

Stability of a Gleevec and immune model with delays

Frédéric Mazenc, Peter S. Kim, and Silviu-Iulian Niculescu

Abstract—This paper focuses on the stability analysis of a delay-differential system encountered in modeling immune dynamics during Gleevec treatment for chronic myelogenous leukemia. A simple algorithm is proposed for the analysis of delay effects on the stability. Such an algorithm takes advantage of the particular structure of the dynamical interconnections of the model. The analysis shows that the model yields three fixed points, two of which are always unstable and one of which is sometimes stable. The stable fixed point corresponds to an equilibrium solution in which the leukemia population is kept below the cytogenetic remission level. This result implies that, during Gleevec treatment, the resulting anti-leukemia immune response can serve to control the leukemia population. However, the rate of approach to the stable fixed point is very slow, indicating that the immune response is largely ineffective at driving the leukemia population towards the stable fixed point. To extend the stability analysis with respect to the delay parameter, we conduct a global nonlinear analysis to demonstrate the existence of unbounded solutions. We provide sufficient conditions based on initial cell concentrations that guarantee unbounded solutions and comment on how these conditions can serve to predict whether Gleevec treatment will result in a sustained remission based on a patient's initial leukemia load and initial anti-leukemia T cell concentration.

I. INTRODUCTION AND PRELIMINARIES

The stability analysis of delay differential equations (DDEs) that model biological phenomena is of recurring interest [9], [17]. In particular, we are concerned with delay models involving the immune response to chronic myelogenous leukemia (CML). A simple DDE model for the immune response in CML is due to [19]. This work tried to explain the transition of leukemia from the stable chronic phase to the erratic accelerated and acute phases. A more recent work is of [16]. They devised a CML model composed of a system of ODEs (without delays). The main goal was to examine which parameters are the most important in influence the success of cancer remission. [3] formulate a system of DDEs to model the dynamics of anti-leukemia T cells during Gleevec treatment for CML. The model is derived by taking the original Gleevec model of [14] and adding a DDE to simulate the population dynamics of anti-leukemia T cells. In the paper, we analyse the DDE system from the Chen model.

Gleevec works by inhibiting the ablytyrosine kinase that drives CML [1] and has become the first-line therapy for

CML. With Gleevec, nearly all patients achieve hematologic remission [4], [11]; however, patients relapse upon Gleevec discontinuation [4]. Thus, strategies to enhance Gleevec's efficacy are needed. Combining Gleevec with immunotherapy represents a promising strategy; however, the role of the immune response remains unclear. In vitro, imatinib renders leukemic cells immunogenic [15], [20]. More specifically, low frequency (generally < 1%) CD8+ T cell responses to 4 leukemia-associated antigens (LAAs) were detected in CML patients after therapy with Gleevec [7]. [3] conduct further experiments to follow the time evolution of anti-leukemia T cells during Gleevec treatment. With this data, they formulate a DDE model based on the observed dynamics. The time delay in [3] corresponds to the duration of T cell proliferation cycles. Their mathematical model is formulated as a nonlinear delay-differential system. Its linearization around the equilibrium point of interest writes as follows:

$$\dot{x}(t) = A_0 x(t) + bc^T x(t - n\tau), \quad (1)$$

under appropriate initial conditions defined on $[-n\tau, 0]$, where τ represents the delay, and n some averaging factor. In our case study ($A_0 \in \mathbb{R}^{5 \times 5}$, $b, c \in \mathbb{R}^{5 \times 1}$), the system (1) has the following "limit" properties: (a) the system free of delays is asymptotically stable ($A_0 + bc^T$ Hurwitz), and (b) the "reduced" system including only the "instantaneous" part is *hyperbolic*, that is A_0 has no eigenvalues on the imaginary axis.

In this paper, we seek to find simple conditions for characterizing the delay effects on stability of the linearized Gleevec model. In addition, we establish the existence of unbounded solutions for the nonlinear system.

Consider the following meromorphic function $q : \mathbb{C} \times \mathbb{R}_+ \mapsto \mathbb{C}$ associated to (1):

$$q(\lambda, h) = 1 - a(\lambda)e^{-\lambda h}, \quad (2)$$

where $a(\lambda) = c^T(\lambda I_n - A_0)^{-1}b$, and $h = n\tau$. By exploiting the rank-one structure of the delay matrix bc^T , we have the following results [18]:

Proposition 1: Assume that A_0 has no eigenvalues on the imaginary axis, and that $1 - a(0) \neq 0$, where $a(\lambda) = c^T(\lambda I_n - A_0)^{-1}b$. Define now the function $f : \mathbb{R} - \{0\} \mapsto \mathbb{R}$, $f(\omega) = 1 - |a(j\omega)|$. Under these conditions the following statements are true:

