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# Advances and Frontier Prospects of Computational Detection Methods for Chromatin Loops

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**Abstract:** The eukaryotic genome exists in a highly folded three-dimensional structure within the nucleus. As the core functional unit of the 3D genome, chromatin loops are formed via the loop extrusion mechanism mediated by CTCF proteins and cohesin complexes. They directly facilitate the spatial interaction between distal enhancers and gene promoters, and precisely regulate essential biological processes including gene transcription, DNA replication and damage repair. Structural abnormalities of chromatin loops are closely associated with the occurrence and progression of numerous diseases, such as cancers, developmental defects and neurodegenerative disorders. Chromosome conformation capture technologies represented by Hi-C, ChIA-PET and HiChIP have laid a critical foundation for the experimental identification of chromatin loops, yet they suffer from inherent limitations including high sequencing costs, limited data resolution, prominent noise interference and obstacles in single-cell detection. Computational detection methods for chromatin loops eliminate the reliance on large-scale experimental expenditures. These approaches can automatically mine characteristic patterns from DNA sequences, epigenomic profiles and 3D genomic contact matrices, enabling efficient, accurate and low-cost chromatin loop identification, and have emerged as a vital solution to compensate for the shortcomings of experimental techniques. This review systematically summarizes the molecular formation mechanisms, biological functions of chromatin loops, and technical characteristics of mainstream experimental detection methods. Following the trajectory of technological evolution, existing computational detection approaches are classified into three categories: statistical methods, conventional machine learning methods and deep learning methods. The algorithmic principles, input data types, core advantages and application limitations of each category are elaborated respectively. Furthermore, this paper integrates emerging chromatin loop detection technologies developed since 2023 based on diffusion models, multimodal data fusion, nanopore sequencing, self-supervised learning and single-cell 3D genomics, and details their technological innovations and performance breakthroughs. It also concludes major challenges in this field, including data imbalance, low-resolution adaptation, cross-cell line generalization, the absence of universal gold standards, and the dynamic analysis of single-cell chromatin loops. In addition, future research directions are prospected from the perspectives of multimodal fusion, weakly supervised learning, single-cell dynamic modeling, disease correlation analysis, and lightweight interpretable models. This review aims to provide a comprehensive reference for researchers in the field of 3D genomics regarding computational detection methods of chromatin loops, and promote the in-depth integration of algorithm development and biomedical applications.

**Keywords:** Chromatin loops, 3D genome, Statistics, Machine learning, Deep learning, Multimodal fusion.

## 1. Introduction

Eukaryotic genetic material does not exist in a linear form within the nucleus but undergoes multi-level folding to form a four-level three-dimensional structure: chromatin territories, A/B compartments, Topologically Associating Domains (TADs), and chromatin loops. Among them, chromatin loops are the basic functional units directly involved in gene expression regulation. By shortening the spatial distance between regulatory elements and target genes that are far apart in the linear genome, they achieve spatiotemporally specific gene expression regulation, serving as the core molecular basis for cell differentiation, tissue development, and cell identity maintenance. In recent years, numerous studies have confirmed that abnormalities in chromatin loop formation, anchor point mutations, or interaction disorders can lead to the activation of proto-oncogenes and silencing of tumor suppressor genes, thereby triggering various malignant tumors. Meanwhile, the disruption of chromatin loop structure is also closely associated with congenital developmental disorders, cardiovascular diseases, neurological diseases, and other pathological processes. Therefore, the accurate and efficient identification of chromatin loops across the entire genome, as well as the analysis of their dynamic changes and regulatory mechanisms, is a core research topic in the fields of 3D genomics and disease biology.

The emergence of Chromosome Conformation Capture (3C) technology has opened a new era in the study of three-dimensional genome structure. Its derivative technologies, such as Hi-C, 4C, 5C, ChIA-PET, Capture Hi-C, and HiChIP, have gradually realized the detection of chromatin interactions from locus-specific to genome-wide scales, and from low to high resolution. Among these, Hi-C technology can capture genome-wide chromatin spatial interaction information and is the core experimental method for detecting chromatin loops; ChIA-PET and HiChIP can specifically capture chromatin loops mediated by specific proteins, greatly reducing the background noise; Capture Hi-C can target and enrich interaction signals in specific regions, enabling high-resolution analysis under limited sequencing costs; Pore-C technology, combined with long-read nanopore sequencing, can detect multi-way chromatin interactions and simultaneously retain epigenetic information such as DNA methylation, providing more comprehensive data support for the study of chromatin loops. However, these experimental

technologies still have insurmountable limitations: high-resolution Hi-C requires billions of sequencing reads, resulting in extremely high costs; all 3C-derived technologies have technical noise such as enzyme digestion bias, cross-linking efficiency differences, and sequencing errors; single-cell 3D genomic data is extremely sparse, making it difficult to stably identify single-cell-specific chromatin loops; there is no unified gold standard for judging the authenticity of chromatin loops detected by different experimental technologies, leading to inconsistent results between different studies.

The rapid development of computational science and bioinformatics has provided a new solution to the above problems. Computational methods for chromatin loop detection can directly mine characteristic patterns of chromatin loops from experimental data, realizing efficient, accurate, and low-cost identification of chromatin loops without relying on massive sequencing data. Over the past decade, chromatin loop computational detection methods have undergone three rounds of technological iteration: the initial statistical methods based on background modeling, the traditional machine learning methods based on manual feature engineering, and the deep learning methods based on automatic feature extraction. These methods have continuously improved in terms of detection accuracy, applicable scenarios, and generalization ability. Since 2023, with the integration of frontier technologies such as diffusion models, multi-modal data fusion, and self-supervised learning, chromatin loop detection methods have achieved breakthroughs in single-cell data processing, cross-species generalization, and biological interpretability, further narrowing the gap between computational prediction and experimental verification. This review systematically summarizes the research progress of computational methods for chromatin loop detection, focuses on the core principles and characteristics of various methods, analyzes the advantages and limitations of different technical routes, and looks forward to the future development trend, aiming to provide a comprehensive and cutting-edge reference for researchers in the field of 3D genomics.

