Multi-scale Modeling in Clinical Oncology: Opportunities and Barriers to Success

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Abstract.

Hierarchical processes spanning several orders of magnitude of both space and time underlie nearly all cancers. Multi-scale statistical, mathematical, and computational modeling methods are central to designing, implementing and assessing treatment strategies that account for these hierarchies. The basic science underlying these modeling efforts is maturing into a new discipline that is close to having its first clinical successes. The purpose of this review is to capture the state-of-the-art as well as the key barriers to success for multi-scale modeling in clinical oncology. We begin with a summary of the long-envisioned promise of multi-scale modeling in clinical oncology, including the synthesis of disparate data types into models that reveal underlying mechanisms and allow for experimental testing of hypotheses. We then evaluate the mathematical techniques employed most widely and present several examples illustrating their application as well as the current gap between pre-clinical and clinical applications. We conclude with a discussion of what we view to be the key multi-scale modeling challenges and opportunities for multi-scale modeling in clinical oncology.

Key terms. cancer, mathematical modeling, predictive oncology, numerical modeling, computational modeling, agent-based modeling, cancer screening, epidemiology

Introduction

Cancer involves spatial scales ranging from RNA to gene networks to patients to entire populations, and mathematical modeling has provided valuable insights at each level. Successes include uncovering the impact of genetic regulatory circuits on spatial dynamics at cell and tissue levels[1], identifying molecular targets for therapeutic interventions[2,3], establishing tumor angiogenesis as a therapeutic target[4-6], and uncovering the potential of cancer immunology[7]. Cancer also involves diverse temporal scales ranging those of gene expression and receptor-ligand interactions (minutes to hours) to tumor growth and metastasis (months to years). Multi-scale modeling that transforms diagnosis and treatment by bridging these diverse spatio-temporal scales has long been pursued, and is now maturing to the point where it shows strong promise for solving critical problems in biology in general (REF), and clinical oncology in particular.

The review begins with overviews of the role that multi-scale modeling can play in oncology, before discussing several of the common mathematical techniques used to attack those problems. The overarching goal of these models is to make a prediction which can then be tested against experiment (either *in silico*, *in vitro*, or *in vivo*) which can lead to model improvement and, eventually, clinical application. We then examine the various areas that are currently barriers to success in applying the methods of multi-scale modeling to clinical oncology. The review is designed for members of the cancer biology and oncology communities who are interested in learning more about multi-scale modeling, as well as those in the modeling community who have recently become interested in using their tools to study cancer.

The role of multi-scale modeling in cancer

Dissecting the multiscale character of cancer to identify therapeutic targets

The long-envisioned promise of multi-scale modeling in clinical oncology revolves around quantification of the hierarchical disease process and the multi-scale feedback structures that enable genetic abnormalities to manifest at the levels of tissues, organs, and systems (see **Figure 1** for an overview), and **Figure 2** for the specific case of Barret's Esophagus where multi-scale effects of inflammation on the development and subsequent behavior of a tumor is described). A goal of multi-scale modeling is to identify how perturbations at each level can affect the system as a whole, and then to exploit this to attack cancers. The genomic level provides a means of tumor sub-stratification, which is a first step between identifiers and potential function. Well-known genetic mutations can initiate oncogenesis as these genes translate to the scale of molecular processes, which in turn translate to cellular behavior. These molecular processes can be seen as functional consequences of genetic abnormalities, and involve changes in cell signaling, receptor status activation, genetic regulation, cellular movement and interactions with the extracellular *milieu*. A key role of multi-scale modeling at this level has been developing knowledge of how "normal" molecular control structures function and, by contrast, how genetic abnormalities produce dysfunction.

At the cellular level, tumors are increasingly recognized as complex, non-clonal cell populations with their own internal dynamics arising from multi-scale interactions between mutated cells and the normal cells exposed to an abnormal signaling

environment. This manifests in inappropriately contextual cell-cell interaction, and is a byproduct of and further enhances intra-tumor heterogeneity[8]: cells housing mutations can “hijack” healthy neighbors into propagating a tumor. This in turn fosters selection within tumor cell populations, bringing in evolutionary and ecological factors into the behavior of cancers, and defines the context by which tumors interact with their surrounding host tissue. Multiscale models hold the potential to reveal therapeutic targets arising from the ways that cells interact with their neighbors and with their physical environment during these processes.

At the tissue level, all tumors all start to develop within normal tissue, and therefore have access to an “Interaction space” at the border with the host that presents a potential area for “hijacking” normal processes and cellular populations. This interaction space not only directly affects the growth and selection within the tumor, but also selects for tumor processes best able to release cells into the blood stream and initiate the process of metastases. The modeling of interactions across the cell, tumor and tissue hierarchy therefore holds the potential for unlocking additional therapeutic targets.

