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Mathematical modeling and control for cancer treatment with cold atmospheric plasma jet

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Abstract

Cold atmospheric plasma (CAP) jet exhibits remarkable properties that trigger cell death in cancer cells. The effect of CAP on cancer cells is influenced by several factors including plasma jet discharge voltages, gas composition and cancer cell type. Consequently in clinics it becomes challenging to plan plasma cancer treatments for a particular cancer types. To address this, we present preliminary results for an *in vitro* model which includes an optimal feedback control scheme that can adjust treatment conditions based on the actual cancer cell response. Translation to an *in vivo* model will be the next objective of the presented project. First, a mathematical model is presented for the dynamic response of cancer cells to CAP jets based on experimental data that provide temporal measurements of cancer cell viability after CAP treatments. A differential equation is developed to model the influence of CAP on the viability of two cancer cell lines, U-87 MG and MDA-MB-231, under varying treatment duration and plasma discharge voltages. Subsequently, a control scheme is presented to determine CAP treatment conditions in an optimal fashion by reducing cancer cell viability less than a prescribed goal while minimizing a weighted sum of the treatment duration and the discharge voltage. This is further extended to a model predictive control framework such that a pre-planned CAP treatment schedule is revised according to the actual cancer cell response. The efficacy of the proposed approach is illustrated by numerical simulations based on experimental data.

Keywords: adaptive plasma, cold atmospheric plasma, model predictive control

(Some figures may appear in colour only in the online journal)

1. Introduction

Cold atmospheric plasma (CAP) jet is formed by ionization of a noble gas (such as helium and argon) when the gas jet flows through a high electric field. As its temperature remains close to the room temperature, it is also referred to as non-thermal plasma jet or non-equilibrium plasma jet [1, 2]. For the mechanism of the CAP jet, the streamer propagates by ionizing neutral particles at the front and it leaves a plasma column behind [3–5]. This process is also called ionization wave. At the wave front region, the ion cloud called streamer head, with a positive potential for cathode directed streamer discharge, roughly equals the discharge voltage near the nozzle and gradually decreases along the jet [6, 7]. The photons emitted from the ionization region make the wave front area visible, and it is usually named as plasma bullet for its bullet shape [6, 8]. It accelerates electrons into nearby atoms and molecules leading to a cascade effect of ionization, excitation, and dissociation processes, ultimately creating a unique environment of positive and negative charges, UV radiation, reactive species, and neutral molecules [8–10].

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CAP jet has attracted a lot of attention in the past decade due to its potential application in cancer therapy. CAP has been reported to trigger cell death in cancer cells while leaving normal cells unharmed. Several researchers have linked its therapeutic effect with some of the species generated by it including: the reactive oxygen and nitrogen species (RONS), including atomic nitrogen and oxygen, hydroxyl (OH), singlet delta oxygen, superoxide and nitric oxide (NO) [11–17]. For instance, Kim *et al* used a micro plasma cancer endoscope for lung carcinoma treatment [18]. The result showed that the CAP jet was capable of inducing apoptosis in both cultured mouse lung carcinoma and fibroblast cells. Ahn *et al* investigated the effect of CAP jet in cancer cell death by utilizing air and nitrogen from a micro nozzle array [19]. Dezest *et al* reported apoptotic cell death in human cervical cancer HeLa cells, simultaneously with depolarization of mitochondrial membrane potential [20]. Wang *et al* investigated a CAP-based therapy *in vitro* for bone metastatic breast cancer treatment and it showed that breast cancer cells are more sensitive to CAP treatment than mesenchymal stem cells (MSCs). CAP jet was reported to selectively ablate metastatic breast cancer cells without damaging healthy MSCs at the metastatic bone site [21].

Despite success in various *in vitro* and *in vivo* experiments, there are several challenges that need to be addressed with CAP treatment [22]. First, the therapeutically effect of the CAP jet is susceptible to the variability of plasma parameters such as discharge voltage, flow rate and frequency and exogenous disturbances such as temperature, target properties, and gas composition of surrounding environment [23–27]. Second, different types of cancers exhibit different responses when exposed to the same CAP treatment conditions. Change in (1) cancer type, (2) properties of the cell culture medium when in contact with the CAP jet and (3) the duration of CAP exposure, can drastically influence the characteristics of plasma and its effect on the cancer cell viability [28]. Consequently the well-known linear dynamic systems theory for time-invariant systems is not sufficient for describing the plasma effect on cancer cells. The theory indicates that the time-integral property of plasma exposure makes the treating effect irreversible once the CAP jet is applied to cancer cells [29]. In cancer the underlying biological mechanisms of novel therapy approaches have not been fully understood and guidelines on how to schedule these therapies still need to be established. Additionally, due to the complexity of clinical trials the scheduling of treatments is often guided by exhaustive and expensive trial-and-error approaches. The problems above prompt researchers in plasma medicine to investigate adaptive and traceable treatment control schemes. The idea of adaptive plasmas for medical application was proposed recently in [30, 31].

Graves *et al* presented control schemes for a device that generates atmospheric pressure plasma jet (APPJ) for plasma medicine. Their approach was to control the temperature of the target [32, 33]. A model predictive control (MPC) strategy was proposed for real-time feedback control of a radio-frequency APPJs in argon. Challenges for reproducible and therapeutically effective application were pointed out and included: nonlinear nature of system dynamics, constraining operating region and cumulative dose metrics to control the temperature. A lumped-parameter, the physics-based model was developed for describing the jet dynamics. The closed-loop performance of the MPC strategy was compared to that of a basic proportional-integral control system. It was indicated that the MPC strategy provided a versatile framework for dose delivery in the presence of disturbances. Additionally, Graves *et al* conducted the feedback control of a kHz-excited APPJs in helium using a PI control scheme and an MPC scheme. The real time result revealed that feedback control is crucial for effective operation in the presence of step disturbances. The MPC scheme can more effectively regulate the multivariate dynamics of the APPJ for effective setpoint tracking and constraint handling in the face of disturbances. However, the objective of these work was to maintain treatment conditions of a device producing CAP jet, such as substrate temperature, plasma current and power at a certain desired level, and the actual cellular and/or living tissue response constant.

