IMA Journal of Applied Mathematics Advance Access published July 3, 2016

IMA Journal of Applied Mathematics (2016) **00**, 1–16
doi:10.1093/imamat/hxw032

Adapting the Kärger model to account for finite diffusion-encoding pulses in diffusion MRI

HOUSSEM HADDAR, JING REBECCA LI AND SIMONA SCHIAVI*
INRIA-Saclay, Equipe DeFI, CMAP, Ecole Polytechnique, Route de Saclay, 91128, Palaiseau Cedex, France
*Corresponding author: simona.schiavi@inria.fr, houssem.haddar@inria.fr, jingrebecca.li@inria.fr

[Received on 16 June 2015; revised on 15 January 2016; accepted on 1 May 2016]

Diffusion magnetic resonance imaging (dMRI) is an imaging modality that probes the diffusion characteristics of a sample via the application of magnetic field gradient pulses. If the imaging voxel can be divided into different Gaussian diffusion compartments with inter-compartment exchange governed by linear kinetics, then the dMRI signal can be described by the Kärger model, which is a well-known model in Nuclear Magnetic Resonance. However, the Kärger model is limited to the case when the duration of the diffusion-encoding gradient pulses is short compared to the time delay between the start of the pulses. Under this assumption, the time at which to evaluate the Kärger model to obtain the dMRI signal is unambiguously the delay between the pulses. Recently, a new model of the dMRI signal, the Finite-Pulse Kärger (FPK) model, was derived for arbitrary diffusion gradient profiles. Relying on the FPK model, we show that when the duration of the gradient pulses is not short, the time at which to evaluate the Kärger model should be the time delay between the start of the pulses, shortened by one third of the pulse duration. With this choice, we show the sixth order convergence of the Kärger model to the FPK model in the non-dimensionalized pulse duration.

Keywords: diffusion MRI; kärger model; njarrow pulse assumption; finite-pulse.

1. Introduction

The image contrast in water proton diffusion magnetic resonance imaging (dMRI) comes from the differing water diffusion characteristics in the imaged tissue at different spatial positions (Le Bihan *et al.*, 1986). A major application has been in acute cerebral ischemia (stroke) (Moseley *et al.*, 1990; Warach *et al.*, 1992). dMRI has been used to detect and differentiate a wide range of physiological and pathological conditions, including, in the brain, tumors (Sugahara *et al.*, 1999; Tsushima *et al.*, 2009; Maier *et al.*, 2010), myelination abnormalities (for a review, see Le Bihan & Johansen-Berg (2012)), as well as in the study of brain connectivity (for a review, see Lazar (2010)) and in functional imaging (LeBihan *et al.*, 2006).

A standard way to encode diffusion using MRI is by applying the pulsed gradient spin echo (PGSE) (Stejskal & Tanner, 1965) sequence. In an ideal experiment, the gradient magnetic field, $B = \mathbf{g} \cdot \mathbf{x}$, is applied during two very short pulses, each of duration δ, with a time delay of Δ between the start of the two pulses (Fig. 1). There is also a 180-degree spin reversal between the two pulses.

Under the assumption that the pulse duration is short, $\delta \ll \Delta$, if additionally, the imaging voxel can be spatially divided into different Gaussian diffusion compartments with inter-compartment exchange governed by linear kinetics, then the dMRI signal can be described by the Kärger model (Kärger, 1985), which is a well-known model in NMR that has been also used for biological tissue dMRI

© The authors 2016. Published by Oxford University Press on behalf of the Institute of Mathematics and its Applications. All rights reserved.

Downloaded from http://imamat.oxfordjournals.org/ at University of Lethbridge on August 25, 2016

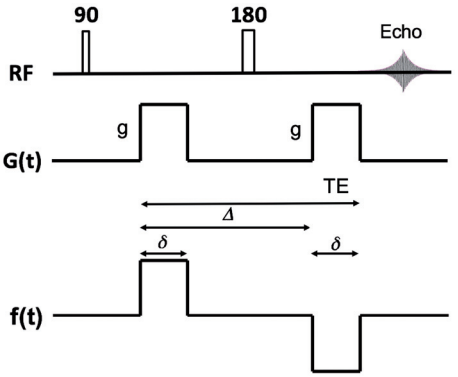

FIG. 1. The PGSE sequence. G is the gradient profile and $f(t)$ is the effective gradient profile after taking into account the 180° pulse.

(Waldeck *et al.*, 1997; Stanisz *et al.*, 1997; Pfeuffer *et al.*, 1998; Lee & Springer, 2003; Quirk *et al.*, 2003; Meier *et al.*, 2003; Roth *et al.*, 2008; Åslund *et al.*, 2009; Nilsson *et al.*, 2009). The Kärger model describes the evolution of the transverse magnetization using coupled, constant coefficient, ordinary differential equations (ODEs). The analytical solution of the ODEs system can be obtained by a matrix eigen-decomposition. Under the assumption that $\delta \ll \Delta$, the time at which to evaluate the Kärger model to obtain the dMRI signal is unambiguously the delay between the pulses.

In physically realistic MRI experiments, the condition $\delta \ll \Delta$ is rarely satisfied. Recently, a new model of the dMRI signal, the finite-pulse Kärger (FPK) model (Coatléven *et al.*, 2014), was derived for arbitrary gradient profiles and takes the form of a coupled ODE system with time-dependent coefficients. The term 'finite-pulse' was used to mean not requiring $\delta \ll \Delta$. In this article, relying on the FPK model, we show that for finite pulses, the time at which to evaluate the Kärger model should be shortened by one third of the pulse duration. For this choice, we prove that the convergence of the Kärger model to the FPK model is of order six in the pulse duration.

The article is organized as follows. In Section 2 we describe the Kärger and the FPK models. In Section 3 we prove that the signal of the Kärger model, when evaluated at $t = \Delta - \frac{\delta}{3}$, converges to the FPK signal with order 6 in the pulse duration. We also show two other possible choices of the evaluation point, $t = \Delta$ and $t = \Delta + \delta$, result only in third-order convergence. In Section 4 we validate our convergence results by numerical simulations. Section 4 contains our conclusions.

2. Description of the models

In order to provide a clear presentation of the Kärger and the FPK models, we begin here by describing them for the simple case where there are two Gaussian diffusion compartments in the tissue. For us, the two compartments will be as follows:

1. The intra-cellular compartment, comprising the ensemble of all the biological cells in a voxel.
2. The extra-cellular compartment, comprising the space in the exterior of all the cells in a voxel.

Downloaded from http://imamat.oxfordjournals.org/ at University of Lethbridge on August 25, 2016

In the more general case, different types of cells and cell components can be separated into several different diffusion compartments. Our later results will be valid for the general case of multiple diffusion compartments.

2.1. *FPK model*

The FPK model for two Gaussian diffusion compartments of total volume $|Y|$ has been proposed in Coatléven *et al.* (2014) and takes the form of two coupled ODEs with time-dependent coefficients:

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}t} m_{\mathrm{e}}^{\mathrm{FPK}}(t) + q^2 F_\delta^2(t)\sigma_{\mathrm{e}} m_{\mathrm{e}}^{\mathrm{FPK}}(t) + \eta_{\mathrm{e}} m_{\mathrm{e}}^{\mathrm{FPK}}(t) - \eta_{\mathrm{c}} m_{\mathrm{c}}^{\mathrm{FPK}}(t) = 0 \\ \dfrac{\mathrm{d}}{\mathrm{d}t} m_{\mathrm{c}}^{\mathrm{FPK}}(t) + q^2 F_\delta^2(t)\sigma_{\mathrm{c}} m_{\mathrm{c}}^{\mathrm{FPK}}(t) + \eta_{\mathrm{c}} m_{\mathrm{c}}^{\mathrm{FPK}}(t) - \eta_{\mathrm{e}} m_{\mathrm{e}}^{\mathrm{FPK}}(t) = 0 \\ m_{\mathrm{e}}^{\mathrm{FPK}}(0) = \theta_{\mathrm{e}}\,; \quad m_{\mathrm{c}}^{\mathrm{FPK}}(0) = \theta_{\mathrm{c}}, \end{cases} \tag{2.1}$$