At the system level, the progression of a tumor from a local phenomenon to a system-level one represents another key point in the control of cancer, and motivates a desire to individualize the representation of tumor characteristics to better determine the specific factors involved in a particular tumors progression. Personalized tumor modeling might integrate baseline molecular potential arising from identified genetic profiling of the primary tumor cells or tumor stem cells with the set of possible behavioral trajectories possible in a multi-cellular tumor that is actively interacting with

its host. These latter characteristics might be represented by tumor-level properties determined by different modalities, such as histology or imaging, which would provide calibration targets for the lower-level mechanisms incorporated into such a model, and then be used to project multiple possible outcomes based on other personal factors, such as health status or interventions.

Finally, at the patient population level, the ability to potentially "simulate" an individual tumor provides a pathway to the generation of simulated populations of cancer patients. These simulated populations, which would provide a more sophisticated accounting for mechanisms than traditional population modeling, would be key to represent and account for the fact of the "rarity" of cancer events, thereby accounting for stochastic processes involved in mutational events, allow the generation of finer grained data sets for identification of more subtle patterns in the pre-cancerous and early stage conditions. Ultimately, these models would form the basis of *in silico* clinical trials for potential therapeutic regimens, and provide another potential pathway for the design and development of cancer therapeutics.

Characterizing drug targets

Molecular targets that are cancer drivers are ultimately part of a mechanistic cascade[9]. Antitumor effects can be caused by many pharmacological interventions, both direct (e.g., kinase inhibition[10]) or indirect (e.g., immune-mediated therapy[11]). Given the broad landscape of potential pharmacological agents, modeling and simulation has a fundamental role in facilitating the investigation of potential targets. Systems pharmacology[12] is an emerging and powerful approach tool in the quantitative modeler's toolbox for guiding the early stages of discovery[13], especially when tool

compounds are unavailable and information is sparse about target properties such as abundance in target tissues and turnover[14]. Pharmacokinetic-pharmacodynamic (PK-PD) models incorporate compartmental[15], or physiologically-based[16], models of drug distribution and empirical or semi-mechanistic models of drug action[17]. They are most suited for investigating the effects of drugs on molecular targets when tool molecules are available to probe disease pathways. At the other end of the scale, pharmacometric[18] models, which incorporate statistical and mechanistic features of the patient population being studied, can be used to quantify the effects of a particular treatment on populations. The statistical technique of mixed effects modeling can be applied to find explanatory variables (covariates) or PK, PD and eventually, as in cancer trials, clinically significant endpoints such as overall or progression-free survival[19]. All these modeling approaches ultimately characterize drug targets across the spectrum[20] of target qualification (cell and tissue), pharmacology (nonclinical models and humans) and disease effect (populations).

Adverse side-effects and lack of efficacy are the two major sources of attrition in drug design field (REF). Substantial efforts have been devoted to tackling this challenge, among which the systems biology approaches have been playing increasingly important roles in addressing the lack of efficacy and undesired off-targets effects (REFS). Recent advances in structural bioinformatics have enabled the reliable prediction of drug off-target binding sites across the proteome (REF). Large-scale network models have also been widely applied to predict the functional effects of various therapeutics (REF). And these two approaches have been integrated to provide a framework for assessing drug responses *in silico* (REF). A recent effort incorporated

the signaling pathway information for the evaluation of side effects on primary human hepatocytes, and obtained insightful results with clinical benefits (REF). Collectively, the traditional experiment-based screening strategy to reduce drug off-target effects is becoming time- and cost-consuming, while a variety of recently developed computational models have begun to make significant contributions to the rational drug design. In addition, many computational tools established on ordinary differential equations (ODEs) systems have been widely used to model and predict the effects of therapeutics on intracellular signaling pathways (REFS). These model tools were developed based on protein-protein interaction networks with applications on exploring optimal therapeutic strategies. Collectively, the ODE models with perturbations can be used to explore *in silico* candidate condition, screen out critical factors, and guide biological experiments, by investigating the drug combination effects with well-known evaluation indexes such as Loewe additivity (REF) and Bliss independence (REF). Finally, using agent-based modeling techniques which integrating multiple biological scales together especially including intracellular signaling pathways, multi-scale modeling frame plays a crucial role in developing optimal drug therapies in cancer research (REF).

Computing the design of anticancer drugs

It is increasingly clear that there must be an extension from the “rational discovery” of potential drug candidates, often based on molecular-level assumptions of effect, to a “rationale design” process, that moves beyond target identification towards characterizing the larger scale consequences of interfering with a particular target gene. This necessarily incorporates recognition of the multi-scale nature of cancer, where

there are higher-order properties that involve accounting for the behavior of multi-cellular populations within a tumor, as well as the interactions of that tumor with its host environment. Given this understanding, it is critical to account for compensatory processes that remain in either the tumor or adjacent host tissue in any attempt to understand the potential downstream consequences of a molecular level intervention (as is the case with many anti-cancer drugs). Quantitative models that can contextualize the multi-scale processes involving the development and behavior of cancer have an important role to play in this line of investigation[21].

