BAUTIN BIFURCATION IN A MINIMAL MODEL OF IMMUNOEDETING

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(Communicated by Shigui Ruan)

ABSTRACT. One of the simplest model of immune surveillance and neoplasia was proposed by Delisi and Resigno [6]. Later Liu et al [10] proved the existence of non-degenerate Takens-Bogdanov (BT) bifurcations defining a surface in the whole set of five positive parameters. In this paper we prove the existence of Bautin bifurcations completing the scenario of possible codimension two bifurcations that occur in this model. We give an interpretation of our results in terms of the Immuno Edition Theory (IET) of three phases: elimination, equilibrium and escape.

1. Introduction. Immune Edition Theory conceptualizes the development of cancer into three phases [8]. In the first one, formerly known as immune surveillance, the complex of the immune system eliminates cancer cells originating from an intrinsic fail in the suppressor mechanisms. When some part of cancer cells are eliminated, an equilibrium between the immune system and the population of cancer cells is achieved, leading to a dormant state. In the second phase, the cancer cells accumulate genetic and epigenetic alterations in the DNA that generate specific stress-induced antigens. When a unbalance of the cancer population occurs, an explosive phase appears with the fast growth of tumor cells. One of the simplest models in the first stage of the Immune Edition framework, based on a previous model of Bell [3], is due to Delisi and Resigno [6]. They model the population of cancer cells and lymphocytes as a predator–prey system. The cancer tumor grows in the early stage as a spherical tumor that protects the inner cancer cells. Only the cancer cells on the surface of the tumor interact with the lymphocytes. Under
Table 1. Parameters value of system (1), [6], [10].

| Parameter-Definition       | Dimension | Value     | Scaled   |
|---------------------------|-----------|-----------|----------|
| $\lambda_1$: Lymphocyte growth rate | $\frac{1}{day}$ | 0.01      | 0.01     |
| $\lambda_2$: Death rate of cancer cells | $\frac{1}{day}$ | 0.020016  | 0.006672 |
| $\alpha_1$: Rate of interaction | $\frac{1}{day}$ | $1.5 \times 10^{-7}$ | 0.297312 |
| $\alpha_2$: Rate of interaction | $\frac{1}{day}$ | $4.6135 \times 10^{-9}$ | 0.00318  |
| $x_c$: Saturation level    | volume    | $2.5 \times 10^{11}$ | 2500     |

Years after, Liu, Ruan and Zhu [10], studied the nonvascularized model of [6] and prove that a Takens–Bogdanov bifurcation of codimension two occurs.

The nonvascularized model of Delisi is

$$\frac{dx}{dt} = -\lambda_1 x + \frac{\alpha_1 x y^2}{1+x} \left(1 - \frac{x}{x_c}\right),$$
$$\frac{dy}{dt} = \lambda_2 y - \frac{\alpha_2 x y^2}{1+x}$$

where $x$ is the number of free lymphocytes that are not bounded to cancer cells, $y$ is the total number of cancer cells in adimensional variables. The fractional power is the result of assuming an allometric law of the number of cancer cells on the surface of a spherical tumor. Obviously, the model is not well suited for $y = 0$ which correspond to the initial tumor cell being a point. In fact, the theorem of uniqueness of solutions does not hold for initial conditions of the form $(x_0, 0)$.

In the original Delisi model 1 (see [6]) the total number of lymphocytes and cancer cells $L$ and $C$, satisfy

$$\frac{dL}{dt} = -\lambda_1 L + \frac{\alpha_1' \gamma C^{3/2} L}{1 + KL} \left(1 - \frac{L}{L_c}\right),$$
$$\frac{dC}{dt} = \lambda_2 C - \frac{\gamma C^{3/2} L}{1 + KL} [\lambda_2 K + \alpha_2']$$

with all parameters being positive: $L_c$ is the saturation population of lymphocytes, $K$ the equilibrium constant for tumor cell interaction between free and bound lymphocytes; $\gamma$ is a constant of proportionality of allometric growth; $\lambda_1$, $\lambda_2$ are the rates of death and birth of lymphocytes and cancer cells, respectively; $\alpha_1'$ and $\alpha_2'$ are constant of interaction between free lymphocytes and cancer cells. Populations are then rescaled as $x = KL$, $y = KC$, $x_c = KL_c$ and parameters as $\alpha_1 = \alpha_1' \gamma / K^{2/3}$, $\alpha_2 = \gamma K^{1/3} (\lambda_2 + \alpha_2' / K)$.

Table 1 shows typical parameter values for the model according to [6], [10].

After a change of variables $\bar{x} = x$, $\bar{y} = y^{1/3}$, performing the reparametrization

$$\frac{d\bar{t}}{dt} = 1 + x,$$

and dropping the bars, the system (5) is written in polynomial form

$$\frac{d\bar{x}}{d\bar{t}} = -\lambda_1 \bar{x} (1 + x) + \alpha_1 \left(1 - \frac{x}{x_c}\right) x y^2$$
$$\frac{d\bar{y}}{d\bar{t}} = \lambda_2 (1 + x) y - \alpha_2 x.$$
Figure 1. The catastrophe surface in coordinates $(\psi, x_c, x_0)$, where $x_0$ is the abscissa of the critical point. For a given value of $(\psi, x_c)$ there are up to two critical points with $x_0 > 0$ and the trivial critical point corresponding to $x_0 = 0$. Notice that there are critical points with $x_0 < 0$ that are not considered. The folding of the surface projects into the saddle-node curve given by (10) in the plane $\psi-x_c$.

