3D Construction of Chromosomes using Reinforcement Learning

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Abstract

The research uses a method for reconstructing 3D chromosome structures from HiC data. It starts by preprocessing the data and converting it into distance matrices to handle experimental biases. Next, it transforms the normalized data into a spatial distance matrix using a conversion factor. Creating a weighted graph ensures adherence to the triangle inequality principle. The method utilizes probability distributions and divergence measurements for 3D structure reconstruction.

The study investigates reinforcement learning (RL) techniques to enhance the accuracy of reconstructed structures. RL helps in refining these structures. Utilizing techniques like Deep Q-Networks (DQN) boosts the precision of 3D structure reconstruction through refining predicted coordinates to closely align with actual ones. Evaluation metrics like Pearson and Spearman correlation coefficients offer insights into the improved quality of generated structures with RL methodologies.

Introduction

Chromosomes help with tasks such as reading genes, copying DNA, and safeguarding genes. Still, there's a lot to understand about how chromosomes fold in 3D and what it means for cells. Modern techniques like 3C, Hi-C, and ChIA-PET aid in enhancing understanding. Deciphering the 3D arrangement of chromosomes is challenging because of limited data and the dynamic nature of their organization.

In 2002, chromosome conformation capture (3C) techniques revolutionized understanding of the genome's 3D shape. These techniques demonstrated the positioning and folding of chromosomes inside cells, as well as their influence on gene activity. While 3C methods reveal how often different genome parts touch, don't show the full 3D picture, making it hard to understand chromosome structures from 2D data. New models, both physical and statistical, have emerged to tackle this problem. These models help link genome shape to its function, offering researchers ways to suggest and try out new ideas.

Studying how chromosome structure and gene expression connect is crucial for tackling genetic diseases. Fluorescence in Situ Hybridization (FISH) technology enables the visualization of chromosome structures in 3D, making the study of their arrangement in cells easier. But at first, this method only looked at small-scale structures, which couldn't show the detailed 3D arrangements. Hi-C technology is now here, and it's great for measuring how often different parts of chromosomes interact. This aids in understanding chromosome organization in detail, regardless of the scale.

Several methods exist for reconstructing 3D chromosome structures from Hi-C data, but often encounter resolution limitations due to time-consuming processes and sparse data. However, researchers developed a 3D chromosome reconstruction algorithm. It works well at both low and high resolutions, matching FISH structures and doing better than other reconstruction algorithms. The relationship between chromosome structure and gene expression affects cell activities a lot. Recent advancements in Hi-C data have facilitated a deeper understanding of chromatin organization within the nucleus.

Reconstructing chromosome structures from Hi-C data is challenging and requires sophisticated computer methods. Traditional approaches struggle to accurately depict complex arrangements. The study of how chromosome structure and gene expression connect is gaining increased attention in the fight against genetic diseases. RL seems promising for improving chromosome structure reconstruction. It learns and improves 3D chromatin structures over time. Integrating RL into chromosome structure reconstruction aims to reveal more about the genome's arrangement and its impacts on gene control and cell activities.

Background

Understanding the 3D folding of the genome is essential for studying cell activities. Deciphering the 3D arrangement of chromosomes from data like Hi-C presents a significant challenge. The data itself is uncertain and sparse, while chromosomes exhibit dynamic and random behavior. Hi-C data shows how often parts of the genome interact, which helps with 3D reconstruction.

Methods like multidimensional scaling (MDS), ChromSDE, ShRec3D, and miniMDS try to solve these challenges. Translating interaction frequencies into distances often involves making assumptions, which might introduce biases and errors in the reconstructed structures.

New genomic technologies, especially Hi-C, have changed the study of chromatin architecture. RL is a promising method for learning from Hi-C data. Algorithms like

3DMax, GEM, and Orca are trying to improve how to capture chromosomal organization.

