Influence of Parameterization on Tracer Kinetic Modeling in DCE-MRI

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Abstract

Tracer kinetic modeling in dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is commonly performed using least squares algorithms. The convergence of such algorithms and the repeatability of the estimates are affected by the curvature of the model’s expectation surface. An adequate choice of the parameterization can reduce curvature and thus improve parameter estimation. This study analyzes the influence of two parameterizations on the curvature of the Tofts model. The influences of the total acquisition time and the sampling period are evaluated. Analysis results show that using (kₑ, vₑ) can significantly reduce the curvature in a large area of the parameter space, suggesting that curvature analysis could guide the choice of the best local parameterization in Gauss-Newton-based algorithms. In addition, increasing the total acquisition time and decreasing the sampling period reduce the curvature. However, only slight improvements are obtained for a total time longer than about 6 min and a sampling period shorter than approximately 10 s. [Coloured figures are available in the on-line version of the manuscript]

Keywords: Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), Tracer kinetics modeling, Model manifold curvature, Nonlinear regression, Least squares

1. Introduction

Tracer kinetic modeling in dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) (Fig. 1) can provide quantitative information about key biological processes such as tumor angiogenesis [1-4]. In general, tracer kinetic modeling is used for deriving quantitative parameters strictly related to the physiological characteristics of interest. These parameters should be independent from the specific clinical protocol to allow useful comparisons among studies [1-4]. However, the effective use of tracer kinetic parameters as imaging biomarkers can be severely hampered by a lack of reliability [5].

Given a specific model, the reliability of the estimated parameters (obtained by fitting a model to the measured data) can be affected by several factors [6,7], including the curvature of the model manifold, the specific parameterization, and the algorithm used for regression. The present study focuses on the influence of the properties of the specific model used and in particular on the curvature of the model manifold. Since the estimation of tracer kinetic parameters is mostly made using the Tofts model [4] and is usually performed using least squares (LS) algorithms [8-16], the focus is on these issues. As is well known, the accuracy of the estimates and the convergence properties of LS algorithms are affected by the curvature of the model manifold [6,7].

Figure 1. After intravenous injection, the contrast medium (usually Gadolinium) travels through the vessels walls toward the extravascular extracellular fluid and subsequently returns to the main blood flow. MRI signal intensity changes according to contrast medium concentration within voxels. The time course of Gadolinium concentration (tracer kinetics) can be adequately described using proper models whose parameters are strictly related to the angiogenic activity.

Bates and Watts introduced the concept of the curvature of the model manifold in 1980 [6,7]. It is based on the geometric properties of the model manifold or the expectation surface of the model (see Section 2). The main idea is that if the expectation surface is locally planar then its curvature is zero whereas if the expectation surface is not planar then its curvature is not zero (see Fig. 2). Local planarity is an essential condition for local approximation via the Taylor series. The
advantage of a locally planar expectation surface is that more reliable estimates of the parameters can be obtained; moreover, LS algorithms can efficiently find best estimates on planar surfaces.

The curvature of the model manifold comprises two components: the intrinsic curvature, explained by the mathematical form of the model, and the parameter-effect curvature, which is due to the specific parameters used. While the intrinsic curvature is not modifiable, the parameter-effect curvature can be reduced if parameters are properly chosen (see Fig. 2) [6,7].

In DCE-MRI, two parameterizations are commonly used, namely \((K^\text{trans}, k_p)\) [12,15,17] and \((K^\text{trans}, v_p)\) [5,13]. Little guidance exists for the optimal choice of parameterization [7] and no guidelines have been proposed specifically for DCE-MRI [18].

The present study analyzes the influence of the two commonly used parameterizations on the curvature of the Tofts model. The influences of the total acquisition time and the sampling period are also evaluated.

The paper is organized as follows. The tracer kinetics model and the corresponding parameterizations considered in the present study are described in Section 2. This section also introduces the concept of curvature and formulas used for its computation and reports the specific ranges of the parameters and the predetermined level of noise for which the curvature is computed. The values of curvature corresponding to the different regions of the parameter space are presented in Section 3. Some guidelines for the choice of some of the parameters to reduce curvature are given in Section 4. Section 5 contains the conclusions.

