Published in final edited form as:

Magn Reson Med. 2017 March ; 77(3): 1329–1339. doi:10.1002/mrm.26189.

Are complex DCE-MRI models supported by clinical data?

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Abstract

Purpose—To ascertain whether complex DCE-MRI tracer kinetic models are supported by data acquired in the clinic and to determine the consequences of limited contrast-to-noise.

Methods—Generically representative in silico and clinical (cervical cancer) DCE-MRI data were examined. Bayesian model selection evaluated support for four compartmental DCE-MRI models: the Tofts model (TM), Extended Tofts model (ETM), Compartmental Tissue Uptake model (CTUM), and Two-Compartment Exchange model (2CXM).

Results—Complex DCE-MRI models were more sensitive to noise than simpler models with respect to both model selection and parameter estimation. Indeed, as contrast-to-noise decreased, complex DCE models became less probable and simpler models more probable. The less complex TM and CTUM were the optimal models for the DCE-MRI data acquired in the clinic. [In cervical tumors, K^{trans} , F_p , and PS increased after radiotherapy ($P = 0.004$, 0.002 , and 0.014 , respectively)].

Conclusion—Caution is advised when considering application of complex DCE-MRI kinetic models to data acquired in the clinic. It follows that data-driven model selection is an important prerequisite to DCE-MRI analysis. Model selection is particularly important when high-order, multi-parametric models are under consideration. (Parameters obtained from kinetic modelling of cervical cancer clinical DCE-MRI data showed significant changes at an early stage of radiotherapy.)

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Keywords

DCE-MRI; tracer kinetic modeling; pharmacokinetics; model selection; Bayesian inference; cervical cancer

INTRODUCTION

Dynamic Contrast Enhanced (DCE) MRI is being used increasingly in the assessment of cancer, both pre- and post-therapy (1–9). Both semi-quantitative (1–4) and quantitative analyses (4–9) of time-resolved DCE-MRI data are used to derive information about tumor microcirculation and microvasculature. Semi-quantitative analyses, which derive measures directly from MR signal intensities, depend on MR hardware and the pulse sequences used to acquire the data, making it challenging to compare results between studies. In addition, the derived parameters, including signal-intensity plateau, contrast-enhancement ratio, and area under the curve, have no clear physiological meaning (4,10). By contrast, quantitative analysis employing tracer kinetic models yields physiological parameters related to tissue perfusion and capillary permeability.

Many tracer kinetic models have been applied to describe the behavior of administered contrast agent in DCE-MRI experiments. The first generation of DCE-MRI models, including the widely used Tofts model (TM) (11), were designed for tissues with negligible blood volume, and were used to characterize the permeability of the tissue vasculature. To account for intravascular signal contributions, the Extended Tofts Model (ETM) (12,13) was introduced for highly-perfused tissues, including tumors. Improvements in scanner hardware and software, which have led to higher-quality DCE-MRI data, have motivated the development of models with greater complexity (14,15) that more fully describe tissue perfusion and capillary permeability. Such models are physiologically more accurate (fewer assumptions/constraints regarding tissue structure) compared to reduced, simpler models that make physiological assumptions or introduce constraints that may not be appropriate for the tissue of interest and will, thus, generate bias in kinetic parameter estimates. However, in practice, it remains unknown whether these more complex models are supported by a given clinical DCE-MRI dataset with specific data quality (e.g., time resolution, acquisition time window, and contrast-to-noise ratio (CNR)). Thus, it is important to apply model selection, a data-driven process that balances the goodness of the fit and the stability of parameter estimation, to choose which kinetic model within a family of competing models best characterizes (is best supported by) the data.

The importance of selecting an appropriate DCE tracer kinetic model for measurement of tissue perfusion and capillary permeability has been examined in previous reports from other laboratories (16,17). Model selection algorithms, including Chi-square (18), Akaike information criterion (AIC) (18–20), F-test (21–23), and the Durbin-Watson statistic (18), have been applied to evaluate tracer kinetic models commonly used in DCE-MRI data analyses. However, very few of these studies have tested the stability of complex models as a function of data quality in the context of a pool of competing models. Luytjens et al. (25), and Murase et al. (26), investigated the effect of noise on the parameter estimation of

individual DCE-MRI tracer kinetic models, but did not compare the accuracy and uncertainty of parameter estimation between models.

Bayesian probability theory (27) provides a rigorous statistical formalism for performing model-selection calculations. Advances in computational power and the development of Markov-chain Monte Carlo (MCMC) methods have greatly increased the applicability of Bayesian inference to a range of problems. Using a Bayesian approach, the model-selection problem is addressed by treating the model itself as a parameter, for which the posterior probability, given the data and prior information, is computed.

