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Modeling tumor growth and treatment response based on quantitative imaging data

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Abstract

We review current approaches to predicting tumor growth and treatment response that combine non-invasive imaging data with mathematical models of cancer progression, and propose some new directions for integrating quantitative imaging measurements with such numerical analyses. Historically, tumor modeling has been described by parameters that are measurable by invasive methods only or in isolated *in vitro* or *ex vivo* systems. This limits the practical usefulness of such models because it is not possible to test their predictions experimentally. Recent advances in three-dimensional magnetic resonance imaging, single photon emission computed tomography, and positron emission tomography techniques provide new opportunities to acquire measurements of relevant molecular and cellular features of tumors non-invasively and with high spatial resolution. Such data can be incorporated into mathematical models of tumors. We highlight some recent examples of this approach and identify several simple examples that allow for conventional mathematical models of tumor growth to be recast in terms of parameters that can be measured by imaging, thus raising the possibility of designing and constraining models that can be tested in clinical practice. It is our hope that this Perspective will stimulate further work in this evolving and exciting field.

Introduction

The application of mathematical models to describe how tumors grow has a long and rich history.¹ These models may have various degrees of complexity and applicability ranging from simple exponential growth of an avascular tumor, to more complex mechanical models

of tumor growth, to systems of partial differential equations describing invasion and angiogenesis. As recently noted,² such models can be divided into three categories: cellular and microscopic models that describe individual cells (discrete models), macroscopic models that describe temporal changes in cell density (continuous models), and hybrid discrete-continuum approaches (see, *e.g.*, ref. 3). These approaches have provided useful insights into tumor biology, as well as predictions that could then be checked experimentally. Modeling of tumor growth may also allow for investigating the likely response of tumors to treatments that can be appropriately simulated.² Unfortunately, the majority of models of tumor growth rely on knowledge of cellular or molecular level processes that are difficult or impossible to measure in an intact living system (*e.g.*, measurements of chemotaxis, haptotaxis, growth factor gradients, gene expression levels, *etc.*). Consequently, the general limitation of these models is that they are almost uniformly driven by parameters that can be measured only by highly invasive methods (surgery, biopsy, or animal sacrifice) or within idealized (*in vitro*) systems. In addition to the difficulty of measuring these parameters *in vivo* and in three dimensions at even a single time point, it is extremely difficult to measure such quantities serially with reasonable spatial or temporal resolution in the clinical setting. Thus, a significant limitation of current approaches is that they are typically not patient-specific.² The need for having patient specific information relates to the ability to accurately predict treatment response.

Insight, innovation, integration

Mathematical models of tumor growth are usually described in terms of parameters that are measurable by invasive methods only or in isolated *in vitro* or *ex vivo* systems. In recent years there have been significant increases in the quality and range of information available from new non-invasive imaging methods particularly for assessing tumor growth and predicting treatment response. In this Perspective we describe how such imaging data may be integrated into mathematical models of tumor growth, and offer several illustrative examples of how this approach can potentially be used to refine quantitative analyses of tumor dynamics. A combined imaging-mathematical modeling approach has the potential to provide new biological insights and enable predictive modeling of treatment response.

Many investigators are searching for ways to establish if an individual will respond to therapy early in the course of treatment. The current state-of-the-art for predicting treatment response is based on the RECIST (Response Evaluation Criteria in Solid Tumors) guidelines.^{4,5} RECIST divides patient response into one of four categories (complete response, partial response, stable disease, and progressive disease) based upon one-dimensional changes in tumor size. While this provides practical guidelines for the clinical community, it has been acknowledged that this method is not without its limitations. One of the fundamental issues with the technique is that the metric for evaluating response is based upon morphological changes that are temporally downstream of the underlying molecular, cellular, and physiological. What are needed are methods to report on those underlying phenomena that will predict the changes in size. One potential way to accomplish this is through mathematical modeling of tumor growth. However, since each patient presents a different set of (initial) conditions, patient specific information is required; data from the literature is suboptimal for driving a mathematical model to predict the growth or response of an *individual's* tumor. Thus, data must be acquired in a noninvasive manner and imaging is an attractive candidate for obtaining such data. There is growing evidence that more practical mathematical models of tumor growth may be constructed so that they can be driven by data obtained from non-invasive imaging studies—and these approaches can be made to be patient-specific.

