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Abstract. The therapy operating characteristic (TOC) curve, developed in the context of radiation therapy, is a plot of the probability of tumor control versus the probability of normal-tissue complications as the overall radiation dose level is varied, e.g., by varying the beam current in external-beam radiotherapy or the total injected activity in radionuclide therapy. This paper shows how TOC can be applied to chemotherapy with the administered drug dosage as the variable. The area under a TOC curve (AUTOC) can be used as a figure of merit for therapeutic efficacy, analogous to the area under an ROC curve (AUROC), which is a figure of merit for diagnostic efficacy. In radiation therapy, AUTOC can be computed for a single patient by using image data along with radiobiological models for tumor response and adverse side effects. The mathematical analogy between response of observers to images and the response of tumors to distributions of a chemotherapy drug is exploited to obtain linear discriminant functions from which AUTOC can be calculated. Methods for using mathematical models of drug delivery and tumor response with imaging data to estimate patient-specific parameters that are needed for calculation of AUTOC are outlined. The implications of this viewpoint for clinical trials are discussed. © 2016 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: 10.1117/1.JMI.3.2.023502]

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1 Introduction

The term precision medicine is commonplace in current dialogue, and it is frequently offered as a modern synonym for personalized medicine, but it is fair to ask whether either designation is apt in the context of cancer therapy. One marvels at the efficiency and precision of mapping a patient's genome, but it is less obvious that the subsequent treatment meets the standards of quantitative accuracy implied by the term “precision,” or that the treatment is personalized to any significant degree beyond selection of the drug for a particular patient. Consider the following critical open questions:

1. What biological and statistical models can be used to determine the optimum amount of a therapeutic agent to administer to a patient, taking into account the probability of tumor control and the potential occurrence of toxic side effects? Can the tradeoff between beneficial and deleterious effects of a drug be made quantitatively for an individual patient?
2. A major uncertainty in chemotherapy and targeted radionuclide therapy or immunotherapy is the amount of drug delivered to the tumor bed and, for targeted agents, how much of the drug is bound to receptors on tumor cells and how much is internalized into the

cells. How can quantitative measures of drug delivery and targeting efficiency be incorporated into estimates of probability of tumor control for an individual patient?

3. Therapeutic efficacy^{1–3} is defined for populations of patients and measured by clinical trials, so what does it even mean to optimize a therapy for a particular patient? How can you verify that you have done so? This is the fundamental conundrum of precision medicine. How can it be resolved?

Answers to these questions in the context of chemotherapy are given in this paper. In Sec. 2, we review the concept of therapy operating characteristic (TOC) curves,^{4,5} which can provide an answer to question 1. In radiation therapy, a TOC curve is a plot of the probability of tumor control versus the probability of specified normal-tissue complications as the overall radiation dose level is varied, e.g., by varying the beam current in external-beam radiotherapy or the total injected activity in radionuclide therapy. As we show in Sec. 2, the TOC can be applied to chemotherapy with the administered drug dosage as the variable. The area under a TOC curve, denoted AUTOC, can be used as a figure of merit for therapeutic efficacy, analogous to the area under an ROC curve (AUROC), which is a figure of merit for diagnostic efficacy.³

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In radiation therapy, we have shown^{4,5} that AUTOC can be computed for a single patient by using image data along with radiobiological models for tumor response and adverse side effects. Extension of TOC to chemotherapy requires mathematical models for drug transport and binding, which we review briefly in Sec. 3. These models afford a rigorous approach to answering question 2.

In Sec. 4, we introduce the concept of posterior probability, which underlies all forms of personalized therapy. The word “posterior” in this context refers to our knowledge of an individual patient “after” we have acquired the images and clinical or genomic data needed to plan the personalized therapy. We show how the fundamental conundrum, question 3, can be resolved by distinguishing posterior and prior ensembles. Though often associated with Bayesian statistics and hence regarded as subjective, we argue in Sec. 4 that posterior probabilities and conclusions drawn from them are amenable to verification by clinical trials.

In Sec. 5, we exploit the analogies to ROC theory further and develop methods for computing the posterior probabilities and relating them to probability of tumor control. A summary and recommendations for future research are given in Sec. 6.

There is substantial overlap between this paper and an earlier report in *Proc. SPIE*.⁶

2 Metrics of Therapeutic Success: Therapy Operating Characteristic Curves

2.1 Radiation Therapy with External Beams

Tumors can be treated with beams of photons, electrons, protons, neutrons, or heavy ions. Clinical practice with these therapies is to use images of the patient to identify the regions occupied by the tumor and by normal organs, and then to plan a therapy that will deliver a cytotoxic radiation dose to the tumor and tolerable doses to critical normal organs. In this sense, routine external-beam radiation therapy is already much more personalized than most chemotherapy.

Another key difference is that delivery of a radiation dose is much more precise than delivery of a chemotherapeutic dose. The distribution of the electron density in a patient can be derived from a CT scan and then the spatial and temporal distribution of the absorbed dose, measured in Grays, can be computed from basic physics and knowledge of the beam parameters for the particular patient. The uncertainties in delivery of a radiation dose are much less significant than the uncertainties in delivering a chemotherapeutic dose. Moreover, the uncertainties in the biological effects of the radiation dose can be assessed with some precision through the use of mathematical radiobiological models.

2.2 Therapy Operating Characteristic Curves and their Application in Radiation Therapy

As noted in Sec. 1, a TOC curve is a plot of the probability of tumor control, denoted $\text{Pr}(\text{TC})$, versus the probability of normal-tissue complications, $\text{Pr}(\text{NTC})$, as the overall radiation dose level is varied. The mathematical and computational aspects of TOC curves are treated in detail in Barrett et al.,⁵ the sixth in a series of theoretical papers on Objective Assessment of Image Quality, hence referred to as OAIQ VI. Two schematic TOC curves are depicted in Fig. 1.

