MATHEMATICAL MODEL OF CHIMERIC ANTI-GENE RECEPTOR (CAR) T CELL THERAPY WITH PRESENCE OF CYTOKINE

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Abstract. In this paper, we reconstruct a mathematical model of therapy by CAR T cells for acute lymphoblastic leukemia (ALL) with the injection of modified T cells to the body, then some signs such as fever, nausea and etc appear. These signs occur for the sake of cytokine release syndrome (CRS). This syndrome has a direct effect on result and satisfaction of therapy. So, the presence of cytokine will be playing an important role in modeling process of therapy (CAR T cells). Therefore, the model will include the CAR T cells, B healthy and cancer cells, other circulating lymphocytes in the blood, and cytokine. We analyze stability conditions of therapy. Without any control, the dynamic model evidences sub-clinical or clinical decay, chronic destabilization, singularity immediately after a few hours and finally, it depends on the initial conditions. Hence, we try to show by which conditions, therapy will be effective. For this aim, we apply optimal control theory. Since the therapy of CAR T cells affects on both normal and cancer cell; so the optimization dose of CAR T cells will be playing an important role and added to the system as one controller $u_1$. On the other hand, in order to control of cytokine release syndrome which is a factor for the occurrence of singularity, one other controller $u_2$ as tocilizumab, an immunosuppressant drug for cytokine release syndrome is added to the system. In the end, we apply the method of Pontryagin’s maximum principle for optimal control theory and simulate the clinical results by Matlab (ode15s and ode45).

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1. Introduction. Acute lymphoblastic leukemia (ALL) is diagnosed in approximately 100,000 people worldwide per year and 70% of the patients are children. Almost 80% of children will be cured, however, only 30% of adults are cured [?].

The CD19 expression is restricted to B-cells and is found on the surface of most B-cell cancers. CD19 is not expressed on bone marrow stem cells which is shown in figure ?? [?].

Engineered T-cell therapy is a new strategy for the treatment of relapsed and refractory acute lymphoblastic leukemia, which is associated with an extremely poor prognosis in adults and a high cure rate in children which remains a leading cause of death amongst childhood cancers. Chimeric antigen receptor (CAR) T cell is a modified T cell which targets the CD19 antigen is presented on the surface of all B cells. Therefore they work like antibodies that persist and expand in the body and act like “living drug.” Efficacy seems dependent on the ability of the cells to expand and persist in the body after infusion into the patients.

Chimeric antigen receptor-modified T cells with specificity for CD19 have shown promise in the treatment of chronic lymphocytic leukemia (CLL). It remains to be established whether chimeric antigen receptor T cells have clinical activity in acute lymphoblastic leukemia. In initial proof-of-principle clinical trials involving patients with chronic lymphocytic leukemia (CLL), Chimeric antigen receptor-modified T cells that target CD19 produced a durable complete remission in a small number of patients [?, ?]. Shannon L. Maude and his group [?] and others then extended these findings to relapsed and refractory B-cell ALL, and they found profound responses in a small number of children and adults [?].

In addition, since Chimeric antigen receptor-modified T-cell therapy against CD19 was effective in treating relapsed and refractory ALL; CTL019 was associated with a high remission rate, even among patients for whom stem-cell transplantation had failed, and durable remissions up to 24 months were observed [?].

Three and a half years after beginning a clinical trial which demonstrated the first successful and sustained use of genetically engineered T cells to fight leukemia, a research team from the Perelman School of Medicine at the University of Pennsylvania and the Children’s Hospital of Philadelphia will today announce the latest
results of studies involving both adults and children with advanced blood cancers that have failed to respond to standard therapies. The findings from the first 59 patients who received this investigational, personalized cellular therapy, known as CTL019, have been presented during the American Society of Hematology’s Annual Meeting and Exposition in New Orleans.

The new research results include an 89 percent complete response rate among adult and pediatric patients with acute lymphoblastic leukemia (ALL) (Penn Medicine team reports finding from research study).

Also, Stephan A. Grupp et al. infused CTL019 to two children with relapsed and refractory pre-B-cell ALL received infusions of a dose of $1.4 \times 10^6$ to $1.2 \times 10^7$ CTL019 cells per kilogram of body weight. In both patients, CTL019 T cells expanded to a level that was more than 1000 times as high as the initial level, and the cells were identified in bone marrow. In addition, the chimeric antigen receptor T cells were observed in the cerebrospinal fluid (CSF), where they persisted at high levels for at least 6 months. Complete remission was observed in both patients and is ongoing in one patient at 11 months after treatment. The other patient had a relapse, with blast cells that no longer expressed CD19, approximately 2 months after treatment. Chimeric antigen receptors-C modified T cells are capable of killing even aggressive, treatment-refractory acute leukemia cells in vivo [?].

In addition, in the Children’s Hospital of Philadelphia (CHOP) trial, which is being conducted in collaboration with researchers from the University of Pennsylvania, a complete response appeared in 27 of the 30 patients treated in the study, nineteen of the 27 patients with complete responses have remained in remission which 15 of these patients receiving no further therapy and 4 patients withdrawing from the trial to receive other therapy [?].

Daniel W Lee et al. showed a complete response rate in six of six patients with primary chemorefractory ALL. Their study showed that CD19-CAR therapy is feasible in a very high proportion of patients with ALL, with an acceptable toxicity profile [?].

This new, highly method exhibit an improved activity compared to chemotherapy or transplantation. In addition, it could be used sequentially or in combination with other treatment modality, to potentiate the overall treatment efficacy. Thus, CAR T cell therapy was developed mainly for B-lineage but not T-lineage ALL [?].

