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Assessment of Tumor Blood Flow Distribution by Dynamic Contrast-Enhanced CT

T. S. Koh*, W. Shi, C. H. Thng, J. T. S. Ho, J. B. K. Khoo, D. L. H. Cheong, and T. C. C. Lim

Abstract—A distinct feature of the tumor vasculature is its tortuosity and irregular branching of vessels, which can translate to a wider dispersion and higher variability of blood flow in the tumor. To enable tumor blood flow variability to be assessed *in vivo* by imaging, a tracer kinetic model that accounts for flow dispersion is developed for use with dynamic contrast-enhanced (DCE) CT. The proposed model adopts a multiple-pathway approach and allows for the quantification of relative dispersion in the blood flow distribution, which reflects flow variability in the tumor vasculature. Monte Carlo simulation experiments were performed to study the possibility of reducing the number of model parameters based on the Akaike information criterion approach and to explore possible noise and tissue conditions in which the model might be applicable. The model was used for region-of-interest analysis and to generate perfusion parameter maps for three patient DCE CT cases with cerebral tumors, to illustrate clinical applicability.

Index Terms—Cerebral tumors, dynamic contrast-enhanced (DCE) CT, perfusion imaging, tracer kinetic modeling.

I. INTRODUCTION

DYNAMIC contrast-enhanced (DCE) CT or perfusion CT is a functional imaging technique that can be used for *in vivo* assessment of tumor blood flow and vascularity [1]–[5]. The technique involves the intravenous injection of iodinated contrast agent (tracer) and sequential imaging to monitor the traversal of tracer within the tissue of interest. Analysis of DCE CT data can be performed by fitting a tracer kinetic model to the sampled tracer concentration-time curves to yield quantitative estimates of physiological parameters pertaining to tissue microcirculation, such as blood flow, vascular volume, vessel permeability, etc., [1]–[5].

It is known that tumor microvasculature is morphologically and functionally distinct from that of normal tissues [4]–[6]. The

angiogenic tumors possess a tortuous vasculature with increased number of microvessels and irregular branching. Such rapidly proliferating capillaries have poorly formed endothelial walls, which constitute the structural basis of tumor microvascular hyperpermeability. These features of the tumor microvasculature can be reflected as an increase in blood flow, vascular volume and permeability when assessed by DCE imaging [4]–[6]. However, the distinct characteristics of random (irregular) branching of vessels, which should result in a wider dispersion in blood flow distribution (i.e., increased variability of blood flow) within the tumor vasculature, is not accounted for by the tracer kinetic models commonly employed for analysis of DCE imaging data. Although a typical tissue voxel on a DCE CT image may consist of a bunch of capillaries, conventionally most tracer kinetic models for DCE imaging adopt the central volume approach [2], [4], [7]–[9] and only account for an average blood flow through the tissue vasculature when fitted to a tracer concentration-time curve.

Bassingthwaighe *et al.* [10], [11] have previously devised a multiple-pathway model capable of accounting for a distribution of blood flow in the tissue vasculature for analysis of tracer data acquired from arterial-venous sampling experiments. In this study, we implemented Bassingthwaighe's multiple-pathway approach and proposed modifications for it to be applicable to DCE imaging clinically. The multiple-pathway model was applied on DCE CT studies of patients with cerebral tumors to explore the feasibility of quantifying the increase in variability of blood flow in tumors as compared with normal tissue.

II. THEORY AND METHODS

A. Multiple Pathway Model of Blood Flow

A schematic illustration of the multiple-pathway approach proposed by Bassingthwaighe *et al.* [10], [11] is provided in Fig. 1(a). Tissue vasculature is modeled as a number (N) of pathways, with each pathway consisting of three component structures: an arteriole, a capillary–tissue exchange unit, and a venule. In Fig. 1(a), each component structure is represented by its impulse outflow response $h(t)$ [7]–[11], which describes the component's tracer output due to an impulse input. Blood flow rate in this hypothetical parallel network is governed by a distribution (or probability density function) of relative flows $w(f_i)$, such that the i th pathway is specified by a relative flow $f_i = F_i/F$, where F_i is the plasma flow rate in the i th pathway and F denotes the mean blood (plasma) flow of the entire network [10], [11]. In this way, the mean relative flow of the network is normalized, i.e., $\sum_1^N \Delta f_i w_i(f_i) f_i = 1$ [10], [11].

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In the original work by Bassingthwaite *et al.* [10], [11], the impulse outflow response of the capillary–tissue exchange unit is described by a two-region distributed parameter model given by [10]

$$h_{cap,f_i}(t) = u(t - t_{cap}) \exp\left(-\frac{PS}{f_i F}\right) \times \left[\delta(t - t_{cap}) + \exp\left(-\frac{PS}{v_e}(t - t_{cap})\right) \times \sqrt{\frac{PS}{v_e} \frac{PS}{f_i F} \frac{1}{t - t_{cap}}} \times I_1\left(2\sqrt{\frac{PS}{v_e} \frac{PS}{f_i F}}(t - t_{cap})\right) \right] \quad (1a)$$

where $u(t)$ is the unit step function, $\delta(t)$ is the Dirac delta function and I_1 is the modified Bessel function. PS denotes the capillary permeability surface area product, v_e is the fractional extravascular extracellular volume, and t_{cap} is the capillary transit time for the i th pathway, which is related to its plasma flow $f_i F$ and fractional capillary volume v_{cap} by $t_{cap} = v_{cap}/f_i F$. The parameters PS , v_e and v_{cap} are assumed to be the same for all pathways, while t_{cap} varies with the plasma flow $f_i F$ in each pathway.

