Time-Efficient Fourier Domain Evaluation of Pharmacokinetic Model in Dynamic Contrast-Enhanced Magnetic Resonance Imaging

Michal Bartoš, Michal Šorel, and Radovan Jiřík

Abstract

Dynamic contrast-enhanced magnetic resonance imaging obtains information about tissue perfusion and permeability. Following the administration of a contrast agent, concentration-time curves measured in each voxel are fitted by a pharmacokinetic model formulated as a time-domain convolution of an arterial input function (AIF) and an impulse residue function (IRF). Since the measurement window contains hundreds of time samples, the discrete convolution is demanding, even when it is performed via discrete Fourier transform (DFT). Additionally, its discretization causes convergence complications in the curve fitting and it is not applicable to functions without a closed-form expression in the time domain, e.g. tissue homogeneity model IRF. Both issues can be solved by formulating the functions in a closed form in the Fourier domain. In the Fourier domain, the model transforms to multiplication of IRF and AIF, followed by the inverse DFT. To avoid time-domain aliasing, the number of samples in the Fourier domain must be higher than the sum of supports of the functions in the time domain. If the functions are slowly decaying exponentials, the support is theoretically infinite, which dramatically reduces the computational performance. In this contribution, we propose a modification of IRF in the Fourier domain to consider the measurement window. Our solution reduces the required number of samples to three times the measurement window compared to dozens needed without the modification and reduces the number of DFTs. This provides faster evaluation of the pharmacokinetic model and its derivatives for each voxel in each iteration of the curve fitting.

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Keywords

DCE-MRI • Tracer kinetic modelling • Tissue homogeneity model

1 Introduction

Dynamic contrast-enhanced magnetic resonance imaging has become an established tool to obtain information about tissue perfusion and capillary permeability. Following the administration of a contrast agent, a set of images in time is acquired using an MRI scanner. These images are related to concentration of the contrast agent in each voxel in each time-instant of the measurement. These concentration-time curves are fitted by a pharmacokinetic model to obtain the perfusion and permeability parameters of interest. These parameters are useful in diagnostics and monitoring of treatment effects, mostly in oncology.

The pharmacokinetic model is usually formulated as a time-domain convolution of an arterial input function (AIF) and an impulse residue function (IRF). Since each concentration-time curve contains hundreds of samples equal to the number of image frames, the discrete time-domain convolution is demanding, even when it is performed in the frequency domain via the discrete Fourier transform (DFT). Additionally, it causes convergence complications in the curve-fitting procedure, because the imprecise time-domain discretization causes local optima [1, 2, 3]. Furthermore, this approach is not applicable to the functions without closed-form expression in the time domain as e.g. the tissue homogeneity (TH) IRF model [4]. Despite these problems, the time-domain approach of evaluation of the pharmacokinetic model is widely used mostly in connection with basic IRFs such as the Kety/Tofts model and its extension containing a vascular contribution (see review [5]).

Use of advanced IRF models instead of the basic ones provides estimation of a more complete set of perfusion parameters. The requirement to use these advanced models

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however puts higher demands on the precise evaluation of the convolution. One possibility is to find a closed-form expression for the convolution and was shown in [2] for adiabatic approximation of TH model (ATH) [6] and a specific closed-form AIF [7]. Because the particular form of the functions involved can be limiting, a correction scheme for evaluation of the convolution was also proposed [2]. Another interesting approach of the pharmacokinetic model evaluation was introduced by Garpebring [1]. It also naturally overcomes the problem with the nonexistent closed-form expression of the IRF in the time domain. As above, the convolution is performed as a multiplication in the Fourier domain but the IRF is evaluated directly in the Fourier domain in contrast to the DFT case. Unfortunately, the remaining problem of this approach is the speed of its evaluation. Although it removes some of slow forward DFTs, the number of function samples must be increased to avoid a time-domain aliasing.

