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Enhancement of the Immune Response to Chronic Myeloid Leukaemia via Controlled Treatment Scheduling

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***Abstract*— We study the differential equations describing the chronic myeloid leukaemia. We propose a novel drug scheduling method to enhance the T-cell mediated immune response. The control strategy relies on the understanding of the immune boosting mechanism. The feasibility of the strategy is illustrated via simulations.**

I. INTRODUCTION

In this paper we evaluate the applicability of the control idea developed in [2], [3] to the model of chronic myeloid leukaemia (CML) proposed in [12]. The main purpose of the paper is to derive a new drug scheduling methodology for CML patients on the basis of the properties of the immune dynamics. The basic control idea stems from a simple graphical analysis and in turn leads to the design of a feedback control strategy.

The CML dynamic model considered in this paper has been introduced in [9]. The cancer cell progression dynamics and the immune dynamics are based on the CML mathematical model in [14] and the immune model in [5], respectively. Low-order models for CML are also studied and discussed in [6], [13]. Some theoretical results on a simplified CML model, derived from the model in [9], have been presented in [11], [15].

The role of the immune response in CML is justified by clinical data. For example, in [4], experimental data show some anti-leukaemia effect due to CD4+ and CD8+ T cells during the use of the CML drug *imatinib*$^{\text{TM}}$. In addition, the work in [4] suggests that anti-leukemia immune response can be boosted in-vitro by means of the patient's cryopreserved blood with irradiated cancer cells even when the anti-leukemia immune response is too weak to be detected. In particular the work in [9] assumes that a similar stimulation of the immune response can be achieved in-vivo, and this method is denominated "cancer vaccine" in [9]. Number, dosage, and timing for the vaccine scheduling are also studied in [9].

The paper is organised as follows. In Section II we recall the CML dynamic model of [9]. In Section III we present the control idea of [2], [3] and the application of the proposed control method to the model of CML. Finally we provide conclusions and further remarks in Section IV.

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II. THE CML MODEL

We consider the CML dynamic model of [9], which includes the T-cell mediated immune response, namely

$$\dot{y}_0 = [r_y(1-\epsilon) - d_0]y_0 - q_C p(C,T)y_0, \tag{1}$$
$$\dot{y}_1 = a_y \eta_a y_0 - d_1 y_1 - q_C p(C,T)y_1, \tag{2}$$
$$\dot{y}_2 = b_y \eta_b y_1 - d_2 y_2 - q_C p(C,T)y_2, \tag{3}$$
$$\dot{y}_3 = c_y y_2 - d_3 y_3 - q_C p(C,T)y_3, \tag{4}$$
$$\dot{z}_0 = (r_z - d_0)z_0 + r_y y_0 \epsilon - q_C p(C,T)z_0, \tag{5}$$
$$\dot{z}_1 = a_z z_0 - d_1 z_1 - q_C p(C,T)z_1, \tag{6}$$
$$\dot{z}_2 = b_z z_1 - d_2 z_2 - q_C p(C,T)z_2, \tag{7}$$
$$\dot{z}_3 = c_z z_2 - d_3 z_3 - q_C p(C,T)z_3, \tag{8}$$
$$\dot{T} = s_T - d_T T - p(C,T)C + Q(C_{n\tau}, T_{n\tau}), \tag{9}$$

where

$$p(C,T) = p_0 e^{-c_n C} kT, \qquad C = \sum_{i=0}^{3} y_i + \sum_{i=0}^{3} z_i,$$
$$C_{n\tau} = C(t - n\tau), \qquad T_{n\tau} = T(t - n\tau),$$
$$Q(C_{n\tau}, T_{n\tau}) = 2^n p(C_{n\tau}, T_{n\tau}) q_T C_{n\tau}.$$

The states describe the populations of specific cells in a unit volume of blood. In particular, y_0, y_1, y_2, and y_3 describe the concentrations of leukemia haematopoietic stem cells, progenitors, differentiated cells, and terminally differentiated cells without resistance mutations while z_0, z_1, z_2, and z_3 describe the respective concentrations of leukemia cells with resistance mutations. T denotes the concentrations of anti-leukemia T cells. Model (1)-(9) includes the anti-leukemia T cell response, modelled by equation (9). Accordingly this system can describe comparatively slow relapse and the immunological data from [4] can be fitted into the model [9]. For a detailed explanation of the system (1)-(8) see [14], and for further details on the dynamics (9) see [5].

