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Optimal Drug Administration in Cancer Therapy using Stochastic Non-linear Model Predictive Control

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Abstract— **There has been significant interest in using advanced control strategies for medical treatments in recent years. This study proposes a two-fold approach to enhance drug dosing in cancer treatment. Firstly, a stochastic model predictive control (SMPC) is designed to address the uncertainties inherent in patient responses. Secondly, this SMPC is formulated as a sequential quadratic programming (SQP) MPC to manage the system's non-linearities. Therefore, this study proposes a stochastic SQP-MPC drug delivery framework to enhance patient outcomes and reduce side effects. The effectiveness of the proposed strategy is assessed via simulations and compared with other strategies.**

I. Introduction

Cancer is a predominant cause of mortality worldwide, exerting a substantial strain on health systems, economies, and societal frameworks. Projections indicate that in the next century, 40-50% of people may develop cancer at some point in their lives [1], [2]. The therapeutic approach to cancer is contingent upon the tumor's nature, its progression stage, and the patient's overall health. Established treatments include radiotherapy [3], immunotherapy [4], surgical procedures, and, notably, chemotherapy [5]. This last treatment, while effective, is non-discriminative and often results in adverse side effects, necessitating meticulous planning to ensure the patient's well-being.

Currently, the integration of engineering and mathematical methodologies in devising cancer treatment strategies is on the rise. In this regard, drug pharmacokinetics models examine tumor-drug-side effect interactions, as seen in the work of [6], which offers an overview of various models. Such techniques are instrumental in forecasting tumor trajectories [7], [8] and discerning their probabilistic behavior [9].

Leveraging mathematical models and control algorithms can enhance drug delivery. For instance, the study in [10] employs a PID controller to orchestrate chemotherapeutic regimens. Similarly, the research presented in [11] adopts a two-degree-of-freedom fractional order PID system for drug dosing. Furthermore, the work in [12] integrates linear quadratic regulators to refine chemotherapy-centric cancer treatments.

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This work is focused on Model Predictive Control (MPC), a well-established control strategy for dynamical systems. MPC employs a mathematical model to predict the future trajectory of system variables and optimize an objective function subject to constraints on both input and output variables along a prediction horizon [13], which renders it apt for safety-critical applications. For instance, MPC is used to compute the optimal thermal dose employed in the ultrasonic heating treatment of cancer in [14], [15].

Generally, MPC controllers using linear models achieve satisfactory results, even when dealing with non-linear systems. However, in some cases where the non-linearities are particularly severe, the response obtained through a linear MPC is unacceptable. In such cases, non-linear MPC (NMPC) formulations are required [16]. In this way, some NMPC approaches have been utilized in biomedical systems. For instance, in reference [17], a dosing strategy for a combined regimen of chemotherapy and immunotherapy is carried out. Also, an NMPC in tandem with a moving-horizon estimator to achieve an optimal drug administration scheme is proposed in [18].

NMPC typically involves solving computationally intensive optimization problems that are nonconvex. An alternative to address this issue is to incorporate Sequential Quadratic Programming (SQP) into MPC, which is recognized as an essential improvement, particularly in managing non-linear applications, as seen in [19], [20]. The SQP-MPC approach is an iterative technique that solves an approximation of the non-linear problem. At each time step, the solution is obtained by replacing the objective function with a quadratic approximation and replacing the non-linear constraints with their linear approximations [21]–[23].

Another issue when developing a control strategy for cancer therapy is to address stochastic uncertainties that may significantly impact therapy outcomes. This fact leads to Stochastic MPC (SMPC) methodologies. Among SMPC techniques, Chance-constrained MPC (CC-MPC) is noteworthy for its ability to manage the probabilistic constraints inherent in the optimization problem [24], translating them into their deterministic equivalent concerning risk violation. The biomedical domain has highlighted the effectiveness of this approach, as seen in works like [25], which employs this kind of controller to calculate chemotherapy dosage.

The main contribution of this work is the combination of SQP-MPC with CC-MPC applied to tumoral growth, resulting in improved effectiveness of chemotherapy treatment. The goal is to optimize the therapeutic impact, minimize side effects, and safely reduce tumor size as much as possible.