As well as, in August 2012, the University of Pennsylvania (Penn) and Novartis announced a research and licensing agreement aimed at expanding the use of personalized T cell therapy using chimeric antigen receptors (CARs) for other cancers.

In different times, researchers have made mathematical models of treatment base on immunotherapy, chemotherapy and so on and also they have applied optimal control on some of those models. For example, Pillis and Radunskaya presented a competition model of cancer tumor growth that includes both the immune system response and drug therapy. Using optimal control theory with constraints and numerical simulations, they obtained new therapy protocols. The optimal control generated therapies produce larger oscillations in the tumor population over time. As well as, at the end of the treatment period, total tumor size was smaller than that achieved through traditional pulsed therapy, and the normal cell population had nearly no oscillations [?].

Also, Lisette de Pillis et al. 2006 Mixed immunotherapy and chemotherapy of tumors and constructed a model involves tumor cells, specific and non-specific immune cells (natural killer (NK) cells, CD8+ T cells and other lymphocytes) and
employs chemotherapy and two types of immunotherapy (IL-2 supplementation and CD8+ T-cell infusion) as treatment modalities. Despite the overall success of their model, the problem of illustrating the effects of IL-2 on a growing tumor has remained open [?]. Again, Pillis et al. updated the model and then carefully identified appropriate values for the parameters of the new model according to recent empirical data. They determined new NK and tumor antigen-activated CD8+ T-cell count equilibrium values; completed IL-2 dynamics; and modified the old model in de Pillis et al. in order to allow for endogenous IL-2 production, IL-2-stimulated NK cell proliferation and IL-2-dependent CD8+ T-cell self-regulations. Finally, they showed that the potential patient-specific efficacy of immunotherapy may be dependent on experimentally determinable parameters[?].

We made a mathematical model for immunotherapy by CAR T cell for treatment of B cell ALL. Then we investigated under which condition cure is stable and successful. We considered the injection of CAR T cell as a drug (control variable) in patients body and applied Pontryagin’s maximum principle for optimal control.

In this paper, the line of research that we follow begins with the extension of modeling in treatment for CAR T cells. At first, we consider a mathematical model for CAR T cells from Reihaneh Mostolizadeh et. al. [?]. So we add a new equation as cytokine equation to the former model. Since all the patients have the cytokine-release syndrome in this therapy. Severe cytokine-release syndrome, which developed in 27% of the patients, was associated with a higher disease burden before infusion and was effectively treated with the anti-interleukin-6 receptor antibody tocilizumab. Then we control this new system with two controllers as optimal injection of CAR T cell and drug tocilizumab.

This paper organizes as follows: In section 2 we give a brief explanation of CAR T cell and make a mathematical model of therapy, then we compute its equilibria. Section 3 is devoted to definitions and theorems of optimal control and analysis of system such that under which conditions, therapy will be successful. In section 4, we apply our results to simulate system by clinical data as an example and compare the status of therapy without optimal control and with control.

2. Mathematical Model.

2.1. Description of Model. Normal autologous or allogeneic T cells can be harvested from patients or normal donors to be genetically modified to recognize specific targets on leukemic cells, then expanded and reinfused in the patient to exert anti-leukemic activity. These T cells are first collected from the patient, then modified to recognize an antigen-binding site on the cancer cell and infuse into the patient. This receptor allows the T cell to recognize and bind to a target in the cancer cells (a protein called CD19) when they bind, the T cell can attack the cancer cells. The receptor that is made on T cells is called a Chimeric Antigen Receptor (CAR) T Cells. T cells are engineered to target the CD19 antigen which is present on the surface of nearly all B cells both normal cells and cancer cells.

After injection of CAR T cells, in the trials for ALL, all responding patients experienced a cytokine release syndrome which researchers have learned this reaction can be managed, if necessary, using tocilizumab, an immuno-suppressant drug which tamps down elevated levels of the inflammatory cytokine IL-6, which have been found during the most robust phase of the engineered cells’ expansion in the body. Tests of ALL patients who experienced complete remissions also show that normal B cells, which express the CD19 protein, have been eliminated along with
their tumors. The researchers note that persistent loss of normal B cells is a good surrogate marker for continued activity of the gene-modified T cells. In this way, the cells appear to be providing long-term vaccine-like activity preventing B cells and likely tumor cells from growing back. B cells are important for the body’s immune system to fight infection by making antibodies, though it is possible to replace antibodies with gamma globulin treatments as a preventive measure.

In particular, there has been uncertainty about whether chimeric antigen receptor T cells would expand in vivo in patients with ALL and whether they would have anti-leukemic efficacy in patients with relapsed disease, high tumor burdens, or both.

