Quantitative Imaging of Tumor Vascularity with DCE-MRI

Z. Jane Wang, Zhu Han, K. J. Ray Liu, and Yue Wang*
Department of Electrical and Computer Engineering and Institute for Systems Research,
University of Maryland, College Park.
*Department of Electrical and Computer Engineering,
*Virginia Polytechnic Institute and State University
e-mail: wangzhen,hanzhu,kjrliu@eng.umd.edu; yuewang@vt.edu

Abstract

Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) is a noninvasive functional imaging technique capable of assessing tumor microvasculature clinically. To determine the kinetic parameters characterizing tumor vascular activity, compartmental model analysis is usually performed. Major limitations associated with conventional region-of-interest (ROI) based methods include the requirement of invasive acquisition of the input function and labor-intensive identification of the ROIs. In this paper, we propose a novel blind system identification approach for quantitative imaging of tumor vascularity by simultaneously estimating the input function and the spatial and temporal characteristics about the underlying tumor microvasculature. New Approach is based on a more general statistical model on the pixel domain, whose parameters are initialized using a sub-space based algorithm, and further refined by an iterative maximum likelihood estimation procedure. Using Monte Carlo simulations, the performances of the proposed scheme is examined extensively under several quantitative measures. The results on both the simulated and real DCE-MRI data sets show a good performance in determining the time activity curves and the underlying factor images when applying the proposed algorithm.
I. Introduction

With rapid advances in developing functionally-targeted contrast agents and imaging probes, new functional imaging techniques promise powerful tools for the visualization and elucidation of important disease-causing physiologic processes in living tissues [10], [11], [16], [17]. For example, dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) is a noninvasive functional imaging technique, utilizing various molecular weight contrast agents to access tumor microvascular characteristics which provide information about tumor microvessel structures and functions [16], [17]. The extravascular retention of intravenous contrast medium correlates to the accumulation at sites of concentrated angiogenesis mediating molecules or microvessels (permeability). Kinetic (perfusion) changes following the treatment have correlations with histopathological outcomes and patient survival, and shall potentially be able to assess or predict the response to the treatment particularly by using anti-angiogenic drugs [7].

In dynamic imaging, a time sequence of images are acquired to track the changes in the tracer concentration over time and reflect the underlying microvessel structures and functions. The physiological kinetic parameters (i.e. the exchange rates of the tracer between blood and tissue) characterize the tissue responses, provide diagnostic clinical information such as regional blood flows and distribution volumes. Therefore, an accurate determination of these kinetic parameters is of essential clinical importance, for instance, in the diagnosis of disease. The use of the tracer kinetic modelling technique in dynamic imaging enables quantification of physiological and biochemical processes in humans.

Compartmental analysis forms the basis for tracer kinetic modeling in quantitative dynamic imaging [18], [19]. In conventional compartmental modelling, for each region of interest (ROI) $i$ on the images, the measured concentration of the tracer over time of the tissue within this ROI, referred to as tissue time-activity curve (TAC) of ROI $i$, is often well modeled as the summation of a convolution of the regional tissue response with the tracer concentration in plasma (i.e. the input function) plus the noise due to the measurement process. It was shown in [19] that a two-compartment model fits dynamic MRI of extracellular Gd-based contrast agents, where the tissue impulse response for ROI $i$ is modelled as

\[ h^{(i)}(t) = k_I^{(i)} e^{-k_O^{(i)} t}, \]

in which the kinetic parameters $k_I$ and $k_O$ represent the washin rate constant and the washout rate constant, respectively. Most current research on determination of the kinetic parameters has been concerned with this simple model [2]-[5]. For a single ROI, estimation of the kinetic parameters
requires the input function, usually obtained by taking blood samples invasively at the radial artery or from an arterialized vein, which, however, poses health risks and is not compatible with the clinical practice [6]. Therefore, it is of great interest to estimate both the kinetic parameters and input function simultaneously. Only a few works for this purpose have been reported in literature [2]-[5]. Most recently, a Monte Carlo method called simulated annealing was studied in [4] and found more insensitive to noise than the nonlinear least square method in [3]. The authors in [5] studied three blind identification schemes and reported that the iterative quadratic maximum likelihood (IQML) method yielded the most accurate kinetic parameter estimates.

Although great efforts have been taken to assess the dynamic imaging data by estimating both the kinetic parameters and input function simultaneously [1]-[5], compartment analysis suffers from several problems and there are still a number of challenges that must be taken care of before dynamic imaging can become mainstream diagnostic tools [7]. Briefly speaking, the problem of identifying different ROIs itself remains an essential challenge, and most often we are interested in the underlying heterogeneity characterization of a tumor. Moreover, clinical observations suggest that multiple biomarkers (e.g. tissue components with different vascular kinetics, and molecules with specific/nonspecific bindings) affect the tissue impulse response simultaneously. We therefore propose to work on the pixel domain directly while keep the base of compartment modeling, where thus no pre-process for identifying different ROIs is required. We plan to construct a hybrid approach for estimating the input function and estimating the spatial/temporal patterns of multiple biomarkers simultaneously.

We begin, in Section II, by highlighting the motivation for our integrated blind system identification scheme. We then introduce a system model on the pixel domain, representing the multiple dynamic parameters and the input function. In Section III, we construct the proposed scheme, where a computationally efficient algorithm based on subspace analysis is developed to obtain the initial estimates of the parameters, and an iterative maximum likelihood (IML) technique is then applied to improve the estimation accuracy. Further, the identifiability of the proposed scheme is examined by both using Monte Carlo simulations in Section IV and using the real data set of DCE-MRI studies of breast cancer patients in Section V. Finally, we present conclusions in Section VI.
II. Motivation and System Model

A. Motivation

In this section, we discuss some challenges focusing on the quantification and interpretation of dynamic imaging data. Further, we investigate the mechanisms that provides a more general view for characterizing multiple biomarkers in functional imaging. In particular, we can improve by considering the following issues:

- **Availability of multiple ROIs:** So far, the ROI-based approach is a popular way of processing the dynamic image data, which requires operator pre-defined homogeneous ROIs characterized by different kinetic parameters (thus the tissue impulse response function). With assuming the same input function and further requiring that the washout rate constant parameters for different ROIs are different, the kinetic parameters and the input function can be uniquely estimated based on the tissue TACs from two or more ROIs. The inherent drawback of the ROI-based method is that the ROIs must be drawn in advance. Moreover, identifying different ROIs itself remains an essential challenge. Those externally supervised pre-operations in distinguishing ROIs can often lead to a discrepancy between the true and claimed regions on the images. To tackle this problem with the previous ROI-based compartmental analysis, we plan to explore a pixel by pixel compartmental analysis instead.