The goal of this study was to test four compartmental tracer kinetic models against generically representative DCE-MRI data. Both *in silico* DCE-MRI data -- simulated based on each of the four models -- and clinical DCE-MRI cervical cancer data acquired pre-treatment and two-to-three weeks following the start of radiotherapy (RT) were utilized. Bayesian-based model selection and parameter estimation algorithms were applied to evaluate the noise tolerance to data analysis for each kinetic model and the dependence of the accuracy and uncertainty of parameter estimation on both model complexity and signal contrast-to-noise. Finally, applying model selection to clinical DCE-MRI cervical cancer data on a voxel-by-voxel basis, optimal models for the data were determined and then employed to estimate physiological parameters, including perfusion metrics and vascular permeability.

METHODS

The DCE-MRI Tracer Kinetic Models

Tracer kinetic modeling of vascular leakage and conservation of mass allow the tissue contrast-agent concentration (C_t) obtained following the administration of a contrast agent bolus to be written as:

$$C_t(t) = C_p(t) \otimes I(t), \quad (1)$$

where $C_p(t)$ is the concentration of the contrast agent in the plasma of the capillary inlet of any region-of-interest (ROI), commonly approximated by a measured upstream arterial input function (AIF), and $I(t)$ is the tissue impulse-response function to the contrast agent input, which depends on the specific DCE-MRI tracer kinetic model. In this expression, " $\otimes$ " denotes the convolution operation.

Springer and colleagues (28) have pointed out that, *in principle*, "tracer kinetic" models are inappropriate for DCE-MRI data because C_t is not directly measured. Rather, it is the tissue water ^1H relaxation enhancement caused by the agent that is monitored. Under some circumstances, the relaxation enhancement will be a non-linear function of C_t , requiring consideration of additional parameters not generally included in tracer kinetic models, e.g., the rate constant(s) governing water exchange across the relevant compartment boundaries. Such models are more complex than those considered herein. *In practice*, under conditions that approximate the MR-relaxation fast-exchange limit (29), the relaxation enhancement

reasonably approximates a linear function of C_b and tracer kinetic models are appropriate simplifications of a more complex system. Data described herein are consistent with this simplification.

Four compartmental DCE tracer kinetic models were included in this model selection study: (i) the four-parameter (F_p , v_e , v_p , and PS) Two-Compartment Exchange Model (2CXM), (ii) the three-parameter (F_p , v_p , and PS) Compartmental Tissue Uptake Model (CTUM); (iii) the three-parameter (K^{trans} , v_e , and v_p) Extended Tofts Model (ETM); and (iv) the two-parameter (K^{trans} and v_e) Tofts Model (TM). In these models, F_p is blood flow, v_e is the extracellular-extravascular volume fraction, v_p is the plasma volume fraction, PS is the permeability-surface area product, and K^{trans} is the forward volume transfer-rate constant. Figure 1 and Table 1 summarize the hierarchy and impulse response functions of these models. Further details about the relationships among these models are given in Sourbron et al. (16). In addition to the DCE tracer kinetic models, a “no signal” model, in which the data are assumed to consist only of noise, was also included, by default, in the model-selection calculation.

Clinical DCE-MRI data

De-identified clinical DCE-MRI cervical cancer data were acquired from patients enrolled in the EMBRACE study (<https://www.embracestudy.dk>), an international study of MRI-guided brachytherapy in locally advanced cervical cancer. All protocols were approved by the local medical ethics research board. Ten patients with advanced-stage cervical tumors (International Federation of Gynecology and Obstetrics: IIA/IIB/IIIB/IVA – 1/5/3/1) were scanned prior to, and two-to-three weeks after, the start of RT. This patient population was previously described in Kallehauge et al. (19).

Data were acquired on a 3-T Philips Achieva scanner *via* a 3D, saturation-recovery spoiled gradient-echo sequence (TR = 2.9 ms, TE = 1.4 ms, saturation time = 25 ms, flip angle = 10°, centric k-space sampling, matrix size = 176 X 176). A total of 120 dynamic scans (18 baseline scans, SNR $\approx$ 5) for 20-to-24 5-mm-thick slices were obtained with 2.1 sec temporal resolution and 2.3 mm x 2.3 mm in-plane resolution.