## 2. Biological Basis and Experimental Detection Technologies of Chromatin Loops

(1) Molecular Formation Mechanism and Biological Function of Chromatin Loops

Chromatin loops refer to cyclic structures with high-frequency spatial interactions formed by two genomic loci that are linearly distant on the genome. Their formation follows the loop extrusion model: the cohesin complex binds to DNA sequences, slides bidirectionally along the DNA strand and extrudes chromatin, and stops when encountering convergent CTCF (CCCTC-binding factor) binding sites, ultimately forming a stable chromatin loop structure. As a key insulator protein, CTCF can mediate loop formation only at binding sites in convergent orientation, serving as the core sequence signature of chromatin loop anchors. Subunits such as RAD21 and SMC3 in the cohesin complex are responsible for maintaining loop stability, and the two factors together constitute the core molecular machinery for chromatin loop formation.

The biological functions of chromatin loops run through the entire process of genome regulation. On the one hand, they mediate spatial interactions between distal regulatory elements and gene promoters, precisely connecting regulatory elements such as enhancers and silencers to target gene regions to achieve cell-type-specific and spatiotemporal transcriptional regulation. On the other hand, they define the boundary range of topologically associating domains, restrict cross-domain interference of internal regulatory elements, and maintain the stability of the three-dimensional genome structure. Meanwhile, they provide essential spatial scaffolds during DNA replication, homologous recombination and DNA damage repair, ensuring the stable transmission of genomic genetic information. Cell-type-specific chromatin loop patterns act as crucial molecular markers for maintaining cell identity and regulating cell differentiation processes, and their dynamic changes directly determine the developmental direction and functional state of cells.

(2) Experimental Detection Technologies and Limitations of Chromatin Loops

Current experimental detection of chromatin loops relies entirely on the derivative system of 3C-based technologies, and distinct differences exist in their principles, application scenarios and technical performance. As the gold standard for genome-wide chromatin interaction detection, Hi-C technology fixes the spatial structure of chromatin through formaldehyde crosslinking, cuts DNA fragments by restriction enzyme digestion, labels ligation ends with biotin, and acquires contact matrices via high-throughput sequencing. It enables the simultaneous identification of topologically associating domains, A/B compartments and chromatin loops, possessing the core advantages of genome-wide coverage and high-throughput detection. Nevertheless, the acquisition of high-resolution data requires extremely high sequencing costs, accompanied by substantial technical noise, and its resolution is highly dependent on sequencing depth. Combining chromatin immunoprecipitation with paired-end tag sequencing, ChIA-PET can specifically capture chromatin loops mediated by specific proteins such as CTCF and RNAPII, effectively reducing detection background and false positive signals. However, it only focuses on interaction signals of a single target protein, requires a large number of cell samples, and involves complicated and cumbersome experimental procedures.

Based on conventional Hi-C libraries, Capture Hi-C introduces an additional targeted capture step to specifically enrich chromatin interaction signals in genomic regions of interest, achieving higher detection resolution at the same sequencing cost. It is suitable for the refined analysis of candidate gene loci and disease risk regions, but cannot realize genome-wide chromatin loop detection. Integrating the technical strengths of Hi-C and ChIP, HiChIP directly enriches protein-bound chromatin interaction fragments through in situ crosslinking, which greatly reduces cell consumption, improves information output efficiency and lowers noise levels, while its detection scope is still limited to protein-mediated interactions targeted by specific antibodies. Combining nanopore long-read sequencing with chromosome conformation capture, Pore-C can simultaneously detect multi-way chromatin interactions and retain epigenetic modifications such as DNA methylation. It exhibits unique advantages in the analysis of complex genomes and multi-locus interactions, but it is confronted with difficult data analysis procedures and relatively high experimental and sequencing costs.

The inherent limitations of experimental techniques have

become the bottleneck for large-scale analysis of chromatin loops, and have directly promoted the rapid development and widespread application of computational detection methods. Compared with experimental approaches that rely on high costs and complicated operations, computational methods can efficiently complete genome-wide chromatin loop detection based on public datasets, and adapt to complex data conditions such as low resolution and sparse noise. Gradually, they have become indispensable core tools in three-dimensional genomic research.

# 3. Statistical Methods for Chromatin Loop Detection

Statistical methods represent the early technical system and the most fundamental computational solution for chromatin loop detection. Centered on probability and statistics theory, such approaches construct mathematical models based on the inherent distribution characteristics of experimental data including Hi-C and ChIA-PET. They screen significant interaction loci through hypothesis testing, standardized correction, background fitting and other strategies. With prominent strengths such as high computational efficiency, strong interpretability and independence from labeled samples, statistical methods served as the mainstream choice for early three-dimensional genomic data preprocessing and preliminary loop identification, and have laid a solid foundation of data processing for the subsequent development of machine learning and deep learning algorithms.

Mango [1] is an early chromatin loop detection tool tailored for ChIA-PET data. It is developed to process paired-end tag (PET) data and identify protein-mediated chromatin interaction loops. This method constructs a background model based on the binomial distribution to correct genomic distance deviation, sequencing depth deviation and enzyme digestion bias. Meanwhile, it eliminates noise signals caused by random ligation through a multi-step filtering workflow, so as to effectively distinguish genuine interactions from background noise. In addition, Mango is embedded with PET clustering and significance test modules, which can simultaneously detect intrachromosomal and interchromosomal chromatin loops. Its output contains key indicators such as interaction strength and significance level, providing solid basic data for subsequent functional analysis of ChIA-PET data.

CHiCAGO [2] is developed for targeted chromatin loop detection based on Capture Hi-C data. It addresses sequence bias and enrichment bias in capture-based data, and provides a robust statistical framework for interaction analysis of candidate genomic regions. This method builds a convolution background model integrating negative binomial distribution and Poisson distribution, which can well fit the interaction frequency distribution of Capture Hi-C data. Moreover, it eliminates distance-dependent deviation and capture efficiency deviation through a hierarchical background correction strategy. Besides, CHiCAGO is equipped with a multi-step filtering pipeline to remove low-quality interactions and technical noise, and finally outputs high-confidence chromatin loops in targeted regions. It has been widely applied in the analysis of disease risk loci and candidate gene interactions.

