

# A novel framework for deciphering 3D genome structure in colorectal cancer

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## Abstract

3D chromatin organization plays a critical role in gene regulation and cancer progression. Conventional Hi-C data analysis faces challenges with resolution and noise. To address challenges associated with the resolution and variability of Hi-C technique, we applied a novel workflow, HiC-ECC (HiC Enhance, Compare, and Call). This approach not only enhances Hi-C data quality but also enables the identification of biologically significant chromatin interactions and genome structural features.

We applied HiC-ECC to enhance Hi-C data quality and identify biologically significant chromatin interactions in colorectal cancer (CRC). This framework enables the identification of distinct epigenomic subtypes in CRC organoids with potential implications for patient stratification and therapeutic targeting. By analyzing the spatial organization of chromatin - a fundamental determinant of epigenomic landscape - we provide new insights into the heterogeneity of 3D genome architecture in CRC and its relationship to tumor progression and metastatic potential.

HIC-ECC	
Enhance	Enhancing quality using deep learning methods (e.g., DeepLoop, DeepHiC or HiC-Plus)
Compare	Comparison of multiple HiC datasets using tools (e.g., multiHiCCompare, dCHiC, CHESS)
Call	Calling chromatin structures using various tools (e.g., TADtool)

Figure 1. Schematic representation of the HiC-ECC workflow for enhancing, comparing, and calling significant chromatin interactions in colorectal cancer samples.

## Contact

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## Methods and Materials

We applied HiC-ECC to 19 patient-derived CRC organoids from primary tumors and metastatic sites. The workflow involved initial data preprocessing to generate high-quality chromatin contact matrices and ensure rigorous quality control. To enhance the resolution of Hi-C datasets, we utilized deep learning-based methods, enabling more accurate identification of chromatin interactions. Comparative analyses were conducted to identify differential chromatin interaction patterns and conserved structural features across the cohort. Chromatin architecture was further characterized by delineating topologically associating domains (TADs) and clustering them to reveal common and sample-specific interaction networks, offering insights into the hierarchical organization of 3D genome structures.

