Pharmacokinetic analysis of tissue microcirculation using nested models: Multimodel inference and parameter identifiability

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The purpose of this study is to evaluate the identifiability of physiological tissue parameters by pharmacokinetic modeling of concentration-time curves derived under conditions that are realistic for dynamic-contrast-enhanced (DCE) imaging and to assess the information-theoretic approach of multimodel inference using nested models. Tissue curves with a realistic noise level were simulated by means of an axially distributed multipath reference model using typical values reported in literature on plasma flow, permeability-surface area product, and volume fractions of the intravascular and interstitial space. The simulated curves were subsequently analyzed by a two-compartment model containing these physiological quantities as fit parameters as well as by two reduced models with only three and two parameters formulated for the case of a permeability-limited and a flow-limited scenario, respectively. The competing models were ranked according to Akaike's information criterion (AIC), balancing the bias versus variance trade-off. To utilize the information available from all three models, model-averaged parameters were estimated using Akaike weights that quantify the relative strength of evidence in favor of each model. As compared to the full model, the reduced models yielded equivalent or even superior AIC values for scenarios where the structural information in the tissue curves on either the plasma flow or the capillary permeability was limited. Multimodel inference took effect to a considerable extent in half of the curves and improved the precision of the estimated tissue parameters. As theoretically expected, the plasma flow was subject to a systematic (but largely correctable) overestimation, whereas the other three physiological tissue parameters could be determined in a numerically robust and almost unbiased manner. The presented concept of pharmacokinetic analysis of noisy DCE data using three nested models under an information-theoretic paradigm offers promising prospects for the noninvasive quantification of physiological tissue parameters. © 2009 American Association of Physicists in Medicine. [DOI: [10.1118/1.3147145](https://doi.org/10.1118/1.3147145)]

I. INTRODUCTION

Technical developments in both magnetic resonance imaging (MRI) and computed tomography (CT) have helped to reduce scan times and expedited the introduction of dynamic-contrast-enhanced (DCE) imaging techniques into clinical routine. Since the temporal change in the image signal following the administration of an appropriate extracellular contrast agent (CA) is related to the local blood supply and the extravasation of the CA into the interstitial space, DCE imaging can be used for the assessment of tissue microcirculation and microvasculature. Given that it does not expose patients to ionizing radiation, MRI, in particular, opens promising prospects for DCE imaging.

While various simplistic but robust approaches for DCE imaging (e.g., Refs. 1–5) are successfully applied both in

biomedical research and health care, there are still serious problems hampering the application of DCE imaging for the absolute quantification of well-defined physiological parameters such as plasma flow, capillary permeability, and volume fractions of the plasma and interstitial space.⁶ Besides the accurate determination of tissue concentrations of the administered CA from measured DCE image data, the development and selection of appropriate pharmacokinetic models for the analysis of the derived concentration-time courses pose a central problem. There is always a trade-off between the complexity of the model, which should describe the relevant physiological transport processes in as much detail as possible, and the identifiability (or estimability) of model parameters from real data.⁷ It generally applies that the number of physiological tissue parameters that can be identified with

FIG. 1. Nested compartment models describing the transport of an extracellular contrast agent through microvessels and its bidirectional diffusion between blood plasma (average concentration $\bar{C}_p$; volume V_p) and the interstitial space (average concentration, $\bar{C}_i$; volume, V_i). $C_A(t)$ is the plasma concentration in a tissue-feeding artery, F_A is the apparent plasma flow, and PS is the permeability-surface area product. The reduced models 2 and 3 are derived under the additional assumption of high plasma flow [$\Rightarrow C_p(t) \equiv C_A(t)$] or fast bidirectional diffusion [$\Rightarrow C_i(t) \equiv C_p(t)$], respectively. The quantities plotted in bold are the free model parameters to be fitted.

high accuracy and precision (or in statistical terms, with a low bias and variance) from DCE data, and thus the complexity of the underlying model, is limited.

At present, the issue of model selection and parameter identifiability cannot be investigated on the basis of DCE data measured in animals or humans since there is no generally accepted noninvasive measurement technique for absolute quantification of all of the aforementioned physiological tissue parameters that can serve as reference method. Therefore, we adapted a simulation-based approach used by Buckley.⁸ By means of a well-established physiological reference model—that accounts for flow dispersion and heterogeneity and models capillaries as axially distributed blood-tissue exchange units⁹—concentration-time curves (referred to in the following as “tissue curves”) were simulated for an extracellular CA by varying the physiological quantities plasma flow, capillary permeability, plasma volume, and interstitial volume. Unlike Buckley, however, a measured arterial input function was used for the simulations, and tissue curves were generated with a realistic noise level to evaluate the numerical stability of data analysis.