In order to deal with drug dosage as control input, we modify the terms η_a and η_b of the model. A similar modification can be found in [1], [17]. In particular, we rewrite η_a and η_b as

$$\eta_a(t) = 1 - \eta_a^* u(t), \qquad \eta_b(t) = 1 - \eta_b^* u(t),$$

where η_a^* and η_b^* are the maximum effect of the drug and u is the control input. Note that we use the same u in η_a and η_b because the imatinib treatment has influence over η_a and η_b simultaneously. From a control perspective the input u represents the drug dose, which takes values between zero

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TABLE I

PARAMETERS FOR CANCER EVOLUTION [5], [9], [10], [14], [16].

d_0	0.00225	d_1	0.006	d_2	0.0375	d_3	0.75
r_y	0.008	a_y	1.6	b_y	10	c_y	100
η_a^*	0.99	η_b^*	0.9987	r_z	0.023	a_z	1.6
b_z	10	c_z	100	ϵ	4×10^{-8}	k	1
p_0	0.8	q_C	0.75	q_T	0.5	τ	1

TABLE II

PARAMETERS FOR IMMUNE RESPONSE AND INITIAL CONDITIONS FOR THE PATIENT 'P4' IN [4], [9].

n	2.2	d_T	0.0022	s_T	9×10^{-7}
c_n	7	$y_0(0)$	2.4×10^{-6}	$y_1(0)$	6.4×10^{-4}
$y_2(0)$	0.1707	$y_3(0)$	22.7556	$z_0(0)$	0
$z_1(0)$	0	$z_2(0)$	0	$z_3(0)$	0
$T(0)$	4.09×10^{-4}				

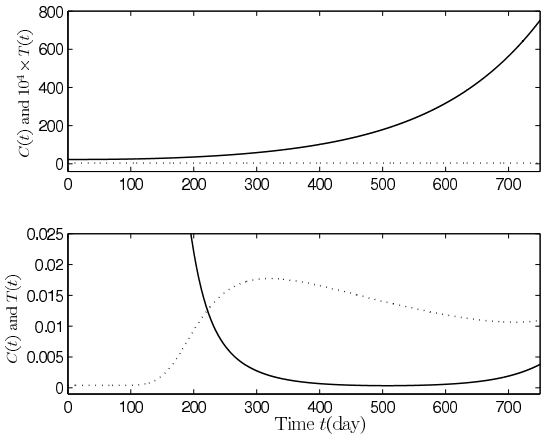

Fig. 1. State histories of $C(t)$ and $T(t)$ for simple treatment examples. The top graph and the bottom graph correspond to the cases with zero-dosage ($u(t) = 0$) and full-dosage ($u(t) = 1$), respectively. The solid lines and the dotted lines indicate the state $C(t)$ and $T(t)$, respectively. Note that $T(t)$ is re-scaled by a factor 10^4 in the top graph.

and one. If $u = 1$ a patient receives maximum dose, while $u = 0$ means no medication. The parameters η_a^* and η_b^* are set based on the parameters η_a and η_b during imatinib treatment [14]. Note that we do not need to introduce control input term for the equation (4) because the parameter c_y does not vary as a consequence of the imatinib treatment [14]. u is restricted to be either 0 or 1 because the values of η_a and η_b are known only when full-dosage imatinib treatment or zero-dosage imatinib treatment are administered.

From the works [9], [14] we assume that the system parameters involving the evolution of the cancer cell are identical for all CML patients. See Table I for these parameters. These parameters are based on the works [5], [9], [10], [14], [16].

We assume that the parameters for the immune dynamics are different for each CML patient. In [9] estimation of the immune related parameters of three patients is carried out exploiting the experimental data of [4]. In this paper we consider the so-called patient 'P4' of [4], [9]. The corresponding parameters are summarised in Table II. The initial conditions considered in this paper are also listed in the same table with the assumption $z_0(0) = 0$ of [9].

