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New Method for Tumor Growth Modeling: Software Environment and Mathematical

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Abstract
Understanding tumor development crossing multiple spatial-temporal scales is of great practical importance to better fighting against cancers. It is hard to attack this problem with pure biological means. In recent decades, computer-based modeling and simulation techniques have been playing an increasingly important role in addressing it. After reviewing the literature, however, we notice that existing tumor models are either highly simplified or too complicated to be scaled to large tumor systems. In light of these problems, we have developed a software environment TUGME to facilitate the multi-scale modeling and simulation of tumor development based on the agent-based method. The most important feature of this software environment is its flexibility which enables straight-forward model reuse and extension. Tumor models of TUGME are hybrid as discrete and continuous approaches are coupled to model the discrete and continuous nature of the tumor system. TUGME is highly modularized, thus changing one module only requires few or no modifications to the others.

Keywords: Cancer, Hybrid models, micro-environmental.

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1. Introduction

Basic cancer research by biologists is mainly carrying out experiments in the laboratory (the so-called wet-lab experiments [1]). In general, the experimental materials are various types of cancer cells, which are either injected into living animals like mice to induce tumors within them (In vivo tumors) or cultivated in culture medium with properly supplied nutrients like glucose (in vitro tumors). Research directly based on in situ and metastasis tumors within the body of persons with a cancer can seldom done as a set of very strict regulations have to be passed. In vivo environment (the body of animals) is obviously mostly similar to human bodies. Hence, experimental results drawn based on the in vivo tumors are usually believed more reliable.

However, many aspects of the in vivo environment are hardly controllable to researchers, especially the individual-tumor dependent factors as well as the intrinsic randomness. Compared with in vivo environment, the environment of in vitro tumors can be better controlled, but it is relatively less real for the absence of normal tissue cells that surround in vivo tumor tissues. In general, easy to control and limited effects of secondary factors of in vitro environment allow a more direct investigation of individual factors (univariate analysis), which makes the in vitro tumors popular among experimental oncologists. Tumor monolayer is prevalent in vitro, where tumor cells grow on a Petri dish with necessary nutrients for sustaining cell growth and proliferation. One important characteristic of tumor monolayers is that all cultured cells have basically the even accessibility to nutrients, hence, distinct tumor cell dynamics are considered as the result of all other factors except nutrients. It is an important experimental means for investigating and analyzing the growth and invasion mechanisms of tumors [5, 6, 7]. Besides, tumor monolayers have been widely used as test systems to investigate the curative effects of anti-cancer drugs, radiotherapy, and chemotherapy etc [8].

Unfortunately, tumor monolayers cannot represent many aspects of actual tumor cell aggregates, for example, the 3D structure and the biological and biophysical properties of closely related to the 3D structure as it has been discussed in [5]. Multicellular tumor spheroids (MTSs) first used to investigate the effects of radiotherapy on tumor cells by Sutherland et al. in 1971 [6], are now prominently applied to cancer research. MTSs are thought to be more real and suitable in vitro tumor models for preserving the 3D structure of real tumor cell aggregates. Furthermore, significant differences or even contradictory phenomena have been indeed observed by conducting comparative experiments using tumor monolayers and MTSs [7]. MTSs provide an alternative with intermediate complexity between tumor monolayers and in vivo tumors, and more importantly, they can be used to model the avascular growth of real tumors that are too small to detect clinically. In addition, quantitative measurements of MTSs are very important references for validating the in silico cancer models.

2.Tumor Models and Cell Representation

Generally there are three classes of approaches for cancer modeling: namely the continuum, the discrete and the hybrid [7]. Each type of approach has its own characteristics which make it proper for investigating certain features of tumors and tumor cells. Continuum models are generally realized by Ordinary differential Equations (OREs) or Partial Differential Equations (PDEs). They are usually applied to study the large scale properties, such as the population and the volume of tumor tissues [6] or the density of tumor cells [9]. Reaction-Diffusion Equations (RDEs) are commonly adopted to model the transport and metabolism of nutrients [10], where the diffusion term and the reaction term correspondingly model the molecular diffusion and consumption by cells.