Adding more information, like the shape of the nucleus, can make models more reliable. Recent studies show that using imaging techniques along with Hi-C data can give better reconstructions of chromatin structures. Combining both types of data can refine models and make them more accurate.

Advancements in RL are offering new ways to reconstruct 3D chromatin structures from Hi-C data. RL algorithms help computers learn from interaction frequencies and spatial rules. By adjusting model settings through trial and error, RL methods could fix the issues with traditional reconstruction methods.

Key Terminology

High-throughput chromosome conformation capture (HiC) serves as a method in biology to study the organization of chromosomes within a cell, uncovering interactions among various segments of an organism's DNA within the nucleus.

Chromosome arrangement occurs in a cell's nucleus in specific ways, impacting cell functions such as gene expression and DNA copying. HiC experiments explore these arrangements.

Genomic loci are specific spots on a chromosome, like genes or control areas. HiC experiments check how these spots interact with each other, showing spatial relationships and possible functions.

Pairwise interactions in HiC data indicate the physical contact between two genomic loci. When a particular location on chromosome 1 frequently contacts another location on chromosome 2, it signifies a pairwise interaction.

Interaction frequency shows how often two genomic loci meet in the nucleus. Lots of meetings suggest proximity, while few meetings mean more separation.

The spatial arrangements of chromosomes refer to their positioning within a cell's nucleus. It's comparable to arranging furniture in a room, and it influences gene activity and cellular operations. HiC experiments help us understand these arrangements by seeing how different chromosome parts connect, revealing the 3D shape of DNA in cells.

Related Work

Several significant methodologies and algorithms have been developed for reconstructing chromosome structures from Hi-C data. One notable approach is the Oluwadare et al. (2018), which utilizes gradient ascent optimization to reconstruct chromosome structures. This algorithm optimizes the log-likelihood objective function by incorporating factors such as contact maps, resolution, and interaction frequencies derived from the Hi-C data. Another notable study by Trieu et al. (2014) focuses on the large-scale reconstruction of the 3D structures of human chromosomes from chromosomal contact data. This approach involves preprocessing Hi-C data to reduce biases, removing contacts with low likelihood ratios, and representing chromosome structures based on observed contacts and non-contacts. These methodologies provide essential insights into the reconstruction of chromosome structures from Hi-C data, contributing to advancements in genomics and biomedicine research.

The GEM framework, as outlined by Zhou (2022), offers a method for reconstructing 3D spatial organizations of chromosomes through manifold learning techniques. The framework embeds neighboring affinities from Hi-C space into 3D Euclidean space, aiming to preserve local structure while mapping from Hi-C space. The Orca model architecture, as described by Zhu et al. (2018), presents a hierarchical sequence encoder and multilevel cascading decoder for multiscale 3D genome prediction. Trained on processed micro-C datasets for H1-ESCs and HFF cells, the model predicts interaction matrices representing pairwise genome interactions at varying resolutions. These diverse methodologies and algorithms contribute to the growing body of research in chromosome structure reconstruction, providing valuable insights and applications for understanding genomic organization and function.

The research paper by Li et al. (2016) outlines a method to reconstruct chromosome 3D structures from Hi-C data using computational techniques and reinforcement learning principles. The dataset includes both simulated and real Hi-C data from mouse embryonic stem cells (mESC) and human GM06990 cells. The methodology entails representing states using 3D coordinates, implementing actions like the shortest-path method and multidimensional scaling (MDS), and optimizing rewards by minimizing the discrepancy between predicted and experimental contact frequencies.

In Gong et al. (2023), the NeRV-3D-DC framework is presented for reconstructing 3D chromosome structures from Hi-C data. The dataset encompasses simulated and actual Hi-C data from GM12878 and IMR90 cell lines. The methodology includes converting contact matrices into distance matrices, reconstructing structures using divide-and-conquer strategies, and evaluating structures using metrics such as root mean square error (RMSE) and Pearson correlation coefficient (PCC).

