



Applied Mathematics and Nonlinear Sciences

<https://www.sciendo.com>

Mathematical analysis of a B-cell chronic lymphocytic leukemia model with immune response

Youcef Belgaid¹, Mohamed Helal¹, Ezio Venturino^{2†}

¹ Biomathematics Laboratory, Univ Sidi-Bel-Abbès, Sidi-Bel-Abbès, Algeria

²Dipartimento di Matematica “Giuseppe Peano”, Università di Torino, via Carlo Alberto 10, 10123 Torino – Member of the INdAM research group GNCS, Italy

Submission Info

Communicated by Juan Luis García Guirao

Received June 23rd 2019

Accepted September 26th 2019

Available online December 26th 2019

Abstract

A B-cell chronic lymphocytic leukemia has been modeled via a highly nonlinear system of ordinary differential equations. We consider the rather important theoretical question of the equilibria existence. Under suitable assumptions all model populations are shown to coexist.

Keywords: Leukemia, Descartes rule, Local stability.

AMS 2010 codes: AMS 2010 MSC primary: 92D40; secondary: 92D25, 92D30.

1 Introduction

In [1] a thorough study of B-cell chronic lymphocytic leukemia (B-CLL) has been undertaken by means of a highly nonlinear mathematical model based on ordinary differential equations. The relevance of this investigation is apparent from the realistic situations that have been scrutinized via numerical simulations, based on published data of B-CLL patients.

While there is nothing to add to this comprehensive study from the applicative point of view, in this short paper we would reconsider the model to tackle one issue that is still missing in the analysis of [1]. Specifically, we consider a rather important theoretical question, namely the issue of the equilibria existence of the mentioned

[†]Corresponding author.

Email addresses:

youcfb079@gmail.com

mhelal_abbes@yahoo.fr

ezio.venturino@unito.it

model. This point has not been addressed in [1] and, although the simulations show the validity of the statement, from the mathematical point of view, something is still lacking.

In this paper we fill the gap, by providing a proof showing that all the model populations can always coexist, under suitable and meaningful assumptions.

The paper is organized as follows. The mathematical model is briefly summarized in Section 2. In the following Section 3, its coexistence equilibrium is analytically found with an explicit form for almost all its components, while one of the populations appears to be the root of an algebraic equation. Section 4 further characterizes this coexistence equilibrium, by providing its local stability analysis.

2 Mathematical model

For the benefit of the reader, we summarize here the basic model presented in [1].

The cell population of B-CLL is denoted by B while N , T , T_H indicate the three immune responses in the peripheral blood, namely: the natural killer cells N that are not B-CLL-specific, which are present in the body at all times; the cytotoxic T cells, e.g., $CD8^+T$, which respond specifically to the B-CLL and the helper cells T_H which are part of the specific immune response. The latter assume an essential role in the recruitment, proliferation and activation of cytotoxic T cells. These different populations are all measured by their concentrations expressed in units of cells per microliter (μl). Time is denoted by t and measured in days.

The model is fully described in [1]. We just outline here the basic relationships between the various compartments and refer the reader to the above paper for a fuller description.

Basically, the first equation models the B-CLL dynamics originating the disease. These cells are mainly produced by bone marrow, can replicate, die naturally and, when detected, are killed by the immune response of the organism, which is performed by the N and T cells. The second equation translates the fact that the natural killer cells are produced in the body continuously at a constant rate, die naturally and become deactivated once they attack the B-CLL cells. The cytotoxic T cells, described in the third equation, are the specific response of the organism to the B-CLL cells: they also are constantly produced, die and are deactivated upon killing the B cells, but are also produced by the activated helper cells. This mechanism is modeled via a saturating sigmoid function, whose shape is described by the integer parameter $L \in \mathbf{Z}_+$. This response of the T_H cells is triggered when they encounter the B-CLL cells. A fraction k of this production rate results also in new T cells. The T_H helper cells dynamics is written in the fourth equation. Beside the above triggering boosting, they are also continuously produced at a constant rate and experience natural mortality.

