Reviewer Report

Title: Loop detection using Hi-C data with HiCExplorer

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Reviewer Comments to Author:

This paper provided a loop detection method using continuous negative binomial function combined with donut approach. To test the performance of this method, the authors used in-situ Hi-C data by Rao 2014 in GM12878, K562, IMR90, HUVEC, KBM7, NHEK and HMEC cell lines. This method showed comparable results with HiCCUPS and cooltools and better outputs than HOMER and chromosight. The significant advantage is the utilization of modern computational resources. The following are my comments:

1. The author claimed the advantages in utilizing computational resources. The authors need to clarify how their algorithm contributes to this advantage.
2. It will be helpful for the users to know the performance of the software at various sequencing depths, which can be achieved by down-sampling the high resolution datasets.
3. The authors need to compare (or at least discuss) Fit-Hi-C and Peakchachu. A table showing the strength and limitation of each method will be helpful. To be honest, I don't think any method is clearly better than the other. They are just different approaches.
4. It is better to use other types of orthogonal data like HiChIP, ChIA-PET to evaluate the loops called by these methods. There are H3K27ac HiChIP, SMC1 HiChIP, CTCF ChIA-PET and RAD21 ChIA-PET data in GM12878.
5. Just a minor suggestion. There are a lot of tables in the manuscript, which makes it hard for the readers to compare. It might be better to use figures instead.

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