A promising and mathematically rigorous way to deal with the issue of model selection is to analyze tissue curves using competing models under an information-theoretic paradigm derived by Akaike as an extension of Fisher’s likelihood theory.¹⁰ Akaike’s information criterion (AIC) is an objective means for the selection of the best approximating model from a set of candidate models. In contrast to other approaches to comparing models, such as the F or likelihood ratio test, the AIC also allows formal inference to be based on more than one model [multimodel (MM) inference] leading to more robust parameter estimates.⁷ Within the context of medical physics, the information-theoretic approach was recently applied to the pharmacokinetic analysis of blood activity data.¹¹

The aim of the present study was threefold: (i) To formulate a consistent concept for the analysis of DCE data within the framework of pharmacokinetic modeling, (ii) to evaluate the identifiability of model parameters on the basis of noisy tissue curves simulated for different physiological scenarios (excluding systematic errors in the measurement process),

and (iii) to assess the potential of multimodel inference of physiological tissue parameters from DCE data using nested pharmacokinetic models.

II. MATERIAL AND METHODS

II.A. Nested pharmacokinetic models

For pharmacokinetic analysis of DCE data, three nested pharmacokinetic models were formulated: A full two-compartment model and two reduced models dedicated to specific physiological scenarios. A graphical representation of the models is given in Fig. 1.

The *full two-compartment model* [CM1, Fig. 1(a)] describes the transport of a CA through the plasma compartment (with mean CA concentration $\bar{C}_p$ and volume V_p) and its diffusion into the interstitial space (with mean CA concentration $\bar{C}_i$ and volume V_i) by the following pair of mass-balance equations derived in the Appendix:

$$V_p \frac{d\bar{C}_p(t)}{dt} = F_A(C_A - \bar{C}_p) - PS(\bar{C}_p - \bar{C}_i) \quad (1)$$

and

$$V_i \frac{d\bar{C}_i(t)}{dt} = PS(\bar{C}_p - \bar{C}_i), \quad (2)$$

where $C_A(t)$ is the CA concentration in a tissue-feeding artery, F_A the apparent capillary plasma flow, and PS the permeability-surface area product. The total tissue concentration is given by $\bar{C}_T(t) = v_p \bar{C}_p(t) + v_i \bar{C}_i(t)$, where $v_p = V_p/V_T$ and $v_i = V_i/V_T$ are the volume fractions of the plasma and interstitial distribution space within the examined tissue volume, V_T , respectively. Based on these model equations, the following four independent tissue parameters can be determined from the measured concentration-time curves $C_A(t)$ and $\bar{C}_T(t)$: F_A/V_T , PS/V_T , v_p , and v_i . As shown in the Appendix, the apparent plasma flow $F_A = RF$ is systematically higher than the true plasma flow F by a factor of $1 \leq R \leq 2$. Under the additional assumption of a unidirectional diffusion of the CA from the capillaries into the interstitial space

(Renkin-Crone model), an analytical expression is derived in the Appendix [Eq. (A5)] for this tissue-specific factor R that can be used to calculate a corrected plasma flow F_C from the fitted model parameters F_A/V_T and PS/V_T .

The *permeability-limited compartment model* [CM2; Fig. 1(b)] is dedicated to a scenario in which the plasma flow is so high that the concentration-time curve in the intravascular plasma compartment cannot be distinguished from the arterial input [$C_p(t) \equiv C_A(t)$] given the limited temporal resolution and the noisy output of the measurement technique. It can be realized numerically by fixing the plasma flow in Eq. (1) at a very high value that is sufficient to replenish loss of the CA into the interstitial space. Accordingly, the number of estimable model parameters is reduced to 3 (PS/V_T , v_p , v_I).

The *flow-limited compartment model* [CM3, Fig. 1(c)] describes the complementary scenario that the transfer of the administered CA between the intravascular and interstitial compartment is fast when compared to the capillary plasma flow so that the distribution space of the CA in the tissue of interest can be approximated by a single tissue compartment with the relative distribution volume $v_D = v_p + v_I$. This one-compartment model is described by only two parameters (F_A/V_T , v_D). It is also applicable to tissues with a small interstitial space ($v_I \ll v_p$) or a low capillary permeability ($PS \approx 0$, e.g., when using an intravascular CA). In this case, the distribution volume approximates the plasma volume ($v_D \approx v_p$).