In this paper, we present a feedback control scheme for CAP cancer therapy where the cancer cell response is monitored and plasma operational parameters are adjusted accordingly. The CAP treatment can be adjusted in real-time such that the plasma therapy is tailored to the particular type of cancer cell undergoing treatment. We develop a mathematical model that represents the temporal variation of cell viability under varying CAP exposure time and plasma discharge voltages obtained in [34]. This is used to predict cancer cell response to CAP under a nominal condition. Subsequently, an optimal control problem is formulated to regulate the minimum parameters which include treatment duration and voltage, while constraining cancer cell viability under a prescribed acceptable range Finally, it is extended to a MPC such that CAP cancer treatment is scheduled for multiple sessions and each session is optimized according to the response of the prior session. The presented modeling and control framework are further discussed for their potential application in the development of an adaptive CAP platform. In short, the main contribution of this paper is in utilizing dynamic system modeling and optimal feedback control in CAP cancer therapy for constructing an independent cancer therapy that can be adjusted adaptively to a specific cancer cell type.

2. Modeling for CAP treatments

A mathematical model is developed to represent the dynamic response of cancer cells under CAP treatment, based on the data from the *in vitro* experiments presented in [34]. The model predicts the temporal response of cancer cell viability for varying treatment conditions in CAP exposure time and discharge voltage. The proposed dynamic model will be used for the development of optimal feedback controls in the subsequent sections.

2.1. Experimental data

The experimental data presented in [34] is utilized for the development of a mathematical model. Cell response to CAP

Table 1. Optimized modeling parameters for U-87 MG.

Δt (s)	U (kV)	p_0	c_1	c_2	c_3	c_4
0	N/A	1.0000	68.8271	−6.8402	0.9985	1.2934
30	3.16	0.3015	15.2595	0.1902	0.9955	1.1302
60	3.16	0.2109	14.9141	0.9523	0.9898	1.1116
90	3.16	0.1972	8.3086	1.7457	0.9373	0.7472
180	3.16	0.3344	9.1859	2.9777	0.9008	0.7701
60	3.71	0.1546	6.1859	0.9777	0.9537	0.7701
90	3.71	0.1277	4.8930	0.7820	0.9430	0.5860

treatment is monitored in two types of cancer cell lines, U-87 MG and MDA-MB-231. In the *in vitro* experiments conducted in [34], CAP-induced cell death was investigated by the RealTime-Glo MT Cell Viability Luminesce Assay from Promega with a continuous read method for up to 48 h after CAP exposure. The assay measures cell metabolic activity which served as a proxy for cell viability and was indicated by the intensity of the luminescent signal which was proportional to the number of live cells. Duration of CAP exposure varying from 0 to 180 s and plasma discharge voltages of 3.16 kV and 3.71 kV were investigated in the study to identify the correlation between cell viability, CAP exposure time and discharge voltage.

2.2. Exponential growth model

A phenomenological model for the growth of cell population can be written in the following form [35],

$$\dot{p} = pF(t,p). \tag{1}$$

In general, $p \in \Re$ denotes the population of cancer cell measured in terms of the number viable cells. To have the consistent value of p for several experiments presented in [34], we normalize the cancer cell viability under CAP treatments with the initial cancer cell viability just before the CAP exposure. Therefore the initial value always is $p(0) = 1$ and the variable p is unit-less. This variable p is simply referred to as *cancer cell viability*. Next, $F : \Re \to \Re$ models its net exponential proliferation rate, which is the difference between the rate of proliferation and death. It is difficult to infer the proliferation rate and death rate separately from experimental data, and thus often the net proliferation rate is used.

Here we present an expression of the net proliferation rate corresponding to the above experimental data presented in [34]. There are common patterns in the viability of cancer cells under CAP treatment as reported in [34]:

- immediately after CAP treatment, an instantaneous reduction of cell viability is observed (more than 50%);
- from 0 min to 6 h, the cell viability increases rapidly;
- from 6 h to 24 h, the cell viability decreases when the treatment duration is sufficiently large;
- from 24 h to 48 h, the cell viability approaches its steady state value
- for the effect of treating duration and voltage, the cell numbers decrease with the increase of the treating duration and voltage.

Based on these common features, we formulate an expression for the net proliferation rate. The experimental data is normalized such that the initial cell viability before CAP treatment is one, i.e. $p(0) = 1$. To represent the instantaneous reduction of the cell viability, the cell viability immediately after the treatment is given by $p(0^+) = p_0$ for $p_0 \in \Re$. Afterwards, the cell viability evolves according to (1), where the net proliferation rate is chosen as

$$F(t,p) = (c_1 - c_2 t)\exp(-c_3^{-t} p^{c_4}) - c_5, \tag{2}$$

where $c_1, c_2, c_3, c_4, c_5 \in \Re$ are parameters determined by the CAP treatment duration and the plasma discharge voltage. The above expression is applied to both types of cancer cells, namely U-87 MG and MDA-MB-231, but c_5 is set to zero for U-87 MG.

2.3. System identification

Next, we identify the values of the free parameters in (2) and (3), according to optimal system identification [36]. The discrepancy between the mathematical model and experimental data is described by the following objective function,

$$J(c) = \sum_{i=1}^{n} \int_0^{48} \|p_{exp_i}(t) - p(t;c)\|^2 dt, \tag{3}$$

where $p_{exp_i}(t)$ denotes the cell viability at t for the ith experimental data, and $p(t;c)$ corresponds to the value obtained by the mathematical model (1) with a given parameter $c = (c_1, c_2, c_3, c_4, c_5) \in \Re^5$.