- **Spatial heterogeneity of biomarkers:** The ROI-based approaches in previous research assume that the tissue in each ROI is homogeneous in terms of its kinetics. Because of this implied homogeneous nature of each ROI, the ROI-based compartmental analysis approaches do not generally provide spatial information for different tissue kinetics, meaning that they lack spatial resolution. However, it is known that many tumors are highly heterogeneous in structures, and the spatial heterogeneity is often essential in understanding the underlying angiogenesis. For instance, some researchers have commented that ROI-based methods may not be appropriate to evaluate the malignant lesions where heterogeneous areas of enhancement are diagnostically important [20]. Therefore, we need to address the spatial heterogeneity issue in our analysis of dynamic imaging data. A pixel-by-pixel heterogeneity analysis of Fluorodeoxyglucose (FDG) kinetics was proposed in [21], but the procedure is complex and requires highly computational cost. Based on the statistical analysis, we plan to develop an effective pixel-based approach to study the tumor heterogeneity characterization.

- **Composite signal resulting from multiple biomarkers:** As commented in [18], most of the previous works have been based on the simple compartmental model in (1) where each ROI is characterized by one biomarker in imaging, i.e., the tissue impulse response is represented by one pair
of washin and washout rate constants. This model concerns with the measurement of the content of individual biomarker. Little attention in literature has been given to characterize the weighted sum of the contents of multiple biomarkers of the system. However, as a common feature in functional imaging, because of the tissue heterogeneity and limited imaging resolution, the measurements represent a composite of more than one distinct biomarkers even for a single pixel. Moreover, clinical observations suggest that multiple biomarkers often affect the tissue impulse response simultaneously. For example, DCE-MRI reveals the heterogeneous mixture of tumor microvessels associated with different perfusion rates (e.g., fast vs. slow flow). As a result, the overlap of multiple biomarkers can severely decrease the sensitivity and specificity for the measurement of functional signatures associated with different disease processes. Therefore, we need to extract the factor images of individual biomarkers for accurate quantification of dynamic imaging data.

By considering these issues, we plan to work on the pixel domain directly instead of ROI domain, starting by describing a general system model representing multiple biomarkers. The proposed scheme needs to estimate the kinetic parameters of each biomarker and reveal the spatial distributions of multiple biomarkers. Since the input function is normally not available in practice, we need to estimate the input function simultaneously.

B. System Model

In this paper, without loss of generality, we focus on the two-compartment model due to its popularity in literature and in practical use. However, the schemes developed in this paper can be generalized to cover a more general compartment model.

We first review the conventional compartment modelling (CCM); we further describe the factored compartment modelling (FCM) and a model of the plasma input function. In the linear CCM, tracer characterization within a ROI leads to a set of first order differential equations. For the two-compartment model [11], its kinetic description is given by:

$$\frac{d}{dt} c_f(t) = k_{1f} c_p(t) - k_{2f} c_f(t),$$
$$\frac{d}{dt} c_s(t) = k_{1s} c_p(t) - k_{2s} c_s(t),$$
$$c_m(t) = c_f(t) + c_s(t) + V_p c_p(t),$$

(2)

where $t \geq 0$, $k_{2f} > k_{2s} > 0$, $c_f(t)$ and $c_s(t)$ are the tissue activities in the fast turnover and slow turnover pools, respectively, at time $t$; $c_p(t)$ is the tracer concentration in plasma (i.e. the input function); $c_m(t)$ is the measured total tissue activity with the ROI, consisting of fast, slow, and vascular
components; $k_{1f}$ and $k_{1s}$ are the unidirectional transport constants from plasma to tissues in the fast-flow and slow-flow pools, respectively (permeability in ml/min/g: spatially-varying); Similarly, $k_{2f}$ and $k_{2s}$ are the washout rate constants (perfusion in /min: spatially-invariant). Note that $c_f(t)$, $c_s(t)$, $c_p(t)$, and $c_m(t)$ are all called TACs. Based on the above differential equations, we have

$$c_f(t) = k_{1f}a_f(t), \text{ with } a_f(t) = c_p(t) \otimes e^{-k_{2f}t},$$  \(3\)

$$c_s(t) = k_{1s}a_s(t), \text{ with } a_s(t) = c_p(t) \otimes e^{-k_{2s}t},$$

where $\otimes$ denotes the convolution operation.

Linear system theory suggests a simple method to convert temporal kinetics to spatial information [12]. For pixels $i = 1, ..., N$ within a tumor region, by using the three factors $a_f(t)$, $a_s(t)$, and $c_p(t)$, as illustrated in Fig. 1, we can describe the dynamics of pixel $i$ as the measured pixel TAC $c_m(i,t)$, where

$$c_m(i,t) = k_{1f}(i)a_f(t) + k_{1s}(i)a_s(t) + v_p(i)c_p(t) + \epsilon(i,t),$$  \(4\)

with $k_{1f}(i)$ and $k_{1s}(i)$ being the local permeability parameters associated with pixel $i$ (i.e., the permeability of fast and slow turnover (perfusion) regions in the pixel, respectively); $v_p(i)$ means the plasma volume in pixel $i$; and the noise term $\epsilon(i,t)$ is due to the measurement process. Let $t = \{t_1, t_2, ..., t_n\}$ indicate the sampling times of the measurements, and write the observation vector
measured input functions. To remove the redundant parameters, we normalize this model has been widely used in correcting the contaminated input function and the indirectly set a TAC as consisting of multiple biomarkers. For each pixel with the vector proposed in [22], where the parameter dimension of the problem, in this paper we consider a parametric model of the input function \( c \) is fully characterized by parameters \( \lambda \) and the coefficients. Now we note that the signal-matrix \( A \) for each pixel \( i \), we have the discrete model

\[
c_m(i) = As(i) + \epsilon(i).
\]  

The plasma input function \( c_p(t) \) is usually represented by a sequence of blood samples. In our problem, \( c_p(t) \) also needs to be estimated based on the pixel measurements \( c_m(i, t) \)'s. To reduce the parameter dimension of the problem, in this paper we consider a parametric model of the input function proposed in [22], where \( c_p(t) = (a_1 t - a_2 - a_3)e^{\lambda_1 t} + a_2 e^{\lambda_2 t} + a_3 e^{\lambda_3 t} \) with \( \lambda_1 < \lambda_2 < \lambda_3 < 0 \). This model has been widely used in correcting the contaminated input function and the indirectly measured input functions. To remove the redundant parameters, we normalize \( c_p(t) \) by \( a_1 \), i.e., we set \( a_1 = 1 \) in the model. Consider the discrete version, we have

\[
c_p = \begin{pmatrix} t_1 e^{\lambda_1 t_1} & e^{\lambda_2 t_1} & e^{\lambda_3 t_1} \\ t_2 e^{\lambda_1 t_2} & e^{\lambda_2 t_2} & e^{\lambda_3 t_2} \\ \vdots & \vdots & \vdots \end{pmatrix} \begin{pmatrix} 1 \\ -a_2 - a_3 \\ a_2 \\ a_3 \end{pmatrix} \triangleq B(\lambda)b
\]

with the vector \( \lambda = \{\lambda_1, \lambda_2, \lambda_3\} \), where \( \lambda_j \)'s (in \( \text{min}^{-1} \)) and \( a_j \)'s (in \( \mu\text{Ci/ml/min} \)) are the model parameters representing the eigenvalues and the coefficients. Now we note that the signal-matrix \( A \) is fully characterized by parameters \( k_{2f}, k_{2s}, \lambda_j \)'s, and \( a_j \)'s, since

\[
A = [H(k_{2f})B(\lambda)b, H(k_{2s})B(\lambda)b, B(\lambda)b].
\]