Zhang et al. (2024) explore the analysis of 3D genomic mapping data, particularly focusing on Hi-C data to identify structural features like compartments, topologically associating domains (TADs), and loops. The paper emphasizes the challenges of achieving consistent feature identification across different methods and datasets.

Wang et al. (2023) introduce the EVRC algorithm for reconstructing chromosome 3D structures from Hi-C data. The dataset comprises simulation data and published Hi-C datasets. The methodology involves converting interaction frequencies into spatial distances, integrating the coclustering coefficient, and refining structure fit using reinforcement learning.

Song et al. (2021) present the DQN x-drop algorithm for local sequence alignment utilizing deep reinforcement learning. The dataset consists of DNA sequence pairs. The methodology includes representing alignment states, selecting actions based on alignment directions, and enhancing alignment scores using reinforcement learning.

Li et al. (2016) discuss methods for reconstructing 3D chromosome structures from Hi-C data, considering various techniques such as distance-based and contact-based methods. The paper underscores rewards based on the accuracy of reconstructed structures compared to experimental data and outlines methodologies involving state initialization, action selection, reward calculation, policy update, iteration, and validation.

Methodology

Dataset

HiC files

HiC files are specifically formatted to store HiC experiment data, documenting the frequency of interactions among different genomic loci. This format encompasses experiment settings and the precise chromosomal spot locations analyzed.

Within HiC files, rows represent genomic loci or regions, and columns denote the interactions between these loci, with each entry indicating the interaction frequency or strength.

In biology, HiC files contain data from experiments examining chromosomal positioning, revealing interactions among various genome segments. These files offer insights into interaction frequencies between genome segments, along with additional metadata like experimental settings and genomic coordinates.

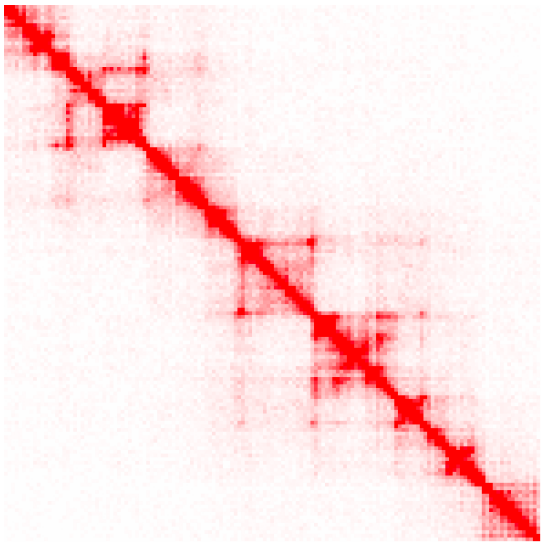

Figure 1: HiC contact map. Image source: Homer et al., retrieved from http://homer.ucsd.edu/homer/interactions2/HiCmatrices.html

Preprocessing

Conversion to Distance Matrix

Distance Matrices represent a square matrix where each entry denotes the distance between two points in a dataset. Widely applied across scientific disciplines, including molecular biology, they quantify relationships or dissimilarities between data points. In Hi-C experiments, distance matrices reveal the proximity or frequency of interactions among different genomic loci, offering insights into chromosomal organization and spatial relationships within cells.

