Multiscale Tumor Modeling with Drug PK/PD Profile Using Stochastic Hybrid System

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***Abstract*—Effective cancer treatment strategy requires an understanding of cancer behavior and development across multiple temporal and spatial scales. This has resulted into a growing interest in developing multiscale mathematical models that can simulate cancer growth, development and response to drug treatments. This study thus investigates multiscale tumor modeling that integrates drug pharmacokinetic and pharmacodynamic (PK/PD) information using stochastic hybrid system modeling framework. Specifically, (1) pathways modeled by differential equations are adopted for gene regulations at the molecular level; (2) A cellular automata is proposed for cellular scale; and (3) the multicellular scale model follows a transit compartment tumor model. Markov chains are used to model the cell behaviors by taking into account the gene expression levels, cell cycle and the microenvironment. The proposed model enables the prediction of tumor growth under given molecular properties, microenvironment conditions and drug PK/PD profile. Simulation results demonstrate the effectiveness of the proposed approach and the results agree with observed tumor behaviors.**

***Index Terms*— Multiscale Modeling, Stochastic Hybrid System, PK/PD, Genetic Regulatory Network, Drug Effect Modeling**

I. Introduction

The complexity and heterogeneity of cancer makes it highly difficult to develop effective cancer therapeutics. Mathematical models can help in designing effective cancer therapy and predicting cancer behavior in a more tractable, efficient and inexpensive manner [1]–[3]. There is an increasing interest in developing multiscale mathematical models that can simulate and predict cancer growth, development and response to drug treatments due to its potential for enabling patient-oriented predictions, treatment design, planning and drug delivery [4]–[9]. This is because cancer is a complex disease and its evolution cuts across multiple temporal and spatial biological scales. The spatiotemporal scales are characterized by processes ranging from reactions at the molecular scale to interactions within and among the cells, and to cancer growth, development and metastasis at the tissue level [10]. The multiscale and complex nature of cancer thus calls for modeling frameworks that are able to capture the molecular, cellular, tissue and organ level processes involved across the spatio-temporal scales adequately.

Recent studies have highlighted the significance of multiscale modeling to cancer behavior and treatment strategies. For instance, multi-cellular modeling of the growth and development of cancer through the alteration in the mechanical property of mutant cells has been investigated in [4]. It provides insights into how mutations affect the structures of cells and an approach for the inclusion of cell phenotypic properties with diverse mechanical features associated with Cellular Potts Models is given [4]. Yan $et\ al.$ [7] developed a 3D multiscale model to examine the progression of glioblastoma (GBM) by exploring tumor development under diverse microenvironment conditions. The effect of feedback among diverse types of cell and crosstalk between vascular endothelial cells and glioma stem cells were explored. A partial disruption of the crosstalk link results in tumor size reduction but does not increase the invasive potential. Thus, the crosstalk link may be exploited as a new therapeutic target for GBM therapy [7]. To show that telomerase inhibitions represses the rate of cell death detects and increases the cell senescent rate, a cell compartment approach was implemented to investigate the time-dependent and dose-based impacts of the anti-cancer agent (RHPS4) on the cancer cell lines HCT116 [8].

The dynamic behavior and phenotypic properties of a single tumor cell to an external therapeutic agent may be influenced by the cell's interaction with the diverse neighboring cells, hence, the effect of treatment(s) may deviate significantly from the expected outcome based solely on the individual cell's phenotypic features. Thus Brown $et\ al$ [9] investigated four beneficial and detrimental aggregation effects in cancer cell populations by applying the evolutionary and ecological concept to multiscale mathematical modeling while accounting for the relationships among diverse group of tumor cells. The model shows the importance of exploiting the detrimental aggregation effects in designing evolutionary-based drugs that can take advantage of the deleterious effects that neighbor cells might have on one another [9].

In cancer system modeling and drug therapeutics, it is vital to understand the response of the system to perturbations and how to obtain a desired effect via a modification to the system. For effective drug discovery and intervention, it is critical to have an understanding of the complex mapping between genotype and phenotype, an evaluation of the regulatory interaction among genes, proteins and other molecules and the effect of perturbations and other biological processes at the molecular, cellular, and tissue/organ scales [11]–[14]. Thus, it is imperative to have models that can predict and provide functional insights into disease-drug interactions and pharmacokinetics/ pharmacodynamics (PK/PK) information, to ensure that therapeutic intervention becomes a more systematic and faster process. A major challenge is linking drug PK characteristics with PD information for a better grasp of the time-course of drug effects after drug intake. Mathematical

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modeling [15] and simulation tools are indispensable in integrating PK/PD information and optimizing drug regimen. Thus this study presents a systematic and multiscale mathematical model to study drug effects under the assumption that the drug(s) target corresponds to a gene(s) or protein(s) in the proposed model [16], [17]. The goal is to investigate the system responses at various scales under drug perturbations and provide suggestion for effective therapeutic intervention.

