}(\hat{b}) &= \lambda + \hat{k}m\hat{b} \\
\tilde{J}(x,y) &= \varepsilon \Delta_T k\hat{k}mxy^2 \\
\hat{J}(x,y,\hat{b}) &= J + \tilde{J}\hat{b} \\
\hat{L}(y,\hat{b}) &= L + \hat{k}m\hat{b}y \\
\tilde{N}(x,y) &= (M + \Delta_R xy)\hat{k}my \\
\hat{N}(x,y,\hat{b}) &= N + \tilde{N}\hat{b} \\
\tilde{Q}(x,y) &= (k\gamma xy + T_{input})\hat{k}my \\
\hat{Q}(x,y,\hat{b}) &= Q + \tilde{Q}\hat{b} \\
U(x,y) &= (k - \Delta_T)Lx + Q \\
V(x,y) &= kLx + (k - \Delta_T)\hat{k}mxy + \tilde{Q} \,.
\end{aligned}
\tag{67}
$$

Theorem 4. *Let $\hat{b}(x,y)$ be the tuned antigen function, let $a(\hat{b}) = a_0 + m\hat{b}$ and let $x(y)$ (or $y(x)$) be as in Theorem 2. The approximate level of antigenic stimulation of T cells is a zero of the third degree polynomial $\hat{b}(x,y)$, when the system is at equilibrium (stable or unstable).*

$$
\begin{aligned}
&(\hat{k}mxy\tilde{J} - k\hat{k}mxy\tilde{N})\hat{b}^3 \\
&+(\hat{k}mxyJ + x\tilde{J}L - k\hat{k}mxyN - \tilde{N}V)\hat{b}^2 \\
&+(xJL - NV - \tilde{N}U)\hat{b} - NU = 0.
\end{aligned}
\tag{68}
$$

Conversely, given an antigenic stimulation level b of T cells, the approximate concentration x of T cells and the approximate concentration y of Tregs are zeros of polynomials that can be explicitly constructed.

Remark: $\hat{b}(x,y)$ is a polynomial of degree three in x and degree five in y. Note that Theorem 3 can be obtained as a corollary of theorem 4 by assuming that the antigenic stimuli a and b are independent, i.e. by setting $m = 0$.

Proof of Theorem 4:
The equalities in (67) are obtained by applying (66) to equation (59). Replacing these in (65) we get

$$
\begin{aligned}
&\hat{b}(J + \tilde{J}\hat{b})(L + \hat{k}m\hat{b}y)x \\
&= (N + \tilde{N}\hat{b})\Big((k(1 + \hat{b}) - \Delta_T)(L + \hat{k}m\hat{b}y)x\Big) \\
&+ (N + \tilde{N}\hat{b})(Q + \tilde{Q}\hat{b}).
\end{aligned}
\tag{69}
$$

Expanding the products to obtain polynomials in $\hat{b}$ and using (67), we get

$$
\begin{aligned}
&\hat{k}mxy\tilde{J}\hat{b}^3 + (\hat{k}myJ + \tilde{J}L)x\hat{b}^2 + xJL\hat{b} \\
&= k\hat{k}mxy\tilde{N}\hat{b}^3 + (\tilde{N}V + k\hat{k}mxyN)\hat{b}^2 \\
&+ (NV + \tilde{N}U)\hat{b} + NU \,.
\end{aligned}
\tag{70}
$$

Reordering the terms of the previous expression we obtain (68).

$\square$

5 Discussion

In this paper, we examined a mechanism proposed in [1] (and also presented in [2], [3], [4] and reviewed in [10]) of Treg control of immune responses through regulation of cytokine dependent T cell proliferation. In particular, we study here the asymmetry introduced in [3], [4]. When we analyse the model in the absence of Tregs we already observe an hysteresis, similar to the result presented in [1]. This is shown by the approximate formula in Theorem 1. In Theorem 2, we determine the analytic formula that describes approximately the fine balance between Regulatory T cells and T cells, in particular at controlled and immune response equilibrium states. We

observe that, for the parameter values chosen, the maximum concentration of Tregs is found for concentrations of T cells around $10^4 - 10^5$. In Theorem 3, we determine the explicit formula that relates approximately the antigenic stimulation of T cells, the concentration of T cells and the concentration of Tregs. For our parameter values, we observe that the relation between the antigenic stimulation of T cells and the concentration of T cells is an hysteresis. By changing some of the parameters, it is possible to reach a cusp bifurcation point where a drastic change in the dynamical behavior occurs: the unfold of the hysteresis. In particular, the hysteresis is unfolded when the homeostatic concentration of T cells T_{hom} is high enough to override the control structure constituted by the thresholds b_L and b_H. The unfold of the hysteresis is already present in model with symmetry [1], [2], here we observe that it unfolds for large values of $\frac{d_R}{d_T}$. The correlation between the antigenic stimulation b of T cells and the antigenic stimulation a of Tregs was modeled by the linear relation from [4] to simulate the effect of the antigen presenting cells. In Theorem 4 we present an explicit formula that relates the approximate relation between the antigenic stimulation of T cells with the concentration of Tregs y and the concentration of T cells x. This formula is a polynomial of third order in b. By contrast, the formula from Theorem 3, is linear in b. Therefore, in Theorem 4 it may be possible to find three solutions where only one solution would be found if Theorem 3 was applied. Therefore, Theorem 4 explains the appearance of an isola and the transcritical bifurcation that occurs in [4].

Acknowledgments

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