The impulse outflow responses of the arteriole and venule in the i th pathway can be modeled as conductive delays [10] given by

$$h_{art,f_i}(t) = \delta(t - t_{art}) \quad (1b)$$

and

$$h_{ven,f_i}(t) = \delta(t - t_{ven}) \quad (1c)$$

respectively. Here, t_{art} and t_{ven} are the corresponding transit times for the arteriole and venule, which are related to their respective fractional volumes by $t_{art} = v_{art}/f_i F$ and $t_{ven} = v_{ven}/f_i F$. Again, v_{art} and v_{ven} are assumed to be the same for all pathways, while t_{art} and t_{ven} differ in each pathway due to its plasma flow $f_i F$. The combined fractional vascular volume for each pathway is given by $v_p = v_{art} + v_{cap} + v_{ven}$. The volume ratio for arterioles: capillaries: venules in human tissues is typically 15:30:55 [12], [13], from which the values for v_{art} , v_{cap} and v_{ven} can be inferred once v_p is specified. Using the central volume principle [2], [7]–[9] with the mean blood (plasma) flow F through the vasculature, the mean vascular transit time MTT can be specified by $MTT = v_p/F$.

The impulse outflow response for the i th pathway is the convolution $\otimes$ of the individual impulse outflow responses of the arteriole, capillary–tissue exchange unit and venule, as follows:

$$h_{f_i}(t) = h_{art,f_i}(t) \otimes h_{cap,f_i}(t) \otimes h_{ven,f_i}(t). \quad (2)$$

The net impulse outflow response of the multiple pathways in parallel is the sum of the individual impulse outflow responses weighted by the relative amount of flow through each pathway [10]

$$h(t) = \sum_i^N \Delta f_i w_i(f_i) f_i h_{f_i}(t). \quad (3)$$

Fig. 1. (a) Schematic diagram of the multiple-pathway model consisting of a network of parallel pathways [10], [11]. Each pathway is associated with a relative flow f and consists of an arteriole, a capillary–tissue exchange unit and a venule. The distribution of relative blood flow among the pathways $w(f)$ is modeled by a lagged normal density function [14] and the effects of RD and skew on $w(f)$ are shown in (b). Simplified model of the capillary–tissue exchange unit in each pathway can be given by a standard (conventional) two-compartment model as depicted in (c). For a pathway associated with a relative flow f , the actual flow supplying the vascular compartment is fF , where F denotes the mean blood flow of the entire network. The effects of varying RD and skew on the impulse residue function $R(t)$ derived from the multiple-pathway model are shown in (d), where F , v_p , PS and v_e are kept constant at 50 mL/min/100 mL, 10 mL/100 mL, 40 mL/min/100 mL, and 20 mL/100 mL, respectively. It can be appreciated in (d) that the effect of skew on $R(t)$ is minimal.

The distribution of relative flow $w(f)$ can be modeled by a lagged normal density function given by the convolution of a standard normal distribution with an exponential function [14]. As the mean relative flow is normalized ($=1$), $w(f)$ can be characterized by another two parameters, the relative dispersion (RD) and skew. RD provides a measure of the degree of variability in blood flow within the vascular network, and skew reflects the degree of asymmetry in the flow distribution, as shown in Fig. 1(b).

B. Modifications for Practical DCE CT Implementation

Bassingthwaighte *et al.* have employed the multiple-pathway model for analysis of arterial-venous sampling experiments, with the number of pathways N typically fixed at 10 or 20, due to considerations for speed and computer memory [10], [11]. To implement the multiple-pathway approach for analysis of DCE CT data and allow for parametric mapping, the following modifications are proposed.

Instead of specifying a fixed number of pathways, we expressed the overall impulse outflow response (3) as an integral over infinite pathways [i.e., $h(t) = \int_0^\infty df w(f) f h_f(t)$], such that the corresponding impulse residue response $R(t)$ can be given by

$$R(t) = 1 - \int_0^t h(\tau) d\tau = 1 - \int_0^t d\tau \int_0^\infty df w(f) f h_f(\tau) \quad (4a)$$

which specifies the amount of tracer remaining in the tissue after an impulse input. For analysis of DCE imaging data, $R(t)$ is required in the fitting of the operational equation [2], [9]

$$C_{\text{tiss}}(t) = F C_A(t) \otimes R(t) \quad (4b)$$

where $C_{\text{tiss}}(t)$ and $C_A(t)$ denote tracer concentrations in the tissue and feeding artery, respectively. In particular, $C_A(t)$ denotes tracer concentration in arterial blood plasma. As $C_{\text{tiss}}(t)$ and $C_A(t)$ are sampled from the DCE images, $F R(t)$ contains the unknown parameters which are estimated through model-fitting.