Based on the above assumptions, the mathematical translation of the system dynamics just described thus is expressed by the set nonlinear system of ordinary differential equations stated below:

$$\frac{dB}{dt} = b_B + (r - d_b)B - d_{BN}BN - d_{BT}BT \tag{1}$$

$$\frac{dN}{dt} = b_N - d_NN - d_{NB}NB \tag{2}$$

$$\frac{dT}{dt} = b_T - d_TT - d_{TB}TB + ka_{TH} \frac{B^L}{s + B^L} T_H \tag{3}$$

$$\frac{dT_H}{dt} = b_{T_H} - d_{T_H}T_H + a_{T_H} \frac{B^L}{s + B^L} T_H. \tag{4}$$

The parameters are all assumed to be positive and their meaning is defined in Table 1. Specific assumptions on some of the parameters are

$$d_{BT} \ll 1, \quad r > d_B. \tag{5}$$

3 Coexisting Equilibrium

In view of the fact that there are constant source terms in (1), no equilibrium with any vanishing compartment can exist. Therefore the model can possibly have only the equilibrium point at which all populations have a constant nonvanishing value. The study of this equilibrium, $E^*(B^*, N^*, T^*, T_H^*)$, is indeed our main goal in this paper. To evaluate it, we need to satisfy the equilibrium equations, which are obtained from (1) by setting the derivatives to zero. The resulting algebraic equations give three of the variables in terms of the fourth one, which here is taken to be the B-CLL cells concentration B . Namely, solving the equations (2), (3), (4) we find:

$$N^* = \frac{b_N}{d_N + d_{NB}B^*}, \quad T_H^* = \frac{(b_{T_H})(s + B^{*L})}{B^{*L}(d_{T_H} - a_{T_H}) + sd_{T_H}}, \quad T^* = \frac{B^{*L}[b_T(d_{T_H} - a_{T_H}) + ka_{T_H}b_{T_H}] + sb_T d_{T_H}}{(d_T + d_{TB}B^*)[B^{*L}(d_{T_H} - a_{T_H}) + sd_{T_H}]} \tag{6}$$

Now, substituting these values of N^* , T^* , T_H^* into the first equation of the system (1) and simplifying we obtain the following equation:

$$\alpha_{L+3}B^{*L+3} + \alpha_{L+2}B^{*L+2} + \alpha_{L+1}B^{*L+1} + \alpha_L B^{*L} + \alpha_3 B^{*3} + \alpha_2 B^{*2} + \alpha_1(B^*) + \alpha_0 = 0 \tag{7}$$

where the coefficients are explicitly known:

$$\begin{aligned} \alpha_{L+3} &= (r - d_B)d_{NB}d_{TB}(d_{T_H} - a_{T_H}), & \alpha_{L+2} &= (d_{T_H} - a_{T_H})[b_B d_{NB} d_{TB} + (r - d_B)(d_N d_{TB} + d_{NB} d_T)], \\ \alpha_{L+1} &= (d_{T_H} - a_{T_H})[b_B(d_N d_{TB} + d_{NB} d_T) + (r - d_B)d_N d_T + d_{BN} d_{TB} b_N - d_{BT} d_{NB} b_T] - kd_{NB} d_{TB} b_{T_H} a_{T_H}, \\ \alpha_L &= (d_{T_H} - a_{T_H})b_B d_N d_{TB} + (d_{T_H} - a_{T_H})[b_N d_{BN} d_T - d_{BT} d_N b_T] - kd_{BT} d_N b_{T_H} a_{T_H}, & \alpha_3 &= (r - d_B)sd_{NB}d_{T_H}d_{TB}, \\ & & \alpha_1 &= b_B s d_{T_H}(d_N d_{TB} + d_{NB} d_T) + s d_{T_H}[(r - d_B)d_N d_T + d_{BN} b_N d_{TB} - d_{BT} b_N d_T], \\ & & \alpha_2 &= b_B s d_{NB} d_{T_H} d_{TB} + (r - d_B) s d_{T_H}(d_N d_{TB} + d_{NB} d_T), & \alpha_0 &= s d_{T_H} d_T [d_{BN} b_N + (1 - d_{BT})d_N]. \end{aligned} \tag{8}$$

3.1 The case $L = 2$

In [1], the value of the parameter L is taken to be $L = 2$. It thus follows:

$$a_5 B^{*5} + a_4 B^{*4} + a_3 B^{*3} + a_2 B^{*2} + a_1(B^*) + a_0 = 0. \tag{9}$$

