An Efficient Method for Controlling of CML Treatment System

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Abstract—Chronic myelogenous leukemia (CML) is a kind of blood cancer, which produces abnormal white blood cells uncontrollably. Modeling of this type of disease can help for treatment of it to physicians. In this paper we proposed an efficient method for CML treatment. In this method, a nonlinear multivariable system is considered as the plant of the CML treatment. Then an efficient centralized multi-input multi-output proportional and integral (CMIMOPI) controller is proposed for this system. Results show that proposed CMIMOPI controller can control CML disease well, by using low dosage of drugs. Although the real plant is nonlinear, however the controller has good robustness and can stabilize the system for various conditions. Simulation results show that the steady state population of cancer cells at the end of treatment period is highly reduced and the rate of cancer improvement is independent from reproduction of cancer cells.

Keywords—Chronic Myelogenous Leukemia (CML) treatment, Disease Modelling, MIMO system, Centralized controller, PI controller.

I. INTRODUCTION

Leukemia is a kind of blood cancer. This disease affects the production of white blood cells, causing abnormal white cells to displace existing healthy cells uncontrollably. These abnormal white cells “overpopulate” the bone marrow and circulate into the blood stream, which ultimately leads to cancer [2]. Leukemia has four major types, Acute Myeloid Leukemia (AML), Chronic Myeloid Leukemia (CML), Acute Lymphoblastic Leukemia (ALL) and Chronic Lymphocytic Leukemia (CLL). The leukemia is called “Lymphocytic”, if the cancerous change occurs in a type of marrow cell that forms lymphocytes. The leukemia is called “Myeloid”, if the cell change occurs in a type of marrow cell that normally leads to the formation of red blood cells, some kind of white blood cells and platelets. “Acute” type of leukemia progresses quickly and primarily has effect on the cells that are partly or totally underdeveloped. “Chronic” leukemia is a slowly progress disease, that allows larger number of developed cells to grow [3]. Statistics indicate that approximately 15–20% of all cases of leukemia are CML, with a prevalence of 1–1.5 cases per 100,000 persons per year [4].

CML is the result of mutation in the DNA of a single cell in the bone marrow. Chromosomes, number 9 and number 22, are abnormal in CML cells. Parts of these two chromosomes change places with each other. The end part of chromosome 22 sticks to the chromosome 9. Besides, the end part of chromosome 9 sticks to the bottom of chromosome 22.

Chronic, accelerated and blast are three separate phases of CML. The chronic phase is the longest with averaging 3–5 years. In the course of this phase, cell counts grow steadily. The length of accelerated and blast phases can last just a few months. Rapid increase in cell counts is a characteristic of these two phases that followed by death of the patient [1]. Since treatments for CML focus on the chronic phase and also the quantified data of the accelerated and blast phases is unreliable (because of the rapid changes in cell counts in these two phases), thus chronic phase is considered for our model. Most patients who have CML chronic phase can live good with drug therapy.

There are two types of drug therapies. One is targeted therapy such as imatinib, and the other is broad cytotoxic therapy such as cytarabine. According to the studies, combination of these two therapies is better than targeted therapy alone [5, 6]. Since the action of these therapies is against a broad class of cells, treatments usually results in severe side effects, e.g. the more common imatinib side effects include fluid retention (edema), collection of fluid in the chest (pleural effusion), puffiness around the eyes, nausea and vomiting, muscle cramps, diarrhea and rash [3] and the more common cytarabine side effects include nausea, mouth sores, diarrhea, loss of appetite, skin rash, redness and itching [7].
There are different developed works which studied drug therapies for cancer disease that involve tumors [8-14]. Recently Maki and Pujo-Menjouet [15] developed a periodic model for CML. A nonlinear mathematical model with three non-linear ordinary differential equations (ODEs) is generated by Moore and Lee [1]. Michor et al. [16] incorporate treatment of CML by imatinib and cell lines with resistance to imatinib. They used linear ODEs of the systems in a four-compartment model. In [17] an optimal control for treatment of CML has presented. Neuro-adaptive approach which leads to good results has been proposed in [2]. Optimal control for resistance and suboptimal response in CML was showed in [18]. One of the main drawbacks of these efforts is that they usually use a high dosage of drugs for their treatments, which leads to severe side effects. Also in the different conditions, for example for different patients the proposed systems will be re-tuned.