where

- $m_{\mathrm{e}}^{\mathrm{FPK}}$ and $m_{\mathrm{c}}^{\mathrm{FPK}}$ are the transverse water proton magnetization of the extra-cellular compartment and of the intra-cellular compartment, respectively;
- q is the intensity of the diffusion-encoding magnetic gradient multiplied by the gyro-magnetic ratio of the water proton;
- σ_{e} and σ_{c} are the effective diffusion coefficients for the two compartments in the direction of the diffusion-encoding gradient. The definition and meaning of these coefficients are quite subtle. For a periodic medium these coefficients can be unambiguously defined as infinite time limits and can be obtained after solving Laplace equations in the compartments. In particular, when the compartment is closed (restricted), then the effective diffusion coefficient would be 0. For details, see Li *et al.* (2014);
- $\eta_{\mathrm{e}} = \frac{\kappa|\Gamma_m|}{|Y_{\mathrm{e}}|}$ and $\eta_{\mathrm{c}} = \frac{\kappa|\Gamma_{\mathrm{m}}|}{|Y_{\mathrm{c}}|}$, with $|Y_{\mathrm{e}}|$ and $|Y_{\mathrm{c}}|$ being the volume of the extra-cellular and intra-cellular compartment, respectively, $|\Gamma_{\mathrm{m}}|$ the total surface area of the biological cell membranes and κ the permeability of the membrane;
- $\theta_{\mathrm{e}} = \frac{|Y_{\mathrm{e}}|}{|Y|}$ and $\theta_{\mathrm{c}} = \frac{|Y_{\mathrm{c}}|}{|Y|}$ are the volume fractions of the two compartments;
- δ is the pulse duration and Δ is the time delay between the start of the two pulses of the classical PSGE sequence, for which the time profile is given by

$$f(t) = \begin{cases} 1 & \text{if } 0 < t \le \delta \\ -1 & \text{if } \Delta < t \le \Delta + \delta \\ 0 & \text{elsewhere} \end{cases}; \tag{2.2}$$

and we define

$$F_\delta(t) := \int_0^t f(s)\mathrm{d}s = \begin{cases} t & \text{if } 0 < t \le \delta \\ \delta & \text{if } \delta < t \le \Delta \\ \Delta + \delta - t & \text{if } \Delta < t \le \Delta + \delta \\ 0 & \text{elsewhere} \end{cases};$$

Downloaded from http://imamat.oxfordjournals.org/ at University of Lethbridge on August 25, 2016

The dMRI signal is the sum of all the compartment magnetizations at the end of the second pulse:

$$S^{\mathrm{FPK}} := m_{\mathrm{e}}^{\mathrm{FPK}}(\Delta+\delta) + m_{\mathrm{c}}^{\mathrm{FPK}}(\Delta+\delta). \tag{2.3}$$

When there is only one compartment, with the effective diffusion coefficient σ, it is easy to show that the analytical signal is:

$$S^{\mathrm{FPK}} = \mathrm{e}^{-b\,\sigma}, \tag{2.4}$$

where b is a commonly used quantity in dMRI called the b value that is defined as:

$$b(q,\delta,\Delta) := q^2\delta^2\left(\Delta - \frac{\delta}{3}\right). \tag{2.5}$$

When $\delta \ll \Delta$ it is easy to interpret Δ as the measured diffusion time.

2.2. *Kärger model*

The Kärger model (Kärger, 1985) was formulated heuristically, originally for microporous crystallites and later applied to biological tissue dMRI, on the basis of phenomenological modeling of the experimentally obtained signal curves. Using the same notation as for the FPK model above, the Kärger model for two diffusion compartments of total volume $|Y|$ takes the form of two coupled ODEs with 'constant' coefficients:

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}t} m_{\mathrm{e}}^{\mathrm{KAR}}(t) + q^2\delta^2\sigma_{\mathrm{e}} m_{\mathrm{e}}^{\mathrm{KAR}}(t) + \eta_{\mathrm{e}} m_{\mathrm{e}}^{\mathrm{KAR}}(t) - \eta_{\mathrm{c}} m_{\mathrm{c}}^{\mathrm{KAR}}(t) = 0, \\ \dfrac{\mathrm{d}}{\mathrm{d}t} m_{\mathrm{c}}^{\mathrm{KAR}}(t) + q^2\delta^2\sigma_{\mathrm{c}} m_{\mathrm{c}}^{\mathrm{KAR}}(t) + \eta_{\mathrm{c}} m_{\mathrm{c}}^{\mathrm{KAR}}(t) - \eta_{\mathrm{e}} m_{\mathrm{e}}^{\mathrm{KAR}}(t) = 0, \\ m_{\mathrm{e}}^{\mathrm{KAR}}(0) = \theta_{\mathrm{e}}\,; \quad m_{\mathrm{c}}^{\mathrm{KAR}}(0) = \theta_{\mathrm{c}}. \end{cases} \tag{2.6}$$

Being a system of constant coefficient ODEs, the Kärger model (2.6) can be solved by matrix eigendecomposition and we give the explicit solution for two compartments:

$$m^{\mathrm{KAR}}(t) = m_{\mathrm{e}}^{\mathrm{KAR}}(t) + m_{\mathrm{c}}^{\mathrm{KAR}}(t) = v^f(q)\,\mathrm{e}^{-D^f(q)q^2\delta^2 t} + v^s(q)\,\mathrm{e}^{-D^s(q)q^2\delta^2 t}, \tag{2.7}$$

where

$$D^{f,s}(q) = \frac{1}{2}\left(\sigma_{\mathrm{e}} + \sigma_{\mathrm{c}} + \frac{1}{q^2\delta^2}(\eta_{\mathrm{e}} + \eta_{\mathrm{c}}) \pm \sqrt{\left(\sigma_{\mathrm{e}} - \sigma_{\mathrm{c}} + \frac{1}{q^2\delta^2}(\eta_{\mathrm{e}} - \eta_{\mathrm{c}})\right)^2 + \frac{4\eta_{\mathrm{e}}\eta_{\mathrm{c}}}{q^4\delta^4}}\right),$$

$$v^f(q) = \frac{1}{D^f(q) - D^s(q)}\left(\theta_{\mathrm{e}}\sigma_{\mathrm{e}} + \theta_{\mathrm{c}}\sigma_{\mathrm{c}} - D^s(q)\right),$$

$$v^s(q) = 1 - v^f(q).$$

Downloaded from http://imamat.oxfordjournals.org/ at University of Lethbridge on August 25, 2016

The Kärger model appears as a special case of FPK model when the time profile of the diffusion-encoding magnetic field gradient sequence is the PGSE (2.2) and the pulse duration δ is very small compared to the time delay between the start of the two pulses, in other words, $\delta \ll \Delta$. One of the purposes of this article is to specify in which sense the Kärger model can be seen as an approximation of the FPK model.

We first observe that

$$\lim_{\delta\to 0} \frac{1}{\delta} F_\delta(t) = F(t) = \begin{cases} 1 & 0 \le t \le \Delta, \\ 0 & t > \Delta. \end{cases}$$

The Kärger model can then be interpreted as a pointwise limit of the FPK model as $\delta \to 0$. However, the convergence is not uniform since,

$$\sup_{t\in[0,\Delta+\delta]} \left| \frac{1}{\delta} F_\delta(t) - F(t) \right| \underset{\delta\to 0}{\longrightarrow} 1.$$

This is why it is not guaranteed that the Kärger model provides an accurate approximation of FPK as $\delta \to 0$.

The main purpose of this article is to clarify what has been already observed by the numerical simulations (Li *et al.*, 2014): if we compute the total magnetization using the Kärger model

$$m^{\mathrm{KAR}}(t) := m_e^{\mathrm{KAR}}(t) + m_c^{\mathrm{KAR}}(t),$$

it is better to evaluate m^{KAR} at time $t = \Delta - \frac{\delta}{3}$ instead of $t = \Delta$ (the time delay between the pulses, as suggested in the original Kärger paper (Kärger, 1985)) or at $t = \Delta + \delta$ (at the end of the second pulse). In other words, $m^{\mathrm{KAR}}(\Delta - \delta/3)$ is closer to S^{FPK} than either $m^{\mathrm{KAR}}(\Delta)$ or $m^{\mathrm{KAR}}(\Delta + \delta)$. Certainly in the homogeneous case where there is only one compartment, it is easy to see that $m^{\mathrm{KAR}}(\Delta - \frac{\delta}{3})$ is exactly S^{FPK} (2.4). In the following we shall prove rigorously that evaluating m^{KAR} at $t = \Delta - \frac{\delta}{3}$ gives a much better approximation to S^{FPK} than evaluating it at the two natural alternatives: $t = \Delta$ or $t = \Delta + \delta$.

