AWARD NUMBER: W81XWH-16-1-0524

TITLE: Non-Uniformly Sampled MR Correlated Spectroscopic Imaging in Breast Cancer and Nonlinear Reconstruction

PRINCIPAL INVESTIGATOR: Michael Albert Thomas

CONTRACTING ORGANIZATION: University of California, Los Angeles
Los Angeles, CA 90095

REPORT DATE: October 2017

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE Oct 2017	**2. REPORT TYPE** Annual	**3. DATES COVERED** 30 Sep 2016 - 29 Sep 2017

4. TITLE AND SUBTITLE

Non-Uniformly Sampled MR Correlated Spectroscopic Imaging in Breast Cancer and Nonlinear Reconstruction

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-16-1-0524

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Michael Albert Thomas

E-Mail:athomas@mednet.ucla.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of California, Los Angeles

Radiological Sciences/UCLA Geffen School of Medicine 10833 Le Conte Avenue, CHS#BL428, Los Angeles
CA 90095

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT: Magnetic Resonance Imaging (MRI) is an excellent anatomical tool to image tissue non-invasively. Dynamic contrast enhanced MRI (DCE-MRI) has excellent sensitivity but with varying specificity. MR Spectroscopy (MRS) enables biochemical characterization non-invasively of metabolites. Three major hypotheses are: (1) Accelerated 5-dimensional (5D) echo-planar imaging based correlated spectroscopic imaging (EP-COSI) acquisition produces multi-slice based multi-voxel two-dimensional (2D) MRS in a clinically feasible time. (2) Incorporating non-uniform under sampling (NUS) for spectral/spatial sampling into the 5D EP-COSI data acquisition and the group sparsity (GS)-based reconstruction will reduce the total acquisition time by at least a factor of 12. (3) ADC values derived from the multi-slice DWI data will correlate negatively with choline groups and positively with lipids quantified by the EP-COSI technique. Three goals are proposed: i) NUS schemes will be combined with 5D EP-COSI sequence. ii) GS- based CS reconstruction schemes will be developed for accelerated acquisition and optimized to reconstruct the NUS EP-COSI data with better reliability . iii) Alterations in metabolite and lipid levels will be correlated with ADC changes in breast cancer patients compared to healthy women which will improve the diagnostic accuracy. The study patient cohort will include 50 patients with malignant breast carcinoma, 20 patients with benign breast tumor and 20 healthy women.

15. SUBJECT TERMS
Dynamic contrast enhanced (DCE) MRI, MR Spectroscopy (MRS), echo-planar imaging based correlated spectroscopic imaging (EP-COSI), five-dimensional (5D), two-dimensional (2D), apparent diffusion coefficient (ADC)

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			**19b. TELEPHONE NUMBER** *(include area code)*
Unclassified	Unclassified	Unclassified	Unclassified	9	USAMRMC

Table of Contents

Page

1. Introduction: Breast cancer death rates are higher than those for any other cancer, besides lung cancer in US. More than 232,670 new cases are diagnosed annually (1). Diagnostic accuracy and effective therapeutic management of the breast tumor remain significant medical challenges, hence early detection, diagnosis, and timely treatments are essential to successful health care (2-6). Currently, histological classification from biopsy specimens is generally used as the gold standard to determine malignancy. Hence, optimal imaging methods will enable predicting whether a tumor is going to behave in a benign or aggressive fashion. The proposed Breakthrough Step I grant application will focus on three specific goals: 1) To implement and optimize the NUS based 5D EP-COSI sequence on a 3T Prisma MRI scanner to accelerate the acquisition by an order of magnitude. 2) To develop GS- and total variation (TV)- based CS reconstruction schemes for accelerated acquisition and optimized to reconstruct the NUS EP-COSI data with better fidelity. 3) To record changes in metabolite and lipid levels will be correlated with ADC changes in breast cancer patients compared to healthy women to improve the diagnostic accuracy. Next to lung cancer, breast cancer is the leading cause of death in women in the US. Improving the specificity of malignant and benign tumors using accelerated MRI techniques will be a major outcome. Compressed sensing (CS)-based multi-dimensional magnetic resonance spectroscopic imaging (MRSI) will significantly increase the speed of data acquisition with minimal discomfort for breast cancer patients leading to improved diagnostic accuracy and early detection. In this proposal, we will develop a novel technique for identifying breast cancers more robustly and with greater accuracy than methods currently available.

