Proceedings of the 4th International Conference on Computing Innovation and Applied Physics
DOI: 10.54254/2753-8818/79/2025.20106

The Mathematical Model Comparison Between Regular Immunogenic Tumor and Chronic Myelogenous Leukemia (CML)

Jiayi Wan[1,a,*]

[1]*Rutgers University, School of Public Health, New Brunswick, 08901, USA*
a. jenniferwan123@outlook.com
**corresponding author*

Abstract: T cell plays important role in lymphocytic leukemia. And the understanding of T cells would help people to modify the growth of leukemia and administrate the dosage to patients. This paper discussed the use of two different models of ordinary differential equations to analyze leukemia. Although the models may have some differences, both of them focused on analyzing the model to calculate the equilibrium state of the tumor in its absence and presence. Regular Immunogenic tumors use a more basic mathematical model, while the chronic myelogenous leukemia (CML) model adds more complex deformations to it. This study compares the steady states of the models proposed by Kuznetsov et al. and Moore and Li, and incorporates the parameter values used in Moore and Li to compare the disparity between them. The research concluded that there were no significant differences in health trials but there were substantial disparities in disease trials between two models.

Keywords: Chronic myelogenous leukemia, ODE, Effector cells, Stability analysis.

1. Introduction

Cancer ranks as the second most prevalent cause of mortality globally, characterized by the uncontrolled proliferation of cells within the human body [1]. The escalation of cellular proliferation associated with tumor development serves as the fundamental framework for understanding tumorigenesis[2]. Different types of cancer have distinct causes, pathologies, course of disease and growth patterns. Therefore, personalized treatment approaches are necessary for each specific type of cancer. So, understanding the growth and change of cancer is a significant process to study. The mathematical model serves as a valuable instrument for characterizing, quantifying, and forecasting the behavior of complex systems, particularly in the context of understanding tumor growth and progression[3]. Kuznetsov et al. were pioneers in elucidating the model of effector cell interactions within tumor environments [4]. Following that, the framework developed by Moore and Li employed ordinary differential equations to quantify the dynamics of naive T cells, effector T cells, and chronic myeloid leukemia (CML) cells [5]. The preceding model examined the precursors of T cells within the bone marrow. Subsequently, Fokas et al. shifted their focus to the maturation and proliferation of T cell precursors [6]. This research focuses on whether Kuznetsov et al. 's model is still available in current research analysis by examing the steady state and utilizing the data employed in Moore and Li's previous study. The study concludes that the growth rate and natural

DOI: 10.54254/2753-8818/79/2025.20106

death rate of CML cancer cells are critical parameters that significantly impact the treatment of CML cancer cells, as estimated by Moore and Li.

2. Mathematical model development

Since the chronic phase is usually the main stage of CML treatment, and the quantity of CML cancer cells in the chronic phase is sufficient for quantitative calculation and prediction using the law of mass action, this mathematical model is more suitable for chronic CML disease.

The rate of change of effector cells (cytotoxic T lymphocytes) and tumor cells from Kuznetsov et al.:

$$\frac{dE}{dt} = s - dE + pE\frac{T}{g+T} - mET \tag{1}$$

$$\frac{dT}{dt} = aT(1 - bT) - nET \tag{2}$$

In the model, E is effector cells and T is tumor cells. For effector cells, s is the produce rate and d is the death rate. mET is the death rate result of killing tumor cells from effector cells, and nET is the dynamic action of this interaction. For tumor cells, a means the maximum growth rate includes the death rate of tumor cells. b^{-1} is the maximum carrying capacity of tumor cells.

The rate of change of naïve T cells, effective T cells, and (CML) cancer cells model from Moore, H., & Li, N. K.:

$$\frac{dT_n}{dt} = s_n - d_n T_n - k_n T_n\left(\frac{C}{C+\eta}\right) \tag{3}$$

$$\frac{dT_e}{dt} = \alpha_n k_n T_n\left(\frac{C}{C+\eta}\right) + \alpha_e T_e\left(\frac{C}{C+\eta}\right) - d_e T_e - \gamma_c C T_e \tag{4}$$

$$\frac{dC}{dt} = r_c C \ln\left(\frac{C_{max}}{C}\right) - d_c C - \gamma_c C T_e \tag{5}$$

In this model, T_n is naive T cells, T_e is effective T cells specific to CML, and C means chronic myelogenous leukemia (CML) cancer cells with unit cells per μl. s_n is bone marrow that could decrease the production of naïve T cells. d_n is naive T cells' death rate. r_c means CML cancer cells' growth. C_{max} is the maximum CML cancer cell. d_c is the death rate of CML cancer cells. γ_c is CML cancer cell loss due to the CML-specific effector T cells. T_e is effector T cells specific to CML.