If the inequality

$$C(t) < 10^{-10} \tag{10}$$

holds then the cancer is eliminated. Note that a cancer cell concentration level below 10^{-10} implies that less than one cancer cell remains in the human body (approximately the concentration of half a cancer cell in the patient's blood), so the leukemia population is totally eradicated [9]. Thus inequality (10) is one of the main criteria to evaluate treatment.

Fig. 1 shows the state histories of $C(t)$ and $T(t)$ for 750 days for simple treatment examples. In this paper we use the DDE command 'dde23' of MATLAB to solve the time-delay differential equations numerically. The top graph and the bottom graph in Fig. 1 correspond to the cases with zero-dosage ($u(t) = 0$) and full-dosage ($u(t) = 1$), respectively.

In the case $u(t) = 0$, in the top graph of Fig. 1, the cancer $C(t)$ grows unboundedly and the immune response $T(t)$ stays at the initial level $T(0) = 4.0909 \times 10^{-4}$ for $0 \leq t \leq 750$. For the case with full-dosage intake, as seen in the bottom graph of Fig. 1, $C(t)$ increases again about 500 days after the treatment starts and the immune response $T(t)$ does not grow enough to eliminate CML thoroughly. Although the drug therapy of full-dosage for all t can force the cancer cell concentration below a low level, it cannot eliminate CML. Note that the minimum value of $C(t)$ for $0 \leq t \leq 750$ is 3.5171×10^{-4}, which does not satisfy inequality (10).

III. CONTROL METHOD AND CANCER VACCINE

We can regard model (1)-(9) as the interconnection of two subsystems: the cancer population dynamics and the immune system. The cancer population dynamics are eight-dimensional nonlinear dynamics described by equations (1)-(8). The immune system is a one-dimensional nonlinear dynamical system described by equation (9). The goal of the control is to enhance immunity, and this is equivalent to boosting the state T. Note that the immune state T must be enhanced to suppress the leukemia concentration due to the cancer population dynamics.

Consider[1] the function of C

$$F_i(C) = e^{-c_n C} C.$$

Note that $F_i(C) \leq F_i(1/c_n)$ $(= M)$ for all C. If $m \leq F_i(C)$ and $m \leq F_i(C_{n\tau})$, then

$$\dot{T} \geq s_T - [d_T + (M - 2^n q_T m) p_0 k] T,$$

which implies that $T \geq s_T / [d_T + (M - 2^n q_T m) p_0 k]$ in finite time (see [8, Lemma 3.4]). Thus, if we can select the value of m *as large as possible*, then the immune response T will be boosted. Note that $F_i(C)$ and $F_i(C_{n\tau})$ depend upon the variables $C(t)$ of the cancer population dynamics, and this

[1]If $n\tau = 0$, then equation (9) can be rewritten as $\dot{T} = s_T + K(C)T$, with $K(C) = (2^n q_T - 1) p_0 k e^{-c_n C} C - d_T$. Note that, for the given parameters, $2^n q_T - 1 > 0$. A similar structure of immune dynamics is discussed in one of the examples of [2], [3].

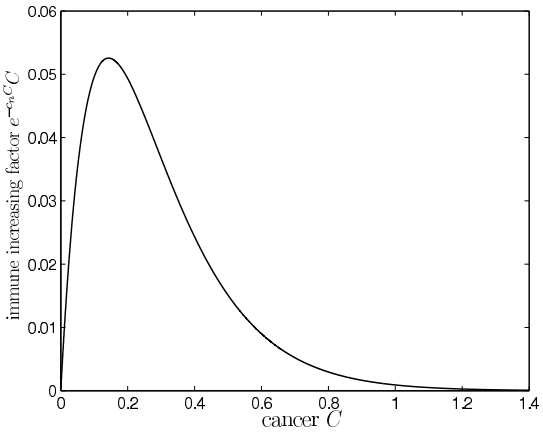

Fig. 2. Graph of the function $F_i(C) = e^{-c_n C}C$, which is derived from (9).

eight-dimensional subsystem is affected by the drug input u. Accordingly we can control $\dot{T}$ indirectly via the input u.

