Mapping Myocardial Perfusion with an Intravascular MR Contrast Agent, A Robust Estimation by a Spatially Constrained Approach

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Abstract

Evaluation of quantitative parameters such as regional Myocardial Blood Flow (rMBF), Blood Volume (rMBV), and Mean Transit Time (rMTT) by MRI is gaining acceptance for clinical applications, but still lacks robust post-processing methods for map generation. Pixel by pixel analysis leads to high variance of the estimates and variance reduction by posterior spatial averaging does not produce satisfactory results. We propose a parametric estimation technique that smoothes the variance of the estimates within parametric homogeneous regions while preserving discontinuities (in the sense that smoothing is not performed across regions with different parametric contents). Our approach lies within the Bayesian framework. It is based on local autoregressive moving average (ARMA) estimation, constrained by an edge-preserving smoothness prior. The prior stems from Markov random fields (MRF) modeling and involves non-quadratic potential functions. The output of the resulting algorithm is a regularized rMBF map. The method is validated on synthetic MR kinetics and tested on first-pass T1 images of an isolated pig heart using an intravascular contrast agent. Comparison of our results with pixel by pixel estimates clearly demonstrate the ability of the proposed approach to improve parametric estimation in terms of variance reduction and discontinuity preservation.

1. Introduction

Functional exploration of the heart is based on the study of contractility and perfusion of the myocardium. These are both needed and are complementary in the diagnosis and follow-up of coronary artery diseases (CAD). MR imaging provides a unique non-invasive method to study myocardial blood flow. With the advent of ultra-fast MRI, it is now possible to assess regional myocardial perfusion during the first-pass of an intravenous-injected contrast agent bolus. To observe the heart during the same cardiac phase (end-diastole), the acquisition is synchronised with the electrocardiogram (ECG). The clinical standard exam consists in a visual analysis of the first pass perfusion sequence by an expert. Diagnosis is based on the assumption that down-stream to a stenosed coronary artery, the myocardial territory presents a delayed arrival of the contrast media and a lower signal intensity compared to normally perfused myocardium.

To improve clinical interpretation, parametric analyses of myocardial distribution of the contrast agent have been described. A classical technique is to compute time signal intensity (SI) curves derived from each myocardial pixel or regions of interest (ROIs) in order to define normal and ischemic areas. First-pass curves of the tissue and the arterial input are analyzed using a physiologic-based model to provide perfusion-related parameters. When an intravascular contrast agent is used, blood flow can be directly obtained from first-pass kinetics using physiological models. Previous studies has validated the use of different deconvolution techniques for mapping quantitative parameters, such as regional blood flow, blood volume, and mean transit time in the myocardium [1], [2], Nevertheless, deconvolution techniques and parameter identification are very sensitive to contrast noise ratio CNR defined as the difference between peak signal intensity and baseline divided by the standard deviation of noise at baseline. To increase CNR, myocardial regions of interest (ROIs) are to be considered, instead of pixel, to compute time signal intensity (SI) curves. Thus, myocardial inner and outer contours are manually drawn but this operation is time consuming and tedious. Therefore, the purpose of the present study is to process quantitative parameters map of myocardial perfusion by mean of robust local estimation spatially constrained.

Increased robustness in parameter identification can be achieved by introducing prior constraints. Existing approaches consider time-domain regularization [3], [4], [5]. Our approach differs in the sense that we perform regularization of perfusion parameters in the spatial domain, which allows to smooth the parameter estimates in homogeneous regions while preserving discontinuities between different tissues or different perfuse myocardial territories. Our method is based on constrained ARMA estimation in a Bayesian framework (similar work include [6] and [7] in the ultrasonic field). It leads to a Maximum

a posteriori (MAP) estimate whose computation translates to the minimization of a non-quadratic cost function. This cost function is the sum of a likelihood cost function that measures fidelity to the data and a prior cost function resulting from simple Markov random field (MRF) modeling.

2. Methods

2.1. Perfusion equations

For intravascular contrast agents, under the assumption of linear relationship between MR measurements and contrast agent concentrations, a relationship between the regional myocardial blood Flow *rMBF*, the left ventricle blood MR temporal signal SI_{in} and the myocardium MR signal SI_{tis} can be written:

$$SI_{tis}(t) = rMBF \cdot SI_{in}(t) \otimes R(t) \qquad (1)$$

where $\otimes$ is the convolution operator, and $R(t)$ the residue function represents the fraction of contrast agent remaining in the tissue at time t for an idealized instantaneous unit bolus input.