In this paper, we describe the above-mentioned approaches of pharmacokinetic model evaluation and propose an efficient modification of the Fourier domain approach (FDA) [1]. This eliminates the increase in the number of samples required to avoid the time-domain aliasing.

2 Pharmacokinetic Model

The pharmacokinetic model is in general described by a system of partial differential equations. Using the Laplace transform with boundary conditions taking the AIF into account, the solution has the form:

$$C_t(s) = c_a(s)h(s) \tag{1}$$

where C_t is contrast-agent concentration in a tissue unit, c_a is concentration in the arterial input of the tissue unit, i.e. the AIF, and h is the IRF. s is the Laplace variable. If the functions involved have a closed form in the time domain, (1) can be written as a time-domain convolution of AIF and IRF.

Equation (1) can also be formulated in the Fourier domain using the substitution: $s \to j\omega$, where j is the imaginary unit and ω is the angular frequency. The substitution is possible for stable functions. It was used for the TH model [1] but it is valid for all IRFs because of their decaying-exponential-like character guaranteeing stability.

2.1 Time Domain Approach—Discrete Convolution

The most usual approach to evaluate (1) as the convolution is based on the DFT. Here, the IRF is parametrized in the discrete-time domain. The AIF is either directly measured in the discrete-time domain or the discrete-time model is used. The discrete convolution is then solved using the multiplication of their DFTs and the subsequent inverse DFT. This approach is possible for any AIF and for IRFs with a closed-form temporal-domain formulation, i.e. not for the TH model.

2.2 Time Domain Approach—Analytic Evaluation

As the IRF models are mostly formulated and parametrized in the continuous-time domain, a straightforward approach to evaluation of (1) is to use an analytic expression of the convolution of the IRF and AIF. This is possible only when analytic time-domain formulations of both the AIF and IRF are available (i.e. not for the TH model nor for a measured nonparametric AIF). The feasibility of such solution was shown in [2] for the AIF of [7] (*Model 2*) and the ATH model [4]. Tractability of this approach for other AIF and IRF models is not guaranteed.

2.3 Fourier Domain Approach

Another option is to use Fourier version of (1) with the AIF and IRF represented directly in the Fourier domain with the subsequent inverse DFT as proposed in [1]:

$$C_t[n] = \mathcal{F}_{\mathrm{DFT}}^{-1}\{c_a[w]h[w]\}, \forall\, w \in \left\{0, 1, \ldots \frac{N - \mathrm{mod}(N,2)}{2}\right\} \tag{2}$$

where "mod" is modulo. For an arbitrary function f in the Fourier domain holds:

$$f[w] = f(j\Delta\omega w), \Delta\omega = \frac{2\pi}{N\Delta t} \tag{3}$$

The output of $\mathcal{F}_{\mathrm{DFT}}^{-1}$ should be real, thus it is assumed that $\mathcal{F}_{\mathrm{DFT}}^{-1}$ also includes necessary complex conjugate symmetrization. The necessary number of samples N of the resulting function is analyzed in the following section.

Time-domain aliasing. The use of (2) requires special care about time-domain aliasing [1]. The aliasing effect (folding of the end of $C_t[n]$ back to its beginning) is avoided, if the number of samples in the time domain is: $N = N_{\mathrm{AIF}} + N_{\mathrm{IRF}}$, where $N_{\mathrm{AIF}}, N_{\mathrm{IRF}}$ are lengths of the respective functions in the time domain. In theory, the lengths $N_{\mathrm{AIF}}, N_{\mathrm{IRF}}$ are infinite, because of their decaying-exponential-like character. In practice, the functions fall to zero with a time constant defined by the respective exponentials. As proposed in [1] for the TH model, this length of the IRF can be assumed:

$$N_{\mathrm{IRF}} = \frac{6}{k_{\mathrm{ep}}\Delta t} \tag{4}$$

where k_{ep} is one of the TH model parameters and the time constant of the decaying "exponential". Because most of the known IRFs have similar decaying character, (4) can be used in general.

