# CCNS Transition Workshop
# May 4-6, 2016

## SPEAKER TITLES/ABSTRACTS

**Tirthabir Biswas**
Loyola University

"A New Template for Walking"

Despite the complex dynamics that underlie the kinematics of individual legs and joints during legged locomotion, the motion of the center of mass (COM) is relatively simple and can qualitatively be described by simple models called templates. Two of the commonly used templates are the inverted pendulum (IP) template - in which the COM vaults over stiff legs, and its extension, the spring-loaded pendulum (SLIP) template in which the COM bounces along on a spring-loaded leg. While IP has been successful to describe walking, SLIP has been the preferred model for running. Neither however seems to be able to explain slow walking motion quantitatively. In our work we will present a new template that can describe slow walking motion and test its viability with data from slow walking fruit flies. We will then go on to discuss how such a template can be integrated with neuromuscular models.

**Andrew Brown**
Clemson University

"Efficient Markov Chain Monte Carlo Methods for Hierarchical Bayesian Inverse Problems"

Ill-posed inverse problems arise in many areas of neuroimaging, including EEG, MEG, CT, and PET. There has been much work focusing on efficiently computing the maximum a posteriori (MAP) solution to such problems. To quantify reconstruction uncertainty, and to estimate the regularization parameters, we adopt a hierarchical Bayesian approach to sample the posterior distribution via MCMC. However, sampling costs can be quite high and the choice of a good proposal distribution is critical to the performance of a Metropolis-Hastings-within-Gibbs algorithm. We propose computational techniques to speed up such algorithms and demonstrate the performance of our approach on simulated examples motivated by neuroimaging applications.

**Iain Bruce**
Duke University Medical Center

"Quantifying Correlations Artificially Induced in fcMRI Data by the SENSE pMRI Model"

In functional connectivity magnetic resonance imaging (fcMRI), spontaneous functional activity is estimated throughout the brain by observing fluctuations in blood oxygenation levels over a time series of images. As the discrete and serial fashion by which these images are acquired places constraints on both the spatial and temporal resolution of the time series data, parallel MRI models that sub-sample the spatial frequency domain have been widely adopted. However, as accelerating data

acquisition is the primary focus of almost all parallel MRI studies, the statistical implications of such models and techniques have been broadly overlooked. Sensitivity Encoding (SENSE), arguably the most common of these models, utilizes spatial sensitivity profiles from each coil in a phased array to reconstruct the sub-sampled/aliased coil images into a single un-aliased image. To precisely quantify the statistical implications of the SENSE model in f(c)MRI data, the complex-valued model is represented in terms of a real-valued isomorphism. It is shown through both theoretical and in-vivo illustrations that the reconstruction of aliased coil images into a full field of view image through SENSE induces an artificial correlation between previously aliased regions of the image. As these correlations are present in all SENSE reconstructed data, they can ultimately result in misleading inferences drawn from fcMRI data if unaccounted for.

**Jian Cheng**
NIH

"Mapping Tissue Microstructure using Spherical Polar Fourier Diffusion MRI"

In diffusion MRI (dMRI), local reconstruction is to estimate biologically meaningful quantities from diffusion signal samples. It is normally also the first step to generate structural connectivity network via fiber tracking. In this talk, I will present a novel method, called Spherical Polar Fourier Imaging (SPFI), which is a generalization of diffusion tensor model to deal with more complicated micro-structures like crossing fibers. With SPFI, we can estimate ensemble average propagator (EAP), diffusion orientation distribution function (dODF), fiber directions, and some meaningful scalar maps. I will also briefly introduce our open source software called dmritool which is used for synthetic data generation, local reconstruction and sampling scheme design.