OAIQ VI uses the AUTOC as a figure of merit for radiation therapy planning and for the imaging components that affect the plan. An AUTOC of 1.0 is ideal, and $\text{AUTOC} = 0.5$ corresponds to a treatment scenario in which the probability of tumor control can be increased only at the expense of an identical increase in the probability of normal-tissue complications. In contrast to ROC, an $\text{AUTOC} \ll 0.5$ can also occur, in the case of a very bad treatment plan where there is a large probability of damage to normal tissues with little chance of tumor control.

Much work has gone into estimating $\text{Pr}(\text{TC})$ and $\text{Pr}(\text{NTC})$,^{7–12} and standardized modules for their calculation are freely available.^{13,14}

As detailed in OAIQ VI, AUTOC can be used for

- Evaluation of image quality in terms of therapeutic efficacy
- Comparison of treatment regimes for a population of patients
- Evaluation of segmentation algorithms⁴
- Study of the effects of patient motion during beam therapy
- Study of the usefulness of auxiliary data, such as hypoxia images
- Evaluation of stem cells and viruses as vectors for radio-nuclide therapy
- Optimization of the treatment plan for an individual patient

To use AUTOC as a figure of merit for personalized radiation therapy, we need

- Image data from an individual patient
- Treatment plan tailored to the patient
- Calculated distribution of radiation absorbed dose (in Gy)
- Credible radiobiological models for $\text{Pr}(\text{TC})$ and $\text{Pr}(\text{NTC})$

Fig. 1 Schematic therapy operating characteristic curves for two treatment plans on the same patient. The plan corresponding to the upper curve will give a higher probability of tumor control for a given probability of normal-tissue complication; different complications would give different TOC curves.

2.3 Extension of Therapy Operating Characteristic Methodology to Chemotherapy

To compute $\text{Pr}(\text{TC})$ as function of administered chemotherapeutic dose for a specific patient, we need

- Mathematical models for drug delivery
- Mathematical models for drug response
- Image data from which to estimate free parameters in the models
- Efficient estimation methods
- Methods to estimate uncertainty of parameter estimates and resulting uncertainty in delivery and response

This appears to be a daunting list, but the models are not intended to predict the patient response *ab initio*; rather, the goal is to provide a robust parametric description of the mechanisms that control that response, specifically extravasation, transport, binding, and internalization. The parameter estimates are intended to serve as approximate sufficient statistics for estimation of $\text{Pr}(\text{TC})$.

One way to get the needed image data for estimating $\text{Pr}(\text{TC})$ is to use radiolabeled therapeutic agents, or validated surrogates, at a subtherapeutic dose and acquire dynamic positron emission tomography (PET) or single-photon emission computed tomography (SPECT) images. For example, there is considerable current interest in antibody–drug conjugates, in which a monoclonal antibody can be linked to either a radionuclide or a chemotherapy drug. The ability of the antibody to target its antigen is essentially unchanged by the addition of a small molecule, provided the binding site is not obstructed by the conjugate.

The concept of radiolabeling chemotherapy agents to assess targeting is not new. Pilot studies go back to the mid-1970s, when Walter Wolf at the University of Southern California proposed using Pt-195m-labeled cisplatin,^{15–17} and a group at the University of Arizona used Co-57 bleomycin (although not specifically to evaluate targeting).^{18,19} The related approach of using the same agent at low dose for diagnostic imaging and at high dose for therapy is also not new. The best exemplar is probably I-131 sodium iodide in differentiated thyroid carcinoma (or, alternatively, I-123 for diagnosis and I-131 for therapy). A variation on this theme is exemplified by I-131 tositumomab (Bexxar) in B-cell lymphoma, where the initial low dose provides quantitative image data for radiation-dose estimation, and the therapy dose is derived from these data so as to limit bone-marrow toxicity. Another variation on this theme is In-111-ibritumomab (Zevalin) for imaging and Y-90-Zevalin for therapy of B-cell lymphoma and certain other non-Hodgkin lymphomas. Zevalin has another interesting property, namely that the molecule without Y-90 and its chelating linker is essentially the same as rituximab (Rituxan), a standard chemotherapy drug for lymphoma.

The abscissa on a chemotherapy TOC curve, $\text{Pr}(\text{NTC})$, depends on the type and amount of the therapeutic drug, and of course on the patient and the particular adverse effect considered, but it does not depend on the parameters that drive $\text{Pr}(\text{TC})$. The only apparent way of getting a personalized $\text{Pr}(\text{NTC})$ is to make use of databases of adverse effects in chemotherapy and stratify them according to the clinical history, tumor stage, and other characteristics of the patient. Other information that contributes to personalized $\text{Pr}(\text{NTC})$ includes renal function and baseline bone-marrow function; both of these are commonly taken into account in planning dosage of chemotherapy agents.

3 Mathematical Models for Drug Delivery

Factors that impede drug delivery include the complicated, tortuous nature of tumor vasculature; the biochemical signals that control the vessel permeability; and the fibrotic stroma that results from desmoplastic reaction in the extracellular space. For targeted chemotherapeutic agents, we must also consider the “end-game” processes of receptor binding; internalization of the drug into the cell; catabolism (breakdown of the drug) and residualization back into the extracellular space.

The patient-to-patient variations in drug delivery are potentially very large. Gurney²⁰ estimates that there is a 4- to 10-fold variation among individuals in cytotoxic drug clearance from serum, and there is further variation in vascular permeability, internal tumor pressure, and transport of the drug to the tumor cells. This enormous range of patient-specific variation means that some patients will suffer unnecessary toxic side effects and others will get less than the requisite therapeutic dose to the tumor. In clinical trials, this same variability can lead to a drug being declared ineffective when it would, in fact, be very effective if administered with the proper dosage and route for each patient. Current practice in medical oncology is personalized by attempting to tailor the drug to the tumor genomics, but there is a need to quantify and optimize the amount of drug delivered.

