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# On the global dynamics of a chronic myelogenous leukemia model

Alexander P. Krishchenko [a], Konstantin E. Starkov [b,*]

[a] Bauman Moscow State Technical University, 2-aya Baumanskaya ul., 5, Moscow 105005, Russia
[b] Instituto Politecnico Nacional, CITEDI, Avenida IPN N 1310, Mesa de Otay, Tijuana 22510, B.C., Mexico

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ABSTRACT

In this paper we analyze some features of global dynamics of a three-dimensional chronic myelogenous leukemia (CML) model with the help of the stability analysis and the localization method of compact invariant sets. The behavior of CML model is defined by concentrations of three cellpopulations circulating in the blood: naive T cells, effector T cells specific to CML and CML cancer cells. We prove that the dynamics of the CML system around the tumor-free equilibrium point is unstable. Further, we compute ultimate upper bounds for all three cell populations and provide the existence conditions of the positively invariant polytope. One ultimate lower bound is obtained as well. Moreover, we describe the iterative localization procedure for refining localization bounds; this procedure is based on cyclic using of localizing functions. Applying this procedure we obtain conditions under which the internal tumor equilibrium point is globally asymptotically stable. Our theoretical analyses are supplied by results of the numerical simulation.



## 1. Introduction

Mathematical models describing interactions between chronic myelogenous leukemia (CML) and the immune system attract attention of many researchers during the last decade, see e.g. papers [1–8]. One of the most popular CML models is the model described in [8] by Moore and Li. This CML model is given in the form of ordinary differential equations of the type

$$\begin{aligned}\frac{dT_n}{dt} &= s_n - d_n T_n - k_n T_n \frac{C}{C+\eta},\\ \frac{dT_e}{dt} &= \alpha_n k_n T_n \frac{C}{C+\eta} + \alpha_e T_e \frac{C}{C+\eta} - d_e T_e - \gamma_e C T_e,\\ \frac{dC}{dt} &= r_c C \ln\left(\frac{C}{C_{max}}\right) - d_c C - \gamma_c C T_e.\end{aligned} \tag{1}$$

In Eq. (1) by $T_n/T_e/C$ we denote concentrations of populations of naive T cells/effector T cells specific to CML/CML cancer cells respectively which circulate in the blood system.

Further, $s_n$ is the source term for new T cells entering the blood system; $d_n$ is the naive T cells death rate; $k_n$ is the constant of the Michaelis–Menten term (MM-term) which is responsible for the $T_n$ population change due to encounters with CML antigen in

* Corresponding author. Tel.: +526646231344; fax: +526646231388.
*E-mail addresses:* apkri@bmstu.ru (A.P. Krishchenko), konst@citedi.mx, kstarkov@ipn.mx, konstarkov@hotmail.com (K.E. Starkov).

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the lymph; parameters $\alpha_n$ and $k_n$ entering into the first MM-term of the second equation characterize the activation encounters between $T_n$ and professional antigen-presenting cells (APC); next MM-term in the second equation describes how the proportion of effector T cells will recruit other immune cells to aid in killing CML cells; $d_e$ is the death rate for $T_e$; $\gamma_e$ is the loss rate of $T_e$ due to encounters between $T_e$ and cancer cells; in the third equation the first term describes the growth of $C$ cells in the form of the Gompertz law; $C_{max}$ is the estimate of the maximal possible concentration of CML; $d_c$ is the CML death rate; $\gamma_c$ the loss rate of CML due to encounters with $T_e$. More details including the diagram of cell populations events and typical range of parameters may be found in [8]. Following [8] we apply the normalization of parameters

$$\zeta_1 = \frac{k_n}{d_n}; \quad \zeta_2 = \frac{\gamma_e \eta}{d_n}; \quad \zeta_3 = \frac{\alpha_n k_n s_n \gamma_c}{d_n^3}; \quad \zeta_4 = \frac{\alpha_e}{d_n}; \tag{2}$$
$$\zeta_5 = \frac{d_e}{d_n}; \quad \zeta_6 = \frac{r_c}{d_n}; \quad \zeta_7 = \frac{\gamma_e C_{max}}{d_n}; \quad \zeta_8 = \frac{d_c}{d_n};$$

