PCA of combined DCE-MRI data from a large cohort can be used to assess treatment effects with similar sensitivity to pharmacokinetic model fitting

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Introduction: DCE-MRI is widely used in clinical trials of antiangiogenic and vascular disrupting agents in the assessment of treatment response. The simplest quantitative metric associated with DCE-MRI uptake curves is area under the curve (IAUGC). IAUGC is both robust and easy to compute, but different underlying physiologies leading to the same IAUGC imply the metric lacks specificity. Fitting pharmacokinetic (PK) models gives more specific measures of vascular function, but difficulties in obtaining a patient specific arterial input function (AIF) can cause additional errors on PK metrics - e.g. in a paediatric population where large variations in AIF are likely. The hypothesis of this work is that principal component analysis (PCA) can also detect post treatment changes in a cohort such as a clinical trial with the same sensitivity as PK modeling. This will be demonstrated using a subset of data from a clinical trial that includes repeat baseline measurements and post-treatment measurements at two time-points. Unlike PK modeling, PCA is a model-free approach that is entirely data-driven.

	DAY 7	DAY 28
Median ΔMH – PK	12.1	8.9
Median ΔMH - PCA	5.5	4.9
Median ΔIAUGC	-60%	-53%
Median ΔKtrans	-64%	-62%
Number of patients with significant changes from baseline (p = 0.95)		
Multivariate PK	11	15
Multivariate PCA	13	15
KTrans	11	12
IAUGC	9	14

Table 1 – comparison of multiparametric PCA and PK techniques for both post-treatment time points

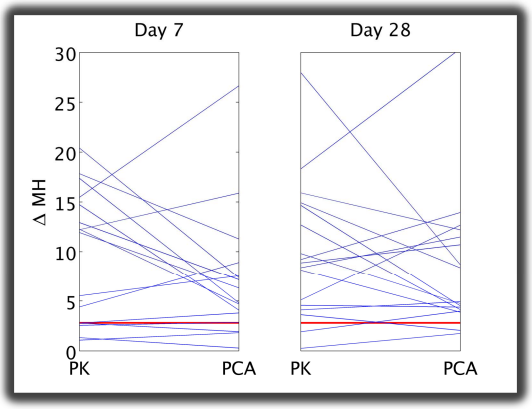

Figure 1 – Comparison of PK and PCA metrics at both time points. Blue lines compare ΔMH for individual patients between both techniques. The 95% significance level for baseline repeatability is shown in red, so that statistically significant changes from baseline are above this line.

Methods and Materials: *Image Acquisition[1]:* With ethical approval, 18 patients with metastatic disease (see *ref 1*) had an abdominal metastatic lesion imaged twice at baseline and after commencing treatment (16 imaged at day 7 and 17 at day 28). A sequential breath-hold protocol was used, each 12s imaging cycle consisting of 2 image volumes acquired over a 6 second breath hold followed by a 6 second free breathing interval. The imaging cycle was repeated to obtain 40 image volumes in total. *Data Preparation:* Gadolinium uptake curves for each voxel within each VOI were obtained (599,680 curves), converted to gadolinium concentration curves, and the extended Kety[2] model was fitted to each voxel with a population AIF using established techniques[3]. Onset time was a significant source of variation across VOIs and therefore the uptake curves were pre-processed to align the onset times across VOIs. The curves were interpolated with a sampling frequency of 3s to give 80 data points. The onset time was manually defined for each VOI by visual inspection of the mean VOI uptake curve. Each curve was then cropped to 63 data points with the 5th data point corresponding to the VOI onset time. The IAUGC (60 sec) for each curve was found. PCA was conducted on the cropped uptake curves. For each VOI, the median of the PC scores and the PK parameters, K^{trans}, v_e and v_p; was found. *Data Analysis:* Our goal was to compare the proposed technique to PK modeling in terms of sensitivity to changes from baseline. This is possible using a multivariate extension of the standard univariate approach, where the difference between repeat baseline measurements are used to define insignificant differences from baseline. The Mahalanobis distance (ΔMH) is suitable for this because it accounts for potential correlations between parameters. For vector x and y, $\Delta MH = \sqrt{(y-x)^T \Sigma^{-1}(y-x)}$, where Σ is the covariance of baseline differences. When used to assess treatment effects x = mean baseline parameter vector and y = post-treatment parameter vector. In summary, the larger ΔMH, the more significant the change is from baseline measurements. To allow direct comparison between PK and PCA methods, the dimensionality of vector spaces must be the same and so the analysis was restricted to the first 3 PCs. This choice was also justified as the variation in the data described by the PCs significantly reduced beyond 3 PCs.

Results: The first 3 PCs described 88%, 4% and 1% of the variance in the data respectively. The 4th PC onwards individually described less than 0.5%. The Spearman correlation between the 1st PC score and IAUGC across all curves is 0.9997. For reference, the % change and number of patients with significant changes from baseline are also shown for univariate K^{Trans} and IAUGC. *Figure 1* compares ΔMH for both techniques for each patient – statistically significant ΔMH with respect to baseline fall above the red line. Comparing the median ΔMH for the PCA and PK techniques using a Wilcoxon signed rank test gives p-values of 0.13, and 0.46 for the post treatment time points, indicating the sensitivity of the techniques to post treatment changes is not statistically different.

Discussion: Although ΔMH is smaller for multiparametric PCA than multiparametric PK, the difference is not statistically significant. The PCA technique classifies more patients as statistically significant at both time points than IAUGC or K^{trans} alone. Because this analysis has reduced 3 PCs to a single metric, multiple changes to PCs may result in the same ΔMH, and therefore the specificity of PCA over IAUGC has not been improved. Further analysis is needed to identify if individual PCs may yield more specific measures. Previous methods of PCA applied to DCE-MRI Gd curves have either not assessed all curves from a large cohort of patients together as one dataset[4] or have not included pre and post treatment data[5]. Conducting PCA across a large cohort in this way means that the PCs retain their meaning across patients and time points. PCA is an attractive technique as it is model free and does not require an AIF, allowing for its potential use in cohorts such as a paediatric population, where an accurate AIF is difficult to obtain and a population AIF may be inappropriate.

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References: [1]*Messiou et al 2012 Radiology –* [2]*Kety SS, Pharmacol. Rev 3 1-41 -* [3]*Orton et al 2009 Phys. Med. Biol. 54 2197 -* [4]*Buonaccorsi, proc. ISMRM 2011 -* [5]*Gwilliam et al, proc. ISMRM 2012*