2. Keywords: Dynamic contrast enhanced (DCE) MRI, MR Spectroscopy (MRS), echo-planar imaging based correlated spectroscopic imaging (EP-COSI), five-dimensional (5D), two-dimensional (2D), apparent diffusion coefficient (ADC). Group sparsity (GS), compressed sensing (CS), total variation (TV)

3. Accomplishments:
Three major goals are the following**: 1**) To further optimize a novel five-dimensional (5D) technology called accelerated echo-planar based correlated spectroscopic imaging (EP-COSI) on a 3T Prisma MRI/MRS scanner (using the Siemens IDEA compiler running on the latest VD13D platform). **2**) To implement and optimize non-linear reconstruction methods such as group sparsity and total variation. **3**) To record i) the 5D NUS EP-COSI data, and ii) DWI and to evaluate ADC maps in the malignant and benign breasts, and healthy women and to correlate the MRSI findings with that of DWI in differentiating benign from malignant breast cancers, and to calculate specificity, sensitivity and accuracy of multi-voxel based 2D MRS and DWI data to differentiate benign from malignant tumors.

What was accomplished Under these goals:

To accomplish the above mentioned goals, we proposed the following ten tasks:

Task 1: To implement and evaluate a novel five-dimensional (5D) technology called accelerated echo-planar based correlated spectroscopic imaging (EP-COSI) on a 3T Prisma MRI/MRS scanner (using the latest Siemens IDEA compiler running on the latest VE11 platform). (**Months 1-6**).

The 5D EP-COSI sequence as shown in Fig.1 was implemented on three different platforms (VE11A, VE11B and VE11C): top row: the analog-to-digital converter (ADC); 2nd row: the radio-frequency (RF) wave forms used to the slice localization along 3 spatial dimensions; 3rd through 5th rows represent X, Y and Z gradient wave forms.

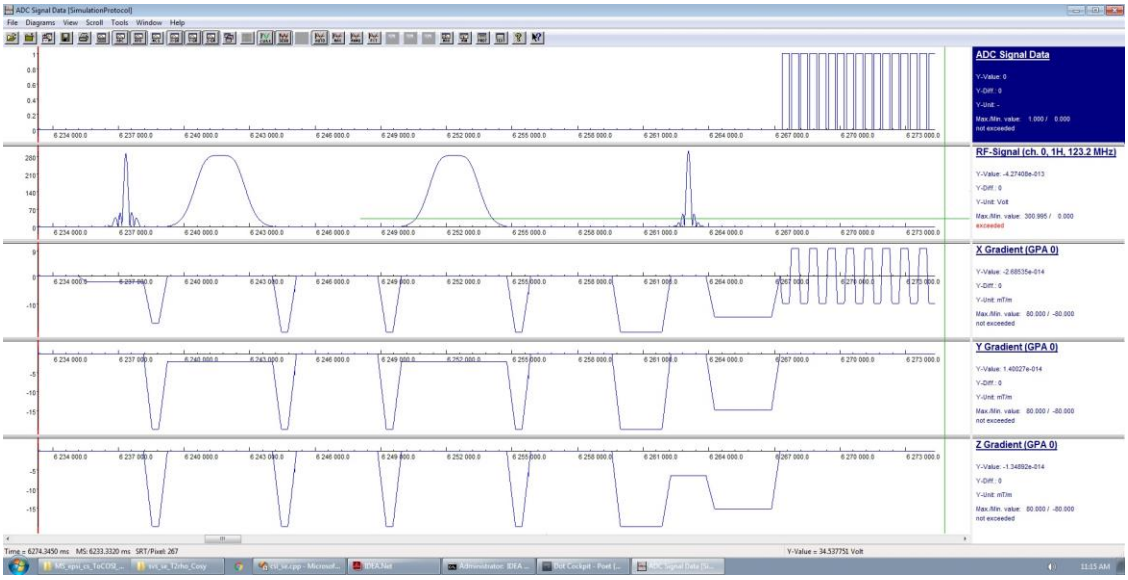

Fig.1. The 5D EP-COSI sequence showing the ADC, RF and gradient waveforms.