A critical point of the system $(x_0, y_0)$ satisfies

$$y_0 = \frac{\alpha_2 x_0}{\lambda_2 (1 + x_0)} \quad (6)$$

$$\frac{\lambda_1 \lambda_2^2}{\alpha_1 \alpha_2^2} = \frac{x_0^2 (1 - x_0/x_c)}{(1 + x_0)^3} \quad (7)$$

Therefore the abscissa $x_0$ of the critical points are determined by the roots of the cubic polynomial (7). In what follows the combination of parameters

$$\psi = \frac{\lambda_1 \lambda_2^2}{\alpha_1 \alpha_2^2}, \quad \lambda = \frac{\lambda_2}{\lambda_1} \quad (8)$$

will be very useful. In particular, the critical points can be described by the catastrophe surface

$$\Sigma = \{(\psi, x_c, x_0) \mid x_0^2 (1 - x_0/x_c) - \psi (1 + x_0)^3 = 0\}. \quad (9)$$

in the space of parameters $\psi$, $x_c$, $x_0$. This surface is shown in Figure 1. The plane $x_0 = 0$ correspond to the trivial critical point $(0,0)$ and is a saddle. The red line shows a case of the value of the parameters $(\psi, x_c)$ such that there are three critical points determined by their $x_0$ abscissa. At a point where the surface folds back, the number of critical points is three, counting the trivial one. The projection of this folding is given by the discriminant of the cubic,

$$\Delta = 4x_c^2 - 27(1 + x_c)^2 \psi = 0, \quad \text{or} \quad \psi = \frac{4x_c^2}{27(1 + x_c)^2}, \quad (10)$$

and defines a curve in the parameter plane $\psi-x_c$ where the projection $(\psi, x_c, x_0) \mapsto x_0$, restricted to $\Sigma$, loses range.
The rest of the paper is organized as follows: In section 2 we summarize the results of Liu et al [10] regarding the existence of saddle–node and Takens–Bogdanov bifurcations. In section 3 we state the main result of this paper, the existence of Bautin bifurcations and describe it explicitly in terms of a proper parametrization. In section 4 we describe the phase portraits derived from the global bifurcation diagram and represented schematically in Figure 3. Finally, in Section 5 we give an interpretation of our results.

In order to keep the mainstream of the paper, we postpone to the section of the Appendices some complementary computations. The main idea of the proof and details of the computation of the first and second Lyapunov coefficients are given in Appendix A. In Appendix B we perform the blow-up of infinity in order to complete the phase portraits of Section 4. The global bifurcation diagram is completed numerically with MatCont using the local diagrams of the Takens-Bogdanov and Bautin bifurcations as described in the Appendix C.

2. Saddle node and Hopf bifurcations. The following two results summarize the results by Liu et al [10].

**Proposition 1** (Liu et al). The parameter set

\[ SN = \left\{ (\lambda_1, \lambda_2, \alpha_1, \alpha_2, x_c) \mid \psi = \frac{4x_c^2}{27(1 + x_c)^2}, \lambda \neq \frac{2(3 + x_c)}{3(1 + x_c)} \right\} \]

are saddle–node bifurcations of the system (5). The phase portrait consists of two hyperbolic and one parabolic sectors.

Using (10) we can obtain, for fixed values of \( \alpha_1, \alpha_2, \) and \( x_c \) the saddle–node curve in the plane of parameters \( \lambda_1 - \lambda_2 \) in the form

\[ \lambda_1 \lambda_2^2 = \frac{4x_c^2\alpha_1\alpha_2^2}{27(1 + x_c)^2}, \] (11)

or in parametric form with parameter \( \lambda_1 \),

\[ \lambda_1 = \frac{1}{3} \left( \frac{4x_c^2\alpha_1\alpha_2^2}{(1 + x_c)^2} \right)^{1/3}, \quad \lambda_2 = \frac{1}{3} \left( \frac{4x_c^2\alpha_1\alpha_2^2}{\lambda(1 + x_c)^2} \right)^{1/3}. \]

Takens-Bogdanov bifurcations are given as follows:

**Theorem 2.1** (Liu et al). The parameter set

\[ BT = \left\{ (\lambda_1, \lambda_2, \alpha_1, \alpha_2, x_c) \mid \psi = \frac{4x_c^2}{27(1 + x_c)^2}, \lambda = \frac{2(3 + x_c)}{3(1 + x_c)} \right\} \] (12)

are non-degenerate Takens-Bogdanov bifurcations of system (5).

For a choice of parameters in \( BT \) the critical point undergoing a BT bifurcation is given by (6) and (7). As a previous construction towards proving our main result, we first characterize the Hopf bifurcations locus.

**Proposition 2.** The parameter set

\[ H = \{ (\lambda_1, \lambda_2, \alpha_1, \alpha_2, x_c) \mid (13) \text{ holds} \} \]

