**Reviewer Report**

**Title:** Sim3C: Simulation Of HiC And Meta3C Proximity Ligation Sequencing Technologies

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**Reviewer name:** Ming Hu

**Reviewer Comments to Author:**

In this paper, the authors developed a software package Sim3C to simulate Hi-C data and other 3C-based data. This work addresses a very important research question, and has the potential to become a useful computational tool in genomics research. However, the authors need to provide more explanations and technical details to further improve the current manuscript. Here are my specific comments:Major comments:1. Figure 3. It is better to plot Figure 3 in log scale for both x-axis and y-axis. In log scale, the slope of contact probably has direct biophysical interpretation, as described by the first Hi-C paper (Lieberman-Aiden et al, Science, 2009). I am very curious to see how biophysics model contributes to the data generation mechanism.2. In Rao et al, Cell, 2014 paper, they identified chromatin loops anchored by CTCF motifs. In Sim3C, the authors considered the 1D genomic distance effect and hierarchical TAD structures. It would be great if Sim3C can also take chromatin loops into consideration.3. Hi-C data can help to detect allelic-specific chromatin interactions. Is Sim3C able to simulate allelic specific proximity ligation data?4. It is very important to rigorously evaluate the data reproducibility. Using Sim3C, if users simulate Hi-C data multiple times with different random seeds, would the reproducibility between two simulated datasets be comparable to the reproducibility between two real biological replicates?5. The authors showed simulated contact matrices of bacteria (Figure 6) and budding yeast (Figure 7). They also need to simulate both human and mouse genome-wide contact matrices, and compare the simulated contact matrices with real data.Minor comments:1. Please replace all 'HiC' by 'Hi-C'.2. Page 6, line 116, "sciHiC" should be "scHi-C".

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**Quality of Written English**

Please indicate the quality of language in the manuscript: Acceptable

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