Sampling frequency dependent identifiability of pharmacokinetic parameters for small and large molecular contrast agents

K. Jaspers[1,2], M. J. Post[2,3], T. Leiner[1,2], and W. H. Backes[1,2]

[1]Radiology, Maastricht University Hospital, Maastricht, Netherlands, [2]Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, Netherlands, [3]Physiology, Maastricht University, Maastricht, Netherlands

Introduction

Dynamic contrast-enhanced MRI (DCE-MRI) is a promising technique to detect muscle ischemia and monitor perfusion recovery. Most DCE-MRI protocols are based on the extravasation of small molecules, e.g. Gd-DTPA (molecular weight, 0.5 kDa). Currently, larger molecules such as dendrimers (e.g. Gadomer, apparent molecular weight, 30-35 kDa [1]) are attractive contrast agents, as they have a lower extravasation rate (K^{trans}). This might allow slower dynamic sampling with higher signal-to-noise ratio (SNR) and/or spatial resolution.

In this study we investigated the influence of the sampling rate and SNR on the identifiability, i.e. the bias and spread, of the pharmacokinetic parameters, i.e. the transfer constant K^{trans}, extracellular extravascular fraction (v_e), and plasma fraction (v_p), as determined with the Kety model [2], and discussed the implications on the design of a DCE-MRI protocol.

Methods

In vivo MRI. First, in vivo DCE-MRI experiments were performed in a male New Zealand White rabbit to estimate an arterial input function (AIF) and the noise level. Imaging was performed on a 3T MRI scanner (Philips Medical Systems, Best, The Netherlands). A dynamic 3D fast gradient echo recalled pulse sequence (TR/TE 6.1/0.9 ms, FA 20˚) was used. Dynamic acquisition time was 4.1 s per dynamic phase and the total scan time was 15 minutes. Cranio-caudal FOV was 250 mm, covering the aorta bifurcation and upper and lower hind limbs. Measured voxel size was 2.5 × 2.5 × 5.0 mm. A bolus of 0.9 mL Gd-DTPA was injected at 0.05 mL/s.

Data extraction. To determine the noise level in the concentration curves, signal was measured at precontrast and maximum tissue enhancement in the lower hind limb muscles and noise was measured in an adjacent air region. The signal curve measured in the aorta was converted to a concentration curve and numerically fitted to a biexponential function.

Simulations. To investigate the influence of sampling frequency and SNR on the identifiability of pharmacokinetic parameters a Monte Carlo simulation was performed [3]. A triexponential AIF was constructed by adding a fast exponential component representing the first pass peak, because this peak is often not detected due to the low sampling frequency, but does contribute to the tissue response of the system.

Pharmacokinetic parameters that mimic muscle tissue were taken as follows: K^{trans} 2.5 10^{-3} min^{-1} and 0.13 min^{-1}, representing a large (Gadomer) and small (Gd-DTPA) molecular contrast agent, respectively, and v_e and v_p were set at 0.09 and 0.025 [4,5]. Based on the AIF and predefined pharmacokinetic parameters a tissue concentration time curve was calculated. Both the AIF and the tissue response curve had a high temporal resolution (10 Hz). Subsequently, both curves were down sampled at either random frequencies (range: 0.5 – 60 min^{-1}) or a preset frequency (6 min^{-1}) by linear interpolation. Gaussian noise (SNR = 35, or randomised range: 10 - 1000) was added to the signal. For parameter estimation based on these curves a Marquardt-Levenberg optimization algorithm was run in MATLAB (The MathWorks, Natick, MA).

Results

The intrinsic properties of the Kety model make estimation of all parameters less dependent on sampling frequency for large molecular contrast agents, as shown for K^{trans} in panel a. Both the precision (i.e. less spread) and accuracy (i.e. less bias) are better for a large molecular contrast agent. Adding noise increased the uncertainty of the estimated parameters (panel b). Panel c demonstrates that for large molecular contrast agents the maximum precision in estimation of K^{trans} was reached at higher SNR compared to small molecular contrast agents. Overestimation of K^{trans} at sampling frequency of 1 min^{-1} is due to the low number of samples during the steep rise of tissue concentration.

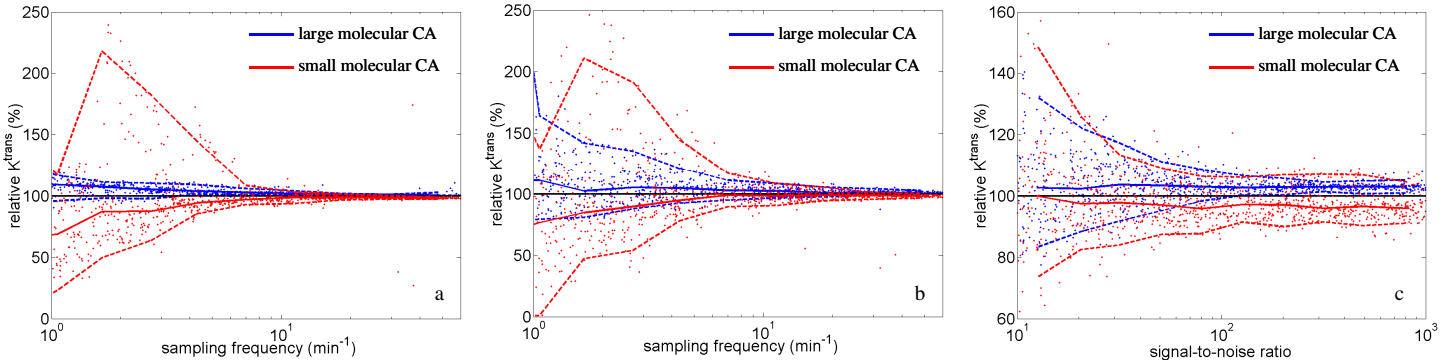

Fig. 1: Estimated relative K^{trans} with respect to sampling frequency (panels a and b) or signal-to-noise ratio (panel c) for a large (K^{trans} = 2.5 e^{-3} min^{-1}, blue) and a small molecular contrast agent (K^{trans} = 0.13 min^{-1}, red). For panel a no noise was added, and for panel b the SNR equals 35. Solid lines represent the mean estimate in an interval, and dashed lines represent the upper and lower 95 % confidence interval. At relative K^{trans} = 100 % the estimated K^{trans} is equal to the input K^{trans} (horizontal black lines)

Conclusions

A simulation assessment was demonstrated that enables determination of the identifiability of pharmacokinetic parameters in terms of bias and variance when varying the sampling rate and noise level. Low sampling rates resulted in strongly biased and unreliable estimations of K^{trans}. The identifiability for K^{trans} at the lower frequencies was better for large than for small molecular contrast agents. This would allow lower sampling rates for large molecular contrast agents, and concomitant increase of spatial resolution, provided that sufficient SNR is obtained.

References

[1] Misselwitz B et al., MAGMA 2001; 12:128-134
[2] Tofts PS et al., JMRI 1999; 10:223-232
[3] Lopata RGP et al, MRM 2007; 58:425-429
[4] Faranesh AZ et al., MRM 2006; 55:1114-1123
[5] Yankeelov TE et al. MRI 2005; 23:519-529