Convergence and basin geometry in the NK–CTL model

A note for Victor Garcia

Summary. This note proves two results about the tumor–NK–CTL model of Garcia, Bonhoeffer and Fu [1], Eqs. (21)–(23), with the immune constants of its Table 3. First (Theorem 2): for every tumor growth rate $0 < a \le 2$ and all $b, U, V > 0$, every finite nonnegative solution converges to an equilibrium, so the model has no sustained oscillations or other recurrent motion. Second: at the printed values $a = 257/500$ and $b = 51/50000000000$, the model has two hyperbolic sinks (the tumor-free state and the larger positive equilibrium) exactly when $a < U < U_*$ and $0 < V < V_s(T(U))$; within the strictly positive octant, their basins are open and their common relative boundary is exactly the saddle's two-dimensional stable manifold. Here U, V are the rescaled immune strengths and U_*, V_s are explicit thresholds, all defined below. The paper already had the quintic stationary reduction and showed the bistability numerically (Fig. A2); what is new here is the proofs.

Garcia, Bonhoeffer and Fu [1], Eqs. (21)–(23), describe tumor cells T, natural killer cells N, and cytotoxic T lymphocytes E. Set $y = N/\sigma$, $z = E/(\sigma\omega)$, $U = c\sigma$ and $V = k\sigma\omega$, where $c, k, \sigma, \omega > 0$ are the paper's parameters. Time (in days) and T are unchanged. This rescales the immune variables; it does not make all variables dimensionless. All growth thresholds below use this same time unit. The normalized system is

$$\dot T = T[f(T) - Uy - Vz], \qquad \dot y = 1 - n(T)y, \qquad \dot z = Ty - e(T)z, \qquad f(T) = a(1 - bT). \tag{1}$$

Here $a, b, U, V > 0$. Dots denote time derivatives; primes denote derivatives in T. At the ten literal immune constants of Table 3,

$$n(T) = 1 - \frac{3T}{2(10000 + T)} + \frac{T}{1000 + T}, \qquad e(T) = 2 - \frac{T}{500 + T} + \frac{2T}{25000 + T}. \tag{2}$$

The parameters $\mu, b_n, d_n, d, b_e, d_e$ keep their Table 3 names and have values $1, 3/2, 1, 2, 1, 2$, respectively. We write $(K_b, K_d, H_b, H_d) = (\kappa_{bn}, \kappa_{dn}, \kappa_{be}, \kappa_{de}) = (10000, 1000, 500, 25000)$ for the four saturation constants. Table 3 also gives $a = 257/500$ and $b = 51/50000000000$. Appendix C, Eqs. (76)–(78), gives the immune nullclines and the rational stationary reduction. Define

$$F(T) = f(T) - \frac{U}{n(T)} - \frac{VT}{n(T)e(T)}.$$

This rational per-capita residual differs from the polynomial called F in Appendix C. Positive equilibria are $(T, 1/n(T), T/[n(T)e(T)])$ with $F(T) = 0$. The boundary equilibrium is $(0, 1/n(0), 0)$. The paper already gives the quintic reduction and numerical bistability (Fig. A2). Its discussion preceding Eqs. (79)–(80) correctly distinguishes stability along the nullcline from stability in three dimensions.

A sufficient criterion for variable rates. The following criterion concerns actual trajectories of (1).

Theorem 1. *Let n, e be positive C^1 functions on $[0, \infty)$. Suppose positive constants M_n, m_e, M_e, m, γ satisfy*

$$n \le M_n, \quad m_e \le e \le M_e, \quad ne \ge m, \quad |Tn'/n^2| \le \gamma.$$

Suppose F has finitely many positive zeros. Put

$$L = \max\{aM_n(a + M_e),\ aM_n \max(M_n - m_e, 0)\}.$$

If $\gamma L < m$, every solution with finite nonnegative initial state converges to one equilibrium. The equilibrium can depend on the initial state.