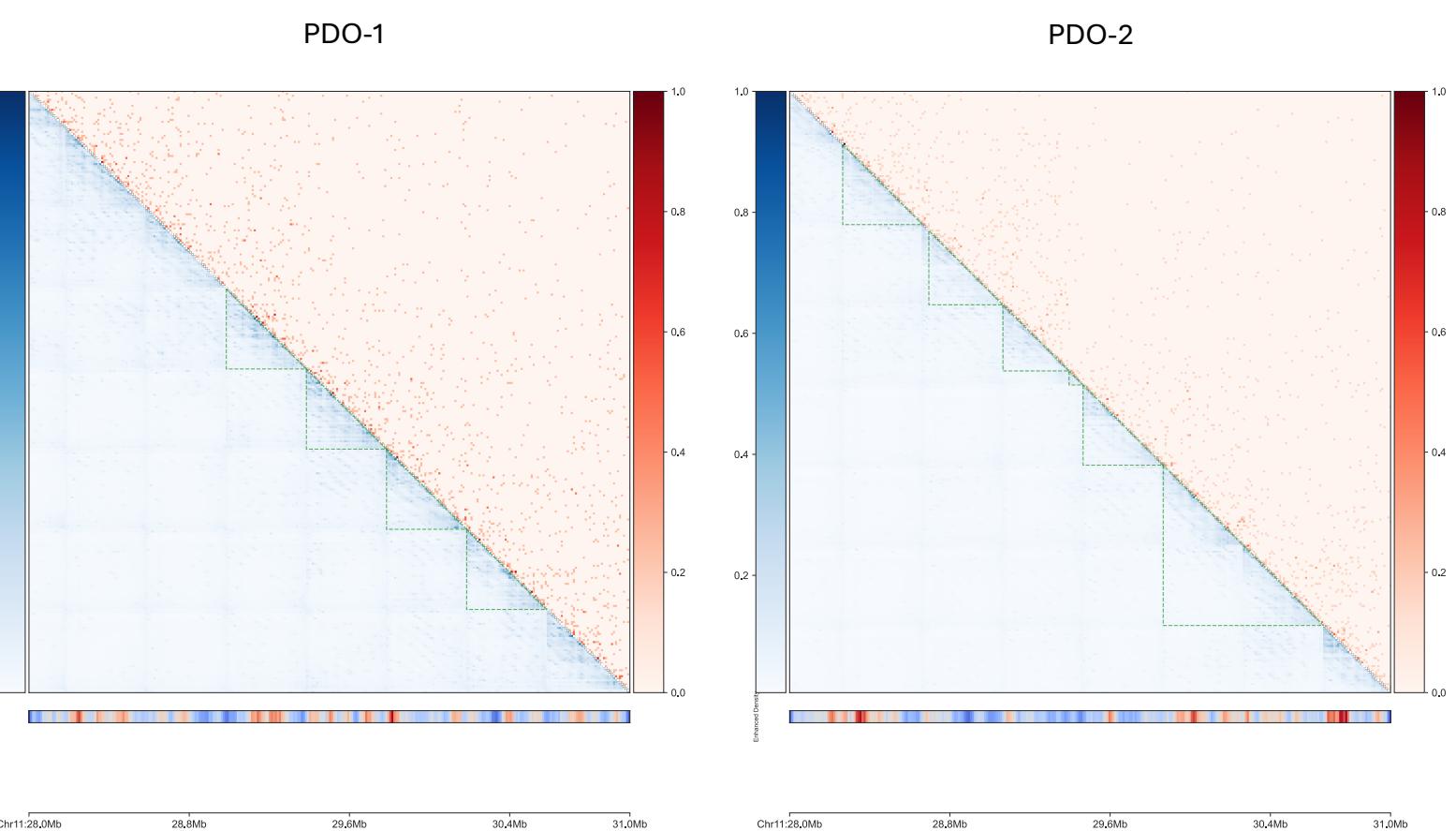


Figure 2. Split-view comparison of enhanced (blue, lower triangle) versus regular (red, upper triangle) Hi-C contact maps at chromosome 11 (28.0-31.0Mb), with dashed lines indicating TAD boundaries, and density heatmaps demonstrating improved signal clarity and TAD boundary detection.

## References

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## Results

Our analysis revealed four distinct subtypes of CRC organoids based on their 3D genome architecture, revealing a novel approach to interrogate heterogeneity within CRC. This subtyping was driven by differential chromatin interaction patterns and structural features, including unique TADs and conserved regulatory elements.

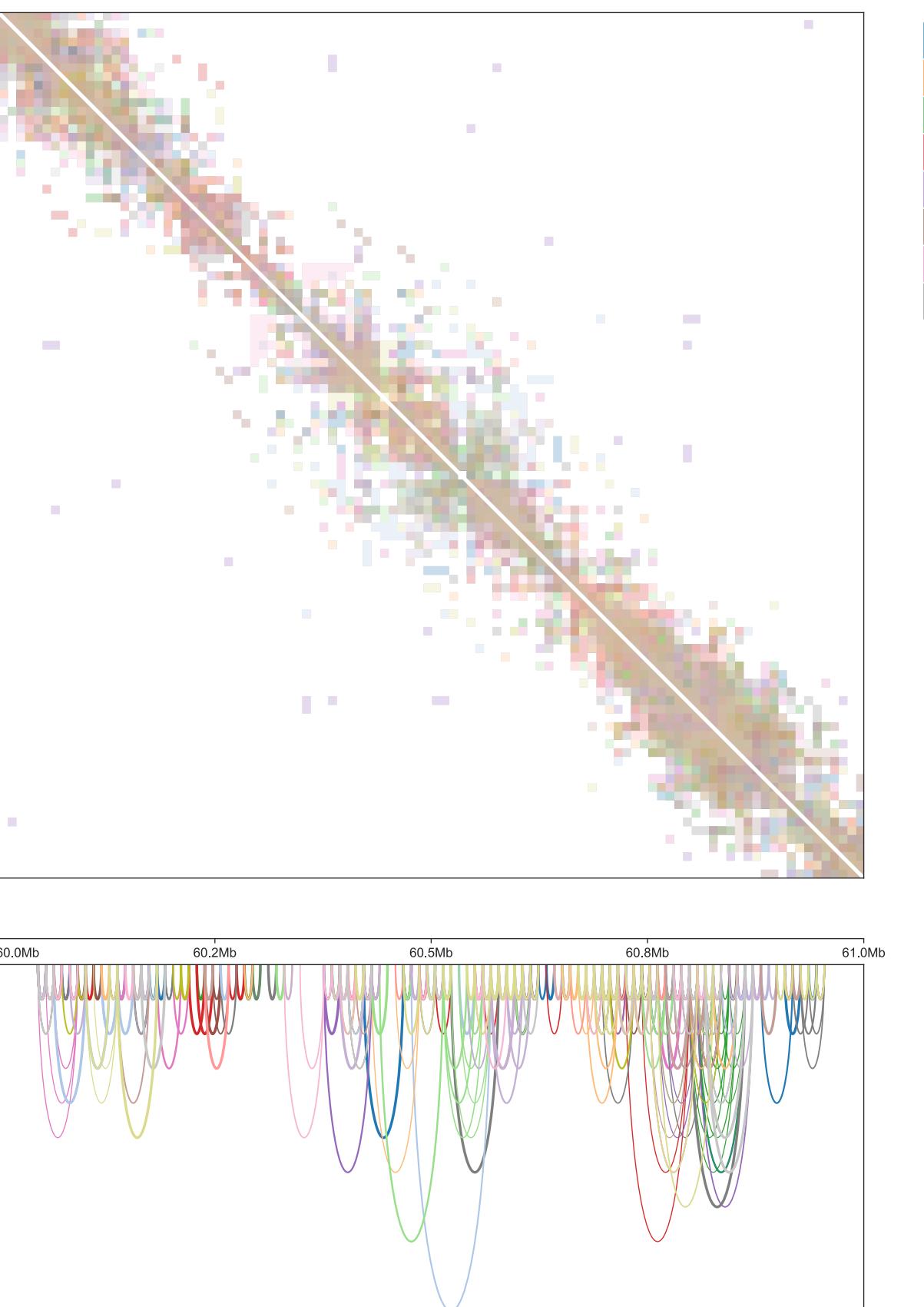


Figure 3. Overlay of significant chromatin loops (top 0.5 percentile interactions) from all samples at a given locus (chr11:60.0-61.0Mb), showing sample-specific and conserved long-range chromatin interactions.