ChIAPoP [3] is a specialized chromatin loop detection tool designed for ChIA-PET data. It adopts a zero-truncated Poisson distribution model to fit the interaction frequency of PET data, and effectively resolves the over-dispersion problem existing in ChIA-PET datasets. Firstly, this method preprocesses raw PET data to remove low-quality and duplicate sequences. Then it establishes a background distribution model based on genomic distance, and identifies high-confidence chromatin interaction loops via significance testing. Meanwhile, it integrates a multi-omics data module, which can incorporate prior information such as CTCF binding signals to improve detection accuracy. It exhibits excellent performance in detecting CTCF and RNAPII-mediated chromatin loops, and has become one of the commonly used tools for loop identification from ChIA-PET data.

Considering the characteristics of Capture Hi-C data, ChiCMaxima [4] is developed to simplify the loop detection pipeline and improve the detection sensitivity of small-scale functional chromatin loops. This method first performs loess smoothing on Capture Hi-C data to convert discrete interaction signals into continuous curves. Afterwards, it adopts a local maximum search algorithm to identify peak positions on the smoothed curves, which correspond to the locations of chromatin loops. A built-in peak significance test module enables it to distinguish true interactions from background noise efficiently. Compared with conventional methods, it greatly reduces computational complexity and presents superior performance on Capture Hi-C data with small sample sizes, delivering an efficient solution for rapid targeted interaction analysis.

To overcome the limitations of traditional uniform genome binning strategies in identifying narrow chromatin loops from low-resolution Hi-C data, HiCORE [5] is proposed to recognize high-confidence core chromatin interaction regions and enhance loop detection sensitivity under low-depth sequencing conditions. It innovatively designs a multi-layer offset genome segmentation strategy. By generating multiple sets of slightly offset genomic intervals and integrating interaction signals from all layers, it can effectively capture narrow interaction peaks neglected by conventional binning methods. Furthermore, it combines the Fit-HiC2 algorithm to construct a background model for distance-dependent bias correction, and verifies the biological validity of candidate loops through aggregate peak analysis, so as to generate a final set of high-confidence core chromatin loops. In the tests of low-resolution Hi-C datasets, HiCORE significantly improves the detection rate of short-range chromatin loops in comparison with traditional tools. It can stably adapt to Hi-C data across different cell types, offering an efficient approach for three-dimensional genome analysis of low-depth sequencing samples.

As a classic early tool for chromatin loop detection in Hi-C data, HiCExplorer [6] is designed to standardize Hi-C interaction data and identify chromatin interaction loci with statistical significance, offering a reliable solution for loop detection in low-complexity research scenarios. This tool utilizes a continuous negative binomial distribution model to fit normalized Hi-C interaction frequency data, and removes the interference of genomic linear distance on interaction signals through the Wilcoxon rank-sum test. It also establishes a complete multi-step filtering process: candidate interaction regions are first screened based on local background signals, and credible chromatin loop positions and intensities are finally determined through background noise discrimination and statistical significance verification. To adapt to Hi-C data with different sequencing depths and

resolutions, HiCExplorer provides diverse built-in normalization strategies to effectively correct technical biases including enzyme digestion preference and sequencing deviation. Its output results can be directly used for subsequent aggregate peak analysis and functional annotation, making it one of the fundamental and widely adopted tools in three-dimensional genomics research.

Statistical methods were widely used in early research due to their high efficiency and interpretability. However, such approaches rely heavily on predefined data distribution assumptions and show poor adaptability to high-noise and multi-dimensional omics data. They fail to capture nonlinear correlation features embedded in sequence and epigenetic data, and their detection accuracy cannot meet the requirements of refined research, which has prompted researchers to turn to more flexible machine learning methods.

# 4. Traditional Machine Learning-Based Methods for Chromatin Loop Detection

Traditional machine learning methods address the inherent limitations of statistical methods and break away from the constraints of fixed distribution assumptions. They extract structured features from DNA sequences, epigenomic profiles and Hi-C contact matrices through manual feature engineering, and adopt classification, clustering, regression and other algorithms to learn latent patterns of chromatin loops. Such methods can effectively mine nonlinear relationships among multi-omics data, achieving a substantial improvement in detection accuracy compared with statistical approaches. They have established the second-generation core technology for chromatin loop computational detection, and also act as a critical transitional bridge connecting basic statistical methods and advanced deep learning techniques.

HiCCUPS [7], serving as the core loop detection module in the Juicer analysis pipeline, is designed for the identification of high-confidence chromatin loops from Hi-C data and realizes pixel-level significance evaluation based on local enrichment statistical tests. This method recognizes significantly enriched interaction loci by comparing the contact frequency of the target pixel with its four neighborhood backgrounds, including bottom-left, horizontal, vertical and annular regions. It adopts multiple testing correction to control the false positive rate and requires the contact intensity of candidate loops to be at least 50% higher than the expected value. As a classic baseline method in this field, HiCCUPS has provided a standardized performance evaluation benchmark for subsequent machine learning and deep learning approaches.

TargetFinder [8], a milestone work in the machine learning-based detection of chromatin loops, is developed to predict enhancer-promoter interaction loops and constructs a multi-omics feature integration framework based on the random forest algorithm. This method integrates hundreds of genomic and epigenomic datasets covering multi-dimensional features such as sequence conservation, transcription factor binding signals and chromatin states. It determines the minimal and optimal feature subset through feature screening to effectively eliminate redundant features, and optimizes model parameters with a cross-validation strategy. In tests across multiple cell lines, TargetFinder exhibits remarkably better performance in enhancer-promoter interaction prediction than traditional methods. It has laid a technical framework for subsequent machine learning-based loop detection methods and provided a reliable tool for the functional analysis of distal regulatory elements.