The two-region distributed parameter model presented in (1a) is mathematically complicated and requires considerable computation. In order to reduce processing time, the capillary-tissue exchange unit is replaced by a standard (conventional) two-compartment model [15]–[17]

$$h_{\text{cap},fi}(t) = -A s_1 \exp(s_1 t) - (1 - A) s_2 \exp(s_2 t) \quad (5a)$$

where

$$\begin{aligned} \begin{pmatrix} s_1 \\ s_2 \end{pmatrix} &= \frac{1}{2} \left[- \left(\frac{PS}{v_{\text{cap}}} + \frac{PS}{v_e} + \frac{1}{t_{\text{cap}}} \right) \right. \\ &\quad \left. \pm \sqrt{\left(\frac{PS}{v_{\text{cap}}} + \frac{PS}{v_e} + \frac{1}{t_{\text{cap}}} \right)^2 - 4 \frac{PS}{v_e} \frac{1}{t_{\text{cap}}}} \right] \end{aligned} \quad (5b)$$

and

$$A = \frac{s_1 + \frac{PS}{v_{\text{cap}}} + \frac{PS}{v_e}}{s_1 - s_2}. \quad (5c)$$

The standard two-compartment model has been previously employed in several DCE imaging studies [15]–[17] and a schematic of the model is provided in Fig. 1(c). By assuming well-mixed compartments, the standard two-compartment model yields a simpler expression for $h_{\text{cap},fi}(t)$ (5) than the distributed parameter model (1a) which accounts for tracer concentration gradients in the vascular and interstitial regions [9], [10].

At this point, the free parameters in the operational equation (2) are F , PS , v_p , v_e , RD, and skew. To reduce the number of free parameters, we consider the influence of the additional parameters, RD, and skew, on the impulse residue function $R(t)$, as shown in Fig. 1(d). RD governs the spread in the flow distribution $w(f)$ and has a substantial effect on the width of $R(t)$. However, skew determines the degree of asymmetry in $w(f)$ and only has a minimal effect on the overall shape of $R(t)$ [Fig. 1(d)]. $R(t)$ appears to be relatively insensitive to changes in skew, which implies the possible reduction of the number of free parameters to 5 by constraining skew to a fixed nominal value. Monte Carlo simulation experiments were performed to further investigate this possibility.

C. Monte Carlo Simulations

To explore whether RD or skew can be omitted in curve-fitting, the full multiple-pathway model with all six free parameters was used as the generating model (GM) to simulate different realizations of tissue concentration-time curves (that mimic DCE CT imaging of 50 time-points at 1 s interval), which were fitted using reduced (nested) versions of the multiple-pathway model by keeping either RD or skew fixed, or by removing both parameters. Fittings by the reduced models were compared using the Akaike information criterion (AIC) approach [18] to select the best approximating model. The three reduced models are (as shown in Table I): 1) model 1 (M1) with skew fixed at the nominal value of 1, 2) model 2 (M2) with RD fixed at the nominal value of 0.3, and 3) model 3 (M3) is the standard two-compartment model without the multiple-pathway formalism.

Two Monte Carlo (MC) simulation experiments were performed, as detailed in Table II. MC experiment (1) attempts to compare the reduced models in the context of a “nominal” brain tumor by generating 100 concentration-time curves with F , v_p , PS , and v_e fixed at their typical (average) values for brain tumors encountered in patient studies, and for various values of RD and skew randomly selected within realistic parameter ranges using a uniform distribution (i.e., every value within the parameter range has an equal chance of being selected). MC experiment (2) compares the reduced models over a wider range of tissue types by generating 500 concentration-time curves with all GM parameters randomly selected (with a uniform distribution) from within their respective physiological ranges.

Both MC experiments were performed with various levels of noise, where the signal-to-noise ratio (SNR) is taken to be the ratio of the maximum value of the tissue concentration-time curve (before noise was added) and the standard deviation of Gaussian noise added. An actual arterial input function [Fig. 4(a)] obtained from one of the patient study cases was used in the simulation of tissue concentration-time curves by the

TABLE I

LIST OF FREE AND FIXED PARAMETERS IN THE VARIOUS MODELS USED IN MONTE CARLO SIMULATIONS, TOGETHER WITH THE RESPECTIVE PARAMETER RANGES USED IN MODEL-FITTING. GM WAS USED TO SIMULATE DIFFERENT REALIZATIONS OF TUMOR CONCENTRATION-TIME CURVES, WHICH WERE FITTED USING THE REDUCED MODELS M1, M2, AND M3. FITTINGS BY M1, M2, AND M3 WERE THEN COMPARED USING THE AKAIKE INFORMATION CRITERION APPROACH TO SELECT THE BEST APPROXIMATING MODEL