II.B. Simulation of tissue curves

In order to investigate the identifiability of physiological tissue parameters from DCE data under an information-theoretic paradigm, tissue concentration curves were simulated using MMID4 (multiple indicator, multiple path, indicator-dilution 4 region model) running under JSim (National Simulation Resource, Department of Bioengineering, University of Washington, Seattle, WA). MMID4 is based on the multiple indicator-dilution theory and enables the simulation of tissue curves for different tissue variables such as plasma flow, capillary permeability, plasma volume, and volume of the interstitial space. Transport processes within a tissue region are subdivided into three functional components: Tracer molecules enter through an arterial vessel, flow through parallel pathways (each consisting of an arteriole, an exchange unit, and a venule), and then leaves the system through a common vein. Whereas tracer in all parts contributes to the tissue curve, transfer of tracer to the interstitial space is limited to the exchange units. They are subdivided into a series of axially distributed segments in order to model capillary flow and exchange of tracer by a Lagrangian sliding fluid element algorithm. The resulting capillary-tissue convection-permeation model is spatially distributed and accounts for axial variation in tracer concentrations within capillaries, transport through and around endothelial cells, exchange with the interstitium, and heterogeneity of regional flows. A detailed description of the concepts implemented in MMID4 is given in the literature.^{9,12,13} For our simulations, it was assumed that the tissue of interest consists of arterioles,

venules, and the exchange units, which means that arteries and veins were excluded from calculating the tissue curves. The volume fractions of the three vascular components taken into account were fixed at 15:55:30.¹⁴

Tissue curves with $N=126$ data points were simulated using a representative arterial input function (C_A) derived from DCE-MRI data measured in a previous patient study¹⁵ over 6 min with a temporal resolution of 2.88 s after short-time infusion (over 30 s) of the paramagnetic CA Gd-DTPA [Fig. 2(a)]. Since fluctuations of the measured input function are dominated by physiological variations of the CA concentration arising from arterial pulsing, the measured input function and not a fit to the measured data was used for the simulation of tissue curves. Dispersion and a time shift of the arterial input measured in the aorta on its way to the tissue region of interest were not taken into account. The maximum of the arterial input was set to an arbitrary value of 100. In total, 40 tissue curves were computed for different combinations of the physiological variables F/V_T , PS/V_T , v_p , and v_I . The values used for the simulations are summarized in Table I. They cover a range that is representative for most normal and tumor tissues. For the simulated curves, the ratio between trans- and intracapillary CA transport was in the range $0.02 \leq PS/F \leq 2$, which corresponds to $1.99 \geq R \geq 1.52$. The mean residence and transit times (in s) defined in the Appendix were in the ranges $1.2 \leq MRT_p \leq 24$, $2.4 \leq MRT_I \leq 60$, and $7.2 \leq MTT_S \leq 84$.

Although the input function is affected by physiological “noise,” the simulated tissue curves are almost noise-free since the tissue (model) acts as a low-pass filter. Therefore, a Gaussian-distributed system noise, obtained from a random number generator, was added to the simulated curves in order to analyze the numerical stability of our modeling approach.¹⁶ The variance of the noise signal ($\sigma_{\text{noise}}=0.15$) was identical for all simulations and adapted to the noise level of the tissue curves determined from patient DCE imaging studies.^{15,17} In total, ten tissue curves with a different noise pattern were generated for each combination of the model variables.

II.C. Parameter estimation

For each of the 400 generated tissue curves (10 curves with different noise pattern for each of the 40 simulated physiological scenarios), the model parameters related to the three pharmacokinetic models CM1, CM2, and CM3 were estimated with the extended least-squares modeling program package MKMODEL (version 5.0, Biosoft, Cambridge, UK) using the same input function as was used for the simulations. The algorithm employed for the numerical integration of the differential equations is based on the Kutta-Merson method, whereby step size selection and local error control are provided automatically. All fits were performed using a constant variance model. To evaluate the goodness of fit for each of the three fitted models, the maximized log likelihood

FIG. 2. Representative selection of concentration-time curves (data points, 126; temporal resolution, 2.88 s). (a) Arterial input function used for the simulation and analysis of the tissue curves. The vertical lines indicate the period of CA administration. (b) Concentration-time curve of the reference tissue ($v_p = 0.04$, $v_l = 0.1$, $F/V_T = 0.5$ ml/ml/min, $PS/V_T = 0.2$ ml/ml/min). The concentration curves plotted in the lower four rows were simulated for tissues that differ from the reference tissue in one microcirculatory quantity: [(c) and (d)] $v_p = 0.02, 0.09$, [(e) and (f)] $v_l = 0.04, 0.30$, [(g) and (h)] $F/V_T = 0.2, 0.9$ ml/ml/min, and [(i) and (j)] $PS/V_T = 0.05, 0.8$ ml/ml/min. The curves give the results of the pharmacokinetic analysis using the three nested models CM1 (solid line), CM2 (dotted line), and CM3 (dashed line). Please note that the fit curves for CM1 and CM2 widely overlap.

