Sequential Therapeutic Response Modeling for Tumor Treatment Using Computational Hybrid Control Systems Approach

Wasiu Opeyemi Oduola, Xiangfang L. Li, Chang Duan, Lijun Qian, and Edward R. Dougherty

***Abstract*—Objective: Tumorigenesis is due to uncontrolled cell division arising from mutations and alterations in the proliferative controls of the cell population. The fight against tumor growth and development has often relied on combination therapy that has been acclaimed as one of the main standards of care in cancer therapeutics and prevention of drug-related resistances. The toxicity of the combinatorial drugs raises a significant concern whenever patients take two or more drugs concurrently at the maximum tolerated dose. A promising solution in tumor treatment involves the administration of the drugs in an alternating or sequential fashion rather than a simultaneous manner. In this paper, we investigate how feasible such an approach is from a mathematical perspective and propose a switched hybrid control systems framework. Methods: We explore the response of tumor cells dynamics to sequential drugs administration with the aid of a time-dependent switching strategy. A transit compartmentalized model is employed to describe the tumor cells progression to death. Results: The design of the time-based drug switching logic ensures the proliferating tumor cells are repressed. Conclusions: Simulation results are provided using the tumor growth dynamics with sequential drugs intake to demonstrate the effectiveness of the proposed method in reducing the tumor size. Significance: This paper is the first attempt to provide a switched hybrid control systems framework on sequential drug administration to biomedical researchers and clinicians.**

***Index Terms*—Cancer treatment, combination therapy, mathematical modeling, sequential drug intake, switched hybrid control system.**

I. Introduction

TUMOR growth and development is due to uncontrolled cell division arising from mutations and alterations in the proliferative controls and regulation mechanisms of the cell population. The tumor cells may grow uncontrollably to a size of about one million cells and they may metastasize by invading the surrounding tissues. Several cancer treatment methods are based on combination therapy in which patients take two or more drugs that target the tumor cells. The mechanism of action of those drugs is such that they function in a cooperative fashion to interrupt specific phase of the cell reproduction cycle [1]. Additionally, it is a widespread belief that combinatorial targeted therapy is one of the most effective treatment options for tackling several solid tumors. Targeted drug therapeutics in the treatment of tumors has substantially improved the patients' survival rates, but the additive toxicity of combination drugs could be counterproductive if not carefully taken into consideration [2]. Hence, a crucial step in the direction of an effective and personalized cancer treatment is to comprehend the effects of drug combinations on the tumor growth dynamics and design the drug administration to reduce toxicity.

Toxicity is largely a function of reduced immune system performances of the patients, bodyweight losses, pains and some other side-effects encountered by patients. Drug toxicity is one of the main concerns whenever combinations of drug agents are administered concurrently at the maximum tolerated dose (MTD) [3]. For example, Metastatic Renal Cell Carcinoma (mRCC) therapies are focusing on agents that block tumor and vascular growth pathway [4]. In such case, the cancer drug Sunitinib is directed to inhibit the vascular endothelial growth factor receptor (VEGFr) while Temsirolimus blocks the mammalian target of rapamycin (mTOR). Temsirolimus and Sunitinib are agents that are certified by the US Food and Drug Administration (USFDA) for the treatment of mRCC. However, toxicity increases whenever patients take such drugs at the same time. The hope is that such drugs can be safely taken *sequentially* at full doses with reduced toxicity [4]. In this work, we attempt to investigate the problem of sequential drug administration from a mathematical modeling point of view, using switched hybrid system control modeling framework.

Mathematical models can help in enhancing the effectiveness of combinatorial targeted therapy and maintaining tolerable toxicity levels by providing a systematic way to design drug treatment schedules. Thus, they can result in intuitive and insightful mechanisms on how to efficaciously reduce the tumor size while limiting the toxicity to the population of normal cells. Several computational and mathematical modeling frameworks

Manuscript received March 6, 2017; accepted June 29, 2017. Date of publication July 6, 2017; date of current version March 19, 2018. This work was supported in part by the US National Science Foundation Awards 1238918, 1464387, 1601126, and 1736196, and in part by the Texas A&M University System Chancellor's Research Initiative. *(Corresponding author: Wasiu Opeyemi Oduola.)*

W. O. Oduola is with the Department of ECE, Prairie View A&M University, Prairie View, TX 77446 USA (e-mail: woduola@student.pvamu.edu).

X. L. Li and L. Qian are with the Department of ECE, Prairie View A&M University.

C. Duan is with the Department of ME, Prairie View A&M University.

E. R. Dougherty is with the Department of ECE, Texas A&M University.

Digital Object Identifier 10.1109/TBME.2017.2723957

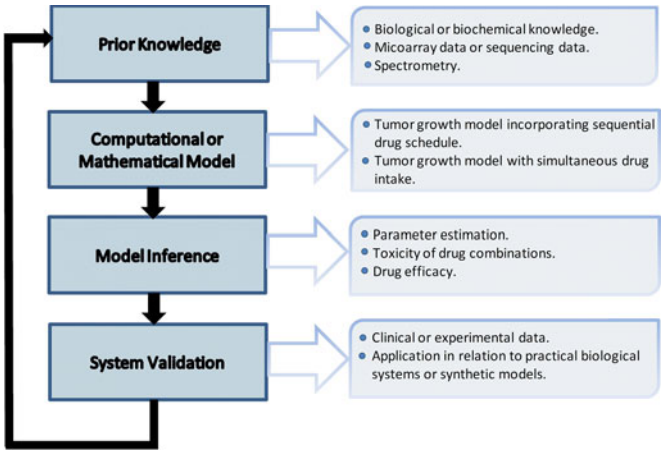

Fig. 1. Predictive therapeutic system modeling.

have been proposed in studying the growth of tumor cells and the corresponding response of tumor cells to different types of treatment. Such models have been used to study tumor growth and tumor-induced neovascularization [5], effect of tumors' microenvironment on tumor development [6] and the impact of the heterogeneity of metabolism on tumor growth, progressions and effects of treatments [7]. Continuous and discrete mathematical models have been used to investigate tumor angiogenesis and vessel-based networks [8]. One of the main objectives of these models is to provide a way to develop new prediction on future experimental guidelines, precision medicine and developing new therapeutic methods to block invasive tumor cells [6]. They are equally vital to the understanding of the mechanisms of drug actions and designing better and effective drugs [2].