Compared to previous works mentioned above, this article attempts to bridge the gap between handling non-linear mathematical models and accounting for the stochastic nature of biological systems. It is important to note that this proposed methodology is intended to aid practitioners in designing and administering chemotherapy. Further study and validation on real subjects would be required before its use in clinical treatment.

This article is organized as follows. Section II describes the non-linear mathematical model detailing tumor dynamics, the pharmacokinetics of tamoxifen (TM), and its associated side effects. Section III develops the formulation of the SQP CC-MPC to deal with uncertainties. Section IV highlights the advantages of the controller by comparing it with other alternative treatments. Conclusions and future directions are discussed in Section V.

II. Non-linear mathematical model of the system

The non-linear mathematical model presented below analyzes different aspects of cancer treatment. Firstly, it is essential to note that the model is based on TM cycles administered to a common mouse with an advanced tumor. As mentioned above, the equations of this model, alongside their parameters, have been taken from the work in [26].

The first part of the model relates to the cellular growth of the cancerous cells in the tumor. This process is divided into three stages for mathematical simplicity, as stated in reference [27]: X_g, which corresponds to the volume of cells in the quiescence and growing states; X_s, which is the volume of cells in the DNA synthesis state; and X_m, which represents the volume of cells in mitotic preparation and in mitosis itself. They are described according to the following equations:

$$\dot{X}_g(t) = -k_g X_g(t) \ln\left(\frac{\Theta}{N(t)}\right) + 2k_m X_m(t) \ln\left(\frac{\Theta}{N(t)}\right) - k_d X_g(t)\left(\frac{X_2}{V} + c\frac{X_3}{V}\right), \quad (1)$$

$$\dot{X}_s(t) = -k_s X_s(t) + k_g X_g(t) \ln\left(\frac{\Theta}{N(t)}\right), \quad (2)$$

$$\dot{X}_m(t) = -k_m X_m(t) \ln\left(\frac{\Theta}{N(t)}\right) + k_s X_s(t), \quad (3)$$

with k_g, k_m, and k_s being the transfer rates between the three stages. Moreover, Θ is the plateau population, k_d is the chemotherapy-induced cellular death rate, V represents the total blood volume, and c corresponds to the higher efficiency of X_3. All of the values for these parameters can be consulted in [26]. Moreover, the total tumor size is represented by

$$N(t) = X_g(t) + X_s(t) + X_m(t). \quad (4)$$

The pharmacokinetics of TM are modeled in four stages: X_0, X_1, X_2, and X_3. The set of equations describing this part of the model are:

$$\dot{X}_0(t) = -k_{01} X_0(t) + u_c(t), \quad (5)$$

$$\dot{X}_1(t) = -k_{12} X_1(t) + k_{01} X_0(t), \quad (6)$$

$$\dot{X}_2(t) = -k_{r2} X_2(t) - k_{23} X_2(t) + k_{12} X_1(t), \quad (7)$$

$$\dot{X}_3(t) = -k_{r3} X_3(t) + k_{23} X_2(t), \quad (8)$$

where $u_c(t)$ is the daily injected dose of chemotherapy, each k_{xx} represents the transfer between different stages of the metabolization, and k_{rx} are the consumption rates for X_2 and X_3. It is important to note that the daily dose of TM should not exceed 800 µg.

As mentioned above, chemotherapy is not a selective treatment, meaning the drug will also affect healthy cells. One of TM's most potentially dangerous side effects is the degradation of the immune system. This work considers circulating lymphocytes as an indicator of this degradation, following the evolution described by the following equation:

$$\dot{C}(t) = \alpha_C - \beta_C C(t) - k_C C(t)\left(\frac{X_2(t)}{V} + b\frac{X_3(t)}{V}\right). \quad (9)$$

Here, $C(t)$ is the quantity of circulating lymphocytes, which should always remain above 40% of its initial value ($C(0) = 10^7$) to ensure the safety of the treatment [26]. Furthermore, α_C and β_C respectively represent the natural generation and death of lymphocytes, k_C is the TM-induced lymphocyte death, V is the total blood volume, and b represents the increased effect of X_3 when compared to X_2. As stated above, these values can be found in [26].