In recent years there have been dramatic increases in the range and quality of information available from non-invasive imaging methods including the ability to quantitatively measure relevant properties such as cellular proliferation, apoptosis, blood flow, metabolism, and oxygenation.⁶ Building models based primarily on imaging data represents a relatively new research direction that could be a powerful and general approach by which to increase our ability to make useful predictions regarding treatment response. The integration of the unique information obtainable from imaging with mathematical descriptions of tumor growth and evolution has considerable potential to improve our understanding of tumor biology and provide new tools for predicting tumor response to treatments. Furthermore, the success and validity of the models can be tested *in vivo* and refined as additional information from different measurements is incorporated. The long term goals of such an approach would be modeling strategies that reliably predict and report on the response to therapy of individual patients.

The rest of this Perspective is organized as follows. We first briefly review several emerging magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), and positron emission tomography (PET) techniques which report on relevant cellular aspects of cancer, as well as discuss some recent developments that enable accurate registration of data obtained from multiple imaging modalities into a common image space. We then offer a brief literature review of some exciting and relevant approaches other investigators have taken at the interface of mathematical modeling and *in vivo* cancer imaging. Next we describe how co-registered, multi-modality imaging data can be used to re-interpret several existing models, and then introduce one new model constructed from the “ground up” explicitly in terms of imaging data. Finally, in the Discussion section, we enumerate some limitations of the approach and discuss some longer term possibilities. Our goal is not to offer an exhaustive review, but to offer insights into how future research may develop in order to exploit this promising new field.

Imaging methods

There are several imaging measures that report on aspects of cancer that may be incorporated into tumor modeling. We begin by discussing high resolution structural imaging provided by MRI. We then proceed to briefly review emerging techniques reporting on tumor cellularity (by MRI), apoptosis (by SPECT), and cell proliferation, metabolism, and hypoxia (by PET). (For convenience, the Table summarizes the salient features of each imaging technique described in this contribution.) Models may be further extended to incorporate other features such as the recruitment of blood vessels as briefly mentioned in the Discussion.

High resolution MRI and computed tomography

As stated above, the current standard-of-care for radiological assessment of treatment response is the Response Evaluation Criteria in Solid Tumors. The evaluation is based on uni-dimensional changes in tumor size that are visible on high resolution computed tomography (CT) or MR images.^{4,5} High resolution morphological data are readily available for most solid tumors and if data are available at multiple time points then degrees of tumor growth or shrinkage can be assessed.

Mapping cell density by diffusion weighted MRI

The microscopic thermally-induced motion of molecules moving in a random pattern is referred to as self-diffusion or Brownian motion. The rate of diffusion of water molecules in cellular tissues is usually described by means of an apparent diffusion coefficient (ADC) which is lower than in free solution and which largely depends on the number and separation

of barriers that restrict or hinder free movements that a diffusing water molecule encounters in a specific measurement time interval. Diffusion weighted MRI (DW-MRI) methods have been developed to map the ADC, and in cellular preparations *in vitro* variations in ADC have been shown to correlate inversely with tissue cellularity.⁷ The common interpretation of ADC values in cancer studies is that the higher the cell density present within a section of tissue, the greater the number of restricting barriers present and thus the smaller the ADC.^{8,9}

In some tissues, the above discussion of ADC may be too simplistic. This is especially true in tissues that exhibit anisotropic water diffusion as is observed in, for example, the brain¹⁰ and skeletal muscle.¹¹ In these cases, the water diffusion must be characterized by a third order tensor, hence, diffusion tensor imaging (DTI). Within the brain, DTI has been used extensively to map fiber tracts and their orientations and there have been recent efforts at using these data to predict the migration patterns of brain tumors (see below).

