The Blurred Line between Genes and Environments: Insights from GWAS of Family Members' Phenotypes

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ABSTRACT

Genome-wide association study (GWAS) methodologies have become quite standard for complex trait genetic research. Today, a modern GWAS typically correlates a phenotype with tens of millions of genetic variants in large cohorts of millions of individuals to reveal genotype-phenotype associations. However, this seemingly standard approach can give largely biased and/or confounded results in various applications. In this talk, I will discuss a new study design which associates genetic data of a cohort with their family members' phenotypes. That is, the genotypic and phenotypic variables in the GWAS are collected from different individuals. Through three separate applications, focusing on offspring, parental, and spousal phenotypes, I will discuss several challenges and new insights in genetic nurture, ascertainment bias, and assortative mating. The phenotypes discussed in this talk will include socioeconomic outcomes, neurodegenerative disease risk, as well as human partner choice.

Keywords: GWAS; within-family genomic analysis; assortative mating; social genomics.

Inferring Cell-Type-Specific Co-Methylation Networks from Single-Cell DNA Methylation Data

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ABSTRACT

The recent development of single-cell DNA methylation (scDNAm) technologies has enabled the detailed collection of cell-type-specific epigenetic regulation data. Yet, co-methylation network estimation and inference remain challenging due to data sparsity, zero-one inflation, and complex dependencies. Here we present scCoNet, a novel statistical framework for cell-type-specific co-methylation inference using a copula model with zero-one-inflated beta marginal distributions. Our approach flexibly captures both the marginal and joint methylation distributions while accounting for sparsity and leveraging copulas for dependence modeling. We identify distinct epigenetic modules and regulatory pathways by integrating cell type information and covariates. We demonstrate the utility of our method on simulated and real scDNAm data, uncovering biologically meaningful co-methylation patterns linked to cell functions. This work offers a powerful tool to decipher the epigenetic landscape at single-cell resolution and illuminates cell-type-specific regulatory mechanisms.

Keywords: Statistical genomics; DNA methylation; single cell; network

Single-Cell Multiomic Analysis of Circadian Rhythmicity

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ABSTRACT

Circadian rhythms are remarkably widespread across most organisms, regulating hormonal, metabolic, physiological, and behavioral oscillations through molecular clocks that orchestrate the rhythmic expression of thousands of genes. Here, we generate single-cell RNA and ATAC multiomics data to simultaneously characterize gene expression and chromatin accessibility of mouse liver cells across the 24-hour day. We interrogate multimodal circadian rhythmicity in both discretized cell types and transient sub-lobule cell states, capturing space-time omics profiles. We delve beyond mean cyclic patterns to characterize stochastic transcriptional bursting and infer spatiotemporal gene regulatory networks that control circadian rhythmicity and liver physiology. Our findings apply to existing single-cell data of mouse and Drosophila brains and are validated by time-series single-molecule fluorescence in situ hybridization and vast amounts of orthogonal omics data. Altogether, our study constructs a comprehensive map of the time-series transcriptomic and epigenomic landscapes that elucidate the function and mechanism of the liver peripheral clocks.

Keywords: circadian rhythm; single-cell multiomics; RNA expression and DNA accessibility; transcriptional regulation

mist: A Hierarchical Bayesian Framework for Detecting Differential DNA Methylation Dynamics in Single-Cell Data

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ABSTRACT

Recent advancements in single-cell DNA methylation (scDNAm) sequencing technologies have enabled the profiling of epigenetic landscapes at unprecedented resolution, offering insights into cellular heterogeneity, differentiation and evolution. Trajectory inference, which orders cells along pseudotime, allows researchers to track genomics changes across continuous cell states and identify key loci exhibiting differential methylation. However, no methods currently exist to model methylation changes along pseudotime in scDNAm data. Here, we present a hierarchical Bayesian framework for scDNAm data analysis. Our method, named mist (methylation inference for single-cell along trajectory), models stage-specific biological variations, identifies genomic features with significant methylation changes along pseudotime, and performs Differential Methylation (DM) analysis across phenotypical groups. Simulations demonstrate its superior accuracy in detecting DM genes along pseudotime compared to existing methods. Applied to multi-omics datasets of mouse embryonic development and developing human brain, mist identifies key developmental regulators, whose methylation patterns align with lineage transitions. mist is publicly available as an R/Bioconductor package at https://bioconductor.org/packages/mist.

Keywords: epigenetics; bioinformatics; computational biology; biostatistics