3. Convergence of the Kärger model to the FPK model

In this section we analyze the convergence of $m^{\mathrm{KAR}}(\Delta - \delta/3)$, $m^{\mathrm{KAR}}(\Delta)$ and $m^{\mathrm{KAR}}(\Delta + \delta)$, respectively, to S^{FPK}. For this purpose we introduce a dimensionless parameter

$$\zeta = \frac{\delta}{\Delta}$$

that goes to zero under the narrow pulse assumption ($\delta \ll \Delta$). Moreover, we shall consider the general case of N different compartments, with $N \ge 2$. In order to do the analysis for time-dimensioneless coefficients we also make the change of variables

$$t \to \frac{t}{\Delta}, \qquad q \to q\Delta, \qquad \sigma_\ell \to \sigma_\ell \Delta \qquad \text{and} \qquad \eta_\ell \to \eta_\ell \Delta \quad \ell = 1, \cdots N. \tag{3.1}$$

Downloaded from http://imamat.oxfordjournals.org/ at University of Lethbridge on August 25, 2016

We rewrite the models for N compartments in matrix notation as

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}t} M^{\mathrm{KAR}}(t) + q^2 \zeta^2 \boldsymbol{\sigma} M^{\mathrm{KAR}}(t) + \boldsymbol{\eta} M^{\mathrm{KAR}}(t) = 0 \qquad t \geq 0, \\ M^{\mathrm{KAR}}(0) = M_0 \in \mathbb{R}^N \end{cases} \tag{3.2}$$

for the Kärger model and

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}t} M^{\mathrm{FPK}}(t) + q^2 F_\zeta^2(t) \boldsymbol{\sigma} M^{\mathrm{FPK}}(t) + \boldsymbol{\eta} M^{\mathrm{FPK}}(t) = 0 \qquad t \geq 0, \\ M^{\mathrm{FPK}}(0) = M_0 \in \mathbb{R}^N, \end{cases} \tag{3.3}$$

for FPK model, where

$$F_\zeta(t) \quad := \quad \begin{cases} t & \text{if } 0 < t \leq \zeta \\ \zeta & \text{if } \zeta < t \leq 1 \\ 1 + \zeta - t & \text{if } 1 < t \leq 1 + \zeta \\ 0 & \text{elsewhere} \end{cases} \quad \left(= \quad \frac{1}{\Delta} F_\delta(\Delta t) \right),$$

$$M^{\mathrm{KAR}}(t) := \begin{pmatrix} m_1^{\mathrm{KAR}}(t) \\ \vdots \\ m_N^{\mathrm{KAR}}(t) \end{pmatrix}, \quad M^{\mathrm{FPK}}(t) := \begin{pmatrix} m_1^{\mathrm{FPK}}(t) \\ \vdots \\ m_N^{\mathrm{FPK}}(t) \end{pmatrix}, \quad M_0 := \begin{pmatrix} m_0^1 \\ \vdots \\ m_0^N \end{pmatrix},$$

and $\boldsymbol{\sigma}$ and $\boldsymbol{\eta}$ are matrices with dimension $N \times N$. We define the total magnetization at time t by

$$m^{\mathrm{KAR}}(t) := \sum_{n=1}^{N} m_n^{\mathrm{KAR}}(t) \quad \text{and} \quad m^{\mathrm{FPK}}(t) := \sum_{n=1}^{N} m_n^{\mathrm{FPK}}(t). \tag{3.4}$$

To enforce mass conservation, we impose the condition that the sum of the entries of $\boldsymbol{\eta}$ is zero for each column, i.e.

$$\sum_{n=1}^{N} \boldsymbol{\eta}_{nj} = 0 \qquad \forall j = 1, \ldots, N. \tag{3.5}$$

For the two compartments models (2.1) and (2.6) $N = 2$ and

$$\boldsymbol{\sigma} = \frac{1}{\Delta} \begin{pmatrix} \sigma_e & 0 \\ 0 & \sigma_c \end{pmatrix} \qquad \text{and} \qquad \boldsymbol{\eta} = \frac{1}{\Delta} \begin{pmatrix} \eta_e & -\eta_c \\ -\eta_e & \eta_c \end{pmatrix}.$$

We observe in particular that assumption (3.5) is satisfied in this case.

Downloaded from http://imamat.oxfordjournals.org/ at University of Lethbridge on August 25, 2016

3.1. *Asymptotic expansion in ζ*

In order to compare the total magnetizations coming from the solutions of (3.2) and (3.3) we expand $M^{\mathrm{KAR}}(t)$ and $M^{\mathrm{FPK}}(t)$ using asymptotic expansions with respect to ζ. More precisely we shall prove that

$$M^{\mathrm{KAR}}(t) = \sum_{i=1}^{\infty} \zeta^i M_i^{\mathrm{KAR}}(t) \quad t \geq 0 \tag{3.6}$$

and

$$\begin{cases} M^{\mathrm{FPK}}(t) = \displaystyle\sum_{i=1}^{\infty} \zeta^i M_i^{\mathrm{F}-}\big(t/\zeta\big) & 0 \leq t \leq \zeta \\ M^{\mathrm{FPK}}(t) = \displaystyle\sum_{i=1}^{\infty} \zeta^i M_i^{\mathrm{F}}\big(t\big) & \zeta \leq t \leq 1 \\ M^{\mathrm{FPK}}(t) = \displaystyle\sum_{i=1}^{\infty} \zeta^i M_i^{\mathrm{F}+}\big((t-1)/\zeta\big) & 1 \leq t \leq 1+\zeta, \end{cases} \tag{3.7}$$

where M_i^{KAR}, $M_i^{\mathrm{F}-}$, M_i^{F} and $M_i^{\mathrm{F}+}$ are functions independent of ζ and the series converge with respect to the C^0 norm on any bounded interval.

The aim of such expansions is to facilitate the comparison between the magnetizations in terms of ζ. To simplify the analysis we make the change of variables

$$\tilde{M}^{\mathrm{KAR}}(t) = \mathrm{e}^{\eta t} M^{\mathrm{KAR}}(t) \quad \text{and} \quad \tilde{M}^{\mathrm{FPK}}(t) = \mathrm{e}^{\eta t} M^{\mathrm{FPK}}(t)$$

in problems (3.2) and (3.3) to obtain

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}t}\tilde{M}^{\mathrm{KAR}}(t) + q^2\zeta^2 \mathrm{e}^{\eta t}\boldsymbol{\sigma}\mathrm{e}^{-\eta t}\tilde{M}^{\mathrm{KAR}}(t) = 0 \qquad t \geq 0, \\ \tilde{M}^{\mathrm{KAR}}(0) = M_0 \end{cases} \tag{3.8}$$

and

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}t}\tilde{M}^{\mathrm{FPK}}(t) + q^2 F_\zeta^2(t)\mathrm{e}^{\eta t}\boldsymbol{\sigma}\mathrm{e}^{-\eta t}\tilde{M}^{\mathrm{FPK}}(t) = 0 \qquad t \geq 0, \\ \tilde{M}^{\mathrm{FPK}}(0) = M_0. \end{cases} \tag{3.9}$$

For the Kärger model (3.8) we observe that we can write the solution as

$$\tilde{M}^{\mathrm{KAR}}(t) = \mathrm{e}^{t\eta} \exp\left(-t\left(q^2\zeta^2\boldsymbol{\sigma} + \boldsymbol{\eta}\right)\right) M_0.$$

One can expand the exponential term using the Taylor series as

$$\exp\left(-t\left(q^2\zeta^2\boldsymbol{\sigma} + \boldsymbol{\eta}\right)\right) = 1 + \sum_{h=1}^{\infty} \frac{\left(-t\left(q^2\zeta^2\boldsymbol{\sigma} + \boldsymbol{\eta}\right)\right)^h}{h!}$$

Downloaded from http://imamat.oxfordjournals.org/ at University of Lethbridge on August 25, 2016

It is then clear that $\tilde{M}^{\mathrm{KAR}}$, and therefore M^{KAR}, can be expanded as in (3.6). For the FPK model, we define

$$\begin{cases} \tilde{M}^{\mathrm{F}-}(\tau) := \tilde{M}^{\mathrm{FPK}}(t) & \tau = \frac{t}{\zeta} \quad \text{for } t \in [0, \zeta], \\ \tilde{M}^{\mathrm{F}}(t) := \tilde{M}^{\mathrm{FPK}}(t) & \text{for } t \in [\zeta, 1], \\ \tilde{M}^{\mathrm{F}+}(\tilde{\tau}) := \tilde{M}^{\mathrm{FPK}}(t) & \text{and} \quad \tilde{\tau} = \frac{t-1}{\zeta} \quad \text{for } t \in [1, 1+\zeta]. \end{cases}$$