Parameter	Model				Fitting Range
	GM	M1	M2	M3	
F (mL/min/100mL)	free	free	free	free	$(10^{-4} - 200)$
v_p (mL/100mL)	free	free	free	free	$(10^{-4} - 99)$
PS (mL/min/100mL)	free	free	free	free	$(10^{-4} - 200)$
v_e (mL/100mL)	free	free	free	free	$(10^{-4} - 99)$
RD	free	free	fixed at 0.3	nonexistent	$(10^{-2} - 1)$
skew	free	fixed at 1	free	nonexistent	$(10^{-2} - 2)$

TABLE II

DETAILS OF THE TWO MC SIMULATION EXPERIMENTS PERFORMED. EXPERIMENT (1): GM WAS USED TO SIMULATE CONCENTRATION-TIME CURVES PERTAINING TO A "NOMINAL" BRAIN TUMOR ($F = 50$, $v_p = 10$, $PS = 40$, $v_e = 20$) WITH VARIOUS VALUES OF RD AND SKEW RANDOMLY SELECTED WITHIN THEIR RESPECTIVE PHYSIOLOGICAL RANGES. EXPERIMENT (2): TISSUE CONCENTRATION-TIME CURVES CORRESPONDING TO A WIDER RANGE OF MICROCIRCULATORY STATES WERE GENERATED BY GM WITH ALL PARAMETERS RANDOMLY SELECTED FROM THEIR RESPECTIVE PHYSIOLOGICAL RANGES

Parameter	MC Experiment 1 (100 GM curves)	MC Experiment 2 (500 GM curves)	Physiological Range Explored
F (mL/min/100mL)	fixed at 50	randomly selected	$(10 - 100)$
v_p (mL/100mL)	fixed at 10	randomly selected	$(1 - 20)$
PS (mL/min/100mL)	fixed at 40	randomly selected	$(0.01 - 80)$
v_e (mL/100mL)	fixed at 20	randomly selected	$(5 - 40)$
RD	randomly selected	randomly selected	$(0.1 - 0.5)$
skew	randomly selected	randomly selected	$(0.2 - 1.5)$

generating model. Fitting of each simulated concentration-time curve was restarted 10 times with initial parameter values randomly selected (uniform distribution) from within their respective fitting ranges, to avoid convergence to a local minimum. The parameter fitting ranges (Table I) are wider than and encompass the physiological ranges (Table II).

The corrected AIC (cAIC) was used for the ranking of models [18]

$$cAIC = n \ln \left(\frac{SSR}{n} \right) + 2k \left(\frac{n}{n - k - 1} \right) \quad (6a)$$

where n is the number of sample points on the tissue concentration-time curves, k = number of model free parameters + 1, and SSR denotes the sum-of-squared residues in the model-fitting. Here, cAIC is used instead of AIC because $n/k < 40$ [18].

In a particular simulation run, cAIC can take either positive or negative values and it is the relative values of cAIC among the competing models that matters, with the best model yielding the smallest (or most negative) cAIC [18]. The relative strength of evidence in favor of model m can be given by the Akaike weight [18]

$$w_m = \frac{\exp \left(\frac{-\Delta_m}{2} \right)}{\sum_{i=1}^3 \exp \left(\frac{-\Delta_i}{2} \right)} \quad (6b)$$

with the Akaike distance

$$\Delta_m = cAIC_m - cAIC_{\min} \quad (6c)$$

where $cAIC_{\min}$ is the smallest cAIC value among the models. In (6b), i refers to each of the three models being compared.

D. Patient and Imaging Protocols

Informed consent was obtained from three patients with cerebral tumors (meningioma) recruited in a DCE CT study of intracranial lesions approved by the local institutional review board. The patients were examined using a slip-ring, helical CT scanner (HiSpeed; GE Medical Systems) with the dynamic CT images obtained on a single section at the level of the largest tumor diameter identified on noncontrast CT scans. 50 contrast-enhanced images were acquired with a scanning time of 1 s per image and with the intravenous injection of 50 ml of nonionic iodinated contrast medium (Omnipaque 300 mgI/ml) at a rate of 4 mL/s using an automatic injector. Parameters for the CT scans were 80 kVp, 190 mAs, 512×512 matrix, 20–22 cm field-of-view and at 10 mm collimations.

E. Analyses of DCE CT Data

The CT images were transferred to a Pentium IV personal computer for further processing. The images were registered (SPM software package; University College, London, U.K.) relative to the first image as a template, to correct for any patient movement during the scans. As a common preprocessing step to reduce noise, a 5×5 median filter kernel was applied to the DCE CT images. Regions-of-interests (ROIs) were manually drawn over the tumor and normal tissue on the contralateral side by a radiologist. The arterial input function $C_A(t)$ for each patient was sampled from a ROI manually drawn over an artery consisting of one or more voxels and which showed an early bolus arrival time, before median filtering of the dataset. The sampled $C_A(t)$ was divided by a factor of $(1 - Hct)$ where Hct is the large vessel hematocrit (assumed 0.4) to account for the tracer concentration in blood plasma. The tissue concentration-time curve $C_{tiss}(t)$ corresponding to each voxel within the ROIs of tumor and contralateral tissue was fitted using the reduced multiple-pathway model selected in the Monte Carlo simulation experiments based on AIC. To account for the difference in bolus arrival time between $C_{tiss}(t)$ and $C_A(t)$, an additional adjustable parameter t_0 was included in the expression of $C_{tiss}(t)$ to impose an adjustable delay relative to the $C_A(t)$. We note that the delay t_0 is dependent on the relative locations where $C_{tiss}(t)$ and $C_A(t)$ were sampled, and it is not a property of the multiple-pathway model. The volume ratios of 15:30:55