Proof. Since $n \ge m/M_e$, logistic and linear comparisons bound T, y, z and give global existence. The face $T = 0$ converges directly. For $T > 0$, put $p = f - Uy - Vz$, $r = y - 1/n$, $C = Tn'/n^2$, $D = e + abT$, and $B = U(n - e) - VT$. Then

$$\dot r = -nr + Cp, \qquad \dot p = -Dp + eF + Br. \tag{3}$$

Comparison gives $\liminf y \ge 1/M_n$. Since $p \le f \le a$, $(z/T)' = y - (e+p)z/T \ge y - (M_e + a)z/T$, $\liminf z/T \ge 1/[M_n(a+M_e)]$. If $U \ge aM_n$, then for each $\epsilon > 0$, eventually $\dot{T} \le T(\epsilon - abT)$. Thus $\limsup T \le \epsilon/(ab)$, which proves $T \to 0$, including equality. Otherwise

$$\limsup T \le \frac{a - U/M_n}{ab + V/[M_n(a+M_e)]} < \frac{1}{b}, \qquad \limsup VT \le (aM_n - U)(a + M_e). \tag{4}$$

The upper bound is $B \le U\max(M_n - m_e, 0) \le L$. The lower bound is $B \ge -UM_e - VT \ge -aM_n(a+M_e) + Ua - \varepsilon$ eventually, by (4). Thus eventually $|B| \le L + \varepsilon$. Set $\delta = m - \gamma L > 0$, $q = L/\gamma$, and $\varepsilon = \min\{L, \delta/(5\gamma)\}$. For $Q_0' = -eF/T$, the energy $\mathcal{E}_0 = p^2/2 + qr^2/2 + Q_0(T)$ satisfies

$$\dot{\mathcal{E}}_0 = -Dp^2 - qnr^2 + (B + qC)pr, \quad 4qnD - (B+qC)^2 \ge 3L\delta/\gamma > 0.$$

Indeed $nD \ge m$ and $|B + qC| \le 2L + \varepsilon$, so $4qnD - (B+qC)^2$ is at least $4L\delta/\gamma - 4L\varepsilon - \varepsilon^2 \ge 3L\delta/\gamma$. On the bounded tail this is strict quadratic damping. The boundary and invariance argument in the boundary section completes the proof. □

Open sufficient rate regions. Here is an explicit way to apply Theorem 1 without fixing decimals. Write

$$n = \mu - \frac{b_n T}{K_b + T} + \frac{d_n T}{K_d + T}, \qquad e = d - \frac{b_e T}{H_b + T} + \frac{d_e T}{H_d + T}.$$

All ten constants are positive. Assume $K_d < K_b$, $H_b < H_d$, $d > b_e$, $d_e > b_e$, and $n_\infty = \mu + d_n - b_n > 0$. Put $e_\infty = d + d_e - b_e$ and choose

$$m_e = d - b_e, \quad M_e = e_\infty, \quad m = \tfrac{14}{15} n_\infty e_\infty, \quad \gamma = \tfrac{1}{2\mu},$$
$$M_n = \max\left\{\mu, n_\infty + \frac{\max(\sqrt{b_n K_b} - \sqrt{d_n K_d}, 0)^2}{K_b - K_d}\right\}.$$

Define $D_n = (K_b + T)(K_d + T)$, $D_e = (H_b + T)(H_d + T)$, $\mathcal{N} = nD_n$ and $\mathcal{H} = eD_e$. Require every coefficient of $\mathcal{N}\mathcal{H} - mD_nD_e$ to be positive. For each quartic $\gamma\mathcal{N}^2 \pm T(\mathcal{N}'D_n - \mathcal{N}D_n') = \sum_{j=0}^4 p_j T^j$, require $p_0, p_1, p_2, p_4 > 0$ and $p_3 > -2\sqrt{p_2 p_4}$. Together with $\gamma L < m$, these are strict, continuous sufficient conditions. They define an open region in the elementary rates. The bounds follow by maximizing the difference of the two reciprocal saturation terms and grouping $p_2T^2 + p_3T^3 + p_4T^4$. They are sufficient, with no maximality assertion.

At (2) one may use $M_n = 3/2$, $m_e = 1$, $M_e = 3$, $m = 7/5$, $\gamma = 1/2$. All coefficient conditions hold, and for $0 < a \le 13/25$, $\gamma L \le 858/625 < 7/5$. Every $b, U, V > 0$ is allowed. At these exact rates this range is subsumed by Theorem 2. The purpose of the open region is robustness to changes in the immune rates.