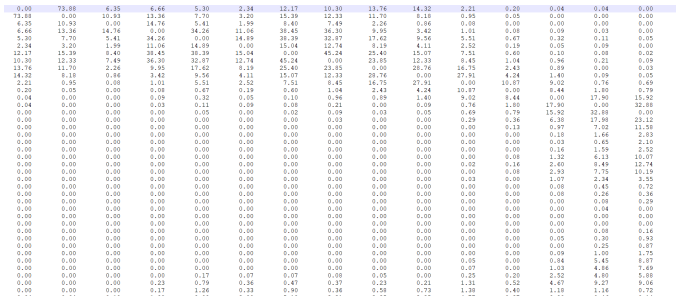

Figure 2: Snapshot of a HiC file

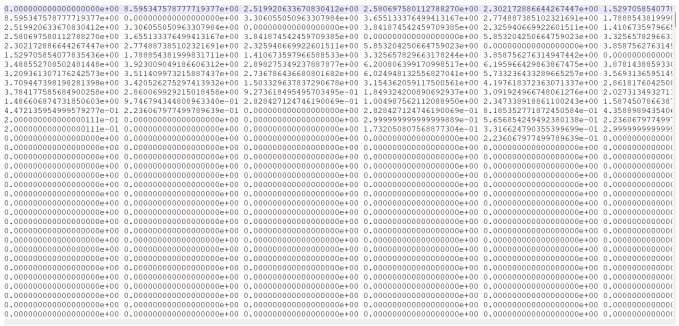

Figure 3: Snapshot of the converted pairwise distance matrix

The first formula, $d_{ij} = \sqrt{H_{ij} - C_{ij}}$, calculates the distance between points i and j based on the difference between corresponding elements in matrices H and C. This computation occurs within the context of a distance matrix.

The second formula, $d_{ij} = (normalized H_{ij} - C_{ij})^{-\alpha}$, determines the pairwise distance between points i and j by normalizing the difference between corresponding elements in matrices H and C, then raising it to the power of $-\alpha$. This calculation applies to all pairs of points within a pairwise distance matrix.

Normalization of Hi-C Data

The Hi-C contact matrix has been normalized using the Knight-Ruiz (KR) algorithm to eliminate systematic biases. This normalization method ensures that the resulting matrix retains the same patterns as the original Hi-C data but with reduced noise and more distinct features. The KR normalization process involved:

1. Calculating row and column sums with a small constant added to avoid division by zero.
2. Determining row and column scaling factors.
3. Applying these scaling factors to normalize the Hi-C data.

Transforming Distance Matrix into Weighted Graph

The transformation converts the distance matrix into a weighted graph, where genomic regions act as points and the distances between them represent the cost of moving from one point to another. This graph undergoes checking to ensure that all pairs of genomic regions adhere to the triangle rule. This verification process utilizes the Floyd-Warshall shortest path algorithm.

Floyd-Warshall's Algorithm finds the shortest paths between all pairs of points in a graph. It's useful for graphs with negative edge weights and many points. It's fast, even for big graphs, with a time complexity of $O(V^3)$.

3D Coordinate Estimation

First, random 3D coordinates are set up. Then, the model is trained using the provided distance matrix and the lambda value. Finally, the predicted 3D coordinates are saved to a text file. This process involves measuring distances between points, transforming them into probability patterns, comparing these patterns for similarity, and tweaking the 3D coordinates to improve fit. The following are the steps involved:

Pairwise Distance Calculation: Computes the distance between every pair of points (bins) in a 3D space. It employs the Euclidean distance formula, which you may recall from geometry. This formula measures the straight-line distance between two points.

Probability Distribution Calculation: Given a distance matrix D, this function calculates a probability distribution. Points closer receive higher probabilities, while those farther apart receive lower probabilities.

Neighborhood Probability Calculation: This function finds the probability of two bins being neighbors in 3D space. Like the previous function, it turns distances into probabilities, but it focuses more on nearby points' connections.

Kullback-Leibler Divergence Calculation: Finds the difference between two probability distributions using KL divergence. This measure shows how one distribution differs from the expected one. It helps compare how similar the two distributions are.

Cost Function Calculation: The function mixes the forward and reverse KL divergences into one cost function. The lambda_value parameter balances between them. This cost function shows how well the model matches the data and its internal representation.

Improving 3D Coordinates: The main training function improves the 3D coordinates (S) to reduce the cost function. It updates the coordinates using an iterative method, following the cost function's gradient. This process continues until the change in coordinates becomes sufficiently small (below a certain limit) or until it reaches the maximum number of iterations.