3DepiLoop [9] is proposed to predict three-dimensional chromatin loops within Topologically Associating Domains merely relying on one-dimensional epigenomic data, and addresses the preference bias in cross-cell-type prediction. Adopting a supervised random forest model, this method extracts features such as chromatin accessibility and histone modifications from one-dimensional epigenomic data to establish a prediction framework for intra-TAD chromatin loops. By conducting independent training for each cell type, it effectively reduces cross-cell-type preference bias and achieves genome-wide unbiased loop detection without requiring prior information about regulatory elements and protein motifs. Tested in various cell lines, 3DepiLoop successfully identifies a large number of chromatin loops consistent with Hi-C results, offering a feasible loop detection solution for cell types lacking high-resolution Hi-C data.

CTCF-MP [10] is developed to predict chromatin loops mediated by convergent CTCF motifs, and establishes a sequence feature learning framework based on gradient boosting classifiers to break the limitations of conventional k-mer features. Firstly, word2vec is utilized to convert CTCF binding motifs and their flanking sequences into continuous vector features, which replace traditional k-mer frequency features and effectively capture context-dependent sequence information. Combined with auxiliary features such as genomic distance and CTCF binding intensity, a gradient boosting classifier is constructed to accurately predict CTCF-mediated chromatin loops. In both intra-cell-type and cross-cell-type prediction tests, CTCF-MP outperforms conventional motif orientation-based prediction methods significantly, delivering an efficient tool for the analysis of CTCF-mediated chromatin loops.

cLoops [11] is designed for chromatin loop detection using paired-end tag data, and builds an unsupervised loop detection framework based on the optimized cDBSCAN clustering algorithm to reduce distance-dependent bias effectively. Directly processing PET data, it estimates the statistical significance of interactions through local background permutation without the need for Hi-C contact matrices. The cDBSCAN clustering algorithm is applied to detect high-density interaction regions, which is compatible with both sharp and broad peak signals. It shows strong robustness in ChIA-PET and Hi-C data, and provides a unified loop detection scheme for diverse types of three-dimensional genomic data.

Lollipop [12] is developed to integrate multi-omics features for the prediction of CTCF-mediated chromatin loops, solving the problem of insufficient prediction accuracy caused by motif orientation-based methods alone. This method constructs a multi-dimensional feature space by integrating genomic sequence features, epigenomic profiles and CTCF motif orientation information, and learns the characteristic patterns of chromatin loops via the random forest algorithm. It is embedded with a feature importance analysis module to clarify the contribution of key factors to loop formation and improve the biological interpretability of the model. Evaluated in multiple cell lines, Lollipop achieves superior accuracy in detecting CTCF-mediated loops and offers a new approach to exploring the role of CTCF in chromatin loop formation.

Peakachu [13] is built to directly detect chromatin loops

from Hi-C contact matrices. It establishes a pixel-level feature learning model under the random forest classification framework and adapts to Hi-C data with varying sequencing depths. Without additional multi-omics data, this method directly extracts pixel intensity and rank features from Hi-C matrices and learns the spatial patterns of chromatin loops through the random forest algorithm. With model parameters optimized by cross-validation, it maintains high precision and recall rates in Hi-C data of different sequencing depths, and can efficiently identify high-resolution short-range chromatin loops. It has become one of the commonly used machine learning tools for Hi-C-based loop detection.

LoopPredictor [14] is developed to predict chromatin loops for cell types without high-resolution Hi-C data. It adopts an ensemble learning strategy to construct a dual-module framework consisting of anchor prediction and confidence evaluation. Firstly, a random forest anchor predictor is used to recognize potential chromatin loop anchors, and a gradient boosting regression tree confidence evaluator is applied to assess the interaction confidence between anchors, enabling the prediction of chromatin topological structures without long-range contact maps. Equipped with a cross-cell-line transfer learning module, it trains models using Hi-C data of well-characterized cell lines and performs prediction on uncharacterized cell lines, providing a reliable loop detection strategy for samples deficient in high-resolution Hi-C data.

Mustache [15] is designed for multi-scale chromatin loop detection in Hi-C and Micro-C data, and realizes the recognition of blob-shaped structures based on the scale-space theory in computer vision. It adopts the Difference of Gaussians (DoG) operator to construct multi-scale representations of contact maps, and identifies candidate loops by detecting local maxima in the three-dimensional space composed of x-coordinate, y-coordinate and scale σ. It can simultaneously detect short-range and long-range interactions at diverse resolutions. Combined with the validation of CTCF binding sites as well as enhancer-promoter associations, it greatly improves the biological reliability of detected loops. Compared with HiCCUPS, Mustache can complete genome-wide analysis at 5 kb resolution within only a few minutes on ordinary CPUs, with 2 to 3 times more detected loops and higher reproducibility, which supports high-throughput analysis of chromatin loops efficiently.

Chromosight [16] is established as a computer vision-based pattern recognition tool for chromosomal contact maps, and realizes automated chromatin loop detection through template matching technology. It calculates cross-correlation between predefined loop templates and normalized contact matrices, and quantifies pattern similarity using Pearson correlation coefficients. It supports the simultaneous identification of multiple chromatin structures including loops, TAD boundaries and centromeres, and adjusts detection sensitivity by threshold optimization. With stable detection performance in both Hi-C and Micro-C data, Chromosight provides a general framework for pattern recognition-based chromatin loop detection.

Traditional machine learning methods have effectively broken the distribution limitations of statistical methods and shown remarkable advantages in multi-omics data adaptation and nonlinear feature mining. However, such approaches rely heavily on manual feature engineering, and the completeness and efficiency of feature extraction are restricted by researchers' experience. Meanwhile, they require large-scale and high-quality labeled samples and are prone to overfitting. The interpretability of model decision-making also remains insufficient. These shortcomings have promoted the practical application of deep learning technologies in this research field.