Mapping cell proliferation by fluorodeoxythymidine PET

The thymidine analogue [¹⁸F]-fluorodeoxythymidine (FLT) is a PET tracer that reports on the increased cellular proliferative activity of tumor cells. Thymidine is a native nucleoside which is taken up by cells *via* surface nucleoside transporters. Once inside the cell, thymidine is phosphorylated by the enzyme thymidine kinase 1 (TK1) into thymidine monophosphate and is trapped. Both the quantity and activity of TK1 are known to be upregulated during the DNA synthase phase, so there may be preferential uptake of thymidine in malignant tumors where cells are rapidly proliferating. After treating a tumor with a drug designed to inhibit proliferation, regulatory mechanisms may decrease TK1 gene transcription and the amount of FLT retained within the tumor may decrease as TK1 activity declines.^{12,13}

Mapping apoptosis by ^{99m}Tc-annexin-V SPECT

A fundamental mechanism of action for a large number of anticancer drugs is to induce apoptosis. When a cell undergoes apoptosis, phosphatidyl serine becomes exposed to the external leaflet of the plasma membrane. The human protein annexin A5 (anxA5) binds to phosphatidyl serine with great affinity and the tracer ^{99m}Tc-HYNIC-anxA5 has proven to be a useful probe for the assessment of apoptosis in cell culture, in preserved tissues, and more recently in live animals and humans. SPECT images of ^{99m}Tc-HYNIC-anxA5 obtained after treatment with an apoptosis inducing drug may show increased retention of the tracer when the tumor responds favorably.¹⁴

Hypoxia imaging *via* FMISO-PET

A growing body of evidence supports the hypothesis that hypoxia may trigger aggressive cell behavior¹⁵ and it is well known that hypoxia can affect the outcome of treatments. Measures of tumor hypoxia may reflect tumor aggressiveness and therefore are an important predictor of tumor responsiveness¹⁶ and an indirect measure of tumor cell migratory behavior. The clinical detection of hypoxia is possible using PET imaging of ¹⁸F-fluoromisonidazole (FMISO). The method is based upon imaging an analogue of misonidazole which is reduced and retained in hypoxic conditions but exits cells with normal oxygenation. Studies have demonstrated the prognostic value of FMISO in several organ sites.¹⁷

Combining data from multiple imaging modalities

Advances in hardware and software allow for the precise alignment and correlation of data obtained by disparate imaging methods so that structures seen in both image sets are co-aligned. While integrated PET/CT, SPECT/CT,¹⁸ and MRI/PET¹⁹ systems are becoming

common, a large literature on co-registration of images acquired from independent devices also exists.²⁰ Algorithms are also available to compare and combine images obtained at different times. We propose that by combining such multimodal data on a voxel-by-voxel basis, sufficient information can be extracted to develop and constrain mathematical models of tumors of practical utility. Some examples of this approach are given below.

Brief review of the literature

There has been much important work at the interface of imaging and mathematical modeling in a number of non-cancer areas including, for example, musculoskeletal modeling,²¹ brain segmentation,²² aortic injury,²³ and cardiovascular mechanics.²⁴ There have also been several exciting recent applications of mathematical modeling to cancer imaging data, some of which we now briefly discuss.

Modeling based on morphological data

High resolution MRI allows for accurate characterization of tumor volumes and dimensions at multiple time points in a tumor's development and there have been efforts to use this data to drive models of brain tumor growth. For example, in their review article, Mandonnet *et al.*²⁵ discussed the use of computational models to allow for characterizing WHO grade II glioma dynamics from serial MRI scans. They reported on the measurement of the linear evolution of the mean tumor diameter in a group of 27 patients and employed this information as a prognostic indicator. The authors then propose that two MRI data sets obtained three months apart could then be used to segment patients into different surgery and chemotherapy regimens based on the rate at which the tumor diameters increased. The paper also describes how a common reaction–diffusion equation could be used to describe cell movement; this model (see below) incorporates parameters for tumor cell diffusion and proliferation. In their conclusion, the authors commented on the fact that using the imaging data to solve the inverse problem and extract the cell diffusion and proliferation parameters is a logical next step.