The state T is regarded as the immune term and $F_i(C)$ is regarded as the immune increasing factor. With these definitions it is possible to apply directly the control steps proposed in [2], [3], as described below. Fig. 2 shows the graph of $F_i = F_i(C)$ as a function of C, for the given parameters. In the control steps we aim at increasing the minimum values of the immune increasing factor because this control action helps increasing the value of m.

Control Steps

Initialization: Select a positive number T_s. T_s denotes the sampling time for the computation of the control input. Let T and $F_i(C) = e^{-c_n C}C$ denote the immune term and the immune increasing factor, respectively. X_I is the initial condition of model (1)-(9), as discussed above.

STEP 1: Integrate model (1)-(9) with initial condition X_I for T_s time instants with full medication and with no medication. Let $\Xi_{F,fm}$ and $\Xi_{F,nm}$ be the values of the immune increasing factor of the model (1)-(9), at the end of the integration period, with full medication and with no medication, respectively.

STEP 2: If $\Xi_{F,fm}$ is greater than $\Xi_{F,nm}$, then set $u = 1$. Otherwise set $u = 0$.

STEP 3: The input determined in STEP 2 is applied to the model (1)-(9) with initial point X_I for T_s time instants. Let X_F be the values of the state at the end of the integration period.

STEP 4: Set $X_I = X_F$ and go to STEP 1.

Fig. 3 shows the results of the application of the control procedure with $T_s = 1$ (day). The control input converges to zero and $C(t)$ converges to zero. The state histories of $C(t)$, $T(t)$ and of the controlled drug input are depicted in the top and middle graphs, respectively. $C(t)$ is displayed in logarithmic scale in the bottom graph. The criterion (10) holds for $t \geq 339$ and the maximum value of $T(t)$ for $0 \leq t \leq 750$ is 1.0809.

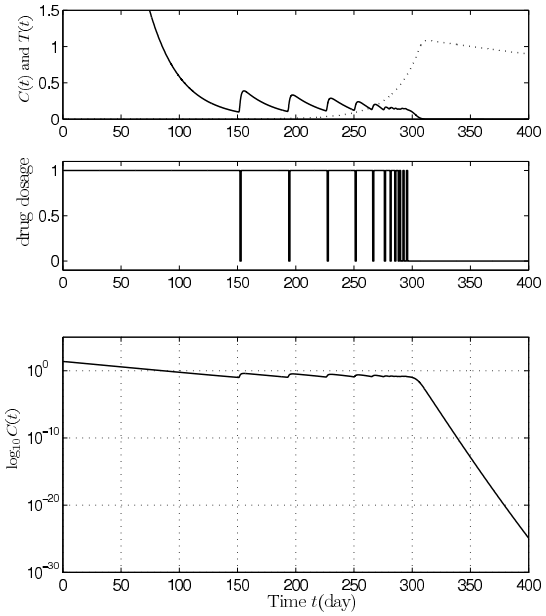

Fig. 3. The results of the application of the control procedure to model (1)-(9) with $T_s = 1$ (day). In the top graph the solid line and the dotted line indicate the state histories of $C(t)$ and $T(t)$, respectively. The controlled drug input and the logarithm of $C(t)$ are displayed in the middle and bottom graphs, respectively.

A. Discussion on Cancer Vaccine

The experimental work in [4] suggests that autologous leukemia cell of a CML patient can be gathered, inactivated, and transfused back in order to boost the immune response using anti-leukemia T-cell. The work in [9] shows that this cancer vaccination effect can enhance the T-cell immune response to a level that would suppress the leukemia population to zero. In [9] the vaccination problem is regarded as an optimisation problem to deliver vaccinations, with fixed dosage, at constant time intervals in order to achieve the criterion (10). To study the feasibility of this approach the dynamical equation describing the population of the inactivated leukemia cells is added to the model (1)-(9). In particular, the model is modified by adding

$$\dot{V} = -d_V V - q_C p(C,T)V + s_V, \tag{11}$$

and by replacing equation (9) with

$$\dot{T} = s_T - d_T T - p(C,T)(C+V) + Q_V(C_{n\tau}, T_{n\tau}, V_{n\tau}), \tag{12}$$

where

$$V_{n\tau} = V(t-n\tau), \qquad s_V = s_V(t),$$
$$Q_V(C_{n\tau}, T_{n\tau}, V_{n\tau}) = 2^n p(C_{n\tau}, T_{n\tau})(q_T C_{n\tau} + V_{n\tau}).$$