III. SQP CC-MPC Approach applied to Tumor Growth through Chemotherapy

In order to obtain a control-oriented model, to compute the law control of the MPC, and to integrate the SQP method, the non-linear mathematical model presented in Section II has been discretized using the Backward Euler method with a sample time of one hour. This non-linear system can be expressed as:

$$x[k+1] = f(x[k], u[k], k), \quad (10a)$$

$$y[k+1] = g(x[k], u[k], k) + \tilde{y}[k], \quad (10b)$$

where f and g are non-linear functions, $u[k]$ represents the manipulated variable, in this case, the daily dose of TM (in µg), and the uncertainties of the system are described by $\tilde{y}[k]$. The set of state variables in this non-linear model is $x[k]$, while $y[k]$ denotes the outputs of the system, which are expressed, respectively, as:

$$x = [X_g\ X_s\ X_m\ C\ X_0\ X_1\ X_2\ X_3]^T,$$
$$y = [N\ C\ X_2\ X_3]^T.$$

The control action $u[k]$ is calculated daily with the use of a linear CC-MPC; this implies that the non-linear system presented in Equation (10) needs to be linearized and can be written as:

$$x[k+1] = A_k x[k] + B_k u[k], \quad (11a)$$

$$y[k] = C_k x[k] + \tilde{y}[k]. \quad (11b)$$

Matrices A_k, B_k, and C_k are obtained through linearization for each operating point (op = $[x_k, u_k, k]$) at which the MPC controller is invoked [28]:

$$A_k = \left.\frac{\partial f}{\partial x}\right|_{\text{op}},\ B_k = \left.\frac{\partial f}{\partial u}\right|_{\text{op}},\ C_k = \left.\frac{\partial g}{\partial x}\right|_{\text{op}} \tag{12}$$

subject to

$$0 \leq u_c[k] \leq 800\,\mu\text{g}. \tag{13}$$

Furthermore, the output variables have to fulfill the following constraints, which reflect the biological requirements and limitations of the chemotherapy administration design [26], [29]:

$$X_2[k] \geq 0\ \mu\text{g/mL}, \tag{14a}$$
$$X_3[k] \geq 0\ \mu\text{g/mL}, \tag{14b}$$
$$N[k] \geq 0\ \text{mm}^3, \tag{14c}$$
$$C[k] \geq 4 \times 10^6. \tag{14d}$$

The main goal of this work is to implement an automatic controller that achieves the largest tumor reduction compliant with the system's safety constraints. In that sense, the cost function for the optimization problem can be defined as:

$$\begin{aligned} J(y[k],\, u[k]) =& (y_{\text{ref}} - y[k])^T R_y (y_{\text{ref}} - y[k]) + \\ & u[k]^T Q_u u[k], \end{aligned} \tag{15}$$

where y_{ref} is the reference array for the output variables, R_y is the weight matrix for each output's error signal, and Q_u is the weight factor for the input variable. All of these values were adjusted by trial and error.

A. SQP-MPC formulation

Integrating SQP into MPC represents a considerable advance in managing complex and non-linear optimization challenges. As stated above, MPC operates on a strategy that utilizes an internal model for predicting a system's future behavior. However, non-linear dynamics in many systems complicate this process, necessitating a more sophisticated approach. This way, SQP breaks the more significant problem into smaller and more manageable segments. All in all, establishing a sequence of quadratic approximations, each designed to move closer to the most favorable outcome, ensuring a systematic approach to problem-solving [30].

To implement this control scheme, it is necessary to calculate, employing Equation (12), a linear model around the current state vector (x_k), resulting in a linear time-varying model [31]. Thus, this approach allows for incorporating linear formulations of an MPC controller in non-linear dynamical systems.

Once matrices A_k, B_k, and C_k are known for the prediction horizon, the optimization problem to be solved by the SQP-MPC controller at each k can be formulated as:

$$\min_{u[k:k+N_{\text{p}}-1]} \sum_{l=k}^{k+N_{\text{p}}-1} J\left(y[l], u[l]\right), \tag{16}$$

subject to (11)-(14), $\forall l \in [k, k+N_{\text{p}}-1]$, where N_{p} is the prediction horizon, in this case 7 days. The SQP-MPC strategy applied is described in Algorithm 1.

Algorithm 1 SQP-MPC scheme.