The system identification problem is formulated to find the optimal value of the parameters minimizing the above cost function as follows.

$$c_{opt} = \arg\min\{J(c)\}. \tag{4}$$

This is solved by the nonlinear programming solver, namely `fmincon` in MATLAB for each discharge voltage of $U = 3.16$ kV and 3.71 kV. For $U = 3.16$ kV, the experimental data are available in [34] for five cases of treatment duration, namely 0, 30, 60, 90, 180 s. There are two cases of 60, 90 s available for the higher plasma discharge voltage $U = 3.71$ kV. An additional bound on the parameters are specified for numerical stability, and the termination tolerance on the function value is set to 10^{-6}. Tables 1 and 2 summarize the optimized parameters for U-87 MG and MDA-MB-231, respectively.

Table 2. Optimized modeling parameters for MDA-MB-231.

Δt (s)	U (kV)	p_0	c_1	c_2	c_3	c_4	c_5
0	N/A	1.0000	9.9801	0.0987	1.0074	0.8482	0.4394
30	3.16	0.2730	9.9655	0.1611	0.9980	1.0162	0.1300
60	3.16	0.2872	6.3320	0.1633	0.9820	1.1613	0.0176
90	3.16	0.1795	8.1645	3.4716	0.8083	0.7222	0.0057
180	3.16	0.2203	7.2578	3.2766	0.7982	0.7638	0.0049
60	3.71	0.1735	6.2233	0.9562	0.9351	1.0194	0.0253
90	3.71	0.1561	6.5352	3.3511	0.7851	1.8486	0.0179

Figures 1 and 2 illustrate the cell viability for four groups of experimental data and the identified mathematical model for U-87 MG and MDA-MB-231 when the plasma discharge voltage $U = 3.16$ kV. It is shown that the proposed mathematical model captures the dynamic characteristics of the experimental data successfully.

Figure 3 summarizes the results of the mathematical model for both U-87 MG and MDA-MB-231 for varying treatment duration when $U = 3.16$ kV. For U-87 MG, for the control group with no treatment and the CAP treatment duration of $\Delta t = 30$ s, the normalized cell viability increases monotonically, but the growth rate is smaller for $\Delta t = 30$ s. For $\Delta t = 90$ s and $\Delta t = 180$ s, the cell viability decreases after 6 h, and then converges to a steady-state value from 24 h to 48 h. The responses for MDA-MB-231 exhibits similar characteristics, but the peak of the viability appears sooner at around 3–6 h. For both cases, the normalized cell viability at 48 h decreases as the CAP treatment duration increases. Next, figure 4 illustrates the cell viability from the mathematical model when $U = 3.71$ kV.

2.4. Generalization

While the mathematical model in the preceding section is constructed for a selected set of CAP treatment duration and plasma discharge voltages provided in [34], it can be used to predict the dynamic response of cancer cells for arbitrary values of treatment conditions. This is based on the assumption that the parameters of the mathematical model vary piece-wise linearly with respect to the treatment conditions. More explicitly, the values of parameters in tables 1 or 2 can be interpolated with respect to Δt and U.

Figure 5 illustrates the resulting cell viability when the CAP treatment duration is varied from 0 s to 180 s continuously when $U = 3.16$ kV. It is shown that the proposed mathematical model can predict the cellular response under CAP treatment reasonably for arbitrary treatment duration. The irregularity around $\Delta t = 140$ for MDA-MB-231 can be resolved if more experimental data sets are available. Also, varying the treating duration while keeping the actual time fixed, it is obvious to find that cell viability decreases with increased CAP treatment duration.

Next, the variation of cell viability with respect to the plasma discharge voltage is explored. Figure 6 illustrates the cell viability for four plasma discharge voltages. For both of U-87 MG and MDA-MB-231, generalization with respect to the plasma discharge voltage is reasonable as the cell viability gradually decreases as the discharge voltage increases. However, this model will be valid when the treatment duration is between 60 and 90 s where the experimental data for the higher discharge voltage of $U = 3.71$ kV are available, and generalization beyond this range is unreliable.

In short, the presented mathematical model characterizes the dynamic response of two types of cancer cells, namely U-87 MG and MDA-MB-231 under CAP treatment. This is valid for the treatment duration up to 180 s when the plasma discharge voltage is $U = 3.16$ kV, and it is further generalized to the higher discharge voltage of $U = 3.71$ kV when the treatment duration is between 60 and 90 s.

3. Optimal cancer treatment

Optimal control aims to minimize a certain objective function formulated on a dynamical system subject to constraints. An optimal control problem is formulated by a mathematical description of a dynamic system and an objective function that measures the performance of the controlled system. The framework of optimal control is common in aerospace engineering, for example in minimal fuel orbital transfer of a satellite. As introduced in [35], the objective function is often selected such that its value becomes smaller as the control system behaves in a more desired way. Optimal control theory addresses the question of minimize this objective function to determine the optimal control input. Once the computed optimal control input is applied, the corresponding dynamic response is be monitored and its performance is evaluated by calculating the objective function. Naturally, the actual response is also influenced by external disturbances, and may be different from those calculated by the dynamic model. Adjusting the control input based on the actual response leads to the framework for optimal feedback control, which will be discussed later in this section.

The above dynamic model for the cancer cell response to CAP exposure shows that the treatment duration and the plasma discharge voltage are one of the dominant factors that determine the cancer viability. In this section, we aim to find the optimal value of those parameters to guarantee that the cancer cell viability after 48 h is suppressed within a prescribed desired level.