In this section, we survey models that have been used or suggested as descriptions of the major intratumoral processes: extravasation, diffusion, binding, and internalization. To set the stage, we begin with a discussion of the three-dimensional (3-D) time-dependent diffusion equation.

3.1 Diffusion Equation

The time-dependent diffusion equation for an infinite uniform medium is

$$\left[\frac{\partial}{\partial t} - D \nabla^2 \right] f(\mathbf{r}, t) = s(\mathbf{r}, t), \quad (1)$$

where $f(\mathbf{r}, t)$ is the concentration of the diffusing species (e.g., a radiotracer) at point $\mathbf{r}$ and time t , $s(\mathbf{r}, t)$ is the source of this species, and D is the diffusion coefficient. Note that $f(\mathbf{r}, t)$ has units of inverse volume or inverse length cubed, which we write as $[f] = 1/L^3$, where $[\dots]$ is read “dimensions of $\dots$ ”. The source $s(\mathbf{r}, t)$, on the other hand, is a rate of change of concentration, $[s] = 1/(L^3 T)$ (T = time). Thus, $[D] = L^2/T$.

We can solve this equation in terms of the Green’s function, $G(\mathbf{r}, \mathbf{r}'; t, t')$, which must satisfy

$$\left[\frac{\partial}{\partial t} - D \nabla^2 \right] G(\mathbf{r}, \mathbf{r}'; t, t') = \delta(\mathbf{r} - \mathbf{r}') \delta(t - t').$$

It can be shown that

$$G(\mathbf{r}, \mathbf{r}'; t, t') = \frac{\text{step}(t - t')}{[4\pi D(t - t')]^{3/2}} \exp \left[-\frac{|\mathbf{r} - \mathbf{r}'|^2}{4D(t - t')} \right],$$

where $\text{step}(t - t') = 1$ if $t > t'$ and 0 if $t < t'$. If the source function is known, the solution to Eq. (1) is

$$f(\mathbf{r}, t) = \int_{-\infty}^{\infty} d^3 r' \int_{-\infty}^t dt' G(\mathbf{r}, \mathbf{r}'; t, t') s(\mathbf{r}', t'), \quad (2)$$

where the subscript ∞ on the integral indicates that it runs over the infinite 3-D domain.

To illustrate the results of this equation, we considered diffusion of an antibody of molecular weight 150 kDa from the point of extravasation in the tumor to an observation point 100, 200, or 400 μm away. In accord with Nugent and Jain,²¹ we took the diffusion coefficient in the tumor to be $10^{-7} \text{ cm}^2/\text{s}$, and we considered spherical shells of capillaries surrounding the observation point, so that the source strength in the diffusion equation was proportional to $|\mathbf{r} - \mathbf{r}'|^2$. The resulting plots of antibody concentration versus time are shown in Fig. 2. Note that the horizontal axis in this plot extends to 100 min; though equilibration of the drug concentration in major blood vessels might occur rapidly, equilibration within the tumor capillary bed is quite slow.

If the diffusion coefficient is a function of location within a tumor, Eq. (1) becomes

$$\frac{\partial}{\partial t} f(\mathbf{r}, t) - \nabla \cdot [D(\mathbf{r}) \nabla f(\mathbf{r}, t)] = s(\mathbf{r}, t).$$

For small deviations of D about a constant value, it is useful to write $D(\mathbf{r}) = D_0 + \delta D(\mathbf{r})$, and in this case, the solution can be approximated by a Born series, possibly retaining only the first term.²²

3.2 Application to Radiotracer Diffusion in Solid Tumors

In emission imaging with radioactive materials, the object is often defined as activity per unit volume, where activity is expressed in becquerels (Bq) or nuclear disintegrations per second. If we denote the time-dependent activity per unit volume as $a(\mathbf{r}, t)$, then $a(\mathbf{r}, t) = f(\mathbf{r}, t)/\tau$, where τ is the exponential-decay time constant of the radioisotope, in seconds. The more familiar half-life is given by $T_{1/2} = \tau \ln 2$. In what follows we denote the object as $f(\mathbf{r}, t)$. If there is one radioactive nucleus per tracer molecule, then $f(\mathbf{r}, t)$ is the mean number of molecules per unit volume at point $\mathbf{r}$ and time t .

Fig. 2 Concentration of a monoclonal antibody as a function of time following an impulse injection at $t = 0$ [i.e., $s(\mathbf{r}, t) \propto \delta(t)$]. Spatially, the impulse source was a thin, spherical shell surrounding the observation point, but except for a scale factor on the ordinate, the same result would be obtained for injection at a point.

In kinetic studies with a radiotracer, $f(\mathbf{r}, t) = 0$ before the injection of the tracer, which we take to be at time $t = 0$. After this time, the concentration of the tracer in blood vessels is denoted $c(\mathbf{r}, t)$.

The rate at which the tracer escapes from the vessels and enters the interstitium depends on both the vascular permeability and the tumor vascularity. The vascular permeability is defined as the molecular flux (molecules per unit area per second) through the vessel wall divided by the concentration (molecules per unit volume) within the vessel. Thus, the permeability has dimensions of L/T , and it is frequently expressed in cm/s .

The source term in the diffusion equation must account for the plasma concentration, the permeability and the total capillary area per unit volume through which the extravasation can occur. Within a given volume, this area depends on the number of capillaries and their average diameter. Thus, we can write

$$s(\mathbf{r}, t) \equiv c(\mathbf{r}, t)v(\mathbf{r}), \quad (t \geq 0), \quad (3)$$

where the “vascular factor” $v(\mathbf{r})$ (assumed to be independent of time during an imaging session) can be interpreted as the average permeability times the average number of vessels per unit volume times the average area-to-volume ratio of the vessels, so that $[s] = 1/(L^3T)$, as required for dimensional consistency in Eq. (1).

