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HiCAN update: a reference-based estimation of the interaction between nuclear bodies and chromosomes

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Higher-order chromosomal structures organized around distinct nuclear bodies are a substantial part of the spatial genome arrangement, yet the lack of efficient experimental and computational methods to detect the interactions between nuclear bodies and chromosomes hinders the investigation of the underlying mechanisms and biological functions. We previously developed Hi-C inter-chromosomal contact map analysis with NMF (HiCAN) to systematically characterize nuclear body-associated chromosomal interactions from *in situ* Hi-C results. Although HiCAN showed robust performance across various cell types, there is ample room to further improve the method to effectively eliminate the biases caused by batch effect, capture efficiency, and inter-chromosomal translocation. Here, we introduce a reference-based HiCAN (rHiCAN) to overcome these limitations of the original HiCAN method. rHiCAN first generates a human reference of nuclear body-associated chromosomal structures, by extracting cell-type-conserved HiCAN basis from 8 different high-quality human cell line in-situ Hi-C data. Instead of performing NMF iteration on samples individually, rHiCAN estimates each basis using the reference bases. rHiCAN successfully captures speckle-/nucleolus-associated chromosomal interactions from SEM and HeLa Hi-C data, which were unable with the original HiCAN due to large number of inter-chromosomal translocations. In addition, rHiCAN reduces unwanted variations across samples and enables robust comparison of each basis between different cell types. With rHiCAN, we not only recapitulate the impact of MAZ depletion on speckle-associated chromosomal interactions but also detect more genomic regions affected by MAZ. Strikingly, we observe that the MAZ depletion can also lead to strengthened nucleolus association for some regions. Together, rHiCAN enables more sensitive and robust detection of nuclear body-associated chromosomal interactions, facilitating the study of the underlying mechanisms and biological functions.