1) Use Equation (12) at time k along with the current state vector x_k and control variable u_k to calculate the Jacobian matrices of the linear model.
2) Solve the optimization problem defined in Equation (16).
3) Apply the first element of the sequence $u[k : k+N_{\text{p}}-1]$.
4) Repeat the process for $k+1$.

B. Chance-Constraint formulation

One key issue to consider is the stochastic nature of the system at hand. The closed-loop control of tumoral growth is affected by the error associated with the measuring process of the system's output variables. Thus, output variables y_j have been modeled as normal independently and identically distributed stochastic process, $\bar{y}_j \sim \mathcal{N}(0, \sigma_j^2)$ with $j \in \{1, 2, 3, 4\}$ and a standard deviation of σ_j.

The use of the CC-MPC deals with the stochastic nature of the system. This proposed control strategy assumes a certain risk of violating the constraints affected by uncertainty described by the following inequality:

$$\mathbb{P}\left[y_j[k] \geq y_{j,\min}\right] \geq 1 - \delta_y,$$

Here, $\mathbb{P}[\cdot]$ is the probability operator, $y_{j,\min}$ is the minimum acceptable value of output y_j, and δ_y represents the risk violation of the constraints. In this study, δ_y has been set to 0.1, which allows for constraint violations up to 10% of the time. This value is a compromise between tumor reduction speed and safety, achieved through trial and error. Moreover, this probabilistic constraint can be transformed into its deterministic equivalent according to this process [32]:

$$\begin{aligned} &\mathbb{P}\left[y_j[k] \geq y_{\min_j}\right] \geq 1 - \delta_y \Leftrightarrow \\ &\mathbb{P}\left[C_{(j)}\, x[k] + \tilde{y}_j[k] \geq y_{\min_j}\right] \geq 1 - \delta_y \Leftrightarrow \\ &\mathbb{P}\left[\tilde{y}_j[k] \geq y_{\min_j} - C_{k(j)}\, x[k]\right] \geq 1 - \delta_y \Leftrightarrow \\ &\mathbb{P}\left[\tilde{y}_j[k] < y_{\min_j} - C_{k(j)}\, x[k]\right] < \delta_y \Leftrightarrow \\ &\phi_j\left(y_{\min_j} - C_{k(j)}\, x[k]\right) < \delta_y \Leftrightarrow \\ &y_{\min_j} - C_{k(j)}\, x[k] < \phi_j^{-1}\left(\delta_y\right) \Leftrightarrow \\ &C_{k(j)}\, x[k] \geq y_{\min_j} + \phi_j^{-1}\left(1 - \delta_y\right). \end{aligned} \tag{17}$$

Here, $C_{k(j)}$ represents row j of the matrix C_k, which corresponds to each output y_j. Additionally, ϕ_j is the cumulative distribution function of the uncertainty impacting each output. Equation (17) can then be applied to each time

TABLE I: Comparison among the different controllers employing KPIs.

Controller	KPI_1 mm^3	KPI_2 mg	KPI_3
Open-Loop	$\mathbf{115.13}$ $(\mathbf{9.68})$	255.50 (0)	$3.59 \cdot 10^6$ $(5 \cdot 10^4)$
MPC	148.66 (10.33)	231.36 (1.07)	$4.11 \cdot 10^6$ $(6 \cdot 10^4)$
SQP-MPC	164.78 (11.17)	219.51 (0.64)	$4.23 \cdot 10^6$ $(6 \cdot 10^4)$
SQP CC-MPC	175.34 (8.65)	$\mathbf{215.63}$ $(\mathbf{0.56})$	$\mathbf{4.26 \cdot 10^6}$ $(\mathbf{5 \cdot 10^4})$
Controller	KPI_4 mm^3/mg	KPI_5 h^{-1}	KPI_6
Open-Loop	3.463 (0.038)	$3.67 \cdot 10^5$ $(1 \cdot 10^5)$	70.42 (0.11)
MPC	3.680 (0.044)	$1.38 \cdot 10^5$ $(8.8 \cdot 10^4)$	52.48 (2.78)
SQP-MPC	3.805 (0.055)	$1.08 \cdot 10^5$ $(7.4 \cdot 10^4)$	34.14 (1.30)
SQP CC-MPC	$\mathbf{3.824}$ $(\mathbf{0.040})$	$\mathbf{5.21 \cdot 10^4}$ $(\mathbf{4.47 \cdot 10^4})$	$\mathbf{9.23}$ $(\mathbf{0.46})$

instant along the prediction horizon $i \in [0,\ N_p - 1]$ and be rewritten as:

$$C_{(j)}\, x[k+i] \geq y_{\min_j} + \phi_{j,i}^{-1}\,(1 - \delta_y)\,. \tag{18}$$