# 5. Classical Deep Learning-Based Methods for Chromatin Loop Detection

From 2020 to 2022, deep learning technologies began to be widely applied in the field of chromatin loop detection. Such methods can directly extract deep-level features from raw data through multi-layer neural networks without manual feature design. They are capable of fusing multi-source data such as DNA sequences, epigenomic profiles and Hi-C contact matrices, and maintain superior performance even on low-resolution and high-noise data, marking the entry of this field into the third-generation technical stage. This chapter focuses on the classic deep learning models proposed during this period, covering research directions including sequence-to-structure prediction, multimodal feature fusion and super-resolution reconstruction, which lay a solid foundation for the subsequent emerging integrated technologies.

Akita [17] is established as the first end-to-end deep learning model to directly predict three-dimensional genomic contact maps from DNA sequences. It constructs a multi-scale sequence encoder based on dilated convolutional neural networks (dilated CNN) to realize the prediction of chromatin organization at the megabase scale. Adopting the Basenji architecture as the backbone network, this method processes 1 Mb input sequences and outputs chromatin contact matrices at 2 kb resolution. It utilizes the exponential receptive field expansion property of dilated convolutions to capture long-range sequence dependencies. With a multi-task learning framework, it synchronously predicts the three-dimensional structures of multiple cell types and supports in silico saturated mutation analysis to evaluate the effects of sequence variations on chromatin conformation. Akita reveals the decisive role of the orientation of CTCF binding sites in genome folding, and provides a fundamental framework for sequence-driven 3D genomic modeling.

DeepC [18] is designed for the prediction of three-dimensional genome structure at the megabase scale, and achieves high-resolution chromatin tissue modeling across cell types based on deep transfer learning. This method firstly employs convolutional modules to extract one-dimensional epigenetic features such as chromatin accessibility and histone modifications. Then, it integrates megabase-scale sequence contexts through dilated convolutional layers, and finally predicts chromatin contact frequencies at 5 kb resolution via fully connected layers. It adopts the percentile-based skeleton normalization strategy to correct distance-dependent bias, and combines transfer learning to effectively improve the prediction accuracy for low-coverage data. DeepC achieves consistent results comparable to experimental Hi-C data in multiple cell lines. It can finely resolve the impacts of variants ranging from single-nucleotide mutations to structural variations on genome folding, providing an efficient tool for the computational analysis of large-scale chromatin organization.

LOOPbit [19] is developed for chromatin loop recognition based on the topological classification of CTCF-CTCF interactions, and realizes high-precision loop detection by combining self-organizing map (SOM) clustering and CNN

models. This method first conducts self-organizing map clustering on CTCF-CTCF interaction signals to identify distinct topological interaction patterns. A CNN classifier is then trained based on clustering results, and chromatin state information is integrated to complete loop detection. Meanwhile, it is embedded with a feature visualization module, which can identify the key features for model decision-making and enhance the biological interpretability of the model. In Hi-C data tests across various cell lines, LOOPbit exhibits excellent performance in both detection accuracy and interpretability, offering a new tool for analyzing the regulatory mechanisms of CTCF-mediated chromatin loops.

DeepLUCIA [20] is proposed to predict tissue-specific chromatin loops. It abandons the dependence on transcription factor binding profiles and constructs a deep learning framework merely based on epigenomic information. This model consists of a sequence motif module, an epigenetic state module and a feature integration module, which separately extract features from DNA sequences and epigenomic data. Information is further integrated through fully connected layers to complete loop prediction. Equipped with a tissue-specific feature learning module, it can capture the differences in chromatin loop patterns among diverse tissues and greatly expand the application scope of the model. Evaluated on multiple tissue samples, DeepLUCIA outperforms conventional methods in the detection of tissue-specific chromatin loops, and provides a novel approach for the analysis of disease-associated chromatin loops.

GILoop [21] is tailored for chromatin loop detection applicable to Hi-C data with different sequencing depths, and builds a dual-branch neural network architecture for multi-scale feature learning. It designs a U-Net branch and a graph convolutional network branch. The U-Net branch extracts image-based features from Hi-C matrices to capture local spatial dependencies, while the graph convolutional network branch mines graph structural features of DNA sequences to identify long-range sequence dependencies. A dual-branch feature fusion module is applied to integrate the two types of features, enabling the high-precision identification of CTCF-mediated chromatin loops. It is adaptable to Hi-C data with various sequencing depths and presents outstanding performance on low-depth datasets.

DeepLoop [22] is developed for chromatin loop detection using sparse and low-depth Hi-C data. It establishes a collaborative dual-module framework composed of the LoopDenoise autoencoder and the LoopEnhance U-Net to greatly boost the signal-to-noise ratio of raw data. Firstly, the LoopDenoise autoencoder is used to eliminate technical noise in Hi-C data. The LoopEnhance U-Net model is then adopted to enhance valid interaction signals. In addition, a built-in multi-scale feature learning module can capture chromatin interaction patterns at different genomic distances. In tests on sparse low-depth Hi-C data and single-cell Hi-C data, DeepLoop achieves fine mapping of chromatin loops at kilobase resolution, delivering an efficient solution for three-dimensional genomic analysis of low-quality datasets.

DLoopCaller [23] is designed to integrate Hi-C contact matrices and chromatin accessibility data for genome-wide chromatin loop prediction. It builds a dual-path CNN architecture to realize multimodal feature fusion. Two independent pathways are constructed to process Hi-C contact matrices and chromatin accessibility data respectively. Convolutional layers are used to extract spatial interaction features and chromatin state features, and a feature fusion module integrates information from both pathways to establish a unified loop prediction framework. Furthermore, it contains a cross-cell-line transfer learning module, and shows far superior generalization performance to traditional methods in cross-cell-line and cross-species tests, providing new insights for multimodal data-driven chromatin loop detection.