Each DCE-MRI dataset consisted of two dynamic MRI sub-datasets: (i) the AIF dataset obtained from monitoring the external iliac artery and (ii) the tissue response dataset obtained from monitoring the cervix. An AIF for each patient (pre- and post-RT) was obtained by averaging multiple contrast agent concentration *vs.* time curves measured in the external iliac artery. All concentration *vs.* time curves were inspected manually to exclude curves that were affected by partial-volume effects.

Following the work of Fram et al. (30), a T_1 relaxation time-constant map was constructed using the variable flip angle method (flip angles = 5°, 10°, 15°, 20°, and 25°) *via* a 3D, spoiled gradient-echo sequence before contrast-agent administration, allowing conversion of DCE-MRI signal intensity into contrast-agent concentration as described in Kallehauge et al. (31). Because a short echo time (TE = 1.4 ms) was used to collect the data, T_2^* dephasing was ignored for this conversion. To avoid the inflow artefacts in the iliac artery, a literature value of 1660 ms (32) for pre-contrast blood T_1 was used. Tumor tissue was identified and

segmented on T₂-weighted images by an experienced radiologist. Figure 2 shows four representative single tumor-voxel DCE datasets.

In silico DCE-MRI data

In silico DCE-MRI data were generated based upon clinical pre-treatment DCE-MRI data from four cervical cancer patients. Both whole-tumor average (mean C_t across all voxels) and single-voxel DCE time courses (one tumor voxel from each patient) were examined for these four patients (eight DCE time course datasets in total). The four whole-tumor average DCE datasets provided high contrast-to-noise at the expense of averaging DCE responses from a heterogeneous tissue (cancer). The four single-voxel DCE datasets provided a local DCE response at the expense of reduced contrast-to-noise. These two data-analysis strategies (region-of-interest and voxel-wise) are common to literature reports. Together with the measured upstream AIFs for each patient, these eight different DCE datasets -- a whole-tumor ROI and a single tumor-voxel from each of four patients -- were then each modeled by Bayesian-based algorithms (*vide infra*) using each of the four tracer kinetic models (eight DCE datasets x four DCE kinetic models).

For each of the eight DCE datasets, the estimated parameter values obtained for each of the four DCE kinetic models (2CXM, CTUM, ETM, TM; see Supporting Figure S1 for parameter ranges) were then used to generate four noiseless in silico DCE datasets, corresponding to each of the four kinetic models. Summarizing, based on analysis of the clinical data, eight, noiseless, differently parameter-valued, in silico, DCE datasets were generated for each of the four DCE kinetic models.

For each of the simulated datasets, the temporal resolution, T_s (2.1 sec), and total acquisition time, T_{acq} (250 sec), were identical to those of the clinical DCE-MRI data-acquisition protocol. Normally distributed (Gaussian) noise (standard deviation from 0 to 0.2 mM in 0.005 mM steps) was then added to each of the simulated noise-free dataset. As such, the contrast-to-noise ratio (CNR), defined as the ratio of the *maximum* contrast-agent concentration to the noise standard deviation, ranges from infinity (no noise added) to approximately three. For each noise power, 100 different noise representations were simulated. Gaussian noise was used for two reasons. First, Gudbjartsson and Patz (33) have shown that MRI data noise distributions are nearly Gaussian for SNR larger than 2, which is very likely to be true for most DCE-MRI scans. Second, the distribution of baseline signal, i.e., “baseline contrast agent concentration” (essentially pure noise), calculated for all of the cervical tumor voxels was well fit by a Gaussian model (see Supporting Figure S2).

Bayesian-based model selection (and parameter estimation)

Bayesian probability theory was used to compute the posterior probabilities for all models on a voxel-by-voxel basis, using Bayes' Theorem (27),

$$P(M|DI) = \frac{P(M)P(D|MI)}{P(D|I)} \quad (2)$$

where $P(M|DI)$ is the posterior probability for the M th model, given the data, D , and all of the prior information, I . On the right-hand side of this equation, $P(M|I)$ is the prior probability for the M th model and $P(D|M)$ is the marginal direct probability for the data, given the model and the prior information. Finally, $P(D|I)$ is the direct probability for the data, given the prior information, and serves as a normalization constant.