2. Materials and methods

2.1 Tracer kinetic modeling

The time course of contrast agent (CA) concentration (typically Gd-DTPA in DCE-MRI) within the tissue is typically modeled using the following equation [4]:

\[
C_i(t, K^\text{trans}, k_p, v_p) = v_p C_f(t) + C_p(t) \Theta K^\text{trans} e^{-k_p t}
\]  

(1)

where \(C_i(t, K^\text{trans}, k_p, v_p)\) is the CA concentration within the voxel of interest; \(C_p(t)\) is the CA concentration within the plasma, also known as arterial input function (AIF); \(K^\text{trans}\) is the volume transfer constant from plasma to the extracellular-extravascular space (EES); \(k_p\) is the diffusion rate constant from the EES to plasma; \(v_p\) is the plasma fraction. \(K^\text{trans}\) and \(k_p\) satisfy Eq. (2), where \(v_p \in (0,1)\) is the volume fraction occupied by the EES.

\[
v_p = \frac{K^\text{trans}}{k_p}
\]  

(2)

The model in Eq. (1) requires a specific \(C_f(t)\). This study uses a computationally efficient AIF, recently proposed in [19] on the basis of a population-based AIF measured by [20]:

\[
C_p(t) = A_0 t e^{-\gamma t} + A_{15} (e^{-\beta t} - e^{-\gamma t})
\]  

(3)

The meaning of the constants in Eq. (3) can be found elsewhere [19]; the specific values of the constants are given in section 2.4.

2.2 Parameterizations

Combining Eq. (1) and Eq. (3) yields a complete model with parameterization \((K^\text{trans}, k_p, v_p)\):

\[
C_i(t, K^\text{trans}, k_p, v_p) = v_p C_f(t) + \frac{A_0 K^\text{trans}}{k_p - \mu_b} (e^{-\gamma t} - e^{-\beta t}) + \frac{A_{15} K^\text{trans}}{k_p - \mu_b} (e^{-\beta t} - e^{-\gamma t})
\]  

(4)

Similarly, a complete model with parameterization \((K^\text{trans}, v_p, v_p)\) is obtained by combining Eq. (2) and Eq. (4).

2.3 Curvature

The main issues of the theory, which is extensively dealt with in [6,7], are briefly discussed here. Consider a model function \(C_i(t, \theta)\) with \(\theta = [\theta_1 \cdots \theta_L]\) model parameters; consider also a set of noisy measures \(y_i = C_i(t_i, \theta) + \epsilon_i\) with \(i = 1, \ldots, N\) \((T = t_1, t_2, \ldots, t_N\) is the sampling period), where \(\epsilon_i\) is random zero-mean noise (i.i.d.). Let \(\eta(\theta) = [C_i(t_1, \theta) \cdots C_i(t_N, \theta)]\).

Then, the measured data can be written as \(y = \eta(\theta) + \epsilon\) (with \(y = [y_1 \cdots y_N]\) and \(\epsilon = [\epsilon_1 \cdots \epsilon_N]\)); it is clear that \(y\) belongs to the \(N\)-dimensional space of measured data (see Fig. 2). The \(p\)-dimensional surface \(\Omega = \{\eta(\theta) : \theta \in \Sigma\}\), embedded in the space of measured data, contains all possible values of the expectation \(E[y]\) and is called the expectation surface \(\Sigma\) is the space of parameters, see Fig. 2). Nonlinearity of the expectation surface at a specific point \(\theta_0\) is commonly quantified by means of the maximum intrinsic curvature \(K^\text{intr}_{\max}\) and the maximum parameter-effect curvature \(K^T_{\max}\) [15]:

\[
K^\text{intr}_{\max} = \max_{k=1}^N \frac{N!}{h^N} \left| \frac{\partial^N \eta}{\partial h^N} \right|_{h=\theta_0} \leq \max_{h=\theta_0} \eta(h) - \eta(\theta_0)
\]  

(5)
where $\mathbf{F}$ is the first derivative matrix (Jacobian) of $\eta(\theta)$ with respect to the parameters, and $\mathbf{F}^T$ and $\mathbf{F}^N$ are the projections of the second derivative matrix $\mathbf{F}$ onto the planes tangent and orthogonal to $\Omega$, respectively (all the derivatives are evaluated at $\theta_0$).

When the parameter $\theta$ varies in the neighborhood of $\theta_0$, along a direction in the parameter space (e.g., $h$ in Fig. 2), the corresponding points $\eta(h)$ on the expectation surface trace a curve passing through $\eta(0)$, and have a tangent vector $\eta(h_t)$ belonging to the space spanned by the columns of $\mathbf{F}$ (plane tangent to $\Omega$ at $\theta_0$). The traced curve has a curvature that can be computed using differential geometry [6,7]. The maximum curvature is computed from the set of all such curvatures considered for all the directions $h$.

In summary, when expanding $\eta(\theta)$ in the Taylor series in the neighborhood of $\eta(\theta_0)$, curvatures quantify the weight of the second-order terms with respect to the first-order (linear) terms. Typically, the expectation surface can be considered approximately linear in a neighborhood of $\theta_0$ if [6]:

$$\max \{K_{\max}^T, K_{\max}^N\} < \frac{1}{2\sigma^2} \theta h(\sigma)$$

(7)

where $\sigma$ is the noise standard deviation, $F_{p,n-p}$ is the (100-$\theta$)-th percentile of the Fisher distribution with $p$ and $N-p$ degrees of freedom. $\theta h(\sigma)$ holds for the threshold level corresponding to $\sigma$. In this study, $\alpha = 0.05.$

2.4 Curvature computation

Both the intrinsic curvature and the parameter-effect curvature were calculated for several points in the parameter space and for several values of the sampling period and total acquisition time. The calculations were performed for both examined parameterizations.