With Eqs. (3) and (2) becomes

$$f(\mathbf{r}, t) = \int_V d^3r' \int_0^t dt' G(\mathbf{r}, \mathbf{r}'; t - t') c(\mathbf{r}', t') v(\mathbf{r}'),$$

where V is the volume occupied by the tumor.

3.3 Models for Tumor Vascularity and Permeability

Many current models of drug delivery trace back to the 1919 work of Nobel Laureate August Krogh on oxygen transport. The Krogh cylinder model^{23–25} represents the capillaries as a regular array of uniform cylinders, and it assumes that any point in the tumor is perfused by only one such model capillary.

More realistic models of tumor capillaries are given in numerous papers by Rakesh Jain and coworkers, and in particular, the fractal model given by Baish and Jain²⁶ captures the complexity of the problem with a small number of free parameters. Secomb²⁷ has recently used a Green’s function method to model drug transport in realistic microvascular networks.

Compartmental pharmacokinetics (CPK) is also commonly used, but it is not well suited to the purposes of this paper. A compartment is a defined volume of tissue within which there are no spatial gradients (there are no spatial derivatives in the CPK equations) and where equilibrium concentrations within the compartments are reached essentially instantaneously. Moreover, it is assumed that the plasma concentration of the drug is the same at all points in the subject. Departures from the CPK assumptions, including nonequilibrium processes and spatial gradients, can result in heterogeneity of the drug distribution and reduced efficacy of the therapy. Treating the tumor cells collectively as a single compartment is unrealistic, and doing CPK on a voxel-by-voxel basis neglects communication between voxels by routes other than the common arterial supply. The time scales in Fig. 2 show that there are long delays between a change in arterial concentration and delivery of a drug to a point in a tumor; the arterial input function, a critical part of CPK analysis, has

very little to do with the time dependence of the interstitial concentration within a tumor capillary bed.

3.4 Binding and Internalization in Targeted Therapy

Binding of a ligand to a receptor is conventionally parameterized by the receptor number $B_{\max}$ (receptors per cell), the affinity K_d , and the binding potential $B_{\max}/K_d$. In equilibrium, there is a simple relation between K_d and the fraction of targeted drug molecules or other ligands bound to their receptors, but it is difficult to know whether equilibrium conditions prevail.

Nonequilibrium reaction-diffusion models, such as the Smoluchowski and Doi models, are reviewed by Agbanusi and Isaacson.²⁸

Internalization takes place through endocytosis or transmembrane receptors; for a discussion of the mathematics of endocytosis and its relation to signaling, see Birtwistle and Kholodenko.²⁹

3.5 Concentration Distribution in a Tracer Study

When all of these processes are active in a radiotracer study, we can write the total concentration (molecules per unit volume) of the radionuclide as

$$f(\mathbf{r}, t) = f^c(\mathbf{r}, t) + f^d(\mathbf{r}, t) + f^b(\mathbf{r}, t) + f^i(\mathbf{r}, t), \quad (4)$$

where the four terms represent, respectively, the concentrations in the capillaries (superscript c); diffusing in the tumor interstitium (d); bound to cell-surface receptors (b), and internalized into the cytoplasm (i). In a dynamic PET or SPECT study, all of these terms contribute to the image data but with different time dependences, so in principle they can be separated.

4 Posterior Probabilities

We now return to the basic problem of personalized medicine, as posed in Sec. 1: both diagnostic and therapeutic efficacies are defined for a large population of patients. What does it mean to optimize the results for one patient? How can we verify that we have done so? Specifically, for personalized chemotherapy, how can we vary the administered drug dosage or regimen so as to get the best possible therapeutic outcome for an individual patient?

Similar questions arise in diagnostic imaging: how can we vary the imaging system configuration or data-acquisition protocol so as to get the best possible diagnostic information for an individual patient? A general approach to answering this question for adaptive (personalized) SPECT imaging was given by Barrett et al.,³⁰ and it was extended to more general adaptive and multimodality imaging systems by Clarkson et al.³¹

The general schema for personalized medicine is illustrated, for both diagnostic imaging and therapy, in Table 1. The key is

to define two theoretical infinite ensembles of patients, called the “prior ensemble and the posterior ensemble.”

One way to think of a prior ensemble is that it is a population on which clinical trials can be performed. For a trial of a chemotherapy drug, for example, a set of inclusion criteria is specified and some endpoint or outcome is defined. The set of all patients who satisfy the inclusion criteria is the prior ensemble, in the present language, and the actual cohort for the trial is a random sample from this ensemble. Often, this cohort is divided into two groups (arms), in one of which the patients receive the drug under test and in the other, they receive a different drug. The two drugs may have different standard dosages (mg/m²) and administration schedules and other protocol factors, but all patients in the same arm receive identical treatment.

In personalized chemotherapy, by contrast, we perform genetic profiling, blood tests, and imaging studies to obtain detailed information on each patient, and we use that information to alter the protocol. Depending on what information is acquired, the protocol alterations can include changing the dosage or administration schedule; pharmacological interventions such as P-gp suppressors or stromal modulators; methods of increasing oxygenation or pH of the tumor, or even choosing different drugs or drug combinations.

With this approach, we have a different protocol for each patient. Does that rule out the possibility of clinical trials? No. We just have to rephrase the question to be answered by the trial. A conventional drug trial asks whether drug A with protocol 1 is better than drug B with protocol 2. Now we can ask whether drug A with a protocol adapted to the patient is better than drug A with a fixed protocol. In other words, does personalized therapy really work? The adaptation (personalization) strategy is an algorithm for deciding how to change the protocol from patient to patient, much as we now adapt the dosage to body surface area. We can think of the adaptation strategy as a metaprotocol, and we can perform clinical trials not with fixed protocols but with fixed metaprotocols. With two drugs, we can adapt each to the patient and ask if drug A with a protocol adapted to the patient is better than drug B with a different protocol adapted to the same patient.