The overall iterative steps towards an effective and mathematically predictive sequential therapeutic modeling is shown in Fig. 1. The prior knowledge of the system will point towards the appropriate mathematical model that can capture the sequential drug design paradigm with respect to the available biological information. There may be need to estimate the parameters of the chosen mathematical model and to quantify the efficacy and toxicity associated with the treatment plan. Validation of the model is based on further experimental or clinical data that helps in checking the prediction accuracy and performance of the designed therapeutic schedule. This study examines a mathematical modeling framework that focuses on the response of proliferating tumor cells to sequential drugs administration by casting the problem as a switched hybrid control system. The proposed model is analyzed using the time-dependent switching method. The switching function is designed such that it guarantees the stability of the system and the reduction of proliferating tumor cells when the drugs are administered sequentially.

The tumor model and problem formulation is detailed in Section II. Section III discusses the time-dependent drug switching mechanism. Simulation case studies are presented inSection IV. Section V contains additional discussion and Section VI provides the conclusion of the paper.

Fig. 2. The sequential drug administration paradigm.

II. Tumor Modeling With Sequential Drug Treatment

The computational systems biology modeling framework is applicable in studying the response of tumor cells to sequential drug treatment. One approach involves using dynamic switched hybrid system modeling to study the drug anti-tumor effects from a sequential drug treatment perspective. The process starts with the generation of a quantitative model of biological systems, then by integrating pharmacology-related data pertinent to the target systems, one can build a new computational hybrid system modeling structure under sequential drug perturbations. The sequential drug intake is such that the patient takes one drug for a certain period of time followed by a period of rest before switching to the next drug and another period of rest and so on as shown in Fig. 2. This is to ensure that the toxicities of the drugs are tolerable and not adding up.

The traditional way to calculate anticancer drug dosage is by a normalization of the dose to body surface area (BSA), which is usually calculated from the patient's weight and height [9]; however, this has been shown to be inadequate [10]. For instance, BSA-based dosing is linked with significant variability in plasma levels by as high as 100 folds [10], and such variabilities are a main contributor to therapeutic failure and toxicity [9]. The problem becomes more pronounced when multiple drugs are taken simultaneously at the MTD. Thus, a systematic approach that facilitates quantitative thinking to sequential drug treatment is required. It is our belief that with the aid of the modeling structure proposed in this paper and a refined model by iterative processes with the experimentalists (See Fig. 1), the proposed methodology is potentially able to provide better recommendation for sequential drug administration in clinical practice.

A. Tumor Growth Modeling With Switched Systems

Tumor study has provided a fertile foundation for mathematical models. Several computational tumor growth modeling frameworks that reflect various paradigms have been reported in the body of knowledge. Tumor growth curves are described using empirical models that employ mathematical equations but they lack thorough mechanistic descriptions of the hidden physiological process. Originally, mathematical models were adapted in conceptualizing the simple exponential tumor growth and development [11]. Afterwards, sigmoid-based formalisms such as Gompertz, Verhulst and logistic mathematical models were used for describing the reduced growth in later stages after the tumor cells outgrow their blood supply, thereby inducing central necrosis [12]. A shortcoming of these classes of mathematical

models is the associated difficulty in predicting the modification to the tumor growth dynamics under drug perturbations.

On the other hand, functional modeling frameworks are focused on understanding biological processes underlying the growth of tumor cells using mechanistic descriptions. Such modeling approaches need a number of assumptions that involve cell cycle kinetics (quiescent vs. proliferating cells) and biochemical processes, like those based on immunological and/or anti-angiogenic responses [13]. Due to the biological complexity being captured, functional models are associated with a much higher number of model parameters in comparison with empirical models. The problem is even more complicated when considering the treatment effect with anti-cancer drugs because of the incomplete knowledge of the mechanisms of drug-agent action $in\,vivo$. Thus, it is usually problematic to maintain an appropriate balance between functional and empirical models.

The model in this paper is built on a system of ordinary differential equations (ODEs) that link the sequential treatment to the tumor growth model using switched control system. The tumor growth without drug treatment is expressed by an exponential growth phase followed by a linear growth phase. Since the proliferating cells make up a large portion of the neoplastic tissue, whenever a drug is administered, the rate of tumor growth reduces proportionally to both the number of proliferating tumor cells and the concentration of drugs [14], [15]. This study therefore proposes a model that dynamically links tumor progression and drug effect, whereby switched hybrid control system is used in accommodating tumor progression and sequential therapeutic response. We specifically modify the tumor growth modeling approach proposed in [15], [16] to switched hybrid control system model in order to account for the tumor growth dynamics at various phases and enhance it with the sequential drug perturbation model shown in Fig. 2. The biological setup is similar to those found in [15], [16]. The $perturbed$ and $unperturbed$ growth modeling frameworks are developed in modeling the dynamics of tumor growth with sequential drug treatment and without treatment.

B. Unperturbed Tumor Growth Model - Without Drug Intake

In the case of unperturbed growth model, tumor growth modeling is formulated based on an exponential growth stage followed by a linear growth stage. We propose a switched hybrid control system modeling approach to account for the dynamics of tumor growth in different phases. The model is as follows:

$$\dot{w}_u = \alpha w_u s^-(w_u, \theta_w) + \beta s^+(w_u, \theta_w) \tag{1}$$

where w_u represents the unperturbed tumor weight, α and β are both model parameters that define the rates of growth exponentially and linearly. $s^+(.)$ denotes the unit step function that is expressed as follows:

$$s^+(x, \theta) = \begin{cases} 0 & x < \theta \\ 1 & x \geq \theta \end{cases}, \tag{2}$$

$s^-(.) = 1$ - $s^+(.)$, and θ_w is the threshold value that corresponds to the instance at which the tumor growth dynamics switches from exponential to linear growth. The continuity of the differentiation in (1) can be guaranteed at θ_w by setting $\theta_w = \beta/\alpha$. Due to recent advancement in tumor growth models, the tumor growth features might entirely differ in different situations. The modeling framework proposed based on switched hybrid control system can be extended to incorporate more complex scenarios, for instance, more growth phases with varying growth rates.