First, we consider the mathematical model of CAR T cells \[ ? \] as

\[
\begin{align*}
\dot{c}_T &= d_1c_T - d_2c_T - \alpha_1c_Tl - \beta_1c_T \dot{h} \\
\dot{l} &= kl - \alpha_2c_Tl \\
\dot{h} &= ah(1 - bh) - d_3h - \beta_2c_Th \\
\dot{c} &= \lambda - \sigma c + \frac{\epsilon_Tc}{\beta_3 + c_T}
\end{align*}
\]

Which this model describes a system of four populations (CAR T cells, B leukemia cells, B healthy cells and other circulating lymphocytes) using a system of ordinary differential equations. The populations at time \( t \) are denoted by

- \( c_T(t) \), CTL 019 population,
- \( l(t) \), total B leukemia cell population with CD19 molecule,
- \( h(t) \), total B healthy cell population with CD19 molecule,
- \( c(t) \), number of circulating lymphocytes (or white blood cells),

Note that the cytokines are chemically made by immune system cells which one of their important roles is regulating the growth and activity of other immune cells and blood cells. The patient with the multiplying of cytokine typically experiences varying degrees of flu-like symptoms, with high fevers, nausea, muscle pain, and in some cases, low blood pressure and breathing difficulties. We have cytokine release syndrome in this therapy which affects on remission or relapse of disease. Cytokine elevations are measurable in most patients, but the degree of elevation may not correlate with severity of CRS or response to therapy. The most significantly elevated cytokines in the CRS associated with CART19 are IL-10, IL-6, and IFN-\( \gamma \). IL-6 is an inflammatory cytokine involved in a large number\[?] of patients. Then we make a model for dynamics of the cytokines \( s \) by the ordinary differential equation

\[
\dot{s} = \alpha_4 - \beta_4 s
\]

where \( \alpha_4 \) is the maximum rate which cytokines are secreted, altered by a negative feedback mechanism corresponding to the term \( -\beta_4 s \). In addition, since cytokine-release syndrome, a systemic inflammatory response that is produced by elevated levels of cytokines are associated with T-cell activation and proliferation, therefore we add a term \( d_4(\frac{c_T}{c_T + m}) \) as secretion of cytokine base on stimulation of CAR T cells. So we have

\[
\dot{s} = \alpha_4 - \beta_4 s + d_4(\frac{c_T}{c_T + m})
\]
Therefore, we reconstruct the following new model for CAR T cells with cytokine release syndrome

\[
\begin{align*}
\dot{c}_T &= d_1 c_T - d_2 c_T - \alpha_1 c_T l - \beta_1 c_T h \\
\dot{l} &= k l - \alpha_2 c_T l \\
\dot{h} &= a h (1 - b h) - d_3 h - \beta_2 c_T h \\
\dot{c}_T &= \frac{\lambda - \sigma c + \alpha_3 \beta_3 + \beta_3 + c_T}{c_T + m} \\
\dot{s} &= \alpha_4 - \beta_4 s + d_4 \frac{c_T}{c_T + m}
\end{align*}
\] (2)

The system (2) can be rewritten as

\[
\begin{align*}
\dot{c}_T &= d c_T - \alpha_1 c_T l - \beta_1 c_T h \\
\dot{l} &= k l - \alpha_2 c_T l \\
\dot{h} &= a_1 h (1 - b_1 h) - \beta_2 c_T h \\
\dot{c}_T &= \frac{\lambda - \sigma c + \alpha_3 \beta_3 + \beta_3 + c_T}{c_T + m} \\
\dot{s} &= \alpha_4 - \beta_4 s + d_4 \frac{c_T}{c_T + m}
\end{align*}
\] (3)

where \(d = d_1 - d_2\), \(a_1 = a - d_3\) and \(b_1 = \frac{ab}{a-d_4}\).

Now, for simplicity we consider system (3) as

\[
\begin{align*}
\dot{x} &= dx - \alpha_1 xy - \beta_1 xz \\
\dot{y} &= ky - \alpha_2 xy \\
\dot{z} &= a_1 z (1 - b_1 z) - \beta_2 xz \\
\dot{w} &= \lambda - \sigma w + \alpha_3 \frac{\beta_3 + x}{c_T} \\
\dot{v} &= \alpha_4 - \beta_4 v + d_4 \frac{c_T}{c_T + m}
\end{align*}
\] (4)

In order to analyze the stability of therapy CAR T cell; first, we compute the equilibriums of system (3).

2.2. Equilibria. To consider the system (3), It has equilibrium points as

\[
E_0 = (0, 0, 0, \frac{\lambda}{\sigma}, \frac{\alpha_4}{\beta_4})
\]

Where the equilibrium \(E_0\) is called a free-cancer cell, free-treatment and free-healthy cell equilibrium. In this case, we have other circulating lymphocytes in the blood which also leads to the production of the cytokine.

The second equilibrium corresponds to positive levels of B healthy cell, other circulating lymphocytes, and cytokine, but no cancer cell and no therapy.

\[
E_1 = (0, 0, \frac{1}{b_1}, \frac{\lambda}{\sigma}, \frac{\alpha_4}{\beta_4})
\]

The equilibrium \(E_2\) shows that the treatment is unstable because the population of healthy cells is zero. B healthy cells are important for the body’s immune system to fight infection by making antibodies, though it is possible to replace antibodies with gamma globulin as a preventive measure. But in here, we focus on keeping of B healthy cells in a reasonable level without using other drugs.

\[
E_2 = \left(\frac{k}{\alpha_2}, \frac{d}{\alpha_1}, 0, \frac{\lambda (\alpha_2 \beta_3 + k)}{\sigma \alpha_2 \beta_3 + \sigma k - k \alpha_3}, \frac{m \alpha_2 \alpha_4 + k \alpha_4 + k d_4}{\beta_4 (m \alpha_2 + k)}\right)
\]
Only equilibrium $E_3$ shows the positive level of all components. Later on, we focus more on this equilibrium for analysis of system.