V and T denote the concentrations of inactivated leukemia cells and anti-leukemia T cells, respectively. The time function $s_V(t)$ is defined below. The parameters for equations (11) and (12) and the vaccine strategy to be used for the patient 'P4' in [9] are listed in Table III.

The function $s_V(t)$ in equation (11) represents the supply rate of inactivated leukemia cells. When the vaccine is

TABLE III

VACCINE STRATEGY FOR THE PATIENT 'P4' AND PARAMETERS FOR INACTIVATED CANCER CELLS [9].

$Timing$	233	$Pacing$	10	$Number$	5
$V(0)$	0	d_V	0.35	q_V	0.1
t_V	0.01				

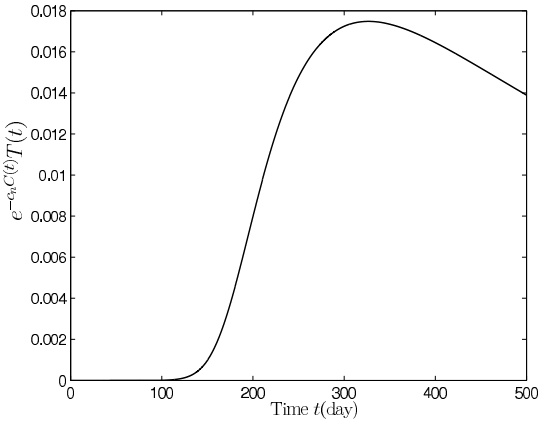

Fig. 4. The graph of $e^{-c_n C}T$ for the case of drug therapy without vaccination.

injected the vaccine dosage q_V should be delivered for the duration t_V. Thus $s_V(t)$ is defined as [9]

$$s_V(t) = \begin{cases} q_v/t_V, & t \in [T_i, T_i + t_V], \\ 0, & \text{otherwise}, \end{cases}$$

where the T_i's are the vaccination times.

In [9] it is assumed that the patient is treated by full-dosage drug therapy ($u(t) = 1$) for all t when the cancer vaccine is considered. It is also assumed that no mutations in the CML model takes place, hence $\epsilon = 0$.

Thus equation (12) can be rewritten as

$$\dot{T} = D_O - p_0 e^{-c_n C} kTV + 2^n p_0 e^{-c_n C_{n\tau}} kT_{n\tau} V_{n\tau},$$

where $D_O = D_O(T, T_{n\tau}, C, C_{n\tau})$ describes the right-hand terms in the equation (9). Thus both V and $V_{n\tau}$ are multiplied by $p_0 k e^{-c_n C(t_m)} T(t_m)$ with $t_m = t$ and $t_m = t - n\tau$, respectively. Note also that $2^n > 1$ for the given parameter n. This implies that the vaccine effect in the long run is affected by the value of $e^{-c_n C}T$ at the vaccination time.

For the case of drug therapy without vaccination, the graph of $e^{-c_n C}T$ is presented in Fig. 4. Note that this case is not the same as in Fig. 1, since $\epsilon = 0$ in the current case. From this graph we have some insight into optimisation for vaccination strategies. For example we infer that if the vaccine starts after 300 day with the same pacing and number, then the immune boosting effect is much better than that of the vaccine strategy in Table III. In such a case the maximum $T(t)$ for $0 \leq t \leq 500$ is 0.2892, which is higher than that discussed in [9], and the criterion (10) holds for $t \geq 435$(day) (the simulation graph is not presented in this paper).