Table 1: Parameter information from Moore and Li

Parameter	Description	Value	Units	Reference
S_n	T_n source term	0.073	$\frac{cells/\mu l}{day}$	Mohri et al. [7]
d_n	T_n death rate	0.04	day^{-1}	Mohri et al. [7]
d_e	T_e death rate	0.06	day^{-1}	Kuznetsov et al. [8]
d_c	C death rate	0.3	day^{-1}	Duvall and Perry [9]
k_n	T_n differentiation	0.001	day^{-1}	Essunger and Perelson [10]
η	Michaelis-Menten	100	$cells/\mu l$	Moore and Li [5]
α_n	T_e proliferation	0.41		Janeway et al. [11]
α_e	T_e recruitment	0.2	day^{-1}	Moore and Li [5]
C_{max}	Maximum C	3×10^5	$cells/\mu l$	Moore and Li [5]
r_c	C growth	0.03	day^{-1}	Afenya and Calderón [11]

DOI: 10.54254/2753-8818/79/2025.20106

Table 1: (continued).

γ_e	T_e loss (due to C)	0.005	$day^{-1}(\frac{cells}{\mu l})^{-1}$	Moore and Li [5]
γ_c	C loss (due to T_e)	0.005	$day^{-1}(\frac{cells}{\mu l})^{-1}$	Essunger and Perelson[10]

To assess the rate of change in CML cancer cells, it is essential to utilize the Gompertz law, which provides the most effective means of modeling cancerous tumors. It states that CML cancer cell's rate of change is the cancer cells' growth minus the death of cancer cells by the effect T cells and minus the natural death of CML cancer cells. Therefore, $r_c C \ln\left(\frac{C_{max}}{C}\right)$ means the growth of CML cancer cells, $d_c C$ means natural death, and $\gamma_c C T_e$ means the death of CML cancer cells by effect T cell contact.

3. Discussion and explanation of models

3.1. Model from Kuznetsov et al.

Firstly, the simplification should be used to derived two new models with a reduced number of parameters.

$$\frac{dx}{d\tau} = \sigma - \delta x + \rho x \frac{y}{y+\eta} - \mu x y \tag{6}$$

$$\frac{dy}{d\tau} = \alpha y(1 - \beta y) - xy \tag{7}$$

Where $x = \frac{E}{E_0}, y = \frac{T}{T_0}, E_0 = T_0 = 10^6, \tau = nT_0 t, \sigma = \frac{s}{nT_0E_0}, \delta = \frac{d}{nT_0}, \rho = \frac{p}{nT_0}, \alpha = \frac{a}{nT_0}, \eta = \frac{g}{T_0}, \beta = bT_0, \mu = \frac{m}{n}$.

3.1.1. Healthy states

The health state means that there is no cancer in the body. By substituting y equals 0 into the rate of change of effector cells, we can get $\sigma - \delta x = 0$, and $x_0 = {}^{\sigma}/_{\delta}$.
If the y is very small under this condition,

$$\lim_{y \to 0} \alpha \beta y^2 = 0, \frac{dy}{dt} = \alpha y - xy \tag{8}$$

To make it stable, $\alpha < x = {}^{\sigma}/_{\delta}$. To check the stability, use the Jacobian:

$$J = \begin{pmatrix} -\delta - \mu y + \rho \frac{y}{y+\eta} & \rho x \frac{\eta}{(\eta+y)^2} - \mu x \\ -y & \alpha(1 - \beta y) - \alpha \beta y - x \end{pmatrix}. \tag{9}$$

Since it is under healthy states, $y = 0$, and $x = x_0$, and we can get

$$J_0 = \begin{pmatrix} -\delta & \frac{\rho x_0}{\eta} - \mu x_0 \\ 0 & \alpha - x_0 \end{pmatrix}. \tag{10}$$

The J_0 will be negative which implies that the healthy tumor-free equilibrium is stable under the condition of $\alpha < x_0 = {}^{\sigma}/_{\delta}$.

