Review

Cancer systems biology and modeling: Microscopic scale and multiscale approaches

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ARTICLE INFO

Keywords:
Cancer
Systems biology
Multiscale modeling
Cell proliferation and survival

ABSTRACT

Cancer has become known as a complex and systematic disease on macroscopic, mesoscopic and microscopic scales. Systems biology employs state-of-the-art computational theories and high-throughput experimental data to model and simulate complex biological procedures such as cancer, which involves genetic and epigenetic, in addition to intracellular and extracellular complex interaction networks. In this paper, different systems biology modeling techniques such as systems of differential equations, stochastic methods, Boolean networks, Petri nets, cellular automata methods and agent-based systems are concisely discussed. We have compared the mentioned formalisms and tried to address the span of applicability they can bear on emerging cancer modeling and simulation approaches. Different scales of cancer modeling, namely, microscopic, mesoscopic and macroscopic scales are explained followed by an illustration of angiogenesis in microscopic scale of the cancer modeling. Then, the modeling of cancer cell proliferation and survival are examined on a microscopic scale and the modeling of multiscale tumor growth is explained along with its advantages.

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1. Introduction

Cancer is a disease mainly derived from mutations in single somatic cells that deviate from the normal routes of proliferation, migrate to adjacent normal tissues, and end in secondary tumors (metastasis) on sites different from the initial origin. In human beings, cancer refers to at least 100 versions of a disease that can develop in almost any tissue in the body. Despite the fact that each cancer type has unique attributes, all these different tumors evolve according to a common scheme of progression that includes genetic and epigenetic incidents in addition to a complex network of interactions between cells and the extracellular matrix in the host tissue. Cancerous cells communicate with their micro-environment in a way that can promote their growth, survival and the manifestation of distant metastasis [1].

Successful treatments for cancer stems from an iterative process that depends on experimental research advances as well as feedback from clinical trials in which it is feasible to learn whether fundamental ideas and related theoretical and biological models are demonstrating a therapeutic benefit [2]. Due to the complexity of biological systems it is hard to merely rely on experimental observations in order to predict the behavior of such systems [3]. Therefore, an increased use of mathematical modeling to understand tumor progression, directs the design of new experiments by introducing likely candidates for further clinical investigation, and presents novel approaches to cancer therapy. Consequently, it is necessary to generate appropriate models for simulation purposes [3]. Models are based on various levels of abstraction, for instance to represent DNA, Protein or RNA, the sequences of predefined letters are used. Chemical structures are depicted as graphs and complex protein structures are represented by graph-theoretical descriptions [4,5]. For network depiction, wireframe graphs are used. Such graphs are differentiated using various definitions of vertices, edges and corresponding labels. For dynamic properties, mathematical theorems are used at distinct levels of abstraction. In this regard logical formalisms are usually used for Boolean modeling, differential equations are often applied for continuous properties, discrete formalisms are utilized for Petri net modeling and stochastic principles are mainly employed to deal with the stochastic properties of chemical reaction networks.

http://dx.doi.org/10.1016/j.semcan.2014.03.003
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Recently, data-driven cancer modeling has emerged as an important field in cancer research [6,7]. Especially, some of the current cancer models that include an array of different time-space scales, i.e. multiscale cancer models have become in the limelight. This is mainly because such multiscale models are capable of using diverse patient data to make exclusive predictions for each patient [8]. From another angle of view, such formalisms are divided into two main categories. A bottom-up (bottom–top) approach investigates the constituent elements to prepare the necessary foundation to predict the whole system behavior. The bottom-up formalisms are appropriate to simulate cancer-related traits caused by cell–host and cell–cell interactions including signaling pathways [9]. Conversely, a top-down approach tries to propose detailed explanations on an observed behavior or characteristic [10].

2. Modeling algorithms

Biological pathways are naturally versatile. To understand the interactions of these pathways, beside the need for the identification of the constituent elements and their interactions, we also need to know how their dynamics evolve over the time. Different modeling and simulation techniques used in systems biology are the systems of differential equations, stochastic methods, Boolean networks, Petri nets, π-calculus, cellular automata methods, agent-based systems, and hybrid approaches.

Methodologies for computational analysis encompass a wide range depending on the problem to be dealt and the experimental data at hand, ranging from highly abstracted models generated by correlative regression to highly deterministic models on the basis of differential equations. Network component interaction and logic modeling techniques lie between the ones mentioned above [11]. Main modeling formalisms are briefly explained below.