In Eq. (2), $P(D|M)$ is a marginal direct probability because no kinetic model parameter appears in this probability. To compute this direct probability, the parameters appearing in the M th model must be reintroduced into this equation. Taking the Tofts Model, with parameters K^{trans} and v_e as an example, equation (2) can be rewritten as,

$$P(M|DI) \propto P(M|I) \int dK^{trans} dv_e P(K^{trans} v_e | MI) P(D | K^{trans} v_e MI) \quad (3)$$

where the normalization constant has been dropped. $P(K^{trans} v_e | MI)$ is the joint prior probability for K^{trans} and v_e , given the model M (in this case, the TM) and the prior information; and $P(D | K^{trans} v_e MI)$ is the direct probability for the data (the likelihood function), given K^{trans} , v_e , the model M , and the prior information. A key feature of Bayesian-based model selection is that it integrates over the joint posterior probability for all of the parameters, thereby taking into account all of the possible parameter-value combinations. The importance/weight (“penalty”) assigned to each parameter derives naturally from that parameter’s contribution to the likelihood function of the modeled data (i.e., its posterior probability), which distinguishes the Bayesian approach from other constrained optimization methods.

The posterior probability for the model indicator, given the data and the prior information, $P(M|DI)$, was approximated using a MCMC calculation with simulated annealing (i.e., the MCMC calculation and simulated annealing were used to approximate the complex, analytically intractable, multidimensional integral in Eq. [3]). Initial values for all of the parameters, including the model indicator, were sampled from the prior probabilities for each parameter and the model indicator. Uniformly distributed prior probabilities, bounded by appropriate physiologic ranges, were assigned to all of the parameters (see Supporting Table S1) and to the model indicators (i.e., all four models were assumed to be equally likely). In simulated annealing, an annealing parameter, β , which varies from 0 to 1, is introduced by raising the direct probability of the data to the β power. When $\beta = 0$, the direct probability of the data is zero and the priors are sampled independent of the data. The data are then slowly brought into the simulation as β increases and, when $\beta = 1$, the full joint posterior probability for the parameters and model indicators is sampled. In this MCMC calculation, the model is varied by proposing a new model indicator and then simulating (i.e., drawing samples for) the new model parameters. After this new proposed model has reached equilibrium, i.e., the distributions of the drawn model parameter values in MCMC are stationary, the proposed model is either accepted or rejected using the Metropolis-Hastings acceptance criteria (34). If the proposed model is accepted, the annealing step is complete. However, if the proposed model is rejected, the calculation returns to the original model and new values for the model parameters are proposed. At the completion of the

calculation, the posterior probabilities for all the models and their parameters are approximated by the distributions of the Markov chain samples.

All model-selection calculations for in silico and clinical DCE-MRI data were performed using a Bayes Data-Analysis Toolbox (<http://bayesiananalysis.wustl.edu>) developed by G. Larry Bretthorst. All DCE-MRI contrast agent concentration signal models were written in Fortran and then loaded into the Image Model Selection package within this Toolbox. Computations were carried out on Dell PowerEdge R900 servers (Dell, Inc., Round Rock, TX), vintage 2008. All MCMC calculations were performed with 48 simulations and 50 repetitions; a total of 2400 simulations were run for each dataset (one voxel). For each simulation, a minimum of 50 annealing steps was employed. Using a server with 24 CPUs, the average computation time for one patient was about 12 hours.

Statistical analysis

All traditional (frequentist) statistical analyses were performed in Matlab (The Mathworks, Inc., Natick, MA). For changes in gross tumor volume, model selection, and parameter estimation on the clinical DCE-MRI data, a paired, two-sided Wilcoxon signed rank test was used to compare the pre- and post-RT time points in a matched fashion. Statistical significance was set at $P = 0.05$.

RESULTS

In silico data were generated based on the clinical cervical cancer DCE-MRI data from four different patients. Figure 3 summarizes the model selection and parameter estimation results for in silico data simulated based on the whole-tumor average DCE-MRI data of patient #1. In Figure 3a, model selection was employed to analyze in silico data simulated based on each of the four DCE models. At each noise power, 100 independent simulations (i.e., different noise sets) were performed and the number of “correct” selections, in which model selection chose the model used to simulate the data, were recorded. The number of correct model selections varied as a function of both model complexity and noise power (i.e., CNR). When the added noise standard deviation (SD) < 0.015 mM (i.e., CNR > 36), which is small compared to our clinical data (baseline noise SD = 0.04 mM, as shown in supplementary Figure 2), Bayesian model selection always chose the correct model, independent of the complexity of the model. However, as the CNR decreased, simpler data representations were preferred relative to more complex models. For data created based on the 2CXM, the number of correct selections dropped when the noise SD > 0.015 mM. For data created based on the ETM, the number of correct selections dropped when the noise SD > 0.055 mM (i.e., CNR < 10); for data based on the CTUM, the threshold was a noise SD > 0.10 mM (i.e., CNR < 5). By contrast, for the TM, the simplest model, model selection chose the correct model even when the noise SD increased to 0.2 mM (i.e., CNR = 3). For CNR much lower than 3, model selection chose the “no signal” model (data not shown). Figure 3b shows the model selection results for in silico data created based on the 2CXM. The number of correct model selections dropped rapidly as noise SD > 0.015 mM, with a concomitant increase in the selection of the CTUM, a simplified version of the 2CXM. However, with decreasing CNR (CNR < 7 , Noise SD > 0.08 mM), Bayesian model selection most often