In this paper we aimed to propose a system for CML treatment that uses low dosage of drugs in order to minimize their side effects and can be applied to different patients with different parameters. So, in this paper, a nonlinear multivariable system is considered as the plant of the CML treatment. Then an efficient centralized multi-input multi-output proportional and integral (CMIMOPI) controller is proposed for this system.

The rest of paper is organized as follows. Section 2 presents the nonlinear model of CML and linearization of it. Section 3 discusses about the stability of the linear system and designing of the CMIMOPI controller for it. Section 4 shows some simulation results. Finally, section 5 concludes the paper.

II. MODEL AND LINEARIZATION

A. Model

The model of CML disease is developed by Helen Moore and Natasha K. Li [17]. This nonlinear multivariable system is considered as the plant of the CML treatment, and it is presented in (1) to (3). In this model, number of cancer cells is shown by C. Tc, denotes the naive T cell population and Te denotes the number of effector T cells. In (1) to (3) parameters u1 and u2 are presenting the dosage of drug treatment, imatinib and cytarabine respectively. Actually u1 and u2 are control inputs of the plant and we use them for controlling the disease. The initial condition of the differential Equation in t=0 is assumed as C(0)=10,000, Tc(0)=10, Te(0)=1510 as it is considered in [17]. The other parameters are described in Table I. Subtracting u1=0 and u2=1 describe the cancer dynamic without treatment.

\[
\frac{dT_c}{dt} = \alpha C
\]

\[
\frac{dT_e}{dt} = \frac{u_2(t)}{2} d e^{-\gamma C T_e} - \gamma C T_e
\]

\[
\frac{dC}{dt} = (1-u_1(t)) r C \ln(\frac{C_{max}}{C}) - u_2(t) d e^{-\gamma C T_e}
\]
rug treatment (u1) in system with two control inputs and two outputs. After information is obtained from the Jacobian matrix of the system (More [19]). This system has three different variables and two inputs. We consider the plant as a MIMO system with two control inputs and two outputs. After linearization and simplification the A, B, C and D matrixes calculated as in (4).

\[
A = \begin{bmatrix}
-u_2^* d_n - k_n \left( \frac{C^*}{C^* + \eta} \right) & 0 \\
\alpha_n k_n \left( \frac{C^*}{C^* + \eta} \right) - u_2^* d_n - \gamma e C^* & (\alpha_n k_n + \alpha e T_e^*) \left( \frac{\eta}{(C^* + \eta)^2} \right) - \gamma e T_e^*
\end{bmatrix}
\]

\[
B = \begin{bmatrix}
0 & -\frac{k_n T_e^*}{C^* + \eta} \\
-r e C^* \ln \left( \frac{C_{\max}}{C^*} \right) - d e C^* & 0
\end{bmatrix}
\]

\[
C = \begin{bmatrix}
0 & 1 & 0 \\
0 & 0 & 1
\end{bmatrix},
\]

\[
D = \begin{bmatrix}
0 & 0 \\
0 & 0
\end{bmatrix},
\]

\[
x = \begin{bmatrix}
T_n^* \\
T_e^*
\end{bmatrix},
\]

\[
(4)
\]

**TABLE II**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>s_n</th>
<th>d_n</th>
<th>k_n</th>
<th>a_n</th>
<th>d_e</th>
<th>a_e</th>
<th>r_e</th>
<th>c_e</th>
<th>d_c</th>
<th>C_max</th>
<th>\eta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>0.073</td>
<td>0.040</td>
<td>0.001</td>
<td>0.41</td>
<td>0.06</td>
<td>0.2</td>
<td>0.005</td>
<td>0.03</td>
<td>0.005</td>
<td>0.2</td>
<td>(3 \times 10^5)</td>
</tr>
</tbody>
</table>