DOI: 10.54254/2753-8818/79/2025.20106

3.1.2. Disease states

In the disease states, there are tumor cells in the body which means that y>0. Setting up the rate of change of cancer cells into 0, we can get:

Equilibrium B: $x = \alpha(1 - \beta y)$, for the rate of change of effector cells. And for cancer cells:

$$x = \frac{\sigma}{\delta + \mu y - \frac{\rho y}{\eta + y}}$$

After calculation, we can get $\mu y^2 + (\mu\eta + \delta - \rho)y + \delta\eta$. And let $\mu\eta + \delta - \rho = c$, the equilibrium C and D would be

$$y = \frac{-c \pm \sqrt{c^2 - 4\mu\delta\eta}}{2\mu}$$

Using the Jacobian to check the stability of equilibrium B, C and D:

$$J_2 = \begin{pmatrix} -\sigma/x & x(-\mu + \rho\frac{\eta}{(\eta+y)^2}) \\ -y & -\alpha\beta y \end{pmatrix}. \tag{11}$$

The equilibrium B and D are negative and stable, but point C is unstable.

3.2. Model from Moore and Li

Since there are a total of twelve parameters in three models and five parameters in the CML cancer cells' rate of change model, it is necessary to simplify the number of parameters for observation and analysis. After simplification, it becomes:

$$\frac{dT_n}{dt} = 1 - T_n - a_1 T_n \left(\frac{C}{C + a_2}\right) \tag{12}$$

$$\frac{dT_e}{dt} = a_3 T_n \left(\frac{C}{C + a_2}\right) + a_4 T_e \left(\frac{C}{C + a_2}\right) - a_5 T_e - C T_e \tag{13}$$

$$\frac{dC}{dt} = a_6 C \ln\left(\frac{a_7}{C}\right) - a_8 C - C T_e. \tag{14}$$

Where $a_1 = k_n/d_n$, $a_2 = \gamma_e\eta/d_n$, $a_3 = \alpha_n k_n \gamma_c/{d_n}^3$, $a_4 = \alpha_e/d_n$, $a_5 = d_e/d_n$, $a_6 = r_c/d_n$, $a_7 = \gamma_e C_{max}/d_n$, $a_8 = d_c/d_n$, T_e is rescaled by γ_c/d_n.

3.2.1. Healthy states

In order to get a steady state, the equilibrium should be figured out first. After setting three simplification solutions into 0, and let C=0 which means it's a healthy trial that the patient does not have any CML cancer cells. The rate of change of naive T cells will become 1-Tn=0, which means Tn=1, Te=0. Then, let $P_1 = (T_{n1}, T_{e1}, C_1)$ become the equilibrium solution. According to the previous calculation, P1=(1, 0, 0) can be obtained.

3.2.2. Disease states

If the patient is unhealthy, which indicates the existence of CML cancer cells in the body, C cannot be 0. We can get $T_n = \frac{C + a_2}{C + a_2 + a_1 C}$, and $T_e = \frac{a_3 C(C + a_2)}{(C + a_2 + a_1 C)[(C + a_2)(C + a_5) - a_4]}$. Putting T_e into the rate of change of CML cancer cells, we can get $\frac{d^2C}{dt^2} = a_8 - a_6 \ln(a_7) + a_6 \ln(C) + \frac{a_3 C(C + a_2)}{(C + a_2 + a_1 C)[(C + a_2)(C + a_5) - a_4]} = 0$. It means that when the equilibrium occurs, C is equal to 0 in this

DOI: 10.54254/2753-8818/79/2025.20106

equation, $a_8 - a_6 \ln(a_7)$ must be less than 0 if the steady state exists. Therefore, we can get that $\frac{dc}{dr} < \ln\left(\frac{\gamma_e C_{max}}{d_n}\right)$ for $P_2 = (T_{n2}, T_{e2}, C_2)$.

To get cell populations' behavior near every equilibrium solution, which also means to get the trend of steady state to see if it is stable. Setting up matrix A by Jacobian, we can get:

$$A = \begin{Bmatrix} -1 - a_1\left(\frac{C}{C+a_2}\right) & 0 & -a_1 T_n\left(\frac{C}{(C+a_2)^2}\right) \\ a_3\left(\frac{C}{C+a_2}\right) & a_4\left(\frac{C}{C+a_2}\right) - a_5 - C & a_3 T_n\left(\frac{C}{(C+a_2)^2}\right) + a_4 T_n\left(\frac{C}{(C+a_2)^2}\right) - T_e \\ 0 & C & a_6 \ln\left(\frac{a_7}{C}\right) - a_6 - a_8 - T_e \end{Bmatrix}. \quad (15)$$

Put P1 into Matrix A, we can get $A = \begin{Bmatrix} -1 & 0 & -\frac{a_1}{a_2} \\ 0 & -a_5 & \frac{a_3}{a_2} \\ 0 & 0 & -a_6 - a_8 \end{Bmatrix}$. Since all parameters are natural real positive constant numbers, all as are positive. By using the eigenvalues of Matrix A, $\lambda_1 = -1, \lambda_2 = -a_5, \lambda_3 = -a_6 - a_8$. It shows that P1 is stable because $\lambda_1, \lambda_2, \lambda_3$ are all negative.