- (i) Suppose $f(\omega) = 0$ has no strictly positive roots. Then if (1) is stable (unstable) at $h = 0$, it remains stable (unstable) for all $h \geq 0$ and no roots cross the imaginary axis when h increases in \mathbb{R}_+ .
- (ii) Suppose $f(\omega) = 0$ has at least one positive root, and that each root is simple. Then as h increases, stability switches

F. Mazenc is with Analyse des Systèmes et Biométrie, INRA, 2 pl. Viala, 34060 Montpellier, France, mazenc@supagro.inra.fr

P.S. Kim is with the Laboratoire des Signaux et Systèmes (LSS), CNRS-Supélec, 3 rue Joliot Curie, 91192 Gif-sur-Yvette, France, pkim@math.stanford.edu

S-I. Niculescu (corresponding author) is with the Laboratoire des Signaux et Systèmes (LSS), CNRS-Supélec, 3 rue Joliot Curie, 91192 Gif-sur-Yvette, France, Silviu.Niculescu@lss.supelec.fr

may occur, and there exists a positive number h^* , such that (1) is unstable for all $h > h^*$. As h varies from 0 to h^* , at most finitely many stability switches may occur. Furthermore, if for $\omega = \omega_0$ one pair of roots lies on the imaginary axis, then the roots will cross the imaginary axis from left to right (right to left) iff:

$$\Re \left[\frac{a(j\omega_0)}{j\omega_0 c^T b} \right] < 0 \quad (> 0). \quad (3)$$

II. LINEAR ANALYSIS

Mathematical model. [3] formulated a DDE model combining the Gleevec dynamics of [14] with a T cell response. For this analysis, we exclude the possibility of Gleevec-resistance mutations and analyse the following DDE system:

$$\dot{y}_0 = [r_y - d_0]y_0 - q_C p(C, T)y_0, \quad (4)$$

$$\dot{y}_1 = a_y y_0 - d_1 y_1 - q_C p(C, T)y_1, \quad (5)$$

$$\dot{y}_2 = b_y y_1 - d_2 y_2 - q_C p(C, T)y_2, \quad (6)$$

$$\dot{y}_3 = c_y y_2 - d_3 y_3 - q_C p(C, T)y_3, \quad (7)$$

$$\dot{T} = s_T - d_T T - p(C, T)C + 2^n p(C_{n\tau}, T_{n\tau})q_T C_{n\tau}, \quad (8)$$

where

$$p(C, T) = p_0 e^{-\gamma C} k T, \quad C = y_0 + y_1 + y_2 + y_3, \\ C_{n\tau} = C(t - n\tau), \quad T_{n\tau} = T(t - n\tau).$$

The variables y_0 , y_1 , y_2 , and y_3 denote the concentrations of leukemia stem cells (SC), progenitors (PC), differentiated cells (DC), and terminally differentiated cells (TC). The constants a_y , b_y , and c_y correspond to differentiation rates, and the constants d_i correspond to death rates. The variable C denotes the total concentration of all leukemia cells. The variable T denotes the concentration of anti-leukemia T cells.

We assume the law of mass action, stating that two populations interact at a rate proportional to the product of their concentrations. We denote the proportionality constant by k . At every interaction, p_0 is the probability that a T cell engages the cancer cell, and q_C is the probability that the cancer cell dies from the T cell response. Furthermore, leukemia cells suppress immune responses, and while the precise mechanism is unknown, we assume that immune activity decays exponentially with respect to the cancer population. In particular, we model that the probability of an effective interaction between a T cell and a cancer cell is $p_0 e^{-\gamma C}$ where γ is the rate of decay.

In (8), s_T denotes the constant T cell supply rate into the system from stem cells. The second term is the natural death rate of T cells. The third term is the rate that T cells engage leukemia cells and commit to n rounds of division. The final term represents the population increase due to n T cell divisions where τ is the average duration of one division, and $C_{n\tau}$ and $T_{n\tau}$ are the time delayed cancer and T cell concentrations. The coefficient q_T is the probability that a T cell survives the encounter with a leukemia cell. This method of modeling T cell proliferation using delays is the same as that used in [6]. As in [3], we kept the parameter estimates from [14] where applicable, and estimated the remaining parameters based on patient data.