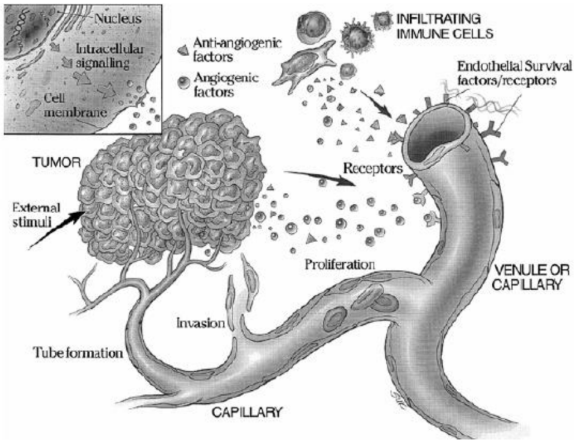

Figure 1. Growth Tumor [8]

Continuum models have many valuable advantages. First of all, they can be scaled to very large tumors without substantially increasing the computational cost of modeling solving. Secondly, they can be solved efficiently on computers, since

there are many classical methods particularly for solving complex PDEs numerically. The disadvantage of continuum models is that the discreteness of individual tumor cells is di cult to explicitly model. As the basic building units of a tumor tissue, cells are discrete by nature. Cellular membranes separate the inner cell world from the surroundings. Behaviors of cells, such as growth, proliferation, movement and death, are individual-cell- based. Furthermore, tumor cells are heterogeneous [11]. To take into account the discrete nature, the discrete approach has been proposed naturally. The discrete approach enables much higher flexibility in representing individual tumor cells compared with the continuum approach. Its basic idea is to treat each tumor cell as an individual object, where cell growth, proliferation, motion, death, interactions can be explicitly modeled as the behaviors of the individual cell objects. ABM is naturally adopted. However, the discrete approach isn't versatile in representing all the aspects of tumors or tumor cells. For example, the transport and metabolism of biochemical molecules are too nescient to realize with the discrete approach. The hybrid approach, which naturally integrates the continuum and discrete approaches, gradually becomes the favor of tumor modelers in recent years [1].

3. The Mathematical Method and Software Tools

ABM is a powerful technique for model design in computer-based simulations. On the one hand, simulation is often utilized to investigate agent systems, for example multi-agent systems (MAS) [11]. On the other hand, ABM has been widely used as a standard model design method for a wide range of applications in computer-based simulations [1]. An agent is a computer system capable of autonomous action in its environment. Agents can be thought as objects with strong notion of autonomy. Normal objects of systems encapsulate states and corresponding state-updating operation methods. In contrast, an agent has the ability to actively sense the changes in its environment, to deal with the perceived information and to make decision for its further actions (see figure 1). In a word, an agent is not only passively affected by environment, but also actively change the environment for its own preference.

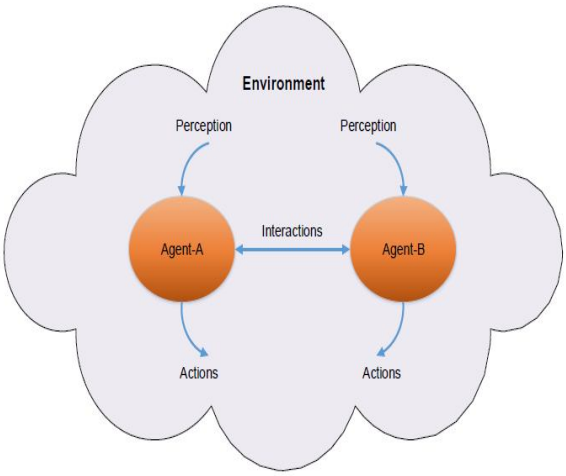

Figure 2.Diagram illustrating agent-agent and agent-environment interactions [9].

Mathematical based applications basically consist of a common environment and a set of agents within it. In an agent-based system, an agent interacts with other agents (its neighbors) as well as its environment [12]. Like a society, an agent-based system allows agents to achieve collective goals via cooperation's and coordination's, and to achieve individual aims through competitions. ABM is very powerful for model description. Agents of an agent-based system may share some properties and also can vary significantly in some properties and behaviors. Besides, a complex agent can be further decomposed into sub-agents too. With such high flexibility and strong description capability, ABM has a wide range of applications, which has stimulated the emergence of software environments or toolkits to facilitate construction of agent-based models. Here, some of them are briefly reviewed from the perspective of the possible application in agent-based cancer modeling. The software tools are representative with respect to the way of constructing an agent-based model. One may fund more software tools for general applications of agent-based modeling and simulation like FLAME or SWARM.