Table 1 Model parameters and their meaning

| | |
|-----------|---|
| b_B | constant source rate of B-CLL produced by bone marrow |
| r | replication rate of the leukemic B cells |
| d_B | natural mortality rate of the leukemic B cells |
| d_{BN} | killing rate of B-CLL cells by N cells |
| d_{BT} | killing rate of B-CLL cells by T cells |
| b_N | constant source rate of N cells |
| d_N | mortality rate of N cells |
| d_{NB} | deactivation rate of N cells by contact with B-CLL cells |
| b_T | constant production rate of T cells |
| d_T | natural mortality rate of T cells |
| d_{TB} | T cells activity suppression rate by contact with B-CLL cells |
| k | fraction of T_H cell activation that results in T cells recruitment |
| a_{T_H} | maximal T_H cells activation rate by contact with B-CLL cells |
| b_{T_H} | constant production rate of T_H cells |
| d_{T_H} | natural mortality rate of T_H cells |
| s | half saturation constant |
| L | parameter shaping the saturating sigmoid response |

The new coefficients are in part the same of those in (8), in part need to be recalculated. We find:

$$\begin{aligned}
 a_5 &= \alpha_{L+3}, & a_4 &= \alpha_{L+2}, & a_0 &= \alpha_0, & a_1 &= \alpha_1, \\
 a_3 &= (d_{T_H} - a_{T_H})[b_B(d_N d_{T_B} + d_{N_B} d_T) + (r - d_B)d_N d_T + d_{B_N} d_{T_B} b_N - d_{B_T} d_{N_B} b_T] \\
 &\quad - k d_{N_B} d_{T_B} b_{T_H} a_{T_H} + (r - d_B) s d_{N_B} d_{T_H} d_{T_B}, \\
 a_2 &= (d_{T_H} - a_{T_H})[b_B d_N d_{T_B} + b_N d_{B_N} d_T - d_{B_T} d_N b_T] \\
 &\quad - k d_{B_T} d_{N_B} b_{T_H} a_{T_H} + b_B s d_{N_B} d_{T_H} d_{T_B} + (r - d_B) s d_{T_H} (d_N d_{T_B} + d_{N_B} d_T).
 \end{aligned}$$

By the model assumptions (5), a_0 turns out to be always positive. Note that using the actually estimated parameter values of [1], it turns out that according to the parameter ranges given, there might be situations in which $d_{T_H} > a_{T_H}$ holds. This inequality may also not be satisfied, giving the following condition

$$d_{T_H} - a_{T_H} < 0. \tag{10}$$

From the latter, the negativity of two more coefficients follows, namely $a_5 < 0$, $a_4 < 0$. We proceed now by applying Descartes rule of signs to equation (9). Our aim is to find at least a positive root of the quintic algebraic equation. There are several cases that need to be discussed, based on the possible signs of the remaining coefficients:

- (i) if $a_3 < 0, a_2 < 0, a_1 < 0$, then there is just one change of sign, so there exists one positive roots of Eq.(9);
- (ii) if $a_3 < 0, a_2 < 0, a_1 > 0$, there is one positive roots of Eq.(9);
- (iii) if $a_3 < 0, a_2 > 0, a_1 > 0$, there is one positive roots of Eq.(9);
- (iv) if $a_3 < 0, a_2 > 0, a_1 < 0$, there exist three or one positive roots of Eq.(9);
- (v) if $a_3 > 0, a_2 > 0, a_1 > 0$, there exist one positive roots of Eq.(9);
- (vi) if $a_3 > 0, a_2 > 0, a_1 < 0$, there exist three or one positive roots of Eq.(9);
- (vii) if $a_3 > 0, a_2 < 0, a_1 > 0$, there exist three or one positive roots of Eq.(9);
- (viii) if $a_3 > 0, a_2 < 0, a_1 < 0$, there exist three or one positive roots of Eq.(9);

Therefore, since in all these cases there is at least one sign change, the existence of a positive root B^* of equation (9) is unconditionally ensured. The extra two roots that arise in cases (iv), (vi), (vii) and (viii) may or may not be real. The occurrence of these multiple roots is related to the sigmoid function used in (3) and (4). This also entails the possible appearance or disappearance of these equilibria, through saddle node bifurcations. This issue will not be further investigated here.

Feasibility of the coexistence equilibrium further hinges on the nonnegativity of the remaining populations, namely we need to require $T_H^* \geq 0$ and $T^* \geq 0$. If condition (10) is not satisfied, it ensures the positivity only of T_H^* , but not the one of T^* . In view of this fact, in general we therefore need to impose both the above further nonnegativity conditions, that give the requirements:

$$d_{T_H} B^{*L} + s d_{T_H} > a_{T_H} B^{*L}, \quad B^{*L} [b_T d_{T_H} + k a_{T_H} b_{T_H}] + s b_T d_{T_H} \geq a_{T_H} B^{*L}. \tag{11}$$

In summary, we have the following result.