Stability of fixed points. To solve for fixed points $(\bar{y}_0, \bar{y}_1, \bar{y}_2, \bar{y}_3, \bar{T})$, where $\bar{C} = \bar{y}_0 + \bar{y}_1 + \bar{y}_2 + \bar{y}_3$, we set all the derivatives in (4) - (8) to zero. We immediately obtain one fixed point corresponding to the case when there are no cancer cells and given by $(\bar{y}_0, \bar{y}_1, \bar{y}_2, \bar{y}_3, \bar{T}_0) = (0, 0, 0, 0, s_T/d_T)$. After a series of algebraic manipulations, we also obtain the expression

$$e^{-\gamma \bar{C}} (\kappa_1 + \bar{C}) - \kappa_2 = 0. \quad (9)$$

where

$$\kappa_1 = \frac{s_T q_C}{(r_y - d_0)(2^n q_T - 1)}, \quad \kappa_2 = \frac{d_T}{k p_0 (2^n q_T - 1)}.$$

Furthermore, we can calculate that $\alpha \bar{C} = \bar{y}_0$ where

$$\alpha = \frac{a_y}{r_y + d_1 - d_0} \left(1 + \frac{b_y}{r_y + d_2 - d_0} \left(1 + \frac{c_y}{r_y + d_3 - d_0} \right) \right).$$

Substituting the parameter values that, due to space limitation, we do not give, and solving the implicit equation (9) numerically, we obtain values for \bar{y}_0 . From \bar{y}_0 , we can obtain the other components, \bar{y}_1 , \bar{y}_2 , \bar{y}_3 , \bar{T} . We find that every patient has three fixed points. These fixed points correspond to equilibrium states where the T cell response controls the leukemia population. For every patient, fixedpoint 1 represents the case when cancer cells are completely eliminated. Fixed point 2 represents a highly controlled state where leukemia is kept below the cytogenetic remission level of about 0.01k/ μ L. Fixed point 3 represents a stalemate scenario when the cancer and anti-leukemia T cell populations are sustained a moderately high levels. Thus, for medical purposes, fixed points 1 and 2 are much more desirable ending places for the dynamical system. Next, for any fixed point $(\bar{y}_0, \bar{y}_1, \bar{y}_2, \bar{y}_3, \bar{T})$, with $\bar{C} = \bar{y}_0 + \bar{y}_1 + \bar{y}_2 + \bar{y}_3$, the linearization of (4) to (8) can be written as $\dot{\mathbf{x}}(t) = \mathbf{A}\mathbf{x}(t) + \mathbf{b}e^{-\gamma \bar{C}} \mathbf{x}(t - n\tau)$ where $\mathbf{x} = (y_0, y_1, y_2, y_3, T)^T$.

Next, by analyzing the system in light of Proposition 1, one can prove the following results:

Proposition 2: The stability of the fixed points with respect to the (non-negative) delay parameter τ are

- (1) Fixed point 1: Never stable for any $\tau \geq 0$.
- (2) Fixed point 2: For one of the patients, stable for $\tau \in [0, 11.6337)$ and not stable otherwise. For another, not stable for any choice of τ . For the last patient, stable for $\tau \in [0, 12.6734)$ and not stable otherwise.
- (3) Fixed point 3: Never stable for any $\tau \geq 0$.

Due to space limitation, the proof of this result is omitted. The proof of Proposition 2 follows the same reasoning as in [18]. However, due to an updated estimate of the parameter λ , we obtain slightly different results, most noticeably that fixed point 2 is now unstable.

Biologically τ represents the duration in days of one round of T cell division and is estimated to be around one day [8], [10], [12]. Hence, from a biological point of view, the upper limit for stability is unattainable, and hence, the stability of fixed point 2 is independent of any reasonable error in the estimation of the delay τ . However, note that the real part of rightmost eigenvalues for fixed point 2 are of the order

negative 10^{-3} to 10^{-4} . Hence, the solution converges to the fixed point very slowly. As τ increases from 0 to τ_c and greater, the rightmost roots of p travel from \mathbb{C}_- across $j\mathbb{R}$ and into \mathbb{C}_+ .

III. NONLINEAR ANALYSIS: UNBOUNDED TRAJECTORIES

In this section, we conduct a nonlinear analysis of the system (4)–(8) to show that it admits unbounded trajectories.

To begin, let us introduce the following constants:

$$L_1 = \frac{M_2}{4} \min \left\{ \frac{1}{M_1}, \frac{1}{G_2} \right\}, \quad L_2 = \frac{2M_1}{M_2}, \quad (10)$$

$$M_1 = \frac{q_c p_0 k}{(r_y - d_0)^2} s_T, \quad M_2 = \frac{d_T}{r_y - d_0}, \quad (11)$$

$$G_1 = \frac{p_0 k}{c_n (r_y - d_0)}, \quad G_2 = \frac{2^n q_T p_0 k}{c_n (r_y - d_0)}.$$

Notice that M_1, M_2, G_1, G_2 are positive real numbers. The main result of this section is

