Measurement of morphological biomarkers using highly under-sampled *k*-space data without image reconstruction: application in left-ventricular end-diastolic volume assessment

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TARGET AUDIENCE Researchers interested in sub-Nyquist uses of *k*-space data, and those interested in the use of MR for morphological and functional biomarker measurement, particularly in cardiology.

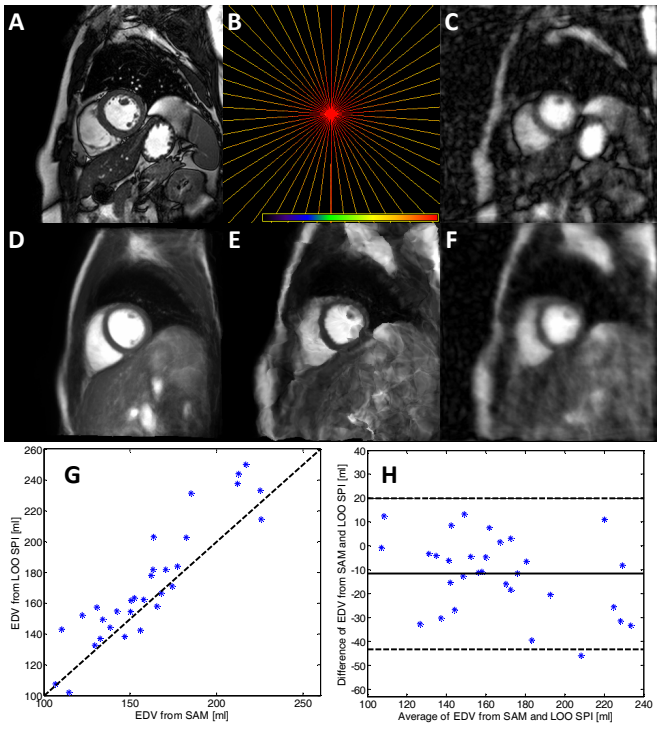
PURPOSE Since the development and application of compressed sensing (CS) in MRI[1], there has been great interest in exploiting under-sampled *k*-space measurements. Increasingly, however, imaging is becoming a quantitative science in which measurements of structures of interest (i.e. biomarkers) are required. One approach would be to reconstruct images and then analyze them using existing methods. We present an alternative in which a morphological biomarker is estimated directly from highly under-sampled *k*-space data without needing to reconstruct a high fidelity image. We call this technique Sparse Parametric Imaging (SPI), and demonstrate the use of SPI to estimate left ventricular (LV) end-diastolic volume (EDV).

THEORY CS uses a highly general nonparametric model of image appearance, in which the image is assumed to be sparse under a suitable transform, and image reconstruction is framed as a relatively complicated optimization problem. SPI uses a highly specific parametric model, in which image appearance is captured by a relatively small number of parameters that are trivially related to the biomarker of interest, and biomarker estimation is framed as a relatively simple fitting process of the model to the data, followed by a transform from the model parameter estimate to the biomarker of interest. If the biomarker of interest is a function of the length, area or volume of a biological structure, one suitable model is the statistical appearance model (SAM)[2]. Briefly, a SAM is a low-dimensional principal component representation of the locations of landmark points and the grey-level textures of regions between them. A SAM is built by annotating a training set of images, placing landmarks at corresponding locations across the set. Because the landmarks correspond to anatomical features, lengths, areas or volumes of those features can be easily obtained. Corresponding landmark locations can be determined automatically using group-wise registration[3]. Given under-sampled *k*-space measurements $\mathbf{k}_u$, an SPI estimate of a morphological biomarker is obtained via Eq 1, in which an objective function f is optimized with respect to the SAM parameter $\mathbf{b}$, to give the best fitting parameter $\mathbf{b}^*$; having obtained $\mathbf{b}^*$ the biomarker can be calculated from the resulting landmark coordinates. The function f measures agreement between data $\mathbf{k}_u$ and predictions from the SAM.

$$\mathbf{b}^* = \arg\operatorname{opt}_{\mathbf{b}} f\left(\mathbf{k}_u, \mathbf{k}_p\right) \quad (1)$$

$$f(\mathbf{k}_u, \mathbf{k}_p) = \sqrt{\frac{1}{n}\sum_{i=1}^{n}\left(\left|F_u^{-1}(\mathbf{k}_u)_i\right| - \left|F_u^{-1}\left(\mathbf{k}_p\right)_i\right|\right)^2} \quad (2)$$