chose the TM, the simplest model. Figures 3c–d (and Supporting Figure S3) show how the accuracy and uncertainty of estimations of v_e , the only common parameter between the simplest model, the TM (Figure 3c), and the most complex model, the 2CXM (Figure 3d), varied as Gaussian noise was added to each noiseless in silico dataset. While the accuracy of the v_e estimation for each model remained stable as CNR decreased, the uncertainties (i.e., error bars) of the estimated v_e were much smaller for the TM relative to the more complex 2CXM.

Similar to Figure 3a&b, Figures 4 and 5 illustrate graphically the model selection results for the 32 in silico datasets (eight differently parameter-valued datasets x four DCE kinetic models). The general qualitative trends are the same as shown in Figure 3a&b (Qualitatively similar results are also obtained for kinetic parameter values extracted from the perfusion literature, and for a different set of DCE models, see Supporting Figure S4). As CNR decreased, the number of correct model selections varied as a function of both CNR and model complexity. Consistently, correct selection of complex models required higher CNR (lower noise power) than simpler models. CTUM and ETM, despite having the same number of model parameters, behaved consistently differently. As CNR decreased, the complex 2CXM was replaced by the simpler CTUM, and, eventually, by the simplest TM. However, for each model, the specific noise power at which the number of correct selections started to decrease depended on the kinetic model's parameter values, which were derived from the original clinical DCE data used to simulate the in silico data. Note that the kinetic model's parameter values affect the MRI contrast agent entering the tissue, which also influence the CNR of the acquired DCE-MRI data.

Bayesian model selection was then applied to the full set of clinical DCE-MRI cervical cancer data acquired from ten patients. Figure 2 illustrates example contrast-agent concentration *vs.* time curves from four individual voxels within a single cervical tumor (Patient #1), in which the 2CXM (Figure 2a), CTUM (Figure 2b), ETM (Figure 2c), or TM (Figure 2d), respectively, are the Bayesian-preferred tracer kinetic models. While each of the four models was preferred in some individual voxels, Figure 6a shows that the TM and CTUM were overwhelmingly selected as best representing cervical cancer DCE-MRI data acquired both pre-treatment and two-to-three weeks following the start of RT (see Supporting Figure S5 for optimal-model maps of example tumor slices). After two-to-three weeks of therapy, the percentage of voxels best fit by the TM dropped by 19% ($P = 0.16$), while the percentage of voxels best fit by the CTUM increased by 14% ($P = 0.19$). Based upon a paired, two-sided Wilcoxon signed rank test, neither of these changes is statistically significant. Defining CNR as the ratio of the *maximum* contrast-agent concentration to the baseline noise standard deviation (calculated prior to the arrival of the main contrast-agent bolus), Figures 6b–c illustrate the CNR distributions of voxels across ten subjects (pre-treatment in Figure 6b, and two-to-three weeks following the start of RT in Figure 6c), in which either the TM or CTUM were the optimal models. For cervical cancer data collected both pre-treatment and two-to-three weeks following the start of RT, the median CNRs for data best modeled by the CTUM were larger than for data best modeled by the TM (18.9 *vs.* 14.3, and 21.4 *vs.* 15.0, respectively).

Next, the two dominant models, TM and CTUM, were used to estimate pharmacokinetic parameters for cervical tumor voxels in which each was preferred. Three pharmacokinetic parameters (K^{trans} from the TM, and F_p and PS from the CTUM) relating to tissue perfusion and capillary permeability increased two-to-three weeks into RT. Figure 7 shows that K^{trans} increased (mean $\pm$ SD) from $0.60 \pm 0.48 \text{ min}^{-1}$ to $1.56 \pm 1.08 \text{ min}^{-1}$ ($P = 0.004$), F_p increased from $0.69 \pm 0.37 \text{ min}^{-1}$ to $1.46 \pm 0.95 \text{ min}^{-1}$ ($P = 0.002$), and PS increased from $0.058 \pm 0.024 \text{ min}^{-1}$ to $0.078 \pm 0.024 \text{ min}^{-1}$ ($P = 0.014$). Representative parametric maps and corresponding uncertainty maps were shown in Supporting Figure S6.