3. Petri nets

Petri nets denote a refinement of monopartite graph models to bipartite directed graphs that are employed to model concurrent causal systems. This formalism has been satisfactorily applied in many areas of biology, e.g. to simulate metabolic networks [12–15], signal transduction pathways [16] and also gene regulatory systems [17,18]. The pivotal ideas in Petri nets are the consecutive distinction between active and passive nodes and the utilization of discrete movable objects to define system’s dynamics. The set of nodes includes places for the passive part, indicating biochemical species, and transitions as the active part, denoting chemical reactions. The movable objects are named tokens. According to firing rules, tokens are transferred by means of the PN from one place to another. Originally, PNs were limited to qualitative simulation within discrete time steps. However, advanced PNs are capable of mimicking Boolean, timed-discrete [19], Bayesian, Fuzzy [20], stochastic [21–23], continuous systems of ordinary differential equations [24], and even hybrid systems [25,26].

4. Bayesian networks

Another computational formalism for modeling, based on a graph representation, is Bayesian network (BNs). Bayesian networks that describe both direct and indirect pathway interactions in terms of stochastic influences of specific components on other components, have been proved useful for disclosing the operation of cell signaling networks but has not been widely applied to cancer biology problems [27]. Bayesian modeling is beneficial because biology is intricate and biological data are accompanied with noise. Bayesian network models explain the effects of pathway elements upon each other in an influence diagram format. Boolean networks can only manage discrete values, however, the Bayesian formalism can handle continuous values as well. In Bayesian network, a node denotes a random variable for the conditional probability distribution of each pathway element. Bayesian modeling provides the possibility to describe stochastic processes and to handle uncertainty, incomplete knowledge and also noisy observations. In such networks, restrictions are the static and the acyclic nature of Bayesian networks [28]. In BNs, the relationships between variables, e.g. proteins and genes are represented by conditional probability distributions (CPDs) of the form \( p(G_j|G_i) \), i.e. the probability of \( G_j \) given \( G_i \). Regarding discrete variables, probability distributions are represented as conditional probability tables (CPTs) including probabilities that are the model parameters. For BNs using continuous variables, conditional probability densities are used in a similar manner as CPTs [29].

5. Cellular automata

Cellular automata (CA) is a discrete dynamical system that means time, space and the space of the system are discrete. Any point assumed in a regular spatial lattice, i.e. a cell, may have each one of a finite number of states. The states of the cells in the mentioned lattice are updated in accordance with a local rule. In other words, the state of a cell at a particular time is merely dependent on its own state and the states of its nearby neighbors at the previous time step. Every cell on the lattice is updated synchronously.

Extensive studies of CA have been carried out by S. Wolfram commencing in the 1980s [30]. Use of CA in biology is primarily focused on systems biology subjects, such as shape space simulations of the immune system [31], artificial brain development [32], the study of morphogenesis in simple cellular systems [33], modeling the competitive growth of two underwater species Chara aspera and Potamogeton pectinatus [34] and the modeling of an enzymatic reaction [35].

Additionally, there is another type of CA, named Dynamic CA (DCA), which varies from conventional CA in that the DCA model tries to simulate real motions by using Brownian dynamics [36], that is to say, the motions of particles are intended to imitate the motions found in real macromolecules. Consequently, random objects cannot be taken up and randomly scattered over the lattice in each time step as they are in the majority of CA models. Instead, DCA needs regular time steps in which the lattice size and time steps could be small enough to fulfill physical laws or experimentally measured parameters such as diffusion rates.

6. Multi-agent systems

An agent is an interactive computer system, which is put in some environment conditions and is autonomously able to perform in such conditions to satisfy its design objectives. Agents are autonomous and interactive entities and may be mobile. They have the potentiality for adaptation and learning. Multi-agent systems (MAS) are a set of agents that undergo interactions in a certain dynamic environment. A comprehensive introduction to MAS can be found in [37]. MASs are able to handle the complexity of solutions through modeling, decomposition and managing the interrelationships between components [38]. Multi-agent systems yield abstractions that facilitate the decomposition of a biological system to a set of agents; multi–agent systems are inherently powerful tools when it comes to modeling complex systems [38]. Modeling complex systems necessitates a profound understanding of the system both regarding its structure and its behavior.
7. Ordinary differential equations

One of the most ubiquitously used formalisms for modeling biological systems is based on ODEs. A differential equation is defined as an equation declaring the relationship between a function and some of the first or higher order derivatives of it. Basically, a differential equation defines how a variable, such as the initial concentration of a substance, changes by the passing of time. This happens through interrelating the rates of changes with respect to the simultaneous concentrations [39–42].