The proposed multiscale model is highlighted in Fig. 1, where three scales are considered, namely, the molecular level, cellular level, and the tumor level. An Ordinary Differential Equation (ODE) pathway model is adopted at the molecular level, where the concentration of proteins and gene expression levels are treated as continuous values. Cellular automata of a 2D grid at the cellular level is used. Each individual cell is treated as a discrete entity, and cell fate is derived using a Markov chain. The transition probability of the Markov chain is determined by the downstream gene expression levels of the pathway of interest and the microenvironment (mE). The tumor model follows a transit compartment model with progressive degrees of decay from the surface to the core assuming a solid tumor. From the biological signal transduction perspective, biological signals and drug perturbation at the molecular scale trigger intra-cellular signaling in various pathways. At the cellular scale, the biological signals coupled with the cell cycle and microenvironment cues determine cell fate such as proliferation, apoptosis etc. At the multicellular scale, the population of cells and their behavior determines the structure and behavior of the resulting tumor.

The detailed model set up is discussed in Section II. Simulation studies are presented in Section III. Section IV presents additional discussions while Section V provides a conclusion to the paper.

II. Multiscale Model Formulation

Mathematical cancer models usually follow the discrete, continuous or hybrid modeling methods [18]. Discrete modeling approaches involve the explicit representation of individual cells for instance by using biological rules. Discrete modeling methods are usually based on the lattice-free modeling (Agent-based modeling (ABM)) or the lattice-based modeling (Cellular automata (CA)) approaches [19]–[21]. These techniques have the capability to describe the evolving population-level dynamics without prior knowledge of tumor behaviors.

Continuous mathematical models describe the large-scale tumor growth dynamics by treating the tumor size as a continuous medium instead of the resolutions of individual cells. Hybrid modeling approaches involve the integration of both the continuous and discrete entities used to describe the concentrations or density fields and the individual cells respectively. Continuum mathematical modeling methods are commonly based on ordinary and partial differential equations. These modeling methods have the ability to describe the common behaviors of tumors, simulate experimental observations and recommend modification as well as test theoretical hypotheses.

Hybrid models combine the strengths of both continuous and discrete modeling approaches. Stochastic hybrid system

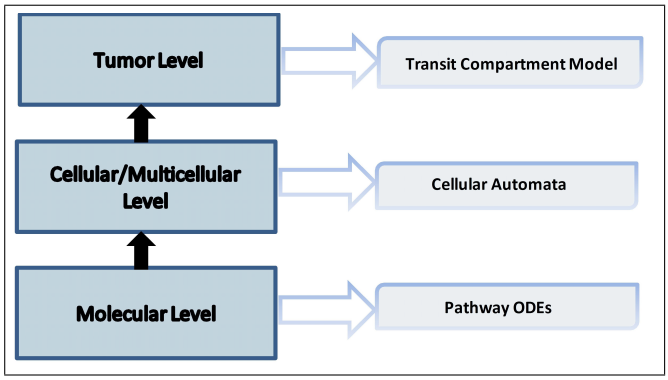

Fig. 1. The schematics of the proposed multiscale model.

can also model randomness that may be inherent to the system being modeled. In this work, stochastic hybrid modeling method is proposed to integrate randomness and exploit the advantages of both the discrete and the continuous modeling frameworks to stochastically simulate the behavior of the tumor cells [6], [7].

Since cancer tumor cells divide uninhibitedly and they often grow and develop with the goal of optimizing their proliferation potentials, they are categorized as proliferating, quiescent, or decaying/dead in the proposed model. It is assumed that each proliferating cell from the cancer cell population may produce daughter cells with similar kinetic characteristics when the cell cycle and microenvironment permit. It is also assumed that cancer tumor cells will go through a series of decay until dead when damaged.

A. Molecular Level: Proliferation and Survival Pathway Modeling

In this study, the proliferation and survival pathway (see Fig. 2 and Table I) are considered. The RAS/RAF/MEK/ERK pathway is usually associated with cell proliferation, prevention of programmed cell death, and resistance to therapies. This pathway is exploited by growth factors and mitogens in transmitting signal(s) from the receptors for regulating gene expression and preventing apoptosis or programmed cell death. Some of the proliferation pathway's components (for instance, RAS, B-RAF) undergo mutations or over-expressions in human cancer (for instance, breast and prostate cancers) [24]. On the other hand, PI3K/AKT/mTOR pathway signifies a proto-typical survival pathway which is activated in various types of cancer. The pathway is usually activated by diverse processes some of which include mutations or amplifications of the PI3K, loss of the tumor suppressor (PTEN) function, activations of the growth factor receptors, amplifications or mutations of AKT, exposure to carcinogen and so on. After it is activated, signaling through AKT may propagate to various array of substrates, that includes mTOR, a crucial regulator of protein translation. The survival pathway functions as an appealing drug target for cancer therapy because it serves as a point of convergence for various growth stimuli. It is equally responsible for the regulation of cellular processes that contribute to cancer growth and development via the downstream