Theorem 1: Consider a solution of (4)–(8) with an initial condition $(\phi_{y_0}, \phi_{y_1}, \phi_{y_2}, \phi_{y_3}, \phi_T)$ satisfying

$$\phi_{y_{i+1}}(t) - h_{i+1} \phi_{y_i}(t) = 0, \quad (i = 0, 1, 2, 3) \quad (12)$$

and

$$\phi_{y_3}(t) \geq \frac{1}{L_1 c_n A_3}, \quad 0 < \phi_T(t) \leq L_2 \frac{r_y - d_0}{q_c p_0},$$

for all $t \in [-\rho, 0]$, where $h_1 = \frac{a_y}{r_y - d_0 + d_1}$, $h_2 = \frac{b_y}{r_y - d_0 + d_2}$, $h_3 = \frac{c_y}{r_y - d_0 + d_3}$. Then this solution is unbounded. In particular, the y_3 component of this solution is unbounded.

Proof. Consider the following coordinate transformation:

$$\eta_i = y_{i+1} - h_{i+1} y_i, \quad (i = 0, 1, 2) \quad (13)$$

$$T = T.$$

Then

$$\begin{aligned} \dot{\eta}_0 &= a_y y_0 - d_1 y_1 - q_c p(C, T) y_1 \\ &\quad - h_1 [(r_y - d_0) y_0 - q_c p(C, T) y_0] \\ &= -d_1 y_1 + a_y y_0 - h_1 (r_y - d_0) y_0 - q_c p(C, T) \eta_0 \\ &= -[d_1 + q_c p(C, T)] \eta_0. \end{aligned} \quad (14)$$

Next, observe that

$$\begin{aligned} \dot{y}_1 &= a_y y_0 - d_1 y_1 - q_c p(C, T) y_1 \\ &= (r_y - d_0 + d_1)(-\eta_0 + y_1) - d_1 y_1 - q_c p(C, T) y_1 \\ &= (r_y - d_0) y_1 - q_c p(C, T) y_1 - (r_y - d_0 + d_1) \eta_0, \end{aligned} \quad (15)$$

$$\begin{aligned} \dot{\eta}_1 &= b_y y_1 - d_2 y_2 - q_c p(C, T) y_2 \\ &\quad - h_2 [(r_y - d_0) y_1 - q_c p(C, T) y_1 - (r_y - d_0 + d_1) \eta_0] \\ &= b_y y_1 - d_2 y_2 - h_2 (r_y - d_0) y_1 - q_c p(C, T) \eta_1 \\ &\quad + h_2 (r_y - d_0 + d_1) \eta_0 \\ &= -d_2 y_2 + b_y \left[1 - \frac{r_y - d_0}{r_y - d_0 + d_2} \right] y_1 - q_c p(C, T) \eta_1 \\ &\quad + h_2 (r_y - d_0 + d_1) \eta_0 \\ &= -(d_2 + q_c p(C, T)) \eta_1 + h_2 (r_y - d_0 + d_1) \eta_0, \end{aligned} \quad (16)$$

$$\begin{aligned} \dot{y}_2 &= b_y y_1 - d_2 y_2 - q_c p(C, T) y_2 \\ &= (y_2 - \eta_1)(r_y - d_0 + d_2) - d_2 y_2 - q_c p(C, T) y_2 \\ &= y_2 (r_y - d_0) - q_c p(C, T) y_2 - \eta_1 (r_y - d_0 + d_2), \end{aligned} \quad (17)$$

$$\begin{aligned} \dot{\eta}_2 &= c_y y_2 - d_3 y_3 - q_c p(C, T) y_3 \\ &\quad - h_3 [y_2 (r_y - d_0) - q_c p(C, T) y_2 - \eta_1 (r_y - d_0 + d_2)] \\ &= -d_3 y_3 + c_y y_2 - y_2 h_3 (r_y - d_0) - q_c p(C, T) \eta_2 \\ &\quad + h_3 (r_y - d_0 + d_2) \eta_1 \\ &= -d_3 y_3 + c_y \frac{d_3}{r_y - d_0 + d_3} y_2 - q_c p(C, T) \eta_2 \\ &\quad + h_3 (r_y - d_0 + d_2) \eta_1 \\ &= -[d_3 + q_c p(C, T)] \eta_2 + h_3 (r_y - d_0 + d_2) \eta_1, \end{aligned} \quad (18)$$

$$\begin{aligned} \dot{y}_3 &= c_y y_2 - d_3 y_3 - q_c p(C, T) y_3 \\ &= (y_3 - \eta_2)(r_y - d_0 + d_3) - d_3 y_3 - q_c p(C, T) y_3 \\ &= (r_d - d_0) y_3 - \eta_2 (r_d - d_0 + d_3) - q_c p(C, T) y_3. \end{aligned} \quad (19)$$