Modeling based on diffusion data

In a 2008 study, Swanson *et al.*²⁶ showed how a realistic model of glioblastoma growth could be characterized in terms of net tumor cell proliferation (ρ) and dispersal (D). They showed how these parameters could be estimated using only *in vivo* post-contrast T_1 -weighted and T_2 -weighted MRI data. They then used these data to predict survival of individual patients. The authors point out that though there are numerous molecular and cellular events preceeding tumor cell proliferation and migration, these two “pathways” contribute an enormous amount of information that can be used to model tumor growth. The important thing to note is that, currently, very few of the molecular and cellular events that contribute to proliferation and migration are accessible non-invasively and *in vivo*, their downstream effects can be incorporated into accurate models of tumor status. It is encouraging that they are able to achieve such promising results using only anatomical data and it seems plausible that incorporating more specific imaging techniques (like those described in the preceding section) into mathematical modeling of tumor growth would enhance the predictive power.

Diffusion tensor MRI data have also been used to model glioma growth patterns and overall tumor burden.^{27,28} In general these efforts make use of a brain atlas, fiber tract orientations, a model of tumor cell diffusion, and a mechanical model of brain parenchyma; given appropriate assumptions, the approach can then be used to predict tumor size at a later time point. For example, Bondiau *et al.* begin by noting that glioblastoma multiforme show a preferential growth pattern along white matter fibers and propose to use DTI data to

generate the background architecture along which a tumor may grow and invade.²⁷ Using the DTI data obtained from an individual patient in conjunction with a mechanical model of tumor growth, they simulate the tumor at a later period and compare it to the actual tumor status. This is an exciting result where “imaging initial conditions” were used to predict the tumor status at a later time point. Their results showed a good correlation between the simulated and actual tumor and therefore allowed the authors to conclude that the approach is feasible and further work is warranted.

Hogea *et al.* recently introduced a technique to use imaging data to estimate parameters within a reaction–diffusion glioma growth model with mass effects.²⁹ They combined a reaction–diffusion model for tumor growth with an elastic material to characterize the brain tissue. They showed how to formulate the problem, described the solution method, and performed numerical experiments. Their paper also contained results exploring an initial application of their model in high-resolution 3D T_1 -weighted MRI data obtained 2.5 years apart from a patient with a low grade glioma. By registering the early and late imaging data, the authors were able to invert the model to capture four parameters related to tumor density, tumor cell diffusivity, tumor growth rate, and tumor mass-effect strength. They illustrate the power of using noninvasive imaging data to characterize fundamental tumor characteristics. Again, it should be stressed that these results were obtained with only anatomical imaging data. By incorporating more specific imaging measurements, such models can no doubt be expanded.

Incorporating hypoxia data into tumor modeling

A recent report by Szeto *et al.*³⁰ considered more advanced imaging techniques in which they correlated hypoxia (from PET measurements) with the net invasion rate (from modeling) obtained from their extended reaction–diffusion model. Using their methods for obtaining proliferation and invasion parameters (ρ and D , respectively) from T_1 - and T_2 -weighted anatomical MRI data, the authors found a high positive correlation between these parameters and relative hypoxia as measured by FLT-PET. These data were obtained in 11 glioblastoma multiforme patients and, though the PET data were not explicitly incorporated into the mathematical model of tumor growth, the high correlation between model parameters and the PET data suggest that such an approach is feasible.

