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Combining pharmacological therapy and vaccination in Chronic Myeloid Leukemia via Model Predictive Control*

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Abstract— **This paper describes a simulation study which aims at optimizing the therapy for the control of Chronic Myeloid Leukemia according to the following objectives: the reduction of the administered drug and vaccine amounts, the establishment of a auto-immune response and the long-term control of disease without reducing the effective of therapy with respect to the full treatment. A therapy optimization method is developed defining and solving a Model Predictive Control algorithm, preceded by an accurate Initial Guess search based on Monte-Carlo like approach. Simulation results show that the suggested procedure achieves the proposed goals.**

I. Introduction

A. Chronic Myeloid Leukemia: disease and treatments

Chronic Myeloid Leukemia (CML) is a slowly growing cancer characterized by the overproduction of white blood cells (WBC) within the bone marrow and their accumulation in the blood [1], [2]. In particular, CML is characterized by the overproduction of immature blood-forming cells, the myeloid precursors, or myeloid blasts [3]. The evolution of CML is grouped into three phases:

1) *Chronic*, which can last for months or years if treated with drugs. During this phase, patients may have few or no symptoms.
2) *Accelerated*, during which the myeloid precursors grow more quickly and patients show several symptoms. Without drug treatment this phase lasts 1-6 months before progressing into terminal phase.
3) *Blast crisis*, the last phase characterized by rapid progression and short survival.

The standard treatment for CML is the drug therapy [4], and the most used drug is Imatinib. Imatinib is a tyrosine kinase inhibitor (TKI), so it induces the bone marrow to stop or reduce the overproduction of white blood cells. Imatinib reduces the number of leukemic cells, but it is not able to fully eradicate the cancerous cells from body. These residual cells are a source of relapse, especially if drug therapy is stopped. Unfortunately, the TKI drugs have several side effects. Recently, some preliminary clinical studies [5] showed that a vaccination therapy may be able to reduce or eliminate the last residual cancerous cells in some CML patients under Imatinib treatment. The researchers say that, probably, the vaccine may stimulate an immune system attack against the cancerous cells.

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B. CML treatments modeling

In the last years, several mathematical models have been developed to describe the dynamic between CML and drugs [6], [7], [8], [9]. In our work we use the model developed by [9] that is based on [6]. In [6] it was proposed to model the differentiation of leukemia cells in four stage: stem cells (SC), progenitor cells (PC), differentiated cells (DC) and terminally differentiated cells (TC). In their model, during Imatinib therapy, the leukemic stem cells are not depleted by significant amounts, because they are not affected by Imatinib action. In this way leukemic stem cells continue growing, so leukemia inevitably persists. The model developed in [9] combines the Imatinib action with the immune system stimulation in order to control the CML progression, so it includes anti-leukemia (T-cells) immune response. The authors hypothesize an in-vivo stimulation of anti-leukemia immune response by irradiated autologous leukemia cells or lysates (taken from blood from the patient before Imatinib therapy). This procedure is referred to as *vaccination*. This model is formulated as a system of delayed differential equations, compactly represented as:

$$\dot{\chi}(t) = f(\chi(t), \upsilon(t), \chi(t - n\tau)), \qquad \psi = h(\chi) \quad (1)$$

where $\chi = [y_0\ y_1\ y_2\ y_3\ z_0\ z_1\ z_2\ z_3\ T\ V]^T$ is the state vector, $\upsilon = [I\ s_V]^T$ is the input vector, $\psi = [C\ T]^T$ is the output vector. In particular, the states y_0, y_1, y_2, and y_3 indicate the concentrations of SC, PC, DC and TC, whereas z_0, z_1, z_2, and z_3 indicate the same cell concentrations with resistance mutations to Imatinib. The terms T, C and V denote the concentrations of anti-leukemia T-cells, leukemia cells and inactivated leukemia cells, respectively. The term I represents the normalized Imatinib input and the term s_V is the supply rate of inactivated leukemia cells. The model equations, the values of each parameters and the initial conditions are available in detail in [9] and are not described in this paper for the sake of brevity.