**Julianne Chung**
Virginia Tech

"Computational Methods for Large-Scale Inverse Problems"

Reconstructing images from indirect measurements is a central problem in many applications. The process of image reconstruction typically requires solving an inverse problem that is ill-posed and large-scale, making it challenging to solve. This talk will focus on recent advances in inverse problems. We will describe analytic tools that can be used to investigate underlying ill-posedness and apply them to various reconstruction problems such as image deblurring, super-resolution, and tomographic reconstruction. We will discuss state-of-the-art computational tools and methods for image reconstruction, including regularization approaches and regularization parameter selection methods.

**Michele Guindani**
MD Anderson

"Integrative Bayesian Modeling Approaches to Imaging Genetics"

Imaging genetics has rapidly emerged as a promising approach for investigating the genetic determinants of brain mechanisms that underlie an individual's behavior or psychiatric condition. By combining single-nucleotide polymorphism (SNP) arrays and functional magnetic resonance imaging (fMRI), we propose two approaches for integrative Bayesian analysis that allow us to discriminate between individuals with schizophrenia and healthy controls, based on a sparse set of discriminatory regions of interest (ROIs) and SNPs. We use simulation studies to assess the performance of our methods and apply it to data collected from individuals with schizophrenia and healthy controls.

**Alexander Hoover**
Tulane University

"Neuromuscular Control of Jellyfish Turning"

In order for an organism to have a robust mode of locomotion, the underlying neuromuscular organization must be maneuverable in a changing environment. In medusae, the activation and release of muscular tension is governed by the interaction of pacemakers with the underlying motor nerve net that communicates with the musculature. This set of equally-spaced pacemakers located at bell rim alter their firing frequency in response to environmental cues, forming a distributed mechanism to control the bell's muscular contraction. To turn, pacemakers induce an asymmetrically timed contraction with the bell musculature. In this work, we explore the control of neuromuscular activation with a model jellyfish bell immersed in a viscous fluid and use numerical simulations to describe the interplay between active muscle contraction, passive body elasticity, and fluid forces. The fully-coupled fluid structure interaction problem is solved using an adaptive and parallelized version of the immersed boundary method (IBAMR). This model is then used to explore the interplay between pacemaker firings, fluid dynamics, and the material properties of the bell.

**Mary Kociuba**
Marquette University

"A Method to Mitigate Inter-slice Signal Leakage in SMS-fMRI"

A higher sampling rate of the BOLD time-course increases the statistical power of the fMRI analysis, and higher volume acquisitions prevent image distortion from motion artifacts. Fast imaging methods like simultaneous multi-slice (SMS) acquisitions, where multiple slice planes are simultaneously magnetized for a single reconstructed image of superimposed slice images, often focus on speed rather than accuracy. Increasing temporal resolution while mitigating inter-slice signal leakage and the correlation induced from suboptimal slice separation methods, is a significant challenge of SMS-fMRI. The Multi-Coil Separation of Parallel Encoded Complex-valued Slices (mSPECS) method minimizes residual artifacts from time-series slice un-aliasing, while maintaining an optimal speed-up of scan time and preserving the BOLD signal for the fMRI activation statistics. To implement the mSPECS reconstruction, the SMS-fMRI time-series is acquired with a Hadamard EPI sequence, and the method combines coil encoding with the orthogonal properties of Hadamard matrices to disentangle the aliased slices. The mSPECS method is expanded to achieve a higher acceleration, with the mSPECS with In-Plane Acceleration (mSPECS-IPA) method, to separate aliased slices both in-plane and through-plane. These approaches implement a bootstrap sampling algorithm of calibration images to minimize induced correlation and residual artifacts in the separated image time-series. The mitigation of inter-slice signal leakage in SMS-fMRI acquisition and reconstruction schemes is critical to appropriately model brain networks.

