Estimation of Physiological Parameters in the Subspace of Arterial Input Function in Dynamic Contrast-Enhanced Magnetic Resonance Imaging

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Abstract — Estimation of physiological parameters by fitting data to a proper pharmacokinetic model plays a fundamental role in application of DCE-MRI for characterization of tissue microvasculature in diagnosis and prognosis of various diseases. In this study, by allowing asymmetric permeability a generalized two-compartment exchange model (G2CXM) is presented that uniformly includes the extensively applied Patlak model, Tofts model, and extended Tofts model as special instances. The identifiable physiological parameters in the G2CXM for various tissue types determined by the boundary values of physiological parameters are indicated by analyzing its impulse response function. To obviate failures occurring at times in the conventional fitting method, an approach of estimating physiological parameters in the subspace of arterial input function (SAIF) is proposed. Simulation result shows that the SAIF can obviate failure, significantly increase accuracy and decrease bias of estimated physiological parameters in a wide signal to noise ratio range.

Keywords — DCE-MRI; pharmacokinetics; physiological parameters; biomarker; tumor

I. INTRODUCTION

Characterization of tissue microvasculature by dynamic contrast-enhance magnetic resonance imaging (DCE-MRI) has potential extensive clinical applications for noninvasive diagnosis and prognosis of diseases such as tumor and atherosclerotic plaques. To extract physiological parameters a number of pharmacokinetic models have been developed to capture the dynamics of tracer that perfuses though capillaries, permeates through capillary walls, and diffuses in the extravascular extracellular space (EES) in a tissue. The most extensively applied pharmacokinetic models are the Patlak model (PM) [1],

\[ C'(t) = v_p C_a(t) + K_{pm} C_a(t) \]  
(1)

Tofts model (TM) [2] [3],

\[ C'(t) = K_{trans} C_a(t) - K_{ep} C(t) \]  
(2)

and extended Tofts model (ETM) [4]

\[ C'(t) = v_p C_a(t) + (K_{trans} + v_p K_{ep}) C_a(t) - K_{ep} C(t) \]  
(3)

where \( K_{ep} = K_{trans}/v_e \) and the meanings of the symbols will be explained in the next section. A large number of experiments on animals and patients in DCE-MRI have been carried out and the interpretation of their results are largely relied on the PM, TM, and ETM. However, Sourbron and Buckley [5] recently developed a two-compartment exchange model (2CXM) (the same model was also recently presented by Koh et al. [6]) and proved that the TM and ETM are only special instances of the 2CXM at the low vasculature and high perfusion boundaries of the physiological parameter space. The 2CXM provides a useful means in estimating physiological parameters in a broad spectrum of tissue types.

This study is two-fold. First, by allowing asymmetric permeability a generalized two-compartment exchange model (G2CXM) is presented that uniformly includes the PM, TM, ETM, and 2CXM as special instances. Then the identifiable physiological parameters in the G2CXM for various tissue types are indicated by analyzing its impulse response function (IRF). Second, to obviate the failures occurring at times in the conventional model fitting method, an approach of estimating physiological parameters in the subspace of arterial input function (SAIF) is proposed. Simulation result shows that the SAIF can obviate failure, significantly increase accuracy and decrease biases of estimated physiological parameters in a wide signal to noise ratio (SNR) range.

II. IDENTIFIABLE PHYSIOLOGICAL PARAMETERS

A. G2CXM and IRF

As illustrated in Fig. 1, the G2CXM is defined by the system of equations

\[ v_p C'_a(t) = F_p C_a(t) + P_s S C_a(t) - (F_p + P_p S) C_p(t), \]  
(4)

\[ v_v C'_v(t) = P_p S C_p(t) - P_v S C_v(t), \]  
(5)

\[ C(t) = v_p C_p(t) + v_v C_v(t) \]  
(6)

with \( C_p(0) = C_v(0) = 0 \). Here, \( F_p \), \( v_p \), \( v_v \), \( S \) are the plasma flow, intravascular volume fraction, extravascular extracellular volume fraction, and capillary surface area, respectively. \( P_p \) and \( P_v \) are the permeability from the plasma to the EES and the converse, respectively. \( C_p(t) \) is the arterial input function (AIF) feeding to the tissue, \( C(t) \) is the total tissue tracer concentration,
and $C_p(t)$, $C_e(t)$ are the tracer concentration in the plasma and in the EES, respectively. Compared with the 2CXM, the G2CXM allows $P_p \neq P_e$ and so includes the PM, TM, ETM, 2CXM as special instances.