TABLE I. Values of the physiological variables used for the simulation of 40 tissue concentration-time curves. One of the specified quantities was always varied over the ten values given in the respective column while the three other variables were fixed at the reference values printed in bold.

v_P	v_I	F/V_T (ml/ml/min)	PS/V_T (ml/ml/min)
0.01	0.02	0.1	0.01
0.02	0.04	0.2	0.05
0.03	0.06	0.3	0.1
0.04	0.08	0.4	0.2
0.05	0.10	0.5	0.3
0.06	0.15	0.6	0.4
0.07	0.20	0.7	0.5
0.08	0.25	0.8	0.6
0.09	0.30	0.9	0.8
0.10	0.35	1.0	1.0

$$\log \mathcal{L} = -\frac{N}{2} [\log(\hat{\sigma}^2) + \log(2\pi) + 1] \quad (3)$$

was computed, with N the sample size and $\hat{\sigma}^2 = RSS/N$ the normalized residual sum of squares (RSS).

The choice of appropriate initial values is a crucial step in iterative parameter estimation. A poor choice may not only result in a very slow convergence (in our implementation, the maximum number of iterations was limited to 200) but may also lead to convergence to a local minimum. In case of the more complex models CM1 and CM2, fits were thus performed for several sets of initial values, namely, the nine combinations of $v_P=0.05$, $v_I=0.15$, $F_A/V_T=0.5/1.5/3.0$ ml/ml/min, and $PS/V_T=0.05/0.75/1.5$ ml/ml/min for CM1 and the three combinations of $v_P=0.05$, $v_I=0.15$, and $PS/V_T=0.05/0.75/1.5$ ml/ml/min for CM2. For CM3, we used $v_D=0.1$ and $F/V_T=1.0$ ml/ml/min. In general, two or more sets of initial values yielded almost comparable fit results. To take advantage of this fact, parameter estimates for fits with a $\log \mathcal{L}$ value that do not differ by more than 0.5% from the maximum $\log \mathcal{L}$ value were averaged.

II.D. Model ranking and multimodel inference

Selection of the “best approximating model” from the set of candidate models was performed by an extension of AIC containing a (second-order) bias-correction term for small sample sizes,⁷

$$cAIC = -2 \log \mathcal{L} + 2K \left(\frac{N}{N-K-1} \right), \quad (4)$$

where K is the number of the estimated model parameters (including $\hat{\sigma}^2$). It is advocated to use the corrected AIC when the ratio N/K is small (<40). The absolute $cAIC$ value for a given model is not meaningful in itself; relevant are only the differences

$$\Delta_m = cAIC_m - cAIC_{\min} \quad (5)$$

calculated over a set of $1 \leq m \leq M$ alternative models, with $cAIC_{\min}$ being the smallest $cAIC$ value in the set. They bal-

ance the change in goodness of fit as assessed by the log-likelihood values to the change in the number of parameters to be fitted and so can be used for model ranking.¹⁶ The model estimated to be the best has $\Delta_m \equiv 0$.

The relative strength of evidence for each of the considered models, i.e., the posterior model probabilities in a Bayesian sense, can be quantified by the so-called Akaike weights⁷

$$w_m = \frac{\exp(-\Delta_m/2)}{\sum_{r=1}^M \exp(-\Delta_r/2)}. \quad (6)$$

These weights form the information-theoretic basis for multimodel inference:⁷ Given a set of $1 \leq m \leq M$ nested models, each having the parameter X as the predicted value of interest, a model-averaged parameter estimate $\hat{X}$ can be obtained by

$$\hat{X} = \sum_{m=1}^M w_m X_m. \quad (7)$$

Figure 1 reveals that the three nested compartment models investigated in this study contribute in different combinations to the considered tissue parameters:

CM1, CM2, and CM3: $v_D = v_P + v_I$,

CM1 and CM2: PS/V_T , v_P , and v_I ,

CM1 and CM3: F_A/V_T . (8)

For each of the three cases, specific weights were calculated for parameter averaging according to Eq. (6).

In order to quantify the relative importance of the parameter X_j for modeling measured or simulated data, Burnham and Anderson suggested to use the sum of the Akaike weights over all models in which that parameter appears:⁷

$$w_+(j) = \sum_{m=1}^M w_m I_j(g_m), \quad (9)$$

where $I_j(g_m) = 1$ if the parameter X_j is defined in model g_m and 0 otherwise.

To evaluate the performance of the MM as compared to the single-model (CM1) approach for each of the $1 \leq i \leq 40$ different physiological scenarios, we finally calculated the mean value ($\bar{X}_i^m$), the standard deviation ($\sigma_{X,i}^m$), and the relative standard deviation ($RSD_{X,i}^m = \sigma_{X,i}^m / \bar{X}_i^m$) of the fit parameters ($X_{i,j}^m$) estimated by both approaches ($m = \text{MM, CM1}$) from the $1 \leq j \leq 10$ corresponding tissue curves simulated with a different noise signal.