This process can be repeated for multiple patients drawn from the same prior ensemble in order to answer the questions posed in the previous paragraph, and standard methods can be used to assess the statistical significance of the conclusions.

Similar considerations apply to adaptive diagnostic imaging, as indicated in Table 1, and we can summarize the paradigm in both cases as

- obtain patient-specific images and other data;
- adapt the final imaging system or therapy regimen for the posterior ensemble;
- evaluate the result with samples from the prior ensemble.

Table 1 Paradigm for adaptive imaging and personalized therapy.

	Adaptive imaging	Personalized therapy
Prior ensemble	Set of all patients presenting for a given diagnostic study with a given modality	Set of all patients with a given cancer and undergoing therapy with a given drug
Posterior ensemble	Set of all patients in prior ensemble and consistent with initial “static” imaging studies on a particular patient	Set of all patients in prior ensemble and consistent with initial “dynamic” imaging studies on a particular patient

A key point is that the second step requires mathematical or heuristic models for diagnostic or therapeutic efficacy, perhaps as expressed by AUROC or AUTOC.

With this paradigm, the outcome of the clinical trial will be a “joint” evaluation of the quality of the patient-specific data; the strategy for adapting the imaging system or therapy regimen to the patient, and the models that connect the data and the strategy. “The only thing one can ever evaluate in a clinical trial for personalized medicine is the combination of the patient-specific data, the model and the adaptation strategy.”

5 Computational Methods

In Sec. 2.3, we suggested collecting dynamic SPECT or PET images with a small, subtherapeutic amount of a radiolabeled chemotherapy drug in order to obtain information about drug delivery for a particular patient, denoted patient j . Let the set of all such dynamic images acquired for patient j be denoted $\mathbf{G}_j$. For actual therapy, we would use the same drug, probably without the radioactive label, and administer a much larger amount. If we assume that mass M_j of the drug will be administered to this patient for the therapy, then both the probability of tumor control and the probability of a normal-tissue complication will increase monotonically with M_j , so we can take M_j as the control variable on a TOC curve for chemotherapy.

To construct the TOC curve for patient j , we need the conditional probabilities $\Pr(\text{TC}|M_j, \mathbf{G}_j, j)$ and $\Pr(\text{NTC}|M_j, \mathbf{G}_j, j)$. The tumor-control probability $\Pr(\text{TC}|M_j, \mathbf{G}_j, j)$ is the probability of tumor control given that images $\mathbf{G}_j$ were obtained in the tracer study and that mass M_j of the drug was administered to patient j in the therapeutic step. The final j in $\Pr(\text{TC}|M_j, \mathbf{G}_j, j)$ is included so that clinical or genomic data about patient j can be used, along with the image data, in estimating the TC probability.

Current clinical practice in chemotherapy is to choose the administered dose to be proportional to the patient’s body surface area, with no information about the processes that limit dose delivery to the tumor cells. As databases become ever larger and more accessible, it should be possible to construct good estimates of $\Pr(\text{TC}|M)$ and $\Pr(\text{NTC}|M)$ for the prior ensemble of all patients who have received a specific drug for a specific type, stage, and grade of tumor. These estimates will depend on the definition of tumor control and the type and magnitude of the normal-tissue effects considered, and of course, they vary with the administered mass (or mass per unit patient surface area) of the drug, but they should provide a reasonable characterization of the prior ensemble.

Moreover, if we assume that the dynamic images cover just the tumor region, then these same clinical data immediately give us the “posterior” probability of normal-tissue complications, after the dynamic ECT images are acquired, simply because the images provide no information relevant to normal-tissue complications. Posterior and prior are identical in this case, so $\Pr(\text{NTC}|M_j, \mathbf{G}, j) = \Pr(\text{NTC}|M_j, j)$. Again, the final j in this expression indicates that $\Pr(\text{NTC})$ can still depend on characteristics of the specific patient; for example, cardiac function tests can be used to assess the patient’s propensity for cardiotoxicity after doxorubicin therapy.

5.1 Analogy to Receiver Operating Characteristic Analysis; Linear Discriminants

ROC analysis is used to measure the performance of some observer or decision maker on binary classification tasks,

where a dataset must be associated with one of two possible classes, say class C_1 and class C_2 (e.g., tumor absent and tumor present). In medical imaging, the observer can be radiologist, a computer algorithm, or a mathematical construct called the “ideal observer,” and the data consist of one or more images, denoted as $\mathbf{g}$.

Under broad conditions,²² it can be shown that the decision strategy of any algorithmic observer given data $\mathbf{g}$ can be construed as first computing a scalar-valued functional of the data, denoted $\tau \equiv T(\mathbf{g})$ and then making the decision by comparing it to a decision threshold τ_0 as follows:

$$\begin{array}{c} D_2 \\ \tau > \tau_0 \\ D_1 \end{array}$$

This inequality is to be read, “make decision D_2 (i.e., choose class C_2) when the greater-than sign holds; make decision D_1 (choose class C_1) when the less-than sign holds.” Human observers fit into this same paradigm if we allow a random component, called “internal noise,” in the decision variable τ . The scalar τ is called the “test statistic,” and $T(\mathbf{g})$ is the “discriminant function.”

The probability of the observer making decision D_2 when the dataset was produced from an object in class C_2 , known as the true positive fraction or TPF, is given by²²

$$\begin{aligned} \text{TPF} \equiv \Pr(D_2|C_2) &= \Pr(\tau > \tau_0|C_2) = \int_{\tau_0}^{\infty} d\tau \text{pr}(\tau|C_2) \\ &= \int_{\tau_0}^{\infty} d\tau \int d\mathbf{g} \text{pr}(\tau|\mathbf{g}) \text{pr}(\mathbf{g}|C_2), \end{aligned} \quad (5)$$

where $\text{pr}(\cdot)$ denotes “probability density function” (PDF) and $\text{pr}(\cdot|\cdot)$ is a conditional PDF.