TABLE III
RESULTS OF MONTE CARLO SIMULATION EXPERIMENT 1. NUMBER OF TIMES (FREQUENCY) EACH MODEL WAS SELECTED AS THE BEST MODEL BY THE CORRECTED AKAIKE INFORMATION CRITERION IS EXPRESSED AS A PERCENTAGE OVER 100 SIMULATED REALIZATIONS

SNR	Model	Frequency as Best Model (%)	Δ_m median (17 th , 83 rd percentile)	w_m median (17 th , 83 rd percentile)
50	M1	80	0.000 (0.000, 0.028)	0.582 (0.495, 0.760)
	M2	20	0.672 (0.000, 2.342)	0.416 (0.236, 0.503)
	M3	0	23.147 (11.024, 36.211)	0.000 (0.000, 0.002)
20	M1	63	0.000 (0.000, 0.870)	0.463 (0.288, 0.579)
	M2	11	0.585 (0.056, 2.155)	0.372 (0.216, 0.445)
	M3	26	2.916 (0.000, 10.047)	0.107 (0.004, 0.464)
10	M1	36	1.000 (0.000, 2.419)	0.278 (0.188, 0.494)
	M2	5	1.256 (0.328, 2.452)	0.261 (0.184, 0.367)
	M3	59	0.000 (0.000, 3.016)	0.458 (0.114, 0.628)

TABLE IV
RESULTS OF MONTE CARLO SIMULATION EXPERIMENT 2. NUMBER OF TIMES (FREQUENCY) EACH MODEL WAS SELECTED AS THE BEST MODEL BY THE CORRECTED AKAIKE INFORMATION CRITERION IS EXPRESSED AS A PERCENTAGE OVER 500 SIMULATED REALIZATIONS

SNR	Model	Frequency as Best Model (%)	Δ_m median (17 th , 83 rd percentile)	w_m median (17 th , 83 rd percentile)
50	M1	64.2	0.000 (0.000, 0.325)	0.516 (0.380, 0.666)
	M2	20.6	0.470 (0.000, 2.609)	0.416 (0.186, 0.500)
	M3	15.2	19.600 (0.771, 52.450)	0.000 (0.000, 0.265)
20	M1	49.2	0.006 (0.000, 2.182)	0.425 (0.205, 0.549)
	M2	13.2	0.633 (0.055, 2.514)	0.335 (0.185, 0.472)
	M3	37.6	1.800 (0.000, 13.549)	0.175 (0.001, 0.606)
10	M1	32.6	1.040 (0.000, 2.512)	0.276 (0.183, 0.483)
	M2	5.4	1.356 (0.239, 2.566)	0.259 (0.178, 0.396)
	M3	62.0	0.000 (0.000, 3.259)	0.464 (0.097, 0.640)

for arterioles, capillaries and venules are typical of human tissues and are assumed to be fixed in both tumors and normal tissues.

Model-fitting was performed using a constrained nonlinear optimization algorithm (“fmincon,” Matlab, The Mathworks, Natick, MA, USA) which yields the SSR as a measure of the goodness-of-fit, and output flags reflecting the status of the optimization search. Fitting failures with exceedingly large SSR (greater than a stipulated threshold) and negative output flags (indicating no feasible solution) were excluded.

III. RESULTS

A. Monte Carlo Simulations

Results of Monte Carlo simulation experiment (1) are shown in Table III, and some examples of simulation runs are shown in Fig. 2. At SNR = 50, among the 100 simulated concentration-time curves pertaining to a “nominal” brain tumor with various (randomly chosen) values of RD and skew, M1 was able to approximate the full model (GM) better than M2 in 80 instances [an example is shown in Fig. 2(a) and (b)], by yielding lower SSR and hence cAIC. The 20 simulation runs in which M2 was ranked better than M1 corresponded to situations when the actual (randomly chosen) value of RD in the GM was close to 0.3 [an example is shown in Fig. 2(c) and (d)]. Because M2 has RD fixed at 0.3 and a variable skew, such situations favor the fitting of M2 over M1, especially when the actual skew in the GM is

far from the value of 1 (to which M1 was constrained). However, for a wide range of values of RD and skew, M1 was found to be more versatile than M2 in approximating the full model, under various noise conditions.

In experiment (1), M3 was not selected at SNR = 50 and began to improve in ranking at SNR = 20, eventually overtaking M1 at SNR = 10. An example of M3 as the best model at SNR = 20 is shown in Fig. 2(e) and (f). The second term in the cAIC expression (6a) favors a smaller number of free parameters, and can offset the ranking by SSR under noisy conditions. As the impulse residue function $R(t)$ for M3 is a biexponential function [see Fig. 2(b), (d), and (f)] which differs in curvature from that of GM, parameter estimates by M3 tend to deviate more from those of the GM, as compared with M1 and M2 [Fig. 2(b), (d), and (f)].