C. Perturbed Tumor Growth Model - With Drug Intake

In the unperturbed modeling dynamics, the assumption is that all tumor cells are proliferating. In the perturbed model, the expectation is that the tumor cells that are being affected by the drugs stop proliferating and go through various phases distinguished by the progressive degree of damages and they die eventually [14], [16]. With sequential drug treatment, the following transit compartmentalized model is employed to describe the cells progression to death. For two drugs taken sequentially, $i = \{1, 2\}$:

$$\dot{x}_1 = \alpha_i x_1 s^-(w_p, \theta_w) + \beta_i \frac{x_1}{w_p} s^+(w_p, \theta_w) - \gamma_i^u x_1 \tag{3}$$

$$\dot{x}_2 = \gamma_i^u x_1 - k_1 x_2 \tag{4}$$

$$\dot{x}_3 = k_1 (x_2 - x_3) \tag{5}$$

$$\vdots \tag{6}$$

$$\dot{x}_n = k_1 (x_{n-1} - x_n) \tag{7}$$

$$w_p = \sum_{j=1}^{n} x_j \tag{8}$$

$$x_1(0) = w_0 \tag{9}$$

$$x_2(0) = x_3(0) = \ldots x_n(0) = 0 \tag{10}$$

where w_0 denotes the tumor weight at the inoculation time $(t = 0)$ while w_p denotes the total tumor weight, which is the addition of cells in the different phases. x_1 denotes the fraction of proliferating tumor cells within the total tumor weight w_p with sequential drug treatment. $x_1(t)$ will pass through exponential growth followed by linear growth in identical manner to the unperturbed tumor growth model. α_i and β_i represent the respective growth parameters of the model. Since not all the tumor cells are proliferating, the rate of linear growth is reduced by the ratio of the proliferation cells to the total tumor cells x_1/w_p. Where γ_i^u, $i = \{1, 2\}$, represents the drug effect coefficients. It is assumed that the drugs target the proliferating cells. The damaged cells go through n phases distinguished by the progressive degree of damages with rate constant k_1. The weight of tumor cells that die each time is denoted by $k_1 x_n$.

It is observed that the changes in the number of all the cells with drug treatment is dominated by the changes in the number of proliferating cells. Hence, one can focus the analysis on the number of proliferating cells. The growth stage is thus decoupled into two phases based on the weight of tumor [14], [16]. Whenever the tumor weight is less than the threshold value, $x_1 < \theta_w$, the system dynamics with sequential drug intake, $i = \{1, 2\}$, is as given in (11) shown at the bottom of next page. For instance,

suppose that $w_p < \theta_w$, then the following are the matrices for sequential drug treatment when the first and second drugs are respectively administered sequentially:

$$A_1 = \begin{bmatrix} \alpha_1 - \gamma_1^u & 0 & 0 & \dots & 0 \\ \gamma_1^u & -k_1 & 0 & \dots & 0 \\ 0 & k_1 & -k_1 & \dots & 0 \\ \vdots & 0 & \ddots & \ddots & 0 \\ 0 & 0 & 0 & k_1 & -k_1 \end{bmatrix},$$

$$A_2 = \begin{bmatrix} \alpha_2 - \gamma_2^u & 0 & 0 & \dots & 0 \\ \gamma_2^u & -k_1 & 0 & \dots & 0 \\ 0 & k_1 & -k_1 & \dots & 0 \\ \vdots & 0 & \ddots & \ddots & 0 \\ 0 & 0 & 0 & k_1 & -k_1 \end{bmatrix}.$$

Comment 1: It can be observed that the eigenvalues of matrix A_i, $i = \{1, 2\}$, are the diagonal terms, $\alpha_i - \gamma_i^u$, $-k_1$, $-k_1$, $\dots$, $-k_1$. Since k_1 is a positive constant, $\alpha_i - \gamma_i^u$ completely determines the solution. Thus, for effective drugs, $\alpha_i < \gamma_i^u$, and matrix A_i has negative eigenvalues. This implies that the number of cells in all the phases will reduce. On the other hand, whenever $\alpha_i > \gamma_i^u$, the very first eigenvalue of A_i will be positive and the solutions will be exponentially growing. Thus, the number of cells in all the phases will be dependent upon the dynamics of the proliferating cells x_1.

III. Time-Driven Switching Design and Stability Analysis for Tumor Growth Dynamics With Sequential Drug Administration

This section focuses on designing the switching of the drugs to be administered sequentially to target and repress the proliferating tumor cells. This is otherwise known as global asymptotic stability. Switched hybrid systems are composed of difference equations or differential equations and a corresponding rule that captures the switching mechanism between them [17], [18]. Switched systems could consist of stable sub-systems [19], unstable sub-systems [20] or a mix of both unstable and stable sub-systems [21]. The stability analysis and switching design for each case is different. The switching approach employed in this study is known as the time-based switching mechanism in which all the sub-systems or system modes are stable based on the matrices of the tumor growth dynamics.

Comment 2: For tumor growth dynamics with or without drug intake, stability of the sub-systems is contingent upon the assumption that, for each sub-system, though the weight of the proliferating cells could be large yet it does not grow out of bound as time $t \to \infty$, due to space and nutrition limitations.

A. Time-Driven Switching Design for Tumor Growth Dynamics

For tumor growth dynamics with sequential (or switched) drugs intake and having all the sub-systems as being asymptotically stable, the approach in [19] is modified to aid the analysis of the switching logic design and asymptotic stability of such systems. Geromel *et al.* [19] investigated the stability analysis for continuous-time switched linear systems with stable subsystems by deriving the minimum dwell-time needed for the system's stability. The analysis is based on the existence of a class of quadratic Lyapunov function that is not required to decrease uniformly at each switching instant as a condition for its stability. We represent piece-wise Lyapunov function as $V_\sigma(x)$. At every switching instant, to bound the increment of the Lyapunov function, it is required that, $V_i(x) \leq \mu V_j(x)$ where $\mu > 1$ and i, j are sub-system's index before and after the switching.

For switched hybrid systems in which the sub-systems are stable, the dwell time constraint depends on the idea that at the instant of switching, the potential increments of the Lyapunov functions are being compensated for by the decrement of the Lyapunov functions within the dwell time. There is equally the relaxed conditions on the Lyapunov functions that at every switching instant t_k, the sequence $V(x(t_k))$ for k = 0 , . . . , ∞, converges uniformly to zero.