The analysis cannot be tested due to the complex system. Therefore, researchers use large random sampling to calculate that P2 is asymptotically stable.

According to two equilibriums, when $\frac{dc}{dr} < \ln\left(\frac{\gamma_e C_{max}}{d_n}\right)$ happens, there are two stable steady state at P1 and P2. Otherwise, there is only P1 for patients in a healthy state.

4. Numerical analysis

In order to determine the feasibility of the model proposed by Kuznetsov et al., it is necessary to align the parameters utilized by Moore and Li with the steady states of Kuznetsov et al. to compare whether the two models are identical or how they differ from each other.

Firstly, for the healthy states from Kuznetsov et al., $x_0 = \frac{E}{E_0} = \frac{s/nT_0E_0}{d/nT_0}$ can be obtained. In Moore and Lis' research, $E_0 = 600, T_0 = 1080, g = 100, S_e = 0$ can be got. Therefore, $E = \frac{0/600}{0.04} = 0$ can be derived. It means steady state A=(0, 0) which is the same as the steady state P1=(1, 0, 0) from Moore and Li under the healthy trial.

Comparing with two different types of model, it is necessary to first determine whether the two models define the same parameters or formulas to transform. After the cooperation, $p = \alpha_e, m = \gamma_e, b = \gamma_c$ can be obtained. Since we already have

$$y = \frac{-c \pm \sqrt{c^2 - 4\mu\delta\eta}}{2\mu}, \quad (16)$$

Where $c = \mu\eta + \delta - \rho$, we can solve:

$$\frac{d}{nT_0} + \frac{m}{n} \cdot \frac{g}{T_0} - \frac{P}{nT_0} = \frac{0.04}{0.005 \cdot 1080} + \frac{0.005}{0.005} \cdot \frac{100}{1080} - \frac{0.02}{0.005 \cdot 1080} = 0.096. \quad (17)$$

Putting c into the equation we can have:

$$y = \frac{-0.096 \pm \sqrt{(-0.096)^2 - 4 \cdot \frac{0.005}{0.005} \frac{0.04}{0.005 \cdot 1080} \frac{100}{1080}}}{2 \cdot \frac{0.005}{0.005}} = \frac{-0.096 \pm 0.081}{2} < 0, \quad (18)$$

According to the definition, y is the tumor size and cannot be less than 0, which means that the steady states do not exist.

DOI: 10.54254/2753-8818/79/2025.20106

To test the steady states data from the disease trial in Moore and Li, it can be assumed that $\lim_{C\to\infty} \frac{C}{C+\eta} = 1$ with a large enough sample. From $\frac{dT_n}{dt} = 0$, $T_n = \frac{S_n}{d_n + k_n \frac{C}{C+\eta}} = \frac{S_n}{d_n + k_n}$. From $\frac{dT_e}{dt} = 0$, $T_e = \frac{-\alpha_n k_n T_n \frac{C}{C+\eta}}{\alpha_e \frac{C}{C+\eta} - d_e - \gamma_c C} = \frac{-\alpha_n k_n T_n}{\alpha_e - d_e - \gamma_c C}$, putting T_n and parameter number into it to get $T_e = \frac{-0.41 \cdot 0.001 \cdot \frac{0.073}{0.04+0.001}}{0.2-0.06-0.005C} = \frac{0.748}{0.005C-0.14}$.

Since $\frac{dC}{dt}$ also come from $aC(1-bC) - \gamma_c T_e C$, set it to be 0, $T_e = \frac{a(1-bC)}{\gamma_c}$ can be derived, where $a = 36, b = 1/30{,}000$. The final equation could be:

$$\frac{36(1-bC)}{0.005} = \frac{0.748}{0.005C-0.14} \tag{19}$$

$$bC^2 - 0.998C + 90.8 = 0 \tag{20}$$

$$C = \frac{0.998 \pm \sqrt{0.998^2 - 4 \cdot 90.8/30{,}000}}{2/30{,}000} \tag{21}$$

Therefore, $C_1 = 90, C_2 = 29850$, which is different from the Kuznetsov et al.'s result.