Let $C_p(t) = \delta(t)$. By the Laplace transform, the IRF of the G2CXM can be obtained in the Appendix as

$$h(t) = A_e e^{-D_p t} + A_f e^{-D_p t},$$

where

$$A_e = \frac{F_p \sqrt{(r_p + r_p + r_e)^2 - 4r_p r_e \pm (r_p - r_e)}}{2 \sqrt{(r_p + r_p + r_e)^2 - 4r_p r_e}},$$

$$D_e = \frac{1}{2} \left( r_p + r_p + r_e + \sqrt{(r_p + r_p + r_e)^2 - 4r_p r_e} \right).$$

The IRF is completely determined by $r_p = F_p / v_p$ – the perfusion per plasma volume, $r_p = P_p S / v_p$ – the plasma to EES permeability surface product per plasma volume, $r_e = P_e S / v_e$ – the EES to plasma permeability surface product per EES volume, and $F_p$. It can be verified that when $P_p = P_e = P$, the G2CXM IRF degenerates to the 2CXM IRF [5] [6].

**Fig. 1.** The generalized two-compartment exchange model (G2CXM) for the tissue of interest (the shaded region).

### B. Identifiable physiological parameters

It can be shown that by estimating the model parameters $A_e$, $D_e$, from the G2CXM the physiological parameters are identifiable up to

$$F_p = A_e + A_1,$$

$$v_p = \frac{(A_e + A_1)^2}{A_e D_e + A D_e},$$

$$P_p S = \frac{A_e A_1 (A_e + A_1) (D_e - D_0)^2}{(A_e D_e + A D_e)^2},$$

$$r_e = \frac{(A_e + A_1) D_e D_0}{A_e D_0 + A D_0}.$$ (13)

If the tissue type is prior known to have symmetric permeability $P_p = P_e = P$, then the physiological parameters are identifiable up to

$$F_p = A_e + A_1,$$

$$v_p = \frac{(A_e + A_1)^2}{A_e D_e + A D_e},$$

$$PS = \frac{A_e A_1 (A_e + A_1) (D_e - D_0)^2}{(A_e D_e + A D_e)^2},$$

$$v_e = \frac{A_e A_1 (D_e - D_0)^2}{D_e D_0 (A_e D_e + A D_e)}.\] (17)

The space of physiological parameter is

$$0 \leq F_p, P_p S, P, S \leq \infty,$$

$$0 \leq v_p, v_e \leq 1, v_p + v_e \leq 1.$$ (18)

At a boundary of the physiological parameter space where a number of physiological parameters take their boundary values, the G2CXM degenerates to a particular tissue type of a special instance model, of which the IRF can be obtained by taking the boundary values of physiological parameters in the G2CXM IRF.

**C. Example 1**

If $P_p S = 0$, then

$$h(t) = A_e + A_1 e^{-D_p t},$$

where

$$A_e = \frac{F_p r_p}{r_p + r_p},$$

$$A_1 = \frac{F_p r_e}{r_p + r_p},$$

$$D_e = r_p + r_p.$$ (21)

By estimating $A_e$, $A_1$, $D_e$, the physiological parameters can be identified up to

$$F_p = A_e + A_1,$$

$$v_p = \frac{(A_e + A_1)^2}{A_e D_e},$$

$$P_p S = \frac{A_e (A_e + A_1)}{A_e},$$

but $v_e$ is unidentifiable.

**D. Example 2**

If $F_p = \infty$, the G2CXM IRF degenerates to

$$h(t) = \lim_{F_p \to \infty} F_p e^{-(r_p/v_p) t} + P_p S e^{-(r_p/v_p) t}$$

$$= v_p \delta(t) + P_p S e^{-(r_p/v_p) t},$$

which further degenerates to the PM

$$h(t) = v_p \delta(t) + K^{trans},$$

with $K^{trans} = P_p S$ if $P_p S = 0$, or to the ETM
\[h(t) = v_p \delta(t) + K^{\text{trans}} e^{-(K^{\text{trans}}/v_p)t},\]  
(27)

with \(K^{\text{trans}} = PS\) if \(P_p = P_r = P\). Clearly, the identifiable physiological parameters for the PM are \(v_p, K^{\text{trans}} = P_pS\), and for the ETM are \(v_p, v_r, K^{\text{trans}} = PS\).

Similarly, the IRFs for all other types of tissues each correspond to a set of boundary values of physiological parameters can also be obtained and the identifiable physiological parameters can be derived accordingly.

