Can the two-compartment model for DCE-MRI fit contrast concentration curves accurately over a heterogeneous region of interest?

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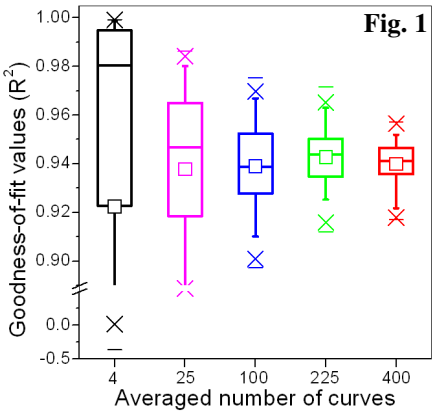
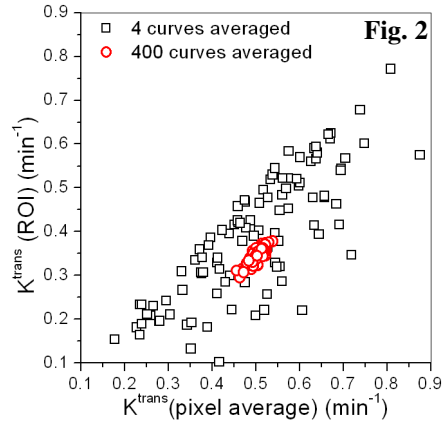
Target audience – This study will benefit people who are interested in the two compartment model (TCM) for dynamic contrast enhanced MRI (DCE-MRI) that is commonly used in both pre-clinical research and clinical detection of cancers.

Purpose – DCE-MRI plays an important role in clinical detection and diagnosis of cancers. A simple two-compartment model (TCM) of tissue [1] is commonly used to characterize the redistribution of contrast agent following a bolus injection. Normally a region of interest (ROI) is drawn to generate the contrast media concentration v.s. time curve (C(t)), which is then fitted with the TCM to extract physiological parameters, such as the volume transfer constant (K^{trans}) and the volume of contrast distribution (v_e). However, even when the C(t) for each pixel within an ROI satisfies the TCM, C(t) averaged over a heterogeneous ROI ($C(t)_{ROI}$) may not satisfy the TCM due to non-linearity of the model. The goal of the present work is to evaluate the effect of heterogeneity on physiological parameters generated by the TCM.

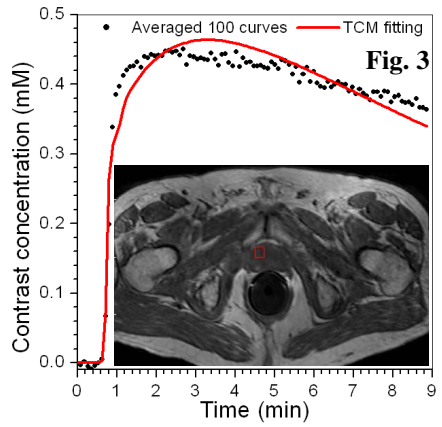
Methods – The computer simulations and clinical prostate DCE-MRI data were used to evaluate the accuracy of TCM fits of $C(t)_{ROI}$. For computer simulations, we used the population arterial input function (C_p), of Parker et al. [2]. To study the effects of nonlinearity of the TCM, we used the random number generator in IDL (ITT Visual Information Solutions) to generate K^{trans} and v_e for each pixel first, and thereafter to obtain C(t) for each pixel ($C(t)_{pixel}$) satisfying the TCM using the following equation: $C(t) = K^{trans}\int_0^t C_p(\tau)\exp\left(-K^{trans}/v_e(t-\tau)\right)d\tau$, where 't' is time. The following steps were used in the computer simulations: (**i**) The temporal resolution was 3 seconds, and the contrast concentration curves were sampled for 20 min. (**ii**) The K^{trans}(pixel) (min^{-1}) and v_e(pixel) were generated randomly in the ranges of $0.005 \le K^{trans} \le 1.0$ and $0.005 \le v_e \le 0.75$ (based on Langer et al. [3]). (**iii**) ROI's were simulated with 4, 25, 100, 225, and 400 different pixels (each with randomly generated $C(t)_{pixel}$). For each case, the simulations were run for 100 times. (**iv**) For each case, we took the K^{trans} and v_e values over all pixels in the ROI to get K^{trans}(pixel average) and v_e(pixel average), as well as the average of $C(t)_{pixel}$ over the ROI ($C(t)_{ROI}$). (**v**) Finally, the TCM was used to fit the $C(t)_{ROI}$ obtained in step (iv) to extract best-fit values of K^{trans} and v_e (K^{trans}(ROI) and v_e(ROI)).





For one clinical DCE-MRI prostate scan, we selected an ROI with 100 pixels. C(t) for each pixel ($C(t)_{pixel}$) was fitted by the TCM to extract the K^{trans}(pixel) and v_e(pixel) first, then C(t) averaged over 100 pixels was also fitted with the TCM to obtained best-fit values of K^{trans}(ROI) and v_e(ROI).

Results – For 100 simulations, the range of the goodness-of-fit values (R^2) was reduced as data from more pixels were averaged (**Fig. 1**), suggesting that the dominant source of error becomes systematic rather than random, when many pixels are used. **Fig. 2** compares the K^{trans}(pixel average) (obtained by fitting C(t) for each pixel) with K^{trans}(ROI) (from C(t) averaged over the ROI) from 100 simulations for 4 and 400 pixels. The K^{trans}(ROI) derived from fitting $C(t)_{ROI}$ with the TCM was on average 20% to 30% smaller than the K^{trans}(pixel average). The fitted v_e(ROI) was only an average of 5% smaller than the v_e(pixel average). As the number of curves increases, i.e., the ROI gets larger, the range of values of K^{trans}(ROI) decreased. Finally, **Fig. 3** shows clinical DCE-MRI data with the TCM fit to C(t) averaged over the tumor ROI (red box in the image with 100 pixels). The K^{trans}(pixel average) = 0.22±0.08 (min^{-1}) and v_e (pixel average) = 0.35±0.06 was larger than the K^{trans}(ROI) = 0.20 (min^{-1}) and v_e(ROI) = 0.33 over the ROI. More importantly, K^{trans}(ROI) and v_e(ROI) were based on relatively poor fits to $C(t)_{ROI}$, as demonstrated in Fig. 3.



Discussion – Even when C(t) for each pixel satisfies the TCM, C(t) averaged over a heterogeneous ROI may not satisfy the TCM. The K^{trans} derived from fitting $C(t)_{ROI}$ significantly underestimates the K^{trans}(pixel average). As data from more pixels were averaged, the K^{trans}(ROI) and v_e(ROI) more closely approximate K^{trans}(pixel average) and v_e(pixel average), but underestimation is still significant. To increase the sensitivity and specificity of diagnosis cancer using DCE-MRI, a smaller ROI or pixel-by-pixel analysis would be preferred in clinical practice. However, heterogeneity is likely to produce significant errors when small ROI's are used.

Conclusion – These results demonstrate that the TCM provides good fits for C(t) averaged over an ROI only when each individual curve within ROI satisfies the TCM and all pixels have similar contrast uptake and washout rate. Heterogeneity leads to poor TCM fits and errors in K^{trans} and v_e. This limits diagnostic accuracy of parameters derived from the TCM.

Reference: [1] Tofts et al. J Magn Reson Imaging. 1999; [2] Parker et al. Magn Reson Med. 2006; [3] Langer et al. Radiology. 2010.