Finally, we can rewrite (4)–(8) as

$$\begin{aligned} \dot{\eta}_0 &= -[d_1 + q_c p(C, T)] \eta_0, \\ \dot{\eta}_1 &= -[d_2 + q_c p(C, T)] \eta_1 + h_2 (r_y - d_0 + d_1) \eta_0, \\ \dot{\eta}_2 &= -[d_3 + q_c p(C, T)] \eta_2 + h_3 (r_y - d_0 + d_2) \eta_1, \\ \dot{y}_3 &= (r_y - d_0) y_3 - q_c p(C, T) y_3 - (r_d - d_0 + d_3) \eta_2, \\ \dot{T} &= s_T - d_T T - p(C, T) C \\ &\quad + 2^n p(C(t-r), T(t-r)) q_T C(t-r), \end{aligned} \quad (20)$$

with $r = n\tau$. Besides, since $C = \sum_{i=0}^3 y_i$, and

$$\begin{aligned} y_2 &= \frac{1}{h_3} y_3 - \frac{1}{h_3} \eta_2, \\ y_1 &= \frac{1}{h_2} y_2 - \frac{1}{h_2} \eta_1 = \frac{1}{h_2 h_3} y_3 - \frac{1}{h_2 h_3} \eta_2 - \frac{1}{h_2} \eta_1, \\ y_0 &= \frac{1}{h_1} y_1 - \frac{1}{h_1} \eta_0 \\ &= \frac{1}{h_1} \left(\frac{1}{h_2 h_3} y_3 - \frac{1}{h_2 h_3} \eta_2 - \frac{1}{h_2} \eta_1 \right) - \frac{1}{h_1} \eta_0 \\ &= \frac{1}{h_1 h_2 h_3} y_3 - \frac{1}{h_1 h_2 h_3} \eta_2 - \frac{1}{h_1 h_2} \eta_1 - \frac{1}{h_1} \eta_0, \end{aligned}$$

one has

$$C = A_3 y_3 + A_2 \eta_2 + A_1 \eta_1 + A_0 \eta_0,$$

where

$$\begin{aligned} A_3 &= \frac{1}{h_1 h_2 h_3} + \frac{1}{h_2 h_3} + \frac{1}{h_3} + 1, \\ A_2 &= -\frac{1}{h_1 h_2 h_3} - \frac{1}{h_2 h_3} - \frac{1}{h_3}, \\ A_1 &= -\frac{1}{h_1 h_2} - \frac{1}{h_2}, \\ A_0 &= -\frac{1}{h_1}. \end{aligned}$$

This expression of C and the explicit expression of $p(C, T)$, imply that we can rewrite the (y_3, T) -subsystem of (20) as

$$\begin{aligned} \dot{y}_3 &= (r_y - d_0) y_3 - q_c p_k e^{-c_n A_3 y_3} \Lambda(\eta) T y_3 - (r_d - d_0 + d_3) \eta_2, \\ \dot{T} &= s_T - d_T T - p_k e^{-c_n A_3 y_3} \Lambda(\eta) T \left(A_3 y_3 + \sum_{j=0}^2 A_j \eta_j \right) \\ &\quad + 2^n q_T p_k e^{-c_n A_3 y_3(t-r)} \Lambda(\eta(t-r)) T(t-r) \\ &\quad \cdot \left(A_3 y_3(t-r) + \sum_{j=0}^2 A_j \eta_j(t-r) \right), \end{aligned}$$

where $p_k = p_0 k$ and

$$\Lambda(\eta) = \exp \left\{ -c_n \sum_{j=0}^2 A_j \eta_j \right\}.$$

Let us introduce the new coordinates

$$Z = c_n A_3 y_3, \quad x = \frac{q_c p_k}{r_y - d_0} T.$$

Then,

$$\begin{aligned} \dot{Z} &= (r_y - d_0)Z - (r_y - d_0)e^{-Z} x Z \Lambda(\eta) \\ &\quad - c_n A_3 (r_d - d_0 + d_3) \eta_2, \\ \dot{x} &= \frac{q_c p_k}{r_y - d_0} s_T - d_T x - p_k e^{-Z} x \left(\frac{Z}{c_n} + \sum_{j=0}^2 A_j \eta_j \right) \Lambda(\eta) \\ &\quad + 2^n q_T p_k e^{-Z(t-r)} x(t-r) \\ &\quad \cdot \left(\frac{Z(t-r)}{c_n} + \sum_{j=0}^2 A_j \eta_j(t-r) \right) \Lambda(\eta(t-r)), \end{aligned}$$