Finally, the optimization problem can be redefined using the operator $\mathbb{E}[\cdot]$, which is the expected value of the cost function described in Equation (15):

$$\min_{u[k:k+N_\mathrm{p}-1]} \sum_{l=k}^{k+N_\mathrm{p}-1} \mathbb{E}\left[J\left(y[l], u[l]\right)\right], \tag{19}$$

subject to (11), (13)-(14), (18), and $\forall l \in [k, k+N_\mathrm{p}-1]$. During the one-year treatment, this process is carried out daily for each linearization step.

IV. Results and discussion

This section presents the results obtained for the control strategy shown above. Four different scenarios were evaluated: (i) aggressive open-loop treatment (consisting of a daily administration of 700 µg of TM), (ii) an MPC controller based on the linearized state-space model at the initial operating point of the system ($X_g = 900$ mm^3, $X_s = 50$ mm^3, $X_m = 50$ mm^3, $C = 10^7$, $X_0 = 0$ µg, $X_1 = 0$ µg, $X_2 = 0$ µg, $X_3 = 0$ μg), (iii) an SQP-MPC, and (iv) the SQP CC-MPC.

Furthermore, 300 one-year simulations have been performed for the different approaches. To carry out these control strategies, the standard deviation values for each output variable are $\sigma_1 = 20$ mm^3, $\sigma_2 = 10^5$, $\sigma_3 = 0.001$ µg/mL, and $\sigma_4 = 0.001$ µg/mL, which are based on [26]. Moreover, the values of the reference vector are $y_\mathrm{ref} = [0$ mm^3, 10^7, 0 µg/mL, 0 µg/mL$]$.

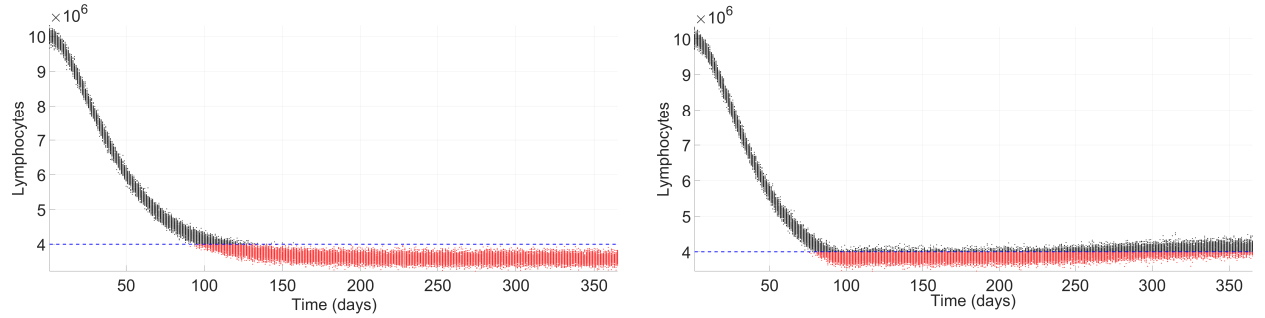
Furthermore, the weight matrix R_y has the following values for each output variable: $2.9 \cdot 10^{17}$, 0.001, 10^{-5}, and 10^{-5}, respectively. The matrix Q_u has a factor of 10^{-5}. Several Key Performance Indicators (KPI) have been defined to characterize each case's behavior:

- KPI$_1$: Final tumor size.
- KPI$_2$: Total use of TM.
- KPI$_3$: Final quantity of lymphocytes.
- KPI$_4$: Volume of $N(t)$ eliminated per mg of TM.
- KPI$_5$: Number of lymphocyte constraint violations for every case in which these occur.
- KPI$_6$: Percentage of hours in constraint violation. This metric tracks constraint violations regardless of severity; i.e., one lymphocyte below constraint is equivalent to one million in this case.