4. Role of Mathematical and Software Method's in cancer therapy

Mathematical modeling and simulation is a versatile tool in comprehending the system behavior and has been used for di errant applications in natural science and engineering disciplines. A mathematical model is an abstraction of a process system. It is composed of model equations and parameters. Usually, available experimental data is used for estimating the model parameters and for validating

its prognostic ability. Then, parametric analysis (sensitivity analysis with respect to parameters) of the model is performed to understand the domain and variations of the system behavior with the variation in the parameters. With understanding of the system and a valid model, one can pursue model based process control and optimization. In a similar fashion, the applications of the tumor growth modeling are many. Firstly, cancer growth can be predicted and the main parameters responsible for it can be better understood. Secondly, these models can be combined with pharmacokinetic and pharmacodynamics models of the therapeutic agents to study their impact on cancer growth. Thus, the combination model can serve as a decision-making tool for planning and scheduling of the different therapies. In addition, inter-patient and intra-patient variability scenarios can be imitated by perturbing the parameters and optimization techniques can be used to schedule a therapy accordingly. Modeling and in silico experiments can provide new insights and over different possibilities to understand and treat cancer. Experimentalists and clinicians are becoming increasingly aware of the role of mathematical modeling and its value-addition along with medical techniques and experimental approaches in order to accelerate our understanding in distinguishing various possible mechanisms responsible for the tumor growth.

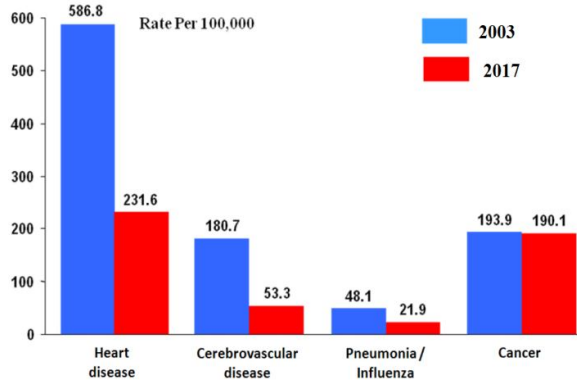

Figure 3. Change in death rates of different diseases in US from 2003 to 2017 [10].

5. Discussion

Cancer is a global issue and an important multidisciplinary field of research with a lot of open ended and challenging problems. The main thrust of this thesis is to highlight that application of process systems engineering techniques can play an important role in addressing the problems related to cancer dynamics and its treatment. The main focus of this thesis is to study the initial stages of cancer progression avascular tumor growth and its interaction with the therapeutic agents. In the first two chapters, the role of modeling in cancer, broader review of works which were done hitherto, challenges and contributions of this thesis were introduced. The second objective was to propose a therapeutic protocol for a given patient while considering practical multiple objectives associated with cancer therapies. Chemotherapy is the common adjuvant therapy given to the patient at stage or another during the course of cancer treatment and, nowadays, they are combined with the targeted therapies to reduce the side effects. Thus, the multiple objectives can be broadly related to tumor reduction and reduction of side effects. This scenario is dealt in chapter 4 by formulating a multi-objective optimization problem using a tumor immune-chemo model (patient representation) adapted from the literature. NSGA -II was used to find the solution set known as Pareto set and the decision variables represented the timing and dosage of the interventions. Then, post-Pareto-optimality analysis was done to choose a solution from Pareto set. The results for the considered patient have shown that the performance of the proposed chemotherapy protocol was better than the standard protocol employed in medical practice. However, at the end of the treatment course the number of tumor cells were in the range of 105 cells. Alternatively, the combination of chemotherapy and immunotherapy resulted in almost complete elimination of tumor cells. Also, post-treatment analysis based on tumor relapse time has indicated that combination therapy is better than chemotherapy. As a whole, this work suggests that the immunogenicity factor (intensity of tumor-immune interactions) must be taken into account prior to every therapeutic intervention.