Comment 3: The Lyapunov function is used to derive the condition(s) which ensures that a certain drug intake interval or

$$\dot{x} = A_i x, \quad i = 1, 2. \tag{11}$$

where

$$A_1 = \begin{bmatrix} \alpha_1 s^-(w_p, \theta_w) + \beta_1 \frac{s^+(w_p, \theta_w)}{w_p} - \gamma_1^u & 0 & 0 & \dots & 0 \\ \gamma_1^u & -k_1 & 0 & \dots & 0 \\ 0 & k_1 & -k_1 & \dots & 0 \\ \vdots & 0 & \ddots & \ddots & 0 \\ 0 & 0 & 0 & k_1 & -k_1 \end{bmatrix} \quad x = \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ \vdots \\ x_n \end{bmatrix}$$

$$A_2 = \begin{bmatrix} \alpha_2 s^-(w_p, \theta_w) + \beta_2 \frac{s^+(w_p, \theta_w)}{w_p} - \gamma_2^u & 0 & 0 & \dots & 0 \\ \gamma_2^u & -k_1 & 0 & \dots & 0 \\ 0 & k_1 & -k_1 & \dots & 0 \\ \vdots & 0 & \ddots & \ddots & 0 \\ 0 & 0 & 0 & k_1 & -k_1 \end{bmatrix} \quad x = \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ \vdots \\ x_n \end{bmatrix}$$

the drug dwell-time is quite effective to drive the tumor size to a desired weight, That is, to drive the tumor growth dynamics to a desired steady state.

Considering the following switched closed loop tumor growth system,

$$\dot{x}(t) = \big(A + B\eta_{\sigma(t)}\big)x(t) + C_{\sigma(t)}\nu(t) \tag{12}$$

The state is represented by $x \in \mathbf{R}^n$ and $\nu(t)$ is the outward disturbance. $\sigma(t)$ is the time-based switching rule and it is dependent on the presence or absence of the drug of interest and therefore selects the appropriate sub-system's sequence from among the available N_p defined as $\{A_i, B_i, C_i\}, i \in \mathbf{I}[1, N_p]$. The sub-systems are assumed to be stable.

The paper uses the following standard notation: The set of real $m \times n$ matrix is $\mathbf{R}^{m\times n}$, $\mathbf{S}^{n\times n}$ represents real, symmetric $n \times n$ matrix, and $\mathbf{S}_+^{n\times n}$ denotes positive-definite matrices. I denotes the identity matrix with the appropriate dimensions. The transpose of a vector or matrix is represented as ('). For integers k_1, k_2, with $k_1 < k_2$, we express $\mathbf{I}[k_1, k_2] = \{k_1, k_1 + 1, \ldots, k_2\}$.

Definition 1: The switching rule σ is said to have a dwell time (DT) τ_D if $t_{k+1} - t_k \geq \tau_D$, $\forall k$ where t_k, t_{k+1} denotes the successive instants of switching.

Comment 4: The dwell time can be interpreted as the smallest interval of time between two successive drug administrations that ensures the tumor weight ultimately decays to a desired equilibrium weight when the drugs are administered sequentially.

B. Stability Analysis Based on Time-Driven Switching

The multiple quadratic Lyapunov function (MLF) is:

$$V_i(x) := x^T P_{i_q} x, \qquad i_q \in \mathbf{I}[1, N_p], \tag{13}$$

where $P_{i_q} > 0$. The active sub-system's index is i_q. Each subsystem has a Lyapunov function associated with it. The MLF must form a converging sequence to guarantee the stability of the switched system.

There has to be restrictions on the switching signal $\sigma(t)$ when switching between the sub-systems, to ensure the stability of the system. Fig. 3(a) illustrates that the stability of the underlying sub-systems does not guarantee that the switched system will be stable unless with a carefully designed switching sequence that ensures the MLF $V_i(x)$ converges uniformly to zero or forms a decreasing sequence. Fig. 3(b) shows that it is possible to have unstable sub-systems with a switching signal that guarantees the stability of the switched system. Thus, the stability of switched systems is heavily dependent on the dynamics of each of its sub-systems as well as the nature of the switching signals.

The objective of the proposed drug switching mechanism is to obtain the minimum dwell time $T^* > 0$ that ensures the asymptotic stability of the equilibrium point of the tumor growth system in (12). In other words, asymptotic stability is guaranteed if $\sigma(t)$ is not changed for a period of time $t \geq T^*$. The following proposition is modified from Geromel *et al.* [19] that provides a theorem characterizing an upper bound on T^* as a feasible solution to the problem.

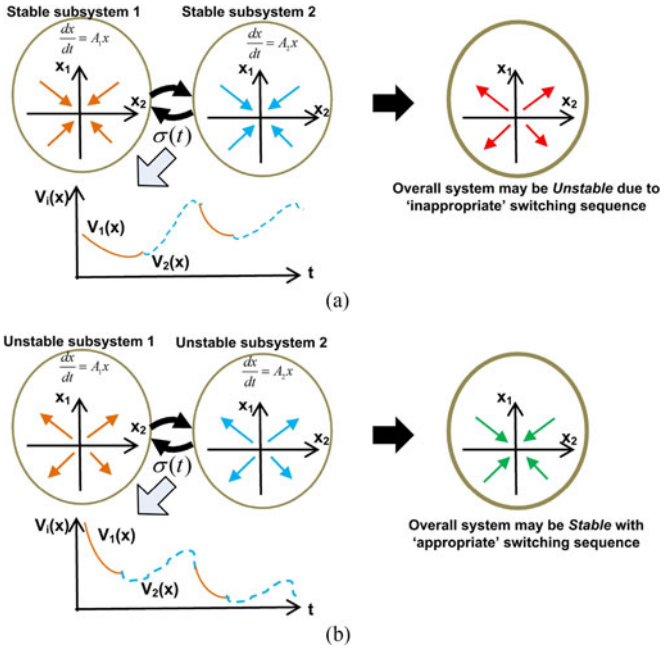

Fig. 3. Vector field trajectory for different switching sequences based on the multiple Lyapunov function (MLF). (a) Switching between two stable subsystems resulting in an overall unstable system because the MLF $V_i(x)$ forms a diverging sequence (b) Switching between two unstable subsystems resulting in a stable system because the MLF $V_i(x)$ converges uniformly to zero or forms a decreasing sequence.

Proposition 1: [19]. Assume that for some $T > 0$, there exists positive-definite matrix $P_i \in \mathbf{S}_+^{n\times n}$, $i \in \mathbf{I}[1, N_p]$ such that

$$(A_i + B_i\eta_\sigma)'P_i + P_i(A_i + B_i\eta_\sigma) < 0\,\forall i = 1, ..., N_p \tag{14}$$

$$e^{(A_i+B_i\eta_\sigma)'T} P_j e^{(A_i+B_i\eta_\sigma)T} - P_i < 0\,\forall i \neq j = 1, ..., N_p \tag{15}$$

Hence in accordance with the dwell-time switching mechanism $\sigma(t)$ with $t_{k+1} - t_k \geq T$, the switched system (12) is said to be globally asymptotically stable.