It is worth mentioning that the analysis presented above can be extended to a more general model consisting of multiple biomarkers. For each pixel \( i \) within a tumor region, we can represent the pixel TAC as

\[
c(i, t) = \sum_{j=1}^{M} k_{1,j}(i) a_j(t) + \nu(i) c_p(t) + \epsilon(i, t), \quad \text{with} \quad a_j(t) = e^{-k_{2,j} t} \otimes c_p(t),
\]
where $M$ is the number of biomarkers, $k_{1,j}(i)$ is the local washin rate of pixel $i$ due to biomarker $j$, $k_{2,j}$ is the washout rate of biomarker $j$, and $\epsilon(i,t)$ is the noise. The estimated washout rates $k_{2,j}$'s represent different dynamic characterizations of biomarkers, which can be linked to the underlying clinical natures. The recovered image of the factors, represented by $\{k_{1,j}(i)\}$, will reveal the tumor heterogeneity characterization due to each biomarker $j$. Based on this general model, the matrix $A$ has a formulation whose $j$-th column vector can be represented as $H(k_{2,j})c_p$. The scheme developed in the next section can be generalized to cover this general model.

III. Proposed Scheme

We first study the likelihood function of the pixel TAC measurements and formulate the corresponding high-dimensional optimization problem.

We assume that the noise is both temporally and spatially white Gaussian distributed, meaning that $\epsilon(i,t)$ follow iid Gaussian distribution with zero mean and unknown variance $\sigma^2$. Therefore, the complete parameter set is described as $\theta = \{k_{2,f}, k_{2,s}, c_p, s(1), ..., s(N), \sigma^2\}$ in our problem. We write the whole observations as a matrix $X = [c_m(1), c_m(2), ..., c_m(N)]$ with $c_m(i) = [c_m(i, t_1), c_m(i, t_2), ..., c_m(i, t_n)]^T$. As a consequence of the statistical assumption of the noise, we observe that the pixel TAC $c_m(i)$ follows a Gaussian-vector distribution $N(As(i), \sigma^2 I_n)$, and the overall likelihood function of the observations $X$ is

$$f(X; \theta) = \prod_{i=1}^{N} (2\pi\sigma^2)^{-n/2} \exp\left(-\frac{||c_m(i) - As(i)||^2}{2\sigma^2}\right).$$

One of the most well-known and frequently used model-based approach in signal processing is the maximum-likelihood (ML) techniques for its accuracy and robustness. We are interested in the ML estimate of the unknown parameters $\theta$, which coincides with the least-square estimate due to the iid Gaussian assumption.

For the measurements $X$, the logarithm of (9) leads to the log-likelihood function

$$\Lambda(\theta) = -\frac{Nn}{2} \log(2\pi\sigma^2) - \frac{1}{2\sigma^2} \sum_{i=1}^{N} (c_m(i)^T c_m(i) - 2c_m(i)^T As(i) + s(i)^T A^T A s(i)).$$

With $A$ is fixed, for each pixel $i$, the ML estimate of $s(i)$ is obtained by equating the partial differential result $\frac{\partial \Lambda(\theta)}{\partial s(i)}$ to be zero, i.e.,

$$\hat{s}(i) = (A^T A)^{-1} A^T c_m(i).$$

Similarly, equating the partial differential result with respect to $\sigma^2$ to zero gives to

$$\hat{\sigma}^2 = \frac{1}{nN} \sum_{i=1}^{N} ||c_m(i) - As(i)||^2.$$
Substituting the estimate of \( s(i) \), we have

\[
\hat{\sigma}^2 = \frac{1}{nN} \sum_{i=1}^{N} c_m(i)^T (I - A(A^T A)^{-1}A^T) c_m(i)
\]

\[
= \frac{1}{nN} \sum_{i=1}^{N} \text{Tr}\{ (I - A(A^T A)^{-1}A^T) c_m(i)c_m(i)^T \}
\]

\[
= \frac{1}{nN} \text{Tr}\{ (I - A(A^T A)^{-1}A^T) \sum_{i=1}^{N} c_m(i)c_m(i)^T \} = \frac{1}{n} \text{Tr}\{ (I - A(A^T A)^{-1}A^T) \hat{\mathbf{R}} \},
\]

(13)

where \( \text{Tr} \) means the trace operation, \( \hat{\mathbf{R}} \) is the sample covariance matrix expressed as

\[
\hat{\mathbf{R}} = \frac{1}{N} \sum_{i=1}^{N} c_m(i)c_m(i)^T.
\]

(14)

Writing \( \theta_s = \{k_{2f}, k_{2s}, \lambda_1, \lambda_2, \lambda_3, a_2, a_3\} \), we note that \( \mathbf{A} \) is fully characterized by parameters \( \theta_s \).

Substituting the ML estimates of \( \sigma^2 \) and the coefficient vectors \( s(i) \)'s into the overall likelihood, we can show that the ML estimates of \( \theta_s \) are obtained by solving

\[
\hat{\theta}_s = \{\hat{k}_{2f}, \hat{k}_{2s}, \hat{\lambda}_1, \hat{\lambda}_2, \hat{\lambda}_3, \hat{a}_2, \hat{a}_3\} = \arg \max_{\theta_s} \Lambda(\theta) = \arg \max_{\theta_s} \left\{ -\frac{Nn}{2} \log(2\pi \hat{\sigma}^2) + \frac{1}{nN} \right\}
\]

\[
= \arg \min_{\theta_s} \text{Tr}\{ (I - A(A^T A)^{-1}A^T) \hat{\mathbf{R}} \} \triangleq \arg \min_{\theta_s} L(\theta_s),
\]

(15)

with the constraints: \( k_{2f} > k_{2s} > 0 \) and \( \lambda_1 < \lambda_2 < \lambda_3 < 0 \). Therefore, our problem is fully characterized by the parameter set \( \theta_s \). Our goal is to simultaneously estimate all these unknown parameters minimizing the cost \( L(\theta_s) \). As we can see, our estimation problem is modelled as a high-dimensional optimization problem. We can show that the gradient with respect to each parameter is in a good form. Different numerical algorithms can be applied to obtain the ML estimate by solving the above seven-dimensional optimization problem. For instance, we may apply the commonly used Gauss-Newton method [24]. However, a sufficient accurate initial estimate is a key for the performance. We may also apply a Monte Carlo method called simulated annealing to estimate the parameters. In this paper, we employ RFSQP (Reduced Feasible Quadratic Programming) algorithm to solve the above constrained nonlinear optimization problem. As in many numerical problems, the algorithm may converge to a local minimum, depending on the initial guess. Therefore, we may start from parallel feasible initial points and use the one yielding the smallest cost as the final estimate.