METHODS *Imaging*: Cardiac MR data were acquired in 31 healthy adult male volunteers recruited prospectively (age: median 23 years, range 18-60 years; BMI: median 24 kg/m^2, range 20-32.5 kg/m^2) on a Philips Achieva 1.5 T scanner using a 5-channel cardiac surface coil (Philips Healthcare, Best, The Netherlands). Approval was granted by the local research ethics committee and volunteers gave written informed consent. The protocol included a multi-slice LV volume horizontal short-axis cine image stack (LV stack) at end-diastole, which was acquired using 2D balanced-TFE: TR 3.4 ms, TE 1.68 ms, breathold 12 to 14 s/slice, slice thickness 8 mm, no gap, slices 17, FOV 320 mm, acquired matrix 196×190, reconstructed matrix 320×320, cardiac phases 30, phase percentage 62%, retrospective ECG-triggering, SENSE off, k-t BLAST off, Cartesian acquisition, total acquisition time approx. 4 minutes plus resting periods, complex data exported. *Objective function*: We measured agreement between $\mathbf{k}_u$ and model predictions $\mathbf{k}_p = F_u(g(\mathbf{b}))$ — where g yields a model instance image of the SAM parameter $\mathbf{b}$, and F_u is the Fourier transform from image space to under-sampled *k*-space — using the objective function in Eq 2. *LV EDV calculation*: Given best-fitting parameter $\mathbf{b}^*$, the left-ventricular end-diastolic volume can be calculated as the volume of the convex hull of the landmark points defining the LV blood pool. *Ground truth*: A SAM was built using images from all 31 individuals. The LV from one volunteer's image was manually annotated and warped to every other volunteer's image using the warps learned from building the SAM, allowing us to obtain accurate ground truth measurements of LV EDV. *Leave-one-out validation*: To evaluate how accurately LV EDV could be estimated using SPI from highly undersampled *k*-space data, a leave-one-out validation was performed. Data for each volunteer was omitted in turn and group-wise registration used to build a SAM for the left-in volunteers. The *k*-space data from the left-out volunteer was retrospectively under-sampled using an in-plane uniform radial pattern (Fig B), repeated for each slice (totaling just 8% of *k*-space). SPI was used to estimate the SAM parameter, $\mathbf{b}^*$, that best explained under-sampled data, $\mathbf{k}_u$, and from this the volume of the convex hull of the landmark points defining the LV blood pool was calculated to estimate LV EDV. Agreement between the ground truth and SPI estimates was summarized using a scatter plot, a Bland-Altman plot, and the (Pearson) correlation coefficient. We tested the null hypothesis of zero bias in the SPI estimates using a two-sided *t*-test.



RESULTS While SPI does not aim to reconstruct high fidelity images, the objective function may be defined in terms of image space "reconstructions" (e.g., Eq 2), even though those will be of low fidelity; viewing images corresponding to the various stages of the SPI process provides insight into the method. Fig A shows a middle slice of the LV stack in one volunteer. Fig B shows the 8% sparse *k*-space sampling of Fig A (intensities are on a log scale; the very left of the color scale (black) is 0 and the very right (red) is 11 or greater, arbitrary units). Fig C shows the zero-filled Fourier reconstruction of the *k*-space data in Fig B. Fig D shows a middle slice of the group-wise mean reference image, which demonstrates accurate representation of the heart, lungs, chest wall, etc., but a blurred representation of other organs/tissues (because no direct anatomical correspondences exist across the volunteers in these regions). Fig E shows a SAM instance resulting from an SPI fit to the undersampled *k*-space data in Fig B. Fig F shows the zero-filled Fourier reconstruction of the *k*-space data for Fig E using the same radial sampling scheme. While Fig F would appear to be a very poor reconstruction of Fig A, we will now see that there is sufficient information to allow accurate estimation of LV EDV. Fig G shows a scatter plot (with a line of identity, dashed), and Fig H a Bland-Altman plot (with the mean bias line, solid, and limit of agreement lines, dashed), of the agreement between the ground truth (i.e., SAM) and SPI estimates of LV EDV, from the leave-one-out (LOO) validation experiment. Pearson's correlation coefficient was r = 0.91 ($p < 0.001$). The 95% confidence interval on the bias, calculated using the *t*-test, was (-5.9 ml, -17.4 ml), indicating that SPI systematically overestimates EDV. However, generally, this bias was much less than 10%.

CONCLUSION We have demonstrated that it is possible to measure LV EDV in healthy volunteers, using just 8% of *k*-space, with a mean bias of just 11 ml, without explicit high fidelity image reconstruction. The ability to parameterize features in this way allows for much faster, tailored quantitative imaging. SPI may allow other morphological or functional biomarkers to be measured (e.g., ejection fraction in cardiology, hippocampal volume in Alzheimer's, and knee cartilage thickness in osteoarthritis). Future work should evaluate the method in patients.

REFERENCES 1. Lustig *et al*, *Magn Reson Med* 58:1182, 2007. **2.** Cootes *et al*, *IEEE PAMI* 23:681, 2001. **3.** Cootes *et al*, *IEEE PAMI* 32:1994, 2010.

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