Digital screening of anticancer drugs

Traditional drug discovery replies upon either rational design or high-throughput screening using a library that contains millions of compounds selected for and then screened for efficacy against a target of interest. While this approach has been successfully used to discover many effective anticancer drugs, it can be enhanced through digital drug screening, a powerful drug discovery technology in the post genome era. In addition to advances in chemoinformatics[22] and the deciphering of the human genome sequence there has been an enormous increase in the types of chemical compounds, biological and physiological systems, and diseases that have been digitized, stored and archived in publically accessible databases, such as PubChem, ChemSpider and ChEBI[23]. These databases offer a platform for releasing and publishing experimental data on chemical compounds and their associated structure and functional data. They also offer user-driven search engines that allow users to define and search a particular or class of chemical compounds.

Conversely, while large sets of biological and medical data are frequently generated, the validation and further standardization of these data remains significant challenge. One of the difficulties is the poor reproducibility and reliability of these biological and clinical data due to complexity of biological systems and hard-to-access human samples. The development of bioartificial tissue and organ-on-a-chip[24] system could help accumulate more clinically-relevant biological and physiological data for digital anticancer drug screening. The digitalization of cancer diagnoses offers another opportunity to deposit and publish clinical and oncological data through internet. Some of these databases (e.g., Therapeutic Targets Darabase and PharmGKB) are available today for drug screening.

Another critical element of digital drug screening is the computational models that bridge the data to a cancer target. Such models must be multi-scale and target-driven due to the multiple spatial and temporal scales at which the motivating biological and clinical data are collected. Algorithms also need to be developed to predict whether compounds or biological agents including proteins or peptides can be translated into anticancer drugs. For example, BioMap® (human primary cell phenotypic profiling services developed by DiscoveRx Co.) consists of primary human cell-based assay systems, a database of reference compound profiles, and computational data mining and analysis tools. This computational model will allow users to virtually correlate a compound's activity to clinical outcomes. A ChemScore system that uses reactivity based fingerprints of compounds as filters has been developed to determine a reactant-like and a product-like score for virtual drug screening[25].

Taken together, the combination of available databases and computational models, offers unprecedented opportunities to build computational models for drug screening, thereby enabling a fundamental shift from traditional high-throughput screening to data-driven screening of potential anticancer drugs.

Optimizing dosage, drug combinatorics, scheduling, and safety

A critical challenge in the development of anti-cancer drugs is the optimization of the dosing strategy including the proper dosing, timing, and scheduling of drug administration (REF). Optimally selecting treatments for a particular cancer subtype, particularly treatments that involve combination therapy, is an extraordinary challenge for the number of potentially relevant adjustable parameters is too large to adequately investigate in clinical trials. Thus, to accelerate progress on this fundamental problem, a robust and practical theoretical-experimental approach is required. Having an accurate—and clinically useful—multi-scale modeling approach can reduce the number of experiments that must be performed by dramatically reducing the space that must be searched to test a given hypothesis.

The classical “maximal tolerated dose” (MTD) approach currently used in early Phase 1 clinical trials of anticancer drugs (REF) can be irrelevant in many situations. For example, some compounds simply do not present a toxicity profile such as reaching the MTD in a dose finding phase. For other compounds with a well-identified MTD, the upper-limit dose may not be appropriate when the compound is given in combination with other therapeutics—which is commonly the case (REF). Efficacy and toxicity are central issues in design of patient-specific chemotherapy regimens, but do not lend themselves well to trial-and-error approaches. A broad range of coupled *in vitro* and

numerical modeling techniques are becoming available that offer much promise for rapid efficacy and toxicity screening.

Cellular and tumor-level responses may be deduced from the responses of bioartifical tissues, organ-on-a-chip systems, *in vitro* tumor models, and murine systems in typical screening procedures. These systems also show promise for assessing toxicity of drug regimens. A particularly promising avenue is screening of compounds on bioartificial tissues whose cells derive from a patient's own induced pluripotent stem cells[26].

Computer models could play a pivotal role in determining efficacy, regimen and safety of drug combinations. Multi-scale modeling can anticipate potential synergies between compounds' mechanisms of action, thus providing a rational method for selecting a dose that would improve efficacy without affecting safety. Progress has already been made using bioinformatics algorithms[27]; however, applications of multi-scale modeling to solving this very important clinical problem remain to be fully explored.