TOC analysis for chemotherapy has this same structure. The tumor itself can be regarded as the observer, and the dataset to which it responds is the drug distribution in the tumor, which we denote as $F(\mathbf{r}, t)$. If the administered dose in both the radiotracer step and the therapy was small enough to avoid saturating the receptors, $F(\mathbf{r}, t)$ would be just the ratio of the injected masses times the tracer concentration $f(\mathbf{r}, t)$ discussed in Sec. 3, but a nonlinear relation is expected in general.

As in Eq. (4), the drug distribution consists of molecules in the capillaries, freely diffusing molecules and ones either bound to receptors or internalized into the cytoplasm, so we can write

$$F(\mathbf{r}, t) = F^c(\mathbf{r}, t) + F^d(\mathbf{r}, t) + F^b(\mathbf{r}, t) + F^i(\mathbf{r}, t).$$

A useful shorthand is to think of this distribution as a vector in a Hilbert space and write $\mathbf{F} = \mathbf{F}^c + \mathbf{F}^d + \mathbf{F}^b + \mathbf{F}^i$.

If the drug must be internalized to be cytotoxic, only $\mathbf{F}^i$ contributes to the probability of tumor control, and the test statistic for patient j is given by $\tau = T(\mathbf{F}_j^i)$. The TOC analog of Eq. (5), for a single patient j rather than a class, becomes

$$\begin{aligned} \Pr(\text{TC}|M_j, j) &= \Pr(\tau > \tau_0|M_j, j) = \int_{\tau_0}^{\infty} d\tau \text{pr}(\tau|M_j, j) \\ &= \int_{\tau_0}^{\infty} d\tau \int d\mathbf{F}_j^i \text{pr}(\tau|\mathbf{F}_j^i) \text{pr}(\mathbf{F}_j^i|M_j, j). \end{aligned} \quad (6)$$

For chemotherapeutic agents that are effective without internalization and for targeted radionuclide therapy, $\mathbf{F}^i$ should be replaced by $\mathbf{F}^i + \mathbf{F}^b$ in this equation and the following ones.

In both ROC analysis and TOC analysis, linear discriminants play a key role. For digital images with N elements, the general linear discriminant is a scalar product of the form $T(\mathbf{g}) = \mathbf{w}^t \mathbf{g} = \sum_{n=1}^N w_n g_n$, where $\mathbf{w}$, called a template, is a vector the same size as the image. Linear discriminants are often good models of human observers, and they describe the ideal observer if the data statistics are multivariate normal and the signal to be detected is weak.

In TOC analysis for chemotherapy, the general linear discriminant is also a scalar product, but now in terms of continuous variables:

$$T(\mathbf{F}_j^i) = \int_0^\infty dt \int_V d^3r F_j^i(\mathbf{r}, t) S(\mathbf{r}, t),$$

where V is the volume of the tumor. The template $S(\mathbf{r}, t)$ in this case can be interpreted as the sensitivity of the tumor cells at point $\mathbf{r}$ and time t to the intracellular component of the drug; the spatial variation of $S(\mathbf{r}, t)$ is the relevant description of the heterogeneity of the response, and the temporal variation over a long time scale is descriptive of evolving sensitivity to the drug.

An important special case of linear discriminants in both ROC and TOC is where the template is a constant over some spatial region and temporally. In image-quality studies, this case is called the nonprewhitening matched filter, and for TOC, setting $S(\mathbf{r}, t)$ to the constant $1/V$ yields

$$T(\mathbf{F}_j^i) = \frac{1}{V} \int_0^\infty dt \int_V d^3r F_j^i(\mathbf{r}, t) \equiv \int_0^\infty dt C_j^i(t), \quad (7)$$

where $C_j^i(t)$ is the spatial average of the intracellular drug concentration as a function of time.

Dimensionally, the linear discriminant defined in Eq. (7) is a concentration times a time, and it is a familiar construct in the chemotherapy literature, referred to there as AUC, meaning the area under a curve of drug concentration versus time. In clinical oncology, however, the concentration is determined from blood samples at a sequence of times, because that is all that can be measured directly on a patient or experimental animal. We refer to this common clinical metric as serum AUC, or sAUC for short, and in Eq. (7), we are defining the intracellular AUC, denoted iAUC. For patient j , iAUC is a monotonically increasing but not necessarily linear function of M_j , so we write it as $\text{iAUC}_j(M_j)$.

Because linear discriminants are sums or integrals of a large number of more-or-less independent random variables, they tend to have univariate normal PDFs, and the integral over τ in Eqs. (5) or (6) can be expressed in terms of an error function, $\text{erf}(\cdot)$. For chemotherapy with $\tau = \text{iAUC}_j(M_j)$ as the test statistic for patient j , Eq. (6) becomes

$$\begin{aligned} \Pr(\text{TC}|M_j, j) &= \Pr(\text{iAUC}_j(M_j) > \tau_0) \\ &= \frac{1}{2} + \frac{1}{2} \text{erf}\left(\frac{\text{iAUC}_j(M_j) - \tau_0}{\sqrt{2}\sigma}\right). \end{aligned} \quad (8)$$

Since $\text{erf}(0) = 0$, we can interpret τ_0 as the value of iAUC for which $\Pr(\text{TC}) = 1/2$, and the parameter σ determines the steepness of the curve of $\Pr(\text{TC})$ versus iAUC through this point.

