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Detecting Regions of Concurrent and Differential Methylation with coMethDMR

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Background: Global changes in DNA methylation have been observed among opioid users. Instead of searching through *individual CpGs* to detect this differential methylation, modern analyses search for differential methylation in *regions* of concurrent methylation. However, identifying differentially methylated regions (DMRs) remains a challenge due to the complex interdependencies inherent to epigenomics data.

Significance: Current methods of DMR detection rely on finding regions with a few highly significant differentially methylated CpGs. These approaches fail to detect regions with small but pervasive differential methylation patterns. Additionally, these methods lose statistical power after multiple comparison corrections due to the massive volume of probes to test. To address these issues, we developed the coMethDMR R/Bioconductor package and DNA methylation analysis pipeline.

Methods: The first step involved is to perform unsupervised clustering on the methylation data to detect regions of contiguous co-methylation. M-values in these clusters are then tested against the phenotype of interest via a linear mixed model that models both variations between CpG sites within the region and differential methylation with a numeric phenotype simultaneously. The overall slope of the cluster is tested against 0, so that statistical significance for a genomic sub-region indicates the DMR is associated with the phenotype.

Results: DNA methylation was analyzed within 64 black heroin users and 32 healthy controls, adjusting for age and sex. Eight protein-encoding genic regions of differential and concurrent methylation were identified with false-discovery rate < 0.05, six of which were in or near CpG islands.

Discussion: Our novel analysis package successfully identified several differentiated and concurrent methylation regions.