Assessing intervention, prevention, and cancer screening strategies

Multi-scale frameworks that explicitly model clinical outcomes in terms of underlying biological processes in conjunction with the physical and physiological characteristics of the instrumentation used for screening or drug delivery are likely to suggest improvements that cannot be gleaned from traditional natural history models of cancer development and drug response. Such traditional models typically ignore important biological processes and time scales in the formation of cancer and its precursors. In contrast, multi-scale models are poised to provide a more comprehensive

understanding of the underlying mechanistic processes as well as the spatio-temporal characteristics of cancer screening and surveillance protocols (e.g., using high-resolution imaging, biopsies, brushings (collecting cells from the epithelial surface using a cytosponge), blood tests). An illustrative example of this reasoning is presented in **Figure 3**[28]. Although regular biopsy-based surveillance is the recommended standard of clinical care for most Barrett's Esophagus (BE) patients who have not progressed to dysplasia or cancer, it is not clear whether screening under current guidelines is clinically optimal and cost-effective. Curtius et al. describe a computational cell-level mutliscale model for the neoplastic progression of Barrett's metaplasia to esophageal adenocarcinoma allowing for variation in segment length, presence of dysplastic cells in the crypt-structured epithelium and their potential detection by biopsy[28]. Thus, multi-scale-based screening models can potentially be used to better understand the clinical performance (sensitivity/specificity) of various screening methods and the sources that limit their clinical utility.

State-of-the-art multi-scale approaches to cancer

Multi-scale Network signaling models

Advances in mechanistic modeling of signaling networks present opportunities for better understanding of therapeutic targets, designing therapeutic regimen including combination therapies, as well as the *de novo* design of drugs. Models of growth factor signaling networks, such as vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF), have been particularly well developed. The VEGF models describe molecular-detailed kinetic interactions between different splice isoforms of VEGF and

their cognate receptors VEGFR1 and VEGFR2 and co-receptors neuropilins-1 (NRP1) and NRP2; the models comprise three compartments: blood, normal and tumor and they also take into account VEGF binding to the extracellular matrix, and soluble factors such as soluble VEGFR1[29,30]. Molecular-detailed intracellular signaling models that include receptor dimerization, internalization, recycling, and degradation can potentially be used for simulating intracellular drug targeting with, for example tyrosine kinase inhibitors[31]. The kinetic receptor-ligand interaction model has been extended to describe PK/PD of VEGF-neutralizing anti-angiogenic drugs including the antibody bevacizumab[30], and aflibercept[29], a fusion of specific domains of VEGFR1 and VEGFR2. They were compared with extensive available clinical data. The difference between these molecular-detailed PK/PD models and more conventional models is in the mechanistic level of detail with which the molecular interactions are represented. Therefore, the model predicts the amounts not only of the drug in the compartments, but also the detailed distribution of the different ligands (e.g., those bound to the cell-surface receptors, extracellular matrix, and free in the interstitium)[32]. For the EGF system a molecular-detailed approach has been used to design and optimize an antibody for cancer applications[33].

Pharmacometrics

A popular definition of pharmacometrics is “the science of developing and applying mathematical and statistical methods to: a) characterize, understand, and predict a drug's pharmacokinetic and pharmacodynamic behavior, b) quantify uncertainty of information about that behavior, and c) rationalize data-driven decision making in the drug development process and pharmacotherapy”[34]. In practice,

pharmacometrics employs nonlinear mixed effects modeling techniques[35] that combine structural models (algebraic or differential equations) that are nonlinear in their parameters with nested variability in the clinical observations (i.e., variation among and within patients) and trial execution components (i.e., patient adherence and dropout rate). There have been many applications of nonlinear mixed effects models to clinical PK-PD, also in oncology[36,37]. What has made its impact possible is the early availability of computer software[38] and frequent application to situations where other techniques would have been difficult to deploy, such as clinical studies where the number of patients is large, but the measurement and sampling schedule is sparse. Since this class of models is informed by data, mechanistic detail is a function of available information. However useful, nonlinear mixed effects are not the only tool that can be used to understand dose-exposure-response relationships *in vivo*. It is through the combination and use of multiple, "fit for purpose" modeling approaches, depending on the appropriate biological scale, that we can hope to understand cancer etiology and pharmacotherapy[39].

Partial differential equations

For handling clinical data that have spatial dimensions as independent variables (i.e., data that do not depend solely on time), mathematical models based on partial derivative equations (PDEs) may be more appropriate than those based on ordinary differential equations (ODEs) which are more amenable to the applications described in the previous two sections. For example, medical images which are composed of rectangular, spatially-resolved voxels describing the shape, location, and texture of the tumor in addition to underlying physiological processes[40], cannot be readily handled by

ODE models. More generally PDE models could be useful when the available data is multidimensional[41]. Most spatial models describe the movement of cancer cells through reaction-diffusion[42] or advection[43] terms. The applications are numerous, ranging from monitoring the evolution of slowly evolving tumors such as lung metastases[44] to defining surgery or irradiation margins[45,46], improving the insight offered by images[47]. (See **Figure 4**). PDE models have also been used to evaluate the spatio-temporal distribution of metastases over time[48], as well as mutations and resistance to treatment[49]. However, most applications require being able to recover the parameters of the model from clinical data in order to perform patient-specific simulations or predict patient-specific outcome.