or equivalently

$$\begin{aligned} \frac{1}{r_y - d_0} \dot{Z} &= Z - e^{-Z} x Z \Lambda(\eta) + K_1 \eta_2, \\ \frac{1}{r_y - d_0} \dot{x} &= M_1 - M_2 x - G_1 e^{-Z} x Z \Lambda(\eta) - K_0 e^{-Z} x \alpha(\eta) \\ &\quad + G_2 e^{-Z(t-r)} x(t-r) Z(t-r) \Lambda(\eta(t-r)) \\ &\quad + K_2 e^{-Z(t-r)} x(t-r) \alpha(\eta(t-r)), \end{aligned}$$

where

$$K_0 = \frac{p_k}{r_y - d_0}, \quad K_1 = -\frac{c_n A_3 (r_d - d_0 + d_3)}{r_y - d_0}, \quad K_2 = \frac{2^n q_T p_k}{r_y - d_0},$$

and

$$\alpha(\eta) = \left(\sum_{j=0}^2 A_j \eta_j \right) \Lambda(\eta). \quad (21)$$

We deduce that, after a time rescaling, (20) becomes

$$\begin{aligned} \dot{\eta}_0 &= -\frac{1}{r_y - d_0} [d_1 + q_c p(C, T)] \eta_0, \\ \dot{\eta}_1 &= -\frac{1}{r_y - d_0} [d_2 + q_c p(C, T)] \eta_1 + \frac{r_y - d_0 + d_1}{r_y - d_0} h_2 \eta_0, \\ \dot{\eta}_2 &= -\frac{1}{r_y - d_0} [d_3 + q_c p(C, T)] \eta_2 + \frac{r_y - d_0 + d_2}{r_y - d_0} h_3 \eta_1, \\ \dot{Z} &= Z - e^{-Z} x Z \Lambda(\eta) + K_1 \eta_2, \\ \dot{x} &= M_1 - M_2 x - G_1 e^{-Z} x Z \Lambda(\eta) - K_0 e^{-Z} x \alpha(\eta) \\ &\quad + G_2 e^{-Z(t-\rho)} x(t-\rho) Z(t-\rho) \Lambda(\eta(t-\rho)) \\ &\quad + K_2 e^{-Z(t-\rho)} x(t-\rho) \alpha(\eta(t-\rho)), \end{aligned}$$

where $\rho = (r_y - d_0)r$.

We start our proof of the existence of unbounded trajectories, by observing that the finite escape time phenomenon does not occur for the system (20) and that, if the initial condition satisfies (12), then $\eta_0(t) = 0$, $\eta_1(t) = 0$, $\eta_2(t) = 0$ for all $t \geq 0$. Thus, from now on, it suffices to study the two dimensional system:

$$\begin{cases} \dot{Z} &= Z - e^{-Z} x Z, \\ \dot{x} &= M_1 - M_2 x - G_1 e^{-Z} x Z \\ &\quad + G_2 e^{-Z(t-\rho)} x(t-\rho) Z(t-\rho). \end{cases} \quad (22)$$

Next, we state a theorem

Theorem 2: Consider a solution of the system (22) with its initial condition belonging to the set

$$\mathcal{E} = \left\{ (\phi_Z, \phi_x) \in C^0([-\rho, 0]) \mid \phi_Z(t) \geq \frac{1}{L_1}, \right. \\ \left. 0 < \phi_x(t) \leq L_2, \forall t \in [-\rho, 0] \right\}. \quad (23)$$

Then, for all $t \geq 0$,

$$Z(t) \geq \frac{1}{L_1}, \quad 0 < x(t) \leq L_2 \quad (24)$$

and

$$\lim_{t \rightarrow +\infty} Z(t) = +\infty. \quad (25)$$

which allows us to deduce that if the initial conditions of (22) belong to the set \mathcal{E} then the solutions satisfy

$$Z(t) \geq \frac{1}{L_1}, \quad 0 < x(t) \leq L_2, \quad \forall t \geq 0 \quad (26)$$

and

$$\lim_{t \rightarrow +\infty} Z(t) = +\infty.$$

Now, one can easily complete the proof of Theorem 1.

Proof of Theorem 2. Consider the system (22). With the variable $b = 1/Z$, we obtain

$$\begin{aligned} \dot{b} &= -\left(1 - e^{-\frac{1}{b}} x\right) b, \\ \dot{x} &= M_1 - M_2 x - G_1 e^{-\frac{1}{b}} \frac{x}{b} + G_2 e^{-\frac{1}{b(t-\rho)}} \frac{x(t-\rho)}{b(t-\rho)}. \end{aligned} \quad (27)$$

The easy proof of the existence of $(b(t), x(t))$ over $[0, +\infty)$ and the positiveness of the components $b(t)$ and $x(t)$ is left to the reader.