Task 2: To evaluate the accelerated 5D EP-COSI data using a breast phantom containing two concentric spheres, the inner one containing several metabolites (choline and ethanolamine groups, creatine, lactate and more amino acids) which have been reported in breast tissues surrounded by the outer phantom containing corn oil to mimic fatty tissues known to be in breast tissues, and to optimize the echo speed-factor and other acquisition parameters using the phantom (**Months 1-6**).

As shown in Fig.2, we prepared a corn oil phantom (left) containing saturated and unsaturated lipids to mimic infiltrating fit in the breast tissue and a quad phantom (right) containing N-acetylaspartate, lactate, creatine and choline. Eight slices from the oil phantom localized by the 5D EP-COSI sequence is shown on the left and similarly, 8 slices from the quad phantom on the right side. Extracted 2D COSY spectra from the corn oil and lactate are also shown.

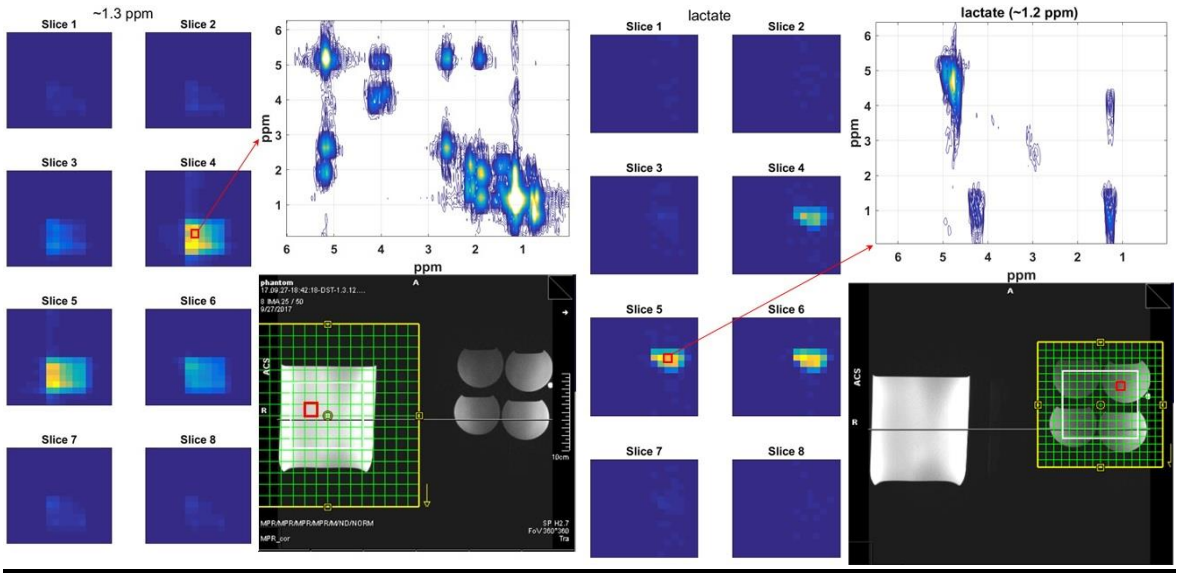

Fig.2. A corn oil and a quad phantom containing metabolites are shown.

Task 3: To implement and optimize non-linear reconstruction methods (group sparsity and total variation). (**Months 3-9**).

Using the above corn oil and the metabolite (quad) phantoms, the undersampled data at 8X and 12X were reconstructed using two different non-linear reconstruction methods: 1) total variation and 2) group sparsity (GS). The GS method was able to retain the fidelity even when higher acceleration schemes were used (12X and 16X).

Task 4: To continue to evaluate/optimize the accelerated 5D EP-COSI data using the breast phantom containing two concentric spheres, to optimize the echo speed-factor and other acquisition parameters using the phantom (**Months 7-18**).

We will purchase a spherical flask containing two layers in which the corn oil will be inside one layer and breast metabolites (choline, phosphoryl and glycerylphosphoryl choline, uridine phosphate) from Sigma-Alrich.