The proof is provided in Appendix A. An upper bound for the minimum dwell-time T^* is determined from the optimum solution to the optimization problem [19]:

$$\begin{aligned} T^* = \inf_{T>0,\, P_1>0,\ldots,\, P_{N_p}>0} \{\, & T : (A_i + B_i\eta_\sigma)'P_i \\ & + P_i(A_i + B_i\eta_\sigma) < 0,\ e^{(A_i+B_i\eta_\sigma)'T} P_j e^{(A_i+B_i\eta_\sigma)T} \\ & - P_i < 0\,\forall i \neq j = 1, \ldots, N_p\} \end{aligned} \tag{16}$$

Comment 5: Equations (14)–(16) provide the constraints on the modeling parameters of the tumor growth dynamics as well as the smallest drug administration interval (dwell-time) that guarantees the proliferating cells are repressed as time $t \to \infty$. This implies the conditions for which the total tumor weight is reduced to a certain weight with a particular sequential drug administration schedule.

Comment 6: The mathematical framework provided assumes that a time factor (alternately or sequentially) is critical in allowing the body to react appropriately to toxicity. This is

because a patient typically requires a few days of rest between cancer drugs. But the drug effects are usually cumulative (for skin, kidney, liver, heart, brain etc.) depending on the drugs administered.

IV. Simulation Case Studies

We examine simulation of the tumor model with sequential drug intake employing a sequential administration of two drugs using MATLAB/SIMULINK based on the tumor growth dynamics provided in Section II and the analytical results obtained in Section III.

A. Results for Tumor Models With Sequential Drug Intake

To validate the proposed time-based switching algorithm on the sequential drug treatment for tumor cells, we carry out numerical simulation using estimated and pre-defined parameters similar to those in [16]. The numerical results are focused on the detailed transit compartment model given from (3) to (7). The cells that are affected by action of the sequential drugs stop proliferating and go through four different phases, x_1, x_2, x_3 and x_4 that are distinguished by progressive degrees of damages. x_1 represents the fraction of proliferation tumor cells affected by the sequential drugs. w_p denotes the total tumor weight. The model parameters [16] are $\alpha_i = 1.0$, $\beta_i = 0.2$, $k_1 = 1.0$, $\theta_w = 40$, $x_1(0) = w_0$, $x_2(0) = x_3(0) = \ldots x_n(0) = 0$.

Fig. 4(a) shows the drug switching signal. A, B, C, D are the first four drug switching points and Fig. 4(b) depicts the quantitative characterization of the decay of tumor cells under sequential drug intake. The figure also shows some of the sequential drug switching points A, B, C and D similar to Fig. 4(a). The points indicate the time instances at which the treatment changes from the first drug to the second drug and vice versa. The tumor cells initially grow exponentially, then the weight of the proliferating tumor cells declines progressively as the drugs are taken sequentially. The change in number of proliferating cells x_1 follows identical pattern with the change of the total tumor weight and both group of cells are reduced effectively. The sequential drug intake also reduced the tumor size effectively to approximately 40% after about ten switching instances between the two drugs. It is observed that the entire tumor begins to grow slower and ultimately decreased and reached steady tumor weight.

Figs. 4(c) and 5 respectively show the quantitative characterization of the decay of tumor cells under simultaneous drug intake and tumor weight comparison between the sequential and simultaneous drug intake methods. The observation is that even though the sequential drug intake option reduces toxicity, it takes a little longer than the simultaneous counterpart to reduce the tumor weight to a given percentage. This appears to be a tradeoff between toxicity reduction and length of treatment time.

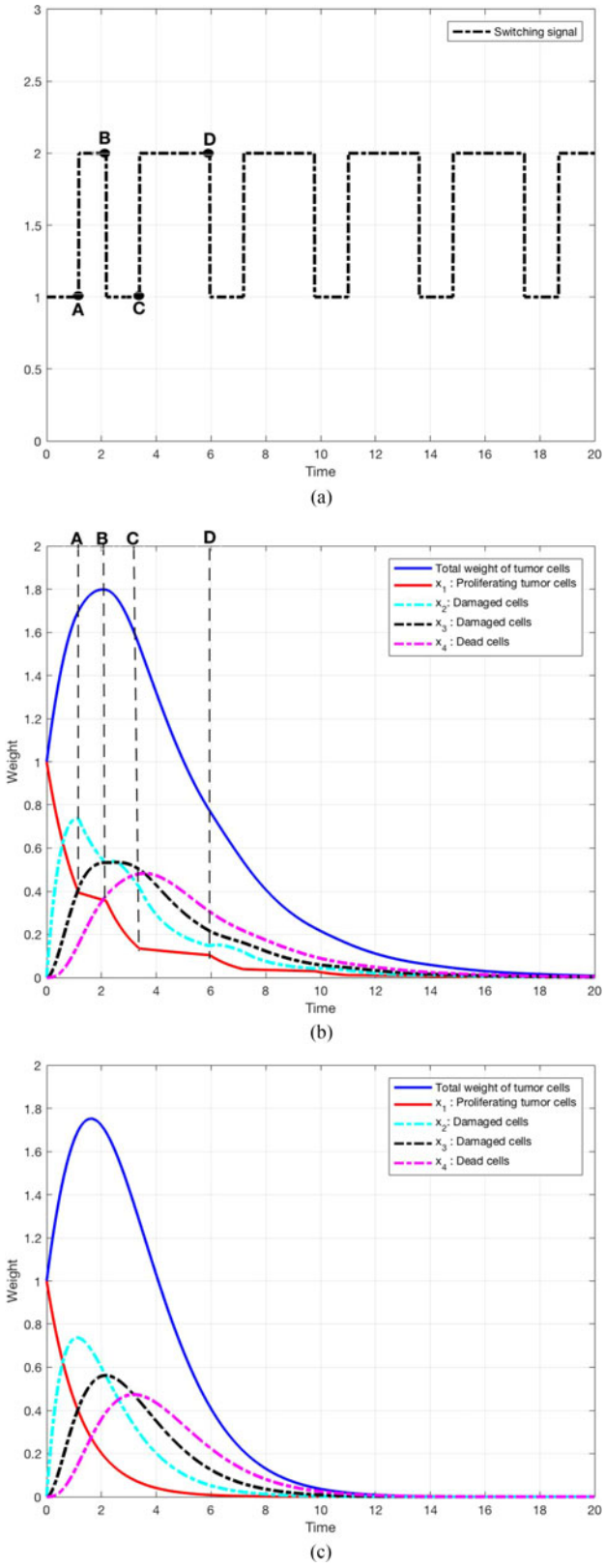

Fig. 4. The drug switching function and response of tumor cells under sequential and simultaneous drug intake. (a) The drug switching signal, e.g., A, B, C, D are the first four switching points. (b) Quantitative characterization of the decay of tumor cells under sequential drug intake and the corresponding switching points A, B, C, D. (c) Quantitative characterization of the decay of tumor cells under simultaneous drug intake.