Let us define the set

$$\mathcal{D} = \left\{ (\phi_b, \phi_x) \in C^0([-\rho, 0]) : 0 < \phi_b(t) \leq L_1, \right. \\ \left. 0 < \phi_x(t) \leq L_2, \forall t \in [-\rho, 0] \right\}, \quad (28)$$

Next, we have the lemma

Lemma 1: Consider a solution (b, x) of (27) with initial condition $(\phi_b, \phi_x) \in \mathcal{D}$. Then, for all $t \geq 0$,

$$\begin{cases} 0 < b(t) &\leq L_1, \\ 0 < x(t) &\leq L_2. \end{cases}$$

Due to space limitation, the proof of this lemma is omitted.¹

One can easily deduce from Lemma 1 that for all t , relation (24) is satisfied. We easily deduce that, for all $t \geq 0$,

$$\dot{Z}(t) \geq \frac{1}{2} Z(t).$$

Consequently, (25) holds.

¹In the present version, we give for the referees the proof of this theorem in Appendix. It will be removed from the final version.

IV. ILLUSTRATIVE EXAMPLE

To apply Theorem 1 to a particular example, we substitute our estimated parameters into (23) and account for the coordinate transformations to obtain the following conditions for an unbounded solution to (4)–(8):

$$y_3(0) \geq 765.2912\text{k}/\mu\text{L} \quad \text{and} \quad T(0) \leq 0.0088\text{k}/\mu\text{L}. \quad (29)$$

In Figure 1, we show three examples of solutions to (4)–(8). In each example, the T cell supply rate, s_T , is varied to set the initial T cell concentration, $T(0)$, as desired. Also, the initial leukemia stem cell concentration, $y_0(0)$, is varied to obtain the desired initial value of terminally differentiated cells, $y_3(0)$.

In Figure 1a, the initial conditions fall within the basin of attraction, and the solution asymptotically approaches the stable fixed point. In Figure 1b, the initial conditions fall satisfies (29), and hence the solution leads to an unbounded trajectory. We note that condition (29) requires the initial leukemia concentration to exceed $750\text{k}/\mu\text{L}$, which is biologically unreasonable. However, this condition is only sufficient, not necessary, and it is possible to find initial conditions that lead to unbounded solutions for reasonable initial leukemia loads. One such example is shown in Figure 1c. Indeed, the sufficient condition established in Theorem 1 is not as strong as possible. In fact, the bounds for $y_3(0)$ and $T(0)$ are dependent, and lower initial T cell concentrations, $T(0)$, allow lower initial leukemia loads to result in unbounded trajectories.

V. INTERPRETATIONS AND CONCLUSIONS

From the linear analysis, we find that in all three cases, fixed point 1 is robustly stable for a wide range of τ . The leukemia concentrations for all fixed points 1 fall well below the level of cytogenetic remission. This robust stability implies that, as long as conditions remain similar, the immune response is able to control the leukemia population and gradually drives it to a sustained cytogenetic remission. On the other hand, the rate of convergence to this fixed point is very slow. This rate of convergence is inadequate, and biological conditions are likely to change over time.

One method to improve the effectiveness of Gleevec therapy is to induce the system to settle down to the stable fixed point more quickly. This may be done by continually measuring a patient's leukemia load and modulating the Gleevec dosage to ensure a stabilized cancer population oscillations. Such a method would involve formulating a delayed-feedback control mechanism, a possible direction for future work.

From the nonlinear analysis, we find that the system admits unbounded trajectories, and we also establish conditions regarding the initial T cell and cancer cell concentrations that guarantee unbounded solutions. In principle, if one can predict from initial conditions whether a system will result in stable or unbounded solutions, one can assess whether Gleevec treatment is appropriate. However, this requires an accurate characterization of the stable basin of attraction. In this paper, Theorem 1 demonstrates an effective method

of using coordinate transformations to determine sufficient instability conditions for the nonlinear system. By strengthening this result we can obtain stronger conditions that guarantee the existence of unbounded solutions.

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APPENDIX

Appendix

Proof of lemma 1. We proceed by contradiction. Assume that

$$t_c = \sup\{t \geq 0 : 0 < b(t) \leq L_1, 0 < x(t) \leq L_2, \forall l \in [-\rho, t]\} \quad (30)$$

is a finite number. Necessarily, $t_c \geq 0$. Next, let us distinguish between several cases.