\[
E_3 = \left( \frac{k}{\alpha_2} \frac{d\alpha_1 \alpha_2 b_1 + k\beta_1 \beta_2 - a_1 \alpha_2 \beta_1}{\alpha_2 b_1 a_1}, \frac{-k \beta_2 - a_1 \alpha_2}{\alpha_2 b_1 a_1}, \frac{\lambda (\alpha_2 \beta_3 + k)}{\sigma \alpha_2 \beta_3 + \sigma k - k \alpha_3}, \frac{m \alpha_2 \alpha_4 + k \alpha_4 + k d_4}{\beta_1 (m \alpha_2 + k)} \right)
\]

In equilibrium $E_4$, cancer cells don’t appear; therefore we can’t use this equilibrium point, because we want to consider the efficacy of therapy on cancer cells.

\[
E_4 = \left( -\frac{a_1 (db_1 - \beta_1)}{\beta_2 \beta_1}, 0, \frac{\lambda (da_1 b_1 - \beta_1 \beta_2 \beta_3 - a_1 \beta_1)}{\sigma a_1 b_1 - da_1 \alpha_3 b_1 - \sigma \beta_1 \beta_2 \beta_3 - \sigma a_1 \beta_1 + a_1 \alpha_3 \beta_1}, \frac{da_1 \alpha_4 b_1 + da_1 b_1 d_4 - ma_4 \beta_1 \beta_2 - a_1 \alpha_4 \beta_1 - a_1 \beta_1 d_4}{\beta_4 (da_1 b_1 - m \beta_1 \beta_2 - a_1 \beta_1)} \right)
\]

Note that in order to investigate the stability of equilibrium points $E_i$, $i = 0, 1, 2, 3, 4$, we apply the following theorem:

**Theorem 2.1. (Routh-Hurwitz criteria)** The Routh-Hurwitz stability criteria is a mathematical method that is a necessary and sufficient condition for determining whether a system is stable or not. That is, for an $n$-order polynomial $P(\Lambda) = \Lambda^n + p_1 \Lambda^{n-1} + \ldots + p_{n-1} \Lambda + p_n = 0$, all the following Hurwitz arrangements $\Delta_i$ ($i = 1, 2, \ldots, n$) should be positive (for proof see [?]).

\[
\Delta_1 = p_1,
\Delta_2 = \begin{vmatrix} p_1 & p_0 \\ p_3 & p_2 \end{vmatrix}, \\
\vdots \\
\Delta_n = p_n \cdot \Delta_{n-1}
\]

(5)

Since only equilibrium $E_3$ has the positive level of all components, so we only discuss its details. At first, we suppose that equilibrium $E_3$ doesn’t satisfy in Routh-Hurwitz criteria and as a result, the solution would be unstable. Therefore we have the following condition which shows Routh-Hurwitz criteria doesn’t satisfy for equilibrium $E_3$,

\[
- (k \beta_2 - a_1 \alpha_2) k \left( \frac{dka_1 \alpha_2 b_1 \beta_2 - da_1^2 \alpha_2^2 b_1 + k^2 \beta_1 \beta_2^2 - 2ka_1 \alpha_2 \beta_1 \beta_2 + a_1^2 \alpha_2^2 \beta_1}{\alpha_2 \beta_1^2 b_1} \right) + \frac{k (da_1 \alpha_2 b_1 + k \alpha_2 \beta_1 \beta_2 - k \beta_1 \beta_2^2 - a_1 \alpha_2^2 \beta_1 + a_1 \alpha_2 \beta_1 \beta_2)}{a_1 \alpha_2^2 b_1} < 0
\]

(6)

Also, we have the following remark:

**Remark 1.** Since all of the equilibrium should be positive for being meaningful in biology, so the values of parameters should be chosen such that they satisfy the following conditions:

1) $\frac{da_1 \alpha_2 b_1 + k \beta_1 \beta_2 - a_1 \alpha_2 \beta_1}{\alpha_2 b_1 a_1 \alpha_1} > 0$
Here, we will show the analysis of system. The numerical values for system (??) are as
\[ d = 10000, \quad \alpha_1 = 900, \quad \beta_1 = 1200, \quad k = 62, \quad \alpha_2 = 1000, \quad a_1 = 80, \quad b_1 = 50, \]
\[ \beta_2 = 80, \quad \lambda = 110, \quad \sigma = 65, \quad \alpha_3 = 150, \quad \beta_3 = 800, \quad \alpha_4 = 20, \quad \beta_4 = 15, \quad d_4 = 10, \]
\[ m = 8. \]

These values for parameters are chosen based on clinical data [?], positivity of all equilibrium points (conditions of remark (??)) and condition (??).

Equilibrium \( E_3 \) is evaluated with values (??) as
\[ E_3 = (0.080, 11.086, 0.018, 1.692, 1.339). \] (7)

Note that the characteristic polynomial of system (??) for equilibrium \( E_3 \) should not satisfy in Routh-Hurwitz criteria (??) (unstability of \( E_3 \)), i.e. the relation (??) should satisfy in the following inequality:
\[
\begin{aligned}
- \left( k\beta_2 - a_1\alpha_2 \right) & \left( d\alpha_1\alpha_2 b_1 \beta_2 - d\alpha_1^2 \alpha_2^2 b_1 + k^2 \beta_1 \beta_2^2 - 2k\alpha_1\alpha_2\beta_1 \beta_2 + a_1^2 \alpha_2^2 \beta_1 \right) \\
+ & \frac{k \left( d\alpha_1\alpha_2^2 b_1 + k\alpha_2 \beta_1 \beta_2 - k\beta_1 \beta_2^2 - a_1 \alpha_2^2 \beta_1 + a_1 \alpha_2 \beta_1 \beta_2 \right)}{a_1 \alpha_2^2 b_1} = -4323201106.944 < 0
\end{aligned}
\]