Orca [24] is developed to directly predict multi-scale three-dimensional genome structures from DNA sequences. It constructs a hierarchical sequence encoder and cascaded decoder framework for fully reference-free de novo prediction. This method firstly converts DNA sequences into multi-scale features via a hierarchical sequence encoder. Cascaded decoders are then used to predict three-dimensional genome structures from local to global scales, which can accurately identify CTCF-mediated and Polycomb-mediated chromatin loops. Meanwhile, the embedded multi-scale feature learning module captures sequence dependencies at different length scales, supporting 3D structure prediction ranging from kilobase to chromosomal scales. Tested in multiple cell lines, Orca successfully predicts chromatin loops highly consistent with Hi-C observations, offering a new perspective for reference-free three-dimensional genomic research.

Deep learning methods completely eliminate the reliance on manual feature engineering that troubles traditional approaches and achieve qualitative leaps in multimodal data fusion and the adaptation to low-quality sequencing data. Nevertheless, such methods still suffer from high computational resource consumption, inherent black-box characteristics, and limited cross-cell-line generalization ability. In particular, there remains considerable room for improvement in research scenarios such as multi-way chromatin interactions, single-cell dynamic regulation, and cross-species prediction, which also provides innovative directions for the integration of cutting-edge technologies after 2023.

# 6. Chromatin Loop Detection Technologies Based on Cutting-edge Integration (2023–2026)

Since 2023, cutting-edge technologies including diffusion models, nanopore sequencing, self-supervised learning, single-cell modeling, multimodal fusion and foundation models have been deeply integrated with three-dimensional genomics, breaking through the performance boundaries of classic deep learning methods. This chapter focuses on innovative approaches proposed in this period, covering emerging directions such as cross-species generalization, multi-way interaction analysis, single-cell dynamic tracking and foundation model pre-training. These advances promote the rapid development of this field toward ultra-high resolution, multi-way interaction identification, single-cell dynamics research and disease-targeted application.

InferLoop [25] is developed to address the challenging problem of chromatin loop detection caused by the extreme sparsity of single-cell Hi-C data. By integrating single-cell chromatin accessibility data, it provides a reliable loop inference strategy for sparse single-cell samples. This method first conducts cell grouping based on single-cell chromatin accessibility data and enhances interaction signal intensity through grouping. It then deduces chromatin loop signals by

adopting the perturbed Pearson correlation coefficient metric, enabling loop inference without relying on high-depth Hi-C data. Meanwhile, a built-in data perturbation strategy effectively reduces the impact of technical noise on detection results and improves model stability. Tested on various single-cell Hi-C datasets, InferLoop successfully identifies numerous chromatin loops consistent with bulk Hi-C data. It fills the technical gap of statistical loop detection at the single-cell level, provides new insights for the study of single-cell three-dimensional genomic regulation, and lays a foundation for the application of subsequent deep learning methods in single-cell scenarios.

C.Origami [26] is designed for the prediction of cell-type-specific chromatin loops. It constructs a multimodal model integrating 1D CNN and Transformer to simultaneously process DNA sequences, CTCF binding signals and ATAC-seq data, achieving high-precision loop detection and in silico genetic perturbation analysis. This method extracts local features of DNA sequences through 1D CNN, captures long-range sequence dependencies via Transformer, and integrates epigenomic features through a multimodal fusion module to build a unified loop prediction framework. Equipped with an in silico genetic screening module, it can simulate the effects of genetic variations on chromatin loops and support in silico perturbation analysis. In tests across multiple cell lines, the AUROC of C.Origami in cell-type-specific loop detection reaches 0.92, offering a powerful tool for resolving the three-dimensional genomic mechanisms underlying disease-related genetic variations.

RefHiC-SR [27] is developed to improve the resolution of low-depth Hi-C data and optimize the detection performance of chromatin loops and TADs via an attention-based super-resolution model. It first learns the spatial dependencies of Hi-C matrices through the attention mechanism, and enhances matrix resolution via an upsampling module to effectively strengthen weak interaction signals in low-depth data. Meanwhile, an embedded noise filtering module removes technical artifacts and improves the signal-to-noise ratio. In tests on clinical samples with insufficient sequencing coverage, RefHiC-SR markedly increases the detection rate of chromatin loops, delivering an efficient solution for three-dimensional genomic analysis of low-quality Hi-C data.

Be-1DCNN [28] is proposed for chromatin loop prediction based on Hi-C data. It adopts a Bagging ensemble strategy to integrate multiple one-dimensional CNN models, so as to enhance the stability and accuracy of loop detection. This method first converts Hi-C contact matrices into one-dimensional sequential data, and automatically mines spatial features through three convolutional layers without manual feature intervention. With the Bagging ensemble strategy, multiple base models are trained and their prediction results are integrated to avoid the bias of a single model and effectively improve the generalization ability. Evaluated on diverse Hi-C datasets, Be-1DCNN achieves superior loop detection performance compared with traditional CNN models, providing a lightweight and efficient scheme for low-complexity deep learning-based loop detection.

HiCDiffusion [29] is designed for deblurring and fidelity enhancement of Hi-C matrices. It integrates an encoder-decoder architecture, Transformer and diffusion model to reduce artificial artifacts and improve both visualization quality and quantitative accuracy of chromatin loop detection. The encoder first extracts latent features from Hi-C matrices, the diffusion model denoises and enhances the extracted features, and the decoder finally reconstructs high-fidelity Hi-C matrices. Moreover, the embedded Transformer attention module captures long-range spatial dependencies within the matrix and strengthens the model's feature learning capability. In comprehensive tests on various Hi-C data, HiCDiffusion greatly improves the detection accuracy and visualization performance of chromatin loops, representing a landmark application of diffusion models in three-dimensional genomics.

CD-Loop [30] is developed for chromatin loop detection on low-depth Hi-C data. It builds a pre-trained denoising framework based on the diffusion model to learn the prior probability distribution of Hi-C data and realize generalized prediction across species and cell types. The diffusion model is pre-trained on large-scale unlabeled Hi-C data to capture inherent data distribution patterns, and then fine-tuned on target datasets to adapt well to low-depth sequencing data. A cross-species transfer learning module is embedded to further boost model generalization by utilizing Hi-C data from different species. In cross-species and cross-cell-type generalization experiments, CD-Loop outperforms conventional deep learning models, bringing new perspectives for cross-species three-dimensional genomic research with low-depth data.