Methodology for Reinforcement Learning in 3D Chromosome Structure Reconstruction

Input data

Input data consists of actual and predicted coordinates loaded from text files. These coordinates represent positions in 3D space. Separate files are used to read both sets of coordinates, making sure their shapes match before proceeding with setting up and training the RL environment.

States

Each state is a vector representing the position in 3D space. The size of the state space depends on how many coordinates are in the predicted coordinate array.

At the beginning of each episode, the RL environment resets to its initial state, which is the first predicted coordinate in the sequence. Subsequently, as the agent interacts with the environment, the current state updates to the next predicted coordinate until the episode terminates.

Actions

Actions in the RL environment correspond to adjustments made to the predicted coordinates along the x, y, and z axes. The action space is discrete, with three possible actions: adjusting the coordinates along each axis.

At each point, the agent picks what to do. If a random number is smaller than the exploration rate (epsilon), the agent tries a random action. If not, it follows what it learned before and picks an action based on what the neural network says.

Rewards

Each step calculates the reward based on the Euclidean distance between the adjusted predicted coordinates and the actual coordinates. Using the negative norm of the distance as the reward shows that the agent earns a reward for reducing the difference between the predicted and actual positions.

Each episode adds up all the rewards gained at each step to calculate the cumulative reward. It serves as a measure of the agent's performance over the entire training episode.

Environment

The Environment is defined by the Environment class, which encapsulates the interaction between the agent and the coordinates. It maintains the actual and predicted coordinates, manages the current index to track progress through the coordinates, and provides methods for resetting and advancing through the coordinates based on the agent's actions.

Algorithm

In each training episode, the agent interacts with the environment by selecting actions, observing rewards, and transitioning between states until the episode terminates. At each step, the agent stores the experienced tuple in memory for learning through experience replay.

DQN The neural network model is a DQN consisting of densely connected layers with ReLU activation. The model learns to predict Q-values for state-action pairs, making it easier for the agent to choose actions.

Architecture of Neural Network The neural network architecture comprises an input layer with the state size, followed by two hidden layers with 64 neurons each and ReLU activation. The output layer has nodes equal to the action size, representing the Q-values for each action.

Replay Memory The agent utilizes a replay memory with a maximum capacity of 2000 experiences. Experience replay helps stabilize and improve training by randomly sampling past experiences to train the neural network.

Gamma Gamma, the discount factor, influences the agent's consideration of future rewards. A higher gamma value emphasizes long-term rewards, while a lower value prioritizes immediate rewards. Gamma is set to 0.95.

Epsilon Epsilon determines the balance between exploration and exploitation during action selection. A higher epsilon encourages more exploration, while a lower value favors exploitation. The initial epsilon value is set to 1.0.

Epsilon_min Epsilon_min defines the minimum exploration rate, ensuring that the agent continues to explore to some extent even after extensive training. The epsilon_min is set to 0.01.

Epsilon_decay Epsilon_decay controls the rate at which the exploration rate decreases over time. A higher decay value leads to a faster exploration rate reduction. The epsilon_decay is set to 0.995.

Output

The output of the training process is adjusted coordinates, aiming to better match the actual coordinates in 3D space. Additionally, the final Pearson and Spearman correlation coefficients between the actual and adjusted coordinates are computed and printed as indicators of the quality of the adjustment.

Evaluation

Pearson correlation coefficient

The Pearson correlation coefficient, denoted as r, is a statistical measure used to assess the strength and direction of the linear relationship between two continuous variables. It quantifies the degree to which a change in one variable corresponds to a proportional change in another variable.

With values ranging between -1 and 1, Pearson's coefficient provides insights into the linear association between variables:

- A correlation of -1 indicates a perfect negative linear relationship, where one variable increases as the other decreases linearly.
- A correlation of 0 signifies no linear relationship between the variables.
- A correlation of 1 reflects a perfect positive linear relationship, indicating that as one variable increases, the other variable also increases proportionally.

