Reviewer Report

Title: **A workflow for simplified analysis of ATAC-cap-seq data in R**

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Reviewer name: **James Lewis**

Reviewer Comments to Author:

Shrestha et al. developed an R software package designed specifically for determining differential enrichment of ATAC-seq reads from target capture ATAC-seq data. Their package includes three different test options (the edgeR Fisher's exact test, a Bayes factor t-test, and a bootstrap t-test). The authors apply each test to a range of simulated datasets, and find that edgeR performs best with low replicate counts, while the Bayes factor and bootstrap tests perform better as replicate numbers and the number of differentially enriched loci increase.

I like the idea of the manuscript, and entirely agree with the authors that more method-specific analysis pipelines are needed to address specific biases, rather than relying on software designed for RNA-seq studies. I would like to see more information about the ATAC-cap-seq assay included in the manuscript to better relate the analysis pipeline to the assay method. A quick search didn't show any publications for ATAC-cap-seq and no citation is given. I am assuming the protocol uses a target capture approach to enrich for DNA fragments after tagmentation but prior to amplification, allowing the researcher to test specific loci at high sequencing depth and relatively low cost. It would be nice if the method was more explicitly stated, as well as when and how the method would be more beneficial than alternatives (such as just doing ATAC-seq). It might also be worth explicitly stating that a capture approach would be able to detect differences in signal at previously identified loci, but would not show that the chromatin is "open" per se unless target capture probes were tiled across a locus.

I have no concerns with the software package as described. Providing differential enrichment test options and results for each test on simulated data is great and allows researchers to use the most appropriate test for their dataset and project. It would be nice, however, to see the authors test their software on data simulated from actual ATAC-seq libraries in addition to the RNA-cap-seq data they currently use.

Level of Interest

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