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# Kalman filtering for reliable estimation of BBB permeability

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**Abstract**

**Introduction:** The blood–brain barrier (BBB) plays an important role in the pathophysiology of a number of central nervous system disorders. In the past, a number of laboratory techniques have been proposed to quantify permeability coefficient $k_i$, an important index of barrier function. Recently, magnetic resonance imaging (MRI) has been used to estimate $k_i$ based on graphical plot technique. The MR technique was found to be in good agreement with the gold standard, quantitative autoradiography (QAR). However, a reduced image signal-to-noise ratio, among other factors such as partial volume effects, did not allow reliable estimation of permeability coefficients. This proof-of-principle study proposes the use of Kalman filter as a filtering technique for a reliable estimation of permeability coefficients. The results are compared to those obtained using the Wiener filter technique.

**Materials and Methods:** MRI experiments were performed in Wistar rats ($N=2$) using a 4.7-T Bruker Biospec MR system (Bruker Biospin, Billerica, MA). After acquiring localizer images, $T_2$-weighted diffusion-weighted imaging images were acquired. Finally, a rapid $T_1$ mapping protocol was implemented to acquire one pre-gadolinium diethylenetriamine pentaacetic acid baseline data set followed by postinjection data sets at 3-min intervals for 45 min. Data were postprocessed with and without the application of Kalman and Wiener filters to obtain an estimate of $k_i$.

**Results and Discussion:** Comparing $T_1$ maps, Patlak plots and permeability maps with and without the Kalman filtering presented several interesting observations. Kalman-filtered Patlak plots, compared to nonfiltered plots, showed that discrete data points on the plot were closer to the line fit. The number of time points used for the construction of the graphical plot had no effect on permeability coefficient estimates when the Kalman filter was used. A box-and-whiskers plot showed longer $Y$-error bars for nonfiltered and Wiener data compared to Kalman-filtered data. These observations suggest that it may be possible to obtain reliable permeability coefficient estimates in a short study time by applying the Kalman filter to the data. Future work involves investigating the application of this filter on a large-sample-size animal study and evaluating the role of partial volume effects on BBB permeability estimation.


*Keywords:* MRI; Patlak plot; Kalman; Filter; $T_1$; Map; TrueFISP; Permeability coefficient; BBB

## 1. Introduction

The blood–brain barrier (BBB) is a system of tissue sites that restrict and regulate the movement of hydrophilic solutes between the vascular compartment and the central nervous system (CNS). The brain capillary endothelium serves as the diffusion barrier between blood and extracellular fluid in the brain. The main function of BBB is to protect brain cells from the neurotoxic effects of infective and noninfective exogenous agents. The component of the BBB that plays an important role in this protective function is the tight junction present between cerebral endothelial cells. It is understood from BBB physiology that solutes move across the BBB predominantly by transcellular route due to the presence of tight junctions [1].

Animal models of brain injury (such as trauma) or disease (such as vascular stroke) have been used for assessing barrier function [2–6]. A quantitative method for evaluating barrier function is to calculate the BBB transfer constant or barrier permeability coefficient $k_i$ using standardized techniques. The most commonly used laboratory techniques for $k_i$ estimation include quantitative autoradiography (QAR) with radiolabeled sucrose [7] and Evans-blue-tagged albumin [8]. Recent technological advancements in the field of magnetic resonance imaging (MRI) and

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the availability of dedicated high-field research scanners for animal studies have allowed the development of sophisticated techniques for evaluating BBB function using MRI [9]. The MRI technique for estimating barrier permeability coefficient $k_i$ is based on the graphical analysis method developed by Patlak et al. [10]. The technique was shown to be in good agreement with the gold standard QAR, using $^{14}$C sucrose for permeability coefficient estimates [9]. Since the MRI technique for $k_i$ estimation requires rapid data acquisition for time-series data collection, signal-to-noise ratio (SNR) is severely compromised. As a result, there is a reduction in the sensitivity of the technique for a reliable detection of BBB opening [11]. Since $k_i$ is estimated on a pixel-by-pixel basis, SNR loss has a pronounced effect on reliably quantifying BBB permeability. An improvement in SNR can be achieved albeit at the cost of reduced temporal resolution (such as increased signal averages that may not be acceptable in dynamic studies).