variables

$$x = \frac{d_n}{s_n} T_n; \quad y = \frac{\gamma_c}{d_n} T_e; \quad z = \frac{\gamma_c}{d_n} C; \quad t := d_n t$$

and come to the system

$$\dot{x} = 1 - x - \frac{\zeta_1 x z}{\zeta_2 + z}, \tag{3}$$
$$\dot{y} = \frac{\zeta_3 x z}{\zeta_2 + z} + \frac{\zeta_4 y z}{\zeta_2 + z} - \zeta_5 y - y z,$$
$$\dot{z} = (\zeta_6 \ln \zeta_7 - \zeta_8) z - \zeta_6 z \ln z - y z.$$

Since the biologically feasible domain for our model is $\mathbf{R}^3_{+,0} = \{(x, y, z)^T \in \mathbf{R}^3 : x \geq 0, y \geq 0, z \geq 0\}$ all our objects (trajectories, sets, functions etc.) appeared below for the system (3) are considered only in $\mathbf{R}^3_{+,0}$.

The function $z \ln z$ in Eqs. (3) is well-defined and differentiable with $z > 0$. The value $z \ln z$ at the point $z = 0$ is taken as 0. This corresponds to the extension by continuity on the right. As a result, this function is not Lipschitzian at $z = 0$ and Lyapunov stability theorems are not applicable to studies of local dynamics of the system (3) around the equilibrium point in the plane $z = 0$.

The goal of this paper is to provide dynamical analysis of Eqs. (3). Our approach is based on using the stability analysis and the localization method of compact invariant sets; the latter one is described in [9–11]. Here a localization means a description of the location of all compact invariant sets in the chosen domain by means of equations and inequalities which depend on parameters of the system. It is worth to notice that localization method of compact invariant sets has been used in dynamical analysis of various cancer tumor growth models under immunotherapy in articles [12–17].

The novelty of this paper and the significance of obtained results consist in the following.

1. The dynamics of the CML model (3) is rigorously studied at the tumor-free equilibrium point where this CML model is not lipschitzian. We prove in Section 3 that the tumor-free equilibrium point is locally unstable. As a consequence, tumor clearance cannot be reached at all, even in small. This situation takes place for all positive values of parameters. We notice that local stability analysis based on computing linearization which was provided in [8] is not correct in the non-lipschitzian case. It leads to the erroneous conclusion that the CML model (3) is locally stable at the tumor-free equilibrium point and local asymptotic tumor clearance is realized.
2. The localization method of compact invariant sets elaborated by us in various papers is extended here for the class of systems containing polynomial and rational terms in its right side hand and logarithmic terms as well. As a result, there are derived ultimate upper bounds for the density of all cells populations included into (3) and ultimate lower bound for the density of $T_n$ cells population. This is important for the prediction of global dynamics of tumor; $T_n$; $T_e$ cells in a long-term and for a possible correction or modifications of the model (3).
3. Here we firstly describe on the nontrivial important example of the CML model (3) how to apply the iterative procedure with infinitely many steps for refining the localization domain. This provides the better understanding of ultimate behavior of (3) as well as the proof of global asymptotic stability of the internal tumor equilibrium point in the positive orthant.
4. Currently there are many published cancer tumor growth models in which the tumor free equilibrium point is not lipschitzian, see e.g. paper [3] and references therein. We believe that the local stability analysis fulfilled in our work may be useful in studies of these models.

Our paper is organized as follows. In Section 2 we formulate necessary results which are useful for our analysis. In Section 3 we give a few preliminary observations relating to the behavior of the system (3). The main one consists in the proof that the tumor-free equilibrium point is unstable. In Section 4 we prove the existence of the globally attracting set in $\mathbf{R}^3_{+,0}$ and derive formulas for upper and lower bounds for the ultimate behavior in $\mathbf{R}^3_{+,0}$. In Section 5 we describe the iteration procedure which provides ultimate bounds for positive half trajectories in $\mathbf{R}^3_+ := \{x > 0; y > 0; z > 0\}$. This procedure has infinitely many steps and gives the sequence of embedded globally attracting polytopes in $\mathbf{R}^3_+$. Based on this procedure we present conditions under which the internal tumor equilibrium point is globally asymptotically stable. Section 6 contains results of a numerical simulation