3.1. Problem formulation

The control parameters are the CAP treatment duration Δt, and the plasma discharge voltage U. In future, control

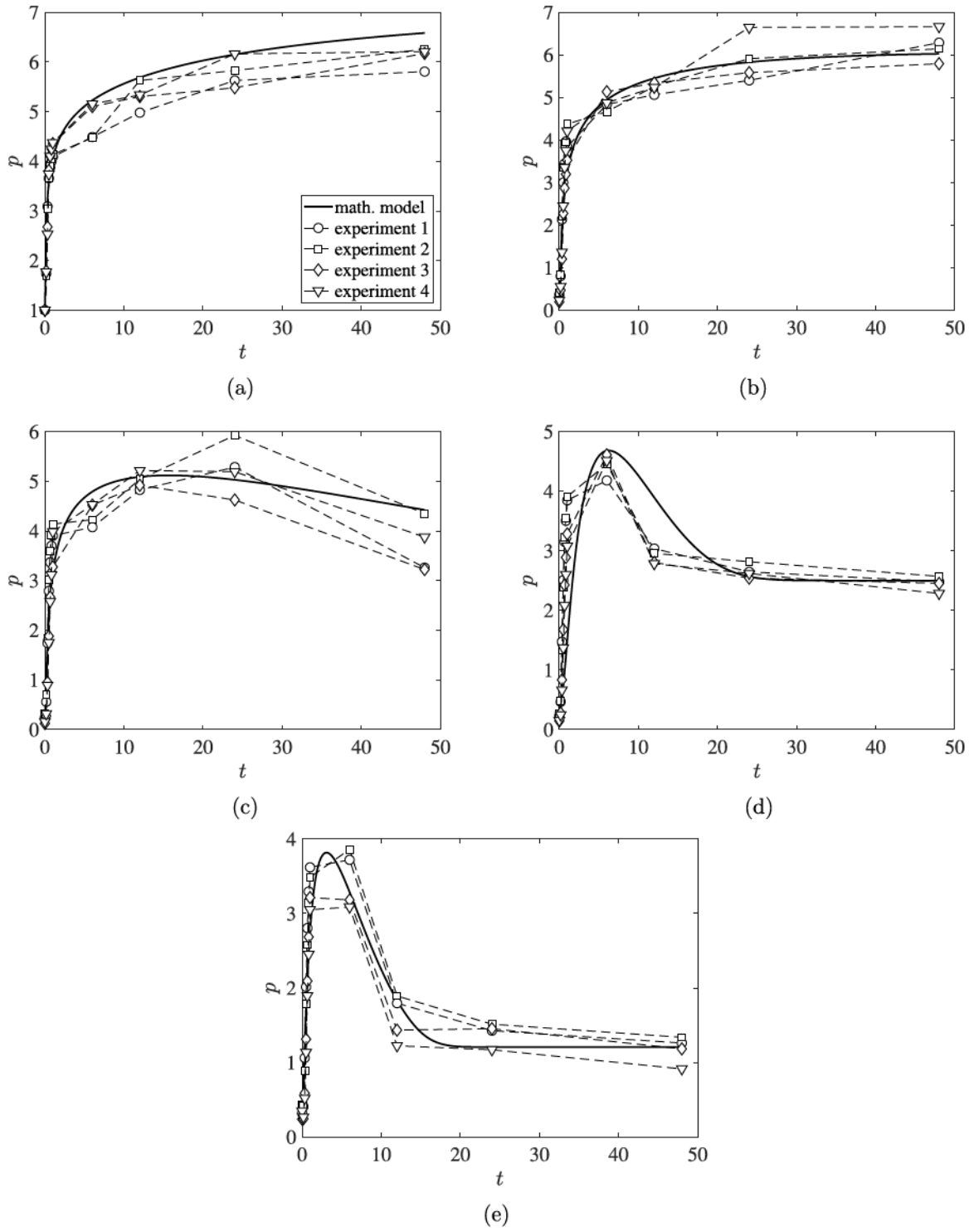

Figure 1. Dynamic response of cancer cell viability for U-87 MG with $U = 3.16$ kV (solid: mathematical model; dashed: experiments). (a) $\Delta t = 0$. (b) $\Delta t = 30$. (c) $\Delta t = 60$. (d) $\Delta t = 90$. (e) $\Delta t = 180$.

parameters will be extended to gas flow rate, composition and humidity. An optimal control problem is formulated to minimize a weighted sum of the CAP exposure and the discharge voltage, while ensuring that the cancer cell viability is reduced to the desired level. This is to maximize the therapeutic effect of CAP treatments for a prescribed level of cancer growth inhibition.

More specifically, the objective function is chosen as the weighted sum of those two,

$$J(\Delta t, U) = w_1(\Delta t)^2 + w_2 U^2, \tag{5}$$

where $w_1, w_2 \in \Re$ are positive weighting factors that determine the relative contribution of the CAP exposure duration and the discharge voltage to the objective function. An inequality