DISCUSSION

The central goal of this study was to test the performance of complex DCE-MRI models in the context of a pool of competing models against: (i) in silico DCE-MRI data simulated based on each of the four models and (ii) clinical DCE-MRI data acquired prior to and two-to-three weeks following the initiation of RT in a cohort ($n = 10$) of advanced-stage, cervical cancer patients. For the clinical data, parameters were estimated, on a voxel-by-voxel basis, employing the selected, optimal kinetic model for each voxel.

The determination of an appropriate kinetic model is essential for extracting quantitative tissue perfusion and vascular permeability parameters from DCE-MRI data. Complex models (i.e., those with more parameters) will always provide better fits in terms of residuals alone (e.g., Chi-square). However, the inclusion of additional parameters may not be well supported by the acquired DCE-MRI data, and may, consequently, increase the uncertainty (variance) in the estimation of the parameters within the model.

Our simulation study shows that complex DCE-MRI models are more sensitive to CNR than simpler models with respect to both model selection (Figure 3a–b, Figures 4&5) and parameter estimation (Figure 3c–d, Supporting Figure S5). As noise standard deviation increases (i.e., CNR decreases), Bayesian model selection chooses simpler data representations (Figure 3b and Figure 5), a statistically rigorous manifestation of Occam's razor. Similarly, as CNR decreases, uncertainties in parameter estimates for highly parameterized models increase much more rapidly than for simpler models (Figure 3c&d) and Bayesian model selection chooses simpler models. For two models having the same complexity (i.e., the same number of model parameter), the CTUM is more robust than the ETM (Figure 3a, Figure 4) for the data examined herein.

Although each of the four models is preferred in some individual tumor voxels (Figure 2), the TM and CTUM are the two dominant models for the acquired cervical cancer DCE-MRI data (Figure 6a). The 2CXM and ETM were seldom selected, a finding that agrees well with our in silico results. As shown in Figures 3b and Figure 5, as CNR decreases, the general 2CXM reduces to the CTUM and eventually to the TM. Amongst the two preferred kinetic models, selection of the three-parameter CTUM generally requires higher CNR than the two-parameter TM (Figure 6b–c). However, choice of the optimal (most probable) model also depends on other factors beyond CNR, including kinetic/compartamental constraints imposed by physiological conditions, which explains the overlap of CNR distributions between the TM and CTUM in Figures 6b–c. For example, when the total acquisition time

course is short or the extracellular extravascular space (EES) is large, the forward contrast-agent flux from plasma to EES is much larger than the contrast-agent backflux from EES to plasma. Under such conditions, the CTUM, which ignores the backflux, is the physiologically more appropriate model (16) and, thus, better represents the acquired dynamic curves.

In heterogeneous tissue such as cancer, DCE model selection poses the “mixed tissue conundrum”. This is illustrated in the current case where different tumors, the same tumors at different times (e.g., before and after treatment), different tumor regions, and different tumor voxels support different DCE models, making it difficult to compare modeling results (e.g., intermodal comparison of estimated model-specific parameter values). However, in highly heterogeneous tissues such as cancer, this is not an unexpected result. Different tumors, different tumor regions, and different tumor voxels possess different physiologic and microstructural characteristics. Indeed, to a large extent, it is the competing models themselves that provide the desired tissue discrimination/characterization. In this light, transformation from one model to another in the face of therapy or other physiologic challenge may provide an important metric for patient care.

Choosing one commonly used “simpler” pharmacokinetic tracer model (without model selection justification) for data analysis would not avoid but hide the underlying mixed tissue conundrum by losing information and biasing parameter estimates. Whether DCE voxel-wise data of sufficient quality could be obtained such that a “more complex” model would be the most probable for all (or the substantial majority of) voxels in a truly heterogeneous tissue such as cancer is an interesting but open question. However, data from voxels that are well-fit by a simple model are likely to be inadequate to support a more complex model vis-à-vis Occam’s razor.

In addition to CNR investigated in this study, both temporal resolution and acquisition time window will also affect the ability of the kinetic models to fit the data, which will consequently affect model selection results. An extensive examination of how each of these factors affects model selection results is beyond the scope of this study. Therefore, it is impossible to draw universal conclusions regarding whether a given DCE model can be supported or not at a specific noise power (or temporal resolution or acquisition time). For each individual DCE-MRI dataset, data-driven model selection must be performed for the identification of voxel-specific optimal (most probable) models.