5.2 Estimation of $\Pr(\text{TC})$ from Image Data

The free parameters in Eq. (8), τ_0 and σ , are characteristics of the tumor type and the drug, and in principle, they can be determined from databases or *in vitro* studies; an analytic approach to predicting cell response from *in vitro* data is given by Gardner.³²

The patient-specific part of Eq. (8) is $\text{iAUC}_j(M_j)$, which we have to estimate from the dynamic images acquired in the radio-tracer study on patient j . We denote the resulting estimated tumor-control probability as $\hat{\Pr}(\text{TC}|\mathbf{G}_j, M_j, j)$, which is a posterior probability in the sense of this paper because it is computed from the image data that distinguish the posterior ensemble from the prior ensemble.

As a starting point for discussing the estimation, we can go back to the tracer-stage concentration expression in Eq. (4). Within a constant, the left-hand side is the total activity per unit volume in the tumor as a function of position and time, which is the object being imaged in the tracer study. Within the limitations imposed by the spatial and temporal resolutions of the imaging system and the duration of the scan, $f_j(\mathbf{r}, t)$ is directly observed in the image data $\mathbf{G}_j$. Other information that can be obtained from the images includes the gross anatomy of the tumor and surrounding tissues and measures of the heterogeneity of the tracer distribution at various time points.

Following the ground-breaking work of Wittrup, Schmidt, Orcutt, Thurber, and Weissleder,^{33–38} we assume that the image data $\mathbf{G}_j$ are used to estimate a set of K drug-delivery parameters, $\Theta_k, k = 1, \dots, K$; these parameters can include tumor vascularity, capillary permeability, diffusion coefficient, receptor density, binding potential, internalization rate, and residualization rate. For patient j , we can assemble these parameters into a $K \times 1$ vector denoted Θ_j . In practice, $K \sim 5$ to 10. In the work cited above, Θ_j is estimated by nonlinear least-squares fitting of the drug-delivery model to the image data. An alternative is maximum-likelihood (ML) estimation, which is basically least-squares fitting modified to account for the statistical properties of the image noise. In either case, we denote the estimated parameter vector for patient j by $\hat{\Theta}_j(\mathbf{G}_j)$. This is a random vector in the sense that different realizations of the image data for the same patient will produce different estimates of the components of Θ_j .

With the estimates $\hat{\Theta}_j$ and knowledge of the tumor anatomy from the images, we want to estimate $\text{iAUC}_j(M_j)$. The simplest approach is to neglect receptor saturation and assume that $F_j^i(\mathbf{r}, t)$ is just the intracellular radiotracer distribution, $f_j^i(\mathbf{r}, t)$, scaled by M_j/m_j , where m_j is the administered mass of the radiotracer. Receptor saturation makes the drug-delivery equations nonlinear, but in principle, we can use the estimated parameters and knowledge of the tumor anatomy from the images to perform Monte Carlo simulations to estimate $\text{iAUC}_j(M_j)$.

With either linear scaling of the activity or correction for nonlinear effects, we can run the drug-delivery model with $\hat{\Theta}_j(\mathbf{G}_j)$ as input and generate corresponding estimates of the time-activity curves for each of the four drug-distribution components (capillary, diffusing, bound, and intracellular). From the intracellular component, we can numerically integrate over time to obtain an estimate of $\text{iAUC}_j(M_j)$, which we denote as $\widehat{\text{iAUC}}_j(M_j)$. Within the assumptions outlined in Sec. 5.1, we can then use Eq. (8) to get the desired estimate of the probability of tumor control:

$$\widehat{\Pr}(\text{TC}|M_j, j) = \frac{1}{2} + \frac{1}{2} \operatorname{erf}\left(\frac{\widehat{\text{iAUC}}_j(M_j) - \tau_0}{\sqrt{2}\sigma}\right). \quad (9)$$

This equation is a useful approximation for any estimation rule, but it follows rigorously if we assume that $\hat{\Theta}_j$ is obtained from $\mathbf{G}_j$ specifically by ML estimation.^{3,22} In that case, we can invoke the ML invariance theorem, which states that the ML estimate of a function of a random variable is that same function of the ML estimate of the random variable itself. Because the prescription outlined above for going from image data to parameter vector to iAUC to probability of tumor control is not probabilistic, it can be regarded as a functional mapping from $\mathbf{G}_j$ to $\widehat{\Pr}(\text{TC}|M_j, j)$, and the invariance theorem applies.

The similarity of this procedure to TOC analysis in radiation therapy should not be overlooked. In that case, the “data” to be read by the tumor are the distribution of absorbed radiation dose, $d(\mathbf{r}, t)$, and it is not necessary to distinguish total and intracellular dose. Estimates of probabilities of tumor control and normal-tissue complications are based on linear discriminants, referred to as total dose, equivalent uniform dose or effective dose, all of which are linear functionals of $d(\mathbf{r}, t)$. The response models are all based on univariate cumulative distribution functions as in Eqs. (5) and (6), and often they assume univariate normals that lead to exactly the same expression as in Eq. (8). Tables of the free parameters, like our τ_0 and σ , have been compiled for many kinds of tumor and many different adverse responses in normal tissues.^{13,14}

5.3 Comments on Clinical Applicability of iAUC

Though more general treatments are possible and may be needed, Eqs. (8) and (9) depend on the premise that iAUC is a good predictor of tumor response. Cell-cycle-independent drugs, such as alkylating agents (cyclophosphamide, cisplatin, and so on), may be the best case for this hypothesis, but there are some important caveats:

1. Cell-cycle-specific drugs such as the antimetabolites (5-FU, methotrexate, gemcitabine, and so on) tend to reach a dose plateau beyond which higher doses are not more effective. Integrating intracellular AUC over a long-enough time to cover multiple cell cycles might get around this problem (recognizing the cells in the tumor will be at different points in the cycle at any one time).
2. Most chemotherapy is given as combination therapy rather than monotherapy (although there are important exceptions). Combining cell-cycle-independent and -dependent drugs is probably the most common regimen, and the resulting response should be greater than the sum of the individual responses. The combination could be difficult to model, although the premise of AUC over an entire chemotherapy cycle might still hold.
3. Multiple clones in a tumor may respond very differently to different chemotherapy agents. For example, ER+ cells in breast cancer may have a rapid and durable response to anti-estrogens, which will do nothing to ER− cells in the same tumor. As different clones are selected as a consequence of therapy, new agents

(in this example, cytotoxic chemotherapy) would have to be modeled; antihormonal therapy and chemotherapy would not be given together at the outset, since the chemotherapy would blunt the response to antihormonal therapy.