The signal $rMBF \cdot R(t)$ can be estimated from $SI_{in}(t)$ and $SI_{tis}(t)$ by means of a deconvolution technique. This allows to obtain *rMBF* (as $R(0)=1$), the mean transit time $rMTT = \int_0^\infty R(t)dt$, and the regional blood volume $rMBV = rMTT \cdot rMBF$ (central volume principle).

In practice SI_{in} and SI_{tis} are only known for equally spaced time samples. A time discrete linear model ARMA describing the convolution equation (1) with input $SI_{in}(k)$, and tissue response $SI_{tis}(k)$ is [1]:

$$SI_{tis}(k) = b_0 SI_{in}(k) + b_1 SI_{in}(k-1) + \ldots + b_m SI_{in}(k-m) - \\ - a_1 SI_{tis}(k-1) - \ldots - a_n SI_{tis}(k-n) \qquad (2)$$

This relation for $k \in \{1,\ldots,N\}$ can be summarized by the linear system:

$$\mathbf{A} \cdot \Theta = \mathbf{B} \qquad (3)$$

with $\Theta = (b_0,\ldots,b_m,-a_1,\cdots,-a_n)^t$; $\mathbf{B} = (SI_{tis}(1),\cdots,SI_{tis}(N))^t$

$$A = \begin{pmatrix} SI_{in}(1) & 0 & \cdots & 0 & SI_{tis}(0) & \cdots & 0 \\ SI_{in}(2) & SI_{in}(1) & \cdots & 0 & SI_{tis}(1) & SI_{tis}(0) & \vdots \\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\ SI_{in}(N) & SI_{in}(N-1) & \cdots & SI_{in}(N-m) & SI_{tis}(N-1) & \cdots & SI_{tis}(N-n) \end{pmatrix}$$

Estimation of ARMA parameters Θ and discrete convolution computed with an impulse input gives *rMBF* $R(k)$ and thus the perfusion parameters, leading to $rMBF = b_0$.

2.2. ARMA Estimation Applied to Perfusion Image

Temporal data are split into a set of "cells", each cell $s=(i, j)$ contains the contrast agent temporal signal $\mathbf{y}_s$ corresponding to pixel (i, j) of the perfusion image we are willing to obtain. This gives the so-called time-space image $Y = \{\mathbf{y}_s ; s \in S\}$ where S is the set of cells, and $\mathbf{y}_s$ denotes the time signal SI_{tis} associated with cell s.

The global ARMA estimation problem consists in finding the ARMA coefficients associated with each signals $\mathbf{y}_s$, which is to solve the system (3) corresponding to each cell s or, equivalently:

$$\underbrace{\begin{bmatrix} \mathbf{A}_{s_1} & 0 & \cdots & \\ 0 & \mathbf{A}_{s_2} & & \vdots \\ \vdots & & \ddots & 0 \\ 0 & \cdots & 0 & \mathbf{A}_{s_{|S|}} \end{bmatrix}}_{\mathbf{U}} \cdot \underbrace{\begin{bmatrix} \Theta_{s_1} & 0 & \cdots & \\ 0 & \Theta_{s_2} & & \vdots \\ \vdots & & \ddots & 0 \\ 0 & \cdots & 0 & \Theta_{s_{|S|}} \end{bmatrix}}_{\mathbf{X}} = \underbrace{\begin{bmatrix} \mathbf{B}_{s_1} & 0 & \cdots & \\ 0 & \mathbf{B}_{s_2} & & \vdots \\ \vdots & & \ddots & 0 \\ 0 & \cdots & 0 & \mathbf{B}_{s_{|S|}} \end{bmatrix}}_{\mathbf{Y}}$$

Where |S| is the number of pixel in the image. In this approach, the set of ARMA parameters modeling the signal in cell s, is estimated independently from other cells. This yields perfusion parameter estimates with high variance [1].