Results for Monte Carlo simulation experiment (2) are shown in Table IV. These simulations explored a wider range of tissue parameters and reveal certain tissue conditions when M3 can be ranked as the best model at SNR = 50 (an example is shown in Fig. 3). A small vascular volume (v_p) and high blood (plasma) flow (F) results in a very rapid vascular transit time (MTT), such that venous outflow occurs almost immediately and the initial plateau in the $R(t)$ of GM diminishes. Such an $R(t)$ of GM appears to be monotonically decreasing and can be well approximated by M3, as shown in Fig. 3(b). Results in both simulation experiments (1) and (2) are largely consistent and suggest that M1 may be generally applicable for SNR $> \sim 20$,

Fig. 2. Examples of simulation runs from Monte Carlo experiment 1. Model fittings for a simulation run at $SNR = 50$ which yields M1 as the best approximating model are shown in (a) and the corresponding impulse residue functions scaled by blood flow (i.e., FR) are shown in (b). Example of a simulation run at $SNR = 50$ which yields M2 as the best model is shown in (c) and (d). At $SNR = 20$, there are instances when M3 is selected as the best model and an example is shown in (e) and (f). In the legends of FR plots (b), (d), and (f), the 6 numbers within brackets for GM, M1 and M2 are (F mL/min/100 mL, v_p mL/100 mL, PS mL/min/100 mL, v_e mL/100 mL, RD and skew) and the four numbers within brackets for M3 are (F mL/min/100 mL, v_p mL/100 mL, PS mL/min/100 mL, v_e mL/100 mL).

and that it may not be preferred over M3 for tissue types with very high flow and small vascular volumes.

B. Patient Studies

Examples of fitting M1 to voxel-level concentration-time curves in the tumor and contralateral normal tissue are shown in Fig. 4(a), with their fitted parameter values listed in the figure caption. Effects of the different parameter values in tumor and normal tissue on the corresponding impulse residue functions scaled by blood (plasma) flow $FR(t)$ are shown in

Fig. 4(b). As the impulse residue function $R(t)$ is a characteristic function of the tracer and tissue system [9], differences in perfusion characteristics between the tumor and normal tissue are also reflected in the features of the corresponding $R(t)$. Higher values of vascular volume (v_p), permeability (PS), and interstitial volume (v_e) for the tumor resulted in a broader $R(t)$ that approaches zero slowly, while $R(t)$ for the normal tissue is narrower and approaches zero more rapidly.

An example of parameter maps generated by the proposed model is shown in Fig. 5(a). These parameter maps reveal that

Fig. 3. Example of a simulation run from Monte Carlo experiment 2 which yields M3 as the best model at $\text{SNR} = 50$. Model fittings and corresponding impulse residue functions scaled by blood flow (FR) are shown in (a) and (b), respectively. In the legend of (b), the six numbers within brackets for GM, M1 and M2 are (F mL/min/100 mL, v_p mL/100 mL, PS mL/min/100 mL, v_e mL/100 mL, RD , and skew) and the four numbers within brackets for M3 are (F mL/min/100 mL, v_p mL/100 mL, PS mL/min/100 mL, v_e mL/100 mL).

the tumor exhibit increased values for all parameters as compared with the contralateral tissue. Tumor demarcation is more obvious on the maps of parameters associated with the extravasation (leakage) of contrast medium in the tumor, namely PS and v_e , which are close to zero in the surrounding normal tissues due to an intact blood-brain barrier. Histograms of the various parameters are presented in Fig. 5(b) to show that parameter distributions within the tumor and contralateral normal tissues are also remarkably different. Some of the parameter distributions appear to be Gaussian-like and others are clearly skewed. These histograms suggest that simple statistics based on the mean and standard deviation would not be adequate and more advanced nonparametric statistics might be required to fully account for the differences. To explore possible association or dependency of the additional parameter RD on the other parameters during fitting, scatter plots of the various parameters with RD are shown in Fig. 5(c). These scatter plots show that RD is not correlated with the other parameters for both the tumor and normal tissues.

Mean and standard deviation values of these parameters in the tumors and contralateral tissues of all three study cases are tabulated in Table VI. RD was found to be generally higher in the tumors, indicating that the tumor vasculature exhibited a higher

Fig. 4. (a) Examples of voxel-level fittings of the multiple-pathway model (M1) to tracer concentration-time curves derived from tumor and contralateral normal tissue. Values of the free parameters $\{F$ (mL/min/100 mL), v_p (mL/100 mL), PS (mL/min/100 mL), v_e (mL/100 mL), RD \} obtained for the tumor and normal tissue are $\{42.7, 7.9, 33.3, 32.1, 0.23\}$ and $\{25.2, 1.7, 0.0, 0.0, 0.01\}$, respectively. The corresponding impulse residue functions $R(t)$ scaled by the respective flow values are shown in (b).

degree of flow variability than the normal tissues. However, statistical significance could not be established due to the small number of study cases.