is the Hopf and symmetric saddle bifurcation surface of system (5),

\[(1 + x_c)^3\psi\lambda^3 - (\psi x_c^3 + (1 - \psi)x_c^2 - 5\psi x_c - 3\psi)\lambda^2 + (x_c^2 + 4x_c + 3)\psi \lambda + (1 + x_c)^2(1 + x_c\psi) \psi = 0. \] (13)
Proof. Let \( f, g \) denote the right hand sides in (5), then we look for a common root of the polynomial equations \( f = g = \text{tr} \mathbf{A} = 0 \), where \( \mathbf{A} = \frac{\partial (f, g)}{\partial (x, y)} \) and \( \text{tr} \mathbf{A} \) denotes the trace of \( \mathbf{A} \). We compute \( R_1 = \text{Resultant}[\text{tr} \mathbf{A}, f, y_0] \), \( R_2 = \text{Resultant}[\text{tr} \mathbf{A}, g, y_0] \) which are polynomials in \( x_0 \). A necessary condition for \( \text{tr} \mathbf{A} = 0 = f \) to have a common root is that \( R_1 = 0 \), and similarly a necessary condition for \( \text{tr} \mathbf{A} = g = 0 \) to have a common root is that \( R_2 = 0 \). Then compute \( R = \text{Resultant}[R_1, R_2, x_0] \) which is a polynomial in the parameters. A necessary condition for \( R_1 = R_2 = 0 \) to have a common root is that \( R = 0 \). If we exclude trivial factors, we end up with (13).

Liu et al [10] prove that a non–degenerate Takens-Bogdanov bifurcation occurs for any values of the positive parameters, thus excluding the possibility of codimension three degeneracy. Adam [1] gives sufficient conditions for the system (5) to undergo a Hopf bifurcation, although no explicit computation is done. Liu et al describe the Hopf bifurcation locus in terms of parameters involved in the normal form computation, but not explicitly. The expression in Proposition 2 gives an explicit parametrization of the locus of Hopf and symmetrical saddle bifurcations in the parameters.

3. Bautin bifurcation. We now give the main idea to compute the first Lyapunov coefficient for a critical point undergoing a Hopf bifurcation. Let \((x_0, y_0)\) be such a critical point. Then we shift the critical point to the origin \( x = x_0 + \epsilon x_1, y = y_0 + \epsilon y_1 \) and expand in powers of \( \epsilon \) in order to collect the homogenous components of the vector field. We first consider the linear part

\[
\begin{align*}
x'_1 & = a_1 x_1 + a_2 y_1, \\
y'_1 & = b_1 x_1 + b_2 y_1
\end{align*}
\]

and perform the linear change of variables \( Y_1 = b_2 x_1 - a_2 y_1, Y_2 = (a_1 b_2 - a_2 b_1) x_1 \).

Under the hypothesis of complex eigenvalues and the determinant \( a_1 b_2 - a_2 b_1 > 0 \) the system reduces to an oscillator equation \( Y'_1 = Y_2, Y'_2 = -\omega^2 Y_1 + 2\mu Y_2 \), with eigenvalues \( \lambda = \mu \pm i \sqrt{\omega^2 - \mu^2} \) and the Hopf condition becomes \( \mu = 0, \omega^2 = a_1 b_2 - a_2 b_1 \) (see Appendix A). We compute right and left eigenvectors \( q_0, p_0 \) such that \( \mathbf{A} q_0 = i\omega q_0, \mathbf{A}^T p_0 = -i\omega p_0 \), \( (p_0, q_0) = 1 \) and \( (p_0, q_0) = 0 \). Let \( Y = \epsilon q_0 + \bar{z} q_0 \). Then the nonlinear system reduces to (setting \( \epsilon = 1 \)) \( z' = \lambda z + G_2(z, \bar{z}) + G_3(z, \bar{z}) + \cdots \) then we compute \( \ell_1 \) by the formula given by [9, p.309–310].

As shown in appendix A, \( \ell_1 \) becomes a polynomial in \( x_0, y_0, \omega \) and after elimination of \( \omega^2 \) and \( \omega^4 \) which are the only powers appearing there, and of \( y_0 \) using (5), a polynomial in \( x_0 \) of degree 19 results. The main difficulty is that computing the abscissa \( x_0 \) of the critical point amounts to solving a cubic polynomial. Therefore we compute the resultant of \( \ell_1 \) with the cubic polynomial (9) and eliminate \( x_0 \). Taking a non–trivial factor of this, we then compute its resultant with the Hopf equation (13). There are two factors. One of these leads to the solution for \( \lambda = \lambda_2/\lambda_1 \),

\[
\lambda = \frac{-3 + x_c}{3(1 + x_c)}
\]

Substituting this value in the Hopf equation (13) we solve for \( \psi \) in an appropriate factor. We then get the following
Theorem 3.1. The parameter set
\[ \text{Bau} = \left\{ (\lambda_1, \lambda_2, \alpha_1, \alpha_2, x_c) \mid \psi = \sqrt{x_c \left( (-27 + x_c) \sqrt{x_c} + (9 + x_c)^{3/2} \right) / 27(1 + x_c)^2}, \lambda = -3 + x_c / (3(1 + x_c)) \right\} \] (16)
are Bautin points of codimension 2 of system (5), for an open set of values of \( x_c \).

Remark 1. The proof of the Theorem is given in Appendix A.

The computation of the first Lyapunov coefficient yields the parametrization (16). The calculation of the second Lyapunov coefficient is more involved but uses similar ideas. In Appendix A we reduce the problem to that of finding the roots of a high order polynomial in \( x_c \). We find numerically three roots \( x_c > 3 \), compatible with \( \lambda > 0 \) in (16), but for larger values of \( x_c > 88.79 \ldots \), approximately, we found that the second Lyapunov coefficient remains negative. This is the reason why we can only state the result for an open set of values of \( x_c \). Nevertheless, these small values of \( x_c \) are of no biological interest according to Table 1 in the Introduction.