Based on the estimate of \( \theta_s \), we can reconstruct the curves \( a_f(t), a_s(t) \) and \( c_p(t) \), and it is straightforward to estimate \( s(i) \)'s, which represent the factor images and reveal the tissue spatial heterogeneity.

\[1\] RFSQP is the implementation of the algorithm developed in [25] for nonlinear constrained optimization. For Academic Institutions, the free source code is available from the website http://www.aemdesign.com/.
However, solving high-dimensional optimization problems numerically is computational expensive, in spite of the fact that the gradient vector and Hessian matrix of our parameters show good structure, and divergences could occur. In addition, finding a good initial estimate itself is challenging and problem dependent. Therefore, we shall find a good initial guess by taking advantage of the signal structure involved in this problem. It is of great interest to find an effective scheme to estimate the kinetic and input parameters with less computational requirement and acceptable accuracy. We shall propose such a scheme in this section.

We propose an integrated blind source separation and system identification scheme consisting of iterative steps. First, we carry out space-time processing analysis and develop a subspace based algorithm to obtain the initial estimates of the parameters. Since these methods do not always yield sufficient accuracy, we need to exploit more the underlying data model. Secondly, with the initial guess, the iterative ML technique is applied to improve the estimation accuracy, where each iteration includes five sub-steps by performing minimization with respect to different sub-sets of parameters. Thirdly, any prior information (belief) will be further evaluated to adjust the estimations. For instance, the underlying factor images are expected to be non-negative and locally homogeneous.

A. Sub-Space Based Algorithm

Based on the data model, our goal is to estimate the parameters by fusing temporal and spatial information, represented by pixel TACs. Here, by taking advantages of the special structures of the tissue impulse response functions and the input function, we propose a sub-space based algorithm to estimate such exponent parameters as $k_2f$, $k_2s$ and $\lambda_i$’s.

According to the system model in (4), our further analysis on Laplace-transform shows that the signal sub-space of our observations is characterized by exponential decaying signals and the first order derivation of an exponential decaying signal over the parameter $\lambda_1$. Now we show the details. Based on (4), we define $f(t) = k_1f(i)a_f(t) + k_1s(i)a_s(t) + v_p(i)c_p(t)$. We have the Laplace transform of $c_p(t)$ as:

$$\mathcal{L}\{c_p(t)\} = \frac{a_1}{(s-\lambda_1)^2} - \frac{a_2 + a_3}{s - \lambda_1} + \frac{a_2}{s - \lambda_2} + \frac{a_3}{s - \lambda_3},$$

(16)

and thus applying the linearity theorem and the convolution theorem, we have the Laplace transform of $f(t)$ as

$$F(s) = \mathcal{L}\{f(t)\} = k_1f(i)\mathcal{L}\{c_p(t)\}\mathcal{L}\{e^{-k_2f t}\} + k_1s(i)\mathcal{L}\{c_p(t)\}\mathcal{L}\{e^{-k_2s t}\} + v_p(i)\mathcal{L}\{c_p(t)\}$$

$$= \left(\frac{k_1f(i)}{s + k_2f} + \frac{k_1s(i)}{s + k_2s} + v_p(i)\right)\mathcal{L}\{c_p(t)\}.$$
The denominator of the function $F(s)$ has a 2-fold real zero $\lambda_1$, and the remaining zeros $-k_{2f}$, $-k_{2s}$, $\lambda_2$, and $\lambda_3$ are simple. Suppose these zero values are different, the partial fraction decomposition of $F(s)$ has the following form:

$$
F(s) = \frac{c_1}{s + k_{2f}} + \frac{c_2}{s + k_{2s}} + \frac{c_3}{s - \lambda_1} + \frac{c_4}{(s - \lambda_1)^2} + \frac{c_5}{s - \lambda_2} + \frac{c_6}{s - \lambda_3},
$$

(18)

in which the coefficients $c_i$’s are calculated accordingly. Therefore, we can represent $f(t)$ by six signal components via applying the inverse Laplace transform

$$
f(t) = \mathcal{L}^{-1}\{F(s)\} = c_1e^{-k_{2f}t} + c_2e^{-k_{2s}t} + c_3e^{\lambda_1t} + c_4te^{\lambda_1t} + c_5e^{\lambda_2t} + c_6e^{\lambda_3t}, \quad \text{for } t \geq 0.
$$

(19)

With the sampling time vector $t$, we define $f_0(\alpha) = [e^{\alpha t_1}, ..., e^{\alpha t_n}]$, the values of $e^{\alpha t}$ sampled at the time vector $t$, similarly define $f_1(\alpha)$ as the values of $te^{\alpha t}$ sampled at the time vector $t$, and write the signal space $S = [f_0(-k_{2f}), f_0(-k_{2s}), f_0(\lambda_1), f_1(\lambda_1), f_0(\lambda_2), f_0(\lambda_3)]$. Thus, for each pixel $i$, we have the discrete signal model

$$
c_m(i) = [f_0(-k_{2f}), f_0(-k_{2s}), f_0(\lambda_1), f_1(\lambda_1), f_0(\lambda_2), f_0(\lambda_3)]c(i) + \epsilon(i),
$$

(20)

where the coefficient vector $c(i)$ indicates the weight of each signal component at pixel $i$. Based on this analysis, we observe that the sample covariance matrix $\hat{R}$ can be expressed by using all pixel TACs:

$$
R = E\{c_m(i)c_m(i)^T\} = \frac{1}{N} \sum_{i=1}^{N} c_m(i)c_m(i)^T = SDS^T + \sigma^2 I_m = Q_s\Lambda_s Q_s^T + \sigma^2 Q_w Q_w^T, \quad \text{with } D = E\{c(i)c(i)^T\},
$$

(21)

where the last equation is due to the eigen decomposition, $Q_s$ and $Q_w$ consist of signal and noise eigenvectors respectively, and the diagonal matrix $\Lambda_s$ contains the $M$ largest eigenvalues. If $D$ (thus $SDS^T$) is of full rank, then $M = 6$ and the eigenvectors in $Q_w$ are orthogonal to $S$. However, in our problem, since the signal components represented in $S$ are coherent as a natural result of the original convolution data model in (4), there is a rank deficiency in matrix $D$.