Although it is possible to represent the AIF in the Fourier domain as described in [8], here we assume, that $c_{\mathrm{a}}[w]$ is the DFT of measured K samples of the AIF zero-padded to length $N = K + N_{\mathrm{IRF}}$ as proposed in [1].

3 Methods

The drawback of the Fourier domain evaluation is the variable length of the functions in the Fourier domain, which depends on the support of the IRF, N_{IRF}, which changes during the iterations based on the current parameters of the IRF. The number of samples can become very high during the curve fitting. This reduces the performance, since the evaluation of $C_{\mathrm{t}}[k]$ is repeated several time for every voxel in every iteration to evaluate the criterion function and its partial derivatives with respect to its parameters. In this section, a closed-form expression for a windowed IRF is derived. This allows us to keep the number of samples to be: $N = 2K$, where K is the required number of samples in the time domain.

3.1 Derivation of Windowed IRF

The windowed IRF in the time domain can be written as $h^{\mathrm{w}}(t) = h(t)\mathcal{H}(t_{\mathrm{w}} - t)$, where $\mathcal{H}(x)$ is the Heaviside step function and t_{w} is a length of the measurement window. However, the transformation of $h^{\mathrm{w}}(t)$ to the Laplace domain can be intractable. Also if the IRF does not exist in the time domain in a closed form as the TH model, it can be impossible to find its Laplace-domain windowed variant.

The presented solution is based on a simple consideration that the Laplace transform of the windowed function is equal to the original function minus the original function outside the window.

The TH model IRF is parametrized by: $\boldsymbol{p}_{\mathrm{TH}} = \{F_{\mathrm{p}}, v_{\mathrm{p}}, v_{\mathrm{e}}, PS, \tau\}$, including the bolus arrival time τ and it is defined by [1]:

$$h_{\mathrm{TH}}(s, \boldsymbol{p}_{\mathrm{TH}}) = \frac{\left(\mathrm{e}^{-(a+bs)} - 1\right)(a+bs)\left(av_{\mathrm{e}} + v_{\mathrm{p}}(cbs + a)\right)}{a^2\left(\mathrm{e}^{-(a+bs)} - 1\right) - (a+bs)sb(c(a+bs)+a)}\mathrm{e}^{-s\tau},$$
$$a = \frac{PS}{F_{\mathrm{p}}}, b = \frac{v_{\mathrm{p}}}{F_{\mathrm{p}}}, c = \frac{v_{\mathrm{e}}}{v_{\mathrm{p}}} \tag{5}$$

To use the above-mentioned consideration, it is necessary to formulate the IRF part outside the window. It seems impossible to formulate it exactly but it can be approximated based on the general knowledge about the IRFs. All IRFs in the time domain have the form of a decaying-exponential-like function. Thus if this is assumed together with $t_{\mathrm{w}} \gg v_{\mathrm{p}}/F_{\mathrm{p}}$, i.e. vascular phase takes only a short part of the measured window, the windowed version of the TH model can be approximated by the TH model minus decaying exponential:

$$h^{\mathrm{w}}_{\mathrm{TH}}(s, \boldsymbol{p}_{\mathrm{TH}}, t_w) = h_{\mathrm{TH}}(s, \boldsymbol{p}_{\mathrm{TH}}) - FE\mathrm{e}^{-k_{\mathrm{ep}}(t_{\mathrm{w}} - \tau - T_{\mathrm{c}})}\frac{\mathrm{e}^{-st_{\mathrm{w}}}}{s + k_{\mathrm{ep}}} \tag{6}$$

where the extraction fraction: $E = 1 - \exp\left(-PS/F_{\mathrm{p}}\right)$ and the mean capillary transit time: $T_{\mathrm{c}} = v_{\mathrm{p}}/F_{\mathrm{p}}$. The expression $1/\left(s + k_{\mathrm{ep}}\right)$ is the Laplace transform of the decaying exponential, $\exp(-st_{\mathrm{w}})$ is its time shift to t_{w} and the rest is a constant correcting its amplitude. The derived windowed function can be sampled using (3) with $N = K + N_{\mathrm{AIF}}$, which turns into $N = 2K$, if used together with time-domain AIF.