3.1. Bifurcation diagram around a Bautin point. According to Theorem 8.2 [9, p. 311], there exists a parameter–depending change of variables, a reparametrization, and a change of parameters that reduces the system to the normal form
\[
\dot{z} = (\beta_1 + i)z + \beta_2|z|^2z + s|z|^4z + O(|z|^6) \tag{17}
\]
where \( s = \text{sign}(\ell_2(0)) = \pm 1 \) is the sign of the second Lyapunov coefficient at the critical value of the new parameters \( \beta_1 = \beta_2 = 0 \). We remark that in the proof of the aforementioned Theorem, a smooth change of parameters \( \beta_i = \beta_i(\lambda_1, \lambda_2) \), for \( i = 1, 2 \) has to be performed to obtain the normal form (17), but is not known explicitly.

The local bifurcation diagram around a Bautin point is shown in Figure 2 (see [9, p. 313]), in the plane of transformed parameters \( \beta_1, \beta_2 \), as explained in the previous paragraph, for \( s = 1 \) (if \( s = -1 \) the bifurcation diagram is obtained by the transformation \( (\beta, t) \mapsto (-\beta, -t) \), so in particular the stability of the limit cycles are exchanged). There are two components of the Hopf curve \( H_\pm \) corresponding to the sign of the first Lyapunov coefficient \( \ell_1(\beta_2) \) in the diagram. Thus when crossing the component \( H_- \) from positive values of \( \beta_1 \), a stable limit cycle appears and similarly, when crossing the component \( H_+ \), there appears an unstable limit. Therefore, in the cusp region marked as 3, there coexist two limit cycles, the exterior one being stable, the interior unstable, and both collapse along the LPC (limit point of cycles) curve.

These local pictures of the Bautin bifurcation (Theorem 2), Takens–Bogdanov (Theorem 1) and the global curve of Hopf bifurcations (Proposition 2) will be completed in the following section by numerical continuation. Finally, we obtain the qualitative phase portraits by adding the flow at infinity as explained in Appendix B.

4. Global dynamics. Figure 3 shows schematically the bifurcation diagram as computed numerically with MatCont in Figure 10-b of Appendix C. There are shown three generic lines of constant values of \( \lambda_2 \), varying \( \lambda_1 \). We will now describe the qualitative phase portrait along these lines. For the upper line \( CT \) corresponding to a value of \( \lambda_2 \) just below the Takens–Bogdanov point \( BT \), the dynamics can be described as follows: In passing from a point \( C \) to a point \( D \) the trivial critical point
connects to the saddle point along a heteroclinic orbit. This happens at the point marked as $K$. Indeed a curve of heteroclinic connections is depicted along with the points $KK'K''$ although we have not computed it numerically. In Figure 4, it is shown the transition along $CT$. In–between $C$ and $D$, a heteroclinic connection $K$ occurs, and then a limit cycle bifurcates from a homoclinic connection at $P$; this limit cycle persist along the open interval $A$ and disappears at a transcritical Hopf bifurcation, at the intersection of the Hopf curve, and finally ends up at the saddle–node $T$. For completeness, we have included in Figure 10-b the flow at infinity as described in Appendix B. The critical points at infinity $y = \infty$ are shown as blue points. Notice the hyperbolic sector for $x = 0$ and the attractor at $x = x_c$.

Similarly, the evolution of the phase portrait along the line $C'T'$ is described in Figure 5. The evolution along the part $C'K'D'P'A'$ is the same as $CKDPA$ in Figure 4, the difference is at the further development of an unstable limit cycle inside the stable limit cycle previously created by a homoclinic bifurcation at $P'$; this cycle persists along the interval $A'$ and then a new cycle appears through a Hopf bifurcation and both cycles continue existing in the interval $R'$ to finally coalesce and disappear at $T'$, a limit point of cycles.

Finally the evolution along the line $C''T''$ is described as follows: The phase portrait along $C''K''D''$ is the same as in $C'K'D'$. In comparison to the previous case, after $D''$ a Hopf bifurcation occurs and an unstable limit cycle continues along $A''$; then a second stable limit cycle originating in a homoclinic bifurcation coexists with the previous limit cycle along $R''$. The whole evolution along the line $C''T''$ is shown in Figure 6 where only the phase portraits different from the previous case are denoted as $A''$ and $P''$.

Figure 7-(a) and (c) shows in detail the evolution along $C'T'$ in the triangular region of coexistence of two limit cycles, with $\lambda_1$ as the $z$-axis. Notice that along
Figure 3. Schema of the bifurcation diagram computed numerically in Figure 10-b. The codes of the lines are as follows: SS (blue) symmetric–saddle; H (green) Hopf; SN (black dotted) saddle–node; LPC (red) limit point of cycles; Hom (magenta) homoclinic. Special points are BT(Takens–Bogdanov) and GH(Bautin).

Figure 4. Qualitative phase portrait along the line $CKDPAT$ of the bifurcation scheme in Figure 3.

with increasing values of $\lambda_1$, first, a limit cycle bifurcates from a homoclinic and then the second cycle bifurcates from a Hopf point. In comparison, Figure 7-(b) and (d) shows the evolution along $C''T''$ where first, a limit cycle originates from a Hopf bifurcation and then a second cycle through a homoclinic bifurcation.

5. Implications of the model on the equilibrium phase of IET. In what follows we will be interested in non–negative values of the parameters and $x$ within the range $0 < x < x_c$. Since $x' < 0$ if $x = x_c$ and $y' < 0$ if $y = 0$, it follows that
Figure 5. Qualitative phase portrait along the line $C'K'D'P'A'T'$ of the bifurcation scheme in Figure 3. The phase portrait along the segment $C'K'D'P'A'$ is the same as $CKPDA$.

the region $0 < x < x_c$, $0 < y$ is invariant. This delimits the region of real interest (ROI) in the model.