Biophysical properties not investigated in this study, but which may also affect the signal response in clinical DCE-MRI studies, include T_2^* dephasing, water exchange, inter-voxel convection (contrast agent flux from highly leaky voxel to less leaky voxels), and AIF accuracy (bolus dispersion and partial volume effects). All of these effects may influence the acquired DCE signal and, thus, affect the tracer kinetic modeling and model selection. Models that fully account for these effects, which were not included in this study, must incorporate more free parameters and thus have higher model complexity. Even though such models are physiologically more correct and more general in terms of applicability, it is likely that data quality would have to be exceptionally high to justify their use vs. less

complex models. In this context, for any given DCE-MRI dataset, data-driven model selection is a necessary prerequisite.

It is worth stressing here that there is no substitute for a well-considered data acquisition protocol, i.e., high quality data. Without such a protocol, even the most sophisticated post-acquisition analysis is left with effects that cannot be estimated in a reasonably small set of model parameters, but which will influence parameter estimates. Importantly, DCE signal effects related to T_2^* dephasing, water exchange, and AIF bolus dispersion and partial voluming can be minimized by optimizing the data acquisition protocol. For instance, T_2^* dephasing can be computed *via* a dual-echo sequence (35), and the water exchange effect can be suppressed by a careful selection of flip angle (36). In addition, the AIF accuracy can be improved by the selection of a reference region (37).

We note here that the estimated values for parameter shared amongst these DCE models are different from model to model, and that some of the computed values in some models are apparently non-physical (e.g., large 2CXM and CTUM v_p). The model selection and parameter estimation algorithms described herein are not the source of such biases. Our *in silico* simulation study (Figure 3), in which parameter values were estimated accurately, but with decreasing precision, as contrast-to-noise decreased, provides *prima facie* evidence that parametric biases in our study are not due to the modeling algorithms. Rather, the models are unavoidably wrong (i.e., are simplifications of a very complex tissue physiology), the data collection is unavoidably constrained/compromised by scanner capabilities, and the clinically achievable contrast-to-noise is unavoidably modest. Thus, while the estimation procedure is unbiased, the models and the data are biased. Therefore, that some parameter estimates seem physiologically implausible is not surprising and is not limited to this study but occurs throughout the literature. For example, while the ETM (also known as the Extended Patlak Model) usually produce v_p less than 0.1, studies (19,21,38–41) employing the newer 2CXM produce substantially higher v_p (up to 0.44). Whether the parameters so obtained are of clinical value in cancer detection and management is beyond the scope of this investigation. Nevertheless, the continued presence of such studies in the peer-reviewed literature suggests that the DCE-MR community feels such studies do have value, a manifestation of Box's dictum (42).

The use of quantitative pharmacokinetic parameters to evaluate the therapeutic response of tumors has been demonstrated in several studies (43–46). Our data showed that F_p , PS , and K^{trans} , which is a mixture of F_p and PS (16), increased during the early stages (two-to-three weeks) of RT (Figure 7). These changes are consistent with DCE-MRI results from previous studies (44,45) on pre- and post-radiotherapy cervical cancer. We caution that changes observed herein are only for voxels defined as tumor based on T2-weighted images. Further, it has been shown that possible underlying biological processes that are secondary to the radiotherapy (47), such as inflammation, may confound quantitative DCE-MRI measures of tumor perfusion and permeability, especially at early stages of treatment. Monitoring long-term patient outcomes, including both MR and clinical tumor indices, is necessary before making inferences regarding therapeutic response.

In conclusion, we have applied Bayesian-based algorithms to DCE-MRI tracer kinetic model selection and parameter estimation. Both DCE-MRI model selection and parameter estimation are sensitive to model complexity and data quality. Highly parameterized, complex models require higher data quality for accurate and stable model parameter estimation. In the absence of performing a model-selection calculation, these complex models should be employed cautiously. The two-parameter TM and the three-parameter CTUM were found to be the two dominant models for the clinical DCE-MRI cervical cancer data examined herein. Beyond other physiological factors, the three-parameter CTUM required higher CNR than the two-parameter TM. Significant changes in tumor perfusion and permeability (K^{trans} , F_p , and PS) were found during the early stages of RT. Correlating pre-treatment pharmacokinetic parameters with long-term treatment outcomes, such as local control and disease-specific survival, will be the subject of future work.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This project was supported by funding from the Alvin J. Siteman Comprehensive Cancer Center (P30 CA091842), research grants from CIRRO – the Lundbeck Foundation Centre for Interventional Research in Radiation Oncology, and funding from the Danish Research Council. We gratefully acknowledge the anonymous reviewers for their helpful comments.