There is also a distinct system suggested by the released scalar NK helper: replace n by $n_c = \mu - b_nT/(K_b + T^2) + d_nT/(K_d + T)$ and retain e. If

$$d_nK_b - b_nK_d > \frac{b_n^2}{4d_n}, \qquad d > b_e, \quad d_e > b_e, \quad H_b < H_d,$$

one may take $M_n = \mu + d_n$, $m_e = d - b_e$, $M_e = e_\infty$, $m = \mu(d - b_e)$, and $\gamma = [d_n/4 + b_n/(2\sqrt{K_b})]/\mu^2$. The first inequality proves $n_c \ge \mu$ by completing a square; $|Tn_c'| \le d_n/4 + b_n/(2\sqrt{K_b})$ proves the derivative bound. At the Table 3 fixture, $\gamma = 103/400$ and $m = 1$. For $0 < a \le 27/50$, $\gamma L \le 492237/500000 < 1$. These rational models have finitely many equilibrium zeros because F is nonzero and tends to $-\infty$.

Fold and basin geometry at the printed growth rate. Now fix the rates in (2) and the printed a, b. Let $g = e - Te'$, so $g \ge 1$. All positive multiple equilibria are parametrized by

$$V_s(T) = \frac{e^2(fn' - abn)}{g}, \qquad U_s(T) = fn - \frac{T}{e}V_s(T), \qquad 0 < T < T_*. \tag{5}$$

Here T_* is the unique positive zero of $(1 - bT)n' - bn$, lying in $(0, 2200)$. Exactly, $V_s' < 0$, $U_s' = -(T/e)V_s' > 0$, $U_s(0) = a$ and $V_s(0) = 10922486893/12500000000000$. Put $U_* = f(T_*)n(T_*)$. For $a < U < U_*$, there are two positive equilibria when $0 < V < V_s(T(U))$, where $T(U)$ is the inverse of U_s on $(0, T_*)$. There are none above this curve; on it there is one double root. For $U \ge U_*$ there is none. For $U < a$ there is one. For $U = a$ there is one precisely when $V < V_s(0)$. For orientation, $T_* \approx 2132.60$ and $U_* \approx 0.7284$; the checker bounds them by $(2132.60, 2132.61)$ and $(0.72839, 0.72840)$.

To justify the count, clear the positive rational denominators in F. The quintic has at most two positive roots counted with multiplicity. Write its coefficients as $\alpha_j - \beta_j U - \gamma_j V$. For $0 \le j \le 4$, $\beta_j > 0$ and the thresholds $(\alpha_j - \gamma_j V)/\beta_j$ form a unimodal sequence. Thus positive coefficients form one block; the leading coefficient is negative. Descartes' rule applies. The checker proves the threshold ordering and fold signs exactly. Along the fold, differentiating $F = F' = 0$ gives $F'' = gV_s'/(ne^2) < 0$, so these roots are exactly double. For $U = a$, put $\Phi = nF$. Then $\Phi(0) = 0$ and $\Phi'(0) = an'(0) - ab - V/2$. There is no positive double root at $U = a$, since $U_s(T) > a$ for $T > 0$ on the positive fold. For large V there is no positive root, since $\sup_{T>0}(fn - a)e/T$ is finite. Root counts can therefore change only at $V_s(0)$. Below it $\Phi'(0) > 0$ and Φ is negative for large T, so a root exists. A positive root at $V_s(0)$ would be simple and persist above it; hence there is none there.

Full stability at the printed growth rate. Put $A_0 = abT$, $C_0 = U/n$, $K_0 = VT/(ne)$ and $X = Tn'$ at a positive equilibrium. For relative perturbations $(\delta T/T, \delta y/y, \delta z/z)$, its Jacobian is

$$J = \begin{pmatrix} -A_0 & -C_0 & -K_0 \\ -X & -n & 0 \\ g & e & -e \end{pmatrix}.$$