V. Further Discussion

The difficulty usually encountered in cancer treatment is due to the heterogeneity of the cell population, their complexity

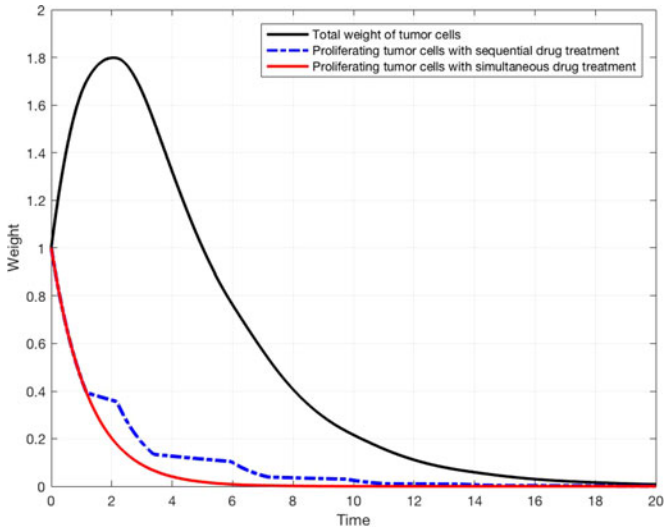

Fig. 5. Quantitative characterization of the response of tumor cells by comparing sequential versus simultaneous drug intake.

and the microenvironment. It also makes it difficult to translate research advancements in molecular biology and cancer cell biology into viable cancer treatments. Thus, there is a need for multidisciplinary efforts that can integrate drug information with drug therapeutics response models and cellular and molecular biological information using computational systems biology framework and experimental methodologies. This will include efficient mathematical modeling at the drug development phase, integrating pre-clinical and clinical information, effective *in silico* modeling approach, translation to clinical practice, collaboration among medical, science, engineering professionals and other related fields. Computational systems biology has emerged as a viable tool in modeling drug therapeutics and cancer biology. This tool helps to functionally understand the interactions existing between the diseases and the drugs and it signals a switch from the traditional "black box" methodology to a more rational design and functional approach. This work is a step in the direction of integrating drug information with drug therapeutics response models and cellular and molecular biological information using computational systems biology framework. The mathematical model proposed in this study could accelerate the design of better sequential treatment options that drive the weight of the tumor cells to a more desirable size.

First line therapeutics is often able to reduce the tumor size by a certain percentage but the accompanying cells death create a fierce evolutionary dynamics used in selecting the resistant clones. Second to fourth line therapeutics are usually ineffective, thus tumor progression happens very rapidly because the resistance mechanism of the cells broadens in a progressive manner [22]. Hence the importance of an effective treatment regimen cannot be overemphasized. There is the need to design optimal treatment schedules that can limit toxicity, enhance clinical trials pathway for new anti-cancer agents and accelerate progress towards precision healthcare [23], [24]. As a consequence of the increase in toxicity level associated with combination therapies, clinical trials and studies that focus on sequential drug administration are being investigated by various research teams. One of the key findings from the clinical trials is that toxicity (at the MTD) is less when the cancer drugs are taken sequentially as contrasted with simultaneous or concomitant intake of the anti-cancer drugs [25]–[27]. Therefore, sequential treatment methods are potentially lowering toxicity on one hand, and providing a way to optimally deliver single-drug therapy and improve the quality of patient's life [28]. A good review of clinical trials providing a comparison between sequential regimen and combination therapy is presented by Miles *et al.* [28]. Additional reviews of clinical trials and pre-clinical evidences supporting each approach are provided by Felici *et al.* [29].

The growth of tumor cells are usually modeled using discrete, continuous or hybrid computational modeling methodologies. The continuous modeling frameworks are the obviously appropriate candidate for modeling large-scale systems. Since they have the ability to describe large-scale behaviors of the growth and development of tumor cells at a very little computation cost; but the main shortcoming is that they tradeoff the resolutions of individual cells, especially when attribute of the cell varies over small spatial and temporal scales. Discrete modeling methods provide spatial and temporal depictions of individual cells in addition to the cell to cell relations. A major shortcoming of discrete modeling framework is that the computational cost required is directly proportional to the number of cells under consideration. This limitation restricts such modeling framework to cases where the number of cells is very small. Hybrid modeling methods exploit the merits of both discrete and continuous modeling methods. They have the ability to capture the stochasticity that may be associated with the system being considered. They have a wide appeal for modeling tumor growth dynamics under drug perturbations since the dynamics of biological systems are typically non-linear, have highly varying regulatory constraints, and maintain a broad range of control mechanisms. In the tumor growth dynamics example, we utilized the widely accepted ODE modeling frameworks which are commonly used in modeling tumors.

Combinatorial therapeutics is widely believed to be the standard of care in preventing the mutations of genes and resistance of drugs. The multiple drugs administered in attacking the tumor cells function synergistically in disrupting specific stages of the cell reproduction cycles [1]. The merits of this treatment type includes the enhancement of patient's compliance resulting from the reduced number of administrations, reduction in drugs doses with accompanying decrease in toxicity to healthy tissues, synergy or additive impacts of drug interaction and overcoming or delaying the resistances due to multiple drugs. The strength of combination therapy one of the motivations behind various combinatorial therapeutic research studies [1]. They equally inspired us to investigate such treatment paradigm mathematically for tumor cells and from a sequential drug administration point of view. The control theory analytics presented in this paper provides a computational tool with potential applications to sequential treatment for variety of tumor types as a means to reduced toxicity and enhancement of patients' quality of life.

A couple of challenges are associated with the proposed modeling methodology. The first is that the proposed model is general and not specific to a particular type of tumor. This may create difficulty in parameterization and validation with experimental data obtained from distinct tumor cells. In spite of this challenge, the modeling framework has the potential to improve the quality of cancer therapeutics that may be geared towards personalized medicine. Another issue is that assuming that the effects of the drugs will not *overlap* may be unrealistic [1]. A good understanding of the drugs' biological half-life may assist in a schedule of the sequential drug intake in such a way that the toxic effects of one drug would have reduced substantially before administering the second drug [30]. For example, a traditional tyrosine kinase inhibitor typically has a prolonged half life that causes a continuous inhibition of the targets and this must be taken into account when designing the drug switching. Worthy of note is the approach adopted in [4] in which one of the drugs is administered for a given time period (e.g., 4 weeks) then accompanied by a lengthy period of rest (2 weeks), then the second drug is similarly administered to ensure that the toxic effects of the drugs do not overlap. For best result, modeling structure should be chosen based on the underlying mechanisms of drugs actions.