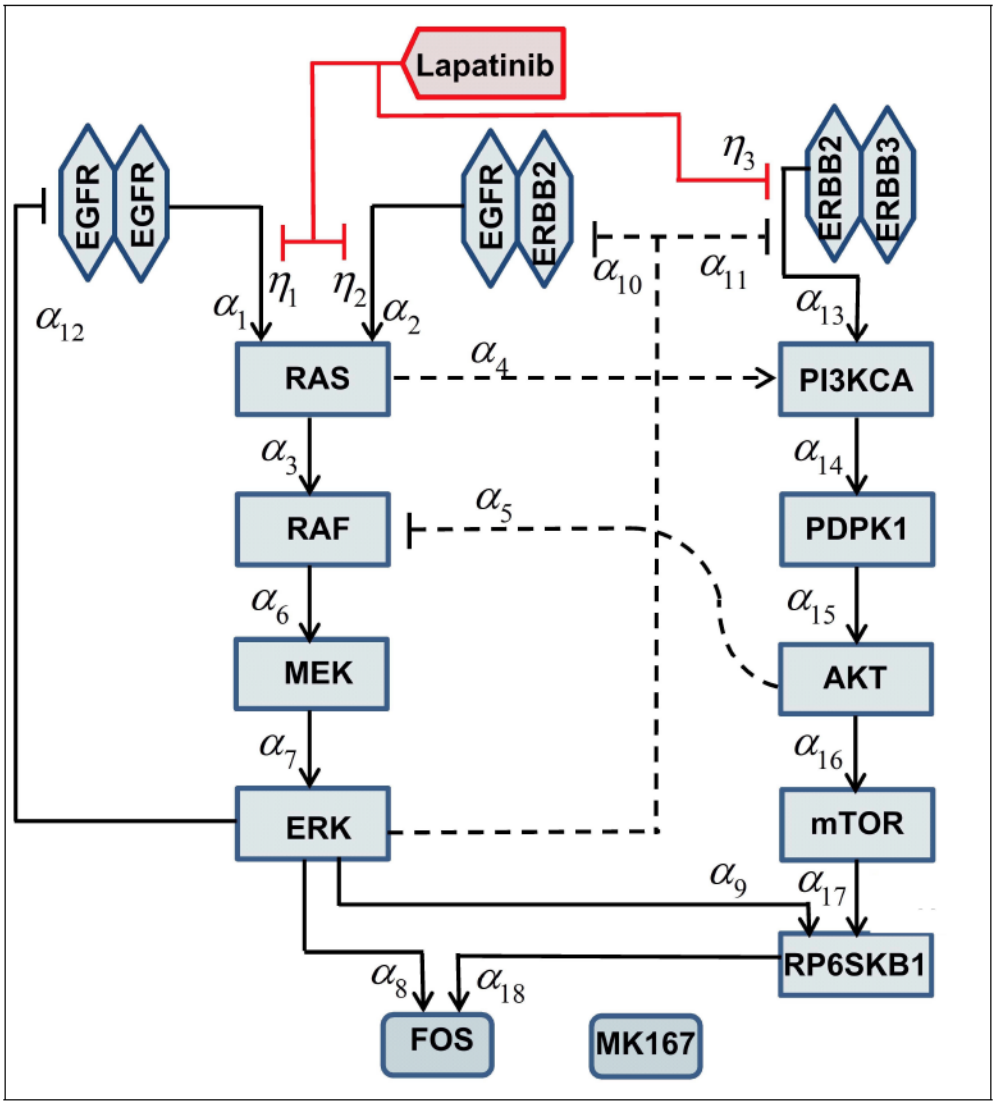

Fig. 2. The proliferation and survival pathways used in the model [22].

TABLE I

NOTATIONS AND PATHWAY EQUATIONS/DYNAMICS (η_{drug1}, η_{drug2}, AND η_{drug3} REPRESENT COEFFICIENTS DUE TO DRUG LAPATINIB APPLIED TO DIFFERENT PROTEINS/COMPLEXES [22], [23].)