Table I shows the values of each KPI for each case as well as their standard deviation in parentheses. The best behavior for each KPI is bolded. For instance, the results obtained for KPI_1 demonstrate that the SQP CC-MPC approach is more conservative than the other control strategies (it presents the highest value of the final tumor size). However, the SQP CC-MPC obtains the best results for every other KPI. Moreover, KPI_3, KPI_5, and KPI_6 demonstrate how this approach offers the safest treatment regarding side effects. For instance, KPI_3 shows how the SQP CC-MPC has, on average, the highest final value of lymphocytes, while KPI_5 indicates that this last algorithm achieves the lowest mean magnitude of constraint violation. Furthermore, as evidenced by KPI_6, this controller can keep the percentage of violation below 10%, as intended by the value set for δ_y. Additionally, as seen by KPI_2 and KPI_4, the implementation of the SQP CC-MPC results in lower TM consumption and higher drug administration efficiency, respectively. Therefore, the SQP CC-MPC controller facilitates efficient drug administration to the mouse and significantly reduces the amount of drug needed for comparable tumor volume reduction.

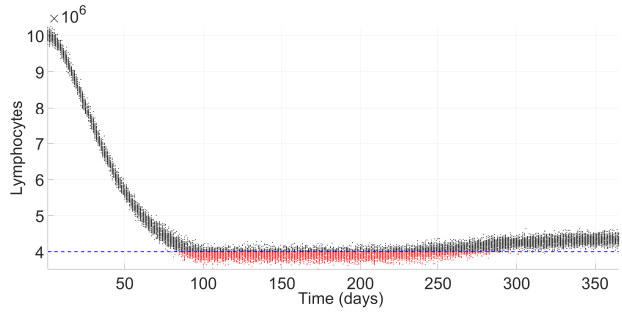
To illustrate an example of the constraint violation, Figure 1 represents the evolution of the lymphocytes, $C(t)$, for all simulations. It can be appreciated how, in the case of the open-loop system, the number of lymphocytes falls below the safety threshold (Figure 1a). As evidenced by KPI_6 in Table I, Figure 1d shows how the SQP CC-MPC controller achieves fewer constraint violations, rendering a much safer treatment for the patient.

After analyzing different approaches, it is clear that open-loop oncologic treatment is highly aggressive and can result in uncontrollable side effects. However, MPCs can help improve the results, even if they achieve slightly lower tumorous cell elimination. It is important to note that the deterministic SQP-MPC cannot fully account for the stochastic nature of the system. Since mathematical modeling and

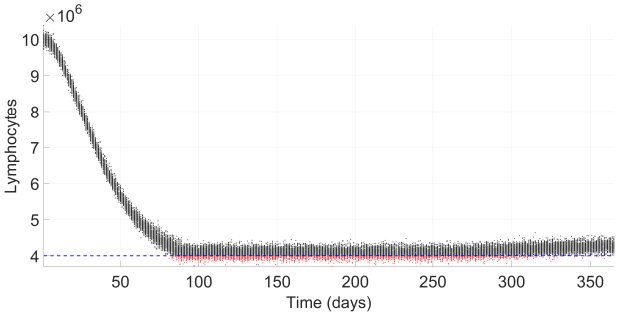


(a) Open-Loop constraints

(b) MPC constraints



(c) SQP-MPC constraints



(d) SQP CC-MPC constraints

Fig. 1: Constraint compliance map.