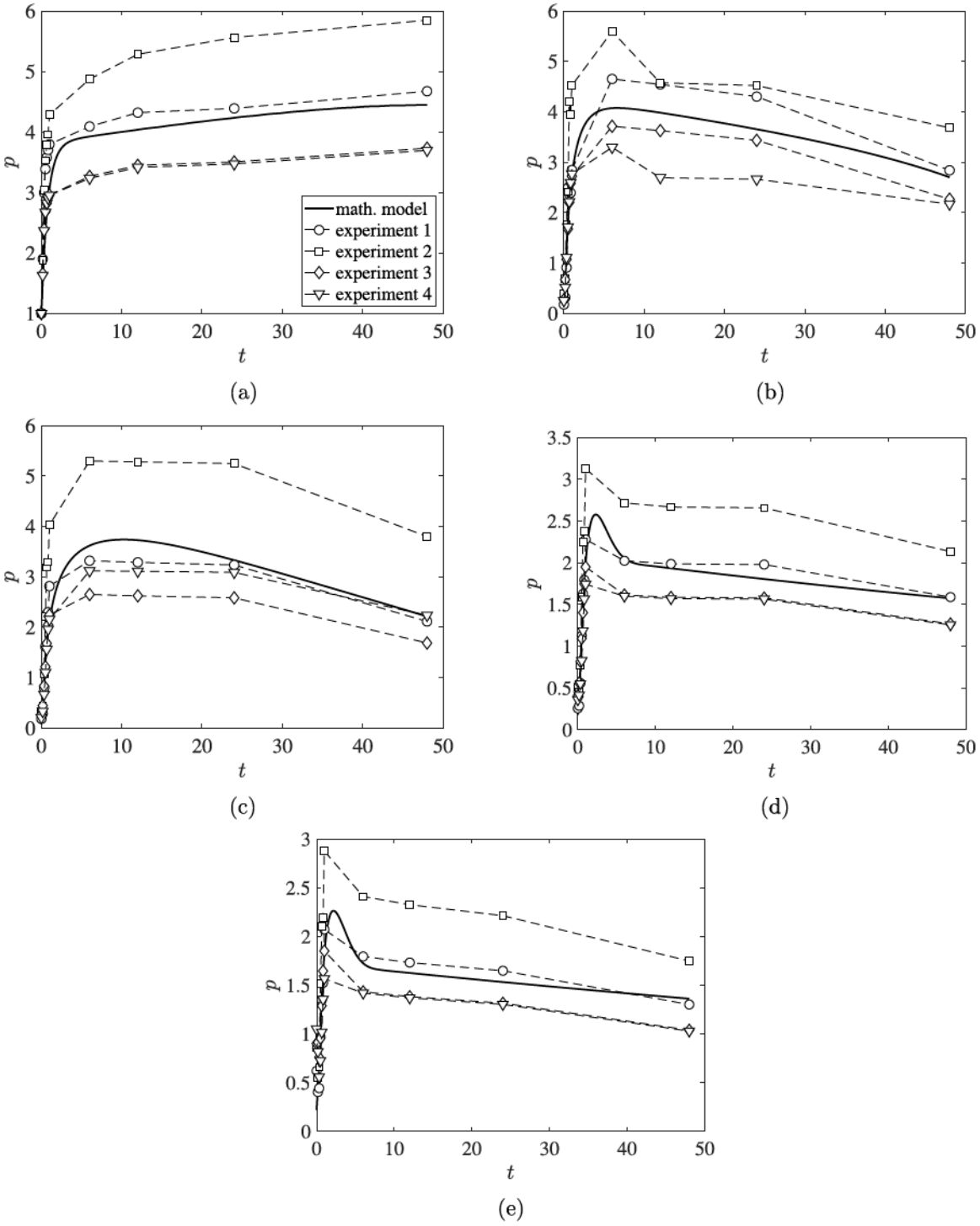

Figure 2. Dynamic response of cancer cell viability for MDA-MB-231 with $U = 3.16$ kV (solid: mathematical model; dashed: experiments). (a) $\Delta t = 0$. (b) $\Delta t = 30$. (c) $\Delta t = 60$. (d) $\Delta t = 90$. (e) $\Delta t = 180$.

constraint is also imposed to suppress the ratio of the terminal cancer cell viability to that of the untreated case as follows.

$$\frac{p(t = 48\text{ h}; \Delta t, U)}{p(t = 48\text{ h}; \Delta t = 0, U = 0)} \leqslant r_d, \tag{6}$$

where $r_d \in \Re$ is the desired ratio of the cancer cell viability less than one.

3.2. Optimal cancer treatment

Once the value of $(\Delta t, U)$ is given, the above objective function and the inequality constraint can be evaluated by integrating the dynamic model (1). As such, the presented optimization can be addressed by any numerical parameter optimization tool. We use the function, `fmincon` of MATLAB to solve it with

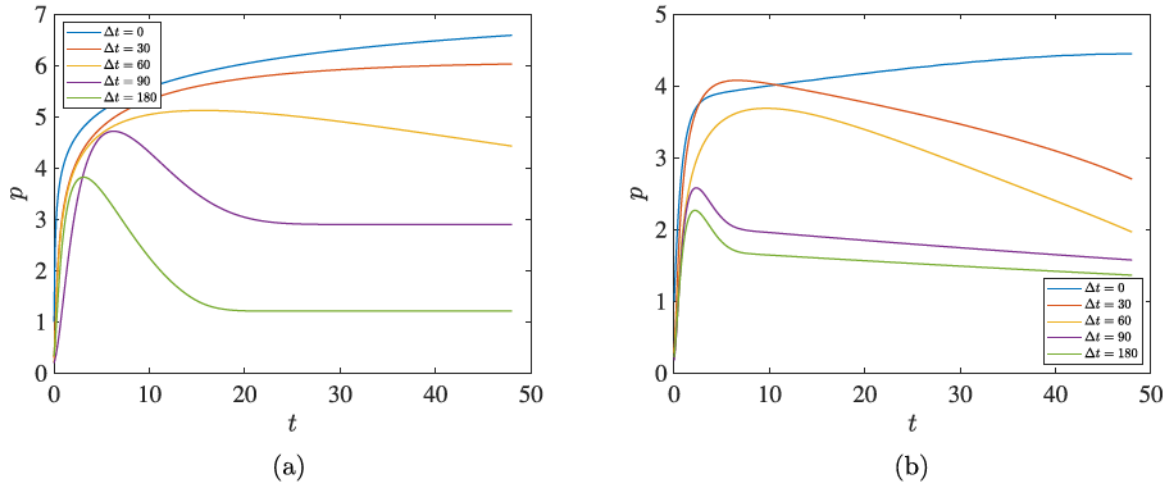

Figure 3. Summery of dynamic response from mathematical model for varying CAP treatment duration Δt when $U = 3.16$ kV. (a) U-87 MG. (b) MDA-MB-231.