Variable	Protein or Complex	Pathway Dynamics
y(1)	EGFR2	$\frac{dy(1)}{dt} = \beta_1[EGFR][EGFR] \quad \alpha_1 y(1)\eta_{drug1}S \quad \alpha_{12}y(7)$
y(2)	EGFR+ERBB2	$\frac{dy(2)}{dt} = \beta_2[EGFR][ERBB2] \quad \alpha_2 y(2)\eta_{drug2}S \quad \alpha_{10}y(7)$
y(3)	ERBB2+ERBB3	$\frac{dy(3)}{dt} = \beta_3[ERBB2][ERBB3] \quad \alpha_{13}y(3)\eta_{drug3}S \quad \alpha_{11}y(7)$
y(4)	RAS	$\frac{dy(4)}{dt} = \alpha_1 y(1)\eta_{drug1}S + \alpha_2 y(2)\eta_{drug2}S \quad \alpha_3 y(4) \quad \alpha_4 y(4)$
y(5)	RAF	$\frac{dy(5)}{dt} = \alpha_3 y(4) \quad \alpha_5 y(10) \quad \alpha_6 y(5)$
y(6)	MEK	$\frac{dy(6)}{dt} = \alpha_6 y(5) \quad \alpha_7 y(6)$
y(7)	ERK	$\frac{dy(7)}{dt} = \alpha_7 y(6) \quad \alpha_8 y(7) \quad \alpha_9 y(7) \quad \alpha_{10} y(7) \quad \alpha_{11} y(7) \quad \alpha_{12} y(7)$
y(8)	PI3K	$\frac{dy(8)}{dt} = \alpha_{13}y(3)\eta_{drug3}S \quad \alpha_{14}y(8) + \alpha_4 y(4)$
y(9)	PDPK1	$\frac{dy(9)}{dt} = \alpha_{14}y(8) \quad \alpha_{15}y(9)$
y(10)	AKT	$\frac{dy(10)}{dt} = \alpha_{15}y(9) \quad \alpha_5 y(10) \quad \alpha_{16}y(10)$
y(11)	mTOR	$\frac{dy(11)}{dt} = \alpha_{16}y(10) \quad \alpha_{17}y(11)\eta_6 S$
y(12)	RP6SKB1	$\frac{dy(12)}{dt} = \alpha_{17}y(11) + \alpha_9 y(7) \quad \alpha_{18}y(12)$
y(13)	FOS	$\frac{dy(13)}{dt} = \alpha_8 y(7) + \alpha_{18}y(12) \quad \alpha_{19}y(13)$
$\eta_{drugi}S$	drug coeff.	$\eta_{drugi}S = \begin{cases} 1 & \text{Drug is not present} \\ \eta_{drugi} & \text{Drug is present} \quad \text{i=1,2,3} \end{cases}$

substrates. Additionally, activation of the AKT/mTOR pathway bolsters resistances to many cancer treatment approaches, and it thus constitutes one of the poor prognostic factors for several types of cancer [25].

Genetic regulation in a pathway with drug perturbation can be modeled with rate equations that express the differences between production and degradation rates [11], [26] as follows

$$\begin{cases} \dot{x}_i = \alpha_j x_j - \alpha_i x_i, & \textit{switch is off.} \\ \dot{x}_i = \alpha_j x_j \eta_{drug} - \alpha_i x_i, & \textit{switch is on} \end{cases} \quad (1)$$

where x_i and x_j represent gene (protein) expression levels, $\alpha_j > 0$ is a synthesis factor and $\alpha_i > 0$ is a degradation factor. η_{drug} represents the drug-effect factor which is determined by the pharmacological model of the drug input. The state of the switch depends on the drug perturbation.

Using the rate equations, the proliferation and survival pathways that biologists currently understand, for example the Kegg collection of pathways (http://www.genome.jp/kegg/pathways.html) and the NIH BioCarta pathway collections (https://cgap.nci.nih.gov/Pathways/BioCarta_Pathways), are illustrated in Fig.2 as well as Table I [22], [23], [27]. For our model set up, Table I provides the pathway dynamics (following equation(1)) for the proteins and complexes together with input from drug Lapatinib [22]. The expected effect of the drug (Lapatinib) is the suppression of the pathway, that is, reducing the concentration level of ERK and thus preventing the tumor cells from proliferation. It is expected that the lower the ERK concentration level, the more effective the drug is and the lower the number of proliferating cells.

B. Pharmacokinetics(PK) and Pharmacodynamics(PD) model

Pharmacokinetics describes the drug dose concentration-time response, i.e., how the drug is absorbed, distributed, metabolized and excreted, while pharmacodynamics describes the concentration-response of drug effects [1]. Our model includes a drug-effect factor η_{drug} in equation (1) and Table I that is related to the time course of drug effects (PK/PD) after drug perturbation (i.e. η_{drug} links PK and PD as described in the following sections). An integrated PK and PD model is vital in adequately describing the time course of drug effects since such model bridges between a pair of classical topics in pharmacology [28].