III. RESULTS

A selection of tissue curves that are representative for the entire set of data investigated in this study is shown in Fig. 2. Visual inspection of the plots reveal two nontrivial facts that constitute necessary (but not sufficient) prerequisites for the identifiability of model parameters with high accuracy (low bias) and high precision (low variance): (i) The tissue curves

FIG. 3. Akaike weights giving the relative strength of evidence for the three nested models CM1, CM2, and CM3 defined in Fig. 1. Data are grouped for tissue curves simulated for varying values of (a) plasma volume v_p , (b) interstitial volume v_I , (c) plasma flow, F/V_T , and (d) permeability-surface area product, PS/V_T . The values of the physiological variables used for the simulations are presented in the same order in Table 1.

are sensitive under the realized experimental conditions (CA administration, temporal sampling) to variations in the physiological tissue parameters v_p , v_I , F/V_T , and PS/V_T . (ii) The models CM1 and CM2 fit all tissue curves very well whereas model CM3 yields some misfits.

The second aspect is verified on a quantitative basis by a residual analysis. The mean (maximum) value of the normalized residual sums of squares, $\hat{\sigma}^2 = RSS/N$, determined for all 400 simulated tissue curves was 0.0262 (0.0346) for CM1, 0.0303 (0.0625) for CM2, and 0.136 (0.616) for CM3. The mean values determined for CM1 and CM2 are very close to the variance of the simulated noise signal ($\sigma_{\text{noise}}^2 = 0.0225$), which indicates that their error variance is small.

Quantitative ranking of the three nested compartment models used for data analyses was performed by means of the Akaike weights, w_m ($m=1, 2, 3$). The computed weights for each of the 40 simulated scenarios are plotted in Fig. 3. From the information-theoretic point of view, CM1 performed best in 32 cases, CM2 in 5 cases, and CM3 in 3 cases. In comparison to CM1, the two reduced models yielded equivalent or even superior results for tissue curves that were simulated for a scenario in which one of the physiological quantities was very low or very high. For example, CM3 performed best when the interstitial volume was very

small [$v_I = 0.02$, Fig. 3(b)] or the PS/F ratio was high [$F/V_T = 0.1$ ml/ml/m, $PS/V_T = 0.2$ ml/ml/min, Fig. 3(c); $F/V_T = 0.5$ ml/ml/m, $PS/V_T = 1$ ml/ml/min, Fig. 3(d)]. This is in line with the theoretical considerations leading to the formulation of model CM3. A strong evidence of $w_1 > 0.9$ in favor of CM1 was determined for only 20 of the 40 curves. In the other 20 cases, the concept of multimodel inference took effect to a considerable extent resulting in a reduction in the maximum RSD from 44% to 34% for v_p , from 50% to 23% for v_I , and from 64% to 32% for PS/V_T . In contrast, no effect was found for v_D (7%) and F_C/V_T (65%).

Averaged over all simulated scenarios, the relative importance of the model parameters for the description of the simulated tissue curves was $w_+(F_A/V_T) = 0.81$, $w_+(v_p) = w_+(v_I) = w_+(PS/V_T) = 0.95$, and $w_+(v_D) = 1.0$.

In order to assess the accuracy of the model parameters estimated by the multimodel approach from the simulated tissue curves, they are plotted in Fig. 4 versus the physiological variables used for the simulations. The absolute values determined for v_p , v_I , v_D , and PS/V_T agree quite well with the true physiological values. In contrast, F_A values are markedly overestimated as theoretically expected. However, their accuracy could be substantially improved using the proposed correction algorithm. The computed correction factors

Fig. 4. Tissue parameters ($\bar{X} \pm \sigma_X$) estimated by the multimodel approach for 40 tissue curves simulated with MMID4 for different values of (a) plasma volume v_p , (b) interstitial volume v_i , (c) plasma flow, F/V_T , and (d) permeability-surface area product, PS/V_T . The solid lines represent the theoretically expected model parameters, whereas the different symbols indicate the model that contributes most to the estimated parameter values (CM1: ●, CM2: ▼, CM3: ▲). The open and full symbols in the flow plots (fourth row) give the apparent (F_A/V_T) and the corrected plasma flow (F_C/V_T), respectively.

were in the range $1.24 \leq R \leq 1.99$. Averaged over all simulated scenarios, the accuracy, i.e., the relative deviation of the estimated from the true parameter values, was 17% for v_p , 8% for v_i , 3% for v_D , 31% for F_C/V_T , and 11% for PS/V_T . The error bars ($\pm \sigma_X^{MM}$) given in the parameter plots of Fig. 4 characterize the precision of the multimodel approach. It was fairly high for v_i (average RSD , 6%), v_D (0.6%), and PS/V_T (7%), whereas larger uncertainties occurred for v_p (14%) and F_C/V_T (24%). Reduced accuracy and precision were observed, in particular, for low v_p (0.01) and v_i (≤ 0.04) values

as well as for high F/V_T and PS/V_T values (≥ 0.8 ml/ml/min).