Write its characteristic polynomial as $\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3$. Then $a_1 = A_0 + n + e > 0$, $a_3 = -TneF'$, and $a_2 = A_0(n+e) + ne - C_0X + K_0g$. The rate bounds give $-3/8 \le X \le 1/4$, $g \ge 1$, $n > 1/2$, $e > 1$, and $C_0 + K_0 = f \le a$. In particular,

$$a_2 \ge ne - a/4 \ge 1/2 - a/4 = 743/2000.$$

The exact identity for $a_1a_2 - a_3$, grouped by A_0, n, K_0, gives

$$\begin{aligned} a_1a_2 - a_3 &= A_0^2(n+e) + A_0[(n+e)^2 - C_0X] \\ &\quad + n[e(n+e) - C_0X] + K_0[g(A_0+e) + eX] \\ &\ge n[3/2 - a/4] \ge 3/4 - a/8 = 2743/4000. \end{aligned}$$

Here $(n+e)^2 - a/4 > 0$ and $g(A_0+e) + eX \ge A_0 + 5e/8 > 0$. These inequalities are analytic; the checker verifies their identities and rate bounds. Routh–Hurwitz gives a sink when $F' < 0$ and a saddle with one unstable direction when $F' > 0$. Thus at the printed rates the nullcline stability test suffices for full stability at every simple positive equilibrium.

Hyperbolic bistability occurs exactly for $a < U < U_*$ and $0 < V < V_s(T(U))$. The sinks are the tumor-free equilibrium $(0, 1, 0)$ and the larger positive equilibrium. The boundary equilibrium has eigenvalues $a - U, -1, -2$ and is a hyperbolic sink exactly when $U > a$. The common boundary of the two sink basins, inside $(0, \infty)^3$, is exactly the saddle's two-dimensional stable manifold. This is a manifold assertion, not a graph in specified coordinates. The argument excluding a saddle return is given in the boundary section.

Convergence through growth rate two.

Theorem 2. *For the literal rates (2), every $0 < a \le 2$ and every $b, U, V > 0$, every finite nonnegative initial state of (1) converges to one equilibrium. This includes repeated equilibrium roots and $a = U$.*

This statement excludes nonconstant periodic or recurrent limiting motion. It neither asserts uniqueness of equilibrium nor classifies basins for this whole growth interval. The endpoint 2 is sufficient; sharpness is not asserted. It is not a measured growth value or a replacement for Table 3's 0.514.

Proof. The exact rate bounds are $1/2 < n < 3/2$, $1 < e < 3$, and $|C| < 1/2$. If $U \ge 3a/2$, the extinction argument above applies. Otherwise, on the bounded T range, choose $n_- > 1/2$, $n_+ < 3/2$ with $n_- \le n \le n_+$. Linear comparison gives $\limsup y \le 1/n_- < 2$ and $\liminf y \ge 1/n_+ > 2/3$. Also (4) gives $\limsup T < 1/b$. Its positive ab term gives $\limsup VT < (3a/2 - U)(a+3)$. These strict gaps give finite-time entry into

$$2/3 \le y \le 2, \quad 0 \le x = abT \le a, \quad 0 \le U \le 3a/2, \quad 0 \le w = VT \le (3a/2 - U)(a+3). \tag{6}$$

No upper bound on z/T is needed. Use (3) and define

$$G = -eF, \quad q = 32, \quad \kappa = \frac{T + 3420000}{30(T + 200000)}, \quad \kappa_x = T\kappa', \quad v = p - \kappa r, \quad H = \kappa G/n.$$

The weight q and function κ were fitted within the family $\kappa_\infty + (\kappa_0 - \kappa_\infty)\ell/(\ell + T)$ to obtain positive damping at the control matrices below, with positive fitting constants $\kappa_0, \kappa_\infty, \ell$. They have no biological interpretation. This is

one sufficient choice; no uniqueness is asserted. The proof uses only the displayed rational values. Here the subscript in κ_x denotes a logarithmic derivative, not differentiation in the variable $x = abT$. Choose primitives $P' = G/T$ and $R' = -HC/T$ on $T > 0$. The energy

$$\mathcal{E} = \tfrac{1}{2}v^2 + \tfrac{q}{2}r^2 + P(T) + H(T)r + R(T)$$

has the exact derivative

$$\begin{aligned}
\dot{\mathcal{E}} &= -Av^2 + Kvr - Qr^2,\\
A &= D + \kappa C + \kappa_x r,\\
K &= B - \kappa(D-n) + (q-\kappa^2)C + H_x - \kappa\kappa_x r,\\
Q &= q(n-\kappa C) - \kappa H_x, \qquad H_x = TH'.
\end{aligned}$$