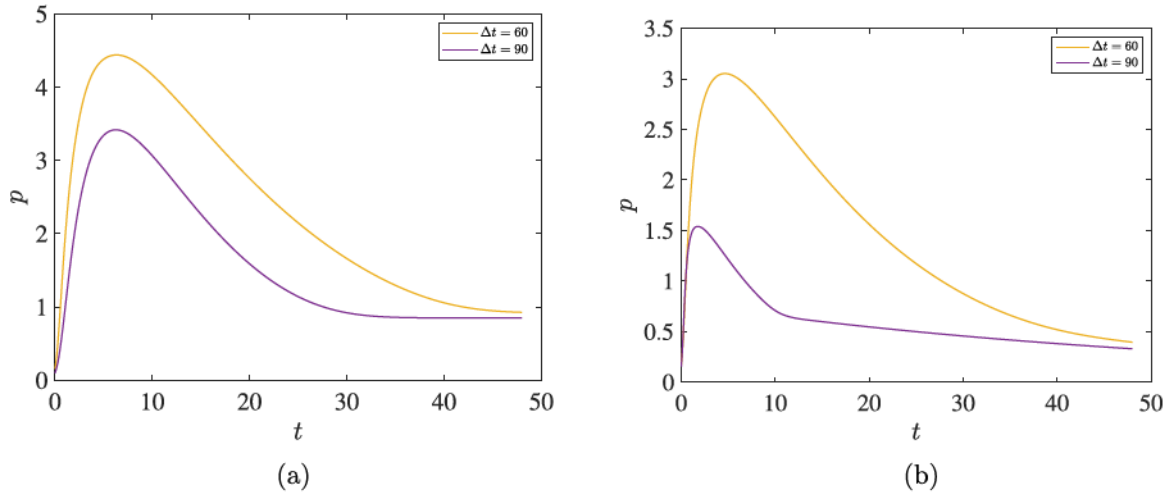

Figure 4. Summery of dynamic response from mathematical model for varying CAP treatment duration Δt, when $U = 3.71$ kV. (a) U-87 MG. (b) MDA-MB-231.

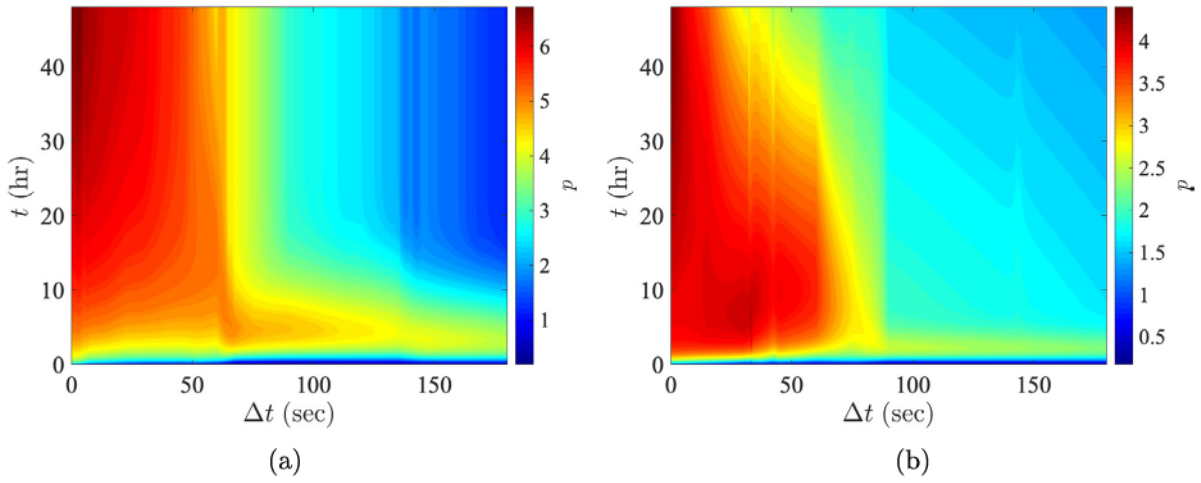

Figure 5. Dynamic response of cell viability from generalized mathematical model for arbitrarily varying CAP treatment duration Δt, when $U = 3.16$ kV. (a) U-87 MG. (b) MDA-MB-231.