IV. DISCUSSION

Anatomically and physiologically realistic tracer kinetic models account for the spatial gradients in tracer concentrations within blood-tissue exchange units, while compartmental models simplify the equations by using spatially averaged concentrations. Since both types of models are derived from

the same ideas, the physiological quantities are usually the same; their differences are in the ability to describe tissue microcirculation quantitatively correct as well as in their computability.¹⁸ In the present study, we used a publicly available axially distributed multipath reference model (MMID4) to simulate tissue microcirculation under conditions realistic for DCE imaging. The simulated data were subsequently analyzed by means of nested compartment models to evaluate the reliability of these lumped models for the analysis of DCE data and the identifiability of physiological tissue parameters. In this way, independent models with a substantially different degree of complexity in describing tissue physiology were used for the generation and analysis of tissue curves.⁸

As arterial input, a representative concentration-time course measured in the aorta of patients by DCE-MRI after administration of Gd-DTPA over 30 s was used. Since the injection time is slightly longer than the circulation time in the human body of about 25 s, the CA is much better mixed in the central blood pool than in the case of a rapid bolus injection. On the other hand, it is short enough to ensure that the measured tissue curves are dominated by the CA in the intravascular compartment during the initial enhancement phase, which improves parameter identifiability. The input function used in this study may be affected to some extent by MRI-specific measurement errors such as susceptibility effects resulting in an underestimation of the peak region. This is, however, of no relevance for our investigation since the same arterial input was used both for the simulation and the analysis of tissue curves.

Adapting a concept presented by Morales and Smith, an open two-compartment model was implemented for the analysis of DCE data that separately describes intra- and transcapillary transport processes of diffusible ionic or non-ionic tracer molecules. This linear model is based on a rather weak assumption regarding the concentration profiles between the inlet and the outlet of capillaries and allows an unbiased estimation of three tissue parameters from DCE data: the transport parameter PS/V_T as well as the volume fractions v_p and v_l . The prize to be paid for these advantages is a systematic overestimation of the true plasma flow, F/V_T , by a factor of $1 \leq R \leq 2$. The theoretical concept is fully verified by the model parameters estimated from the simulated tissue curves (Fig. 4). As compared to the related, but mathematically much more ambitious, adiabatic solution to the tissue homogeneity model published by StLawrence and Lee in 1998 (Ref. 19) for the separate estimation of F/V_T and PS/V_T , our approach offers two advantages from the practitioners point of view: (i) It is fully consistent with the principles of pharmacokinetic modeling and can thus be implemented in commercially available pharmacokinetic software packages and (ii) it clearly indicates which physiological tissue parameters are affected (and to what degree in the worst case) by the underlying model assumptions and which are unbiased.

In order to correct for the systematic error in the apparent plasma flow, $F_A = RF$, estimated from a tissue curve by our compartment approach, an analytical expression was derived

for R under the assumption of a unidirectional diffusion of the CA from the capillaries into the interstitial space (Renkin-Crone model). At first sight, this seems to be a rather crude assumption for DCE imaging given the fact that the contrast enhancement is typically measured over some minutes following CA administration. It has to be noted, however, that the model parameter F_A/V_T is numerically determined from the data measured during the very early phase of CA uptake, in which the above assumption holds in good approximation. This is confirmed by the satisfactory results achieved by applying Eq. (A5) for first-order flow correction for a variety of physiological scenarios (cf. Fig. 4). The accuracy of the corrected flow data presented in Fig. 4(c) is better than 35% in the range $0.1 \leq F/V_T \leq 0.8$ ml/ml/min, which is representative for the majority of normal and pathological tissues. Markedly higher errors of up to 85% occurred for tissue curves simulated for $F/V_T > 0.8$ ml/ml/min or $v_p = 0.01$. In these cases, the mean residence time for CA particles passing through the intravascular plasma compartment is less than $MRT_p = v_p(F/V_T)^{-1} \leq 3$ s, i.e., in the order of or less than the temporal sampling interval of the curves of 2.88 s. To avoid this “undersampling” error, the temporal resolution of the measurement process has to be adapted to the mean residence times of the tissues to be examined. But besides that it has to be recognized that the plasma flow is the least accurate and precise fit parameter. This is in line with the result that the relative importance of the plasma flow, $w_+(F_A/V_T)$, in modeling the simulated tissue curves is somewhat lower than the corresponding values determined for the other model parameters.