We then can rewrite (3.9) as

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}\tau}\zeta^{-1}\tilde{M}^{\mathrm{F}-}(\tau) + q^2\zeta^2\tau^2 \mathrm{e}^{\eta\zeta\tau}\boldsymbol{\sigma}\mathrm{e}^{-\eta\zeta\tau}\tilde{M}^{\mathrm{F}-}(\tau) = 0 & \tau \in [0,1] \\ \tilde{M}^{\mathrm{F}-}(0) = M_0 & \\ \dfrac{\mathrm{d}}{\mathrm{d}t}\tilde{M}^{\mathrm{F}}(t) + q^2\zeta^2 \mathrm{e}^{\eta t}\boldsymbol{\sigma}\mathrm{e}^{-\eta t}\tilde{M}^{\mathrm{F}}(t) = 0 & t \in [\zeta, 1] \\ \tilde{M}^{\mathrm{F}}(\zeta) = \tilde{M}^{\mathrm{F}-}(1) & \\ \dfrac{\mathrm{d}}{\mathrm{d}\tilde{\tau}}\zeta^{-1}\tilde{M}^{\mathrm{F}+}(\tau) + q^2\zeta^2(1-\tilde{\tau})^2 \mathrm{e}^{\eta\zeta(1-\tilde{\tau})}\boldsymbol{\sigma}\mathrm{e}^{-\eta\zeta(1-\tilde{\tau})}\tilde{M}^{\mathrm{F}+}(\tilde{\tau}) = 0 & \tilde{\tau} \in [0,1] \\ \tilde{M}^{\mathrm{F}+}(0) = \tilde{M}^{\mathrm{F}}(1) & \end{cases}.$$

For $\tau \in [0, 1]$, we observe that

$$\tilde{M}^{\mathrm{F}-}(\tau) = M_0 + \zeta^3 \int_0^\tau q^2 z^2 \mathrm{e}^{\eta\zeta z}\boldsymbol{\sigma}\mathrm{e}^{-\eta\zeta z}\tilde{M}^{\mathrm{F}-}(z)\mathrm{d}z,$$

which first proves that, for ζ sufficiently small, $\tilde{M}^{\mathrm{F}-}(\tau) = M_0 + O(\zeta^3)$ uniformly for $\tau \in [0, 1]$. This allows us to prove by induction the first asymptotic expansion in (3.7) by adding and substracting (at step k of the induction) the truncated asymptotic expansion (at step $k-1$ of the induction) inside the integral and expanding the exponential function in power series with respect to $\boldsymbol{\eta}\zeta z$.

For $t \in [\zeta, 1]$ it is convenient to extend $\tilde{M}^{\mathrm{F}}$ to a function defined on $[0, 1]$ such that it verifies

$$\frac{\mathrm{d}}{\mathrm{d}t}\tilde{M}^{\mathrm{F}}(t) + q^2\zeta^2 \mathrm{e}^{\eta t}\boldsymbol{\sigma}\mathrm{e}^{-\eta t}\tilde{M}^{\mathrm{F}}(t) = 0 \quad t \in [0,1]$$

and using the Taylor expansion replace the initial condition $\tilde{M}^{\mathrm{F}}(\zeta) = \tilde{M}^{\mathrm{F}-}(1)$ with

$$\tilde{M}^{\mathrm{F}}(0) = \tilde{M}^{\mathrm{F}-}(1) - \sum_{i=1}^{\infty} \frac{\zeta^i}{i!}\frac{\mathrm{d}^i}{\mathrm{d}t^i}\tilde{M}^{\mathrm{F}}(0).$$

Similarly as for the Kärger model, we have that the analytic solution is given by

$$\tilde{M}^{\mathrm{F}}(t) = \mathrm{e}^{t\boldsymbol{\eta}} \exp\left(-t\left(q^2\zeta^2\boldsymbol{\sigma} + \boldsymbol{\eta}\right)\right)\tilde{M}^{\mathrm{F}}(0).$$

Downloaded from http://imamat.oxfordjournals.org/ at University of Lethbridge on August 25, 2016

The second part of (3.7) then follows from the fact that $\tilde{M}^{\mathrm{F}-}(1)$ (and therefore $\tilde{M}^{\mathrm{F}}(0)$) can be expanded as a convergent power series in terms of ζ. Finally for $\tilde{\tau} \in [0,1]$ we make similar arguments as for $\tilde{M}^{\mathrm{F}-}(\tau)$, by writing

$$\tilde{M}^{\mathrm{F}+}(\tilde{\tau}) = \tilde{M}^{\mathrm{F}}(1) + \zeta^3 \int_0^{\tau} q^2(1-z)^2 \mathrm{e}^{\eta\zeta(1-z)} \boldsymbol{\sigma}\, \mathrm{e}^{-\eta\zeta(1-z)} \tilde{M}^{\mathrm{F}+}(z)\mathrm{d}z$$

and using the expansion in terms of ζ of $\tilde{M}^{\mathrm{F}}(1)$ to initiate an induction argument (following the same lines as for $\tilde{M}^{\mathrm{F}-}$).

3.2. *Error estimates*

The goal of this section is to prove that

$$m^{\mathrm{KAR}}\left(1-\tfrac{\zeta}{3}\right) - m^{\mathrm{FPK}}(1+\zeta) = O(\zeta^6).$$

We remark that this convergence holds only for the sum of the magnetizations m and not for each of the compartment magnetizations. In fact one only has $M^{\mathrm{KAR}}\left(1-\frac{\zeta}{3}\right) - M^{\mathrm{FPK}}(1+\zeta) = O(\zeta)$. For arbitrary $\boldsymbol{\sigma}$, the convergence result does not hold for a general choice of the initial data M_0 but only for those such that

$$\boldsymbol{\eta} M_0 = 0. \tag{3.10}$$

This condition is indeed verified for dMRI applications where the components of M_0 are the volume fractions of the compartments. We observe that as a direct consequence of (3.5) and (3.10) we have the following identities.

LEMMA 3.1 Let $\boldsymbol{\eta}$ satisfy (3.5) and $M_0 \in \mathbb{R}^N$ such that $\boldsymbol{\eta} M_0 = \mathbf{0}$. Then for all $\boldsymbol{\alpha} \in \mathbb{R}^{N\times N}$, the following properties are satisfied

$$\sum_{n=1}^{N} (\boldsymbol{\eta}^h \boldsymbol{\alpha} M_0)_n = \sum_{n=1}^{N} (\boldsymbol{\alpha}\boldsymbol{\eta}^h M_0)_n = 0 \quad \text{for all } h \in \mathbb{N}, h \geq 1; \tag{3.11}$$

$$\sum_{n=1}^{N} (\boldsymbol{\alpha} e^{-\boldsymbol{\eta}} M_0)_n = \sum_{n=1}^{N} (\boldsymbol{\alpha} M_0)_n \quad \text{and} \quad \sum_{n=1}^{N} (\boldsymbol{\alpha}\boldsymbol{\eta} e^{-\boldsymbol{\eta}} M_0)_n = 0. \tag{3.12}$$

The proof is staightforward.

We now state and prove the main theorem of this section.