Incorporating imaging data in simple models of tumor growth

While the above approaches have shown considerable and exciting promise, the field developing at the interface of mathematical tumor modeling and cancer imaging is still quite young. In the following sections we suggest how three common models of tumor growth may be re-interpreted by incorporating imaging data and then we introduce a fourth that was constructed in terms of data only available from MRI, PET, and SPECT imaging techniques. After the introduction of each model, we mention a few illustrative examples of how it may be used to provide new biological insights and research directions.

The logistic growth model

The logistic growth model can be described by a differential equation that predicts the time course of the number of tumor cells at any time. At first the cells grow exponentially, but later their number asymptotically approaches a limit, the cellular carrying capacity. This model is explained in detail in several places (*e.g.*, ref. 31), and the relevant differential equation is:

$$\frac{dN}{dt} = k(r)N(r, t) \left(1 - \frac{N(r, t)}{\theta} \right), \quad (1)$$

where $N(r, t)$ is the number of cells per voxel at position r and time t , $k(r)$ is the cell proliferative rate at position r , and θ is the carrying capacity of the population. The solution to eqn (1) is:

$$N(r, t) = \frac{\theta N(0)}{N(0) + (\theta - N(0))e^{-k(r)t}}, \quad (2)$$

where $N(r, 0)$ is the number of cells present at $t = 0$. There are several ways in which eqn (2) can be interpreted from an imaging perspective and here we explore two possibilities.

First, we consider how to obtain maps of the proliferation rate, $k(r)$, from available imaging data. From a variety of studies of the apparent diffusion coefficient for water in cells and tissues, we can write:

$$ADC(r, t) = ADC_w - \lambda N(r, t), \quad (3)$$

where ADC_w is the ADC of free water, and λ is a proportionality constant that (most likely) varies with cell type. This relationship has been shown to hold in well-controlled settings.⁷ Note that $ADC_{\min}$ occurs when $N(r, t) = \theta$.

$$ADC_{\min} = ADC_w - \lambda\theta. \quad (4)$$

Now, after recasting eqn (2) as:

$$\frac{\theta - N(r, t)}{N(r, t)} = \frac{\theta - N(r, 0)}{N(r, 0)} e^{-k(r)t}, \quad (5)$$

we can substitute eqn (3) and (4), into eqn (5) to capture (after regrouping)

$$\left(\frac{ADC(r, t) - ADC_{\min}}{ADC(r, t) - ADC_w} \right) = \left(\frac{ADC(r, 0) - ADC_{\min}}{ADC(r, 0) - ADC_w} \right) e^{-k(r)t}. \quad (6)$$

Thus, we have eliminated cell number and replaced it with ADC which can be directly obtained in 3D and at multiple time points. $ADC(r, t)$, ADC_w , and $ADC(r, 0)$ can be directly measured by imaging so it is possible to fit eqn (6) to measured ADC data to extract $k(r)$ and $ADC_{\min}$ on a voxel-by-voxel basis, thereby yielding a proliferation rate map. As proliferation is a fundamental characteristic of tumors, a method to non-invasively measure it is of great interest. The approach outlined above provides a means to measure proliferation at high spatial resolution, *in vivo*, and in 3D. In general, this yields a measure of the proliferative capacity of a given cell type under given conditions and this could provide new biological insights into any treatment or phenomena that would alter proliferation. In particular, this method would allow for the determination of how tumors respond to both existing and novel treatment regimens. For example, rats from treated and untreated groups should display different k distributions and these distributions may then be used to separate responders from nonresponders in subsequent experiments. Moreover, the carrying capacity can be interpreted as the maximum number of cells that can be contained within a given volume. For imaging, the relevant volume scale is a voxel and therefore $\theta = (\text{voxel volume})/$

(cell volume). The voxel volume and the individual cell volume (for a given cell species) are relatively well-defined quantities, so θ can be calculated.