Task 5: To record the 5D EP-COSI spectra in the fatty, glandular and ductal areas of healthy breasts. Twenty healthy female volunteers (25-70 years old) with no previous history of breast cancer will be investigated. (**Months 9-36**).

As shown in Fig.3, the accelerated (8X) 5D EP-COSI data was acquired in a healthy subject and the reconstructed data using TV and GS are shown. The chemical shift multi-slice images were of good quality using both reconstruction methods.

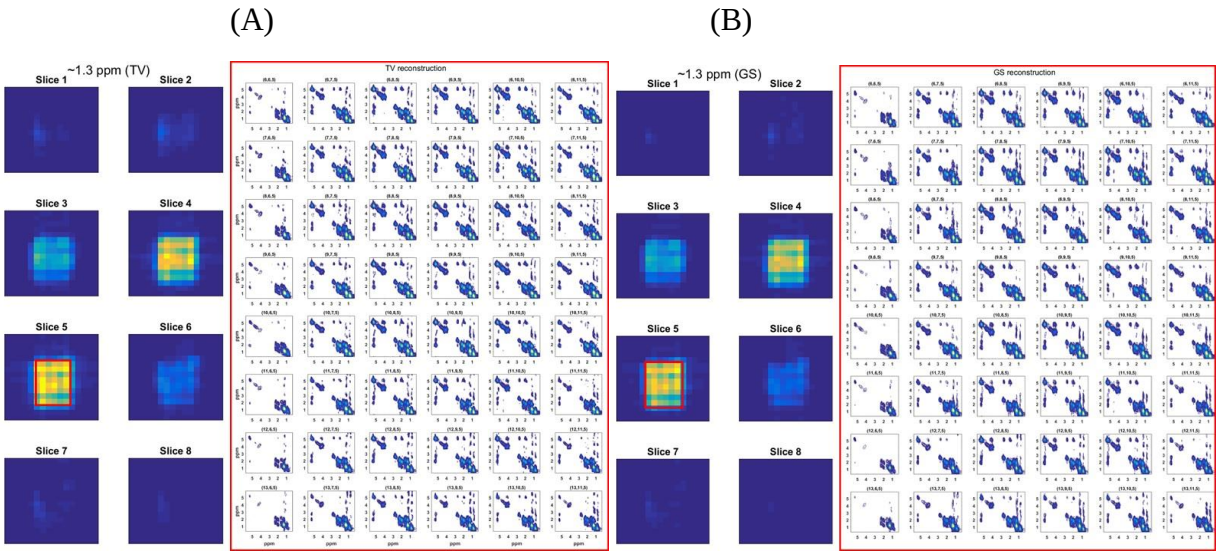

Fig.3. The accelerated 5D EP-COSI data acquired in a healthy volunteer and reconstructed using TV (A) and GS (B)

Eight healthy women (age range of 26-58 years) were screened for the MRI scans. One subject declined to continue with the scan due to claustrophobia. Hence, the 5D EP-COSI data have been successfully scanned in 7 healthy using the Siemens 3T Skyra MRI scanner currently running on the VE11C platform.

Task 6: To record multi-slice DWI in twenty healthy breasts, and to calculate the ADC maps. (**Months 9-36**).

Diffusion weighted MRI data have been successfully recorded in 7 healthy subjects using the Siemens 3T Skyra MRI scanner currently running on the VE11C platform.

Task 7: To record the 5D EP-COSI spectra in twenty patients with benign breast tumor (fibroadenoma, proliferative fibrocystic change and papillomas) (**Months 9-36**).

The 5D EP-COSI and diffusion weighted MRI data have been successfully scanned in 5 benign breast cancer subjects using the Siemens 3T Skyra MRI scanner currently running on the VE11C platform.

Task 8: To record the 5D EP-COSI spectra in fifty patients with biopsy-proven breast cancer (ductal carcinoma and invasive lobular cancer) (**Months 9-36**).

Four malignant breast cancer patients have been screened so far out of which one patient was investigated using the 5D EP-COSI sequence.

Task 9: To record multi-slice DWI in fifty malignant patients with biopsy-proven breast cancer and twenty benign breast cancer, and to calculate the ADC maps. (**Months 9-36**).