Regarding signal transduction network models, analytical methods indicate the more realistic moiety of the model spectrum. The mentioned models involve nonlinear systems of ordinary differential equations, where each variable represents the concentration of a certain gene product [43]. As an instance, assume the succeeding reaction in which the product $P_1$ is produced: $\varnothing \xrightarrow{k_1} P_1$. This ordinary reaction does not include any catalyst and can be modeled by using mass action kinetics. Mass action describes the behavior of reactants and products in a simple chemical reaction. Mass action kinetics explains such a behavior through an equation by which the rate of a chemical reaction is directly kept in proportion to the concentrations of the reactants, where $k_1$ symbolizes the reaction rate constant. The above reaction is called a zero-order reaction. In a first-order reaction, the reaction rates are proportional to the concentration of one reactant, here $S$. As an example, assume the reaction below in which the substrate $S$ is changed into the product $P$: $S \xrightarrow{k_2} P_2$. The reaction rate goes on as follows: $v = k_2[S]$. It is clear that the reaction rate $v$ is directly proportional to some factors such as $[S]$, i.e. the more the concentration of the $S$, the higher the reaction rate. According to the mentioned equation, it should not be difficult to present differential equations to define the rate of change in $[S_1]$ and $[P_2]$: $d[S_1]/dt = -k_3[S_1]; d[P_2]/dt = k_3[S_1]$. In order to model and simulate reactions, it is indispensable to know substrates’ and products’ initial concentrations. A second-order reaction is proportional to the square of the concentrations of an individual reactant or both reactants. It is possible to model reversible reactions by two specific reactions or by one reaction. For example: $A + B \xrightarrow{k_3} C$. The reaction rate of $C$ production is: $v = k_3[A][B] - k_2[C]$, where $k_3$ denotes the rate constant of the forward direction and $k_2$ is related to the reverse one. The above enzymatic reaction rate, with respect to the Michaelis–Menten equation is: $v = V_{max}[S]/(K_m + [S])$, where $[S]$ presents the concentration of substrate, $V_{max}$ denotes the maximum rate. The Michaelis constant $K_m$ indicates the substrate concentration at which the reaction rate approaches half the $V_{max}$ [44]. Different models which are usually employed in the literature can be classified from the calculus point of view: ordinary differential equations (ODEs) [44], delay differential equations (DDEs), Fredholm integral equations (FIES) (in the estimation of parameter problem), stochastic differential equations (SDEs), partial differential equations (PDEs) and integro-differential equations (IDEs) [45]. Different software packages can be applied for different types of models for simulations and numerical analysis. Table 1 illustrates some of the systems biology simulation tools concisely.

8. Cancer modeling

Tumors are notable examples of complex systems that can undergo self-organization. Because of their intrinsic complexity, it is essential to analyze their growth at different scales. It involves a number of phenomena that take place over a variety of spatial scales encompassing from tissue (for instance, tissue invasion and angiogenesis) up to molecular length scales (for example, gene silencing, mutations and signal transduction). The timescales range from seconds for signaling to years for prostate cancer.

The complexity of cancer development expresses itself at least in three scales that can be distinguished and described using mathematical models, namely, microscopic, mesoscopic and macroscopic scales [46] as described further below:

- 1) The microscopic scale represents molecular and sub-cellular phenomena taking place within the cell or at its plasma membrane. Instances are gene mutations or modifications in gene expression patterns, variations of signaling cascades and/or metabolic pathways, cytoskeleton rearrangements and altered membrane activities, protein traffic within the cell, cell cycle progression and the control of the cell cycle, etc. Biological networks can be categorized into four main types: Metabolic networks, gene regulatory networks (GRN), protein–protein interaction (PPI) networks and signal transduction networks. Metabolic networks are applied to describe the basic biochemistry in a cell. Biologically important reactions have been explained in terms of reaction pathways catalyzed by enzymes, and metabolic networks are systematic collections of such biochemical data. The metabolic process can be defined as a repertoire of biochemical transformations ending in the consumption as well as the production of one or more metabolites [47]. GRNs are characterized as directed graphs. They involve