A second possible method of applying imaging data to eqn (2) is to obtain estimates of $k(r)$ directly from FLT-PET images and use that information to predict tumor growth and treatment response. For example, eqn (2) directly predicts the number of cells provided the carrying capacity and proliferation rate are known. It may be an insightful exercise to measure the proliferation rate from FLT-PET data and then estimate the number of cells available at a later time point and compare that estimate to measurements from DW-MRI. Thus, the model can provide hypotheses that can be tested experimentally. The downstream effect of any drug that is designed to reduce (or increase) cell number could be studied with this technique, thereby making available measurements that are typically very difficult to obtain in an intact system. More specifically, this approach allows for studying the *in vivo* temporal and spatial effects of a particular drug (e.g., cytotoxic agents) on cell number. It is well known that tumors contain areas of increased cell density, so this approach would allow for making absolute determinations of that density and predictions of how that density will change in time. This would provide (quantitative) insights into how effective a drug is at reducing tumor cell burden.

Incorporating treatment in the logistic growth law

It is straightforward to include treatment within the logistic growth law.³¹ We merely amend eqn (1) by adding a term that characterizes the amount of a chemotherapeutic drug present at time t and position r , $A(r,t)$:

$$\frac{dN}{dt} = k(r)N(r,t) \left(1 - \frac{N(r,t)}{\theta}\right) - \mu A(r,t)N(r,t), \quad (7)$$

where μ is the rate at which the drug kills tumor cells. Solving eqn (7) yields

$$N(r,t) = \frac{N(r,0)\theta(k(r) - \mu A(r,t))}{N(0)k + (\theta(k(r) - \mu A(r,t)) - N(r,0)k)e^{(-t(k(r) - \mu A(r,t)))}} \quad (8)$$

It is possible to label anticancer drugs with a radionuclide so that $A(r,t)$ can be measured with nuclear imaging, and an estimate of μ can be obtained from *in vitro* studies. However, a more direct method, provided the treatment is designed to induce apoptosis, would be to employ ^{99m}Tc-Annexin-V SPECT to estimate apoptosis and therefore infer a quantity proportional to $\mu A(r,t)N(r,t)$. Thus, the approaches described above are again applicable as it is possible to estimate $N(r,t)$ and $\mu A(r,t)N(r,t)$ so that a fitting process can be employed to characterize the proliferation, $k(r)$, of the tumor. Alternatively, one could predict tumor cell number at a later time point given knowledge of $A(r,t)$, μ , and $k(r)$ (from FLT-PET as described above) at an initial time point, and then compare the prediction with actual experimental values obtained by DW-MRI.

Fig. 1 displays a schematic of how the data integration and comparison between simulated and experimental results could be implemented. The top row indicates data that could be acquired at the start of an experiment; imaging measurements of cellularity (from DW-MRI), apoptosis (from ^{99m}Tc-Annexin-V SPECT), and cell proliferation (from FLT-PET). These data could then be input into, for example, the model described by eqn (8) and then run forward to see how the model predicts tumor status at a future time point. The simulated data could then be compared to the actual tumor status. In this way, the theory behind the modeling can actually be tested experimentally in a rather straightforward fashion.

The biological insights that can be provided by this model are again the ability to quantitatively assess the effect of an anticancer drug on the tumor characteristics of cell density and proliferation. Additionally, by systematically holding some terms constant in eqn (8) and varying others, insights can be gained into the way the parameters interact. For example, by studying the relative contributions of proliferation and apoptosis, the model has the ability to simulate the distribution and accumulation of drug required to offset the cell proliferation in order to obtain tumor control.

A partial differential equation model

Here we focus on a model frequently applied to model the growth and diffusion of tumor cells within a glioma.³²