**Proposition 3** (Elimination threshold). Given $\alpha_1$, $\alpha_2$, $\lambda_2$, $x_c$, there exists $\lambda_1^*$ such that if $\lambda_1 > \lambda_1^*$, there exists a curve $y = h(x)$ such that for any initial condition $(x_0, y_0)$ such that $y_0 < h(x_0)$ then there exists $T > 0$ such that $y(T) = 0$.

**Proof.** Fix $\alpha_1$, $\alpha_2$, $\lambda_2$ and $x_c$. Since the saddle–node curve is the hyperbola $\lambda_1 \lambda_2^2 = \text{const}$ (see Proposition 1), then for $\lambda_1$ large enough the unique critical point is the origin and is a saddle with the positive $y$ axis as a branch of the unstable manifold. Let us consider the rectangular region within the ROI

$$R = \{(x, y) \mid 0 < x < x_c, \quad 0 < y < k\}$$

We have seen that on the boundary $x = x_c$, $x' < 0$; on the boundary $y = 0$, $y' < 0$. Let us analyze the upper boundary $y = k$; since $x$ remains bounded, it follows that $y' = \lambda_2 y (1 + x) - \alpha_2 x$ is positive for $y = k$ large enough. We now follow the unstable manifold $W^s(0, 0)$ backwards in time. A straightforward computation of the stable eigenvalue shows that a small components of $W^s(0, 0)$ belongs to $R$, since there are no critical points within $R$ it follows that it must intersect the line $x = x_c$. It remains to show that in fact the component of $W^s(0, 0)$ within the region $0 < x < x_c$ can be expressed as the graph of a function $y = h(x)$. Now from the
first equation \( x' = -\lambda_1 x(1 + x) + \alpha_1 x(1 - x/x_c)y^2 \), since \( x, y \) remain bounded and \( \lambda_1 \) is large enough, it follows that \( x' < 0 \), and the result follows. \( \square \)

Proposition 3 defines a threshold value of the population of cancer cells \( y_c \) given by the intersection of \( W^s(0, 0) \) and the line \( x = x_c \), namely \( y_c = h(x_c) \): let \( y_0 \) be an initial population of cancer cells \( y_0 < y_c \), for a given growth parameter \( \lambda_2 \) and interaction constants \( \alpha_{1,2} \) then there exists \( x_0 = h^{-1}(y_0) \) such that for \( x_0' > x_0 \) the evolution of cancer cells \( y(t) \) with initial condition \((x_0', y_0)\) becomes zero. Geometrically, the horizontal line \( y = y_0 \) in phase space intersects the graph of the curve \( y = h(x) \) at a point \((\bar{x}_0, \bar{y}_0)\) and for an initial population of lymphocytes large enough \( x_0 < x_0' < x_c \), the solution with initial condition \((x_0', y_0)\) crosses the line \( y = 0 \) for some finite time \( T \) and \( y(T) = 0 \). See Figure 9.

Notice that the above dynamics occurs in the scaled variables \((x, y)\). The branch of the stable manifold \( y = h(x) \) transforms back to the original variables \((x, \bar{y})\) into a curve \( \bar{y} = h(x)^3 \) however, in the original variables the locus \( \bar{y} = 0 \) does not make sense for two reasons: the first one is that the model breaks down because of the hypothesis of a spherical tumor. The second is that the system (1) is not Lipschitz for \( \bar{y} = 0 \). Indeed one expects non–uniqueness as in the well–known example \( \bar{y}' = \bar{y}^{2/3} \). Nevertheless the threshold curve is still defined in the original variables \((x, \bar{y})\), and since the change or variables is of class \( C^1 \) outside this singular locus \( \bar{y} = 0 \), the same dynamical behavior occurs in the non–scaled variables.
According to the Immune Edition Theory (IET) the relation between tumor cells and the immune system is made up of three phases (commonly known as the three E’s of cancer): elimination, equilibrium and escape [7]. Although not in this terminology, Delisi and Resigno [6], describe these phases in terms of regions delimited by the zeroclines. For example the authors mention that within the region $x’ < 0, y’ > 0$, denoted by $A$ in [6], solution evolves eventually to escape to $x = x_c, y = \infty$. According to the Threshold Proposition 3, this is true for initial
conditions above the curve $y = h(x)$. Here we describe in more detail the three phases according to the regions delimited by the invariant manifold and basins of attraction. For example, the elimination phase is described as the region below the threshold curve; the explosive phase as the basin of attraction of the point at infinity obtained by the compactification of phase space along the $y$ direction (see Appendix B). The equilibrium phase is constituted by the basins of attraction of either a stable anti–saddle or a stable limit cycle.

The existence of a Bautin bifurcation and the global bifurcation diagram continued numerically, implies the existence of a triangular region in the plane of parameters $\lambda_1–\lambda_2$ delimited by the Hopf, LPC and homoclinic curves, for fixed values of $\alpha_1$, $\alpha_2$, and $x_c$ as shown in Figure 10. Within this region, two limit cycles exist and the detailed analysis of the phase diagrams along the lines $CT$, $C'T'$ and
In Figure 3, leads to the conclusion that the inner limit cycle is unstable and the exterior one is stable. These two limit cycles are shown in Figure 7, the corresponding plots against the time are shown in Figure 8. This implies that for an initial condition within the interior of the inner limit cycle, the solution tends asymptotically to the values of the stable equilibrium. This would correspond to the escape phase in the IET. Meanwhile, for an initial condition just outside the unstable inner cycle, the population of cancer cells and lymphocytes grow in amplitude and tends towards a periodic state but of larger amplitude. This yields a new type of qualitative behavior predicted by the model.