All derivatives here hold at fixed parameters a, b, U, V. In particular, when differentiating $G/n = -(e/n)(a-x) + Ue/n^2 + w/n^2$, one must use $Tx' = x$ and $Tw' = w$. This same energy fails the domain test at $a = 5/2$: at $T = 100000$, $x = w = 0$, $U = 15/4$, $y = 2$, one has $4AQ - K^2 < 0$. This failure limits the certificate, not the dynamics.

On (6), $|r| \le 4/3$, $0 < \kappa \le 57/100$ and $|\kappa_x| \le 161/1200$, so $A \ge 193/360$. For fixed T, the symmetric matrix with entries $A, -K/2, Q$ is affine in y and jointly affine in a, x, U, w. It suffices to check $y = 2/3, 2$, $x = 0, a$, and the three vertices of the (U, w) triangle in (6). At each such choice its dependence on a has degree at most two. In the degree-two Bernstein basis for $a/2 \in [0,1]$, the three coefficient matrices are obtained from

stage	a	x	U	w
0	0	0	0	0
1	1	θ	$(3/2)u$	$(9/2)(1-u)\eta$
2	2	2θ	$3u$	$15(1-u)\eta$

where $\theta = 0, 1$ and $(u, \eta) = (0,0), (0,1), (1,0)$. Indeed $w = (3a/2)(a+3)(1-u)\eta = (9s + 6s^2)(1-u)\eta$ for $s = a/2$. Its degree-two Bernstein controls are $0, 9(1-u)\eta/2, 15(1-u)\eta$. These are coefficient matrices, not values sampled at three growth rates. There are 36 control choices and 26 distinct tuples, since the stage-zero choices coincide. For all of them the checker proves $4AQ - K^2 > 0$ for every $T \ge 0$. It clears positive denominators, maps $T = 10000s/(1-s)$, and uses exact Bernstein subdivision on $0 \le s \le 1$. Convexity of positive definite matrices then proves strict damping throughout (6). Continuity gives a uniform positive margin on each compact trajectory closure. The boundary argument now proves convergence. □

Boundary limits and the basin argument. For Theorem 1, put $F_0 = a - U/n(0)$. Near zero the potential is $Q_0(T) = -e(0)F_0 \log T + O(1)$. For Theorem 2, $n(0) = 1$, $e(0) = 2$, and the only singular term in $\mathcal{E}$ is $P(T) = -2(a-U)\log T + O(1)$. Indeed $C = O(T)$, H stays bounded and R' stays bounded. The other energy terms stay bounded along any bounded trajectory.

If $F_0 > 0$, decreasing energy excludes approach to $T = 0$. If $F_0 < 0$, the energy either has a finite lower limit, which again excludes approach to zero, or tends to $-\infty$. In the latter case its lower bound on each region $T \ge \epsilon > 0$ forces $T \to 0$. The linear immune equations then give the boundary equilibrium. If $F_0 = 0$, the apparent singularity in the potential derivative is removable. In the shifted energy, $G, H = O(T)$ as well. The energy extends as a C^1 function to $T = 0$.

In each remaining case, for sufficiently large t_0, the set $\mathcal{K} = \overline{\{(T(t), y(t), z(t)) : t \ge t_0\}}$ is compact and positively invariant. LaSalle's Theorem 1, p. 522, [3] applies on $\mathcal{K}$, including the boundary in the critical case. Zero damping gives $p = r = 0$ (or $v = r = 0$, hence $p = 0$). Invariance at $T > 0$ also requires $F = 0$. At $T = 0$, these identities give $y = 1/n(0)$ and $z = 0$. Thus the largest invariant zero-damping set consists of equilibria. Their finiteness is essential. A bounded trajectory has a connected omega-limit set, so that set is a single equilibrium. This proves both theorems even at multiple roots.