6. Mathematical Hybrid Modeling

Mathematical and computational modeling of tumor growth is not new—in fact it goes back over 50 years. However, to some extent it has largely been ignored by the biological and medical communities. There are multiple reasons for this but two of the most significant revolve around the reductionist focus of biology and the lack of directly testable hypotheses from the models. By necessity, much of the models of cancer were general, phenomenological, and not Specific to a type of cancer and therefore were plagued by a lack of experimental data to both parameterize and validate. That is not to say they were not useful. At their heart most mathematical models are mechanistic focusing on the core processes that drive tumor growth and integrating them leading to predictions that are holistic by definition [13].

This further contributed to the lack of biological interest in combining laboratory experiments with computational simulations. Most of the experimental biologists working in this field were more focused on the reductionist route revolving around specific genetic mutations or signaling pathways that were found to be important in cancer development. This led to the data explosion that motivated the advent of early systems biology and the development of bioinformatics. Mathematical biology and the mechanistic cancer models it produced were somewhat left behind, but little by little they have matured moving from simple non-spatial growth laws (gompertz) all the way to hybrid multi-scale models discussed in this review. See also a list of previously published reviews in the Future Reading section [14, 15].

In the last few years, mathematical and computational models of cancer have become more accepted by the biological community both as means to motivate experimentation but also as a route to integrate multiple experimental measurements to generate testable predictions. This shift has been partly driven not only by the emergence of new modeling approaches (such as hybrid models) but also by the refocusing of the biological community on cancer as a system. Mathematical and computational models of cancer have almost always viewed cancer as a system of multiple interacting variables and processes and therefore should really be considered part of systems biology. In this review, we will focus on the recent development of hybrid models of tumor growth. While not an exhaustive review we have tried to incorporate all of the most up-to-date models, constraining our search to key references within the last 5 years. Hybrid models integrate both continuous and discrete variables and are able to incorporate biological phenomena on various temporal and spatial scales. These models represent cells as individual discrete entities and often use continuous concentration or density fields to model cell intracellular and extracellular environments. By their very nature, hybrid models are ideal for examining direct interactions between individual cells and between the cells and their microenvironment, but they also allow us to analyze the emergent properties of complex multicellular systems (such as cancer). It is worth noting that as these interactions take place on the intracellular and intercellular levels, but are manifested by changes on the tissue level, the emergent behavior of growing multi-clonal tumors are almost impossible to infer intuitively. Hybrid models can facilitate our understanding of the underlying biophysical processes in tumor growth. For example, by using high-throughput simulation techniques, we can examine the impact that changes in specific cell interactions (or their microenvironment) have on tumor growth and treatment. Hybrid models are often multi-scale by definition integrating processes on different temporal and spatial scales, such as gene expression, intracellular pathways, intercellular signaling, cell growth, or migration [16].

There are two general classes of hybrid-models, those that are defined upon a lattice and those that are off-lattice. The structure of this review will be to view these two broad classes in terms of increasing cellular complexity. We will then revisit these models in terms of the level of biological detail of the tumor growth process they recapitulate. Finally, we will discuss the critical role that integration needs to play if we want to make a direct impact on cancer research and treatment both from the perspective of integrating models with experiments but also from the perspective of integrating multiple modeling approaches.

7. Hybrid Models Complexity

Hybrid models can be divided into two classes that depend reciprocally on the number of cells these models can handle and the included details of each individual cell structure, i.e., models dealing with large cell populations but with simplified cell geometry, and those that model small colonies of fully deformable cells (Figure 1). Simplified geometry models are capable of handling large number of cells (thousands to millions) and still treat them as individual entities that can both act independently of other cells (individual cell cycle, cell mutations, cell phenotype) and interact with their

immediate neighbors (cooperate or compete). With these kind of models, one can simulate tumor growth up to clinically relevant sizes, thereby allowing for incorporation of different kinds of tumor treatments, and enabling us to test in silicon new and preexisting treatment protocols.