2.3. Edge-preserving Spatial Smoothing using a Bayesian Approach

In the Bayesian framework, the maximum a posteriori (MAP) estimate (the most popular estimate in image processing [6], [7]) leads to the minimization of a cost function of the form $U_{like}(Y/X) + U_{prior}(X)$ where $U_{like}(Y/X)$ measures the likelihood of a candidate solution X with respect to the data Y. Assuming that MRI measurements are corrupted by additive white Gaussian noise and that time signals $\mathbf{y}_s$ are statistically independent from each other, the likelihood cost function writes::

$$U_{\text{like}}(Y/X) = \sum_s U_{\text{like}}(\mathbf{y}_s/\Theta_s) = \sum_s \left\|\mathrm{B}_s - \mathrm{A}_s \cdot \Theta_s\right\|^2 = \left\|\mathbf{Y} - \mathbf{U} \cdot \mathbf{X}\right\|^2$$

Uprior measures how well X matches our prior knowledge about the solution. It is derived under the assumption that signals associated with neighboring cells have similar perfusion parameters. In other words, regional blood flow *rMBF* of neighboring cells are expected to be close when they correspond to the same tissue; in this case, only slow and smooth variations are expected. This prior knowledge is incorporated by means of an Markov random fields (MRF) model, which leads to a prior cost function of the form $U_{prior}(X) = \lambda \sum_{\{s,t\} \subset S} \Phi(\Theta_s - \Theta_t)$, where the sum is over pairs of adjacent cells in the 4 or 8 nearest neighbor system and the function Φ is taken to be even, increasing in $\Re+$ and such that $\Phi(0)=0$. The weighting parameter λ allows adjusting the relative influence of prior and likelihood cost functions. Since *rMBF* is the only physiological parameter that has a simple relationship with the ARMA parameters ($rMBF = b0$), we set:

$$\Phi(\Theta_s - \Theta_t) = \Phi(rMBF_s - rMBF_t) = \Phi\left((b_0)_s - (b_0)_t\right)$$

Φ is known as the potential function. Thikonov regularization uses conventional quadratic smoothing (i.e., $\Phi(u) = u^2$) and the MAP estimator is given by

$$\tilde{X} = \left(\mathbf{U}^T\mathbf{U}\right)^{-1}\left(\mathbf{U}^T\mathbf{Y} + \lambda\Delta\Theta\right) \quad (9)$$

where Δ is a matrix that represents a weighted discrete approximation of the Laplacian operator.

Thikonov regularization over-smoothes estimates around discontinuities. Instead, we use the function $\Phi(u) = 2\sqrt{1-u^2} - 2$ introduced by Charbonnier [8], which behaves like |*u*| for high values of *u*, but is differentiable at *u=0*. The estimation of the resulting cost function is performed using the half-quadratic approach proposed in [8].

Initialization : $\tilde{X} = \left(\mathbf{U}^T\mathbf{U}\right)^{-1}\mathbf{U}^T\mathbf{Y}$

Do (alternate estimation)

Evaluate:

$$\Delta_{\text{pond}} = \begin{pmatrix} 0 & \lambda^{\text{N}} & 0 \\ \lambda^{\text{W}} & -\sum & \lambda^{\text{E}} \\ 0 & \lambda^{\text{S}} & 0 \end{pmatrix}$$

Evaluate: $\tilde{X} = \left(\mathbf{U}^T\mathbf{U}\right)^{-1}\left(\mathbf{U}^T\mathbf{Y} + \lambda\Delta_{\text{pond}}\Theta\right)$

Until convergence,

Where $\lambda^{V_S} = \varphi'(u_{V_S})/2u_{V_S} = 1/\sqrt{1+u_{V_S}^2}$, $u_{V_S} = (\Theta_s - \Theta_t)/\delta$ for the adjacent cells in the neighborhood system. δ is a spatial scaling factor for the regularization and $\sum = \lambda^{\text{W}} + \lambda^{\text{S}} + \lambda^{\text{E}} + \lambda^{\text{N}}$.

3. Results

3.1. Simulation Results

Simulated series of MRI images are generated. The myocardium was represented as a ring region. The inner region constitutes the left ventricle (LV). For each point of the image a temporal response corresponding to the MRI signal variation during the first pass of an intravascular contrast agent was generated. For points in the LV, considered as the arterial input, a Fermi function was chosen [1] $SI_{in}(t)=t^{\alpha}\, exp(-t/\tau)$ if $t \geq 0$ and 0 if $t<0$, with $\alpha=2$; $\tau=4.6s$; in order to get a mean transit time for the arterial input of 7s corresponding to the arterial input under stress condition.