Since from the subspace decomposition point of view, our problem is analogous to array signal processing problems widely faced in radar, sonar and communications [23], we can apply similar techniques to re-store the rank of the source covariance matrix $D$ and develop subspace-based algorithms correspondingly. A well-known technique to re-store the rank of the signal covariance matrix is the so-called smoothing [8], [23], in which the antenna array are split into a number of overlapping
subarrays, and the covariance matrices of the subarrays are then averaged. The smoothing process introduces a random phase modulation which helps to decorrelate the source signals causing the rank deficiency. In our problem, we assume that the pixel TACs are uniformly sampled for simplicity. To achieve the full rank of $D$, we employ the smoothing idea by splitting the TACs into a number of overlapping sub-TACs with length $n_s$. We can show that the signal components in the sub-TACs are identical up to different scalings, and the covariance matrices based on sub-TACs are then averaged. Employing this temporal smoothing, we can make $D$ with a full rank $M = 6$. As long as $D$ (thus $SDS^T$) is of full rank, due to the property of eigen-decomposition, we notice that the eigenvectors in $Q_w$ are orthogonal to $S$, meaning

$$S^T q_m = 0, \text{ for } m = M + 1, ..., n_s,$$

where $q_m$ are noise eigenvectors. Based upon the eigen-structure of the covariance matrix, we can develop different subspace based algorithms for our estimation problem. Here we are particularly interested in the MUSIC (Multiple Signal Classification) algorithm because of its wide success in many areas [23]. Therefore, utilizing this orthogonality property in (22), we compute a MUSIC-like algorithm as

$$S_0(\alpha) = \frac{1}{\sum_{m=M+1}^{n_s} |q_m^T f_0(\alpha)|^2}$$

$$S_1(\alpha) = \frac{1}{\sum_{m=M+1}^{n_s} |q_m^T f_1(\alpha)|^2}$$

(23)

where $0 < e^\alpha < 1$. Similar to MUSIC spectrum which exhibits peaks in the vicinity of true frequency components, here the peaks correspond to the exponent parameters of interest, as shown in Fig. 2 for a noiseless example.

We use the constraints ($k_{2f} > k_{2s} > 0$ and $\lambda_1 < \lambda_2 < \lambda_3 < 0$) to help the mapping between the peaks and the exponent parameters. Normally $-\lambda_1 > k_{2f}$ is also assumed since the input function is expected to behave similarly to a delta function at the early stage. Based on the mapping, several sets of the estimates of the exponent parameters can be used as parallel initial estimates. We need to further estimate the coefficients of the input model $a_2$ and $a_3$. For each set of the estimate of $k_{2f}, k_{2s}, \lambda_1, \lambda_2$, and $\lambda_3$, we fix these parameters in the cost function and find the estimate of $a_2$ and $a_3$ by minimizing the cost function $\text{Tr}\{(I - A(A^T A)^{-1} A^T)\hat{R}\}$ as defined in (15). We then use the set of parameters which yields the minimum cost as the initialization for further adjustment in the next stage.
Fig. 2. An example to estimate the exponent parameters using the subspace-based algorithm. Here $N = 10^3$, $n = 41$ and the TACs are uniformly sampled every 15 seconds.

B. Iterative Likelihood Maximum (ILM)

Since the subspace based method may not always yield sufficient accuracy, we need to fully exploit the underlying data model and apply the ML technique to improve the accuracy.

We can apply a seven-dimensional search to find the ML estimates according to (15). However, to further reduce the computational cost of the overall ML approach, here we propose an iterative alternative, called the iterative likelihood maximization or iterative minimization, where each iteration includes five sub-steps by decoupling the effects of unknown parameter sets. The main idea is to achieve multidimensional minimization (or maximization) by solving successive lower-dimensional minimization (or maximization) problems iteratively. This idea has its root in the Alternative Maximization (AM) technique [26]. AM is conceptually simple and appears to be a good competitor to the computationally expensive ML method. The key idea of AM is to iteratively update the estimates by successively performing a maximization with respect to each single parameter while all other parameters are held fixed. In our case, considering the structure of input $c_p$, we feel it is more reasonable to treat the pair $(\lambda_2, a_2)$, similarly the pair $(\lambda_3, a_3)$, as a subset of parameters and update their estimate simultaneously. Therefore, let $\theta_s^{(k)}$ denotes the estimated values of $\theta_s$ at iteration $k$, at iteration $(k + 1)$, the update of the estimate $\theta_s^{(k+1)}$ is obtained by solving the following one- or two-dimensional minimization problems:

- **Sub-step 1:** We update the ML estimates of the parameter pair $(\lambda_2, a_2)$, according to the cost
function in (15):

\[
(\hat{\lambda}_2^{(k+1)}, \hat{a}_2^{(k+1)}) = \arg \min_{(\lambda_2, a_2)} L(\hat{\theta}_s^{(k+1)}), \text{ subject to } \lambda_1^{(k)} < \lambda_2 < \lambda_3^{(k)},
\]

meaning a two-dimensional minimization (or equivalently a maximization of the likelihood function) is performed with respect to \(\lambda_2\) and \(a_2\), while all other parameters are held fixed.

- **Sup-step 2:** With the above estimated \((\hat{\lambda}_2^{(k+1)}, \hat{a}_2^{(k+1)})\), we update \(\hat{\theta}_s\) accordingly. We then update the ML estimates of the parameter pair \((\lambda_3, a_3)\) as

\[
(\hat{\lambda}_3^{(k+1)}, \hat{a}_3^{(k+1)}) = \arg \min_{(\lambda_3, a_3)} L(\hat{\theta}_s), \text{ subject to } \lambda_2^{(k+1)} < \lambda_3,
\]

by solving a simple 2-dimensional estimation problem.

- **Sub-step 3:** With the above estimated \((\hat{\lambda}_3^{(k+1)}, \hat{a}_3^{(k+1)})\), we update \(\hat{\theta}_s\) accordingly. We then update the ML estimates of the parameter \(\lambda_1\) as:

\[
\hat{\lambda}_1^{(k+1)} = \arg \min_{\lambda_1} L(\hat{\theta}_s), \text{ subject to } \lambda_1 < \lambda_2^{(k+1)}.
\]

- **Sub-step 4:** We update \(\hat{\theta}_s\) accordingly. We then update the ML estimates of the kinetic parameter \(k_{2f}\) of fast flow as

\[
\hat{k}_{2f}^{(k+1)} = \arg \min_{k_{2f}} L(\hat{\theta}_s), \text{ subject to } k_{2f} > k_{2s}^{(k)}.
\]

- **Sub-step 5:** Updating \(\hat{\theta}_s\) accordingly, we then obtain the update the ML estimates of the kinetic parameter \(k_{2s}\) according to

\[
\hat{k}_{2s}^{(k+1)} = \arg \min_{k_{2s}} L(\hat{\theta}_s), \text{ subject to } k_{2s}^{(k+1)} > k_{2s}.
\]

We thus obtain the updated estimate \(\hat{\theta}_s^{(k+1)}\). These sub steps are iteratively applied until the convergence is achieved.