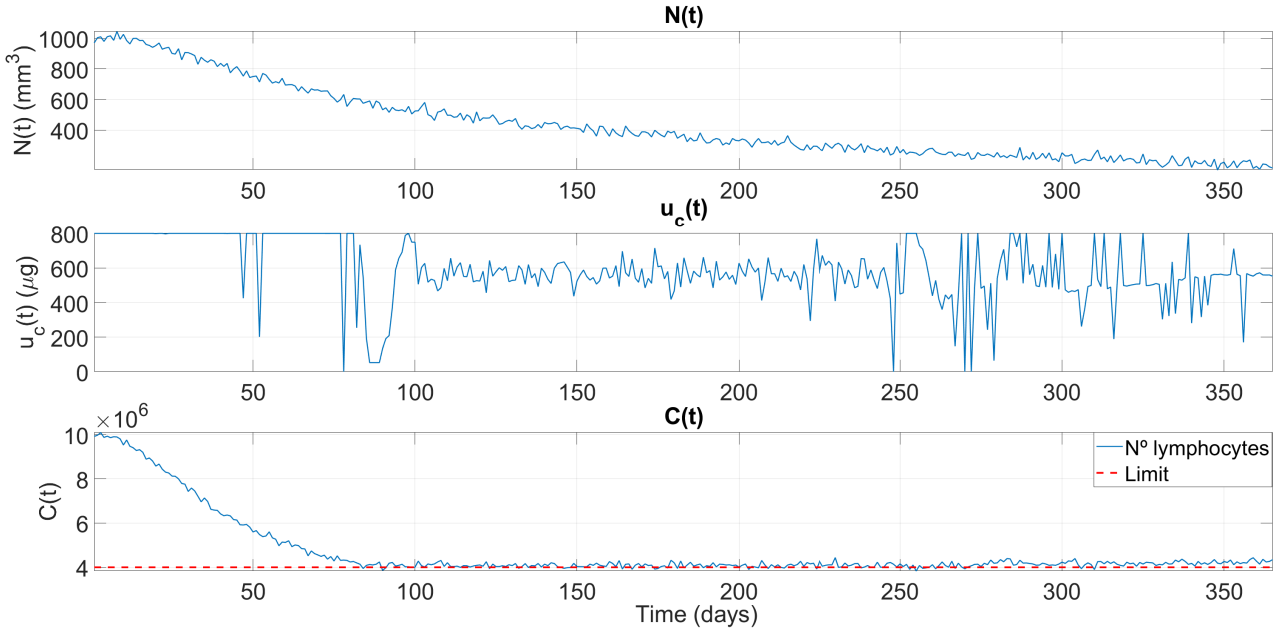


Fig. 2: Evolution of the treatment (SQP CC-MPC).

control of biological systems are affected by uncertainty, it is crucial to consider this uncertainty while attempting to control it.

Finally, Figure 2 portrays the evolution of one of the 300 SQP CC-MPC-controlled one-year chemotherapeutic treatments. The first subplot illustrates the change in tumor size, $N(t)$, during the one-year treatment. As seen in the figure, approximately 80% of the tumor during the TM cycle, represented by $u_c(t)$, is eliminated. It is also worth pointing out that the controller uses an already-established strategy of administering a loading dose of TM during the first 70 days of treatment. This drug administration scheme could significantly improve the chemotherapeutic cycle's prognosis and reduce its associated risks. This is portrayed in the last subplot, which represents the evolution of the lymphocytes, $C(t)$.

V. Conclusions and Future Work

Implementing Stochastic SQP-MPC controllers represents a crucial step forward in achieving a significant reduction

in tumor volume, while also maintaining strict adherence to essential safety standards throughout treatment. This control algorithm improves the effectiveness of therapeutic protocols and may limit severe side effects that often accompany chemotherapy.

The results presented in this work point to the conclusion that the SQP CC-MPC can limit the degradation of the patient's immune system while achieving an impressive reduction in tumor size and a significant decrease in the administered drug. This approach can lower the economic costs associated with oncologic treatment, freeing up resources and increasing treatment availability to patients.

All in all, employing SQP-MPC jointly with chance constraints allows a more appropriate investigation of the stochastic aspects of biological systems, leading to more reliable, safe, and practical strategies in drug dosing related to cancer therapy. It is important to note that these strategies can lead to more adaptive treatments, offering a robust drug dosing scheme that adjusts to changes in the patient's condition.

Future works will be aimed at the sophisticated evolution of Stochastic SQP-MPC controllers within cancer therapy. A key goal is to expand the scope of mathematical models by considering essential aspects, such as genetic indicators, metabolic data, and immune system responses. These are expected to have a significant impact on the effectiveness of treatments. Moreover, there is an imperative for creating advanced algorithms with the capacity for real-time responsiveness to the nuances of patient reactions.

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