Theorem 1. *The coexistence equilibrium $E^*(B^*, N^*, T^*, T_H^*)$ of the system (3)-(4) with $L = 2$ exists unconditionally and it is feasible if conditions (11) are satisfied.*

3.2 The case $L = 3$

In this case, we have the equation

$$a_6B^{*6} + a_5B^{*5} + a_4B^{*4} + a_3B^{*3} + a_2B^{*2} + a_1(B^*) + a_0 = 0. \tag{12}$$

It is easy to see that $a_k = \alpha_k$ for $k = 0, 1, 2, 4, \dots, 6$. For a_3 we find instead

$$a_3 = (d_{T_H} - a_{T_H})b_B d_N d_{T_B} + (d_{T_H} - a_{T_H})[b_N d_{B_N} d_T - d_{B_T} d_N b_T] - k d_{B_T} d_N b_{T_H} a_{T_H} + (r - d_B) s d_{N_B} d_{T_H} d_{T_B},$$

which is of uncertain sign. For the remaining coefficients we find

$$a_0 > 0, \quad a_2 > 0, \quad a_5 < 0, \quad a_6 < 0$$

on using (5) and (10). Combining all the possible cases, we have the situations described in Table 2.

Table 2 Signs of the coefficients of equation (12) for the case $L = 3$

| a_6 | a_5 | a_4 | a_3 | a_2 | a_1 | a_0 | sign variations | positive roots |
|-------|-------|-------|-------|-------|-------|-------|-----------------|----------------|
| - | - | + | + | + | + | + | 1 | 1 |
| - | - | + | + | + | - | + | 3 | 1 or 3 |
| - | - | + | - | + | + | + | 3 | 1 or 3 |
| - | - | + | - | + | - | + | 5 | 1 or 3 or 5 |
| - | - | - | + | + | + | + | 1 | 1 |
| - | - | - | + | + | - | + | 3 | 1 or 3 |
| - | - | - | - | + | + | + | 1 | 1 |
| - | - | - | - | + | - | + | 3 | 1 or 3 |

We have thus proven the following result.

Theorem 2. *The coexistence equilibrium $E^*(B^*, N^*, T^*, T_H^*)$ of the system (3)-(4) in the case $L = 3$ exists unconditionally. Once again, for it to be feasible, conditions (11) need to be satisfied. Multiple roots are possible, arising possibly through saddle-node bifurcations, in the cases listed in Table 2.*

3.3 The general case $L \geq 4$

In this situation, the equation is in general of order L . Therefore we need to study directly the characteristic equation (7) whose coefficients are then $a_k = \alpha_k, k = 0, \dots, 3, k = L, \dots, L + 3$, the only 8 ones that do not vanish. Furthermore, from (5) and (10) we once again find

$$a_0 > 0, \quad a_2 > 0, \quad a_3 > 0, \quad a_{L+2} < 0, \quad a_{L+3} < 0$$

The vanishing ones do not influence Descartes' rule, for which now the situations described in Table 3 arise.

Again, the multiple equilibria seen to arise in some cases of Table 3 would be originated by saddle-node bifurcations.

In summary we can state the following claim.

Theorem 3. *The coexistence equilibrium $E^*(B^*, N^*, T^*, T_H^*)$ of the system (3)-(4) in the general case $L \geq 4$ exists unconditionally. Once again, for it to be feasible, conditions (11) need to be satisfied.*

Table 3 Signs of the coefficients of equation (7) for a general value of L

| a_{L+3} | a_{L+2} | a_{L+1} | a_L | a_{L-1} | \dots | a_4 | a_3 | a_2 | a_1 | a_0 | sign variations | positive roots |
|-----------|-----------|-----------|-------|-----------|---------|-------|-------|-------|-------|-------|-----------------|----------------|
| - | - | + | + | 0 | 0 | 0 | + | + | + | + | 1 | 1 |
| - | - | + | + | 0 | 0 | 0 | + | + | - | + | 3 | 1 or 3 |
| - | - | + | - | 0 | 0 | 0 | + | + | + | + | 3 | 1 or 3 |
| - | - | + | - | 0 | 0 | 0 | + | + | - | + | 5 | 1 or 3 or 5 |
| - | - | - | + | 0 | 0 | 0 | + | + | + | + | 1 | 1 |
| - | - | - | + | 0 | 0 | 0 | + | + | - | + | 3 | 1 or 3 |
| - | - | - | - | 0 | 0 | 0 | + | + | + | + | 1 | 1 |
| - | - | - | - | 0 | 0 | 0 | + | + | - | + | 3 | 1 or 3 |

4 Stability Analysis

In this section we investigate the local stability of the coexistence equilibrium, in the particular case $L = 2$ and in the general one $L \geq 3$.