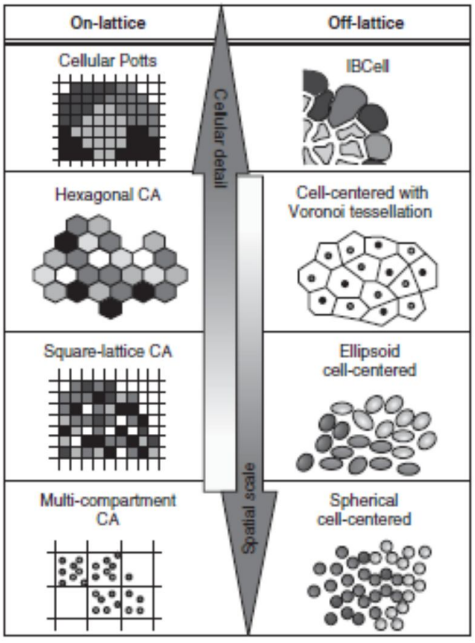

Figure 1. Reciprocal relation between the number of cells handled [13]

Models with deformable cells allow us to investigate the intimate interactions between individual cells and between cells and their environment. Various cellular processes can be represented in these models in a more realistic way, by incorporating, e.g., the time- and space-dependent enlargement of growing cells, the orientation of cell division, the elongation during cell migration. Both classes, however, can be coupled with additional equations, such as ordinary differential (ODE), partial differential (PDE), and/or stochastic equations, to describe signaling or metabolic pathways, as well as mechanical or molecular details of cell life processes [17]. Technically, hybrid models can also be divided into two classes, on- and off-lattice (Figure 2), however, this term actually refers only to the imposed positions of the cells [a square, hexagonal, or cubic lattice versus unconstrained locations in the two- (2D) or three-dimensional (3D) space], but the underlying chemical or physical fields are typically defined on regular grids in both kinds of models (as the simplest way to solve standard reaction-diffusion equations). We elaborate on both classes of model below, discussing in briefly the different models that fit in each class and how they have been applied to tumor growth [18].

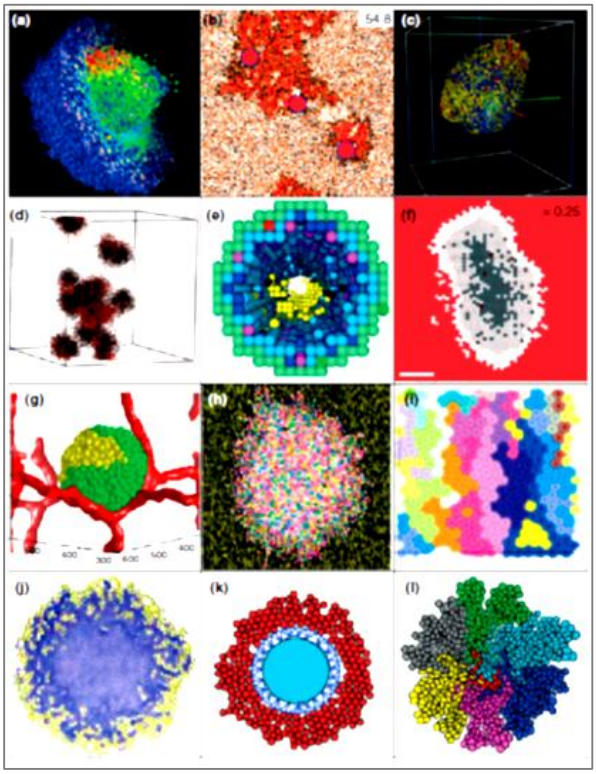

Figure 2. Snapshots from simulations of various hybrid models of tumor growth. (a) Three-dimensional (3D) tumor spheroid simulated by ahybrid cellular automaton (Reprinted with permission from Ref 12. Copyright 2007 Birkhauser-Verlag).