Escape phase in the IET corresponds to the basin of attraction of the point at infinity \( x = x_c, y = +\infty \). The analysis in Appendix B shows that this point is stable, so there is an open set of initial conditions leading to the escape phase. The basin of attraction of the point at infinity is delimited by the threshold curve and by the unstable manifolds of the saddle point with positive coordinates, here denoted as \((x_s, y_s)\). The structure of its stable and unstable branches delimits three types of behavior leading to escape. In the first one, for an initial condition \( x_0 > x_s \) and \( y_0 \) large enough, there is a transitory evolution of diminishing values of cancer cells \( x(t) \) less that \( x_s \) but finally leading to escape. This region is delimited by the unstable branch connecting \((x_s, y_s)\) and the point at infinity and the stable branch crossing the line \( x = x_c \). The second type of evolution leading to escape occurs for an initial condition of large values of the initial population of lymphocytes \( x_0 \) with a great diminishing of \( x(t) \), namely less than \( x_a \), the abscissa of the anti–saddle critical point \((x_a, y_a)\), following an increase of cancer cells and lymphocytes leading finally to escape. This kind of solutions can be described as a turn around the anti–saddle before escaping. A third and more complex behavior occurs when the initial condition lies on the boundary of the basin of attraction of a limit cycle. In this situation, a small perturbation can lead to oscillations of increasing magnitude and finally the solution tends to escape.

**Appendix A. Computation of the first and second Lyapunov coefficients.**

In this Appendix we give the proof of Theorem 2. We first give Lyapunov coefficient at a Hopf point.

Let \((x_0, y_0)\) be a critical point of (5). Replacing \( x = x_0 + x_1, y = y_0 + y_1 \) in (5),

\[
\begin{align*}
\frac{dx_1}{dt} &= -\lambda_1 (x_0 + x_1)(1 + x_0 + x_1) + a_1 \left(1 - \frac{x_0 + x_1}{x_c}\right) (x_0 + x_1)(y_0 + y_1)^2 \\
\frac{dy_1}{dt} &= \lambda_2 (y_0 + y_1)(1 + x_0 + x_1) - a_2 (x_0 + x_1),
\end{align*}
\]

and expanding we have

\[
\begin{align*}
x'_1 &= a_0 + a_1 x_1 + a_2 y_1 + a_3 x_1^2 + a_4 y_1^2 + a_5 x_1 y_1 + a_6 x_1^2 y_1 + a_7 x_1 y_1^2 + a_8 x_1^2 y_1^2 \\
y'_1 &= b_0 + b_1 x_1 + b_2 y_1 + b_3 x_1 y_1,
\end{align*}
\]

where

\[
\begin{align*}
a_0 &= -\lambda_1 x_0 (1 + x_0) + a_1 \left(1 - \frac{x_0}{x_c}\right) x_0 y_0^2, \\
b_0 &= \lambda_2 y_0 (1 + x_0) - a_2 x_0.
\end{align*}
\]

Of course \( a_0 = b_0 = 0 \) yields the equations for the critical points. The rest of the coefficients are

\[
\begin{align*}
a_1 &= -\lambda_1 (1 + 2x_0) + a_1 \left(1 - \frac{2x_0}{x_c}\right) y_0^2, \\
a_2 &= 2\alpha_1 x_0 y_0 \left(1 - \frac{x_0}{x_c}\right),
\end{align*}
\]
\[a_3 = -\lambda_1 - \alpha_1 x_0, \quad a_4 = \alpha_1 x_0 \left( 1 - \frac{x_0}{x_c} \right),\]
\[a_5 = 2\alpha_1 y_0 \left( 1 - \frac{2x_0}{x_c} \right), \quad a_6 = \alpha_1 \left( 1 - \frac{2x_0}{x_c} \right),\]
\[a_7 = -2\alpha_1 y_0 \frac{x_0}{x_c}, \quad a_8 = -\frac{x_0}{x_c},\]
\[b_1 = \lambda_2 y_0 - \alpha_2, \quad b_2 = \lambda_2 (1 + x_0),\]
\[b_3 = \lambda_2.\]

Consider the linear part \(x' = Ax\) where \(x = (x_1, y_1)^T\) and
\[A = \begin{pmatrix} a_1 & a_2 \\ b_1 & b_2 \end{pmatrix}\]
Perform the linear change of coordinates
\[Y = Mx, \quad (19)\]
where \(Y = (Y_1, Y_2)^T\) and
\[M = \begin{pmatrix} b_2 & -a_2 \\ a_1 b_2 - a_2 b_1 & 0 \end{pmatrix}\]
then the linear system is transformed into
\[Y' = RY, \quad R = \begin{pmatrix} 0 & 1 \\ -\det(A) & \tr(A) \end{pmatrix}.\]
Then \(R\) has the canonical form
\[R = \begin{pmatrix} 0 & 1 \\ -\omega^2 & 2\mu \end{pmatrix}\]
where we have supposed and set that \(0 < \det(A) \equiv \omega^2, \tr(A) = 2\mu\) and \(\mu^2 - \omega^2 < 0\) so we have complex eigenvalues \(\lambda = \mu \pm i\sqrt{\omega^2 - \mu^2}\).