4.1 The case $L = 2$

The Jacobian matrix of system at the coexisting equilibrium E^* is given by

$$J_2(E^*) = \begin{pmatrix} (r - d_B) - d_{BN}N^* - d_{BT}T^* & -d_{BN}B^* & -d_{BT}B^* & 0 \\ -d_{NB}N^* & -d_N - d_{NB}B^* & 0 & 0 \\ -d_{TB}T^* + ka_{TH} \frac{2B^*s}{(s + B^{*2})^2} T_H^* & 0 & -d_T - d_{TB}B^* & ka_{TH} \frac{B^{*2}}{s + B^{*2}} \\ a_{TH} \frac{2B^*s}{(s + B^{*2})^2} T_H^* & 0 & 0 & -d_{TH} + a_{TH} \frac{B^{*2}}{s + B^{*2}} \end{pmatrix} \tag{13}$$

We have the following result:

Theorem 4. For $L = 2$, The coexistence equilibrium $E^*(B^*, N^*, T^*, T_H^*)$ of the system (3)-(4) is locally asymptotically stable if $b_0 > 0, b_1 > 0, b_2 > 0, b_3 > 0$, where these coefficients are defined in the proof.

Proof. We use the linearization method [2], followed by another application of Descartes’ rule of signs. From (13), the eigenvalues of the characteristic equation of $J(E^*)$ are the solution of the following equation:

$$P(\lambda) = \lambda^4 + b_3\lambda^3 + b_2\lambda^2 + b_1\lambda + b_0 = 0 \tag{14}$$

whose coefficients are

$$\begin{aligned}
 b_3 &= d_N + d_{NB}B^* + d_{BN}N^* + d_{BT}T^* - r + d_B + d_T + d_{TB}B^* - a_{TH} \frac{B^{*2}}{s + B^{*2}} + d_{TH}, \\
 b_2 &= \left[d_T + d_{BT}B^* - a_{TH} \frac{B^{*2}}{s + B^{*2}} + d_{TH} + d_{BN}N^* + d_{BT}T^* - r + d_B \right] (d_N + d_{NB}B^*) \\
 &\quad - d_{NB}d_{BN}N^*B^* + \left[d_T + d_{TB}B^* - a_{TH} \frac{B^{*2}}{s + B^{*2}} + d_{TH} \right] [d_{BN}N^* + d_{BT}T^* - r + d_B] \\
 &\quad - (d_T + d_{TB}B^*) \left(a_{TH} \frac{B^{*2}}{s + B^{*2}} - d_{TH} \right) + d_{BT}B^* \left(ka_{TH} \frac{2B^*s}{(s + B^{*2})^2} T_H^* - d_{TB} \right), \\
 b_1 &= -d_{NB}d_{BN}N^*B^* \left[d_N + d_{TB}B^* - a_{TH} \frac{B^{*2}}{s + B^{*2}} + d_{TH} \right] \\
 &\quad - (d_N + d_{NB}B^*) \left[(d_T + d_{TB}B^*) \left(a_{TH} \frac{B^{*2}}{s + B^{*2}} - d_{TH} \right) - (d_T + d_{TB}B^*) \right. \\
 &\quad \left. - \left(a_{TH} \frac{B^{*2}}{s + B^{*2}} - d_{TH} \right) [d_{BN}N^* + d_{BT}T^* - r + d_B] - d_{BT}B^* \left(ka_{TH} \frac{2B^*s}{(s + B^{*2})^2} T_H^* - d_{TB} \right) \right] \\
 &\quad - [d_{BN}N^* + d_{BT}T^* - r + d_B] (d_T + d_{BT}B^*) \left(a_{TH} \frac{B^{*2}}{s + B^{*2}} - d_{TH} \right) \\
 &\quad - d_{BT}B^* \left[\left(ka_{TH} \frac{2B^*s}{(s + B^{*2})^2} T_H^* - d_{TB} \right) \left(a_{TH} \frac{B^{*2}}{s + B^{*2}} - d_{TH} \right) + \left(a_{TH} \frac{2B^*s}{(s + B^{*2})^2} T_H^* \right) ka_{TH} \frac{B^{*2}}{s + B^{*2}} \right], \\
 b_0 &= d_{NB}d_{BN}N^*B^* (d_T + d_{BT}B^*) \left(a_{TH} \frac{B^{*2}}{s + B^{*2}} - d_{TH} \right) \\
 &\quad - (d_N + d_{NB}B^*) \left[[d_{BN}N^* + d_{BT}T^* - r + d_B] (d_T + d_{BT}B^*) \left(a_{TH} \frac{B^{*2}}{s + B^{*2}} - d_{TH} \right) \right] \\
 &\quad + d_{BT}B^* \left[\left(ka_{TH} \frac{2B^*s}{(s + B^{*2})^2} T_H^* - d_{TB} \right) \left(a_{TH} \frac{B^{*2}}{s + B^{*2}} - d_{TH} \right) - \left(a_{TH} \frac{2B^*s}{(s + B^{*2})^2} T_H^* \right) ka_{TH} \frac{B^{*2}}{s + B^{*2}} \right].
 \end{aligned}$$