**TABLE III**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>By increasing (u_2^*)</th>
<th>By increasing (u_1^*)</th>
<th>By increasing (C^*)</th>
<th>By increasing (T_n^*)</th>
<th>By increasing (T_e^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eigenvalues of matrix A</td>
<td>0.1878</td>
<td>-0.1009</td>
<td>-0.0102</td>
<td>0.0521</td>
<td>0.0926</td>
</tr>
<tr>
<td></td>
<td>-0.0045</td>
<td>-0.2849</td>
<td>-0.0045</td>
<td>-0.0050</td>
<td>-0.0045</td>
</tr>
<tr>
<td></td>
<td>-0.4136</td>
<td>-0.5675</td>
<td>-0.4173</td>
<td>-49.8180</td>
<td>-1.3084</td>
</tr>
</tbody>
</table>

In (1) \(S_n\) denotes the birth of the naive T cells (T_n), the other two terms represent decreasing naive population, one by \(u_2\) drug treatment and natural death, and the other by transforming to the effector T cells. Equation (2) shows increasing and decreasing effector T cells population. First term in (2) points to the naive cells transformed to the effector T cells by \(a_n\) coefficient. Second term in (2) is a recruitment term, which it is assumed that a proportion of effector T cells will recruit other immune cells to aid in killing CML cells [1]. The two last terms represent declining cancer population, by \(u_2\) treatment, natural death and effector T cells.

**B. Linearization**

To design the controller for the nonlinear plant, linearization of the system is needed. Linear system is obtained from the Jacobian matrix of the system (More information is in [19]). This system has three different variables and two inputs. We consider the plant as a MIMO system with two control inputs and two outputs. After linearization and simplification the A, B, C and D matrixes calculated as in (4).

Parameters \(C^*, T_n^*, T_e^*, u_1^*\) and \(u_2^*\) denote operating points for each variable. Between two outputs \(T_n\) and \(C\), \(C\) is more important than \(T_n\), since \(C\) shows the number of cancer cells and the progress of diseases. These variable matrices become numerical by selecting typical parameters for operating point and considering a general patient proposed in [1] (Table II). Numerical matrices for patient “G” are presented in (5).

Although accordance to the recommendation of a specialist reasonable values are chosen for the operating point, but the system presented in (5) is extremely sensitive to the selection of the operating points. Variables \(u_2^*, u_1^*\), \(C^*, T_n^*\) and \(T_e^*\) have important effect on eigenvalues of matrix A respectively. Parameters \(u_2^*\) and \(u_1^*\) have more effect on the eigenvalues of matrix A, such that they can displace all the eigenvalues of matrix A to left half plane (LHP) and stable it. In Table III the effect of changing parameter on the eigenvalues of matrix A is discussed; In each column just one parameter has changed and the others are constant (Patient “G” value).

It is visible that by increasing \(u_2^*, u_1^*\) one of the eigenvalues of A go to the LHP and the system becomes stable. The other three parameters can displace eigenvalues of A, but this displacement has no significant effect on system stability.
III. Nyquist Stability and Controller Design

In this section firstly, Nyquist diagram of the plant is investigated, and then a controller for the system is designed in order to achieve stability and good performance.

\[
A = \begin{bmatrix}
-0.0045 & 0 & -0.0001 \\
0.0002 & -0.4060 & -0.0090 \\
0 & -0.5 & 0.1802
\end{bmatrix},
B = \begin{bmatrix}
0 & -0.8 \\
0 & -0.12 \\
-24.01 & -20
\end{bmatrix}
\]

\[
C = \begin{bmatrix}
0 & 1 & 0 \\
0 & 0 & 1
\end{bmatrix},
D = \begin{bmatrix}
0 & 0
\end{bmatrix}
\]

(5)

A. Nyquist Stability

Since one of the important specifications of each plant is its stability, Nyquist diagram has been studied for our CML model stability. Our plant is a MIMO system therefore we use MIMO Nyquist [20]. Transfer function of plant (7) is calculated from (6).

\[
G(s) = C(sI - A)^{-1}B + D
\]

(6)

\[
G(s) = \frac{1}{\text{det}} \begin{bmatrix}
-8.327 \times 10^{-17}s^2 + 0.2157s + 0.0009708 \\
-0.12s^2 + 0.2005s + 0.0009352 \\
-24.02s^2 - 9.86s - 0.04388 \\
-20s^2 - 8.15s - 0.03619
\end{bmatrix}
\]