Spearman correlation coefficient

The Spearman correlation coefficient, denoted as ρ, is a statistical measure used to evaluate the strength and direction of the monotonic relationship between two variables. Unlike Pearson's correlation coefficient, Spearman's coefficient does not assume that the relationship between variables is linear; instead, it assesses how well the relationship can be described using a monotonic function.

Spearman's coefficient is based on the ranks of the data rather than their raw values. It ranges from -1 to 1, where:

- $\rho = -1$ indicates a perfect negative monotonic relationship, meaning that as one variable increases, the other variable consistently decreases.
- $\rho = 0$ implies no monotonic relationship between the variables.
- $\rho = 1$ signifies a perfect positive monotonic relationship, indicating that as one variable increases, the other variable consistently increases.

Results

3D Structure Reconstruction

The 3D chromosome structures were constructed. Pearson and Spearman correlation coefficients provided insights into the accuracy and consistency of the reconstructed structures.

5.593517379034445014e+00	-7.286316926486159140e+00	-3.170423409298598116e+00
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5.828009927596567330e+00	-2.197268913611325480e+00	2.955282790941653470e+00

Snapshot of the x, y, and z coordinates of the predicted structure

Conclusion

This study explores how to reconstruct 3D chromosome structures from Hi-C data using reinforcement learning (RL)

Table 1: Correlation Coefficients

Statistic	Value
Pearson correlation coefficient	0.99
Spearman correlation coefficient	0.99

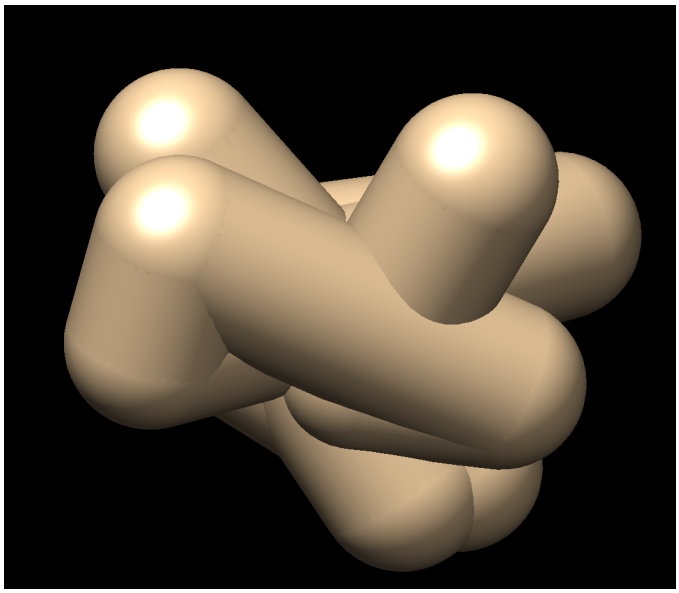

Figure 5: 3D reconstruction of the chromatin

techniques. Integrating RL algorithms improves the accuracy and efficiency of 3D chromatin reconstruction, solving problems with traditional methods.

The research shows how Hi-C data captures spatial relationships and interaction frequencies between genomic loci, revealing chromatin organization. The process converts Hi-C data into distance matrices. The graph theory algorithms, like Floyd-Warshall's algorithm, refine these matrices to enhance input for 3D structure reconstruction.

The reconstruction process involves calculating probability distributions based on distances. It also involves optimizing 3D coordinates using conjugate gradient algorithms and evaluating structures against actual coordinates using correlation coefficients. RL iteratively refines structures, improving fidelity.

Extensive evaluation, including Pearson and Spearman correlation coefficients, assesses the quality of the generated 3D structures. The study demonstrates RL's effectiveness in accurate reconstruction.

This study advances chromatin architecture studies by introducing a data-driven approach using RL techniques. Future research may optimize RL algorithms, integrate multi-omics data, and experimentally validate methods.

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