IV. DISCUSSION

Although the multiple-pathway approach for modeling flow distribution has been proposed by Bassingthwaite *et al.* [10], [11] since the 1980s, it is rarely implemented in DCE imaging studies to-date, possibly due to its requirements of substantial computer memory and processing time. Kroll *et al.* [19] and Jerosch-Herold *et al.* [20] have applied Bassingthwaite's multiple-pathway model (MMID4, Multiple indicator, Multiple path, Indicator Dilution, 4-region model running under JSim, National Simulation Resource, Department of Bioengineering, University of Washington, Seattle, WA, USA) in DCE MRI

Fig. 5. Parameter maps of a study case (Patient 1) are shown in (a), with the mean contrast-enhanced image depicting ROIs for the tumor and contralateral normal tissue in red and blue, respectively.

studies of myocardial perfusion. They showed that failure to account for blood flow heterogeneity may result in systematic underestimation of flow. Brix *et al.* [12], [13] have recently used the MMID4 software for simulation studies to compare tracer kinetic methods employed for DCE imaging. The MMID4 software computes a distributed parameter model for each pathway using a Lagrangian sliding fluid element algorithm (with the meshing of time and space into calculation grids) but only allows a finite number of pathways N (up to

TABLE V
PERCENTAGE UNCERTAINTY (COEFFICIENT OF VARIATION) IN THE
PARAMETERS OF M1 ESTIMATED FROM THE SIMULATION
RUNS OF MONTE CARLO EXPERIMENT 2

Parameter	SNR		
	50	20	10
F	8.3	14.0	23.2
v_p	6.5	10.3	16.4
PS	10.7	22.6	35.3
v_e	12.8	31.2	44.1
RD	11.4	27.5	43.7

about 30) due to memory constraints, in the modeling of the tissue impulse outflow response function $h(t)$.

The present modified approach devised the corresponding tissue impulse residue response function $R(t)$ by the integration of infinite pathways and replaces the distributed parameter model in each pathway by a standard two-compartment model which is much simpler to compute. On a personal computer (Intel Core i7 Processor), MMID4 with $N = 20$ (single tracer, two regions: one vascular and one interstitial space, number of spatial grids = 1001, time steps of 0.1 s up to 100 s) takes about 120 s to compute while the present simplified model takes about 0.1 s to generate a corresponding $R(t)$. Application of the present model for analysis of DCE imaging data becomes feasible with the substantial reduction in computation time.

Another advantage of the present infinite pathway formulation over a finite number of pathways is illustrated in Fig. 6. A finite number of pathways results in a corresponding number of discontinuities in $R(t)$ which could pose difficulties during curve-fitting. It has been reported that a single discontinuity in the adiabatic tissue homogeneity (ATH) model could result in convergence problems and reduced parameter precision in curve-fitting [21], [22]. Such problems of convergence can be attributed to inaccuracies in the estimation of the convolution integral (4b) due to the fact that DCE imaging data are sampled at discrete points in time [23]. Although effective correction methods have been proposed to address such convergence problems for a single discontinuity in the ATH model [23], the occurrence of multiple discontinuities due to multiple pathways would render such correction methods impractical.

An alternative formulation of $R(t)$ with infinite pathways has been previously proposed by incorporating a distribution of capillary transit time, instead of a distribution of flow in Bassingthwaite's approach [24]. Various possible distributions for capillary transit time has been previously explored, which included a corrected normal, skewed Gaussian [24] and gamma distributions [25], [26]; and for capillary-tissue exchange units described by the ATH [24], [26] and distributed parameter [25] models. Both the flow-distributed and transit time-distributed multiple-pathway approaches suffer from the common drawbacks of mathematical complexity and increased computational burden. However, each approach has its strengths. The transit time-distributed approach formulates $R(t)$ into physiological phases with vascular and parenchyma components separable in time and readily allows for a transition of $R(t)$ between single and multiple pathways [24]–[26]. On the other hand, the flow-distributed approach explicitly specifies the blood flow distribution in $R(t)$ and readily yields a parameter (RD) that describes

Fig. 5. (Continued.) Histograms of the parameters sampled from these ROIs are shown in (b). Scatter plots to explore correlation between RD and the other parameters are shown in (c) with Spearman's r .

variability of flow, allowing the user to directly characterize blood flow heterogeneity within the tissue.