If the image noise in a dynamic data set corresponds to a white noise model for temporal errors in signal, correlation techniques maybe suitable for the analysis of this type of data. An attractive option is the Kalman filter that uses a generalized linear model approach, as it is precisely an incremental solver for least squares linear regression problems. The Kalman filter technique has been used in the past for the detection of time-varying brain activation signals in real-time functional MRI (fMRI) data-series acquisition [12]. In an fMRI experiment, the combination of short data acquisition time and small changes in brain activation signals in response to hemodynamic events causes noise to be dominant in the fMRI data set. The Kalman filter works to extract the true state of the system (i.e., the fMRI signal) by combining information on system dynamics with probabilistic information on noise [13].

In this study, a digital Kalman filter, an adaptive filter technique, has been applied to MRI data, allowing an optimal estimation of permeability coefficient. The Kalman filter is a set of mathematical equations that provides efficient computational means to estimate the state of the system through observed noisy data in a way that minimizes the mean squared error. The aims of this work were twofold: (a) to apply this digital filter technique to raw MRI data in order to obtain a pixel-by-pixel estimate of $k_i$, and (b) to compare the results in Aim 1 with the results obtained after the application of the Wiener filter technique [14] — a linear filter technique used for image restoration to filter out noise that has corrupted a signal or an image.

## 2. Theory

### 2.1. MRI technique

The MRI technique for estimating BBB permeability coefficient is based on the graphical analysis method of a time series of tissue and arterial concentrations of an injected MR contrast agent [gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA)] proposed by Patlak et al. [10]. The working equation is

$$C_{\text{tiss}}(t) = k_i \int_0^t C_{\text{pa}}(\tau)\mathrm{d}\tau + C_{\text{pa}}(t)V_{\text{p}} \tag{1}$$

where $C_{\text{tiss}}(t)$ (mM $\text{l}^{-1}$) is the tissue concentration of an indicator (per unit tissue weight) at time $t$, $C_{\text{pa}}(\tau)$ (mM $\text{l}^{-1}$) is the arterial plasma concentration of the indicator (per unit plasma volume) over the duration of the experiment, $k_i$ (ml $\text{g}^{-1}$ $\text{min}^{-1}$) and $V_{\text{p}}$ (ml) represents the permeability coefficient and tissue distribution volume of Gd-DTPA prior to crossing the BBB, respectively. Based on Eq. (1), the plot of $\frac{C_{\text{tiss}}(t)}{C_{\text{pa}}(t)}$ vs. $\frac{\int_0^t C_{\text{pa}}(\tau)\mathrm{d}\tau}{C_{\text{pa}}(t)}$ fit to a straight line, the slope of which is an estimate of the permeability coefficient. $k_i$ can be defined as the ratio of the total amount of contrast agent accumulated in a tissue region after an infinite amount of time to the integral of the plasma time–activity curve (TAC) from $t=0$ to infinity. The tissue volume $V_{\text{p}}$ is the $y$-axis intercept of the line fit in the Patlak plot.

The Patlak plot method requires an estimation of tissue and arterial concentrations of injected contrast agents at multiple time points in order to perform a fit. Since $T_1$ relaxation time is directly related to contrast agent concentration, a $T_1$ map provides a useful and direct way of obtaining a concentration map of the tissue of interest. In this study, plasma concentration values of Gd-DTPA at various time points were obtained from the sagittal sinus, since it has been shown to be a good estimate of arterial concentration in this type of study [10]. However, an important prerequisite of this study is short acquisition time per time point for an efficient sampling of Gd-DTPA TAC in the tissue region and the sagittal sinus.

The MR protocol consisted of a rapid MRI technique for $T_1$ mapping based on the method proposed by Look and Locker (L–L) [15]. True Fast Imaging with Steady state Precession (TrueFISP) was used as a readout sequence for the L–L method for this study. The $T_1$ map for each time point was reconstructed from raw data on a pixel-by-pixel basis using a three-parameter fit to the following signal intensity equation [16]

$$S(nT_{\text{r}}) = S_{\text{s}}\left[1 - \text{INV} \times \text{e}^{-\left(\frac{nT_{\text{r}}}{T_1^*}\right)}\right] \tag{2}$$

where $T_{\text{r}}$ represents the time between gradient echoes, $T_1^*$ represents the apparent $T_1$ relaxation time from which the true $T_1$ relaxation time can be calculated, $S_{\text{s}}$ represents steady-state signal and INV is a fit factor that depends only on the flip angle and $T_1/T_2$. True $T_1$ times were calculated from $T_1^*$ using the following equation

$$T_1 = T_1^*\left[\cos^2\frac{\alpha}{2} + (A \times \text{INV} + B)\sin^2\frac{\alpha}{2}\right] \tag{3}$$