Quantitative Methodologies Pilot Program 2021 Awardees

In October 2021, the Quantitative Methodologies Pilot Program (QuMP) awarded three interdisciplinary, translational research projects involving quantitative methodologies, such as mathematical modeling, statistics, biostatistics, and epidemiology. Each project will receive $25,000 in funding for a 12 month award period.

Decision strategies during speech perception in aging

$25,000 Awardee

Team: Bharath Chandrasekaran, PhD (PI), Jacie McHaney (Co-PI), Casey Roark, PhD, Catherine Palmer, PhD, Tobias Teichert, PhD.

Abstract: Hearing impairment in middle-aged adults is considered the number one modifiable risk factor for dementia in later life, presenting a critical need to understand auditory sensory-cognitive interactivities in aging individuals. We will develop and test computational models of speech processing derived from a set of models we have developed in an NSF-funded grant and will allow the rapid determination of the extent to which an individual's hearing difficulties arise from sensory or cognitive processes (which require different aural rehabilitation approaches). Leveraging quantifiable tools for the assessment of speech perceptual difficulties is an unmet research need that can significantly alter diagnostic and clinical practice. We propose to collect data from middle-aged adults with normal hearing thresholds. We plan to utilize patients from the greater Pittsburgh community and our established collaboration with the UPMC Eye and Ear Clinic. Out of the 47,000 clinic patients in the last five years at UPMC Eye and Ear Clinic, more than 15% had normal hearing thresholds (but still had concerns regarding their hearing health and in many cases the ability to understand in complex listening environments). Participants will complete a number of behavioral SPIN tasks, where they will categorize phonemes in challenging listening environments. Traditionally, analyses of SPIN performance involve an estimate of listening accuracy. Our novel extension of drift diffusion models will assess the underlying sensory-cognitive process in SPIN. Our computational model will examine the extent to which noisy sensory evidence is accumulated by the individual until enough evidence is accrued to make perceptual decisions across a variety of listening conditions. Our model will also account for accuracies and the time taken to respond to uncover the extent to which performance is driven by sensory versus cognitive processes and the extent to which these processes are driven by top-down biases. The development of such computational models proposes a major shift in behavioral SPIN research and successful implementation will lead to a precision medicine approach to aural rehabilitation.

Modern factor analysis for metabolic data

$25,000 Awardee

Team: Chris McKennan, PhD, (PI), Weiqiong Huang (co-PI), Joshua Cape, PhD, Kedir Turi, PhD.

Abstract: Metabolomics is the high-throughput study of tissue- or body fluid-specific small molecule metabolites. As a relatively nascent area of research, metabolomics has the potential to elicit new insights into the origin of human disease and drug metabolism. Like when analyzing other 'omic' data, factor analysis is an indispensable tool when attempting to interpret high-dimensional metabolomic data. Factor analysis is routinely used to identify co-regulated metabolites, cluster samples, denoise data, and correct for latent confounds, all of which are critical steps towards metabolic biomarker discovery and uncovering meaningful biological variation. While it is tempting to apply existing methods designed for other omic data to perform factor analysis in metabolomic data, several features unique to metabolomic data make this imprudent. To this end, we propose three related problems with the goal of performing interpretable factor analysis in metabolomic data. First, we will consider the problem of performing PCA with non-ignorable missing observations, which is critical in mass-spectrometry-based metabolomic data. Second, we will define an estimator for the number of latent factors that facilitates optimal latent confounder correction. Lastly, we propose incorporating *a priori* metabolic pathway information into a factor analysis algorithm to facilitate interpretable factor analysis in metabolomic data. All three of our methods will be the first to solve these problems, and will aid in metabolomic biomarker discovery.

Quantifying molecular circadian time and dysfunction for mental health and precision medicine

$25,000 Awardee

Team: George Tseng, ScD (PI), Michael Gorczyca (Co-PI), Colleen McClung, PhD.

Abstract: Biological rhythms in living organisms influence cellular and organ system function as well as enable environmental adaptation. In particular, the circadian rhythm regulates a variety of biological processes, and alterations of this rhythm are associated with morbidities such as cancer and mental disorders. The critical influence of the circadian rhythm in overall health has stimulated several research efforts, leading to identification of circadian genes and their roles in biological processes. These findings have facilitated the development of translational therapies. However, our knowledge of associations between intracranial circadian rhythm abnormalities and psychiatric disorders is limited and conclusions about circadian associations are complicated by unobserved factors that can cause variation in the circadian rhythm between experimental subjects. This variation can bias statistical inference. In this work, we propose to develop a circadian error-in-variables model from transcriptomic or methylation data that estimates the molecular circadian time (MCT) while accounting for this bias. We also develop a measure of overall molecular

circadian dysfunction (MCD) for each subject, defined as the omics aggregation of differences in observed circadian gene expression and estimated circadian expression level. Larger molecular circadian dysfunction reflects greater unhealthiness in circadian rhythm. We will test for novel associations between the quantified abnormal rhythmicity and mental health. Finally, we will develop an open-source and user-friendly software package for other researchers to use the developed methodologies.

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