5. Discussion

From the analysis and derivation of the two model formulas, it can be seen that both models have a steady state in healthy trials. This may be due to the fact that when individuals have few or no cancer cells, they typically do not develop the disease. Additionally, effector T cells tend to target tumor cells. However, the two models have numerous differences in disease trials. Initially, the equilibrium values differ between the studies. Analysis reveals that Kuznetsov et al. identify two distinct steady states, while Moore and Li recognize only one. However, when applying the parameters from Moore and Li in their calculations, Kuznetsov et al. observed that all outcomes were negative, signifying an absence of a steady state. In contrast, the model introduced by Moore and Li demonstrated the possibility of achieving a steady state in disease trials. This divergence indicates that the two models produce fundamentally different results. One possible explanation is that Moore and Li's model incorporates naïve T cells, which impact effector T cells and consequently influence the overall rate of change in effective T cells. At the same time, it is worth noting that Moore and Li primarily focus on the CML model, while this is not a primary consideration for Kuznetsov et al..

6. Conclusion

By analyzing the formula and calculating the data, it is can be found that in the state of good health, the steady states of the model are both 0. When impacting by the cancer cells, different models will have distinct equilibrium. The benefit of this study is that it provides a comparison of mathematical models for leukemia to help people understand the differences between models. It also provides data that more intuitively reflects the differences in equilibria analyzed by different models. In evaluating the critical parameters, the proliferation and apoptosis rates of cancer cells are paramount in regulating chronic myeloid leukemia (CML) across both models. This indicates that prioritizing these factors will be more beneficial in exploring CML treatment strategies. Furthermore, this analysis yields an estimated mutation rate for CML, which can be leveraged to forecast the optimal dosing regimen throughout the course of treatment.

The study's limitation lies in the use of different analysis cell types in the two models, incorporating only the parameters defined, which results in an inadequate evaluation of naïve T cell

DOI: 10.54254/2753-8818/79/2025.20106

parameters. This may explain the notable disparity in steady states observed across the two disease trials. This study offers new insights for model selection when utilizing mathematical models to analyze cancer cells. In future research, greater attention should be devoted to addressing parameter-matching issues in order to minimize errors in calculations.

References

[1] *Mamat, M., Subiyanto, & Kartono, A. (2013). Mathematical model of cancer treatments using immunotherapy, chemotherapy and biochemotherapy. Applied Mathematical Sciences, 7, 247–261. https://doi.org/10.12988/ams.2013.13023*

[2] *Tomlinson, I. P., & Bodmer, W. F. (1995). Failure of programmed cell death and differentiation as causes of. tumors: Some simple mathematical models. Proceedings of the National Academy of Sciences, 92(24), 11130–11134. https://doi.org/10.1073/pnas.92.24.11130*

[3] *Kronik, N., Kogan, Y., Elishmereni, M., Halevi-Tobias, K., Vuk-Pavlović, S., & Agur, Z. (2010). Predicting. outcomes of prostate cancer immunotherapy by personalized mathematical models. PLoS ONE, 5(12). https://doi.org/10.1371/journal.pone.0015482*

[4] *Kuznetsov, V., Makalkin, I., Taylor, M., Perelson, A., 1994. Nonlinear dynamics of immunogenic tumors: parameter estimation and global bifurcation analysis. Bull. Math. Biol. 56 (2), 295–321.*

[5] *Moore, H., & Li, N. K. (2004). A mathematical model for chronic myelogenous leukemia (CML) and T Cell. Interaction. Journal of Theoretical Biology, 227(4), 513–523. https://doi.org/10.1016/j.jtbi.2003.11.024*

[6] *Fokas, A. S., Keller, J. B., & Clarkson, B. D. (1991). Mathematical model of granulocytopoiesis and chronic. myelogenous leukemia. Cancer research, 51(8), 2084–2091.*

[7] *Mohri, H., Perelson, A., Tung, K., Ribeiro, R., Ramratnam, B., Markowitz, M., Kost, R., Hurley, A., Weinberger, L., Cesar, D., Hellerstein, M., Ho, D., 2001. Increased turnover of T lymphocytes in HIV-1 infection and its reduction by antiretroviral therapy. J. Exp. Med. 194 (9) (November 5), 1277–1287.*

[8] *Duvall, C.P., Perry, S., 1968. The use of 51-chromium in the study of leukocyte kinetics in chronic myelocytic. leukemia. J. Lab. Clin. Med.*

[9] *Essunger, P., Perelson, A.S., 1994. Modeling HIV infection of CD4þ T-cell subpopulations. J. Theor. Biol. 170, 367-391.*

[10] *Janeway, C.A., Travers, P., Walport, M., Shlomchik, M., 2001. Immunobiology: The Immune System in. Health and Disease. Garland Publishing, New York.*

[11] *Afenya,E.,Calderón,C.,2000.Diverseideasonthegrowthkineticsof disseminated cancer cells. Bull. Math. Biol. 62, 527–542.*