It is important to note that PDE models are (relatively) computationally expensive to solve. Even if they can take more from available data (e.g., every voxel value of an image could be used for calibrating) this makes data assimilation challenging. Classical optimization techniques can often be too expensive to be realistically used. More advanced techniques relying on reduced-order models[50] or exploiting the features of the solution to a model[51], may prove more successful for assimilating clinical data.

Spatially discrete/cellular agent models

One class of computational modeling that has recently increased in popularity is the representation of biological structures with spatially discrete, cell-as-agent models. Methods that fall into this category are agent-based models (ABMs), individual based models (IBMs), cellular automata, and cellular Potts Models. For simplicity's sake, these methods will be globally described as agent-based modeling, and can be generally described as discrete event, object oriented, rule based, and often spatially explicit

methods for dynamic computer modeling that represent systems as a series of interacting components[52]. ABMs are computer programs that generate populations of discrete computational objects (or *agents*) that correspond to the component-level at which the reference system is being examined. These computational agents are organized into *agent classes* representing groupings of agents of a similar type defined by shared properties and characteristics. Agents are governed by *agent rules,* which are a series of instructions that allow the agent to be treated as an input-output object. Individual agents incorporate the properties and rule-structures of their parent agent class, but are able to manifest diverging behavioral paths based on the differing local inputs, generating population/system level outputs from the heterogeneous behavioral trajectories of individual agent instances that embody lower-level knowledge and mechanisms. ABMs intrinsically cross scales of biological organization, utilizing behavioral rules (scale 1) to determine individual agent behavior (scale 2), and then aggregating individuals into population dynamics of the global system (scale 3). When applied to biological systems, cells form a natural agent level within this organizational structure. Subcellular components (e.g., genes, enzymes, receptors, and structural elements) are represented as state variables for the cellular agents. Their behavior and interactions (e.g., gene transcription, intracellular signaling, protein synthesis) for the rules for the cellular agents, and can be represented by a wide range of mathematical and computational formulations including (for example) ordinary, partial or stochastic differential equations, discrete event processes, conditional statements, and Boolean algebra. Individual cellular agents interact with each other by manipulating state variables of their neighbors or their shared environment, resulting in cell-population

dynamics. **Figure 5** depicts an ontological description of an agent-based model, with an emphasis on its generality that can be tailored to specific modeling tasks. Given these framework, ABMs have been extensively used to study tumor growth and behavior (see ref. (1)-(3)) for a recent reviews of the use of ABM to study cancer).

Multi-scale, agent based modeling has been used to generate high-fidelity replications of tumor structure. The natural spatial representation of ABMs allows them to generate “realistic” tumor structures incorporating multiple cell types and capturing the heterogeneity increasingly recognized as a part of cancers[53]. This permits a more detailed investigation of the multi-scale consequences of genetic or molecular perturbations, and offers the promise of potentially personalizing models based on histological features[54].

ABMs also allow examination of fundamental processes involved in oncogenesis by facilitating a parsimonious approach that provides insight into fundamental processes involved in tumor growth and development[55]. ABMs can also provide linkages to the role of general biological processes, like inflammation, in the development and progression of cancer[60].

Finally, ABMs can bridge cancer mechanism to simulated populations. The intrinsic stochasticity seen in ABMs allows them to be used to generate simulated, *in silico* populations of virtual patients. This is a critical capability, particularly in cancer, where the development and progression of tumors can span years and decades. ABMs of this type can be used to add increased mechanistic detail to traditional population-level, epidemiological models, thus far used to explore more basic processes in

oncogenesis[56], but also providing a potential means of performing *in silico* clinical trials for both preventative and therapeutic modalities.

As with all modeling methods, agent-based modeling is not without its limitations. Most of these stem from the fact that ABMs do not have a common formal description, which limits the ability to subject them to formal analysis. Their "similarity" to biological systems, particularly in terms of the heterogeneity and non-linearities in their behavior, makes formal, comprehensive exploration of their parameter space difficult and essentially only able to be accomplished using very large sets of simulations. Added to this is the fact that ABMs are relatively computationally expensive and difficult to distribute across modern, distributed computing architectures, with the result that very often biomedical ABMs are treated more akin to experimental objects where their use is dependent upon finding some subset of parameters that can provide "realistic" behavior. Despite this limitation, however, ABMs can serve a very useful purpose as transitioning models that can serve as bridges between biological objects/knowledge and more formal mathematical representations.