1) **The PK model:** The concentration of the drug at the effect site is vital for the pharmacological effect of the drug. As illustrated by Kuh *et al.* [29], the drug's intra-cellular concentrations increase exponentially when the drug is absorbed following each intake of the drug. The concentration of the drug may change slowly (this is approximated as a flat line in our model) when the drug's intra-cellular and extra-cellular concentrations approach equilibrium. Then the concentration decreases exponentially as the drug elimination rate is higher than the rate of entering the effect site, resulting in diminishing effects. According to Kuh *et al.* [29], a widely used modeling curve for the concentration-time profile of the drug is shown in Fig. 3. The proposed modeling approach

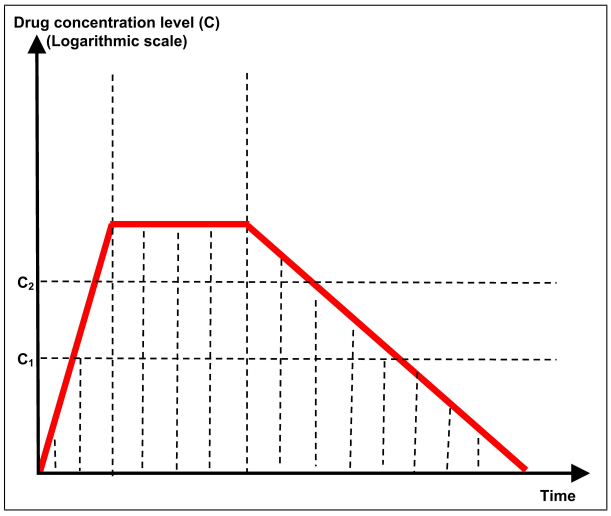

Fig. 3. The PK model: drug concentration versus time profile (in log scale).

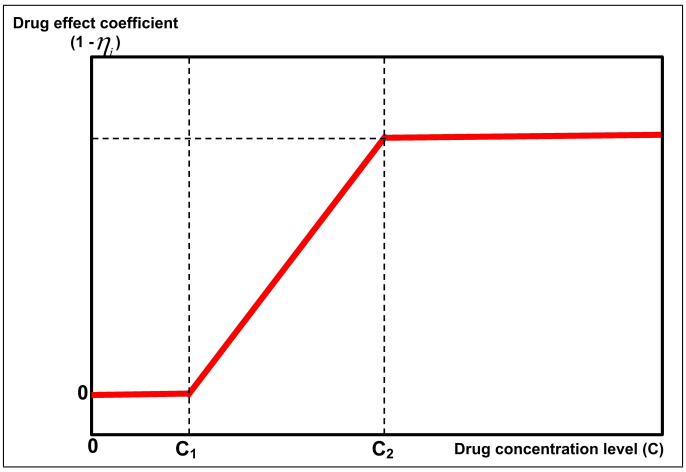

Fig. 4. The PD model: drug concentration-response characteristics.

is generalized enough to handle diverse cases even though different drugs function differently. The concentration increase stage may be ignored if the drug concentration increases very rapidly, or the equilibrium phase may be neglected if it is very short. By adjustment of the model's parameters, one can represent specific drug characteristic.

2) **The PD model:** Generally, drug pharmacological effect magnitude is directly proportional to the dose before it eventually reaches saturation [30]. The most widely used concentration response model is the logistic model or the Hill equation, equally referred to as the sigmoidal E_{max} model [31]. It is assumed in our model that the drug effect coefficient η_{drug} (where the drug target is x_j according to equation(1)) relates to the concentration via a sigmoidal function approximated by the plot in Fig. 4, where the drugs only begin to be effective after the concentration level exceeds a lower threshold (C_1) and the effect of the drug reaches saturation after the concentration level rises above an upper threshold (C_2).

C. Cellular/Multicellular Level

A cellular automata model is proposed at the cellular level in an $N \times N$ grid to describe the intracellular and intercellular interactions among the cells, drug profile and the microenvironment (mE) conditions. Specifically, It is assumed that each cell is in one of the states at a given time. For each cell, the gene expression levels and the microenvironment conditions such as nutrients and the number and types of neighboring cells, as well as the current cell states and cell cycle determine the transition probabilities in the proposed Markov chain as shown in Fig. 5. For instance, If [ERK] is above a threshold, it is expected that P_{12} and P_{22} will be high since high ERK concentration implies that more cells are expected to be in a proliferating state. It is assumed that once a cell enters the decaying state, it will never transition back to the quiescent or proliferating state and it is eventually dead based on the progressive degree of decay from the transit compartment model [32], [33]. Proliferation of cells potentially increase the number of cells in the grid. It results in a cell duplicating into a pair of similar offspring cells. The proliferating cells with a good microenvironment condition search for an empty space to deliver their offspring. Since each grid site may be occupied by a single cell, one offspring cell resides in the mother's grid site and the second is situated in the empty grid site comprising the Moore neighborhood of the mother [34]. The procedures for simulating the above process is illustrated in Algorithm 1.