The Monte Carlo simulation results indicated that one should be cautioned against the use of the present multiple-pathway model (M1) under noisy conditions of $\text{SNR} \sim 10$, and for tissue types with very high flow and small vascular volumes. Although the normal brain tissues have small vascular volumes

($\sim 1\text{--}2$ mL/100 mL), their blood (plasma) flows are not exceedingly high (typically range from about 10 to 50 mL/min/100 mL), such that the corresponding $R(t)$ can still exhibit a plateau [as shown in Fig. 4(b)], which may not be well approximated by the biexponential form of M3 [16]. SNRs estimated for the tumor and normal tissue concentration-time curves shown in Fig. 4(a) are 36 and 11, respectively. While the vascular tumors

TABLE VI
STATISTICS (MEDIAN, MEAN $\pm$ STANDARD DEVIATION) FROM REGION-OF-INTEREST ANALYSIS OF EACH
PARAMETER IN THE TUMOR AND CONTRALATERAL NORMAL TISSUES OF EACH STUDY CASE

	Patient 1		Patient 2		Patient 3	
	Tumor	Normal	Tumor	Normal	Tumor	Normal
F (mL/min/100mL)	38.8, 41.7 $\pm$ 14.7	22.6, 29.0 $\pm$ 23.3	27.7, 32.7 $\pm$ 25.5	24.7, 28.7 $\pm$ 9.9	34.9, 43.1 $\pm$ 31.8	23.9, 30.5 $\pm$ 23.0
v_p (mL/100mL)	7.0, 7.4 $\pm$ 2.8	1.4, 1.5 $\pm$ 0.5	6.6, 6.9 $\pm$ 2.0	1.4, 1.5 $\pm$ 0.7	3.5, 3.5 $\pm$ 1.4	1.1, 1.3 $\pm$ 0.7
MTT (sec)	11.0, 10.9 $\pm$ 2.5	4.2, 4.6 $\pm$ 2.7	14.8, 14.9 $\pm$ 3.8	3.9, 3.7 $\pm$ 1.9	6.6, 6.7 $\pm$ 3.2	3.4, 3.4 $\pm$ 1.8
PS (mL/min/100mL)	37.9, 42.8 $\pm$ 20.4	1.4, 2.1 $\pm$ 2.8	45.8, 55.1 $\pm$ 34.6	1.1, 2.7 $\pm$ 5.4	16.1, 18.0 $\pm$ 14.3	0.8, 1.7 $\pm$ 3.0
v_e (mL/100mL)	17.8, 21.5 $\pm$ 20.8	0.0, 2.8 $\pm$ 10.3	9.6, 19.4 $\pm$ 25.0	0.0, 2.0 $\pm$ 8.4	4.3, 5.1 $\pm$ 6.2	0.1, 2.5 $\pm$ 10.6
RD	0.03, 0.12 $\pm$ 0.20	0.01, 0.07 $\pm$ 0.15	0.1, 0.18 $\pm$ 0.23	0.01, 0.11 $\pm$ 0.19	0.05, 0.13 $\pm$ 0.22	0.01, 0.09 $\pm$ 0.17

Fig. 6. An example of the presence of discontinuities in the impulse residue function $R(t)$ for a finite number of pathways, while the proposed multiple-pathway approach incorporates infinite pathways to yield a smooth $R(t)$.

are associated with higher SNRs $> \sim 20$ on DCE CT, normal tissues are usually less enhanced with lower SNRs of ~ 10 , and parameter estimates by the multiple-pathway model would be associated with much larger errors for the normal tissues than tumors. Percentage uncertainty (coefficient of variation) in the parameters of M1 were estimated from Monte Carlo experiment (2) and shown in Table V. Parameter errors in PS , v_e and RD can deteriorate to more than 40% at SNR = 10, as compared to the more acceptable level of about 10%–30% at SNR = 20.

Parameter maps generated by M1 [Fig. 5(a)] and ROI analysis (Table VI) indicated higher values for blood (plasma) flow (F), vascular volume (v_p), vascular mean transit time (MTT) and permeability (PS) in the tumors than the normal tissues, which are consistent with the current understanding of the process of neo-angiogenesis in human neoplasms. The leaky tumor vasculature allows the tracer to access the tumor interstitial space and yield estimates of the fractional interstitial volume (v_e). In contrast, the surrounding normal cerebral tissues are associated with an intact blood-brain barrier and the data-fittings yielded near-zero values for PS and v_e [as shown in Fig. 4(a)]. However, this does not mean that the interstitial volume of the normal

tissue is actually zero, but that the interstitial space is simply not assessable by DCE CT with the tracer (contrast agent) used. The mapping of these extravasation parameters can therefore more clearly reveal the location and extent of the tumor. This is consistent with the findings of Roberts *et al.* [27] who show that tumor conspicuity is highest on the PS map, as compared with the maps of blood flow and vascular volume.

The main advantage of the present multiple-pathway model is its ability to account for blood flow distribution in tumors, which is known to be heterogeneous and associated with a higher degree of randomness. The present model thus offers the possibility of assessing an additional aspect of the tumor vasculature, and potentially allow for a more complete characterization of the tumor microenvironment by DCE imaging. It is plausible to postulate that a higher grade tumor could be associated with a higher value of RD, but a larger number of patients with different grades of a particular type of tumor would be required to further explore this conjecture.

V. CONCLUDING REMARKS

In summary, a modification of the multiple-pathway model is proposed that allows for substantial improvement in computation speed and facilitates its application in the analysis of DCE imaging data. In the cerebral perfusion CT study cases, parameter maps generated using the present model provided both spatial and functional information with sufficient clarity. With the incorporation of a blood flow distribution, the present multiple-pathway model yields an additional parameter (RD) pertaining to blood flow variability that can potentially be used for differential diagnosis and characterization of tumors by DCE imaging.

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