The convolution (1) of the arterial input *SItis(t)* with an exponential residue function $R(t) = exp(-t/rMTT)$ is then multiply by *rMBF* to give the tissue response. Exponential residue function describes the vasculature as a single, well-mixed compartment with a time constant, *rMTT=rMBV/rMBF*, *rMBF=300ml/min/100g*, and *rMBV=6%*. Gaussian white noise was added to yield the specific CNR of 15 for the arterial input and 6 for tissue. On the quarter top left of the myocardium an hypoperfused region was simulated using *rMBF=10 ml/min/100g*, and *rMBV=1%*. The same magnitude of noise in a perfused region was added to the hypoperfused signal.

In the two *rMBF* maps the gray level intensity was assigned to the parameter value at the pixel location. Figure 1 shows a pixel by pixel and a regularized map using a first order ARMA model (n=m=1). Regularisation parameters are λ =200; δ=0.0005 and a 4-conexity is used. The profile of identified rMBF along a circle situated in the myocardium is also given. Table 1 give the min/max and the mean±std value of the identified rMBF in each normal and hypo-perfused myocardium using or not regularisation.

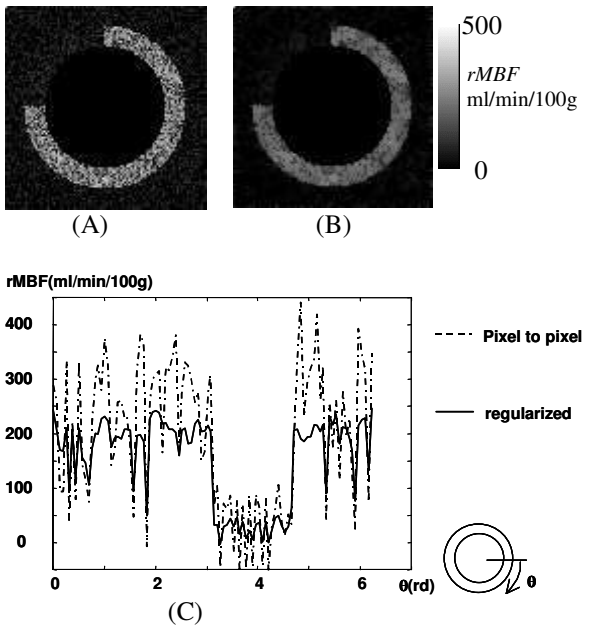

Figure 1. Pixel by pixel (A) and regularized (B) rMBF map using a first order ARMA model (n=m=1). Profiles of identified rMBF along a circle situated in the myocardium (C)

rMBF (ml/min/100g)		min/max	mean±std
No regularization	Hypo.	-74.0/111.2	24.6±48.1
	Normal	-10.8/423	221.3±82.6
With regularization	Hypo.	-62.2/75.2	18.7±14.4
	Normal	25.5/230.5	190.7±35.0

Table1. mininum/maximum and mean±std value of the identified rMBF in hypoperfused and normal myocardium using or not regularisation (theoretical values are respectively 10 and 300ml/min/100g)

3.2. Experimental Results

In this phase, using the non-beating isolated pig heart preparation [1] first-pass T1 MR images were analyzed to obtain maps representative of local tissue perfusion. A region-of-interest (ROI) was manually positioned on the cannula input to acquire the arterial input function. In the two rMBF maps, the gray level intensity was assigned to the parameter value at the pixel location. A normal myocardial region was manually delineated and the spatial mean ±SD of each parameter for normal myocardium was then calculated for pixel by pixel map rMBF=250.11±92.15 ml/mn/100g and regularized map rMBF=239.32 ±75.77 ml/mn/100g.

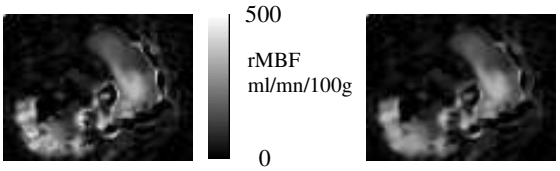

Figure 2. Pixel by pixel (A) and regularized (B) rMBF maps using a first order ARMA model.

4. Discussion and conclusions

Simulation and experimental results shows that the variance of the identified blood flow decreases using the spatial regularization. Regularization enables obtaining myocardium regions with locally constant blood flow. This result is obtained without penalization of the perfusion discontinuity within two different perfusion regions. In consequence it increases the ability of parametric perfusion map for detection and quantification of abnormal perfusion.

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