$$\frac{dN}{dt} = \nabla \cdot (D(r) \nabla N(r, t)) + k(r)N(r, t), \quad (9)$$

where $N(r, t)$ is the number of cells at position r and time t , $k(r)$ (in units of inverse time) is the net rate of cell growth at position r , and $D(r)$ (in units of length² per time) is the cellular diffusion coefficient of tumor cells which measures cell motility along gradients of cell density. We described above how one could assess $N(r, t)$ and $k(r)$, but here we must also assess $D(r)$. Swanson *et al.* have used this approach to calculate D values in individual patients³² based on T_2 and post-contrast T_1 weighted MRI. There are at least three additional approaches to employing this model with imaging data. $N(r, t)$ may be estimated using multiple ADC maps and $D(r)$ may then be determined as just described. These data could then be used to calculate $k(r)$. Alternatively, FLT-PET data may be used to obtain knowledge of $k(r)$ and combined with an estimate of $D(r)$ to predict $N(r, t)$ at later times. The third approach would be to employ DW-MRI and FLT-PET to assess $N(r, t)$ and $k(r)$ and then use this knowledge to derive $D(r)$. This is a particularly attractive option as $D(r)$ has heretofore been extremely difficult to measure.

This model also provides novel and valuable information about tumor growth and response to treatment. Additionally, this model provides the opportunity to investigate how tumor cells migrate, as characterized by $D(r)$. The ability to measure $D(r)$ *in vivo* and in individual patients could provide new insights into how tumor cells migrate. For example, they may have preferred directions of motility²⁹ in particular tissues or metabolic conditions, and this model may be able to study and predict those motions.

An “imaging mathematical model”

Here we present a new model that is built exclusively in terms of parameters that can be measured by noninvasive imaging. We consider the cells within a voxel as proliferating, undergoing apoptosis, or migrating into or out of the voxel. Mathematically, we write:

$$\frac{dN_i}{dt} = \mu_{p,i}N_i(t) - \mu_{d,i}N_i(t) + \sum_{m=1}^{26} k_{im}N_m(t), \quad (10)$$

where $N_i(t)$ is the number of tumor cells in the i th voxel at time t , $\mu_{p,i}$ and $\mu_{d,i}$ are the proliferation and death rates of the tumor cells in the i th voxel, respectively, k_{im} represents the net “transfer constant” of cells from the i th voxel to the m th voxel. (The sum runs from 1 to 26 to account for all 26 nearest neighbors in 3D.) Here we assume that k_{im} is proportional to the difference in pO₂³³ as estimated by FMISO-PET, though it could be amended to indicate other factors that determine cell movement. In terms of the accumulation of a PET tracer as estimated by the standard uptake value, SUV,³⁴ we have:

$$k_{im} = \frac{SUV_{FMISO}^i - SUV_{FMISO}^m}{SUV_{FMISO}^i + SUV_{FMISO}^m}, \quad (11)$$

where the terms on the right hand side of eqn (11) represent the SUV of FMISO in the i th and m th voxels, respectively, and we have assumed that cells will tend to move in the direction of increased pO_2 . In this model we can use imaging to provide estimates of cell proliferation (via FLT-PET), apoptosis (via ^{99m}Tc -Annexin-V), and hypoxia (via FMISO-PET). If this is combined with an initial estimate of cell number (via DW-MRI), then the model will make predictions for both cell number and spatial distribution as a function of time which can readily be tested.

The model described by eqn (10) and (11), is particularly attractive since it offers the ability to investigate how the relative contributions of proliferation, apoptosis, and migration contribute to tumor life cycles. Such data can be provided by imaging so it is possible to learn how initial values predict tumor aggressiveness. These predictions could be compared to patient outcome. It should be noted that, in addition to being able to be immediately applied to experimental data, simulations with this (and the above) models(s) may also be informative. Indeed, this is how many current mathematical models of tumor growth are actually studied. Simulations can lead to predictions and biological insights related to how proliferation, apoptosis, cellularity, and migration are linked and thereby can lead to new hypotheses. The hypotheses are generated from the combination of the models and *in vivo* imaging data so they may tested directly to validate or reject the models. In this way, it may be possible to mathematically identify imaging data that can actually predict how a given tumor will grow or respond to treatment.