C. Model Predictive Control

Model Predictive Control (MPC) denotes a class of control algorithms in which a dynamic model of the system to be controlled is used to forecast the system evolution under a planned control trajectory. Based on this predictive model, an optimal control trajectory is computed by minimizing an objective function, which usually measures the control effort and the deviation of the system variables from desired targets, while respecting constraints on the system variables and control inputs.

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MPC strategies were initially developed in the late '70s to meet the optimization needs of large-scale process industries, but they have now become attractive control algorithms in many other contexts, including biomedical applications and drug therapy optimization (see e.g. [10], [11], [12], [13] and references therein).

II. Method

A. Therapeutic Objectives

Based on the results of the CML model described in [9] in terms of drug and vaccination usage, the therapy objective has been defined in terms of minimization of 3 quantities: the C cells concentration, the total vaccination dosage and the total amount of Imatinib. The reduction of the vaccination dosage is desirable since the injection of deactivated cancer cells represents a risk factor for the patient. The minimization of the Imatinib has two main objectives: i) to avoid mutation process involving drug resistance in sub-populations of C cells; ii) to modulate the drug amount in order to reach the *optimal load zone* (OLZ) for the C cells population. Using a scheduled modulation of the Imatinib, the proliferation of C cells can be hold within an interval (OLZ) that enables the maximum T cells reproduction by vaccination. Within the OLZ, it is possible to reach the same (or better) immune response using a less vaccination dosage.

B. Problem Formulation

As briefly recalled, the predictive control algorithm requires the definition of a suitable cost function (to be minimized) and of a set of constraints (to be fulfilled). On the clinical side, the cost function minimization means to drive the evolution of the pathology into the chronic state. In our formulation, the cost function was defined into a decision space identified by the *control* variable vector θ:

$$\theta = \begin{bmatrix} t_s & t_e & \nu & \zeta \end{bmatrix} \tag{2}$$

where t_s and t_e are the day of the first and the last vaccination respectively, ν is the total dosage of the vaccine. The variable ζ has been defined as: $\zeta = \begin{bmatrix} \zeta_1 & \zeta_2 & \cdots & \zeta_n \end{bmatrix}$, in which each ζ_i represents the i-th drug modulation (i.e., reduction) in the i-th period between the $(i-1)$-th and the i-th vaccination. Note that $\zeta_i = 0$ means maximal drug use and $\zeta_i = 1$ means no drug use. The cost function is:

$$\begin{aligned} J = \min_{\theta} \Big[& \nu + \alpha_1 \log\big(C(t^\star)\big) + \alpha_2 \|\eta(\cdot)\| \\ & + \alpha_3 \|1-\zeta\| + \alpha_5 \|\overline{\varphi}(\cdot)\| + \alpha_6 \|\underline{\varphi}(\cdot)\| \Big] \end{aligned} \tag{3}$$

the set of constraints is:

$$t_s \geq t_{\min} \quad t_e \leq t_{\max} \quad t_s \leq t_e \tag{4a}$$
$$\nu_{\min} \leq \nu \leq \nu_{\max} \tag{4b}$$
$$\log(T) \geq \log(T_{\min}) - \eta(t) \tag{4c}$$
$$\eta(t) \geq 0 \tag{4d}$$
$$\log(C_{\min}) - \underline{\varphi}(t) \leq \log\big(C(t)\big) \leq \log(C_{\max}) + \overline{\varphi}(t) \tag{4e}$$
$$\overline{\varphi}(t) \geq 0 \quad \underline{\varphi}(t) \geq 0 \tag{4f}$$
$$0 \leq \zeta_i \leq 1 \quad i = 1, \ldots, n \tag{4g}$$

in which t_0 and $t^\star$ are starting and ending times of the predictive window, $t_{\min}$ and $t_{\max}$ represent the minimum and maximum delay needed in starting the therapy to reach a considerable immune response. The term $C(t^\star)$ is the final concentration of leukemia cells, the penalty term $\|1-\zeta\| = \sum_{i=1}^{n} |1-\zeta_i|$ is used to "encourage" drug modulation, $T_{\min}$ is the lowest possible value for the anti-leukemia concentration, $C_{\max}$ and $C_{\min}$ are the higher and lower bound of the OLZ defined around the optimal value $1/c_T$ (c_T is a subject-dependent parameter that regulates the T cell interaction with a cancer cell [9]), explicitly:

$$C_{\max} = \frac{1}{c_T} + \xi; \quad C_{\min} = \frac{1}{c_T} - \xi \tag{5a}$$