Let us consider that the real part of the eigenvalues is zero \((\mu = 0)\), then
\[R_0 = \begin{pmatrix} 0 & 1 \\ -\omega^2 & 0 \end{pmatrix},\]
and we want to find vectors \(q_0\) and \(p_0\), such that \(R_0 q_0 = i\omega q_0, R_0^T p_0 = -i\omega p_0, \langle p_0, q_0 \rangle = 1\) and \(\langle p_0, q_0 \rangle = 0\). We find
\[q_0 = \frac{1}{2i\omega} \begin{pmatrix} 1 \\ i\omega \end{pmatrix}\]
and
\[p_0 = \begin{pmatrix} -i\omega \\ 1 \end{pmatrix} .\]

Let us transform the complete system (18) at a critical point with complex eigenvalues \(\lambda \pm i\omega\)
\[x' = Ax + H_2(x) + H_3(x) + \cdots,\]
by means of the change of variables (19), then
\[Y' = MA_0 x + MH_2(x) + MH_3(x) + \cdots,\]
\[= MA_0 (M^{-1} Y) + MH_2 (M^{-1} Y) + MH_3 (M^{-1} Y) + \cdots\]
\[= R \begin{pmatrix} Y_1 \\ Y_2 \end{pmatrix} + K_2 \begin{pmatrix} Y_1 \\ Y_2 \end{pmatrix} + K_3 \begin{pmatrix} Y_1 \\ Y_2 \end{pmatrix} + \cdots\]
where \(K_l = MH_l M^{-1}\), for \(l = 2, 3, \ldots\)
Now introduce the complex variable $z$ by
\[
\begin{pmatrix}
Y_1 \\
Y_2
\end{pmatrix} = zq_0 + \bar{z}\bar{q}_0,
\]
then system is reduced to the normal form
\[
z' = \lambda z + \langle p_0, K_2(zq_0 + \bar{z}\bar{q}_0) \rangle + \cdots
\]
\[
= \lambda z + G_2(z, \bar{z}) + G_3(z, \bar{z}) + \cdots
\]
where
\[
G_l = \langle p_0, K_l(zq_0 + \bar{z}\bar{q}_0) \rangle, \quad l = 2, 3, \ldots
\]
and $g_{ij} = \frac{1}{i!j!} \frac{\partial G_i}{\partial z^i \partial \bar{z}^j}$, for $i, j = 0, 1, \ldots$. For the computation of the first Lyapunov coefficient we will need the expansion up to third order terms and for the second coefficient up to the fifth order.

We will compute the first Lyapunov coefficients using the formulas (3.18) in [9] for the coefficient $c_1(0)$ of the Poincaré normal form and
\[
\ell_1(0) = \frac{\text{Re}(c_1(0))}{\omega}
\]
where
\[
c_1(0) = \frac{g_{21}}{2} + \frac{g_{20}g_{11}i\omega}{2\omega^2} - i \frac{g_{11}g_{11}}{\omega} - i \frac{g_{02}g_{02}}{6\omega}.
\]

Observe that the change of coordinates (19) contains the coordinates of the critical point $(x_0, y_0)$ and so the coefficients $g_{ij}$. Therefore, we have to impose on the formal expression we get using (20) from the coefficients $g_{ij}$ up to third order, the restriction of a critical point, with zero real part and positive determinant equal to $\omega^2$. We achieve this as follows: The expression (20) is a polynomial expression depending on $(x_0, y_0)$ and the parameters $P(x_0, y_0, \lambda_1, \lambda_2, x_c, \alpha_1, \alpha_2)$. First we eliminate $y_0$ using (6) and obtain a polynomial expression in $x_0$ of order 19 and the parameters and still denote by $P(x_0, \lambda_1, \lambda_2, x_c, \alpha_1, \alpha_2)$. The abscissa $x_0$ of the critical point satisfy the cubic equation (7) written here as $Q(x_0, \lambda, \psi, x_c)$. Surprisingly, the coefficients of $P$ and $Q$ can be expressed solely in terms of the combination of parameters $\lambda, \psi$ and $x_c$. Next we eliminate $x_0$ using the resultant
\[
R_{P,Q}(\lambda, \psi, x_c) = \text{Resultant}[P(x_0, \lambda, \psi, x_c), Q(x_0, \lambda, \psi, x_c), x_0].
\]
Also the Hopf surface can be expressed in terms of the same combination of parameters as shown in (13) as $R(\lambda, \psi, x_c) = 0$, then we compute
\[
R_3(\lambda, x_c) = \text{Resultant}[R_{P,Q}(\lambda, \psi, x_c), R(\lambda, \psi, x_c), \psi]
\]
and we get from a non trivial factor of $R_3$
\[
\lambda = \frac{-3 + x_c}{3(1 + x_c)}.
\]

Finally, substituting (21) in the Hopf surface $R(\lambda, \psi, x_c) = 0$ we get the nonnegative solution
\[
\psi = \frac{\sqrt{x_c} \left( (-27 + x_c) \sqrt{x_c} + (9 + x_c)^{3/2} \right)}{27(1 + x_c)^2}. \quad (22)
\]
Expressions (21) and (22) are those given in (16).