The state space modeling framework used hitherto is based on the assumption that the dynamics of the tumor cells are time-invariant. Realistically, biological systems involve many diverse but interconnected processes, that are dynamical, nonlinear, random and may occur at several temporal and spatial scales [31]. However, a totally non-linear continuous modeling structure of biological systems may be too large and complex for analyses and simulations. A method to partially handle this problem is by the extension of the current time-dependent switching algorithm to consider randomness in the analysis provided in Section III-A. It is expected that, despite the challenges listed, the promising result obtained from the sequential therapeutic modeling provides a progressive step towards a pre-clinical model and help in supporting the decision making processes in the therapeutic planning stage. It is vital to note that all system models have their limitation, inclusive of system modeling frameworks in oncology: simple system models can give us insight and they can intuitively describe existing data, but simple models are faced with the issue of over-simplification and omission of critical variables; conversely, it is ordinarily difficult fitting functional models to experimental data because over-parametrization can only be averted if additional "microscopic" observation is available. Therefore, constructing multiscale computation-intensive and predictive models that is linked to biological-based evidence and parameterized with biomedical data will certainly be very crucial. Advanced experimental technologies and computational methodologies can be applied mutually in a synergistic fashion to address some of the aforementioned issues.

VI. Conclusion

This study is an attempt to provide a systematic way of elucidating the evolution of tumor growth and its interactions with sequential drug treatment. It provides a quantitative model of sequential (switched) intake of the drugs and how to design an appropriate treatment schedule in combination therapy to avoid high toxicity while still repressing the proliferating tumor cells. Analytical results are derived for the sequential drugs administration and validated by simulations. The sequential drug intake based on time-driven switching function is linked with tumor cells growth dynamics to evaluate the effectiveness of such therapeutic strategy from a mathematical modeling perspective. The design and analysis provided are based on multiple Lyapunov function and Linear Matrix Inequalities (LMI). For linear approximations of the models, closed-form solutions of the time-based switching rule and hence the sequential (switched) administrations of the drugs are obtained. This is one of our first attempts towards mathematical modeling of sequential drug effects for cancer treatment. The sequential drug intake framework proposed is flexible enough to accommodate various models of tumor growth. However, with more complex models, analytical results may be unattainable.

Experimental data suggests that maximum tolerated dose for combinatorial therapeutic drugs differ from that of monotherapy drugs where the drugs are administered in a sequential or individual manner [25]–[27] and the toxicity of multiple combination of drugs is higher than those of single drug therapy. The mathematical model provided in this study is focussed on such investigations as in [25]–[27]. It is already shown that drug-related toxicity is lower in the sequential treatment regime as compared with simultaneous drug administrations [4]. Future work aims to investigate the extension of the current time-driven switching strategy to analyzing the stability of tumor models with built-in stochasticity and other external constraints when the drugs are given sequentially. This is to ensure that the model gets as close as possible to what obtains in wet lab experiment on tumor models with drug consideration and it will involve collaboration with experimental and clinical professionals.

Appendix A
Proof of Proposition

Proof: The proposition is proved based on the analysis of the stability of switched systems by utilizing the multiple Lyapunov function framework. The objective is to get the minimum dwell time $T^* > 0$ existing between drug iadministration that ensures the asymptotic stability of the equilibrium point of (12) based on the time-driven switching function,

$$\sigma = i_q \in \mathbf{I}[1, N_p], \qquad t \in [t_k, t_{k+1}) \tag{17}$$

Let $\tau = t_{k+1} - t_k$ with $\tau \geq T > 0$. At the time instant $t = t_{k+1}$, the time-driven switching function changes to

$$\sigma(t) = j_q \in \mathbf{I}[1, N_p] \tag{18}$$

Examine (14), the differential of the Lyapunov function $V(x) = x' P_{i_q} x$ along an arbitrary trajectory of (12) satisfies

$$\dot{V}(x) = x' \left[(A_i + B_i \eta_\sigma)' P_i + P_i (A_i + B_i \eta_\sigma) \right] x < 0 \tag{19}$$

This means that there exists a positive scalar $\lambda > 0$ and $\mu > 0$ satisfying

$$||x(t)||^2 \leq \mu e^{-\lambda(t-t_k)} V(x(t_k)) \quad \forall t \in [t_k, t_{k+1}) \tag{20}$$

Also, by considering inequality (15), we have

$$\begin{aligned} V(x(t_{k+1})) &= x(t_{k+1})' P_j x(t_{k+1}) \\ &= x(t_k)' \left[e^{(A_i + B_i \eta_\sigma)' \tau} P_j e^{(A_i + B_i \eta_\sigma)\tau} \right] x(t_k) \\ &< x(t_k)' \left[e^{(A_i + B_i \eta_\sigma)' \tau_k} P_i e^{(A_i + B_i \eta_\sigma)\tau_k} \right] x(t_k) \\ &< x(t_k)' P_i x(t_k) \\ &< V(x(t_k)) \end{aligned} \tag{21}$$

Inequality (15) is satisfied due to the fact that for each $\tau_k = \tau - T \geq 0$, the following inequality holds

$$e^{(A_i + B_i \eta_\sigma)' \tau_k} P_i e^{(A_i + B_i \eta_\sigma)\tau_k} \leq P_i \tag{22}$$

The outcome is that there exists $\alpha \in (0, 1)$ such that

$$V\big(x(t_k)\big) \leq \alpha^k V(x_0) \ \ \forall k \tag{23}$$

Equations (20) and (23) ensures the asymptotic stability of the equilibrium solution of (12). ■

REFERENCES

[1] P. Hamberg *et al.*, "Impact of pazopanib on docetaxel exposure: Results of a phase I combination study with two different docetaxel schedules," *Cancer Chemotherapy Pharmacology*, vol. 75, no. 2, pp. 365–371, 2015.

[2] M. Li *et al.*, "Nanoscale quantifying the effects of targeted drug on chemotherapy in lymphoma treatment using atomic force microscopy," *IEEE Trans. Biomed. Eng.*, vol. 63, no. 10, pp. 2187–2199, Oct. 2016.