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<tr>
<th>Name</th>
<th>Category</th>
<th>Model representation</th>
<th>Function</th>
<th>URL</th>
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<tbody>
<tr>
<td>MATLAB, with SimBiologyToolbox</td>
<td>Continuous and stochastic</td>
<td>Mathematical (e.g. ODE)</td>
<td>General-purpose mathematical environments, simulation and analysis</td>
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<td>Continuous and stochastic</td>
<td>ODE</td>
<td>General purpose; simulation, analysis</td>
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<td>Continuous and stochastic</td>
<td>ODE</td>
<td>Simulation and analysis</td>
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</tr>
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<td>Systems Biology Worldbench, including Jarnac and Designer</td>
<td>Discrete, continuous and stochastic</td>
<td>ODE/SBML</td>
<td>Data-exchange framework for modeling, simulation and analysis</td>
<td>sbw.kgi.edu</td>
</tr>
<tr>
<td>E-CELL</td>
<td>Continuous</td>
<td>Graphical, ODE-based</td>
<td>Modeling and simulation</td>
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<td>Stochastic</td>
<td>Object-oriented</td>
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<td>Discrete and continuous</td>
<td>Logical + kinetic models</td>
<td>Reasoning, hypothesis testing</td>
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<td>General purpose; Analysis</td>
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interrelated genes by directed edges in such way that one gene regulates the transcription of the other one [48]. PPI networks are depicted as undirected graphs. In these networks, an undirected edge is drawn between each couple of proteins for which there is evidence of physical or biochemical interactions. A PPI network mainly embraces information about how different proteins operate in coordination with others to facilitate biological processes within the cell. Protein function prediction is still a bottleneck in computational biology research and many experimental and computational methods have been devised to infer protein function from its interactions with other biomolecules [49]. In signal transduction networks, reactions mainly denote complex formation, phosphorylation, dephosphorylation, activation, deactivation and so forth. The processes involved in this complex system comprise many interacting molecules and cannot be deduced by the reductionism approach alone. In fact, signal transduction networks perform as a bridge between the extracellular environment and the intracellular response [50,51].

2) The mesoscopic scale indicates cellular interactions between host and tumor cells such as endothelial cells, lymphocytes, macrophages and also the local components of the extracellular matrix (ECM) [52]. Moreover, this level includes cell–matrix and cell–cell adhesion mechanisms that determine the invasive traits of cancer cells, tumor growth and so forth.

3) The macroscopic scale deals with processes happening at the tissue level such as cell migration, convection and diffusion of chemical factors and nutrients, mechanical stress, invasion of nearby tissues, rupture of capsules or basement membranes and so forth.

Therefore, cancer growth is indeed a multiscale, nonlinear dynamical problem whose basic evolution is impossible to be quantitatively explained without the aid of mathematical models [1]. Models usually fall into two main categories: they are either discrete or continuum with respect to the fact that how the tumor tissue is represented. Discrete models represent distinct cells on the basis of a specific set of biophysical and biochemical rules, which is especially useful for studying genetic instability, carcinogenesis, natural selection and cell–cell in addition to cell–microenvironment interactions. Continuum models look upon tumors as an assemblage of tissue and herein, the principles from continuum mechanics are used to describe cancer-related variables (e.g. cell volume fractions, nutrients and concentrations of oxygen) as continuous fields by using PDEs and IDEs [53]. On a microscopic scale ODEs are commonly applied for continuum modeling where quantitative data are available. The third modeling method employs a hybrid combination of both discrete and continuous representations of tumor cells and microenvironment components, in order to develop multiscale models.

Fig. 1 shows that three scales, namely, macroscopic, mesoscopic and microscopic are interrelated because the tumor growth is dependent to cell population density, nutrient concentration and chemical factors, cell–cell communication, cell behavior, intracellular mechanisms, pressure, etc. each of the mentioned items are modeled on specific scales.

Biological networks in subcellular compartments are modeled on a microscopic scale. These networks are often modeled using ODE, Petri net, Boolean network and hybrid methods. Cellular automata and agent-based approaches are used as well. The produced output and the calculated parameters through subcellular modeling are used in cellular, cellular communications and tissues models on a mesoscopic or macroscopic scale. Moreover, the production of the proteins that are involved in the cell junctions and the cell–matrix connections and the production of the molecules to be secreted and diffused on the tissues are also considered as important modeling parameters for the mesoscopic and macroscopic scales. The mentioned parameters are obtained from microscopic models.

As an instance, assume the functional state \( F \) of a cell is defined by the molecular concentrations of EGFR, PLC gamma and EGF such that the cell immigration, proliferation and apoptosis are dependent on the increase or the decrease of the mentioned factors in the cell [54]. Suppose that a cell population size is \( N \) and for each cell the functional state \( F \) exists. The rate of the cell number change, the cells being of a specific type, and in the \( F \) state at the time \( t \) depends on: (1) \( I_t \) that denotes the sum of all cellular processes such as the increase and the decrease of the gene expression, mutation, interaction alterations, etc. which change the \( F \). (2) \( J \) indicates cell–cell connections which lead to the \( F \) in one or more interacting cells and the proliferative interactions \( (P_t) \) or deadly interactions \( (D_t) \) are observed. (3) \( S \) that is related to the external sources and leads to the formation of \( L \) cells. Herein, the assessment of the cell internal changes which end in the determination of the \( F \), manifested

![Fig. 1](image-url). The connection between macroscopic, mesoscopic and microscopic scales. The arrows show the reciprocal interdependence between the levels in multiscale modeling of cancer growth, indicating that models (subsystems) at a specific scale apply information from other scales [60].
on microscopic scale. The evaluation of the cell population changes with size $N$ occurs on a mesoscopic scale which is fully dependent on the changes to $F$. This fact demonstrates that there's a mutual dependency between the mesoscopic and the microscopic scales.