**Xi Luo**
Brown University

"Estimating Brain Pathway Effects Using Large-scale Multilevel Models"

The brain can be conceptualized as a dynamic network of connected nodes, and information, such as external stimuli, is processed while passing through series of brain nodes that form pathways. Structural equation modeling (SEM) is usually employed to quantify the brain information flow. However, strong empirical evidences suggest that fMRI measured activities are influenced by stimulus

unrelated factors, and thus violating the assumption for causal interpretation of SEM results. We propose a new two-layer SEM framework that provides valid causal inference even if structured unmeasured confounding factors are present. We develop a constrained optimization approach to estimate the model coefficients, and analyze the nonidentifiability issue due to unmeasured confounding. Because this model leverages large multilevel fMRI data to help remove the confounding effects, we show that the causal effects are identifiable and can be estimated consistently using our multilevel method, without performing sensitivity analysis. Using extensive simulated data and a large cohort fMRI dataset, we demonstrate the improvement of our approach over existing methods. This is joint work with Yi Zhao.

**Chintan Mehta**
Yale University

"Identifying Genetic Variants for Learning Ability with Neuroimaging"

Specific learning disorders (SLD) are an archetypal example of how clinical neuropsychological traits can differ from underlying genetic and neurobiological risk factors. Disparate environmental influences and pathologies impact learning performance assessed through IQ-achievement exams and clinical valuations, the primary diagnostic tools for SLD. Here we present a novel method to quantify neurobiological risk for learning problems with neuroimaging biomarkers. We then integrate this risk into a genomewide association study (GWAS) predicated on a learning performance composite score derived from cognitive exams. Regions in the temporal lobe and anterior cingulate best characterized the brain morphology of those diagnosed with learning problems in a cohort of 479 typically developing European individuals between 8 and 21 years of age. In this cohort, single nucleotide polymorphisms in a gene on chromosome 15 had significant association with learning performance at a genomewide level. We validated this finding in an independent cohort of 2,327 individuals of the same demographic profile. Our statistical approach for integrating genetic and neuroimaging biomarkers can be extended into studying the biological basis of other neuropsychological traits.

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**Amanda Mejia**
Johns Hopkins University

"PCA Leverage: Outlier Detection for High-Dimensional fMRI Data"

Outlier detection for high-dimensional data is a popular topic in modern statistical research. However, one source of high-dimensional data that has received relatively little attention is functional magnetic resonance images (fMRI), which consists of 100,000 or more measurements, sampled at hundreds to thousands of time points. At a time when the availability of fMRI data is rapidly growing—primarily through large, publicly available grassroots datasets consisting of hundreds of subjects collected at different sites—automated quality control and outlier detection methods are greatly needed. I propose PCA leverage and demonstrate how it can be used to identify outlying time points in an fMRI scan. Furthermore, PCA leverage is a measure of the influence of each observation on the estimation of

principal components, which forms the basis of independent component analysis (ICA) and seed connectivity, two of the most widely used methods for analyzing resting-state fMRI data. I also propose an alternative measure, PCA robust distance, which is less sensitive to outliers and has controllable statistical properties. The proposed methods are validated through simulation studies and are shown to have high sensitivity and specificity. A reliability study using resting-state fMRI data from the Autism Brain Imaging Data Exchange (ABIDE) shows that removal of outliers using the proposed methods results in more reliable estimation of subject-level resting-state networks using ICA.

**Laura Miller** and **Katie Newhall**
University of North Carolina

"Modeling the Muscular Response to Motor Neuron Spike-Trains"

An important component of locomotion is sensing the environment and controlling movement accordingly. The nervous system is a fundamental component of actuating and controlling this movement. We therefore seek an understanding of how spike-train signals from motor neurons result in dynamic force generation in muscles. We discuss adaptations to a model linking calcium dynamics to a Hill model for muscular force generation. This model is then used to investigate different relationships between spike-train frequency, intracellular calcium dynamics in the muscle cells, and the resulting force generation. This model connecting spike trains to force generation could then be coupled to a model of locomotion. One potential application would be the control of effective muscles attached to an inverted pendulum, as has been used to model insect walking.

**Hernando Ombao**
University of California, Irvine

"The Future Outlook in EEG Analysis"

I will discuss the specific areas in EEG analysis that require novel methods. I will point out existing work in the statistics and signal processing communities, discuss their limitations and possible extensions.