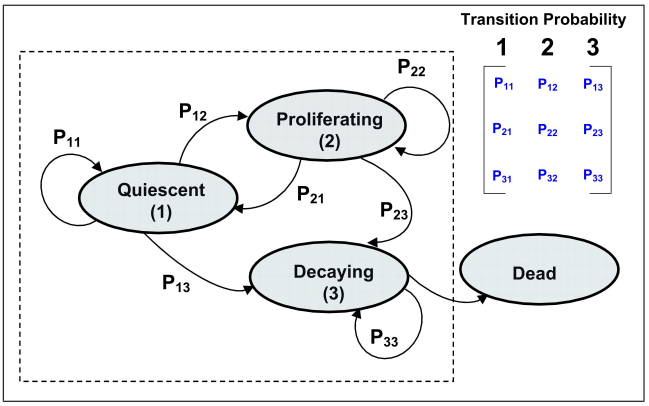

Fig. 5. The proposed Markov chain where the transition probability is a function of the expression level of ERK, cell cycle, and the microenvironment.

Algorithm 1 : Procedures for simulating the phenotypic decision process for cancer cells

Input: Pathway parameters, drug dosage, initial transition probabilities P_{ij}, initial number of cells, initial gene expression levels
Output: Cell phenotype, percent of non-proliferating cells
for *each observation interval* $(t = t_i)$ **do**
  for each cell **do**
    Get $\eta_{drug}(t_i)$ from drug PK/PD curve
    Solve pathway ODEs and obtain [ERK]
    if ([ERK] $\geq$[ERK]$_{threshold}$) **then**
      adjust P_{ij}
      Sample Markov chain
      $Cell\ phenotype \leftarrow state\ of\ markov\ chain$
    end if
    if $Cell\ phenotype \leftarrow Proliferating$ **then**
      if $mE \leftarrow Good$ & $Space \leftarrow empty$ **then**
        Add new cell
      end if
    end if
return Number of cells

III. Simulation Results

Simulations have been performed in MATLAB using the proposed model. The simulations incorporate a baseline run of the pathway equations by following the procedures in Algorithm 1. Three scenarios have been simulated using the proposed model, namely, with no drug input, low dose drug input, and high dose drug input. The output results correspond to the time series data of the number and type of cells as well as the state of each individual cell.

As a solid tumor grows and develops, the cells at the core of the tumor may often be starved of nutrients and thus become dead cells (Fig. 6) which are the typical characteristic of solid tumors. Taking into account the typical duration of the cell cycle (about 24 hours) [35], [36] and the effective drug half-life (approximately 24 hours for Lapatinib) [37], the Markov chain of cell state is sampled in about every 10-hour interval divided into time slots of one hour each. The growth patterns of the cells can be observed in Fig. 6 from the snapshots of spatial and temporal evolutions of cancer cells with different inputs, namely, no drug perturbation and with drug administration (low dose and high dose). Simulation depicts a tumor having a necrotic core that is surrounded by cells in quiescent or proliferating state. Under periodic drug intake with high dose, the constant drug concentration in plasma is high enough to cause the drug PD value falling into the effective region. In contrast, the drug being administered periodically at low dose causes the drug PD value to fall in the ineffective range. Thus, the growth of cancer cells is repressed under high dose drug administration (Fig. 6C) as compared with the case with low dose drug administration (Fig. 6B) where limited drug effect is observed, although it is better than the case of no drug input given in Fig. 6A. This demonstrates that the administered drug being effective in inhibiting the proliferation pathway indicated by the expression level of ERK. The spatial and temporal patterns in Fig. 6 depict a tumor having a compact shape and a boundary that is irregular, as it has been observed in some solid tumors [21].

Fig. 7 shows the evolution of the different cell types with and without drug intakes. It is observed that the proliferating cell population grow exponentially when they are not exposed to any drug (Fig. 7A). When the drug intake has low dose, proliferating cell population will still grow (Fig. 7B) since the drug PD value falls in the ineffective range. It is also shown that cancer cell proliferation happens at a much greater speed in comparison with tumor cell death when there is no drug administered or when the administered dose is too low. With a