A central issue in modeling physiological data is the bias versus variance trade-off: Inferences under models with too few parameters can be biased, while there may be poor precision with models having too many fit parameters. The aim is thus to select a parsimonious model that provides an accurate approximation to the structural information in the data at hand.⁷ Accordingly, three nested pharmacokinetic models of different complexity were investigated in this study with respect to the *a priori* or structural identifiability of tissue parameters using simulated data free of systematic errors.²⁰ In case that it turns out in this context that the models are too complex for the particular set of ideal data, there is no way in a real situation that the parameters can be identified. Besides a full two-compartment model with four parameters (CM1) two reduced models were investigated: A “permeability-limited” model with three parameters that holds for a very high plasma flow (CM2) and a “flow-limited” model with only two parameters that holds for $PS \gg F$ and/or $v_p \gg v_l$ (CM3). As an objective way of determining which of these models is most parsimonious in approximating a given tissue curve, the AIC was used that penalizes for the number of model parameters in order to balance bias against variance. As expected, given the limited temporal resolution and the noisy output of the “measurement” process (Fig. 3), the two reduced models yielded equivalent or even superior results for physiological scenarios where one microcirculatory pa-

parameter becomes very small or large and so has only a negligible effect on the shape of tissue curves.

In order to utilize the information available from all three models to come to an inference, model-averaged parameters were estimated using Akaike weights that express the relative strength of evidence in favor of a particular model in a mathematically rigorous way. The concept of multimodel inference took effect ($w_1 < 0.9$) in half of the tissue curves investigated in this study and improves the precision of the estimates for v_p , v_f , and PS/V_T . In contrast, inference of the parameters v_D and F/V_T does not benefit from the multimodal approach for two completely different reasons: In the first case, the three nested models yielded almost identical estimates of v_D when the Akaike weights were comparable, whereas, in the second case, there were only three physiological scenarios with $w_3 > w_1$ (note that $w_2 \equiv 0$ because F/V_T is not defined in CM2).

The latter case reveals that multimodel inference is not a panacea. If the Akaike weight computed for one of the two reduced models is comparable to that of the full model, it indicates that the structural information in the analyzed tissue curve on either the plasma flow (CM2) or the capillary permeability (CM3) is limited. In these instances, inference of the “critical” parameter under model CM1 is not improved by the information-theoretic approach, since the parameter considered is not defined in the competing reduced model yielding a comparable Akaike weight. On the other hand, the complementary reduced model containing the parameter generally yields a much smaller Akaike weight (cf. Fig. 3).

In conclusion, the presented concept of pharmacokinetic analysis of DCE data using three nested models under an information-theoretic paradigm offers promising prospects for the noninvasive quantification of well-defined physiological parameters that characterize tissue microcirculation and microvasculature. As a major advantage, the multimodel approach avoids the *a priori* selection of a particular model. Instead, the relative strength of evidence in favor of competing models is computed for a given set of DCE data. The analysis of noisy tissue curves simulated for a variety of physiological conditions demonstrated that tissue parameters (with the exception of plasma flow, which is subject to a systematic but largely correctable overestimation) can be determined in a numerically robust and almost unbiased manner.

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APPENDIX: PHARMACOKINETIC MODELING

The following analysis is based on a single-capillary model. It is further assumed that (i) the solubility of the employed extracellular CA in the interstitial fluid is the same as in plasma, (ii) the permeability of the capillary wall is the same in both directions, and (iii) the physiological tissue parameters are constant over the duration of measurement

(stationary system). Under these assumptions, the transport of the CA through capillaries and its diffusion into the interstitial space can be described by the following pair of mass-balance equations derived from Fick’s first law:²¹

$$V_P \frac{d\bar{C}_P(t)}{dt} = F(C_A - C_V) - PS(\bar{C}_P - \bar{C}_I) \quad (A1)$$

and

$$V_I \frac{d\bar{C}_I(t)}{dt} = PS(\bar{C}_P - \bar{C}_I), \quad (A2)$$

where C_A is the arterial plasma concentration at the inlet of the capillaries (i.e., the arterial input), C_V is the venous concentration at their outlet, $\bar{C}_P$ is the spatially averaged CA plasma concentration in the capillaries (volume V_P), $\bar{C}_I$ is the averaged CA concentration in the interstitial space (volume V_I), F is the plasma flow through the capillaries, and PS is the permeability-surface area product. However, since the venous concentration C_V cannot be measured noninvasively, these equations cannot be solved directly and so additional assumptions must be made in order to simplify the problem.