Since a minimization is performed at every sub-step, the value of the cost function \(L(\theta_s)\) keeps decreasing with the index of the iteration \(k\). Intuitively, the algorithm reaches the bottom of the cost function \(L(\theta_s)\) along lines parallel to the axes. Thus, the above algorithm is to converge to a local minimum, which depends on the initial condition. It is worth mentioning that this algorithm is easy to implement, and it is computationally attractive since we only need to solve simple one- or two-dimensional optimization problems. We will demonstrate later via extensive simulations that the initial obtained via the subspace based scheme yields good estimation results.
C. Further Adjustment

In this section, we propose to investigate the approach that can improve the accuracy of factor images by exploiting the non-negative property of the underlying factor images in our dynamic imaging problem. With the parameters are estimated, we can estimate the TACs $a_f$, $a_s$ and $c_p$ (thus the matrix $A$) correspondingly. Given that $A$ is fixed and that the inequality constraints $k_1 f(i) \geq 0, k_1 s(i) \geq 0$ and $v_p(i) \geq 0$, for each pixel $i$, due to the assumption that $c_m(i)$ follows a $N(As(i), \sigma_2 I)$ distribution, estimating the factor coefficients $s(i)$ equals to solve a constrained optimization problem

$$\hat{s}(i) = \arg \min_{s(i)} ||c_m(i) - As(i)||^2 \text{ subject to } s(i) \geq 0.$$  \hspace{1cm} (29)

We can apply the Lagrange multiplier theorem to solve this problem [?], where the Lagrangian function is defined as

$$L(s(i), \mu) = ||c_m(i) - As(i)||^2 - \sum_{j=1}^{3} \mu_j s(i, j).$$  \hspace{1cm} (30)

D. The Integrated Approach

Based on the above discussions, our proposed hybrid approach is summarized as following:

- **Initialization:** Any computationally attractive methods can be applied to obtain the initial estimates of the parameters. We propose subspace based algorithms to estimate the parameters as initialization. Since heavy noise is usually observed in real DCE-MRI data, the subspace based algorithm may not find all peaks when processing all image data together. Intuitively, we can see that the fast-flow component is demonstrated more clearly in images collected in the earlier time period, while the slow-flow component exists all over the time and is demonstrated more clearly in images of the later stage. Therefore, we apply a simple method to overcome the above problem, where early time and later time static images are processed separately and the estimated exponent parameters are then combined together. Our preliminary simulation study illustrates that the initial estimates itself is very accurate in many cases.

The estimates from any fast algorithms can be used as initial estimates. Moreover, we can compare and combine the estimates from different algorithms to yield the better estimates.

- **Iterative minimization:** To further reduce the computational cost of the overall ML approach, we apply an iterative likelihood maximization (ILM) approach to improve the estimation accuracy of the unknown parameters, as described in Section III-B. This approach performs the following substeps iteratively: performing minimizations with respect to the parameter pair $(\lambda_2, a_2)$, the pair $(\lambda_3,$
a_3), the input parameter \( \lambda_1 \), the kinetic parameter for the fast-flow \( k_{2f} \) and the kinetic parameter \( k_{2s} \) successively at each iteration.

- **Further adjustment based on prior information:** One principle for enhancing the estimation accuracy of a problem is to take advantage of any prior knowledge about the parameters and the underlying model. For instance, in our dynamic imaging problem, the underlying factor images are expected to be non-negative and locally homogeneous. We explore this prior information to further adjust the estimates as in Section III-C.

If necessary, go back to Stage-2 until the estimates are converged. However, our experience in preliminary study suggests that further iteration is usually not necessary. It is worth mentioning that this approach is easy to implement and normally provide good performance comparable to that of RFSQP algorithm.

**IV. Simulation Results**

Due to the complex nature of the dynamic imaging problem and the multiple goals of our interpretation of the dynamic imaging data, it is impossible to characterize the performance of an algorithm analytically. Hence, performance demonstrations are based on simulations.

**A. Some Performance Measures**

In this dynamic imaging problem, we aim to estimate the input function, estimate the kinetic parameters and TACs of the multiple biomarkers, and figure out the spatial heterogeneity characterizations simultaneously. Therefore, the proposed scheme should provide for each parameter an accurate estimate; it should accurately estimate the three factor TACs associated with the extracted from the whole-tumor tissue kinetics (i.e., \( a_f(t), a_s(t) \) and \( c_p(t) \)); and it should locate the tumor heterogeneity characterization due to each biomarker reasonably accurate.

With regard to the first objective, a measure of the performance in terms of the parameter estimation error, we many examine various statistical criteria, such as mean, standard deviation, coefficient of variation, and bias. In this paper, as in [3], we consider the coefficient of variation (CV) and the relative bias

\[
CV(p) = \frac{std(\hat{p})}{\bar{p}}; \quad bias(p) = \left| \frac{p - \bar{p}}{p} \right|
\]

in which \( p \) represent the true value of the individual parameter, \( std \) means standard deviation operation, \( \bar{p} \) is the empirical mean value obtained from simulations. It is clear that \( CV(p) \) and \( bias(p) \) make more sense than the simple average and standard deviation of the estimated parameter, since
the later criteria could obscure large fluctuations in the estimation. The above criteria $CV(p)$ and $bias(p)$ will be used to evaluate the estimation performance for each individual parameter.

Let $y$ and $\hat{y}$ be the true and estimated factor TAC with length $n$, respectively. To evaluate performance with regard to the second objective, we calculate the correlation coefficient (CC) between the estimated factor TACs $\hat{y}$ and the true ones $y$. We also study the norm of the corresponding residuals defined as $(\hat{y} - y)$, since it is desirable for an estimator to fit the real factor curve in a least-square sense. The histogram of the above criteria will be studied using Monte Carlo simulation runs. To make a fair comparison, we perform “centering” and “normalization” on the three factor TACs over time $t$ before we calculate the above performance measures, where the vector $\tilde{y}$ after “centering” and “normalization” satisfies

$$\sum_{j=1}^{n} \tilde{y}_j = 0; \quad \sum_{j=1}^{n} \tilde{y}_j^2 = \text{constant}. \quad (32)$$

The larger the CC and the smaller the residual norm, the better the estimation performance.