The terms $\underline{\varphi}(t)$, $\overline{\varphi}(t)$ are slack variables used to represent violations of the OLZ boundaries. The term $\eta(t)$ is the violation of the minimum concentration bound of T-cells required as safe specific during the whole therapy. Their norms appearing in the cost function are computed as follows:

$$\begin{aligned} \|\eta(\cdot)\| &= \int_{t_0}^{t^\star} \eta(t)dt \\ &= \int_{t_0}^{t^\star} \max\left[0,\ \log\big(T_{\min}\big) - \log\big(T(t)\big)\right] dt \end{aligned} \tag{6a}$$

$$\begin{aligned} \|\overline{\varphi}(\cdot)\| &= \int_{t_s}^{t_e+\Delta t} \overline{\varphi}(t)dt \\ &= \int_{t_s}^{t_e+\Delta t} \max\left[0,\ C(t) - C_{\max}\right] dt \end{aligned} \tag{6b}$$

$$\begin{aligned} \|\underline{\varphi}(\cdot)\| &= \int_{t_s}^{t_e+\Delta t} \underline{\varphi}(t)dt \\ &= \int_{t_s}^{t_e+\Delta t} \max\left[0,\ C_{\min} - C(t)\right] dt \end{aligned} \tag{6c}$$

Notice that the integration are structured in such a way that they are non-zero only if their related constraints are violated. Note that windows of integration in (6b) and (6c) are limited onto period between the first scheduled vaccination and the last one plus the shifting term Δt in order to consider also the effect of the last estimated drug amounts. The Imatinib modulation has allowed only during vaccination, in order to avoid periods in which no controls are active.

C. Initial Guess Search

Due to the complexity of the cost function expressed in (3), an Initial Guess (IG) algorithm has been devised to provide a good initial set of values for parameters. The IG algorithm uses a *Monte-Carlo like* approach. The cost function value is evaluated for different values of the decision parameters. In particular, the IG search can be described in 3 steps: 1) definition of a finite set of values for the each parameter; 2) evaluation of cost functions for each combination of values; 3) setting as IG the parameters with the lower cost function value. The IG procedure will return a *sub-optimal* therapy vector (θ_r^{IG}), not including the Imatinib modulation, consisting of a therapy timing (t_s^{IG}, t_e^{IG}), scheduler of vaccination

(providing total dosage (ν^{IG}), number of vaccinations Nv^{IG} and inter-vaccination time f^{IG}):

$$\theta_r^{IG} = \left[t_s^{IG} \;\; t_e^{IG} \;\; \nu^{IG} \;\; Nv^{IG} \;\; f^{IG}\right]. \tag{7}$$

D. Closed-loop Implementation

The first issue to address in a closed-loop implementation is represented by the mismatch between the real process evolution and the predicted one. When modeling real processes, several sources of error (ideal model equations, parameter identification, experimental measurement errors, etc.) are often introduced. In order to cope with all sources of mismatch, it is customary in MPC design to use an additive disturbance term, estimated at each measurement time. Such disturbance is used to modify future nominal model predictions. Assuming that measurements are available regularly every Δ days, let ψ_j be the output vector at time $t_j = \Delta j$, with $j = 1, 2, \ldots$:

$$\psi_j = \left[C(t_j) \quad T(t_j)\right]^T \tag{8}$$

At each time t_j an *output disturbance* is estimated as:

$$d_j = \psi_j - h(\chi_j) \tag{9}$$

Then, the prediction for future times $t \geq t_j$ will be performed using the *corrected* model:

$$\dot{\chi}(t) = f(\chi(t), \upsilon(t), \chi(t - n\tau)), \quad \hat{\psi} = h(\chi) + d_j \tag{10}$$