3.2 Experiments

Validation. To validate our windowed TH model (6), 10,000 evaluations using (3) was repeated and transformed to the time domain using the inverse DFT. The time axis was defined by, $t = \{0, 1, \ldots, N-1\} \cdot 1.5/60$ min, where $N =$ 10000 samples, i.e. 0–250 min, to simulate an infinitely long measurement avoiding aliasing effect. The length of the window was set $t_{\mathrm{w}} = 10$ min, i.e. $K = 400$. The IRF parameters were generated uniformly from intervals: $F_{\mathrm{p}} \in \langle 0.06, 0.75\rangle$, $v_{\mathrm{p}} \in \langle 0.01, 0.20\rangle$, $v_{\mathrm{e}} \in \langle 0.05, 0.70\rangle$, $PS \in \langle 0.05, 0.50\rangle$, $\tau = 0$ as in [1]. For each evaluated function, a ratio (R) of energy of the folded part (E_{f}) to energy inside the window (E_{w}) as a function of the number of samples in multiples of the window length was computed:

$$R(q) = \frac{E_{\mathrm{f}}[m]}{E_{\mathrm{w}}} = \frac{\sum_{n=0}^{N-1} h^{\mathrm{w}}_{\mathrm{TH}}[n]^2 - \sum_{0}^{m} h^{\mathrm{w}}_{\mathrm{TH}}[m]^2}{\sum_{k=0}^{K-1} h^{\mathrm{w}}_{\mathrm{TH}}[k]^2}, \forall m < N-1,$$
$$q = \frac{m+K}{K} \tag{7}$$

If (6) is a sufficient approximation of the windowed IRF, $R(2) \to 0$, thus there will be no energy contaminating the result of the convolution with the AIF. This should hold for any combination of the parameters. The collected 10,000 ratios $R(q)$ were statistically processed. The result was plotted and visually analyzed.

Table 1 Tested variants of the pharmacokinetic model

Variant		IRF				No. of DFT
#	Description	Model	$h(\cdot)$	Equation	No. of samples	Forward/inverse
2.1	TDA—DFT	DCATH	t	[10] (2)	K	1/1
2.2	TDA—closed form	ATH	t	[2] (A1)	K	0/0
2.3	FDA—[1]	TH	ω	(5)	$(K+f(k_{ep}))/2$	0/1
3.1	FDA—proposed	TH_w	ω	(6)	$3K/2$	0/1

Evaluation time. The evaluation time of (6) in (2) was compared to other evaluation variants discussed (see Table 1). For each variant and each parameter set, 1000 function evaluations were repeated to stabilize the measurement of the evaluation time. Their average represented the evaluation time. The time scale t was generated similar to previous experiment with N_{IRF} defined in Table 1 (Number of samples). The AIF model and its parameters were fixed and same as in [7] (*Model 2*). The IRF parameters were fixed to: $F_p = 0.06\,\mathrm{min}^{-1}$, $v_p = 0.04$, $PS = 0.031\,\mathrm{min}^{-1}$, $\tau = 0.1\,\mathrm{min}$; except k_{ep}, where 10 values were generated on a logarithmic scale from 10^{-2} to $1\,\mathrm{min}^{-1}$. In variants "2.1" and "2.2", the TH model had to be replaced by the distributed capillary adiabatic tissue homogeneity model (DCATH) [9] and the ATH model [2], [6], respectively. The DCATH IRF instead of the ATH was used, because the ATH in the time-domain approach (TDA) using DFT causes convergence problems in practice. The additional DCATH parameter was set to approximate the ATH model, $\sigma = \Delta t$, as explained in [10, 11]. The number of samples in the variant "3.1" reflects the result of the previous validation experiment.