, \text{det} = s^3 + 0.2303s^2 - 0.07663s - 0.0003494

(7)

Two eigenvalues loci (More information is in [21]) are calculated from (8).

\[
\text{det}(sI - G(s)) = 0
\]

(8)

Since \(G(s)\) is a MIMO system, calculation of its poles is not as simple as Single-Input Single-Output (SISO) systems (More information is in [22]). The place of the poles can be calculated from \(\text{den}=0\), but their repeating is not gathered. Since dimension of matrix \(A\) is three so we conclude that the plant has three poles at maximum. Thus the poles of \(G(s)\) are -0.0045, -0.4136 and +0.1878 and they have not been repeated. One right half plain (RHP) pole makes the open loop system unstable. Eigenvalues loci of \(G(s)\), \(\lambda_1\) and \(\lambda_2\) are showed in Fig. 2. Because the plant has one RHP pole, then in the Nyquist (9), \(p\) parameter is one. Since we want to have a stable close loop system, therefore \(z\) parameter in (9) should be zero; thus \(n=-1\) which means that the diagram should circle point -1 counter clock wise once.
can improve cancer disease and decrease number of cancer cells in a short period of treatment.

\[ K_p = \begin{bmatrix} -0.1 & 0 \\ 0 & -0.1 \end{bmatrix} \]  

(10)

B. Controller Design

According to (4) our model for CML is MIMO, also the parameters of the model are different for various patients and can change the stability of the system; in addition real system is nonlinear. PI controller has robustness against changing parameters and more performance than the simple proportional controller. Some methods for designing a decentralized MIMOPI controller have been presented, in [24-27]. These methods usually design PI controller according to decentralized control concept, but since two channels of output plant are not decoupled our control method should be centralized (CMIMOPI), which is more complicated to design. Fig. 5 shows a MIMO feedback structure with a CMIMOPI controller. The controller which is applied to the system is presented in (11), the parameter of the controller are obtained by considering two properties together: Robustness of the close loop system and decreasing using drug dosage in treatment period.

\[
CMIMOPI = \begin{bmatrix} K_{p11} + \frac{K_{11}}{s} & K_{p21} + \frac{K_{12}}{s} \\ K_{p21} + \frac{K_{21}}{s} & K_{p22} + \frac{K_{22}}{s} \end{bmatrix} = \begin{bmatrix} \frac{37 + 0.01}{s} & 10 + \frac{0.1}{s} \\ \frac{26 + 0.0005}{s} & 100 + \frac{0.01}{s} \end{bmatrix}
\]  

(11)

In Fig. 5, parameter \( K_{p0} \) is a simple negative gain for tuning loop gain. CMIMOPI controller presented in (11)
TABLE IV
PARAMETERS OF PATIENTS “G” AND “A”

<table>
<thead>
<tr>
<th>Parameter</th>
<th>( s_n )</th>
<th>( d_n )</th>
<th>( k_n )</th>
<th>( a_n )</th>
<th>( d_a )</th>
<th>( a_a )</th>
<th>( y_e )</th>
<th>( r_c )</th>
<th>( y_c )</th>
<th>( d_c )</th>
<th>( C_{\text{max}} )</th>
<th>( \eta )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient “G”</td>
<td>0.073</td>
<td>0.040</td>
<td>0.001</td>
<td>0.41</td>
<td>0.06</td>
<td>0.2</td>
<td>0.005</td>
<td>0.03</td>
<td>0.005</td>
<td>0.2</td>
<td>( 3 \times 10^6 )</td>
<td>100</td>
</tr>
<tr>
<td>Patient “A”</td>
<td>0.29</td>
<td>0.35</td>
<td>0.066</td>
<td>0.39</td>
<td>0.4</td>
<td>0.65</td>
<td>0.079</td>
<td>0.011</td>
<td>0.058</td>
<td>0.012</td>
<td>( 1.6 \times 10^5 )</td>
<td>140</td>
</tr>
</tbody>
</table>

TABLE V
PARAMETERS OF PATIENTS “M”, “N”, “O” AND “P”