At each measurement time, the corrective term d_j will be then estimated and used to improve the model accuracy. In principle, we could use a more general (state and output) disturbance observer, see e.g. [14], [15], [16], but this is omitted because it would add technicalities not justified by the scope of this paper. To reduce the model and real system mismatch, the frequency of measurements ($1/\Delta$) has been increased during vaccination therapies, in which the system dynamic is more sensible to measure uncertainty. As can be seen from the Fig.1, at each step the corrective term is estimated from the measurements (of the real process) and the prediction of system evolution evaluated during optimization. At the next step, the corrective term is used at the optimization level to improve the model accuracy, as above mentioned.

A dedicated code was written in MATLAB (version 2010a) for the solution of the IG searching problem. For MPC formulation, the MATLAB nonlinear constrained minimization function *fmincon* was used to find the solution of (3) at each sampling time.

III. Results and discussion

The combined MPC-IG formulation was applied to 3 different simulated patients (named P1, P2 and P3), by using the parameters reported in [9]. For each patient, we set 1500 days as total time of simulation; to be compatible with clinical practice, we supposed that the time interval between each measures (Δ) is 7 days (between t_s^{opt} and t_e^{opt}) and 30 days (during non treatment period), and that the Imatinib dosage can switch each 30 days. To simulate the mismatch between the real process and the modeled one, we use the model parameters of P2 as the internal model for the MPC formulation of P1 and P3. In table I the results of controlled variables at the ending time of predictive window ($C(t^\star)$ and $T(t^\star)$), drug reduction with respect to the uncontrolled protocol and θ^{opt} (except for drug vector) of closed-loop simulation, are reported for each patient after both IG and optimization stages. Notice that the best compromise (high level of T cells but low values of vaccination, Imatinib dosage and C cells) is related to P2. The evolutions of both controlled variable and drug modulation are shown in figure 2. In figure 2, only the time widows focused over t_s^{opt} and t_e^{opt} are reported during which the drug is modulated. From the data of figure 2, it is clear that the best evolution of the CML are obtained for the patient P2 with low noise level (1%), in fact the amount of drug usage is the lower with respect to the other simulations and, at the same time, the T cell population reaches high level and the C cell amount is drastically reduced at the end of simulation. This goal for P2 is due to the fact that the MPC algorithm is able to drive and keep the C cell population into the OLZ when C cells are in higher concentration. In this way, lower amounts of drug and vaccination are required to drive the Leukemia into the chronic state. The performances of the control strategy get worse with the increase of noise level (from 1% to 10%),

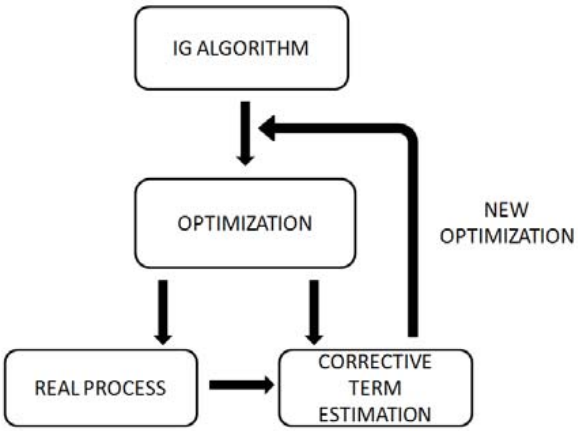

Fig. 1. Whole implementation of MPC and IG stages

TABLE I
RESULTS OF SIMULATION FOR EACH PATIENT (P1, P2 AND P3).