4 Results

Validation. The plot (Fig. 1) of the approximation error based on the folding energy revealed that in most cases, the derived windowed TH model is sufficient. Only in less than 10% of the cases, the result of the convolution inside the measurement window would be contaminated by the ratio of folding energy ranging from 10^{-4} to 10^{-2}. It was discovered, that this happened for the cases where the extraction fraction E was close to 1 in combination with low flow F_p. It is a regime, where the contrasted agent travels mainly through an extracellular extravascular space. Although the ratio is small and such cases are rare, it is recommendable to use $N = 3K$ for sampling of the windowed TH model.

Evaluation time. The evaluation times for each variant in Table 1 are plotted in Fig. 2. As expected, only method "2.3" does not have a constant evaluation time. That is caused by (4) defining the necessary number of samples to avoid aliasing. Other variants have a constant number of samples as listed in Table 1. The number of samples with its

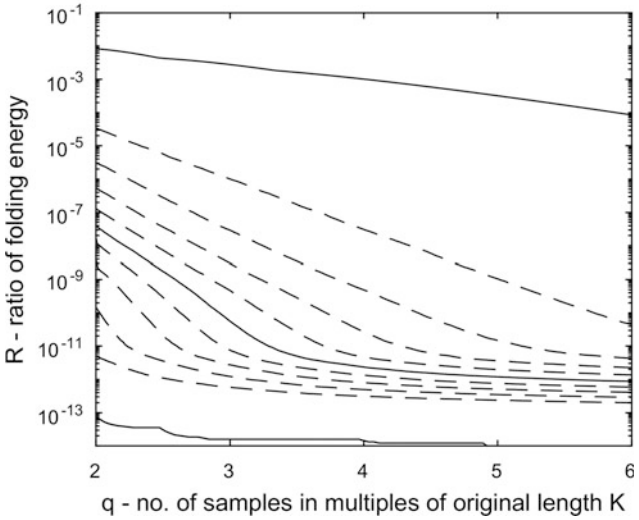

Fig. 1 Ratio of folding energy as a function of the addition of samples. Solid lines are maximum, median, minimum and the dashed lines are the resting 10-quantiles

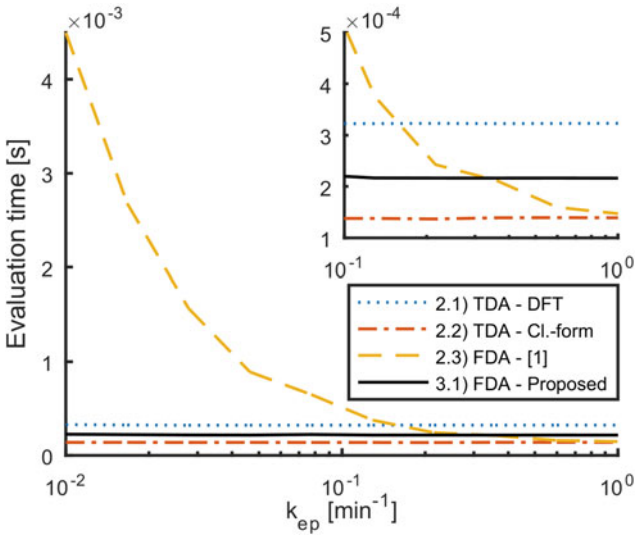

Fig. 2 Comparison of the possible variants of the pharmacokinetic model evaluation in terms of their evaluation time. The top-right plot is a close-up

type (real/complex) is not the only factor influencing the evaluation time. The second factor is the number of needed DFT operations, which is the most demanding operation and its speed depends on the number of samples. The faster evaluation of "2.3" in comparison with "3.1" for high k_{ep} is in the area, where the proposed windowing is not needed and thus can be eliminated in practice.