In simulation of system (??), when we analyze the system for a duration of 1 month (4 weeks); we will see that the system experiences singularity (a singularity is, in general, a point at which a given mathematical object is not defined, or a point of an exceptional set where it fails to be well-behaved in some particular way, such as differentiability), i.e. the patient faces to case of singularity a few days (almost 2 days) after injection \( t = 0.07 \). In fact, the singularity can occur when one form of growth outpaces another. From the viewpoint of biology, this case will be satisfied completely for this therapy; because after injection of modified T cells, the patient will experience the intensive increase of cytokine which leads to cytokine release syndrome. Therefore, the high growth of cytokine will establish singularity in this therapy and after the time of singularity, the behavior of system will not be predictable. Hence, in this system, the results will be shown only for interval \( t = [0, 0.07] \), i.e. for a few days after injection (see figure ??).

In fact, figure ?? is shown a decrease for leukemia cells and an increase for circulating lymphocytes. But the most important issue is that B healthy cells destroy as leukemia cells are taking down. As we mentioned, the aim of this therapy to remain the B healthy cells while B cancer cells are destroying. In addition, the CAR T cells after injection go down and as well cytokine is increasing which it leads to the singularity.

Generally, in meaning of singularity, we have the singularity is a common point among many trajectories, the dynamics of the system, after the singular point is
interacted, is not in any way determined by the dynamics before, and thus, in conclusion, this system will exhibit a dynamics that may no longer be considered to be deterministic (in the classical sense); therefore the results of system (??) only will be considered until time of singularity ($t = 0.07$).

Note that for system (??) with singularity, its equations will be stiff; so ode15s will be applied for simulation.

Since the singularity implies non-deterministic behavior of the system after a singular point, so some systems show the features similar to deterministic-chaos, i.e. whenever a phase space trajectory comes near the singular point, any arbitrary small perturbation will put the trajectory on a completely different solution [?]. Therefore, it means that if one change the initial conditions for the system, then the singularity may move or eliminate (it will be shown in ??). So system (??) with a new initial condition will not experience the singularity any longer, i.e. the system is sensitive to initial conditions.

However, in ?? with the change of initial conditions, system (??) faced to singularity no longer; but also the results were not reasonable because the whole B healthy cells have removed. Therefore, therapy cannot be effective and can not control the viral load and in final, the cancer cells remain at a high level.

As we mentioned, the dynamics for a singular point will not be deterministic; So for such non-deterministic system, as the various solutions move away from the singularity, they will evolve very differently and will tend to diverge. In general, we have a continuum of different solutions intersecting at a single point. Control may be realized in this case via an appropriate perturbation, so we will have the possibility of the optimization for the behavior of the system in the proximity of
the singularity. Away from the singularity, the solution is well defined\[?\]. Therefore we will apply the optimal control theory and control the behavior of the system by optimization dose of injection CAR T cells and drug of tocilizumab for cytokine in order to destroy the cancer cells and keep the healthy cells in a reasonable level.

In the biological analysis of CAR T cell therapy, the stable conditions for this therapy depend on the following factors:

- Randomized, phase II dose optimization study
- Cytokine release syndrome
- Humoral Immunity and plasma cell changes in patient

Hence, we try to control the factors which affect the stability of therapy by the optimal control which will be described in next section.

3. Optimal Control Problem. Generally, optimal control (OC) is an extension of the calculus of variations. We consider the system

\[ \dot{x}(t) = f(t, x(t), u(t)) \]  

where the state \( x(t) \) is an \( n \) vector and the control \( u(t) \) is an \( m \) vector with \( m \leq n \).

The dynamic equation is solved over the time interval \((t_0, t_f)\) subject to assumed initial conditions, \( x(t_0) = x_0 \). The state and control are subject to inequality constraints, \( x \geq 0, u \geq 0 \).

A typical OC problem requires a performance index or cost functional, \( J[x(\cdot), u(\cdot)] \); a set of state variables, \( x(\cdot) \in X \); and a set of control variables, \( u(\cdot) \in U \). The main goal consists in finding a piecewise continuous control \( u(t), t_0 \leq t \leq t_f \), and the associated state variable \( x(t) \), to maximize the given objective functional.
**Definition 3.1.** (Basic OC Problem in Lagrange form) An OC problem is:

\[
\max_{u(t)} J[x(t), u(t)] = \int_{t_0}^{t_f} f(t, x(t), u(t)) dt, \tag{9}
\]

s.t. \( \dot{x}(t) = g(t, x(t), u(t)) \), \( x(t_0) = x_0 \). \tag{10}

Note that we can switch back and forth between maximization and minimization, by simply negating the cost functional:

\[ \min J = -\max J. \]

Pontryagin introduced the idea of adjoint functions to append the differential equation to the objective function. Adjoint functions have a similar purpose as Lagrange multipliers in multivariate calculus, which append constraints to the function of several variables to be maximized or minimized.

**Definition 3.2.** (Hamiltonian) Consider the OC problem (9). The function

\[
H(t, x, u, \lambda) = f(t, x, u) + \lambda g(t, x, u) \tag{12}
\]

is called the Hamiltonian (function), and \( \lambda \) is the adjoint variable [?, ?].

We are ready to formulate the Pontryagin Maximum Principle (PMP) for problem (9).