Patient	P1	P2	P3
$t_s^{opt}[days]$	350	316	350
$t_e^{opt}[days]$	602	480	602
Nv^{opt}	10	10	10
$f^{opt}[days]$	5	5	5
ν^{opt} $[k/\mu l]$	0.41	< 0.01	5
$\log(C(t^\star))$	-15.7	< -20	< -20
$T(t^\star)$ $[k/\mu l]$	0.0165	0.0165	0.0082
drug reduction [%]	-11.7	-7.6	-16.8

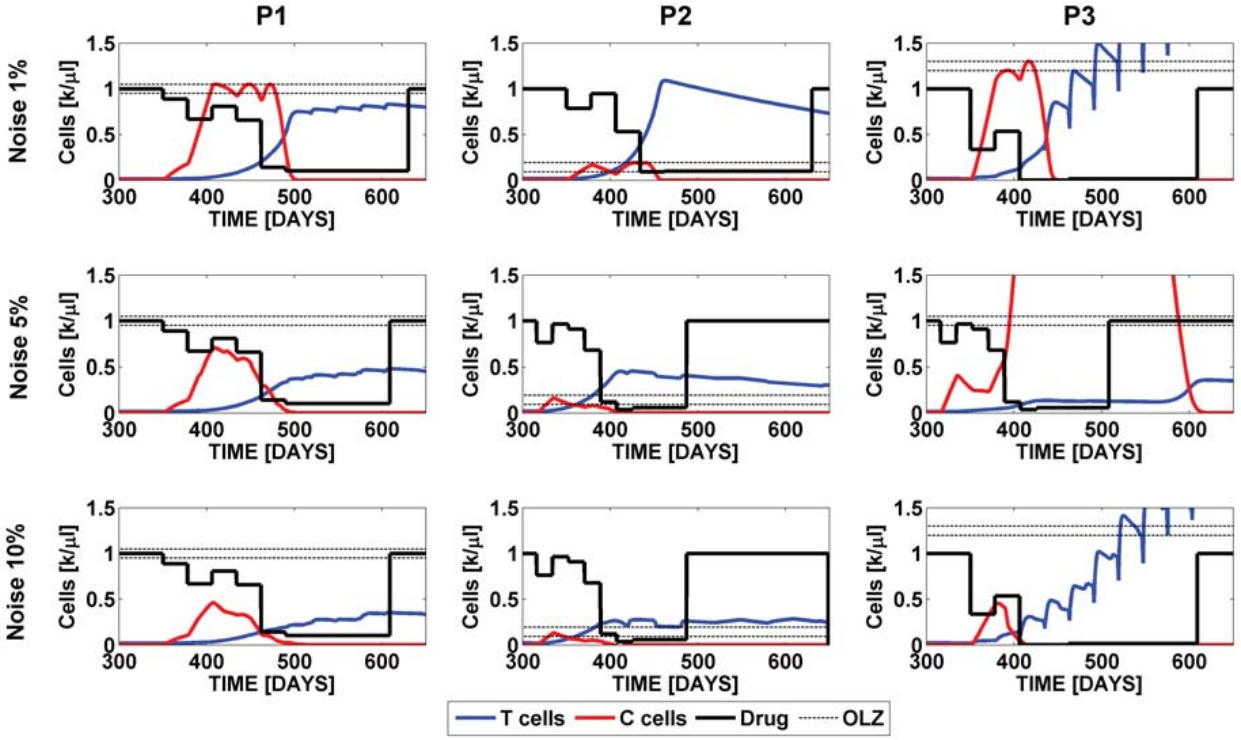

Fig. 2. Closed-loop evaluation for 3 simulated patients (P1,P2 and P3)

but the used amount of drug is still reduced compared to the standard pharmacological therapy. On average, the patients P1 and P3 are lower overall performances then P2, but it is still possible to improve the therapeutic protocols for each patient with respect to the standard ones.

IV. Conclusions

In this work we have devised a Model Predictive Control strategy, preceded by a initial guess (IG) searching, to an ODE model describing the interaction between the drug and vaccination administrations and the Chronic Myeloid Leukemia. We showed how this approach is well suited for this kind of application, since the simulations demonstrated that the MPC-IG combined strategy is able to optimize the standard therapeutic approaches by minimizing the drug and vaccination amounts but, at the same time, keeping under control the disease.

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