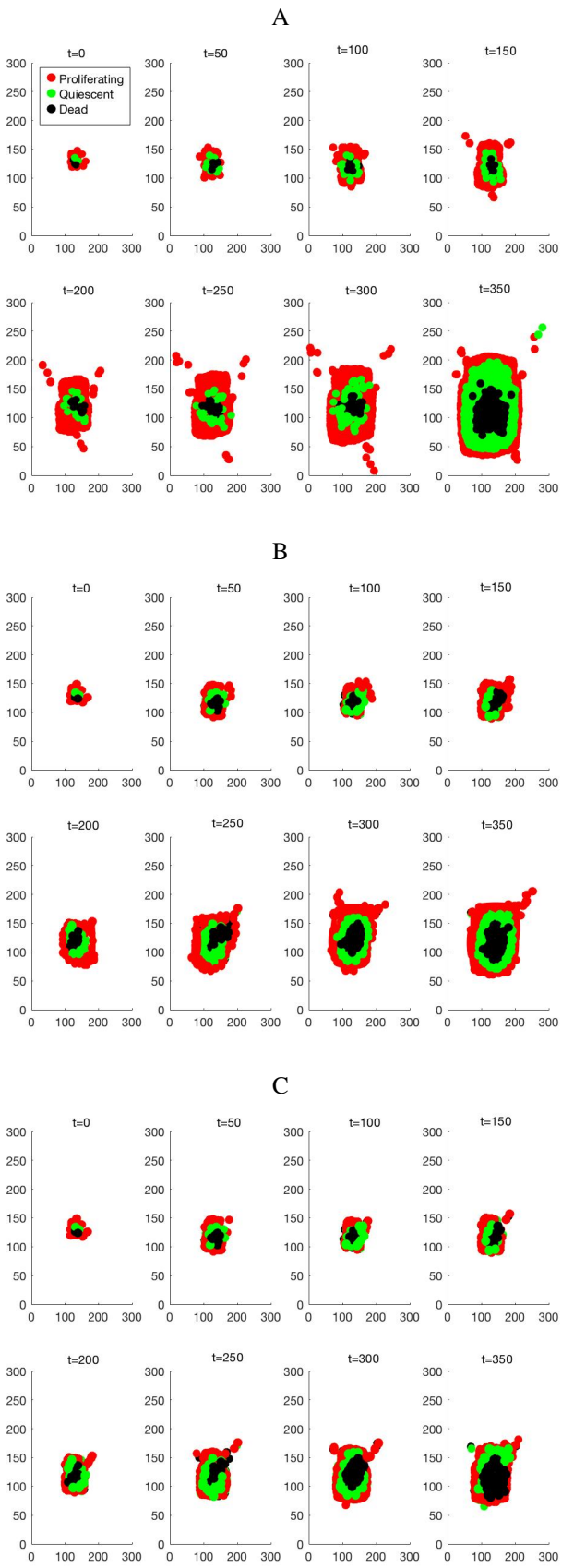

Fig. 6. Growth patterns of the cancer cells after 50, 100, 150, 200, 250, 300 and 350 iterations. Snapshots of spatial and temporal evolutions of cancer cells are given for (A) with no drug perturbation; (B) with low dose drug intake; (C) with high dose drug intake.