8. Biological Complexity

Cancer development is a complex multi-scale process that depends on both the intrinsic factors (such as genetic mutation, gene expression, cell adaptability, robustness, and phenotypic evolution) and on extrinsic cues sensed from the cell microenvironment (such as multiple metabolite and nutrient gradients, different densities and alignments of ECM fibers, or diverse tissue architectures). Experimentally, cancer evolution and development are generally only considered at the gene or protein scale; however, recently there has been a great deal of interest in the impact of this evolution at the cellular scale. After all, selection occurs upon the cellular phenotype even if mutations take place in the genotype. This selection pressure is often driven by the changes in the tumor microenvironment. Hybrid models seem particularly well suited to investigate

the evolutionary aspects of cancer and various strategies have been developed to model evolution of both cell phenotypes and genotypes, as well as the complex interactions between cancer cells and their surrounding microenvironment. Evolution of cell phenotypes is often modeled using deterministic flow charts in which a decision to enter the specific cellular process (such as cell growth, division, death, or movement) is determined sequentially by comparing cell status (e.g., cell age, nutrients level, the number of cell neighbors, or the configuration of cell membrane receptors) to predetermined thresholds [19]. Another approach involves the introduction of random mutations that determine the evolution of a given cellular phenotype (e.g., doubling time, death rate, or sensitivity to contact inhibition) or cell interactions with external factors (such as concentration of metabolites or ECM degradation). Such interactions can be also modeled using the neural networks18,21 or systems of ODEs defining certain signaling pathways or protein networks. Evolution of cell phenotypes depends not only on cell genotype but also on cues sensed by the cells from their neighborhood.

Moreover, the evolving cells modify also their immediate vicinity, and these mutual interactions may lead to the emergence of certain microenvironments promoting tumor development. The establishment of a three-layered structure (consisting of a proliferating rim, a ring of quiescent cells, and a necrotic core) that arises in tumor spheroids as a consequence of nutrient depletion has been reproduced by virtually every kind of modeling approach, and has become a test problem for every newly developed mathematical model of solid tumor growth. Gradients of nutrients, such as oxygen or glucose, are not the only chemical species present in the stroma surrounding normal and tumor tissues. In fact, tumor cells are exposed to various enzymes [more than 20 kinds of matrix metalloproteinase (MMPs) and tissue inhibitors of matrix metalloproteinase (TIMPs), a multitude of growth factors and a range of chemokine's. Mathematical models were used extensively to investigate the relations between gradients of various metabolites and the emerging morphologies of developing tumors. In addition to responding to various chemical factors, tumor cells can mechanically interact with other tumor cells as well as with various other stromal cells, such as fibroblasts, macrophages, and immune cells [20].

Tumor cell behavior depends also on the interactions with its physical environment, e.g., variable densities and alignment of different ECM fibers (such as collagen, laminin, elastin, or fibronectin). The intimate adhesive relations between neighboring tumor cells, cells and the ECM, and the interactions between tumor cells and other stromal cells have been addressed by multiple investigators. The initiation and progression of most tumors depends strongly on the architecture of the host tissue. Various computational models have addressed the issues arising from confined microenvironments such as the structure of epithelial ducts or brain geometry [21].

9. Bridging Scales and Models

In principle, it is possible to build a model that will span multiple scales from the genotype and various biochemical reactions to the details on cell morphology, and the collective behavior of millions of individual cells forming the whole tumor tissue. However, such a model may acquire structural complexity that is comparable with biological cells and far less effective computationally than the real living organism. It is therefore more desirable to find ways to bridge independent models rather than build a single 'mega-model' that encompasses all the complexity of tumor development. This bridging may be in terms of separate models that consider distinct parts of the cancer process or the same process but on different scales. Our group has undertaken such an approach to address genetic, mechanistic, and evolutionary mechanisms of disruption of tissue homeostasis and initiation of tumor growth, as well as to investigate how the local tumor microenvironment can select for cells with an invasive advantage. Similarly, the questions of vascular endothelial growth factor (VEGF) transport in healthy and cancerous vascular systems were investigated by Popel and collaborators using a multi-compartment model [22].

The emergence of glycolytic phenotype in carcinogenesis was addressed by Gatenby and colleagues using a combination of approaches including CA, evolutionary dynamics, information, or competition theories. The advantage of applying several distinct models in answering the same scientific question is manifold. If these models produce similar (or comparable) outcomes, the common assumptions underlying the investigated phenomena can be identified, and used to infer underlying mechanisms that can then be further investigated experimentally. If these models result in different outcomes, further investigation can be carried to determine which features specific to each model have influenced the contrasting results and how this relates to the underlying biology. Again, this may lead to further experimentation to confirm or rule out the contrasting results.