THEOREM 3.1 Under the hypothesis of Lemma 3.1 there exists two constant $C_{\boldsymbol{\sigma},\boldsymbol{\eta},M_0} > 0$ and ζ_0 that only depends on $\boldsymbol{\sigma}$, $\boldsymbol{\eta}$ and M_0 such that, for all $0 \leq \zeta \leq \zeta_0$,

$$\left| m^{\mathrm{KAR}}\left(1-\tfrac{\zeta}{3}\right) - m^{\mathrm{FPK}}(1+\zeta) \right| \leq C_{\boldsymbol{\sigma},\boldsymbol{\eta},M_0}\, q^4 \zeta^6,$$

Downloaded from http://imamat.oxfordjournals.org/ at University of Lethbridge on August 25, 2016

where

$$C_{\sigma,\eta,M_0} := \sum_{n=1}^{N} \frac{2}{9}\left(\sigma^2 M_0\right)_n - \frac{5}{36}\int_0^1 \left(\sigma\eta e^{\eta(s-1)\sigma M_0}\right)_n ds + \left(\frac{2}{9}\sigma e^{-\eta}\sigma M_0\right)_n + \left(\frac{1}{4}\sigma\eta\sigma M_0\right)_n.$$

Proof. The proof relies on the expansions (3.6) and(3.7) and the explicit expressions of the terms of these expansions. In order to compute these terms, we found it easier to follow another route than the one used for proving the existence of these expansions. More precisely we shall first identify the set of differential equations satisfied by these terms by inserting the asymptotic expansions into the differential equations then match the terms in front of the same power of ζ. We then solve (inductively) these equations to obtain the desired explicit expressions of the expansions in terms of the data. In the case of the Kärger model, inserting expansion (3.6) in (3.2) we obtain the following problems for $i \geq 0$

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}t} M_i^{\mathrm{KAR}}(t) + q^2\sigma M_{i-2}^{\mathrm{KAR}}(t) + \eta M_i^{\mathrm{KAR}}(t) = 0 \\ M_0^{\mathrm{KAR}}(0) = M_0 \text{ and } M_i^{\mathrm{KAR}}(0) = 0 \text{ for } i \geq 1, \end{cases} \tag{3.13}$$

where we used the convention that the terms with a negative index are 0. Then one easily verifies that $M_{2i+1}^{\mathrm{KAR}}(t) = 0$ for all $i \geq 0$ and

$$M_0^{\mathrm{KAR}}(t) = e^{-\eta t} M_0, \quad M_2^{\mathrm{KAR}}(t) = -q^2 \int_0^t \left(e^{\eta(s-t)}\sigma M_0^{\mathrm{KAR}}(s)\right) \mathrm{d}s,$$

$$M_4^{\mathrm{KAR}}(t) = -q^2 \int_0^t \left(e^{\eta(s-t)}\sigma M_2^{\mathrm{KAR}}(s)\right) \mathrm{d}s \quad \text{and} \quad M_6^{\mathrm{KAR}}(t) = -q^2 \int_0^t \left(e^{\eta(s-t)}\sigma M_4^{\mathrm{KAR}}(s)\right) \mathrm{d}s.$$

For a vector $V \in \mathbb{R}^N$ we denote $\overline{V} := \sum_{n=1}^{N} V_n$. Using Taylor's expansion we obtain

$$m^{\mathrm{KAR}}\left(1-\frac{\zeta}{3}\right) = \sum_{i=0}^{\infty} \zeta^i \overline{M_i^{\mathrm{KAR}}}\left(1-\frac{\zeta}{3}\right) = \sum_{i=1}^{\infty} \zeta^i \left(\overline{M_i^{\mathrm{KAR}}}(1) + \sum_{h=1}^{i} \frac{1}{(-3)^h (h!)} \frac{\mathrm{d}^h}{\mathrm{d}t^h} \overline{M_{i-h}^{\mathrm{KAR}}}(t)|_{t=1}\right).$$

Therefore,

$$\begin{aligned} m^{\mathrm{KAR}}\left(1-\frac{\zeta}{3}\right) = {} & \overline{M_0^{\mathrm{KAR}}}(1) + \zeta^2 \overline{M_2^{\mathrm{KAR}}}(1) - \frac{\zeta^3}{3}\left(\frac{\mathrm{d}}{\mathrm{d}t}\overline{M_2^{\mathrm{KAR}}}(1)\right) + \zeta^4 \overline{M_4^{\mathrm{KAR}}}(1) \\ & - \frac{\zeta^5}{3}\left(\frac{\mathrm{d}}{\mathrm{d}t}\overline{M_4^{\mathrm{KAR}}}(1)\right) + \zeta^5 \left(\overline{M_6^{\mathrm{KAR}}}(1) + \frac{1}{18}\frac{d^2}{dt^2}\overline{M_4^{\mathrm{KAR}}}(1)\right) + O(\zeta^7). \end{aligned}$$

Using the analytic expression of the solutions and properties (3.5), (3.10) and (3.12) we finally obtain

$$\begin{aligned} m^{\mathrm{KAR}}\left(1-\frac{\zeta}{3}\right) = {} & \overline{M_0} - \zeta^2 q^2 \overline{\sigma M_0} + \zeta^3 \frac{q^2}{3}\overline{\sigma M_0} \\ & - \zeta^4 q^4 \int_0^1 \int_0^s \left(\overline{e^{\eta(s-1)}\sigma e^{\eta(t-s)}\sigma M_0}\right) \mathrm{d}t\mathrm{d}s - \zeta^5 \frac{q^4}{3}\int_0^1 \left(\overline{\sigma e^{\eta(s-1)}\sigma M_0}\right) \mathrm{d}s \end{aligned}$$

Downloaded from http://imamat.oxfordjournals.org/ at University of Lethbridge on August 25, 2016

$$+\zeta^6\left[q^6\int_0^1\left(\overline{\mathrm{e}^{\eta(s-1)}\boldsymbol{\sigma}\int_0^s\left(\mathrm{e}^{\eta(z-s)}\boldsymbol{\sigma}\int_0^t\left(\mathrm{e}^{\eta(z-t)}\boldsymbol{\sigma}M_0\right)\mathrm{d}t\right)\mathrm{d}z}\right)\mathrm{d}s\right.$$
$$\left.+\frac{q^4}{18}\left(\overline{\boldsymbol{\sigma}^2M_0}-\int_0^1\left(\overline{\boldsymbol{\sigma}\boldsymbol{\eta}\mathrm{e}^{-\eta(s-1)}\boldsymbol{\sigma}M_0}\right)\mathrm{d}s\right)\right]+O(\zeta^7).$$

To get the analytic expansion of the signal given by the FPK model in terms of ζ we have already observed that it is convenient to split the time interval in three different parts in which the F_ζ has different expressions and to extend the one in the middle as a function in the time interval $[0,1]$. We then rewrite the problem (3.3) as

$$\begin{cases}\dfrac{\mathrm{d}}{\mathrm{d}\tau}\zeta^{-1}M^{\mathrm{F}-}(\tau)+q^2\zeta^2\tau^2\boldsymbol{\sigma}M^{\mathrm{F}-}(\tau)+\boldsymbol{\eta}M^{\mathrm{F}-}(\tau)=0 & \tau\in[0,1],\\ M^{\mathrm{F}-}(0)=M_0,\\ \dfrac{\mathrm{d}}{\mathrm{d}t}M^{\mathrm{F}}(t)+q^2\zeta^2\boldsymbol{\sigma}M^{\mathrm{F}}(t)+\boldsymbol{\eta}M^{\mathrm{F}}(t)=0 & t\in[0,1],\\ M^{\mathrm{F}}(0)=M^{\mathrm{F}-}(1)-\displaystyle\sum_{i=1}^{\infty}\frac{\zeta^i}{i!}\frac{\mathrm{d}^i}{\mathrm{d}t^i}M^{\mathrm{F}}(0),\\ \dfrac{\mathrm{d}}{\mathrm{d}\tilde{\tau}}\zeta^{-1}M^{\mathrm{F}+}(\tilde{\tau})+q^2\zeta^2(1-\tilde{\tau})^2\boldsymbol{\sigma}M^{\mathrm{F}+}(\tilde{\tau})+\boldsymbol{\eta}M^{\mathrm{F}+}(\tilde{\tau})=0 & \tilde{\tau}\in[0,1],\\ M^{\mathrm{F}+}(0)=M^{\mathrm{F}}(1).\end{cases}\tag{3.14}$$