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Figure 1.

The hierarchy of the four compartmental tracer kinetic models and their corresponding model parameters (16). Under various physiological conditions, the general 2CXM, in which contrast agent is distributed into two separate compartments (vascular and extracellular-extravascular spaces), reduces to the simpler ETM, CTUM and TM. PS_{c_p} is the permeability-surface area product of the vascular wall multiplied by the concentration of contrast agent in the blood plasma; and PS_{c_e} is the permeability-surface area product of the vascular wall multiplied by the concentration of contrast agent in the extracellular-extravascular space.

Figure 2.

Example DCE-MRI contrast agent concentration vs. time curves (circles) within a single cervical tumor, with optimal model fitting (solid line). For these example voxel-specific data sets, the optimal models were 2CXM (**Panel a**), CTUM (**Panel b**), ETM (**Panel c**), and TM (**Panel d**). Residuals are shown as dotted lines. All four kinetic models were selected as preferred models for some individual voxels within one cervical tumor. The measured AIF for this patient is shown in **Panel e** (note the change of the y-axis scale).

Figure 3.

Bayesian DCE-MRI model-selection and parameter-estimation results for in silico datasets created based on the whole-tumor averaged ROI DCE time course from patient #1. **Panel a:** for each of the four in silico DCE-MRI data models, the number of “correct” model-selections (out of 100 different noise representations), as a function of the noise standard deviation (SD). **Panel b:** for the two-compartment exchange in silico DCE-MRI data model (the most complex model of the four models examined), the number of times a given model was selected (out of 100 different noise representations) as a function of the noise SD. **Panels c & d:** relative percent error of v_e estimated from initially noiseless simulated TM (**Panel c**) and 2CXM (**Panel d**) as a function of added noise.

Figure 4. Pooled model selection results for in silico datasets created for each of the four DCE models -- **Panel a:** 2CXM; **Panel b:** CTUM; **Panel c:** ETM; and **Panel d:** TM. For each model, the 5th, 50th, and 95th percentiles of numbers of correct selections are plotted.

Figure 5.

Pooled model selection results for in silico datasets created for the 2CXM only. The numbers of selections for each model are shown in **Panel a**: 2CXM; **Panel b**: CTUM; **Panel c**: ETM; and **Panel d**: TM, respectively. Similar to Figure 4, the 5th, 50th, and 95th percentiles of the numbers of selection for each model are plotted.

Figure 6.

Bayesian DCE-MRI model selection results for a cohort of cervical cancer patients ($n = 10$).

Panel a: The average percent distribution of the optimal DCE-MRI model from the cohort of ten patients (39,365 total tumor voxels). The uncertainty bars indicate the standard deviation of the model distribution across all ten subjects.

Panel b & c: Pooled CNR distribution of pre-treatment (**Panel b**) and two-to-three weeks following the start of RT (**Panel c**) tumor voxels that are best represented by TM (solid black) or CTUM (crosshatch) DCE-MRI models.

Figure 7.

Pharmacokinetic parameters estimated using the optimal DCE-MRI kinetic models for all ten subjects in this study. **Panels a–c:** Paired scatter plots of median pharmacokinetic parameter estimates, both pre-treatment and two-to-three weeks following the start of RT, for tumor voxels in which the TM is the optimal model (K^{trans} in **Panel a**) and those in which the CTUM is the optimal model (F_p in **Panel b** and PS in **Panel c**). Here, * indicates $P < 0.05$, and ** indicates $P < 0.01$, as calculated by a paired, two-sided Wilcoxon signed rank test.

Table 1

Impulse response functions for the four tracer kinetic models.

	Impulse response function
2CXM ^a	$I(t) = F_p^*(A * \exp(-\alpha t) + (1 - A) * \exp(-\beta t))$
CTUM ^b	$I(t) = F_p^*((1-E) * \exp(-\gamma t) + E)$
ETM	$I(t) = K^{trans} * \exp(-K^{trans} * t) + v_p * \delta(t)$
TM	$I(t) = K^{trans} * \exp(-K^{trans}/v_e * t)$

^aFor the 2CXM, the impulse response function parameters A , α , and β are fully characterized by F_p , v_e , v_p , and PS (16).

^bFor the CTUM, the impulse response function parameters E and γ are fully characterized by F_p , v_p and PS (16).