For the basin assertion at the printed a, b, there is a particularly simple energy: take $q = 8$ in $\mathcal{E}_0$. Eventually $-1355147/500000 \le B \le 771/2000$ and $T < 1/b$. At both endpoints, clearing denominators in $32n(e + abT) - (B + 8C)^2 - 1$ gives a degree-13 polynomial with strictly positive coefficients. Convexity of the square covers the interval. The damping matrix has determinant $> 1/4$ and trace $< 15 + a$; hence $\dot{\mathcal{E}}_0 \le -(125/7757)(p^2 + r^2)$.

Eventual damping alone does not exclude a saddle homoclinic. On a bounded complete positive trajectory, start the comparisons arbitrarily far in the past and drop nonnegative initial terms. The bounds for $y, z/T$ and T then hold at every time. Thus the whole saddle unstable branch has strict damping. Equal endpoint energies exclude a return to the saddle. Global convergence and the full local classification leave only the tumor-free sink and the larger positive

sink as destinations for these branches. In the connected positive octant both sink basins are nonempty, open and proper. The tumor-free sink has a neighborhood attracting positive states because $U > a$. Each basin therefore has a nonempty relative boundary. A boundary point cannot converge to either sink, since both basins are open; it must converge to the saddle. Forward invariance and closedness of the boundary then put the saddle on each boundary. If both unstable branches reached the same sink, the local saddle exit map would put a punctured neighborhood off the stable manifold in that basin, a contradiction to both basins accumulating at the saddle. Thus the two branches reach different sinks. Every point on the local stable manifold has both basin sides arbitrarily close. Pulling these sides back by the flow proves the stated common-boundary identity. This assertion requires hyperbolic bistability and does not extend here to degenerate parameters.

Scope. In `analysis_FengNKCTL.R` [2], line 35 reads

```
N.stimul = parameters$g*T_w/(parameters$hg + T_w^2).
```

Thus its NK helper (lines 34–38) uses $T/(K+T^2)$, where Eq. (22) uses $T/(K+T)$; $K > 0$ denotes a saturation constant. The CTL helper is at lines 63–68. The R-to-paper parameter maps are $(g, hg, p, hp, dN, sN) = (b_n, K_b, d_n, K_d, \mu, \sigma)$ and $(m, hm, q, hq, dE, r) = (b_e, H_b, d_e, H_d, d, \omega)$. The n_c system agrees with these NK and CTL nullclines. The sourced files `Rscripts/params_FengNKCTL.R` and `Rscripts/stoch_cancer_model_FengNKCTL.R` are absent from the release. Their absence prevents identifying the historical figure dynamics. No full legacy replay is asserted. The paper already supplies stationary elimination and numerical bistability. Descartes' rule and Routh–Hurwitz give the algebraic classification here; the energy and LaSalle arguments establish convergence of trajectories. The growth interval through 2 is a sufficient mathematical range in the paper's time unit, with no biological interpretation. Theorem 2 gives no quantified uncertainty box around its ten exact immune constants. The open sufficient regions concern smaller growth ranges. There is no empirical, physiological, clinical or priority claim. Polynomial checks do not formalize the compactness, invariance or manifold proofs.

References

[1] V. Garcia, S. Bonhoeffer and F. Fu (2020). Cancer-induced immunosuppression can enable effectiveness of immunotherapy through bistability generation: A mathematical and computational examination. *J. Theor. Biol.* 492, 110185. doi:10.1016/j.jtbi.2020.110185.

[2] V. Garcia, S. Bonhoeffer and F. Fu (2020). Official code release, `analysis_FengNKCTL.R`. doi:10.6084/m9.figshare.11536824.v1.

[3] J. P. LaSalle (1960). Some extensions of Liapunov's second method. *IRE Trans. Circuit Theory* 7, 520–527. doi:10.1109/TCT.1960.1086720.

Checker. Run `python3 -I check_victor.py` (Python 3.9+, standard library). It checks rate bounds, endpoint products, differential and Jacobian identities, fold signs, coefficient ordering for the root count, and energy damping for 36 control choices (26 distinct tuples). The Routh inequalities, comparison bounds, compactness, invariance and basin geometry are proved analytically in the text. SHA-256 (concatenate the two lines):
`dfe5d33c499d87d6c3ac65f72a64c9bb`
`370f22dc9c7d4e72c7dc218642a3760d`.