## Discussion

Comparative analysis highlighted subtype-specific chromatin interaction networks, suggesting distinct epigenomic landscapes that correlate with tumor progression and metastatic potential.

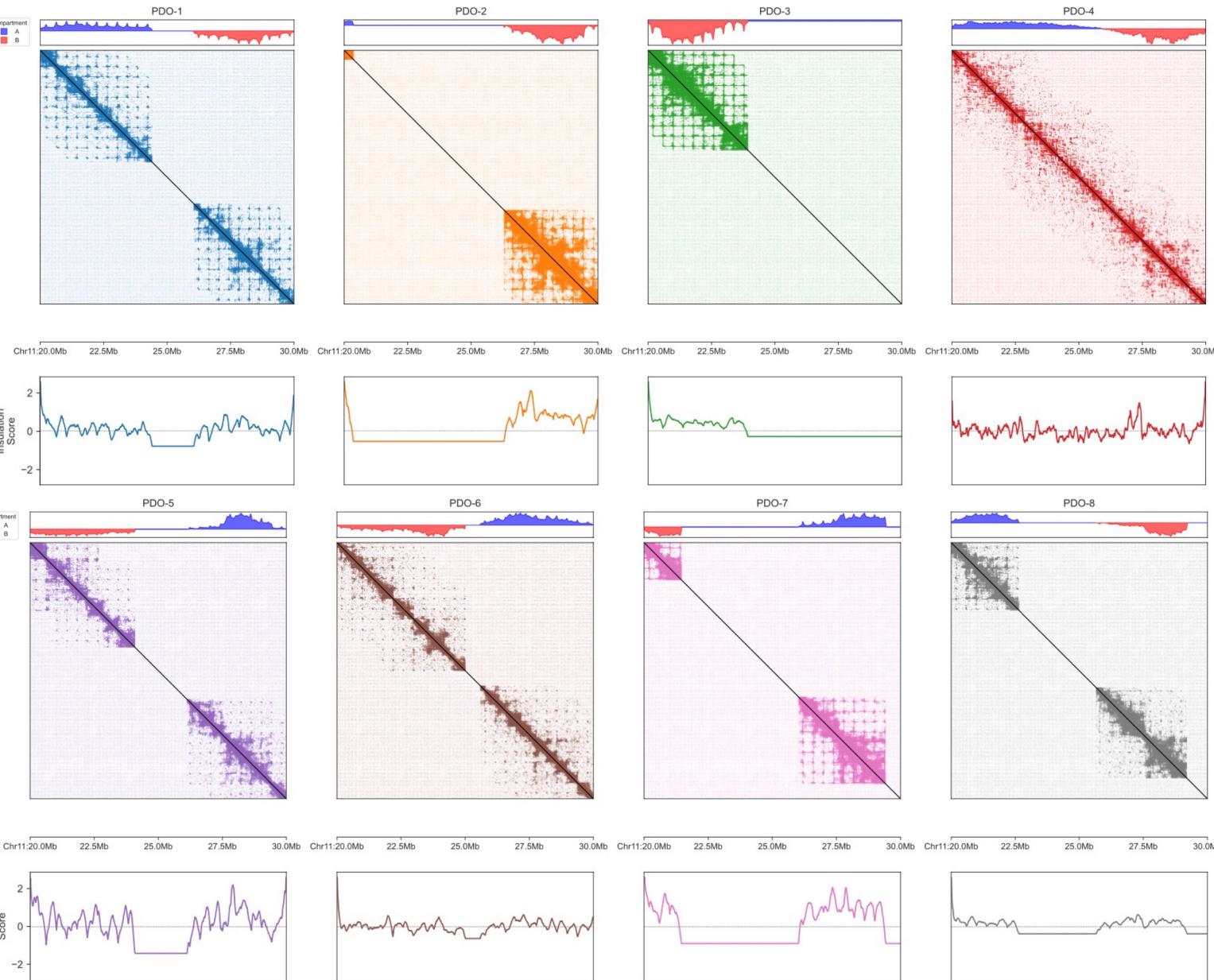


Figure 4. Individual chromatin interaction maps for 8 of the CRC organoid samples at chromosome 11 (20-30Mb) showing sample-specific patterns with corresponding insulation scores and compartment annotations.

## Conclusions

Our study identifies distinct 3D genome architecture subtypes in colorectal cancer. These epigenomic signatures provides a novel method for patient stratification and create opportunities for targeted therapeutic approach based on chromatin structure.