<table>
<thead>
<tr>
<th>Parameter</th>
<th>( s_n )</th>
<th>( d_n )</th>
<th>( k_n )</th>
<th>( a_n )</th>
<th>( d_a )</th>
<th>( a_a )</th>
<th>( y_e )</th>
<th>( r_c )</th>
<th>( y_c )</th>
<th>( d_c )</th>
<th>( C_{\text{max}} )</th>
<th>( \eta )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient “M”</td>
<td>0.35</td>
<td>0.12</td>
<td>0.1</td>
<td>0.71</td>
<td>0.005</td>
<td>0.023</td>
<td>0.1</td>
<td>0.023</td>
<td>0.01</td>
<td>0.19</td>
<td>( 2.5 \times 10^5 )</td>
<td>20</td>
</tr>
<tr>
<td>Patient “N”</td>
<td>0.073</td>
<td>0.39</td>
<td>0.01</td>
<td>0.041</td>
<td>0.48</td>
<td>0.7</td>
<td>0.05</td>
<td>0.23</td>
<td>0.08</td>
<td>0.42</td>
<td>( 4 \times 10^6 )</td>
<td>800</td>
</tr>
<tr>
<td>Patient “O”</td>
<td>0.45</td>
<td>0.21</td>
<td>0.07</td>
<td>0.01</td>
<td>0.05</td>
<td>0.23</td>
<td>0.002</td>
<td>0.045</td>
<td>0.043</td>
<td>0.148</td>
<td>( 3.2 \times 10^5 )</td>
<td>364</td>
</tr>
<tr>
<td>Patient “P”</td>
<td>0.045</td>
<td>0.012</td>
<td>0.01</td>
<td>0.51</td>
<td>0.15</td>
<td>0.83</td>
<td>0.02</td>
<td>0.001</td>
<td>0.003</td>
<td>0.048</td>
<td>( 3.2 \times 10^5 )</td>
<td>541</td>
</tr>
</tbody>
</table>

will decrease fewer than 2,000, which is showed in Fig. 6. Also disease of patient “G” is improved in almost less than 50 days. (Fig. 6)

The CMIMOPI controller is tuned such that uses cytarabine \((u_2)\) less than imatinib \((u_1)\), since cytarabine cannot be used high dosage in practice. Dosage of each drug for controlling cancer of patient “G” and “A” is showed in Fig. 7. Since disease is aggressive in patient “A”, imatinib \((u_1)\) is used to the end period of treatment. And cytarabine \((u_2)\) is used for about 65 days with a decreasing trend. But for patient “G” cytarabine is used just for less than 5 days and imatinib treatment continued for about 50 days and after that, using of it will be continued with a very low dosage to the end period of treatment.

We claim that our controller has better result for patient “A” than optimal controller proposed in [17]. Since their optimal controller uses a high dosage of cytarabine \((u_2)\) for treatment which has side effects, while our CMIMOPI controller uses cytarabine fewer. Nevertheless the results of these two controllers are almost the same and cancer cell population decrease nearly to the 2,000 after 250 days for both two controllers. On the other hand our controller is robust and can be applied to different patients with different parameters, while their controllers is dependent on patient’s parameters and should be designed for each patient separately.

The other output of the system (Fig. 8) which is not as important as the first one is effector \(T\) cell population. Effector \(T\) cell population decrease to zero among the treatment very quickly which has three major reasons according to the (2). First, it will be decreased as the disease improves and finally after diminishing cancer cell population, it will become zero. Second, many of effector cells are disappeared by cancer cells daily and using cytarabine \((u_2)\) (which is necessary for treatment) destroys effector cells, too. Last, effector cells don’t have enough time to be replaced, since their replacement is much less than their deaths. Fig. 8 shows effector cell populations for patient “A” and “G”.

B. Simulation of Patients with Different Parameters

The optimal controller proposed in [17], is dependent on patient’s parameters. But the designed CMIMOPI controller is independent from patient’s parameters. So we applied our controller for many different patients to ensure its robustness and performance. Results showed that it operates well for different patients, and the disease improved in few days.