Capricorn [31] is proposed for the resolution enhancement of Hi-C contact matrices. It integrates small-scale chromatin features through a multi-view diffusion model to improve matrix fidelity across cell lines and chromosomes. Taking one-dimensional epigenetic profiles such as chromatin accessibility and CTCF binding signals as additional views of Hi-C matrices, this method generates high-coverage contact maps via a diffusion probabilistic model. It achieves a 26% improvement in F1-score in cross-cell-type settings and a 14% improvement in combined cross-chromosome and cross-cell-type scenarios. The enhanced matrices generated by Capricorn can identify CTCF-supported loops that are undetectable by conventional methods, providing critical technical support for in-depth mining of low-coverage Hi-C data.

HiCFoundation [32] is established as the first Hi-C foundation model. It is pre-trained on 118 million submatrices of contact maps based on the Transformer architecture, enabling universal three-dimensional chromatin architecture analysis across species and cell types. This model achieves state-of-the-art performance in multiple tasks including loop detection, super-resolution reconstruction and reproducibility analysis. Its F1-score of loop detection reaches 81.6% for high-coverage data and 75.1% for low-coverage data, which is significantly better than HiCCUPS and Chromosight. HiCFoundation can predict diverse epigenomic activities and resolve conformation-function associations, and also supports single-cell Hi-C analysis. It provides a unified, interpretable and generalized fundamental computational framework for three-dimensional genomic research.

CGLoop [33] is developed for chromatin loop prediction. It constructs a multimodal model integrating CNN, convolutional block attention module (CBAM) and bidirectional gated recurrent unit (BiGRU), to simultaneously capture local spatial features and long-range sequential dependencies and improve the precision and stability of loop detection. The CNN extracts local spatial features from Hi-C matrices, BiGRU captures long-range dependencies of sequential information, and the CBAM module weights different features to highlight the contribution of key

regulatory elements. Density clustering is further adopted to filter false-positive loops and reduce the false discovery rate. In multi-cell-line evaluations, the AUROC of CGLoop exceeds 0.91, offering an efficient solution for high-precision chromatin loop identification.

DconnLoop [34] is designed for chromatin loop detection using Hi-C data. It builds a deep learning framework with dynamic convolution and multi-scale feature fusion to overcome the limitations of traditional convolutional models in capturing long-range interaction patterns. It first adopts dynamic convolution layers to adaptively adjust kernel weights according to input data, so as to effectively capture local spatial dependencies in Hi-C matrices. A multi-scale feature pyramid module is then applied to extract interaction features at different genomic distances, covering both short-range and long-range chromatin interaction patterns. The embedded attention mechanism highlights feature contributions of key interaction regions and strengthens feature learning capability. To address the class imbalance problem in chromatin loop detection, DconnLoop combines oversampling and undersampling strategies to balance positive and negative sample distribution, and introduces focal loss to optimize model training and reduce false positives. Tested on Hi-C data of multiple cell lines, DconnLoop achieves outstanding loop detection performance compared with traditional CNN models, and presents strong robustness especially for low-depth Hi-C data. It provides a unified loop detection scheme for Hi-C data with variable sequencing depths.

CellLoop [35] is developed for rapid chromatin loop detection in single-cell Hi-C data. Based on the density center detection algorithm and re-voting strategy, it realizes efficient identification of chromatin loops in sparse single-cell contact maps. This method integrates interaction signals within individual cells and between adjacent cells, and enhances sparse signals through the re-voting strategy. It achieves an average detection time of only 0.99 seconds at 100 kb resolution and approximately 13 seconds at 10 kb resolution. With ultra-fast processing speed, it can meet the large-scale analysis requirements of tens of thousands to hundreds of thousands of single cells. CellLoop successfully identifies cell-type-specific chromatin loops and reveals their spatial correlations with gene expression, providing an efficient tool for the study of single-cell three-dimensional genomic heterogeneity.

NanoLoop [36] is tailored for chromatin loop detection by integrating Pore-C nanopore sequencing data. It simultaneously utilizes DNA sequence features and DNA methylation epigenetic features to mine methylation modification patterns at loop anchors, and identifies long-range multi-way chromatin loops that cannot be detected by conventional methods. This method first preprocesses raw Pore-C data to extract DNA sequence and methylation features, and integrates the two types of features via a multimodal fusion neural network to construct a prediction framework for multi-way chromatin interactions. The built-in multi-locus interaction recognition module enables the detection of spatial interactions among multiple genomic loci, filling the technical gap in multi-way interaction analysis. In tests on various Pore-C datasets, NanoLoop identifies a large number of novel multi-way chromatin loops, providing an effective tool for dissecting the regulatory mechanisms of multi-way chromatin interactions.

These emerging methods have thoroughly broken through the bottlenecks of conventional technologies and achieved leapfrog improvements in low-data dependence, multi-way interaction analysis, single-cell resolution and cross-species generalization, providing brand-new technical support for both basic research and clinical translation of chromatin loops.

# 7. Comprehensive Comparison and Core Challenges of Existing Methods

(1) Performance Comparison of Different Method Categories

The performance comparison of different method categories is presented in Table 1.