In macroscopic scale, for obtaining the rate of the cell concentrations changes, the cell generation parameters are needed as well as those related to the cell death, the lack of the cell conditions fluctuations from one state to another, cell migration, materials distribution and absorption. The materials distribution pertains to the materials such as oxygen, nutrients and so forth [55,56]. These items disclose the relationships between the three scales are inevitably woven together.

9. Angiogenesis in microscopic scale of the cancer modeling

Angiogenesis is defined as the development of new blood capillaries with the origin of preexisting vessels, which is a pivotal step in tumor growth and metastasis. Many growth factor complexes take part in angiogenesis regulation, involving the vascular endothelial growth factor (VEGF) system of minimum five ligands, i.e. VEGF-A, PI GF, VEGF-B, VEGF-C and VEGF-D, in addition to three receptors, i.e. VEGFR1, VEGFR2 and VEGFR3, the fibroblast growth factor (FGF) system including at least 18 ligands, namely, FGF1 to FGF10 and FGF16 to FGF23, and four receptors, i.e. FGFR1 to FGFR4, the angioptin (Ang) system involving at least four ligands, i.e. ANG1 to ANG4 and two receptors, i.e. TIE1 and TIE2, the platelet-derived growth factor (PDGF) system comprising at least four ligands, i.e. PDGF-A to PDGF-D and two receptors (PDGFR-alpha and PDGFR-beta), and the insulin-like growth factor (IGF) system expressing at least two ligands, i.e. IGF1 and IGF2 and two receptors, i.e. IGF1R and IGF2R [57].

An ODE simulation of the result of the mentioned vascular remodeling on tumor growth has been performed [58]. This model included starvation-induced VEGF expression in tumors as the only angiogenic factor, while considering the destabilization of the mature vessels and the regression of the immature vessels by Ang2. Hypoxic cells secrete angiogenic factors in the vicinity of the center of the necrotic region of the tumor. The alpha subunit of the HIF1 largely regulates the cellular response to hypoxia. In a hypoxic situation the cytosolic HIF1a skips being hydroxylated and penetrates into the nucleus. Then it binds HIF1β/ARNT and triggers the angiogenic pathway, involving VEGF and its receptor VEGFR2/Flk1.

The hypoxic response pathway has been modeled using a system of ODEs indicating the molecular kinetics of 17 compounds and the data have been validated from several other [59]. The model proved both a rapid, switch-like response to low oxygen concentrations as well as a slower one, depending on the existence of cytosolic iron, ascorbate and PDH2 [60]. Finley et al. proposed a model of VEGF transport and kinetics in the mice that had developed tumor, which gave a simulation of the interactions between the VEGF isoforms and receptors, i.e. VEGFR1 and VEGFR2, in addition to co-receptors, i.e. NRP1 and NRP2. This is perceived as a complementary study along with experimental investigations in mice and brings a framework with which it is feasible to examine the effects of anti-angiogenic agents. It can lead to the optimization of anti-angiogenic therapeutics parallel to clinical data analysis [61].

In another study, an experiment-based model of VEGF kinetics and transport was suggested to examine the distribution of the major VEGF isoforms, i.e. VEGF121 and VEGF165 in the body. The model has predicted that the free VEGF in the tumor interstitium is seven to 13 times higher than that of plasma and is mainly in the form of VEGF121 (more than 70%). These predictions were validated by experimental data. The model has additionally predicted that the tumor VEGF would increase or decrease with anti-VEGF treatment being contingent upon tumor microenvironment, denoting the significance of personalized medicine. The study suggested that the rate of VEGF secreted by the tumor cells could serve as a biomarker in order to predict the number of patients that were probable to respond to anti-VEGF treatment [62].

The VEGF–Bcl–2–CXCL8 pathway introduces new targets for the creation of anti-angiogenic approaches involving short interfering RNA (siRNA) that can silence the CXCL8 gene and small molecule inhibitors of Bcl-2 [63]. Jain et al. presented a validated mathematical model to predict the result of the therapeutic blockade of VEGF, CXCL8 and Bcl-2 at various stages of the tumor progression. In accord with the experimental evidence, the model predicted that reducing the production of CXCL8 in the early stages of development can lead to a lag in the tumor growth rate and vascular development, however, it had no significant effect when put to use at the late stages of the tumor progression. Moreover, numerical simulations have demonstrated that blocking Bcl-2 up-regulation, be it at early stages or after the full tumor development, confirms that both tumor cells and microvascular density are stabilized at low values indicating growth control. These findings have provided a deeper understanding of the facets of the VEGF–Bcl–2–CXCL8 pathway, which are crucial mediators of tumor growth and vascular development both independently and in combination [64].

