Functional Liver Imaging Using Partial Least Squares (PLS) Analysis

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Introduction:

The liver plays important roles in biochemical transformations and blood detoxification. A number of techniques are now available to evaluate liver function. However, these methods are either invasive, expose the patient to ionizing radiation or have limitations with regards to sensitivity and specificity. We are therefore proposing the use of Blood Oxygen Level Dependant (BOLD) imaging to evaluate liver function non-invasively. We have developed a liver challenge procedure that relies on modulating the BOLD signal with hyperoxia and meal intake. The collected images are subsequently analyzed using two approaches: a general linear model (GLM) and a model free approach based on partial least squares (PLS). It was hypothesized that following food ingestion, healthy livers will show a decrease in signal response (due to increased portal venous blood flow and increased portal oxy:deoxyhaemoglobin ratio **[1]**). Diseased livers were postulated to respond differently; either showing no significant change, or an increase in signal response after the meal. Using PLS to analyze the images, our liver challenge procedure is able to accurately differentiate between healthy individuals and those with liver disorders. However, this is not true when GLM analysis is applied to the data.

Methods:

In a research ethics board approved study, healthy human subjects (n=8) and patients with biopsy-proven liver disorders (mild chronic hepatitis and fibrosis) (n=3) were scanned following an overnight fast using a GE Signa HDX 3T short-bore MR scanner (GE Healthcare, Milwaukee, WI, USA) and an 8-channel torso coil. Images were sagittally acquired with a single-shot GRE-EPI sequence (TE/TR=35/1000ms, 8mm thickness, 64x64 matrix, 1248 phases) before and following the intake of a controlled meal (235 ml of Ensure Plus, Ross Prod. Div., Abbott Labs, Saint-Laurent, Que., Canada) while modulating the BOLD contrast with 100% O_2 (15L/min) and medical air (21.8% O_2) in a cyclic manner (**Fig. 1**). A 32x32 matrix from the centre of the images were extracted from the data and motion corrected using a template mating algorithm **[2]**. Motion corrected images were analyzed using 2 techniques: GLM (with either a positive or a negative sawtooth hemodynamic model response function) and local PLS. The variability of the liver BOLD hemodynamic response function (HR) across subjects necessitated that a positive or negative function be used in the GLM (**Fig. 1**). The appropriate function for a subject was selected based on which HRF produced more active pixels. Signal response level was determined by the uncorrected Z-scores from the regression analysis thresholded at p=0.05. At each pixel, PLS signal response level was based on a Bhattacharyya distance between the centers of 2 clusters in a 2D score space. These clusters were formed from the center portions of the time courses measured while the subject was breathing oxygen and air, respectively. The mean pre and postprandial signal response values were compared using the Student's t-test.

Results/ Discussion:

Table 1 shows the percent change in mean response between pre and postprandial states for healthy individuals (1-8) and patients suffering from liver disease (9-11). PLS results indicate that there was a significant decrease in signal response in all healthy subjects ($p<0.05$) following intake, and that 2 of the patients (10-11) showed significant increase ($p<0.05$), while 1 patient showed no significant change in signal response. Using GLM for the analysis, however, 1 patient (11) showed significant reduction in signal response following intake ($p<0.05$), while 1 healthy subject (1) did not show any significant changes between the two states (hi-lighted in red). These results were inconsistent with the hypothesis. **Fig. 2** shows the pre and postprandial signal response maps for these 2 subjects using GLM and PLS. It should be noted that besides providing inconsistent changes across subjects, GLM was unable to identify certain regions in the liver that were considered "active" as seen in the BOLD time series, while the PLS technique indicated activity in these areas (**Fig. 3**).

Conclusion:

Using our liver challenge procedure and applying local PLS to analyze the images, we have developed a technique that can differentiate between healthy subjects and patients with a liver disorder, such as hepatitis-C with fibrosis. Our results also indicate that modeling the hemodynamic response function of the liver, using GLM, is not a reliable technique due to the complex dual blood supply to the liver.

References: **[1]** Li *et al.* (1997) *Radiology* 204:71-77. **[2]** Noseworthy *et al.* (2007) *JCAT* 31:193-197.

	% Change	
Subject	**GLM**	**PLS**
1	1.3	-5.8
2	-17.1	-5.9
3	-11.3	-5.1
4	-98.6	-5.9
5	-65.4	-12.0
6	-50.3	-0.4
7	-69.4	-11.0
8	-88.1	-6.1
9	109.5	-0.9
10	30.7	7.6
11	-26.0	0.2

Table 1. % Change in signal response between pre and postprandial states for healthy (1-8) and diseased (9-11) subjects. Red indicates results inconsistent with hypothesis.

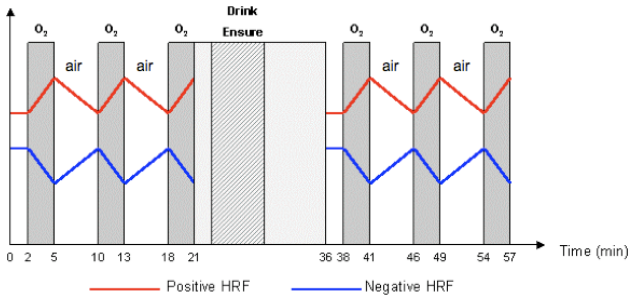


Figure 1. Timing of the study showing hyperoxia cycling and Ensure intake. Both negative and positive HRF responses are also shown.

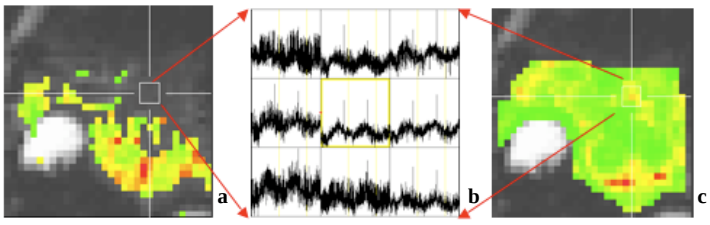
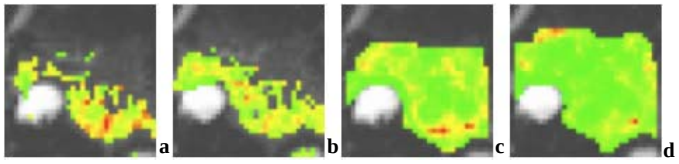


Figure 3. a) GLM is unable to identify an active region in the liver shown in b) while PLS c) indicates response.



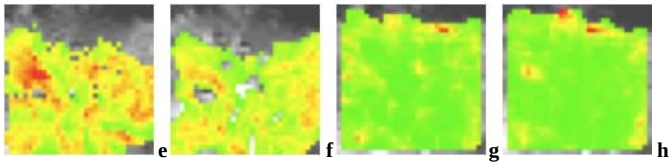


Figure 2. Pre and postprandial signal response maps using GLM (a,b) and (e,f) for subjects 1 and 11 respectively and using PLS (c,d) and (g,h) for subjects 1 and 11 respectively.