Four malignant breast cancer patients have been screened out of which one patient was investigated using the DWI sequence.

Task 10: To correlate the accelerated 5D EP-COSI findings with that of DWI in differentiating benign from malignant breast cancers, and to calculate specificity, sensitivity and accuracy of the MRSI and DWI data in differentiating benign from malignant tumors. (**Months 12-36**).

This task will be investigated after successfully recording 20 malignant, 20 benign and 20 healthy women and repeated at the end of the proposed study.

Major Activities: 1) Our protocol was approved by both UCLA IRB and HRPO. The HRPO approval was received on June 8, 2017. 2) The 5D EP-COSI sequence has been compiled on the Siemens VD13D, VE11A, VE 11B and VE 11C platforms and it was tested using a phantom containing several metabolites at physiological concentrations and also, at pH of 7.2 and a corn oil phantom containing oil

Significant Results/Key Outcomes: After testing the 5D EP-COSI sequence using phantom solutions, 8 healthy women (age range of 26-58 years) and 5 benign breast cancer subjects (age range of 26-67 years) were screened for the MRI scans. One subject declined to continue with the scan due to claustrophobia. However, the 5D EP-COSI and diffusion weighted MRI have been successfully scanned in 7 healthy and 5 benign breast cancer subjects using the Siemens 3T Skyra MRI scanner currently running on the VE11C platform.

What Opportunities for training and professional development has the project provided?: Nothing to Report

How were the results disseminated to communities of interest: Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?: We will continue to screen malignant and benign breast cancer patients and healthy subjects. After screening the subjects for MRI safety and other related issues, they will be scanned using the 3T Skyra MRI scanner equipped with a dedicated breast coil. After compiling the data in 12 healthy and 12 malignant/benign cancer subjects, we plan to submit an abstract to the2018 Radiological Society of Northern America (RSNA) or cancer related conferences.

4. Impact:

What was the impact on the development of the principal disciplines of the project?: Nothing to Report

What was the impact on other disciplines? Nothing to Report

What was the impact on technology transfer? Nothing to Report

What was the impact on society beyond science and technology? Nothing to Report

5. Changes/Problems: Nothing to Report

6. Products:

1) Publications, Conference papers and Presentations: An ePoster on the abstract entitled "Correlation of Diffusion Weighted Imaging and Echo planar Correlated Spectroscopic Imaging of Breast Cancer at 3T" was prepared and submitted to the ISMRM website on April 14th. The ePoster was presented at the 25th International Society of Magnetic Resonance in Medicine (ISMRM) in Honolulu, HI April 22-27, 2017.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name	**M. Albert Thomas Ph.D.**
Project Role	P.I.
Researcher Identifier	0000-0001-9037-2585
Nearest person month worked	12 months
Contribution to Project	Design of the project and supervision of the MRI data acquisition and pos-processing
Funding Support	Dr. Thomas is currently funded by NIH and VA Merit grant also
Name	**Melissa Joines M.D.**
Project Role	Co.I.
Researcher Identifier	None
Nearest person month worked	5 months
Contribution to Project	Study Subject Recruitment and review of MRI
Funding Support	None
Name	**Nanette DeBruhl M.D.**

Project Role	Co.I.
Researcher Identifier	None
Nearest person month worked	5 months
Contribution to Project	Study Subject Recruitment and review of MRI
Funding Support	None
Name	**Manoj Sarma**
Project Role	Co-I
Nearest person month worked	4 months
Contribution to Project	Sequence Development and Data Processing
Funding Support	Partly funded by NIH grants also
Name	**Andres Saucedo M.S.**
Project Role	Graduate Student Researcher
Research Identifier	None
Contribution to Project	Data Acquisition and Post-processing
Funding support	Partly funded by NIH grants
Name	**Stephanie Gilbert B.S.**
Project Role	Study Coordinator
Nearest person month worked	5 months
Contribution to Project	IRB protocol renewal/amendment, recruitment
Funding Support	Radiology Departmental funds

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period? Nothing to Report

What other organizations were involved as partners? Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS: Nothing to Report

9. Appendices: Nothing to Report.