Branching processes

Disruption of normal cell proliferation and differentiation is the *sine qua non* of the malignant state. However, numerous experimental and clinical studies provide evidence that the proliferation and differentiation kinetics in normal and premalignant cells are also of critical importance in the carcinogenic process. This notion was further enforced by analytic findings from mathematical modeling of cancer incidence patterns[57]. A prototype branching process model of cancer is the two-stage clonal expansion (TSCE) model[58]. Initially, this model was formulated with stochastic clonal expansions of both

normal and intermediate (or premalignant) stem cells. However, due to the typically very large (and highly regulated) size of the normal tissue stem cell pool, the version most frequently used assumes a deterministic number of normal tissue stem cells. The basic TSCE model is characterized by two rate-limiting events in normal tissue stem cells (premalignant tumor initiation and malignant transformation) together with a stochastic growth process of premalignant cells that can undergo malignant transformation. Various extensions of this model have been put forward (multistage clonal expansion (MSCE) models) to better explain cancer incidence patterns in registries and cohort studies[59]. The availability of analytical tools and likelihood expressions for population-level clinical observations (e.g., cancer incidence, prevalence of a precursor such as colonic adenoma or dysplasia in Barrett's esophagus patients) greatly facilitates likelihood-based parameter estimation *via* gradient methods or Markov-Chain Monte Carlo (MCMC) techniques. The 'mathematical bridge' that connects the cellular-level with the tissue-level is a filtered Poisson process. The tissue-level is further connected to the population level observation (cancer occurrence) through the model hazard function.

Homogenization approaches

Linear homogenization approaches comprise the simplest techniques for estimating parameters describing cell health and function from measurements conducted on a tissue construct. From the perspective of screening for safety, the desired outcomes are parameters describing electrophysiological and mechanical functioning of individual cells. From the perspective of screening for efficacy, cancer culture models such as the Xu model[60] exist, and the challenge is determining how

chemotherapy agents affect the tumor periphery and factors promoting malignancy. Models estimating tissue and cellular mechanics from multiple loadings of tumor models are capable of estimating these changes[61], and for estimating effects on cells, protein structures, and networks[62]. Although techniques are preclinical at present, the capacity to test chemotherapy regimens on both heart tissue equivalents from a patient's own transdifferentiated cells and tumor equivalents from a patient's own tumor cells shows much promise. Ongoing challenges relate to refinement of electrophysiological and mechanical models to account for local variations within tissues, and to include nonlinear phenomena.

Hybrid models

Multi-scale hybrid models combine different modeling methodologies; e.g., intracellular signaling described by ODEs combined with 3D distributions of oxygen, growth factors and cells described by PDEs, or oxygen and growth factor distributions described by PDEs combined with discrete cell dynamics represented by agent-based modeling. In principle, hybrid models could include all types of models. The advantage of hybrid modeling is that different parts of the system can be described using the methodologies most appropriate for the biological question to be answered, and with a spatial and temporal resolution that makes the problem tractable.

Barriers to and opportunities for progress

Technical/methodological issues

Mathematical complexity

There is a tradeoff between mathematical and computational complexity in modeling oncological problems, especially when the problem involves a large number of interacting components (cell-types), non-linear signaling between components (feedback loops), and stochastic behavior (noise). The main challenge in developing useful multi-scale models is therefore the choice of mathematical abstraction (continuum, discrete, lattice) and choice of relevant (rate-limiting) processes, which may operate at different time and length scales. However, these scales may not be known *a priori* and the appropriate choice may require preliminary studies and/or additional bio-mechanistic information. A case in point is the problem of emerging resistance to chemotherapy in heterogeneous tumors, whether or not the 'resistance conferring' alterations are preexisting, a result of the tumor and its microenviroment being under selection pressure caused by the drug, or simply due to the hypermutability or genomic instability of the tumor. Each of these causes requires a distinct mathematical description. For example, the size fluctuations of preexisting mutants may well be captured by a Luria-Delbrück type of distribution, which allows for mutational jackpots, while a drug-induced response is unlikely to do so given the much shorter time scale of treatment (REFS).

Mathematical complexity in oncologic applications of multi-scale modeling arises primarily in the formulation of the dynamics of bulk behavior and description of underlying constituent processes in the forms described above. It is important to note that only in exceptional cases (and often only with many simplifying assumptions) are closed form solutions available and parameter identifiability issues limited. Further adding to the mathematical complexity is the stochastic nature of many cell-level and

sub-cellular processes requiring the proper formulation and solution of discrete or continuous-time Markov processes, which capture important fluctuations in the data with time. Although the implementation and mathematical treatment of the stochastic process may be complex, a considerable advantage is that it lends itself to likelihood-based methods for parameter estimation and hypothesis testing.

