S3V2-IDEAS: a package for normalizing, denoising and integrating epigenomic datasets across different cell types

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Abstract

Summary: Epigenetic modifications reflect key aspects of transcriptional regulation, and many epigenomic datasets have been generated under different biological contexts to provide insights into regulatory processes. However, the technical noise in epigenomic datasets and the many dimensions (features) examined make it challenging to effectively extract biologically meaningful inferences from these datasets. We developed a package that reduces noise while normalizing the epigenomic data by a novel normalization method, followed by integrative dimensional reduction by learning and assigning epigenetic states. This package, called S3V2-IDEAS, can be used to identify epigenetic states for multiple features, or identify discretized signal intensity levels and a master peak list across different cell types for a single feature. We illustrate the outputs and performance of S3V2-IDEAS using 137 epigenomics datasets from the VISION project that provides validated systematic integration of epigenomic data in hematopoiesis.

Availability and implementation: S3V2-IDEAS pipeline is freely available as open source software released under an MIT license at: https://github.com/guanjue/S3V2_IDEAS_ESMP.

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Supplementary information: Supplementary data are available at Bioinformatics online.

1 Introduction

The tens of thousands of epigenomic datasets now available are potentially great resources to better understand the associations of epigenetic modifications with mechanisms of transcriptional regulation (Bernstein et al., 2010; ENCODE Project Consortium, 2012; Martens and Stunnenberg, 2013; Moore et al., 2020; Stunnenberg et al., 2016; Xiang et al., 2020a, b; Yue et al., 2014). However, integrating these resources for global inferences about regulation is challenging for many reasons. In this application note, we focus on two issues. First, technical differences in procedures and biological samples analyzed in different laboratories introduce noise and biases that can obscure true biological differences (Meyer and Liu, 2014; Shao et al., 2012; Xiang et al., 2020a, b). Second, certain combinations of epigenetic modifications often appear together, but those combinations of modifications (epigenetic states) need to be learned from integrative modeling across epigenomic datasets simultaneously across multiple cell types (Ernst and Kellis, 2012; Hoffman et al., 2012; Zhang et al., 2016).

Here, we introduce a package, named S3V2-IDEAS, that builds upon our prior works and provides an improved, integrated workflow that will facilitate usability. In this pipeline, we address the first issue (noise and bias in data) by incorporating an improved version of the S3norm method (Xiang et al., 2020b), which can simultaneously normalize signals in foreground and signals in background. In contrast to S3norm, in which each 200 bp bin was assessed as either foreground (peak) or background, in the improved version (S3V2) the reads within each bin are split into foreground reads and background reads. For the background noise track, both non-zero mean and non-zero standard deviations are matched across datasets, which can reduce the noise in some datasets (Fig. 1A, Supplementary Methods and Supplementary Figs S1D and S2). To address the second challenge (integration across multiple features and cell types), we performed genome segmentation using...
the Integrative and Discriminative Epigenome Annotation System (IDEAS), which learns epigenetic state models from the normalized epigenomic signals simultaneously along the genome and across cell types to improve consistency of state assignments across different cell types (Zhang et al., 2016; Zhang and Hardison, 2017). Moreover, the IDEAS model can jointly estimate the state of a genomic region by using the information in a set of similar cell types, so that the state can be accurately estimated even for cell types with missing data (Zhang and Malony, 2019). The S3V2-IDEAS pipeline incorporates both S3V2 normalization and IDEAS segmentation so that the advantages of both methods can be used to normalize, denoise and integrate multi-dimensional epigenomic datasets across different cell types.

2 Implementations

The inputs to S3V2-IDEAS are (i) average read counts of each epigenetic feature in each cell type (bigWig), (ii) an annotation file that includes the names of the cell types and the epigenetic features of bigwig files and (iii) information about the mapped genome, such as chromosome sizes and black-listed regions (Amemiya et al., 2019; Boyle et al., 2014; Kent et al., 2002, 2010; Yue et al., 2014).

The S3V2-IDEAS incorporates two major modules. First, it uses the S3V2 method to normalize and denoise the epigenomic datasets (Fig. 1A). The second module of the package incorporates the IDEAS genome segmentation model to integrate the epigenomic signal into tracks of epigenetic state assignments for each bin in each cell type (Fig. 1B and C). The second module can operate in either of two modes. When the input data include multiple epigenetic features, the module executes an epigenetic states mode (ES mode), which integrates the signals of multiple epigenomic features into epigenetic states as done previously (Fig. 1B). When the input data include one epigenetic feature, the module executes a signal intensity state mode (IS mode) to quantize the signal of that one epigenetic feature into discrete signal levels (Fig. 1C). In the IS mode, a master peak list (Fig. 1D) can be extracted from the signal intensity state tracks by a novel hierarchical method which provides way to integrate the epigenomic information across cell types (Supplementary Figs S5 and S6).

3 Results and discussion

The S3V2-IDEAS produces three outputs: the normalized signal tracks and the \(-\log_{10} P\)-value tracks based on the background model (Fig. 1A); a list of epigenetic states or signal intensity states and the corresponding state track in each cell type (Fig. 1B and C). An additional master peak list can be produced in the IS mode (Fig. 1D).

To illustrate these results, we applied the S3V2-IDEAS to datasets compiled by the Validated and Systematic integratION of epigenomic data project (VISION) (Hardison et al., 2020; Heuston et al., 2018; Xiang et al., 2020a,b). The ES mode can integrate seven epigenetic features to a 27 epigenetic states model (Fig. 1B). Compared with our previous analysis (Xiang et al. 2020a,b), the genome segmentation tracks from this S3V2-IDEAS are more consistent between biological replicates (Supplementary Figs S2C, D and S3D). The de-noising by S3V2 improves the accuracy of peak calling in ChIP-seq datasets (Supplementary Fig. S2E).

We illustrate the IS mode by limiting our analysis to only the ATAC-seq. In the IS mode, the ATAC-seq signal tracks can be first normalized and discretized into tracks of signal intensity levels (Fig. 1C). Then, a master peak list can be extracted from these state tracks (Fig. 1D). A master peak list is a straightforward way to obtain a coherent set of chromatin accessible peaks across cell types, which can be challenging for larger numbers of cell types (Meuleman et al., 2020). Comparing with the one produced by simply pooling and merging the MACS2 peaks in all cell type (Zhang et al., 2008), the IS mode master peak list pinpoints functional elements with higher accuracy (Supplementary Figs S6 and S7).

These results indicate that the S3V2-IDEAS should be versatile and effective tool for integrative analyses of epigenomic datasets.

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