III. ESTIMATION METHODS

A. Conventional method

In a practical scan of MRI at temporal resolution \(\Delta\) (min), only the noisy tissue concentration can be acquired

\[y(n) = C(n) + z(n)\]

\[= \sum_{k=0}^{n} C_a (n-k) h(k) + z(n), \quad n = 0, 1, \ldots, N-1\]  
(28)

where \(C(n\Delta)\) is simply denoted by \(C(n)\), and the noisy AIF is acquired as

\[x(n) = C_y (n) + w(n), \quad n = 0, 1, \ldots, N-1.\]  
(29)

Due to the fact that \(y(n)\) and \(x(n)\) are usually practically acquired at different places of body the noise processes \(z(n), w(n)\) are mutually independent, and due to tracer enhancement \(z(n), w(n)\) can be well approximated as white Gaussian processes [7] with mean zero and variance \(\sigma^2\). Conventionally, the model parameters \(A_x, D_x\) are directly estimated by

\[(A_x, D_x) = \arg \min \sum_{n=0}^{N-1} \left[ \sum_{k=0}^{n} \sum_{i=0,j=0}^{N-1} (x(n-k)h(k) - y(n))^2 \right]^2\]  
(30)

where \(h(n)\) is generated by the G2CXM IRF and then the identifiable physiological parameters are obtained from \(A_x, D_x\).

Stacking \(y(n), h(n), z(n)\) into column vectors \(y, h, z\), respectively, and \(x(n)\) into matrix \(X\) with the \((i,j)\)th element

\[X_{i,j} = \begin{cases} \Delta x(i-j), & 0 \leq j \leq i \leq N-1, \\ \Delta x, & 0 \leq i < j \leq N-1, \end{cases} \]  
(31)

then the conventional method is to directly estimate \(A_x, D_x\) by

\[(A_x, D_x) = \arg \min \| Xh - y \|^2.\]  
(32)

However, the conventional method may be failed at times in that one of estimated \(A_x\) is close to zero, resulting in a monoeponential (instead of biexponential) function of IRF. The failure rate increases as SNR decreases. The reason is that the AIF is usually low-pass and so the initial value \(h(0)\) that needs a high-pass AIF to retain in \(y(n)\) is significantly decreased.

B. SAIF

To obviate the failure problem, we propose to (i) estimate IRF \(h'\) by

\[(A_x, D_x) = \arg \min \| Xh' - y \|^2,\]  
(33)

(ii) properly modify \(h'\) to \(h^*\) and then (iii) estimate \(A_x, D_x\) by

\[(A_x, D_x) = \arg \min \| h - h^* \|^2.\]  
(34)

The AIF matrix can be expressed in the form of singular value decomposition

\[X = UAV^T\]  
(35)

where the columns of \(U, V\) are the left and right singular vectors and

\[A = \text{diag}(\lambda_0, \lambda_1, \ldots, \lambda_{M-1}), 0, \ldots, 0)\]  
(36)

if \(X\) has \(M\) nonzero singular values (SVs) \(\lambda_0 \geq \lambda_1 \geq \ldots \geq \lambda_{M-1} > 0\). Properly selecting \(0 < m < M\) and letting

\[A^* = \text{diag}(\lambda^{-1}_0, \lambda^{-1}_1, \lambda^{-1}_{M-1}, 0, \ldots, 0),\]  
(37)

then

\[X^* = VA^*U^T\]  
(38)

is an approximated pseudoinverse of \(X\). A solution of (1) is therefore

\[h' = X'y,\]  
(39)

which is an estimate of \(h\) in the subspace of AIF \(X\). To properly select \(m\) the methods of Picard plot and L-curve with a regularization term in the objective function have been proposed in literature [see [8] and references therein]. However, these methods aim at suppressing noise effect and discard the dimensions where the SVs are small relatively to the noise level, which further significantly underestimates \(h(0)\) in addition to the low-pass effect of \(X\). Because of this, we propose to (a) select \(m\) such that almost all spectral power (say 99.9999%) of \(X^*X\) is retained, i.e.

\[\sum_{n=0}^{M-1} \lambda^2_n \leq 0.999999 \sum_{n=0}^{M-1} \lambda^2_n,\]  
(40)

which is contradictory to the methods in literature [8], though;

(b) after estimating \(h'\) by (39), find \(n^*\) at the peak value of \(h'(n)\);

(c) use only the backward delayed partial data

\[h'(n) = h'(n+l), n = n^*-l, \ldots, N-1-l,\]  
(41)

say \(l = 1\), in estimation of \(A_x, D_x\) by (34).