Lack of necessary data available from standard clinical studies

It is important to acknowledge that while the multi-scale cancer modeling community is rich in models from the nanoscale to the macroscale, we are quite poor in data. This a fundamental, if not *the* fundamental, challenge facing the validation and clinical application of multi-scale modeling (REFS). This is particularly true for cases in which electrophysiological, transport, and mechanical factors of cells and a pericellular region are of interest. For the case of the screening of chemotherapy agents, the key difficulties are measuring in the mesoscale range, characterizing the pericellular region, and sampling a sufficient number of cells to overcome the high cell-to-cell variability so inherent to three dimensional culture. These challenges results in modeling approaches that require many (often heuristic) assumptions on model parameters. Consequently, application of such models to make clinically relevant predictions is quite limited (REF). More directly, the field of multi-scale modeling in cancer has largely been developed independent of the data types that are typically available in the clinical setting. The community needs to acknowledge that it is not simply enough to test a myriad of modeling approaches *in silico* by systematically varying parameters, coupling constants, etc. Rather, to be of clinical utility, the community needs to build multi-scale models that can be initialized and constrained with patient specific data that is readily available in

the clinical setting (REF). Only by proceeding along this route will we be able to test hypotheses about patients that directly testable. One area that is underexplored in making progress is the utility of medical imaging data (REFS).

The medical imaging technologies of magnetic resonance imaging, x-ray computed tomography, positron emission tomography, single-photon emission computed tomography, and ultrasound can quantify, at multiple time points and in 3D, tumor characteristics at the physiological, cellular, and molecular levels[63]. Furthermore, the images themselves present a natural gridding (i.e., the image pixel or voxel) that enables direct application of finite difference and finite element methods. While using such data in statistical and informatics driven approaches has launched the fields of radioomics and radiogenomics[64], such data are only beginning to be incorporated into mechanism-based, predictive models of tumor initiation, growth, invasion, and response to treatment[45,65].

Limited rigorous assessment of clinical problems

Another barrier—and opportunity for progress—is that there is frequently a limited, or absent, rigorous assessment of the clinical problem from the available literature. This plays an equally important as modeling approaches in the success of multi-scale modeling in clinical oncology. As has been described[66] if a mathematical model is likened to a building, assumptions are the ground beneath, and if the underlying soil is swamp, the edifice—the model and its resulting inferences—is doomed to failure. Therefore, to remove an important barrier towards the success of multi-scale modeling in clinical oncology, the community must substantially reduce conflicts between model assumptions and clinical problem by rigorous assessments of

the clinical literature. As an illustrative example, if the development of a tumor subtype is particularly linked to immune response or neoavascularization, but is not incorporated into the model system as a basic model assumption, then projected spatiotemporal evolution of the tumor fail to capture significant portions of tumor biology. Thus, it is of critical important to have a rigorous, biological understanding of the tumor type under investigation when designing a multi-scale model. Unfortunately, limited tissue data are available for designing multi-scale modeling approaches[67].

Mathematical models of tissue health and function

There is a pressing need for multi-scale modeling techniques that enable the use of *in vitro* tissue surrogates and organ-on-a-chip models for safety and efficacy screening of chemotherapy agents. Although well-established methods exist for applying integrated multi-scale modeling and experiment to assess subtle, drug-induced changes to the health and function of cells within simple bioartificial tissue constructs[68], advances are required to account for such tissues and organ-on-a-chip systems with heterogeneous cell populations. With these models in place, the potential to, for example, test a regimen of chemotherapy agents on bioartifical tissues mimicking a patient's own tissues will become possible, enabling rapid optimization for both efficacy against a patient's malignant cells and for tolerance by a patient's healthy cells through quantitative evaluation of changes to cell function.

Scientific "social" issues

Intrinsic to any trans-disciplinary endeavor is the need to reconcile different ways of viewing the world, and the terms that are used to reflect those views. This is

particularly notable in the attempt to link biology with the physical sciences/engineering/mathematical fields. Of course it is recognized that biology, as it currently stands, is too “complex” for the identification of abstractions that can approximate “natural laws.” However, it has been proposed that, until sufficiently powerful mathematics is discovered, dynamic computational models representing sets of mechanistic hypotheses can stand in for formal mathematical theories for a defined context and for a constrained use[69]. Within this context the importance of specific methods is lessened: sufficiently strong hypothesis structures should perform equally well when instantiated in a multiplicity of modeling methods; this is the principle of cross platform validation. Of course, the quality of the implementation is crucial to establishing the trustworthiness of a particular computational model, and there needs to be accounting for the relative strengths, weaknesses, and representational capabilities of the different methods. There also needs to be some means by which the appropriate use-context of a particular model is explicitly defined and determined, in order to avoid the misapplication and misinterpretation of a particular model. These issues are common to the general use of models and simulations, and have been pragmatically addressed through the establishment of guidelines and standards for model credibility, testing, and reporting in a domain specific fashion. As with many aspects of computational modeling in biomedicine, this process is in its infancy. However, there are several initiatives (e.g., the Committee on Credible Practice in Modeling and Simulation in Healthcare[70]) that have started the process by which biomedical models can be categorized by their use and purpose. This initiative is of particular importance as the field recognizes its eventual goal of using model-aided design and testing in the

regulatory arena (for testing of drugs and devices) and for personalized/precision decision support.