10. Cancer cell proliferation and survival in microscopic scale modeling

EGFR overexpression has been reported in neck and head, colon, non small cell lung cancer (NSCLC), breast, bladder, stomach, esophagus, cervix, ovary and endometrium cancers which is considered as an indication for cancer prediction. EGFR mutations in kinase domain are commonly known as activating mutations as they seem to trigger an increase in the kinase activity of the receptor. It has been shown that ligand induced EGFR phosphorylation kinetics among wild type and mutant EGFR are dissimilar. More over, it is confirmed that activation-kinetics of downstream factors such as ERK, Akt and STAT3/5 are also different. EGFR signaling sets off Ras/ERK, PI3K/Akt and STAT activation pathways (Fig. 2). These three pathways are the main ones for cell proliferation and survival. Accordingly, mutations that lead to excessive activation of the mentioned pathways may lead to cancer. In one of our previous studies mathematical (ODE-based) models were developed representing EGFR signaling in normal and NSCLC EGFR signaling pathways, and different dynamics and behaviors of these models were examined. For the first time we have simultaneously analyzed the mutation in both EGFR and PTEN and over-expression of PI3K, EGFR, Akt, STAT3 and Ras in NSCLC EGFR signaling in one study. Our simulation denoted the effect of EGFR mutations and increased expression of certain factors in NSCLC EGFR signaling on each of three pathways where levels of pERK, pSTAT and pAkt are increased. The over activation of ERK, Akt and STAT3 that are the main cell proliferation and survival factors act as promoting factors for tumor progression in NSCLC. In case of the loss of PTEN, Akt activity level is considerably increased. Simulation results showed that in the presence of erlotinib, downstream factors, i.e. pAkt, pSTAT3 and pERK are inhibited. However, in case of the loss of PTEN expression in the presence of erlotinib, pAkt level would not decrease which demonstrates that these cells are resistant to erlotinib [44].

Comparable to the EGFR family members, insulin-like growth factor type 1 (IGF1R) is a transmembrane tyrosine kinase receptor, which is encoded by the IGF1R gene [65]. Both activated EGFR and IGF1R prompt the signal transduction events involving the Ras/ERK and PI3K/Akt pathways. The biological relationship between the proteins existing in EGFR and IGF1R signaling pathways and the downstream PI3K and MAPK networks has been modeled applying a set of ordinary differential equations (ODEs) to study the
time behavior of the overall system, and the functional interdependencies between the receptors, the proteins and kinases that were involved. Bianconi et al. suggested a systems biology approach to model EGFR and IGF1R pathways in NSCLC. They proposed an in silico model (on the basis of ordinary differential equations) of the pathways and examined the dynamic effects of receptor alterations on the time behavior of the MAPK cascade down to ERK that governs proliferation and cell migration. Moreover, a sensitivity analysis of the proposed model was carried out and a simplified model was proposed which allowed them to infer a similar relationship between EGFR and IGF1R activities and disease the disease aftermath [66].

In 2004, Brown et al. established computational models of the EGFR and NGF activated ERK pathway in PC12 cells [67]. The topological structure of the model was initially constructed and then a novel ensemble method was used to automatically assign values to model parameters on the basis of accessible experimental time course data. By means of this approach, models of the EGFR and NGF activated ERK pathway were generated and afterwards were used to make a number of interesting predictions; for example the fact that knocking out Akt would have little effect on ERK activation was predicted. The study by Orton et al. was focused on investigating what effects different cancerous alterations exert on signaling through the EGFR activated ERK pathway [68]. They generated a new model of the EGFR activated ERK pathway, which was verified by their own experimental data. Afterwards, they altered their model to represent various cancerous situations such as Ras, B-Raf and EGFR mutations, as well as EGFR overexpression. Analysis of the models demonstrated that different cancerous situations ended in different signaling patterns through the ERK pathway, particularly when compared with the normal EGF signal patterns. Moreover, the model points out the importance of receptor degradation in normal and cancerous EGF signaling, and indicates that receptor degradation is a key contrast between the signaling from the EGF and nerve growth factor (NGF) receptors [68].