**Theorem 3.3.** (Pontryagin’s Maximum Principle for (9)) If \( u^*(t) \) and \( x^*(t) \) are optimal for problem (9), then there exists a piecewise differentiable adjoint variable \( \lambda(t) \) such that

\[
H(t, x(t), u(t), \lambda(t)) \leq H(t, x^*(t), u^*(t), \lambda(t))
\]

for all controls \( u(t) \) at each time \( t \), where \( H \) is the Hamiltonian (12), and

\[
\lambda(t) = -\frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x},
\lambda(t_f) = 0.
\]

**Proof.** See [?]

**Remark 2.** The last condition of theorem (9), \( \lambda(t_f) = 0 \), is called the transversality condition, and is only used when the OC problem does not have the terminal value in the state variable, i.e., \( x(t_f) \) is free.

Theorem (9) converts the problem of finding a control which maximizes the objective function subject to the state ODE and initial condition, into the problem of optimizing the Hamiltonian pointwise. As a consequence, we have

\[
\frac{\partial H}{\partial u} = 0 \tag{13}
\]

at \( u^* \) for each \( t \), that is, the Hamiltonian has a critical point at \( u^* \). Usually, this condition is called the optimality condition.

**Remark 3.** If the Hamiltonian is linear in the control variable \( u \), it can be difficult to calculate \( u^* \) from the optimality equation, since \( \frac{\partial H}{\partial u} \) would not contain \( u \). Specific ways to solve such kind of problems can be found, for [?]
Note that for a minimizing problem, $f$ would have a convex property and the inequality of $f$ would be reversed (coercivity).

**Definition 3.4.** (OC problem with bounded controls) An OC problem with bounded control, in Lagrange form, is:

$$
\max_{u(\cdot)} J[x(\cdot), u(\cdot)] = \int_{t_0}^{t_f} f(t, x(t), u(t)) dt,
$$

s.t. $x(t) = g(t, x(t), u(t))$, $x(t_0) = x_0$,

$$
a \leq u(t) \leq b,
$$

where $a$ and $b$ are fixed real constants with $a < b$.

**Theorem 3.5.** (Pontryagin’s Maximum Principle for (??)) If $u^*(\cdot)$ and $x^*(\cdot)$ are optimal for problem (??), then there exists a piecewise differentiable adjoint variable $\lambda(\cdot)$ such that

$$
H(t, x^*(t), u^*(t), \lambda(t)) \leq H(t, x^*(t), u^*(t), \lambda(t))
$$

for all admissible controls $u$ at each time $t$, where $H$ is the Hamiltonian (??), and

$$
\lambda(t) = -\frac{\partial H(t, x^*, u^*, \lambda(t))}{\partial x}, \quad \text{(adjoint condition)}
$$

$$
\lambda(t_f) = 0. \quad \text{(transversality condition)}
$$

The following proposition is a direct consequence of theorem (??). The proof can be found in [?, ?].

**Proposition 1.** The optimal control $u^*$ to problem (??) must satisfy the following optimality condition:

$$
u^*(t) = \begin{cases} a & \text{if } \frac{\partial H}{\partial u} < 0 \\ \bar{u} & \text{if } \frac{\partial H}{\partial u} = 0 \\ b & \text{if } \frac{\partial H}{\partial u} > 0 \end{cases}
$$

where $a \leq \bar{u} \leq b$, is obtained by the expression $\frac{\partial H}{\partial u} = 0$. In particular, the optimal control $u^*(\cdot)$ maximizes $H$ pointwise with respect to $a \leq u \leq b$.

Note that if we have a minimization problem instead of maximization, then $u^*$ is instead chosen to minimize $H$ pointwise. This has the effect of reversing $<$ and $>$ in the first and third lines of the optimality condition (??).

3.1. **Optimal control of system (??).** The process of treatment for the disease is interpreted as a problem of optimal control in dynamical systems. As we mentioned, the dynamic model of therapy evidenced destabilization and, the stability of model depended on the dose of injection for CAR T cells and control of cytokine release syndrome. Then, we will use an optimal dose of injected CAR T cells as a control variable $u_1$ and drug of tocilizumab for control of cytokine release syndrome which we show adding of a drug as $8 - u_2$. If $u_2 = 8$, a patient is fully drug dosed and for $u_2 = 0$, we have no medication. The drug of tocilizumab affects on cytokine produced by proliferation of CAR T cells.
Hence, the system (16) convert to

\[
\begin{aligned}
\dot{x} &= dx - \alpha_1 xy - \beta_1 xz + u_1 \\
\dot{y} &= ky - \alpha_2 xy \\
\dot{z} &= a_1 z(1 - b_1 z) - \beta_2 xz \\
\dot{w} &= \lambda - \sigma w + \alpha_3 \beta_3 + x \\
\dot{v} &= \alpha_4 - \beta_4 v + (8 - u_2)(\frac{x}{x + m})
\end{aligned}
\]  

(16)

Since CAR T cell therapy kill both B healthy cells and cancer cells, so our aim is the minimization of the population of cancer cells while keeping the population of healthy cells above the reasonable level. Hence our problem is to minimize the objective functional

\[ J = \int_0^T y(t) \, dt \]  

(17)

where \( T \) is the specified final time and \( y(t) \) is the solution of system (16).

Also, the inequality constraints are

(I) \[ g(z, t) = (z(t) - D) \geq 0 \quad 0 \leq t \leq T \]  

(18)

where is constraint for the number of healthy cells and \( D \) is the lowest value of B healthy cells.

