AIChE Webinar Series

Computing & Systems Technology Division (CAST) Welcomes

Juergen Hahn

Professor and Department Head

Department of Biomedical Engineering
Department of Chemical & Biological Engineering

Center for Biotechnology and Interdisciplinary Studies
Rensselaer Polytechnic Institute

Towards the Development of a Diagnostic Test for Autism Spectrum Disorder: Big Data Meets Metabolomics

Autism Spectrum Disorders (ASD) are a group of neurological disorders that present with limited social communication/interaction and restricted, repetitive behaviors/interests [1]. The current estimate is that approximately 1.5% of children in the US are diagnosed with ASD [2]. While this is a high prevalence and the economic burden by ASD is significant [3], there is still considerable debate regarding the underlying pathophysiology of ASD. Because of this lack of biological knowledge, autism diagnoses are restricted to observational behavioral and psychometric tools. Subsequently, the average age at which children receive an ASD diagnosis is four years [2], while it is generally acknowledged that diagnosis between 18-24 months is possible [4]. Furthermore, disparities by race/ethnicity in estimated ASD prevalence as well as disparities in the age of earliest comprehensive evaluation and presence of a previous ASD diagnosis or classification, suggest that access to treatment and services might be lacking or delayed for some children [2]. Thus, confirmation and expansion of the unique metabolic abnormalities in children with autism that accurately distinguishes them from neurotypical children would not only strengthen diagnostic accuracy, but also provide insights into underlying pathophysiology and a personalized approach to treatment options.

Stepping towards this goal of incorporating biochemical data into ASD diagnosis, we analyzed measurements of metabolite concentrations of the folate-dependent one-carbon metabolism and transulfuration pathways taken from blood samples of 83 participants with ASD and 76 age-matched neurotypical peers. Fisher Discriminant Analysis enabled multivariate classification of the participants as on the spectrum or neurotypical which results in 96.1% of all neurotypical participants being correctly identified as such while still correctly identifying 97.6% of the ASD cohort [5]. Furthermore, kernel partial least squares was used to predict adaptive behavior, as measured by the Vineland Adaptive Behavior Composite score, where measurement of five

metabolites of the pathways was sufficient to predict the Vineland score with an R2 of 0.45 after cross-validation. This level of accuracy for classification as well as adaptive behavior prediction far exceeds any other approach in this field.

In addition to classification and adaptive behavior prediction, we have developed a steady state model of the metabolic pathways. We estimated flux parameters for every participant of the study and derived a probability density function for each parameter for the neurotypical participants and, separately, for participants with an ASD diagnosis. Comparison of the parameter distributions between neurotypical study participants and those on the autism spectrum revealed significant differences for four model parameters [6]. Sensitivity analysis identified the parameter describing the rate of glutamylcysteine synthesis, the rate-limiting step in glutathione production, to be particularly important in determining steady-state metabolite concentrations.

These computational studies enhance the analysis obtained from traditional population-level statistics and suggest that folate-dependent one carbon metabolism and transsulfuration may play an integral role in ASD pathophysiology. Although these results need to be replicated in independent studies, these analyses suggest combinations of metabolites in these pathways as potential biomarkers for ASD.

Speaker Biography

Juergen Hahn is the department head of the Department of Biomedical Engineering at Rensselaer Polytechnic Institute in addition to holding an appointment in the Department of Chemical & Biological Engineering. He received his Diploma degree in engineering from RWTH Aachen, Germany, in 1997, and his MS and Ph.D. degrees in chemical engineering from the University of Texas, Austin, in 1998 and 2002, respectively. He was a post-doctoral researcher at the Chair for Process Systems Engineering at RWTH Aachen, Germany, before joining the Department of Chemical Engineering at Texas A&M University, College Station, in 2003 and moving to the Rensselaer Polytechnic Institute in 2012. His research interests include systems biology and process modeling and analysis with over 125 peer-reviewed publications in print. Dr. Hahn is a recipient of a Fulbright scholarship (1995/96), received the Best Referee Award for 2004 from the Journal of Process Control, the CPC 7 Outstanding Contributed Paper Award in 2006, was named Outstanding Reviewer by the journal Automatica in 2005, 2006, 2007, and 2010 CAST Outstanding Young Researcher, and has been elected as an AIMBE fellow in 2013. He served on the IEEE CSS Board of Governors in 2016 and has been a CACHE Trustee since 2014. He is currently serving as associate editor for the journals Control Engineering Practice, Processes, and the Journal of Process Control.

References

[1] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washing-ton, D.C.: American Psychiatric Association, 2013.

[2] D.L. Christensen, J. Baio, K.V. Braun, et al. “Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities

Monitoring Network, 11 Sites, United States, 2012." MMWR Surveill Summ, vol. 65 (no. SS-3):1–23, 2016.
[3] J. P. Leigh and J. Du, "Brief Report: Forecasting the Economic Burden of Autism in 2015 and 2025 in the United States," J. Autism Dev. Disord., vol. 45, no. 12, pp. 4135–4139, Dec. 2015.
[4] M. L. McPheeters et al., "Screening for Autism Spectrum Disorder in Young Children: A Systematic Evidence Review for the U.S. Preventive Services Task Force," Rockville, Maryland, 13-05185-EF-1, Feb. 2016.
[5] D.P. Howsmon, U. Kruger, S. Melnyk, S.J. James, and J. Hahn. Classification and Adaptive Behavior Prediction of Children with Autism Spectrum Disorder based upon Multivariate Data Analysis of Markers of Oxidative Stress and DNA Methylation. PLoS Computational Biology 13(3): e1005385, 2017.
[6] T. Vargason, D.P. Howsmon, S. Melnyk, S.J. James, and J. Hahn. Mathematical Modeling of the Methionine Cycle and Transsulfuration Pathway in Individuals with Autism Spectrum Disorder. Journal of Theoretical Biology 416, pp. 28-37, 2017.

Join Webinar on Feb 6, 2017 at 11 AM Eastern Time at http://goo.gl/5ySqO4