An Extended Graphical model for analysis of Dynamic Contrast-Enhanced MRI

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Introduction

Kinetic modeling of dynamic contrast-enhanced MRI (DCE-MRI) permits the measurement of physiological parameters, such as the transfer constant, K^{trans}. One challenge in kinetic analysis is that the most commonly used model – the modified Kety/Tofts model (1) – is subject to fit failures, particularly when the data acquisition period is too short. Thus, long duration acquisitions are required to obtain stable estimations in this model. An alternative analysis approach that does not lead to such fit failures is the graphical solution proposed by Patlak (2). Because the Patlak model neglects reflux, however, its estimates can be highly inaccurate (3). In this investigation, we sought to develop a new model that produces stable, unbiased estimates of K^{trans} within acquisitions of short duration. By exploring the mathematical relationship between the modified Kety/Tofts model and the Patlak model, we found that the latter is a linear approximation based on an infinite expansion of the former. A higher order approximation based on this expansion is found to correct for reflux, while retaining the central advantages of the Patlak model – it is linear in the parameters to be estimated, leads to a simple graphical interpretation, and has a stable fitting procedure. Simulated and in vivo experimental data were used to investigate whether the new "extended graphical model" can outperform the Patlak and modified Kety/Tofts models and under what circumstances.

Methods and Materials

Theory With the assumption of bi-directional exchange of contrast agent between plasma and extravascular extracellular space (EES), the modified Kety/Tofts model is given by (1):

$$C_t(t) = v_p C_p(t) + K^{trans}\int_0^t C_p(\tau)\exp(-k_{ep}(t-\tau))d\tau \quad [1]$$

where $K^{trans}=v_e k_{ep}$; C_p and C_t are the contrast agent concentration in plasma and tissue; v_p and v_e are the fractional volumes of plasma and EES; k_{ep} is the transfer rate between the plasma and EES. Assuming that the contrast agent can only wash in from plasma to EES, yields the Patlak model (2):

$$C_t(t) = v_p C_p(t) + K^{trans}\int_0^t C_p(\tau)d\tau\,. \quad [2]$$

If we expand Eq. [1] using integration by parts, we observe that the Patlak model [2] accounts for the first two terms in the expansion:

$$C_t(t) = v_p C_p(t) + K^{trans}\int_0^t C_p(\tau)d\tau + K^{trans}\sum_{i=1}^{n=\infty}(-k_{ep})^i\int_0^t\cdots\int_0^{\tau_i} C_p(\tau_{i+1})d\tau_{i+1}\cdots d\tau_1\,. \quad [3]$$

Thus, the infinite sum term in Eq. [3] corrects for contrast agent reflux. As with other expansions, a more accurate approximation can be expected if more additional terms are included from Eq. [3]. In particular, if only the first order correction term is chosen, the resulting model is our linear extended graphical model, given by:

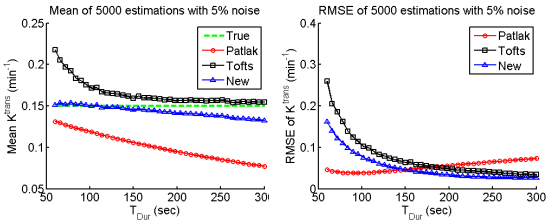
$$C_t(t) = v_p C_p(t) + K^{trans}\int_0^t C_p(\tau)d\tau - k_{ep}K^{trans}\int_0^t\int_0^{\tau_1} C_p(\tau_2)d\tau_2 d\tau_1\,. \quad [4]$$

Simulation To test this model, we simulated an arterial input function using an existing model (4):

$$C_p(t)=(A_1+A_2)(t/t_0) \text{ when } t<7s \qquad C_p(t)=A_1\exp(-K_1(t-t_0))+A_2\exp(-K_2(t-t_0)) \text{ when } t\geq 7s \quad [5]$$

where A_1=3.4mM, A_2=1.81mM, K_1=2.7min^{-1}, K_2=0.09min^{-1}. Tissue uptake curves were generated with Eq. [1] using k_{ep}=0.3 min^{-1}, v_e =0.5, v_p =0.05 and sampling interval =3s. The fitting procedure of each model was then repeated 5000 times with 5% random noise added to each sample (standard deviation is 5% of the maximum C_p value). The mean values and root mean square error (RMSE) of the K^{trans} estimates were computed for duration times (T_{Dur}) ranging from 60s to 300s with a step of 6s.