For example four different patients “M”, “N”, “O” and “P” with different parameters are presented in Table V. We have selected these patients such that show different possible situations. For example, look at \(s_n\) for patients “M”, “N”, “O” and “P”, it has values from 0.045 to 0.45 (Table V). We know that \(s_n\) allowed range is (0, 0.5) according to Table I. So, for patients “M” to “P” \(s_n\) has various values which approximately cover all of its allowed range. By examining Table V, it is obvious that each parameter of patients “M” to “P” approximately cover all of its allowed range, (i.e. presented in Table I). Fig. 9 and Fig. 10 show the system’s outputs for patients “M” to “P” under treatment with CMIMOPI controller.

Patient “M” and “P” has better health. Although number of cancer cells decreases with a slow rate for patient “P”, but number of cancer cells decreased to zero for both patients “M” and “P” and the drug treatment stopped after 10 days for patient “M” and after 100 days for patient “P” (according to Fig. 11). Patients “N” and “O” have worse health. Although number of cancer cells decreases with fast trend in first days of treatment for both patients, but some cancer cells remained for patient “N” and “O” after 250 days and the drug treatment continued (just imatinib \((u_1)\)).

The results of simulating these patients show that not only our controller can control cancer disease in different patients well, but also it uses a low dosage of cytarabine \((u_2)\) which is indeed practical. Fig. 11 shows the dosage of each drug which is used for treatment of patients “M” to “P”.

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C. Effect of \( r_c \) and \( d_c \) on Patient Health

In this section we study the effect of parameters \( r_c \) and \( d_c \) on system’s response. Since the system is nonlinear, it is not easy to predict its behavior. But parameters \( r_c \) and \( d_c \) have more effect on the system behavior than the other parameters, as it is mentioned in [1]. Many simulations for different patients show that the overall behavior of system can be predicted using these two parameters, as follows:

1) First point, steady state population of cancer cells

We introduce an important ratio which determines the steady state population of cancer cells at the end of treatment period. This ratio is presented in (12).

\[
\text{Reproduction Ratio for cancer cells } = \frac{r_c}{d_c} \quad (12)
\]

Whatever reproduction ratio of cancer cell (\( RR_c \)) increases, the number of cancer cells at the end of the treatment period is bigger (other parameters are constant). On the other hand, whatever this ratio decreases, the number of cancer cells at the end of the treatment period is smaller. In order to show the effect of \( RR_c \) on the number of cancer cells at the end of treatment period, we consider “P” and other three different patients (“P1”, “P2” and “P3”) which has the same parameters as patient “P” except \( r_c \) and \( d_c \). The parameters \( r_c \), \( d_c \) and \( RR_c \) are presented in Table VI for these patients.

Fig. 12 shows the result of simulation for patients “P”, “P1”, “P2” and “P3”. As you see parameter \( RR_c \) of patients “P”, “P1”, “P2” and “P3” is 0.02, 0.1, 0.2 and 0.5 respectively, and according to Fig. 12.b the number of cancer cells at the end of treatment period is nearly 0, 70, 650 and 1750 respectively. These results show that (12) is an important ratio and confirms our discussion in first point (i.e. whatever reproduction ratio of cancer cell (\( RR_c \)) increases, the number of cancer cells at the end of the treatment period is bigger and vice versa).

2) Second point, the rate of disease improvement at the beginning of treatment

It is obvious that number of cancer cells decreases in different patients with different rates at the beginning of treatment. The question is that “Among \( r_c \), \( d_c \) and the other parameters, which one has critical effect on this rate? And causes the number of cancer cells achieves to its steady state, rapidly?”
Rate of disease improvement at the beginning of treatment is approximately dependent on magnitude of parameter $d_c$, and is independent from parameter $r_c$ and other parameters. Whatever $d_c$ parameter is bigger, rate of disease improvement is better, and vice versa. In order to show this effect, Patients “P”, “P3”, “P4”, “P5”, “P6” and “P7” from Table VI are considered. Fig. 13 shows the results of simulation for these patients.

In Fig. 13, we need a criterion in order to compare the rate of improvement of each patient. Let’s consider the number of days, which cancer cell population of each patient achieved from 10,000 to 3,000 as a criterion for rate of disease improvement.