Inserting the expansion (3.7) in (3.14) and equating the same powers of ζ yields for $i\geq 0$

$$\begin{cases}\dfrac{\mathrm{d}}{\mathrm{d}\tau}M_i^{\mathrm{F}-}(\tau)+q^2\tau^2\boldsymbol{\sigma}M_{i-3}^{\mathrm{F}-}(\tau)+\boldsymbol{\eta}M_{i-1}^{\mathrm{F}-}(\tau)=0,\\ M_0^{\mathrm{F}-}(0)=M_0 \text{ and } M_i^{\mathrm{F}-}(0)=0 \text{ for } i\geq 1,\end{cases}\tag{3.15}$$

$$\begin{cases}\dfrac{\mathrm{d}}{\mathrm{d}t}M_i^{\mathrm{F}}(t)+q^2\boldsymbol{\sigma}M_{i-2}^{\mathrm{F}}(t)+\boldsymbol{\eta}M_i^{\mathrm{F}}(t)=0,\\ M_i^{\mathrm{F}}(0)=M_i^{\mathrm{F}-}(1)-\displaystyle\sum_{h=1}^{i}\frac{1}{h!}\frac{\mathrm{d}^h}{\mathrm{d}t^h}M_{i-h}^{\mathrm{F}}(t)|_{t=0},\end{cases}\tag{3.16}$$

$$\begin{cases}\dfrac{\mathrm{d}}{\mathrm{d}\tilde{\tau}}M_i^{\mathrm{F}+}(\tilde{\tau})+q^2(1-\tilde{\tau})^2\boldsymbol{\sigma}M_{i-3}^{\mathrm{F}+}(\tilde{\tau})+\boldsymbol{\eta}M_{i-1}^{\mathrm{F}+}(\tilde{\tau})=0,\\ M_i^{\mathrm{F}-}(0)=M_i^{\mathrm{F}}(1),\end{cases}\tag{3.17}$$

where we again use the convention that the terms with a negative index are 0. We hereafter shall not detail all the calculations (which are lengthy but not difficult) and restrict ourselves to the main steps and results. Since we are interested in the signal

$$m^{\mathrm{FPK}}(1+\zeta)=\overline{M^{\mathrm{F}+}}(1)=\sum_{i=0}^{\infty}\zeta^i\overline{M_i^{\mathrm{F}+}}\tag{3.18}$$

Downloaded from http://imamat.oxfordjournals.org/ at University of Lethbridge on August 25, 2016

we focus on evaluating $\overline{M_i^{\mathrm{F}+}}$. For $i = 0$, one straightforwardly gets

$$M_0^{\mathrm{F}-}(\tau) = M_0, \quad M_0^{\mathrm{F}}(t) = \mathrm{e}^{-\eta t} M_0 \text{ and } M_0^{\mathrm{F}+}(\tilde{\tau}) = \mathrm{e}^{-\eta} M_0,$$

which implies, using (3.12)

$$\overline{M_0^{\mathrm{F}+}}(1) = \overline{M_0}.$$

The solutions of (3.15)–(3.17) for $i = 1$ are

$$M_1^{\mathrm{F}-}(\tau) = -\tau \boldsymbol{\eta} M_0, \quad M_1^{\mathrm{F}}(t) = 0 \text{ and } M_1^{\mathrm{F}+}(\tilde{\tau}) = -\tilde{\tau} \boldsymbol{\eta}\, \mathrm{e}^{-\eta} M_0.$$

Using (3.12) one then gets

$$\overline{M_1^{\mathrm{F}+}}(1) = 0.$$

For $i = 2$ the solutions are

$$M_2^{\mathrm{F}-}(\tau) = \frac{\tau^2}{2} \boldsymbol{\eta}^2 M_0, \quad M_2^{\mathrm{F}}(t) = -q^2 \int_0^t \left(\mathrm{e}^{\boldsymbol{\eta}(s-t)} \boldsymbol{\sigma}\, \mathrm{e}^{-\eta s} M_0 \right) \mathrm{d}s,$$

$$M_2^{\mathrm{F}+}(\tilde{\tau}) = \frac{\tilde{\tau}^2}{2} (\boldsymbol{\eta}^2 \mathrm{e}^{-\eta} M_0) + M_2^{\mathrm{F}}(1).$$

Then, using (3.11) and (3.12), one gets

$$\overline{M_2^{\mathrm{F}+}}(1) = -q^2 \overline{\boldsymbol{\sigma} M_0}.$$

For $i = 3$ one obtains

$$M_3^{\mathrm{F}-}(\tau) = -\frac{q^2}{3} \tau^3 \boldsymbol{\sigma} M_0 - \frac{\tau^3}{6} \boldsymbol{\eta}^3 M_0, \quad M_3^{\mathrm{F}}(t) = \frac{2}{3} q^2 \mathrm{e}^{-\eta t} \boldsymbol{\sigma} M_0,$$

$$M_3^{\mathrm{F}+}(\tilde{\tau}) = \frac{q^2}{3} ((1-\tilde{\tau})^3 - 1) \boldsymbol{\sigma}\, \mathrm{e}^{-\eta} M_0 - \frac{\tilde{\tau}^3}{6} \boldsymbol{\eta}^3 \mathrm{e}^{-\eta} M_0 + \tilde{\tau} \boldsymbol{\eta} M_2^{\mathrm{F}}(1) + \frac{2}{3} q^2 \mathrm{e}^{-\eta} \boldsymbol{\sigma} M_0$$

Then, using (3.11) and (3.12) one gets

$$\overline{M_3^{\mathrm{F}+}}(1) = \frac{q^2}{3} \overline{\boldsymbol{\sigma} M_0}.$$

For $i = 4$ one has

$$M_4^{\mathrm{F}-}(\tau) = \frac{q^2}{4} \tau^4 \boldsymbol{\sigma} \boldsymbol{\eta} M_0 + \frac{q^2}{12} \tau^4 \boldsymbol{\eta} \boldsymbol{\sigma} M_0 + \frac{\tau^4}{24} \boldsymbol{\eta}^4 M_0,$$

$$M_4^{\mathrm{F}}(t) = -q^2 \int_0^t \left(\mathrm{e}^{\boldsymbol{\eta}(s-t)} \boldsymbol{\sigma} M_2^{\mathrm{F}}(s) \right) \mathrm{d}s - \frac{q^2}{4} (\boldsymbol{\sigma} \boldsymbol{\eta} M_0 - \boldsymbol{\eta} \boldsymbol{\sigma} M_0),$$

$$M_4^{\mathrm{F}+}(\tilde{\tau}) = q^2 \frac{\tilde{\tau}^2}{12} \left(3\tilde{\tau}^2 - 8\tilde{\tau} + 6 \right) \boldsymbol{\sigma} \boldsymbol{\eta} \mathrm{e}^{-\eta} M_0 - \int_0^{\tilde{\tau}} \boldsymbol{\eta} M_3^{\mathrm{F}+}(s) \mathrm{d}s + M_4^{\mathrm{F}}(1)$$

Downloaded from http://imamat.oxfordjournals.org/ at University of Lethbridge on August 25, 2016

and using again (3.11) and (3.12),

$$\overline{M_4^{\mathrm{F}+}}(1) = -q^4 \int_0^1 \int_0^s \left(\overline{\mathrm{e}^{\eta(s-1)}\boldsymbol{\sigma}\mathrm{e}^{\eta(t-s)}\boldsymbol{\sigma}M_0}\right) \mathrm{d}t\mathrm{d}s.$$

For $i = 5$ to find the solutions in the last two time intervals it is better to first take the sum of the equations in order to directly cancel the terms that are right multiplied by $\boldsymbol{\eta}$. One then gets

$$\begin{aligned}
M_5^{\mathrm{F}-}(\tau) &= -\frac{q^2}{10}\tau^5\boldsymbol{\sigma}\boldsymbol{\eta}^2M_0 - \frac{q^2}{20}\tau^5\boldsymbol{\eta}\boldsymbol{\sigma}\boldsymbol{\eta}M_0 - \frac{q^2}{60}\tau^5\boldsymbol{\eta}^2\boldsymbol{\sigma}M_0 - \frac{\tau^5}{120}\boldsymbol{\eta}^5M_0,\\
\overline{M_5^{\mathrm{F}}}(t) &= -\frac{2}{3}q^4\int_0^t (\overline{\boldsymbol{\sigma}\mathrm{e}^{-\eta s}\boldsymbol{\sigma}M_0})\,\mathrm{d}s,\\
\overline{M_5^{\mathrm{F}+}}(\tilde{\tau}) &= \frac{q^4}{3}((1-\tilde{\tau})^3 - 1)\int_0^1 \overline{\boldsymbol{\sigma}\mathrm{e}^{\eta(s-1)}\boldsymbol{\sigma}\mathrm{e}^{-\eta s}M_0}\,\mathrm{d}s + \overline{M_5^{\mathrm{F}}(1)}.
\end{aligned}$$