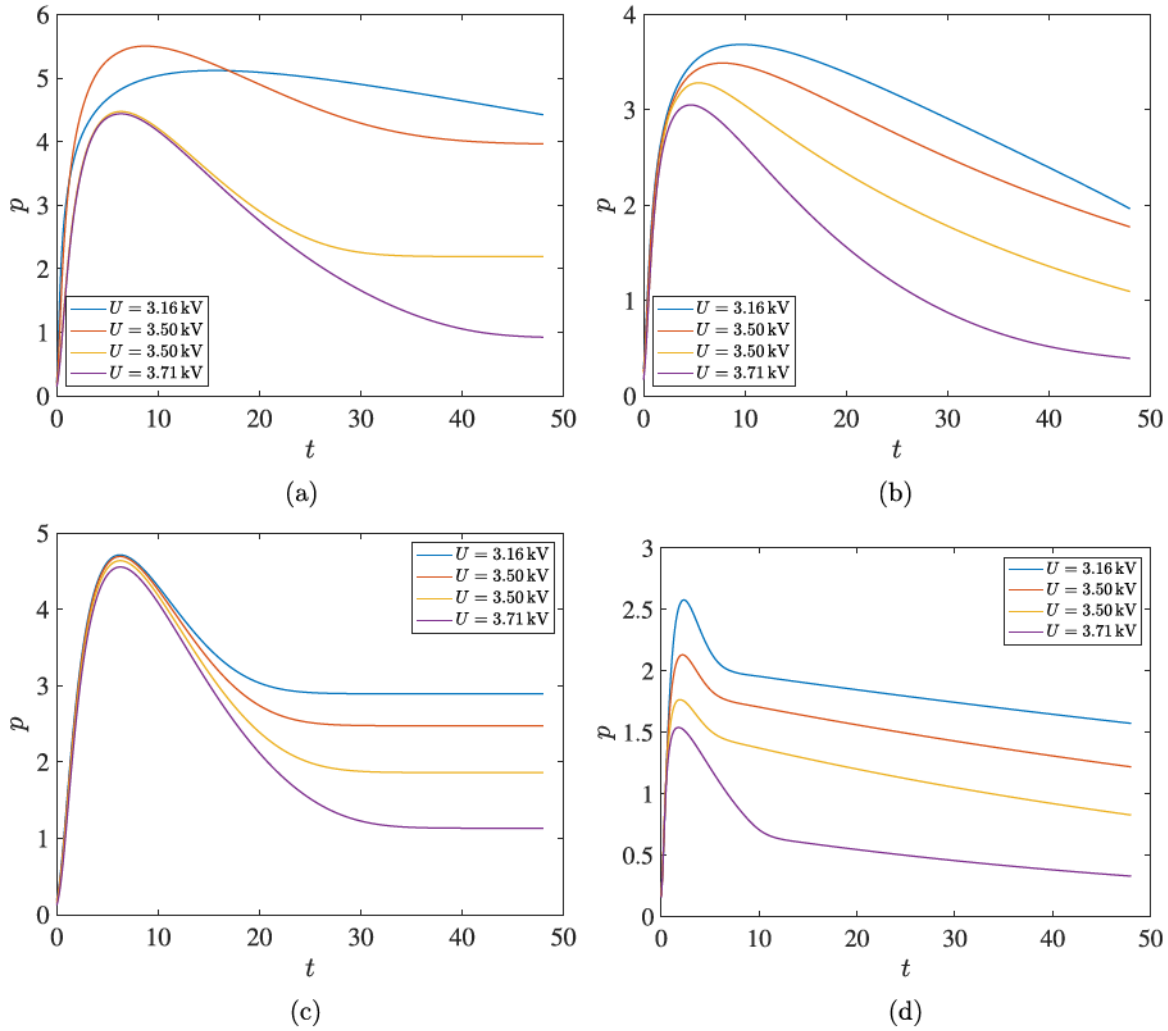

Figure 6. Dynamic response of cell viability from generalized mathematical model for varying plasma discharge voltage U. (a) U-87 MG, $\Delta t = 60$. (b) MDA-MB-231, $\Delta t = 60$. (c) U-87 MG, $\Delta t = 90$. (d) MDA-MB-231, $\Delta t = 90$.

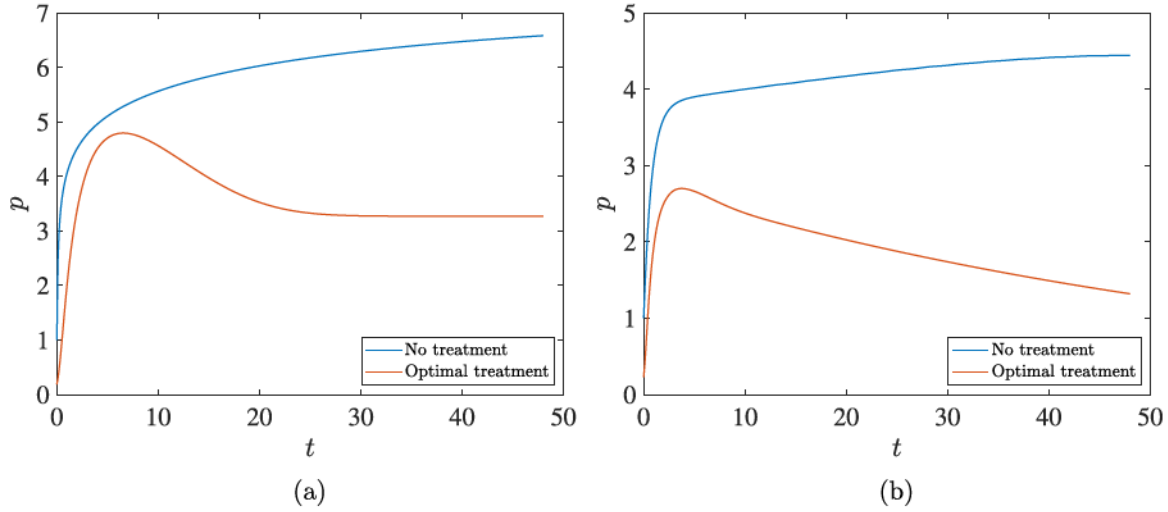

Figure 7. Simulation results of the proposed optimal control for U-87 MG and MDA-MB-231. (a) U-87 MG. (b) MDA-MB-231.

the tolerance on the objective function of 10^{-6}. The weighting factors are chosen as $w_1 = 1/(180)^2$ and $w_2 = 1/(3.71)^2$.

Two cases are considered. For U-87 MG, the desired ratio of the cancer cell viability is chosen as $r_d = 0.5$, and the corresponding optimal treatment duration and the plasma discharge voltage are obtained as

$$(\Delta t, U) = (65.1\ \mathrm{s}, 3.367\ \mathrm{kV}).$$

Table 3. Model predictive control of U-87 MG.

	Ideal case			MPC		
Treatment	r_d	Δt	Relative viability	r_d	Δt	Relative viability
1	0.56	78.47	$0.56 = 0.1^{1/4}$	0.56	70.34	0.62
2	0.56	78.47	$0.31 = 0.1^{2/4}$	0.45	80.38	0.33
3	0.56	78.47	$0.17 = 0.1^{3/4}$	0.47	75.38	0.22
4	0.56	78.47	0.10	0.40	82.95	0.11

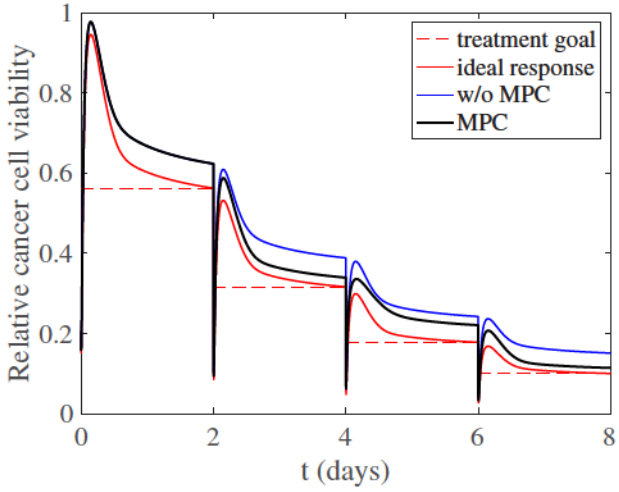

Figure 8. Simulation results of the proposed MPC for U-87 MG.