[3] N. Lamanna *et al.*, "Sequential therapy with fludarabine, high-dose cyclophosphamide, and rituximab in previously untreated patients with chronic lymphocytic leukemia produces high-quality responses: Molecular remissions predict for durable complete responses," *J. Clin. Oncology*, vol. 27, no. 4, pp. 491–497, 2009.

[4] L. D. Lewis, Phase II study of alternating sunitinib and temsirolimus, 2015. [Online]. Available: https://clinicaltrials.gov/ct2/show/NCT01517243

[5] H. Yan *et al.*, "Multiscale modeling of glioblastoma suggests that the partial disruption of vessel/cancer stem cell crosstalk can promote tumor regression without increasing invasiveness," *IEEE Trans. Biomed. Eng.*, vol. 64, no. 3, pp. 538–548, Oct. 2016.

[6] Y. Kim *et al.*, "The role of the tumor microenvironment in glioblastoma: A mathematical model," *IEEE Trans. Biomed. Eng.*, vol. 64, no. 3, pp. 519–527, Dec. 2016.

[7] M. Robertson-Tessi *et al.*, "Impact of metabolic heterogeneity on tumor growth, invasion, and treatment outcomes," *Cancer Res.*, vol. 75, no. 8, pp. 1567–1579, 2016.

[8] A. R. A. Anderson and M. A. J. Chaplain, "Continuous and discrete mathematical models of tumor-induced angiogenesis," *Bull. Math. Biol.*, vol. 60, no. 5, pp. 857–899, Sep. 1998.

[9] M. Saif *et al.*, "Pharmacokinetically guided dose adjustment of 5-fluorouracil: A rational approach to improving therapeutic outcomes," *J. Nat. Cancer Inst.*, vol. 101, no. 22, pp. 1543–1552, 2009.

[10] S. Baker *et al.*, "Role of body surface area in dosing of investigational anticancer agents in adults, 1991-2001," *J. Nat. Cancer Inst.*, vol. 94, no. 24, pp. 1822–1823, 2002.

[11] S. Kusama *et al.*, "The gross rates of growth of human mammary carcinoma," *Cancer*, vol. 30, no. 2, pp. 594–599, 1972.

[12] L. A. Norton, "Gompertzian model of human breast cancer growth," *Cancer Res.*, vol. 48, pp. 7067–7071, 1988.

[13] J. Steimer *et al.*, "Modelling the genesis and treatment of cancer: The potential role of physiologically based pharmacodynamics," *Eur. J. Cancer.*, vol. 46, no. 21–32, 2010.

[14] M. Simeoni *et al.*, "Predictive pharmacokinetic- pharmacodynamic modeling of tumor growth kinetics in xenograft models after administration of anticancer agents," *Cancer Res.*, vol. 64, pp. 1094–1101, 2004.

[15] P. Magni *et al.*, "A mathematical model to study the effects of drugs administration on tumor growth," *Math. Bio Sci.*, vol. 200, pp. 127–151, 2006.

[16] X. Li *et al.*, "A systems biology approach in therapeutic response study for different dosing regimens—A modeling study of drug effects on tumor growth using hybrid systems," *Cancer Informat.*, vol. 11, pp. 41–60, 2012.

[17] H. Lin and P. Antsaklis, "Stability and stabilizability of switched linear systems: A survey of recent results," *IEEE Trans. Autom. Control*, vol. 54, no. 2, pp. 308–322, Feb. 2009.

[18] D. Liberzon and A. Morse, "Benchmark problems in stability and design of switched systems," *IEEE Control Syst. Mag.*, vol. 19, no. 5, pp. 59–70, Oct. 1999.

[19] J. C. Geromel and P. Colaneri, "Stability and stabilization of continuous-time switched linear systems," *SIAM J. Control Optim.*, vol. 45, no. 5, pp. 1915–1930, 2006.

[20] W. O. Oduola *et al.*, "Analysis and control of genetic regulatory systems with switched drug inputs," in *Proc. 2016 IEEE-EMBS 3rd Int. Conf. Biomed. Health Informat.*, Feb. 2016, pp. 533–536.

[21] G. Zhai *et al.*, "Disturbance attenuation properties of time-controlled switched systems," *J. Franklin Inst.*, vol. 338, pp. 765–779, 2001.

[22] J. Brown *et al.*, "Aggregation effects and population-based dynamics as a source of therapy resistance in cancer," *IEEE Trans. Biomed. Eng.*, vol. 34, no. 3, pp. 512–518, Nov. 2016.

[23] E. Pefani *et al.*, "Chemotherapy drug scheduling for the induction treatment of patients with acute myeloid leukemia," *IEEE Trans. Biomed. Eng.*, vol. 61, no. 7, pp. 2049–2056, Jul. 2014.

[24] N. Emaminejad *et al.*, "Fusion of quantitative image and genomic biomarkers to improve prognosis assessment of early stage lung cancer patients," *IEEE Trans. Biomed. Eng.*, vol. 63, no. 5, pp. 1034–1043, May 2016.

[25] C. D. Santos *et al.*, "Effects of preset sequential administrations of sunitinib and everolimus on tumour differentiation in Caki-1 renal cell carcinoma," *Brit. J. Cancer*, vol. 112, no. 1, pp. 86–94, 2015.

[26] L. Galli *et al.*, "Phase II study of sequential chemotherapy with docetaxel-estramustine followed by mitoxantrone-prednisone in patients with advanced hormone-refractory prostate cancer," *Brit. J. Cancer*, vol. 97, no. 12, pp. 1613–1617, 2007.

[27] J. Y. Bruce *et al.*, "A phase I pharmacodynamic trial of sequential sunitinib with bevacizumab in patients with renal cell carcinoma and other advanced solid malignancies," *Cancer Chemotherapy Pharmacology*, vol. 73, no. 3, pp. 485–493, 2014.

[28] D. Miles *et al.*, "Combination versus sequential single-agent therapy in metastatic breast cancer," *Oncologist*, vol. 7, no. suppl. 6, pp. 13–19, 2002.

[29] A. Felici *et al.*, "Sequential therapy in metastatic clear cell renal carcinoma: TKI-TKI vs TKI-mTOR," *Expert Rev. Anticancer Therapy*, vol. 12, no. 12, pp. 1545–1557, 2012.

[30] W. O. Oduola *et al.*, "Time-based switching control of genetic regulatory networks: Toward sequential drug intake for cancer therapy," *Cancer Informat.*, vol. 16, pp. 1–11, 2017.

[31] X. L. Li *et al.*, "Integrating multiscale modeling with drug effects for cancer treatment," *Cancer Informat.*, vol. 5, pp. 21–31, 2016.