In vivo DCE MRI of carotid artery To evaluate the performance of the model in vivo, the dependence of parameter estimation on T_{Dur} was also tested with DCE-MRI of carotid plaque. We obtained 8 MRI data sets from subjects with advanced carotid artery disease consisting of axial 2D spoiled gradient recalled echo images (8 slices, slice thickness 2 mm, FOV 140*140 mm, Matrix 256*256, TR= 95ms, TE=4.6ms). Coincident with the second image in the sequence, 0.1 mmol/kg of a gadolinium-based contrast agent was injected at a rate of 2 ml/s by a power injector. A spatial saturation band was applied to induce a T1-dependent blood signal on images prior to contrast bolus arrival. After bolus arrival, images were acquired at 20 time points separated by a repetition interval of 13s. These data were analyzed using the method described by Kerwin et al. (5) to obtain average measurements of K^{trans} and v_p within the carotid artery wall. We applied each of the three kinetic models (Patlak, modified Kety/Tofts, and extended graphical model) for T_{Dur} ranging from 78s (first 6 time points) to 260s (all 20 time points). For each T_{Dur}, we computed the RMSE of K^{trans} estimates using the values estimated by the modified Kety/Tofts model with full duration as a gold standard.



(a) (b)

Fig. 1. (a, b) Comparison of the mean value (a) and RMSE (b) of estimated K^{trans} with different T_{Dur} in 5000 estimations with 5% random noise among the three models.

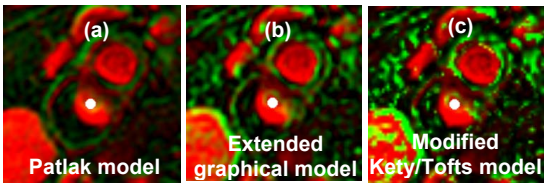


Fig. 2. Examples of the generated vasa vasorum image of carotid plaque using the Patlak model (a), the extended graphical model (b), and the modified Kety/Tofts model (c). The white spot pointed the internal carotid artery.

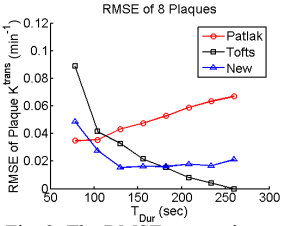


Fig. 3. The RMSE comparison of the estimated K^{trans} in the three models using in vivo DCE-MRI of carotid plaque

Results

In the simulation, the mean error plots in Fig. 1(a) show that the Patlak model exhibits substantial bias that varies with T_{Dur}. Interestingly, the modified Kety/Tofts model also exhibited heavy bias in estimates of K^{trans} when T_{Dur} is short, which we attribute to asymmetric response to noise that favors higher estimates of K^{trans}. Our new, extended graphical model, on the other hand, exhibited minimal bias across the full range of T_{Dur} tested. In the RMSE comparison (Fig. 1(b)), the Patlak model exhibited generally low error attributable to its simpler 2-parameter formulation, but the error increased with T_{Dur} as bias dominated the error. In comparison, both the new model and the modified Kety/Tofts model exhibited lower errors as T_{Dur} increased. Notably, the extended graphical model had lower error than the modified Kety/Tofts model for all the tested T_{Dur} values, suggesting the former is less sensitive to noise. For the in vivo data, Fig. 2 shows examples of kinetic parameters with v_p in the red channel and K^{trans} in the green channel to produce "vasa vasorum images" (5). Qualitatively, the Patlak result has lower values, which is attributable to bias. The new extended graphical model result appears less noisy than the modified Kety/Tofts result. In the T_{Dur} dependence test (Fig. 3), the new extended graphical model showed good agreement with the full duration modified Kety/Tofts model for durations down to 130s. In contrast, the modified Kety/Tofts rapidly degraded as T_{Dur} decreased. The Patlak model produced generally poorer estimates of K^{trans} for all durations.

Conclusion

The newly proposed extended graphical model was shown to address the bias inherent in the Patlak model and produce more stable estimates of K^{trans} than the modified Kety/Tofts model for short duration experiments. The extended graphical model could permit DCE-MRI acquisition durations to be shortened while maintaining stable, accurate estimates of K^{trans}. Furthermore, in applications where the duration of the DCE-MRI acquisition is forced to be short, the new extended graphical model might be a better choice of models than the modified Kety/Tofts.

References:

1. Tofts P et al., J Magn Reson Imaging 1997, 7:91-101; 2. Patlak C et al., J Cereb Blood Flow Metab 1983, 3:1-7; 3. Li K et al., Magn Reson Med 2003, 50:1286-1295; 4. McGrath D et al., Magn Reson Med 2009, 61:1173-1184; 5. Kerwin W et al., Magn Reson in Medicine 2008, 59: 507-514.