Consider patients “P” and “P3”. Parameter $d_c$ of these two patients is the same, but their $r_c$ parameter is 0.001 and 0.024 respectively (Table VI). As Fig. 13.b shows, cancer cell population of both patients achieved from 10,000 to 3,000 in the same period of time (nearly 25 days). This result confirms our discussion in second point (i.e. the rate of disease improvement for these two patients is dependent on parameter $d_c$ and independent from parameter $r_c$ at beginning period of treatment). Also for patients “P4” and “P5” parameter $d_c$ is the same, but their $r_c$ parameter is different. Fig. 13.b shows, cancer cell population of both patients achieved to 3,000 in the same period of time (nearly 185 days). Patients “P6” and “P7” have the same result too (Fig. 13.b). All these results show independency of disease improvement rate from parameter $r_c$, which confirm our discussion in second point.

On the other hand, second point says that “whatever $d_c$ parameter is bigger, rate of disease improvement is better”. Consider patients “P4”, “P” and “P6”. Parameter $d_c$ for these three patients is 0.0048, 0.048 and 0.48 respectively (Table VI). Fig. 13 shows that the rate of disease improvement at the beginning of treatment for these three patients is influenced by their $d_c$ parameter. It is obvious that whatever parameter $d_c$ is bigger, the rate of disease improvement is better and cancer cells achieve to their steady state rapidly. And it is completely independent from parameter $r_c$.

Now let’s take a look at section 4.1. Parameter $RR_{RC}$ for patients “G” and “A” is 0.15 and 0.92 respectively (according to Table IV). According to first point the cancer cell population for patient “G” should be much less than...
patient “A” at the end of treatment period (see Fig. 6). On the other hand parameter \( d \), for patients “G” and “A” is 0.2 and 0.012 respectively (Table IV). And due to second point the rate of disease improvement at the beginning of treatment for patient “G” should be much better than “A” (see Fig. 6). These two points confirm that disease of patient “A” is more aggressive than patient “G”.

V. CONCLUSION

In this paper a multivariable nonlinear model is considered for CML disease. The stability of the system is investigated from Nyquist diagram. Our goal is to improve the disease by decreasing cancer cell populations, and using low dosage of drugs. So, an efficient centralized multi-input multi-output proportional and integral (CMIMOPI) controller method is proposed for this system. The CMIMOPI controller, can overcome uncertainties in patient parameters. Using CMIMOPI controller not only causes the nonlinear system to be stable, but also improves the performance of disease treatment. Simulations show that the proposed CMIMOPI method has a good robustness against parameter uncertainties. Also the proposed controller uses fewer dosages of drugs than the other controllers, while can reduces the cancer cell population as controller uses fewer do

In order to implement the proposed controller and practical usages, the information obtained from daily blood samples can be used. Using this information, the number of cancer cells and effector cells feedbacks to the controller, and then the controller determines the dosage of two different drugs which should be used by patients.

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ارائه ی روشی کارآمد برای کنترل درمان بیماری CML

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چکیده- بیماری (CML) نوعی سرطان خون می‌باشد. که منجر به تولید نامحدود گل‌بوله‌های سفید در خون می‌شود. مدل سازی این بیماری می‌تواند به پژوهش‌های درمان آن کمک کند. در این مقاله روش پیشنهادی یک سیستم غیرخطی چندمتغیره به عنوان یک روش آماده درمان CML کارآمدی به شکل کنترل دیجیتال یکپارچه‌ای متعلق به کنترل‌کننده مناسب انتگرالی با چنین برای درمان CML پیشنهاد شد. نتایج نشان می‌دهد که این روش پیشنهادی در مورد مصرف دارویی بیماری کنترل می‌کند. با وجود غیر خطی بودن مدل بیماری، کنترل کننده بهینه سنجی به دقت بسیار بالا نسبت به تغییر پارامترها نشان می‌دهد. با کاهش قدرت و ایجاد شرایط غیرخطی، سیستم یکپارچه‌ای به‌طور مؤثر تغییر می‌کند. شبیه‌سازی نشان می‌دهد که جمعیت سلول‌های سرطانی در حالت دائمی، در پایان دوره درمان به شدت کاهش می‌یابد و نرخ بهبود بیماری مستقل از نرخ تولید مثل سلول‌های سرطانی می‌باشد.

واژه‌ها: کلیدی: درمان CML، مدل سازی بیماری، سیستم‌های یکپارچه‌ای، کنترل متمرکز، کنترل تناسبی انگرالی.