Considering a measure of adherence to the third objective above is not straightforward, since the spatial structure of the resulting factor image due to each biomarker is of great interest. As such, we calculate the CC between the estimated factor image $\{\hat{k}_{1i}\}$ and the true one. In addition, we propose $PM$, the relative distance between the true and the estimated factor coefficients (i.e., $k_{1f}(i)$, $k_{1s}(i)$ and $v_p(i)$’s). Based on the factor image of the fast flow, we calculate $PM$ as

$$PM_f = \frac{1}{N} \sum_{i=1}^{N} \frac{|\hat{k}_{1f}(i) - k_{1f}(i)|}{k_{1f}(i)}. \quad (33)$$

The $PM$ of the components of the slow-flow and the input function can be similarly defined. The smaller $PM$ is, the better performance a scheme provides on revealing the spatial heterogeneous structure of a tumor.

**B. Results**

Monte Carlo simulation runs are used to test the accuracy and reliability of the proposed scheme. The input function $c_p(t)$ is generated from the parametric model proposed in [22], with the values of the parameters set as $\lambda_1 = -4.1339, \lambda_2 = -0.2191, \lambda_3 = -0.0104, a_1 = 851.1225, a_2 = 21.8798$ and $a_3 = 20.8113$. We consider a multi-region significantly-overlapped case. The simulated tumor phantom consists of three underlying components as shown in Fig. 3(a), including the fast factor image $\{k_{1f}(i)\}$, the slow factor image $\{k_{1s}(i)\}$, and the input factor image $\{v_p(i)\}$. The grey level represents the amplitude of these component values, where a lighter color means a high amplitude.
As we can see, each factor image includes a light and a darker sub-region, where the coefficients (e.g. \( \{k_1f(i)\} \)) are randomly drawn from one of the two uniform distributions. In our simulation, the coefficients \( \{k_1f(i)\} \) and \( \{k_1s(i)\} \) are randomly drawn from the uniform distributions \( U(0.1, 0.4) \) and \( U(0.8, 1) \), and the coefficients \( \{v_p(i)\} \) are randomly drawn from the distributions \( U(0.2, 0.3) \) and \( U(0.4, 0.8) \). Adding Gaussian noise with zero mean and variance \( \sigma^2 \) to each pixel kinetics, we simulate the pixel time activity curve for each pixel \( i \) according to (4), where the values of the washout constant rates are set as \( k_{2f} = 2.5/min \) and \( k_{2s} = 0.4/min \). The TACs are sampled from 0 to 10 minutes with the uniform sampling period 15 seconds. In our simulation, the noise level is chosen as \( \sigma^2 = 30 \) to yield a similar SNR observed in real image data. Fig. 4 shows the TACs observed by using the above set of parameters and sampling schedule, where we note that the fluctuations in observations represent approximately the noise level observed in the patient studies.

Based on 100 simulations runs, we study the performance measures discussed above. Table I shows the statistical results of estimating the kinetic parameters, in terms of the coefficient of variation and the relative bias defined in (31). As mentioned earlier, we only report the estimate of the ratios \( a_2/a_1 \) and \( a_3/a_1 \) to avoid the redundant parameter. Within each cell of the table, we report the
corresponding result of RFSQP before the sign | and that of the proposed scheme after the sign |. For instance, 0.266|0.227 means that the relative bias 0.266 of \( k_{2f} \) obtained from the RFSQP algorithm is 0.266, which it is 0.277 from the proposed scheme. From this table, we can see that the resulting CVs and relative biases are reasonably small. Although the RFSQP yields more stable estimates of parameter since smaller CVs are observed in RFSQP, overall the proposed scheme provides comparable performance in estimating parameters. More specifically, it is noted that the RFSQP provides much more accurate estimate of the kinetic parameter \( k_{2s} \), while the proposed scheme is more accurate in estimating the parameter \( \lambda_1 \). However, it is worth mentioning that the accuracy in estimating individual parameter is of less importance in our problem, since the signal components are characterized by the parameters together. We are more interested in identifying different signal components and find out their space patterns within a tumor region.

<table>
<thead>
<tr>
<th>parameter ( p )</th>
<th>( k_{2f} )</th>
<th>( k_{2s} )</th>
<th>( \lambda_1 )</th>
<th>( \lambda_2 )</th>
<th>( \lambda_3 )</th>
<th>( a_2/a_1 )</th>
<th>( a_3/a_1 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>true value</td>
<td>2.5</td>
<td>0.4</td>
<td>-4.1339</td>
<td>-0.2191</td>
<td>-0.0104</td>
<td>0.0257</td>
<td>0.0245</td>
</tr>
<tr>
<td>bias(( p ))</td>
<td>0.266</td>
<td>0.196</td>
<td>-0.061</td>
<td>-0.061</td>
<td>-0.061</td>
<td>0.062</td>
<td>1.618</td>
</tr>
<tr>
<td>CV(( p ))</td>
<td>0.138</td>
<td>0.179</td>
<td>-0.061</td>
<td>-0.061</td>
<td>-0.061</td>
<td>0.312</td>
<td>0.381</td>
</tr>
</tbody>
</table>

**TABLE I**

Estimation performance of the input function and kinetic parameters for the noise level \( \sigma^2 = 30 \). The CVs and the relative biases are calculated from 100 simulation runs.

To evaluate the performance of the proposed scheme in estimating the three factor TACs (i.e.
Fig. 5. The true and the estimated factor TACs \( a_f(t) \) (left), \( a_s(t) \) (middle) and \( c_p(t) \) (right).

\( a_f(t), a_s(t) \) and \( c_p(t) \), we first show a typical example by plotting the “centered and normalized” true factor TACs and the fitted factor TACs estimated by the proposed scheme in Fig. 5. It is noted that the estimated slow-flow curve matches very well with the true one \( a_s(t) \), while the estimated fast-flow curve and the input curve are underestimated before 1 minute and overestimated after 1 minute. However, the estimated curves agree well with the true ones in terms of their shapes. To further evaluate the estimation performance, we then study the resulting correlation coefficient (CC) and the residual norm. For each factor TAC, the empirical means and standard deviations of these two performance measures are also shown in Table II. We note that the proposed scheme provides a little worse but very close performance to that of RFSQP. An interesting observation is that both schemes works well in estimating the slow-flow factor curve \( a_s(t) \), although it was noted earlier that the proposed scheme works much worse in estimating the kinetic parameter \( k_{2s} \). Based on simulation realizations, the pdfs (normalized histograms) of CC and the residual norm are obtained for the proposed scheme, as illustrated in Fig. 6. It can be seen from the figures that the proposed scheme provides high accuracy in estimating the curves \( a_f(t), a_s(t) \) and \( c_p(t) \) which characterize the underlying components in this tumor phantom case.