**Mark Reimers**
Michigan State University

"Issues in Data Analysis for Optical Imaging"

The BRAIN initiative aims to measure functional activity in living brains at high resolution. Although several technologies are being developed a result of this program, the most promising technologies are the high-throughput optical imaging technologies, which generate movies of brain activity, up to terabytes of data per experiment. However the statistical methods to analyze and interpret these data are largely undeveloped. This session will discuss four kinds of issues in analyzing optical data. The issues are: pre-processing to remove artifacts and reduce noise; exploratory analysis and visualization; state-space dynamics; and inference of network connections.

**Ben Risk**
SAMSI

"Examination of Artifacts from Multiband Imaging"

Multislice acquisition techniques can be used to decrease the time between acquisition of fMRI volumes, which can increase statistical power and better characterize the temporal dynamics of the blood-oxygen level dependent (BOLD) signal. However, multislice techniques result in signal leakage between aliased voxels, which can lead to false positives. We examine the Slice-GRAPPA algorithm for image reconstruction at different acceleration factors. We illustrate potential issues with slice leakage and induced correlations via simulation. We also analyze fMRI data from the Human Connectome Project, which uses a high acceleration factor and thus may be susceptible to false positives.

**Daniel Rowe**
Marquette University

"A Gentile Introduction to Image Processing and Reconstruction in FMRI"

An outline of the talks in this session will be given. A brief introduction to inverse Fourier transform image reconstruction for fMRI will be presented followed by an isomorphism representation of inverse Fourier image reconstruction. Several image processing operations will be described as matrix multiplications and integrated into the isomorphism representation. Basic statistical consequences of these image processing operations including modified mean and induced correlation will be highlighted.

"The Current State of Image Processing and Reconstruction with Future Directions"

The current state of image processing and reconstruction will be summarized including the talks in this session. Future avenues of possible exploration along with open questions will be presented.

**Sean L. Simpson**
Wake Forest School of Medicine

"Disentangling Brain Graphs: The Conflation of Network and Connectivity Analyses"

Understanding the human brain remains the Holy Grail in biomedical science, and arguably in all of the sciences. Our brains represent the most complex systems in the world (and some contend the universe) comprising nearly one hundred billion neurons with septillions of possible connections between them. The structure of these connections engenders an efficient hierarchical system capable of consciousness, as well as complex thoughts, feelings, and behaviors. Brain connectivity and network analyses have exploded over the last decade due to their potential in helping us understand both normal and abnormal brain function. Functional connectivity (FC) analysis examines functional associations between time series pairs in specified brain voxels or regions. Brain network analysis serves as a distinct subfield of connectivity analysis in which associations are quantified for all time series pairs to create an interconnected representation of the brain (a brain network), which allows studying its systemic properties. While connectivity analyses underlie network analyses, the subtle distinction between the two research areas has generally been overlooked in the literature, with them often being referred to synonymously. However, developing more useful analytic methods and allowing for more precise biological interpretations requires distinguishing these two complementary

domains. Here we briefly delineate methods for (static) connectivity and network analyses and discuss the importance of joint and hybrid methodology for expanding the scope of neuroscience research.

**Hoang Duy Thai**
SAMSI

"Simultaneous Image Segmentation and Deconvolution"

Given a noisy and blurred piecewise smooth signal, e.g. brain imaging, image reconstruction tries to recover its clean version. Image segmentation turns a piecewise smooth signal into a piecewise constant. In this work, we simultaneously address two issues using approximation theory in function space. This constrained non-convex minimization problem in the Banach space (in the discrete setting) is tackled using convex relaxation. A piecewise smooth component is measured by the \ell_1 norm of its directional mean curvature which can reduce the so-called "stair-case effect". Both theoretical results and demonstrations on images of relevance to neuroscience will be discussed.