The parameter space was sampled as follows: $K_{\text{trans}}$ ranged from 0.05 to 2 min$^{-1}$ (step: 0.1 min$^{-1}$); $\nu_c$ ranged from 0.05 to 1 (step: 0.05). These ranges should encompass the physiological conditions found in both normal and diseased tissues [9,17]. $k_{\text{op}}$ was obtained from Eq. (2).

Regarding $\nu_p$, it is worth noticing that the first and second derivative matrices in Eqs. (5) and (6) do not depend on $\nu_p$. Accordingly, our simulations considered only $K_{\text{trans}}, k_{\text{op}},$ and $\nu_c$.

The sampling period $T$ was varied from 5 to 20 s in steps of 5 s; the total acquisition time was varied from 3 to 12 min in steps of 3 min.

Noise level $\sigma$ was varied from 0.01 to 0.1 mM in steps of 0.01 mM. The noise level for the CA concentration in DCE-MRI data depends on the specific pulse sequence utilized. Therefore, it is difficult to find a general relationship between the noise superimposed on CA concentration time-course and the noise on MR images. However, in order to give an idea of the noise level that can be tolerated on MR images, we consider the following particular case:...
Figure 3. Maximum intrinsic curvature ($K_{\text{max}}$). Total acquisition time: 6 min. Sampling period $T$: (a) 5 s, (b) 10 s, (c) 15 s, (d) 20 s. Curvatures less than $\sigma$ are colored according to the color bar.

Figure 4. Comparison between the curvatures of ($K_{\text{trans}}^v$, $v_e$) and ($K_{\text{trans}}^k$, $k_{ep}$). In the red area, the curvature of the parameterization ($K_{\text{trans}}^v$, $v_e$) is less than that for ($K_{\text{trans}}^k$, $k_{ep}$). Total acquisition time: 6 min. Sampling period $T$: (a) 5 s, (b) 10 s, (c) 15 s, (d) 20 s.
Figure 5 shows the $\max(K_{N_{\text{max}}}^{\text{T}}, K_{T_{\text{max}}}^{\text{T}})$ for the parameterization $(K_{\text{trans}}, v_e)$ for total times of 3, 6, 9, and 12 min, respectively, and $T = 5$ s. It is worth noticing that while a great improvement is obtained when the total time is increased from 3 to 6 min, little further improvement is obtained for a total time longer than 6 min. From this figure, it can be inferred that the curvature is always above the threshold when $v_e < 0.4$: this is because $v_e$ mainly affects the $C_t$ peak amplitude and therefore the signal to noise ratio. Similar behavior was observed for $(K_{\text{trans}}, k_{\text{ep}})$.

Figure 6 shows the $\max(K_{N_{\text{max}}}^{\text{T}}, K_{T_{\text{max}}}^{\text{T}})$ for the parameterization $(K_{\text{trans}}, v_e)$ for a total time of 6 min and $T = 10, 20$ s. As the sampling period increases, the curvature becomes very large, particularly for small values of $v_e$ or $K_{\text{trans}}$. Similar behavior was observed for $(K_{\text{trans}}, k_{\text{ep}})$.
4. Discussion

Estimation of tracer kinetic model parameters in DCE-MRI is commonly performed via LS fitting of the measured time course of CA concentration. The convergence properties of LS algorithms and the repeatability of the estimates are affected by high values of the total curvature (comprising intrinsic and parameter-effect curvatures) of the model used. Adequate choice of parameterization can reduce the curvature. There are currently no guidelines for optimal choices of parameters for DCE-MRI; studies use one of two parameterizations for the Tofts model [4].

The present study analyzed the influence of the two commonly used parameterizations on the curvature of the Tofts model. The influences of the total acquisition time and the sampling period were also evaluated. Specifically, \( K_{\text{trans}}^{\text{max}} \) and \( K_{\text{ep}}^{\text{max}} \) were calculated for a range of parameters \( K_{\text{trans}}^{\text{max}}, k_{\text{ep}} \) and \( v_e \), encompassing the values encountered in clinical practice.