Consequently, using a change of variable and the property (3.12) in order to simplify the first integral, one ends up with

$$\overline{M_5^{\mathrm{F}+}}(1) = \frac{q^4}{3}\int_0^1 \overline{\boldsymbol{\sigma}\mathrm{e}^{\eta(s-1)}\boldsymbol{\sigma}\mathrm{e}^{-\eta s}M_0}\,\mathrm{d}s - \frac{2}{3}q^4\int_0^1 \overline{\boldsymbol{\sigma}\mathrm{e}^{-\eta s}\boldsymbol{\sigma}M_0}\mathrm{d}s = -\frac{1}{3}q^4\int_0^1 \overline{\boldsymbol{\sigma}\mathrm{e}^{-\eta s}\boldsymbol{\sigma}M_0}\mathrm{d}s.$$

Finally for $i = 6$ it is again better to first take the sum of the equations in order to directly cancel the terms that are right multiplied by $\boldsymbol{\eta}$ in the last two intervals. One then gets

$$\begin{aligned}
M_6^{\mathrm{F}-}(\tau) = {} & \frac{q^4}{18}\tau^6\boldsymbol{\sigma}^2M_0 + \frac{q^2}{36}\tau^6\boldsymbol{\sigma}\eta^3M_0 + \frac{q^2}{60}\tau^6\boldsymbol{\eta}\boldsymbol{\sigma}\boldsymbol{\eta}^2M_0 + \frac{q^2}{120}\tau^6\boldsymbol{\eta}^2\boldsymbol{\sigma}\boldsymbol{\eta}M_0\\
& + \frac{q^2}{360}\tau^6\boldsymbol{\eta}^3\boldsymbol{\sigma}M_0 + \frac{\tau^6}{720}\boldsymbol{\eta}^6M_0\\
\overline{M_6^{\mathrm{F}}}(t) = {} & -q^2\int_0^{\tilde{t}} \overline{\mathrm{e}^{\eta(s-\tilde{t})}\boldsymbol{\sigma}M_5^{\mathrm{F}}(s)}\mathrm{d}s + \frac{2}{9}\overline{\boldsymbol{\sigma}^2M_0}\\
\overline{M_6^{\mathrm{F}+}}(\tilde{\tau}) = {} & \frac{q^4}{18}\tilde{\tau}^2(\tilde{\tau}^2 - 3\tilde{\tau} + 3)^2\overline{\boldsymbol{\sigma}^2M_0} + \frac{q^4}{12}\tilde{\tau}^2(3\tilde{\tau}^2 - 8\tilde{\tau} + 6)\int_0^1 \overline{\boldsymbol{\sigma}\mathrm{e}^{\eta(s-1)}\boldsymbol{\sigma}M_0}\\
& - \frac{2}{9}q^4\tilde{\tau}(\tilde{\tau}^2 - 3\tilde{\tau} + 3)\overline{\boldsymbol{\sigma}\mathrm{e}^{-\eta}\boldsymbol{\sigma}M_0} + \overline{M_6^{\mathrm{F}}}(1)
\end{aligned}$$

and using again (3.11) and (3.12):

$$\overline{M_6^{\mathrm{F}+}}(1) = \frac{5q^4}{18}\overline{\boldsymbol{\sigma}^2M_0} + \frac{q^4}{12}\int_0^1 \overline{\boldsymbol{\sigma}\mathrm{e}^{\eta(s-1)}\boldsymbol{\sigma}M_0}\mathrm{d}s - \frac{2}{9}q^4\overline{\boldsymbol{\sigma}\mathrm{e}^{-\eta}\boldsymbol{\sigma}M_0} - q^2\int_0^1 \overline{\mathrm{e}^{\eta(s-1)}\boldsymbol{\sigma}M_4^{\mathrm{F}}(s)}\mathrm{d}s.$$

We thus have proved that $m^{\mathrm{FPK}}(1+\zeta)$ has the same asymptotic expansion as $m^{\mathrm{KAR}}(1-\frac{\zeta}{3})$ up to but not including $O(\zeta^6)$ terms, which yields the claim of our theorem. □

REMARK 3.2 We remark that, for $i = 1, \ldots, 5$, the magnetizations M_i^{FPK} are different from M_i^{KAR}.

Downloaded from http://imamat.oxfordjournals.org/ at University of Lethbridge on August 25, 2016

THEOREM 3.3 Under the hypothesis of theorem 3.1 we have that

$$m^{\mathrm{KAR}}(1) - m^{\mathrm{FPK}}(1+\zeta) = O(\zeta^3)$$

and

$$m^{\mathrm{KAR}}(1+\zeta) - m^{\mathrm{FPK}}(1+\zeta) = O(\zeta^3).$$

Proof. With the previous theorem we have proved that

$$m^{\mathrm{KAR}}(1-\zeta/3) - m^{\mathrm{FPK}}(1+\zeta) = O(\zeta^6).$$

Following a similar approach it can be also easily shown that if we evaluate the Kärger model at $t = 1$ or $t = 1 + \zeta$ the order of convergence drops to $O(\zeta^3)$ because the constants of the expansions in front of ζ^3 become different. □

4. Numerical results

We provide numerical validation of our results of the previous section using a two compartments example. The parameters of the FPK and Kärger models come from a simple tissue geometry consisting of cylindrical biological cells, with the diffusion-encoding direction being transverse to the cylinder axes.

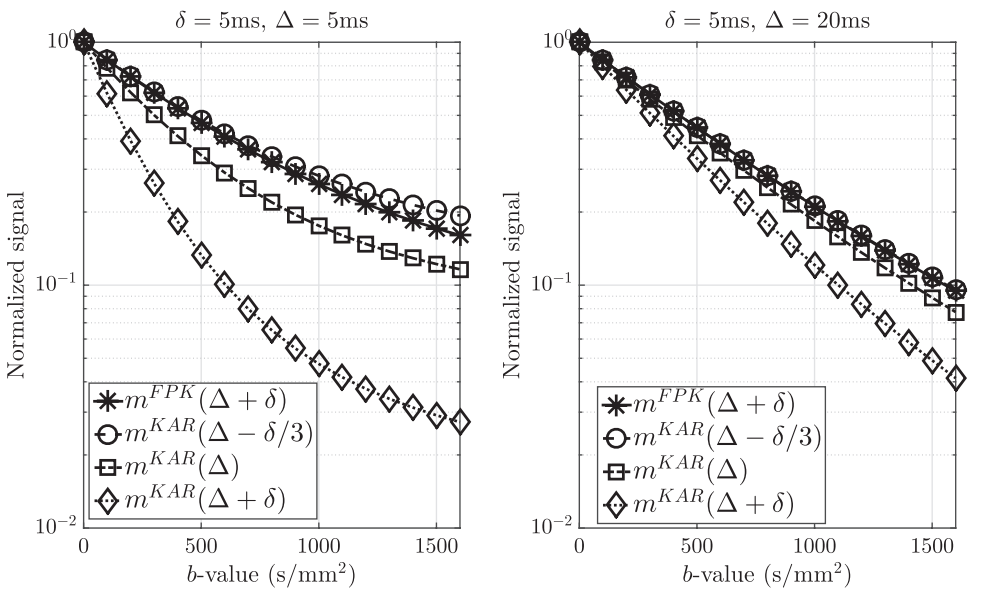

FIG. 2. dMRI signals given by FPK model and by the Kärger model at three different evaluation times, $\delta = 5$ ms, left: $\Delta = 5$ ms, right: $\Delta = 20$ ms, for various b values.

Downloaded from http://imamat.oxfordjournals.org/ at University of Lethbridge on August 25, 2016

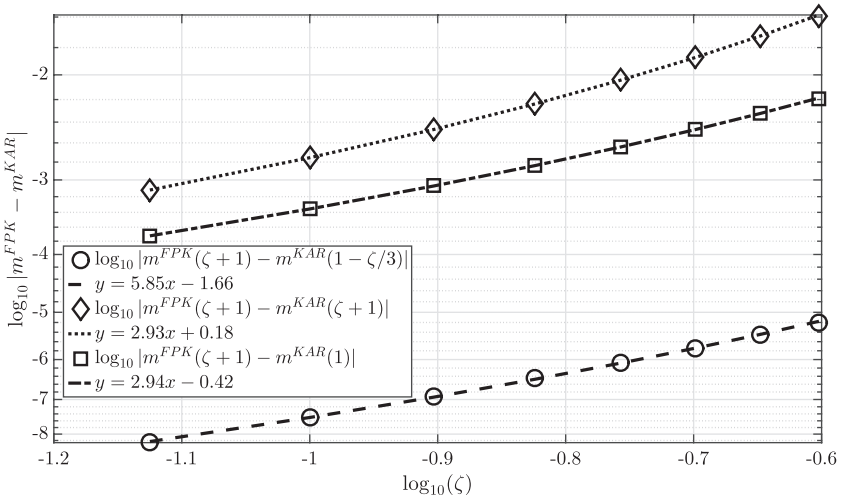

FIG. 3. The convergence of $m^{KAR}(\Delta-\delta/3)$, $m^{KAR}(\Delta+\delta)$ and $m^{KAR}(\Delta)$ to S^{FPK} as $\zeta=\delta/\Delta$ goes to 0. $q=1\times10^{-5}\mu\text{m}^{-1}\text{ms}^{-1}$, $\Delta=20$ ms, for various $\delta\in[1.5,5]$ ms.