5 Discussion and Conclusion

It was shown, that the fastest approach to evaluate the pharmacokinetic model in DCE-MRI is to use the closed-form evaluation "2.2" [2]. This is not surprising, since it does not use the DFT and the number of real samples is the lowest possible, i.e. equal to the number of the time-domain samples. The limitation of this variant is the necessity to have a specific parametrized form of AIF (it is not possible to use measured AIF directly) and also the IRF is limited to specific models to derive a closed-form formula.

Our Fourier domain approach "3.1" allows both to use a measured AIF or a parametrized one. Our derived closed-form expressions for windowed IRF dramatically speed up the evaluation in comparison with the original FDA "2.3" [1] and with the conventional time domain approach "2.1" using the DFT, although only 1.5 times. However, this factor grows with the time resolution because of the DFT. Additionally, the evaluation of the pharmacokinetic model together with its derivatives is repeated many times in the iterative estimation procedure for each voxel, thus even a slight speed up can save a lot of time.

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Disclosure

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Garpebring, A., Ostlund, N., Karlsson, M.: A Novel Estimation Method for Physiological Parameters in Dynamic Contrast-Enhanced MRI: Application of a Distributed Parameter Model Using Fourier-Domain Calculations. IEEE Trans. Med. Imaging. 28(9), 1375–1383 (2009).
2. Koh, T.S., Cheong, D.L.H., Hou, Z.: Issues of discontinuity in the impulse residue function for deconvolution analysis of dynamic contrast-enhanced MRI data. Magn. Reson. Med. 66(3), 886–92 (2011).
3. Bartoš, M., Keunen, O., Jiřík, R., Bjerkvig, R., Taxt, T.: Perfusion Analysis of Dynamic Contrast Enhanced Magnetic Resonance Images Using a Fully Continuous Tissue Homogeneity Model with Mean Transit Time Dispersion and Frequency Domain Estimation of the Signal Delay. In: Analysis of Biomedical Signals and Images. pp. 269–274. Brno University of Technology, Brno, Czech Republic (2010).
4. Lawrence, K.S. St., Lee, T.-Y.: An Adiabatic Approximation to the Tissue Homogeneity Model for Water Exchange in the Brain: I. Theoretical Derivation. J. Cereb. Blood Flow Metab. 18(12), 1365–1377 (1998).
5. Sourbron, S.P., Buckley, D.L.: Classic models for dynamic contrast-enhanced MRI. NMR Biomed. 26, 1004–27 (2013).
6. Johnson, J.A., Wilson, T.A.: A model for capillary exchange. Am. J. Physiol. Heart Circ. Physiol. 210(6), 1299–1303 (1966).
7. Orton, M.R., D'Arcy, J.A., Walker-Samuel, S., Hawkes, D.J., Atkinson, D., Collins, D.J., Leach, M.O.: Computationally efficient vascular input function models for quantitative kinetic modelling using DCE-MRI. Phys. Med. Biol. 53(5), 1225–39 (2008).
8. Bartoš, M.: Advanced Signal Processing Methods in Dynamic Contrast Enhanced Magnetic Resonance Imaging, https://www.vutbr.cz/www_base/zav_prace_soubor_verejne.php?file_id=93420, (2014).
9. Koh, T.S., Zeman, V., Darko, J., Lee, T.-Y., Milosevic, M.F., Haider, M., Warde, P., Yeung, I.W.: The inclusion of capillary distribution in the adiabatic tissue homogeneity model of blood flow. Phys. Med. Biol. 46(5), 1519–38 (2001).
10. Kratochvíla, J., Jiřík, R., Bartoš, M., Standara, M., Starčuk, Z., Taxt, T.: Distributed capillary adiabatic tissue homogeneity model in parametric multi-channel blind AIF estimation using DCE-MRI. Magn. Reson. Med. 75(3), 1355–1365 (2016).
11. Bartoš, M., Jiřík, R., Kratochvíla, J., Standara, M., Starčuk, Z., Taxt, T.: The precision of DCE-MRI using the tissue homogeneity model with continuous formulation of the perfusion parameters. Magn. Reson. Imaging. 32(5), 505–13 (2014).