Next we compute the second Lyapunov coefficient similarly, but with minor differences. We use formula (8.23) of [9, p. 310] and we obtain the polynomial
We eliminate $y_0$ using (6) and obtain $P_2(x_0, \lambda_1, \lambda_2, x_c, \alpha_1, \alpha_2)$. This expression can also be given in terms of $\psi$, $\lambda$, $x_c$ and $x_0$; write this as $P_2(x_0, \lambda, \psi, x_c)$. Next we compute the resultant with the cubic polynomial (9) for the abscissa of the critical point with respect to $x_0$. Thus we obtain

$$R_{P_2,Q}(\lambda, \psi, x_c) = \text{Resultant}[P_2(x_0, \lambda, \psi, x_c), Q(x_0, \lambda, \psi, x_c), x_0].$$

We evaluate $R_{P_2,Q}$ at the Bautin points parametrized by (16), eliminating $\psi$ and $\lambda$. The resulting expression is algebraic in $x_c$ but can be written in polynomial form in terms of an auxiliary variable. Denote any of the non trivial factor of the resulting expression as $D_2(x_c)$ which is a product of two polynomials of orders 39 and 106. This polynomial has the following roots $x_e > 3$ up to 16 decimal figures (other roots are negative or $x_e < 3$ which give negative values of $\lambda$ in (16) and are discarded):

$$3.9452439348678707\ldots, \quad 7.984380476628895\ldots, \quad 88.79056679626245\ldots$$

For $x_e > 88.79056679626245\ldots$, $D_2(x_e)$ remains negative.

We remark that due to the high order of the polynomial $D_2(x_e)$, a small numerical error in the determination of a root produces a drastic change in its value, so we cannot verify that effectively $D_2(x_e)$ vanishes at the above roots approximated to this order. Instead we verify that a change of sign of $D_2(x_e)$ occurs in a neighborhood of these roots. Moreover, since $x_e$ represents the number of lymphocytes (see Table 1 in the Introduction) such small values are of no oncological interest. This completes the proof of Theorem 2.

**Appendix B. Blow up of infinity.** In order to study solutions that escape to infinity in the direction $y \to \infty$ we perform a blow up of infinity by the change of variables $(x, y) \mapsto (x, v = x/y)$, a further rescaling of time $dt/dt' = v^2$ extends the system up to $v = 0$ corresponding to infinity $y = \infty$, $x > 0$ (5)

$$\frac{dx}{dt'} = -\lambda_1 x(1+x)v^2 + \alpha_1 x^3 \left(1 - \frac{x}{x_c}\right),$$
$$\frac{dy}{dt'} = vx \left(\lambda_1 x \left(1 - \frac{x}{x_c}\right) - \lambda_2\right) + \alpha_2 v^2 - v^3(\lambda_1 (1+x) + \lambda_2).$$

(23)

We see that $v = 0$ becomes invariant and the reduced system at infinity is

$$\frac{dx}{dt'} = x^3(1-x)$$

showing that along $v = 0$, $x > 0$, $x = x_e$ an attractor.

To determine the local phase portrait of system (23) at the critical point $x = x_e, v = 0$, we compute its linearization

$$A = \begin{pmatrix} -x_e^2 \alpha_1 & 0 \\ 0 & -x_e \lambda_2 \end{pmatrix}$$

thus $(x_e, v = 0)$ is an attractor. The origin $x = 0 = v$ is also a degenerate critical point with zero linear part with terms of third order the least. Performing a radial blow using polar coordinates $x = r \cos \theta$, $v = r \sin \theta$ we get

$$\frac{dr}{dt} = r(-\lambda_1 + \alpha_1 \cot^2 \theta - \lambda_2 \sin^2 \theta) + r^2 \left(-\lambda_1 \cos^2 \theta + \alpha_2 \sin^3 \theta - \frac{\alpha_1}{x_e} \cot^2 \theta - (\lambda_1 + \lambda_2) \cos \theta \sin^2 \theta\right)$$
which shows that $r = 0$, $0 < \theta < \pi/2$ is invariant. Setting $r = 0$ we get
\[
\frac{d\theta}{dt} = -\lambda_2 \cos \theta \sin \theta
\]
which is always negative for $0 < \theta < \pi/2$. Thus the origin is a degenerate critical point with a hyperbolic sector.

**Appendix C. Numerical continuation.** Following [6], [10] we take the numerical values

\[
\lambda_1 = 0.01, \quad \lambda_2 = 0.006672, \quad \alpha_1 = 0.297312, \quad \alpha_2 = 0.00318, \quad x_c = 2500
\]

satisfying conditions (12) for a BT bifurcation of (5), and the coordinates $x_0 = 1.9976$, $y_0 = 0.317619$ for the critical point computed from (6) and (7). The scaled values (24) correspond to dimensional parameters shown in Table 1.

Figure 10 (a)–(b) shows the family of homoclinic connections in phase space, originating from the BT critical point. Since continuing the family of homoclinics from the BT point sometimes is difficult (see [2]), for the computation of the initial member of the family of homoclinics we use the homotopy method near the previous values of $\lambda_1$, $\lambda_2$ and then continue forward and backward to assure that the family originates from the BT point. The curve of homoclinics is shown in Figure 10-b as the violet curve. The Bautin point (GH) is detected by continuing the Hopf curve from the BT point.

The numerical bifurcation diagram of Delisi model is shown in Figure 10 (b). The saddle-node bifurcation curve is shown in black, the green corresponds to the Hopf bifurcation, the curve in red corresponds to the saddle-node bifurcation of periodic orbits (limit point of cycles) and the blue one to symmetric saddles.

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Figure 10. Numerical continuation of bifurcation diagram with MatCont. Saddle-node: black; Hopf: green; limit point of cycles: red; symmetric saddles: blue; homoclinic: violet.

Received July 2018; 1st revision April 2019; 2nd revision May 2019.

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