Discussion

In this Perspective we have suggested how several (three existing and one novel) mathematical models of tumor growth can be described quantitatively in terms of imaging measures that can be serially obtained noninvasively and in 3D. It is important to note that these particular models involve only existing imaging techniques and therefore can immediately be tested in simulations and experiments. Furthermore, they underscore the point of having models that actually make predictions on tumor growth which can be directly tested for individual animals or patients. The longer term goal is not only to synthesize existing methods, but also to incorporate information from new, more advanced imaging techniques. As the parameters that most clearly predict treatment response emerge from experiments, they can be incorporated into appropriate and more sophisticated models.

We acknowledge that the analyses presented here are quite simple, represent only an initial step, and need to be adjusted to increase their biological relevancy. For example, in eqn (9), we have taken oxygen gradients to be a driver of cell migration, and this process is certainly more complicated than what we have assumed.¹⁵ Indeed, given that different cell lines and tumor types have different characteristics, different terms may need to be incorporated to reflect specific cell characteristics. Potentially these can be obtained by alternative molecular imaging techniques. Another limitation is that all of the models described above are avascular, while it is well known that tumors can not grow past a few cubic millimeters in size without acquiring a blood supply.³⁵ However, angiogenesis can be incorporated using, for example, data from dynamic contrast enhanced MRI³⁶ or high resolution angiography.³⁷ Some of these approaches may be relevant only for pre-clinical applications, when multi-modality techniques are more practical, but advances in hybrid technology suggest several may be translated to clinical application.

Another research track that may prove to be insightful is to more explicitly incorporate imaging data into multi-scale mathematical models of tumor growth.³⁸ For example, efforts like the “Phsyiome Project”³⁹ aim to develop modeling frameworks that incorporate biochemical, biophysical, and anatomical from the cellular to organism levels. We anticipate that quantitative, *in vivo* imaging will help to fill the void between molecular/cellular level data afforded by invasive techniques (*e.g.*, biopsy, tissue sampling, *etc.*) and the morphology level data afforded by anatomical imaging (*i.e.*, clinical CT, US, MRI). This may be of particular interest when relevant data on tumor status (*e.g.*, receptor expression, growth factor concentrations, *etc.*) is not available from imaging but required for modeling. Initial efforts at multi-scale modeling exist and are quite promising (see, *e.g.*, ref. 40–42).

There are a number of obstacles that will be encountered in pursuing the investigations outlined in this contribution. Perhaps the most pressing issue is the construction of reasonable models that only include parameters that are accessible by noninvasive imaging. Furthermore, these parameters must be related to tumor growth in well-defined ways. Even though there has been tremendous growth in both the quantity and quality of imaging metrics, many key measurements are still not well understood. A second fundamental problem is that the currently available spatial resolution that imaging data is acquired (~0.1–2 mm, depending on the modality) might be too coarse for precise modeling. A more practical issue to address is that since imaging techniques have inherent strengths and weaknesses, multi-modality approaches will most likely be the most informative for guiding mathematical models of tumor growth. Though there is an increase in the number of small animal imaging centers that have multiple modalities and the capability of registering/fusing such data, the ability to get the corresponding data from clinical studies is currently limited.

While there are several groups making exciting contributions at the interface of cancer imaging and mathematical modeling, we believe there is much room for growth. We have outlined various simple approaches whereby multi-modality imaging data can be synthesized and integrated in order to drive simple mathematical models of tumor growth. (The interested reader is encouraged to consult ref. 43 for a preliminary exploration through simulations of several of the models presented in this contribution). We suggest that using imaging data in this manner may prove to be a powerful approach to increase our understanding of tumor growth and treatment response and to enhance the practical import of mathematical modeling. It is our hope that this Perspective will stimulate further work in this direction.

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Fig. 1.

The figure displays how the data integration of imaging data can be used to study tumor growth. The top row displays data that could be acquired at the start of an experiment; imaging measurements of cellularity, apoptosis, and cell proliferation. These data could then be input into eqn (8) and run forward to see how the model predicts tumor status at a future time point. The simulated data could then be compared to the tumor status measure experimentally.