IV. CONCLUSION

We have discussed a unified control methodology for drug scheduling for disease dynamics. We have shown its applicability to CML dynamics by means of computer simulations. The method relies on the intuitive idea that the control action has to boost the immune system and it is based on a simple graphical analysis of the immune system model.

Compared to the research in [9] we use only the drug imatinib as control input without the autologous inactivated cancer cells and our controlled system corresponds to a closed-loop structure which is desirable in view of its potential robustness. Note that the control strategy can be implementable even in the case of no detectable immune response in the patients with CML, because the strategy is based on the immune increasing factor and it is possible to measure the precise level of the leukemia load using PCR tests [7], [12].

REFERENCES

[1] B.M. Adams, H.T. Banks, M. Davidian, H. Kwon, H.T. Tran, S.N. Wynne, and E.S. Rosenberg. HIV dynamics: Modeling, data analysis, and optimal treatment protocols. *J. Comp. Appl. Math.*, 184:10–49, 2005.

[2] H. Chang and A. Astolfi. Immune response's enhancement via controlled drug scheduling. In *Proc. of Conference on Decision and Control*, pages 3919–3924, 2007.

[3] H. Chang and A. Astolfi. Activation of immune response in disease dynamics via controlled drug scheduling. *IEEE Trans. Automation Science and Engineering*, 6:248–255, 2009.

[4] C.I.U. Chen, H.T. Maecker, and P.P. Lee. Development and dynamics of robust T-cell responses to CML under imatinib treatment. *Blood*, 111(11):5342–5349, 2008.

[5] R. DeConde, P.S. Kim, D. Levy, and P.P. Lee. Post-transplantation dynamics of the immune response to chronic myelogenous leukemia. *Journal of Theoretical Biology*, 236(1):39–59, 2005.

[6] D. Dingli and F. Michor. Successful therapy must eradicate cancer stem cells. *Stem Cells*, 24(12):2603–2610, 2006.

[7] S. Hughes and A. Moody, editors. *PCR*. Scion Publishing Ltd, 1st edition, 2007.

[8] H.K. Khalil. *Nonlinear Systems*. Prentice-Hall, third edition, 2002.

[9] P.S. Kim, P.P. Lee, and D. Levy. Dynamics and potential impact of the immune response to chronic myelogenous leukemia. *PLoS Comput Biol*, 4:e1000095, 2008.

[10] T. Luzyanina, K. Engelborghs, S. Ehl, P. Klenerman, and G. Bocharov. Low level viral persistence after infection with LCMV: a quantitative insight through numerical bifurcation analysis. *Mathematical biosciences*, 173(1):1–23, 2001.

[11] F. Mazenc, P.S. Kim, and S.-I. Niculescu. Stability of a Gleevec and immune model with delays. In *Proc. of Conference on Decision and Control*, pages 3317–3322, 2008.

[12] M. McPherson and S. Møller. *PCR*. Taylor & Francis Ltd, 2nd edition, 2006.

[13] F. Michor. The long-term response to imatinib treatment of CML. *British Journal of Cancer*, 96:679–680, 2007.

[14] F. Michor, T.P. Hughes, Y. Iwasa, S. Branford, N.P. Shah, C.L. Sawyers, and M.A. Nowak. Dynamics of chronic myeloid leukaemia. *Nature*, 435(7046):1267–1270, 2005.

[15] S.-I. Niculescu, P.S. Kim, P.P. Lee, and D. Levy. On stability of a combined Gleevec and immune model of chronic myelogenous leukemia: exploiting delay system structure. In *IFAC Symp. on Nonlinear Control Systems Design (NOLCOS)*, pages 796–801, 2007.

[16] E. Olavarria, C. Craddock, F. Dazzi, D. Marin, S. Marktel, J.F. Apperley, and J.M. Goldman. Imatinib mesylate (STI571) in the treatment of relapse of chronic myeloid leukemia after allogeneic stem cell transplantation. *Blood*, 99(10):3861–3862, 2002.

[17] R. Zurakowski and A.R. Teel. A model predictive control based scheduling method for HIV therapy. *J. of Theoretical Biology*, 238:368–382, 2006.