(II) \[ U = \{ u = (u_1, u_2) : \frac{1}{2} \times 10^7 = u_{1\min} \leq u_1(t) \leq u_{1\max} = 1 \times 10^8, \]

\[ 0 = u_{2\min} \leq u_2(t) \leq u_{2\max} = 8, \quad t \in [0, T] \} \]  

(19)

where \( u_{1\min} \) and \( u_{1\max} \) are low and high dose for injection of CTL019 and \( u_{2\min} \) and \( u_{2\max} \) are the dose of tocilizumab approved for adults which is 4 to 8 mg/kg every 4 weeks, and the pediatric recommended dose which is 8 to 12 mg/kg every 2 to 4 weeks.

We use theorems (17) and (18) in order to find the best possible control for taking a dynamical system from one state to another, especially in the presence of constraints for the state or input controls.

Since we have constraints on this problem, we make the Lagrangian function which is a strategy for finding the local maxima and minima of a function subject to equality constraints in mathematical optimization.

Next, we form the Lagrangian function

\[ L(t, X, u, \lambda, \mu) = H(t, X, u, \lambda, \mu) + \mu^T g(t, X, u) \]

with the Hamiltonian function

\[ H(t, X, u, \lambda, \mu) = J(t, X, u) + \lambda^T f(t, X, u) \]

where \( \mu^T \) and \( \lambda^T \) are the vectors of adjoint functions, \( X = (x, y, z, w, v) \) is state variable, \( f(t, X, u) \) is vector field of system (16) and \( g(t, X, u) \) is as constraint of (18).

Therefore, the Lagrangian function for system (16) is as

\[ L(t, x^*(t), y^*(t), z^*(t), w^*(t), v^*(t), u_1, u_2, \lambda, \mu) = y^*(t) + \lambda_1(x^*) + \lambda_2(y^*) + \lambda_3(z^*) + \lambda_4(w^*) + \lambda_5(v^*) + \mu(z^*(t) - D). \]  

(20)
For analysis of Lagrangian function of (??), we have

I) $\mu \equiv 0$ when $g(z^*, t) \geq 0$

II) $\mu \leq 0$ when $z^*$ is tight.

Since minimizing $L$ with respect to the control $u$, violating the constraint (??) would increase $L$ and not be optimal, so we have [?]

$$\mu(t) \ g(z^*, t) = 0 \implies \mu(t) \ (z^*(t) - D) = 0. \quad (21)$$

Then we have the adjoint equations and transversality condition

$$\begin{cases}
\dot{\lambda}_1 = -\frac{\partial L}{\partial x^*} = -\lambda_1(d - \alpha_1 y^* - \beta_1 z^*) - \lambda_2(-\alpha_2 y^*) - \lambda_3(-\beta_2 z^*) - \lambda_4\left(\frac{\alpha_3 w^* \beta_3}{(\beta_3 + x^*)^2}\right) - \lambda_5(d_4(8 - u_2)(\frac{m}{x^* + m})) \\
\dot{\lambda}_2 = -\frac{\partial L}{\partial y^*} = -\lambda_1(-\alpha_1 x^*) - \lambda_2(k - \alpha_2 x^*) + 1 \\
\dot{\lambda}_3 = -\frac{\partial L}{\partial z^*} = -\lambda_1(-\beta_1 x^*) - \lambda_3(a_1 - 2a_1 b_1 z^* - \beta_2 x^*) - \mu \\
\dot{\lambda}_4 = -\frac{\partial L}{\partial w^*} = -\lambda_4(-\sigma + \frac{\alpha_3 x^*}{(\beta_3 + x^*)}) \\
\dot{\lambda}_5 = -\lambda_5(-\beta_4) \\
\lambda_1(T) = 0, \ \lambda_2(T) = 0, \ \lambda_3(T) = 0, \ \lambda_4(T) = 0, \ \lambda_5(T) = 0
\end{cases}$$

as well as the optimality condition

$$\frac{\partial L}{\partial u_1} = \lambda_1 = 0, \quad \frac{\partial L}{\partial u_2} = \lambda_5(-d_4(\frac{x^*}{x^* + m})) = 0 \quad (22)$$

which is independent of control variable, $u = (u_1, u_2)$. Since we assumed that the amount of CTL injected to the patient and drug of tocilizumab at time $t$ are bounded, therefore we conclude from the proposition (??),

$$u_1 = \begin{cases}
u_{1\text{min}} & \lambda_1 > 0 \\
u_{1\text{max}} & \lambda_1 < 0 \\
[u_{1\text{min}}, u_{1\text{max}}] & \lambda_1 = 0
\end{cases} \quad (23)$$

$$u_2 = \begin{cases}
u_{2\text{min}} & \lambda_5(-d_4(\frac{x}{x^* + m})) > 0 \\
u_{2\text{max}} & \lambda_5(-d_4(\frac{x + y_t}{x + m})) < 0 \\
[u_{2\text{min}}, u_{2\text{max}}] & \lambda_5(-d_4(\frac{x + y_t}{x + m})) = 0 \quad (24)
\end{cases}$$

Thus, the variables, $\lambda_1, \lambda_2$ are the switching functions for system and our aim is to estimate the number of switching of optimal control $u_1$ and $u_2$. This problem is equivalent to estimate the number of zeroes of the corresponding switching functions $\lambda_1$ and $\lambda_2$.

Therefore, CTL019 should be injected at the maximum rate, $u_{1\text{max}}$ if $\lambda_1$ is negative and if $\lambda_1$ is positive, then CTL019 will be injected at the minimum rate, $u_{1\text{min}}$ [?] and for the drug of tocilizumab is conversely.