4. Preparing radiolabeled chemotherapy drugs may pose certain challenges. A few chemotherapy drugs such as bleomycin, cisplatin, and also 5-FU can be radiolabeled by substituting a radioactive isotope for the corresponding stable isotope in the molecule, as noted in Sec. 2.3. Most chemotherapy drugs will require a linker to bind the radionuclide label, but significant chemical modification may affect the pharmacokinetics of the drug. Radiolabeled drugs will, of course, have to meet standard pharmaceutical criteria for safe human administration as well as various regulatory requirements.

Another important clinical issue regards the route of administration of the therapeutic drug. Though intravenous administration is by far the most common route, there may be large advantages in intraperitoneal (IP) administration for abdominal tumors.^{39–43} The formalism of this paper should be immediately applicable to IP administration, and iAUC should still be a useful predictor.

6 Summary and Conclusions

The use of TOC curves in cancer therapy is introduced in Sec. 2, and some models of drug delivery needed to implement it are reviewed in Sec. 3. New methodologies to calculate the TOC curve and metrics derived from it are discussed in Secs. 4 and 5, where we apply concepts from image science to the analysis and optimization of cancer therapy.

In Sec. 4, we discuss the conceptual and mathematical dilemma confronting all forms of personalized medicine. If diagnostic or therapeutic efficacy is defined in terms of average outcome over a population (ensemble) of patients, what does it mean to optimize the process for an individual, and how do we validate the optimization? The answer, taken from the literature on adaptive imaging,^{30,31} is to acquire supplementary data (often images) on a particular patient and use them to refine the statistical description of the population under study. The resulting posterior ensemble is defined as the subset of all patients in the prior ensemble who could have given the same supplementary data within the uncertainty of the measurement. The suggested (and possibly only) approach to rigorous personalized medicine is to optimize the therapy or diagnostic test for the posterior ensemble, but to test the usefulness of the optimization with conventional clinical trials or other assessment based on the prior ensemble.

Following this paradigm requires mathematical models and statistical estimation methods that allow us to make statements about the posterior probabilities and the extent to which the posterior ensemble is “smaller” than the prior ensemble, in the sense of including less patient-to-patient variability.

The methodology for this purpose is borrowed from statistical decision theory, especially as applied to objective, task-based, assessment of image quality.²² The essential steps are sketched in Sec. 5 for the specific case of personalized chemotherapy. We treat the tumor as an observer reading a dataset and responding by continuing to grow or by stopping or shrinking.

Without loss of generality, the response can be construed as computing a scalar-valued functional of the data, called a test statistic, and comparing it to a threshold. The loss of generality comes from an assumption frequently made in many different fields that this test statistic is a linear functional of the data, and we are led to discuss linear discriminants.

In chemotherapy, the dataset in question is the distribution of the drug within the tumor, and if the drug is cytotoxic only when it is incorporated into the cytoplasm, the linear discriminant must be a weighted integral of the intracellular distribution of the drug. The simplest weighting factor is a constant, and in this case, the discriminant function is the area under a curve of average intracellular drug concentration versus time, which we denote as iAUC. Methods of estimating iAUC from imaging data on a particular patient are discussed, and a simple final expression for probability of tumor control for the posterior ensemble defined by that patient is derived in Sec. 5.1. The expression depends on two free parameters, which must be determined by clinical or laboratory studies on the prior ensemble.

Many questions remain. An immediate issue related to data acquisition is that the time course of the distribution of the radio-tracer can extend over hours or days, so a radioisotope with a long half-life is required. PET isotopes Zr-89 (half-life 78.4 h) and I-124 (100 h) and SPECT isotope In-111 (67 h) have been suggested for labeling antibodies, but there are logistical difficulties in acquiring multiple images of a patient over this time scale. The optimum choice of number and timing of the imaging sessions can be determined by use of the Fisher information matrix and Cramer–Rao bound for the estimation of iAUC.²²

Once the imaging data are acquired, the recommended next step is to perform ML estimation of the drug-delivery parameters. Accurate likelihood functions with careful attention to null functions and nuisance parameters are needed for this purpose.

The parameters estimated from the radiotracer study provide information about the distribution of the drug only when it is administered at trace concentrations so that the transport equations are linear. New analytic methods involving nonlinear differential equations or Monte Carlo simulation are needed to get the distribution at higher concentrations where receptor saturation can occur.

Considerable research is also needed to develop experimental and analytic approaches to determining the tumor-response parameters τ_0 and σ , introduced in Sec. 5. It is not uncommon for tumor specimens from a patient to be used in chemotherapy sensitivity/resistance assays for multiple drugs; quantitative results from these assays could be used to get personalized estimates of the response parameters,³² but many details must be worked out.

Animal and clinical studies are clearly needed to validate this whole approach, and there are many variants and refinements of the methodology and many possible mathematical models from which to choose. The ultimate goal is to demonstrate that personalized chemotherapy with precision estimation of patient-specific parameters for drug delivery and tumor response results in improved clinical outcomes, as quantified by an increase in area under the TOC curve. Useful intermediate steps are to quantify the precision and accuracy of the estimates of the drug-delivery parameters, to validate the response models and establish values for the parameters that occur in them, and to either validate iAUC as the appropriate test statistic or to consider more general linear or nonlinear formulations.

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