First case: Assume that $b(t_c) = L_1$ and $x(t_c) = L_2$. Then,

$$\begin{aligned} \dot{b}(t_c) &\leq -\left(1 - e^{-\frac{1}{L_1} L_2}\right) L_1 \\ &\leq -\left(1 - L_1 L_2\right) L_1 \leq -\frac{1}{2} L_1 < 0. \end{aligned}$$

On the other hand,

$$\begin{aligned} \dot{x}(t_c) &< M_1 - M_2 L_2 + G_2 e^{-\frac{1}{b(t_c - \rho)}} \frac{1}{b(t_c - \rho)} L_2 \\ &< M_1 - M_2 L_2 + 2G_2 b(t_c - \rho) L_2 \\ &< M_1 + \left(-M_2 + 2G_2 \frac{M_2}{4} \min\left\{\frac{1}{M_1}, \frac{1}{G_2}\right\}\right) \frac{2M_1}{M_2} \\ &< M_1 + \left(-1 + G_2 \frac{1}{2} \frac{1}{G_2}\right) 2M_1 = 0. \end{aligned}$$

We deduce easily that there exists $h > 0$ such that $0 < b(l) \leq L_1$ and $0 < x(l) \leq L_2, \forall l \in [t_c, t_c + h]$. This contradicts the definition of t_c .

Second case: Assume that $b(t_c) < L_1$ and $x(t_c) = L_2$. Then,

$$\begin{aligned} \dot{x}(t_c) &< M_1 - M_2 L_2 + G_2 e^{-\frac{1}{b(t_c - \rho)}} \frac{1}{b(t_c - \rho)} L_2 \\ &< M_1 - M_2 L_2 + 2G_2 b(t_c - \rho) L_2 \\ &< M_1 + \left(-M_2 + 2G_2 \frac{M_2}{4} \min\left\{\frac{1}{M_1}, \frac{1}{G_2}\right\}\right) \frac{2M_1}{M_2} \\ &< M_1 + \left(-1 + G_2 \frac{1}{2} \frac{1}{G_2}\right) 2M_1 = 0. \end{aligned}$$

Third case: Assume that $b(t_c) = L_1$ and $x(t_c) < L_2$. Then,

$$\begin{aligned} \dot{b}(t_c) &= -\left(1 - e^{-\frac{1}{L_1} x(t_c)}\right) L_1 \\ &< -\left(1 - e^{-\frac{1}{L_1} L_2}\right) L_1 < -\frac{1}{2} L_1 < 0. \end{aligned}$$

We deduce that $\dot{b}(t_c) < 0$. Therefore there exists $h > 0$ such that $0 < b(l) \leq L_1$ and $0 < x(l) \leq L_2, \forall l \in [t_c, t_c + h]$. This contradicts the definition of t_c .

Fourth case: Assume that $b(t_c) < K_1$ and $x(t_c) < K_2$. Then there exists $h > 0$ such that $0 < b(l) \leq L_1$ and $0 < x(l) \leq L_2, \forall l \in [t_c, t_c + h]$. This contradicts the definition of t_c .

All the possible cases lead to a contradiction. This concludes our proof.

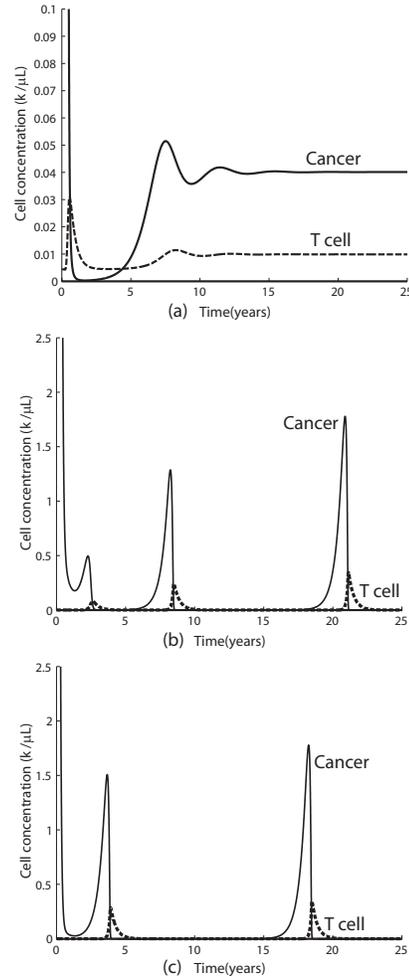


Fig. 1. Time evolution of cancer and T cell concentrations in the DDE system (4)–(8). (a) The initial conditions $y_3(0) = 113.78\text{k}/\mu\text{L}$ and $T(0) = 0.0044\text{k}/\mu\text{L}$ fall within the basin of attraction and lead to a stable solution. (b) The initial conditions $y_3(0) = 948.15\text{k}/\mu\text{L}$ and $T(0) = 1.43 \times 10^{-6}\text{k}/\mu\text{L}$ satisfy the condition given by (29) and lead to an unbounded trajectory. (c) The initial conditions $y_3(0) = 142.22\text{k}/\mu\text{L}$ and $T(0) = 1.43 \times 10^{-6}\text{k}/\mu\text{L}$ do not satisfy the sufficient condition given by (29), but they still lead to an unbounded trajectory.