**Sarah Vallélian**
SAMSI

"Reduced Order Modeling in Photoacoustic Tomography"

Photoacoustic tomography combines a rich optical contrast with the high resolution of ultrasound tomography. Mathematically it is an ill-posed inverse coefficient problem for a coupled wave equation and diffusion equation pair. To accelerate the inversion in multispectral settings, we use a POD-based reduced order model for the wavelength dependence. We demonstrate the computational gains on a synthetic problem motivated from neuroscience.

**Lu Wang**
Duke University

"Bayesian Network-Response Regression"

In order to better understand how the brain network varies according to phenotypes (behavioral traits, neurological disorders, etc.), novel statistical methods are needed for analyzing network-valued data consisting of a different network for each individual. We develop a Bayesian semiparametric model, which combines low-rank factorizations and Gaussian process priors to allow flexible shifts of the conditional expectation for a network-valued random variable across the values of a predictor. We demonstrate the good performance of our model in edge prediction and network goodness-of-fit assessments. The model is applied to learn changes in the brain network across intelligence scores and we find that intelligence score is positively correlated with average connection probability of potential edges connecting the left and right frontal lobes.

**Jasmine Yang**

"Imaging Genetic Analysis for PNC Behavioral Data"

The Philadelphia Neurodevelopmental Cohort (PNC) is a research initiative focusing on characterizing brain and behavior interaction in youths, with the availability of participants' genomic, neuroimaging and behavioral data. Both Genome-Wide Association Study(GWAS) and the Joint and Individual

Variation Explained (JIVE) methodology were used to identify significant genes and pathways associated with differentiating subject neurophenotypes.

**Qunqun Yu**
University of North Carolina

"Joint and Individual Variation Explained (JIVE) Integration of HCP Data"

As noted on the Human Connectome Project (HCP) website, mapping the human brain is one of the great scientific challenges of the 21st century. The Project is tackling a key aspect of this challenge by elucidating the neural pathways that underlie brain function and behavior data. Our study applies the joint and independent variation explained method on task functional MRI data and behavioral data from Human Connectome Project. Motivated by recent developments in the joint and individual variation explained (JIVE) method, we propose to simultaneously explore the joint and individual variations within image and behavioral data. Our results show that JIVE has a good performance in separating the behavior related and unrelated variations in the image data and thus provides a new insightful view of brain function. One example where task variations are strong, one where task variations are weak and a reference case where the behavior is not directly related to the image are provided to see the different levels of signals found in the joint variation. This is a new indication of the efficiency of JIVE on decomposing the joint and individual variations.

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**Zhengwu Zhang**
SAMSI

"Robust Human Brain Structural Connectivity Analysis"

Structural connection in an individual brain plays a fundamental role in how the mind responds to everyday tasks and challenges. Modern imaging technology such as diffusion MRI (dMRI) makes it easy to peer into an individual brain and collect valuable data to infer the structural connectivity. The difficulty for current statistical analysis and inference of the connectivity of human brain is to extract robust and high-resolution connectivity network from dMRI. In this talk, I will present a state-of-the-art dMRI processing pipeline to process dMRI data and to reliably construct the structural connectivity from dMRI. The pipeline includes three different module: (1) reliable streamline construction, (2) robust connectivity analysis, and (3) multi-scale connectivity analysis.

**Yihong Zhao**
New York University

"Imaging Genetics toward Mechanistic Understanding of Psychiatric Disorders"

To more effectively treat neuropsychiatric disorders and identify high-risk groups for targeted interventions, it is essential to understand the underlying biological mechanisms that are specific or shared across disorders. With rapid development of technologies, large-scale genetic data such as genome-wide SNP and epigenome, structural and functional brain imaging data, and various phenotypic data at behavioral level have been collected. This motivated the pursuit of understanding pathophysiological processes by integrative analysis of data at genetic, brain, and behavioral levels. We will highlight current major challenges in psychiatric research and discuss how big data and discovery science can advance our understanding in this field.