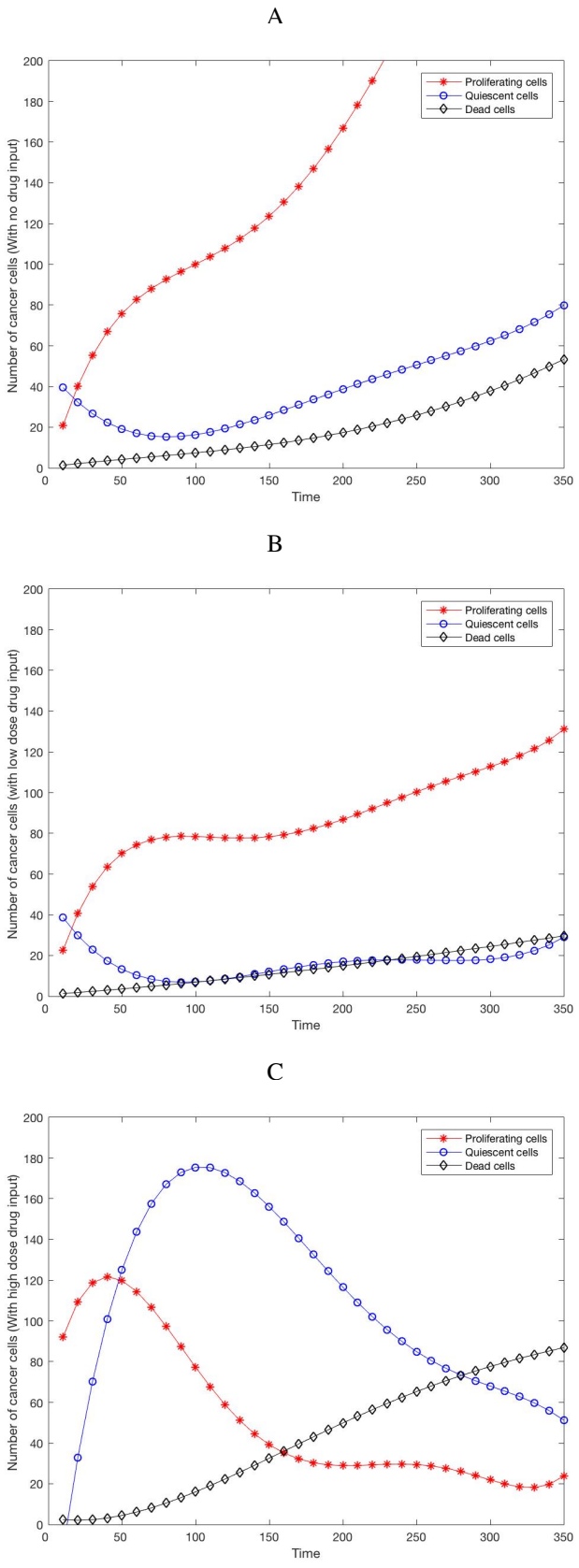

Fig. 7. Dynamic evolution of proliferating, quiescent and dead cells (A) with no drug administration (B) with lower dose drug administration (C) with high dose drug perturbation.

high dose drug intake, an initial warm-up period is observed in Fig. 7C given the drug's PK, then the number of proliferating cells starts to go down after the drug effect kicks in, i.e., the constant drug concentration in plasma is high enough to eventually cause the drug PD value fall within the effective region. Fig. 7C also shows that the cancer cell proliferation initially happens at a much greater speed than that of tumor cell death, then the trend is reversed as the drug becomes more effective in repressing the proliferating cells. Overall, the results show that gene(s) or protein(s) network perturbation by drug at the sub-cellular level manifests as functional changes at the inter-cellular and tumor scales.

IV. Discussions

Mathematical models are increasingly being used in the area of quantitative multiscale cancer modeling. Although several modeling approaches have been explored in the literature, the actual bio-systems are far more complex to the point that current available computational tools are not able to sufficiently describe all the details. In addition, such mathematical models are usually computationally demanding and should therefore be designed in a way that maintains a balance between model complexity and mathematical tractability or simplicity with the aid of clinical or experimental data. In modeling such type of integrated systems and experimental modeling method, associated challenges that researchers may encounter includes availability of pertinent biomedical/experimental data, model validation, estimation of model parameters, uncertainty and sensitivity analyses, variable choice for model inclusions and access to data standards facilitating sharing of results and information [38]. Access to proven biomedical or experimental data, model validation against *in vivo* experiments and high-level innovative mathematical and simulation tools may help to mitigate some of the challenges.

To limit the complexity of the model and to focus primarily on system modeling, we have not incorporated processes such as angiogenesis, vascularization, cell heterogeneity, drug resistance, 3D tumor morphology and several other biological and biochemical mechanisms into the proposed model. There have been many studies integrating some of these processes into multiscale tumor models and interested readers may refer to [6], [39]–[42]. However, many existing models do not usually integrate the relevant and detailed modeling of the regulatory networks or signaling pathways and the drug pharmacology information. The proposed model is simulated on a fixed grid size for the sake of simplicity and in the case of real cells, the regulation and interaction processes are much more complicated since several hundreds of biochemical reactions occur in the cells. The proposed multiscale model is conceptual and the model parameters are not directly estimated from clinical/experiment data. They are obtained based on general understanding of tumor behavior and via literature search. Availability of various clinical or *in vivo* data and assays (for instance, drug delivery and metabolism data) may help improve the prediction accuracy of the model. For a more realistic application towards precision medicine, future work on the model could incorporate detailed descriptions of some of these processes and the dynamic changes in

tissue morphology resulting from the evolutionary competition among the cells.

V. Conclusions

This study has proposed a multiscale mathematical model depicting the dynamics of cancer cell population with different drug perturbations. The model has been implemented at the sub-cellular, cellular and multicellular hierarchical levels. It is shown by simulations that the tumor cell population typically grow exponentially when they are not exposed to anti-cancer drug or low dosage of drugs, while the growth of tumor cells is repressed with high dose of drugs. The proposed multiscale model could provide vital insight into tumor growth, development and therapeutic strategies while taking into account specific PK/PD profiles and genetic pathway information. As further experimental/biomedical data becomes available, the model parameters could be better refined, estimated and calibrated. Additional study is needed to extend the modeling approach to describe cancer cells in primary cultures and tumor tissues. This may provide further insights into the growth dynamics and response to drug-treatments of cancer cell population *in vivo*.

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