Next, we consider treatment of MDA-MB-231 with $r_d = 0.3$, and the resulting optimal treatment conditions are given by

$$(\Delta t, U) = (71.6\ \text{s}, 3.315\ \text{kV}).$$

Figure 7 illustrates the dynamic response of cell viability under the optimal treatment for both U-87 MG and MDA-MB-231. It is shown that the terminal relative cancer cell viability is reduced as specified by the inequality constraint (6).

3.3. Model predictive control for optimal feedback treatment

The above formulation of optimal control provides CAP treatment schedule for a specific level of cancer cell growth inhibition. However, cancer cell response to CAP treatments depends on various intrinsic and extrinsic factors, and the presented mathematical model may not accurately characterize the actual response of the cancer cells under treatments. This may cause that the terminal value of the relative cancer cell viability becomes greater than the desired level, or it may yield unnecessarily intensive CAP treatments.

We address this by optimal feedback framework based on MPC. The objective is to adjust the treatment parameters adaptive based on the actual cell response. The key idea of MPC is solving an optimal control problem repeatedly over a finite time horizon, where each optimization is initialized by the actual response at the beginning of the time horizon considered. While each optimization is completed in an open-loop fashion, MPC is a feedback mechanism as it is repeatedly applied based on the actual response. In control system engineering, MPC is one of the most popular methods to extend the results of optimization into an optimal feedback control. It is desirable as nonlinear constraints can be easily imposed in feedback controls.

We consider a case of *in vitro* CAP treatments for U-87 MG, where cancer cells in a petri dish are exposed to CAP jet four times at the interval of 48 h. It is assumed that the cancer cell viability is measured at the end of each 48 h period, and the treatment at the next period is determined accordingly. The weighting factors for the objective function is chosen as $w_1 = 1$ and $w_2 = 0$, and the plasma discharge voltage is fixed at $U = 3.16$ kV. This is to explore a wide range of treatment duration Δt in feedback controls without being restricted by the limit of 60–90 s for higher discharge voltages. For cancer growth inhibition, it is required that after completing four treatments the relative cancer cell viability defined as r_d in (6) is less than 0.1. Ideally, the desired relative cell viability can be chosen as $r_d = (0.1)^{1/4} \simeq 0.56$ for the optimization of each treatment period such that the terminal relative viability is reduced to 0.1 after the course of four treatments. Instead, in the presented MPC, the desired relative cell viability is chosen as

$$r_d = \begin{cases} 0.1^{1/4} & \text{first treatment} \\ 0.1^{1/4} \times \frac{\text{(predicted ratio of cell viability)}}{\text{(actual ratio of cell viability)}} & \text{remaining treatments} \end{cases}. \tag{7}$$

This is to reduce the desired viability of the next treatment further if the actual cell viability at the end of the preceding treatment is greater than its predicted value.

The proposed approach is verified by a numerical simulation, where the preceding mathematical model is considered as the actual cancer response, and the parameters of the mathematical model are altered to represent a mathematical model available to MPC. Therefore, the mathematical model available to the controller is different from the dynamic model representing the actual cancer cell response.

The corresponding simulation results for U-87 MG are illustrated in table 3 and figure 8. In table 3, the three columns from the second to the fourth correspond to the ideal case when the exact model is available to MPC. In this case, the relative cancer viability reduces exactly by the desired factor r_d at each treatment. The treatment duration for all four treatments are identical to $\Delta t = 78.47$ s, and the terminal relative viability after four treatments is 0.1 as desired. The next three columns are the results of MPC when the exact model is not available to MPC. Due to the modeling error, the first treatment duration is $\Delta t = 70.34$ s, which is less than the ideal value. Consequently, at the end of the first treatment, the relative viability becomes greater than the desired value, i.e. $0.62 > 0.52 = r_d$. In MPC, the treatment goal and the duration of the second treatment are adjusted accordingly, and it is repeated at each treatment. After four treatment, the terminal relativity viability for MPC is 0.11.

Figure 8 illustrates the temporal response of the relative cell viability. The red, dotted lines show the desired relative cell viability at the end of each period. The red, solid curves illustrate the ideal case when the mathematical model for the actual response is available to optimization. In this ideal case, the cell viability of the U-87 MG is reduced to the desired level at the

end of each period, as observed in the above table. Here we consider an additional case when the mathematical model available to optimal control is not identical to the actual model, but the proposed MPC scheme is not applied. This is illustrated by blue curves in figure 8, and it is shown that the cell viability becomes greater than the desired level always, resulting in the terminal ratio of 0.15 that is 50% greater than the desired value. Finally, when the proposed MPC is introduced, as illustrated by black lines, the controlled cell viability reduces close to the desired level even with the discrepancy in the mathematical modeling. As such, this simulation result suggests that by adjusting CAP treatment conditions adaptive to the actual cancer response, the adverse effects of modeling errors can be mitigated.

4. Conclusion

This work proposes a mathematical model for describing the dynamic response of cancer cell to CAP by utilizing the optimal feedback control. A mathematical model, which reflects the cell viability variation with respect to time, is developed based on the experiments presented in [34]. The proposed differential equation describes the influence of the CAP on two particular cancer cells, namely U-87 MG and MDA-MB-231, based on two key factors, plasma treatment duration and discharge voltage. It was observed that from 0 h to 1 h, the plasma exposure promotes cell division, then such promotion effect gradually shifted to inhibition effect, and the proliferation rate ratio became negative from 2 h to 48 h. Additionally, an optimal control problem is formulated to minimize a weighted sum of the treatment duration and the discharge voltage while guaranteeing that cancer cell viability is reduced to the desired level. This is further generalized to an optimal feedback framework according to model predictive controls, so that the CAP treatment is adaptively adjusted based on the actual cancer cell response. Future works include the validation of the proposed approach with *in vitro* experiments, and incorporation of the dynamic response of health cells to maximize the selectivity of CAP treatment.

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