Conclusion

No shortage of powerful—and promising—computational techniques exists for use in the multi-scale modeling of cancer and cancer treatments. What is lacking, however, is access to relevant clinical data and practical modeling approaches to incorporating such data into relevant models. This will allow modelers, experimentalists, and oncologists to effectively close the "build model -test-refine cycle" by directly testing the predictive power of a particular model and then improving upon it to the point where it can, ultimately, be applied to clinical problems. We also need a more rigorous understanding of the key components that go into the growth and response to treatment of individual tumor subtypes. Both of these issues are exacerbated by the social constructs in academia. In practice, future progress in clinically relevant multi-scale modeling in oncology requires interdisciplinary collaborations between clinicians, experimentalists (biologists, physiologists, biophysicists, bioengineers, etc.), and mathematical and computational modelers. Although this truth is clearly recognized at the level of the funding agencies, the difficulty in developing such collaborations is generally underappreciated. However, a corollary of successfully working across multiple disciplines is the education and training of the next generation of students and postdocs who are accomplished at both the bench and computer thereby allowing them to explore and integrate their data into clinically useful models. Fortunately, this is happening as we speak and therefore the future utility of multi-scale modeling in clinical oncology is bright.

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Figure legends

Figure 1. The continuum of multi-scale components of cancer pharmacological therapy, and the role of each of the modeling techniques described in the text. The process starts with discovery and characterization of a target, followed by drug lead optimization and extensive in vitro and pre-clinical testing. A new medicine will also require successful testing in the clinical setting. Public domain image credits (bottom to top): NCI Center for Cancer Research (Luana Scheffer, Stephen Lockett, Jairaj Acharya); Wikimedia Commons; NCI Center for Cancer Research (Thomas Ried); National Cancer Institute (Leidos Biomedical Research, Inc.); National Cancer Institute (Rhoda Baer); photo courtesy photos-public-domain.com.

Figure 2. Proposed Generative Hierarchies for Cancer and the Effect of Inflammation. A depiction of an example of the multi-scale effects of inflammation on the development and subsequent behavior of a tumor, incorporating evolutionary and selection effects across the scales from DNA to cellular populations. This paradigm posits that increased and accumulating genetic damage in an inflammatory milieu leads to a progressive loss of the cellular and molecular control structures that govern stable multi-cellular organization. The loss of these control structures in the tumor leads a more “colony-like” behavior, where the genetic plasticity of the increasingly disordered tumor cells provides a potential selection benefit when subjected to therapeutic interventions. The incorporation of these concepts into a multi-scale computational model allows the exploration of various fundamental processes and behaviors involved in this hypothesis. Reprinted with permission from ref. 56.

Figure 3. The Multi-scale nature of screening in Barrett’s esophagus (BE). The standard screening protocol for BE involves scales from stem cells in the crypt (left) to the BE cylindrical segment of the esophagus depicted (right) with rectangles representing biopsy samples taken during endoscopy. The BE segment may have dysplasia and/or malignant tissue patches that may be missed. During histological preparation, portions of each biopsy are sliced by microtome and placed on slides for pathologic assessment. A diagnosis is made by microscopic interpretation of crypt and cellular architecture, reflecting the most severe tissue grade found from all slides. Given the multi-scale nature of the problem, it is natural that a multi-scale-based screening model would have great clinical utility. (EAC = Esophageal Adenocarcinoma; HGD = High Grade Dysplsia.)

Figure 4. This illustrative example uses serial diffusion weighted magnetic resonance imaging data to estimate tumor cellularity before and after the first cycle of neoadjuvant therapy. The top row indicates the apparent diffusion coefficient (ADC) obtained from diffusion weighted MRI data at three time points during therapy. Given the known relationship between ADC values and cellularity, this data is then converted to tumor cell number (middle row). The cell number data from the initial and post one cycle time points are then fit to a biomechanical model of tumor growth to estimate patient-specific

parameters of tumor cell proliferation and migration. The model, calibrated with the patient-specific parameters determined from the fitting procedure, is then run forward in time to predict residual tumor burden at the conclusion of neoadjuvant therapy. Model predicted cell number can be compared to cell number imaging observations at the final time point in order to assess predictive performance. Details are presented in ref. X.

Figure 5. A schematic of an Agent-based modeling format (ABM). The structure of an ABM intrinsically incorporates at least three representational scales of the system being modeled. For most biomedical ABMs, cells are used for the middle level representation (the *agent* level). Figure reprinted with permission from Elsevier Ltd.

Figure 6. Patient-specific drug and cardiotoxicity systems are available, but require integrated multi-scale modeling and experiment to apply. Tumor cells can be multiplied in systems like the Xu system (REF) for patient-specific drug screening. Commercial systems exist for testing patient-specific cardiotoxicity on tissue constructs derived from induced pluripotent stem cells (iPSCs); for example. Multi-scale models are required to derive metrics of cellular health from measurements of the mechanical function of tissue constructs, and for scaling dosages. Image credits: Top center and top right: ref. 71; bottom left and bottom center: Invivosciences, LLC. All images used with permission.