The results of this study can be summarized in two points. First, for both parameterizations, the parameter-effect curvature is predominant over the intrinsic curvature and the curvature of the parameterization \( (K_{\text{trans}}^{\text{max}}, v_e) \) is lower than that of \( (K_{\text{trans}}^{\text{max}}, k_{\text{ep}}) \) (see Fig. 4) for a large range of parameters (the extension of this range is little affected by the sampling period). In essence, this means that using \( (K_{\text{trans}}^{\text{max}}, v_e) \) in a well chosen range of parameters, higher levels of noise can be tolerated before the curvature becomes unacceptable and therefore unreliable estimates are obtained. Second, when considering \( (K_{\text{trans}}^{\text{max}}, v_e) \) only, the range of parameters with a below-threshold curvature increases with increasing total acquisition time (although little difference is observed for total acquisition times longer than 6 min). However, the opposite occurs when the sampling period is increased. Thus, optimal settings for \( (K_{\text{trans}}^{\text{max}}, v_e) \) should use long acquisition times (from about 6 min to 9 min) and short sampling periods (shorter than about 10 s).

Our analysis is in line with previous studies on the subject. A number of papers have tackled the issue of the repeatability of parameter estimates for the Tofts model for DCE-MRI. Lopata et al. [21] used a frequency analysis approach in order to establish optimal experimental conditions; however, they used a bi-exponential AIF, which is an excessively simplified model, and their results were be completely adequate for shorter sampling periods. Dale et al. [22] used an error propagation approach in order to analyze the influence of several factors comprising \( T_{\text{10}} \) (\( T_{\text{1}} \) of the tissue before contrast injection) and the flip angle; however, their analysis identified only the instrumental source of errors, and did not take into account modeling issues. Henderson et al. [23] studied the influence of the sampling period for breast DCE-MRI, concluding that fast sampling is a strict requirement for accurate parameter estimation. They used the first derivative matrix \( F \) as a tool of analysis, but they did not extend the analysis to the curvature of the model. Ahearn et al. [8] investigated the fitting failures due to the Levenberg-Marquardt fitting algorithm implemented in IDL (RSI Inc., Boulder, CO, USA) and proposed a multiple starting points procedure in order to improve results; however, they used the parameterization \( (K_{\text{trans}}^{\text{max}}, v_e) \) and did not investigate \( (K_{\text{trans}}^{\text{max}}, k_{\text{ep}}) \).

It is worth noting that our approach is complementary to existing ones. In each of the mentioned studies, a single parameterization was chosen. The curvature properties of both parameterizations have not been considered before. However, the analysis of curvature can shed light on the intrinsic properties of the Tofts model and can suggest an optimal choice of the parameters. Although \( (K_{\text{trans}}^{\text{max}}, v_e) \) has the lowest curvature in a large range, our study indicates that none of the examined parameterizations can work well in the whole parameter space. This suggests that a new search strategy should be included in Gauss-Newton-based algorithms for nonlinear regression of the Tofts model for DCE-MRI. The evaluation of the local curvature can indicate which parameterization to use in order to obtain the best results in terms of repeatability.

As known, DCE-MRI guidelines [18] have proposed \( K_{\text{trans}}^{\text{max}} \) as the primary endpoint because it seems directly related to the perfusion of the tissues and the permeability of the vessels; \( v_e \) has been proposed as a secondary endpoint because it may reflect the cellular density. However, the parameterization to be used has not been suggested. On the basis of our analysis, both the parameterization used and the values of all the parameters should be reported because the curvature, and consequently the accuracy of the estimates, depends on both parameters. The importance of considering both parameters simultaneously has been evidenced also from a clinical point of view in a recent study [17], which showed that for an effective separation between benign and malignant tumors in the breast, \( K_{\text{trans}}^{\text{max}} \) only is not sufficient and thus another parameter should be used. In fact, as reported in [24], tumor aggressiveness and response to therapy are also influenced by the EES fraction \( v_e \) of the malignant tissue. In this regard, it is worth mentioning that, often, clinical studies report neither the parameterization they used nor the values for all parameters.

Although the results of the present study apply mainly to LS fitting, our findings can also shed light on other methods for non-linear regression because of the similarities among different approaches. Least squares coincides with the maximum likelihood method when Gaussian noise is hypothesized; further, Bayesian methods coincide with maximum likelihood estimation when a uniform prior probability is assumed. Bayesian methods in DCE-MRI have been reported, for example in [25,26]. Moreover, \textit{ad hoc} reformulations of the Tofts model are possible and were used in [22,27]. However, it should be noted that the LS approach is the most commonly used and has been implemented in most computational packages.

5. Conclusion

The specific parameterization used in tracer kinetic modeling in DCE-MRI affects the curvature of the model. Our analysis gives some insight into the curvature properties of the Tofts model: a) none of the examined parameterizations has low curvature in the whole parameter space, but each of them works well in a specific range, suggesting that a curvature-
based local parameterization could be a valid searching approach in Gauss-Newton algorithms; b) both increasing the total acquisition time (up to about 6 min) and decreasing the sampling period (shorter than about 10 s) reduce the curvature.

References