Now, the necessary condition for the characteristic equation to have roots with negative real parts is $b_0 > 0$. Therefore, by using Descartes rule of signs, all the roots of equation (14) are real negative if $b_1 > 0$, $b_2 > 0$, $b_3 > 0$.

4.2 The case $L \geq 3$

The Jacobian in this case is slightly modified from the expression (13), in that it becomes, using also the first three equilibrium equations to simplify some of the diagonal entries:

$$J_L(E^*) = \begin{pmatrix} -\frac{b_B}{B^*} & -d_{BN}B^* & -d_{BT}B^* & 0 \\ -d_{NB}N^* & -\frac{b_N}{N^*} & 0 & 0 \\ -d_{TB}T^* + ka_{T_H}T_H^* \frac{sLB^{*L-1}}{(s+B^{*L})^2} & 0 & -d_T - d_{TB}B^* ka_{T_H} \frac{B^{*L}}{s+B^{*L}} & \\ ka_{T_H}T_H^* \frac{sLB^{*L-1}}{(s+B^{*L})^2} & 0 & 0 & -\frac{b_{T_H}}{T_H^*} \end{pmatrix} \tag{15}$$

We now show that $-J_L(E^*)$ is positive definite, under suitable conditions. This will ensure the stability of the coexistence point E^* . We consider in turn the signs of the principal minors of all possible order, $\Delta_j, j = 1, \dots, 4$, imposing that they are all positive. We thus find

$$\Delta_1 = \frac{b_B}{B^*} > 0, \quad \Delta_2 = \frac{b_N}{N^*} \frac{b_B}{B^*} - d_{NB}N^*d_{BN}B^*, \quad \Delta_3 = (d_T + d_{TB}B^*)\Delta_2 - b_Nd_{BT} \frac{B^*}{N^*} \left[d_{TB}T^* - ka_{T_H}T_H^* \frac{sLB^{*L-1}}{(s+B^{*L})^2} \right].$$

For the determinant, we finally have

$$-\det J_L(E^*) = \frac{b_{T_H}}{T_H^*} \Delta_3 + k^2 a_{T_H}^2 \frac{T_H^*}{N^*} b_N d_{BT} \frac{sLB^{*L^2}}{(s+B^{*L})^3} > 0.$$

Thus the conditions ensuring positivity of the remaining above minors are

$$b_B b_N > d_{BN} d_{NB} B^{*2} N^{*2}, \quad (d_T + d_{TB} B^*) \Delta_2 + b_N d_{BT} ka_{T_H} \frac{T_H^*}{N^*} \frac{sLB^{*L}}{(s+B^{*L})^2} > b_N d_{BT} \frac{B^*}{N^*} d_{TB} T^*. \tag{16}$$

In summary we have the desired stability result:

Theorem 5. For $L \geq 3$, The coexistence equilibrium $E^*(B^*, N^*, T^*, T_H^*)$ of the system (3)-(4) is locally asymptotically stable if conditions (16) hold.

References

[1] Nanda, S., dePillis, L., Radunskaya, A., (2013) B cell chronic lymphocytic leukemia - a model with immune response, *Discrete and Continuous Dynamical Systems*, B, 18(4), 1053-1076.
 [2] Perko, L., (1991) *Differential Equations and Dynamic Systems*, Springer Verlag.