Also, we consider $h \in H$ as an arbitrary variable; then by directly solving for $x, y, w, v$, and integrating their equations of system (??), $x(t), y(t), w(t)$ and $v(t)$.
can be expressed as
\[
x(t) = x(0)e^{\int_0^t (d-\alpha_1 y(s) - \beta_1 z(s)) \, ds}
\]
\[
y(t) = y(0)e^{\int_0^t (k-\alpha_2 x(s)) \, ds}
\]
\[
w(t) = e^{\int_0^t (-\sigma + \frac{\alpha_3 x(s)}{\beta_3 + x(s)}) \, ds}(w(0) + \lambda \int_0^t e^{\int_0^h (-\sigma + \frac{\alpha_3 x(h)}{\beta_3 + x(h)}) \, dh} \, ds)
\]
\[
v(t) = e^{\int_0^t (-\beta_4 + d_4 \frac{x(s)}{x(s) + m}) \, ds}(v(0) + \alpha_4 \int_0^t e^{\int_0^h (-\beta_4 + d_4 \frac{x(h)}{x(h) + m}) \, dh} \, ds)
\]
and hence \( x(t) > 0, y(t) > 0, w(t) > 0 \) and \( v(t) > 0 \) for all \( t \in [0,T] \). The third equation of the system (19) is the Bernoulli equation, integrating yields
\[
z(t) = \left[(a_1 b_1 t + z_0)e^{(\frac{\alpha_1 t + \beta_2}{a_1}) x(s) ds}\right]^{-1}. \quad (26)
\]
Since that for a biological model, only positive initial conditions are considered; therefore we have \( x(0) > 0, y(0) > 0, z(0) > 0, w(0) > 0 \) and \( v(0) > 0 \).

The formulas (19) and the positiveness of \( x(t), y(t), w(t) \) and \( v(t) \) imply the boundedness, positiveness and continuity of system (19) on the entire interval \([0,T]\) which satisfy in the following inequalities:
\[
x_{min} < x(t) < x_{max}, \quad y_{min} < y(t) < y_{max},
\]
\[
w_{min} < w(t) < w_{max}, \quad v_{min} < v(t) < v_{max}, \quad t \in [0,T]
\]
where \( x_{min}, x_{max}, y_{min}, y_{max}, w_{min}, w_{max}, v_{min}, v_{max} \) are positive constants \([?]\), so solutions \( x(t), y(t), z(t) \) and \( w(t) \) of system (19) on the interval \([0,T]\) are defined and bounded.

3.2. Numerical Simulation. In this section, we apply the reasonable values of parameters (19) as well as controllers \( u_1 = 5 \times 10^6 \) for the dose of optimized injection and \( u_2 = 8 \) for drug tocilizumab. Therefore, as figure 20 shows, CTLs have oscillation, i.e. CTL019 increases and decreases regularly. As far as, researchers show the quick growth of CTL019 make a cytokine release syndrome, then two controllers \( u_1 \) and \( u_2 \) have controlled the growth of CTL019 and the release of cytokines, i.e. nor CTL019 increase very fast and neither cytokines. As the figure 20 shows, they have an oscillation behavior.

Also, the B leukemia cells decreased dramatically and tended to zero, while, the number of B healthy cells have remained at a reasonable level. As well as, the number of circulating lymphocytes are at a certain level too.

Figure 5 points to function of controllers.

Therefore, the model with controller showed the satisfactory results of therapy, though model without control pointed to instability, singularity, sensitivity to initial conditions and briefly, the therapy couldn’t be successful.

3.3. Conclusion. For years, there were some different methods for treatment of leukemia such as chemotherapy, radiotherapy, bone marrow and so on. In the last decades, the using of drugs like imatinib and trastuzumab have been extended.

And now, the immunotherapy therapies are growing which harness the power of a patient’s immune system to combat their disease.
One approach of immunotherapy involves engineering patients’ own immune cells to recognize and attack their tumors. Engineered T-cell therapy is a new strategy for the treatment of relapsed and refractory acute lymphoblastic leukemia (ALL).

Treatment of a pathogenic disease process is interpreted as the optimal control of a dynamic system, i.e. the dynamic equations are controlled by therapeutic agents that affect the rate of change of system variables. It is shown that optimal control
theory can point the way toward new protocols for treatment and remediation of human diseases and as well, this theory can help develop clinical insight in monitoring and treating illness.

In fact, the present research focused on the modeling of CAR T cell therapy for acute lymphoblastic leukemia (ALL) with consideration of cytokine. Then we applied optimal control theory for this model. We introduced controller $u_1$ as the dose of injection for CAR T cells and controller of $u_2$ as the drug of tocilizumab for control of cytokine. The objective of the control for the model was, minimizing the level of cancer cells with keeping the level of healthy cells above of desirable level over a given time period. The aim was attainable when an appropriate tolerable dose was administered. These results were shown as numerical simulation. We considered two cases for the model, the untreated model without any control which faced all critical situations and model with controllers which implied an effective therapy. The optimal control theory as a commonly employed strategy determined a treatment method that guaranteed a minimum of harm to the patient (such as the keeping of healthy cells population) while minimizing the cancer cell population after 1 month (after 1 month, the drug should be re-injected).

Finally, this question also will be remained that what is the relationship of cancer cells burden to CAR T cells proliferation?

Since the solution of this question can help to model and as a result, to a better therapy for cancer, so we hope the medical science can reply to this question in future.

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