IV. SIMULATION RESULT

In the simulation, three methods are tested: the SAIF that uses 99.9999% total spectral power, the SAIF that uses the Fourier-domain transition point of Picard plot as \(m\), and the conventional method that directly estimates \(A_x, D_x\), \(F_p = 0.75 /\text{min}, v_p = 0.15, v_r = 0.50, P_pS = 0.65 /\text{min}, P_rS = 0.85 /\text{min}, and then \(r_z = 1.7 /\text{min}\) are considered. A bolus AIF is used

\[C_v(t) = 18t e^{-2t} + 1.1(1-e^{-5t})e^{-0.04t} \text{ (mM)}\]  
(42)

for \(0 \leq t \leq 12 \text{ min}\) with \(\Delta = 2\text{ s}\), which is ordinary in the literature [9]. The AIF SNR defined by

\[\text{SNR} = 10\log_{10} \left( \frac{\sum_{n=0}^{N-1} C_v^2(n) / \sigma^2}{1} \right) \text{ (dB)}\]  
(43)
is used as the SNR reference. Simulation is carried out in Matlab and the embedded function ’lsqcurvefit’ is used in the nonlinear model fitting (32), (34) where \( A_x, D_x \) are bounded to \([0, \infty]\). At each SNR, the three methods are run two hundred times, in each of which the Gaussian noise and the initial values of \( A_x, D_x \) with the uniform distribution over \([0, 5]\) are randomly generated. Fig. 2 illustrates The AIF, trace concentrations in plasma, EES, tissue, respectively, G2CXm IRF, and the noisy samples of AIF and tissue tracer concentrations at SNR = 20 (dB). As shown in Table 1, the conventional method results in a high failure rate, particularly in the middle and low SNR regime, and low accuracy of estimated parameters. The Picard method cannot improve the estimates. In contrast, the proposed SAIF can effectively obviate the failure and obtain accurate estimates. Moreover, as SNR increases, the SAIF can decrease the biases of estimated physiological parameters while the conventional and Picard methods cannot.

V. CONCLUSION

By allowing asymmetric permeability, the G2CXm uniformly includes the PM, TM, ETM, and 2CXm as special instances. Through estimating the model parameters in the IRF, the identifiable physiological parameters for various tissue types each corresponding to a set of constraints in the physiological parameters are indicated. While the conventional model fitting method has a high failure rate and low accuracy in estimated physiological parameters, the proposed approach of estimating physiological parameters in the subspace of arterial input function (SAIF) can obviate the failure, significantly increase accuracy and decrease biases of estimated physiological parameters in a wide SNR range.

APPENDIX

Let \( C_o(t) = \delta(t) \) the impulse function, and then \( C(t) = h(t) \) is the impulse response function. Taking the Laplace transform on (4), (5), we obtain

\[
v_pC_o(s) = F_p + P_pC_o(s) - (F_p + P_pS)C_p(s), \quad (A1)
\]

\[
v_sC_o(s) = P_pSC_p(s) - P_sSC_p(s). \quad (A2)
\]

Eq. (A2) can be written as

\[
C_p(s) = \frac{P_pS}{v_s + P_pS}C_o(s). \quad (A3)
\]

Substituting \( C_o(s) \) in (A1) by (A3) produces

\[
C_p(s) = \frac{v_s + P_pS}{v_s + P_pS + (F_p + P_pS + v_pP_pS)s + F_pP_pS} (A4)
\]

Taking the Laplace transform on (6) and substituting \( C_o(s) \) and \( C_p(s) \) by (A1) and (A3), we obtain the Laplace transform of the impulse response function

\[
H(s) = v_pC_p(s) + v_sC_o(s) \quad (A5)
\]

\[
= \frac{v_pv_s + v_pP_pS + v_sP_pS}{v_s + P_pS}C_p(s)
\]

which by the inverse Laplace transform leads to the impulse response (7)-(9).

REFERENCES


Fig. 2. The AIF, trace concentrations in plasma, EES, tissue, respectively, G2CXM IRF, and the noisy samples of AIF and tissue tracer concentrations at SNR = 20 (dB).

Table 1. Failure rates and estimates of identifiable physiological parameters with mean ± standard deviation in simulation.

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<th>SNR (dB)</th>
<th>Failure rate (%)</th>
<th>$P_a = 0.75$</th>
<th>$P_a = 0.15$</th>
<th>$P_a = 0.65$</th>
<th>$t_a = 1.7$</th>
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<td>1.5</td>
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<td>0.52±0.4</td>
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<td>10</td>
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