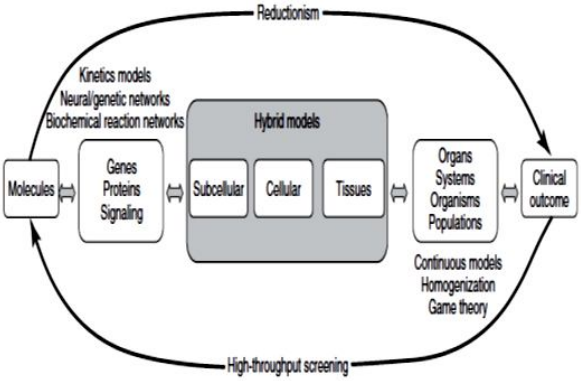

Figure 3. A schematic of modeling scales and techniques. Multiple biological scales can be bridged by various types of mathematical models [23].

10. Discussion

As we hinted at in the opening section of this article, computational models developed and implemented without real experimental data to neither parameterize nor validate their predictions was one of the major limitations in them gaining biological acceptance. What has recently become clear is that there is not only a need for greater integration between models and experimentation but also a requirement. This dialogue must go both way experiments should drive models and models should drive experiments. Models can utilize experimental data and produce novel hypotheses but without the experimental testing to validate or negate such hypotheses, it becomes a very limited academic exercise. Although to be fair, it can be very difficult to find appropriate collaborators motivated to provide such experimental support.

Models need to drive experimentation and to some extent this requires an understanding of the experimental systems that are currently being used by the cancer research community. The schematic presented in Figure 3 highlights the multiple scales that are experimentally studied in cancer research by means of the experimental systems that are utilized. If we truly want to build integrated models, then we need to think of what sort of experiments will be needed to drive our models and validate them. From our personal experience, this leads to a significant shift in thinking in relation to which components are incorporated into a model and which are not. It also dictates what type of model should be utilized and this review would not be about hybrid models if we did not believe that hybrid approaches are perfectly suited to facilitate such integration. Owing to their cell-centric nature, hybrid models naturally connect with cell biology and readily incorporate micro environmental components.

11. Conclusion

Cancer is a complex, multi-scale process in which genetic mutations occurring at a subcellular level manifest themselves as functional changes at the cellular and tissue scale. The multi-scale nature of cancer requires mathematical modeling approaches that can handle multiple intracellular and extracellular factors acting on different time and space scales. Hybrid models provide a way to integrate both discrete and continuous variables that are used to represent individual cells and concentration or density fields, respectively. Each discrete cell can also be equipped with sub-models that drive cell behavior in response to micro-environmental cues. Moreover, the individual cells can interact with one another to form and act as an integrated tissue. Hybrid models form part of a larger class of individual-based models that can naturally connect with tumor cell biology and allow for the integration of multiple interacting variables both intrinsically and extrinsically and are therefore perfectly suited to a systems biology approach to tumor growth.

The interface between tumor cells and their microenvironment being one of the critical drivers of cancer progression, the other being the intracellular changes that result from mutations, altered intracellular and intercellular signaling or protein trafficking, which can also be captured using hybrid models. It is worth restating that cancer is a multi-scale process, whereby mutations at the molecular scale effect protein formation that effects signaling pathways, which modulate cell behavior that transforms the tissue leading to damaged organs and potentially death. This complex multi-scale process can be broken down into smaller units that are more amenable to both experimental and theoretical approaches. This again brings into focus the bridging nature of mathematical models that are critical for understanding how the different biological scales of cancer impact upon one another. The models we have focused on this review bridge several scales both above and below the fundamental unit of the cell (Figure 3), however, they cannot bridge all—this most certainly will require different modeling approaches such as continuous or statistical models. In addition, there is an unspoken void between in vitro and in vivo models and between in vivo and the clinic. In silico models have the power to link these approaches and in doing so can give some insight into the processes that translate well between them and those that do not. This is a severely understudied area for modeling in cancer research and should be a ripe focus for future work.

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