

THE GIS SPEAKER SERIES

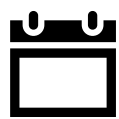


Sequence-based Machine Learning for Modeling Cell State Transitions in Development and Disease

Prof. Michael A. Beer

Departments of Biomedical Engineering, Genetic Medicine, and Oncology, Johns Hopkins University

Host: Shyam Prabhakar



Tuesday 4 June 2024
10.00am – 11.00am



GIS Seminar Room (Level 2)
60 Biopolis Street, Genome, Singapore 138672

About The Speaker

Dr. Michael Beer received his Ph.D. in theoretical physics from Princeton University and switched fields into genomics following the sequencing of the human genome. He now puts his physics training to good use at Johns Hopkins University where he directs the Computational Regulatory Genomics Laboratory in the Dept of Biomedical Engineering and the McKusick-Nathans Department of Genetic Medicine. He uses machine learning algorithms to discover how DNA sequence encodes cell-specific enhancer activity, and builds quantitative models of the mechanisms of enhancer-promoter interaction, nonlinear gene regulatory network models of how enhancers control cell fate, and how regulatory element perturbation and genetic variation contributes to human disease and evolution. He has published over 100 scientific papers, was a Searle Scholar, and is a member of the ENCODE and IGVF consortia.

About The Seminar

Enhancers control cell state transitions in development and disease, but validation of disease associated enhancers has been slow and difficult. Using CRISPRi-based enhancer perturbation during a dynamic cell state transition, we discovered the set of enhancers controlling each of the core transcription factors. Most enhancers had strong effects mid-transition but weak effects post-transition. We developed a simple dynamic gene regulatory network (GRN) model to predict the effect of enhancer perturbation based on properties discovered from DNA-sequence based machine learning. This GRN model predicts nonlinear temporal responses and hysteresis in cell state transitions, and explains the difficulty of observing the effects of enhancer perturbation in the post-transition state. These findings suggest that disease associated variants can contribute sensitively to determine the threshold stimulus of a cell state transition without strongly affecting established cell states, potentially explaining the difficulty of validating disease enhancer variants and suggesting more effective future strategies for precision medicine.