Tumor genome sequencing has generated many genomic alterations, it is a big challenge to dissect, prioritize and uncover the functional importance of the genomic alterations and the underlying mechanism that drive cancer development, progression and metastasis. Zaman et al. have constructed breast
cancer subtype-specific (i.e. luminal and basal subtypes) survival networks by integrating genome-wide RNAi screening data and exome-sequencing data [69]. These networks elucidate underlying signaling mechanisms governing cancer cell survival and proliferation, and imply selective pressures for evolutionary convergence of cancer genomic alterations. Differential network modeling of these networks showed that signaling mechanisms of the two subtypes are different. A set of network genes (i.e. genes are differentially different between the two subtype-specific networks) whose genomic alteration profiles (amplification and mutating status) are able to significantly distinguish breast tumor samples into luminal and basal subtypes, and furthermore, these networks predicted subtype-specific drug targets. Importantly, most (~80%) of the predicted drug targets have been experimentally validated [69].

11. Modeling of multiscale tumor growth

In spite of the astronomically increasing molecular data, the growth of tumors, the metastasis of tumors toward healthy tissues, and the response of tumors to therapies are not considerably understood [70]. Therefore, mesoscopic and macroscopic modeling allow us to examine the cancerous cells behavior in tissue and to model the tumor growth and the whole tumor behavior in order to obtain the crucial parameters involved in different conditions.

Delsanto et al. have investigated multicellular tumor spheroids (MTS) on mesoscopic and macroscopic scales and suggested an intermediate model to fill the gap between a macroscopic formulation of tumor growth and a mesoscopic one. In mesoscopic MTS model the space is divided into concentric isovolumetric shells \( n = 0, \ldots, N \), where \( n = 0 \) labels the central sphere of radius \( r_0 \), and the growth is controlled by local nutrient availability and pursues according to reproduction, migration, death and feeding. Nutrients are diffused from the \( n \)th shell to the ones in the vicinity at a rate of \( \alpha_V \), available nutrient units \( V_0 \) per unit area. Applying the WBE model (first proposed for tumors by Guiot et al. [71]), they assumed that the central core of the dead cells (region \( Z_0 \)) is surrounded by an inner layer, \( Z_1 \), of quiescent cells, and by an outer layer, \( Z_2 \), of active cells. Their assumption temporarily neglected any wrong positioning. It is important to emphasize that the central core \( Z_0 \) and the other two layers \( Z_1 \) and \( Z_2 \) do not need to be spherical, which means not only can the macroscopic model be used to describe MTS’s, but it can also model almost any type of prevascular in vivo solid cancers [72]. Ferreira et al. have integrated the cellular (mesoscopic) and tissue (macroscopic) scales. Moreover, their study introduces an effective stochastic cell kinetics managed by local probabilities for cell division, migration and death to provide a strategy to connect the macroscopic diffusion equations for nutrients and/or growth factors to cell response and interactions at the macroscopic scale. In this model each tumor cell was selected at random, with equal probability, and one of three actions was carried out: Division, Migration, Cell death. The mentioned system comprised a tissue fed by a single capillary vessel. The tissue was depicted as a square lattice of size \( (L + 1) \times (L + 1) \) with the lattice constant of \( \Delta \). The capillary vessel, being localized at the top of the lattice at \( x = 0 \) is the only source that acts as a nutrients diffusion center from the tissue toward individual cells. Only three cell types were considered: normal, cancerous and tumor necrotic cells. As the initial “seed”, a single cancerous cell in the middle of the lattice \( (x = L/2) \) and at a distance \( Y \) from the capillary vessel was introduced in the normal tissue, which is in accord with the theory of the clonal origin of cancer. Periodic boundary conditions down the horizontal axis were used. The row \( i = 0 \) indicated a capillary vessel and the sites with \( i = L + 1 \) showed the external border of the tissue. The simulated tumors comprise a spatial structure including a central necrotic core, an inner rim containing quiescent cells and a thin outer rim of proliferating cells in accord with biological data [73].

Lymphoma tumor growth was modeled through merging the experimental and the computational models in which the rate of change of the growth, apoptosis, necrosis, blood vessel density, the VEGF and oxygen diffusion as well as the cell velocity were estimated in accord with the experimental data. Their method to constrain the computational model comprises both cell and tumor-scale methods as described in Fig. 3. Then the model was calibrated on the basis of the mentioned cell scale parameters so that the tissue scale parameters such as size and growth rate could be estimated. Their model predicted that the tumor growth reaches \( 5.2 \pm 0.5 \) mm up to the 21th day, which was in accord with in vivo data. Additionally, the angiogenesis behavior in cancerous tissue was also modeled which showed that the simulated endothelial tissue density was higher in tumor core and the results revealed that the difference in spatio-localization of the cells and vasculature, as well as in the transportation in the tumor microenvironment may have a serious role in the tumor behavior [74]. In a similar study but more computational (using agent-based modeling) melanoma was modeled in a multiscale manner. They examined angiogenesis at the level of the melanoma tumor by using the intracellular functional state and intercellular scale and with respect to the VEGF concentration [75].