One approach was presented by Kety for inert gases that are rapidly distributed in the interstitial and intracellular space.²² Since the capillary volume is small when compared to the extravascular volume in most tissues, it is reasonable to assume that changes in the mean tissue concentration of the tracer during the time it takes for an element of blood to pass through the tissue are negligible in comparison with the concentration change occurring in the blood itself. Using this postulate, Kety derived an analytical solution for the total amount of tracer in a tissue region, from which the transfer coefficient $K = F \cdot E / V_e$ can be determined with V_e being the partition volume of exchangeable tracer and $E = 1 - \exp(-PS/F)$ being the extraction fraction. Whereas the Kety model can also be applied to activity-time courses measured with positron emission tomography after the administration of a freely diffusible tracer (e.g., ¹⁵O-labeled water), its application to extracellular CA administered in CT and MRI studies is questionable, at least for tissues with V_I not much larger than V_P .

A more general approach was presented by Morales and Smith for inert gases in 1942 (Ref. 23) and adapted to DCE-CT studies using an extracellular CA by our group in 1999.¹⁷ It is based on the rather weak assumption that the spatially averaged tracer concentration $\bar{C}_P$ is between the concentrations at the arterial inlet and the venous outlet of the capillaries, which implies the relation

$$C_A - C_V = R(C_A - \bar{C}_P), \quad (A3)$$

with $R \geq 1$ being a tissue-specific factor that is independent of time over the duration of measurement. Substituting this in Eq. (A1) yields

$$V_P \frac{d\bar{C}_P(t)}{dt} = F_A(C_A - \bar{C}_P) - PS(\bar{C}_P - \bar{C}_I), \quad (A4)$$

where $F_A = RF \geq F$ is the *apparent* plasma flow. The model described by Eqs. (A2) and (A4) is fully consistent with the basic assumptions of linear pharmacokinetic modeling,²⁴ namely that (i) the tissue-specific model parameters are independent of time, (ii) each compartment can be described by a uniform—i.e., spatially averaged—tracer concentration, and (iii) the flow of tracer out of a compartment is proportional to the average concentration in the compartment (first-order kinetics). In contrast to the Kety model, the approach formulated by Morales and Smith makes it possible to independently characterize both the apparent plasma flow F_A and the permeability of the capillary endothelium, PS .

For an arbitrary blood-tissue exchange unit, the tissue-specific factor R introduced in Eq. (A3) decreases from 2 to 1 as PS/F increases over the interval $(0, \infty)$ as the following considerations substantiate: In the limit $PS/F \ll 1$, the concentration profile along a capillary decreases only slightly and can thus be approximated by a linear (first-order) Taylor expansion of the exact functional relationship, which directly yields $C_A - C_V \approx 2(C_A - \bar{C}_P)$. In the limit $PS/F \gg 1$, the concentration profile drops immediately at the beginning of the capillary to the venous concentration, which implies $\bar{C}_P \approx C_V$ and thus $C_A - C_V \approx C_A - \bar{C}_P$. An explicit functional relationship can, of course, only be derived by making additional assumptions. For example, if the backflow of administered CA into the intravascular compartment is negligible compared to its outflow into the interstitial compartment (e.g., during the initial enhancement phase after CA administration in DCE imaging), then the capillary concentration falls exponentially along the capillary from C_A to $C_V = C_A \exp(-PS/F)$ as shown by Renkin²⁵ and Crone.²⁶ For this scenario, we derive the following expression (for $C_A - \bar{C}_P \neq 0$, i.e., $PS > 0$):

$$R(PS/F) \equiv \frac{C_A - C_V}{C_A - \bar{C}_P} = \frac{E}{1 - E(PS/F)^{-1}} \quad (A5)$$

with $E = 1 - \exp(-PS/F)$,

which decreases—in accordance with the general considerations—strictly monotonically from $R=2$ for $PS/F \rightarrow 0$ to $R=1$ for $PS/F \rightarrow \infty$. Based on this fact, Eq. (A5) in combination with the relation $F_A = RF_C$ can be used to calculate a corrected plasma flow F_C from the numerical estimates derived for F_A and PS from measured DCE data. Alternatively, Eq. (A5) can be used during the fitting procedure in order to directly estimate the corrected blood, F_C .

According to the sophisticated mathematical analysis presented in Refs. 27 and 28 the mean residence times for CA particles passing through the plasma compartment and the interstitial compartment are given by

$$MRT_P = \frac{V_P}{F} \quad \text{and} \quad MRT_I = \frac{V_I}{F}. \quad (A6)$$

The sum is the system mean residence time MRT_S ,

$$MRT_S = \frac{V_P + V_I}{F} = MTT_S, \quad (A7)$$

which equals the system mean transit time MTT_S . Whereas the mean transit time gives the average time required by a CA particle to flow from the inlet of a (sub)system to its outlet (by whatever path), the residence time refers to the time that a particle remains in the compartment under study. Transit and residence times are identical for (sub)systems if all material leaving cannot re-enter.

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