**Table 1.** Performance and Characteristics Comparison of Different Chromatin Loop Detection Methods

| Method Category | Representative Tools | Computational Efficiency | Feature Dependence | Detection Accuracy | Applicable Data | Interpretability |
|---|---|---|---|---|---|---|
| Statistical Methods | HiCExplorer, CHiCAGO | Extremely High | Data Distribution | Low-Medium | Hi-C / Capture Hi-C | Strong |
| Traditional Machine Learning | TargetFinder, Peakachu | High | Manual Features | Medium-High | Multi-omics Integrated Data | Moderate |
| Classical Deep Learning Methods | DeepLoop, GILoop, DeepLUCIA | Medium | Automatic Features | High | Multimodal / Low-resolution Data | Weak |
| Cutting-edge Integrated Technologies | CD-Loop, NanoLoop, HiCFoundation | Medium-Low | Automatic Features | Extremely High | Multi-way / Single-cell / Cross-species Data | Weak-Moderate |

(2) Core Technical Challenges in the Field

Although computational detection methods for chromatin loops have undergone multiple rounds of technological iteration and achieved dual breakthroughs in detection accuracy and application scenarios, the field still faces a number of common technical bottlenecks. These interrelated and mutually restrictive challenges have become core obstacles hindering the clinical translation and large-scale application of relevant technologies. Chromatin loop annotation data suffers from severe class imbalance between positive and negative samples. The number of positive samples representing functional genuine loops is far lower than that of background negative samples, making model training prone to bias toward majority classes. Consequently, final detection results are accompanied by a high false positive rate, which fails to meet the accuracy requirements of clinical practice and refined biological research. Conventional Hi-C data generally has a resolution ranging from 5 kb to 100 kb, which is insufficient for identifying small-sized functional chromatin loops. The adaptation and resolution enhancement of low-resolution data remain unsolved technical difficulties.

Meanwhile, chromatin loops detected by different experimental technologies show poor consistency, and there is no universally recognized gold standard dataset in this research field. This leads to the lack of objective criteria for model training, performance evaluation and horizontal method comparison. Insufficient cross-cell-line generalization is also a prevalent limitation. Most models perform well on cell lines used for training, while their accuracy drops sharply when applied to unseen cell types, restricting their large-scale application across multiple cell lineages. In addition, single-cell three-dimensional genomic data is extremely sparse, and traditional methods cannot stably identify dynamically changing single-cell chromatin loops. The black-box nature of deep learning models makes their decision-making processes difficult to interpret from a biological perspective, and the molecular connections between key features and loop formation cannot be clearly clarified. Moreover, there is a lack of time-series detection and prediction methods for dynamic loop alterations during cell cycle progression, stress response and disease development, and the analysis of dynamic regulatory mechanisms is still in its initial stage. Collectively, these issues restrict the advancement and practical implementation of computational chromatin loop detection technologies.

# 8. Future Research Directions and Development Trends

The future development of computational chromatin loop detection will center on three core directions: technological breakthrough, mechanistic analysis, and clinical translation, gradually realizing the transformation from basic computational tools to core technologies for disease diagnosis and precision medicine.

The in-depth fusion of multimodal data will become a core technological trend. By integrating multi-dimensional datasets such as Hi-C, Pore-C, epigenome, transcriptome and proteome, researchers can construct a unified framework for feature fusion and prediction. This enables the comprehensive capture of sequence, epigenetic, spatial and functional characteristics underlying chromatin loop formation, thereby further improving detection accuracy and generalization performance.

Foundation models and self-supervised pre-training will emerge as a new paradigm for chromatin loop detection. Pre-training on large-scale unlabeled Hi-C data enables models to learn universal principles of three-dimensional genome organization, followed by fine-tuning for specific cell types or disease states. This strategy can greatly reduce the reliance on annotated data and enhance cross-species and cross-cell-line generalization capabilities. The emergence of foundation models such as HiCFoundation marks a pivotal shift in this field from task-specific models to general-purpose foundation models. Combined with weak learning strategies, these models can further adapt to chromatin loop detection in clinically scarce samples and partially annotated datasets, breaking the technical limitations caused by insufficient sample size.

Specialized loop detection methods tailored for single-cell three-dimensional genomes will continue to achieve breakthroughs. Through technologies such as sparse data denoising, signal enhancement and temporal modeling, it will realize the dynamic tracking and mechanistic analysis of chromatin loops at the single-cell level, and reveal the three-dimensional genomic basis of cellular heterogeneity.

Lightweight and interpretable artificial intelligence technologies will promote the practical deployment of relevant models. Model compression and knowledge distillation can reduce computational resource consumption, while interpretable algorithms can clarify the biological basis for model decision-making, transforming deep learning models from black-box tools into biologically understandable analytical instruments.

Targeted mining of disease-associated chromatin loops will serve as a key application focus. Focusing on samples from cancer, genetic disorders and other diseases, researchers will develop disease-specific loop detection and annotation tools, and identify molecular biomarkers applicable to disease diagnosis, prognostic evaluation and targeted therapy.

The modeling of temporal dynamic chromatin loops will be gradually improved. The construction of time-series three-dimensional genomic models covering cell cycle, differentiation and disease progression will support the accurate prediction and functional annotation of dynamic chromatin loop changes, advancing the in-depth transformation of chromatin loop research from basic biology to precision medicine.

# 9. Conclusion

As the core functional unit of three-dimensional genome regulation, chromatin loops are critically important for deciphering gene regulatory mechanisms and revealing the molecular pathogenesis of human diseases, and their accurate detection has always been a key scientific issue in this field. Computational methods for chromatin loop detection have undergone three major technological iterations, including statistical algorithms, traditional machine learning and deep learning. These advances have achieved leapfrog development: from fixed distribution assumptions to automatic feature learning, from single-data input to multimodal integration, and from low-sensitivity detection to ultra-high-resolution identification. Since 2023, the integration of cutting-edge technologies such as diffusion models, nanopore sequencing, self-supervised learning and single-cell modeling has further broken the performance limitations of conventional approaches, providing innovative technical solutions for the analysis of multi-way interactions, single-cell dynamics and disease-specific chromatin loops.

At present, this research field still faces core challenges including severe data imbalance, the lack of unified gold standards, limited cross-cell-line generalization, technical obstacles in single-cell analysis, and poor model interpretability. With the continuous in-depth integration of artificial intelligence and three-dimensional genomics, multimodal fusion, weak supervised learning, interpretable modeling and disease-oriented application will become mainstream research directions. Gradually, computational chromatin loop detection technologies will move beyond basic research toward practical scenarios such as clinical diagnosis and precision medicine, offering a brand-new three-dimensional genomic perspective and core technical support for the prevention and treatment of human diseases.

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