Cell-based models incorporate a class of agent-based models that imitate molecular and biophysical interactions between cells. One of the most common cell-based modeling approaches is the cellular Potts model (CPM), a multi particle cell- and lattice-based formalism. The CPM has emerged as a popular and accessible approach for modeling mechanisms of multicellular processes involving cell sorting, angiogenesis or gastrulation. For a more comprehensive review of the cellular Potts modeling of tumor growth, tumor invasion and tumor evolution, please refer to reference [70].

Daub and Merks have modeled endothelial cells applying a cellular Potts model (CPM) to examine the possible role of extracellular matrix (ECM) guided cell motility in angiogenesis. The stochastic cell motility was simulated by iteratively contracting and expanding the defined domains with respect to a set of cell behavior rules. They used a partial-differential equation (PDE) representation for the fields of extracellular matrix materials, diffusing growth factors and proteolytic enzymes. Three PDEs described the concentrations of VEGF, ECM and MMP components. The model explained the cell–matrix interactions at the level of distinct cells. They have disclosed that an array of biologically-motivated cell behavioral rules, namely, haptotaxis, chemotaxis, haptotaxis and ECM-guided proliferation is adequate for constructing sprouts and branching vascular trees [76]. Sun et al. proposed a novel multiscale, agent-based computational model including both angiogenesis and EGFR modules to investigate the brain cancer response under tyrosine kinase inhibitors (TKIs) treatment [77]. The angiogenesis module, which was integrated into the agent-based tumor model, consisted of a set of reaction–diffusion equations that explained the spatio-temporal evolution of the distributions of micro-environmental factors like glucose, TGfalfa, oxygen and fibronectin. The simulations proved that the entire tumor growth profile is an integral behavior of the cells, which is regulated by the cell cycle and EGFR signaling pathway [77].

In epithelial tissue, a complex interplay between inhibitory mechanisms and growth stimulating signals regulates normal growth. Many tumors begin to develop when cells undergo a transition from stable epithelial behavior to expanding mesenchymal growth [78]. A lattice-free DCA biophysical model has facilitated the simulation of cell- and tissue-shape changes under the pressures of adhesion and deformation from surrounding cells and underlying extra-cellular matrix. Displacement and deformation forces were modeled applying Langevin equations through the coupling of both deterministic intercellular and stochastic forces with constants obtained from the literature or directly from
Fig. 3. Schematic illustrating integrated computational/experimental modeling approach including both cell- and tumor-scale measurements. (A) Functional relationships containing cell-scale parameters, i.e. proliferation (Ki-67), apoptosis (Caspase-3), and hypoxia (HIF-1α) are defined on the basis of experimental observations, as an instance, from immunohistochemistry the density of viable tissue is shown as a function of vascularization in the third panel (red: highest density; yellow: lowest; blue: vessels). The mentioned functional relationships in addition to parameter values were measured experimentally and were used as the input for the model to simulate the lymphoma growth. A sample was applied to simulate tumor cross-section depicting vascularized viable tissue, shown on the far right (highest density in red, lowest in yellow, with vessel cross-sections as small blue dots). (B) Lymphoma observations related to the size, morphology, and vasculature from macroscopic imaging of an inguinal lymph node in live mice specify part of the tumor-scale information used as validation of the model. Consider the pre-existing vasculature in the lymph node, being in the center, from which the tissue is provided with oxygen and nutrients (all the data related to this figure and the corresponding legend were taken from Friebes HB, et al.) [74].

12. Conclusion

Despite the fact that cancer is a complex disease with different attributes and the potential to develop in various tissues, it follows a common plan of progression [1] making it feasible to seek for appropriate modeling approaches at various time and space scales using extra- and intracellular contributing factors. The validation of the emerging models and simulations of cancer are chiefly dependent on mutual cooperation between experimental researches and clinical results [2]. Consequently, further improvement in mathematical modeling of cancer can lead to the design of more sophisticated cancer therapy approaches. In addition, the more accurate the raw data, i.e. transcriptional and/or translational, the more actual and predictive the corresponding models. To present more actual models, there are different levels of abstraction and simplification. One should exercise great care to ensure that the formalisms along with their levels of abstraction and simplification are chosen in a way that the least amounts of crucial data be lost. Lately, multiscale cancer models have proved to be more advantageous in that they can simultaneously incorporate more aspects of complex diseases such as cancer, hence the improvement of more predictive data-driven models. The mentioned approach along with the experimental and clinical trial achievements can provide us with the foundations that facilitate the future design of patient-specific cancer therapy, which could be perceived as great strides toward entering an era of personalized medicine [81].

Conflict of interest

No conflict of interest exists.

References