One example of the estimated factor images is shown in Fig. 3, where good matches are observed. We are particularly interested in the factor images which reveal the underlying spatial heterogeneity characterization. With this regard, we study the statistical behave of the correlation coefficient between the true and estimated factor images and the performance measure \( PM \) defined in (33). Correspondingly, Table III shows their empirical means and standard deviations based on the estimate of factor images from 100 simulation runs. Again, we note that the proposed scheme provides
Fig. 6. Normalized histograms of the correlation coefficients (left plots) and the residual norms (right plots) for estimating the factor TACs $a_f(t), a_s(t)$ and $c_p(t)$.

<table>
<thead>
<tr>
<th>factor TAC</th>
<th>$a_f(t)$</th>
<th>$a_s(t)$</th>
<th>$c_p(t)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>(0.973,0.079)</td>
<td>(0.995,0.003)</td>
<td>(0.973,0.025)</td>
</tr>
<tr>
<td>residual norm</td>
<td>(0.053,0.159)</td>
<td>(0.010,0.006)</td>
<td>(0.053,0.049)</td>
</tr>
</tbody>
</table>

TABLE II

PERFORMANCE OF ESTIMATING THE FACTOR TACs $a_f(t), a_s(t)$ AND $c_p(t)$. HERE THE MEAN AND STANDARD DEVIATION OF THE . THE CORRELATION COEFFICIENTS AND THE RESIDUAL NORMS ARE CALCULATED FROM 100 SIMULATION RUNS, WITH THE NOISE LEVEL $\sigma^2 = 30$.

comparable performance to that of RFSQP in estimating the underlying factor images. The histograms of $PM$ are also illustrated in Fig. 7 for the proposed scheme. It can be seen from the figures that the proposed scheme provides high accuracy in estimating the factor images which demonstrate the spatial heterogeneity of each component.

V. REAL DATA CASE

We now examine the performance of our proposed scheme when applied to the DCE-MRI study of breast cancer patients. The data was acquired at NIH laboratory, as illustrated in Fig. 8, where
TABLE III

Performance of estimating the factor images, in terms of the mean and standard deviation of $PM$. Here the noise level $\sigma^2 = 30$.

<table>
<thead>
<tr>
<th>factor</th>
<th>fast</th>
<th>slow</th>
<th>input</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>(0.962,0.041)</td>
<td>(0.955,0.100)</td>
<td>(0.980,0.016)</td>
</tr>
<tr>
<td>$PM$</td>
<td>(0.388,0.113)</td>
<td>(0.320,0.188)</td>
<td>(0.207,0.054)</td>
</tr>
</tbody>
</table>

we observe an advanced tumor (breast cancer) showing highly spatial heterogeneity. We assume appropriate masking is operated to obtain the tumor region. 3-D scans of DCE-MRI were performed every 30 seconds for a total of 11 minutes after the injection.

Blind estimations of the kinematic parameters performed by the integrated scheme give the following results: $\hat{k}_{2,f} = 0.583$, $\hat{k}_{2,s} = 0.103$. Furthermore, the proposed scheme gave the following estimates of the parameters representing the input function $c_p(t)$: $\hat{\lambda}_1 = -14.20$, $\hat{\lambda}_2 = -0.864$, $\hat{\lambda}_3 = -0.033$, $\hat{a}_2 = 0.123$, and $\hat{a}_3 = 0.044$. To validate the blind estimation, our work further should involve the performance comparison to a gold-standard.

Fig. 9 shows the input function estimated by the proposed scheme. In addition, we also plot the estimated factor curves for the fast-flow and the slow flow. To further examine the results, based on the above estimate of the parameters, we reconstruct the factor images (i.e. $s(i)$’s) in Fig. 10. It is noted that the boundary region is dominated by the fast flow, while the inside region is dominated by the slow flow. Meanwhile, the input signal component is observed everywhere in some sense, with
Fig. 8. Images of advanced breast tumor obtained by DCE-MRI. The masking operation is processed to separate the tumor region out.

Fig. 9. The factor TACs $a_f(t)$ (left), $a_s(t)$ (middle) and $c_p(t)$ (right) estimated by the proposed scheme based on the real breast cancer data.

stronger energy around edges. The observations match with the clinical opinions. An interesting sub-region is noticed around the coordinate (10,22), where strong coefficients are observed in all three factor images. Recall that our tumor region is separated from normal tissue region by employing a masking process, which is experience based in many situations. By referring to the factor images shown here, we suspect that this sub-region is not belong to tumor region. Future work will involve studies with a microsphere based gold standard of flow to validate the proposed scheme.
VI. CONCLUSION

There are clinical needs to develop noninvasive imaging analysis schemes for tumor angiogenesis. The goal of this research is to develop efficient methods for characterizing multiple biomarkers and estimating the input function in dynamic imaging. We investigated the system model on the pixel domain consisting of multiple biomarkers, therefore, no pre-processing for identifying different ROIs is required. We developed an integrated scheme including iterative steps to estimate the kinetic parameters and the input function simultaneously. By taking advantages of the specific signal structure involved in our problem, we employed a subspace based algorithm to obtain an initial estimate of parameters. Then, an iterative ML technique was developed to refine the estimation results, where the parameters are divided into sub-sets and minimization with respect to parameters of each sub-set of parameters is performed iteratively until convergence.

The performance of the proposed scheme was tested by using Monte Carlo simulations. We studied several performance measures to examine the results of the proposed scheme in estimating the parameters, in estimating the three factor TACs, and in revealing the underlying spatial heterogeneous structures (e.g. the factor images). The results illustrated that the proposed scheme is able to quantify all the unknown parameters, provides reliable estimations of factor TACs, and proves very promising in examining the spatial heterogeneity in tumor dynamics on pixel-by-pixel basis. Overall, simulations showed that the proposed scheme provides comparable performance to that of RFSQP, which serves as a performance bound in our estimation problem. Furthermore, we studied the result on breast tumor of DCE-MRI. It was noted that the estimated factor images clearly reveal...
the spatial heterogeneity in tumor structure which matches with the clinical belief. According to the simulation and real image results, we conclude that the scheme proposed in this paper is useful for the noninvasive quantification analysis of biomarker kinetic parameters, spatial heterogeneity of the tumor structure, and the input function. In other words, the proposed scheme is promising as a practical alternative to tradition methods, which either requires the input function obtained by taking blood samples invasively, or requires pre-processing to identify different ROIs.

To validate the proposed scheme, our future work will involve DCE-MRI small animal studies of tumor vascularity, and we will correlate our results with that from histopathological analysis of tumors. In addition, we plan to generalize the approach to estimating the number of biomarkers characterizing a tumor region, since such information may not be available in practice. We plan to examine the traditional model order estimation techniques, such as information criteria [8], and the minimum description length (MDL) principle [9]. It is worth mentioning that other computationally efficient methods can be applied to obtain the initial estimates of the parameters. For instance, we can employ the independent component analysis (ICA) based methods [14], [15].

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