The first compartment is the cylindrical cells compartment and the second compartment is the extracellular space. For details on how to obtain FPK and Kärger model parameters using homogenization, we refer to reader to Coatléven *et al.* (2014). Here, we only give the values of these parameters:

$$\sigma_e=1.7\times10^{-3}\text{mm}^2/\text{s},\ \sigma_c=0\text{mm}^2/\text{s},\ \kappa=5\times10^{-5}\text{m/s},$$
$$\theta_e=0.72,\ |\Gamma|=1.8842\,\mu\text{m}^2,\ \eta_e=1.3\times10^{-1}\text{ms}^{-1},\ \eta_c=3.34\times10^{-1}\text{ms}^{-1}.$$

We compute the dMRI signal of the FPK model and the total magnetization of the Kärger model evaluated at three different times: $t=\Delta$, $t=\Delta+\delta$ and $t=\Delta-\delta/3$, for several b values (defined in (2.5)). In Fig. 2 we see that for both $\Delta=5$ ms and $\Delta=20$ ms the Kärger signal evaluated at $t=\Delta-\frac{\delta}{3}$ is much closer to S^{FPK} over the entire range of the b values than the other two choices.

Next we verify numerically the order of convergence with respect to the dimensionless parameter $\zeta=\delta/\Delta$. We fix $\Delta=20$ ms and vary δ in the interval [1.5, 5]ms. In Fig. 3 we see that $m^{\text{KAR}}(\Delta-\delta/3)$ converges to S^{FPK} with order 6, whereas $m^{\text{KAR}}(\Delta+\delta)$ and $m^{\text{KAR}}(\Delta)$ converge to S^{FPK} with order 3.

Conclusion

By expanding the solutions of the Kärger and the FPK models we showed that in the case of finite pulses (when the duration of the gradient pulses is not short compared to the delay between the start of the pulses) the time at which to evaluate the Kärger model should be the time delay between the start of the pulses, shortened by one third of the pulse duration. We showed that with this choice, the convergence of the Kärger model to the FPK model is of order six in the pulse duration. This result helps to clarify the longstanding question of how to adapt the Kärger model to account for finite diffusion-encoding pulse sequences.

Downloaded from http://imamat.oxfordjournals.org/ at University of Lethbridge on August 25, 2016

References

Åslund, I., Nowacka, A., Nilsson, M. & Topgaard, D. (2009) Filter-exchange PGSE NMR determination of cell membrane permeability. *J. Magn. Reson.*, **200**, 291–295.

Coatléven, J., Haddar, H. & Li, J.-R. (2014) A macroscopic model including membrane exchange for diffusion MRI. *SIAM J. Appl. Math.*, **74**, 516–546.

Kärger, J. (1985) NMR self-diffusion studies in heterogeneous systems. *Adv. Colloid Interface Sci.*, **23**, 129–148.

Lazar, M. (2010) Mapping brain anatomical connectivity using white matter tractography. *NMR Biomed.*, **23**, 821–835.

Le Bihan, D., Breton, E., Lallemand, D., Grenier, P., Cabanis, E. & Laval-Jeantet, M. (1986) MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. *Radiology*, **161**, 401–407.

Le Bihan, D. & Johansen-Berg, H. (2012) Diffusion MRI at 25: exploring brain tissue structure and function. *NeuroImage*, **61**, 324–341.

LeBihan, D., Urayama, S.-i., Aso, T., Hanakawa, T. & Fukuyama, H. (2006) Direct and fast detection of neuronal activation in the human brain with diffusion MRI. *Proc. Natl. Acad. Sci USA*, **103**, 8263–8268.

Lee, J.-H. & Springer, C. S. (2003) Effects of equilibrium exchange on diffusion-weighted NMR signals: the diffusigraphic shutter-speed? *Magn. Reson. Med.*, **49**, 450–458.

Li, J.-R., Nguyen, H. T., Nguyen, D. V., Haddar, H., Coatléven, J. & Bihan, D. L. (2014) Numerical study of a macroscopic finite pulse model of the diffusion MRI signal. *J. Magn. Reson.*, **248**, 54–65.

Maier, S. E., Sun, Y. & Mulkern, R. V. (2010) Diffusion imaging of brain tumors. *NMR Biomed.*, **23**(7), 849–864.

Meier, C., Dreher, W. & Leibfritz, D. (2003) Diffusion in compartmental systems. I. A comparison of an analytical model with simulations. *Magn. Reson. Med.*, **50**, 500–509.

Moseley, M. E., Kucharczyk, J., Mintorovitch, J., Cohen, Y., Kurhanewicz, J., Derugin, N., Asgari, H. & Norman, D. (1990) Diffusion-weighted MR imaging of acute stroke: correlation with T2- weighted and magnetic susceptibility-enhanced MR imaging in cats. *AJNR Am. J. Neuroradiol.*, **11**, 423–429.

Nilsson, M., Latt, J., Nordh, E., Wirestam, R., Stahlberg, F. & Brockstedt, S. (2009) On the effects of a varied diffusion time in vivo: is the diffusion in white matter restricted? *Magn. Reson. Imaging*, **27**, 176–187.

Pfeuffer, J., Flogel, U., Dreher, W. & Leibfritz, D. (1998) Restricted diffusion and exchange of intracellular water: theoretical modelling and diffusion time dependence of 1H NMR measurements on perfused glial cells. *NMR Biomed.*, **11**, 19–31.

Quirk, J. D., Bretthorst, G. L., Duong, T. Q., Snyder, A. Z., Springer, C. S., Ackerman, J. J. H. & Neil, J. J. (2003) Equilibrium water exchange between the intra- and extracellular spaces of mammalian brain. *Magn. Reson. Med.*, **50**, 493–499.

Roth, Y., Ocherashvilli, A., Daniels, D., Ruizcabello, J., Maier, S., Orenstein, A. & Mardor, Y. (2008) Quantification of water compartmentation in cell suspensions by diffusion-weighted and T2-weighted MRI. *Magn. Reson. Imaging*, **26**, 88–102.

Stanisz, G. J., Wright, G. A., Henkelman, R. M. & Szafer, A. (1997) An analytical model of restricted diffusion in bovine optic nerve. *Magn. Reson. Med.*, **37**, 103–111.

Stejskal, E. O. & Tanner, J. E. (1965) Spin diffusion measurements: spin echoes in the presence of a time-dependent field gradient. *J. Chem. Phys.*, **42**, 288–292.

Sugahara, T., Korogi, Y., Kochi, M., Ikushima, I., Shigematu, Y., Hirai, T., Okuda, T., Liang, L., Ge, Y., Komohara, Y., Ushio, Y. & Takahashi, M. (1999) Usefulness of diffusion-weighted MRI with echo-planar technique in the evaluation of cellularity in gliomas. *J. Magn. Reson. Imaging*, **9**, 53–60.

Tsushima, Y., Takahashi-Taketomi, A. & Endo, K. (2009) Magnetic resonance (MR) differential diagnosis of breast tumors using apparent diffusion coefficient (ADC) on 1.5-T. *J. Magn. Reson. Imaging*, **30**, 249–255.

Waldeck, A., Kuchel, P. W., Lennon, A. J. & Chapman, B. E. (1997) NMR diffusion measurements to characterise membrane transport and solute binding. *Prog. Nucl. Magn. Reson. Spectro.*, **30**, 39–68.

Warach, S., Chien, D., Li, W., Ronthal, M. & Edelman, R. R. (1992) Fast magnetic resonance diffusion-weighted imaging of acute human stroke. *Neurology*, **42**, 1717–.

Downloaded from http://imamat.oxfordjournals.org/ at University of Lethbridge on August 25, 2016